Navigating GIST Clinical Trials

The Life Raft Group
June 12, 2008
Some observations:

“Annually, only 3% of adult patients participate in cancer clinical trials.”

http://jco.ascopubs.org/cgi/reprint/23/36/9282

“Of all patients approached with a trial, 75% consented but no more than 20% of patients who were eligible were offered a trial....”

Siminoff, Thomas; Why Learning to Communicate With Our Patients Is So Important: Using Communication to Enhance Accrual to Cancer Clinical Trials Journal of Clinical Oncology, Vol 26, No 16 (June 1), 2008: pp. 2614-2615  
http://jco.ascopubs.org/cgi/content/full/26/16/2614
GIST Treatment Trials Starting 2000-2008
(From clinicaltrials.gov)

Planned Accrual (% of Total) by Trial Phase

Worldwide Planned Accrual 2000-2008
7,365 patients in Phases 1-3
Includes Adjuvant Trials
Planned Accruals by Trial Start Year, Phase 1-3 GIST Treatment Trials Worldwide in ClinicalTrials.gov

Gleevec -1692 1st Line, No Control

Tasigna – 240 3rd Line, Gleevec Control

IPI-504 (Intravenous) – 195 3rd or 4th Line, Placebo

Sutent – 312 2nd Line, Placebo
Planned Accruals by Trial Start Year, Phase 1-3 GIST Treatment
Trials Worldwide in ClinicalTrials.gov

- Gleevec or Sutent – 200
  2nd Line, No Control
- Sutent – 312
  2nd Line, Placebo
- Avastin (Intravenous) + Gleevec – 572
  1st Line, Gleevec Control
- Tassigna – 240
  3rd Line, Gleevec Control
- IPI-504 (Intravenous) – 195
  3rd or 4th Line, Placebo
Today’s Objectives

- What are clinical trials?
- How do I find GIST trials?
- What do you look for in a trial?
- What are the LRG Tools for finding Trials.
- How do You Decide on a Trial?
- What is new in GIST Trials?
What are clinical trials?

- Phases: I-4
- Types: Interventional, Observational
- Designs:
  - Inclusion Criteria: Newly Diagnosed vs. Pre-Treated
  - Controls: Active, Placebo
  - Neo-Adjuvant/Adjuvant
Phase 1

- Is the drug safe?
  - Usually 20-60 patients at one or a few sites
  - First use of drug in humans
  - Determines whether patient can tolerate the dosage given *MTD – Max Tolerable Dose*
  - Early patients may not get a therapeutic response because they are on the lowest dosage.
  - Later patients may have increased risk of side effects due to a very high dosage level.
Phase 2

- Is the drug effective in treating GIST?
  - Usually 100-300 patients at 3-10 sites
  - Can be combined with Phase 1

*Gleevec was approved for GIST based on Phase II trial results*
Phase 3

- Is the treatment better than current standard?
  - Compare trial treatment to current standard of treatment for GIST
  - Usually 300-1,000 patients at 10-100 sites
  - Often Randomized
    - Active Control
    - Placebo Control
Phase 3

- Is the treatment better than current standard?
  - Compare trial treatment to current standard of treatment for GIST
  - Usually 300-1,000 patients at 10-100 sites
  - Often Randomized
    - Active Control
    - Placebo Control

Current Phase III Trials in GIST

- Gleevec with/without Avastin, Gleevec Control – US, Canada
- Sutent or Gleevec, Gleevec Control – US and International
- IPI-504, Placebo Control – US and International (pending)
Phase 4

- Post Approval
  - Studies long-term side effects and efficacy
Clinical Trial Phases

1. Pre-Clinical Evidence of Effect in GIST
   - Safety
   - Drug Candidates

2. Sometimes Combined
   - Effect

3. Effective in GIST
   - Compare
   - Regulatory Approval
   - Further Study

4. Long Term Effects
   - After Approval

• Approx 10% of drugs that start get approved
Types of Trials

- Intervention
  - Drug – 98% of GIST Trials
  - Radiation
  - Procedure
  - Observation
FDA Procedures that look like trials

- Expanded access
- Treatment IND
- Compassionate access
Trial Designs

Newly Diagnosed vs. Pre-Treated

Initial Diagnosis
- Gleevec 400 mg
- Gleevec 800 mg
- Sutent

Front Line: “Newly Diagnosed”, or “Naive”
Second Line:
Third Line: “Refractory to available therapy”
Newly Diagnosed vs. Pre-Treated

