

Second webcast is resounding success: Fletcher reports on 'Pathway to a Cure'

Dr. Jonathan Fletcher, lead investigator for the Life Raft Group research team was the keynote lecturer at our second web cast. Titled "Pathways to a Cure," Dr. Fletcher reviewed the ten priority projects that the LRG researchers are pursuing to find a cure for GIST. Although the material presented was not for the light hearted, it was geared to help the lay person understand the mechanisms of resistance that a relatively small percentage of GIST patients immediately display in response to treatment with Gleevec (imatinib) and the patterns of resistance displayed by most GIST patients following an initially

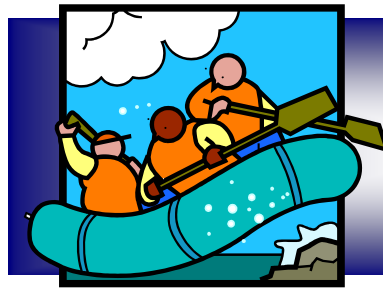


positive response to such treatment.

After a 45 minute presentation, Dr. Fletcher had

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Battling gastrointestinal stromal tumor



LIFE RAFT GROUP

August 2007

In memory of Herb Flom, Marilyn Bohan, Laura-lee Bucholtz, Dick Singleton & Wokie David

Vol. 8, No. 8

GIST Research Progress



By **Dr. Jonathan Fletcher**
Brigham & Women's Hospital

The LRG is committed to funding research programs for identification and validation of synergistic targeted therapies that counteract Gleevec-resistance in

GIST. Despite remarkable clinical responses to tyrosine kinase inhibition, we are seeing relapses of GIST, even in patients with spectacular initial response to Gleevec. We expect that most GIST patients currently benefiting from Gleevec treatment will eventually develop resis-

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Patient group reps meet in Germany

By **Norman Scherzer**
Executive Director, LRG

GIST and CML patient group representatives convened the weekend of June 29 for the fifth annual patient summit in Bad Nauheim Germany. Representing GIST organizations in Belgium, France, Germany, Israel, Italy, Norway, Poland, Romania, Switzerland, United Kingdom and the United States, over twenty delegates had the opportunity to hear plenary sessions on Strategic Alliances and meeting the challenges of coping with a chronic disease. They also attended a series of GIST medical workshops presented by three expert GIST

specialists, Drs. Peter Hohenberger, surgeon, Germany, Peter Reichardt, oncologist, Germany and Jean-Yves Blay, oncologist, France.

The three presentations, along with a combined expert panel discussion, provided an excellent review of the state of the art in GIST management, including an overview, the role of surgery, meeting the challenge of managing progressive disease and updates on clinical trials. Reviewing my notes from these lectures and importantly, from informal discussions afterwards. These are the highlights:



- A significant number of reports of disease progression turn out to be false, particularly during the first year of treatment. It was important for the clinician to listen carefully to the patient to see how they are feeling and to seek a re-evaluation of the CT Scan readings by an experienced radiologist.
- When progression does occur it is important to try to understand whether this is caused by pharmacokinetics or by genetic resistance. In the former situation the patient is not getting enough drug, sometimes because of compliance issues (the patient does not take all the drug that is prescribed). In the latter situation, the patient may be resistant to treatment

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More highlights from ASCO 2007

By Jerry Call

Science Coordinator, LRG

Wound Healing

Dr. C.P. Raut and his Dana-Farber colleagues presented a poster about wound healing and surgery during sunitinib treatment. They compared complications from wound healing after surgery in patients on sunitinib therapy versus those on imatinib therapy.

Their conclusions were:

1. In this study, there were no significant differences in wound-healing complication following cytoreductive procedures between patients with metastatic GIST on sunitinib or imatinib therapy, despite the broader spectrum of RTK inhibition by sunitinib.
2. Given the relatively small sample size (sunitinib = 26, imatinib = 46), and the retrospective nature of this analysis, further studies will be required to confirm these results.
3. The current practice is to continue sunitinib until 1-2 days prior to surgery and to resume as soon as possible after hospital discharge, which usually coincided with the patient's first postoperative visit.

For details, see abstract #10044.

Congestive Heart Failure

Dr. A. Y. Khakoo and colleagues at MD Anderson presented a poster describing the "Rare incidence of congestive heart failure in GIST and other sarcoma patients receiving imatinib therapy". They reviewed 219 patients enrolled on imatinib trials and concluded congestive heart failure was rare and only observed in one elderly patient with known prior cardiac disease. They also recommended that patients who develop potential cardiac adverse events (PCEs) while on imatinib should be treated with diuretics, ACE-inhibitors and beta-blockers with continuation of imatinib as clinically indicated.

