Molecular Decision-making
In GIST Therapy

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GIST Molecular Overview

- About 5,000 newly diagnosed GIST patients per year in the US
- **Kit mutation** ~80% of GISTs
  - Exon 11 (~70%), Exon 9 (~10%)
- **PDGFR mutation** ~10% of GISTs
  - Exon 18 D842V imatinib/sunitinib resistant
- **SDH-B** deficient
- **Raf V600E**
- **NF-1, Ras**
- **PI3K**
- “**wild-type**”
Molecular Decision-Making in GIST

- Initial therapy for GIST patients requires molecular decision-making:
  - Kit exon 9
  - PDGFR D842V
  - SDH-B deficiency
  - Raf V600E
  - NF-1, Ras
  - PI3K
GIST Patient Initial Therapy

**KIT Exon 9 Mutation**

- Imatinib 400 mg
- Imatinib 800 mg
Initial Imatinib Dose Selection

*Kit Exon 9 mutation*

**Graph B**

Overall Survival (%)

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>400 mg ex9</td>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
<td>60</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>800 mg ex9</td>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
<td>60</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>400 mg other</td>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
<td>60</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>800 mg other</td>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
<td>60</td>
<td>50</td>
<td>40</td>
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**Table**

<table>
<thead>
<tr>
<th>Dose</th>
<th>O</th>
<th>N</th>
<th>22</th>
<th>15</th>
<th>3</th>
<th>0</th>
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<td>400 mg ex9</td>
<td>31</td>
<td>42</td>
<td>34</td>
<td>22</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>800 mg ex9</td>
<td>30</td>
<td>49</td>
<td>42</td>
<td>33</td>
<td>22</td>
<td>6</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 Patient Initial Therapy

PDGFR D842V Mutation
GIST Patient Initial Therapy

**RAF V600E Mutation**

Treatment with RAF inhibitor

Falchook, Trent, Heinrich 2013
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.
Bidimensional response has been observed in SDH-deficient GIST treated with regorafenib.

Waterfall plot of best response of target lesions in SDH deficient GIST:

Median age of patients with SDH deficient GIST: 43 yrs (range 25 – 63)
Molecular Decision-Making in GIST

- Initial therapy for GIST patients requires molecular decision-making
  - Kit exon 9: Imatinib 800mg (or highest tolerated dose)
  - PDGFR D842V: anti-PDGFR trial
  - SDH-B deficiency: Regorafenib ?
  - Raf V600E: Raf inhibitor
  - NF-1, Ras: Raf inhibitor?
  - PI3K: mTOR inhibitor
Molecular Decision-Making in GIST

- Optimal second-line therapy for GIST patients requires molecular decision-making
  - KIT secondary mutations
    - Exon 13 (ATP binding site)
    - Exon 17 (A-loop)
Secondary Mutations in KIT

Regorafenib in Metastatic GIST

**Progression-Free Survival**

Median PFS: 13 months
95% CI (9-18)
Regorafenib in GIST following failure of IM and SU: Baseline patient characteristics (n=33) Median followup 20 months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (% or range)</th>
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<tr>
<td>Median Age, years</td>
<td>56 (25-76)</td>
</tr>
<tr>
<td>Female/Male</td>
<td>14 (42)/19 (58)</td>
</tr>
<tr>
<td>ECOG PS 0/1</td>
<td>23 (70)/10 (30)</td>
</tr>
<tr>
<td>Median number of prior regimens</td>
<td>2 (2-10)</td>
</tr>
<tr>
<td>Primary kinase mutation*:</td>
<td></td>
</tr>
<tr>
<td>KIT Exon 11</td>
<td>19</td>
</tr>
<tr>
<td>KIT Exon 9</td>
<td>3</td>
</tr>
<tr>
<td>Wild type (WT) ** for KIT and PDGFRA</td>
<td>8</td>
</tr>
</tbody>
</table>

*Available for 30 pts. Three pts had insufficient material for analysis
**7 pts were WT for KIT exons 9, 11, 13, 17 and PDGFRA exons 12, 14, 18.
Two of 7 pts were also WT for KIT exons 14,15, 16 and 18
(remaining 5 of 7 pts were not tested for these sites of possible mutation)
Regorafenib
*exon 17 secondary*

<table>
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<th>Pre-regorafenib secondary mutations</th>
<th>N</th>
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<tr>
<td>Exon 17</td>
<td>7</td>
</tr>
<tr>
<td>Exon 18</td>
<td>1</td>
</tr>
<tr>
<td>Exon 13</td>
<td>1</td>
</tr>
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</table>

Pre-enrollment tumor for secondary mutations was available on 9 study participants.

