Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

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KIT & PDGFRA Mutations in GIST: A to Z

By Dr. Michael Heinrich
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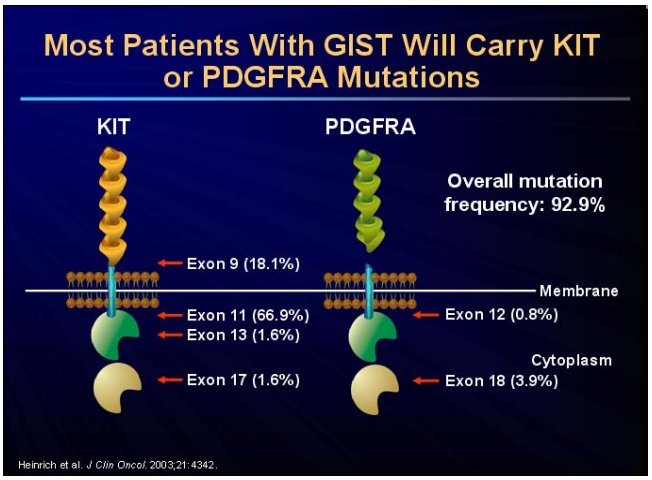
HEINRICH

This is part one of a two-part series on "KIT and PDGFRA kinase mutations in GIST: from A to Z". In this newsletter, Dr. Heinrich will provide a background on the role of kinase mutations in GIST, focusing largely on the biological and clinical implications of these mutations. In part two (which will be featured in the July 2007 edition of the newsletter, following the special "Five-year anniversary" edition), Dr. Christopher Corless will provide a practical, clinically-based commentary on these mutations. In particular, Dr Corless's article will focus on practical aspects of mutation testing as it applies to routine clinical decisions.

In 1988, Dr. Seiichi Hirota and his scientific team in Japan discovered that GISTs express the KIT protein (aka c-Kit or CD117). In addition, they found that in most GISTs the KIT protein has been mutated so that it provides an inappropriately high level of growth stimulation to the tumor cells. These observations revolutionized the field of GIST in two ways: 1) they provided pathologists a new test (immunohistochemical staining for KIT protein) that allowed the distinction of GISTs from other tumors of the GI tract;[1] and 2) they explained what made GIST cells grow. The finding that most GISTs have a mutant, activated KIT enzyme (kinase) immediately raised the possibility that drug treatments that could inhibit KIT enzyme activity would be an effective treatment for malignant

Figure 1



KIT and PDGFRA mutations in GIST.

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Clinical trial confirms Gleevec reduces recurrence

By Norman J. Scherzer
Life Raft Group Executive Director

On April 12, the National Cancer Institute (NCI), the American College of Surgeons (ACOSOG) and Novartis pharmaceuticals announced that a phase III trial studying Gleevec use to prevent recurrence in patients whose primary Gastrointestinal Stromal Tumor (GIST) had been removed by surgery would be ended early because it had met its primary endpoint of increasing recurrence free survival with a statistically significant hazard ratio of 3.1. Information on over 600 patients was used in the analysis. In the study, patients were randomized to either Gleevec or a placebo. Neither the patients nor their physicians were told which group they were assigned to. One group received Gleevec at a dose of 400 mg per day for one year, while the second group received placebo for one year (See Note on page 3).


SCHERZER

While it has been known for several years that Gleevec is an effective first-line treatment for GIST, this is the first reported data demonstrating that Gleevec is also effective in preventing GIST recurrence following surgery. Us-

See GLEEVEC, Page 11

AMN107 (Tasigna) Trial Opens (See page 7)

Immunotherapy trial strives to improve Gleevec response

By Jerry Call

While most GIST patients experience a good initial response to Gleevec, most will eventually relapse. A new phase II GIST trial is set to try to significantly improve the initial response and duration of remission of GIST patients to Gleevec, by combining it with pegylated interferon, described later.

Nearly all of the current clinical trials for GIST involve either trying to prevent a recurrence using the current first-line treatment (Gleevec) or trying to treat the disease after it has become resistant. What has been missing is an attempt to improve upon and lengthen the excellent initial response to Gleevec. Lei Chen, M.D., Ph.D. and Professor of Medicine at the Huntsman Cancer Institute at the University of Utah and her colleagues have planned a new trial to do just that.

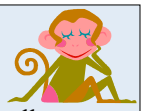
"The two major obstacles of durable remission in cancer patients are acquired drug-resistant clones and tumor stem cells" according to Chen. "Although GIST has initial excellent response, more than half of patients develop Gleevec resistance in less than 2 years. The responders are committed to Gleevec life-long because of the "tumor stem cell", which will regenerate as soon as Gleevec is discontinued. GIST is a great model to prove the concept of combination targeted therapy and immunotherapy." (Note: See the February 2005 LRG newsletter for a discussion about cancer stem cells.)

