Silvia Williams Steinhilber has been a member of the Life Raft Group Board of Directors since 2002. She was born in Germany and moved to Canada when she was 8 to begin a new life in Winnipeg, Manitoba.

Silvia was educated in biochemistry and for a time worked at Winnipeg’s main hospital in the radiopharmacy department, concocting the mix that’s injected for CT scans. She eventually decided to partner with her father to establish an injection-molding firm. She has been doing that for 30 years and loved working closely with her father, until he passed away.

Her leisure activities include camping, getting together with good friends, music, rock gardening, reading and enjoying a glass of good wine. When the first day of spring arrived March 21 of this year, she married her long-time (14 years!) beau, Garry, and became Mrs. Steinhilber.

Silvia became involved with the Life Raft Group after her mother was diagnosed with cancer in 2001. Doctors informed them that nothing could be done.

Silvia didn’t accept that. She searched the Internet, found the Life Raft Web site and some information on Gleevec, and e-mailed Norman Scherzer. He referred her to a doctor at...
Novartis to help patients on Medicare

Novartis will work with new drug coverage to ensure Gleevec supply

Novartis has announced that it will help GIST patients in its financial assistance program in the United States if there is difficulty with the out-of-pocket costs associated with the new Medicare Replacement Drug Demonstration. Patients in the Patient Assistance Program (PAP) accepted into the Demonstration project will remain eligible for PAP support if the co-pay obligation exceeds $60 per year and no alternative source is available to support their co-pay obligation.

One Life Raft Group member recently voiced concern that the new Medicare program could cost them the financial help from Novartis. The issue was that the Novartis assistance program had no out-of-pocket costs whereas the Medicare program did.

"We have had a number of conversations with Novartis about this," said Norman Scherzer, executive director of the Life Raft. "We have been made aware that there is a new foundation to help eligible patients with these out of pocket costs. Novartis' Patient Assistance Hotline has information on how to contact this new foundation."

Scherzer also shared a letter from Barbara Kennedy, executive director of Oncology Scientific Operations for Novartis. Novartis, Kennedy wrote, recognizes the concerns of Life Raft Group members “and wants to assure them that all Medicare-eligible patients currently enrolled in the Novartis Patient Assistance Program (PAP) will remain eligible for PAP support if they are denied coverage under the Demonstration or their co-pay obligation exceeds $60 per year and no alternative source is available to support their co-pay obligation.”

The Novartis program is designed to get Gleevec to patients who lack insurance coverage or the means to pay for the medicine after all other potential avenues are explored. All patients in PAP are re-evaluated every six months to determine continued eligibility. “The Medicare Replacement Drug Demonstration is a potential avenue for coverage of Gleevec,” Kennedy said, “and therefore must be considered before the Novartis PAP.”

Given the complexity of Medicare and Novartis programs, “Novartis is assisting patients, physicians and caregivers with the application for the Demonstration and with information about alternative sources of support for any co-pay obligations,” Kennedy wrote.

Patients who have questions can contact the Gleevec Patient Assistance Program at (866) 884-5906, weekdays from 9 a.m. to 5 p.m. Eastern Standard Time.

ON BOARD!

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the University of Minnesota in Minneapolis who was familiar with GIST and Gleevec.

Her mother’s first appointment with Dr. Keith Skubitz was scheduled the day after Christmas. That holiday was spent in a motel room just outside Minneapolis. Christmas dinner was pizza and a brandy while sitting around a 1-foot tree.

The trip turned out to be a lifesaver. Her mother’s cancer was determined to be GIST and she was given Gleevec. She experienced initial tumor shrinkage and has remained stable since 2002.

Silvia and Garry Steinhilber
Novartis, Pfizer join to co-sponsor the meeting; European trial reviewed

By Marlies Bruinsma

 Members of the Dutch Life Raft Group had their first national gathering Saturday, Sept. 25 in Scherpenzeel, The Netherlands. The meeting began with registration and socializing at 10.30 a.m., followed by a very interesting presentation by Dr. W. Van der Graaf, internist/oncologist at the AZG Groningen, who spoke of new trials in The Netherlands and future possible treatments.

Reactions were positive and new members heard a lot of new information. Van der Graaf was also able to present the group with the outcome of an European trial about Glivec dosage levels which was published a day earlier in The Lancet medical journal.

After the presentation, patients and caregivers had the opportunity to ask questions to a panel with Van der Graaf and M. Van Hattum, Novartis product manager for Glivec.

Novartis and Pfizer kindly sponsored the meeting.

During a lovely lunch, patients, caregivers and participants were able to socialize and get to know each other better.

