NF1 Related Plexiform Neurofibromas

- **NF1**: 1:3000, autosomal dominant, mutation in *NF1* (17q 11.2)
- **PN**: Histologically benign peripheral nerve sheath tumors (50%)
  - Congenital, slow growth, large size, complex shape
  - Disfigurement, pain, functional impairment, life-threatening
  - Transformation to malignant peripheral nerve sheath tumor (MPNST) (15.8%)
  - Poorly understood natural history
  - No effective medical therapy

11 mo.  17 mo.  25 mo.  36 mo.
PN Grow the Fastest in Young Children

Need to develop therapies for young patients

Dombi E...Widemann B. Neurology 2007, Akshintala S. in submission
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) 29.4 months
- Placebo (N=29): 10.6 months

Objective to improve progression free survival

PN volume decrease ≥20% in 2/146 (1.4%) patients

Weiss, Widemann ...Fisher M. Neuro-Oncology, 2014
Widemann et al.: Neuro-Oncology, 2014
Jakacki ...Widemann. Neuro-Oncology, 2016
Widemann, Babovic...Packer. PBC, 2014
**Phase I Trial of the MEK Inhibitor Selumetinib for Children with NF1 PN**

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

**Dose levels and volumes:**
- **Dose level 1:** 20 mg/m²
- **Dose level 1.5:** 25 mg/m²
- **Dose level 2:** 30 mg/m²

**Volume decrease**
- **Progressive PN**

**Anecdotal clinical improvement:**
- Appearance, motor function, pain

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**Graphs and images:**
- Percent change in PN volume
- Volume decrease over time
- Clinical improvement images

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*Dombi E et al. NEJM, 2016*
Phase 2 Selumetinib in NF1 PN

Multi-Institutional NCI CTEP Sponsored Study

Study Objectives:
- **Primary:** Complete and partial response (PR) rate by volumetric MRI
- **Secondary:**
  - Effect on pain, quality of life, disfigurement and physical functioning
  - Long term safety and tolerability
  - Pharmacodynamics (endothelial progenitors, cytokines)

Eligibility:
- Children 2-18 years old with NF1 and inoperable PN causing morbidity

Selumetinib Administration:
- 25 mg/m²/dose BID continuous dosing (1 cycle = 28 days)

Response Evaluations:
- Volumetric MRI every 4 cycles for 2 years (then every 6 cycles)
34/37 PR were confirmed on consecutive restaging scans (4 months apart)
Clinically and statistically significant improvement in pain and function
Orphan drug designation 9/2018, BTD application in progress
Sample Patient Response

Baseline

Outcome Measure | Baseline | Pre Cycle 13
--- | --- | ---
Neck extension | | 
Neck lateral flexion (L) | 42 | 72
 | 10 | 47
Shoulder abduction (L) | 75 | 180
Internal/external rotation | 46/42 | 90/90
Pain meds: Ibuprofen | BID | -
Pain intensity (0-10) | 3 | 0
Global impression of change | - | Much improved

Start Selumetinib

- 27.7% Volume

Time (months)

Parent: “Better mobility with left arm; less swelling; arm is not as red; he is much more active - wrestles with sister; walking with normal gait--not favoring the right side like he used to do; he is more comfortable plus he sleeps better; clothes fit him better”

Patient: “Can move left arm better now; can wrestle a bit with my sister.”
Pediatric Cancers and RASopathies: Unmet Needs / Challenges

- **RAS pathway activation in pediatric cancers** with poor clinical outcomes
  - KRAS, HRAS, and NRAS mutations
  - RMS, NB, melanoma, MPNST, malignant ectomesenchymoma
  - No effective therapy for RAS mutated cancers

- **RASopathies**: Germline mutations in RAS pathway genes (1:1000 to 1:300,000)
  - NF1, cardiofaciocutaneous-, Noonan-, Costello syndrome, others
  - Manifestations include:
    - Congenital heart disease, failure to thrive, developmental delay
    - Cancer risk (up to 42-fold): Sarcomas, leukemias, CNS tumors
    - Incomplete understanding of the natural history of RASopathies
    - NF1 is the only RASopathy with an effective targeted therapy (MEK inhibition)
Advancing RAS/RASopathy Therapies (ART)

Accelerate understanding of RASopathies / RAS mutated tumors
Develop effective therapies / prevention strategies

1. Optimally utilize resources of the NCI RAS Initiative
2. Development of a RASopathy clinic at the NIH Clinical Center:
   - Natural history study: Patient reported and functional outcomes measures
   - Parallel trials with RAS targeting agents for RASopathies and pediatric cancers with somatic RAS mutations / Ras pathway activation:
     - Tipifarnib for Costello syndrome and HRAS mutated cancers
3. Public health genomics approach to RASopathies:
   - Population genomics: Frequency of pathogenic germline variations in RAS pathway genes linked to electronic health record (Geisinger Health system ≥90,000 exomes)
   - Insights into prevalence, penetrance, phenotypes, and prediction of cancer risk
RAS / RASopathy Collaboration

 population genomically-identified patients with RAS pathway mutations

Phenotypically-identified RASopathy patients

Patient Advocates

Patients with sporadic RAS-driven tumors

NIH Clinical Center
RASopathy Clinic

Oncology Clinic

Pre-clinical/ translational research

NCI RAS Initiative

RASopathy natural history

RASopathy clinical trials

RAS pathway driven tumor clinical trials
The NCI Moonshot Initiative Rare Tumor Patient Engagement Network

