Settima edizione di

AIEOP...

...in Lab

G.d.L. Biologia Cellulare Molecolare

AIEOP

ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

CNS Tumors: from the bench to the bedside…

M. Massimino

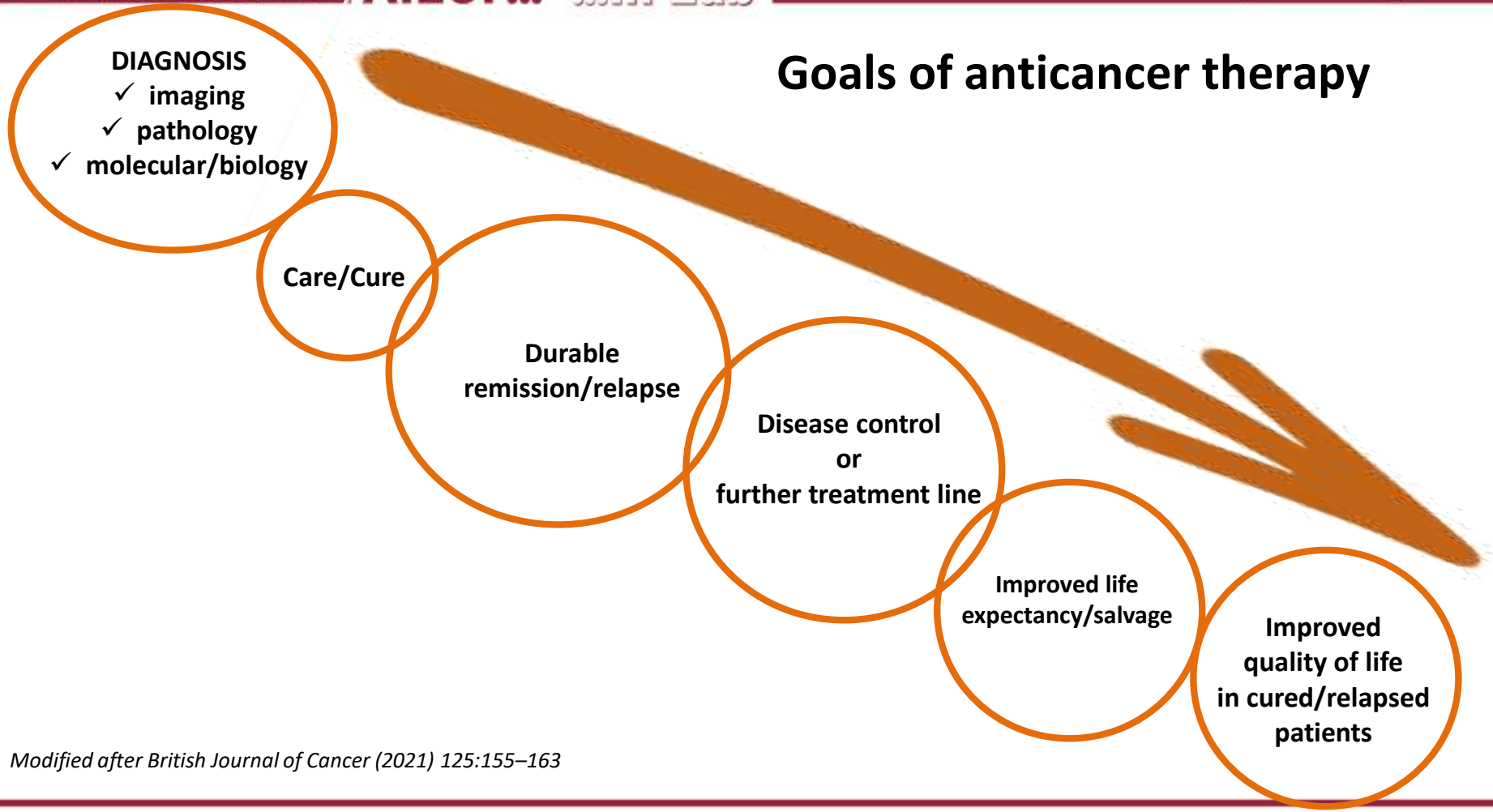
(Milano)

Milano, 22 e 23 maggio 2026

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Oncoscience			X				

Goals of anticancer therapy

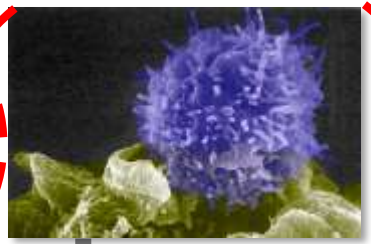


Modified after British Journal of Cancer (2021) 125:155–163

Our weapons against cancer

Surgery 1846

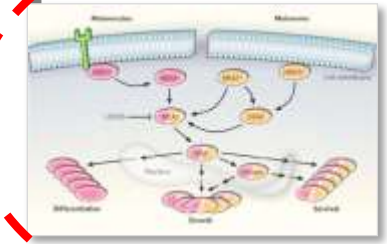
Chemotherapy 1946



Immuno-Oncology 2011

Radiation Therapy 1901

Targeted Therapy 1997



1. DeVita VT Jr, et al. *Cancer Res*. 2008;68:8643–8653; 2. American Cancer Society. http://www.cancer.org/cancer/cancerbasics/thehistoryofcancer/; 3. Hodi FS, et al. *N Engl J Med.* 2010;363:711–723; 4. Sznol M, et al. Presented at ASCO 2013: oral presentation; 5. Kantoff PW, et al. *N Engl J Med*. 2010;363:411–422; 6. Finn OJ. *Ann Oncol*. 2012;23(suppl 8):viii6–viii9.

pediatric brain tumors
EPIDEMIOLOGICAL PREMISES

- BRAIN TUMORS REPRESENT, BY INCIDENCE, THE SECOND PEDIATRIC TUMOR AFTER LEUKEMIA, THE MORE FREQUENT CAUSE OF DYING FOR TUMOR, THE MORE FREQUENT CAUSE OF POST-CANCER DISABILITIES
- 20/25% OF THE TUMORS OF THIS AGE GROUP
- WORLDWIDE, THE INCIDENCE CORRESPONDS TO 2-3 CASES / YEAR / 100,000 CHILDREN UNDER 15 YEARS OLD
- IN ITALY ABOUT 350-400 CASES ARE DIAGNOSED EVERY YEAR
- MORTALITY, IN THE LAST TWO DECADES, HAS REDUCED FROM 2 / 100,000 TO 0.9 / 100,000 EVENTS PER YEAR:

THAT MEANS THAT 60% OF AFFECTED CHILDREN CAN BECOME ADULT

5-year survival

» CEREBELLAR ASTROCYTOMA	95%
» LOW-GRADE ASTROCYTOMA	75%
» MEDULLOBLASTOMA	70%
» EPENDYMOMA	60%
» HIGH-GRADE GLIOMAS	30%
» DIFFUSE INTRINSIC PONTINE GLIOMA	2%
» ALL TOGETHER	60% ca.

What We Would Like From The “Lab”

- A molecular/genetic marker for any tumor
- A risk profile for any single patient
- One or more drugs that could interfere with tumorigenic pathway, therefore with minimal normal tissues damage

medulloblastoma

What we know

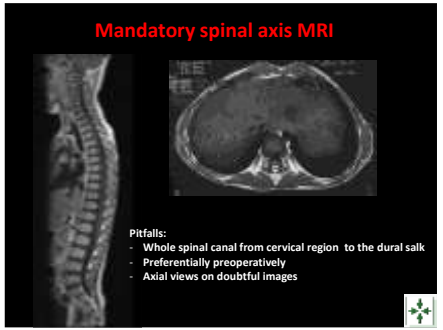
Medulloblastoma (MB) represents the most common malignant brain tumor in children, accounting for approximately 20% of all central nervous system (CNS) tumors.

It also comprises over 60% of intracranial embryonal tumors, a recently characterized entity consisting of atypical teratoid rhabdoid tumors (ATRTs), embryonal tumors with multilayer rosettes (ETMRs), CNS neuroblastoma with FOX2 alteration and malignant neuroepithelial tumors with BCOR alteration.

What we know

» Craniospinal irradiation is needed

– **Dissemination at diagnosis: 20-35% of patients**



Survival improvement

- **Embryonal tumors, from 1980 to 2009**
  - **37% to 60%, as general assessment**

  But, around 2000
  - **Gap between South and East Europe with 40% and EUROCARE-5 consortium with 66%**
  - **Medulloblastoma, from 1959 to 2009**
    - **29% to 73% as general assessment**
    - **In Tunisia less than 27% in 1997**
    - **In Uganda 0% in 2007**

CSI doses

OLD! Standard

- **Standard risk (5 year EFS 55-70%)**

  35-36 Gy, 1.5-1.8 Gy/fraction

- **High risk (5 year EFS 30-50%)**

  36-40 Gy, 1.6-1.8 Gy/fraction

  + metastatic site boosts

Posterior fossa boost: 54-55 Gy

Why We Use CT For MEDULLOBLASTOMA

- **To reduce**, postpone or omit **RT use**
  - **Standard/low-risk medulloblastoma**
  - Youngest children medulloblastoma
  - Low-grade glioma
  - Germ-cell tumors
- To improve survival
  - High-risk medulloblastoma
  - Malignant glioma/DIPG
  - AT/RT
  - All diseases at relapse

CSI doses
A different reached standard

CCG Study: 65 standard risk patients

Surgery

⬇

CSI 23.4 Gy, PF 31.8 Gy + weekly vincristine

⬇

Cisplatin, CCNU, VCR x 8 courses

PFS 86% at 3 years, 79% at 5 years

Packer, JCO 1999

Phase III Study of Craniospinal Radiation Therapy Followed by Adjuvant Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma

Roger J. Packer, Amar Gajjar, Gilbert Vezina, Lucy Rorke-Adams, Peter C. Burger, Patricia L. Robertson, Lisa Bayer, Deborah LaFond, Bernadine R. Donahue, MaryAnne H. Marymont, Karin Muraszko, James Langston, and Richard Sposto

J Clin Oncol 24:4202-4209. © 2006 by American Society of Clinical Oncology

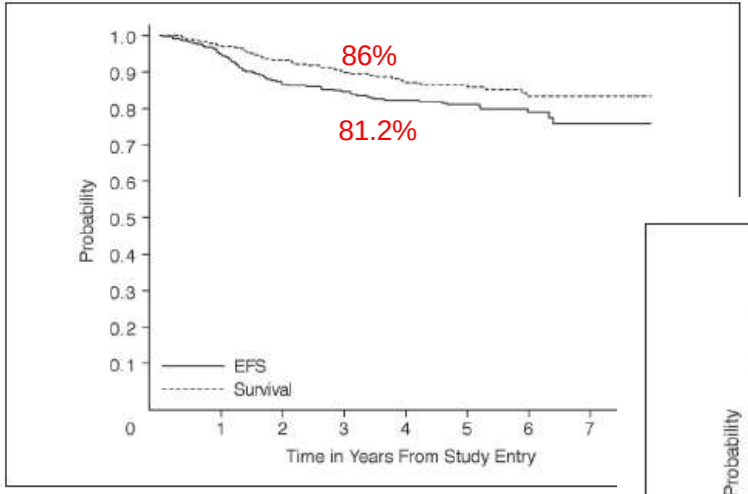


Fig 1. Event-free survival (EFS) and survival from study er

Between December 1996 and December 2000, **421 patients** were enrolled on this study.

Randomized regimen	
A	193
B	186

Table 1. Chemotherapy Regimens

Regimen	Drug	Dosage
A		
Day 0	CCNU	75 mg/m² by mouth
Day 1	CDDP	75 mg/m² intravenously
Day 1, 7, 14	VCR	1.5 mg/m²; max 2 mg intravenous bolus, maximum of eight doses
B		
Day 0	CDDP	75 mg/m² intravenously
Day 1, 7, 14	VCR	1.5 mg/m²; max 2 mg, intravenous bolus
Day 21, 22	Cyclo	1,000 mg/m² intravenously over 60 min daily

Abbreviations: CCNU, lomustine; CDDP, cisplatin; VCR, vincristine; max, maximum; Cyclo, cyclophosphamide; min, minute.

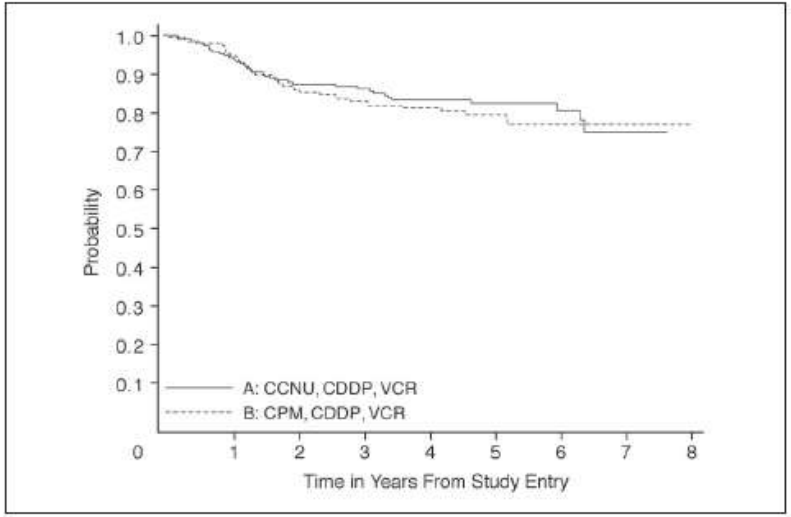


Fig 2. Event-free survival from study entry by treatment regimen. CCNU, lomustine; CDDP, cisplatin; VCR, vincristine; CPM, cyclophosphamide.

How much CSI is needed?

Or, how low can CSI doses be if giving chemotherapy?

Michalski et al., reported that IQ scores of 3–7-year-old patients were significantly better for the reduced dose group (i.e., 18 vs. 23.4 Gy) at the earlier evaluations post RT

Not **type:**

- a 5.4 Gy reduction in the CSI dose (*18 Gy*) was prescribed in patients 3-7 years (COG ACNS0331) with a non-inferiority randomized design
- The 5-year **OS** in SD-CSI and LD-CSI was **85.9% and 78.1%**, respectively
- The 5-year **2.6% and 72.1%,** resp
- **decreasing e risk of recurrence**

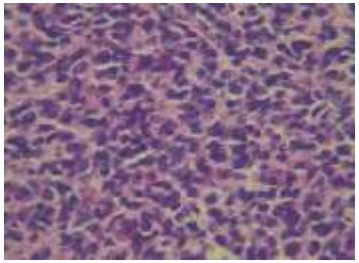
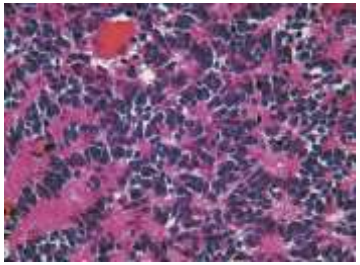
Children's Oncology Group Phase III Trial of Reduced-Dose and Reduced-Volume Radiotherapy With Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma

Jeff M. Michalski, MBA, MD; Anna J. Janss, MD; L. Gilbert Vezina, MD; Kyle S. Smith, PhD; Catherine A. Billups, MS; Peter C. Burger, MD; Leanne M. Embry, PhD; Patricia L. Cullen, PhD; Kristina K. Hardy, PhD; Scott L. Pomeroy, MD, PhD; Johnnie K. Bass, AuD, PhD; Stephanie M. Perkins, MD; Thomas E. Merchant, DO, PhD; Paul D. Colbs, PsyD; Thomas J. Fitzgerald, MD; Timothy N. Booth, MD; Joel M. Cherlow, MD, PhD; Karin M. Muraszko, MD; Jennifer Hadley, MS; Rahul Kumar, PhD; Yuanyuan Han, PhD; Nancy J. Tarbell, MD; Maryam Fouladi, MD; Ian F. Pollack, MD; Roger J. Packer, MD; Yimei Li, PhD; Amar Gajjar, MD; and Paul A. Northcott, PhD

J Clin Oncol 39:2685-2697.

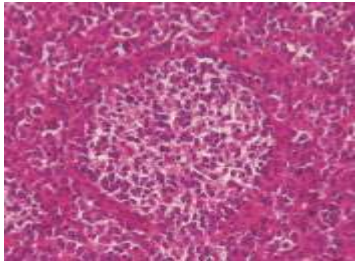
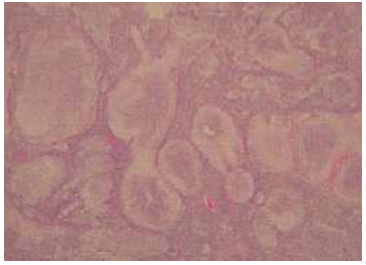
What we have acquired for MEDULLOBLASTOMA
Histological subtypes

Classic (CMB)

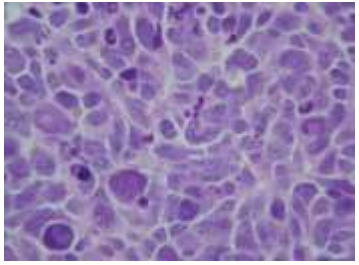
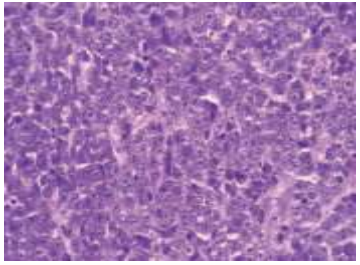



Desmoplastic/nodular (DMB)

Nodular prevalence (MBEN)

Large cell/ anaplastic (LCA)

Acta Neuropathol (2012) 123:465–472
DOI 10.1007/s00401-011-0922-z

Molecular Subgroups of Medulloblastoma

CONSENSUS	WNT	SHH	Group 3	Group 4
Cho (2010)	C6	C3	C1/C5	C2/C4
Northcott (2010)	WNT	SHH	Group C	Group D
Kool (2008)	A	B	E	C/D
Thompson (2006)	B	C', D	E, A	A, C

DEMOGRAPHICS

Age Group: 

Gender: ♀ ♂

CLINICAL FEATURES

	WNT	SHH	Group 3	Group 4
Histology	classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
Metastasis	rarely M+	uncommonly M+	very frequently M+	frequently M+
Prognosis	very good	infants good, others intermediate	poor	intermediate

GENETICS

WNT	SHH	Group 3	Group 4
6-	3q+, 9q-, 10q-	7+, 1q+, 17q+, 18q+, 11p-, 8-, 5q-, 10q-, 16q-	7+, 17q+, 18q+, 11p-, X-, 8-
CTNNB1 mutation	*PTCH1/SMO/SUFU* mutation *GLI2* amplification *MYCN* amplification	i17q *MYC* amplification	i17q *CDK6* amplification *MYCN* amplification

GENE EXPRESSION

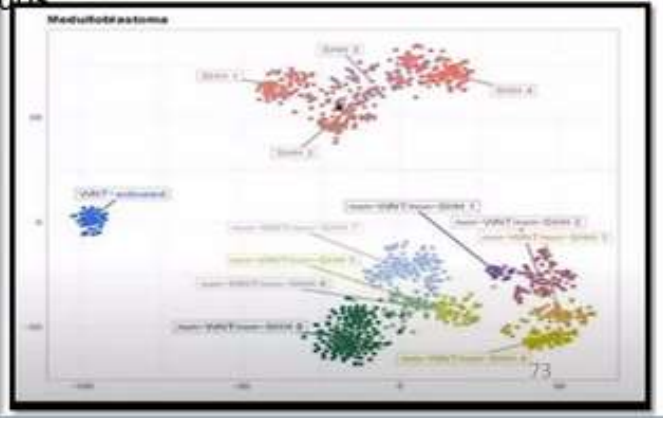
WNT	SHH	Group 3	Group 4
WNT signaling	SHH signaling	Photoreceptor/GABAergic	Neuronal/Glutamatergic
MYC +	*MYCN* +	*MYC* +++	minimal *MYC* / *MYCN*

Changes in Medulloblastoma classification- WHO 5th edition

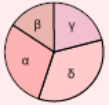
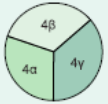
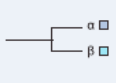
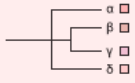
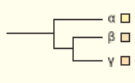
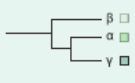
1. The histopathological classification of medulloblastoma listed in the 2016 WHO classification comprised 4 morphologic types: classic, desmoplastic/nodular, medulloblastoma with extensive nodularity (MBEN), and large cell/anaplastic.
2. These have now 2021 been combined into 1 section that describes them as morphologic patterns of an inclusive tumor type, Medulloblastoma, histologically defined.
3. WNT activated is a single entity
4. SHH having 4 subgroups
5. Non-WNT/non-SHH group has 8 subgroups

Embryonal tumors

- Medulloblastoma
  - Medulloblastomas, molecularly defined
    - Medulloblastoma, WNT-activated
    - Medulloblastoma, SHH-activated and *TP53*-wildtype
    - Medulloblastoma, SHH-activated and *TP53*-mutant
    - Medulloblastoma, non-WNT/non-SHH
  - Medulloblastomas, histologically defined

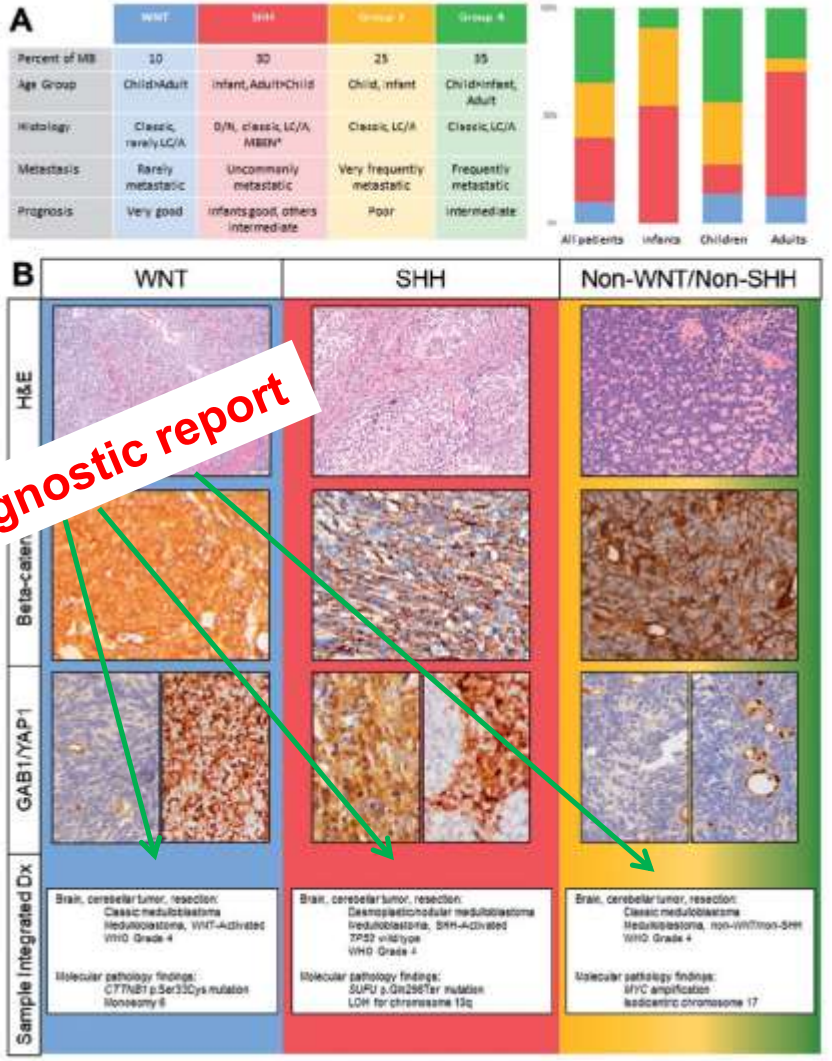


How far we can expand this classification?

