The GIST model: Medical therapy
The clinical challenge of secondary resistance

Peter Reichardt
The challenge of secondary resistance

• Secondary resistance due to
  - Secondary resistance mutations
  - Insufficient drug levels
  - Target overexpression
  - Loss of target
  - Alternate pathway activation
  - Etc.
CT scan: focal progression
Secondary resistance in GIST

- Secondary mutations in target gene
  - Mutation of gatekeeper residue (ATP binding site)
  - Mutation in the p-loop and activation loop leading to stabilization of the activation loop in the active conformation
Secondary KIT mutations in imatinib-resistant GIST

Heinrich et al., J Clin Oncol 24:4764-4774, 2006
Drug Activity in Resistant GIST Cells

Predicted sensitivity profile of regorafenib compared with imatinib and sunitinib

**PRIMARY MUTATIONS**

- **Exon 9:** 12%
- **Exon 11:** 70%
- **Exon 13:** 1%
- **Exon 17:** 1%

**SECONDARY MUTATIONS**

- **Exon 13:** V654A
- **Exon 14:** T670I
- **Exon 17:** D816E
- **Exon 18:** D820A/Y, N822K

**CELL membraen**

**ATP-binding pocket**

**Activatio n loop**

**DRUG SENSITIVITY**

- **Imatinib**
- **Sunitinib**
- **Regorafenib**

- Resistant
- Sensitive

Regorafenib has activity in GIST cells with KIT primary exon 11 mutations and secondary KIT exon 17 imatinib-resistant mutations, but is less active against KIT exon 13 (V654A) mutations compared to sunitinib.

Wide Distribution of Imatinib Exposure without Reliable Correlation with Dose

GIST patients with lowest imatinib blood levels had higher risk for rapid disease progression

Fig 3. Time to progression by imatinib day 29 trough level ($C_{\text{min}}$) quartile (Q).

The challenge of secondary resistance

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• Secondary resistance over time
EORTC 62005: PFS

Overall Logrank test: $p=0.202$

Casali PG et al., CTOS 2013
The challenge of secondary resistance

- Secondary resistance due to
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- Secondary resistance over time

- Secondary resistance and tumor bulk
Overall Survival by Tumor Bulk Quartile – B2222

Log-Rank test $P = 0.0160$

$P=0.0063$ for Q1 vs Q2-Q4

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Number at Risk</th>
<th>Median Time (months)</th>
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<tbody>
<tr>
<td>Quartile 1</td>
<td>36 34 32 29 25 21</td>
<td>N/A</td>
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<tr>
<td>Quartile 2</td>
<td>37 30 27 22 19 12</td>
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<td>Quartile 3</td>
<td>36 33 29 21 15 13</td>
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<tr>
<td>Quartile 4</td>
<td>37 31 23 15 13 8</td>
<td>35</td>
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Adjuvant Imatinib for High-Risk GI Stromal Tumor: Analysis of a Randomized Trial

Heikki Joensuu, Mikael Eriksson, Kirsten Sundby Hall, Annette Reichardt, Jörg T. Hartmann, Daniel Pink, Giuliano Ramadori, Peter Hohenberger, Salah-Eddin Al-Batran, Marcus Schlemmer, Sebastian Bauer, Eva Wardelmann, Bengt Nilsson, Harri Sihto, Petri Bono, Raija Kallio, Jouni Junnila, Thor Alvegård, and Peter Reichardt
The challenge of secondary resistance

- Secondary resistance due to
  - Secondary resistance mutations
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- Secondary resistance over time

- Secondary resistance and tumor bulk

- Heterogeneity of secondary resistance
Fig. 1. Differential immunohistochemical expression patterns for KIT receptor, CD34, bcl-2, and desmin in a progressive peritoneal GIST lesion (case no. 27) with two different acquired KIT mutations in exon 13 (V654A) and exon 17 (Y823D). Different regions were microdissected and mutational analysis was done separately.

Wardelmann et al., Clin Cancer Res 2006
Limitations of Tumor Biopsies – and a Possible New Solution

- Tumor ("tissue") biopsies may be problematic, because tumors are heterogeneous and only certain tumors (or even only certain parts of any given tumor) are sampled.

- Tumor biopsies are invasive in patients with most solid tumors which are deep in internal organs.

- Tumor cells are constantly dying and releasing DNA into the bloodstream.

- A sophisticated assay of blood may be able to document a comprehensive picture of all the mutations in any given patient.

- These "Liquid Biopsies" to assay mutations in circulating free DNA provide a potential alternative that may circumvent the limitations and risks of tumor-based DNA analysis from solid tissue biopsies.
Mutational Analysis of Circulating DNA in Plasma via BEAMing Technology

- **Beads, Emulsions, Amplification, Magnetics (done with Inostics):**
  - laboratory steps: pre-amplification, emulsion PCR, hybridization, flow cytometry
  - detection of tumor-associated mutations using circulating free DNA from plasma
  - Exquisitely sensitive detection: 1 mutant allele in 10,000 normal alleles
  - Ideal concept to detect emergence of multiple gene mutations which can make GIST resistant to targeted therapies

*Richardson and Iglehart, Clinical Cancer Research, May 2012*
BEAMing of GRID plasma DNA: results

- Data obtained from 163 (82%) GRID patients
- *KIT* mutations (primary and secondary) detected in 58% of samples
- Primary *KIT* mutations detected in exon 9 (15%) and exon 11 (12%)
- Secondary *KIT* mutations detected in 47% of samples and of these:
  - 25% were exon 13/14 mutations
  - 64% were exon 17/18 mutations
  - 12% were both
    - Most mutations (76%) in activation loop (imatinib/sunitinib resistance)
- 40% of samples with secondary *KIT* mutations had additional mutations
- Other mutations detected:
  - 1% of samples with *PDGFR* mutation; *KRAS* mutation in 1 of 2 samples tested; no *BRAF* mutations in any samples
The challenge of secondary resistance

• Secondary resistance due to
  - Secondary resistance mutations
  - Insufficient drug levels
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• Secondary resistance over time

• Secondary resistance and tumor bulk

• Heterogeneity of secondary resistance

• Prevention of secondary resistance
Response to Imatinib Correlates with Surgical Result

- Response to imatinib therapy at the time of surgery strongly correlated with surgical result (p<0.0001)
The challenge of secondary resistance

- Use of alternating drugs