

Understanding GIST survival under imatinib treatment

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One of the goals of Life Raft Group research team is to investigate the underlying mechanisms leading to the differences in diverse degree of response to imatinib mesylate treatment. Indeed, while 80 to 85 percent of patients with advanced GISTs show an initial benefit from the treatment, the response level may vary from rapid and gross reduction in tumor volume to no or only minor tumor shrinkage (described as stable disease) (5). Moreover, the heterogeneous type of response from patients carrying multiple nodules is sometimes observed, with certain lesions responding well and



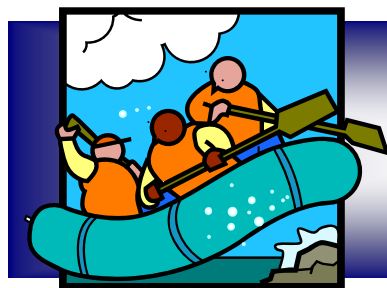
DEBIEC-RYCHTER

some being stable (2, 13). Importantly, the clinical and pathologic complete response is exceedingly rare (3, 4, 11).

The information on the histopathological changes (histopathology is the microscopic study of diseased tissue) in patients treated with imatinib is quite limited, but the overall changes in these patients are very similar. A variable, but often prominent loss of tumor cells is seen and this loss is replaced by a dense hyalinization (a change to hyaline; a cartilage-like consistency) and fibrosis (fibrous connective tissue). In addition, areas of stromal hemorrhages and necrosis are present. Proliferation markers are usually decreased but the seemingly mi-

See GIST SURVIVAL, Page 4

Battling gastrointestinal stromal tumor



LIFE RAFT GROUP

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In memory of John Leary and Shehadeh Moujaes

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Several new Web sites launched about GIST

International Life Raft representatives founded new organizations to add to the GIST community

By Jerry Call

Contributions from Estelle LeCointe and Anna Costato

LRG representatives start new country/language-specific organizations France

Estelle LeCointe has been a very busy woman lately. Estelle is the Director of "Association Française des Patients du GIST: Ensemble contre le GIST" a new organization for French GIST patients. The organization has a new web site which was launched in January 2007 and provides French GIST patients with access to information about GIST in their own language. It is divided

into four parts: basic information about GIST, scientific research, articles, and a discussion forum. The web site was developed by Estelle with the help of GIST experts including Dr. Alex Le Cesne, Dr. Jean Yvets Blay, Dr. B.N. Bui, Dr. S. Bonvalot, Dr. J. Coindre, Dr. S. Cauchy, Dr. F. Duffaud, Dr. C. Le Pechoux, Dr. P. Terrier and Dr. D. Vanel.

In addition to the organization and web site, Estelle is actively involved in the new French national information campaign about cancer organized by the National Institute of Cancer.

The motto of the campaign is "We're two million ordi-

See GIST WEB SITES, Page 6



The screenshot shows the homepage of the French GIST patient association website. At the top, there is a logo with four hands in a circle and the text "Association Française des Patients du GIST" and "ENSEMBLE CONTRE LE GIST". Below the logo is a navigation menu with links for "AAPP", "Informations GIST", "Recherche scientifique", "Informations AAPP", "Espace Membres", and "Liens". The main content area features an "Agenda" section for "24 janvier 2007 : Colloque F.M.O., Paris Gême" with a quote: "Ensemble nous contribuons à développer la connaissance des GIST, ensemble nous serons plus forts, ensemble nous ferons reculer la maladie." A large circular logo with four hands is visible in the bottom right corner of the screenshot.

The French GIST web site was launched in January 2007 by Estelle LeCointe.

Strategies and classes of potential GIST drugs

By Jerry Call

Many new cancer drugs are entering clinical practice and clinical trials. Many GIST patients are no longer responding to Gleevec or Sutent and thus are looking for clinical trials. Understanding strategies and grouping these new drugs into classes with other similar drugs may help patients understand some of their choices for treatment. For additional information, see Dr. Jonathan Fletcher's article in the January 2007 edition of The Life Raft Group newsletter.

The classes of drugs we are talking about are related to one or more strategies to treat GIST. Other strategies may emerge over time, but for now these strategies include:

1. Inhibit KIT (and/or PDGFRA) signaling
2. Antiangiogenesis (impede tumor vascularization)
3. Destroy KIT

4. Inhibit the production of KIT (or PDGFRA)

5. Inhibit, destroy or prevent production of intermediate signaling proteins downstream of KIT (or PDGFRA)

6. Inhibit the cell cycle

7. Induce apoptosis

Strategy: Inhibit KIT signaling

Drug Class: KIT/PDGFR/ABL/SRC inhibitors

This class of drugs includes Gleevec, the drug that is approved for first-line treatment of metastatic GIST. Even in Gleevec-resistant GIST, Gleevec is sometimes used in combination with other drugs and in the absence of another therapy. This is because many tumors may still be sensitive to Gleevec, resulting in a slowing of tumor progression.

One of the primary ways that drugs in this class hope to overcome Gleevec-resistance is by inhibiting the secondary mutations that are the primary cause of

See DRUGS, Page 5

The Life Raft Group

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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40 Galesi Dr., Suite 19
Wayne, NJ 07470

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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.

