New Advances in Research and Clinical Insights in Gastrointestinal Stromal Tumor (GIST)

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Gastrointestinal Stromal Tumor (GIST)

Management
• Surgery mainstay treatment
• Recurrence or metastatic disease - fatal
• Refractory to chemotherapy and radiation

• ~5,000 cases diagnosed per year in the US.

• One of the most common subtypes of soft tissue sarcomas, the most common mesenchymal neoplasm in the GI tract.

• Can arise anywhere from the entire GI tract; stomach is the most common primary site (2/3), then small bowel (1/4), esophagus/colon/rectum (the rest).

• Peak incidence 50-65 year old.

• Familial syndromes
Pre-KIT ERA: GIST - A clinicopathological challenge

GIST has broad morphological spectrum

- Difficult to diagnose!
- Difficult to treat!

Clinicopathologically distinct entity!

Miettinen, M. and Lasota, Arch Pathol Lab Med 2006
GIST originates from ICC and highly expresses KIT

- Originates from the Interstitial Cells of Cajal (ICCs) of the GI tract
- Characterized by KIT positive IHC and activating mutations in KIT or PDGFRA...

A Paradigm: Normal ICC development vs. GIST

Normal ICC development

External stimuli

$\text{KIT/ PDGFRA}$

Signaling

$\text{STAT}$

$\text{PI3K}$

$\text{MAPK}$

$\text{TFs}$

Chromatin

ON/OFF

GIST

$\text{KIT/ PDGFRA mutation}$

Aberrant signaling

$\text{STAT}$

$\text{PI3K}$

$\text{MAPK}$

ON
## Molecular characterization of GIST

<table>
<thead>
<tr>
<th>Genetic type</th>
<th>Relative frequency</th>
<th>Anatomic distribution</th>
<th>Germline examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KIT mutation (relative frequency 75–80%)</strong></td>
<td>Rare</td>
<td>Small bowel</td>
<td>One kindred</td>
</tr>
<tr>
<td>Exon 9 insertion AY502-503</td>
<td>10%</td>
<td>Small bowel and colon</td>
<td>None</td>
</tr>
<tr>
<td>Exon 11 (deletions, single nucleotide substitutions and insertions)</td>
<td>67%</td>
<td>All sites</td>
<td>Several kindreds</td>
</tr>
<tr>
<td>Exon 13 K642E</td>
<td>1%</td>
<td>All sites</td>
<td>Two kindreds</td>
</tr>
<tr>
<td>Exon 17 D820Y,N822K and Y823D</td>
<td>1%</td>
<td>All sites</td>
<td>Five kindreds</td>
</tr>
<tr>
<td><strong>PDGFRA mutation (relative frequency 5–8%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 12 (such as V561D)</td>
<td>&lt;1%</td>
<td>Stomach</td>
<td>None</td>
</tr>
<tr>
<td>Exon 14 N659K</td>
<td></td>
<td>Stomach, mesentery and omentum</td>
<td>None</td>
</tr>
<tr>
<td>Exon 18 D842V</td>
<td>5%</td>
<td>Stomach, mesentery and omentum</td>
<td>None</td>
</tr>
<tr>
<td>Exon 18 (such as deletion of amino acids IMHD 842–846)</td>
<td>1%</td>
<td>All sites</td>
<td>One kindred</td>
</tr>
<tr>
<td><strong>KIT and PDGFRA wild-type (relative frequency 12–15%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>~7–15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDHA, SDHB, SDHC and SDHD mutations</td>
<td>~2%</td>
<td>Stomach and small bowel</td>
<td>Carney–Stratakis</td>
</tr>
<tr>
<td>HRAS and NRAS mutation</td>
<td>&lt;1%</td>
<td>Stomach</td>
<td>Not heritable</td>
</tr>
<tr>
<td>Sporadic paediatric GISTs</td>
<td>~1%</td>
<td>Stomach</td>
<td>Not heritable</td>
</tr>
<tr>
<td>GISTs as part of the Carney triad</td>
<td>~1%</td>
<td>Stomach</td>
<td>Not heritable</td>
</tr>
<tr>
<td>NF1-related</td>
<td>Rare</td>
<td>Small bowel</td>
<td>Numerous</td>
</tr>
</tbody>
</table>

GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type I; PDGFRA, platelet-derived growth factor receptor-α; SDH, succinate dehydrogenase.

