NCI IRP Neurofibromatosis Type 1 (NF1) Program

Brigitte Widemann, M.D.
Neurofibromatosis Type 1 (NF 1)

- Common single gene disorder (1:3500), prototype RASopathy
  - Neurofibromin, 17q11.2, RAS pathway activation
- Cutaneous stigmata:
  - Café au lait macules, cutaneous neurofibromas, skin freckling
- Tumor development:
  - Plexiform neurofibromas (PN)
  - Atypical neurofibroma (AN)
  - 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
<table>
<thead>
<tr>
<th>NF1 Peripheral Nerve Sheath Tumors</th>
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</table>
| **Cutaneous**  
≥ 95% | **Plexiform**  
25-40% | **Atypical**  
Unknown ? | **MPNST**  
15.8% |

- Appearance, pruritus
  Biallelic loss of *NF1*

- Appearance, pain, function loss
  Biallelic loss of *NF1* + loss of *CDKN2A/B* + loss of PRC2, p53, (and others)

⇒ Malignant transformation
NF1 Gene Identified  
Dr. Francis Collins

Semi-Automated Volumetric MRI for measuring PN  
NCI POB  
Dr. Brigitte Widemann

Tipifarnib Clinical Trial

PEG-Interferon Clinical Trial

Sorafenib & Sirolimus Clinical Trials Open

Selumetinib Pediatric Clinical Trial Opens

Selumetinib Adult Clinical Trial Opens

Phase 2 Selumetinib Study Results Presented at ASCO

FDA Grants Selumetinib Breakthrough Therapy Designation

POB NF1 Natural History Study Opened

Successful Mouse Study of Selumetinib in Plexiform Neurofibromas  
Collaboration with Cincinnati Children's Hospital

NEJM Publication of Successful Phase 1 Selumetinib Trial Results

NCI Intramural Program Contributions to NF1 PN Research
Plexiform Neurofibromas (PN)

- Histologically benign, biallelic loss of *NF1*
  - Schwann cells, fibroblasts, mast cells, perineurial cells, highly vascular
  - Involve multiple nerve fascicles/branches
- Congenital, slow growth, large size, complex shape
- Disfigurement, pain, functional impairment, life-threatening
- Transformation to malignant peripheral nerve sheath tumor (MPNST) (10-15%)
- Surgical resection only potentially curative treatment
MRI Volume Measurement of Plexiform Neurofibromas

Solomon, J. et al., Comp. Med. Imaging and Graphics, 2004
Volumetric MRI Analysis to Measure PN

- More sensitive and reproducible than standard solid tumor response criteria
- Progression:
  - ≥ 20% increase in PN volume
- Response:
  - ≥ 20% decrease in PN volume
- Central response evaluation on national multi-site trials

Dombi E … Widemann B: Neurology 2013
Characterization of Plexiform and Atypical Neurofibromas

- Identification of **Distinct Nodular Lesions**
- PN grow most rapidly in young children
- DNL grow independently of age
- Many DNL are atypical neurofibromas

Development of atypical neurofibroma (AN) transforming to MPNST

Akshintala S...Dombi E*, Widemann B*, submitted
Phase II Trial of Tipifarnib for Children with PN

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

Phase A
- Tipifarnib
- Placebo

Phase B
- Tipifarnib
- Placebo

START OF STUDY

END OF STUDY

Widemann B. et al.: J Clin Oncol 2006; Neuro Oncology 2014
Phase II Trial of Tipifarnib for Children with PN

Tipifarnib does not improve PFS

3D analysis to assess progression

No PN volume decrease ≥20% on placebo or tipifarnib arms

Widemann B. et al.: J Clin Oncol 2006; Neuro Oncology 2014
Phase I Trial: MEK Inhibitor Selumetinib in Children with NF1 PN

- NCI CTEP sponsored, POB coordinated, multi-site
- Primary objective: Maximum tolerated dose
- Results:
  - MTD 25 mg/m² PO BID continuous dosing
    - (60% adult recommended dose)
  - Partial response 17/24 (71%) patients
  - Anecdotal clinical benefit

Dombi E….Widemann B., NEJM 2016
# Phase II Registration Trial of Selumetinib for PN

## Study

<table>
<thead>
<tr>
<th>Stratum I (≥ 1 PN morbidity)</th>
</tr>
</thead>
</table>

