The Life Raft GROUP

October 2013 - Vol. 14, Issue 5

Ensuring no one has to face GIST alone

In Loving Memory: Mary Corliss, Dan White, Richard Bartenbach, Stanley Folda, Susan Farmer

Immunotherapeutic Approaches to Cancer

By Dr. Matt van de Rijn
LRG Research Team
Stanford University

With the advent of Imatinib, tremendous progress has been made in the treatment of patients with GIST.

Imatinib is a drug that can be taken orally that inhibits the function of KIT, a protein that is expressed in GIST cells. In these cells, the KIT protein undergoes a mutation (change) in the DNA that causes it to send an activating signal to the GIST cells and induces them to grow.

With Imatinib's ability to inhibit the KIT protein, we have seen a dramatic increase in the life expectancy of patients with this tumor.

Unfortunately, after a period of treatment with Imatinib, other mutations can eventually occur in the KIT molecule, rendering it insensitive to Imatinib. Therefore, a lot of research in past years has focused on the discovery and testing of novel inhibitors that can inhibit KIT proteins that have undergone these secondary mutations.

The Immune System and Cancer

I would like to give a brief description of a different approach to cancer that involves the immune system. Many researchers have been working in this approach for decades, but only in recent years have very promising results been obtained in clinical trials; trials

See Research, Page 7

Amazing Turnout for the 10th Annual Night to Fight Cancer in NYC

By Matthew Mattioli
Events and Design Coordinator

We had some big shoes to fill this year when we started planning our 10th Annual Night to Fight Cancer. It had to be fun, successful, and better then any thing we had done in the past. We knew we had to make this a celebration and wow people. We already had our amazing venue picked out that overlooks the Empire State Building. Those views alone from inside and on the gorgeous terrace are enough to get

See NTFC, Page 5

The Rare 13 Campaign is on it's way to viral success

we're not RARE just people

WHAT IS THE RARE 13 CAMPAIGN?

Five Thousand people are diagnosed with GIST each year in the United States. That's 13 people diagnosed each day.

Thirteen people diagnosed each day may seem small but every day 13 people are added to the organ transplant list, 13 people in the US die of food-borne illness… 13 people are diagnosed with Lou Gehrig's disease.

All of a sudden, 13 people doesn't seem so small after all.
Because of this, the Life Raft Group (LRG) launched a campaign called Rare13, a one-of-a-kind, dynamic, media-driven, awareness campaign to address the misconception surrounding a rare cancer like GIST.

WHY IS IT IMPORTANT?

Over 100 types of cancer are considered rare because fewer than 20,000 people per year are diagnosed.

But what does rare really mean? That you don't have to know about it? Worry about it? Because it may never affect you? Thousands of people are living with GIST, yet many doctors know little to nothing about it. Many GIST patients are unaware of programs and services that may help them and research is not being done on a large enough scale. All of this because this cancer has been labeled rare and therefore, not as important as other diseases.

Check out **therare13.com** for more info about the campaign and ways to get involved in helping it go viral.

Go to page 6 to check out one of our Faces of GIST!

NEW ONCOLOGY INFORMATION!

Launching Soon...

The *GIST* Cancer Journal

The Official Journal of The Life Raft Group

For the first time, a new, peer-reviewed medical journal offering comprehensive and exclusive coverage of Gastrointestinal Stromal Tumors (GIST)

- The official medical journal of The Life Raft Group, the only GIST advocacy organization dedicated to research, patient support, and worldwide educational initiatives
- Published quarterly
- Distributed to medical oncologists, select gastroenterologists, and additional healthcare providers directly involved in GIST
- Editor-in-Chief: Leading research scientist Jonathan C. Trent, MD, PhD, University of Miami
- Presenting essential clinical information on GIST-related issues and new research findings with translational impact
- Expert opinion on diagnostic and treatment trends
- Accessible soon on www.thegistcancerjournal.org

The Life Raft GROUP

The LRG proudly presents six new Local Group Leaders!

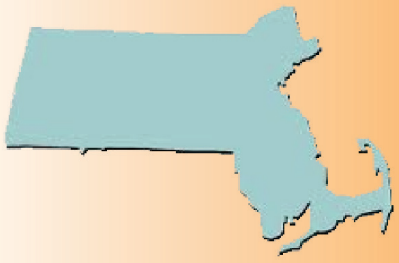
Representing Colorado, Susy Clough – "Having been through a different cancer ten years ago I know that its so important to be in contact with others who are going through the same emotions and feelings. I hope in some way I will be of help to others and to lend an ear. I feel its very important for anyone out there with a gist diagnosis to receive comfort from our group along with information and ideas about the gist journey." Susy can be reached at **susyclough@yahoo.com**

Also representing Colorado, Marge Morgan – Marge has been married to her husband Mike for 19 years, he is a 9 year gist survivor. She enjoys reading, traveling, history and spending time with her 2 grandkids. Marge enjoys working part time at a non-profit that works with at risk youth. Along with Susy Clough, she brings knowledge and compassion to others in Colorado facing life with GIST. Marge can be reached at **mike.d.morgan@comcast.net**

Representing Arizona, Ellen MacDonald – "As the new Arizona LRG Group Leader I look forward to meeting more members of our group and welcoming new members. I have heard that there are GIST patients who can't afford their medication in Prescott where I live. I hope they will contact me so we can direct them to resources that may help them pay for their medication. By communicating with and meeting other Arizona GIST patients I hope to be able to help them with any issues they may be having." Ellen can be reached at **emac1492@gmail.com**

Representing West Texas, Tatiana Avila-Isaias – Tatiana is a wonderful cheerleader and advocate for her husband who was diagnosed last year with GIST, she hopes to bring together a group in West Texas to share and support each other. "It's a privilege to be part of this amazing group. I want to help as much as possible." Tatiana can be reached at **tatianajudith@aol.com**

Representing West Michigan, Cliff Kopp – Cliff is volunteer and event chairperson with the local Special Olympics in Michigan as well as past president of a non-profit organization. Cliff is a terrific organizer and is very excited to bring together Western Michigan members for support. Cliff is also becoming very instrumental in the LRG's efforts to promote The Rare 13 campaign. Cliff can be reached at **gistgroupmichigan@gmail.com**



Representing Massachusetts, Charles Burke – Charles and his wife Suzy are retired and enjoying life in N. Dartmouth Massachusetts, Charles volunteered to become the LRG local group leader where he will bring a unique positive aspect to group meetings. Having survived three different cancers, 'Charlie' doesn't let anything get him down! Charles can be reached at **cfxburke@aol.com**

Susan Farmer, trailblazer for women in Rhode Island politics, dies at 71

Susan Farmer, who broke the glass ceiling in Rhode Island politics by becoming the first woman to be elected secretary of state — and the first female Rhode Islander ever to hold statewide general office — and then went on to run and manage the state's public television station for 17 years, died Monday after a long battle with cancer. She was 71.

