The Life Raft GROUP

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Ensuring no one has to face GIST alone

In Loving Memory: Mary Netting, Eric Krauch, Brian Poe, Jack Marstellar, Morgan Konnick Cronan

New Treatments for GIST: Finding the Right Combinations

By Michael Heinrich
LRG Research Team
Oregon Health and Science University

Prior to 2000, surgery was the only known effective treatment for advanced GIST. Notably, conventional sarcoma chemotherapy yielded response rates of less then 5 percent and very short time intervals before disease progression/treatment failure. In retrospect, these treatments were probably more harmful than helpful.

The GIST world changed dramatically with the discovery of KIT activating mutations in 1998. This discovery set the framework for clinical trials of imatinib (Gleevec) that began in 2000. Over the past 13 years, the use of KIT-targeted therapy has revolutionized the treatment of advanced GIST with high response rates, tolerable side effects, impressive palliative effects on tumor-associated symptoms like abdominal distention/pain, durable disease control, and improved overall survival.

Currently, overall survival is estimated to be in the range of five to seven years for patients with newly diagnosed metastatic GIST. In addition, a sizable minority of patients treated for metastatic GIST will experience durable disease control lasting more than a decade.

However, the majority of metastatic GIST

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Alianza GIST presents at Fifth International Cancer Control Congress

By Piga Fernandez
LRG Global Relations Coordinator

Alianza GIST had the opportunity to give two presentations at the Fifth International Cancer Control Congress (ICCC5) in Lima, Peru at the beginning of November. The ICCC5 is a global cancer control meeting with full participation of government and non-government cancer control practitioners, professionals, patients/advocates, researchers and volunteers committed to learning and sharing experiences, tactics, and best practices on cancer control.

The focus this year addressed the fol-

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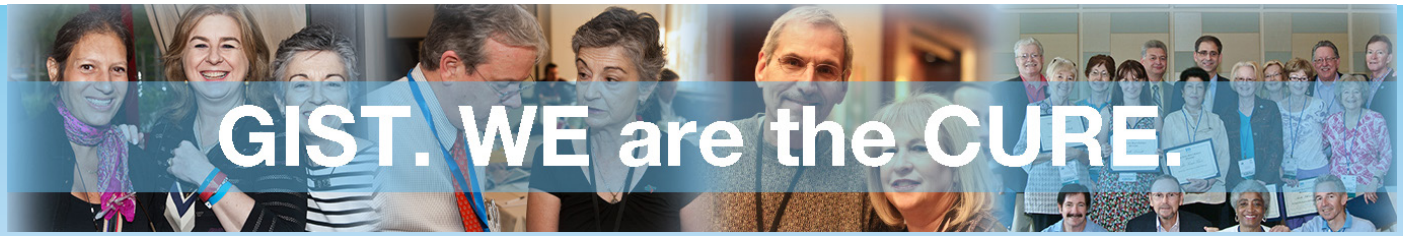

GIST. WE are the CURE. That is name of our holiday fundraising campaign that we just launched. We have switched from our traditional mailing to a new online fundraising system. We did this for many reasons, including, the cost of doing a mailing is so high, and this new way of fundraising allows us to reach so many more people and it helps to spead the word.

The LRG Research Team's pioneering research is in serious danger of grinding to a halt if new funds are not procured. Since institutions like the National Cancer Institute are funding just 4-5% of all research proposals, rare diseases like GIST are lost amongst the roughly 200 cancers competing for funding.

The Life Raft Group is the largest single contributor to GIST research in the world. We can't stop now. We have the cure in our sights. We are not slowing down.

Go to this link for more info and to join the campaign: bit.ly/WEaretheCURE

Treatment of small stomach GISTs

By Jerry Call
LRG Science Director

Some stomach GISTs smaller than 2 cm may pose more risk than previously thought according to a new report from China. In this small retrospective study[1] by Dr. Jianjun Yang and colleagues from Xijing Hospital of Digestive Diseases, the mitotic rate exceeded 5/50 High Power Field (HPF) in 14 of 63 cases (22.2%). Mitotic rate is used with tumor size and tumor location to determine the risk of recurrence after surgery for GIST patients. Several risk assessment methods also add tumor rupture as an additional high-risk factor. 5/50 HPF is frequently used as the dividing line between high and low risk GISTs, with most systems considering tumors of 5/50 HPF or less to be lower risk while tumors above 5/50 HPF are generally higher risk. An exception is the GIST nomogram which considers primary tumors of exactly 5/50 HPF to be of generally higher risk (a complete risk rating also depends on tumor size and location).

Current United States (NCCN) and European (ESMO) treatment guidelines allow for monitoring these tumors without surgery in some cases. For example, in the U.S., surgery is recommended for small tumors when an ultrasound (EUS) shows high-risk features[2]. For tumors without high-risk features, the U.S. guidelines say to "consider endoscopic surveillance at 6-12 month intervals." They note however, that "Endoscopic ultrasonography surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits."

In a study of 1,765 cases of GIST stomach tumors, the Armed Forces Institute of Pathology (AFIP), found 124 cases where the primary tumor was less than or equal to 2 cm (7%). In these small stomach tumors, tumor-related mortality was essentially zero, however, only eight of these tumors had a mitotic rate greater than 5/50 HPF. There was no recurrence information available for the Yang study, so despite the higher frequency of "high-mitotic rate" tumors, the results should be interpreted with caution.

Most patients in the Yang study presented with clinical symptoms despite the small tumor size. Symptoms included pain (29%), bleeding (8%) and discomfort (37%); 27 percent were asymptomatic.

