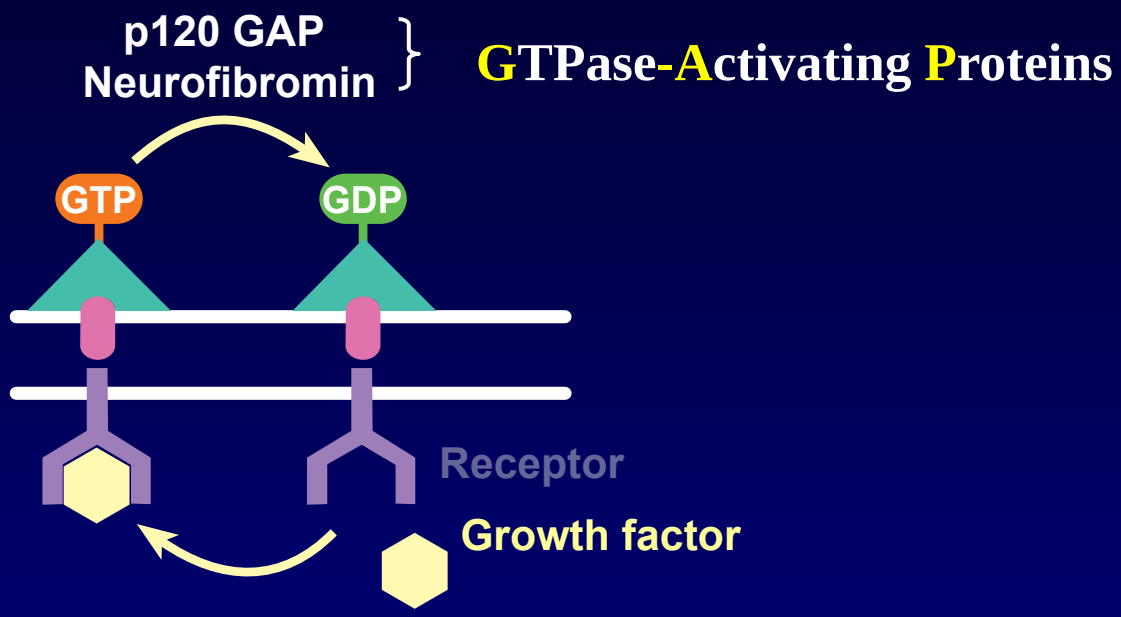
Neurofibromatosis Type 1 (NF 1)

- **Most common single gene disorder (1:3500)**
  - Neurofibromin,17q11.2, tumor suppressor gene
- **Cutaneous stigmata:**
  - Café au lait spots, dermal neurofibromas, skin freckling
- **Tumor development:**
  - Plexiform neurofibromas (PN)
  - 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

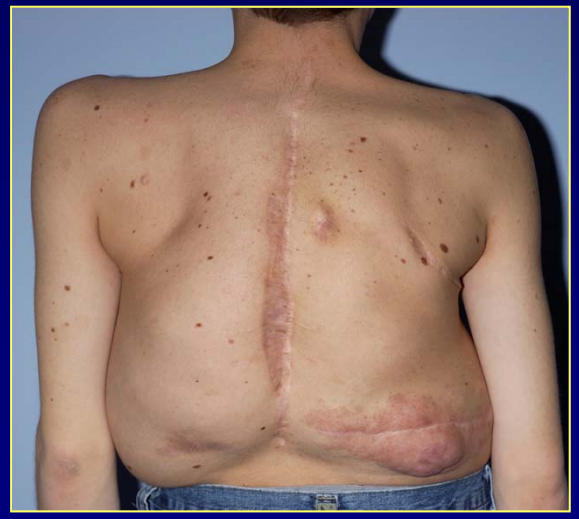
NF1 Tumor Development

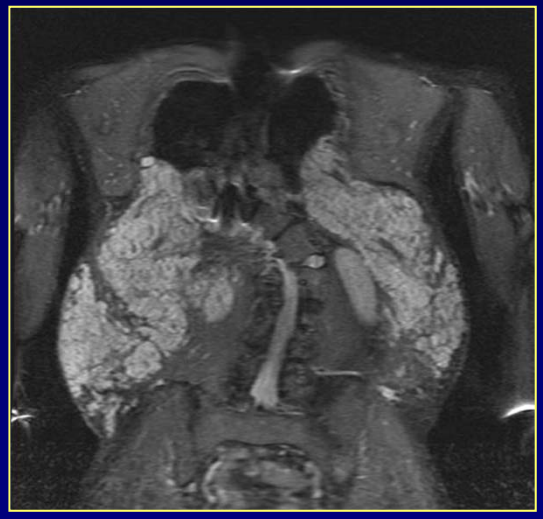


Targets for NF1 Tumors	
Ras pathway	M-TOR
Angiogenesis	EGFR
Mast cell	Kit, TGF- β

