SIOP Hot topics

Childhood brain tumors

Current management
Biological insights
Future directions

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Why brain tumours?

Devastating diagnosis

Results of treatments not satisfactory

Long term effects of treatment

Complexity of the care

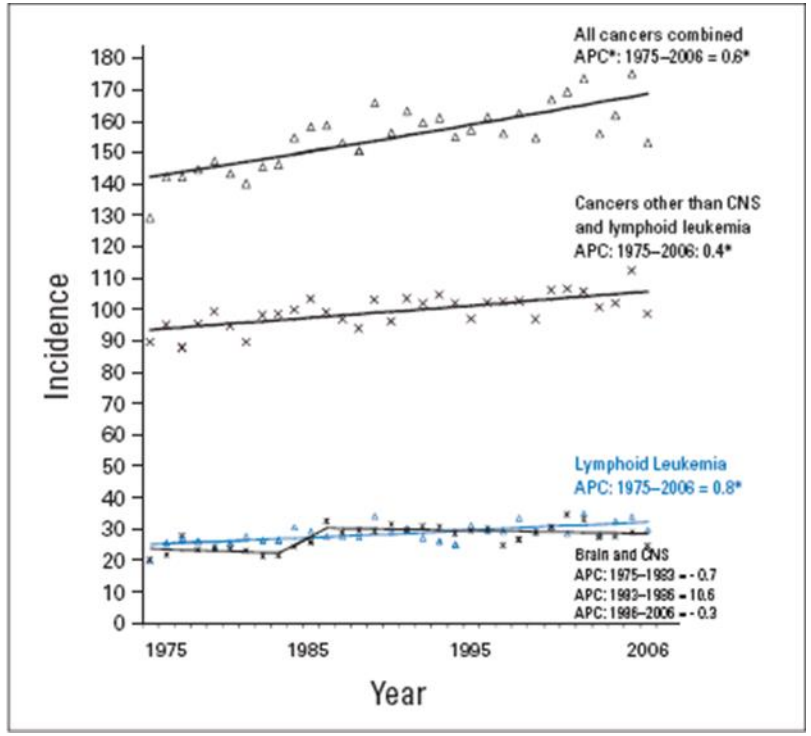
- Multidisciplinary management
- Link hospital-community-school

Palliative care

WHO GICC

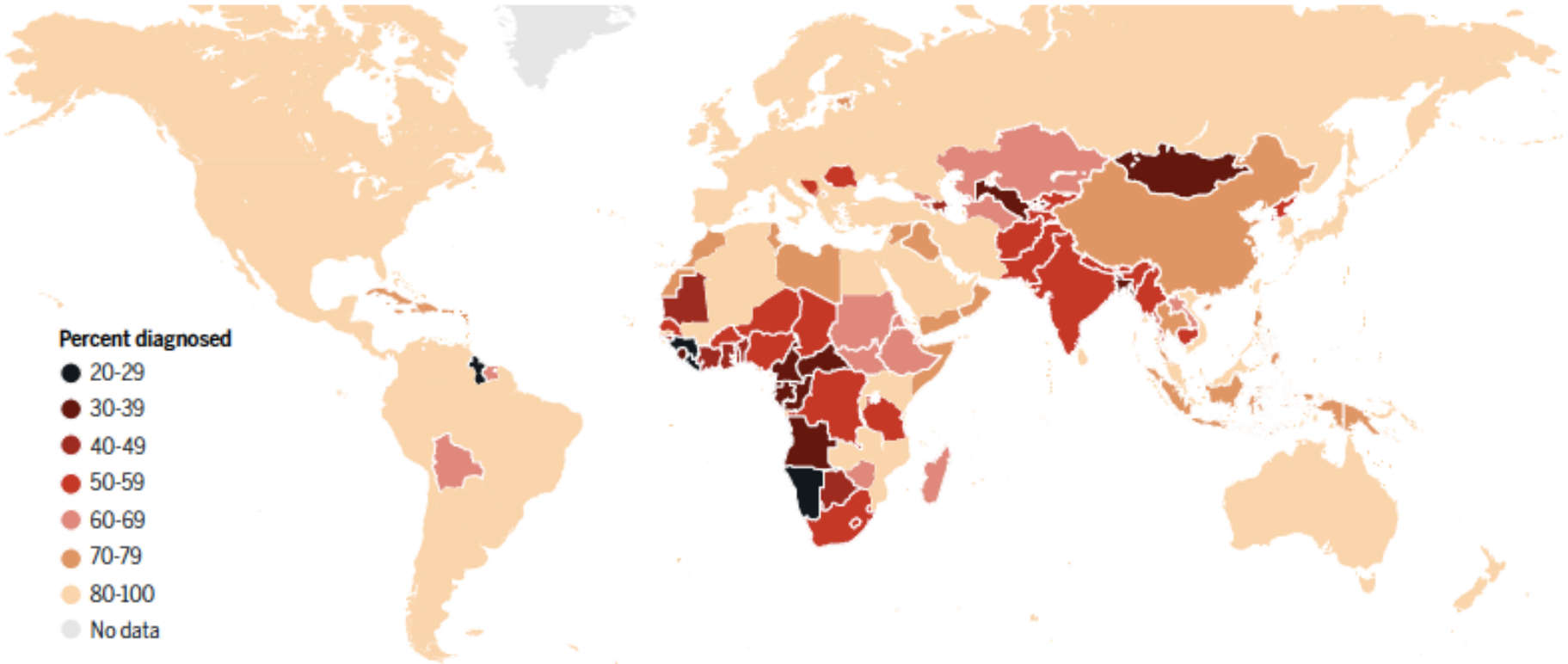
- The World Health Organization (WHO) Global Initiative for Childhood Cancer aims :
  - Improve outcomes for children with cancer around the world
    - The goal is to give all children with cancer the best chance to survive, to live full and abundant lives and to live and die without suffering.

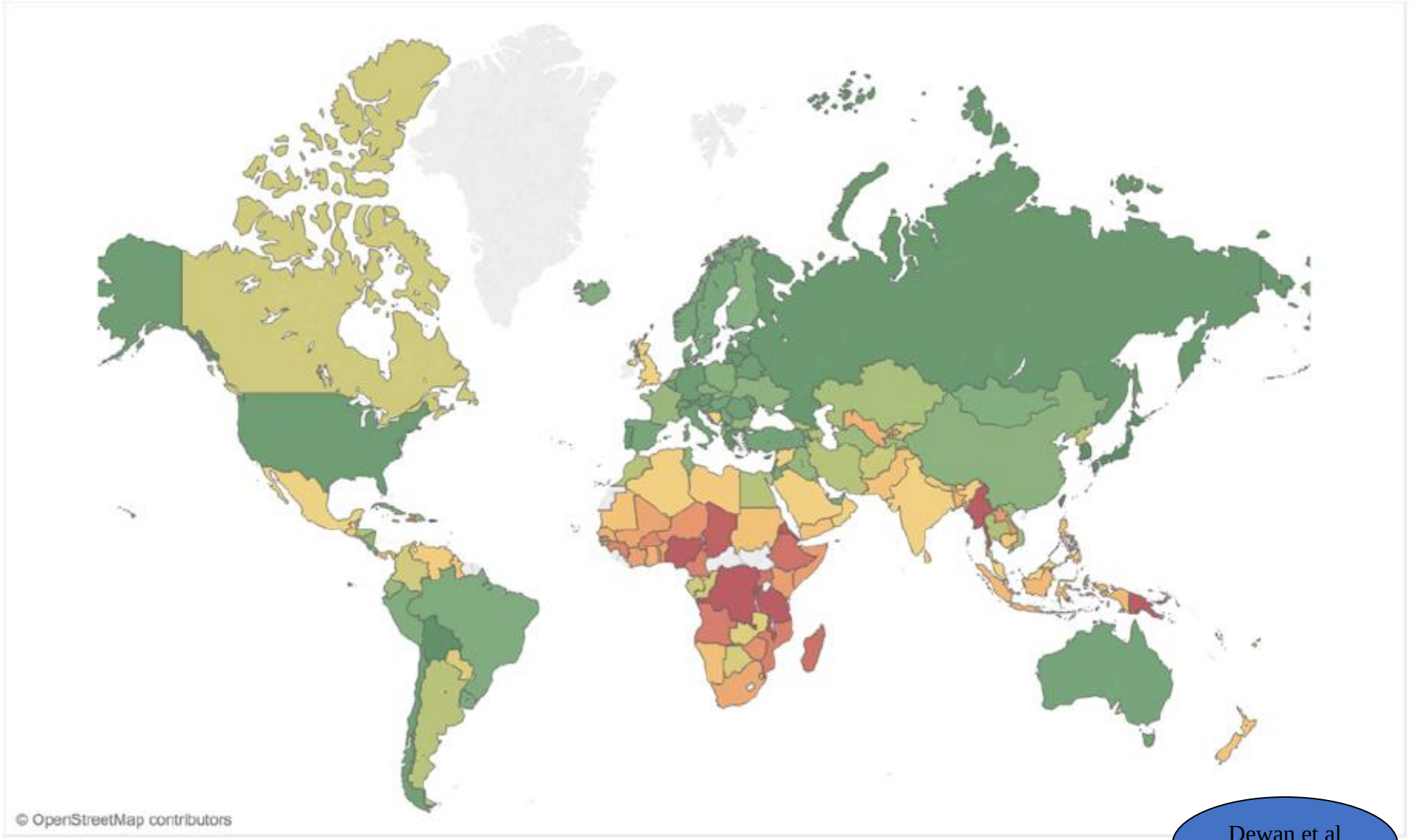
Cancer Death In Children



- Brain tumors are leading cause of cancer related deaths
- Advances in surgical and adjuvant therapy have improved the survival rates of children with medulloblastoma and low-grade glioma (LGG), for which 5-year survival now exceeds
  75%
- Prognosis for other tumors such as diffuse intrinsic pontine glioma (DIPG) and other midline high-grade gliomas (HGGs) remains poor

Percent Diagnosed CNS Tumor





Dewan et al 2018

Survival in paediatric brain tumours

	1980	2010	2022
Medulloblastoma	45	→ 75%	78
Germ cell tumours	50	→ 85%	86
Low grade glioma	70	→ 95%	95
Ependymoma	30	→ 60%	65
High grade gliomas	15%	→ 15%	15
Pontine gliomas	<5%	→ <5%	<5

