GIST warriors left behind a legacy of struggle & triumph

By Erin Kristoff
LRG Newsletter Editor

Access issues come up often enough in America. Depending on the disease, many times there are agencies or organizations in place to help patients in need overcome these hurdles. Outside of the United States, it is not always easy or even difficult to access treatment for a rare cancer. It can be downright impossible. Factors like cost, patient population, and bureaucratic red tape can lead to restrictions on a patient’s ability to afford or even get a prescription for drugs like Gleevec, Sutent and others.

Vera Krstevski was diagnosed with GIST in August 2007 in her native Macedonia, where the Ministry of Health had not prioritized funding treatment costs for rare diseases like GIST. This created a situation in which most patients are left to find other ways to access life-saving treatment.

She had her first gastrectomy shortly after diagnosis; one year later, she had a recurrence and a second operation. Vera started 400mg of Gleevec in January 2009 and spent two years on the drug, managing to increase her dosage to 800mg.

Genetic markers of progression in GISTS and their significance

By Maria Debiec-Rychter
Catholic University of Leuven
LRG Research Team Member

Today there are four major methods of determining risk of recurrence after initial surgery. These methods are pretty good at identifying low-risk and high-risk tumors. However, there is a fairly large group that fall between low-risk and high-risk. Those with so-called “moderate” or “intermediate” risk tumors are faced with the decision of whether or not to take Gleevec. New guidelines exist that recommend taking Gleevec for at least three years, with many experts advocating longer periods for high-risk patients.

Gleevec is an outstanding drug and a lifeline for the majority of GIST patients. However, it does have side-effects and these can be significant for some patients. In addition, like all cancer treatments, it is expensive. Thus it is extremely desirable to find better methods to determine which patients need to take Gleevec and which patients are essentially “cured” by surgery and don’t need to take Gleevec. In this issue of the LRG newsletter, LRG Research Team member, Dr. Maria Debiec-Rychter de-

The 2011 Executive Director’s Report

By Norman Scherzer
LRG Executive Director

The Life Raft Group is coming up on our ten year anniversary. The truth is, we’ve been around longer than that, since 2000 and the early days of Gleevec, when we were just a handful of patients and caregivers trying to make sense of this strange, new world and help each other as best we could.
Ensuring That No One Has To Face GIST Alone — Newsletter of the Life Raft Group — December 2011 — PAGE 2

One Life Rafter chooses a unique way to show support

By William Sumas
LRG Program Associate

Last month, the Life Raft Group took a giant step towards launching the Mike Matthews Legacy Society and planned giving program. Ray Montague, a dedicated Board Member and Treasurer of the Life Raft Group, pledged an incredible $100,000 bequest in memory of his son, Jonathan, in an effort to jumpstart the program.

Ray joined the LRG in December of 2002 after Jonathan lost his battle to pediatric GIST earlier that year. Since joining, Ray’s commitment and support in the struggle to find a cure has been unwavering. In 2007, Ray joined the LRG Board of Directors, giving him the opportunity to broaden the range of his involvement. Of particular importance is the role he plays in promoting numerous pediatric GIST initiatives. These efforts include sponsoring two National Institute of Health (NIH) dinners as well as hosting a pediatric GIST family weekend. His most recent decision to support our planned giving program will enable GIST patients to receive expert care in the future while preserving Jonathan’s memory.

Planned Giving is a method of supporting organizations and/or charities that gives the individual a variety of choices when considering estate planning. Planned gifts are beneficial to the donor because they allow the Life Raft Group to engage in long-term financial planning knowing that resources will be available in the future.

The LRG Planned Giving Program was named in honor of Mike Matthews, a Life Raft Group founding member and GIST patient whose story has been a source of inspiration not only for the Life Raft Group, but for cancer patients everywhere. Mike was devoted to his family, a respected man in his community, and a loving friend.

Mike passed away in 2004 while waiting for a trial that would not come in time. His friends at Purcells Cove Social Club decided to throw him a “Going Away” Party. At this party, Mike asked his wife to dance; everyone in the room knew it was their last. LRG Executive Director, Norman Scherzer was present for this solemn and touching moment and pledged that the LRG would not rest until we live in a world where no man had to ask his wife for one last dance.

Mike Matthews with his grandson.

The Life Raft Group

Who are we, what do we do?

The Life Raft Group (LRG) directs research to find a cure for a rare cancer and help those affected through support and advocacy until we do. The LRG provides support, information and assistance to patients and families with a rare cancer called Gastrointestinal Stromal Tumor (GIST). The LRG achieves this by providing an online community for patients and caregivers, supporting local in-person meetings, patient education through monthly newsletters and webcasts, one-on-one patient consultations, and most importantly, managing a major research project to find the cure for GIST.

How to help

Donations to The Life Raft Group, a 501(c)(3) nonprofit organization, are tax deductible in the United States. You can donate by credit card at www.liferaftgroup.org/donate.htm or by sending a check to: The Life Raft Group 155 US Highway 46, Suite 202 Wayne, NJ 07470

Disclaimer

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

Please advise Erin Kristoff, the Newsletter Editor, at ekristoff@liferaftgroup.org of any errors.

The Life Raft Group chose to honor Mike’s memory and the lives of all those who have lost their battle to GIST by establishing this fund and ensuring that their legacy will live on.

To learn more about the Mike Matthews Legacy Society and planned giving please call Christine Schaumberg, the Life Raft Group’s Director of Development, at 973-837-9092 x116.

You can also read more about Mike’s story in the July 2004 issue of the LRG newsletter.
By Jennie Kim  
LRG Program Associate

Recently, President Obama nominated our Life Raft Group Board Member Marietta Robinson to join the Consumer Product Safety Commission (CPSC). The Commission ensures the safety of over 15,000 domestic consumer products, particularly those of children’s.

Marietta has expressed how honored she is for the nomination and hopes for a quick confirmation from the Senate. Once confirmed she will be the fifth member of the commission, giving leverage to the Democrats once again since Democrat Thomas H. Moore’s absence, according to the Washington Post. Moore left the commission evenly divided between Democrats and Republicans, which caused consequent disagreements and obstacles for the CPSC.

