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Gastrointestinal Stromal Tumor (GIST)

Management:
- Surgery mainstay treatment
- Recurrence or metastatic disease - fatal
- Refractory to chemotherapy and radiation
- Imatinib is the first line therapy for past 15 years…

- ~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

- Spindle
  - Sclerosing
  - Hypercellular
  - Sarcomatous

- Epithelioid
  - Sclerosing
  - Hypercellular
  - Sarcomatous

- Palisaded-vacuolated
- dyscohesive pattern

• 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


Interstitial Cell of Cajal (ICC)- Pacemaker cells of the GI tract

GIST of stomach

H&E

α-KIT
A Paradigm: Normal ICC development vs. GIST

Normal ICC development

- **External stimuli**
- **KIT/PDGFRA**
- **PI3K**
- **MAPK**
- **STAT**
- **TFs**
- **Chromatin**

ON/OFF

GIST

- **KIT/PDGFRA mutation**
- **Aberrant signaling**
- **PI3K**
- **MAPK**
- **STAT**
- **TFs**

ON
Table 1 | Molecular classification of GISTs

<table>
<thead>
<tr>
<th>Genetic type</th>
<th>Relative frequency</th>
<th>Anatomic distribution</th>
<th>Germline examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT mutation (relative frequency 75–80%)</td>
<td></td>
<td>Small bowel</td>
<td>One kindred</td>
</tr>
<tr>
<td>Exon 8</td>
<td>Rare</td>
<td>Small bowel and colon</td>
<td>None</td>
</tr>
<tr>
<td>Exon 9 insertion AY502-503</td>
<td>10%</td>
<td>All sites</td>
<td>Several kindreds</td>
</tr>
<tr>
<td>Exon 11 (deletions, single nucleotide substitutions and insertions)</td>
<td>67%</td>
<td>All sites</td>
<td></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>PDGFRA mutation (relative frequency 5–8%)</td>
<td></td>
<td>All sites</td>
<td></td>
</tr>
<tr>
<td>Exon 12 (such as V561D)</td>
<td>1%</td>
<td>Stomach</td>
<td>Two kindreds</td>
</tr>
<tr>
<td>Exon 14 N659K</td>
<td>&lt;1%</td>
<td>Stomach</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>KIT and PDGFRA wild-type (relative frequency 12–15%)</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.
Imatinib-FDA approved as 1st line therapy for GIST 2002!
Challenges-Imatinib resistance in GIST

14% - Primary resistance; 50% - Develop imatinib resistance after 2 years

Resistome 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
Clinical Challenges in GIST: imatinib/TKI resistance?

- Heterogeneity of resistant tumor clones
- \textit{KIT/PDGFRA} wild-type GIST-primary resistance
- Adaptive responses to tyrosine kinase inhibitors
Tumor heterogeneity in imatinib resistance

Polyclonal Resistance

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

- KIT V560D
- KIT V654A
- MGA P1956Hfs*22
- KIT N822K

Allelic Frequency (Log)

Clinical Correlate

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

Developing custom gene panel with ultra-deep sequencing and bioinformatics

Kelly /Chi & Reichel/Berger Innovation Lab
Heterogeneous resistance mechanisms

Polyclonal Resistance

Resistance Mechanisms:
1. Various secondary mutations (50-65%)
2. Genomic Amplification of RTKs
3. Activation alternative signaling pathways
4. Kit-low, imatinib-resistant GIST stem/progenitors
5. Tumor heterogeneity
6. Tumor adaptation
7. Others…
Precision therapy in imatinib-resistant setting

**Primary KIT mutations:**
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:**
1) SDH-deficient GIST
2) NF1-, BrafV600E or RAS associated
3) Others

**Primary KIT mutations:**
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)

**All comers, Imatinib-resistant GIST**

**Clinical Trials**
Next-Gen KIT/PDGFRa i

1) PLX9486+ PLX3397
2) DCC-2618

1) Imatinib+Binimetinib
2) PLX3397+Binimetinib

1) PLX9486
2) BLU-285
3) DCC-2618

1) BLU-285
2) DCC-2618

Registration trials of BLU-285 and DCC-2618 in imatinib-resistant GISTs 2nd, 3rd and 4th line settings! We see RESISTANCE!
Clinical Challenges: imatinib/TKI resistance?

