Overview of Neurofibromatosis Type 1

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Overview

1. *Neurofibromatosis Type 1*
2. *Plexiform Neurofibromas (PN)*
3. *Atypical Neurofibromas*

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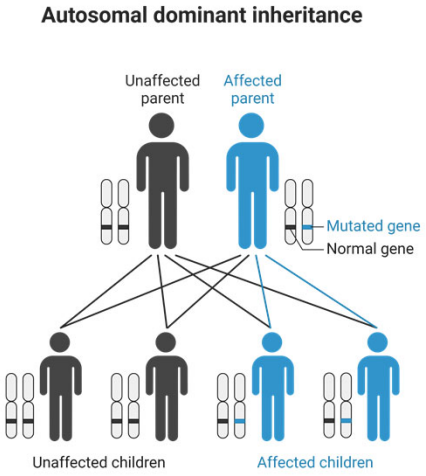
Neurofibromatosis Type 1

- Autosomal dominant inheritance
  - Complete penetrance
  - Highly variable phenotype
- Spontaneous mutations in approximately 50% of cases
- Mutation in *NF1*, tumor suppressor gene on chromosome 17q11.2 (RAS pathway activation)



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Updated NF1 Diagnostic Criteria

- Need ≥2 if no parent with NF1; ≥1 if a parent with NF1

Diagnostic Criteria
≥ 6 café-au-lait macules (>5 mm pre-pubertal, >15 mm post-pubertal)
Freckling in the axillary or inguinal region
Two or more neurofibromas of any type or one plexiform neurofibroma
Optic Pathway Glioma
≥2 Lisch nodules on slit lamp exam or ≥2 choroidal abnormalities
Distinctive Osseus Lesion (sphenoid wing dysplasia, anterolateral bowing of tibia, long bone pseudoarthrosis)
Heterozygous pathogenic *NF1* variant allele fraction of ≥ 50% in normal tissue

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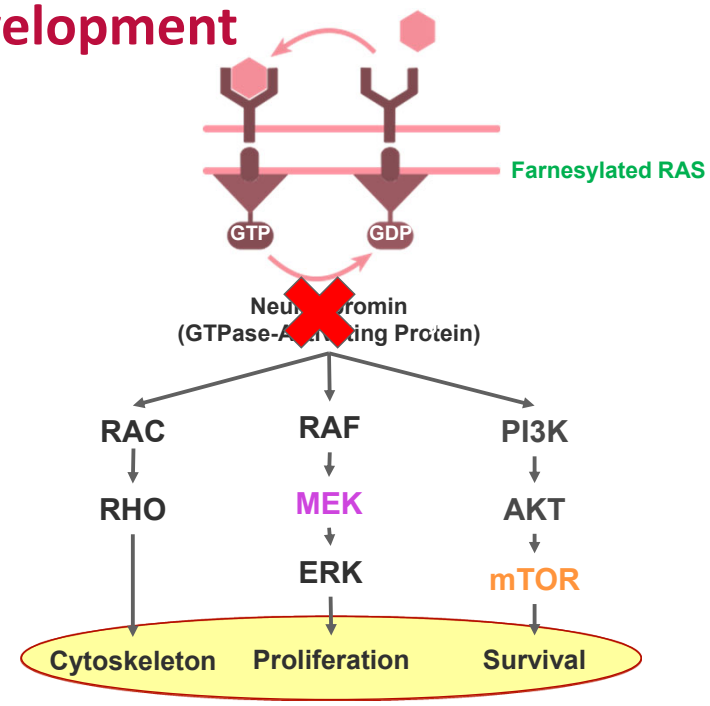
NF1 Tumor Development



Gutmann DH, et al. *Nat Rev Dis Primers.* 2017; Asati V, et al. *Eur J Med Chem*. 2016.

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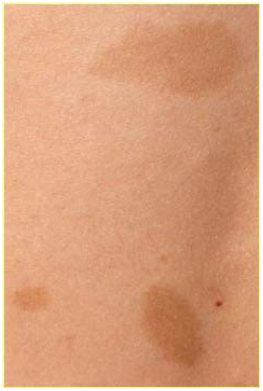
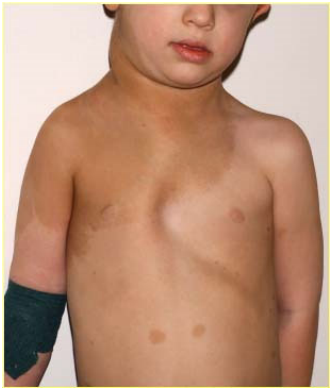
Café au Lait Macules

- Obvious during first 2 years of life
- Macular, regular border, homogenous pigmentation





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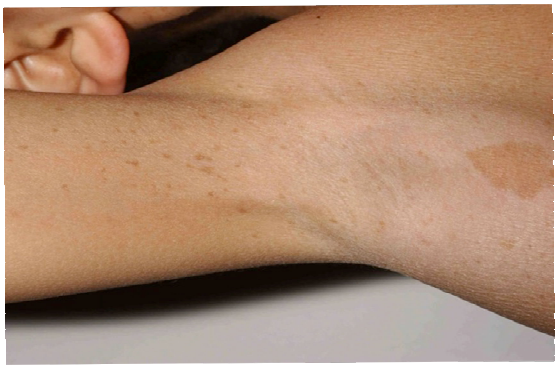
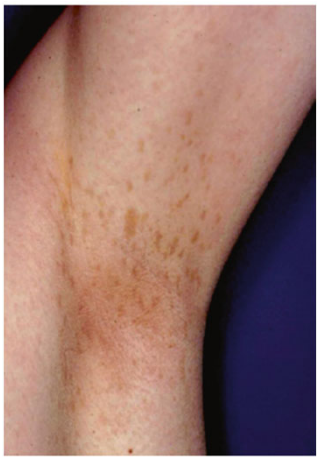
Skinfold Freckling

- Appears during first 5 years of life
- Axillary (64-84%), inguinal (52-56%), trunk, neck, submammary region





(Mautner 2022)

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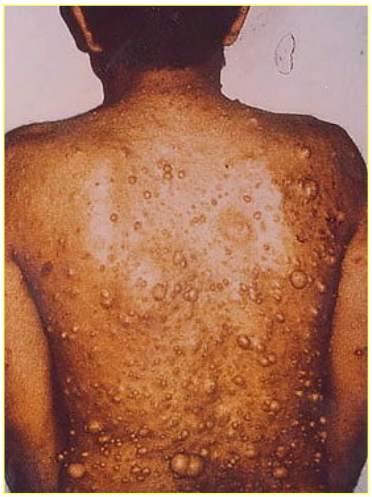
Cutaneous Neurofibromas

- Do not usually develop until preadolescence:
- Frequency:
  - < 10 years: 14%
  - 10-19 years: 44%
  - 20-29 years: 85%
  - >30 years: 94%
- Earlier onset predicts for more severe cutaneous manifestations
- Increase during puberty and pregnancy
- Major cosmetic problem
- No malignant transformation



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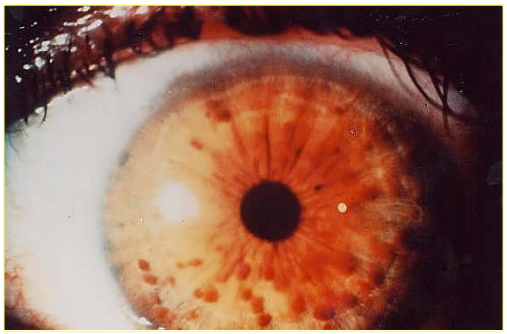
Lisch Nodules

- Dome shaped elevations on the surface of the iris - hamartomas
- Pathognomonic of NF1
- Frequency: 22% at 5 years, 96-100% at 20 years