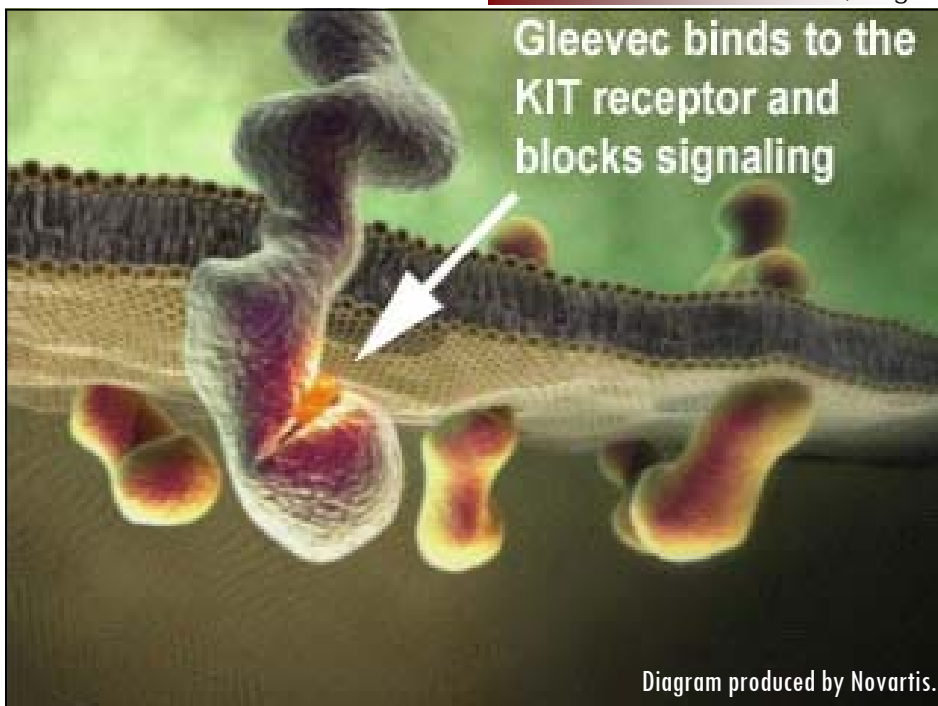


Diagram depicting inhibition of KIT signaling from Gleevec.

Painting transformed Mayer's pain into healing

By Erin Kristoff

This article is part of the "Artists of the Life Raft Group" series. The series focuses on the various talents of our members and how it helps them cope with their cancer.

From the time she was a young girl, Ellen Mayer always loved to draw, this she knew. What she did not know is how much that love would help her in her battle with GIST.

She started out as any child might, drawing sketches on bits of paper. "We didn't have a lot of money and I wanted paper, my mother worked in an office and would bring me back pieces from work." In the seventh grade, Ellen was placed in a special art class and she realized that this was what she wished to do with her life.

After high school, Ellen went on to become a secretary but confesses, "I was a really terrible secretary." She then moved on to a job as a fashion illustrator in Manhattan, "I used to say, 'I can't believe they're paying me for this.'" As she got older, Ellen realized what she wanted to do, "If you don't do what you are passionate about, you're not going to be happy." She even went back to school at age 49 and earned a degree in graphic arts.

When Ellen was diagnosed with GIST, her painting took on a whole new form. "After I was diagnosed and had my surgery. I was in a lot of pain and I was really focused on my art. I started get-

ting shows and my paintings became deeper. It just evolved and since then [art] has been very important to me in coping with GIST. I feel more passionate about it."

Not only does painting help Ellen to express her feelings about GIST, it also helps her to forget. "The moments that I'm so busy with all the pressure of art shows is when I don't think of having GIST."

Ellen likens her work to those of Edvard Munch, her favorite artist. "My paintings are a lot like his, very strong, dark, fast type of work.

While painting is her prime form of expression, Ellen also uses poetry to

she writes, "My smile is low now because I just want to go now." This particular poem creates a window into the world of scans and aided Ellen in getting through them.

Besides the Arts, Ellen finds support in numerous places. "At first it was the GIST groups, [they are] still my support system when I get scared or have questions. The sites are like a security blanket; a year ago I was not happy about something and when I left the hospital I immediately called Norman Scherzer, LRG executive director, and that was very important to me." She also finds the love and support she needs from her husband, Konrad; her two children and

the rest of her family and friends.

Above all else, painting is the focus of her life and Ellen intends to see it all the way through. "I hope that one day I will be famous, in a museum, like Munch," she adds, "and I want to see my grandchildren."

Through painting and poetry, friends and family, good times and

bad, Ellen continues to fight for that peace of mind she gets when not burdened by thoughts of GIST. "Am I still scared? Yes. Am I completely thinking it will never come back? No. I will live my life as best as I can, GIST will not control my life... I feel like I have much more to give. I can't go anywhere yet."



Mayer will be displaying her pieces of art, such as "Girl in Closet" (left) and a portrait of herself (right), from January 18 to March 1 at OrangeArts/Orange County Tourism, 124 Main St, Goshen, NY 10924. For more information, call (845) 291-2136.

Mayer featured in 2002 watercolor illustrations for the gown worn by the actress Renee Taylor at the Academy Awards as well as illustrations for Liza Minnelli's wedding. As an artist, Mayer has successfully versed herself in many mediums.

express her feelings. In one poem she describes getting a CT scan; Ellen changes from being comical to nervous. In the beginning of the poem she comments on the "guck" she must drink, "Today I get to pick between banana-flavored or berry." At a later part she comments, "I start to remember the reason I am here for," and towards the end

GIST SURVIVAL

From Page 1

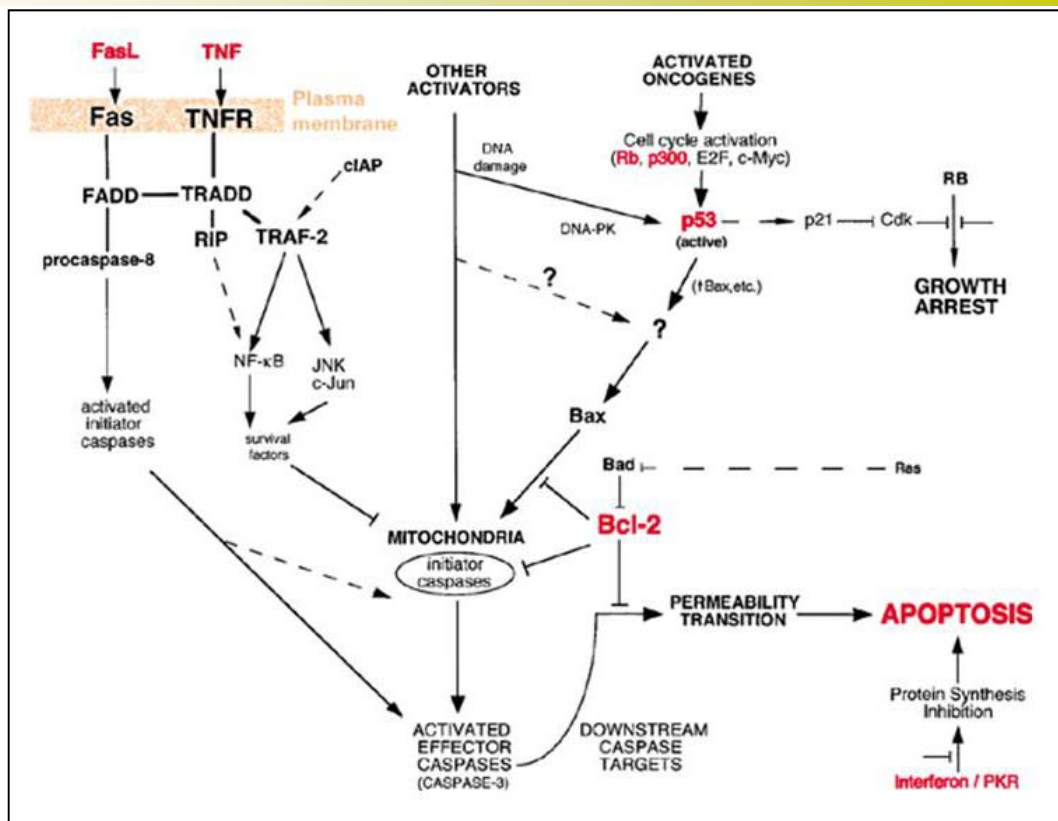
Microscopically viable foci of tumor cells are variable encountered (13, 16). The degree of response does not correlate with the duration of imatinib therapy, with possible variable grade and heterogeneity of response pattern within different tumor areas or tumor lesions of individual patients (13). In concordance with the histopathological analyses, data from most clinical studies show that many patients responding to imatinib eventually progress, indicating that the effect of the drug on residual GIST cells is rather cytostatic (stopping cell growth and multiplication) than cytotoxic (killing the cell) (2, 5, 15).