- Heterogeneity of resistant tumor clones
- KIT/PDGFRA wild-type GIST-primary resistance
- Adaptive responses to tyrosine kinase inhibitors
Human Genetics

KIT
(regulates multiple cell lineages)

- ICC
- Melanocyte
- Germ cell
- Mast cell

Familial GIST

activating KIT mutants

ICC lineage and GIST have special cellular contexts
ETV1- A Lineage specific survival factor in GIST and ICC

ETV1: an “ETS family transcription factor”

Transcription of genes

ExpO (Expression Project for Oncology)

p=5.4x10^-7

ETV1 Normalized Expression (Z-Score)

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

ETV1- A Lineage specific survival factor in GIST and ICC

Chi, P, Chen, Y et al, Nature 2010
Ran L et al., Cancer Discovery, 2015
Tumor adaptation, evolution, and resistance to targeted therapy

LETTER

Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Anirudh Ramakrishnan, Roderick Campbell, and Victor E. Bond

CANCER DISCOVERY

Relief of Feedback Inhibition of HER3 Transcription by RAF and MEK Inhibitors Attenuates Their Antitumor Effects in BRAF-Mutant Thyroid Carcinomas

Cristina Clogston, Asa J. Alterman, and U. Dheeraj Reddy

Relief of Profound Feedback Inhibition of Mitogenic Signaling by RAF Inhibitors Attenuates Their Activity in BRAFV600E Melanomas


1Molecular Pharmacology and Chemistry Program

2Department of Medicine

3Department of Biostatistics

4Department of Oncology

5Department of Genetics
Tumor adaptation and resistance to targeted therapy

Adapted from Lito P, Rosen N & Solit DB, Nat Med 2013; Xie, Y, et al., J Clin Investigation, 2018

ETV1/4/5 (Pea3 ETS)

KIT/PDGFRA or other RTK

Mutant / Wt KIT/PDGFRA

Negative feedback regulators

COP1

MAPK

GIST

Chi, P, Chen, Y et al, Nature 2010;
Ran L et al., Cancer Discovery, 2015, 2018;
Xie, Y, et al., J Clin Investigation, 2018
Synergy of combined MAPK and KIT pathway inhibition

GIST882 cells

MEK162 (1µM)

Time (hr)  0  0.5  1  2  8  24

pKIT
KIT
pERK
ERK
ETV1
ACTIN

Imatinib (nM)  0  62.5  125  1000

MEK162(µM)  0  0.5  1.0  0.5  1.0  0.5  1.0

pKIT
KIT
pERK
ERK
ETV1
ACTIN

GIST882 xenografts

% original tumor size

Days

% viability (% control)

Imatinib (nM)  62.5  125  250  500  1000

MEK162(µM)  0  0.5  1.0  0.5  1.0  0.5  1.0

Viability (% control)

Imatinib+
MEK162

Chi, P, Chen, Y et al, Nature 2010
Ran L et al., Cancer Discovery, 2015
Combination strategy to target ETV1 and KIT

Advantage of targeting the lineage dependence:

- ETV1 is required for GIST growth, survival and tumorigenesis in vitro and in vivo.
- ETV1 is required for growth and survival of GIST precursor ICCs—target the KIT-low stem/progenitor cells
- Bypasses multiple upstream resistance mechanisms
- Break the positive feedback circuit of ETV1/KIT-target KIT expression regardless of mutations
- Block early adaptation and forestall resistance development
Molecular biomarker driven novel therapies in GIST

Proof of Principle Trial:

- KIT/PDGFRA wild-type GIST-primary resistance
- Adaptive responses to tyrosine kinase inhibitors

-A phase Ib/II study of MEK162 (binimetinib) in combination with imatinib in patients with advanced gastrointestinal stromal tumor (GIST) (Clinicaltrials.gov#: NCT01991379)

-A phase Ib/II study of MEK162 (binimetinib) in combination with PLX3397 (pexidartinib) in patients with advanced gastrointestinal stromal tumor (GIST) (Clinicaltrials.gov#: NCT03158103)
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

**2015 ASCO sarcoma oral abstract:**
- Combination is safe with manageable toxicity
- Modest Efficacy in KIT/PDGFRA-mutant multiply refractory GIST