1940

Surgery

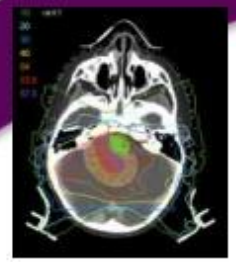
1970

Radiation

Cobalt

Linear accelerator

IMRT



1990

Chemotherapy

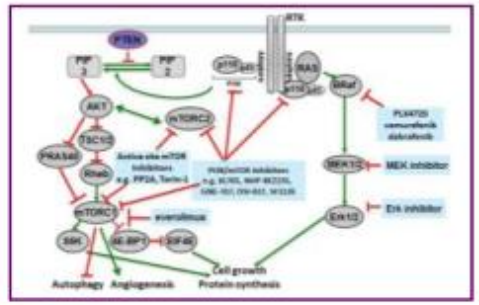
Vincristine + carboplatin

TPCV

Vinblastine

2015

Targeted therapies…

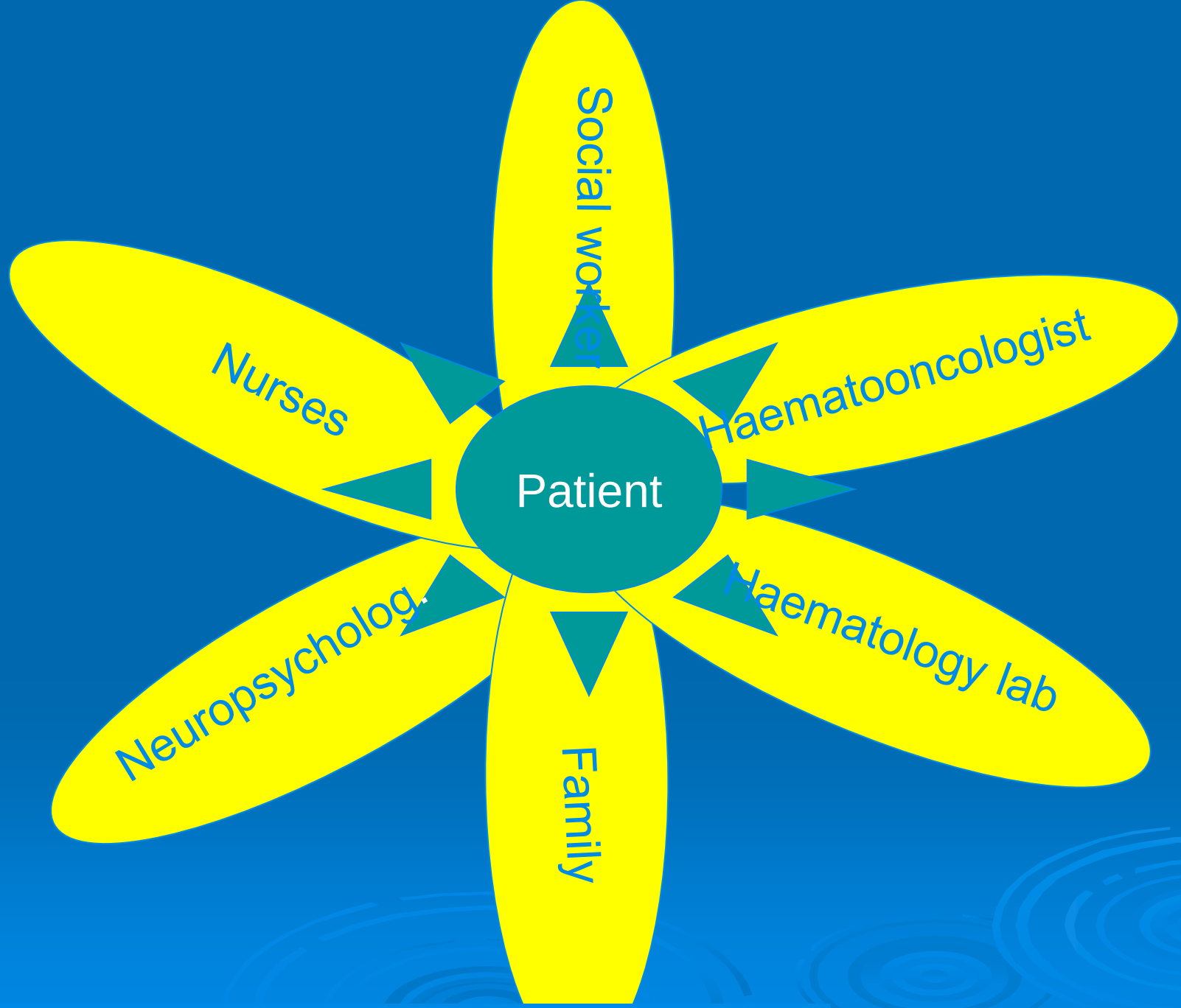


Paediatric Brain Tumours

- Diversity
- Complexity
- Heterogeneity
- It never stops
  - ***Exact role of the neuro-oncologist***
  - ***Extent of the job***

Exact role of the neuro-oncologist

- Just patients with brain tumour who require chemotherapy
- Patients who need postoperative management (radio or chemo or other treatments)
- All patients
- Other patients
  - ***Neurofibromatosis clinic***
  - ***Tuberous sclerosis***
  - ***DI and pituitary stalk thickening***
  - ***Cutaneous melanosis***



Key (players) for a pediatric Leukaemia program

Key (players) for a paediatric neuro-oncology program

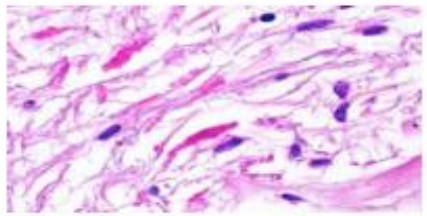
Low-Grade Glioma

- Several subgroups, including :
  - ***Pilocytic***
  - ***Pilomyxoid***
  - ***Subependymal giant cell***
  - ***Diffuse astrocytomas***

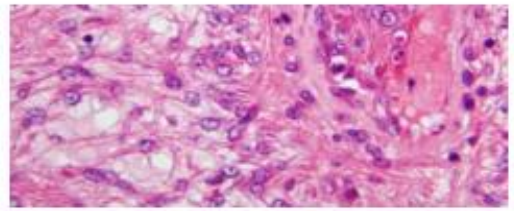
Low grade gliomas

Most common pediatric brain tumors (30-50%)

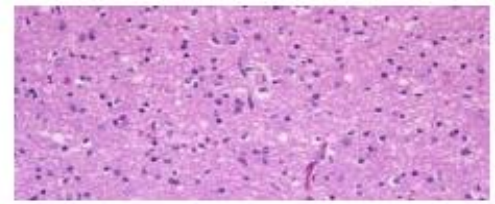
PILOCYTIC ASTROCYTOMA



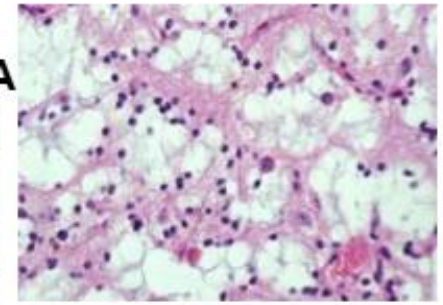
PILOMYXOID ASTROCYTOMA



DIFFUSE ASTROCYTOMA



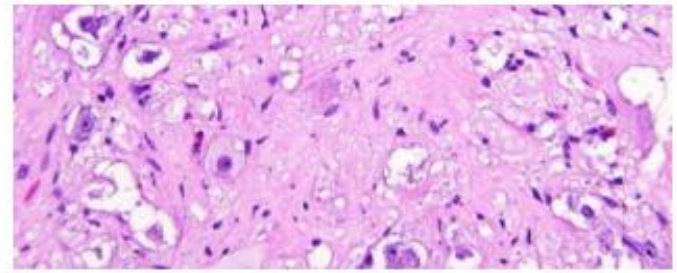
DNET



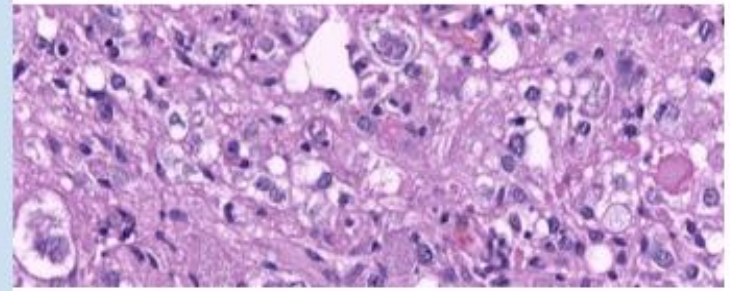
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*

Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3

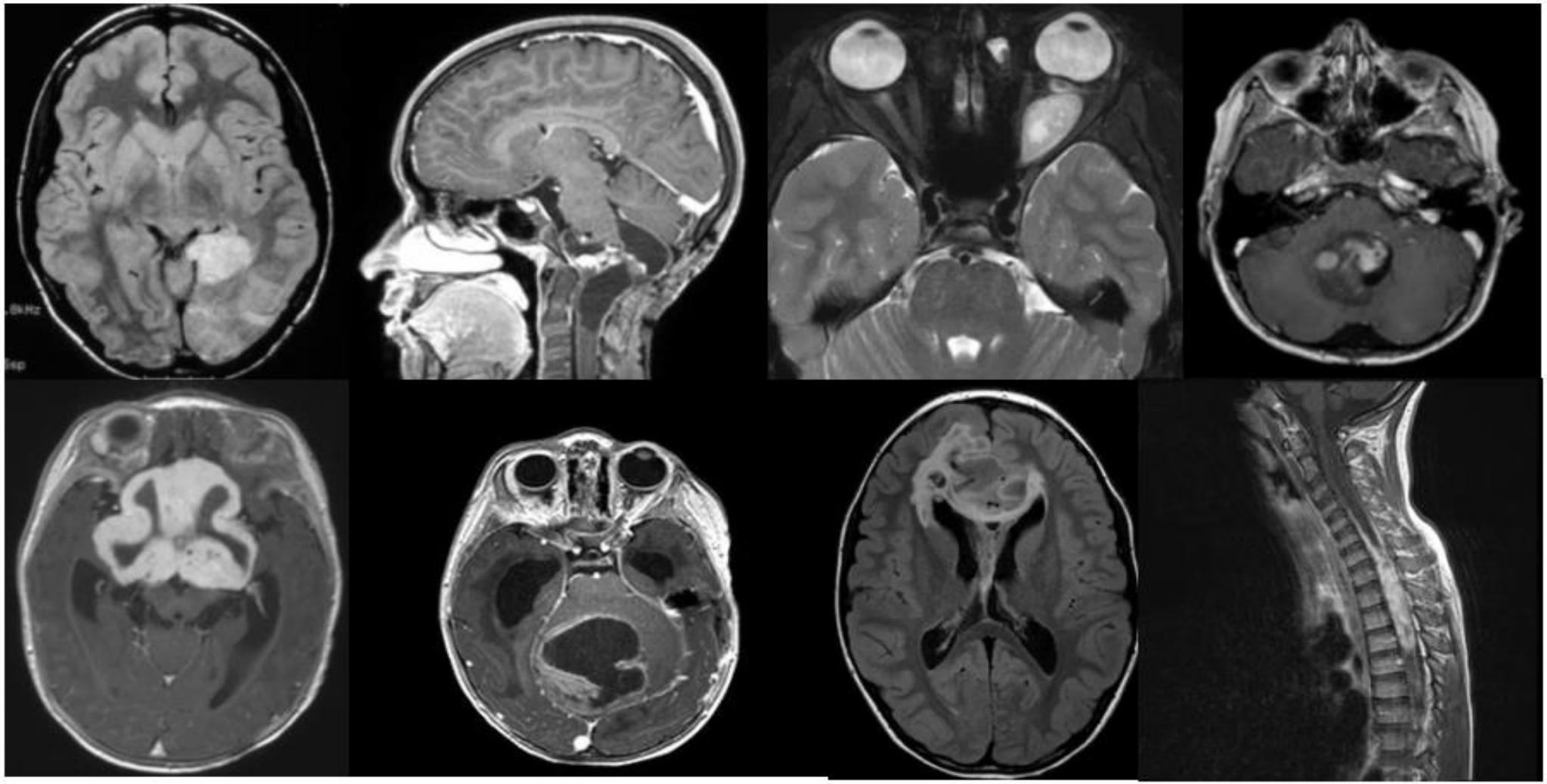
GANGLIOGLIOMA



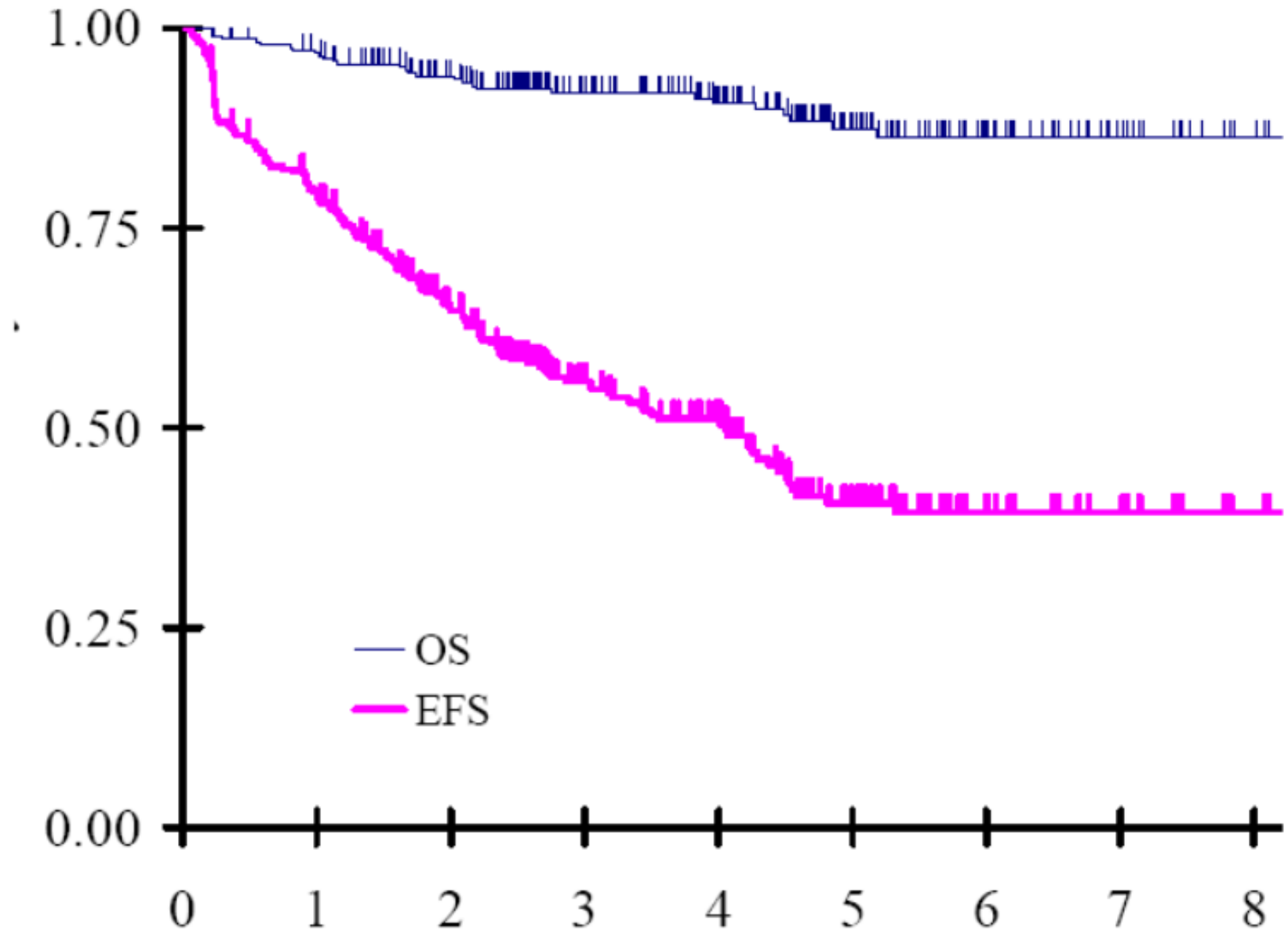
PXA



Pediatric Low Grade Gliomas (PLGG) can arise anywhere around neuroaxis



What did we know on PLGG in 2008?



Low-Grade Glioma

- Two cancer-predisposition syndromes :
  - ***Neurofibromatosis type 1 (NF1)***
  - ***Tuberous sclerosis complex***
- Increased frequency
  - ***Pilocytic Astrocytoma***
  - ***Subependymal giant cell astrocytomas***
- Extensive resection

Progression-Free Survival
PFS

- After complete resection :
  - ***10-year (PFS) Over 85%***
  - ***Less than 50% if there is radiologically visible residual tumor***
- After complete resection, RT or chemotherapy is rarely warranted.

Limitation

- Complete resection is not usually feasible
  - ***Deep-seated***
  - ***Infiltrative tumors***
    - ***Hypothalamus***
    - ***Optic pathways***
- Worse prognosis than superficial lesions
    - ***Challenging***
    - ***large size***
    - ***Frequent occurrence in young children***
    - ***Increasing the risks of adverse late effects from RT***

Issues with PLGG

- Bag of diverse pathology subtypes with heterognous outcomes.
- Inoperable tumors: challenge
- Radiation has long term effects
- Chemotherapy- unsatisfactory results
- Lack of information on long term outcome.
- Lack of targeted therapies.

Past

- Conventional chemotherapy has been used during the last 2 decades to delay or avoid RT in young children
- COG A9952 study randomized :
  - ***Carboplatin and vincristine***
  - ***Thioguanine, procarbazine, lomustine,and vincristine***
- For unresectable or progressive LGGs in children without NF1

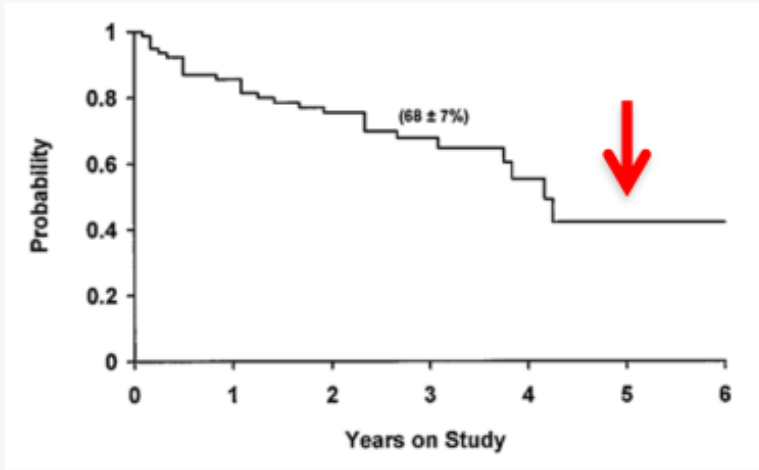
Results

- Patients with NF1-related gliomas received carboplatin and vincristine given concerns regarding alkylator-related second malignancies
- Both regimens delayed tumor progression, although children without NF1 generally experienced disease progression within 5 years of therapy, highlighting the need for additional treatment options.

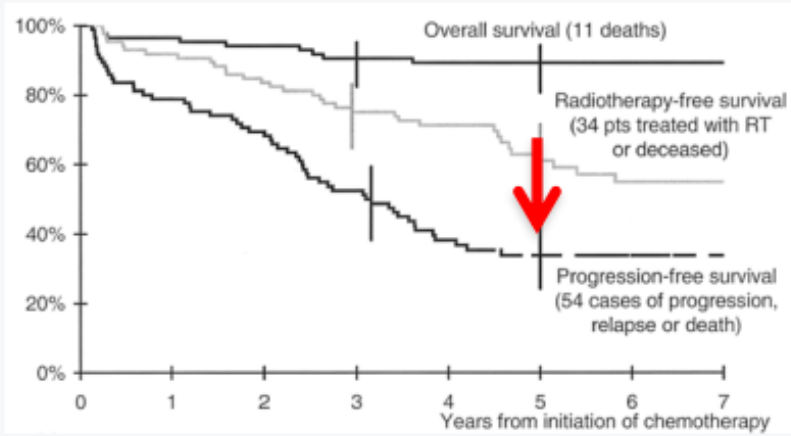
Studies

- Phase III randomized trial (SIOP) :
  - ***Adding etoposide to carboplatin and vincristine did not improve survival***
- Vinblastine
- COG ACNS0221
  - ***Conformal RT benefit in appropriately selected unresectable tumors in children older than 5 years***

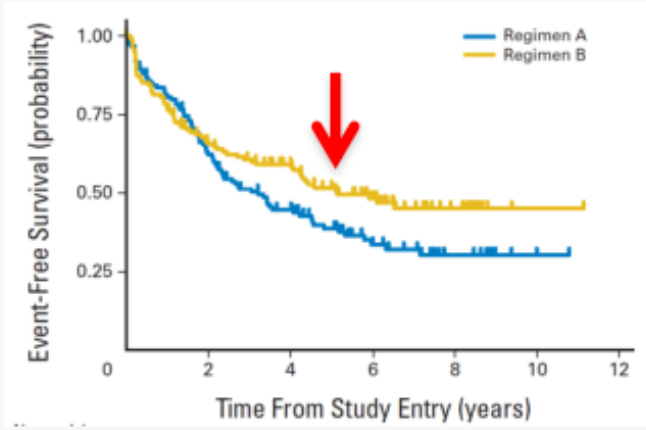
Which chemotherapy? Similar outcome no matter what you give…