After one political writer wrote that she looked like she had just leapt from the pages of the Official Preppy Handbook, friends and foes alike sometimes referred to the always-upbeat secretary of state as "Muffy," a term that she tolerated depending on who was saying it.

She said she never appreciated people using it in a condescending way. After all, she said, she had worked very hard to overcome the fact "that I came from the East Side and went to private school, and that I am blond-haired and blue-eyed and wear pearls."
She was also a Republican. Though another Republican, U.S. Rep. Claudine Schneider, was elected to become the state's first female member of Congress, in 1980, Farmer's election to the secretary of state's position at age 40 in 1982 thrust her into a State House dominated by men. Democrat J. Joseph Garrahy was the governor for her first two years as secretary of state, followed by Republican Edward DiPrete.

In one of her first moves as new secretary of state, she announced she was reorganizing the office, dismissing 14 of its 52 employees. With Democrats crying foul, she was forced to keep the dismissed employees three more months before a federal judge ruled that she had the right to terminate them.
Farmer was asked if she had ever given the firings a second thought. "I've never for a moment thought that I should not do it," she said.

Growing up as the middle child of three children of Ralph Lawson Jr., the retired president of a machine tool plant in Central Falls, and Margaret Lawson, who became prominent in Republican women's circles, the future secretary of state lived in Bristol and went to Wheeler School in Providence, then Stoneleigh-Burnham School in Greenfield, Mass., and finally what's now Simmons College.

With her mother so involved in politics, Farmer said she did all she could to avoid politics, and envisioned a life of caring for children, baking brownies and carpooling.

But then in 1971, she and her husband, Malcolm, who would go on to become a Republican city councilman, became so upset with the Vietnam War and with then-President Richard Nixon that they helped start a dump-Nixon rally that drew thousands to the State House. In 1972, she ran the Rhode Island campaign for California Republican Paul McCloskey, who was trying to deny Nixon another nomination for president.

After becoming then-Sen. John Chafee's finance director in 1976, Farmer ran for and won, in 1979, a seat on the commission drafting a new Home Rule charter for Providence.

After losing her first bid to become Rhode Island secretary of state to incumbent Robert Burns in 1980, she won it two years later by defeating Democrat and future state Supreme Court Justice Victoria Lederberg.
As she would explain it later, "I did all this work to open the door for a woman holding statewide office. I wasn't doing that to hold the door open for another woman to cruise through on the Democratic side."

Farmer cruised to victory again in 1984, and as she put it, would have been perfectly happy to run for secretary of state again when then-Gov. Edward DePrete pressed her to take on Lt. Gov. Richard Licht, at a time when Licht was riding low in the polls.

It was a bitter and nasty campaign — Licht and Farmer would later say they healed their differences and became friends — but the fact was that Farmer lost.

A year later, in 1987, she was offered the job of general manager of Channel 36, the state's public television station. Farmer said she thought the idea was crazy at first but later realized it gave her an opportunity to use her administrative, fundraising and public-relations skills.

She came up with the idea of airing a weekly public-affairs show, "A Lively Experiment," and became a prolific fundraiser for the station. The irony was that the more she raised, the more opportunity politicians had to trim her budget.

Her leadership was not without controversy, as when she approved in 1999 the airing of an hour-long documentary entitled "It's Elementary: Talking About Gay Issues in School," a program that some Christian groups said promoted homosexuality and undermined parents' right to teach morality. Although many public television stations shied away from the program, she said airing the program was a "no brainer."

Farmer, who learned she had cancer in 2001, was mourned across Rhode Island's political establishment on Monday.

"From an early age, Susan Farmer proved she had a big heart and cared for the well being of Rhode Islanders," said Governor Chafee, who called her a dear family friend. Lt. Gov. Elizabeth Roberts called her a woman of great courage and political leadership. "She made a lasting impression on me and so many of my peers," Roberts said. "Women from all walks in this state will be forever indebted to Susan Farmer for her service to Rhode Island state government."

Calendar

18th Annual CTOS Meeting
October 30 - November 2, 2013
New York, NY

Partnering for Cures
November 3 - 5, 2013
New York, NY

Top Ten Flu Tips for Cancer Patients

With flu season starting, we have put together a listing of the top ten flu tips for cancer patients. One day the weather is unseasonably warm, and the next you have a foot of snow on the ground. These types of drastic changes in temperature are just a few of the reasons you may be sick with the flu. Keep reading to learn some handy tips for beating the flu.

1. Get a Flu Vaccine - Take time to get a flu shot. Many local pharmacy's offer flu shots, making it much easier to get a vaccine.
2. Stay Healthy – Maintain healthy habits year round to avoid getting sick.
3. Use a tissue to cover your mouth when coughing or sneezing, and be sure to throw the tissue away after you use it.
4. Wash your hands regularly with soap and water. Use hand sanitizer if soap is not available.
5. Keep your hands away from your eyes, nose, or mouth so germs don't spread.
6. Avoid crowds, but if you have to be around people be sure to stand six feet away from someone that is sick.
7. Stay home for at least 24 hours after your fever is gone except to get medical care or for other necessities.
8. Keep a supply of over-the-counter medicines, alcohol-based hand sanitizer, and tissues.
9. Take Your Meds – Take flu antiviral drugs if your doctor prescribes them.
10. Keep a written record of the type of cancer you have, treatment you have received and when you received it, the name and contact information for your doctor, and a list of medicines you are taking.

