First LRG webcast is successful
By Elizabeth Braun

The Life Raft Group held its first educational webcast on June 19. Over 150 people registered for the event with attendees joining in from 16 different countries.

Dr. Jonathan Trent delivered an outstanding lecture titled, “New Developments in GIST for Patients and their Families”. The presentation answered common questions about GIST including those submitted by viewers. He discussed both Gleevec for the treatment of metastatic GIST and Gleevec as an adjuvant treatment. Some of the other topics covered included dosage, side effects management, and genotyping. Dr. Trent also discussed options for managing Gleevec resistance based on the type of mutation.

Looking for kinase mutations in GISTs: how, when and why?
By Dr. Christopher Corless
Oregon Health & Science University

Note: This is the second of a two-part series on KIT and PDGFRA mutations in GISTs, written collaboratively by Drs. Michael Heinrich and Christopher Corless, LRG research team members. Please refer to the May issue of our newsletter for the first part titled, “KIT & PDGFRA mutations in GIST: A to Z” by Dr. Heinrich.

The significance of mutations in the KIT and PDGFRA genes in the development and growth of GI stromal sarcomas (GISTs) is a topic that has been thoroughly discussed in the pages of this newsletter in an article by my colleague, Dr. Heinrich and in articles by other experts in the field. The Life Raft Group’s Science Coordinator, Jerry Call, has also made significant contributions on this topic. We know that mutations in KIT and PDGFRA occur early in GIST development, are key drivers of tumor growth and serve as the primary targets for kinase inhibitors like imatinib and sunitinib. In this article, I will concentrate on pragmatic issues related to testing GISTs for these mutations, with the goal of providing readers with an understanding of how testing is performed and what information it can (and cannot)

A stitch in time: life with GIST can still exist
By Hollie Ontrop

Time. It was something I never worried about. Really. I didn’t even think about it. I always assumed I had so much of it and I could spend it at my own leisure. I saw no point in settling, rushing down the aisle or starting a family. I had plenty of time to do those kinds of things, later.

When I met Gary five years ago, he shared the same belief. We were young and wanted to have fun while focusing on our careers.

Then a little over a year ago, time stopped. “It’s a rare form of cancer called GIST,” the doctor reluctantly muttered. I remember every detail—the disbelief, shock and terror. Then came the realization that my life will never be normal again. Gary had cancer.

All of our plans immediately changed. Heck, my entire life changed!

I believe it was Oprah who popularized the phrase, “a new normal,” which describes a person’s normal day after a tragic event in his or her life. For me, my “new normal” smacked me in the face when I realized that Gleevec would end any hopes for Gary and I to have children.

ASCQ Report by Jerry Call (See page 2)
Highlights from ASCO 2007

By Jerry Call
Science Coordinator, LRG

This year at ASCO, over 50 posters and presentations were given related to GIST. This newsletter covers two of the GIST highlights.

Adjuvant Treatment of GIST

Ronald DeMatteo, MD, of Memorial Sloan-Kettering Cancer Center in New York, NY., presented late-breaking results from the North American Inter-group phase III trial, ACOSOG Z9001. This was a randomized trial that compared one year of Gleevec to a placebo after complete surgical resection of a primary GIST.

The study found that taking Gleevec for one year after surgery significantly increased the time to a recurrence. Of the patients taking Gleevec, 97 percent had no signs of their cancer returning at one year and 90 percent at two years compared to 83 percent at one year and 71 percent at two years for the patients that received the placebo.

The study began in June 2002 and included 644 patients that were recruited from 230 sites. Based on the highly significant results of the trial, the data safety committee halted further enrollment in April. They recommended that patients in the trial that were on the placebo be offered one year of Gleevec treatment.

At the present time, surgery is the standard treatment for GIST that has not spread. “This highly significant result could prompt re-evaluation of clinical practice recommendations for management of intermediate and high-risk primary resectable GISTs,” said Dr. DeMatteo, the principal investigator of the trial, in a June 4 press release. Based on the results of this trial Novartis expects to file global regulatory submissions for use of Gleevec as adjuvant therapy in GIST patients following surgery to remove primary tumors by early 2008.