“Patients With Gastrointestinal Stromal Tumors (GIST) Who Have Had Progressive Disease While On 400 mg Daily Of Imatinib” Gleevec or Sutent Ph 3

“Refractory to available therapy or for which no therapy is available” SNX5422 Ph 1

“Patients previously treated with imatinib mesylate must have documented progression of disease Untreated disease allowed. Must have ≥ 1 measurable lesion by RECIST” Gleevec + Sutent Ph 1

“Patients with malignant gastrointestinal stromal tumor that progressed during or after previous treatment with imatinib mesylate and sunitinib malate. “ Sorafenib Ph 2

Always ask the clinical trial site....
Newly Diagnosed vs. Pre-Treated

- Prior treatment dose requirements
  - Failed at Minimum 400 mg Gleevec
    \(\text{(AMN107 Phase 3)}\)
  - Failed at Minimum 50 mg Sutent
    \(\text{(Sorafenib Phase 2)}\)

- Restrictions on prior therapies
  - No TKI’s other than Gleevec and Sutent
    \(\text{(AMN107 Phase 3)}\)
  - No prior HSP-90 therapy
    \(\text{(IPI-504 Phase 3)}\)
Trial Design

- Randomized
  - Two + arms – experimental and controls
  - Patients assigned randomly to an arm
  - Double Blinded – Patients and Site team unaware which arm patients are assigned.

- Controlled
  - Active – Usually current standard treatment
  - Active/Historical - Patients continue prior therapy
  - Inactive – Placebo: No treatment
Trial Design

- Neo-Adjuvant
  - Before surgery to reduce the size of the tumors and to reduce the need to remove healthy tissue

- Adjuvant
  - After surgery where all detectable disease has been removed, but where there remains a statistical risk of relapse due to microscopic disease

Remember: Before & After
How do I find GIST trials?

ClinicalTrials.gov
A public service of the US National Institutes of Health
- 23,926 Active trials of all types worldwide
- 7,634 Active cancer trials worldwide
- 4,976 Active cancer trials in US

Cancer.gov
A public service of the National Cancer Institute
- 7,563 Active cancer trials worldwide
- 4,743 Active cancer trials in US

As of 2:30 pm CDST 6/5/08
Guidance for Industry Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions: March 2002, Center for Drug Evaluation and Research (CDER), FDA, USDHHS.

“Section 113 of the Modernization Act requires you (Industry) to submit information to the data bank about a clinical trial conducted under an investigational new drug (IND) application if it is for a drug to treat a serious or life-threatening disease or condition and it is a trial to test effectiveness (42 U.S.C. 282(j)(3)(A)).”

“The data bank was established as required under section 113 of the Food and Drug Administration Modernization Act of 1997 (Modernization Act). “
Standard Searches

- Starting points
  www.clinicaltrials.gov
  www.cancer.gov

- For category searches select:
  “Gastrointestinal Stromal Tumor”

- For keyword searches try the line below with the quotes:
  “gastrointestinal stromal” OR “gastro-intestinal stromal” OR GIST
  - Remember : “You say tumor…I say tumour”
  - So skip the word ‘tumor’. You don’t need it!.... 😊
Registry Comparison

- **NIH/NLM: clinicaltrials.gov**
  - Required by FDA
  - Probably more complete
  - All sites all trials
  - Easy to bookmark a search
  - Map
  - Downloadable data
  - RSS Feed “Changes within last 14 days”

- **NCI: cancer.gov**
  - Cancer only
  - Mirrors NIH/NLM
  - Recruiting sites in active trials only
  - Suggested search terms and lists
  - “Within miles of Zip code” search
  - Patient version
  - Occasionally has more site contact info
  - Good other resources for patients

When in doubt – use both
Standard Searches

- Searching with the pre-defined condition category “Gastrointestinal Stromal Tumor” for Active Trials
  - clinicaltrials.gov - 40 Trials
  - cancer.gov - 53 Trials
  - emergingmed.com - 92 Trials

We are currently reporting on 32 trials of these trials in the US and Internationally.
Standard Search Issues

- Sometimes trials for “Gastrointestinal Neoplasms” *are* included as GIST.
- Some Phase I trials for “Solid Tumors” “Soft Tissue Sarcoma” or Sarcoma will accept GIST patients but *are not* included. (EmergingMed seems to include them all!)
- Trials mentioning GIST but not for GIST get included.
Another observation…

“The Center for Information and Study on Clinical Research Participation (CISCRP)—online survey in 2005 among nearly 5000 (public) registry users

“Registry users most want easy-to-process, summary trial information; details on whether the trials are being conducted in conveniently accessible locations; and investigative site contact information.”

