20th National Congress of Cancer
April 19 - 23, 2013 • Susesi Hotel - ANTALYA
Turkish Pediatric Oncology Group Society
Turkish Medical Oncology Society
Turkish Radiation Oncology Society

Chemotherapy of childhood high-grade gliomas

Maura Massimino

Pediatric Unit

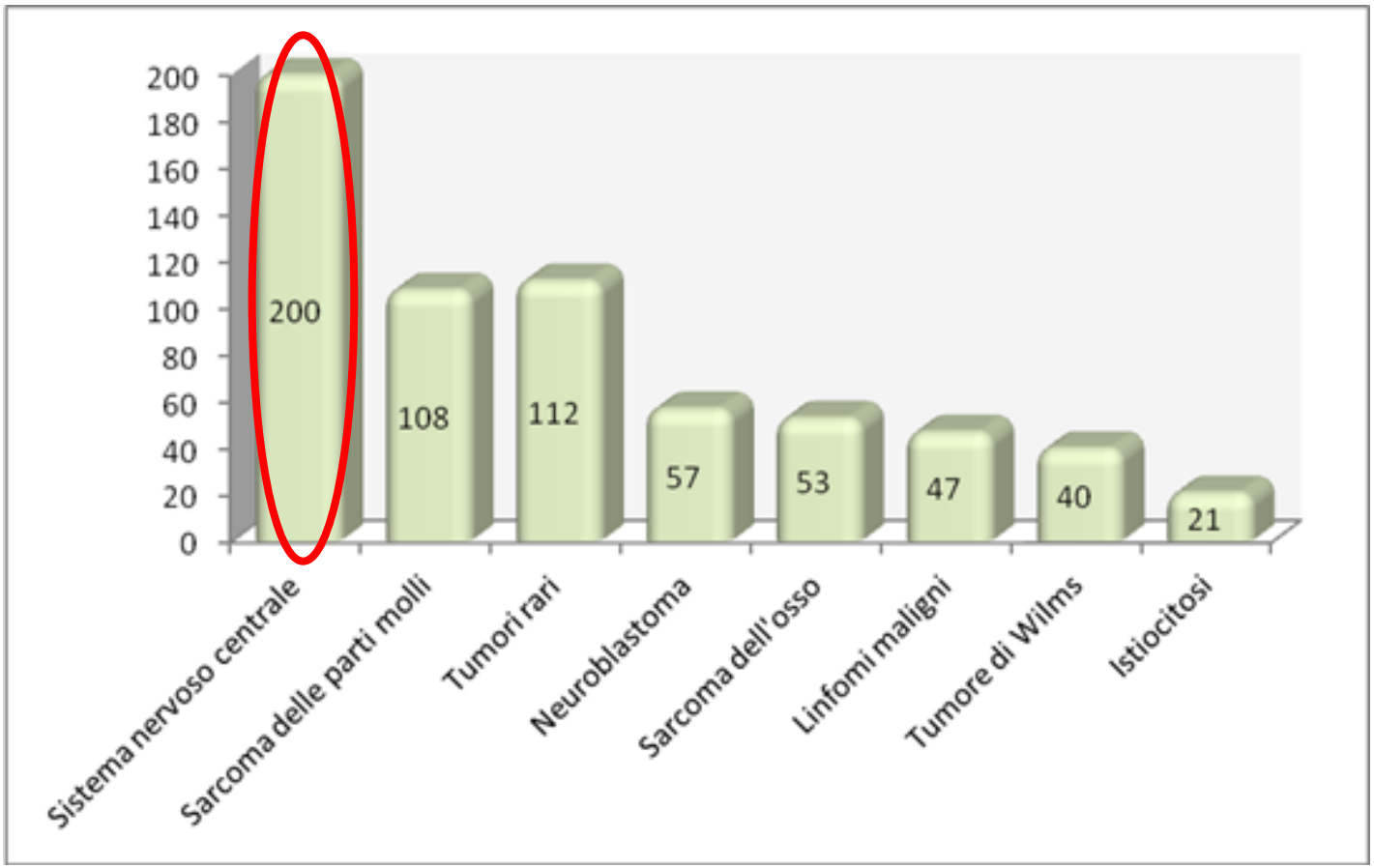
Fondazione IRCCS

Istituto Nazionale dei Tumori

Milano Italy

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Fond IRCCS, INT Milano
Cases treated between 2009 and 2011



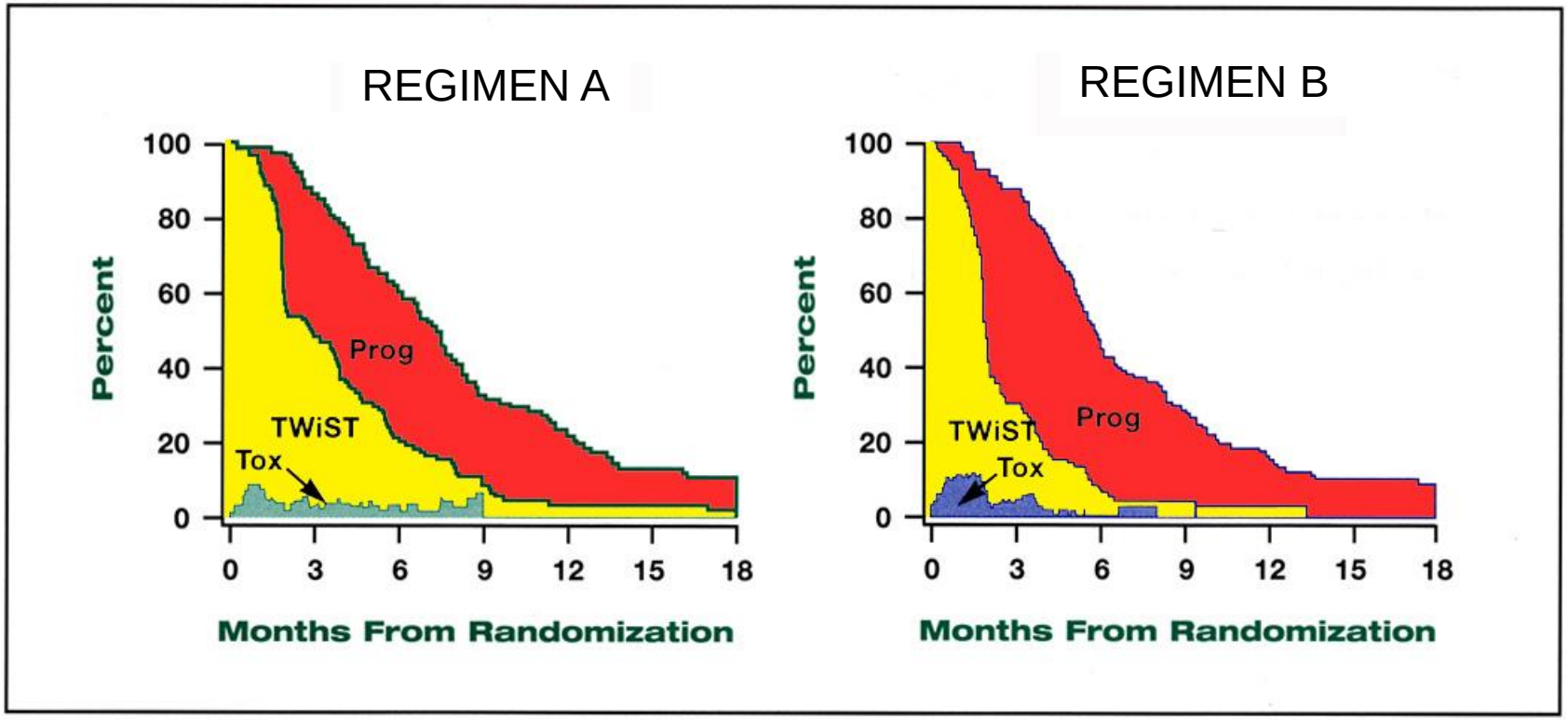
***Neoplasie rare: tumori germinali, epatoblastoma, carcinoma rinofaringe, ca. tiroide, melanoma, retinoblastoma**

TWIST: time without symptoms

Measuring the success of any therapy means measuring *time left to real life* after diagnosis

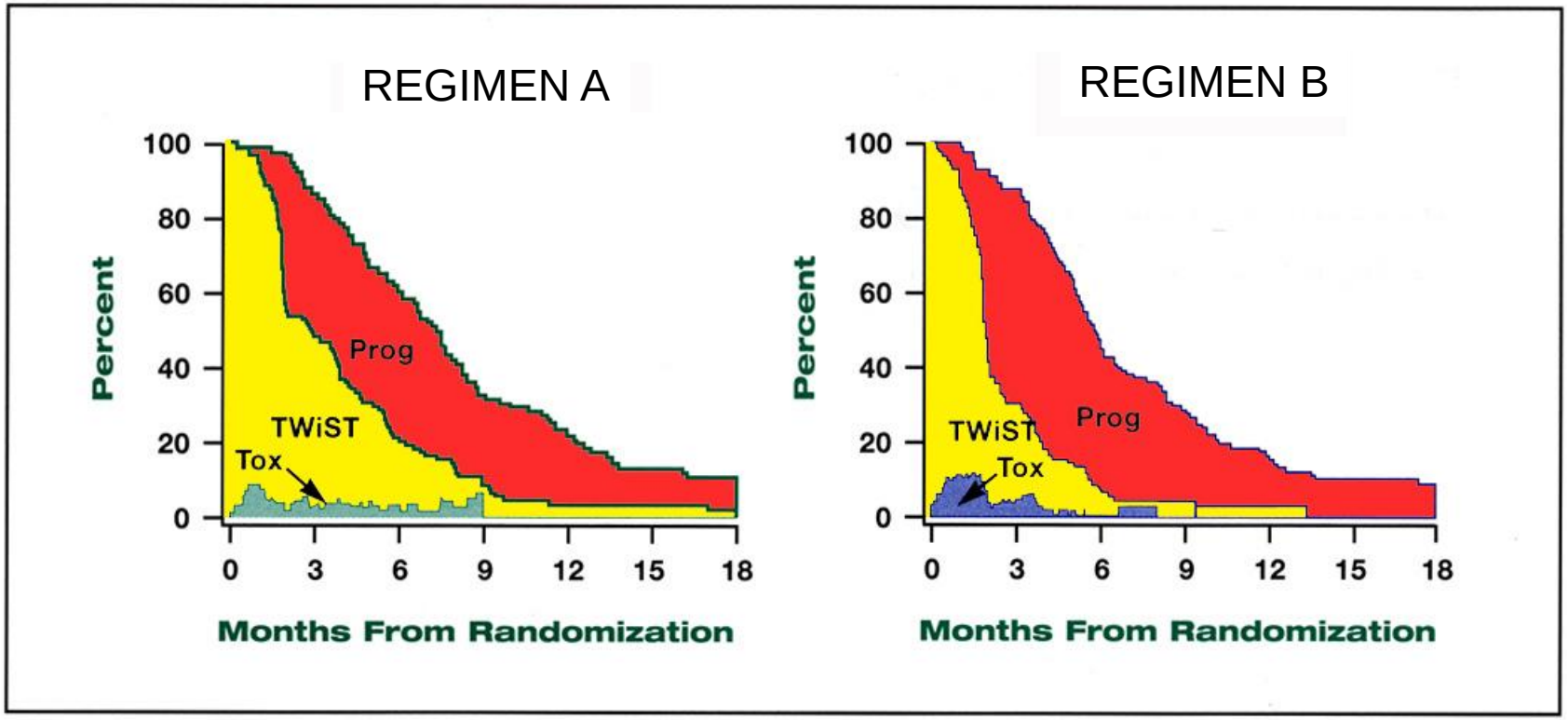
- **Without symptoms (of tumor)**
- **Without toxic events**
- **Without progression**

END POINTS: Response, EFS, OS, TOX, TWIST!!!!



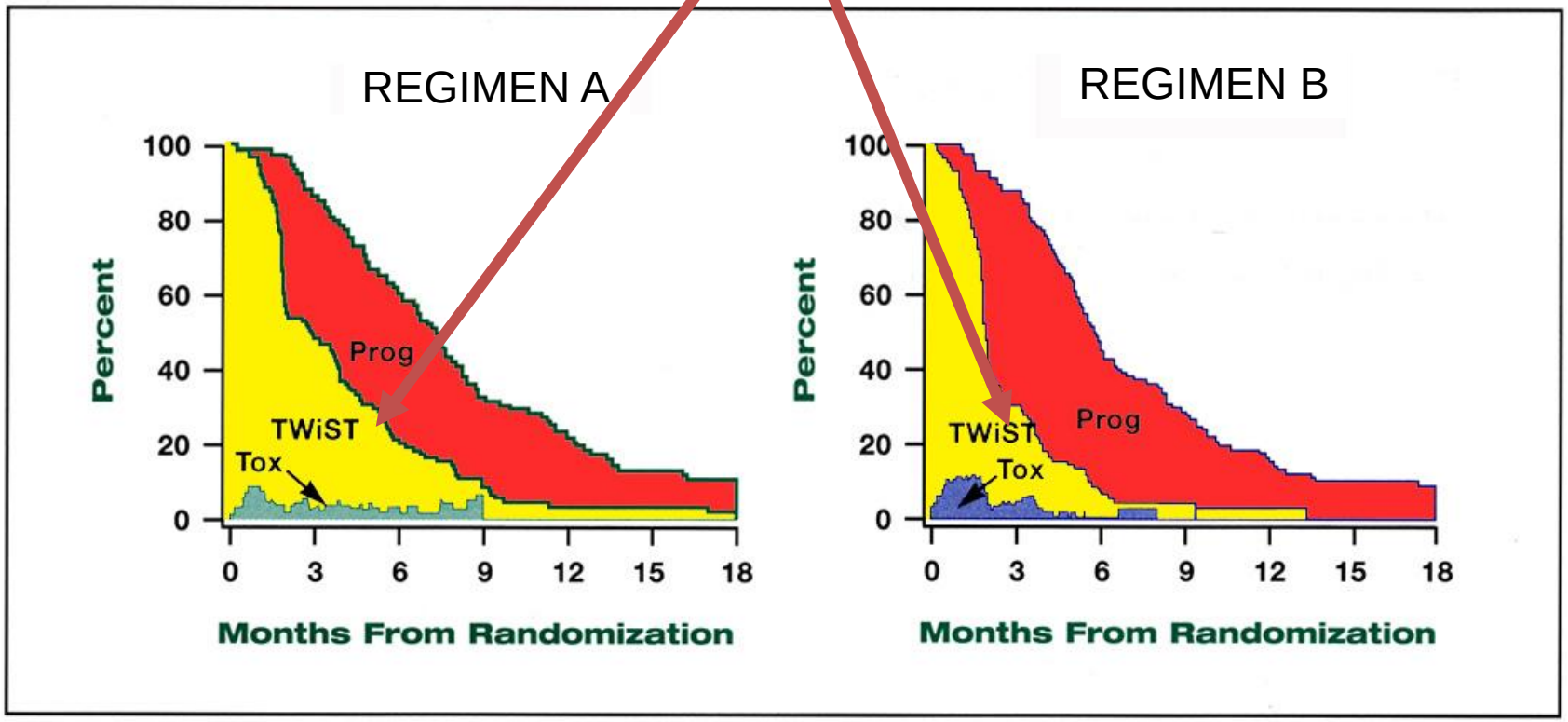
Q-TWiST analysis, partitioned survival—glioblastoma multiforme

END POINTS: Response, EFS, OS, TOX, TWIST!!!!



