Novartis files globally for approval of Glivec

By Norman J. Scherzer
Coordinator, Life Raft Group

Who could imagine that only a very short time ago, we never heard of the disease GIST nor the drug STI571 (Glivec). Instead, patients were diagnosed as having something else (leiomyosarcoma, leiomyoma, leiomyoblastoma), and most were generally failing to respond to any combination of standard chemotherapy.

Many had exhausted their surgical options and some, including my wife, were very close to death.

Now, we are about 50 strong and growing all the time — an international, Internet-based, clinical trial community focused on a new drug (Glivec) for a newly recognized disease (GIST). Although it is quite early in the trials, and no one can predict the future, for most Life Raft Group trial

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Swiss pharmaceutical giant submitting applications worldwide

Novartis is submitting applications with health authorities globally seeking marketing authorization for Glivec (STI571) for the treatment of patients with chronic myeloid leukemia (CML) in the blast crisis, accelerated phase or in chronic phase after failure of interferon-alpha therapy.

These filings, announced March 1 and occurring within approximately one week of each other, continue the company’s efforts to accelerate the rapid pace of this novel agent’s global development.

Submissions have taken place in the U.S. and the European Union, and the filing for Switzerland was expected as of this writing (March 8). The filing will be submitted in Japan and other countries shortly as well.

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Reflections on the Life Raft Group

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STI trial sites

Here are the U.S. clinical trial sites (and Toronto, Canada) trying Glivec (STI571) on patients with gastrointestinal stromal tumor (GIST). For site contact names and phone numbers — or if you know of additional trial sites — e-mail the newsletter editor at linda@interpac.net

California
Jonsson Comprehensive Cancer Center, University of California, Los Angeles

District of Columbia
Washington Cancer Institute, Washington, D.C. 20010

Illinois
University of Chicago Medical Center, Chicago, Illinois

Maryland
Johns Hopkins Oncology Center, Baltimore, Maryland

Massachusetts
Dana-Farber Cancer Institute, Boston, Massachusetts

Michigan
University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan

Minnesota
Mayo Clinic Cancer Center, Rochester, MN

New York
Memorial Sloan-Kettering Cancer Center, New York, NY

Ohio
Cleveland Clinic Cancer Center, Cleveland, OH

Oregon
Oregon Cancer Center at Oregon Health Sciences University, Portland, OR

Pennsylvania
Fox Chase Cancer Center, Philadelphia, PA, U.S.A.

Texas
M.D. Anderson Cancer Center, Houston, TX, U.S.A.

Other countries
Canada
Mount Sinai Hospital, University Health Network, Toronto, Ontario Canada

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participants the experience has been akin to an “epidemic of miracles.” Hardly a week now goes by without someone reporting dramatic results of early tumor shrinkage.

In our last newsletter we presented our first response rate data, which showed over 85 percent of our Life Raft Members achieving significant drug response by the third month. We are currently evaluating the results of our recent side effects survey and will report on these in the near future. It is already clear, however, that these side effects, though serious for some, are far more manageable than those generally experienced during traditional chemotherapy.

Lest we forget, however, our clinical trial adventure is not without very real cost. Two members have died since starting the trial and, although there may not be any relationship between these tragedies and STI571, it is nonetheless very real that two people are no longer with us. Others have been taken off the drug, sometimes for short periods of time and sometimes permanently. Two trial participants have failed to respond and one other may have suffered a relapse. Many have had to overcome financial and emotional hardships. Some have had to overcome trial related mishaps.

Every trial participant has endured the imposition of numerous tests and the inevitable anxiety of waiting to hear whether they are amongst the lucky ones responding to this new drug.

The existence of the Life Raft Group has also created a new paradigm for the conduct of clinical trials. The rapid sharing of knowledge and experiences across national and institutional boundaries has created a situation where informed and empowered patients, and significant others, are becoming greater partners in the management of their care.

Our newsletter, so professionally crafted by our editor, Richard Palmer, is evolving into an important communication forum. Its distribution is growing to include the key clinical researchers managing the STI571 trials for GIST, senior Novartis officials, and others interested in learning from our patient driven data base and from our experiences.