As a lawyer of 33 years, Marietta has worked with various law firms and is well known in Michigan’s political sphere as a successful member of the legal community. Her persistent devotion to the LRG Board provides GIST patients, families, and caregivers hope for a cure. She continues the legacy of her husband of twenty-eight years, the accomplished James K. Robinson who sadly lost his battle to GIST in August 2010, as she remains committed to the cause of the LRG.

The LRG would like to offer a big congratulations to Marietta on this prestigious nomination!

---

LRG introduces GIST Day of Learning in Miami

By Tricia McAleer  
LRG Program Director

The Life Raft Group is launching a new program called GIST Day of Learning.

In response to the requests of previous attendees of our biennial meeting, Life Fest, for more opportunities like this, we have created a one-day program full of education and support for people who have GIST and their caregivers.

By hosting these events regionally throughout the year at different cancer centers we hope to make it easier for people to attend. **Since we will also be hosting Life Fest this year in Las Vegas in early November we are only hosting one GIST Day of Learning event in 2012 in Miami, Fla.**

For our inaugural event, we are very excited to work with Dr. Jonathan Trent and the University of Miami’s Sylvester Comprehensive Cancer Center. The event will be held in the Miami Beach area on May 19, 2012. We will be sending out details about the exact location as soon as they are available. This event will be free for GISTers and their families to attend. You can register by going to www.liferaftgroup.org/gdol.html

For many of you who may not know about these types of meetings, it was almost ten years ago in Cambridge, Mass. when the first educational event was held for people facing a newly defined cancer called GIST. That event grew into what we now call Life Fest. Life Fest has been held in different cities every other year since then. People attend from all over the world to gain a better understanding of their disease, the latest updates on GIST treatment and gain support from other people who are facing the same obstacles they are. Life Fest is our favorite event because even though our bond is through cancer, it is still a joyous event overflowing with support and hope for a cure.

**About Dr. Trent**

Jonathan C. Trent, MD, PhD is the Co-Director of the Musculoskeletal Center, Director of the Sarcoma Medical Research Program and professor of medi-
OCT-1 study shows promise for some CML patients: could there be benefit for GIST?

By Pete Knox
LRG Special Projects Coordinator

An Australian study of newly diagnosed CML patients concentrated on OCT-1 activity as a predictor of molecular response and progression-free survival (PFS) treated with imatinib. The study, entitled, “Chronic phase chronic myeloid leukemia patients with low OCT-1 activity randomized to high dose imatinib achieve better responses, and lower failure rates, than those randomized to standard dose”, is slated to be published in Haematologica in an upcoming issue, and was made available ahead of print as an early release paper (doi: 10.3324/haematol.2011.056457). The study looked at patients who were taking either 400 mg or 800 mg of imatinib daily and attempted to see if levels of OCT-1 activity had any predictive value. For a highly detailed discussion of the relationship between OCT-1 levels and imatinib uptake for CML patients, please see the article “Suboptimal response in CML linked to Gleevec uptake into leukemia cells” written by LRG Science Director, Jerry Call from the February 2008 edition of the LRG newsletter.

OCT-1 (Organic Cation Transporter 1) is a protein that is responsible for transporting imatinib into the target BCR-ABL positive cells (tumor cells). BCR-ABL is the oncogene that causes CML, and mutations in BCR-ABL are the primary means by which a CML patient becomes resistant to imatinib.

The findings of the study were of some interest for CML patients, but also should serve as a prompt for discussion and perhaps a call for further research for GIST. A relationship between imatinib dosage and OCT-1 activity was found for some patients but not for others, as Table 1 shows. (Also see accompanying Figure 1 (page 10) for information about response over time.) Thus, for patients on low dose (400 mg) imatinib, the rate of Major Metabolic Response (MMR) differed significantly among patients with low and high OCT-1 activity levels, with high OCT-1 level patients seeing markedly better results. The significance of this difference did not extend to patients with varying OCT-1 levels that were on a high dose (800 mg) of imatinib. In addition, the researchers looked at trough plasma levels and their relationship to rate of MMR, and found that those patients who had both low trough imatinib levels (defined as <1200 ng/ml) and low OCT-1 activity levels achieved the lowest rates of MMR (47%) when compared to the other patients in the study, and this difference was statistically significant (p=0.009). In addition, this group also had the highest rate of imatinib failure, a finding that has promise for some CML patients: could there be benefit for GIST?

Table 1: Relationship between imatinib dosage and OCT-1 activity

<table>
<thead>
<tr>
<th>Imatinib Dose</th>
<th>OCT-1 activity level</th>
<th>Rate of MMR (24 months)</th>
<th>Statistically Significant? (compared to same dose &amp; different OCT-1 levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (400 mg/day)</td>
<td>High</td>
<td>100% of patients</td>
<td>YES (p&lt;0.001)</td>
</tr>
<tr>
<td>Low (400 mg/day)</td>
<td>Low</td>
<td>57% of patients</td>
<td>YES (p&lt;0.001)</td>
</tr>
<tr>
<td>High (800 mg/day)</td>
<td>High</td>
<td>95% of patients</td>
<td>NO (p=0.073)</td>
</tr>
<tr>
<td>High (800 mg/day)</td>
<td>Low</td>
<td>68% of patients</td>
<td>NO (p=0.073)</td>
</tr>
</tbody>
</table>

First LRG jewelry party is a success

By William Sumas
LRG Program Associate

This holiday season, the Life Raft Group hosted its very first jewelry party in collaboration with our dedicated volunteer photographer Kim Tallau. Kim and her husband Steve joined the Life Raft Group in 2009 when Steve was diagnosed with GIST. They have remained proactive within the GIST community and play important roles in fund-raising for the Life Raft Group.

On December 13, 2011, local Life Raft Group members and our corporate neighbors browsed through an array of designer jewelry provided by Touchstone Crystals Jewelry—a member of the prestigious Swarovski Group. The LRG conference room was temporarily transformed into a winter wonderland as shoppers searched for gifts for their loved ones. For those unable to attend, an online shop was made available for the duration of the month. Overall, the event was a definite success, donating 15 percent of all purchases to the Life Raft Group while spreading the word about GIST to our neighbors. Congratulations to LRG supporter Paula Stover, winner of the eloquent Inspire Necklace!

