Battling gastrointestinal stromal tumor

# Life Raft Group

December 2005 | In Memory of Cordelia Salas, Meng Yen Yee, Eric Irons and Matthew Duran | Vol. 6, No. 9

Life Raft members who have been on Gleevec for five years or longer include, from left, Tania Stutman, Anita Scherzer, Andrea Fuller and Chris Carley.

# GIST and Gleevec: 5 years of progress

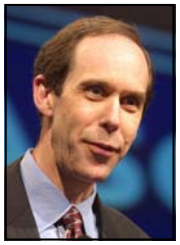
## GIST has been around since 1983, but therapy didn't arrive till 1999

**By Jerry Call**

While the term "GIST" was first used in 1983, the interesting parts of the GIST story begin in 1998. That was the year that a Japanese pathologist, Dr. Seiichi Hirota, found that GISTs often contain mutations in a gene called "c-kit". The c-kit gene contains a "blueprint" for assembling a protein known as "KIT." This protein is a receptor which transmits survival and proliferation signals to cells. Hirota also found that in most GISTs, the KIT protein was "constitutively activated", meaning it was always "stuck" in the on position, continuously signaling GIST tumors to survive and grow.

The second major part of the GIST story starts in the early 1990s, but does not start to become clear until 2000. Novartis scientists including Nicholas Lydon, Alex Matter, Elizabeth Buchdunger, Juerg Zimmermann and others had developed a new kind of drug called a "tyrosine kinase inhibitor." They had developed this drug to inhibit a receptor known as PDGFR. This drug was to prove to be amazingly successful.

Meanwhile, Dr. Brian Druker of Oregon Health Science University (OHSU) had been doing research on a type of leukemia known as chronic myelogenous leukemia (CML). He knew that CML seemed to be caused by a defective protein called bcr/abl. Druker approached Lydon and



**DRUKER**

See GIST REVIEW, Page 3

# Brian Rubin: snowboarder to dedicated pathologist

**By Elizabeth Braun**

Dr. Brian Rubin originally started school as a percussion major. He dreamed of becoming a drummer. His innate curiosity, love for science and fascination with how things work drew him away from music to cell biology. He graduated in 1983 from the University of California, Berkley with a degree in cell biology.

Rubin dedicated the next three years to the Peace Corps in the WHO malaria control program in Thailand. He returned to the United States in 1986 to work with Amgen as a technician. In 1987 he moved on to the Cornell University Medical College to earn his M.D. and PhD, in molecular biology,

See RUBIN, Page 2

Rubin at Whistler, British Columbia.

# Prescription health coverage: A tale of different doughnuts

*Editor's note: This fictionalized incident happens in the future. While a product of imagination, the circumstances surrounding the tale are sadly true. It is offered as food for thought.*

**By Norman Scherzer**

Fast forward to May 3, 2006. Margaret Whitman is visiting her local pharmacy in Washington, D.C. Alongside her is U.S. Sen. Sam Montgomery. Both have prescriptions that cost an average of $562.50 a month. Although slightly higher than the average American, these costs are considerably less than the average that cancer patients are facing for the newest generation of oral cancer drugs — a cost that can easily exceed $3,000 per month.

The drug store they are in is about a mile from where Margaret lives and two miles from where the senator works. It is a friendly place and Fred Sample, the pharmacist, has worked there for many years.

"Good morning, Senator Montgomery. How are you today sir?"

"Just fine, Fred, just fine. How is your daughter doing at that new school?

"Great, Senator. Nice of you to remember."

The pharmacist greets his other customer. "And good morning, Ms. Whitman. I didn't see you standing there. I hope you are doing well today."

"Why yes, thank you, Fred. I am quite well."

Ms. Whitman knows her legislator from previous encounters. "Good morning, Senator," Ms. Whitman says, turning to the tall, well-dressed man standing by her side.

"Why good morning, Ms. Whitman. It is nice to meet you on such a fine day."

"I have both your prescriptions ready, folks," Fred announced.

See MEDICARE, Page 6

## RUBIN

From Page 1

graduating in 1995.

His residency and fellowship at Brigham and Women's Hospital in Boston, Mass., introduced Rubin to both Jonathan Fletcher and Chris Fletcher. Rubin did focused fellowships in soft tissue pathology and a post-doc on genomics of sarcomas including GIST. Brian chose the field of pathology because it provided him with best opportunities to work on cancer research. He has a true passion for understanding how cancers work and how to destroy them. Even as an undergrad, he researched chemotherapy resistance. He has now directed this passion to the field of sarcomas, including GIST. As Rubin states, "Sarcomas are my life."

For the last five and a half years, Rubin has been the director of bone and soft tissue pathology and an assistant professor at the University of Washington. Currently, Rubin's lab is focused on genomics and proteomics of sarcomas, targeted therapies of sarcomas and developing mouse models of sarcomas.

Although Rubin has several other passions outside of work, he rarely has the time to engage in them. He loves to relax and have a good time with his friends. Unfortunately, his time with his friends often includes laundry and his homemade wine because he spends so much time traveling for work. Wine making is another passion of Rubin's. Every year he makes several barrels with a couple of his friends.

When Rubin has the time to sneak off to Whistler, B.C., he enjoys snowboarding. During the warmer months, he often relaxes with a game of golf. Currently, he is reading a book on golf, in preparation for the new season. As an avid reader, he enjoys a true variety of books including science fiction, current popular and travel books.