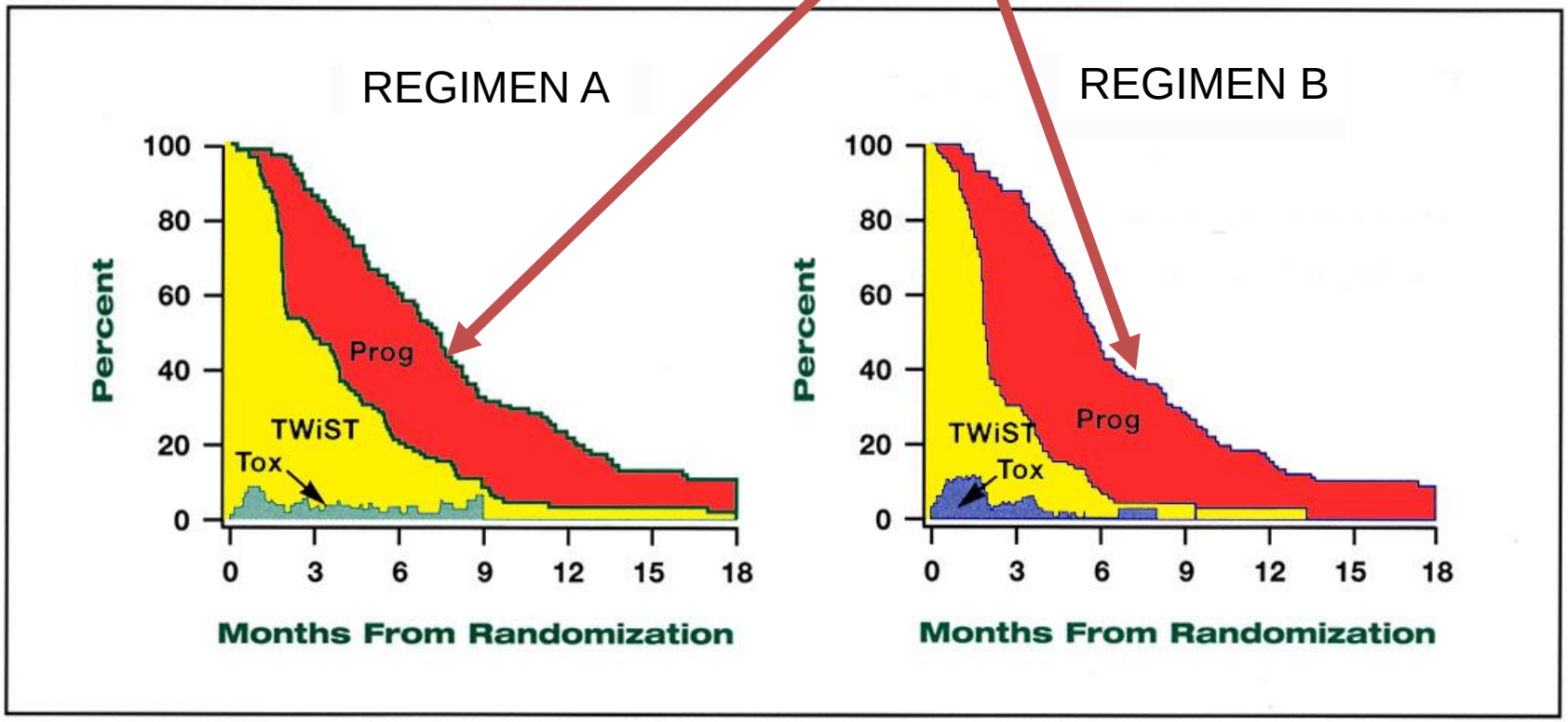
Q-TWiST analysis, partitioned survival—glioblastoma multiforme

END POINTS: Response, EFS, OS, TOX, TWIST!!!!



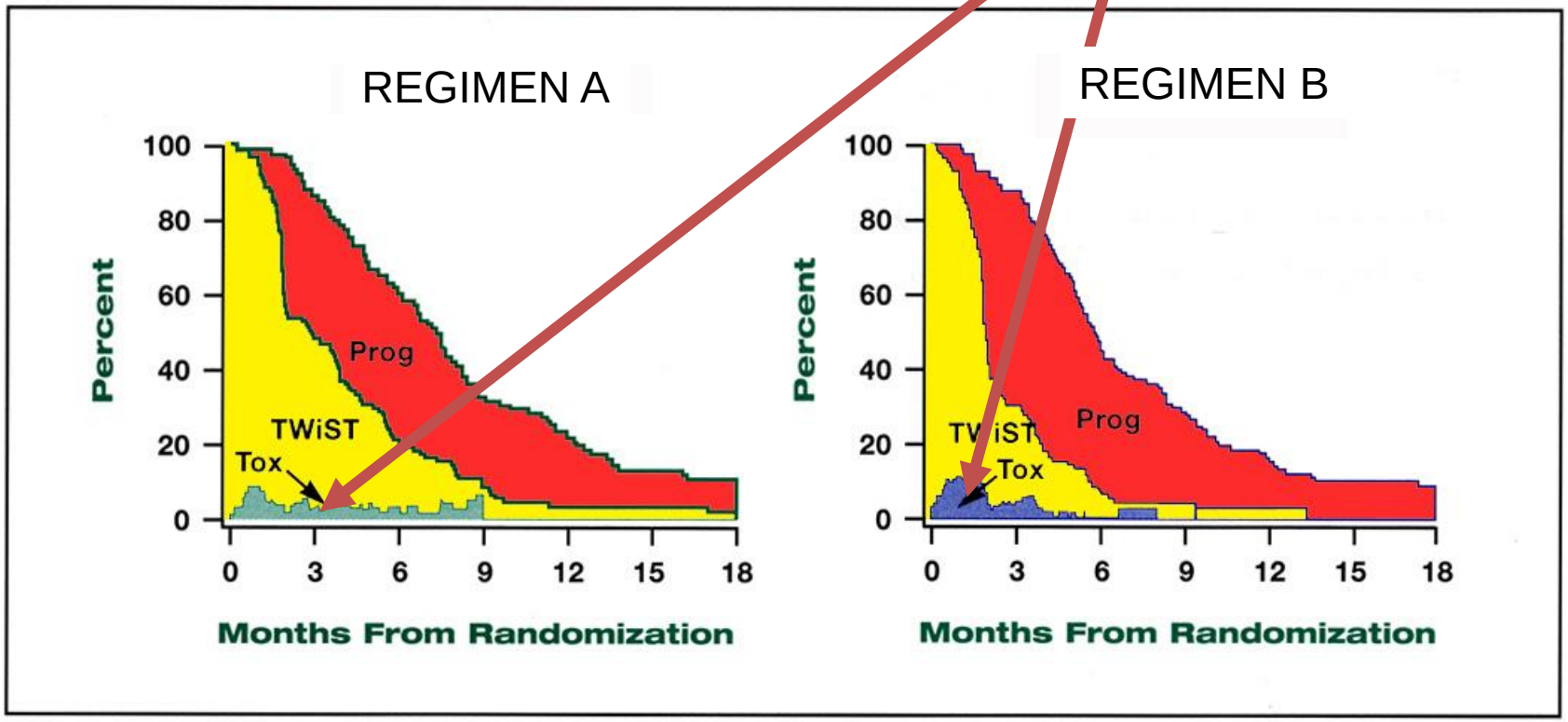
Q-TWiST analysis, partitioned survival—glioblastoma multiforme

END POINTS: Response, EFS, OS, TOX, TWIST!!!!



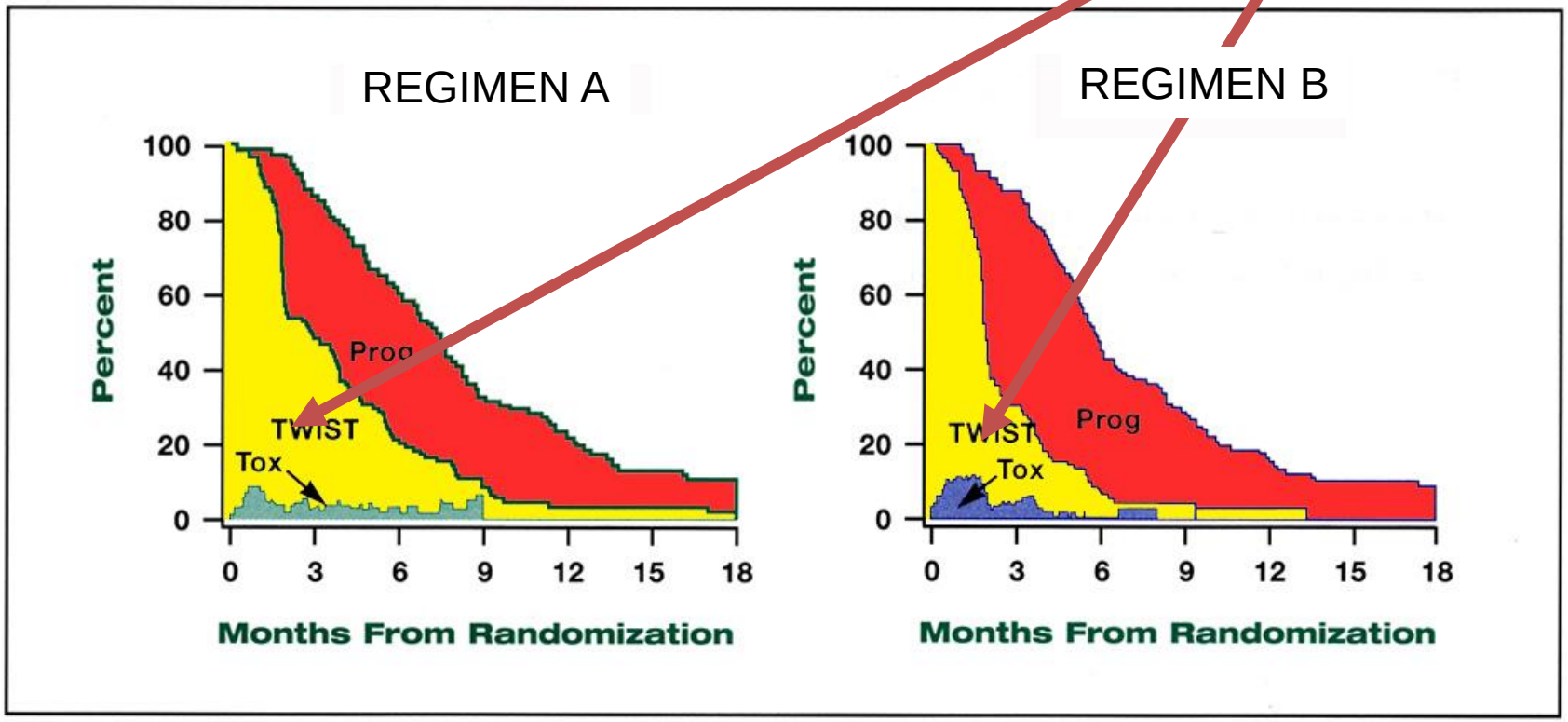
Q-TWiST analysis, partitioned survival—glioblastoma multiforme

END POINTS: Response, EFS, OS, TOX, TWIST!!!!



Q-TWiST analysis, partitioned survival—glioblastoma multiforme

END POINTS: Response, EFS, OS, TOX, TWIST!!!!



Q-TWiST analysis, partitioned survival—glioblastoma multiforme

What we would like for our patients at best ?

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

Giovanni Battista Moroni ca 1522 - 1578/1579

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**
- **One or more drugs “tumor-oriented”, therefore with minimal normal tissues damage**

What about gliomas?

