

She knew all was not right but diagnosis took 5 years

Joan Marie Hayno has been NED thanks to surgery and Gleevec

By Erin Kristoff

Joan Marie Hayno told her doctors in 1997 that something inside of her didn't belong there. She'd experienced a sudden change in bowel functions and had begun having abdominal and pelvic pains.

In 1997, she had a CAT scan that showed an ovarian cyst. A follow-up ultrasound revealed the cyst to be 3 cm. But she was told it was of no consequence. She was diagnosed with IBS — irritable bowel syndrome — and sent on her way.



HAYNO

Over the years she would have bouts of pain and even a few trips to the emergency room. "That's very common with IBS," was a phrase Joan heard all too often. "They give you Motrin and [basically] tell you to go away."

She had no way of knowing that a tumor was growing inside her body.

Joan is a native of Wilkes Barre, Penn., born Feb. 6, 1952. Growing up she enjoyed such sports as basketball, bicycling, volleyball and swimming. She had an "absolutely normal" and "uneventful" youth. During high school Joan decided that she wanted to go into electronics and enrolled at College Misericordia, an all-girl Catholic

See HAYNO, Page 4

Battling gastrointestinal stromal tumor



LIFE RAFT GROUP

March 2005

In memory of Barry Cushing and Maher Samet

Many drugs coming for Gleevec-resistant GIST

Pharma scientists open doors to Life Raft Group

By Norman Scherzer
LRG executive director

During the past month the Life Raft Group has had discussions with several pharmaceutical companies in an ongoing effort to monitor the progress of new and potential treatments for GIST.

Recognition is due Amgen, Ariad, Bristol-Myers Squibb and Novartis for making their key scientists available, for displaying courtesy and respect to Life Raft inquiries, and for continuing their efforts to find new drugs to overcome Gleevec resistance. Thanks is also due to many GIST specialists who spoke both on and off the record.

AMGEN

Amgen continues to recruit patients for its phase II trial of AMG706 for patients with Gleevec-resistant GIST.

Although the Life Raft Group is monitoring the efficacy of this trial drug, there has not been enough time to responsibly report on this.

AMG706 targets three known GIST receptors: c-kit, PDGFRA and VEGFR. One question was whether the six-hour half-life of a 125 mg. daily dose of AMG706 is sufficient to



Life Raft Group Executive Director Norman Scherzer, left, meets March 2 with Tuomo Patsi, center, and Dr. Daniel Stepan of Amgen at the Life Raft office in New Jersey.

inhibit kit. LRG representatives were assured that it was, both at a March 2 meeting with Dr. Daniel Stepan and Tuomo Patsi at the LRG office, and in a follow-up meeting with PK expert Dr. Shekman Wang. LRG science

See PIPELINE, Page 2

PIPELINE

From Page 1

coordinator Jerry Call in Colorado participated in both meetings via teleconference. Our understanding is that the minimum AMG706 concentration is expected to be about 1.5 to 3 times the amount needed to inhibit kit.

The short half-life is said to be able to reach its concentration level more quickly and provide a safety margin if a patient must stop the medication due to toxicity. It is important to take the drug at the same time each day — on an empty stomach — and to be vigilant in not skipping doses.

As VEGF inhibitors are known to increase the possibility of hypertension, Amgen made frequent blood pressure checks part of its protocol. In response to patient concerns about having to travel back and forth to the trial site to have this done, Amgen is arranging for a visiting nurse to do this at the patient's home if they live far from the trial site.

Also discussed were such possibilities as testing AMG706 at a greater dosage, such as 150 mg., and comparing AMG706 to SU11248 in a head-to-head trial.

ARIAD

We recently spoke to Dr. Camille Bedrosian, ARIAD chief medical officer, about the clinical trial status of a drug called AP23573. We expressed our concern that a phase II trial for sarcoma had been started but that it excluded GIST patients. This trial is enrolling 170 patients from four cohorts: leiomyosarcoma, liposarcoma, bone sarcoma and other sarcomas. AP23573 is an I.V. drug that is given for five days followed by a nine-day break.

We were told that ARIAD believes GIST should have a separate trial and that they were still considering this. ARIAD has also committed to having an oral version of AP23573 by June 30, 2005. Therefore, if there is a trial



Participating via teleconference in the Life Raft's March 23 meeting is Dr. Robert LaCaze, Bristol-Myers Squibb's clinical lead person for BMS354825.

for GIST, it would likely include this oral drug.

BRISTOL-MYERS SQUIBB

I traveled to the Bristol-Myers Squibb's pharmaceutical headquarters in Princeton, New Jersey, to meet several officials. Participating via teleconference was the LRG's Jerry Call, and Dr. Robert LaCaze, Bristol-Myer Squibb's vice-president for oncology global marketing, Worldwide Medicines Group. LaCaze is the clinical lead person for BMS354825.

BMS354825 is in phase I clinical trial for sarcoma at Dana-Farber Cancer Institute in Boston, and in Scotland. Most of the Dana-Farber patients have Gleevec- and SU11248-resistant GIST; most of the Scotland patients do not have GIST at all. This is a dose escalation trial. The current dose is 120 mg. twice a day for five days followed by a two-day break. Compared to the experience of chronic myelogenous leukemia patients in earlier trials, some speculated that GIST patients might require a higher dose because of different sensitivity of the target proteins. The current phase II trial for CML uses a dose of 140 mg. per day.

