Gastrointestinal Stromal Tumor

GISTS 2010

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Background
GIST Overview

- Most common GI sarcoma
  - 0.2% of all GI tumors, but 80% of GI sarcomas
- Distinct clinical and histopathologic entity
  - Highest incidence in the 40-60 year age group
  - Similar male/female incidence
  - Many misclassified
- About 5,000 newly diagnosed GIST patients per year in the US
- Clinical presentation is variable
  - pain, hemorrhage, anemia, anorexia, nausea, perforation
Median Overall Survival in Metastatic GIST

Circa 1990

## Chemotherapy Trials

### Advanced GIST

<table>
<thead>
<tr>
<th>Regimen</th>
<th>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/ CDDP/GM–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 Pathology

- GIST share several characteristics with ICC
  - Neuromuscular pacemaker cell of the GI tract
  - Found in myenteric plexus throughout GI tract
  - Expression of CD34 in ~80% of cases
  - Expression of KIT (CD117) in ~95% of cases

ICC = interstitial cells of Cajal.

Kit Receptor Structure

- Extracellular Domain (exon 9, 10.2%)
- Juxtamembrane Domain (exon 11, 66.1%)
- Tyrosine Kinase Domain I (exon 13/14, 1.2%)
- Tyrosine Kinase Domain II (exon 17, 0.6%)

★ = common mutation site
Kit Receptor Phenotype

ADP
+
P
Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

ATP
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 contact point
Marked Biologic Response Revealed by PET Scan

Multiple liver and upper abdominal \[^{18}\text{FDG}\text{-accumulating metastases}]

A marked decrease in \[^{18}\text{FDG}\text{ uptake}]
4 weeks after starting imatinib mesylate

The First GIST Patient: Histology

**H&E** (at diagnosis)

**H&E**

**Ki 67**

**CD117**

**Pretreatment**

**One month of therapy**

What is the chance of imatinib helping me?
Clinical Trials of Imatinib in GIST

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>N</th>
<th>OR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>OS (2 yr)</th>
<th>TTP (median)</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Oosterom, 2001</td>
<td>I</td>
<td>36</td>
<td>53%</td>
<td>0%</td>
<td>53%</td>
<td>36%</td>
<td>11%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>von Mehren, 2002</td>
<td>II</td>
<td>147</td>
<td>63%</td>
<td>0%</td>
<td>63%</td>
<td>19%</td>
<td>12%</td>
<td>-</td>
<td>72 wks</td>
<td>-</td>
</tr>
<tr>
<td>Verweij, 2003</td>
<td>II</td>
<td>27</td>
<td>71%</td>
<td>4%</td>
<td>67%</td>
<td>18%</td>
<td>11%</td>
<td>-</td>
<td>-</td>
<td>73% (1 yr)</td>
</tr>
<tr>
<td>Rankin, 2004</td>
<td>III</td>
<td>746</td>
<td>-</td>
<td>48%</td>
<td>3%</td>
<td>45%</td>
<td>-</td>
<td>-</td>
<td>78%</td>
<td>50% (2 yr)</td>
</tr>
<tr>
<td>-400 mg daily</td>
<td></td>
<td>48</td>
<td>3%</td>
<td>45%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>73%</td>
<td>-</td>
<td>53% (2 yr)</td>
</tr>
<tr>
<td>-800 mg daily</td>
<td></td>
<td>48</td>
<td>3%</td>
<td>45%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>73%</td>
<td>-</td>
<td>53% (2 yr)</td>
</tr>
<tr>
<td>Verweij, 2004</td>
<td>III</td>
<td>946</td>
<td>-</td>
<td>50%</td>
<td>5%</td>
<td>45%</td>
<td>32%</td>
<td>13%</td>
<td>69%</td>
<td>44% (2 yr)</td>
</tr>
<tr>
<td>-400 mg daily</td>
<td></td>
<td>50</td>
<td>5%</td>
<td>45%</td>
<td>32%</td>
<td>13%</td>
<td>69%</td>
<td>-</td>
<td>-</td>
<td>44% (2 yr)</td>
</tr>
<tr>
<td>-800 mg daily</td>
<td></td>
<td>54</td>
<td>6%</td>
<td>48%</td>
<td>32%</td>
<td>9%</td>
<td>74%</td>
<td>-</td>
<td>-</td>
<td>52% (2 yr)</td>
</tr>
</tbody>
</table>

Courtesy Dejka Steinert, M.D.
Phase III dose-randomized study of Imatinib mesylate (Gleevec, STI571) for GIST: NA Intergroup S0033 early results.

