# NCI IRP N*eurofibromatosis* Type 1 (*NF1*) Program

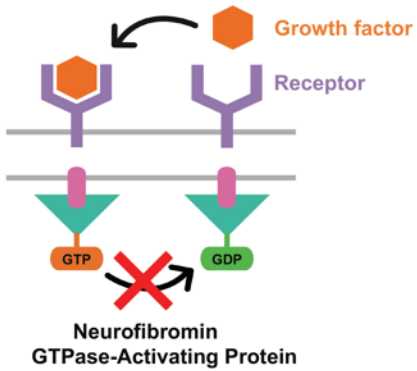
Brigitte Widemann, M.D.

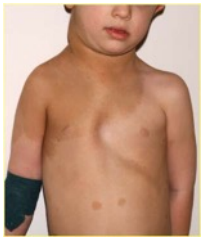
NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

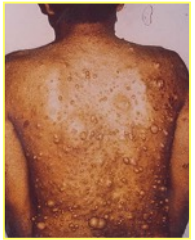
Pediatric ONCOLOGY BRANCH

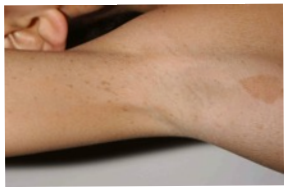
# Neurofibromatosis Type 1 (NF 1)

- 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



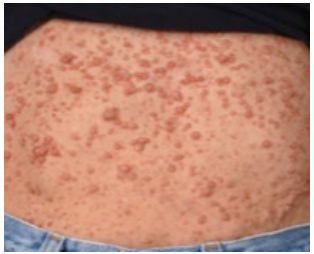
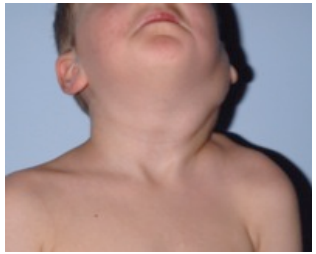
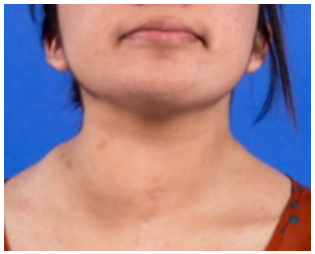
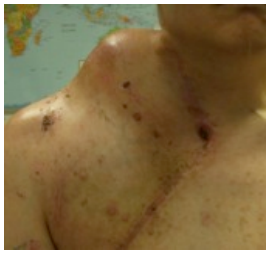
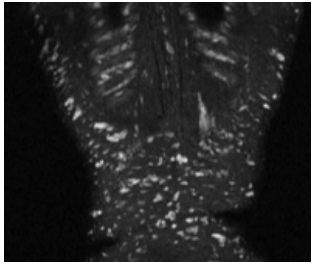
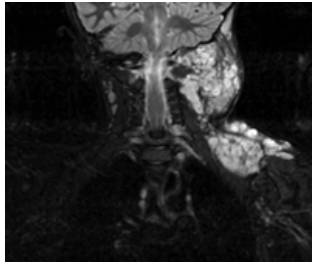
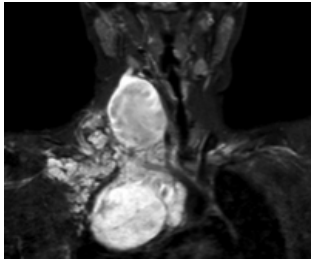
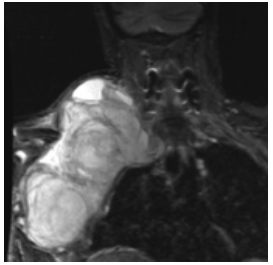
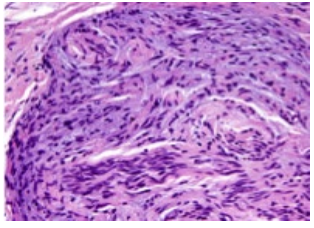
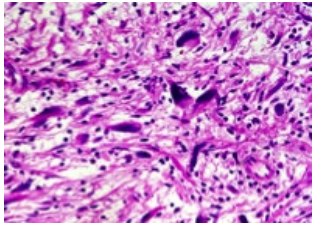
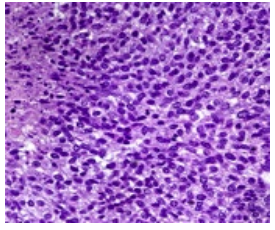







# NF1 Peripheral Nerve Sheath Tumors

| Cutaneous ≥ 95% | Plexiform 25-40% | Atypical Unknown ? | MPNST 15.8% |
|---|---|---|---|

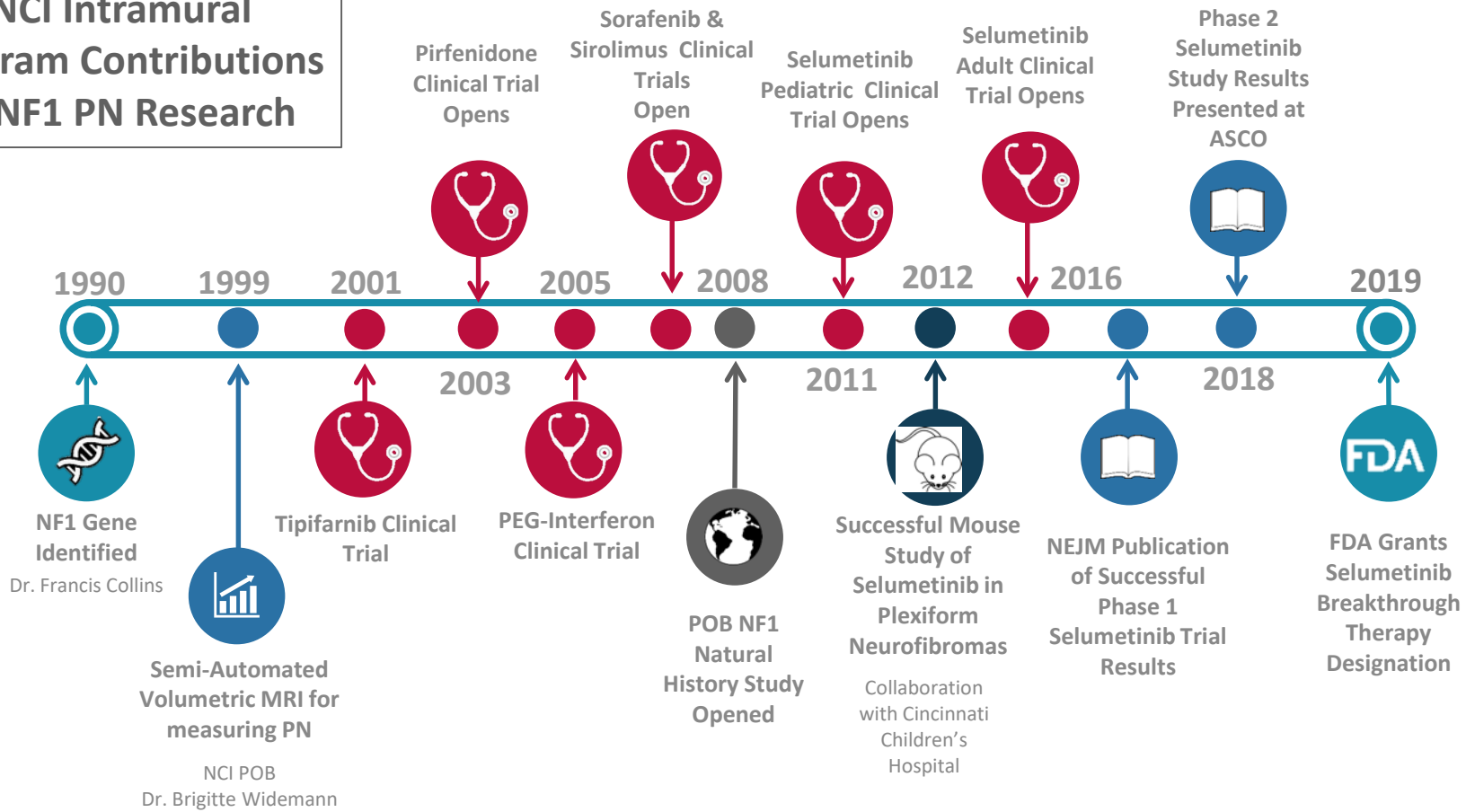
Appearance, pruritus

Biallelic loss of *NF1*

Appearance, pain, function loss ➔ Malignant transformation

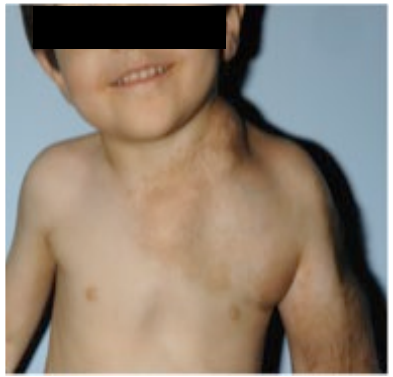
Biallelic loss of *NF1* + loss of *CDKN2A/B* + loss of PRC2, p53, (and others)