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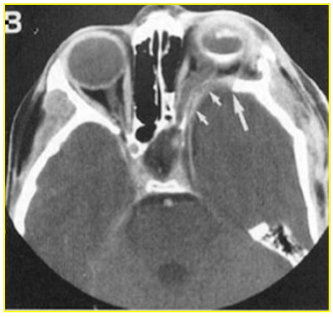
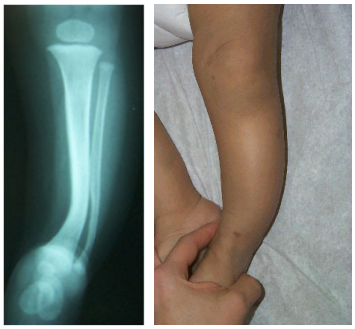
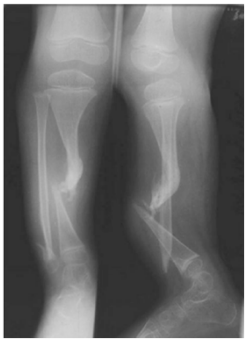
Osseus Lesions

- Sphenoid Wing Dysplasia
- Long bone dysplasia/ Tibial Pseudoarthrosis
  - Congenital; 5% of patients with NF1







(Figure from Mautner 2022)

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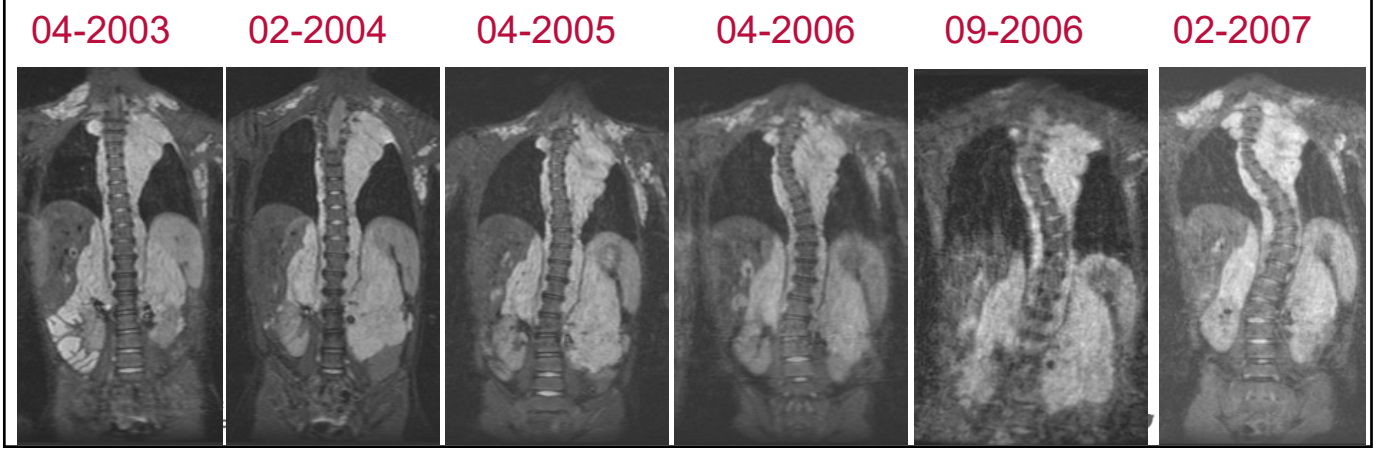
NF1 Scoliosis

- Idiopathic and Dystrophic types
- Dystrophic: Short segmented, sharply angulated wedged vertebrae, apical rib penciling
- Frequency: 15% to 20%, surgery required 5%



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NF1: Signs and Symptoms Timeline

Sign/Symptom (%)	0-2 Yrs	2-6 Yrs	6-16 Yrs	16 Yrs +
Café au lait macules (95)	→			
Plexiform neurofibroma (50)	→			
Tibial dysplasia (5)	→			
Skin fold freckling (65-84)		→		
Lisch nodules (96-100)		→	→	→
Optic pathway glioma (15-20)		→		
Learning deficits (30-60)		→	→	→
Hypertension		→	→	→
Cutaneous neurofibromas (95)			→	→
Scoliosis (12-20)			→	→
MPNST (8-16)				→

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NF1 Oncologic Manifestations

- T2 Hyperintensities (Spongiform gliosis, UBO's)
- Optic pathway gliomas (15-20%)
- Gliomas (cerebellar, cerebral, brain stem) (1.2%)
- Spinal neurofibromas (spinal cord compression)
- Malignant Peripheral Nerve Sheath Tumor (MPNST) (5-13%)
- Plexiform neurofibroma (25%)
- Pheochromocytoma (1%), Gastrointestinal Stromal Tumors (GIST)
- Glomus tumors
- Other malignancies (JMML, RMS)

NF1 Optic Pathway Gliomas

- Most common CNS tumor in NF1 (15-20%)
- **Age at presentation**: Median 4.9 years, new tumors after 6 years of age are rare
- **Symptoms**:
  - Decreased visual acuity, visual field defects, proptosis, strabismus, optic atrophy, HA, nausea, anorexia, hypothalamic dysfunction/ precocious puberty
  - *Only 30-50% of these tumors become symptomatic*
- **Pathology**: Pilocytic astrocytoma (WHO grade I)

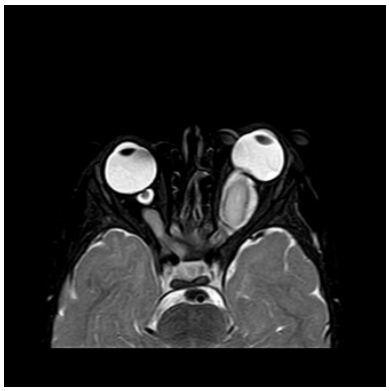

Image courtesy of Sepehr Haghighi, Radiopaedia.org, rID: 64709

NF1 Optic Pathway Gliomas (continued)

- Natural history:
  - Progression is infrequent after diagnosis
  - Spontaneous regression
- Treatment: ***Not necessary*** for most patients
  - For patients with progressive neurological, visual or radiographic disease
  - Chemotherapy: Carboplatin and vincristine (standard regimen)
    - Ongoing trial comparing MEKi to standard chemotherapy up-front
  - Avoid XRT, if possible
- Screening:
  - Ophthalmologic examination: Yearly until 6 years
  - MRI: Utility for screening questioned

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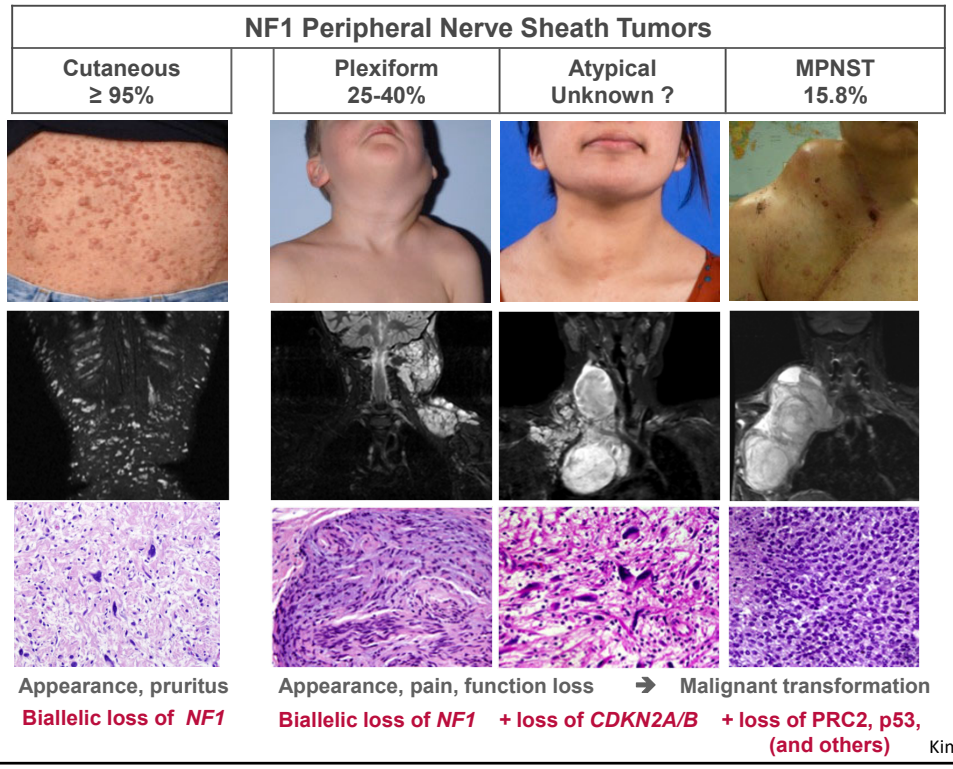

