Desmoid Tumors Biology: Exploiting Estrogen and Notch Signaling


Development Therapeutics- Clinical Pharmacology/Experimental Therapeutics
Poster Discussion Monday June 5, 2018

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Objectives

Highlight these two studies and discuss them within context of desmoid tumors biology and current standard treatment options
Desmoid Tumor

Rare disease affecting ~1200 patients yearly in U.S.

Sarcoma of fibroblastic origin characterized by excess collagen and fibrous stroma.

Median age of presentation is 30

Associated with mutation in CTNNB1 gene in ~85% of cases

Component of Gardner’s syndrome in conjunction with familial adenomatosis polyposis and APC mutation
Desmoid tumors: Canonical Wnt signaling

Diagram showing the process of Wnt signaling.

- **Extracellular matrix**: Wnt is turned OFF.
- **Cell membrane**: Frizzled.
- **Cytoplasm**: GSK-3β, β-catenin (β-cat), APC, CK-1.
  - GSK-3β phosphorylates β-cat.
- **Nucleus**: Transcriptional repressor (Lef/Tcf) binds to DNA, leading to transcription.
- **Degradation**: Ser-Thr residues in β-cat are degraded.

Note: The diagram illustrates the canonical Wnt signaling pathway, including the activation of β-catenin and its role in transcription.
LEVELS OF EVIDENCE

- Case reports
- Case series: retrospective
- Single Institution
- Small sample size ($N = <30 - 40$ pts)
- Non-randomized
## Clinical Outcomes of Systemic Therapy for Patients with Desmoid Tumor

<table>
<thead>
<tr>
<th>Therapy administered</th>
<th>Lines of treatment given</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progressive disease</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline-based</td>
<td>35</td>
<td>13 (37%)</td>
<td>18 (51%)</td>
<td>4 (11%)</td>
<td>Not reached</td>
</tr>
<tr>
<td>Methotrexate (single agent)</td>
<td>12</td>
<td>4 (33%)</td>
<td>6 (50%)</td>
<td>2 (17%)</td>
<td>9.4</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>26</td>
<td>6 (23%)</td>
<td>17 (65%)</td>
<td>3 (12%)</td>
<td>12</td>
</tr>
<tr>
<td>Vinca-containing combination</td>
<td>10</td>
<td>2 (20%)</td>
<td>6 (60%)</td>
<td>2 (20%)</td>
<td>Not reached</td>
</tr>
<tr>
<td>DTIC or temozolamide</td>
<td>16</td>
<td>2 (13%)</td>
<td>12 (75%)</td>
<td>2 (13%)</td>
<td>14.3</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor</td>
<td>35</td>
<td>3 (9%)</td>
<td>25 (71%)</td>
<td>7 (20%)</td>
<td>26.8</td>
</tr>
<tr>
<td>Other cytotoxic agents</td>
<td>8</td>
<td>0</td>
<td>7 (88%)</td>
<td>1 (12%)</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>142</strong></td>
<td><strong>31 (21%)</strong></td>
<td><strong>91 (64%)</strong></td>
<td><strong>30 (21%)</strong></td>
<td><strong>14.1</strong></td>
</tr>
</tbody>
</table>

Alliance A091105: A phase III, double blind, randomized, placebo-controlled trial of sorafenib in desmoid tumors

Sorafenib improves median PFS over placebo

30 PFS events

Median follow up: 27.2 months (IQR 22-31.7 months)

HR = 0.14 (95% CI 0.06 - 0.33)

p-value (adj) < 0.0001
Alliance A091105: Response higher in sorafenib arm, yet 20% of patients on placebo had spontaneous regressions

Sorafenib (N = 49)
ORR: CR/PR: 33% 95% CI 20 - 48%

Placebo (N = 35)
ORR: CR/PR: 20% 95% CI 8 - 37%
17 patients accrued
Sixteen patients (94%) were evaluable for response
• Five (29%) patients confirmed PR (at least 2 years)
• Five patients SD
A Phase I Study of AL101, a Pan-Notch Inhibitor, in Patients With Locally Advanced or Metastatic Solid Tumors

Anthony B El-Khoueiry,1 Jayesh Desai,2 Swaminathan Padmanabhan Iyer,3 Shirish M Gadgeel,4 Suresh S Ramalingam,5 Leora Horn,6 Patricia LoRusso,7 Gaurav Bajaj,8 Georgia Kollia,8 Zhenhao Qi,9 Shashwati Basak,10 Bruce S Fischer,8 Matti Davis,11 Philippe L Bedard12

