Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

May 2009 | In memory of Howard Kemp & Joseph Mirenda, III | Vol 10, No. 5

As the days spring forward, Bannon reflects on her life

By Brenda Bannon
LRG Member

As March ends and April begins, I realize that I have begun my eighth year of knowing that I am living with GIST cancer… and life is good. Seven years ago, misdiagnosed with Neuroendocrine tumors and meeting with a local oncologist, I sat and listened to her... this doctor, this woman … calmly and quietly tell me I was going to slowly die and there was nothing she could do for me. She gently explained to my mom, my sister, my husband and I that although she would supply me with pain medication and other palliative care, I would grow more and more fatigued, experience more and more pain and slowly deteriorate until I died. She didn't think I would see age 40. At the time, I was 36, with three sons, the youngest of whom was 15 months old.


BANNON

As most of you can understand, when we left her exam room and walked in silence side by side down the hall, I asked incredulously, "Did she just say I was going to die?" My loved ones quietly responded in the affirmative. After a moment, I retorted, "Well, she's fired! I can't die!"

In that moment, I decided to live. It's the decision that every single person who hears those dreaded words is forced to make, even while still amid the chaos of his or her entire life being upended. Many choose not to make that decision at that moment, but in doing so have unwittingly opted to die.

I think of that day often, wondering how many cancer patients all

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HSP90 inhibitors and GIST: why this target could work

By Dr. Sebastian Bauer, West German Cancer Center &
Dr. Jonathan Fletcher, Brigham & Women's Hospital
LRG Research Team

Imatinib has revolutionized the treatment of unresectable GIST, with remarkable remissions in most patients, even in the face of widely metastatic disease; the recent worldwide approvals of this agent in the post-surgical adjuvant setting also has promise to improve the outcomes of patients further. This clinical advance is all the more remarkable in that metastatic GIST was previously regarded as among the most untreatable, incurable forms of sarcoma. Nonetheless, as we have learned in the past eight years, most GIST patients eventually develop resistance towards imatinib and that further improvements in our therapeutic approach are needed to achieve the ultimate goal of a cure for all.


BAUER


FLETCHER

One of the major mechanisms for imatinib resistance is the emergence of GIST cells that harbor secondary mutations of the KIT kinase domain [1]. While primary mutations are usually found next to the cell membrane, kinase domain mutations are located in the section of KIT that transfers energy (in the form of phosphorylation) to its downstream signaling intermediates. These secondary mutations have a major impact on the effectiveness of direct KIT inhibitors (i.e. imatinib) in binding and inhibiting KIT and PDGFRA oncoproteins in GIST cells. So far, more than ten different secondary mutations have been found in patients with imatinib-resistant GIST. Imatinib perfectly fits into the Adenosine triphosphate (ATP)-binding pocket, the docking station for the ATP-"battery packs", in mutant KIT with primary mutations only. Secondary mutations still allow ATP to provide energy for KIT to function but decrease to vari-

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Infinity's IPI-504 Phase III trial closes

See Jim Hughes' Clinical Trial update on page 3 for more details about the trial.
You can also read more about HSP90 inhibitors in Drs. Sebastian Bauer & Jonathan Fletcher's article above.

Tips from the Raft: A GIST 'vet' passes on her secrets

By Louise Ladd
LRG Member

Often, in the LRG email community, members have been known to offer suggestions on everything from what to bring with you to the hospital to managing side-effects. Louise Ladd is one of those people and as a 12-year GISTer has picked up many tricks along the way. We thought it might be helpful to repeat some of those tips here.

This picture was taken before Louise was diagnosed with GIST (with the granddaughter of the famed racehorse, Man O' War) as a promotion for her book series, "Double Diamond Dude Ranch".

I just picked up a new supply of Gleevec and it reminded me that I've been meaning to write in, especially for those who are fairly new to managing this cancer thing, with three little tricks I use that make life a bit easier. I think many of us old-timers probably use these ideas.

The first is simply a precaution. When I get a new supply of any meds I MUST take, such as Gleevec, I put two day's worth in an empty pill bottle. If the doctor is late ordering a refill or it's a holiday, or if my meds are held up for any reason, I have an extra 2 days before I need to panic. Makes life easier.

A few years ago I entered a list of all the meds & vitamins I currently take into my computer, with the dosage and frequency, divided into prescription and over-the-counter, plus daily or "as needed." I also list the antibiotics that don't go well with Gleevec (citing the source), and a warning in boldface about the two drugs that give me bad reactions.

Last, I list my Primary Care physician, oncologist and pain specialist with their phone numbers. It all fits on one sheet of paper. I update the list every few months. When I see a new doctor, I check to be sure the list is current, then print it out and hand it to them instead of trying to fill in their questionnaire. This way I don't have to keep it all in my head, which is already overworked, poor thing.