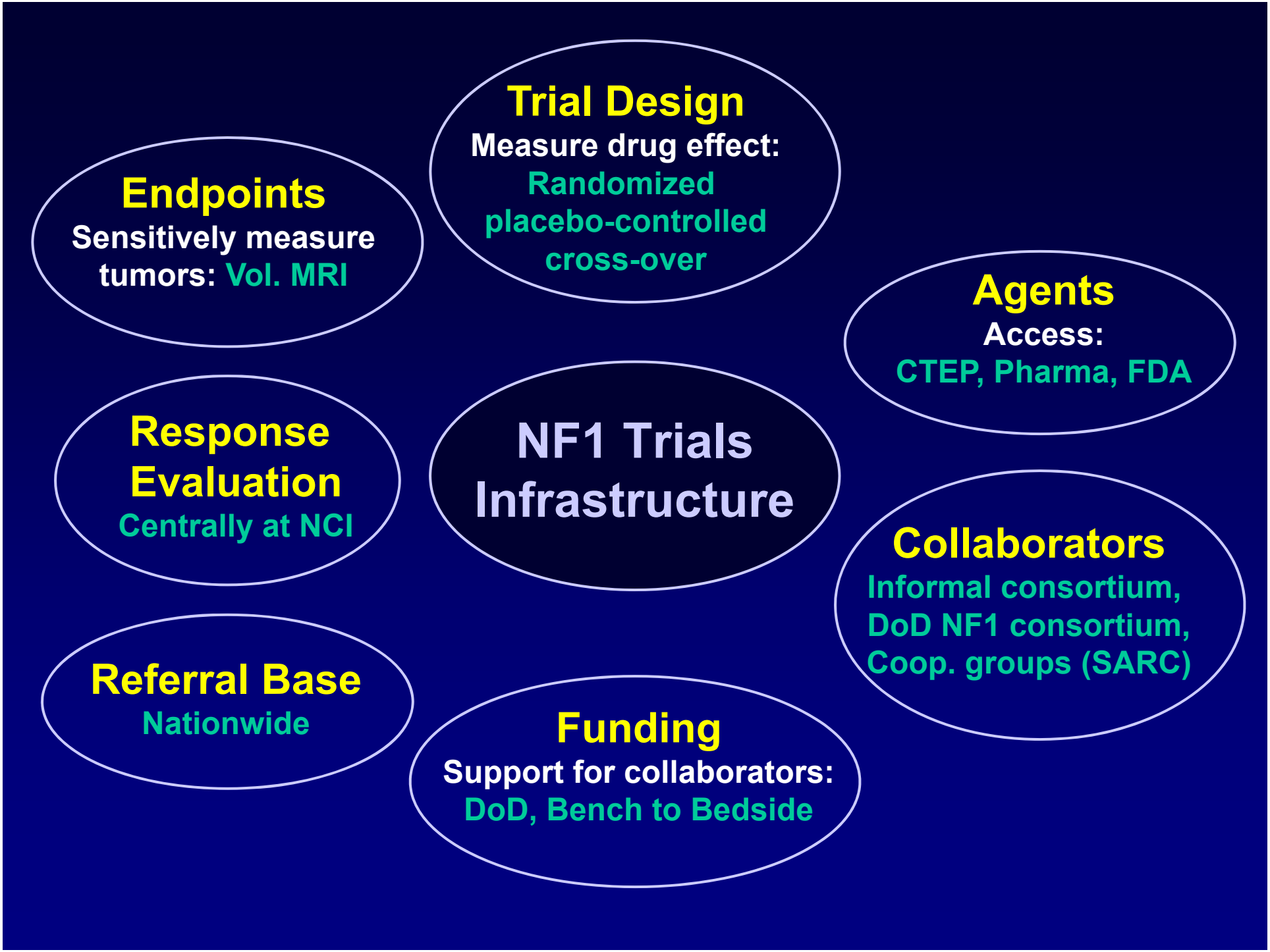
Plexiform Neurofibromas

- Involve multiple nerve fascicles/branches (25%)
- Congenital, erratic growth, large size and complex shape
- Disfigurement, functional impairment, life-threatening
- Malignant transformation to MPNST (8-13%)
- Surgical resection only standard treatment





- Medical treatment may reduce morbidity and prevent cancers

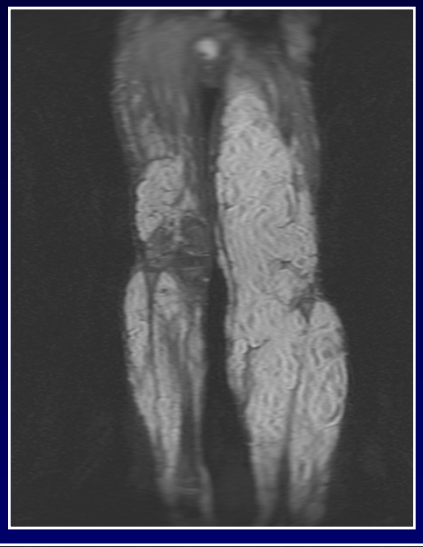

Trial Design
Measure drug effect:
Randomized
placebo-controlled
cross-over
Endpoints
Sensitively measure
tumors: Vol. MRI
Agents
Access:
CTEP, Pharma, FDA
Response
Evaluation
Centrally at NCI
NF1 Trials
Infrastructure
Collaborators
Informal consortium,
DoD NF1 consortium,
Coop. groups (SARC)
Referral Base
Nationwide
Funding
Support for collaborators:
DoD, Bench to Bedside

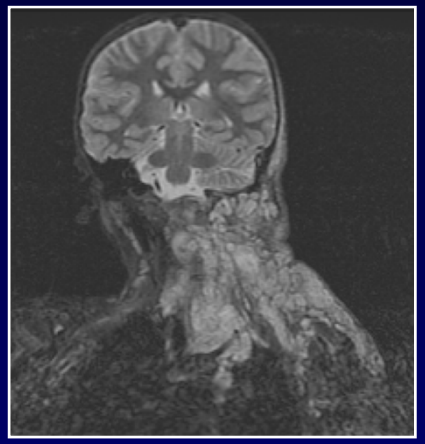
Clinical Drug Development

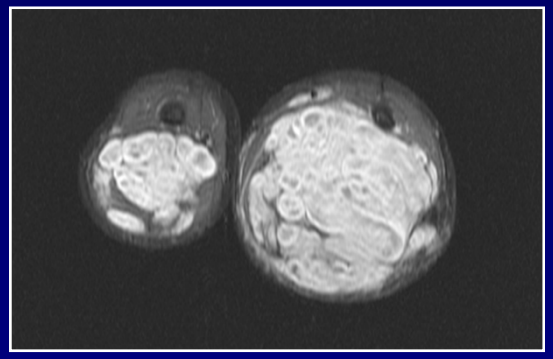
	Cancer		NF1
Study	**Objective**	**Endpoint**	**Trials in NF1**
Preclinical	Start dose human trial	Toxicology in animals	Chronic toxicity Reproduction toxicity
Phase I	MTD PK	Toxicity	Chronic dosing Redefine DLT, MTD
Phase II	Activity	Response TTP	Response unrealistic Progression difficult to measure Unknown NH
Phase III	Efficacy	Survival QOL	Near normal survival QOL

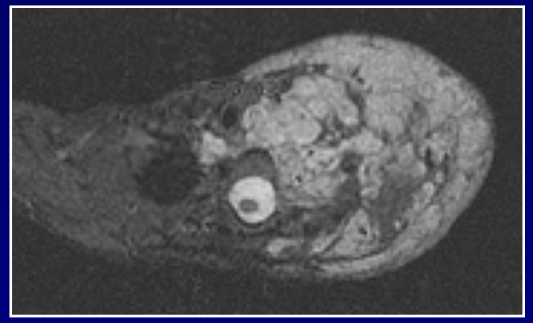
MTD, Maximum Tolerated Dose; DLT, Dose-Limiting Toxicity; TTP, Time To Progression; QOL, Quality Of Life; PK, Pharmacokinetics

Complex Plexiform Neurofibromas





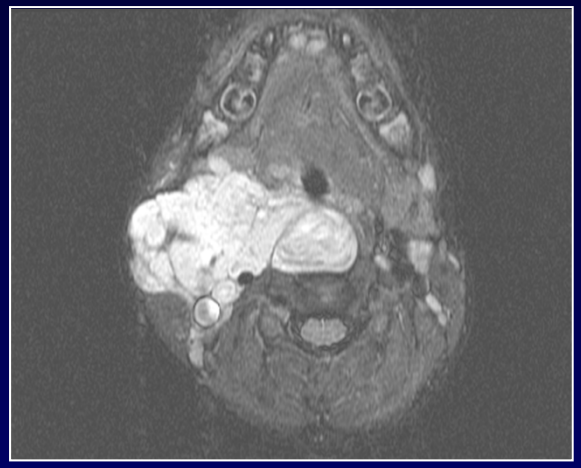




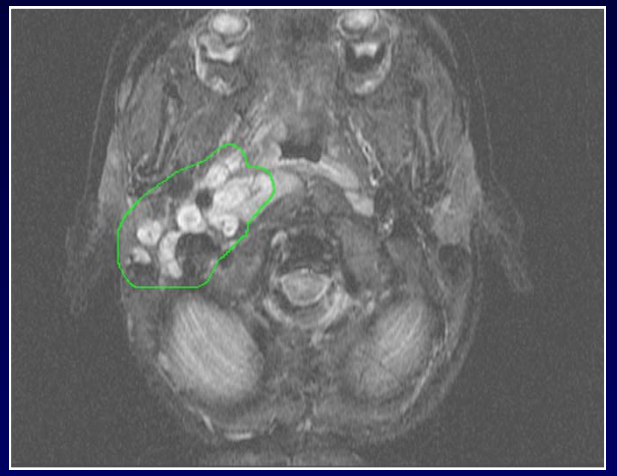
Measuring change in PN size difficult with standard criteria (WHO, RECIST)