Robert S. Benjamin, UT MD Anderson Cancer Center and SWOG, Houston, TX, Cathryn Rankin, SWOG, Christopher Fletcher, Dana Farber Cancer Institute, Charles Blanke, SWOG, Margaret von Mehren, ECOG, Robert Maki, CALGB, Vivien Bramwell, NCIC, Laurence Baker, SWOG, Ernest Borden, SWOG, George D. Demetri, Dana Farber Cancer Institute, CALGB, as the

North American Sarcoma Intergroup

Benjamin et al, ASCO 2003
North American Sarcoma Intergroup Schema

Randomization:
- Low Dose Imatinib 400 mg/d → Progression → Crossover
- High Dose Imatinib 800 mg/d → Progression → Off Protocol Treatment

Crossover:
- High Dose Imatinib 800 mg/d → Progression → Off Protocol Treatment
EORTC Phase III Imatinib for Advanced GIST

Survival Benefit

Verweij, et al 2004
How long do I take imatinib?
The First GIST Patient: Histology

H&E (at diagnosis)

H&E

Ki 67

CD117

Pretreatment

One month of therapy

Phase III Trial: US Intergroup S0033: Time to Progression on Crossover

Data as of November 25, 2003

- Imatinib 800mg/day
- At Risk: 89
- Failed: 60
- Median in Months: 4

Months After Registration
Time to Tumor Progression

- **Sunitinib (N=207)**
  - Hazard ratio = 0.335  \( P < 0.00001 \)
  - Median (95% CI) 6.3 (3.7, 7.6)

- **Placebo (N=105)**
  - Median (95% CI) 1.5 (1.0, 2.3)
BFR14 3-yr randomization

Advanced/metastatic GIST

RC

RP

SD

RANDOMIZATION

STOP

PD

GLIVEC 400 mg

2 ans (analyse intermédiaire programmée pour Juin 2007)

3 yr
BFR14 3-yr randomization
Progression Free Survival

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

**STOP group** 17 evts / 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%

Log-rank test: p < .0001

Median f.u.: 11 m (IC95: 4.8 – 13.8)

Updated sept 07, ECCO 14
What dose of imatinib should I take?
EORTC Phase III Imatinib for Advanced GIST

Progression-free Survival Benefit

Verweij, et al 2004
Progression-free Survival By Imatinib Dose

*Kit* Exon 11 Mutation

Debiec-Rhycte et al, 2007
Progression-free Survival By Imatinib Dose

*Kit* Exon 9 Mutation

Debiec-Rhycter et al, 2007
## Kit Mutation in GIST

### Benefit from 800mg Imatinib

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 11 (n=211)</td>
<td>1.0</td>
<td>0.96</td>
</tr>
<tr>
<td>Exon 9 (n=25)</td>
<td>8.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Wild-type (n=33)</td>
<td>1.5</td>
<td>0.62</td>
</tr>
</tbody>
</table>

*Heinrich et al, ASCO 2005*
Tell me about the side effects.....
## Side effects: 400 vs. 800 mg

<table>
<thead>
<tr>
<th>Toxic Event</th>
<th>Adjusted $p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rash</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.0026</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0.036</td>
</tr>
<tr>
<td>Pleuritic Pain</td>
<td>0.053</td>
</tr>
</tbody>
</table>

*Verweij et al, 2004*
## Interruptions and Reductions of Therapy

<table>
<thead>
<tr>
<th></th>
<th>400 mg</th>
<th>800 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Interruption</strong></td>
<td>40%</td>
<td>64%</td>
</tr>
<tr>
<td>-Hematologic</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>-Non-Heme</td>
<td>23%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Dose Reduction</strong></td>
<td>16%</td>
<td>60%</td>
</tr>
<tr>
<td>-Hematologic</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>-Non-heme</td>
<td>10%</td>
<td>42%</td>
</tr>
</tbody>
</table>
North American Intergroup Phase III Study of Imatinib in Advanced GIST

