New Treatments in the Pipeline for GIST

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How Do We Develop New Treatments?

1. Empiricism – Give a drug to patients, and see if it works (how do you know?)

2. Scientific Approach – Identify the problem in the cancer, design/develop a drug that blocks that process, test in laboratory models (if you have them), test for safety in people, test how well it works, test if it works better than standard treatment (takes a long time!)

3. Combination of (1) and (2)
Step 1: Identify the disease

- Leiomyosarcoma
- GIST
- CD117 (KIT)
Step 2: Identify the abnormality

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
Step 3: Test drug in laboratory models

SHORT REPORTS

STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications

David A Tuveson*,1,2,3,4, Nicholas A Willis1, Tyler Jacks1,2, James D Griffin3,4, Samuel Singer3,4,5, Christopher DM Fletcher6, Jonathan A Fletcher3,4,6 and George D Demetri3,4

These cell-culture-based studies support an important role for c-KIT signaling in GIST and suggest therapeutic potential for STI571 in patients afflicted by this chemoresistant tumor. Oncogene (2001) 20, 5054–5058.
Steps 4 and 5: Test drug for efficacy in patients with GIST

Efficacy and Safety of Imatinib Mesylate in Advanced Gastrointestinal Stromal Tumors

George D. Demetri, M.D., Margaret von Mehren, M.D., Charles D. Blanke, M.D., Annick D. Van den Abbeele, M.D., Burton Eisenberg, M.D., Peter J. Roberts, M.D., Michael C. Heinrich, M.D., David A. Tuveson, M.D., Ph.D., Samuel Singer, M.D., Milos Janicek, M.D., Ph.D., Jonathan A. Fletcher, M.D., Stuart G. Silverman, M.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Beate Kiese, M.Sc., Bin Peng, M.D., Ph.D., Sasa Dimitrijevic, Ph.D., Brian J. Druker, M.D., Christopher Corless, M.D., Christopher D.M. Fletcher, M.D., and Heikki Joensuu, M.D.
Step 6: Test if it is better than standard treatment

- Duh! Nothing else worked. Imatinib did for >80% of patients

- Some things are obvious – don’t need to test whether jumping out of an airplane is safer with a parachute than without one

- FDA granted approval in 2002. This was fast.
But imatinib doesn’t work for all patients, or it stops working

• Steps 1 and 2: Identify the disease/abnormality

  – Additional KIT mutations causing imatinib resistance (about 80%)

  – Other mutations (about 20%):
    • PDGFRA D842V (stomach, epithelioid)
    • NF1 (small bowel, spindle cell)
    • SDH deficiency/“pediatric GIST” (stomach, epithelioid)
    • BRAF
    • Other as of yet unidentified mutations
Next steps

• Test in lab models (if you have them)
• Test for safety (if not already done)
• Test for efficacy
• Test if better than standard of care

• Let’s discuss some pathways and emerging drugs. Most will focus on KIT/PDGFR signaling; brief discussion of SDH-deficient GIST
But first...
Brief foray into clinical trials
and (...gasp...) statistics
Clinical Trials

**What** - Research (experiments) involving people.

**Types** - Therapeutic, Prevention, Quality of Life

**Why** - Find better treatments

**When** - Potentially at any point

**How** – Safety and consent of patient is paramount. Involves oversight of Institutional Review Board (IRB) and FDA. Guided by principles of human rights, ethics, and by Federal Law. Thus, the “protocol”.
Major Types of Drug Studies

- Phase I
  - First time drug administered to patients
  - Study goal is to determine safety, side effects, and maximal safe dose
  - Drug levels (pharmacokinetics/PK) closely measured. Lots of blood draws.
  - Drug effect on body (pharmacodynamics/PD) often measured. Blood draws and biopsies.
  - Frequent safety assessments (blood tests, EKGs, etc). Lots of visits.
  - Patients enrolled in small groups at a given dose level, observed for toxicity, then next group at higher dose level, etc. Few slots.
  - Often the only access to exciting new drugs for patients with rare diseases
  - Outcomes: Maximally tolerated dose (MTD), Recommended Phase 2 Dose (RP2D), side effect profile
Major Types of Drug Studies

• Phase II
  – All patients get same dose of drug. Everyone gets the same drug.
  – Testing efficacy in patients with shared type of disease.
  – Typical Outcomes: Response rate (RR) or progression-free survival (PFS). Stay tuned.
Major Types of Drug Studies

• Phase III studies
  – Testing whether one treatment is better than another, or better than the standard of care
  – Patients are randomly assigned (by a computer) to one treatment group. Sometimes the patient and the doctor do not know what the patient is getting (“double-blind”).
  – Require many patients to participate.
  – If properly done, often viewed as “gold standard” and can lead to FDA approval.
  – RR, PFS, and overall survival (OS) or hazard ratio (HR) are typical endpoints
Some Outcome definitions

How do we report outcomes in clinical studies?

