GIST Support International

http://www.gistsupport.org

GIST Talking!

Summer 2009

Volume 1, Issue 4

Special points of interest:

- Clinical trial news
- Dasatinib
- WILD Ladies at NIH
- Grieving the new normal
- Post surgery furniture recommendations

Inside this issue:

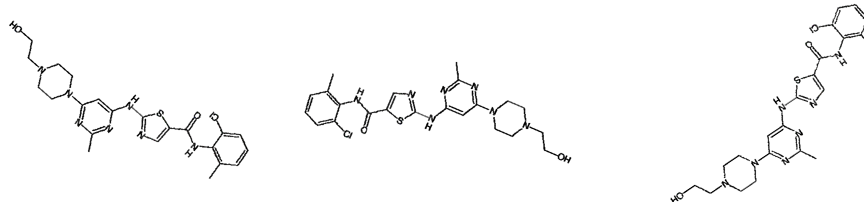
Dasatinib	1,8
Clinical Trials	2-5
Tissue Banks	6
NIH Clinic	7,9
Targeting therapy	8,9
The New Normal	10
St Louis Meeting	11
Project Flag	12
Post-surgery furniture options	13

Dasatinib in Advanced Sarcomas

by Nancy Berezin

Dasatinib is a multi-targeted TK inhibitor that is regarded as being more potent than Gleevec. Recent data suggest that it is active against imatinib-resistant activation loop mutants of KIT as well as against the Gleevec-resistant PDGFR-α D842V mutation.

In order to explore its potential, there is an ongoing Phase II trial (SARC009) to determine patient response and 6-month progression-free survival (PFS) after treatment with dasatinib (Sprycel). Multiple sarcoma types in addition to GIST (e.g., leiomyosarcoma, liposarcoma, osteosarcoma, chordoma, Ewing's sarcoma) are included.



SARC

Partial results were presented at the biannual meeting of the Sarcoma Alliance for Research through Collaboration (SARC) on May 29, 2009, just prior to the 45th annual meeting of the American Society of Clinical Oncology (ASCO).

Investigators

The principal investigator of SARC009 is Scott M. Schuetze, MD, PhD, of the Department of Hematology/Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan.

The GIST Principal Investigator is Jonathan C. Trent, MD, PhD, of the Department of Sarcoma Medical Oncology and Sarcoma Research Center at the MD Anderson Cancer Center, Houston, Texas. Below is a summary of Dr Trent's portion of the presentation:

Eligibilty

In order to be eligible for the GIST portion of the trial, patients must have advanced, KIT- or PDGFR-alpha expressing GIST and be at least 4 weeks out and recovered from the effects of prior therapy (with the exception of other TK inhibitors). Other TK inhibitors are not prohibited, and there is no washout period for them.

Continued on page 8

copyright 2009, GIST Support International

Clinical Trials Offer Treatment Options!   Julie Royster, PhD

Options for More Patients

Several new drugs targeting GIST offer an opportunity for **newly diagnosed GIST patients and patients with new recurrences** to receive drugs and potentially excellent care through clinical trials. This is a change from the last few years, when available trials were recruiting mostly patients who were drug-resistant.

The entry criteria for these trials vary, so patients must read the inclusion criteria closely to determine if they might qualify. In the list below, only the most basic inclusion criteria are listed, but you can read the full criteria at the trial links at www.clinicaltrials.gov

.Adjuvant Imatinib (Gleevec)

The following trial is expected to open very soon.

Five Year Adjuvant Imatinib Mesylate (Gleevec®) in Gastrointestinal Stromal Tumor (GIST)

NCT00867113 http://clinicaltrials.gov/ct2/show/study/NCT00867113

This is a new adjuvant Gleevec trial using a 5-year drug duration (in contrast to the 1-year duration in the ongoing Z9001 trial, and 2- or 3-year durations in European adjuvant trials). To be accepted, patients must be at significant risk of tumor recurrence as defined by either:

a. Primary GIST (any site): ≥ 2 cm and a mitotic rate of ≥ 5 per 50 HPFs

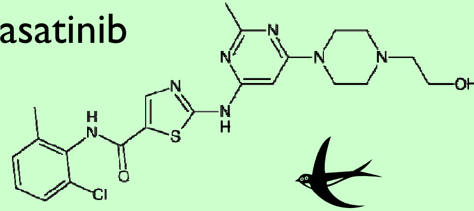
or

b. Non-gastric primary GIST: ≥ 5cm

Patients must have undergone complete gross resection of a primary GIST within 12 weeks prior to first dose of imatinib study drug. The inclusion of R1 resections will be reviewed on a case by case basis by the Study Management Committee.

Patient must have no evidence of metastatic GIST on either 1) a post-operative CT of the abdomen and pelvis with intravenous and oral contrast or 2) MRI of the abdomen and pelvis with intravenous contrast. CT or MRI must be performed within 8 weeks prior to first dose of imatinib study drug.

Dasatinib



Dasatinib (brand name Sprycel, formerly known as BMS-354825) is a potent oral multi-kinase inhibitor that targets ABL, SRC, KIT, PDGFR, and other tyrosine kinases. Dasatinib was approved by the FDA on 6/28/2006 for use in leukemias, and it is now in a new trial against GIST. Dasatinib is structurally dissimilar to imatinib, possibly binding better to KIT, regardless of the conformation of the KIT activation loop. It inhibits KIT and KIT-dependent activation of downstream pathways including RAS/MAPK, PI3K/AKT, and STAT3.

Preclinical cell studies indicate that dasatinib may inhibit imatinib-resistant mutations KIT D816V, D816Y, and D116F, as well as PDGFRA mutation D842V. For more information see our webpage http://www.gistsupport.org/treatments/emerging-treatments/tyrosine-kinase-inhibitors/dasatinib-sprycel.php

Dasatinib as First-Line Therapy in Treating Patients With Gastrointestinal Stromal Tumors

NCT00568750 http://www.clinicaltrials.gov/ct2/show/NCT00568750

This study is being done in Switzerland, and no other locations are listed. Patients will receive dasatinib therapy as their first drug treatment for GIST.

