Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

February 2008 In memory of Andrea Fuller & Ralph Mattison Vol. 9, No. 2

NIH Pediatric GIST clinic is planned for spring 2008.

By Norman Scherzer
LRG Executive Director


HELMAN

The National Institutes of Health (NIH) in Bethesda, Maryland, is planning to host a pediatric GIST clinic in late spring, 2008.

While it is still in the early stages, we are thrilled to announce this plan of action. The intent is to begin with two clinics per year and later to evaluate whether that number will be sufficient. Each clinic will be able to accommodate approximately 15 patients. In order to ensure quality, patients may be asked to come the day before the clinic for any necessary diagnostic tests. Staff might also be asked to come the day before the first clinic to coordinate patient management and care and to remain for a few hours after the clinic to discuss what has been learned. The lead for the NIH will be Dr. Lee Helman, Scientific Director for Clinical Research of the Center for

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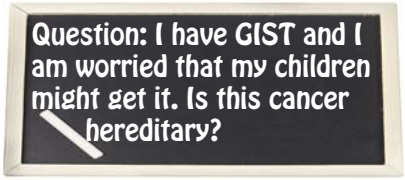
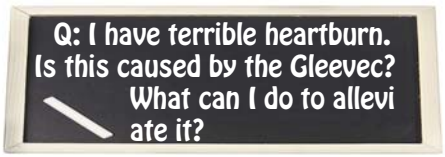
The doctor is in: common patient questions answered

By Dr. Jonathan Trent
MD Anderson Cancer Center

This is part one of a two-part series answering commonly asked questions by GIST patients. We will publish the second part in the next newsletter.



Answer: Hereditary GIST is extremely rare so it is highly unlikely that your children will inherit this cancer. However, if you have several family members that have had GIST, gastrointestinal leiomyosarcoma, or stomach cancer you should notify your physician. If you would like to know more about the inheritance of GIST there are several publications on the topic (*Kleinbaum et al, International Journal of Cancer 2008 Feb 1;122 (3):711-8*).



A: It is not a common side-effect of Gleevec but has been described. It may also be a side-effect of surgical resection. Either way I

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'Hide & go seek': Sarcoma UK director questions politicians

By Roger Wilson
Director, Sarcoma UK

This editorial is part two of a series chronicling vital issues facing GIST patients in the United Kingdom.

Readers of the October 2007 edition of the LRG Newsletter will recall that I wrote about some of the issues we are facing in the United Kingdom with access to new drugs. You may not regard imatinib (Glivec to all of us outside North America) as a new drug by now,

but be assured it comes into that category for us.

Our new Prime Minister Gordon Brown announced the Cancer Reform Strategy on December 3, 2007. This is a review of the Cancer Plan, which dates from 2000, and incorporates a range of new initiatives which would not have been feasible when that Plan was launched. The leadership shown by the United States on survivorship work is acknowledged and will become a big part of the way the UK's National Health Service adapts to the reality of

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Suboptimal response in CML linked to Gleevec uptake into leukemia cells

By Jerry Call
LRG Science Coordinator

Australian researchers have confirmed the protein involved in Gleevec's transport into chronic myelogenous leukemia (CML) cells and have shown that it is the activity of this protein which is a key determinant of response in CML patients.


CALL

Dr. Timothy Hughes, Department of Hematology, Royal Adelaide Hospital, Adelaide, Australia, and his colleagues have recently reported in the journal, *Blood*, that "Most CML patients who have a suboptimal response to imatinib have low OCT-1 activity: higher doses of imatinib may overcome the negative impact of low OCT-1 activity". Debra L. White, a PhD student in Dr. Hughes lab, was the lead author of this paper.

The CML and GIST worlds are closely linked. Gleevec was originally developed for CML and GIST formed the second major indication for Gleevec. New findings in one often have important implications for the other. While the consensus of GIST experts is that 400 mg should be the starting dose for most GIST patients (with the exception of exon 9 patients), The Life Raft Group will present the results of an internal study of LRG patients in the LRG Newsletter next month.

Proteins that move drugs out of cells have been suspected to be a cause of resistance to cancer therapy for many years. "Multi-drug resistance" or MDR is the term used to describe the process where cancer cells are able to "pump" drugs out of the cell before the drug concentration is high enough to kill the cell. The ability of some cancer cells to increase the number/activity of these drug pumps can lead to resistance across a spectrum of drugs, hence the term "multi-drug resistance." Normal genetic variations can also cause some people to have more or less effective "pump" transport.

Understanding of multi-drug resistance proteins has largely been limited to their role in pumping drugs out of tumor cells (drug efflux). Recently, several groups have demonstrated that drug transport into the cell (drug influx) might also be an important factor in multi-drug resistance, especially in patients treated with Gleevec.

In 2004, Julia Thomas and her colleagues at the University of Liverpool in the United Kingdom, were the first to describe the role of OCT-1 (sometimes written as hOCT-1) in transporting Gleevec into cells. They speculated on the clinical implications of their findings. "The net effect of these transport processes may be a decrease in the intracellular concentration of imatinib (Gleevec)." The consequences are that cells might become resistant to Gleevec.

Lucy Crossman, Brian Druker, and Michael Deininger extended the laboratory work of the Liverpool team to CML patients. In a letter to the editor of *Blood*, they gave a short report on their experience with a small group of CML patients. They divided the patients into responders (achieved a complete cytogenetic response to Gleevec within the first year) and nonresponders (remained at least 65% Philadelphia-chromosome positive during the first ten months of Gleevec).