Nilotinib Phase I

Updated results for "a phase I study of nilotinib (AMN107) alone and in combi-

nation with imatinib in patients with imatinib-resistant GIST" were presented in abstract form by Dr. Margeret Von Mehren of Fox Chase Cancer Center. In this study of heavily pretreated patients, 18 patients received nilotinib alone and 35 patients received a combination of imatinib and nilotinib (in different dose combinations).

Median progression-free survival for this phase I trial was 134 days (about 4 ½ months) overall and 178 days (about 6 months) for patients receiving nilotinib alone. Six patients experienced dose limiting hyperbilirubinemia or skin rash. See abstract 10023 for more details.



CALL

NOTE: This phase I trial is now closed. The 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.

Hypoglycemia

Dr. B. Rikhof and colleagues presented an abstract reporting on their experience with non-islet cell tumor induced hypoglycemia (NICTH) in GIST patients. They found that before treatment and/or during follow-up, four of 25 (16%) GIST patients showed increased plasma levels of a protein called 'big'-IGF-II. Three of these four patients developed NICTH. 'Big'-IGF-II is a high molecular weight form of IGF-II. According to Rikhof, "The role of IGF-II in GIST is unknown."

Similar reports of NICTH and hypoglycemia (low blood sugar) have been reported in GIST patients by Davda et al., Escobar et al., Guiteau et al., Hamburg et al. and Pink et al.

Compliance and Medical Costs

Dr. R. Halpern and colleagues presented abstract 6618 describing the relationship between compliance with

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.). This molecularly targeted therapy represents a new category of drugs known as signal transduction inhibitors and has been described by the scientific community as the medical model for the treatment of cancer. Several new drugs are now in clinical trials.

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.

Donations, payable to The Life Raft Group, 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.

FLETCHER

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time to respond to only a handful of the many questions submitted by the international web cast audience. These included explanations of immortal cell lines (they live forever), the possibility of GIST being passed on to the children of patients (called familial GIST, this is quite rare) and whether GIST patients eventually



Fletcher reading questions during July 25 webcast.

develop resistance to Gleevec (most do). Dr. Fletcher also responded to questions about how GIST patients develop resistance to Gleevec and other drugs, whether one could determine if there are still live GIST cells, the importance of preserving tumor tissue and whether surgery could prevent resistance from developing.

Dr. Fletcher also took the opportunity to describe the unique collaborative nature of his research team and their dramatic first year progress in implementing nine of the ten priority projects.

All of Dr. Fletcher's presentation and responses to questions will be available shortly on the LRG website: www.liferaftgroup.org

Note: Dr. Fletcher is only the second scientist to have been honored by the Life Raft Group, the first having been Dr. James Watson, Nobel Prize winner. Dr. Fletcher is certified in internal medicine, cytogenetics as well as oncology and holds faculty positions at Harvard Medical School, Mass General Hospital, Brigham and Women's Hospital and Dana-Farber Cancer Institute.

Funding

The biggest hurdle to continuing this vital research is that the initial funding will run out at the end of the second research year—March 31, 2008. We will need to raise approximately 1.4 million dollars a year for at least three additional

years to continue the current priority efforts plus a few more that have been identified as necessary to complete our pathway to finding a cure for GIST.

The Life Raft Group research is unique in that it is driven by a strategic plan and supported by a core group of the world's best researchers who are willing to cooperate with one another and to be held accountable for results. Research dollars are greatly leveraged by capping the administrative overhead (indirect costs) of funded institutions at 10

percent as opposed to typical charges between 50 and 65 percent. If you wish to help support this battle for survival, please make your donations to:

The Life Raft Group
GIST Research Fund
40 Galesi Drive, Suite 19
Wayne, NJ 07470.

Our Next Webcast

Join us on August 23 at 12:00 EST for "GIST" the Basics. Jerry Call and David Josephy, GIST caregivers, break down the complicated world of GIST and GIST treatment in this understandable presentation.

August 2007 clinical trial update

By Jim Hughes

LRG Science Team Member

AMN107 Phase III

Trial contact information at ClinicalTrials.gov has been updated. The Novartis central contact number is 1-800-340-6843. This number answers at a call center in Tampa, Florida. The ClinicalTrials.gov listing has also been updated to show planned sites for the phase III trial. Each site has contact information. Several sites listed as "Recruiting" are not yet open. Our list of open sites was verified with Novartis as of June 28. We are in the process of contacting each site to further verify status. Between newsletters, we will post updates to the STI571-GIST mail list.

MP470 Safety Study

Trial information is also now available at the ClinicalTrials.gov site. The contact listed there for Virginia Piper Can-

We are looking to create a more "reader-friendly" version of our clinical trial data tables. Please bear with us while we try to bring this very important information to you in a comprehensive and simple format.

cer Center in Scottsdale, AZ is Raoul Tibes, MD, 480-323-1350.

