Placebo: Wrong then, wrong now

By Norman J. Scherzer
LRG Executive Director, on behalf of LRG Board of Directors

The issue of placebo use in clinical trials for GIST patients has resurfaced once again as Infinity Pharmaceuticals proceeds to implement a phase III trial for IPI-504, for patients with refractory GIST.

The Life Raft Group first addressed the issue of placebos at a board of directors meeting in November 2003 when eight directors and LRG members agonized and debated the merits of a placebo: wrong then, wrong now.

Battling gastrointestinal stromal tumor

International GIST community meets in Italy

By Norman J. Scherzer
LRG Executive Director

Baveno, Italy was the site of the sixth patient summit meeting which brought together GIST and CML patients from around the world. This meeting, sponsored by Novartis, exhibited the dramatic growth in maturity of the patient organizations represented. The diversity and level of excellence of their presentations spoke to the progress patients are making in taking control of their own lives and impacting the quality of care that patients receive. A few highlights:

The NIH Clinic: in two perspectives

By Dr. Su Young Kim
National Cancer Institute

The National Institutes of Health (NIH) was proud to host the inaugural Pediatric GIST Clinic. The objective of this clinic was to bring together young patients with national experts in the medical and research realms, in an effort to build a foundation of knowledge upon which to build. From the NIH perspective, the clinic was very successful.

There were four aspects to this clinic. First, we asked patients to send us their medical information prior to their visit. The response we received was incredible. Patients and families went to great lengths to send medical reports, radiographic images and pathology slides to us. This allowed NIH physicians to become familiar with the See NIH1, Page 7

Look Inside!

Don’t forget to register for Life Fest by August

By Jacqui Bromberg
LRG Pediatric GIST Co-Chair for the NIH Planning Committee

On June 18, the very first Pediatric GIST Clinic was held in Bethesda, Maryland at the National Institute of Health (NIH). I am so fortunate to have been able to attend this clinic, which was open to all Pediatric GIST patients. Having been diagnosed with this rare disease for four years now, my mother and I were very excited to learn that there was an interest being taken at the NIH. The clinic was meant to give patients and caregivers the opportunity to meet with a panel of Pediatric GIST experts from all over the country. These experts shared their combined knowledge and provided us with a session to ask questions about our treatments and address any

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What's going on at Life Fest?

This year’s Life Fest in Chicago is shaping up to be a very informative event. We have plenty of general sessions, workshops and distinguished speakers to make your weekend worthwhile. Here is a current list of sessions with a few highlighted for you:

**General Sessions:**
- GIST Update (Dr. Jonathan Trent)
- Pediatric GIST Update (Dr. Lee Helman)
- LRG Research Update (Dr. Brian Rubin)

**Workshops:**
- Survival Strategies (Norman Scherzer/Jerry Call)
- Clinical Trial Update (Jim Hughes)

Please go to page 15 for information about Life Fest registration and room rates.

**Distinguished Honoree: Dr. Lee Helman**

Dr. Lee Helman earned his M.D. at the University of Maryland School of Medicine in 1980. His internship and residency were completed at the Internal Medicine at Barnes Hospital Washington University. His fellowship training was at the National Cancer Institute, where he continues his research. In 1993, he became the head of the Molecular Oncology Section of the Pediatric Oncology Branch. He became the chief of the Pediatric Oncology Branch in 1997 and was named a Deputy Director of the Center for Cancer, National Cancer Institute in 2001. In 2005, Dr. Helman was named Acting Scientific Director for Clinical Sciences, Center for Cancer Research, National Cancer Institute. Currently, Dr. Helman’s laboratory focuses on three major themes related to the biology and treatment of pediatric sarcomas: the role of insulin-like growth factors on these tumors; identification of the molecular mechanisms of metastases using animal models of spontaneously metastatic tumors; and translation of these findings into treatments to improve the patient outcome.

**General Session: Survival Strategies**

There are a number of inter-related strategies that patients can use to optimize their therapy. It is very important to make sure your treatment is on the best possible track to keep GIST at bay for as long as possible. We will discuss some of these strategies including finding the right doctors, getting the right treatment, optimizing Gleevec treatment. Optimizing Gleevec treatment includes the following: knowing your mutation type; understanding dosage issues and finding your optimal dose based on the information that we have today; side effects management; taking Gleevec faithfully; and proper monitoring.

**Workshop: Side-Effects Management**

Side effects can have a negative impact on every day life. Learning how to manage side effects or in some cases, how to live with them, not only improves quality of life, but it also allows patients to be able to take these drugs at the proper dose and schedule, which is key to successful treatment. Pat Neal of MD Anderson will be hosting this workshop.
August 2008 US clinical trials update

By Jim Hughes
LRG Clinical Trials Coordinator

STA9090 Phase I: This trial is now listed in clinicaltrials.gov. It is actually two trials at the same sites. In one trial the drug is administered once weekly. In the other it is administered twice weekly.

Imatinib + Bevacizumab: This trial is now listed in the US report. It was first reported last month. There are over 100 locations listed as recruiting in the U.S. Look up a location near you using the NCT# in clinicaltrials.gov advanced search for contact information

XL820 Phase I: This trial is now listed as “ongoing but not recruiting participants”.

Site information has been updated in nine trials in the table below.

