Sutent given U.S. approval

Pfizer says drug will be available for use Feb. 3

The United States Food and Drug Administration (FDA) announced Jan. 26 that it has approved Sutent (sunitinib) for patients with gastrointestinal stromal tumors (GIST) and advanced kidney cancer.

It was the first time the agency has approved a new oncology product for two cancers simultaneously.

Sutent, which received a priority review and was approved in less than six months, is a tyrosine kinase inhibitor. The once-daily, 50 mg. capsule blocks several enzymes that deprive the tumor cells of the blood and nutrients needed to grow.

"Today's approval is a major step forward in making breakthrough treatments available for patients with rare and difficult to treat forms of cancer," said Dr. Steven Galson, director of FDA's Center for Drug Evaluation and Research. "New targeted therapies such as Sutent are helping FDA expand options for patients for whom there are limited alternatives."

According to the American Cancer Society, about 6,000 new cases of GIST and 32,000 cases of advanced kidney cancer are diagnosed each year.

Sutent won approval for the treatment of Gleevec-resistant GIST and for GIST patients unable to tolerate Gleevec, the current treatment for GIST. In clinical trials, researchers did an early analysis of data that showed Sutent delayed the time it took for tumors or new lesions to grow. Specifically, the median time-to-tumor progression for patients treated with Sutent was 27 weeks compared to six weeks for patients given a placebo.

Of 312 clinical trial participants, 207 received Sutent, while 105 were given placebos.

Typically, patients in cancer trials are not given placebos because it is considered unethical to deny them effective treatments. But Sutent maker Pfizer said a third of the patients were given placebos in this trial because no standard drug is known to work against such stomach tumors once they develop resistance to Gleevec.

When it became clear that patients taking Sutent were surviving longer than the placebo group, all patients in the study were allowed to start taking Sutent.

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Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

January 2006 Volume 7, Number 1

Challenges ahead for the GIST community

Last month's newsletter reviewed the exciting developments that have occurred in the GIST world in the past five years. This month, Jerry Call, Life Raft Science Coordinator, shares his views on the challenges the GIST world is likely to face in the future.

By Jerry Call

Writing about the past is easier to discuss. It deals with people, events, dates and facts. The hard parts are emphasizing the most important events and knowing that many important people were left out of the story, either because I simply was unaware of their role or because of limitations about the level of detail possible in a newsletter article.

CALL

Writing about the challenges that I think the GIST world will face in the future is a more difficult task. At the risk of appearing supremely arrogant, I will peer into my layperson's crystal ball.

Understanding the GIST world is like looking through a prism. When you look through a prism, the whole picture (white light) is separated into distinct colors. Looking at GIST, each of us sees only a piece of the whole story as though we were looking through a prism but can see only

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Infinity launches trial of IPI-504 vs. GIST

Early clinical trial will see if novel treatment addresses Gleevec resistance

Editor's note: In the November newsletter of the Life Raft Group, Science Coordinator Jerry Call wrote about the development of a new inhibitor that targets the protein that stablizes KIT, the driver of GIST. On Jan. 10, the maker of this new inhibitor announced it has started clinical trials for GIST treatment.

CAMBRIDGE, Mass. (PRNewswire) — Infinity Pharmaceuticals Inc. has announced another early clinical trial of IPI-504, the company's heat shock protein 90 (Hsp90) inhibitor and lead investigational anti-cancer agent.

The study will evaluate the safety, pharmacokinetic profile and potential effectiveness of IPI-504 in patients with gastrointestinal stromal tumors (GIST) whose cancer is resistant to Gleevec (imatinib mesylate).

This open-label, dose-escalation phase I clinical trial of IPI-504 is being conducted at Dana-Farber Cancer Institute in Boston, under the direction of Dr. George Demetri, director of the Center for Sarcoma and Bone Oncology.

"We are very excited about this phase I clinical trial of IPI-504 in patients with refractory GIST as it pioneers a novel treatment paradigm for these patients with an unmet medical need," said Demetri. "Previous treatments for GIST have been dramatically effective but over time we have seen the emergence of resistance to targeted therapy such as Gleevec, and this leads to progression of the cancer. IPI-504 has an important new mechanism of action with the potential to treat patients with resistant disease.

"Even more importantly," Demetri noted, "GIST may serve as a bellwether of activity, since the mechanism of action of IPI-504 may also apply to patients with breast cancer resistant to Herceptin, lung cancer resistant to Tarceva, and multiple myeloma resistant to VELCADE."

In preclinical work performed with Dr. Jonathan Fletcher's lab at Brigham and Women's Hospital in Boston, Infinity Pharmaceuticals has demonstrated that IPI-504 kills GIST cancer cells as effectively as Gleevec in vitro (in the test tube). Moreover, when cancer cells have mutations that make them resistant to Gleevec, IPI-504 kills these cells with even greater effectiveness. The more mutated the GIST cells become, the more sensitive they are to IPI-504.

These data were presented in November at the molecular targeting meeting held in Philadelphia by the National Cancer Institute, the American Association of Cancer Researchers, and the European Organization for Research and Treatment of Cancer.

"The initiation of this additional phase I trial of IPI-504 represents an important milestone for our lead product candidate and a significant validation of our strategy to discover and develop therapies that attack cancer cell survival mechanisms," said Julian Adams, Ph.D., Infinity's chief scientific officer. "We are delighted to be collaborating with Dr. Demetri and his outstanding team of scientists and caregivers at the Dana-Farber on this study."

ABOUT IPI-504

IPI-504 is Infinity's novel anti-cancer agent that potently and selectively inhibits Hsp90. IPI-504 has broad anti-tumor activity in animal models as a single agent as well as in combination with existing anti-cancer therapeutics.