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												
	Histology			LCA Desmoplastic	Desmoplastic	MBEN Desmoplastic	Desmoplastic						
	Metastases	8.6%	21.4%	20%	33%	8.9%	9.4%	43.4%	20%	39.4%	40%	40.7%	38.7%
	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)
	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

Cavalli et al., 2017, Cancer Cell *31*, 737–754
June 12, 2017 © 2017 Elsevier Inc.
http://dx.doi.org/10.1016/j.ccell.2017.05.005



The ideal diagnostic report

Medulloblastoma: WHO 2021 and Beyond

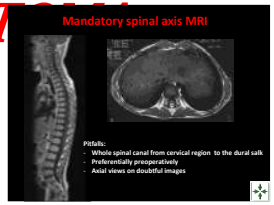
Jennifer A Cotter[1] and Cynthia Hawkins[2,3,4]

… and which is the impact of this refined classification on treatment?

Biology in medulloblastoma SIOPE trials

- **Flexibility**
  - To adopt validated prognostic criteria
  - New designs
- **Predictive biomarkers**
  - *Early use of new drugs in HR diseases*
- **Standardized criteria and cross-validation in Europe**
- **New WHO entities**

What we have acquired for MEDULLOBLASTOMA



» Craniospinal irradiation is needed

– **Dissemination at diagnosis: 20-35% of patients**

» Craniospinal doses can be reduced in **standard risk conditions** if chemotherapy is thereafter given

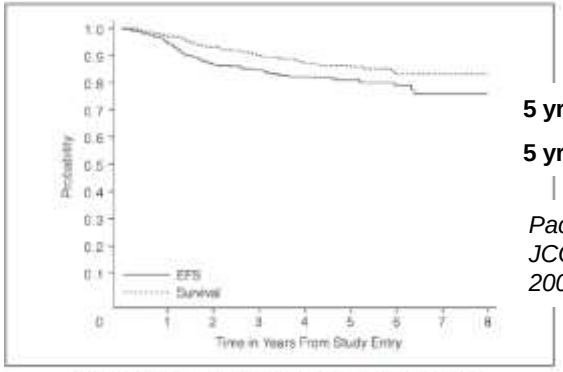
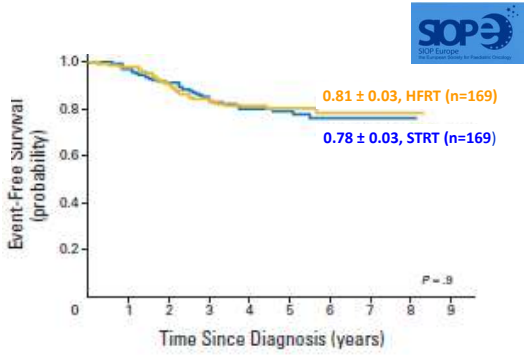


Fig 1. Event-free survival (EFS) and survival from study entry.

5 yrs EFS 81%

5 yrs OS 86%

Packer JCO 9-2006



JCO, 2012

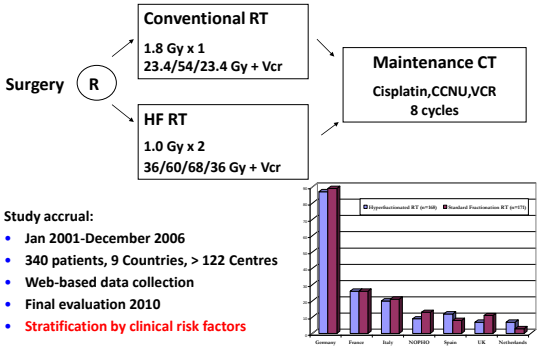
What we have acquired for MEDULLOBLASTOMA
Common strategy in EUROPE

VOLUME 30 · NUMBER 26 · SEPTEMBER 10 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

SIOP Europe
the European Society for Paediatric Oncology

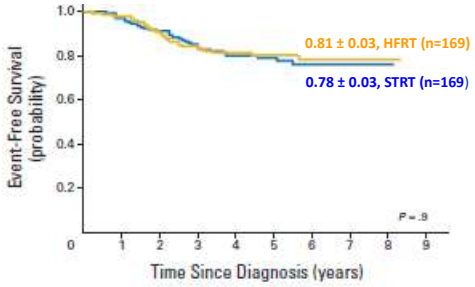
Hyperfractionated Versus Conventional Radiotherapy Followed by Chemotherapy in Standard-Risk Medulloblastoma: Results From the Randomized Multicenter HIT-SIOP PNET 4 Trial

Birgitta La
Maura Ma
Thomas B
Keith Rob
Véronique



Study accrual:

- Jan 2001-December 2006
- 340 patients, 9 Countries, > 122 Centres
- Web-based data collection
- Final evaluation 2010
- Stratification by clinical risk factors

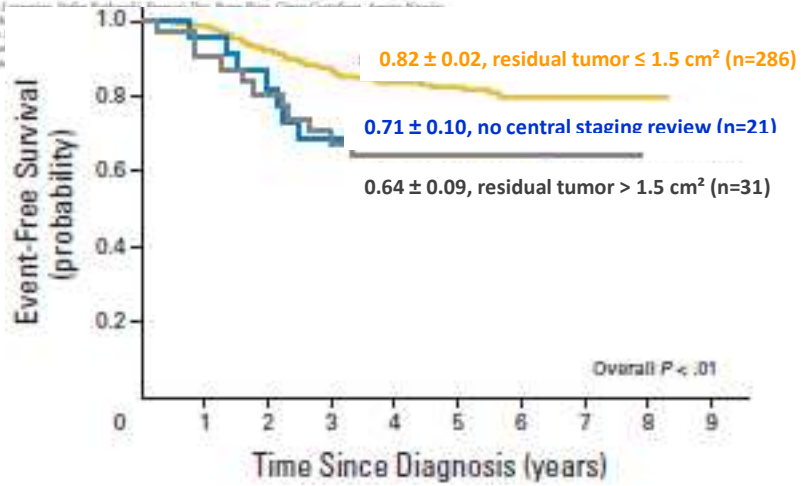


What we have acquired for MEDULLOBLASTOMA
Common strategy in EUROPE

Published Ahead of Print on July 30, 2012 as 10.1200/JCO.2011.39.8719
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2011.39.8719

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Hyperfractionated Versus Conventional Radiotherapy Followed by Chemotherapy in Standard-Risk Medulloblastoma: Results From the Randomized Multicenter HIT-SIOP PNET 4 Trial



SIOP PNET4: Residual tumor and staging

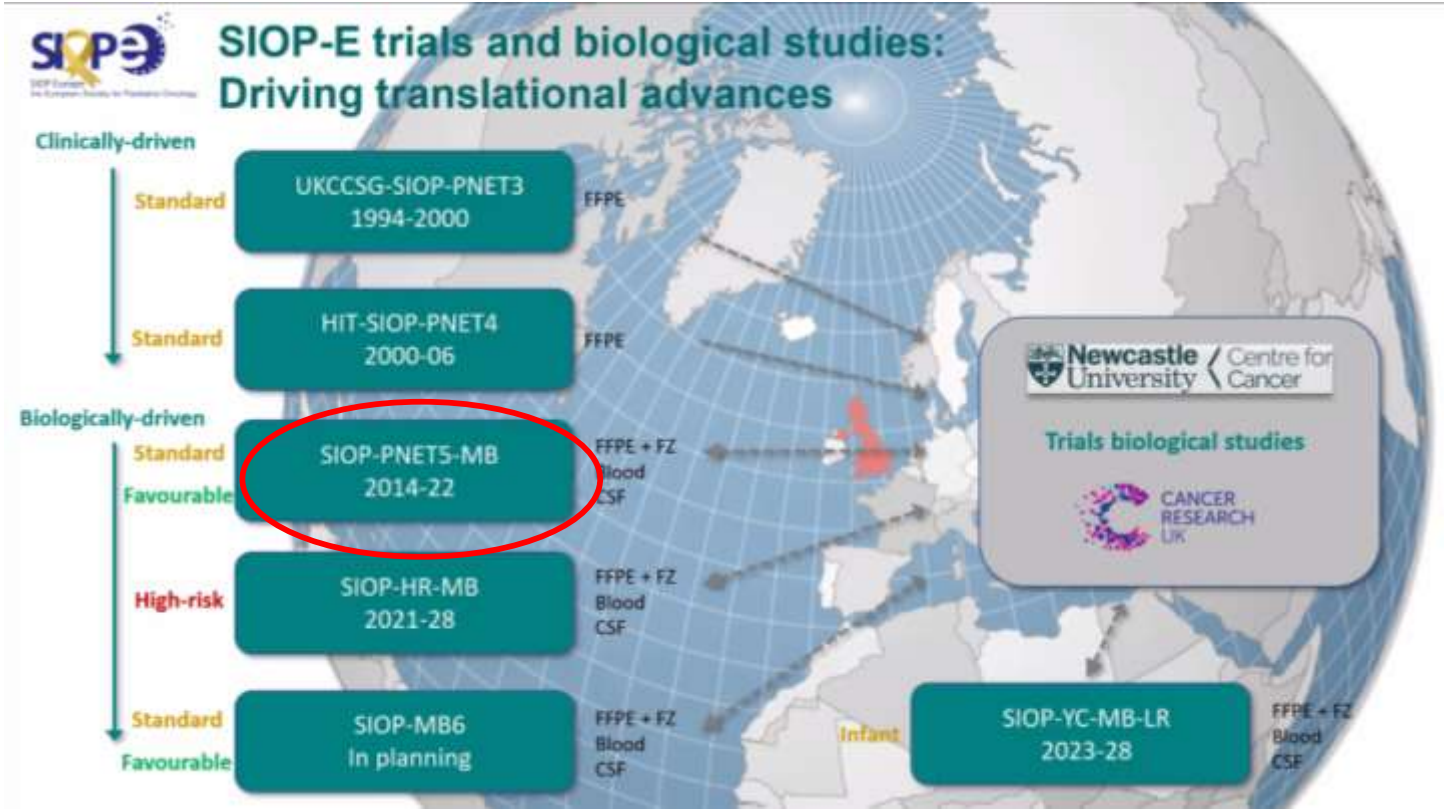
Complete surgery

- » **Extent of resection is still thought of as a prognostic variable** in medulloblastoma when overt metastatic disease is excluded by initial staging
- » Its influence on PFS and OS however is not clear
- » Apart from the CCG-921 trial, done in the pre-magnetic resonance imaging (MRI) era, there are roughly **an equal number of studies that identify, or not, an association between increased extent of resection and OS**
- » It is probable that the prognostic **benefit of a total resection is attenuated after accounting for molecular subgroup affiliation**
- » Residual tumour without any other high-risk factors **cannot be considered high-risk disease**

Histological Variants of Medulloblastoma Are the Most Powerful Clinical Prognostic Indicators

CONSENSUS PAPER

Risk stratification of childhood medulloblastoma in the molecular era: the current consensus



Courtesy of Prof Clifford

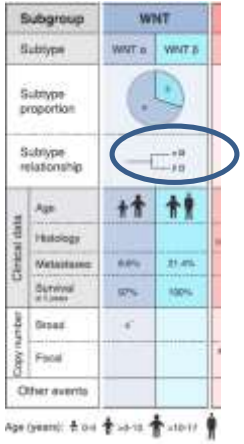
SIOP PNET 5 MB

EudraCT-Nr. 2011-004868-30

- European study (16 countries) for children older than 3 to 5 years
- Stratification according to clinical and biological criteria

- LR: Low-risk medulloblastoma (Phase II; Co-PI: F. Doz)
- SR: Standard-risk medulloblastoma (Phase III)

PNET 5 MB



Patient eligible for PNET 5 MB

Introduction: age

WNT subgroup*

positive | negative

Central labs

* β-catenin IHC (mandatory), ß-catenin mutation (mandatory) and monosomy 6 (optional) analysis

Introduction: aCGH

Age <16.0

Age ≥16.0

PNET 5 MB - LR

PNET 5 MB - SR

Central imaging and RT review

Randomisation

Radiotherapy 18 Gy CSI (without vincristine)

Radiotherapy alone (without vincristine)

Radiotherapy + Carboplatin 35 mg/m² 5 times/week (without vincristine)

Maintenance Chemotherapy ABA_BAB

Maintenance Chemotherapy ABA_BAB_AB

Successful hypothesis in PNET 5

Re: Treatment of patients below 16 years of age presenting with R0M0 WNT group medulloblastoma

As you know, the first results of the PNET5 MB LR arm have been reported at the last SIOP meeting in Amsterdam, October 22, 2025 (See attached abstract)

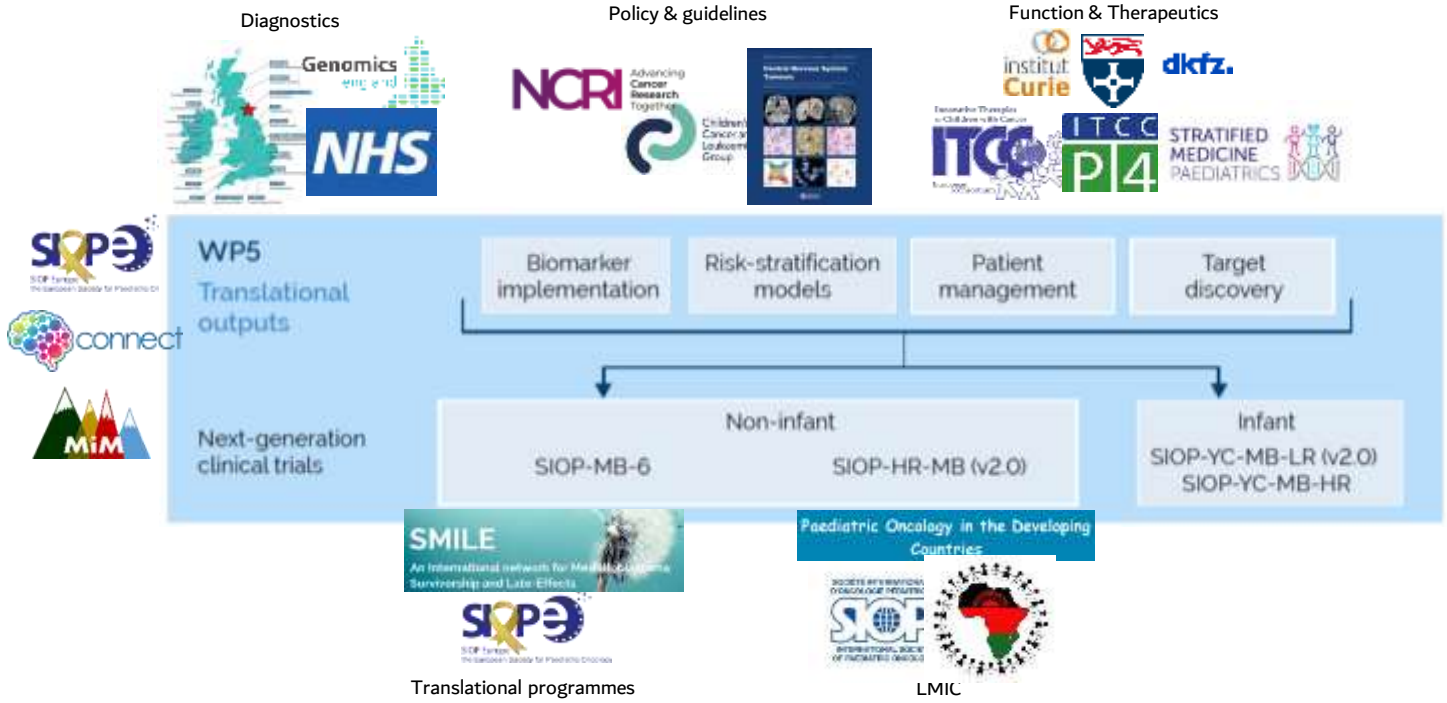
The main objective was reached with a 3-year EFS rate of 91% in the per-protocol analysis (and 88.8% in the intent to treat analysis).

Based on these good results, and before the opening of the future SIOPE MB6 study, we may recommend today the **PNET5 MB LR treatment as a standard in R0M0 WNT group medulloblastoma diagnosed before 16 years** (as we agreed during our recent meeting in Porto).

