Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

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Hereditary GIST explained

By Maria Debiec-Rychter
LRG Research Team

Familial cancer syndrome is a genetic condition that causes an increased risk for specific types of cancers. Familial cancer syndromes account for only five to ten percent of all cancers.


DEBIEC-RYCHTER

Most cancer is not inherited. Cancer is common; each year, more than 1.5 million new cancer cases are diagnosed. Many people have relatives who have had cancer, but most of the time this is due to chance or environmental factors (this represents sporadic form of the disease). In a familial cancer syndrome, an inherited genetic mutation causes a person to be at increased risk for cancer and other physical symptoms. There are many different familial cancer syndromes, and each one has a specific set of characteristic cancers and physical symptoms associated with it.

Hereditary forms of GIST arise in the settings of primary familial GIST syndrome or other hereditary syndromes.

Familial GIST syndrome is a rare genetic disorder, showing a high penetrance and representing a small subset of clinical GISTs. To date, 27 families have

See FAMILIAL, Page 6

Plasma level testing: what we know, what we don't & what we hope to learn

By Jerry Call
LRG Science Coordinator

This month, Novartis Pharmaceuticals (maker of Gleevec) launched a new website designed to help optimize the outcome of GIST patients taking Gleevec. Some of the featured content is about blood level testing for GIST. In addition, the website prominently links to the Avantix labs website (www.bloodleveltesting.com) for testing Gleevec blood levels in CML and GIST.

The GIST Alliance site and related Avantix blood level testing site appear to be a response to the increasing awareness that testing Gleevec levels in the blood, and adjusting dose based on levels, may be superior to the current standard of assigning all patients 400 mg at the start of treatment. This position is based on preliminary data from CML and GIST trials that suggest the adequate plasma levels are critical to prevent progression.

In the GIST trial, a higher concentration of Gleevec in the blood correlates with better clinical outcome according to Dr. George Demetri, Director of the Center for Sarcoma and Bone Oncology at Dana Farber Cancer Institute. Demetri presented this information in January 2008 at the 2008 Gastrointestinal American Society of Clinical Oncology (ASCO) meeting.

In an interview with Peggy Peck on the MedPage Today website, Dr. Demetri said that the imatinib plasma level was not associated with age, gender, disease

Demetri: "We may have been under-dosing some people."

bulk, or body weight. "You really need to do pharmacokinetic testing to determine the level of imatinib because there are no clues," Demetri reported at the Gastrointestinal Symposium. The find-

See PLASMA, Page 5

FDA Approves Gleevec to Prevent Recurrence of GIST

The following press release was reprinted from the Food & Drug Administration website.

The U.S. Food and Drug Administration today approved Gleevec (imatinib mesylate) for a new indication – keeping cancer from growing in patients following surgical removal of a

gastrointestinal stromal tumor or GIST.

GIST is a fairly rare form of cancer that originates in cells found in the wall of the GI tract. These cells, known as interstitial cells of Cajal, are part of the autonomic nervous system, which helps to control the movement of food and liquid through the stomach and intestines. Gleevec, first approved by the FDA in 2001, is one of the first drugs in a class of agents that block cellular communications that result in tumor growth

"Approval of Gleevec offers health care professionals and patients an important new therapeutic option for patients with this uncommon gastrointestinal disease," said Richard Pazdur, M.D., director, Office of Oncology Drug Prod-

See ADJUVANT, Page 14

Treatment strategies & mutational testing among key topics at CTOS 2008

By Jim Hughes
LRG Clinical Trials Coordinator

Several presentations and posters regarding GIST were presented at the Connective Tissue Oncology Society (CTOS) meeting on November 13 to 15 at the Landmark Hotel in London. The key topics were:

- Multiple treatment strategies for mutation-based resistance in GIST
- Planning for a new trial for wild-type GIST. SARC015: Phase II study of R1507 in wild-type GIST
- Dasatinib has a possible new role in resistant GIST
- Radiotherapy is a palliative option in GIST especially in the pelvis
- Pediatric GIST clinic registers largest cohort of young GIST patients
- The protein recycling mechanism - A potential new target in GIST
- Molecular testing growing – but has a long way to go
- Adjuvant Imatinib use growing

CTOS attendees view a presentation at the Landmark Hotel in London.

Multiple treatment strategies for mutation-based GIST resistance

Dr. Jonathan Fletcher of Brigham and Women's Hospital, Boston (and the lead researcher on the LRG Research Team) presented the current status of mutational resistance in GIST and the array of potential counter strategies.

FLETCHER

A key point is that more than one mutation can develop in the same patient in the same or different metastases. In a word or two, GIST mutations are 'heterogeneous' or varied. While the source of these multiple mutations is not fully understood, it is theorized that they are always present and can emerge and become more viable following therapy that suppresses a single dominant primary mutation. The mutations follow some patterns, but can also be highly individual.

The strategies to combat resistance are as varied as the knowledge of how GIST signaling works. Dr. Fletcher outlined the following main strategies:

- Use a broader spectrum and more potent KIT/PDGFRA inhibitor to block multiple mutations. This may also include combination therapy (multiple KIT/PDGFRA inhibitors).
- Block the signal path downstream from mutant KIT/PDGFRA. This strategy theoretically works against all mutations and may also work against wild-type GIST where normal KIT/PDGFRA is over expressed. Targets can include, AKT, PI3K, mTOR, SRC, RAS, RAF1 and PKC theta.
- Degrade (or destroy) mutant KIT by blocking its chaperone (HSP-90) or by interfering with it's transcription from DNA (HDAC and proteasome inhibitors).
- Block KIT/PDGFRA independent pathways. (IGF-1R, BRAF)

SARC015: Phase II study of R1507 in wild-type GIST

Dr. Margaret von Mehren of Fox Chase Cancer Center outlined a potential new target in GIST and the plans for a clinical trial of R1507 an IGF-1R inhibi-

See CTOS, Page 7

The Life Raft Group

Who are we, what do we do?

The Life Raft Group is an international, Internet-based, non-profit organization offering support through education and research to patients with a rare cancer called GIST (gastrointestinal stromal tumor). The Association of Cancer Online Resources provides the group with several listservs that permit members to communicate via secure e-mail. Many members are being successfully treated with an oral cancer drug Gleevec (Glivec outside the U.S.A.).

How to join

GIST patients and their caregivers may apply for membership free of charge at the Life Raft Group's Web site, www.liferaftgroup.org or by contacting our office directly.

Privacy

Privacy is of paramount concern, and we try to err on the side of privacy. We do not send information that might be considered private to anyone outside the group, including medical professionals. However, this newsletter serves as an outreach and is widely distributed. Hence, all articles are edited to maintain the anonymity of members unless they have granted publication of more information.

How to help

Donations to The Life Raft Group, incorporated in New Jersey, U.S.A., as a 501(c)(3) nonprofit organization, are tax deductible in the United States.

To donate by credit card, go to www.liferaftgroup.org/donate.htm

Donations by check can be made to The Life Raft Group and should be mailed to:

The Life Raft Group
40 Galesi Dr., Suite 19
Wayne, NJ 07470

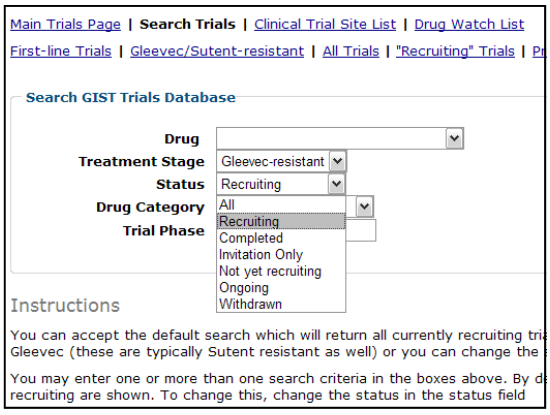
Disclaimer

We are patients and caregivers, not doctors. Information shared is not a substitute for discussion with your doctor. As for the newsletter, every effort to achieve accuracy is made but we are human and errors occur. Please advise the newsletter editor of any errors.

