

# Mutational testing predicts GIST treatment response

By Jerry Call

**T**he ability of mutational analysis to predict the response of GIST tumors to Gleevec has been known since Dr. Charles Blanke's GIST presentation at the plenary session of the 2001 American Society of Clinical Oncology (ASCO) meeting. A new paper by Maria Debiec-Rychter and colleagues from the European Organization for Research and Treatment of Cancer (EORTC) may prove to be a tipping point that causes mutational analysis to become routine for GIST patients, especially if their data is confirmed by the slightly smaller U.S./Canadian phase III study.

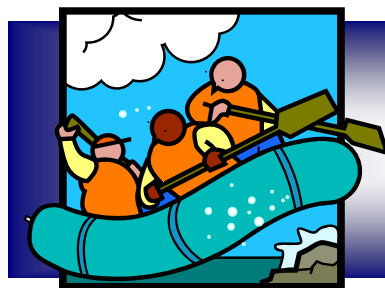
As many oncologists and GIST patients know by now, the most important therapeutic target in GIST is the KIT protein (or for a small minority the PDGFRA protein). Since the 2001 Blanke presentation it has also been known that where the mutation occurs in the c-kit gene (which contains the instructions for making the KIT protein) is also important. Mutations can occur in different parts of the gene called exons.

Dr. Michael Heinrich and Dr. Christopher Corless of Oregon Health & Science University (OHSU) have been two of the pioneers in the field of mutational analysis for GIST. Analysis that identifies the mutated gene as well as the exon where the mutation occurs is known as genotyping and has been available since 2003, but recent data from the GIST reGISTry has shown that only 3.5 percent of GIST patients have had genotyping done. A limited role in the treatment decision process, possible denial of insurance coverage, and a lack of availability in some parts of the world have been the most cited reasons for not having genotype testing done.

Genotype has been shown to be the

See TESTING, Page 3

Battling gastrointestinal stromal tumor



## LIFE RAFT GROUP

July 2006

In memory of Sheila Murphy

Vol. 7, No. 6

## Life Raft meets with Centers for Disease Control and Prevention

By Norman Scherzer  
Life Raft Executive Director

**W**hile in Atlanta at the American Society of Clinical Oncology (ASCO) conference, Jerry Call and I had the pleasure of meeting with Dr. Julie Gerberding, the Director of the Centers for Disease Control and Prevention (CDC), and William Gimson, the Chief Operating Officer. We spent over an hour discussing the work of the Life Raft Group and hearing

about some of the global issues facing CDC. Official pins were exchanged with Jerry and I receiving CDC's and Julie and Bill receiving the Life Raft's. We also presented our CDC colleagues with copies of the Life Raft Group newsletters and pamphlets, along with our official tee shirt. We have reliable information that Dr. Gerberding wore her Life Raft Group pin the entire day.

Following the hour long meeting with Dr. Gerberding, Jerry and I were given a tour of the new CDC bioterrorism facility.

See CDC, Page 10



Dr. Julie Gerberding, left, Director of the Centers for Disease Control and Prevention (CDC), William Gimson, center, Chief Operating Officer of CDC, and Norman Scherzer, right, LRG Executive Director view the Life Raft newsletters.

# Novartis-Schering drug vatalanib produces interesting early results

By Jerry Call

Interesting early results of a phase II trial for GIST were presented at the 2006 American Society of Clinical Oncology (ASCO) meeting. The drug, PTK787/ZK22584 (vatalanib), is being tested for GIST patients that are resistant to Glivec (Gleevec). Only 15 patients have been in the trial long enough to be assessed for response; therefore, the results of this small trial must be viewed with extreme caution.

Two of the 15 patients (13 percent) had a partial response (PR) to the drug and 8 patients (53 percent) had stable disease for more than 3 months. Overall this represents a 67 percent benefit rate for Glivec-resistant patients. The median time to progression (TTP) was 8.9 months. All of these numbers are very similar to the response rate of Sutent, the drug that is currently approved in the United States and Canada for Glivec-

resistant GIST.

The PTK787/ZK22584 project is a joint collaboration between Novartis and Schering AG. It is a multi-tyrosine kinase inhibitor and inhibits all three VEGF receptors as well as KIT and PDGFR.

The investigators for the phase II GIST trial are Heikki Joensuu, M.D., from Helsinki, Finland; Paolo G. Casali, M.D., from Milan, Italy; and Filippo DeBraud, M.D., Milan, Italy. Joensuu was the first doctor to ever treat a GIST patient with Glivec and was one of four investigators in the original phase II trials testing Glivec in GIST.

At the sarcoma poster session at ASCO, Dr. Joensuu hypothesized to me on why PTK787/ZK22584 might have a low toxicity profile. Joensuu showed a dendrogram showing the activity profile of Glivec, Sutent and PTK787. Each dot on the dendrogram indicated a kinase that is inhibited by the drug. The larger

See VATALANIB, Page 9



Dr. Heikki Joensuu from Finland meets with LRG Executive Director Norman Scherzer at the American Society of Clinical Oncology conference.

## The Life Raft Group

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](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., as a 501(c)(3) nonprofit organization, are tax deductible in the United States.

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

The Life Raft Group  
40 Galesi Dr., Suite 19  
Wayne, NJ 07470

### Disclaimer

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.

## TESTING

From Page 1

most important predictor of how GIST patients' tumors will respond to Gleevec. Patients with KIT exon 11 tumors have the best response rate, those with exon 9 tumors have an intermediate response rate and those with wild-type GIST (no mutations in KIT or PDGFRA) have a poor response rate. Patients with a PDGFRA mutation in exon 12 also respond well while those with exon 18 mutations have a poor response rate.

Last year at the 2005 ASCO meeting, Dr. Heinrich presented the first information that patients with KIT mutations in exon 9 have responses to the drug much more often at higher doses of Gleevec. About 15 percent of GIST patients have this type of mutation and these patients have an 8 times greater chance of having a response (shrinkage of their tumor(s) by approximately 50 percent). Even though this data had a very high P value, it was not considered "statistically significant" because it was an "interim analysis."

In a recent paper published in the European Journal of Cancer, Maria De-

biec-Rychter and the EORTC team expanded the work of Heinrich and the U.S./Canadian group to show that the higher doses of Gleevec also significantly prolonged progression-free survival for the exon 9 GIST patients. They reported that "... treatment with the high-dose regimen resulted in a significantly superior progression-free survival ( $P=0.0013$ ), with a reduction of the relative risk of 61 percent.

