

# Current Therapies for Neurofibromatosis Type 1

Laura Klesse MD, PhD  
Assistant Professor of Pediatrics  
UT Southwestern Medical Center  
Children's Medical Center of Dallas

# What is a Clinical Trial?

- Test of a new treatment in humans.
- Two purposes:
  - Test the effectiveness of a therapy in treating the disease process.
  - Testing the safety of the therapy.
- Comes out of both clinical observations and research in the laboratory.
- Approved by local or national Institutional Review Boards (IRB) for safety, potential benefits.

# Phases of Clinical Trials - Early Stages

- Preclinical Trials: work done in the laboratory with cells in culture or with animal models.
  - Often critical in identifying promising agents.
- Phase 0 : Exploratory, first in human trials.
  - Designed to speed development of promising drugs.
  - Smaller doses, usually small numbers of subjects.
  - No real safety or efficacy information.
- Phase I: First stage of testing in humans – goal is to test safety and tolerability.
  - Small numbers, usually 20-80 patients.



## Phases of Clinical Trials - Later Phases

- Phase II: First real test of the drug's efficacy in treating.
  - Larger numbers of patients – 100-300.
- Phase III: Large group, randomized and controlled to fully assess efficacy.
  - Often multi-center.
  - Usually 300-2000 patients.
- Phase IV: Continued safety monitoring.
  - Drug is now marketed for the disease.

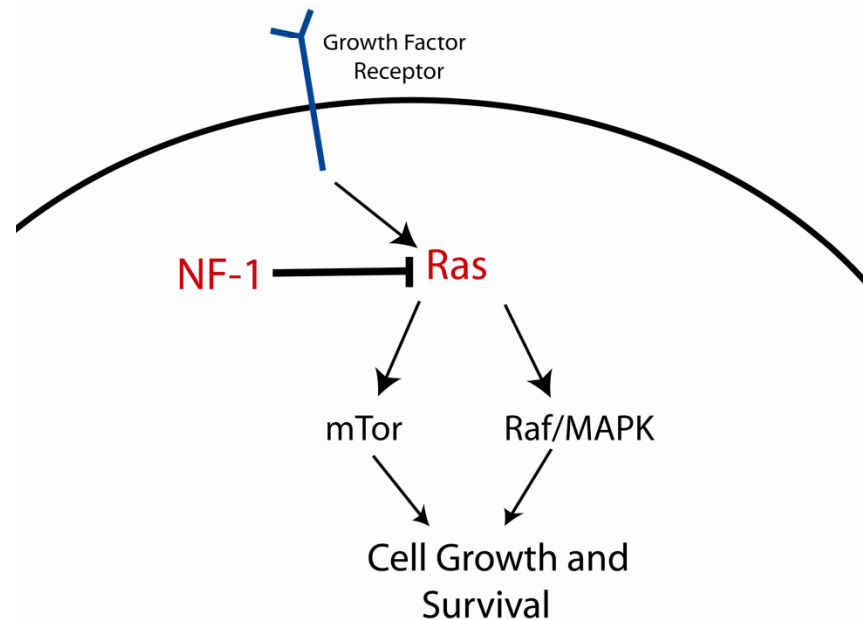


# Clinical Trials Development

- Based on preclinical testing – biology.
  - Using cell culture or animal models.
- Based on clinical observations.
  - Medications given for other indications.

# NF1 and Cancer

- NF1 a classic tumor suppressor.
- Found on Chromosome 17.
  - **Very mutable.**
  - **Mutation does not predict outcome.**
- Negatively regulates Ras signaling.
- Tumor formation requires a second hit.