Rubin is an integral part of the Life Raft Group's research team. He is the priority project leader for the development of murine models and a vital part of many of the projects. His skills and passion are proving invaluable to our research model.

# GIST REVIEW

From Page 1

asked if he had any inhibitors that he could test against the bcr/abl protein. Lydon responded by supplying several inhibitors including one called STI571. This drug proved to work extremely well against the bcr/abl protein. Several years later, clinical trials for CML started. Of course, the drug proved to be a major step forward for CML, but the STI571 story was not over yet.

The idea that STI571 might be used to inhibit KIT in GISTs was substantiated in 1999 in essentially simultaneous experiments at OHSU (Dr. Michael Heinrich) and the Brigham & Women's Hospital in Boston (Dr. Jonathan Fletcher). Heinrich showed that STI571 could block the activity of mutant forms of KIT in the test tube, while Fletcher found that STI571 shut down the growth of GIST cells grown in a petri dish.

**FLETCHER**

In March 2000, STI571 was tried in a single GIST patient and seemed to halt progression of his/her disease. Phase I and phase II GIST trials were started in July of 2000.

The phase II GIST/Gleevec trial proved to be so successful that it was quickly expanded to include a total of 147 patients at three trial sites. Doctors and nurses were clearly excited about the results they were seeing in early patients, and omitted their typical cautious statements given during clinical trials.

Word quickly spread via the internet and among the sarcoma community that there was a new drug in trials for GIST and that, contrary to previous therapies, it seemed to be working very well. Patients with abdominal leiomyosarcoma were urged to have their pathology slides tested for c-kit, as a positive c-kit test in these patients probably meant they actually had GIST instead of leiomyosarcoma. This knowledge did not spread to the general oncology world until Dr. Charles Blanke presented early results of the phase II trial at a plenary session of the American Society of Clinical Oncology (ASCO) meeting in May of 2001. This marked the beginning of a period of time when many GIST patients were often better informed about treatment options than their local oncologists.

Drs. Chris Corless, left, and Michael Heinrich show visitors around their labs at Oregon Health & Science University in Portland.

Within a few months of starting the phase II trials for GIST, sarcoma specialists and GIST patients both knew that something special was happening. In the United States and Canada, phase III trials were quickly organized by Dr. George Demetri and started in the record time of five weeks! A European phase III trial was also quickly organized and began accruing patients by February of 2001.

With no effective therapy prior to STI571, there was a large backlog of metastatic GIST patients in need of effective therapy. Since STI571 was not yet approved, the only way to get it was in the phase III trials. This introduced the GIST patient community to the world of clinical trials in an unprecedented way. Like most cancer patients, few GIST patients had ever participated in a clinical trial before. Now they were dependent on clinical trials for their survival. The extremely high participation rate for GIST patients in clinical trials continues to this day with several thousand patients having participated in one or more clinical trials.

In May 2001, STI571 was approved in the United States for CML patients

See GIST REVIEW, Page 5

# The youngest Life Rafter shares her advice about coping with cancer

*Editor's note: This article is a part of a series on the youth of the Life Raft Group. It was written by Life Raft staffer Erin Kristoff, with help from Josalin Dunn and her mother, Jennifer.*

Josalin Dunn is not your average 8-year-old girl. It's not because she comes from a family of seven children. It is not because she has cancer. It is because she has remained bright-eyed and optimistic — despite the twists and turns she has had to endure during her young life in Fort Meyers, Fla.

One of her favorite phrases among friends and family is, "If you're having a really bad day and you found out you have cancer, dance anyway!"

In January 2005 at age 7, Josalin was diagnosed with Ewings Sarcoma. She had seven rounds of chemotherapy before being taken to Memorial Sloan-Kettering Cancer Center in New York to have her tumor and a third of her stomach removed.

After surgery, Josalin and her family were told that she had been misdiagnosed and that her cancer was actually gastrointestinal stromal tumor (GIST).

When Josalin found out that she had cancer she had mixed feelings, "I felt confused and a little scared because they told me I had to go to the hospital a lot." She goes for her scans every three months and like many Life Rafters, doesn't like it a bit, "I have to go up to St. Petersburg and drink some nasty stuff, [it tastes like] a really disgusting milkshake."

But life is not all scans and hospital visits for Josalin. Not only has she recently entered the third grade, which she admits is a little bit harder than second grade, but she also has many extracurricular activities to keep her happy and busy. "I just finished my soccer season and I'm starting softball and basketball. I also do modern and hip hop [dancing]. I have a little Christmas recital. The outfits are really cute, I'm a little nervous I might do something wrong, but I'm ready to go."

Mom Jennifer is not worried about her daughter's performance. "When she's behind the camera she really cuts loose."

You might not expect this behavior from a middle child. Out of the seven children in the Dunn clan, Josalin is right in the middle. The middle child often clamors for attention that goes to the oldest and youngest siblings, but not Josalin. "Being the middle is special, because lots of people have an even family and they are at the end or at the beginning, I like being half old and half young."


When Dunn is having bad days, she says to herself "calm down, it'll be over pretty soon."

Just as Josalin's days were not always sad, they were also not always this happy. When she was misdiagnosed with Ewings sarcoma, she was subjected to unnecessary chemotherapy. When they finally realized that her doctors had been wrong, she had already undergone seven rounds, which made her hair fall out and caused her to be ill. Her parents experienced the whole range of emotions.