The Crossman team found that baseline expression of hOCT1 (the influx pump) was variable and not significantly different from healthy bone marrow donors. Interestingly however, the pre-Gleevec expression level of hOCT1 in non-responders was one-eighth that was seen in responders (P=.005). Once on Gleevec, six of the non-responders had a further twofold decrease in the expression of hOCT1 compared to baseline. The implications were that in the non-responders, not as much Gleevec was being pumped into the tumor cells.

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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.

February 2008 international clinical trial update

By Jim Hughes
LRG Science Team Member

Though we will feature only international trials in our clinical trials table this month, we thought it important to include some important United States changes that have occurred in the past month. Please remember that while these changes are listed in this text, they are not reflected in the table below, which includes only *international trials.*

International

AZD2171 Phase II: The AZD2171 Phase II Trial in the UK is now listed as "Not recruiting".

Dasatinib Phase II: This new trial for GIST is now open at Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland, CH-1011. Dasatinib (BMS-354825) is approved for leukemia (CML). Dasatinib is a c-KIT inhibitor and has been used in Phase I trials in GIST. At the 2006 Connective Tissue Oncology Society (CTOS) meeting, the international trial team presented a poster showing that four of 18 refractory GIST patients were on the drug for three months or more. The unique aspect of this trial is that dasatinib will be offered to patients who have been diagnosed with GIST but who have not received any tyrosine kinase inhibitor. In other words, this will be a first line trial. Patients receive dasatinib twice daily for two years. This is listed as a multi-center study. But only Lausanne is open so far.

United States and Canada

AMN107 Phase III: Novartis has informed us that Saint Vincent's Hospital in New York City is now open. Principal Investigator is Gerald Rosen, MD. Contact is Larry Giove at 212-367-1729, lgiove@aptiumoncology.com.

Imatinib and Sunitinib Phase I: This Phase I trial combining two approved drugs for GIST has just opened at Vanderbilt-Ingram Cancer Center in Nashville, TN. Contact is the Clinical Trials Office - Vanderbilt-Ingram Cancer Center at 800-811-8480. Principal investigators at Vanderbilt are Jordan D. Berlin, MD and Emily Chan, MD.

STA-9090 Phase I: Manufacturer Synta announced a second STA-9090 Phase I trial on January 17. Patients will be dosed intravenously once a week versus twice in the other phase I trial announced in November. Sites were not mentioned. We recommend contacting the first phase I site at Dana-Farber in Boston, MA via Travis Quigley, RN, 617-632-5117. Geoffrey Shapiro, MD, 617-632-4942, geoffrey_shapiro@dfci.harvard.edu is the principal investigator for the earlier trial.

IPI-504 Phase I: This is now available at Mount Sinai Hospital in Toronto, Ontario, Canada. Contact is Edith Bardi, (416) 586-4800, extension 4795, ebardi@mtsinai.on.ca. Principal investigator is Martin Blackstein, MD.

AMN107 (nilotinib, Tasigna®)

Efficacy and safety of AMN107 compared to current treatment options in GIST patients who failed imatinib and sunitinib

Phase: III
Conditions: GIST
Strategy: Inhibit KIT
NCT#: NCT00471328
Contact: Novartis gives a central contact #
Telephone: 862-778-8300
Sites: We have reports of as many as 32 international sites being open and 10 pending. We were unable to confirm this at the time of this publication. Use the central contact number for the latest information. Study ID CAMN107A2201

Imatinib (Glivec) or Sunitinib (Sutent)

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

Phase: III
Conditions: GIST
Strategy: Inhibit KIT and/or impede tumor vascularization
NCT#: NCT00372567
Telephone: 1-877-369-9753
Sites: Milano, Italy, 20133

Radiation Therapy as Palliative Treatment of GIST (GIST RT)

Phase: I/1l
Conditions: GIST
Strategy: Kill GIST cells (Radiation)
NCT#: NCT00515931
Telephone: 947173208 Ext. 358
Sites: Helsinki Univ. Central Hospital Helsinki, Finland

AZD2171

The biological activity of AZD2171 in GIST

Phase: II
Conditions: GIST, Sarcoma
Strategy: Multiple targets
NCT#: NCT00385203
Sites: No longer recruiting

Dasatinib (BMS-354825)

Dasatinib as first-line therapy in treating GIST patients

Phase: II
Conditions: GIST
Strategy: Inhibit KIT
NCT#: NCT00568750
Telephone: 41-21-314-0150
Sites: Hospitalier Universitaire Vaudois, Lausanne, SwitzerlandCH-1011 Michael Montemurro, MD

Imatinib + RAD001 (everolimus)

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

Phase: II
Conditions: GIST
Strategy: Inhibit target KIT downstream signaling (mToR)
NCT#: NCT00510354
Telephone: 41 6 1324 1111
Sites: Clinicaltrials.gov lists 9 sites as open in Germany. We could not independently verify this at the time this newsletter was published. Please use the Novartis number above for specific site information or visit the German Novartis site (www.novartis.de).

Glivec + Interleukin 2 (IL2)

Phase I trial in solid tumor and GIST resistant to imatinib and/or sunitinib (IMAIL-2)

Phase: I
Conditions: Solid tumors and GIST
Strategy: Kill GIST cells (Immunotherapy)
Contact: Dr. Nathalie Chaput nathalie.chaput@igr.fr
Telephone: +33(0)1 42 11 50 05
Sites: Institute Gustave Roussy Villejuif, France

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Q&A

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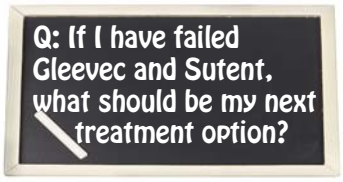
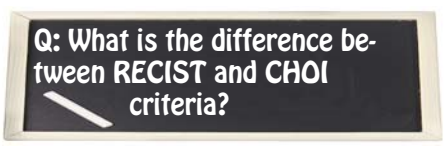
favor the initial use of calcium-containing antacids that are available over the counter. These may help with heartburn but also provide a good source of calcium and may help with muscle cramps that patients get while on Gleevec. If this does not relieve heartburn one should consult their physician for diagnostic evaluation.



