

Novartis CEO: Glivec should clear hurdles

By Daniel Vasella, M.D.
Chairman and Chief Executive Officer,
Novartis

“Dear Dan,
“You were going to write something for our Life Raft Group Newsletter.
“How about by the end of this week?
“Regards,
“Norman”

This was the message I got recently from Norman Scherzer and a few days later, as I had not responded, he reminded me of the deadline.



Dr. Daniel Vasella.

Norman and I have never met. But I know who Norman is and he knows who I am. The first time we wrote to each other it was by letter, but now we send each other short e-mails and the communication is immediate.

There is real power in the Internet as a source of information, but especially as a way to connect with each other, to share experiences, knowledge and help each other. The Internet makes all this possible. These connections across countries and time zones, with English as the common language, has enlarged our horizons, and I would assume this has been of substantial help for all of you. Those who are suffering from a rare disease gain from the sense of community, and there is encouragement in that one may get the feeling that one is not alone, not the only one with a certain condition. Discovering that there are others, getting organized and helping each other with informa-

See Vasella, Page 4

Battling GIST with Glivec (STI571)



LIFE RAFT GROUP

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Real progress with real people, thanks to the global community

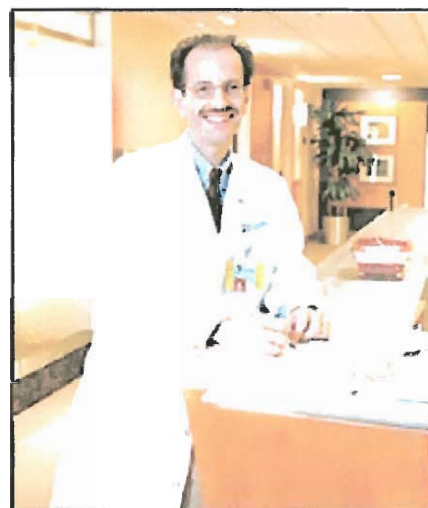
Editor's Note: Dr. Demetri is one of the three principal investigators for the U.S. phase II clinical trial of STI571 for GIST, and is overall principal investigator on the new phase III clinical trial being performed under the auspices of the U.S. National Cancer Institute and the NCI-Canada. He is considered one of the leading sarcoma specialists in the world.

By George Demetri, M.D.

Co-director, Center for Sarcoma and Bone Oncology, Dana Farber Cancer Institute and Harvard Medical School

We live in interesting times. From the south of Australia to the northernmost regions of Scandinavia and Finland, from Oregon to Boston to Belgium and Holland, patients, friends and families are seeing first-hand the power and grace of molecular medicine. With remarkable speed, we are all sharing our observations, learning as we go, and forming a global community. It is truly an honor and a privilege to be part of this near-miraculous series of events.

Dr. Brian Druker's laboratory bench was one floor above mine when we were both finishing our training in Boston in the late 1980s. I will always remember the selfless manner in which he would share antibodies he had developed with any scientist who asked for them — importantly, these antibodies would be some of the very tools which would enable him to rec-



Sarcoma specialist Dr. George Demetri.

ognize the effects of enzyme inhibitors such as STI571. I consider myself fortunate indeed to know him and to collaborate with him in the expanded development of STI571 for GIST.

It was only two short years ago that I found myself at an international meeting with other sarcoma experts worldwide, all of us bemoaning the lack of useful therapies for the gastrointestinal sarcomas known as GISTs. Although we had some ideas in 1999, they could not be translated into testable therapies. Through hard work and teamwork globally, we are now seeing that change, faster than we ever could have dreamed possible.

The project now seems to have taken

See Demetri, Page 2

Demetri

From Page 1

on the energy which must have imbued the early days of the space program (remember when people actually got excited about watching rocket launches, when the Apollo program was providing a sense of hopefulness for the world ...?) -- all of us, together, are now exploring a different frontier, an inner universe too small to see but intricately well described by the schematics of molecular modeling. This is the world of enzymes and cell biology, of regulatory systems gone astray, and cancer cells wreaking havoc in the otherwise tightly controlled order of the human body.

