

# Glivec OK'd for GIST in Japan, Israel

Drug now approved in U.S., Europe and 70+ nations across the globe

**B**ASEL, Switzerland – Novartis announced July 17 that health authorities in Japan have approved Glivec® (Gleevec/imatinib) for the treatment of patients with c-kit positive gastrointestinal stromal tumors.

The Life Raft Group has independently learned, and Novartis has confirmed, that Israel's Ministry of Health approved Glivec for GIST treatment July 17. Historically, GIST is very difficult to treat due to its resistance to available chemotherapy and radiation therapy. Previously, surgery was the only treatment option, resulting essentially in palliation of the disease.

The approval from the Japan's Ministry of Health, Labor and Welfare came only six months after Novartis filed for approval in that country. Glivec was originally granted orphan drug status for the GIST indication in Japan in October 2002. The approval was based on clinical data from studies conducted in Japan and Western countries, including the member states of the European Union and the United States, where Glivec is already approved for GIST.

"This approval enables Japanese patients with kit-positive GISTs to benefit from the remarkable results we've seen with Glivec," said David Epstein, president of Novartis Oncology. "The high response rates in these patients have been extremely encouraging and Novartis is pleased that Japanese regulatory authorities acted swiftly to make the drug available to them."

The Japanese study of Glivec was

**See Approval, Page 9**

Battling gastrointestinal stromal tumor



## LIFE RAFT GROUP

July 2003

In memory of Bill Lawson

Volume 4, Number 7

## Targets, targeted therapy reports abound at AACR

Many speakers mention Gleevec as top example of progress vs. cancer

By David Josephy

**I** attended the 94th annual meeting of the American Association for Cancer Research held July 11-14 in Washington, D. C. This meeting had been set for April in Toronto, Ontario, but was rescheduled due to the outbreak of severe acute respiratory syndrome (SARS).

It's the major annual basic science cancer meeting, with more than 10,000 registrants. Compressed into four days, one could only attend a

fraction of the many parallel presentations. Lots of papers and posters were relevant to GIST and Gleevec, and I tried to get to as many as I could.

Here is a brief report of some of the highlights, based on the abstracts (available at [www.aacr.org](http://www.aacr.org)) and my rough notes. A warning: I have likely introduced a few errors as I rushed to write down the presentations, many of which were given at a very fast pace.

Friday morning I attended some talks in an "educational session." Co-chairman of the session was to have been Dr. Jonathan A. Fletcher of Dana-Farber Cancer Institute in Boston, a pathologist and leading expert

**See AACR, Page 2**

## Life Raft's reach spans the globe

From the Netherlands to Uganda, patients are linked to vital resources

Compiled by  
Norman Scherzer

**T**he Life Raft Group continues to expand its activities around the world. Our membership has expanded to 23 countries and our outreach to several more.

Some recent highlights:

**Netherlands:** We are working with LRG member Ton de Keijser on the development of a Life Raft Group in the Netherlands. Ton will also become our new country representative in the Netherlands.

**Germany:** Ulrich Schnorf, our country representative in Switzerland, is a founding member and our liaison to a new group, Das Lebenshaus (the House of Life) for Glivec patients

**See Going global, Page 6**

## New Zealand Life Rafter's hold first meeting

**T**he New Zealand branch of the Life Raft Group held its first meeting Saturday, June 28.

Present were Carol Donnell (Gister) and her husband Roger and Tom Cooper (Gister) and his wife Maggie.

The meeting place of the Ngatea Water gardens was chosen because it is approximately halfway between Auckland (where the Donnells live) and Waihi (the Cooper's hometown).

Luckily for us, Tom's car was the

only other one in the carpark so we didn't have to knock on car doors asking people's names.

It is winter in New Zealand so the weather was cold and overcast but that didn't slow the conversation. We spent the afternoon sharing anecdotes about our diagnosis, hospital stays, and life with Glivec.

We all enjoyed the comfort of knowing what each other is going through and could laugh at some of the moments we have experienced on this journey.

Tom was the first person in New

Zealand to receive Glivec for GIST and has been on it for 15 months. It is working very well for him and has resulted in a 80 percent shrinkage of his tumor.

For Carol, Glivec hasn't worked so other options are being pursued.

It is amazing that a U.S.-based group could be the way of finding a fellow Gister in New Zealand as both of us are the only GIST patients at our respective hospitals. We are grateful to Life Raft for informing, encouraging and supporting us in this battle with GIST.

## AACR: Lots of talk about targets and targeted therapy

From Page 1

on GIST, but he was unable to attend and Dr. Michael Heinrich from Oregon Health & Science University in Portland took his place. Heinrich gave a talk focused on the molecular analysis of GIST, titled "PDGFRA and KIT gain-of-function mutations are alternative oncogenic mechanisms in GISTs."

