



Nancy and Murton Brock on their farm by Exeter, Ontario, Canada.

Ignorance is bliss, but not about GIST

Nancy Brock has advice for newcomers: Obtain knowledge, be assertive

By Erin Kristoff

Life Raft administrative assistant

Nancy Brock had a CT scan in March; five weeks later the results came back, "I knew something was wrong, the nurse wasn't making eye contact with me."

The tumors in her liver had doubled in size and she had edema in her legs, feet and abdomen. Her doctor said he was slightly concerned with the results and upped her dosage of Gleevec to 800 mg.

Nancy's previous CT scan had been in October, six months earlier. Most

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Battling gastrointestinal stromal tumor



LIFE RAFT GROUP

April-May 2005

In memory of Avraham Anidjar,
Alan L. Fink, Nancy Welsh

Beyond Gleevec: The next-era drugs for GIST

AMN107 could prove to be the next bullet in the Novartis cancer arsenal

(Editor's note: The first part of this article was adapted from an April 19 press release from the American Association of Cancer Research.)

By Jerry Call

Life Raft science coordinator

Patients with chronic myelogenous leukemia (CML) typically respond very well to Gleevec. However, for a small number, their disease eventually becomes resistant to Gleevec. The primary mechanism of resistance identified in these patients is the acquisition of a new secondary mutation in bcr/abl, the oncogene that causes CML. At least 16 secondary mutations have been identified in CML.

In GIST patients, secondary mutations in the target gene, c-kit, are the largest known mechanism of resistance. Secondary mutations in GIST patients also occur in an alternative receptor, PDGFRA.

Structural studies have identified the crystal structure of both bcr/abl and KIT. Using this enhanced understanding of the exact shape/structure of the



Photo courtesy Novartis

The new Novartis drug AMN107 is in phase I clinical trials for chronic myelogenous leukemia, and it could have applications for GIST.

intended target, researchers from the Dana-Farber Cancer Institute in Boston and Novartis Pharmaceuticals have developed a new drug, AMN107, that binds tighter to the bcr/abl target (the kinase domain of the bcr/abl protein).

In an abstract presented April 19 at the 96th annual meeting of the American Association of Cancer Research AACR in Anaheim, Calif., scientists

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NEXT ERA

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at Oregon Health and Science University (OHSU) in Portland compared AMN107 against Gleevec using a panel of cell lines expressing 16 different mutant, Gleevec-resistant versions of bcr/abl.

The OHSU researchers found that 15 of the 16 mutants are predicted to be sensitive to AMN107, while one mutation remains insensitive and will require a different, as yet undiscovered, inhibitor. In the same study, the investigators also tested BMS-354825, the new drug from Bristol-Myers Squibb. This drug was equally impressive, according to Dr. Thomas O'Hare, a research specialist in the lab of Dr. Brian Druker, OHSU's CML pioneer.

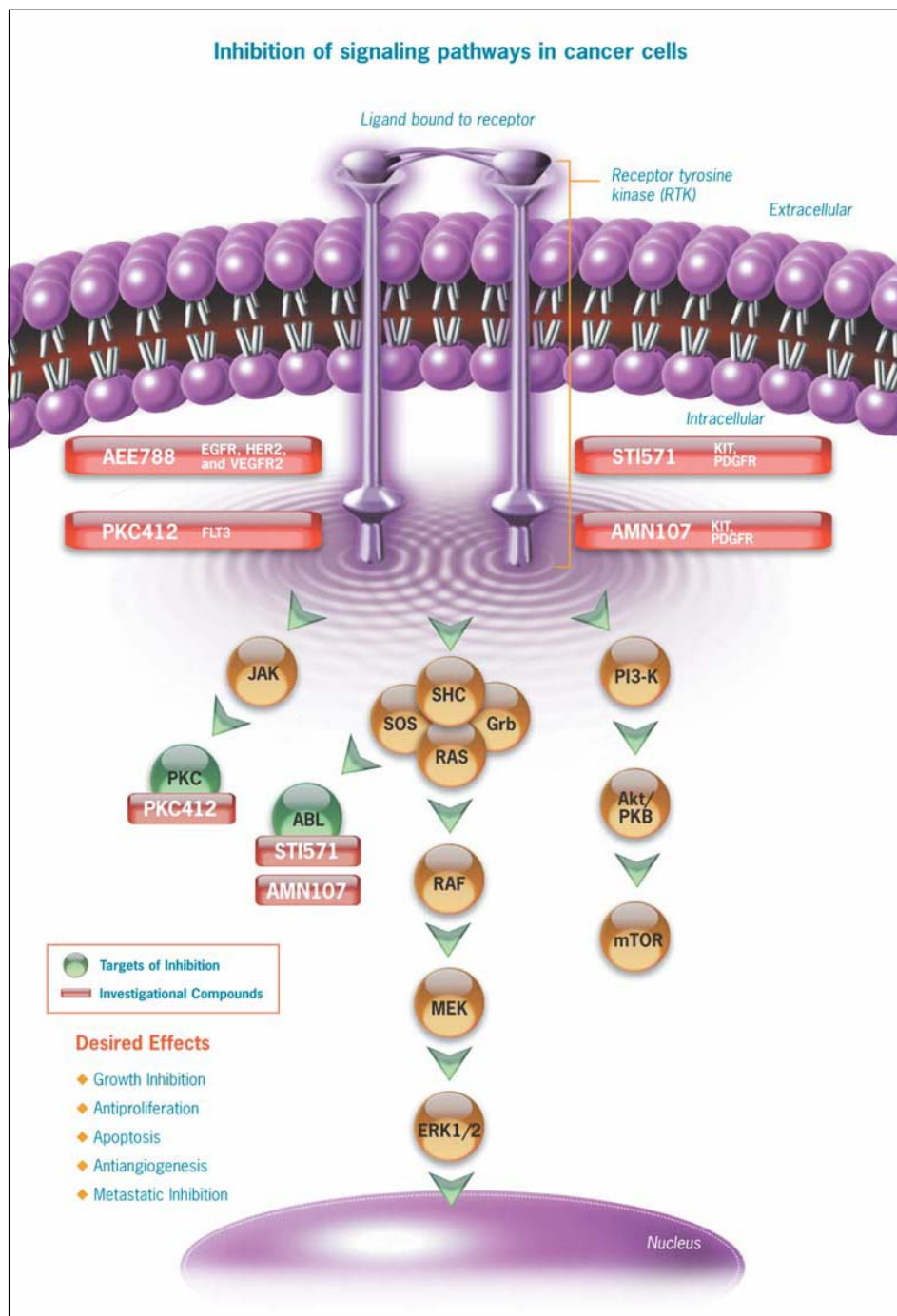
Researchers presented preliminary results of the phase I trial for AMN107 in CML patients. They reported that more than 70 percent of advanced CML patients have responded to the drug — and early CML patients have responded at a rate of more than 90 percent. The researchers noted that the response rate in more than 100 patients enrolled in the clinical trial to date continues to improve, as doses are rapidly increased. The first patients began treatment at 50 mg., but now all are taking 400 mg. twice a day and have not reached a dose-limiting toxicity.

