Preliminary meeting

האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

TEL AVIV UNIVERSITY אוניברסיטת תל אביב

המרכז הרפואי שערי צדק
SHAARE ZEDEK MEDICAL CENTER
120 שנות מצוינות

Meeting agenda

- Pediatric brain tumors: a short introduction:
- Iris Fried- Pediatric neurooncologist-Shaare Zedek Medical Center
- PNOC-preclinical research options:
- Sabine Mueller-Professor of Neurology, Neurosurgery and Pediatrics, UCSF; Co-Leader,PNOC
- Facilitation of preclinical-clinical collaboration in Israel-Discussion:
- Ronit Satchi Fainaro: Head, Cancer Research and Nanomedicine Laboratory. Director, Cancer Biology Research Center Tel Aviv University

Pediatric brain tumors:

Getting to know the field

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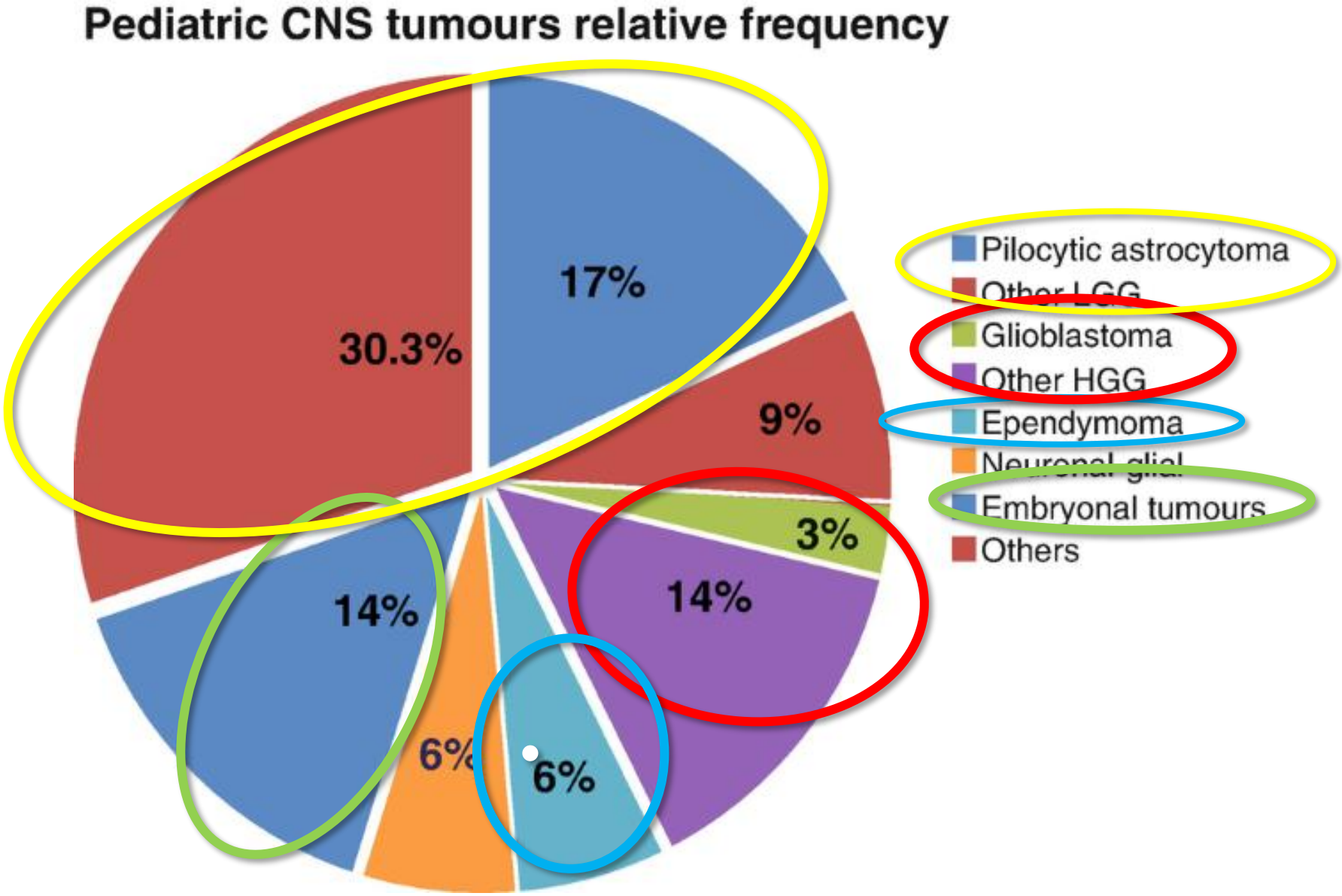
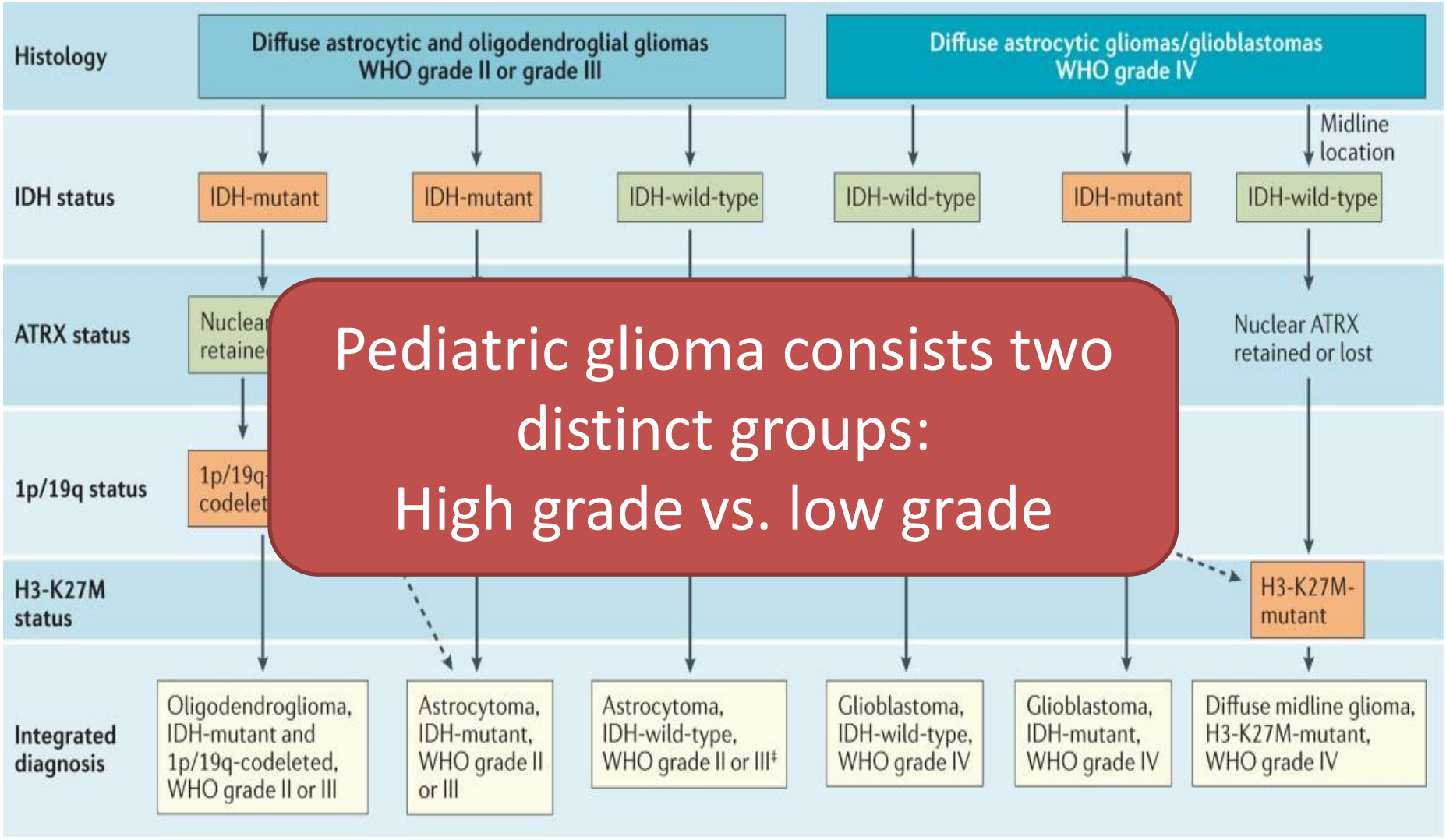


100-120 new patients per year in Israel

brain tumors classification

Adult diffuse glioma



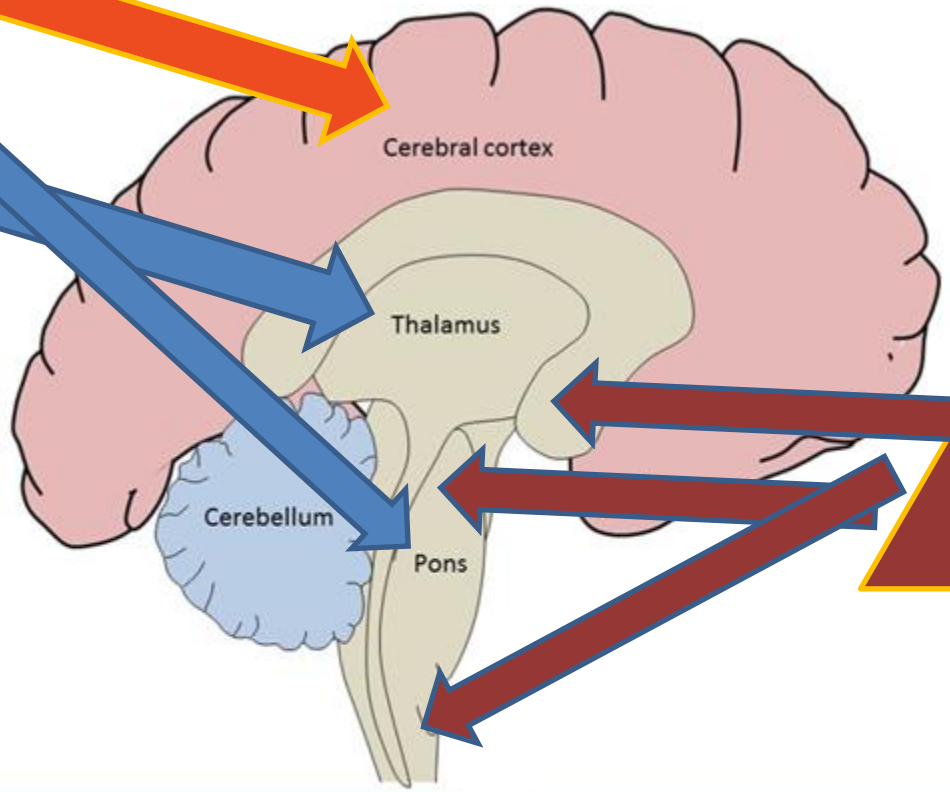
Pediatric glioma consists two distinct groups:
High grade vs. low grade