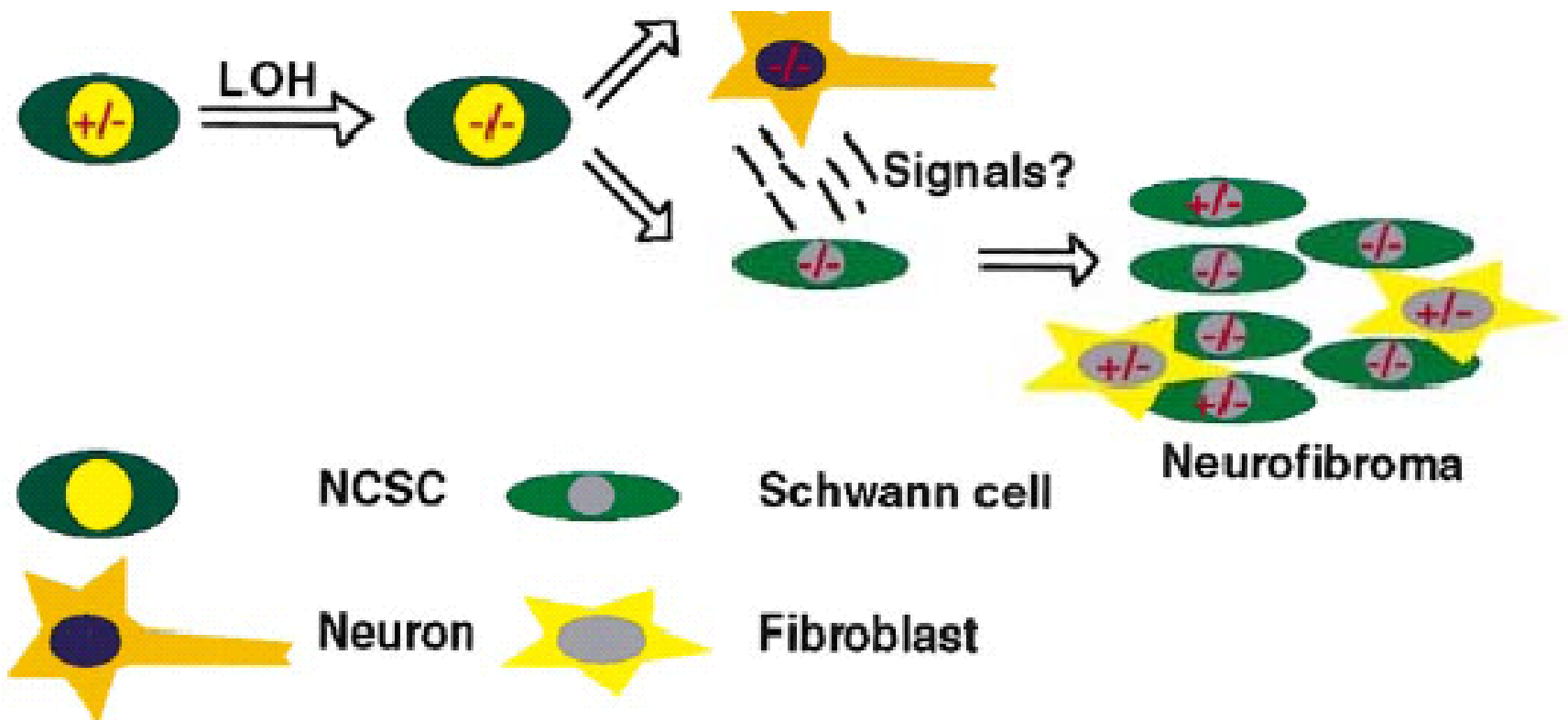


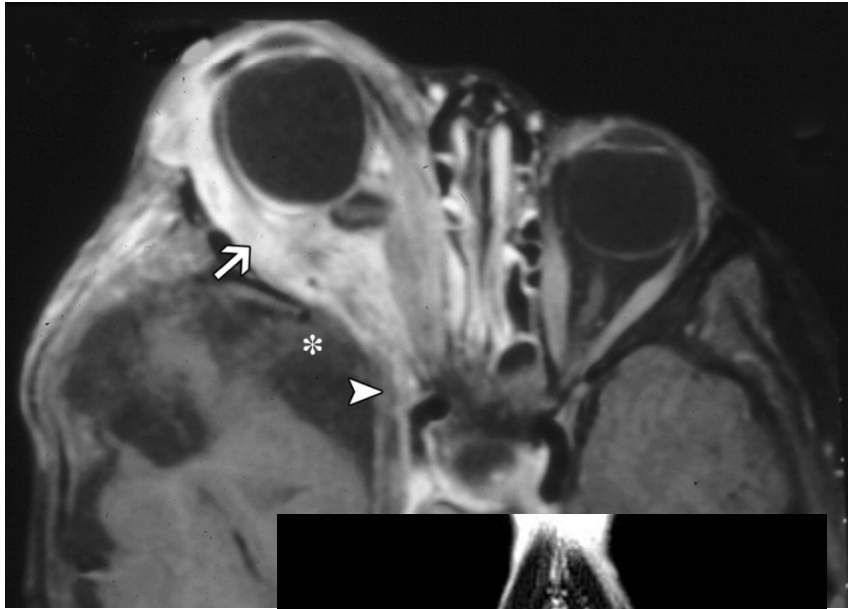
# Clinical Trials in Neurofibromatosis

- Often done at local institutions.
- Often with limited numbers of patients.
- More patients is always better!!
  - Increases the ability to detect efficacy.
- CTF clinical consortium
  - Department of Defense – Phase II
  - 9 centers.
  - Started in 2007.