1. Response Rate

2. Progression-Free Survival

3. Overall Survival
1. **Response Rate (RR)**
   - Proportion of patients whose tumors shrank by some standard amount
   - Response Evaluation Criteria in Solid Tumors (RECIST)
   - Other measures: Choi criteria, EORTC PET criteria, etc.
   - Usually, response = drug effect

2. **Progression-Free Survival (PFS)**
   - Proportion of patients who have not died and whose tumors have not grown by some standard amount
   - If the tumor didn’t grow, is that an effect of the drug, or is the tumor just growing very slowly on its own?
   - Compare to “historical controls” or to a different treatment within the same study to find out
Typical Outcome Measurements

3. Overall Survival (OS)
   • Proportion of patients who are still alive
   • Compare to “historical controls” or to a different treatment within the same study to find out
   • Generally viewed to be the gold standard
How are they reported?

1. Response Rate: percentage (ok, so it’s not really a rate)
   - “The response rate was 45%”

2. PFS and OS: median (different than the mean, or average – see next slide), rate, or hazard ratio
   - “The median PFS was 28 weeks”
   - “The PFS rate at 6 months was 37%”
   - “The hazard ratio was 0.5”
Very Brief Foray into Statistics

• **Mean** = average value
  – Mean of 1,3,5,7,9 = 25/5 = 5
  – Mean of 1,3,5,10,101 = 120/5 = 24
  – Useful for repeated measurements of related values (eg weight of one person)

• **Median** = middle value of a range of values
  – Median of 1,3,5,7,9 = 5
  – Median of 1,3,5,10,101 = 5
  – Useful for measurements of unrelated values so that values at either extreme don’t introduce bias
Just one more stats slide

• p values
  – Represent the probability that the observation was due to chance alone
  – The higher the p value, the less likely the finding is real
  – By convention, a p value < 0.05 (connotes 5%) is typically viewed as “statistically significant”
OK – we got all that out of the way. Now let’s talk about some new drugs.
Normal Activation of KIT/PDGFRA Receptor Tyrosine Kinase Signaling

Activated receptor

Deactivated receptor

Ligand

Outside cell

Activated receptor

Deactivated receptor

Inside cell

Signaling cascades

Transient activation

Receptor complex internalization

Receptor complex dissociation

Receptor recycled to plasma membrane

Normal cell growth and development
Mutations Generate Uncontrolled, Constant Activation in GIST

Constitutive activation

Outside cell

Inside cell

Mutation

Signaling cascades

Cell Proliferation and Survival
Imatinib turns off activated KIT
Imatinib turns off the switch in GIST

ON

Tumor Cell Survival and Growth

OFF

Tumor Cell Growth Arrest and Cancer Regression
Sunitinib Malate – a Different Shaped Key

• Small-molecule receptor tyrosine kinase inhibitor
• Inhibits all VEGFRs, PDGFR-A, PDGFR-B, c-KIT, RET and FLT-3
• Oral administration
• Both antitumor and antiangiogenic activity
Sunitinib Control of Imatinib-Resistant GIST in a Patient with Primary Imatinib Resistance

PET after 7 Days of Sunitinib
- Normal heart
- Normal kidneys

CT after 2 months of Sunitinib

Benefit of Sunitinib on Time to Tumor Progression Following Progression on Imatinib

Demetri et al. Lancet 2006
Other KIT inhibitors studied in GIST

Tumor blood vessel endothelial cell membrane

Tumor cell membrane

Dasatinib
Sorafenib
Nilotinib
Pazopanib
Masitinib
Regorafenib
Imatinib
Sunitinib

PKC

Sunitinib
Sorafenib
Regorafenib
Pazopanib
Dovitinib

KIT
PDGFRA
VEGFR

PI3K
AKT
mTOR

Ras
Raf
Mek
Erk

Nucleus

Transcription factors

Cell proliferation
Cell adhesion
Apoptosis
Cell survival
Angiogenesis
Cell differentiation
# Phase II Studies of 3rd+ Line Therapy (other keys) for GIST (not intended for interstudy comparisons)