Research shows that inhibition of Hsp90 forces cancer cells to "commit suicide" through a process of programmed cell death or apoptosis. In addition to Gleevec-resistant GIST, IPI-504 is currently undergoing evaluation as a monotherapy for relapsed or relapsed, refractory multiple myeloma in a multi-center, phase I, dose-escalation trial. Interim data from the first phase I trial of IPI-504 was presented at the annual meeting of the American Society of Hematology held Dec. 10-13 in Atlanta, Ga.

ABOUT GIST

The American Cancer Society reports that GIST is the most frequent form of gastrointestinal sarcoma, a life-threatening disease highly resistant to traditional chemotherapy or radiation treatment. The ACS estimates that between 4,500 and 6,000 Americans develop GIST each year.

In a majority of cases, specific mutations in cellular signaling enzymes called KIT or PDGFRA allow the survival signal of the mutated cancer cell to be switched "on" all the time. Both KIT and PDGFRA are signaling enzymes that belong to the class of tyrosine kinases and are responsible for sending growth and survival signals inside the cell.

The mutations in KIT or PDGFRA allow the GIST cells to grow uncontrollably and spread (metastasize). The initial identification of tyrosine kinase mutations in GIST has allowed for the development of targeted kinase inhibitors, such as Gleevec, as an effective treatment of the disease.

However, over time new kinase mutations evolve so that the targeted kinase inhibiting drugs are no longer effective at treating the disease.

Fight GIST *and* follow your dream

Mother proud of the accomplishments of her daughter

By Diana Lanza

As the mother of four sons, ages 26 to 36, and a 16-year-old daughter, I worked for 30 years in the employee benefit world to help send our kids to college. Once our boys were through school, I opted to retire and spend more quality time with our daughter.

Two weeks after I retired, she became sick. I was fortunate to be home full-time, although becoming a "nurse," per se, in my retirement was not exactly what I had in mind. However, I would never trade the close bond we've developed as a result.

Kelly was diagnosed with stomach GISTs three years ago at age 13. Kelly had always been a very healthy child with rarely even an ear infection; however, after returning home from a Disney vacation in February 2002, Kelly complained of always being tired.

A checkup and a blood test showed that she had mono but soon she began to suffer abdominal pain. To make a long story short, we went from her team of pediatricians to various gastroenterologists and heard many different diagnoses ranging from "stressed at school" to "abnormalities in her stomach," while she had to deal with six months of invasive tests and weight loss.

After a misdiagnosis where we were advised that her MRI showed everything to be normal, the same films were read by a radiologist at Children's Hospital of Philadelphia (CHOP). This resulted in the need for an additional endoscopy ultrasound and, ultimately, the shocking diagnosis of GIST.

Given how rare this type of cancer is, our team of doctors at CHOP consulted with Dr. George Demetri at Dana-Farber Cancer Institute for advice on Kelly's treatment and surgery. After a baseline PET scan, she was immediately put on Gleevec to see if it would be effective in shrinking her tumors. Three weeks later, a follow up PET scan confirmed the effectiveness. She was then taken off Gleevec to prepare for surgery.

Mom and caregiver Diana Lanza, and her daughter and GIST patient Kelly, 16.

Editor's note: This article is the latest of several articles about young people of the Life Raft Group. It also provides a foundation for a new series: "Caregivers of The Life Raft Group." We do not necessarily choose the roles we get, but the people featured here certainly carry them out with courage. With cancer, the patient receives the empathy and support while the caregiver receives the burden and pretends not to notice the weight. The Life Raft Group welcomes the opportunity to recognize the caregivers of the world.

On Oct. 30, 2002, she underwent a six-hour surgery that resulted in a complete gastrectomy when the surgeon found small GISTs throughout her stomach but, fortunately, not in the margins or anywhere else.

Kelly was put back on Gleevec for a year. Also, a new pouch stomach with a six-ounce capacity was built from a section of her intestines. A J-tube was inserted during the surgery to help her gain back some of the 20 pounds she had lost and to maintain her nutrition while learning to eat on her own.

She was on the J-tube and various pain meds for 18 months but we were gradually able to cut back as she was able to tolerate more foods by mouth. The J-tube was finally removed and she was weaned off the pain meds when her weight exceeded 100 pounds. Luckily, she had tolerated the Gleevec extremely

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one color. I, as a caregiver, might see only the red; a patient might see orange, a researcher a blue color, someone from pharma a violet color. Within each group we must make further divisions, for no two people experience exactly the same circumstances.

So please understand that when you read my opinions on the challenges of the future, they are influenced by what I see through *my* prism; my insight into the GIST world.

SECONDARY RESISTANCE

Despite the large number of GIST patients who initially benefit from Gleevec, most have tumors that will eventually become resistant to Gleevec. This is a common problem with cancer treatments.

Resistance to Gleevec after having an initial response is called "secondary resistance." Overcoming secondary resistance is one of the most important challenges facing GIST researchers.

In GIST patients, secondary mutations in the target gene, c-kit, are the largest known mechanism of resistance. Secondary mutations in GIST patients also occur in an alternate receptor, PDGFRA.

Several approaches to overcoming this resistance are possible. One strategy is to design drugs that bind to KIT just like Gleevec but that have a somewhat altered structure that fits better into the altered binding pocket of KIT. AMN107, for example, is a modified form of Gleevec that may inhibit some secondary mutations in KIT that are insensitive to Gleevec.

A variation of this would be to combine two (or more) inhibitors with activity against different mutations in an effort to inhibit a broad spectrum of mutations.