He reviewed the role of c-kit in GIST and the importance of exon 11 mutations. He mentioned a transgenic mouse "knock-in" animal model in which an exon 11 mutation leads to GIST. Then he focused on the subset of GISTs (about 18 percent of patients) in which KIT mutations are NOT detected. He noted the recent study (Gilliland et al., published in Science) that identified PDGFRA mutations in many of these cases.

PDGFRA sequencing analysis was performed on tumor material from 40 c-kit-negative GISTs. He gave the following statistics for PDGFRA mutations: Point mutation D842V, in the kinase activation loop (exon 18), 9 cases; deletions in exon 18, 3 cases; insertions or deletions in the juxtamembrane domain (exon 12): 3

cases; other or not identified, 25 cases. He noted that about 10 percent of GISTs have no identified mutation in either c-kit or PDGFRA, presumably indicating that additional targets remain to be discovered. Some of the PDGFRA mutant proteins are Gleevec-sensitive, but the D842V mutation is relatively resistant, with an inhibitory constant of 2 micromolar

He reviewed the pattern of c-kit mutations in a spectrum of diseases. Exon 8 mutations are associated with leukemia; exon 9 and 11 mutations with GIST, and exon 17 mutations with mast cell disorders (mastocytosis).

Finally, he discussed the recent (published this year) finding that Gleevec is effective in the extremely rare HES (hypereosinophilic syndrome). In this case, a FIPIL1-PDGFRA fusion protein is responsible, and this protein is exquisitely sensitive to inhibition by Gleevec (inhibitory constant of 5 nanomolar.), explaining why Gleevec is effective at almost "homeopathically" small doses.

The Friday afternoon plenary session at AACR was built around a perspec-

tive of the impact of the 1953 discovery of the structure of DNA. Attendees received a foldout poster showing a time-line of 50 years of cancer research since that discovery, and the introduction of Gleevec was one of the most recent milestones on the chart. Many speakers mentioned Gleevec as a prime example of progress in the war on cancer.

On Saturday, Dr. Brian Druker of Oregon Health & Science University presented a 7 a.m. "Meet-the Expert Sunrise Session," titled "Imatinib as a Paradigm of Targeted Therapies." His focus was on CML but he also discussed GIST. Most of his talk was a review of progress familiar to most LRG members.

After presenting the overall good news of the success of Gleevec therapy for CML, he raised several questions: 1) Is it possible to improve on the present success with treatment of chronic CML patients? 2) Why do some patients relapse? 3) Is the target (Bcr-Abl kinase in CML) actually inhibited? He showed that about half of

See More AACR, Page 5



**Those at the Dutch Life Raft Group meeting included, standing from left, Joke and Peter van der Meer, Koos and Lenie Flaton, Hettie and Rene Kerremans, Gretie Hegge, Hilbrand and Marlies Bruinsma, Angeliqne and Arthur van Krugten. In front: Ton and Ineke de Keijser, Carolien and Hans Verhoogt.**

## Dutch Life Rafter's gather in Ridderkerk

By Marlies Bruinsma

**R**IDDERKERK, The Netherlands — The first Dutch Life Raft Group meeting took place June 28. Eight GIST patients and seven partners arrived between 14.00 and 15.00 hours. Most of the members knew each other by e-mail, so we started by introducing one another. Every patient has its own unbelievable medical history and most fortunately all the treatments by surgery, or with Gleevec were successful.

After consideration with all the Dutch patients, Ton de Keijser had volunteered to select a few questions for Prof. J. Verweij (the “Dutch Dimitri”). Verweij was most willing to cooperate and was very sorry he couldn’t make it to our meeting, due to another commitment.

Verweij wrote back to our questions

that there is more unknown about GIST than known and it is very important that money for research will be available. He also told us that metastases are mostly found in the liver and the abdomen. Diet has no influence on the GIST — either in cancer already existing or in developing GIST.

At this moment there is no reason to presume that our children will inherit the GIST. No inheriting factor is found yet.

Furthermore, Verweij mentioned some side effects of Gleevec, but these are very individual (for example, thin skin, hair turns to gray, etc.). The research about the resistance on Gleevec isn’t very far along at the moment, but Verweij believes surgery is best when possible, because when the entire GIST is removed operatively, the patient stops with the Gleevec. This narrows the chance of resistance and if

the cancer returns treatment with Gleevec is still possible.

Once a patient develops resistance on Gleevec, their options are reduced.

In The Netherlands there is no trial for Sugen or Sugen-related treatments, mostly because there are too many governmental rules and money is always the problem.

The hospitality by Ton and Ineke de Keijser was very fine. The catering was excellent and we had the most beautiful weather so we were sitting in the garden most of the time. In a nice and warm atmosphere we could share our experiences.