Oblimersen (Genasense) + Imatinib Phase II

This trial, which was being run by Dr. Jonathan Trent at MD Anderson in Houston, TX is now closed.

FR910228 Phase II

This trial has only one slot still open and is expected to close shortly.

Imatinib or Sunitinib Phase IIIb

The title of this trial is "Safety And Effectiveness Of Daily Dosing With Sunitinib Or Imatinib In Patients With Gastrointestinal Stromal Tumors". Patients who are failing Gleevec at 400 mg are randomized into two groups. One group is given 37.5 mg of Sutent daily. The other group is given Gleevec at 800 mg daily. Patients are followed for one year to determine progression-free survival. The study expects to enroll 200 patients. Only one site, Milan, Italy, is listed as recruiting. Pfizer is sponsoring the trial and provides a central contact point: Pfizer Oncology Clinical Trial Information Service, 1-877-369-9753, PfizerCancerTrials@emergingmed.com. Contact Pfizer for additional site information.

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Will you run for my daughter?

By Erin Kristoff, Paul Montuori & Carolina Ponce-Williams

Paul's Story

After finishing a brutal training run, Paul Montuori asked himself why any sane person would train for a marathon in Bolivia. "On a whim, I told my brother and sister-in-law that I would attempt to run a marathon with them. Little did I know at the time, how hard it would be.



Paul, Vicky and Libby the dog pause for a photo op with one of Vicky's monkeys in Bolivia.

My legs were sore and I realized that I don't even like to run." One day later Paul had a purpose and an inspiration.

Driving six hours in one day each weekend to find a good altitude did not sound logical to Paul, so he began searching for a place to spend the night. However, no one was willing to board his hyperactive running partner: his Labrador retriever.

The last place he checked was "La Senda Verde Refugio Natural". This is where he met Vicky Ossio, the owner.

Paul told Vicky why he needed to come every weekend, she then asked

him to surprising questions: Why are you running? "Even though I had contemplated this question in my mind many times on those long training runs, I still did not have an answer. I replied with a meaningless response."

Vicky then asked, "Will you run for my daughter?" Paul was speechless.

Before he knew it, Vicky, an active LRG member had run to her car and returned with several LRG bro-

chures, "She proceeded to tell me that her daughter had been recently diagnosed with a rare cancer. As tears ran down her face, Vicky told me Carolina's story of her diagnosis in January 2006 and how the charity on the brochures were like angels sent down from heaven. I tried to console her, but I felt helpless and I did not know what to do."

But Paul did know what to do, "Driving away, I felt like something in me changed. I realized that my problems were insignificant and petty compared to the problems that Carolina faced everyday. One week later I had an answer for Vicky. 'We want to run for your daughter.'"

Carolina's Story

When Carolina Ponce-Williams found out about Paul and her mother's idea she was stunned, "[My husband and I] were both shocked. I showed him the website and he got very excited!"

When she was diagnosed in January 2006, Carolina couldn't believe that her "benign tumor" was in fact, cancer. "I was in denial honestly. I think it took me about a month when it started hitting me. My mom was doing all the research for

me. I didn't realize what it was. When I came to my appointment with my oncologist and saw people doing chemo it first hit me. I was like, 'Okay, oh my god.'"

A year-and-a-half later, Carolina is feeling much better, "I feel great, I was very emotional in the beginning. When I

"I felt like something in me changed. I realized that my problems were insignificant and petty compared to the problems that Carolina faced everyday."

received that email from Paul it was perfect in coming. Before I was a little bitter about being sick. Now I can help others."

She has also found the strength she knew she had inside, "Being strong, I used to think, was to have a thick skin and to survive anything; now I understand that surviving is really accepting the obstacles, learning lessons, and then...teaching them."

Carolina is bright about her future, despite Gleevec side effects affecting her immune system, "You have to enjoy



Carolina on vacation in Aruba.

every day without having to plan for the future. One thing I always tell people is 'Stop and enjoy right now, enjoy the people you have, live in the moment.' I regret sweating the small stuff. It doesn't matter what you have, if you have a positive outlook you can

have anything. I know that my positive

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UPDATE

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tance on the single-regimen therapy.

The ambitious plans and the impressive Year One progress outlined in this report would not be possible in the absence of a closely-knit and highly-interactive GIST scientist research group. Great pains have been taken to enable collaboration without redundancy, such that the team is emphasized over the individual. This carefully coordinated approach continues to maximize the LRG research productivity. The overall objective in this research is to identify combinations of therapies that can provide synergistic benefit with Gleevec in patients with GIST. The specifics of this progress report represents the input of each LRG research team member.

A series of ten “priority” projects were highlighted for immediate funding. The Year One progress for each of these projects is summarized below. With the exception of project B, all have made outstanding progress and are expected to continue in the same fashion for Year

Two.