If you have the following symptoms call your doctor:

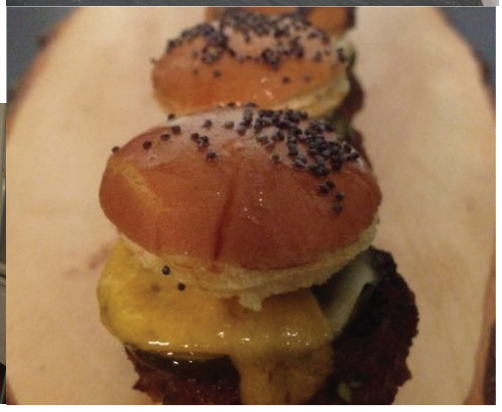
- Earache or drainage from your ear
- Pain in your face or forehead along with thick yellow or green mucus for more than a week
- Temperature higher than 102 degrees Fahrenheit
- Hoarseness, sore throat, or a cough that will not go away
- Wheezing
- Vomiting
- Persistent or worsening symptoms

Go to the doctor immediately if you have trouble breathing, chest pain, confusion, seizure, fainting, or extreme fussiness.

Visit the CDC Website to read even more on tips for dealing with the flu. http://www.cdc.gov/

NTFC, from Page 1

people to show up. It really transports you into a whole new world where you can look at the amazing city and see it's beauty and drown out the craziness below. The overall goal of the evening is to raise money for the Life Raft Group which we certainly did. It was one of our most successful events yet raising over $70,000. Having our new amazing dealers from Big Eastern Casino definitely helped to make this such a successful evening. Our caterer Scoozi from last year made a return to serve up their amazing hors d'oeuvres and specialty Rosemary Lemonade. The food really makes the night special. We had everything from mini crab cakes to mac and cheese with pork belly. The fun didn't stop there. For dessert we wowed everyone with deconstructed s'mores and mini crème brule. We pull out all the tricks to make our guests comfortable and help them connect with new and old friends. We would like to congratulate our winners pictured below. Mike Disant - 1st, Tom Mullarky - 2nd, and Matt Knopman - 3rd



Faces of GIST


Anita Getler


Kim Glass


Marc Wasserman


Sile Bao


Ellen Mayer

Bella Rocco

What is your name?
Bella Rocco

How long have you been living with GIST?
Since I was seven years old. I am twelve now.

What was your first thought when you were diagnosed with GIST?
I didn't know what it was. I just knew I hadn't been feeling well and I was glad the doctors figured out what it was so they could help me feel better and they did.

What grade are you in and what's your favorite class?
I am going into the seventh grade. I love my Italian class and math the best. I was on the honor roll all four marking periods in sixth grade and I hope to do it again in seventh grade.

How are you doing now?
I'm doing great but have to get MRI's done every few months to watch for more tumors.

What is your favorite sport or activity outside of school?
I love softball, field hockey, cheerleading, art classes, amusement parks, the beach, and hanging with my friends and cousins.

GIST is called a "rare" cancer, how do you feel about that term being applied to you?
I think I'm just like most kids. I just have to go to the doctor more than a lot of other kids to make sure I stay healthy. I guess rare is ok because it's like being unique which is a good thing but when it comes to GIST or me having GIST I would rather it not be considered rare so more people would know about it and more doctors would be able to find a cure.

Tell me a little about your special characteristic.
What is special about me is my dimples, my leftie swing when I'm playing softball, and that I am not afraid of anything. My mom says I'm fearless. It doesn't matter if it's an upside down roller coaster, or another needle in my arm, I'm not afraid.
I also think I may want to be a doctor when I grow up or maybe do research to help other people who are sick.

Check out all of the Faces of GIST at **www.therare13.com.** While you are there check out our awesome video explaining the campaign and be sure to like us on Facebook and Twitter and share the campaign with everyone you know. The campaign going viral can only happen if everyone does their part. With this campaign we can finally wipe out the word rare from GIST and get the recognition we need to cure this disease.

Research, from Page 1

that have so far focused on tumors other than GIST. In this approach, different parts of the immune system are used to battle tumors.

The immune system consists of a highly complex collection of different cell types. Each of these cell types can have different or partially overlapping functions with other cell types.

Some examples of the most common cell types in the immune system are T-lymphocytes, macrophages, and B-lymphocytes. T-lymphocytes can have many different functions, including killing normal human cells that have been infected by a virus. Macrophages are generic cleaners that can eat up cells recognized as foreign or that are otherwise labeled as abnormal in a variety of manners. B-lymphocytes make immunoglobulins, which are proteins that can specifically bind to a tumor cell and cause it to be eaten up (phagocytosed) by a macrophage.

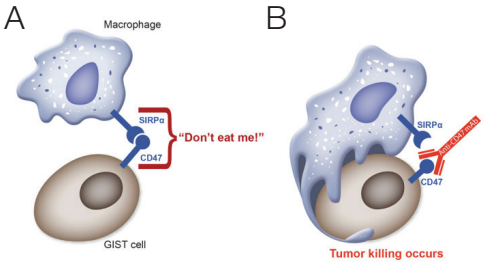


Figure 1: A protein called CD47 on the surface of GIST cells binds to SIRPa, a protein on the surface of macrophages. This sends a powerful "don't (panel A). A therapeutic antibody against CD47 disrupts the binding of CD47 to SIRPa; the "don't eat me" signal is not delivered to the macrophage and tumor killing occurs.

Helping T-lymphocytes Kill Tumor Cells

In past years, a series of antibodies have been developed that can increase the ability of the human immune system, specifically T-lymphocytes, to recognize tumor cells as "foreign" so that they then can be destroyed.

At the recent ASCO meeting, the combination of two of these antibodies, one directed against CTLA-4 and the other against PD-1, showed a response rate of almost 50% in melanoma patients. Although the trial was small, this response rate was very high, and the hope is that this work will continue to provide good results and that this approach will also be tested in patients with GIST. A number of publications describe this approach (1-5).

Helping Macrophages Attack Tumor Cells

Macrophages are cells that clean up debris or destroy cells that are recognized as "foreign". A second approach in immunotherapy is in development in an earlier stage, but hopefully will go to a clinical trial in the next year. This approach relies on the ability of certain antibodies to "uncloak" tumor cells that are hiding from macrophages.

Tumor cells can protect themselves from being seen as foreign and thus from being "phagocytosed" or eaten up by macrophages by expressing a protein called CD47 on their surface. Antibodies against CD47 protein can interfere with this camouflage effect and can allow phagocytosis to proceed (See Figure 1).