Dr. DeMatteo’s presentation also provided the first look at data for different risk categories. The data was broken down into groups by primary tumor size; three cm to six cm, six cm to ten cm and over ten cm. The groups generally represent a range from lower risk (three cm to six cm) to higher risk (over ten cm); however the criteria for these groups is different than other criteria established for risk assessment for GIST (such as the Fletcher/NIH criteria) which almost always includes a measure of how fast the tumor is growing (mitotic rate). This means that while the three cm to six cm group is generally at lower risk of recurrence, there may still be patients in this group that are at an intermediate risk or even at high risk of recurrence and there may even be some patients in the over ten cm group that are at low-to-moderate risk of recurrence (Gastric GISTs over ten cm but with a low mitotic rate are rated as low to moderate malignant potential by the Armed Forces Institute of Pathology Suggested Guidelines). Notably in patients taking Gleevec, in the six-ten cm group and the less than ten cm group, the slope of the recurrence-free survival curves increased at about the one and a half year mark, perhaps starting to show the effects of being off of Gleevec after the one year adjuvant treatment period. Acknowledging the still somewhat short follow-up time, we asked Dr. DeMatteo for his comments about the change in slope. “All that can be said is that once Gleevec is stopped, there appears to be a

See ASCO 2007, Page 7
Once a teacher, always a teacher

By Erin Kristoff

Becky Harper always knew she wanted to be a teacher. “I think you have to be called to it. You have to have a passion to be with kids and you do a lot of giving.” And she did give—22 years to be exact. She taught every first grader who came through her class until 1996 when she was told she had cancer.

Teaching was what Becky loved. “My grandmother was very worried about me, she thought that as a teacher got to be more proficient that she moved up grade levels and she couldn’t understand why I was stuck in the first grade!”

And first grade is where she wanted to stay, “I always knew I wanted to be with the younger kids. They were eager to learn. They come in as babies and leave as kids.”

After Becky received her bachelor’s degree from Washburn University in Topeka, Kansas and her Masters degree from the University of Missouri in Kansas City, she embarked on that 22 year long journey with her first graders and enjoyed every minute of it. “First graders are real big on hugs, even the little boys.”

But in 1996, when she was diagnosed with leiomyosarcoma, the party was over. “They really didn’t think I would live very long when I was diagnosed. They put me in the hospital right away and started chemo.”

After the dreadful chemotherapy, she was eventually correctly diagnosed with GIST. “Once I got on Gleevec it affected my white blood cell count; I realized couldn’t go back to teaching.”

July 2007 clinical trial update

By Jim Hughes

LRG Clinical Trials Coordinator

Five clinical trials were added this month:

AB1010 Phase II
AB1010 or masitinib manufactured by AB Science in France is in Phase II. Dr Axel Le Cesne at Institut Gustave-Roussy in Villejuif, France is the Primary Investigator. Masitinib is a c-Kit/ PDGFRa inhibitor similar to imatinib. This trial continues to be available mainly to patients in France.

MP470 Phase I
MP470 is a multi-targeted tyrosine kinase inhibitor that appears effective in the lab against multiple c-kit mutations resistant to imatinib. MP470 appears to also be an inhibitor of alternate signaling pathways that may take over when c-Kit is blocked by targeted therapy. Lab tests in GIST cell lines have shown that AXL and c-Met pathways are sometimes activated and may be a mechanism of resistance to Gleevec.

Contacts at SuperGen have indicated that trials are expected to start soon at two locations: Johns Hopkins University, Baltimore, Md. under Manual Hidalgo and Wells Messersmith and at the University of Arizona in Scottsdale, Ariz. under Dan Von Hoff.

AMN107 Phase III
The AMN107 Phase III trial is now open at three sites in the U.S. Fox Chase in Philadelphia, Pa., Dana Farber in Boston, Mass. and Washington University in St. Louis, Mo. Ten sites in total are planned in the U.S. Four are planned in Canada. Four sites are open in Europe. One site each is open in Taiwan and Australia. Patients must have had only Gleevec and Sutent to be eligible for this trial. Novartis continues to make AMN107 available through a compassionate access program. Novartis tells us that over 140 patients have been ap-

proved under this program worldwide. Plans are also underway for a second AMN107 trial in the U.S. that will admit patients now excluded because of prior molecular therapy. The protocol is now under review at a clinical trial site and the trial should open within the next six months.

KOS1022 Phase I
This drug by Kosan is a Heat Shock Protein (HSP90) inhibitor. It is designed to inhibit the chaperone protein that protects mutant c-Kit. This enables the cell to destroy the mutant c-Kit. KOS1022 is a second generation HSP90 inhibitor designed to be taken orally. This Phase I trial admits patients with advanced solid tumors and is not exclusive to GIST.