Several of our members are using the Internet to reach out to lay persons and physicians seeking information about GIST and STI571. Gary Golnik, for example, is now serving as our liaison to Jerry Mayfield’s Unofficial STI571 Web site. This site, created for chronic myelogenous leukemia patients, has added a GIST section and Gary regularly responds to questions there. In addition, the Association of Online Cancer Resources has created an interim Web site where the general public can now access our newsletters and other information about GIST and STI571: http://www.acor.org/lrg/

Our philosophy has been to manage this new patient-driven information model in a responsible way and to forge positive and cooperative relationships with clinical researchers. To this end, I expect this newsletter to feature contributions from lead clinical researchers, such as Dr. George Demetri, and from senior Novartis officials, such as their president and CEO, Dr. Dan Vasella, the subject of a February newsletter article.

As we grow in size and wisdom, I believe that we will have a positive influence on the standards of medical practice for GIST, and that we will serve as a model for other clinical trial patient groups.

My thanks to our team of dedicated volunteers: Mia Byrne, list management; John Poss, treasurer; Penny Duke, membership coordinator; Janet Hendrickson, medical librarian; Richard Palmer, newsletter editor; Barry Jordan, Jerry Call, Marina Symcox and Gary Golnik, medical/scientific team.
Who’s new to the Life Raft Group

Welcome to all new members of the Life Raft Group.

Bruce and Roisin G.
Linda H.
Alicia F., for sister Marina
Ophir Z., for father-in-law Ehud
Sam H., for wife Julia
Mustafa and Zarina P., for father and husband Abbus
Bob J., for father-in-law Chet D.
Anne M., caregiver to Darlene V.
Deborah R., for mother Betty R.

GIST survivor Todd, with a lot to live for

Janet and Todd H. had this family portrait taken in September 1999. Todd was scheduled to undergo chemotherapy (MAID) and they weren't sure if he would ever have hair again. He eventually decided against chemo and had one final surgery before STI571.

Writes Janet: “Todd chased this drug from April 2000 to August 2000. He was the first person on the Portland trial thanks to some very hard work by Dr. Druker and Dr. Blanke. When he was given his first dose he was very near the end. He couldn't walk without being hunched over in pain. He had a tumor the size of a football in his abdomen that was terribly painful. He was doped up to the point of being unable to function and needed help in and out of bed.”

Today, Todd has had 75 percent reduction of tumor through his six month checkup, done the end of January.

“We are having the time of our lives enjoying our second chance,” says Janet. “It’s funny but that’s the gift in this awful scenario. You can view things quite differently in a very short time period ... the trick is not to forget.

“Each and every day is a gift,” she adds, “that’s why they call it the present.”

You can figure out who Mom and Dad are; that’s Tyler, 11, on the left, Max, 12, in the middle, and front and center 2-year-old T.J.

Want the newsletter sent via e-mail?

It comes as a PDF (portable document format) file attachment. You’ll need the free Adobe Acrobat Reader installed on your computer. It’s very useful since many things on the Internet are PDF files. It lives hidden in your computer and launches only when you click a PDF file. You’ll find it at www.adobe.com/products/acrobat/ readstep.html Just click “get Acrobat Reader free” and follow the steps; it’s easy.

To add your name to the e-mail mailing list, e-mail the editor at linda@interpac.net
phan drug designation by the U.S., the European Union and Japan.

The applications come in less than three years after the initiation of clinical trials with the agent, ahead of an industry average of nearly five years.

The filing is based on study results from approximately 1,230 patients in 32 centers located in five countries. To date, Glivec has been studied in more than 5,000 patients in 30 countries.

"We believe that Glivec marks the beginning of a new stage in cancer therapeutics development," said Dr. David Parkinson, vice president of clinical research, Novartis Oncology. "By understanding the molecular abnormality causing the cancer — CML in this case — we can design drugs like Glivec that target the fundamental biochemical abnormalities associated with cancers, with better treatment results and fewer toxic effects on normal cells."

About CML and Glivec

CML is one of the four most common types of leukemia. Worldwide, the disease occurs in one to two cases per 100,000 people per year and is responsible for 15 to 20 percent of all adult leukemias.

