STA-9090: Second-generation Hsp90 Inhibitor
Review for Gastrointestinal Stromal Tumors
Hsp90 chaperones “client proteins” that drive many key features of cancer cells

Hsp90 helps maintain the shape and proper functioning of these proteins

Blocking Hsp90 causes degradation of client proteins, leading to tumor cell death

 inactive client → Hsp90 degradation; cell apoptosis

Active client → cell survival, proliferation

Inactive client

(Akt, FLT3, BCR-ABL, HER2, BRAF, c-KIT, EGFR, c-MET, …)

Inactive client

Proteosome degradation; cell apoptosis

STA-9090
Cancer cells can have multiple, redundant drivers of growth and proliferation

The redundancy of growth factors helps cancer cells “evade” treatment by drugs that target one, or a small number, of these proteins
Blocking Hsp90 degrades many of these growth factors simultaneously

Eliminating multiple growth factors can help overcome drug resistance
Blocking Hsp90 can also eliminate mutated client proteins, overcoming drug resistance

Protein X (e.g., kinase) drives a cancer

Treat with Gleevec, Sutent, Tarceva, ...

Resistance can emerge from mutation of the kinase

Treat with STA-9090

The mutated protein also relies on Hsp90 for proper activation
Example: overcoming resistance in GIST

In the two GIST cancer cell lines on the right, mutations have developed that make these cancers drug-resistant – the drug is unable to degrade the form of KIT protein driving the disease (“p-KIT”). STA-9090, however, can degrade the protein and kill the cancer cell.

Sunitinib-resistant KIT mutations retain biochemical sensitivity to STA-9090

J. A. Fletcher et al, G. D. Demetri; Brigham and Women’s Hospital; Dana-Farber Cancer Institute; Harvard Medical School; Oregon Health and Science University: AACR-NCI-EORTC Nov 2009

Fig. 1: Novel IM/SU-resistance mutations are inhibited by STA-9090. HEK293 cells were transfected with various KIT mutants identified in clinically-progressing GISTs. 24 hours after transfection, cells were exposed to varying concentrations of STA-9090 for 6 hours. Whole-cell lysates were immunostained for p-KIT(Y703), p-KIT(Y721), total KIT and ß-Actin. Sunitinib-resistant KIT mutations retain biochemical sensitivity to STA-9090.
Example: overcoming resistance in GIST

The highlighted cancers below, which have developed a form of KIT protein mutation that make them resistant to treatment with Gleevec, are still effectively killed by STA-9090. (“IC50” score is a measure of potency – the concentration of drug needed to kill 50% of cancer cells in a laboratory assay.)

Table 1: Cell viability IC50s in Ba/F3 cells transformed by KIT mutants with primary mutation only (Ex 9) vs primary + secondary mutations (Ex 9 + V654A).

<table>
<thead>
<tr>
<th>Model</th>
<th>IC50</th>
<th>STA-9090 (nM)</th>
<th>17-AAG (nM)</th>
<th>Gleevec (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ba/F3: KIT Exon 9</td>
<td></td>
<td>15</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Ba/F3: KIT Exon 9 + V654A (ABP)</td>
<td></td>
<td>15</td>
<td>200</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

Table 2: Cell viability IC50s in KIT-dependent and KIT-independent (GIST62) GISTs

<table>
<thead>
<tr>
<th>Cell line</th>
<th>IC50</th>
<th>STA-9090 (nM)</th>
<th>17-AAG (nM)</th>
<th>Gleevec (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIST882: KIT Ex 13</td>
<td></td>
<td>40</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>GIST882B (17-AAG resistant)</td>
<td></td>
<td>35</td>
<td>&gt;1000</td>
<td>300</td>
</tr>
<tr>
<td>GIST430: KIT Ex 11 + V654A (ABP)</td>
<td></td>
<td>20</td>
<td>300</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>GIST48: KIT Ex 11 + D820A (AL)</td>
<td></td>
<td>20</td>
<td>100</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>GIST62 (KIT-negative)</td>
<td></td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

HSP90 inhibitor STA-9090 potently suppresses secondary KIT kinase-domain mutations responsible for gastrointestinal stromal tumor (GIST) progression during imatinib therapy. -- J. A. Fletcher et al, G. D. Demetri; Brigham and Women's Hospital; Dana-Farber Cancer Institute; Harvard Medical School; Oregon Health and Science University; Synta. AACR-NCI-EORTC Nov 2009
Hsp90 history: first-generation inhibitors have limitations

- **Heat shock proteins discovered**
- **Geldanamycin** purified for use as antibiotic
- **Antibiotic radicicol** shown to inhibit Hsp90
- **Crystal structure elucidated** for binding pocket in Hsp90
- **First-generation Hsp90 inhibitors** (ansamycins, 17-AAG) shown to have modest potency but relatively toxic
Second-generation inhibitors seek to improve potency, safety

- Heat shock proteins discovered
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- **First-generation** Hsp90 inhibitors (ansamycins; 17-AAG) shown to have modest potency but relatively toxic
- **Second-generation**, small-molecule Hsp90 inhibitors

First-year timeline:
- 1962
- 1970
- 1997
- 1998
- 2000
- 2004
- 2008 …

Second-year timeline:

- STA-9090
STA-9090 Clinical Status Summary

- Currently in six ongoing Phase 1, Phase 2 trials. Initial results from these trials to be presented at medical meetings in 2010
- Phase 2 clinical trial in GIST was initiated in the end of 2009 and is currently enrolling patients
- Information about the Phase 2 trial in GIST can be found at [http://clinicaltrials.gov](http://clinicaltrials.gov) (identifier NCT01039519)