Included in the paper were graphs called "Kaplan-Meier" curves that showed in a more visual way the difference between doses. When we look at

See TESTING, Page 13

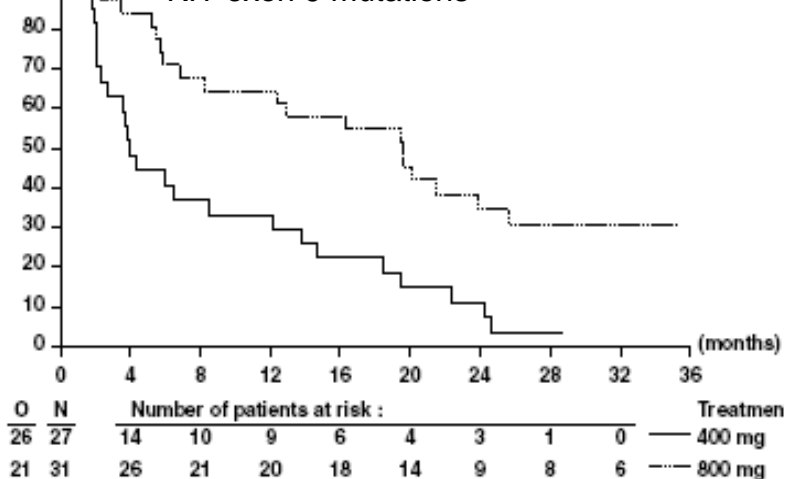
### Figure 1

The impact of the randomly allocated initial dose of imatinib on time to progression: (Figure 1A) for patients with tumorous bearing KIT exon 9 mutations, (Figure 1B) and for patients with tumours with wild-type genotype.

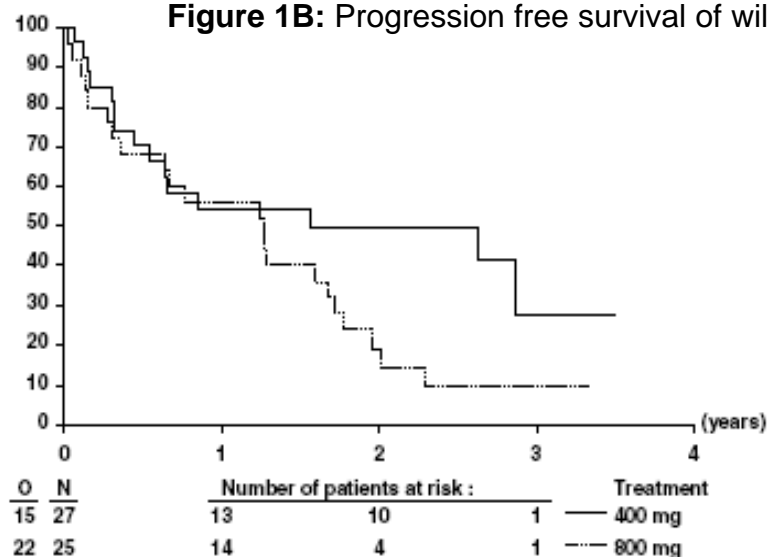
Reprinted from *European Journal of Cancer*, 42, Maria Debiec-Rychter et al., KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours, 1093-1103, 2006, with permission from Elsevier.

Dr. Debiec-Rychter is a key member of the Life Raft Group Research Team. Her story can be found on page 4.

**Figure 1A: Progression free survival of patients harboring KIT exon 9 mutations**



**Figure 1B: Progression free survival of wild-type patients**



# Debiec-Rychter sees research group as an orchestra

**By Dr. Maria Debiec-Rychter  
and Elizabeth Braun**

**D**r. Maria Debiec-Rychter has been exposed to the medical sciences her entire life. Her mother was a pediatric cardiologist and her father was a surgeon, both of whom worked at university hospitals. She expressed her interest in cancer as early as high school. For class, she was asked to write about her dreams for the future. Maria wrote about two, to see the Niagara Falls and to find the cure for cancer. In 1984, sixteen years since writing the essay, Maria visited the Niagara Falls. She has dedicated her life to achieving her second goal.

Dr. Debiec-Rychter attended school in her native city, Lodz, Poland. When she graduated from Medical University in 1978, she moved onto a Ph.D. program with a focus on the genetics of leukemia in children. This is where she discovered her passion for genetics, especially cancer genetics. She completed the program in 1981, and moved on to work as a visiting scientist in the Department of Chemical Carcinogenesis, part of the Michigan Cancer Foundation located in Detroit. Although she enjoyed the position, it made her life like a revolving door. She was continuously traveling between the United States and Poland trying to find the balance among her roles as wife and mother and her professional interests. Neither she nor her husband wanted to leave their native coun-

try at the time.

In 1998, Dr. Debiec-Rychter discovered GIST. At the time she was working in the Armed Forces Institute of Pathology, Washington, D.C. The first reports about activating KIT mutations in GIST were published, sparking significant interest for her colleagues – Dr. Markku Miettinen and Dr. Jerzy Lasota. In 1999, she was appointed to the Department of Human Genetics, University of Leuven, and she happily transferred back to Europe. She continued her study of GIST at the university. The studies were greatly facilitated by their clinical oncology leader, Prof. Dr. Allan Van

support of her friends and colleges from her department (Dr. Anne Hagemeyer, Dr. Jan Cools, Dr. Peter Marynen, Dr. Eric Legius – to name only few) and the clinicians from the Leuven Hospital Sarcoma Group (Dr. Raf Sciote, Dr. Ivo De Wever, Dr. Patrick Schoffski) nothing would be possible.

She strongly believes that team work is more important than individual effort. The unique GIST phase III study was successful due to the collaborative effort of the EORTC (European Organization for Research and Treatment of Cancer) Soft Tissue and Bone Sarcoma Group. Within this group, not only the leading

oncologists but also pathologists (Dr. Raf Sciote, Dr. Pancras Hogendoorn) and statistician (Dr. Martine Van Glabbeke) deserve special recognition. Debiec-Rychter often sees the research group as an orchestra. Each member has special qualities, plays distinct instruments and gives the unique tunes, but the best music is when they play together. Maria's family includes her husband who is a medical doctor and her son who is just finishing up his master's de-



Last summer while hiking on the Austrian and German border in the Alps, Dr. Maria Debiec-Rychter enjoys a moment of relaxation in the mountains.

Oosterom, from whom she learned the enthusiasm for translational research and received unlimited support and help.

Much of Dr. Debiec-Rychter's inspiration comes from the team of experts from different fields that complement and support each other, and from the unique research environment of Leuven University Hospital, whose research efforts focus on the intensive fusion of clinical and basic research. Without the

degree in computer science in Manchester, UK. She is very close to her mother and twin sister, who are back in Poland. Although she doesn't yet have grandchildren, she looks forward to the day that she does.

Dr. Debiec-Rychter is a valuable addition to the LRG's Research Team. With her passion for and dreams about finding a cure for cancer, she is truly an asset to the GIST community.

# Medicare Surprise: Why many seniors could temporarily lose drug coverage

**By Howard Gleckman**  
BusinessWeek Writer

*Note: This article is reprinted with permission from BusinessWeek from the May 1, 2006 issue.*

**S**uffering from asthma, emphysema, and a bad back, Barbara Slawson eagerly signed up for the new Medicare Part D drug benefit. For a premium of \$69 a month, she bought a Blue Cross policy that let her buy generic drugs for just \$5 and brand-name medications for \$38.

Then in late March, the Macedon (N.Y.) resident fell into what congressional staffers dubbed the “doughnut hole,” and her insurance was cut off. Under Part D, once patients spend \$2,250 on drugs, their coverage ends, and they must pay for their medicine themselves. Their benefits resume only after they shell out \$5,100—a \$2,850 gap.

