What’s New For GIST Patients

Jon Trent, MD, PhD
Professor of Medicine
Director, Bone and Soft-tissue Sarcoma
Associate Director, Clinical Research
Sylvester Comprehensive Cancer Center
GIST Center of Excellence

Twitter: @JTrentMDPhD
Email: jtrent@med.miami.edu
The Emerging Role of Circulating Tumor DNA in Gastrointestinal Stromal Tumor

Steve Bialick, DO, MS
Hematology/Oncology Fellow, PGY6
Sylvester Comprehensive Cancer Center
• Most common **GI sarcoma**
  – 1-2% of all primary GI malignancies
  – 4500-6000 cases annually in US
• Treated with **tyrosine kinase inhibitors**
  – Prevalence > incidence
    ▪ Clinical course >10-15yr (from pre-TKI era <12 mo)
• Peak incidence 40-60 yo
  – GISTs unusual in pts <40yo
  – M = F predominance
• High frequency of **metastatic disease**, commonly abdominal

KIT
• 70-80% of GISTs
• Constitutive activation
• Most-common = exon 11, exon 9
• In-frame del*, insertions, substitutions, or combo

PDGFRα
• 5-10% of GISTs
• Constitutive activation
• Most-common = exon 12, exon 14, exon 18

KIT/PDGFR WILD TYPE
• 10-15% of GISTs
• RAF, RAS, SDH, NTRK

KIT and PDGFRA structure and mutations.

GIST DRIVER MUTATIONS

- **KIT exon 11**: imatinib 400 mg
- **KIT exon 9**: imatinib 800mg (or tolerated dose)
- **PDGFR D842V**: avapritinib
- **SDH deficiency**: sunitinib or regorafenib (TMZ trial)
- **RAF V600E**: RAF inhibitor
- **NF-1, RAS**: RAF or MEK inhibitor
- **PI3K**: mTOR inhibitor
- **IGF-1R expressing** – IGF-1R inhibitor trial
- **TRK fusion** – larotrectenib (NTRK inhibitor)
- **KIT resistance mutations**
  - Exon 13 (ATP binding site): sunitinib 37.5 mg daily
  - Exon 17 (A-loop): regorafenib or ripretinib
KIT SECONDARY MUTATIONS

• Optimal therapy for GIST patients requires mutation testing.

• Comprehensive, effective in identifying tumor mutations

• Performed commonly on pretreatment tumor biopsy and resection specimens

• Invasive, requires adequate tissue quantity

• Lengthy turnaround times

MOLECULAR DIAGNOSTIC TESTING

NGS/GIST: *KIT* EXON 11 VS EXON 9

• NAVIGATOR study with BLU-285
• Antitumor activity with avapritinib in patients with PDGFR D842V mutation

**NGS/GIST: PDGFRα EXON 18**

<table>
<thead>
<tr>
<th>Best Response</th>
<th>PDGFRA Exon 18 (n=43)</th>
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<tbody>
<tr>
<td>CR</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>34 (1 pending)</td>
</tr>
<tr>
<td>SD</td>
<td>5</td>
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<tr>
<td>PD</td>
<td>1</td>
</tr>
<tr>
<td>ORR (CR+PR), % (95% CI)</td>
<td>86.0 (72.1–94.7)</td>
</tr>
<tr>
<td>CBR, % (95% CI)</td>
<td>95.3 (84.2–99.4)</td>
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<td>DOR, months (95% CI)</td>
<td>NE (11.5–NE)</td>
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<tr>
<td>PFS, months (95% CI)</td>
<td>NE (13.4–NE)</td>
</tr>
</tbody>
</table>

**86% ORR
95% of patients with tumor reduction**

CBR = clinical benefit rate
CI = confidence interval
CR = complete response
PD = progressive disease
PR = partial response
SD = stable disease

Baseline
4.5x3.2cm
SUV 9.9

C4D21 of regorafenib
3.0x1.6cm
SUV <3

• Radiographic and metabolic response in pt with KIT exon 11 and KIT exon 17 resistance mutation by tissue NGS, treated with next-line regorafenib

NGS/GIST: KIT EXON 17 (D820Y) + REGORAFENIB

SEER review: only ~30% of pts diagnosed with GIST (2010-2015) underwent mutational analysis

GIST MUTATION TESTING IN USA

• Provides a **rapid, noninvasive** analysis of current mutations

• Clinical applications in multiple solid tumor cancers
  – emerging predictive value in patients with **metastatic GIST**

• May help define optimal choice of therapy based on **resistance mutations**
  – **KIT** resistance mutations in **GIST**
    o Exon 13
    o Exon 17

**INTRODUCTION TO LIQUID BIOPSY**

• ctDNA = free, tumor derived DNA in blood (1% of cfDNA)
• cfDNA = free, circulating DNA in blood (of tumor + nontumor origin)