Notably, these preliminary scattered histopathological observations were recently further confirmed by the Agaram et al. study (1). The authors investigated the pathologic response and molecular changes in a largest so far analyzed group of clinically responsive or stable GIST lesions removed by elective surgery. Since the predominant mechanism of acquired resistance to imatinib is via additional mutations in KIT, the authors tried to answer the question whether the secondary mutations are present in GIST cells that are stable under imatinib pressure (which could provide a survival advantage to the tumor cells and which could render the tumor only partially sensitive to the drug). In addition, for the first time the molecular signatures of imatinib-stable/imatinib-responsive lesions were established by the expression profiling study.

The results of this study can be summarized in a few points:

1) The histologic response to imatinib is heterogeneous and does not correlate well with clinical response or imatinib therapy duration.

2) High-abundant, second-site KIT mutations are rare in imatinib-responsive



Molecular pathways with a potential to target apoptosis in cancer.

GISTs compared with imatinib-resistant tumors.

3) Proliferation capacity of tumor cells (which correlate with mitotic activity) does not correlate with the *KIT* genotype or overall response of the tumor to imatinib therapy. Even in tumors with a very good histologic response, small foci of distinctly viable tumor, which were mitotically active, could be identified.

4) Activation of KIT and downstream targets (such as PI3-K, AKT, mTOR, MAPK, and ribosomal S6) was consistent in all tumors analyzed. The temporary cessation of the drug before surgical resection (one to two days before surgery) most likely was a confounding factor for this observation.

5) The gene signature of imatinib-response in GISTs showed down-regulation of cell cycle control regulators as well as up-regulation of genes involved in muscle differentiation and function.

The most important message from

the aforementioned study is confirmation that although imatinib treatment induces apoptosis (a type of cell death) and causes cell cycle arrest of GIST cells, some residual cells usually survive and become active again within a remarkably short time after cessation of treatment. Therefore, either a combination or novel systemic therapeutic approaches are needed to maximize GIST cell death.

Cancer is a manifestation of **six essential alterations in cell physiology** that collectively **dictate malignant growth**: 1) self-sufficiency in growth signals, 2) insensitivity to growth-inhibitory (antigrowth) signals, 3) evasion of programmed cell death (apoptosis), 4) limitless replicative potential, 5) sustained angiogenesis, and 6) tissue invasion and metastasis (9, 10).

Impaired apoptosis signaling is common in cancer cells and plays an impor-

DRUGS

From Page 2

resistance. Secondary KIT (or PDGFRA) mutations, especially in exons 13, 14 and 17, prevent Gleevec from being able to bind to the mutant receptor. Drugs that can bind to the KIT receptor, in spite of the secondary mutations, may overcome Gleevec-resistance.

The SRC protein is downstream of KIT. It has been speculated that inhibition of SRC might be important in GIST. However, recent reports by Bauer et al. suggest that SRC might not be important in GIST. Some drug(s) in this class inhibit SRC (such as BMS-354825) and others do not. This class of drugs could easily be divided into two categories: KIT/PDGFRAs inhibitors With or Without SRC inhibition. Until the importance of SRC becomes better defined in GIST, we are combining all of these drugs into one class (for simplicity). Drugs that inhibit SRC but not KIT (or PDGFRA) should be viewed as a different class of drugs (at least with respect to GIST).

Another potentially important mechanism that these drugs could use to overcome Gleevec resistance is better drug penetration into tumor cells. AMN107 has been shown to enter GIST tumor cells much better than Gleevec (by bypassing multiple multi-drug resistance mechanisms) and BMS-354825 has also been shown to be less affected by one of the multi-drug resistance proteins that appear to affect Gleevec.

Drugs in this class include Gleevec for first-line therapy and AMN107 and BMS-354825. AMN107 is set to enter trials for third-line (failure of Gleevec and Sutent) therapy (scheduled for April 2007). BMS-354825 is in phase I trials for solid tumors with talk of phase II trials for GIST.

Strategy: Inhibit KIT signaling, Antiangiogenesis

Drug Class: KIT/PDGFRAs/VEGF inhibitors a.k.a. Multi-targeted Tyrosine Kinase Inhibitors

This class of drug is similar to the KIT/ABL/SRC inhibitors, except that they also inhibit one or more of the vascular endothelial growth factor receptors

(VEGFR). They may also inhibit additional targets whose role in GIST is undetermined (such as RET). VEGFRs play an important role in the growth of new blood vessels in the body (angiogenesis). Without the growth of new blood vessels, tumors cannot grow beyond a few millimeters in size. In addition to inhibiting PDGFRA, almost all of the drugs in this class also inhibit PDGFRB. PDGFRB is also important in angiogenesis, so these drugs inhibit angiogenesis via at least two pathways (VEGFRs and PDGFRB). It should be noted that the drugs currently listed in the first class also inhibit PDGFRB.