Corless et al, Nat Rev Cancer, 2011
Imatinib (Gleevec) in GIST

- Activity – Abl kinase, KIT, PDGFRA
Imatinib-FDA approved as 1st line therapy for GIST 2002!
Challenges - Imatinib resistance in GIST

14% - Primary resistance; 50% - Develop imatinib resistance

Resistance Mechanisms:
1. Secondary mutations (50-65%)
2. Genomic Amplification of RTKs
3. Activation alternative signaling pathways
4. Kit-low, imatinib-resistant GIST stem/progenitors
5. Others…

Corless et al, NRC, 2011
How to overcome imatinib resistance?

1) More effective first line therapy than imatinib
   • Reduce the persistence of disease
   • Reduce the adaptive responses to imatinib

2) Next generation of targeted therapy for imatinib resistant mutations, KIT exon 14 and exon 17 secondary mutations, PDGFRA D842V mutation
A Clinical Conundrum

What is special about the ICC lineage and GIST?

KIT
(regulates multiple cell lineages)

- ICC
- Melanocyte
- Germ cell
- Mast cell

Familial GIST

GIST

activating KIT mutants

What is special about the ICC lineage and GIST?
ETV1- A Lineage specific survival factor in GIST and ICC

ETV1: an “ETS family transcription factor”

Transcription of genes

ETV1 Normalized Expression (Z-Score)

ExpO (Expression Project for Oncology)

p=5.4x10^{-7}

Bladder  Breast  Cervical  Colorectal  Endometrial  Gastric  Head and Neck  Liver  Lung  Lymphoma  Melanoma  Ovarian  Pancreatic  Prostate  Renal  Sarcoma  Thyroid

GIST

Chi, P, Chen, Y et al, Nature 2010
Ran L et al., Cancer Discovery, 2015

Decreased ICC survival  Normal ICC development  ICC hyperplasia and GIST

Kit wt  Kit wt  Kit mutant

MEK  MEK  MEK

ERK  ERK  ERK

ETV1

ETV1

ETV1

+
ETV1 is required for GIST growth and survival

GIST882 cell (imatinib sensitive)

GIST48 cell (imatinib resistant)

Chi, P, Chen, Y et al, Nature 2010
Ran L et al., Cancer Discovery, 2015
ETV1 and KIT forms a positive feedback circuit in GIST

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**Excised 3T3 allograft tumors**

- Vector
- KITwt
- KITΔ560
- ETV1
- ETV1+KITwt
- ETV1+KITΔ560

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**ETV1 cooperates with KIT/MAPK signaling in GIST**
- KIT/MAPK activation stabilizes ETV1 protein
- ETV1 directly upregulates KIT expression
- Positive feedback (ETV1 and mutant KIT)
- Target the adaptive responses in response to TKIs
- Targeting ETV1 protein stability – novel therapeutic approach

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Chi, P, Chen, Y et al, Nature 2010
Ran L et al., Cancer Discovery, 2015
Unpublished result
Synergy of combined MAPK and KIT pathway inhibition

GIST882 cells

<table>
<thead>
<tr>
<th>MEK162 (1µM)</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>8</th>
<th>24</th>
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</thead>
<tbody>
<tr>
<td>Time (hr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>pKIT</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>KIT</td>
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<td></td>
</tr>
<tr>
<td>pERK</td>
<td></td>
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<tr>
<td>ERK</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ETV1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTIN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GIST882 xenografts

- Vehicle
- MEK162
- Imatinib
- Imatinib + MEK162 (dose 1)
- Imatinib + MEK162 (dose 2)
- Imatinib + MEK162 (dose 3)

% original tumor size

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>35</td>
<td>40</td>
<td>45</td>
<td>50</td>
</tr>
</tbody>
</table>

P < 0.0001

Synergy of combined MAPK and KIT pathway inhibition

Chi, P, Chen, Y et al, Nature 2010
Ran L et al., Cancer Discovery, 2015
Molecular biomarker driven novel therapies in GIST

More effective first line therapy than imatinib

-A phase Ib/II study of MEK162 (binimetinib) in combination with imatinib in patients with advanced gastrointestinal stromal tumor (GIST) (Clinicaltrials.gov#: NCT01991379)
- Phase Ib-completed and defined safety and tolerability and modest efficacy in imatinib-resistant GIST, presented in the 2015 ASCO sarcoma oral abstracts.
- Phase II in imatinib-naïve patient population is actively accruing.
Phase Ib/II study of MEK162 in combination with imatinib in patients with untreated locally advanced and metastatic GIST

**Primary Objective:**

*Phase Ib:* safety and tolerability of combining MEK162 (a MEK inhibitor) and imatinib, MTD and the recommended Phase II dose (RP2D) in GIST patients.

