The state of the Life Raft Group in 2006

Scherzer reviews Life Raft accomplishments over the past year.

By Norman J. Scherzer
LRG Executive Director

The mission of the Life Raft Group remains the survival of patients with GIST… By making sure that no one dies because they cannot access lifesaving treatment… By making sure that no one dies because of ignorance, either their own or that of their physician… By ensuring that no one has to face GIST alone… And, by directing the coordinated implementation of a strategic plan to find a cure for GIST…

The following projects illustrate the new challenges the Life Raft Group continued to take on in 2006:

● Our monthly newsletters, websites, listservs and pamphlets reached growing audiences around the world. We continued to expand our website, including our worldwide GIST Specialist Directory. Our newest website, the Global GIST Network (www.globalgist.org), was extremely cost effective in linking patients and caregivers to resources in their own country and languages.

● Our third annual Life Fest meeting brought patients and caregivers from the United States, Europe and South America together in Dallas, Texas.}

Overcoming treatment resistance in GIST patients

By Dr. Jonathan A. Fletcher
Department of Pathology
Brigham and Women’s Hospital
Boston, Mass.

Note: Dr. Jonathan Fletcher is a member of the LRG Research Team working to understand and overcome GIST treatment resistance. This is the first article in a series to be written by each of the key research team members. In September 2006, Dr. Fletcher was presented with the LRG’s first Researcher of the Year Award by Dr. Daniel Vasella, Chief Executive Officer of Novartis, at a meeting of the Life Raft Group in Dallas, Texas. He is considered by the LRG to be the lead coordinator of the research team.

Most GISTs are “driven” by mutations of the KIT or PDGFRA genes. The mutant KIT or PDGFRA genes produce activated receptor tyrosine kinase proteins, and the activated proteins send signals into the GIST cells, directing the cells to grow. In fact, these activated proteins are largely responsible...
Questions to consider for adjuvant treatment

By Jerry Call

GIST patients face many decisions about their treatment. Many GIST patients have surgery to remove a primary tumor and do not have detectable metastases at the time of surgery. This large group of patients faces the decision of whether or not to take Gleevec to try to prevent or delay a recurrence. Adjuvant therapy refers to additional treatment given after a main mode of therapy (the main treatment is usually surgery). For example, Gleevec given after surgery in hopes of preventing or delaying a recurrence is called adjuvant therapy.

Several adjuvant Gleevec trials are ongoing, but results from these trials will take years. The predominant opinion that I have heard from GIST experts is that adjuvant treatment is a research treatment and should only be given in clinical trials. I respect this opinion and await the results of these trials before I can make any finite judgment about the benefits of adjuvant Gleevec.

Many GIST patients, however, do not have the time to wait for the results of the adjuvant Gleevec trials; they have to make decisions immediately. For some, part of the decision is made for them; they do not have insurance that will cover adjuvant treatment. Their only choice is to enter a trial where some of the trials may contain a placebo. Most patients recognize that the benefit, if any, of adjuvant Gleevec is unknown and many gladly participate to help answer the questions about adjuvant Gleevec.

Some patients do have insurance that will pay for adjuvant Gleevec and these patients have a decision to make. They may receive advice for or against adjuvant treatment. In the absence of clinical trial results, the remainder of this article will attempt to convey some of the potential pros and cons of adjuvant Gleevec for GIST patients. It is written by a layperson and is intended to provide discussion points for patients to talk to their doctors about.

Some limitations of adjuvant trials:

- Most of the trials are still accruing patients. Even after patient accrual is finished, it will take years before the results are final. It is possible that we may see some interim data before this.
- Patients may continue to take Gleevec on their own after the trial period. This may affect the trial results.
- The trials only examine lower doses of Gleevec.
- All of the existing adjuvant Gleevec trials give Gleevec (or placebo) for a fixed period of time (varying from one to three years) and then Gleevec is discontinued.

Does adjuvant Gleevec prevent recurrence?

This is unknown and the subject of the trials. It is well established that patients with measurable disease that stop taking Gleevec have a very high chance of progression. Gleevec does not kill all GIST tumor cells. Some residual cells remain alive after/during Gleevec treatment which become active again after Gleevec is stopped. The number of residual cells may vary greatly from patient to patient. Some may only have a small number of viable cells left and, for others, the vast majority may still be viable.

Does adjuvant Gleevec promote resistance?

This is unknown. Theoretically, for KIT exon 9 patients, the 400 mg dose being used in adjuvant treatment has been shown to be ineffective as a first-line treatment against measurable disease. For patients with measurable disease, Heinrich et al. showed that patients on high-dose Gleevec respond 8 times as often as patients on low-dose Gleevec.
Finding a silver-lining when living with cancer

By Erin Kristoff

This article is part of the “Artists of the Life Raft Group” series. The series focuses on the various talents of our members and how it helps them cope with their cancer.

Rachel Tate is very excited about a new change in her life. She is about to move into a new house that has a studio. Why is this so important? Because Rachel will have a new space to do her favorite activity with her sister, both of whom love the art of silversmithing. Rachel cuts, forges and solders silver. Living in South Carolina, Rachel lives close to silver mines and sometimes she and her sister mine their own stones.