Kim et al, *Sarcoma* 2017

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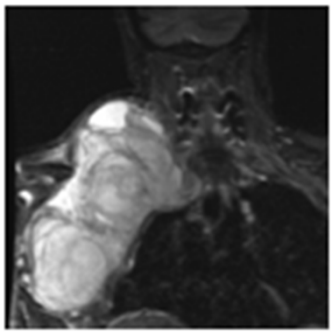
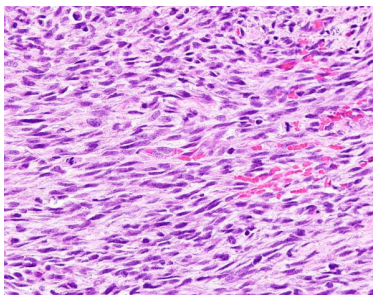
Malignant Peripheral Nerve Sheath Tumor (MPNST)

- Highly aggressive soft tissue sarcoma
- Most common malignancy in NF1
- Lifetime risk: 8-13%
- Treatment:
  - Local control: ESSENTIAL – wide resection with negative margins; radiation therapy
  - Chemotherapy: Ifosfamide/ Doxorubicin/ Etoposide





Mitotic figures >10/10 HPFs), high cellularity

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Pathology photo courtesy of Miettinen

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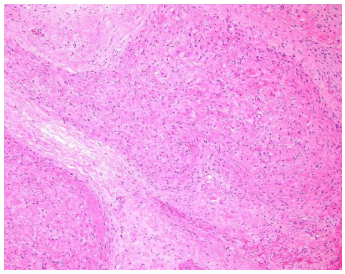
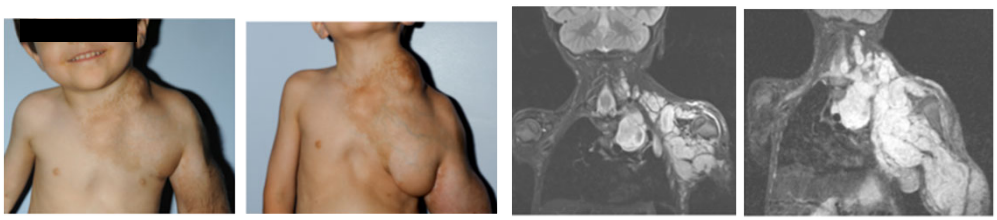
Plexiform Neurofibromas (PN)



- Histologically benign
- Involve multiple nerve fascicles/branches
- Schwann cells, fibroblasts, mast cells, highly vascular
- Young age, slow growth, large size, complex shape
- Disfigurement, pain, functional impairment, life-threatening
- Transformation to malignant peripheral nerve sheath tumor (MPNST) (10-15%)



3 years | 5 years | 3 years | 5 years

Klesse LJ, et al. *Oncologist.* 2020; Kim A, et al. *Sarcoma.* 2017; Korf BR. In: *Advances in Neurofibromatosis Research.* 2012.

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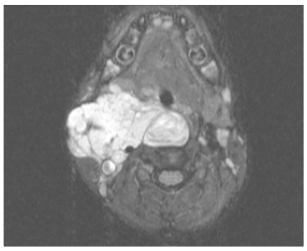
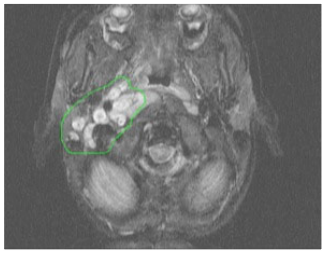
Volumetric MRI Analysis of PN

- Volumetric MRI is the standard methodology for measuring PN on clinical trials (REiNS)

STIR Sequence

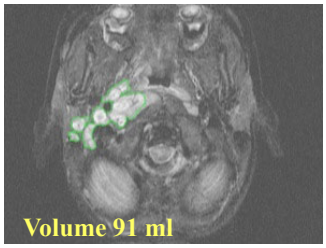


Region of Interest



- Response Criteria:
  - **Partial Response (PR)**: ≥ 20% decrease in tumor volume
  - **Progressive Disease (PD)**: ≥ 20% increase in tumor volume from best response

Tumor border identified



Dombi E, et al. *Neurology*. 2013; Solomon J, et al. *Comput Med Imaging Graph.* 2004; Gross AM, et al. *N Engl J Med.* 2020.

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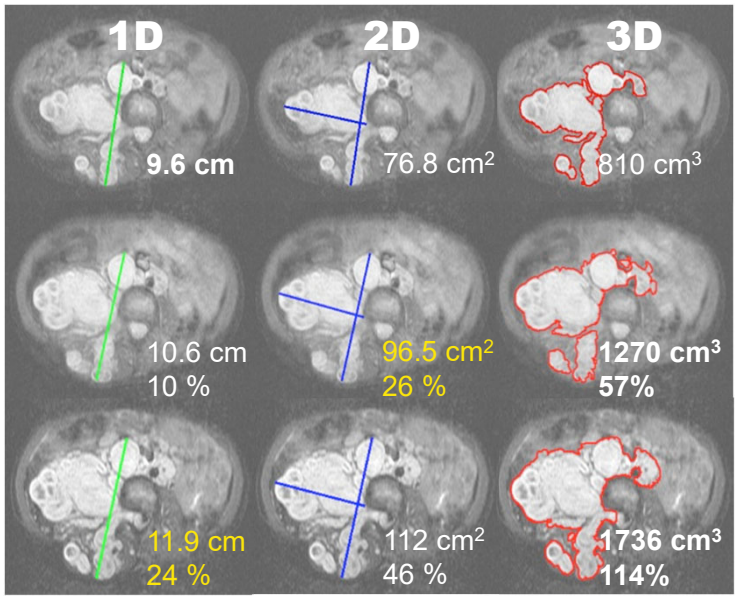
Example of Line and Volume Measurements



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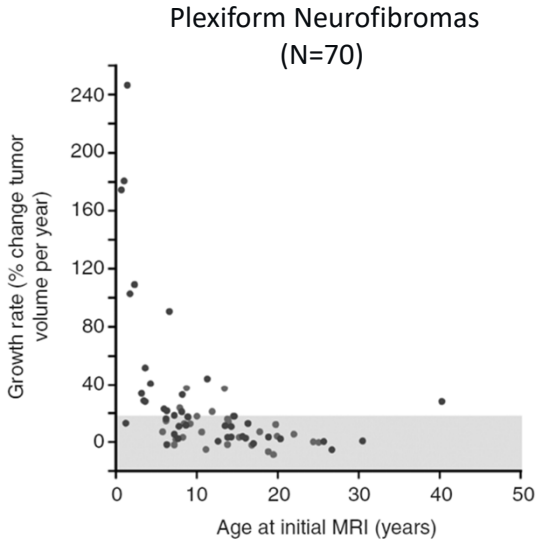
Natural History of PN Growth

- NCI NF1 Natural History Study
- PN Growth Rate:
  - PN grow most rapidly in young children
  - No spontaneous PN shrinkage >20% per year
- PN-Related Morbidity
  - Most PN cause some degree of morbidity at time of first assessment
  - Once PN-related morbidity develops in growing PN, it is very unlikely to resolve spontaneously, thereby reinforcing the need for early intervention



Akshintala S, et al. *Neuro Oncol.* 2020; Gross AM, et al. *Neuro Oncol.* 2018.

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Surgery and Radiation Therapy for PN

- Surgical resection of PN can be a dangerous procedure with risk for significant blood loss
- Younger patients and incomplete resection associated with increased risk of tumor regrowth
- Small retrospective case studies have shown radiotherapy can shrink tumors, however it leads to significant increases in risk of malignant transformation therefore generally **NOT** recommended

Fig. 3. Kaplan-Meier estimates of the proportion of patients without development of tumor progression based on the extent of resection as assessed by the operating surgeon (*n* = the total number of tumors in each arm).