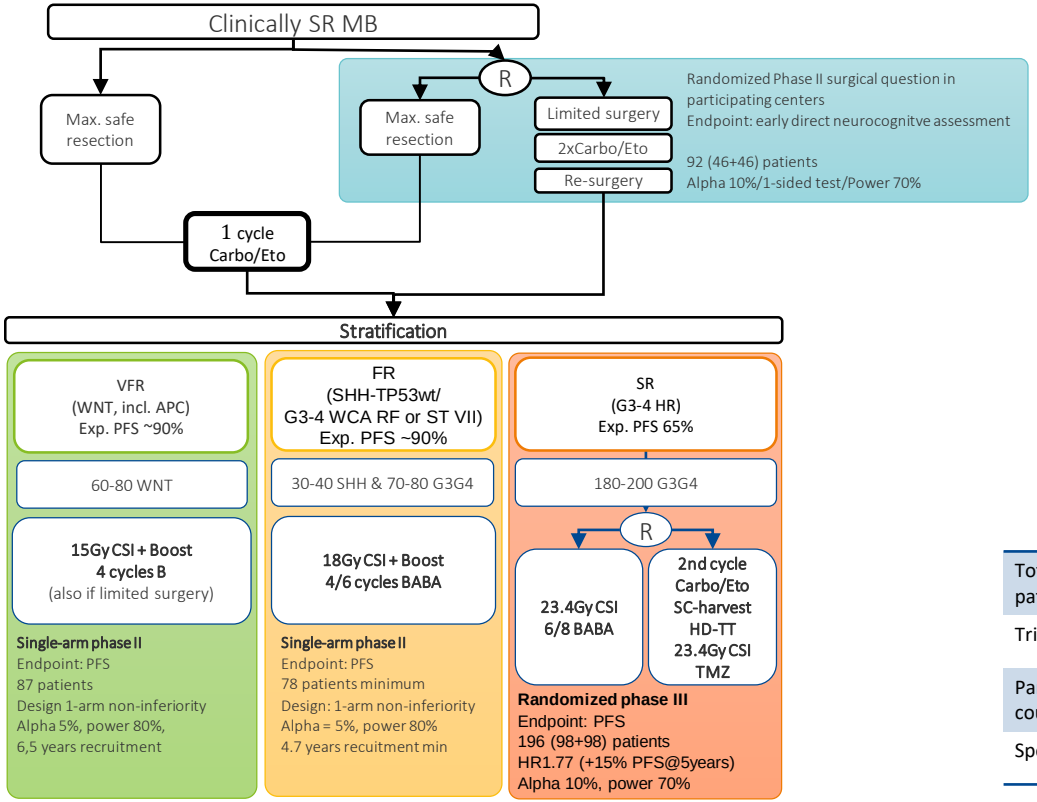
However, this is only true in the conditions of the per-protocol treatment:

- Age <16.0 years at diagnosis
- Confirmed R0 (R<1.5 cm^2)
- Confirmed M0
- Classic or desmoplastic histology
- Confirmed WNT group: *CTNNB1* mutation AND at least one additional molecular feature of WNT medulloblastoma [defined as isolated monosomy 6 and/or WNT methylation group by DNA methylation or RNA expression profiling, using methods accredited according to national requirements], and no other biological parameter incompatible with this diagnosis. Please note: positive nuclear expression of β-catenin is NOT considered a robust marker for the definition of WNT status.
- Radiotherapy to be started within 28 days from surgery (maximum 40 days)
  - Careful review of radiotherapy plans
  - Brain 18 Gy in 10 daily fractions of 1,8 Gy
  - Spine 18 Gy in 10 daily fractions of 1,8 Gy
  - Primary tumor boost 36 Gy in 20 daily fractions of 1,8 Gy (total dose to primary tumor 54 Gy in 30 daily fractions of 1,8 Gy
  - Safety margins according to the PNET5 MB protocol recommendations
- Maintenance chemotherapy: To be started 6 weeks after end of radiotherapy
  - 6 cycles BA_BA_BA
  - Regimen B: Cyclophosphamide (1000 mg/m^2 day 1, 2) Vincristine (1.5 mg/m^2 day 1)
  - Regimen A: Cisplatin (70 mg/m^2 day 1) CCNU (75 mg/m^2 day 1) Vincristine (1.5 mg/m^2 day 1, 8,15)
  - Recommendations of dose adaptation according to PNET5 MB LR should be followed

Translational Outputs



Courtesy of Prof Clifford



SIOP MB6

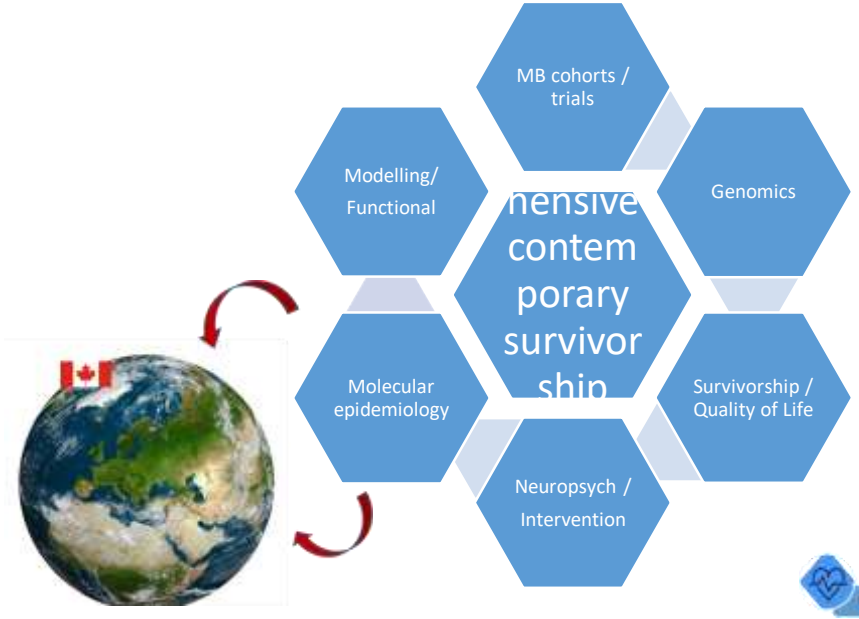
Total No patients	~380
Trial duration	6 (-8) years
Participating countries	SIOP-E
Sponsor	Germany

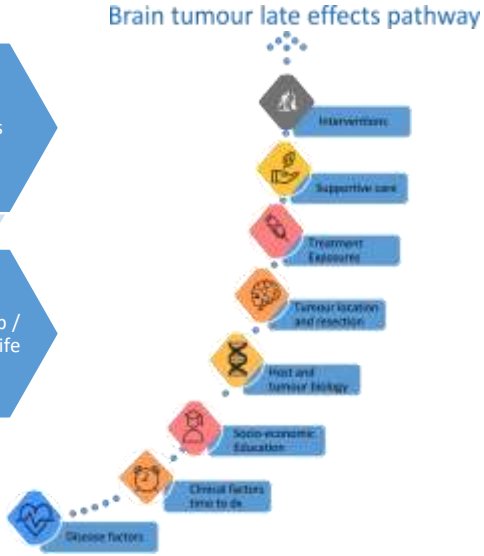
Conclusions: What We Have For Standard Risk Medulloblastoma

- **NO NEW DRUGS but**
  - **Risk tailored protocols**
  - **And NEW way of using old drugs**
    - **Less toxicity forecast for «better» disease**
    - **Shorter duration**
    - **Sinergy (RT + CT/HDCT) evaluation for «less good» diseases**

- **“smaller” surgery?**

SMILE: An International network for Medulloblastoma Survivorship and Late-Effects



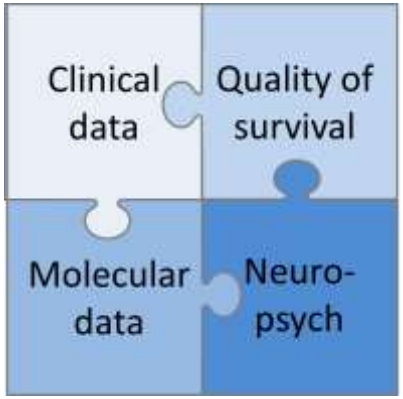


A multidisciplinary network in MB survivorship

Courtesy of Prof Clifford

Best current experience cohort-based molecular survivorship studies

Archival trial data (1990-2006)
> PNET3 and PNET4



PNET3 and PNET4; QoS

Quality of survival

- Health Utilities Index (HUI3)
- Strengths and Difficulties Questionnaire (SDQ)
- Pediatric Quality of Life Inventory (PedsQL)

PNET4; NPS

Cognitive measures

- Full Scale Intelligence Quotient (FSIQ)
- Performance Intelligence Quotient (PIQ)
- Processing Speed Index (PSI)
- Verbal Intelligence Quotient (VIQ)
- Working Memory Index (WMI)

Courtesy of Prof Clifford

Medulloblastoma at relapse is an almost hopeless disease

- » **No cure with surgery + re-irradiation**
- » **No cure with high-dose chemotherapy***
- » **No cure with standard second-line chemotherapy°°**
- » ***metronomic efforts…***

…and target therapies?

*

NO SALVAGE USING HIGH-DOSE CHEMOTHERAPY PLUS/MINUS REIRRADIATION FOR RELAPSING PREVIOUSLY IRRADIATED MEDULLOBLASTOMA

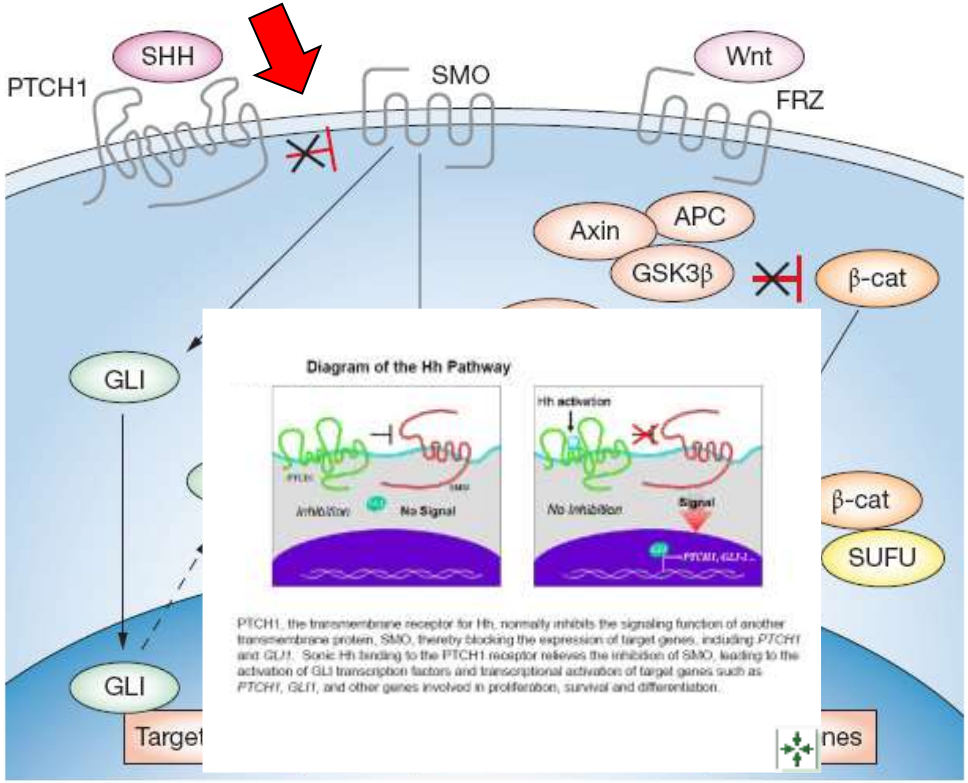
°°

Relapse in medulloblastoma: what can be done after abandoning high-dose chemotherapy? A mono-institutional experience

» *JAMA Oncol. 2023;9(12):1688-1695. doi:10.1001/jamaoncol.2023.4437*

Published online October 26, 2023.

Big Hope Was Put On The Possibility Of New Therapeutic Targets



NATURE CLINICAL PRACTICE ONCOLOGY

MAY 2007 VOL 4 NO 5 POLKINGHORN AND TARBELL

N Engl J Med. 2009 Sep 17;361(12):1173-8

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Treatment of Medulloblastoma with Hedgehog Pathway Inhibitor GDC-0449

Charles M. Rudin, M.D., Ph.D., Christine L. Hann, M.D., Ph.D., John Laterra, M.D., Ph.D., Robert L. Yauch, Ph.D., Christopher A. Callahan, M.D., Ph.D., Ling Fu, M.D., Thomas Holcomb, M.S., Jeremy Stinson, B.S., Stephen E. Gould, Ph.D., Barbara Coleman, R.N., C.C.R.P., Patricia M. LoRusso, D.O., Daniel D. Von Hoff, M.D., Frederic J. de Sauvage, Ph.D., and Jennifer A. Low, M.D., Ph.D.

SUMMARY

Medulloblastoma is the most common malignant brain tumor in children. Aberrant activation of the hedgehog signaling pathway is strongly implicated in the development of some cases of medulloblastoma. A 26-year-old man with metastatic medulloblastoma that was refractory to multiple therapies was treated with a novel hedgehog pathway inhibitor, GDC-0449; treatment resulted in rapid (although transient) regression of the tumor and reduction of symptoms. Molecular analyses of tumor specimens obtained before treatment suggested that there was activation of the hedgehog pathway, with loss of heterozygosity and somatic mutation of the gene encoding patched homologue 1 (PTCH1), a key negative regulator of hedgehog signaling.

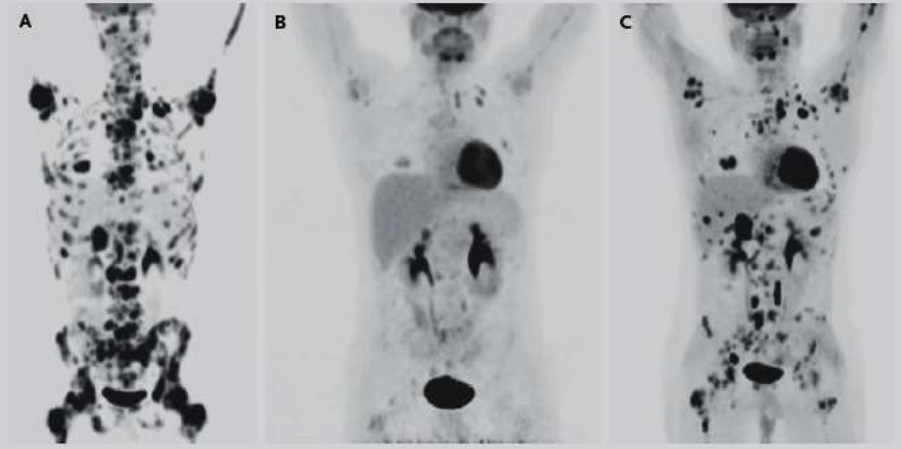


Figure 1. Tumor Response on Positron-Emission Tomographic (PET) Scanning.

Whole-body projections from ^{18}F-fluorodeoxyglucose (FDG)–PET scans are shown. Panel A shows the pretreatment scan; Panel B, the repeat scan after 2 months of therapy with the hedgehog pathway inhibitor GDC-0449; and Panel C, the repeat scan after 3 months of therapy.

Anti-SMO in Europe

The 5-gene Hh Signature

Control genes: *HUWE1, YME1L1, SOD1, LARP1, ZP2**

**ZP2*, up-regulated in normal cerebellum samples, was used to analyze non-tumor sample contamination present in FFPE samples.
GLI1, glioma-associated oncogene homolog 1; HUWE1, HECT, UBA and WWE domain containing 1; LARP1, la ribonucleoprotein domain family, member 1;OTX2, orthodenticle homeobox 2; SHROOM2, shroom family member 2; SOD1, superoxide dismutase 1, soluble;PDLIM3, PDZ and LIM domain 3; SPHK1, sphingosine kinase 1; YME1L1, YME1-like 1; ZP2, zone pellucida sperm-binding protein 2.
Novartis, data on file, 2012.

SHH Inhibition Is Not Enough

- Tumorigenesis is a more complex event
- LDE225/vismodegib resistence correlates with germ-line mutation like SUFU (infants) and amplification of GLI2 e MYCN (and TP53, 5-16 years), «downstream mutations»
- Adults medulloblastoma, the most commonly PTCH and SMO mutated, are the best to obt

Cancer Cell
Article

Genome Sequencing of SHH Medulloblastoma Predicts Genotype-Related Response to Smoothened Inhibition

Marcel Kool,[1,7] David T.W. Jones,[1] Natalie Jäger,[2] Paul A. Northcott,[1] Trevor J. Pugh,[3] Volker Hovestadt,[4] Rosario M. Piro,[5] L. Adriana Esparza,[6] Shirley L. Markant,[3] Marc Remke,[8] Till Milde,[9] Franck Bourdeaut,[6,10] Marina Ryzhova,[11] Dominik Sturm,[1] Elke Pfaff,[1] Sebastian Stark,[1] Sonja Hutter,[1] Huriye Seker-Cin,[1] Pascal Johann,[1] Sebastian Bender,[1] Christin Schmidt,[1] Tobias Rausch,[12] David Shih,[6] Jüri Reimand,[12] Laura Sieber,[1] Andrea Wittmann,[1] Linda Linke,[1] Hendrik Witt,[1,7] Ursula D. Weber,[4] Marc Zapatka,[4] Rainer König,[5,13,14] Rameen Beroukhim,[3,15,16] Guillaume Bergthold,[3,15,17] Peter van Sluis,[18] Richard Volckmann,[18] Jan Koster,[19] Rogier Versteeg,[18] Sabine Schmidt,[19] Stephan Wolf,[19] Chris Lawerenz,[20] Cynthia C. Bartholomae,[21] Christof von Kalle,[21] Andreas Unterberg,[21] Christel Herold-Mende,[21] Silvia Hofer,[22] Andreas E. Kulozik,[7] Andreas von Deimling,[23,24] Wolfram Scheurlen,[25] Jörg Felsberg,[26] Guido Reifenberger,[26] Martin Hasselblatt,[27] John R. Crawford,[28,29] Gerald A. Grant,[30,31] Nada Jabado,[32] Arie Perry,[33] Cynthia Cowdrey,[34] Sydney Croul,[35] Gelareh Zadeh,[36] Jan O. Korbel,[12] Francois Doz,[6,38] Olivier Delattre,[6,9] Gary D. Bader,[12] Martin G. McCabe,[37] V. Peter Collins,[38] Mark W. Kieran,[39] Yoon-Jae Cho,[40] Scott L. Pomeroy,[41] Olaf Witt,[42] Benedikt Brors,[2] Michael D. Taylor,[3] Ulrich Schüller,[43] Andrey Korshunov,[1,23,24] Roland Eils,[2] Robert J. Wechsler-Reya,[5,44] Peter Lichter,[1,45] and Stefan M. Pfister[1,7,46] on behalf of the ICGC PedBrain Tumor Project

Cancer Cell 25, 393–405, March 17, 2014 ©2014 Elsevier Inc.

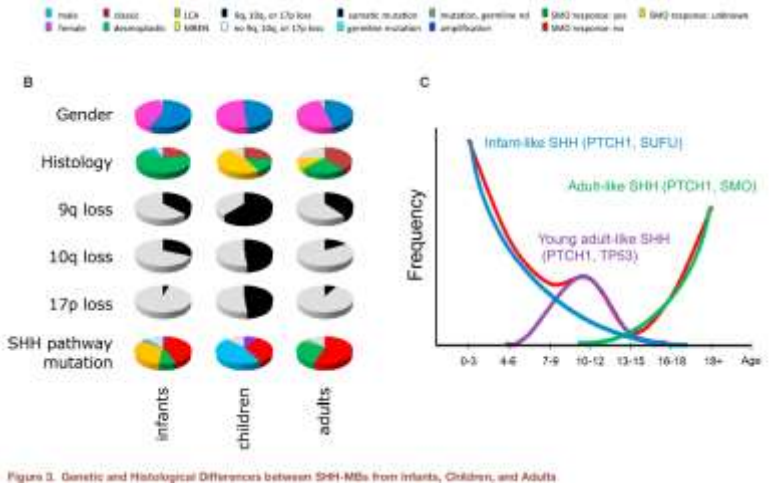


Figure 3. Genetic and Histological Differences between SHH-MBs from Infants, Children, and Adults

doi: 10.1002/cam4.1171

Cancer Medicine

Open Access

REVIEW

Medulloblastoma in children and adolescents: a systematic review of contemporary phase I and II clinical trials and biology update

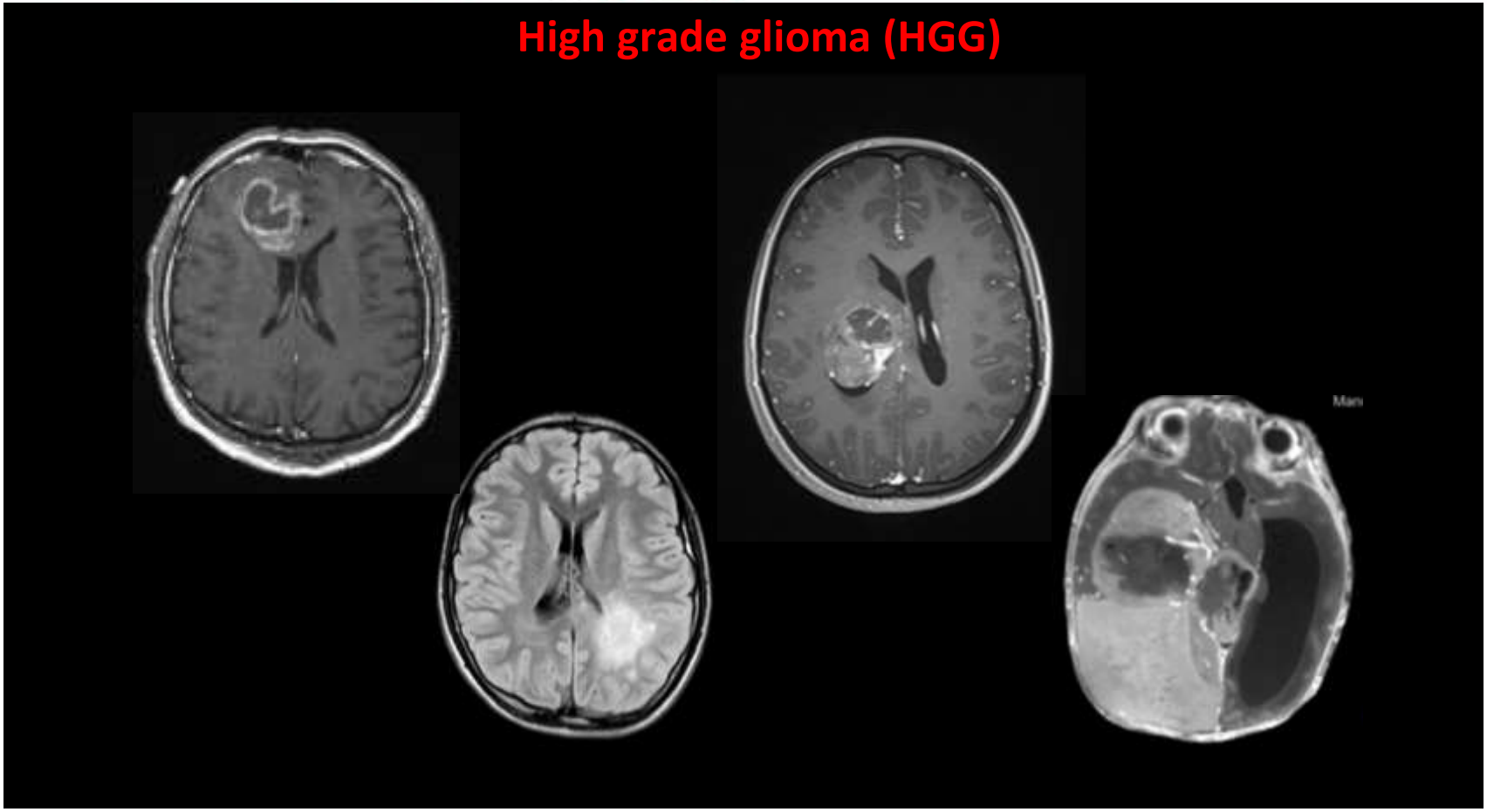
Francisco Bautista[1], Victoria Fioravantti[1], Teresa de Rojas[1], Fernando Carceller[2,3], Luis Madero[1], Alvaro Lassaletta[1] & Lucas Moreno[1,4]