# NCI Intramural Program Contributions to NF1 PN Research

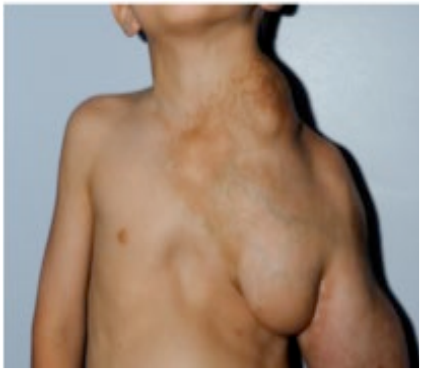


# Plexiform Neurofibromas (PN)

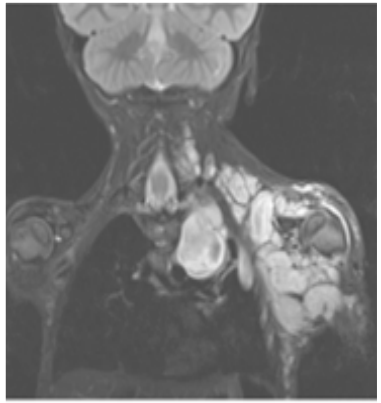
- Histologically benign, biallelic loss of *NF1*
  - Schwann cells, fibroblasts, mast cells, perineurial cells, highly vascular
  - Involve multiple nerve fascicles/branches
- Congenital, slow growth, large size, complex shape
- Disfigurement, pain, functional impairment, life-threatening
- Transformation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



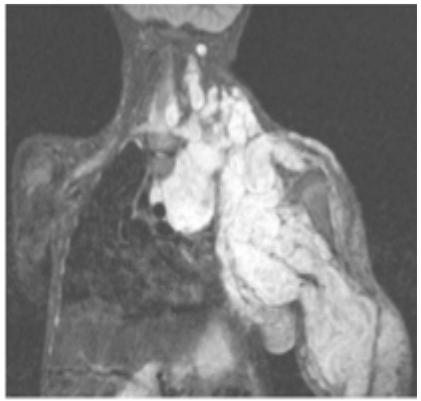
3 years



5 years



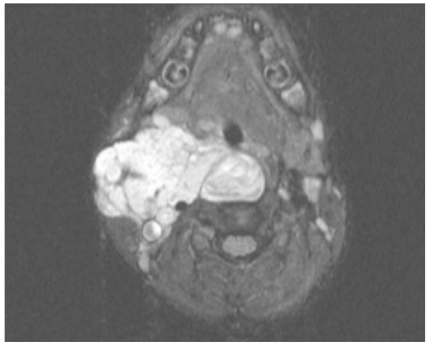
3 years



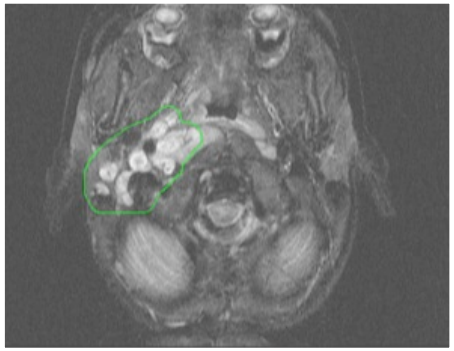
5 years

# MRI Volume Measurement of Plexiform Neurofibromas

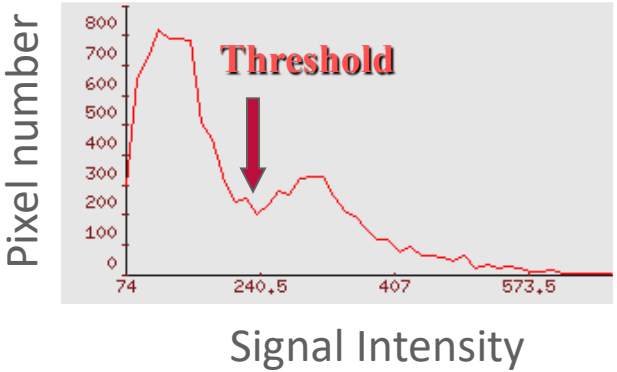
**STIR Sequence**



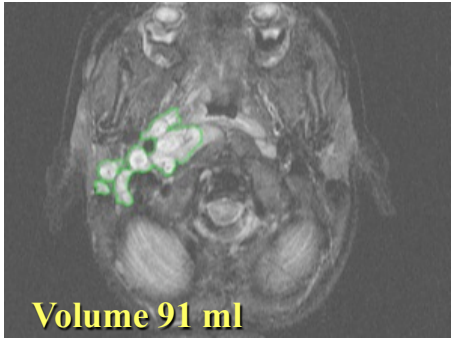
**Tumor Border**



**Histogram Analysis**

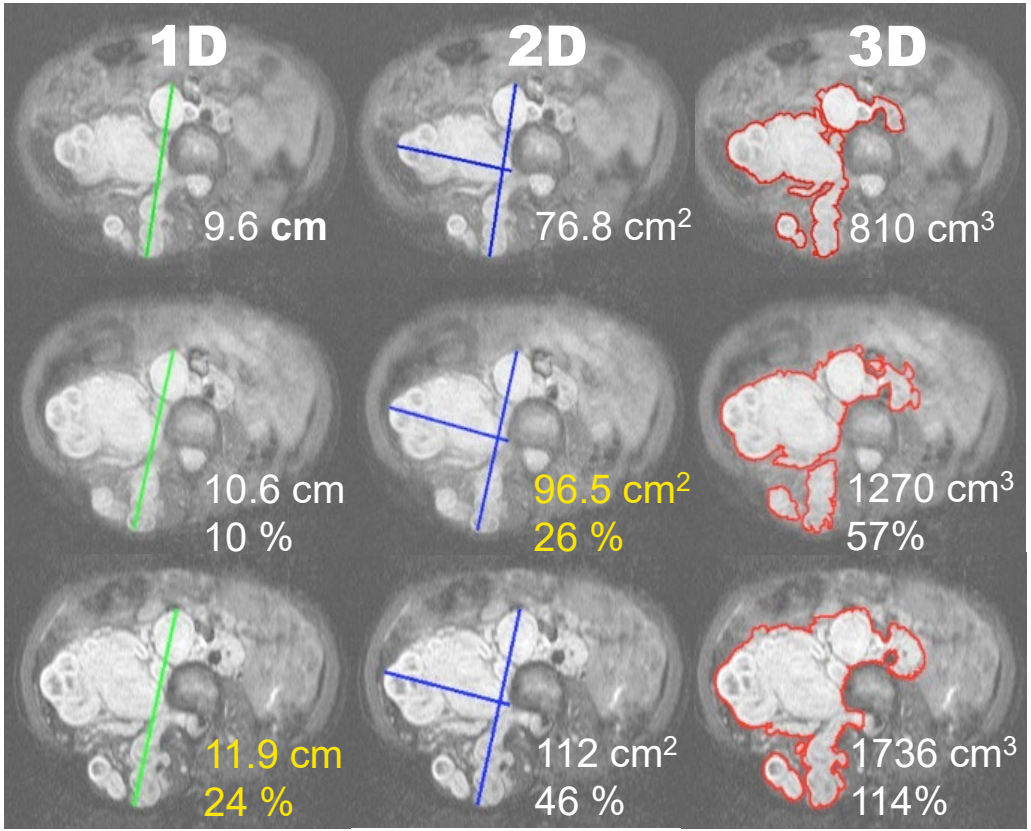



**Tumor Border Identified**




*Solomon, J. et al., Comp. Med. Imaging and Graphics, 2004*

# Volumetric MRI Analysis to Measure PN

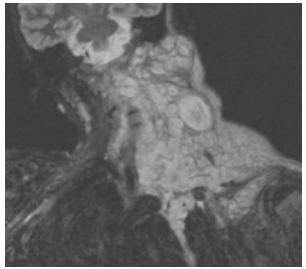


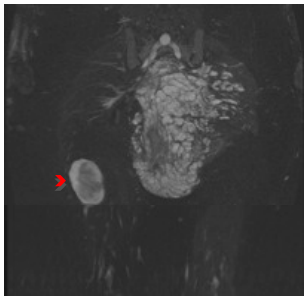

- More sensitive and reproducible than standard solid tumor response criteria
- Progression:
  - ≥ 20% increase in PN volume
- Response:
  - ≥ 20% decrease in PN volume
- Central response evaluation on national multi-site trials

*Solomon J … Widemann B: Comp. Med. Imaging and Graphics, 2004*

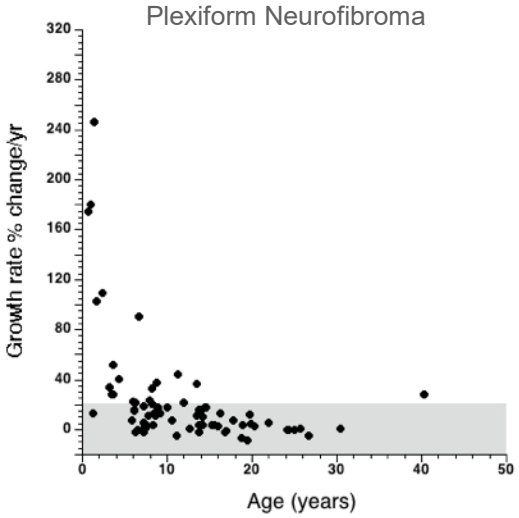
*Dombi E …Widemann B: Neurology 2013*

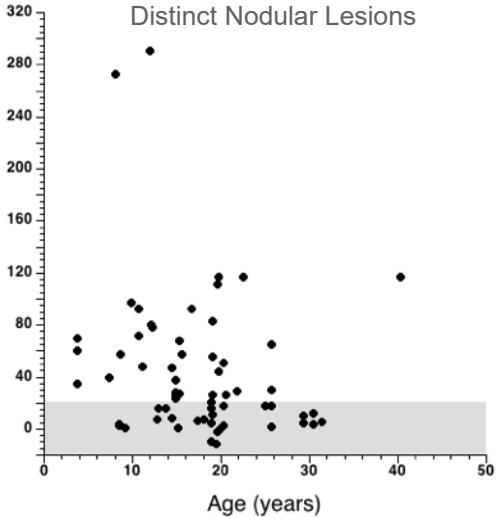
# Characterization of Plexiform and Atypical Neurofibromas