January 2009 International clinical trials

By Jim Hughes
LRG Clinical Trials Coordinator

This month's clinical trial report may look the same as those past, but it is now based on our new clinical trial database. Many changes have been incorporated into the data we collect and how it is published. To access and use the new data got to the Clinical Trials page at www.liferaftgroup.org/treat_trials.html. The eight new menu items at the top provide some of the most common reports as well as a free form search capability and two all new capabilities, a Clinical Trial Site List and a Drug Watch List. You can use the site list to see all GIST trials at a specific site. The Drug Watch List provides information specific to each new trial therapy including molecular targets. On trial and drug pages we have also included links to outside sites providing trial listings and results and background research material on new drugs. **We are interested in feedback on how useful this is and would also like to hear if you have questions or comments.** Please contact Jim at tjhughes43@com cast.net or Jerry Call at jcall@liferaftgroup.org.



United States

XL-820 Phase II: We have received notification from Exelixis that "Exelixis is closing the XL820-201 study for GIST". No explanation was provided. An interim report on this trial was recently published in a poster at CTOS in London on November 15 by Dr. Andrew Wagner at Dana Farber Cancer Center and was based on data collected through Oct. 1, 2008. The conclusions in that poster included "These preliminary data suggest that XL820 may be active in the treatment of imatinib and/or sunitinib resistant GIST." ClinicalTrials.gov lists this trial as "ongoing, but not recruiting participants." XL820 no longer appears on the pipeline page of drugs under development at Exelixis' website. Sixteen patients were reported as having enrolled in the trial.

Study to the optimal duration of therapy with oral angiogenesis inhibitors

Phase: IV
Conditions: GIST
Strategy: Block tumor blood vessel growth
NCT#: NCT00777504
Contact: C.M.L. van Herpen, 31 24 3610353
Sites: **Univ. Medical Center, Njmegen st Raboud,** Njmegen, Gelderland Netherlands

IPI-504

Study of IPI-504 in GSIT patients following failure of at least imatinib or sunitinib

Phase: III
Conditions: GIST
Strategy: Destroy KIT
NCT#: NCT00688766
Contact: GIST Phase 3 Team, 877-504-4634, RINGtrialinfo@infi.com
Sites: Bedford park, SA, Australia
Ashford, SA, Australia

AMN107 (Tasigna, Nilotinib)

First-line treatment of patients with metastatic or unresectable GIST

Phase: II
Conditions: GIST
Strategy: Block KIT
NCT#: NCT00756509
Contact: + 41 61 324 1111
Sites: Saarow, Germany

Imatinib (Glivec) or Sunitinib (Sutent)

Safety and effectiveness of daily dosing with sunitinib or imatinib in patients with GIST

Phase: III
Conditions: GIST
Strategy: Block KIT
NCT#: NCT00372567
Telephone: 1-877-369-9753
Contact: Pfizercancertrials@emergingmed.com
Sites: **Christie Hospital NHS Trust,** Manchester, Lancashire, UK
Royal Marsden Hospital, London, UK
The Beatson Institute, Glasgow, UK
Hamburg, Germany
Hong Kong SAR
Milano, Italy
Bologna, Italy
San Giovanni Rotondo, Foggia, Italy
Seoul, Republic of Korea
Barcelona, Spain
Valencia, Spain

Imatinib + RAD001 (everolimus)

Treatment with everolimus + imatinib in progressive GIST and imatinib-resistance

Phase: II
Conditions: GIST
Strategy: Block KIT+Block KIT signal path
NCT#: NCT00510354
Telephone: 41-6-1324-1111
Sites: Clinicaltrials.gov lists 9 sites as open in Germany. Use the Novartis number above for specific site information or go to the German Novartis site at www.novartis.de.

Dasatinib (BMS-354825)

Dasatinib as first-line therapy in treating GIST patients

Phase: II
Conditions: GIST
Strategy: Block KIT + Block KIT signal path
NCT#: NCT00568750
Telephone: 41-21-314-0150
Sites: **Hospitalier Universitaire Vaudois,** Lausanne, Switzerland CH-1011
Michael Montemurro, MD

AMN107 (Tasigna, Nilotinib)

Efficacy & Safety of AMN107 in GIST patients who have failed imatinib & sunitinib

Phase: II
Conditions: GIST
Strategy: Block KIT
NCT#: NCT00718562
Contact: Novartis Japan 81 3
Sites: Japan: Hokkaido, Niigata, Chiba, Tokyo, Kyushu, Aichi, Osaka

AMN107 (Tasigna, Nilotinib)

Phase II study evaluating efficacy & safety of AMN107 in GIST patients

Phase: II
Conditions: GIST
Strategy: Block KIT
NCT#: NCT00633295
Contact: Novartis Basel 41 61 324 111
Sites: Israel: Tel Aviv, Tel Hashomer

See TRIALS, Page 9

Twenty year battle brings feelings of luck and determination to Presnall

By Michelle Presnall
LRG Member


PRESNALL

My name is Michelle Presnall; I am 45 years old now, but my story starts back in 1988.

During my teenage years I experienced a lot of stomach problems. In 1988 I was traveling in the US when a doctor visit led to the discovery of a 6cm x 9cm tumor in my stomach. I had a laporotomy at Panarama Community Hospital in Los Angeles, and was sent home to Sydney, Australia for my recovery. At the time, my diagnosis was leiomyoma with an uncertain malignant potential. Within three months, the tumor was back and had doubled in size and in pain. The next year I had a partial gastrectomy which removed the tumor and the top half of my stomach. This was a huge operation that nearly cost me my life.

Thankfully I was still young at the time and was able to recover quite quickly and was traveling again within three months. In October 1989, I had to have surgery again while I was in London; scar tissue had developed around my small bowel and it was becoming gangrenous. I had to thank my youth once more because I was able to continue backpacking in Britain only ten days later. I suppose I have had the hospital tour of the world.

"I thought it was funny at the time that my gastroenterologist, referred to [my tumor] as 'lumpy'."

At that time, we believed all of the tumors were gone, but I continued to have an endoscopy and CT scan every year, just to be safe. Then, on a visit back to Australia in 1995 (I had moved to California a few years earlier), the tumors came back and had metastasized to my liver. I thought it was funny at the time that my gastroenterologist, referred to it as "lumpy." I continued to have my yearly scans and finally had a biopsy in 1997. Leiomyoma, again. They suggested that we keep an eye on it, so we did.

2003 was a very stressful year for me. My then husband was a Marine serving in Iraq during the first part of the war. My tumors had shrunk to half of their size, and then six months later they and had grown and spread to my abdomen. I had another biopsy done, but this time I received a different diagnosis: GIST.

At this point, my doctors decided to start me on 400 mg of Gleevec. During the course of 18 months I was on and off Gleevec, which kept my tumors stable. The Gleevec was far too toxic for me, so I went off of it and just continued my PET scans. Three years later I was in bad shape. I had received mixed results from my next scan, one tumor was growing and one was shrinking. I tried Sutent for a couple of weeks, but it shot my blood pressure up to 220/130 and the doctors were afraid that I was going to have a stroke. Now I was off of both Gleevec and Sutent and in the meantime I had developed a white stripe in my hair, eyelashes and eyebrows. It of course called for an immediate dye job.

This April, I found out that my tumors were misbehaving again. I entered a clinical trial for ARQ-197, but that only lasted for one month because my heart rate dropped down to 45 beats per minute. Thankfully my cardiologist says that my heart is okay. Since then I have had two more PET scans, and my tumors are still stable. Not shrinking, but not growing or spreading either.

After the lunch in Los Angeles where I was able to meet other GISTers, I feel lucky to still be alive. I believe I have

See PRESNALL, Page 11

LRG in the News!

The LRG has popped up in the news twice in the last week. Executive Director, Norman Scherzer was recently interviewed for a New Jersey paper, the Bergen Record. *Here are some highlights:*

"Norman Scherzer has two basic goals: One is to remake the way cancer research is conducted in order to speed up… treatments and cures. The second is to put his organization out of business. He hopes that by accomplishing the first objective, he'll inevitably achieve the second.

"When we had raised $2 million, I brought four [researchers] together [and] I told them 'We want you to create a strategy and agree to cooperate.' And then I turned to the institutions and told them, 'You can only charge us 10 percent for overhead.' Typically those charges are as much as 75 percent…Not one of them argued with us."

"[Dr. Brian] Rubin explain[s], "Here we assemble a team and carve up the duties...It's not a model a lot of us have used before, but it's a very good idea..."

