Life Raft study presented at CTOS annual meeting

# Starting vs. actual dose significant

A groundbreaking study of cancer patients done by the cancer patients and caregivers themselves was presented at the Nov. 11-13 meeting of the Connective Tissue Oncology Society's in Montreal, Canada.

The study undertaken by the Life Raft Group was presented Friday afternoon, Nov. 12, to over 300 sarcoma and GIST specialists from around the world. It affirmed preliminary results of a large European study on dose levels of Gleevec (imatinib) for GIST (gastrointestinal stromal tumor), and also tackled the thorny issue of clinical trial patients who begin a clinical trial at a certain dose, but then change that dose.

The results of clinical trials are usually based upon the starting, or "intent to treat" dosages – even though patients sometimes have their dosage reduced due to side effects or changed by the patients themselves without notifying the trial clinician. Researchers generally do not take into account these dosage changes when reporting their findings.

The Life Raft study, however, suggests that cancer patients, particularly

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## Fundraising charges on...

GIST patients and supporters walked through the park, ran the New York City Marathon and played Texas Hold'em to help research and support the vital work of the Life Raft Group.

### GIST Walk tops $90,000 for GIST research

More than 300 cancer patients, friends, family and supporters helped raise more than $90,000 to fight GIST at the 4th Annual Walk For A Cure held Oct. 10 in Congers, New York.

According to organizers Tania and Robert Stutman, the fund-raiser was the biggest walk to date and drew people from across the country. Participants came from California, Texas, Florida, S. Carolina, Oklahoma, Virginia, W. Virginia, Connecticut, Massachusetts, and New York, among others.

The walk was again held at Rockland Lake State Park in Congers. Greeting participants was Walk Frazier, one of the greatest players in the history of the National Basketball Association. Now an announcer and analyst for the New York Knickerbockers basketball team, Frazier is a member of the Basketball

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Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

November-December 2004 Vol. 5, No. 11

In memory of Myrtle Brickman, Ray Carbott, Thomas Fredgren and Martin Scharf

## Life Raft Pediatric GIST Meeting

Pictured at the first international pediatric GIST meeting clockwise from lower right are part of the group: Jaap Verweij (back to camera), Tricia McAleer, Cristina Antonescu, David Josephy, Karen Albritton George Demetri, Alberto Papo, Dick Singleton and Daniel Stepan

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# STUDY

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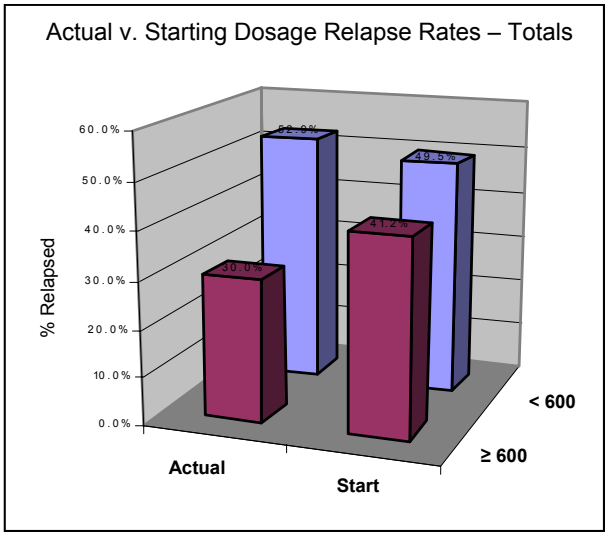
those on long term oral therapy, might be better served if dosage changes were considered as well. In the LRG study of 169 patients with metastatic GIST receiving Gleevec, there was a significant difference in the observation of resistance when the actual dose being taken was considered versus the "intent to treat," or starting dose.

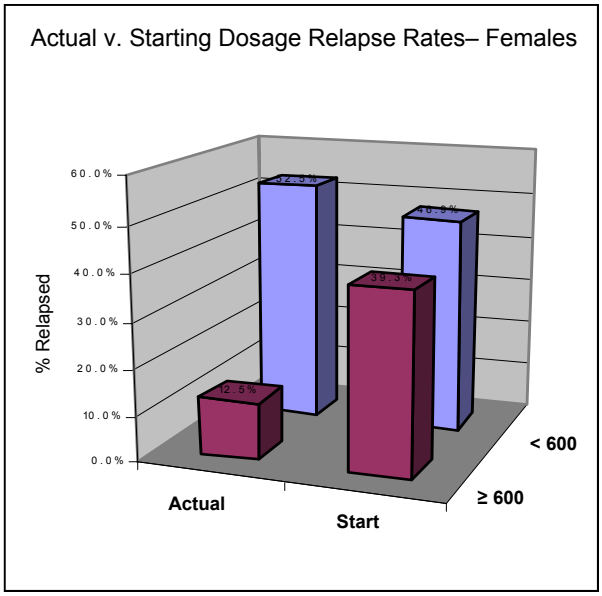



The patients studied all had metastatic GIST, had been on Gleevec one year or longer, and had experienced initial tumor shrinkage. The objective of the study was twofold: to see if there's a correlation in this group between dose and the cancer becoming resistant to Gleevec; and to evaluate the difference in methodology between using starting dosage ("intent to treat") vs. actual dosage.

Of the 169 patients, 91 reported continued stable disease following shrinkage. The other 78 had experienced tumor growth after their initial response. Forty percent of the 169 patients were initially prescribed 600 mg. or more of Gleevec daily, while 60 percent were prescribed less than 600 mg.

When considering starting dosage alone, the LRG study did find a correlation between dosage and relapse, but it was not statistically significant (p = 0.265). The relapse rate for patients taking 600 mg. or more was 41.2 percent, while it was 49.5 percent for those taking less than 600 mg. It is interesting that this 8.3 percent higher relapse rate is not far off the 6 percent higher relapse rate reported in the European/Italian/Australian (EORTC, ISG, AGITG) Phase III study of 946 GIST patients of patients taking 400 mg. or 800 mg. of Gleevec daily. The companion American/Canadian study of a somewhat smaller group of patients has failed to report any relationship between dosage and resistance thus far.