# Plexiform Neurofibromas

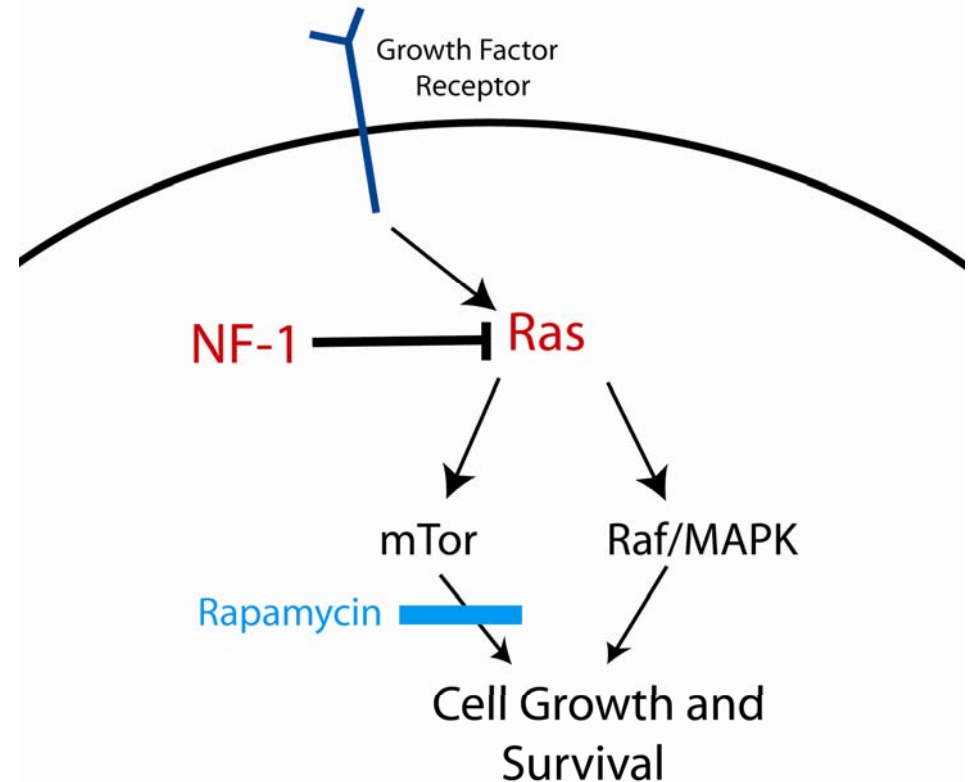
- 25% of patients with NF-1.
  - Masses of Schwann cells, fibroblasts, mast cells and endothelial cells around nerves.
  - Highly infiltrative , disfiguring
  - Potentially life threatening
- No known effective medical therapy!!
- Surgical resection continues to be the standard treatment.
  - Complete resection is often difficult.
    - 44% grow back if subtotally resected.
    - Often have major sequelae.
  - Chemotherapy is not effective.
  - Radiation therapy not effective.





# Sirolimus

- Antibiotic initially developed as an antifungal agent.
- Inhibits mTOR signaling.
- Promising in preclinical work.



