Gastrointestinal Stromal Tumor (GIST)

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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
• About 5,000 newly diagnosed GIST patients per year in the US
• Clinical presentation is variable
  – pain, hemorrhage, anemia, anorexia, nausea, bleeding
• High recurrence rate after surgery (>50%)
• No effective chemotherapy
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.
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%)

ATP

= common mutation site
Kit Receptor Phenotype

ADP + P → ATP

Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis
Metastasis in GIST

- Primary tumor
- Detachment of the primary tumor
- Intravasation
- Migration/invasion
- Colonization/proliferation at the secondary site
- Dormancy/extravasation
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$_{50}$ ≈ 0.1μM)
Kit Receptor Phenotype

Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

ATP

= imatinib contact point
Marked Biologic Response Revealed by PET Scan

Multiple liver and upper abdominal $^{18}$FDG-accumulating metastases

A marked decrease in $^{18}$FDG uptake 4 weeks after starting imatinib mesylate

## 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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg daily</td>
<td></td>
<td></td>
<td>48%</td>
<td>3%</td>
<td>45%</td>
<td>-</td>
<td>-</td>
<td>78%</td>
<td>-</td>
<td>50% (2 yr)</td>
</tr>
<tr>
<td>800 mg daily</td>
<td></td>
<td></td>
<td>48%</td>
<td>3%</td>
<td>45%</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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg daily</td>
<td></td>
<td></td>
<td>50%</td>
<td>5%</td>
<td>45%</td>
<td>32%</td>
<td>13%</td>
<td>69%</td>
<td>-</td>
<td>44% (2 yr)</td>
</tr>
<tr>
<td>800 mg daily</td>
<td></td>
<td></td>
<td>54%</td>
<td>6%</td>
<td>48%</td>
<td>32%</td>
<td>9%</td>
<td>74%</td>
<td>-</td>
<td>52% (2 yr)</td>
</tr>
</tbody>
</table>

*Courtesy Dejka Araujo, M.D.*
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
GIST Response

Pre-Imatinib

Post-Imatinib (8 weeks therapy)
How Long Do I take Imatinib?
BFR14 3-yr randomization

Advanced/metastatic GIST

RC
RP
SD

RANDOMISATION

STOP

PD

GLIVEC 400 mg

3 yr

2 ans (analyse intermédiaire programmée pour Juin 2007)
BFR14  3-yr randomization
Progression Free Survival

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

Log-rank test : p <.0001

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

Median f.u.: 11 m
(IC95: 4.8 – 13.8)

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

Updated sept 07, ECCO 14
What Dose of Imatinib Do 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-Rhycter et al, 2007
Progression-free Survival By Imatinib Dose

Kit Exon 9 Mutation

Debiec-Rychter et al, 2007
Will I Have Side Effects?

How Do I Manage Them?
### 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></td>
<td></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></td>
<td></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
Is My GIST "Responding" To Therapy

Radiographic Efficacy
## 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>
</tbody>
</table>
## Best Response (B222)

<table>
<thead>
<tr>
<th></th>
<th>400 mg (N=73)</th>
<th>600 mg (N=74)</th>
<th>All Patients (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n (%))</td>
<td>(n (%))</td>
<td>(n (%))</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
Good “Response”
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
Survival by Best Response

(B222, Kaplan Meier Estimate)

[CR (n=2; median OS n/a) and unknown/NE (n=7; median OS 144 wks) not included]
Paradoxical Good “Response”

CT and PET findings
Paradoxical Good “Response”

CT and PET findings
Who is reading my CT scan?
What do I do if my GIST is Resistant?
Type of Progression

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

Stable lesion
Progressing lesion
Limited Progression
Nodular Progression
Therapy by Type of Progression

• **Limited or Nodular Progression**
  – Hepatic Artery Chemoembolization
  – Hepatic Radio-frequency Catheter Ablation
  – Surgical Resection
  – Radiation Therapy (esophageal or rectal)

• **Widespread progression**
  – Increase Imatinib to 800 mg daily
  – Sunitinib
  – Clinical Trial
Hepatic Artery Embolization

Pre-embolization

Post-embolization

Courtesy of Dr. R. DeMatteo.
Secondary Mutation

1. V654A, D816H (patient 5 this report)
2. D820E, N822K, N822Y (patient 39 this report)
3. V654A, N822K (Antonescu et al7)
4. D816E, D820V, D820E, N822K (Wardelmann et al12)
5. V654A, T670E, Y823D (Wardelmann et al12)
7. V654A, T670I (Wardelmann et al15)