In looking at the starting dose vs. actual dose issue, the Life Raft study found that 38 percent of patients had a reported change of dosage, most because the clinician had changed the dosage but some because the patient had changed the dosage themselves without notifying the clinician. Most (30.2 percent) reduced their dosage but some (7.7 percent) had a dosage increase.




When the actual dose was considered, the difference in relapse rates between the higher and lower dosage groups was dramatic. Based upon actual dosage there was a significantly lower relapse rate for higher versus lower dose (p = .001)

Going by "intent to treat" dosage, the relapse rate was 49.5 percent for those on less than 600 mg., and 41.2 percent for those on 600 mg. or more. But when the actual dose was considered, the relapse rate was 52.9 percent for those on the lower dose, and just 30 percent for those on the greater dose. Put another way, the lower dose group had an 8% higher relapse rate based upon starting dose but a 23% higher relapse rate based upon actual dose. Further, although not statistically significant, likely due to small numbers, the actual dosage data does suggest a gender difference that needs to be watched in future studies.

When the study looked at relapse rates based upon actual dosage over time, relapse rates were relatively consistent in five six month time periods starting with month 13 (the first study month). Relapse rates overall and separately by gender were significantly lower for higher dose. What this means is that patients on lower doses who have not relapsed cannot take any comfort in that fact and face the same risk of resistance in each six month time period evaluated thus far.

<u>Conclusions:</u>

When looking at actual dosage, patients on 600 mg or more of Gleevec are significantly more likely to have lower relapse rates than do patients on less than 600 mg.

Actual dosage produces substantially different results than starting dosage.

It is important to note that the meth-

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# FUNDRAISING

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Hall of Fame and the NBA's 50th Anniversary All-Time Team.

Some noted GIST specialists joined in the walk, including Drs. Ronald DeMatteo from Memorial Sloan-Kettering and Margaret Von Mehren from Fox Chase Cancer Center. Also represented were pharmaceutical companies Novartis and Pfizer, who helped sponsor the walk.

"You all should be commended for your effort, determination, commitment, kindness and support," said Tania Stutman, a GIST patient since 1998. "The day was great not only because it was a sunny day, but because everyone's face had the most beautiful glow of happiness, and there was the greatest feeling of belonging to such a special family."

This year's walk was held in memory of Dean Gordanier, an attorney and GIST warrior who took part in the clinical trials of both Gleevec and SU11248. Gordanier gained the admiration and respect of fellow patients as he gave generously of his time and shared his experience, knowledge, wit and wisdom with GIST patients worldwide as he participated in GIST cancer support groups. His outlook was always positive and uplifting.

With the latest walk, the GIST Cancer Research Fund has raised more than $215,000. The money goes exclusively to GIST researchers, and has provided grants to Fox Chase Cancer Center in Philadelphia, Dana-Farber Cancer Institute in Boston, Oregon Health & Sciences University in Portland, and Memorial Sloan-Kettering Cancer Center in New York City. Dr. Ephraim Casper of Memorial Sloan-Kettering serves as medical advisor to the GIST Cancer Research Fund.

## Hundreds 'Walk for a Cure'

Nan Mustard, center, and husband, Tim, traveled all the way from the San Francisco Bay Area to participate in the 4th Annual Walk for a Cure held Oct. 10 at Rockland State Park in New York. More than 300 people turned out for the event.

## Team LRG Completes New York City Marathon

On November 7, more than 30,000 athletes ran in the New York Marathon, covering five bridges, five boroughs, and 26.2 miles. Amongst the athletes were Team Life Raft Group's own Michael Byrne and family friend Jennifer Corrao. The Byrne and Corrao team raised over $11,000 for the LRG with a campaign that reached out to family and friends to sponsor them for the run.


Team Life Raft: Jennifer Corrao and Michael Byrne at the finish line of the 2004 ING New York City Marathon

A sea of runners flooded the streets and after they were finished they walked back to their homes and hotel rooms wrapped in a piece of foil and a great sense of accomplishment. Michael and Jennifer made it to the finish line in a little over four hours.

The LRG held a special dinner in Manhattan to honor Michael & Jennifer. Michael & Jennifer arrived exhausted, but they were pumped full of adrenaline from their physical and mental accomplishment.

Norman Scherzer, LRG Executive Director, presented Michael and Jennifer with the LRG Volunteer Award for an astounding effort on their parts.

Several other Life Rafters joined Team Life Raft for their congratulatory celebration.

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# FUNDRAISING

From Page 3

In attendance at the dinner were Michael, Mia and Matthew Byrne, Jennifer & her husband, Phil Corrao, Katie Byrne, LRG members, Dan Cunningham, Rita Raj and Marilen Danguilan, and David and Ruth Portnoy. The LRG staff members present were Norman and Anita Scherzer, Tricia McAleer, Pam Barckett and Matt Mattioli.

Special thanks to the Byrne and Corrao families and all those who supported them!


Michael Byrne and Jennifer Corrao receive the LRG volunteer award

The line to enter was literally out the door. Jerry Cudzil and his wife, Lorie, made an opening announcement introducing the Life Raft Group, explaining their connection and thanking everyone for their help and support.

It was time to play poker! They were playing Texas Hold'em. There would only be one winner so the serious players had their heads in the game immediately. By the end, only one man was left standing.

The 1st place winner was Ken Kiarash, followed by Steve Duncker in 2nd place and Michael Levine in 3rd place.

Many generous players and invitees made contributions to the LRG in addition to their initial $500 entrance fee. Jerry and Lorie conducted a 50/50 raffle as well during the game. The winner of the 50/50 donated $500 of his winnings back to the LRG.

