Sugen offers option when Gleevec fails

Novel compound works when cancer develops resistance to imatinib

WASHINGTON, D.C. – Two new therapies for metastatic cancer are showing significant clinical activity, according to research presented July 14 at the 94th Annual Meeting of the American Association for Cancer Research (AACR).

The studies examined the potential anti-tumor benefits of a combination therapy for colorectal cancer and a multi-targeted oral therapy for Gleevec- (imatinib) resistant gastrointestinal stromal tumors.

In one study, the addition of the anti-angiogenesis agent bevacizumab (Avastin) to traditional IFL chemotherapy proved both safe and effective in patients with advanced colorectal cancer, according to researchers at Duke Comprehensive Cancer Center.

“We feel confident that this novel combination therapy offers a new and improved therapeutic option for colorectal cancer patients,” said lead author John DeSantes, M.D., associate professor of Oncology.

In the other study, the multi-targeted oral therapy SU11248 (Sugen), administered alone or in combination with Gleevec, significantly delayed tumor growth in patients with advanced GIST who had stopped responding to Gleevec.

“As Gleevec becomes more widely used, it is important to develop new therapies for patients who become resistant to it,” said lead author Eric Foster, M.D., associate professor of Oncology.

GIST patients see new clinical trials

Gleevec, SU11248 will be joined by other new therapies in near future

By Jerry Call

Gleevec, SU11248 will be joined by other new therapies in near future. It has also set a very high bar for other treatments.

Gleevec has also introduced many patients in the Life Raft Group to clinical trials. I am not sure what the percentages are, but I am confident that many more Life Raft Group patients participate in clinical trials now than in the pre-Gleevec era.

As wonderful as Gleevec is, some GIST patients do not respond to it and some eventually stop responding to it. We recommend that whenever possible, patients failing Gleevec participate in a clinical trial. There are many possibilities for each patient. It is important to have options for new drugs.

Finding doctors who are knowledgeable about gastrointestinal stromal tumor and how to treat it should become a lot easier in the future. Two organizations, the Connective Tissue Oncology Society and the Life Raft Group, are combining forces to create an international directory of physicians specializing in GIST and sarcoma. This directory will be maintained on the Life Raft Group Web site and in the Life Raft Group office in New Jersey.

The CTOS, headquartered in Alexandria, Virginia, U.S.A., is the only medical organization that focuses upon
combination will be beneficial for patients with colorectal cancer,” said Dr. Herbert Hurwitz, assistant professor of medicine at Duke, the study’s lead investigator. Continued research is needed, he said, to see if bevacizumab combined with other chemotherapy regimens will apply to other cancers.

In a study of patients with advanced gastrointestinal stromal tumor whose cancer had develop resistance to the standard therapy Gleevec, use of the multi-targeted tyrosine kinase inhibitor SU11248 proved effective for many patients, according to a study at Dana-Farber Cancer Institute in Boston, Mass.

“While imatinib induces objective responses and can control GIST in the majority of patients, the incidence of resistance to imatinib increases over time, and alternative strategies to control this life-threatening disease are needed,” said lead investigator Dr. George Demetri, associate professor of medicine at Harvard Medical School and director of the Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Boston, Mass.

Imatinib has captivated the scientific and medical communities by the impressive ability of this oral drug to shrink and control even the most massive abdominal tumors of GIST patients by inhibiting a specific uncontrolled enzyme known as a kinase.

“SU11248 was developed to target multiple signaling “switches” called kinases within cells, and our data indicate that this agent can molecularly target the cancer cells of GIST differently than imatinib, thereby allowing these resistant patients to be successfully treated.”

SU11248 not only targets the tumor cells themselves, but it is also a very powerful anti-angiogenesis agent, blocking the growth of blood vessels that might otherwise feed the tumors.

This phase I study was designed to test the best way in which to administer SU11248, as well as to assess the differences in biological activity between SU11248 and imatinib in GIST patients. Groups of patients were treated at starting doses of 25, 50, or 75 mg per day for two to four weeks, followed by a 14-day rest period. The molecular mechanisms by which SU11248 affects the tumor cells have been carefully studied and these show important differences in the inhibition of uncontrolled signaling molecules such as the KIT receptor tyrosine kinase and related targets in comparison with the standard Gleevec therapy.