According to Dr. Francis Giles, leader of the AMN107 study at M.D. Anderson Cancer Center in Houston, the potential success of AMN107 represents a "phenomenal rate" of drug development since Gleevec was introduced in 1999.

"We have been able to take the knowledge of how Gleevec works — where, exactly, it binds to bcr/abl — and tweak it to be as much as 30 to 100 times more potent."

DISCUSSION

CML and GIST occur with very similar frequencies, 10 to 20 people per million per year for CML and



AMN107 is an oral tyrosine kinase inhibitor that targets Bcr-Abl, KIT and PDGFR. This Novartis illustration shows how signaling pathways in cancer cells may be inhibited by targeted chemotherapies. For more, see the Novartis Web site, <http://www.novartis oncology.com/page/amn107.jsp>

14.5 people per million per year in GIST. Relapse rates to Gleevec are higher in GIST than in early stage CML, and relapse rates in advanced CML are probably higher than in GIST. AMN107 was designed for Gleevec-resistant CML patients. BMS-354825 was designed as a Src

inhibitor. Its excellent efficacy in CML is perhaps just a fortunate coincidence. While the Pfizer drug SU11248 has shown some efficacy in Gleevec-resistant GIST patients, there is still an unmet need for a new KIT/

Pediatric GIST family gathering near

Parents and children from California to the United Kingdom are planning to meet in northern New Jersey state the weekend of May 20.

The Life Raft Group will welcome about a dozen pediatric GIST families. Starting with a family-style Italian dinner on Friday night in Little Falls, New Jersey, the program will move Saturday morning to Gilda's Club in Hackensack, New Jersey. There the parents will have an opportunity to meet one another and talk to a number of medical experts about the management and treatment of pediatric GIST.

Simultaneously, the young adults will meet with staff from Tomorrow's Children that have achieved wide recognition for their work with adolescents trying to cope with their cancer, including body image, interrupted school and social schedules and coping issues.

After lunch, parents and children will be picked up by bus and head to New York City for a tour that will include Rockefeller Center, Times Square, and Madame Tussauds Wax Museum and



Trish McAleer, Life Raft Group executive assistant, left, and Susan Cohen of Tomorrow's Children plan the May 20 pediatric GIST family gathering.

wind up with hamburgers, french fries and hot fudge sundaes at the Hard Rock Café in Manhattan.

A wrap-up buffet breakfast Sunday

morning will pull the weekend's events together and send each family off with new friends, great memories and hugs.

GIST DRUGS

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PDGFRA inhibitor that, using currently available structural data of the KIT/Gleevec interaction, has been engineered to overcome secondary mutations in KIT/PDGFRA.

A phase I clinical trial to include Gleevec-resistant GIST patients is underway for BMS-354825. Trials with AMN107 are planned. It remains to be seen whether either of these drugs, which were not optimized for KIT or PDGFRA mutations, will prove to be more effective than currently available therapies. Phase II trials are underway for the Amgen drug AMG706, but it is

too early to speculate on the response of Gleevec-resistant GIST patients.

So the question becomes, "Where's the optimized drug for GIST?" Perhaps a half-dozen or more new drugs that inhibit either KIT or PDGFRA were reported in abstracts at the AACR meeting. Most of these drugs also inhibit various forms of VEGF. Thus, their primary target indications may be based upon their ability to inhibit angiogenesis. As such, it is unlikely that they have been specifically engineered to overcome the secondary KIT/PDGFRA mutations that

cause GIST to resist Gleevec. It's possible that one or more of these drugs will be effective in resistant GIST due to chance. Another possibility might be attacking KIT/PDGFRA using a different or perhaps complementary method, such as anti-sense therapy or HSP-90 inhibitors.

GIST seems to be a more complex disease than CML. It is possible that the response rate to more effective optimized KIT/PDGFRA inhibitors still might not be as high as in CML, and that combinations of drugs might be more effective than single agents.

BROCK

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GIST patients are scanned every three months.

"I think my oncologist was overly optimistic, all his other GIST patients did so well, that may be why he didn't push harder for a CT every three months." Nancy doesn't blame any of her doctors for her situation, though.

"I am a passive person; this is not a disease to be passive about." That's why, when diagnosed four years ago when she was 34, Nancy went on the Internet in search of answers and found the Life Raft Group.

"I was surprised to see that there were so many people like me that were my age or younger. They had things in common with me and we're struggling together."