Imatinib or Sunitinib

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

| Phase: III |
| Conditions: GIST |
| Strategy: Inhibit KIT and/or impede tumor vascularization |
| NCT#: NCT00372567 |
| Contact: Pfizer |
| pfizercancertrials@emergingmed.com |
| Telephone: 1-877-369-9753 |
| Sites: FCCC, Philadelphia, Penn. Dana-Farber Cancer Institute (DFCI), Boston, Mass. Memorial Sloan-Kettering Cancer Center (FCCC), New York, NY |

Imatinib + Bevacizumab

Imatinib with or without Bevacizumab in patients with metastatic/unresectable GIST

| Phase: III |
| Conditions: GIST |
| Strategy: Inhibit KIT |
| NCT#: NCT000324987 |
| Contact: Over 120 US contacts. Check clinicaltrials.gov or cancer.gov for this NCT# |

Imatinib + Pegylated Interferon-a 2B

Phase II study combines targeted therapy with immunotherapy, Imatinib + Pegylated Interferon-a 2B in imatinib-naive GIST patients

| Phase: II |
| Conditions: GIST |
| Strategy: Kill GIST cells |
| NCT#: NCT00585221 |
| Contact: Huntsman Cancer Institute |
| University of Utah, Salt Lake City, Utah |
| Jessica Moehle |
| 801-587-4438 |
| Suzanne Dodd |
| 801-587-9834 |
| Lei Chen, MD |

Perifosine + Imatinib

Phase II study of Perifosine + Gleevec in GIST patients

| Phase: II |
| Conditions: GIST |
| Strategy: Multiple Targets |
| NCT#: NCT00455559 |
| Contact: Online Collaborative Onc. Group |
| ococtrials@ocog.net |
| Telephone: 415-946-2410 |

Doxorubicin + Flavopiridol

Doxorubicin and Flavopiridol in treating patients with metastatic or recurrent unresectable sarcomas

| Phase: I |
| Conditions: GIST/Sarcoma |
| Strategy: Inhibits production of KIT |
| NCT#: NCT 00098579 |
| Contact: David D’Adamo, MD |
| Telephone: 212-639-7573 |
| Sites: MSKCC, NY, N.Y. |
Infinity's IPI-504 enters phase III

By Jim Hughes
LRG Clinical Trials Coordinator

The heat shock chaperone protein (HSP-90) has emerged as a promising target for cancer therapy. Infinity Pharmaceuticals’ IPI-504 is one of many experimental heat shock protein inhibitors vying for a spot in the cancer market. Data from the recently completed Phase I trial of this drug was presented at the 2008 American Society of Clinical Oncology conference (ASCO) in May. Based on this information, Infinity Pharmaceuticals has announced plans to initiate an international Phase III registration trial of its HSP-90 inhibitor, IPI-504, in patients with refractory GIST in the third quarter.

The Phase III protocol has been granted a Special Protocol Assessment agreement by the Food and Drug Administration (FDA). The European Medicines Evaluation Agency has provided scientific advice consistent with that of the FDA regarding the Phase III trial design. To participate in this trial, patients must have failed both imatinib and sunitinib therapy. There will be no limit to the number of prior therapies patients may have received. The company has also assured us that patients will be screened according to the inclusion/exclusion criteria to make certain that patients with large tumor loads will be excluded and not subject to undue risk.

More GIST highlights from ASCO 2008

By Paula Vettel
LRG Science Team Member

Quantitative functional imaging by dynamic contrast enhanced ultrasonography (DCE-US) in patients with GIST treated by tyrosine kinase inhibitor (TKI)

L. Chami, N. Lassau, S. Koscielny, B. Benatsou, A. Roche, and A. Le Cesne
(Institute Gustave Roussy)

The investigators have developed an ultrasound technique to study GIST tumors in 20 patients in France. Contrast was given, but no radiation was involved. Ultrasound was able to show the difference between live GIST and necrotic tissue. This is very useful in the early stages of drug treatment to measure efficacy of treatment. The study is being expanded to 650 patients with various solid tumors.

Cardiotoxicity associated with the cancer therapeutic agent sunitinib alate

Melinda L. Telli, MD1, Ronald M. Witteles, MD2, George A. Fisher, MD, PhD1, Sandy Srinivas, MD1
Stanford University School of Medicine, Divisions of Oncology1 and Cardiovascular Medicine2

Cardiotoxicity was studied in a group of 48 patients on Sutent therapy, including seven GIST patients. Grade 3-4 LVEF (Left Ventricular Ejection Fraction) (<40%) was found in 15 percent of patients. Of these, 81 percent were dosed at 50 mg for four weeks on and two weeks off, and 19 percent were dosed at 37.5 mg continuous. Identified risk factors were low body mass, congestive heart failure, and coronary heart disease. Most cardiac events were diagnosed in less than 100 days after the start of treatment. The authors recommend cardiac monitoring of patients on Sutent. Similar results were found in a previous study showing reduced LVEF and congestive heart failure in 11 percent of patients in Sutent clinical trials. (T. Chu, et.al; Lancet 2007; 370: 2011-2019)

Interobserver variability of size and density measurements on CT in patients with metastatic GISTs on imatinib mesylate (IM)