Glivec represents a new type of anti-proliferative agent called a signal transduction inhibitor (STI), which has been shown to have the potential to interfere with intracellular signaling pathways that have implications in tumor development.

Glivec molecularly targets an abnormal protein produced by the specific chromosomal abnormality called the Philadelphia chromosome, which is present in a majority of patients with CML.

The filing is supported by data from three Phase II studies. The endpoints of the studies included both hematologic and cytogenetic response rates. A cytogenetic response indicates the disappearance or reduction of Philadelphia chromosome-positive cells.

"The development of Glivec has been a tremendous experience for the investigator community," said Dr. Brian Druker, professor of medicine at Oregon Health Sciences University in Portland and principal investigator for the Phase I CML study. "Glivec has offered us not just an opportunity to provide a drug to patients that has truly changed the course of their lives, but has allowed us to evaluate a drug that may be the first of many that may radically change how cancer is treated."

- Dr. Brian Druker, principal investigator

In clinical trials, Glivec has been generally well tolerated, with side effects including nausea, muscle cramps, edemas, skin rash, diarrhea, heartburn, and headache, which have been largely mild or moderate in intensity.

Fewer than 3 percent of patients have experienced serious side effects such as the potential for liver toxicity, fluid retention syndrome, and hemorrhages.

Additional research underway

The Philadelphia chromosome involved in CML is present less commonly in patients with acute lymphocytic leukemia (ALL). Some patients with these rare forms of leukemia were included in the Glivec clinical trials.

Additionally, in a program of small-scale, proof-of-concept studies, Novartis recently began investigating the role of Glivec in select types of solid tumors where the biological mechanisms suggest potential activity. These pilot studies are intended to establish the basis for further clinical trial study.

Novartis accelerated development

As a result of the highly promising Phase I results, which eventually drew widespread demand for Glivec (STI571 at that time) by CML patients, Novartis recognized the potential impact this agent could have on the CML community and prioritized and accelerated the compound’s development with all diligence. Additional resources were devoted to supporting, expediting and expanding the clinical program. Novartis also increased the technical resources and capacities devoted to the product, transferring production of Glivec directly to large, commercial-scale manufacturing facilities.

Manufacturing Glivec entails many processes to ensure a high purity and reproducible drug substance, and the company initiated measures that decreased the complex procedures to a production time of approximately 9 to 12 months.

"Since the first promising data emerged on Glivec, Novartis began taking extraordinary steps to expedite..."
When we were dating, Jim told me his goals were to be a husband, a father and a judge,” says Betsye Ackerman. “I told him I wanted to be happy. We both accomplished our goals with each other and the help of our children, Tom and Jill.”

Life Raft Group member Jim Ackerman died Jan. 16, 2001, 10 months after he was diagnosed with cancer, a year after he was appointed a judge on the Arizona Court of Appeals. He was remembered Jan. 22 at a special session held in the Arizona Supreme Court, the first time such an event was ever held there.

“One of the qualities he will be most remembered for here is his good cheer,” said E.G. Ted Noyes Jr., chief judge of the appeals court. “You could hear his laughter several chambers away. … Jim’s laughter could leap out, too, surprising even him. … you’d soon be roaring too, and having a better day than before he came in. Jim had a way of doing that for people and for situations — making them better than before he came in.”

Ackerman was born Dec. 29, 1951, the son of Charles and Martha Ackerman of Lincoln, Neb. He grew up in Phoenix, and after an initial stint at college, tried his hand as a painting contractor. After a bid miscalculation earned he and his partner just $300 for three weeks work, he became inspired to study.

He earned his bachelor’s degree, summa cum laude, from Arizona State University in 1979, then graduated magna cum laude from the ASU College of Law in 1982.

He clerked for Judge William Canby, U.S. Court of Appeals, Ninth Circuit, and there found out that he, too, wanted to be an appellate judge.

He joined the law firm of Jennings, Strouss & Salmon in 1983. For several years he headed the firm’s legal clinic at a Food City store in Phoenix. Betsye said that many of the pro bono clients still sent him Christmas cards.

“They appreciated so much that he had helped them,” she said.