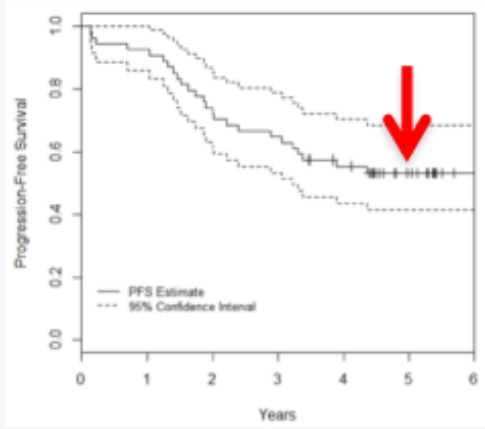
Vincristine+carboplatin
Packer 1997



Pro+Carbo/Cis+VP16/V+CFM
Laithier 2003



TPCV Ater 2012

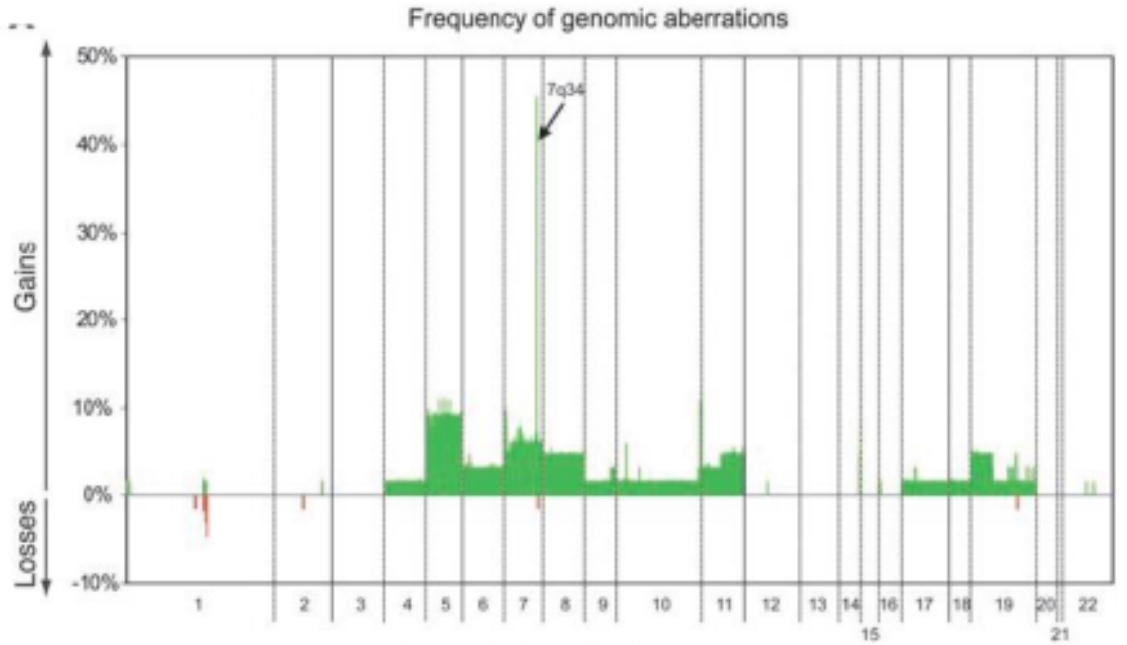


Vinblastine Lassaletta 2016

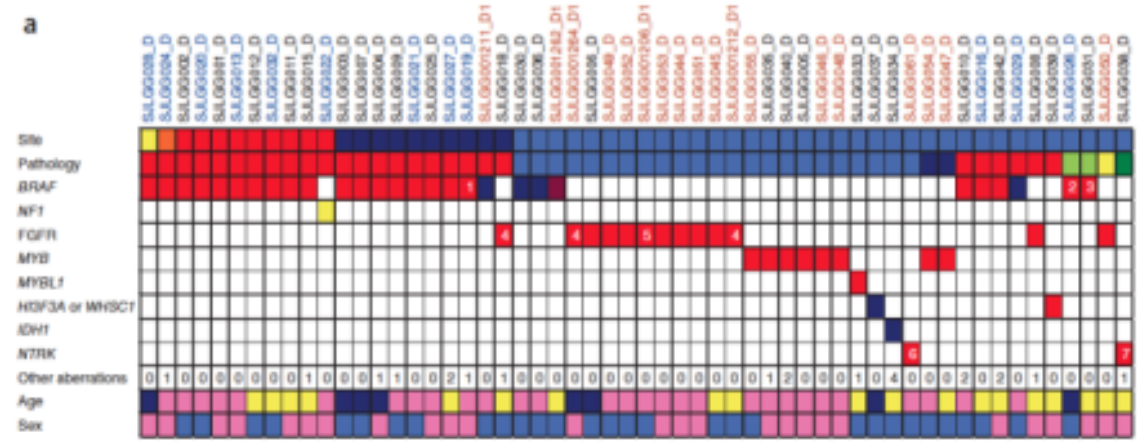
Genomic landscape of PLGG – A single pathway disease

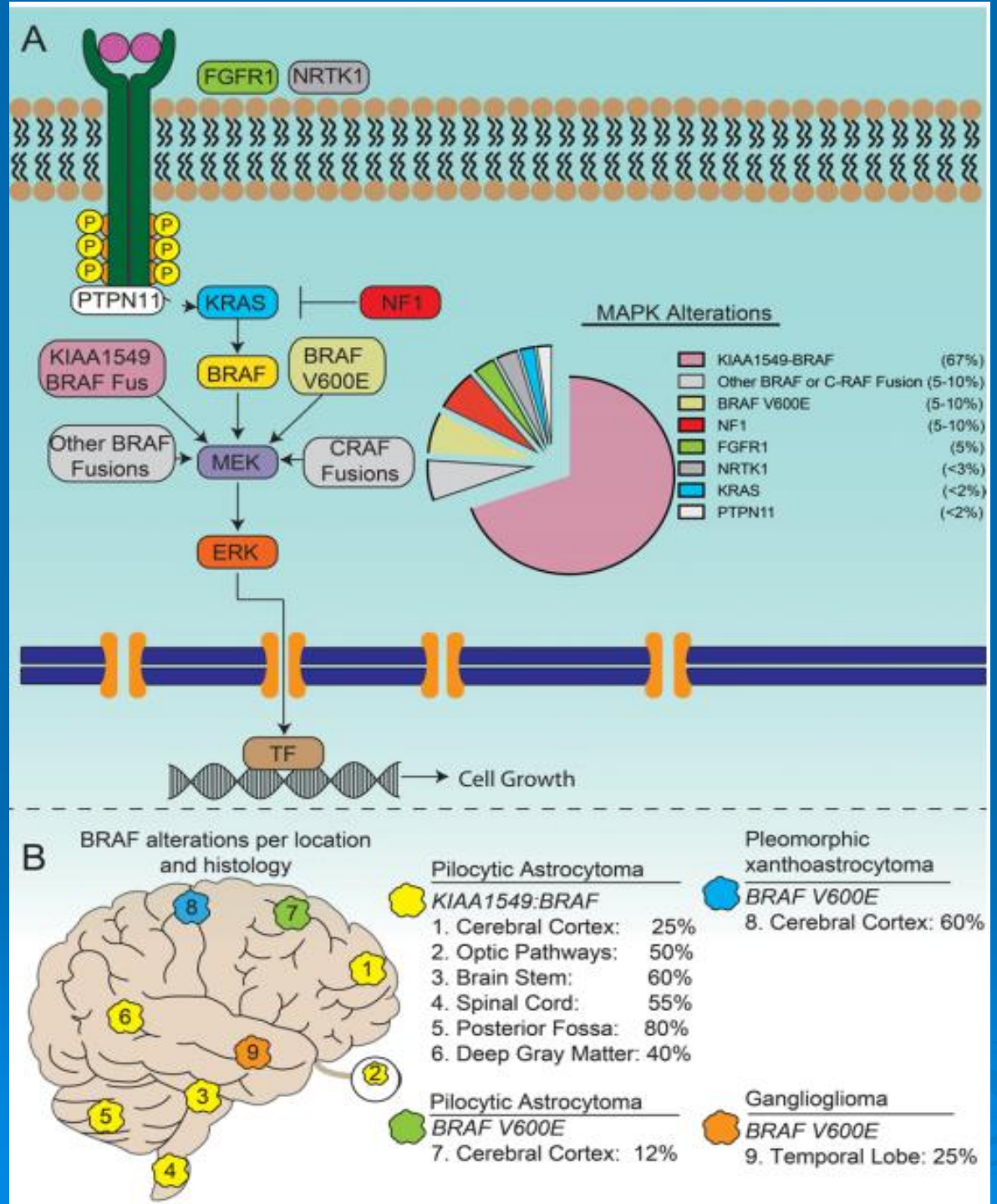
Prior 2008: Germline *NF1* mutations associated with PLGG development.

Pfister *et al.* 2008: Duplication of *BRAF* gene most frequent aberration (later identified as *BRAF-KIAA1549* fusion event).



Genomics era: Gene fusions, activating mutations and loss of function mutations in the mitogen-activating protein kinase pathway (MAPK), including *BRAF*, *FGFR1*, *NF1*, *MYB*, *MYBL1*.



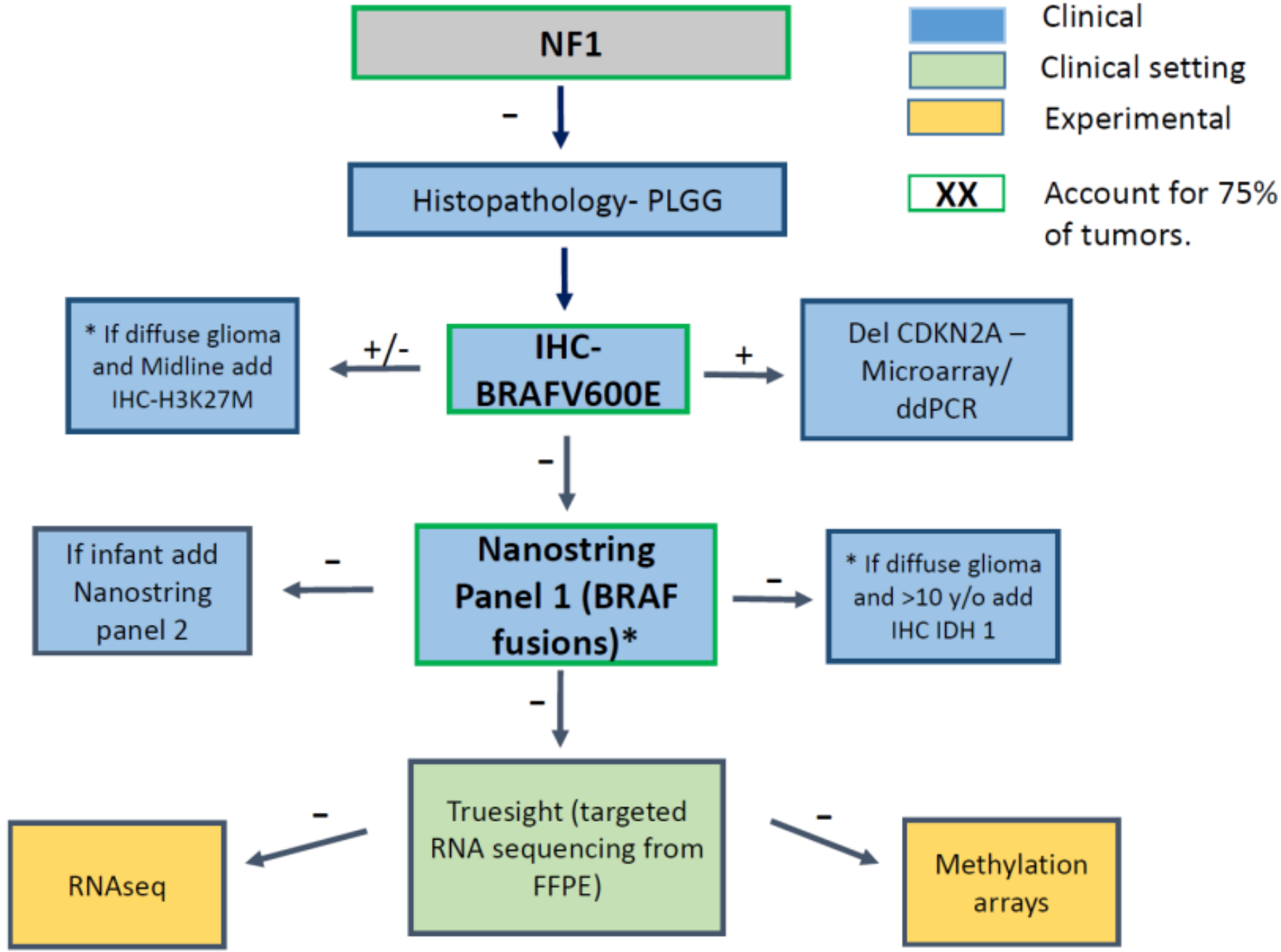

A
FGFR1
NRTK1
P
PTPN11
KRAS
NF1
KIAA1549
BRAF Fus
BRAF
BRAF
V600E
Other BRAF
Fusions
MEK
CRAF
Fusions
ERK
TF
Cell Growth
MAPK Alterations
KIAA1549-BRAF (67%)
Other BRAF or C-RAF Fusion (5-10%)
BRAF V600E (5-10%)
NF1 (5-10%)
FGFR1 (5%)
NRTK1 (<3%)
KRAS (<2%)
PTPN11 (<2%)
B
BRAF alterations per location
and histology
Pilocytic Astrocytoma
KIAA1549:BRAF
1. Cerebral Cortex: 25%
2. Optic Pathways: 50%
3. Brain Stem: 60%
4. Spinal Cord: 55%
5. Posterior Fossa: 80%
6. Deep Gray Matter: 40%
Pleomorphic
xanthoastrocytoma
BRAF V600E
8. Cerebral Cortex: 60%
Pilocytic Astrocytoma
BRAF V600E
7. Cerebral Cortex: 12%
Ganglioglioma
BRAF V600E
9. Temporal Lobe: 25%