<table>
<thead>
<tr>
<th>Drug</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib</td>
<td>3</td>
<td>32</td>
<td>3</td>
<td>8</td>
<td>Montemurro 2009</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>3</td>
<td>23</td>
<td>4</td>
<td>10</td>
<td>Sawaki 2011</td>
</tr>
<tr>
<td>Dasatinib (Choi criteria)</td>
<td>8</td>
<td>30</td>
<td>2</td>
<td>19</td>
<td>Trent ASCO 2011</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>12</td>
<td>56</td>
<td>5</td>
<td>12</td>
<td>Kindler ASCO 2011</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>10</td>
<td>54</td>
<td>5</td>
<td>10</td>
<td>Ruy ASCO 2011</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>9</td>
<td>82</td>
<td>10</td>
<td>NR</td>
<td>George ASCO 2011 and JCO 2012</td>
</tr>
</tbody>
</table>

Adapted from Verweij ASCO 2011.
Regorafenib (BAY 73-4506) is a Structurally Distinct Oral Inhibitor of Multiple Kinases Relevant to GIST and Other Cancers


Biochemical activity

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC$_{50}$ (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT</td>
<td>7</td>
</tr>
<tr>
<td>VEGFR-1</td>
<td>13</td>
</tr>
<tr>
<td>Murine VEGFR-2</td>
<td>4</td>
</tr>
<tr>
<td>PDGFR-β</td>
<td>22</td>
</tr>
<tr>
<td>RET</td>
<td>1.5</td>
</tr>
<tr>
<td>B-RAF</td>
<td>28</td>
</tr>
<tr>
<td>FGFR1</td>
<td>202</td>
</tr>
</tbody>
</table>

Demetri ASCO 2012
Preclinical GIST models demonstrate antitumor activity of regorafenib

Preclinical GIST models demonstrate antitumor activity of regorafenib

- Regorafenib 50 mg/kg PO daily

Sort-term response: PET/CT imaging after 3 doses

% Change in Tumor SUV

Anti-tumor efficacy: tumor volume

Tumor Volume (mm³)

Days of Treatment

Regorafenib in GIST following failure of IM and SU: Best Responses To Date

<table>
<thead>
<tr>
<th>Objective response</th>
<th>n (%)</th>
<th>Clinical Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>3 (9)</td>
<td>n = 24 (73%)</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>95% CI: 55%-87%</td>
</tr>
<tr>
<td>≥16 weeks</td>
<td>21 (64)</td>
<td></td>
</tr>
<tr>
<td>&lt;16 weeks</td>
<td>6 (18)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1 (3)</td>
<td></td>
</tr>
</tbody>
</table>

Regorafenib in GIST following failure of IM and SU: Significant target inhibition of KIT phosphorylation

- Pre- and post-treatment tumor biopsies in a patient with baseline KIT exon 11 mutation and secondary resistance mutation in KIT exon 17 (D820V)

- Significant inhibition of KIT phosphorylation

- No significant change in total KIT

Regorafenib in GIST following failure of IM and SU: Progression-free survival

Median PFS: 10.0 months
95%CI (7.3 mo - …)

Randomized Phase III Trial of Regorafenib in Patients (pts) with Metastatic and/or Unresectable Gastrointestinal Stromal Tumor (GIST) Progressing Despite Prior Treatment with at least Imatinib (IM) and Sunitinib (SU): The GRID Trial


Ludwig Center at Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; HÉLIOS Klinikum, Bad Saarow, Germany; Asan Medical Center, Seoul, South Korea; Centre Léon Bérard, Lyon, France; Helsinki University Central Hospital, Helsinki, Finland; Mount Sinai School of Medicine, New York, NY, USA; Maria Skłodowska-Curie Memorial Cancer Center, Warsaw, Poland; Mannheim University Medical Center, Mannheim, Germany; Leiden University Medical Center, Leiden, Netherlands; Christie NHS Foundation Trust, Manchester, UK; Fox Chase Cancer Center, Philadelphia, PA, USA; Université de Liège, Belgium; Mount Sinai Hospital, Toronto, Canada; Institut Gustave Roussy, Villejuif, France; University of Palermo, Italy; Affiliated Hospital of Academy Military Medical Sciences, Beijing, China; Department of Surgery, Osaka Police Hospital, Osaka, Japan; Bayer HealthCare Pharmaceuticals, Berlin, Germany; Istituto Nazionale dei Tumori, Milan, Italy
GIST – Regorafenib In Progressive Disease (GRID): Study Design

