GIST:
Medical and Multidisciplinary Therapy

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DISCLOSURES FOR
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Consulting fees received from Janssen, Bayer, EMD-Serono (Merck KGA), Lilly, Sanofi, Daiichi-Sankyo, Pfizer, Novartis, Ziopharm, Ariad, Polaris, KyMab, Genocea, Nektar, Caris Life Sciences, WCG

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Equity in Blueprint Medicines, Kolltan, and G1 Therapeutics

Board of Directors of Blueprint Medicines
SOLVING CANCER
YOU CAN’T CURE WHAT YOU DON’T UNDERSTAND

(X + Y = -C) (X + Y = -C) (X + Y = -C) (X + Y = -C)

In the war against cancer, the enemy remains poorly defined. This group of scientists is hoping to change that—and is making enemies of its own. Priest + Grace
The Disease is the Medium, 
The *Mechanism* is the Message

- Understanding the basic mechanisms of GIST at the molecular level
- Diagnosing patients correctly
- Understanding clinically relevant GIST variations
- Understanding resistance to overcome barriers to cure
Research has helped us to understand which mechanisms drive cancer cells

Adapted from Dawelbait G et al. Bioinformatics 2007;23:i115-i124
Tumor cells are only one part of an ecosystem – How to make the whole ecosystem extinct?
We need to identify the switches that sustain cancer cell survival and growth.
There was no effective systemic medical therapy for GIST prior to Kinase Inhibitors.
The Enabling Discovery Linking KIT to GIST

Gain-of-Function Mutations of c-kit in Human Gastrointestinal Stromal Tumors

Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiro Kitamura†

Science 279:577-580, 1998
Detection of KIT by Immunohistochemical Staining in GIST

H+E Stain

CD117 IHC Stain

CDM Fletcher, MD

Normal Small Intestine
The first GIST patient on imatinib: January 2000
Clinical Development

STI571/STI571B

Protocol No. CSTI571B2221

An Individual Supply, Pilot Study to Determine the Efficacy and Safety of STI571 in a Patient with a Progressing Metastatic Gastrointestinal Stromal Tumour

Document Type: Clinical Study Protocol
Development Phase: I
Document Status: Final
Release Date: February 18 2000
Imatinib Induces Major Response in the First Patient with Metastatic GIST

March 3, 2000

April 5, 2000

Joensuu H, et al. NEJM 2001; 344: 1052-6
GIST liver metastases disappear after 4 weeks of treatment with STI571 (imatinib, Glivec)
SARCOMA & GIST CONFERENCE 2016

GIST Biopsy Before Imatinib

H+E

Ki-67 (proliferation)

CD117 (KIT)

GIST Biopsy After Imatinib

H+E

Ki-67

CD117

Rapid movement to the next big step: April 2000
Clinical Development

Compound STI 571

Protocol No. CSTI571B2222

A Phase II Study of STI571 in Patients with Unresectable or Metastatic Malignant Gastrointestinal Stromal Tumors Expressing c-kit

Author(s): George D. Demetri, M.D.; Renaud Capdeville M.D.; Sasa Dimitrijevic, Ph.D.
The First U.S. GIST Patient Treated with Imatinib: Dana-Farber Cancer Institute and Harvard Medical School

Baseline

Active Tumor
## Imatinib Benefits the Majority of Patients with Metastatic GIST

<table>
<thead>
<tr>
<th>Best Response</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 147 (%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>97 (66%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>25 (17%)</td>
</tr>
<tr>
<td>Progression or Non-evaluable</td>
<td>25 (17%)</td>
</tr>
</tbody>
</table>

83% Benefit

*Demetri et al. Update from N Engl J Med 2002*
Significant improvement in overall survival for metastatic GIST patients treated with imatinib

J Clin Oncol. 2008;26:620-625
Long Term Survival in GIST Patients: S0033 Intergroup US-Canada Trial
Different Structural Variants of Kinase Targets in GIST

**KIT**
- Single Dominant Mutation per patient:
  - Site of mutation differs between patients

- Exon 9 (8%) - SENS
- Exon 11 (76%) - SENSITIVE
- Exon 13 (1%) - +/-SENS
- Exon 17 (1%) - RES

**PDGFRA**
- WILD TYPE in both KIT and PDGFRA (13%) – RESISTANT
- Exon 12 (0.3%) - SENS
- Exon 18 D842V (0.6%) - RES

Membrane

Cytoplasm
Describing and Dissecting Imatinib Failure

Different Genotypic and Structural Variants Fail Imatinib Therapy at Different Rates

Heinrich, Corless, Blanke, Joensuu, von Mehren, Demetri 2006
There are clinically important differences in GIST between patients

**GIST**

- **KIT mutations*** (75% to 80%)
- **PDGFRA mutations*** (approx 10%)
- **SDH mutations or deficiency** *(SDHA, SDHB, SDHC)* (approx 10%)
- **BRAF or NF1 mutations** (<2%)