V. Bulusu, S. Fawcett, P. Moyle, and N. Carroll

The authors measured 27 GIST tumors from CT scans with contrast by longest measurement and tumor density in 2007. The same tumors were measured again three months after the start of drug therapy. In 2008, two of the authors repeated their measurements and assessments of the same tumors. The second set of measurements were within 10 percent of the original measurements in 81 to 92 percent of the cases for length and 81 to 88 percent for density. The authors feel that this variation is acceptable, but caution that these evaluations should be carried out by radiologists with experience in assessing response to drug therapy.
Pfizer clinical trial for SU11248 (Sutent) that included a placebo in its protocol (A photo of this group can be found on page five of our March 2004 newsletter in a eulogy to Dean Gordanier, the first of three members of this group to die from GIST). In January 2004 our editorial headlined, “Placebo use in Pfizer trial is simply wrong”. In August 2004 our front page article headlined, “More placebo clinical trials predicted for cancer patients-Patient advocacy concerns presented about potential ethical dilemmas”. Once again we shared our concerns and made the following major points:

- “Nothing about us, without us”, stealing a mantra from our colleagues at ECPC (European Patient Cancer Coalition).
- The burden of proof must be upon those proposing to use a placebo.
- If a drug being tested is likely to produce stability rather than tumor shrinkage, then how could any progression which occurs due to a placebo be reversible?

This new trial comes a step closer to addressing our concerns. We note that the trial protocol attempts to strengthen the monitoring of participants to enable earlier cross-over to the trial drug for those progressing on the placebo. We note that the use of a placebo may well reduce the number of trial participants needed and that this may expose fewer patients to the unknown risks of an unproven drug. We note that the smaller number of participants may mean a shorter trial period and, should the trial demonstrate drug efficacy, that this may allow earlier approval for the drug and earlier access to it by GIST patients. Finally, we note that Infinity is a progressive company with a high degree of transparency and a sincere motivation to do right by patients. We appreciate that the company plans to help trial patients with transportation costs. We appreciate the time and attention we have been accorded from the President, Julian Adams, on down.

We have once again invested a considerable amount of time and energy investigating the complex issue of placebos and deliberating what our position should be. We are particularly indebted to the comprehensive work of the Canadian National Placebo Initiative published in July 2004.

We do understand the challenge posed to a pharmaceutical company to design a clinical trial which can demonstrate the safety and efficacy of a new drug to the satisfaction of government regulators. This must be done while still meeting the financial needs of its investors and the medical needs of the patients for whom the drug is intended. This is no small task, particularly for smaller companies.

We are also particularly sensitive to the realistic world of drug development and the need to encourage companies to invest in drugs for a rare disease like GIST.

What is at stake today is not just the Infinity trial but the precedent that it sets for others to come. We could continue to weigh the pros and cons indefinitely and engage in an ongoing lively dialogue with a vast community of ethicists, scientists, scholars and others regarding a subject that brings great passion to the table, but the time is once again at hand to take a position.

The Life Raft Group respectfully disagrees with the use of a placebo in the Infinity clinical trial for IPI-504.

We feel that the burden of proof for using such a placebo, which must be assumed by those proposing it, has not been met for the following reasons:

1. Poor Science: There is a sufficient body of knowledge that removing a GIST patient from whatever treatment they are on may accelerate the cancer progression. Hence, the issue is not whether a drug is better than nothing, but whether it is better than the current treatment.

We are also concerned that the RECIST criteria being used to demonstrate progression is not the best methodology available and has in fact been discredited by a number of GIST specialists over the past few years. CHOI criteria, on the other hand, identifies progression sooner and could be substituted for RECIST.2,3.

2. Irreversible Disease Progression: Early data strongly suggests that the major benefit of IPI-504 may be tumor stability rather than tumor shrinkage (Figure 1). Should that be the case, we submit that the progression required to qualify for cross-over to the drug may well be irreversible and therefore is potentially life-threatening.

3. Failed Ethics: Many ethicists hold that placebo use cannot be justified solely on scientific grounds. We agree, especially in the case of terminally ill cancer patients whose judgment may be clouded. Indeed, a placebo-based trial exploits their vulnerability.

The Life Raft Group remains committed to its mission to ensure the survival of every GIST patient. We cannot condone a situation in which terminally ill patients and their families are asked to choose between a placebo and a drug.
### Imatinib + Sunitinib

**Imatinib & sunitinib in treating GIST patients**

**Imatinib + Sunitinib**

A phase I/II study of BGT226 in patients with advanced solid malignancies including those with advanced breast cancer

- **Phase:** I
- **Conditions:** Solid Tumors, Breast Cancer, Cowden Syndrome
- **Strategy:** Target KIT downstream signal (PI3K)
- **NCT#:** NCT00600275
- **Contact:** Novartis
- **Telephone:** 800-340-6843
- **Sites:**
  - Nevada Cancer Institute
  - Las Vegas, Nev.
  - Sunil Sharma, MD

### Sorafenib (Nexavar)

**Sorafenib in treating patients with malignant GIST that progressed during or after previous treatment with imatinib and sunitinib.**

**Sorafenib (Nexavar)**

A Phase I/II multi-center, open-label study, administered orally on a continuous daily schedule in adult patients with advanced solid malignancies.

- **Phase:** I/I
- **Conditions:** Adv. Solid Malignancies/ Adv. Breast Cancer
- **Strategy:** Target KIT downstream signal (PI3K)
- **NCT#:** NCT00620594
- **Contact:** Novartis
- **Telephone:** 862-778-8300
- **Sites:**
  - Nevada Cancer Institute, Las Vegas, Nev.
  - Sarah Cannon Res. Institute, Nashville, Tenn.
  - Howard Burris, MD, 615-329-7274

### BGT226

A phase I/II study of BGT226 in patients with advanced solid malignancies including those with advanced breast cancer

- **Phase:** I
- **Conditions:** Solid Tumors, Breast Cancer, Cowden Syndrome
- **Strategy:** Target KIT downstream signal (PI3K)
- **NCT#:** NCT00600275
- **Contact:** Novartis
- **Telephone:** 800-340-6843
- **Sites:**
  - Nevada Cancer Institute
  - Las Vegas, Nev.
  - Sunil Sharma, MD

### BEZ235

A Phase I/II multi-center, open-label study, administered orally on a continuous daily schedule in adult patients with advanced solid malignancies.