1University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA; 2Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia; 3The Methodist Cancer Center Weill Cornell Medical School, Houston, TX, USA; 4University of Michigan, Ann Arbor, MI, USA; 5Winship Cancer Institute, Emory University, Atlanta, GA, USA; 6Vanderbilt University Medical Center, Nashville, TN, USA; 7Yale University School of Medicine–Yale Cancer Center, New Haven, CT, USA; 8Bristol-Myers Squibb, Princeton, NJ, USA; 9Bristol-Myers Squibb, Pennington, NJ, USA; 10Aurigene Discovery Technologies Ltd, Bangalore, India; 11Ayala Pharmaceuticals, Rehovot, Israel; 12Princess Margaret Cancer Centre, Toronto, ON, Canada
Notch is a Proven Oncogenic Driver in Defined Cancers

**Notch Pathway In Normal State**
- ADAM family protease
- γ-secretase complex
- Mutated state allows γ-secretase to cleave Notch without ligand binding
- Mutations, fusions or translocations
- NICD
- AL101 inhibits Notch Activation

**Notch Activation in Cancer**
- Mutated state allows γ-secretase to cleave Notch without ligand binding
- Mutations, fusions or translocations
- NICD

**AL101 inhibits Notch Activation**
- AL101 inhibits Notch Activation (eg, Hes1)

**Study Design**

**Escalation phase (3+3 design) (n = 58)**

- AL101 IV QW (n = 47)
  - 0.3 mg (n = 4)
  - 0.6 mg (n = 3)
  - 1.2 mg (n = 4)
  - 2.4 mg (n = 4)
  - 4 mg (n = 7)
  - 6 mg (n = 14)
  - 8.4 mg (n = 11)

- AL101 IV Q2W (n = 11)
  - 4 mg (n = 4)
  - 6 mg (n = 7)

**Follow-up**

- DLTs: 4 patients receiving 6 mg (diarrhea 3, vomiting 1)
  - 3 receiving 8.4 mg (infusion rxn, vomiting, hepatic failure)

**Expansion phase (n = 36)**

- AL101 IV QW
  - MTD: 4 mg (n = 36)

**Follow-up**

- 1 DLT (diarrhea)

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**Prespecified maximum dose level.**

**Follow-up will end 30 days after the final dose or when adverse event resolves, stabilizes, or is deemed irreversible.**

IV = intravenous; MTD = maximum tolerated dose; QW = once weekly; Q2W = once every 2 weeks.
### Best Overall Response

<table>
<thead>
<tr>
<th>Response</th>
<th>All treated patients (n = 94)</th>
<th>Patients treated with AL101 QW (n = 83)</th>
<th>Patients treated with AL101 Q2W (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOR, n (%)</td>
<td>CR 1 (1)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>PR 3 (3)</td>
<td>2 (2)</td>
<td>1 (9)</td>
</tr>
<tr>
<td></td>
<td>SD 10 (11)</td>
<td>9 (11)</td>
<td>1 (9)</td>
</tr>
<tr>
<td></td>
<td>PD 64 (68)</td>
<td>55 (66)</td>
<td>9 (82)</td>
</tr>
<tr>
<td></td>
<td>ND 16 (17)</td>
<td>16 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Confirmed ORR, n (%)</td>
<td>4 (4)</td>
<td>3 (4)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.2, 10.5</td>
<td>0.8, 10.2</td>
<td>0.2, 41.3</td>
</tr>
</tbody>
</table>

*Confirmed complete response plus confirmed partial response.

BOR = best overall response; CI = confidence interval; CR = complete response; ND = not determined; ORR = overall response rate; PD = progressive disease;
PR = partial response; SD = stable disease; QW = once weekly; Q2W = once every 2 weeks.

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1/2 GE jx (APC splice-site/notch 1 mut)
2/3 desmoids
1/2 adenoid cystic (notch 1 mut)
Phase I Trial of Z-Endoxifen with Estrogen Receptor Imaging in Adults with Advanced Hormone Receptor–Positive Solid Tumors Including Desmoid and Gynecologic Tumors

N. Takebe1,2, G. O'Sullivan Coyne1,2, S. Kummar1,2, Reid JM3, Lindenberg L2, Piekarz R1, Harris L1, Juwara L4, Quinn M2, Moore N2, Choyke P2, Mena E2, Lin F2, Goetz MP3, McGovern RM3, Streicher H1, Covey J1, Collins J1, Doroshow JH1,2, Chen AP1,2

1Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD 20892, USA; 2Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892, USA; 3Department of Oncology, Mayo Clinic, Rochester, MN 55905, USA; 4Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD 21702

Sandra P. D’Angelo, MD
Background

Response to tamoxifen in hormone receptor-positive cancer may be due to variations in tamoxifen metabolism.

Z-endoxifen is a potent metabolite of tamoxifen.