Needle MN, et al. *J Pediatr*. 1997; Canavese F, et al. *J Pediatr Orthop*. 2011; Wentworth S, et al. *Int J Radiat Oncol Biol Phys*. 2009; Grill J, et al. *Int J Radiat Oncol Biol Phys*. 2009; Chopra R, et al. *Am J Clin Oncol.* 2005.

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Treatment Targets in NF1

Farnesyltransferase inhibitors:
- Tipifarnib

RTKi / Angiogenesis / TME
- Thalidomide
- Sorafenib
- Cediranib
- Imatinib
- Cabozantinib
- Peg-Interferon Alpha 2b
- Pirfenidone
- Pexidartinib

mTOR inhibitors:
- Sirolimus

MEK inhibitors:
- Selumetinib
- Trametinib
- Binimetinib
- Mirdametinib

Gutmann DH, et al. *Nat Rev Dis Primers.* 2017; Asati V, et al. *Eur J Med Chem*. 2016.

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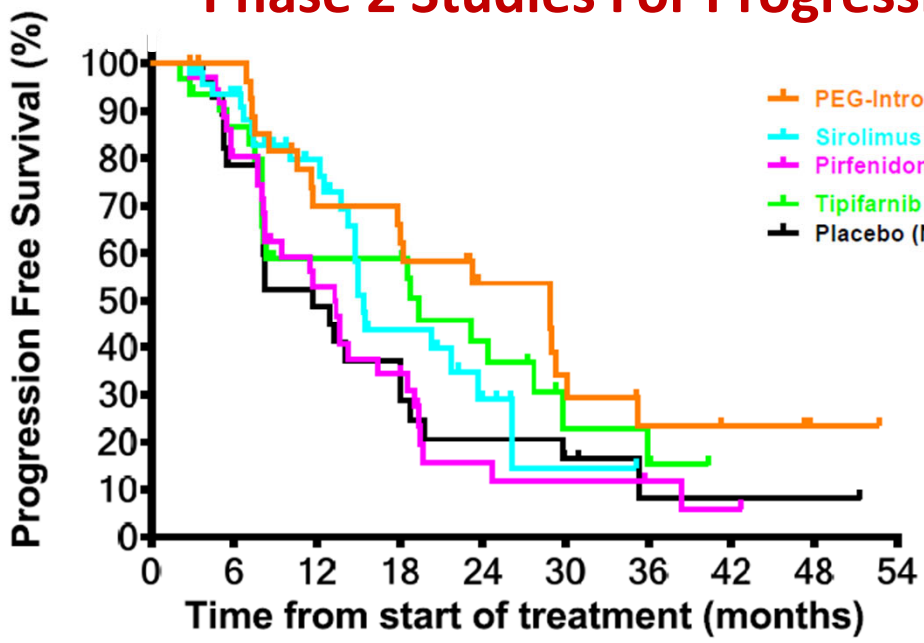
Phase 2 Studies For Progressive PN



Only 2 of 175 patients with confirmed partial response (both on PEG-Intron study)

Weiss BS, et al. *Neuro Oncol.* 2015; Widemann BC, et al. *Neurol Oncol.* 2014; Jakacki RI, et al. *Neuro Oncol.* 2017; Widemann BC, et al. *Pediatr Blood Cancer.* 2014.

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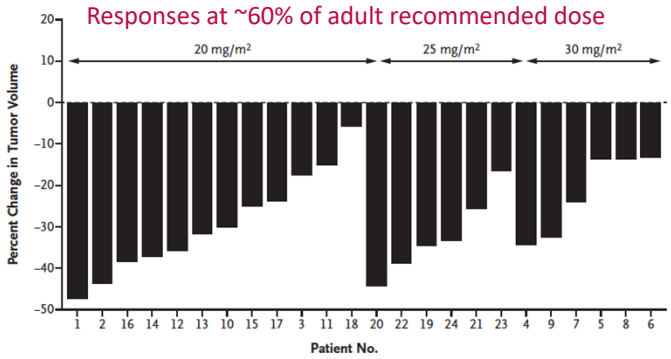
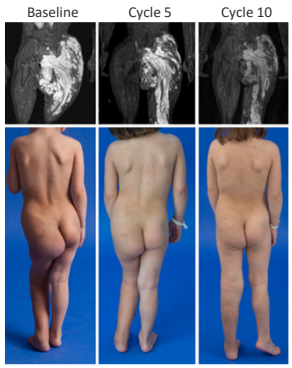
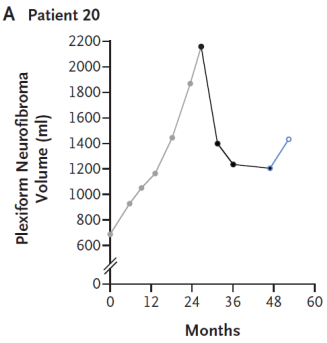
Phase I Trial of Selumetinib

- Taken twice daily on a continuous dosing schedule (1 cycle = 28 days)
- Primary Objective: Define the maximum tolerated dose (MTD) of selumetinib for pediatric patients with inoperable PN
- First treatment to show shrinkage of plexiform neurofibromas in NF1
  - Partial response in 17/24 patients







Anecdotal clinical benefit but no prospective functional measures in this study

Dombi E, et al. *N Engl J Med.* 2016.

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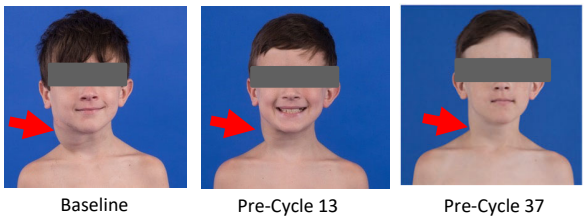
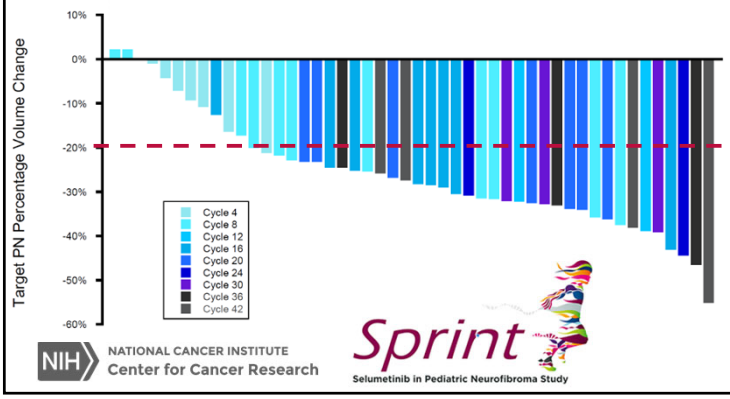
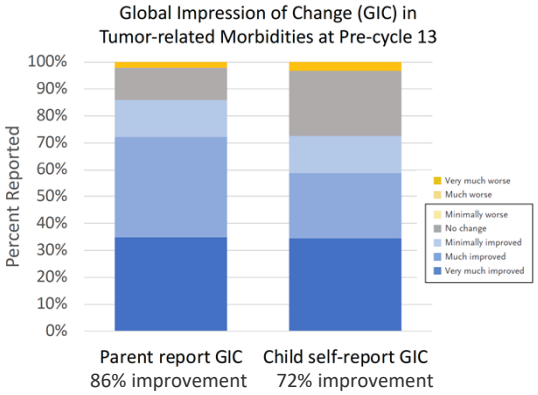
Phase 2 Trial: Selumetinib in Children with NF1 PN

- **Primary objective:** Overall Response Rate
- **Key Secondary Objectives:**
  - Functional and Patient Reported Outcomes
- **Results**:
  - Confirmed Partial response 34/50 (68%) patients
  - Clinical benefit with improvement in pain and function







Gross AM, et al. *N Engl J Med.* 2020.