In addition to their antiangiogenic effects, drugs in this class may also fit into the binding pocket of KIT (or PDGFRA) differently than Gleevec. To be effective against Gleevec-resistant GIST, it is widely believed that, in addition to their antiangiogenic effects, these drugs must also be effective at inhibiting the secondary mutations that cause Gleevec-resistance. The effects of multi-drug resistance proteins on drugs in this class have generally not been well characterized in the literature.

Approved drugs in this class include:

- Sutent (approved for Gleevec-resistant GIST)
- Nexavar (not approved for GIST, but in phase II trials for Gleevec and/or Sutent-resistant GIST). NOTE: Inhibition of PDGFRA by Nexavar has not been reported.

Drugs in this class that are unapproved, but available in clinical trials include:

- PTK787 – Phase II trials for GIST
- AZD2171-Phase II trials for GIST
- OSI-930-Phase I trials for solid tumors
- XL-820-Phase I trials for solid tumors

Strategy: Antiangiogenesis

Drug Class: VEGF monoclonal antibody inhibitor

In addition to being able to be inhibited by tyrosine kinase inhibitors (like Sutent), VEGF signaling can be inhibited in other ways as well. One method is to use a drug that binds to the exterior portion of the VEGF receptor(s) and prevents the binding of the VEGF growth factor(s) to the VEGF receptor. Avastin is a drug in this class that is ap-

proved for colon cancer. A phase III trial that combines Avastin + Gleevec compared to Gleevec alone is planned for first-line therapy in GIST.

Strategy: Destroy KIT

Drug Class: HSP90 inhibitors

Heat Shock Protein 90 (Hsp90) is a protein that has several functions in cells. It is an emerging therapeutic target of interest for the treatment of cancer. Proteins are the mainstay of structural and signaling elements of all cells. Hsp90 is a molecule that maintains the conformation and activity of specific proteins in the cell, also called "client proteins" of Hsp90. KIT is one of the client proteins of Hsp90. Hsp90 enables cancer cell survival by maintaining the function of their mutated client proteins including the KIT and PDGFRA proteins in GIST. Inhibition of Hsp90 therefore has the potential to destroy the activated KIT/PDGFRAs proteins resulting in a therapeutic effect in GIST. Since the target of these drugs are Hsp90 and not KIT or PDGFRA, they should be unaffected by the secondary mutations that commonly cause resistance to Gleevec. In fact, preliminary work has suggested that the stronger KIT is activated, the better they work.

Drugs in this class include both oral and intravenous drugs. Some of the intravenous drugs, such as IPI-504, are also being developed as an oral version.

Drugs in this class include:

- IPI-504 - Currently in phase I trials for GIST
- CNF2024 - A drug in phase I trials for solid tumors
- 17-DMAG - In phase I trials for solid tumors. It is a second generation version of 17-AAG with better solubility than 17AAG.
- 17AAG - In phase I and phase II trials for a variety of cancers. This drug has poor solubility.
- KOS-1022 – An oral or intravenous drug in phase I trials for solid tumors.

Strategy: Inhibit the production of KIT (and possibly other important proteins)

Class: Transcription inhibitors

While flavopiridol is widely known as an inhibitor of cyclin-dependent kinase

GIST WEB SITES

From Page 1

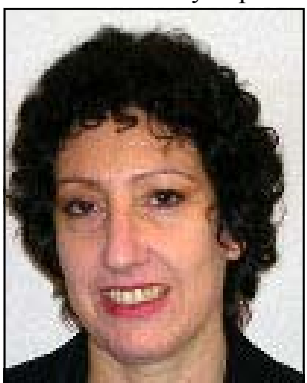
nary heroes.” The aim is to change people’s vision of cancer through the account of survivors or people on their way to survival. Estelle has done three commercials for the campaign as well as appearing on billboards. To learn more, visit www.e-cancer.fr.

Estelle has been busy behind the scenes as well. She has been developing relationships with key physicians and researchers in France. In December, she was invited to the Gustave Roussy Institute where she met with Dr. Cedric Mé- nard to discuss their ongoing research into GIST, Glivec and immunotherapy. Next month Estelle will share this interview and information about their upcoming trial with the members of Ensemble contre le GIST, and in the Life Raft Group newsletter. For more information, please contact Estelle LeCointe at gist.estelle@laposte.net or visit www.ensemblecontrelegist.org.

Italy

Italian LRG representative Anna Costato just founded and announced in October 2006 the new GIST organization in Italy called “Associazione Italiana GIST.” At a medical summit on rare tumors held in Milan, Italy, GIST expert, Dr. Paolo G. Casali, announced the start up of the new Italian Gist patient group during his speech.

Dr. Casali launched, in 1997, an organization called The Rare Tumor Network. It is a network among hospitals and facilities throughout Italy, gathering more than 100 oncology units and representing a permanent link among oncologists. Through this internet-based network, oncologists from different locations consult each other and share decisions on treatment and therapies on specific cases. Patients are requested to give permission for their personal data to be shared within the network, which is restricted to oncologists.



COSTATO



LeCointe poses in one of the cancer survivor billboards in France.

During 2007 it is forecasted that radiological and histological materials can be “virtually” shared through the network. Patients whose oncologists belong to the network have in fact “second opinions by experts” all the time, with no need to

move from their own facilities. It is easy to understand what a great service cancer patients are getting through this network.

The idea to try and start a GIST

advocacy patient group in Italy, where there are a few hundred Gisters, started in Spring 2006. Novartis helped to finance the start up of the group and the National Cancer Institute greatly contributed to the educational material for the web site. Anna Costato has accepted this responsibility with pleasure.

Costato says, “Patient advocacy groups

have offered me tremendous help, that’s why I think it is fair that I return [the favor] now. I am glad I have the opportunity to start a patient group in my own country and share knowledge, support and hope.” She hopes to reach nearly one thousand GISTers identified in her country. For more information, please contact Anna Costato at info@gistonline.it or visit www.gistonline.it.

New GIST web site focuses on physician education

In December 2006, a new GIST web site aimed at physician education was launched. The web site, GIST GOLSCME.com, contains a number of webcasts from the third GIST Global Opinion Leader Summit (GOLS) meeting which was held October 27-29, 2006 in Prague, Czech Republic. GIST GOLS is an international gathering of more than 500 physicians and a distinguished faculty of GIST authorities. In addition to the webcasts, a highlights e-newsletter and a highlights panel discussion will be added to the web site in January and February respectively.