After lots of discussion about all sorts of things, from hospital treatments (eight patients, five different hospitals) to private situations, reactions and more, we closed our first Dutch Life Raft Group Meeting around 21.00 hours.

## Letters to the editor



# LifeLine Pilots: The shortest distance between home and hope

**L**ifeLine Pilots is a not-for-profit, charitable flying organization that arranges free air transportation for financially stressed individuals who are seeking medical treatment or other specialized services at locations far from their homes. We also provide planned organ transplant recipient travel assistance and fulfill other specialized humanitarian needs. All of our services are provided free of charge to our passengers.

Founded in 1981, LifeLine Pilots has matured into a network of more than 400 volunteer pilots located throughout the upper Midwest that includes North and South Dakota, Nebraska, Kansas, Minnesota, Iowa, Missouri, Arkansas, Wisconsin, Illinois, Michigan, Indiana, Ohio, Kentucky, and Tennessee. Pilots donate their time, aircraft (usually 4- to 6-seat craft), and all related flying expenses including fuel. A small support staff located in our Peoria, Ill., headquarters coordinates all missions, recruits pilots, provides education and outreach services, and performs all the other services that keep us operational.

Our passengers come from all walks of life, ages and ethnic backgrounds, and a majority of them are facing some form of life-threatening disease. During the past year our volunteer pilots flew well over 500,000 miles transporting their passengers to their destination. Whether it's a small child going for cancer treatment, a homemaker going for a kidney transplant, or a child going for laser surgery, our underlying mission is the same ... to "Make A Difference," to help relieve some of the suffering in the lives of those we serve. In addition to medical needs, the common denominator among the people we serve is financial distress, and if not for our service and our generous volunteer pilots, most would experience extreme hardship in getting to the treatment they needed.

A phone call to 1-800-822-7972 is all it takes to apply for our service.

Our financial support comes from many areas, including corporate and private foundations, gifts, grants, individual contributions, and a variety of in-kind contributions. We also receive outreach and education support from various organizations, including ser-

vice clubs, the health care industry, media and others. These organizations help disseminate information about our services and identify the people we strive to serve.

LifeLine Pilots works with other volunteer pilot organizations (VPOs) throughout the country to provide comprehensive nationwide service. We are also part of the Air Care Alliance that provides autonomous VPOs with a forum by which we all work toward improving the mission we share. The ACA plays an increasingly important role as our target population grows and as their medical needs become more diversified.

The board of directors, volunteer pilots, and entire staff are grateful for your interest in our organization and in our mission. We would be happy to provide you with additional information. Please give us a call or e-mail at the address below.

**Robert C. Hultgren,**

Executive Director, LifeLine Pilots

1-800-822-7972

bhultgren@lifelinepilots.org

www.lifelinepilots.org

## Mark your calendar for these coming Life Raft events

**Saturday, Aug. 23:** The first meeting of the Florida chapter of the Life Raft group is being organized by Life Rafter Vince Luce and Stan Bunn, president of the Life Raft Group's board of directors.

The meeting, from 11 a.m. to 1 p.m., will be held in Bunn's office in Tampa, 5925 Benjamin Center Drive, located directly behind Tampa International Airport. Lunch and

refreshments will be provided.

E-mail Luce or Bunn to reserve a seat. Bunn may be reached at sbunn@bstsoftware.com; Luce at javagate@hotmail.com

**Saturday, Aug. 23:** The Chicago chapter of the Life Raft Group meets at the Wellness Place, a cancer support center in Inverness, Ill. Contact Dick Kinzig, RJKinz@aol.com, for details.

**Sunday, Sept. 7:** Another meeting of

Southern California Life Rafter will take place at the Lakewood home of Floyd Pothoven, the So Cal area coordinator for the Life Raft. For details, contact him at floyd@lasersealer.com.

**Sunday, Oct. 19:** The third annual Walk for a Cure organized by Tania and Robert Stutman for their GIST Cancer Research Fund will take place at Rockland Lake State Park in Congers, New York state. Details to come.