Volumetric MRI Analysis: MEDx

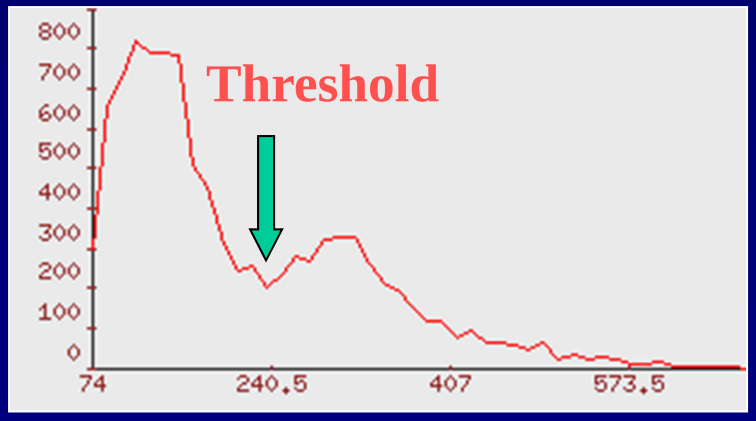
STIR Sequence



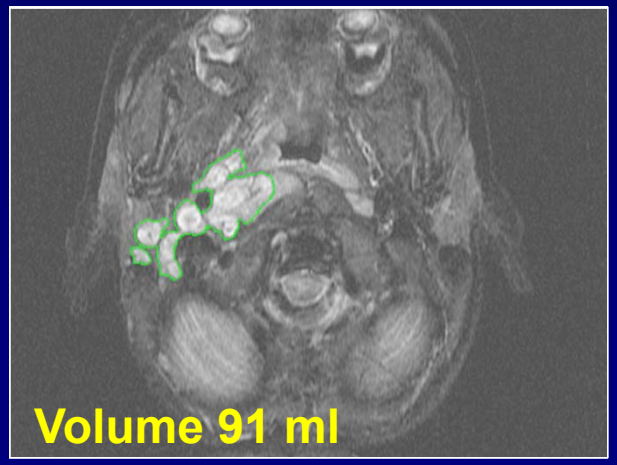
Define Border



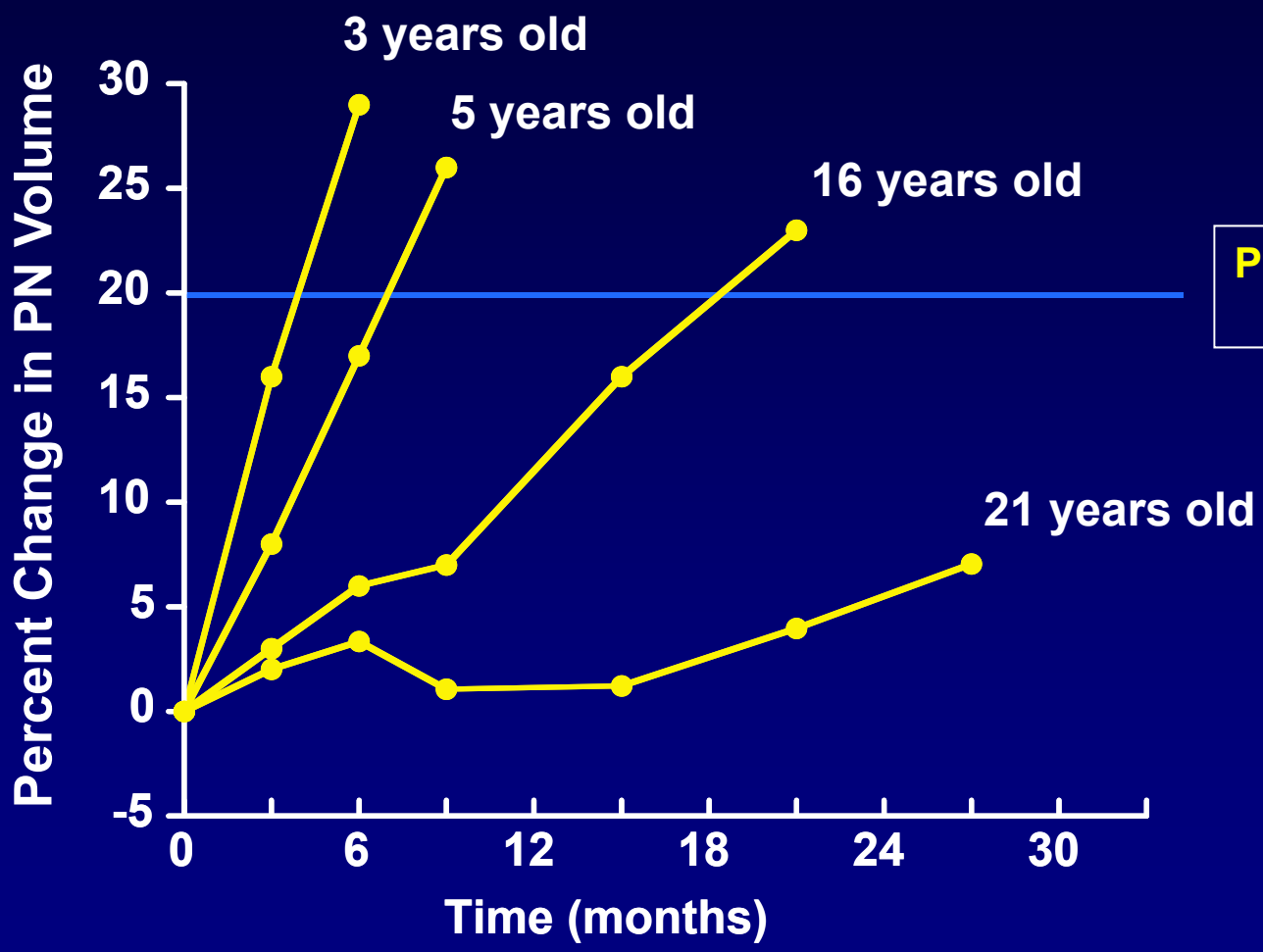
Histogram Analysis



Final Tumor Border



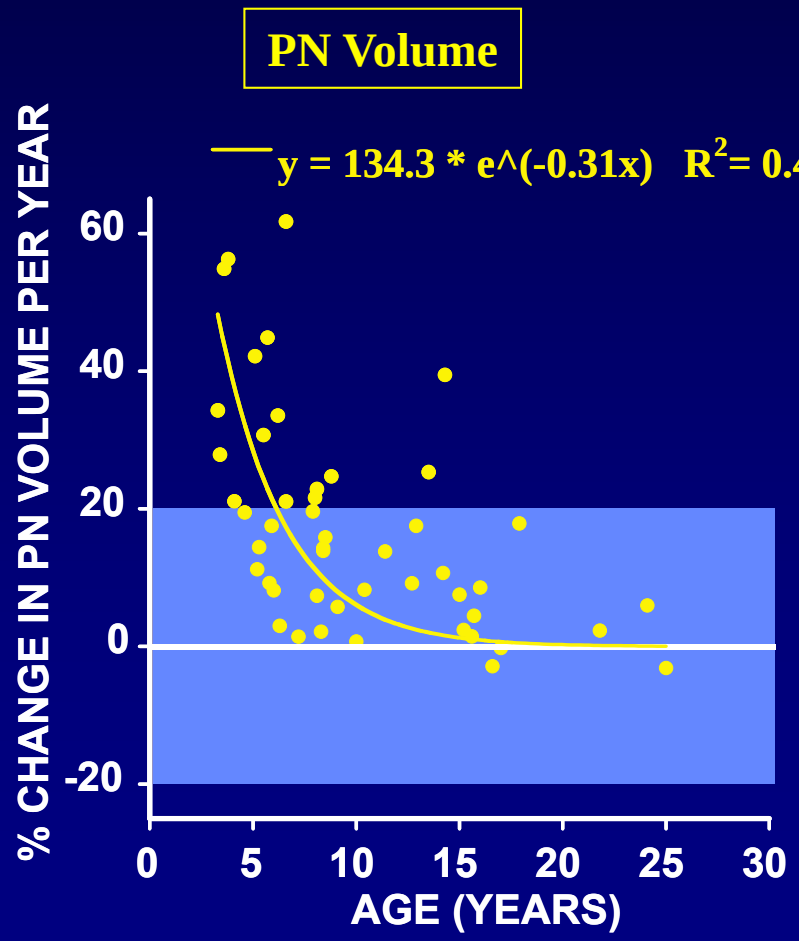
Growth Rate and Pattern of PNs