A. Oncogenic signaling mechanisms as novel therapeutic targets: Substantial progress has been made in identifying “downstream” proteins which play crucial roles in channeling the KIT activation stimulus into the GIST cell which are alternate therapeutic targets in GIST. The Year One research highlighted the crucial rolls of PI3-K and AKT proteins in maintaining cell growth and has begun to catalog comprehensively the cell proteins that bind to the KIT/PDGFRα oncoproteins in GIST.

B. KIT/PDGFRα Wildtype GISTs: These studies have been hampered by the availability of frozen GIST specimens that lack KIT and PDGFRα mutations. The LRG board of directors and research team discussed strategies for obtaining additional frozen GIST specimens that lack KIT and PDGFRα mutations for Year Two. *This project is suspended until suitable samples can be obtained.*

C. Primary Resistance: Progress has been made in establishing laboratory models for GIST mutations that show primary resistance to Gleevec, and potent alternative KIT kinase inhibitors of such mutants. Future studies will con-

tinue to focus on identifying and validating novel KIT kinase inhibitors that are effective against primary KIT/PDGFRα Gleevec-resistant mutations.

D. Stable disease after imatinib: Stable disease, i.e. GIST cells that are suppressed but not killed by Gleevec, remains a major problem for most patients. Year 1 studies show that clinically stable GIST – in patients receiving Gleevec or Sutent – can contain abundant KIT secondary mutations, which are the starting point for progression to eventual outright Gleevec resistance. Future studies of stable GIST will address KIT/PDGFRα mutational heterogeneity, evaluate new therapies that more effectively induce apoptosis (cell death), and identify new therapeutic targets by gene expression profiling and proteomic methods.

E. Secondary resistance mechanisms & clinical evaluation: Great progress has been made in the past year by developing new human GIST and non-GIST cell lines and mouse xenografts of human GISTs that contain various KIT and PDGFRα kinase domain Gleevec and Sutent resistance mutations. These diverse GIST “models” have enabled identification and preclinical validation of novel small molecule kinase inhibitors with expanded efficacy against the Gleevec-resistant KIT and PDGFRα mutations.

F. Kit Degradation: The Year 1 studies have validated the concept that HSP90 and similar proteins are required to protect KIT in GIST cells. HSP90 can be inhibited by various drugs, resulting in substantial destruction of the KIT oncoproteins in all GIST cell lines tested to date, cessation of growth, and induction of death, in the GIST cells. Future studies will focus on identifying HSP90 inhibitors with greater potency and selectivity for KIT/PDGFRα in GIST.

G. Murine Models: The proposed studies are well underway, with Dr. Besmer’s group having shown that the PI3-K pathway is crucial to KIT oncogenic signaling in the murine GISTs, and that therapeutic inhibition of mTOR can reduce the growth of these GISTs. Continuing studies from Drs. Besmer

Why Not Do Some Good With Your Search?

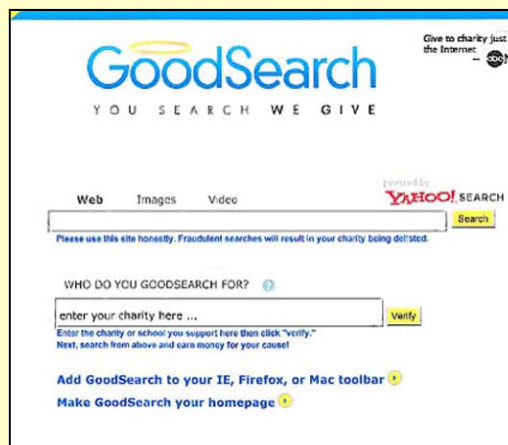
GoodSearch is a search engine powered by Yahoo! It was designed to help raise money for non-profits. Each search you do donates a penny or more to the non-profit of your choice. Enough people using this search engine can make a big difference.

Using GoodSearch for the first time is very simple:

- Go to www.goodsearch.com
- Underneath “Who Do You GoodSearch For?” type in “Life Raft Group” and click verify. You are now ready.

There are many ways to spread the word. You can send an email to your friends and family or add a toolbar to your web browser. You

can also make it your homepage. You can find these and many other ideas by clicking on “Spreading the Word” at the bottom of www.goodsearch.com. Thank you to member, Debbie Chang for this information.



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TRIALS

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Strategy Table (The color of trial row indicates the trial's treatment strategy)

The information below does not include location information. Please visit our website at www.liferaftgroup.org/treat_trials.html for more in-depth coverage of each trial.