- Multicenter, randomized, double-blind, placebo-controlled phase III study
  - Global trial: 17 countries across Europe, North America, and Asia-Pacific
  - Stratification: treatment line (2 vs >2 prior lines), geographical location (Asia vs “Rest of World”)

Demetri ASCO 2012
GRID Study: Progression-Free Survival (primary endpoint per blinded central review)

Regorafenib significantly improved PFS vs placebo (p<0.0001); primary endpoint met

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GRID Study: Overall Survival
(following 85% cross-over of patients on placebo arm)

Because of the crossover design, lack of statistical significance between regorafenib and placebo was not unexpected

Demetri ASCO 2012
### Disease Control and Overall Response Rates

<table>
<thead>
<tr>
<th>Disease control rate</th>
<th>Regorafenib (N=133) n (%)</th>
<th>Placebo (N=66) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + PR + durable SD (≥12wks)</td>
<td>70 (52.6)</td>
<td>6 (9.1)</td>
</tr>
</tbody>
</table>

### Objective response rate

<table>
<thead>
<tr>
<th>Objective response rate</th>
<th>Regorafenib (N=133) n (%)</th>
<th>Placebo (N=66) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>6 (4.5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Stable disease (at any time)</td>
<td>95 (71.4)</td>
<td>22 (33.3)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>28 (21.1)</td>
<td>42 (63.6)</td>
</tr>
</tbody>
</table>

Responses based on modified RECIST v1.1

**Regorafenib improved rates of disease control vs placebo**

Demetri ASCO 2012
Drug-Related Treatment-Emergent Adverse Events in ≥10% of Patients During Double-Blind Treatment

<table>
<thead>
<tr>
<th>Demetri ASCO 2012</th>
<th>Regorafenib (N=132), % Median 23 wks exposure</th>
<th>Placebo (N=66), % Median 7 wks exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>All 3 4 5</td>
<td>All 3 4 5</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>56.1 19.7 0 0</td>
<td>15.2 1.5 0 0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48.5 22.7 0.8 0</td>
<td>16.7 3.0 0 0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40.9 5.3 0 0</td>
<td>7.6 0 0 0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38.6 2.3 0 0</td>
<td>27.3 1.5 0 1.5</td>
</tr>
<tr>
<td>Mucositis, oral</td>
<td>37.9 1.5 0 0</td>
<td>9.1 1.5 0 0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>23.5 1.5 0 0</td>
<td>3.0 0 0 0</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>22.0 0 0 0</td>
<td>4.5 0 0 0</td>
</tr>
</tbody>
</table>

Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Treatment

<table>
<thead>
<tr>
<th>Regorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 (6.1%)</td>
<td>5 (7.6%)</td>
</tr>
</tbody>
</table>
Conclusions and Questions: Regorafenib in GIST

• Novel KIT/VEGFR kinase inhibitor significantly increases PFS compared with placebo in GIST progressing despite prior therapy with at least imatinib and sunitinib
  – **PFS: median 4.8 vs 0.9 months, HR 0.27, p<0.0001**

• No new or unexpected safety findings with regorafenib

• Regorafenib has the potential to fulfill an unmet need for advanced GIST patients progressing after imatinib and sunitinib

• **Which patients will benefit from regorafenib?**

• **Can other KIT kinase inhibitors be effective as 4\textsuperscript{th}+ line of therapy?**
  – **Will other keys fit, or do we need other approaches?**
HSP90 helps proteins fold
Other Approaches to Target Specific Molecular Pathways in GIST

HSP90 inh.

Nucleus

Transcription factors

Cell proliferation
Cell adhesion
Apoptosis
Cell survival
Angiogenesis
Cell differentiation
Without HSP90, mutated KIT is destroyed.