At 2:30 p.m., members were divided in small groups to talk about diagnoses, hospital treatments, communications with and between oncologists, social changes and more.
GIST mutation top cause Gleevec failure

Secondary mutation appears the most likely reason for resistance

While Gleevec initially works very well for most GIST patients, cancer can eventually become resistant to the drug. Dr. Jonathan Fletcher of Dana-Farber Cancer Institute in Boston, and others presented some preliminary data about this problem at the 2003 convention of the American Society of Clinical Oncology. They noted four types of resistance in GIST:

1. Resistance due to acquisition of a secondary mutation (evolution of secondary KIT or PDGFRA mutants).
2. Resistance through overexpression (the tumor cells produce greater amounts of c-kit, the target kinase).
3. Activation of alternate mechanisms (kinase switching [e.g. KIT] to unknown kinase).
4. Functional resistance: Little is known about this type of resistance. It includes intrinsic (initial) resistance and may include undetermined factors.

Further research has found that acquisition of a secondary mutation appears to be the most common reason for resistance. As reported extensively in other articles, the primary genetic defects that drive GIST tumors are mutations in the c-Kit gene (in about 80 to 90 percent of cases) and the PDGFRA gene (about 5 percent of cases). Mutations can occur in different parts of the gene called “exons.” The c-Kit and PDGFRA genes contain information (a code or blueprint) that determines how the KIT receptor and the PDGFR receptor are assembled. These receptors are a type of protein. Proteins have complex three-dimensional shapes that allow them to carry out their normal function (such as signaling) in the cell. A mutation in the gene changes the shape of the protein, which changes its ability to function correctly. The mutations that occur in the c-Kit and PDGFRA genes typically result in the respective receptor being converted into a “constant-on” state.

For the KIT or PDGFRA receptors to perform normal signal transduction functions, a chemical called ATP (adenosine triphosphate) must bind to a site in a section of the receptor called the kinase domain. The kinase domain has a three-dimensional shape and, like a key fitting into a lock, Gleevec fits into the ATP binding site in the kinase domain and blocks ATP. This prevents KIT- or PDGFRA-mediated signaling. Some mutations in the kinase domain apparently alter the shape of the binding site and prevent Gleevec from binding. The key (Gleevec) no longer fits into the lock (the ATP binding site in the kinase domain), and resistance to Gleevec develops.

Dr. Michael Heinrich at Oregon Health & Sciences University and others reported that of 112 GIST tumors studied, none had more than one activating mutation in KIT or PDGFRA prior to starting Gleevec. Several different groups of researchers are now reporting that many resistant tumors have a secondary mutation as well as...
Pamela Bowden was a dancer, figure skater

Pamela Bowden, figure skater, dancer, and lifetime Citibank employee, died Aug. 30, 2004, nearly five years after being diagnosed with GIST. Daughter of the late Alfred F. and Emily C. Bowden, Pamela was 54 and lived in Garden City, New York.

A graduate of Molloy College in Rockville Centre, New York, Pamela served as a Senior Systems Analyst at Citibank. She had been involved with Citibank’s home banking system since its inception during the mid-1980s.

Pamela thoroughly enjoyed her work, and was determined to put in a full day at the office (driving 25 miles each way) no matter how much she was struggling with fatigue or other side effects. She worked up until the day before her hospitalization in late August.

An accomplished figure skater, Pamela had devoted a great deal of time to skating lessons and practice sessions, passing several levels of tests as a young woman. Later in life she turned her boundless energy to tap dancing, working with an outstanding instructor to develop a unique and graceful combination of tap and ballroom dancing.

Along the way, Pamela also found time for tennis, swimming, diving, cross-country skiing and kayaking, participating in these sports with much vigor and joy.

Pamela had a great affection for Lake Placid, New York, where she spent both winter and summer vacations. It was in the Adirondacks that she acquired several pairs of antique ice skates to add to her significant collection of such artifacts. It was also in this part of the world that Pamela befriended “Smitty,” a young black bear who had been converted into a “piano bear” for the Hotel Saranac restaurant, following an unfortunate confrontation with an automobile. A few years ago she brought Smitty home to Garden City, where he became an important part of the Bowden household, seated happily at the player piano in the living room. Subsequently, Smitty became known to many as the subject of several delightful narratives written by Pamela.

Pamela participated in the phase II clinical trials of both Gleevec (Dana-Farber Cancer Institute, December 2000), and SU11248 (Memorial Sloan-Kettering, January 2003).

She is survived by her three older sisters, Barbara, Juliana Schmitt and Emily. A Mass of Resurrection was celebrated Sept. 3 at St. Joseph’s Church in Garden City.

John Mabee is survived by his wife of 18 years, four children

John Edward Mabee of Toronto, Ontario, Canada, died Saturday morning, Oct. 9, 2004, surrounded by his loved ones. He is survived by his beloved wife of 18 years, Beatrice (nee Borenstein); grown children Bryan, 34, and Kim 32; and Stephanie, 16, and James,14; two brothers, George and Bill; three sisters, Pat, Gail and Lynda, as well as his brothers- and sisters-in-law, cousins, nephews, nieces, friends and family.