Goetz et al. JCO 2017
Of 41 enrolled patients, 38 were evaluable for MTD determination.
- Patients received endoxifen once daily at seven dose levels (20 to 160 mg).
- Dose escalation ceased at 160 mg per day given lack of MTD and adequate endoxifen concentrations.
- Overall clinical benefit rate (SD x 6 months [n = 7] or PR [n = 3]) was 26.3%
**Trial Design**

- Refractory gynecologic tumors
- Hormone-positive breast
- Desmoid tumors
- Other solid tumors

**Cycle 1 (28 days)**

**Z-endoxifen**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Z-endoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20mg/day</td>
</tr>
<tr>
<td>2</td>
<td>40mg/day</td>
</tr>
<tr>
<td>3</td>
<td>60mg/day</td>
</tr>
<tr>
<td>4</td>
<td>100mg/day</td>
</tr>
<tr>
<td>5</td>
<td>140mg/day</td>
</tr>
<tr>
<td>6</td>
<td>200mg/day</td>
</tr>
<tr>
<td>7</td>
<td>300mg/day</td>
</tr>
<tr>
<td>8</td>
<td>360mg/day</td>
</tr>
</tbody>
</table>

**PK sampling**

**FES PET/CT**

D1  D2  D28
No DLTs observed

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 2</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>9</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>2</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>2</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>3</td>
</tr>
</tbody>
</table>

Events observed in ≥5% of patients shown; the worst grade (≥ 2) at least possibly related to study drug is shown for each patient.
Prolonged disease stabilization in patients with desmoid fibromatosis:

- Patient 23 achieved slow tumor regression of 25% after 55 cycles.
- Patient 35 reported a subjective response (softening of the tumor allowing for bending of the knee joint) starting around cycle 10.
\(^{18}\text{F-fluoroestradiol (FES) PET}\)

9 patients with FES-positive lesions demonstrated a 2\%-76\% reduction in average FES standard uptake values following 2-5 days of Z-endoxifen treatment.
## Summary

<table>
<thead>
<tr>
<th></th>
<th>AL101</th>
<th>Z-endoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2 dose determined</td>
<td>4 mg/week</td>
<td>MTD not reached</td>
</tr>
<tr>
<td>PK data: dose proportional and effective concentrations</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Toxicity acceptable</td>
<td>Drug-related diarrhea</td>
<td>hypophosphatemia, elevated ALT</td>
</tr>
<tr>
<td>Biomarker</td>
<td>Dysregulated Notch/Wnt signaling</td>
<td>FES PET Hormone positivity</td>
</tr>
<tr>
<td>Preliminary evidence of efficacy</td>
<td>1 CR/3PR GE jx, desmoid, ACC</td>
<td>PR 1 fallopian &amp; breast cancer</td>
</tr>
<tr>
<td>Next steps/ ongoing studies</td>
<td>Adenoid cystic carcinoma</td>
<td>On-going efforts in breast ca</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expansion in other tumors?</td>
</tr>
</tbody>
</table>

### Table:
- **Phase 2 dose determined**: 4 mg/week
- **MTD not reached**: Yes
- **PK data**: dose proportional and effective concentrations
- **Toxicity acceptable**: Drug-related diarrhea
- **Biomarker**: Dysregulated Notch/Wnt signaling
- **Preliminary evidence of efficacy**: 1 CR/3PR GE jx, desmoid, ACC
- **Next steps/ ongoing studies**: Adenoid cystic carcinoma

**Notes:**
- **Sandra P. D’Angelo, MD**
- **Presented at: 2018 ASCO Annual Meeting**
- **Presented by: Sandra P. D’Angelo, MD**
- **#ASCO18**

**Keywords:**
- AL101
- Z-endoxifen
- Dose determination
- Toxicity
- Biomarker
- Efficacy
- Next steps/ongoing studies
Unknown
FAP
Pregnancy
Trauma

Anti-
estrogen

NSAIDS

NOTCH
inhibitor

Desmoid
Inflammation
& Release of
cytokines

Activation of mutated
MSC_{APC/CTNBB1}

Recruit
endothelial cells

Sorafenib

Recruit
normal fibroblasts

Differentiate and
proliferate to myo/
fibroblast

Chemo

1. Recruitment of
normal fibroblasts
2. Differentiate and
proliferate to myo/
fibroblast

Gounder M, Cancer 2015
Conclusions

Well designed, interesting data that warrant further study in specific patient population
- AL101/Z-endoxifen: Predictable pK, manageable toxicity, signal of activity

Biomarker work will be important to tease out appropriate patient population
(? FES PET, ? Wnt/notch signaling)

For desmoid tumors
- AL101: responses are encouraging and not surprising, but small numbers
- Z-endoxifen: prolonged disease stability, no responses
- Tumor biology vs true drug effect