The Life Raft Group wishes to thank all of our members who participated in this year’s Holiday Campaign. Though it is still underway (look for final results in the next newsletter), this important campaign has raised over $47,000 to support our patient education & support, advocacy, and research to find a cure GIST. In addition, this yearly fundraiser has become vital in raising awareness about GIST.

GISTer’s daughter holds third annual ball for GIST

By Julie Cramer

GIST has had a profound impact on my life even though I am not a patient myself. My father, Mark Becker, bravely fought his battle with GIST for 12 years before he died in 2009. Research and clinical trials are the two things that kept my dad alive long enough to see both of his daughters graduate high school and college, get married and have children. Though my children will never get to know him, I continue to feel that I need to do something to help people who are still fighting with this disease.

The GIST Benefit Ball is an opportunity for GIST patients from all walks of life to gather with other patients and supporters to enjoy a fun evening while supporting a fantastic cause.

Please join us next month at the third GIST Benefit Ball which will be held on February 18, 2012 at the Rittenhouse Ballroom in Philadelphia from 7 pm to 10 pm. There will be casino gambling (for prizes), silent and Chinese auctions, live entertainment, an art auction, and much more—all to benefit Fox Chase Cancer Center in Philadelphia!

Visit our website, www.gistbenefitball.weebly.com to purchase tickets or for more information. Use discount code “survivor” at checkout to get a special deal!
In April 2011, AROG Pharmaceuticals initiated a phase II trial of crenolanib (CP-868,596) for GIST patients with PDGFRA-D842V mutation. The current status of the trial was presented at CTOS 2011, and includes data regarding a metabolic response that was observed in a patient. The trial is currently ongoing at Fox Chase Cancer Center (Principal Investigator (PI): Dr. Margaret von-Mehren) and Oregon Health Sciences University (PI: Dr. Michael Heinrich). To ensure that crenolanib is not given to the patients at a sub-optimal dose, AROG has escalated the current dose by approximately 1.7 fold. Also, in an effort to provide therapeutic benefit to a maximum number of patients, AROG has increased the sample size and also allowed the patients that had discontinued from the study to re-enroll in the study at the higher dose. Currently available drugs like imatinib and sunitinib have no activity against the PDGFRA-D842V mutated GIST. AROG is hopeful that crenolanib will help provide therapeutic benefits to these patients that currently have no treatment.

Did you Know?

In April 2011, AROG Pharmaceuticals initiated a phase II trial of crenolanib (CP-868,596) for GIST patients with PDGFRA-D842V mutation. The current status of the trial was presented at CTOS 2011, and includes data regarding a metabolic response that was observed in a patient. The trial is currently ongoing at Fox Chase Cancer Center (Principal Investigator (PI): Dr. Margaret von-Mehren) and Oregon Health Sciences University (PI: Dr. Michael Heinrich). To ensure that crenolanib is not given to the patients at a sub-optimal dose, AROG has escalated the current dose by approximately 1.7 fold. Also, in an effort to provide therapeutic benefit to a maximum number of patients, AROG has increased the sample size and also allowed the patients that had discontinued from the study to re-enroll in the study at the higher dose. Currently available drugs like imatinib and sunitinib have no activity against the PDGFRA-D842V mutated GIST. AROG is hopeful that crenolanib will help provide therapeutic benefits to these patients that currently have no treatment.

Did you Know?

In April 2011, AROG Pharmaceuticals initiated a phase II trial of crenolanib (CP-868,596) for GIST patients with PDGFRA-D842V mutation. The current status of the trial was presented at CTOS 2011, and includes data regarding a metabolic response that was observed in a patient. The trial is currently ongoing at Fox Chase Cancer Center (Principal Investigator (PI): Dr. Margaret von-Mehren) and Oregon Health Sciences University (PI: Dr. Michael Heinrich). To ensure that crenolanib is not given to the patients at a sub-optimal dose, AROG has escalated the current dose by approximately 1.7 fold. Also, in an effort to provide therapeutic benefit to a maximum number of patients, AROG has increased the sample size and also allowed the patients that had discontinued from the study to re-enroll in the study at the higher dose. Currently available drugs like imatinib and sunitinib have no activity against the PDGFRA-D842V mutated GIST. AROG is hopeful that crenolanib will help provide therapeutic benefits to these patients that currently have no treatment.

Did you Know?

In April 2011, AROG Pharmaceuticals initiated a phase II trial of crenolanib (CP-868,596) for GIST patients with PDGFRA-D842V mutation. The current status of the trial was presented at CTOS 2011, and includes data regarding a metabolic response that was observed in a patient. The trial is currently ongoing at Fox Chase Cancer Center (Principal Investigator (PI): Dr. Margaret von-Mehren) and Oregon Health Sciences University (PI: Dr. Michael Heinrich). To ensure that crenolanib is not given to the patients at a sub-optimal dose, AROG has escalated the current dose by approximately 1.7 fold. Also, in an effort to provide therapeutic benefit to a maximum number of patients, AROG has increased the sample size and also allowed the patients that had discontinued from the study to re-enroll in the study at the higher dose. Currently available drugs like imatinib and sunitinib have no activity against the PDGFRA-D842V mutated GIST. AROG is hopeful that crenolanib will help provide therapeutic benefits to these patients that currently have no treatment.
Retired horse trainer seeks to “Harness a Cure” through Dover Downs fundraiser

By Christine Schaumburg  
LRG Development Director

Twelve years ago, Life Rafter Bobby Kinsey began his own battle against GIST. Since then, he has helped countless people with GIST across the world. Most of you know Bobby as an LRG member who posts advice and words of encouragement in our email community. Now, Bobby has decided that he wants to do more to help fight this cancer.

A retired horse trainer and former record-holding lead driver in harness racing, Bobby continues to groom horses at the Dover Downs in Delaware. He is combining his passion for harness racing with his determination to find a cure for GIST. On March 25, 2012, Bobby will host a fundraiser at the Dover Downs, Harness a Cure, to support the LRG’s research efforts.

Planning is underway; please email Christine for more information: cschaumburg@liferafgroup.org.

Swiss pathologist wins the 2011 GIST prize

The following is an excerpt from a press release distributed by the Swiss GIST Group.