## “Doughnut Hole” Danger

Once seniors spend

**\$2,250**

For prescription drugs under Medicare’s new Part D drug insurance this year, they’ll have to pay the next

**\$2,850**

Out of their own pockets until coverage kicks back in at **\$5,100.**

Although policymakers were aware of the doughnut hole when they passed the law, many seniors are stunned. “It came up all of a sudden,” Slawson says. “My medications were covered. Then I hit the hole, and they weren’t.”

About 38 percent of Medicare benefi-

ciaries are at risk, reckons Bruce Stuart, director of the Peter Lamy Center on Drug Therapy & Aging at the University of Maryland. This means 7 million to 10 million seniors and disabled could lose coverage for part of this year.

Many will stumble into the gap in late summer or early fall—just before the November elections. This could be bad news for Republicans, who pushed the Medicare drug law. According to an Apr. 6-9 Washington Post/ABC NEWS poll, just 41 percent of seniors approve of the program today. If many face a gap in coverage, that support could plummet. “There will be a lot of angry people—and they’ll be very negative toward the politicians,” says Robert J. Blendon, a professor at Harvard University School of Public Health.

Seniors such as Slawson fall into the hole because they take many costly drugs. But it took just one to push in Bob and Marge Naylor of Covina, Calif. Bob takes Betaseron to treat multiple sclerosis, and it costs him up to \$800 a

See MEDICARE, Page 11

## Editorial: The time for routine mutational testing has come

**By Norman Scherzer**

**R**eports continued at the American Society of Clinical Oncology (ASCO) meeting about various aspects of the relationship between mutational status and treatment efficacy. Heinrich et al. reported that Sunitinib (Sutent) response in Gleevec resistance GIST correlates with KIT and PDGFRA mutation status. Janeway et al. reported on wild-type pediatric GIST (i.e., no detectable mutation) responding to Sutent. Kleinbaum et al. reported on a familial GIST cluster with an exon 11 deletion. Blanke et al. reported on the long term follow-up of

the first Gleevec trial for GIST, once again confirming that patients with an exon 11 mutation had the best responses. Other reporters noted that GIST tumors outside of the abdomen (prior reports have noted that exon 9 tumors are more likely to occur outside of the abdomen) contributed to a higher risk for recurrence.

These reports are but the latest in an accumulation of information about the relationship between mutational status and treatment efficacy.

What do we know now:

- Gleevec works best with exon 11
- Sutent works best with exon 9 and with wild-type kit (thus accounting for

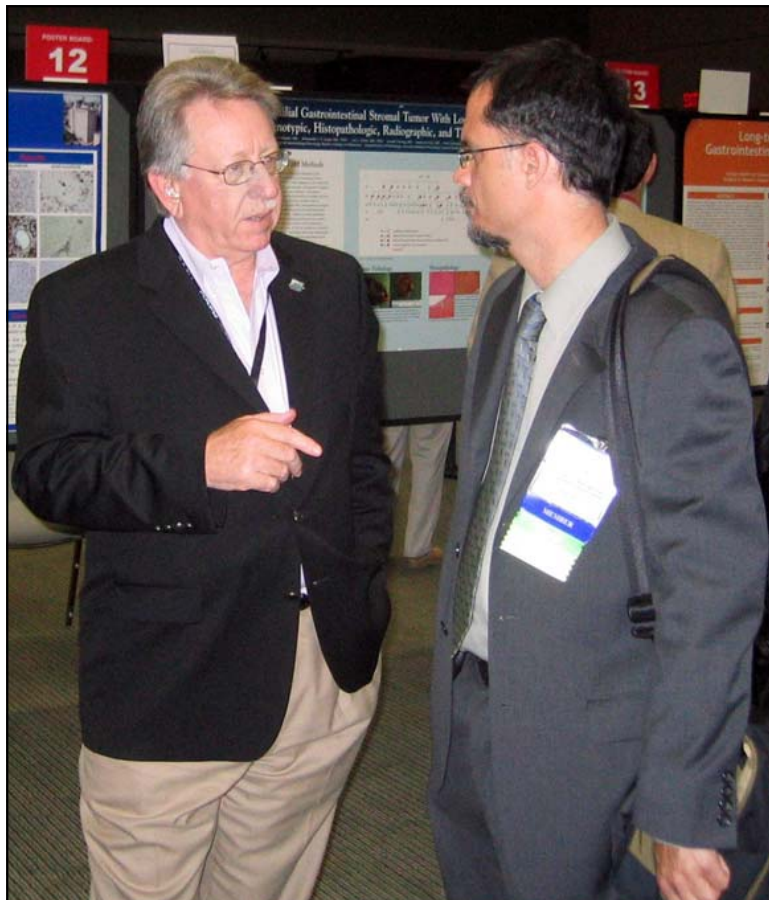
the Pediatric GIST response).

- Exon 9 mutations respond better to higher doses of Gleevec
- There is some suggestion that exon 11 mutations may respond to higher doses of Gleevec.

At ASCO Jerry Call and I spoke to a number of researchers and clinicians about routine mutational testing of GIST patients as part of their diagnosis. We could not find anyone who did not agree that this was a good idea. We submit that the time has come to move such mutational testing from occasional research to routine clinical management. That would accomplish two major re-

See EDITORIAL, Page 9

## Networking at American Society of Clinical Oncology



Networking is an overused term but we know of no better one to describe a major reason why we attend meetings such as American Society of Clinical Oncology (ASCO). Our objectives are to learn what is going on, to create and to develop strategic relationships, and to influence and advocate for the needs of GIST patients. As we mature as an organization we find that we are increasingly being networked by others. New GIST specialists seek us out to introduce themselves and to be listed in our Specialist Directory. Pharmaceutical companies seek our advice and our support for their clinical trials. Researchers seek our financial support for their projects. Marketing firms seek our patient advocacy group input for their pharmaceutical clients. ASCO was an incredible opportunity to listen, to learn and to advocate.