Nature Reviews | Clinical Oncology

Pediatric glioma: two distinct groups

HGG
H3.3G34M

DMG
H3.3K27M



LGG
BRAF associated

Hemispheric HGG harbor:
H3G34R/V mutations with alterations of
- *ATRX/DAXX* (high frequency)
- *TP53*
- *MYCN*
- *BRAF V600E*
- *PDGFRA*

***SETD2* mutations**
***IDH* mutations**

Midline HGG harbor:
H3K27M mutations with alterations of
- *TP53* (high frequency)
- *ATRX/DAXX* (low frequency)
- *FGFR1* (Thalamus)
- *ACVR1*
- *NF1*
- *PDGFRA*

***BRAF V600E* mutations**

Pediatric low grade glioma

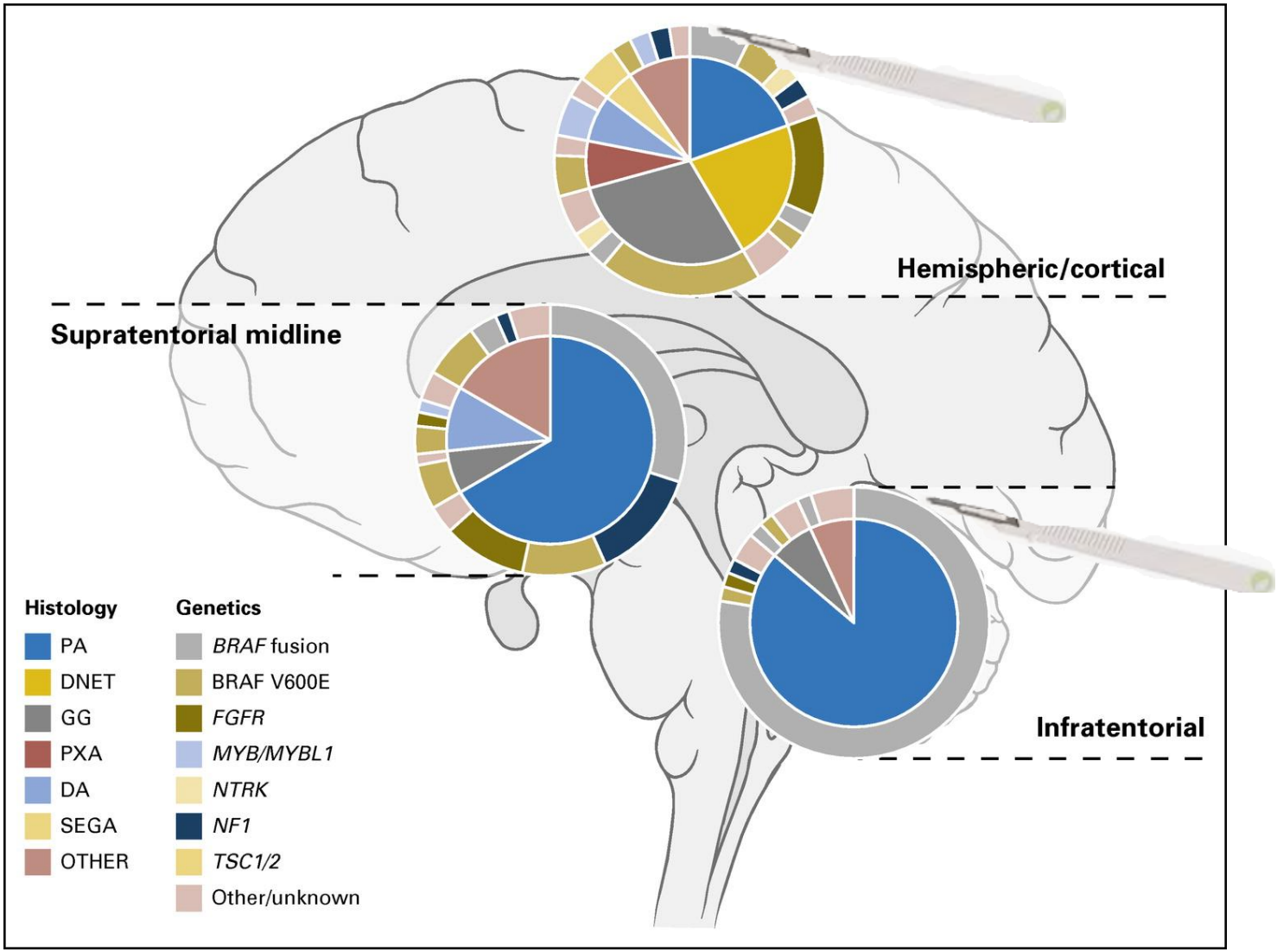
H. Was diagnosed with OPG at the age of 6 months old

regardless of several lines of chemo and targeted therapy, followed by partial resection- she lost her vision

Pediatric Gliomas: Current Concepts on Diagnosis, Biology, and Clinical Management

Sturm D, Pfister SM, Jones DTW.

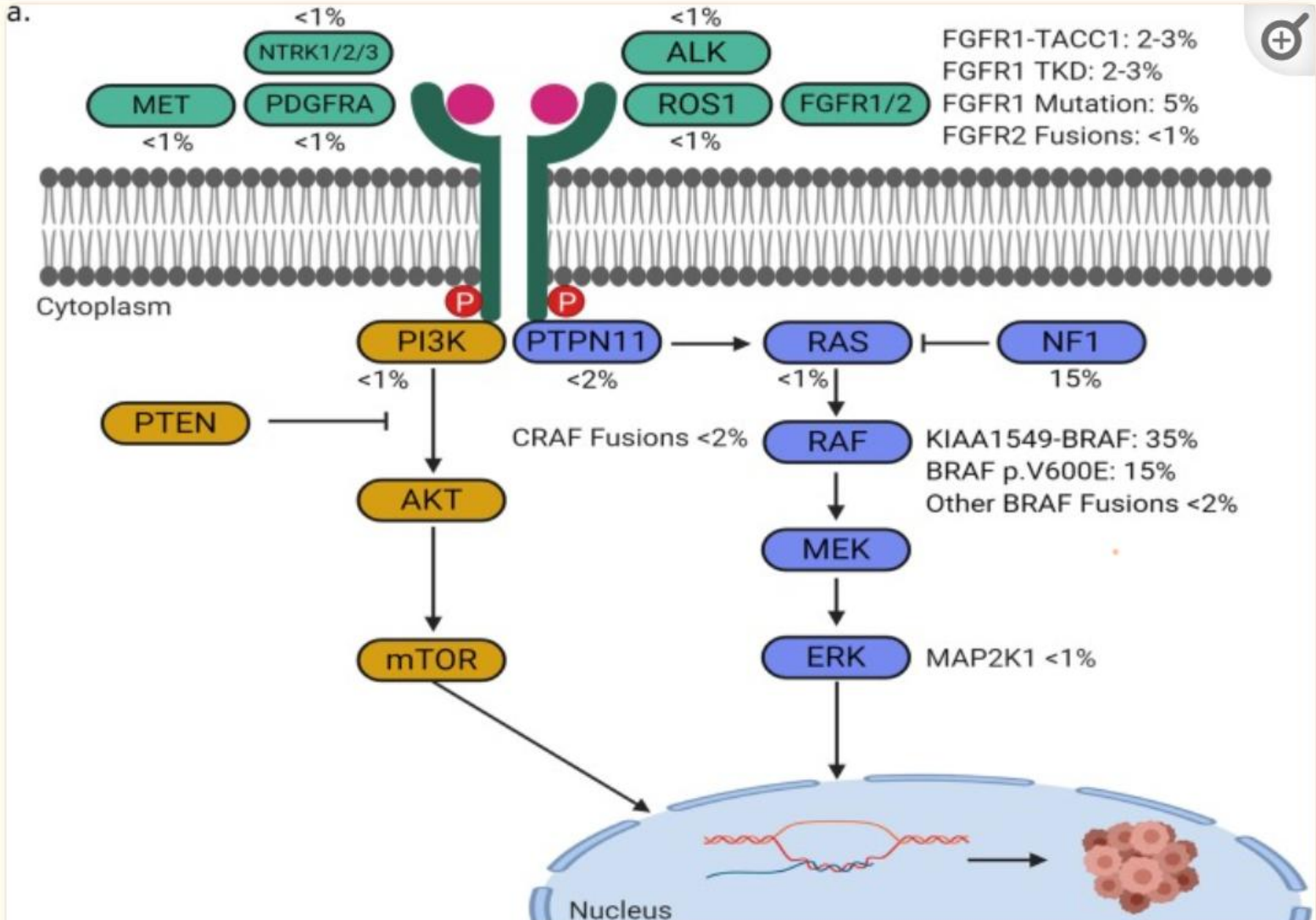
J Clin Oncol. 2017 Jul 20;35(21):2370-2377.



Pediatric low-grade glioma in the era of molecular diagnostics.