Even histological diagnosis is not so easy

- **Classifying glioma requires judgment, experience, meticulous adherence to established nosological guidelines**

  Pollack I, Neuro-oncology 2003

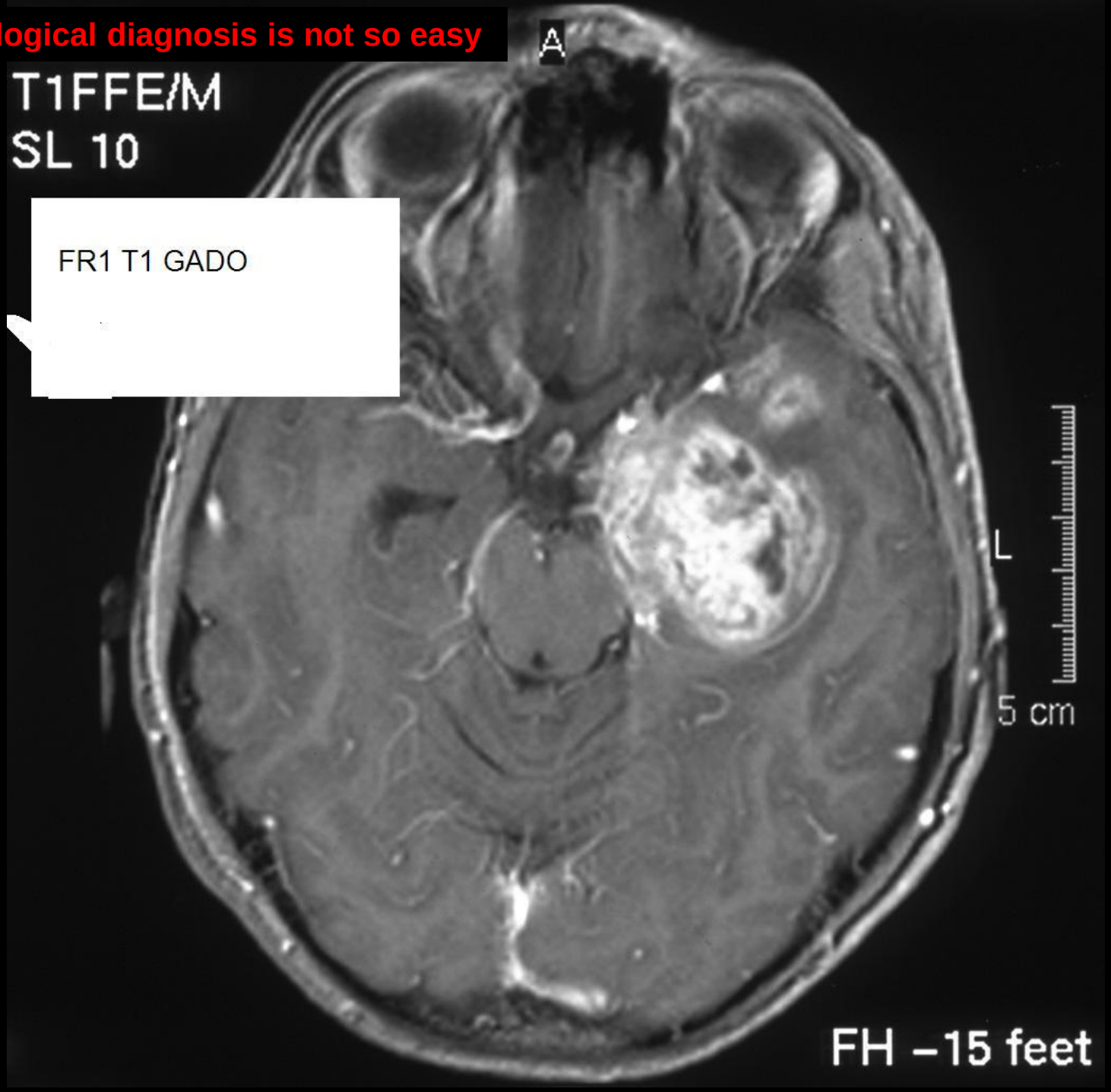
- **The rarity and the histological heterogeneity of these tumors can bring also experienced reviewers to reach different diagnoses from different specimens of the same tumors**

what has been done in SIOP group

- **13 sets of HE slides received have been sent, together with pertinent clinical forms, and in 8 instances with significant MRI images, to the neuropathologists involved**
  - 1st mail April **2003** (Italy)
  - 2nd mail November 2003 (Italy)
  - 3rd mail January 2004 (France)
  - 4rd mail June 2004 (Germany)
  - 5th mail March 2005 (Spain)
  - 6th mail December **2005** (USA)

Maura Massimino, Nicola Zucchini, Didier Frappaz, Paola Collini, Adela Caňete, Isabella Morra, Dominique Figarella Branger, Thorsten Pietsch, Johannes Wolff, Alessandro Sandri, Manuel Hernandez, Peter Burger and Felice Giangaspero, on behalf of the high-grade glioma SIOP brain tumor sub-subcommittee

Even histological diagnosis is not so easy



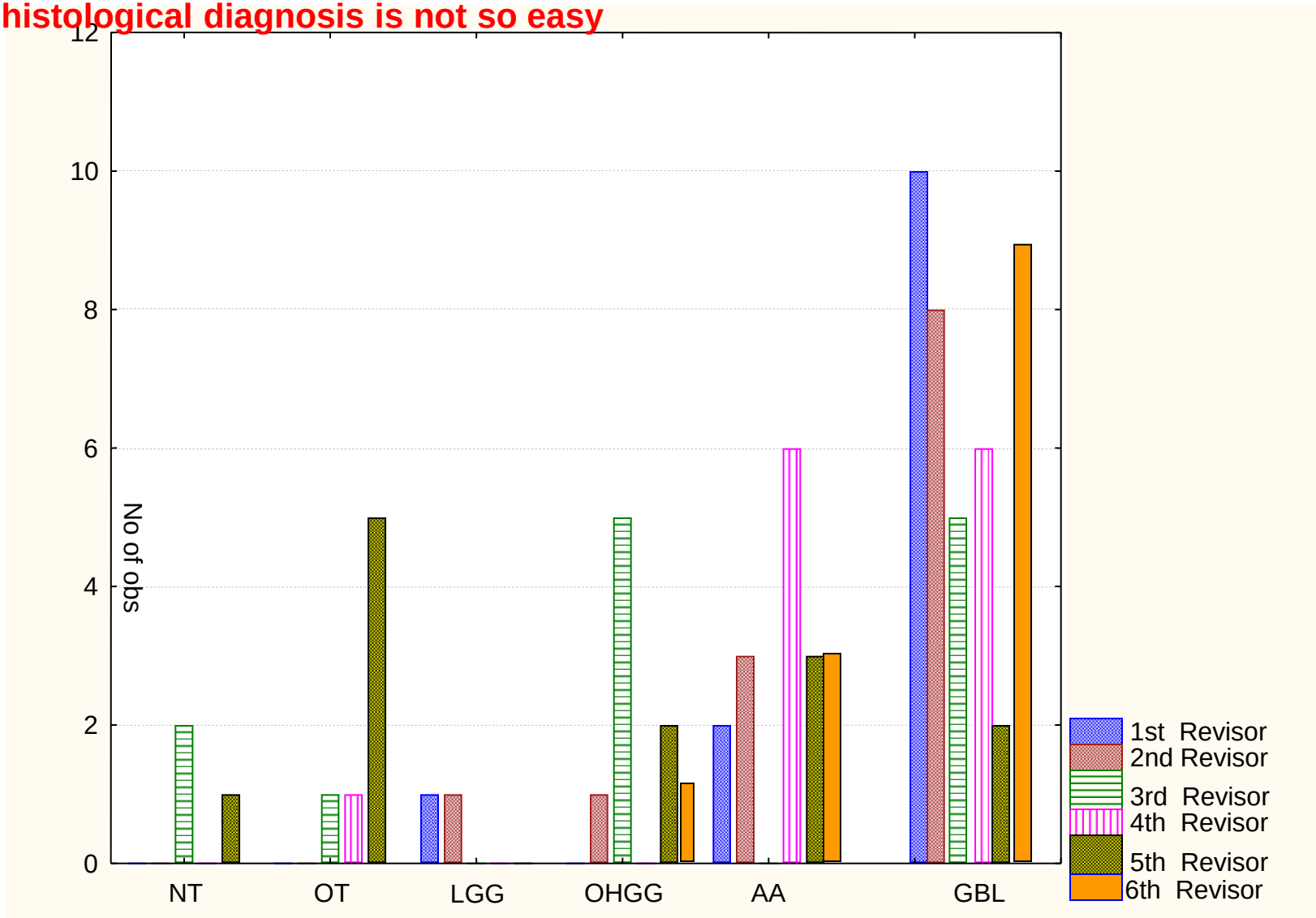
Even histological diagnosis is not so easy

Other diagnoses

CASES	ORIGINAL DIAGNOSIS						
IT1	Glioblastoma	Glioblastoma*	Glioblastoma*	Anaplastic oligodendro.	Glioblastoma	PNET	Glioblastoma
IT2	Anaplastic astro*.	Anaplastic astro.	Anaplastic astro*.	Anaplastic oligodendro.	Anaplastic astro.	Anaplastic oligodendro	Anaplastic astro.
IT3	Glioblastoma	Glioblastoma	Glioblastoma*	Glioblastoma*	Glioblastoma	Glioblastoma	Glioblastoma
IT4	Anaplastic astro.	Low grade glioma	Low grade glioma*	Anaplastic oligodendro.	Pylo.astro/anaplastic astro	Pineoblastoma	Anaplastic astro.
SP1	Anaplastic astro.	Glioblastoma	Anaplastic astro*.	Glioblastoma*	Pleomorphyc xantoastro/ anaplastic astro	Anaplastic astro.	Glioblastoma
SP2	Anaplastic astro*.	Glioblastoma	Glioblastoma	Unconclusive	Glioblastoma	Anaplastic astro*.	Glioblastoma
SP3	Glioblastoma	Glioblastoma	Glioblastoma	Unconclusive	Glioblastoma	Glioblastoma	Glioblastoma
GE1	Glioblastoma	Glioblastoma	Glioblastoma	Glioblastoma*	Glioblastoma	Meningocerebral melanosis	Glioblastoma
GE2	Anaplastic ganglioglio.	Anaplastic astro.	Anaplastic astro.	Anaplastic oligoastro.	Anaplastic astro.	…..	Anaplastic astro.
FR1	Anaplastic oligodendro.	Glioblastoma	Anaplastic oligodendro	Anaplastic oligodendro	Anaplastic astro/ anapl.ganglioglio	Anaplastic oligodendro	Glioblastoma
FR2	Anaplastic xantoastro.	Glioblastoma	Glioblastoma	AT/RT	AT/RT/ rhabdoid meningioma	Anaplastic xantoastro with rhabdoid f.	Malignant glioma rhabdoid type
FR3	Glioblastoma	Glioblastoma	Glioblastoma	Glioblastoma*	Anaplastic astro.	PNET	Glioblastoma
FR4	Glioblastoma	Glioblastoma	Glioblastoma	Glioblastoma*	Glioblastoma	Pineoblastoma	Glioblastoma

some details have been cut to semplify definition: ie. large cell glioblastoma= glioblastoma
anaplastic astrocytoma with glioblastoma areas = anaplastic astrocytoma
pylocitic astrocytoma = low-grade astrocytoma

Even histological diagnosis is not so easy



NT no tissue, OT other tumors, LGG low grade gliomas, OHGG other high grade gliomas, AA anaplastic astrocytomas, GBL glioblastoma

Results

- **Six pathologists (or panel of) expressed their diagnoses**
- **A total of *75* diagnoses on 13 slides were done**
  - **(3 lacked because HE stain was not considered enough for two and one set was lost during the last journey)**
- **Concordance was *71%* for grade IV lesions and *56%* for grade III ones**

CONCLUSIONS

- Pathology revision was a quite hard and time consuming effort
- Diagnostic reproducibility was average as far as “extreme lesions” (glioblastoma)
- Poorer for grade III gliomas
- Think about when designing a common study, when reading literature, when comparing results

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

- **Paediatric malignant gliomas have long been considered to be the same as adult disease**
- **Diffusely infiltrating malignant lesions arising in the ventral (DIPGs) generally occur in children only**
- **Differences in DNA copy number and gene-expression profiles have provided evidence that paediatric high-grade glioma (HGG) and DIPG have different developmental origins and are biologically distinct from the corresponding adult tumours**

TOPOGRAPHIC DIFFERENCES

ADULT HGG		CHILDREN HGG
BRAINSTEM	**1%**	**50%** 80% DIPG 20% not-DIPG
THALAMIC	**rare**	**10-15%**
SUPRATENTORIAL	**90%**	**20-30%**
SPINAL	**3%**	**3%**

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

- **Although childhood HGG seem to be similar histologically to their adult counterparts, they have some distinctive molecular features**
  - **frequent p53 mutations,**
  - **rare EGFR amplification / overexpression,**
  - **rare PTEN deletion that render them similar to adult "secondary" glioblastoma**
- **Moreover HGG from adolescents and children older than six years have significantly higher frequencies of 19q and/or 22q deletions than those from younger children**

Table 2 | 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.

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

- **Histone H3 mutations have been identified in 78% of DIPG and 22% of non DIPG HGG**

  Nature Genetics, Wu G, 2012, Nature 2012

- **while they are absent in adult HGG**

  Parsons DW, Science 2008

- **These mutations in H3H could be the pathogenetic event of pediatric HGG**

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

N Engl J Med 2005;352:987-96.