Nanostring panel 1(main alterations):
KIAA1549_Ex13-BRAF_Ex9
FAM131B_Ex1-BRAF_Ex10
RNF130_Ex3-BRAF_Ex9 MKRN1_Ex4-BRAF_Ex11
GNAI1_Ex1-BRAF_Ex10
CLCN6_Ex2-BRAF_Ex11
FXR1_Ex13-BRAF_Ex10
BRAF_Ex7-MACF1_Ex19
FGFR1_Ex17-TACC1_Ex7
SRGAP3_Ex11-RAF1_Ex8
ST6GAL1_Ex2-WHSC1_Ex4
QKI-Ex2:MYB-Ex16
MYB-Ex9:PCDHGA1-Ex2
QKI-Ex1:RAF1-Ex14
NACC2-Ex4:NTRK2-Ex13

Nanostring panel 2(main alterations):
ALK FUSIONS:
i.e.: ALK_MUT2_Ex23; PPP1CB_Ex5-ALK_Ex20
ROS FUSIONS:
i.e.:ROS1_WT1_Ex27; GOPC_Ex4-ROS1_Ex37
NTRK FUSIONS
i.e.: ETV6_Ex4-NTRK3_Ex14
QKI-RAF FUSIONS
i.e.:QKI_Ex3-RAF1_Ex9-Intron
MET fusions:
i.e:CLIP2_Ex11-MET_Ex15
MYB_QKI FUSIONS:
i.e.:MYB_Ex9-QKI_Ex5
FGFR2 FUSIONS:
i.e.:FGFR2_Ex17-ERC1_Ex3

Truesight panel:
More than 1000 genes

BRAF	FLI1	KIAA
ALK	FGFR	MYB
ROS	JAK	WT1
NTRK	Stat	CTNNB1
IDH	HRF3A	HOX
BCOR	HIST1H	MYB
EGFR	MSH2/3/6	CDKN
EWS	RELA	DICER



Molecular Insights

- BRAF-KIAA fusions:
  - ***Optic pathway pilocytic tumors***
  - ***Gangliogliomas***
  - ***Pleomorphic xanthoastrocytomas***
  - ***Cerebral pilocytic astrocytomas***
    - ***Vemurafenib(NCT01748149)***
    - ***Dabrafenib (NCT01677741)***
  - ***Specifically target tumors with BRAFV600E***
  - ***Sorafenib (end)***

Mitogen-Activated Protein Kinase (MAPK)

- NF1
- RAF
  - ***Selumetinib***
- Durable partial (> 50%) response

MEK inhibitor

- Phase II randomized clinical trial:
  - ***Dabrafenib and Trametinib***
  - ***Carboplatin and vincristine***
- Children with newly diagnosed BRAFV600E-mutated LGGs (NCT02684058).
- Cobimetinib
- Binimetinib

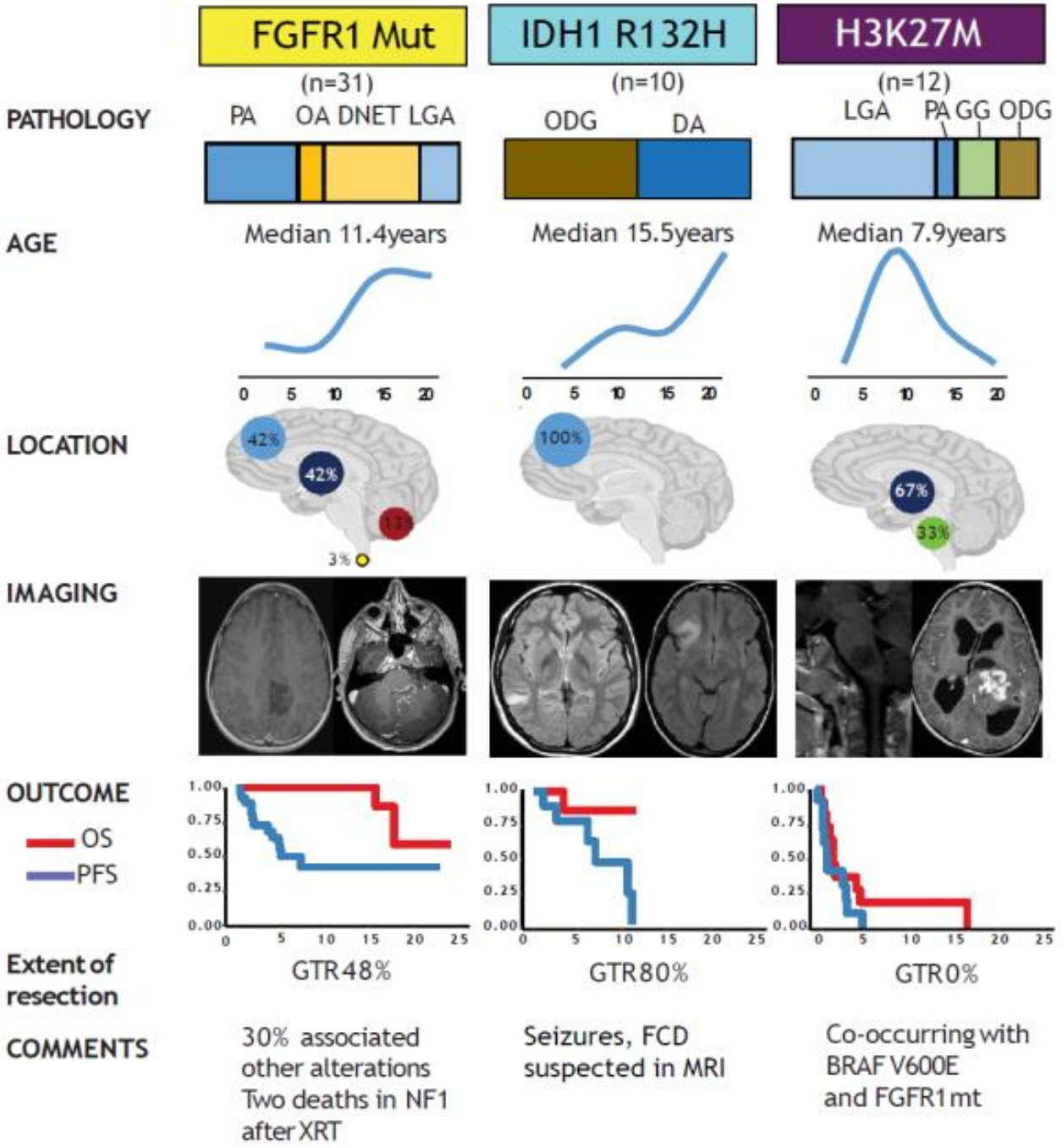
mTOR

- **Tuberous sclerosis have activated mTOR signaling**
  - ***Everolimus***
- **Antiangiogenic in all LGG**
  - ***Bevacizumab***
- ***FGFR1 :***
  - ***AZD4547 (NCT02824133)***
- ***ALK/ROS1/NTRK Inhibitors:***
  - ***Crizotinib (NCT00939770)***
  - ***Ceritinib (NCT02336451)***
  - ***Cabozantinib(NCT00704288)***
  - ***Brigatinib (ALK/ROS1)***
  - ***Entrectinib (ROS1/TRK)***
  - ***larotrectinib (TRK)***

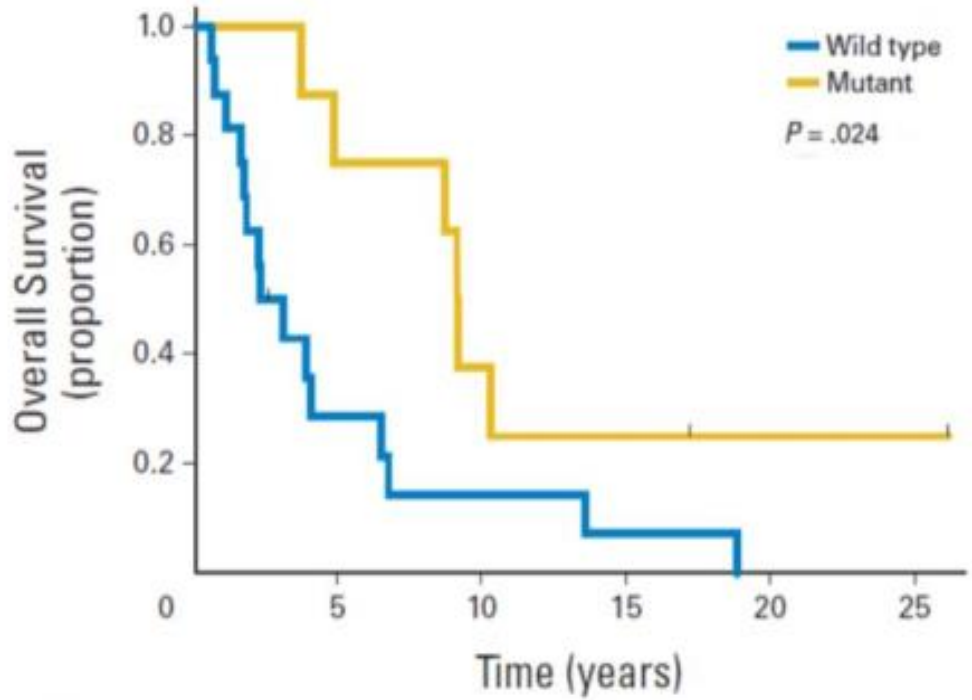
TABLE 1. Current experimental protocols for recurrent LGG

Therapeutic Approach	Study Design	Clinical Trial Identification
Use of oral vinorelbine	Phase II	NCT02197637
Vinblastine vs vinblastine & bevacizumab	Phase II randomized	NCT02840409
Weekly carboplatin & vincristine vs carboplatin every 4 wks	Phase III randomized	NCT02455245
Oral everolimus (mTOR inhibitor)	Phase II	NCT01734512
Oral MEK162 (MEK inhibitor)	Phase II	NCT02285439
Immunotherapy w/ HLA-A2–restricted tumor antigen peptide vaccine administered w/ poly ICLC	Phase II	NCT02358187
Oral TAK-580 (pan-RAF kinase inhibitor)	Phase I/II	NCT03429803