So she checked her e-mail from the LRG. "It [helped] get me through."

Nancy lives on the outskirts of the small town of Exeter in Ontario, Canada. Even though Exeter boasts a large population of the town mascot, the majestic white squirrel, the human population is only around 4,400.

"I guess because I come from a small town, I felt really isolated. In day-to-day life I feel singled out, like 'that girl in town with that weird disease.'"

However, the people of Exeter have been very supportive of Nancy. In just one week she received a gift certificate for a massage, two apple pies, soup, cookies, muffins and more. "The community is amazing."

One day Nancy was pulling into her driveway when she saw a woman at her door with a casserole and cookies. "She said to me, 'I don't really know you, but I've heard of you and I just want you to know you are in our thoughts.'"

The people of Exeter and the Life Raft Group aren't the only ones behind Nancy. Her husband, Murton, 12-year-old daughter Jessica, and 10-year-old son Madison are also helping her out. "We've got a great family," Nancy



The Brock family — Nancy, Murton, Jessica, 12, (holding the family dog, Scout) and Madison, 10.

says. "They always want to be with us."

"I think because they're farm kids, they see a lot of life and death happening every day, they are strong children, and they're willing to help with anything."

Last Christmas, Nancy decided to reward her family with a trip to the Dominican Republic. "It was a good time to go; I just thought 'I need to take my kids snorkeling.'" Despite the malaria scare that occurred while they were there, "it was amazing."

Nancy has had her share of dark days. "Sometimes it's hard to just be a good little cancer patient." Not long ago she felt like she had had enough. "I shut myself in my room for three days," she recalls. "I just wanted it all to go away, but I saw what it did to the kids and that was worse."

"I hate putting my family through this. I could deal with it easier if I didn't have to look in their eyes and tell them about bad reports. I hate to see my mom cry and cause grief to anybody. I try to keep smiling and

having fun and doing the best I can." And she is.

Shes involved with Jessica and Madison's lives. The children are very involved in sports. Jessica plays ringette, a game like hockey but played with a stick and a ring (instead of a puck). Madison enjoys curling, a game similar to shuffleboard but played on on ice. It's customary for the winners to buy the losers a beer or, given Madison's age, root beer.

Life on their 600-acre farm is interesting too. With a dog, Scout; a horse, Dakota, and a pet chicken, Lucky Larry (saved from a county fair), the Brock family has it all.

"Jessica always wanted a horse," and in March, she got one. Only nine months old, Dakota is too young to ride but he's still fun. "His father was a champion barrel racer, and he runs around like a spoiled puppy."

The family also canoes, and Nancy has begun gardening at additional farmland her husband has purchased.

Nancy had a diploma as a graphic

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Progress against GIST inches ahead

Advances in diagnosis, treatment reported by American Association for Cancer Research

Editor's note: Jerry Call, science coordinator for the Life Raft Group, attended the 96th annual meeting of the American Association for Cancer Research held April 16-20 in Anaheim, Calif. This is his report on the handful of sessions that he was able to attend.

By Jerry Call

Life Raft science coordinator

A potentially useful way for testing anti-GIST drugs aimed at KIT mutation that sparks cancer was unveiled by Dr. Brian Rubin, a pathologist at the University of Washington Medical Center in Seattle.

He presented a poster, abstract no. 1977, "A Mouse Model of Gastrointestinal Stromal Tumor." This mouse model may be useful for testing new anti-KIT based therapies.

Rubin, Dr. Christina Antonescu of Memorial Sloan-Kettering Cancer Center, and their colleagues used a genetic "knock-in" strategy to replace one normal Kit allele with a mutate allele (for each characteristic or trait, organisms inherit two alternative forms of that gene, one from each parent. These alternative forms of a gene are called alleles). The KIT mutation introduced was K641E, which is equivalent to an exon 13 mutation found in a human familial GIST syndrome family.



RUBIN



ANTONESCU

The mice developed hyperplasia in interstitial cells of cajal (ICC) and GIST tumors that are histologically, immunohistochemically, ultrastructurally and biochemically identical to human GISTs, and thus represent an excellent model for the study of ICC biology and the pathogenesis of GIST.

FLAVOPIRIDOL

Dr. Elliot Sambol and Dr. Samuel Singer, et al, from Memorial Sloan-Kettering presented a poster, abstract no. 1504, "Flavopiridol is an active agent in the treatment of gastrointestinal stromal tumor (GIST) cells with relative resistance to imatinib mesylate via both transcriptional suppression and inhibition of autophosphorylation of KIT."

While flavopiridol is widely known as an inhibitor of cyclin-dependent kinase (CDK2 and CDK1), its effects may be mediated more by inhibition of transcription than anything else (Cell Cycle review, December 2004).

The Sloan-Kettering team used a GIST 882 cell line for their experiments. They found that total KIT protein was significantly diminished in flavopiridol-treated cells after 24 hours. This resulted in an indirect reduction in KIT autophosphorylation, comparable to Gleevec. They confirmed that transcriptional downregulation was the reason for reduced total KIT protein, by using quantitative real time RT-PCR.

Compared to control cells, KIT mRNA was reduced by 18.25 percent and 61.1T at 150nM and 300nM of flavopiridol, respectively, after 24 hours. They also found that flavopiridol, at clinically achievable doses, induces a high level of apoptosis (cell death) in GIST cells. They believe

their findings justify a clinical evaluation of flavopiridol in treating patients with Gleevec-resistant GIST.

The way flavopiridol works against KIT is different than Gleevec. Flavopiridol reduces the total amount of KIT protein, where Gleevec inhibits the activation (phosphorylation) of the KIT protein present without lowering the amount of KIT protein. One of the mechanisms of Gleevec-resistance is overexpression of KIT or PDGFRA (too much KIT or PDGFRA protein).