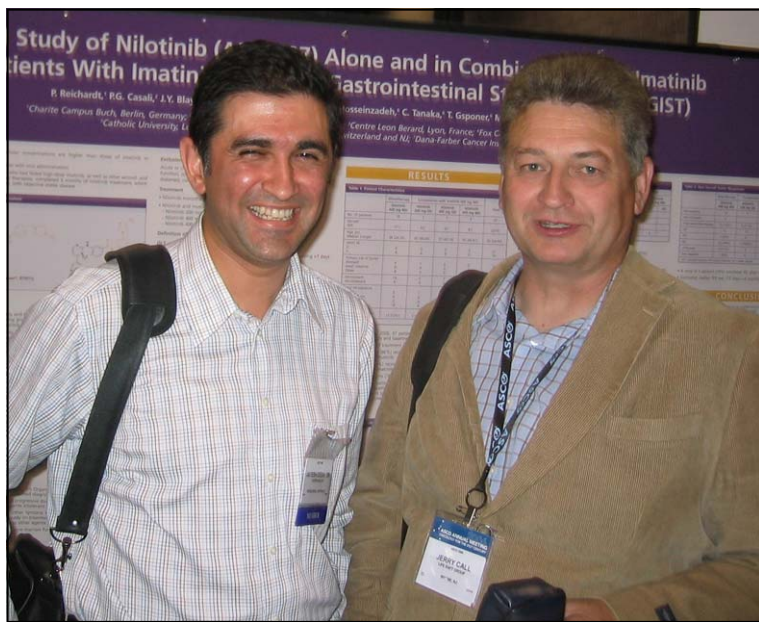
Pictured on top (from left to right): Dr. Robert Maki from Memorial Sloan-Kettering Cancer Center, Dr. Lee Helman from the National Cancer Institute, Jerry Call from the Life Raft Group, and Dr. Robert Benjamin from M.D. Anderson Cancer Center. Pictured to the left (from left to right): Norman Scherzer from the Life Raft Group talking with Dr. Jonathan Trent from M.D. Anderson Cancer Center. **Dr. Trent will be a featured speaker at the LRG membership meeting from September 15-17.**

## Meeting GIST experts at American Society of Clinical Oncology



Above (left photo): Norman Scherzer discusses with Dr. Alex LeCesne, from the Institute Gustave-Roussy in France, GIST clinical trials in France . Above (right photo): Dr. Susan George from Dana Farber Cancer Institute meets with Jerry Call about the latest news about Sutent.

## Discussing international efforts in GIST treatment



Above (left photo): Dr. Jayesh Desai, medical oncologist with Austin Health in Victoria, Australia, discusses treatment options for GIST patients in Australia with Jerry Call. Above (right photo): Dr. Alberto Pappo, from the Hospital for Sick Children in Toronto, Ontario, discusses new developments in pediatric GIST with Norman Scherzer.

# Life Raft meets with Infinity about IPI-504

By Norman Scherzer and  
Jerry Call

**W**hile at the American Society of Clinical Oncology (ASCO) 2006 meeting in Atlanta, Life Raft

Group members Norman Scherzer and Jerry Call had the opportunity to meet with Julian Adams, Ph.D., and David Grayzel M.D., of Infinity Pharmaceuticals. Infinity has a new drug, IPI-504, that is being tested in a phase I trial in GIST patients. Adams is the President and Chief Scientific Officer at Infinity and Grayzel is the Vice President, Clinical Development and Medical Affairs.

Prior to joining Infinity, Dr. Adams discovered and successfully brought to market two drugs, Viremune® for HIV and Velcade® for cancer. Adams received a B.S. from McGill University and a Ph.D. from the Massachusetts Institute of Technology in the field of synthetic organic chemistry. He has received many awards, including the 2001 Ribbon of Hope Award for Velcade® from the International Myeloma Foundation.

Dr. Grayzel obtained his medical degree at Harvard Medical School where, working in the Department of Genetics investigating familial inheritance of cardiovascular disease, he assisted in identifying the gene causing Holt-Oram Syndrome.

IPI-504 belongs to a new class of drugs known as heat shock protein 90 (Hsp90) inhibitors. Articles about this drug and the phase I trial have appeared in the November 2005 and January 2006 editions of this newsletter. The Hsp90 protein binds to and protects the KIT protein (Activated KIT protein is the primary driver behind the great majority of GIST tumors). Inactivating the Hsp90 protein causes degradation of the KIT protein and results in tumor cell death. In-vitro tests have shown activity of this class of drugs in GIST cells lines that have secondary mutations that are typi-



From left to right: Jerry Call, LRG Science Coordinator; Dr. Julian Adams, President and Chief Scientific Officer at Infinity; Dr. David Grayzel, Vice President, Clinical Development and Medical Affairs of Infinity; and Norman Scherzer, LRG Executive Director.

cally insensitive to Gleevec and other drugs.

IPI-504 is given intravenously twice per week for two weeks followed by one week off. As in any phase I trial the investigators primary concerns are looking for toxicities and establishing the right schedule and dose. As Hsp90 is an important protein that interacts with many other proteins besides KIT, investigators must proceed cautiously when establishing the right schedule and dose. Much of the experience with similar drugs in this class is with a schedule similar to the one used in the IPI-504 trial.

IPI-504 is not the only drug given to GIST patients in an on drug/off drug schedule. Sutent, the only drug currently approved for Gleevec-resistant GIST, is given in a four week on/two week off schedule. The on/off schedule of Sutent has been the subject of concern as some patients and some doctors feel that tumors can become “reactivated” during the off drug period. This has resulted in a phase II trial for Sutent to test whether

Sutent given continuously might be safe with increased effectiveness over the on/off schedule. The off drug period is commonly called a “washout period.”

One of the topics that we discussed at the meeting with Infinity was the washout period of IPI-504. Similar to the washout period with Sutent, some patients have reported difficulties with the washout period on IPI-504. Infinity acknowledged the concerns with the washout periods in GIST patients and had plans to discuss the IPI-504 washout with the trial investigators immediately after our meeting.

Infinity is a very promising start-up pharmaceutical company that is targeting an interesting protein, Hsp90. They seem committed to working with investigators and patients to bring their compound to patients. With Gleevec-resistant GIST, it might be a case of having found the right disease for their drug rather than a much longer term process of developing a specific drug solely for GIST.

# Murphy battled GIST for 7 years

## EDITORIAL

From Page 5

**S**heila Norene Murphy died Thursday, June 8, 2006, at McMaster Hospital in Hamilton, Ontario, Canada. She was 52.

Sheila was born Feb. 17, 1954. She held a degree in wildlife biology, but worked as a business systems analyst. She and her husband, Al, and their children, Andrea and Evan, enjoyed cross-country skiing, hiking, camping, sailing and canoeing. Sheila was also active in both school and church. The family made their home in Jordan Station, in the wine region of southern Ontario.

Services were held June 13 at Jordan Station United Church, followed by cremation. Survivors include her siblings, Randy and Janet Brown, Karen Brown, and Paul Harris. She was the daughter of Ken and Shirley Brown, and sister of Randy and Janet Brown, Karen Brown and Paul Harris. Special thanks to sister-

in-law Linda Murphy.

Memorial donations can be made to the Canadian Cancer Society, Ontario Division, 1639 Yonge St., Toronto, ON M4T 2W6.



MURPHY

sults: First, it would give each clinician critical information needed to determine the choice of drugs and the dosage level of drugs for each GIST patient. Second, it would permit future researchers to have this information and to be able to incorporate it into their analysis of their clinical trial data. At this time each researcher has to repeat mutational testing for patients that were previously tested in an earlier trial.

The time for routine mutational testing has come.

*Note: At the present time mutational testing can be performed by Oregon Health & Science University for a fee. Information about this process can be found on our website at [http://www.liferaftgroup.org/treat\\_gleeve\\_response.html](http://www.liferaftgroup.org/treat_gleeve_response.html).*

## VATALANIB

From Page 2

the dot, the more potently it is inhibited. Glivec is somewhat of a “cleaner” drug (in that it hits a single target), but it still has about 5 medium to large dots and about 11 smaller dots. Sutent (SU11248) is a relatively “dirty” drug (in that it hits multiple targets) and has some affinity for 74 different kinases. PTK787 was one of the “cleanest” drugs tested in this study by Milea Fabian et al., which was published in Nature Biotechnology.