Strategy	Description
A	Inhibit KIT (PDGFRA signaling)
B	Impede tumor vascularization (Antiangiogenesis) (PDGFRb, VEGF, VEGFR)
C	Destroy KIT (HSP90)
D	Inhibit the production of KIT
E	Target KIT downstream signaling (i.e. AKT, mTOR, BCL-2, SRC, RAF-1, etc.)
F	Destroy KIT plus Inhibit the cell cycle plus Induce apoptosis (HDAC)
G	Multiple Targets
H	Kill GIST cells

Therapy	Description	Trial #	Phase	For
AMN-107 (nilotinib, Tasigna)	Efficacy and safety of AMN107 compared to current treatment options in patients with GIST who have failed both imatinib and sunitinib	NCT00471328	III	GIST
Imatinib (Gleevec) or Sunitinib (Sutent)	Safety And effectiveness of daily dosing with sunitinib or imatinib in patients with GIST	NCT00372567	III	GIST
Perifosine + Imatinib	Phase II Study of Perifosine plus imatinib mesylate for patients with resistant GIST	MDACC 2004-0968, NCT00455559	II	GIST
Sorafenib (Bay 43-9006, Nexavar)	Sorafenib in treating patients with malignant GIST that progressed during or after previous treatment with imatinib and sunitinib	NCT00265798	II	GIST
FR901228 (romidepsin)	FR901228 in treating patients with metastatic or unresectable soft-tissue sarcoma	NCT00112463	II	GIST/Sarcoma/Ewings
IPI-504	Safety study of IPI-504 for GIST	NCT00276302	I	GIST
Oblimersen (Genasense) + Imatinib (Gleevec)	Oblimersen and imatinib in treating patients with advanced GIST that cannot be removed by surgery <i>(As we go to press we are advised that this trial has closed)</i>	NCT00091078	I	GIST
MP470	MP470 in treating patients with unresectable or metastatic solid tumor or lymphoma	NCT00504205	I	GIST
Perifosine + Sunitinib (Sutent)	Perifosine + sunitinib for patients with advanced cancers	NCT00399152	I	GIST/RCC
Doxorubicin + Flavopiridol	Doxorubicin and flavopiridol in treating patients with metastatic or recurrent sarcoma that are unresectable	NCT00098579	I	GIST/Sarcoma
OSI-930	Dose escalation study of daily oral OSI-930 in patients with advanced solid tumors - Sarcoma	EmergingMed	I	Advanced Solid Tumors - Sarcoma
LBH589	A Phase IA, two-arm, multi-center, dose escalating study of LBH589 administered through IV on two dose schedules in patients with advanced solid tumors & non-Hodgkin's lymphoma.	Nevada Cancer Institute	I	Advanced Solid Tumors
CNF2024	Study of Oral CNF2024 in advanced solid tumors or lymphomas	NCT00345189	I	Tumors/Lymphoma
KOS1022	Phase 1 study of oral KOS-1022 in patients with advanced solid tumors	Univ of Colo COMIRB 05-0627	I	Advanced Solid Tumors
XL820	Study of XL820 given orally daily to subjects with solid tumors	NCT00350831	I	Cancer/Solid Tumor

GERMANY

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Patient group representatives gather for a picture in Bad Nauheim, Germany at the Patient Summit Meeting

(for Gleevec, this includes most patients with a mutation higher than exon 11) or may require higher doses (for Gleevec, patients with an exon 9 mutation).

- Two best practice recommendations would be for the clinician to ask each patient in a non threatening way if they have taken all their medication and for routine plasma testing to become a standard adjunct to treatment. (Note: The Life Raft Group has asked Novartis to follow-up on the subset of patients in the early Gleevec clinical trials who were given routine plasma testing over several days to retest them to determine whether there have been any changes in their plasma levels-i.e., in the level of Gleevec in their body).
- Some drugs may not make it to the marketplace even though they show efficacy for some GIST mutations. An example may be the Novartis drug PKC412 which seems to work for exon 18 mutations in PDGFRA. The irony is that Gleevec does not seem to work for such exon 18 mutations.

Several new clinical trials were noted:

- An EORTC randomized trial com-

paring Gleevec to Gleevec plus surgery at the point of best response within one year

- A new trial for 600mg of Gleevec plus RAD001
- A single agent trial for 800mg of Nilotanib (AMN107)

The high point of the meeting may well have been the adoption of the Bad Nauheim Declaration by the assembled GIST community to promote access to state-of-the-art treatment for all GIST patients wherever they may live.

The Bad Nauheim Declaration

Background Statement

1. Gastrointestinal stromal tumour (GIST) is a rare cancer of the mesenchymal (connective) tissues of the stomach, gastrointestinal tract and related organs. The incidence of this cancer is approximately 12 -15 per million of population, and it is regarded as a rare disease. It accounts for less than one half of one percent of all cancers diagnosed.
2. In the early years of the twenty first century the treatment of GIST was revolutionized by the introduction of tyrosine kinase inhibitors. Prior to

their introduction a patient diagnosed with advanced GIST had a life expectancy of less than two years. With tyrosine kinase inhibitors (e.g. imatinib for first-line therapy) the prognosis of patients has improved significantly. Over 85 percent of patients respond to these drugs and benefit for many years.

