Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

June 2005 | In memory of James Boucher, Rob Danielson, Carol Donnell, Daniel Hoffman, Matina Maisu | Vol. 6, No. 5

Rachel Knopp, left, and Julie Gilbert hug goodbye as the pediatric GIST meeting comes to a close.

$2 million pledged for GIST research

Life Raft will use grant from Novartis to focus on resistant tumors

Novartis, the Swiss pharmaceutical giant, is giving $2 million for research to identify and overcome GIST resistance to therapy.

Novartis CEO Dr. Daniel Vasella made the commitment in Boston after hearing a plea from Life Raft Executive Director Norman Scherzer. The $2 million grant is the largest single donation for GIST cancer research in history.

Scherzer made his pitch over breakfast with Vasella and David Epstein, president of Novartis Oncology. Scherzer noted that despite the remarkable clinical responses to tyrosine kinase inhibition, this therapy often fails, even in patients who had spectacular initial response to Gleevec. Scherzer noted this outcome is not surprising, as single-agent therapy has never controlled widely-metastatic solid tumors.

VASELLA

Because treatment of metastatic or unresectable GIST rarely, if ever, induces complete remission, most GIST will eventually develop resistance

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Young GIST patients find unity, hope

Families find strength in numbers, form bonds at pediatric GIST gathering

By Tricia McAleer

Families traveled from as far as the United Kingdom to meet one another in New Jersey for a pediatric GIST meeting held May 20-21.

GIST patient Rachel Gilbert and her mother, Julie, flew in from England. The Knopp family — GIST patient

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Advances reported at 2005 ASCO meeting

By Jerry Call

GIST patients with a particular genetic mutation are more likely to respond to Gleevec than those without the mutation, reported Dr. Michael C. Heinrich at one of plenary sessions of the annual conference of the American Society of Clinical Oncology, held May 14-17 in Orlando, Florida.

The results confirm previous observations and provide a foundation for molecular testing that can predict who will best respond to treatment with Gleevec.

A professor of medicine at Oregon Health & Science University in Portland, Heinrich's presentation was titled "Correlation of target kinase genotype with clinical activity of imatinib mesylate (IM) in patients with metastatic GI stromal tumors

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$2 MILLION

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mechanisms in the residual tumor cells. That's why funding is urgently needed to develop research programs to find targeted therapies to counteract GIST treatment resistance.

Dr. Dan Vasella, left, Norman Scherzer, center, and David Epstein meet for breakfast in Boston.

UNIQUE RESEARCH PARADIGM PLANNED

In response, Vasella agreed to provide the Life Raft Group with $2 million to develop a unique research plan and carry it out. Instead of researchers pursuing individual interests, often with minimal or no coordination with their peers, the Life Raft will recruit experts who'll draft a research plan to identify and overcome the mechanisms of GIST resistance.

The experts will be asked to identify key research components, including specific timetables, mechanisms for evaluation, and communications and coordination to include shared databases and publications. The experts will be asked to share data on an ongoing basis and agree to maximum collaboration and coordination.

Once this strategic plan is created, the Life Raft Group will seek proposals to carry out the plan's components, and fund the most promising.

"The hope is to create a new, proactive and coordinated research paradigm that will attract other research dollars looking for a faster and more effective way to achieve scientific breakthroughs," Scherzer said. "We are running out of time and we must think smarter about how to leverage limited resources to achieve major discoveries."

RESEARCH OBJECTIVES and PRIORITIES

The overall goal is to find combinations of therapies that benefit GIST patients. While the focus is GIST, the studies should provide insights in developing strategies for other types of metastatic solid tumors. Importantly, these studies will provide the biological rationale to guide clinical evaluations of multi-agent targeted therapies.

Researchers will see if there are advantages in attacking multiple targets simultaneously, whether this better kills the tumor and if it stops relapse.

Three main priorities have been identified:

Synergestic Drug Targets — Determine the critical signaling pathways that are activated when GIST progression begins during therapy. Expression and activation of receptor tyrosine kinase proteins, and crucial signaling intermediates, will be compared in GIST biopsies taken before therapy, and at time of GIST progression/ relapse while the patients are still receiving treatment. These analyses will be performed using cDNA profiling and phosphoproteome methods, which have been extensively validated in GIST models.

Preclinical validation of synergistic therapies — Do preclinical GIST cell line and mouse model studies to determine which combinations of targeted therapies show particular promise. These evaluations will be performed in primary and immortalized treatment-resistant GIST cultures, in non-GIST cell lines (Ba/F3 and NIH3T3) transformed by treatment-resistant kinase oncogene constructs, and in transgenic mice that develop GISTs. The laboratory identification and validation of synergistic therapeutic targets will drive the clinical translation of this work, leading to evidence-based algorithms for management of treatment-resistant GIST patients.

Pediatric GIST — Ten percent of funds will be prioritized to determine mechanisms of treatment resistance in pediatric GIST. Clinical responses to treatment are uncommon in pediatric GIST, where the biology of the disease is different — and often more indolent — than in adults. Yet several studies have shown that pediatric GISTs nonetheless feature strong expression of activated KIT proteins and it is likely that combination therapies involving novel drugs will ultimately prevail in this underserved group of GIST patients.

The studies will be useful in defining the scope, and limitations, of targeted therapies in GIST in particular and metastatic solid tumors in general. Such insights are essential for progress in targeted therapies, and will likely reveal that combinations of such therapies are needed to consolidate initial remissions, and to forestall the emergence of clinical resistance.