**Updates and manuscript in preparation:**
- One exceptional responder in SDH-deficient GIST (case-presentation), remains on trial (>5 years)
- Expanded to enroll additional 4 SDH-deficient GISTs, two patients remain on trial for >18 months; one patient came off study after 8 months on trial due to CVO (recovered); one patient came off study after ~14 months on trial with POD.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>Median: 60; Range: 30-74</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Female: 8; Male: 10</td>
</tr>
<tr>
<td><strong>ECOG status</strong></td>
<td>0-1</td>
</tr>
<tr>
<td><strong>Number of prior therapy</strong></td>
<td>Median: 3; Range: 1-6; 15/18 pts ≥ 3 prior therapies</td>
</tr>
<tr>
<td><strong>Prior therapies:</strong></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>Linsitinitib trial</td>
<td>1</td>
</tr>
<tr>
<td><strong>Molecular characteristics:</strong></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.**

![Chart showing Choi responses and progression free survival](chart.png)

<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><strong>Imatinib 400mg QD + MEK162 45mg BID</strong></td>
<td>4</td>
<td>Imatinib, Sunitinib, Linsitinib trial</td>
<td>SDHA R31X; SDHB loss by IHC</td>
<td>&gt;270 (active)</td>
<td>SD (-20%)</td>
<td>PR</td>
</tr>
<tr>
<td>8</td>
<td>Imatinib, Sunitinib, Sorafenib</td>
<td>KIT exon11, L576P</td>
<td>56</td>
<td>SD (-16%)</td>
<td>PR</td>
<td></td>
</tr>
</tbody>
</table>

Expanded to enroll additional 4 SDH-deficient GISTs. (Imatinib 400mg QD+MEK162 30mg BID)
- Two patients remain on trial for >18 months
- One patient came off study after 8 months on trial due to CVO (recovered);
- One patient came off study after ~14 months on trial with POD.
Phase Ib/II study of MEK162 in combination with imatinib in patients with untreated locally advanced and metastatic GIST

Primary Objective:

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**Advanced GIST (progressed on imatinib)** → **RP2D**

**Phase Ib**

- Untreated advanced GIST → Imatinib alone lead in (2-week)
  - Pretreatment baseline evaluation (FDG PET, CT/MRI, blood, Echo/MUGA)
  - Pretreatment biopsy
- Blood for imatinib trough x2

**Phase II**

- Imatinib/ MEK162 1 cycle=4wks
- FDG PET at wk4
- Blood for imatinib trough x2 (wk3 and wk5)
- Post-treatment biopsy wk 1
- Post-treatment biopsy document recurrence

**Disease progression**

**Completed**

**Ongoing**

Accuring well, readout in about 6 months
Phase II Imatinib & binimetinib treatment response

5/9/2017 1/23/2018
A phase Ib/II study of MEK162 (binimetinib) in combination with PLX3397 (pexidartinib) in patients with advanced gastrointestinal stromal tumor (GIST)

59 year-old woman with NF1 and metastatic GIST, progressed on imatinib
(NF1 exon 42 (pX2143_splice); TSC1 exon 15 (pV531M); SPEN intragenic deletion)

8.4cm
7/19/2017

6.0cm
4/30/2019
Future Directions

Precision Personalized Medicine:

- Improving front-line therapy
- Developing treatment for KIT/PDGFRA-wild type GIST (SDH-deficient, NF1-deficient, BRAFV600E-mutant, FGFR-mutant, NTRK fusion…)
- Multiple refractory disease (e.g. Alternative targets, tumor microenvironment, newer generation of TKIs, combination strategy)
- Developing “liquid biopsies” and identify appropriate clinical application in GIST- e.g., tumor heterogeneity, treatment response, MRD, radiographic imaging studies.
- …..
Patients and Family!

MSKCC
Ping Chi (HOPP)
Leili Ran (former)
Yuedan Chen (former)
Yuanyuan Xie
Jessica Sher (former)
Devan Murphy (Former)
Elissa Wong
Amish Patel
Sarah Warda
Cindy Lee
Juan Yan
Miguel Miranda-Roman

Yu Chen (HOPP)
Zhen Cao (former)
Dong Gao (former)
Amanda Moore (former)
Youxin Guo (former)
Shipra Shukla
Tyler Hitchman
Gabriella Baystock
Dan Li
Aaron Wang

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