

The background features a dark blue gradient with faint, light blue circular patterns and a scale on the left side. The scale has markings from 140 to 260 in increments of 10. The main title is centered in large, bold, yellow capital letters.

FUNCTIONAL MEASUREMENTS IN CLINICAL TRIALS FOR PLEXIFORM NEUROFIBROMAS

ANDREA GROSS, MD

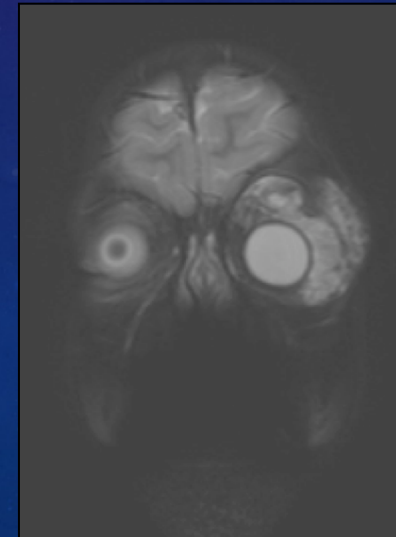
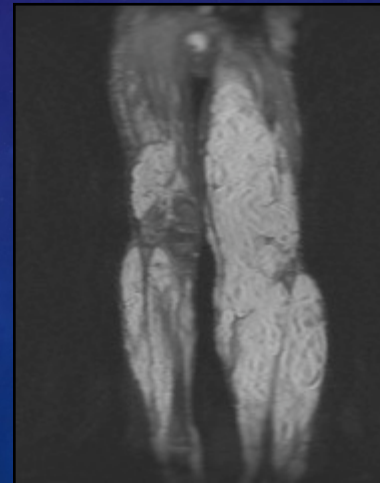
PEDIATRIC ONCOLOGY BRANCH, NCI

NF FORUM

MAY 5, 2018

PLEXIFORM NEUROFIBROMAS (PN)

- ❖ Tumors (not cancer) which come from nerves
- ❖ 20-50% of patients with NF1 will have PN
- ❖ Many patients are born with PN
- ❖ NOT cancer but can cause lots of problems!
 - Can cause pain, loss of function, disfigurement
 - May change into malignant (cancerous) tumors called “MPNST”



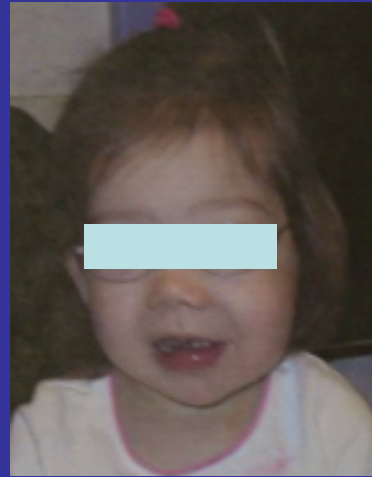
GROWTH OF PN OVER TIME



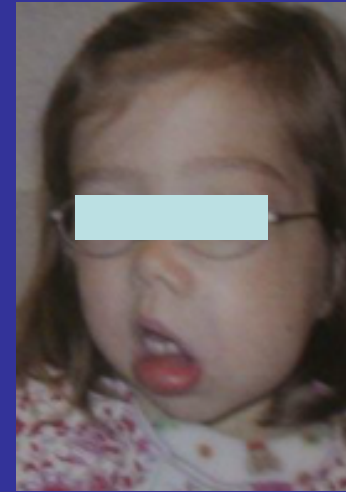
11 mo.



17 mo.



25 mo.



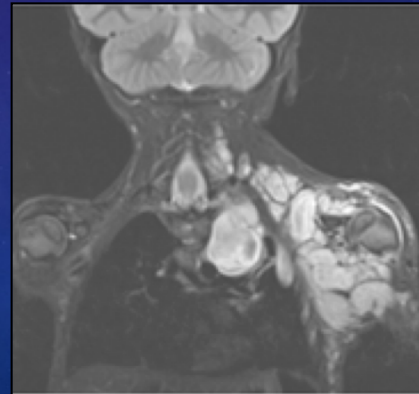
36 mo.