He was a man of love, integrity and loyalty who always strived to do the best he could, and was an inspiration loved by many.

Services were held Oct. 12 in Toronto; interment was at York Cemetery.

Mark the date:

- Oct. 22-23: Das Lesbenhaus GIST forum at Novotel, Frankfurt, Germany.
- Oct. 24: Life Raft Group Board of Directors meeting.
- Nov. 7: Team Life Raft runs New York City marathon to raise money for the Life Raft Group; members gather afterwards at place to be announced.
- Nov. 12: Life Raft Group relapse study presented to the Connective Tissue Oncology Society in Montreal, Canada.
- Nov. 18: Poker tournament fund-raiser for the Life Raft Group; New York City site to be announced.
the original primary mutation.

Dr. Lei Chen and others at M.D. Anderson Cancer Center in Houston have identified a secondary mutation that occurs in KIT kinase domain 1 (exon 13). This secondary mutation correlates with resistance to Gleevec.

Among the 130 patients in the M.D. Anderson study, 12 who had an excellent initial response were chosen for further study. Seven of these patients originally had exon 11 mutations and five had exon 9 mutations. Five of these patients developed resistance in a total of six tumors. In each case, in addition to the original exon 11 or exon 9 mutation, a new secondary exon 13 mutation, Val654Ala, was identified. In each of these cases, the secondary mutation was identical and the resistant tumors now contained both the primary mutation (exon 11 or exon 9) and the new exon 13 mutation. In the seven patients who did not develop resistance no secondary mutations were found.

Dr. T. Wakai and others of Niigata University Graduate School in Niigata City, Japan, recently published a short article identifying a patient who developed a second KIT mutation in exon 17 (the tyrosine kinase domain 2). This secondary mutation was not present in the primary tumor and resulted in Gleevec resistance in the tumor with the secondary mutation.

Dr. George Demetri of Dana-Farber and others reported early results of the SU11248 trials at the 2004 ASCO meeting. In 57 patients with Gleevec-resistant GIST:

- 22 (39 percent) had a mutation in KIT only
- 1 (2 percent) had a mutation in PDGFRα only
- 9 (16 percent) had no detectable mutations (wild type)
- 25 (44 percent) had two or more mutations in KIT

Despite being resistant to Gleevec, many of the tumors with two or more KIT mutations did respond to SU11248 with either shrinkage defined by RECIST criteria or stable disease lasting more than six months thus far. Of those tumors with a secondary KIT mutation in exon 13 or exon 14, nine patients (56 percent) received benefit (response + stable > 6 months) and two patients (13 percent) achieved shrinkage. Secondary mutations in
Deep in the heart of Texas

The Southwest Life Raft Group met Sept. 18 in Dallas, Texas. Seated from left are Glenda Zick, Dee Hawkins, Betty Arnett, Betty Avant, Melinda Poss and Jim Arnett; standing from left, Sue Waggoner, Tim Cline, John Stinson, Barbara Stinson, Norman Scherzer, Jeryl Golden, Donna Golden, Kerry Hammett, Kurt Molitor, David Epstein and Gayne Ek. The next meeting of the Southwest Life Raft Group will be Jan. 22, 2005 at Gilda’s Club of North Texas. For more information or to suggest program ideas, contact Kerry Hammett at yaloow@gvtc.com.

RESISTANCE II
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exon 17 were less sensitive to SU11248, but three patients (38 percent) still achieved stable disease for more than six months. No RECIST response occurred in the seven patients with secondary exon 17 mutations.

In his ASCO presentation, Dr. Demetri speculated on why SU11248 might work when Gleevec fails:
  • SU11248 could interact differently with structural variants of new kinase mutants in GIST clones resistant to Gleevec.
  • The simultaneous inhibition of multiple signaling pathways by SU11248 may be important for controlling GIST (such as VEGF, in addition to KIT and PDGFRA).

Dr. Jayesh Desai of Dana-Farber reported on a novel pattern of clonal evolution in certain GIST tumors at the 2003 Connective Tissue Oncology Society (CTOS) meeting in Barcelona, Spain. This pattern was termed a “nodule within a mass,” and was noted in approximately half of patients (22 of 42) with progressive GIST in a study by the Dana-Farber team.

These “nodules” often appeared before the development of progressive disease. Conventional tumor measurements will not detect this type of progression unless expansion of the nodule causes a very significant increase in the size of the surrounding mass. The nodule within a mass is a subtle but important early marker of GIST progression, according to Desai.