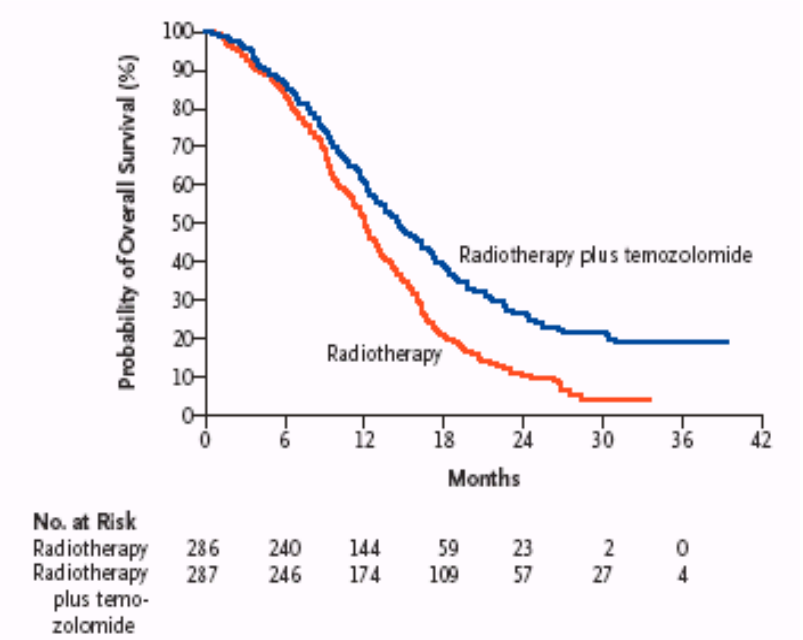


Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

- **methylation of the *MGMT* promoter, which results in gene silencing, is associated with a striking survival benefit in patients treated with radiotherapy plus temozolomide.**

- **This characteristics in adults glioma is in good part responsible for the "favourable" results of this trial**

→ Does this "nowadays standard" apply to children/adolescents as well?

- **The majority of pediatric primary brain tumors express MGMT activity**

  Clinical Cancer Research 2001; 7:613–619

- **Overexpression of MGMT in childhood HGG is strongly associated with an adverse outcome in children treated with alkylator-based chemotherapy**

  Pollack IF, et al. J Clin Oncol 2006; 24: 3431-3437

- **These results have been confirmed in ACNS0126, where 2-years EFS was 17 5% for patients without MGMT overexpression and 5 4% when MGMT was overexpressed (p=0.045)**

  Cohen et al. J Clin Oncol 2011

→ Can we apply the adult model to children/adolescent?

WHICH STANDARD CHEMOTHERAPY?

- **There is no standard chemotherapy backbone that is universally acknowledged in the setting of pediatric HGG**
- **Very few randomized trials of adjuvant chemotherapy have shown benefit**
  - **Post-surgical use of lomustine, vincristine and prednisone has been cosidered an adjuvant standard therapy with 5-year EFS 46% vs 18%**

Sposto R 1989

WHICH STANDARD CHEMOTHERAPY?

- **… but lower difference was found when central histological review was adopted**

  Fouladi M 2003

- **No superiority was found with «8 in 1» regimen**

  Finlay J 1995

WHICH STANDARD CHEMOTHERAPY?

- **Doubtful benefit of chemotherapy given together and post-radiation in presence of gross tumor residual even with intensive regimens**

  HIT-GBM-C protocols results in Wolff JE Cancer 2010

- **The strongest prognostic indicator is infact the presence of tumor residual after surgery**

Pediatric studies with Temozolomide

at relapse

CCG	**Previous radiotherapy**	**180 mg/sqm x 5**
	No radiotherapy	**215 mg/sqm x 5**

No response in either low or high grade relapsing astrocytoma

JCO 1998: 16 3037-3043

U.K./SFOP	**No radiotherapy**	**200 mg/sqm x 5**

No activity in relapsing high grade gliomas

JCO 2002: 20 4684-4691

Italian study

No activity in 24 relapsing high grade glioma

200 mg/sqm x 5

(divided in 3 doses)

Cancer Chemother Pharmacol. 2003;52:459-64

Pediatric studies with Temozolomide

at first diagnosis

- **COG**
- **concomitant to radiation and as adjuvant**
  - **no evidence that temozolomide therapy resulted in improved EFS**
- **neither in non-pontine glioma**

  Neuro Oncol 2011:13 317-23
- **or in DIPG**

  Neuro Oncol 2011:13 410-6

- **Also the addition of O6-benzylguanine to temozolomide did not increase response numbers in relapsed HGG or newly diagnosed DIPG**

  Warren KE, J Neurooncol 2012

- **It is difficult to develop trials randomizing children to a control arm when overall survival is known to be less than 10%**
  - But, on the other hand, use of historical control arms is dangerous especially if reporting patients treated two decades earlier
- **Drugs that are found to be active or inactive in adult HGG trials cannot be assumed to have similar activity in pediatrics**

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

- **Differences outlined between adult and pediatric HGG seem to be crucial**
- **Therefore they should deserve different treatment strategies**
- **Or, at least…**

  ….to think about

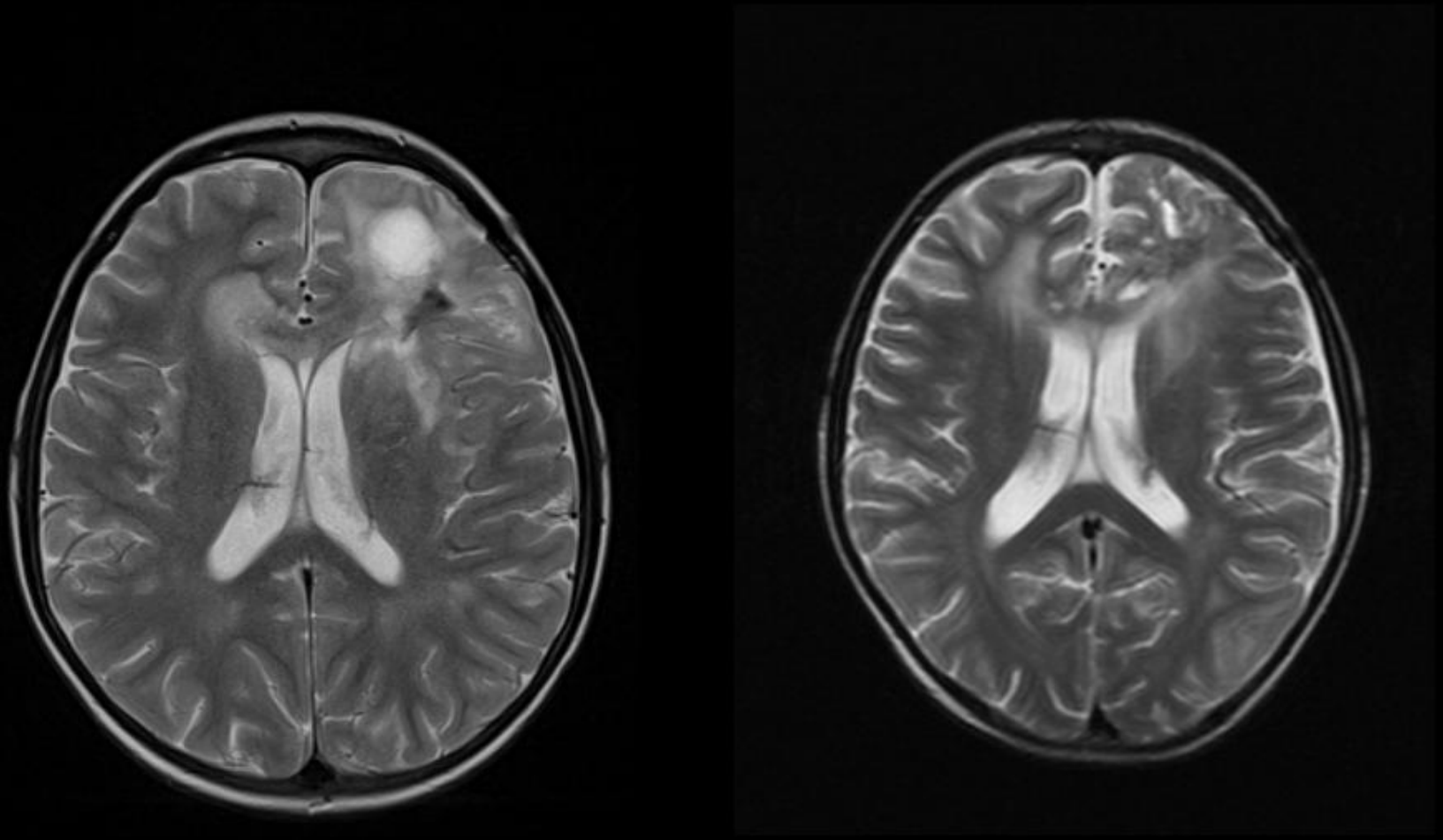
ANY ROLE FOR HIGH-DOSE CHEMOTHERAPY?

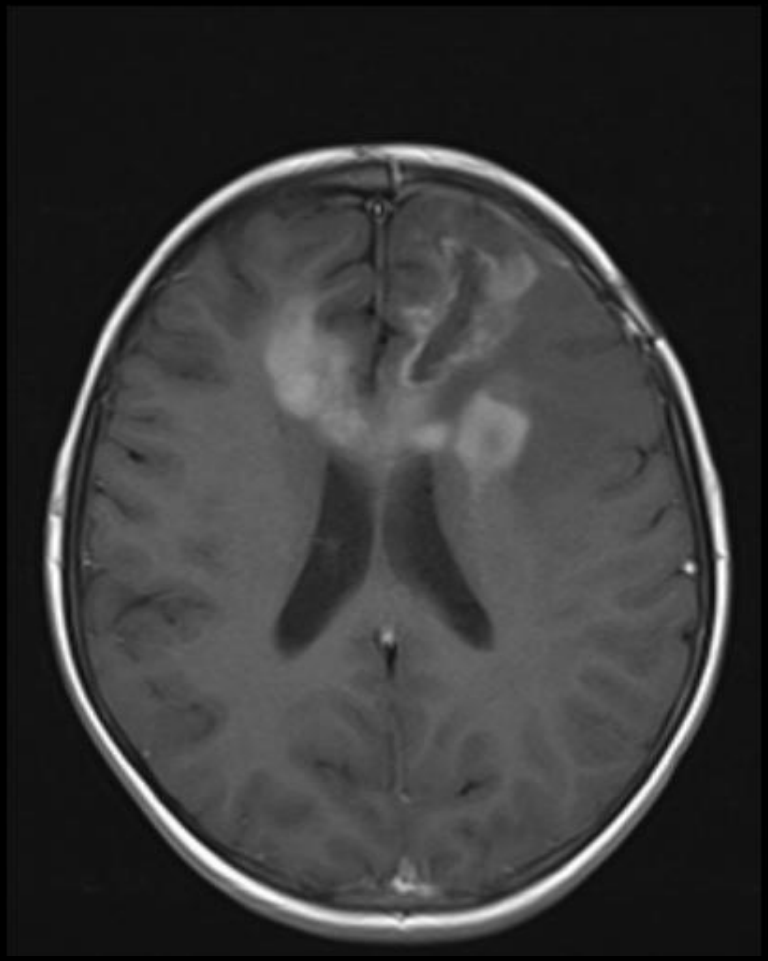
- **No effect in DIPG**
- **Doubtful in other contexts**
- **The associated side effects and resultant poor quality of life have led many investigators to question the benefit of high-dose chemotherapy despite the potential for better disease control…**