Go to www.northjersey.com/business/nonprofits/Innovating_cancer_research.html for the full article.

A recent issue of CancerWorld magazine featured GIST specialist, Paolo Casali. In the article, Dr. Casali discussed cancer advocacy groups' future role in research:

"People who will be doing less wondering and taking more action, says Casali, are patients. 'We can now add advocacy groups as a third category of trial sponsor… I believe they will drive a lot of research in future. More and more patients will not join studies that the groups do not approve of…'

"He was...taken a back when, at a GIST meeting, patients presented a study disregarding the 'intent to treat' principle in analyzing data. 'I said I'd never heard in any medical congress someone challenging the principles of clinical research…'

A particularly active advocacy group is the US-based Life Raft, which is laying down its own model for allocating GIST research funds.

Go to http://www.cancerworld.org/cancerworld/home.aspx?id_sito=8&id_stato=1 for the full article.

PLASMA

From Page 1

ings suggest that "we may have been under-dosing some people," he said.

The report is based on analysis of the pharmacokinetic data from the original phase II Gleevec trial for GIST (B2222), which started in July 2000. These plasma levels were grouped into quartiles according to imatinib trough plasma concentrations (the level of drug in the blood at its lowest point during the day, just before taking that day's Gleevec). The plasma levels and response rates of these groups are listed in the table below.

The authors concluded that, "Exposure to adequate drug levels of imatinib appears to correlate with clinical benefit; patients with the lowest imatinib levels show lowest objective response and shortest time to progression. These results suggest that monitoring PK/PD relationships may provide novel predictive markers and that exposure to adequate imatinib trough plasma concentrations (>1,110 ng/mL) is important for optimal clinical response."

Table 1: B2222 phase II trial data: Plasma levels affect response

	Objective response	Median time to progression	Objective response exon 11 patients
Quartile 1 <1,110 ng/ml	44%	11.3 months	55.6%
Quartile 2+3 >1,110 ng/ml-<2,040 ng/ml	67%	30.6 months	94.1%
Quartile 4	74%	33.1 months	92.3%

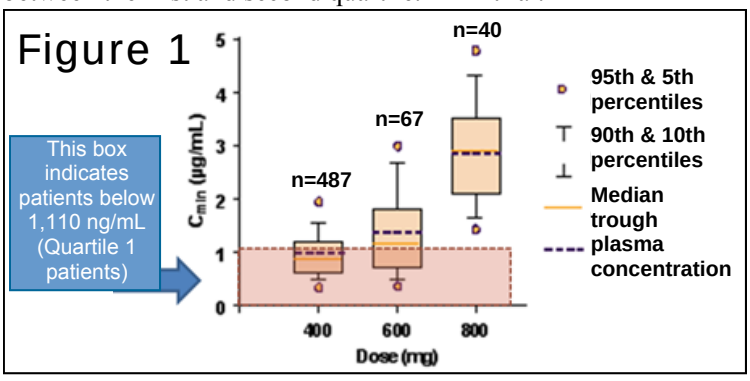
NOTE: The phase II plasma analysis divided the patients into four groups based on plasma levels (4 "quartiles"). This creates a somewhat arbitrary dose level of 1,110 ng/mL at the break point between the first and second quartile. This gives an impression that this precise number is a sort of "magic figure" (i.e., that one should feel safe to be above it, and panicked if one is below it). The data show that lower plasma levels are generally less effective, but biological common sense says that there is not a precise "safe level" for all patients. Because of this we prefer to use the approximate number of 1,100 ng/mL and will do so throughout the remainder of this article.

In the MedPage Today interview, Demetri went on to explain, "It's possible that we could have done this analysis and found nothing at all, but in fact, we saw something that is a bit worrisome for the patients with the lowest levels of the drug." According to Demetri, the next step will be to "… talk with our colleagues, decide exactly how much this is worth pursuing, [and] decide how to mount a large trial."

A closer look at both the B2222 trial results and other data shed light on why a trial might be needed to clarify the preliminary data that Dr. Demetri presented in 2008. In the B2222 trial, plasma levels were taken 29 days after starting Gleevec. Results were available for 73 of the 147 patients enrolled in the trial.

Table 2: Median Plasma Levels at Different Time Points

Study/Series	Timepoint	400 mg	600 mg	800 mg
B2222 Phase II	Day 29	1476 ng/mL	1659 ng/mL	N/A
		39% to 46% difference	28% difference	
Egorin/Novartis	Mixed	900 ng/mL	1200 ng/mL	2900 ng/mL
French CML	Mixed	825 ng/mL		
LRG	Mixed	879 ng/mL (8 pts)	1250 ng/mL (7 pts)	1970 ng/mL (3 pts)



In addition to the fact that the patients were not randomized, two other factors tend to confuse the data. First, Professor Ian Judson and colleagues from the European Organization for Research and Treatment of Cancer (EORTC) have raised **concerns that Gleevec drug levels may fall as much as 42 percent within the first year after starting Gleevec**. Table 2 presents data that supports the EORTC data. This raises concerns that comparing the B2222 "Day 29" levels to plasma levels that might have been obtained at any time point may be an "apples to oranges" comparison. Still, this type of error would tend to overestimate getting an adequate amount of the drug.

The second major factor that mystifies the B2222 plasma data is that we don't know how many of these patients remained on the dose that they were taking at day 29. This data was not reported for the phase II trials. It may be that a significant number of patients (more likely in the 600 mg arm) had permanent dose reductions after day 29. This type of error would tend to be in the opposite direction of the first factor and tend to underestimate the actual plasma level needed to prevent progression.

Imperfect as the plasma level data from the B2222 trial may be, it is the only plasma level/response data that we have for GIST. Additional plasma level data compiled by Novartis suggests that the majority of patients (includes CML, GIST and others) on the standard dose of Gleevec (400 mg) are below the 1,100 ng/mL level (See Figure 1).

Thus far, only a small percentage of LRG members have had plasma testing and shared the results with the LRG. Those results appear in Table 3 (Page 12). Although only a small dataset, the results are similar to the larger dataset from Novartis. Only three of the eight

See PLASMA, Page 12

FAMILIAL

From Page 1

been reported. Germline KIT or PDFGRA gene mutations cause most familial cases of GIST. Individuals affected with familial GIST syndrome typically have one normal KIT gene (called wild-type) and one mutant KIT gene. KIT or PDGFRA mutations are similar to those found in sporadic (not familial) form of disease. Familial GIST syndromes show autosomal dominant inheritance, which means that an affected person has a 50 percent chance of passing on the genetic mutation to each of his or her children.

Familial GIST syndrome associated with germline KIT mutation is characterized by certain medical and physical features, which are distinct from sporadic GISTs. Patients with this syndrome develop GISTs at a younger age (median – 46 years). The primary tumors are usually multiple in number (3 to >100 tumors) (see Figure 1, Page 10). The predominant site of tumors development is in the stomach and small intestine, but other gastrointestinal locations are also reported. In addition to GIST predisposition, germline KIT mutations result in other types of gastrointestinal pathology, particularly in disrupted bowel motility, such as difficulty in swallowing (dysphagia), constipation or gastro-esophageal reflux (regurgitation). Symptoms associated with gastrointestinal bleeding, such as fatigue, anemia (loss of blood) and melanea (blood in feces) are common and may be the only manifestation of the disease. Additional abnormalities may be present, with a substantial clinical variability. A significant number of familial GIST patients have skin hyperpigmentation, particularly around the mouth, in the perineum, on the face, neck, digits, axillae, groin and knees. Other features that are linked with the dysfunction of melanocytes (pigment producing cells), such as melanocytic moles (colored spots on the outer layer of the skin), lentigines (multiple, tiny, hyperpigmented skin spots), café au lait spots (a pale tan patches of skin) and vitiligo (white patches of skin or hair due to a loss of pigment in the cells) can also be seen. Abnormalities of mast cells, mainly urticaria pigmentosa (a skin rash that is marked by itching and small pale or red swellings) or systemic mastocytosis (abnormal over-production of mast cells) in infancy are less frequently reported.

Germline mutation in the gene encoding PDGFRA has been reported only in three families. In one of these families, a unique combination of multiple fibrous tumors and lipomas of the small intestine and several gastric GISTs was described. This was the second family presented with multiple intestinal tumors. Notably, none of the additional components of familial GIST syndrome (such as hyperpigmentation, dysphagia, or mast cell abnormalities) previously described in germline KIT mutation kindreds were present in the PDGFRA mutation carriers. In two families, all affected family members displayed unusually large hands.