Imatinib or sunitinib Phase III
This trial is now recruiting GIST patients. Patients experiencing progression at 400 mg of imatinib are offered either 800 mg daily of imatinib or 37.5 mg daily of sunitinib.
As discussed in Dr. Heinrich’s article, genes are somewhat like books, each one divided into a series of exons (chapters) that are made up of codons (words), which in turn are made up of bases (letters). In GISTs, mutations can occur in any of 5 different exons of KIT or three different exons of PDGFRA. Additionally, the mutations vary from a single base change (substitution of one letter by another) to deletions of up to a dozen or more codons (words) in a row. Sometimes there is a combination of a deletion and a substitution, which is like deleting part of a sentence and altering the meaning of the remainder.

The infamous KIT exon 9 mutation, for which there is evidence that a higher dose of imatinib may be appropriate, is caused by a duplication of two codons back-to-back, as though someone forgot to proofread the gene when it was copied during the routine division of a cell into two daughter cells.

Finding any of the above types of mutations within the 3.2 billion letters (bases) that comprise the library of DNA within a tumor cell is truly akin to finding a needle in a haystack. Fortunately, we have PCR (polymerase chain reaction) technology. This Nobel-prize winning approach to the analysis of DNA revolutionized molecular biology in the early 1980’s is now the mainstay in all laboratory testing for tumor mutations. The details of this approach are beyond the scope of this article, but one can think of PCR as a means of finding and Xeroxing selected chapters (exons) in any book (gene) in the DNA library. Considering that the DNA library is submicroscopic and quite fragile, this is quite a trick!

Before PCR can be employed, however, it is first necessary to extract and purify the DNA from a tumor. If fresh tumor tissue is available, this is a simple process that can be done in a couple of hours and yields high quality material for testing. Unfortunately, it is not customary to collect and store fresh tumor tissue outside of university hospitals. Instead tumor tissue is put into formaldehyde (to prevent it from rotting), then dehydrated and embedded into a block of wax (Figure 1). The purpose of creating such blocks is so that thin sections can be cut from them and mounted onto microscope slides (Figure 1). This 150-year old approach to the microscopic diagnosis of tumors may seem a bit dated, but it remains cost-effective and accurate, so pathology departments continue to use it worldwide. Given that nearly all GIST tissue available for mutation screening is embedded in paraffin blocks, it has become necessary for molecular testing laboratories to adopt methods that allow recovery of the tumor DNA from the wax.

The standard protocol for extracting DNA from paraffin-embedded tumor tissue takes 24 to 72 hours, and involves the use of organic solvents. The resulting DNA is of poorer quality than that which can be recovered from fresh tumor tissue, but it still serves as a reasonable starting point for PCR-based testing of KIT and PDGFRA exons. Our laboratory has recently been experimenting with a new extraction protocol that may shorten the whole procedure to just 3 hours.

Once tumor DNA has been prepared and PCR reactions performed, the final step is to ‘read’ the amplified (Xeroxed) exons and look for a mutation. This can be done by several approaches. Many laboratories use standard DNA
resistance seen in the patient.
Here is some of the feedback the Life Raft Group has already received:

I signed on from my office computer and thought the web seminar was excellent...Thank you and I look forward to the next one. Great job. – Glen Banks, Maryland.

As a newly diagnosed patient with GIST, I found the program very informative. Continuing education on this subject only helps patients like me to better understand the disease as well as taking some of the unknowns out of our mindset. The more we understand, the better able we can handle some of the adversities that can occur, both physical and mental. Please continue to provide programs like this when possible. - Robert Grossmann, California.

Thank you. I attended this morning and learned that I was pretty much up to date on my information. Great way to meet and I hope we are able to continue to do this kind of thing. - Ron McClelland, Canada.

It was a very interesting experience, useful and time and money saving. Glivec is an unaffordable drug in Romania and the waiting lists are old and long. Next time I shall invite the healthcare professionals from the expert’s commission which approve the Glivec treatment for solid tumors. - Simona Ene, Global GIST Network Representative for Romania.

Just wanted to say thank you for a wonderful broadcast. It is very reassuring to hear things explained by an expert in the field. Dr. Trent has a gift of being able to impart very technical information in a way that patients can comprehend. Thank you so much. I learned a lot and look forward to more broadcasts in the future. – Debbie Chang, Texas.

The LRG has planned several more of these webcasts. Please see below for further information on the July and August seminars. Those that missed the June broadcast can view it at the Life Raft Group website.

Fletcher’s webinar, “Pathway to a Cure” will take place July 25 at 12 PM EST. Dr. Jonathan Fletcher reports on the outstanding success of the LRG’s strategic plan to find a cure for GIST by identifying and overcoming the causes for treatment resistance. In spite of amazing clinical responses to imatinib, GIST patients are still developing resistance to treatment, leading to life-threatening relapses. It’s anticipated that most GIST patients with metastatic or unresectable disease will eventually develop such resistance. In 2005, the LRG initiated a research program committed to developing synergistic molecularly-targeted therapies to counteract imatinib resistance. Through the identification of additional therapeutic targets it may be possible to develop a treatment protocol that prevents such relapses - or even cures - GIST.