My third trick is another computer list, this one of my medical history, beginning with the rupture of my tumor in 1997. I very briefly state all the important events and update this list, also adding new events of significance, with the date, doctor's name and the hospital involved, if there is one. I also edit it for extra words, trying to keep the facts as succinct as possible. It now has spilled over onto a fourth page, no matter how hard I try to state, "Just the facts, Ma'am." I take this to every new doctor also, no matter what type of doctor he or she is.

The Life Raft Group

Who are we, what do we do?

The Life Raft Group (LRG) directs research to find a cure for a rare cancer and help those affected through support and advocacy until we do. The LRG provides support, information and assistance to patients and families with a rare cancer called Gastrointestinal Stromal Tumor (GIST). The LRG achieves this by providing an online community for patients and caregivers, supporting local in-person meetings, patient education through monthly newsletters and webcasts, one-on-one patient consultations, and most importantly, managing a major research project to find the cure for GIST.

How to help

Donations to The Life Raft Group, a 501(c)(3) nonprofit organization, are tax deductible in the United States.
You can donate by **credit card** at www.liferaftgroup.org/donate.htm or by sending a **check** to:
The Life Raft Group
40 Galesi Dr., Suite 19
Wayne, NJ 07470

Disclaimer

We are patients and caregivers, not doctors. Information shared is not a substitute for discussion with your doctor.

Please advise Erin Kristoff, the Newsletter Editor, at ekristoff@liferaftgroup.org of any errors.

Did you Know...

Sunday, June 7 is the 22nd annual observance of "National Cancer Survivors Day". Communities all over the world will host events like parades, carnivals and contests to celebrate life and honor the strength and courage of cancer survivors.
For great event ideas and step-by-step instructions, contact the National Cancer Survivors Day Foundation at info@ncsdf.org, or call (615) 794-3006.

May 2009 US clinical trials update

By Jim Hughes
LRG Clinical Trials Coordinator

Infinity IPI-504 Phase 3 RING trial in resistant GIST terminated:
Infinity Pharmaceuticals Inc. announced April 15 that it had elected to terminate the IPI-504 phase 3 RING trial in resistant GIST upon the recommendation of its independent data monitoring committee (IDMC). The IDMC's recommendation to halt the trial was based on an early review of safety data from the first 46 patients enrolled in the study, which showed a higher than anticipated mortality rate among patients enrolled in the treatment arm. Infinity also announced that patients participating in the trial would no longer receive IPI-504. The Life Raft Group continues to explore the options available for RING trial participants and will report additional details as they are available and can be verified. Patients who participated in (or were planning on entering) the RING trial and are now seeking options can call the LRG office at 973-837-9092 or email us at liferaft@liferaftgroup.org

Novartis Imatinib or Nilotinib Phase 3 first line advanced GIST now recruiting in US:
This is a large international trial designed to ascertain if nilotinib is a better therapy for newly diagnosed advanced GIST patients. GIST patients who have not received prior TKI (tyrosine kinase inhibitor) therapy will be randomly assigned to receive either imatinib or nilotinib. The primary goal is to determine progression-free survival in both groups. Sites are now open in Southern California (City of Hope), Austria, Canada, Spain and Thailand. This trial plans to accrue over 700 participants in North and South America, Europe, Africa and South-East Asia. And will be collecting data for over ten years.

First-line trials are for patients that have never had Gleevec before. The intent of these trials is to try to improve on the initial response to therapy.

Astex Therapeutics AT13387 Phase 1 HSP-90 inhibitor added for resistant solid tumors:
This phase 1 trial is designed to determine the maximum tolerable dose and the safety of AT13387. AT13387 is a small molecule HSP-90 inhibitor. It differs from IPI-504 in that it was designed specifically for HSP-90 inhibition. IPI-504 is a soluble refinement of the drug 17-AAG which in turn is a synthetic form of the antibiotic Geldanamycin. Geldanamycin has HSP-90 inhibition properties but also exhibits hepatotoxicity. Astex describes their fragmented drug design platform which they claim uses as starting points very small, low molecular weight, drug fragments. Astex asserts that these fragments have the potential to keep the overall complexity and molecular weight of each drug candidate low. Astex also claims that this results in "high ligand efficiency" and "results in drug candidates having lower molecular weight, reduced metabolic liability, improved target selectivity and ease of chemical synthesis." This trial is running at three closely related centers in the Longwood medical area of Boston. The Principal Investigator is Geoffrey Shapiro, MD, PhD and Director of the Early Drug Development Center at Dana Farber Cancer Institute (DFCI) a position similar to George Demetri's at the Sarcoma Center. We are publishing all contact information but would suggest contacting Dana-Farber first and coordinating participation with the Sarcoma Center.

