Selumetinib for the Treatment of NF1 Plexiform Neurofibromas

Brigitte Widemann, M.D.
Pediatric Oncology Branch
National Cancer Institute
Center for Cancer Research
Neurofibromatosis Type 1 (NF 1)

- Most common single gene disorder (1:3500)
  - Neurofibromin, 17q11.2, tumor suppressor gene
- Cutaneous stigmata:
  - Café au lait macules, cutaneous neurofibromas, skin freckling
- Tumor development:
  - Plexiform neurofibromas (PN)
  - Malignant peripheral nerve sheath tumors (MPNST)
  - Optic pathway and low-grade gliomas
  - Leukemias (JMML)
- Organ manifestations:
  - Skin, CNS, peripheral nerves, cardiovascular, gastrointestinal, endocrine, skeletal, growth, hematological
Plexiform Neurofibromas (PN)

- Involve multiple nerve fascicles/branches (50%)
  - Schwann cells, fibroblasts, mast cells, highly vascular
- Congenital, slow growth, large size, complex shape
- Disfigurement, pain, functional impairment, life-threatening
- Transformation to malignant peripheral nerve sheath tumor (MPNST) (15.8%)
- Surgical resection only standard treatment

Medical treatment may reduce morbidity and prevent MPNST
Plexiform Neurofibromas (PN)

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NF1 Natural History

Knowledge of the natural history of PN required for meaningful clinical trials
  • NCI NF1 Longitudinal Natural History Trial:
    • Detailed standardized clinical evaluations
    • MRI evaluations to evaluate tumor burden
    • Development of morbidity

Reproducible and sensitive measurement of PN to assess activity in clinical trials
  • Development and validation of volumetric MRI analysis of NF1 PN

Novel trial designs
  • Randomized, double-blind, placebo control, cross-over
  • Target improvement in progression free survival

Novel endpoints are required to measure efficacy
  • Patient reported outcomes, appearance, functional assessments
  • Response Evaluation in Neurofibromatosis and Schwannomatosis international working group (REiNS)
Morbidity Plexiform Neurofibromas

- Difficulty measuring change in PN size (complexity, slow growth)
- WHO/RECIST not applicable

Cord compression

Pain, disfigurement, dysfunction
Volumetric MRI Analysis: MEDx

STIR Sequence

Define Border

Histogram Analysis

Final Tumor Border

Pixel signal intensity

Pixel number

Threshold

Volume 91 ml

Solomon, J. et al., Comp. Med. Imaging and Graphics, 2004
Age Dependent Growth of Plexiform Neurofibromas

- Measurable PN Growth
- Percent PN change

3 years old
5 years old
16 years old
21 years old

Measurable PN Growth ↑ 20%

Time (Months)
Relationship of PN Growth Rate and Age

• PN grow most rapidly in young patients
• PN growth ≥20% per year is rare in ≥ 15 year-old patients

Dombi E...Widemann B. Neurology 2007.  Akshintala S. in submission
Phase II Trial Farnesyltransferase Inhibitor Tipifarnib

Double-blinded, placebo-controlled, flexible cross-over

Dose and schedule: 200 mg/m^2 PO BID x 21d q 28 d

Endpoint: Time to progression (PN volume \( \uparrow \geq 20\% \))
Progression Free Survival Phase A and B

- Placebo (n=47): 13 mo.
- Tipifarnib (n=53): 18.2 mo.
Median Time to Progression (Phase A)

60 Patients

- 1D RECIST
- 2D: WHO
- 3D: 14.3 months
- 3D: 52.5 months

PFS (%)

TTP (months)
Phase II Trials for Progressive PN

Objective to improve progression free survival

- **Tipifarnib (N=31)**: 19.2 months
- **Pirfenidone (N=36)**: 13.2 months
- **Sirolimus (N=49)**: 15.4 months
- **PEG-Intron (N=30)**: 22.6 months
- **Placebo (N=29)**: 10.6 months

PN volume decrease ≥20% in 2/146 (1.4%) patients
Phase I Trial of Selumetinib (AZD6244) in NF1 PN

Specific MEK inhibitor

Objectives:
- MTD: Cycles 1-3 (1 cycle = 28 days)
- Pharmacokinetics; 3D MRI of PN

Eligibility:
- Children 3-18 y/o with NF1 and inoperable PN

Results:
- 24 patients: median age 10.9 years (3-18 years)
- Median PN volume: 1205 mL (29-7,210 mL)
- MTD: 25 mg/m²/dose (60% of adult MTD)
- DLTs: CK ↑, cellulitis, rash, LVEF ↓, all reversible
- Most frequent AEs: Acneiform rash, CK ↑, GI

Dombi E…Widemann B. NEJM, 2016
Phase I Trial NF1 PN: MEK Inhibitor Selumetinib

- **Confirmed partial response:** 17 of 24 patients (71%)
- **Continue on study:** 19 of 24 patients after median of 30 (23-56 cycles)

Dose level 1: 20 mg/m²

Dose level 1.5: 25 mg/m²

Dose level 2: 30 mg/m²

**Baseline, Cycle 5, Cycle 10**

**Volume decrease progressive PN**

Anecdotal clinical improvement:
Appearance, motor function, pain

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Best response (cy. #)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>46 46 28 22 22 22 10 16 22 22 10 10 5 16 22 22 10 16 28 16 5 5 10 5</td>
</tr>
</tbody>
</table>
Completed Phase II Studies for Progressive PN

