Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

August 2011 | In memory of Kaye Thompson, Richard Lowry, Matthew Guthrie, Charles McCurdy. RoseMarie Jackson & Michael Lightle | Vol 12, No. 4

Dutch Group marks one year anniversary of D-Day fundraising in Amsterdam

By Christine Schaumburg
LRG Director of Development

Life Raft Group Research Team member, Dr. Brian Rubin and Life Raft Group's Development Director, Christine Schaumburg, visited Amsterdam in June to recognize the one year anniversary of the launch of Project D-Day with Jeroen Pit and his colleagues who, combined, raised $2.1 Million for the D-Day project in a matter of weeks.

Part of the famed Amstel River in Amsterdam's Dam Square.

See D-DAY, Page 10

Adjuvant Gleevec star of ASCO: What we learned

By **Jerry Call**, LRG Science Director & **Jim Hughes**, LRG Clinical Trials Coordinator

Results of the Scandinavian Sarcoma Group (SSG 18) adjuvant imatinib (Gleevec/Glivec) trial in high risk GIST were presented on June 5, during the Plenary Session of the 2011 American Society of Clinical Oncology conference (ASCO). The Plenary or "all members' session" highlights "abstracts deemed to have the highest merit and greatest impact on oncology research and practice".

Dr. Heikki Joensuu of Helsinki University in Finland was principal investigator for the trial and presented the results. Dr. Joensuu should be familiar to many GIST patients as he treated the first GIST patient with imatinib. He was also one of the principal investigators in the 2001 phase two trial that resulted in approval of imatinib for GIST.

The primary endpoint of the study was to assess recurrence-free survival (RFS) in high-risk GIST (greater than 50 percent estimated risk of disease recurrence) within the first five years following the diagnosis and treatment with adjuvant imatinib for 12 or 36 months. The secondary endpoints included overall survival (OS) and treatment safety.

Four hundred KIT positive GIST patients entered the study. Half were given imatinib for one year and half were giv-

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First GIST tumor board convenes for Latin American docs

By Sara Rothschild
LRG Global Relations Director

Alianza GIST, in partnership with the Life Raft Group, The Max Foundation, and Tecnológico de Monterrey hosted an event for Latin American physicians on Sunday June 5 at the American Society of Clinical Oncology conference (ASCO). The meeting drew physicians from many countries as they discussed best practices in Latin America for Gastrointestinal Stromal Tumor (GIST) and convened a Tumor Board with case discussions. Panelists included Dr. Matías Chacón, Instituto Alexander Fleming (Buenos Aires, Argentina); Dr. Christopher Corless, Oregon Health and Science Universi-

The Panel: Dr. Chris Corless, Eduardo Guzmán, Matías Chacón, & Jonathan Trent.

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Case Study: challenges of long-term therapy in GIST

By Jerry Call
LRG Science Director

Bob (not his real name) was one of the patients in the original B2222 phase 2 trial for metastatic GIST patients, a trial that has been running since 2000.

CALL

For 10 years Gleevec (at 600 mg) had been controlling his GIST, but Bob was struggling with the day-to-day side-effects of Gleevec. Most troubling were the muscle cramps, especially in the arms, that made it difficult to function effectively. Aching in the bones was also a problem; dealing with the side-effects of Gleevec had become a daily battle. Despite being treated at one of the best GIST centers in the country and despite taking supplements, such as calcium, the side-effects continued.

Due to the long-term grind of taking Gleevec and the toxicity he experienced, Bob explained to the LRG that he got "lazy" regarding his dose and started to miss taking his dose more frequently, perhaps once per week.

But then Bob ruptured his Achilles tendon and had to have surgery. With the surgery came inactivity. The nausea that he had more or less successfully battled for 10 years by getting up and moving around after taking his Gleevec, got worse and became harder and harder to tolerate. It was the final straw according to Bob. What began as missing his dose once per week escalated into missing his dose at least three or four times a week. This was not necessarily a conscience decision to skip his dose, it just sort of happened. Perhaps Bob had been lulled into a sense of security, after all Gleevec had been controlling his disease for 10 years.

About six months after his Achilles surgery and after he started frequently not taking his Gleevec, Bob got unexpected news; his latest CT scan showed new tumors in his liver. Bob was removed from the trial as the Gleevec appeared to no longer be working.

Bob decided it was time to talk to his doctor and tell him how much Gleevec he had been missing.

When Bob was able to take his Gleevec, he took it as prescribed six 100 mg pills taken all at one time. With the help of his doctors, Bob now breaks the dose into two, taking 300 mg in the morning and 300 mg in the evening and this has tremendously reduced his nausea.

At this point, it's too early to tell if Bob will again respond to Gleevec now that he is once more faithfully taking his Gleevec or if his GIST has become resistant. What is certain is that Bob is not the only patient that struggles with the side-effects of Gleevec. Long-term therapy requires determination, persistence, great side-effects management and the knowledge/belief that Gleevec is what stands between you and GIST.