Getz; Forgotten Voices in the Transparency Debate; Applied Clinical Trials, April 1, 2006; http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=316473&pageID=1&sk=&date=
LRG Resources

- The LRG Newsletter
June 2008 US clinical trials update

By Jim Hughes
LRG Science Team member

AMN107 Phase III: This trial has met accrual goals and enrollment is now closed.

Sunitinib or Imatinib: Five new sites have been added in the United States. Four new international sites have also been added:
1. Lai Chi Kok, Kowloon, Hong Kong
2. Tsuen Man, New Territories, Hong Kong
3. Milano, Italy, 20133,
4. Seoul, Republic of Korea, 135-710

Imatinib + Pegylated Interferon-a 2B:
This trial now has an NCT number and the contact information has changed.
Contact Jessica Moehle, 801-587-4438 at the Huntsman Cancer Institute.

Sorafenib Phase II:
Contact information has been updated.

Perifosine + Imatinib:
Trial is ongoing but not recruiting.

Sorafenib (Nexavar): Sorafenib in treating patients with malignant GIST that progressed during or after previous treatment with imatinib and sunitinib.

Phase II
Conditions: GIST
Strategy: Multiple Targets
NCT#: NCT00265708
Contact: Univ. Of Chicago Cancer Res. Center, Chicago, Ill.
Ravi Salgia, MD
rsalgia@medicine.bsd.uchicago.edu
Rasha Polite, MD
rpolite@medicine.bsd.uchicago.edu
Telephone: 773-834-7424
Sites: City of Hope, Duarte, Calif.
Warren Chow, MD, 626-256-4673
USC-Norris Cancer Center, Los Angeles, Calif.
Hein-Josef Lenz, MD, 323-865-3955
UC-Davis, Sacramento, Calif.
David Gandara, MD, 916-734-3771
Decatur Memorial Hospital, Decatur, Ill.
James Wade, MD, 217-876-6617
Oncology/Hematology Assoc., Peoria, Ill.
John Kugler, MD, 309-671-5180
James Knost, MD,
jknost@ohaci.com
Central Illinois Hem/Onc, Springfield, Ill.
Edem Agamah, MD, 217-525-2500
Univ. of Michigan, Ann Arbor, Mich.

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

Phase II
Conditions: GIST
Strategy: Kill GIST cells
NCT#: NCT00585261
Contact: Huntsman Cancer Institute
University of Utah, Salt Lake City, Utah
Jessica Moehle
Telephone: 801-587-4438

Perifosine + Sunitinib:
Safety and effectiveness of daily dosing with sunitinib or imatinib in patients with GIST

Phase III
Conditions: GIST
Strategy: Inhibit KIT and/or impede tumor vascularization

Oncology Specialists
Kathy Tolzein, RN
847-268-8200
Grand Rapids, Mich.
Sara Down

Phase II
Conditions: GIST
Strategy: Multiple Targets
NCT#: NCT00455559
Contact: Online Collaborative Onc. Group
ocogtrials@ocog.net
Telephone: 415-946-2410
Sites: Los Angeles, Calif.
Sant Chawla, Md.
Coeur D’Alene, Idaho
Park Ridge, Ill.

Oncology Specialists
Kathy Tolzein, RN
847-268-8200
Grand Rapids, Mich.
Sara Down
LRG Resources

The Web Page:
http://www.liferaftgroup.org/treat_trials.html
LRG Resources

- LRG Brochure – “Navigating GIST Clinical Trials”
  http://www.liferaftgroup.org/docs/Pamphlets/Clinical_Trials.pdf

Five-Year GIST Survivors at Life Fest 2006

You do not face GIST alone

The Life Raft Group was formed in 2000 by GIST patients, many of whom were participants in the Phase II trial of STI-571 (Gleevec/Glivec). Many of those patients are still here today because they made the choice to participate. Gleevec is available today because of those first GIST patients who stepped forward. To have GIST is to be a member of a community actively pursuing a cure.

International Patients

Patients outside the United States who try to enter a clinical trial in another country may have a different process to go through than U.S. citizens. To learn more about international access to clinical trials, visit the Global GIST Network at www.globalgist.org.

Navigating GIST Clinical Trials

An easy-to-use guide about GIST clinical trials and tips to help you decide which trial to choose.

Special Thanks

The production of educational materials would not be possible without the generous contributions from companies such as Amgen, Bristol-Myers Squibb, Novartis, OSI Pharmaceuticals, and Pfizer.