Fun was had by all players as well as spectators. The participants were extremely generous. Even those who lost left with a good feeling

It was a night not to be forgotten.

Again, thank you to the Cudzil and Roth families and all those who attended for all your support!!

## Life Raft Group Second Annual Fundraising Drive Off To Good Start

The second annual LRG Thanksgiving campaign is up and running. To date we have raised over $30,000!

LRG members have pitched in to ask their family and friends to lend a hand to the Life Raft Group.

We would like to thank everyone who has contributed as well as those who continue to put in the footwork needed to keep the Life Raft afloat.

Last year, Life Rafters raised over $100,000 dollars We are trying to surpass that goal this year.

Over 100 men and women sat down to play Texas Hold'em for the Life Raft Group

## Poker Tournament Nets over $47,000 for Life Raft

On Thursday, November 18, Life Raft Board member Jerry Cudzil hosted a poker tournament in New York City to raise money for the Life Raft Group. Over 100 family, friends and colleagues poured into the Park Avenue Country Club for a night of friendly play and a chance to win a ticket to the E.S.P.N. World Series of Poker in Atlantic City, NJ in January 2005. The event raised over $47,000 for the Life Raft Group.

## Putting Gleevec tablets in glycerin capsules raises serious concerns

**By Jerry Call and Norman Scherzer**

Last month we published a short article in our October Newsletter headlined "Life Rafter members find solution to Gleevec tablet nausea."

We reported that several GIST patients who had switched from the original orange Gleevec capsules to the tablet form had experienced increased side effects, including nausea.

The article went on to cite a possible solution-namely, to put the Gleevec tablets inside empty glycerin capsules. The rationale was that this would allow the tablets to travel further down the gut before dissolving, bypassing sensitive regions where nausea arises. The source of this advice was said to be an oncology nurse and an oncologist.

We have since spoken to several people at Novartis who had concerns about our article, most noteworthy Dr. Bin Peng, MD, PhD, the Senior Clinical Pharmacokineticist in the Department of Clinical Pharmacology. Dr. Peng received his medical degree from Sun Yet-sen University of Medical Sciences in China. He completed his postdoc- fellowship in Manchester University, UK with Prof. Malcolm Rowland. He has authored and co-authored more than 50 papers and abstracts on clinical pharmacokinetics/ pharmacodynamics in the field of anti-cancer drugs. As a clinical pharmacokineticist, he has been involved in the first investigations of the pharmacokinetics/pharmacodynamics of Glivec (STI571) in man.

Dr. Bing Peng, Novartis, Jerry Call, LRG and Barbara Kennedy, Novartis

Based upon Dr. Peng's input we would like to withdraw our recommended solution. These are the reasons:

First, it is unknown if the solubility of the glycerin capsules would compare to that of the original orange Gleevec capsules.

Second, it is not known how placing the tablets into the capsules affects the solubility of the tablets. Our understanding is that the patient would probably take a pill cutter and cut the capsule in half. This may produce quite a different result than the original powdered form of Gleevec that went into the original orange capsules.

The bottom line is that we do not know how this suggested procedure would affect the absorption of the drug and hence affect the efficacy of the drug.

Given that most patients have reported that the increase in side effects accompanied by the switch from capsules to tablets resolves over time, it does not seem that this suggested procedure is worth the potential risks.

# Life Raft Research Team meets with European researchers

## Methodology to assess actual dosage compared

**By Jerry Call**

At 7:00 a.m. on Friday morning, prior to the start of the formal CTOS agenda, the Life Raft Group met with Dr. Jaap Verweij, Erasmus University Medical Center, Rotterdam, the Netherlands and Dr. Martine Van Glabbeke, EORTC Data Center, Brusssels, Belgium. Verweij and Van Blabbeke were two of the investigators in the large phase III European Gleevec trial for GIST patients. The primary purpose of the meeting was to discuss some of the methodology differences between the European phase III study and the Life Raft Group (LRG) study on relapse. Another great benefit of the meeting was just a chance to meet and strengthen relationships with some of the top European researchers.

The LRG study had found a significant difference in relapse rates in GIST patients using Gleevec when comparing actual higher doses (600 mg/day or more) to actual lower doses (less than 600 mg/day). The European study also found a significant difference (in "progression-free survival") when looking at high vs. low starting doses. A companion phase III trial

Patients Progressing on Gleevec: The effect of starting dosage.

| **Patients Progressing At:** | 400mg | 600mg or more |
|---|---|---|
| European phase III trials | 56% | 50% |
| LRG study | 49% | 41% |
| The median follow-up was 760 days in the European trial, and was not computed for the LRG study. The higher dose was 800mg in the European Study and 600mg or more in the LRG Study. | | |

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# Life Raft Hosts First Pediatric GIST Conference

On November 12, 2004 in Montreal Canada, the Life Raft Group hosted a meeting on pediatric GIST, the first such comprehensive meeting ever held. Chaired by LRG Executive Director Norman Scherzer, the two hour conference brought together key players from around the world (there are no experts per se yet for pediatric GIST, only a small number of clinicians and researchers who share some experience with pediatric GIST patients and an interest in learning more). Attending the meeting were:
*Dr. Karen Albritton, Dana-Farber; Dr. Cristina Antonescu, Memorial Sloan Kettering; Dr. Camille Bedrosian, ARIAD Pharmaceuticals; Mr. Jerry Call, LRG; Dr. Chris Corless, OHSU; Dr. Sean Daly, ARIAD Pharmaceuticals; Dr. George Demetri, Dana-Farber; Dr. Jonathan Fletcher, Brigham and Women's Hospital; Mr. Jim Hughes, LRG; Ms. Margi Hughes, LRG; Dr. David Josephy, LRG; Dr. Ian Judson, Royal Marsden, London; Mr. Kalvin Kochhar, Novartis Pharmaceuticals; Ms. Tricia McAleer, LRG; Mr. David Murphy, Sarcoma Alliance; Dr. Alberto Pappo, Hospital for Sick Children, Toronto; Mr. Norman Scherzer (Chair), LRG; Dr. Richard Singleton, LRG; Dr. Daniel Stepan, AMGEN Pharmaceuticals; and Dr. Jaap Verweij, Erasmus Univ. Medical Center, Netherlands.*