The LRG research team consists of:
- Dr. Cristina Antonescu of Memorial Sloan-Kettering Cancer Center, N.Y.
- Dr. Peter Besmer of Memorial Sloan-Kettering Cancer Center, N.Y.
- Dr. Christopher Corless of Oregon Health and Science University, Ore.
- Dr. Maria Debiec-Rychter of Catholic University Leuven, Belgium
- Dr. Jonathan Fletcher of Brigham and Womens Hospital, Mass.
- Dr. Michael Heinrich of Oregon Health and Science University, Ore.
- Dr. Brian Rubin of Cleveland Clinic Foundation, O.H.
- Dr. Matt van de Rijn of Stanford University, Calif.

This unique team has made significant progress on the pathway to a cure. Since the initiation of this venture, scientific plans have been outlined to augment research progress through cooperation and collaboration. Members of the team were selected based on their prior commitment to GIST research and willingness to fully participate in this program without creating redundant research efforts.

On March 24, 2007, the LRG research team gathered in San Diego to evaluate the progress of the individual research efforts. Future research opportunities that might further advance the program were identified for prospective funding. In this webcast, Dr. Jonathan Fletcher summarizes and reports on this meeting and the achievements from the team’s first year of research.

Don’t miss our July 25 webinar ‘Pathway to a Cure’ featuring Dr. Jonathan Fletcher

Up Next...
Our August webinar will be called “GIST: the Basics”. Jerry Call and David Josephy break down the complicated area of GIST treatment in this amazingly understandable presentation.
### Strategy Table (The color of trial row indicates the trial’s treatment strategy)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
<th>Trial #</th>
<th>Phase</th>
<th>For</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Inhibit KIT (PDGFRA signaling)</td>
<td>NCT00471328</td>
<td>III</td>
<td>GIST</td>
</tr>
<tr>
<td>B</td>
<td>Impede tumor vascularization (Antiangiogenesis) (PDGFRb, VEGF, VEGFR)</td>
<td>NCT00372567</td>
<td>III</td>
<td>GIST</td>
</tr>
<tr>
<td>C</td>
<td>Destroy KIT (HSP90)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Inhibit the production of KIT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Target KIT downstream signaling (i.e. AKT, mTOR, BCL-2, SRC, RAF-1, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Destroy KIT plus Inhibit the cell cycle plus Induce apoptosis (HDAC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>Multiple Targets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Kill GIST cells</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Therapy Description

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
<th>Trial #</th>
<th>Phase</th>
<th>For</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMN-107</td>
<td>AMN107 compared with current treatment options in patients with GIST who have failed both imatinib and sunitinib</td>
<td>NCT00471328</td>
<td>III</td>
<td>GIST</td>
</tr>
<tr>
<td>Imatinib or Sunitinib</td>
<td>Safety and effectiveness of daily sunitinib or imatinib in patients with GIST</td>
<td>NCT00372567</td>
<td>III</td>
<td>GIST</td>
</tr>
<tr>
<td>Perifosine + Imatinib</td>
<td>Phase II study of Perifosine plus imatinib for patients with resistant GIST</td>
<td>MDACC 2004-0968, NCT00455559</td>
<td>II</td>
<td>GIST</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Sorafenib in treating patients with GIST that progressed during or after previous treatment with imatinib and sunitinib</td>
<td>NCT00265798</td>
<td>II</td>
<td>GIST</td>
</tr>
<tr>
<td>FR901228</td>
<td>FR901228 in treating patients with metastatic or unresectable soft tissue sarcoma</td>
<td>NCT00112463</td>
<td>II</td>
<td>GIST/Sarcoma/Ewing</td>
</tr>
<tr>
<td>IPI-504</td>
<td>Safety study of IPI-504 for GIST</td>
<td>NCT00276302</td>
<td>I</td>
<td>GIST</td>
</tr>
<tr>
<td>Oblimersen + Imatinib</td>
<td>Oblimersen and imatinib in treating patients with advanced unresectable GIST</td>
<td>NCT00091078</td>
<td>I</td>
<td>GIST</td>
</tr>
<tr>
<td>MP470</td>
<td></td>
<td></td>
<td>I</td>
<td>GIST</td>
</tr>
<tr>
<td>Perifosine + Sunitinib</td>
<td>Perifosine + sunitinib for patients with advanced cancers</td>
<td>NCT00399152</td>
<td>I</td>
<td>GIST/RCC</td>
</tr>
<tr>
<td>Doxorubicin + Flavopiridol</td>
<td>Doxorubicin and Flavopiridol in treating patients with unresectable metastatic or recurrent sarcoma</td>
<td>NCT00098579</td>
<td>I</td>
<td>GIST/Sarcoma</td>
</tr>
<tr>
<td>OSI-930</td>
<td>Dose escalation study of daily oral OSI-930 in patients with advanced solid tumors - sarcoma</td>
<td>EmergingMed</td>
<td>I</td>
<td>Advanced Solid Tumors - Sarcoma</td>
</tr>
<tr>
<td>LBH589</td>
<td>Dose escalating study of IV LBH589 on two dose schedules for advanced solid tumors &amp; non-Hodgkin’s lymphoma.</td>
<td>Nevada Cancer Institute</td>
<td>I</td>
<td>Advanced Solid Tumors</td>
</tr>
<tr>
<td>CNF2024</td>
<td>Study of oral CNF2024 in advanced solid tumors or lymphomas.</td>
<td>NCT00345189</td>
<td>I</td>
<td>Tumors/Lymphoma</td>
</tr>
<tr>
<td>KOS1022</td>
<td>Oral KOS-1022 in patients with advanced solid tumors</td>
<td>Univ of Colo COMIRB 05-0627</td>
<td>I</td>
<td>Advanced Solid Tumors</td>
</tr>
<tr>
<td>XL820</td>
<td>Study of XL820 given orally daily to subjects with solid tumors</td>
<td>NCT00350831</td>
<td>I</td>
<td>Cancer/Solid Tumor</td>
</tr>
</tbody>
</table>