Table 1

Tumor location	AFIP	Xijing Hospital
Fundus	124	28
Gastroesophageal junction/cardia	50	8 (cardia)
Upper gastric body	45	
Mid-body	48	
Distal gastric body	13	
Antrum	261	
Body		27
≤2 cm ≤5/50 HPF	116 (93.5%)	49 (78%)
≤2 cm >5/50 HPF	8 (6.5%)	14 (22%)
Symptomatic		46 (73%)

Some questions about small stomach GISTs remain. Dr. Heikki Joensuu, the principal investigator of the one year versus three year adjuvant imatinib trial, has written a brief communication to the Lancet journal about this question (due out in a few weeks). We asked Dr. Joensuu these questions:

1. How many patients with small gastric GISTs are symptomatic?

Dr. Joensuu: "This percentage depends on the size, but the great majority are unsymptomatic. The most common symptom is anemia."

2. Should symptomatic patients have surgery?

Dr. Joensuu: "-In my opinion yes, unless there are co-morbidites or risks related to surgery."

3. Should patients with small tumors in the cardia consider surgery and/or should location within the stomach be considered when deciding on surgery?

Dr. Joensuu: "I am not convinced about the location in the stomach yet. Mitotic count is probably a more important parameter."

4. Do biopsy procedures (when surgery is not performed) used for small stomach GISTs accurately assess mitotic rate (does a needle or small sample size hit the most mitotically active part of the tumor)?

Dr. Joensuu: "I do not think mitotic count can ever be regarded accurate, since there are differences between pathologists in identification of the mitotic figures, the fields-of-views of the microscopes vary, there are sampling variations, and fixation variations. Yet, perhaps paradoxically, mitotic counting is still the best prognostic factor we have. Using a single cut-off value (5 mitoses/50 HPFs) does not make much sense, since the mitotic count is clearly a continuous variable, and prognosis does not change abruptly from good too bad at five mitoses/50 HPFs. I prefer to use the continuous scales for prognostication."

This article pertains to small stomach tumors. Small tumors located in a different organ may have different risk criteria. In particular, high mitotic rate is more common in small rectal GISTs and many of these may have a high risk of recurrence (Miettinen et al.).

[1] Yang, J. et al. Surgical resection should be taken into consideration for the treatment of small gastric gastrointestinal stromal tumors. World Journal of Surgical Oncology 11, 273 (2013)

[2] Possible high-risk EUS features include irregular border, cystic spaces, ulceration, echogenic foci and heterogeneity.

Reasons why GISTer's are on no treatment

By Magdalena Sarnas
LRG Patient Registry Supervisor

One of the frequently asked questions from the GIST Community is "Why are there some GIST patients who do not take any medication to treat GIST?" The assumption is made that there a number of individuals who have a low risk of recurrence and don't need to take Gleevec, while this is true, there are a multitude of other reasons why patients are not taking Gleevec or any drug to treat GIST.

We will present two different views of this data. For the first, we looked at all 377 living patients that are not on treatment. This was particularly helpful for looking at risk and mutational status as decision points for treatment or no treatment. In the second analysis, we wanted to look at other reasons, including what patients were telling us the reasons were. For this analysis, we looked at a sub-set of 235 cases with the most complete data.

Data from all living LRG registry patients

When looking at the data, regardless of any patient-supplied comments, an interesting pattern emerges. It becomes clear that two things have a heavy influence in whether or not a patient is on no treatment. The first is their disease stage including their risk of a recurrence. In keeping with current guidelines, such as NCCN and ESMO, lower risk patients (including intermediate risk) are on no treatment far more often than high risk or metastatic patients (table 1).

Table 1 – Last reported treatments of living patients from the LRG registry based by stage/risk category

Risk	Ablation	Medication	No Treatment	Other	Radiation	Surgery	(blank)	Grand Total
Frankly malignant	2	150	29 (14%)	6		20		207
High risk	1	241	119 (30%)	6	1	30	1	399
Intermediate risk		15	27 (60%)			3		45
Low risk	1	14	43 (72%)			2		60
Unknown	1	193	154 (41%)	5		17	3	373
Very low risk			5 (83%)			1		6
Grand Total	**5**	**613**	**377 (35%)**	**17**	**1**	**73**	**4**	**1090**

We took a closer look at the data to help understand what those reasons may be. Living LRG registry members were analyzed that listed their most recent status as no treatment. This data was extracted from the LRG's Registry on October 7, 2013. The Modified National Institute of Health (NIH) Method was used to calculate risk. There were some records that did not provide complete diagnostic information to calculate this figure and/or did not provide us enough information to state a concrete reason why treatment was either halted or the patient was not taking a drug. It is important to also mention that patients receiving no drug treatment include patients who have been disease-free and patients that have had a recurrence of disease. It should be noted that, in general, patients in the LRG registry form a higher risk group than the entire GIST population (based on comparisons to population-based studies).

The second thing that becomes apparent is that mutational status also affects the decision to be on medication/treatment (table 2). Patients with PDGFRA mutations and wildtype GIST are much less likely to be on active treatment than other patients. The PDGFRA data is probably heavily influenced by PDGFRA D842V patients, which make up two thirds of PDGFRA patients and are non-responsive to most current treatments. Of 53 living patients classified as "pediatric or likely pediatric" (forming much of the wildtype GIST group), 32 (60%) reported no treatment at last report. In comparison, 345 of 1037 (33%) living patients classified as non-pediatric reported no treatment at last report.