Plans are underway for a phase II GIST trial and consideration is also

being given to administering this drug on a continuous basis as opposed to the five-day-on, two-day-off schedule.

The costs of travel and lodging for patients that do not live in the Boston area were discussed. BMS officials said they're working with Cancer Care to try to provide some assistance. Also discussed was the frequency of EKG tests and, particularly, that these tests must be done in Boston. We asked BMS to consider allowing such tests to be done near the patient's home. As was the case with Amgen, we brainstormed other trial possibilities, including combining it with Gleevec.

NOVARTIS

March 14, I traveled to Novartis Oncology in Florham Park, New Jersey to meet with several officials; Jerry Call again joined from Colorado via teleconference. There were also several follow-up discussions over the next several days to address issues regarding AMN107. More than 15 different Novartis officials participated in these discussions.

Adjuvant Gleevec: Dr. Laurie Letvak, Novartis Global Medical Affairs, reviewed the status of four adjuvant clinical trials.

These trials range from one to three years and address different risk groups, but all patients take 400 mg. of Gleevec. We expressed concern that these trials do not address higher dosage levels and briefly discussed plans of the Life Raft Group to conduct its own study — retrospective rather than randomized — of preventive treatment that considers higher dosage levels.

PKC412: Dr. Pamela Cohen, PKC clinical team lead, reviewed this trial. As previously reported, this combination Gleevec+PKC412 trial has taken



LETVAK



Gathered Feb. 18 in Amsterdam, the Netherlands, are Life Raft members, from left, Peter Verhaagen, Peter van der Meer, Marlies Bruinsma-Bol, Norman Scherzer, Lennie Flaton and Matthew Mattioli.

Life Rafter's meet in Amsterdam, Prague

By Norman Scherzer

Recently I had the wonderful experience of traveling with my 15-year-old grandson, Matthew to Prague, Czech Republic and Amsterdam, the Netherlands. Although we were traveling on personal business as part of a youth group that Matt belongs to, we nonetheless crossed paths with the Life Raft Group in both countries.

Matt works part time after school at the Life Raft Group office and is the reason we were initially able to hook up all our computers and equipment.

In Prague, I got to go out to dinner with Joe Carrigan. The connection?

Joe is living in Prague working under contract for a company there. He is the husband of Life Raft Group member Nengar, who lives in Canada. She is the daughter of a GIST patient in Tehran, Iran, whom the Life Raft Group has helped to obtain Gleevec under difficult circumstances.

In Amsterdam, members of the Netherlands Life Raft Group came from throughout the country to meet and visit with Matt and myself. They included Peter van der Meer, Peter



Joe Carrigan, left, and Norman Scherzer meet Feb. 18 in Prague.

Verhaagen, Marlies Bruinsma-Bol and Lennie Flaton.

It is indeed a small world.

HAYNO

From Page 1

school in Dallas, Penn., where she majored in math.

After college, Joan worked as a customer service representative for the local gas and water company, and did other secretarial and data-processing work. But working in electronics was what Joan wanted to do. So in 1979, at 27, Joan joined the Navy.

It was a good match. Over the next 20 years, Joan was stationed in Homestead and Pensacola, Fla.; San Diego, Calif., Fort Meade, Md., and in Scotland and Puerto Rico. She was an electronics technician and worked her way up to become a technician with top secret clearance for the National Security Agency, working on cryptographic and signals collection equipment.

“[The Navy] was very interesting for the first 10 years, but the longer you are in and the more senior you become in rank, the less you actually do the technical part of your job,” said Hayno.

In June 1999, Joan retired from the Navy. In 2001 her husband’s last set of orders brought them back to Pensacola, where she and Butch have remained. They have a 5-year-old Jack Russell terrier named Fred and a 3-year-old beagle named Buddy, whom they rescued from an abusive owner.

In January 2003, doctors discovered what they again thought was an ovarian cyst and Joan was shooed off to a doctor at Keesler Air Force Base Medical Center in Biloxi, Miss.

“When the examination was over, he informed me that something didn’t ‘feel quite right’ and ordered a pelvic ultrasound,” says Joan. “I almost cancelled, thinking that everything was OK, then thought ‘what the heck – just keep the appointment’.”

The ultrasound revealed what



Joan Marie Hayno gives a buss to beagle Buddy, held by husband Butch. They rescued 3-year-old Buddy from an abusive owner.

Joan’s doctor believed to be an ovarian tumor.

“My head was spinning. Two short days ago I was a reasonably healthy woman with no serious medical problems.”

Within the week, Joan had surgery to remove the “ovarian” tumor. It turned out to be a 12 cm. GIST.

Joan’s surgeon was an ob/gyn who’d been expecting to find ovarian cancer, but found the tumor was indeed attached to the small intestine. “The surgeon was quite surprised when he opened me up.”

“They tried to get another surgeon in there,” Joan says. “Nobody could do it, everyone was busy!”

She was in surgery for eight hours. The tumor was removed, intact, along with a foot of small intestine and more than over 50 mets throughout the omentum and colon. Every bit of visible disease was removed.

Joan has been on 600 mg. of Gleevec ever since. Her first post-op CT scan was NED (no evidence of disease) and she remains so to this day.

“I have some Gleevec side effects: periorbital edema and poor vision associated with that, a lot of fatigue,

and nausea,” she says. “Small price to pay for the gift of life.”

Along this rocky road, Butch has been very supportive and helpful. “[He] has been my rock throughout this GIST journey,” says Joan. “Always there to care, to comfort me and give me his words of wisdom. After my surgeries he would come home from work several times each day to check on me. I don’t know what I would have done without him.”