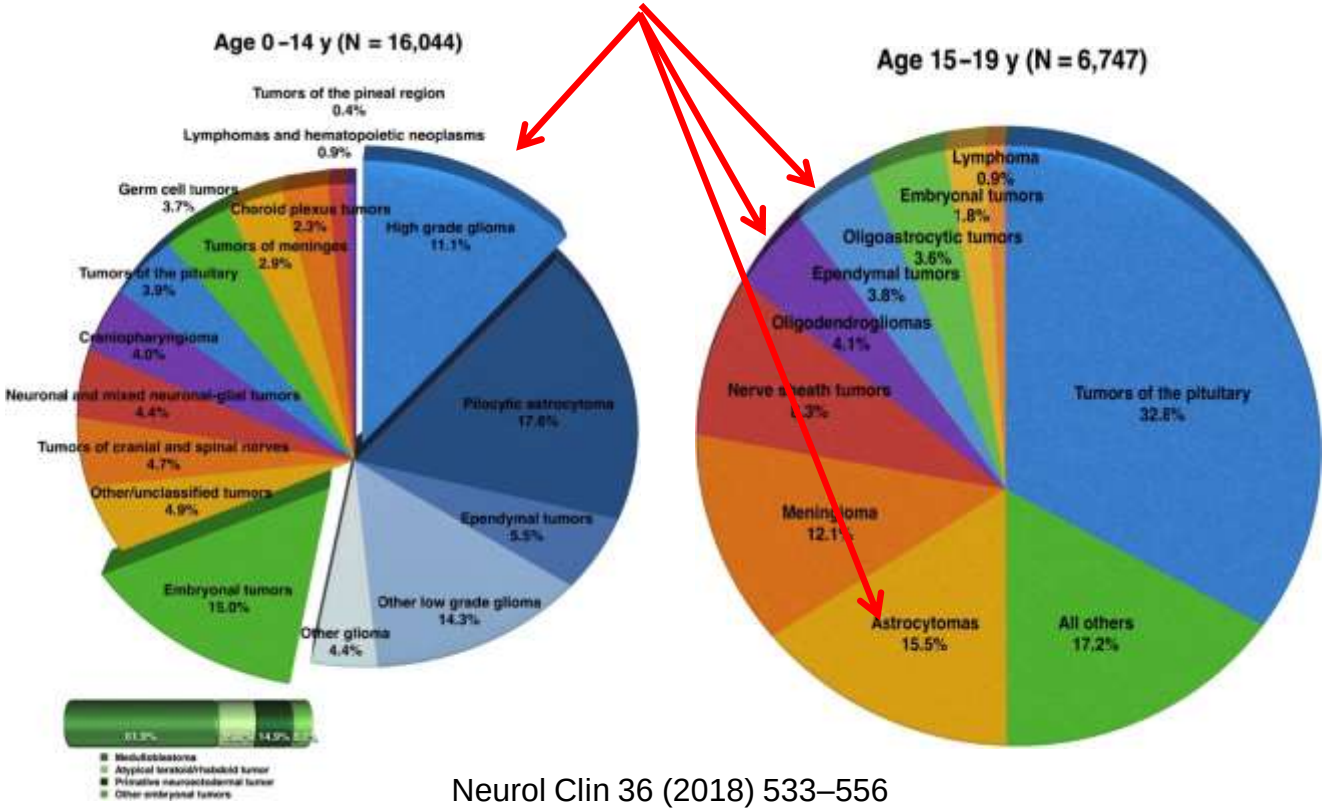
[1]CNIO-HNJ Clinical Research Unit, Pediatric Oncology, Hematology and Stem Cell Transplant Department, Hospital Infantil Universitario Niño Jesús, Avenida Menéndez Pelayo, 65, 28009, Madrid, Spain
[2]Pediatric and Adolescent Drug Development, Children and Young People's Unit, The Royal Marsden NHS Foundation Trust, London, UK
[3]Division of Clinical Studies and Cancer Therapeutics, The Institute of Cancer Research, London, UK
[4]Instituto de Investigación La Princesa, Madrid, Spain

- Overall, 662 patients with medulloblastoma/primitive neuroectodermal tumors were included
- Median (range) objective response rate (ORR) for patients with medulloblastoma in phase I/II studies was **0%** (0–100) and **6.5%** (0–50), respectively
- **Temozolomide** containing regimens had a median ORR of **16.5%** (0–100).
- Smoothened inhibitors trials had a median ORR of **8%** (3–8)

Novel drugs have shown limited activity against relapsed medulloblastoma

High grade glioma (HGG)





Neurol Clin 36 (2018) 533–556

Also diagnosis is very difficult

- **The classification of a glioma requires judgment, experience, meticulous adherence to guidelines**
  - *Pollack I, Neuro-oncology 2003*

- **The rarity and histological heterogeneity of these tumors can put even experienced pathologists in difficulty**
- **They will be able to make different diagnoses on different samples of the same tumor**

Paediatric and adult malignant glioma: close relatives or distant cousins?

Jones, C. *et al. Nat. Rev. Clin. Oncol.* 9, 400–413 (2012); published online 29 May 2012; doi:10.1038/nrclinonc.2012.87

Chris Jones, Lara Perryman and Darren Hargrave

» **HGGs in children have long been considered the same disease as adults**

Not true… beginning from topographic differences

HGG Adults		HGG Children
brainstem	1%	50% 80% DIPG 20% non-DIPG
Basal nuclei	rare	10-15%
Supratentorial	90%	20-30%
Spinal	3%	3%

Adult and childhood HGG... Close relatives or distant cousins

- Although children's HGGs appear to be histologically similar to their adult counterparts, they follow different genetic pathways from those that operate in adults

•Nature Genetics, Wu G, 2012

- The association between age and genetic alterations between pediatric glioblastomas indicates the probable existence of distinct pathways of molecular tumorigenesis in younger than in older children

They both look daisies

The seeds are however different

daisy

chrisantemus

Adult and childhood HGG... Close relatives or distant cousins

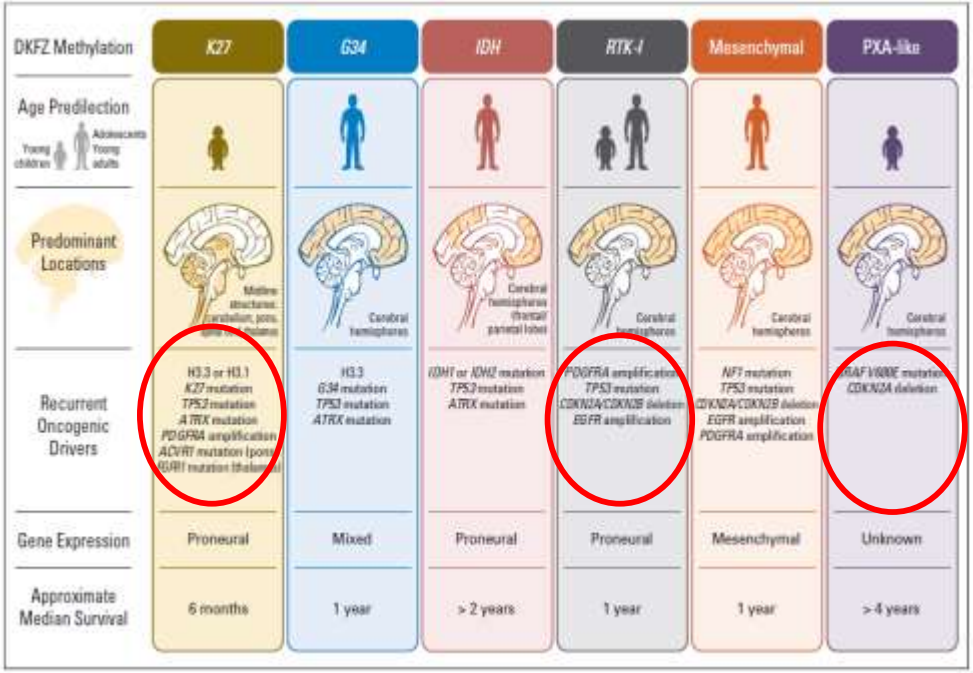
- **Mutations of histone H3 were identified in 78% of intrinsic pons tumors (DIPG) studied and in 22% of non-pontine gliomas**
  - **Nature Genetics, Wu G, 2012, Nature**
- **These mutations in the single histone H3 are associated with the assembly of chromatin and may represent the pathogenetic event of children's pons gliomas**

Table 2 | Location-specific and age-specific genetic differences in malignant glioma

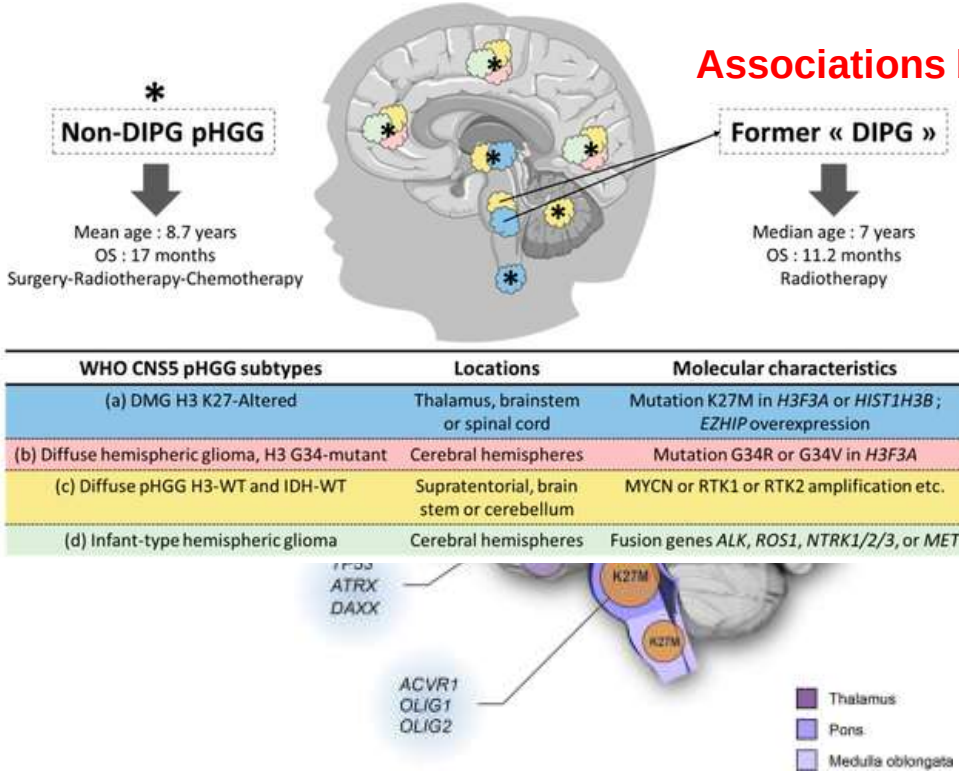
Genetic abnormality	DIPG*	HGG‡				
		Infant (<3 years)	Child (3–14 years)	Adolescent (14–21 years)	Young adult (21–44 years)	Older adult (>45 years)
Transformation	NR	–	–	+	+++	+
Number alterations	++	–	+	+	++	+++
Gain of 1q	++	++	++	++	+	–
Loss of 16q	+	++	++	++	–	–
Stable genomes	–	++	++	++	–	–
Gain of 7	+	–	–	–	++	+++
Loss of 10q	++	+	+	+	++	+++
EGFR amplification	+	–	+	+	++	+++
PDGFRA amplification	+++	–	++	++	++	+
CDKN2A or *CDKN2B* deletion	–	+	++	++	+++	+++
p53 pathway alterations	+++	+++	++	++	++	++
PI3K pathway alterations	++	+	++	++	++	+++
Rb pathway alterations	++	+	+	+	++	+++
BRAF V600E	–	–	+	++	+	–
IDH1 R132X	–	–	–	+	+++	+
H3F3A K27M	+++	NR	+++	++	+	–
H3F3A G34R/V	–	NR	+	++	+	–
HIST1H3B K27M	++	NR	–	–	–	–

*Peak age 4–9 years. Grade not specified; infratentorially located. ‡Supratentorially located. Abbreviations: –, low; +, moderate; ++, high; +++, very high; DIPG, diffuse intrinsic pontine glioma; HGG, high-grade glioma; NR, not reported.

Many Different High-grade Glioma



Associations between sites and gene mutations



WHO CNS5 pHGG subtypes	Locations	Molecular characteristics
(a) DMG H3 K27-Altered	Thalamus, brainstem or spinal cord	Mutation K27M in *H3F3A* or *HIST1H3B*; *EZHIP* overexpression
(b) Diffuse hemispheric glioma, H3 G34-mutant	Cerebral hemispheres	Mutation G34R or G34V in *H3F3A*
(c) Diffuse pHGG H3-WT and IDH-WT	Supratentorial, brain stem or cerebellum	MYCN or RTK1 or RTK2 amplification etc.
(d) Infant-type hemispheric glioma	Cerebral hemispheres	Fusion genes *ALK*, *ROS1*, *NTRK1/2/3*, or *MET*

Rishi R. Lulla et al. Sci Adv 2016;2:e1501354

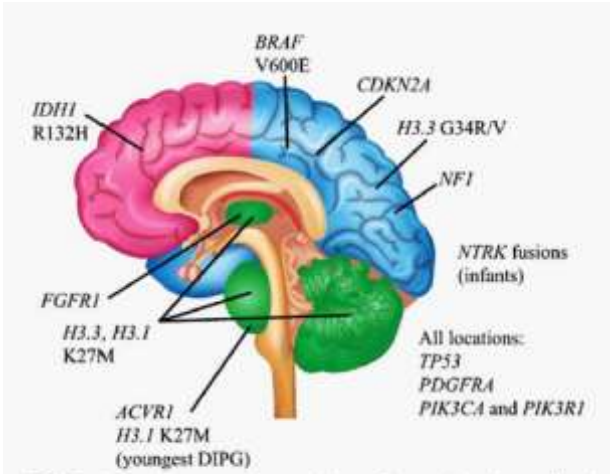


FIGURE 4: Spatiotemporal association of mutations in pediatric high-grade glioma. Clear associations between specific mutations and age- and location-dependent subgroups of pediatric HGG

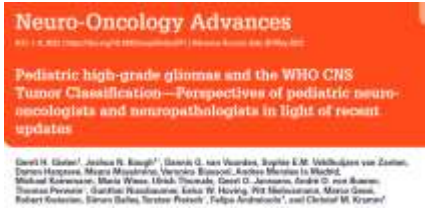
Baker SJ, Ellison DW, Gutmann DH. Pediatric gliomas as neurodevelopmental disorders.
Glia. 2016 Jun;64(6):879-95

Table 2. Comparisons Between Participant Feedback on the Revised CNS4 in 2016 and Changes Implemented in the CNS5 in 2021

Paediatric HGG WHO 2016	Relevant Survey Questions Addressing the Issue	Problem Confirmed By Survey Results	Addressed by Pediatric HGG WHO 2021?	
1.				
2.				with loss
Ar as wi Gl wi				high- a, IDH/ 34 ew infants
Pi wi ar				is ade es not ocytic
				astrocytoma
Gliomatosis cerebri removed as a neuroradiological diagnosis	Neuroradiological defined diagnosis of gliomatosis cerebri still needed?	Yes: 58.7% No: 40.0%	No	No change

New: "DMG, H3 K27-altered", WHO grade 4

- Subtype 1: H3 K27M-mutant (most common)
- Subtype 2: EGFR-mutant
  - Often bithalamic
  - Occasionally with superimposed H3 K27M mutation
- Subtype 3: H3-wildtype with EZHIP over-expression
- Loss of H3K27me3 by IHC in all 3 subtypes
- Most commonly young kids for DIPGs and AYAs for thalamus and spinal cord
- All WHO grade 4 by definition



But What Is The Standard Therapy?

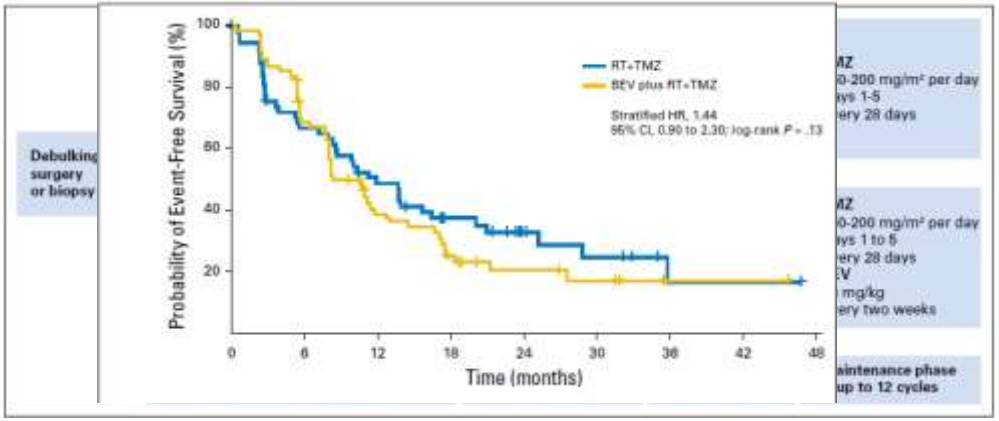
- **There is no universally recognized chemotherapy standard on which the history of pediatric HGG therapy can be built**
- **Very few randomized trials have shown an advantage in the use of chemotherapy**
- **The adjuvant use of lomustine, vincristine and prednisone was considered the standard of the 90s with EFS 46% vs 18% at 5 years with or without the use of chemotherapy**
- *Sposto R 1989*

Which Standard Chemotherapy?

- … But the differences were much smaller after the histopathological review
  - Fouladi M 2003
- Doubtful benefit of concomitant chemotherapy and subsequent radiotherapy in the presence of large residual disease even with intense treatments
- In fact, the most solid prognostic indicator remains the presence of the post-surgical residue

- **It is difficult to develop randomized trials when the OS of the standard arm is less than 10%**
- **But, otherwise, the use of historical control arms is dangerous especially when comparing patients treated one or two decades earlier**
- **Drugs found active or inactive in adult HGG trials cannot be assimilated for efficacy in the treatment of pediatric HGGs**

Something new and successful available?



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II, Open-Label, Randomized, Multicenter Trial (HERBY) of Bevacizumab in Pediatric Patients With Newly Diagnosed High-Grade Glioma

VOLUME 36 · NUMBER 10 · APRIL 1, 2018

Not bevacizumab …!

Many mutations…but drivers?