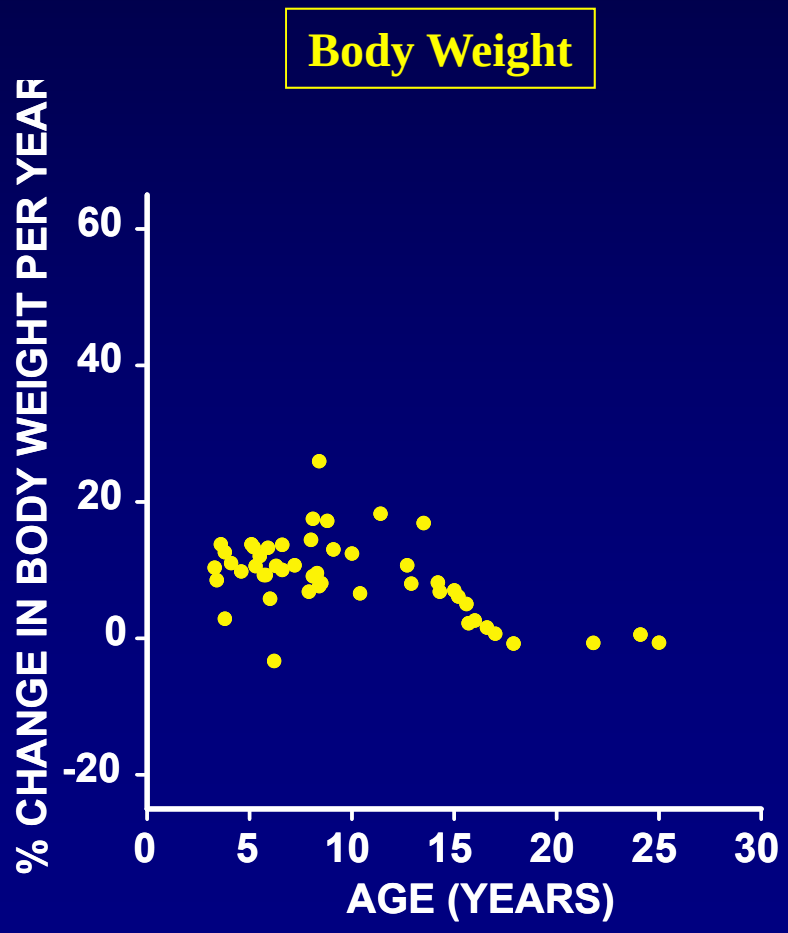


Progressive Disease:
PN Volume ↑ 20%

Longitudinal Volumetric MRI of PN

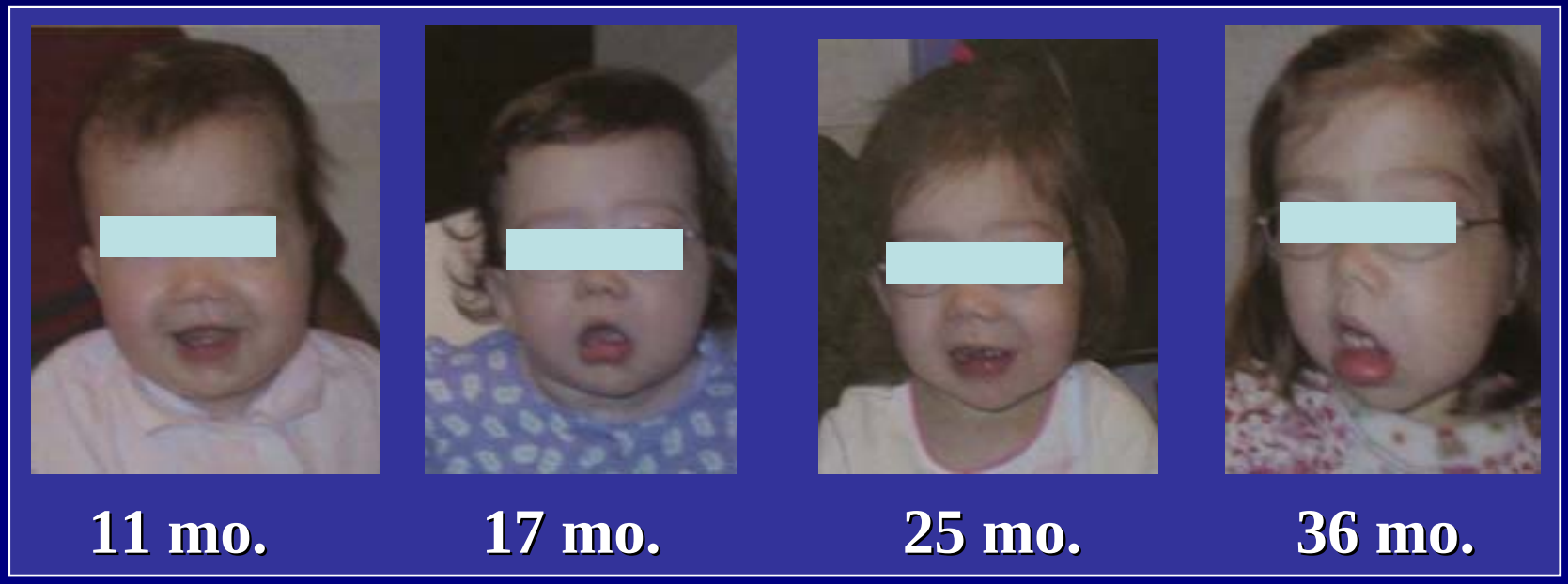
- 49 patients with 61 PN, median age 8.3 years (3.3-25)
- Observation period 34 months (18-70 months)
- PN volume at baseline 471 ml (31-5573 ml)