A: When I see patients with GIST who have failed Gleevec and Sutent I start over at the beginning. Our sarcoma pathologists review the tumor specimen to make sure it is truly a GIST. Sometimes patients may have other types of sarcoma such as leiomyosarcoma, desmoid tumor, or schwannoma rather than GIST. These types of sarcoma are treated very differently than GIST so the diagnosis is important. A number of investigators are trying to improve upon diagnostic accuracy of GIST (*for an example see Price ND, Trent JC, El-Naggar AK, Cogdell D, Taylor E, Hunt KK, Pollock RE, Hood L, Shmulevich I, Zhang W. Highly accurate two-gene classifier for differentiating Gastrointestinal Stromal Tumors and Leiomyosarcomas. PNAS 2007 104: 3414-3419*).

TRENT



A: RECIST uses tumor size to quantitatively define shrinkage or growth of a tumor. Choi Criteria uses tumor size (similar to RECIST) but also includes changes in the internal characteristics of a GIST, namely intravenous contrast uptake. These are used in clinical trials to define complete response, partial response, stable disease, and progression of disease.

GIST care perspectives from a 'student' of GIST

By John C. McAuliffe, PhD
MD Anderson Cancer Center

John is a MD/PHD student at the University of Texas Medical School at Houston, Texas working as a Post Doctoral Fellow in the department of sarcoma medical oncology in the sarcoma research center at the University of Texas, MD Anderson. He returns to medical school for his fourth year this summer. After graduation, he will become a surgical resident with the ultimate goal of being a surgical oncology clinical-investigator.

Each particular patient is unique. Likewise, each patient has a unique GIST that responds to targeted therapy (such as Gleevec or Sutent, among others) for a variable duration. Likewise, some patients that undergo surgery for their primary GIST become "No Evidence of Disease" (NED) while others relapse quickly. In Sarcoma Medical Oncology and the Sarcoma Research Center at the University of Texas, MD Anderson Cancer Center, we are implementing molecular studies to better determine the best possible treatment for an individual GIST patient.

For instance, when we see a new patient with GIST who requires therapy with imatinib we routinely perform *kit* mutation testing. The patient is provided educational materials and personalized discussion about GIST and Gleevec. The patient then begins therapy with Gleevec at a dose of 400mg daily for one month after which time they return for a follow-up visit. At this follow-up visit the patient and physician discuss the side-effects of imatinib and how to manage them for the best quality of life. Additionally, the results of mutation testing are discussed with the patient. If the patient is tolerating Gleevec and the patient has a GIST with *kit* exon 9 mutation the dose of Gleevec is escalated to 800 mg daily or the highest dose that the patient can tolerate well. Patients whose tumor has the exon 11 or other mutation continue at 400 mg of Gleevec daily. This approach is supported by publications showing that the 800mg daily dose is better for patients whose GIST has *kit* exon 9 mutation and that dose escalation is better tolerated after an increase from 400 mg rather than starting at 800mg as the first dose.

MCAULIFFE

Another factor that appears to be important in predicting long-term survival on Gleevec is a protein called vascular endothelial growth factor (VEGF). This protein helps tumor blood vessel formation. Some kinase inhibitors block the activity of the VEGF-receptor and KIT while others do not block the activity of VEGF receptor.

We recently published an article in *Clinical Cancer Research* (November 15 issue) demonstrating that patients with GIST whose tumors make VEGF (17% of all GIST patients) had a shorter survival than patients whose GIST did not express this protein when treated with Gleevec. Perhaps this small subset of GIST patients whose tumor produces VEGF should be treated with Gleevec plus a VEGF receptor inhibitor or with a multi-targeted kinase that inhibits both *kit* and VEGF receptor. We continue to strive for a better understanding of the molecular characteristics of GIST in order to better care for each unique patient with the ultimate goal of curing this disease.

LAF Presidential Cancer Forum represents you

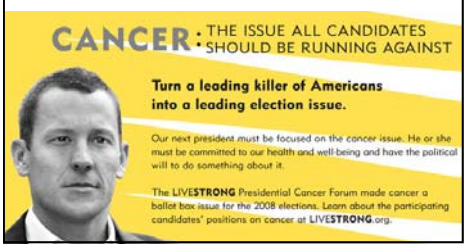
If you live in the United States you know that it is hard to go a day without hearing something about the 2008 Presidential Election. Platforms are being disputed, issues are being dissected, candidates are being challenged. Everyone seems to have an opinion about who can best run this country.

The Life Raft Group does not wish to endorse and offer an opinion of the candidates. However, it is important for cancer patients and caregivers to remember the issues that affect them during this campaign.

The Lance Armstrong Foundation (LAF) has shown great leadership in this effort to make cancer a national priority by hosting the LIVE**STRONG** Presidential Cancer Forum on August 27-28. All candidates were invited and six candidates pledged to renew the war on cancer and to make cancer a national priority. "We began an important conversation today and demonstrated that cancer should be part of the national dialogue as we choose our next leader," said Lance Armstrong, founder and chairman of the LAF.

Visit livestrong.org to see what each candidate had to say about "the issue all candidates should be running against", to read the Forum blog or to view details about the two-day event sponsored by the LAF.

The LRG will continue to present important political issues affecting GIST patients and positions of the candidates over the coming months.



GI symposium offers interesting abstracts

By Jerry Call
LRG Science Coordinator

Thirteen GIST abstracts were presented this year at the 2008 Gastrointestinal Cancers Symposium, sponsored by the American Society of Clinical Oncology (ASCO). Space limitations will not permit us to report on all of these abstracts.