Table 2- Last reported treatment of living patients from the LRG registry based on mutation

Mutation	Ablation	Medication	No Treatment	Other	Radiation	Surgery	Blank	Total
KIT	1	233	63 (19%)	8		29	1	335
PDGFRA		7	29 (78%)			1		37
SDHA		1						1
SDHB		1	3 (75%)					4
SDHC			1 (50%)	1				2
SDHD			1 (100%)					1
Unknown	4	343	244 (38%)	7	1	37	3	639
Wildtype		28	36 (51%)	1		6		71
Grand Total	**5**	**613**	**377 (35%)**	**17**	**1**	**73**	**4**	**1090**

What Patients Reported

When we focused in on the 235 records with the most complete data (including anecdotal comments) we found ten of the most common reasons that a patient is not taking drug or other treatment to treat GIST. There are some records that had compounding reasons listed for not taking medication.

Summary

In summary, there are many reasons that GIST patients may not be on treatment. These include: low risk of a recurrence, not on treatment after adjuvant Gleevec, no treatment influenced by a non-responsive or less responsive mutation type, family planning/pregnancy, end of life/hospice, intolerance to medications and stopped GIST treatment to treat another condition (such as a secondary cancer).

For deceased patients, 50 (10%) reported no treatment at last report and 26 reported hospice. When combined, this represents 15 percent of patients reporting no treatment at the end of life.

Please feel free to email me with your questions regarding this analysis and if you have suggestions for other statistical observations that can be made from the LRG Patient Registry.
msarnas@liferaftgroup.org

To view the entire article please see the online version.

Table 3 - Why Patients are not on treatment

Reasons	Grand Total
No treatment after Adjuvant Therapy (watchful waiting)	**60**
After 1 Year Adjuvant	35
After 3-5 Years Adjuvant	**11**
1 Year Adjuvant**Treating other condition	1
Clinical trial ended - 0-1 year on treatment	1
Doctor Initiated - Modified Adjuvant Therapy	12
Unknown	**38**
Low Risk	**34**
Low Risk	27
Very low risk	2
Low Risk and Financial reason	1
Doctor Initiated - Classified as Low Risk	4
Other	**19**
Shared Decision	**18**
Patient Initiated Decision	14
Doctor Initiated - Unknown Reason	4
Side Effects	**23**
Surgery	**15**
Treating another condition	**13**
Mutation (as the reason *stated* by the patient)	**11**
Placebo	**4**
Grand Total	**235**

IRBs and the LRG Patient Registry

By Roberto Pazmino
LRG Admin Director

Institutional Review Boards (IRBs) are the core of the well-established U.S. system for the protection of human research participants. IRBs were initially created to provide independent review of research conducted by researchers at their own institutions, impartial assessment of the ethical acceptability of proposed research, and a check on investigators' interests.

Under FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

The purpose of IRB review is to assure that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human subjects of research.

What is the purpose of the LRG Patient Registry?

Patients and their families or caregivers may choose to participate in one or any number of LRG sponsored activities, one of which is the LRG Patient Registry. The LRG Patient Registry's roots started in late 2000 when members of an online listserv community began sharing information about the first clinical trial with Gleevec for GIST patients. The software used to record data has gone through several evolutions, including a change from Excel to Microsoft Access. Currently the data is stored in Microsoft Access and shortly we will release a secure online version.

The purpose of the LRG Patient Registry is to collect and store medical information and other information from individuals with GIST. Information from patients in this registry will be used for medical research to better understand GIST. Scientists studying GIST need more accurate, real-world information to understand how the disease affects people.

Data from the LRG Patient Registry has been and will continue to be used to provide real-world information about GIST patients. This information includes implementation rates of suggested testing such as mutational testing rates, drug plasma testing, off-label and clinical trial drug usage, and how different factors affect survival (such as mutation, age, gender, GIST type, mutational testing, etc.). The goals include comparing real world usage to existing guidelines, generating hypotheses for testing using more rigorous methods (such as clinical trials) and providing demographic information (such as variations in gender ratios by age, mutation type by primary tumor site, etc.). This data is published using various types of media including, but not limited to, medical journals and medical conferences.

What does it mean to the patient that LRG Patient Registry is IRB approved?

The mission of an IRB is to ensure the protection, safety, and welfare of human subjects (study participants).

Having an IRB approval means that an appropriately constituted research ethics board certified that they have reviewed every single step in the LRG Patient Registry Protocol and have found it ethical and privacy compliant, the study does not involve any physical risk to the patient and it may help researchers understand GIST better.

IRBs ensure that research protocols involving human subjects are ethical and that the rights of participants are protected, IRBs evaluate the following:

- The nature and purpose of the research;
- Proposed procedures involving human subjects;
- Risks or harms to the subjects - (including physical, psychological, sociological, economic, and legal);
- Benefits;
- Risk/benefit relationship;
- Subject population;
- Subject recruitment;
- Process of obtaining informed consent;
- Research data processing and storage; and
- Need and frame for IRB follow-up.

Any participant of the LRG Patient Registry needs to consent; they need to not only sign the form, but also understand the consent process, once the consent is signed, the person is considered enrolled in the study.

Who can I talk to about this?

If you have any questions, do not hesitate to contact the principal investigator or any study staff.

Study Title: Life Raft Group GIST Registry Protocol
Study #: LRG2013PR112
Sponsor: Life Raft Group, Inc.
Privacy Officer: Roger Campbell
Quality Control Officer / Co-Investigator: Jerry Call
Principal Investigator: Roberto Pazmino (rpazmino@liferaftgroup.org)

Patient Registry Research Team:
- Magda Sarnas – Patient Registry Supervisor
- Michelle Durborow – Patient Registry Coordinator
- Janeen Ryan – Outreach Coordinator

Caregiver support group in Illinois

By Janeen Ryan and Marlene Nei
LRG Outreach Coordinator
Illinois Caregiver Support Group Leader

After her husband Bill was diagnosed with GIST in November 2010, Marlene and Bill entered the frightening and confusing world of doctors, hospitals, treatments and uncertainty. Bill's oncologist recommended they reach out to The Life Raft Group, and in January 2011 Marlene did just that and found the support and encouragement they had been looking for.