<table>
<thead>
<tr>
<th>Dose Reduction</th>
<th>400 mg (376 pts)</th>
<th>800 mg (370 pts)</th>
<th>800 mg X-Over</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10%</td>
<td>44%</td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td>7%</td>
<td>26%</td>
<td>5%</td>
</tr>
<tr>
<td>3</td>
<td>2%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>1%</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Dileo et al, ASCO 2005
How do I know if imatinib is working?
## Confirmed Overall Responses with Gleevec

<table>
<thead>
<tr>
<th>Total patients</th>
<th>N</th>
<th>Confirmed partial response (%)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>400mg</td>
<td>73</td>
<td>33</td>
<td>22-45</td>
</tr>
<tr>
<td>600mg</td>
<td>74</td>
<td>43</td>
<td>32-55</td>
</tr>
<tr>
<td>Total</td>
<td>147</td>
<td>38</td>
<td>30-46</td>
</tr>
<tr>
<td></td>
<td>400 mg N=73 n (%)</td>
<td>600 mg N=74 n (%)</td>
<td>All Patients N=147 n (%)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Complete Response</td>
<td>0</td>
<td>2 (2.7)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>50 (68.5)</td>
<td>48(64.9)</td>
<td>98 (66.7)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>10 (13.7)</td>
<td>13 (17.6)</td>
<td>23 (15.6)</td>
</tr>
<tr>
<td>Progression</td>
<td>11 (15.1)</td>
<td>6 (8.1)</td>
<td>17 (11.6)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>2 (2.7)</td>
<td>5 (6.8)</td>
<td>7 (4.8)</td>
</tr>
</tbody>
</table>
Time to PR by RECIST

Cumulative incidence of CT responses

2 Months

3 Months

6 Months

Verweij et al, ASCO 2003
CT Scan Results

Jun 27, 2000

Before Imatinib

Oct 4, 2000

After Imatinib
Decrease in GIST intravenous contrast uptake after patient is treated for 8 weeks with imatinib mesylate
Overall Survival by Best Response

(B222, Kaplan Meier Estimate)

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Weeks: 0</th>
<th>40</th>
<th>80</th>
<th>Median Duration</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>N/A</td>
<td>172</td>
</tr>
<tr>
<td>PR</td>
<td>98</td>
<td>97</td>
<td>92</td>
<td>248 Wks</td>
<td>226</td>
</tr>
<tr>
<td>SD</td>
<td>23</td>
<td>22</td>
<td>20</td>
<td>N/A</td>
<td>149</td>
</tr>
<tr>
<td>PD</td>
<td>17</td>
<td>7</td>
<td>4</td>
<td>36 Wks</td>
<td>15</td>
</tr>
<tr>
<td>UNK</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>144 Wks</td>
<td>18</td>
</tr>
</tbody>
</table>

SD (n=23): Median n/a

PD (n=17): Median 36 wks

PR (n=98): Median 248 wks

[CR (n=2; median OS n/a) and unknown/NE (n=7; median OS 144 wks) not included]
Effects of Imatinib on GIST: CT and PET findings
Pseudoprogression Early During Treatment With Imatinib Mesylate

Effects of Imatinib on GIST: CT findings

1/12  3/30  5/24
Modified RECIST for GIST

CT Size + Density (Choi)

- Tumor size decrease of \( >10\% \) or tumor density decrease of \( >15\% \) were highly correlated with decrease in SUV by \( >70\% \) to a value \( <2.5 \) on PET.

- RECIST criteria substantially underestimate, at least initially, the value of therapy with imatinib for GIST.
How do I know if my GIST comes back?
Type of Progression

- Limited progression
- Stable disease
- Nodular progression
- Widespread progression

Stable lesion
Progressing lesion
Limited Progression
Resistance to Imatinib Mesylate: Recognition of Clonal Evolution
Secondary Mutation

Heinrich et al, JCO 2006
Should I take imatinib after my GIST was removed?
# Risk Stratification of Primary GIST by Mitotic Index, Size, and Site