Being a “dirty” drug is not necessarily a bad thing. Just how dirty a drug should be was the topic of an editorial in the October 13 issue of *Nature*. Dr. Michael Heinrich, M.D., a noted GIST expert, was featured in the article. “The trick is that most cancers have more than one target. They might have five or six targets and you have to knock out three to stop the cancer,” Heinrich said. “This is where dirty drugs come into play. You might be able to develop one dirty drug

with three targets instead of three clean drugs with one target each.” Glivec was thought to be a clean drug. “CML has just one target. At first, Gleevec seemed to be a very specific drug that affected the single mechanism of action behind CML. We thought Gleevec was a clean drug, but it turned out to be dirty,” Heinrich said. “Gleevec for CML was not an accident. Druker (Dr. Brian Druker) understood both the drug and the target. And because we knew how Gleevec worked, we made the step to GIST,” Heinrich said. “In the case of GIST, we are using a side effect of Gleevec to treat cancer.”

It is an interesting question whether or not a relatively clean drug like PTK787 that hits a few vital targets will be as effective as a dirty drug that strongly inhibits those vital targets and may or may not inhibit other important targets.

As presented by Dr. George Demetri, M.D., at a previous ASCO meeting, the ability of Sutent to overcome secondary resistance to Gleevec probably comes from two factors; its inhibition of addi-

tional kinases that may be important to GIST (perhaps especially VEGFRs) and its ability to inhibit the secondary mutations that can occur in exons 13 and 14 of the c-kit gene. Dr. Michael Heinrich updated the activity profile of Sutent at the 2006 ASCO conference and confirmed that Sutent has activity against the secondary mutations that occur in exons 13 and 14, but not against the exon 17 and exon 18 secondary mutations that were tested.

If the early impressive results of PTK787 continue to hold up with larger numbers of patients, it will be interesting to see the activity profile against the secondary mutations that are the primary cause of resistance to Glivec.

*Note: At a more recent meeting, Norman Scherzer spoke to another investigator connected to the vatalanib trial who reported some concerns with side effects, although not necessarily toxic in nature. This is a very early trial and we need a lot more data to draw any reliable conclusions.*

# AMG706 continues testing as second line drug for Gleevec-resistant GIST patients

By Norman Scherzer

**W**e were disappointed that no data was presented on the phase II trial for AMG706. Now entering its second year, AMG706 is being tested as a second line drug for GIST patients resistant to Gleevec. A number of Life Raft Group GIST patients continue in this trial and report positive responses to this drug.

At our meetings with AMGEN at American Society of Clinical Oncology (ASCO) we were impressed with their continuing interest in AMG706 for GIST patients. A practical dilemma for this company is that clinical trials for another second line drug for GIST patients resistant to Gleevec, Pfizer's drug Sutent, are far ahead of those for AMG706 and, in fact, Sutent has been approved by the Food and Drug Administration (FDA) for GIST treatment. That raises tactical issues for AMGEN and practical questions for the GIST patient community. The lack of a clinical trial with two treatment arms (in this case Sutent versus AMG706) makes it diffi-



From left to right: Kathryn West from Amgen, Norman Scherzer, LRG Executive Director, and Dr. Greg Rossi from Amgen meet at ASCO.

cult to compare the efficacy and side effects of these two drugs. This is a common problem when two drugs are made by two different pharmaceutical companies.

AMGEN will need to decide whether it can compete with Pfizer in producing

another second line drug for GIST or whether it can compete with Novartis in producing another first line drug by going head to head with AMG706 versus Gleevec in a clinical trial. GIST patients will need to decide how they can survive in the interim.

## CDC

From Page 1

ties, including their new state of the art crisis operations center and new multi-level hot labs.

*Personal Note:* Prior to the Life Raft Group, I spent 25 years working for the Centers for Disease Control and Prevention. After my retirement I became an Assistant Commissioner of Health for the City of New York and later the head of a consulting firm, 22<sup>nd</sup> Century Health Concepts. The sense of urgency and the high state of coordination of public health are in marked contrast to the situation with regard to cancer research, a subject I will write about in a future Newsletter.

## Life Fest 2006 in Dallas, TX September 15-17, 2006

The Life Raft Group is hosting the third membership meeting in Dallas, Texas at the Adams Mark Hotel. All GIST patients and caregivers are welcome to join the LRG for the weekend.

Educational sessions with the LRG Research Team, key medical professionals, and some of our own Life Rafterers who have volunteered to facilitate the flow of life-saving information will be presented. Additionally, Dr. Daniel Vasella, CEO of Novartis, will be a featured speaker at the event.

Registration/check-in opens at 3 p.m. and reception starts at 6 p.m. on Friday, September 15. General session ends at noon on Sunday, September 17.

For reservations, call 1-800-444-2326. For international reservations, call 314-993-2326. Inform the reservation specialist that you are attending the Life Raft Group meeting.

Check the LRG website at [http://www.liferaftgroup.org/members\\_lifestfestregistration.php](http://www.liferaftgroup.org/members_lifestfestregistration.php), for more details about registration and updates to the agenda and guest list.

## MEDICARE

From Page 5

month. He's now in the gap, and when he fills his next prescription, he may have to pay as much as \$3,400 for a three-month supply.

Why did Congress invent such a mess? Lawmakers first decided they wouldn't spend more than \$400 billion over 10 years. Then they wanted to cover those with high drug costs. They also wanted to do something for ordinary seniors. That left nothing for those whose spending falls in the middle. "They had to make it look good for people who don't use many drugs, and with that \$400 billion limit, they pretty quickly ran out of money," says Joseph R. Antos, a health economist at the American Enterprise Institute, a conservative Washington think tank.

Not everyone is at risk. Very poor seniors get full insurance. So do most of those covered by former employers. And insurers can fill in the gap, though usually only with generic drugs. About 13 percent of Medicare plans offer coverage in the hole. But seniors pay for that extra protection. In Maryland the monthly premium for Humana Inc.'s basic drug plan is \$6.44. A policy that fills the gap costs \$52.88.

Many health experts worry that those who lose coverage, even temporarily, will skip dosages or not fill prescriptions at all to save money. That could make them sicker in the long run. "It is pretty clear that people are going to cut back when they are in the doughnut hole," Stuart says. Others may try to buy cheap drugs from Canada or shop for lower prices online or at chain discount stores. But that can be a bad idea, because if they buy from a pharmacy that doesn't

take their insurance, the spending doesn't count toward the \$5,100 level that gets them out of the hole again.

Major drugmakers, smelling a round of bad publicity once seniors start falling into the gap, are considering special discounts for those who lose coverage. But they have not yet figured out a way to offer them. So for now, millions of unsuspecting seniors, who thought they were buying a full year's worth of drug insurance, are about to have a nasty surprise.