"Initially we were thrilled that it was different and the chemo was over," says her mom. "Then we were like, wait, she never needed it in the first place? She had to suffer all that and, in terms of long term effects, we have issues we may have to deal with? We thought: Is there somebody we should be suing, I know it's a sue-happy society, but when an injustice is done to your child, you are hurt."

After speaking to the doctors, the Dunns reevaluated their position, "They weren't looking for GIST, so when it matched up with Ewings, they had no reason to run the other tests. What's gotten me and [Troy] through all of this is faith — maybe we were supposed to experience this for a reason. Josalin's future looks brighter now and the end result could have been much worse. Everybody did the best they could with the knowledge they had. We just found a way to deal with it."

See DUNN, Page 10

# Cordelia Salas, devoted wife and mother

**By Rodrigo Salas**

Cordelia, the 10th of 11 children, was born in 1964 in Monterrey, Mexico. Both Cordelia's family and my family were always very close. We began dating when she was 13 and I was 16. She was my only girlfriend and I her only boyfriend. We got married in 1984, and she blessed me with five beautiful children: Rodrigo, 20, José Miguel, 17, Cordelia, 14, Paulina, 12, and Emilio, 11.

Cordelia was diagnosed with leiomyosarcoma in January 1999 and had an operation to take out a 4-inch tumor in the small bowel. In June 2000, the cancer had metastasized to her liver and we traveled to Houston, Texas, for her second surgery. The surgeon took out four tumors, and found many small spots of cancer throughout her abdomen and pelvis.

Anita Scherzer with Cordelia Salas.

It was tragic to hear the words of the oncologist: "It's unfortunate your wife has this kind of cancer; there is no cure available and it looks as if she has six months to live."

I just couldn't accept that Cordelia was going to die at age 36 and with five kids then ages 6 to 15. We went to M.D. Anderson in Houston for a second opinion just to hear the same prognosis — except for a small comment by the oncologist about a new clinical trial of an experimental drug that might help.

I asked him for information about the trial, but he just said it was impossible to get in because there were no spots available, they were all taken for many months ahead, and that it was impossible that someone from another country could get in. I insisted and he gave me the magic word: "STI 571".

We went back to Mexico and I started getting contacts in the pharmaceutical industry in Mexico. My family has been in the drug store business for generations. I found out the new drug was manufactured by Novartis and got in contact with the medical director and later with the CEO of No-

See SALAS, Page 9

## GIST REVIEW

From Page 3

and, in February 2002, for GIST patients with inoperable or metastatic disease. Approval in other countries soon followed. It received a few new names, Gleevec in the U.S. and Glivec internationally. GIST had gone from a cancer that was notorious for its resistance to chemotherapy, to a cancer where taking a few pills every day provided substantial benefit to about 85 percent of patients. These responses were longer lasting than most responses to standard types of cancer therapy.

During his 2001 ASCO presentation, Blanke presented information about the response rate of GIST tumors to Gleevec. He noted that GIST tumors having mutations in different parts of the gene (called exons) responded differently to Gleevec, with KIT exon 11 mutations responding the best, KIT exon 9 mutations having an intermediate response and GISTs with no KIT mutations (wild-type for KIT) responding the worst. The identification of exon mutations, called genotyping, was developed to a high degree of accuracy in the OHSU labs of Heinrich and Dr. Christopher Corless. This process moved from the lab to the clinic in early 2003.

By early 2003, Heinrich and Corless, along with Fletcher, had put together another piece of the GIST puzzle. They had found that some of the tumors that did not have c-kit mutations did have mutations in a closely related gene, PDGFRA. Almost simultaneously, this observation was confirmed by Hirota, who first discovered KIT mutations in GIST.

While Gleevec inhibits some of these mutations, the most common PDGFRA mutation, D842V, is resistant to Gleevec. The current estimates are that from 5 percent to 7 percent of GISTs have PDGFRA mutations. There are some data to suggest that these tumors are less aggressive than other GISTs, but this remains controversial.

Unfortunately, as with most types of chemotherapy, resistance to Gleevec eventually becomes a problem for most GIST patients. By two years after starting Gleevec, only about half of the patients are still responding to it.

Fletcher provided the first reports (that we are aware of) of why GIST tumors might become resistant to Gleevec at the 2003 ASCO meeting. These mechanisms of resistance were:

1. The acquisition of a new KIT or PDGFRA point mutation, superim-

See GIST REVIEW, Page 7

# MEDICARE

From Page 2

"Senator, your prescription comes to $600 and your co-pay today will be $15. Will that be cash or charge?"

"Cash, and I will also take that box of chocolates that my wife likes so much."

"Ms. Whitman, your prescription also comes to $600 … but I'm afraid that your co-pay today will be the entire amount of $600," he says haltingly. "Will that be cash or charge?"

"I don't understand," Ms. Whitman asked, her right hand beginning to tremble. "I thought I had prescription drug coverage."

"Perhaps the Senator could explain," Fred volunteered.

On the spot, the lawmaker has no choice but to respond.

"Well, it gets a tad complicated, but I am afraid that you may have reached what folks call a 'doughnut hole' in your coverage."

"What does that mean?" Ms. Whitman replied, her petite body beginning to shake.

"Well, it means that when your annual prescription costs exceed $2,250, you have to pay the next $2,850 out of your own pocket."

"I just don't understand," Ms. Whitman responded.

"Well, let me try to explain," the Senator said.