This approach has been quite successful in experiments where human tumors were grown as subcutaneous nodules in mice. While it remains to be seen whether these results can be translated to the human setting, the findings are quite exciting.

In addition to the range of cancers that were examined by the Weissman laboratory, we collaborated in a study to look at the treatment of leiomyosarcoma tumors in this manner. We showed that antibodies directed against CD47 could inhibit the growth of human leiomyosarcoma (LMS) cells in mice. The LMS cell lines were obtained from the laboratory of Dr. Jonathan Fletcher. The mice receiving the anti-CD47 antibodies did much better in that their tumors became smaller and they had many fewer lung metastases (6).

These experiments still need to be performed with GIST cells, but if successful, they could ultimately lead to a novel therapeutic approach in patients with GIST.

Recently, we collaborated in a study to show that in addition to antibodies against CD47, one could also inhibit the function of CD47 by a synthetic protein that was generated to bind the CD47 protein at a very high level of strength. This so-called "synthetic variant" of a protein called SIRPa was also highly successful in animal experiments and in vitro experiments in a range of tumors, and hopefully we will extend these studies to include GIST cells in the future (7).

So far, these studies have been performed in carcinomas, lymphomas, and leiomyosarcoma. So, we hope to start similar experiments using GIST cell lines.

Using Antibodies in Immunotherapy, ROR2 As a Candidate Target

A third approach in immunotherapy relies on the use of antibodies. Antibodies are proteins that are synthesized by B-lymphocytes, a cell type specialized in generating these proteins. B-lymphocytes can generate immunoglobulins in such a way that they only react with one specific protein, like one key may fit only one specific lock. As a result, an antibody against the KIT protein will react only with KIT and not with the other thousands of other proteins in the body, for example.

Antibody therapy has become widely used in the past decades, and some of the currently best-selling drugs are antibodies. Some examples are Rituximab, an antibody that is used in treating leukemias and lymphomas and Trastuzumab, an antibody that is used to treat patients with breast cancer.

For antibody treatment to be successful, it is useful if the protein targeted by the antibody is expressed at low levels in normal human tissues but is expressed at fairly high levels in tumor samples.

One such protein is called ROR2, which is an example of a protein that is found in very few adult human tissues, but is expressed at high levels in some (but not all) GIST and LMS tumors. Just like the KIT protein, the ROR2 protein is a member of the family of receptor tyrosine kinases (RTK), molecules that are present on the surface of the cells. The RTKs can be activated when a specific protein called a ligand binds to them on the cell surface, resulting in an activating signal that is then transmitted to the cells. For ROR2, the ligand is Wnt5A (See Figure 2).

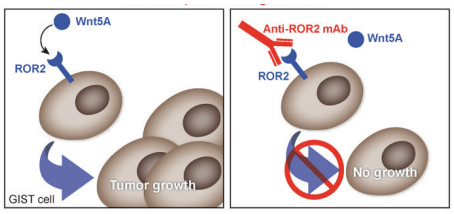


Figure 2: Activation of ROR2 occurs when Wnt5A binds to it, causing cells to grow. An antibody against ROR2 could prevent the binding of Wnt5A and stop tumor growth.

The significance of ROR2 is supported by the fact that we found that tumors that expressed this marker behaved more aggressively than tumors that did not (8).

We are currently developing a monoclonal antibody that can target the ROR2 protein. This antibody will initially be studied in cell culture for its effect on GIST cell growth. If successful, the study will be performed in mice bearing GIST tumors. Finally, if these are successful, we hope to develop an ROR2-based clinical trial for GIST patients.

See Research, Page 11

ASCO 2013 Report

By Jim Hughes
Clinical Trials Coordinator

American Society of Clinical Oncology (ASCO) was held in Chicago again this year. Over 32,000 medical professionals and exhibitors participated in what has become an international event, and 53 percent of attendees now come from outside the US.

The information presented at ASCO is not peer-reviewed like journal articles, so the level of information is not the same. Peer review can come later as ASCO reports are submitted for publication.

However, ASCO reports are screened by a Scientific Program Committee of medical professionals who are familiar with each cancer type. GIST falls under the track "sarcoma."

The four MDs on the Sarcoma Program Committee have significant GIST experience. The abstracts submitted for review by the Sarcoma Program Committee are then given a place in the overall conference based on merit and likely impact. The order from highest to lowest is:

- Plenary Session
- Oral Abstract
- Discussion Poster
- General Poster
- Abstract only

Most of the new information collected by The Life Raft Group (LRG) comes from oral abstracts, discussion posters, and general posters.

The LRG and Poster Sessions

The LRG is represented by both staff and volunteer reporters who attend the presentations and walk through the poster sessions. The LRG reporters meet via teleconference before the meeting to review the GIST abstracts and plan to see important posters and presentations. At the ASCO meeting they collect paper copies of posters, take photos of posters, talk with authors, attend oral presentations (sometimes ask questions), and interview authors and principle investigators. The LRG reporters also carefully review the online video and audio archives of session material made available by ASCO for attendees. Other activities include meeting with other patient groups, attending education sessions, and attending off-site meetings. The ASCO meeting usually starts on a Friday and goes through Tuesday morning. GIST oral abstracts are typically presented on Monday afternoon.

Phase 2 Trial of Regorafenib Leads Discussion Posters at ASCO 2013; Improved Benefit in Wild Type Reported and Combination Trials Indicated

The Phase 2 trial of Regorafenib in 33 GIST patients conducted in 2010 continues to produce data advancing our knowledge of GIST. Two posters based on Phase 2 trial data led the poster discussion session on Saturday morning.

Suzanne George, MD of the Dana-Farber Cancer Institute in Boston presented updated Phase 2 results showing prolonged disease control in patients with Exon 11. The median Progression Free Survival (PFS) was 13 months and the median Overall Survival (OS) was 25 months. For Exon 11 primary patients, these were improvements over similar results from the Phase 2 Sunitinib trial shown in Table 1.