Heinrich et al, JCO 2006
Phase III Trial: US Intergroup S0033: Time to Progression on Crossover

Data as of November 25, 2003

- Months After Registration
- At Risk: 89
- Failed: 60
- Median in Months: 4
Time to Tumor Progression

Estimated TTP probability (%)

Sunitinib (N=207)
Placebo (N=105)

Median (95% CI)
6.3  (3.7, 7.6)
1.5  (1.0, 2.3)

Hazard ratio = 0.335
P<0.00001
Background - Regorafenib

- Regorafenib (BAY 73-4506) is a structurally distinct oral TKI with inhibitory activity against several kinases including KIT, PDGFRA, FGFR, VEGFR 2,3, TIE-2, and B-RAF.

- Regorafenib is physiologically processed into at least two bioactive metabolites, each with long half-lives (approximately 24 hrs), allowing target kinase inhibition with promising pharmacodynamics.

George et al ASCO 2103
<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Trial Phase</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT Inhibitors</td>
<td>Sorafenib</td>
<td>II</td>
<td>PR=13%, SD=58%, PFS=5 mos.</td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td>II</td>
<td>PR=22%, SD=24%, PFS=2 months</td>
</tr>
<tr>
<td></td>
<td>Nilotinib</td>
<td>I/II/III</td>
<td>PR=10%, SD=37%, PFS=3 mos.</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>II</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Axitinib</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Ponatinib</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Raf Inhib.</td>
<td>Vemurafenib</td>
<td>NA</td>
<td>ND</td>
</tr>
<tr>
<td>IGF-1R inh.</td>
<td>Linsitinib</td>
<td>II</td>
<td>Ongoing (Pedi/WT)</td>
</tr>
<tr>
<td>mTOR inh.</td>
<td>Everolimus</td>
<td>II</td>
<td>PR=2%, SD=43%, PFS=3.5 mos.</td>
</tr>
<tr>
<td>HDAC inh.</td>
<td>vorinostat</td>
<td>NA</td>
<td>ND</td>
</tr>
<tr>
<td>Placebo</td>
<td>Various</td>
<td>III</td>
<td>PR=0%, PFS=1-1.5 months</td>
</tr>
</tbody>
</table>
Gastrointestinal Stromal Tumor (GIST)

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

<table>
<thead>
<tr>
<th>Mitotic Index</th>
<th>Size</th>
<th>Gastric</th>
<th>Duodenum</th>
<th>Jejunum/Ileum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 per 50 hpf</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>&gt; 5 per 50 hpf</td>
<td>≤ 2 cm</td>
<td>None*</td>
<td>(Insuff. data)</td>
<td>High*</td>
<td>High (54%)</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.

Adjuvant Imatinib

# 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>

Recurrence-Free Survival (ITT)
(Joensuu et al. Plenary Session: Abstract #LBA1)
Overall Survival Benefit

Overall Survival (ITT)
(Joensuu et al. Plenary Session: Abstract #LBA1)

Hazard ratio 0.45
(95% CI, 0.22–0.89)

P=0.019

Percentage

Years

No. at risk (n=397)

36 months of imatinib  198  192  184  152  100  56  13  0
12 months of imatinib  199  188  176  140  87  46  20  0
Referral of Patients With GIST to Specialists

- Radiologists
  - Perform imaging studies: CT, MRI, and PET
- Surgeon: Biopsy and Surgical Evaluation
- Gastroenterologist: Biopsy
- Pathologist: Diagnosis and Mutation Testing
- Medical Oncologist: PCP, Systemic Therapy
- Nurse and Mid-Level: evaluate side-effects

GIST Evaluation

- Every 2-3 months (extend over time)
- History and Physical Examination
- Laboratory Testing
- Abdominal/pelvic CT with contrast
  - Recommended for diagnosis and staging
  - Also useful for assessing common sites of metastasis (eg, liver, peritoneum)
  - Every 2-4 months while on therapy
- Chest X-ray
- $^{18}$FDG-PET
- MRI with gadolinium

$^{18}$FDG-PET=fluorine-18-fluorodeoxyglucose positron emission tomography.
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