"Medicare prescription drug coverage went into effect this year. Like other insurance, if you join, you will pay a monthly premium, which varies by plan, and a yearly deductible which will be no more than $250 in 2006.

"After you pay the $250 deductible, Medicare will pay 75 percent of all drug costs, up to $2,250. Then there is a gap in coverage — some people call it the 'doughnut hole.' What this means is that when your total drug costs reach $2,250, you will need to pay the next $2,850 yourself until you reach $3,600. After $3,600, Medicare will pay 95 percent of your drug costs.

"Because private companies are setting up the plans for Medicare, each plan will be a bit different. The monthly fee is estimated to average around $32."

"I see," Ms. Whitman nodded. "I don't understand much of what you just said but I do understand about doughnuts. Tell me Senator, just what is the doughnut hole in your prescription drug plan, the one we taxpayers pay for?"

The Senator looks uncomfortable. "Umm, we don't have a doughnut hole."

"So that means I get to eat the hole in the center of the doughnut while you and the other Senators who passed this bill get to eat the actual doughnut."

"Kind of," the Senator replied.

"I understand that," Ms. Whitman replied. "I will just have to pass on my prescription this month, Fred." Turning to the Senator, "Hope your wife enjoys her candy, Senator."

---

Confused? We present a summary table below.

If you have limited income and resources, and you qualify for extra help, you may be able to get assistance from a number of sources, including the federal and state government. For additional information see the Web site at www.medicare.gov.

If you are a GIST patient on Gleevec, and you qualify for extra help, you may be able to get assistance from Novartis. For additional information see the Web site at www.gleevec.com or call 1-877-Gleevec (453-3832).

Regardless, if you have modest income or assets, you may have to learn to live with eating the hole in the center of the doughnut while your legislators get to eat the actual donut.

We have asked Novartis to investigate whether there may be a cap on the amount of Gleevec covered by the new Medicare formulary. Right now the Medicare Web site seems to cap the dosage covered at 400 mg.

**Medicare Prescription Drug Coverage**

| Drug Costs | You Pay | Cumulative Total Out of Your Pocket | Medicare Pays |
|---|---|---|---|
| $0-$250 | $250 (100%) | $250 | $0 |
| $251-$2,250 | $500 (25%) | $750 | $1500 (75%) |
| $2,251-$5,100 | $2,850 (100%)—the donut hole | $3,600 | $0 |
| Costs above $5,100 | No limit (5%) | $3,600 + 5% of costs above $5,100 | 95% |
| In addition, you pay an annual premium of about $400, depending upon the plan you choose. | | | |

# GIST REVIEW

From Page 5

posed on the baseline mutation in that gene.

2. Resistance by overexpression of the target protein (KIT).

3. Activation of an alternate receptor tyrosine kinase protein.

4. Functional resistance by KIT or PDGFRA activation, in the absence of a secondary genomic mutation, and with baseline KIT or PDGFRA mutations being outside the juxtamembrane hotspot regions.

There is a great deal of ongoing research to try to understand and overcome these mechanisms of resistance. Similar mechanisms of resistance have been reported in CML patients and in non small-cell lung cancer (NSCLC) patients taking a drug, Iressa, which is similar to Gleevec. This is one example of how GIST and CML are models for molecularly targeted therapy. Primary mutations were found in the target gene (EGFR) of Iressa sensitive tumors in NSCLC patients and secondary mutations caused resistance to Iressa—both were lessons learned from GIST and Gleevec.

By 2002, phase I trials had started for a new drug that would eventually prove to be effective for about 60 percent of GIST patients that became resistant to Gleevec. This new drug was called SU11248 and was developed by Sugen, one of the early leaders in the signal transduction field. To many patients this drug became known simply as "Sugen." Sugen was purchased by Pharmacia which was then purchased by Pfizer. It was Pfizer that brought the drug to clinical trial. SU11248 is now known as "Sutent."

In addition to being a powerful KIT and PDGFR inhibitor, Sutent also inhibits the VEGF receptors. These receptors are important for the growth of new blood vessels (angiogenesis) which are required for tumors to grow.

Sutent also appears to interact differently with the area where tyrosine kinase inhibitors like Gleevec and Sutent bind to the target protein. Mutations in different parts of the c-kit gene produce slightly different conformations of the KIT protein. A small difference in shape can make the difference between a drug being able to bind to the protein and not being able to bind to the protein. Sutent appears to be able to inhibit some types of mutations that Gleevec cannot inhibit.

The activity profile of Sutent appears to be somewhat different than Gleevec. Gleevec-resistant patients that go on to take Sutent and have KIT exon 9 mutations have the best chance of responding (in the Gleevec-resistant setting, most responses are stabilization of disease), while patients with exon 11 mutations have a significantly lower chance of responding. Patients that are wild-type for KIT and PDGFRA have an intermediate response rate.

After showing clear activity in Gleevec-resistant patients in the phase I trial, the Sutent trials expanded to include phase II and phase III trials. The phase III trials were controversial because of the use of a placebo.

By early 2005, the data monitoring board for the phase III Sutent trial had concluded that the drug had met its efficacy endpoints and that the trial could stop seven months early. In August of 2005, Pfizer submitted Sutent for governmental approval in the United States.

Sutent was not the only drug to be tested in resistant GIST. Early "targeted therapies" such as Herceptin for breast cancer proved to have moderate success. But it was the astonishing success of Gleevec in CML and GIST that really moved the field of molecularly targeted therapies into high gear. Buoyed by success, a new wave of enthusiasm swept through the world of oncology. This enthusiasm extended to the drug manufacturers who were eager to try their drugs using this new way of fighting cancer.