Anti-BRAF Trials also in HGG

- BRAF V600E mutations were detected in approximately 10% of pediatric HGGs
  - Roth, 2014; Schiffman, 2010; Nicolaides, 2011
- The prognostic significance of BRAF V600 mutations is not known in this setting

Title:	Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects with Advanced BRAF V600-Mutation Positive Solid Tumors

Efficacy of dabrafenib alone

»Historical data suggests ORR of 11% for chemotherapy in this disease

»**HGG with BRAFV600 (N=31) – ORR 45%**

–Historical data not available for BRAFV600 mutant HGG ORR

–**Unselected HGG ORR is less than 12% - most reports less than 5%**

–Duration of response in HGG is significantly greater than 4 months (7.7)

–Data from Heidelberg suggests favorable prognosis for BRAFV600 mutant HGG patients (PXA methylation like)


Neuro-Oncology Practice

12(6), 1099–1111, 2025 | https://doi.org/10.1093/nop/npaf061 | Advance Access date 16 August 2025

Dabrafenib in pediatric patients with *BRAF* V600 mutation–positive high-grade glioma: Results from a phase 1/2a single-arm study

Birgit Geoerger, Lucas Moreno, Eric Bouffet, Santhosh A. Upadhyaya, Nicolas André, Isabelle Aerts, Ashley S. Plant-Fox, Michael Roughton, Mark Russo, and Darren Hargrave

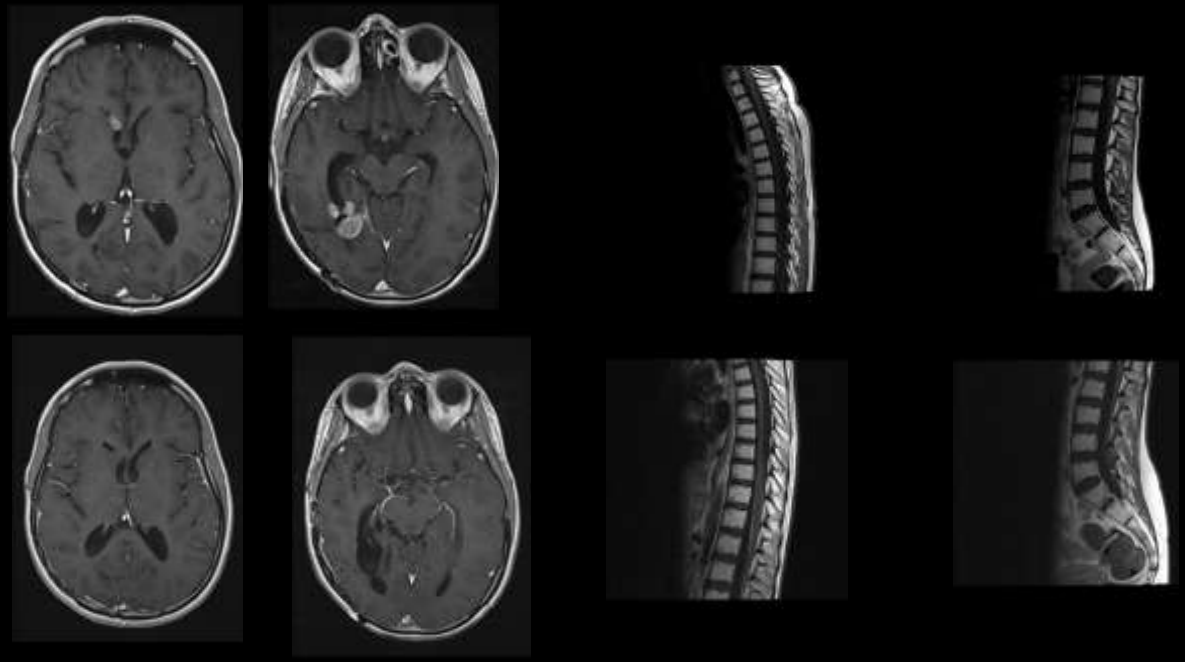

Original Reports | Pediatric Oncology

Phase II Trial of Dabrafenib Plus Trametinib in Relapsed/Refractory *BRAF* V600–Mutant Pediatric High-Grade Glioma

Darren R. Hargrave, MD, MBChB, MRCP, FRCPCH[1]; Keita Terashima, MD, PhD[2]; Junichi Hara, MD, PhD[3]; Uwe R. Kordes, MD[4]; Santhosh A. Upadhyaya, MD[5]; Felix Sahm, MD, PhD, MBA[6,7,8]; Eric Bouffet, MD[9]; Roger J. Packer, MD[10]; Olaf Witt, MD[8]; Larissa Sandalic, MSc[11]; Agnieszka Kieloch, MSc[12]; Mark Russo, MD, PhD[13]; and Kenneth J. Cohen, MD, MBA[14]; on behalf of all the Investigators involved in the high-grade glioma cohort

DOI: https://doi.org/10.1200/JCO.23.00558

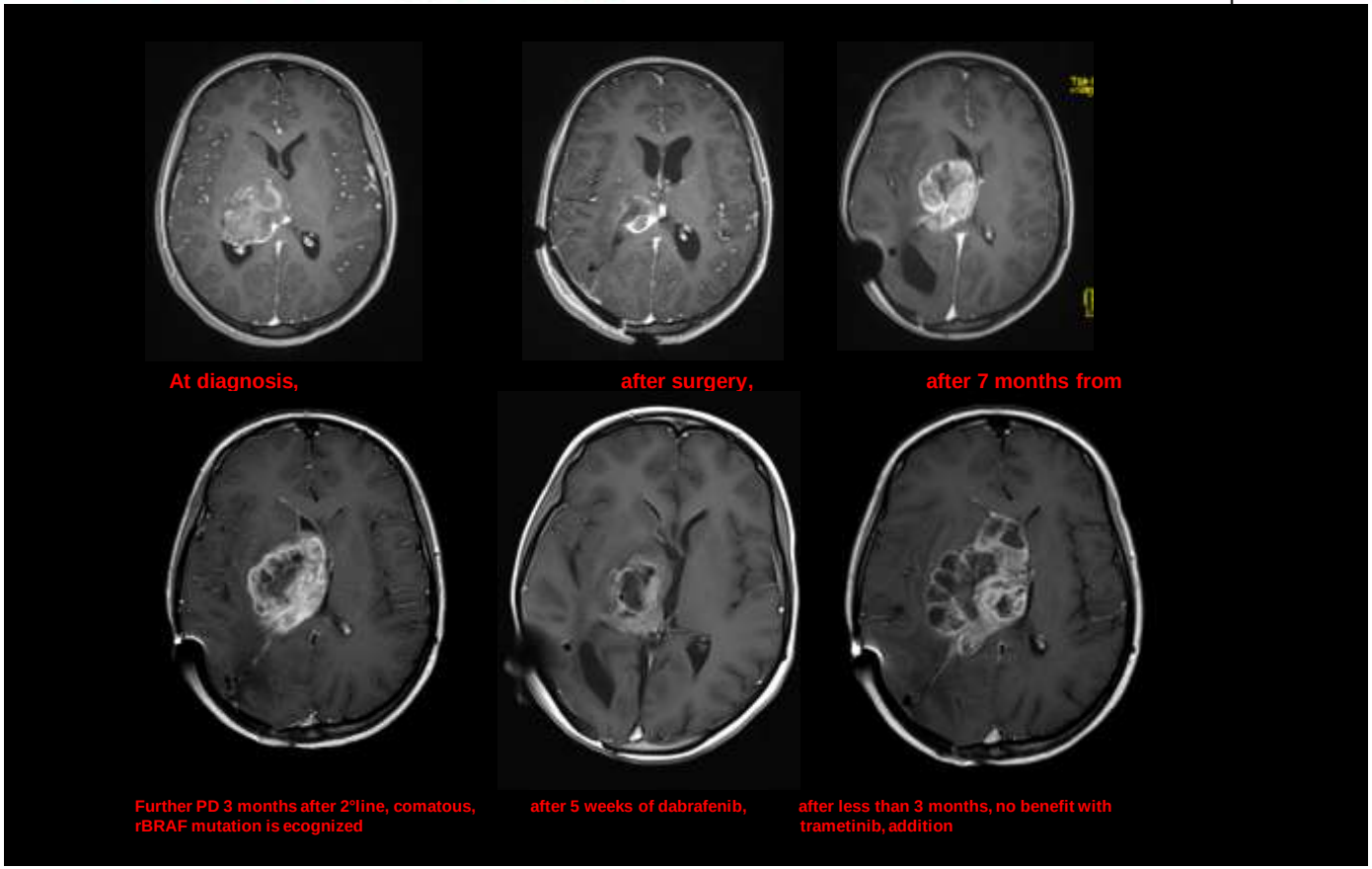
Inhibitor of BRAF In a Disseminated Glioblastoma

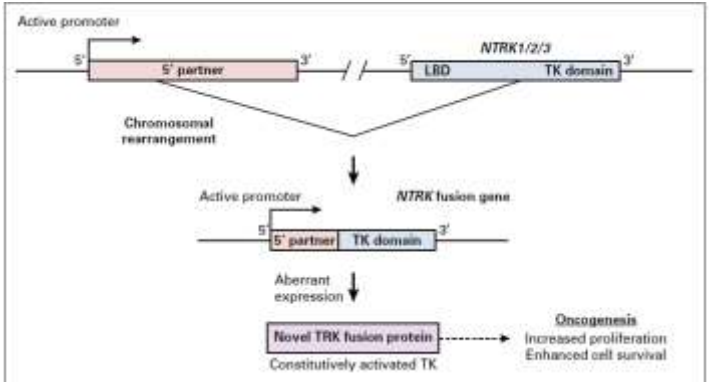


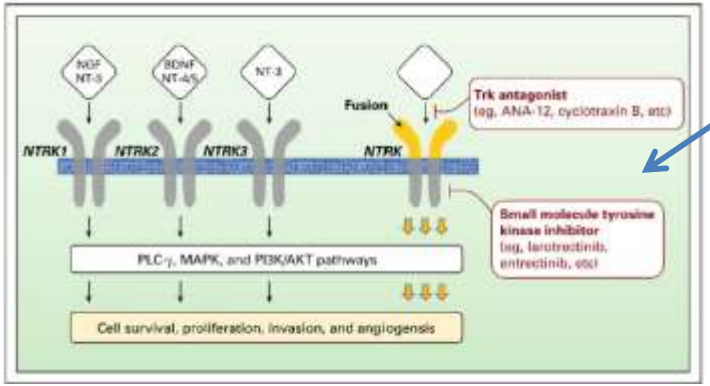
One year of excellent remission

histone H3-K27M is not mutually exclusive with BRAF-V600E mutation

- histone H3-K27M mutation rarely co-occur with BRAF-V600E mutation, and is commonly associated with p53 overexpression, ATRX loss (except in pontine gliomas), and monosomy 10 (*Childs Nerv Syst . 2018;34:107-116)*
- Better prognosis according to *Brain Tumor Pathol. 2019;36:162-168*
- Not confirmed by *Neuropathol Appl Neurobiol. 2015;41:403-8*
- **These results indicate some overlap between the genetic alterations of paediatric LGG and HGG**
- All authors describes entities histologically difficult to characterize


At diagnosis,
after surgery,
after 7 months from
Further PD 3 months after 2°line, comatous, rBRAF mutation is ecognized
after 5 weeks of dabrafenib,
after less than 3 months, no benefit with trametinib, addition





TRK fusion

- Some tumors express TRK gene fusions, even in the pediatric field
- Sarcomas, papillary thyroid tumors, nevi, inflammatory myofibroblastic tumors, leukemias ... and gliomas
- The latter are mainly in young children
- This is a rare occurrence (0.34%), but "targettable"

- Larotrectinib resulted in 76% responses in various cancers
- Entrectinib 79% (with interest also in ALK and ROS1 rearrangements)
- There are also drugs for already resistant tumors

ASCO 2019

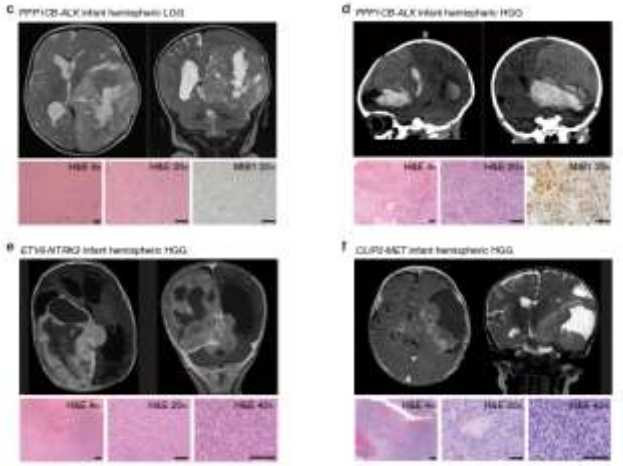
nature COMMUNICATIONS

ARTICLE

OPEN

Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas

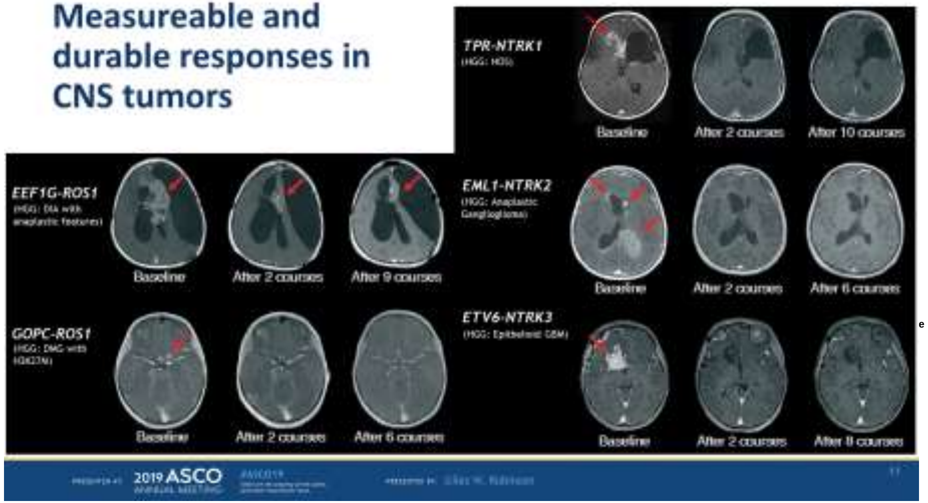
Ana S. Guerreiro Stucklin@et al.#



Infantile gliomas are mostly single-driver tumors and they are particularly suitable for precision medicine treatment approaches

Presented By Giles Robinson at 2019 ASCO Annual Meeting

Measureable and durable responses in CNS tumors

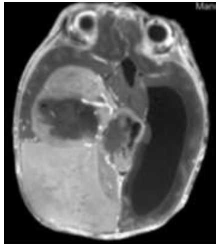


Through proper evaluation in clinical trials we will learn how make the most of these new therapeutic approaches, improve rates survival and reduce toxicity for children with cancer

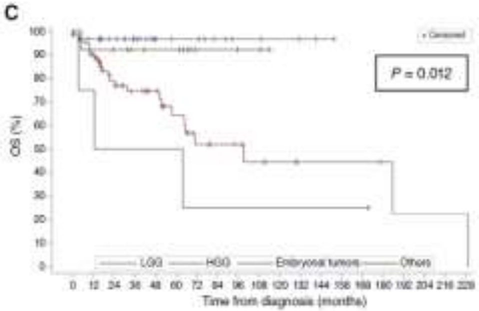
CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Clinical Characteristics and Outcomes of Central Nervous System Tumors Harboring NTRK Gene Fusions

Audrey-Anne Lamoureux, Michael J. Fisher, Lauriane Lemelle, Elke Pfaff, Pouneh Amir-Yazdani, Christof Kramm, Bram De Wilde, Bernarda Kazanowska, Caroline Hutter, Stefan M. Pfister, Dominik Sturm, David T. W. Jones, Daniel Orbach, Gaëlle Pierron, Scott Raskin, Alexander Drilon, Eli L. Diamond, Guilherme Harada, Michal Zapotocky, Josef Zamecnik, Lenka Krskova, Benjamin Ellezam, Alexander G. Weil, Dominic Venne, Marc Barritault, Pierre Leblond, Hallie Coltin, Rawan Hammad, Uri Tabori, Cynthia Hawkins, Jordan R. Hansford, Deborah Meyran, Craig Erker, Kathryn McFadden, Mariko Sato, Nicholas G. Gottardo, Hetal Dholaria, Dorte Schou Nørøxe, Hiroaki Goto, David S. Ziegler, Frank Y. Lin, Donald Williams Parsons, Holly Lindsay, Tai-Tong Wong, Yen-Lin Liu, Kuo-Sheng Wu, Andrea T. Franson, Eugene Hwang, Ana Aguilar-Bonilla, Sylvia Cheng, Chantal Cacciotti, Maura Massimino, Elisabetta Schiavello, Paul Wood, Lindsay M. Hoffman,

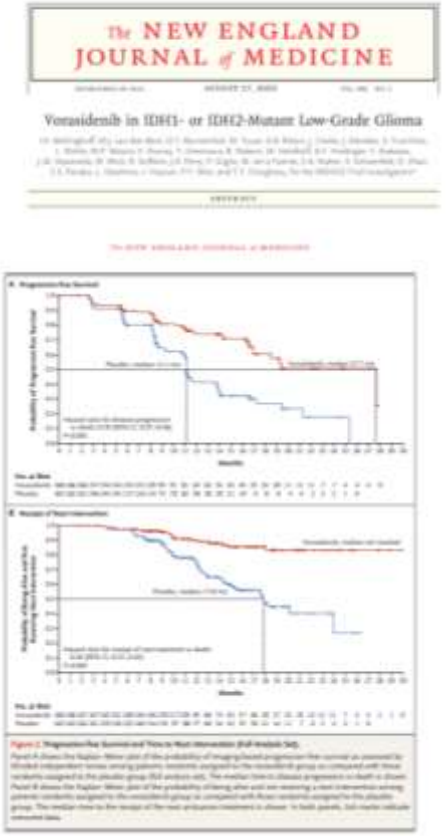


No heroic surgery is needed

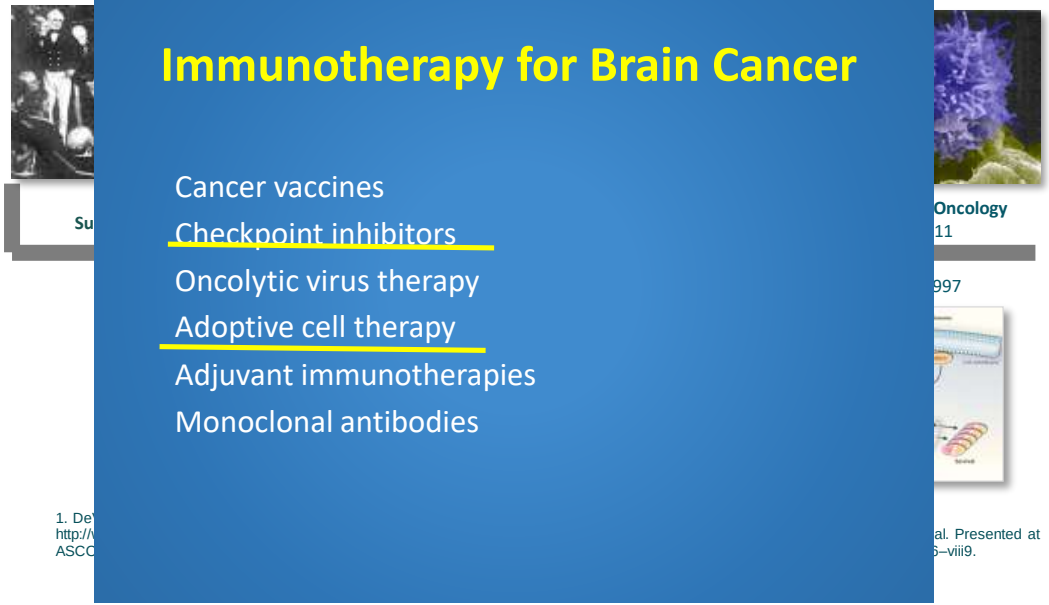


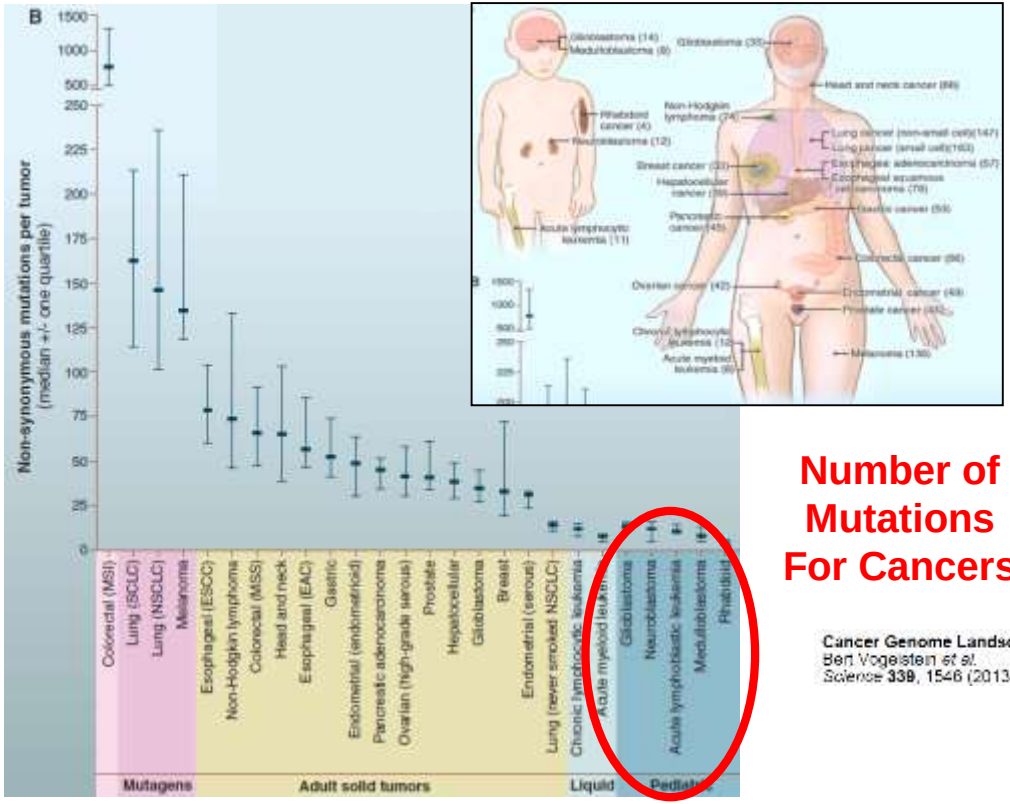
Very rare subtypes

For the **IDH mutant pHGG subgroup**, blood–brain barrier penetrant IDH inhibitors have been developed for glioma trials (NCT02273739, NCT03343197, NCT02073994 and NCT04056910). These may be specific to IDH-1 (ivosedinib), IDH-2 (enasidenib) or both (**vorasidenib**).
In addition, the use of PARP (poly-adenosine 50-diphosphate-ribose) inhibitors alongside temozolomide as a radiosensitizer is being explored



Immuno-onco-therapy is a "new" therapeutic weapon against cancer





Number of Mutations For Cancers

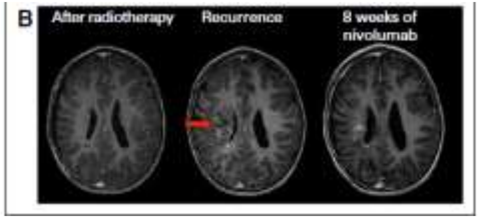
Cancer Genome Landscapes
Bert Vogelstein *et al.*
Science **339**, 1546 (2013)

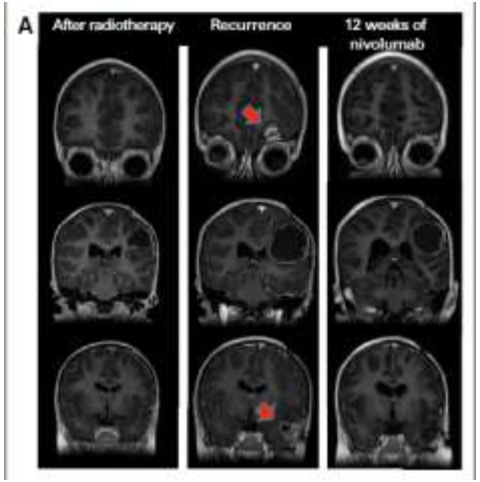
Check point inhibitors: Concrete benefit in HGG due to Germline Biallelic Mismatch Repair Deficiency