Selected Inclusion Criteria:

a. Histologically confirmed gastrointestinal stromal tumor (GIST)

b. No prior therapy for GIST, particularly tyrosine kinase inhibitors at any time

Also see Dasatinib article Pages 1 & 8

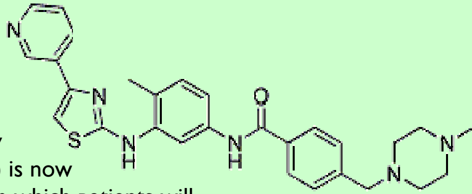
GIST patients needing to make sense of the clinical trials available can look at GSI's website where there are descriptions of trial drugs:

www.gistsupport.org/treatments/emerging-treatments.php

copyright 2009, GIST Support International

Clinical Trials—Masitinib

Masitinib



Masitinib (formerly known as AB1010) is now in a Phase III trial in which patients will receive either masitinib or imatinib. Masitinib inhibits both the KIT and PDGFRA receptors. It may have greater activity than imatinib against wild-type GIST and juxta-membrane KIT mutations in exon 11.

According to a 2009 presentation at ASCO (http://www.abstract.asco.org/AbstView_65_33199.html), in a prior Phase II trial 85% of patients showed PET response at 2 months, and 97% of patients showed clinical benefit at 23 months (6.7% Complete Response, 43.3% Partial Response, 46.7% Stable Disease) whereas 3.3% showed Progressive Disease.

The average time to response was 5.7 months (0.8 to 23.3 months). The median Progression-Free Survival was 27.2 months with PFS rates of 68.8% at 1 year and 60.2% at 2 years. Earlier results and links are included on our website page http://www.gistsupport.org/treatments/emerging-treatments/tyrosine-kinase-inhibitors/masitinib-ab1010.php

Efficacy and Safety of Masitinib (AB1010) in Comparison to Imatinib in Patients With Gastro-Intestinal Stromal Tumour: NCT00812240

http://clinicaltrials.gov/ct2/show/NCT00812240

Patients in this trial will receive either masitinib or imatinib.

Selected Inclusion Criteria:

a. Histologically proven, metastatic or locally advanced non-resectable GIST, or recurrent GIST after surgery.

b. Either no prior drug treatment *OR* patient previously treated with imatinib as neoadjuvant/adjuvant and relapsed after imatinib discontinuation.

Selected Exclusion Criterion:

No previous treatment by tyrosine kinase inhibitors except imatinib in case of inclusion criterion b.

Personalized Treatment

Fox-Chase recently launched the Institute for Personalized Medicine for using personal genetic analysis in selecting drugs for cancer patients, aiming to advance the development of genetically targeted cancer treatments.

A poster was presented at ASCO (May 2009) by Rink and colleagues showing how Fox-Chase's tumor bank tissues aided in research on GIST. Tumor samples from 63 patients in the RTOG trial, who were given Gleevec before surgery for primary or recurrent tumors were analyzed.

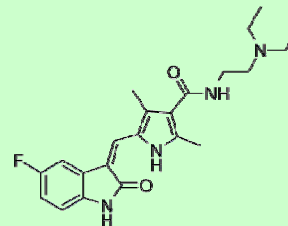
The gene profiles of gene expression was compared to how well the tumors had responded to short term Gleevec treatment. Gene signatures of 38 genes were identified which were expressed higher in tumors that did not respond well to Gleevec. Rink hopes that with these findings the effectiveness of imatinib treatment may be enhanced.

See http://www.fccc.edu/news/2009/2009-05-14-rink.html

Sutent Call Center

Pfizer has launched a patient call center where patients can get information about Sutent and its potential side effects from oncology nurses. You can learn more from the PDF at the following link.

http://www.sutent.com/imports/Sutent_Patient_Call_Center.pdf



You can find this and other useful resources (including patient assistance programs, the Novartis gistalliance website, and professionally prepared consensus treatment guidelines for GIST) on the GSI website at this link:

http://www.gistsupport.org/for-new-patients/best-links.php

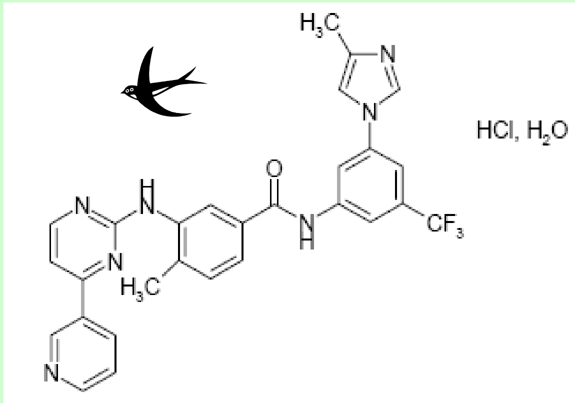
For a comprehensive overview of which clinical trials are available see:

www.gistsupport.org/treatments/clinical-trials.php . The GSI telephone number is: 215-340-9374

copyright 2009, GIST Support International

Clinical Trials—Nilotinib

Julie Royster, PhD



Nilotinib (brand name Tasigna)

Sold as Tasigna, nilotinib (manufactured by Novartis) is closely related in chemical structure to imatinib (Gleevec) but has improved binding with the KIT receptor protein and with leukemia targets.. This drug is already approved by the FDA for use in chronic myelogenous leukemia, so its safety is already established. It has fewer side effects than imatinib. Nilotinib has been found to build up higher concentrations of drug within cancer cells than imatinib. Two new trials testing nilotinib in GIST are open.

Phase III, Open-Label Study of Nilotinib Versus Imatinib in GIST Patients: NCT00785785

http://clinicaltrials.gov/ct2/show/study/NCT00785785

This trial is for patients with unresectable and/or metastatic GIST either newly diagnosed OR newly detected after surgery and adjuvant imatinib.

Inclusion criteria:

a. No prior therapy with imatinib, sunitinib, or any investigational therapies. Note: newly diagnosed patients may have received up to 14 days imatinib treatment for disease management while awaiting study start.
b. Recurrent GIST after stopping adjuvant treatment with imatinib and no subsequent treatment with any other investigational therapies (for example sunitinib).

Exclusion Criteria:

a. Prior treatment with nilotinib or any other drug in this class or other targeted therapy agents with the exception of adjuvant imatinib.

b. Disease progression during adjuvant therapy with imatinib

Patients will be randomized to receive either imatinib or nilotinib.