### INTERNATIONAL TRIALS

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
<th>Trial #</th>
<th>Phase</th>
<th>For</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKT787</td>
<td>PTK787/ZK222584 in the treatment of metastatic GIST resistant to imatinib</td>
<td>NCT00117299</td>
<td>II</td>
<td>GIST</td>
</tr>
<tr>
<td>AZD2171</td>
<td>The biological activity of AZD2171 in GIST</td>
<td>NCT00385203</td>
<td>II</td>
<td>GIST</td>
</tr>
<tr>
<td>AB1010</td>
<td></td>
<td></td>
<td>I</td>
<td>GIST</td>
</tr>
</tbody>
</table>

The information below does not include location information. Please visit our website at [www.liferaftgroup.org/treat_trials.html](http://www.liferaftgroup.org/treat_trials.html) for more in-depth coverage of each trial.
higher chance of recurrence”.

To date, there has been no difference in overall survival for patients in the two groups, although it is too early to make a definitive conclusion about how adjuvant Gleevec impacts survival. Although all of the groups seemed to benefit, according to DeMatteo, “From what has been analyzed so far, it appears that those at highest risk (defined by large tumors) benefited the most (See table 2).”

We asked Dr. DeMatteo what he would like patients and their doctors to know about this trial and adjuvant Gleevec for GIST. “While there has been considerable investigation of the role of Gleevec in metastatic GIST, we are just beginning to understand its use in the adjuvant setting. Our ultimate goal of course is to prevent, or at least dramatically delay, the development of tumor recurrence after the resection of a primary GIST. Obviously, we would like to thank all the patients who participated in this randomized trial as well.”

“There should be a lot more coming out in the next year from our studies,” said DeMatteo. “The two European studies will take at least several more years.” These studies will look at different durations of adjuvant Gleevec. The EORTC trial will compare two years of Gleevec (Glivec outside the U.S.) to no treatment and the Scandinavian Sarcoma Group trial compares one year of adjuvant Gleevec to three years of adjuvant Gleevec.

**Gleevec dosage/MetaGIST Project**

Martine Van Glabbeke presented the results of the MetaGIST project. The two large phase III GIST trials, the US/Canadian (US-CDN) and European/Australasian (EU-AUS) trials were originally planned to allow the data to be combined to increase the power and precision of the trials. The US-CDN trial had 746 patients and the EU-AUS trial had 946 patients.

The purpose of both trials was to compare two doses of Gleevec; 400 mg vs. 800 mg for both safety/tolerability and efficacy. The MetaGIST analysis showed a small but statistically significant progression-free survival (PFS) benefit for the higher dose arm as shown in Table 3.

However, there was no difference in overall survival between the two arms, with a median overall survival of 49 months for both 400 mg and 800 mg. Approximately 60 percent of patients survived for three years. The hazard ratio was 1.00 (no difference) with a P value of 0.97.