Another tactic may be to bypass the problem of drug binding to the many different conformations possible in KIT or PDGFRA, and inhibit these proteins using a different technology. Some possibilities include antisense technology, siRNA technology, or HSP90 inhibitors. Of these possibilities, HSP90 inhibition took the lead when a phase I trial for IPI-504, an HSP90 inhibitor by Infinity Pharmaceuticals, began this month (see article on Page 2). The antisense and siRNA technologies don't appear to be very far along at present.

Targeting proteins downstream of KIT or PDGFRA is another direction considered to overcome Gleevec resistance.

Further defining and overcoming other methods of secondary resistance such as protein overexpression and activation of an alternate receptor also remain a challenge.

PRIMARY RESISTANCE

Initial resistance to Gleevec occurs in about 15 percent of GIST patients. Some of the problems dealing with primary resistance are similar to secondary resistance and some are quite different. One particular PDGFRA mutation, D842V, is insensitive to Gleevec. What's needed is a drug that fits into the binding pocket of this mutation. While this mutation is rare, it's still the most common PDGFRA mutation.

KIT exon 9 mutations don't respond to Gleevec as well as the most common exon 11 mutation. Exon 9 mutations are somewhat of a problem from both the primary and secondary resistance aspects. While more research is needed to better understand exon 9 mutations, Sutent already offers some clinical relief, as it is effective in about 80 percent of Gleevec-resistant exon 9 mutations.

The third major type of primary resistance occurs with GIST tumors that don't have KIT or PDGFRA mutations. These tumors are called "wild-type" (for) KIT/PDGFRA. Part of the "wild-type" mystery was solved when researchers discovered the PDGFRA mutations that occur in 5 to 7 percent of GISTs (see the "GIST and Gleevec: 5 years of progress" article in last month's newsletter). More research is needed to find the "driver" for the remaining wild-type GISTs.

GIST AS A CHRONIC DISEASE

There is a lot of talk about moving away from the concept of curing cancer and moving towards treating cancer as a

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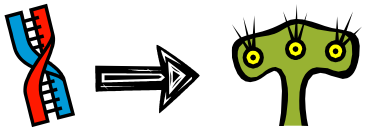
GIST 101: Cell division and cancer

• Mutations in critical genes cause cells to become cancerous.

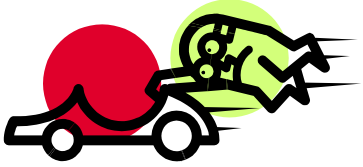


• Cell division in normal genes is controlled.

• "Oncogenes" promote cell division. They are like gas pedals. on your car.

• "Tumor suppressor genes" inhibit cell division; these are like brakes in the car.

• BUT cell mutations change these functions. They activate oncogenes and make them like stuck gas pedals ... and they inactivate tumor suppressor genes, meaning they cut the brakes.



This process is like a car out of control and contributes to or causes cancer development.

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"chronic disease." Gleevec is one of the best examples of how this may be possible.

Gleevec does not cure GIST (or chronic myelogenous leukemia), it just keeps it under control. About half the GIST patients who take Gleevec will have significant tumor shrinkage, while about a third will have less significant shrinkage, or stability.

Gleevec has been one of the most important milestones ever in the war on cancer. It marked the beginning of the molecularly targeted era. It is also a prime example of treating cancer as a chronic disease.

Treating metastatic GIST as a chronic disease is likely to continue for quite some time, and the historic gains made using this concept should be loudly acknowledged.

Despite this incredible success, treating GIST as a chronic condition should only be an intermediate goal. Research into ways to overcome secondary resistance is *vital* and should be supported to the best of our ability.

At the same time, I believe that it is possible to pursue a *parallel path* that tries to improve upon the effectiveness of Gleevec with an ultimate goal of curing GIST.

While many (perhaps most) GIST patients would be quite happy to take Gleevec or a similar therapy forever to control their disease, there are several concerns. The first is that Gleevec resistance (in GIST more so than chronic phase CML) is proving far too common.

The second concern with the "GIST as a chronic disease" philosophy is that while most GIST patients can maintain a reasonable quality of life, a few can't, either because of side effects from Gleevec or the advanced stage of their cancer. Side effects such as fatigue, nausea and diarrhea can be difficult to live with if they continue long-term. One symptom that is difficult to manage in a chronic fashion is bleeding. Although rare, bleeding represents a significant challenge for some patients.

A third concern with treating cancer as a chronic condition is the cost. Gleevec has dramatically extended the survival of GIST patients with metastatic disease. But the cost is significant. Gleevec (most patients take other medications as well) and other targeted therapies such as Avastin (for colon cancer) and Nexavar (for kidney cancer) are very expensive. Then there are the CT scans, blood monitoring and visits to doctors. I'm not suggesting we throw away 30 years of (slow) progress in the war on cancer because treating cancer as a chronic condition is too expensive; that would be foolhardy. I merely acknowledge the fact that this philosophy is expensive.

The good news and an argument for the "treat as chronic disease" philosophy is that the mechanisms of resistance in GIST are becoming fairly well understood. The incredible *focus* that results from having a single target (*either* KIT or PDGFRA) being so important to the proliferation and survival of GIST, and having an effective inhibitor (Gleevec), is what allows the biology of GIST and the mechanisms of resistance to Gleevec to be dissected so thoroughly. Add to that the comparisons that can be drawn from the Gleevec for CML story and you end up with GIST, CML and Gleevec creating models for molecularly targeted cancer therapies.

As more progress is made in the war on cancer, we can expect that more common cancers will be increasingly treated with molecularly targeted therapies. As this happens, huge costs will be incurred as patients, governments and insurance companies try to fund these advances in treatments.