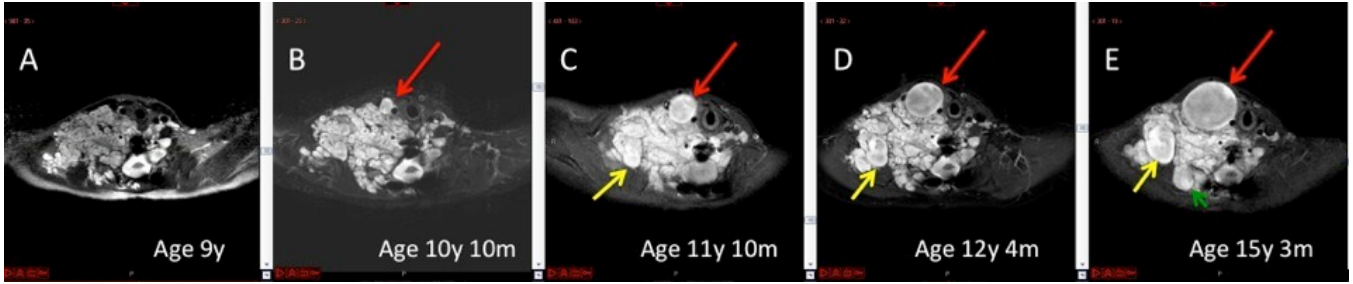


- Identification of **D**istinct **N**odular **L**esions
- PN grow most rapidly in young children
- DNL grow independently of age
- Many DNL are atypical neurofibromas



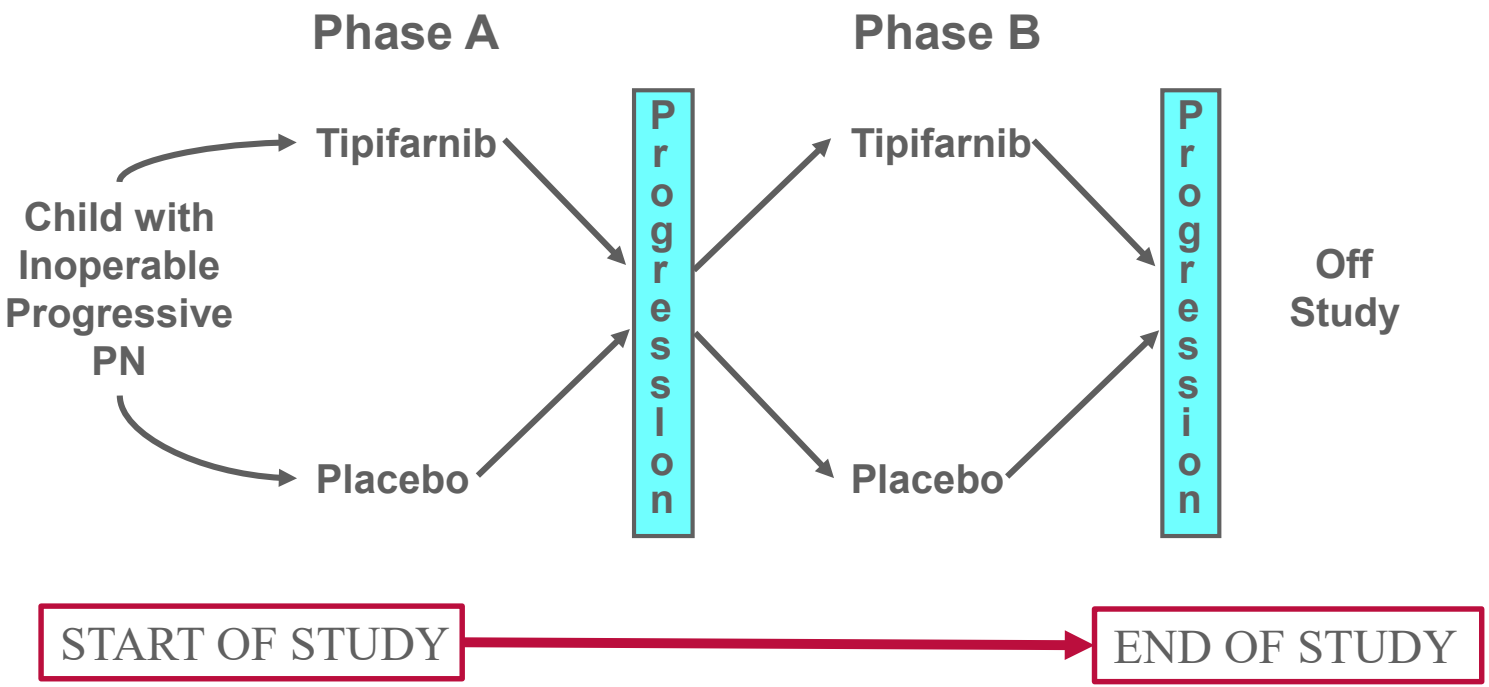

Development of atypical neurofibroma (AN) transforming to MPNST




*Akshintala S…Dombi E*, Widemann B*, submitted*

# Phase II Trial of Tipifarnib for Children with PN

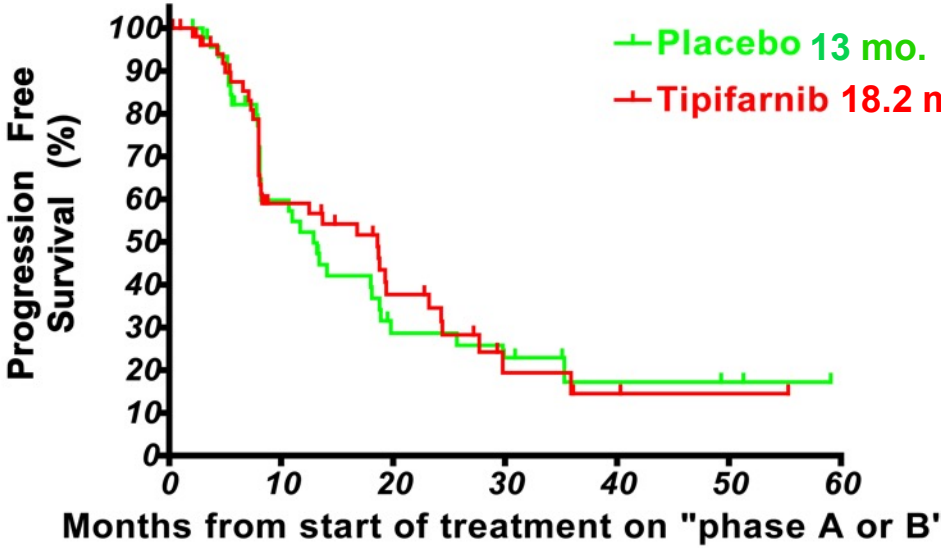
*Double-blinded, placebo-controlled, flexible cross-over*



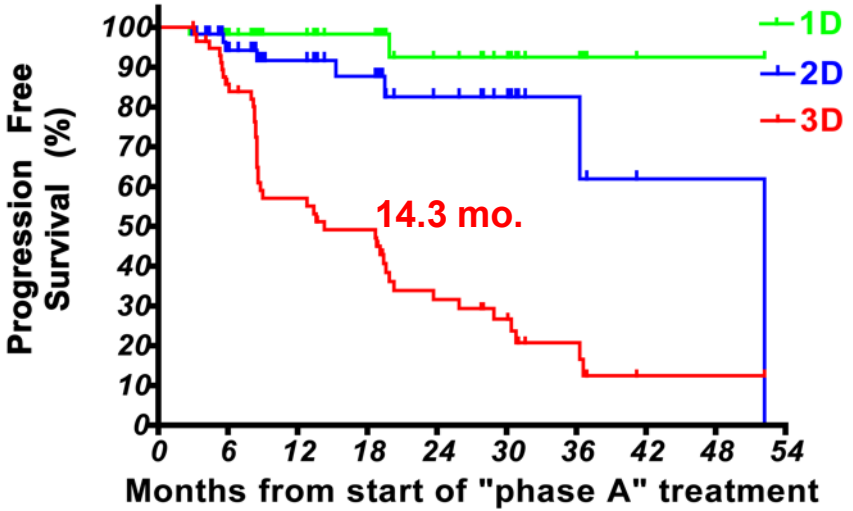

*Widemann B. et al.: J Clin Oncol 2006; Neuro Oncology 2014*

# 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*

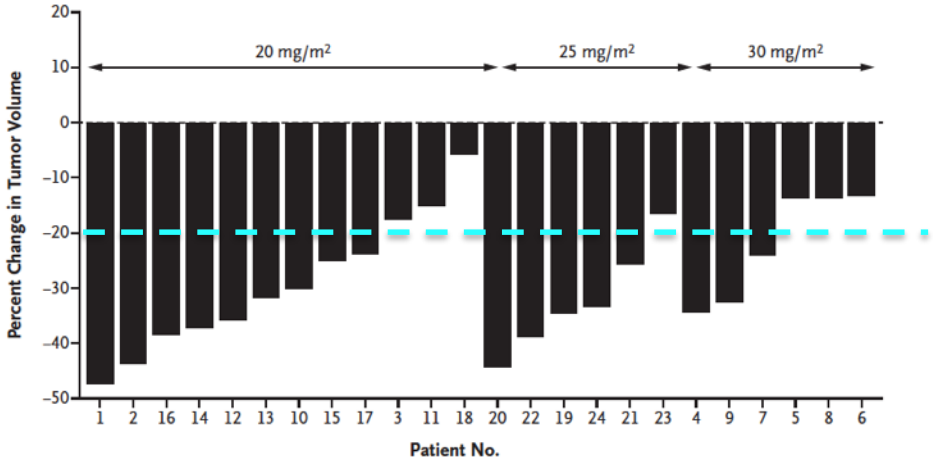
# Phase I Trial: MEK Inhibitor Selumetinib in Children with NF1 PN