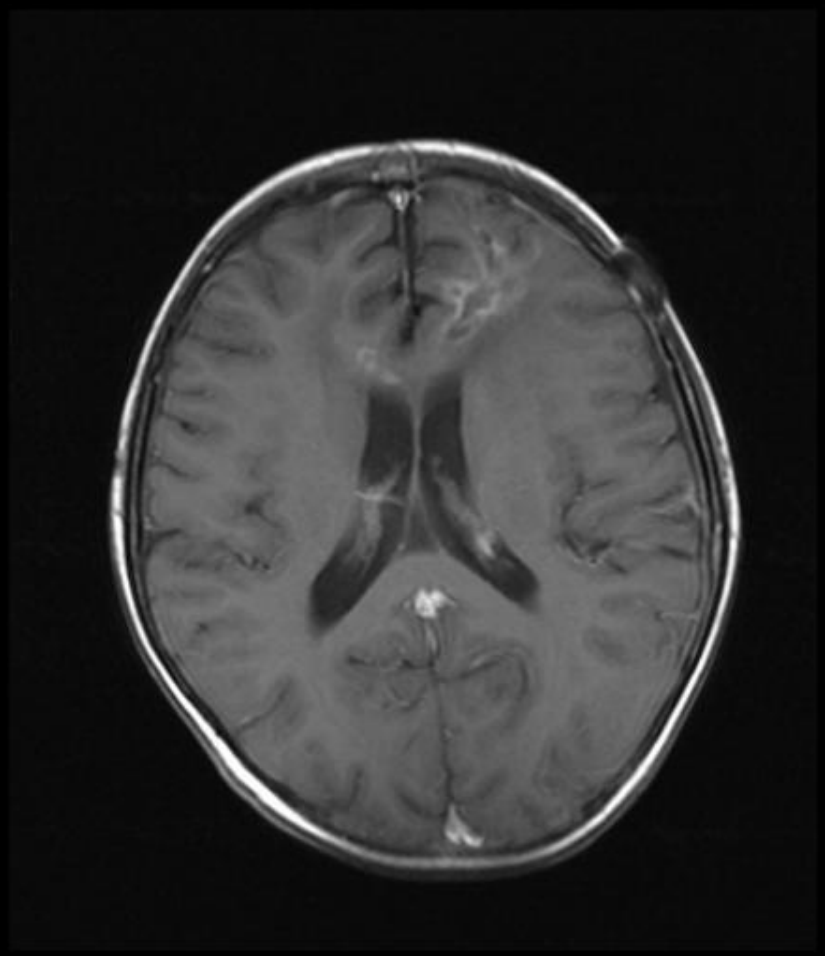
  Cage TA Neurosurg Clin N Am 2012

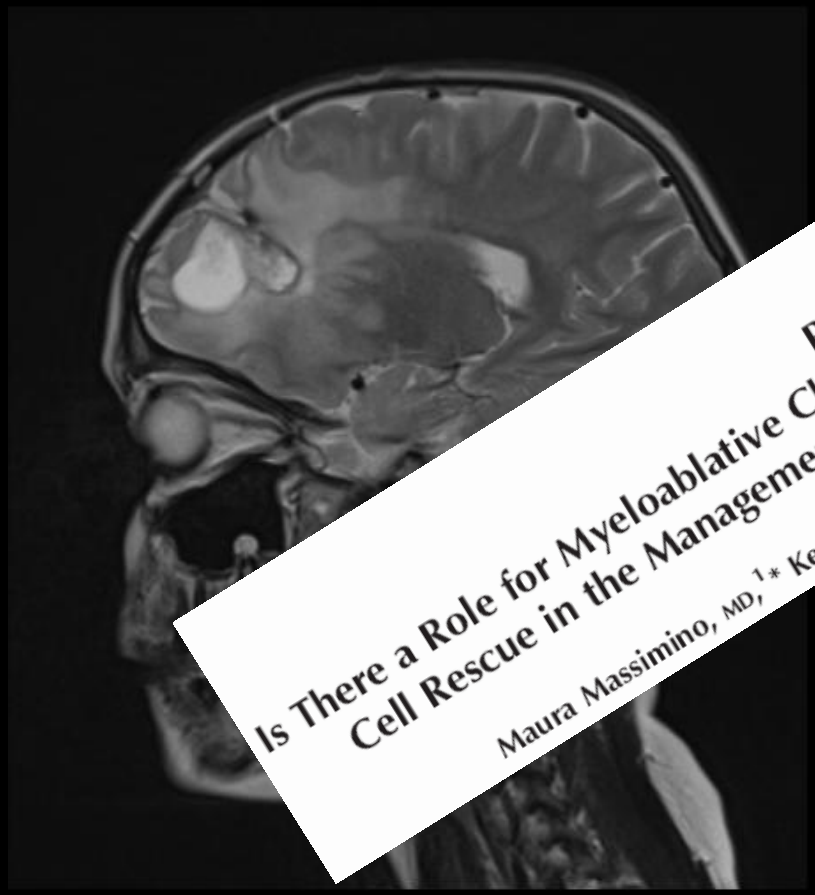
- **….but we have tried!**

“SEDUCTIVE” response to high dose thiotepa of radio-induced glioblastoma







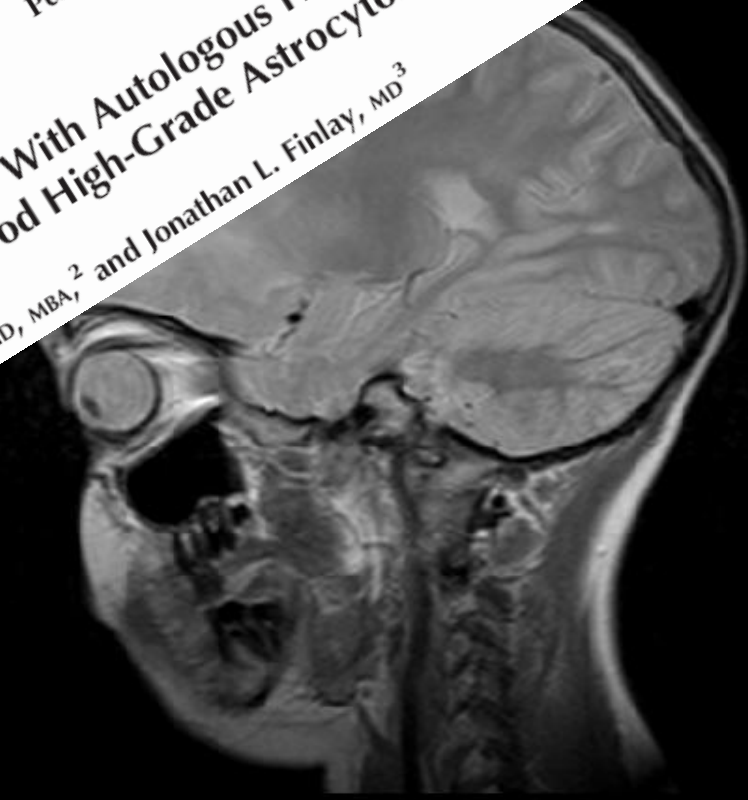


Pediatr Blood Cancer 2010;54:641–643

REVIEW

Is There a Role for Myeloablative Chemotherapy With Autologous Hematopoietic Cell Rescue in the Management of Childhood High-Grade Astrocytomas?

Maura Massimino, MD,[1]* Kenneth J. Cohen, MD, MBA,[2] and Jonathan L. Finlay, MD[3]



Neuro-Oncolo

CONSENSUS AND STATE-OF-THE-ART WORKSHOP

ARROW ABLATIVE CHEMOTHERAPY WITH
IATOPOIETIC CELL RESCUE FOR MALIGNANT
TUMORS OF CHILDHOOD AND ADOLESCENCE

Milan (Italy), 13-15 September 2006

Sequential chemotherapy, high-dose thiotepa, circulating progenitor cell rescue, and radiotherapy for childhood high-grade glioma

2005

Maura Massimino,[1] Lorenza Gandola, Roberto Luksch, Filippo Spr
Carlo Solero, Felice Giangaspero, Franco Locatelli, Marta Podda, F
Emanuele Pignoli, Paola Collini, Graziella Cefalo, Marco Zecca, Mi
Andrea Ferrari, Monica Terenziani, Cristina Meazza, Daniela Polast
Scaramuzza, Fernando Ravagnani, and Franca Fossati-Bellani

Review

Use of high-dose chemotherapy in front-line therapy of childhood malignant glioma

New concepts in the treatment of brain tun young child

*Maria Luisa Garre'[1], Arn
Gandola, Maura Massin*

Pediatr Blood Cancer 2010;54:634

COMMENTARY

A Consensus and State-of-the-Art Workshop: Marrow Ablative Chemotherapy With Hematopoietic Cell Rescue for Malignant Brain Tumors of Childhood and Adolescence

Jonathan L. Finlay, MB, ChB[1]* and Maura Massimino, MD[2]

Pediatr Blood Cancer 2010;54:641–643

REVIEW

Is There a Role for Myeloablative Chemotherapy With Autologous Hematopoietic Cell Rescue in the Management of Childhood High-Grade Astrocytomas?

Maura Massimino, MD,[1]* Kenneth J. Cohen, MD, MBA,[2] and Jonathan L. Finlay, MD[3]

Neuro-Oncology 2005 ■ Volume 7, Issue 1

Massimino, M., Gandola, L., Luksch, R., Spreafico, F., Riva, D., Solero, C., Giangaspero, F., Locatelli, F., Podda, M., Bozzi, F., Pignoli, E., Collini, P., Cefalo, G., Zecca, M., Casanova, M., Ferrari, A., Terenziani, M., Meazza, C., Polastri, D., Scaramuzza, D., Ravagnani, F., and Fossati-Bellani, F. Sequential chemotherapy, high-dose thiotepa, circulating progenitor cell rescue, and radiotherapy for childhood high-grade glioma. *Neuro-Oncology* [serial online]. Doc. 04-030. December 1, 2004. URL http://neuro-oncology.mc.duke.edu; DOI: 10.1215/

SEQUENTIAL CHEMOTHERAPY, HIGH-DOSE THIOTEPA, CPC RESCUE AND RADIOTHERAPY FOR CHILDHOOD HIGH-GRADE GLIOMA: A PAUCI-INSTITUTIONAL STUDY

update 2013

and Physics (E.G., E.F.), Pathology (F.C.), and Radiology (D.S.) Departments and Translational Service (F.R.), Istituto Nazionale Tumori, Milan; Developmental Neurology (D.R.) and Neurosurgery (C.S.) Units, Istituto Neurologico C. Besta, Milan; Neuropathology Department, Università La Sapienza, Rome (F.G.); Pediatric Department, Policlinico S. Matteo, University of Pavia (F.L., M.Z.); Italy

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Treatment program

Week 1 **CDDP (40 mg / sqm / d x 3) / VP16 (150 mg / sqm / d x 3 d)**
+ G-CSF & CPC harvesting

Week 4 **CDDP / VP16**
RM evaluation

Week 7 **VCR (1.4 mg / sqm) / EDX (1.5 g / sqm) / MTX (8 g / sqm)**

Week 10 **VCR / EDX / MTX**
RM evaluation

Week 13 **THIOTEPA (300 mg / sqm x 3 in one d) + CPC reinfusion**
RM evaluation

Week 18 → 23 **RADIOTHERAPY**
RM evaluation

Week 27 → 52 **VCR (every 3 wks), CCNU (80 mg / sqm / 9 wks p.o.)**

Patients

Accrual: 08/96 - 2011

62 children (34 F, 28 M; 4-19 yrs, median 10)

53 evaluable for response to CT

(with residual disease after surgery)

Histology

Glioblastoma multiforme	31
Anaplastic astrocytoma	20
Anaplastic oligodendroglioma	4
Anaplastic xanthoastro	4
anaplastic ganglioglioma	1
anaplastic pylo astrocytoma	1
anaplastic astroblastoma	1

Site

supratentorial (ST)		53
	thalamo-mesencephalon 18	
spine		6
posterior fossa (PF)		3
	multicentric 9	
	(ST 7; PF 2)	

Results

18/62 alive

TIME *BEFORE RT:

planned	**18 wks**
median elapsed	**22 wks**

Hospital stay for treatment and complications: 54 days (range 32-86)

Follow-up 20 - 182 mos, median 72

***five early RT for radiological and clinical progression before HD-thiotepa**

Results

62 patients

12 mos PFS 63 ± 6%

12 mos OS 76 ± 5%

Median PFS 18 mos

Median OS 26 mos

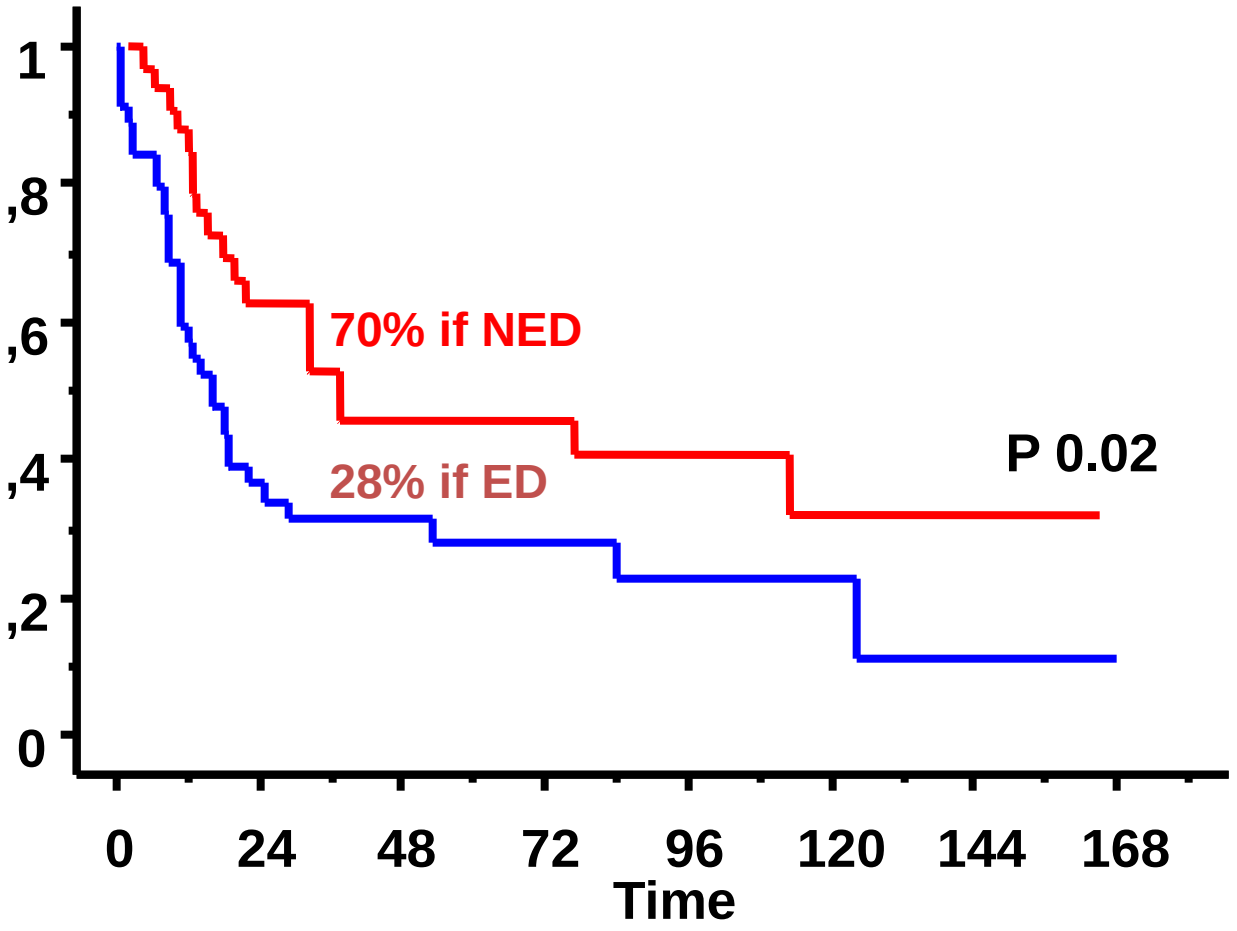
3 yrs PFS grade 3 glioma: 45 ± 9%

3 yrs PFS glioblastoma: 26 ± 8%

3 yrs OS grade 3 glioma: 48 ± 9%

3 yrs OS glioblastoma: 32 ± 8%

EFS OF THE SERIES ACCORDING TO POST SURGICAL TUMOR



Conclusions

- **Results of this series, where all histological samples were centrally reviewed, compare favourably with other published ones**
- **The role of high-dose chemotherapy is however not estabilished in this subset**

Something new available?