We are learning together the fact that our ways of conceptualizing the problems of cancer may, occasionally, be right on target. We now know that CML cells have rogue signals which stem from the mutant enzyme product of the BCR-ABL fusion gene: Dr. Duker and his colleagues have convincingly demonstrated with STI571 that by shutting these signals down, the CML cells which rely upon those signals can disappear. Studies from laboratories led by scientists such as Kitamura, Fletcher, Miettinen, Tuveson and others also show that the majority of GIST cells suffer from a related, though distinct, enzyme disorder. In these cells, a different enzyme known as KIT becomes, shall we say, hyperactive. Unruly. Troublesome. It continually signals the cells, and the cells grow and never seem to stop in a normal way. Stop the signaling with STI571, and for many GIST cells, the normal controls seem to resume. We are all learning together what that means in clinical terms, as well as in human terms. This is not a mouse model. This is real life, for real people.

Perhaps one of the most exciting aspects of this work is the renewed sense of enthusiasm and justifiable hopefulness this all has brought to the world of medical research. We now see the

possibilities, we can envision the future strategies to explore other targets. S(ignal) T(ransduction) I(nhibitor) 571 is just that -- the 571st compound in a "chemistry set" of compounds aimed at inhibiting a class of enzymes. How many other such compounds are already sitting in laboratories and medicinal chemistry departments around the world? A lot. Might some of these hold promise for other types of diseases? Of course. Many of our younger trainees have told me that this reinforces the notion that science can lead to powerful therapies. So many others have yet to be discovered, have yet to be developed.

We are all grateful to Novartis for making the investments to scale up production of STI571 (now pronounced as GLEE-vec, although spelled "Glivec"). One can imagine a take-off on the well-known Visa advertisements:

- Vats: 5 million Swiss francs
- Chemists: 10 million Swiss francs
- Regulatory costs: 20 million Swiss francs
- Saving lives and proving a new paradigm: priceless

We stand together in this work as one global community against the common enemy of disease. Even if a rare disease, the global reach of the excitement has galvanized doctors, patients, and families to seek out novel options. This is particularly important given the negative tone often taken to describe clinical research in the lay press in recent months. There is no doubt that clinical research must protect human subjects, but we should all be supporting well-designed and promising clinical research so that patients now and future generations can benefit.

It is truly heartening to see the tremendous enthusiasm with which the GIST community has embraced clinical

research to provide insights to this disease. By working together on a worldwide basis, we will quickly gain the experience needed to understand better how best to approach this disease. And this will be a model for the study of other diseases, no matter how rare or how daunting they may be.

The reach of the Internet to bring together people is extraordinary. I hear every day about patients directed to access trials from other families and patients half a world away. The era of patient and family empowerment is most certainly arrived, and we physicians can welcome the collaboration of our patients and their supportive caregivers.

I cannot express in words the depths to which this work has moved me. I consider myself very fortunate to have this collaborative team with whom to work. I would like to list here many of the individuals without whose contributions we would not have been where we are today (many more have been a part of this work, but space would allow only a partial listing):

Boston Team STI: David Tuveson, Jonathan Fletcher, Sam Singer, Chris Fletcher, Travis Quigley, Amy Potter, Priscilla Merriam, Adriana Torre, Joan Canniff, Jeff Morgan, David Ryan, David Harmon, Milos Janicek, Annick van den Abbeele

Oregon Team STI: Brian Druker, Mike Heinrich, Charles Blanke, Chris Corless

Philadelphia Team STI: Meg von Mehren, Burt Eisenberg

Finland Team STI: Heikki Joensuu, Peter Roberts

Novartis Team STI: Sasa Dimitrijevic, Sandra Silberman, David Parkinson, Greg Burke, Renaud Capdeville, Alex Matter, Elisabeth Buchdunger

European Team STI (separate projects, but we are trying to share data and ideas globally to move the field ahead as quickly as possible): Allan van Oosterum (Leuven, Belgium), Jaap Verweij (Rotterdam, the Netherlands), Ian Judson (London, England).