STABLE DISEASE

Most people consider stable disease to be a huge victory in the war on cancer. I do as well, but I also consider it a challenge. For many GIST patients, Gleevec kills many — perhaps even most — of their tumor cells. For some GIST patients, Gleevec kills few tumor cells but it does keep them from proliferating — resulting in "stable disease." No matter what type of response patients have, Gleevec seldom, if ever, kills all of their cancer cells. This means that patients will have to continue taking Gleevec as long as it continues working.

Efforts to improve initial responses to Gleevec and responses in "stable patients" has the potential for gain in several areas. One is simply improved symptomatic relief. In a few patients this symptomatic relief could be substantial, even profound.

If we acknowledge that resistance arises in tumor cells that drugs don't kill, then attacking stable disease may be beneficial. One question is whether the residual stable tumor cells are easier to kill than cells that become resistant to Gleevec. While intuition would suggest this is true, I'm not convinced it is. However, I *am* convinced that trying to understand and (eventually) target both gives the maximum chance of success.

The more we understand residual disease, the better chance we have of developing effective adjuvant therapies.

While acknowledging that residual/stable disease may turn out to be more complex (especially more heterogeneous) than we'd like, I still believe that the potential benefits justify research into this area. I was glad to see that researchers involved in The Life Raft Group resistance project seem to agree and have made "stable disease" one of their priority areas for research.

PEDIATRIC GIST

The primary cause of GIST is a mutation in c-kit (that affects the KIT protein) in 80 to 85 percent of adults, or PDGFRA in 5 to 7 percent of patients. Knowing the primary cause in adults provides the rational for therapy. And, thankfully, Gleevec is an effective therapy.

In pediatric GIST, the primary cause isn't known. Hence understanding the biology of pediatric GIST and, specifically, finding the most important mutations is the most important challenge facing GIST researchers. Understanding pediatric GIST may also reveal clues

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Navigating Medicare Prescription Drug Plan D

By Elizabeth Braun

Care is required when selecting a Medicare Prescription Drug Plan D. Not all plans have the same formularies — that is, the list of commonly prescribed medications. It is used by insurance companies to determine coverage. Co-pays, quantity limits and coverage vary significantly.

To determine if the drug plan you're looking at is right for you, start by going to www.medicare.gov. There will be a link, "Compare Medicare Prescription Drug Plans."

Close to the bottom of the screen there will be a heading, "Where would you like to begin?" Under that heading will be "Find a Medicare Prescription Drug Plan." Click on the orange arrow to the right of this line.

This new page has a couple of sections; these are the directions for using section B: "General Search." Go ahead and click on the box that says "General Search."

There are three components to fill out: your zip code, what type of coverage you now have, and eligibility for additional help. Fill them out as best as you can.

For this exercise, "07470", "None of the above" and "No" were used. Click "Continue." (It may ask for your county.)

Follow these Steps to Navigate this Complex System

1. Go to www.medicare.gov.
2. Click on "Compare Medicare Prescription Drug Plans."
3. Click the orange arrow next to "Find a Medicare Prescription Drug Plan."
4. Click the box "General Search."
5. Answer the three questions and click "Continue."
6. Click "Choose a Drug Plan Type."
7. Click "Search for Medicare Prescription Drug Plans."
8. Click "Enter my Medications."
9. Type drug name and click "Search for Drug."
10. Click "Continue with Selected Drugs."
11. Click "Change/Update My Drug Dose & Quantity."
12. Adjust dosage and click "Update Dosage/Quantity."
13. Click "Continue with Selected Drugs."
14. Click "Continue to Plan List."
15. The Plan List is on this page.
16. If you have gotten this far, you deserve an award!

On the new page, scroll and click "Choose a Drug Plan Type." Scroll to section C and click "Search for Medicare Prescription Drug Plans." In section B, click "Enter my Medications." In section A, type the name of your drug and click "Search for Drug." You may repeat this step for each drug you take.

When you are done, click "Continue with Selected Drugs." A new box will appear that says "Change/Update My Drug Dose & Quantity." Click it. Adjust the dosage and click, "Update Dosage/Quantity." If you are taking six 100 mg. tablets a day, you would put in Gleevec TAB 100mg and 180. This is the tablet and number of them that you require in a month.

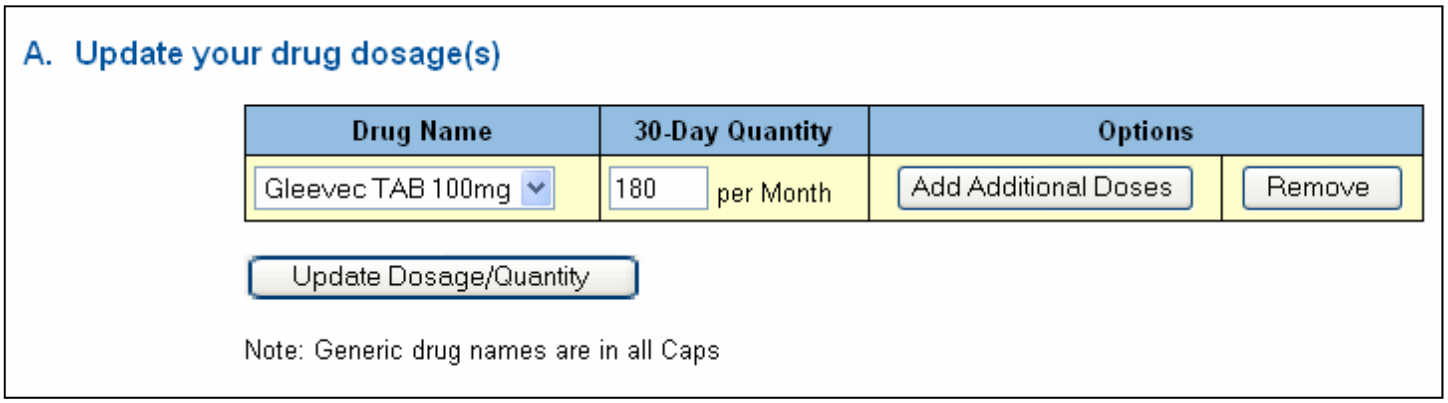
Now click "Continue with Selected Drugs," then "Continue to Plan List." Here is the list of plans available in your area. There is a lot of information here, but don't feel overwhelmed. If you click on the title of a column, it will provide a description of the column at the bottom of the table.