## More AACR: Talk about targets and targeted therapy

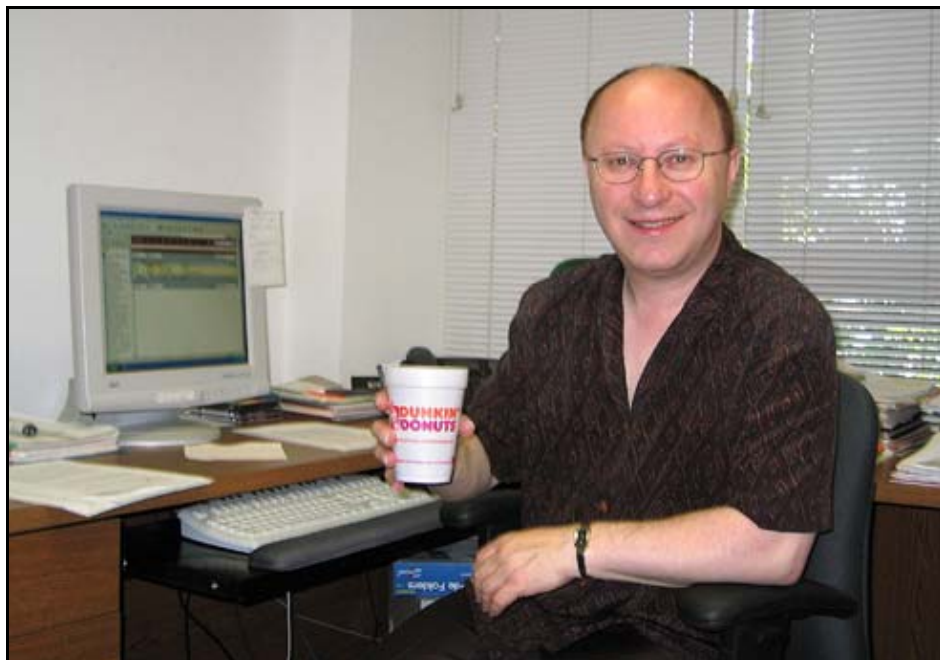
From Page 2

CML patients who become Gleevec-resistant have acquired new mutations in the kinase domain of Abl, with the Y351I (tyrosine to isoleucine) mutation being one of the most troublesome, because the mutant protein is insensitive to Gleevec and also to the investigational drug PD180970. With respect to GIST, he estimated that there are 5,000 new cases of GIST per year in the U.S. — far more than was thought a few years ago. He cited Dr. George Demetri's work and the recent study of Gilliland et al. (see above).

After his talk, I asked a question about dosing strategies — does he feel that doses should be pushed higher, or dropped lower, in patients who appear to be doing well on Gleevec. He was certainly well aware of the surrounding issues, and mentioned the controversy regarding the comparison of results between the (nominal) 400 and 800 mg. dose regimens for GIST, which has been discussed in these pages, and he agreed that analysis of these results is difficult, in view of the differences between the intent-to-treat doses and the actual delivered doses.

Dr. Andrey Frolov, working with Fletcher and others at Fox Chase and Dana-Farber, gave a talk titled "Gleevec and GISTs: Identification of response markers and the molecular mechanisms of action." The goal of his work is to identify "surrogate" markers, that is, proteins other than c-kit which might be used to measure a patient's responsiveness to Gleevec. He compared gene expression in human GIST cell line (GIST882) with and without exposure to Gleevec, looking for proteins whose expression was changed by exposure to the drug. Two proteins were discovered to be strongly down-regulated in response to Gleevec: a signaling molecule called SPRY4A ("sprouty") and another protein called MAFbx.

Finally, needle biopsies of GIST pa-



**David Josephy, Ph.D., at the Life Raft Group office in Totowa, New Jersey. Josephy spent three days there in June helping update the medical content of the Life Raft's Web site. Josephy is on the chemistry and biochemistry faculty at the University of Guelph, Ontario, Canada.**

### Quote:

**"With respect to GIST, he estimated that there are 5,000 new cases of GIST per year in the U.S. — far more than was thought a few years ago."**

**— David Josephy, citing Dr. Brian Druker's talk titled "Imatinib as a Paradigm of Targeted Therapies."**

tients before and after Gleevec treatment were analyzed for expression of these proteins. He concluded that these proteins are highly-reliable predictors

of response, because they became down-regulated only in those patients who, clinically, responded well to Gleevec.

Sunday morning, Dr. Sharyn D. Baker gave a sunrise talk, "Pharmacokinetic Variability of Anti-cancer Agents." Gleevec was among the many drugs she covered. Her most important message was that there is still no substitute for clinical and analytical observation of the response of the individual cancer patient to a drug. For most studies, there are no significant correlations between response and variables such as body mass, body surface area, age, or polymorphisms of specific enzymes such as P450 3A4. Inter-individual variation in drug metabolism is multi-factorial and usually too complex to be reduced to any single predictive variable. This explains why most doctors believe that it is not useful to adjust Gleevec doses

**See AACR III, Page 6**

## Going global: Each country has unique bureaucracy

From Page 1

(both chronic myeloid leukemia and GIST) in Germany. We will be providing them with medical information and other support.

**Poland:** We recently succeeded in getting Glivec to a Polish GIST patient, the father of Life Raft member Bartosz Szczesny. He will become our country representative in Poland and we will be working together to get Glivec to other patients there.

**Eastern Europe:** We are working with a key Novartis representative in a new initiative to reach GIST patients in Eastern Europe.