*Phase II:* ORR (CR + PR) by both RECIST 1.1

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### Pretreatment Evaluation

- **Pretreatment biopsy**
- **Pretreatment baseline evaluation (FDG PET, CT/MRI, blood, Echo/MUGA)**
- **Blood for imatinib trough x2**
- **Blood for imatinib trough x2 (wk3 and wk5)**
- **FDG PET at wk4**
- **Post-treatment biopsy wk 1**
- **Post-treatment biopsy document recurrence**

### Treatment Protocols

1. **Advanced GIST (progressed on imatinib)** → **RP2D** → **Untreated advanced GIST** → **Imatinib alone lead in (2-week)** → **Imatinib/ MEK162 1 cycle=4wks** → **Disease progression**

2. **Phase Ib**

3. **Phase II**

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**Completed**

**Ongoing**
## Patient Characteristics (Phase Ib)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>Median: 60; Range: 30-74</td>
</tr>
<tr>
<td>Sex</td>
<td>Female: 8; Male: 10</td>
</tr>
<tr>
<td>ECOG status</td>
<td>0-1</td>
</tr>
<tr>
<td>Number of prior therapy</td>
<td>Median: 3; Range: 1-6; 15/18 pts ≥ 3 prior therapies</td>
</tr>
<tr>
<td>Prior therapies:</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>18</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>16</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>9</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>7</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>4</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>1</td>
</tr>
<tr>
<td>Dasatinib/Ipilimumab trial</td>
<td>2</td>
</tr>
<tr>
<td>Linsitinib trial</td>
<td>1</td>
</tr>
<tr>
<td>Molecular characteristics:</td>
<td></td>
</tr>
<tr>
<td>KIT(13, 10/13 with known imatinib-resistant KIT mutations); NF1 loss (1); BRAFV600E/NF1 loss (1); SDH-deficient (1), Unknown (2)</td>
<td></td>
</tr>
</tbody>
</table>
**Efficacy signal from phase Ib trial of MEK162+Imatinib in GIST**

### Patients who have imatinib-resistant *KIT* mutations all progressed within 16 weeks.

<table>
<thead>
<tr>
<th>Dose Escalation Cohort</th>
<th>Pt #</th>
<th>Prior Therapies</th>
<th>Mutational Status</th>
<th>Duration (wks)</th>
<th>Best RR (RECIST)</th>
<th>Best RR (CHOI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib 400mg QD + MEK162 45mg BID</td>
<td>4</td>
<td>Imatinib, Sunitinib, Linsitinib trial</td>
<td>SDHA R31X;SDHB loss by IHC (active)</td>
<td>&gt;135</td>
<td>SD (-20%)</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Imatinib, Sunitinib, Sorafenib</td>
<td>KIT exon11, L576P</td>
<td>55</td>
<td>SD (-16%)</td>
<td>PR</td>
</tr>
</tbody>
</table>

**Graph a:**
- **Choi responses 7/17 (41%)**

**Graph b:**
- Median PFS: 8 weeks
- 95% CI: 7 to 56 weeks

**Graph c:**
- Median PFS: 8 weeks
- 95% CI: 7 to 56 weeks

**Table:**
- Efficacy signal from phase Ib trial of MEK162+Imatinib in GIST
- Patients who have imatinib-resistant *KIT* mutations all progressed within 16 weeks.
ETV1 is highly expressed in KIT/PDGFRα wild-type GIST

Ostrowski J et al., BMC Cancer 2009
CT scans of the liver lesions (liver window)

**Timeline of Rx**

- **POD on Debulking Sunitinib, & Imatinib (11/20/2012)**
- **Started trial (1/28/2014)**
- **Biopsy (11/5/2015)**

<table>
<thead>
<tr>
<th>Months:</th>
<th>22</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linsitinib</td>
<td>imatinib+ binimetinib (MEK162)</td>
<td></td>
</tr>
</tbody>
</table>

**Target lesion #1**

Before treatment

~12 months (RECIST: -20%)

~24 months (RECIST: -4%)
Exceptional response in a patient with SDH-deficient GIST