# Sirolimus (Rapamycin)

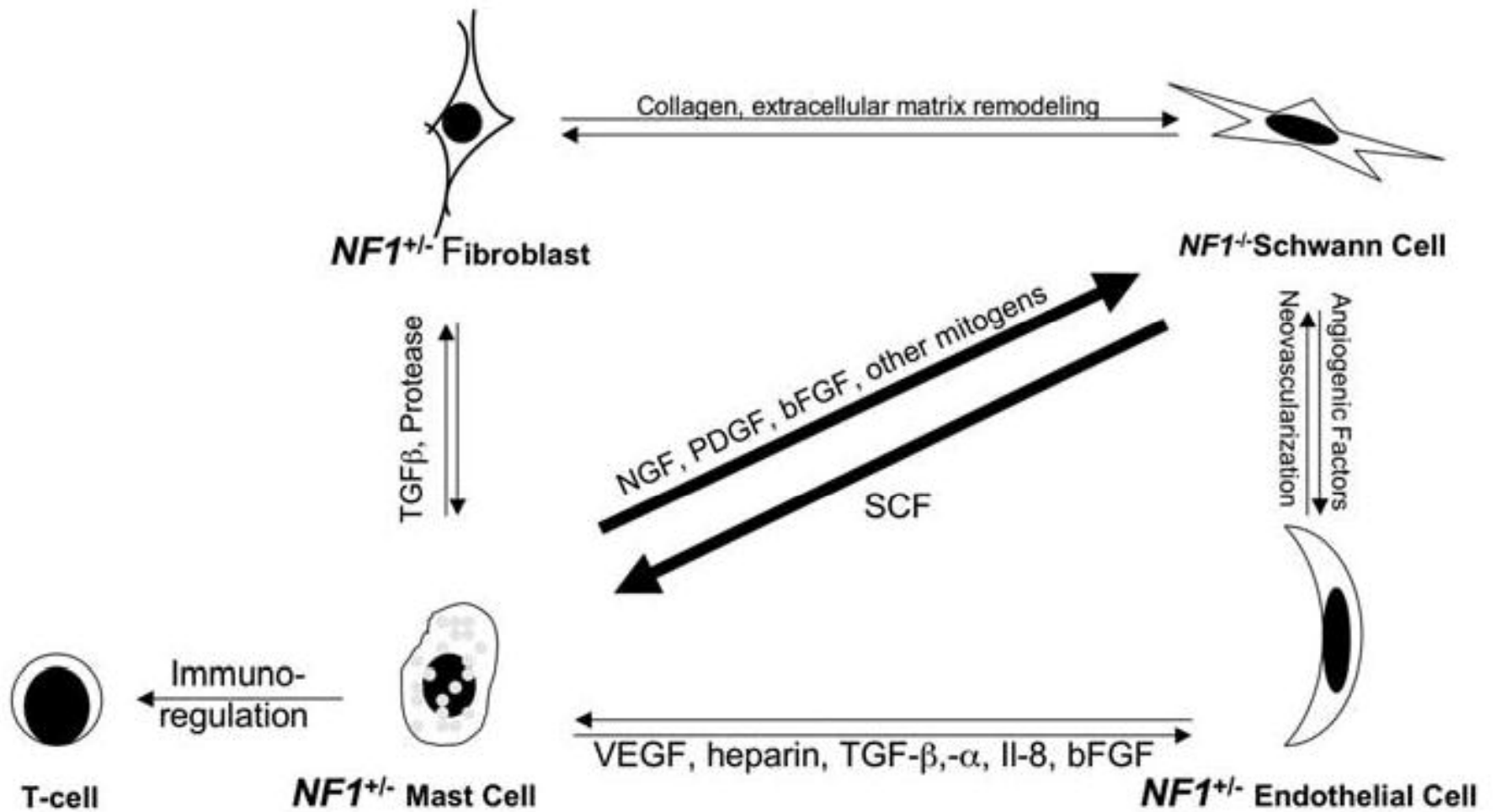
- Phase II clinical trial currently open at CTF Clinical Consortium Centers.
  - Enrolling patients older than 3 years of age.
  - Stratum 1: inoperable, progressing
  - Stratum 2: High risk
- Preliminary evidence:
  - Time to progression around 10 months.
    - Stratum 1: 36 of 46 enrolled.
    - Stratum 2: 13 enrolled – all removed after 6 cycles.
      - 11 without response, 1 with progression.
  - Toxicity noted.
    - Decreases in doses, 3 removed for toxicity.

# PEG-Interferon

- Inhibits growth.
  - Inhibits blood vessels.
  - Immune modulation.
  - Not specific.
- In early trials with  $\alpha$ -interferon:
  - 5/27 patients reported clinical improvement.
  - 26/27 had stable plexiforms on MRI scan.
  - Few objective clinical responses.
  - Get rebound growth after stopping.
- Administered under the skin once per week.
- Open to patient 18 months to 21 years.
  - Plexiforms increasing in size or in dangerous locations.
- Currently open in Pittsburg, NCI, Chicago and Seattle.