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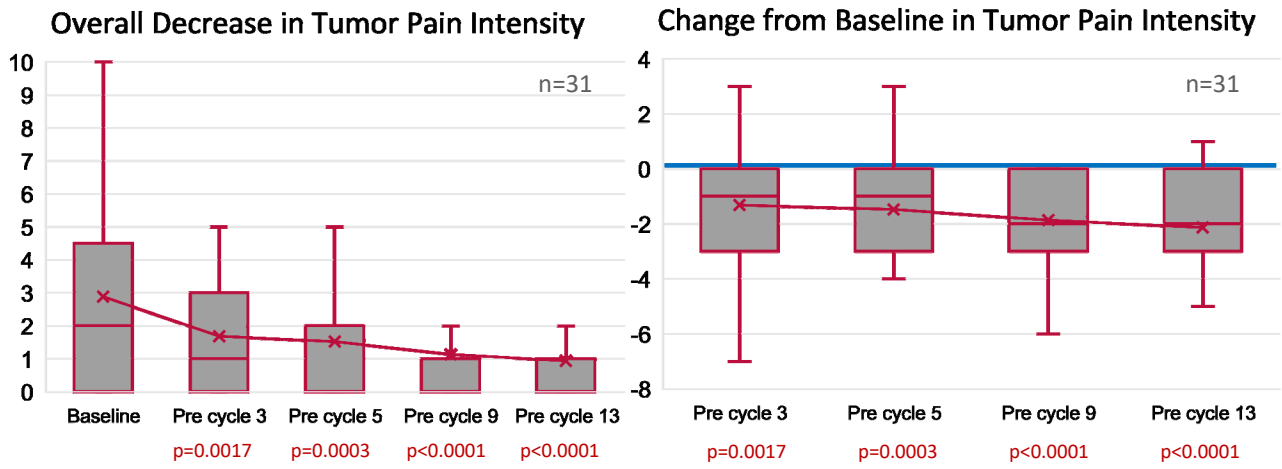
NRS-11 Self-report of Tumor Pain Intensity



- Includes 5 patient's ratings of 0 (no pain) at baseline
- Excludes 2 patients with only baseline ratings

- By pre-cycle 13, 52% of NRS-11 tumor pain intensity ratings decreased ≥2 points

Slide Courtesy of Dr. Pamela Wolters

Gross AM, et al. *N Engl J Med.* 2020.

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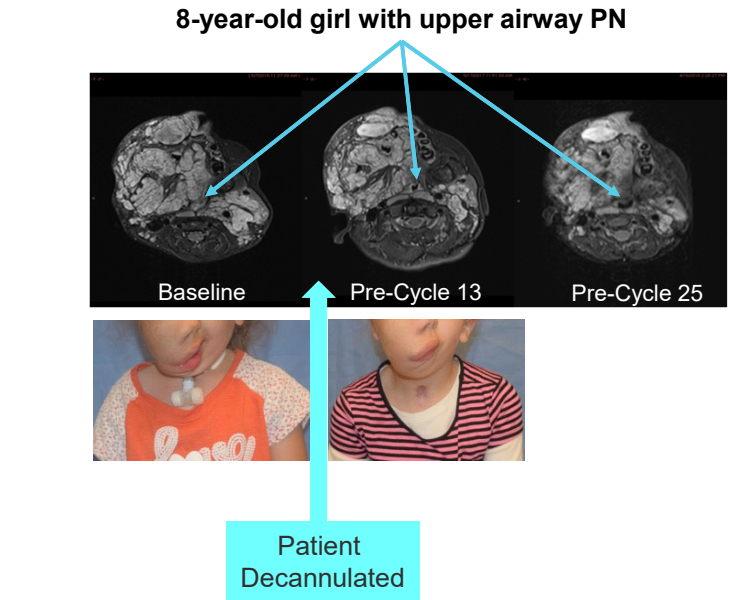
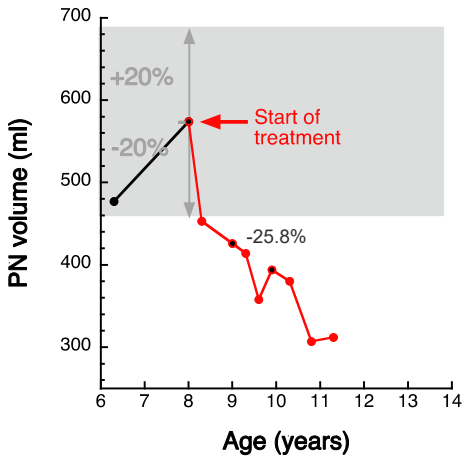
Improvement in Airway Function with Selumetinib





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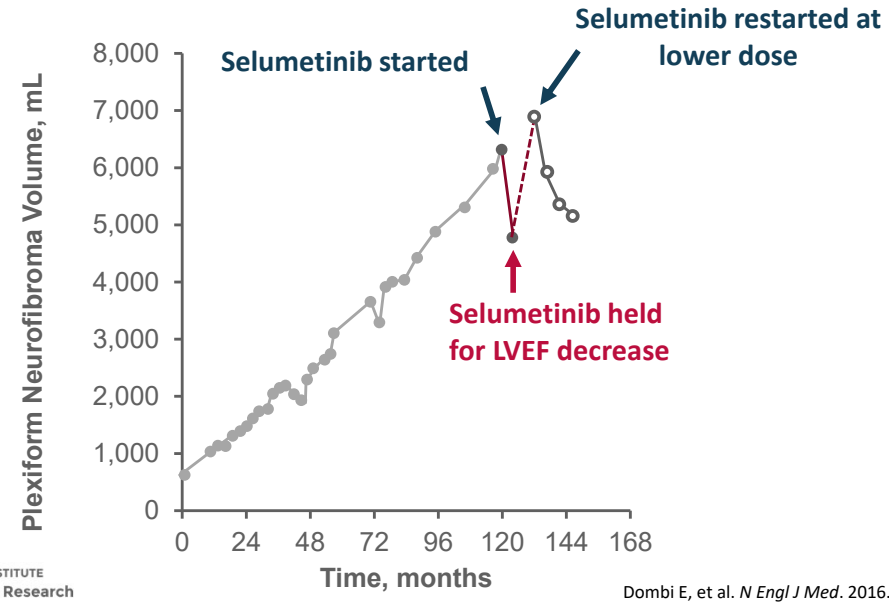
Continuous Selumetinib Needed for Sustained Response



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Dombi E, et al. *N Engl J Med*. 2016. @NCIResearchCtr 29

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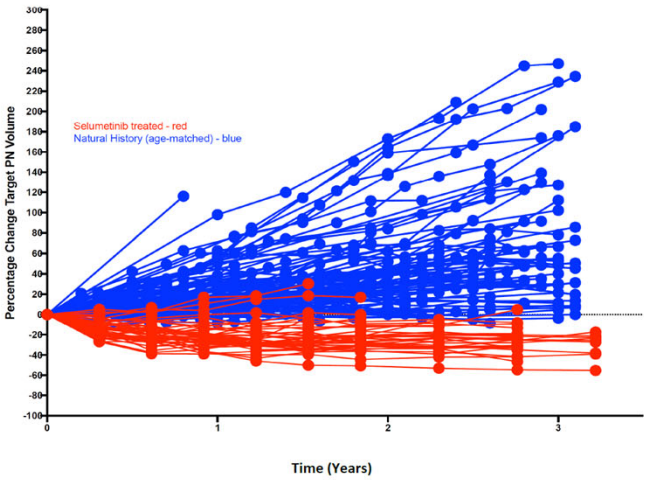
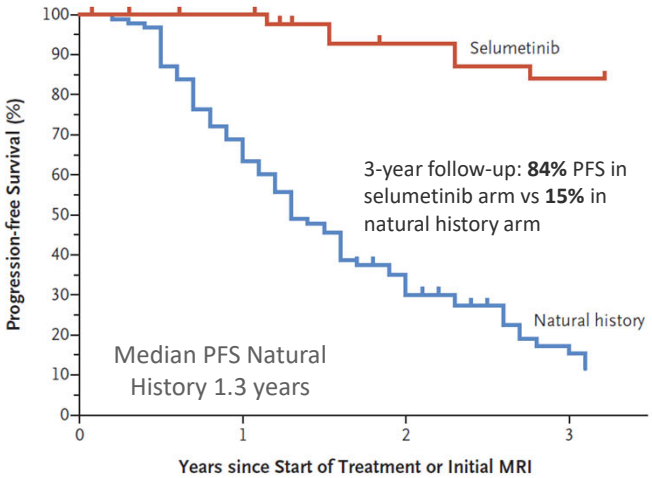
PN on Selumetinib vs Natural History

Age matched control: NCI Natural history and selumetinib





Gross AM, et al. *N Engl J Med*. 2020.

