GIST Overview

- GIST have an incidence of 3-6,000 annually and a prevalence of ~40,000 individuals
- 0.2% of all GI tumors, but 80% of GI sarcomas
- Highest incidence in the 40-60 year age group
- Similar male/female incidence
- Clinical presentation is variable
  - Pain, hemorrhage, anemia, anorexia, nausea, perforation
  - May be asymptomatic

GIST Overview

GIST may occur anywhere along the GI tract or elsewhere in the abdomen or retroperitoneum

- Stomach: 60%
- Small intestine: 25%
- Colon/Rectum: 5%
- Esophagus: 2%
- Other (mesentery, retroperitoneum): 8%

Major sites of GIST metastases:
- Liver
- Peritoneum
- Bone
- Lung

## GIST Chemotherapy Trials

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of Patients</th>
<th>Partial Response n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOX + DTIC</td>
<td>43</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>DOX + DTIC +/- IF</td>
<td>60</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>IF + VP-16</td>
<td>10</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>15</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>17</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Liposomal DOX</td>
<td>15</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>DOX</td>
<td>12</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>DOX or docetaxel</td>
<td>9</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>High-dose IF</td>
<td>26</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>EPI + IF</td>
<td>13</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Various</td>
<td>40</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>DTIC/MMC/DOX/DTIC/MMC/DOX/CSF</td>
<td>21</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Temozolamide</td>
<td>19</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>280</strong></td>
<td><strong>19 (6.8%)</strong></td>
</tr>
</tbody>
</table>
GIST: Therapy

- KIT is expressed on GIST cells
- Gene mutation in most cases
  - KIT: 80%-85%
  - PDGFRA: 5%-7%
  - Wild Type: 12%
- Gene mutation results in constitutively activated receptor tyrosine kinase activity
- Imatinib is effective in CML

Marked Biologic Response Revealed by PET Scan

Multiple liver and upper abdominal \( \text{\textsuperscript{18}} \)FDG-accumulating metastases  A marked decrease \( \text{\textsuperscript{18}} \)FDG uptake 4 weeks after starting imatinib mesylate

Extracellular Domain (exon 9, 10.2%)

Juxtamembrane Domain (exon 11, 66.1%)

ATP

Tyrosine Kinase Domain I (exon 13/14, 1.2%)

Tyrosine Kinase Domain II (exon 17, 0.6%)

★ = common mutation site
Imatinib Mesylate

- **Formula:** \( \text{C}_{30}\text{H}_{35}\text{N}_7\text{SO}_4 \)
- **MW:** 589.7

- Rational drug design
  - 2-phenylamino pyrimidine
  - Based on structure of ATP binding site
  - Highly water soluble
  - Oral bioavailability

- Inhibitor of selective tyrosine kinases
  - bcr-abl
  - PDGF-R
  - c-kit

- Potent (IC\(_{50}\) ≈ 0.1\(\mu\)M)
Kit Receptor Phenotype

Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

Imatinib

ATP

= imatinib contact point
Low KIT Expression Correlates With Benefit From Imatinib

Chirieac, Trent. Cancer 2006
Apoptosis After Imatinib (5 DAYS)

Baseline

5 days post-imatinib
Familial GIST

Kleinbaum et al, ASCO 2006
Progression-free Survival By Imatinib Dose

*Kit* Exon 9 Mutation

Debiec-Rychter et al, 2007
A Clinical Trial is a Scientific Study in Humans
A Clinical Trial Must Be Ethically and Scientifically Sound
A Clinical Trial Should Be Ethically and Scientifically Sound, While Providing a Therapeutic Option For Patients
Clinical Trial Elements

- Objectives
- Background
- Patient Eligibility
- Pretreatment Evaluation
- Treatment Plan
- Evaluation During and after Treatment
- Criteria for Response
- Criteria for Removal from Study
- Laboratory Correlates
- Statistical Considerations
- Informed Consent
What Are The Objectives of The Clinical Trial?
Objectives

• **Phase I**
  - To determine maximum tolerated dose
  - To assess safety
  - To assess efficacy

• **Phase II**
  - To assess efficacy
  - To assess safety
  - Laboratory Correlates

• **Phase III**
  - To assess small differences in efficacy between therapies (drug, dose, formulation, BSC)
Background

- Provide an overview of the disease and the drug.
- Why are the objectives important?
- How will this improve patient care?
- What are the risks and benefits to the patients?
Phase II Study Design

- Patient population
- Selection of agent(s)
- Dose
- Definition of endpoints
- Statistical design
Eligibility Criteria

Selection of Patients

- Patient population
  - Type of cancer
  - Prior therapy
  - Stage of disease
  - Presence of drug target
Eligibility Criteria

Selection of Patients

Select patients who have progressing disease
Should not be overly strict on exclusion criteria

- Prior therapy
- Prior cancer history
Selection of Study Drug

- Phase II studies in advanced GIST
  - Perifosine (AKT/MapK/p21 inhibitor) + Imatinib
  - Tasigna: Kit and Abl inhibitor
  - HSP90 inhibitor vs. Placebo (randomized)
BFR14  3-yr randomization  
Progression Free Survival