Nilotinib (brand name Tasigna)

Treatment of Patients With Metastatic or Unresectable Gastrointestinal Stromal Tumors in First Line With Nilotinib NCT00756509

http://clinicaltrials.gov/ct2/show/study/NCT00756509

This trial is for GIST patients newly diagnosed with unresectable or metastatic disease. All trial subjects will receive nilotinib.

Selected Inclusion Criteria:

a. Age ≥18 years

b. Histologically confirmed diagnosis of GIST that is unresectable and/or metastatic and therefore not amenable to surgery or combined modality treatment with curative intent prior to or at Visit 1

c. Various lab results in acceptable ranges

Selected Exclusion Criteria:

a. Prior treatment with nilotinib

b. Treatment with any cytotoxic and/or investigational cytotoxic drug ≤ 4 weeks (6 weeks for nitrosurea or mitomycin C) prior to Visit 1 with the exception of imatinib targeted therapy as an adjuvant therapy.

Other Options: GIST patients whose disease progresses on treatment with Gleevec and Sutent have various options. Sorafenib and Tasigna are obvious next choices, and both could potentially be obtained via prescription off-label by patients who could not travel to trial sites.

Some others: Various other HSP90 inhibitors in clinical trial, for which you can see descriptions on GSI's website at: www.gistsupport.org/treatments/emerging-treatments.php

There are various trial combinations of sorafenib, including a combination of Sorafenib and a MEK inhibitor; http://clinicaltrials.gov/ct2/show/NCT00785226

There is a trial for the Roche IGF-1R inhibitor in combination with other drugs—for a GIST pt, the relevant combination is with Sorafenib; www.clinicaltrials.gov/ct2/show/NCT00811993?term=R1507&rank=2

Finally, there is a trial of vorinostat + bortezomib combined, each of which is already approved for other purposes; www.clinicaltrials.gov/ct2/show/NCT00227513

It would be possible for an oncologist to prescribe this combo off-label. Neither one acts on KIT or PDGFRA, so neither would be affected by mutations that cause resistance to TKIs.

copyright 2009, GIST Support International

GIST—Diagnosis Onwards

Julie Royster, PhD

Diagnosis

GIST is diagnosed by a pathologist examining samples of the tumor by using a stain test to see if the cells show KIT protein (also called CD117). If this is negative (KIT-expression-negative) but the tumor otherwise appears to be consistent with GIST, then other tests can be used, including DOG-1 and PKC-theta. A small percentage of GISTs are not positive for KIT protein (KIT expression-negative GISTs).

Most GISTs have mutations in the ***KIT*** gene that contains the instructions for making the KIT protein (the receptor for a growth factor called stem cell factor). A small percentage instead have mutations in the ***PDGFRA*** gene (containing instructions for making the alpha receptor for platelet-derived growth factor). GISTs with mutant ***PDGFRA*** are more likely to have low or no KIT protein expression, but some KIT-expression-negative GISTs still do have mutations in the ***KIT*** gene. The mutant receptors are activated all the time, causing cell division (tumor growth).

Treatment (with or without surgery)

Imatinib (Gleevec) usually works for both ***KIT***-mutant and ***PDGFRA***-mutant GISTs because it usually stops the activation of the growth factor receptors. However, it works better for some particular mutations than others. The most common exception is that about a third of GISTs that develop in the small intestines have an "exon 9" mutation, and these patients benefit more from a higher dose of Gleevec.

Exons are just locations within the gene instructions for making the relevant protein. Depending on which part of the instructions is wrong (mutated) then different parts of the protein will be constructed wrong.

http://www.gistsupport.org/for-new-patients/mutation-testing.php

Mutational Analysis

You can find out what type of mutation your GIST has through extra tests for mutation analysis. These are not required to diagnose GIST so they are not on the regular pathology report.

Reasons to get mutation testing include:

i. you had a GIST with a high risk of recurrence

ii. you had a GIST arising from the small intestines (a chance of exon 9 mutation)

iii. your GIST was negative for **KIT** expression

iv. your GIST had already metastasized at diagnosis

We have a page on mutation testing at this link:

http://www.gistsupport.org/for-new-patients/mutation-testing.php

Eventually I think mutation testing will become the norm for all GISTs, but at present it is not. Currently imatinib (Gleevec) is the first drug to try regardless, so your doctor would not do anything different based on mutation analysis except to prescribe a higher dose for exon 9. However, some treatment centers do mutation testing on all GIST patients now.

"Wildtype"

About 12-15% of GISTs do not have mutations in either of the above genes, and these are called "Wildtype." This is a catch-all category, and it is quite likely that it contains more than one type of GIST.

For example, some but not all adult Wildtype GISTs show high expression of insulin-like growth factor (IGF) and its receptor, and this alternative growth factor probably drives those GISTs.

Imatinib (Gleevec) works in a smaller percentage of Wildtype GISTs. Drugs that inhibit the IGF system are in trials now.

Team Sarcoma July 18-26th 2009

The Liddy Shriver Sarcoma Initiative website has been moved to

www.SarcomaHelp.org

The 2009 Team Sarcoma Initiative (i.e., the 2009 International Sarcoma Awareness Week) will take place during July 18-26, 2009. Please consider being a part of it. Our goal this year is to have over 10,000 people involved worldwide.

Please see **www.team-sarcoma.net**

The 2009 Team Sarcoma Bike Tour of western Maryland's Allegany Mountains will also take place during July 18-25, 2009. You and your family are welcomed to join us on it as well; see

http://tinyurl.com/9qxbf3

copyright 2009, GIST Support International

Donating Tissues for Research into GIST

Researchers seeking better GIST treatments and ultimately a cure need GIST tissue samples for their work.

Tissue banks or repositories provide permanent storage of valuable samples and a mechanism for them to be shared by other researchers (based on the worthiness of their applications).

Storing your tissue in a bank also ensures that it can always be accessed for your own clinical needs, whereas pathology departments would discard your samples after a specified time period (such as 10 years).

We are compiling a list of tissue banks for GIST on our webpage :

www.gistsupport.org/for-new-patients/gist-tissue-banks.php

Here are the programs from which we have received responses so far. For full details please see the website as above, and keep checking for updates.