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Size</th>
<th>Gastric</th>
<th>Duodenum</th>
<th>Jejunum/Ileum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic Index</td>
<td>≤ 2 cm</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 ≤ 5 cm</td>
<td>Very low (1.9%)</td>
<td>Low (8.3%)</td>
<td>Low (4.3%)</td>
<td>Low (8.5%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 ≤ 10 cm</td>
<td>Low (3.6%)</td>
<td>(Insuff. data)</td>
<td>Moderate (24%)</td>
<td>(Insuff. data)</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>Moderate (10%)</td>
<td>High (34%)</td>
<td>High (52%)</td>
<td>High (57%)</td>
</tr>
<tr>
<td>Mitotic Index</td>
<td>≤ 2 cm</td>
<td>None* (Insuff. data)</td>
<td>High*</td>
<td>High (54%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 2 ≤ 5 cm</td>
<td>Moderate (16%)</td>
<td>High (50%)</td>
<td>High (73%)</td>
<td>High (52%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 ≤ 10 cm</td>
<td>High (55%)</td>
<td>(Insuff. data)</td>
<td>High (85%)</td>
<td>(Insuff. data)</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>High (86%)</td>
<td>High (86%)</td>
<td>High (90%)</td>
<td>High (71%)</td>
</tr>
</tbody>
</table>

*Defined as metastasis or tumor-related death. *Denotes small numbers of cases.

Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.

ACOSOG Phase III Trial
Adjuvant Imatinib in Patients with High Risk Primary GIST

Primary Kit + GIST (≥ 3 cm) → Complete Gross Resection 14-70 days prior

Placebo x 1 year → Recurrence → Gleevec 400mg x 2 yrs

Recurrence → Gleevec 400mg x 1 year

Recurrence → Gleevec 800mg x 2 yrs

Primary Objective: Recurrence Free Survival (RFS)

10 years or until death

Adjuvant Imatinib

Adjuvant Imatinib

Number at risk:

- Placebo: 354
- Imatinib: 359

Total:
- Placebo: 354
- Imatinib: 359

Events:
- Placebo: 70
- Imatinib: 30

HR 0.35 (95% CI 0.22–0.53); p<0.0001
Adjuvant Imatinib

18 Months
## Postoperative Imatinib Studies

<table>
<thead>
<tr>
<th>Postoperative Imatinib Trial</th>
<th>Recurrence-Free Survival at 1 y</th>
<th>Recurrence-Free Survival at 2 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOSOG Z9001 (Imatinib)</td>
<td>98%</td>
<td>91%</td>
</tr>
<tr>
<td>ACOSOG Z9001 (Placebo)</td>
<td>83%</td>
<td>71%</td>
</tr>
<tr>
<td>MDACC-0023 (ITT)</td>
<td>94%</td>
<td>87%</td>
</tr>
<tr>
<td>MDACC-0023 (completed 2 y)</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

### Other Ongoing Adjuvant Trials in GIST (2010)

<table>
<thead>
<tr>
<th>Study (Planned Accrual)</th>
<th>Inclusion*</th>
<th>Treatment/ Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSG XVIII [NCT00116935] Phase 3 (N=400)</td>
<td>&gt;10 cm or mitoses &gt;10 &gt;5 cm + mitoses &gt;5</td>
<td>1 vs 3 y imatinib RFS</td>
</tr>
<tr>
<td>EORTC-62024 [NCT00103168] Phase 3 (N=750)</td>
<td>&gt;5 cm or mitoses &gt;10 &lt;5 cm + mitoses 6-10</td>
<td>0 vs 2 y imatinib OS</td>
</tr>
<tr>
<td>CSTI571BUS282 [NCT00867113] Phase 2 (N=133)</td>
<td>≥2 cm + mitoses ≥5 (≥5 cm only for non-gastric GIST)</td>
<td>5 y imatinib Time to recurrence</td>
</tr>
</tbody>
</table>

*Tumor size in cm; number of mitoses per 50 HPFs.  
SSG = Scandinavian Sarcoma Group.  
Effect of Imatinib on Apoptosis

Immunofluorescent TUNEL Assay

Pre-Imatinib

Post-Imatinib (3 days of therapy)
Will my kids get GIST?
Familial GIST
Gastrointestinal Stromal Tumors

GISTS 2010

Jon Trent, MD, PhD
jtrent@mdanderson.org

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

The University of Texas
MD Anderson Cancer Center
Making Cancer History™