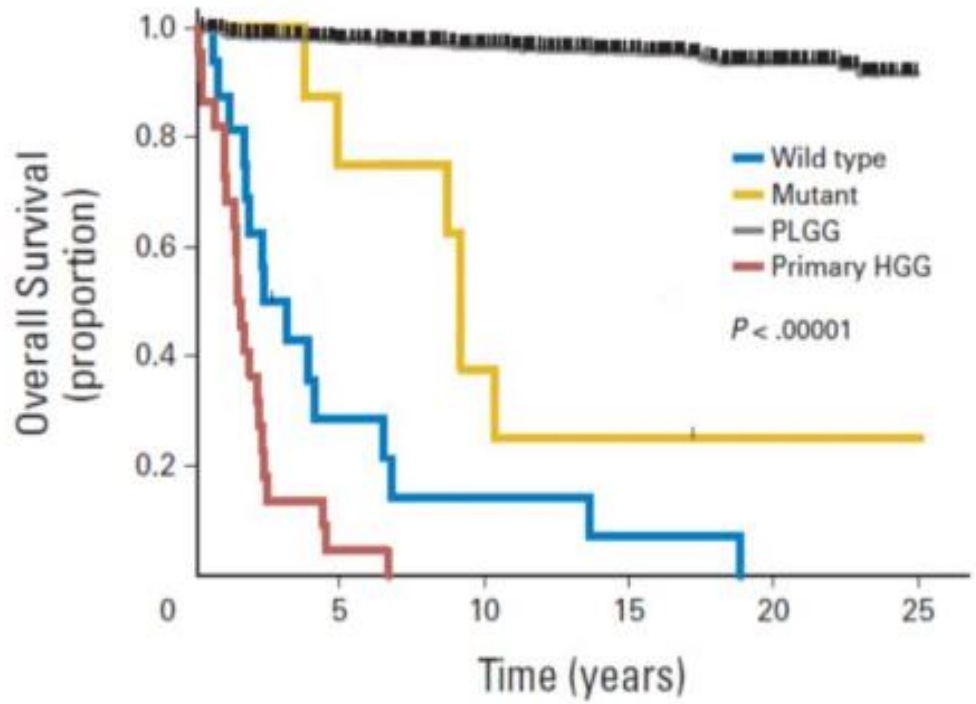
Clinical and molecular characteristics of LGG harboring point mutations



Results: BRAF V600E patients have improved survival following initial diagnosis



No. at risk						
Wild type	16	4	2	1	0	0
Mutant	8	6	3	2	1	1

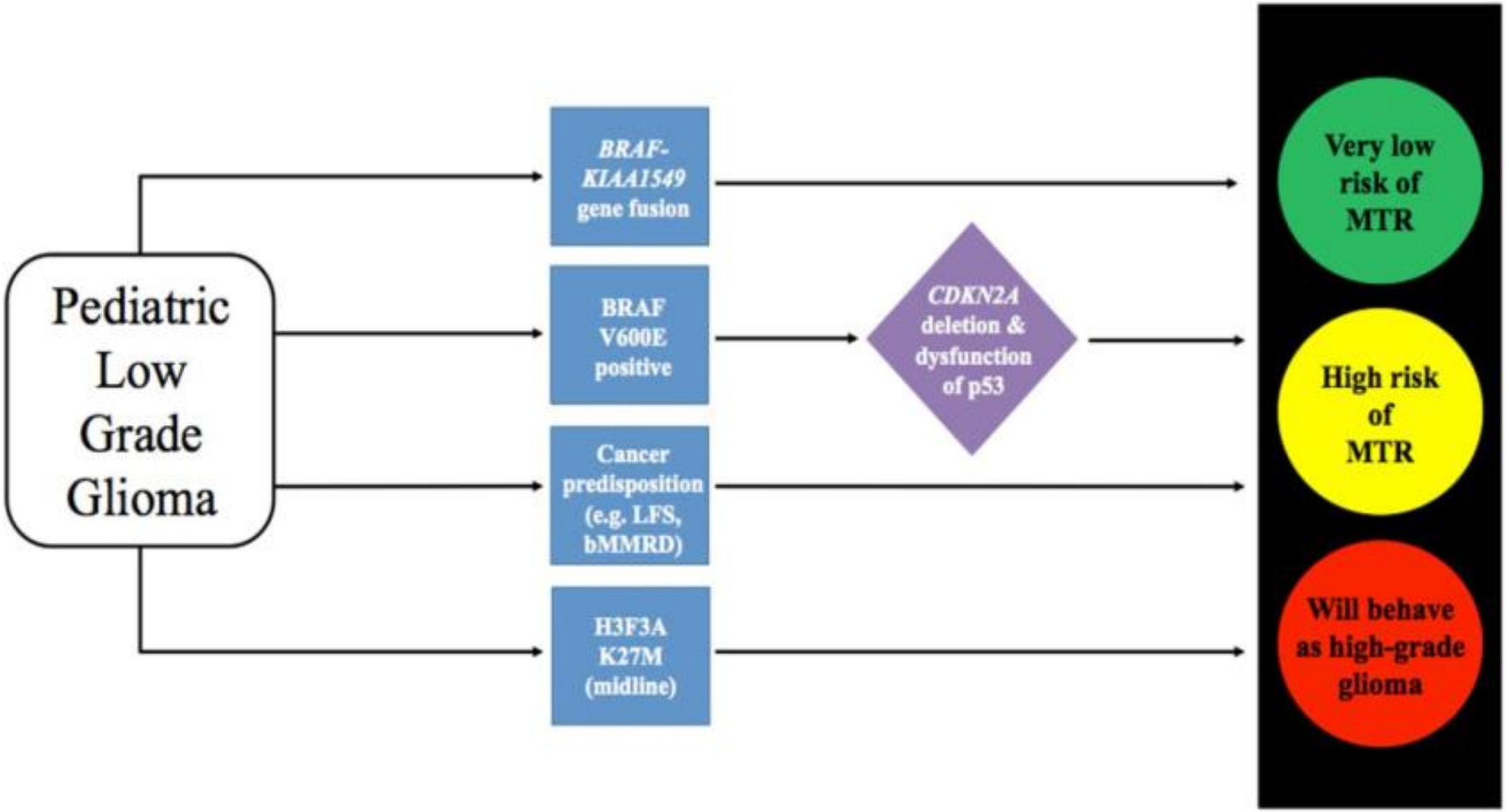


No. at risk						
Wild type	16	4	2	1	0	0
Mutant	8	6	3	2	1	1
PLGG	814	653	507	351	183	36
Primary HGG	22	1	0	0	0	0

<u>5-yr overall survival:</u>
BRAF mutant patients: **75% ± 15%**
BRAF wildtype patients: **29% ± 12%**
(P=0.024)

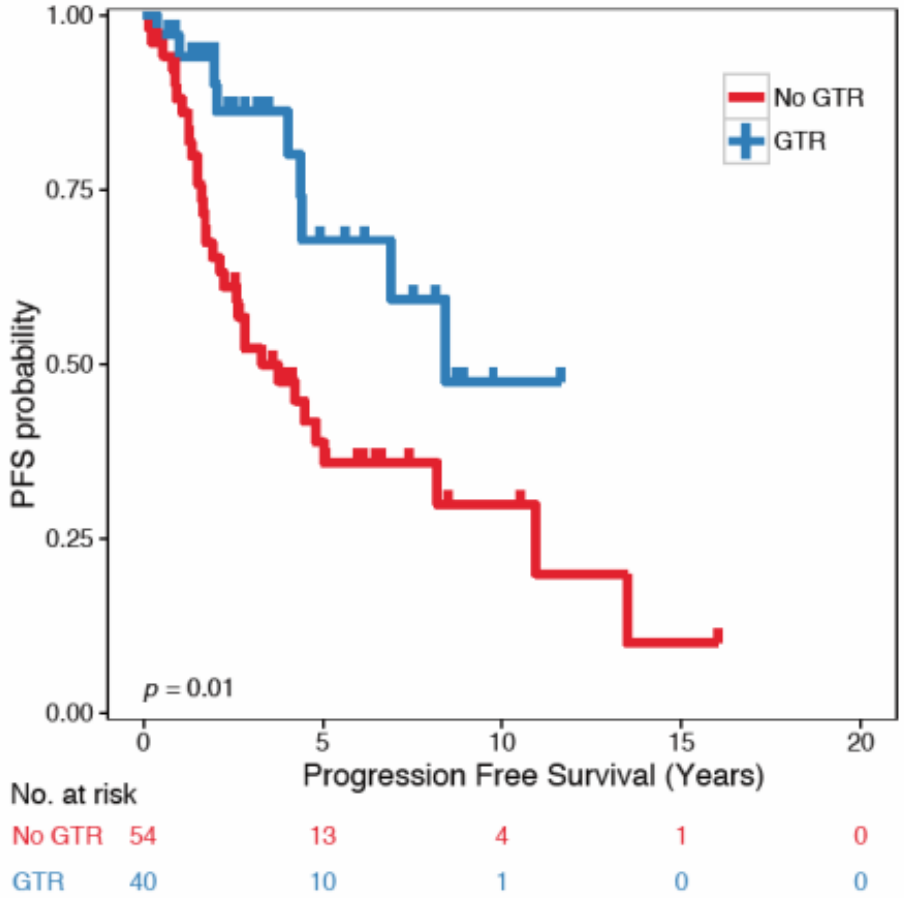
<u>5-year overall survival:</u>
BRAF wildtype patients: **29% ± 12%**
Primary HGG patients: **5% ± 4% (P=0.0163)**