The point of this story is not simply "Take your Gleevec". There are very real challenges that patients face every day. Long-term therapy is a daunting challenge that should not be underestimated. Many of us have heard, "You're lucky, you only have to take a pill every day." As most patients know, the reality is different. Gleevec, Sutent and other drugs have side-effects and they can be significant. Taking these drugs every day "to eternity" can be extremely difficult, both from a physical and a psychological standpoint.

Unlike other chemotherapies, oral cancer drugs like Gleevec can often feel like a life sentence. In our next issue we will offer tips and insights into coping with the emotional and physical issues that come with long-term survivorship.

The Life Raft Group

Who are we, what do we do?

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

How to help

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

Disclaimer

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

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

Do you have your own tips for coping with a long-term therapy like Gleevec?

Email us at liferaft@liferaftgroup.org and we might just put it in the LRG newsletter!

Trips & transitions: Where our specialists landed

By Erin Kristoff
Newsletter Editor

GIST is a tricky disease. It's important for patients to find the right doctor, one who understands the disease biology, treatment options and individualized treatment techniques like mutational and plasma testing. In most cases, we encourage our members to seek a GIST specialist.

Recently, there have been a number of shifts in our close-knit GIST physician community and it's making some people a little nervous.

Here, we are breaking down some of these transitions and getting information from the sources themselves.

The moves:

- Dr. Robert Maki has left Memorial Sloan-Kettering Cancer Institute (MSKCC) and is now at Mount Sinai Hospital, both in New York City.
- Dr. William Tap has left UCLA and is now at MSKCC.
- Dr. David D'Adamo has left MSKCC and is now at Dana-Farber Cancer Institute in Cambridge, Mass.
- Dr. Jonathan Trent has left MD Anderson Cancer Center (MDA) in Houston, Texas and as of September 18, will be at Sylvester Cancer Center in Miami, Flor.

I managed to get a hold of Drs. Tap and Trent for discussion.

Dr. Tap can now be reached at MSKCC at the following number: (212) 639-5720.
To get an appointment for **Dr. Trent** after **September 18,** you can call 305-243-5302 or 1-800-545-2292, Monday through Friday from 8:30 to 5PM.
Since his last day is August 8, Dr. Trent has offered his personal email for any patients who need to contact him: jonctrent@gmail.com

Dr. Tap understands the patients' anxiety, "This is a tight community, but GIST remains an area where we will always interact. We're going to make sure they get the best care."


TAP

As for his move, Tap is very excited about working in a facility like MSKCC as the Section Chief of Sarcoma.

"It really offers a lot of different opportunities that you can't find other places. It's one of the largest sarcoma programs in the country and I think some of the basic science research here has a way to advance GIST research. Some of the best surgeons and pathologists in world are here."

Dr. Tap will sincerely miss the patients who could not come with him but is trying to remain in touch through email.


TRENT

But they are still receiving great care at UCLA, he states, "UCLA remains a top notch place and the sarcoma program has tremendous support from the Department of Medicine. Dr. Eilber is there and Dr. Bartoz Milowsky, who I worked with for three years is taking over for me."

Farther west, Dr. Trent is busy preparing himself for his move to Sylvester.

"There is a real need for [GIST specialists] in the Southeast United States," he declares.

While Trent is enthusiastic about his new position, Program Director of the Sarcoma Center at Sylvester, he is having difficulty letting go of his patients in Houston.

"The most difficult aspect of this situation is to move away from so many wonderful patients. I honestly apologize for any difficulties or anxiety this move has caused."

Trent is doing his best to ensure a seamless transition for patients following him and those remaining at MDA.

Drs. Bob Benjamin, Dejka Araujo & Satesh Patel are just a few of the respected physicians currently at MD Anderson.

Both Tap & Trent are energized by the their futures at their respective institutions.

Trent is working to renew mutational testing soon and hopes to include plasma testing as part of his program. Tap is particularly motivated by the collaborative nature of the sarcoma team.

"There are several new sarcoma specialists who are coming [to MSKCC] this year. I'm excited to have them and get them involved in GIST," raves Tap.

Regardless of where these specialists are practicing, they want to assure all of the GIST survivors out there that they will never have to look far for a GIST physician.

"The doctors have shifted around," says Tap, "But they're still out there and they are dedicated to GIST patients."

Member uses fun in the sun to raise funds

LRG Director of Development, Christine Shaumburg was fortunate enough to be in attendance at member, Jason DeLorenzo's annual "DeLoBQ". She said, "He has raised nearly $1,000 so far to support Life Raft's work and will be running in a marathon on October 30 to raise additional funds!"

GIST Research: Articles on the Science of GIST

ASCO 2011: GIST Overview

By Jim Hughes
LRG Clinical Trials Coordinator

This year's American Society of Clinical Oncology conference (ASCO), held in Chicago in June, produced a number of interesting and informative GIST-relevant presentations. Instead of printing them all here and deluging our readers, we are posting them all to our website and you will receive an email alert very soon. Below is a brief summary of these articles.