Most tumors can induce the patient's immune system into becoming "tolerant" of the tumors and paralyze the patient's anti-tumor immunity. Cytotoxic chemotherapeutic agents can cause bone marrow suppression and a low white cell count. Targeted therapy, e.g. Gleevec, does not cause significant white cell count suppression, thus preserving the patient's immune system during treatment. According to Dr. Chen:

"Gleevec can result in effective and rapid apoptosis and necrosis of Gleevec-sensitive cells. This rapid killing of GISTs will allow 'restoration' of patients' previously paralyzed anti-tumor im-

See CHEN, Page 7

Definitions:



Antigen: Antigen is a molecule that binds to an antibody or a cytotoxic T-cell receptor. T cell receptors bind only peptide fragments of proteins that are complexed with MHC molecules. Cytotoxic T cells that recognize "tumor-specific antigens" will attack tumor cells only but not normal cell.

Endogenous: Endogenous means "arising from within" as oppose to exogenous. Endogenous anti-tumor immunity means that it is developed by patients themselves.

Cytokine: Proteins produced by many different cell types that mediate inflammatory and immune reactions. They are principal mediators of communication between cells of the immune system.

Milieu: The physical or social setting in which something occurs or develops.

Cytokine milieu: A panel of different combinations of cytokines (present in our serum or in the microenvironment of different cell-cell interactions). Depending on the combination of different cytokines, they can either promote immune tolerance, or promote the development of antibodies or NK cells or cytotoxic T-lymphocytes to fight infection or to kill tumor cells. For example, pregnancy is a natural "immune tolerance" state. Tumors can secrete proteins and cause patients to sustain an "immune tolerance" state and prevent the development of "anti-tumor immunity". For a healthy individual, there is a dynamic delicate balance between immune stimulation and immune tolerance. Without immune tolerance, we can develop autoimmune disease. Without immune stimulation, we can get life threatening bacteria and virus infection and allow tumor progression.

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:

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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.

Adjuvant Gleevec Q&A with Jonathan Trent and Jerry Call

Following the Gleevec announcement briefed on page one, LRG Science Coordinator Jerry Call asked Dr. Jonathan Trent of MD Anderson Cancer Center in Houston, TX follow-up questions as clarification on the trial.

JC: Are there some patients that should/ should not be taking adjuvant Gleevec?

JT: A formal subset analysis from this study may help us answer that question. I approach patients with the general thought that they should take Gleevec after resection of a primary GIST in order to give them the best chance of being cured. With that said, patients are individuals and there are situations where I may not recommend adjuvant Gleevec. Even with this new data the decision should be individualized between a patient and their physician taking into consideration the many risks and benefits.

TRENT

JC: No mutational data is available for the trial. In light of the data about exon 9 patients having a dramatically higher response rate to higher doses of Gleevec and to Sutent, should these patients receive adjuvant therapy? With what drug and at what dose?

JT: If I recommend Gleevec, then I recommend the 800mg dose for those patients with exon 9 mutation in the KIT gene. We perform mutation analysis on all GIST patients so we have this infor-

See Q&A, Page 10

For the next issue...

Next month, the Life Raft Group will be celebrating its five-year anniversary. Therefore, our June issue will be a very special one—with a look back at the last five years in GIST, "staff pick" articles, LRG milestones and much more. Other regular newsletter content will be printed in the July issue. We are grateful to everyone sharing in this anniversary with us. Also, we ask anyone who has a suggestion for the five-year issue to please email Erin Kristoff at ekristoff@liferaftgroup.org.

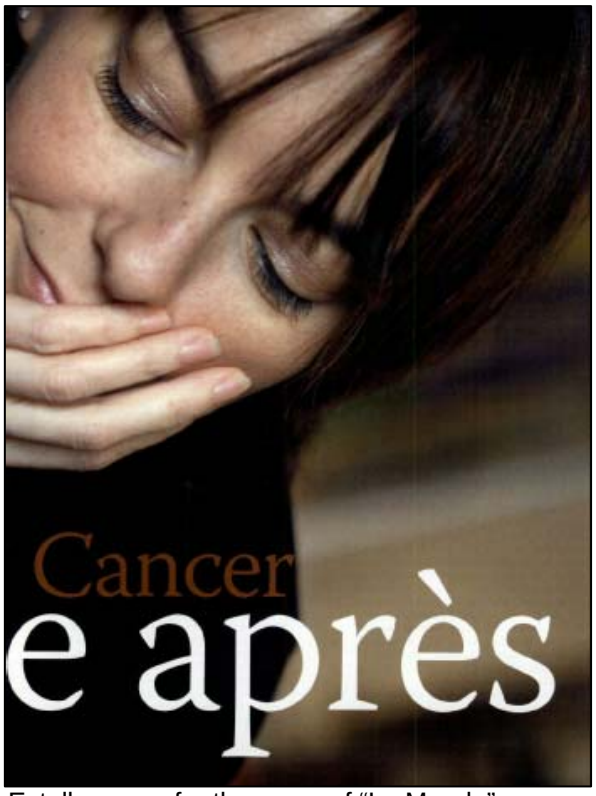
From the 'Elysée' to 'Le Monde', Lecointe can do it all

So close, yet so far; Estelle poses near Chirac.