**Uganda:** Our efforts here launch the beginning of our medical specialist assistance program: Dr. Mary Louise Keohan, a sarcoma specialist at Columbia Presbyterian in New York City — and the doctor I credit for saving my wife Anita's life by diagnosing her with GIST and telling us about Gleevec — has volunteered to serve as a consultant to a physician in Uganda. We will be expanding this type of consultation to physicians in developing nations.

**India:** Although we have temporarily helped negotiate for the manufacturer of a generic version of Glivec to supply GIST patients in need, we are concerned about being able to maintain this and are monitoring the situation closely.

**Morocco:** Morocco has now ap-

### Quote:

**“The Internet has indeed made for a much smaller world.”**

Norman Scherzer,  
executive director,  
Life Raft Group



proved Glivec for CML patients, but not yet for GIST patients. In the interim we will work behind the scenes with Novartis to supply GIST to patients in need. (As we go to press we are advised that this situation has changed and that Novartis now has a patient assistance program in place administered by the MAX Foundation.)

**Australia and the U.K.:** In both countries we are working to try to get the government to approve Glivec for GIST patients.

**Israel and Japan:** Both countries have just approved providing Glivec for both CML and GIST.

**United States:** U.S. legislators are still fighting over the details of a prescription coverage plan, which does

not now include interim coverage (for the two year period before the proposed comprehensive prescription plan would take place) of oral cancer drugs like Gleevec. We are an active member of an ad hoc coalition trying to change this, but it remains an uphill battle.

**Observations:** Each country has its unique culture and bureaucracy. In countries where Glivec is approved for GIST and where there is no government coverage (socialized medicine) Novartis contracts with the MAX Foundation to provide drugs to patients in need. In countries where Glivec is not approved for GIST or where there is supposed to be government coverage, the MAX Foundation does not operate.

The Life Raft Group has increasingly been called upon to fill that void. For example, in countries like Poland we have to deal with a catch-22 situation: Theoretically, the government will provide drugs to everyone; in reality, their budget does not meet the need.

Polish press visiting the U.S. recently interviewed people at Novartis as well as Life Raft member Dan Cunningham and myself. The resulting news articles and television broadcasts generated almost immediate requests for assistance from both patients and doctors. The Internet has indeed made for a much smaller world.

## AACR III: Many researchers follow Gleevec's example

From Page 5

based on factors such as body mass.

Another prominent theme at the AACR meeting was the large number of researchers who are trying to develop new drugs that act by mechanisms similar to that of Gleevec; that is, inhibiting c-kit and other tyrosine kinases. The real number of such ongoing studies must be even larger, because much of the work will be pro-

prietary projects at drug companies, but several academic researchers reported their work at the meeting.

I won't go into too much detail about these studies, because the new compounds are generally at a very early stage of development. An example was a talk by Daruka Mahadevan (Arizona Cancer Center, Tucson) titled "Structure-based design and synthesis

of c-kit tyrosine kinase inhibitors targeting GIST." He showed a series of new compounds that inhibit c-kit at concentrations similar to that at which Gleevec acts, and can kill GIST882 cells in vitro.

Novartis researchers displayed a poster titled "Antitumor activity of RAD001 in combination with cyto-

See AACR IV, Page 7

## William Lawson, 56, lifelong resident of Lafayette

**W**illiam “Bill” Lawson, of Lafayette, Indiana, died Thursday, July 3, at Home Hospital after a near two-year battle with GIST. He was 56.

Bill was a lifelong resident of Lafayette. He worked as a realtor for ERA and Select Homes, and was previously employed at General Foods and Great Lakes Chemicals.

He was a member of Saint James Lutheran Church, Beta Phi Sigma fratern-

ity and the John Purdue Club. He enjoyed playing and coaching softball. He also followed Purdue football.

He married Gwen Schultz on July 21, 1973. She survives him, as does his mother, Gloria Wolf of Americus; a son, C. Cory Lawson of Lafayette; two daughters, Jennifer Brook Lawson of Lafayette and Rhonda Kay Lawson of West Point; two sisters, Cathy Geier of Lafayette and Connie Spall and her husband, Ron, of Lafayette; a brother, Fred Lawson of Kentucky, and three

grandchildren, Alexa, Andrew and Garrett. He was preceded in death by his father, Elwood Lawson.

Services were held July 7 at Saint James Lutheran Church, Pastor David French officiating. Interment was at Rest Haven Cemetery. Memorial contributions can be made to Saint James Lutheran Church, 800 Cincinnati St., Lafayette, IN 47901-1073, or to the Life Raft Group, 555 Preakness Ave., Level Two East, Suite 2, Totowa, NJ 07512.