Over time, Joan’s life began to resume a sense of normalcy. She returned to work and began to enjoy hobbies like quilting, sewing and baking.

Normal ended Sept. 16, 2004 — not due to cancer but Hurricane Ivan. From televised reports, Joan and Butch thought they were far enough north to avoid the brunt of the storm. But when it hit, Joan ended up in the closet with Buddy the dog, riding it out, terrified.

Three dozen people in Pensacola died and the damage was considerable. Joan and Butch’s home had significant damage, losing part of the roof. Joan focused on repairs: hiring

See MORE HAYNO, Page 11

PKC412 fights Gleevec-resistant GIST

Novartis drug can inhibit secondary KIT mutations

By Jerry Call

Life Raft Group science coordinator

Recently reported research further defines the mechanisms of resistance that GIST tumors use to thwart Gleevec. The researchers also report that the Novartis drug, PKC412, may be able to overcome this resistance in some cases.

Maria Debiec-Rychter was the lead author of the research article in the journal "Gastroenterology." Peter Marynen, Ph.D., heads up the Center of Human Genetics - Molecular Genetics lab that was involved in this research.

This study investigated the mechanisms of resistance to Gleevec in 26 GIST patients treated at the oncology department of University Hospital in Leuven, Belgium.

The resistance mechanisms noted in this study were similar to those previously reported by Dr. Jonathan Fletcher and others. The KIT protein was activated (phosphorylated) in eight of 10 progressive tumors that could be analyzed during treatment with Gleevec. In half of these cases, KIT was reactivated because the progressive tumors had a second KIT mutation in addition to the original KIT mutation. In the other half, the cause for reactivation of KIT remains unknown.

It was speculated that sequencing of the complete open reading frame of KIT in these samples might identify novel mutations in unexpected regions of KIT. An alternative proposal was that factors influencing drug delivery into the cell or alterations in drug clearance from the body could result in inadequate amounts of drug in the tumor and could cause reactivation of

KIT and progression. Thus, resistance could be divided into KIT-dependent (KIT protein was activated) and KIT-independent categories, with reactivation of KIT as the most important mechanism of resistance.

The most frequent cause for reactivation of KIT appears to be secondary mutations in KIT. Overall, 12 of 26 patients (46 percent) in this study were found to have secondary mutations in KIT.



DEBIEC-RYCHTER



MARYNEN

One patient with a primary KIT mutation (KIT G565R) developed a secondary PDGFRA mutation (PDGFRA D842A) that was not present in the primary tumor. Activation of an alternate receptor has previously been cited as a mechanism of resistance in GIST, but this is the first report that we are aware of that has found a second gene mutation that caused the activation of the second receptor (PDGFRA

in this case).

Most GIST tumors have mutations in either exon 11 (most common) or exon 9 (second most common). Patients with exon 11 mutations generally have the best response rate to Gleevec. Patients with exon 9 mutations have a lower response rate to Gleevec. When resistance is caused by secondary mutations, patients will generally have at least two types of tumors in their body:

- Those that only have the original mutation (typically in exon 11 or exon 9 of KIT).

These tumors are typically still being controlled by Gleevec.

- Those that have the original muta-

tion in addition to a new (secondary) mutation, typically in exon 13, exon 14, exon 15, or exon 17.

It is these tumors that have two KIT mutations that stop responding to Gleevec.

In some cases, it may just be one or two rogue tumors that can be surgically removed, or controlled a local treatment such as radiofrequency ablation (RFA). Gleevec is then continued to control the remaining, sensitive tumors. In other cases this is not possible, and a clinical trial with a drug active against both types of tumors might be one solution. Another trial to be considered would be combining Gleevec, to control the tumors with only a primary mutation, with a second drug that had activity against the tumors with two KIT mutations.

The secondary mutations found in KIT were; V654A (N=4 tumors), D716N (N=1), T670I (N=3), D820E (N=1), D820Y (N=1), N822K (N=1), and D816G (N=1). The secondary PDGFRA mutation was D842V.

Using a combination of resistant GIST tumor cells, and a Ba/Fe mouse cell line engineered to express mutant forms with KIT primary and secondary mutations, the research team demonstrated that Gleevec was not able to inhibit KIT but PKC412 was able to inhibit KIT in a number of cells containing both primary and secondary mutations.

The Gleevec resistant mutations that were tested were KIT-V654A, KIT-T670I, and PDGFRA-D842V. All of these proved sensitive to PKC412. These mutations include what may turn out to be the most common secondary mutations (KIT-V654A, and KIT-T670I), and some of the more resistant mutations, KIT-T670I, and PDGFRA-D842V.

The KIT-V654A mutation (in exon 13) was the most common secondary

PKC412

From Page 5

mutation in this small group of patients. In another study at M.D. Anderson Cancer Center in Houston, Texas, U.S., all six resistant secondary mutations noted in the study were this type of mutation.

The KIT-T670I mutation (in exon 14) was the second most common secondary mutation and, in test tube experiments, was inhibited by PKC412. This mutation corresponds to the T315I mutation in bcr/abl in CML patients and the T674I mutation in PDGFRA.

The T315I mutation has proved to be the most difficult mutation to treat in CML patients. For example, the new Bristol-Myers Squibb drug, BMS-354825, that is proving so effective in Gleevec-resistant CML patients, inhibits basically all known bcr/abl mutants except the T315I mutation.