DEMETRI

The first abstract by Dr. George Demetri is particularly timely as next month The Life Raft Group will report on an update of its 2004 dosage study which adds to the concern that some GIST patients (perhaps most GIST patients) are not receiving an adequate dose of Gleevec.

Correlation of imatinib plasma levels in GIST patients

A higher concentration of Gleevec in the blood correlates with better clinical outcome according to George Demetri, M.D., of the Dana-Farber Cancer Institute. In an interview with Peggy Peck on the medpageTODAY website, Dr. Demetri said that the imatinib plasma level was not associated with age, gender, disease 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 Symposium. The findings suggest that "we may have been under-dosing some people," he said.

This report is based on analysis of the pharmacokinetic data from the original phase II Gleevec trial for GIST (B2222), which started in July of 2000. Plasma levels (plasma is one component of blood) taken after 29 days of Gleevec, were available for 73 of the 147 patients enrolled in the trial. 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 the daily Gleevec capsule). 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 pharmacokinetic/ pharmacodynamic relationships may provide novel predictive markers and that exposure to adequate IM trough plasma concentrations (>1,110 ng/mL) is important for optimal clinical response."

Plasma levels and response rates

	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) >2,040 ng/ml	74%	33.1 months	92.3%

A video report is available on the medpageTODAY website. In the interview, Dr. Demetri explained that "when you give Gleevec or any other kinase inhibitor to a group of patients, they will handle it very differently, some people will have high levels and some people will have low levels… The important part about that is whether we for years might be underdosing people, and whether we perhaps should develop a blood test to

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PEDIATRIC

From Page 1

Doctors and patients met up in Seattle, Washington for a meeting to discuss the planning of an NIH pediatric GIST clinic.

Cancer Research, who came up with the plan and fought for its implementation.

One ongoing complication with pediatric care has been that clinical trials often have age requirements. While a pediatric GIST patient over the age of 18 can join a trial and have their medical information, an underaged patient is completely off-the-radar. There will be no age cut-off for patients at this NIH clinic. Instead, patient selection will be determined by biology (mutational analysis) in addition to the ages of diagnosis and projected disease onset.

The Life Raft Group will coordinate outreach and pre-registration to the pediatric GIST community.

The intent of the NIH clinic is not to replace the care a patient has been receiving. Patients will be encouraged to maintain an ongoing relationship with a local oncologist. The intent will be to provide that oncologist with consultation and support. Similarly the intent would be for any necessary surgery to be provided outside of the NIH.

Staff will also be credentialed by the NIH. Currently, plans are to include the following:

• Dr. Alberto Pappo, Oncologist at Texas Children's Cancer Center
• Dr. Constantine Stratakis, Endocrinologist at the NIH. His specialty is Carney's Triad and Carney's Diad
• Dr. Michael LaQuaglia, Surgeon at Memorial Sloan-Kettering Cancer Center (MSK)
• Dr. Cristina Antonescu, Pathologist at MSK and coordinator of the LRG pediatric tissue bank
• Dr. Katherine Janeway, Oncologist at Brigham and Women's Hospital, Dana-Farber Cancer Institute
• Lori Weiner, Psycho-Social Expert
• A Pain Management team from NIH
• A Nutritionist from NIH

Plans for tissue and research coordination include:

• Dr. Cristina Antonescu of MSK
• Dr. Constantine Stratakis of NIH
• Dr. Andy Godwin of Fox Chase Cancer Center

NIH will pay for the travel and lodging for the patient (child) and one parent if it is required. Reimbursed travel would have to begin within the United States or its territories. An attempt will be made to house participants at the Children's Inn. Patients will not receive a bill for services, including any tests. Drugs like Gleevec and Sutent may have to be provided by the appropriate pharmaceutical company or by the patient's insurance company.

Thus far, the NIH and the LRG have co-sponsored an initial discussion with medical professionals, patients and caregivers at a meeting in Seattle and several follow-up teleconferences. The LRG has begun to form a patient advisory group that will serve to collaborate with the clinicians to ensure best practices. Patients' Ashley Young and Jacqui Bromberg have already enthusiastically signed up for the task.

Ashley Young's thoughts on... being a part of the patient advisory group

Every difficult situation makes you stronger if you use it correctly. I have been waiting for something amazing to come from my experience with GIST and this is it. Now is my time to finally use my experience for something that is going to do some good for me and for others in my situation.

We will be building a lifeline for those who desperately need it. The information we give these doctors will be available for other doctors and there will be no reason for misdiagnosis or ignorance. What an absolutely amazing concept! This is an answer to all of our thoughts and prayers; our hopes and our dreams. I cannot wait to help make a difference in other people's lives through my personal experience. I can't think of anything more meaningful than that.

At times it is really hard and I have to dig deep for a shred of hope. This gives— ensures— hope for us all.

Ashley (right), with mother, Toni

— Ashley Young - 21 - GIST/Carney's Triad

CELLS

From Page 2

Crossman noted in her correspondence to the editor, "Since hOCT1 actively transports imatinib (Gleevec) into cells, patients with low baseline expression of hOCT1 may be unable to achieve adequate intracellular concentrations of imatinib, and hence fail to achieve a cytogenetic response. Although our study is small, our observations add weight to Thomas, et al.'s proposal that differential expression of hOCT1 may affect patients' responses to imatinib. We believe that further work is warranted to explore the interaction of hOCT1 and other drug transporters as a cause of primary cytogenetic resistance to imatinib."

In the current Australian study, White, Hughes and their colleagues designed an assay to measure OCT-1 activity in the blood of CML patients enrolled in either the TIDEL trial or the TOPS trial for CML patients. This assay provides a measure of the actual activity of the OCT-1 protein in the transport of Gleevec into the cell.