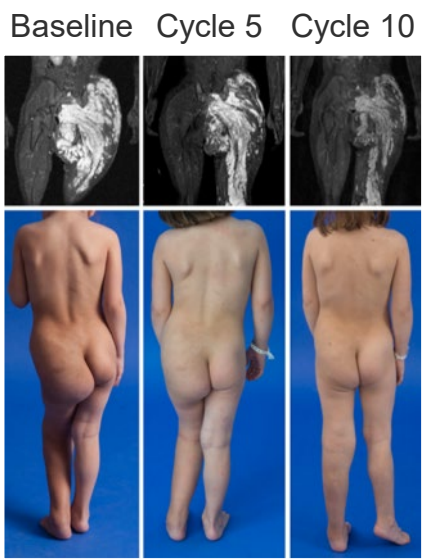
- NCI CTEP sponsored, POB coordinated, multi-site
- Primary objective: Maximum tolerated dose
- Results:
  - MTD 25 mg/m$^2$ PO BID continuous dosing
    - (60% adult recommended dose)
  - Partial response 17/24 (71%) patients
  - Anecdotal clinical benefit

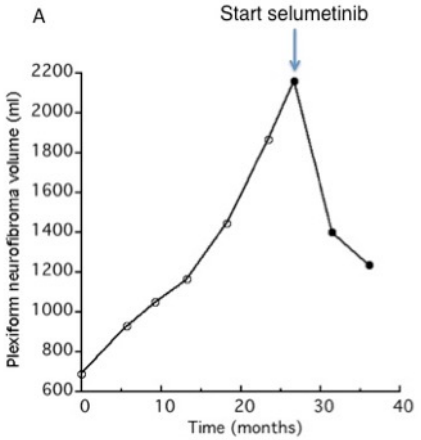
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Activity of Selumetinib in Neurofibromatosis Type 1–Related Plexiform Neurofibromas




*Dombi E….Widemann B., NEJM 2016*

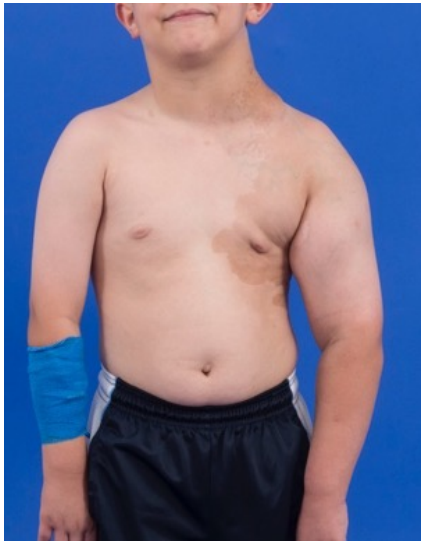
# Phase II Registration Trial of Selumetinib for PN

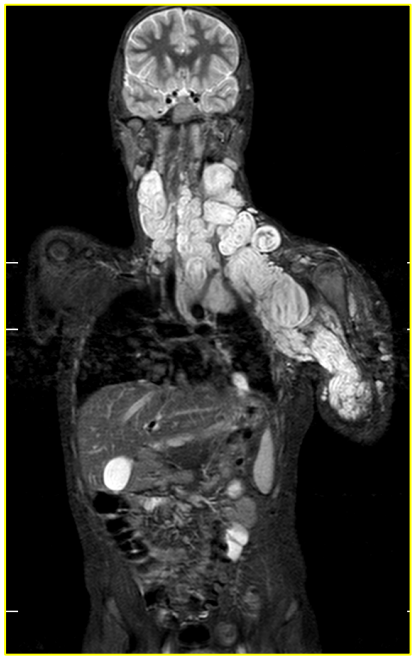
Sprint
Selumetinib in Pediatric Neurofibroma Study

| Study | Stratum I (≥ 1 PN morbidity) |
|---|---|
| **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:<br>Photography / video |
| ***Function*** | Based on PN location:<br>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

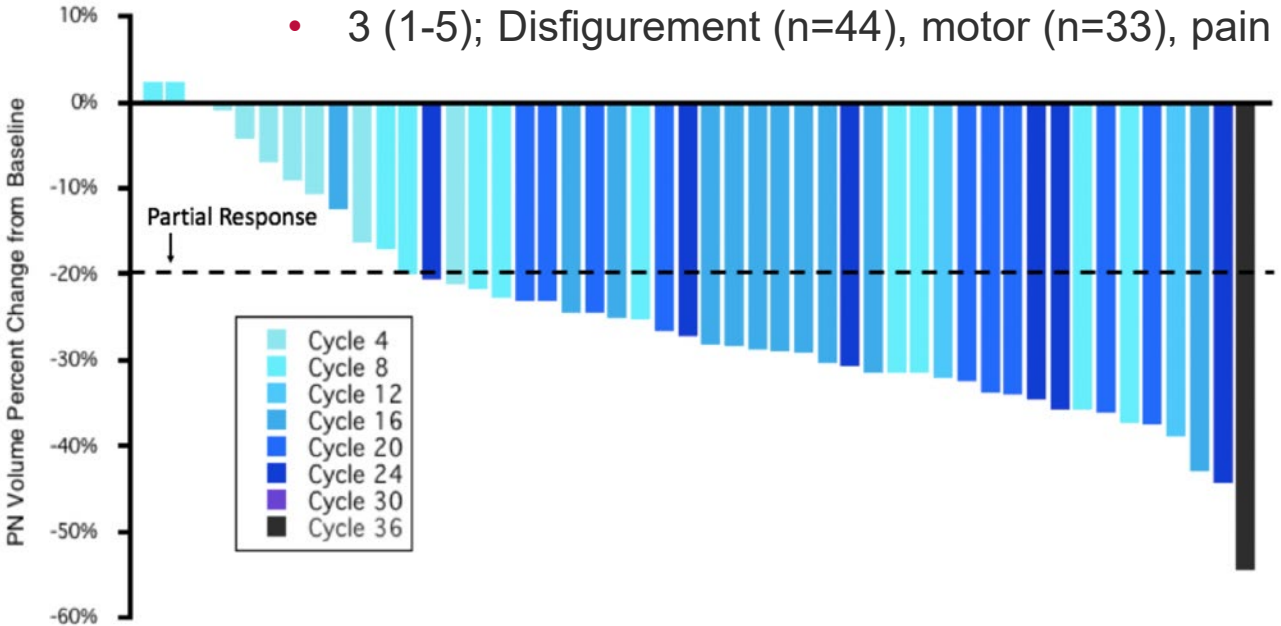
**Motor PN (Upper Extremity)**
- ☐ Strength evaluation
- ☐ ROM evaluation
- ☐ Grooved Pegboard Test (Age ≥5 years)
- ☐ PROMIS

**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%)

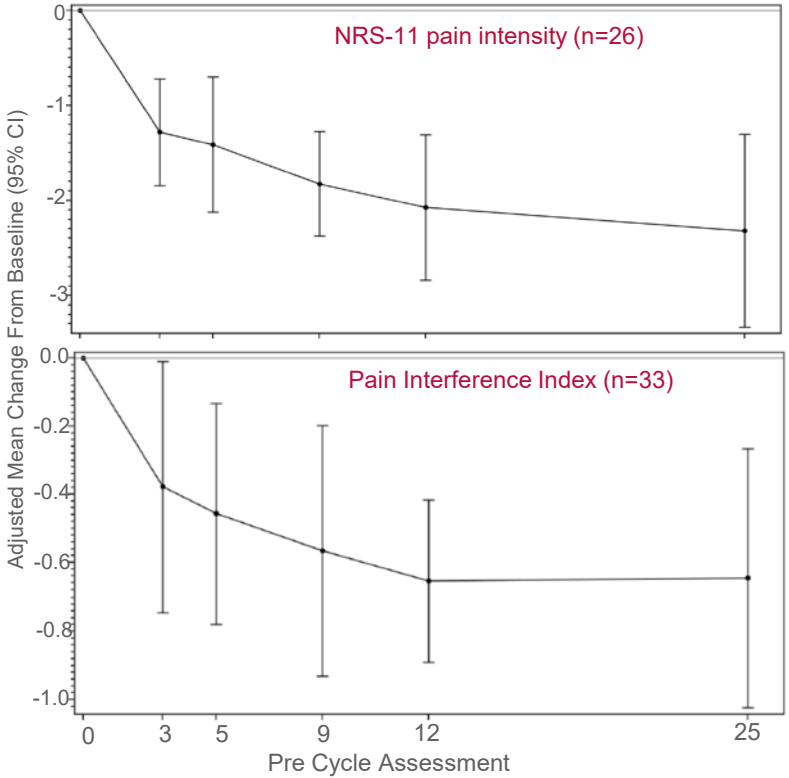
Durable PR (≥ 1 year):
- 28 (56%)