"Three-year therapy with imatinib is now the new gold standard."
-Dr. Charles Blanke
"The disease we formerly called GIST may now be 10 different diseases..."
-Dr. Jaap Verweij

Key findings:

- Three years of adjuvant imatinib therapy improves overall survival.
- Imatinib levels drop significantly at three months of treatment.
- Regorafenib third line on track with improved survival. More survival data is now available for dasatinib, nilotinib, sorafenib and other third line options.
- GIST genotype based therapy is moving into the clinic.

Implications of longer term therapy

The overall survival benefit found in the 36 month adjuvant imatinib trial means that newly diagnosed GIST patients will likely be on therapy for at least three years and possibly much longer for high risk patients. The key to determining who is a candidate for adjuvant therapy is in using the patients primary tumor pathology report detailing tumor location, size, and mitotic index to determine the risk of recurrence. In the ReGISTRy database, the records of over 30 percent of patients on adjuvant treatment did not have a mitotic index; 10 percent did not have tumor size. Since adjuvant therapy can be a longer term commitment that can encroach on lifestyle, it is important for patients to have an accurate and detailed risk assessment using these key data from the original tumor pathology report.

Published results of the 36 month adjuvant trial also showed that patients with exon 11 mutations got an even greater benefit from longer adjuvant imatinib therapy. Mutational analysis now has the potential to help patients make the adjuvant treatment decision.

While risk analysis is now essential, there is still a question about which patients are most likely to have progress without adjuvant therapy. Formal investigation of biomarkers for risk of recurrence is now needed.

Managing long-term imatinib therapy also needs to be easier. There is a need for formal studies of side effects and compliance management for patients who are at increased risk of encountering problems in these areas. Compliance is even more of a survival issue now.

Read more about adjuvant therapy on page 1.

Imatinib blood levels:

The evidence continues to mount supporting a relationship between imatinib blood levels and progression. There is now also evidence that blood levels decline after approximately 90 days of therapy. There is a growing need for a standard imatinib blood level test and a growing need to incorporate blood level testing into standard practice especially for high risk patients and those experiencing debilitating side-effects.

Third line treatment options expanding and benefits better defined:

Reports on five phase II trials in GIST provided new data about prospective and off-label third line options. Regorafenib looks to be on track as phase II data supports the ongoing phase III trial. Although preliminary, data on other phase II trials in sorafenib and dasatinib may help patients and oncologists make trial participation and off-label decisions for second line patients experiencing progression.

Genotype or subgroup-based therapy:

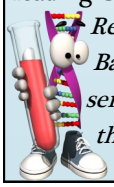
A trial for PDGFRa D842V patients marks the advent of GIST sub-group based therapy. Newly diagnosed patients with stomach primaries have a small but significant chance of having this mutation. Mutation testing for all newly diagnosed patients can help five percent of patients avoid treatment with drugs that are known to have no effect on this mutation.

Treating sub-groups of GIST patients based on mutation will mean smaller target populations for clinical trials and it will be necessary for more trial sites to recruit fewer patients from each site area.

Did you Know?

If the cost of mutational testing is not covered by your insurance agency, you can have your mutational testing done for FREE!

You can do this by participating in the **GIST Collaborative Tissue Bank**. The GIST Collaborative Tissue Bank is a one-of-a-kind tissue bank, where your tumor will help the world's leading GIST researchers search for the cure.



Request more information about the Tissue Bank, by contacting our office. We will send you an instructional package about the program.

Furthering research through the NIH Pediatric GIST clinic

By Carly Smith
National Institutes of Health

From June 15 through June 17, 2011, the National Institutes of Health (NIH) hosted the seventh annual Pediatric and wildtype GIST Clinic. Ten patients from across the United States and Canada attended, accompanied by family members or friends. In total, 80 patients have participated in the NIH Pediatric GIST Clinic, 75 of whom have wildtype GIST. Thirty-five percent of patients have pediatric GIST, currently defined as diagnosis before the age of 19.

The major topics addressed during the clinic included the interpretation of survival data stratified by clinical parameters, the implications of Succinate Dehydrogenase subunit B (SDHB) immunostaining, and how all of this information could help refine the current definition of pediatric GIST.

The average age of patients at the time of diagnosis was 26.6 (range 5-58) and the current average age is 34.3 years with an average follow-up period of 7.3 years (range 0-36).

Sixty percent of patients have now been living with GIST for more than five years, allowing us to generate Kaplan-Meier survival curves. Figure 1 shows the overall survival (OS) and recurrence free survival (RFS) over a five -year period. Although RFS is only 32 percent, overall survival during the same time period is quite high at 93 percent, suggesting that the vast majority of patients have an indolent form of GIST. These values did not vary significantly based on age, with a 24 percent RFS and 88 percent OS for pediatric patients versus 30 percent RFS and 93 percent OS for adult wildtype patients. For those with other types of cancer, recurrence is practically synonymous with poor prognosis. It is very striking that wildtype GIST patients are so different in this regard, in that they continue to do well despite recurrence.