Life Rafter and president of Association Française des Patients du GIST: Ensemble contre le GIST, Estelle Lecointe attended Président Jacques Chirac's speech on cancer at the French Presidential Palace "l'Elysée" on March 27. "There were a lot of journalists there. Some of them knew me as they had already seen the billboards with my picture, or previously interviewed me for magazines or radio, some of them had seen me on TV and just wanted to meet me. The fact that they remembered my face makes me think they now know my story and will then remember GIST too," says Lecointe.

Estelle has not received her picture with Chirac yet, however, she insists that it actually happened and we offer this as a substitute (left).

In the meantime, the French magazine, "Le Monde" has a familiar face on its cover (right). Lecointe is part of an article on cancer in last weekend's edition.



Estelle poses for the cover of "Le Monde".

'Treatments, trials and trails, oh my' but life must go on: Part 2

By Mark Becker

This is the second and final part of Mark's story regarding his experiences with GIST.

I continued regular follow-up visits over the succeeding years always with clear scans. At about three years, my regularly scheduled follow-up CT scan showed a new growth, measuring about 3cm, in the bottom of my pelvis to the right of my anus. Gleevec had stopped working.

BECKER

Dr. Von Mehren offered two options: Sutent or a clinical trial with AMN107 and Gleevec. After reviewing the possible side effects and comments online from various sources regarding Sutent, I decided to try the clinical trial as the noted side effects seemed less offensive. Unfortunately, I was prevented from participating in the trial, as my dosage of Gleevec was below the requirement and they could make no exception regardless of my other qualifications. Dr. Von Mehren increased my dosage of Gleevec to 800 mg but subsequent scans showed no positive results to the dosage increase and we continued looking for alternatives.

A couple of months later, a clinical trial combining a drug called RAD001 and 800 mg of Gleevec opened up. I was qualified, so I volunteered.

I became part of the Clinical Research Unit (CRU Lab), a special facility which exclusively manages patients participating in trials of drug studies. Monica Davey was the nurse managing my study and my point of contact for the trial.

At our first meeting, I received an appointment schedule, including tests I would have to take as part of the study and instructions regarding medication usage. All medications and tests as well as any professional charges were covered by Novartis, the study sponsor. I had to have a PET scan, CT scan, EKG and a lot of blood work prior to beginning the study. During the first two months, I had to visit the CRU every week for blood work and once a month for CT scans. The CRU lab is a separate unit set up with its own reception area, individual areas for seven people and a nurse station with its' own nursing staff who cares for only those patients. Each patient area has a reclining lounge chair, private TV, DVD and VCR players and there are two rest rooms for patient use in the unit. There were times when I was the only patient there. It was actually quite calm, almost quiet there most of the time. I was given access to the wireless internet connection for the duration of the trial so I could do some work and check email while I was there. The accommodations were exceptional.

"Enough was enough; so I told my doctor either we got this under control or I was dropping the study."

I was encouraged to phone in with questions, concerns, and any observations whenever I wanted. Although I had to leave a voice message, the staff was excellent in returning calls in a timely fashion and I got used to the system quickly. Help was always available.

It wasn't long after beginning the medication that I began to experience side effects. I found myself becoming tired easily but actually falling asleep was a challenge, so I began to use Ambien which occasionally helped. Then, my skin color turned an ashen hue and people began to mention I did not look well. My appetite declined and I lost weight. There were plenty of times I skipped meals and did not care. I experienced pain in my bowels, as well as bloody stool and diarrhea.

Diarrhea. Twenty four hours a day. Every day. For months. I began to take spare underwear and baby wipes in my car. It was unrelenting. There was no over-the-counter medication that could stop it. I ended up getting a script for Lonox, a powerful and tiny pill for my new, tormenting side effect. Exceeding the recommended dosage usually worked. I began to withdraw from normal activities as I was consumed with the threat of losing control of my bowels anywhere at any time, even sleeping. I slept on top of towels and wore double underwear. Enough was enough; so I told my doctor either we got this under control or I was dropping the study. Dr. Von Mehren decided to cut all my dosages in half following a week off all drugs. That week was an incredible vacation! I had forgotten what life without medication was like and I liked it! The real world came crashing down a week later and I started on medications again. I only took the RAD001 every other day and 400 mg of Gleevec once a day. We got the diarrhea under tenuous control and I was able to continue on with life in some semblance of normalcy.

After three months, I trekked back to

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MUTATIONS

From Page 1

GISTs. In the nine years since Dr. Hirota's initial report, there have been huge advances in GIST diagnosis and treatment. Notably, two different kinase inhibitors (imatinib and sunitinib) have now been FDA-approved for treatment of GIST and numerous other inhibitors are being tested for treatment of imatinib- and/or sunitinib-resistant tumors.