Sutent appears headed for approval

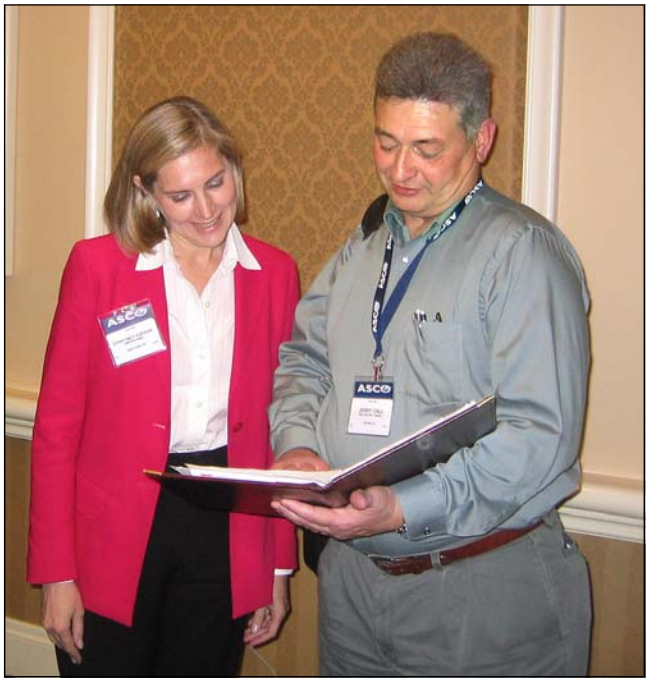
By Norman Scherzer

Each month we try to find out the latest news about clinical trials for GIST, a process that sometimes feels like describing the latest layout of chairs on the Titanic. As the relentless spread of GIST resistance claims an increasing number of lives, the need for a drug that repeats the initial miracle of Gleevec intensifies. So, too, do the conflicts inherent in clinical trials — where drug companies seek a proof of concept that wins government approval and finds a subsequent market niche that's competitive, and what GIST patients need to survive.

Sutent: To date there is one post-Gleevec drug that seems to be heading for FDA approval — SU11248 or Sutent (formerly called Sugen). This Pfizer drug has completed its initial phase III trial and is now available in a growing number of clinical trial locations as a treatment protocol no longer requiring a placebo. Preliminary data has shown that Sutent helps a substantial number of GIST patients whose cancer is resistant to Gleevec, generally by slowing down the progression of disease.

Interestingly, Sutent seems to work best among GIST patients who don't have an exon 11 mutation — the opposite of Gleevec, which works best on patients with an exon 11 mutation.

To improve access to Sutent, Life Raft representatives met with their counterparts at Pfizer and its contractor, Emerging Med, which manages access to its clinical trials, at the annual meeting of the American Society of Clinical Oncology. A special Emerging Med liaison and phone number has been created to help GIST patients and caregivers via the Life Raft Web site (see www.liferaftgroup.org/treat_trials_su11248.html) or call the Life Raft office at 1-973-837-9092).



Courtney Hudson, CEO and founder of Emerging Med, confers with Life Raft Science Coordinator Jerry Call

A pleasant surprise at this meeting was the willingness of Pfizer to open Sutent access to pediatric GIST patients under age 18 on a special need basis. The same Emerging Med liaison person will provide pediatric GIST families with help in getting Sutent.

As we go to press, we learn how important this assistance will have to be. A pediatric GIST family trying to get Sutent was unable to do so at a clinical trial site at major medical center because the trial physician was not comfortable treating a young GIST patient. The family is now searching for an alternative location.

AMG706: Coming out of the clinical trial starting date a little later than Sutent is AMGEN's AMG706. This phase II trial is close to its enrollment target of about 100 patients.

Although there is no published data yet, the Life Raft has anecdotal reports that this drug is active. Some GIST specialists opine that this drug will prove to be as effective as Sutent, perhaps with fewer side effects.

The challenge AMGEN faces is whether it can compete with Pfizer and win government approval. The challenge that GIST patients may face is whether they will be able to retain some access to AMG706 once clinical trial enrollment closes.

(Note: after surveying a dozen GIST specialists in the United States and abroad, the Life Raft found an interest and need for continued access to AMG706 after the clinical trial enrollment closes. This was reported back to AMGEN.)

NEW PHASE II TRIALS

Two new phase II trials have begun enrolling patients with Gleevec- resistant GIST.

Gleevec and Perifosine: Perifosine (KRX-0401), made by KERYX Biopharmaceuticals, is an oral drug that inhibits AKT, an anti-apoptosis protein. Apoptosis is a form of controlled cell death, a type of cellular suicide. A phase II trial is now seeking to enroll GIST patients at M.D. Anderson Cancer Center in Houston, Texas.

CCI-779: Made by Wyeth Pharmaceuticals, CCI-779 is an intravenous mTOR inhibitor. A phase II trial is now seeking to enroll patients at the Mayo Clinic in Rochester, Minn., and in the District of Columbia, Maryland, Michigan, Missouri and Wisconsin. For a complete listing, see the Life Raft Group's Web site at www.liferaftgroup.org.

— Norman Scherzer is executive director of the Life Raft Group

PEDIATRIC

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Clockwise, from left, Gordon Simmons (in black), John and Diana Lanza, Rachel Knopp, Sybil Knopp, Doug and Joy Knopp, Rachel and Julie Gilbert.

Leah, sisters Sybil and Rachel, and parents Doug and Joy, flew in from Seattle, Wash. Others drove: GIST patient Sile Bao and parents, Jennifer and Simon; GIST patient Malorie McBride and parents Brian and Dorothy; Diana and John, parents of GIST patient Kelly Lanza; Patricia and Chris, parents of GIST patient Stephanie Kastner; GIST patient Ashley Young and parents Danny and Toni; Gordon Simmons, father of GIST patient Meredith Simmons; Kanya Pannell, mother of GIST patient Shaun Pannell. Others present included Ray and Sheila Montague of the Arbor Foundation, established in memory of their son, Jonathon, who died from GIST; Life Raft staffers Pamela Barckett, Erin Kristoff, Tricia McAleer and Norman and Anita Scherzer; Ken Schou of GIST Cancer Research Fund; Sue Cohen of Tomorrows Children's Institute; and Drs. Cristina Antonescu and Michael La Quaglia from Memorial Sloan-Kettering Cancer Center.

Showing off their surgical pants fashions are, from left, Sue Cohen, Sybil Knopp, Rachel Knopp, Leah Knopp, Ashley Young, Sile Bao, Malorie McBride and Sheila Montague.