MICROARRAYS in DIAGNOSIS, TREATMENT

Memorial Sloan-Kettering teamed up with Affymetrix Inc. to present a poster, abstract LB-47, "Affymetrix Gene Expression Microarrays as a Tool for Detecting Copy Number Aberrations in Gastrointestinal Stromal Tumors."

Microarrays are a tool for examining the expression of thousands of genes at the same time. By using microarrays and special software to study the expression of different proteins in cells, researchers hope to track down the genetic changes that promote cancer.

One of the changes that can occur in a cancer cell is the loss or gain of genetic material. This can be a whole chromosome, or a smaller segment like a gene. In this study, researchers were able to detect copy number aberrations such as deletions in Chromosome 1p, loss of Chromosome 22, and amplification in Chromosome 3q. Studies are in progress to determine the smallest change that can be reliably detected using this approach.

The potential for microarrays is vast, from diagnosis to personalized treatment. In what appears to be the first small step in moving microarray technology from the lab to the clinic, Affymetrix and Roche announced the availability of the world's first microarray instrument system for clinical



SINGER

AACR

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diagnostics last September. The AmpliChip CYP450 Test will allow diagnostic laboratories to identify certain naturally occurring variations in the drug metabolism genes, CYP2D6 and CYP2C19 (note: CYP2D6 enzyme plays a role in Gleevec metabolism, where CYP3A4 is the major enzyme involved in Gleevec metabolism).

These variations affect the rate at which people metabolize many drugs used to treat depression, schizophrenia, bi-polar disorder, cardiovascular disease and more.

Knowledge of these variations, considered with other factors, can help a physician select the best drug and set the right dose for a patient sooner, as well as avoid drugs that may cause the patient to suffer adverse reactions. This testing is currently approved only in the Europe.

ANTIANGIOGENESIS

Emerging concepts in translating antiangiogenesis therapy to the clinic was the topic of a session led by Dr. Rakesh K. Jain of Massachusetts General Hospital. One of the key hypotheses of this session is that antiangiogenic agents, when used judiciously, can transiently improve the function of tumor vessels and facilitate the delivery of oxygen (a radiation sensitizer) and drugs.

This “vessel normalization” hypothesis underscores the importance of dose and schedule in combining antiangiogenic therapies with cytotoxic therapies. The hypothesis was that normal tissues have normal blood vessels. Blood vessels that feed tumors are abnormal. As antiangiogenic treatment progresses, tumor blood vessels change from abnormal to normal before they start to shrink and deteriorate. The period of transition, when vessels are changing from abnormal to normal, may represent a window of time when both radiation and delivery



of cytotoxic drugs to the tumor may be improved.

The presenters hypothesized that after beginning VEGF blockage (VEGF is one of the most common/important antiangiogenic targets), tumors might be more sensitive to radiation three to six after starting VEGF blockage.

They noted that this might be dependent on tumor type and, in the case of chemotherapy, the window might also be drug and dose dependent. The presenters offered a few other opinions:

That proper dose of antiangiogenic drugs is important for tumor blood vessel normalization.

That antiangiogenic therapies can have different goals, i.e., tumor starvation, improved drug delivery, sensitizer to radiation.

TARGETED CHEMOTHERAPIES

Presentations were given on some newer types of chemotherapy, with specific targets but perhaps rather general or wide-ranging effects. These included heat shock protein 90 (HSP-90) inhibitors, proteasome inhibitors, and histone deacetylase inhibitors (HDAC inhibitors). These classes of drugs were reviewed in our report of the 2004 AACR meeting (see the April 2004 edition of the LRG newsletter).

Another class of drugs, mTOR inhibitors, with a specific target also is similar in some ways to these other drugs, in that it may treat a rather wide range of cancers due to the importance of the target to cancer cells generally. Most notable among these drugs is the addition of at least two drugs with bet-

ter solubility/better formulation in the HSP-90 inhibitor class. These two drugs are IPI-504 from Infinity Pharmaceuticals, and 17-DMAG from Kossan Biosciences. 17-DMAG is in phase I clinical trials, and IPI-

504 should be entering phase I trials very soon. Impressions from the presentations are that these drugs are likely to work better when combined with other drugs (including between the 4 classes listed here) and that they may have not only synergistic benefits, but perhaps synergistic toxicities as well.

Jeffrey Tong from Infinity Pharmaceuticals gave a presentation on Infinity's HSP-90 inhibitor, IPI-504. HSP-90 is a protein that helps fold other proteins into their final shape. Inhibition of HSP-90 prevents proteins (including KIT) from folding into their three-dimensional shape. This indirectly inhibits KIT signaling (presumably by reducing the amount of active KIT protein). Tong described three paths for unfolded proteins.

— They can be refolded by HSP-90 protein.

— They can be degraded by a “cellular machine” called the proteasome.

— They can accumulate in the cell, triggering cell death (apoptosis).

Because the first two items can both be inhibited by different drugs, there exists the possibility that combining the two classes of drugs would lead to more cell death as the unfolded proteins accumulate.

It should be noted that Dr. Julian Adams, formerly of Millennium Pharmaceuticals, developed the first drug approved in the proteasome inhibitor class, Velcade, and has since joined Infinity Pharmaceuticals and was instrumental in developing IPI-504.

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Medical mistakes happen, sometimes in a big way

Error reading CT scans nearly lead to patient's ouster from clinical trial

By Norman Scherzer

Life Raft Group executive director

Most Life Raft Group members have learned that there is a high correlation between managing their own health care (either by the patient or a caregiver) and good medical care.

While respecting the opinion of their doctors, particularly those who are GIST specialists, members have learned that medical care is quite complex and that mistakes do happen.