LRG: Marlene, what brought you to the LRG?

Marlene: My husband's GIST diagnosis and surgery was in November 2010, and his oncologist recommended the LRG website.

LRG: What experience led you to start a caregiver support group?

Marlene: The LRG has a family support group that meets in the Chicago area 3 or 4 times a year for the GIST patients, family and friends. As a caregiver, and knowing from conversations with other caregivers, I felt there was a definite need for an LRG Caregiver Support Group where we can be open in our comments, feelings and thoughts about us, the caregiver. The patient has a wonderful support system (doctors, nurses, family, caregivers, support groups), but us caregivers need a support system strictly for ourselves. We need one where we can speak openly and honestly from a caregiver's perspective.

LRG: What is your hope for other caregivers?

Marlene: It's amazing to me how quickly we have formed a bond with one another in the group. We know we aren't alone and we aren't the only ones having scary thoughts and feelings about our loved ones, ourselves or our family and friends. If a caregiver needs a smile, a hand to hold, someone to listen, a shoulder to lean on, or whatever, whenever, my hope for all is that we will be there for one another. I can't make the GIST go away, but when I see the men and women talking up a storm, eating cookies and laughing 40 minutes after a meeting was supposed to end, it makes my heart feel good and I hope it makes the hearts of the other caregivers feel the same way.

LRG: What are some examples of how a caregiver can cope more easily in their situation?

Marlene: It's important to take care of yourself, the caregiver. If you don't, and something happens to you, who will be there to take over all you do?

Don't be a martyr or be afraid to ask for help. I've seen instances where the caregiver resents that no one helps, yet they never asked for any help. In some cases, when help was offered, the caregiver declined.

Have someone or some place to turn to when you need it, such as a family member, a friend, a therapist, clergy or a support group. Someone or some place to relax, talk if you want, laugh, cry or just sit and listen. The Wellness Place, where our LRG Caregiver Support meetings are held, offers a wonderful variety of free programs for the caregiver: counseling sessions, yoga, massage therapy, exercise and more. Programs are offered both during the day and evening, all with the intent of helping us to cope more easily in our own, individual situation.

The Life Raft Group Caregiver Support Group is held every other month at The Wellness Place in Palatine, Illinois. They give us the space and opportunity to meet for a few hours on a Sunday morning to have the time for ourselves to talk frankly, ask questions, give our perspectives and share our thoughts and feelings with one another.

If you are interested in attending the LRG Caregiver Support Group or starting one of your own, please contact Marlene Nei at marlenenei25@gmail.com or write The Life Raft Group at liferaft@liferaftgroup.org

Mo Collins, comedian and actress, visits the LRG office

Recently, comedienne and actress Mo Collins visited the LRG office while in the area for a Novartis-sponsored GIST webinar.

Mo discussed upcoming events and research with the LRG team. A lot of information and laughter was shared.

Calendar

GDOL Miami
Early 2014

Poker for Hope - Las Vegas
May 17th 2014

Wish Lantern Festival - Worldwide
June 14th 2014

Life Fest 2014 - New Jersey
November 7th - 9th 2014

The Life Raft Group Attends 18th Annual CTOS Meeting in NYC

The Connective Tissue Oncology Society

By Pete Knox
LRG Director of Strategic Planning

From October 30th to November 2nd the Life Raft Group staff members attended the annual Connective Tissue Oncology Society Meeting in New York City. In addition to a number of presentations relevant to GIST, the LRG also took part in some very significant meetings with some of the world's leading GIST experts.

Perhaps the highlight of the meeting from a GIST perspective was the GIST presentation session that took place Saturday afternoon. The session featured a number of relevant presentations:

The role of ABL1 in the therapeutic response of GIST cells to imatinib mesylate - Dr. Anette Duensing of the University of Pittsburgh, who is a member of the LRG Research Team, did this presentation. She noted that imatinib inhibits both KIT and ABL1, but inactivation of ABL1 in turn activates PI3K, which makes imatinib less effective. The implication of the study was that in order to make future therapies that are more effective for GIST, it would be best to develop a KIT inhibitor that does not also inhibit ABL1.

Long-term analysis of a phase III randomized, intergroup, international trial assessing the clinical activity of imatinib at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) – Dr. Paolo Casali of the Istituto Nazionale dei Tumori in Milan, Italy, conducted this presentation. The presentation reported on a long-term study (median follow-up = 10.9 years) comparing patients with advanced disease on 400 mg of imatinib with those on 800 mg. Patients in the 400 mg arm were allowed to cross over into the 800 mg arm if they had progression. The intent of the study was to determine what prognostic factors existed for GIST patients. While dosage was not found to be a statistically significant factor, KIT mutational status (mutations other than exon 11 had worse outcomes) and diameter of the largest tumor (larger tumors had worse outcomes) were significant. When summing up the data, Dr. Casali cautioned, however, that, "We may not be looking at the whole curve, but instead just the top tail of it." He implied that perhaps the patients in this study may not be completely representative of all GIST patients.

Tolerability and anti-tumor activity of the PI3K/MTOR inhibitor GDC-0980 in patients (PTS) with GIST and other SARCOMAS on two phase I studies – Dr. Andrew Wagner of Dana-Farber conducted this presentation that examined a drug from Genentech. This early study examined different dosage schedules (daily and weekly) and levels (2-70 mg daily, 6-200 mg weekly) in an attempt to assess safety and tolerability, PK values, and anti-tumor activity. A number of different sarcomas were featured in the study, including 11 patients with GIST. The study found that the drug was well tolerated in GIST patients, and patients did have disease control greater than those on placebo. The authors believe that this compound warrants further study in GIST patients.