This was not always Rachel’s favorite past time. It took a little push by someone very special for Rachel to discover the joys of silversmithing. “GIST inspired me, really. My sister has been my guardian angel and taken care of me, and has been so wonderful. Right after I had surgery and found out four years ago that I had cancer, she gave me a trip to a folk art school for my birthday and I got to pick which class I wanted, so I picked silversmithing. She went with me and we both got hooked on it. It was really her trying to find something that would inspire me and get my mind off of [GIST].”

And inspire her she did. Rachel and her sister now have their own company named “Oops” (Named for the word they used many times a day when first starting their endeavor) and sell their jewelry and other silver pieces at private showings. They are different from many artists in that they polish their silver and bring it to a nice shine before completion. Most choose to leave their pieces in a dull form, but Rachel and her sister love to take on the difficult task of polishing and making the silver brilliant. “Our favorite instructor used to call us the Shiny Girls!”

This art has also aided Rachel in her battle with GIST. “[I can turn out a beautiful piece of jewelry and it just takes me into another world. One piece in particular always brings a smile to her face. “It was a piece we entered into a national contest. It was a labor of love and it turned out so beautifully. It is an old fashioned garden party hat, when you look at it you just feel like you’re at a garden party. Any time we can bring joy into our lives it lifts us up out of this cancer.” Rachel thinks that everybody fighting GIST can feel this way.

Anybody that has [cancer] should find some kind of outlet to give them a sense of peace. It takes you out of the misery and the worry. Get a hobby!” When Rachel is not busy forging silver, she likes to read and spend time with her seven grandchildren. In fact, on a recent trip to Dana-Farber Cancer Institute, Rachel showed her oldest grandson (age 12) the sites of Boston. “I try to turn those trips into a fun time.” Rachel’s favorite place in Boston is the Museum of Fine Arts and the impressionist gallery, housing famous pieces by Van Gogh, in particular.

When she is home Rachel has her three sons, sister and brother-in-law to help support her and lift her spirits up, as well as her church. “My friends at church—they pray for me and I truly believe in the power of prayer.”

Rachel has no complaints; her art, family and friends have made her life whole, she feels truly blessed and does not fear for her future. “My life is so full, it’s just so wonderful. I would like to see my grandchildren mature and be a part of their lives for as long as possible. But I don’t feel that cloud hanging over my head.”
for causing GISTs to develop from normal cells in the first place.

Most patients with GIST have their lives prolonged and suffering ameliorated using first-line treatment with imatinib mesylate (Gleevec™) which binds directly to the mutant KIT and PDGFRA proteins and inhibits their activity (1;2). The striking clinical responses to imatinib fully validate the essential oncogenic role served by KIT activation is not just essential to the development of GISTs, but actually plays an initiating oncogenic role in a subset of patients (3-5). It is not surprising, therefore, that kinase-targeting therapy with imatinib has profound effects on GIST viability, given that most GIST cells depend on an uninterrupted chain of signals emanating from the constitutively activated KIT or PDGFRA proteins. Unfortunately, even patients with nearly complete clinical responses can develop resistance to imatinib, as manifested by clinical progression of GIST. Such clinical progression typically occurs after a median of approximately 18 to 24 months after the start of imatinib therapy. The alternate small molecule therapeutic, sunitinib malate (Sutent™) which inhibits a broader spectrum of tyrosine kinase signaling proteins, can induce clinical disease control and prolong survival for patients when given second-line following failure of imatinib (6), but many patients with imatinib-resistant GIST do not benefit from sunitinib. Given that few patients have a complete response to imatinib, it is possible that most patients with metastatic GIST will ultimately develop imatinib resistance mechanisms. Several studies have shown that the dominant imatinib resistance mechanisms vary from patient to patient, and that resistance mechanisms can also vary between different metastatic lesions in a given patient (7-9).

KIT oncogenic exon 11 mutations, which are found in approximately 75 percent of GISTs, abrogate juxtamembrane region autoinhibition of the KIT kinase. Virtually all of these KIT exon 11 mutants are highly sensitive to imatinib, and patients with such mutations have better than an 80 percent clinical response rate to imatinib (10;11). At time of clinical progression on imatinib, most GIST patients with “primary” KIT juxtamembrane mutations will demonstrate additional mutations in the kinase domain (7-9;12). These kinase domain mutations are found on the same “alleles” (i.e. the same copies of the KIT gene) as the primary exon 11 mutants, and are presumably present in a small percentage of cells in the untreated GISTs – providing a selective advantage to those cells during imatinib therapy, rather than arising, de novo, as a complication of imatinib. Some of these secondary kinase domain mutations are intrinsically imatinib-resistant, as is the case with the frequently-encountered V654A mutation. However, other secondary kinase domain mutations, including those involving the activation loop N822 residue, are intrinsically imatinib-sensitive, but endow resistance when coupled with a KIT juxtamembrane region mutant, perhaps due to hyperactivation and structural changes in the KIT oncoprotein (7).