SCHERZER

A recent example: A few weeks ago a GIST patient at one of the world's leading medical centers for GIST was told that (s)he was going to be removed from a clinical trial due to disease progression. The patient's written report stated: "The lesions have increased in size... For example, the dominant lesion ... now measures 7.4 cm. x 6.3 cm. ... This lesion is ... larger in comparison to prior (report) where it measured 6.3 x 6.1 cm. The concluding impression paragraph stated that "THE LESIONS HAVE INCREASED IN SIZE SINCE THE PRIOR (REPORT). (The caps have

not been added; they were that way in the report.)

When the report was compared against the actual measurements taken by the radiologist and recorded into the patient's record, quite a different picture emerges. Not only did the other lesions actually decrease in size but the dominant lesion cited changed from 6.3 x 6.1 cm. (that measurement was correct) to 6.1 x 5.0 cm. — not 7.4 x 6.3 cm. In other words, the tumor being measured was smaller, not larger.

Fortunately, for this particular patient, the mistake was caught in time to keep her/him from being removed from the clinical trial. The impact upon the patient's emotional well-being ... well, we will leave to the reader to evaluate.

Life Rafter's gather in Southern California



GIST patients and caregivers gathered April 9 at the Los Angeles-area home of Floyd and Joyce Pothoven. "We had a really great time as usual," reports Floyd. The regular gatherings seem to grow by a face or two each time, even though quite a few people couldn't make this gathering. "We sat in a circle and everyone gave their name and a description of their own individual experience with the discovery that they had GIST and their treatments over the years," says Floyd. "Everyone had lots of questions for each other." Picture, from left, are Pete Kavaloski, Lee Kavaloski, Peter Henning, Judy Henning (holding Mason Henning) Mike Rider, Susan Rider, Beverly Wishon, Glenn Wishon, Ellen MacDonald, Dina Wiley, Sam Wiley, Cindy Dunigan, Gary Kirk, Joyce Pothoven, Lee Kirk, Vadim Schukin, Natasha Shukin (almost hidden), Bobbie Offen, Floyd Pothoven, Henry Offen, Jackie Edwards and Wayne Edwards.

Maher Samet of Tunisia, good friend and father

Maher Samet, Life Raft Group member in Tunisia, died Feb. 24, 2005. Fellow Life Rafter Bertrand de la Comble of France sent this message from his wife, Leila. Some of the words have been changed to smooth the translation from French. If only there was some way to change the pain that his wife and children are feeling.

“Dear friends,

“I am really sad to announce the passing of my husband, Maher. He left with plenty of good memories in our minds and in our hearts.

“Maher was born on the 22nd of August 1961 in Tunisia. He was the oldest son of the Samet family. His parents were very proud of him, because he was a brilliant pupil. He had the opportunity to succeed with excellent scores in high school.

“In 1979, the government sent him to France where he obtained a degree in engineering from Ecole Centrale de Paris. His dream was computing science. He was crazy about computers - it was his passion till the last days of his life.

“We met in the summer of 1991 and we married in February 1992 when we moved to France where our two children were born, Sana in 1994 and Malek in 1997. Then we came back to Tunisia. We chose to live in Sousse, one of the best tourist places in Tunisia. He joined Meublartex Holding as IT manager and he was very happy at his job. In 2001, our third baby was born.

“We were a happy family; he loved his kids, and he was careful to ensure their education, until the 25th of December, 2001, when he discovered that he had a tumour.

“At this time, everything has changed. During these last three years, he used to believe in recovery; he was fighting in all the way, for



Maher Samet of Tunisia died Feb. 24, 2005. He's pictured here in happier times with his wife, Leila, and two of their three children.

himself and mainly for us, I never left him and I do not regret it. For the last two months, his situation became worse, and quickly, he felt that GIST was going to win; he never showed that he was waiting for a miracle; that never happened, or at least in time.

“Now that he's gone too early, at 43 years old, I really suffer; kids too. Maybe God preferred to save him from pain; today I am sure he does not suffer anymore from GIST. He must be in a better place. GIST prevented him from eating, sleeping, working and then living, even with Gleevec in France, then Suglen in Switzerland.

“He was a good friend, everybody loved him, he was a nice guy — that's what people tell me. He was a

fighter, he never gave up, he was an excellent husband and a perfect father.

“I hope that research will find the right solution to GIST

“I'd like to let you know what Professor Levraz wrote when he heard about Maher's passing:”

“Dear Mrs. Samet, Dear Samet Family,

“I am very sad of hearing the bad news you sent, your husband was fighting as a lion, and we all admire his courage and his determination. He did, you did, more than expected. I was very happy to meet such a brilliant person, and to be close to him for the last months. I am really sad, and I am disappointed because we could not do better. Our hearts are you and with your family.”



Alan Fink, above and at right, loved riding, whether it was bicycles or his Harley-Davidson motorcycle.



Alan Fink, 45, loved riding, family and friends

Alan L. “Alf” Fink died Wednesday, April 13, 2005 after a long battle with GIST. He was 45.

Alan was diagnosed in September of 2000. He had surgery weeks later, and also underwent a then-new clinical procedure called photodynamic therapy, which involves using lasers to burn tumor cells after administration of a drug that makes the cancer more sensitive to the laser treatment.

After the cancer returned eight months later, Alan joined the phase III clinical trial of Gleevec for GIST.

When Gleevec failed him after a year, he volunteered for the SU11248 trial, which didn’t work for him. He also tried combining the relatively new antiangiogenesis drug Avastin with

Gleevec, and Avastin with the more traditional chemo Gemzar.

Alan told his story in the January 2003 issue of the Life Raft newsletter.

Originally from Philipsburg, PA, Alan graduated from Penn State University in 1984 and moved to Bear, Delaware, in 1991. He was known for his involvement in First State Harley Owners Group, his participation in many bicycle rides raising money for the MS Society, Habitat for Humanity, the American Cancer Society and several other charities, and for his sense of humor. He will be greatly missed by his family and friends.