Memorial Sloan-Kettering Cancer Center

Sarcoma Tissue Bank

Contact: Cristina Antonescu MD **antonesc@mskcc.org**

Phone: 1-212-639-5721

Names of physicians coordinating GIST research projects:
Cristina Antonescu MD, Ronald DeMatteo MD, Samuel Singer MD, Robert Maki MD, Peter Besmer MD

The types of research include molecular analyses, immunologic analyses, pathologic correlates to clinical outcomes, drug discovery, and signaling studies.

All samples from all types of patients or tumors (genotype, clinical response history, primary, metastatic, imatinib-resistant, etc) are equally valuable. Frozen samples are preferred, but paraffin blocks are acceptable.

Banked tissues are sometimes shared with other qualified researchers.

Fox-Chase Cancer Center Biosample Repository

Director: Andrew K. Godwin, Ph.D.

Co-Leader: Women's Cancer Program

Director: Clinical Molecular Genetics Laboratory

Director: Biosample Repository

Website: **www.fccc.edu/research/facilities/biosample/biosampleRepository.html**

Researchers: Margaret von Mehren, MD (Director, Sarcoma Program, FCCC), Andrew K. Godwin, PhD

Descriptions of GIST research in the Godwin lab can be found at **www.fccc.edu/research/pid/godwin/index.html** under the link "Research" - Pathogenesis and Molecularly Targeted Therapy of GISTS.

Fox Chase Cancer Center Biosample Repository

1-888-831-6466 (Toll-Free)

Mary Gilroy, Recruitment/Intake Coordinator

(215-214-1652) email: **Mary.Gilroy@fccc.edu**

http://www.fccc.edu/research/facilities/biosample/biosampleRepository.html

NIH Pediatric & Wildtype GIST Clinic, National Institutes of Health

Contact: Su Young Kim, MD, PhD

Pediatric Oncology Branch, National Cancer Institute

E-mail: **ncipediatricgist@mail.nih.gov**

phone 301-451-7018 fax 301-480-5906

Types of research being done on GIST and research goals:

The goal is to identify genes and therapies for Pediatric GIST, Wildtype GIST, familial GIST, Carney Triad, and related conditions.

Frozen samples and fresh tissue samples of Wildtype GIST are needed. If a Wildtype or Pediatric GIST patient is scheduling surgery, please contact Dr. Kim and he will make the arrangements for sample collection. Paraffin-embedded tissue blocks or unstained slides are also very helpful in the studies.

The researchers included in the **C**onsortium for **P**ediatric and Wildtype **G**IST **R**esearch (CPGR) are all involved, and this consortium is open to all interested researchers.

www.pediatricgist.cancer.gov/Source/CPGR/CPGR.aspx

copyright 2009, GIST Support International

Wild Ladies at the NIH Clinic

By Vicki Zuber

We self proclaimed Wild Ladies are myself, Jeni Bullard, Becky Bensenhaver and Kath Kimball who have just returned from the 3rd NIH study on pediatric and Wildtype GIST—this time for adults. The "kids" had been studied in the first two sessions.

Suppose you were told that you were part of a medical study group where 65% of the diagnosed GIST patients had a bachelors degree or higher. What would you think? One member of the study group concluded, "If you don't want to get GIST, don't be smart."

We all spent three busy days in Building 10 at the National Institutes of Health in Bethesda, Maryland after the opening night dinner at the "Children's Inn".

Dr Kim: speaking at Dinner

The time at NIH did two things, (a) provided researchers from across the nation with in-depth information about our individual cases and (b) provided us with a thorough update on current directions that treatments and research seem to be taking. It was a very worthwhile experience for all of us.

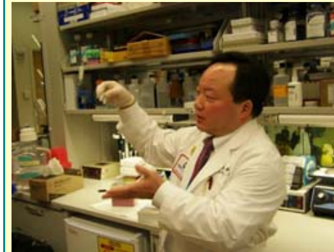
NIH had a complete history on each of our cases. While we were there, each of us was given a physical exam, seen by a dermatologist, seen by a nutritionist, seen by a psychiatrist (not because we were crazy but to see how we and our families were handling the situation), asked to give blood (this ranged from 4 to 12 vials per person), given a bone density scan, photographed from a variety of angles, asked to participate in a facial videography study (a fascinating process), and met with a geneticist. All of this was meant to provide more information for the researchers.

Research team meetings

One of the high points of the visit was an individual meeting with the full research team. In the room were doctors from NIH, Fox Chase, MD Anderson, Dana Farber, Sloan Kettering and probably a couple more I can't remember. Each of them had a full copy of our records and it quickly became evident they were well informed about our cases. In my meeting, we reviewed my current situation and discussed options for future treatment. We also discussed any questions I had. By the end of the session I felt fully informed of my situation and options. It was a wonderful meeting. This was echoed by the other participants.

Research Lab tour

Another highlight was a tour of Dr. Helman's research lab with Dr. Kim as our tour guide. This was an unbelievable experience. We were shown the process used to extract DNA from tumor samples.



Dr. Kim showing us some of the containers used in the lab to isolate DNA, RNA, and proteins.

Below: The robot used to isolate DNA

They have a robotic machine that completes the extraction process in about two hours. A human would take about a week to complete the same process.

We were also shown a process for marking cancer cells so they can be visually followed once they are introduced into a live subject (they use the chemicals that fireflies use to light up and that jelly fish use to floresce). We were also shown how cells move and fill voids, which is an indicator of how cancer cells metastasize. We were also shown the preliminary results of a new approach that restricts cell movement, which Dr. Kim believes will lead to a drug that may slow or stop the metastatic process. Finally, we were shown a microscope that was powerful enough to see inside a mouse, to and follow cells as they move through the mouse's arterial system. This was done without making any incisions.