### In Memoriam

There have been 26 deaths in the Life Raft Group to date:

**Debbie Nance**, 38, Oct. 2, 2000, wife to Eddie, mother of Chris.

**Jim Ackerman**, 49, Jan. 16, 2001, husband to Betsy, father of Jill and Tom.

**Jim Perham**, 63, May 2001, husband to Karen, father of Craig, Kathy, Jennifer.

**Amy Barney**, 25, June 10, 2001, wife to Reed, mother of Joshua.

**Jeff Prichard**, 52, July 11, 2001, husband to Joyce, father of Gregory and Scott.

**Ron Martinez**, 60, July 25, 2001, husband to Jo Ann, father of Ron, Wendy, Natalie.

**Ehud Nehemya**, Aug. 7, 2001, father to Einat Zelinger, father-in-law of Ophir Zelinger, Hadar Nir.

**Bruce Gunn**, 43, Nov. 8, 2001, husband to Roisin, father of Seamus, Liam, Brendan and

Aislinn.

**Robert Carr**, Dec. 30, 2001, father of Robert, Steven, Scott and Melissa.

**Jonathan Montague**, 23, Jan. 19, 2002, son of Ray and Sheila Montague, brother to Jamie, Adam, Meghan.

**Robert Lecca**, 49, Jan. 28, 2002, husband to Diane.

**Jacob Winfield Waller III**, 67, March 31, 2002, husband to Jerry, father to Rita, Richard.

**Mary Golnik**, 50, April 18, 2002, wife to Gary, mother to Timothy.

**Ana Maria Baldor-Bunn**, 30, April 19, 2002, wife to Stan, mother to William.

**Stewart “George” Wolf**, 51, April 19, 2002, husband to Maggy, father to Thomas.

**Michael Cornwell**, April 19, 2002, husband to Cathy.

**Jerry Pat Rylant**, 61, May 5, 2002, husband to Pamela, father of four, grandfather to 10.

**Jill B. Meyer**, 53, June 9, 2002, mother of Aliza.

**Todd Hendrickson**, 44, June 29, 2002, husband to Janet, father to Max, Tyler and T.J.

**Chet Duszak**, 79, Oct. 5, 2002, husband to Kay, father to Lori.

**Nora Shaulis**, 42, Nov. 4, 2002, wife to David, mother to Griffin.

**Howard Delapenha**, 41, Dec. 14, 2002, husband to Sandra, father to Joshua and Hannah.

**Kathy Colwell**, 45, Jan. 5, 2003, wife to Tom, mother of Katherine, Mary and Tom.

**Cynthia G. Whitson**, 64, Jan. 19, 2003, wife to Jerry, mother to Steve, Jill, Randy and Donna.

**Abdul Hai**, 76, Feb. 26, 2003.

**William Lawson**, 56, July 3, 2003, husband to Gwen, father of Cory, Jennifer and Rhonda.

## AACR IV: New RAD drug a derivative of rapamycin

From Page 6

toxic agents” which, although not focused on GIST, may be of interest, since there are ongoing trials of RAD001 for GIST therapy.

I had a chat with the lead author, Dr. Terence O’Reilly, who turned out to be a graduate of the University of Guelph! RAD001 is a derivative of rapamycin. They tested combination therapy of RAD001 with conventional chemotherapy agents such as doxorubi-

cin, cis-platinum and taxol, in tissue culture studies, and found some potentially promising regimens, in terms of synergistic cell killing.

Another poster I looked at was “Plasma and cerebrospinal fluid pharmacokinetics of imatinib in non-human primates,” presented by Dr. Merrill J. Egorin of the University of Pittsburgh Cancer Institute. The poster reported studies in monkeys looking at

Gleevec’s ability to pass through the blood-brain barrier. Gleevec was detected in the brain after oral dosing, but the levels were much lower than in the peripheral blood. Thus, the brain may be a “sanctuary” site, explaining why CML can recur in the brain after Gleevec treatment. (However, I believe that GIST metastasis to the brain

See AACR V, Page 8

## AACR V: Patients tolerate Sugen better than expected

From Page 7

is very rare.)

Egorin told me that his lab ran the analyses of Gleevec serum levels for the NCI clinical trial. He was friendly and approachable and very well-informed about Gleevec pharmacology. While we were talking, another person stopped to look at the poster, Dr. Anthony Murgo from National Cancer Institute, and we chatted for some time. He is one of the key managers for the NCI Gleevec trial.

A highlight of the meeting was one of the last sessions, a mini-symposium on epidermal growth factor receptor inhibitors Monday afternoon. There were three talks in a row about GIST therapy.