The objectives of the meeting were to:
1. Bring visibility to the problem of pediatric GIST by convening such a conference
2. Create a working definition for what constitutes pediatric GIST
3. Briefing and discussion of the protocol for the planned pediatric GIST-Gleevec clinical trial
4. Discuss plans for a pediatric GIST data base
5. Discuss plans for a pediatric GIST tissue bank
6. Discuss a best practices protocol for managing current pediatric GIST patients

Consider how best to coordinate and support further efforts, including research

Visibility: Clearly the first objective of the meeting was achieved by the simple presence and participation of the twenty persons listed.

A working definition of pediatric GIST: The consensus was to use a broad definition now until we learn more. The likely upper age limit for the pediatric GIST-Gleevec trial will be 30. Dr. Judson and others observed that biology might serve as a more appropriate indicator with pediatric GIST patients than an artificial age cutoff. Although there is not a great deal of data available it seems that pediatric GIST patients are likely to be c-kit positive but less likely to have a known genetic mutation-in other words they are likely to be wild type c-kit. Chris Corless shared genetic data from OHSU on 14 GIST patients age 17 or less: 1 had exon 9; 1 had exon 11, 1 had a PDGFA mutation and the rest were all wild type c-kit.

New clinical trial protocol: Drs. Demetri and Pappo, the primary study coordinators, reviewed the still evolving plans for a clinical trial for Pediatric GIST patients. Demetri will likely take lead for patients over 18 and Pappo for patients under 18. Expected to begin early in 2005, the phase ll trial and data registry will attempt to enroll three groups of patients: those with completely resected GIST, those already receiving Gleevec at the time of registration and those with metastatic or unresectable GIST who have not yet begun Gleevec. The objectives would be to collect information on the natural history of the disease, including molecular and pathologic characteristics, to evaluate treatment response rates, to describe Gleevec toxicities and to obtain tissue samples for analysis.

As the discussion evolved there was a strong interest in expanding the scope of participation in the trial beyond the United States and in expanding the principal investigators to include key pathologists that the Life Raft Group has been working with, including Antonescu of Sloan-Kettering, Corless of OHSU and Fletcher of Brigham and Women's Hospital. The Life Raft Group was particularly interested in ensuring that molecular and pathologic testing retain a strong focus in the hands of experienced GIST pathologists.

Pediatric GIST data base: At present a number of centers have small pediatric GIST data bases, with the Life Raft Group probably having the largest. Scherzer reviewed the creation of a LRG internet based data base which presently has access limited only to the families of the pediatric GIST patients who contributed the data. Plans are to expand the size and scope of the data base and to offer access to key clinicians and researchers. As the clinical trial data base begins to take shape and grow, the LRG will reassess the need to continue its own data base. It is not clear from the protocol discussions whether, and if so how, pediatric GIST families and key clinicians will be permitted access to this new data base.

Pediatric GIST tissue bank: The planned clinical trial was the dominant factor in the discussion of pediatric GIST tissue banks. The LRG had been discussing a pediatric GIST tissue bank with several pathologists over the past year and is committed to supporting such a concept. The Life Raft Group was particularly interested in ensuring that molecular and pathologic testing retain a strong focus in the

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# Novartis Scientists Review Status of Drugs in Pipeline

On November 8th Life Raft Group Executive Director Norman Scherzer sat down with 15 key officials and scientists at Novartis Worldwide Oncology headquarters in New Jersey to discuss the status of Novartis drugs that might have applicability to the treatment of GIST patients. Present at this meeting were:
*Pamela Barckett, LRG Med. Rsch. Asst.; Sarah Boyce, Gleevec Brand Director U.S.; Pamela Cohen, Global Leader **PKC412**; Heather Duncan, Director New Product Commercialization; Leslie Fields, Patient Advocacy Relations; Sushant Harkiker, Assoc. Director **RAD** Clinical Research; Barbara Kennedy, Exec. Director Oncology Scientific Operations; Kalvin Kochhar, Assoc. Director Glivec Global Marketing; Mildred Kowalski, Assoc. Director Patient Advocacy Relations; Tracey Lawhon, Intern. Proj. Team Leader **AMN107**; Laurie Letvak Glivec, Global Medical Affairs; Karen McDougal, Clinical Research Mgr. **Gleevec**; Hugh O'Dowd, Global Brand Leader **Gleevic**; Inga Sams, Assoc. Dir **Gleevec** Phase 1V; Norman Scherzer, LRG Exec. Director; Johanna Shulman, Sr. Product Mgr Gleevec; Gloria Stone, Global Communications; Lei Zhang, Assoc. Director PKC Team.*

This level of openness and trust on the part of a pharmaceutical company is quite something extraordinary. Discussions went on for two hours and covered five Novartis drugs, including four adjuvant Gleevec trials. This summary will cover only the four non FDA approved Novartis drugs. We will cover the ongoing adjuvant and neo-adjuvant Gleevec trials in a future edition of this Newsletter.

RAD001 (Everlolimus) Protocol number CRAD001C2206

RAD is an oral mTOR-inhibitor. It is given in combination with Gleevec to

See DRUGS IN PIPELINE, Page 13

From top, left to right: Alex & Nena Smolyer, Elaine Rys, Pam Lewkovich, Paula Vettel, Lucy Madsen, Jennifer and Matthew Kostalek, Bob Book, Corrine Lundell, Jeanne Book, Sue Kinzig; Karen Schmitt, Ken Lundell, Dick Kinzig, Beth Sanchez, Esther Parada and Nestor Sanchez

# Chicago LRG Takes on Fundraising Role

The Chicago Chapter of Life Raft Group held its eighth meeting on November 14 at the Wellness Place in Inverness, Ill. Seventeen people attended from Illinois, and as far as Indiana, and Wisconsin. Three new GIST survivors joined the group, Alex, Lucy, and Jennifer.