The major challenge in confronting imatinib (and sunitinib) resistance mutations clinically is the apparent heterogeneity of such mutations that can be identified amongst individual GIST patients. This clinical reality suggests that although newer generations of broad-spectrum, increasingly potent, KIT/PDGFRA kinase inhibitors will benefit patients progressing on imatinib therapy, such drugs – on their own – are unlikely to cure many patients with imatinib-resistant disease. Therefore, novel therapeutic paradigms are needed urgently, including those whose success is less dependent on the specific mutational mechanisms of KIT/PDGFRA activation. One such approach involves inhibition of the KIT chaperone, HSP90. This strategy, in preliminary studies, was particularly effective against the hyperactivated KIT oncoproteins containing imatinib-resistance mutations (13). Clinical trials of HSP90 inhibitors have begun recently at Dana-Farber Cancer Institute, but much work undoubtedly remains to determine the most effective ways of administering these promising drugs. Another clinical strategy, in patients with imatinib-resistant GIST, might involve transcriptional repression of the KIT oncogenes, as can be accomplished experimentally using flavopiridol (14), and where the presence of imatinib-resistant mutations would appear to be irrelevant to therapeutic efficacy. Still another strategy for imatinib-resistant GIST is drug targeting of intermediate waypoints in the growth-promoting cell communication pathways regulated by KIT and PDGFRA oncoproteins. For example, the kinase pro-

Diagram describing imatinib resistance at the molecular level.
The Life Raft Group would like to thank those members, families and friends who responded to our annual holiday fundraising campaign this year.

The Life Raft Group provides members with supportive e-mail communities and local groups to ensure that no one has to face this crisis alone.

Our websites, newsletters and educational materials provide the leaves of knowledge to ensure that no one has to die from ignorance about the diagnosis and treatment of GIST.

Our advocacy and interventions provide the safety nets to ensure that no one has to die because of a lack of access to treatment.

And, most importantly, our research is focused upon an unprecedented coordinated strategy to find a cure for GIST.

Now, more than ever, the Life Raft Group needs your support and participation in order to continue our life-saving efforts. If you have not yet done so, please help.

You can mail your check payable to the Life Raft Group and send it to: The Life Raft Group, 40 Galesi Drive, Ste. 19, Wayne, NJ 07470. Or you can donate online at www.liferaftgroup.org/about_contribute.html.

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### Defining Risk of Aggressive Behavior in GISTS

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**Other High Risk Factors:** Lack of clear margins, tumor rupture, small bowel may be more aggressive.

**Note:** Recent papers by Meittinen may provide better risk assessment for gastric GISTs. See LRG website for additional information: [http://www.liferaftgroup.org/gist_diagnosis.html](http://www.liferaftgroup.org/gist_diagnosis.html)

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### Magic Leaves Fundraising Campaign

Debiec-Rychter et al. demonstrated that exon 9 patients on high-dose have a median progression-free survival time that is almost 5 times as long as patients on low-dose Gleevec.

In the lab, one of the ways scientists use to produce Gleevec-resistant cell lines (such as the CML cell line, K562/G01) is to culture the cell line in a sub-optimal concentration of Gleevec for several months. Thus, one wonders if giving an exon 9 patient 400 mg of Gleevec when there is no visible tumor to gauge Gleevec effectiveness could lead to premature resistance.

**Know your Risk of Recurrence:**
Not all GIST patients are at high risk of recurrence. Patients at low risk of recurrence may never have a recurrence or they may have a recurrence 10 or more years from now. By that time, it is likely that we will understand GIST much better and have even better drugs that we do today. Adjuvant Gleevec makes much more sense for patients with a high risk of recurrence. The ongoing adjuvant trials are for patients with high and intermediate risk.

**Can we Predict Adjuvant Gleevec Benefit?**
No, but in the absence of clinical trial data, we can generate some hy-

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international experts and researchers. Highlights included key presentations by Dr. Daniel Vasella, Chief Executive Officer of Novartis, David Epstein, President of Novartis Oncology, Dr. Jonathan Trent of MD Anderson Cancer Center, Monica Davey of Fox Chase Cancer Center, Dr. Marie Debiec-Rychter of Catholic University in Leuven, Belgium, Dr. Matthew van de Rijn of Stanford University Medical Center, Dr. Jonathan Fletcher of Brigham & Women’s Hospital and Dana-Farber Cancer Institute, Dr. Chris Corless of Oregon Health and Science University & Portland VA Medical Center, Dr. Brian Rubin of the Cleveland Clinic and Dr. Laurie Letvak of Novartis.

- Our research team completed the first six months of a two year project, funded by the Life Raft Group, to implement a coordinated strategy aimed at finding the reasons for GIST treatment resistance and ways of overcoming them. A copy of this strategic plan, the world’s first, can be found on our website at http://www.liferaftgroup.org/research.html and an article by our lead researcher, Dr. Jonathan Fletcher, can be found in this January 2007 Newsletter on page one.

- We expanded our Science Team and our worldwide surveillance program to track new clinical trials and new drugs.
- We planned the foundation for creating pediatric GIST centers of excellence on two parallel tracks, one virtual and one physical. We are collaborating with the Texas Children’s Cancer Center to provide on-site consults and ongoing care to pediatric GIST patients who can get there. On the virtual track, we have established a core group of specialists in oncology, surgery and pathology who have agreed to review cases by teleconference. We tested the concept recently by successfully arranging a transatlantic surgical consult.
- We continued to form strategic alliances with sister groups throughout the world. We maintain a key alliance with Das Lebenshaus and Association of Online Cancer Resources, with whom we coordinate the Global GIST Network.
- We continue to work behind the scenes to advocate on behalf of patients trying to access treatment, often in remote corners of the world. We occasionally find it necessary to be more confrontational in order to keep patients alive. This is an example of one such intervention:

  A member of the Life Raft Group from another country reached out to us in desperation. He was resistant to Gleevec and needed to start Sutent. The problem was that he had been waiting for several months for his medical center to begin a clinical trial that would permit him to have access to this drug.