Median PFS for patients with tumor which harbors a known secondary exon 17 mutation: 18 months (95% CI 6-NR)
## Summary of secondary exon 17 mutations identified in this patient cohort (n=7)

<table>
<thead>
<tr>
<th>Case</th>
<th>Primary Mutation</th>
<th>Secondary mutation in exon 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Exon 11 V559A</td>
<td>D820Y</td>
</tr>
<tr>
<td>15</td>
<td>Exon 9 Insertion AY502-503</td>
<td>D820Y</td>
</tr>
<tr>
<td>19</td>
<td>Exon 11 KPMYEVQW550-557K</td>
<td>D820Y</td>
</tr>
<tr>
<td>21</td>
<td>Exon 11 deletion 550-558</td>
<td>N822K</td>
</tr>
<tr>
<td>25</td>
<td>Exon 11 W557G</td>
<td>N822K</td>
</tr>
<tr>
<td>30</td>
<td>Exon 9 insertion AY502-503</td>
<td>D820Y</td>
</tr>
<tr>
<td>31</td>
<td>Exon 11 deletion KPMYEVQ 550-556M</td>
<td>N822K</td>
</tr>
</tbody>
</table>
KIT D820Y (exon 17). Radiographic and metabolic response on REGO

Baseline

Pre-REGO biopsy

KIT ex 11 + ex 17 (D820Y)

C4D21
KIT V654A (exon 13). Radiographic and metabolic progression on REGO

Baseline

C12D21

KIT ex 11 + Ex 13 (V654A)
Use of ponatinib to inhibit kinase mutations associated with drug-resistant GIST
Ponatinib binds Kit in the presence of resistance mutations.

Ponatinib binds the inactive conformation deep in the ATP binding pocket.

Ponatinib binding can tolerate key KIT resistance mutations.

Heinrich et al ASCO 2013
Differential Activity of TKIs

IC50 (nM)

Imatinib
- E9
- E9/V654A
- E9/D816H
- V560D
- V560D/V654A
- V560D/D816H
- E11
- E11/V654A
- E11/D816H
- E11/V564A
- E11/T670I
- E11/D820A
- E11/N822K
- E11/A829P
- V560D/V654A
- V560D/D816H

Sunitinib
- E9
- E9/V654A
- E9/D816H
- V560D
- V560D/V654A
- V560D/D816H
- E11
- E11/V654A
- E11/D816H
- E11/V564A
- E11/T670I
- E11/D820A
- E11/N822K
- E11/A829P
- V560D/V654A
- V560D/D816H

Ponatinib
- E9
- E9/V654A
- E9/D816H
- V560D
- V560D/V654A
- V560D/D816H
- E11
- E11/V654A
- E11/D816H
- E11/V564A
- E11/T670I
- E11/D820A
- E11/N822K
- E11/A829P
- V560D/V654A
- V560D/D816H
Ponatinib Potently Inhibits Secondary Mutants In A-Loop

Jon Trent, MD, PhD
Sunitinib Superior If Secondary Mutation Is In ATP-binding Site

**Graph:**
- **X-axis:** Days
- **Y-axis:** Tumor volume (mm$^3$)
- **Lines:**
  - Citrate vehicle
  - Ponatinib 30 mg/kg
  - Sunitinib 80 mg/kg
  - Water vehicle
  - Imatinib 300 mg/kg

**Legend:**
- **KIT ΔEx11/ V654A**
Conclusions

• Ponatinib is clearly active against GIST cell lines including those with secondary mutations in Exon 17 (A-loop) and Exon 14 (Gate Keeper)

• Ponatinib is superior to other TKIs in terms of IC50 in GIST cell lines except those with Exon 13 (V654 ATP binding site) secondary mutation

• Clinical trial in resistant GIST is warranted
Secondary Mutations in KIT

ATP/ADP Binding Site (V654)
Gate Keeper (T670)
Activation Loop (D820)

Detection of mutant free circulating tumor DNA in the plasma of patients with gastrointestinal stromal tumor (GIST) harboring activating mutations of ckit or pdgfra
Ligation-PCR
Rapid Decrease of mutant fcDNA: Predictive for response

cKIT exon 11 del K550-K558
GIST: Progression and response: \textit{Transient increase of mutant fcDNA in Plasma}

cKit exon 11 Del Y553-Q556

LINE DNA

Dr. John Doe

Imatinib

Day 716

Day 806

Day 901

TIME (Days)
Detection of Tumor fcDNA in GIST

**Results**

- 15/38 pts had positive mutant fcDNA
- pts. with active disease: 9/18 positive
- pts. in CR according to Miettinen risk of relapse
  - HR: 5/14 positive
  - MR: 1/3 positive
  - LR/NA: 0/3 positive
Conclusions

• fcDNA is detectable in plasma from GIST patients

• Improved sensitivity may allow early detection of progression and identification of specific secondary mutations allowing drug selection

• May have a role in further stratifying intermediate to low risk GIST patients for adjuvant imatinib therapy
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  - PI3K
  - KIT secondary mutations
    - Exon 13 (ATP binding site)
    - Exon 17 (A-loop)
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- PI3K: mTOR inhibitor
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  - Exon 13 (ATP binding site): Sunitinib 37.5 mg daily
  - Exon 17 (A-loop): Ponatinib?
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