"Preoperative and Postoperative Imatinib Mesylate Study in Patients With c-Kit Positive GIST" at MD Anderson:
This Phase 2 trial has stopped recruiting new patients and is now ongoing.

Mt. Sinai School of Medicine Added Sunitinib & Stereotatic Radiation Phase 2:
This trial will accept GIST patients. It is similar to a trial now running in Helsinki, Finland and another in Australia. Historically, GIST tumors have not responded to radiotherapy. Concurrent TKI therapy and the advent of newer radiation technologies may open the possibility of effectively treating selected tumors with radiation. This trial targets "oligometastatic disease". "Oligo" is a prefix meaning roughly "a few". A recent retrospective of 12 GIST patients treated with radiation therapy at the Royal Marsden in London was presented at the 2008 Connective Tissue Oncology Society (CTOS) conference. The poster concluded that "A dose of 30 Gy in 10# given over 2 weeks appears to give effective, durable symptom control with minimal toxicity and should be considered for selected patients with this diagnosis (GIST)."

Novartis Nilotinib Phase 2 Japan for resistant GIST:
This trial is ongoing and no longer recruiting participants.

Southwest Oncology Group (SWOG) Phase 3 Imatinib & Bevacizumab first line for advanced GIST:
We have added nine major cancer center sites currently recruiting to this listing. This trial adds and changes sites almost daily. Multiple Community Clinical Oncology Program (CCOP) sites are available across the United States. We have chosen to list the CCOP regional contact points and those major centers outside the CCOP. For complete site detail please visit the clinicaltrials.gov website and search for NCT00324987.

The Clinical Trials table has moved to its own publication!
You can find this bulletin at www.liferaftgroup.org/docs/ClinicalTrials/May2009.pdf
If you have any questions, please email us at liferaft@liferaftgroup.org.

U.S. News announces Best Hospital rankings

By Erin Kristoff
LRG Newsletter Editor

The *U.S. News & World Report* has announced its "Best Hospital" rankings for 2008. Now in its 19th year, *U.S. News* judges hospitals, not on routine procedures, but in difficult cases across an entire specialty.

Out of 5,453 hospitals (Military & Veteran's hospital data are unavailable), only 170 scored high enough to be included in the list. Of that 170, only 19 were able to make the *U.S. News* "Honor Roll", which is the list of hospitals that ranked at or near the top in six or more specialties.

Factors involved in ranking include:

Reputation. For 2008, a random sample of 200 physicians for each of the 16 specialties was drawn from the American Board of Medical Specialties database. They were asked to list five hospitals they consider among the best in their specialty for difficult cases, without taking into account cost or location.

Mortality index. This ratio defines the ability to keep patients alive. It compares the number of Medicare inpatients with certain conditions who died within 30 days of admission in 2004, 2005, and 2006 with the number of deaths that would have been expected after adjusting for severity. An index number below 1.00 means the hospital did better than expected; a number above 1.00 means the hospital did worse than expected.

Other care-related factors. This information came from various sources, most prominently the American Hospital Association's 2006 survey of member and nonmember hospitals. It includes technology, volume, nurse staffing, and other patient-related information.

For the full list of ranked hospitals, a more detailed description of the ranking process, as well as a more in-depth look at each hospital's scores (e.g., mortality index, ratio of nurses to patients and patient services) go to www.usnews.com/directories/hospitals/index_html/specialty+IHQCANC/

Best Hospitals for Cancer	Reputation (%)	U.S. News Score
1 University of Texas M.D. Anderson Cancer Center, Houston Houston , TX	64.1	100.0
2 Memorial Sloan-Kettering Cancer Center, New York New York , NY	59.8	93.3
3 Johns Hopkins Hospital, Baltimore Baltimore , MD	33.4	66.6
4 Mayo Clinic, Rochester, Minn. Rochester , MN	27.0	60.8
5 Dana-Farber Cancer Institute, Boston Boston , MA	28.6	49.4
6 University of Washington Medical Center, Seattle Seattle , WA	16.4	47.7
7 Massachusetts General Hospital, Boston Boston , MA	13.3	43.5
8 University of California, San Francisco Medical Center San Francisco , CA	13.0	40.7
9 Stanford Hospital and Clinics, Stanford, Calif. Palo Alto , CA	11.5	39.1
10 Ronald Reagan UCLA Medical Center, Los Angeles Los Angeles , CA	7.2	38.7

The U.S. News "Honor Roll". The order is based on points—a hospital earned 2 points for ranking at or close to the top in a specialty, 1 point if ranked slightly lower.