Families became fast friends over dinner Friday night at Rosa's Family Style Restaurant in Little Falls, N.J. Children and their parents enjoyed the warmth and comfort that is found in meeting other people with the same struggle. Jazzy the Clown and the Amazing Dick the magician donated their time for the evening's entertainment. Adults and children alike were mesmerized by wild balloon sculptures and nifty magic tricks.

The following morning, everyone carpooled to Gilda's Club in Hackensack, N.J. First to greet them was program director Ann Lambert, who provided the facilities for the meeting. The second person to greet the families was Stan Bunn, president of the Life Raft's Board of Directors. He sent his love and best wishes to all the families by phone from a subway station in London. The chances of getting cellular service underground, in a different country, are slim to none — but

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ASCO: Exon 9 mutations more likely to shrink on 800 mg. vs. 400 mg.

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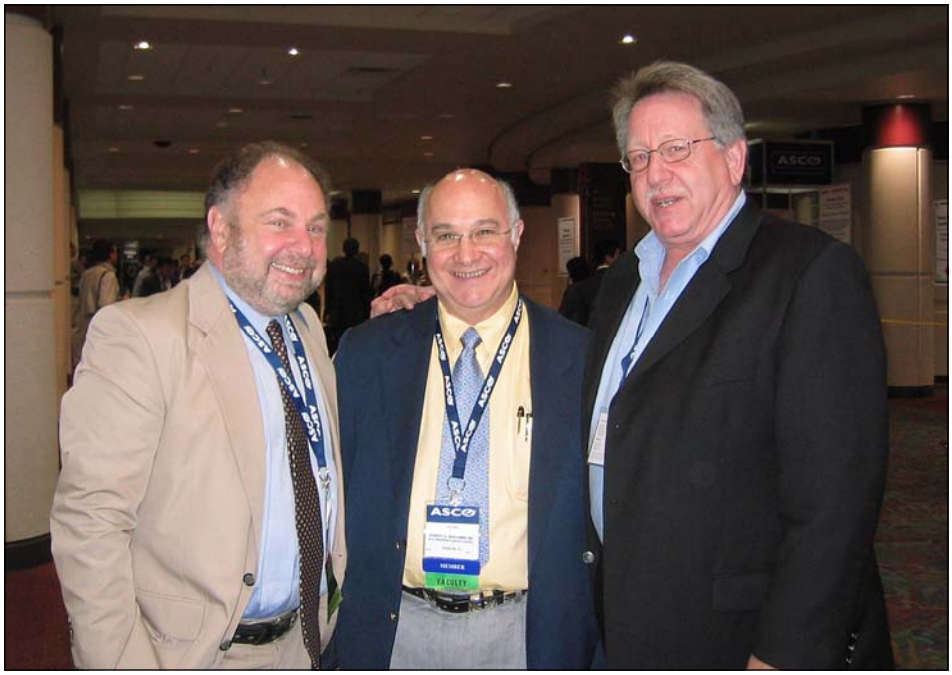
(GISTs) expressing KIT (KIT+)."

The objective of the study he reported on (CALGB 150105/SWOG S0033) was to correlate molecular abnormalities in pre-treatment GIST specimens with clinical response to Gleevec in patients treated in the S0033 phase III NCI trial. Some 344 patients had sufficient tumor samples to be included in this study. This is about 46 percent of the total number of patients in the phase III S0033 trial. The pathology of these 344 patients was reviewed by Dr. Christopher Fletcher of the Brigham & Women's Hospital. Of the 344 patients, 332 of them were confirmed to have GIST, while 12 patients (3.5 percent) were reclassified as non-GIST sarcomas.

Of the 332 GISTs analyzed, 324 (97.5 percent) were "KIT-positive" GISTs, and eight (2.5 percent) were "KIT-negative" GISTs. Heinrich also noted that 98 percent of KIT exon 9 mutations have a small intestine origin and 98 percent of PDFRA mutations have a stomach origin. The study data showed that both KIT-positive and KIT-negative GISTs have either KIT or PDGFRA mutations in about 87 percent of cases; however, the ratio of KIT to PDGFRA mutations was different. KIT-positive GISTs had KIT mutations 86 percent of the time and PDGFRA mutations in only 1.5 percent of cases. KIT-negative GISTs had KIT mutations in 50 percent of the cases, and PDGFRA mutations in 37.5 percent of the cases.

Kinase genotyping (checking for mutations in the various exons of c-kit and PDGFRA), was done by Heinrich and Dr. Christopher Corless, also of OHSU in Portland. Using gene expression profiling, three different groups (Subramanian et at, Antonescu et al, and Kang et al) have reported different molecular signatures for KIT exon 9, exon 11, and "wild-type" GISTs (no KIT or PDGFRA mutations).



Left, ASCO presenter Dr. Michael Heinrich of Oregon Health & Science University. Below, networking at ASCO are, from left, Dr. Lawrence Baker, University of Michigan, Dr. Robert Benjamin, M.D. Anderson Cancer Center in Houston, and Norman Scherzer, Life Raft executive director.

The study looked at c-kit positive patients with KIT exon 11 and exon 9 mutations and patients with no mutations to determine the likelihood of an objective response when comparing low-dose (400 mg.) to high-dose (800 mg.) Gleevec. Note that "objective response" measures tumor shrinkage using RECIST criteria, and does not necessarily equate to how long the therapy will be effective (time to progression).

The study found that there was no effect on dose in patients with an exon 11 mutation. The "odds-ratio" of high-dose vs. low-dose in these patients was 1.0 (p=0.96). This means that low-dose patients had the same odds (1.0) of an objective response as high-dose patients. Yet the study also found that the 25 patients with exon 9 mutations were much more likely to have an objective response on 800 mg. Gleevec than those on 400 mg., with an odds ratio of 8.0 — that is, eight times the chance of having a response.

"However," Heinrich noted, "when adjusting for multiple comparisons, and considering the small sample size, this difference was not statistically

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PEDIATRIC II

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somehow it worked.

The next caller was a surprise for all. Dr. Daniel Vasella, the CEO of Novartis Pharmaceuticals, called to wish the group well – and to say that Novartis would be giving the Life Raft Group $2 million for research, with $200,000 earmarked for pediatric GIST.