Berne, Switzerland 29 November 2011 – The GIST Group Switzerland awarded its Science Prize for the second time. This year’s recipient was Prof. Stephan Dirnhofer, who won the prize for his important work on the pathogenesis of GIST at the University of Basel’s Institute of Pathology. Dr. Michael Montemurro and Helga Meier Schnorf, who made the documentary “Living with GIST”, won the Special Recognition Award.

The Gastrointestinal Stromal Tumors (GIST) Patient Support Group, the GIST Group Switzerland, awarded its Science Prize for the second time. This year’s recipient of the GIST prize, which is worth 10,000 Swiss francs, is Dr. Stephan Dirnhofer, Deputy Head of the Institute of Pathology at the University of Basel. The prize was conferred for his publication “Frequency, phenotype, and genotype of minute gastrointestinal stromal tumors in the stomach: an autopsy study”, published this year in the journal Human Pathology. The award ceremony took place on the 24 November at the semiannual meeting of the Swiss Group for Clinical Cancer Research (SAKK), held in Basel.

The jury, headed by Dr. Urs Metzger, voted unanimously in favor of this decision. GIST is a very rare cancer of the gastrointestinal tract that occurs in 10–15 people per one million
community is bigger. But we’ve never forgotten where we began; we are increasing our reach to ensure that amongst everything else—no one faces GIST alone.

And we are still as dedicated as ever to survival. We have just chosen to imagine a future without GIST—without cancer.

Maybe that’s why it’s so hard to write these reports, because I would rather be looking ahead, not behind. But as I said before and must always remind myself, where you’re going depends a whole lot on where you’ve been.

**Advocacy**

One of the many things the LRG expanded in 2011 was our advocacy efforts. From the early days of helping patients with access issues on a one-on-one basis and reporting on trends we saw in dosage and survival, the LRG has now become an active presence in making change. We still helped patient’s access drugs; we just did it more often and in some cases, in new ways.

Alianza GIST, our Latin American patient group alliance, met (as a formal organization) for the first time in Brazil and committed itself to helping patients in this region become better informed about the disease and its treatments as well as get better access to life-saving drugs.

We put this into effect by creating the first event for “Best Practices in Latin America”, which we held in collaboration with the Max Foundation at the American Society of Clinical Oncology (ASCO) conference in June and brought American & Latin American physicians together with others to study abnormal GIST cases in the region.

We also took a stand on counterfeit and substandard treatment, which plagues much of the world, but especially Latin America, by creating a petition and asking the community to stand with us.

Another goal that we have had for years is the routinizing of mutational and plasma testing. In 2011, we took this further than we ever have by first reestablishing free plasma testing through TDM Pharmaceutical Research, when Novartis was no longer able to support the program. Second, we launched a major survey, targeting both patients and doctors, which aimed to find the root causes for lack of participation in these tests and how we can make it better.

**Patient Support & Education**

I’m constantly amazed at how much our support & education efforts have grown. The ever-changing technological world we find ourselves in continues to come up with new and innovative ways to reach people.

While laying the groundwork for new technology, like a fresh, more interactive website and mobile apps, the LRG reached further and further out. Though we wish there were no need for it, we increased our patient crisis counseling efforts and plan to make these better in the new year.

We also not only expanded our US local groups, but we began efforts to keep our local group leaders more engaged and well-informed in order to increase the benefit from those meetings.

In a similar vein, we created a formal Physician Outreach program, with a goal to reach more patients, especially those who might not be able to find us on the internet, through their doctors.

Additionally, after the tragic loss of LRG member, Bill Buchanan, the LRG was able to honor his last wishes and establish a local support group at John Stroger Hospital a county hospital in Cook County, Illinois, where patients sometimes don’t have access to the internet to learn more about their disease and often have trouble even getting to appointments.

We also reached more patients by getting out of New Jersey! This year, the LRG had its first professional booth at ASCO in Chicago, where we raised awareness about GIST and the Life Raft Group by connecting with oncologists, pharmaceutical representatives and other patient groups from all over the world.

Moreover, we made a fairly simple, but nonetheless brilliant, decision to hire long-time LRG member and very vocal email poster, Janeen Ryan on a part-time basis.

Bringing Janeen on board has helped us support, assist and comfort more patients. We began as a handful of friends trying to help each other and with Janeen and the rest of the committed staff’s help, as large as we become, we will still always feel that way.

This year we saw a new member, Dave Safford, join the LRG and throw himself into supporting the cause by joining the Board and hosting a fantastic piano con-
scribes three new genomic-based methods that appear to significantly outperform current methods of risk assessment:

- CINSARC
- AURKA expression
- Genomic Index

One of these methods, the CINSARC method, appears to have broader applicability to the wider sarcoma community as well. Importantly, the DNA CGH array technique performed by Dr. Debiec-Rychter and colleagues can be performed from paraffin-embedded tumor tissue, the type of tissue that is already available/existing for most GIST patients.

GISTs are heterogeneous tumors in terms of location, histology, molecular profile and prognosis. Although mutations of KIT or PDGFRA are early and most likely initiating tumorigenic events in GISTs, increasing evidence suggest that clinical behavior of GISTs is influenced by accumulation of other genomic/chromosomal alterations (Figure 1). Like in most tumors, a number of chromosomal changes occur during the progression of GIST from low risk to metastatic (Wozniak et al., 2007). By cytogenetic analysis approximately two-thirds of GISTs demonstrate either total (monosomy) of partial loss of chromosome 14q. Loss of the long arm of chromosome 22 is observed in approximately 50 percent of GISTs. Loss of 1p and 15q are common and often coexisting, with higher frequency in high risk GISTs. Losses on chromosomes 1p, 9p (which harbours tumor suppressor genes CDKN2A and B), 9q, 10, 11p and 13q, and gains or amplifications on chromosomes 5p, 3q, 8q, and 17q are associated with malignant behavior (Figure 2*).