Other hospitals of interest to GISTers include: The Cleveland Clinic (13), Fox Chase (15) & the Moffitt Cancer Center (16)

1	Johns Hopkins Hospital, Baltimore 30 points in 15 specialties
2	Mayo Clinic, Rochester, Minn. 28 points in 15 specialties
3	Ronald Reagan UCLA Medical Center, Los Angeles 25 points in 14 specialties
4	Cleveland Clinic 25 points in 13 specialties
5	Massachusetts General Hospital, Boston 24 points in 12 specialties
6	New York-Presbyterian Univ. Hosp. of Columbia and Cornell 22 points in 12 specialties
7	University of California, San Francisco Medical Center 21 points in 11 specialties
8	Brigham and Women's Hospital, Boston 18 points in 11 specialties
8	Duke University Medical Center, Durham, N.C. 18 points in 11 specialties
10	Hospital of the University of Pennsylvania, Philadelphia 18 points in 10 specialties
10	University of Washington Medical Center, Seattle 18 points in 10 specialties

HSP90

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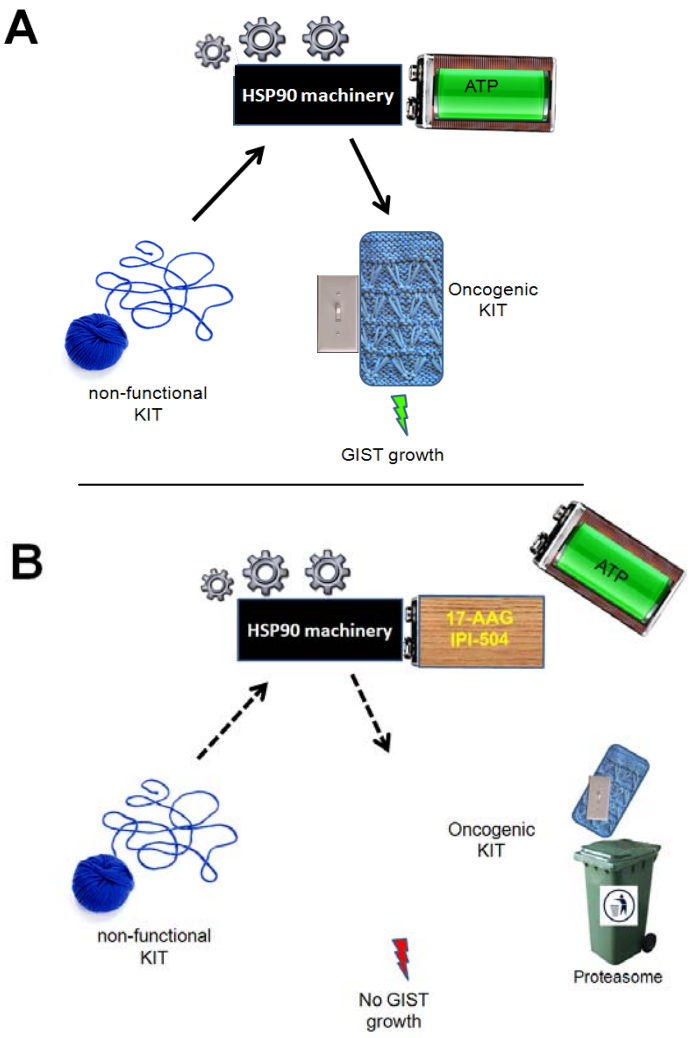
ous degrees the capacity of imatinib to compete with ATP.

Using the large inhibitor libraries used in drug development, several inhibitors were identified that do a better job than imatinib in inhibiting mutant KIT containing secondary mutations. However, none of these drugs (e.g. sunitinib, nilotinib, dasatinib or sorafenib) inhibit all mutations and especially mutations in the kinase-loop part of the kinase domain, which seem to be specifically difficult to inhibit with this class of KIT inhibitors. In addition, the efficacy of these second generation KIT inhibitors is hampered by the fact that different secondary mutations can occur within the same patient [2]. This explains why we often see "mixed responses" in patients treated for imatinib-resistant GIST. While some metastases shrink, presumably with favorable secondary mutations, others continue to grow despite treatment. A solution to this problem of genomic heterogeneity might either be a combination of several KIT inhibitors or a single drug that inhibits KIT regardless of the type of secondary mutation.