One of the advances was the 2003 discovery that a subset of GISTs have mutations in a sister kinase called PDGFRA.[2] This observation, the result of a collaboration between Drs. Jonathan Fletcher and George Demetri in Boston and our labs at OHSU, helped to explain the origin of at least some of the GISTs that lack KIT mutations. Several lines of evidence support the hypothesis that activating mutations of KIT or PDGFRA are the initiating event in most adult GISTs: 1) KIT mutations are common in small, incidentally discovered GISTs; 2) KIT mutation status does not correlate pathologic grade; 3) inherited KIT or PDGFRA mutations are associated with familial GIST syndromes (in humans); 4) expression of mutant KIT in mice results in GISTs; 5) KIT mutations precede other genetic abnormalities that contribute to GIST growth and malignancy. Overall, KIT or PDGFRA mutations are found in 80 to 85 percent and five percent of GISTs, respectively. These mutations are mutually exclusive (i.e., there are no reported cases of both KIT and PDGFRA mutations in the same tumor). What accounts for the growth of GISTs lacking kinase mutations (so-called "wild-type" GISTs), remains unknown but is the subject of intense investigation. From the standpoint of standard pathology tools such as immunohistochemistry and light microscopy, these tumors are indistinguishable from GISTs with kinase mutations.

Table 1. Molecular Classification of GISTs

Genetic type	Relative Frequency	Anatomic Distribution	Familial Examples
***KIT* Mutation**	**80%**		
Exon 8	Rare	Small bowel	1 Family
Exon 9	10%	Small bowel, colon	None
Exon 11	67%	All sites	Several families
Exon 13	1%	All sites	2 Families
Exon 17	1%	All sites	2 Families
***PDGFRA* Mutation**	**5-8%**		
Exon 12	1%	All sites	1 Family
Exon 14	<1%	Stomach	None
Exon 18 D842V	5%	Stomach, mesentery, omentum	None
Exon 18 other	1%	All sites	1 Family
Wild-type	**12-15% Adult > 90% Pediatric GIST**	All sites	None
Carney triad-related	Rare	Stomach	Not inherited
NF1-related	Rare	Small bowel	Numerous

The KIT and PDGFRA genes are contained in a large section of DNA on chromosome 4. Like most genes in our DNA, the KIT and PDGFRA genes are comprised of approximately twenty exons (if a gene is a book, an exon is a chapter). Each exon consists of a string of words (codons), and each word is represented by three DNA letters (bases A, T, G or C). The precise sequence of the letters/bases in the exons represents the blueprint for production of normal KIT or PDGFRA protein, assembled from building blocks called amino acids.

Mutations of KIT or PDGFRA found in GISTs are localized to certain exons (exons 8, 9, 11, 13 or 17 in KIT; 12, 14, or 18 in PDGFRA). In addition, within a given exon, only certain mutations can result in abnormal kinase enzyme activation. These mutations can be as simple as substitution of one DNA letter/base with another, or more complicated alterations involving deletion or insertion of a whole string of DNA bases. Figure 1 (see page 1) depicts the reported frequency and location of KIT and PDGFRA mutations in GIST, based on work in the Heinrich-Corless laboratory.

In addition to the presumed role of kinase mutations in giving rise to GISTs, there is also strong evidence of a correlation between tumor biology and the presence and/or type of kinase mutation. For example, 98 percent of GISTs with KIT exon 9 mutations arise from the small bowel or colon, whereas most GISTs with PDGFRA mutations arise from the stomach. In contrast, GISTs with KIT exon 11 mutations can arise from any portion of the GI tract. Additionally, the type of mutation correlates with global changes in the pattern of genes expressed in GISTs, as assessed by sophisticated "gene chip" technology in the laboratories of Dr. Antonescu and Dr. van de Rijn. Finally, the underlying malignant potential of GISTs may be influenced not only by the presence or absence of a mutation, but potentially by the class of mutation (e.g. exon involved, deletion vs. single base substitution).

The above commentary refers to GISTs arising in adult patients. In contrast, GISTs arising in children, adolescents, or young adults have a much lower frequency of mutations in KIT or PDGFRA (less than 10% of cases).[3] As detailed in the literature and other LRG newsletters, GISTs arising in younger patients have other distinctive features when compared to GISTs arising in adult patients. Based on the above considerations, a molecular classification of GISTs has been developed (See Table 1).