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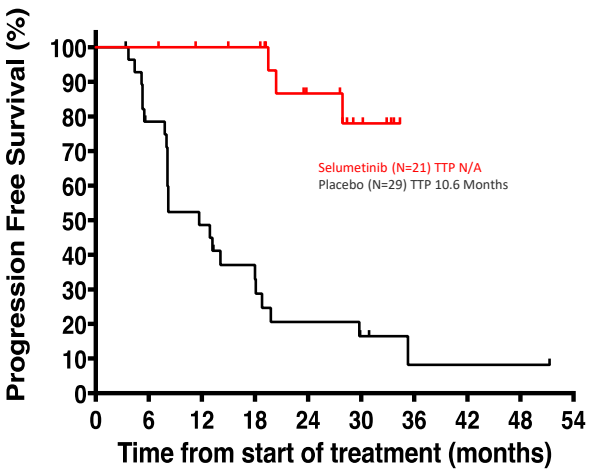
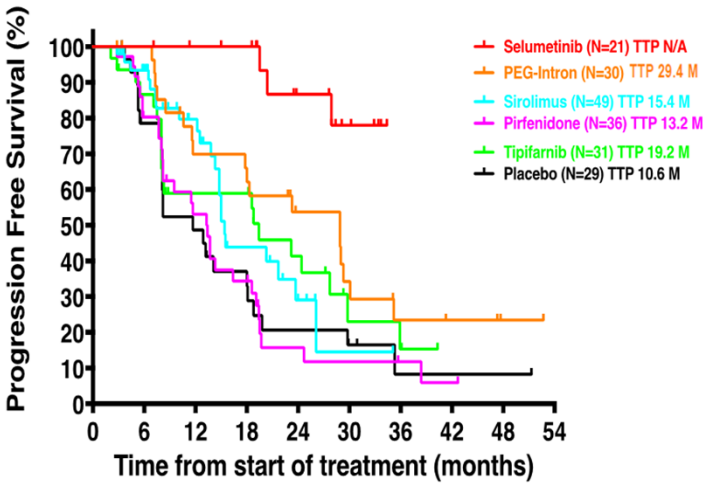
PN on Selumetinib vs Prior Clinical Trials

Tipifarnib placebo/SPRINT progressive PN



Prior studies/SPRINT progressive PN



Gross AM, et al. N Engl J Med. 2020; Weiss BS, et al. *Neuro Oncol.* 2015; Widemann BC, et al. *Neurol Oncol.* 2014; Jakacki RI, et al. *Neuro Oncol.* 2017; Widemann BC, et al. *Pediatr Blood Cancer.* 2014.

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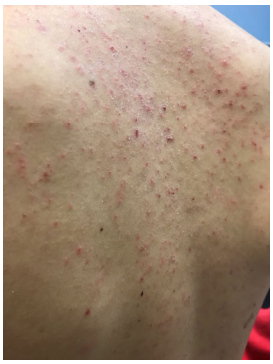
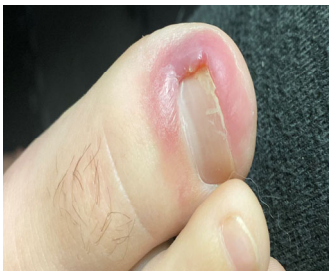
Safety and Tolerability of Selumetinib

- All subjects had at least 1 selumetinib related toxicity
  - Majority (97%) were mild (grade 1 or 2)
- All toxicities were reversible
- Most common toxicities:
  - Gastrointestinal (nausea, vomiting, diarrhea)
  - CPK Increase (asymptomatic)
  - Rash
  - Paronychia
- As of 2/27/21, median 55.5 cycles treatment
  - 5 of 50 subjects off treatment for drug-related adverse event





12/7/2022

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Regulatory Agency Approval of Selumetinib (Koselugo™)

April 10, 2020

"The Food and Drug Administration (FDA) approved selumetinib for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN)."

April 22, 2021:

"Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional1 marketing authorisation for the medicinal product Koselugo2, intended for the treatment of paediatric patients with neurofibromatosis type 1 (NF1) plexiform neurofibromas (PN)."

FDA Prescribing Information; FDA Press Release, April 10, 2020.
https://www.ema.europa.eu/en/medicines/human/summaries-opinion/koselugo (April 22, 2021)

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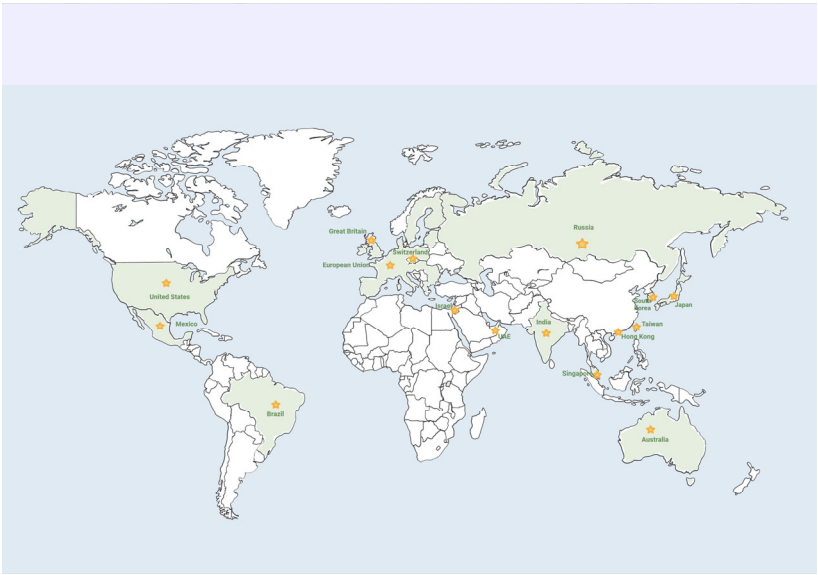
Regulatory Agency Approval of Selumetinib (Koselugo™) - October 2022



1. USA
2. Brazil
3. United Arab Emirates
4. South Korea
5. European Union (27 member countries)
6. Israel
7. Singapore
8. Great Britain
9. India
10. Mexico
11. Russia
12. Australia
13. Taiwan
14. Hong Kong
15. Switzerland
16. Japan

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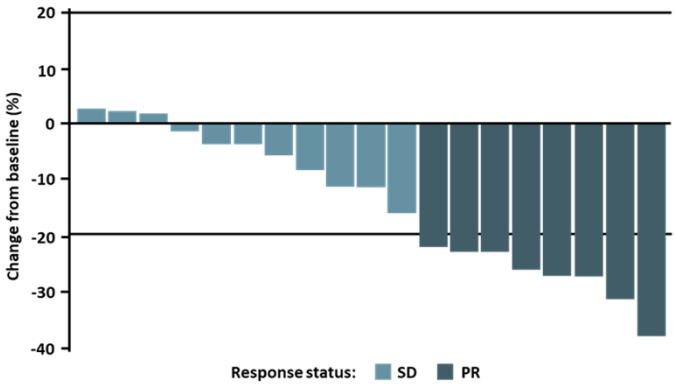
Other Treatments For PN:

- Other MEK Inhibitors have caused PN shrinkage:
  - **Binimetinib**
  - **Trametinib**
  - **Mirdametinib**
- **Cabozantinib:** Multi-receptor Tyrosine Kinase Inhibitor (TKI)
  - First non-MEK inhibitor to show tumor shrinkage

Phase 2 Trial of Cabozantinib

Multiple RTK inhibitor: MET, VEGFR2, c-KIT, RET



Fisher MJ, et al. *Nat Med*. 2021.
Mueller S, et al. *ISPNO*. 2020. Abstract NFB-17.
McCowage GB, et al. *J Clin Oncol*. 2018
Weiss B, et al. *J Clin Oncol*. 2021.