The study next looked at whether there were other factors that might affect progression-free survival (PFS) and overall survival independently of the treatment arm. They found that four factors adversely affected both:

- Poor performance status (patients that were sicker at the start of the trial did worse)
- High neutrophil count at trial entry
- Absence of KIT exon 11 mutations
- Male gender

Factors that adversely affected PFS but not overall survival were:

- Small bowel origin
- Low hemoglobin at trial entry

Factors that adversely affected overall survival but not PFS were:

- Advanced age
- Low albumin at trial entry
- Large lesions

Since the benefit that could be demonstrated with the intent-to-treat analysis was limited to four months of additional progression-free survival, the investigators wanted to see if there was a subset of patients that would benefit the most from high-dose Gleevec. The only group that was statistically significant was pa-

---

**Table 2: Greater Benefit in Higher-Risk Groups**

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Gleevec</th>
<th>Placebo</th>
<th>Recurrence-Free Survival</th>
<th>Gleevec</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 cm</td>
<td>100%</td>
<td>95%</td>
<td>100%</td>
<td>Est. 88%</td>
<td>Est. 73%</td>
</tr>
<tr>
<td>6-10 cm</td>
<td>96%</td>
<td>80%</td>
<td>Est. 87%</td>
<td>Est. 73%</td>
<td>Est. 73%</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>96%</td>
<td>67%</td>
<td>Est. 80%</td>
<td>Est. 30%</td>
<td>Est. 30%</td>
</tr>
</tbody>
</table>

Note: The recurrence-free survival numbers at 2 years are less accurate because of smaller numbers and because they are estimated (Est.) from survival curves.

**Table 3: PFS MetaGIST results**

<table>
<thead>
<tr>
<th></th>
<th>400 mg/800 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>19/23</td>
</tr>
<tr>
<td>3-year estimate (%)</td>
<td>30/34</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.89 (11% increased risk in low-dose arm)</td>
</tr>
<tr>
<td>P value (logrank test)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

---

See ASCO 2007, Page 10
It wasn’t until we left the doctor’s office and I was on the way to work that I realized what the Gleevec’s warning label really read. “Do not get pregnant or get anyone pregnant while using Gleevec.” One would have thought that a nurse, a doctor, somebody would have said something about the fact that a young couple would lose the ability to have biological children. But no one did.

I left messages and had conversations with nurses, but nobody could give me answers. The only advice offered was to make sure he took his Gleevec that night. That was a Friday. I finally received a suggestion on Monday, “We should consider banking [sperm and an egg] before starting Gleevec.” This came a little too late since Gleevec can have such immediate effects.

I was devastated. I was mourning the loss of an unborn child but didn’t want Gary to know. He was going through enough and I didn’t want him to feel worse because of me. So I would secretly throw perfectly clean clothes, hit pillows and randomly stop in parking lots to cry, scream and feel sorry for myself. It was my way of dealing (Granted, anyone who drove by me while I was throwing my tantrum most likely thought I was crazy but in a way I was)

Months went by when I would run to the nearest bathroom to cry after seeing a picture of friends’ children or when someone would ask me when Gary and I were going to settle down and have children. It seemed that babies and cancer were the only things on TV and the only topics that crossed people’s lips.

I was a closet mourner. No one really knew. People knew I was going through a lot and would occasionally see a tear shed but no more. At the time I was attending college and interning. I remember my friends, classmates and co-workers commenting on how I was going full speed and no one could believe my strength. I would often comment that there was no time to slow down. I had to keep researching about GIST, attending school, going to work and care for Gary. I had to appear strong for Gary and myself.

Then I became obsessed. I changed from Gary’s girlfriend to Gary’s mother and live-in nurse. I needed to absorb all the facts and information I could. If I was at home, I was on the computer reading about GIST or asking Gary if he was feeling okay. If I was at work or school, I would sneak off to research or call Gary. It was driving him crazy. He would often say if he wanted to live with a mother he’d move back to his parents. I would just blame it on denial.

Looking back, I was actually more in denial then he was. Not about cancer but about us ever living a half-way normal life again. I thought the joy in my life was over; I couldn’t see past the cancer. I had to deal with insurance, medical bills, prescriptions and doctors, things that I really never dealt with before – at least not to this extent. And no one would take me seriously, probably because of my age.

Finally I ran across Cynthia, an insurance agent, who understood me. She knew I was scared, confused and usually had no clue how to handle things. We’d spend hours on the phone and together we’d call doctors’ offices to figure out what was going on. She’d tell me secrets of the trade, how to get straight answers and ways to save money on all of Gary’s tests. More importantly, Cynthia would ask me how I was handling everything. It was something that most people I knew forgot to do. They all assumed I was handling it fine because I appeared to be. I still call Cynthia if I have a question and she’ll ask “Are you holding your ground?”