Survey: Gender plays role in side effects

By Norman Scherzer
with Janet Hendrickson

The February newsletter presented drug response rate data for the first 16 Life Raft members completing three months on the ST1571 (Glivec) trials. More than 85 percent reported significant tumor shrinkage, with more than half of the participants experiencing 50 percent or greater shrinkage by their third month. This group was in the Phase II trials and on a randomly assigned dosage of either 400 or 600 mg per day.

As for side effects, each Life Raft Group member patient was asked to list up to three significant side effects and to rank each on a scale of low, medium or high. Where reported side effects were similar to problems experi-

enced before starting the trial, patients were asked to describe the differences since beginning to take Glivec. Non-respondents were aggressively followed up, the result being an enviable 100 percent response rate.

Of the 34 member patients surveyed, all have been on the trial for at least one month, and 27 (79 percent) on the trial more than three months. Excluded from the survey was anyone on the trial less than one month (one person with serious liver toxicity who was removed from the trial after two weeks was part of this excluded group).

Also excluded were a few member patients who have been on 800 mg per day because their numbers were too small to be statistically meaningful. Where there was a dosage change, the starting dosage was used, but respon-

dents were asked to report their side effects both on the initial dosage and on the subsequent dosage. This data is based upon the initial dosage.

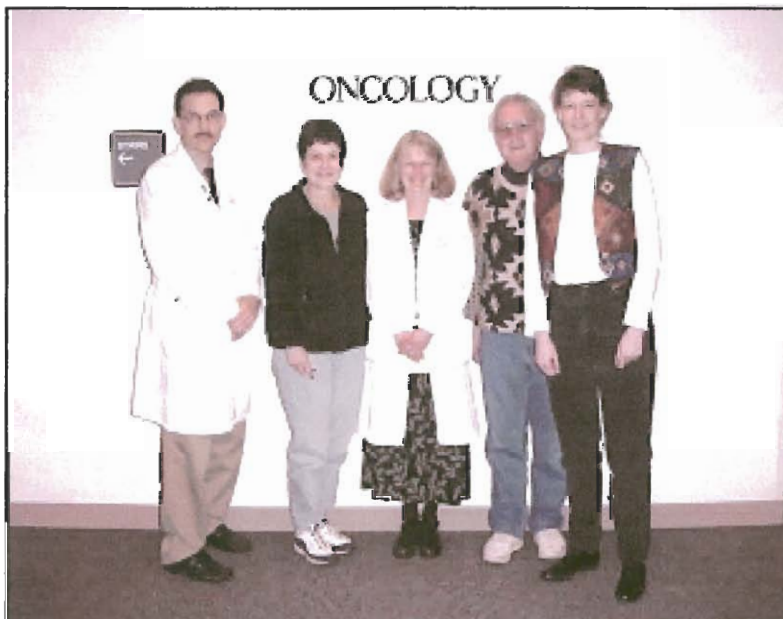
Caveats: *The authors are not professional researchers and the data collected is subject to the twin demons of inaccuracy and distortion. Although we tried to be careful, we should be cognizant that patient-based reporting may not always be accurate. Also, there is no way of knowing how representative we are of the clinical trials as a whole. Finally, beware the pitfalls of small numbers. A small change can have a large statistical effect.*

Added to this caveat is that, unlike the earlier response survey where patients were repeating the results they received from their trial doctors, this survey of side effects is based directly and entirely upon the patient's own assessment. It is a snapshot of the side effects experienced at a point in time. Patient assessments of severity are somewhat subjective, as is the process of communicating such observations. Finally, the fact that there are no placebos, nor control groups, makes the process of measuring side effects more difficult. This is likely to be a problem for the clinical researchers as well.

On the other side of the coin, however, it can be argued that side effect data provided by patients whose anonymity and confidentiality is protected may well be more accurate than that provided to the trial doctors. This may be particularly the case when describing the severity of side effects. In addition to the tendency of some to tell the doctor that things are better than they really are — particularly given the euphoria of dramatic drug responses — there is also a real concern by some that reporting certain side effects to the trial doctor may jeopardize

See Side effects, Page 5

Life Rafter's meet in Portland



Meeting April 5 at Oregon Health Sciences University in Portland were, from left, Dr. Charles Blanke, principal researcher (he hadn't had his Kona coffee yet that morning); Joan A., trial nurse Lora Wilson, Gary Kirk of California, and Marina Symcox of Oklahoma.