What's Next for Plexiform and Atypical Neurofibromas?

- Combination trials to try to improve the amount of PN tumor shrinkage
- Alternative dosing schedules to try to decrease side effects
- Prevention study – should we be treating young children with PN BEFORE they develop symptoms?
- Other treatment options for atypical neurofibromas?

Any Questions?

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Extra Slides

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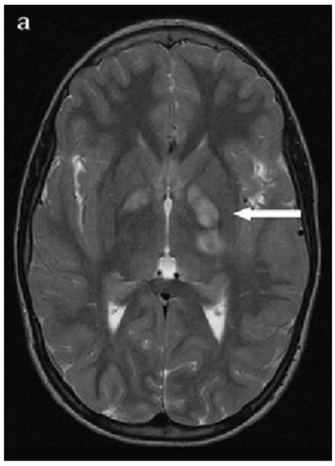
T2 Hyperintensities (aka Spongiform Gliosis, UBOs)

- Increased signal intensity on T2 weighted MR images (60%-70%)
- Isointense on T1 weighted MRI no mass effect, no contrast enhancement
- Pathology: Dysplastic glial proliferation, vacuolation of myelin sheets
- Location: Basal ganglia, optic tract, brainstem, cerebellum
- Clinical significance: No clear association with cognitive defects
- Spontaneous resolution in 2nd to 3rd decade



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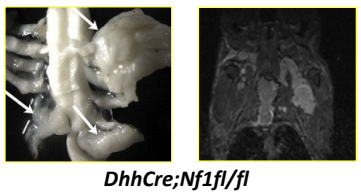
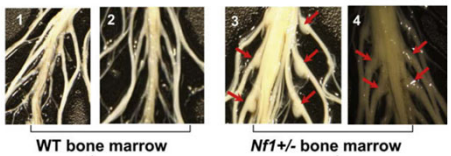
Pre-Clinical Models of Plexiform Neurofibromas

- Genetically engineered mouse models of NF1 neurofibroma predict for activity
- MEK Inhibitor (MEKi) is first active therapy

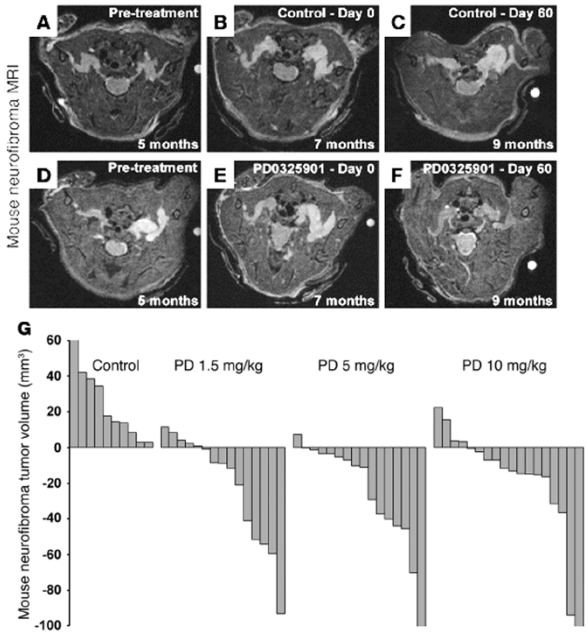
Mouse Neurofibromas



DhhCre;Nf1fl/fl



Krox20;Nf1$^{flox/flox}$



Wu J, et al. *Cancer Cell*. 2008; Yang FC, et al. *Cell*. 2008; Jessen WJ, et al. *J Clin Invest*. 2013.

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Few Genotype-Phenotype Correlations in NF1

Genotype	Phenotype
1.4 Mb microdeletion	Coarse face, ptosis, hypertelorism, broad nose, multiple neurofibromas, ADHD, cognitive impairment, macrocephaly, heart defects, connective tissue dysplasia, scoliosis, pectus, bone cysts, and increased risk for malignancy (i.e., MPNST)
Missense mutations in NF1 codons 844–848	Higher risk for OPGs, plexiform neurofibromas, spinal neurofibromas, superficial neurofibromas, and higher risk for scoliosis and skeletal anomalies
NF1 pMet992del	Mild phenotype—café-au-lait and freckling only
NF1 codon 1809 missense mutations	Café-au-lait, learning delays, and pulmonic stenosis (Noonan features), but lower risk of plexiform neurofibromas and OPG

Kayes LM, et al. *Am J Hum Genet.* 1994; Koczkowska M, et al. *Am J Hum Genet*. 2018; Koczkowska M, et al. *Genet Med*. 2019; Rojnueangnit K, et al. *Hum Mutat.* 2015.

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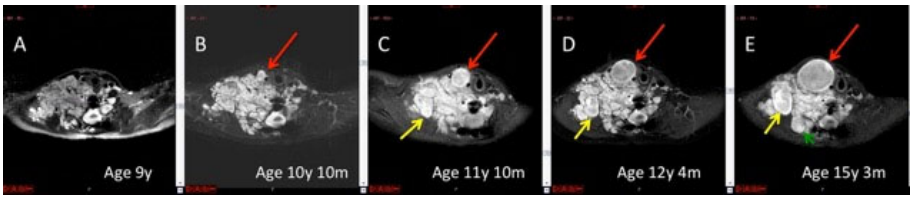
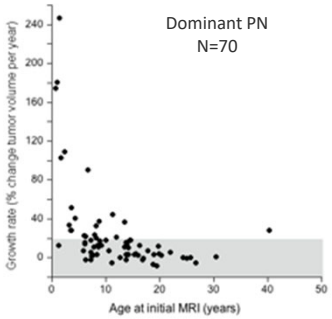
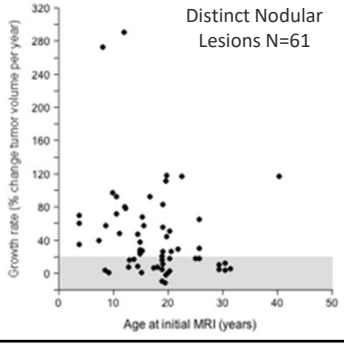
Characterization of Atypical Neurofibromas

- Distinct imaging, clinical, and genomic (*CDKN2A* loss) characteristics

Distinct nodular lesion







Pathology:
- Atypia,
- Loss of neurofibroma architecture
- Mitosis
- Increased cellularity
- ANNUBP:
  - **A**typical
  - **N**eurofibromatous
  - **N**eoplasm of
  - **U**ncertain
  - **B**iologic
  - **P**otential

Akshintala S…Widemann B: Neuro Oncol 2020
Reilly K…Stewart D: JNCI 2017
Miettinen M…Perry A: Humpath 2017

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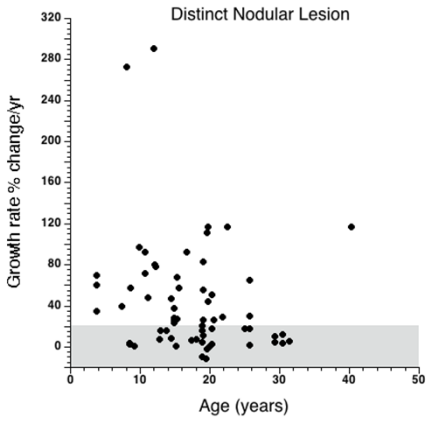
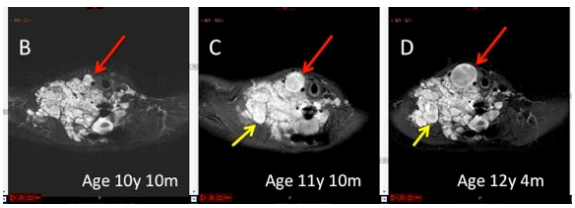
NF1 Juvenile Myelomonocytic Leukemia (JMML)