*Note: Every GIST patient who relies upon Medicare to help pay for Gleevec will hit this doughnut hole. As noted in our December 2005 newsletter, U.S. senators and congressional representatives do not themselves face similar prescription doughnut holes. Ironically, their health insurance is paid for by the U.S. taxpayers, including those on Medicare.*

## Dutch Life Raft Group receives national recognition

By Anja Long

Dutch Life Raft Group

### *National recognition for the Dutch Life Raft Group*

On May 12, 2006 the Life Raft Group Nederland officially became the 25th Cancer Patient Group to join the NFK (Dutch Federation of Cancer Patient Organisations). The NFK started in 1991 and is the umbrella organisation linking and representing 25 cancer patient groups all dealing with specific types of cancer. It supports the 25 patient groups in offering them services and information such as training, supportive administrative and secretarial services and professional advice in website management. The NFK publishes a quarterly magazine as well as a digital newsletter.

Four members of the Dutch Life Raft Group Committee had the agreeable duty of receiving the welcome package from the Chairman of the NFK, Mrs. Els Borst, to seal this official introduction of the LRG Nederland as the 25th member to the NFK.

The official welcome took place at the office of the NFK in Utrecht. Mrs. Els



From left to right: Carolien Verhoogt, Peter van der Meer, Ton de Keijser (LRG Committee), Els Borst (Chair NFK), Hilbrand Bruinsma (LRG) and Patricia Huijbregts (Director NFK).

Borst is a well-known public figure in the Netherlands; she was the Minister for Public Health in the previous government for 4 years. Also present was the Director of the NFK, Patricia Huijbregts. During this introductory meeting discussions were held as to the purpose and activities of both the NFK

and the LRG Nederland, and how these organisations can complement one another.

The Life Raft Group Committee hopes that by being part of the umbrella organisation it will be better able to represent the interests of GIST patients

See DUTCH LRG, Page 15

## ASCO reports Sutent as important drug for pediatric GIST

By Norman Scherzer

For the first time at the American Society of Clinical Oncology (ASCO) conference, a poster was presented with a report about pediatric GIST patients responding to a drug. Although quite preliminary and limited to three patients, the report noted that, after 5 cycles of Sutent (sunitinib malate), there was important anti-tumor activity in pediatric GIST patients with Gleevec (imatinib) resistance therapy. All GIST lesions were reported to have stabilized or decreased in size with complete regression of two lung nodules in one patient.

The data presented is consistent with internal reports that the Life Raft Group

has been receiving from pediatric GIST patients, some of whom may have been included in the poster presentation. Pediatric GIST patients generally seem to have no detectable KIT or PDGFR- $\alpha$  mutations ("wild type GIST"). In earlier studies with adult GIST patients who had a similar genotype (i.e., wild type GIST), significant clinical benefit was reported for Gleevec resistant patients treated with Sutent.

The authors of the poster conclude that an expanded phase I/II trial of Sutent in pediatric GIST is warranted.

*Note: While at ASCO we also received an update about a pending clinical trial for treating pediatric GIST patients with Gleevec. This trial has been in the discussion and planning stage for about*

*two years. It does not currently have a component for testing pediatric GIST patients with Sutent. Although there is insufficient data about the efficacy of either drug, we have not observed responses by pediatric GIST patients to Gleevec similar to those reported about for Sutent. Although we recognize that the Life Raft Group database of about 25 pediatric GIST patients is hardly a substitute for any randomized clinical trial, we submit that any such trial that does not include a Sutent arm does not take advantage of our most current information that strongly suggests that wild-type GIST patients (both adult and pediatric) do not seem to respond to Gleevec and do seem to respond to Sutent.*

### Massachusetts Life Raft Group



Back from left is Jack and Judy Leary, standing is Kathleen Konicek-Moran and seated holding purple ribbon is Dick Konicek-Moran, Maura and Mike Cesarini, Janice and John Leary holding Christopher, kneeling in front on the left in blue shirt is Ray Lofstrom on right in front of baby Christopher is Kristen Lofstrom.

## TESTING

From Page 3

the graph for exon 9 patients (see page 3, Figure 1A) we see that the median progression time (time point at which half of the patients have progressed) is only about 4 months for the low dose group. In stark contrast, the median time to progression for the higher dose group is about 20 months. This represents tumor control for five times as long as the low-dose regimen.

Even though the exon 9 high-dose group's median progression-free survival is five times as long, we do not know the full story because 57 percent of the patients on the lower dose were able to "cross-over" to a higher-dose of Gleevec. The length of benefit for these crossover patients was not given in the paper.

The EORTC paper concluded that "... These results suggest that imatinib (Gleevec) should be dosed at 400 mg twice a day in patients with tumours bearing KIT exon 9 mutations." The only way to tell which patients have an exon 9 mutation (and need the higher dose) is to do mutational testing (genotyping) on all GIST patients (or at least all new GIST patients).

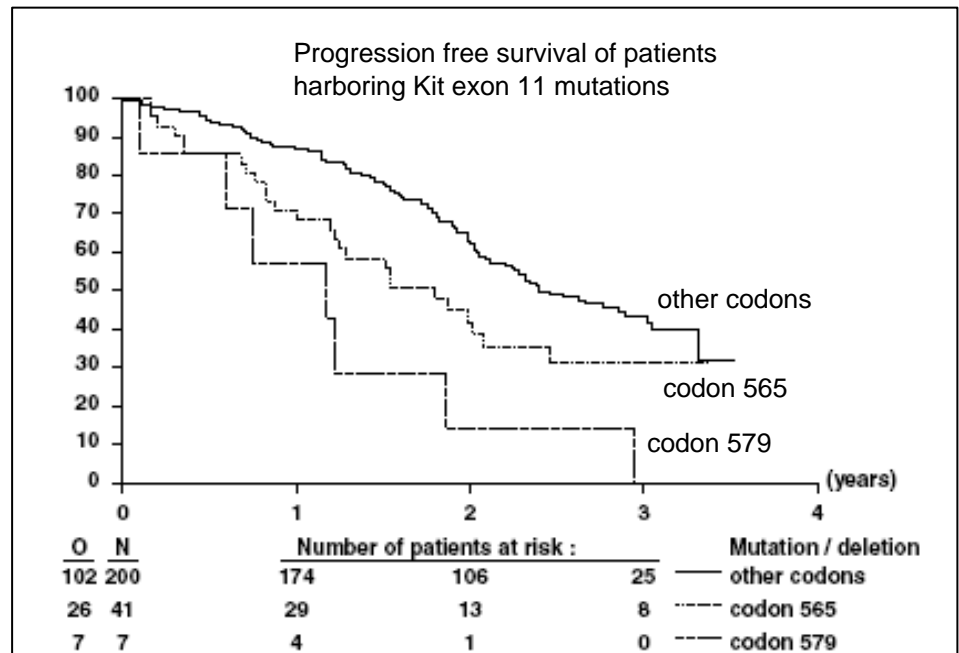
Additionally, the EORTC study showed that for wild-type GISTs "... higher dose did not significantly change the progression-free survival, with a trend even toward the benefit for the lower dose" (see page 3, Figure 1B). The authors concluded that interpretation of response in this group was difficult because of the diversity of wild-type GISTs. Hopefully when the data is merged between the two phase III trials the picture will become a little clearer.