MyPART: My Pediatric and Adult Rare Tumor Network

Mission:
To increase patient and patient family involvement in rare tumor research and develop new therapies for rare pediatric and adult solid tumors through increased understanding of tumor biology and natural history

Vision:
Rapid progress and effective therapies for rare tumors

Core Values:
- Commitment to the unmet needs of patients with rare tumors
- Patient-focused approach to cancer research
- Inclusion of underrepresented and minority populations
- Commitment to excellence in patient care and research
- Wide dissemination and timely sharing of research materials and data
Comprehensive Engagement and Analysis of Rare Tumor Patients

Patient Advocacy

Patient Engagement Portal

Repeat sampling over patient trajectory

Access to Data
Clinical Trial Recommendations
Education and Support

Biospecimens from Patient
(and family members when possible)

Outcomes Measures

Clinical History
Family History
Patient reported Outcomes

• Biorepository and database
• Rapid dissemination
• New model systems
Natural History Study of Rare Tumors – Protocol Schema

- Consent to the Natural History Study of Rare Tumors Master protocol (off-site)
  - Collect clinical information, pathology, imaging reports, PRO
  - Multidisciplinary review
    - Provide opinion to patient and physician
    - Molecular/genetic analysis
  - Enrollment on treatment protocol at NCI
  - Enrollment on sub-protocol at NCI
  - Follow up on master protocol off site / at NCI

Sub-Protocols:
- SDH-deficient Tumors (GIST, pheo...)
- Sarcomas (ASPS, LS, DSRCT, SS...)
- Neuroendocrine tumors
- NF1 (PNF, MPNST)
- Chordoma
- Rare Liver Tumors (FLHCC, HB)
- Others: Melanoma, Neuroblastoma
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  - Kara Heisey
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Genetically Engineered Mouse Models of NF1 Neurofibroma Predict for Activity

Ratner Lab

Mouse Neurofibroma $Dhh\text{Cre};Nf1^{fl/fl}$

Clapp Lab

Use of preclinical trials to evaluate:
- Optimal dose
- Schedule
- Pharmacodynamic effect (pERK)

Clapp lab, unpublished confidential data
# Neurofibroma / Nerve Sheath Tumor

<table>
<thead>
<tr>
<th></th>
<th>Dermal ≥ 95%</th>
<th>Plexiform (PN) 25-40%</th>
<th>Atypical (ANF) Unknown?</th>
<th>MPNST 15.8%</th>
</tr>
</thead>
</table>

- **Appearance, pruritus**
- **Appearance, pain, function loss, → Malignant transformation**

- Loss of *NF1* → + *CDKN2A/B* → + *PRC2, P53, others*
NIH Wild-type GIST Clinic: Intramural-Extramural-Advocacy Collaboration

- **GIST**: Connective tissue tumor in the GI tract; *KIT* or *PDGFRA* mutations
- “**Wild-type**” GIST: Lack *KIT* or *PDGFRA* mutations, no effective medical therapies
- **Pediatric and Wild-type GIST Clinic**:
  - Brings patients, clinicians (multidisciplinary expertise), and clinical and basic researchers (intramural – extramural) to NIH
  - Collaborates with patient support groups
  - Obtains clinical history and evaluations
  - Provides expert clinical advice
  - Collects biospecimens for molecular analysis
- **Accomplishments include**:
  - Genomic characterization of wt-GIST:
    - SDH mutations, promotor hypermethylation
  - Increased clinical understanding of wt-GIST
    - Has led to changes in clinical management
  - Clinical trials with targeted agents ongoing:
    - Phase II study of guadecitabine

Janeway...Helman, Stratakis, PNAS, 2011
Miettinen...Helman, Meltzer, Am J Surg Pathol 2013
Killian...Helman, Meltzer, Cancer Dicovery, 2013
Killian...Helman, Meltzer, Sci Transl Med, 2014
Boikos...Helman. JAMA Oncol, 2016
Phase II Selumetinib Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients Enrolled</td>
<td>50</td>
</tr>
<tr>
<td>First/Last Patient Enrolled</td>
<td>August 2015/August 2016</td>
</tr>
<tr>
<td>Median Age at Enrollment, years (range)</td>
<td>10.2 (3.5 – 17.4)</td>
</tr>
<tr>
<td>Sex: Male / Female (n)</td>
<td>30 / 20</td>
</tr>
<tr>
<td>Progression Status of Target PN at Baseline (n)</td>
<td>21 / 15 / 14</td>
</tr>
<tr>
<td>Target PN Classification (n)</td>
<td>45 / 4 / 1</td>
</tr>
<tr>
<td>Median Target PN Volume, mL (range)</td>
<td>487 (5 – 3820)</td>
</tr>
<tr>
<td>Median number of baseline morbidities (range)</td>
<td>3 (1-5)</td>
</tr>
</tbody>
</table>
Statistically and clinically meaningful improvement in:

- Motor function (strength and range of motion) seen between baseline and pre cycle 13 evaluation
- Pain related patient reported outcomes
  - Pain Interference Index
  - Pain Intensity (NRS-11 Scale)
- Analysis of additional functional and PRO measures is ongoing