After settling in, the young adults went into a private session facilitated by volunteer Sue Cohen. They discussed individual backgrounds, issues that affect them and Malorie McBride's stylish purse. They designed their own personal surgical pants with themes of hope and survival and autographed each pair.

Parents and others, meanwhile, met in an informative session led by the Life Raft's executive director, Norman Scherzer. Expert opinions were heard from pathologist Antonescu, pediatric surgeon La Quaglia, pathologist Dr. Jonathan Fletcher from Brighams & Women's Hospital in Boston, and Life Raft Science Coordinator Jerry Call. Anna Costato, mother of GIST patient Claudia, also called in from Italy to participate in the discussion.

Above, Norman Scherzer, Rachel Knopp, right, Leah Knopp, front, and Daniel. Participating in activities at Gilda's Club, are, clockwise from far left, Sue Cohen (in black shirt), Sheila Montague, Ashley Young, Sybil Knopp, Leah Knopp, Sile Bao (at least her hands), Malorie McBride and Rachel Knopp.

"To be able to touch, hug and commiserate with other parents at one time was, I used to think, an impossible dream," said Gordon Simmons. "And to watch as the pediatric kids slowly but surely formed bonds was beyond words."

Before the group broke for lunch, Ashley Young led off in the "Surgical Pants Fashion Show." The girls waited patiently outside, whispering and giggling together, until introduced by Sue Cohen and Sheila Montague.

"As they lined up next to each other to get photos, bright smiles lit faces and made me weep as I saw these brave young souls who have endured so much pain and suffering," said Toni Young. "I saw their awesome resiliency shine through and the connection they made with each other was obvious."

The pants will be exhibited this coming November at ArtWorks Express Yourself-NJ, created by the Naomi Cohain Foundation to support art exhibitions by children and young adults with life-threatening illness.

After lunch, the group boarded a bus to tour New York City. The first stop

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ASCO II: Gleevec shown to work on KIT-negative GIST

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significant (p=0.62).

Heinrich presented data showing that patients with exon 11 mutations had a much longer median time to treatment failure (576 days) compared to patients with exon 9 mutations (308 days) or patients with no mutation (251 days).

The study concluded that there is no effect of Gleevec dose on objective response of KIT exon 11 mutant GIST. However, further study is needed to determine if KIT exon 9 mutant GISTs respond better to high-dose imatinib. Also, the study concluded that kinase genotyping is useful for:

— Confirming the diagnosis of GIST, particularly for c-kit negative GIST;

— Predicting response and duration of response to Gleevec;

— The design and interpretation of clinical trials to study new treatments for GIST.

NETWORKING WITH NOVARTIS: Getting together at the May 14-17 meeting of the American Society of Clinical Oncology is Norman Scherzer, Life Raft executive director, second from right, and Novartis officials, from left, Michael Boehler, Christian Hosius (Germany), Kalvin Kochhar (USA) and, right, Aydin Dortok (Poland).

GLEEVEC MAY WORK ON KIT-NEGATIVE GIST

In another presentation (abstract No: 9010), Dr. Martin Blackstein presented data showing the response rate and progression-free survival in KIT-negative GIST is not significantly different than KIT-positive GIST (43 percent vs. 49 percent progression-free survival at two years); however, a significant difference in survival was noted for KIT-positive vs. KIT-negative GIST (77 percent vs. 57 percent, estimated overall survival at two years).

The conclusions of this study are that Gleevec therapy can provide clinical benefit for patients with KIT-negative GIST and the high incidence of kinase mutations in KIT-negative GIST support a therapeutic trial of Gleevec for all GIST patients regardless of CD117 (KIT) expression. It should be noted that many indications for Gleevec only include patients with KIT-positive GIST — thus patients with KIT-negative GIST who could benefit from Gleevec might not be able to get it.

SUTENT BOOSTS SURVIVAL IN GLEEVEC-RESISTANT GIST

Dr. George Demetri reported that the new Pfizer drug Sutent (SU11248 or sunitinib malate) more than doubled survival and significantly reduced tumor growth and spread in patients with Gleevec-resistant GIST.

Demetri, of Dana-Farber Cancer Institute in Boston, presented phase III clinical trial data[1] for Sutent, an oral, multi-targeted kinase inhibitor. Sutent inhibits multiple signals including KIT, PDGFRA, PDGFRB, VEGFR1, VEGFR2, VEGFR3, Fms, FLT3, and CSR1R.

This study accrued 312 patients within one year and was conducted at 56 sites in the United States, Australia, Europe and Singapore. One out of every three patients received a placebo. Patients progressing were unblinded and those receiving the placebo were allowed to cross over and receive SU11248.

The primary study objective was to compare time to progression (defined by RECIST criteria) between the two arms. Secondary goals included objective response rates and overall survival, patient-reported outcomes, including pain control, safety monitoring, correlation of drug exposure with efficacy and safety, and evaluation of biomarkers and molecular target studies including kinase genotyping.

The first interim analysis for efficacy was done in January. At that time the primary endpoint (time to progression) was found to be statistically significant between SU11248 and the placebo. After discussions between Pfizer and the independent data and safety monitoring board, treatment was unblinded and all patients receiving the placebo were allowed to cross over.

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ASCO III: Tumors grew quickly for Pfizer patients on the placebo

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Patients receiving SU11248 had an 8 percent partial response rate vs. 0 percent for the placebo group. Stable disease was noted in 58 percent of SU11248 patients and in 50 percent of the placebo patients — but it is not clear from the data at what time point this was the case, particularly given the report that patients receiving SU11248 had a significantly longer median time to progression vs. placebo (6.3 months vs. 1.5 months). Progressive disease occurred in 20 percent of SU11248 patients and 39 percent of placebo patients. Some patients were not evaluable (too early or missing).

DEMETRI

SU11248 also lengthened overall survival in spite of the placebo group being able to cross over after progression. Finally, although all patients on the placebo were given the option of crossing over to the drug after being unblinded following progression, 46 of the 105 placebo patients did not. No explanation for this group was given.

AMG706 active vs. solid tumors

Dr. Lee Rosen of the John Wayne Cancer Institute in Santa Monica, Calif., presented abstract no. 3013, "Safety and pharmacokinetics of AMG706 in patients with advanced solid tumors."