  We were asked to write a letter to the head of the hospital. This is what happened.

  This is an excerpt from the letter we wrote:

  Dear Dr. _____

  “…(Patient’s) medical condition is deteriorating rapidly as you go through your internal procedures….In other words, he is dying as you, and your staff, are working on the paperwork for this trial….The progression of life threatening illnesses like GIST may not…wait for the normal deliberative process….and may require that a responsible person intervene…I take personal responsibility for holding you accountable to that end…We shall be covering this story in our Newsletter…”

  This is an excerpt from the response of the Hospital Director:

  Dear Mr. Scherzer,

  I received with astonishment your letter…it seems that what you are really after ….is circumventing legal proce-
potheses from what we already know:

**Most likely to benefit**
- High-risk patients with:
  - Exon 11 mutations
  - Exon 9 patients taking high-dose Gleevec on an adjuvant basis

**Least likely to benefit**
- Low-risk patients
- High-risk patients with:
  - Exon 9 mutations while taking low-dose Gleevec on an adjuvant basis
  - Non-responsive mutations
    - PDGFRA D842A, etc
  - Wild-type GIST (Note: This is more speculative than others.)

Note: Sutent has also shown good activity for exon 9 mutations in second-line therapy; however, no adjuvant trials have tested Sutent for GIST.

Recommended or not, many patients are taking adjuvant Gleevec outside of clinical trials. By understanding some of the issues regarding adjuvant Gleevec, patients and their doctors can make more informed choices about adjuvant Gleevec.

### Surgery and Imatinib for GIST: Clinical Trials*

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<tr>
<td><strong>Phase II Study of Adjuvant Imatinib Mesylate in Patients With Completely Resected High-Risk Primary GIST (ACOSOG-Z9000)</strong></td>
<td>End points: survival, 2- and 5-year recurrence rates, toxicity; imatinib therapy initiated within 84 days of surgical resection, continuing for 1 year; enrollment complete (N = 110) <em>Note: This trial is closed. The first interim analysis is expected in 2006.</em></td>
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<td><strong>Phase III Randomized Study of Adjuvant Imatinib Mesylate in Patients With Resected Primary GIST (ACOSOG-Z9001)</strong></td>
<td>End points: overall, recurrence-free survival; imatinib or placebo administered postoperatively for 1 year, with crossover to imatinib if recurrence; projected enrollment <em>has been expanded from 489 patients to 732 patients.</em></td>
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<tr>
<td><strong>EORTC Soft Tissue and Bone Sarcoma Group (EORTC-62024) randomized phase III trial</strong></td>
<td>End points: overall, recurrence-free survival; risk stratification/randomization after complete GIST resection to imatinib or no treatment for 2 years; projected enrollment = 400</td>
</tr>
<tr>
<td><strong>Scandinavian Sarcoma Group Trial SSGXVIII</strong></td>
<td>End points: recurrence-free survival, safety, overall survival; imatinib administered postoperatively for 12 or 36 months; projected enrollment = 80</td>
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<td><strong>Phase II Study of Neoadjuvant and Adjuvant Imatinib Mesylate in Patients With Primary or Recurrent Potentially Resectable Malignant GIST (RTOG-S0132)</strong></td>
<td>End points: progression-free survival, objective response rate, safety; 8 weeks of imatinib therapy, then surgical debulking of all gross tumor and reinstitution of imatinib for 2 years; projected enrollment = 63</td>
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<td><strong>Post-Marketing Clinical Study of Postoperative Adjuvant Therapy With Imatinib Mesylate in Patients With Gastrointestinal Stromal Tumors (GIST) (CNT00171977)</strong></td>
<td><em>End points: relapse-free survival in high-risk GIST patients receiving 400 mg of Gleevec for one year, and survival for three years after surgery for their primary tumors. Location: Tokyo, Japan</em></td>
</tr>
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<td><strong>Phase II Study of Neoadjuvant Imatinib Mesylate in Patients With Locally Advanced Gastrointestinal Stromal Tumor (Germany/Austria)</strong></td>
<td><em>End points: Primary: objective response rates and histological response rates. Secondary: R0-resectability and organ-preserving resectability, correlate radiographic and metabolic imaging with response; projected enrollment = 40</em></td>
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GIST indicates gastrointestinal stromal tumor; ACOSOG, American College of Surgeons Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group.

*Clinical Management of GIST-Highlights Newsletter-Understanding the New Paradigms (Highlights from the Helsinki and Barcelona Conferences)
*Represents new information added after the Helsinki and Barcelona Conferences.

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### Cancer Care Teleconference

On Tuesday, January 30 from 1:30 p.m.-2:30 p.m., CancerCare will be hosting a free telephone education workshop for people living with gastrointestinal stromal tumors, their families, friends and health care professionals.