The newcomers were given the opportunity to ask many questions and they learned about the various treatments recommended by the member's doctors.

Dick Kinzig, Chicago LRG Chapter Coordinator, discussed the Thanksgiving campaign and urged the members to reach out to friends and family. He explained that funds are much needed to continue the fine work of the international LRG.

Bob Book, LRG director, asked everyone in attendance to investigate local hospitals foundations that would consider contributing to a community cancer organization such as the LRG. Members were asked to identify the hospital, the address, and a contact person.

It was reported that Medicare now covers one PET scan per year and more insurance companies are following suit. This is important for those denied coverage in the past.

Bob Book informed members of a new CT scan machine that is being installed in many area hospitals that is faster and more accurate for reliable imaging. Patients should inquire with their own facility.

A social hour was enjoyed by all and holiday greetings were exchanged. The next meeting will be held Sunday, March 20, 2005.

**By Dick Kinzig**

# Life Raft in Warsaw for Patient Advocacy Conference

The day after Thanksgiving, I found himself on a plane bound for Warsaw Poland to participate in a meeting of Eastern European patient organizations. A nine hour plane ride was to take me from turkey, family and t.v. football to a first visit to the country where my parents were born and to a meeting quite unlike any I had attended before.

"Hello, my name is Stanislaw Kulisz. I am a GIST patient from Poland and the head of the new GIST Patient's Society. I have been looking for you." In his hand he had written *Norman Scherzer, the Life Raft Group*.

Just a brief while before I had checked into the conference hotel-the meeting had already started but the sole post Thanksgiving flight had landed only an hour or so before. It was about 10:00 a.m. in Warsaw; about 4:00 p.m. in New Jersey; and about neverland in my head. I had dropped my luggage off in my room and skimmed through the program and the listing of attendees.

In my hand I had written *Stanislaw Kulisz, Polish GIST Patient Society*. Stanislaw's English was modest and my Polish was disgracefully much less than that but language and culture was not an issue that moment. The emotional connection broke across all those barriers.

Jolanta Kwasniewska, First Lady of Poland, addresses patient groups

Stanislaw Kulisz, Head of Polish GIST Patient's Society and Norman Scherzer, LRG Executive Director

I was to go on to make two formal presentations to the 200 delegates from Poland and Malta, Bulgaria, Romania, Croatia, Czech Republic, Hungary, Greece, Slovakia, Serbia and Montenegro, and a few colleagues from Western Europe. Thank goodness I studied those geography maps my elementary school teacher pulled down from the roll up holders on the wall each day. It didn't hurt of course to have grown up on a street in New York City where I, along with all my friends, were first generation Americans and where the mothers of Europe bathed our kitchens with the scents of history.

I was the only American at the meeting and my mandate was to talk about organization building and networking. But the real meeting, as is almost always the case, took place in the breakout sessions and over meals and socializing. Imagine my joy at being partnered with Elzbieta Kozak for a breakout session to strategize increasing resources for Eastern European cancer patients and their organizations. This, after a call to arms by the wife of the President of Poland who had attended several hours of the meeting.

Elzbieta is a breast cancer survivor and the president of a group called the Amazonki-the Amazons of Poland. She and 25 or her colleagues joined me in a wonderful work session assisted by this great translator who sat by my side and simultaneously translated this fast paced discussion, often with several persons talking at once. At the wrap up Elzbieta and her colleagues deferred to me, the articulate American, to make our presentation to the plenary session, a presentation that would call upon the health ministers of Poland and the European Union to join us at our next session to explain to us in person why they had inadequately funded cancer support organizations and to explain what they intended to do to redress that, particularly in Poland. I would have nothing of that undeserved charge to speak and instead when our turn came walked over to Elizbieta and took her by the hand so that we could walk together to the podium. And that is when I learned what the President of Amazonki is capable of doing as she took charge of the room and delivered the core of our presentation.

I could talk about the endless details of the meeting but that is not the real point of all this. I went as a teacher and instead became the student. You will hear more in the future about Stanislaw and Elzbieta and Agnes Vadnai from Hungary and Francois Houyez from Eurodis (the European Organization for Rare Diseases) and the European Cancer Patients Coalition and our special friends from Das Lesbenhaus (Markus and I toured old Warsaw together after the meeting ended).

The Life Raft just got a little more crowded and a little more diversified and that is as it should be.

# Life Raft Group at CTOS 2004 Montreal, Canada

## Presents two papers, hosts first pediatric GIST conference and hosts meeting with European researchers

**By Jim Hughes**

It is something we have all wanted to do.

In the throes of fighting GIST, I suspect each of us has probably had communication problems with multiple doctors and wanted to just get them all together at one time to get on the same page.

Apparently that is exactly what happened 10 years ago when a wealthy sarcoma patient got involved in researching his own cancer. After consulting many experts independently, it was the patient's contention that although there were experts, communication among those experts was suboptimal and that poor communication ultimately detracted from the optimization of patient care. He pulled the experts together for a meeting and, as they say in Quebec, "Voila" the Connective Tissue Oncology Society (CTOS) was formed. You can read about it at www.ctos.org "About CTOS".

Now, ten years later, there is an on-going scientific discussion among the world's leading sarcoma and GIST experts focused on key scientific and clinical research topics. But, as we learned, this patient's mission is far from completed and much optimization still needs to occur. At this year's CTOS meeting the Life Raft Group continued that first sarcoma patient's mission on the behalf of GIST patients worldwide.