An examination of 132 patients enrolled in both trials revealed a wide variation in OCT-1 activity (range 0 to 31.2 with a median of 8.2). Five of the patients had negligible OCT-1 activity.

Survival in imatinib-treated chronic phase CML (the initial phase of CML) has been previously shown to correlate with the depth of response to imatinib. Patients with more residual disease during treatment do not do as well. Difference landmarks have been established in CML to indicate when a patient is having a "suboptimal response". In this study, the Australian team showed that most of the CML patients that had a suboptimal response had low OCT-1 activity resulting in inadequate concentrations of Gleevec in cells.

The OCT-1 activity was compared with molecular response over the first 24 months of imatinib therapy in 56 patients in the TIDEL trial. The median OCT-1 activity level was 7.2 ng/200,000 cells for this group of patients. Patients were grouped into high and low OCT-1 activity with the upper half of patients considered high OCT-1 activity and the lower half of patients considered to have low OCT-1 activity. Patients with high OCT-1 activity achieved significantly higher molecular response compared to patients with low OCT-1 activity (P=0.005 at 24 months).

To assess whether a higher dose of Gleevec could overcome the effects of low OCT-1 activity (poor Gleevec transport into tumor cells), the authors looked at the actual Gleevec dose patients received. They noted that "Separating patients into those averaging 600 mg and those failing to do so revealed patients with a high OCT-1 activity achieved good molecular responses regardless of dose. In contrast, the molecular response of those patients with low OCT-1 activity was highly dose dependent; with patients receiving 600 mg achieving significantly better molecular response by 24 months (*P* =.005)… These data indicate that dose is a critical determinant of long-term molecular response in the low OCT-1 activity cohort, but patients with a high OCT-1 activity generally perform well regardless of dose."

In the study, only 18 percent of patients receiving 600 mg or less of Gleevec and having low OCT-1 activity had a Major Molecular Response (MMR) by 24 months compared to 83 percent of patients in the same dose range but having high OCT-1 activity.

The Australian Group had previously shown that in 62 CML patients, there was a marked variability in their intrinsic sensitivity to Gleevec. When their cancer cells were tested to see how much Gleevec was required to inhibit the Crkl protein (inhibition of Crkl is used as a surrogate for inhibition of Bcr/Abl, the protein that drives CML) by 50 percent (IC50), they found that the IC50 ranged from 0.375 to 1.8 µM (median, 0.6 µM). In a latter paper, they reported that reduced OCT-1 activity was the cause of low in-vitro sensitivity to imatinib.

In summarizing their work, the authors noted that "The data presented here demonstrates clearly that dose is an im-

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Figure 1

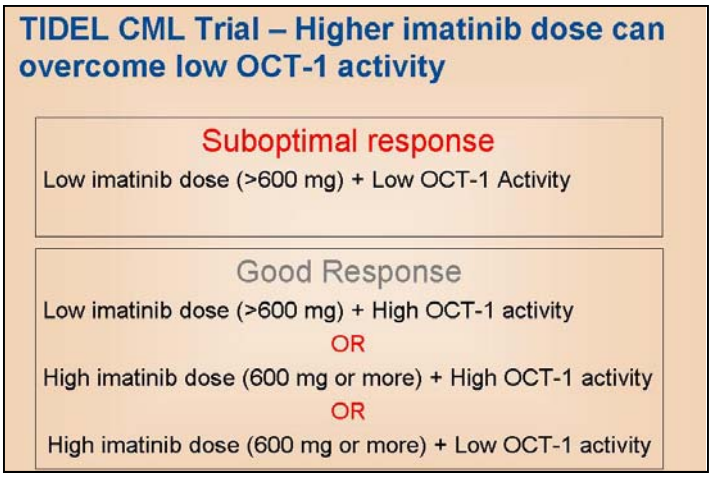
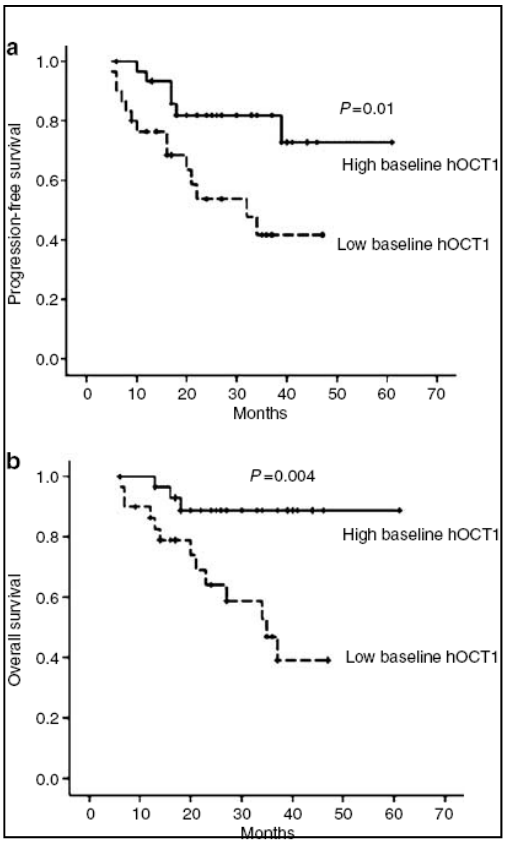


Figure 2



Correlation between baseline hOCT1 levels and survival. *Adapted by permission from Macmillan Publishers Ltd: CLINICAL PHARMACOLOGY & THERAPEUTICS, copyright 2007*

PCTs

From Page 1

WILSON

improved cancer survival. The importance of psychological support for patients (and their families) is part of the plan as well, alongside a range of new work on improving diagnosis, developing radiotherapy services, bringing new surgical techniques into widespread use, and reducing in-patient time in hospitals.