Mast cell disease or mastocytosis is a chronic hematological disease that is characterized by the presence of too many mast cells. As in GIST, the growth of these cells is often driven by constitutively activated KIT, which often harbors mutations in the KIT kinase-loop. In 2004, researchers from the National Cancer Institute (NCI) showed that a drug called 17-AAG, or 17-Allylamino-17-demethoxygeldanamycin, effectively inhibited KIT at low doses even in mast cells that contained the kinase-loop mutation, D816V. Notably, this particular KIT mutation causes resistance to imatinib in a subset of GIST patients. It has been estimated that inhibition of the D816V mutant KIT by imatinib would presumably require doses of more than 10 grams per day, which cannot be given to patients.

Inspired by this work, we investigated 17-AAG as a potential KIT-inhibitor in GIST cells and found – similar to the aberrant mast cells—GIST cells harboring mutant KIT were highly sensitive to 17-AAG [3]. At the same time, a new water-soluble derivative of 17-AAG called IPI-504 (now known as retaspimycin) [4-5] was about to enter clinical trials. This fortunate availability of a clinically useful compound allowed the treatment of a first GIST patient by our clinical colleague, Dr. George Demetri, of Dana Farber Cancer Institute, only few months later. The initial results were promising, and in short order a worldwide multicenter phase III trial (called the RING trial, for "Retaspimycin In GIST") was begun in an attempt to rapidly prove the effectiveness of this therapeutic approach in patients with imatinib- and sunitinib-refractory GIST.

Figure 1



What is 17-AAG and why is HSP90 inhibition a therapeutic opportunity in GIST?

In 1970, researchers searching for new antibiotics first described a new bacteria strain (Streptomyces hygroscopicus var. geldanus) that they found in the soil of Kalamazoo, Michigan. These bacteria produced an antibiotic which they called Geldanamycin[4]. 17-AAG is a chemically-modified version of Geldanamycin which has turned out to be more chemically stable and exhibit a better therapeutic window. Initially, Geldanamycins were thought to be kinase inhibitors, but it later turned out, that their kinase-inhibition effects were a consequence of inhibiting a protein called HSP90, Heat Shock Protein 90.

HSP90 is one of the most abundant proteins in human cells and belongs to a broad family of proteins, known as "chaperones". Chaperones are vital in maintaining the normal functions of cells, and are especially needed after environmental stresses that induce protein damage. Experiments in which cells are stressed by heat exposure have demonstrated strong induction of chaperone synthesis, and for this reason many chaperones are known as "heat shock proteins". However, this name is misleading, as almost every abrupt change in the cellular environment induces chaperones, and their cellular functions

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are multifaceted.

HSP90 is responsible for controlling the conformation, stability, activation, intracellular disposition, and disposal (proteolytic turnover) of many important proteins that are involved in cell growth, differentiation and survival (Figure 1A, pg 5). Transcription and translation of genes results in a string of amino acids that, left on their own, assume a 3-dimensional configuration (like a self-inflatable life raft). However, those proteins don't optimally configure on their own and rather assemble into something like an unkempt ball of wool, which would be identified as useless and be disposed into the cells' trash can, by the "proteasome" (Figure 1, pg 5). Proteins such as mutant KIT, which rely on the help of the HSP90 chaperone machinery, are called HSP90 clients and HSP90 ensures that these clients are properly folded and protected from premature destruction.

Cancer researchers have been intrigued by HSP90 inhibitors for many years, since the list of HSP90 clients contains the "celebrity A-list" of oncogenes, such as the EGF-Receptor, which is commonly deregulated in many types of epithelial cancer. When used in test tubes, HSP90 inhibitors such as 17-AAG, selectively kill cancer cells but not normal cells at low doses. This phenomenon has been explained by the fact that cancer cells are addicted to the oncogenic HSP90 clients and normal cells are not. 17-AAG shows a 100-fold higher affinity to HSP90 in tumor cells compared to the HSP90 protein in normal control cells . This can be explained by the fact that tumor cells are usually permanently stressed by their high demands for nutrients and oxygen. Therefore, oncogenic clients are in permanent need of the actively supporting ATP-consuming HSP90 complex, the so-called super-chaperone complex [5], which can be inhibited by ATP-competitive drugs, such as 17-AAG.

In theory, this sounds like a miracle drug. However, the first 12 trials of 17-AAG in cancer patients involving more than 300 patients showed not a single objective clinical remission. This seeming discordance between laboratory concept and clinical reality can be explained, in part, by the fact that cancer cells in lab test tubes are fully exposed to the drug being tested, whereas cancer cells in a human can be protected from the same drug by various physiological barriers. In the case of 17-AAG or other geldanamycin-based drugs (ansamycins), clinical applications have been constrained by the challenging pharmacology of the drugs. They need to be administered intravenously and due to their low water solubility have needed to be dissolved in a solvent (until recently) which on its own had substantial side-effects. In addition, most of the patients treated in these clinical trials had been randomly selected and had usually been heavily pretreated for epithelial cancers, which in part might explain the poor response rates.

