Children’s Oncology Group
AREST1921
Phase 2 Study of a γ-Secretase Inhibitor, Nirogacestat (PF-03084014), in Children and Adolescents with Progressive, Unresectable Desmoid Tumors

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Desmoid Tumors

• Wide range of behaviors
  – Spontaneous regression, stable to rapidly growing
  – Low potential to metastasize, but can be locally aggressive

• Most have mutation in β-catenin and less commonly in APC gene (regulator of β-catenin)

• Treatment
  – Surgery (first line, if feasible)
  – Radiation
  – Ablation techniques
  – Systemic therapy: cytotoxic chemotherapy, anti-estrogen, NSAIDS, hydroxyurea, tyrosine kinase inhibitors (e.g. sorafenib), and recently γ-secretase inhibitor
Notch Signaling

- Inhibit differentiation
- Promote survival
- Accelerate proliferation

Borggreffe et al. Biochimica et Biophysica Acta 2016
Nirogacestat (PF-03084014)

- Potent, selective, reversible inhibitor of γ-secretase at IC50 < 10 nM
  - Initially developed for Alzheimer’s Disease
    - Development stopped due to poor CNS penetration
- Growth inhibition in xenograft models of T-ALL, pancreatic CA, breast CA, CRC
- Initially developed by Pfizer/Pfizer Cures, now Springworks Therapeutics
Adult Phase I Study with Dose Expansion Cohort

- Relapsed solid tumors, including desmoid tumors
- 64 patients enrolled
  - 41 patients in dose-finding
- Tested doses range of 20-330 mg PO BID in 21 day cycles
- 3+3 design

Messersmith et al. CCR 2014
## DLTs by Dose Level
### Adult Phase I

<table>
<thead>
<tr>
<th>Dose (mg BID for 21d)</th>
<th>No. Patients Evaluable for DLT</th>
<th>DLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>40</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>80</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>100</td>
<td>6</td>
<td>Grd 4 analphylaxis</td>
</tr>
<tr>
<td>130</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>150</td>
<td>6</td>
<td>Grd 3 diarrhea</td>
</tr>
<tr>
<td>220</td>
<td>6</td>
<td>Grd 3 diarrhea</td>
</tr>
<tr>
<td>330</td>
<td>2</td>
<td>Grd 3 rash(1); Unable to complete 80% dose due to palpitations (grd 1) and mouth pain (grd 1)</td>
</tr>
</tbody>
</table>

MTD: Maximum Tolerated Dose, RP2D: Recommended Phase 2 Dose
## Treatment-related AE in ≥5% Patients
### Adult Phase I

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All grades n (%)</th>
<th>Grade 3 n (%)</th>
<th>Grade 4 n (%)</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>↓ PO4</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</td>
<td>13 (20.3)</td>
<td>2 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</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>↓ Potassium</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>
Desmoid Tumors:
5 of 7 with PR; 2 SD
Median time to response = 11.9 mo (range, 2.5-21.4)
Duration of Response = 48 and 73+ months

Messersmith et al. CCR 2014
Nirogacestat: Adult Phase II

- Single institution (NCI)
- Inclusion:
  - Age ≥ 18 years
  - Desmoid tumor not amenable to surgery or RT and PD with at least one line of standard therapy
- 17 patients enrolled (16 evaluable for response)
  - Median age 34 years (range 34 – 69)
- 150 mg BID in 21 day cycles
- Response by RECIST after 3 weeks then every 18 weeks

Kummar et al. JCO 2017
Tumor Response and Mutation Status

- 5 PR (29%)
- 11 SD (5 prolonged)
Future Development

• Adult randomized phase 3 study
  – Age ≥ 18 years

• Phase 2 pediatric study through the Children’s Oncology Group
## Pediatric Clinical Trials in Desmoid Tumors

<table>
<thead>
<tr>
<th></th>
<th><strong>POG 9650</strong> Skapek et al. JCO 2007</th>
<th><strong>COG ARST0321</strong> Skapek et al. PBC 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>VBL/MTX (52 weeks)</td>
<td>Tamoxifen/Sulindac (12 mo)</td>
</tr>
<tr>
<td><strong>Duration of study</strong></td>
<td>8/1997-2/2001 (35 mo)</td>
<td>2004-2009 (63 mo)</td>
</tr>
<tr>
<td><strong>No. of patients enrolled</strong></td>
<td>28 (27 eligible)</td>
<td>70 (59 eligible)</td>
</tr>
<tr>
<td><strong>Median age in years</strong></td>
<td>11.5 (0.6-20.5) (at enrollment)</td>
<td>13 (&lt;1-18) (at diagnosis)</td>
</tr>
<tr>
<td><strong>2-yr PFS (range)</strong></td>
<td>46 % (25-65)</td>
<td>36% (23-48)</td>
</tr>
<tr>
<td><strong>Tumor response (%)</strong></td>
<td>26 evaluable</td>
<td>59 evaluable</td>
</tr>
<tr>
<td><strong>CR+PR</strong></td>
<td>19 % (CI: 6.6 – 43.7)</td>
<td>8%</td>
</tr>
</tbody>
</table>
Primary Objectives

• To determine the objective tumor response rate of Nirogacestat in children with progressive, surgically unresectable desmoid tumors

Secondary Objective

• To estimate the 2-year PFS rate
• To describe the toxicities of Nirogacestat in children and adolescents
• To characterize the PK of Nirogacestat in children and adolescents
Inclusion Criteria

- Age at enrollment 12 month to < 18 years
- Primary or recurrent desmoid tumor not amenable to surgery without significant morbidity and demonstrating progression in the past 12 months
- Measureable disease by WHO criteria
- Able to swallow tablets
- No prior γ-secretase inhibitor or anti-NOTCH receptor antibody
Treatment Plan

- Nirogacestat 90 mg/m²/dose PO BID daily (Adult RP2D, assuming adult BSA 1.7 m²)
- One cycle = 28 days
- Disease evaluation at baseline then following every 3 cycles
- Therapy will continue until evidence of disease progression or unacceptable toxicity
Statistical Considerations

• Primary Endpoint: Overall Response Rate
  – Target response rate (CR+PR) by WHO criteria of 30%; no worse than 10%
• Estimated sample size: 28 evaluable patients
• Estimated duration of study: 3.5 years
Exploratory Objectives

• To explore the relationship between patient reported outcomes (PROs) and tumor response and PFS
• To compare assessment of tumor response using WHO criteria with RECIST 1.1 and T2 and volumetric changes using MRI
• Correlative biology studies
Correlative biology studies

- Mutational analysis for CTNNB1 and APC genes
- Genetic profiling of archival tumor samples
- Assess changes in NOTCH and WNT pathway-related signaling genes in peripheral blood cells at baseline, during treatment and at the time of progression
- Assess effect of nirogacestat on immune cells, chemokines and cytokines

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Thank you
Questions/Comments