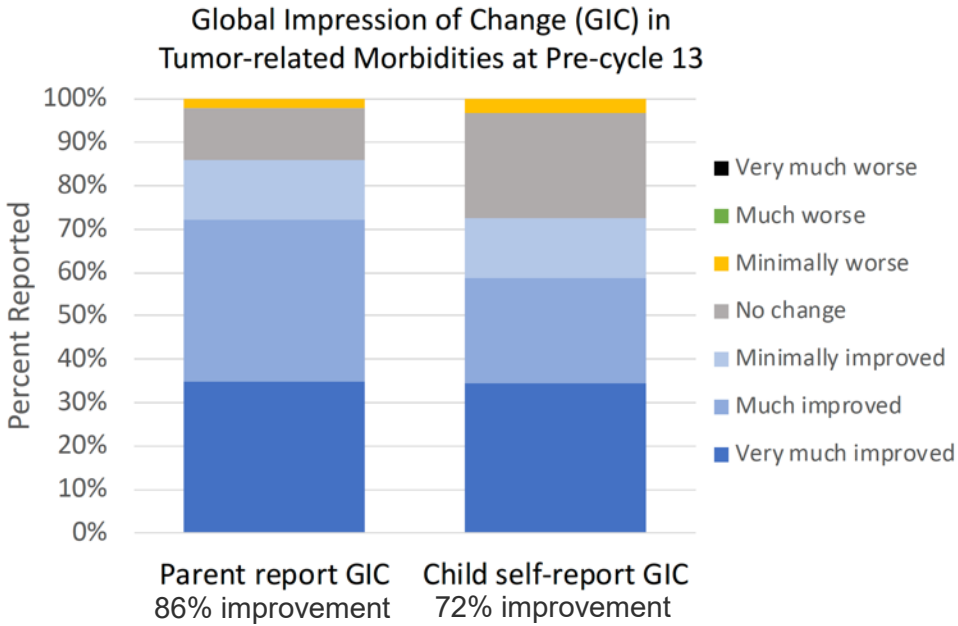
Progressive disease:
- 4 (8 %)

*Gross A…Widemann B: NEJM prov. accepted*

# SPRINT: Improvement in PN Pain and PRO

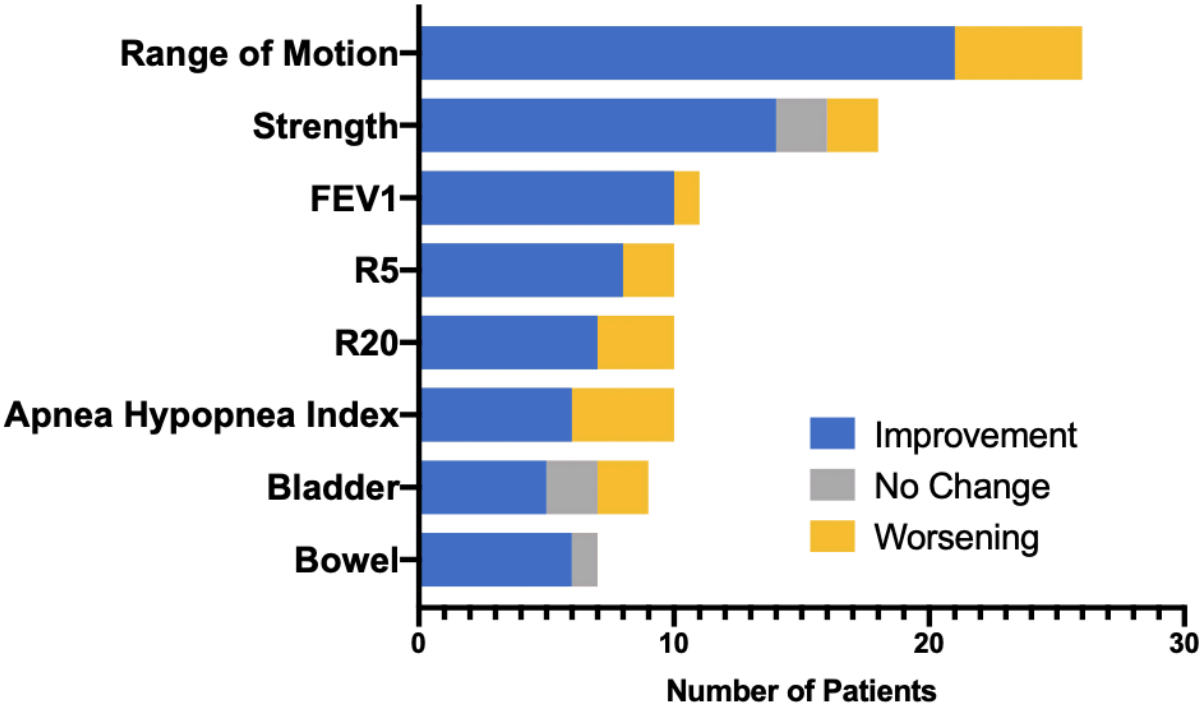
Pamela Wolters



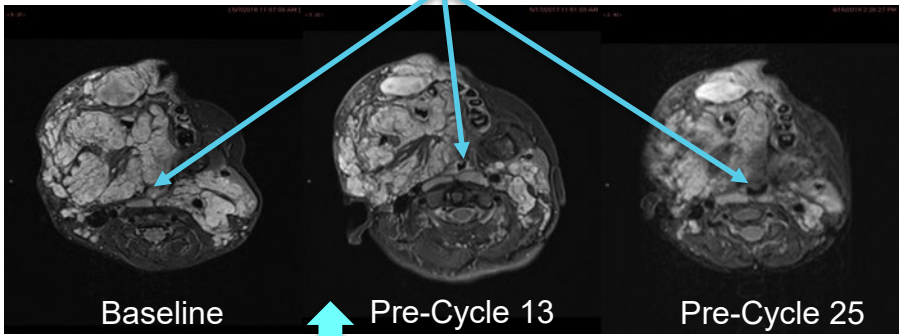

*Gross A…Widemann B: NEJM prov. accepted*

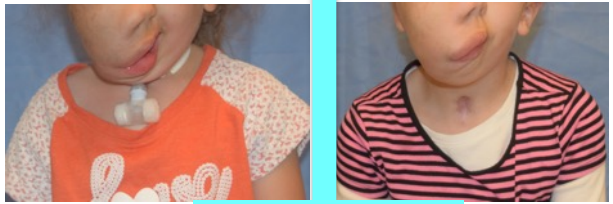
# SPRINT: Improvement in Functional Morbidities



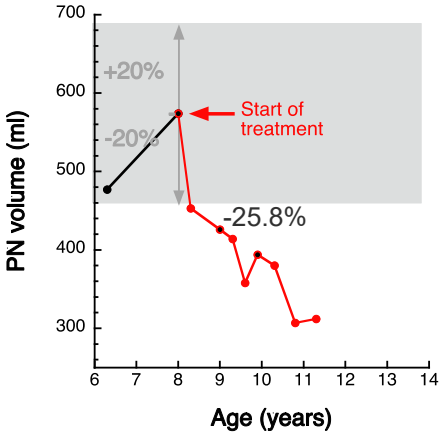
# Example: Improvement in Airway Function