- **Phase:** I/I
- **Conditions:** Adv. Solid Malignancies/ Adv. Breast Cancer
- **Strategy:** Target KIT downstream signal (PI3K)
- **NCT#:** NCT00620594
- **Contact:** Novartis
- **Telephone:** 862-778-8300
- **Sites:**
  - Nevada Cancer Institute, Las Vegas, Nev.
  - Sarah Cannon Res. Institute, Nashville, Tenn.
  - Howard Burris, MD, 615-329-7274

### GDC-0941

An open-label phase I, dose-escalation study in patients with locally advanced or metastatic solid tumors for which standard therapy is ineffective, intolerable or does not exist

- **Phase:** I
- **Conditions:** Tumors/Lymphoma
- **Strategy:** Target KIT downstream signal (PI3K)
- **NCT#:** NCT00345189
- **Contact:** Biogen Idec
- **Telephone:** 862-778-8300
- **Sites:**
  - National Cancer Institute, Bethesda, Md.
  - Los Angeles, Calif.
  - Scottsdale, Ariz.

### MP470

MP470 in treating patients with unresectable or metastatic solid tumor or lymphoma

- **Phase:** I
- **Conditions:** Solid Tumors/Lymphoma
- **Strategy:** Multiple Targets
- **NCT#:** NCT00504205
- **Contact:** Biogen Idec
- **Telephone:** 800-340-6843
- **Sites:**
  - UCLA, Los Angeles, Calif.
  - DFCI, Boston, Mass.
  - Virginia Piper Cancer Center, Scottsdale, Ariz.

### BIIB021 (CNF2024)

Once or twice daily administration of BIIB021 to solid tumor subjects

- **Phase:** I
- **Conditions:** Advanced Solid Tumors
- **Strategy:** Destroy KIT (HSP-90)
- **NCT#:** NCT00618735
- **Contact:** Biogen Idec
- **Telephone:** 862-778-8300
- **Sites:**
  - National Cancer Institute, Bethesda, Md.
  - Los Angeles, Calif.
  - Scottsdale, Ariz.

### CNF2024

Oral CNF2024 in advanced solid tumors

- **Phase:** I
- **Conditions:** Tumors/Lymphoma
- **Strategy:** Destroy KIT (HSP-90)
- **NCT#:** NCT00345189
- **Contact:** Biogen Idec
- **Telephone:** 862-778-8300
- **Sites:**
  - National Cancer Institute, Bethesda, Md.
  - Los Angeles, Calif.
  - Scottsdale, Ariz.

### AUY922

Phase I-II study to determine the MTD of AUY922 in advanced solid malignancies and efficacy in HER2+ or ER+ locally advanced or metastatic breast cancer.

- **Phase:** I
- **Conditions:** Breast Cancer/Solid Malignancies
- **Strategy:** Destroy KIT (HSP-90)
- **NCT#:** NCT00526045
- **Contact:** Novartis
- **Telephone:** 800-340-6843
- **Sites:**
  - UCLA, Los Angeles, Calif.
  - DFCI, Boston, Mass.
  - Virginia Piper Cancer Center, Scottsdale, Ariz.

### See TRIALS, Page 9
NIH1

From Page 1

medical history prior to seeing the patient.

The second objective of the clinic was to discuss the patient’s history with GIST clinicians and researchers. We were fortunate to have several doctors, in various specialties, volunteer their time and expertise in this endeavor. This included Dr. Cristina Antonescu, pathologist; Dr. George Demetri, medical oncologist; Dr. Katherine Janeway, pediatric oncologist; Dr. Michael LaQuaglia, pediatric surgeon; and Dr. Alberto Pappo, pediatric oncologist. Hosting the session was Dr. Lee Helman, pediatric oncologist at the National Cancer Institute, Dr. Constantine Stratakis, geneticist and pediatric endocrinologist at the National Institute of Child Health and Human Development, and myself. During this meeting, we were able to discuss interesting aspects of each patient’s history and to assimilate elements that were common to many cases.

The third part of the clinic was the most satisfying, in that we had the chance to meet with patients and their families. In a short period of time, we addressed the major concerns of each patient. This was made possible since we were familiar with each history, and patients came prepared with a list of questions. Patients also had the opportunity to speak with a range of specialists at the NIH, including Genetics, Pain Management, Nutrition, Psychology, Social Work, Recreation Therapy, Art Therapy and Alternative Medicine teams. Our hope is that the patients and families found these sessions as helpful to them as we found their medical information helpful to us. All of the families were extremely delightful and it was truly a pleasure interacting with all of those who attended.

The fourth aspect of the clinic involved discussion of the present state of GIST. The Office of Rare Diseases (NORD) and the National Cancer Institute (NCI) graciously provided funding for this conference. We were fortunate to be joined by Norman Scherzer and Tricia McAleeer of the Life Raft Group and Phyllis Gay and Rebecca Bensenhaver of GIST Support International. This provided a great mixture of advocates, parents and patients. Based on the information that we obtained from the patient records and the cumulative knowledge of those present, we were able to comment about certain aspects of pediatric GIST. This included recommendations on treatment, imaging and research.