The clinical behavior of familial GIST associated with germline KIT or PDGFRA mutations is the same as sporadic GIST, varying from clinically benign to overtly malignant disease. Imatinib may be effective in the prevention of tumor development as well as in the treatment of familial GISTs. The careful monitoring for the development of tumors is indicated, but the multifocality of the disease suggests that surgical intervention should be avoided in the absence of large tumors or complications.

Other hereditary syndromes associated with an increased risk for GIST are neurofibromatosis type 1 (NF-1), as well as von Recklinghausen's disease, and Carney–Stratakis syndrome.

Neurofibromatosis type 1 is a condition characterized by changes in skin coloring (pigmentation) and the growth of tumors along nerves in the skin, brain, and other parts of the body. The signs and symptoms of this condition vary widely among affected people. Beginning in early childhood, almost all people with NF-1 have multiple café-au-lait spots, which are flat patches on the skin that are darker than the surrounding area. Freckles in the underarms and groin typically develop later in childhood. Most adults with NF-1 disease develop neurofibromas, which are noncancerous (benign) tumors that are usually located on or just under the skin. These tumors may also occur along nerves elsewhere in the body. People with NF-1 disease also have an increased risk of developing other cancers, including malignant peripheral nerve and brain tumors and leukemia. Neurofibromatosis type 1 is caused by mutations in the NF1 gene. The NF1 gene provides instructions for making a protein called neurofibromin. This protein is produced

See FAMILIAL, Page 10

Hereditary Glossary

Autosomal dominant genetic conditions: These are conditions whereby a person needs only to inherit one changed (mutated) copy of the gene in order to be affected by the condition, or become affected by the condition later in life. The changed gene is dominant over the normal gene.

Autosomes: We have 23 pairs of chromosomes. Pairs number 1 to 22 are called autosomes and look the same in men and women. Pair number 23 are different in men and women and are called the sex chromosomes (X and Y chromosomes).

Carrier: A person who is generally not affected with the condition (at that moment), but carries one fault copy of a gene. In the case of dominant conditions, the person may become affected at a later stage.

Catecholamines: Any of several compounds occurring naturally in the body that serves as hormones or as neurotransmitters in the sympathetic nervous system.

Germ-line mutation: Originating from the germ cells (sperm in males or egg in females) and passed from parent to child.

Penetrance: A term used in genetics that describes the extent to which the properties (phenotype) controlled by a gene will be expressed. A high penetrance means that children that inherit the mutant KIT gene have a high chance of developing GIST sometime during their life.

Prenatal diagnosis: Test during a pregnancy for the presence or absence of a genetic condition in the baby.

Proband: The first affected person that seeks medical attention for a genetic disorder.

CTOS

From Page 2

tor. The IGF-1R receptor has been identified as over expressed in a number of cancers which now include wild-type GIST. Unlike KIT, IGF-1R mutations have not yet been found. High levels of IGF-1R may be partly due to gene amplification. Research is needed to find the cause. It is clear that inhibition of IGF-1R can lead to cell death in both KIT wild-type and mutant GIST in the lab. Fox Chase is leading the effort to design a trial of R1507 in pediatric and adult wild-type GIST in early 2009. The trial will be called SARC015.

Dasatinib has a possible new role in resistant GIST

Dr. Scott M. Schuetze, at the University of Michigan presented the interim status of the SARC 009 Phase II trial in Dasatinib for advanced sarcoma. GIST has recently been added as a condition acceptable for accrual. As of report cutoff, 22 GIST patients have enrolled. The trial is available at 19 sites across the United States. Dasatinib has had renewed interest since it was shown in a paper earlier in 2008 that it is active against a common PDGFRA mutation (D842V) and also against KIT mutations in exon 17 in GIST cell lines in the lab.

Radiotherapy is a palliative option in GIST especially in the pelvis

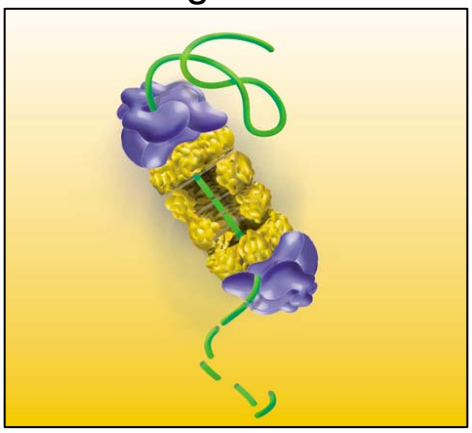
A research team in at the Royal Marsden in London examined the effect of radiation therapy on 12 GIST patients from 2001 to 2008. Eleven of twelve GIST patients experienced clinically relevant symptomatic improvement. This suggests that radiation therapy can be useful in the palliative setting for symptomatic GIST. Four patients received radiation for bone mets, seven for intra-abdominal /pelvic disease and one to the abdominal wall.

Pediatric GIST clinic registers largest cohort of young GIST patients

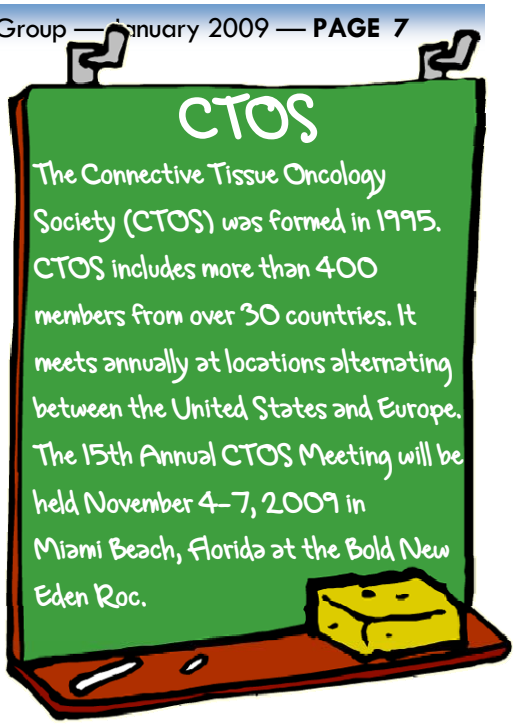
A poster authored by the Consortium for Pediatric and Wild-Type GIST Research (CPGR) outlined the activity of the pediatric GIST clinic at the National Institute of Health in Bethesda, MD. The first clinic was held June 19, 2008. Out of 21 patients registered, 14 were seen at the clinic and patient ages ranged from 11 to 35. The second pediatric clinic will take place on January 21 to 23, 2009. A goal of the clinic is to see all patients with pediatric or wild-type GIST. On clinic day one, patients will have the opportunity to meet health care specialists is a variety of fields, such as dermatology, genetics, nutrition, pain management and psychosocial services. On clinic day two, patients will meet with members of the CPGR. Throughout the day there will be a series of seminars that address subjects such as alternative/complimentary approaches, nutrition tips, recreational/art therapy and relaxation techniques. In addition to developing a database of patients with this rare form of GIST, current CPGR projects include assessment of germline mutations of the succinate dehydrogenase gene previously identified in patients with Carney-Stratakis Syndrome, measurement of tumor size and growth rates and development of a protocol using an IGF-1R antibody for wild-type GIST.

CPGR has a webpage (www.pediatricgist.cancer.gov) for more info and an email address (ncipediatricgist@nih.cancer.gov) for patients who would be interested in registering for the clinic.

Figure 1



A green protein is captured by the Proteasome where it is disassembled into smaller components that are released back into the cell and are available for reuse.



The protein recycling mechanism - a potential new target in GIST

Dr. Annette Duensing recently joined the LRG Research Team. Her work on GIST cell death mechanisms was the subject of a presentation. Duensing presented lab evidence that inhibiting the proteasome causes apoptosis (natural cell death) in a GIST exon 13 mutation cell line.

DUENSING

The proteasome (See Figure 1) is basically a recycling machine. It disassembles large proteins into their component protein building blocks so they can be reused within the cell. In this role it can move the cell directionally either toward renewal or natural death. It comes into

See CTOS, Page 14

A man inspired, a family remembers

By Lorie Cudzil, Lisa Roth Fleming, LRG Members & Erin Kristoff, LRG Newsletter Editor

It's difficult to write the story of a man like Bill Roth.

