

Care for Your Child with NF1

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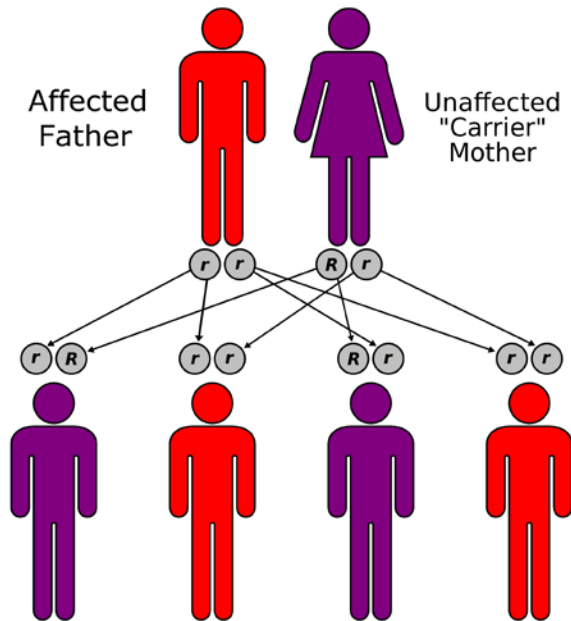
Disclosures

Consultant to AstraZeneca (AZD6244)- Plexiform neurofibromas

What is NF1?

NF1 is a syndrome that affects approximately 1:3000 people

50%



50%

De novo

(D)



Father has mutation in a single sperm cell and transmits it to the child. Child is heterozygous in every cell.

(E)



Mutation occurs in zygote within first few cell divisions. Child is heterozygous in every cell.