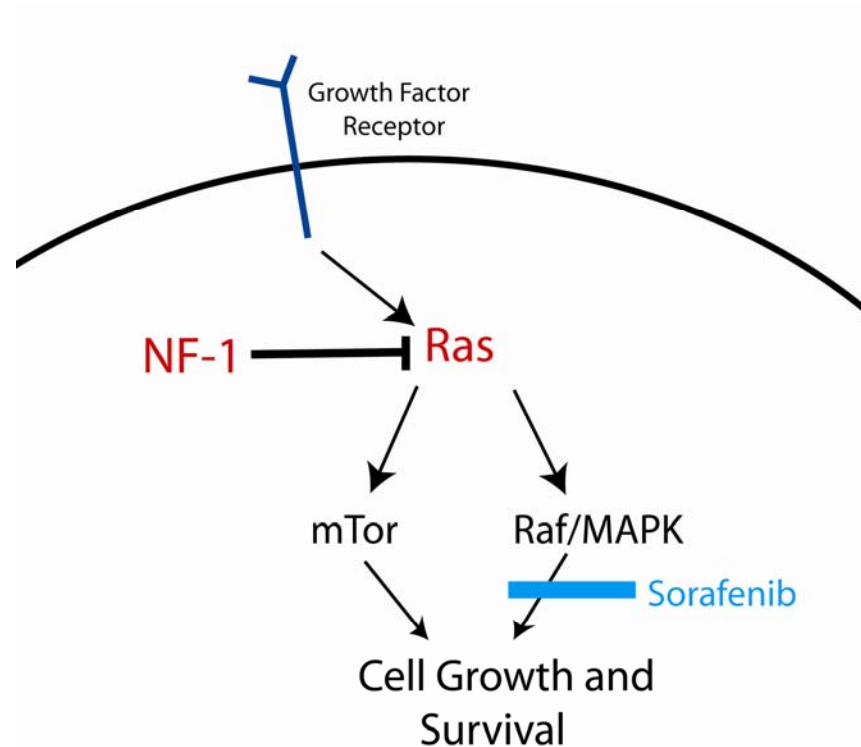
# Gleevac

- Drug initially designed for leukemia.
- Inhibits cell surface receptors which are involved in the development of plexiform neurofibromas.
  - Work done in Luis Parada's lab at UT Southwestern the basis for this trial.
  - Inhibits PDGF, c-kit and c-abl.
  - 1 patient had >50% reduction in tumor size.
- Phase II study – principle investigator Kent Robertson at Indiana University.
- Recently closed, awaiting results.



# Sorafenib

- Phase I study.
- Given by mouth twice per day for 28 days – plan 6 months.
- Inoperable, growing or in dangerous area.
  - Head or neck or eye.
- Ages 3-18.
- Has toxicity – significant increase in pain, hand/foot syndrome.



# Studies which demonstrated no effect

- Pifenidone
  - Inhibits fibroblast growth.
  - Tested as a Phase II.
  - No improvement over controls.
    - Time to progression was 13.2 mths versus 10.6 for placebo.
- Tipfarnib
  - Inhibited the activation of ras.
  - No improvement over controls.

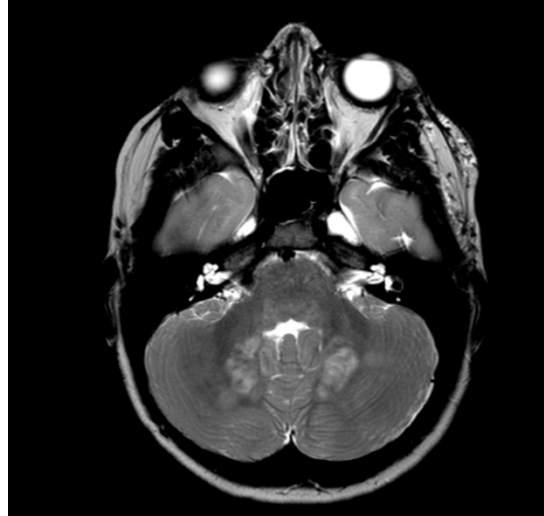
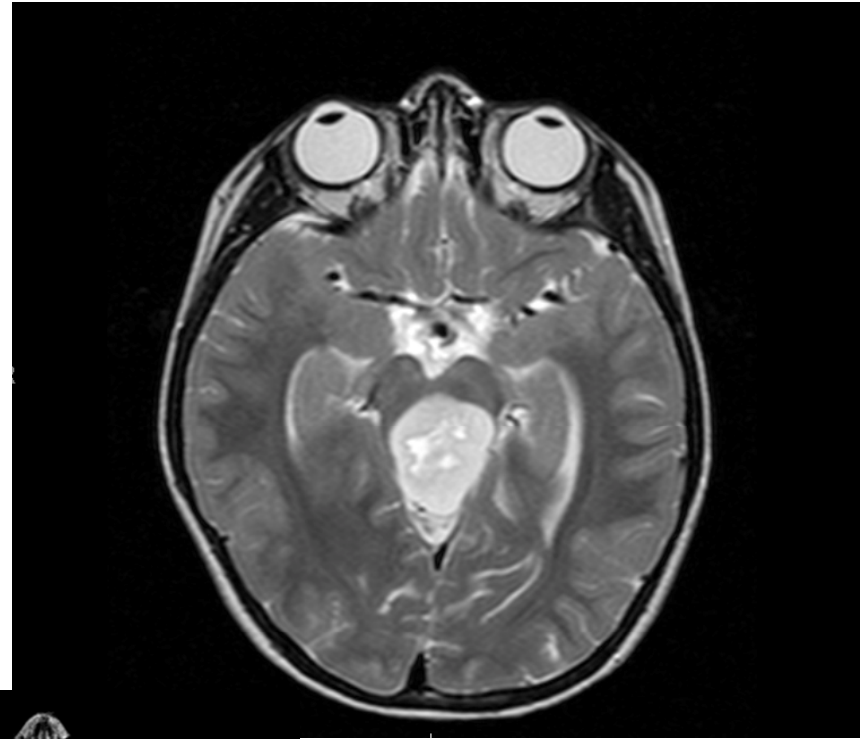


# Difficulties of Plexiform Trials

- Erratic growth:
  - Increased in early childhood.
  - Likely have growth throughout lifetime.
- Invasiveness:
  - Difficulty with accurate measurements.
- Difficulty measuring growth:
  - Improved with 3D measurements

# Pilocytic Astrocytomas

- Low grade, benign tumors of the central nervous system.
- Derived from glia, the support cells of CNS.
- 35-40% of childhood brain tumors.
- Overall survival very good - >90% at 5 years.
- Surgical resection usually curative.
- Neurofibromatosis type 1 patients at increased risk.