GIST represented a number of opportunities for testing new drugs. Most importantly perhaps, the primary target, KIT, was extremely well validated. Stop KIT signaling and you have an excellent chance of controlling GIST. This was true with new patients and most patients that were resistant to Gleevec.

Pfizer and Amgen were the first two drug companies to try their KIT inhibitors in Gleevec-resistant GISTs. The Amgen drug, AMG706, is in many ways similar to Sutent. They both inhibit KIT, PDGFR, and the VEGF receptors. One difference is that Sutent is given in a four week on, two week off schedule, while AMG706 is given continuously. A phase II trial is underway to see if patients can tolerate a lower dose of Sutent given continuously.

Amgen concentrated their initial phase II trial in Gleevec-resistant GIST. While we have anecdotal reports of some efficacy, we understand that formal results will not be presented until the 2006 ASCO meeting. We also understand that Amgen is planning a phase III trial to compare AMG706 to Gleevec as front-line therapy for GIST. This is expected to be a European trial.

One of the important innovations that Amgen used was to make the drug more widely available by having more trial sites. It is likely that this contributed to the rapid accrual of patients in their trial.

Combining Gleevec with other drugs represented another method to attack GIST tumors. Novartis, the maker of Gleevec, took the lead in this area. Their first two combinations included Gleevec + PKC412 and Gleevec + RAD001. PKC412 and RAD001 are also made by Novartis.

See GIST REVIEW, Page 8

# GIST REVIEW

From Page 7

PKC412 inhibits a number of targets including KIT, PDGFR, VEGF, FLT3, and several forms of protein kinase C (PKC). PKC412 has interesting in-vitro activity in a number of Gleevec-resistant mutations. Drug interactions between PKC412 and Gleevec have slowed this trial.

RAD001 is an mTOR inhibitor. Early reports from this trial indicate moderate success in Gleevec-resistant GIST. Some drug interaction issues have been resolved and it remains to be seen which type(s) of resistant patients this combination could help.

Another trial that combines Gleevec and Perifosine has recently started at M.D. Anderson Cancer Center in Houston, Texas. Perifosine inhibits AKT (and other targets), an important protein downstream from KIT. M.D. Anderson has been planning another combination trial with Gleevec and Genasense (a Bcl-2 inhibitor) but this trial has just gotten off the ground.

One method of overcoming Gleevec resistance is to design a Gleevec-like drug with a different shape so that it fits better into the binding pocket of the target protein. Two new drugs used this strategy for CML patients. BMS-354825 (Bristol-Myers Squibb) and AMN107 (Novartis) both proved to be *very* effective in Gleevec-resistant CML patients with response rates approaching 90 percent. These drugs were able to overcome almost all of the known secondary mutations that account for the majority of Gleevec-resistance in CML. The exception was one specific mutation, T315I. Other drugs are being tested against this mutation. BMS-354825 and AMN107 not only were active against secondary mutations, they also were many times more potent than Gleevec at inhibiting the bcr/abl protein.

BMS-354825 and AMN107 both inhibit bcr/abl, the protein responsible for CML, but they also inhibit KIT and PDGFRA, the proteins responsible for GIST, although neither drug appears to be as potent at inhibiting KIT as they are at inhibiting bcr/abl. Both of these drugs are in early trials for GIST: BMS-354825 as a single agent and AMN107 in combination with Gleevec. With the AMN107 + Gleevec combination, it is hoped that the two drugs will have a broad spectrum of activity against secondary mutations.

The latest drug to enter clinical trials for GIST is BAY 43-9006 or Nexavar. This drug has some similarities to Sutent and AMG706, but it adds another downstream target, RAF. It is in phase II trials at the University of Chicago and several other sites. There are a few anecdotal reports of responses in Gleevec-resistant GIST from previous sarcoma and solid-tumor trials. This drug won U.S. approval for treatment of renal cell cancer on December 21.

One of the newest strategies to treat resistant GIST is to try to bypass the problem of drug fit into multiple different types of mutations; in other words, to block KIT signaling by inhibiting a different protein that KIT is dependent on. This protein is HSP90, a protein that is required to stabilize KIT. Blocking HSP90 causes the mutated KIT protein to degrade and be destroyed by the cell. A new phase I trial testing IPI-504 should start very soon at Dana-Farber Cancer Institute in Boston. IPI-504 is a HSP90 inhibitor made by Infinity Pharmaceuticals.

In the summer of 2005, armed with a generous $2 million dollar start-up grant from Novartis, the Life Raft Group began strategic planning into GIST resistance research. This planning began with a core group of the most respected GIST researchers. The core group created an initial outline of projects and identified personnel that would form a larger research group.

The group recommended that the project be divided into two phases. In the first phase the research would be directed at high-priority research projects. The second phase would incorporate a more traditional research approach and be directed at developmental research projects. The second phase has not been funded at this time.

With the help of the entire GIST resistance research group, eight priority research areas were identified for adult GIST, with pediatric GIST forming the last priority area. In these priority areas there was an expectation that the research would quickly translate to the clinic.

