GIST Research Update: What’s New and Promising?

Location of Gastric GIST Predicts Mutation Profile

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- Deciphera
- Foundation Medicine
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- Merck
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The evolution of GIST genomics

**KIT**
Gain-of-function mutations
Hirota et al., *Science.*

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Activating mutations in 35% of non-KIT mutant GIST
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**GEF**

**RAS**

**NF1**

**BRAF**

**GDP**

**GTP**
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- GIST in pts with NF-1

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7 families with SDH mutations
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**SDHC “Epimutation”**
- SDHC promoter hypermethylation
  - Killean et al., *Sci Trans Med*.
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  - Quadruple WT (KIT/PDGFRA/ RAS-P/SDH) have ETV6-NTRK3 fusion
  - Brenca et al., *J Pathol*
  - Shi et al., *JTM*.

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**FGFR1 fusions**
Quadruple WT (KIT/PDGFR/ RAS-P/SDH) have FGFR1-HOOK3 & FGFR1-TACC1 fusions
Shi et al., *JTM*. 2016
Mutation Profile Associated with Location

- **Small Intestine**
  - KIT Exon 11/9 Gene Fusions
  - Germline NF1

- **Stomach**
  - KIT exon 11
  - PDGFRA
  - Germline SDHx
  - Epimutant SDH

- **Colon**
  - KIT

- **Ligament of Treitz**
  - KIT
  - BRAF V600E
  - Germline NF
  - Somatic NF1

References:
Burgoyne et al. JCO Precision Oncology, 2017.
Tumor Location within Organs Correlates with Mutation Profile

**CIN - Chromosomal Instability**
- Intestinal histology
- TP53 mutation
- RTK-RAS activation

**GS - Genomically Stable**
- Diffuse histology
- CDH1, RHOA mutations
- CLDN1S-ARHGAP fusion
- Call adhesion

**MSI - Micro Satelite Instability**
- Hypermutation
- Gastric-CIMP
- MLH1 silencing
- Mitotic pathways

**EBV - Epstein Barr Virus**
- PIK3CA mutation
- PD-L1/2 overexpression
- EBV-CIMP
- CDKN2A silencing
- Immune cell signaling

Caris Life Sciences. *ASCO*. 2017
Hypothesis

GIST arising from distinct regions within the stomach may possess unique genomic profiles.
Location of Gastrointestinal Stromal Tumor (GIST) in the Stomach Predicts Tumor Mutation Profile and Drug Sensitivity

Ashwyn K. Sharma\textsuperscript{1,2}, Jorge de la Torre\textsuperscript{1,2}, Nikki S. IJzerman\textsuperscript{3,4}, Thomas L. Sutton\textsuperscript{5}, Beiqun Zhao\textsuperscript{1,2}, Tahsin M. Khan\textsuperscript{6}, Sudeep Banerjee\textsuperscript{1,2,7}, Christina Cui\textsuperscript{1}, Vi Nguyen\textsuperscript{1}, Maha Alkhuziem\textsuperscript{1,2}, Petur Snaebjornsson\textsuperscript{8}, Hester van Boven\textsuperscript{8}, Annemarie Bruining\textsuperscript{9}, Chih-Min Tang\textsuperscript{1,2}, Hyunho Yoon\textsuperscript{1,2}, Alexa De la Fuente\textsuperscript{1}, Shumei Kato\textsuperscript{2,10}, Hitendra Patel\textsuperscript{2,10}, Michael C. Heinrich\textsuperscript{11}, Christopher L. Corless\textsuperscript{12}, Santiago Horgan\textsuperscript{13}, Adam M. Burgoyne\textsuperscript{2,10}, Paul Fanta\textsuperscript{2,10}, Jill P. Mesirov\textsuperscript{2,14}, Andrew M. Blakely\textsuperscript{6}, Jeremy L. Davis\textsuperscript{6}, Skye C. Mayo\textsuperscript{5}, Winan J. van Houdt\textsuperscript{15}, Neeltje Steeghs\textsuperscript{3}, and Jason K. Sicklick\textsuperscript{1,2}
National Cancer Database (NCDB)

$N = 2418$ patients

GIST Databases

Study Cohort

Gastric Location

NGS

Demographics & Pathology

Location in Stomach

Driver Mutation(s)

NIH National Institutes of Health
TransAtlantic GIST Collaborative (TAGC)