8 year-old girl with
upper airway PN



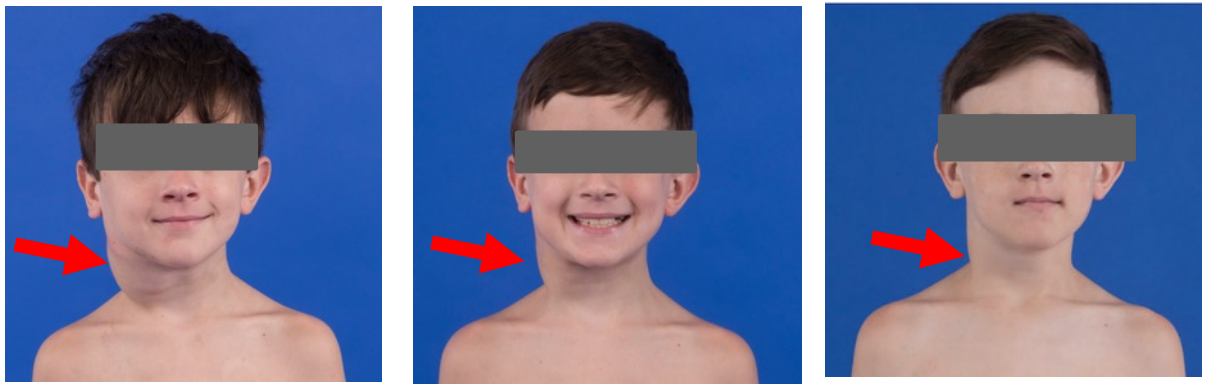



Patient
Decannulated

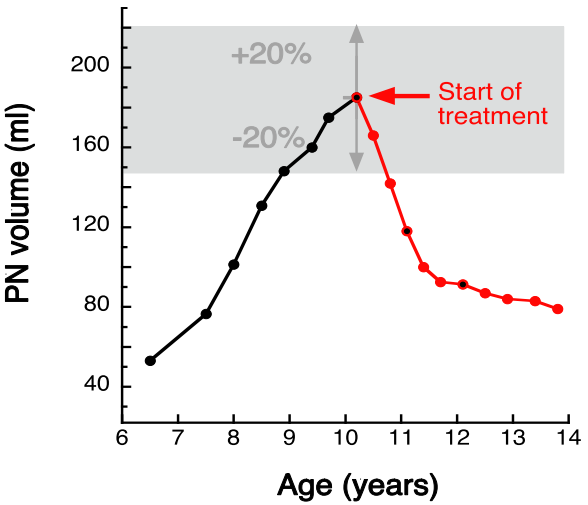


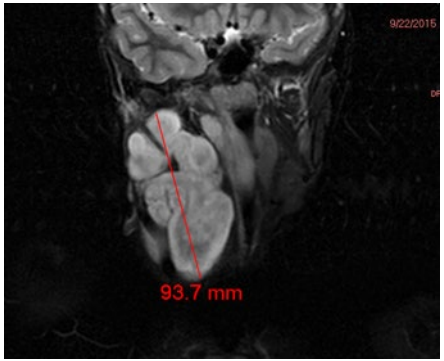
# Example: Improvement in Appearance

10 year-old boy with right neck PN



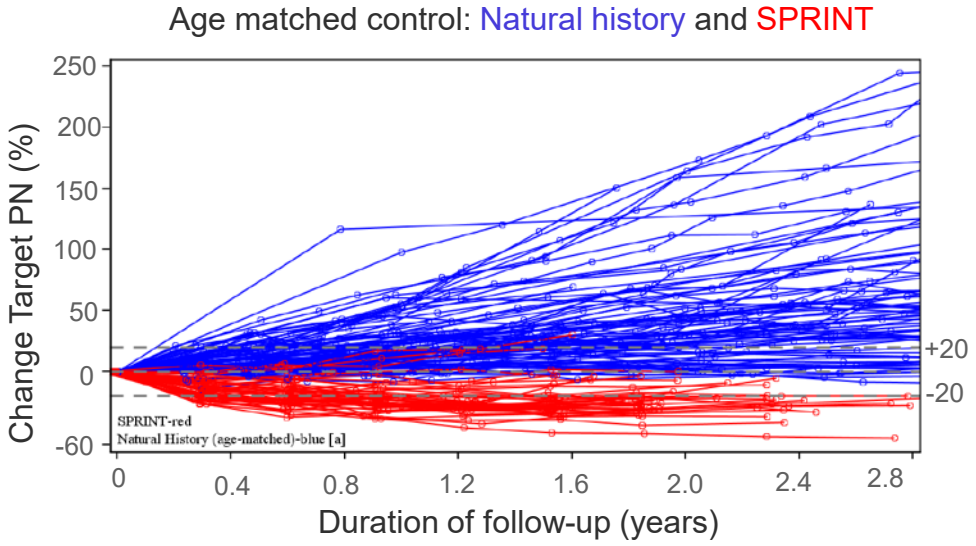
Baseline | Pre-Cycle 13 | Pre-Cycle 37

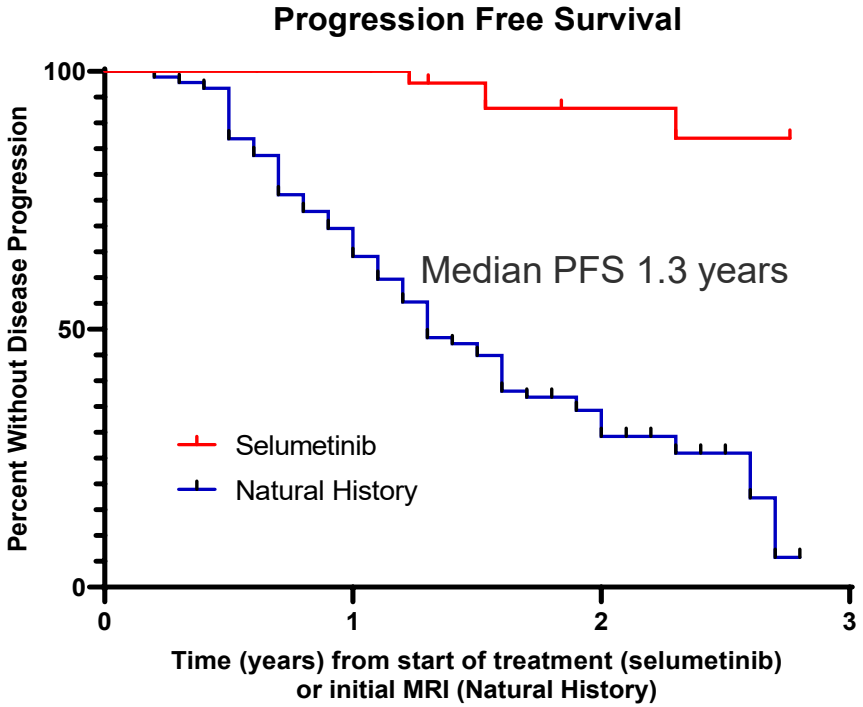


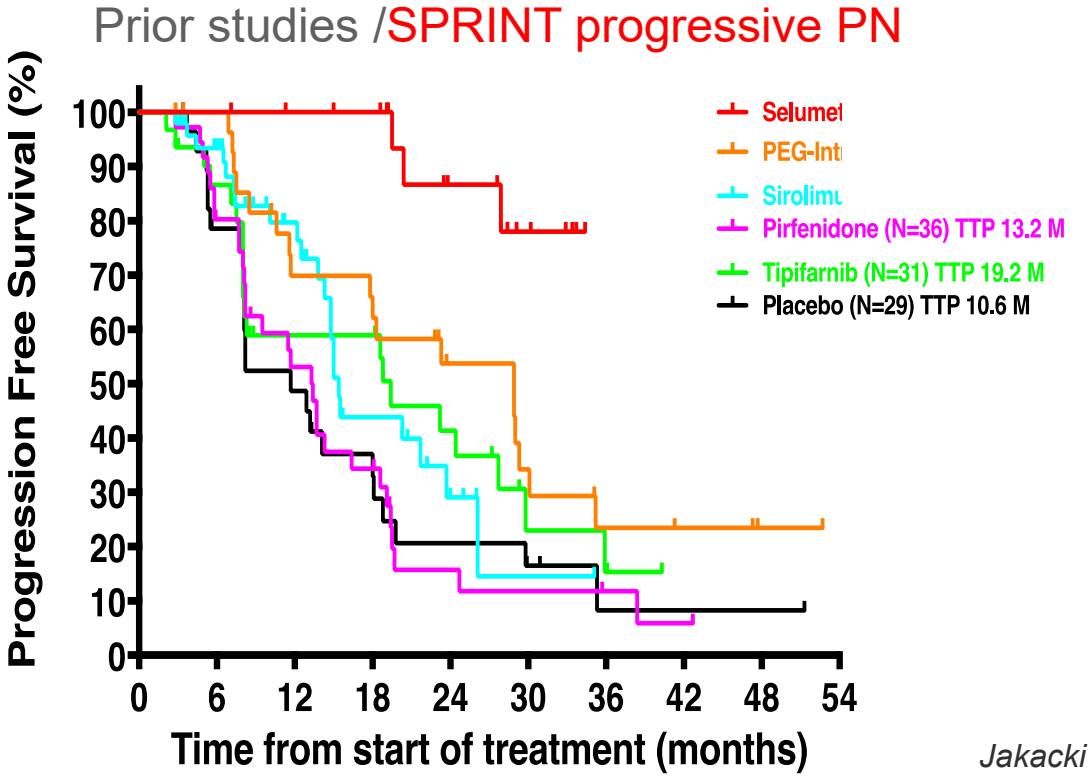

Prevention of morbidity: Airway compromise

# SPRINT External Control NF1 Natural History Study



# SPRINT versus Prior Phase II Trials for Progressive PN

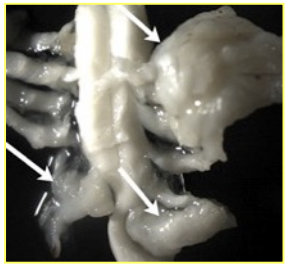


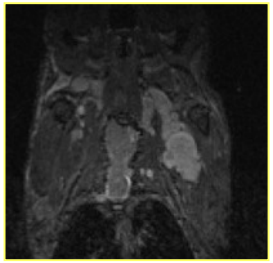

*Jakacki R,…Widemann B. Neuro-Oncol, 2017*
*Weiss B, Widemann B…Fisher M. Neuro-Oncol, 2015*
*Widemann B…Balis F: Neuro-Oncol 2014*
*Widemann B, Babovic D…Packer R. PBC, 2014*

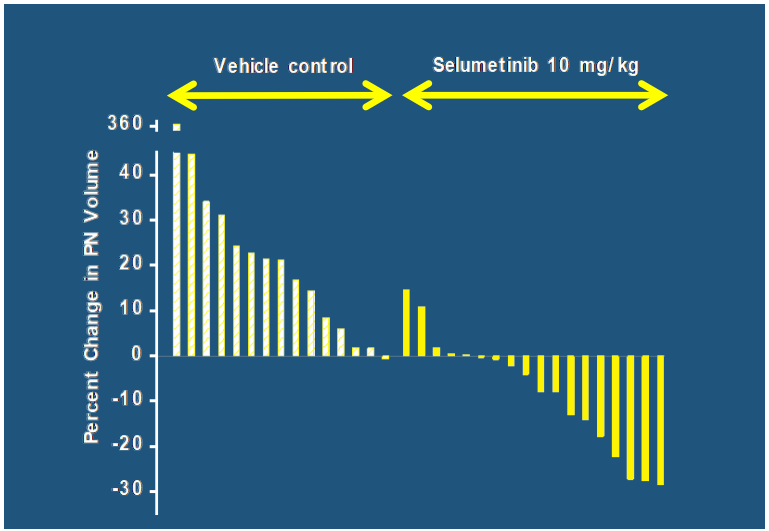
# Genetically Engineered Mouse Models of NF1 Neurofibroma Predict for Activity