Caused by a "spelling error" in the NF1 gene

BIG

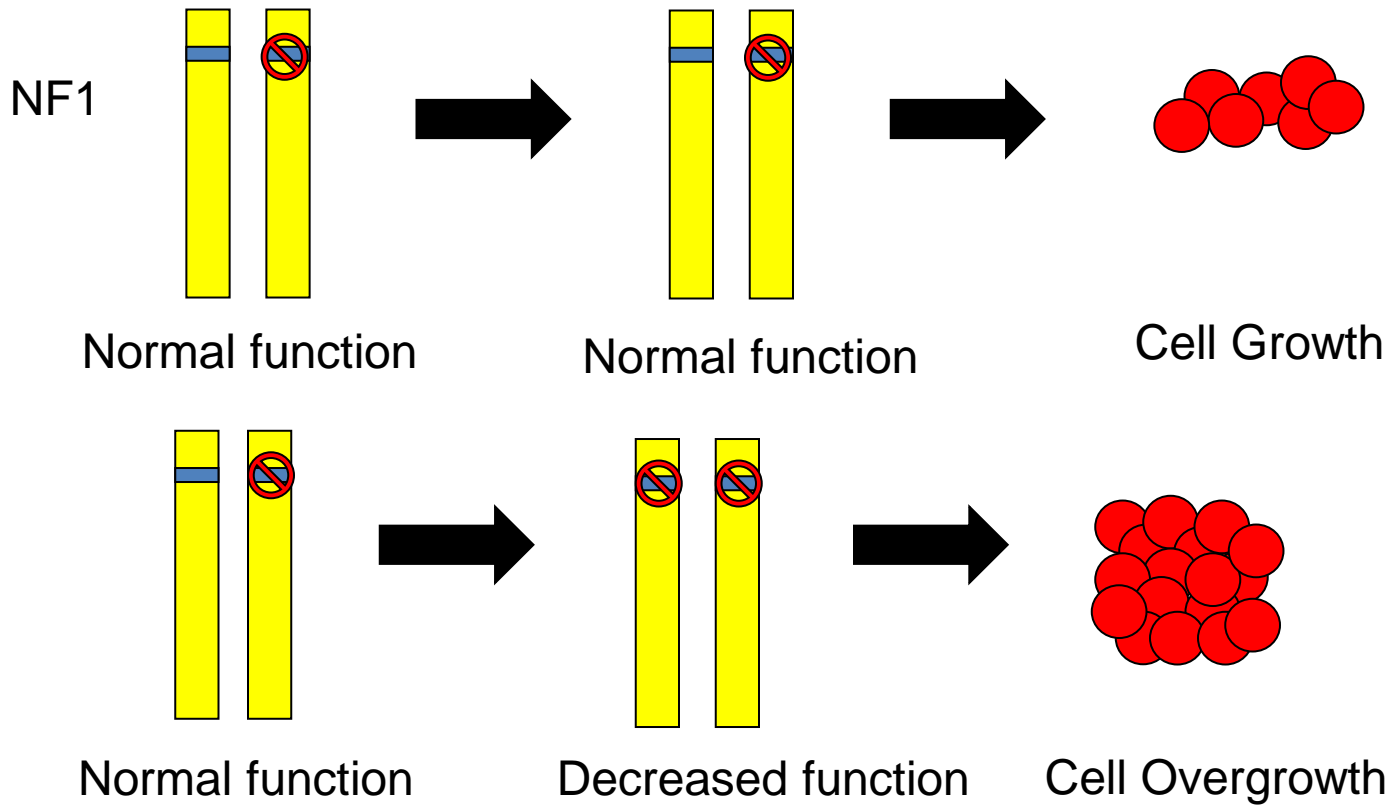
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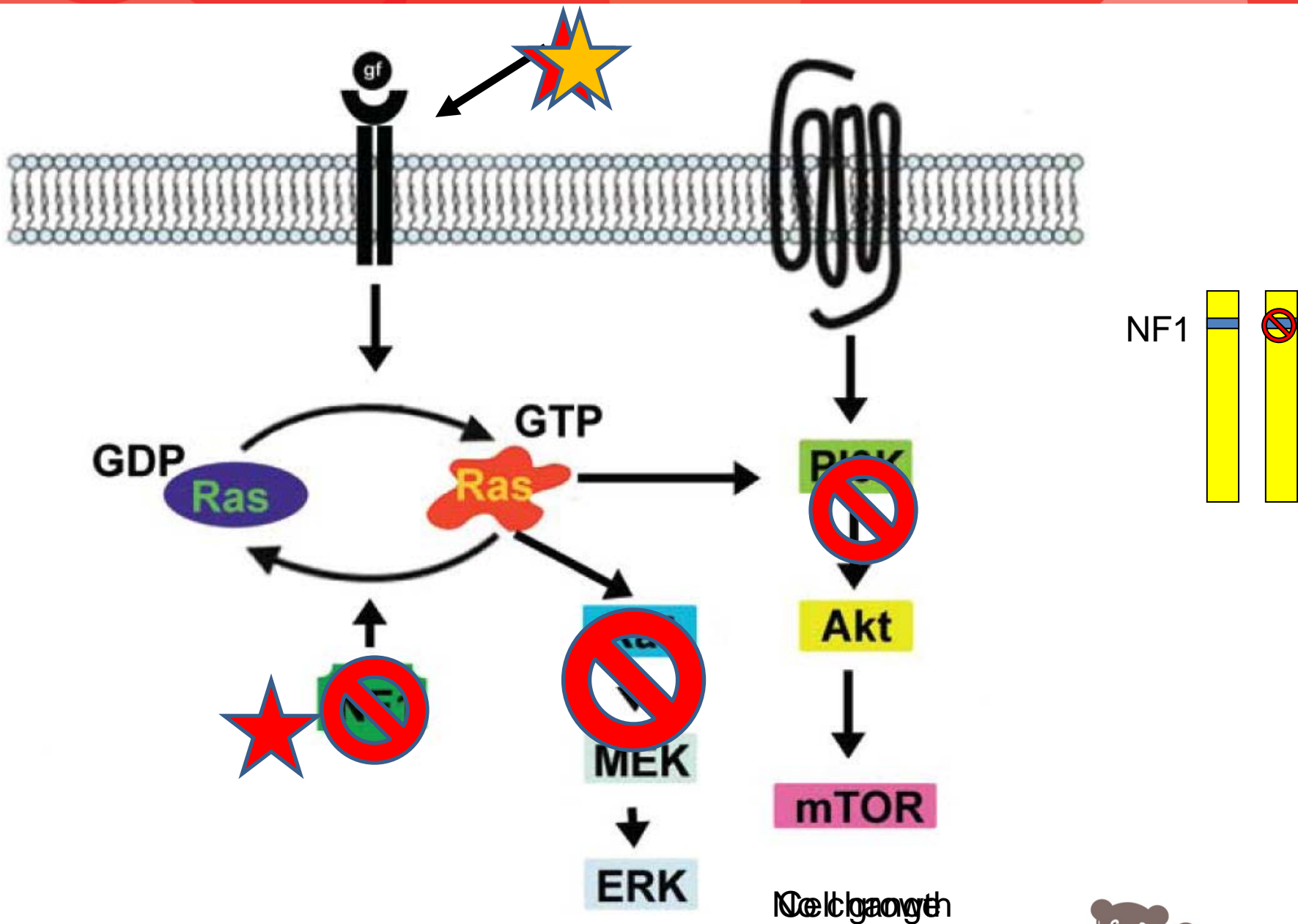
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