Genetic alterations stratify PLGG into several risk groups

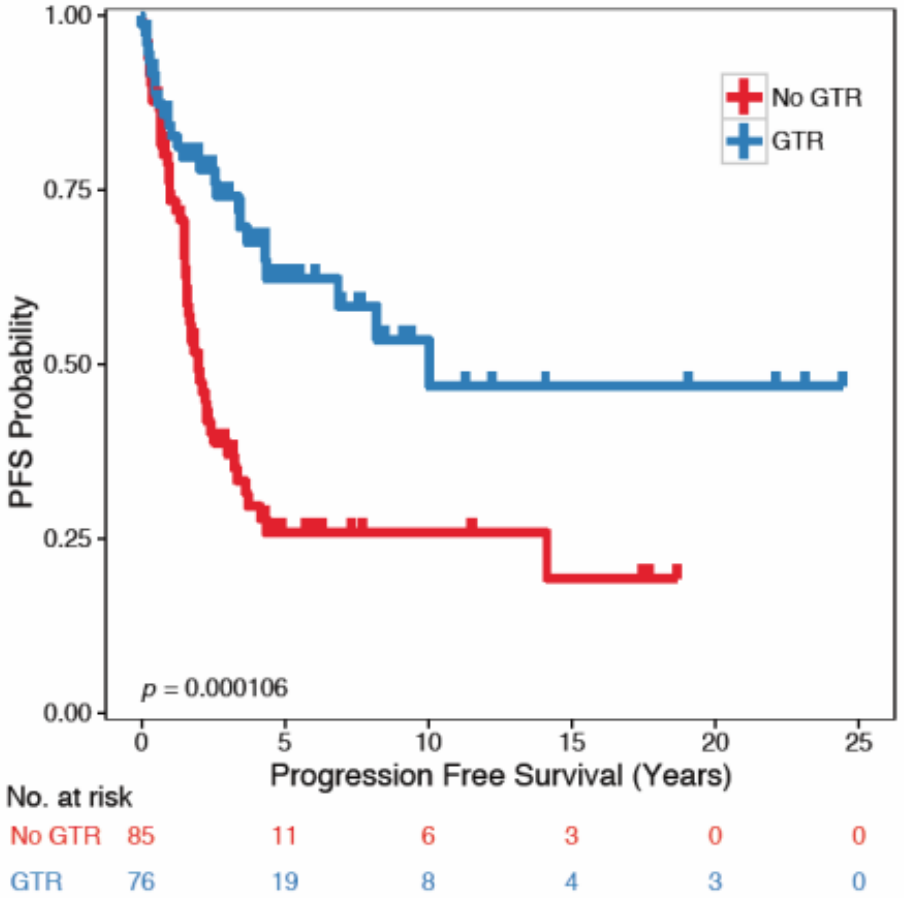


Gross total resection in BRAF V600E PLGG

Discovery



Validation

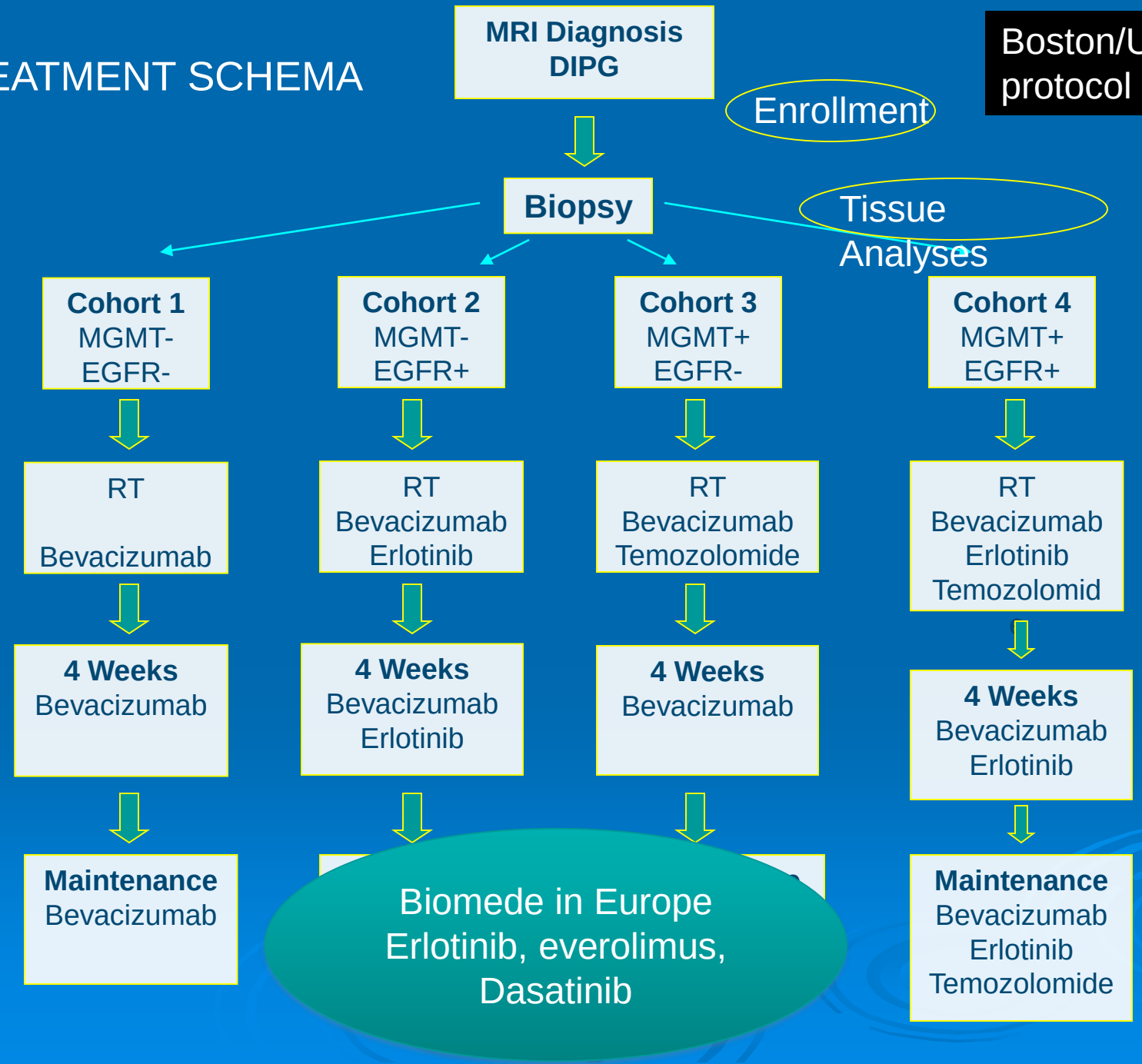


41% patients GTR

Lassaletta A, Zapotocky M et al. JCO 2017

TREATMENT SCHEMA

Boston/UCSF protocol



Brainstem Gliomas Trials

- COG: No protocol
- PBTC studies:
  - PARP inhibitor + Temozolomide + radiation (closed for futility)
  - Pembrolizumab (closed for toxicity)
  - Panabinostat (HDAC inhibitor) ongoing
- PNOC studies
  - H 3.3 vaccine
  - Convection enhanced delivery
- CONNECT studies
  - Ribociclib and everolimus trial
  - PTC596 trial (phase I)

Re-irradiation of DIPG

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RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer | SIOP | aspho

Reirradiation in patients with diffuse intrinsic pontine gliomas: The Canadian experience

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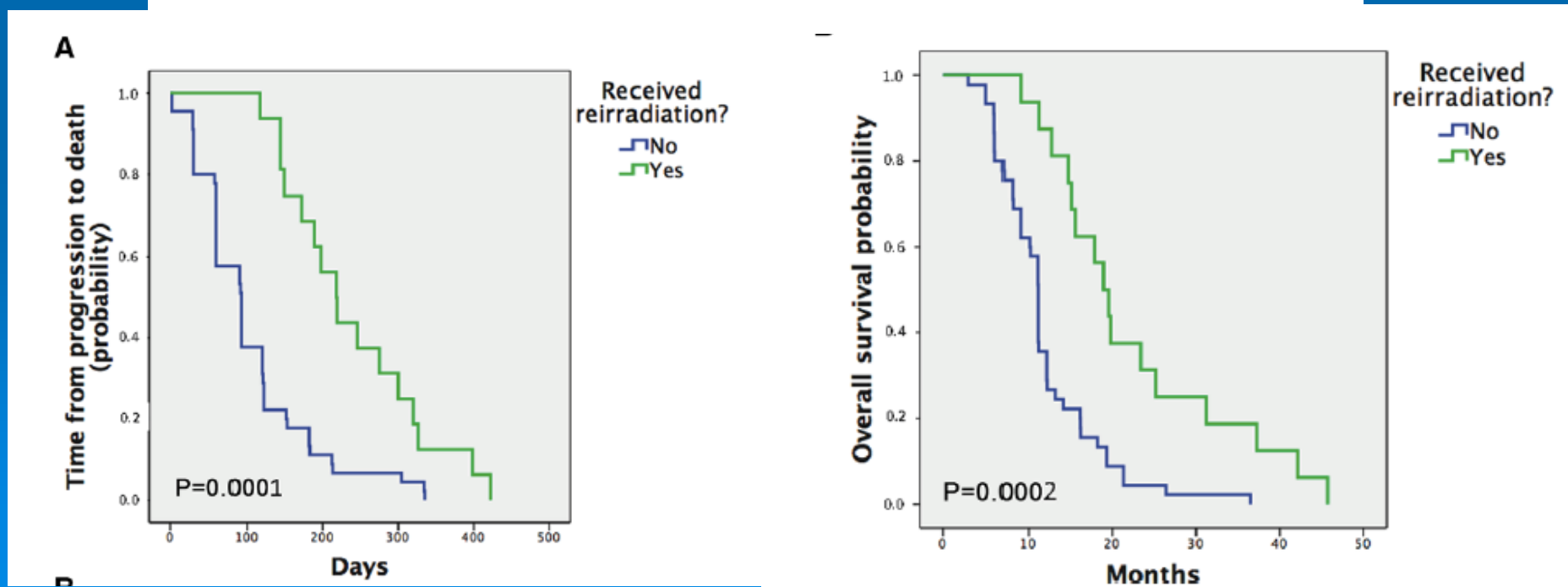
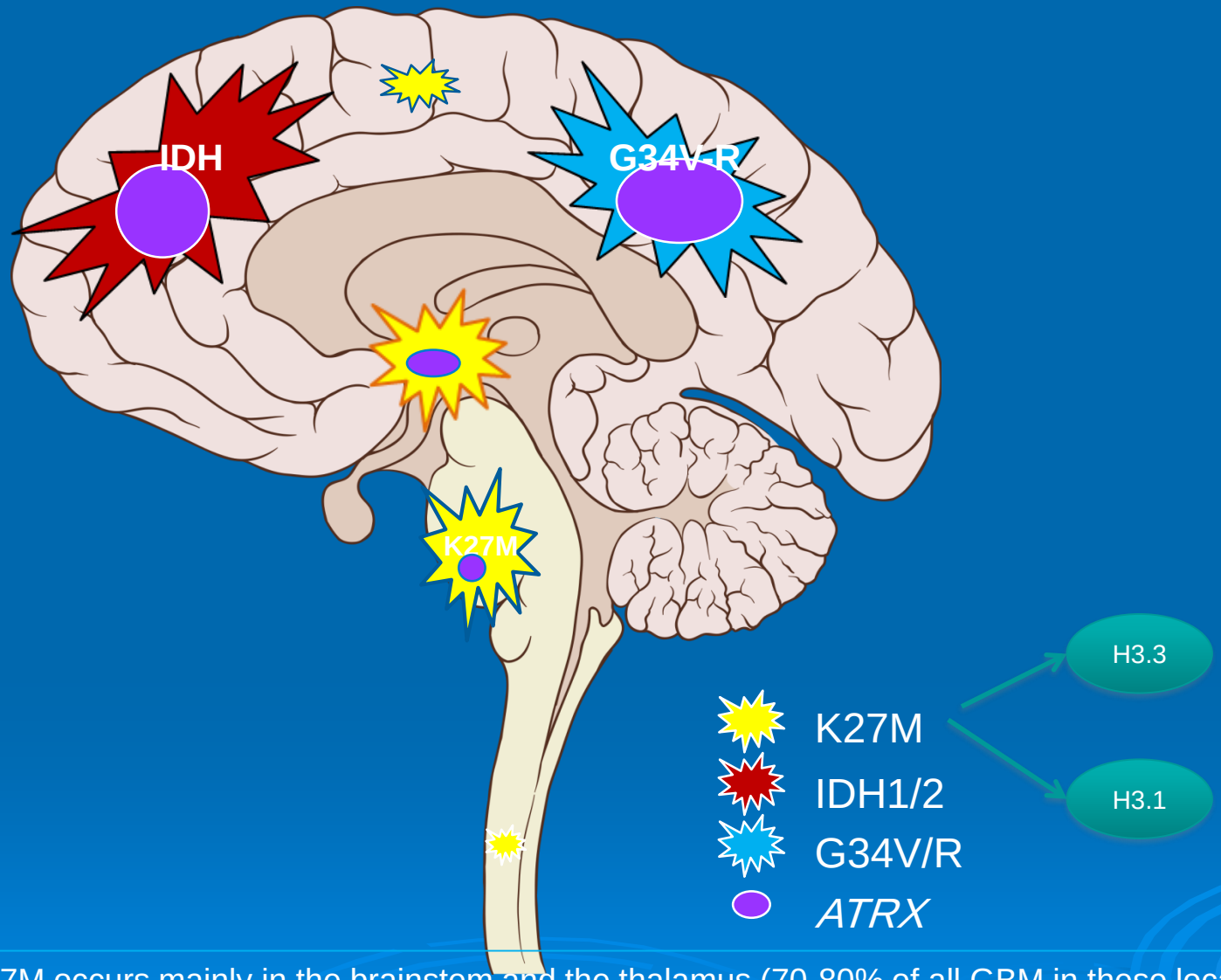