You can view more information for each plan by using the pull down menu under "More About this Plan." Once you have narrowed down the plans, if you click on the name of the drug plan, contact information is provided for that company.

Call the company and confirm their drug plan is the right one for you.

If you need more help navigating the system, you may call Novartis' Gleevec Help Line at 1-877-Gleevec (453-3832) or on the internet at www.gleevec.com. Medicare can be contacted at 1-800-Medicare (633-4227).

Should you have a prescription plan that either limits or doesn't cover Gleevec, there is an appeal process that will be covered in a future article.



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that fill in some of the knowledge gaps in adult GIST.

The most difficult obstacle for pediatric GIST researchers is probably the scarcity of resources, specifically tumor tissue samples. Consolidating the limited resources and getting them to the right researchers is a top priority of the Life Raft Group, as is a dedicated pediatric tissue bank and basic research into finding the causes of pediatric GIST.

CLINICAL TRIALS

The early and tremendous success of Gleevec introduced GIST patients to the world of clinical trials. Prior to Gleevec there was no effective therapy for metastatic or inoperable GIST. There was a window of time — from July of 2000 until February of 2002 — when Gleevec was only available in clinical trials (although it was available "off-label" in 2001).

With 85 percent of participants benefiting in the early clinical trials of Gleevec, GIST patients came to depend on these clinical trials for survival. Most of these responses were fairly long-lasting as well with a median time-to-progression of about two years.

By 2002, as some of the early GIST patients were becoming resistant to Gleevec, Sutent entered clinical trials for GIST. While Gleevec-resistant patients didn't see the same spectacular results, they were still good (see Sutent below).

As GIST patients stopped responding to Gleevec, they sought out new clinical trials. These included AMG706, Gleevec plus RAD001, Gleevec plus PKC412, BMS-354825, Gleevec plus AMN107, Gleevec plus Perifosine, BAY 43-9006, CCI-779, and the latest drug, IPI-504.

SUTENT

Sutent (formerly known as SU11248) has won U.S. approval for Gleevec-resistant GIST, and it is a welcome addition to the GIST treatment arsenal. It is particularly nice that it seems to be most effective in patients that typically have primary resistance to Gleevec, specifically patients with KIT exon 9 mutations and "wild-type" patients.

Sutent seems to significantly benefit 60 to 65 percent of patients, most of whom experience stable disease. About half of Sutent patients will progress in slightly over six months. Many will have significantly more than six-months' benefit.

THE 'CURSE OF THE CURE'

There was a recent editorial in the journal, "Nature Clinical Practice Oncology" by Vincent T. DeVita Jr., titled "The curse of the cure." He wrote: "We are in some ways victims of our own success in the management of childhood leukemia and advanced Hodgkin's disease (HD). Leukemia was the first childhood malignancy to be cured by chemotherapy, and HD was the first tumor of a major organ system in adults, in its advanced stages, to be cured by chemotherapy. In both instances, as the majority of patients respond to chemotherapy, investigators are faced with the challenge of reducing the toxicity of treatment while still offering patients the maximum chance of cure."

In other words, it was hard to make further progress in treating these diseases because the existing treatments were successful, but toxic.

In GIST, a potential "curse of the cure" looms, albeit a bit differently. While Sutent has been approved in the U.S., it is *not a cure* and only about half of the patients get more than six months' benefit from it. We still need much better treatments for Gleevec-resistant GIST. These treatments must be proven in clinical trials.

Gleevec-resistant patients are harder to treat than patients who've never had Gleevec. Patients who are resistant to both Gleevec and Sutent are harder to treat than patients resistant only to Gleevec.

While it's risky to generalize too much, my impression is that as you treat cancer with therapy after therapy, it becomes harder to treat with each failure.

It's possible that a drug with good to excellent activity against Gleevec-resistant GIST might have marginal activity in Gleevec- and Sutent-resistant GIST. How would you know if you only tried it in Gleevec/Sutent-resistant GIST?

With Sutent's approval, we have a new challenge: How do we maximize the patient's therapy and at the same time maximize advances in GIST treatment in general? Should all patients try Sutent after failing Gleevec? Or should some patients go directly into other clinical trials? How do you choose? And will Sutent's approval — clearly good news for patients — slow overall progress in the war on GIST? Can the GIST community avoid "the curse of the (not quite) cure?"

MOVING TOWARDS INDIVIDUALIZED THERAPY

When we hear the word cancer, we think of one disease, but cancer is really made up of many, many types of cancer, each of which could be thought of as a separate disease. Six years ago, most doctors and almost all patients thought of leiomyosarcoma (LMS) and GIST as the same disease or they thought of GIST as a subset of LMS. Today we know that GIST and LMS are quite different and require totally different treatments.