Bevacizumab
antiVEGF MoAb

Rationale

- **High response rate of the drug alone or in combination even with a moderately effective drug like CPT-11**

  Vredenburgh, J Clin Oncol 2007

- **Tumor stem cells are also sensitive to antiangiogenetic drugs**

  Bao, Cancer Res 2006

- **Can be combined with most chemotherapies without dose modification**
- **Phase I available in children**

  Bender, J Clin Oncol 2008

- **and phase II started in pediatric sarcomas**

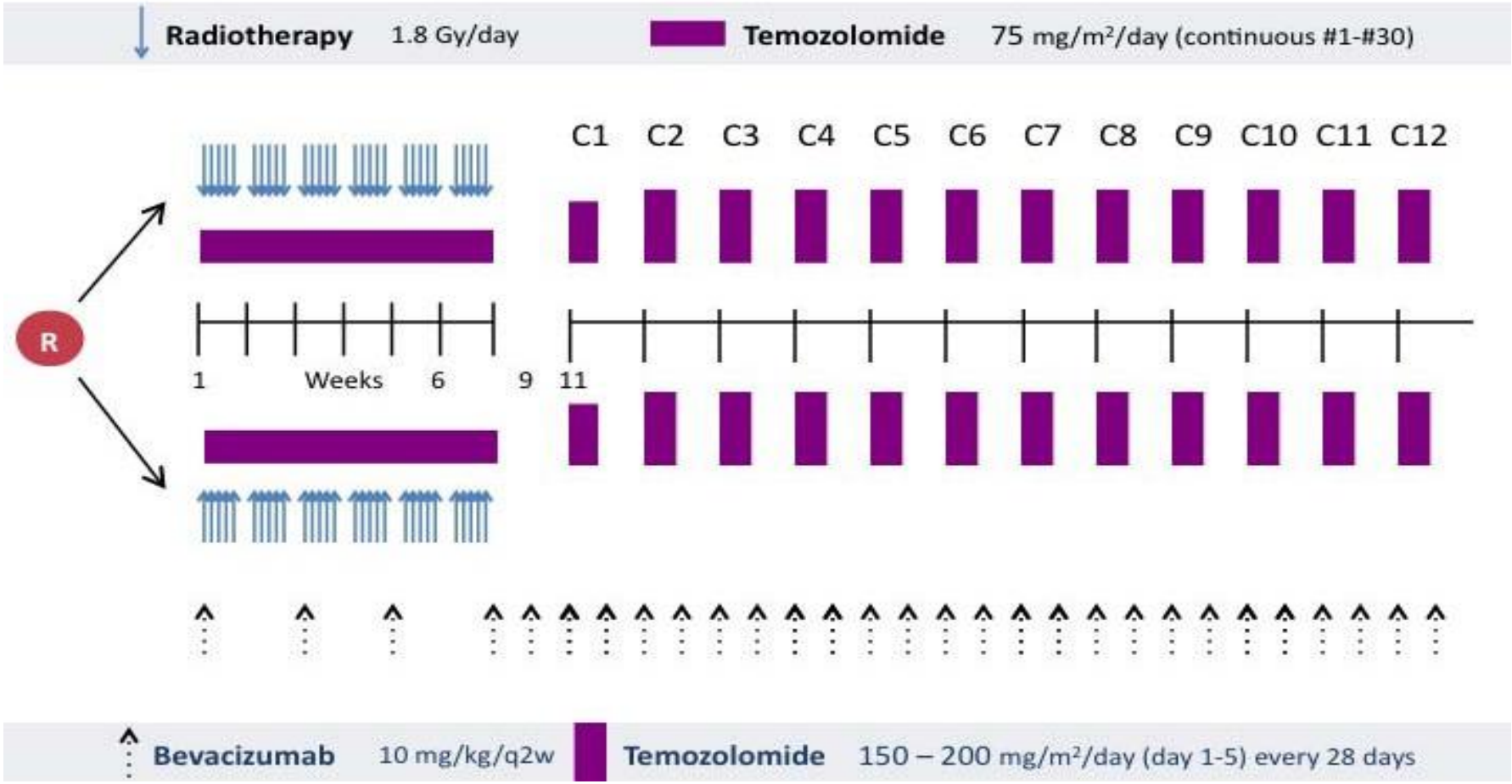
- **VEGF pathway is activated in pHGG.**
- **VEGFA = target of bevacizumab is present in pHGG.**
- **Factors associated with response, ie IGFBP2, also present in pHGG.**

Evaluation of bevacizumab in pHGG

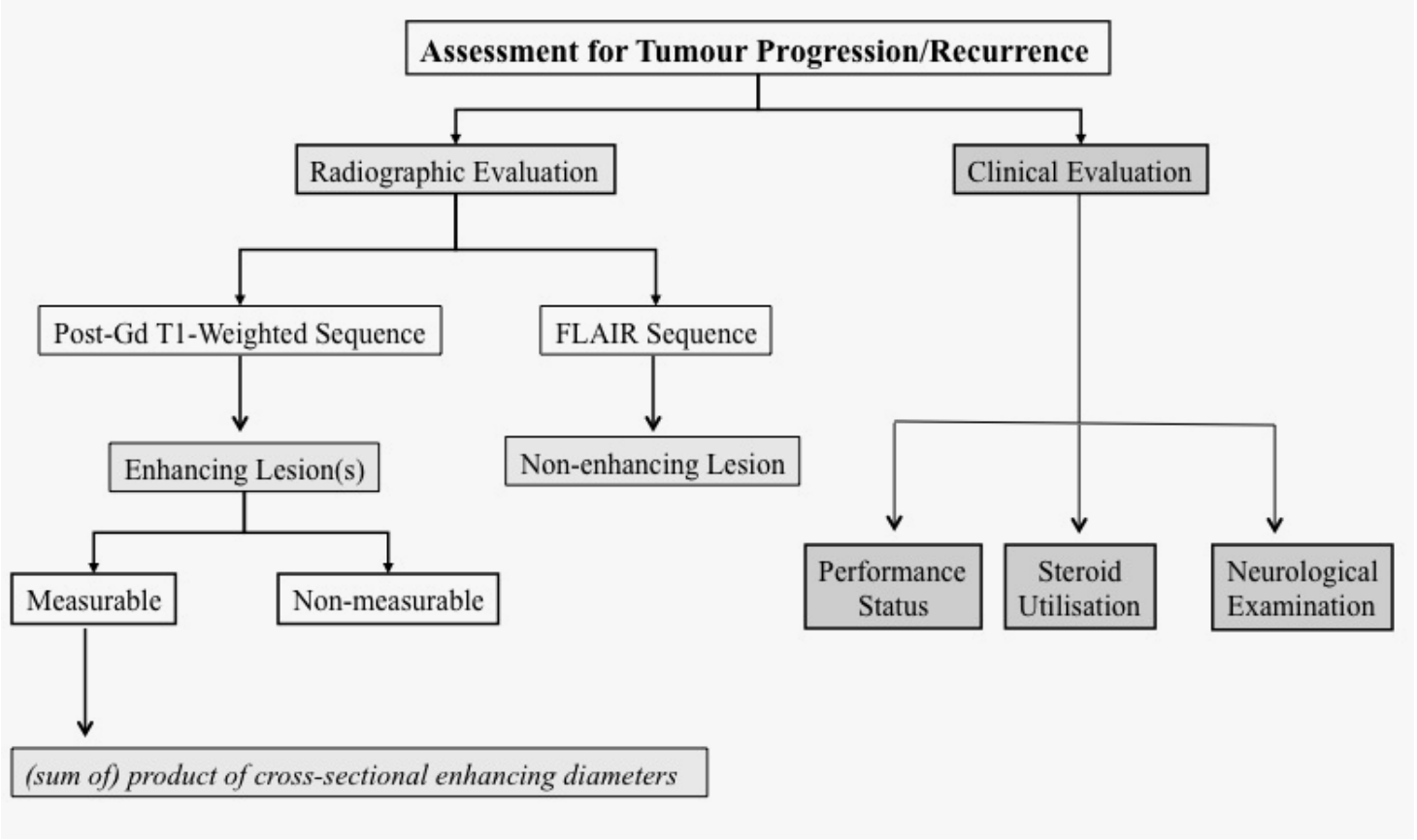
SIOP-ITCC-ACCT trial (+ Canada/Australia)

Over 70 centers

HERBY trial


Radiotherapy 1.8 Gy/day
Temozolomide 75 mg/m²/day (continuous #1-#30)
C1 C2 C3 C4 C5 C6 C7 C8 C9 C10 C11 C12
R
1 Weeks 6 9 11
Bevacizumab 10 mg/kg/q2w
Temozolomide 150 – 200 mg/m²/day (day 1-5) every 28 days

- **120 patients in three years**
- **fMRI evaluation (pseudoprogression)**



SOMETHING AT RELAPSE

- **Oral temozolomide/Vp 16**

  Korones DN,. Pediatr Blood Cancer 2006;47:37–41

  some activity in non-DIPG

- **Nimotuzumab**

  Bode U. Pediatr Blood Cancer, 39th Annual SIOP Congress 49: 435, 2007

  some activity in DIPG

- **Bevacizumab/irinotecan**

  Gururangan S JCO 2010, Narayama 2010

  disappointing, poor activity

RE-IRRADIATION

– Well known among adults

- Largest series published so far

Fogh SE JCO 2010

Median dose 35 Gy into 147 adult patients

Good tolerance

No addictive benefit of resection/chemotherapy

– **Possible tool for children too**

– **SIOP-E group ongoing project**

AND DIPG?

Estimated European DIPG Incidence

Country	Population	DIPG / year*
Russia	142008838	45 - 68
Germany	82217800	26 - 39
France	63601002	20 - 30
United Kingdom	60587000	19 - 29
Italy	59715625	19 - 29
Spain	46777373	15 - 22
Ukraine	45396470	15 - 22
Poland	38625478	12 - 19
Romania	22303552	7 - 11
Netherlands	16757000	5 - 8
Kazakhstan	16400000	5 - 8
Greece	11606813	4 - 6
Czech Republic	10674947	3 - 5
Portugal	10617192	3 - 5
Belarus	10335382	3 - 5
Belgium	10274595	3 - 5
Hungary	10075034	3 - 5
Sweden	9076744	3 - 4
Austria	8169929	3 - 4
Bulgaria	7621337	2 - 4
Serbia	7498001	2 - 4

Country	Population	DIPG / year*
Switzerland	7301994	2 - 3
Slovakia	5422366	2 - 3
Denmark	5368854	2 - 3
Finland	5302545	2 - 3
Georgia	4960951	2 - 2
Norway	4942700	2 - 2
Croatia	4490751	1 - 2
Moldova	4434547	1 - 2
Ireland	4234925	1 - 2
Bosnia and	3964388	1 - 2
Lithuania	3601138	1 - 2
Albania	3544841	1 - 2
Armenia	3262200	1 - 2
Latvia	2366515	1 - 1
Macedonia	2054800	1 - 1
Slovenia	2048847	1 - 1
Estonia	1415681	0 - 1
Cyprus	803147	0 - 0
Iceland	312384	0 - 0

SIOPE DIPG network

Europe total: 243 - 364 per year

142 - 213 = 58%

**) Estimation based on projected incidence of 100-150 patients in USA (0,32-0,48 per million)*

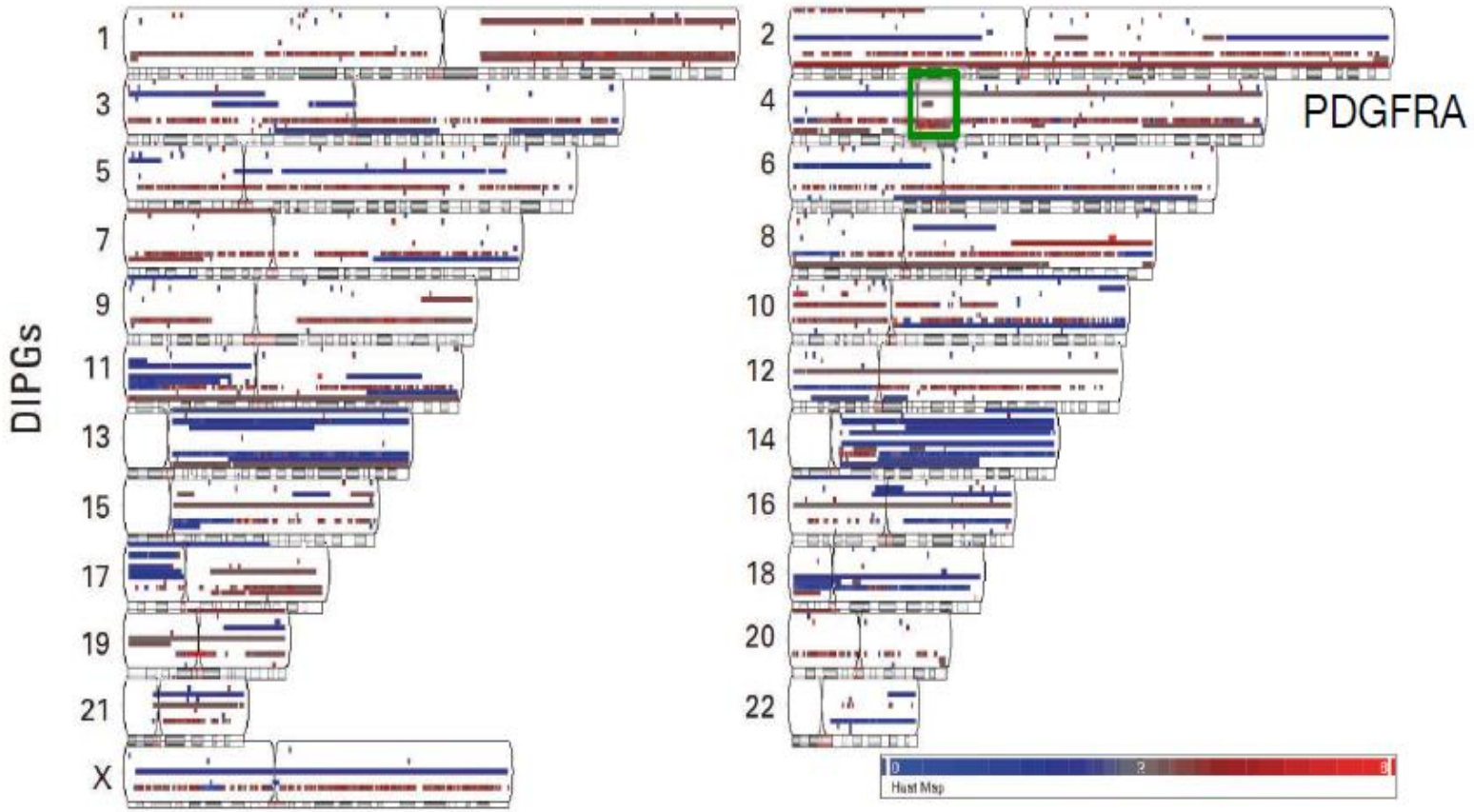
Autopsy:	WHO grades 3 and 4 predominate	Packer, 1983 Silbergeld, 1988
Stereotactic & open biopsies	36 biopsy specimens 13 LGA 13, 20 AG, 2 GBM	CCG, Albright, 1993
Biopsy	71 children 75% WHO 2, 25% HGG	Selvapandian, 1999
retrospective study	48 specimens, Pons, Diffuse features; predominate Fibrillary A	Fisher PG, 2000
Stereotactic biopsy	18 DPG patients 5 LGA, 5 AA, 8 GBM	Cartmill M, Punt J,1999
Stereotactic biopsy	(CT diagnosis) 20 Pontine gliomas 50% LGG/HGG, other	Chico-Ponce de León, 2003
18 surgical biopsy 10 postmortem specimens	12 WHO grades II 9 WHO III, 7 WHO IV	Gilbertson, 2003
stereotactic biopsy	22 WHO III or IV 1 JPA, 1 WHO II	Roujeau, Sainte-Rose, 2007
Retrospective study	Fibrillary 2 (5%) AA 6 (15.5%) GBM 1 (2.5%) No histology 30 (77%)	Hargrave, 2007
Autopsy	WHO III or IV	HSJD