Neuroanatomical specificity of IDH, H3.3-K27M and G34V-R in the brain

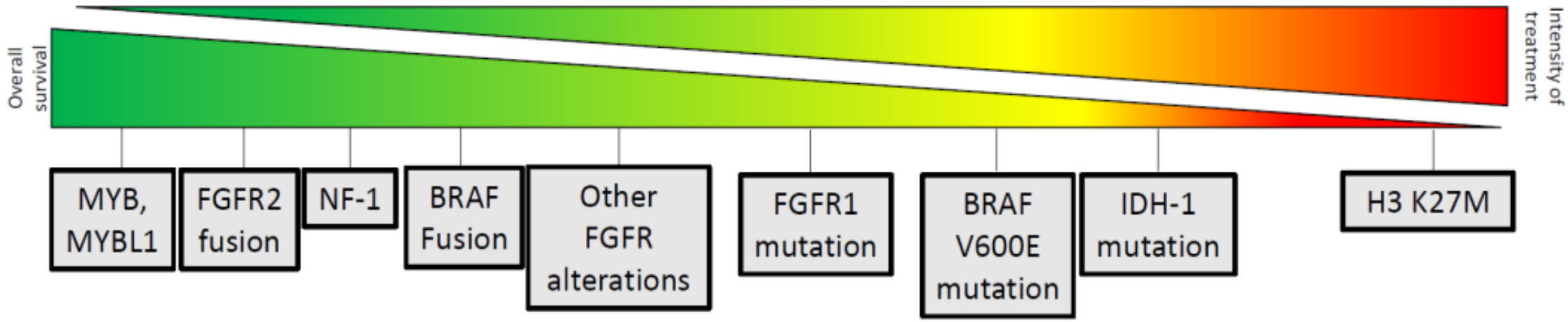


K27M occurs mainly in the brainstem and the thalamus (70-80% of all GBM in these locations). It is inconsistently associated with ATRX mutations. G34V-R occurs mainly in the cerebral hemispheres similar to IDH mutations that have a predilection for the frontal cortex. Both are strongly and significantly associated with ATRX mutations. (references 2,3,6,7,12).

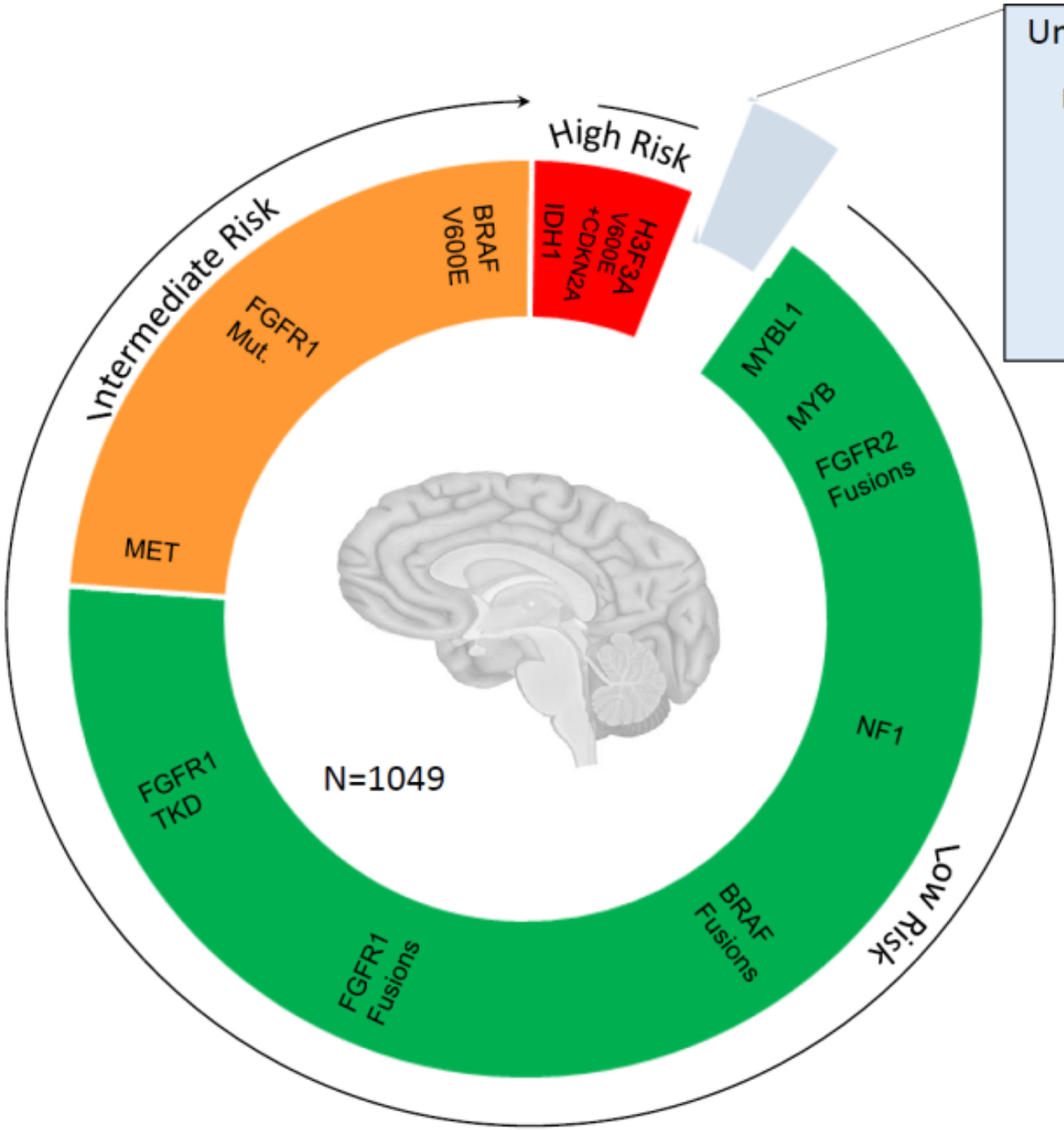
CONCLUSIONS

- Pediatric DIPGs are one of the main causes of brain tumor death in children
- After decades of clinical trials, largely based on protocols for adult brain tumors, no effective treatment has yet been found
- A lot going on in the preclinical setting…
- You may be the first generation to see a change in survival!!!

Novel stratification of PLGG?

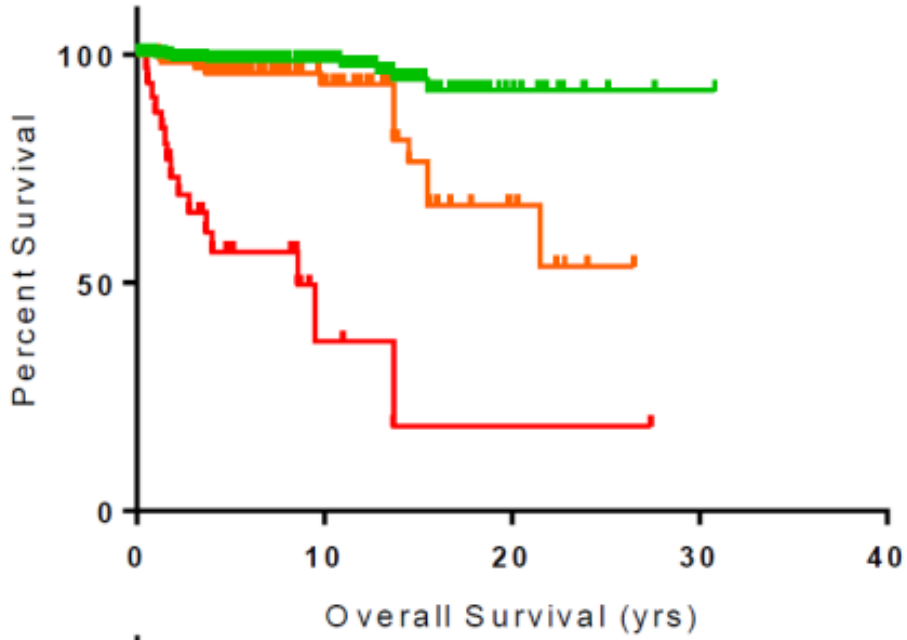


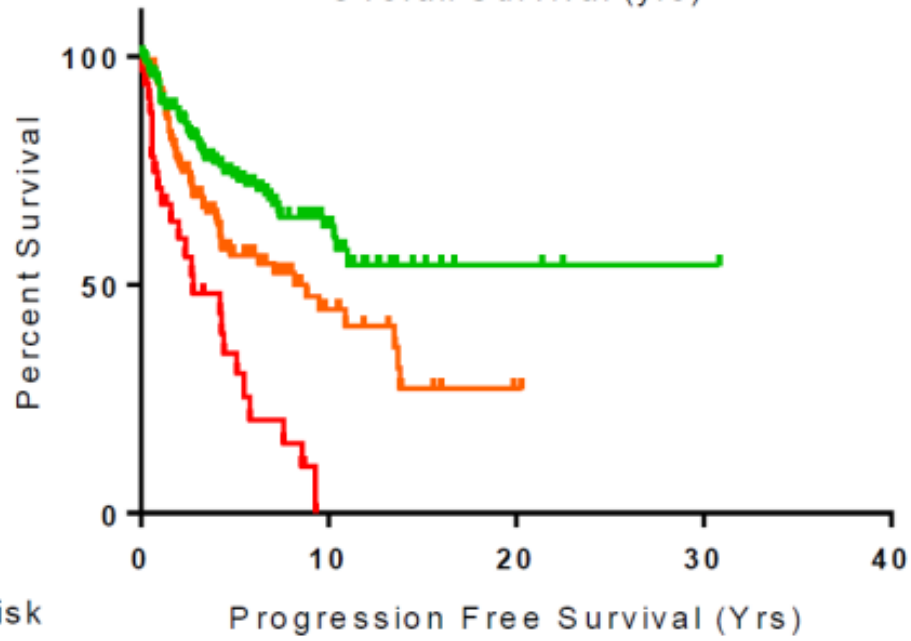
Observation	+	+	+	+	+	-	-	-	-
Chemotherapy	?	?	+	+	?	?	+	+	-
Targeted therapy	?	+	+	+	+	+	+	-	-
Radiation	-	-	-	-	-	-	-	+	+
Suggested WHO Grade	1	1	1	1	1			2	4



Unknown Risk

PDGFR
RAF1 Fusion
PIK3CA
ALK/
ROS1/
NTRK
Kras
MAP2K1
GANI1





Low Risk
Intermediate Risk
High Risk

Ryal et al. Cancer Cell in press

Take home messages:

- PLGG is mostly benign, take your time and avoid aggressive therapy in most cases.
- Biopsy should be considered in most PLGG due to molecular classification which determines therapy.
- Infants and AYA should be addressed with specific cautions.
- Targeted therapies are here and may replace chemo-rads soon.
- Methylation arrays should be used with caution with PLGG.

cure all

World Health Organization

WHO Global Initiative for Childhood Cancer: **An Overview**


thank
you