# Low-Grade Gliomas: Influence of Neurofibromatosis-1

Figure 2. Event-Free and Overall Survival for Randomized Patients

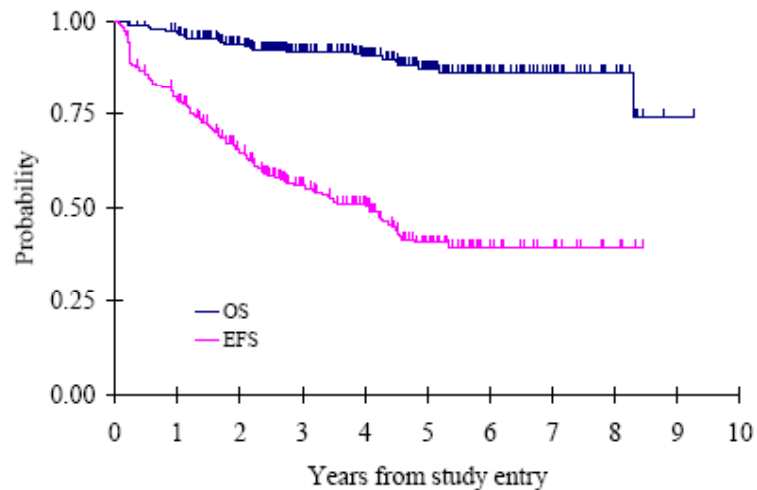
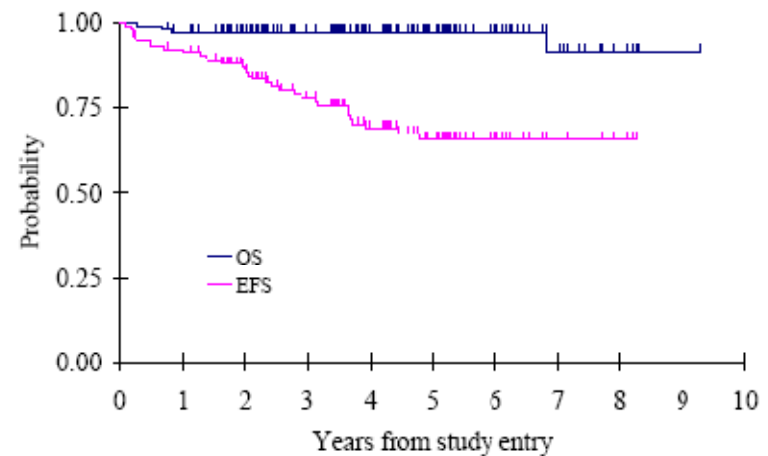


Figure 3. Event-Free and Overall Survival for Neurofibromatosis Patients





# Treatment for low grade gliomas

- If treatment is required – discussion is often surgical resection versus chemotherapy.
  - Based on the ability to resect without significant consequences.
  - Radiation is avoided.

# Optic Gliomas

- Affects 15- 25 % of patients with NF-1.
- Is most commonly identified in patients less than 10 years of age.
- Can cause significant morbidity.
  - Proptosis, vision loss, endocrine abnormalities.
- Are low grade tumors –
  - Often do not impact vision.
  - Often have limited growth.
  - Only 25% require treatment.

# Optic Gliomas

- Screening:
  - Yearly ophthalmology examination until age 8, then every 2 years.
  - Limited evidence in children less than 1 year of age.
  - Changes in visual acuity or visual fields need further evaluation.
- Role of MRI?
  - Screening MRIs not recommended.



# Current Therapy for OPG

- When to treat:
  - No clear guidelines.
  - Loss of vision.
  - Radiographic progression, endocrine changes, patient age.
- Often watchful waiting.
- First line treatment: Chemotherapy.
  - Carboplatin and vincristine.
  - Second line – vinblastine, avastin/irinotecan.

# OPG treatment

- **Surgery:**
  - Biopsy not necessary for diagnosis.
  - Often used for patients with significant proptosis when vision is lost.
  - Chiasmal tumors may require surgical debulking.
- **Radiation Therapy:**
  - Felt to have unacceptable sequelae.
  - 9 of 18 NF pts with progressive OG treated with radiotherapy had 12 secondary malignancies. (Sharif et al., JCO 2006).
  - Also at risk for significant cerebral occlusive vasculopathy (Grill et al., Ann Neurol 1999).

