Desmoid tumor trial using a gamma secretase inhibitor PF-03084014

Victor M. Villalobos, M.D., Ph.D.
Assistant Professor
Director, Sarcoma Medical Oncology
Division of Medical Oncology
Disclosures

• Advisory capacity:
  • Lilly, Novartis, Janssen
Gamma secretase inhibition in desmoid

- Gamma secretase is an integral membrane protein that cleaves multiple different transmembrane protein complexes including:
  - NOTCH
  - E-CADHERIN
  - Amyloid Precursor Protein
  - others
- PF-03084014 is a noncompetitive, reversible, targeted agent that selectively inhibits gamma secretase
- Activation of WNT pathway through B-Cat or APC mutations appears to be primary driver in desmoid tumors
- Hypothesis that cooperativity exists between WNT pathway activation and active NOTCH signaling.
- Inhibition of NOTCH may reverse activation of B-catenin due to mutations in Bcat or APC.

A Phase I, Dose-Finding Study in Patients with Advanced Solid Malignancies of the Oral γ-Secretase Inhibitor PF-03084014

- 64 patients (solid tumors) enrolled in 3+3 dose escalation design.
- MTD: 220 mg BID orally (n=16)
- RP2D was 150 BID orally (n=23)
- A total of 9 desmoid patients were enrolled (7 at UC Denver)

Table 3. Treatment-related adverse events in ≥5% patients on study

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All grades&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Grade 3&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Grade 4&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>35 (54.7)</td>
<td>6 (9.4)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (37.5)</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (29.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>17 (26.6)</td>
<td>15 (23.4)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (23.4)</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Rash&lt;sup&gt;d&lt;/sup&gt;</td>
<td>13 (20.3)</td>
<td>2 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11 (17.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>6 (9.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5 (7.8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (7.8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4 (6.3)</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (6.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4 (6.3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> No grade 5 treatment-related adverse events were reported.
<sup>b</sup> One patient experienced grade 3 drug hypersensitivity.
<sup>c</sup> One patient experienced grade 4 anaphylactic shock.
<sup>d</sup> Rash included erythematous rash, maculo-papular rash, macular rash, and pruritic rash.

PF-03084014 in Desmoid tumors

- 7 desmoids accrued at UCD (9 total)
- Overall RECIST response rate of **71.4%**
- Median TTP – **Not met**
- Median DOR – **49.8+ mo.** (47.9-67+ mo.)
- Mean time to response - **8.7 mo.**
- Effective even at low doses (80 mg BID)

**Known germline APC mutation**

- Spontaneous desmoid
- ▲ 80 mg BID
- × 100 mg BID
- ◆ 130 mg BID
- ● 150 mg BID
- ■ 220 mg BID

**Arrows:**
- Patients stopped therapy, maintained disease stability despite no further intervention
- Patient was biopsied at end of study and pathology showed paucicellular tissue with prominent collagenous fibrosis
Treatment effects

- Even in absence of RECIST response, there were considerable treatment effects.
- Arrow – came off study at 42 months due to patient preference.
Pathologic response to therapy

2012 Biopsy prior to treatment

Desmoid fibromatosis

2015 End of treatment biopsy

Paucicellular fibroconnective tissue with prominent collagenous fibrosis
Time to treatment failure of therapies (chronologic)

- PF-03084014 (GSI)
- Off Rx Free of Progression
- Tamoxifen/Sulindac
- Surgery
- Methotrexate/Vinblastine
- Vinorelbine
- Imatinib
- Indomethacin
- Liposomal Doxorubicin

Treatment duration (years)
Time to treatment failure of therapies (chronologic)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Time to Failure (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF-03084014 (GSI)</td>
<td>42</td>
</tr>
<tr>
<td>Off Rx Free of Progression</td>
<td>15</td>
</tr>
<tr>
<td>Tamoxifen/Sulindac</td>
<td>54</td>
</tr>
<tr>
<td>Surgery</td>
<td>9.5</td>
</tr>
<tr>
<td>Methotrexate/Vinblastine</td>
<td>15</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>47</td>
</tr>
<tr>
<td>Imatinib</td>
<td>13</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>53</td>
</tr>
<tr>
<td>Liposomal Doxorubicin</td>
<td>78</td>
</tr>
</tbody>
</table>

Treatment duration (years)
4/28/11 baseline

Week 63
Taken off study for patient protocol violation

10/8/14 Week 142

5/12/16 Week 262

RECIST 17 cm
% Change ----
WHO 171.7 cm^2
% Change -----  

RECIST 11.7 cm
% Change -31%
WHO 34.6 cm^2
% Change -80%

RECIST 12 cm
% Change -30%
WHO 24.7 cm^2
% Change -85%

RECIST 12.3 cm
% Change +5%
WHO 27.1 cm^2
% Change + 10%
Conclusions – PF-03084014
gamma secretase inhibitor

• Exciting potential for use in desmoid patients
• 72% RECIST response rate
• Active at even low doses (as low as 80mg BID)
• Tolerable side effect profile (primarily diarrhea, hypophosphatemia)
• Clinical benefit in 100% of patients (only patient with progression had mild regression lasting 12 months)
• Even if no response by size criteria, evidence of tumor activity on pathology
• Working on further clinical development
Acknowledgements

• Phase I team
  • Wells Messersmith MD
  • Antonio Jimeno MD, PhD
  • Lia Gore MD

• Sarcoma Team
  • Anthony Elias MD
  • Brianna Hoffner NP

• Pfizer
T1 post Pretreatment

6 weeks after starting

T1 post 4 years after starting

T2 pre Pretreatment

6 weeks after starting

T2 pre 4 years after starting