Vasella

From Page 1

tion and support is often critical, both physically and mentally.

Briefly, after the first results of the Glivec therapy in the first trial with 31 patients suffering from CML became known, I received a petition signed by hundreds of patients. They requested faster access to Glivec. We were acutely aware of this need and the tremendous therapeutic potential of Glivec. These became critical factors driving us to faster development of this breakthrough product. Concern for patients' needs encouraged us to make early investment commitments and to ask colleagues in production and development to do their utmost to rapidly move the product ahead. They achieved a slightly impossible task, working around the clock seven days a week, and they felt happy and proud to make a positive impact on the lives of many people.

Of course, this would not have been possible without our researchers, who — sometimes against internal company resistance — persisted in moving Glivec ahead. It would not have been possible without the crucial vision and determination of Dr. Brian Druker. It would also have been impossible without people like Norman and many of you, who go out of their way, routinely, day after day, to persist and overcome obstacles in order to make things happen.

Recently there were three articles on Glivec in the New England Journal of Medicine, two on CML by Dr. Druker and his research colleagues and one on GIST by Dr. George Demetri, as well as an editorial in this most prestigious medical publication. These scientists and physicians deserve our congratulation and admiration for pushing the boundaries of medicine forward to the benefit of so many patients.

The regulatory review has started in many countries, and the FDA has granted us an expedited review. We

will hear about their decision within six months. This leaves Novartis little time to deal with some difficult questions. The most difficult one is that of price. We made substantial up-front investments in Glivec. In addition, as Glivec is today only suited for a rela-

‘As some of you may know, but for reasons which escape my understanding, Medicaid does not reimburse oral cancer drugs. So there will be patients who cannot afford the therapy.



At the same time it would be unethical to leave uninsured and indigent patients without access to Glivec. So we will put in place a patient support program ...”

**Dr. Daniel Vasella,
Novartis**

tively small patient population, this means we will have to charge a relatively high price to recoup our costs and to allow us to continue to develop the drug, testing to determine if it would be effective in saving the lives of patients with other cancers. Our price will be lower than the most expensive cancer therapies, but for many it will still be a high price.

As some of you may know, but for reasons which escape my understanding, Medicaid does not reimburse oral cancer drugs. So there will be patients who cannot afford the therapy. At the same time, it would be unethical to

leave uninsured and indigent patients without access to Glivec. So we will put in place a patient support program, hoping that through this measure people will not be denied therapy for financial reasons. At the same time, we hope that — in view of the relatively small number of patients — insurers and governments will quickly agree to cover this innovative and life saving therapy.

On our side we will continue to investigate Glivec's efficacy, looking next to possibilities in additional cancer types. And if we are successful in increasing the number of cancer indications and with it the usage among a broad range of cancer patients, we might be able to lower the price over a period of time.

So, there are many hurdles to leap when a new drug is born. But in the end, what counts is that it works, is well-tolerated and improves people's lives. I thank you all for having accepted Novartis as your partner and having encouraged us in moving forward speedily and with confidence. We will do whatever we can to continue our search to find ever better therapies to ease patients' suffering and save lives.