This phase I trial was open to patients with many different types of solid tumors. AMG706 was generally well tolerated up to 125 mg. per day, every day. A total of 71 patients were entered into the trial. Forty-nine received the dose eventually chosen for further study — 125 mg./day.

In all, 56 patients are evaluable. Three patients have been on the study for more than one year. Four percent of patients had partial responses, and 61 percent had stable disease. The duration of stable disease was not identified in the study.

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) was used to evaluate the permeability of the blood vessels supplying blood to the tumors (tumor vascular permeability).

DCE-MRI showed reductions up to 37 percent in initial "area under the curve" on the third day and up to 61 percent on day 21 of treatment.

Fatigue and high blood pressure were the most common side effects. The high blood pressure was generally fairly easy to manage, with 23 percent of patients requiring some type of blood pressure medication.

The pharmacokinetic profile appeared desirable. Once per day dosing of AMG706 achieved the desired blood concentrations.

There was no evidence of drug accumulation (levels at day 28 were similar to those of the first day). AMG706 was found to be a weak inhibitor of CYP3A enzymes and clinically significant drug interactions are not predicted.

PET SCAN REVEALS EFFECTS OF SUTENT

Dr. Annick D. Van den Abbeele of Brigham and Women's Hospital of Boston presented abstract[2] on using PET scans to reveal kinase target inhibition with SU11248 in patients who have Gleevec-resistant GIST. The study showed that patients responding to SU11248 had a decrease in standard uptake valve (SUV) of the FDG tracer as soon as seven days after beginning SU11248.

A series of PET scans of a patient on a two-week on, two-week off drug schedule was shown. This patient had a dramatic decrease of activity seven days after starting therapy. Another PET scan taken on the last day of the two-week off drug period showed a rebound in activity, although the activity did not appear to be quite as high as a baseline scan. Another PET scan taken seven days after restarting SU11248 showed reduced activity that was similar to the PET scan taken seven days after beginning therapy.

An interesting question from the audience was whether PET scans were done before the patient stopped Gleevec. The answer was yes, and there was "a tremendous flare" in activity on the PET scan taken after the washout period, just before starting SU11248. This wash-out period flare-up suggests that there was still some response to Gleevec in "Gleevec resistant" patients.

GLEEVEC TOXICITY

Dr. Ronald DeMatteo presented an abstract[3] that showed that the toxicity profile of Gleevec for patients with no visible disease is similar to patients with metastatic disease. The notable exception is that doctors are not seeing bleeding in patients with no visible disease, suggesting that bleeding in metastatic patients in probably related more to the GIST tumors themselves

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ASCO IV

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rather than Gleevec irritation of the GI tract. The benefit of adjuvant Gleevec has not yet been defined, but researchers hope to have this data within the next year.

GIST MUTATIONS

Dr. Sebastian Bauer from Dana-Farber presented this poster (abstract 9034), KIT hyperactivation in imatinib-resistant GIST: Implications for salvage therapies. Two new Gleevec-resistant GIST cell lines were established from biopsy specimens and used in this study along with an existing GIST882 cell line. GIST882 has a primary KIT mutation in exon 13 (K642E) and is sensitive to Gleevec.

GIST48, one of the new cell lines, has a primary mutation in exon 11 (V560D). This primary mutation would normally be sensitive to Gleevec. But this cell line also has a secondary mutation in exon 17 (D820A) that causes these cells to become resistant to Gleevec.

GIST430 is the second new cell line. It has a primary mutation in exon 11, and a secondary mutation in exon 13 (V654A). This secondary mutation causes Gleevec resistance.

Levels of KIT protein were equal in all of the cell lines, but KIT activation was three to six times greater in the cell lines with secondary mutations compared to the Gleevec-sensitive GIST882 cells. PKC412 was found to inhibit the cell lines with secondary mutations, but may not inhibit certain Gleevec-sensitive primary mutations.

The study concluded:

— GIST secondary mutations can be associated with KIT hyperactivation and Gleevec resistance.

— Gleevec resistance is not absolute and varies depending on the type of resistance mutation.

— GIST proliferation and survival depend on the absolute (residual) levels of KIT activation after treatment with Gleevec.

— Gleevec resistance may be overcome with alternate KIT inhibitors or by targeting critical downstream signaling proteins, such as PI3K.

— PKC412 effectively inhibits cell lines with secondary Gleevec-resistant KIT mutations but may not inhibit certain Gleevec-sensitive primary mutations.

— The PI3K/AKT pathway is a critical signaling pathway in Gleevec-resistant GISTs and appears to be a relevant therapeutic target.

— JAK/STAT signaling seems to play a minor role for cell survival/ proliferation in GIST.

PKC412+Gleevec: stability for some

Dr. Peter Reichardt was the first author of abstract no. 3016, a phase I/II trial of PKC412 in combination with Gleevec (imatinib mesylate) in patients with Gleevec-resistant GIST.

Secondary kinase mutations represent the most common mechanism of resistance in GIST patients progressing on Gleevec therapy. In-vitro (test-tube) data suggests that PKC412 has activity against many of these secondary mutations. In-vitro data also suggests that PKC412 and Gleevec show synergistic activity when used in combination.

Nineteen patients were given 200 mg. per day of PKC combined with Gleevec at doses ranging from 600 mg. to 1000 mg. Using this combination, Gleevec exposure (blood concentrations) decreased ~70 percent after one month on the combination, either due to enzyme induction (liver enzymes metabolize Gleevec), or protein binding interactions.

REICHARDT

At the same time, PKC levels increased ~twofold by day 28 over those that were expected from previous studies of PKC alone in AML. The study was therefore amended to allow for dose escalation of Gleevec and temporary dose reduction of PKC. This resulted in reduced toxicity and increased levels of Gleevec in the blood equal to 600 mg. of Gleevec alone.

Two of five patients evaluable for response had stable disease at four months. The authors concluded that the preliminary evidence indicates the combination of PKC412 and Gleevec for Gleevec-resistant GIST works, and the study is ongoing.