Additional clinical aspects that we investigated serve as important prognostic factors for assessing the risk for recurrence in KIT-mutated GIST patients. These features include the mitotic rate, size, and location of the primary tumor. We observed no significant difference in RFS in our wildtype patients based on these characteristics, suggesting that they do not predict the risk for recurrence in the wildtype setting, as they do in KIT-mutated GIST. This result is important because these characteristics are often used to make decisions about beginning adjuvant therapy. It is our

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Figure 1: OS and RFS over 5 years

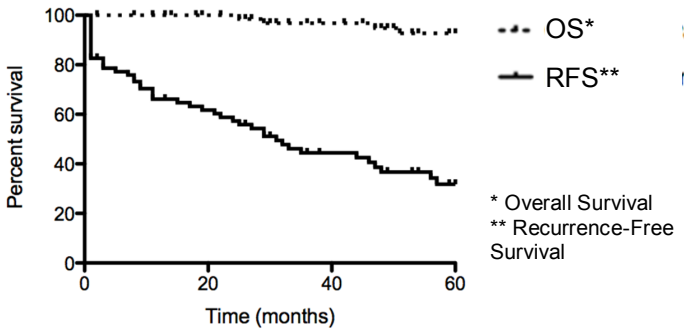
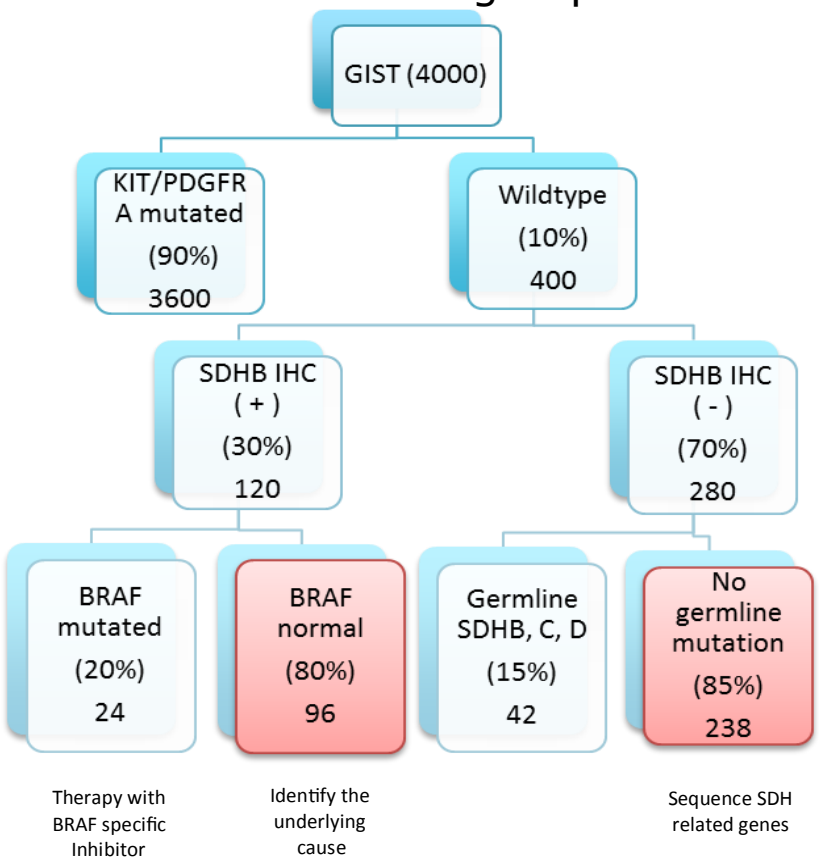


Figure 2: Distinctions between subgroups



Beloved wife, mother & GIST support leader passes at 68

Caroline "Kaye" Thompson, age 68, of Lancaster, died Monday, July 25, 2011 at her residence. Born July 20, 1943 in Pickaway County to the late John J. & Margaret "Margie" (Brungs) Seyfang, she was a 1961 graduate of Walnut High School. Survived by her husband of 46 years, Terry N. Thompson, Sr.; sons, Terry N. (Gianna) Thompson, Jr., Gerry R. Thompson, and Larry L. (Julie) Thompson; grandchildren, John Jacob Thompson, Tyler N. Thompson, Ryan A. Thompson, Samantha C. Thompson & Jack W. Thompson; nepews, John Seyfang, Christopher Seyfang & Shannon Seyfang. In addition to her parents, she was preceded in death by grandparents, Raymond, Sr. & Edna Brungs; brother, John David Seyfang; and niece, Stephanie Seyfang.

Online condolences can be made at www.spencefuneralhome.com

Mark your calendars!

- This year's annual NYC Poker Tournament, hosted by LRG Board President, Jerry Cudzil will be held earlier than usual, on **September 22** (See page 8). Visit www.liferaftgroup.org/poker2011.html for details and registration.
- Jason DeLorenzo (See Page 3) will be running a marathon on **October 30** to raise funds for the LRG. Keep a lookout in the coming months for ways to support him!

Look in your mailboxes for this year's Annual Report!

ADJUVANT

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"The findings mean very simply: The risk of dying within five years of first diagnosis of an operable high-risk GIST is actually halved by 36 months of adjuvant imatinib compared to 12 months of treatment."