The other mutation inhibited by PKC412 (but not Gleevec) was the D842V mutation in exon 18 of PDGFRA. While this mutation occurred as a secondary mutation in this series of patients, it is also a primary type of mutation. In the U.S./Finland phase II study, this mutation occurred in two patients (1.6%), or 10% of those that had initial resistance to Gleevec. The D842V mutation is the most common form of PDGFRA mutation. Patients that have PDGFRA mutations tend to have primary tumors located in the stomach.

It is tempting to hypothesize that in this small group of patients with primary D842V mutations, PKC412 given alone might be as effective as PKC412 plus Gleevec, since Gleevec is not effective against this mutation. Thus for patients with initial resistance to Gleevec, clinical testing to identify the type of mutation in KIT or PDGFRA has an approximately 10% chance (this percentage estimate is based on small numbers) or identifying the PDGFRA D842V mutation, which

might then suggest PKC412 as a strong clinical candidate drug.

In another study just pre-published online as a Blood First Edition Paper, Joseph Growney and others reported that PKC412 was able to inhibit a number of other Gleevec-resistant mutations that occur in human mast cell disease and acute myeloid leukemia. The most notable of the mutations inhibited by PKC412 in this study were the KIT D816V and D816Y mutations in the c-KIT activation loop.

Other mechanisms of resistance noted in the Leuven study included:

- Two patients completely lost KIT expression, indicating a KIT-independent mechanism of resistance. These tumors no longer stained positive for c-kit (CD 117) and they inverted their histologic appearance from spindle to epithelioid type.
- Two cases where resistance was associated with amplification of KIT or PDGFRA genes. In the PDGFRA case, the patient was resistant to initial Gleevec therapy.

Phase I/II trials combining Gleevec and PKC412 are underway in Berlin, Germany, and Portland, Oregon, U.S. These trials are for GIST patients that are resistant to Gleevec. Lead researchers are Dr. Peter Reichardt at the Robert-Rössle-Klinik, Charité Campus Buch in Berlin, and Dr. Charles Blanke at Oregon Health & Science University in Portland. When given together, a significant interaction between PKC412 and Gleevec has been noted.

Our understanding is that PKC412 causes Gleevec to leave the body faster than when Gleevec is given alone. This combination trial thus requires a higher-than-anticipated dose of Gleevec to achieve normal levels of Gleevec in the body (perhaps 1,000 mg. to 1,200 mg./day). The need to

adjust the dose of Gleevec in interaction with PKC412 is one of the major reasons that this trial has moved so slowly.

The Gastroenterology article concluded with the following summary: "... our study confirms the existence of KIT-dependent and -independent mechanisms of imatinib resistance in patients with GISTs and shows novel imatinib-resistant KIT mutant isoforms. It points to the acquisition of imatinib-resistant PDGFRA mutations as a cause of secondary resistance in a KIT-positive tumor and indicates KIT amplification as the possible explanation not only for a secondary but also for a primary resistance to the drug. Moreover, our results prove the sensitivity of KIT-T670I and KIT-V654A and of PDGFRA-D842V mutations to PKC412. Given that individual kinase domain mutations exhibit differential sensitivity to alternative kinase inhibitors, it will be crucial to tailor second-line therapy precisely to the underlying mechanism of resistance."

Many GIST patients use clinical trials to survive. The challenge is how to match the resistance mechanism that causes Gleevec to fail, to the drug/trial that gives patients the best chance of responding. The current paradigm favors enrolling a diverse group of resistant patients into clinical trials and examining mechanisms of resistance at the end of a trial. Patients often select a trial based on geography, or whatever trial happens to be running at the institution they visit.

There is one advantage in enrolling a diverse patient population into clinical trials; after the trial you can analyze data and you might get lucky and find some patient population that was not expected to benefit, but did. On the other hand, enrolling patients into a trial that has the best rationale for benefit also offers some advantages. When

Plans laid for global GIST network

Life Raft, ACOR and Das Lebenshaus will join to create multilingual site

Plans for a global, multilingual network for GIST patients, caregivers, doctors and researchers were finalized March 17 in New York City.

The objective is to dramatically increase the flow of information about GIST around the world and to facilitate the development of GIST patient groups in different countries.

At the March 17 meeting was Gilles Frydman, president of ACOR (Association of Cancer Online Resources); Markus Wartenberg, spokesperson for Das Lebenshaus in Germany, and Norman Scherzer, executive director of the Life Raft Group.

The plan builds upon the strengths of the three organizations and will include the creation of a new Web site, appropriately called the “Global GIST Network.” This Web site will provide FAQs (frequently asked questions) about GIST in several languages and links to any groups or formal organizations speaking each language.



Life Raft Group's Norman Scherzer, left, and Markus Wartenberg of Das Lebenshaus, center, and Gilles Frydman of the Association of Cancer Online Resources meet March 17 in New York City.

Equally important will be the creation of foreign language listservs to be hosted by ACOR — the leading online cancer organization — that will permit GIST patients to speak to one another in their own language. These listserv

groups will be hosted by ACOR and will be linked to the scientific and support expertise of the Life Raft Group, including its international directory of GIST experts and its international listing of clinical trials.

Life Raft joins European Cancer Patient Coalition

By Erin Kristoff

The Life Raft Group has been accepted as a member of the European Cancer Patient Coalition. The ECPC was launched in September 2003 in Copenhagen to represent the views of cancer patients in the European healthcare debate and to provide a forum for European cancer patients to exchange information and share best practice experiences.