The teleconference, “Treatment Update on GIST,” will include:
- Overview of GIST
- Current Standard of Care
- New Treatment Approaches
- Clinical Trials
- Pain and Symptom Management
- Communicating with Your Health Care Team
- Quality-of-Life Considerations
- Questions For Our Panel of Experts

To register, call 1-800-813-HOPE (4673) or register online at www.cancercare.org.
teins PI3-K and AKT seem to play crucial roles in translating KIT activation signals into GIST cell growth and survival: these “downstream” kinase proteins continue to be activated and important in GISTs that have developed imatinib and sunitinib resistance (7;15). Clinical trials of the AKT inhibitor, Perifosine, are ongoing at MD Anderson Cancer Center, and one expects that additional trials will commence once effective and selective PI3-K inhibitors—whose development is an extremely active effort at many pharmaceutical companies—are available for testing. These and other observations suggest a scenario in which patients will benefit ultimately from combinations of GIST therapies that biochemically inactivate KIT and PDGFRα (e.g. imatinib, sunitinib, nilotinib, and others), destroy KIT and PDGFRα (e.g. flavopiridol), and block the ability of KIT and PDGFRα to send activating signals into the cells (e.g. AKT and PI3-K inhibitors).

In all, the complexity and heterogeneity of imatinib-resistance mutations can seem a daunting clinical challenge, but the good news is that this challenge is being met head-on by many GIST research groups and with expectations of success. New therapeutic approaches are certainly in order, and several such are already in the works, with others to follow in the next few years. Combinations of targeted therapies should ultimately serve the goal of fully shutting down KIT and PDGFRα oncogenic signaling pathways in GIST, thereby transitioning the dramatic successes of imatinib more routinely into long-term GIST control and cure.

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In all, the complexity and heterogeneity of imatinib-resistance mutations can seem a daunting clinical challenge, but the good news is that this challenge is being met head-on by many GIST research groups and with expectations of success. New therapeutic approaches are certainly in order, and several such are already in the works, with others to follow in the next few years. Combinations of targeted therapies should ultimately serve the goal of fully shutting down KIT and PDGFRα oncogenic signaling pathways in GIST, thereby transitioning the dramatic successes of imatinib more routinely into long-term GIST control and cure.
dures and trying to influence legal judgment...Furthermore, I consulted with our legal advisors and we are all in the view that your letter should it get published constitutes...slander...Our institution shall take all necessary legal measures in that event...

This is an excerpt of an e-mail received from the patient less than 24 hours later:

"Dear Norman,

The good news reached us just now!!!! Your letter...has done it...although Dr. ___ is upset...This news was given to us today by an official of the...Cancer Association, calling from home...If you manage to move Dr. ___, I am sure you could move the Rocky mountains to Egypt...May God bless you...."

Although we are proud of our accomplishments in 2006 and pleased to report on the positive state of the Life Raft Group, we are also saddened by the death of so many members and the imminent prospect of so many more.

On a personal note:

Great wars are defined by their vastness of scope and casualty such as was the case in World Wars One and Two. Although such wars are often subject to continuous debate about the moral imperatives of the combatants, they all have in common that sooner or later they end, either with one side declaring surrender or both sides, as was the case in Korea, deciding that there was nothing to gain by further combat. In either event the survivors are often awarded medals and the dead are often buried with high ceremony and honor. In most wars, certainly the great ones, memorials are erected with care, and attended with respectful reverence on the anniversary of their cessation.

The war against cancer was formally declared by then President Nixon in 1971. It too could be defined by its vastness in scope and casualty as a Great War. But there the comparison ends. Its casualties are not tallied in daily media reports. Its heroes are not presented with medals. Its dead are not marked by memorials or commemorations. Certainly victory has not been declared and for too many will not come in time.

In a future newsletter we will discuss how the Life Raft Group’s research plan to find a cure for GIST can serve as a model for curing other cancers.

Howe fought GIST courageously

Peggy Lee Howe, 60, of Boynton Beach passed away peacefully on Monday, December 11, 2006. Peggy was born on March 31, 1946. Formally of Michigan, she moved to South Florida in the early 80's. Peggy is survived by her loving daughter, Marsha Lynn Plesko and beloved grand-daughter, Jamie Lynn Plesko; 12 devoted brothers and sisters: Jack, Sandy, Kathy, Brenda, Ross, Kim, Donna, Jerry, Ronnie, Judy, Scott and Danny; and ex-husband Richard Howe. Peggy fought cancer courageously with the help of family, friends and an invaluable support group. For those wishing to make a donation to the support group in memory of Peggy, contact Life Raft Group 973-837-9093 or visit www.liferaftgroup.org. To express condolences and/or make donations, visit PalmBeachPost.com/obituaries. Published in The Palm Beach Post on 12/13/2006.

Lee Cousins, age 58

Leonie (Lee) Anne Cousins died peacefully on Thursday, December 14, 2006 at Mount Sinai Hospital at the age of 58.

Lee is survived by her beloved sister Jane and brother John. She is the loving daughter of Janet and the late Gerald. She will sadly be missed by Don.