GLEEVEC plus RAD001

Dr. Allan van Oosterom was lead author of the abstract[4] on the phase I/II trial combining RAD001 and Gleevec. The original phase of this trial combined 600 mg. Gleevec with weekly 20 mg. doses of RAD001. Only one of 13 patients had progression-free survival of four months or more. So this phase I study was amended to a daily dosing of RAD001 and the interruption of Gleevec for PK sampling was eliminated. The amended protocol compared 600 mg. Gleevec plus either 5 mg/day or 2.5 mg/day of RAD001. Seven of 18 patients demonstrated clinical benefit (four months or more of progression-free survival) and one

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PEDIATRIC III

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Young people with GIST and their parents get to know each other at dinner at Rosa's in Little Falls.

was Rockefeller Center. The girls joined Sheila Montague and pro-bono tour guide Marian Deal Smith for Bobby Brown makeovers at Sax Fifth Avenue. The ladies then moved on to see St. Patrick's Cathedral — and even managed to crash a wedding.

Hopping back on the bus, stories were traded while George, the friendly driver, navigated the coach through Times Square. For the younger Life Rafters, the highlight of this trip came when the bus passed the MTV Total Request Live studios.

The next stop was Madame Tussauds, a world-renowned wax museum. Jennifer Lopez and Brad Pitt greeted the group at the "opening night party." The girls got their pictures taken with the likes of *NSYNC, Lucille Ball, Oprah, Yoko Ono, John Travolta and the Spice Girls. Sybil and Rachel Knopp proved they could outpose Paris Hilton while Sile Bao proved she could out-laugh Robin Williams. The real show was when Rachel Gilbert sang on stage as the "American Idol" — and won!

After boarding the bus again, Leah Knopp, although she was starving, shared her very first New York pretzel with all her new friends. The coach made its way to the Hard Rock Café for dinner. The rain that had threatened to ruin the tour finally came down after everyone had nestled in for dinner — perfect timing.

Surrounded by rock 'n' roll memorabilia, all enjoyed good music, good food and good friends. Dessert arrived at the table with a candle and everyone burst into song to celebrate Sheila Montague's upcoming birthday. Husband Ray had leaked the information.

"It was so terrific to be able to meet other families facing the same nasty disease …," said Diana Lanza. "We feel so lucky to have this new extended family both at the Life Raft Group and all around the world, all pulling together for the same cause — to stamp out GIST in our loved ones."

Sunday morning, a tired but empowered group enjoyed breakfast at the hotel. The group discussed the weekend and the future of pediatric GIST research and treatment. With Gordon Simmons on trumpet, Rachel Gilbert sang "Amazing Grace" — truly unforgettable.

"Meeting with all the families and medical experts, hearing Rachel sing with Gordon on the trumpet, watching the girls get made up at Saks Fifth Avenue, and having a wonderful tour of NYC while candy was being tossed around the bus — what can I say," said Joy Knopp. "This meeting offered our family a unique opportunity to feel not alone in dealing with this disease."

After heartfelt goodbyes, all departed but the Knopps and the Gilberts who joined Norman and Anita at the Scherzer home for a laid-back barbecue to unwind before their long journey home.

"For us, this was the first time we had met anyone else with the disease and, as Rachel is the only child in the UK with GIST (as far as we know), she certainly has never met anyone around her own age with GIST," said Philip Gilbert. "Rachel summed it up perfectly on the way home. She said it was so nice being able to discuss symptoms and side effects with the other kids, and she no longer thought she was going mad." Added Toni Young: "I am uplifted by the fact that people do care about finding a way to treat this disease, and we patients and caregivers are not alone."

The Life Raft Group would like to express special thanks to Rosa's Family Style Restaurant, Dick and Judy Post for their phenomenal performance as Jazzy the Clown and the Amazing Dick the magician; Gilda's Club Hackensack and program director Ann Lambert for lending their facilities; Sue Cohen of Tomorrow's Children for an incredible morning working with our young GIST patients; Daniel Vasella for speaking with the families and bestowing enormous generosity for GIST research; Drs. Cristina Antonescu, Michael La Quaglia and Jonathan Fletcher for sharing their expertise; Ray and Sheila Montague, who were an integral part of planning and coordinating the gathering, and their Arbor Foundation for sponsoring the bus tour of New York; and Marian Deal Smith of Alternative Tours for donating her time to serve as an all-knowing tour guide; Bobby Brown, Sax Fifth Avenue for donating makeovers for the ladies, and to all the families who shared their experience, strength and hope with each other.

— Tricia McAleer is executive assistant of the Life Raft Group

In memoriam

Carol Donnell's gift: Seeing potential in others

Carol Maree Donnell died June 7, 2005, at her home after a 2½-year battle with GIST.

A resident of Auckland, New Zealand, she helped advanced cancer research by participating in an Australian trial of the Pfizer drug Sutent.

Carol was born June 6, 1957 in Auckland, the second daughter of Pat and Phil. She was exceptional at sports and would develop into a top badminton, squash and tennis player. Her first marriage at 18 was blessed with two sons, Paul and Mark. When her marriage ended, she went through a lonely and difficult time.

Carol met Roger when he was transferred to the bank where she worked. If it wasn't love at first sight it was pretty close; they were married 10 months later in November 1987.

Roger introduced Carol to God and they started attending Northwest Baptist Church in 1992. Shy by nature, Carol's desire to serve God was stronger than her timidity. She started off by helping in the Sunday school and ended up leading music at the church, singing in front of up to 300 children a week and their parents and caregivers.

"Carol loved what she did and she genuinely cared for the children and their families and her helpers," said Debbie, Carol's friend of 13 years, at her funeral. "She encouraged others to develop their gifts of service. too.

"My four oldest children each had very important tasks as helpers. It didn't matter how small the job was -- a 4-year-old handing out lollipops, a 12-year-old who laid out the biscuits and dried dishes, a 10-year-old who did the overhead and music and an 8-year-old who handed out the drinks. All were made to feel that they had a very important part to play in the running of the session.

The Donnell family in 2003, from left: Aimee-Rose, Carol, Rebecca and Roger. They'd been tossing petanque balls on the beach in front of their Te Atatu home.