Table 1: KIT Exon 11 Primary Mutation Survival (Months) in Phase 2 Trials. CI – Confidence Interval, NR – Not Recorded

Drug	Patients	Median Follow-Up	Median PFS	95% CI	Median OS	95% CI
Regorafenib	19	20	13	10.0-21.0	25	16.0-NR
Sunitinib[1]	44	Not rep.	5.1	4.5-7.8	12.3	8.8-19.6

Regorafenib was noted for potent inhibition of KIT Exon 17 and 18 secondary mutations In GIST cell lines. The data presented by Dr. George showed this benefit is now in the clinic. The data from the Sunitinib Phase 2 trial was used again for comparison and can be seen online. PFS and OS were significantly improved for patients known to have Exon 17 secondary mutations. In the lab, Sunitinib was not as effective against Exon 17 mutations and this is reflected in the Phase 2 trial data published in 2008.

Whether this data is sufficient to raise the question (i.e. a proposed clinical trial) of which drug should be given first based on secondary mutation remains to be seen.

Perhaps the most notable data was for what we have historically called Wild Type GIST. Wild Type GIST is now sub-divided into those whose tumors express normal levels of SDHB and those whose tumors are SDHB-Deficient, indicating a disruption or mutation in the SDH complex. This important distinction was first identified in 2007 by a team led by Constantine Stratakis. It occurs in approximately 40 percent of Wild Type patients.

Dr. George reported that of the six patients in the study with this deficiency, all had clinical benefit and two had partial responses (30 percent+ tumor shrinkage).

Wild Type historically has been noted for slow growth and a mixed response to therapy with stability typically the best response. These results raise the question of the mechanism of action of Regorafenib in SDHB-deficient GIST.

The Phase 3 trial of Regorafenib included 29 Wild Type patients reported by George Demetri in his presentation on plasma DNA. Hopefully, SDHB-Deficient data will be available to see if this improved outcome was seen there as well in this subset of Wild Type patients.

Reports of the Phase 2 trial of Regorafenib continue to show longer PFS compared to reports from the Phase 3 trial. The Phase 3 PFS results (median 4.8 months) are less than half the Phase 2 (median 13.0 months). This is a significant difference since the 95 percent confidence limits do not overlap.

A possible explanation could be the mix of mutation types. In the Phase 3 trial, only about half the patients had primary mutation analysis. Given the potential for differential response by primary (and now secondary) mutation, it is becoming increasingly relevant in clinical trial settings to have complete subgroup analysis of these biomarkers to validate responses, avoid false negative results due to confounded data, and find patients who benefit the most.

In the second poster, Cèsar Serrano-Garcia, MD, also of Dana-Farber, presented data showing the relative effectiveness of Sunitinib and Regorafenib against the most common secondary KIT mutations. Sunitinib is particularly good for Exon 13/14 ATP binding pocket (Gateway) mutations and Regorafenib is effective against Exon 17/18 "kinase activation loop" mutations. The thrust of the poster is that some combination of the two would produce the best result.

As a result of his work, Serrano-Garcia will receive a $50,000 Young Investigator

Award from Conquer Cancer Foundation of ASCO for "Cycling Multi-Kinase Inhibitors in Imatinib-resistant GIST to Maximize Clinical Response." It is anticipated that this work will eventually result in a combination clinical trial in GIST .

A third poster presented by Heikki Joensuu, MD of Helsinki University reported the details of the sub-group analysis of patient characteristics for the Regorafenib Phase 3 trial. ll sub-groups showed significant benefit on Regorafenib compared to their counterparts on placebo. These included groups divided by age, sex, treatment history, mitotic index-,and KIT mutational status. Only patients on Imatinib for less than six months showed a benefit that was not significant. Regorafenib typically reduced risk of progression by 70 percent or more compared to placebo in these sub-groups.

Re-challenge with Imatinib Better Than No Therapy

Yoon K. Kang, MD, PhD of Asan Medical Center, Seoul, ROK presented results of a randomized study comparing re-challenge with Imatinib in 70 advanced resistant patients who had failed both Imatinib and Sunitinib, but had prior clinical benefit from Imatinib. Many failed more than Sunitinib but none had Stivarga.

The results showed that the Imatinib arm had significantly longer progression free survival. Patients on placebo were allowed to cross over to Imatinib on progression and saw a similar level of disease control. Although it was a small benefit (median PFS 1.8 months) it was twice that of the patients on placebo.

When asked if he would use Imatinib instead of Stivarga for patients failing Sunitinib, Dr. Kang replied that he would recommend Stivarga because of the longer progression free survival reported in trials. He stated that he would reserve Imatinib re-challenge for use when all else had failed.

In his remarks discussing this report, Shreyaskumar Patel, MD of MD Anderson took up the implications for clinical trial design in GIST: "So if the patient has run out of all sorts of options, randomizing them to imatinib instead of placebo, certainly slows down the rate of progression even in the absence of a response and certainly can impact on their quality of life and their overall natural history…This now validates what is fairly standard global practice of keeping these patients on a kinase inhibitor when all else has failed…But, more importantly, I would hope that this resets the tone and when the next anti-GIST agent comes on to the market for clinical trial we will use a kinase inhibitor of choice as a control arm and get rid of the placebo arm."

Nilotinib Phase 3 Versus Imatinib Fails in First Line GIST

In April, 2011, Novartis announced that the Phase 3 trial of Tasigna in newly diagnosed GIST patients had been halted after an independent data monitoring committee said that continuing the trial was unlikely to show that patients given Tasigna would live longer than those taking Imatinib.

Jean-Yves Blay, MD of Centre Léon Bérard, Lyon, France, presented the data from this trial. Patients in the Imatinib arm had better progression free and overall survival than those on Tasigna. Much of the difference was attributed to Exon 9 patients who did significantly worse on Tasigna than on Imatinib. The analysis for Exon 11 patients showed Imatinib was slightly better than Tasigna in PFS and OS.

Dr. Blay indicated that there would be further analysis of the OS data to understand the impact of cross-over since the question was raised as to why there was an OS difference. Wild Type patient data was not presented. Dr. Blay, however, said that the numbers were too small to analyze, but the few wild type in the trial did not show superiority on Tasigna.

Imatinib Failure Free Survival—Relapes vs. Resistance

The EORTC sponsored Phase 3 trial "Imatinib Mesylate or Observation Only in Treating Patients Who Have Undergone Surgery for Localized Gastrointestinal Stromal Tumor" accrued 900 patients in 3.5 years from 2005 to 2008 primarily in Europe. The median follow up is currently 4.5 years. Paolo Casali, MD of Istituto Nazionale dei Tumori, Milan, Italy presented the results at ASCO.