The response to crossover from a lower dose of Gleevec to the higher dose was highly dependent on genotype as well. Responses (as measured by the growth modulation index) after crossover were:

- Exon 11, 7%
- Exon 9, 57%
- Wild-type 83%

Because KIT exon 11 tumors are the

Figure 2-Not all exon 11 mutations are the same



The progression-free survival in patients harbouring KIT exon 11 mutations: without mutation/deletion of codon 579 or 565 versus with mutation/deletion of codon 565 but not 579 versus with mutation/deletion of codon 579.

Reprinted from *European Journal of Cancer*, 42, Maria Debiec-Rychter et al., KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours, 1093-1103, 2006, with permission from Elsevier.

most common, an exploratory subset analysis of this group was possible. It turns out that not every exon 11 tumor has the same chance of responding to Gleevec (see Figure 2). Debiec-Rychter et al. discovered that patients with mutations in "the more distal end of exon 11" did not seem to respond as well as the total group of exon 11 patients. The hazard ratio for progression was significantly higher in tumors with mutations in codons 562-567 and particularly high in tumors with mutations at codons 577-579. The authors hypothesized that "It is possible that mutations inducing conformational changes, such as large deletions or insertions (the latter being reported mainly in the distal 3' end of exon 11) may reduce the affinity of KIT for imatinib and moderate the efficacy of the drug." Mutation/deletion of codon 579 was the most significant factor in a univariate analysis and had a hazard ratio of 3.37 ( $P > 0.0013$ ).

Genotyping also plays a prognostic role for Sutent response as well, how-

ever, our understanding of response to Sutent is limited to Gleevec-resistant GIST.

Gleevec-resistant patients with exon 9 mutations have the highest response rate to Sutent, those with wild-type GIST have an intermediate response rate and those with exon 11 mutations have a lower response rate.

Sutent has also been tested against the secondary mutations that seem to be the largest cause of secondary resistance. As reported by Dr. Michael Heinrich at 2006 ASCO, Sutent is active against secondary mutations in exons 13 and 14, but not in the exon 17 and exon 18 mutations that were tested.

The Heinrich 2005 ASCO presentation and the Debiec-Rychter/EORTC paper are the most compelling arguments to date for moving genotyping from a research procedure to a routine clinical procedure. The difference in response between low-dose and high-dose Gleevec for exon 9 patients is simply too large to ignore.

## Global GIST Network adds new GIST representatives



**Australia**  
**Katharine Kimball**  
katharine\_kimball@hotmail.com



**Bolivia\***  
**Vicky Ossio**  
vossiop@acelerate.com  
\*correction made from June 2006 newsletter



**Kenya**  
**Francis Kariuki**  
bridgestone@coopkenya.com



**Russia**  
**Tanya Soldak**  
tsoldak@citihope.org

Visit the Global GIST Network  
at [www.globalgist.org](http://www.globalgist.org)

## Three Survivors



From left to right: Catherine Roberts, Anita Scherzer, and Tania Stutman meet at Fox Chase Medical Center and celebrate being stable on Gleevec for over five years.

## New Jersey Life Raft Group



Back Row (from left to right): Jan Becker, Amy Spires, Charles Roberts, Catherine Roberts, Deborah Rinehart, Jennifer Bao, and Simon Bao. Front Row (from left to right): Mark Becker, John Napoli, and Claudia Seresko.

# The benefits of Health Savings Accounts

**By Richard Ware**  
Life Raft Member

**D**oes thinking about your next medical appointment cause you to involuntarily reach for the checkbook? Do you stop at the ATM machine before picking up your prescriptions? As cancer survivors, many of us are experiencing similar reactions. These are symptoms of 'Rising Health Care Costs.' No one is immune to this malady but there is a strategy that can help you deal with its ill-effects. A tax advantage strategy called the Health Savings Account can help you stretch the value of each health care dollar.

Health Savings Accounts (HSAs) were created to help rein in rising health care costs and allow consumers more control over how their medical dollars are spent. HSAs have three important features: 1) An account into which tax-free dollars are set aside to pay current or future medical expenses, 2) Account balances and earnings grow tax-free and 3) Disbursed funds remain tax-free when used to pay qualified medical expenses. Depending on your tax bracket, the 'Bill Paying Power' of each contribution dollar can become worth roughly \$1.15 to \$1.35 just by opening/funding an HSA.

The "Key" to stretching the value of each health care dollar is that contributions are tax-free, grow tax-free and remain tax-free when used for qualified medical expenditures.

Health Savings Accounts are designed to work in tandem with qualified High Deductible Health Policies (HDHPs). As the name suggests, HDHPs feature higher upfront deductibles in exchange for lower premiums. Premium savings of 20 to 80 percent are common and it is anticipated that these 'saved monies' will be used to open and fund HSAs. Most HDHPs emphasize well-being and preventative health care services and are either fully covered or subject to a small co-pay. For 2006, qualified HDHPs must have: 1) A minimum deductible of \$1,050 for Self and \$2,100 for Family and 2) A maximum out-of-pocket limit of \$5,250 for Self and \$10,500 for Family enrollment. For cancer survivors, maximum out-of-pocket limits provide protection against catastrophic loss.

Contributions to HSAs are tax deductible\*. For 2006, contributions are limited to the HDHP deductible amount up to a maximum of \$2,700 for Self and \$5,450 for Family. Both you and your employer can contribute to an HSA and individuals over 55 are permitted catch-up contributions of \$700. At year's end, HSA balances roll over and not a penny is

lost. Financial institutions can act as HSA trustees and offer checking or debit card services for fund disbursements. When Medicare eligible, HSAs are closed to contributions but balances continue to grow tax-free and can be used to pay for medical expenses. Non-healthcare disbursements must be reported as regular income.

In conclusion, HSAs make health care coverage more affordable and allow consumers control over how their medical dollars are spent. Contributions to an HSA are tax-free\* (even if you do not itemize deductions) and both you or your employer may contribute. Importantly, HSA balances roll over at year's end and earnings continue to grow tax-free until disbursed. Accounts are portable and move with you if you change employers or leave the work force. HSAs have maximum out-of-pocket limits which provide protection against catastrophic health care losses. This protection feature is crucial to us as individuals with chronic/serious health problems. An excellent web site for additional information on HSAs is [www.treas.gov](http://www.treas.gov).

*\*HSA contributions are free from federal income tax. Note that a few states may not permit tax-deductible contributions.*

## DUTCH LRG

From Page 11

and their partners, family and friends as 1) able to reach more patients in this way, and 2) able to bring GIST more to the attention of a wider audience such as medical specialists and nursing staff.