One of the notable features of the clinical studies of imatinib for treatment of

See MUTATIONS, Page 8

May 2007 clinical trial update

Fox Chase Cancer Center has begun their phase III AMN107 trial. Further details are on page seven. We ask anyone interested in more information than the table below to view it in the science section of the Life Raft Group website: http://www.liferaftgroup.org/treat_trials.html

Strategy

- Inhibit KIT (PDGFRA signaling)
- Inhibit KIT (PDGFRA signaling) plus Impede tumor vascularization (Antiangiogenesis)
- Impede tumor vascularization (Antiangiogenesis)
- Destroy KIT
- Inhibit the production of KIT
- Target KIT downstream signaling
- Destroy KIT plus Inhibit the cell cycle plus Induce apoptosis

Therapy	Title	Trial #	Phase	For
AMN-107			III	GIST
FR901228	FR901228 in treating patients with metastatic or unresectable soft tissue sarcoma	NCT00112463	II	GIST/Sarcoma/Ewings
Perifosine + Imatinib	Phase II Study of Perifosine plus imatinib mesylate for patients with resistant Gastrointestinal Stromal Tumor	MDACC 2004-0968	II	GIST
Sorafenib	Sorafenib in treating patients with malignant Gastrointestinal Stromal Tumor that progressed during or after previous treatment With imatinib mesylate and sunitinib malate	NCT00265798	II	GIST
CNF2024	Study of oral CNF2024 in advanced solid tumors or lymphomas	NCT00345189	I	Tumors/Lymphoma
Doxorubicin + Flavopiridol	Doxorubicin and flavopiridol in treating patients with metastatic or recurrent sarcoma that cannot be removed by surgery	NCT00098579	I	GIST/Sarcoma
IPI-504	Safety study of IPI-504 for Gastrointestinal Stromal Tumors	NCT00276302	I	GIST
LBH589	A phase IA, two-arm, multi-center, dose escalating study of LBH589 administered intravenously on two dose schedules in adult patients with advanced solid tumors & non-Hodgkin's lymphoma.	NVCI	I	Advanced Solid Tumors
Oblimersen + Imatinib	Oblimersen and imatinib mesylate in treating patients with advanced Gastrointestinal Stromal Tumors that cannot be removed by surgery	NCT00091078	I	GIST
OSI-930	Dose escalation study of daily oral OSI-930 in patients with advanced solid tumors - sarcoma	EmergingMed	I	Advanced Solid Tumors -Sarcoma
Perifosine + Sunitinib	Perifosine + sunitinib malate for patients with advanced cancers	NCT00399152	I	GIST/RCC
XL820	Study of XL820 given orally daily to subjects with solid tumors	NCT00350831	I	Cancer/Solid Tumor

AMN107 (Tasigna) now open at Fox Chase Cancer Center

The AMN107 phase III trial is now open at Fox Chase. The contact number is 1-888-FOX-CHASE. Patients will be seen every two weeks for the first two months and every two months thereafter. They will be randomized to receive either AMN107 at 400 mg twice a day or best supportive care. Best supportive care allows the treating physician to continue administering Gleevec, Sutent, or other supporting care, however, the patient will be allowed to cross over to receive AMN107 at time of progression.

The AMN107 phase III trial is not expected to open at Dana-Farber for several weeks. Between eight and 12 sites are expected to open in the United States and three are expected to open in Canada. We understand there are several sites open in Europe as well.

CHEN

From Page 2

CHEN

munity. The massive release of tumor-specific antigens from apoptosis and necrosis can stimulate NK cells and modulate antigen-presenting cells toward development of effective adaptive anti-tumor activity if we provide help to improve the cytokine milieu and empower the endogenous anti-tumor immunity by appropriate coordination of immunotherapy with targeted therapy. Effective endogenous anti-tumor immunity can recognize and kill the Gleevec-resistant clones and tumor stem cells that escaped Gleevec, the cells that eventually cause Gleevec resistance."

In order to stimulate/optimize an immune response against GIST, the new phase II trial will add pegylated interferon α 2b (PEG-intron, Schering Plough) to Gleevec. "If given at the right dose, [with the] right timing, combined with the right drug, interferon α holds the greatest potential in breaking immune tolerance and shifting to immune stimulation against patients' tumors," said Chen, "with pegylated interferon α 2b we expect much improved toxicity."

PEG-intron differs from interferon α 2b by having molecules of polyethylene glycol (PEG) attached to them. PEG causes the interferon α to remain in the body longer and prolong the effects of the interferon α and its effectiveness. It also greatly improves the tolerability and requires only once-a-week treatment.

The Trial

Dr. Chen at Huntsman Cancer Institute plans to enroll approximately thirty GIST patients for a phase II trial. The trial is expected to open in May 2007, initially as a single institute trial. It is expected to expand later to a multi-center trial. Because the intent is to build upon capture of the tumor-specific antigen release from Gleevec-sensitive tumors, the trial will be targeted to patients that have never received Gleevec before. In addition, GIST patients that received Gleevec as adjuvant (preventative) treatment and later developed a recurrence, are eligible only if the disease-free survival is greater than or equal to six months after completion of adjuvant Gleevec.

Because this trial uses immunotherapy, there are certain restrictions. Patients must have a relatively healthy immune system. They cannot have autoimmune disease or be immunosuppressed and they must have a spleen. (Note: GIST patients may have had their spleens removed during surgery.)