As expressions of sympathy, donations to the Canadian Cancer Society or the Mount Sinai Hospital Foundation would be appreciated by the family. Online condolences may be made at earlyfuneralhome.com
January 2007 clinical trial update

By Jim Hughes
Member of LRG Science Team

XL820 (Exelixis)
This drug inhibits c-Kit, PDGFRb and VEGFR. It is similar to the OSI-930 drug below. Data presented by Exelixis in a poster at EORTC in October 2006 showed results for 23 evaluable patients in phase I, including one GIST patient. The GIST patient had stable disease after 3.5 months on XL820. Exelixis has a phase I trial listed in the clinicaltrials.gov database to assess “the safety and tolerability of XL820 when given orally.” The listing says it is not open but we checked with one of the sites (Texas) and understand that it is now open. The sites are: The Cancer Institute of New Jersey, New Brunswick, N.J.- Mark Stein, M.D., and the Cancer Therapy and Research Center, San Antonio, Texas- Kyriakos P. Papadopoulos, M.D. This trial is open to patients with solid tumors failing standard therapy.

OSI-930
OSI Pharmaceuticals has begun a phase I trial of the compound OSI-930 at two locations in the United States and one in Europe. The trial is for patients with advanced solid tumors, but will admit GIST patients. Locations include:
- Dana-Farber Cancer Institute- Boston, Mass. (Dr. George Demetri, Principal Investigator)
- Colorado University- Denver, Colo.
- Royal Marsden Hospital- London, UK (Dr. Michelle Scurr, Principal Investigator)
OSI-930 is a new small molecule tyrosine kinase inhibitor. It inhibits c-Kit, VEGFR and PDGFRb. The trial began in August. Up to 60 patients are expected to be accrued.

Sutent
In the United States, Canada, the United Kingdom and the European Union countries Sutent is now approved for patients failing Gleevec or those who cannot tolerate Gleevec. In addition, Sutent continues to be available to patients via the “Treatment Use Protocol,” which is “four weeks on/two weeks off” (50 mg). There are many sites open throughout the world. Site information changes frequently; for the most current information, contact EmergingMed at 1-877-416-6248 (outside the United States) or at 1-800-620-6104 (inside the United States). If international patients have problems with the listed number, use email at: sutent@emergingmed.com.

In September Pfizer posted a new phase III trial on the NIH website. This study will compare 37.5mg daily of Sutent with 800mg daily of Gleevec for patients progressing on 400mg of Gleevec. Anticipated enrollment is 212. Site information has not yet been announced. According to the listing this trial is not yet recruiting and is scheduled to start November 2006. It had not yet started when we last checked on November 17.

AMN107 + Gleevec
The combination of AMN107 and Gleevec may have a broad spectrum of activity against primary and secondary mutations in GIST. The generic name for AMN107 is nilotinib and our understanding is that the brand name will be Tasigna. The phase I trial is now closed at all sites. A phase III trial is planned. In the meanwhile, access to AMN107 is available through a compassionate use process.

IPI-504
The IPI-504 phase I trial is open for patients resistant to prior therapies and is accruing patients at Dana-Farber Cancer Institute. It undergoes fairly frequent start/stop periods as cohorts accrue.

IPI-504 is an inhibitor of Heat Shock Protein 90 (HSP90) and has been the subject of articles in the November 2005 and January 2006 editions of the Life Raft Group newsletter.
Ensuring That No One Has To Face GIST Alone — Newsletter of the Life Raft Group — January 2007 — PAGE 11

TRIALS

Raft Group newsletter. This is an intravenous drug which is administered twice a week for two weeks followed by a one week off period. IPI-504 is administered without Gleevec. We understand that a second schedule of treatment without a one week off period is beginning.

**Genasense + Gleevec**

A phase II trial testing the combination of Genasense plus Gleevec in patients with Gleevec-resistant GIST recently opened.

Genasense (Genta Inc.) is an antisense drug that inhibits bcl-2. Bcl-2 is a protein involved in cellular survival. This drug is administered intravenously. It is hoped that Genasense may help Gleevec kill tumor cells by making them more sensitive to Gleevec. This trial is currently open only at M.D. Anderson. Several other trial sites are planned including: Dana-Farber Cancer Institute, Boston, Mass.; University of Michigan Comprehensive Cancer Center, Ann Arbor, Mich.; Mayo Clinic Cancer Center, Rochester, Minn.; and Memorial Sloan-Kettering Cancer Center, New York, N.Y.

**Perifosine (Keryx Biopharmaceuticals)**

Keryx Biopharmaceuticals has perifosine (KRX-0401), an oral drug that inhibits the AKT protein. AKT is an antiapoptosis protein. It is speculated that inhibition of AKT might enhance therapy. Apoptosis is a form of controlled cell death, a type of cellular suicide where the cell issues its own death warrant.

**Perifosine + Gleevec Phase II**

A phase II trial, which combines Perifosine with Gleevec, is open at M.D. Anderson Cancer Center, Houston, Texas; Oncology Specialists, Park Ridge, Ill.; and under Dr. Sant Chawla at the Cancer Center at Century City in Los Angeles, Calif. This trial is accruing Gleevec-resistant GIST patients.

**Perifosine + Sutent Phase I**

This phase I trial is primarily for renal cell cancer and GIST patients. It has two parts. The first part will determine the maximum tolerable dose (MTD) in a four week “on,” two week “off,” six week cycle. The second part of the phase I trial will use the MTD to determine if a larger group of patients can remain on the drug for two six week cycles. The inclusion criteria includes the following caution:

“The physician must believe that the patient’s course and the growth rate of the tumor are such that the patient would feel comfortable continuing treatment for 12 weeks even if there is a transient period of modest tumor growth during the first weeks following the initiation of perifosine and sunitinib malate treatment.”