Selumetinib improves PFS

- Placebo (N=29): 10.6 months
- Tipifarnib (N=31): 19.2 months
- Pirfenidone (N=36): 13.2 months
- Sirolimus (N=49): 15.4 months
- PEG-Intron (N=30): 22.6 months
- Selumetinib (N=9): Median cycle number 26 (23-46)
Continuous Selumetinib Required for Sustained Response

Baseline: 7210 ml
Cycle 5: 5479 ml (-24%)

Drug held for LVEF decrease
Drug restarted at reduced dose

Patient 7

Graph showing the comparison of different treatments over time in terms of plexiform neurofibroma volume.
Preclinical Trials in NF1 *DhhCre;Nf1fl/fl*
Mouse Neurofibroma Model

Mouse PN

Human PN

Vehicle control
Selumetinib 10 mg/kg

PN volume (mm$^3$)

Percent Change in PN Volume


Jessen ...Ratner. JCI, 2012
# PN Phase II Trials of Selumetinib

## Eligibility

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Pediatric Registration Study</th>
<th>Adult Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-18</td>
<td>2-18</td>
<td>&gt;18</td>
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</table>

## Primary objective

- Confirmed response rate by volumetric MRI

## Secondary objectives

### PRO: Pain, QOL, function

- All patients

### Disfigurement

- All patients with visible PN: Photography / video

### Function

- All patients based on PN location: Orbit, airway, motor, bowel, bladder, other

### PK, PD: Cytokine, PBMC

- All patients pre selumetinib and on treatment

### Study specific

- Long term safety
- Bone mineral density
- Optic glioma
- Paired biopsy: PN, DNF, pERK, pAKT, pMEK, kinome, transcriptome, PDX, immune infiltrate

### Target response rate / pts.

<table>
<thead>
<tr>
<th>Pediatric study</th>
<th>Adult Study</th>
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<tr>
<td>36%, 50 patients (stratum 1)</td>
<td>45%, max 35 patients (two-stage design)</td>
</tr>
</tbody>
</table>

- Pediatric study completed enrollment in stratum 1 in September 2016
- Plan for data submission to FDA 2018
Patient Example: 8 y/o Boy with Motor / Airway PN

Baseline pain: on pain medication

<table>
<thead>
<tr>
<th>Specific Evaluations Based on PN Location/Morbidity:</th>
<th>Form Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orbital PN</strong></td>
<td></td>
</tr>
<tr>
<td>☐ Ophthalmologic functional evaluations</td>
<td>☐ Appendix VII</td>
</tr>
<tr>
<td><strong>Airway PN</strong></td>
<td></td>
</tr>
<tr>
<td>☑ Sleep study</td>
<td>☐ Appendix VIII</td>
</tr>
<tr>
<td>☑ PFTs/Oscillometry</td>
<td>☐ Appendix VIII</td>
</tr>
<tr>
<td>☑ Endurance evaluation: 6-Minute Walk-Run Test</td>
<td>☐ Appendix IXA</td>
</tr>
<tr>
<td><strong>Motor PN (Lower Extremity)</strong></td>
<td></td>
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<tr>
<td>☐ Strength evaluation</td>
<td>☐ Appendix IXB</td>
</tr>
<tr>
<td>☑ ROM evaluation</td>
<td>☐ Appendix IXC</td>
</tr>
<tr>
<td>☑ Leg length evaluation</td>
<td>☐ Appendix IXD</td>
</tr>
<tr>
<td>☑ Endurance evaluation: 6-Minute Walk-Run Test</td>
<td>☐ Appendix IXA</td>
</tr>
<tr>
<td>☐ PROMIS</td>
<td></td>
</tr>
<tr>
<td><strong>Motor PN (Upper Extremity)</strong></td>
<td></td>
</tr>
<tr>
<td>☑ Strength evaluation</td>
<td>☐ Appendix IXB</td>
</tr>
<tr>
<td>☑ ROM evaluation</td>
<td>☐ Appendix IXC</td>
</tr>
<tr>
<td>☑ Grooved Pegboard Test (Age ≥5 years)</td>
<td>☐ Appendix IXE</td>
</tr>
<tr>
<td>☑ PROMIS</td>
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<tr>
<td><strong>Bowel/Bladder PN</strong></td>
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<tr>
<td>☐ Bowel/Bladder Questionnaire</td>
<td>☐ Appendix X</td>
</tr>
<tr>
<td><strong>Visible PN, Disfigurement (or Potential Disfigurement)</strong></td>
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### Comprehensive Response Evaluation

#### Baseline vs Pre Cycle 5

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Baseline</th>
<th>Pre Cycle 5</th>
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<tbody>
<tr>
<td>Neck extension</td>
<td>42</td>
<td>70</td>
</tr>
<tr>
<td>Neck lateral flexion</td>
<td>10</td>
<td>61</td>
</tr>
<tr>
<td>Shoulder abduction</td>
<td>75</td>
<td>180</td>
</tr>
<tr>
<td>Internal/external rotation</td>
<td>46/42</td>
<td>90/84</td>
</tr>
<tr>
<td>Strength (Trapezius)</td>
<td>4+ pain</td>
<td>5</td>
</tr>
<tr>
<td>Pain meds: Ibuprofen</td>
<td>BID</td>
<td>-</td>
</tr>
<tr>
<td>Pain intensity (0-10)</td>
<td>3</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Pain interference patient (0-6)</td>
<td>2</td>
<td>2.16 (0.33)</td>
</tr>
<tr>
<td></td>
<td>3.66</td>
<td>1.33 (0.33)</td>
</tr>
<tr>
<td>Pain interference parent (0-6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global impression of change</td>
<td>-</td>
<td>Much improved</td>
</tr>
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#### 3D MRI Analysis
- Decrease: 25%