The ECPC's goals are to campaign for better patient representation, equity



EUROPEAN
CANCER
PATIENT
COALITION

of access to high quality cancer treatment, facilitating interested patients to develop or improve their advocacy skills and ensure that all European cancer patients have access to well-designed clinical trials.

“The coalition hopes to become the natural first point of reference for European institutions when seeking the opinions of cancer patients,” said Lynn F. Wood, chairman of the ECPC.

of access to high quality cancer treatment, facilitating interested patients

The group plans to hold its second annual Masterclass in Cancer Patient Advocacy May 28-29 in Milan, Italy. It is for cancer patients and their representatives who want to campaign more actively and effectively for improvements in health policy and services. The first Masterclass drew representatives from 33 countries.

For more on the coalition, see its Web site at www.ecpc-online.org/

The Life Raft Group's international role continues to grow with representatives in 10 countries and Life Raft members in more than 30 countries.

Life Raft Group calendar of coming events

April 9: Southern California LRG meets at 1 p.m. at the Lakewood home of coordinator Floyd Pothoven, e-mail floyd@keralum.com or phone (562) 920-6411.

April 16-19: American Association for Cancer Research (AACR) meets in San Diego, Calif., U.S.

April 19: Life Raft Group to announce Challenge Grant

April 20: London GIST Group meets. For more information e-mail Dave Cook at D.Cook@sheffield.ac.uk

April 29: Swiss LRG meets. For more information contact Ulrich Schnorf at

Ulrich.schnorf@bluewin.ch

April 30: The Detroit area LRG meets at Gilda's Club in Royal Oak. For more information e-mail Allan Tobes at atobes@comcast.net

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

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

June 12: Chicago LRG meets

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

Druker updates stem cell research

By Jerry Call
LRG scientific coordinator

Last month's issue of the Life Raft Group newsletter reported that researchers are working to understand and target stem cells in leukemia. After the newsletter was published, we found a relevant interview with Dr. Brian Druker in Medscape by Sally Church, Ph.D. (See the Medscape Web site, www.medscape.com/viewarticle/496015).

Druker is credited with bringing Gleevec into clinical practice for chronic myelogenous leukemia (CML). The following excerpt is presented because it may have important implications for GIST patients.

Church interviewed Druker in conjunction with the American Society of Hematology's 46th annual conference held in December. The interview is titled: "Imatinib and Beyond — New Developments in the Treatment of CML: An Interview with Brian Druker, M.D."

Medscape's Church: In terms of this conference, what presentations have excited you?

Dr. Druker: "Within CML, the most exciting have been the AMN107 and BMS-354825 compounds, because the response rates in imatinib-resistant patients have been so high. The other presentation, which I think was, in some respects, overlooked, was Tessa Holyoake's poster. She was addressing what I view as the most pressing problem in CML patients, and that it is not the issue of relapse, but what I would call molecular persistence. So, if you look at imatinib, 98 percent of patients have normal blood counts, 84 percent of patients have a complete cytogenetic response, but only 5 percent of patients are molecularly negative or have undetectable levels of the bcr-abl transcript. Thus, I would consider the majority of patients having molecular

persistence, meaning good responses, but still they have molecularly detectable disease. The issue is, why can't you eradicate the disease?"

"What Dr. Holyoake has been doing is purifying progenitor cells from CML patients and looking to see, much like we did in relapse patients, whether the bcr-abl kinase is "on" or "off." It looks, from her early studies, that the bcr-abl kinase is "on."

"She also has some data that suggest that some of the CML progenitor stem cells may be resistant to imatinib. The issue is: with a more potent inhibitor, will you be able to achieve a higher rate of molecular negativity? Certainly, from the dose escalation studies, there is a suggestion that we may be able to, and to me ultimately the excitement of the new kinase inhibitors that are coming along is that we may be able to achieve a higher rate of molecular negativity, but it may be more complicated than just a more potent inhibitor.

"Some of her data suggest that quiescence of stem cells may also contribute to molecular persistence, so it may well be that, with a more potent inhibitor, we will get a higher rate of molecular negativity, but we may not yet eradicate the clone. And we may yet need other targets or other mechanisms to attack the leukemic cell to eradicate the disease and cure patients.

"These are very exciting times; we may see higher remission rates, high rates of molecular negativity, but we still may have to learn how to eradicate those last few cells. Ultimately, the work looking at why we can't eradicate the last, few cells will be critical to designing the best strategies to eradicate the disease."



DRUKER

MORE PIPELINE

From Page 2

some time to work out due to the interaction of the two drugs. Basically, higher doses of Gleevec are needed to offset



COHEN

this interaction. Although it's still too early to draw solid conclusions, there are reports of stable disease. Jerry

Call explores PKC412 in this newsletter; see page 5.

RAD: Dr. David Lebowitz, RAD clinical team lead, reviewed this trial, which seems to be progressing very slowly. RAD, an mtor inhibitor, is

given along with 600 mg. of Gleevec. There are three trial sites, in Boston, Berlin and Belgium.

AMN107: Dr. M. Luisa Veronese, AMN107-GIST clinical team lead based in Basel, Switzerland, reported on this trial in a series of communications following the meeting. The protocol had been delayed but at last report had received all internal scientific approvals and is expected to be at trial sites very soon.

The protocol calls for a phase I trial.