It is not stated that tumor growth or failure on a current treatment is a necessary condition for entry into this trial. Patients who have received prior Sorafinib or Sutent are eligible for this trial.

On December 6, the first meeting of the Georgia LRG Group took place at Emory University Hospital Winship Cancer Center. Dr. Michael Fanucchi, a GIST expert, was guest speaker and listened intently and answered questions of many GISTers and their family members.

Standing from left to right: Claire Davis, Anne George, Pat George, Sue Rink and Pat Lemeshka. Seated from left to right: Gary Stayer, Hollie Ontrop, Ginger Stayer and Jennie Stayer.
CLINICAL TRIALS
From Page 11

RAD001 + Gleevec
RAD001 is an mTOR inhibitor. We have been informally advised that the RAD001 plus Gleevec phase II trial for GIST patients has completed accrual. We are awaiting word from Novartis on the outcome of the trial and on future plans for this drug. RAD001 is available outside the United States as Certican® for heart and kidney transplant patients. A similar mTOR inhibitor from Wyeth called Rapamune® is available in the United States for kidney transplant patients. We have received reports from GIST patients who have been prescribed Rapamune “off-label” with Gleevec.

PTK787/ZK222584
This is a phase II study being conducted at the University of Helsinki in Finland and in Milan, Italy. This trial is for patients progressing on Gleevec. PTK787 is administered without Gleevec. A seven day washout period is required.

BMS-354825 (Dasatinib)
BMS-354825 is a tyrosine kinase inhibitor of Src, abl, KIT, and PDGFR. Dasatinib is available in a phase I trial at Dana-Farber and Glasgow, Scotland. In June the Karmanos Cancer Center in Detroit, Mich. also began recruiting patients. Future plans include a SARC phase II trial. We will update trial sites and the scope of the trial as this information becomes available.

BAY 43-9006 (known as Sorafenib and by trade name Nexavar)
This drug was approved in December 2005 for kidney cancer. BAY 43-9006 inhibits several kinases including KIT, VEGFR-2, VEGFR-3, PDGRF-β, RAF, FLT3, and RET.
The phase II trial for BAY 43-9006 is open and recruiting patients. Three trial sites are open in Illinois and one in New York:
- University of Chicago- Chicago, Ill.
- Decatur Memorial Hospital-Decatur, Ill.
- Oncology/Hematology Associates of Central Illinois- Peoria, Ill.
- Memorial Sloan-Kettering Cancer Center-New York, N.Y.
Several sites are also pending.

Sarcoma trials that also allow GIST patients:
The last two trials listed are sarcoma trials that allow GIST patients. There are several ways to attack GIST tumor cells with drugs. The most common method is to inhibit KIT and/or PDGFRA signaling.

Bayer FR901228
This is a phase II trial for sarcoma patients, including GIST patients, with metastatic or unresectable disease. FR901228 (depsipeptide) belongs to a new class of chemotherapy drugs called histone deacetylase inhibitors (HDAC inhibitors). This is a class of drugs that works at a higher level within the cell acting on the genome, which is like the master control room for all of the genes in a cell.

Patients must be at least 18 and have a performance status of ECOG 0-2 or Karnofsky 60-100 percent. Projected accrual is 18 to 36 patients.

Tran, 39, traveled across the world to find a cure for GIST

By Erin Kristoff

W hen Vietnam-born, four-foot-tall Thuy Tran would walk along the streets, she would own the sidewalk. At least that’s what Doug Gans says and what better source of information than the man who loved her for over six years. Thuy passed away on November 5 at the age of 39 in Vietnam with her mother by her side.

“[Thuy] was just the brightest, neatest, Wittiest person you would ever want to meet,” according to Doug. She loved theater and music, especially John Lennon.

Thuy came to America at age twelve. She received her degree in Human Resources from Sacramento State College and was a Human Resources manager until October of last year. Her mother brought her to Vietnam to try alternative medicines after all conventional means had stopped working and she died not long after. Though Doug could not be with her, he asks only one thing, “I hope she saves me a seat next to her.”

Hospital tips: the small stuff can add up

By Louise Ladd, LRG Member, with Alison Woodman

Note: Some of this information pertains particularly to women, but anyone can benefit from reading these helpful tips.

Planning:

If at all possible, schedule your surgery for early in the week. That way you should have the regular staff taking care of you during the major part of your recovery. Once the weekend comes you may find a number of new faces, plus your doctor might be off, his partner covering for him. Normally all will go smoothly but in case of problems, I find it’s better to recover during the weekdays.

Also: request the first operation of the day, if possible. Your doctor and the OR team are freshest, and complications won’t delay the start of surgery. The only time I accepted the second appointment of the day I had to wait 4 hours when the patients ahead of me tied up all the operating rooms. Yikes!