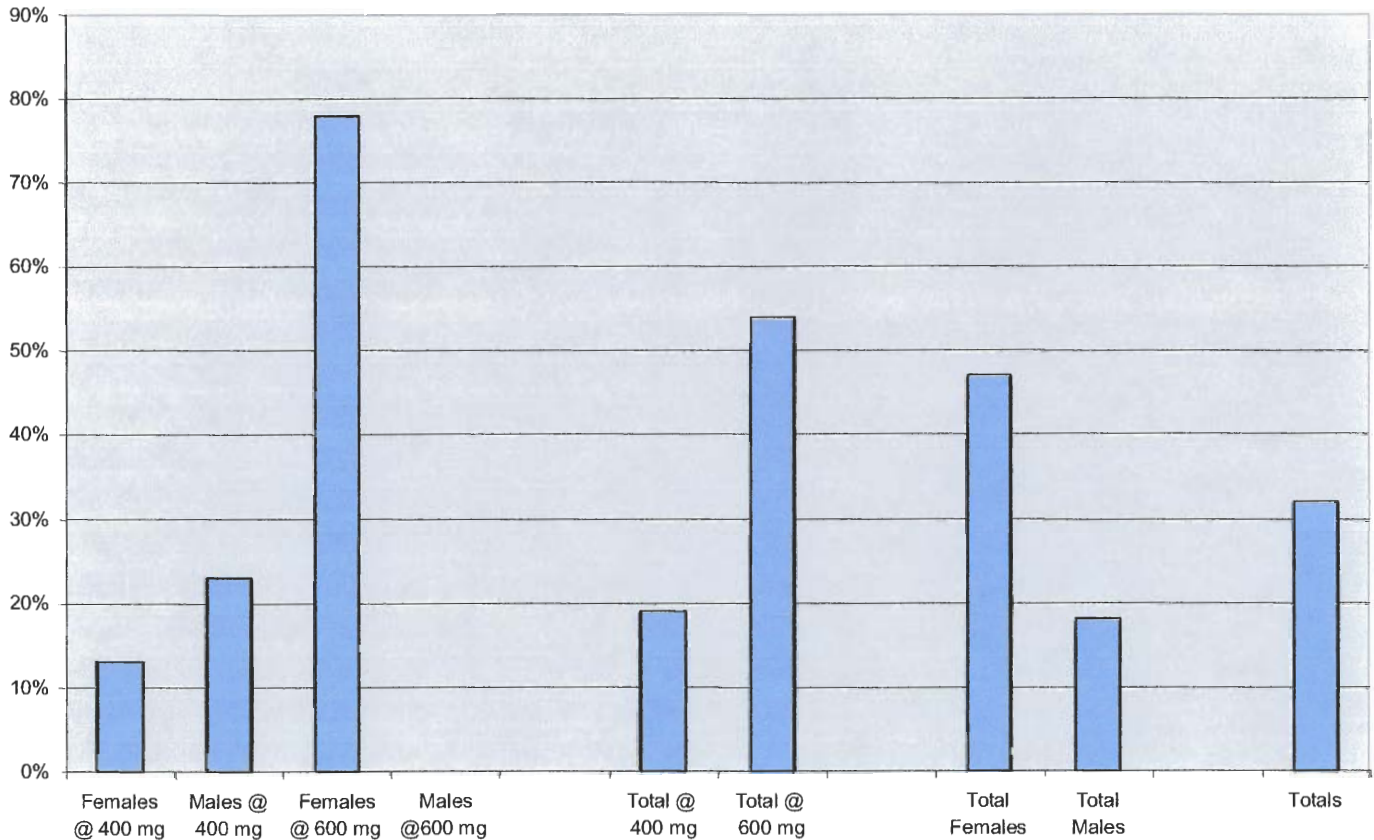
Editor's note: It looks like the Life Raft Group may have to launch a new effort — lobbying Medicaid to cover oral cancer drugs.

Want the newsletter sent via e-mail?

It comes as a PDF (portable document format) file attachment. You'll need the free Adobe Acrobat Reader installed on your computer. You'll find it at www.adobe.com/products/acrobat/readstep.html Just click "get Acrobat Reader free" and follow the steps; it's easy.

To subscribe, e-mail the newsletter editor at linda@interpac.net

Chart 1: Percent Reporting Severe Side Effects



Side effects

From Page 3

their staying in the trial. Given that there is no other treatment alternative for GIST patients other than Glivec, this can be a very real survival issue.

There was one situation where a patient reverted to a different dosage on his/her own without telling the trial doctor. (This article reports the actual dosage being used and, although such behavior is not encouraged nor condoned, that person’s confidentiality will be maintained.)