Meeting March 24 at the Life Raft Group office in New Jersey were, from left, Life Raft Executive Director Norman Scherzer, Novartis representatives Susanna Leto, Leslie Fields and Barbara Kennedy, and LRG Executive Assistant Tricia McAleer.

The first part will have just six patients taking 400 mg. of AMN107 twice a day. The second part will combine AMN107 and Gleevec. This will be a dose escalation trial combining 800 mg. of Gleevec with 200 mg. of AMN107 in the first cohort, with 400 mg. of AMN107 in the second cohort, and with 800 mg. of AMN107 in the third. All three cohorts will have three patients.

There may be a simultaneous cohort of six patients who had disease pro-

gression on 600 mg. Gleevec and were intolerant of 800 mg. Gleevec. These patients would take 400 mg. AMN107 twice a day.

Gleevec-resistant patients will be accepted regardless of whether they have tried other drugs.

The Life Raft Group has learned this trial may be available at Dana-Farber and Fox Chase Cancer Center in Philadelphia, and in Belgium, France, Germany, Italy, and the Netherlands. These sites are subject to change.

MORE PKC412

From Page 6

a patient does well, both the patient and the trial sponsor benefit.

Note: Dr. Charles Blanke, GIST specialist at OHSU and the principal investigator for PKC412 in the United States, was asked to comment on this article. His response: "The article looks great. You hit the nail on the

head. I just gave H/O grand rounds at OHSU and I said that the ultimate goal in GIST is to match the individual patient to his/her best GIST drug ... "

footnote:

Mechanisms of Resistance to Imatinib Mesylate in Gastrointestinal Stromal Tumors and Activity of the PKC412 Inhibitor Against Imatinib-Resistant

Mutants Maria Debiec-Rychter, Jan Cools, Herlinde Dumez, Raf Sciot, Michel Stul, Nicole Mentens, Hilde Vranckx, Bartosz Wasag, Hans Prenen, Johannes Roesel, Anne Hagemeyer, Allan Van Oosterom, And Peter Marynen (Gastroenterology 2005:128:270-279).



At the GIST Cancer Research Fund presentation are, from left, Robert Stutman, Dr. Ron DeMatteo, Ken Schou, Dr. Robert Maki, Tania Stutman, Mark Landesman and Dr. Christina Antonescu. The Stutmans are the founders of GIST Cancer Research Fund; Landesman and Schou are directors of the fund.

GCRF presents first \$25,000 gift

Money will pay for GIST research; separate \$10K to study pediatric GIST

More than a dozen GIST patients and caregivers attended the March 16 presentation of \$25,000 by the GIST Cancer Research Fund to Memorial Sloan-Kettering Cancer Center in New York City, specifically for GIST research.

The GIST Cancer Research Fund presentation by Tania and Robert Stutman was immediately followed by a \$10,000 Life Raft Group check for pediatric GIST, presented by Dorothy and Brian McBride. Their daughter, Malorie, has been fighting GIST five years. Students at Malorie's school, St. John Villa Academy High School on Staten Island, N.Y., were inspired by Malorie's courage and raised this money to battle pediatric GIST.



Enjoying a moment together at Memorial Sloan-Kettering are, from left, Dr. Tianhua Guo, Tania Stutman, Dr. Christina Antonescu and Dr. Knarik Arkun.

Accepting on behalf of Memorial Sloan-Kettering were Drs. Cristina Antonescu, Murray Brennan, David D'Adamo, Robert Maki and Ronald DeMatteo, signal transduction researcher Peter Besmer, Ph.D., senior research technicians Dr. Knarik Arkun and Dr. Tianhua Guo and, from the hospital's development department, Joan Roseman and Mindy Weintraub.

The formal presentation was fol-

lowed by an informal roundtable discussion. The doctors lingered for nearly two hours to make sure all questions were addressed.

GIST patients, caregivers and friends joining in the discussion were Myron and Ora Gelberg, Donna and Patrick Geraghty, Chris Keller, Mark Landesman, Pam Lewkovich, Ellen Mayer, Ken Schou, Bruce Torres, Sandra

See GCRF GIFT, Page 11

GCRF GIFT

From Page 10

Watkins, the Stutmans and the McBrides.

Antonescu, the head of the GIST research lab, related her involvement and the path her career took a number of years ago when she was recruited from her pathology work with other sarcomas and was asked to direct her efforts exclusively to GIST. While she had some initial apprehension, she now believes it was the best move she ever made as she is now in the forefront of the most exciting advances in the field of oncology.

Antonescu introduced Besmer, her mentor, who related his personal journey. He began his career in virology, and with Dr. Bill Hardy discovered the role of the viral kit gene in producing a mutated KIT protein in feline sarcoma. At this point he began wondering if mutated KIT played a role in human oncology, and thus began the odyssey that led to the worldwide collaboration.

Several points were made during the roundtable:

First, everyone seemed to reiterate the idea of genetic mutational status being extremely important in determining the behavior of the tumor vis-a-vis response to therapy as well as prioritizing treatment modalities.

Antonescu said that her lab will test anyone's tumor for mutational status free of charge. All that is needed is a paraffin block or 10 unstained slides of representative tumor tissue. As the FDA has not yet approved this testing at MSK the results that will be given to patients must be considered informal. Further information will be posted at the websites of the GIST Cancer Research Fund's Web (www.gistinfo.org) and the Life Raft Group (www.liferaftgroup.org).