Whole-Genome Profiling of Pediatric Diffuse Intrinsic Pontine Gliomas Highlights Platelet-Derived Growth Factor Receptor α and Poly (ADP-ribose) Polymerase As Potential Therapeutic Targets

n=11

Maryam Zarghooni, Ute Bartels, Eric Lee, Pawel Buczkowicz, Andrew Morrison, Annie Huang, Eric Bouffet, and Cynthia Hawkins

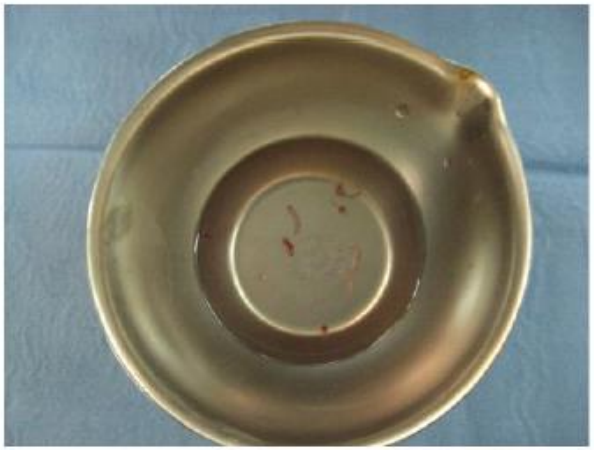
J Clin Oncol. 2010 Mar 10;28(8):1337-44

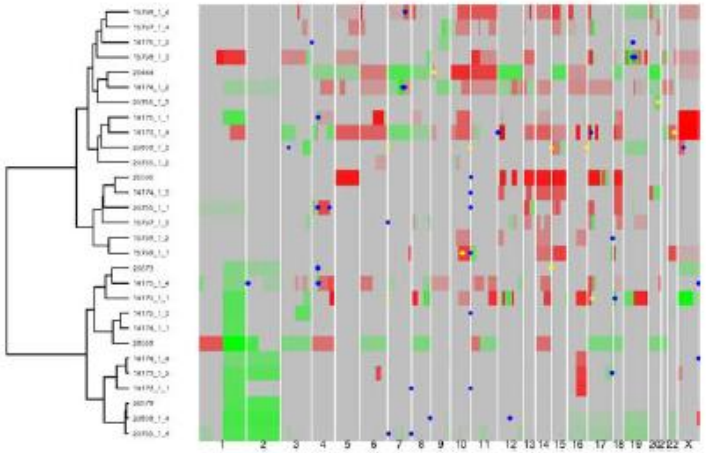


Innovative Therapies for Children with Cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors

Birgit Geoerger, Darren Hargrave, Fabienne Thomas, Anna Ndiaye, Didier Frappaz, Felipe Andreiuolo, Pascale Varlet, Isabelle Aerts, Riccardo Riccardi, Timothy Jaspan, Etienne Chatelut, Marie-Cecile Le Deley, Xavier Paoletti, Christian Saint-Rose, Pierre Leblond, Bruce Morland, Jean-Claude Gentet, Valérie Méresse, and Gilles Vassal, on behalf of the ITCC (Innovative Therapies for Children with Cancer) European Consortium

Neuro Oncol. 2011 Jan;13(1):109-18



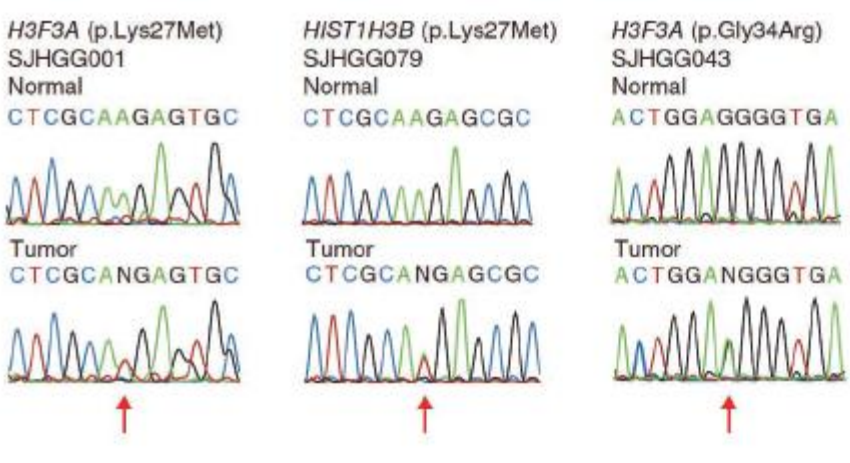


Biopsies can give sufficient quantity macromolecules for profiling

Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas

n=7

Gang Wu[1,8], Alberto Broniscer[2,8], Troy A McEachron[3,8], Charles Lu[4], Barbara S Paugh[3], Jared Becksfort[5], Chunxu Qu[5], Li Ding[4], Robert Huether[1], Matthew Parker[1], Junyuan Zhang[3], Amar Gajjar[2], Michael A Dyer[3], Charles G Mullighan[6], Richard J Gilbertson[3], Elaine R Mardis[4], Richard K Wilson[4], James R Downing[6], David W Ellison[6], Jinghui Zhang[1] & Suzanne J Baker[3] for the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project[7]



J Clin Oncol. 2011 Oct 20;29(30):3999-4006

Table 1 Frequency of recurrent somatic mutations in DIPG and GBM

Gene	Amino acid change	DIPG[a] (%)	non-BS-PG[b] (%)
H3F3A	p.Lys27Met	30 (60)	7 (19)
H3F3A	p.Gly34Arg	0	5 (14)
HIST1H3B	p.Lys27Met	9 (18)	1 (3)
All H3		39 (78)	13 (36)

[a]For DIPGs, total $n = 50$. [b]For non-BS-PGs, total $n = 36$.

Title

Mesenchymal transition and PDGFRA amplification/mutation are key distinct oncogenic events in pediatric diffuse intrinsic pontine gliomas

n=32

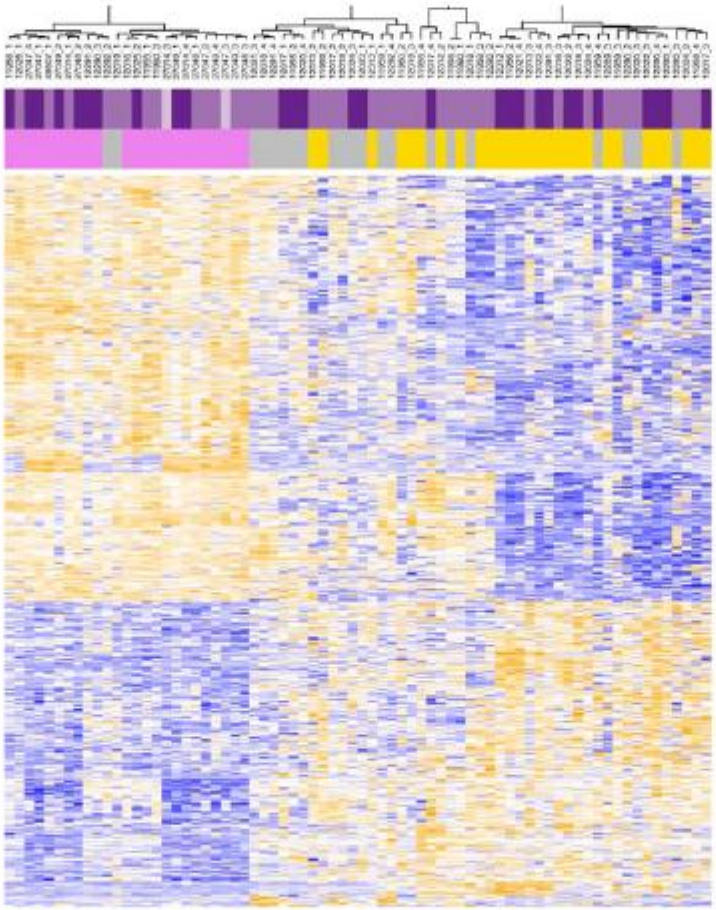
Authors

Puget S[1,2#], Philippe C[2#], Bax DA[3], Job B[4], Varlet P[5], Junier MP[5], Andreiuolo F[2], Jubert C[2], Opolon P[2], Carvalho D[3,6,7], Reis R[6], Guerrini-Rousseau L[2], Roujeau T[1], Dessen P[4], Richon C[8], Lazar V[8], Le Teuff G[9], Sainte-Rose C[1], Vassal G[2], Jones C[3], Geoerger B[2,10*], Grill J[2,10*].

PLoS One. 2012;7(2):e30313

Thalamus / midline

Pons



Hemispheric

RADIOTHERAPY: the only standard of care

- **54 Gy divided into 1.8 Gy daily fractions**

- **Clinical improvement in 70-80% :**
- ***Regression of neurological impairment***
- ***Tapering of steroids***

- **Radiological improvement 50-80%**
- **Clinical and radiological response not always homogeneous**
  - **And median PFS below 6 months, median OS below 9 months**

CHEMOTHERAPY

Tumour Review

Diffuse intrinsic pontine gliomas: A systematic update on clinical trials and biology

M.H.A. Jansen [a,c,*], D.G. van Vuurden [a,c,1], W.P. Vandertop [b,c,2], G.J.L. Kaspers [a,c,3]

[a] Department of Pediatrics, Division of Pediatric Oncology/Hematology, VU University Medical Center, Amsterdam, The Netherlands
[b] Neurosurgical Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
[c] Neuro-Oncology Research Group, Cancer Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

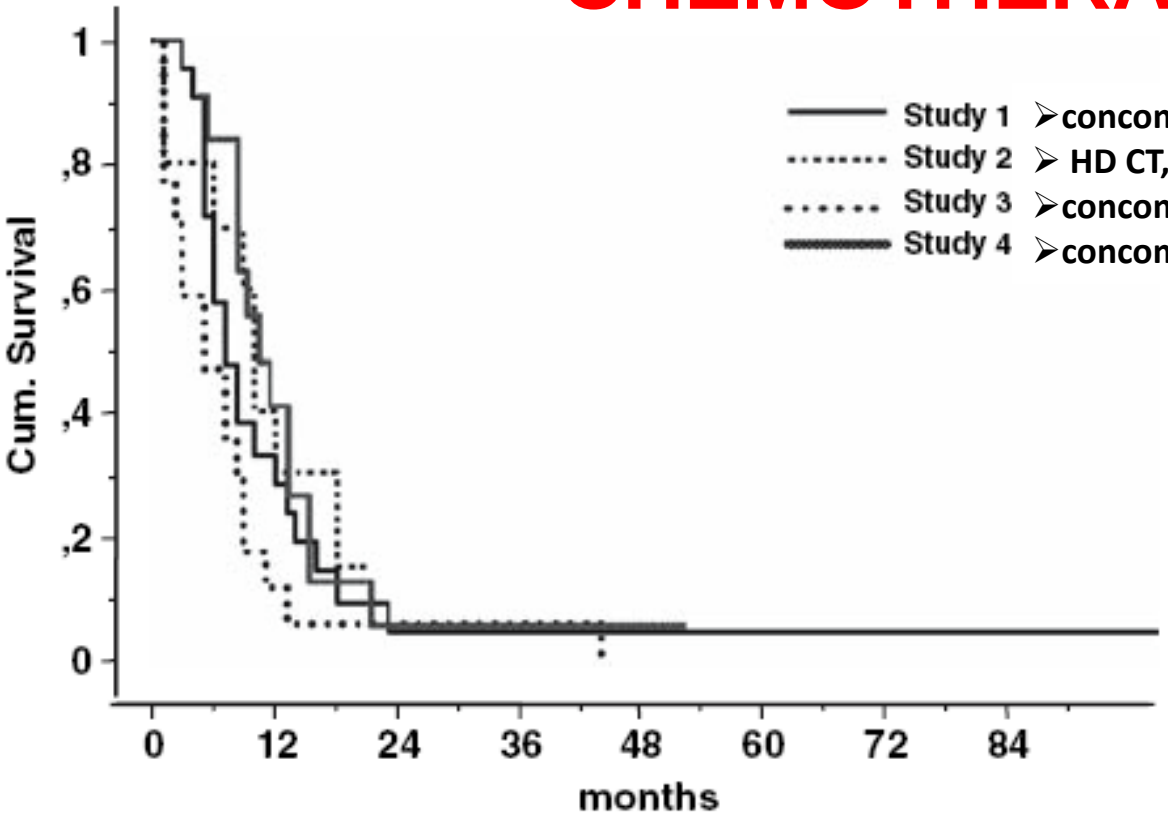
Response and survival rates of published studies including newly diagnosed DIPG patients from 2005.