The priority areas identified (in no particular order) included:

1. Oncogenic signaling mechanisms as novel therapeutic targets
2. KIT/PDGFRA wild-type GISTs
3. Primary resistance
4. Stable disease
5. Secondary resistance
6. KIT degradation
7. Murine (mouse) models
8. Resource development
9. Pediatric GIST

Six developmental research groups were identified. These areas were felt to have the same ultimate importance as the “priority” groups, but clinical translation might take longer. They were:

1. Pharmacology
2. KIT/PDGFRA antagonists
3. Genetic progression mechanisms
4. ICC/stem-cell biology
5. KIT synthesis
6. Maximizing therapeutic response

This new GIST resistance research project has researchers and patients working more closely together than ever before. It also requires the participating researchers to work very closely together and share their findings with each other on an ongoing basis.

It will be up to the GIST patient community to find a way to continue to fund the priority areas (the current funding is for two years) as well as to begin funding the developmental research areas that are currently not funded.

# SALAS

From Page 5


Cordelia with her family at her daughter Cordelia's 14th birthday party on July 2, 2005.

vartis Mexico. They did not know what I was talking about, but, due to the business relationship with my family, they promised to do some research at Novartis headquarters in Basel, Switzerland.

At the same time I started to make contact with friends, with international banks and any kind of company that I thought would have some kind of relationship with Novartis in Switzerland. I sent Cordelia's clinical history all over the world.

As soon as I found out that the trial was going to be held in three different cities in the United States (Boston, Portland and Philadelphia), I received the first news from Novartis Mexico: "We have a spot ready for Cordelia — but it's in Helsinki." That was too far away, but if it was the only option available ….

I decided to call the oncologist at M.D. Anderson and asked him to choose one of the three centers in the United States. He told me that in Boston there was a very knowledgeable doctor in GIST, George Demetri. Now our efforts were towards getting Cordelia into Dana-Farber Cancer Institute. Calls to Bank of Boston, First Boston — there was someone in the board of directors of Dana-Farber. Great!

Two weeks later, we received a call from Dana-Farber giving us an appointment with Dr. Demetri. This had taken two months. We started the STI 571 (later named Gleevec) trial in September 2000.

Every time the drug stopped working, Cordelia went through surgeries (three all together) and tried every clinical trial imaginable: increased dosages of Gleevec, Sugen, BMS, Gleevec+RAD, and the AMN drug. Until after battling tumor infections all this past year which led to multiple trips to the hospital and transfusions, Cordelia was hospitalized in Boston for nine weeks, from August through October. Odds were she was not going to make it, but Cordelia continued to amaze every doctor with her strength and desire to live.

Nevertheless, her health was very diminished from this entire episode in which she did not have any cancer treatment. Her GIST advanced, she lost a lot of weight and was very weak.

In late November, during a check-up at Dana-Farber, she was hospitalized again with a powerful pneumonia. After an intense battle, Cordelia died Dec. 3. I, our five children, her four sisters and her mother were at her side.

What we learned from these years fighting GIST were the following:

1. **Never** ever give up.
2. Learn as much as you can about your cancer.
3. Always try to get second opinions and advice from someone with experience (LRG).
4. Question your doctors. They are not always right.
5. Take as much control of your treatments as possible. Don't leave everything to your doctors. Gather all the information and **you** take the decisions.

Cordelia was the bravest fighter, but I will always remember Cordelia not just for her beauty, but for her capacity to love. Her love for the kids and her family was her motivation.

She touched a lot of lives wherever she was. She was always admired. Always humble and caring. During her life she always participated in different charity activities; she was always involved in her son's schools — she was a very devoted mother and wife.

Her presence here will be missed. She is in a better place now, where she will never suffer again. Now we must learn to live with her in a different way until we meet again.

# Second national contact day for the Life Raft Group Nederlands

**By Anja Long**

On a misty autumn morning on Oct. 8, 2005, the Dutch LRG held their second national meeting in the town of Wageningen. The organizers were slightly apprehensive as to how it would all turn out, but when the number of attendees had doubled from last year, they knew it would be a success.

More than 70 patients and their partners, friends or family came, ranging in age from a young baby to people in their 70s and not only from Holland, but also from Belgium and Germany.

See DUTCH LRG, Page 11


Dr. van Coevorden, Dr. Gelderblom, J. Smeets, and M. van Hattum spoke on the question-and-answer panel at the Dutch meeting.

## DUNN

From Page 4

Josalin posing at the Holiday Dance Show this year.

Josalin was very glad to hear she had the "better cancer." The idea of any more surgery made her cry. When she was told that the chemo was unnecessary, her response was simple and poignant, "I went to all this trouble for nothing?"

Josalin does not take her "better cancer" for granted. She wants to keep herself and others informed about her disease, "I think I know a bunch, me and my teacher read [the Life Raft Group Pediatric GIST pamphlet] to the students. I think they understood part of it and there were a few questions, but they mostly got it. I want to learn as much as I can, so if anything comes up, I'm ready!"

Josalin's perseverance has helped her conquer the problems that came her way. She even has different techniques to tackle them. "[When I have bad days] I like to stick my face in my pillow and say, 'Calm down, it'll be over pretty soon.'"

Her mother reflects on her strength by recalling one of the many visits Josalin made to Memorial Sloan-Kettering, "She had surgery on a Monday, she was discharged on a Friday and was walking around Time Square on Saturday. She seemed to bear it all fairly well."