Updating previous summaries of this work, Demetri reported on the ongoing results from this active trial. Forty-five patients with GIST have been treated with SU11248. Early results have been reported from 39 of these patients via biopsies and correlative imaging studies. Of these patients, the majority (72 percent) exhibited reductions in tumor-associated metabolic activity as seen via PET scanning.

After one week on SU11248, routine pathology exams (looking at a tumor biopsy sample under a microscope) failed to detect these biological changes; however, by using a more sensitive marker to study the tumors before and after treatment, the researchers were able to see clearly the impact of this therapy: the rate of tumor cell growth (as measured by the Ki-67 proliferation index) decreased in 12 of 17 patients (71 percent) with matched tumor biopsy specimens.

These results have already translated into clinical anti-tumor activity in these imatinib-resistant GIST patients for whom no other therapy existed before.

The development of SU11248 as a potential treatment for imatinib-resistant GIST “is an exciting example of the new world of targeted therapy,” Demetri said. “We can analyze cancer cells to identify mutations, then screen drugs in the laboratory that target those specific mutations. The resulting therapies should be more effective and less toxic than traditional chemotherapy, which attacks normal cells as well as cancerous ones.”

Directory: Physicians are invited to sign up via Internet

Physicians should sign up for this online directory by going to www.liferaftrgroup.org/doctor.htm and completing the simple form.

“Any sarcoma/GIST specialist in the world is welcome to sign up,” said Scherzer. “We expect to have this new directory up and running in about one month, and we expect that it will become a valuable resource for patients, and their doctors, around the world.
Global sales of Gleevec up 102% in first half of ’03

BASEL, Switzerland – With sales of $7.6 billion, Novartis’ pharmaceuticals business delivered double-digit growth of 18 percent in the first half and second quarter of this year, outpacing the global market.

Novartis’ overall share of the global healthcare market has risen to 4.3 percent from 3.9 percent a year ago.

Sales of Gleevec/Glivec for chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST), rose 102 percent worldwide, and 43 percent in the U.S.

Gleevec is now Novartis’ second biggest product, benefiting from recent approvals in Europe and the U.S. for first-line treatment in CML and for GIST, and for U.S. approval of juvenile CML.

As sales continued to exceed expectations, the number of patients on the Gleevec/Glivec Patient Assistance Program rose to 4,300, providing many needy patients access to treatment at reduced or no cost.

Life Rafters hold New Jersey luau

Norman and Anita Scherzer hosted a gathering of Life Rafters on Sunday, Aug. 3 at their New Jersey home. Not just any old summer barbecue, but a luau.

“The celebration was lively and upbeat with a great theme,” reports Life Rafter Dan Cunningham. “Chef Nor and Miss Anita did a bang-up job of delivering an assorted delicious menu, and (Scherzer) grandson Matt Mattioli was an excellent mixologist for some tasty pina coladas. Tricia McAleer, the Life Raft’s administrative assistant, arranged for some gentle, intermittent showers to keep us cool!”

Life Rafters are, clockwise from bottom left: Frank, caregiver to Martine Godleski; Mickey, caregiver to Dan Cunningham; Dan Cunningham; Norman, caregiver to Anita Scherzer; Tricia McAleer, caregiver to us all; Danny, caregiver to Ashley Young; David Portnoy; Ruth, caregiver to David Portnoy; Bernie Kaplan; Bracha, caregiver to Bernie Kaplan; Bill Roth; Francis, caregiver to Bill Roth; Carole, caregiver to Joan Angerer; Joan Angerer; Toni, caregiver to Ashley Young; Ashley Young; Martine Godleski and Anita Scherzer.

Adds Norman Scherzer: “Dan Cunningham and Bernie Kaplan volunteered to coordinate the New York City area Life Raft Group. As is always the case with gatherings like this, you cannot tell the patients from the caregivers.”

Ensuring That No One Has To Face GIST Alone — Monthly Newsletter of the Life Raft Group — August 2003 — PAGE 3
Clinical trials: They may be a GIST patient’s best hope

From Page 1

advantages to this such as:

• A medical team that is familiar with GIST.
• Clinical trials move GIST research forward.
• Medical treatment and monitoring are usually better.
• This is generally the only way to access drugs that have not yet been approved.

Like many with cancer, GIST patients join clinical trials in a bid to survive, and often do not have the time to wait for more conclusive results.

We do recognize however, that participation in clinical trials is difficult, if not impossible, for some patients. Some may not be eligible. Some live in places where clinical trials are limited. With this in mind we have attempted to list some current options that might be considered.