# New Therapies:

- Tarceva and Rapamycin
  - Phase 1 therapy
  - Blocks mTOR signaling and EGFR signaling.
    - 87% of low grade gliomas have increased expression of EGFR.
    - 77% of LGGs have increased mTOR.
  - Synergy noted in animal models.

# New Therapies

- 7 patients with NF treated.
  - 16 patients overall treated.
- Eight patients in remission from 1 to 18 months.
  - 6 patients off therapy secondary to progression.
  - All patients with NF1 had stable disease or response.
  - 2 patients with NF1 with stable disease for over one year.
  - Packer, RJ.

# Malignant Peripheral Nerve Sheath Tumors

- Account for 10% of soft tissue sarcomas.
  - Rare in pediatrics:
    - Only 20% of MPNSTs are diagnosed in the first 2 decades of life.
- Strong association with NF1 – 50% are in patients with NF1.
- In NF1 patients, most arise from pre-existing plexiform neurofibromas.
  - Both have loss of NF1, but MPNST associated with loss of second tumor suppressors – including p53, p16.
  - Present with persistent pain, rapid growth, change in consistency or new neurologic finding.
- Patients with NF1 have a 10% risk of developing MPNST over their lifetime.

# MPNSTs and NF1

- Patients with NF1 present with MPNSTs at a younger age.
  - 20 instead of 40-50s.
- Patients with NF1 and MPNSTS have less response to chemotherapy.
  - In combined Italy/Germany experience:
    - 126 patients over 25 years
    - Response to chemotherapy was 55% without NF1; 18% in patients with NF1
    - Overall survival at 5 years was 55% vs 32%.
- Patients with NF1 are more likely to present with large, unresectable tumors or distant metastases.



# MPNSTs therapy

- Surgery is the corner stone of therapy.
- For high grade lesions, even with surgery have a high local recurrence rate (32-65%).
- Radiotherapy after surgery improves control rates and is recommended for high grade lesions and intermediate lesions >5 cm.
  - Radiotherapy alone (without resection) only has control rates of 30-40% reported.
    - Gupta et al., 2008

# Future Directions for MPNST.

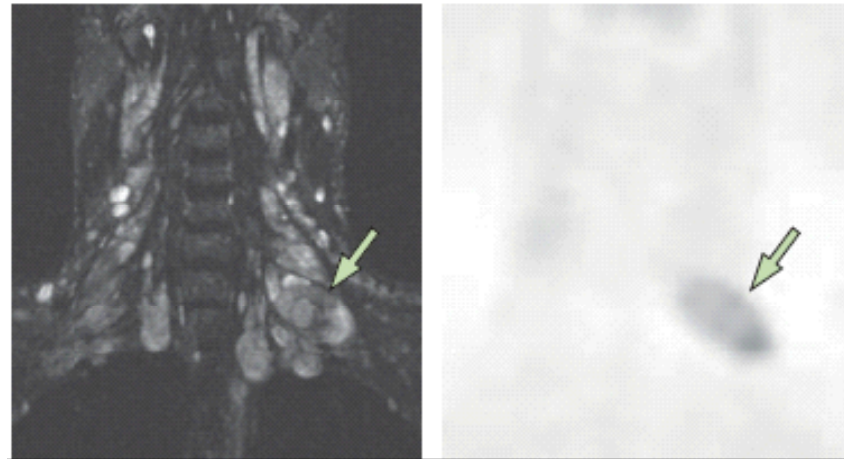
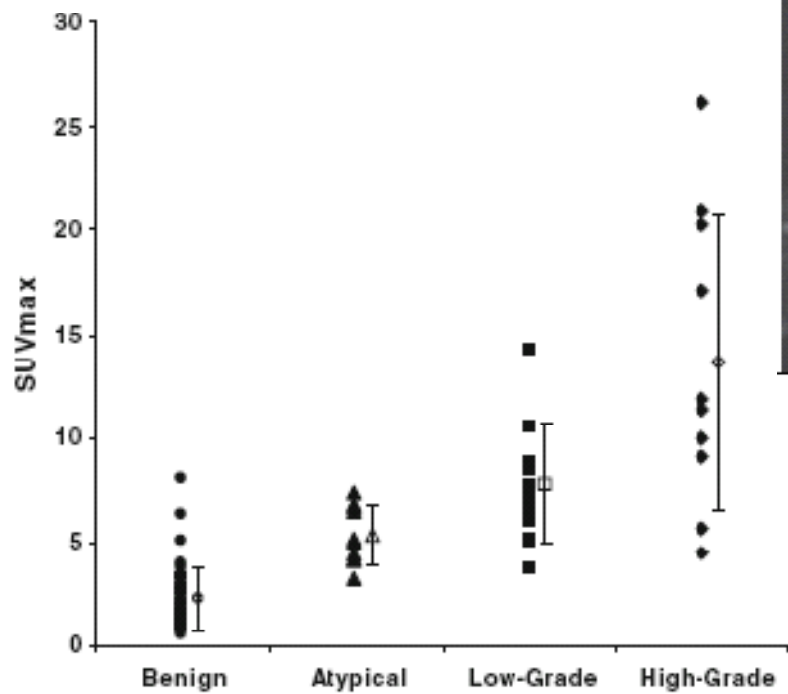
- Clearly need better therapies.
- New chemotherapy approaches:
  - Currently NCI open Phase II for chemotherapy naïve, unresectable MPNSTs using doxorubicin, ifosfamide and etoposide.
- New biological approaches:
  - Epidermal Growth Factor?
    - EGFR is expressed on a substantial percentage of human MPNSTs and its expression is associated with a worse prognosis. Keizman, et al, 2009
    - Preclinical studies demonstrate a potential role.
      - Ling et al., 2005.