In the new drugs area, the Strategy has a lot to say, although it is constrained by the political realities of the National Health Service (NHS). We were never going to get the decision making processes on whether new drugs will get funded or not changed, but it is going to improve. The National Institute of Health and Clinical Excellence (NICE) is to accelerate its appraisal of new technologies and the aim will be to respond to the issue of the marketing license by the regulators with a decision on use of that drug in the NHS within two to four weeks.

In those instances where NICE Guidance does not exist, Primary Care Trusts (PCTs) hold the right of approval and here the Strategy is also proposing an improved process. PCTs are local and hold the funding for the treatment of the patients in their area. In England, there are 153 PCTs and because decisions can vary between them, we have what is known as the "postcode lottery". This means that it is possible for two patients in one neighborhood to be receiving different treatments for the identical condition, even to the extent where one might have a life-saving drug like Glivec and the other may be receiving so-called "best supportive care".

In future, PCTs will have to refer to the advice of specific professional bodies who have undertaken clinical reviews of new treatments. We tried quite hard to get the decision making on cancer drugs taken away from PCTs but it was quite clear that government policy was not going to be changed to that extent. Politically, the PCT must be seen to be in charge. The problem we have with PCTs is that the quality of their decision processes is poor. There may be some good ones; we haven't come across them – yet. Last October I wrote about the case we have been fighting in Bromley (a district of south-east London) for a GIST patient who had been seeking an escalated dose of 800 mg of imatinib.

In late 2006, we were able to get the then Secretary of State, Mrs. Patricia Hewitt, involved and she requested the top level NHS body in London (called NHS London) to investigate. Their investigation started well but stalled. It took a request under the Freedom of Information Act to reveal what was happening and what has unfolded since has been astonishing. Indeed, some of it looks so bad you could not include it in a novel without the reader finding it totally unbelievable.

It is quite clear that NHS London got out of its depth. It commissioned three independent reviews of the work of Bromley's decision making panel on our patient's case. All three of the reviewers were damning, criticizing the process, the review of clinical evidence, and considerations of such issues as cost and human rights. Although only one of them thought the decision was actually wrong (the other two refused to comment on the decision itself), it was clear that it was deeply flawed.

NHS London did not know how to handle this. Its approach with Bromley was highly selective and it decided to cover up all the bad behavior (some of it probably illegal) that it had found. It did not report back to the Secretary of State and as a new Secretary of State came into the post in the summer, it could hope that it would get forgotten there too. They refused to provide us with any information. Only our Freedom of Information Act request revealed it.

In October, we asked the Chairman of NHS London, Dr. George Greener, to re-open the investigation. He refused. We asked the new Secretary of State, Mr. Alan Johnson, to take an interest. He agreed to do so; his personal letter acknowledges that an important issue had been raised.

You might wonder what has happened since then, it does not usually take three months for a senior (indeed a very senior) politician to make up his mind about such things.

The actions of NHS London and Bromley PCT went from bad to worse within days of Mr. Johnson writing to me. They have created a problem of the kind even a senior politician does not like to have to resolve.

The chairman of NHS London, Dr. George Greener, wrote to me saying that his final decision was that the investigation was closed and he had agreement from a senior official in the ministry backing his decision. I pointed out that he was endorsing unethical, unprofessional, prejudicial and illegal behavior. He effectively said he did not care.

Who could the senior official be? We have asked the ministry whether it could be the Chief Executive of the NHS. It would be no surprise if it was; he used to be the Chief Executive of NHS London and worked closely with its current Chairman. We have not yet had an answer to our question.

What has happened at Bromley PCT is even more astonishing. As part of what it was requested to do, following the NHS London aborted investigation, it reconstituted the panel to review our patient's case. This took place on October 17, 2007. We received the minutes of the

"Other evidence was distorted and assumptions about clinical matters were made on the basis of those distortions by people who had no experience or qualifications to make them."

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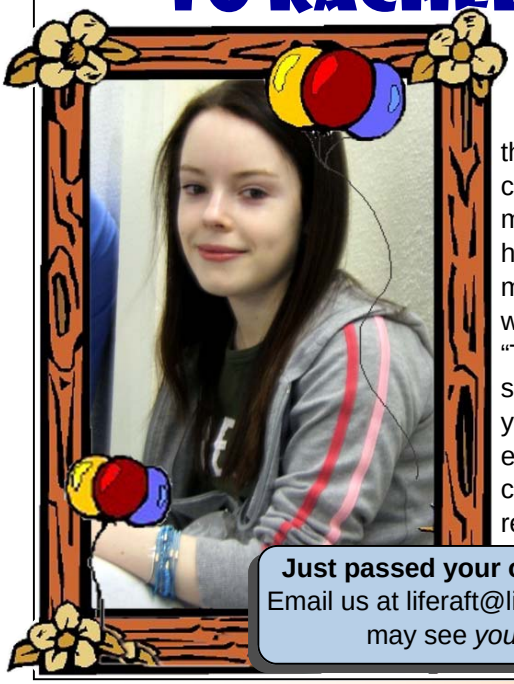
HAPPY CANCER-VERSARY TO RACHEL GILBERT!



If you've been to pediatric GISTer, Rachel Gilbert's blog, www.rachelemma.blogspot.com then you know that she recently celebrated a very important milestone in her survivor-hood. December 23, 2007 marked six years since she was diagnosed with GIST.

"That day I took my Glivec with pride! It seems strange that it has been six years, sometimes I think it's been forever and I can't remember life before cancer and other times I think it's gone really quickly. Whatever, I'm still here, still fighting and still loving and living life."