Unlike many epithelial cancers, GISTs are genetically rather stable and mutant forms of KIT/PDGFRA are the dominant oncogenic driver, which explains why imatinib or sunitinib works so well in GIST. We have shown that HSP90 inhibition results not only in the inhibition but also the proteasomal degradation (Figure 1, pg 5) of oncogenic KIT irrespective of the imatinib-resistance mutations present [6]. **In theory, GIST should therefore represent an ideal disease model for HSP90 inhibitor**

Table 1: HSP90 drugs in development

Chemical class	Lead compound	Compounds/ Drug names	Trade name	Route	Developmental Status	Company name
Natural antibiotic-based HSP90-Inhibitors	Radicicol					
	Benzochinon Ansamycins	17-AAG (NCI-formulation)		IV	Phase II	
		17-AAG (cremaphor and suspension formulation)	Tanespimycin (KOS-953)	IV	Phase II	Kosan
		IPI-504	Retaspimycin	IV	Phase III in GIST	Infinity
		IPI-493		Oral	Phase I	Infinity
		17-DMAG	KOS-1022, Alvespimycin,	IV and oral	Phase II/III	Kosan
		CNF-1010 (oil in water emulsion)		IV	Phase I/II	Biogen
		Macbecin		N.A.	preclinical	Biotica
Pyrazoles	Resorcinol	CCT018159				
		VER-49009 (CCT-129397) and others				
		BIIB021 (CNF 2024)		Oral	Phase I/II in GIST	Biogen-Idec
Purine-based		AT-13387		N.A.	Phase I in solid tumors	Astex
Other small molecule inhibitors		PF-04928473		Oral	Phase I in solid tumors	Pfizer
		STA9090		Oral	Phase I, solid tumors	Synta
		AUY922			Phase I, solid tumors	Novartis

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New York GISTers meet!

New York-area GISTers met on Saturday, April 25 at the LIJ Plainview Hospital in Long Island. Front row, from left to right: Judith Cohen, Pat Bonda-Swenson, Maureen Paladino & Eleanor Svedi. Back row, from left to right: John Tarantino, Edward Cohen & Norm Scherzer.

A Cure Is In Our Reach Update

The updated total for the "Cure Is In Our Reach" campaign has now exceeded **$50,000**! Anyone wishing to contribute to the LRG can contact the LRG at liferaft@liferaftgroup.org for information and materials.

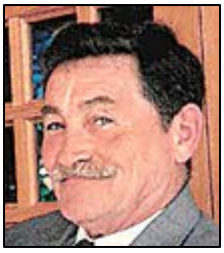
As always, you can show what a cure for cancer means to you by uploading your photo to www.acureisinourreach.org and letting us know!

Mirenda, man of the outdoors, passes away at 68

Joseph R. Mirenda III, 68, husband of the late Margaret E. (Reese) Mirenda, Old Swede Road, Douglassville, died April 16, 2009, of natural causes in his residence.

Born in the Bronx, N.Y., he was a son of the late Joseph Mirenda Jr. and Josephine (Fischelli) Mirenda.

He worked more than 25 years at Venezia Trucking, Limerick, as a senior mechanic.



Joseph was a Navy veteran.

While in the Navy, Joe played on the All-Navy softball team, which played other branches of the service at that time. He was also an avid skier, making a number of trips to Europe over the past number of years.

In addition to skiing, he was an avid bicyclist, kayaker and outdoorsman.

Surviving are three sons: Joseph Mirenda IV, Las Vegas; Michael T. Mirenda, Exeter Township; and Jamie P. Mirenda, Birdsboro; and two daughters, Joleen Mirenda-Alaniz, Greensburg; and Christine A. Strocen, Birdsboro.

Other survivors include one brother, Robert Mirenda, Altoona; 14 grandchildren and six great-grandchildren.

Condolences can be made at www.catagnusfuneralhomes.com

Did you catch Dr. Heinrich's Plasma Testing webcast?

If not, you can view the archived webcast at www.liferaftgroup.org/library_videos.html#plasmatesting. Dr. Mike Heinrich, of Oregon Health & Science University, concluded an hour-long webcast with a question & answer period on April 28, titled, "Optimizing Gleevec Therapy with Plasma Testing". In the presentation, Heinrich delves into the role of plasma testing, its logistics, who might benefit from this testing, and how to interpret the results.

Kemp was faithful volunteer & vet

Howard W. Kemp, 85, of Meadowcrest, Fla., formerly of Holden, died Friday, March 27, 2009 in Inverness, Fla. He was born in Worcester, son of Howard L. and Jennie (Bates) Kemp, and graduated from Wentworth Institute and Boston University. Mr. Kemp owned and managed the Marsh-Kemp Insurance Agency in Worcester until retirement in 1986. He resided in Hadley and in Florida since 1987.