The 100 percent response rate lends credibility to this data. Finally, although the author of this article is not a professional researcher, he is a public health professional with many years of disease management experience with the Centers for Disease Control and as assistant commissioner of health for New York city.

Table 1— Trial participants reporting side effects

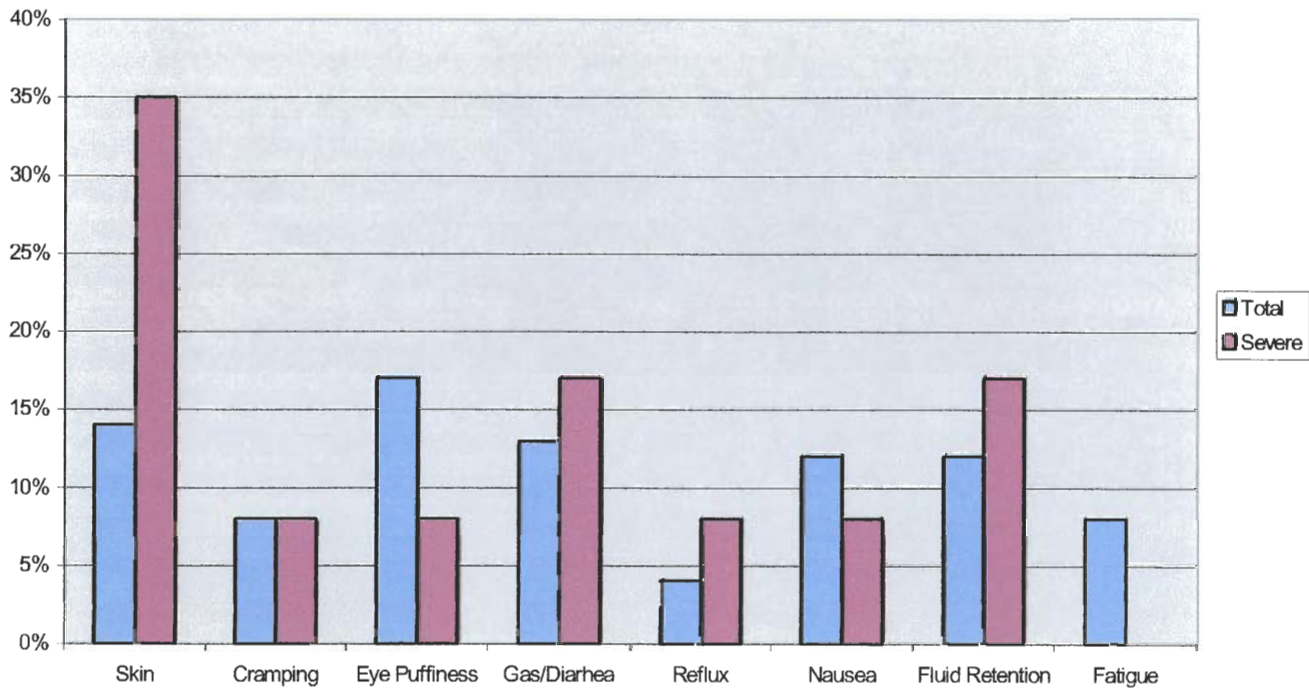
<i>A Total Of 34 Trial Participants Reported 78 Side Effects, With 11 Ranking One or More As Severe</i>			<i>No. Side Effects Reported Per Trial Participant</i>	
Categories Of Participants	% Of Total Participants	% Reporting Severe Side Effects	Total Side Effects	Severe Side Effects Only
Females @ 400 mg	24%	13%	2.00	.13
Males @ 400 mg	38%	23%	2.31	.31
Females @ 600 mg	26%	78%	2.33	.78
Males @ 600 mg	12%	-0-	2.75	-0-
Totals, 400 mg	62%	19%	2.19	.24
Totals, 600 mg	38%	54%	2.46	.54
Totals, Females	50%	47%	2.18	.47
Totals, Males	50%	18%	2.41	.24
Grand Total	100%	32%	2.0	.35

The Results: A total of 34 trial participants reported 78 occurrences of side effects, most of them falling into nine categories, with 32 percent rank-

ing one or more as severe (high). Although, as might be expected, there were more side effects reported by

See More side effects, Page 6

Chart 2: Distribution Of Side Effects By Category



More side effects

From Page 5

those on the 600 mg compared to the 400 mg dosage, the difference in the number of side effects per participant was only 2.46 at 600 mg compared to 2.19 at 400 mg, (a difference of only 12 percent).