Before the operation:

● Stop aspirin/ibuprofen, etc. one-two weeks prior, to help control bleeding.
● Stop vitamin C and E for the same reason.
● Ask ahead for the post-op pain prescription so you can have it filled and waiting, to prevent a gap between when you leave the hospital and someone bumbles to the pharmacy.
● Delegate a friend/relative to call or email people with news about the operation, visiting info, and when you’ll be released.
● Put important papers where they can be found or leave a note as to where they are.
● Do all the personal grooming that requires bending or reaching, as it will likely be a while before you’re able to this again in comfort. For instance, shave your legs, and have a pedicure if needed.
● Shampoo your hair as close to departure as possible. There is nothing worse than greasy hair when you can’t wash it. Shortly before surgery have it cut or highlighted etc. because you won’t feel up to dealing with such procedures for some weeks. Some who wear their hair short prefer to have it trimmed extra close, as it means less to deal with during recovery.
● If you are a having bowel clean-out, get some Gatorade or Pedialite (not red) to drink. It replaces potassium which is lost in the process. Hemorrhoid ointment (better than cream) helps if delicate areas are irritated.
● If you are able to manage it, do any housework or chores that require bending or stretching up, trying to anticipate future needs for a month or two. For instance, take down a few vases from high storage, as you may have flowers to put in them if friends don’t send pre-made arrangements. People don’t realize that arranging flowers in a post-op condition is not a pleasant chore.
● In sum, put anything you usually need where you can easily reach it when you get home.
● Before you leave for the hospital, put clean sheets on the bed, or arrange for a friend to do so. Nothing beats coming home to your own bed with fresh sheets. Same with towels. Put out your thickest, most luxurious, and forbid anyone else to touch them.
● Stock up on essentials, of course. You’ll probably have people to run errands, but some things you want to do for yourself, such as choosing products that you’re particular about. Make sure you have enough on hand so you don’t have someone shopping for you and bringing home a disappointment.

Suggestions on what to take in your purse and toiletries bag (in random order):

See CHECKLIST, Page 14
Sometimes they feel like sandpaper.

Sheets are lovely and worn and soft; your own sheets. Sometimes the hospital to the hospital with you. If your skin is

roommate.

Light will help you see without waking a

thing, or check areas you can't see with

around your bed space if you drop some-

necessary, but the mirror can help you see

tv. CD players may disappear. You want to listen and not watch

tuck in the night table drawer in case

home you can get in!

medications (see below).

shoes, loose-hanging shirt/pants/dress,

daily get into for the return trip. Slip-on

your own sheets (see below).

Some of these items might be unnec-

Nightgown, robe and slippers

Comfortable clothes that you can eas-

around to making arrangements.

This is vital! Do not allow anyone to

move your nightstand or bedtable with

the phone, your cup—whatever impor-
tant is on it—without putting it back

where you can easily reach it. This is the

to the phone, your cup—whatever impor-
tant is on it—without putting it back

or using it to plump up a pillow. That

You may want to check areas you can't see

lights, or open the blinds, add or take

away blankets, chores that spare the

staff should have orders to give you the

meds you require, but if orders get

worked and don't have time to eat prop-

to the staff. They're often over-

nt to share with the staff. They're often over-

ing around in halls. (Hospitals some-

ultra-sensitive like mine, you might want

Your house key, so if a friend takes

home you can get in!

A good book

Perhaps a little radio that you can

not watch TV. CD players may disappear.

Some of these items might be unnec-

sary, but the mirror can help you see

around your bed space if you drop some-

thing, or check areas you can’t see with

the fixed mirrors in bath and bed-

able. The string can tie objects to the bed

so you can retrieve them, and the flash-

light will help you see without waking a

roommate.

Usually you can take your own pillow to the hospital with you. If your skin is

living in those hospital johnnies makes you feel (and look) more like a

patient, not a person. Take a soft, pretty

nightgown with short sleeves that don't

interfere with IVs, spring or summer- weight because most hospitals are very

warm and dry. (Some hospitals don't al-

them.) Pack a non-bulky robe for

walking the halls, and slip-on but secure

slippers. A bed jacket is nice, if you

have one, or a light sweater or shirt can

substitute.

Important: The instant you think of a

question for the doctor, write it down

immediately on your notepad. Amazing

how these important questions slip away

which can also cut tape, paper, etc.)—your vital needs—

nail scissors (which can also cut tape,

or using it to plump up a pillow. That

You may want to check areas you can't see

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away blankets, chores that spare the

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have one, or a light sweater or shirt can

substitute.

Important: The instant you think of a

question for the doctor, write it down

immediately on your notepad. Amazing

how these important questions slip away

when faced with a surprise 6 a.m.

visit. Doctors always seem to arrive

when you least expect them, and they

don't stay long, so grab your list of ques-
tions and ask them quickly, but don't

settle for incomplete answers. One ques-
tion I've recently added to my list:

“Doctor __, what questions haven't I

asked that I should be asking?” I try to

rewrite my list at the end of the
day, placing the most urgent questions

first. A friend/caretaker can help with

this, if needed.

Take along small doses of any medica-
tions you normally use. The hospital

staff should have orders to give you the

meds you require, but if orders get

 messed up, the busy doctor must author-

ize anything that has been missed. Better
to take your own, in case, rather than

waiting a day or two for them to get

around to making arrangements.

I keep my purse or toiletries bag in the

bed with me, tucking it under the covers

or using it to plump up a pillow. That

way you always have your most essen-
tial valuables—notepad and pen, glasses,
nail scissors (which can also cut tape,

string, paper, etc.)—your vital needs—

where you can reach them without a

stretch or fuss.

In Summary:

We hope you find this help-

ful. Sometimes it's the small stuff that can make a big difference.
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Learn more about the Global GIST Network: www.globalgist.org