Purpose

1. The worldwide advocacy groups supporting patients with GIST are all concerned about the differences that exist in the way in which patients are treated, and the ways in which health-care systems often delay access to new treatments.
2. We believe that all patients should be treated equally regardless of race, nationality, faith, age, sex or economic status.
3. This document is a consensus declaration from the GIST patient advocacy groups assembled at Bad Nauheim, Germany on Sunday 1 July 2007. It identifies a set of basic standards which we call on doctors, other health care practitioners, hospital administrators and health care funders to adopt and to build upon for the benefit of the

Katharine Kimball faces GIST one surgery at a time

By Katharine Kimball

My journey with GIST is a long haul that has taken me from Brisbane, Melbourne and Canberra, Australia to San Antonio, Texas. It is a journey that began in October 2002 when I found a rather large mass in my abdomen and was concerned enough that I phoned my GP for an appointment. When she felt the mass, she immediately made an appointment for a CT scan. I had the scan done within an hour and then returned to my GP's office. After consulting with her partner, she informed me that they thought I had a lymphoma. She wanted me to go to Urgent Care at Princess Alexandra Hospital (PAH) "to get into the system."

The following week I met with a surgeon at PAH who thought I either had a lymphoma or a sarcoma. A week later I had surgery to remove an 8.5cm GIST tumor from my small intestine. I was in hospital for one week. My discharge papers read "unfavorable prognosis". I didn't know what that meant. So when I arrived home, I got on the Internet and googled gastrointestinal stromal tumor. That is how I found the Life Raft Group. I joined and sent an email asking for

information and soon felt I belonged to a special family. That was in December 2002.

Not long after my diagnosis, my husband, Ian left. It was at this time that an opportunity arose for me to accept a three-month teaching position in Shanghai, China. I left for China in October 2003. This was a perfect opportunity for me, as I would return just in time for my next scans. After scans in January, I went to Nanjing, where I had been offered another job and shortly thereafter, Beijing. I spent a wonderful year in

China teaching mathematics and was able to forget about GIST until my return to Australia in October 2004. My scan that month revealed I had a recurrence and was once again scheduled to have surgery at PAH in November.

By the time I had my next scans at the end of January, I had two new tumors. This time it was recommended that I begin Glivec. However, in Australia this is not just a matter of having your oncologist write a prescription. The prescription had to be approved by Medicare at their office in Tasmania.

costs across all patients were lower and less variable with good compliance (\$22,882 ± 22,791) than with medium (\$40,366 ± 68,186), $p=0.007$ and poor (\$104,961 ± 190,559), $p<0.001$). Mean medical costs for GIST patients were: good=\$28,318 (±24,781); medium=\$33,270 (±35,356, $p=0.584$); and poor=\$62,235 (±68,751, $p<0.001$). The authors concluded "Good imatinib compliance was associated with significantly lower medical costs. Mean total medical costs were 78 percent lower with good compliance relative to poor. Compliance is an important treatment issue for both clinical and medical cost outcomes."

Sutent Resistance

Dr. Michael Heinrich gave an oral presentation "Mechanisms of sunitinib malate (Sutent) resistance in (GISTs)."



Kimball pictured with her sons, Matt (left) and Ray (right) during Matt's enlistment into the Air Force.

In the meantime I moved to Australia's capital, Canberra, to stay with my father as I wanted to visit with him before returning to the U.S. where my children (2 boys and 3 girls) were anxious for me to return. I also had to make the decision as to whether to have surgery in Australia or in the U.S. After some consideration and consulting with my third surgeon, I decided to have surgery in Canberra. It went well; five tumors were removed along with part of my bladder. A few

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imatinib and medical costs for patients with CML and GIST. They reviewed past claims data from a large national US health plan. Compliance was measured with a medication possession ratio ((days of imatinib during follow-up / days of follow-up)*100). The compliance categories were; good compliance was equal to or better than 90 percent; medium compliance was between 70 and 89.9 percent and poor compliance was less than 70 percent. Only 35 percent of GIST patients had "good compliance". The compliance was rated as poor in 46 percent of GIST patients and in 40 percent of CML patients. Mean medical

In this study of two GIST patients (one with an exon 11 primary mutation and one with an exon 9 primary), a total of 11 lesions (tumors) were analyzed; nine of the eleven were progressing lesions. As Dr. Heinrich and colleagues have previously reported, resistance to sunitinib was highly correlated with secondary mutations. Lesions with secondary mutations in the drug binding pocket (exons 13 and 14) become insensitive to imatinib but retain their sensitivity to sunitinib. Lesions that developed secondary mutations in the KIT activation loop (exons 17 at codons 816, 820, 822 and 823) and in the extended activation loop (exon 18) were resistant to both imatinib and sunitinib.