GIST itself can be subdivided in several different ways — by major gene mutation (KIT or PDGFRA), then by the location of the mutation within the gene

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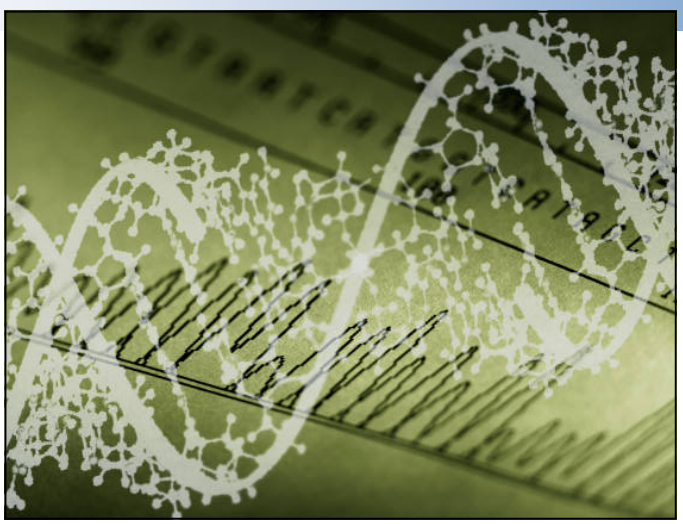


(exons). These mutations can be analyzed in the lab. The process of determining the gene and exon mutation is called genotyping, and it may represent the next major method of subdividing GISTs.

Testing tumors to see if they "stain positive" for the KIT protein has been possible (clinically) since approximately 2000. This helped establish the diagnosis of GIST and make GIST distinct from other cancers such as LMS. In a way, we could think of this as the beginning of "individualized therapy" for LMS/GIST patients. There was a good reason to separate the two as there was a powerful drug in clinical trials (Gleevec) that targeted the mutant KIT receptors.

Mutations in different parts (exons) of the gene result in proteins that have a different shape than normal proteins. These changes in shape can result in "short-circuiting" the protein, causing it to be continuously activated. These activated proteins (receptors) continually provide an abnormal growth and survival signal to cells, resulting in GIST.

Mutations in some exons can change the way drugs bind to the target proteins (KIT and PDGFRA) and cause the drugs to be ineffective.

Mutations in different exons can also change the activation pattern of downstream signaling proteins. Some drugs work better against one type of mutation while other drugs work better against other types of mutations:

1. It is well established that mutational status (genotyping) can predict how well patients will respond to Gleevec:

- GIST highly sensitive to Gleevec
  - □ KIT
    - Exon 11
  - □ PDGFRA
    - Exon 12
- GIST with intermediate sensitivity to Gleevec
  - □ KIT
    - Exon 9
- GIST with lower sensitivity to Gleevec
  - □ PDGFRA
    - Exon 18
  - □ Wild-type for KIT and PDGFRA (no mutations)

2. Clinical trials have also defined the response rate (at least partially) of Sutent (in Gleevec-resistant GIST) by exon status including secondary mutations:

- Gleevec-resistant GIST highly sensitive to Sutent
  - □ KIT
    - Exon 9
    - Wild-type for KIT & PDGFRA
    - Secondary exon 13 or 14
- Gleevec-resistant GIST less sensitive to Sutent
  - □ KIT exon 11
  - □ KIT secondary exon 17 mutation

If testing for KIT expression is the first step in individualized therapy for GIST patients, genotyping is clearly the second step. In addition to predicting response to drugs, genotyping can help diagnose GISTs that don't express the KIT protein (KIT negative GIST) as most of these tumors do have either KIT or PDGFRA mutations. It could help in deciding whether to have surgery and whether a patient would be likely to benefit from neoadjuvant Gleevec (Gleevec before surgery).

The role of genotyping will continue to expand as sensitivity profiles are developed for more drugs. I believe any patient who has access to genotyping (through insurance, etc.) should strongly consider having this testing done.

The other step patients can take toward individualized therapy is simply finding the best GIST experts, preferably an institution with a multidisciplinary team. For that matter, this may be the most important thing a patients can do. While we can make generalizations about treatments from details like KIT expression and genotyping, the details are all important. It takes a GIST expert to interpret all aspects of a patient's care, from his or her general health to CT scans to surgery and many other details.

One challenge will be to extend the use of genotyping. Some possible questions/scenarios:

- A patient has a mutation that is known to be insensitive to Gleevec (such as PDGFRA D842A); should that person be required to fail Gleevec before being allowed to participate in a clinical trial? What if the trial drug has demonstrated in-vitro (test tube) activity against this mutation?
- Should patients be directed towards clinical trials based on matching their mutation to in-vitro activity of the drug?

Beyond genotyping exists the next generation of individualized therapy. How do we match the patient with the best therapy possible? Should we know the activation status of KIT and/or downstream signaling proteins? Given that GIST biology is extremely well understood, it seems logical the GIST should be at the forefront of individualized therapy.

FINAL THOUGHT

The introduction of Gleevec sparked a revolution in the way cancer is treated. The gains made by researchers and pharmaceutical companies are great, but there are challenges ahead — not just the ones I've mentioned, but ones we haven't even dreamed of.