So what did we learn? We determined that pediatric GIST is not a single entity and that there are more aggressive forms and less aggressive forms. In most cases, we found that tumor growth was very slow and that the interval between scans could be increased. We found that treatment for patients has not been uniform and one of our goals is to try to determine the natural course of pediatric GIST and evaluate the many different regimens that patients have received. We talked about Dr. Antonescu’s and Dr. Janeway’s recent findings that levels of Insulin-like Growth Factor Receptor 1 (IGF-1R) are

NIH2

From Page 1

other concerns. My mother and I flew down the day before the clinic and following a registration, were finally able to meet other GIST patients and caregivers. These amazing individuals shared with one another hope and encouragement. Everyone gathered for a meeting where the doctors and those representing support groups introduced themselves and spoke, including myself and Ashley Young, on behalf of the LRG and Phyllis Gay on behalf of GSI. There was a very informative presentation on new research and the excitement regarding a promising chemotherapy treatment com-

Mothers & daughters unite: Jennifer & Sile Bao, Toni & Ashley Young, Stephanie & Patty Kastner, Phyllis & Kara Gay.

Top row from left: Dr. Constantine Stratakis, Nora Winstead, Stefanie Peyk, Sile Bao. Bottom row from left, Jacqui Bromberg, Liz Skree, Jason DeLorenzo & Stephanie Kastner.
France: Estelle Lecointe presented a booklet on patient compliance which is being translated into other languages and will serve as a template for other organizations.

Canada: David Josephy presented an update on the formation of a new patient organization, GIST Sarcoma Life Raft Group Canada and the logistics of coordination in such a vast country.

U.S.A.: Norman Scherzer presented on behalf of Tricia McAleer and Sara Rothschild a review of the first year of Life Raft Group’s live educational webcasts which are archived on the LRG website.

Germany: Markus Wartenburg presented the experience of Das Lebenshaus in conducting round table ring tests for pathologists as a quality control and training technique.

U.K.: Judith Robinson presented a grassroots telephone system developed by her son to facilitate communications with GIST patients and caregivers at their homes.

Switzerland: Ulrich Schnorf presented the progress in establishing a network of clinics staffed by GIST specialists.

The quality of the expert panels contributed greatly to the material presented and to the extraordinary interaction between patients and physicians. Contributing faculty included: Dr. Jonathan Fletcher, USA; Dr. Maria Debiec-Richter, Belgium; Dr. Peter Reichardt, Germany; and Dr. Paolo Casali of Italy.

The Life Raft Group was also invited to present its latest data on the relationship between imatinib dosage levels and survival (Highlighted in our March 2008 newsletter). The focus of the presentation was the link between higher doses and lower progression which in turn was linked to lower mortality. Of great concern was the lack of any drug (or combination of drugs) that significantly impacts upon survival once imatinib-progression occurs. The discussion then turned to the differences between using starting dosage (the formal MetaGIST study) and actual dosage (the Life Raft Group Study). The concern was that only a new clinical trial could resolve these statistical differences between the LRG and the traditional MetaGIST consortium; that such a trial was unlikely and at best would take another ten years to produce new survival data.

Attention then turned to a call to action, the cornerstone of which was to introduce routine plasma level testing of imatinib as a practical way of determining which of the low dosage patients actually might require an increase. The result was the Global GIST Patient Community Declaration:

Baveno, Italy 28th June 2008

The GIST patient advocacy community is concerned about the current dosage levels of imatinib which patients are receiving.

We propose as a first step that for each patient being treated data are gathered about

• KIT/PDGFR mutational testing at diagnosis
• Routine plasma testing of imatinib levels

We expect doctors treating GIST patients to use these data to inform decisions on the appropriate dose level of imatinib for all patients.

Signed by patient representatives from: Brazil, Canada, France, Germany, Hungary, Italy, Lithuania, Poland, Switzerland, U.K., U.S.A. (both GSI and LRG)

Plasma Testing

Plans are now underway to conduct routine mutational and plasma testing of patients on imatinib. The Life Raft Group has joined forces with a number of patient organizations to implement the aforementioned declaration. Plans include hosting an international development conference with key American and European laboratories currently performing plasma level testing to create a common testing protocol and to identify...
OSI-930

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

Phase: I
Conditions: Solid Tumors/Sarcoma
Strategy: Multiple Targets
NCT#: NCT00513851
Contact: OSIP Medical Information
Medical-information@osip.com
Telephone: 800-572-1932 xt 7821
Sites: Univ. of Colorado, Aurora, Colo.
Mary Kay Schultz, 303-266-1740
DFCI, Boston, Mass.
Melissa Hobos, RN, 617-632-2201

SNX5422

Safety and pharmacology of SNX-5422 in patients with refractory solid tumor malignancies

Phase: I
Conditions: Solid Tumor Malignancy
Strategy: Destroy KIT (HSP-90)
NCT#: NCT00506805
Contact: Catherine A. Ross
Telephone: 919-376-1330
Sites: TGen Clinical Res. Services
Scottsdale, Ariz.
Joyce Ingold, RN, 480-323-1339
Ramesh Ramanathan, MD
Sarah Cannon Res. Institute
Nashville, Tenn.
Howard Burris III, MD