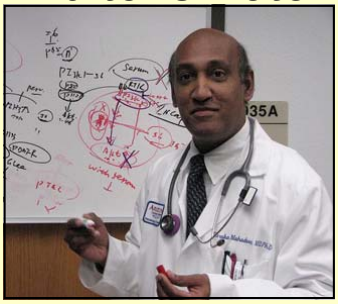
In addition to the attempt to improve response and remission to Gleevec, the trial has several other innovative aspects. Patients will initially receive PEG-intron plus 400 mg of Gleevec. They will then have genotyping performed and patients that have an exon 11 mutation will continue taking 400 mg. All other patients will have their Gleevec dose increased to 800 mg. In addition, if the patient has resectable disease after 24 weeks of treatment the patient will undergo surgery at week 24-25.

This trial is the first to take advantage of recent data about the mutation/dose relationship as well as an emerging trend to evaluate patients for surgery at the time of maximum response. The trial will also measure response, not only with RECIST (the current standard), but also using the "Choi criteria". The Choi criteria seems to be one of the leading candidates to replace, or at least supplement the RECIST standard, which has proven problematic with GIST.

PEG-intron will be given at 4mcg/kg subcutaneously once per week for seven weeks. The dose will then be decreased to 1 mcg/kg weekly for 49 weeks. Like all trials, protocols are built-in to allow dose reductions for excessive toxicity.

Chen and colleagues have taken the challenge of drug-resistant clones and tumor stem cells and designed a trial combining targeted therapy and immunotherapy. They are aiming high for a long-term remission or cure and are truly offering a new and interesting opportunity to GIST patients.

Editor's Note



Last month, we published an article discussing the work of Dr. Daruka Mahadevan, M.D., Ph.D., Associate Professor of Medicine, with AXL. We are including a picture of Dr. Mahadevan that was regrettably not included last month.

Dr. Mahadevan also had the following to say, "The MP470 Phase I clinical trial will open at two sites this month. It is open to all solid tumor patients including patients with Gleevec-resistant GIST. We in the lab are developing new combination therapies with MP470 based on over-expressed targets discovered in our gene expression profiling studies."

BECKER 2

From Page 4

Mark Becker poses for the camera with wife, Janet.

Fox Chase for my monthly CT scan to check on the tumor. I showed progression. The trial was not working for me and we had to abandon it and look to a new option. I felt somewhat empty and that the painful experiences of the last few months were a waste of time-- time lost that the cancer had used to convalesce and grow. For a brief time, I was depressed but I told myself that I had to put that behind me. Get over it and move on. The options were few and another bad choice on my part was not going to be part of my plan for surviving. I had to trust that I had an excellent medical team working with me and a family who loves me and wants me around as long as possible. Even my coworkers were a constant source of encouragement. There was much to be grateful for in life despite the constant threat of losing to the disease. Life was good.

In her gentle way, Dr. Von Mehren said we were going to move on to Sutent. We discussed the potential side effects, the same side effects that prompted me to try a different clinical trial all those months past. I found it interesting that now those same side effects did not sound so bad. While she was talking, I recall thinking to myself, "Okay Doc, let's get it on!"

So here I am, several months down the Sutent trail (not a trial) and I am happy to report that my disease is stable. My side effects are the least and most tolerable to date since the recurrence in 2003. There has been no metastasis.

The Sutent will not work forever. I know that and have a backup plan in the works. I am aware of upcoming clinical trials at Fox Chase, and am also a patient at Memorial Sloan Kettering in New York. I have discussed upcoming clinical trials there with Dr. D'Adamo for which I may be a candidate in the event I need to make that move. And in the small world of GIST, Dr. Von Mehren knows Dr. D'Adamo and supports my contingency plan.

Life, once again, is good.

MUTATIONS

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GIST is the consistent observation that genotypically-defined subsets of GIST have different outcomes during treatment with this drug. Listed in Table 2 are the correlations between tumor genotype and tumor response (complete and partial responses) in four trials (phases 1-3). Based on 509 genotyped GISTs, the response rate for KIT exon 11 mutant, KIT exon 9 mutant, and wild-type GISTs is 74 percent, 38 percent, and 22 percent, respectively. Likewise, the probability of primary resistance to imatinib for KIT exon 11, KIT exon 9, and wild-type GISTs is 4 percent, 16 percent and 25 percent, respectively. An even more striking observation is that kinase genotype correlates with progression-free and overall survival, with superior survival seen for patients whose GIST harbors a KIT exon 11 mutation. For example, the median time to tumor progression for patients whose GIST has an associated KIT exon 11 mutation is more than one year longer than patients whose tumors have KIT exon 9 or wild-type kinase genotypes. A similar overall survival benefit is seen for patients with KIT exon 11 mutations versus the other common genotypic subsets.[4-6]

Table 2. Relationship Between Kinase Genotype, Response And Outcome During Imatinib Therapy