He was the beloved husband of Betty (Fedorkowicz), loving son of William and Doris (Stranko) of Osceola Mills, Penn., father of Matthew Fink of

Waldwick, N.J., and Jessica Okarski of Wilmington, Del. He is also survived by his brothers-in-law, Pete Fedorkowicz, Paul Fedorkowicz and Dan Fedorkowicz; sisters-in-law, Gladie Brogan, Joanne Nichols, Mary Anderson and Barbara Brothers; his great aunt, Anne Galvin of Conn.; along with many loving aunts, uncles, cousins, nieces and nephews.

Services were held April 18 at Hope Lutheran Church, 230 Christiana Road, New Castle, Del. In lieu of flowers, the family asks for donations to be sent to Vitas Hospice, 100 Commerce Drive, Suite 302, Newark, DE 19713; or to the American Cancer Society, 92 Reads Way, New Castle, DE 19720. To send online condolences, please visit www.dohertyfh.com

**Life Raft Web site
visitors hail from
the U.S., Canada
— and Japan**

In the last newsletter, readers were asked if they could name the third-leading country from which the Life Raft receives visitors to its Web site, the first two being the United States and Canada.

The correct answer was Japan,

The Life Raft Web site has recorded almost 1,000 visitors from Japan in the past 50 weeks.

Unfortunately, no one got the right answer and the accompanying prize — a Life Raft Group T-shirt and pin.

Nancy Welsh, 37, survived GIST for more than 14 years

Nancy Welsh, 37, of Evanston, Illinois, died April 28, 2005. Nancy survived GIST for more than 14 years, being first diagnosed with leiomyosarcoma in January 1991, then correctly diagnosed with GIST 10 years later.

She is survived by her husband, Randall Welsh; her parents, Jim and Margi Hughes; a sister, Jamie

Hughes, and many aunts, uncles, cousins and friends.

A funeral Mass was held May 3 at the Church of St. Mary in Lake Forest. Interment was at St. Mary Cemetery, Lake Forest.

In lieu of flowers contributions may be made to Shannon's House, 10 Maplewood Road, Medfield, MA, 02052 or The Life Raft Group, 40 Galesi Drive, Wayne, NJ 07470.



Portrait of Nancy Welsh, taken by Life Raft member Mark Thomas

Life Raft Group directors accept challenge grant

The Life Raft Group Board of Directors has accepted the challenge of a family whose loved one died of GIST that could raise \$720,000 over the next five years.

The offer was accepted April 19. The anonymous family pledged \$72,000 a year for five years if board members committed a like amount. The combined family and board pledge would raise \$144,000 a year for the next five years.

In turn, the board will ask Life Raft Group members to match the board's pledge.

The challenge grant is in memory of the Life Raft Group members whose candles inspire the group to continue the battle against GIST. This money will be used to support the four major components of the Life Raft Group's mission: information and support, treatment surveillance and research, patient consultation and assistance, and advocacy. The goal is to ensure the survival of GIST patients while maintaining the quality of their lives.

Battle with GIST brought Avraham Anidjar to the U.S.

Life Raft member Avraham Anidjar of Los Angeles died April 17 after a seven-year battle with GIST. He was 51, and leaves his wife, Sara, and four children. This was the message she sent to the Life Raft.

"Today I lost my dearest husband, Avraham Anidjar, who fought GIST for seven years. He died on his 51st birthday. The irony is that my husband died not from GIST but from inexperienced doctors, young and ignorant, who never saw a GIST patient in their lives.

"It was a weekend, his doctor was in New York and we fell into a deep dark hole.

"Seven years ago, in Israel, my husband was diagnosed with sarcoma. The doctors were very pessimistic and did not give us any hope or chance of survival (the tumor was huge).

"My husband was a prominent lawyer and I was teaching math and biology in high school and university.

We, with our four small children — boys age 4 and 5, and girls age 9 and 11 — came to the United States. We came full of hope, determined to defeat the illness with a sum of a quarter-million dollars.

"My husband was operated on successfully. A year later, the cancer metastasized to the liver. At the end of 2002 we discovered Gleevec. The Gleevec never caused any shrinkage but the mets were stable.

"The last months we were fighting low blood pressure and low hemoglobin. My husband was not ready to die and we were not ready to let him go. We were optimistic and had many plans for the future that, unfortunately, will be without him.

"This coming Hanukkah my son will celebrate his bar mitzvah (a Jewish celebration of a boy coming of age at 13) alone.

"My friends, light a candle for us — a candle of protest, of despair, of shock, of hope that never will be fulfilled.



“Jessica always wanted a horse,” says Nancy, and in March, she got one. Only nine months old, Dakota is too young to ride but he’s still fun. Dakota joins the family dog, Scout, and a pet chicken, Lucky Larry (saved from a country fair) along with cattle and other assorted animals on the family’s 600-acre farm on the outskirts of Exeter, Ontario, Canada.

MORE BROCK

From Page 4

artist but currently works part time at a clothing store and caters at night with a friend. “I don’t think I’ll ever want to work full time again. I like the variety. Life’s not all about material things, and I want to enjoy my time with the kids.”

At this point in her life, Nancy knows what is important to her.

“My goal in life is to hold my grandchildren. I want to see them pedal up my driveway on their bikes and I want to be as great a grandma as my mom has been. She’s my role model.”

Nancy does have some advice for people new to GIST. “Find out about your disease. Ignorance can be bliss but knowing about what’s going in your body is better than not knowing, because I’ve fallen through the cracks. You have to be aggressive and



The Brock family enjoys a quiet moment on the porch of their home in Canada.

assertive about what you want or expect. Keep optimistic.”

