Gastrointestinal Stromal Tumor
GISTs 2019

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Associate Director, Clinical Research
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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
Metastasis in GIST

Primary tumor → Detachment of the primary tumor → Intravasation → Migration/invasion → Colonization/proliferation at the secondary site → Dormancy/extravasation
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

ATP
Kit Receptor Phenotype

ADP + P

Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

ATP
Imatinib Mesylate

Kinase Inhibitor, TKI

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$_{50} \approx 0.1\mu$M)
ATP = imatinib contact point

Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= 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>
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<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>
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<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>
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<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>
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<tr>
<td>Rankin, 2004</td>
<td>III</td>
<td>746</td>
<td></td>
<td></td>
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<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>
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<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>
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<td>44% (2 yr)</td>
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<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

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)

Courtesy Jon Trent and Alex Lazar
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 (e.g., liver, peritoneum)
  - Every 2-6 months while on therapy
- Chest X-ray
- $^{18}$FDG-PET
- MRI with gadolinium

$^{18}$FDG-PET=fluorine-18-fluorodeoxyglucose positron emission tomography.
What if my GIST does not have a KIT mutation?
GIST Subtypes of GIST

- Kit exon 11
- Kit exon 9
- PDGFR D842V
- SDH deficiency
- Raf V600E
- NF-1, Ras
- PI3K
- IGF-1R expressing
- TRK fusion
- KIT resistance mutations
  - Exon 13 (ATP binding site)
  - Exon 17 (A-loop)

Personal Communication Jon Trent, MD, PhD (Sylvester Comprehensive Cancer Center)
GIST Subtypes and Treatment

- Kit exon 11: Imatinib 400 mg
- Kit exon 9: Imatinib 800 mg (or tolerated dose)
- PDGFR D842V: anti-PDGFR trial (avapritinib, crenolanib)
- SDH deficiency: Sunitinib or Regorafenib
- Raf V600E: Raf inhibitor
- NF-1, Ras: Raf or Mek inhibitor
- PI3K: mTOR inhibitor
- IGF-1R expressing – IGF-1R inhibitor trial
- TRK fusion – LOXO-101 NTRK inhibitor trial
- KIT resistance mutations
  - Exon 13 (ATP binding site): Sunitinib 37.5 mg daily
  - Exon 17 (A-loop): Regorafenib 120 mg daily

Personal Communication Jon Trent, MD, PhD (Sylvester Comprehensive Cancer Center)
GIST Precision Medicine

Advanced GIST Patient

Tissue Sent For NGS or NGS available

Weekly Molecular Tumor Board

Actionable mutation
- Targeted Drug
  - FDA Approved (Off-Label)
  - External Targeted trial

No actionable mutation
- SDH Expression Loss
  - Sunitinib
  - Regorafenib
  - DNMTi

Options

SCCC Targeted Trial

NCI MATCH

External Targeted trial

FDA Approved (Off-Label)

Options

SCCC Immunotherapy Trial

SCCC Non-Targeted Trial

External Non-Targeted trial
How Long Do I take Imatinib or Other Kinase Inhibitor?
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**

<table>
<thead>
<tr>
<th>Time</th>
<th>Probability</th>
<th>1-year PFS</th>
<th>CI95</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOP group</td>
<td>3 evts / 25 patients</td>
<td>25.2%</td>
<td>6.3 - 44.0</td>
</tr>
<tr>
<td>CONT group</td>
<td>3 evts / 25 patients</td>
<td>87.7%</td>
<td>71.6 - 100.0</td>
</tr>
</tbody>
</table>

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%

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-Rhycker 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>
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</table>

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

<table>
<thead>
<tr>
<th></th>
<th>400 mg</th>
<th>800 mg</th>
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<tbody>
<tr>
<td><strong>Treatment Interruption</strong></td>
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</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>
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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>
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<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
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
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

Courtesy Jon Trent
Secondary Mutations in KIT


- ATP/ADP Binding Site (V654)
- Gate Keeper (T670)
- Activation Loop (D820)
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
  - Regorafenib
  - Clinical Trial
Hepatic Artery Embolization