When a distinction is made about the severity of side effects, however, the difference increases dramatically to 125 percent (.54 per participant at 600 mg versus .24 at 400 mg).

Dosage Changes: Another way of measuring the relationship of side effects to dosage is to evaluate changes that occur after dosage levels are changed. There were three respondents in the study group who had their drug dosage lowered from 600 to 400 mg. All three reported a subsequent reduction in the severity of their side effects. In addition, there were three respondents who reported an increase in dosage from 400 to 600 mg. All three reported a subsequent increase in

Table 2. Types Of Side Effects Reported

	78 Total Side Effects	12 Severe Side Effects
Skin	14%	35%
Cramping	8%	8%
Fatigue	8%	-0-
Eye Puffiness	17%	8%
Gas/Diarrhea	13%	17%
Reflux	4%	8%
Nausea	12%	8%
Insomnia	1%	-0-
Fluid Retention	12%	17%
Miscellaneous *	13%	-0-
	100%	100%

* Includes watery eyes, blurred vision, headache, dizziness, hunger pangs, loss of appetite, metallic taste.

the severity of their side effects.

Gender: What may not have been expected was that gender was such a significant predictor of side effects. On the one hand, males were some-

what more likely to report side effects — 2.41 per male patient compared to 2.18 per female patient, a dif-

See Even more, Page 7

Rafters rendezvous at Dana Farber in Boston



Above is Cordelia S. (on far right), with her husband Rodrigo (they're the couple everyone at D-F said looked like movie stars) with Cordelia's sister Claudia and mother Virginia.



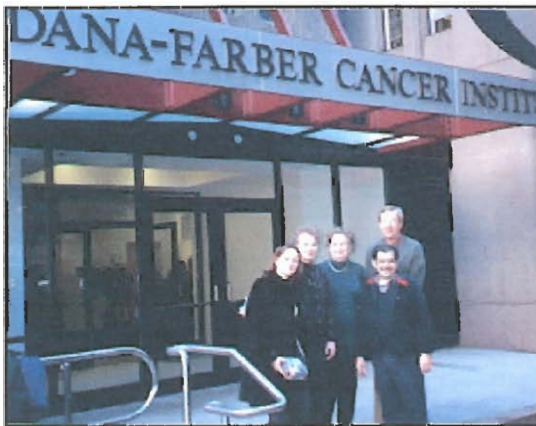
At right, that's Peggy and Chuck Korte of Raleigh, North Carolina who met other Life Rafters in March.

*Photos courtesy
Cynthia Whitson*

In photo at right is Evelyn D. (left) with daughter Penny Duke, membership coordinator for the Life Raft Group.



In front of Dana-Farber in Boston are, from left, Cordelia, Cynthia, Evelyn and Chuck. The shorter guy in front is a prospective member they happened to meet.



At left is Cynthia Whitson and her wonderful husband Jerry (that's Chuck Korte in back at right)

Even more

From Page 6

ference of 11 percent. The opposite was true, however, when looking at severe side effects, with females twice as likely as males to categorize side effects as high. (See Table 1 on Page 5).

Chart 1 (Page 5) illustrates this quite clearly. Gender is almost as significant as dosage levels in predicting severe side effects. Females at the higher dosage of 600 mg have a dramatically greater chance of experiencing more severe side effects. Males at 600 mg report no severe side effects.

Types Of Side Effects: The types of side effects reported mirror those reported in the trials for chronic myelogenous leukemia. Added to this assessment is a determination of severity. (See Table 2 on Page 6)

Chart 2 on Page 6 lays out the major categories of side effects. When severe side effects only are examined, three categories — skin, fluid retention and gas/diarrhea — account for 69 percent of the total side effects ranked as high. Noteworthy is that all of the severe skin and fluid retention

problems were reported by females.