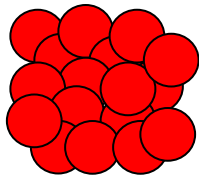
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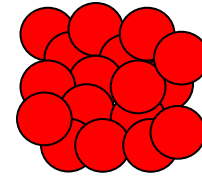
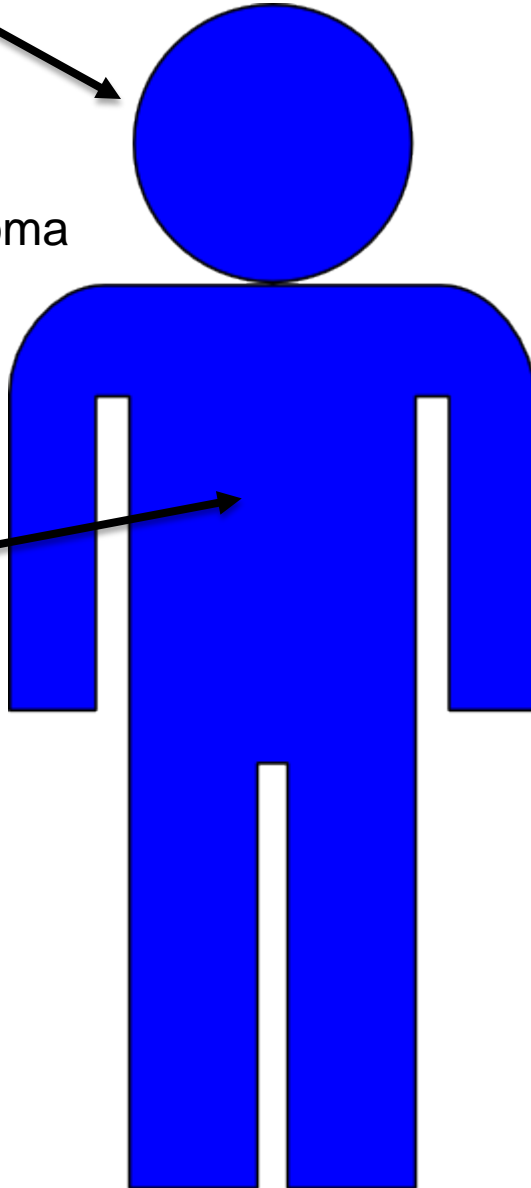
“Two-hit Hypothesis”