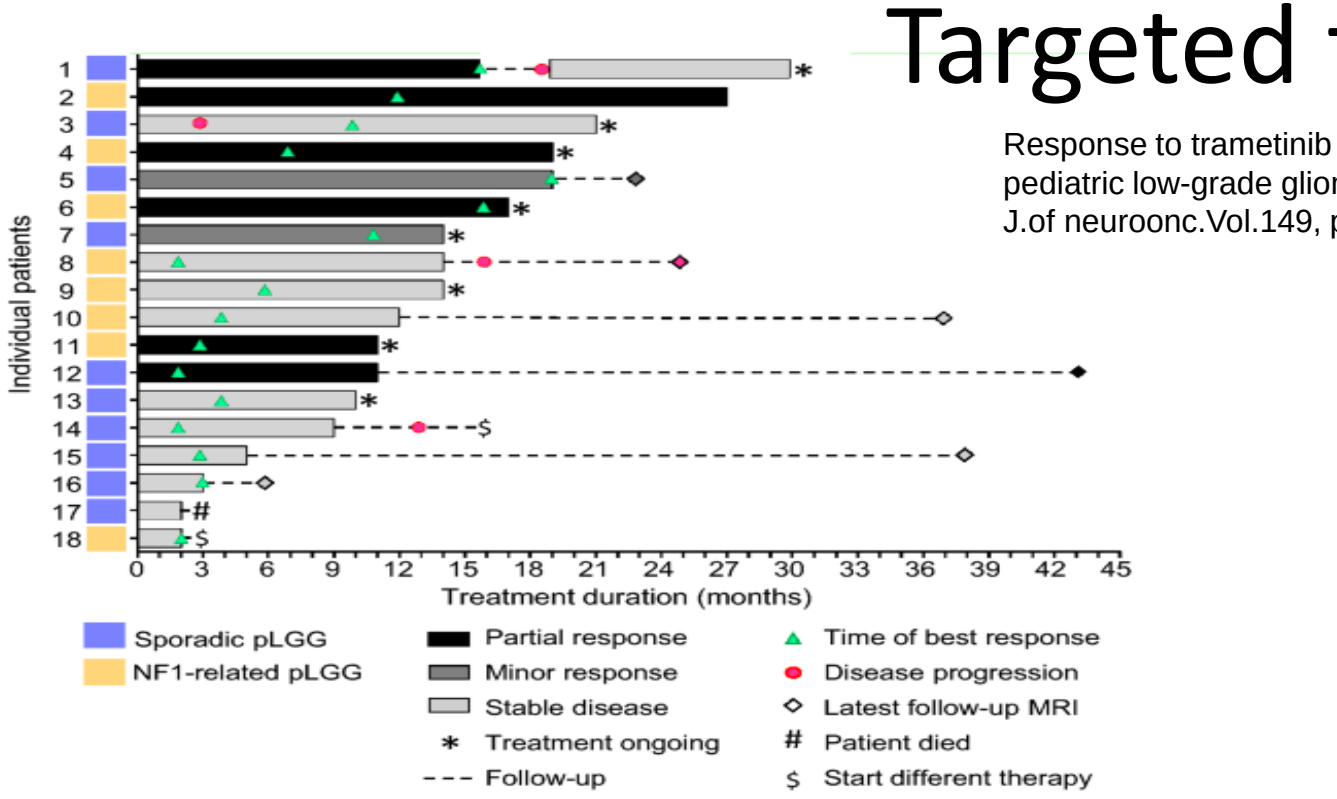
Ryall S, Tabori U, Hawkins C.

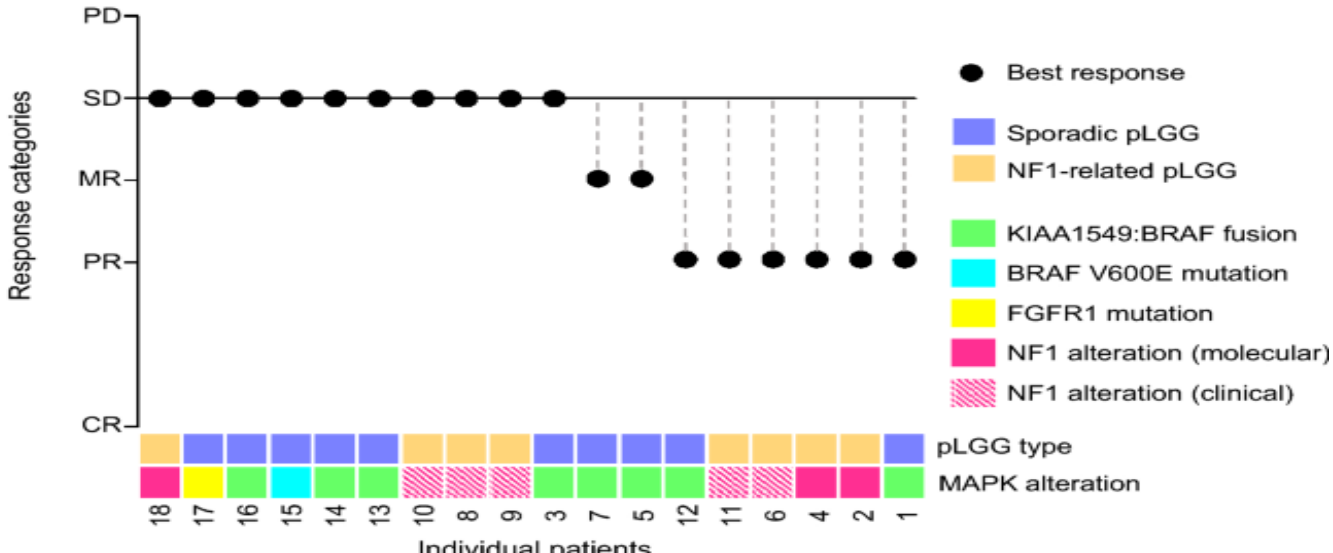
Acta Neuropathol Commun. 2020 Mar 12;8(1):30.

- 

Targeted therapy?

Response to trametinib treatment in progressive pediatric low-grade glioma patients
J.of neurooncVol.149, pages 499–510, (2020)

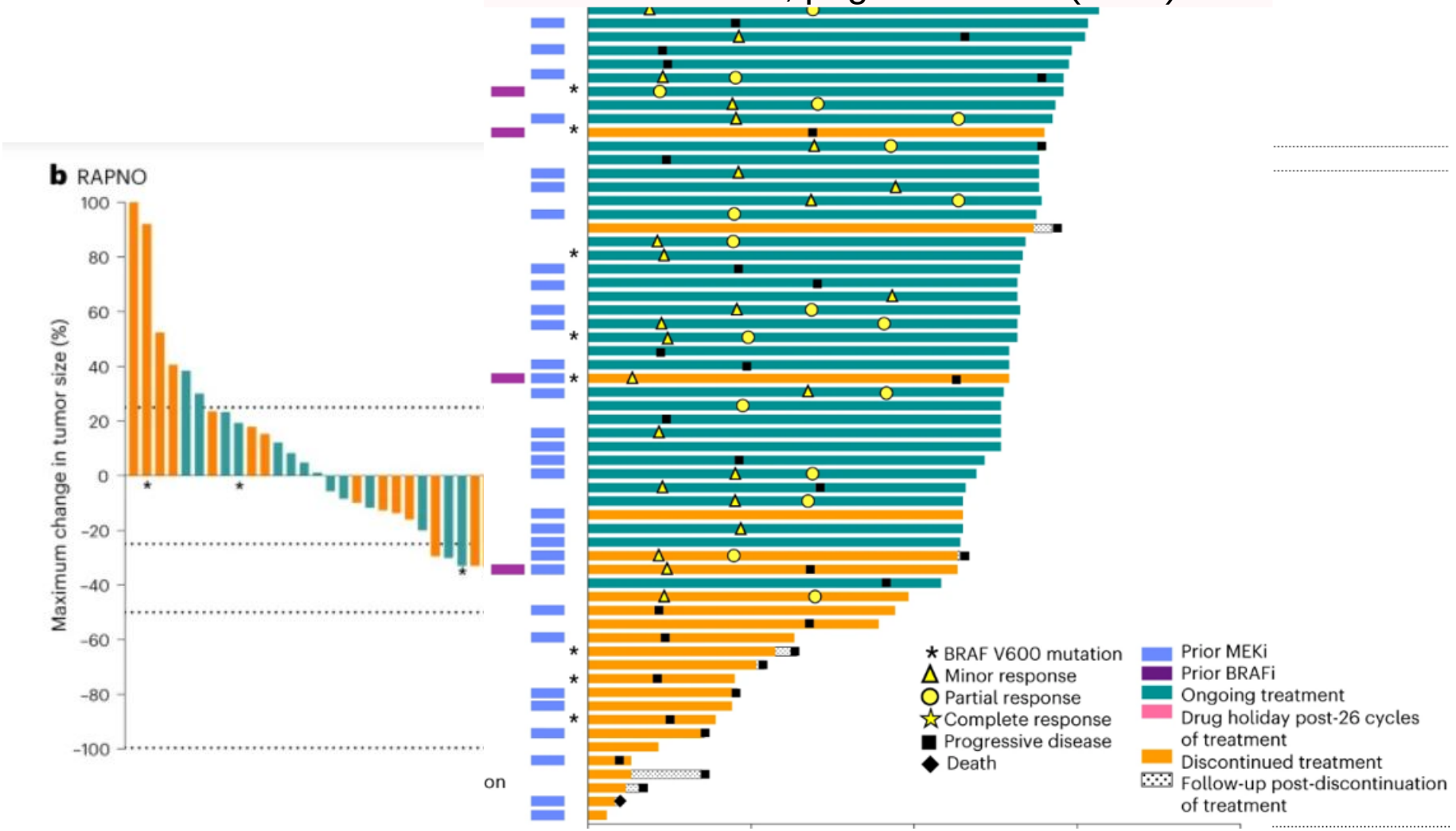




The type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: the phase 2 FIREFLY-1 trial

Lindsay B. Kilburn et al.

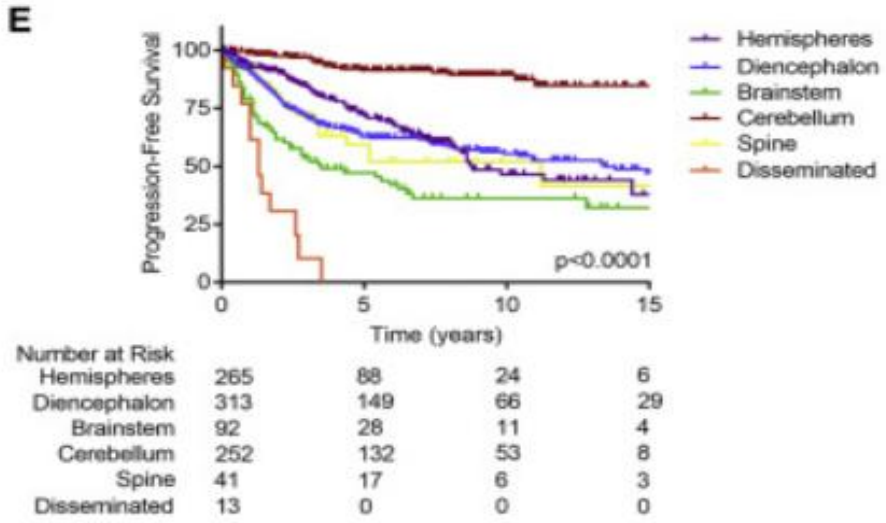
Nature Medicine volume 30, pages207–217 (2024)