We have long known that patients who complete adjuvant Imatinib therapy have a risk of recurrence. Upon recurrence, patients are typically given Imatinib and can often regain control. This recurrence would be a considered a relapse of Imatinib sensitive tumor. At some point, however, patients might experience new or existing tumor growth while on Imatinib. This type of recurrence would be considered resistance and would typically warrant a switch to another TKI – Sunitinib.

In this trial the initial intent was to measure Overall Survival. However, the trial was amended due to the fortunately low frequency of deaths in the control group, which was the group not receiving Imatinib and getting "observation only." It was decided to use a new end point more fitting to the improved prognosis. Imatinib Failure Free Survival (IFS), which is defined as either death or the point when a patient switched from Imatinib to another tyrosine kinase inhibitor, was chosen.

Dr. Casali reported that overall there was no difference in IFS between the adjuvant group receiving Imatinib and the observation only group. He then showed results for the Intermediate and High-Risk patient subgroups. Intermediate-risk patients showed no difference. In the High-Risk group there was increased benefit for the Imatinib group but it was not statistically significant.

In his conclusions, Dr. Casali made the following points:

- IFS use supports the notion that, by substantially delaying relapse in High-Risk GIST, adjuvant therapy may provide some benefit in duration of survival.
- Adjuvant imatinib does not appear to hasten the emergence of resistant clones.
- IFS is a tentative surrogate end-point for Overall Survival and deserves validation.

At the end of the last session on GIST, Dr. Shreyaskumar Patel from MD Anderson summed up the current status of GIST Management:

Adjuvant:
- Post Primary Removal: Three years Imatinib is better than one for high-risk GIST.

Advanced:
- First Line: Imatinib prevails. Masitinib in Phase 3 trial.
- Second Line: Sunitinib is approved. Masitinib is in Phase 3 trial.
- Third Line: Stivarga is approved. All patient subsets benefit.
- Fourth line and greater: Re-challenge with Imatinib is better than no treatment (for those who had prior clinical benefit from Imatinib).

Future:
- Circulating DNA biomarkers may improve understanding and management of GIST

Exon 11 Primary Mutations Predict Progression-Free Survival:

Jean- François Emile, MD, PhD of Hôpital Ambroise Paré, Boulogne, France presented the poster "Relationship of the topography of Exon 11 alterations and predictive value for PFS in patients with advanced GIST: Results of the BFR14 prospective French Sarcoma Group randomized phase III trial."

This trial has produced many reports at ASCO over the years.

In this prospective study 167 Advanced GIST Patients with Exon 11 mutations were grouped by mutation codon location.

Interestingly this cohort of Exon 11 patients who were recruited after the initial B2222 Phase 2 imatinib trial in 2000-2001 showed longer median PFS than that reported earlier 30 to 63 months versus 20 months.

Dr. Emile reported that patients in group 2 had better response to imatinib but significantly lower progression free survival

Table 1

Group	Codons	# of Patients	Median PFS (Mos.)
1	556 and below	41	49.4
2	557-558	74	30.6
3	559 and above	52	63.3

Dr. Emile's conclusion outlined the next steps and the potential impact in the clinic: "These results deserve confirmation in other prospective series in advanced GIST and could be translated in the adjuvant setting."

Sunitinib Effective in Patients Over 65 Years; Monitoring Important

Florence Duffaud, MD, PhD of La Timone University Hospital, Marseille, France presented the poster titled "Clinical experience with sunitinib (SU) in patients over age 65 with metastatic gastrointestinal stromal tumors (GIST): A retrospective study from the French Sarcoma Group (FSG)."

In this retrospective study the charts of 71 elderly patients (≥65 years) treated with Sunitinib on routine clinical practice were reviewed in 11 French Centers of the French Sarcoma Group to evaluate safety and efficacy. The median age was 74. Roughly half received Sunitinib at 37.5 mg daily and half received 50 mg daily for 4 weeks then 2 weeks off in six week cycles.

69 of 71 patients experienced some level of adverse event during the first three months of therapy. Of all events 76 percent were grade 1-2 and were medically manageable. The more serious grade 3-4 events represented 23 percent of all events.

Most frequent Grade 1-2 events were:

Grade 1-2 Event	Frequency of all Grade 1-2
Fatigue	20%
Diarrhea	12%
Mucositis	9%
Abdominal pain	8%
Hand foot syndrome	6.40%
Hypertension	4.70%

Dr. Duffaud concluded that Sunitinib treatment is effective in elderly GIST patients yet dose reductions and interruptions for intolerance were frequent. Careful follow-up regarding tolerances should be considered in elderly GIST patients.

Frequency of Follow-up Favorably Impacts Outcome

Erica Palesandro, MD of the Institute for Cancer Research and Treatment – Candiolo, Turin, Italy presented a poster titled "A risk-based individualized follow-up after complete surgery as an effective procedure to reduce the relapse (R) impact in GIST patients (pts)."

In this study, 140 patients who had all tumor removed by surgery were grouped by risk of recurrence. For two years, high-risk patients had CT scans every three months and all others every four months. Scan frequency gradually decreased to annual for high-risk at year six and annual at year five for all others. Patients who had recurrence during the study were further categorized as high and low tumor burden at recurrence. 58 recurrences were observed. 26 percent had recurrences within six months and 50 percent within 16 months. Patients with low tumor burden had significantly longer overall survival (112 months for low burden versus 87 months for high burden).

The study provides some rationale for guidelines on follow-up which currently lack data on optimal methodology. Dr. Palesandro concluded that this study shows in principle that follow-up can detect low burden tumor recurrence and that this might affect outcome and therefore justify the added cost.

Surgery After Imatinib Response Improves Outcome

Baek-Yeol Ryoo, MD, PhD of the University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea presented the General Poster titled: "The role of surgical resection following imatinib treatment in patients with metastatic or recurrent GIST." This data had been presented earlier at ASCO-GI in February 2013.

This poster noted that there is no study (clinical trial) to prove the benefit of surgical resection after imatinib response in comparison to imatinib treatment alone and that prospective Phase 3 trials (of this question) have been terminated due to poor enrollment.