-Dr. Peter Reichardt
In June 6, 2011 SPAEN News Release

en imatinib for three years; the median follow-up was four and a half years. The five-year RFS was 66 percent for patients in the three-year group versus 48 percent for those in the one-year group. Patients assigned to 36 months of imatinib also had longer overall survival.

Five-year OS was 92 percent versus 82 percent. Thirty-six months of adjuvant imatinib compared to 12 months essentially halved the risk of recurrence and death. Joensuu reported that imatinib was generally well-tolerated and that the proportion of patients who discontinued imatinib during the assigned treatment period for reasons other than GIST recurrence was 26 percent in the 36-month group and 13 percent in the 12-month group.

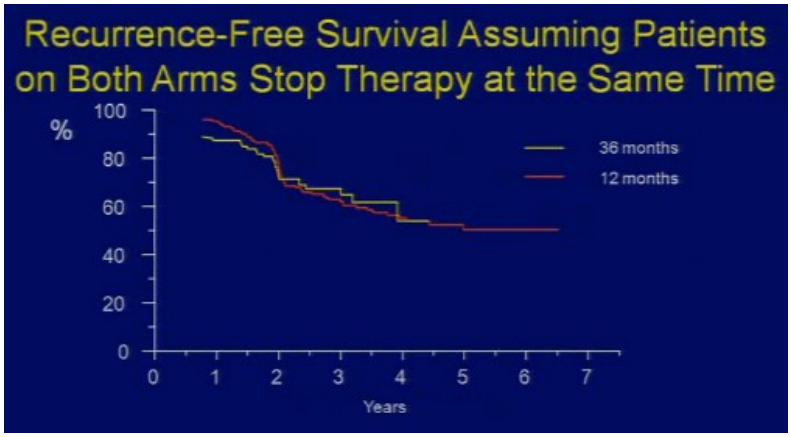
Is three years enough?

Dr. Charles Blanke, one of the four doctors in the first trial of imatinib in GIST (B2222) was the discussant for Dr. Joensuu's presentation. Dr. Blanke addressed the question of the optimal duration of adjuvant therapy for GIST patients. To examine this question, Dr. Blanke first looked for answers in the metastatic GIST setting. He noted that 35 percent of patients enrolled in the longest running metastatic GIST trial, B2222, are still alive at nine years and then posed the question of whether or not these patients were cured. His conclusion was that "No, they are not (cured)".

Dr. Blanke presented two slides from the BFR14 trial comparing metastatic GIST patients that either continued imatinib treatment or interrupted imatinib treatment after one, three or five years. In all cases, the patient groups that interrupted treatment rapidly progressed and the groups that continued imatinib had few progressions. The authors of the BFR14 study concluded that even five years of imatinib was not enough in patients with advanced GIST in complete remission and they wondered whether the findings would be the same for adjuvant use.

In his presentation, Dr. Blanke next talked about previously published results from the Z9001 trial that compared one year of adjuvant imatinib to placebo. In that trial, there were very few recurrences while on active treatment, but once patients stopped imatinib, recurrences

Figure 1



Dr. Charles Blanke, ASCO Plenary Session Discussant, From Here to Eternity: Optimal Duration of Post-Operative Therapy for Patients with Resected Gastrointestinal Stromal Tumors.

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ADJUVANT

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quickly started to occur with a recurrence rate that was similar to the placebo arm. He then showed both the recurrence-free survival slide and a slide that had been altered to show the recurrence curves of the SSG 18 trial, so that both curves started at the point of imatinib discontinuation (the three year curve was shifted to the left), see Figure 1. Just like in the metastatic trial (BFR14), the Z9001 adjuvant trial, patients starting relapsing (having a recurrence) six to 12 months after stopping imatinib.

So the question Dr. Blanke posed was, "Is a three-year treatment duration (versus one year) delaying recurrence two years longer without increasing cure rates?" According to Blanke, "To derive the best interval, we would still need to test multiple possible durations. Of course economic issues and factors related to numbers of patients available . . . limit the feasibility of doing so. In fact, the NCI (National Cancer Institute) rejected the five versus 10 year versus lifelong imatinib trial that was recently proposed. "

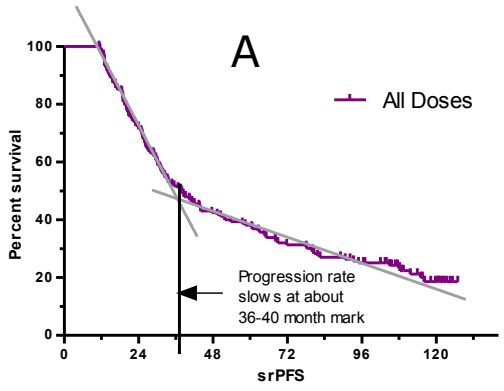
The Plenary Hall seated 14,000 and had 15 projection screens. It was nearly full when Drs. Heikki Joensuu and Charles Blanke presented the SSG 18 adjuvant imatinib study results and the discussion.

Do relapses still occur in patients that have responded to imatinib for over five years?