Multiple small nodules developed in some patients over a period of months. In most patients, the nodule arose from the edge of the mass, whereas both the mural surface and the tumor matrix were involved in a subset of patients.

In an interview at the 2003 CTOS meeting, Desai indicated that the keys
A survival paradigm for GIST

Rethinking the standard of keeping inoperable patients on 400 mg.

By Norman Scherzer
Executive Director, Life Raft Group

Almost every day the Life Raft Group office gets calls from GIST patients and doctors asking for information. Most are seeking ways to stay alive, or keep patients alive.

As the research on GIST grows, including the critical research that the Life Raft Group conducts itself, a paradigm for survival is evolving for patients on Gleevec with inoperable tumors.

A few weeks ago European researchers released their latest report about dosage and resistance. They reported that larger doses are related to longer times to disease progression.

In November the Life Raft Group will present a research paper to the Connective Tissue Oncology Society on relapse rates amongst metastatic GIST patients who initially responded to Gleevec. This data will show that higher doses are related to lower relapse rates.

Some researchers may take the position that patients should continue on lower doses (400 mg.) until all research has determined that this is unwise. (U.S. studies are ongoing and have not found any relationship between dosage and resistance.) We understand this but prefer to operate on the side of caution and see patients on a greater dosage until research proves it is safe to do otherwise.

Accordingly we offer our survival paradigm for GIST patients with inoperable tumors who are on Gleevec:

- Start patients at 400 mg. per day.
  - There is no difference in initial response to Gleevec related to dosage levels. Instead, initial response seems to be related to the type of mutation.
  - Side effects are often minimized by starting on a lower doses and phasing in higher doses.

- Gradually increase the dosage to at least to 600 mg. per day, perhaps higher.
  - Higher doses are related to lower resistance rates.
  - Higher doses can prevent resistance from subsequently occurring in metastatic GIST patients who had initial shrinkage.
  - This finding is consistent with the recent European report on progression and with earlier data from Europe suggesting that clearance of Gleevec — the rate at which the drug leaves the body — increases over time. This may explain why side effects get better over time.
  - Current research has shown that

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increasing dosage after resistance is generally not successful in reversing resistance, though it does help some patients by halting disease progression.

Therefore, it is easier to prevent the development of resistance with higher doses than to try to reverse resistance with higher doses after the fact.

- Exercise caution before reducing dosage in response to side effects.
  - Side effects are related to dosage levels.
  - They usually get better over time.

- The development of resistance does not seem to slow over time — at least not so far — so patients at lower doses should not find false comfort in the fact that they have not yet developed resistance.

This is not a perfect blueprint and others may disagree. This paradigm is based on what we have learned from the research community, our own research and from more than 500 Life Raft Group case records. Be warned, however, that we are not physicians and we urge patients to use this information only as the basis for an informed discussion with their own doctors.

Also, these remarks pertain only to GIST patients on Gleevec with tumors that are not amenable to surgery. Patients with operable tumors should talk to their physicians about surgery.

We do not have enough data yet regarding the efficacy of Gleevec — at any dose — in patients who have had surgery and are taking Gleevec on a preventive (adjuvant) basis.

* European Organization for Research and the Treatment of Cancer (EORTC), the Italian Sarcoma Group (IRG) and Australasian Gastrointestinal Trials Group (AGITG).

** The European study compared 400 mg. to 800 mg. and concluded that the higher dose had a longer rate to progression. They did not look at 600 mg. The Life Raft Group has compared 400 mg. to 600 mg. and more; we did not have enough data to distinguish between 600 mg and 800 mg.
Who are we, what do we do?
The Life Raft Group is an international, Internet-based, non-profit organization providing support through education and research to patients with a rare cancer called GIST (gastrointestinal stromal tumor). The Association of Cancer Online Resources provides the group with several listservs that permit members to communicate via secure e-mail. Many members are being successfully treated with an oral cancer drug Gleevec (Glivec outside the U.S.A.). This molecularly targeted therapy inhibits the growth of cancer cells in a majority of patients. It represents a new category of drugs known as signal transduction inhibitors and has been described by the scientific community as the medical model for the treatment of cancer. Several new drugs are now in clinical trials.

How to join
GIST patients and their caregivers may apply for membership free of charge at the Life Raft Group’s Web site, www.liferaftgroup.org or by contacting our office directly.

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, including medical professionals. However, this newsletter serves as an outreach and is widely distributed. Hence, all articles are edited to maintain the anonymity of members unless they have granted publication of more information.

How to help
Donations to The Life Raft Group, incorporated in New Jersey, U.S.A., as a 501(c)(3) nonprofit organization, are tax deductible in the United States. Donations, payable to The Life Raft Group, should be mailed to:

The Life Raft Group
40 Galesi Dr.
Wayne, NJ 07470

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