Noting the difficulty of doing this kind of study as a clinical trial the authors attempt to improve on prior retrospective analysis by using a statistical analysis technique called propensity scoring. Propensity scoring matches patients that do and do not receive surgery based on the characteristics that indicate a likeliness to respond. It is a way of countering likely bias in a non-randomized population. Bias becomes more likely in a single site study due to the limited patient population and the unique aspects of the medical center.

This was a retrospective study that included 134 patients treated from 2001 to 2010 at Asan Medical Center. Patients must have had initially metastatic GIST or a recurrence of GIST after only surgery. Patients also must have had some benefit (PR or SD) while on imatinib and the benefit must have lasted for at least six months. This sub-set of patients was then divided into those who benefited from imatinib and then had surgery (42) and those who benefited from imatinib but did not have surgery (92).

Patient characteristics included some significant differences between the two groups. he surgery arm was younger (51 vs. 58) and the imatinib only arm had more tumors located in the peritoneum (45 percent vs. 23 percent of tumor sites). One could expect these characteristics in the clinic because younger patients are more able and likely to undergo surgery and multiple mets in the peritoneum make surgery difficult.

Despite these limitations the authors reported that surgery provides significant benefit even after adjusting for statistical bias. Patients who had surgery were had significantly improved Progression Free and Overall Survival.

"In general, one-third of patients are candidates for surgical removal of residual lesions, depending on the tumor size and other tumor and patient characteristics," said Dr. Park at an ASCO GI press conference in February.

Although this study sheds light on the value of surgery after Imatinib, existing US guidelines have already adopted the recommendation that surgery may be indicated in these advanced patients.

In the US the NCCN Guidelines for Surgery in GIST contain the following recommendation:

- Limited disease progression refractory to imatinib.
- Locally advanced or previously unresectable tumors after a favorable response to preoperative imatinib.

According to the US guidelines, the level of evidence supporting this recommendation is recognized as not at the highest level but there is uniform NCCN consensus that the intervention is appropriate.

The authors concluded: "These results strongly suggest that surgical resection of the residual lesions after disease control with imatinib may be beneficial in patients with metastatic or recurrent GIST. This treatment strategy can be recommended in clinical

practice, if there are experienced multi-disciplinary team, skillful surgeons and/or interventional radiologists."

The emphasis on experience, surgical skill, and a multi-disciplinary team is important to note. Advanced GIST patients who might qualify for surgery after imatinib are well advised to seek out a major GIST center.

When commenting about the study, Neal J. Meropol, MD, professor and chief of the division of hematology and oncology at Case Western Reserve University School of Medicine, noted that although GISTs are an uncommon type of gastrointestinal tumor, they have been a triumph of molecularly targeted therapy with imatinib, with imatinib providing disease controls for years in many patients.

"Unfortunately resistance ultimately develops to imatinib, so this study provides provocative evidence that taking an aggressive approach with surgical treatment, in addition to medical treatment with imatinib, may result in an even longer survival in patients with GIST," Dr. Meropol said.

Mitchell Posner, MD, Thomas D. Jones Professor and chief of general surgery and surgical oncology, University of Chicago, said the study is "interesting but not groundbreaking" because it is not a randomized trial. The study will not change clinical practice as "almost everyone" is already resecting patients with residual disease or those with tumors that stop responding to imatinib, he said.

Based on previous retrospective trials, most experts agree that patients with GIST benefit from surgical removal of residual tumors. However, the previous studies did not provide sufficient evidence that surgery is beneficial because they assessed clinical outcomes in patients who had received surgery without comparison to patients who did not undergo surgery (J Clin Oncol 2006;24:2325-2331; J Surg Oncol 2008;98:27-33; Ann Oncol 2010;21:403-408).

Research, from Page 11

The development of these reagents is unfortunately a very slow process and it will be several years before we will know how successful this approach can be.

Using Antibodies in Immunotherapy, the KIT Protein As a Target

While the ROR2 protein is expressed on only about 30% of GIST tumors, there is of course one protein that is expressed on almost all GIST tumors: the KIT protein.

A mutation in the gene coding for the KIT protein is what causes the GIST tumors to grow. While KIT can be successfully inhibited with small molecule inhibitors such as Imatinib, the KIT protein itself also forms a potential target for immunotherapy with antibodies.
We believe that we may have found strong support for this approach (9). Using cell lines made of GIST tumors that we received from Dr. Jonathan Fletcher's lab, we could show that adding an anti-KIT antibody called "SR1" to cultures of these cell lines would decrease their growth rate. In addition, when we isolated macrophages from a mouse, we could show that addition of this antibody to GIST cells "tagged" the cells in such a way that they became more easily phagocytosed by the macrophages. Finally, when we grew the GIST cell lines in the abdominal cavity of mice, we found that treatment of these mice with the SR1 antibody resulted in much smaller tumors than when a control antibody was used (See Figure 3).

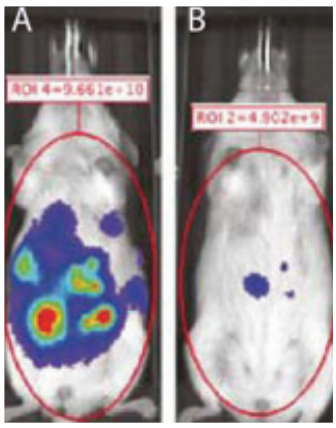


Figure 3: Mice were injected with GIST tumor cells into the abdominal cavity. Mice treated with control antibody grew large tumors (panel A) while the tumor were much smaller in those receiving anti-KIT monoclonal therapy (panel B).

While the results are very inspiring, many issues need to be resolved. First, the antibody we used was made in a mouse and this cannot be used a therapeutic drug in humans. The human body will recognize the protein from the mouse as foreign and will immediately destroy it before it can start its therapeutic effect.

A solution to this problem is to obtain an antibody that has been "humanized." What this means is that all the fragments of the antibody that are specifically for a mouse and that will be recognized by the human body as foreign will be replaced by protein material that is found in humans.
Another concern for this therapy is that the KIT protein is expressed on an important subset of cells in the bone marrow. This cell is called the "hematopoietic stem cell" and it is the cell from which all blood elements are derived. Clearly, one would not want to destroy that cell compartment. Many experiments will be needed to see whether this negative side effect can be avoided or to which extend bone marrow transplantation given after treatment with anti-KIT antibody can restore the blood forming cells.