UTILITY OF ctDNA IN GIST

<table>
<thead>
<tr>
<th></th>
<th>ctDNA Mutation+</th>
<th>Tumor FFPE Mutation+</th>
<th>Detection Rate</th>
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<tbody>
<tr>
<td>All Patients</td>
<td>22</td>
<td>36</td>
<td>61%</td>
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<tr>
<td>Primary Tumor</td>
<td>0</td>
<td>6</td>
<td>0%</td>
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<tr>
<td>Metastatic Low Volume</td>
<td>1</td>
<td>6</td>
<td>16%</td>
</tr>
<tr>
<td>Metastatic and Responding</td>
<td>0</td>
<td>3</td>
<td>0%</td>
</tr>
<tr>
<td>Metastatic, Large, and Progressive</td>
<td>21</td>
<td>21</td>
<td>100%</td>
</tr>
</tbody>
</table>

* Large = sum of 3 largest lesions ≥ 10 cm
12 months from ctDNA testing (n = 39):

**OS** = 79.5%; CI 0.66-0.92

**PFS** = 46.2%; CI 0.32-0.65
55yo Caucasian male with **stage IV gastric GIST** (*KIT* exon 11 W557-558del), **liver and intraabdominal metastases**

Progressive disease w/

1. Imatinib
2. Sunitinib
3. Regorafenib **→** Referred to hospice
4. Pazopanib
5. Nilotinib

Liquid biopsy via ctDNA

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<thead>
<tr>
<th>PRIMARIES</th>
<th>8</th>
<th>9</th>
<th>11</th>
<th>13</th>
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**Sensitive**  | **Resistant**  | **Intermediate**

Kit secondary mutations:

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<th>KIT SECONDARY MUTATIONS</th>
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Heinrich et al, ASCO 2013 Poster/Abstract 10509
Baseline; before ponatinib

After 6 months of ponatinib

After 12 months of ponatinib

DISEASE RESPONSE
ctDNA analyses in phase III VOYAGER trial: KIT mutational landscape and outcomes in pts with advanced GIST

Serrano et al. ASCO 2022.
Patients with **Kit exon 13 resistance mutations** are progression free longer when treated with *regorafenib* over *avapritinib*.
Patients without KIT exon 13 resistance mutation remain progression free on avapritinib compared to regorafenib
ctDNA AND *KIT* RESISTANCE MUTATIONS

*KIT* Resistance Mutations Identified by Circulating Tumor DNA and Treatment Outcomes in Advanced Gastrointestinal Stromal Tumor.

*Poster discussion session at ASCO 2022.*

Steve Bialick, DO, MS  
Hematology/Oncology Fellow, PGY6  
Sylvester Comprehensive Cancer Center
• *KIT*-mutant GIST patients benefit from first-line (1L) imatinib

• *KIT*-resistance mutations confer differential sensitivity to subsequent TKI
Patients with common driver mutation (n=83)
Patients with KIT mutation (n=64)
SPECIFIC KIT ALTERATIONS DETECTED
Patients with Kit exon 13 resistance mutations do twice as well on sunitinib then regorafenib
CONCLUSIONS

• ctDNA is a noninvasive tool for detecting driver and resistance mutations in pts with advanced GIST.

• GIST pts with ctDNA is an emerging technology which may impact therapeutic decision-making

• ctDNA-guided therapy warrants evaluation in a prospective clinical trial: Phase II Study of ctDNA-guided Sunitinib and Regorafenib Therapy for Gastrointestinal Stromal Tumor (GIST)
**Medical Oncology**
- Jon Trent
- Gina D'Amato
- Emily Jonczak
- Aditi Dhir (ped)

**Nurse Practitioner**
- Morgan Smith
- Solange Sierra
- Alisette Naveda

**Pathology**
- Andrew Rosenberg
- Elizabeth Montgomery
- Daniel Cassidy
- Jay-Lou Velez Torres

**Radiology**
- Ty Subhawong
- Francesco Alessandrino

**Orthopedic Oncology**
- Fran Hornicek
- Tom Temple
- Sheila Conway
- Frank Eismont
- Juan Pretell
- Mo Al Maaieh

**Surgical Oncology**
- Nipun Merchant
- Alan Livingstone
- Neha Goel
- Dido Franceschi

**Radiation Therapy**
- Raphael Yechieli
- Aaron Wolfson
- Laura Freedman

**Thoracic Surgery**
- Dao Nguyen
- Nestor Villamizar

**Head & Neck Surgery**
- Zoukaa Sargi
- Frank Civantos

**Interventional Radiology**
- Shree Venkat
- Felipe Desouza

**Gynecologic Oncology**
- Matt Schlumbrecht
- Matt Pearson
- Marilyn Huang

**Clinical Research**
- Josefina Sanchez
- Melissa Serana
- Mirna Gonzalez
- Karyms Luna

**Nursing**
- Arlen Pita
- Elizabeth Hagen
- Rosie Jara

**Lab Research**
- Zhefeng Duan, PhD
- Luyuan Li, PhD
- Karina Galoian
- Josie Eid, PhD

**Fellows/Residents**
- Priscila Barreto-Coelho

**Steve Bialick**
- Philippos Costa
- Andrea Espejo-Freire