The 2006 GIST GOLS meeting was co-chaired by Jean-Yves Blay, M.D., Ph.D and Peter Reichardt, M.D., Ph.D.

In his introduction to the web site, Dr. Blay notes that “. . . This is the focus of a new web site for sharing the excitement of one of the most scientifically interesting and medically rewarding developments in cancer;

the potential to provide many patients with GIST years of additional life.”

The GISTGOLSCME web site provides some of the latest information about GIST to physicians worldwide and will be available for at least the next three years. Physicians can earn continuing medical education (CME) credits



GIST WEB SITES

From Page 6

through the web site.

The 26 presentations are divided into four sections:

- Changing Paradigms in the Treatment of Advanced GIST: Efficacy of Tyrosine Kinase Inhibition
- Practical management of GIST Patients
- Surgery and Emerging Treatment

DRUGS

From Page 5

(CDK2 and CDK1), it's effects may be mediated more by inhibition of transcription than anything else (Cell Cycle review, December 2004).

Work done at Memorial Sloan-Kettering found that in a GIST cell line, total KIT protein was significantly diminished in flavopiridol-treated cells after 24 hours. This resulted in an indirect reduction in KIT autophosphorylation, comparable to Gleevec. They confirmed that transcriptional down regulation was the reason for reduced total KIT protein. They also found that flavopiridol, at clinically achievable doses, induces a high level of apoptosis (cell death) in GIST cells. They believe their findings justify a clinical evaluation of flavopiridol in treating patients with Gleevec-resistant GIST.

The way flavopiridol works against KIT is different than Gleevec. Flavopiridol reduces the total amount of KIT protein, where Gleevec inhibits the activation (phosphorylation) of the KIT protein present without lowering the amount of KIT protein. One of the mechanisms of Gleevec-resistance is overexpression of KIT or PDGFRA (too much KIT or PDGFRA protein).

A combination of flavopiridol and doxorubicin is in phase I trials for Sarcoma. This trial also allows GIST patients.

Strategy: Target KIT downstream signaling

Classes: The drugs using this strategy come from several different classes.

Targeting signals downstream from

Modalities

- New Insights and Practical Management of Resistance

The presentations have a heavy focus on the practical management of GIST including 9 case studies. Surgery, adjuvant Glivec, the role of genotyping, dose optimization and resistance are also discussed in detail. Dr. Charles Blanke is

KIT and PDGFRA is one strategy being investigated for Gleevec-resistant GIST and for many cancers in general. Some of the most promising targets appear to be:

PI3K – However, because of its widespread use in the human body, it remains a difficult protein to target. Drugs that inhibit specific portions of PI3K may enter clinical trials in the near future.

PKC theta – Remains a desirable target, but we are unaware of any drugs that currently target PKC theta.

AKT – A protein involved in the prevention of apoptosis (it may have other functions as well). An AKT inhibitor, Perifosine, is in phase II trials in several combinations. One trial combines Gleevec + Perifosine and another combines Sutent + Perifosine.

mTOR – Inhibiting mTOR may have multiple effects in cancer cells. mTOR is involved in cell growth, angiogenesis and cellular survival. A phase I/II trial for the mTOR inhibitor RAD001 + Gleevec is underway in GIST. It is unclear if this trial will proceed to more advanced stages. There are at least 3 other mTOR inhibitors either approved (Rapamune) or in clinical trials (CCI779 and AP23573).

BCL-2 – This protein is a very important anti-apoptosis protein. Genasense is a drug that inhibits the production of bcl-2 through an “antisense” mechanism. Phase II trials are underway with a combination of Genasense and Gleevec.

Strategy: Induce apoptosis, inhibit cell cycle, Destroy KIT

one of the featured presenters who discusses the



LRG and its Patient Registry.

The GISTGOLSCME web site is jointly sponsored by Elsevier Office of Continuing Medical Education and ProHealth Communications and is supported by an unrestricted educational grant from Novartis Oncology. It can be found at www.gistgolscme.com.

Class: HDAC inhibitors

Work recently presented at the Life Fest meeting in Dallas, showed that a histone deacetylase (HDAC) inhibitor was able to cause significant regression in a Gleevec-resistant xenografts model (mouse model). HDAC inhibitors are a new class of drugs that have shown anti-cancer activity in three major ways:

1. Inducing apoptosis
2. Arresting the cell cycle
3. By destabilizing certain cancer-causing proteins such as bcr-abl (and possibly KIT).

This may occur because HDAC inhibitors cause hsp90 to become inactive, possibly resulting in the destruction of the KIT protein.

Another way that HDAC inhibitors might accomplish their effects is by “turning on” some tumor suppressor genes that have been silenced.

HDAC inhibitors are in various stages of development and none are in GIST specific trials:

- FR901228, is in phase II trials for sarcomas. This trial does allow GIST patients.

- Zolinza (vorinostat) was recently FDA approved for cutaneous T-cell lymphoma (CTCL).

- LBH589 – Is in phase I trials for solid tumors.

- Others

Summary

In summary, a number of different strategies are being tried to overcome Gleevec resistance. Different classes of drugs use different strategies to accomplish this. Some classes of drugs use multiple strategies. Understanding the classes and strategies may help patients evaluate their treatment options.

GIST SURVIVAL

From Page 4

tant role in tumor initiation, progression and metastasis, as cells with genomic damage or deregulated cell cycle are normally eliminated by apoptosis (6, 7, 8). Resistance of cancer cells to apoptosis is especially deleterious, because it results in a higher survival capacity under adverse conditions, enhancing the malignant potential of the tumor, favoring accumulation of mutations, metastasis and rendering tumor cells resistant to therapy as well as to host defense mechanisms.

Cancer cells invent numerous ways to inactivate the apoptotic machinery in order to survive and thrive. Included among these are the activation of PI3-K and AKT firing, the increase in the levels of anti-apoptotic BCL-2-related proteins, the inactivation of p53 protein through changes in the p53 gene, interference with cytochrome c release from mitochondria, and inhibition of caspases (which are enzymes that initiate cell death process) (10).