Pre-embolization

Post-embolization
What happens if imatinib is no longer helping?
Secondary Mutation

- 1. V654A, D816H (patient 5 this report)
- 2. D820E, N822K, N822Y (patient 39 this report)
- 3. V654A, N822K (Antonescu et al\textsuperscript{7})
- 4. D816E, D820V, D820E, N822K (Wardemann et al\textsuperscript{12})
- 5. V654A, T670E, Y823D (Wardemann et al\textsuperscript{12})
- 6. V654A, D820G (Wardemann et al\textsuperscript{15})
- 7. V654A, T670I (Wardemann et al\textsuperscript{15})

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

Data as of November 25, 2003

0%  20%  40%  60%  80%  100%

0  6  12  18  24  30

Months After Registration

At Risk  Failed  Median in Months

Imatinib 800mg/day  89  60  4
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
Time to Tumor Progression

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

- **Placebo (N=105)**
  - Median (95% CI): 1.5 (1.0, 2.3)
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.
Regorafenib vs. Placebo

![Graph showing progression-free survival probability over months from randomization for Stivarga (N=133) and Placebo (N=66).]

**Patients at Risk**
- Stivarga: 82, 72, 27, 9
- Placebo: 12, 5, 0, 0
Clinical Trials
## Off-Label

FDA-approved but not for GIST

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Trial Phase</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>KIT Inhibitors</strong></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Sorafenib</td>
<td>II</td>
<td>PR=13%, SD=58% PFS=5 months</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 months</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>II</td>
<td>PazoGIST, PFS-1.9 months</td>
</tr>
<tr>
<td></td>
<td>Ponatinib</td>
<td>II</td>
<td>Exon 11 CBR 37%, PFS 4.3 months</td>
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<td></td>
<td>Axitinib</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td><strong>RAF Inhibitors</strong></td>
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<td>Vemurafenib</td>
<td>ND</td>
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<td>Dabrafenib</td>
<td>ND</td>
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<td><strong>mTOR Inhibitors</strong></td>
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<tr>
<td></td>
<td>Everolimus</td>
<td>II</td>
<td>PR=2%, SD=43% PFS=3.5 months</td>
</tr>
<tr>
<td></td>
<td>Temsirolimus</td>
<td>ND</td>
<td>ND</td>
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</table>
Circulating Tumor DNA
Mutation Testing From Blood (Liquid Biopsy)

Nurwidya et al, 2018
Ponatinib

Case: KIT Exon 11(W557-K558del), KIT Exon 17 (Y823D) ctDNA

Baseline 6 months 12 months
Sarcoma and GIST Team

- **Medical Oncology**
  - Jon Trent
  - Breelyn Wilky
  - Matteo Trucco (Pediatric)
- **Pathology**
  - Andrew Rosenberg
  - Darcy Kerr
- **Radiology**
  - Ty Subhawong
  - Jean Jose
- **ARNP**
  - Morgan Smith
  - Ali Naveda
- **Nursing**
  - Eryka Lacayo
  - Yolanda Roper
- **Social Work**
  - Marlene Morales
- **Orthopedic Oncology**
  - Sheila Conway
  - Frank Eismont
  - Juan Pretell
  - Mo Al Maaieh
- **Surgical Oncology**
  - Nipun Merchant
  - Alan Livingstone
  - Danny Yakoub
- **Radiation Therapy**
  - Raphael Yechieli
  - Aaron Wolfson
- **Head & Neck Surgery**
  - Zoukaa Sargi
  - Frank Civantos
- **Thoracic Surgery**
  - Dao Nguyen
  - Nestor Villamizar
- **Interventional Radiology**
  - Shree Venkat
  - Ivan Chaitowitz
  - Evelyn Wempe
- **Gynecologic Oncology**
  - Brian Slomovitz
  - Marilyn Huang
- **Clinical Research**
  - Tamara Leon
  - Liz Bornote
  - Junet Alvarez
- **Lab Research**
  - Josie Eid
  - Joanna DeSalvo
  - Luyuan Li
  - Karina Galoian
  - Shuchao Zhang
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GISTs 2019

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