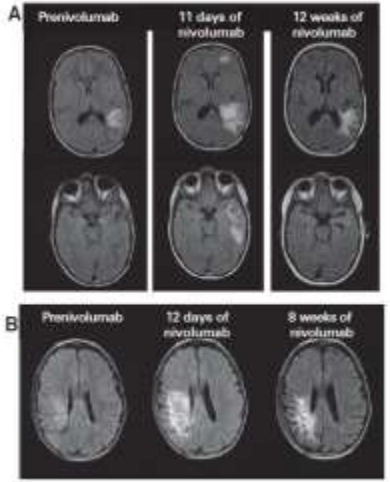
- cMMRD is a high penetrance pro-cancer syndrome
- "His" glioblastoma has the highest mutational burden of human cancers, much higher than melanoma, lung and GI cancers
- All neoantigens are hypothetically responsive to checkpoint inhibitors due to the activation of T cells
- Hence the possible therapeutic response of glioblastoma

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

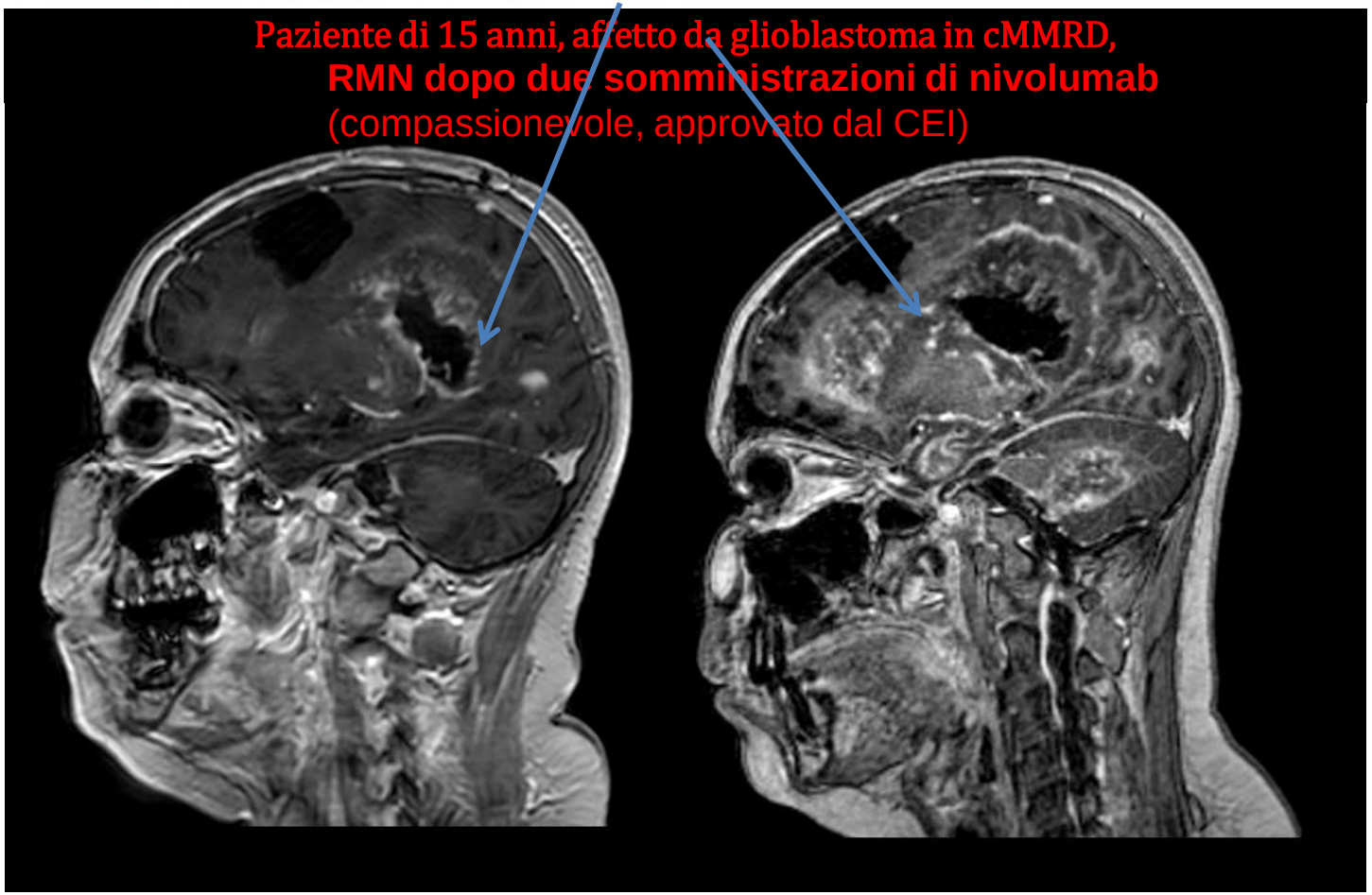
Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency

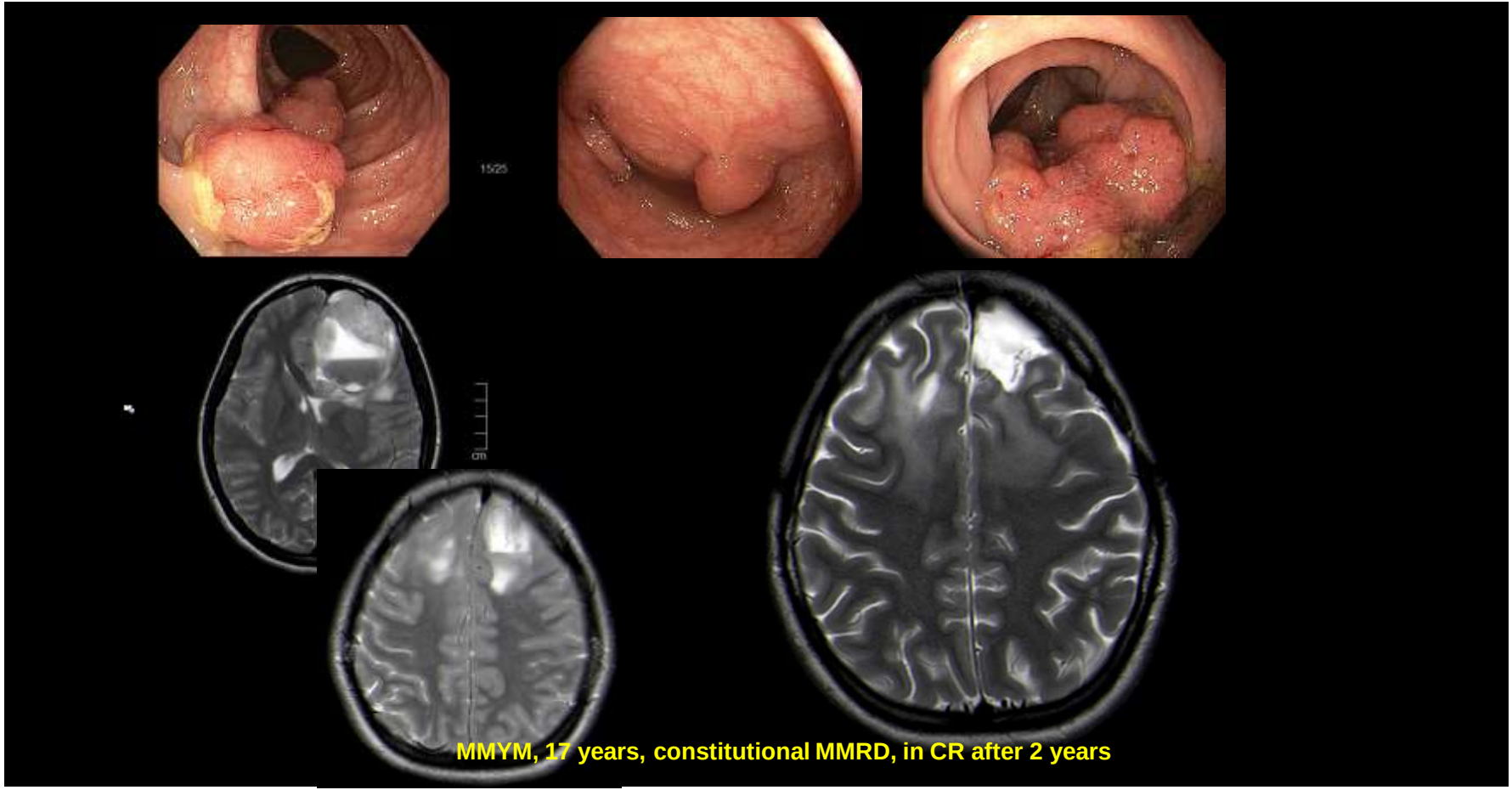






- **Treatment of two brothers with relapsed glioblastoma**
- **Clinical and radiological response lasting at least 5 and 9 months**


Paziente di 15 anni, affetto da glioblastoma in cMMRD,
RMN dopo due somministrazioni di nivolumab
(compassionevole, approvato dal CEI)

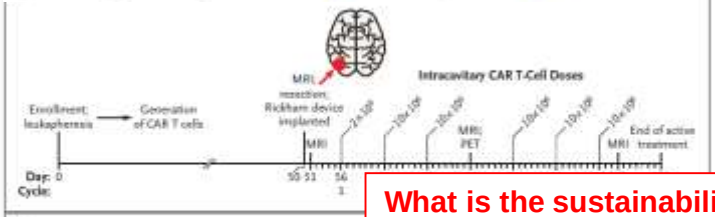


MMYM, 17 years, constitutional MMRD, in CR after 2 years

LETTERS nature medicine

Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M+ diffuse midline gliomas

Christopher W. Mount[1,2,11], Robbie G. Majzner[4,11], Shree Sundaresh[1], Evan P. Arnold[1], Meena Kadapakkam[4], Samuel Haile[4], Louai Labanieh[4,5], Esther Hulleman[6], Pamelyn J. Woo[1], Skyler P. Rietberg[6], Hannes Vogel[7,8,10], Michelle Monje[1,4,5,9,10,*] and Crystal L. Mackall[1,4,5,*]



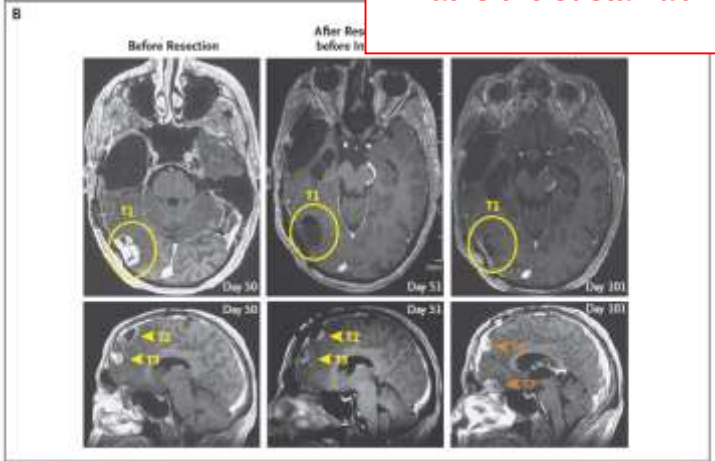


Figure 1. Local Tumor Control after Intracavitary Delivery of IL13Bζ-Chimeric Antigen Receptor (CAR) T Cells.

ort published in the Nev
e possibility of using CAR
glioblast
glioblastoma had
e of the five intra
of CAR T cells tar
cation of a previo
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weekly intracavi
he right lateral ventricl
cerebrospinal flui
s had a dramatic effect:
th response maintained

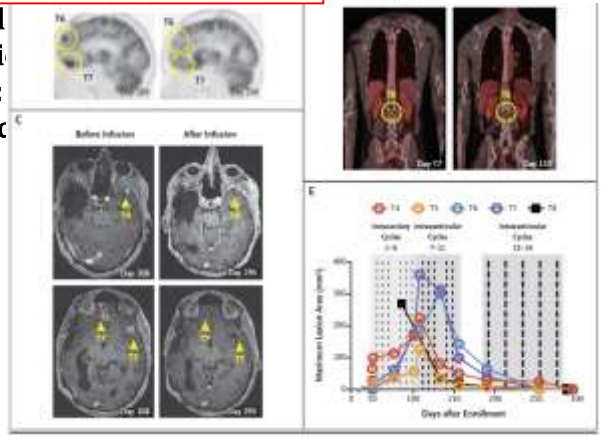
What is the sustainability of such a complex and daring project?

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy

Christine E. Brown, Ph.D., Darya Alizadeh, Ph.D., Renate Starr, M.S., Lihong Weng, M.D., Jamie R. Wagner, B.A., Araceli Naranjo, B.A., Julie R. Ostberg, Ph.D., M. Suzette Blanchard, Ph.D., Julie Kilpatrick, M.S.N., Jennifer Simpson, B.A., Anita Kurien, M.B.S., Saul J. Priceman, Ph.D., Xiuli Wang, M.D., Ph.D., Todd L. Harshbarger, M.D., Massimo D'Apuzzo, M.D., nsen, M.D., Michael E. Barish, Ph.D., ow, M.D., Stephen J. Forman, M.D., Badie, M.D.



Low-grade glioma

- Management of pLGG is intimately related to surgical resection, and **complete resection remains the most favorable predictor of patient outcome**
- **achievable for superficial lesions**
  - the cerebral hemispheres or posterior fossa,
  - not always feasible for deep seated or highly infiltrative tumors

- Progressive residual disease has historically been treated with adjuvant chemotherapy or radiotherapy
- These treatments are associated with longterm sequelae and, particularly for radiation, increased mortality
- **Up to 50% of patients will require adjuvant treatment**

  - Acta Neuropathologica Communications 2020; 8:30

cerebellar astrocytomas

- the tumors are generally well circumscribed and non-invasive
  - Large cysts with a solid mural nodule
  - Solid with smaller cysts throughout the tumor substance
  - **Wall is mostly reactive and not-neoplastic tissue**

- Growth behaviour in the first two years from diagnosis can be predictive of future progressiveness and death

  - Journal of Cancer 2019; 10:6314-6326

Indications to start non-surgical treatment in unresectable LGG.

Indications to start non-surgical treatment in unresectable LGG

Radiologic criteria

- Increase of tumour volume of > 25 % (the increase of the diameter of the optic nerve should be indicated separately) as per RAPNO working group guidelines
- Involvement of previously uninvolved areas
- Appearance of new lesions
- Increase of the number and/or size of metastases

Neurologic symptoms

- Diencephalic syndrome
- Focal neurologic deficits subsequent to tumour growth
- Drug resistant seizures with or without tumour growth
- (Focal) increased intracranial pressure subsequent to tumour growth
- Symptomatic metastases

Infants

– Infants below 12 months of age with chiasmatic-hypothalamic tumours

Ophthalmologic symptoms:

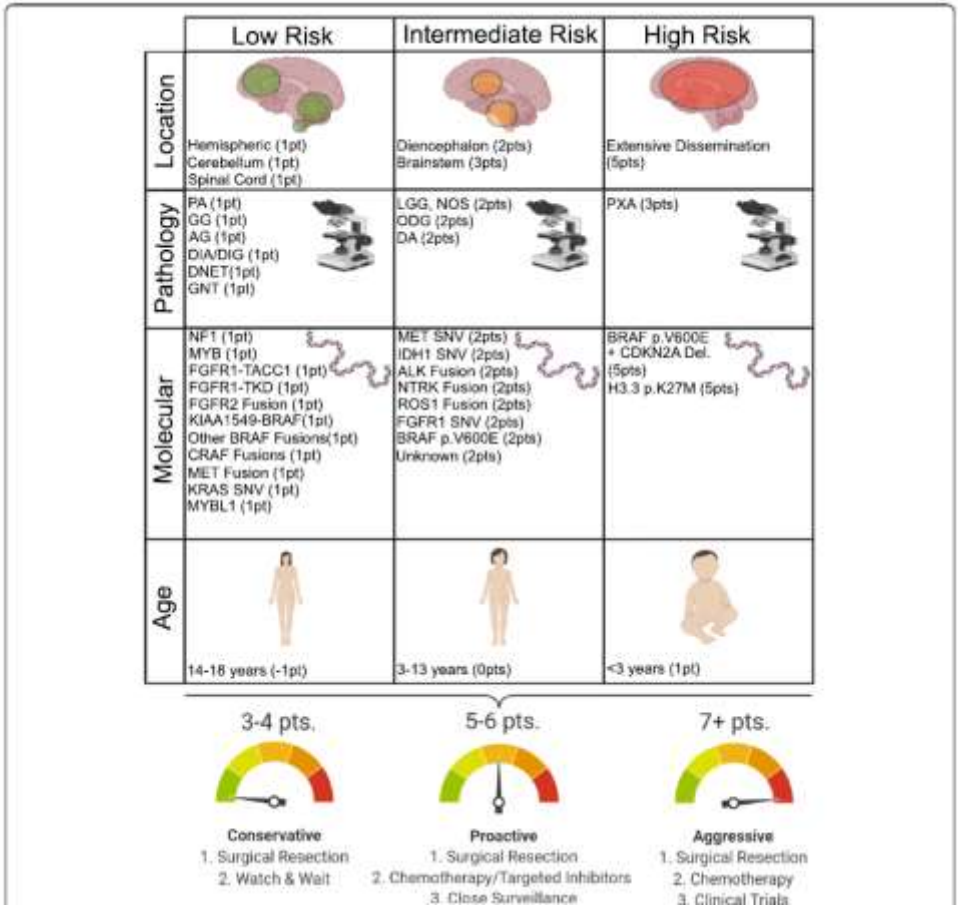
- Definitive loss of vision
- Borderline vision ("Threat to vision")
- Reduction of residual low level vision/visual field
- Nystagmus as a result of visual impairment in infants
- Any visual loss in the second eye when the first eye is blind
- Visual deterioration on follow-up, a significant loss is defined as more than or equal to 0.2 LogMAR

For patients with SEGA(s) mTOR inhibitor is indicated when they require intervention and:

1. The tumour is not amenable to surgery
2. Surgery is contraindicated
3. Surgical approach does not allow complete resection
4. In case of bilateral fornix lesions.

EJC Paediatric Oncology

European standard clinical practice recommendations for primary pediatric low-grade gliomas



Pediatric low-grade glioma in the era of molecular diagnostics

Ryall *et al. Acta Neuropathologica Communications* (2020) 8:30

Low-grade gliomas

BRAF/MAPK Alterations in Most LGG/PA "Converging" Mutations in a Single Pathogenetic Pathway

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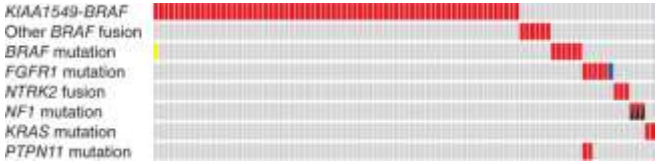
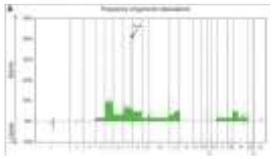
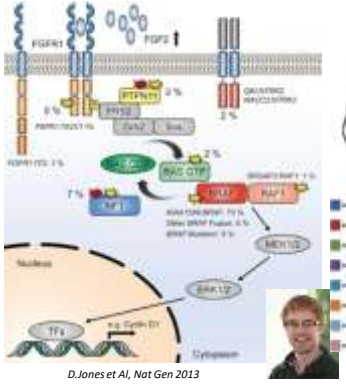
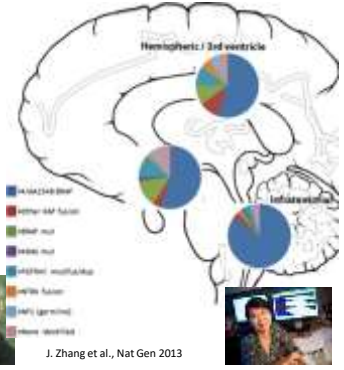




S. Pfister et Al, JCI 2008



D.Jones et Al, Nat Gen 2013



J. Zhang et al., Nat Gen 2013

The Journal of Clinical Investigation http://www.jci.org Volume 118 Number 5 May 2008
Research article

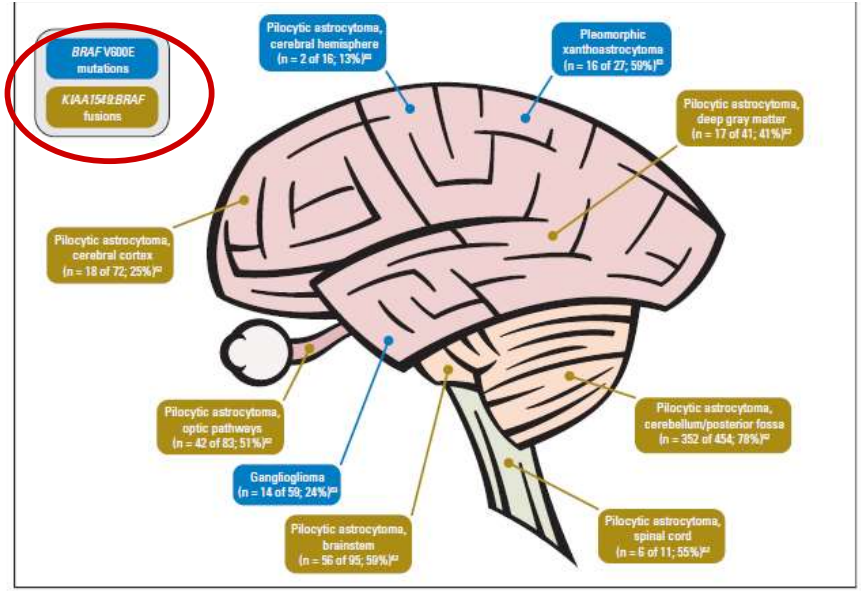
BRAF gene duplication constitutes a mechanism of MAPK pathway