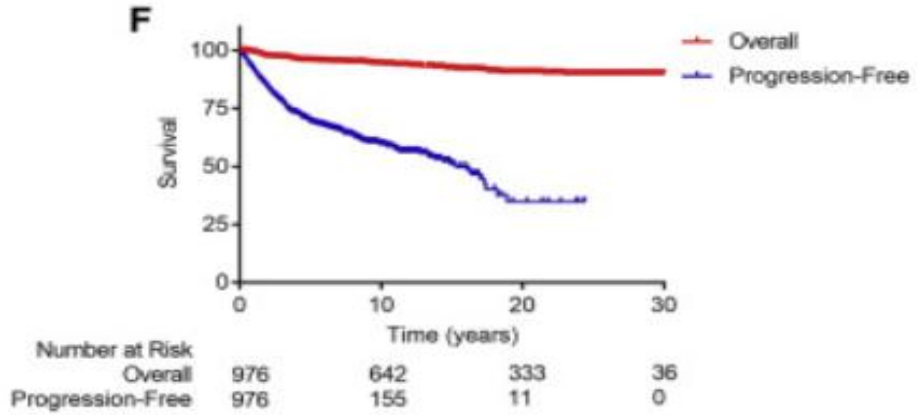


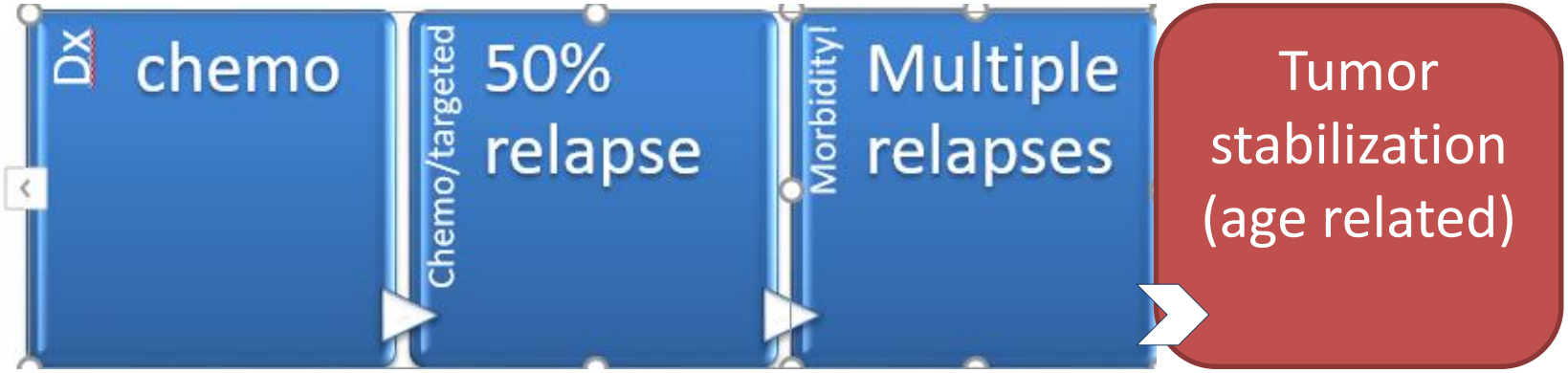
Integrated Molecular and Clinical Analysis of 1,000 Pediatric Low-Grade Gliomas.

Ryall S, Bouffet E, Karajannis MA, Santi M, Ellison DW, **Tabori U**, Hawkins C.

Cancer Cell. 2020 Apr 13;37(4):569-583.e5

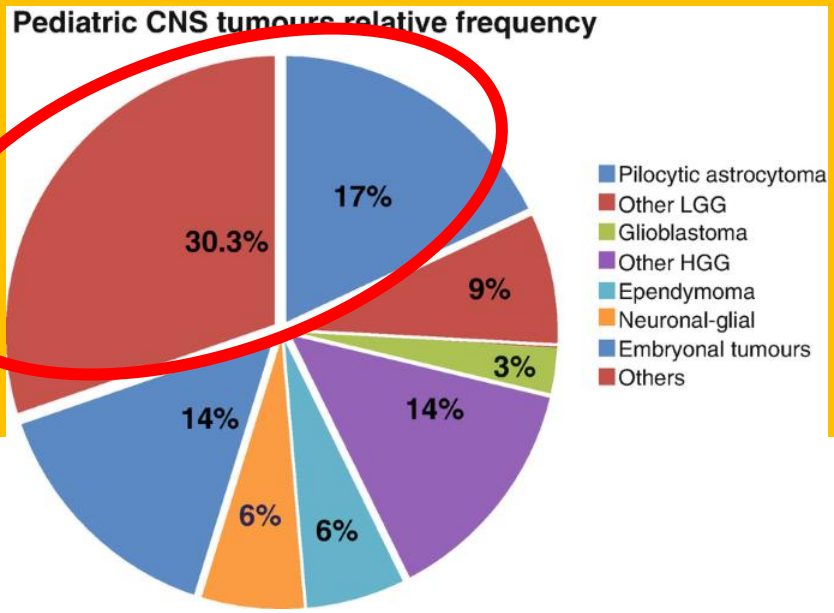






The need:

- 30-35 new children yearly
- 10-12 children with progressive LGG per year in Israel
- Non resectable LGG with multiple progressions (mainly OPG)
- Long term outcome of multiple progressions: functional deficits



Pediatric high grade glioma

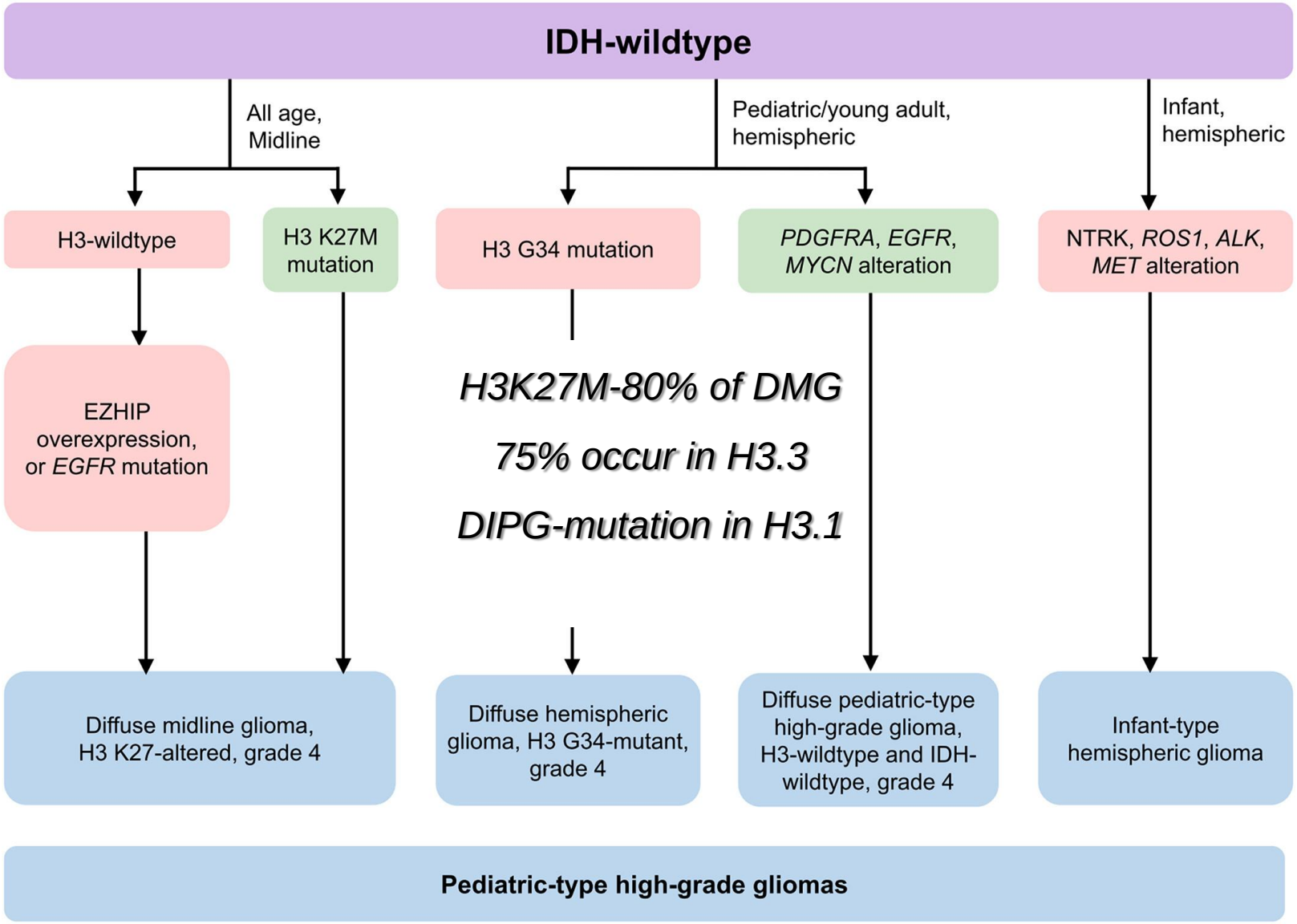
Ch. was diagnosed with a GBM involving the ventricular system and the hypocampus with a secondary massive bleed and quadriplegia. following rads Ch underwent intensive rehabilitation. The picture was taken when he regained his ability to walk eat and speak.

Unfortunately a month later disease recurred.

The 2021 WHO Classification for Gliomas and Implications on Imaging ..