Live tissue samples desperately needed

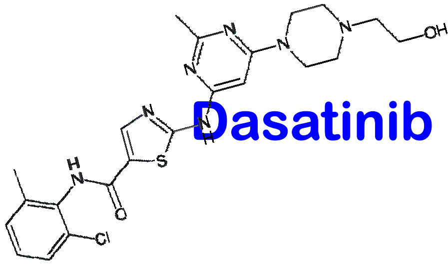
All of this was a lead up to the real reason for the tour and our inclusion in this study. In order for researchers to study Wildtype GIST and develop effective treatments and possible cures, the researchers need to have living cell lines of Wildtype GIST. These cell lines, once developed, will continuously generate new GIST cells so researchers can try all sorts of experiments with them. To date there are no Wildtype GIST cell lines to use in this critical research. The only way cell lines can be developed is to extract cells from tumors immediately after they are removed from the body. This has to happen in the operating room at the time of surgery. To date, no surgeries on Wildtype GIST patients have occurred at NIH. However, Dr. Kim said that if a patient was having surgery and the hospital where the surgery was taking place had the necessary equipment, he would come to the facility, and use the harvested cells to start the process. The key is for the patient to inform him of the surgery so he could contact the hospital and make the necessary arrangements. Until the development of the needed cell lines, research on Wildtype GIST will be limited .

I know all of us who went to NIH had a very positive experience. We learned a lot about our cases and about our options. We also learned a lot about what the experts are doing to address our disease. If we all make the effort to work with NIH to get the needed cell lines established, the future will look bright for research into our disease.

See also Jeni Bullard's article, page 9

See: www.pediatricgist.cancer.gov

copyright 2009, GIST Support International



Dasatinib in Advanced Sarcomas cont. from p.1

by Nancy Berezin

All patients must have experienced progression on Gleevec (as defined by an increase in unidimensional tumor size of >10% and/or new lesions, including new tumor nodules in a previously cystic tumor).

Thirty-seven GIST patients have been enrolled in the trial. Data from 35 patients (19 men, 16 women) are currently available for evaluation of toxicity and demographics, while data from 32 patients are available for evaluating PFS. Median patient age is 59 (range, 20-79 years).

Patients receive 70 mg oral dasatinib twice daily in 28-day cycles. Radiographic evaluation is performed every 2 cycles. Toxicity is assessed by NCI Common Toxicity Criteria (CTC) and efficacy by Modified RECIST (Choi Criteria).

Toxicity results.

Nine of 35 evaluable patients experienced Grade 3 or 4 toxicity, including nausea/vomiting, GI hemorrhage, cerebrovascular ischemia, electrolyte abnormality, deep vein thrombosis, gastritis, fever, renal failure, and pneumonia.

Efficacy results.

Dasatinib appears to be well tolerated. Overall response during the study period was 8%. At 6 months, PFS was 17.6% in the evaluable cohort. Median PFS was 2 months. Genotype data are pending.

Future considerations.

Important points that need clarification include:

What is the optimum dose of dasatinib and dosing schedule?

Are there specific KIT/PDGFR mutations to treat with dasatinib, for instance KIT L576P, PDGFR-alpha D842V?

How important are other TK targets of dasatinib, such as EPHA-2 or the Src family kinases (SFK), in GIST?

Toward Personalized, Targeted Therapy

The concluding section of Dr Trent's SARC presentation echoed an article he published last year in *Gastrointestinal Cancer Research*, entitled "Toward Personalized, *Targeted* Therapy of Gastrointestinal Stromal Tumor" (*Gastrointest Cancer Res*. 2008; 2(5): 256–257.) In that article, he discussed the goal of individualized therapy for GIST and reviewed some of the major scientific insights that have edged investigators closer to that goal. They include:

Mutation status of the KIT or PDGFR-α gene is both a prognostic factor and a major predictor of imatinib response. Patients with GIST tumors harboring exon 11 mutations generally realize the greatest benefit from Gleevec. In contrast, patients with tumors harboring KIT exon 9, 13, or 17 mutations are generally less sensitive to Gleevec. However, not all mutations of exon 13 are alike: while mutation at codon 654 is associated with Gleevec resistance and poor rates of survival, patients with mutations at codon 642 appear to benefit from Gleevec therapy. Thus, a detailed knowledge of mutational status is important when making predictions about therapeutic outcome. Moreover, other TK inhibitors such as Nexavar (sorafenib) and Sutent (sunitinib) have shown activity in patients with Gleevec-resistant mutations. Thus, the identification of specific mutations in KIT or PDGFR-α may allow early selection of active therapies over ones that are inactive.

Data supporting this come from sister studies performed in North America (Intergroup study S0033) and Europe with Australasia (EORTC trial 62005). Both studies compared 400 mg with 800 mg of Gleevec daily, with provisions to cross over to 800 mg if the patient progressed on the 400 mg daily dose.

Comprehensive KIT mutational analysis was performed on 377 of the EORTC 62005 study patients, leading to the observation that the exon 9 mutation resulted in inferior rates and duration of Gleevec response compared to the exon 11 mutation. Risk of progression was increased by 171% ($P < .0001$) and risk of death by 190% ($P < .0001$) for patients with KIT exon 9 vs. exon 11 mutations.

Patients with Exon 9 mutations

Importantly, patients with exon 9 mutations who were treated with Gleevec at 800 mg daily had a statistically superior median PFS ($P < .0013$) compared to those treated with 400 mg daily. A meta-analysis combining data from the two studies showed a benefit in progression-free survival when patients with exon 9 mutations were treated with 800 mg of Gleevec daily ($P < .017$).

It is possible that Gleevec dosage may be optimized by measurement of plasma concentration.

Specific KIT genotypes are known to have different binding affinities for imatinib. Thus, the optimal plasma concentration is likely to vary based on the genotype of the individual patient. Measurement of plasma trough concentrations may play a particularly important role in patients with primary GIST without additional features to guide the appropriate dose of therapy.

However, the connection between Gleevec dosage and plasma concentration still remains to be clarified. For example, although the standard of care is to increase Gleevec dose at the time of GIST progression,

Continued bottom page 9

copyright 2009, GIST Support International

WILD Ladies at The 3rd NIH Clinic

by Jeni Bullard

It is Day Two for me and I have met so many wonderful people!

Yesterday was filled with flights and paperwork. Lots of signing and sitting!! Then meeting and greeting. We were part of a webcast which was exciting. Today I went to all of my clinic appointments. The meeting with the NIH team was great—all of the doctors participating are kind and grateful for our participation.