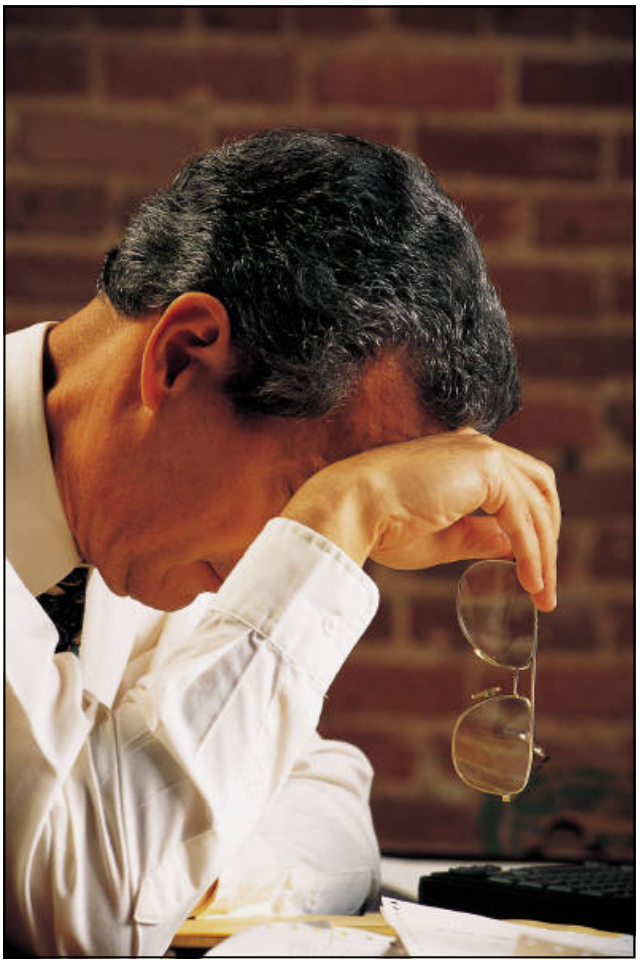
Battling fatigue after the holidays

Many of our members have voiced their frustration about experiencing fatigue while on Gleevec. This time of year happens to be most difficult due to the cold winter weather making it difficult for mobility as well as recuperating from the holiday shopping season.

There are many reasons for why patients experience tiredness and exhaustion but a major contributor is that Gleevec lowers the red blood cell count, a condition known as anemia. When you take Gleevec, it can reduce the amount of red blood cell production—this varies among patients. This low blood count causes a lack of oxygen to be carried to the tissues, in turn, causing weakness and exhaustion.

One way of treating this side effect is taking Procrit or Aranesp which increases the number of red blood cells enabling more oxygen to be carried to the tissues. These drugs will help elevate the hemoglobin to above 12 (normal range). Transfusions may be used in extreme cases as well, but a doctor needs to determine which of these methods is appropriate.

If you are still experiencing fatigue, here are some practical suggestions to help cope with such exhaustion:



• Plan your day so that you have time to rest.

• Take naps or rest during the day (but not within six hours of bedtime if you have problems sleeping).

• Save your energy for the most important things or reduce nonessential tasks.

• Try easier or shorter versions of activities you enjoy.

• Take short walks or do light exercise if possible. You may find this helps with fatigue.

• Talk to your health care provider about ways to save your energy and treat your fatigue.

• Try activities such as meditation, prayer, yoga, guided imagery, visualization, etc.

• Eat as well as you can and drink plenty of fluids. Eat small amounts at a time, if that is helpful.

• Join a support group. Sharing your feelings with others can ease the burden of fatigue. You can learn how others deal with their fatigue.

• Limit the amount of caffeine and alcohol you drink.

• Allow others to do some things for you that you usually do.

• Keep a diary of how you feel each day. This will help you plan your daily activities.

• Report any changes in energy level to your doctor or nurse.

• Meditate. Sit quietly with your eyes closed and imagine sights and sounds of things that make you happy.

• Don't keep it to yourself. Talk with friends and family members about your stress.

• Learn to say "no." You can't do it all, so don't try.

• Try to get the right amount of sleep. For most people, it's between seven to 10 hours a night.

GIST Resistance Strategic Plan Completed

Excitement abounds at the Life Raft Group offices in Wayne, NJ.

In just a matter of weeks, the first formal grant awards for GIST resistance research will be going out.

Over the past few months, the LRG research team has completed the world's first strategic plan to address the causes of GIST treatment resistance. In addition to detailing the many specific tasks that need to be carried out in each of the individual participating research institutions, lead investigators have completed cross-cutting priority projects to coordinate the collaboration of multiple institutions. The strategic plan is now going through the final check of our outside reviewers.

We are grateful for the selfless work of our investigators and particularly of the leadership of Jonathan Fletcher.

LANZA

From Page 3

well and all of her blood counts and weight were steadily improving.

Kelly missed most of the eighth grade through all of this, but through home schooling she was able to move on to high school with her class, returning in the ninth grade. This didn't really bother us as we were so concerned about her having so much pain.

Meanwhile, she has been monitored every three months via CT scans at CHOP, which fortunately have all been disease free. She is now off all medications. Over time, Kelly has learned what foods she cannot tolerate (sweets, chocolate, popcorn, and pepperoni seem to be the worst) and how much she can eat/drink at a time to minimize the pain of overloading her six-ounce stomach. Liquids, however, continue to be her biggest challenge.

Hearing that Kelly had a rare stomach cancer was devastating news for our entire family, we went through all of the emotions: fear, anger, stress; "why us" and "why her." The hardest thing I ever had to do was call my mother and tell her about it. But we had to be really strong for Kelly and we are fortunate to have not only a wonderful family, but many friends who helped us with their love, support and prayers.

Every student in the middle school made Kelly a get-well card (which arrived by the shoe box full each week) and friends came or called to check on her regularly. She was flooded with flowers, balloons, gifts and love. For me personally, daily exercise and staying calm was vital in my ability to get through this nightmare and help Kelly even after sleepless nights spent caring for her.

Kelly is an amazing girl with many talents that were not to be denied, despite her illness. Kelly spent her younger years attending her brothers' many sports events and listening to them play guitar. She also developed an interest in music through piano, flute and, like her mother, dance.

However, while she was sick at home, she searched for a way to utilize her interest in the arts. She spent hours online trying to distract herself from the pain and managed to find a Web site where she could help other teens design their bedrooms. She eventually formed a Web site of her own that got thousands of hits.