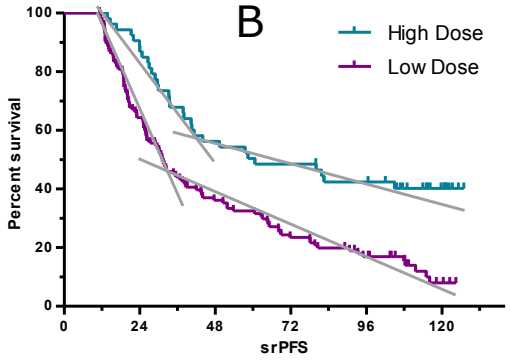
We have heard speculation that perhaps patients reach a plateau at which they no longer have progressions and that this might suggest a cure. Both long-term data from the B2222 trial and internal LRG data suggest that although the rate of progressions may slow, it does not stop. The LRG data supporting this is shown in Figure 2. In Figure 2A, the progression rate of all 169 patients in our study appeared to slow starting at about the three year mark, but progressions still continued, even at the ten year mark. The data presented for the B2222 trial used a different method (the Life-Table Method) and had different patient characteristics (it included a more diverse patient group). When divided into two year progression time points, progression in this group slowed significantly for patients with greater than six years of treatment. Using a similar method, the LRG patients also showed fewer progressions beyond the six year mark, although not as low as the B2222 data.

Figure 2

169 metastatic GIST patients in the LRG registry that reported some shrinkage and responded to imatinib for at least one year.



Combined self-reported progression of 169 patients



Comparison of progression on low/standard dose imatinib vs. high dose (>400 mg) when actual dose is considered

Note: Even at 10 years, there is no point at which progressions stop, even while on imatinib therapy.

In summary, Dr. Blanke addressed three main questions:

1. "Can we administer imatinib for prolonged periods in the adjuvant setting?" He concluded that "the high dropout rate on the three year arm of SSG 18 may have strong implications for the ability to give imatinib for even longer intervals." (i.e. longer than 36 months)

2. "Who should receive adjuvant imatinib?

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NIH

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recommendation that physicians do not use any of the above risk factors alone to determine the need for adjuvant therapy.

Our recent research has focused on the expression of SDH in GIST. A study performed by members of the NIH consortium revealed that 12 percent of patients with wildtype GIST alone had germline mutations in one of the subunits of SDH[1]. More interestingly, when assessed by immunohistochemistry, 70 percent of wildtype patients and all pediatric patients were SDHB negative. These results strongly suggest loss of SDH function is a major determinant in the majority of patients. In light of these new findings, we feel that the current definition of pediatric and wildtype GIST needs to be re-worked in order to better reflect the distinctions between these subgroups.

Figure 2 (Page 5)highlights these differences.

1) Out of the approximately 4,000 new cases of GIST diagnosed every year, only 400 are wildtype.

2) Those 400 cases can be further classified by whether the tumor is SDHB IHC positive or negative.

3) If the tumor is SDHB IHC (+), BRAF mutational testing should be performed. If a mutation is discovered, treatment using a BRAF-specific inhibitor should be initiated. We have observed that tumors with BRAF mutations are more likely to be located in the small bowel, have spindled histology, and occur more frequently in males.

4) The other 80 percent of SDHB IHC (+) GISTs that do not have a BRAF mutation will be the focus of our research initiatives to discover the underlying cause of disease. We have started germline sequencing analysis on patients with SDHB (+) GIST and their parents, to attempt to identify genes that are mutated or deleted that may play a role in tumorgenesis.

5) The majority (70%) of patients with wildtype GIST will be SDHB IHC (-). All of these patients should undergo germline testing of SDH subunits B, C, and D (also A when it becomes CLIA certified). Fifteen percent of patients will have mutations, at which point we recommend genetic screening of immediate family members. Affected family members should then undergo biochemical and radiographic surveillance.

6) Eighty-five percent of patients who are SDHB IHC (-) will not have germline mutations in subunits B, C, and D. One hypothesis is that mutations in other genes important in proper SDH formation and function result in the loss of SDHB staining. Thus, we are currently sequencing tumor samples for all seven recognized components of SDH to test this hypothesis.

The rationale for subclassification is to direct treatment and to focus our research efforts to identify new therapeutic targets. Our goal is to open a treatment protocol with SDHB IHC (-) GIST, targeting the SDH pathway.

LRG BOD member Ray Montague sponsored dinner for the patients & families attending this NIH Clinic at the Children's Inn. Pictured from left: Tricia McAleer, Ray Montague and Maribeth Olt.

Thanks to the continued support of Life Raft Group and the patients who have participated in our clinics, we have made great progress so far. Both continue to provide essential help as we strive toward our common goal.

References:

1. Janeway KA, Kim SY, Lodish M, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl Acad Sci USA 2011;108:314-8.

LRG arrives at ASCO in style!

The Life Raft Group did a full exhibit this year at the annual ASCO meeting in Chicago, Il. The booth was designed and constructed thanks to Board Member Ray Montague (pictured on page 8) and his team at Art Guild, Inc. We would like to extend very heartfelt thanks to Ray & Co. for donating the booth and all of the materials.