## Ratner Lab

Mouse Neurofibroma *DhhCre;Nf1fl/fl*





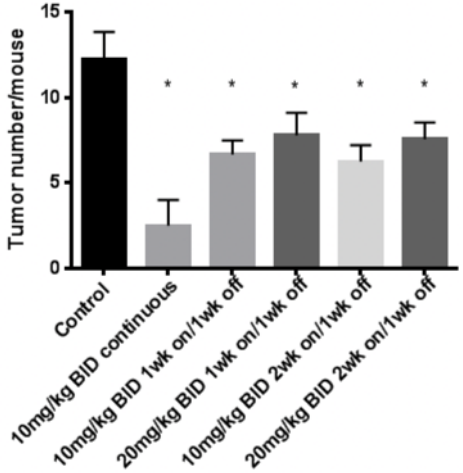



*Wu...Ratner. Cancer Cell, 2008. Jessen …Ratner. JCI, 2012*

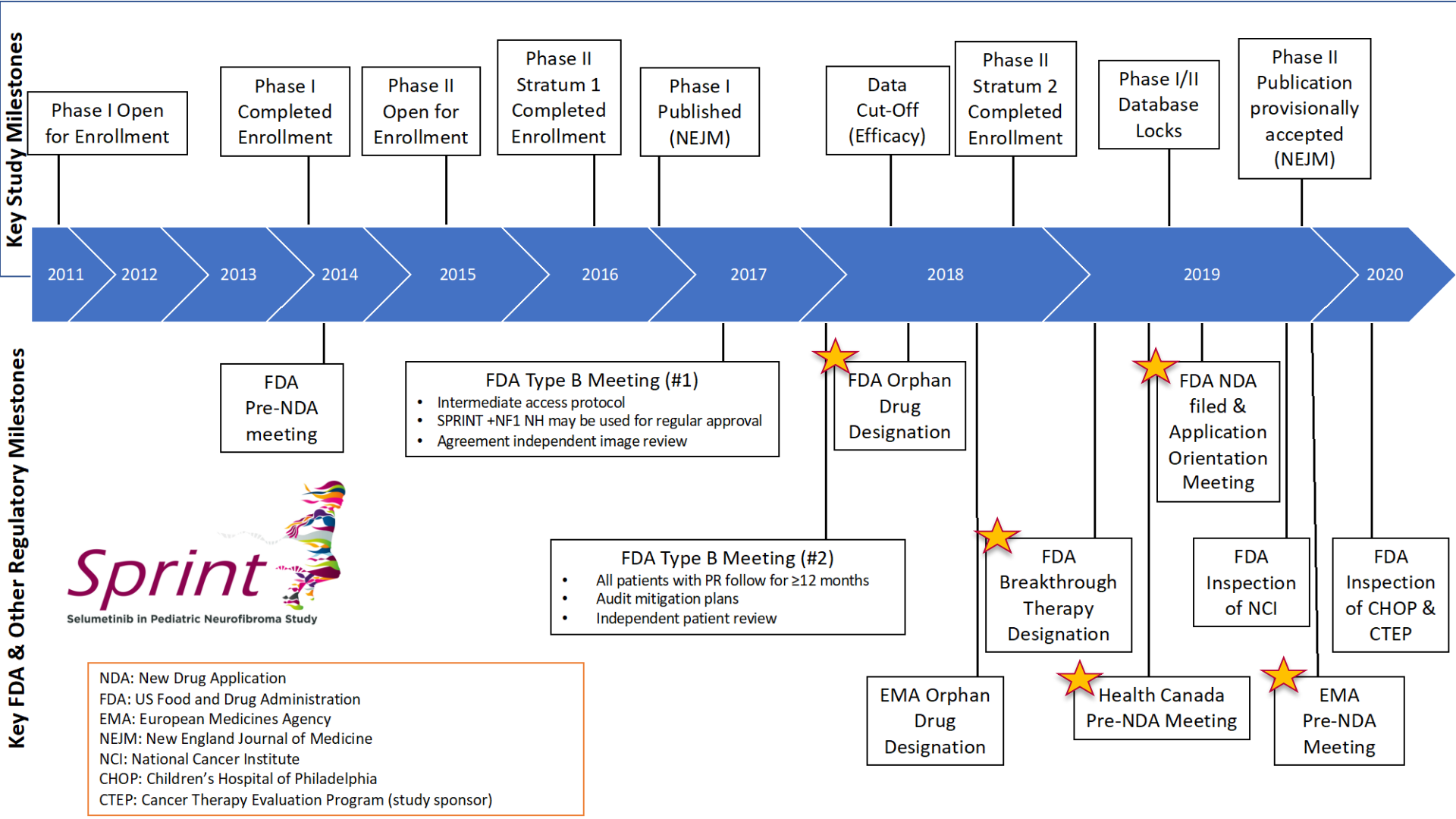
## Clapp Lab: Hyperactive RAS SPORE

Use of preclinical trials to evaluate:

- Optimal dose
- Schedule
- Pharmacodynamic effect (pERK)



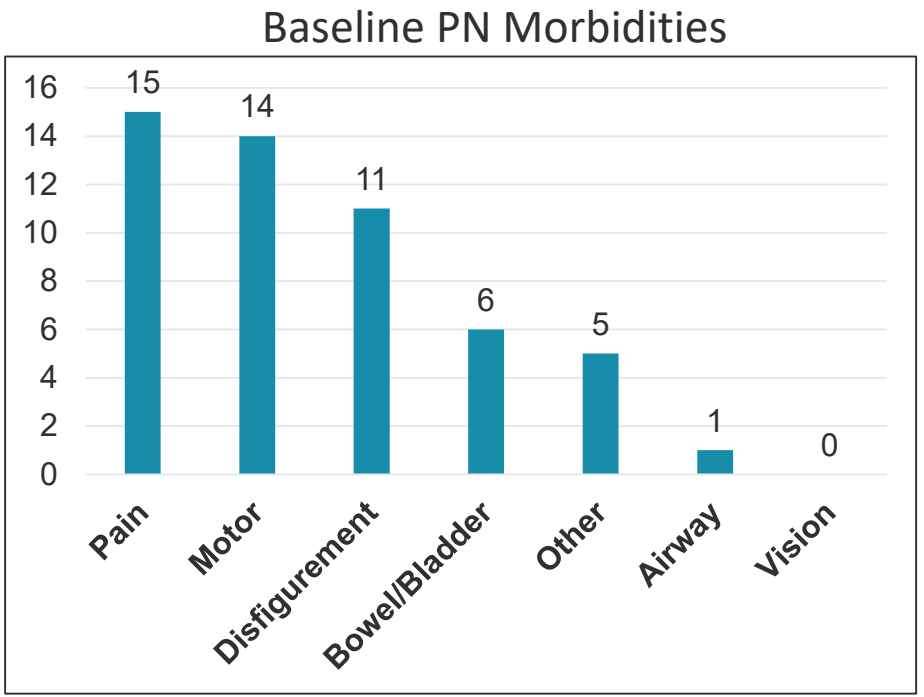

*Clapp lab, unpublished confidential data*


Key Study Milestones
Phase I Open for Enrollment
Phase I Completed Enrollment
Phase II Open for Enrollment
Phase II Stratum 1 Completed Enrollment
Phase I Published (NEJM)
Data Cut-Off (Efficacy)
Phase II Stratum 2 Completed Enrollment
Phase I/II Database Locks
Phase II Publication provisionally accepted (NEJM)
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
Key FDA & Other Regulatory Milestones
FDA Pre-NDA meeting
FDA Type B Meeting (#1)
Intermediate access protocol
SPRINT +NF1 NH may be used for regular approval
Agreement independent image review
FDA Orphan Drug Designation
FDA NDA filed & Application Orientation Meeting
FDA Type B Meeting (#2)
All patients with PR follow for ≥12 months
Audit mitigation plans
Independent patient review
FDA Breakthrough Therapy Designation
FDA Inspection of NCI
FDA Inspection of CHOP & CTEP
EMA Orphan Drug Designation
Health Canada Pre-NDA Meeting
EMA Pre-NDA Meeting
Sprint
Selumetinib in Pediatric Neurofibroma Study
NDA: New Drug Application
FDA: US Food and Drug Administration
EMA: European Medicines Agency
NEJM: New England Journal of Medicine
NCI: National Cancer Institute
CHOP: Children's Hospital of Philadelphia
CTEP: Cancer Therapy Evaluation Program (study sponsor)