## Eligible Ages (years)
2-18

## Primary objective
Confirmed response rate 3D MRI

## Target response rate
36%, 50 patients

## Secondary objectives

### PRO/ObsRO
Pain, QOL (≥ 8 years old), Function

### Disfigurement
Patients with visible PN:
Photography / video

### Function
Based on PN location:
Orbit, airway, motor, bowel, bladder, other

### PK, Cytokine, PBMC
Baseline and on treatment

## Long term safety
5-7 years
Example: Complexity of Functional Evaluations

8 y/o with left neck, arm, airway PN

**Airway PN**
- Sleep study
- PFTs/Oscillometry
- Endurance evaluation: 6-Minute Walk-Run Test

**Motor PN (Upper Extremity)**
- Strength evaluation
- ROM evaluation
- Grooved Pegboard Test (Age ≥ 5 years)
- PROMIS

**Visible PN, Disfigurement (or Potential Disfigurement)**
- Photography
- +/- Video

MRI, PRO, functional evaluation, photography every 4 cycles during first year
SPRINT Phase II: Best Response through June 29, 2018

- Enrollment stratum 1: 50 patients 8/2015-8/2016
- Median age: 10.3 years (3.5-17.4)
- Median target PN volume: 487.5 mL (5.6-3820)
  - 21 progressive, 15 non-progressive PN
- Median number of PN morbidities:
  - 3 (1-5); Disfigurement (n=44), motor (n=33), pain (n=26), airway (n=16)

- Partial response (PR):
  - 37/50 (74%)
- Confirmed PR:
  - 34 (68%)
- Durable PR (≥ 1 year):
  - 28 (56%)
- Progressive disease:
  - 4 (8%)

Gross A...Widemann B: NEJM prov. accepted
SPRINT: Improvement in PN Pain and PRO

Pamela Wolters

Gross A...Widemann B: NEJM prov. accepted
SPRINT: Improvement in Functional Morbidities

- Range of Motion
- Strength
- FEV1
- R5
- R20
- Apnea Hypopnea Index
- Bladder
- Bowel

Legend:
- Improvement
- No Change
- Worsening

Number of Patients
Example: Improvement in Airway Function

8 year-old girl with upper airway PN

Baseline Pre-Cycle 13 Pre-Cycle 25

Patient Decannulated

PN volume (ml)

Start of treatment

-25.8%
Example: Improvement in Appearance

10 year-old boy with right neck PN

Baseline  |  Pre-Cycle 13  |  Pre-Cycle 37

Prevention of morbidity: Airway compromise
SPRINT External Control NF1 Natural History Study

Age matched control: **Natural history** and **SPRINT**

![Graph showing progression-free survival](image)

- **Progression Free Survival**
- **Median PFS 1.3 years**

![Graph showing change in target PN](image)

- Change Target PN (%): -60, 0, 50, 100, 150, 200, 250
- Duration of follow-up (years): 0, 0.4, 0.8, 1.2, 1.6, 2.0, 2.4, 2.8
- Percent Without Disease Progression

*SPRINT-red, Natural History (age-matched-blue)*
SPRINT versus Prior Phase II Trials for Progressive PN

Prior studies / SPRINT progressive PN

- Selumet
- PEG-Int
- Sirolimus
- Pirfenidone (N=36) TTP 13.2 M
- Tipifarnib (N=31) TTP 19.2 M
- Placebo (N=29) TTP 10.6 M

Time from start of treatment (months)
Progression Free Survival (%)

Jakacki R, Widemann B. Neuro-Oncol, 2017
Widemann B…Balis F: Neuro-Oncol 2014
Widemann B, Babovic D…Packer R. PBC, 2014
Genetically Engineered Mouse Models of NF1 Neurofibroma Predict for Activity

Ratner Lab
Mouse Neurofibroma DhhCre;Nf1fl/fl

Clapp Lab: Hyperactive RAS SPORE
Use of preclinical trials to evaluate:
• Optimal dose
• Schedule
• Pharmacodynamic effect (pERK)


Clapp lab, unpublished confidential data
Phase II Selumetinib: Adults with Growing or Symptomatic PN

- Treatment: Selumetinib 50 mg PO BID continuous dosing
- Evaluations: Paired tumor biopsies (baseline and pre cycle 2 or 3)
- Simon 2-stage design: Target response rate 45%