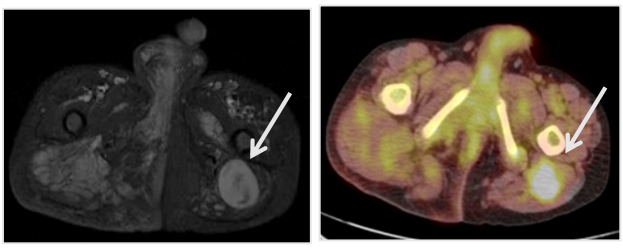
- Rare myeloproliferative disorder of early childhood (<1% of all childhood leukemias)
- Clinical diagnosis of NF1 in 10% to 14% of children with JMML
- Activating RAS mutations in 18-25%(not in NF1)
- NF 1 mutations in approximately 30% of patients with JMML
- Hypersensitivity to GM-CSF
- GM-CSF stimulation associated with elevated ras-GTP
- Only HCT has resulted in extended survival
- Ongoing clinical trial with MEK inhibitors

Distinct Nodular Lesions

- Distinct Nodular Lestions (DNL):
  - Identified by imaging
  - Round/oval, well demarcated, ≥ 3 cm,
  - Within or outside a PN
  - Often FDG-Avid
  - Growth rates different from PN



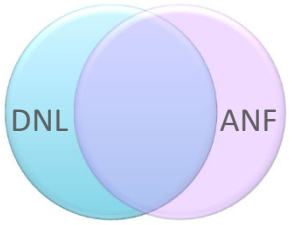




(Figures from Akshintala 2020)

Atypical Neurofibromas

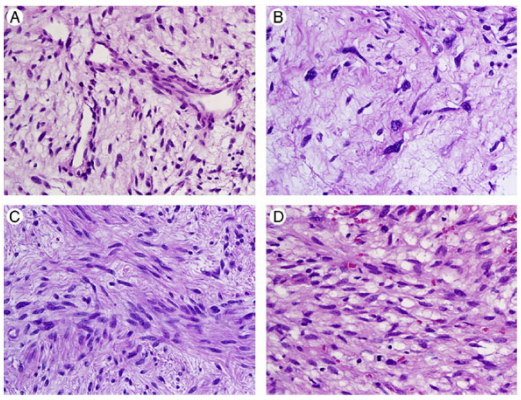
- Atypical Neurofibromas (ANF): Histopathologic diagnosis based on nuclear atypia, hypercellularity, loss of neurofibroma architecture and rare mitosis
  - MAY be Distinct Nodular Lesion on imaging (but not always!)



Pathology of ANF:
- Atypia
- Loss of neurofibroma architecture
- Mitosis
- Increased cellularity

ANNUBP: At least 2 of the ANF pathology features
- **A**typical
- **N**eurofibromatous
- **N**eoplasm of
- **U**ncertain
- **B**iologic
- **P**otential

Figure from Miettinen 2017



(Miettinen, 2017)

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Atypical Neurofibromas are MPNST Precursors

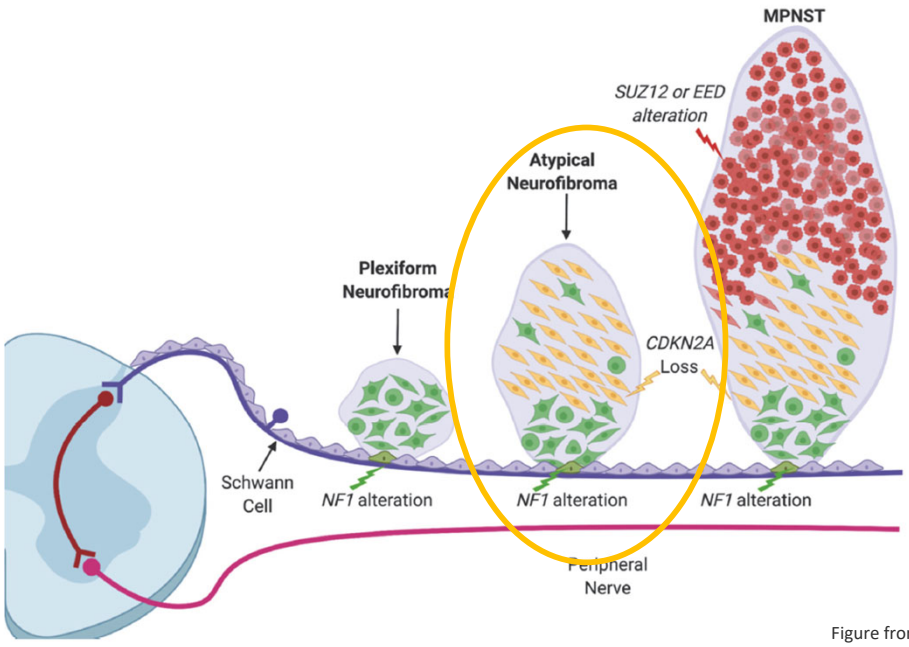

Figure from *Zhang, X…Shern J, Genes 2020*

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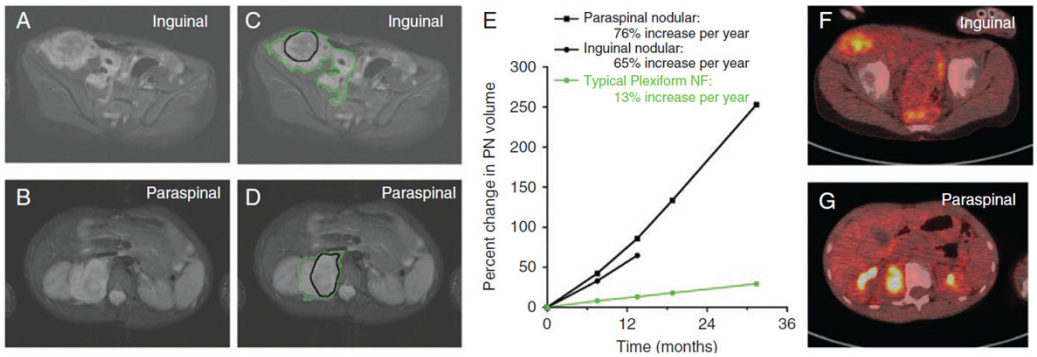
ANF management- an unmet need for clinical trials

- ANF Require close observation and imaging with MRI and FDG-PET
- Recommendations of recent consensus conference:
  - Surgical resection IF feasible without substantial morbidity
  - Due to locations, often cannot be easily surgically removed
  - Patients may have multiple ANF
- **No previous clinical trials specifically targeting ANF have been conducted**



Pemov A…Stewart D, Neuro-Oncology 2019

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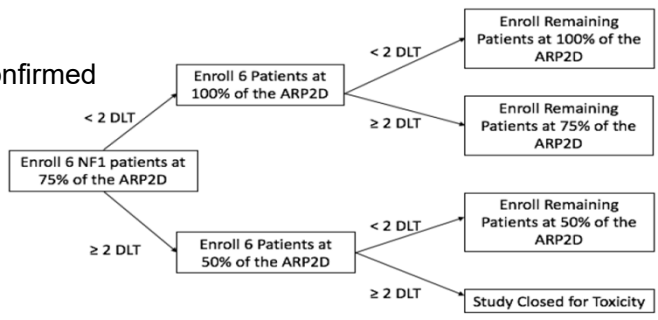
Phase I/II Study of the Cyclin-Dependent Kinase (CDK)4/6 Inhibitor Abemaciclib for Neurofibromatosis Type 1 (NF1) Related Atypical Neurofibromas (ANF)

- Primary Objectives
  - **Phase I:** To determine the recommended Phase II dose (RP2D) of abemaciclib in patients with NF1 and a measurable ANF
  - **Phase II:** To determine the objective response rate (ORR) in the target ANF; complete and partial response (CR + PR), response determined by volumetric MRI analysis (≥ 20% volume reduction) compared to baseline
- Key Eligibility Criteria:
  - ≥12 years old with NF1
  - Presence of ≥ 1 atypical neurofibroma, biopsy confirmed
- Goal Sample Size: 27 subjects
- Study Status: **ENROLLING!**



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