A novel mutation was discovered in

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INTERNATIONAL TRIALS

Therapy	Description	Trial #	Phase	For
AMN107 (nilotinib, Tasigna)	Efficacy and safety of AMN107 compared with current treatment options in patients with GIST who have failed both imatinib and sunitinib	NCT00471328	III	Gastrointestinal Stromal Tumors
PKT787 (vatalanib)	For treatment of metastatic GISTs resistant to imatinib	NCT00117299	II	GIST
AZD2171	The Biological Activity of AZD2171 in GIST	NCT00385203	II	GIST
AB1010 (masitinib)	Evaluation of the efficacy and the tolerance of AB1010 in first line treatment for inoperable, locally advanced or metastatic GIST.	Masitinib	II	GIST
LBH589	LBH589 in adult patients with advanced solid tumors or cutaneous T-Cell Lymphoma	NCT00412997	I	Advanced Solid Tumors
BMS-354825 (dasatinib, Sprycel)	A Phase I Study of BMS-354825 in patients with solid tumors	NCT00339144	I	Tumors

Be sure to check out our Clinical Trials Map

The LRG Clinical Trials map allows patients to clearly identify trials of interest based on location and what they offer. Here is how the map works:



Sites with one GIST trial.



Allow GIST patients and those with other tumor types.



Multiple trials ongoing

You can find the map, along with all of our information on clinical trials at http://www.liferaftgroup.org/treat_trials.html.



UPDATE

From Page 1

and Rubin will produce mice with Gleevec-resistant inherited mutations, which will be very useful in screening for novel therapies against Gleevec-resistant GIST.

H. Resource Development (imatinib sensitive & resistant): Exceptional progress has been made in developing new immortal cell lines. Future efforts will be devoted to expanding the panel of immortal cell lines available for drug testing.

I. Tissue Banks: Excellent progress has been made in establishing a central repository for frozen and paraffin-embedded GISTs to enable the collective research efforts in the LRG program. Future efforts will focus on genomic and gene expression annotations for the banked specimens, and histopa-

thologic annotation to assure that GISTs from patients already treated with Gleevec include both clinically stable and progressing specimens.

Pediatric GIST: Dr. Antonescu has identified several genes that are uniquely active in pediatric GISTs, rather than adult GISTs. Future studies will determine whether these genes can be targeted successfully with drugs, producing therapeutic advances for pediatric GIST. This work is particularly crucial because pediatric GIST patients do not respond as well as adult GIST patients to Gleevec.

Gleevec resistance studies are essential to therapeutic progress in GIST. We hope to substantially expand select studies in the following two years. These studies will likely reveal that combinations of GIST therapies are needed to consolidate initial remissions, forestall the emergence of clinical resistance, and enable increased cure rates.

ASCO 2007

From Page 8

exon 16 (L783V) of one progressing lesion. sunitinib was able to achieve 50 percent inhibition of the in-vitro signaling of this type mutation at a fairly low concentration, however; it was unable to achieve 90 percent inhibition (IC90), even at high doses. The exon 16 mutation was clinically resistant to sunitinib, but the biochemical data for this was less clear according to Dr. Heinrich.

In his conclusions, Dr. Heinrich noted that sunitinib activity in imatinib-resistant GIST is affected by the type of secondary KIT mutation as shown by in-vitro and clinical data. Dr. Heinrich also hypothesized that the anti-angiogenic effects of sunitinib may be insufficient to inhibit GIST progression when the targeted oncogenic kinase (KIT) remains active.

MARATHON

From Page 4

attitude will hopefully one day cure me. I want to have kids and have grandchildren. I want to be here for all of that. I want it all.”

Carolina is from La Paz, Bolivia and currently lives in Plano, Texas with her husband, Terrance. She is a fourth grade teacher and is looking forward to telling her grandkids how she once had to take a medicine called Gleevec.



Mother and daughter share a moment with the camera at Carolina's wedding in 2004.

The Marathon

Paul has set up a web page so that he and his family can use

the marathon (which will be held in Long Beach, Calif. on October 14, 2007) to raise money for the LRG. Please go to

<http://3montys4cure.pledgepage.org/> to view the page. Paul, his brother Chad and sister-in-law Kira have set a goal of \$10,000 to be raised. “Even though it is high it is important to shoot high and think big and actually make a difference. If we give \$10,000 it can actually make a difference in something. The key is encouraging people to donate because we are not going to be able to do it alone, we have to extend



and encourage other people. I think that we will make the dent. Money talks. Money drives everything.”

You can visit the Long Beach Marathon's page at <http://www.runlongbeach.com/site5.aspx>

If you are interested in donating to the LRG in the name of Paul's cause please visit http://www.liferaftgroup.org/about_support.php or send a check to

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

The LRG would like to wish good luck to Paul and his family.