LBH589

Phase IA, two-arm, multi-center, dose-escalation study, by IV on two dose schedules in adult patients with advanced solid tumors and non-Hodgkin’s lymphoma

Phase: I
Conditions: Adv. Solid Tumors/Lymphoma
Strategy: Destroy KIT, Inhibit Cell Cycle, Apoptosis
Contact: Nevada Cancer Institute, Las Vegas, Nev.
Donna Adkins, RN, 702-822-5173

STA-9090

Administered once-weekly in solid tumor patients

Phase: I
Conditions: Solid Tumors
Strategy: Destroy KIT (HSP-90)
Sites: DFCI, Boston, Mass.
Melissa Hobos, RN, 617-632-2201
Geoffrey Shapiro, MD, 617-632-4942
Premiere Oncology, Santa Monica, Calif.
Lee Rosen, MD, 310-633-8400
Karmanos Cancer Institute, Detroit, Mich.
Pat LoRusso, MD 315-576-8716

STA-9090

Administered twice-weekly in solid tumor patients

Phase: I
Conditions: Solid Tumors
Strategy: Destroy KIT (HSP-90)
Sites: DFCI, Boston, Mass.
Melissa Hobos, RN, 617-632-2201
Geoffrey Shapiro, MD, 617-632-4942
Premiere Oncology, Santa Monica, Calif.
Lee Rosen, MD, 310-633-8400
Karmanos Cancer Institute, Detroit, Mich.
Pat LoRusso, MD 315-576-8716

SF1126

Phase I open label, safety, pharmacokinetic & pharmacodynamic dose escalation study of SF1126 given twice weekly by IV to patients with advanced or metastatic tumors

Phase: I
Conditions: Solid Tumors
Strategy: Target KIT downstream signaling (PI3-K)
Sites: Arizona Cancer Center,
Tucson, Ariz.
Daruka Mahadevan, MD 530-626-0191
Indiana University, Indianapolis, Ind.
Elena Chiorean, MD 919-376-1330

Adult GIST pamphlet translated into URDU!
The Adult GIST information pamphlet is now available online and for order in Urdu.

What is Urdu?
Well, according to our friends at Wikipedia, “Standard Urdu has approximately the twentieth largest population of native speakers, among all languages. It is the national language of Pakistan as well as one of the 23 official languages of India.”

Adult GIST and Pediatric GIST pamphlets can be viewed in English and Spanish. Plans are in effect to add more languages. If you want to volunteer to help us in our efforts, please email Sara at srothschild@liferaftgroup.org.
much higher in wildtype KIT tumor samples, compared to that of mutated KIT samples. Regardless of age, we believe that patients with wildtype GIST will have more in common than those with gene mutations. We then discussed Dr. Demetri’s and Dr. Janeway’s plan to initiate a treatment protocol for patients with pediatric or wildtype GIST. The study agent will be an IGF-1R antibody. These were some of the many issues that we addressed. Specifics details of this meeting and other aspects of the Clinic will be presented in the coming months on our website.

As a consequence of this clinic, we are proud to announce the formation of the Consortium for Pediatric and wildtype GIST Research (CPGR). Member institutes include Dana-Farber Cancer Institute, Memorial Sloan-Kettering Cancer Center, Texas Children’s Hospital and the National Institutes of Health. All clinicians and researchers with an interest in pediatric and wildtype GIST are encouraged to join.

CPGR will meet twice yearly at the NIH. The second Pediatric and Wildtype GIST Clinic is scheduled for January 21 and 22, 2009.

Updates of results from Pediatric GIST Clinics will be posted quarterly on our website at www.pediatricgist.cancer.gov, which is expected to open on October 1, 2008. There will also be a parallel series of articles that addresses research. The first of these will explain what happens to a tumor sample, how it is processed and what types of experiments are performed. Every article will be written in a way that a medical dictionary will

Did you Know...

Being far from home for treatment is difficult enough with traveling, leaving jobs and/or school behind and separating family members. Lodging can be an added annoyance and expense that you may not be able to cope with. Here are a few choices:

- Joe’s House-Site lists hundreds of cancer treatment centers and lodging facilities (www.joeshouse.org)
- National Association of Hospital Hospitality Homes Incorporated-Provides lodging and more for patients and families during medical emergencies (www.nahhh.org)
- Ronald McDonald House—Provides a home away from home for families of seriously ill children (www.rmhc.org)

To use centralized CT scan review to insure both consistency and accuracy in measuring potential progression and timely turn-around. Plans include scans at two, five, and eight weeks with a one week turn-around. Four to six radiologists will read the scans and compare results. Results will be transmitted electronically for review by the primary site (Dana-Farber Cancer Institute). Infinity has provided assurance of best effort in monitoring all patients for progression so that crossover can be timely for those patients on placebo.

This article is based on a May 30 meeting with Norman Scherzer, Jim Hughes and representatives from Infinity Pharmaceuticals and subsequent telephone discussions with Infinity.

Please see, “Placebo: Wrong then, wrong now” on page 1, for the LRG’s position on this trial.
PFS: Patient Benefit or Lower Standard?

By Eleanor Mayfield
National Cancer Institute

The U.S. Food and Drug Administration (FDA) recently granted bevacizumab (Avastin) accelerated approval for use in combination with paclitaxel (Taxol) to treat some patients with metastatic breast cancer. The decision cast a spotlight on a somewhat controversial clinical trial endpoint that the agency used to support its decision. Though the combined therapy improved progression-free survival (PFS) by 5 months compared with the control group, which received only paclitaxel, there was no significant improvement in patients’ overall survival (OS).

