Mistakes I See in GIST Management, and Ethical Issues In Clinical Trials

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Effects of Imatinib on GIST: CT findings
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Now you see it

Now you don’t
Effects of Imatinib on GIST: CT findings - Size

Baseline

8 Weeks
Effects of Imatinib on GIST: CT findings - Density

Baseline with Density Measurement

8 weeks with Density Measurement
Effects of Imatinib on GIST: CT findings - Size

Baseline

8 Weeks
We Should Desist Using RECIST at Least in GIST
SU11248 in Advanced GIST

Sunitinib Malate, Sutent

Stop imatinib
4 weeks

PD on imatinib

Randomize

SU11248 (207)

6 weeks

Placebo (105)

PD
Off

PD
Figure 2   Kaplan-Meier estimates of time to tumour progression  Results represent central radiology assessment of ITT population.

George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verw...

Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial

The Lancet Volume 368, Issue 9544 2006 1329 - 1338

http://dx.doi.org/10.1016/S0140-6736(06)69446-4
Figure 4  Kaplan-Meier estimates of overall survival  Results represent central radiology assessment of ITT population and include open-label treatment subsequent to crossover after progression.

George D  Demetri , Allan T  van Oosterom , Christopher R  Garrett , Martin E  Blackstein , Manisha H  Shah , Jaap  Verw...
EORTC 1st Line Chemotherapy: Active Single Agents or Combinations

Time to progression
1st line - leiomyosarcoma

- extr
- abdo
- gyn
- gi
- oth.st
- oth.vi

(months)

[Graph showing time to progression for different categories of leiomyosarcoma patients]
Phase III Trial: US Intergroup S0033: Time to Progression on Crossover

Data as of November 25, 2003

- At Risk: 89
- Failed: 60
- Median in Months: 4

Months After Registration
Time to Tumor Progression

- **Sunitinib (N=207)**
  - Median (95% CI): 6.3 (3.7, 7.6)
  - Hazard ratio: 0.335
  - P < 0.00001

- **Placebo (N=105)**
  - Median (95% CI): 1.5 (1.0, 2.3)
GIST – Regorafenib In Progressive Disease (GRID): Study Design

- Metastatic/unresectable GIST pts progressing despite at least prior imatinib and sunitinib (n=236 screened; n=199 randomized)
- Randomization: 2:1
- Regorafenib + best supportive care (BSC)
  - 160 mg once daily
  - 3 weeks on, 1 week off (n=133)
- Placebo + BSC
  - 3 weeks on, 1 week off (n=66)
- Disease progression per independent blinded central review
- Unblinding: Crossover offered for placebo arm or continued regorafenib for treatment arm
- Regorafenib (unblinded) until next progression

- 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
Figure 2   Kaplan-Meier survival analysis after treatment with regorafenib or placebo.  (A) Progression-free survival, per central review (primary endpoint, final analysis).  (B) Overall survival (interim analysis). HR=hazard ratio.

George D Demetri, Peter Reichardt, Yoon-Koo Kang, Jean-Yves Blay, Piotr Rutkowski, Hans Gelderblom, Peter H...

Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial

The Lancet Volume 381, Issue 9863 2013 295 - 302

http://dx.doi.org/10.1016/S0140-6736(12)61857-1
GRID Study: Progression-Free Survival (primary endpoint per blinded central review)

<table>
<thead>
<tr>
<th>Regorafenib, N=133</th>
<th>Placebo, N=66</th>
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<tbody>
<tr>
<td>Median PFS (95% CI)</td>
<td>4.8 months (4.1–5.8)</td>
</tr>
<tr>
<td>Number of events</td>
<td>81 (60.9%)</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI): 0.27 (0.19–0.39)
1-sided p-value: <0.0001

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

Demetri, ASCO 2012
Study Design: RIGHT
(Rechallenge of Imatinib in GIST Having no effective Treatment)

Patients with 1) Prior clinical benefit from 1st-line imatinib, and 2) Progression with both 1st-line imatinib and 2nd-line sunitinib, (Prior use of 3rd-line TKI is permitted)

Randomization

1:1

Placebo

Imatinib

Cross-over to Imatinib

Stop or continue Imatinib

Stratification:
1) ECOG PS: 0-1 vs 2-3
2) Use of 3rd line TKI: yes vs no

Presented by: Yoon-Koo Kang
Progression-Free Survival
(Primary endpoint per blinded external review)

- **Imatinib**
  - HR: 0.45
  - (95% CI, 0.27-0.76)

- **Placebo**
  - 40
  - Event: 34
  - Median PFS (95% CI):
    - Imatinib: 1.8 (0.9-2.8)
    - Placebo: 0.9 (0.8-0.9)

**P = 0.00075 (1-sided)**
Overall Survival

![Graph showing overall survival with comparison between Imatinib and Placebo. The Kaplan-Meier estimator is used to plot the survival fraction over months. The hazard ratio (HR) is 0.99 (95% CI, 0.57-1.72) with a p-value of 0.4912 (1-sided).]

<table>
<thead>
<tr>
<th>Arm</th>
<th>Total</th>
<th>Event</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>41</td>
<td>25</td>
<td>8.2 (5.0-11.3)</td>
</tr>
<tr>
<td>Placebo</td>
<td>40</td>
<td>26</td>
<td>7.5 (4.7-10.3)</td>
</tr>
</tbody>
</table>

Presented by: Yoon-Koo Kang