GIST882
Imatinib Sensitive

GIST48
Imatinib Resistant
(secondary mutation)

See also S. Bauer, J. Fletcher, et al. (2006)
Cancer Res. 66:9153 (17-AAG)
Phase 1 Trial of IPI-504 in Patients with Metastatic GIST Refractory to Tyrosine Kinase Inhibitors
Metastatic GIST responding to Hsp90 Inhibitor in Phase 1 Study
Progression Free Survival in GIST

Median PFS 12 weeks (n=36)\(^1\)
Phase III Study of IPI-504 in GIST (RING Study)

- IPI-504 or placebo, 400 mg IV twice weekly, 2 weeks on/1 week off

- Stopped early because of 4 cases of death from liver failure in the treatment group

- Studies with other HSP90 inhibitors are ongoing

- HDAC inhibitors also likely work through HSP90
If the switch is stuck on, unscrew the lightbulb

Tumor Cell Survival and Growth
Other Approaches to Target Specific Molecular Pathways in GIST

- KIT
- PDGFRA
- VEGFR
- Tumor blood vessel endothelial cell membrane

- Tumor cell membrane

- P13K
- AKT
- mTOR
- PKCθ
- Ras
- Raf
- Mek
- Erk

- GDC-0941
- BKM120
- GDC-0980
- BEZ235

- Nucleus
- Transcription factors

- Cell proliferation
- Cell adhesion
- Apoptosis
- Cell survival
- Cell differentiation
- Angiogenesis

- Sirolimus
- Everolimus
- Temsirolimus
Phase I Study of PI3K/mTOR Inhibitor

Figure 8. Best $^{18}$FDG-PET Response by Patient

- Sarcoma: 36d
- Neuroendocrine: 87d
- Giant cell sarcoma: 36d
- GIST: 64d
- PDGFR mt: 299d
- 70 mg/50 mg: 108d
- 50 mg: 299d

Mean % Change from Baseline in SUVmax

Days on study

GDC-0980 Dose

Wagner et al. ASCO 2011
Phase I Study of PI3K/mTOR Inhibitor

Figure 9. Best RECIST Response by Evaluable Patient

* Patient on study as of 18 April 2011

Wagner et al. ASCO 2011
What about combining drugs? Is it safe? Does it work?

- Imatinib + mTOR inhibitor
  - Schoffski, Hohenberger
- Imatinib + HDAC inhibitor
  - Bauer – too toxic
- Imatinib + HSP90 inhibitor
  - Ongoing
- Imatinib + PI3K inhibitor
  - Ongoing
What about PDGFR mutant GIST?

• Imatinib is ineffective against D842V mutation

• Responses seen with HSP90 inhibitors

• Studies ongoing of crenolanib (PDGFR kinase inhibitor) and IMC-3G3 (anti-PDGFR antibody)
  – Results are not yet available
SDH-Deficient GIST ("pediatric-GIST") and VEGFR inhibitors

• Accumulation of succinate in cells leads to stabilization of HIF1α
• HIF1α turns on other genes such as VEGF

• Some activity reported with sunitinib and observed with regorafenib and pazopanib in patients with SDH-deficient GIST
SDH-Deficient GIST (“pediatric-GIST”) and IGF1R inhibitors

• Insulin-like Growth Factor Receptor (IGF1R) is expressed in “wild-type” GIST
• Role of IGF1R signaling in GIST is not yet established
• IGF1R inhibitor study is opening for wt GIST

• Recent papers have shown that IGF1R is only expressed in SDH-deficient GIST
Pipeline Summary

• Other kinase inhibitors
  – Regorafenib now available in “expanded access”, hopefully will be approved soon
  – Pazopanib study ongoing
  – Masitinib studies ongoing

• Combination studies for safety and efficacy
  – Imatinib + HSP90 inhibitor
  – Imatinib + PI3K inhibitor

• Studies for specific subtypes
  – PDGFR inhibitors/IGF1R inhibitor
Acknowledgements-DF/BWHCC Sarcoma

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Dr. Chandrajit Raut
Michelle Lapidus, PA

Pediatric Oncology
Dr. Katherine Janeway
Dr. Carlos Rodriguez-Galindo

Pathology
Dr. Christopher Fletcher
Dr. Jason Hornick
Dr. Jonathan Fletcher and Lab

Radiology
Dr. Jyothi Jagannathan
Dr. Nikhil Ramaiya

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