The difference between PFS and OS is that PFS measures the time from a patient’s random assignment to one treatment arm or another until the patient’s cancer begins to grow again or the patient dies from their cancer; whereas OS measures the time from randomization until death from any cause.

Central to the controversy over the use of PFS as an endpoint in cancer clinical trials is whether delaying disease progression matters if a cancer treatment doesn’t also lengthen patients’ lives. Put another way, which matters more: longer life or better quality of life?

FDA considers OS the most reliable cancer endpoint. It is a universally accepted direct measure of the benefit of an experimental drug or other treatment, and it is unequivocal and easy to measure. Demonstrating in a clinical trial that a drug improves OS, however, is no easy feat. It often requires trials with hundreds of patients that take years to complete.

Furthermore, with multiple treatment options now available for many types of cancer, patients can switch to other therapies if the treatment they are receiving in a clinical trial stops working. That’s good for patients, but it creates a conundrum for those who must interpret trial results: If a patient’s OS improved, how much of that improvement was due to the study drug and how much was due to subsequent treatments?

In this respect, explains Dr. Daniel J. Sargent, a biostatistician with the North Central Cancer Treatment Group (an NCI-sponsored clinical trials cooperative group) who has authored numerous articles about endpoints in cancer clinical trials, PFS offers an advantage over OS because it requires patients to be followed only until their disease progresses. PFS, therefore, measures only the effect of the study drug and is not diluted by subsequent treatments patients receive, as OS may be.

“Most patients stop taking the study drug when their disease begins to progress,” he says, “so the PFS clock stops at that point.” This also means that trials using PFS as an endpoint can be completed more quickly than trials using OS, and they generally require fewer patients.

A key advantage of PFS as a clinical trial endpoint, says Dr. Sargent, is that “it captures both a tumor-shrinkage and a tumor-stabilization effect.” This is important because, unlike conventional chemotherapeutic drugs that kill cancer cells, causing tumors to shrink, many new targeted drugs (including bevacizumab) work by other mechanisms, which may stop tumors from growing but don’t always cause them to shrink.

A concern with using PFS as a trial endpoint, says Dr. Sargent, is that it’s more subjective than OS and can be influenced by outside factors, including how disease progression is defined and measured, which may vary from one trial to another. For example, because progression is measured by X-rays or computerized tomography (CT) scans, measures of PFS can differ depending on how frequently those assessments are performed.

Other questions surrounding PFS include: What magnitude of improvement in PFS is clinically meaningful? And is an improvement in PFS beneficial to patients in and of itself, regardless of whether OS is also improved?

Dr. Jo Anne Zujewski, head of Breast Cancer Therapeutics in NCI’s Division of Cancer Treatment and Diagnosis, is emphatic that, at least in advanced breast cancer, an improvement in PFS is beneficial to patients in and of itself. “In advanced breast cancer, disease progression is often symptomatic and uncomfortable, so if we can delay that, it’s a...
not be required to understand the document. In addition, there will be a section that contains published scientific articles, in an easy, downloadable PDF format.

The website will also contain restricted access subpages, accessible only by the patient, the patient’s doctor and CPGR members. The delay in opening this website is to ensure security and maintain confidentiality. Medical records, radiographic images and scanned pathology slides can be uploaded to this site. This will allow CPGR members the opportunity to correlate clinical care with research endeavors. As CPGR grows, the ability to help promote patient care via this web interface will also increase.

All of the above was made possible by the willingness of patients and support groups to participate in the inaugural Pediatric GIST Clinic. We would like to thank everyone who contributed time and effort to help in this endeavor. You are truly the pioneers who have established the foundation for scientific pro-

plasma reference levels through a collaborative effort.

Other plans include forming a subgroup with the French organization, En-semble Contre le GIST, the Swiss organization, GIST-Selbsthilfegruppe Schweiz) and several other patient organizations to draft a working protocol for consideration by the entire international GIST community.

In addition, the LRG is setting up a comprehensive survey that includes evaluating long-term side-effects, patient compliance, mutational testing and plasma level testing and attempts to correlate the relationships between these four components. Priority will be given to evaluating long-term survivors to try to determine what sets them apart, particularly with reference to plasma level and mutational status.

Drum roll please...

Have you seen the new LRG Newsroom?

The Life Raft Group is proud to present the new LRG Newsroom! Here you can find a multimedia gallery, including webcasts, blogs, videos and member stories. You can also check out past LRG annual reports, recent news and educational GIST materials. Check back often for the most up-to-date GIST & LRG news!
which might save their lives.

4. **There is an alternative to this placebo protocol:** Although it may take more patients, time and money, there is no disagreement that a clinical trial for IPI-504 could be created with current best treatment substituting for a placebo.

In an October 2006 article on the efficacy and safety of sunitinib, and which was co-authored by George Demetri, the sunitinib principal investigator, the authors commented that “subsequent preliminary data suggest that discontinuation of imatinib in patients with GIST increases risk of disease progression and is associated with accelerated disease progression in some patients…With this perspective, continuing imatinib despite progression might have served as an alternative approach for the (placebo), for reasons of patients’ well being and because discontinuation of imatinib therapy might not represent the most current standard of palliative care. In the absence of a trial directly comparing sunitinib with continuing imatinib treatment after imatinib failure no definitive conclusion about the superiority of switching to sunitinib can be reached.”

We would submit that his words hold true for this new clinical trial as well.