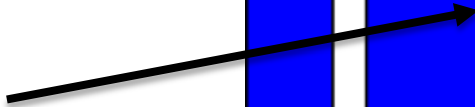




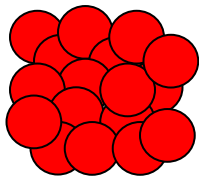
Optic nerves=
Optic Pathway Glioma



Peripheral nerves=
Neurofibroma



Skin=
Cutaneous neurofibroma



NF1 Presentation

When should my child have their first MRI?

Infants (0-1)	Toddler/Pre-School (2-5)	Children (6-10)	Adolescents (11-16)	Adults (16+)
Café au lait spots	Decreased growth			MPNST
Pseudoarthrosis	Macrocephalus	Lisch nodules	Skin neurofibromas	
Plexiform neurofibroma			Scoliosis	Gliomas-other
Developmental Delays	Gliomas (Optic)	Neuropsychological deficits		Breast cancer (female)
	Other malignancies			
	T2 Hyperintense MRI lesions of unknown significance			
	Freckling			

How do I know if I/my child needs medical attention?

Headache (early AM)

Frequent vomiting

Abnormal movements

Weakness

Pale/easy bruising

Joint/bone swelling

Vision Changes

Abnormal eye movements

Abdominal Pain

Diarrhea (bloody)

Worsening tumor pain

Not acting right

Tumors: Treatment

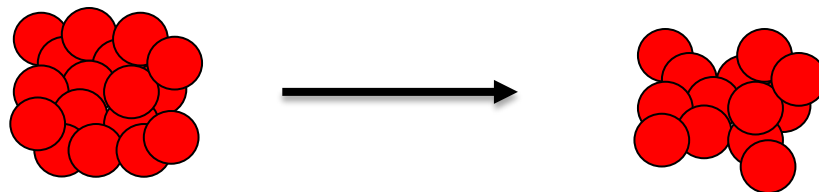
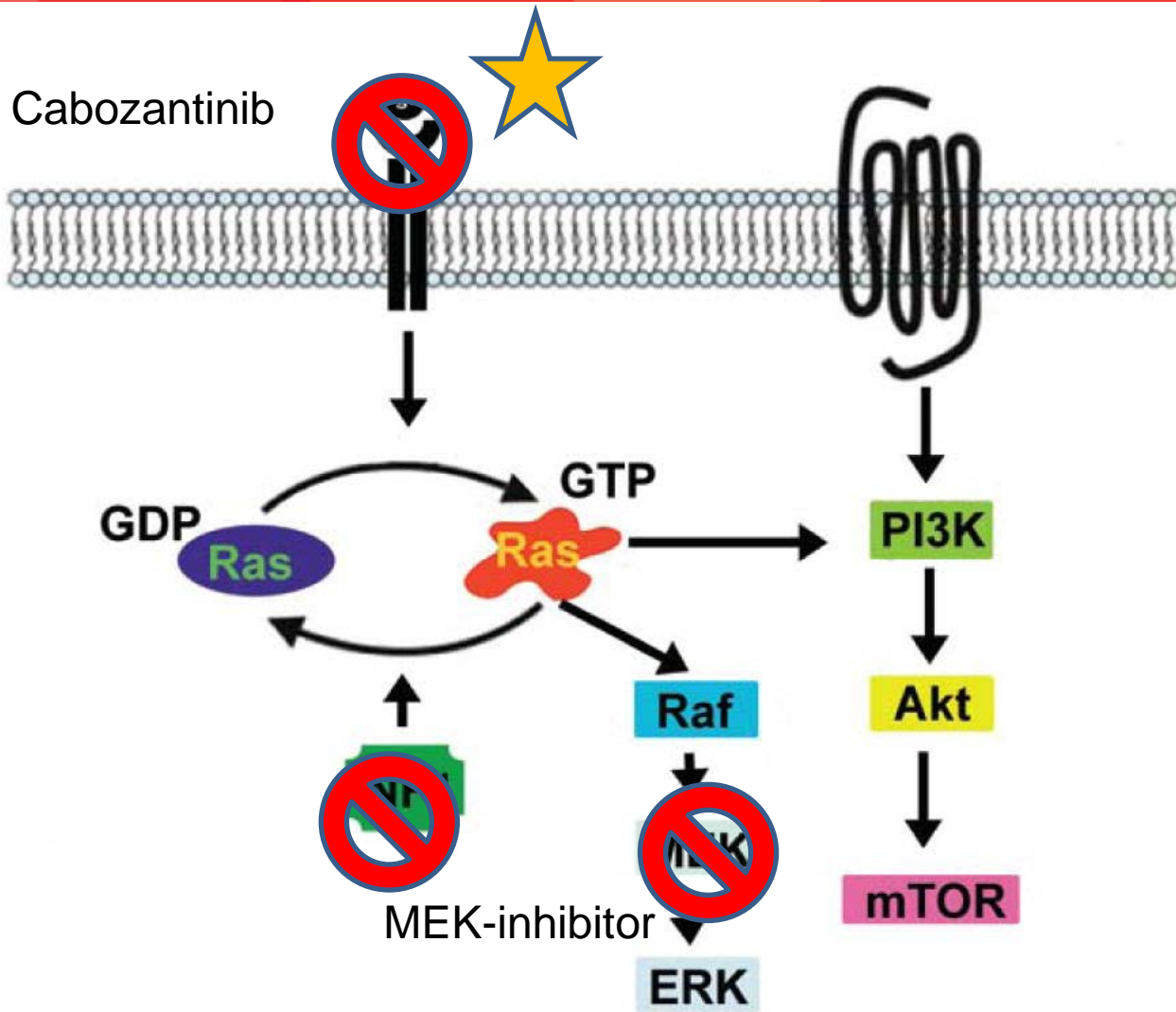
Plexiform Neurofibroma