## Role of PET scans

- Significant difficulty in distinguishing symptomatic plexiform neurofibromas from MPNSTs.
- Biopsies can be difficult and may have sampling error.
- Early detection may benefit NF patients.
- PET has 95% sensitivity and 87% specificity in detecting MPNSTs.

# PET scans and NF1



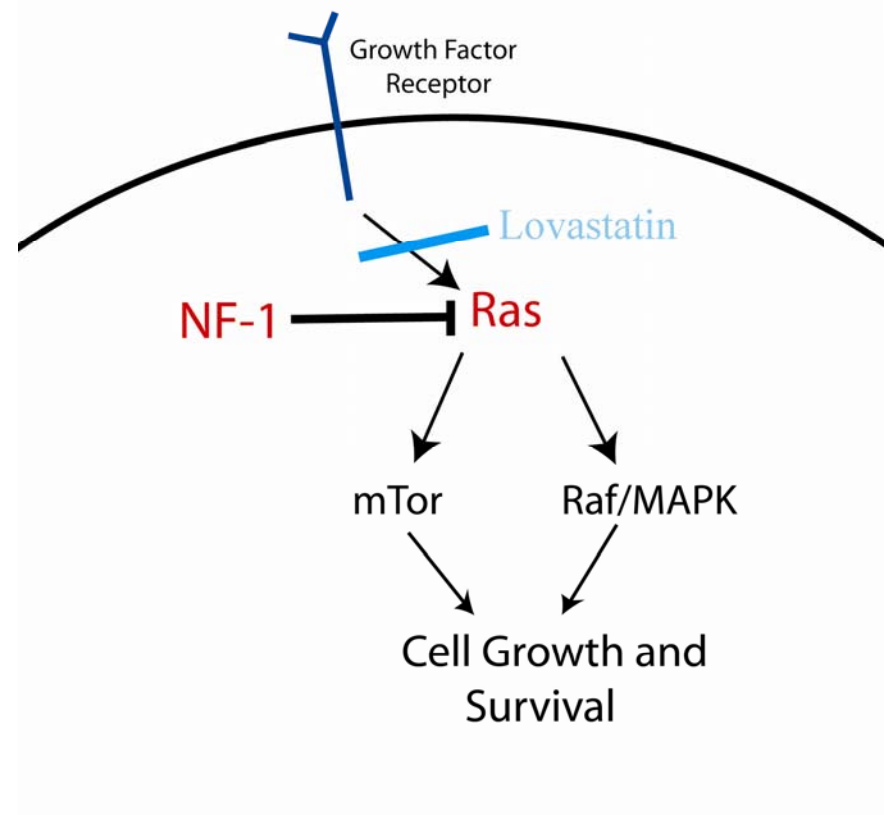
Tucker et al., 2009

# Learning Disabilities

- Neuro-developmental problems found in over 50% of NF patients.
  - Only a very small proportion have severe mental retardation (8%)
- Learning Disabilities overall 5 times more common in NF patients than the general population.
  - Speech abnormalities (esp. articulation issues).
  - Attention deficient disorders.
  - Impaired performance in at least 1 area of academic achievement.
  - Visual-spatial-perceptual problems.
  - Motor disorders.

# Statins

- Commonly utilized for cholesterol control.
- Well tolerated.
- Inhibits ras activation.
- Currently in phase II study for patients 10-16 years of age, open at CTF organizations.
- In initial study in Netherlands:
  - Found improvements in one measure.
  - Larger US study is planned to open.
- In animal models, demonstrated improvements in spatial learning and memory.





## Further information

- Children's Tumor Foundation website.
  - [www.ctf.org](http://www.ctf.org)
  - Also listings for tissue donation, etc.
- Clinical Trials website – National Cancer Institute.
  - [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Questions?