Please see Jim Hughes’ article on page 4 for more information on the trials’ protocol.

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**Figure 1**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dose (mg/m²)</th>
<th># of pts</th>
<th>Best Response by RECIST</th>
<th># of Cycles per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30</td>
<td>6</td>
<td>SD, PD, PD, SD, SD, SD</td>
<td>3, 2.1, 1.3, 5</td>
</tr>
<tr>
<td>A</td>
<td>150</td>
<td>3</td>
<td>SD, PD, SD</td>
<td>0.2, 2</td>
</tr>
<tr>
<td>A</td>
<td>225</td>
<td>3</td>
<td>SD, SD, SD</td>
<td>5.7, 3</td>
</tr>
<tr>
<td>A</td>
<td>300</td>
<td>3</td>
<td>SD, PD, SD</td>
<td>5.2, 6</td>
</tr>
<tr>
<td>A</td>
<td>400</td>
<td>6</td>
<td>SD, n/e, SD, SD, SD, SD</td>
<td>3, n/e, 5, 3, 4, 4</td>
</tr>
<tr>
<td>B</td>
<td>150</td>
<td>3</td>
<td>SD, SD, SD</td>
<td>2.1, 3</td>
</tr>
<tr>
<td>B</td>
<td>225</td>
<td>4</td>
<td>SD, n/e, teta, teta</td>
<td>1.1, 1.1</td>
</tr>
</tbody>
</table>

This chart shows data from the IPI-504 Phase I trial. The best response by RECIST for any given patient is stable disease (SD), implying the drug works by stabilizing the tumor rather than shrinking it.

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**Pennsylvania GISTers meet!**

Kim Trout, Pennsylvania local group leader was a little disappointed when only one person showed up to the July 12 meeting. However, as Kim says, it was a “small, but mighty” day, because she was able to help another GIST patient, Ellen Baker (pictured, left). “I thought I was able to share important information with her and encouraged her to be her own advocate. I was glad to make a new friend and it was Ellen’s first time meeting anyone else who has GIST.”

The next Pennsylvania meeting is tentatively scheduled for **October 11**. Mark your calendars now, folks!

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**Global GIST Network adds new GIST representatives**

- **Cyprus**
  - George Constantinou
  - george@gnora.com

- **Dominican Republic**
  - Alejandro Miranda
  - ma.689.1215@gmail.com

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**Citations**


Schade offered a warm smile and a love of life

Jan “Butch” Patrick Schade of San Diego passed away peacefully at home on Sunday, June 29, 2008, he was surrounded by his loved ones. Butch was born on February 11, 1970 and raised in Cranford, New Jersey, before moving to San Diego. He was an avid surfer, loved motorcycles and had a passion for classic cars. He was employed as an estimator at Magnesite Specialties, Inc. He made the world a better place, his smile put everyone at ease. Butch brought happiness to the lives of everyone lucky enough to be part of his life. Butch was a loving fiancé to Kerry O’Sullivan with whom he shared his life for the past 14 years, the devoted son of Janet and James Stivale. He leaves behind brothers James, Brian and Patrick, Aunt Phyllis and many dear friends that he revered as family including his loyal friends, Brutus and Ozzy. In lieu of flowers please offer donations in Butch’s honor to the oncologists that cared for Butch so that their research can continue to battle this disease.

Donations can be made through the Dana-Farber Cancer Institute, c/o Andrew J. Wagner, MD, PhD, for GIST Research or UCLA Jonsson Cancer Center, c/o William Tap, MD, for GIST Research. Please visit www.butchschade.com for instructions on giving.

Mark your calendars!

- A gathering of GIST patients in California will be held, Saturday, August 16. Please contact Martha at 408-247-1045 or john.martha@sbcglobal.net for more information.

- Don’t forget! Life Fest is being held September 12-14 in Chicago. See page 2 for details and page 15 for a registration form.

Here is a photo from LRG member, Ellen Mayer’s (pictured, left) recent art show, “Evolution of the Original Eye”.

Congratulations Ellen!
Life Fest
September 12-14, 2008

Hyatt Regency O'Hare
9300 Bryn Mawr Ave.
Rosemont, IL 60018

For hotel reservations, please call the Hyatt Regency O'Hare at (847) 696-1234 *Indicate that you are with the Life Raft Group. The LRG rate is $109 (+tax) per night for single and double occupancy rooms.

You can also register online at: www.liferaftgroup.org

Name: ....................................................................................
Patient's Name (If different): ....................................................
The Patient is my: ...................................................................
Email: ....................................................................................
Address: ..................................................................................
..............................................................................................
City: ....................................................................................... State: ..............................................................................
Postal Code: .............................................................................
Country: ..................................................................................
Phone Number: ....................................................................... Email: .............................................................................

Please check all the apply:
LRG Member: ____  Gist Patient: ____  Caregiver: ____
Number Attending: _____ x $135= _____

☐  I would like to pay by credit card:
Please Circle One: AMEX   VISA   MSTRCARD
Credit Card Number: ................................................................. Exp. Date:.........................

The meeting schedule is as follows:

Friday: 6 p.m. Dinner Reception
Saturday: 8 a.m.— 5 p.m. Breakfast, Presentations, Lunch & Workshops
Sunday: 9 a.m.—1 p.m. Breakfast, Presentations, Candle Ceremony
Ensuring That No One Has To Face GIST Alone — Newsletter of the Life Raft Group — July 2008 — PAGE 12

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