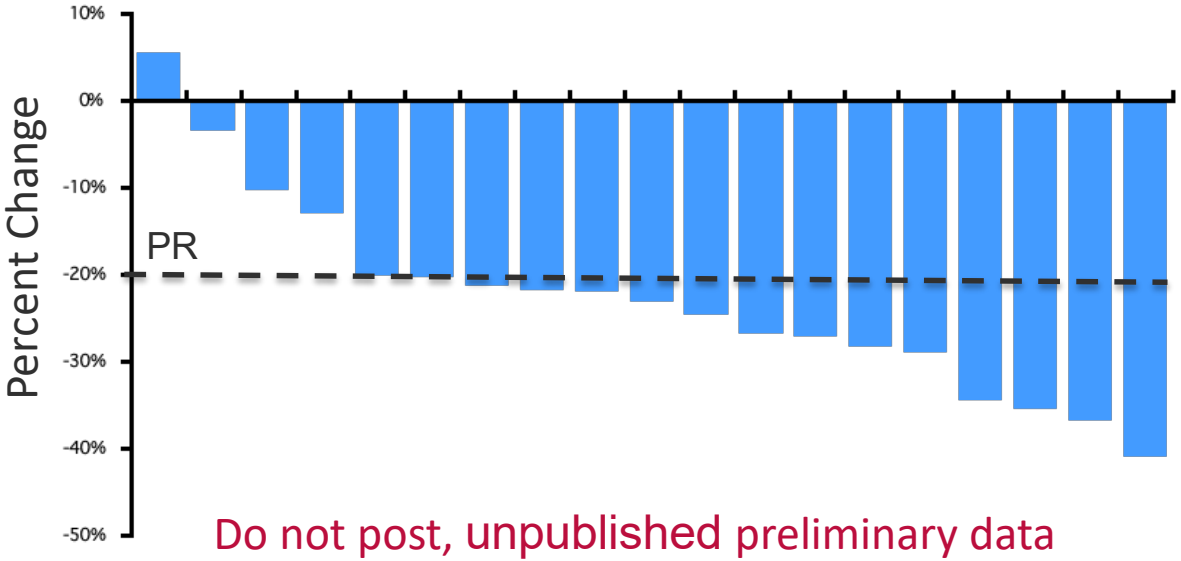
# Phase II Selumetinib: Adults with Growing or Symptomatic PN

- 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%

| Patients | (N=21) |
|---|---|
| Age in yrs., median (range) | 33 (18-60) |
| Sex: F/M | 6 / 15 |
| Target PN | |
| Typical | 17 |
| Solitary Nodular | 4 |



# Selumetinib Adult PN: Activity through October, 2019

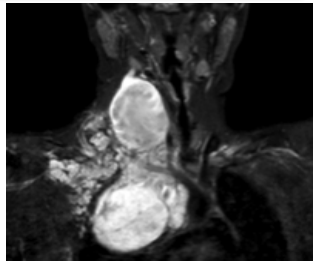



Do not post, unpublished preliminary data

| Best Response | n=21 |
|---|---|
| Partial Response | 15 (71%) |
| Confirmed PR | 12/15 |
| Stable Disease | 4 |
| Non-evaluable | 2 |
| Progressive Disease | 0 |

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

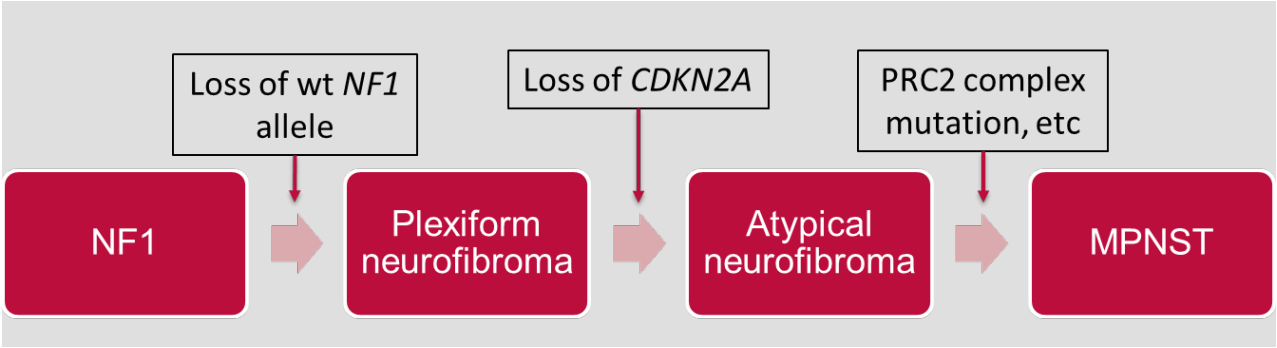
# Atypical Neurofibromas Are MPNST Precursors



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

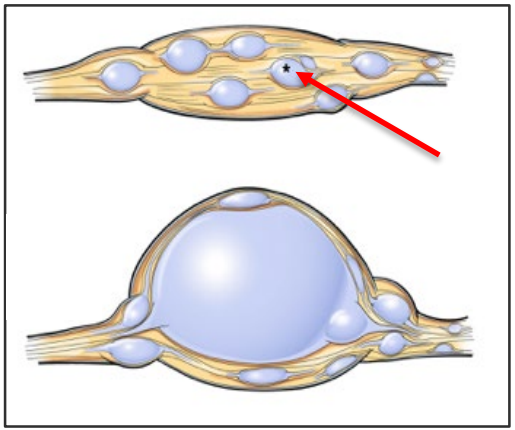
Hypothesis: Most MPNST arise from preexisting AN and not directly from PN




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: **A**typical **N**eurofibromatous **N**eoplasm of **U**ncertain **B**iologic **P**otential (**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*

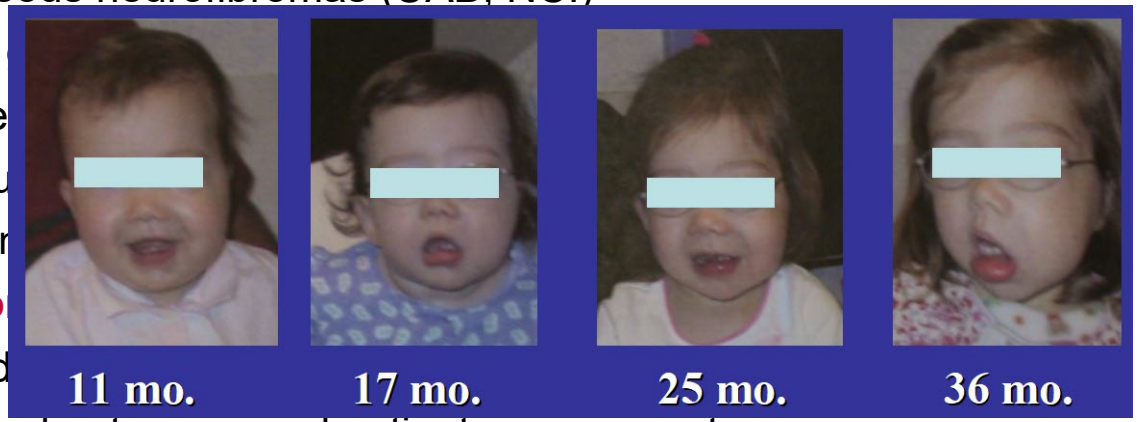
# NCI IRP NF1 Program Future Considerations

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
- Effect of se
- Atypical neu
- Combinatior




Develop tools fo

- Medication ad
- 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

# Acknowledgements


Patients and families

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  - patient care coordinator support
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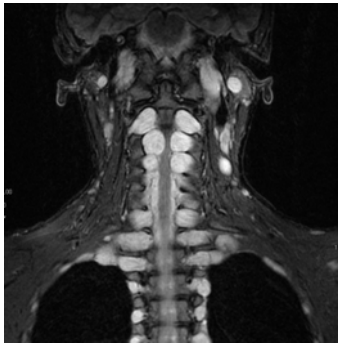
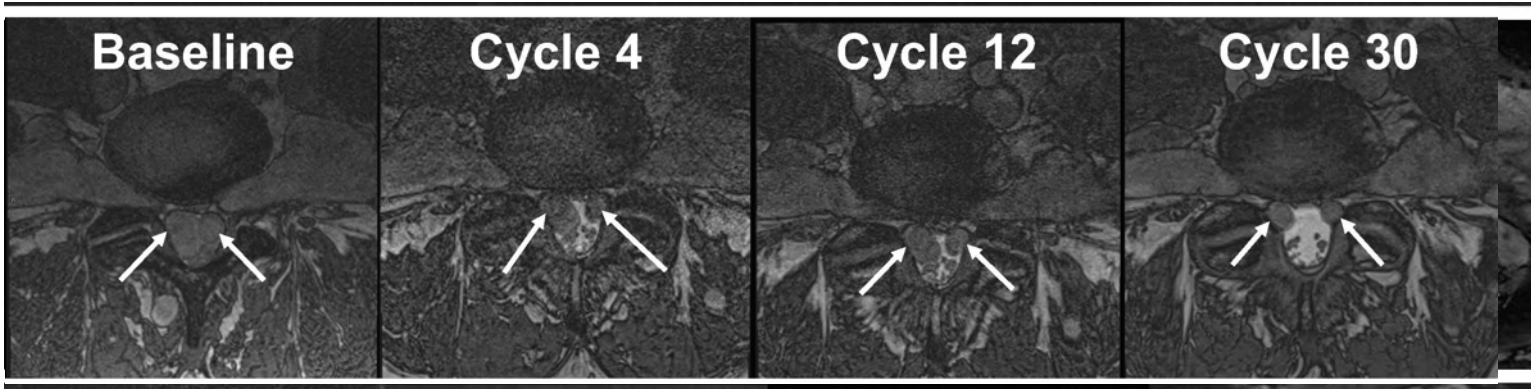
  - Douglas Stewart, Sharon Savage, NCI DCEG

# 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*