Treatment Paradigms for Primary and Resistant Gastrointestinal Stromal Tumor (GIST)

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DISCLOSURES

- Speaker’s Bureau: Eli Lilly, Eisai
- Advisory Role: Eli Lilly
- Founder: PDOX LLC.
WHERE DOES GIST START?

- Stomach (60%).
- Small intestine (30%).
- Rectum (3%).
- Colon (1–2%).
- Esophagus (<1%).
- Omentum/mesentery (rare).
# Treatment planning

## Must haves

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidisciplinary team</td>
<td></td>
</tr>
<tr>
<td>Medical history and physical exam</td>
<td></td>
</tr>
<tr>
<td>Biopsy if</td>
<td>- &lt;2 cm stomach tumor,</td>
</tr>
<tr>
<td></td>
<td>- ≥2 cm GI tumor and may have other types of treatment before surgery,</td>
</tr>
<tr>
<td></td>
<td>- ≥2 cm GI tumor and can’t have surgery but will have other treatment</td>
</tr>
<tr>
<td>Imaging of abdomen and pelvis</td>
<td>- CT (computed tomography) for &lt;2 cm stomach tumors</td>
</tr>
<tr>
<td></td>
<td>- CT or MRI (magnetic resonance imaging) for ≥2 cm tumor</td>
</tr>
<tr>
<td>KIT and PDGFRA testing for ≥2 cm tumor</td>
<td></td>
</tr>
</tbody>
</table>

## Sometimes useful

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging of chest</td>
<td></td>
</tr>
<tr>
<td>Endoscopy ± ultrasound</td>
<td></td>
</tr>
<tr>
<td>PET (positron emission tomography)</td>
<td></td>
</tr>
<tr>
<td>SDH (succinate dehydrogenase) gene testing</td>
<td></td>
</tr>
</tbody>
</table>
GIST CATEGORIES

Resectable
- Eilber

Unresectable
- Chemotherapy (<5% RR)
  - Radiation Therapy
<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><strong>≤5 per 50 high-power fields (HPF)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitotic Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</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>(Insufficient data)</td>
<td>Moderate (24%)</td>
<td>(Insufficient 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></td>
<td></td>
<td>None##</td>
<td>(Insufficient 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>(Insufficient data)</td>
<td>High (85%)</td>
<td>(Insufficient 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 number of cases.
GIST MUTATIONS

KIT

- Exon 9 (11%)
- Exon 11 (67.5%)
- Exon 13 (0.9%)
- Exon 17 (0.5%)

PDGFRα

- Exon 12 (0.9%)
- Exon 14 (0.3%)
- Exon 18 (6.3%)

Membrane

Cytoplasm

BRAF: 2%
RAS: ?
NF1: 2%
SDHB/C: 3%
WHAT DOES IT MEAN TO HAVE A MUTATION?
Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

Heikki Joensuu, M.D., Peter J. Roberts, M.D., Maarit Sarlomo-Rikala, M.D., Leif C. Andersson, M.D., Pekka Tervahartiala, M.D., David Tuveson, M.D., Ph.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Sasa Dimitrijevic, Ph.D., Brian Druker, M.D., and George D. Demetri, M.D.

Figure 1. Transaxial Gadolinium-Enhanced T1-Weighted MRI Studies of the Upper Abdomen.
Before ST1571 therapy (Panel A), multiple metastatic lesions were present in the liver. Contrast enhancement of the metastases was highly heterogeneous, with strong enhancement at the periphery. Enhancement was less intense in the central parts of the metastases, suggesting necrosis. After four weeks of treatment with ST1571 (Panel B), the metastases had a cyst-like appearance. After eight months of treatment (Panel C), the metastases were smaller, and some had disappeared.
EFFICACY AND SAFETY OF IMATINIB MESYLATE IN ADVANCED GASTROINTESTINAL STROMAL TUMORS

George D. Demetri, M.D., Margaret von Mehren, M.D., Charles D. Blanke, M.D., Annick D. Van den Abbeele, M.D., Burton Eisenberg, M.D., Peter J. Roberts, M.D., Michael C. Heinrich, M.D., David A. Tuveson, M.D., Ph.D., Samuel Singer, M.D., Milos Janicek, M.D., Ph.D., Jonathan A. Fletcher, M.D., Stuart G. Silverman, M.D., Sandra L. Silverman, M.D., Ph.D., Renaud Capdeville, M.D., Beate Kiese, M.Sc., Bin Peng, M.D., Ph.D., Sasa Dimitrijevic, Ph.D., Brian J. Druker, M.D., Christopher Corless, M.D., Christopher D.M. Fletcher, M.D., and Heikki Joensuu, M.D.
<table>
<thead>
<tr>
<th>Best Response</th>
<th>400 mg (N=73)</th>
<th>600 mg (N=74)</th>
<th>Either Dose (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>36 (49.3 [37.4–61.3])</td>
<td>43 (58.1 [46.1–69.5])</td>
<td>79 (53.7 [45.3–62.0])</td>
</tr>
<tr>
<td>Stable disease</td>
<td>23 (31.5 [21.1–43.4])</td>
<td>18 (24.3 [15.1–35.7])</td>
<td>41 (27.9 [20.8–35.9])</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12 (16.4)</td>
<td>8 (10.8)</td>
<td>20 (13.6)</td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>2 (2.7)</td>
<td>5 (6.8)</td>
<td>7 (4.8)</td>
</tr>
</tbody>
</table>
Figure 1. Kaplan–Meier Estimates of Overall Survival and Time to Treatment Failure for All Patients. Each arrowhead represents the point at which a patient’s data were censored.
What is the right dose of Gleevec?