First, Dr. Samuel DePrimo of Sugen Inc., presented “Decreases in circulating levels of soluble KIT in patients with imatinib-resistant GIST receiving the novel kinase inhibitor SU11248: Correlative analysis of blood and plasma biomarkers.” This paper reported a study of a possible biomarker of response to treatment in GIST, carried out in the patients enrolled in the phase I trial of Sugen (SU11248) in Gleevec-refractory, -resistant, or -intolerant GIST patients. The goal is to find markers in the blood which could be used to predict or evaluate response to therapy in GIST patients. C-kit is a membrane-bound protein found in the tumor cells but not circulating in the blood. “S-kit” is a soluble fragment of kit that corresponds to the extra-cellular domain of the protein. It is generated by cleavage of membrane-bound c-kit, carried out by an unidentified protease enzyme. The researchers measured s-kit in the blood of patients in the SUGEN trial. S-kit levels decreased during treatment, and there was a good correlation between the s-kit level and response to therapy. So this may be a promising and rapid new way to assess patient response to treatment.

### Quote:

**“A clear lesson was that CAT scans are a poor indicator of response to the Sugen drug.”**

— David Josephy

Dr. Anette Duensing, in collaboration with Drs. Fletcher, Demetri, et al., gave a talk “Oncogenic KIT signaling in GISTs.” They used biochemical techniques to look for proteins involved in c-kit-dependent signaling in GIST patients and in GIST cell lines. This was a rather technical talk and I did not discern any direct implications for GIST therapy.

Dr. George Demetri gave the next talk, “Biological activity of the multi-targeted tyrosine kinase inhibitor SU11248 in patients with malignant GIST refractory to imatinib mesylate.” Among the points he made: He reviewed results with Gleevec for GIST, stating that 63 percent of patients show a partial response, 20 percent are stable, and 17 percent fail to respond. However, resistance emerges with time among the responding patients.

So far, median survival time of the metastatic GIST patients in the U.S./Finland trial is 1.4 years. SUGEN (SU11248) is being tested in a phase I dose-escalating study in metastatic GIST patients “with disease that was objectively progressing despite continuation of imatinib therapy, plus one patient who could not tolerate imatinib.”

The study has developed into a phase II trial. Safety and tolerability of the drug is being studied, as well as many correlative science studies (one of which is the DePrimo et al. study mentioned previously).

The SUGEN starting dose is 25, 50, or 75 mg. a day for 14 days, followed by a 14-day rest period per cycle. Patients undergo CT, MRI and PET scans, biopsies and blood work. Forty-five patients were enrolled from April 2002 to March 2003, 40 of whom had developed resistance to Gleevec after an initial response. He showed evidence that kit phosphorylation (activation) and tumor cell proliferation drop dramatically following Sugen treatment. Some 72 percent of patients showed a response, as measured by PET scans. He emphasized one patient who is “doing great” after one year on Sugen.

The overall conclusion is that Sugen shows promising activity. He also showed cases where a dramatic response was evident by PET scans and by evaluation of diminishing proliferative index in biopsy cells, even though there was no clear evidence of response on CAT scans.

A clear lesson was that CAT scans are a poor indicator of response to the Sugen drug. A phase III trial is “coming.”

During questions, the dose schedule was discussed. The two-week-on/two-week-off regimen was used because previous trials of Sugen for other cancers had shown that patients had trouble tolerating the drug, with a fatigue syndrome developing. The two-week rest period allows patients to recover. However, Demetri said, GIST patients are tolerating the drug better than had been anticipated, and the study may switch to continuous drug dosing.

This was a very encouraging presentation. Thanks to Laura Cooley for letting us know about a report, stemming from Demetri’s talk, available on MSN (<http://content.health.msn.com/content/article/71/81203.htm>).

*David Josephy, Ph.D., is a professor of chemistry and biochemistry at the University of Guelph, Ontario, Canada.*



## Life Raft board meeting held in Dallas



**Members and directors of the Life Raft Group gathered May 17 for a board meeting in Dallas, Texas, U.S. Pictured from left are Director Silvia Williams, Executive Director Norman Scherzer, President Stan Bunn, Director Rodrigo Salas, Life Rafter Cordelia Salas, Chief Financial Officer John Poss, Life Rafter Gayne Ek, Gerry Knapp (fund-raising co-chairman) and Anita Scherzer, and Christy Garrison, Poss' assistant.**

## Approval: Glivec for GIST used in more than 70 countries

**From Page 1**

conducted in 74 patients who received either 400 mg. or 600 mg. Glivec once a day. The overall response rate was 51 percent at the time of the data cut-off for the submission.

The Japanese data support the findings of a study that was the basis for marketing approval in the EU and U.S. In this open-label, multinational study conducted in 147 patients with unresectable and/or metastatic malignant GISTs, patients were randomized to receive either 400 mg. or 600 mg. of Glivec daily. The overall response was 38 percent, based on confirmed partial

responses after a median follow-up of approximately seven months.

Updated data from the multinational study, after a median follow-up of 15 months, was presented in May 2002 at the annual meeting of the American Society of Clinical Oncology (ASCO). The data showed that more than 60 percent of GIST patients achieved a confirmed partial response with Glivec, and an additional 20 percent attained some degree of tumor shrinkage or stabilization of their disease.