Just passed your own GIST milestone?
Email us at liferaft@liferaftgroup.org and you may see *your* name in print.

TRIALS

From Page 3

Dasatinib (BMS-354825)

Study of dasatinib(BMS-354825) in patients with solid tumors

Phase: I
Conditions: Tumors
Strategy: Inhibit KIT
NCT#: NCT00339144
Contact: For participation information at a US site, use a phone number below. For site information outside the USA please email Clinical.Trials@bms.com. First line of email MUST contain NCT# & Site#. Only trial sites that are recruiting have contact information at this time.
Sites: Contact Site 00, Koto-Ku, Tokyo, Japan, 135-0063.
Contact Site 02, Osakasayama City, Osaka, Japan, 589-0014

LBH589

LBH589 in patients with advanced solid tumors or cutaneous T-Cell lymphoma

Phase: I
Conditions: Tumors
Strategy: Destroy KIT + Inhibit cell cycle + Induce apoptosis (HDAC)
NCT#: NCT00412997
Telephone: +81-3-3797-8748
Sites: Tokyo, Japan

OSI-930

Dose escalation study of daily oral OSI-930 in patients with advanced solid tumors

Phase: I
Conditions: Solid Tumors/Sarcoma
Strategy: Multiple Targets
NCT#: NCT00513851
Contact: ContactUs@emergingmed.com
Telephone: (877) 601-8601
Sites: Dept. of Cancer Therapeutics Institute of Cancer Research Sutton, Surrey, United Kingdom

XL765

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

Phase: I
Conditions: Cancer
Strategy: Target KIT downstream signaling (PI3-K)
NCT#: NCT00485719
Contact: Gemma Sala
gsala@vhebron.net
Telephone: +34 93 489 4158
Sites: Hospital Universitario Vall d'Hebron, Barcelona, Spain, 08035
Jose Baselga, MD, PhD

SYMPOSIUM

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check the levels of this drug in people's blood and have more certainty that there's actually therapeutic levels in the blood." Demetri went on to explain that "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." The next step according to Demetri will be to "… talk with our colleagues, decide exactly how much this is worth pursuing, (and) decide how to mount a large trial."

Sorafenib (Nexavar)

Preliminary results of the phase II trial for sorafenib in GIST were presented. Sorafenib was approved in the United States in December of 2005 for kidney cancer. Sorafenib is also known as Nexavar or BAY 43-9006.

The sorafenib trial originally required only that GIST patients be resistant to Gleevec. In August of 2006, after FDA approval of Sutent, the trial was amended to require that patients be resistant to both Gleevec and Sutent.

This abstract reports on six Gleevec-resistant and 15 Gleevec- and Sutent-resistant GIST patients. Sixteen of these patients were evaluable for response (five too early). Two of the patients (one Gleevec-resistant and one Gleevec- and Sutent- resistant) had partial responses (significant shrinkage of their tumors) while nine patients had stable disease (duration unspecified).

The median progression-free survival for this small group of patients was 13.3 months. Although this trial is small, it should be noted that the reported median progression-free survival exceeds that of any previously reported drug after the failure of Gleevec. However, it should also be noted that median progression-free survival is not the only measure of benefit and not necessarily the best measure of benefit.

The phase II trial for BAY 43-9006 is open and recruiting patients. The University of Chicago maintains a central contact point for this trial at the University of Chicago Clinical Trials Office,

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CELLS

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portant factor for overcoming suboptimal response in low OCT-1 activity patients. These findings indicate a potential role for increased imatinib dose up front in those patients found to have low OCT-1 activity prior to imatinib start. Intolerance to higher dose imatinib in these patients may be a trigger to switch to an ABL kinase inhibitor that is not dependent on OCT-1 for its uptake into cells (AMN107 is not dependent on OCT-1 activity for cellular uptake)…. Importantly, using this functional assay to determine OCT-1 activity at the time of diagnosis may identify patients likely to respond well to standard-dose imatinib and those who would be most likely to benefit from a higher dose of imatinib."

Further support for the importance of OCT-1 in CML was provided by the University of Liverpool group (with L. Wang as the lead author), in an article published in June 2007 in *Clinical Pharmacology & Therapeutics*. In analyzing 70 consecutive imatinib-naïve CML patients seen between October 2000 and 2005 Wang and colleagues report that the pretreatment expression level of hOCT1 is critical in determining outcome. The authors suggest "that a crucial determinant of cytogenetic response may be the early achievement of high intracellular imatinib concentrations. Finally, in regression analysis, we demonstrate that hOCT1 expression is a critical determinant of the outcome of imatinib therapy, in comparison with other easily measured clinical and hematological parameters." The results of their study are reported in Figure 2.

While the OCT-1 story is less developed as it pertains to GIST, it seems reasonable that the same mechanisms are applicable. As a practical measure, Dr. Hughes offered this advice "I would certainly avoid OCT-1 inhibitors (prazosin, procainamide, progesterone) if I were on imatinib and looking for better efficacy.

Alert: Based on the apparent importance of OCT-1 in getting Gleevec into tumor cells, it seems prudent that patients talk to their doctors about avoiding inhibitors of OCT-1 activity. Known inhibitors of OCT-1 are listed below.

• Prazosin (trade names Minipress®,Vasoflex® and Hypovase®) is a medication used to treat high blood pressure. It belongs to the class of alpha-adrenergic blockers, which lower blood pressure by relaxing blood vessels.

• Procainamide (trade names Pronestyl®, Procan®, Procanbid®) is a pharmaceutical antiarrhythmic agent used for the medical treatment of cardiac arrhythmias. Procanbid® will no longer be manufactured.

• Progesterone is a C-21 steroid hormone involved in the female menstrual cycle, pregnancy and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen. Progesterone should not be confused with progestins, which are synthetically produced progestogens.