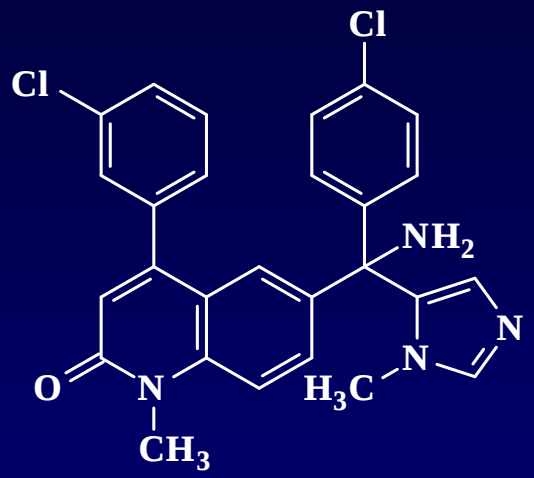
Conclusions Volume Analysis PN

- Volumetric MRI sensitively measures PN growth
- PN growth rate varies among patients, but is constant within a patient
- PNs grow more rapidly in younger patients
- Age stratification for treatment trials is indicated
- Body growth does not account for more rapid growth of PN in young children
- Drug development for PN should target young patients



Tipifarnib

Farnesyltransferase Inhibitor



Mechanism of Action: Targets RAS farnesylation

Route of Administration: Oral, twice daily for 21 days

Toxicity Profile: Myelosuppression, rash, GI

Cancer Development: Leukemias/MDS, breast

Pediatric Phase I Trial of Tipifarnib

Eligibility: Age 2-18 years
NF1 and solid tumors

Endpoints: MTD, toxicities, PK, PD

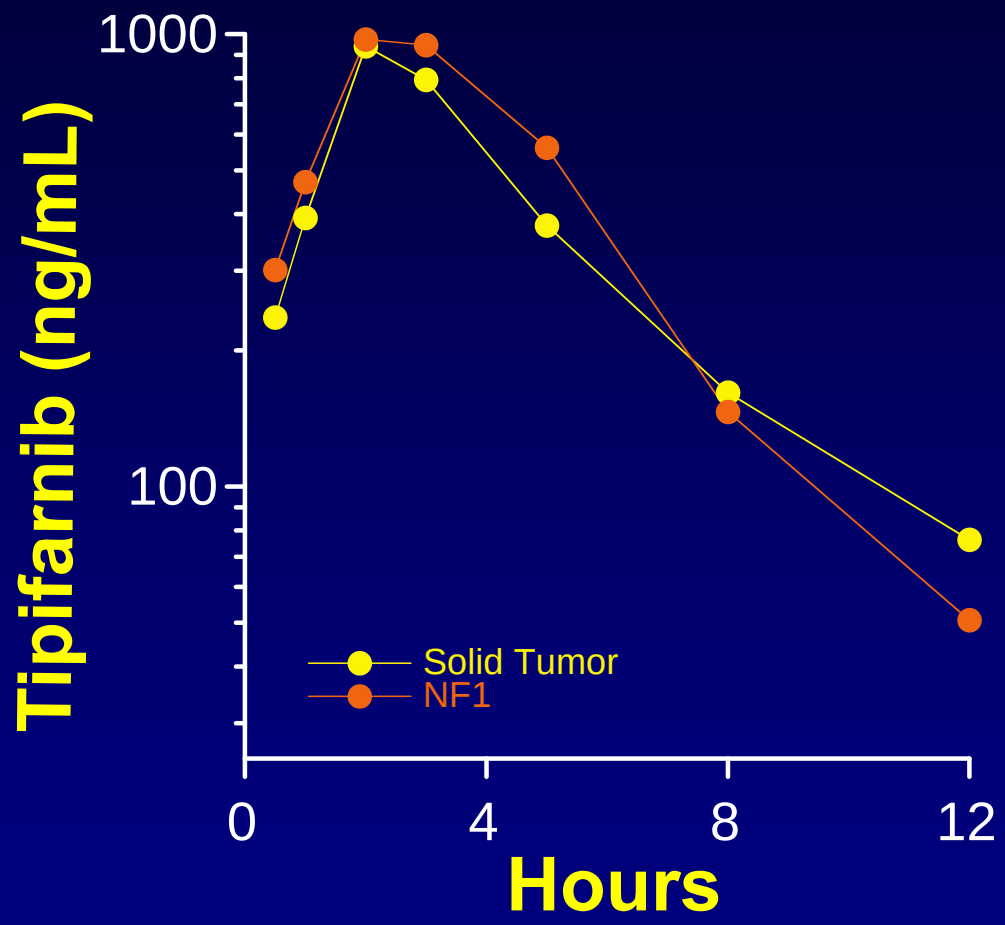
Schedule: Oral every 12 hours for 21 days followed by 7 days rest

Dose levels: 150 (n=4), 200 (n=13) MTD, 275 (n=12), 375 (n=7) mg/m^2/dose

Pediatric Tipifarnib Phase I Trial

Characteristics	NF1	Solid Tumor
Patients entered (N)	21	25
Median (range) Age (yr)	7 (5-16)	15 (5-18)
DLT	Diarrhea (1) ANC (1), Rash (1)	Plt (3), ANC (2), Rash (1) NV (1), FN (1)
ANC baseline (/μL)	2968 (1495-8520)	3570 (2330-7200)
ANC nadir (% decrease)	32 (0-87)	37 (0-100)
CL/F (mL/min/m^2)	819 (280-2070)	680 (162-4310)
Median (range) cycle #	10 (1-32)	1 (1-4)
Cumulative toxicity	None	Not evaluable

Tipifarnib Pharmacokinetics (200 mg/m^2)