: Part 2—Summary of Imaging Findings on Pediatric-Type Diffuse High-Grade Gliomas, Pediatric-Type Diffuse Low-Grade Gliomas, and Circumscribed Astrocytic Gliomas

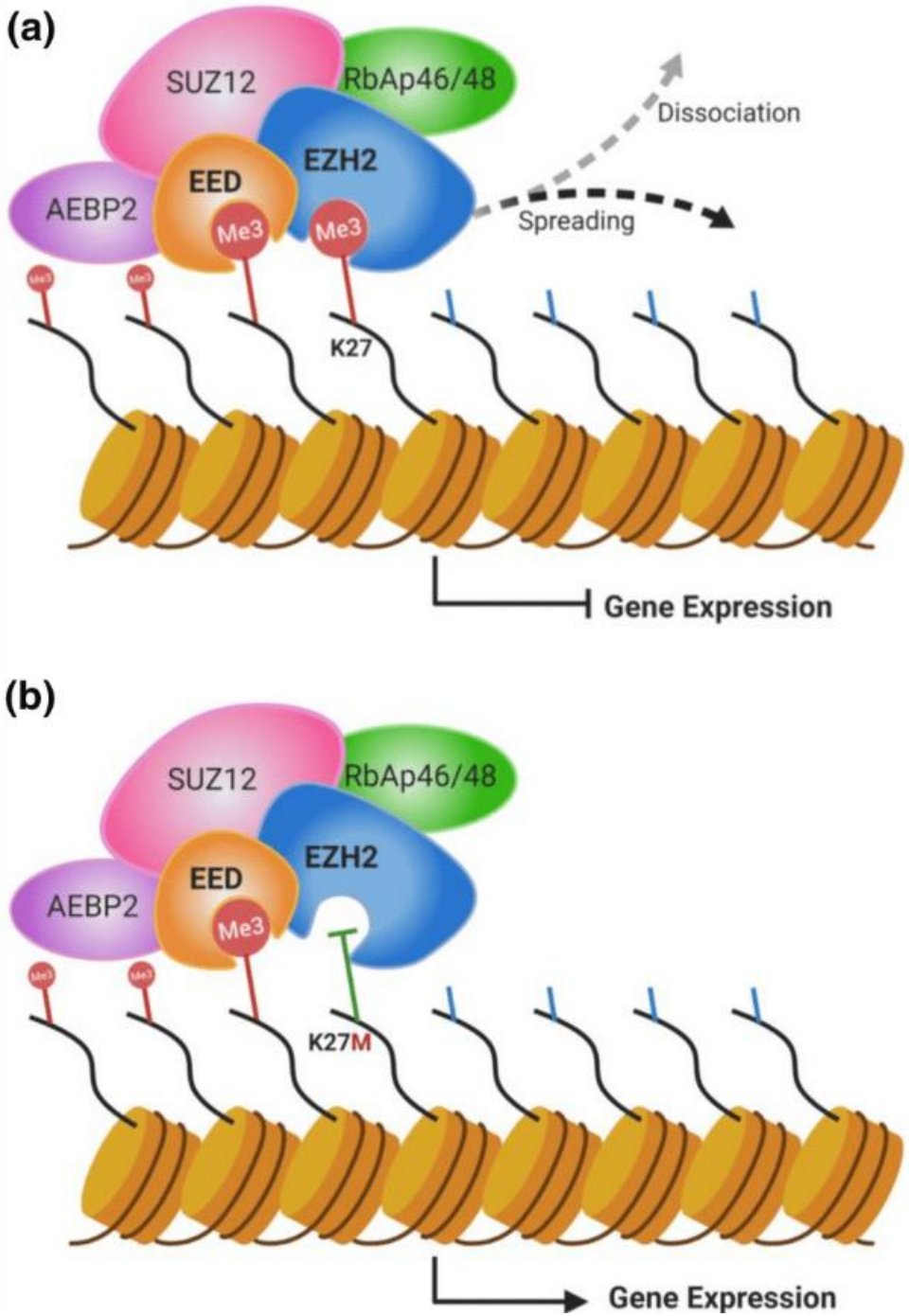
Yae Won Park etc.,



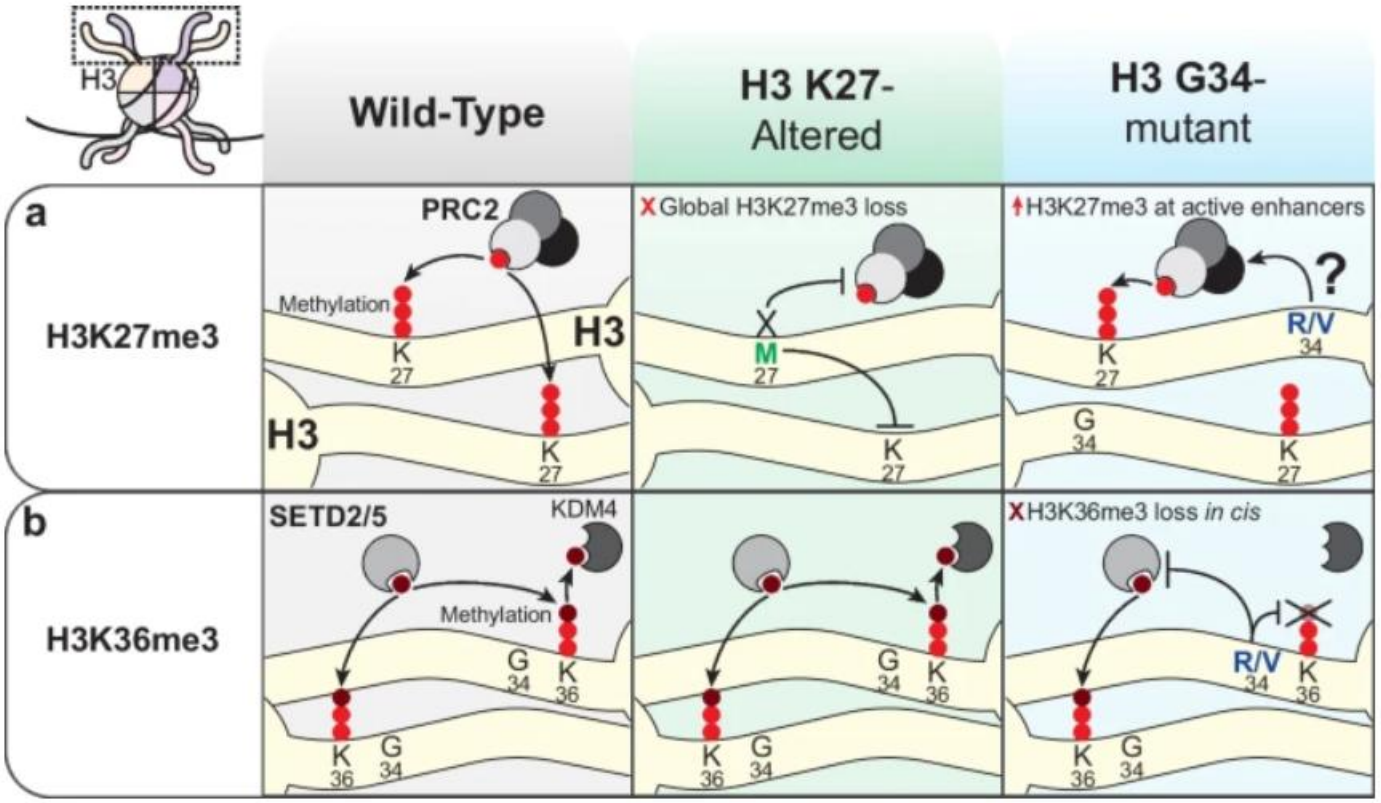
The result of H3k27m

and PRC2 complex

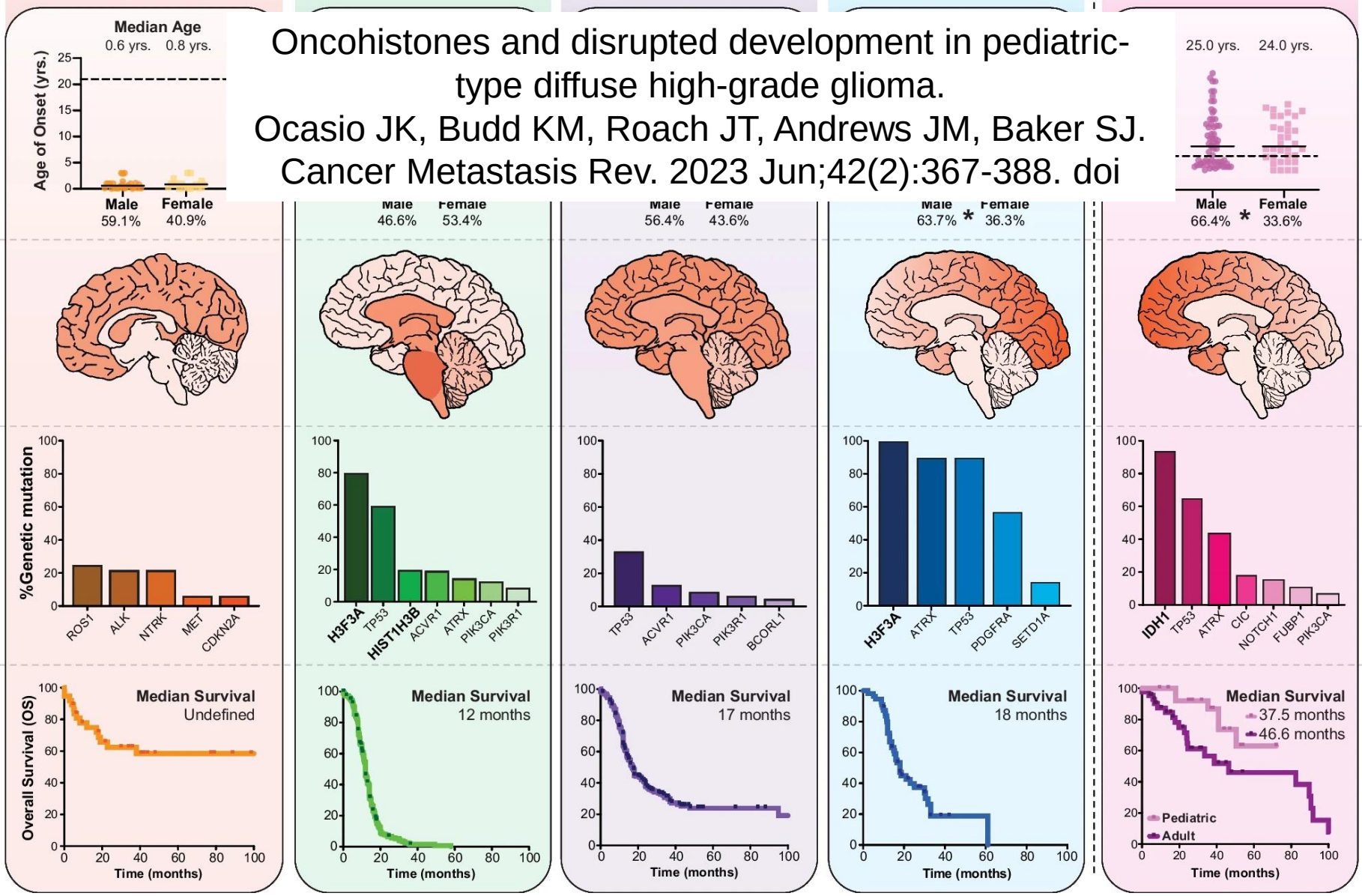
DMG



Result of oncohistone mutation:



Oncohistones dysregulate histone methylation patterns. **a**) PRC2 deposits methyl groups (red circles) at H3K27 in wild-type cells. H3 K27M causes global loss of H3K27me3 while H3 G34R/V increases H3K27me3 at active enhancers. **b)** SETD2 and SETD5 deposit the third methyl group at H3K36 (dark red circles), which can be removed by KDM4 (KDM4A, KDM4B, and KDM4D). H3K36me3 is unaffected in H3 K27-altered tumors while H3 G34R/V causes a loss of H3K36me3 in cis

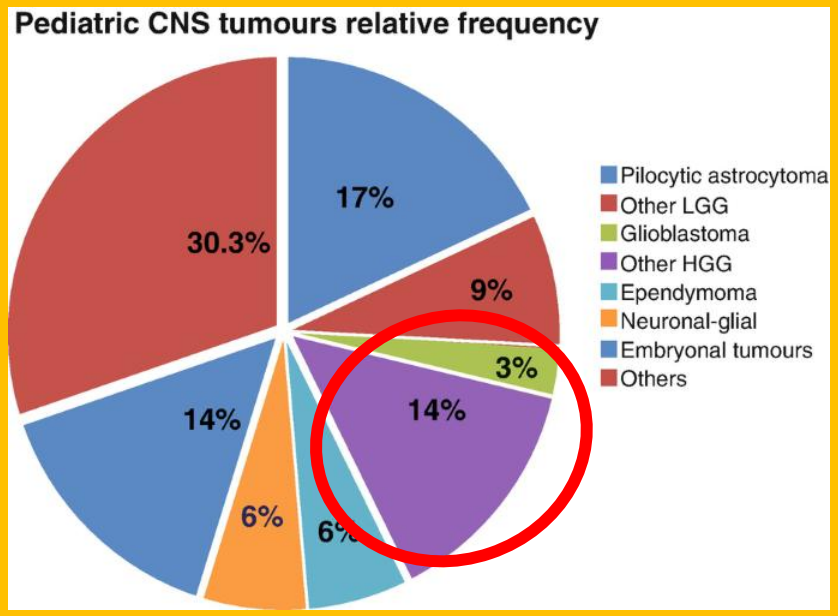


Oncohistones and disrupted development in pediatric-type diffuse high-grade glioma.

Ocasio JK, Budd KM, Roach JT, Andrews JM, Baker SJ. Cancer Metastasis Rev. 2023 Jun;42(2):367-388. doi

The need:

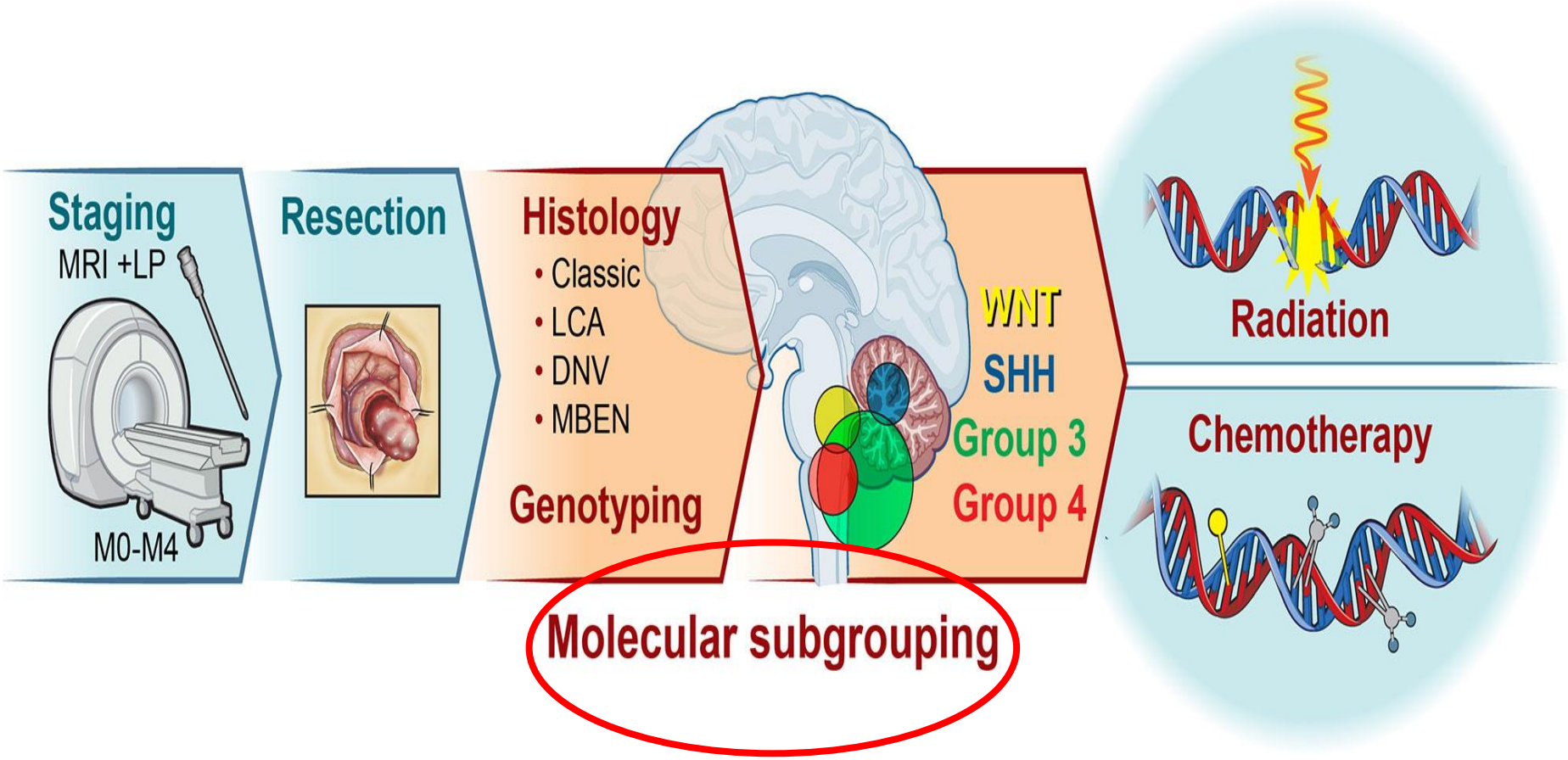
- 20 children with HGG/DMG per year in Israel
- On current therapies :median survival-12-15 months

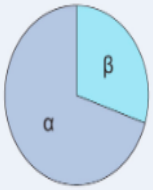
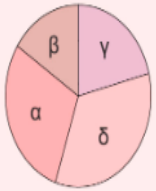
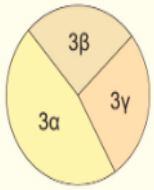
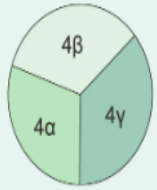
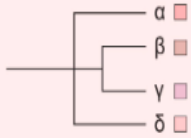
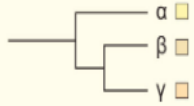
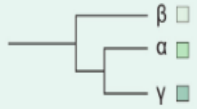


medulloblastoma

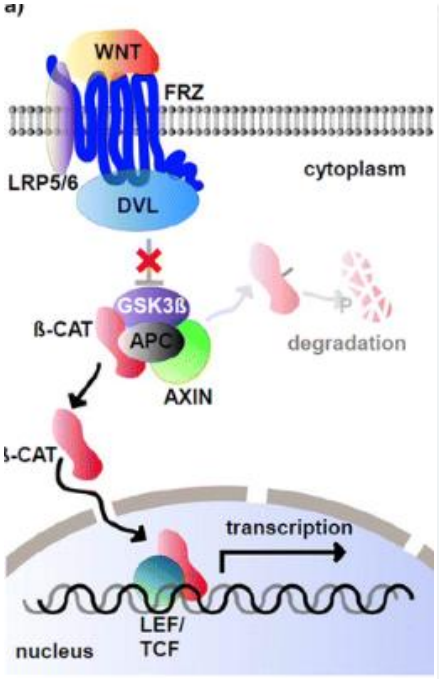
A. is an 18 months years old child . Just learned how to walk. On January this year she startedfalling. A huge mass was Dx stemming from the cerebellum with multiple mets. The primary mass was resected. She received aggressive chemo followed by partial response only an she is currently a happy 2 years old..

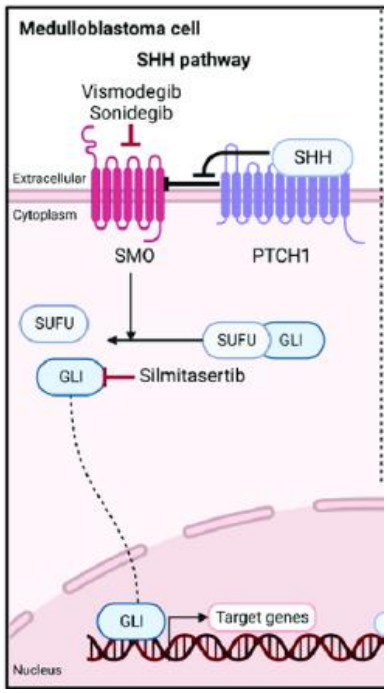
Diagnosis and therapy



Subgroup	WNT		SHH				Group 3			Group 4		
Subtype	WNT α	WNT β	SHH α	SHH β	SHH γ	SHH δ	Group 3α	Group 3β	Group 3γ	Group 4α	Group 4β	Group 4γ
Subtype proportion												
Subtype relationship												
Clinical data: Age												
Clinical data: Histology			LCA Desmoplastic	Desmoplastic	MBEN Desmoplastic	Desmoplastic						
Clinical data: Metastases	8.6%	21.4%	20%	33%	8.9%	9.4%	43.4%	20%	39.4%	40%	40.7%	38.7%
Clinical data: Survival at 5 years	97%	100%	69.8%	67.3%	88%	88.5%	66.2%	55.8%	41.9%	66.8%	75.4%	82.5%
Copy number: Broad	6$^-$		9q$^-$, 10q$^-$, 17p$^-$		Balanced genome		7$^+$, 8$^-$, 10$^-$, 11$^-$, i17q		8$^+$, i17q	7q$^+$, 8p$^-$, i17q	i17q	7q$^+$, 8p$^-$, i17q (less)
Copy number: Focal			*MYCN* amp, *GLI2* amp, *YAP1* amp	*PTEN* loss		10q22$^-$, 11q23.3$^-$		*OTX2* gain, *DDX31* loss	*MYC* amp	*MYCN* amp, *CDK6* amp	*SNCAIP* dup	*CDK6* amp
Other events			*TP53* mutations			*TERT* promoter mutations		High *GFI1/1B* expression				

Age (years): 0-3 >3-10 >10-17 >17





?