	EORTC phase I/II (n=37)	B2222 Phase II (n=127)	EORTC-Austral-Asian Phase III (n=363)	Overall Average
Objective response[#]	% (n)	% (n)	% (n)	% (n)
KIT exon 11	83% (24)	*83% (85)	*70% (248)	74% (378)
KIT exon 9	25% (4)	48% (23)	35% (58)	38% (85)
No mutation	33% (6)	0% (9)	25% (52)	22% (61)
Progressive disease				
KIT exon 11	4%	5%	3%	4%
KIT exon 9	0%	17%	17%	16%
No mutation	33%	56%	19%	25%

The above results reflect pooled data from clinical studies in which imatinib doses ranged from 400-800 mg per day. In a recent subset analysis of the EORTC/AustralAsia phase III trial, Dr. Debiec-Rychter and colleagues found that the progression-free survival of GIST patients with KIT exon 9 muta-

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MUTATIONS

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tions was significantly better when they were treated with 800 mg per day as compared with 400 mg.[6] In contrast, patients whose GIST had KIT exon 11 mutations had a similar progression-free survival on either dose. Many GIST experts now recommend routine tumor genotyping and dose selection based on the presence or absence of a KIT exon 9 mutation. Similar correlative analyses are underway using genotyping data and outcomes from the North American phase III study. A meta-analysis (statistical aggregation) of data from both trials will be completed in late 2007.

A minority of patients experience continued tumor growth on imatinib within the first six months of treatment, which is referred to as primary resistance. Compared with patients who have KIT exon 11-mutant tumors, those with exon 9-mutant or wild-type tumors are overrepresented in this group. Amongst patients who benefit from treatment beyond six months, a significant fraction will show growth in one or more tumors between 12 and 36 months of treatment. This is called secondary resistance. Recent studies from a number of laboratories have established that in most such tumors there are new, acquired mutations in KIT or PDGFRA that directly interfere with the ability of imatinib to block the kinase.[7-10] This phenomenon is similar to bacteria becoming resistant to an antibiotic, and it tells us that we need to be smarter in the design of new drugs and that we must consider combinations of drugs in the future.

Sunitinib is FDA-approved for the treatment of GIST patients who are intolerant of, or resistant to, imatinib. Based on an extended phase II trial, it appears that the best responses to this drug are in patients with KIT exon 9-mutant or wild-type tumors.[11] There is a lesser benefit to patients whose tumors have acquired imatinib-resistance mutations associated with secondary kinase mutations, as many of these mutations (particularly those in exon 17) confer cross-resistance to sunitinib. Predictably, patients who initially respond well to sunitinib may develop secondary resistance, and preliminary studies in our laboratories indicate that sunitinib-specific resistance mutations occur in this setting.

Based on the fundamental importance of kinase mutations to GIST pathogenesis, biology, and response to kinase inhibitors, it is expected that basic science and translational research efforts will continue to devote substantial resources to understanding how such mutations may be further exploited as therapeutic targets. As noted above, characterization of these mutations is increasingly important for routine clinical diagnosis and management.

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Global GIST Network adds new GIST representative

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Biomarkers presentation sparks interest at Dutch meeting

By Anje Long
The Contactgroup GIST / Life Raft Group

At the Dutch patient meeting, "Cancer Genomics Market Plaza" held on March 10, in Utrecht, a report was presented called "Biomarkers and the fight against cancer".

This report was published by the Dutch Cancer Society (KWF Kankerbestrijding) and was written by what is called the Signalling Committee Cancer, under the chairmanship of Dr. Laura van 't Veer, head of molecular pathology at the The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI-AvL). It highlights the current situation in regards to available biomarkers for well-known types of cancer. Biomarkers allow for research into characteristics of a tumor cell. Every human being has his or her own DNA, but every tumor cell is also unique. Biomarkers make it possible to predict tumor behavior and the risk of forming metastases. This could save patients, as well as the healthcare system, unnecessary, prolonged and expensive treatments. It was made clear in the presentations that research into GIST has been a role model here for other cancers. The committee wishes to promote the enormous importance of the application of biomarkers in clinical practice because of the importance for patients. The report highlights the state of affairs regarding the application of biomarkers in prevention, research into heredity, diagnostics and the treatment of cancer, for the present as well as in the future**.** The report also cites some downsides to this development, namely that the use of biomarkers should only be appropriate and supported by scientific research.

Discussion panel at the "Cancer Genomics Market Plaza". From left to right: Dr. Brenda Hermsen, Dr. Els Borst-Eilers and Dr. Laura van 't Veer.

The report was presented to inform cancer patients of these promising new developments, as it signals the future of cancer treatment: individualised treatment for every patient.