With all that Josalin endured, she has never been alone. Her support system is vast and generous. Not only is her family a part of this network but also several teachers, an elderly couple from her church and all of her friends, "I have quite a few friends, I think I might have five best friends: Danielle, Maddie, Lauren, Camri, Brady, and Sami K. I'm getting support from lots of people! When I wasn't feeling good, Sami K got me a present and came to the hospital. Everyday that I had to get a shot, my brother came to the hospital and held my hand so I could squeeze it."

Josalin's experiences have given her a fresh outlook on her future, "I hope that I'll have some wavy hair that's pretty long and I hope I won't have to get anymore scans and I hope that other people in my family don't get cancer."

More than 70 GIST patients and their partners, family and friends gathered for the second annual Life Raft Group Nederlands gathering held Oct. 8 in of Wageningen.

# DUTCH LRG

From Page 10

After coffee, Peter van der Meer addressed the gathering by introducing the speakers, but also by asking for a moment of silence to commemorate all those who died the previous 12 months from GIST.

Then Dr. Hans Gelderblom, medical oncologist with the University Hospital in Leiden, gave his presentation on how the treatment of GIST has developed over the past years. He used a very apt analogy of a boat: only a few years ago the boat was small and contained few survivors, but with the advent of Glivec the boat has grown much bigger and crowded. He highlighted in particular both Glivec and the c-KIT test as big steps forward, and talked about the results so far with Sutent and how combinations of treatments are used nowadays including RFA (radio frequency ablation).

The second speaker of the day was Dr. Frits van Coevorden, oncological surgeon with the Antoni van Leeuwenhoek Hospital/Netherlands Cancer Institute in Amsterdam. Since his presentation was the first after lunch he made it not only informative but also funny in parts so that everybody would stay awake. He talked about the use of surgical methods for either curative or palliative reasons and in particular highlighted the technique of RFA.

Both speakers made the point very firmly to the audience that treatment via a multidisciplinary team based in specialist centers is the best approach to treating patients with GIST.

After both presentations, a panel of both speakers plus J. Smeets (Pfizer) and M. van Hattum (Novartis) answered a wide range of questions from the audience.

The last speaker of the day was Hans van Pelt, social worker and committee member of the Dutch Society for Psychosocial Oncology, who did an interactive session with lots of discussion. He touched on the mental aspects of cancer, such as how you cope with it yourself as a patient but also how your direct circle of family, friends and coworkers deal with it.

In between the sessions there was a course time for everybody to meet each other (in a lot of cases this was for the first time) and socialize, which was much appreciated. Favorable comments were: this was my first time and I was impressed with the quality of the speakers; the atmosphere was great; it was good to finally be able to match up e-mails and faces; I am looking forward to next year's gathering; shouldn't we have next year's meeting on a boat?

The day was nicely rounded off with a lovely buffet dinner. And as the chairman for the day said: "There is light on the horizon for all of us, we just have to persevere."

# Clinical trial updates as of December 2005

**AMG 706**

A new phase II trial testing AMG 706 in Japanese patients with Gleevec-resistant GIST opened in February in Japan. Patients must be at least 20 years old to participate. Interested patients should contact the Research Center, Japan or the Amgen Call Center at 866-572-6436 or mit@amgen.com The expected total enrollment of this trial is 35 patients.

AMG 706 is a potent, oral, multi-kinase inhibitor with anti-angiogenic and anti-tumor activity achieved by selectively targeting all known as VEGF, PDGF, KIT and Ret receptors.

**Gleevec + Genasense**

A new phase II trial testing the combination of Gleevec plus Genasense in patients with Gleevec-resistant GIST recently opened.

The principal investigator for this trial is Dr. Jonathan Trent of M.D. Anderson Cancer Center in Houston, Texas. Patients 18 and over with an ECOG status of 0-2 are eligible for this study.

Genasense (Genta Inc.) is an antisense drug that inhibits bcl-2. Bcl-2 is a protein involved in cellular survival. It is hoped that Genasense may help Gleevec kill more tumor cells by making them more sensitive to Gleevec.

Trial locations include:

• Dana-Farber Cancer Institute, Boston, Mass.

• University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan

• Mayo Clinic Cancer Center, Rochester, Minnesota

• Memorial Sloan-Kettering Cancer Center, New York, New York

• M.D. Anderson Cancer Center, Houston, Texas

**FR901228**

This is a phase II trial for sarcoma patients, including GIST patients, with metastatic or unresectable disease. FR901228 (depsipeptide) belongs to a new class of chemotherapy drugs called histone deacetylase inhibitors (HDAC inhibitors). This is a class of drugs that works at a higher level within the cell-acting on the genome, which is like the master control room for all of the genes in a cell.

Patients must be at least 18 and have a Performance status of ECOG 0-2 or Karnofsky 60-100 percent. Projected accrual is 18 to 36 patients.

The principal investigator is Dr. Paul D. Savage, Comprehensive Cancer Center of Wake Forest University. Trial locations include:

• CCOP - Western Regional, Arizona, Phoenix, Arizona

• CCOP - Bay Area Tumor Institute, Oakland, California

• Regional Radiation Oncology Center, Rome, Georgia

• CCOP - Central Illinois, Decatur, Illinois

• Kentuckiana Cancer Institute, PLLC, Louisville, Kentucky

A number of sites in North Carolina include:

• Alamance Cancer Center, Burlington, N.C.

• Brody School of Medicine at East Carolina University, Greenville, N.C.

• CCOP - Southeast Cancer Control Consortium, Goldsboro, N.C.

• Comprehensive Cancer Center at Wake Forest University, Winston Salem, N.C.