Keep in mind this disclaimer: We are not doctors and information we offer should be discussed with your doctor. Because patients may be trying to survive the lethal time gap of clinical research, we have pushed the envelope of verifiable information. Extra caution is therefore needed and we invite the clinical researchers to comment or clarify.

Sugen SU11248

More is known about the results of the Sugen SU11248 clinical trial than any other alternative to Gleevec. About two-thirds of patients that fail Gleevec respond to SU11248. It is by far the best-understood option and is the current clinical trial of choice for patients failing Gleevec. Failure to respond to Gleevec has been a prerequisite for acceptance into this trial.

This trial requires staying in Boston (Dana-Farber Cancer Institute) or New York (Memorial Sloan-Kettering Cancer Center) for a considerable time, due in part to the extensive testing required for phase I patients.

To date, 11 of 18 patients (61 percent) have exhibited disease regression or stable disease (2-28 percent tumor reduction) lasting more than four months, and objective anatomic responses continue to evolve over time.

It is our understanding that this trial is now moving into phase II at Dana-Farber. The initial period patients must spend there should be less for phase II patients than phase I patients. Phase II trials may start at other locations in the near future.

The following message was sent June 6 to the Life Raft Group from Dr. George Demetri:

“Dear members of the GIST community,

“Now that the ASCO meeting is over, we can all more fully discuss the current state of the art in the newer options for GIST patients.

“As you have probably heard, we are planning to move the SU11248 treatment option quickly into a global clinical trial. This will represent a logistical challenge, since we would ideally wish to do this very, very fast, and we will be drawing up these plans soon. In the meanwhile, our plan is to continue the current clinical trial which is open here in Boston at Dana-Farber Cancer Institute and was also recently opened in New York City at the Memorial Sloan-Kettering Cancer Center.

“We have heard that Pfizer is supportive of our plans, and for that we are most grateful.

“Other promising options also exist and will be explored in a variety of strategic clinical trials. However, the SU11248 is by far the most well-explored option for patients with GIST at this time.

“Thank you all for the support that you have shown to our team and to the investigative teams interested in GIST worldwide. This sort of collaboration should enable the research to continue to move forward as rapidly as possible and advance the field with positive therapeutic results and with a greater understanding of the directions we should take in the future.”

We wish to thank Demetri, Pfizer, and all of the other behind the scene people involved in organizing these trials. We hope that trials will be globally available since this drug seems so promising.

While SU11248 is the most proven drug for those that fail Gleevec, several other clinical trials have either started or will start in the near future for GIST. The first of these is the combination of Gleevec and RAD001 (RAD).

RAD001 plus Gleevec:

Both RAD001 and Gleevec are manufactured by Novartis. RAD001 is
an mTOR inhibitor that may improve the effectiveness of Gleevec. mTOR is a downstream target in the AKT pathway. AKT is a survival pathway that is activated by KIT and many other receptors. It is hoped that simultaneous inhibition of KIT and mTOR will result in increased effectiveness over Gleevec alone.

Trials have already started in Belgium and at Dana-Farber. Patients accepted at Dana-Farber are those who stopped responding to both Gleevec and Sugen. In Belgium, there is no Sugen trial hence patients selected are those who stopped responding to Gleevec.

It has long been speculated that GIST — and most cancers in general — will eventually be treated with a “cocktail” of various drugs. This is the first such combination to come to clinical trials for GIST.

PKC787
This is another Novartis drug. It is an inhibitor of KIT, PDGFR, and VEGFR. Although we are not aware of any current trials solely for GIST, the targets of this drug would be relevant to GIST. On paper this drug appears to be similar to SU11248.

AMG706
This drug was developed by Amgen.
More new drugs: Some aimed at a variety of cancers
From Page 5

Phase I trials will be at the John Wayne Cancer Institute in Santa Monica, California and at M.D. Anderson Cancer Center in Houston, Texas. We have heard that this drug is similar to SU11248, however, we have not verified the targets of this drug. These early phase I trials are open to many different types of cancer besides GIST.

**PKC412 plus Gleevec:**
This trial has not started yet.
PKC412 is another Novartis drug. It is an inhibitor of KIT, as well as protein kinase C (PKC); however PKC is probably the main target of this drug. Recently it has been suggested (Duensing et al, 2003) that protein kinase C theta is constitutively activated in all GISTs including those which are c-kit negative.