Traditional methods of karyotyping have enabled rough analysis of chromosomal aberrations, but are imprecise and low-throughput. To map chromosomal changes with superior precision, researchers have turned to oligonucleotide-based comparative genomic hybridization (DNA array-CGH) (Figure 3*). By DNA array-CGH analysis, it was found that benign (more commonly referred to as very low- to low-risk) GISTs had a mean number of 2.6 aberrations per sample; malignant primary GISTs had a mean number of 7.5 aberrations per tumor, whereas the mean number of aberrations per metastatic GIST was 9 (El-Rifai et al., 2000; Wozniak et al., 2007). Genes targeted by these chromosomal changes and their contribution to clinical progression of GISTs are only partially known.

Alteration in DNA copy number is one of the many ways in which gene expression and function of cancer cells may be modified. In the past, several efforts have been made to establish biologic differences at the levels of gene expression profiles according to tumor’s KIT/PDGFRA genotypes, their anatomic site of origin and histopathologic grade of malignancy (low-risk vs. intermediate vs. high-risk), based on the whole-genome expression profiling of heterogeneous cohorts of GISTs (Rubin et al., 2001; Antonescu et al., 2004; Ylipää et al., 2011). A variety of genes encoding oncogenes, tumor suppressors, proteins involved in cell 

![Figure 1](image1)

GIST progression is a multistep process that involves tumor initiation, progression, and metastasis. A malignant GIST develops as a result of an acquired mutation in KIT or PDGFRA & a series of sequential genomic abnormalities.

### Glossary

**GIST**: Gastrointestinal stromal tumor

**KIT**: Encoding the receptor tyrosine kinase KIT

**PDGFRA**: Encoding the receptor tyrosine kinase PDGFRA

**KIT/PDGFRA oncoprotein**

**Loss of chromosome 14 and 22**

**Gain of chromosome 9q, 10p, 15q, 19q, 1p, 9p, 13, 19q, 1p, 9p, 13, 19q, 1p, 9p, 15q, 19q, 1p, 9p, 13, 19q, 1p, 9p, 15q, 19q**

**Gain of 5p, 8q, 17q, 20q**

**Kit/Pdgfra oncogenic mutation**

**Loss of gain in 5p, 8q, 17q, 20q**

**Low-Risk (Benign)**

**High-Risk (Malignant)**

**Metastatic GIST**

**Array comparative genomic hybridization**: DNA array comparative genomic hybridization (DNA array-CGH) is an efficient approach to scanning the entire genome for alterations in DNA copy number.
was also statistically significant (p<0.001).

White and colleagues have provided a much better picture of which CML patients might benefit from a higher dose of Gleevec. Using a combination of OCT-1 activity, imatinib plasma levels and imatinib dose, they were able to demonstrate that those with low OCT-1 activity (2/3 of patients), adjusting dose for patients with low plasma levels could significantly improve results.

The findings of this study are important for CML patients, but also raise a few questions for the GIST community to consider as well. While OCT-1 activity levels were not correlated with MMR for all CML patients, they were a good predictor of outcomes for one particular subset of patients: those on a low dose of imatinib that had high levels of OCT-1 activity fared much better than those on the same dose with low levels of activity. For these patients, knowing the levels of OCT-1 activity is an important factor that, in the words of the researchers, “provides a valuable prognostic tool to determine the up-front dose of imatinib in newly diagnosed chronic phase chronic myeloid leukemia patients.” In summary, for CML patients, this test may become extremely important in the future.

The question then, is what about GIST patients? Would testing for OCT-1 activity levels be just as beneficial? Is there a similar relationship between these levels, Imatinib dose, and progression-free survival? What about the role of plasma levels for imatinib and OCT-1 activity? At this point, there are no definitive answers to these questions. While CML and GIST do have their similarities, there are of course differences as well, and it is possible that OCT-1 plays a different role in each disease.

One fundamental difference has to do with drugs available beyond the first line of treatment. CML pa-

---

**Did you See?**

Some of you may have seen this picture before, but we just couldn’t resist posting when LRG member Nina Johns forwarded it to us.

Nina found this while site seeing in Oregon during her first trip to see Dr. Blanke, when he was at Oregon Health & Science University.

She saw it as her husband passed by and yelled for him to stop. They backed up, turned around and she got a picture with the sign.

What a coincidence!

---

**Figure 1**


---

**Did you See?**

Some of you may have seen this picture before, but we just couldn’t resist posting when LRG member Nina Johns forwarded it to us.

Nina found this while site seeing in Oregon during her first trip to see Dr. Blanke, when he was at Oregon Health & Science University.

She saw it as her husband passed by and yelled for him to stop. They backed up, turned around and she got a picture with the sign.

What a coincidence!
cycle progressions, and proteins involved in the control of cell motility have been found to be aberrantly expressed and/or amplified in GISTs.

In most expression profiling studies in sarcomas, the purpose has been to identify new diagnostic markers or to obtain better understanding of sarcoma pathogenesis. Only a few studies to date have tried to correlate expression profiles with the outcome of the disease. Recently, using a new methodological approach, Dr. Fredric Chibon and co-workers from the Bergonie Institute (France) have performed integrated genomic and expression profiling analysis of a large set of different sarcoma types, including 32 GISTs (Chibon et al., 2010). By analysing expression profiles according to genome complexity (reflected by the number of chromosomal aberrations in a given tumour) and tumor’s histological grade (established by routine histopathological criteria), the researchers were able to identify a prognostic gene expression signature. This signature includes 67 genes involved with cell division (mitosis), chromosome management and, ultimately, genomic stability as a predictor of metastatic potential. The authors proposed the use of this system, which they termed CINSARC (Complexity Index in Sarcomas), as an adjunct to the current histologic grading system. Based on the system the tumors could be divided into two CINSARC classes of “good” or “poor” prognosis. The results were compelling as the authors showed that CINSARC is more sensitive in assigning risk group than currently used procedures and can be applied to many tumor types including GISTs. Subsequently, through the collaborative efforts between French and Belgian sarcoma groups, these results were confirmed and extended by a more recent study, in which DNA array-CGH and expression profiling analysis was performed on 67 primary untreated GISTs (Lagarde et al., 2011). As a result not only the value of CINSARC signatures was validated (Figure 4*) but also several important correlates were found. Firstly, the gene whose expression was most strongly associated with metastasis was AURKA (which maps to chromosome 20q), even though the AURKA locus was not amplified. Secondly, the deletion of the p16 (CDKN2A) and retinoblastoma (RB1) genes were identified, and these were mutually exclusive and likely causal events leading to increased AURKA and CINSARC gene expression, to chromosome rearrangement and ultimately to metastasis. In addition, the so-called Genomic Index that integrates the number and type of DNA copy number alterations was established. This index is a strong prognostic factor in GISTs (Figure 5*). The CINSARC class, level of AURKA expression and Genomic Index all outperform the currently used histopathologic grading system in determining the prognosis of patients with GISTs.