The manifestation was attended by nearly one thousand cancer survivors and their caregivers and consisted of plenary sessions in the morning where the growing role of genomics in cancer care was discussed. Highlights were the presentation of the report on biomarkers to Dr. Els Borst- Eilers, chair of the NFK (Dutch Federation of Cancer patients' organizations), and workshops in the afternoon, titled "Ask the experts". There were a total of nine workshops, which included one on "Bowel and stomach cancer and GIST". In this workshop the developments in the management of GIST and the fact that GIST serves as a model for other cancers were discussed by Prof. Jaap Verweij and Prof. Winette van der Graaf.

In the Expo Hall the Contactgroup GIST / Life Raft Group (Netherlands - Belgium) was represented amongst the many other patient organization information stalls.

Q & A

From Page 3

mation routinely available. If side-effects are a problem then I recommend the highest dose of Gleevec tolerated up to 800 mg. Sutent and Gleevec have not been compared head to head yet. This trial is in development and it is possible that Sutent might be a better choice but we don't know yet.

JC: The trial allowed some patients with tumors that might be considered "low-risk". Should patients with low-risk tumors take adjuvant Gleevec?

JT: Yes. Patients with low-risk tumors were included so the current data supports use of adjuvant Gleevec in that population. Moreover, low-risk does not mean "no-risk".

I have personally been recommending adjuvant Gleevec for intermediate to high-risk patients for the past several years. I only enrolled low-risk patients on the ACOSOG Z9001 trial for reasons of equipoise. Basically, I could not ethically risk putting an intermediate or high-risk GIST patient on a study where they might receive a placebo. Our ongoing study of preoperative plus postoperative Gleevec includes 2 years of adjuvant Gleevec with absolutely no placebo arm.

And, once again, low-risk features of the GIST are part of the individualized risk-benefit decision between a patient and their physician.

JC: How long should patients take Gleevec on an adjuvant basis?

JT: The data support one year. The next generation of studies will hopefully focus on duration of adjuvant therapy. Our study of preoperative plus postoperative Gleevec for resectable GIST includes 2 years of adjuvant therapy with Gleevec and is open for patients. This may be a more appropriate study for patients with high-risk tumors or exon 9 mutation.

The Liddy Shriver Sarcoma initiative has made a video presentation, "A Forgotten Cancer", that integrates information about sarcoma and the Team Sarcoma Initiative. You can access the video directly at http://www.liddyshriversarcomainitiative.org/Initiatives/TS%202007/forgotten.htm.

Ohio local group meets

The Ohio local group held its meeting on April 21. In attendance were, from left to right: Bob Hall, Helen Hall, Kaye Thompson, Terry Thompson, Jeannette McIntosh and Russell McIntosh. The Ohio group is spearheading GIST awareness by distributing pamphlets to their oncologists. We encourage other patients to do this too. If you are interested in obtaining materials, please contact the Life Raft Group at liferaft@liferaftgroup.org.

GLEEVEC

From Page 1

ing a drug like Gleevec to try to prevent recurrence is called adjuvant treatment. The interim analysis showed a 97 percent recurrence-free survival rate for the Gleevec group as opposed to an 83 percent survival rate for those on the placebo. While it has been known for several years that Gleevec is an effective first-line treatment for GIST, this is the first reported data demonstrating that Gleevec is also effective in preventing GIST recurrence following surgery. There was no difference in overall survival for patients in the two study groups.

We look forward to seeing the data from this trial analyzing any differences between different subgroups based upon mutational type and between different clinical profiles based upon original tumor size. The latter analysis may provide some guidance for adjuvant treatment based upon the patient's risk of recurrence, to the extent that is driven by tumor size.

Although the trial protocol also permitted patients whose primary tumor resection did not result in clear margins, we do not know if there were sufficient numbers of such patients enrolled to permit meaningful analysis.

Amongst the critical questions this clinical trial was not designed to answer:

Note: Despite the fact that neither patients nor their physicians were told whether they were assigned to a placebo or treatment group some may have guessed which group they were in based upon whether they were experiencing any of the well known side-effects of Gleevec. Some on Gleevec experience no side-effects and some on the placebo report side-effects, making this an imperfect system. But what is not known is whether any patients who correctly concluded that they were on a placebo left the clinical trial in order to secure definite access to Gleevec.

- How long should patients remain on Gleevec on an adjuvant basis? This trial was for one year. We hope that an ongoing Scandinavian study, which is comparing one to three years, will provide more answers.
- Would a dosage higher than 400mg of Gleevec make any difference? As there is no ongoing clinical trial designed to answer this question, we are planning to use the Life Raft Group GIST patient registry to try to find some information on dosage and adjuvant treatment.
- Would Gleevec help to prevent recurrence following surgery for metastatic GIST? Once again, as there is no ongoing clinical trial designed to answer this question, we are going to use the Life Raft Group GIST patient registry to try to shed some light on this question.

Trial investigators are in the process of notifying all the clinical trial patients about these developments. Patients that were receiving a placebo at the time the trial ended will be given the opportunity to receive one year of Gleevec at no cost. It is not clear as we go to press whether placebo patients who completed the one year clinical trial period prior to the end date will also be offered free Gleevec.

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