"You see, Carol's greatest gift wasn't singing or dancing. It was encouragement. It was the ability to make people feel important and special and loved. Carol saw the potential in people and helped them reach that potential. She had the ability to make people believe in themselves."

In March 2004 Carol spoke at her church, talking frankly about her cancer. She told how she gained strength from the story of Shadrach, Meshach and Abednego from the book of Daniel, how they refused to worship a statue and were threatened with being thrown into a blazing furnace.

They responded by saying their God could save them from the fiery furnace. But even it He didn't, they told the king they would not worship the golden image.

"For me," Carol said, "cancer is like being thrown in the furnace. Most of the time I can feel God's arms around me and I can't feel the flames. But sometimes, I do feel the flames of grief and despair and sadness.

"I know God can heal me, and if that happens, praise Him, but if He chooses to take me to heaven, where I will be healed, He is still my God."

She was the wonderful and loving wife of Roger, and a caring mum to Paul, Mark, Rebecca and Aimee-Rose; a treasured sister to Jenny, Rosemary, Jane and Andrea; sister-in-law of Len, Bryan, Dave and Jason, loved aunty of Sarah, Sam, Frazer, Max, Ben and Oliver, dearly loved daughter of Pat and Roy.

Roger says Carol left behind a memories book for each daughter with photos and her memories of what each photo meant to her. "Carol also left a book to each girl in which she had written her favorite Bible verses, quotes and poems, and another book in which she had written the girls' favorite recipes."

Services were held June 10 at Te Atatu Baptist Church in Auckland.

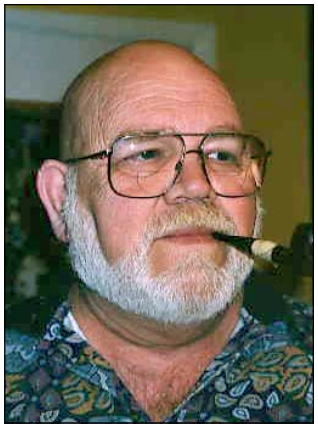
In memoriam

Jim Boucher was the favorite teacher of many

James M. Boucher, 70, of Indiana died Wednesday, May 18, 2005 at home.

He was born April 17, 1935 in Clairton. He graduated from Dormont High School in 1953 and Indiana State Teachers College, now Indiana University of Pennsylvania, in 1957.

He was a teacher by profession and passion. He instilled a respect for education and teachers in all he met. Says his daughter, Libby, "I can't tell you how many times and in how many places he was approached by a former student, grown men and women, who always said, 'Mr. Boucher, you were my favorite teacher.' He was my favorite teacher too."



James M. Boucher

He taught seventh grade social studies for 37 years with the Apollo-Ridge Area School District, retiring in 1995.

He was a quiet man who didn't talk much about his feelings, but expressed them through actions and through his willingness to do anything for his wife, his children and his friends.

Recalls Libby: "He joked with my mom, 'I told you I loved you on our wedding day. If anything changes, I'll let you know.' He had a great sense of humor, but it was dry and quiet, the kind you'd miss if you weren't really listening."

He enjoyed spending time with his family. "He loved golf and he played cards every other week with a group of other teachers, some still working and some retired," Libby says.

Boucher was a true optimist, holding on to hope until just the last couple months. "His final gift to us was going through with the BMS trial," says Libby, "moving to Boston, submitting himself to the constant needles and tests, all because we wanted a few more months with him."

He is survived by his wife, Mary R'Dell Williams Boucher, whom he married Dec. 28, 1960; two sons and three daughters: Steven and wife, Janet, of Tolland, Conn.; Janet Ann Boucher of Collinsville, Va.; Perry Schrello and husband, Dino, of South Park; Robert and wife, Lori, of Allison Park; and Elizabeth Miner and husband, Arthur, of Baton Rogue, La.; five grandchildren, Eric, Adam and Noah Boucher, and Michael and Mark Schrello; a sister, Bonnie Thomas and her husband, David, of Bethel Park, and his mother-in-law, Alice W. Constable of St. Marys.

He was preceded in death by his parents and a brother, Robert Boucher.

Memorial contributions may be made to Shannon's House, 76 Sewall Ave., Brookline, MA, 02446, or online at www.shannonhouse.org.

Rob Danielson, 54, survived 12 years

Robert William Danielson, 54, died May 20, 2005, in California after a 12-year battle with GIST.

A resident of Santa Clarita, Calif., he was born on Sept. 29, 1950, in St. Louis, Mo. He was a diesel mechanic.

He is survived by his wife, Jeannette Danielson; three daughters, Ivy, Ciara and Briana; a son, Ryan; his mother, Ethel Danielson, and a brother, Fred (Sylvia) Danielson.

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patient had a partial response. The regimen selected for phase II studies was 600 mg. Gleevec plus 2.5 mg/day of RAD001. The study is continuing.

The study did note that clinical benefit was not apparent in patients with known exon 9 mutations in the primary tumor (n=5). However, one Life Raft Group member with an exon 9 primary tumor resistant to Gleevec, SU11248 and BMS-354824, now appears to be responding (with shrinkage) to Gleevec plus RAD001.

GLEEVEC PRIOR TO SURGERY YIELDS RESULTS

Dr. Jonathan C. Trent of M.D. Anderson Cancer Center in Houston Texas, reported on apoptotic and antivascular activity of imatinib in GIST patients (abstract 9001).

Patients with planned resections of tumors were treated with a short course of 600 mg. Gleevec a day prior to surgery. Before Gleevec, patients had biopsies to acquire baseline tumor samples. The effects of short-term Gleevec administration were examined. The researchers noted both a direct anti-tumor effect of apoptosis (programmed cell death) and an antivascular effect. It is interesting to note

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ASCO VI: In one trial, Gleevec continued until 6 hours before surgery

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that Gleevec was continued to within six hours (yes, hours) of surgery.