GISTs are the most frequent mesenchymal tumors of the gastrointestinal tract and are among the rare tumors to benefit from a targeted therapy. Thus, the development of a method for GIST prognostication has become essential for the proper clinical management of GIST patients, especially in the context of adjuvant treatment, where many patients are exposed to drug while only a small proportion will likely benefit from such treatment. In the past, many pathological criteria based on tumor site, tumor size, cell type, degree of necrosis and mitotic rate have been proposed for predicting the outcome of patients with GISTs. A consensus grading scheme based on tumor size and mitotic count was proposed by the US National Institutes of Health (NIH) in 2001 to estimate the prognosis.

Importantly, Genomic Index was able to predict metastatic outcome in GISTs in the intermediate-risk group of the AFIP (Miettinen) classification. The results obtained based on DNA isolated from frozen tumor tissue and tissue embedded in paraffin for routine histopathologic evaluation (FFPE block) gave identical results, indicating that array-CGH karyotyping is amenable to routine clinical use.
Cert. Long-time member and Pediatric GIST survivor, Jason DeLorenzo, who has always struggled with GIST complications, ran an entire marathon this year to support GIST research.

New or just arrived, I consider every GIST survivor my friend and I am immensely proud of all they have achieved.

Research

In 2011, the LRG made several strides in the search for a cure.

We sustained our support and participation in endeavors like the NIH Pediatric & Wildtype GIST Clinic which continues to make discoveries in the understanding of this rare subset of GIST.

We were honored to present a poster and a paper on the relationship between Gleevec dosage and long-term survival at the prestigious Connective Tissue Oncology Society (CTOS) conference in November. We’ve come a long way from a small group of dedicated patients looking for trends in treatments and practices.

This year, we also saw the first progress report of our D-Day initiative.

This research project was the result of years of knowledge building, and bringing together the best in their fields to consider and plan every next step. As I’ve said before, a perfect storm created this effort. The funding arrived just as costs for vital tests lowered and the research team had gained enough knowledge and resources to make a strong push for the cure.

I for one was terribly excited to see what they came up with and the results were better than I expected.

Our team identified several new mutations besides KIT in its Sequencing group; an important gene-critical for GIST cell survival- was identified by the Gene Knock-Down group, as well as more relevant targets and resistance factors;

Perhaps, it is more than preferring to look forward. Perhaps the brighter the future looks, the harder it is to look back.

When we do, we are reminded of how far we still need to go. We lost friends this year- people like Richard Palmer, Dan Cunningham, Rachel Tate and Butch Eller- who supported us as we supported them. It’s easy to let these heartbreaks discourage you and rob you of hope.

But in those moments, all I need do is look around at Anita Getler, who is celebrating her six-year cancerversary this month; Tim Mansfield, who has passed 17 years, Floyd Pothoven, Marina Symcox, Tania Stutman and Paula Vet-tel—Anita, my wife of 50 years, 18 of which have been spent living with GIST.

Devoted wife, mother & grandmother passes

DeLorenzo is tired but still smiling at the end of the marathon.

DeLorenzo is tired but still smiling at the end of the marathon.

Surviving in addition to her husband are a daughter, VaughnDe K. Peterson and her husband, Terry; two sons, Brack Kirk Smith, Jr. and his wife Sharon J. and Carl A. Smith; a sister, Kay Johnson; a brother, William H. Grahl, Jr. and his wife, Brenda; 6 Grandchildren, Stephanie Gorss, Matthew and Sarah Peterson, Cameron and Megan Smith and Kelsey Smith.

In addition to her parents, she was preceded in death by a brother-in-law, Leroy C. Johnson.

Condolences may be expressed online at www.robinsonfuneralhomes.com.

Mark your calendars!

- The GIST Benefit Ball, hosted by Julie Cramer (Page 5) will be held on February 18.
- The next Cook County meeting will be held on March 3 from 1-3 PM. Please email Jim Hughes at j Hughes43@comcast.net for details.
- The LRG researchers are meeting in Belgium, March 18-23.
- Harness a Cure” (Page 7) is set for March 25. Details coming soon!
- Alianza GIST’s next meeting is scheduled for March 26-28. Email srathschild@liferaftgroup.org for info.
- GIST Day of Learning (Page 3) in Miami, Fl. Will be held on May 19. Contact the LRG for information.
- Look out for Life Fest 2012 in Las Vegas in the beginning of November. More details to come!
mg (after discovering an exon 9 mutation) through perseverance and donations from generous friends and patients (You can read more about this story in our April 2010 newsletter issue).

Eventually Vera was shifted to Sutent and then on to other drugs when the progression continued. Though she tried tremendously to get ahead the disease, Vera passed away peacefully on December 17, 2011.

It may seem as if for the duration of her illness, she knew only struggle and financial hardship, and that may be true. However, through the exhaustive endeavors of Vera and her family, collaboration with the CML community, talks with health authorities and a huge media campaign to create more awareness about access, Gleevec was put on the treatment reimbursement list and future GIST & CML patients have been left with the gift of access to a lifesaving drug.

What Vera and her devoted son, Dejan inspired in Macedonian GISTers and non-GISTers alike was nothing short of a miracle.

“The GIST & CML communities in Macedonia really came together. What they were able to do was an inspiration to patient advocates everywhere,” said LRG Global Relations Director, Sara Rothschild, who worked with closely with Dejan on this campaign, “The passion and the steadfastness that Dejan had for saving his mother motivated me as I continued working with the global GIST community.”

Dejan, too, is not done yet, “We have another fight ahead of us that will be much harder, putting Sutent on the reimbursement list. We have already started [working] together with RCC patients that are also affected by lack of access to Sutent. The fight goes on.”

Rafael Becerra was never highlighted in our newsletter, but he was well known in the GIST community and widely loved by all who knew him.