DeMatteo gave an update on the adjuvant Gleevec trials. The phase II trial has reached its patient goal. The phase III trial is still accruing patients at a rate far exceeding initial expectations; there are more than 320 patients currently enrolled. At this point in time, as part of correlative studies, all adjuvant patients are having their tumors genotyped at Memorial Sloan-Kettering, so conclusions can be related specifically to molecularly de-

Can you name that country?

The Life Raft Group tracks the countries of visitors to its Web site. During the past 50 weeks, the two leading countries were the United States and Canada. Can you name the third leading country that had almost 1,000 visitors to our Web site?

Send an e-mail with your guess to liferaft@liferaftgroup.org by April 10. The first 3 people with the correct answer win a Life Raft Group pin and T-shirt.

finer subsets. It may be several years before statistically accurate conclusions may be drawn.

The role of adjuvant Gleevec was discussed. Also, it was noted that patients are being accrued in Europe for a study of adjuvant use of Gleevec for two years to see if there would be added benefit of taking the drug an additional year.

See MORE GIFT , Page 12

MORE HAYNO

From Page 4

the roofer, people to replace the walls, insulation and floor.

About this time, Joan wasn't feeling that great. "The first time I thought it was food poisoning, then I thought it was the flu or maybe gastritis."

One episode in October was so painful it sent Joan to the hospital. The diagnosis was partial small bowel obstruction. Next month saw Joan in surgery again. "He successfully removed the adhesions and scar tissue AND meticulously examined my entire GI system up close and personally during the surgery for any signs of GIST recurrence," Joan said. Happily, all was NED.

These days Joan isn't nervous about

her scans, "Getting all upset about it won't change the outcome."

She doesn't even mind the four-hour trip to and from Keesler. Joan has high regard and admiration for her oncologist, Dr. Douglas Nelson, and her surgeon, Dr. W. Cannon Lewis. "They are caring and compassionate men as well as fantastic doctors. I trust them implicitly -- I trust them with my life. It is very important to have that kind of confidence in your medical team. It gives you peace of mind."

Joan is also thankful that Gleevec has kept her GIST at bay. "When I read about an unfortunate situation with one of our LRG listmates, I al-

ways feel so sad. Then I think, there but for the grace of God go I. I take each day as it comes and try to enjoy every minute doing the things I love to do. I don't take things for granted anymore. I hope one day to see this dragon slayed and a cure found!"

March 16 was the six-month anniversary of Hurricane Ivan. Joan's house is nearly finished and she remains hopeful for the future.

"I want to stay clean of disease, remain disease free; I look forward to a long life. I know it will take years to see this community rebuilt and I want to see that."

Erin Kristoff is administrative assistant for the Life Raft Group.

My name is Tom, I am not a member of the LRG elite ... just a GIST patient who is still on his feet.

The tri-states Michigan, Indiana and Ohio have been my stompin' grounds, Neigh full circle from Detroit, Kalamazoo, Fort Wayne, Bloomington and now Toledo.

I have lived in all these towns. I have some GISTs and they're stable in my liver... sometimes it scares me and just makes me shiver. Other times I forget that I ever had cancer ... and put it away, don't even look for the answer. Small bowel resection and Gleevec and now RFA, Grace bought me four years and I am with you today.

I found my way to this list by misdiagnosis of LMS, through a lady from South Africa who looks good in a dress ... a Kevlar breast plate, she has her own armor, and the strength of 10 oxen, wit and spunk of a charmer. For two years post surgery, I was tumor free, she warned me to "hedge my bet," she did ... my friend Dr. Dee.

The list had just opened to non-gobblers of Gleevec, so I wrote on and enlisted ... I thought, "what the heck." It was only a matter of time, for my onco genes, to "met" to my liver. You all know what that means. And so it began, my affair with orange caps, and I hoped and I prayed my insurance wouldn't lapse. I began to write poems about Gleevec and white guck, and to the Life Raft I clung, from then I was stuck. Perhaps some bright day, from this raft we'll be free, but until that great day, you are all stuck with me.

White shirt and a tie, by the day, I am a lawyer, by night, I play songs of the heart, with the soul of a vo-year. Inside and outside, we look for the best, that each moment can bring, and skip all the rest. And late every evening, I get on the list,

Toledo Daze

By Tom Overly

to read of the status of caretakers and friends who have GIST. You see I see through you and you see through me ... for we live in the now, and we

run, but don't flee. The events of our life, perhaps we see clearer, the times with our friends and our families are dearer. The things that we say and the way that we act, are disturbing to some because of the urgency they lack. The words of the heart ... don't know their fate, but if they are not spoken, it might be too late. We share words of wit and wisdom and love, all full of support, with the heart of a dove. This list has lengthened my life, I am sure, I'll cling to this raft, till science finds a cure.

Some folks think it's a curse to have the big "C," but it is bigger to them than it is now to me. I faced my mortality and came out pretty well, and conquered the fear and came through the GIST hell. But I have to give credit where credit is due, I couldn't have made it without all of you. A blessing it's true to have found this fine boat, Knowledge is power and keeps it afloat. But the love and support and group-centered sharing, Keeps us on track and maintains steady bearing. We all found this raft, just as we should, In the boat together, it feels pretty good.

If I should let go, and my time has come, don't think I won't miss you, it's been a fine run. Oh, please when I am dying, talk to me from your heart, and we'll share our beliefs until I depart ... from this world to beyond, I've no fear of leaving, so please light your candle ... but don't bother grieving. I will be OK and you will be too. Just remember this fact in the things that you do. Give thanks were they are due, and run this fine race, and try to do something. Make the world a better place. I've gone on too long with this bio-poem of mine, so ... As my mom use to write, I'll hang my close on this line.