“Keep on communicating,” she

adds. “The more we can learn and share with each other, the better we all will be.”

Setting the record straight

In an early edition of the March 2005 newsletter, a photo caption incorrectly identified a teleconference meeting participant from Bristol-Myers Squibb as Dr.

Robert LaCaze. The person pictured was actually Dr. Claude Nicaise, BMS clinical lead person for the BMS354825 clinical trial.

In brief

GLEEVEC+KRX-0401

Jerry Call, Life Raft Group science coordinator, reports that a **new phase II trial** combining **Gleevec** and **KRX-0401**, or Perifosine, has been approved by the institutional review board at M.D. Anderson Cancer Center in Houston, Texas. The trial is for Gleevec-resistant GIST. Activation is pending; start date to be announced.

KRX-0401 is an oral inhibitor of AKT, a protein downstream from KIT and PDGFRA, made by Keryx Pharmaceuticals headquartered in New York. It is activated in most metastatic GIST, but typically inhibited by Gleevec in patients whose cancer is responding to Gleevec.

AMN107

As this newsletter goes to press, Norman Scherzer, Life Raft Group execu-

tive director, says he's been advised that the long-awaited GIST trial for Novartis' AMN107 may become a reality this coming June.

AMN107 is a drug that binds tighter than Gleevec to the target bcr/abl oncogene that causes chronic myelogenous leukemia. As Gleevec was originally developed to fight CML but also proved exceptionally potent against GIST, it is hoped that AMN107 will perform the same way.

RAD

This just in: we report that a GIST patient who had developed resistance and then failed to respond to SU11248 and BMS354825 has now demonstrated significant tumor shrinkage after approximately one month in a combination of Gleevec plus RAD. Both are Novartis drugs.

MARK YOUR CALENDAR

Walk for a Cure: The GIST Cancer Research Fund will hold its fifth annual walk on Sunday, Oct. 2.

"The Walk" will once again be held at the picturesque Rockland Lake State Park, in Congers, NY. Additional information about the walk will soon be posted on the GIST Cancer Research Fund Web site, www.gistinfo.org.

The **American Society of Clinical Oncology** (ASCO) meets May 14-17 in Orlando, Fla., U.S.

Pediatric GIST families meet May 20-22 in northern New Jersey, U.S.

Chicago area Life Rafters meet June 12. Details: Dick Kinzig, rjkinz@aol.com.

The **International Patient Summit** for CML and GIST meets June 17-19 in Dublin, Ireland.

MORE AACR

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THE FUTURE

Dr. Charles Sawyers was the chair of the session "The future of oncology drugs in the new era of molecularly targeted drugs." Part of this discussion reviewed the history of Gleevec. Researchers initially had wondered if the early results of Gleevec in CML could be duplicated. They wondered whether CML, which is a genetically simple type of cancer, was in fact "real cancer." They got their answer in the Gleevec for GIST trials. Gleevec worked very well in GIST, and GIST was indeed a "real cancer." A PET scan of the first GIST patient that responded to Gleevec was a part of the presentation. This scan was described as "One of the most famous PET scans in oncology" by the presenter.

Some of the challenges highlighted in this session were:

- Selecting the right targets
- Discovering the right biomarkers

to enable selection of the right patients — Smarter trials

Some of the speculation is that biomarkers will evolve to pathway markers, and many of the next generation targets will not have to be activated to be crucial targets.

Presenters also discussed the concept of "synthetic lethality." Researchers are looking for synthetic lethal interactions (such as targeting the most important, and second most important genes/targets).

Several new KIT and/or PDGFRA inhibitors had poster displays. Many of these are just starting or almost ready to start phase I trials. Since there is no indication that they were specifically designed to overcome Gleevec-resistant secondary mutations in GIST, it is unknown whether any of these will have applications in GIST.

In addition to AMG706, BMS-354825 and AMN107, which have

ongoing or planned GIST trials, inhibitors included: OSI-930 from OSI Pharmaceuticals, SU14813 from Pfizer, BAY 43-9006 from Bayer Pharmaceuticals, ABT-869 from Abbott, JNJ-10198409 (RWJ-540473) from Johnson & Johnson, AZD2171 from Astra-Zeneca, and CHIR-258 from Chiron Oncology.

Montigen Pharmaceuticals and the University of Arizona also had a poster that found that in two patients and one GIST cell line, KIT was downregulated and another protein, AXL, was upregulated. A lead compound that inhibits AXL was presented. This work requires further validation.

One group (abstract 4956) found that glucose uptake in GIST cells (such as in PET scans) is dependent on AKT, but that GIST cell survival isn't dependent on AKT. AKT is a protein downstream in GIST.

Gleevec, vitamin C and insulin slows disease

Gleevec-resistant GIST patient is helped by a unique combination

By Jerry Call and Norman Scherzer

We report the case of a Life Raft Group member, a man whose GIST was resistant to Gleevec and twice responded positively when Gleevec was combined with vitamin C and insulin.

This patient was 51 when diagnosed with a GIST of the small bowel. No metastases were present at the time of diagnosis. Seven months after surgery removed the primary tumor, a CT scan showed a liver metastasis.

When the liver met was discovered, he started on 400 mg. Gleevec. The dose was raised to 600 mg. about two weeks after starting Gleevec. His initial response was stability and slight shrinkage. After 11 months on Gleevec, a CT scan showed the cancer was starting to progress. This was verified at the next scan (three-and-a-half months later) when several liver lesions, a moderate-sized mesenteric mass, and a moderate-sized pelvic mass were noted.

A twice-weekly intravenous regimen of vitamin C (75 grams) and

insulin (5 units) was added to the 600 mg. of daily Gleevec. The herbal supplement artemisinin (300 mg./day) was also added. A CT scan three months later showed a fairly significant improvement of the pelvic mass, and the mesenteric mass was also slightly smaller. There was little change in the liver masses.