Mammals have evolved a receptor/ligand mechanism that enables the organism actively to direct individual cells to self-destruct through the presence of **cell surface death receptors**, which transmit apoptosis signals initiated by specific **death ligands** (7, 12). Apoptosis-targeted therapy through activation of death receptors can engage an apoptotic response that bypasses the action of sensors, such as p53, and therefore their frequent mutant state in cancer should be irrelevant to this therapeutic approach. Death receptors are members of the tumor necrosis factor (TNF) receptor gene superfamily, which consists of more than 20 proteins with a broad range of biological function, including the regulation of cell death and survival, differentiation or immune regulation (7). The best-characterized death receptors in their potential to induce apoptosis are Fas, TNF receptor 1 (TNFR1), and TNF-related apoptosis-inducing ligand (TRAIL) receptors (death receptor 4/DR4 and death receptor 5/DR5). Hence, the corresponding death ligands TNF,

Fas ligand (FasL) and TRAIL are interesting candidates for antitumor therapy (12, 14, 17). Targeting death receptors, such as Fas, is a promising anticancer strategy by which apoptotic cell death can be induced. It is expected that already existing small molecules targeting these death receptors will be designed to lower toxicity and increase antitumor activity.

References

1. Agaram NP, Besmer P, Wong GC, Guo T, Socci ND, Maki RG, DeSantis D, Brennan MF, Singer S, DeMatteo RP, Antonescu CR. Pathologic and Molecular Heterogeneity in Imatinib-Stable or Imatinib-Responsive Gastrointestinal Stromal Tumors. *Clin Cancer Res* 2007;13(1): 170-181
2. Antonescu CR, Besmer P, Guo T, Arkun K, Hom G, Koryotowski B, Leversha MA, Jeffrey PD, Desantis D, Singer S, Brennan MF, Maki RG, DeMatteo RP. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res* 2005; 11:4182-4190
3. Bauer S, Hartmann JT, de Wit M et al. Resection of residual disease in patients with metastatic gastrointestinal stromal tumors responding to treatment with imatinib. *Int J Cancer* 2005; 117:316-325
4. Chacon M, Roca E, Huertas E, et al. CASE 3. Pathologic complete remission of metastatic gastrointestinal stromal tumor after imatinib mesylate. *J Clin Oncol* 2005; 23:1580-1582
5. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol* 2004; 22:3813-3825.
6. Danial NN, Korsmeyer SJ. Cell death: critical control points. *Cell* 2004; 116:205-219
7. Debatin KM, Krammer PH. Death receptors in chemotherapy and cancer. *Oncogene* 2004; 23:2950-2966
8. Green DR, Evan GI. A matter of life and death. *Cancer Cell* 2002; 1:19-30
9. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000; 100:57-70
10. Igney FH, Krammer PH. Death and anti-death: tumour resistance to apoptosis. *Nat Rev Cancer* 2002; 2:277-288
11. Melichar B, Voboril Z, Nozicka J, Ryska A, Urminska H, Vanecek T, Michal M. Pathological complete response in advanced gastrointestinal stromal tumor after imatinib therapy. *Internal Medicine* 2005; 44:11
12. Mollinedo F, Gajate C. Fas/CD95 death receptor and lipid rafts: New targets for apoptosis-directed cancer therapy. *Drug Resist Update* 2006; 9:51-73
13. Raut CP, Posner M, Desai J, Morgan JA, George S, Zahrieh D, Fletcher CD, Demetri GD, Bertagnoli MM. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. *J Clin Oncol* 2006; 24:2325-31
14. Shankar S, Srivastava RK. Enhancement of therapeutic potential of TRAIL by cancer therapy and irradiation: mechanisms and clinical implications. *Drug Resist Update* 2004; 7:139-156
15. Sciot R, Debiec-Rychter M. GIST under imatinib therapy. *Semin Diagn Pathol* 2006; 23(2):84-90.
16. Wardelmann E, Thomas N, Merkelbach-Bruse S, Pauls K, Speidel N, Buttner R, Bihl H, Leutner CC, Heinicke T, Hohenberger P. Acquired resistance to imatinib in gastrointestinal stromal tumours caused by multiple KIT mutations. *Lancet Oncol* 2005; 6:249-251
17. Van Geelen CMM, de Vries EGE, de Jong S. Lessons from TRAIL-resistance mechanisms in colorectal cancer cells: paving the road to patient-tailored therapy. *Drug Resist Update* 2004; 7:345-358

Norwegian FAQs up on Web sites!

Our Norway LRG representative, Jan-Einar Moe, has graciously provided new FAQs in Norwegian for two web sites! To view, please visit: http://www.liferaftgroup.org/faqs_norwegian.html and http://www.globalgist.org/faq_norway.html.



February 2007 clinical trial update

By Jim Hughes

Member of LRG Science Team

AZD2171 (AstraZeneca International)



This investigational drug is in early trials for a number of cancers. It inhibits KIT and VEGFR-1, VEGFR-2 and VEGFR-3. This phase II trial is being sponsored by AstraZeneca in the United Kingdom (The Royal Marsden NHS Foundation Trust in London and Christie Hospital NHS Trust in Manchester). This study deals with patients with “Histological or cytological confirmation of GIST which is resistant or intolerant to imatinib mesylate...which is refractory to standard therapies or for which no standard therapy exists,” and “will exclude patients on treatment with an investigational drug within 30 days prior to starting AZD2171 45mg, with the exception of SU11248 and imatinib mesylate which should be stopped at least 14 days before starting AZD2171.” Biologic tumor activity is evaluated by FDG/PET response at eight days and four weeks.

Sutent (Pfizer)



In the United States, Canada, the United Kingdom and the European Union

countries Sutent is now approved for patients failing Gleevec or those who cannot tolerate Gleevec. In addition, Sutent continues to be available to patients via the “Treatment Use Protocol,” which is “four weeks on/two weeks off” (50 mg). There are many sites open throughout the world. Site information changes frequently; for the most current information, contact EmergingMed at 1-877-416-6248 (outside the United States) or at 1-800-620-6104 (inside the United States). If international patients have problems with the listed number,

use email at: sutent@emergingmed.com.