Mr. Kemp led numerous professional, community and church organizations. He was an Army veteran, serving during World War II, and a lifetime member of the Boylston Masonic Lodge. He was a member of the First Baptist Church of Holden and later was an active member of the First Presbyterian Church of Crystal River, Fla.

Mr. Kemp was predeceased by his wife, Norma L. Kemp, and his former wife, Jean Hugo Kemp; a brother, Arthur Kemp; and a daughter, Christine A. Kemp. Survivors include a daughter, Andrea J. Morris of Hadley; a grandchild, Scott Morris of Westfield; and a sister, Carol Bingham of Renton, Wash.

BANNON

From Page 1

across the globe have heard similar prognoses, believed them, and surrendered to them as if they were a death sentence written in stone.

Since that day I have watched friends and friends of friends as they heard similar words, "It's malignant," or, "It's cancer," and in the panic of wanting the offending disease out and gone, have rushed into surgeries or treatments without seeking a consult or second opinion from one of the many cancer treatment centers we New Yorkers are so incredibly fortunate to have within a day's drive.

"We assume that tomorrow we'll greet the day as we did today. We take for granted that the people we know and love will be in our tomorrows as well."

I have also comforted their loved ones and cried tears of grief as they lost the battle against this beast we call cancer. Sometimes because the surgery that was thought to have had clear margins clearly did not, sometimes because, like me, they were misdiagnosed by the local oncology team and treated for the wrong cancer. Sometimes it's because they decided the battle against the cancer presented to them was less desirable than the choice of simply saying goodbye, letting go and going home.

After seven years, I still hate cancer. I've become a faithful advocate for anyone who is recruited into this war, using the knowledge and skills I acquired in my own battle to help others in theirs. After seven years, I still shed tears for those people whom I've grown to love along the way, who have lost the battle against the beast. Yet, after seven years, I have come to realize how immensely blessed I have been, knowing each day that I live with cancer.

Having cancer means living every day knowing that it's a gift. We are all one day closer to the end of our life when we awaken to greet a new day, but most of us live in the wonderful world of denial, completely ignoring that basic fact. We assume that tomorrow we'll greet the day as we did today. We take for granted that the people we know and love will be in our tomorrows as well. Very few of us ever question whether the loved ones in our lives will be there to answer our next email or phone call; we simply assume they will be. We plan for the future as if it's a given. We live like tomorrow is already ours.

I am blessed to live gazing every day into eternity from its threshold. When I become angry with a friend or hurt someone for whom I care, I am acutely aware that I may not have the luxury of time to wait to repair the rift or apply balm to the injury.

"I am blessed to live gazing every day into eternity from its threshold."

I know altogether too well that each sunrise and sunset is precious. I cherish the snowflakes as they dance in the cold winter air and I watch in wonder as a butterfly flutters on the soft spring breezes. The rain falling on my skin and the sun's warmth on my face are different now than they were seven years ago. I enjoy them. I stop and notice them. My children's laughter so fills my heart with joy that I am nearly always moved to tears.

I no longer worry about how things might appear, and I take chances I may not have taken in the past. I say things and do things that other people—people who don't have a cancer living inside them trying to kill them—will either delay or not say or do at all for fear of feeling foolish. I don't care about that anymore. I feel things more intensely, cherish people more deeply, know the futility of "things" and the incalculable value of a simple smile or hug. Having cancer, living with cancer, allows me to remember that I am alive and what a precious gift each moment of my life is.

It's sad really. Even if I didn't have the cancer, I was not yet forty when a stroke took part of my vision and made simply remembering things an enormous challenge. Those tiny emboli that showered my brain could easily have ended my life that day. What would I have wished I had said or done? What lives would I have wished I had touched? It's sad because not one of us knows what the next hour might bring, let alone if we'll have a tomorrow on this earth. I have been given an incredible, amazing, wonderful gift with this belly full of tumors with which I live and hope to someday defeat.

And I've realized that having a 22 inch waist is nice, but not if it means I am not here to enjoy it. So I don't mind my "pregnant" belly, as long as I can still laugh and love, walk and run and swim and dance.

As long as I still have time to watch my boys and the other children in my life who I dearly love, grow and learn and experience this wonderful life and have the opportunity to influence them.

As long as I can still hope for and dream of knowing that once-in-a-lifetime love, that someday I will look into the eyes of my future husband and see my best friend, my lover, my life partner, the one who makes me better because he loves me and shares his life with me.

As long as I can imagine what my grandchildren will look like and be like and as long as I can hope to be here to hold each one as they are born into this incredible world.