Age 3



Age 5



Age 3



Age 5

SELUMETINIB (AZD6244) PHASE 1 IN NF1 PN

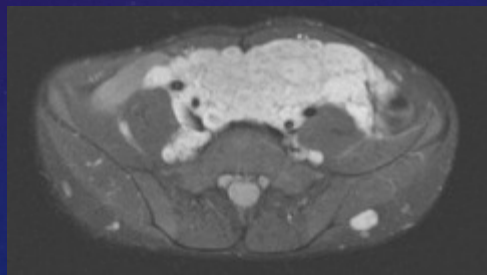
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

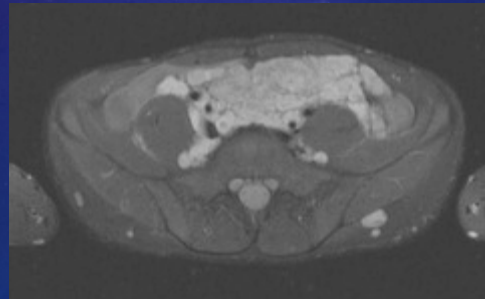
Activity of Selumetinib in Neurofibromatosis Type 1–Related Plexiform Neurofibromas

Patient 1

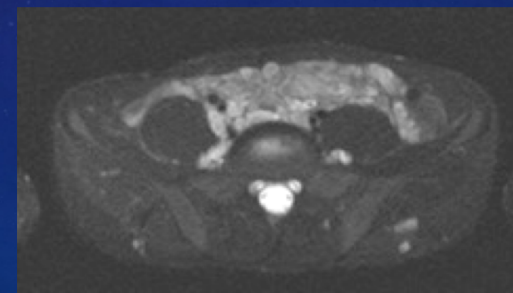
Abdominal Plexiform Neurofibroma



Baseline: 2449 ml



Cycle 5: 2038 ml
- 17%



Cycle 22: 1477 ml
- 40%

DEVELOPMENT OF SELUMETINIB FOR PN

❖ *Anecdotal* clinical benefit

❖ **Approval strategy:**

- Collaboration with CTEP, FDA, AstraZeneca, NTAP, academic institutions (NCI, CHOP, CNMC, CCHMC)

❖ **FDA Approval Depends On Clinical Benefit:**

- Show PN volume reduction AND
- Improvement in pain, function, disfigurement



WHAT IS A “FUNCTIONAL” MEASURE?

- Objective measurement of ability to perform a task
- Impacted area of function depends on location of tumor
 - Airway
 - Bowel/Bladder
 - Vision
 - Motor
- Provide better data than “anecdotal” reports

Specific Evaluations Based on PN Location/Morbidity:

Form Completed

Orbital PN

- Ophthalmologic functional evaluations

- Appendix VII

Airway PN

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

- Appendix VIII
- Appendix VIII
- Appendix IXA

Motor PN (Lower Extremity)

- Strength evaluation
- ROM evaluation
- Leg length evaluation
- Endurance evaluation: 6-Minute Walk-Run Test
- PROMIS

- Appendix IXB
- Appendix IXC
- Appendix IXD
- Appendix IXA

Motor PN (Upper Extremity)

- Strength evaluation
- ROM evaluation
- Grooved Pegboard Test (Age ≥5 years)
- PROMIS

- Appendix IXB
- Appendix IXC
- Appendix IXE

Bowel/Bladder PN

- Bowel/Bladder Questionnaire

- Appendix X

Visible PN, Disfigurement (or Potential Disfigurement)

- Photography
- Video

- Appendix IV

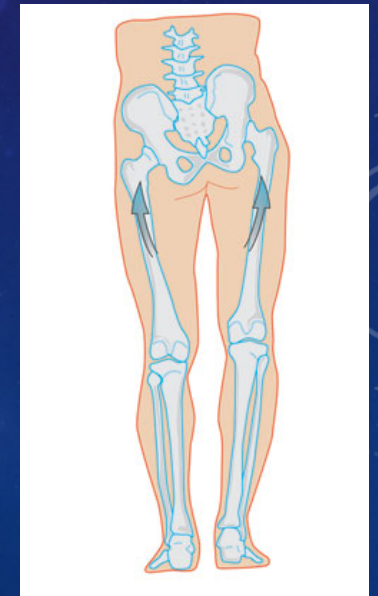
Other PN

- PN affecting speech/swallow: Speech Pathology Assessment
- PN affecting auditory system: Audiology and/or ENT Assessment