It is also noteworthy that most respondents report that their side effects seem to get better over time.

Editor's note: Norman Scherzer, Life Raft Group coordinator, prepared this article. The data was provided by the members of the Life Raft Group and tabulated and entered into a spreadsheet by Janet Hendrickson, Life Raft Group medical librarian. Janet is to be credited for achieving a 100 percent response rate.

THE LIFE RAFT GROUP

Coordinator: Norman J. Scherzer
e-mail: normanjs@bellatlantic.net
List Management: Mia B.
e-mail: mebmcb@peoplepc.com
Medical Librarian: Janet Hendrickson.
e-mail: delmar@visi.com
Membership: Penny Duke.
e-mail: pduke@magicnet.net
Newsletter Editor: Richard Palmer
e-mail: linda@interpac.net
Treasurer: John Poss
e-mail: jcpoos@swbell.net
Medical/Scientific Team
Barry Jordan, M.D.
e-mail: bgjordan@attglobal.net
Jerry Call.
e-mail: jcall10365@aol.com
Marina Symcox.
e-mail: keith-symcox@bamard.utulsa.edu
Gary Golnik.
e-mail: ggolnik@earthlink.net

Who are we and what do we do? We are a group of GIST patients and caregivers (spouses and others) in the STI571 (Glivec) clinical trials who have come together to share our experiences and support each other. Persons not in the trial are encouraged to seek support from the broader leiomyosarcoma (LMS) community. We focus on side effects, symptoms and other drug-related issues. Members correspond privately to each other and to the wider group as appropriate.

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. To assist in that goal, the secure e-mail listserv does not include professional members of the various study sites. However, this newsletter does serve as an outreach and is widely distributed. Hence, all items in the newsletter are edited to maintain the anonymity of members, unless members have granted publication of more detailed information.

Method: Our primary means of communication is through a confidential, secure listserv operated by the Association of Cancer Online Resources, ACOR (www.acor.org).

Disclaimer: We are patients and caregivers, not doctors. Any information shared among the group should be used with caution, and is not a substitute for careful discussion with your doctor.

Newsletter note: Read at your own risk! Every effort to achieve accuracy is made, but we are human and errors occur. Please advise the newsletter editor of any errors you may find.

STI571/GIST trials at 200+ U.S. hospitals

After remarkable success in the phase II trials at three cancer centers in the United States, Glivec (STI571) has entered phase III trials at nearly 300 cancer centers.

These clinical trial sites can be found on the Web at ClinicalTrials.gov, a service of the National Health Institutes, (see <http://www.clinicaltrials.gov>).

Listed are 208 U.S. sites, 77 in Canada, two in Puerto Rico, one each in England and South Africa.

NOT on the ClinicalTrials site are the following, provided by Life Raft member Ophir:

Prof. Dr. Van Oosterom - Department of Oncology - Universitaire Ziekenhuizen, Leuven, Belgium.

Prof. Jaap Verweij - Department of Oncology - Rotterdam Cancer Institute

and University Hospital - Rotterdam, The Netherlands.

On the Novartis Web site is the following: "Novartis has expanded its trials ... based on a collaborative, worldwide effort to treat more than

1,000 patients and will include clinical trials in conjunction with cancer cooperative groups in the United States, Canada, Europe, Australia, and potentially other organizations in Latin America and throughout the world.

Who's new to the Life Raft Group

Welcome to all new members of the Life Raft Group.



Ronna L.

Abbas P., patient whose wife and son are already on the list.

Reed B., whose wife Amy is on the trial.

Carolyn L. and husband/caregiver Frank, on the trial in Illinois.

Jerry R. and wife/caregiver Pamela on the trial in Texas.

Nancy W., on the trial in Illinois.

Steve L., whose mother Eleanor is on the trial in Arizona.

Nancy B., whose father Henry L. is on the trial in Texas.

Dan C., who is on the trial in New York.

Jeanette and husband/caregiver Bernie S., on the trial in Canada.