In September Pfizer posted a new phase III trial on the NIH web site. This study will compare 37.5mg daily of Sutent with 800mg daily of Gleevec for patients progressing on 400mg of Gleevec. Anticipated enrollment is 200. Site information has not yet been announced. According to the listing this trial is not yet recruiting and is now scheduled to start July 2007 per the clinicaltrials.gov database listing as of January 17. Contact: Pfizer Oncology Clinical Trial Information Service at 1-877-369-9753 or PfizerCancerTrials@emergingmed.com.

AMN107 + Gleevec (Novartis)

The combination of AMN107 and Gleevec may have a broad spectrum of activity against primary and secondary mutations in GIST. The generic name for AMN107 is nilotinib and our understanding is that the brand name will be Tasigna. The phase I trial is now closed at all sites. A phase III trial is planned starting in April.

A small number of GIST patients have been able to obtain AMN107 via an individual expanded access program.

IPI-504 (Infinity)



The IPI-504 phase I trial is open for patients resistant to prior therapies and is accruing patients at Dana-Farber Cancer Institute. It undergoes fairly frequent start/stop periods as cohorts accrue.

IPI-504 is an inhibitor of Heat Shock Protein 90 (HSP90) and has been the subject of articles in the November 2005 and January 2006 editions of the Life Raft Group newsletter. This is an intravenous drug which is administered twice a week for two weeks followed by a one week off period. IPI-504 is administered without Gleevec. We understand that a second schedule of treatment without a



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one week off period is beginning.

Genasense + Gleevec (Genta, Inc.)

A phase II trial testing the combination of Genasense plus Gleevec in patients with Gleevec-resistant GIST recently opened.

Genasense (Genta Inc.) is an antisense drug that inhibits bcl-2. Bcl-2 is a protein involved in cellular survival. This drug is administered intravenously. It is hoped that Genasense may help Gleevec kill tumor cells by making them more sensitive to Gleevec.

This trial is currently open only at M.D. Anderson. Several other trial sites are planned including: Dana-Farber Cancer Institute, Boston, Mass.; University of Michigan Comprehensive Cancer Center, Ann Arbor, Mich.; Mayo Clinic Cancer Center, Rochester, Minn.; and Memorial Sloan-Kettering Cancer Center, New York, N.Y.

Perifosine (Keryx Biopharmaceuticals)

Keryx Biopharmaceuticals has perifosine (KRX-0401), an oral drug that inhibits the AKT protein. AKT is an antiapoptosis protein. It is speculated that

TRIALS

From Page 9



inhibition of AKT might enhance therapy. Apoptosis is a form of controlled cell death, a type of cellular suicide where the cell issues its own death warrant.

Perifosine + Gleevec Phase II (Keryx)

A phase II trial, which combines Perifosine with Gleevec, is open at M.D. Anderson Cancer Center, Houston, Texas; Oncology Specialists, Park Ridge, Ill.; and under Dr. Sant Chawla at the Cancer Center at Century City in Los Angeles, Calif. This trial is accruing Gleevec-resistant GIST patients. To contact M.D. Anderson patients should call: 1-800-392-1611 (in U.S.) or (713) 792-6161 (outside U.S.).

Perifosine + Sutent Phase I (Keryx)

This phase I trial is primarily for renal cell cancer and GIST patients. It has two parts. The first part will determine the maximum tolerable dose (MTD) in a four week "on," two week "off," six week cycle. The second part of the phase I trial will use the MTD to determine if a larger group of patients can remain on the drug for two six week cycles. The inclusion criteria includes the following caution:

"The physician must believe that the patient's course and the growth rate of the tumor are such that the patient would feel comfortable continuing treatment for 12 weeks even if there is a transient period of modest tumor growth during the first weeks following the initiation of perifosine and sunitinib malate treatment."

It is not stated that tumor growth or failure on a current treatment is a necessary condition for entry into this trial.

Patients who have received prior Sorafenib or Sutent are eligible for this trial.

Sites currently open include: Tower

Hematology and Oncology, Beverly Hills, Calif., and Oncology Specialists, Park Ridge, Ill. Contact Jonathon Fendelman, M.A., M.B.A. at (415) 946-2410 or ocogtrials@ocog.net, or Robert Birch, Ph.D at (901) 869-3844 or b.birch@ogoc.net, for more information.



Bristol-Myers Squibb

RAD001 + Gleevec (Novartis)

RAD001 is an mTOR inhibitor. We have been informally advised that the RAD001 plus Gleevec phase II trial for GIST patients has completed accrual. We are awaiting word from Novartis on the outcome of the trial and on future plans for this drug. RAD001 is available outside the United States as Certican® for heart and kidney transplant patients.

A similar mTOR inhibitor from Wyeth called Rapamune® is available in the United

States for kidney transplant patients. We have received reports from GIST patients who have been prescribed Rapamune "off-label" with Gleevec.

PTK787/ZK222584 (Novartis)

This is a phase II study being conducted at the University of Helsinki in Finland and in Milan, Italy. This trial is for patients progressing on Gleevec. PTK787 is administered without Gleevec. A seven day washout period is required.

PTK787/ ZK222584 was synthesized and developed by Novartis AG and Schering AG. It is a tyrosine kinase inhibitor and inhibits VEGF receptors as well as KIT and PDGFRB. See the July 2006 Life Raft Group newsletter for an article about this trial. Contact for more information: Heikki Joensuu, M.D. at 358-9-471 73208 or heikki.joensuu@hus.fi, or Mia Viskari at 358-9-4711 or mia.viskari@hus.fi.

BMS-354825 (Bristol-Myers Squibb)

BMS-354825 (Dasatinib) is a tyrosine

kinase inhibitor of Src, abl, KIT, and PDGFR.

Dasatinib is available in a phase I trial at Dana-Farber and Glasgow, Scotland.

In June the Karmanos Cancer Center in Detroit, Mich. also began recruiting patients.

Future plans include a SARC phase II trial. We will update trial sites and the scope of the trial as this information becomes available.

This trial is for patients with progression on Gleevec. The BMS drug is administered without Gleevec. For more information, contact the BMS Call Center at 1-866-892-1BMS, Ext. 131 or the BMS Call Center (outside the U.S. and Canada) at (941) 906-4711, Ext. 131.

BAY 43-9006 (Bayer) (known as Sorafenib and by trade name Nexavar)

This drug was approved in December 2005 for kidney cancer. BAY 43-9006 inhibits several kinases including KIT, VEGFR-2, VEGFR-3, PDGFR-β, RAF, FLT3, and RET.