The 10th annual scientific meeting of CTOS was held Nov. 11-13, 2004 in Montreal, Quebec, Canada. The goal of the society is to advance the care of patients with connective tissue tumors and to increase knowledge of all aspects of the biology of these tumors, including basic and clinical research. Approximately 250 medical professionals attended from around the world.

This was definitely a hard working information filled event. Dinner Thursday night concluded with a working session on the use of the RECIST criteria. RECIST is used to measure disease progress in GIST clinical research. RECIST is the source of the 50% shrinkage and 20% growth criteria associated with trials. The consensus seems to be that RECIST should be replaced. It was an animated discussion led by Drs. Larry Baker and George Demetri that lasted past 9:00 pm. It became apparent as the discussion went on that there were more issues than conclusions about replacing RECIST. This is going to take either more time or a follow-up committee. One key issue was the definition of "progressing disease" It was felt that a new criteria should include molecular (PET and cellular activity) and clinical criteria (how does the patient feel) as well as the current RECIST biological criteria (CT scans and tumor size). An encompassing new definition will hopefully come soon.

Thanks to all the LRG team members who attended the meeting in Montreal: Jerry Call, David Josephy, Margi Hughes, Trish McAleer, Norman Scherzer and Dick Singleton.

# A Review of the posters and papers at CTOS

The CTOS (Connective Tissue Oncology Society) meeting in Montreal had about 250 attendees. It was held as a single plenary session (no concurrent sessions) in a hotel ballroom setting. There was also a small poster session. This is my report on those scientific presentations that I attended at the meeting. Other LRG attendees will report on the LRG-sponsored discussions (Friday early morning meeting with Jaap Verwiej, Netherlands; Friday morning pediatric GIST meeting; Saturday evening meeting with Dr. Fletcher, etc.) and LRG outreach activities. In general, GIST was a very hot topic at the CTOS meeting, and the focus of numerous presentations.

**Posters:**

1. One of the posters (Blay et al.) described the results of a randomized clinical trial study in France, in which glivec treatment was stopped in GIST patients who had been treated with the drug. The objective was to see whether continued treatment (for the patient's lifetime) is advisable. The results were, in retrospect, obvious: the rate of disease progression was drastically higher in the patients who stopped glivec. This effect was so dramatic that the trial was stopped and all the remaining patients were returned to glivec treatment.

2. Martin Blackstein et al. (Mt. Sinai, Toronto) put up a poster entitled "Neoadjuvant imatinib therapy for rectal GISTs". Three cases of rectal GIST were treated with glivec prior to surgery (neoadjuvant treatment). The study concluded that this is an effective treatment approach; glivec induced debulking of the tumours had

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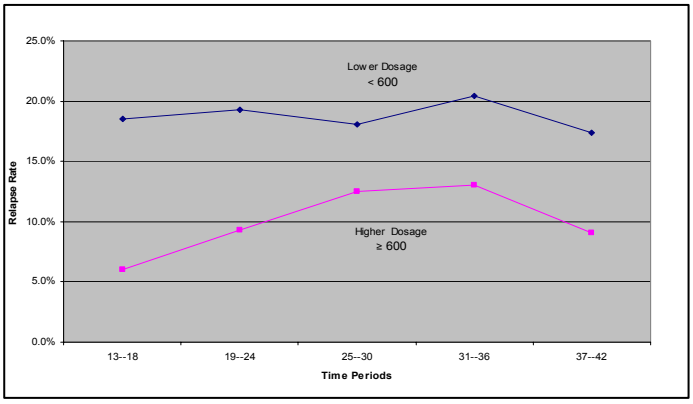
# STUDY

From Page 2

odology used by the Life Raft Group is subject to bias in that there was not a non-random assignment of subjects to dosage groups. On the other hand the Life Raft Group methodology takes into consideration the actual dosage that patients were on, including those situations in which the patients themselves changed their dosage without reporting this to their clinicians.

The Life Raft Group study was led by Norman Scherzer, executive director, with science coordinator Jerry Call, research assistant Pamela Barckett, biochemist David Josephy, Ph.D.; mathematician Michael Josephy, MSc., and statistician Richard Singleton, Ph.D.

Relapse Rates Over Time— Actual Dosage




This was a milestone event for CTOS and the LRG. For CTOS it was the first patient led scientific study and presentation. Dr Larry Baker commented at the end that this was an "extraordinary event. …that much other retrospective work had been presented at the CTOS meeting and the LRG's was as provocative as any". For the LRG this was a major learning event.

**By Richard Palmer, Norman Scherzer and Jim Hughes**

# RESEARCHERS

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done in the United States and Canada did not find a significant difference in its early interim analysis.

Pictured from left to right are: Dick Singleton, Martine Van Glabbeke, Jerry Call, Norman Scherzer and Jaap Verweij

When looking at the dose patients started on (also known as "intent-to-treat" dose), the results for the European study and the LRG study were similar.

The LRG study also found a larger difference when comparing the actual dose patients took vs. the starting dose prescribed to the patient. The LRG study had found that patients receiving a lower dose of Gleevec had an 8% higher relapse rate based on *starting* dose, but a 23% higher relapse rate based on the *actual* dose.

Dr. Verweij had previously informed the LRG that their study *did not* find a difference when comparing starting dose to actual dose. Why these different findings occurred was one of the primary items that we wanted to discuss at this meeting. There were several differences between the European and LRG methodologies that could explain this difference:

1. The European study was a randomized controlled clinical trial and the LRG study was a non-randomized retrospective study. Non-randomized trials/studies may be biased as a result.
2. The patient population that each looked at when comparing actual dose vs. starting dose was different. The Europeans looked at all patients from 6 months of treatment forward. The LRG looked at patients from 12 months of treatment forward. The Europeans chose the 6 month starting point because of their assumption that almost all dosage changes would occur within the first 6 months.
3. The European study looked *at all* patients that completed 6 months of the trial, and the LRG only looked at patients that had *initial shrinkage* on Gleevec. Patients who were judged to be "stable" during initial treatment stages were not included in the LRG study.
4. The LRG attempted to consider dose changes done by the patients themselves. If a patient reported that they were prescribed a higher dose, but they actually took a lower dose, then that patient was considered in the low dose group when looking at actual dosage. A new unpublished study on Gleevec compliance suggests that patient compliance in taking Gleevec may be considerable worse than that reported by patients to the LRG. It seems likely, even though the LRG attempted to consider this issue, that it was probably underreported in our study.