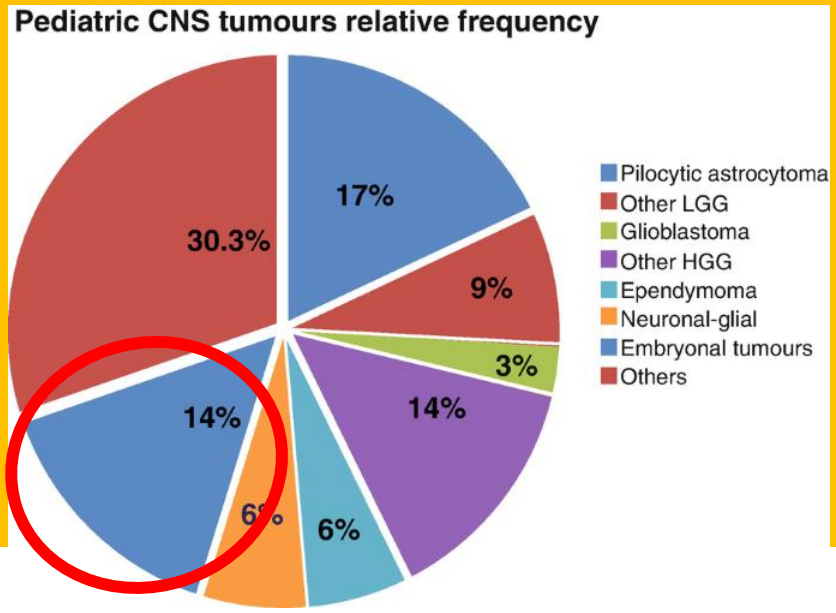
Old fashioned clinical trials

Targeted therapy-limited effect

The need:

- 15-16 children with medulloblastoma per year in Israel
- Children per year Relapse:4-5
- Specific subgroups:

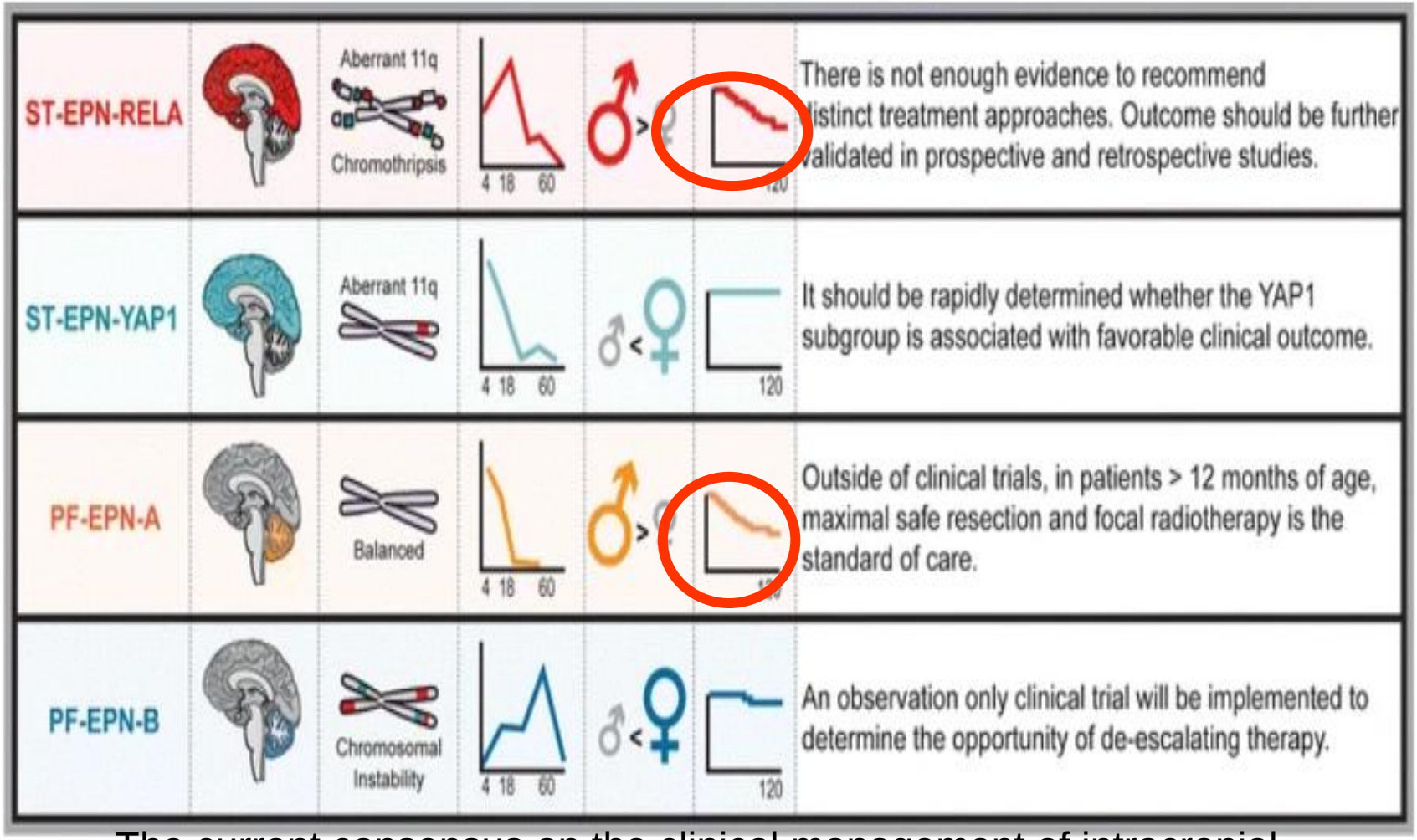
(3-cure rates – 50%)



Ependymoma

R. Was Dx 5 years ago with a huge Rt. Hemispheric ependymoma with ZFTA fusion. He had 4 surgeries, two rounds of radiation , chemo and a year on targeted therapy.he had just completed a 5th surgery and we are looking for new treatment options. Since last week R is back in his class

Main pediatric subtypes



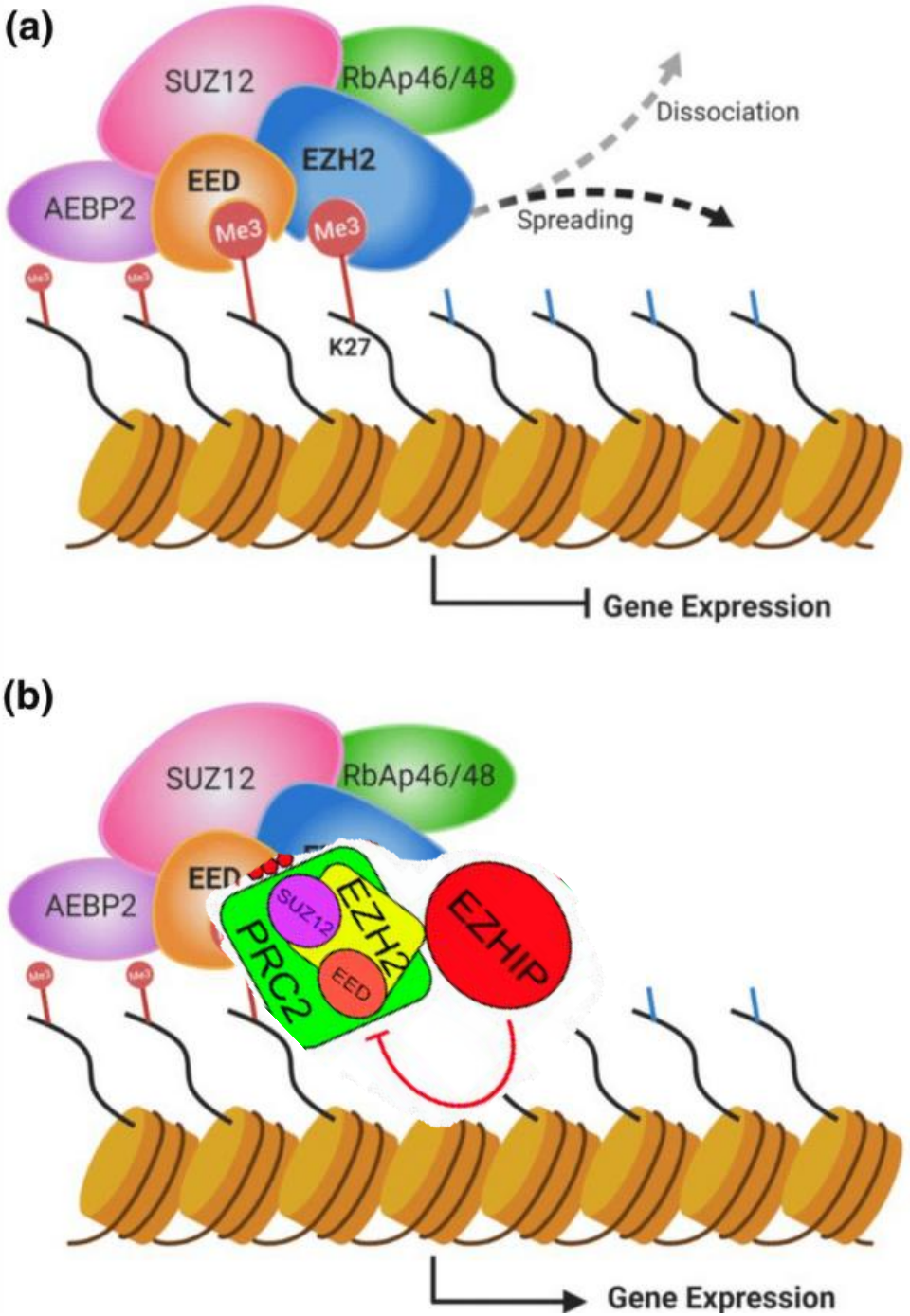
The current consensus on the clinical management of intracranial ependymoma and its distinct molecular variants
Acta Neuropathologica Volume 133, pages 5–12, (2017)