He started out like many GIST patients, faced with a diagnosis they were not prepared for. After his initial surgery, he continued his normal life, but in his spare time he began to study his disease, to learn what treatments were available and how to manage the side-effects they produce. In a relatively short amount of time, Rafa, as he was known to his friends and colleagues, accomplished much.

In his comings and goings to treatment appointments, Rafa began to meet other people who had the same disease, like Rafael Vega. Together, they decided to create the Colombian GIST Foundation (www.fundaciongistcolombia.org ), for the purpose of educating and informing patients and medical providers and raising awareness about treatments and side-effects management.

Never tiring, “The Raefals” and

fixed paraffin-embedded samples. Genomic array-CGH profiling could therefore be a powerful tool to manage imatinib therapy for intermediate-risk GIST patients.

*Due to the length restrictions of a newsletter such as this, we were forced to remove some information from Dr. Debiec-Rychter’s article. You can find more figures and a full list of references on our E-News site, www.gistnews.org.
Ensuring That No One Has To Face GIST Alone — Newsletter of the Life Raft Group — December 2011 — PAGE 14

HAPPY CANCER-VERSARY TO ANITA GETLER!

This month, LRG member Anita Getler (pictured below with her grand-daughter Oriannah) will be celebrating two important days. Her birthday is on February 5, followed closely by her cancer-versary on February 14. Valentine’s Day & GIST? That doesn’t seem to go together, but Miss Anita never stops smiling...

“Wow! It's hard to believe all this time has passed since my diagnosis with GIST and I have been truly blessed to be cancer-free and dancing with NED for six years now! I even had the joy of another grandchild, Mariellah, born this past June….very thrilling for me and my family to celebrate another new life joining us! My wish is to find a cure for GIST and all other cancers this year so we can all relax a little bit, but in the meantime always live life to the fullest and enjoy each day!”

Congratulations Anita….and Happy Birthday!

OCT-1
From Page 10

Patients that don’t respond well to imatinib have second and third line drugs that are very effective for most patients. While GIST patients do have treatment options beyond imatinib, and they are effective for some patients, they are not as effective for as broad a group as with CML. Because of this, resistance is a bigger issue for GIST patients, who do not have as many broadly effective drugs beyond the first-line to fall back on, and for most patients, is extremely hard to overcome once it has developed. Thus, the best approach may be to try to prevent resistance before it happens, as opposed to trying to reverse it when it occurs. Further research into which patients need a higher dose (or plasma level) of imatinib is one of the most promising ways to prevent resistance, and this study may help provide some clues to help drive that research.

The only way to determine the role of OCT-1 is to conduct further research, both on GIST tumors, to get a general understanding of what role OCT-1 may play, and through clinical trials, to see if there is any correlation between these levels, plasma levels of imatinib, and increased survival among GIST patients. A collaborative effort may be the best approach, with GIST researchers working with their CML counterparts to augment existing research and help determine if additional research can be conducted that would directly benefit GIST patients.

Janice loved life & family

Janice Garrison Aubert, 76, of Spencer, died December 21, 2011. Born January 2, 1935 in Pond Creek to William and Maxine Garrison, Janice loved life and family, especially her grandchildren. Janice was preceded in death by her parents; sister, Billie Rarrick; and grandson, Mike Bastianelli. She is survived, by husband, Ray Aubert of Spencer; children: Nancy West of Coraopolis, PA; Don West of Oklahoma City; and Paul West of Dammam, Saudi Arabia; stepson, Marty Aubert of Oklahoma City; seven grandchildren and four great-grandchildren.

The family would like to thank Hospice Quality Care for their loving care during Janice's final weeks. In lieu of flowers, please send donations to The Life Raft Group, which is working to find a cure for G.I.S.T., a rare form of cancer, at 155 US Hwy. 46, Ste. 202, Wayne, NJ 07470, or www.liferaftgroup.org
inhabitants per year. In their investigation, the authors discovered a so-called mini-GIST in 2.9 percent of the cases studied, i.e. in 17 of 579 autopsies. This is still well below the rate of 20–30 percent that has been published by other authors in smaller-scale studies. Together with the extensive molecular genetic investigations, these findings provide important insights into the molecular mechanisms leading to GIST.

The jury was impressed not only by the indisputable quality of the work submitted but also by Prof. Dirnhofer’s commitment to the study of this rare disease. In the past seven years, he has published ten papers on this topic that are listed in Medline, eight of them containing original research. GIST is a sarcoma, a group of malignant tumors that occur in connective tissue, bones and muscles. As a non-profit organization, SAKK also conducts studies on such rare forms of cancer.

Film makers win Special Recognition Prize

A second award, the Special Recognition Prize, was conferred on Helga Meier Schnorf and Dr. Michael Montemurro of the GIST Group Switzerland for their documentary “Living with GIST”. “The film strikes a delicate balance between appealing to the emotions and conveying information and focuses on delivering a message about a difficult topic. It neither wrings the heartstrings and nor becomes bogged down in technical details. The film succeeds in maintaining this quality for 50 minutes,” said Urs Metzger on behalf of the jury. Using patient histories from real life, “Living with GIST” impressively illustrates the path from the correct diagnosis to therapy and dealing with the disease and with cancer. It also throws light on the worldwide network of patients and physicians and their cooperation across medical disciplines and in research. Yet the patient is always the focal point of the documentary.

“Living with GIST” won the EDI 2011 Silver Medal just a few days ago. EDI is the Swiss prize awarded to the best advertising, industrial and corporate films and is sponsored by the Swiss Federal Department of Home Affairs.

Show the LRG some love!

Valentine’s Day is coming up, a perfect time for your friends and family to show GISTers some love! Please send out your Holiday Fundraising Campaign note cards. All donations go directly to support patients & GIST research (You can read more about this year’s campaign on page 5).

You can also go to www.acureisinoureach.org, upload a photo (you and your sweetie, perhaps?) and tell the world what a cure would mean to you. Won’t you be our valentine?

The first steps towards finding a cure for GIST can start with you!