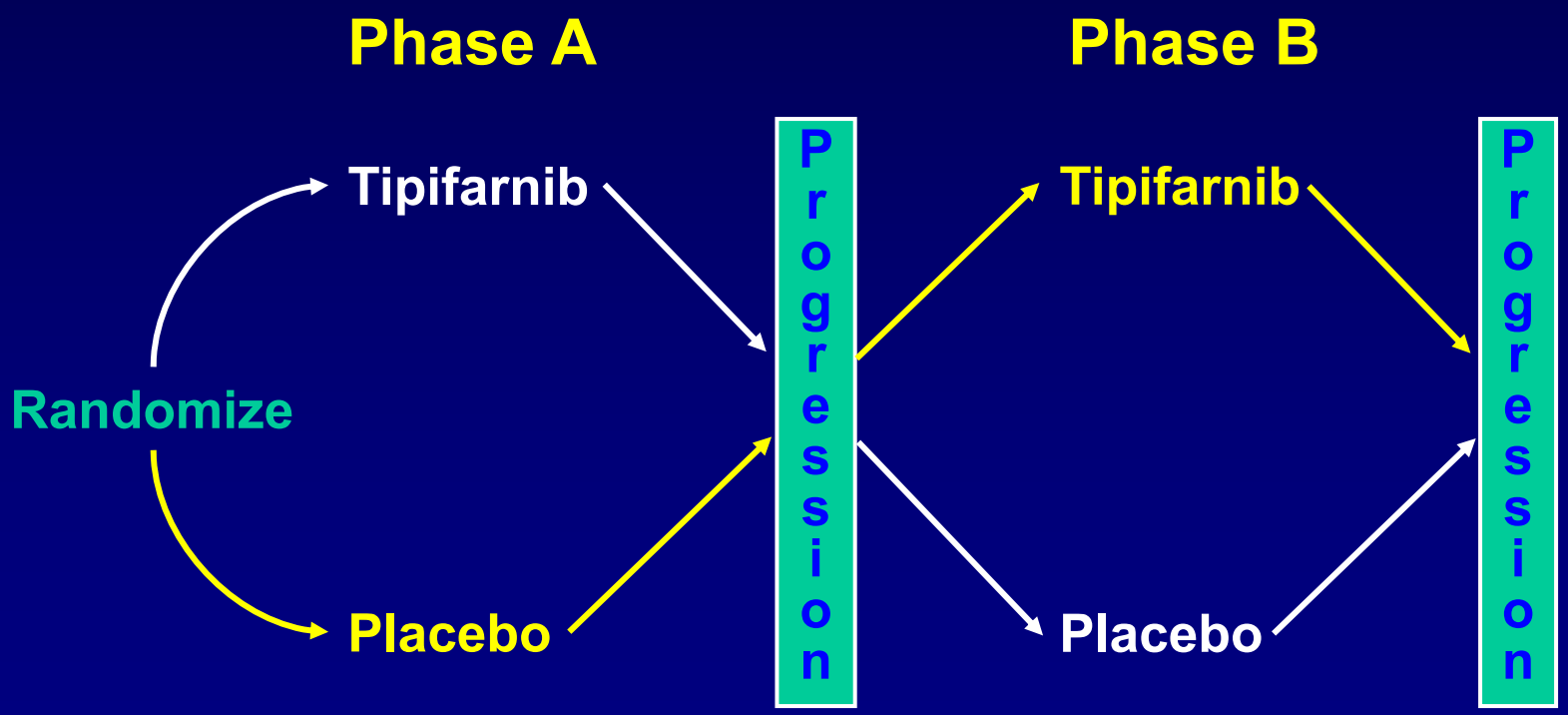
$C_{12\ h}$: 146 nM
C_{12h}: 103 nM

- 70% inhibition of FTase in PBMCs

Phase II Trial of Tipifarnib for PN

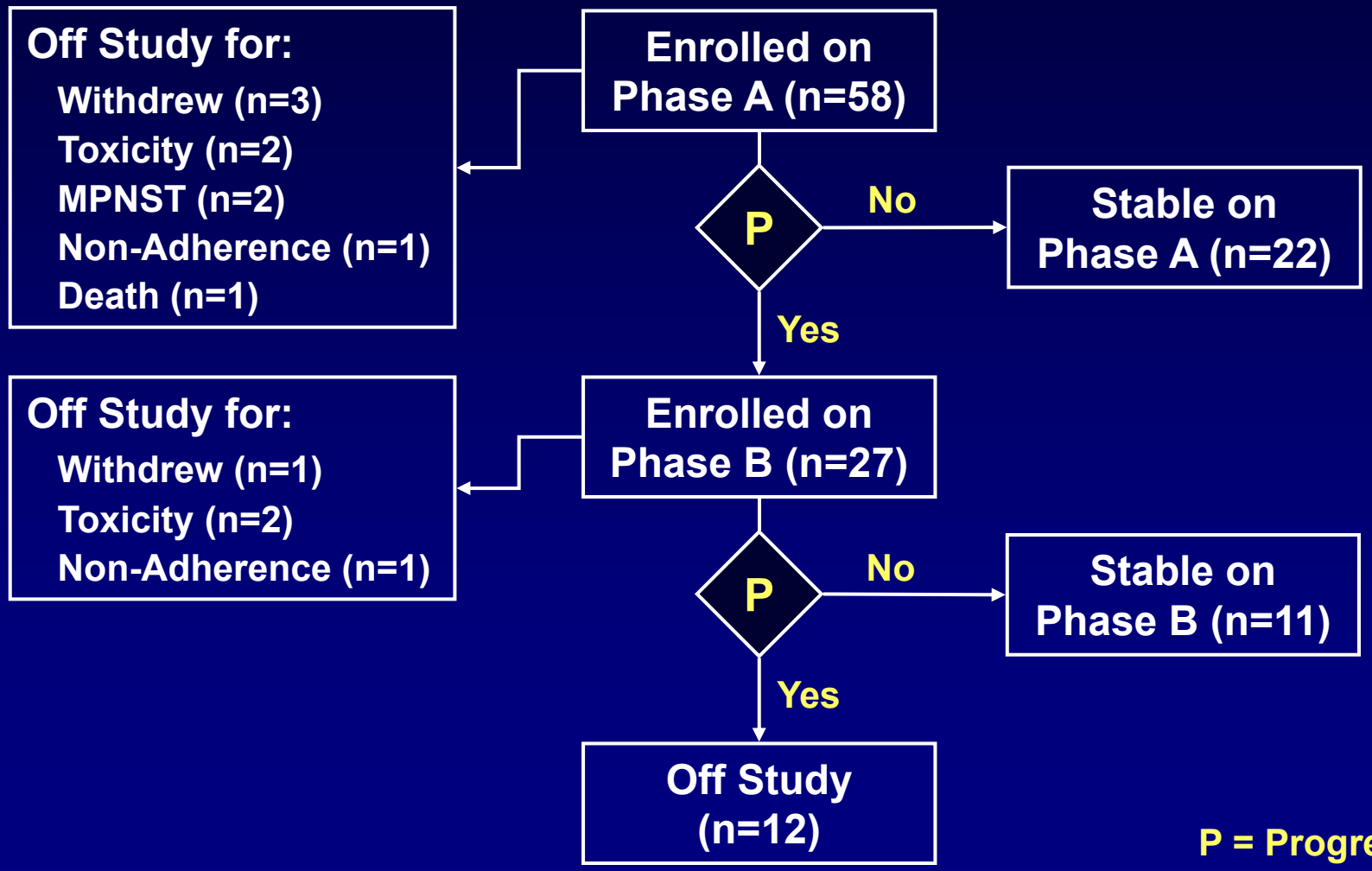
Double-blinded, placebo-controlled, flexible cross-over

Endpoint: Time to progression (PN volume ↑ ≥ 20%)