A phase I trial is anticipated at Oregon Health & Science University in Portland this October. Details are lacking, but our early understanding is that PKC412 may be given together with Gleevec in this trial.

**Gleevec + Gentasense**
Genta Inc. makes Gentasense, an antisense drug. These drugs are small, chemically modified strands of DNA. Gentasense inhibits the production of bcl-2. Bcl-2 is an anti-apoptosis protein. In one recent study, 11 of 11 GIST tumors expressed bcl-2.

It is postulated that inhibition of bcl-2 might tip the balance of pro-apoptosis/anti-apoptosis proteins toward apoptosis. Apoptosis is a form of controlled cell death, a type of cellular suicide where the cell issues its own death warrant.

Our understanding is that a phase I trial with this combination may start soon at Dana-Farber.

An overview of antisense drugs can be found at the Genta Web site: http://www.genta.com/genta/Products/antisense.html

The following two trials are much more speculative than the preceding trials. They are listed because they use somewhat novel approaches that differ from the preceding trials in their mechanisms of action:

**Carboxyamidotriazole (CIA)**
CIA is an anti-angiogenic drug being developed by the National Cancer Institute. It inhibits calcium (Ca2) influx into the cell. It addition to being anti-angiogenic, inhibition of calcium influx may also be cytotoxic to some types of cancer cells.

This drug is in phase I trials for solid tumors. This trial also includes the more traditional chemotherapy, Paclitaxel. It is also in phase III trials for patients with non-small cell lung cancer.

One of the potential advantages of this drug is that, in theory, it might work against several of the known mechanisms of resistance of Gleevec treatment of GIST. These include mutations that render Gleevec ineffective. One concern with this trial is that we are not aware of any pre-clinical evidence of in-vitro effectiveness in GIST tumor cells.

**17-AAG**
This is a benzoquinoid ansamycin antibiotic, currently in clinical trials, which binds to heat shock protein 90 (hsp90), causing de-stabilization of various hsp90-dependent kinases involved in proliferation and survival of malignant cells, (including KIT).

17-AAG, by a novel mechanism, may be effective in the treatment of mastocytosis. In addition, 17-AAG may have a role in the treatment of other diseases where c-kit plays a crucial role in pathogenesis, including GIST, mast cell leukemia, some types of acute myelogenous leukemia and testicular cancer.

One of the theoretical advantages of targeting hsp90 is that GIST tumors that harbor mutations outside of exons 9 and 11 might still be sensitive to the effects of hsp90 inhibition.

Our concerns with this drug (and hsp90 inhibitors in general) are:
- Limited oral bioavailability and solubility. Second generation HSP90 inhibitors may be designed to overcome some of the drawbacks of 17-AAG. They could also be engineered to target specific functions of hsp90, which may not only provide greater molecular selectivity and clinical benefit but may also increase understanding of the complex functions of this molecular chaperone.
- The drug is difficult to use, with an unsatisfactory formulation, and is currently limited in its availability.
- It does not appear to be very specific. Drugs that do have very specific targets (like Gleevec) tend to have fewer side effects and less toxicity.

Life Raft on the move!

The Life Raft Group office is moving! It will close Aug. 28 and reopen Sept. 3 at 40 Galesi Dr., Wayne, NJ, 07470. The new phone will be (973) 837-9092.

Mark your calendars:
**Southern California** Life Rafters will meet Sunday, Sept. 7, at the Lakewood home of Floyd Pothoven, the SoCal area coordinator for the Life Raft. For details, contact him at floyd@lasersealer.com.

**Detroit Life Rafters** will meet Saturday, Sept. 13 at Gilda’s Club. Contact Alan Tobes at atobes@comcast.net. Guests will include Norman Scherzer, Tricia McAleer, John Poss and Gerald Knapp.
Laura Marie Blanchette of St. Albert, Alberta, Canada, died Aug. 4 after a long and courageous battle with GIST. She was 47. She entered Heaven’s gates in the loving arms of her husband of 25 years, Mitch, as well as her children, Sarah and Curtis. Laura and Mitch joined the Life Raft Group in January of this year. She is also survived by her brothers, Dennis (Barb) and Randy; father-in-law and mother-in-law, Albert and Yvonne; brothers-in-law, Clem (Zeny) and Guy (Ginger); sister-in-law, Jackie (Gil) Coulombe; she also leaves behind her mother, Anne (Pat) Sheridan; as well as many relatives and friends. She was preceded in death by her father, Carl, and by three aunts.