MORE GIFT

From Page 11

Robert Maki made several interesting comments about the dosage levels for Gleevec. To permit these to be placed within context, the Life Raft Group will invite Dr. Maki along with a number of GIST Specialists from the United States and Europe to offer their points of view in a forthcoming Newsletter.

The next GIST Cancer Research

Fund presentation will be Wednesday, April 6, at Dana-Farber Cancer Institute in Boston. Presentations will also be made at noon April 12 at Fox Chase Cancer Center in Philadelphia, and April 28-29 at Oregon Health & Sciences University in Portland.

GIST patients and caregivers are invited. Those interested should contact the Stutmans via e-mail at Tania5kids@aol.com

As Robert Stutman said at the presentation, we all hope we won't have to return next year because a cure has

been found.

[A note from the Life Raft Group Executive Director:](#) The work of the GIST Cancer Research Fund is a testament to what a few motivated people can do to change the world. The impact of the funds raised is leveraged way beyond its dollar amounts by the attention it brings to the critical research we need to find answers to Gleevec resistance and ultimately to a cure itself. I confess to being an early skeptic of these fundraising efforts. I was wrong. Well done Tania!

Barry Cushing, distinguished professor, was 59

Barry E. Cushing of Salt Lake City, Utah, died March 1 after a four-year battle with GIST. He was 59.

Colleagues at the University of Utah, where he taught accounting, hailed him as a “distinguished professor” who made a lasting impression on his students, fellow professors and co-workers.

Jack Brittain, dean of the university’s David Eccles School of Business, said Cushing helped establish university’s School of Accounting as one of the top programs in the West. The school’s stature today is Cushing’s academic legacy, which included hiring dedicated scholars with excellent research skills who are committed to students, Brittain said.

“This was Dr. Cushing’s vision, and the school’s ongoing achievements are an important legacy,” Brittain told the Salt Lake Tribune.

Cushing joined the faculty in 1977.



CUSHING

He served as chairman of the Accounting Department from 1982 to 1985, leaving in 1986 for a position at Pennsylvania State University. He returned to Salt Lake City in 1991, and was named university’s David Eccles Professor of Accounting in 1996.

He was born July 6, 1945, in Lansing, Mich., to William and Abigail Cushing. He graduated with honors from Grand Ledge High School and studied accounting at Michigan State University, obtaining his bachelor of arts degree with high honors in 1966, and his doctorate in 1969.

He married his lifetime partner, Cherry Lee Barker, on June 25, 1966.

Barry celebrated his life by traveling around the world with his family. He showed his passion for being a professor by authoring numerous textbooks and research articles. Barry received various national and university awards recognizing the excellence of his research and teaching contributions.

In addition to his wife, he is survived by two sons, Dennis (Kristin) and Andy; two daughters, Becky and Christy; brothers, Eldon (Maxine) and William (Marion), and grandchildren Travis, Kady, and Camden.

The Cushing family has expressed sincere thanks to both The Huntsman Cancer Institute and VistaCare hospice for their excellent care.

A celebration of life was held March 5 at the home of his dear friend, Professor D. Gerald Searfoss. Donations in Barry’s name are preferred to The Huntsman Cancer Institute or to VistaCare hospice.

Chicago area Life Rafterers meet at Wellness Place

By Dick Kinzig

The Chicago area meeting of Life Rafterers took place March 20 at the Wellness Place in Palatine, Ill., U.S.A.

Among the 21 in attendance were newcomers Ron and Paula from Grayslake, and Bill from Palatine.

Two members of the Life Raft’s Board of Directors, Bob Book and Jim Hughes, gave presentations. Book brought the group up to date on fund-raising, noting a new program will soon be launched seeking donations for a matching funds grant.

Hughes attended the Connective Tissue Oncology Society convention last November and gave a summary of the Life Raft Group’s presentation Nov. 12 on Gleevec dosage at the CTOS meeting. (Details appeared in the No-

vember/December newsletter.)

Pediatric GIST was discussed, including the Life Raft’s meeting with Dr. Jonathan Fletcher of Dana-Farber Cancer Institute in Boston. The Life Raft is compiling information on this rare patient group and has found 18 pediatric GIST patients through its outreach efforts. Hughes speculated that there may be 100 pediatric GIST patients in the U.S. Pediatric GIST is a different creature from adult GIST, with no standard of drug therapy.

Hughes also gave a summary on the importance of stem cells; more on this topic can be found in the February newsletter article by the Life Raft’s science coordinator, Jerry Call.

Guest speaker was Dr. Heather Brown, a pathologist from Northwest Community Hospital in Arlington Heights. She gave a slide presentation

on her role in managing the various tests done in surgical pathology, and showed slides of a GIST tumor, microscopic GIST with CD117, and one with mitotic cells.

There was a good deal of discussion during the question-and-answer period and attendees voiced their appreciation of Brown’s insight and Hughes’ presentation.

Special thanks to those who provided snacks, including Esther P., Beth S., Marianne M., Elaine R. and Doris D..

The next meeting of the Chicago area group is set for Sunday, June 12 at Wellness Place. Guest speaker will be Norman Scherzer, Life Raft executive director.

Dick Kinzig is the Chicago area coordinator of the Life Raft Group. E-mail him at RJKinzig@aol.com.

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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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