The Pediatric clinic was our meeting point every day

I am still not sure where I fit in. I hope this trip will tell me as the doctors have yet to figure out what category I fit in. Adult? Wild-type? or Pediatric? Dr Kim is testing to find out at the clinic. So the answers to my genetic or mutation questions are in the works. I will be having my tumor blocks tested and the information I am looking for will be shared with me when it becomes available.

One of the highlights was participating in the audience for Dr Stratakis' webcast, which you can see at: http://videocast.nih.gov/summary.asp?live=7742 The subject is "Genetic Syndromes Associated with KIT or PDFGRA Non-Mutant Pediatric GISTs". I really recommend you look up this fascinating talk, in which he explains everything so well.

Dr Stratakis

Live webcast of Dr Stratakis' talk

Tonight some old friends from the GSI list (the Wild Ladies!) and some new friends just met, are having dinner on the town. So more socializing is to come! For me the clinic was largely about meeting others, who share "my story" , to join forces in forwarding research. To that I say "Mission accomplished!" ***See also Vicki Zuber's article, page 7***

See: www.pediatricgist.cancer.gov

Toward Personalized, Targeted Therapy cont.

there are no data that the increase results in higher plasma trough concentrations. It also has not been clearly demonstrated that patients who undergo gastrectomy or small-bowel resection are able to absorb adequate levels of the drug.

The TK inhibitors available in the United States include, in addition to Gleevec, Sutent, Nexavar, Tasigna (nilotinib), and Sprycel (dasatinib). These drugs differ in their ability to block signaling through the VEGF receptor.

The vascular endothelial growth factor (VEGF) pathway appears to play a significant role in GIST pathogenesis.

A recent study found that approximately 20% of patients with GIST have tumors that express high levels of VEGF, and they have inferior outcomes when treated with Gleevec compared to patients who do not express VEGF or express it only weakly. (These observations were independent of the patients' KIT genotype.) Thus, it is clear that patients whose tumors express VEGF are in need of better therapies, possibly including anti-VEGF drugs such as Sutent, Nexavar, or Avastin (bevacizumab) in combination with Gleevec.

In summary, the rationale exists for an individualized approach to the therapy of GIST using KIT genotype, tumor VEGF expression, and imatinib plasma trough concentration. Personalized, targeted cancer therapy with Gleevec and other TK inhibitors will improve clinical outcomes and minimize toxicity for patients with GIST.

Note: The University of Texas, MD Anderson Cancer Center Department of Sarcoma Medical Oncology and Sarcoma Research Center will perform GIST mutation testing and Gleevec plasma level testing for all patients who request the information and agree to be tested.

By Nancy Berezin

Formerly senior editor of Hospital Practice, Nancy Berezin is currently senior medical researcher at King Brown Partners, a strategic market research firm in Sausalito, CA..

copyright 2009, GIST Support International

Grieving the Loss of Normal

By Jane Moses, Licensed Clinical Professional

A cancer diagnosis brings a world of changes we don't want and didn't ask for. One of them is losing a sense of normality, of what life always was, of what we could always count on.

What do we mean by "normal"?

Although it is defined differently by everyone, normal is what we never question. It is the set of assumptions we use to live our days, things we take for granted. For example --

- When/how we wake up, and how we feel
- What we eat and drink
- How we plan our day -- our work, families, fun
- Who we interact with, what we talk about

Things like these make up our normal days. They make it possible to predict what will happen -- whether we will spend the day reviewing cases, or teaching children, or mending fence or running errands. We have all had our normal days disrupted for a time, by vacations, or out-of-town visitors, or changes at work. But these disruptions are temporary, and normal life usually returns in a way that feels reassuring.

With a cancer diagnosis, normal can be permanently disrupted. Suddenly, many of the things that made our lives stable and predictable are turned upside down. The regular routines are gone, and in their place are new problems, thoughts, feelings and fears. As treatment progresses, some people feel they have lost friends, although this is rarely true. "My friends shouldn't have to go through my illness with me. I don't want to bother anyone with this -- it's too hard." This is just one of the reasons a cancer diagnosis can be so disruptive. We feel as though we lose the ability to manage our lives and our relationships with the people we care about. This is especially hard for people who like feeling in control -- and that's most of us.

Grieving is normal, necessary

As humans, we're pretty good at denial, especially when what we're avoiding is painful or unpleasant. For some people, it works well. But denying a painful reality -- like losing life as we know it in the face of a cancer diagnosis -- prolongs suffering for many people. Accepting and grieving a loss can be painful in itself, but it can also clear the emotional decks for the hard work of getting on with life.

Grieving is not a linear process. You can't start at the beginning, follow the steps until you come to the end, and then stop. Grieving is not tidy. And we all do it differently. One day you may feel pretty much OK, like you'll be able to manage, and the next day you're knocked flat.

One woman said, "I was fine for a while, really -- taking care of the house, working, talking with friends . . . It was good. Then my eight-year-old son started talking about playing football when he gets to high school, and it hit me. What if I'm not here? I can't even look forward to my son's high school days. And then I really started seeing how nothing's the same."

Allowing yourself to go through this kind of pain, and not side step it, is exhausting and important work. Feel what you feel, when you're ready to feel it. There isn't a right or wrong way to grieve.

Loss of the life you planned

While it isn't true that life before cancer was carefree, it was possible to make plans and assume you'd be around to take part in them. You may have felt you could look forward to a long and healthy life, the way many in your family have before you. If you have children, you could assume you'd be around to watch them grow up, to watch their lives unfold. If you are young, you may have to grapple with the possible loss of plans you had for the future -- continuing a job, or college, or vocational training, or travelling with friends. Not being able to predict what will happen, feeling like there's no point in making plans, can lead to hopelessness and despair. It can help to stay focused on today and tomorrow, and draw your thoughts away from the distant future.

"New normal"

For a time, a new sense of normal can settle in. It may include planning life around treatment, which is especially hard for families in rural areas who have to travel long distances for appointments and treatments, often leaving important farm and ranch work undone. A "new normal" might also include planning around the feelings that go with treatment -- fatigue and nausea, for example -- and knowing that on some days you will simply have to stay home and not get much accomplished. It may include accepting help with dinners, or housework, or with seasonal chores on the ranch or farm. Gradually, some people begin to think of life Before Cancer and After Cancer.