He was appointed an appellate judge by Gov. Jane Hull and took the oath of office in January 2000. Ackerman, said Charles “Bud” Jones, justice of the Arizona Supreme Court, “was on a virtual cloud when he was appointed to the court.”

He was diagnosed with leiomyosarcoma two months later. Despite his illness, Ackerman wrote some 40 decisions while fighting the disease.

“The only sense I can make of this is that he has been called up to the highest court where he will shed his light and wisdom upon us,” says Betsye. “He never gave up hope and he would want the same for you.”

A fund has been established in Ackerman’s honor: The ASU Foundation, Ackerman Fund, c/o Susan Matthews, ASU College of Law, P.O. Box 877906, Tempe, AZ 85287-7906.

More FDA approval
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the development program,” said David Epstein, president of Novartis Oncology. “The enthusiasm surrounding this drug has been incredible.

"Filing the registration package in just 32 months after the first human dosing demonstrates the dedication of Novartis employees and investigators who have devoted themselves to making Glivec available to patients in need," Epstein added. "The outpouring of support from the patient community has provided a real boost to all of us."

In the U.S., patients and physicians interested in more information on these studies can contact the Novartis Oncology Clinical Trials Hotline at 1-800-340-6843, or the company's Web site, www.novartisoncology.com.

The company did qualify its "forward-looking statements," pointing out the use of such terminology as "believe," "highly promising," "potential impact," "may drastically change" or similar expressions. "Such statements," said the company's press release, "reflect the current views of the company with respect to future events and are subject to certain risks, uncertainties and assumptions. Many factors could cause the actual results, performance or achievements of Glivec to be materially different ..."
**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 listserv 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.

There was discussion among the patients present about the use of vitamins with STI-571. Several said they take their supplements at the same time as STI-571 and have not had any adverse reaction. Others take their supplements at a different meal than they take STI-571. Wilson said as far as they know, basic multiple vitamins (but no megadoses) do not interfere with the assimilation of STI-571.

Adds Scherzer: The Life Raft Group is completing its own study on side effects and will report on the results in the next newsletter. A preliminary review of the still-incomplete data is revealing that the worst side effects seem to be skin problems, cramping, eye puffiness and reflux. There appears to be a pattern emerging, with those on the greater 600 mg dose reporting a greater degree in the severity of side effects. There also seems to be some early evidence that the gender of the patient plays a role in side effects.

**OHSU notes**

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speaker at the March meeting. She told the CML patients that GIST stands for gastrointestinal stromal tumor and is a soft-tissue cancer which produces tumors in the abdomen. The characteristics that set GIST apart from other leiomyosarcomas are significant and still being studied.

The first trial for treatment of GIST with STI571 was opened at Oregon Health Sciences University in Portland, Fox Chase in Philadelphia, Dana Farber in Boston, and the University of Helsinki in Finland with a total of 36 patients. This trial was sponsored by the maker of STI571, Novartis, which is marketing the drug as Glivec. It has since been expanded to 142 openings. A new Phase III trial sponsored by the National Cancer Institute has begun and is expected to serve an additional 600 GIST patients within 24 months. Both trials are virtually identical, with the major difference being drug dosages. The earlier trial is comparing 400 mg and 600 mg dosages, while the new phase III trial is comparing 400 and 800 mg doses. (Note: Neither trial has a control group receiving another treatment or a placebo, as there is no other effective treatment for GIST and using a placebo would be both unwarranted and unethical.)

The benefits reported to date include decreases in tumor size, reduced need for pain medication and improved endurance. To Wilson’s knowledge, though some patients at OHSU have had to stop taking the drug temporarily, no one has been removed from the trial due to low blood counts.

Since there is no marker in the blood for GIST as there is for CML, tumor tissue is tested to determine if it expresses a protein (oncogene) called c-kit which regulates the enzyme tyrosine kinase. STI-571 works to inhibit this enzyme, thereby stopping the growth of tumor cells. Where CML patients are monitored through bone marrow biopsies, GIST patients are primarily monitored with CT scans which show changes in tumor mass.

Research has found other cancers that express c-kit including some brain tumors, small cell lung cancer and prostate cancer. Discussion is taking place about the possibility of a trial open to other cancer patients with tumors expressing c-kit.

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