# PEDIATRIC GIST

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hands of experienced GIST pathologists and will be watching the conduct of this trial closely to ensure that this happens.

It was noted that there is existing infrastructure at the Cooperative Human Tissue Network (CHTN) which manages a pediatric division at the Columbus Children's Hospital in Columbus, OH. The CHTN has a process that oncology centers of excellence use today. "Investigators just need to identify the protocol and the CHTN takes care of the rest".

The CHTN seemed to be a good solution, except it could potentially limit tumor tissue access to just those investigators on the individual protocols supplying the tissues. While the CHTN seems like a good existing solution, there is still a need to provide full access to key investigators who express interest in studying pediatric GIST. In the case of patients who are not in trials, Norman Scherzer offered that the LRG could help educate these patients to get tissue to the right places.

Pictured clockwise from left side of table: Alberto Papo, Dick Singleton, Daniel Stephan, Jerry Call, Norman Scherzer, Ian Judson, Jaap Verweij, and Cristina Antonescu. Back row: Camille Bedrosian, Sean Daly, David Murphy, Kalvin Kucher, and Margi Hughes. Back to camera: George Demetri.

Best practices protocol for current pediatric GIST patients: Few specifics emerged to address how to currently handle the clinical management of pediatric GIST patients. There was a consensus that such patients should be seen by physicians connected with the proposed clinical trial but there seemed no clear correlation between that and the availability of demonstrated expertise. One issue that did seem to be clarified was that treatment within the clinical trial protocol would be quite similar to that given to adults-at least for children over 12- with a "usual dosage" of between 400 and 600 mg per day and the possibility of going to 800 mg per day. As a number of the pediatric GIST patients the LRG is monitoring are currently receiving less than 400 mg per day this best practice should be quite helpful.

Coordinate and support further efforts: The Life Raft Group committed to making pediatric GIST patients aware of this new data registry and trial and to support it by education and referrals. The clinical community present offered to refer pediatric GIST families to the Life Raft Group for support and to work closely with the LRG in implementing this and other projects. We will offer the key players present access to our pediatric GIST data base and hope that they will be able to reciprocate.

We will also work together to try to lower the age limit for most clinical trials to below 18 for GIST patients as no one present could cite a sound medical or scientific base for the general 18 year cut-off. It was proposed that future GIST study protocols be written to specifically include patients less than 18 years of age. It was also noted by Dr. Alberto Pappo that the Children's Oncology Group (COG) has an active program to test new drugs in children as young as 10. In Europe, the direction is to include teenagers of 14 and 15.

We will also work closely with our pharamaceutical colleagues to explore bringing new drugs to trial for pediatric GIST patients.

This meeting was an important first step in launching a coordinated and comprehensive strategy to address the need of pediatric GIST patients. The LRG is planning a first ever meeting of pediatric GIST families in 2005 and expects that many of the key players present at this meeting will participate.

**By Jim Hughes and Norman Scherzer**

# CTOS REVIEW OF POSTERS AND PAPERS

From Page 9

allowed better surgical outcomes, with subsequent resection (surgery) allowing preservation of the anal sphincter.

3. A poster from a group in the UK reported a case study of blood calcium levels and cramps/ spasms as side effects of glivec treatment. (Serum calcium level and involuntary movements in patients treated with imatinib for GIST, Jamal M Zckri et al) concluded that "Treatment with imatinib (glivec) for GIST is associated with statistically significant reductions in serum calcium. This may account for the high reported incidence of myalgia and muscle cramps in these patients."

**Oral Presentations:**

1. Acquired resistance to imatinib in progressive GISTs due to multiple synchronous kinase mutations in different exons of kit. Dr Peter Hohenberger from the Surgical Oncology section of Mannheim University, Heidelberg, Mannheim, Germany representing a team from Germany, presented on secondary resistance to imatinib in GIST. They found that Imatinib treatment of GIST may lead to secondary resistance to new acquired KIT mutations in addition to the primary mutation. In primary tumors with an Exon 9 mutation GIST secondary mutations were noted in exon 17. In primary tumors with exon 11 mutatations GIST secondary point mutations were noted in exons 13, 14 and 17.

2. Early and late resistance to imatinib in advanced GIST are predicted by different prognostic factors: an analysis of the EORTC-ISGAGITG randomized trial; M Van Glabbeke et al. This report from a large international consortium, including some of the leading European authorities (Verweij, Oosterom, Judson) was of considerable interest. Dr. Van Glabbeke presented the paper. The hypothesis was that the biological mechanisms of resistance to glivec may differ between the cases of “early” versus late” development of resistance. They used their clinical trial database and studied the characteristics of 116 cases of early drug resistance/ progression (among 934 at-risk patients) and 347 cases of late drug resistance/ progression (among 818 at-risk patients). They tested whether various factors biological and treatment variables correlated with risk of resistance.

**Lower dose was significantly (p < .01) correlated with late development of resistance but not with early resistance**. Low hemoglobin levels upon entry correlated with poorer response; mechanisms for this effect might include hemoglobin effects on drug pharmacokinetics or a correlation between hemoglobin levels and disease state. Another factor that correlated with both early and late resistance was high blood granulocyte count, perhaps, again, due to more advanced disease state or inflammation.