Summary

In addition to the examples given above for immunotherapeutic approaches, many other approaches are being pursued by research laboratories around the world. Many of those approaches focus on tumors other than GIST, but there is a definite possibility that findings obtained in other tumor types can be applied to GIST care as well.

The few immunotherapeutic approaches described above hopefully will give some insight into novel developments in immunotherapy and show a possible approach to GIST treatment that in the future could be used in addition to the treatment by small molecule inhibitors such as Imatinib.
References can be found online.

THE LIFE RAFT GROUP

LRG STAFF

Executive Director	Norman Scherzer
Deputy Executive Director	Roger Campbell
Science Director	Jerry Call
Strategic Planning Director	Pete Knox
Marketing and Communications Director	Erin Kristoff
Events and Design Coordinator	Matthew Mattioli
Operations Director	Diana Nieves
Administrative Director	Roberto Pazmino
Program Director	Sara Rothschild
Outreach Coordinator	Janeen Ryan
Patient Registry Supervisor	Magda Sarnas
Development Associate	Eola Bakhru
Program Associate	Michelle Durborow
Global Relations Coordinator	Piga Fernandez
Web Programmer	James Lee
Websites Manager	Jim Napier
Program Associate	Elizabeth Pierre
Office Assistant	Samantha Scott

LRG VOLUNTEERS

Newsletter Editor	Monica Barudin
Pediatric GIST	Erin McBean
Database Coordinator	Steven Rigg
Official Greeter	Gail Mansfield
Latin America Liason	Vicky Ossio
Clinical Trials Coordinator	Jim Hughes
Photographer	Kim Tallau
Special Projects Asst.	Eileen Glasser
Special Projects Asst.	Dana Kobloth
Science Team	Tanya DeSanto
	Jim Hughes
	David Josephy
	Michael Josephy
	Rick Ware
	Glenn Wishon
	Paula Vettel

BOARD OF DIRECTORS

Executive Committee
Jerry Cudzil — President
Stan Bunn — Past President
Ray Montague — Secretary/Treasurer

Mia Byrne
Chris Carley
Gary Glasser
Jim Hughes
Jerry Knapp
Dan Miller
John Poss
David Safford
Rodrigo Salas
Larry Selkovits

Life Raft regional chapters: Find your reps info at liferaftgroup.org/find-a-support-group/

Alabama	Pat George
Alaska	Jill Heinrich
Arizona	Ellen MacDonald
California	Dina Wiley
	Martha Zielinski
Colorado	Marge Morgan
	Susy Clough
Connecticut	Pat Whitcomb
Delaware	Cindy Bones
Florida	Skip Ryan
Georgia	Pat Lemeshka
Idaho	Janet Conley
Illinois	Jim Hughes
Inxdiana	Debbie Farmer
Iowa	Barbara Kepple
Louisiana	Jackie Welsh
Maine	Jodi Merry
Maryland	Bonnie Emerson
Massachusetts	Charles Burke
Michigan	Ellen Rosenthal
Michigan - West	Cliff Kopp
Minnesota	Ananth Pai
Missouri	Katie Bloss
Montana	Dirk Niebaum
Nebraska	Sally Norton
Nevada	Joan Smith
New Hampshire	Julie Thorne
New Jersey	Anita Getler
New York	Pat Bonda Swenson
North Carolina	Chuck Korte
Ohio	Maryann Snowbrick
Oklahoma	Jane Rowan
Oregon	Gail Mansfield
Pennsylvania	Jeffrey Bernstein
	Carol Heller
Rhode Island	Susan Farmer
South Carolina	Paula Stover
Tennessee	Alice Sulkowski
Texas	Dee Hawkins
Texas -West	Tatiana Avila-Isaias
Utah	Mike Ginsberg
Virginia	Sally Jackson
Washington	Deanne Snodgrass
Wisconsin	Rick Ware

Life Raft country liasons: Learn more about the Global GIST Network & find contact info for your rep at www.globalgistnetwork.com

Argentina	Melisa Biman
Australia	Roy Neil
Belgium	Kris Heyman
Bolivia	Virginia Ossio
Bulgaria	Juliana Popova
Brazil	Valeria Hartt
Canada	David Josephy
Chile	Piga Fernández
China	Ruijia Mu
Colombia	Maria Helena Matamala
Costa Rica	Michael Josephy
Cyprus	George Constantinou
Czech Republic	Jan Pelouchová
Dominican Rep.	Alejandro Miranda
Finland	Mirja Voutilainene
France	Estelle LeCointe
Germany	Markus Wartenberg
Greece	Lefteris Patapis
Guatemala	Silvia Castillo de Armas
Honduras	Xiomara Barrientos
Hungary	Tünde Kazda
India	Paresh Majmudar
Iran	Negar Amirfarhad
Ireland	Carol Jones
Israel	Avi Zigdon
Italy	Anna Costato
Japan	Sumito Nishidate
Jordan	Mohammed Milhem
Kenya	Godsent Odero
Korea	HyunJung Yang
Macedonia	Dejan Krstevski
Malaysia	Choo Sian Yong
Mexico	Rodrigo Salas
Namibia	Lon Garber
Netherlands	Contactgroep GIST
Nicaragua	Maria Teresa Ponce
Norway	Frode Homb
Pakistan	Muhammad Shahid afique
Peru	Eva Maria Ruiz
Phillipines	Rod Padua
Poland	Piotr Fonrobert
Puerto Rico	Eileen Rolon
Romania	Simona Ene
Russia	Tanya Soldak
Samoa	John Galuvao
Saudi Arabia	Mohamed-Elbagir Ahmed
Scotland	Stacey McAully
Singapore	Robert Richardson
South Africa	Annette Mentasti
South Korea	Hyun Jung Yang
Spain	Luis Herrero
Sudan	Mohamed-Elbagir Ahmed
Switzerland	Helga Schnorf
Thailand	Kittikhun Pornpakakul
Turkey	Haver Tanbay
U.K.	Judith Robinson
Uruguay	Fabrizio Martilotta
Venezuela	María Isabel Gómez

---

155 US Highway 46, Suite 202
Wayne, NJ 07470
p: 973-837-9092
f: 973-837-9095
e: liferaft@liferaftgroup.org
w: www.liferaftgroup.org

Facebook
facebook.com/liferaftgroup

Twitter
twitter.com/liferaftgroup

LinkedIn
http://linkd.in/liferaftgroup