Status of Tipifarnib Phase II Trial

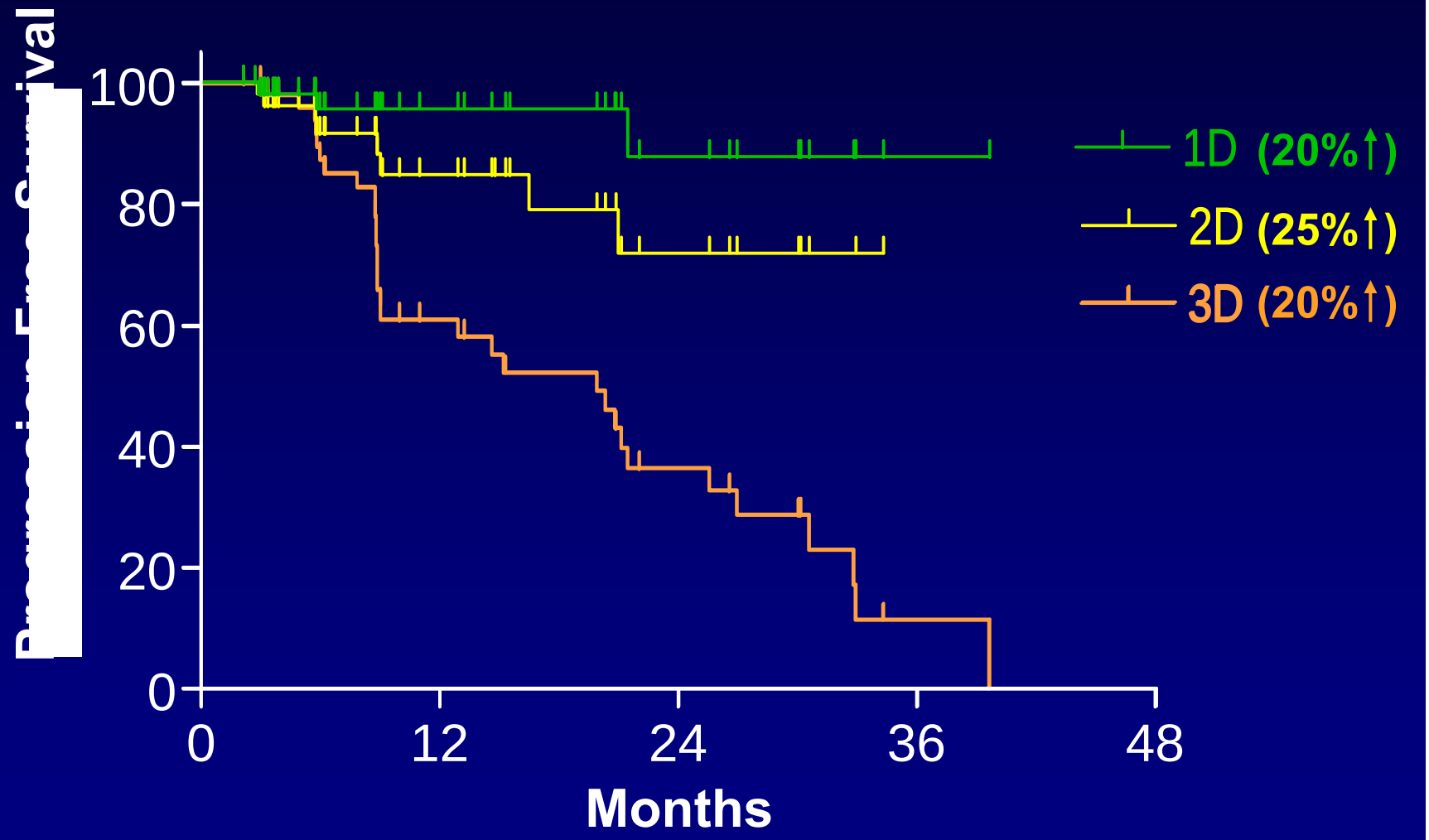
Patients: 58 (35 m, 23 f), median age: 8 years (3-21 yrs.)



P = Progression (≥20% volume increase)

Time to Progression (Phase A)

54 Patients



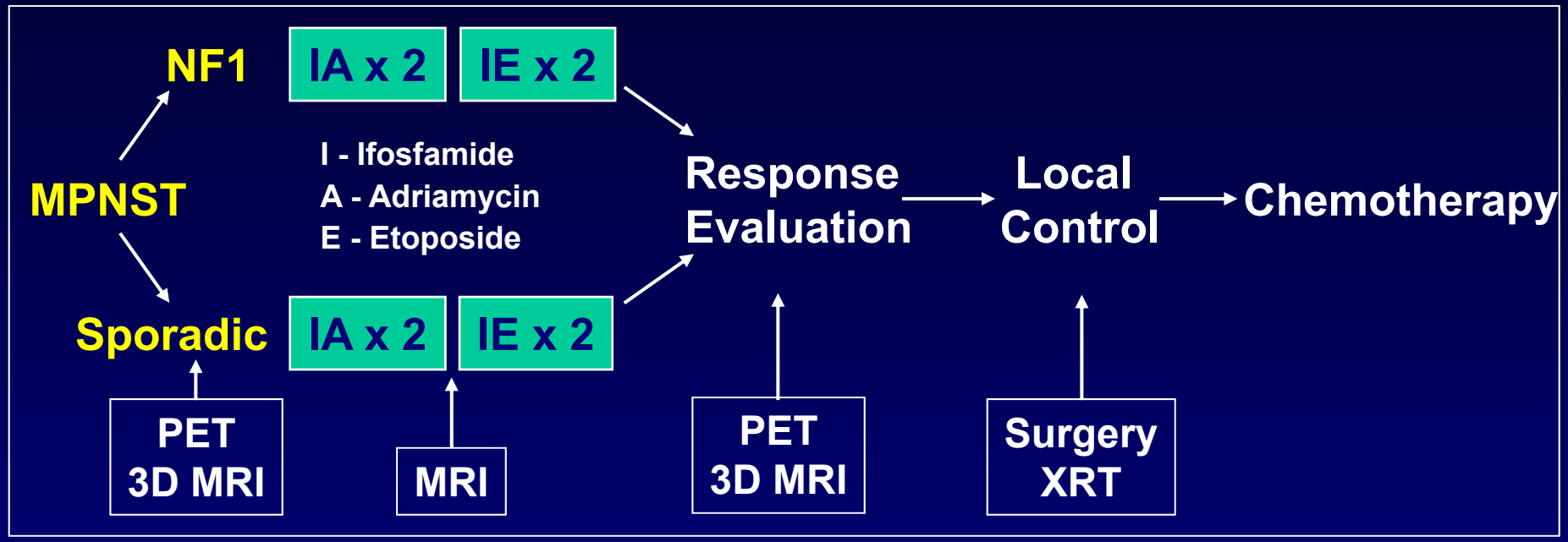
Conclusions Tipifarnib Phase II Trial

- Tipifarnib / placebo toxicity indistinguishable
- Volumetric MRI analysis more sensitive than standard criteria in detecting progression
- Progression by volumetric MRI is a valid endpoint
- Randomized flexible cross-over design is feasible
- Placebo arm will serve as historical control group for other ongoing trials

Malignant Peripheral Nerve Sheath Tumor

Characteristics	MPNST	
	Sporadic	NF1
Incidence (%)	0.001	8-13
Age at diagnosis (yrs.)	40-62	26-36
Development	De novo	In PN
Clinical findings	Pain, rapid growth, neurologic compromise	
Molecular biology	Not distinct	
Chemotherapy response %	55	18
5-year survival %	42-57	16-38

Phase II Trial of Neoadjuvant Chemotherapy in Sporadic and NF1 Associated High Grade Unresectable MPNST



- **Primary objective:**
  - Response rate after 4 cycles of chemotherapy in NF1 and sporadic MPNST
  - Target response rate (CR or PR by WHO criteria): 40%
- **Secondary objectives:**
  - Response evaluation with ^{18}FDG-PET, 3-D MRI, pathology (% necrosis)
  - Molecular biology, tissue microarray, serum proteomics
  - Epidemiology of MPNST (NF1 vs. sporadic)
- **A collaborative effort of** NCI, SARC, and NF1 centers, funded through DoD grant