Interim analysis of SARC022, a phase II study of Linsitinib in pediatric and adult wild type (WT) gastrointestinal stromal tumors) – This presentation, conducted by Dr. Margaret von Mehren of Fox Chase Cancer Center in Philadelphia, reported on the ongoing trial for linsitinib, a drug aimed at pediatric and wild type patients. The study met its first stage accrual target of 20 patients (12 female, 8 male), and per the authors, "demonstrates that studies evaluating agents in Wild-Type GIST can be performed." The drug seemed to be well tolerated, and 55 percent of the patients in the trial had stable disease six months or longer at the time data was collected. As the trial is ongoing, we will be sure to report further results when they are released.

Dr. Jon Trent of Sylvester Cancer Center in Miami was the discussant and summarized all of the presentations quite well. He pointed out that they complemented each other by showing that there are a number of different forms of GIST that vary by mutation, exon, and expression of particular factors like IGF-1R, and that this shows us that these different forms of the disease need to be handled differently in regards to specific drugs and dosage levels.

In addition to the presentations, the LRG had a number of meetings with key GIST experts. Drs. Jon Trent of the U.S., Peter Reichardt of Germany, Matias Chacon of Argentina, and Yoon-Koo Kang of South Korea all met with the LRG to discuss various ongoing projects. All of these doctors also were confirmed as the inaugural members of the LRG's GIST Medical Team – a group of experts throughout the world that the LRG will consult with on various topics related to GIST. In addition, each of these doctors confirmed their participation in the GIST Cancer Journal, the first scholarly journal devoted solely to GIST, which will be released in the coming months. Along with meeting with the GIST Medical Team, the LRG also met with Dr. Lee Helman of the NIH to discuss a project designed to help our pediatric patients. Dr. Helman also updated us, telling us that the term "pediatric GIST" is no longer being used, but has instead officially been changed to "SDH-deficient GIST."

Our final meeting was with two members of the LRG Research Team, who updated us on their research progress. Keep an eye out in the coming months, when we will further update you not only on their progress, but also that of the rest of the research team, and how we can help them continue that progress.

All in all, this year's CTOS meeting was a very productive one for the LRG. Watch for news from us in the months ahead where we will update you on a number of new projects we are currently working on, and also on any updates on the research presented at CTOS and elsewhere.

Make sure to like us on Facebook and follow us on Twitter to get the latest updates about Life Fest 2014 in NJ.

fb.com/liferaftgroup

twitter.com/liferaftgroup

Kie Go Turns Knowledge Into Action

By Kei Go
LRG Singapore Representative

In early 2012, I was having gastric discomfort, so I took over-the-counter medication and it seemed to feel better. But as the days passed, the pain got worse, so after a few months I made an appointment and finally went to see a doctor. During his examination, the doctor suspected that my liver was enlarged and recommended that we immediately go to the hospital for more tests. That was how we found out that I had GIST.

The beginning of our journey as a GIST patient was not an easy one. Even the professionals did not seem to have a good knowledge of GIST. Resources on GIST were hard to come by in Singapore; the national cancer center support group does not have a GIST or sarcoma group. We were lucky to find the Life Raft Group online, and reading the discussions daily

really helped us learn more about what we were dealing with.

Since GIST is a rare type of cancer, the treatment and the needs as a patient seemed to be very different from other cancers. The discussion we had on Skype with Janeen Ryan gave us a better understanding of GIST and the side effects of Gleevec. Furthermore, reading what everyone shared online was a great benefit. Knowing that there are so many GIST patients in the same position as me, on Gleevec, and surviving for many years helped to give me hope.

Through our own experience, we realized that GIST patients in Singapore have very limited resources locally. If we had so much trouble looking for information and assistance, there must be other people that have the same issue. So we decided to contact the Singapore National Cancer Center Support Group and asked them if we can help in forming a local Life Raft Group GIST support group for patients in Singapore. We met with them and discussed the unique issues facing GIST patients and have agreed to serve as the Life Raft Group Singapore Group Leaders. We look forward to meeting others in Singapore and providing assistance where we can.

Kie Go and Yasuyo Arai can be reached at **gkieking@gmail.com** & **su_dj@hotmail.com**

Research, from Page 1

patients treated with imatinib will experience disease progression within three years of starting treatment. Molecular analyses of drug-resistant tumors have identified acquired (secondary) kinase mutations as the cause of drug resistance in most cases. Imatinib, and similar drugs, need to bind to KIT in order to block its activity.

Secondary mutations prevent imatinib (or other drugs) from binding correctly (or even at all). This can be thought of in terms of a lock and key model, where the lock is the KIT protein and the key represents imatinib. If you change the lock, the key will no longer work. Secondary mutations are the cause of most cases of drug-resistant KIT exon-11 mutant GIST. The mechanisms of resistance in patients whose GIST lack KIT or PDGFRA mutations are more complicated and varied, due to the fact that this subset of GIST is actually composed of at least 10 different types of tumors.

"Your LRG Research Team is working hard to identify these combinations. Due to the close collaboration of our group, new findings are freely shared, leading to more rapid progress."

The success of front-line treatment with imatinib, coupled with the discovery that many imatinib-resistant GIST are still "addicted" to KIT, lead to clinical studies of other KIT inhibitors. As of 2013, sunitinib and regorafenib have been clinically validated and approved by health regulatory authorities (e.g. the U.S. Food and Drug Administration) for the treatment of drug-resistant metastatic GIST.