Larger tumours showed poorer response/ more resistance, especially beyond 18 months of treatment. With respect to site of origin, results were better for stomach than for bowel. The authors concluded that factors affecting resistance do indeed differ between early and late resistance. With the possible exception of patients with small bowel primary tumours, dose is an important factor in late resistance, expecially for tumours with less-common sites of origin. In the question period, one doctor asked whether the apparent effect of tumour site of origin might in fact be an effect of exon position of the kit mutation, since that factor is strongly correlated with tumour site of origin, and Dr. Van Glabbeke agreed that this was likely. (exon 9 mutations in GIST occur almost exclusively in the small bowel and not in other sites),

3. The last GIST talk in the session was the LRG presentation: Disease progression in patients with metastatic GIST receiving gleevec (imatinib): the effect of drug dosage P Barckett; J Call; P D Josephy; N J Scherzer; R Singleton The Life Raft Group. Our paper was well-received, and drew compliments from many of the doctors present. See page 1.

**Advocacy Groups:**

This was the very last session at CTOS 2004, but the attendance was good, nonetheless. Presentations were given by Norman Scherzer which focused on the history and role of LRG; by Jody Cummings, Executive Director, the Sarcoma Foundation, which focused on supporting research projects and by David Murphy of the Sarcoma Alliance, which focused on providing patient support.

**By David Josephy, PhD**

*Notice: Our Newsletter Editor, Richard Palmer, was off on a well deserved vacation. This Newsletter was put together by Tricia McAleer and Norman Scherzer, with input from Mia Byrne, Jerry Call, Jerry Cudzil, Jim Hughes, David Josephy and Tania & Robert Stutman, amongst others. Although we had Richard’s orientation, inspiration and layout templates to guide us, any glitches should be attributed solely to us. Nothing makes one appreciate the work of others than to try to step into their shoes. Richard’s are much too big for us and we look forward to him resuming his editorship.*

# Das Lebenshaus Visits the Life Raft Group Office

Andrea Schumann and Markus Wartenberg of Das Lebenshaus, a German GIST organization, flew in to meet with the Life Raft Group for two days: November 16 and 17.

Although they were guests at Life Fest 2004, this was Markus and Andrea's first trip to the Life Raft Group office.

They recently switched the mission of Das Lebenshaus to focus solely on GIST.

The objective of this meeting was to learn more about each other and explore complimentary areas of collaboration and support.

Das Lebenshaus and the Life Raft Group developed a shared vision of a world where: Less patients have to suffer or even die of GIST; Caregivers are supported whenever needed; GIST patients and caregivers experience a life worth living.

The Life Raft Group and Das Lebenshaus plan to work together to unify and strengthen the global GIST community.

**By Tricia McAleer**

# DRUGS IN PIPELINE

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GIST patients resistant to Gleevec. This study is currently in phase l with patients at 5mg per day of RAD plus 600 mg of Gleevec. There are 4 centers in Europe (Germany-2 sites; France and Belgium) and 1 in the U.S. (Dana-Farber).

There have been two phase l cohorts: Each group was given 600 mg of Gleevec. In addition, one group of 13 was given a weekly dose of 20 mg-all 13 progressed and 0 are ongoing. A second group of 13 was given a daily dosage of 5mg-1 has responded, 7 have progressed, and 6 are ongoing.

PKC412 Protocol number CPKC412A2211

PKC412 is an inhibitor of protein kinase C (PKC). The PKC family consists of at least 12 isoforms of serine/threonine kinases that play a major role in signal transduction. It has been shown that PKC inhibitors can also reduce tumor angiogenesis. PKC412 is a very active and more selective derivative of the PKC inhibitor staurosporine. It is given in combination with Gleevec to GIST patients resistant to Gleevec. There are two sites, one in Berlin, Germany and one in Portland Oregon.

The first part of this phase l trial had daily doses of 100 mg PKC412 plus 600 mg Gleevec-this part is closed-all 12 patients are off the study. 8 of the 12 patients had partial progression due at least in part to Gleevec levels being lowered by the interaction with PKC412. The study was then amended.

The amended part of this phase l trial has 3 cohorts: Patients need to be stable on 800 mg of Gleevec for at least 2 months before starting combination treatment. This is a dose escalation trial starting at 200mg of PKC412 per day plus three dose levels of Gleevec, 1000mg per day, 1200 mg per day and 1500mg per day. Planned enrollment is up to 18 patients. There is no wash out period (that is, do not have to stop Gleevec prior to starting the trial). The dosage of PKC412 was initially decreased to 50mg per day and the dosage of Gleevec was then increased from 800 to 1000 per day. 7 patients were enrolled-at cycle four, 2 have dropped out, 2 have stable disease and 3 have partial progression.

This combination drug trial has been quite an ordeal with unexpected and striking interactions between PKC412 and Gleevec. This is demonstrated by the intent to put patients on up to 1500mg of Gleevec per day along with PKC412 because the expected "actual" level of Gleevec will be far below that amount. The interaction of these drugs is good reason to be particularly cautious about early phase l trials.

AMN107

This new drug has been high on the rumor circuit and has aroused great interest. It is currently in a phase l trial for chronic myelogenous leukemia (cml) with promising results. It is planned to be in a combination trial with Gleevec for Gleevec resistant GIST patients in 2005.

PTK787:

We briefly discussed PTK787 but no new information was learned. This drug is not yet in trial for GIST patients.

**By Norman Scherzer**

# The Life Raft Group

**E-mail: liferaft@liferaftgroup.org** • **40 Galesi Drive** • **Telephone: 973-837-9092**
**Internet: www.liferaftgroup.org** • **Wayne, NJ 07470** • **Fax: 973-837-9095**

## Who are we, what do we do?

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

## How to join

GIST patients and their caregivers may apply for membership free of charge at the Life Raft Group's Web site, www.liferaftgroup.org 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.**
**Wayne, NJ 07470**

**International donors should contact the office for electronic transfer instructions.**



## 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.