*SPECIFIC MUTATIONAL SUBTYPES can impact patient outcomes

**KIT** exon 11 mutations predict most benefit with imatinib

**KIT** exon 9 mutations may progress faster on standard dose imatinib

**PDGFRA** D842V mutation:
  - good risk in primary localized GIST, worse outcomes in metastatic GIST

### Variable Affecting RISK of Recurrence for Primary Localized GIST

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>RISK OF RECURRENCE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stomach</td>
</tr>
<tr>
<td>Size</td>
<td></td>
</tr>
<tr>
<td>≤ 2 cm</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 2, ≤ 5 cm</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 5, ≤ 10 cm</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td>12</td>
</tr>
<tr>
<td>Mitotic Count</td>
<td></td>
</tr>
<tr>
<td>≤ 5 per 50 HPFs</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 per 50 HPFs</td>
<td>0*</td>
</tr>
<tr>
<td>≥ 2 cm</td>
<td>16</td>
</tr>
<tr>
<td>&gt; 5, ≤ 10 cm</td>
<td>55</td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td>86</td>
</tr>
</tbody>
</table>

* Too few cases

Adapted from Miettinen and Lasota. *Sem Diag Pathol.* 2006; 23(2):70-83.
Adjuvant Imatinib Improves Recurrence-Free Survival in Primary GIST: ACOSOG Z9001

Not all GIST patients benefit from adjuvant imatinib

NO IMATINIB BENEFIT for GIST with PDGFRA D842V Mutation

% Recurrence-Free and Alive

Time in Months

Imatinib (n=15)
Placebo (n=13)

p=0.9984

Corless et al. ASCO 2010 and JCO online March 17, 2014; DOI:10.1200/JCO.2013.51.2046.
Improved Recurrence-Free Survival with 3 yrs vs. 1 yr of Adjuvant Imatinib in GIST

- **Hazard ratio**: 0.46 (95% CI, 0.32 - 0.65)
- **P value**: < 0.0001
- **Median follow-up time**: 54 months

### Survival Rates
- **3 years IM**: 86.6% (65.6%)
- **1 year IM**: 60.1% (47.9%)

### Table: No. at risk (n=397)

<table>
<thead>
<tr>
<th>Duration</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 Months IM</td>
<td>198</td>
<td>184</td>
<td>173</td>
<td>133</td>
<td>82</td>
<td>39</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>12 Months IM</td>
<td>199</td>
<td>177</td>
<td>137</td>
<td>88</td>
<td>49</td>
<td>27</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

Improved Overall Survival with 3 yrs vs. 1 yr of Adjuvant Imatinib in GIST

Hazard ratio 0.45 (95% CI 0.22-0.89)

P = 0.019

Joensuu H, et al

JAMA. 2012;307(12):1265-1272
Resistance to Kinase Inhibition in *KIT*-Mutant GIST Is Generally Caused by Secondary *KIT* Mutations

**PRIMARY *KIT* Activating Mutations**

GIST is addicted to signals from the primary mutant kinase

**KIT Resistance Mutations**

Clonal expansion of multiple secondary mutations in TKI-resistant GIST

Sunitinib overcomes resistance to imatinib by fitting into the mutated KIT binding pocket

Courtesy of K Gajiwala, Pfizer Oncology
1Gajiwala et al. Proc Natl Acad Sci USA 2009;106:1542
There are now 3 different Tyrosine Kinase Inhibitors (TKIs) approved for therapy of metastatic GIST

Imatinib

Sunitinib

Regorafenib

Overcoming dual resistance to imatinib and sunitinib with regorafenib

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.

Why are GIST patients not cured with TKI Therapy?

- We do not really know…
  - D842V PDGFRα-specific and Exon 17 KIT-specific inhibitors
  - BRAF-specific drugs
  - Metabolic targeting of SDH-mutant GIST
- Insufficient kinase inhibition?
  - BRAF mutants need >95% inhibition for activity
- Other GIST cell survival pathways?
Other New Options for Metastatic GIST

- Mutation-specific therapies
  - D842V PDGFRA-specific and Exon 17 KIT-specific inhibitors
  - BRAF-specific drugs
  - Metabolic targeting of SDH-mutant GIST

- Anti-KIT targeting monoclonal antibodies

- New combinations with TKIs
  - Inhibitors of MEK, FGFR
  - Immuno-oncology approaches

- Consider referral to clinical trials at every step in GIST management
OTHER LEARNINGS

GIST Management has been a model for translational and clinical oncology multidisciplinary research

- The global sarcoma community has worked together effectively to advance research and improve patient outcomes

- Collaborations with regulatory agencies, national groups, patient advocacy groups and biopharma have accelerated progress

- Costs remain a concern for sustainability of cancer care in the era of combinations

- Rapid and focused trials have been the model for efficient development of new therapies

- Thanks to everyone who has been a part of this over nearly two decades!