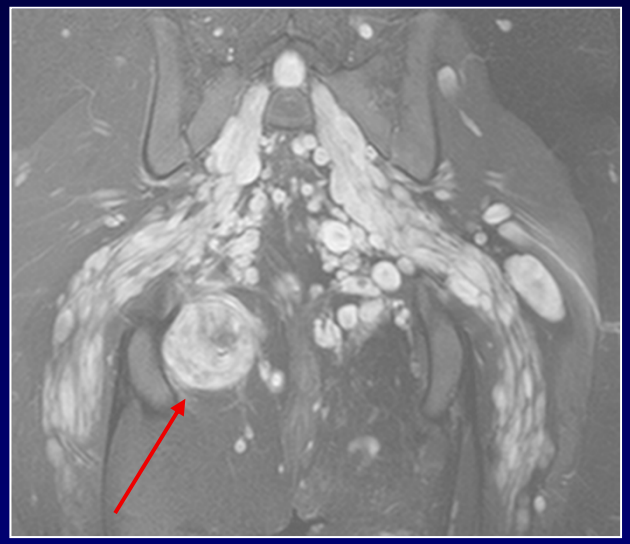
Future Directions in NF1

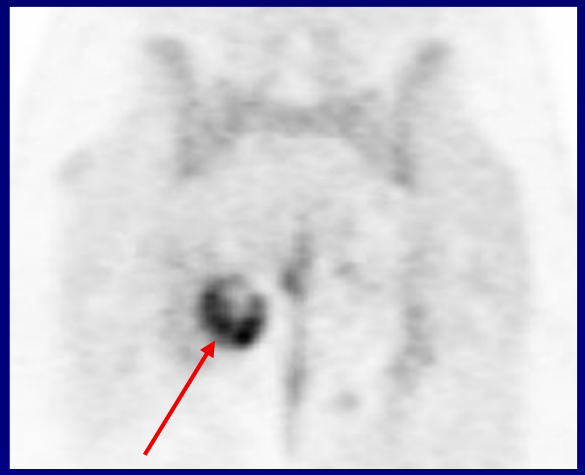
- Collaborative natural history study (Trans-NIH):
  - Geno-, phenotyping, optic gliomas, hormonal influence, cognitive function
- Separate NF1 phase I trials (after cancer trials)
- Phase II PN trials within DoD NF1 Consortium
- FDG-PET for the diagnosis of MPNST within PN
- Phase II trials in recurrent MPNST within DoD NF1 Consortium
- Develop methods to measure dermal and spinal neurofibromas
- Clinical trials for dermal neurofibromas

FDG-PET Imaging of NF1 MPNST

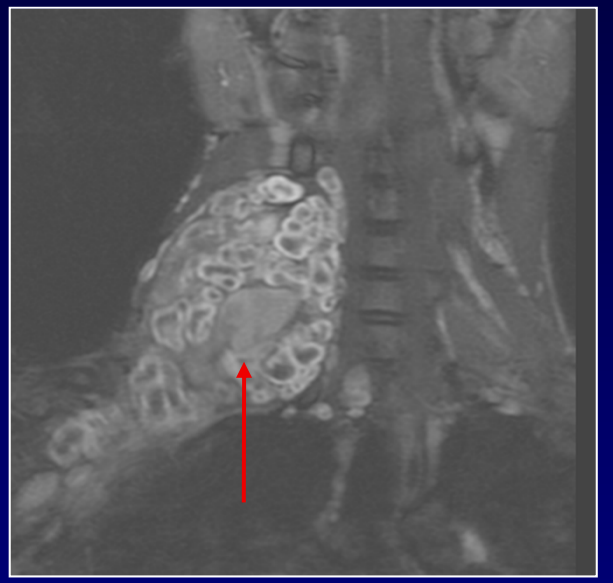
MPNST arising in

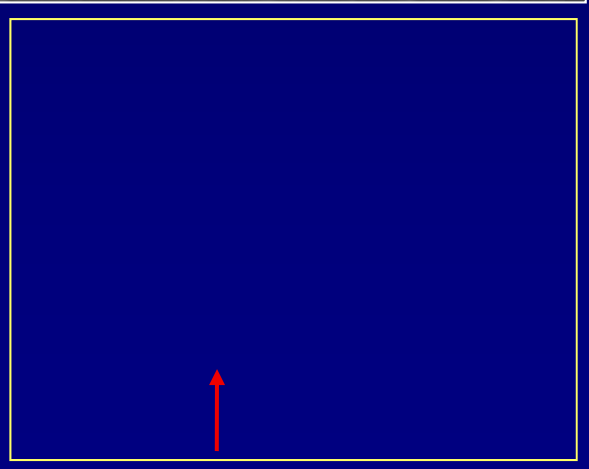
Pelvic PN





Neck PN





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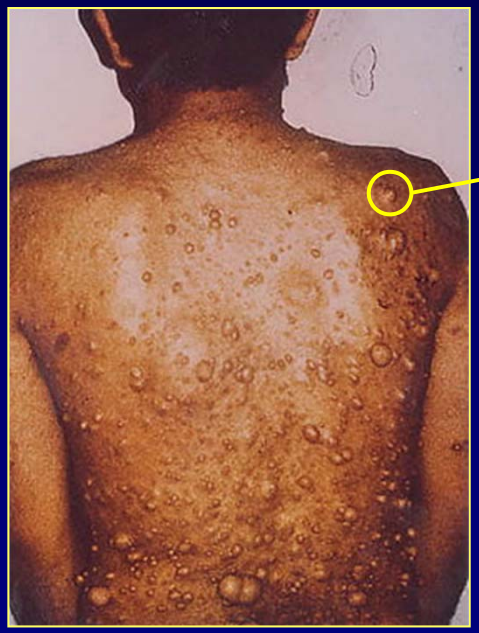
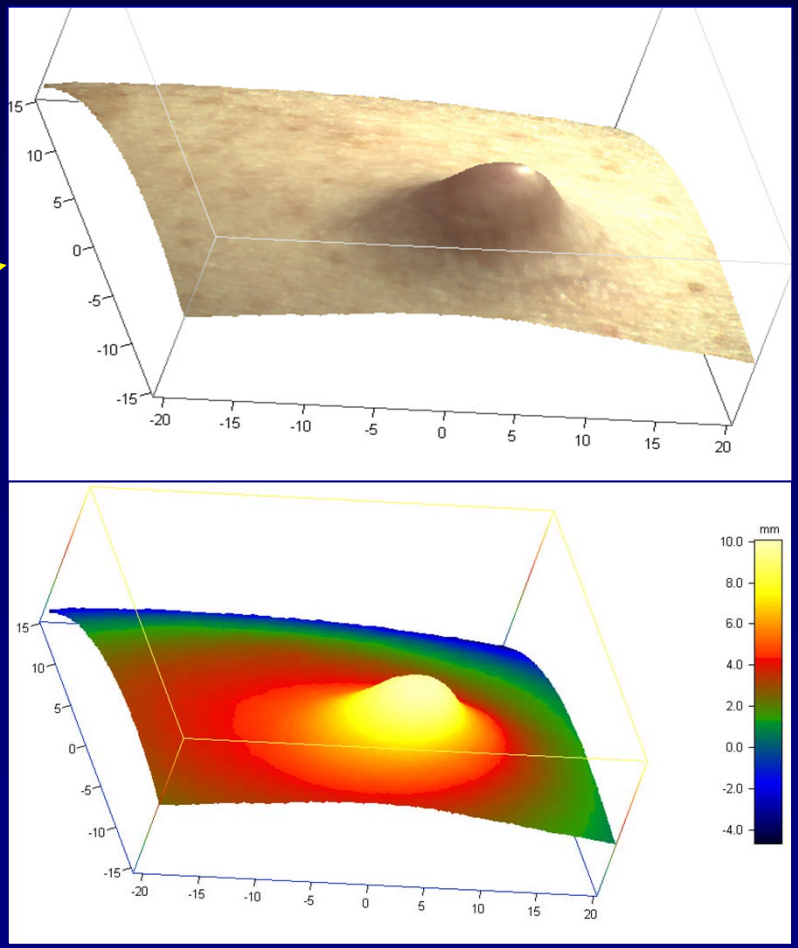
Measurement of Dermal Neurofibromas
Volume photography

3-D measurements of skin surface

Dermal Neurofibroma





Natural history and biology study of dermal neurofibromas NHGRI and NCI collaboration