Once the initial results with imatinib were known, some investigators wondered whether or not continuous treatment was needed to maintain disease control. Historically, patients with advanced cancer have been treated intermittently rather than continuously. This was due in part to the toxicity of continuous chemotherapy treatment, and also because there was no evidence that continuous treatment was better than intermittent treatment. The prevailing cancer treatment paradigm prior to imatinib was chemotherapy treatment to cure patients with minimal disease after surgery (e.g. colon or breast cancer) or to cure patients with highly chemotherapy-sensitive diseases like Hodgkin lymphoma. For most patients with metastatic cancer, chemotherapy was used to halt disease progression and/or extend survival and was given when needed but not continuously.

To determine whether continuous imatinib was needed for optimal GIST disease control, investigators from the French Sarcoma Group randomized long-term responders (1, 3, or 5 years) to either continue imatinib treatment or to stop and undergo close surveillance. The primary endpoint of this study was to determine the effect of stopping vs. continuing treatment on disease control. The results for patients randomized after three years of imatinib treatment are shown in figure 1.(1) As is clearly seen by the separation of the curves, almost all patients who stopped treatment had disease growth within one to two years. In contrast, patients who continued treatment had a much slower rate of disease growth. These data support the need for continuous imatinib treatment and indicate that long-term disease control does not mean that we have eliminated all GIST cells, as tumors start growing within months of stopping treatment.

The two curves from this study identify two different tumor states: 1) the rapid relapse (tumor progression) of the patients who stop treatment is due to persistent disease; and 2) the slow loss of tumor control over time for the patients who continue imatinib-treatment is due to the emergence of resistant disease.

As noted above, drug resistance can arise from multiple mechanisms, most commonly from the development of secondary KIT mutations. In contrast, persistent disease reflects a population of cells whose growth is inhibited by imatinib, leading to some form of cellular "hibernation." These hibernating cells can survive continuous imatinib treatment but, over time, these same cells may develop additional mutations and evolve into drug resistant tumors.

Although the mechanisms underlying these two cellular states are different, they share one central shared feature: in both cases, the clinical attempt to block KIT signaling is insufficient to induce cellular death. In the case of persistent disease, even near-total inhibition of KIT does not cause cellular death, due to the existence of other survival mechanisms. In the case of resistant disease, minimal or sub-optimal KIT inhibition by available drugs like imatinib, sunitinib, or regorafenib is insufficient to cause tumor cell death and in some cases does not even slow the growth of these tumors.

Theoretically, more potent KIT inhibitors with an enhanced spectrum of activity against different resistance mutations would improve upon current treatments, especially in the case of resistant disease. However, even this approach will not solve the problem of persistent disease.

As previously discussed in this forum, many GIST scientists and clinicians feel that a joint solution to treating persistent, as well as resistant, disease is the use of combination treatments. Such an approach would exploit the known benefits of inhibiting KIT enzyme activity and add in the effects of blocking a separate critical survival pathway. Theoretically, some form of combination therapy might eradicate persistent disease, thereby leading to a cure. Finding the right combination to treat GIST has become the goal of many GIST scientists, including all the members of the Life Raft Group Research Team.

To identify targets to include in a combination treatment, one can use either a biased or an unbiased target identification approach. In the biased approach, we use existing knowledge to suggest new drug targets. This approach is exemplified by Dr. Rubin's recent commentary in the June 2013 newsletter. Notably, signaling from KIT tends to be transmitted via two main pathways known as PI3K and MAPK. Both pathways are known to be important to GIST growth and survival and both pathways are activated by KIT signaling. These two pathways are analogous to two main highways that lead out of a large city. If there is a traffic jam on one highway, one can still leave the city by using the other. In the case of GIST, cells manage to figure out a way to restore signaling through one or both pathways.

In his commentary, Dr. Rubin presented evidence that a triple combination of a KIT inhibitor + MAPK pathway inhibitor + a PI3K pathway inhibitor was much more effective than single or dual drug treatment. This result highlights the advantages of using a biased approach: scientists can focus on what is already known about GIST biology and immediately proceed to laboratory studies of combination treatments. However, this approach also has limitations: 1) we have not discovered

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lowing areas: improving and sustaining prevention; mobilizing all of society for effective cancer control; using data and evidence to improve population health; improving integrated approaches to cancer treatment and care; and integrating research, practice and policy priorities to improve cancer control. The congress this year coincided with the anniversary of "Plan Esperanza" ("Plan Hope"), a Peruvian government initiative that seeks to improve comprehensive cancer care and access to oncology services in Peru. The Peruvian President, Ollanta Humala, was featured in the opening ceremony and emphasized the need to create a culture of prevention and promotion of healthy habits. "I think we should all agree that the best time to fight cancer is in the preventive stage" he said.

Addressing an audience of international health experts, President Humala noted the efforts the Peruvian government has done in lowering cancer rates in Peru and thanked the "Plan Esperanza" for the big step it has achieved in providing free coverage to patients fighting against cancer.

Health authorities such as Clarissa F. Etienne, Director of the Pan American Health Organization (PAHO) and Midori De Habich, Peruvian Minister of Health, also participated in the opening session of the Congress.

The Life Raft Group and Alianza GIST participated in two sessions. The first one: "Mobilizing all of Society for Effective Cancer Control" was aimed to understand and strengthen a response from the society to the growing challenges of cancer by achieving a better impact in public policy while informing and engaging all of society. In this framework, we participated in the workshop: "Integration across regions and sectors", in which we presented: "Alianza GIST: Building a Coalition in Latin America". We explained how Alianza GIST was formed, highlighting the importance of the LRG, and its scientific knowledge, technology and resources such as Patient Registry and Tissue Bank. These resources help Alianza GIST achieve its main goal—the survival of GIST patients in Latin America.