Much of what made Bill a wonderful person cannot be articulated, it can only be felt. The subtle generous and supportive nuances of his character and quiet strength of his convictions comforted and compelled every person in his life. Without the tongue of Chaucer or the pen of Shakespeare, how do you explain what makes a man great?

Bill's oldest daughter, Lorie, has read the LRG newsletter for years, "I always pictured writing one of these for dad; now I can't think of anything to say."

What Lorie, Lisa and I hope to do here is not to unravel the vast mural of Bill's life, but to paint you a single portrait of a good man.

Bill was born on May 18, 1950 and owing to a love of the beach, has spent his whole life in the Long Island area. When he was 17, he met the future love of his life, Frances. The two were married soon after he graduated from Hofstra University and went on to have two beautiful daughters, Lorie and Lisa. Bill was a wonderfully doting husband; when he got sick, it was important to him that Frances was always cared for. Around her, Bill was always smiling and he was definitely her whole life.

Bill worked as a wholesale buyer for 30 years and eventually was lucky enough to own his own company, TradeMaster Marketing services. People who did business with Bill respected him, as one man said to Lorie, "This is a tough business, but your dad always did the right thing."

Growing up with a dad like Bill was easy for Lorie and Lisa. Bill had lost his dad to cancer when he was ten and grew up without a father-figure, but as Lorie always says, "He just knew how to be a good dad."

"He always made us feel so good. We owe a lot of our accomplishments to our dad. He always pushed us, but in a gentle way." Bill wanted his daughters to succeed in life and always made himself available to talk and problem solve, "It was important to him that we were self sufficient. He was so proud that it made us more proud to see his face."

The "Roth" family celebrates Christmas. From left: Peter, Lisa, Lorie with baby Abigail, Jerry, Sean, Bill & Frances.

When Bill was diagnosed with GIST in January 2003, he refused to let it keep him down. "He could have a whole lot of stuff going on, but he always just cared about you."

Bill, Jerry and Sean at the car show on Father's Day.

Bill was a family man. On the weekends, he left his business behind and devoted himself to his family and friends. He adored his sons-in-law, Jerry Cudzil, Lorie's husband (and President of the Life Raft Group Board of Directors) and Lisa's husband, Peter Fleming. He also loved to babysit Lorie's children, Sean and Abigail.

He wanted to share what he loved with those around him. Last June, Bill decided to take Jerry and Sean to a car show for Father's Day. Bill had loved cars since he was a little boy. He enjoyed the Indy500 and had taken a racing course once. He wanted to experience this with his grandson. Bill had been looking forward to it for some time and the three boys had a great day together.

Three weeks later Bill could barely walk. He had been much sicker that weekend, but no one knew. He wanted it to be special. That was just the kind of man Bill Roth was.

It seems hard for people to say just one nice thing about Bill, "He was just wonderful and very selfless. He always helped with homework, he was always full of praise and always made us and our mom feel like the most important people. He truly was a family man and an eternal optimist. He wanted everything to always be fun. He was such a good person," Lisa says passionately.

Bill passed away on October 15, 2008. When Lisa and Lorie opened his email to begin the numbing task of notifying friends and acquaintances, she found a staggering 1,000 contacts. Immediately a rush of responses flooded her inbox with messages like, "He was a true gentle man," and "He was the nicest person I knew."

Quietly, Lorie says, "For a lot of people, life isn't the same without Dad here."

See ROTH, Page 9

TRIALS

From Page 3

Glivec + IL2

Imatinib+IL2

Phase: I
Conditions: Solid tumors and GIST
Strategy: Block KIT+Stimulate the immune system
Contact: Dr. Patricia Pautier
Telephone: +33(0)1 42 11 42 10
Sites: **Institute Gustave Roussy,** Villejuif, France

Multi-Bacteria Vaccine

A Phase 1 study of mixed bacteria vaccine in patients with tumors expressing NY-ESO-1 Antigen

Phase: I
Conditions: GIST
Strategy: Stimulate the immune systen
NCT#: NCT00623831
Contact: Krankenhaus
069 7601 4161
neumann.antje@khnw.de
Sites: **Krankenhaus Nordwest,** Frankfurt, Germany

Radiation Therapy as Palliative Treatment of GIST (GIST RT)

Phase: I
Conditions: GIST
NCT#: NCT00515931
Contact: Heikki Joensuu
947173208 Ext. 358
Sites: heikki.joensuu@hus.fi
Helsinki University Central Hospital, Helsinki, Finland

RAD001 (everolimus)

Treatment of patient with RAD001 who have progressive sarcoma

Phase: II
Conditions: Sarcoma
Strategy: Block KIT signal path
NCT#: NCT00767819
Contact: Novartis
Sites: Germany: Berlin, Munchen, Dusseldorf, Mannheim

AUY922

Phase I-II study to determine the MTD of AUY922 in advanced solid malignancies and efficacy in HER2+ or ER+ locally advanced or metastatic breast cancer.

Phase: I
Conditions: Solid Tumors
Strategy: Destroy KIT
NCT#: NCT00526045
Contact: **Novartis**
Telephone: 800-340-6843
Sites: Bellinzona, Switzerland

BGT226

A phase I/II study of BGT226 in patients with advanced solid malignancies including those with advanced breast cancer.

Phase: I
Conditions: Solid Tumors
Strategy: Block KIT signal path
NCT#: NCT00600275
Contact: Novartis
Telephone: 800-340-6843
Sites: **Hospital Vall d'Hebron**, Barcelona, Spain
Princess Margaret Hospital, Toronto, ON, Canada

XL147

Study of safety and pharmacokinetics of XL147 in adults with solid tumors

Phase: I
Conditions: Solid Tumors
Strategy: Block KIT signal path
NCT#: NCT00486135
Contact: Exelixis, 866-939-4041
Sites: **Hospital Universitario Vall d'Hebron**, Barcelona, Spain, 08035
Gemma Sala, gsala@vhebron.net
+34 93 489 4158

XL765

Study of safety and pharmacokinetics of XL765 in adults with solid tumors

Phase: I
Conditions: Solid Tumors
Strategy: Block related tumor signal paths
NCT#: NCT00485719
Contact: Exelixis, 866-939-4041
Sites: **Hospital Universitario Vall d'Hebron**, Barcelona, Spain, 08035
Gemma Sala
+34 93 489 4158

Global GIST Network adds new GIST representatives

Global GIST-Network

Sudan
Mohamed-Elbagir K Ahmed
mohamedelbagir@live.com

Scotland
Helena Koumbouzis
hkoumbouzis@yahoo.com

ROTH

From Page 8

The Fifth Annual NYC Poker Tournament

On November 20, the Life Raft Group held its Fifth Annual Poker Tournament at the Midtown Loft on Fifth Avenue in New York City. It is always a remarkable evening and has become a much-looked-forward-to event for LRG staff and supporters.

Its beginnings were simple. Lorie and Lisa ran a marathon in 2003 to raise money for the LRG in honor of their father. Jerry helped raise a lot of money for their effort. In 2004, Lorie and Lisa had no plans to run another race but Jerry still wanted to raise money. He knew many colleagues in the financial world who donated to charity and thought that a poker tournament would be a fun way for them to contribute. The poker tournament has since become a yearly success.

Players get their heads in the game at the Fifth Annual NYC Poker Tournament.

This year was a little different. In the

See ROTH, Page 11

FAMILIAL

From Page 6

in many cells, including nerve cells and specialized cells surrounding nerves (Schwann cells). Neurofibromin acts as a tumor suppressor, which means that it keeps cells from growing and dividing too rapidly or in an uncontrolled way. Mutations in the NF1 gene lead to the production of a nonfunctional version of neurofibromin that cannot regulate cell growth and division. As a result, tumors such as neurofibromas can form along nerves throughout the body. Neurofibromatosis type 1 is considered to have an autosomal dominant pattern of inheritance. People with this condition are born with one mutated copy of the NF1 gene in each cell. In about half of cases, the altered gene is inherited from an affected parent. The remaining cases result from new mutations in the NF1 gene and occur in people with no history of the disorder in their family.