<table>
<thead>
<tr>
<th>Patients</th>
<th>(N=21)</th>
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<tbody>
<tr>
<td>Age in yrs., median (range)</td>
<td>33 (18-60)</td>
</tr>
<tr>
<td>Sex: F/M</td>
<td>6 / 15</td>
</tr>
<tr>
<td>Target PN</td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>17</td>
</tr>
<tr>
<td>Solitary Nodular</td>
<td>4</td>
</tr>
</tbody>
</table>

Baseline PN Morbidities

- Pain: 15
- Disfigurement: 14
- Bowel/Bladder: 11
- Other: 6
- Airway: 5
- Vision: 1
- Total: 16

Patients with symptoms:
- Pain: 15
- Disfigurement: 14
- Bowel/Bladder: 11
- Other: 6
- Airway: 5
- Vision: 1
- Total: 16
Selumetinib Adult PN: Activity through October, 2019

<table>
<thead>
<tr>
<th>Best Response</th>
<th>n=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>15 (71%)</td>
</tr>
<tr>
<td>Confirmed PR</td>
<td>12/15</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>4</td>
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<tr>
<td>Non-evaluable</td>
<td>2</td>
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<tr>
<td>Progressive Disease</td>
<td>0</td>
</tr>
</tbody>
</table>

Patient-reported target tumor pain intensity and pain interference scores significantly improved (p<0.002)

Do not post, unpublished preliminary data
Atypical Neurofibromas Are MPNST Precursors

Atypical neurofibroma (AN) characterization:
- 63 patients (32 male, 31 female) with 76 AN
- Median age at diagnosis: 27.7 years (7.6-60)
- Most were FDG avid on FDG-PET (56/57)
- 21/63 (33%) of patients with AN had history of MPNST

Hypothesis: Most MPNST arise from preexisting AN and not directly from PN

Clinical challenge: It is unknown if all and when AN transform to MPNST

Higham C, Legius E*, Widemann B*, Ferner R*: Neuro-Oncology 2018
Strategies to Prevent MPNST

1) MPNST State of the Science Conference:
   - Pathology consensus: Atypical Neurofibromatous Neoplasm of Uncertain Biologic Potential (ANNUBP)
   - Recommendation for surgical resection of AN
     - Marginal resection of AN: Safe and feasible
     - Low recurrence risk

2) Biomarkers for malignant transformation: Key collaborator Dr. Jack Shern
   - Serial blood samples for detection of cell-free DNA
   - Genomic dissection of tumor evolution, single cell sequencing

3) Phase I/II trial of CDK4/6 inhibitor abemaciclib:
   - Children and adults with unresectable pathology confirmed AN

Reilly K…Widemann B, Stewart D: JNCI, 2017
Miettinen M…Widemann B, Perry A: Humpath, 2017
Nelson C…Widemann B, Chittiboina P., J Neurosurg, 2019
Can MEK inhibitors prevent the development of PN related morbidities?

- Develop trial to assess the effect of selumetinib on asymptomatic but growing PN

Trials for other NF1 manifestations?

- NF1 cutaneous neurofibromas (UAB, NCI)
- Low grade gliomas
- Effect of selumetinib on cognitive function (DC Children's, NCI)
- Atypical neurofibromas and MPNST
- Combination studies with other targeted agents

Develop tools for NF1 Trials and Patients:

- Medication adherence
- Patient reported outcomes and patient engagement

Evaluation of MEK inhibitors and other RAS targeted agents in other conditions

- Advancing RAS/RASopathy Therapies (ART)
- Rare pediatric solid tumors
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  - Nancy Ratner, Wade Clapp, Karen Cichoeski
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- Advancing RAS/RASopathy Therapies:
  - Marielle Yohe, Andrea Gross
  - Douglas Stewart, Sharon Savage, NCI DCEG
Selumetinib Reduces Spinal Neurofibroma Burden in NF1

- Spinal neurofibromas (SNF) in NF1:
  - Progressive neurologic deficits and require repeat surgeries
- SNF in children and adults on selumetinib trials:
  - 23 of 56 patients enrolled had SNF extending into the central canal
- On selumetinib improvement in canal distortion, CSF distribution and spinal cord deformity in majority of patients

Jackson S., Widemann B, Dombi E, in preparation