Amongst the staffers present - Erin Kristoff, Sara Rothschild, Tricia McAleer, Norman Scherzer, were volunteers Jim Hughes, Board Member & Clinical Trials Coordinator, Sherri Janousky, and Rodrigo Salas (Board Member & President of Fundación GIST México).

Passersby were able to enjoy our lollipop gardens and an abundance of information on supporting GIST patients. In addition, our GIST awareness bracelets went home with medical professionals to the far reaches of the world. Many of our newer friends were excited to see a GIST group that they could direct their patients to or rely on for support.

ALIANZA

From Page 1

ty (Portland, Oregon); Dr. Eduardo Guzmán, Tecnológico de Monterrey (Monterrey, Mexico); and Dr. Jonathan Trent, MD Anderson Cancer Center (Houston, Texas).

A presentation was made by Rodrigo Salas, President of Fundación GIST México, about a new CME accredited training course available in Spanish through Tecnológico de Monterrey. The goal is for physicians from across Latin America to take this educational course to improve their knowledge of treating and managing GIST. For more information, visit www.fundaciongist.org.

Both Dr. Chacón and Dr. Guzmán presented challenging GIST cases for discussion. Misdiagnosis was one key issue and a lengthy dialogue followed regarding ways to optimize this process. The highlighted case underscored the necessity to work with pathologists that see many GIST patients.

SALAS

Causes and possible solutions for progressive disease were also discussed for another case, with many panelists emphasizing the importance of genotyping as a predictor of how GIST tumors respond to drug therapy. The Life Raft Group is able to provide free mutational testing for GIST patients in Latin America through its GIST Collaborative Tissue Bank program. Please visit: www.liferaftgroup.org/TissueBank.html

Cases such as the ones that Dr. Chacón and Dr. Guzmán presented are not rare in Latin America, nor are they in other parts of the world. These problems reach global dimensions and many issues need to be addressed such as:

GUZMÁN

- Incorrect Diagnosis
- Poor Clinical Trial Availability
- Lack of Mutational Testing
- Poor Access to Safe, Effective, and Affordable Treatment

This forum was an important start to closing the information gap among the medical community and increasing the index of suspicion among those that see GIST patients. The tumor board sets a precedent for establishing a more formal structure of physicians to continue the dialogue about regional and global issues that affect patients in Latin America.

D-DAY

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Dr. Rubin presented the latest D-Day project update, first describing the overall goal to leverage the success of tyrosine kinase inhibitors such as Gleevec, which is primarily cytostatic (cells divide but don't die), to discover new gene/protein targets to cure GIST. He highlighted two issues:

- Patients require lifelong therapy with Gleevec or other tyrosine kinase inhibitors
- Patients develop acquired resistance to Gleevec (50% within two years of initiation of therapy)

Dr. Rubin described the four main components of the D-Day project:

1. Sequencing the GIST genome
2. Gene knockdown (RNAi) in GIST models
3. Drug screening
4. Gene target & drug validation

Results were the main focus of Dr. Rubin's presentation in which he reported that **sequencing** is well underway and that the next phase will select the most interesting mutations and validate them on an independent set of GISTs to see if they are common to GIST.

Regarding **gene knockdown**, Rubin reported that population and individual RNA screens have been performed. Analysis is ongoing while validation has been initiated. In addition, new RNA libraries will be obtained to perform additional screens.

Jeroen is the first patient to be inducted into the LRG GIST Hall of Fame. Pictured from left: Rubin; Jeroen's wife, Emelie; Jeroen & Christine Schaumburg

Dr. Brian Rubin presents the LRG Research Team's progress to date to the group of D-Day donors.

The **drug screening** portion of the progress report contained the following:

- The project is screening both compounds that are already developed for clinical use in humans and are even FDA-approved in some cases, but have not been evaluated in GIST along with the evaluation of a library of over 1,000 drug-like molecules that would require further development to become drugs.
- A substantial number of compounds have been evaluated and several KIT inhibitors have been identified and/or validated as well as several compounds that appear to exert activity against GIST without inhibiting KIT. The latter group is interesting because they could potentially be combined with KIT inhibitors such as Gleevec.
- Chemical library screening will be initiated this summer.
- **Validation** of compounds is ongoing.

The D-Day project was launched in 2010, following Jeroen Pit's investigation into the best way to donate to GIST research and perhaps help save his own life. After consulting several leading GIST researchers, the patient decided that the Life Raft Group Research Team gave him the best chance for finding a cure. He raised 2 million dollars and challenged us to accelerate our efforts to keep him and other GIST patients resistant to Gleevec and Sutent alive. We added one million dollars and the result is the aptly named D-Day Project. Like that extraordinary day in 1944, when the Allied forces stormed the beaches of Normandy, our attack on GIST treatment resistance has reached an historic opportunity for success, focusing on the four key areas of sequencing, gene knockdown, drug screening and validation.

An additional $500,000 was raised to supplement the project in early 2011. A portion of this funding allowed for an additional scientist to work on drug screening. The Drug Screening Program will be expedited with two additional scientists added to the team thanks to another $150,000 grant from the Pit family.