Unlike most other autosomal dominant conditions, in which one altered copy of a gene in each cell is sufficient to cause the disorder, two copies of the NF1 gene must be altered to trigger tumor formation in neurofibromatosis type 1. A mutation in the second copy of the NF1 gene occurs during a person's lifetime in specialized cells, such as cells surrounding nerves, interstitial cells of Cajal (ICC, precursor GIST cells) or blood cells. Almost everyone who is born with one NF1 mutation acquires a second mutation in many Schwann cells and develops neurofibromas. However, the risk of developing GISTs is low (only 7%, based on a single Swedish study)[2]. GISTs in NF1 patients tend to be multiple and are located predominantly within the small intestine. Abdominal pain, bowel obstruction and massive gastrointestinal bleeding are the most common presenting clinical manifestations. Although they may fall into any GIST risk category, NF1-associated GISTs usually show low cell proliferation (growth) indicators and they rarely metastasize. Vast majority of GISTs associated with NF-1 do not carry KIT or PDGFRA mutations, and for this reason treatment with tyrosine kinase inhibitor drugs such as imatinib might be less effective in NF-1 GIST patients.

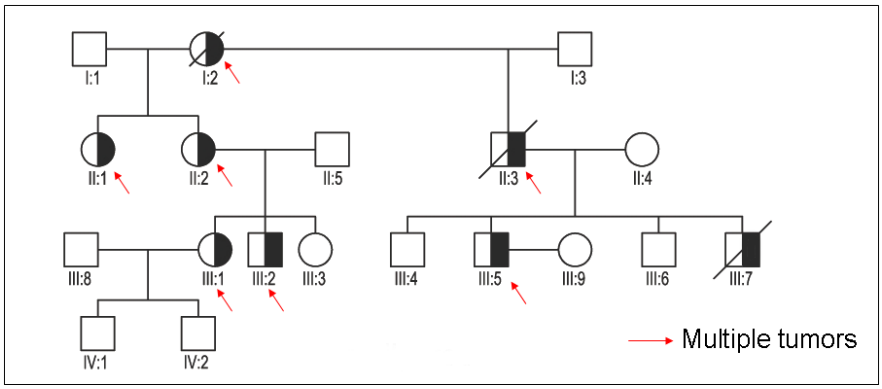
In a subset of patients with gastric GISTs the lesions are associated with paragangliomas (PGLs). The condition referred to as the dyad of "paraganglioma and gastric stromal sarcoma" or the "Carney–Stratakis syndrome" is transmitted as an autosomal-dominant trait with incomplete penentrance (not all carriers of the mutant gene develop tumors). The patients present tumors at a young age (median age 19 years). GISTs are multifocal and paragangliomas multicentric, supporting a genetic link between the two lesions. PGLs are neuroendocrine tumors that may secrete catecholamines. They occur most frequently in the head, neck, adrenal and extra-adrenal sympathetic ganglia. Once the diagnosis is made, patients must be followed carefully in order to detect new lesions as early as possible, since both, GISTs and PGLs, have malignant potential. A functioning paraganglioma may manifest itself by sympathetic effects such as hypertension, increased perspiration, and/or facial flushing. A ^{131}I-MIBG scan is useful for diagnosis, as this agent localizes to catecholamine-producing tissues.

GIST patients with Carney–Stratakis syndrome do not carry the KIT or PDGFRA gene mutations. The underlying hereditary defect of the Carney–Stratakis syndrome has been elucidated recently by identification of germline "loss-of function" mutations in the succinate dehydrogenase subunit B (SDHB), C (SDHC) or D (SDHD) genes in affected patients. The identified mutations had been described before in sporadic or familial paragangliomas. Notably, the abdominal paragangliomas associated with GISTs are uniquely correlated with SDHC mutations. The absence of KIT or PDGFRA somatic mutations and inactivation of one of the succinate dehydrogenase subunits in GISTs/PGLs from patients with the dyad suggests that a deficient mitochondrial tumor suppressor gene pathway is responsible for tumor formation and not constitutively active tyrosine kinases. The role of imatinib as a therapeutic or preventive intervention in Carney–Stratakis syndrome patients remains to be defined.

Below is a list of "clues" in a family tree that make a familial GIST syndrome more suspicious:

a. GIST diagnosed more than once in the same person (more than one primary tumor, not a cancer recurrence).
b. GIST diagnosed at an earlier age than usual (before age 50)
c. Two or more close relatives with GIST (on the same side of the family)
d. One person in the family who has had a GIST and another cancer as well
e. One person in the family with GIST who also has a personal or family history of unusual skin findings, multiple moles, or NF1.

Figure 1



Family tree. Black semicircles indicate family members with inherited germ-line KIT mutation. All affected individuals developed multiple intestinal tumors. Individual III:7 died from a massive gastrointestinal bleeding.

See FAMILIAL, Page 15

Ferris brought joy to everyone she touched

Sarah (Blanche) Ferris was born in Willcox, Arizona on April 27, 1935. She was the youngest of seven children born to Alma (Brown) and Joseph Wootan. Her siblings were Arthur, Harold and Roy (deceased) and she is survived by Dora, David and Gerald. Blanche married Delle Ferris on February 9, 1952. Before Delle's graduation from Arizona State College and the ROTC program, Delle and Blanche had two children, Dennis and Debby. Eighteen months later she gave birth to Lynn and the Ferris family was complete. The Ferris family enjoyed their military life and lived all over the world until 1975 when the second phase of their life began again in Arizona. Blanche was an accomplished wife, mother, grandmother, teacher, role model, life coach, mentor, hostess, artist, tennis player, musician, golfer, seamstress, cook, antique collector and gardener. Blanche was the thread that held the family fabric together. She was a person who lit up every room she entered and brought joy to everyone she touched. Blanche was the person we should all aspire to be. Blanche passed away on Sunday December 14 at the age of 73 after a courageous 6 1/2 year battle with cancer. She was as gracious, selfless and loving through this difficult battle as she was her entire life. She was truly "one in a million". Blanche is survived by her loving husband Delle, her daughters, Debby and Lynn, and will join her son, Dennis, in heaven. Her grandchildren, Kurt, Anthony, Nicole, Alexander and Andrew are all better people because of the influence of this great lady. Her great granddaughter, Ainsley, will know her as we did, through our many wonderful memories. A memorial service was held on Friday, December 19 at the Paradise Valley United Methodist Church. In lieu of flowers, the family asks that donations be made to Hospice of the Valley, 1510 E. Flower Street, Phoenix, AZ 85014. They can also be made at www.hov.org.

FERRIS

PRESNALL

From Page 4

my upbringing to thank for that. A life of small frequent meals combined with moderate exercise, great friends and family, and positive thinking are what has kept me going.

I have always been the type to push myself, and even though it takes more energy now, I am still living my life. Although I can no longer work full time because I am easily tired and overwhelmed, I keep going.

What else can I do? Just lie down and die? No way! I have too many things to do and places to see to do that.

ROTH

From Page 9

midst of an American financial crisis, most non-profits have been concerned about funding. The question of whether people would want to spend their hard-earned money on charitable giving was a pressing one, one that would not be answered until the day of the tournament.

The final three players at this year's tournament. From left: Dennis Lu, Joe Bonavita & Choudhary Yarlagadda.

That night, the LRG greeted 150 guests, over 90 of whom were players who together contributed over 63,000 dollars! Old friends and colleagues enjoyed a night of great food and serious poker in remembrance of a man who knew how to have a good time.

The Life Raft Group would like to congratulate first place winner, Joe Bonavita, who will receive a seat at the World Series of Poker Main Event in Las Vegas, Nevada (valued at $10,000). Taking home second and third place were Choudhary Yarlagadda and Dennis Lu, respectively, who each won dinner for four to famed New York City restaurants, Daniel and Nobu. Johnny Tyler won the night's raffle for dinner for four at another famous New York restaurant, The Palm, donated by previous Poker Tournament winner, Nick Chiara.

We would like to thank Marzena from the Midtown Loft, Worldwide Events, Jerry Cudzil for his tireless dedication, and everyone who supported the event!

PLASMA

From Page 5

patients on 400 mg had plasma levels above 1100 ng/mL. One of those patients at 1121 ng/mL had only been on Gleevec for three months and will bear close monitoring to ensure that the Gleevec level does not decline in the first year.