**CONT group**
- 3 events / 25 patients
- 1-year PFS: 87.7% (CI95 = 71.6 - 100.0)

**STOP group**
- 17 events / 25 patients
- 1-year PFS: 25.2% (CI95 = 6.3 - 44.0)

Rate of PD in STOP group:
- at 6 months: 40%
- at 9 months: 55%
- at 1 year: 75%

Median f.u.: 11 m (IC95: 4.8 – 13.8)
Log-rank test: p < .0001
Imatinib 400mg vs 800mg
Time to Progression on Crossover
Clinical Trial Evaluations

Measuring Efficacy

- **Pre-treatment**
  - Baseline measurement

- **During Treatment**
  - Response assessment (same method as baseline)
  - Survival

- **Post-treatment**
  - “on study” until event
Phase II Study
Design

- Endpoints
  - Response rate
  - Time to progression
  - Progression Free Survival
  - Overall Survival
  - Improved Quality of Life
Phase II Study
Design

- Definition of response
  - Clinical
  - Radiographic
  - Histological
  - Molecular
  - Improved Quality of Life
CT Scan Results

Jun 27, 2000

Before Imatinib

Oct 4, 2000

After Imatinib
Response

Pre-Imatinib

Post-Imatinib (8 weeks therapy)
Effects of Imatinib on GIST: CT and PET findings
### Effect of Imatinib on Vascularity

<table>
<thead>
<tr>
<th>Perfusion Parameter</th>
<th>Pre-Imatinib</th>
<th>Post-Imatinib</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF (mL/100g/min)</td>
<td>36.84</td>
<td>24.55</td>
<td>0.017</td>
</tr>
<tr>
<td>BV (mL)</td>
<td>3.90</td>
<td>2.84</td>
<td>0.005</td>
</tr>
<tr>
<td>MTT (s)</td>
<td>9.47</td>
<td>9.96</td>
<td>0.26</td>
</tr>
</tbody>
</table>
Statistical Considerations

Study Design
Statistical Considerations

- Number of patients
- Rate of accrual
- Power
- Significance
- What can you demonstrate?
Statistical Considerations

- Allow quantitation of objectives
- Require “clinical considerations”
- When done properly ensure a safe, ethical, and successful study
Phase II Study
Design

- Statistical design
  - 1-stage design
  - 2-stage designs
  - Newer Bayesian approaches
Clinical Trials

- Clinically Sound: Ensure the Best Patient Care
- Scientifically rigorous
- Ethical
- Offer a therapy to patients that have no other treatment options
- Learn about the disease and the therapy so that the next Clinical Trial is better.
Why Participate In A Trial?

- No other therapeutic options are available.
- Therapy or testing are free.
- To allow researchers to understand GIST and help future patients.
- Freireich’s Law #6: A good clinical trial offers the best patient care.
Clinical Trials

Jon Trent, MD, PhD

jtrent@mdanderson.org

Associate Professor
Dept. of Sarcoma Medical Oncology
The University of Texas,
M. D. Anderson Cancer Center

Connective Tissue Oncology Society

SARc
Sarcoma Alliance for Research through Collaboration
*What is a clinical trial, and when should a patient consider entering a trial?*

*What are the various phases of trials and their goals?*

*Who sponsors a trial and how does this affect goals? (Government, pharma, intergroup trials, etc)*

*What are the various surrogate endpoints in clinical trials, and what does each imply for a patient (time to progression, overall survival, time to treatment change, time to secondary resistance, etc?)*

*What makes a trial “scientific/unbiased” and how does this differ from voluntary internet polls about pt results?*

*How does a patient find a trial? Who pays for trial participation?*

*What are some key areas of investigational drugs for GIST pts and why are these important? (HSP90i, HDACi, PI3Ki, other KIT inhibitors, non-ATP competitive KIT inhibitors, antibodies, etc)*
Eligibility Criteria

Selection of Patients

- **Imatinib in Sarcomas**
  - Response Rate: 10%

- **Imatinib in Kit + GIST**
  - Response Rate: 85%
Eligibility Criteria

Selection of Patients

- Select Patients whose tumor expresses the target
- Don’t Select Patients whose tumor expresses the target
Phase III Trial of Sunitinib

Time to Progression

Sunitinib
TTP = 6.3 months (n=207)

Placebo (discontinuation)
TTP = 1.5 months (n=105)

Hazard ratio = 0.335
P < 0.00001

EORTC 1st Line Chemotherapy: Active Single Agents or Combinations

Time to progression
1st line - leiomyosarcoma

(months)
Temozolamide in GIST

Overall Survival

TTP 2 months
OS (28 months)

Trent et al, Cancer 2003
Biological Endpoints

Phase II trial to understand the biology of response to therapy
Mechanisms of Activity of Imatinib in GIST
Mechanisms of Activity of Imatinib in GIST
Mechanisms of Activity of Imatinib in GIST

Cohort 1
Imatinib for 3 days

Cohort 2
Imatinib for 5 days

Cohort 3
Imatinib for 7 days

Imatinib Therapy

Pre-imatinib Studies
-Perfusion CT Scan
-PET scan
-Serum collection
-Biopsy

Post-imatinib (preoperative) Studies
-Perfusion CT Scan
-PET scan
-Serum collection

Surgical Resection

-Pathology evaluations
-Bank excess tumor for molecular studies
-Imatinib for 2 years
Early Mechanisms of Activity of Imatinib in GIST

- Apoptosis pathway interrogation
- Anti-Vascular pathway interrogation
- Genomic pathway analysis (Gene Ontology)
- Proteomic analysis of tissue protein changes (RPPA)
- microRNA modulation of genomic changes
- Methylation changes after imatinib therapy