Also during their visit to Amsterdam, Dr. Rubin and Christine Schaumburg had the great privilege of inducting Jeroen Pit into the Life Raft Group's GIST Hall of Fame, which was created as a part of the LRG's GIST 2010: A Decade of Difference Gala to honor the greatest contributions to the GIST community. Previous inductees include Dr. Brian Druker & Dr. George Demetri. The first patient to be inducted, Jeroen was recognized for his contributions to help find a cure for GIST patients like him and challenging GIST research.

ADJUVANT

From Page 7

Dr. Blanke pointed out that historically the high risk category was very broad and included patients with 34 percent to nearly 100 percent risk of recurrence.[1] Instead of these broad categories, GIST oncologists currently combine risk factors and give each patient a numerical chance of recurrence.[2]

Dr. Blanke pointed to the subset analysis in the study. In the subset analysis patients were divided into lower and higher risk groups based on known risk factors such as mitotic rate and tumor size, lower than 10 mitoses versus greater than 10 mitoses per 50 high powered fields (HPF) and less than 10 cm versus greater than 10 cm. The results showed that in all categories, patients on 36 month adjuvant imatinib had lower risk of recurrence. As Dr. Blanke explained, this meant that all risk levels in the study would benefit, "We could thus theoretically apply the trial results to all patients with a one in three or greater chance of recurrence. But should we?"

After answering the next question he would come back to that issue.

The subset analysis also showed that patients with either exon 11 or mitotic counts higher than 10 per 50 HPF did even better on 36 months adjuvant imatinib. At the same time patients with exon 9, wild type and other mutations had benefit but these that were not significant when compared to patients with the same mutation status on 12 months of therapy.

3. "What is the ideal duration for post–operative therapy?"

Dr. Blanke suggested that if there was evidence that adjuvant imatinib therapy cured GIST then a finite period of therapy might be possible. He then reviewed the SSG 18 trial, published lab results and several examples of adjuvant therapy for other cancers but found that no clear evidence of a cure following adjuvant imatinib therapy in GIST.

"There are plenty of reasons to think giving imatinib for a longer period would be better, but that theory remains unproven. For now, if I was a patient with resected GIST and I had a compliant oncologist, I would request more. As a compliant oncologist, I personally will offer patients treatment to eternity—meaning indefinitely."

He then came back to the second question.

"But given the possibility we need to treat for a *very* long time, coupled with the difficulty patients have taking long-duration drug, I probably will recommend adjuvant therapy for those with a 50 percent or greater chance or recurrence following surgery alone. I suspect many of you will choose a lower number."

References:

1. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol*. 2006;23 (2):70-83.

2. Gold JS, Gönen M, Gutiérrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *Lancet Oncol*. 2009;10(11):1045-1052.

Q&A with the man behind the presentation

We asked Dr. Heikki Joensuu about the SSG 18 trial results.

Life Raft Group: Did the magnitude of the survival results surprise you?

Dr. Heikki Joensuu: Regarding recurrence-free survival (RFS) and the drop-out rate, the results turned out to be almost exactly what we anticipated when we planned the trial. We expected a hazard ratio of 0.44 for RFS, and it turned out to be 0.46. We anticipated the drop-out-rate to be 20 percent, and it turned out that 13 percent of the patients in the 12-month group discontinued imatinib early due to another reason than GIST recurrence, and 26 percent in the 3-year group.

I considered finding a significant difference in overall survival possible, and this was the analysis I was waiting for most anxiously. We were very delighted to learn that the overall survival figures were high in both groups. Since only few patients died, the estimate for the size of the survival benefit is not very accurate. In other words, the survival benefit is there but we cannot yet be sure how big it is.

LRG: Would you care to offer some speculation about why adjuvant therapy might improve survival compared to just treating at recurrence?

Joensuu: It often makes a lot of sense to treat cancer early when the tumor volume is still small. Small volume disease is easier to eradicate than large volume cancer. Some scientists believe that GIST metastases contain stem cells that cannot be eradicated with imatinib and that these cells will give rise to a new colony of cancer cells when imatinib administration is interrupted. This may not be the case when the tumor bulk is small, as is the case in the adjuvant setting.

New mutations that make GIST resistant to drugs may arise somewhat randomly at those sites of the cancer cell genome that are most vulnerable and that are functionally most active. When the tumor burden is large there are a lot of cancer cells around, each of which can generate a drug resistance mutation. When imatinib is administered soon after clinically complete surgery there are only few (or no) GIST cells left behind and it will thus likely take a long time for a drug resistance mutation to emerge - or perhaps it will never emerge.

We should not be too pessimistic about novel ways to treat cancer without first testing them. A classic example is tamoxifen that cannot cure anybody who has metastatic breast cancer, but when it is given soon after breast surgery before overt metastases have appeared, permanent cures are frequent. GIST is very different from breast cancer and imatinib is different from tamoxifen, but there may still be some analogy here.

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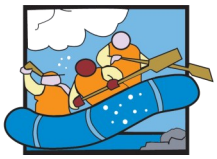

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