None of the pharmaceutical companies who have helped fund the development of this pamphlet have had any role in determining, reviewing or approving its content.

Ensuring that no one has to face GIST alone

GIST stands for gastrointestinal stromal tumor. This pamphlet is intended to answer some of your questions about GIST clinical trials. It is intended to guide those considering options after treatment failure. It is not a substitute for your physician’s guidance and care.
More Details about Clinical Trials

- ClinicalTrials.gov – “Understanding Clinical Trials”
  http://clinicaltrials.gov/ct2/info/understand?flds=Xabj
- Cancer.gov – “Educational Materials”
  http://www.cancer.gov/clinicaltrials/learning
Deciding - What are the benefits?

- Option to access treatment after standard treatment fails
- Receive treatment at major GIST trial center
- Expanded treatment options
- Help future GIST patients
Deciding - What are the risks?

- The new drug may not work for you
- Side effects may occur
- Additional testing, time and travel
- Some costs may not be covered by insurance
How to choose a clinical trial

Decide on a set of criteria that are important to you. This will keep you focused. Examples:

- Proximity to home, job and family
- Sarcoma expertise of physician
- Potential drug risks and benefits
- Follow-up schedule and options
- Newer untried strategy
Ask Questions

- How does the new treatment work differently for you?
- Which trial offers the best chance of survival?
- What are the chances it will benefit you?
- What are the options if the trial does not work for you?
- Will this trial limit future options?
- How much time do you have to decide?
- If phase 1, will the dose be therapeutic?
High Stakes Decision Making*

1. Allow yourself the time to decide.
2. Get emotional support.
3. Make sense of controversies.
4. Manage your decision like you manage other complex projects.
5. Give yourself permission to experiment.
6. Recognize your preferences.
7. Remain vigilant about ignorance. Seek those who will teach and learn with you.
8. Delegate.
10. Keep your sense of humor.

*Top Ten Decision Lessons from the Community Breast Health Project (CBHP) in Palo Alto, CA
By Jeff Belkora, September 1997 http://www.guidesmith.org/top-ten-lessons/
What’s New - ASCO 2008

- HSP-90 inhibitors move to center stage
  - IPI-504 Phase III Placebo Controlled
    - 50 sites
    - 195 Patients
- IGF-1R Identified as a potential target in GIST
  - Wild Type & Pediatric
  - Multiple Phase 1, 2 & 3 trials with IGF-1R inhibitors
    - R-1504 – Roche: Pediatric GIST MSKCC
    - NVP-AEW541 – Novartis: tested against GIST in Vitro
    - CP-751,871 – Pfizer: Phase III Combination trials in carcinoma
Cancer Clinical Trials (CCT) Awareness and Attitudes in Cancer Survivors (Ca. surv.)

Comis, R.L., Colaizzi, D., Miller J.D.
Coalition of Cancer Cooperative Groups, Philadelphia PA;
Northwestern University, Chicago, IL

Poster presented at the American Society of Clinical Oncology Annual Meeting, Atlanta, GA, June 5, 2006
Abstract No. 6061 – Poster No. H1
Perception of Advantages to Enrollment in a CCT Among Survivors Who Were Aware of the Possibility of a Trial at the Time of Diagnosis, and Enrolled

- **65%** Improve personal chances of recovery
- **27%** Advance knowledge
- **3%** More physician attention
- **2%** Reduce costs

Number of survivors = 60

These results are the product of a set of direct questions to each cancer survivor asking about awareness and enrollment. Up to two advantages were coded for each set of open-ended responses.
Perception of Disadvantages to Enrollment in a CCT Among Survivors Who Were Aware of the Possibility of a Trial at the Time of Diagnosis, but Declined

40% New treatment might be less effective
18% Concern about random assignment
11% Side effects or safety
9% Time concerns/delay in treatment
2% Too many additional test/procedures

Number of survivors = 57

These results are the product of a set of direct questions to each cancer survivor asking about awareness and enrollment. Up to two disadvantages were coded for each set of open-ended responses.
### Satisfaction with Participation in a CCT

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>97%</td>
<td>Felt they were fully informed on risks and benefits</td>
</tr>
<tr>
<td>96%</td>
<td>Felt they were treated with dignity and respect</td>
</tr>
<tr>
<td>92%</td>
<td>Had a positive experience</td>
</tr>
<tr>
<td>91%</td>
<td>Would recommend a trial to others</td>
</tr>
<tr>
<td>9%</td>
<td>Felt like a “Guinea Pig”</td>
</tr>
</tbody>
</table>