- Surgery

Optic Pathway Glioma/Glioma

- Monitoring (70%)
- Chemotherapy
 - Vincristine/Carboplatin
 - Vinblastine
 - Avastin

What about oral inhibitors?



Clinical trials

Mek-inhibitor Clinical Trials for NF1-associated Tumors

Gliomas:

PBTC029 (AZD6244) – Currently closed to enrollment

MEK162-Phase 1/2 (CHLA) – Open to enrollment

Trametinib Phase 1/2 (Novartis) – Currently closed to enrollment

AZD6244 vs Carbo/VCR -- COG trial, open to enrollment

Mek-inhibitor Clinical Trials for NF1-associated Tumors

Plexiform Neurofibromas:

PD0325901 Phase 2 – Open to enrollment for children and adults; biopsy required for adults (>18)

NIH AZD6244 Phase 2 – Currently closed to enrollment for children, adult study with biopsy open

MEK162- Phase 1/2 (DOD/PNOC) – Currently closed to enrollment

Trametinib Phase 1/2 (Novartis) – Currently closed to enrollment

Cabozantinib Phase 2 – Open to enrollment for children <16

Koselugo (AZD6244/Selumetinib)

1st ever FDA approved Medication with a NF1 indication

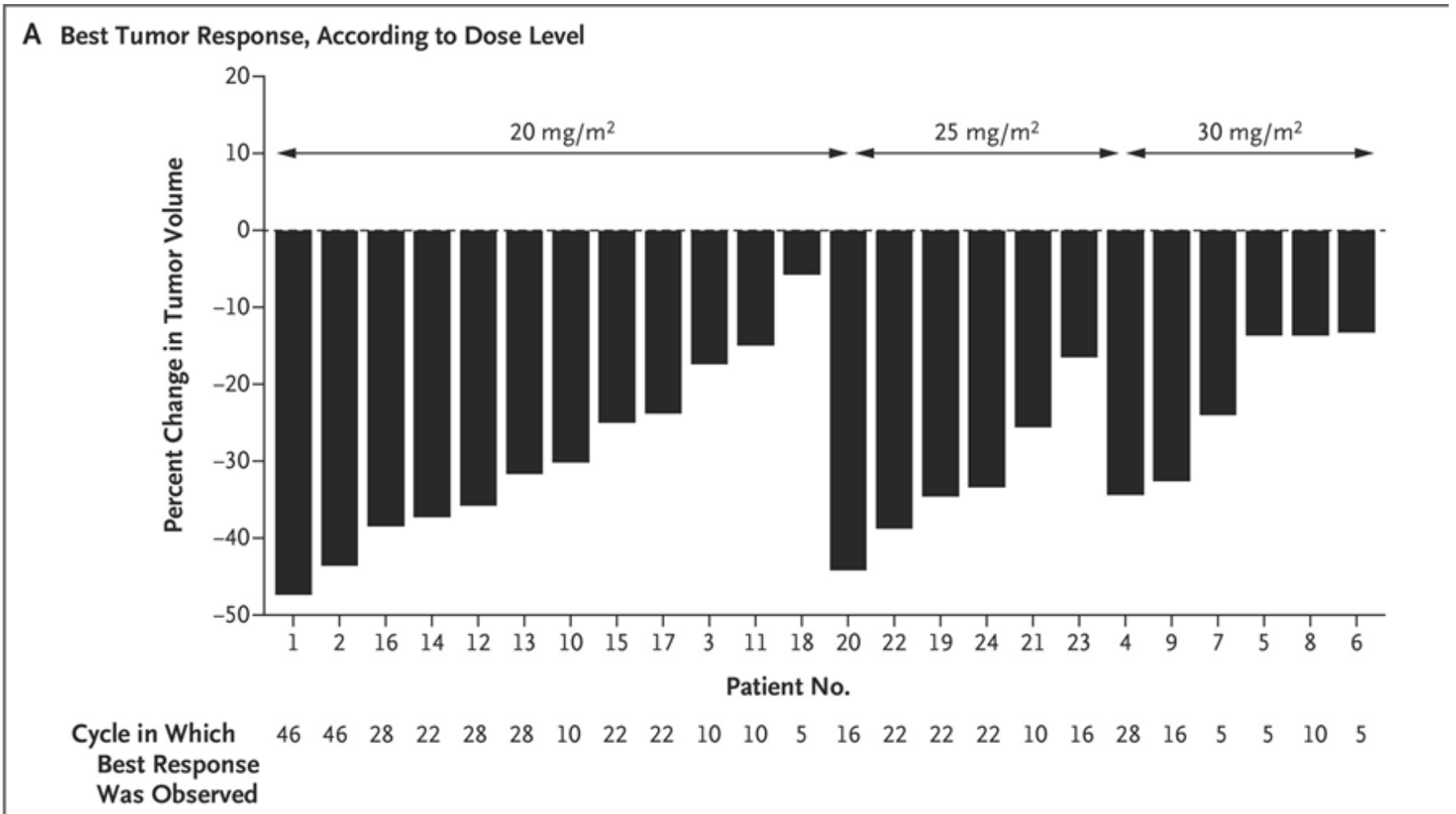
- Plexiform neurofibromas associated with morbidity
- In a phase 2 study, all patients but 2 had shrinkage of their tumor

The most common side effects of KOSELUGO are:

Vomiting, stomach pain, nausea, dry skin, feeling of tiredness, weakness or lacking energy, muscle and bone pain, fever, inflammation of the mouth, headache, redness around the fingernails, itching

AZD6244 Selumetinib Phase I Neurofibroma Trial

Dombi et al. NEJM



Current Research Progress- Treatment

Combination therapy

- MEK-inhibitor + Cabozantinib
- MEK-inhibitor + mTOR

Treatment schedule

- 3 weeks on, 1 week of (PD0325901)
- Other schedules?

Non-medical therapies

- WBMRI screening for atypical neurofibromas
- HIFU
- Gene editing

DIET

There are no current diet recommendations for patients with NF₁

But...we know that patients with NF₁ have different metabolism

Publications:

MedDiet enriched with 1200 mg curcumin (tumeric)

Vitamin D for **cutaneous neurofibromas**