- 1640 pts with advanced GIST
Response by Mutational Status
Response by Genotype

Fig. 3 – Cumulative incidence of response observed in the three largest subgroups of kinase genotypes analyzed in this study.
How does Gleevec compare to Chemotherapy?

Figure 6: Overall survival for total study population
Data are compared with historical (GIST) controls from the EORTC database.
Dox=doxorubicin-based regimen
Adjuvant Treatment = After Surgery
How Long?

396 Patients

1 year (198 pts)

3 years (198 pts)

2/1/2012

FDA Grants Expanded Approval of Gleevec for 36 months in adjuvant setting
Resistance to Imatinib

- 5% primary resistance
- 14% have early resistance
- Secondary /acquired resistance
  - Median of 2 years
KIT and PDGFRA mutations and correlation to protein structure

Pierotti, M. A. et al. (2011) Targeted therapy in GIST: in silico modeling for prediction of resistance
Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial

George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali

- 312 Patients
- 207 Sutent
- 105 Placebo
  - Failed Gleevec
  - Intolerant of Gleevec
Response to Sutent
## Response to Sutent

<table>
<thead>
<tr>
<th>Response</th>
<th>Sutent</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Stable</td>
<td>58%</td>
<td>48%</td>
</tr>
<tr>
<td>Progressed</td>
<td>19%</td>
<td>37%</td>
</tr>
</tbody>
</table>
Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib: an international, multicentre, prospective, randomised, placebo-controlled phase 3 trial (GRID)

Response to Regorafenib=Stivarga

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib, N=133</th>
<th>Placebo, N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (95% CI)</td>
<td>4.8 months (4.1–5.8)</td>
<td>0.9 months (0.9–1.1)</td>
</tr>
<tr>
<td>Number of events</td>
<td>81 (60.9%)</td>
<td>63 (95.5%)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI):</td>
<td>0.27 (0.19–0.39)</td>
<td>1-sided p-value: &lt;0.0001</td>
</tr>
</tbody>
</table>

![Survival distribution function graph showing the comparison between Regorafenib and Placebo.](image)

- Patients at risk:
  - Regorafenib: 82, 72, 27, 9
  - Placebo: 12, 5, 0, 0
Regorafenib, N=133 | Placebo, N=66
---|---
Median PFS (95% CI) | 4.8 months (4.1–5.8) | 0.9 months (0.9–1.1)
Number of events | 81 (60.9%) | 63 (95.5%)

Hazard ratio (95% CI): 0.27 (0.19–0.39)
1-sided p-value: <0.0001

Patients at risk
Regorafenib: 82, 72, 27, 9
Placebo: 12, 5, 0, 0
What about patients who started on placebo and switched to regorafenib?

- Median PFS: 5.0 months
**GIST**
- Imatinib\(^{25,26}\)
- Sunitinib\(^{27}\)
- Regorafenib\(^{28}\)

*Disease progression after imatinib, sunitinib, and regorafenib*
- Sorafenib\(^{29-31}\)
- Nilotinib\(^{32,33}\)
- Dasatinib\(^{34}\) (for patients with D842V mutation)
- Pazopanib\(^{35}\)
Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial

Olivier Mir, Claire Cropet, Maud Toufmonde, Axel Le Cesne, Mathieu Molimard, Emmanuelle Bonpas, Philippe Cassier, Isabelle Roy-Coquard, Maria Rios, Antoine Adenis, Antoine Italiano, Olivier Bousché, Emmanuelle Chouzit, Florence Deffaud, François Bertucci, Nicolas Isambert, Julien Gaubert, Jean-Yves Blay, David Pirol, on behalf of the PAZOGIST study group of the French Sarcoma Groupe-Groupe d’Étude des Tumeurs Ossseuses (GSF-GETO)

4 month PFS
45% vs. 17%

MEDIAN PFS
3.4 vs. 2.3 mo
(HR: 0.59, p=0.03)
THANK YOU!