The data also revealed that at a median follow-up of 15 months, 73 per-

cent of patients remained on the study.

GISTs are the most common sarcoma of the gastrointestinal tract. According to a Swedish study presented at the American Society of Clinical Oncology meeting held May 31-June 3 in Chicago, the incidence of GIST is estimated at 15 per 1,000,000 people annually, more than three times as high as previously suggested.

Glivec is approved in the U.S., the European Union and more than 70 other countries for the treatment of patients with kit-positive unresectable and/or metastatic malignant GISTs.

# THE LIFE RAFT GROUP

E-mail: [liferaft@liferaftgroup.org](mailto:liferaft@liferaftgroup.org)  
 Internet: [www.liferaftgroup.org](http://www.liferaftgroup.org)

● 555 Preakness Ave. ●  
 ● Level Two East, Suite 2 ●  
 Totowa, NJ 07512

Telephone: 973-389-2070  
 Fax: 973-389-2073

## Who are we and what do we do?

The Life Raft Group is an international, Internet-based, non-profit organization providing support through education and research to patients with a rare cancer called GIST (gastrointestinal stromal tumor). The Association of Cancer Online Resources provides the group with several listservs that permit members to communicate via secure e-mail. Many members are being successfully treated with an oral cancer drug Gleevec (Glivec outside the U.S.A.). This molecularly targeted therapy inhibits the growth of cancer cells in a majority of patients. It represents a new category of drugs known as signal transduction inhibitors and has been described by the scientific community as the medical model for the treatment of cancer. Several new drugs are now in clinical trials.

## How to join

GIST patients and their caregivers may apply for membership free of charge at the Life Raft Group's Web site, [www.liferaftgroup.org](http://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.,

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[nscherzer@liferaftgroup.org](mailto:nscherzer@liferaftgroup.org)  
[tmcaleer@liferaftgroup.org](mailto:tmcaleer@liferaftgroup.org)  
[jcpoos@swbell.net](mailto:jcpoos@swbell.net)  
[jroy@liferaftgroup.org](mailto:jroy@liferaftgroup.org)  
[guitarman335@msn.com](mailto:guitarman335@msn.com)  
[dnrgibson@yahoo.com](mailto:dnrngibson@yahoo.com)  
[mebmcb@peoplepc.com](mailto:mebmcb@peoplepc.com)  
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[Jerry.Call@attbi.com](mailto:Jerry.Call@attbi.com)  
[liferaft@attbi.com](mailto:liferaft@attbi.com)  
[jcpoos@swbell.net](mailto:jcpoos@swbell.net)  
[gsknapp@winfirst.com](mailto:gsknapp@winfirst.com)

## Life Raft country representatives

Australia  
 France  
 Netherlands  
 Poland  
 Switzerland  
 United Kingdom

**Greg Ladbrooke** [lad57b@bigpond.com](mailto:lad57b@bigpond.com)  
**Bertrand de la Comble** [bdelacomble@oreka.com](mailto:bdelacomble@oreka.com)  
**Ton de Keijser** [akeijser1@challo.nl](mailto:akeijser1@challo.nl)  
**Bartosz Szczesny** [bsz1974@yahoo.com](mailto:bsz1974@yahoo.com)  
**Ulrich Schnorf** [ulrich.schnorf@dplanet.ch](mailto:ulrich.schnorf@dplanet.ch)  
**David Cook** [D.Cook@sheffield.ac.uk](mailto:D.Cook@sheffield.ac.uk)

## Life Raft area groups

Chicago, U.S.A.  
 Detroit, U.S.A.  
 Los Angeles, U.S.A.  
 Netherlands

**Richard Kinzig** [rjkinz@aol.com](mailto:rjkinz@aol.com)  
**Alan Tobes** [atobes@comcast.net](mailto:atobes@comcast.net)  
**Floyd Pothoven** [floyd@lasersealer.com](mailto:floyd@lasersealer.com)  
**Ton de Keijser** [akeijser1@challo.nl](mailto:akeijser1@challo.nl)

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**Mike Matthews** [mike@caster-rack.com](mailto:mike@caster-rack.com)  
**Rodrigo Salas** [rsalas@webtelmex.net.mx](mailto:rsalas@webtelmex.net.mx)  
**Silvia Williams** [nswplas@mb.sympatico.ca](mailto:nswplas@mb.sympatico.ca)

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## Donations, payable to The Life Raft Group, should be mailed to:

The Life Raft Group  
 555 Preakness Ave.,  
 Level Two East, Suite 2  
 Totowa, NJ 07512

## Disclaimer

We are patients and caregivers, not doctors. Information shared should be used with caution, and is not a substitute for discussion with your doctor.

As for this newsletter, every effort to achieve accuracy is made but we are human and errors occur. Please advise the newsletter editor of any errors.