At this point, the patient decided to continue with the “alternative treatment” of vitamin C, insulin and artemisinin, while discontinuing Gleevec. The next reported CT scan occurred a year later and showed very large liver masses and extensive peritoneal disease.

The patient continued the twice-weekly vitamin C+insulin treatment and restarted Gleevec at 600 mg. a day. He discontinued the artemisinin. A CT scan three-and-a-half months later showed some improvement in the liver masses and quite significant regression of the peritoneal masses.

The next CT scan revealed increases in size of some hepatic masses and decreases in others. The peritoneal masses remain unchanged

and there is slight improvement in soft tissue nodularity in the pelvis.

What is unusual about this case is that, after demonstrating resistance to Gleevec, the patient responded on two separate occasions to a combination of Gleevec, vitamin C and

insulin. The latest report is mixed and demonstrates some progression and some shrinkage.

The Life Raft Group routinely monitors the treatment of GIST patients both in and out of clinical trials. This is the first time the Life Raft has reported on the use

of an alternative therapy. The patient was carefully questioned about his complicated treatment history. In addition, an independent radiologist reviewed and confirmed the results of the last four CT scans. Nonetheless, the Life Raft strongly cautions readers against concluding that this treatment is either safe or effective. Patients are encouraged to discuss their unique situation and treatment options with their doctors.

Jerry Call is the Life Raft Group's science coordinator; Norman Scherzer is the executive director.



Timeline for one GIST patient treated with Gleevec, insulin, artemisinin, vitamin C

8-8-01	3-22-02	9-30-02	2-12-03	6-2-03	8-27-03	9-24-04	1-11-05	4-11-05
Sm. bowel primary resected	Liver mets	Stability to slight shrinkage	Tumor growth	New mets	Significant improvement	Significant growth	Significant improvement	Both growth & shrinkage
No adjuvant treatment	Gleevec started	Continues Gleevec	Continues Gleevec	Artemisinin, vitamin C & insulin added to Gleevec	Artemisinin, vitamin C & insulin but off Gleevec	Resumes Gleevec plus vitamin C & insulin, halts artemisinin	Continues Gleevec, vitamin C & insulin	Consulting with doctor

What does love mean?

By Tricia McAleer

Executive assistant

We get a lot of e-mail at the Life Raft Group. Every once in a while, something out of the ordinary comes in that begs to be shared. The following e-mail had been passed along through so many persons that we no longer know the source but we hope that whoever wrote this would not mind our sharing it:

A group of professional people posed this question to a group of 4- to 8 year-olds, "What does love mean?"

The answers were broader and deeper than anyone could have imagined. See what you think:

"When my grandmother got arthritis, she couldn't bend over and paint her toenails anymore. So my grandfather does it for her all the time, even when his hands got arthritis too. That's love."

— Rebecca, age 8

"When someone loves you, the way they say your name is different. You just know that your name is safe in their mouth."

— Billy, age 4

"Love is when a girl puts on perfume and a boy puts on shaving cologne and they go out and smell each other."

— Karl, age 5

"Love is when you go out to eat and give somebody most of your French fries without making them give you any of theirs."

— Chrissy, age 6

"Love is what makes you smile when you're tired."

— Terri, age 4

"Love is when my mommy makes coffee for my daddy and she takes a sip before giving it to him, to make sure the taste is OK."

— Danny, age 7

"Love is when you kiss all the time. Then when you get tired of kissing, you still want to be together and you talk more. My Mommy and Daddy are like that. They look gross when they kiss"

— Emily, age 8

"Love is what's in the room with you at Christmas if you stop opening presents and listen."

— Bobby, age 7

"If you want to learn to love better, you should start with a friend who you hate."

— Nikka, age 6

"Love is when you tell a guy you like his shirt, then he wears it every day."

— Noelle, age 7

"Love is like a little old woman and a little old man who are still friends even after they know each other so well."

— Tommy, age 6

"During my piano recital, I was on a stage and I was scared. I looked at all the people watching me and saw my daddy waving and smiling. He was the only one doing that. I wasn't scared anymore."

— Cindy, age 8

"My mommy loves me more than anybody. You don't see anyone else kissing me to sleep at night."

— Clare, age 6

"Love is when Mommy gives Daddy the best piece of chicken."

— Elaine, age 5

"Love is when Mommy sees Daddy smelly and sweaty and still says he is handsomer than Robert Redford."

— Chris, age 7

"Love is when your puppy licks your face even after you left him alone all day."

— Mary Ann, age 4

"I know my older sister loves me because she gives me all her old clothes and has to go out and buy new ones."

— Lauren, age 4

"When you love somebody, your eyelashes go up and down and little stars come out of you."

— Karen, age 7

"Love is when Mommy sees Daddy on the toilet and she doesn't think it's gross."

— Mark, age 6

"You really shouldn't say 'I love you' unless you mean it. But if you mean it, you should say it a lot. People forget."

— Jessica, age 8

And the final one — author and lecturer Leo Buscaglia once talked about a contest he was asked to judge. The purpose of the contest was to find the most caring child. The winner was a 4-year-old whose next-door neighbor was an elderly gentleman who had recently lost his wife.

Upon seeing the man cry, the little boy went into the old gentleman's yard, climbed onto his lap, and just sat there.

When the boy's mother asked what he had said to the neighbor, the little boy said, "Nothing — I just helped him cry"

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Who are we, what do we do?

The Life Raft Group is an international, Internet-based, non-profit organization offering 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 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:

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We are patients and caregivers, not doctors. Information shared is not a substitute for discussion with your doctor. As for the newsletter, every effort to achieve accuracy is made but we are human and errors occur. Please advise the newsletter editor of any errors.