Kelly Lanza, third from the left, poses with models wearing outfits she designed.

When she started high school and took a sewing class, she fine-tuned her art skills to fashion design. She started attending the summer high school program at the Fashion Institute of Technology in New York City and loved it. She has continued taking fashion courses at FIT the past three summers, takes a double sewing class in school, and won a "Teens In Fashion" contest last summer, resulting in six of the outfits she designed and sewed being modeled in NYC's prestigious Fashion Week last September.

Since that time she has also designed puppet costumes for a children's educational video business her oldest brother John has begun, and was asked to be one of three designers creating a limited edition back-to-school teen clothing line for "Teens in Fashion." She's currently working on the costume designs for her high school's musical production.

There are a number of other things that she has accomplished: She was inducted into the National Honor Society as a sophomore, started a Design Club at school, writes a regular "trend talk" article for her school newspaper, takes private French and art lessons, and volunteers in our church nursery every Sunday. Unfortunately, she had to give up dance after finding that the jumps and turns made her sick, but she works with a personal trainer in place of physical education.

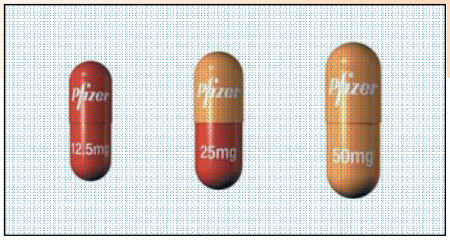
Additionally, after taking a jewelry course, Kelly developed her own jewelry business and has designed and sold jewelry through home parties and craft fairs this past fall. This enabled her to donated more than $800 of her sales to the Make-A-Wish Foundation. Her brother Jeff is building a Web site where she can highlight both her jewelry and fashion design.

I feel really good about all of these extracurriculars as it takes her mind off of when she hurts. She does need to learn how to say "no" gracefully; too

See LANZA, Page 11

SUTENT

From Page 1



Sutent comes in 12.5, 25 and 50 mg.

FDA also granted accelerated approval for Sutent in the treatment of patients with advanced renal cell carcinoma (RCC). In contrast to the approval for GIST, which was based on the drug's ability to delay the growth of the tumors, this approval was based on Sutent's ability to reduce the size of the tumors in patients. An overall response rate ranging from 26 to 37 percent was found in patients with metastatic kidney cancer whose tumors had progressed following cytokine-based therapy.

Pfizer is studying the drug for use in treating other cancers, including colorectal, breast and lung cancer.

Pfizer says it expects the average cost of Sutent per six-week treatment cycle to be about $4,000, putting the annual cost of treatment at about $38,000. The drug is expected to be available to patients Feb. 3, and will come in 12.5 mg., 25 mg. and 50 mg. capsules.

Patients and physicians can visit www.sutent.com or phone FirstRESOURCE at (877) 744-5675 for information about patient assistance for those who don't have drug coverage and for information about reimbursement issues or appeals assistance.

The FDA said in a statement that it has a long-standing commitment of providing patients with serious and life-threatening diseases access to safe and effective treatments, in some cases prior to FDA approval.

In the GIST clinical trial, significant clinical benefit was determined through an interim analysis of data, thereby allowing researchers to convert all patients in the trial to treatment.

FDA worked with Pfizer, maker of Sutent, to offer an expanded access program prior to approval, making the product available to patients not enrolled in a clinical trial. Currently, more than 1,700 U.S. patients are being treated with Sutent through the expanded access program.

"Expanded access programs have proven to be an effective way to get treatment to patients who need it most, especially in cancer," said Ellen Stovall, president of the National Coalition of Cancer Survivorship. "There needs to be a greater awareness among patients and doctors about both the option to participate in clinical research as well as in these expanded access programs in order to make promising new therapies available to as many patients as possible."

Pfizer said the most commonly reported side effects included diarrhea, nausea, stomatitis, dyspepsia, and vomiting. Patients also experienced, fatigue, high blood pressure, bleeding, swelling, and altered taste. Hypothyroidism was also observed.

Skin discoloration possibly due to the drug color (yellow) occurred in approximately a third of patients. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet.

Pfizer, which acquired Sutent in 2003 through its purchase of Pharmacia Corp., has said it intends to become a major player in the oncology arena. It is now far better known for drugs such as Viagra and cholesterol fighter Lipitor.

LANZA

From Page 10

much can be too overwhelming. She cannot take on everything that comes along. But I am still very happy for her. As for fashion, I think she needs to get in there and try it; I am very excited about it.

Currently, Kelly is looking for an internship in fashion design for this summer and, hopefully, part time during her senior year. She also hopes to be accepted as a fashion design major at the Fashion Institute when she graduates next year.

We have so much to be thankful for and are always looking for ways to share with others less fortunate. I spend some of my time volunteering in the pediatric wing of St. Barnabas Hospital, at our school library, and with wish granting at Make-A-Wish Foundation. Kelly's dad dedicates his spare time to taking photos and putting together slide shows of memorable moments for the high school football team's annual banquet.

Kelly feels strongly that focusing on her dream of becoming a fashion designer helps her get through her illness and the pain, and also has given her something to hope for in the future. GIST is a nasty disease, but if there is a way of turning it into a positive by using the time recuperating to build a dream and to carry you through, we think our Kelly did a great job. She has a bright future ahead of her.

Kelly Lanza at her high school formal.

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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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We are patients and caregivers, not doctors. Information shared is not a substitute for discussion with your doctor. As for the newsletter, every effort to achieve accuracy is made but we are human and errors occur. Please advise the newsletter editor of any errors.