In the LRG data, seven patients furnished data at the 600 dose. Only one 600 mg member was clearly well below the recommended threshold with a value of 742 ng/mL. Two members were below but within three percent of the threshold with values of 1080 and 1082 ng/mL. The other four 600 mg members, one member at 700 mg and four members at 800 mg were all well above the minimum threshold.

Opinion: Will plasma testing follow in the footsteps of mutational testing?

Mutational data from the GIST reGISTry was recently presented at the Connective Tissue Oncology Society (CTOS) (See Jim Hughes' CTOS article on page 2). This registry collects data on how GIST patients are being treated. One of the most striking omissions in the treatment of GIST patients is that only one percent of patients treated at local institutions are getting mutational testing. At academic institutions this number rises to four percent and even with Life Raft Group patients we only have about 20 percent of members that have reported their mutational status to us.

There is a tremendous amount of data detailing the value and potential uses of mutational data. It is now "strongly encouraged" for metastatic disease and "can be considered" for patients with primary disease according to the *Journal of the National Comprehensive Cancer Network* (JNCCN) guidelines for GIST (July 2007). In spite of this fact, the LRG regularly hears from members that want to have the test done and are refused by their doctors. With plasma testing, refusals are even more common. Because of this, some patients have turned to their primary care doctor to order the test.

Just as disconcerting as a lack of mutational testing discussion, there were no formal discussions (that we are aware of) about plasma testing at this year's CTOS meeting. The preliminary data suggest that plasma level testing has the potential to significantly alter the course of GIST in many patients. In this preliminary patient group, patients with levels above 1100 ng/mL had three times the duration of response as those below that level. In addition, the current practice of dosing at 400 mg may result in over half of those patients being below 1100 ng/mL as their levels decline over time.

At this time, plasma level testing may be the biggest potential opportunity to significantly improve GIST patient survival in the near future. Second-line treatment to overcome Gleevec-resistance is just not where we want it to be yet.

The question remains: Will plasma testing go the way of mutational testing, with only a lucky few being offered the test? The only way this is likely to be avoided is to have a new trial designed to answer the questions that remain about plasma testing. Such a trial could probably do more and should really be designed to take advantage of all we have learned over the last eight years of Gleevec and may answer the question: What is the best way to treat patients initially?

We need to take the information that we have already learned, but are not acting on and create a first-line optimization trial with different therapies for different mutations and with the dose modified based on plasma levels for exon 11 patients. Only then will mutational testing and plasma testing move into mainstream clinical practice.

In the meantime, patients and their

Table 3: LRG Plasma Testing Results

PT #	Gender	Dosage	Trough Level	Treatment
1	M	100	210	Gleevec
1	M	300	738	Gleevec
2	M	400	972	Gleevec
3	M	400	897	Gleevec
4	F	400	1121	Gleevec
5	M	400	773	Gleevec
6	M	400	591	Gleevec
7	M	400	1380	Gleevec
8	M	400	658	Gleevec (adjuvant)
8	M	600	1082	Gleevec (adjuvant)
9	F	400	861	Gleevec (adjuvant)
10	M	600	742	Gleevec (neoadjuvant)
11	F	600	1080	Gleevec for recurrence
12	F	600	1600	Gleevec
13	M	600	1250	Gleevec
14	F	600	2240	Gleevec
15	F	600	2340	Gleevec (adjuvant) (exon 9)
16	M	700	1460	Gleevec
17	M	800	2280	Gleevec (for recurrence)
17	M	800	2090	Gleevec (for recurrence)
18	M	800	1970	Gleevec
19	M	800	1940	Gleevec

Patient # 1 experienced liver toxicity on 600 mg as indicated by elevated levels of liver enzymes in the blood and is now using dose escalation and plasma monitoring to balance dose and toxicity.
Pt # 6 is unable to increase dose because of current NCCN guidelines.
Pt # 8 increased dose from 400 mg to 600 mg resulting in Gleevec levels that are just below the recommended minimum.
Pt # 10 (neo-adjuvant) now questions whether a higher dose might result in more shrinkage before surgery.
Pt # 15 had an exon 9 primary (removed by surgery) and was unable to tolerate the 800 mg dose recommended by her oncologist. Plasma testing gave some reassurance that the plasma level was indeed quite high on 600 mg. Despite this informative finding, plasma testing is probably of limited value for exon 9 patients (discussed later in this article).

See PLASMA, Page 13

PLASMA

From Page 12

doctors must act on what we know today. With a median Gleevec-sensitive window of two years and no trials underway which include plasma level testing, data from future trials will be too late for most patients that are taking Gleevec right now.

You can read an editorial by Norman Scherzer on routine plasma testing in the September 2008 newsletter and a plasma testing how-to in the December 2008 newsletter. Both issues are available at www.liferaftgroup.org/newsletters.html

Opinion: Plasma testing is not for everyone

The initial data about plasma testing is intriguing, yet there are reasons to believe that some patients could benefit and some would not:

- Patients with the most common mutation, KIT exon 11, appear to be those most likely to benefit. By extension, it seems logical that patients with the closely related exon 12 mutation in PDGFRA, might also benefit.
- Evidence from the phase III GIST trials has already shown that patients with exon 9 mutations need a high dose of Gleevec, preferably 800 mg (if tolerated) so plasma testing should probably not be used in lieu of the 800 mg recommendation.
- Gleevec is not a very good inhibitor of wild-type GIST, so it seems likely that the plasma levels determined in the phase II trials would not be applicable to wild-type GIST (10% to 15% of GIST patients).
- GIST patients with the PDGFRA D842V mutation appear to be insensitive to Gleevec, at least in the test tube so plasma level testing would probably be irrelevant in these patients.
- Patients that are resistant to 400 mg of Gleevec and are moving to a higher dose probably need 800 mg (if tolerated) and plasma testing is irrelevant to these patients.
- The value of plasma level testing in patients taking Gleevec as adjuvant therapy is unknown, but it seems likely that exon 11 patients in this group could benefit as well.

One last ride for Donnie Chadrick

Very shortly after receiving news of the passing of LRG member, GIST patient and wonderful friend, Donnie Ray Chadrick on December 5, the LRG received a letter from his ex-wife and dear friend, Janel Graham. We feel it would be a great disservice to all of Donnie's friends in the GIST community not to share Janel's message.

Donnie before his last ride in September, just outside of Kingsburg, California, at a place called "Riverland". The Harley in the picture is "Dingo", what Janel sometimes called him for fun.

I know that most of you readers from my reading of the daily news, already have heard of the passing of my dear friend Donnie Chadrick.

I am doing what Donnie asked me to do after he was gone which was to let all of his friends on the "Raft" know of his passing to a peaceful place.

We were close friends, both with medical problems (I have Multiple Sclerosis), who could understand a lot. I could do research for him and he for me because four eyes are always better than two. We could laugh and discuss life rather than the daily fears and problems that we both would deal with, but also understand each other better on a bad day, because of our ability to speak very bluntly about very sensitive and personal issues.

"I have a feeling that he still fights alongside you fellow Rafters in spirit."

I had one last Harley ride, and one last very special day with my dear friend. I felt it would be our last; it was. I believe he also knew his limited time left was nearing the end, because he worked at a feverish pace to finish his old truck, or at least get it closer to "finished". Donnie was and will always be a dear friend. He was a hero who fought the monster till his end. And I have a feeling that he still fights alongside you fellow rafters in spirit. That's the kind of man he was.

His last wishes have been taken care of in a style that was his, and his alone. His memory will be forever in the hearts of many, and his courage will hopefully someday help in the curing of GIST.

So with a tearful end to this last request, I wish you all strength, hope and courage. And I want to thank you from Donnie, for all the support you gave him, he was so grateful for all of you.

Mark your calendars!

- The second annual Complimentary and Alternative Cancer Therapies conference will be held in West Palm Beach, Flor. from **January 8-January 10**.
- The NIH Pediatric GIST Clinic will be held January 21-23. Please see www.pediatricgist.cancer.gov for details.
- Julie Cramer's GIST Benefit Ball will be held at The Mansion on Main Street in Voorhees, NJ on **February 14**. Visit www.gistbenefitball.org for more information.
- The Italian GIST group will be meeting on **February 21**, please email Anna Costato at anna.costato@virgilio.it for details.

CTOS

From Page 7

play after another cell process called ubiquitination tags proteins with ubiquitin to identify them for disassembly by the proteasome.