GERMANY

From Page 7

patients they serve.

4. The global GIST patient advocacy groups will monitor the implementation of this declaration and publicize the healthcare systems demonstrating adherence to it.

The Declaration

The GIST patient advocacy groups collectively call on all those responsible for the treatment and care of patients with GIST to:

1. Ensure that patients are diagnosed promptly and accurately.
2. Provide the information and resources which allow patients access to specialist second opinions.
3. Provide treatment and care to GIST patients through the hands of specialist multidisciplinary teams which conform to standards for a center of expertise in rare diseases. All members of these teams should have specialist

knowledge, continuing experience of treating GIST, and participate in national and/or international networking with other centers of expertise.

4. Provide access to expert pathology and mutation analysis services which give doctors and patients the information they need to make an informed clinical decision.
5. Provide accurate and timely information relevant to the patient at each step along the treatment pathway.
6. Provide access to psychological support and treatment.
7. Adopt an internationally accepted treatment guideline (see 8.) and ensure that the resources required to deliver it are available to doctors and patients.
8. Treat patients in line with an internationally accepted treatment guideline informed by the published evidence from scientific and clinical re-



From left: Roger Wilson, Marina Symcox, Anna Costato and Markus Wartenberg

search.

9. Maintain and review funding for treatment so that no patient suffers through failure to treat, or through stopping treatment recommended by specialist doctors.

10. Provide patients with access to clinical trials regardless of race, nationality, faith, age, sex or economic status.

AMN107 Update

The following information was sent to us from Novartis.

Novartis Oncology was expecting approval of Tasigna (AMN107) in the third quarter of 2007.

However, The company was recently notified by the US Food and Drug Administration (FDA) that it has extended the review of Tasigna by three months to complete its evaluation of recent amendments made by Novartis to the NDA.

These amendments allow the agency to review additional longer-term median follow-up of CML patients with nearly a year of Tasigna treatment.

The agency has not required any new studies, but only additional time to complete its review of the amended NDA.

GIST 101: Metastases

What are metastases?

GISTs start as a single tumor somewhere in the GI tract.



Like most other cancers, GISTs can shed cancer cells. This process is called metastasis and the new lesions are called metastases (The original tumor is called the "primary").



They usually metastasize to sites near the primary tumor. Although they may be in a different spot than the primary tumor, they are still GIST.



KIMBALL

From Page 8

days later I was well on the road to recovery. However, by noon I was very nauseated and I began vomiting bile. As luck would have it, my surgeon was away in Sydney all weekend but he was being advised of my situation and giving instructions for my care. I had an NG tube inserted (very uncomfortable) and while it helped with the vomiting, it did not completely stop it.

When my surgeon returned, he immediately came to see me to discuss my situation. He told me I was probably going to have another surgery to repair the leak in my intestine which a CT had confirmed. I didn't want to have another surgery so soon and prayed that it wouldn't be necessary; however, exactly one week after my initial surgery, I was scheduled for another. It turned out to be a blessing after all, as another tumor was found. It was small and may have been missed the week before as tumors often

hide in the folds of the small intestine. By the time I left hospital the next week, I had lost a total of 15 pounds and felt very weak. A couple of weeks later, I resumed taking 400mg Glivec.

In July 2005, I returned to San Antonio, Texas where I had lived many years earlier. I became a patient at Wilford Hall Medical Center (WHMC) on Lackland Air Force Base. I continued to have clear scans until February 2006 when another 4.8 cm tumor was found on my small intestine. I had another surgery

"I didn't want to have another surgery so soon and prayed that it wouldn't be necessary"

and was put on Gleevec at 600 mg. I found the side-effects much more severe at that dose. Two months later, another tumor was found, though this one was small. Another surgery so soon after the last one was no longer an option, so I began taking 50 mg of Sutent but dropped to a four-weeks-on, two-weeks-

off schedule at 37.6 mg because of my neutrophil count.

In October 2006, I received approval to be seen by Dr. Jonathan Trent at M.D. Anderson Cancer Center (MDA) in Houston, Texas. I continued to see my local oncologist but went to MDA every 3 months for scans. I remained stable on Sutent for exactly one year. At my appointment in May of this year, Dr. Trent informed me that my tumor was growing. The recommendation was surgery. My sixth GIST surgery was scheduled at

Brooke Army Medical Center on June 21. It was successful and I was home within a few days. I have resumed 37.5 mg Sutent in the hopes that new tumors will be prevented from forming.

In many respects I am lucky. I now have a wonderful new man in my life, Phillip who has been very supportive. I have great children who care and worry about me. Moreover, I feel very blessed; while many dread surgery, I feel very fortunate that it is still an option for me at this time.

THE LIFE RAFT GROUP

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