Our second participation was in the session: "Improving Integrated Approaches to Cancer Treatment and Care". This session addressed how to highlight integrated approaches to interventional treatment, management and care of patients based on global or Latin American experiences. Alianza GIST presented in the workshop entitled "Mobilizing Communities," which explored ways in which organizations build supportive networks and strengthen advocacy efforts, and reinforce efforts in education and training. Alianza GIST presented "The Rare Disease Movement: The Importance of Collaboration between Academia and Civil Society", in which we explained how Alianza GIST partnered with Instituto Tecnologico de Monterrey, Fundación GIST Mexico and The Life Raft Group, using an inter–sectoral approach to cancer control. This online GIST CME training initiative has been replicated in other countries in Latin America to teach physicians and medical students about diagnosis, treatment and management of GIST.

In the Session about "Improving Population Health: Using Data and Evidence to Support Policies and Programs", we were able to confirm the importance of our Patient Registry Program, hearing international health experts talking about the importance of improving the health of the population, and how can the data be translated into evidence based practice guidelines that health care providers can use to influence health seeking behaviors. All of this confirmed how proud we are about Alianza GIST and the Life Raft Group accomplishments with the Patient Registry.

Other Alianza GIST members participated in this Congress, such as Eva María Ruiz de Castilla, from Esperantra (patient advocacy group in Peru) who was co-chair in the plenary session: Mobilizing all of Society for Effective Cancer Control, in the Workshop "Building Social Movement", and a panelist in the Plenary Session: "Integrating Research, Practice and Policy Priorities to Improve Cancer Control" featuring "The political science perspective: How is policy influenced beyond the health perspective".

Maurice Mayrides, Alianza GIST representative in Peru and Director of Esperantra was also present at the congress with a poster which analyzed the patients' power in Peru.

The closing ceremony featured The First Lady of Peru: Mrs. Nadine Heredia and Dr. Simon Sutcliffe, President of International Cancer Control Congress Association (ICCCA). Both who gave inspiring messages of how we can take the information shared at this Congress and apply it to our global work for the cancer community.

This was an incredible opportunity to participate in this congress and to have Alianza GIST and The Life Raft Group be able to showcase their work with the global cancer community. It also gave us a better understanding of public policy issues and the importance of working with different stakeholders to achieve change. It demonstrated how important it is to collaborate with key partners to achieve our goal of improving survival of the GIST community.

Morgan Konnick Cronan, loses battle against GIST, 28

Morgan Konnick Cronan, 28, formerly of Vestal and most currently of South Portland, ME, passed away peacefully after a long and courageous battle with cancer on October 19, 2013 at Our Lady of Lourdes Hospital in Binghamton.

She was predeceased by her grandfathers, Claude A. Crawford Jr. and Joseph Konnick. She is survived by her husband and best friend, John J. Cronan III; her loving parents, Randy and Corinne (Crawford) Konnick of Vestal; her brother, Corey J. Konnick of Beverly, MA; two grandmothers, Patricia J. Crawford of Clermont, FL and Elizabeth M. Konnick of Johnson City; one great-grandmother, Gertrude Engates of Binghamton; her in-laws, Dr. and Mrs. John (Laurie) Cronan Jr. of Barrington, RI; several aunts, uncles, cousins and friends, too many to mention. She is also survived by her beloved dog, Claire.

After graduating from the Vestal Central School District in 2003, Morgan attended Johnson and Wales University in Providence, RI, graduating with an Associate's Degree in Culinary Arts and a Bachelor's Degree in Hospitality Management. She was a Project Manager for Champion Exposition Services and later a National Account Executive for the Freeman Company. Morgan and John met in 2006, were married in 2011 and eventually settled in South Portland, ME.

In 2005 Morgan was diagnosed with GIST, a rare form of cancer, and over the next eight years battled her disease bravely while working, traveling and living life to the fullest. She was a true inspiration to all whose lives she touched. Morgan will always be remembered for her beautiful smile, her kind and generous spirit and the grace and courage with which she faced her illness over the past several years.

The family would like to thank Dr. Joseph Readling of Broome Oncology, Dr. Michael Fallon of Lourdes Radiation Oncology, Dr. Andrew Wagner of the Dana-Farber Cancer Institute and every member of their staffs for their skilled and compassionate care. They would also like to express gratitude to the doctors, nurses and staffs of the ICU and PCU at Lourdes Hospital for their amazing attention to Morgan's needs over the past week.

FACES OF GIST - ANITA GETLER

What is your name?
Anita Getler

How long have you been living with GIST?
7 1/2 years

What was your first thought when you were diagnosed with GIST?
OMG will I survive?

What do you do?
Receptionist/Administrative Assistant for a Botanical Company in Carlstadt, NJ

How are you doing now?
GREAT! Feel good & live a happy and as close to "normal" life as ever. I work, play tennis, entertain, ride motorcycles, enjoy wine tastings and travel and most of all love playing with my two granddaughters! :) :)

GIST is called a "rare" cancer, how do you feel about that term being applied to you?
I guess I would say "rare" because I had never heard of it before my diagnosis…..thanks to having this "rare cancer" called GIST I have made many new friends on the Life Raft Group to help support me throughout my GSIT Journey and it has been a blessing. I live life to the fullest and one day at a time! :)

Tell me a little about your special characteristic.
I think my most special characteristic would be my positive attitude and happy grateful heart….SMILE! :)

Research, from Page 1

everything we need to know about GIST biology and may not have identified the critical or optimal pathways to drug; and 2) some pathways that we know are important to GIST biology may not provide good drug targets (e.g. transcription factors like ETV1).