The proteasome is active in a chain of events occurring during imatinib therapy. Therapeutic response to imatinib in GIST involves upregulation of histone H2AX. H2AX levels are regulated by the ubiquitin-proteasome machinery in GIST. By blocking the recycling machinery using an approved proteasome inhibitor called Velcade or Bortezomib, Dr. Duensing demonstrated that GIST cell death can occur as a result of higher H2AX levels. Bortezomib is also shown to reduce transcription levels of KIT.

Dr. Duensing concludes that this is a new therapeutic option for GIST.

Molecular testing growing – but has a long way to go.

The GIST 'ReGISTry' began in 2004 as a means of tracking actual delivery of GIST care at multiple sites in the United States. After patient consent, GIST clinicians enter historical data into a web-based database. Every six months the data is collected and summarized. Dr. Jonathan Trent presented the current summary in a poster at CTOS. There are now 753 patients enrolled from 116 treatment centers. Molecular testing (GIST genotype or mutation analysis) is growing but has only been done for four percent of the patients. This is a clear area of concern since genotyping is available and may have predictive value. Hopefully this percentage will grow as clinicians learn of the potential implications for treatment.

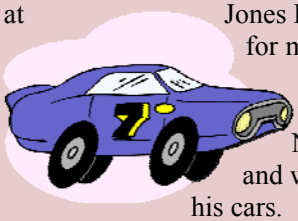
Adjuvant imatinib use among all patients has grown from 14 percent in 2007 to 28 percent in 2008.

Several of the CTOS presentations can now be downloaded at www.ctos.org/meeting/2008/program.asp.

Gjertson was 60

Thomas O. Gjertson, 60, of Fort Atkinson, WI passed away Thursday, Dec. 04, 2008, at his home.

Tom was born on Jan. 10, 1948, in Stoughton, WI. He had been employed at Jones Dairy farm for many years.



Tom enjoyed watching NASCAR and working on his cars.

Tom is survived by his children, Dale Gjertson of Fort Atkinson, Cheryl (Jim) Martinson of Helenville and Angie (Troy) Kratz of Fort Atkinson; grandchildren, Allison and Nicole Gjertson; brother, Marvin (Rosie) Gjertson; sisters, Corinne Hommen of Fort Atkinson and Evelyn Gjertson of Stoughton; Paula Vaughn (mother of Tom's children); nieces; nephews; cousins; and many special friends.

ADJUVANT

From Page 1

ucts, Center for Drug Evaluation and Research, FDA. "It illustrates how the continued study of a once novel drug throughout its product lifecycle can yield new and important uses."

About 5,000 to 6,000 new patients are diagnosed with GIST each year in the United States. Because symptoms of GIST are no different than other GI complaints such as nausea and vomiting, the cancer is difficult to detect early. Patients initially undergo surgery to remove the tumor but GIST commonly recurs. Gleevec is intended to be given to patients following surgery to help prevent tumor recurrence.

The efficacy of Gleevec was established in a clinical trial in which patients received either Gleevec or a placebo for one year after surgical removal of the tumor. The optimal treatment duration is not known.

There were significantly fewer recurrences of GIST in patients receiving Gleevec than in patients who did not. The most frequently reported adverse reactions were diarrhea, fatigue, nausea, swelling of the feet, decreased red blood cell counts, rash, vomiting and abdominal pain.

Gleevec is manufactured by Novartis AG, Basel, Switzerland.

LRG Notes

Although there are still some questions about adjuvant Gleevec for GIST, the new FDA approval has few restrictions. The approval is for "Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST". As noted in the FDA press release, "the optimal treatment duration is not known" and no treatment duration is specified in the revised Gleevec prescribing information. In the Z9001 trial, patients that received Gleevec took it for one year and then stopped the Gleevec. Other trials are underway that examine longer treatment periods. The other limitation in the Z9001 trial was that the resected primary tumor had to be at least three cm in size, but there is no such limitation in the approval.

There are still some questions about which patients might benefit the most from adjuvant treatment. It's easy to speculate that patients with a high risk of recurrence and Gleevec-responsive mutational types will be more likely to benefit than patients with low-risk tumors or less Gleevec-responsive types of mutations.

Ronald DeMatteo, MD, of Memorial Sloan-Kettering Cancer Center in New York was the principal investigator of the pivotal Z9001 trial that led to adjuvant Gleevec approval for GIST in the United States.

According to Dr. DeMatteo, "We may learn more [about those types of questions] in the next year or so as we do subtype analyses."

Wilhelm shined as man and mentor

Dean Francis Wilhelm, 62, of Alexandria, Va., passed away Wednesday, Aug. 6, 2008, from complications of GIST. Mr. Wilhelm served for nearly 25 years as General Manager of Holiday Inn Capitol in Washington, D.C., the seventh largest Holiday Inn in the United States.

Born July 6, 1946 in Norwalk, where he was raised in Norwalk, he graduated from St. Paul's High School in 1964. He received a bachelor's degree from the University of Dayton and joined the hotel business, and worked in that field for nearly 40 years, beginning as a bellman and working his way up. He was recognized in 2007 as the "Best of the Best" General Manager for Holiday Inn Worldwide.

Besides his duties with Holiday Inn, he also served on the Board of Directors of the Hotel Association of Washington, D.C. for 20 years. He advocated the formation of a charter school called Hospitality High School and assisted in the formulation of the curriculum to mentor and prepare inner-city students for college and a career in the hospitality industry. Over the course of the past 10 years, Dean and his staff have mentored 20 students and provided jobs for eight. Because of his commitment to education and the hospitality field, a scholarship has been formed in his name.

Dean's leadership and commitment to the youth of D.C. was once again manifested in his unwavering support of the Bridges Marriott Foundation, a program that assists youth with disabilities with obtaining meaningful employment. In 2006 he was recognized as the Bridges Marriott Foundation's "Employer of the Year" for the hotel's support of the program.

He is survived by his brother, Roger Wilhelm, of Norwalk; and two sisters, Judith Miller, of Bellevue, and Joan Kehrer, of Lakewood, Colo.

Mr. Wilhelm leaves behind many devoted family members.

FAMILIAL

From Page 10

The most important step in determining if a family has a familial cancer syndrome is gathering an accurate family history. For a person who has had cancer, the type of cancer and age at diagnosis should be listed for each cancer. It may be necessary to obtain medical records to confirm what type of cancer a person had since family members may not always be aware of specific information. Birth defects, unusual skin findings, benign tumors, and special screening tests (such as colonoscopy to look for colon polyps) should also be noted. Many hospitals have a "familial cancer unit," which is a team of health professionals with expertise in familial cancer syndromes. Geneticists, genetic counselors, oncologists, and social workers assist individuals and families by providing risk assessment, support, screening and prevention recommendations, and genetic testing options. When a person is diagnosed with a familial cancer syndrome, relatives should be examined for signs of the syndrome. Sometimes a person identified as having a familial cancer syndrome is the first person in the family to be affected. That person is able to pass the condition on to his or her children, but the parents and siblings are not affected. Depending on the syndrome, genetics professionals can determine who in the family is at risk. There are special issues surrounding genetic testing that should be discussed; for example, what age should the test be done (important for children)? How would the results change medical management? Does insurance cover the test? Is prenatal diagnosis indicated? How will the information affect the family? Health professionals familiar with familial cancer syndromes keep up to date with advances in cancer genetics, and work with families to discuss the risks, benefits and limitations of genetic testing.

Points to remember:

• A person only needs to inherit one copy of the changed gene in order to be affected by the condition (50% chance). These outcomes occur randomly. They remain the same in every pregnancy and are the same for boys and girls.

• A changed gene cannot be corrected – it is present for life.

• A changed gene is not something that can be caught from other people. They can still be a blood donor, for example.

• People often feel guilty about a genetic condition which runs in the family. It is important to remember that it is no one's fault and no one has done anything to cause it to happen.

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If you want to learn more about Familial GIST:

• Go to www.projectflag.org for the Project FLAG research study.

• Go to www.liferaftgroup.org/library_videos.html to watch the Familial GIST webcast

• Look out in the coming month for a new LRG Familial GIST pamphlet!

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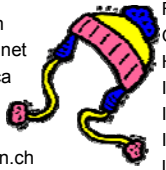

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