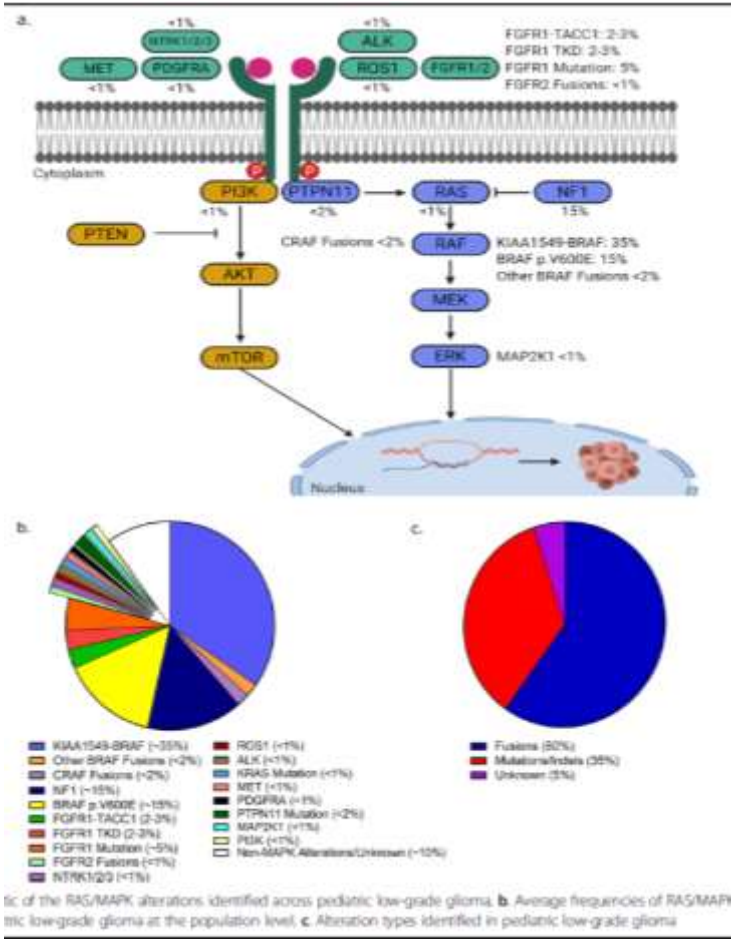
Acta Neuropathol (2011) 121:397–405
DOI 10.1007/s00401-011-0802-6
ORIGINAL PAPER

Analysis of *BRAF* V600E mutation in 1,320 nervous system tumors

BRAF Mutations And Fusion According To Topographic And Histologic Variety

- BRAF Mutations activating MAPK (mitogen-activated protein kinase) pathway represent the most frequent genetic alteration in low-grade glioma
- KIAA1549–BRAF gene-fusions are common in cerebellar pilocytic astrocytomas, but not in cerebral cortex, while BRAFV600E mutations are more frequent in pleomorphic xantoastrocytoma, gangliogliomas and in a small subset of pylocitic astrocytoma

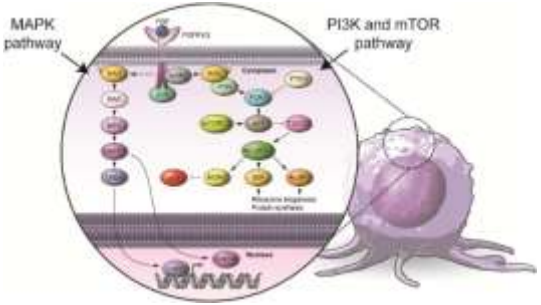




Biology and surgery in LGG

- The last decade has produced unparalleled insights into the underlying biology of pLGG
- we now know that **the majority of pLGG are driven by a single genetic event resulting in up-regulation of the RAS/MAPK pathway**
- Due to its predilection for arising in **highly circumscribed histologies** (pilocytic astrocytoma) **and in surgically amenable locations (cerebellum)** tumors with a KIAA1549-BRAF fusion **are often amendable to complete surgical resection and have excellent overall survival and rarely progress**

- **Kinase inhibitors** have been successful in the therapy of malignant melanoma, including BRAF, MEK and ERK inhibitors targeting the MAPK pathway; PI3K, AKT or mTOR inhibitors targeting the PI3K pathway and some newer FGFR inhibitors are in development
- **It is essential to understand the biology of these oncogenic pathways**, as there are risks of **paradoxical signaling activation via feedback loops** with targeting of some nodes
- Preclinical studies of BRAF V600E-mutated pLGG cell lines treated with a **type 1 BRAF inhibitor** are effective in switching off MAPK signaling, while treatment with the same BRAF inhibitor in **BRAF KIAA1549-rearranged cells can cause paradoxical pathway activation** and increase cell growth



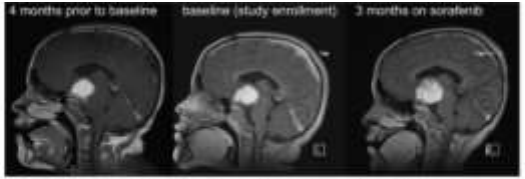


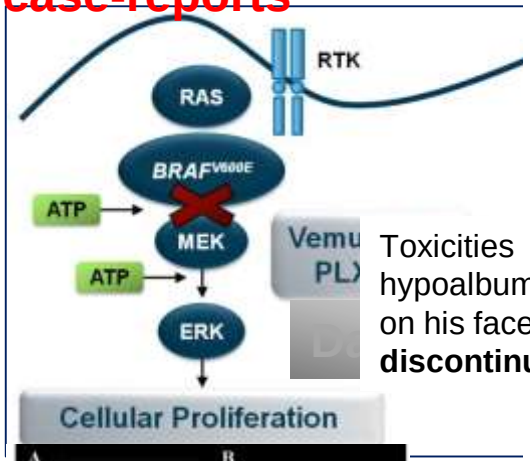
Fig. 2. Sequential gadolinium contrast-enhanced MRI studies showing rapid, accelerated tumor growth of an optic pathway glioma on sorafenib (patient 8). Imaging was obtained 4 months prior to sorafenib, at study enrollment (baseline), and after 3 months on study (sorafenib treatment week 12) showing a large contrast-enhancing suprasellar mass, stable in size prior to sorafenib and significant progression upon treatment.

Neuro-Oncology 16(10), 1408–1416, 2014

Summary of ongoing trials in newly diagnosed/recurrent pLGG with MAPK pathway inhibitors.

Trial	Study start	Population	Intervention
Newly diagnosed disease			
Tadpole G (NCT02684058) [16,68]	2017	Newly diagnosed *BRAF* V600E-mutant pLGG	Randomised phase 2 - dabrafenib (BRAFi) + trametinib (MEK1/2i) versus carboplatin and vincristine
COG ACNS1831 (NCT03871257) [106]	2019	Untreated *NF1*-associated pLGG	Phase 3 - carboplatin + vincristine versus selumetinib (MEK1/2i)
COG ACNS1833 (NCT04166409) [107]	2020	Untreated non-*NF1* and non-*BRAF* V600E mutant pLGG	Phase 3 - carboplatin + vincristine versus selumetinib (MEK1/2i)
LOGGIC (In Preparation)		Newly diagnosed non-*NF1* mutant pLGG patients who need further treatment after initial operation	Phase 3 - MAPK inhibitor versus physician's choice
MEKTRIC (NCT05180825) [108]	2022	Newly diagnosed non-*NF1*, *BRAF* wild-type pLGGs	Randomised phase 2 - trametinib(MEK1/2i) versus weekly vinblastine
Recurrent or Progressive disease			
PNOC026/DAY101-001/FIREFLY-1 (NCT04775485) [109]	2021	Recurrent or progressive *BRAF*-mutant pLGG	Phase 2 - Tovorafenib [DAY101] (Pan-RAFi)
PBTC-055 (NCT04201457) [71]	2019	Recurrent or progressive *BRAF*-mutant pLGG or pHGG	Phase 1/2 - dabrafenib (BRAFi), trametinib (MEK1/2), hydroxychloroquine
COG ACNS1931 (NCT04576117) [110]	2021	Recurrent or Progressive pLGG	Phase 3 - selumetinib versus selumetinib + vinblastine (MEK1/2i)
Paediatric MATCH (NCT03155620) [111]	2017	Ras/Raf pathway activated tumours	Phase 1/2 - ulixertinib (ERK1/2i)
Phase I/II MEK162 Ras/Raf Pathway Activated Tumours (NCT02285439) [112]	2016	Ras/Raf pathway activated tumours	Phase 1/2 - MEK162
SJ901 (NCT04923126) [113]	2021	Recurrent or progressive pLGG	Phase 1/2 - mirdametinib (MEK1/2i)
PNOC021 (NCT04485559) [114]	2020	Recurrent or Progressive pLGG	Phase 1 - trametinib (MEK1/2i) and everolimus

Anti-BRAF case-reports



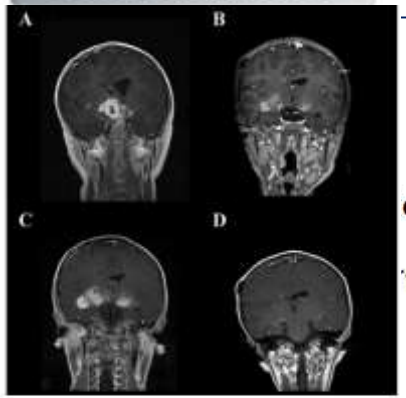
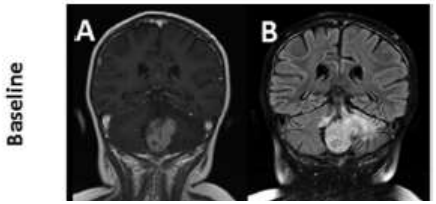


Fig. 1. A 23 month old with a BRAF V600E mutated pilomyxoid astrocytoma treated with vinblastine and vemurafenib. MRI imaging (A) prior to initiation of treatment; (B) 5 months after starting therapy; (C) following interruption of therapy for 2 weeks; (D) 4 weeks after re-initiation of therapy.

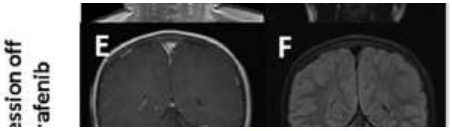


Pediatr Blood Cancer 2016;63:541–543

REPORT
a Refractory Brainstem Ganglioglioma
nurafenib

re Mazewski, MD,[1] Robert Craig Castellino, MD,[1] Barumashish Brahma, MD,[4] Lauren Fogelgren, PA,[5] lacDonald, MD[1]

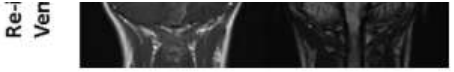
Toxicities included: Grade I hypocalcemia, hypertriglyceridemia, hypoalbuminemia, and pruritus, and Grade II maculopapular rash on his face and chest. All of the side-effects **resolved with** drug **discontinuation** and **recurred to the same degree** with re-administration



Pediatr Blood Cancer 2014;61:2099–2100

BRIEF REPORT
oma Treated Successfully With Vemurafenib

eman, MD,[2] Daniel Guillaume, MD,[3] and Christopher Moertel, MD[1]



Human Pathology (2016) 58, 79–89

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

In this issue

BRAF inhibitor therapy–associated melanocytic lesions lack the *BRAF* V600E mutation and show increased levels of cyclin D1 expression☆,☆☆

during fewer days of targeted therapy. Paradoxical activation of the MAPK pathway in *BRAF*
melanocytes may account for ~15% to 21% of patients developing a second new primary melanor
within a year of starting BRAFi therapy; thus, close clinical surveillance is warranted.

Received: 22 October 2018 | Revised: 17 January 2019 | Accepted: 6 February 2019

DOI: 10.1002/pbc.27682

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer aspho

Cutaneous reactions to targeted therapies in children with CNS tumors: A cross-sectional study

Hannah Song[1] | Connie S. Zhong[2] | Mark W. Kieran[3] | Susan N. Chi[3] | Karen D. Wright[3] | Jennifer T. Huang[2]

TABLE 2 Patient characteristics and skin findings

Targeted therapy	Folliculitis n (%)	Xerosis/eczema n (%)	Photosensitivity n (%)	Hand-foot syndrome n (%)	Eruptive nevi n (%)	Nail changes n (%)	Paronychia n (%)	Alopecia n (%)	Other skin findings n (%)	Grade of reactions median (range)
Dabrafenib (n = 6)	6 (100)	3 (50)	2 (33)	5 (83.3)	1 (16.7)	1 (16.7)	0 (0)	0 (0)	Diffuse dusky erythema multiforme-like reaction 1 (16.7)	1.5 (1–3)
Trametinib (n = 11)	9 (81.8)	8 (72.7)	2 (18.1)	0 (0)	0 (0)	1 (9.1)	4 (36.3)	2 (18.1)	Lightening hair color 1 (9.1) Angular cheilitis 3 (27.3) DRESS-like reaction 1 (9.1) Psoriasiform eruption of scalp 1 (9.1)	2 (1–4)

cancers

Article

Dyslipidemia in Children Treated with a BRAF Inhibitor for Low-Grade Gliomas: A New Side Effect?

Marco Crocco [1,2,*], Antonio Verrico [1], Claudia Milanaccio [1], Gianluca Piccolo [1,2], Patrizia De Marco [3], Gabriele Gaggero [4], Valentina Iurilli [5], Sonia Di Profio [6], Federica Malerba [2], Marta Panciroli [2], Paolo Giordano [2], Maria Grazia Calevo [7], Emilio Casalini [2,8], Natascia Di Iorgi [2,8] and Maria Luisa Garrè [1]

Received: 29 June 2022 | Revised: 12 November 2022 | Accepted: 4 December 2022

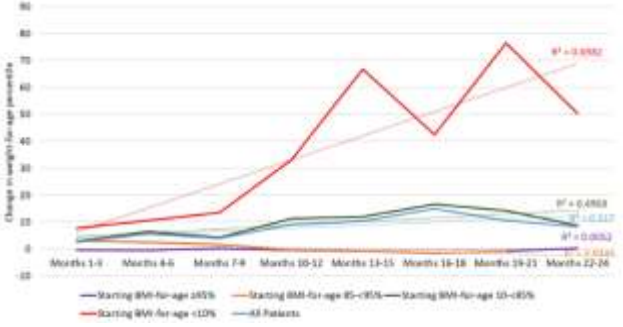
DOI: 10.1002/pbc.30182

RESEARCH ARTICLE

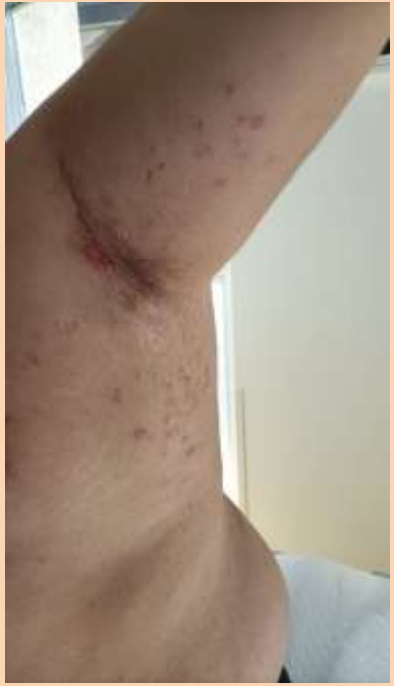
Pediatric Blood & Cancer aspho WILEY

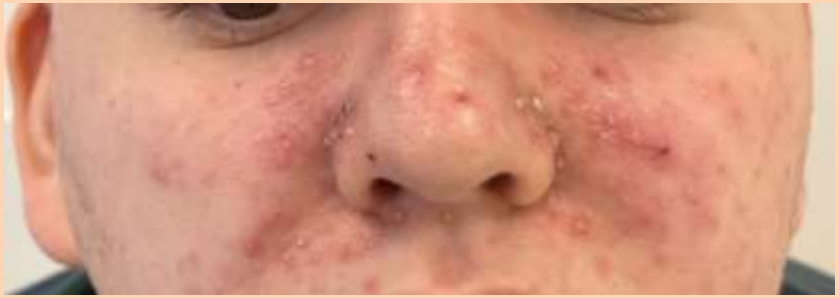
The incidence and characterization of weight gain associated with MEK inhibitors in pediatric patients

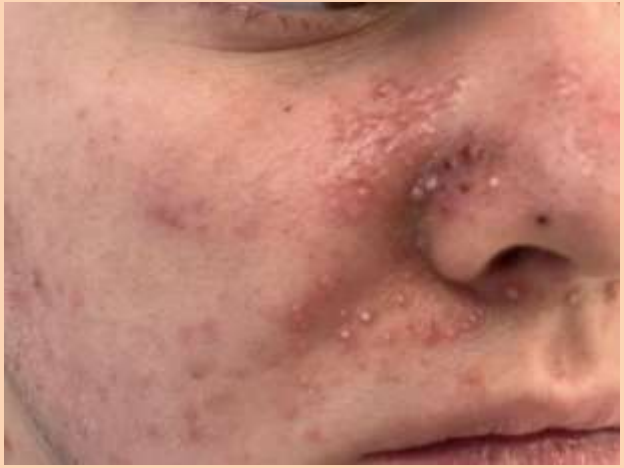
Cassandra Rush[1] | Ashley Sabus[1] | Zanette Kanani Bradley[1] | Maxwell Herbert[1] | Molly Hemenway[2]

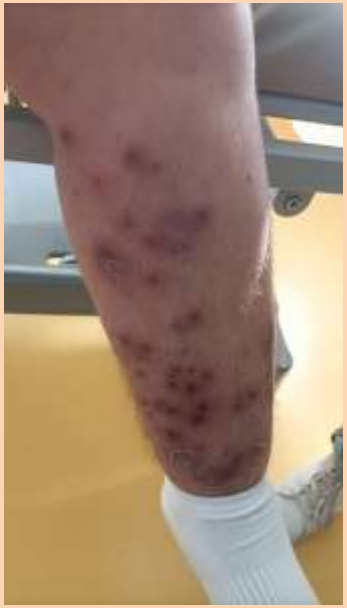


Unpredictable toxicity (anti-RAF, anti-MEK)





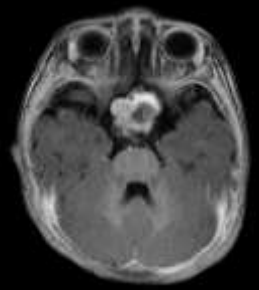




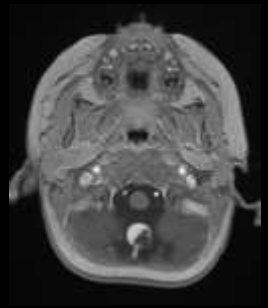
Anti-BRAF Trials Ongoing

- At present, the **optimal duration of therapy is unknown** with response persisting in some patients after drug discontinuation whilst others experience tumour regrowth or progression
- The current pragmatic approach is **to treat clinical benefit until loss of clinical benefit or for a certain specific duration** (typically approximately 2 years) and then stopping therapy
- Additional functional end-points e.g. visual acuity, quality-of-life, motor function and neuro-psychological function are important so that these agents benefit children with paediatric low-grade gliomas and should be included in initial designs and agreed upon prospectively with regulators
- **Long-term follow-up of patients receiving these inhibitors is crucial** in view of their prolonged administration and the involvement of the pathway in normal development
- *European Journal of Cancer 177 (2022) 120e142*

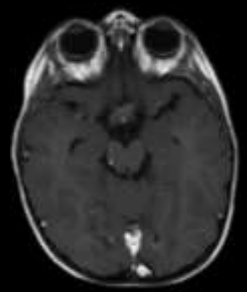
Dabrafenib: approved compassionate use at relapse, pylocitic astro with BRAFV600E mut



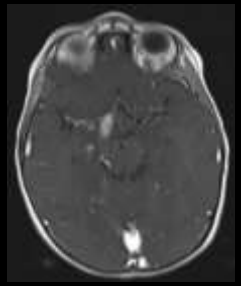
At diagnosis, age 8 months



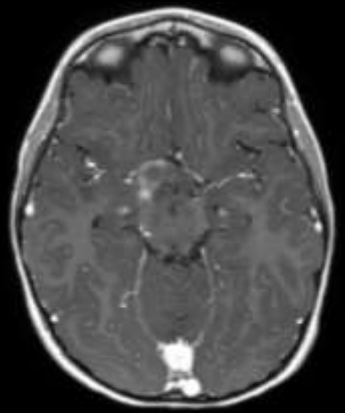
A second lesion after 2 months, biopsy



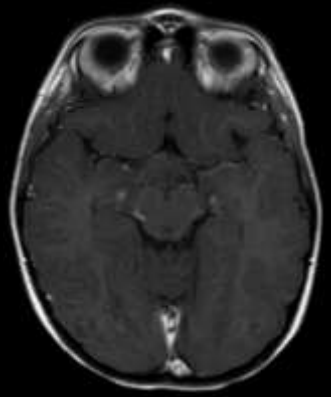
at the end of first line treatment



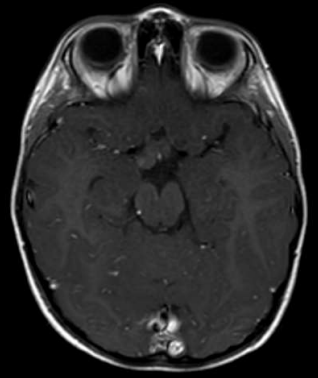
local progression, two years after diagnosis