If you or your loved one has had their tumor removed, you are eligible to participate in the GIST Collaborative Tissue Bank (GCTB). As an added benefit, we also offer free mutational testing with participation. Contact the LRG at 973-837-9092 to learn about GCTB, and how you can help find a cure for GIST.
Ensuring That No One Has To Face GIST Alone — Newsletter of the Life Raft Group — December 2011

The Life Raft Group

Staff

- Executive Director
  - Norman Scherzer
  - Lisa Pereira
  - Jerry Call
- Program Director
  - Tricia McAleer
  - Sara Rothschild
  - Erin Kristoff
- Communications Director
  - Christine Schauburg
- Global Relations Director
  - Roberto Pazmino
- Development Director
  - Magda Sarnas
- Patient Registry
  - Peter Knox
  - Gale Kenny
- Special Projects
  - Matthew Mattioli
  - Diana Nieves
- Office Manager
  - Jennie Kim
- Program Coordinator
  - Janeen Ryan
- Administrative Director
  - William Sumas

Volunteers

- General Counsel
  - Jodi Merry
- Database Consultant
  - Maine
  - Jodi Merry
- Official Greeter
  - Maryland
  - Maura Emerson
- Latin America Liaison
  - Massachusetts
  - Eileen Rosenthal
- Clinical Trials Coordinator
  - Michigan
  - Sharon Boudreau
- Planner
  - Minnesota
  - Katie Campbell
- Media Mailing Distribution Asst.
  - Missouri
  - Dirk Niebaum
- Member Birthday Coordinator
  - Montana
  - Caroline Boudreau
- Special Projects Asst.
  - Nebraska
  - Sally Norton
- Science Team
  - Nevada
  - Erik Krauch
- Mark:
  - New Hampshire
  - Julie Thorne
-钉: New Jersey
  - Anita Getter
- Chuck Korte

Contact the LRG

155 US Highway 46, Ste 202
Wayne, NJ 07470
Phone: 973-837-9092
Fax: 973-837-9095
E-mail: liferaft@liferaftgroup.org

Board of Directors

- Executive Committee
  - Jerry Cudzil, President
  - Stan Bunn, Past President
  - Ray Montague, Secretary-Treasurer

- Norman Scherzer
- Roberto Pazmino
- Matthew Mattioli
- William Sumas

Life Raft regional chapters: Find your reps info at www.liferaftgroup.org/about_support_programs.html

- Alabama: Pat George
- Arizona: Janeen Ryan
- California: Ann Bridgewater
- Colorado: Dina Wiley
- Delaware: Cindy Bones
- Florida: Skip Ryan
- Georgia: Pat Lemeshka
- Idaho: Janet Conley
- Illinois: Tim Hughes
- Indiana: Robert Book
- Iowa: Barbara Kepple
- Louisiana: Jackie Welsh
- Maine: Jodi Merry
- Maryland: Maura Emerson
- Massachusetts: Eileen Rosenthal
- Michigan: Sharon Boudreau
- Minnesota: Katie Campbell
- Missouri: Dirk Niebaum
- Montana: Caroline Boudreau
- Nebraska: Sally Norton
- Nevada: Erik Krauch
- New Hampshire: Julie Thorne
- New Jersey: Anita Getter
- New York: Pat Bonda Swenson
- North Carolina: Chuck Korte
- Oklahoma: Bonnie Emerson
- Oregon: Maura Cesarini
- Pennsylvania: Ellen Rosenthal
- Rhode Island: Sharon Boudreau
- South Carolina: Katie Campbell
- Tennessee: Dirk Niebaum
- Texas: Sally Norton
- Utah: Erik Krauch
- Virginia: Julie Thorne
- Washington: Anita Getter
- Wisconsin: Pat Bonda Swenson

Life Raft country liaisons: Learn more about the Global GIST Network & find contact info for your rep at www.globalgist.org

- Argentina: Sandra Mesri
- Australia: Katharine Kimball
- Austria: Kris Heyman
- Belgium: Virginia Ossio
- Bulgaria: Stefan Mandov
- Brazil: Alexandre Sakano
- Canada: David Josephy
- Chile: Mirja Voutilainen
- China: Ruijia Mu
- Colombia: Rafael Vega
- Costa Rica: Michael Josephy
- Cyprus: George Constantino
- Czech Republic: Jan Pelouchová
- Dominican Rep.: Alejandro Miranda
- Ecuador: Estelle LeConte
- El Salvador: Markus Wartenberg
- Guatemala: George Constantino
- Honduras: Silvia Castillo de Armas
- Hungary: Xiomara Barrientos
- India: Tünde Kazda
- Indonesia: Paresh Majmudar
- Iran: Negar Amirfarhad
- Ireland: Carol Jones
- Israel: Avi Zigdon
- Italy: Anna Costato
- Japan: Sumito Nishidate
- Jordan: Mohammed Milhem
- Kenya: Francis Kariuki
- Kazakhstan: Dejan Kristevski
- Malaysia: Yong Choo Sian
- Mexico: Rodrigo Salas
- Myanmar: Marie Lagaluga
- Netherlands: Contactgroup GIST
- Nicaragua: Maria Teresa Ponce
- Nicaragua: Odd Andreas Tofeng
- Pakistan: Mohammad Shahid affique
- Peru: Eva Maria Ruiz de Castillo Yabar
- Puerto Rico: Stan Kulisz
- Romania: Gerardo Silva
- Russia: Simona Ene
- Samoa: Tanya Soldak
- Saudi Arabia: John Galuvao
- Scotland: Mohamed-Elbagir Ahmed
- Singapore: Helen Kombouzis
- South Africa: Robert Richardson
- South Korea: Jenny Aitken
- Spain: Changhoon Lee
- Sweden: Luis Herrero
- Sudan: Mohamed-Elbagir Ahmed
- Switzerland: Susanna Allgurin Neikter
- Turkey: Helga Schnorf
- Thailand: Kittikhun Pornpakakul
- U.K.: Haver Tanbay
- Uruguay: Judith Robinson
- Venezuela: Fabrizio Martiotta
- Vu: Maria Isabel Gómez

www.liferaftgroup.org
www.globalgist.org

Wayne, NJ 07470
Phone: 973-837-9092
Fax: 973-837-9095
E-mail: liferaft@liferaftgroup.org

www.globalgist.org

E-mail: liferaft@liferaftgroup.org