In contrast, the unbiased screening approach utilizes one or more technologies to identify targets, even those that have never been identified as important to GIST biology, or any cancer for that matter. A number of members of the LRG Research Team are using large scale screens to identify novel pathways and targets in GIST.

Dr. Jonathan Fletcher's group has been using RNA interference (a method of blocking protein function) to systematically inhibit 11,194 different proteins in GIST cells--one protein at a time. By combining RNA interference with imatinib treatment, Dr. Fletcher's group has identified several critical and novel pathways. Their initial results validating CDC37 as a treatment target were recently published by Dr. Marino-Enriquez et al.(2) Their results highlight the main strength of an unbiased screening approach: you can find targets that were not previously known to be important to cancer cells.

Dr. Anette Duensing's laboratory has been using a related but technically distinct screening approach to identify pathways that could be targeted in GIST in conjunction with KIT inhibitors.

In addition to the work described above, Dr. Brian Rubin also has been conducting screening studies using a chemical library of existing cancer drugs (including kinase inhibitors) to try and identify novel combination treatment approaches. By testing many drugs and combinations, we may find a better treatment.

Over the past several years, my laboratory also has been focused on trying to develop combination treatment strategies for GIST. This work has been conducted in collaboration with Dr. Chris Corless, the above LRG investigators, as well as Drs. Debiec-Rychter and Bauer (both members of the LRG Research Team). One of our approaches has been to sequence all the genes in drug-resistant GIST to find which pathways are commonly mutated in addition to the known KIT mutations in these tumors. These types of experiments produce terabytes of data and take many months to analyze. The datasets from these experiments are too large to analyze on a personal computer and must be stored and analyzed in "the cloud." The analysis of several dozen sequenced tumors is still ongoing.

More recently, my group started using a novel methodology to identify pathways important to GIST biology. In these experiments, cells are treated with KIT inhibitors and we measure changes in gene expression using an approach known as RNA-Seq. By identifying pathways that are modulated by KIT inhibitors, we hope to find novel treatment strategies.

In our preliminary work, we have identified several novel pathways for which existing drugs or research grade inhibitors already exist. Using these drugs/compounds as research tools, we hope to find new combination treatments that can be further tested in the laboratory and hopefully advanced to clinical studies. Our preliminary results are promising and suggest that this approach is likely to identify a number of targetable pathways. In some cases, drugs to target these pathways already exist, allowing us to more rapidly advance promising combination treatments to clinical studies.

As outlined above, I believe that combination treatments are the key to finding more effective and, hopefully, curative GIST treatments. Your LRG Research Team is working hard to identify these combinations. Due to the close collaboration of our group, new findings are freely shared, leading to more rapid progress. Our common objective is to find a cure for GIST and we believe that working as a team is the best way to achieve that goal. Hopefully, our work on finding new combination treatments will bring us closer to a cure for GIST.

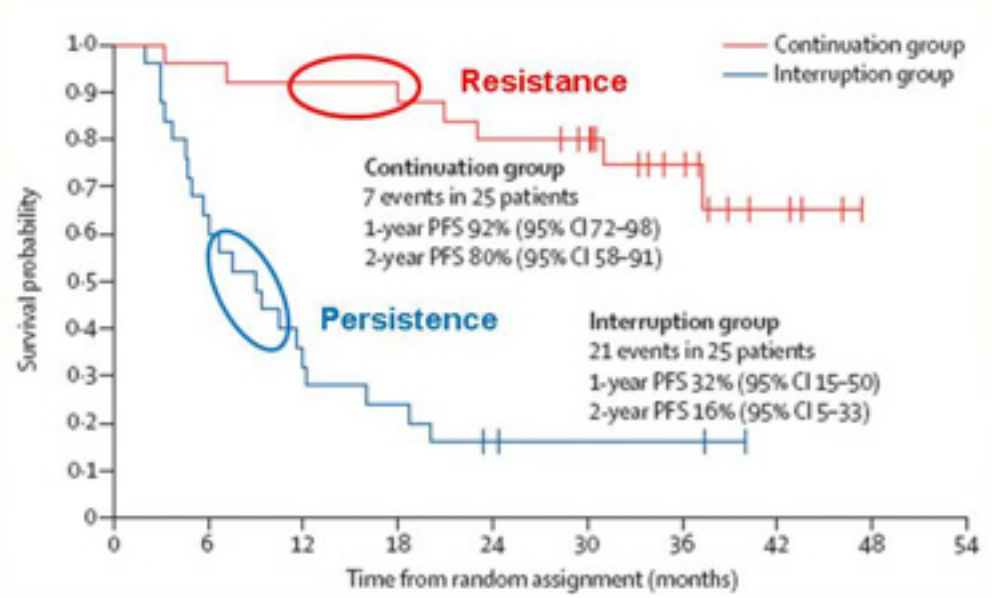

Figure 1. *Results from the BFR14 randomized study of interrupted vs. continuation treatment. Data are shown for patients randomized after three years of successful imatinib treatment (i.e. only those patients who were still responding to imatinib). The blue curve represents outcomes after halting treatment. At one year, only 32% of patients had not experienced detectable tumor growth. The red curve is data from patients who continued their imatinib treatment. At the one year time point, more than 90% of patients continued to respond to imatinib (i.e. no tumor growth). As discussed in the text, patients who continue treatment and have subsequent tumor growth have resistant disease. In contrast, persistent disease is responsible for the growth of tumors in patients who stop treatment. Reference: (1)*

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