See discussions at www.cancerlearning.com/

copyright 2009, GIST Support International

St. Louis GIST Foundation By Ally Klein

In the fall of 2007 Ally Klein, Dennis Luber and Katie Campbell were living and dealing with GIST in St. Louis. We met via the GIST internet support web sites and decided to meet in-person for lunch. We enjoyed our meeting so much we decided to meet for lunch every month. After a few months of lunching, we thought about expanding our little support group. We were successful in developing a great working relationship with a wonderful group at Siteman Cancer Center.

Marilee Kuhrik, Ally Klein, JoAnn O'Neill, Dennis Luber, Katie Campbell, Nancy Kuhrik, Teresa Deshields

Our goal in early 2008 was to find other GIST patients in the midwest, offer support through a meeting or seminar format where we could learn from some knowledgeable speakers and share our disease journey.

The first GIST Gathering was sponsored by Siteman Cancer Center in May, 2008. We had a great working committee assembled through the Patient Education Department. They were very supportive even though there was a lot of scepticism that our obscure disease could draw patients to an all-day seminar in St. Louis. Siteman listed our Saturday seminar in their weekly newspaper ad once. We distributed flyers to all the patient education departments and oncologists offices in area hospitals.

Announcements were made on the GIST support web sites. Siteman Cancer Center registered participants through their 800-line. There were 50 attendees at our first seminar. About half were patients and the balance attending were family members/care givers. The program included an oncologist and nutritionist in the morning. A great lunch was provided by a foundation grant. After lunch, we separated into patient and care giver groups for discussion with a psychologist. It was a very successful and rewarding day for everyone.

The second GIST Gathering convened in November, 2009. Our planning committee secured a great surgeon as a keynote speaker to discuss medical treatments, clinical studies and future drugs related to a GIST diagnosis. Then a panel of experts including a physician, nurse practitioner and a pharmacist fielded disease management questions. There were excellent questions and great discussion. After another delicious lunch, we spent informal time networking and getting to know each other.

Full House!

The most recent GIST Gathering in April, 2009 again supported about 50 attendees with an excellent presentation by a surgeon about small incision gist surgery. Next, we heard from an employment attorney, Medicare specialist and insurance specialist in a panel format. Their topics covered cancer in the workplace and how to pay for treatments which is critical to our survival.

After another delicious lunch, author and Co-Chair of the Board of GIST Support International, Marina Symcox, delivered a riveting story of her GIST journey and inspired everyone with her survival of 12 years with GIST.

Our group of three formed the GIST Foundation of St. Louis and received our 501(c) (3) designation. Our goal is to expand our program and apply for grants to pay for support efforts. We are developing a web site so other GIST patients can find us.

Our partnership with Siteman Cancer center has been critical to our initial success. We have a great committee to work with. They have provided marketing support, a great venue, AV services, speaker resources, meeting supplies and meeting support.

We have all benefitted from a very successful patient education program in a disease group with an unmet need for support. Our partnership has been described in a national magazine as a model for successful patient education. It will continue as we plan another GIST Gathering slated for October 24, 2009.

Look for more information on our web site www.gistl.org

copyright 2009, GIST Support International

Project FLAG

What is Project Flag?

Project FLAG is a study funded by the National Cancer Institute. It is conducted by Dr. Judy Garber, Dr. George Demetri, and Dr. Suzanne George of Dana-Farber Cancer Institute in collaboration with Memorial Sloan-Kettering Cancer Center and with the support of GIST Support International .

One of Project FLAG's goals is to understand GISTs that occur in families. Do only patients with a family history of GIST help FLAG as subjects, or do ALL GIST PATIENTS help by participating?

The participation of All GIST patients 18 years or older is important to Project FLAG! Even if you do not have a family history of GIST, sharing your medical history and your family's medical history is extremely beneficial.

In addition to familial GIST, may FLAG identify patterns of other cancers that are more likely to occur in people who have GIST?

One of the goals of Project FLAG is to gain information about what other types of cancers and symptoms are associated with GIST, even when we don't know the gene mutation.

What is the difference between somatic and germline mutations?

The vast majority of all GIST develop from gene alterations (mutations) that occur in the body, also known as "somatic" mutations. Somatic gene mutations are not heritable, that is to say, they are not inherited from our parents, and there is no risk to pass them on to our children. As with most medical conditions, there are exceptions! A small number of families do have alterations in genes that can be passed from one generation to the next; these are known as "germline" alterations (or germline mutations). Germline mutations are associated with an increased risk to develop GIST. The genes that are known to be altered in either the somatic or the germline mutation type include KIT and PDGFRA. In addition, there may be other genes that we have not yet discovered.

Will FLAG point the way toward a better understanding of all GIST, not just familial GIST?

A goal of Project FLAG is to gather family history information to identify other cancers and symptoms that may be present in the family when there is a diagnosis of GIST. While we know that there can be multiple family members with GIST in the hereditary type, we do not yet know whether GIST can be seen together with other cancers. The best way to capture this information is to look at a large number of families, even if only one family member has GIST.

What are the benefits to participants?

By participating in Project FLAG you will be sharing information that we hope will help clinicians to develop appropriate screening recommendations for early detection in the future.

Does it take much time for people to participate in FLAG?

Participating in Project FLAG will not take up much of the participant's time. If you wish to enrol in FLAG, you will review and sign the study consent form and complete a brief questionnaire about your medical history and your family's medical history. This information will help us determine whether you may be at higher familial risk for one of the GIST-associated mutations. If you are found to be at higher risk, you will have the option to have genetic testing. You will also have the option of whether or not to receive your genetic test results. A FLAG staff member will call you when you enroll to explain the study in more detail and describe your options.

How can you participate?

Participating in Project FLAG does not require you to come to one of the participating cancer centers. You can join Project FLAG by:

Enrolling through our website ***www.ProjectFLAG.org***

Or

Call the FLAG Study Manager toll-free: 1(800) 828-6622, option #1, and request that she mail you the materials to be completed to join Project FLAG. She will also answer any questions or concerns you may have.

copyright 2009, GIST Support International

Furniture Recommendations from GSI Listmates

Carol's Vote

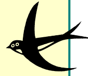
Merv's tumor was high on stomach & resection involved part of esophagus. He has severe reflux and must sleep nearly upright. We tried several things post-op.