Prayers were held Aug. 7 at St. Albert Funeral Home. The Rev. John Hesse celebrated a memorial Mass of Christian burial at Holy Family Church on Friday, Aug. 8, followed by a reception at the Holy Family Catholic Church Hall.

Friends may make memorial donations to the Stollery Children’s Foundation, 4th Floor, 11402 University Avenue, Edmonton, AB T6G 2J3. Arrangements were by St. Albert Funeral Home, (780) 458-2222.

In Memoriam

There have been 27 deaths in the Life Raft Group to date:
- Jim Ackerman, 49, Jan. 16, 2001, husband to Betsy, father of Jill and Tom.
- Amy Barney, 25, June 10, 2001, wife to Reed, mother of Joshua.
- Jeff Prichard, 52, July 11, 2001, husband to Joyce, father of Gregory and Scott.
- Ron Martinez, 60, July 25, 2001, husband to Jo Ann, father of Ron, Wendy, Natalie.
- Bruce Gunn, 43, Nov. 8, 2001, husband to Roisin, father of Seamus, Liam, Brendan and Aislinn.
- Mary Golnik, 50, April 18, 2002, wife to Gary, mother to Timothy.
- Ana Maria Baldor-Bunn, 30, April 19, 2002, wife to Stan, mother to William.
- Stewart “George” Wolf, 51, April 19, 2002, husband to Maggy, father to Thomas.
- Michael Cornwall, April 19, 2002, husband to Cathy.
- Jerry Pat Rylant, 61, May 5, 2002, husband to Pamela, father of four, grandfather to 10.
- Todd Hendrickson, 44, June 29, 2002, husband to Janet, father to Max, Tyler and T.J.
- Nora Shaulis, 42, Nov. 4, 2002, wife to David, mother to Griffin.
- Kathy Colwell, 45, Jan. 5, 2003, wife to Tom, mother of Katherine, Mary and Tom.
- Cynthia G. Whitson, 64, Jan. 19, 2003, wife to Jerry, mother to Steve, Jill, Randy and Donna.
- Laura Blanchette, 47, Aug. 4, 2003; wife of Mitch, mother of Sarah and Curtis.

Setting the record straight

I enjoyed reading David Josephy’s article “Targets, targeted therapy reports abound at AACR.” (July newsletter.) I was glad to see that our studies were included in this article.

However, I would like to point out that Andrey Frolov is a graduate student in my laboratory at the Fox Chase Cancer Center, where all the research was performed. He will be receiving his Ph.D. in September. In fact, Andrey received a Scholar-In-Training Award from the American Association for Cancer Research for this research.

Sincerely,

Andrew K. Godwin, Ph.D.,
Director, Clinical Molecular Genetics Laboratory
Director, Biosample Repository Department of Medical Oncology, Fox Chase Cancer Center
Philadelphia, PA
This photo was taken on Saturday, Aug. 2, in Denton, Texas, U.S.A. at 13,500 feet over a small airport facility that was called “Sky Dive Texas.”

“My son and I do fun things together,” says Life Rafter Andrea Fuller, “like celebrate Christmas in Italy, Acapulco, Mexico City and Mazatlan — this year is Belize. We scuba dive, snorkel with the manatees, and this was on our list of things we wanted to do some day.”

By diving in tandem, Andrea had no control over anything, “which was fine with me,” she says. For that matter, Andrea told her instructor that her eyes would be closed from the time the door was opened until he maneuvered her out of the plane.

“The air rushed past us at 127 miles per hour in the 7,500-foot free fall,” recalls Andrea. “He pulled the chute at 5,000 feet. Gliding down the rest of the way was more gentle, floating over green pastures, a few cows and the grassy air field.

“The landing was an easy sort of short skid with our legs making a four-point soft impact, mine being out in front and his being somewhat flexed backwards.

“Next time you are flying imagine crawling out the window and experiencing every emotion — terror, freedom, ecstasy — and a singular experience with someone you love making a memory that lasts forever.”

What’s more remarkable is that in June of 2000, Andrea was in New York Presbyterian Hospital, in a wheelchair, being pushed to most of her appointments. She’s truly a Gleevec success story.
Who are we and what do we do?
The Life Raft Group is an international, Internet-based, non-profit organization providing 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 inhibits the growth of cancer cells in a majority of patients. It 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:
The Life Raft Group
40 Galesi Dr.
Wayne, NJ 07470

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