Once August came, I was starting to get the hang of everything and the “new car smell” of Gary’s cancer was wearing off. I focused on school; I was graduating at the end of September, which was good for us. With most of my attention being on school, Gary and I once again became the couple we were before GIST. I remember getting into an argument with him and afterwards I started to laugh. I thought, “Finally.” I was never as happy to fight with him as I was then. For me it was a sign that I was comfortable. I’d stopped mothering and protecting him so much and instead I was ready to let him live and give him a piece of my mind. I try to have a more positive attitude these days. When Gary is too tired or sick to go hangout with friends, I tell myself it is a chance for me to focus on myself and have fun. If Gary falls asleep at eight, I spend the evening doing things I enjoy.

We’ve started to once again focus on the future and the time we have together. We talk about places we want to live and the things we want to do with our lives. We’ve started traveling a bit more and actually doing things we’ve always wanted to do but never had the time. Gary and I learned that it doesn’t matter how much time you have – it is what you do with that time that counts.
‘sequencing’, which is essentially reading each exon line for line – a very laborious and time-consuming process. In the Heinrich & Corless laboratories, we adopted a different approach back in 2001 that has since been widely copied by other laboratories doing GIST analyses. Called ‘denaturing HPLC’, it is a method that allows us to ‘speed read’ each exon in 2.5 minutes, looking for any anomalies. This allows us to quickly dismiss the exons that are normal and focus on any that look anomalous (Figure 2, page 4). Such anomalies can then be pinned down by direct DNA sequencing to conclude the exact nature of any mutation that is present.

Denaturing HPLC is a powerful approach to mutation screening, but it is costly ($125,000 per instrument) and time-consuming to set up. For this reason, we have spent the past 18 months working on newer, faster approaches to mutation analysis. These approaches utilize a modified type of PCR in which special ‘probes’ that give off fluorescent light (like phosphorescence) are used to detect the presence of a mutation. An example of one such assay for the KIT exon 13 mutation is shown in Figure 3. The advantage of this assay is that it is very fast yet highly accurate. In combination with our new extraction protocol, we believe that this assay will permit exon 13 mutation screening to be done in a single day, whereas it currently takes 3 or 4 days. Similar assays will shortly be available for KIT exon 9 and PDGFRA exon 18 (including the imatinib-resistant D842V mutation).

Along with our interest in finding primary KIT and PDGFRA mutations, our laboratories are examining secondary mutations that account for the onset of resistance to imatinib and more recently, sunitinib. These mutations are of keen interest to everyone concerned with imatinib resistance, which may develop after 12 to 36 months of treatment. One of the most common questions that I am asked is whether testing for resistance mutations is a good approach to deciding which drug should be used after imatinib. In theory, this is a good idea, because some mutations that cause resistance to imatinib are still sensitive to sunitinib, while others are resistant to both drugs but might respond to a newer agent.

There are, however, two problems with testing for resistance mutations. First, it requires that a patient undergo a biopsy of one or more resistant GIST lesions in order to obtain the DNA needed for testing. Second, there is evidence emerging from a number of different laboratories that different tumor nodules may harbor different resistance mutations. More sobering still, work from our laboratories and that of Dr. Jonathan Fletcher using high-sensitivity assays for resistance indicates that even within a single tumor nodule there may exist up to three different resistance mutations, albeit at varying levels. What this implies is that once a GIST figures out a way to accumulate resistance mutations, it can do so quite prolifically. This undermines the significance of any particular resistance mutation that might be identified in a single biopsy. Indeed, basing treatment decisions on this approach might not be appropriate and could even prove harmful. For these reasons, we have decided not to offer routine testing for resistance mutations until more information from trials becomes available.

The concept that tumors should be subclassified by their mutation status is beginning to spread to other areas of oncology. Imatinib was first developed to treat chronic myelogenous leukemia (CML), a disease that is defined by a unique type of mutation. More recently, mutations in genes that are suitable targets for other imatinib-like drugs have been identified in lung cancer, breast cancer, thyroid cancer and endometrial cancer. Drug development for these targets is moving very quickly. So too, is the field of molecular testing, which may some day supplant the old-fashioned microscope and become the primary means for cancer diagnosis and drug assignment. In the meantime, selected use of molecular testing provides us with a valuable prism for understanding GIST biology and optimizing the treatment of these tumors.