$N = 251$ patients

GIST Databases

Study Cohort

Gastric Location

NGS

Demographics & Pathology

Location in Stomach

Driver Mutation(s)
## NCDB & TAGC Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Median [IQR]</td>
<td>64.5 [56–74]</td>
</tr>
<tr>
<td><strong>Tumor size</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 cm</td>
<td>222 (9.2)</td>
</tr>
<tr>
<td>2.1-5.0 cm</td>
<td>828 (34.3)</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>934 (38.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>420 (17.8)</td>
</tr>
<tr>
<td><strong>Location within stomach</strong></td>
<td></td>
</tr>
<tr>
<td>Cardia/fundus</td>
<td>785 (32.5)</td>
</tr>
<tr>
<td>Body/GC/LC</td>
<td>1,379 (57.0)</td>
</tr>
<tr>
<td>Antrum/pylorus</td>
<td>254 (10.5)</td>
</tr>
<tr>
<td><strong>Gene testing</strong></td>
<td></td>
</tr>
<tr>
<td>KIT only</td>
<td>2,162 (89.4)</td>
</tr>
<tr>
<td>PDGFRA only</td>
<td>22 (0.9)</td>
</tr>
<tr>
<td>Multigene^a</td>
<td>234 (9.7)</td>
</tr>
<tr>
<td><strong>Mutation status</strong></td>
<td></td>
</tr>
<tr>
<td>KIT</td>
<td>2,270 (93.9)</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>81 (3.3)</td>
</tr>
<tr>
<td>KIT/PDGFRA wild-type^b</td>
<td>67 (2.8)</td>
</tr>
<tr>
<td><strong>Baseline mitotic rate</strong></td>
<td></td>
</tr>
<tr>
<td>Low (≤5/5 mm(^2))</td>
<td>1,770 (73.4)</td>
</tr>
<tr>
<td>High (&gt;5/5 mm(^2))</td>
<td>440 (18.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>203 (8.4)</td>
</tr>
</tbody>
</table>

\(^{a}\) Indicates presence of both KIT and PDGFRA mutations.

\(^{b}\) Indicates presence of at least one additional mutation other than KIT and PDGFRA.
Non-\textit{KIT} Mutations are More Common in Distal Stomach
Mutation and Histology

Molecular-Morphologic types GIST

- **KIT mutated**: Spindle/mixed
- **PDGFR mutated**: Epithelioid
- **SDH deficient**: Epithelioid
- **RAS-P mutated**: Spindle
- **Unclassified**

- **c-KIT/DOG1 +ve**
- **DOG1 +ve**
- **SDHB -ve**
- **SDHB +ve**
Location Matters

**Fundus**
- (n=49, 21%)

**Cardia**
- (n=22, 9%)

**Lesser Curvature**
- (n=65, 28%)

**Greater Curvature**
- (n=57, 24%)

**Antrum**
- (n=40, 17%)

**Fundus**
- (n=49)

**Cardia**
- (n=20)

**Lesser Curvature**
- (n=64)

**Greater Curvature**
- (n=57)

**Antrum**
- (n=40)
Morphology & Location More Important than Age

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariable regression</th>
<th>95% CI</th>
<th>p-value</th>
<th>Multivariable regression</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>≤65 years</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>1.500</td>
<td>0.822 - 2.737</td>
<td>0.186*</td>
<td>2.343</td>
<td>1.065 - 5.157</td>
<td>0.034**</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>≤7 cm</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&gt;7 cm</td>
<td>1.029</td>
<td>0.581 - 1.821</td>
<td>0.923</td>
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<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Male</td>
<td>Reference</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.048</td>
<td>0.594 - 1.851</td>
<td>0.871</td>
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</tr>
<tr>
<td>Location</td>
<td></td>
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</tr>
<tr>
<td>Proximal</td>
<td>14.000</td>
<td>4.244 - 46.397</td>
<td>&lt;0.001*</td>
<td>17.735</td>
<td>3.905 - 80.550</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Distal</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Growth pattern</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Endophytic</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exophytic</td>
<td>0.756</td>
<td>0.419 - 1.367</td>
<td>0.355</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mitotic rate</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;5/5 mm²)</td>
<td>1.320</td>
<td>0.657 - 2.649</td>
<td>0.435</td>
<td></td>
<td></td>
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<tr>
<td>Cell morphology</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Spindle</td>
<td>Reference</td>
<td></td>
<td>&lt;0.001*</td>
<td></td>
<td>&lt;0.001**</td>
<td></td>
</tr>
<tr>
<td>Epithelioid</td>
<td>0.029</td>
<td>0.009 - 0.092</td>
<td>0.038</td>
<td>0.011</td>
<td>0.134</td>
<td>0.111</td>
</tr>
<tr>
<td>Mixed</td>
<td>0.106</td>
<td>0.049 - 0.229</td>
<td>0.111</td>
<td>0.047</td>
<td>0.261</td>
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83% accurate when including all tumors
Gastric GISTs are not homogenous and possess somatic mutations that correlate with tumor location.

Summary

- Gastric GISTs are not homogenous and possess somatic mutations that correlate with tumor location.

Clinical Implications

- In resource limited settings where mutation profiling is not widely available, or when time is of the essence to start treatment before profiling, knowing the tumor location & cell morphology may be predictive of K/IT vs non-K/IT mutations and in turn, potential TKI sensitivity or resistance.
THANK YOU!

Jason Sicklick, MD

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