SUTENT FATIGUE TIED TO THYROID FUNCTION

Dr. Jayesh Desai presented an abstract[5] on a study that found some patients (25 of 64) developed abnormal TSH levels after 5.4 months (median) on SU11248. TSH is a measurement of thyroid function. Nineteen of the 25 patients were treated with thyroid hormone replacement. The study found that the thyroid dysfunction noted may account, in part, for fatigue previously described with SU11248. All patients could be effectively treated with thyroid hormone replacement.

AFTER SURGERY, CONTINUE GLEEVEC

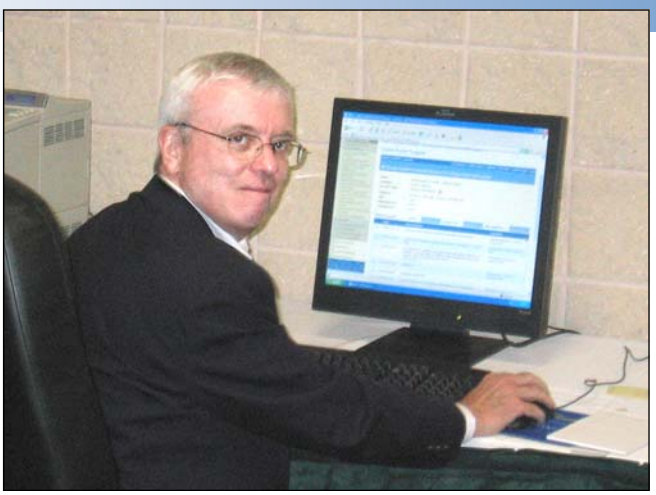
Two abstracts (9037 and 9038) were about the role of surgery and Gleevec. Both found that surgery in patients who were still responding to Gleevec was generally successful as long as Gleevec was continued after the surgery. Surgery in patients with Gleevec-resistant GIST was much less successful. In the 9038 study, six patients with Gleevec-resistant GIST had progression a median 6 months after surgery. The study's authors found that patients with progressive disease are candidates for treatment with second-line molecularly targeted therapies, since surgery is likely of minimal benefit. The 9037 study recommended that in patients with progressive disease, indications for surgery should be individualized.

'NEW' LESIONS MAY NOT BE NEW

Kim M. Linton, MBChB, MRCP, was the first author of a study (abstract 9047) on liver lesions in two GIST patients. In both patients, CT scans taken eight to 12 weeks after the start of Gleevec showed the appearance of new, low-density liver metastases consistent with progressive disease, although other sites of disease had become smaller. Patient 1 had considerable symptomatic improvement despite the CT scan showing "new lesions," so treatment was continued. All sites of disease remained stable for two years at the same dose of Gleevec.

Patient 2 developed new symptoms so treatment was stopped. Later, it was considered that the development of new low-density liver lesions on the early CT scans may have been due to cystic changes within tumors that were already there but not visible on the initial CT scans. Gleevec was therefore restarted two years later (at a time of rapid progression) and a significant response was seen.

The authors conclude that following Gleevec treatment, a fall in lesion density due to cystic change can result in increased conspicuity of liver metastases, which may look like new lesions but were actually pre-existing. This should not be confused with the development of new lesions.



Jim Hughes, member of the Life Raft board of directors, keeps tabs on what's happening via the Internet at the May 14-17 meeting of ASCO.

GLEEVEC CROSSES BRAIN BARRIER?

Dr. Amir Khan gave abstract 9050, "Efficacy of Imatinib in Metastatic GIST to the Brain." This is the case report of a patient with liver metastases who stopped Gleevec after five months of treatment. Within a month, the patient had multiple lesions in the brain, believed to be GIST. The patient restarted Gleevec at 400 mg. a day and improved within two weeks. An MRI done 10 weeks later showed complete resolution of the lesions. This case and another similar case reported earlier suggest that Gleevec can cross the blood-brain barrier, contrary to earlier reports.

Jerry Call is science coordinator of the Life Raft Group. Life Raft members present at 2005 ASCO conference included Penny Duke, Jim Hughes, Norman Scherzer and Marina Symcox. Penny and Marina represented GIST Support International.

[1] Demetri: Abstract 4000, A phase III, multicenter, randomized, double-blind, placebo-controlled trial of SU11248 in patients following failure of imatinib for metastatic GIST.

[2] Van den Abbeele: Abstract 9006-Imaging kinase target inhibition with SU11248 by FDG-PET in patients with imatinib-resistant gastrointestinal stromal tumors (I-R GIST).

[3] DeMatteo: Abstract 9009, Adjuvant imatinib mesylate in patients with primary high risk GIST following complete resection: Safety results from the U.S. Intergroup Phase II trial ACOSOG Z9000.

[4] Van Oosterom: Abstract No. 9033, A phase I/II trial of the oral mTOR-inhibitor everolimus (RAD001) and imatinib mesylate (Glivec/Gleevec) in patients with GIST refractory to imatinib.

[5] Desai: Abstract 3040, Hyprothyroidism may accompany SU11248 therapy in a subset of patients with … GIST and is manageable with replacement therapy.

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Who are we, what do we do?

The Life Raft Group is an international, Internet-based, non-profit organization offering support through education and research to patients with a rare cancer called GIST (gastrointestinal stromal tumor). The Association of Cancer Online Resources provides the group with several listservs that permit members to communicate via secure e-mail. Many members are being successfully treated with an oral cancer drug Gleevec (Glivec outside the U.S.A.). This molecularly targeted therapy represents a new category of drugs known as signal transduction inhibitors and has been described by the scientific community as the medical model for the treatment of cancer. Several new drugs are now in clinical trials.

How to join

GIST patients and their caregivers may apply for membership free of charge at the Life Raft Group's Web site, www.liferaftgroup.org or by contacting our office directly.

Privacy

Privacy is of paramount concern, and we try to err on the side of privacy. We do not send information that might be considered private to anyone outside the group, including medical professionals. However, this newsletter serves as an outreach and is widely distributed. Hence, all articles are edited to maintain the anonymity of members unless they have granted publication of more information.

How to help

Donations to The Life Raft Group, incorporated in New Jersey, U.S.A., as a 501(c)(3) nonprofit organization, are tax deductible in the United States.

Donations, payable to The Life Raft Group, should be mailed to:

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