Timeline of Rx

**POD on Debulking**
- Sunitinib, Surgery & Imatinib (11/20/2012)
- Started trial (1/28/2014)

**Biopsy (11/5/2015)**
- Linsitinib
- imatinib+ binimetinib (MEK162)

**Impact:***
- SDHA exon 2 p.R31X
- KDR exon 30 p.V1334E

**Genetic Alteration***
- Shallow Deletion
- Truncating Mutation
- Inframe Mutation
- Missense Mutation

**WES of FFPE***
- Archer negative for fusion

**Cristina R. Antonescu**
How to overcome imatinib resistance?

1) More effective first line therapy than imatinib
   • Reduce the persistence of disease
   • Reduce the adaptive responses to imatinib

2) Next generation of targeted therapy for imatinib resistant mutations, KIT exon 14 and exon 17 secondary mutations, PDGFRA D842V mutation
Molecular biomarker driven novel therapies in GIST

Polyclonal Resistance – much like CML
Single TKI may only effect one mutation

Next generation of targeted therapy for imatinib resistant mutations
- KIT exon 17 secondary resistant mutations
  PLX9486 (open); BLU-285 (phase I open)
- KIT exon 13/14 mutations
  PLX3397 +/- PLX9486 (open soon)
- PDGFRA D842V mutation
  BLU-285 (phase I open)
- PLX3397 + Pembrolizumab (open soon)
- DCC2618, an allosteric inhibitor of KIT/PDGFRA
  (phase I open)....
**Impact of tissue and liquid biopsies of all GIST**

**Primary KIT mutations (75-80%)**:
1) Exon 8 (D419 del, rare)
2) Exon 11 (deletions, SNV and insertions, 60-70%)
3) Exon 9 (AY 502-502 insertion, ~10%)
4) Exon 13 (K642E, 1%)

**Secondary KIT mutations**:
1) Exon 13 (V654A)
2) Exon 14 (T670I)

**PDGFRA mutations (5-8%)**:
1) Exon 12 (V561D, 1%)

**KIT /PDGFRA wild-type (12-15%)**:  
1) SDH-deficient GIST  
2) NF1-, BRAFV600 or RAS associated  
3) Others

**Primary KIT mutations (75-80%)**:
1) Exon 17 (D820Y, N822K, Y823D).

**Secondary KIT mutations**:
1) Exon 17 (D816A/G/H/V; D820A/E/G/Y; N822H/K; Y823D)
2) Exon 18 (A829P)

**PDGFRA mutations**:
1) Exon 18 (D842V)
2) Exon 14 (N659K)

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**Clinical Trials**

1) PLX3397+Binimetinib
2) PLX3397+Pembrolizumab
3) PLX3397+PLX9486
4) DCC-2618

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**All comers, Imatinib-resistant GIST**
Tumor-derived cfDNA to detect tumor heterogeneity and subclonal dynamics

6/10 patients with detectable tumor-derived cfDNA consistent with IMPACT

Patient #20

- **Clinical Correlate**
  - 4/13/2010: Debulking surgery
  - 6/7/2016: Progressed on Imatinib, sunitinib, regorafenib and pazopanib

Patient #3

- **Clinical Correlate**
  - 3/11/2015: Debulking surgery
  - 4/26/2016: Starting trial
  - 6/24/2016: POD on trial

**Allelic Frequency (Log)**

<table>
<thead>
<tr>
<th>Tumor Tissue</th>
<th>Plasma cfDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KIT V560D</strong></td>
<td>Orange</td>
</tr>
<tr>
<td><strong>KIT V654A</strong></td>
<td>Blue</td>
</tr>
<tr>
<td><strong>MGA P1956Hfs*22</strong></td>
<td>Red</td>
</tr>
<tr>
<td><strong>KIT N822K</strong></td>
<td>Green</td>
</tr>
</tbody>
</table>

**Allelic Frequency (Log)**

<table>
<thead>
<tr>
<th>Tumor Tissue</th>
<th>Plasma cfDNA1</th>
<th>Plasma cfDNA2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAX R35L</strong></td>
<td>Red</td>
<td></td>
</tr>
<tr>
<td><strong>KIT K550_W557delinsIL</strong></td>
<td>Green</td>
<td></td>
</tr>
<tr>
<td><strong>KIT D820A</strong></td>
<td>Orange</td>
<td>Blue</td>
</tr>
<tr>
<td><strong>KIT D820Y</strong></td>
<td>Blue</td>
<td>Blue</td>
</tr>
</tbody>
</table>
Thanks…

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