SYMPOSIUM

From Page 9

773-834-7424.

Adjuvant Gleevec – results of the Z9000 phase II trial

Preliminary results of the phase II Z9000 adjuvant Gleevec trial were presented by Dr. Ronald DeMatteo, a hepatobiliary surgeon at Memorial Sloan-Kettering.

There were 107 evaluable patients enrolled in this trial between September 2001 and September 2003. In contrast to the phase III Z9001 trial, all patients in the Z9000 trial were high risk patients with a primary tumor size of ten cm or more, tumor rupture or less than five peritoneal metastases.

The primary end point of this trial was overall survival. Prior to the availability of Gleevec, patients with a high-risk primary GIST were reported to have a two year overall survival of approximately 50 percent. With a median follow-up of four years, the overall survival rates and recurrence-free survival are:

Overall survival rates

	Overall Survival	Recurrence-free survival
1 year	99%	94%
2 year	97%	73%
3 year	97%	61%

The authors concluded that, "Imatinib given at a daily oral dose of 400 mg for one year following the resection of a high-risk primary GIST prolongs recurrence-free survival and is associated with improved overall survival compared with historical controls.

It's Here!

We are happy to announce the launching of our new website.

We spent many long hours trying to make this new site more user-friendly so that you have an easier time accessing the most important information that you need to survive.

To help you find areas in the site that you may frequently visit, we have highlighted a few of them (All urls begin with **www.liferaftgroup.org/**):

Clinical Trials: treat_trials.html
Medical Updates: members_medical_updates.html
Donate: donate.html
Newsletter:newsletters.html
Webcast Archives: library_videos.html

We also have a few new areas we encourage you to check out:

Blogs: If you have a blog or you would like to create one and place it on our site, visit:
members_blogs.html

Coping: We have expanded are coping section and we will continue to work on it on an ongoing basis. To check out the most up-to-date information, visit: coping/coping.html

Research: To learn more about the Resistance Research Project as well as our internal research, visit: research.html

If you have any comments or suggestions, please send them to liferaft@liferaftgroup.org.

Chicago area GISTers meet

Chicago area GIST patients met Sunday, January 27, at the Wellness Place in Palatine, Illinois. Twenty four patients and support people from Illinois, Indiana and Wisconsin gathered for over three hours to share personal stories, a BYO buffet and to hear a presentation on "Nutrition for GIST Patients" by Christine Tangney, PhD and Cheryl Sullivan, MS from Rush University Medical Center in Chicago. Two new GIST families also joined the group, which is comprised of patients belonging to both LRG and GSI. The next meeting date is set for May 4, 2008, at the same location. The tentative guest agenda item is Chicago Area Phase I trials in GIST. All Chicago area GIST patients are welcome to attend.

PCTs

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meeting on December 6, having long been promised them.

An absolute horror story unfolded as we read them. The only medically qualified person on the panel was a family doctor. The clinical and research evidence the panel needed had been reviewed by a pharmacist. Evidence presented to the meeting included some complete fabrications (the word 'lie' is not used in British public life!). Material evidence about our patient's response to imatinib was not presented – yet PET scans have proven prognostic value. Other evidence was distorted and assumptions about clinical matters were made on the basis of those distortions by people who had no experience or qualifications to make them.

There was an extraordinary diversionary foray discussing the quality of research. The two large scale studies of imatinib for GIST came in for criticism from a panel with no research experience. This was unprofessional at the very least and it would be easy to argue that it is unethical. What was unquestionably unethical was to infer that because the studies were funded by Novartis that influences a doctor's clinical decisions if he was involved in that research.

The meeting failed to consider costs of the treatment in an appropriate way (this is an area where legal judgments have been given) and it did not consider the crucial question of what might happen should the treatment not be funded. This too is the direct inference of a recent High Court judgment.

You will have guessed by now that the earlier decision not to fund an escalated dose of 800 mg per day of imatinib for a locally progressive, unresectable, non-metastatic GIST of the mesentery, shown to be responding to the dose, remained unchanged. I maintain that this is irrational, the behavior of the panel was unreasonable, and the whole structure is unfair.

My report to the Secretary of State ran to twelve pages. My letter to the Chair of Bromley PCT, Mrs. Elizabeth Butler, ran to two tightly packed pages of bullet points with the invitation to ask for the fuller report. She has chosen not to ask for it. She has rebutted our analysis without even considering the evidence. Given her staff's attitude to evidence, that is probably not surprising.

It all raises the question of how many other PCTs have panels as bad as the one at Bromley. As the NHS has never audited these panels it is an unanswerable question – but I would hazard a guess.

So now it is up to the Secretary of State, Mr. Johnson. He can back his senior executives – at NHS headquarters, in NHS London and in Bromley PCT. If he does so he opens himself to public and possibly parliamentary allegations of condoning corrupt behavior in public life which acts directly against the interests of patients.

He could, although it's unlikely, accept our allegations and take executive action to put things right. Somehow I know that the world doesn't work like that.

He might of course take our allegations at face value and commission an independent inquiry. It would put some senior figures at risk and that might be the price that has to be paid.

You never know; he might ring up and want to talk about it.

I'll let you know what happens.

Mark your calendars!

• New York/New Jersey GISTers will meet on **Feb 16** at Gilda's Club in Hackensack, NJ. For more information, contact Anita Getler at agetler2550@hotmail.com.

• Ohio patients will also meet on **Feb 16**. Please contact Kaye at tnt.1@sbcglobal.net for details.

• Dana Farber is holding a GIST Patient Support Forum on **Feb 25** in the Smith Building, Room 764. Contact Sarah Murphy at 617-632-6463 for more information.

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