PFA Ependymoma

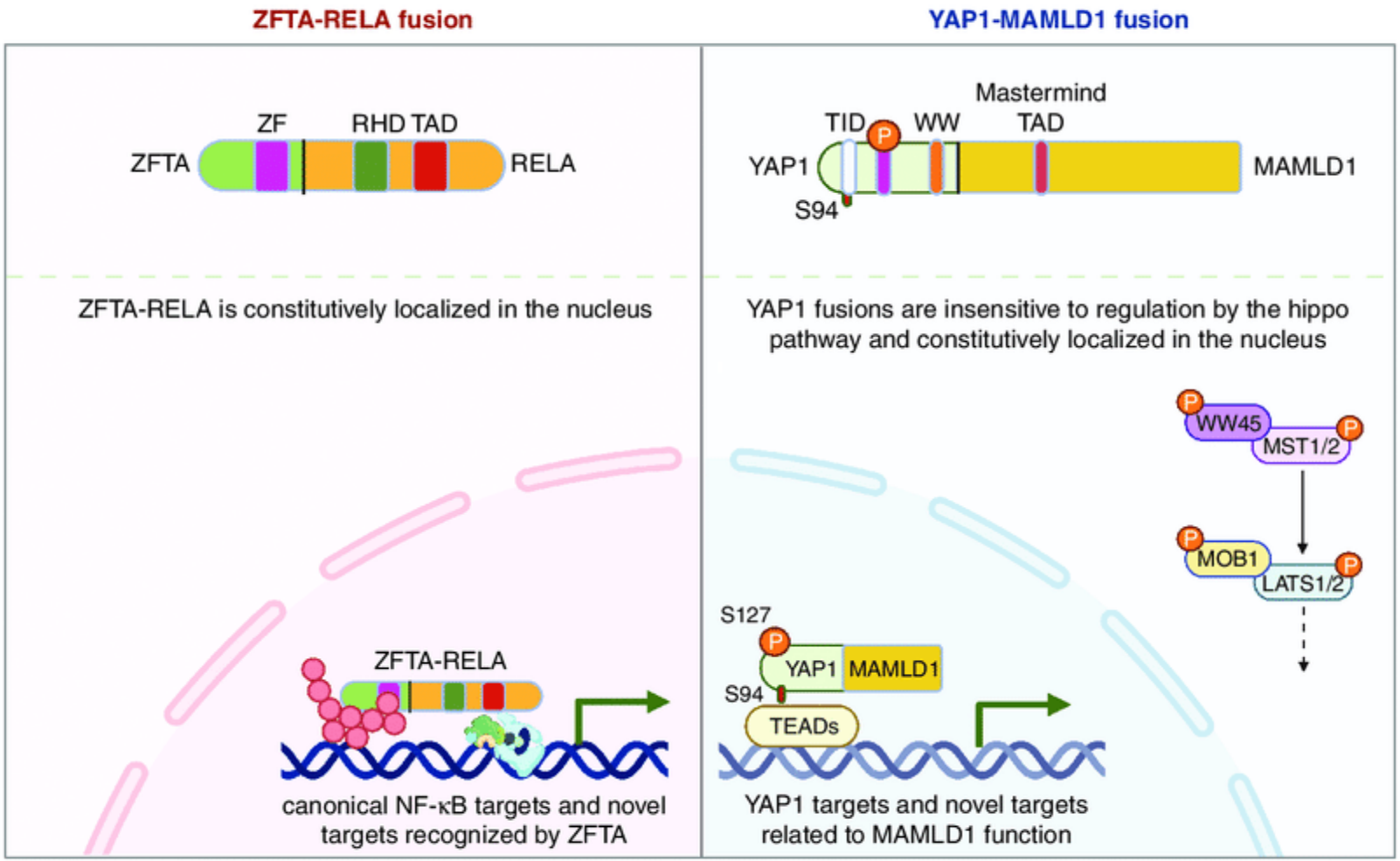
The result of EZHIP mutations

and PRC2 complex

- Global DNA hypomethylation,
- Increased H3K27me3 enrichment at select genomic loci



ST Ependymoma:



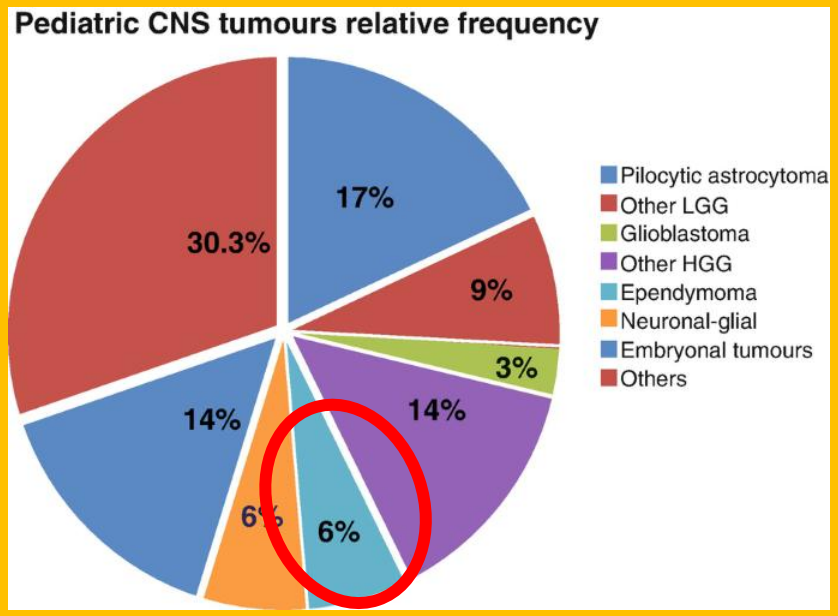
Childhood Ependymoma Treatment (PDQ®)
October 15th 2024

Table 1. Standard Treatment Options for Childhood Ependymoma

Treatment Group	Standard Treatment Options
Newly diagnosed childhood myxopapillary ependymoma (WHO grade 2)	Surgery with or without adjuvant radiation therapy
Newly diagnosed childhood nonmyxopapillary spinal ependymoma	Surgery
	Radiation therapy
Newly diagnosed childhood intracranial (supratentorial or posterior fossa) ependymoma:	Surgery
	Adjuvant therapy:
No residual disease, no disseminated disease	—Radiation therapy
Residual disease, no disseminated disease	—Second-look surgery
	—Radiation therapy
	—Preirradiation chemotherapy
Central nervous system disseminated disease	—Radiation therapy (not considered standard treatment)
	—Chemotherapy (not considered standard treatment)
Children younger than 1 year	—Chemotherapy
	—Deferred radiation therapy
Recurrent childhood ependymoma	Surgery
	Radiation therapy and/or chemotherapy

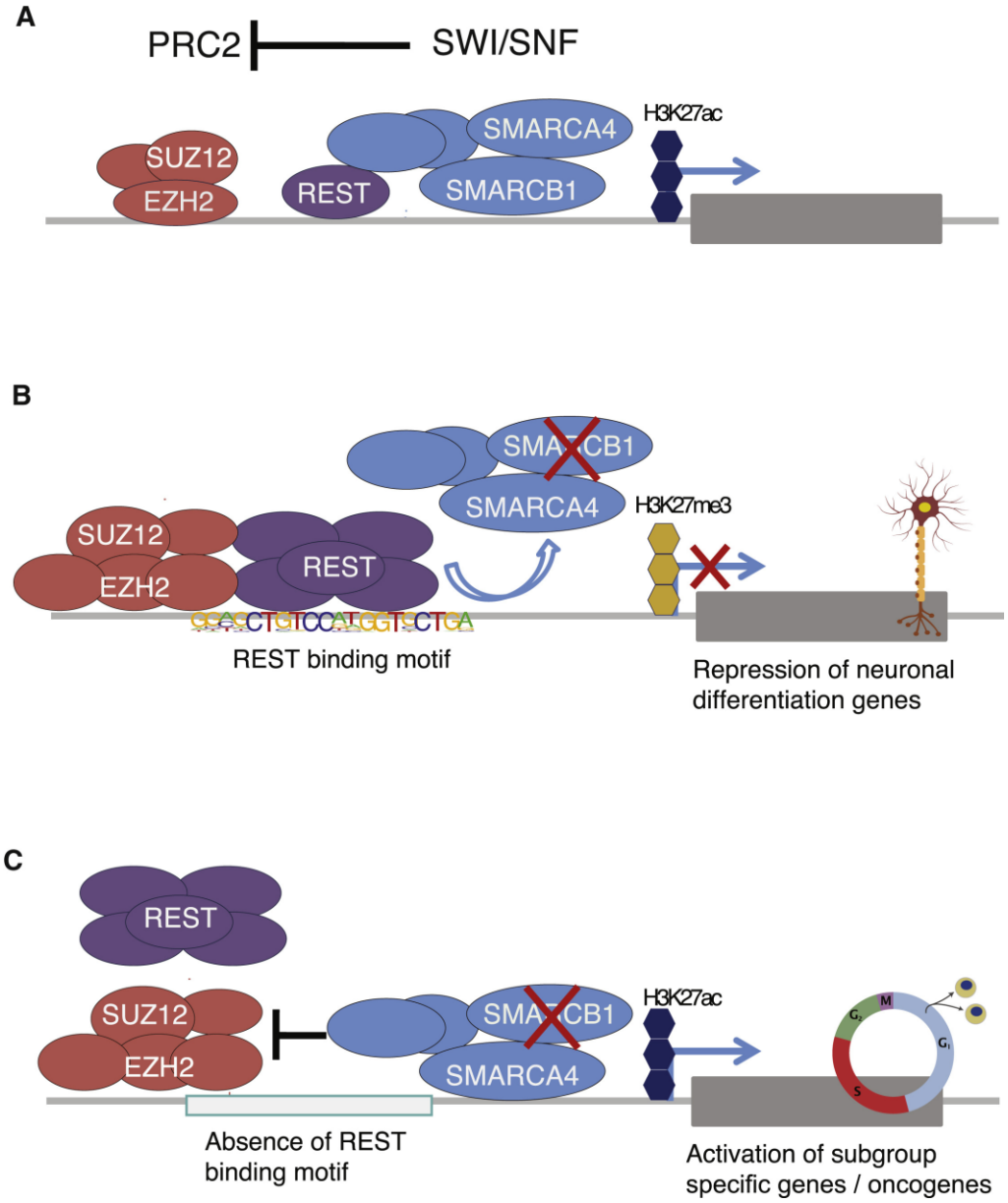
The need:

- 8-10 children with Ependymoma per year in Israel
- 4-5 children relapse/progress



Rare tumors

- ATRT:
- 50% 1 yr survival
- 30% germline mutation with lower survival



Comprehensive Analysis of Chromatin States in Atypical Teratoid/Rhabdoid Tumor Identifies Diverging Roles for SWI/SNF and Polycomb in Gene Regulation
Erkerk S.
Cancer cell . 2019 Jan 14;35(1):95-110.e8.

Immunotherapy

- Intravenous and intracranial GD2-CAR T cells for H3K27M(+) diffuse midline gliomas.