The phase II trial for BAY 43-9006 is open and recruiting patients. Three trial sites are open in Illinois and one in New York:

- University of Chicago-Chicago, Ill.
- Decatur Memorial Hospital-Decatur, Ill.
- Oncology/Hematology Associates of Central Illinois- Peoria, Ill.
- Memorial Sloan-Kettering Cancer Center-New York, N.Y.

Several sites are also pending.

This trial is for patients progressing on Gleevec. It now also will include patients resistant to Sutent. BAY 43-9006 is administered without Gleevec. A fourteen day washout period is required before trial drug start. For more information, contact Clinical Trials Office - University of Chicago Cancer Research at (773) 834-7424.

Sarcoma trials that also allow GIST patients:

See TRIALS, Page 11



TRIALS

From Page 10

The last trials listed are sarcoma trials that allow GIST patients. There are several ways to attack GIST tumor cells with drugs. The most common method is to inhibit KIT and/or PDGFRA signaling.

The protein is still present; it is just inhibited by the drug. This is the method used by Gleevec, Sutent and most of the other new inhibitors being developed (dasatinib, AMN107, etc).

Another way to target GIST is to destroy the KIT or PDGFRA protein. IPI-504 and other HSP90 inhibitors target GIST tumors in this manner.

A third way to target GIST is to try to prevent (or reduce) the formation of KIT or PDGFRA proteins. The following two trials take the approach of inhibiting the formation of a large number of proteins including KIT and PDGFRA.

Doxorubicin + Flavopiridol (Aventis Pharmaceuticals)

This is a phase I trial to determine the maximum tolerated dose of the combination of doxorubicin (a traditional cytotoxic chemotherapy) with flavopiridol (an inhibitor of the cell cycle and an inhibitor of transcription). This trial is for sarcoma patients (including GIST patients) that are 18 years old or older. Patients must have a performance status of ECOG 0-2 or Karnofsky 60-100 percent. Projected accrual is 3 to 36 patients.

The trial is being conducted at Memorial Sloan-Kettering Cancer Center in New York, N.Y. For more information, contact David R. D'Adamo, M.D., Ph.D at (212) 639-7573.

FR901228

This is a phase II trial for sarcoma patients, including GIST patients, with metastatic or unresectable disease. FR901228 (depsipeptide) belongs to a new class of chemotherapy drugs called histone deacetylase inhibitors (HDAC inhibitors). They work by regulating gene transcription to block multiple signaling pathways.

Patients must be at least 18 and have a performance status of ECOG 0-2 or Karnofsky 60-100 percent. Projected accrual is 18 to 36 patients.

Trial locations include: Phoenix, Ariz.; Oakland, Calif.; Rome, Ga.; Decatur, Ill.; Louisville, Ky.; Columbus, Ohio; Greenville, S.C.; Spartanburg, S.C.; Danville, Va.; Burlington, N.C.; Greenville, N.C.; Goldsboro, N.C.; Winston Salem, N.C.; High Point, N.C.; Elkin, N.C.; Goldsboro, N.C. For more information, look-up NCT00112463 in the clinicaltrials.gov database for detailed site contact information.

Phase I solid tumor trials that allow GIST patients:

Although these drugs are only for solid tumors, there is rationale that these drugs might be effective in GIST.

LBH589 (Novartis)

This Novartis drug is a histone deacetylase (HDAC) inhibitor. It works by regulating gene transcription to block multiple signaling pathways. It is in the same class as FR901228 (see end of article). It is not yet available in clinical trial in the United States. A phase I trial has started in Tokyo, Japan for patients with advanced solid tumors. Contact Novartis at 81-3-3797-8748. In the United States, a phase I trial is also available at the Nevada Cancer Institute in Las Vegas for patients with advanced solid tumors. The principal investigator is Dr. Sunil Sharma. To find out more information, contact Donna Adkins at (702) 822-5173.

CNF2024 (Biogen Idec)

CNF2024 is a heat-shock protein 90 (HSP-90) inhibitor. It works by inhibiting the protein that acts as a chaperone for mutant KIT. This results in the destruction of mutant KIT. Unlike Gleevec, this drug works by destroying and not by merely blocking KIT's signaling region. Theoretically, this type of drug can counter KIT mutations that reactivate Gleevec or Sutent responsive

GIST. Phase I trials have started in Scottsdale, Ariz.; New Haven, Conn. and San Antonio, TX for patients with advanced solid tumors. GIST patients resistant to Gleevec and Sutent are being accepted. Contact Biogen Idec at oncologyclinicaltrials@biogenidec.com for more information.

XL820 (Exelixis)

This drug inhibits c-kit, PDGFRb and VEGFR. It is similar to the OSI-930 drug below. Data presented by Exelixis in a poster at EORTC in October 2006 showed results for 23 evaluable patients in phase I, including one GIST patient. The GIST patient had stable disease after 3.5 months on XL820. Exelixis has a phase I trial listed in the clinicaltrials.gov database to assess "the safety and tolerability of XL820 when given orally." The listing says it is not open but we checked with one of the sites

(Texas) and understand that it is now open. The sites are: The Cancer Institute of New Jersey, New Brunswick, N.J.- Mark Stein, M.D. (contact Pamela Scott at (732) 235-7459 or scottpd@umdnj.edu) and the Cancer Therapy and Research Center, San Antonio, TX- Kyriakos P. Papadopoulos, M.D. (contact Pat O'Rourke at (210) 616-5976 or porourke@idd.org). This trial is open to patients with solid tumors failing standard therapy.

(osi) pharmaceuticals

OSI-930 (OSI Pharmaceuticals)

OSI Pharmaceuticals has begun a phase I trial of the compound OSI-930 at two locations in the United States and one in Europe. The trial is for patients with advanced solid tumors, but will admit GIST patients. Locations include:

- Dana-Farber Cancer Institute- Boston, Mass. (Dr. George Demetri, Principal Investigator)
- Colorado University- Denver, Colo.
- Royal Marsden Hospital- London, UK (Dr. Michelle Scurr, Principal Investigator)

OSI-930 is a new small molecule tyrosine kinase inhibitor. It inhibits c-Kit, VEGFR and PDGFRb. The trial began in August. Up to 60 patients are expected to be accrued.

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