Further PD, after 8 months, dabrafenib required, approved and begun

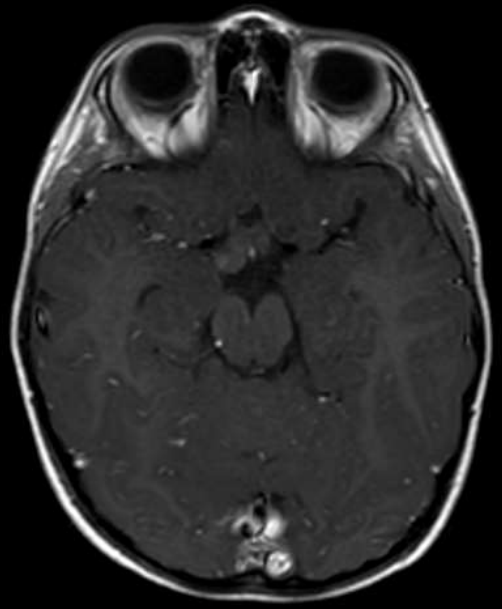


after 3 months of dabrafenib

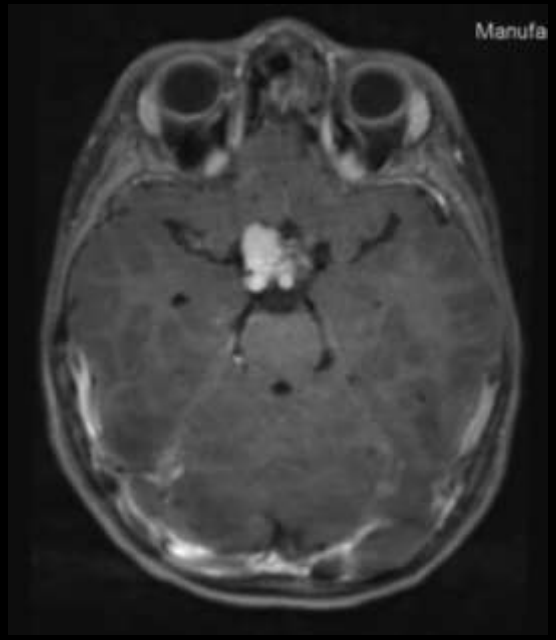


after 1 year treatment stop (cutaneous reaction)

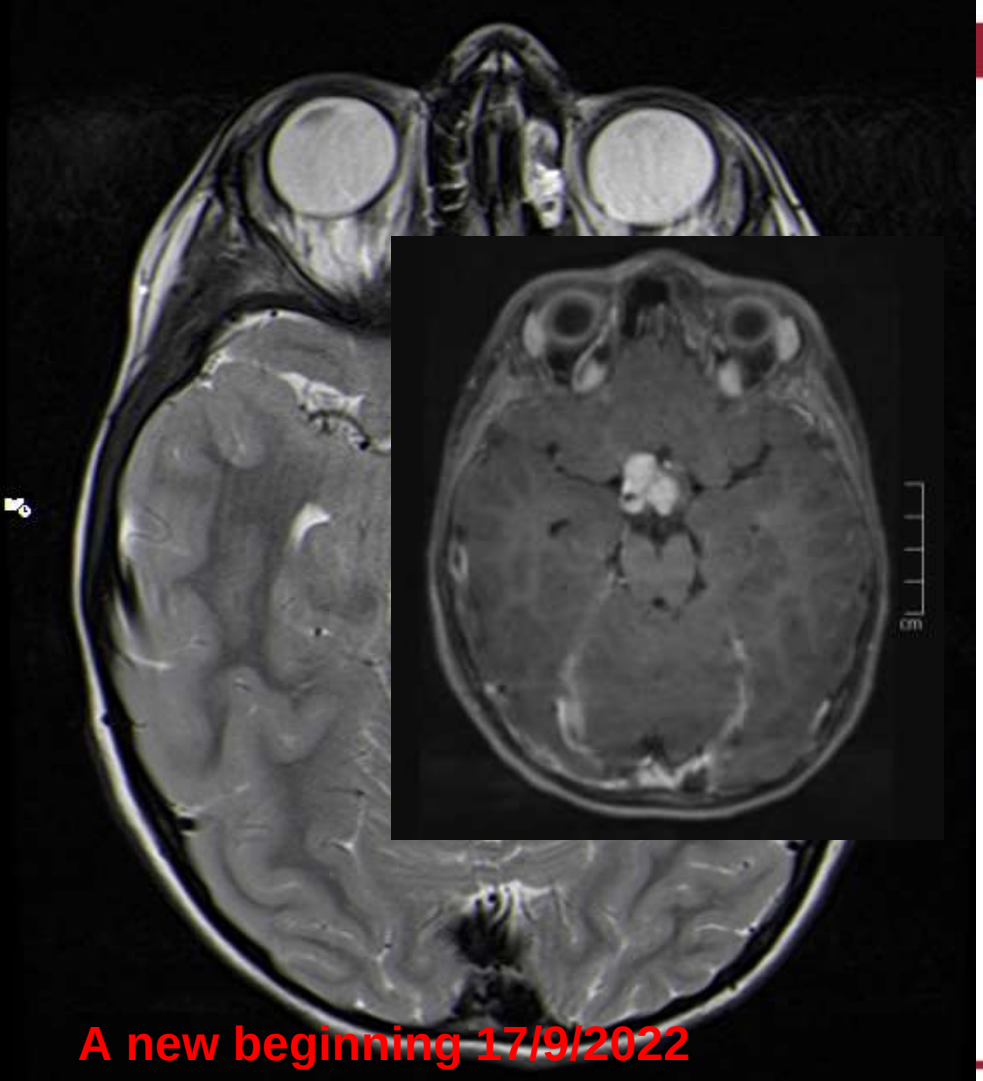
Slow progression after stop



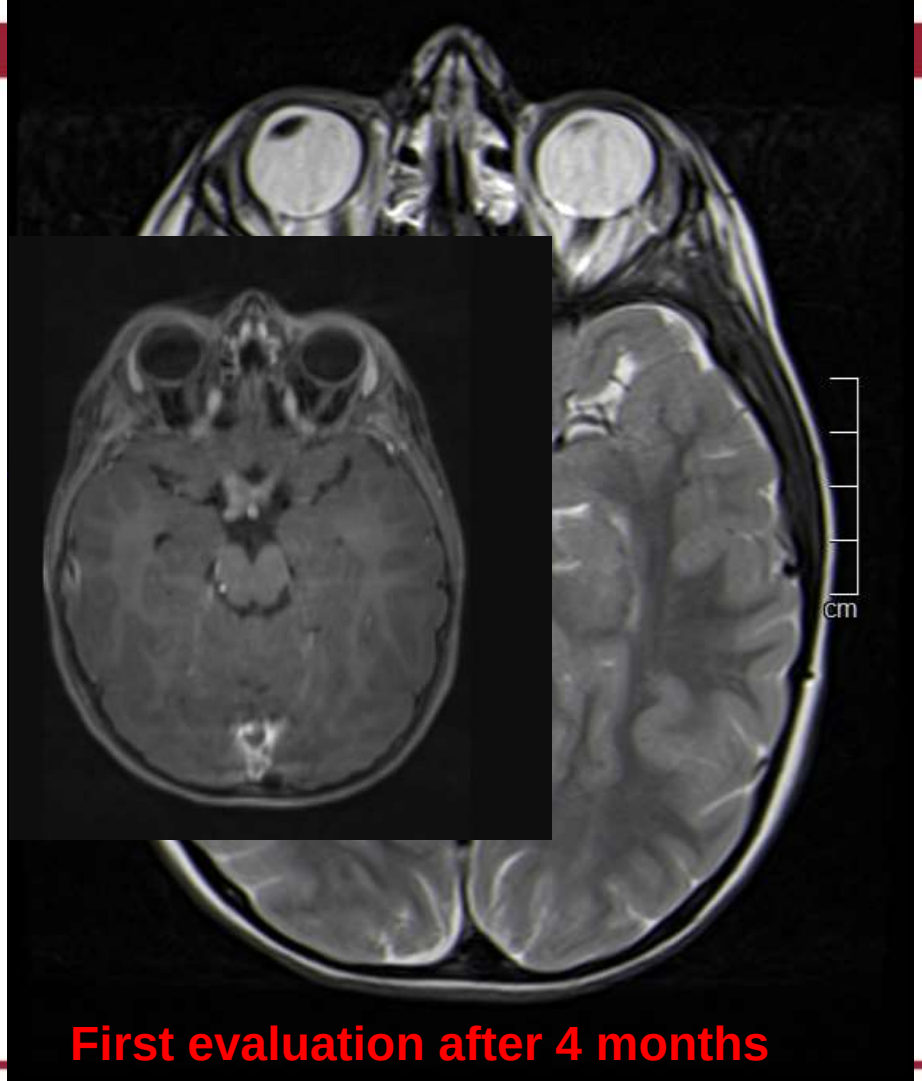
At treatment end, Oct 2020



At overt relapse, July 2022
further compassionate request of the combination



A new beginning 17/9/2022



First evaluation after 4 months

Outcomes of BRAF V600E Pediatric Gliomas Treated With Targeted BRAF Inhibition

Liana Nobre, MD[1]; Michal Zapotocky, MD, PhD[1,2]; Vijay Ramaswamy, MD, PhD[1,3-5]; Scott Ryall, BSc[1]; Julie Bennett, MD[1]; Daniel Alderete, MD[6]; Julia Balaguer Guil, MD, PhD[7]; Lorena Banani, MD[8]; Ute Bartels, MD[1]; Abhishek Bavle, MBBS[9]; Miriam Bornhorst, MD[9]; Daniel R. Boue, MD, PhD[10]; Adela Canete, MD, PhD[7]; Murali Chintagumpala, MD[11]; Scott L. Cohen, DO, MPH[12]; Ofelia Cruz, MD, PhD[13]; Sonika Dahiya, MD[14]; Peter Dirks, MD, PhD[4,15]; Ira J. Dunkel, MD[16]; David Eisenstat, MD[17]; Cecile Faure Conter, MD[18]; Elizabeth Finch, MD[19]; Jonathan L. Finlay, MD[19]; Didier Frappaz, MD[20]; Maria Luisa Garre, MD[20]; Karen Gauvain, MD[21]; Anne Grete Bechensteen, MD, PhD[22]; Jordan R. Hansford, MSc, MBBS[23]; Inga Harting, MD[24]; Peter Hauser, MD, PhD[25]; Lili-Naz Hazrati, MD, PhD[26]; Annie Huang, MD, PhD[1,4]; Sarah G. Injac, MD, PhD[11]; Valentina Iulili, RPh[20]; Matthias Karajannis, MS, MD[16]; Guncharanjeet Kaur, MD[16]; Martin Kyncl, MD, PhD[2]; Lenka Krskova, PhD[2]; Normand Laperriere, MD[3]; Valerie Larouche, MD[28]; Alvaro Lassaletta, MD[27]; Sarah Leary, MD[29]; Frank Lin, MD[11]; Samantha Mascelli, PhD[20]; Tara McKeown, MN, NP[1]; Till Milde, MD[30]; Andres Morales La Madrid, MD[13]; Giovanni Morana, MD, PhD[20]; Helena Morse, MD, PhD[19]; Naureen Mushtaq, MBBS[19]; Diana S. Osorio, MD, MPH[10]; Roger Packer, MD[9]; Zdenek Pavelka, MD[31]; Eduardo Quiroga-Cantero, MD[32]; James Rutka, MD, PhD[4,15]; Magnus Sabel, MD, PhD[33]; Duarte Salgado, MD[34]; Palma Solano, MD[32]; Jaroslav Sterba, PhD[31]; Jack Su, MS, MD[12]; David Sumerauer, MD, PhD[2]; Michael D. Taylor, MD, PhD[1,4,15,23,35,36]; Helen Toledano, MD[27]; Derek S. Tsang, MSc, MD[1]; Mariana Valente Fernandes, MD[34]; Frank van Landeghem, MD[37]; Cornelis M. van Tilburg, MD[23]; Bev Wilson, MD[12]; Olaf Witt, MD[23]; Josef Zamecnik, MD, PhD[2]; Eric Bouffet, MD[1]; Cynthia Hawkins, MD, PhD[4,29,36]; and Uri Tabori, MD[1,4]

Relevance

High response rates to targeted inhibition (partial or complete response, 53%; minor response, 27%) were observed, with PFS at 3 years of 49.6% for BRAF V600E–mutated pediatric low-grade gliomas. This was associated with favorable short-term outcomes. Future prospective clinical trials are required to address long-term management strategies and outcomes in these patients.

JCO Precis Oncol 4:561-571. © 2020 by American Society of Clinical Oncology

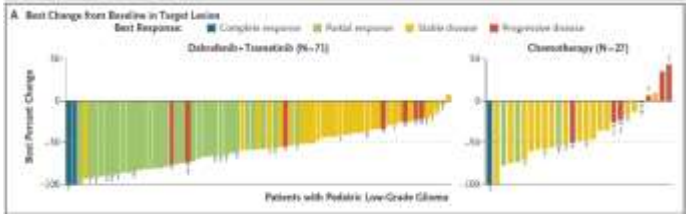
- Objective response was observed in 80% of patients with low-grade gliomas, with progression-free survival (PFS) superior to that seen with chemotherapy
- These responses occurred rapidly (4 months) and were sustained if receiving treatment
- **Upon stopping, rapid progression occurred**.
- Patients who were re-challenged with BRAF V600E inhibition responded again with tumor reduction back to their baseline
- In contrast, BRAF V600E **high-grade gliomas** experienced progression, **even when initial tumor shrinkage was observed, and patient outcomes were poor**

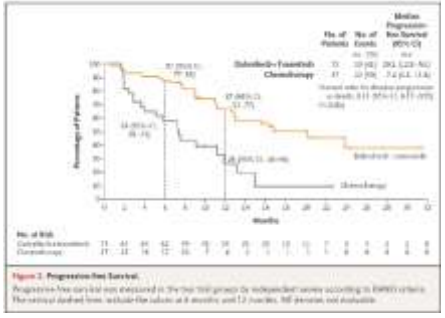
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabrafenib plus Trametinib in Pediatric Glioma with *BRAF* V600 Mutations

Eric Bouffet, M.D., Jordan R. Hansford, M.B., B.S., Maria Luisa Garrè, M.D., Junichi Hara, M.D., Ph.D., Ashley Plant-Fox, M.D., Isabelle Aerts, M.D., Franco Locatelli, M.D., Ph.D., Jasper van der Lugt, M.D., Ph.D., Ludmila Papusha, M.D., Ph.D., Felix Sahm, M.D., Ph.D., Uri Tabori, M.D., Kenneth J. Cohen, M.D., Roger J. Packer, M.D., Olaf Witt, M.D., Larissa Sandalic, M.S., Ana Bento Pereira da Silva, Ph.D., Mark Russo, M.D., Ph.D., and Darren R. Hargrave, M.B., Ch.B., M.D.





Ojemda® approved in the European Union the first targeted therapy in relapsed or refractory pediatric low-grade glioma regardless of BRAF alteration

- New treatment option for rare, life-altering pediatric brain tumors
- Less than 10% of new medicine approvals over the past five years have focused on pe diseases; Ojemda® (tovorafenib) represents a rare achievement that reinforces the urg close the innovation and investment gaps in pediatric therapeutics
- Approval is based on pivotal Phase II FIREFLY-1 data demonstrating meaningful and du responses

PARIS, FRANCE, 22 April 2026 – Ipsen (Euronext: IPN; ADR: IPSEY) today announced that th

nature medicine

Article

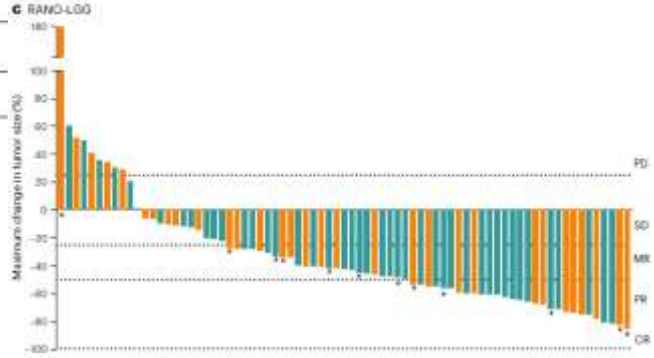
https://doi.org/10.1038/s41591-023-02668-y

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

Received: 15 September 2023

Accepted: 25 October 2023

paper



From the beginning of the story to the take home message

DISCOVERIES

- First observations on patients with cancer predisposition syndrome (i.e. mTOR inhibitors for giant-cell subependymoma)(2002)
- To identification of recurrent RAS/MAPK alterations in low-grade glioma (2008)
- Thereafter BRAF and FGFR discovery in the same tumors (2013-2015)
- Rare alterations including NTRK fusions, ALK rearrangements, recurrent histone mutantions in HGG. Hypermutation in MMRD (2016-2019)

DOUBTS

- **DURABILITY OF RESPONSE**
- **LONG-TERM TOXICITIES (growth delays, bone health..)**
- **FUNCTIONAL OUTCOME i.e vision, school/work performance, endocrine**
- **Re-challenge if progression after treatment suspension**
  - See also Neuro-Oncology Advances Bennet J, Bouffet E, 2026

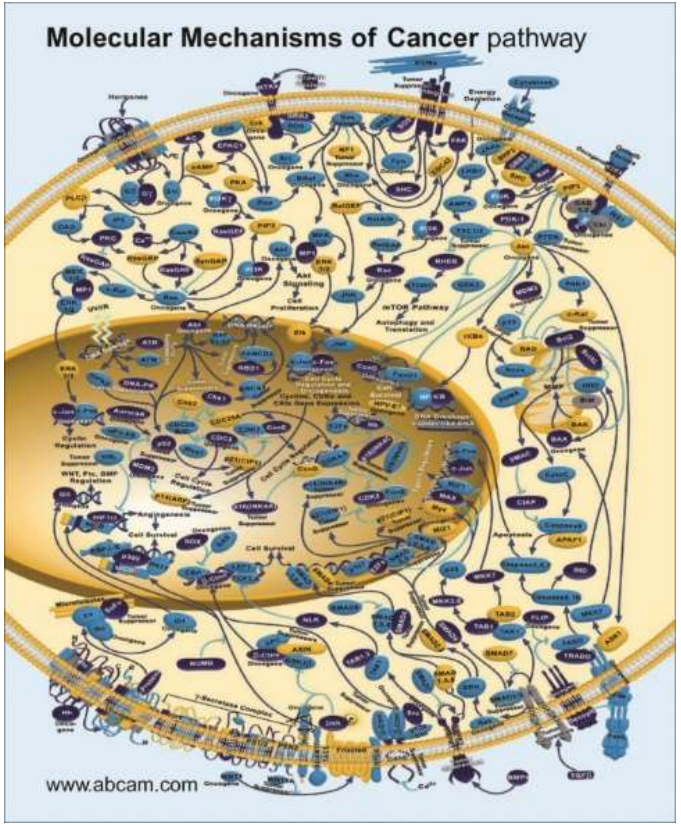
    From blunt tools to bullseyes: The impact of targeted therapy in pediatric neuro-oncology.

In order to reach this prediction for precision medicine, we as physicians

need to use the science that is available,

encourage and participate in basic and clinical research,

and **ask ourselves whether the therapies that we are using are effective or ineffective and in need of a new treatment paradigm**



What we would like for our patients at best ?

A treatment like a perfect tailor-made dress sewed by expert hands of an artist

Giovanni Battista Moroni ca 1522 - 1578/1579

Precision medicine needs to **simultaneously increase and decrease** the expectations of patients and physicians.
We cannot promise what we cannot deliver now.

We need to simultaneously **curb the enthusiasm** about what precision medicine can produce at this time, while increasing the enthusiasm over what precision medicine will eventually deliver in the future.

Although these goals are aspired to, **there is an emerging trend for fit for filing (FFF)** trials to move new and novel commercial products to market faster by incorporating all needed evidence for administrative approval from government agencies around the world

Grazie per l’attenzione!

maura.massimino@istitutotumori.mi.it

nature medicine

Article https://doi.org/10.1038/s41591-026-04354-1

Targeted therapies plus radiotherapy for diffuse intrinsic pontine glioma: the randomized phase 2 BIOMEDE trial

The trial was ended for futility of the primary endpoint following the recommendations of the independent data monitoring committee: **OS from biopsy was not different from the control cohort** (median OS = 10.8 months (95% confdence interval (CI): 9.5−13.0)) in any of the three arms (median OS = 9.7 months (95% CI: 7.8−14.6) for erlotinib; 9.9 months (95% CI: 8.8−11.2) for dasatinib; and 11.9 months (95% CI: 10.7−14.2) for everolimus).

«eterogenesi dei fini»: un trial nato per identificare una terapia target e migliorare la prognosi, fallisce.

Tuttavia va su un giornale con IF 50 descrivendo un fattore prognostico (noto?!):

TP53 mutations, frequently linked to multiple structural chromosomal aberrations, were the strongest predictor for poor survival in multivariate analysis (hazard ratio = 2.8 (95% CI: 1.9−4.2), $P < 0.0001$)