No, my big old belly is a small price to pay for the intensity with which I experience life. I pray that I never lose the lessons this cancer has taught me. I pray that I never stop gazing from the threshold of eternity so I might always remember the value of each moment of this life. May you not need the "blessing" of a cancer to bring you to the realization of what is important, what has value, what a miracle this thing is that we call life.

HSP90

From Page 6

strategies. And, indeed, an initial clinical trial of the HSP90 inhibitor IPI-504 has provided the crucial proof-of-concept that HSP90 works as a master-regulator of KIT in GIST cells. In 66 percent of patients a reduction of glucose metabolism as measured by PET-scans was seen and one-third of patients experienced a prolonged disease stabilization [7].

IPI-504 is a chemically-modified form of 17-AAG which is highly soluble in water, thereby overcoming one of the major pharmacologic problems of 17-AAG. Notably, the phase I and II trials showed that IPI-504 was generally well-tolerated. In these early-phase trials, most of the observed IPI-504 toxicities were Grade 1 or 2, which means they were very mild and mostly required only outpatient management and no hospitalization. Side-effects related to IPI-504 that occurred in more than five patients were asymptomatic— slowing of heart rate, mild diarrhea and mild nausea (30%) and vomiting (14%), which was very responsive to standard anti-emetics. Other side-effects were fatigue (50%), infusion site pain, asymptomatic increased liver enzymes, muscle and joint pain (35%) and mild headache (35%[8]). Moderate or severe side-effects (Grade 3 or 4) were observed in few patients in the initial review of the clinical data from this early phase trial, and the large scale international phase III trial (RING) was designed on this basis.

Sadly, the RING trial was recently closed early due to concerns that the frequency of patients who had severe side-effects in the phase III trial was higher than predicted, perhaps because the patients had more advanced GIST and less normal functional reserve. Although it is too early to speculate on the exact mechanisms for these IPI-504 associated toxicities, it will be crucial to determine whether severe toxicities are inevitable with HSP90 inhibition in subgroups of GIST patients, particularly those who have already been extensively treated with other GIST therapies and who may be in fragile medical condition. Alternately, it is possible that certain toxicities seen in the RING trial were not caused by HSP90 inhibition per se, but rather resulted from unintended "off-target" consequences of IPI-504, which might not be seen with other classes of HSP90 inhibitor drugs. The data that have been collected in this recently closed phase III trial will hopefully help us all to understand how HSP90 inhibition might be developed in the safest possible way as a therapeutic strategy for patients with GIST.

Beyond the potential for severe toxicities, it is also clear that substantial progress must be made in determining the optimal dose and schedule of HSP90 inhibitors for treatment of GIST. IPI-504 has been administered intravenously twice weekly for two weeks with one week off. Comparing PET scans during treatment, a significant glucose reduction was seen at the end of the second week but after one week off drug administration in the first cycle of study, glucose metabolism in the GISTs had returned to near-baseline levels. While IPI-504 is the HSP90 inhibitor furthest along in clinical trials there are limitations, such as the inconvenient schedule (frequent IV treatment) and the fact that HSP90 may not be continuously inhibited. However, IPI-504 might be available in an oral form in the near future and several other synthetic, orally-available HSP90 inhibitors are being developed by other pharmaceutical companies (Table 1, pg 6). Future studies are needed to identify the most potent, safe and clinically useful HSP90 inhibitors for GIST. An urgent priority will be to determine the extent to which HSP90 can be truly shut down by HSP90 inhibitor drugs, and to determine what clinical efficacy and what side effects result when that pharmacologic aim is achieved. Other crucial laboratory studies include development of HSP90 resistance models and testing of strategies to prevent or overcome resistance to HSP90 inhibitors.

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Mark your calendars!

- Chicago-area GISTers are meeting Sunday, **May 3**. Contact Jim Hughes at tjhughes43@comcast.net for meeting information.
- Northern Californians will be meeting on Saturday, **May 16** at 1 p.m. Email Martha Zielinsnki at john.martha@sbcglobal.net for details.
- GIST patients in the St. Louis area will also be meeting on **May 16**; please contact Katie Campbell at campbellksoup@hotmail.com with questions.
- *CancerCare* will be holding a workshop, "The Importance of Nutrition and Physical Activity" on **May 19**. Please visit www.cancercare.org/TEW for further details.
- Arizona GISTers will be meeting on Sunday, **May 24**. Please email Janeen Ryan at tabascocook@yahoo.com for information.

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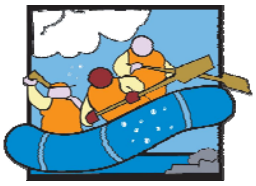

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