• High Point Regional Hospital, High Point, N.C.

• Hugh Chatham Memorial Hospital, Elkin, N.C.

• Southeastern Medical Oncology Center, Goldsboro, N.C.

More sites:

• CCOP - Columbus, Columbus, OH

• CCOP - Greenville, Greenville, South Carolina

• CCOP - Upstate Carolina, Spartanburg, South Carolina

• Cancer Center of the Piedmont Inc., Danville, Virginia

• Danville Hematology and Oncology Inc., Danville, Virginia

**Doxorubicin + Flavopiridol**

This is a phase I trial to determine the maximum tolerated dose of the combination of doxorubicin (a traditional cytotoxic chemotherapy) with flavopiridol (a inhibitor of the cell cycle and a inhibitor of transcription). This trial is for sarcoma patients, including GIST patients, that are 18 years old or older. Patients must have a Performance status of ECOG 0-2 or Karnofsky 60-100%. Projected accrual is 3 to 36 patients.

The trial is being conducted at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, N.Y. U.S.A.

# The Life Raft Group

| | |
|---|---|
| Executive Director | **Norman Scherzer,** nscherzer@liferaftgroup.org |
| Executive Assistant | **Tricia McAleer,** tmcaleer@liferaftgroup.org |
| Administrative Assistant | **Erin Kristoff,** ekristoff@liferaftgroup.org |
| IT Director/Web Master | **James Roy,** jroy@liferaftgroup.org |
| Program Coordinator | **Sara Rubinoff**, srubinoff@liferaftgourp.org |
| Research Coordinator | **Elizabeth Braun**, ebraun@liferaftgroup.org |
| Research Assistant | **Pamela Barckett,** pbarckett@liferaftgroup.org |
| Science Coordinator | **Jerry Call,** Jerry.Call@attbi.com |

**Contact the Life Raft Group**
40 Galesi Drive
Wayne, NJ 07470
Phone: 973-837-9092
Fax: 973-837-9095
Internet: www.liferaftgroup.org
E-mail: liferaft@liferaftgroup.org

## Life Raft volunteers

| | | |
|---|---|---|
| Chief Financial Officer | **Allan Tobes** | atobes@comcast.net |
| General Counsel | **Thomas Overley** | guitarman335@msn.com |
| Accountant | **Allan Tobes** | atobes@comcast.net |
| List Manager | **Mia Byrne** | mebmcb@wowway.com |
| Newsletter Editor | **Richard Palmer** | richardpalmer@hawaii.rr.com |
| Web Designer | **Tami Margolis** | tami@comcast.net |
| Fund-raising co-chairs | **John Poss** | John@PossHaus.com |
| and | **Gerald Knapp** | gsknapp@winfirst.com |

## Life Raft country representatives

| | | |
|---|---|---|
| China | **Ruijia Mu** | mu_ruijia@yahoo.com |
| France | **Bertrand de La Comble** | bdelacomble@oreka.com |
| Iran | **Negar Amirfarhad** | negaraf@sympatico.ca |
| Italy | **Anna Costato** | anna.costato@virgilio.it |
| Mexico | **Rodrigo Salas** | rsalas@maprex.com.mx |
| Netherlands | **Ton de Keijser** | akeijser1@chello.nl |
| Poland | **Bartosz Szczesny** | bsz1974@yahoo.com |
| Switzerland | **Ulrich Schnorf** | ulrich.schnorf@bluewin.ch |
| United Kingdom | **David Cook** | D.Cook@sheffield.ac.uk |

## Life Raft area groups

| | | |
|---|---|---|
| Arizona | **Linda Martinez** | linda.martinez1@cox.net |
| Chicago | **Richard Kinzig** | rjkinz@aol.com |
| Colorado | **Jerry Call** | Jerry.Call@comcast.net |
| Detroit | **Allan Tobes** | atobes@comcast.net |
| Los Angeles | **Floyd Pothoven** | floyd@keralum.com |
| New York | **Dan Cunningham** | CunninghamDA@coned.com |
| Texas | **Kerry Hammett** | yaloo@gvtc.com |
| | & **John Poss** | John@PossHaus.com |

## Board of Directors

**Executive Committee**

| | |
|---|---|
| **Stan Bunn,** President | SBunn@BSTGlobal.com |
| **Allan Tobes,** Secretary-Treasurer | atobes@comcast.net |
| **John Poss,** Fund-raising | John@PossHaus.com |

**Directors**

| | |
|---|---|
| **Robert Book** | RMBook2@aol.com |
| **Mia Byrne** | mebmcb@wowway.com |
| **Chris Carley** | ccarley@fordhamco.com |
| **Jerry Cudzil** | Jerry.Cudzil@DACFunds.com |
| **Jim Hughes** | tjhughes43@comcast.net |
| **Gerry Knapp** | gsknapp@winfirst.com |
| **Dr. Arnold Kwart** | amkbmp@aol.com |
| **Rodrigo Salas** | rsalas@webtelmex.net.mx |
| **Silvia Steinhilber** | nswplas@mb.sympatico.ca |

### Who are we, what do we do?

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

### How to join

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

### Privacy

Privacy is of paramount concern, and we try to err on the side of privacy. We do not send information that might be considered private to anyone outside the group, including medical professionals. However, this newsletter serves as an outreach and is widely distributed. Hence, all articles are edited to maintain the anonymity of members unless they have granted publication of more information.

### How to help

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

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

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.