- Appendix XA

FUNCTIONAL MEASURES: MOTOR PN

- Assessments Performed Before and During Treatment:
 - **Strength**
 - **Range of Motion**
 - **Grooved Pegboard**
 - **Endurance = 6 Minute Walk Test**
 - **Leg Length Discrepancy**

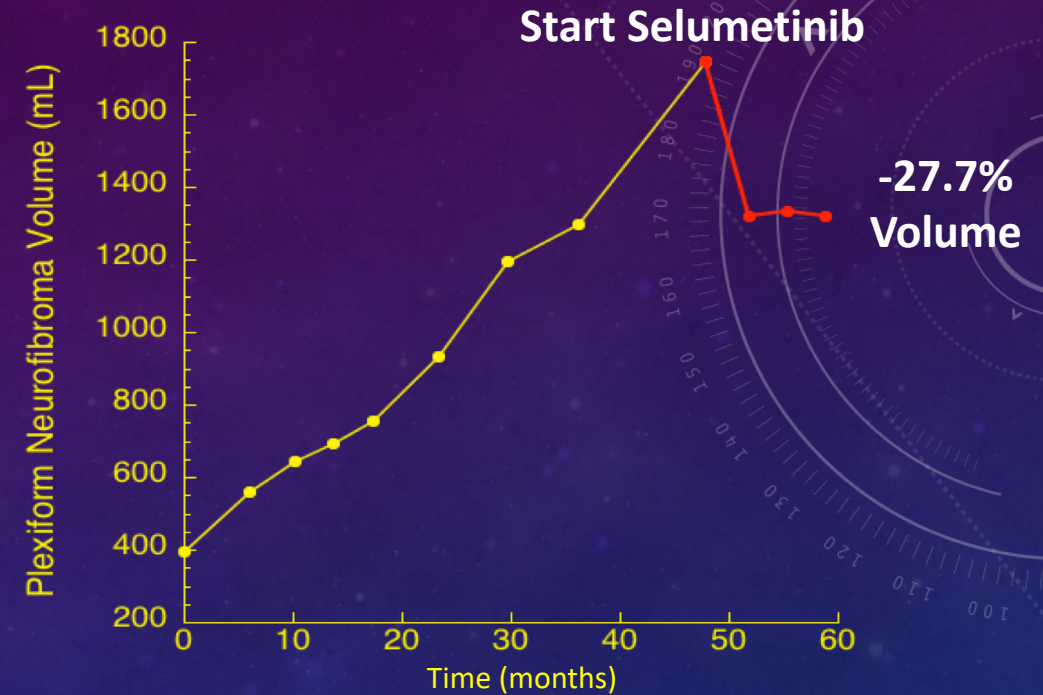
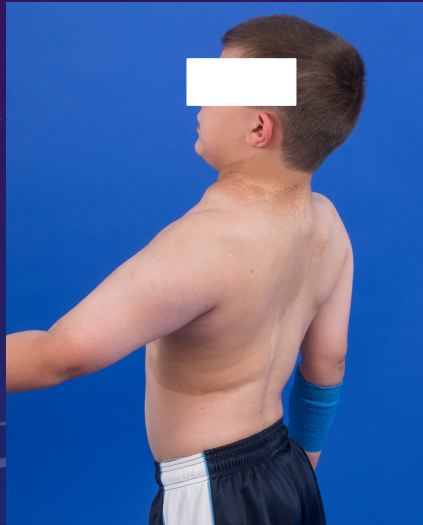


Sample Patient Response

Baseline



Pre Cycle 13



Outcome Measure	Baseline	Pre Cycle 13
Neck extension	42	72
Neck lateral flexion (L)	10	47
Shoulder abduction (L)	75	180
Internal/external rotation	46/42	90/90
Strength (Trapezius)	4+ pain	5
Pain meds: Ibuprofen	BID	-
Pain intensity (0-10)	3	0
Pain interference (0-6): patient	2	1
Pain interference (0-6): parent	2.67	0.83
Global impression of change (Patient and parent)	-	Much improved

CHALLENGES WITH FUNCTIONAL EVALUATIONS

- Picking the best measurement
 - No validated measures in NF1
 - Utility of Measurements
- Clinical meaningfulness of changes
- Burden vs Benefits of testing on patients



KEY POINTS & CONCLUSIONS

- Functional measures will be ESSENTIAL for any drug approval for PN in the future
- Varied locations of PN means functional measures have to be flexible
- Need patient and family input to determine best functional measures
 - Most practical
 - Most meaningful



QUESTIONS?