Our winning entries are:

(1) Recliner. This is Merv's absolute favorite. First thing home from surgery we bought him a Lane recliner from Costco. I've since replaced it with a couple of leather Flexsteel recliners. These are by far his favorite.

(2) Neck pillow. Merv is addicted to the buckwheat-filled U-shaped neck pillows. It keeps his head in position & lots less reflux. He hates the memory-foam versions sold everywhere. He says the foam is too squishy.

(3) Bed Lifters ($10 from Bed Bath & Beyond). These are sold in sets of 4 plastic cup-like items that are generally used to raise dorm-room beds for underbed storage. We use 2 under legs of chairs, sofas, or beds. This is our standby for travel. Cheap and easy to pack.



Our so-so items are:

(1) Zero-gravity lawn chair. We use this occasionally for travelling and staying in hotels.

(2) Foam wedge. The cruise lines have them. Merv had to use 2, but it worked ok for the week.

Our wish-we-hadn't items are:

(1) Selectcomfort dual-king adjustable bed. We spent quite a lot of money on this and Merv only slept in it a couple of nights. Merv needs a lot of incline for sleeping, about 45 degrees or more. The mattress is very thick & buckles at the bend. Merv found it made an uncomfortable "lump" there & he missed having arms to keep him from rolling over. I sleep in it, but am stuck with dual mattresses that require special bedding & controls I never use. I wishing I had my old bed back!

(2) BedLounger. We bought both pieces and hoped to use them for travel. They just didn't fit Merv. He is on the tall side (6'1") and the back didn't support him at the right angle. However, I shipped it to a listmate that seems quite pleased.

Jill reports: Having been an Occupational Therapist prior to surgery and then going through surgery also, I will tell you 3 of the greatest things to have after surgery that I found. Those were a reacher, sock aid and a long- handled bath sponge. Now, many hospitals don't give patients Occupational Therapy after abdominal surgery, especially if they are younger or are able to move fairly well after surgery. Well although I could move after a total gastrectomy and being cut from the top of my breast bone to the bottom of my belly button and having a tube in my nose for days, I couldn't bend for anything!

So the reacher helps you reach things on the floor, or up high or that are too far away when you can't get out of bed.

It also helps a lot once you are home to help with dressing and reaching things, as it is a while before you can bend or reach. The sock aid is a very easy way to put your sock on without bending. And the long handled bath sponge is pretty self explanatory and since you can't get in a tub you will need to wash your back and feet unless you have someone to do it for you, lol!

These were lifesavers for me.

Joan Marie and Susan both recommend: The Tempurpedic adjustable bed. JM says: "It has made a wonderful difference in my life. I sleep better, have less aches and pains, and when I have reflux - I just adjust the bed. I love it and am glad I made the investment."

Marina recommends: a) A large recliner chair, as flat beds are uncomfortable.
b) Night sweats are a problem post-surgery. Use multiple thin blankets that can be peeled back, and a fan to circulate the air.

For more post-surgery recommendations from GSI members, please see (use underscores between the words!)

http://gistsupport.medshelf.org/Returning_Home_Post_Surgery

copyright 2009, GIST Support International

GIST Support International

by Barbara Doré, Newsletter Editor

As this time around I get to hold the stage, I would like to talk about something very close to my heart. Those that know me, know that GIST Support International has won my affections for being a very unusual group. What is unique about us is that we are ALL volunteers, and with no regular funding we operate on a shoestring.

This totally unique position has advantages, but also distinct challenges. Although we are financial minnows in the GIST world, in fact we have by far the biggest membership worldwide. So, we are doing something right, but need to work at it to keep it up.

The most obvious point is that we run on volunteers—GSI literally IS all of us, so more people need to take an active part for it to stay truly representative. And we are not talking minor parts here—the organisation is open to all enthusiasts at all levels. I should know—I am a newcomer, and find myself on the Board. All it takes is the will to help make GSI GSI.

It is quite true that patient advocate groups are making a major difference in the interaction between doctors and patients. Patients come to appointments better prepared, ask insightful questions, and participate in their treatment decisions. Those of us who have a rare condition get to meet others in our predicament and compare treatments, side-effects, coping strategies. And we have also developed a Voice— and are listened to!

I would like to mention a couple of our programs that you may like to use: our Phone Pals, Healing Through Music (HTM) and the Bob Spiegel Second Opinion Fund.

* The HTM program has a very well stocked library just waiting for you to send a request. The CDs of your choice will be delivered to your door without cost, all in memory of our much loved Fla. Bob who set the idea off. Just ask!

* We also have phone pals you can contact if you would really just like to talk to somebody and have a one to one conversation. All you need to do is to call 215 340 9274.

* Finally, I would like to remind you that the Bob Spiegel Second Opinion Fund is there to help patients in need of a second opinion or treatment to travel to a sarcoma expert. GIST Support International offers a one-time grant to those who need financial help with expenses for this travel.

www.gistsupport.org/financial-assistance/assistance-from-gsi.php

Email: gsi@gistsupport.org

Lee Ann Lamb, Co-Manager

Marina Symcox, PhD, Co-Manager

Ginger Sawyer, Treasurer

Joan Marie Hayno, Secretary

Yvonne Blixt, List Manager

Donna Capps, Wiki Team

Barbara Doré, Newsletter Editor

Bradley Clark BS 2nd Opinion Fund

Phyllis Gay, Pediatric Coordinator

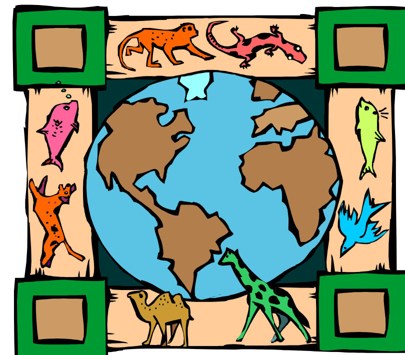
Julie Royster, PhD, Science Comm.

LeeAnn South, Greeting Comm.

Nea Paquet, Phone Pals

Rebeca Porto, MD, Healing thru Music

Lynette Ferguson, Newsletter



GSI needs you—please volunteer !