### ***National Contact Day for the Dutch Life Raft Group on September 30, 2006***

September 30 will be the 3rd National Contact Day for the ever growing Life Raft Group Nederland! The two previous Contact Days were well

received, particularly last year's day which saw an increase in attendees from 35 to 70. The day will consist of a mixture of speakers who are well known in the field of GIST, as well as a meeting of like-minded people be they patients, partners, family and/or friends, all within a friendly relaxed atmosphere.

The location is usually in the center of Holland so that no one has to travel too far. This year it will be in the town of Renswoude at the Restaurant De Hof.

The committee is proud to have two eminent speakers attend the meeting:

- Prof. Dr. Jaap Verweij, medical oncologist at the Erasmus Medical

Centre-Daniel den Hoed in Rotterdam, a well-known GIST expert well versed in the latest developments regarding GIST.

- Prof. Dr. Pancras Hogendoorn, pathologist at the Leiden University Medical Centre. He is an authority on soft tissue as well as bone tumors, and the pathologist with the most experience in diagnosing GIST in the Netherlands.

The social side will again form an important part of the day, including a lunch as well as a dinner.

For more information about this event and reports about the past days please visit the website of LRG Nederland on: <http://www.liferaftgroup.nl>

# THE LIFE RAFT GROUP

## Life Raft staff

Executive Director	<b>Norman Scherzer</b>	nscherzer@liferaftgroup.org
Executive Assistant	<b>Tricia McAleer</b>	tmcaleer@liferaftgroup.org
Administrative Assistant	<b>Erin Kristoff</b>	ekristoff@liferaftgroup.org
Program Coordinator	<b>Sara Rubinoff</b>	srubinoff@liferaftgroup.org
Research Coordinator	<b>Elizabeth Braun</b>	ebraun@liferaftgroup.org
Research Assistant	<b>Pamela Barckett</b>	pbarckett@liferaftgroup.org
Science Coordinator	<b>Jerry Call</b>	Jerry.Call@comcast.net

## Contact the Life Raft Group

40 Galesi Drive  
Wayne, NJ 07470  
Phone: 973-837-9092  
Fax: 973-837-9095  
Internet: [www.liferaftgroup.org](http://www.liferaftgroup.org)  
E-mail: [liferaft@liferaftgroup.org](mailto:liferaft@liferaftgroup.org)

## Life Raft volunteers

General Counsel	<b>Thomas Overley</b>	guitarman335@msn.com
Accountant	<b>Erin Robb</b>	erin@mackeyctas.com
Database Consultant	<b>Steven Rigg</b>	StevenRigg@aol.com
List Manager	<b>Mia Byrne</b>	mebmcb@wowway.com
Newsletter Editor	<b>Sara Rubinoff</b>	srubinoff@liferaftgroup.org
Newsletter Editor Emeritus	<b>Richard Palmer</b>	richardpalmer@hawaii.rr.com
Web Designer	<b>Tami Margolis</b>	tami@comcast.net
Fund-raising co-chairs	<b>John Poss</b>	John@PossHaus.com
	<b>&amp; Gerald Knapp</b>	gsknapp@winfirst.com
Science Team	<b>David Josephy</b>	djosephy@uoguelph.ca
	<b>Michael Josephy</b>	mjosephy@gmail.com
	<b>Richard Singleton</b>	dick@garlic.com
	<b>Antonio Ramos</b>	ramos.antonio@inbox.com

## Life Raft regional chapters

Arizona	<b>Linda Martinez</b>	linda.martinez1@cox.net
Illinois	<b>Richard Kinzig</b>	rjkinz@aol.com
Colorado	<b>Jerry Call</b>	Jerry.Call@comcast.net
California	<b>Floyd Pothoven</b>	floyd@keralum.com
Massachusetts	<b>Janice Leary</b>	jleary@orr.mec.edu
Michigan	<b>Ellen Rosenthal</b>	ebrosenthal@comcast.net
New Jersey	<b>Amy Spires</b>	amy_spires@ml.com
New York	<b>Dan Cunningham</b>	Daniel.Cunningham2@pseg.com
Ohio	<b>Kaye Thompson</b>	tnt.1@sbcglobal.net
Texas	<b>Kerry Hammett</b>	yahoo@gvtc.com
	<b>&amp; John Poss</b>	John@PossHaus.com
Washington	<b>Deanne Snodgrass</b>	g-d-snodgrass@comcast.NET

## Board of Directors

### Executive Committee

<b>Stan Bunn</b> , President	SBunn@BSTGlobal.com
<b>Jerry Cudzil</b> , Secretary-Treasurer	Jerry.Cudzil@DACFunds.com
<b>John Poss</b> , Fund-raising	John@PossHaus.com

### Directors

<b>Robert Book</b>	RMBook2@aol.com
<b>Mia Byrne</b>	mebmcb@wowway.com
<b>Chris Carley</b>	ccarley@fordhamco.com
<b>Jim Hughes</b>	tjhughes43@comcast.net
<b>Gerry Knapp</b>	gsknapp@winfirst.com
<b>Dr. Arnold Kwart</b>	amkbmp@aol.com
<b>Rodrigo Salas</b>	rsalas@maprex.com.mx
<b>Silvia Steinhilber</b>	nswplas@mb.sympatico.ca

## Life Raft country liaisons

Australia	<b>Katharine Kimball</b>	katharine_kimball@hotmail.com	Kenya	<b>Francis Kariuki</b>	bridgestone@coopkenya.com
Bolivia	<b>Virginia Ossio</b>	vossio@acelerate.com	Malaysia	<b>Yong Choo Sian</b>	ycspj2005@yahoo.com
Brazil	<b>Vanessa Passos</b>	vanessa@endo.med.br	Mexico	<b>Rodrigo Salas</b>	rsalas@maprex.com.mx
Canada	<b>David Josephy</b>	djosephy@uoguelph.ca	Netherlands	<b>Ton de Keijser</b>	tdk@liferaftgroup.nl
China	<b>Ruijia Mu</b>	mu_ruijia@yahoo.com	Norway	<b>Jan Einar Moe</b>	jeinmoe@online.no
Columbia	<b>Jaime Peralta</b>	peraltas@etb.net.co	Poland	<b>Stan Kulisz</b>	listy@gist.pl
Costa Rica	<b>Michael Josephy</b>	mjosephy@gmail.com	Romania	<b>Simona Ene</b>	si_mi_ene@yahoo.com
France	<b>Estelle LeCointe</b>	gist.estelle@laposte.net	Russia	<b>Tanya Soldak</b>	tsoldak@cithope.org
Iran	<b>Negar Amirfarhad</b>	negaraf@sympatico.ca	Singapore	<b>Yong Choo Sian</b>	ycspj2005@yahoo.com
Ireland	<b>Carol Jones</b>	roycal-re-gist@hotmail.com	Switzerland	<b>Ulrich Schnorf</b>	ulrich.schnorf@bluewin.ch
Israel	<b>Ben Shtang</b>	ehuds@merkavim.co.il	Turkey	<b>Haver Tanbay</b>	tanbay@tanbay.net
Italy	<b>Anna Costato</b>	anna.costato@virgilio.it	U.K.	<b>David Cook</b>	D.Cook@sheffield.ac.uk