**Editors’ Note**

In the May 2007 issue of the newsletter, the first line of Dr. Heinrich’s article appeared incorrectly. It should have read, “In 1998, Dr. Seiichi Hirota and his scientific team in Japan discovered that GISTs express the KIT protein...”

Thank you to Dick Whiting for the tip.

---

**Figure 3**

**HPLC Profiles of KIT Exon 11 deletion**

<table>
<thead>
<tr>
<th>Time (Minutes)</th>
<th>Relative Absorbence (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wild-type control</td>
</tr>
<tr>
<td></td>
<td>Deletion control</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
</tr>
<tr>
<td></td>
<td>Negative control</td>
</tr>
</tbody>
</table>

**Centers in the United States that offer KIT & PDGFRA gene mutation screening**

- MD Anderson Cancer Center, Houston, TX
- ARUP Laboratories, Salt Lake City, UT
- Fox Chase Cancer Center, Philadelphia, PA
- Oregon Health & Science University, Portland, Ore
dose Gleevec (p = 0.017, logrank test). While the benefit of high-dose Gleevec was statistically significant for exon 9 patients (and even for all patients, but with a smaller benefit), the overall median survival benefit of 28 months (low-dose) vs. 35 months (high-dose) did not reach statistical significance for exon 9 patients (p = 0.15). This may be due to the small number of patients in the trial.

Dr. Reichardt’s Presentation
Peter Reichardt, MD, was the discussant for the GIST presentations. He noted that both phase III trials showed some benefit from crossover to a higher dose after progression at 400 mg. The median benefit was 81 days in the EORTC study and four months in the S0033 trial (US/Canadian). What was noteworthy was that a significant percentage of patients experienced longer-term benefit. In the EORTC trial, 18 percent of patients were progression-free for one year or more after crossover. In the S0033 trial, 20 percent of patients were progression-free for two years or more. Dr. Reichardt noted several limitations that might impact these studies. These included:

- Probable impact of cross-over and second-line (or more) treatment, including surgery on overall survival.
- Small numbers in subgroups other than exon 11.
- Correlation of dose and PFS/OS based on intention-to-treat. Dr. Reichardt showed a slide from the EORTC (courtesy A. Le Cesne) that showed a correlation between increased progression-free survival and the dose of Gleevec that patients actually received (See Figure 1).

In his summary on dose, Dr. Reichardt noted the controversy about dose but remarked, “that’s all we will get” (referring to the MetaGIST project). It is unlikely that such a large trial will be repeated in GIST. He also concluded that in the future, first-line trials with a primary end-point of PFS would need to compare to 800 mg of Gleevec in the exon 9 subgroup. This means, according to Reichardt, that any patients would need mutational analysis at the start of the trial but there is increasing consensus of the necessity of doing this. We can only hope that in the near future, mutational analysis for first diagnosis of GIST or at a minimum, metastatic GIST will become routine, at least in the major GIST centers.

Figure 1.
This chart is adapted from one presented by Reichardt.
Luckily she had a support system to carry her through. “I have been so lucky to have the most wonderful friends. I have a group of church friends who are just so supportive. I study with them and talk with them. If I’m at a sick point they’ve stayed with me and cleaned my house. It is just amazing to have such caring people.”

For Becky, life doesn’t just end when you lose your ability to work. “I miss the kids and the wonderful teachers that I worked with but now I’ve got three grandkids. So they keep me hopping!”

When Becky was diagnosed with cancer she had a granddaughter, Theressa, who was one. The day after she started taking Gleevec a grandson, Max, came into the world. Two years later, when she was having a checkup at Dana Farber Cancer Institute, a second granddaughter, Roni, was born. “I call them my Gleevec babies.”

These days, Becky likes to play with her grandchildren. She hopes to be able to spend a lot of time with them and have input in all of their lives. She also spends a good deal of time with her husband, who also has health issues. “We don’t do a lot of physical things. I buy a book of entertainment coupons each year and we go on coupon adventures; we go and find these places.”

Becky understands the concept of time gotten back. Thirteen years before she was diagnosed with LMS, she had a grapefruit-sized cyst removed from her intestines. The doctors told her to see a doctor if it ever hurt. They didn’t know that it was cancer and that it would come back. Becky did go to a doctor in 1996. “The misdiagnosis probably worked to my advantage, it kept me alive [until I was diagnosed with GIST].”

So Becky takes this time and spends it with those she loves. She tries to be a good wife, mother, grandmother and friend. And yes—even a good teacher to her grandkids.

Does she ever think about those kids whose minds she shaped for 22 years? Of course. “I was in a restaurant last summer and the waitress was one of my former students. I recognized her and could not remember her name. I had to apologize and tell her that my brain is not what it used to be.”