Gastrointestinal Stromal Tumor
Advanced Disease

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Metastasis in GIST
Metastatic Sites

Liver
Peritoneum
Bone
Lymph nodes
Lung
Brain
Heart
Skin
## 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/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>
EORTC 1st Line Chemotherapy: Active Single Agents or Combinations

Van Glabbeke, ASCO 2001
Median Overall Survival in Metastatic GIST

Circa 1990

SWOG S8616/S9627

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\(_{50}\) \( \approx 0.1 \mu\text{M} \))
Ph II Trial: 400 mg/d vs 600 mg/d Imatinib in Advanced GIST

Metastatic or unresectable GIST

Imatinib (400 mg/d) → Follow for PFS

Imatinib (600 mg/d)
Ph III Trials: 400 mg/d vs 800 mg/d Imatinib in Advanced GIST

- US Intergroup SWOG S0033 Study
- EORTC 62005 Study

Metastatic or unresectable GIST

Imatinib (400 mg/d)

Imatinib (800 mg/d)

PD

Follow for Survival, PFS


MetaGIST: PFS

Tumor Genotype and Imatinib Dose Selection


<table>
<thead>
<tr>
<th>Dose Type</th>
<th>O</th>
<th>N</th>
<th>22</th>
<th>15</th>
<th>3</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg ex9</td>
<td>31</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 mg ex9</td>
<td>30</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg other</td>
<td>144</td>
<td>341</td>
<td>304</td>
<td>258</td>
<td>209</td>
<td>94</td>
</tr>
<tr>
<td>800 mg other</td>
<td>146</td>
<td>340</td>
<td>310</td>
<td>252</td>
<td>190</td>
<td>84</td>
</tr>
</tbody>
</table>
GIST Evaluation

- Every 2-4 months
- 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.  
## 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
Response to Therapy
GIST Response

Pre-Imatinib

Post-Imatinib (8 weeks therapy)
GIST Response

Pre-Imatinib

Post-Imatinib (8 weeks therapy)

61.3 HU

11.3 HU
Continuous Target Inhibition
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)

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

Log-rank test : p <.0001

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%
Progression of Disease
Type of Progression

- Stable disease
- Stable lesion
- Progressing lesion
- Nodular progression
- Limited progression
- Widespread progression
Limited 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.
Imatinib-Resistant Metastatic GIST

Limited Hepatic Progression

Hepatic Arterial Embolization

Radiographic Response Rates

- 14 patients with imatinib-resistant GIST and progressive liver metastases
  - Treated with hepatic arterial embolization or chemoembolization
  - 13 patients evaluable for radiologic response

<table>
<thead>
<tr>
<th>Response</th>
<th>Best Response (Choi Criteria)</th>
<th>Best Response (RECIST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>54%</td>
<td>8%</td>
</tr>
<tr>
<td>Complete</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Partial</td>
<td>54%</td>
<td>8%</td>
</tr>
<tr>
<td>Stable</td>
<td>46%</td>
<td>92%</td>
</tr>
<tr>
<td>Progression</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Hepatic Arterial Embolization

Progression-Free Survival

Median = 7.0 Months

Imatinib-resistant GIST

*Disease-Free Survival*

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**Heptatic Resection**

**Hepatic Resection + RFA**

Arch Surg. 2006 Jun;141(6):537-43
Radiotherapy for GIST
Radiotherapy for GIST
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
Association of Intratumoral Vascular Endothelial Growth Factor Expression and Clinical Outcome for Patients with Gastrointestinal Stromal Tumors Treated with Imatinib Mesylate

John C. McAuliffe¹, Alexander J.F. Lazar², Dan Yang¹, Dejka M. Steinert¹, Wei Qiao³, Peter F. Thall³, A. Kevin Raymond², Robert S. Benjamin¹ and Jonathan C. Trent¹
**Sunitinib Efficacy in Patients With Imatinib-Refractory GIST**

- **Primary endpoint**
  - TTP, as defined using RECIST
- **Secondary endpoints**
  - PFS, OS, ORR, TTR, DOR, and duration of PS maintenance
- At RECIST-defined disease progression, pts receiving placebo were eligible for crossover

IM=imatinib; ORR=overall response rate; RES=resistant; TTP=time to progression; TTR=time to tumor response.

Time to Tumor Progression

Estimated TTP probability (%)

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

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

Hazard ratio = 0.335
P<0.00001
## Other Agents for IM-RES GIST

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Trial Phase</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KIT Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>II</td>
<td>PR=13%, SD=58%</td>
<td>PFS=5 months</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>II</td>
<td>PR=22%, SD=24%</td>
<td>PFS=2 months</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>I/II/III</td>
<td>PR=10%, SD=37%</td>
<td>PFS=3 months</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>II</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>Axitinib</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td><strong>Raf Inhibitors</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>I</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td><strong>mTOR inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>II/III</td>
<td>PR=2%, SD=43%</td>
<td>PFS=3.5 months</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>II</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td><strong>HDAC inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAHA</td>
<td>NA</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>Various</td>
<td>III</td>
<td>PR=0%, PFS=1-1.5 months</td>
</tr>
</tbody>
</table>

HDAC=histone deacetylase; IGF-1R=insulin-like growth factor-1 receptor; MKI=multitargeted kinase inhibitor; mTOR=mammalian target of rapamycin.
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Advanced Disease

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