Therapy	CR	PR	SD	PD	MOS (mths)	CI	1-year OS	2-year OS	3-year OS	PFS (mths)	1-year PFS	Ref. No.
Pre-irradiation therapy												
HDC (and adj VCR-lomustine)	–	–	–	–	13	–	70%	10%	–	10	40%	22
Cisplatin, VP-16 (and adj isotretinoin)	–	–	–	–	9	–	29%	12%	–	5	12%	22
Vinorelbine	–	–	–	–	9	–	43%	21%	–	7	21%	22
Carmustine, cisplatin, tamoxifen, HD-MTX	–	–	–	–	17	11–20	65%	22%	4%	–	–	12
Carboplatin, VCR, MTX, cyclophosphamide, cisplatin	–	–	–	–	3.6	–	14%	0%	0%	2.5	0%	15
Radiotherapy												
Hypofractionation	–	–	–	–	8.6	–	–	–	–	5	–	18
Hypofractionation	–	–	–	–	7.6	–	–	–	–	5.7	–	24
Chemo-radiotherapy												
TMZ	–	–	–	–	9.2	–	35%	15%	10%	6.9	–	17
TMZ	–	–	–	–	9.8	–	20%	7%	–	5.1	7%	26
TMZ	0%	31%	34%	14%	9.6	–	40%	3.6%	0%	6.1	14%	11
TMZ and cis-retinoic acid	0%	58%	33%	9%	13.5	6–22	58%	–	–	10.2	–	27
TMZ and thalidomide	0%	83%	8%	8%	12.7	10–15	58%	25%	–	7.2	17%	19
Cisplatin, VP-16, VCR, ifosfamide	3%	22%	46%	30%	13.6	–	–	–	–	4.8	0%	30
Tamoxifen	–	–	–	–	6.3	–	16%	6%	6%	3.9	3%	23
VCR and oral VP-16	–	–	–	–	12	–	45%	18%	–	7	30%	21
VP-16, cytarabin, ifosfamide, cisplatinum, dactinomycin	0%	26%	67%	7%	9	–	27%	3%	0%	–	–	22
Radiosensitizers												
Carbogen	–	–	–	–	9.6	–	–	–	–	8	–	8
Motexafin gadolinium	–	–	–	–	7	8–3	–	–	–	–	–	9
Adjuvant chemotherapy												
Interferon Ý and cyclofosfamide	–	–	–	–	9.6	–	–	0%	0%	–	–	29
Anti-angiogenesis therapy												
Thalidomide	0%	54%	15%	23%	9	–	–	0%	0%	5	–	28
Topotecan, adjuvant thalidomide, celecoxib, etoposide	–	50%[a]	–	–	12.5	–	63%	–	–	11	–	20
Targeted therapy Tipifarnib	–	–	–	–	–	–	36%	–	–	–	–	16
Imatinib	0%	6%	–	–	11	–	45%	–	–	–	24%	25
Gefitinib	–	–	–	–	–	–	48%	–	–	–	16%	14
Vandetanib	–	–	–	–	–	–	38%	21%	–	–	–	10
Erlotinib	0	17%	50%	33%	12	–	50%	19%	–	8	–	13

mths = months, CR = complete response, PR = partial response: >50% decrease, SD = stable disease: <50 decrease and <25% increase, PD = progressive disease: >25% increase, MOS = median overall survival, PFS = progression-free survival, OS = overall survival, Ref. = reference, HDC = high-dose chemotherapy with autologous stem cell transfusion, MTX = methotrexate, VCR = vincristine, TMZ = temozolomide, VP-16 = etoposide.

[a] Partial response was defined as >20% decrease in this study.

CHEMOTHERAPY



- Study 1 ➢concomitant RT/CT vp16/ara-C/ifo/cddp/d-act
- Study 2 ➢ HD CT, TTP, ASCT, RT, vcr/CCNU
- Study 3 ➢concomitant RT/cddp-vp-16
- Study 4 ➢concomitant RT/vnb

J Neurooncol
DOI 10.1007/s11060-008-9525-5

CLINICAL-PATIENT STUDY

Diffuse pontine gliomas in children: changing strategies, changi results? A mono-institutional 20-year experience

Maura Massimino · Filippo Spreafico · Veronica Biassoni · Fabio Simonetti · Daria Riva · Giovanna Trecate · Sergio Giombini · Geraldina Poggi · Emilia Pecori · Emanuele Pignoli · Michela Casanova · Andrea Ferrari · Cristina Meazza · Roberto Luksch · Monica Terenziani · Graziella Cefalo · Marta Podda · Daniela Polastri · Carlo A. Clerici · Franca Fossati-Bellani · Lorenza Gandola

Identical survival despite 4 different Treatment approaches

Possible TARGETED drugs

Drugable targets in DIPG.

Target	Expression/amplification	% of samples	Targeted by drugs[a]
EGFR	Protein expression	27–50%	Erlotinib, gefitinib, nimotuzumab, cetuximab, vandetanib (also VEGFR)
	Amplification	0%	
PDGFR	Protein expression	63–100%	Imatinib, dasatinib
	Amplification	36%	
VEGF(R)	NA	NA	Vandetanib (also EGFR), bevacizumab
MTOR	Protein expression	100%	Everolimus, sirolimus
	Amplification	NA	
PARP	Expression	36%	ABT-888 (study ongoing)
	Amplification	27%	
MGMT	Protein expression	0%	O6-benzylguanine
RAS	NA	NA	Lonofarnib, tipifarnib
avβ3 and avβ5	NA	NA	Cilengitide (EMD121974)
IL-13	NA	NA	IL13-PE38QQR

NA = not analyzed, EGFR = epidermal growth factor receptor, VEGF(R) = vascular endothelial growth factor (receptor), PDGFR = platelet-derived growth factor receptor, MTOR = mammilian target of rapamycin, PARP = poly (ADP-ribose) polymerase, MGMT = methylguanine methyltransferase, RAS = RAt Sarcoma, PE = pseudomonas exotoxin.

[a] The enumeration of drugs is not exhaustive.

why nimotuzumab

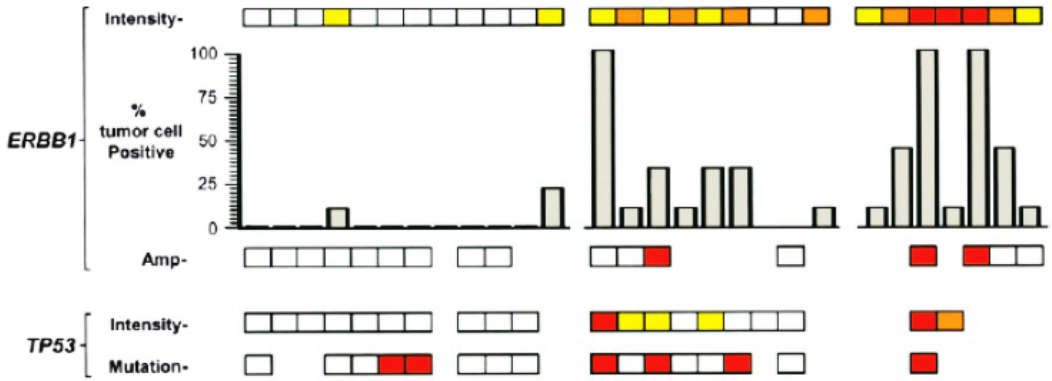
- **Among the few studies providing biological information on DIPG, Gilbertson's group demonstrated a significant increase in EGFR expression (Gilberston R 2003)**

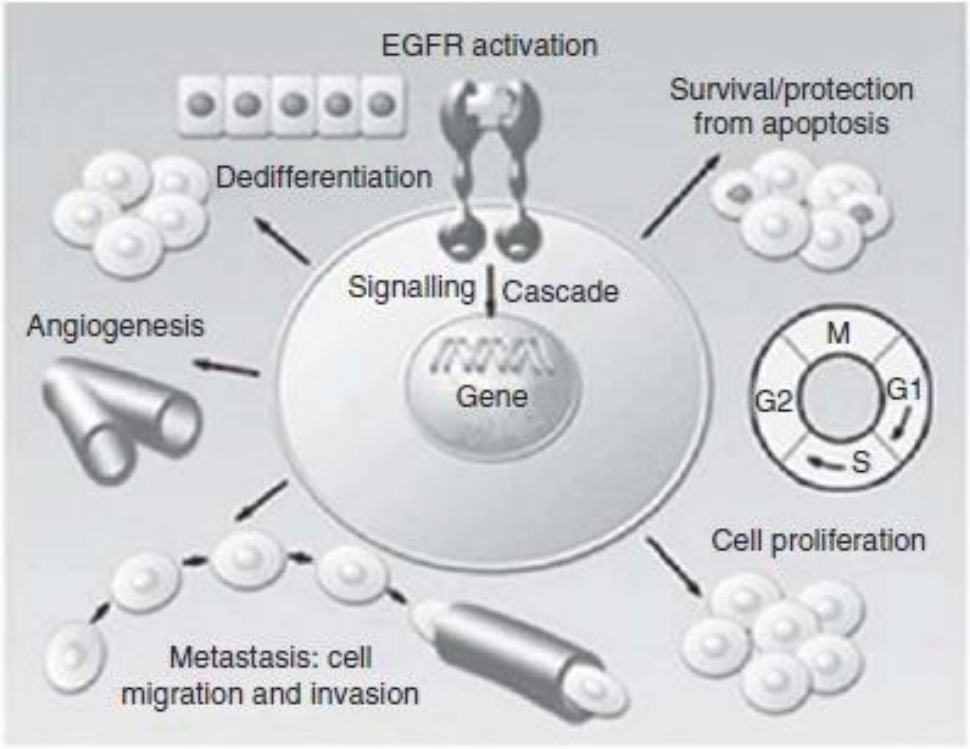
3620 *Vol. 9, 3620–3624, September 1, 2003* Clinical Cancer Research

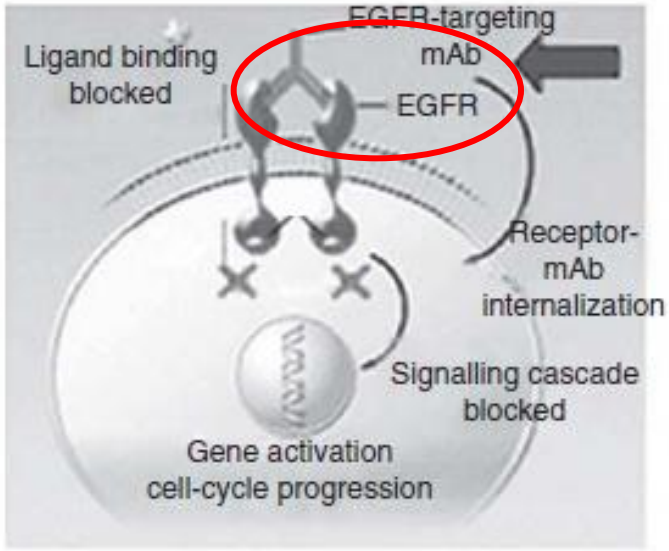
***ERBB1* Is Amplified and Overexpressed in High-grade Diffusely Infiltrative Pediatric Brain Stem Glioma[1]**

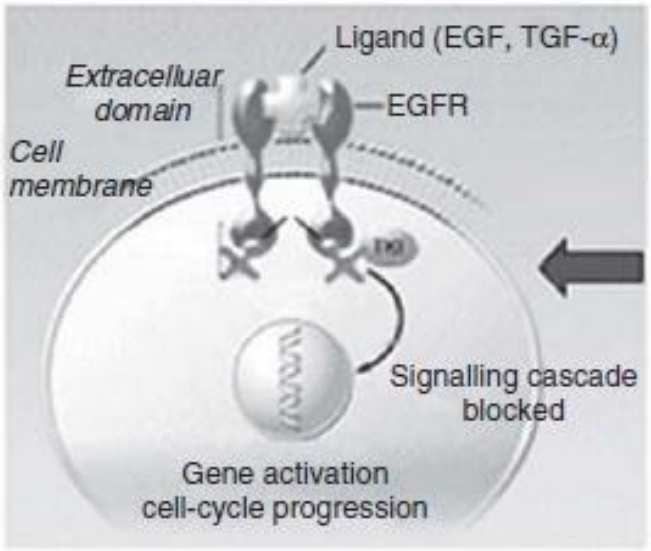
Richard J. Gilbertson,[2] D. Ashley Hill, Roberto Hernan, Mehmet Kocak, Russell Geyer, Jim Olson, Amar Gajjar, Lisa Rush, Ronald L. Hamilton, Sydney D. Finkelstein, and Ian F. Pollack

Mixed of Biopsy/Autopsy samples









- **The activity of nimotuzumab, a humanized anti-EGFR monoclonal antibody, was therefore studied within a Phase II trial in 47 relapsing pediatric patients with DIPG and high-grade gliomas, showing an interesting, persistent response, especially in the first group treated**
  (J Clin Oncol (ASCO Annual Meeting Proceedings) 2007;25(18S):abstract # 2006)

- **A multicenter exploratory study combining nimotuzumab and radiotherapy as first line treatment for DIPG showed disease control and an overall patient survival similar to previous experiences along with an improvement in the quality of patient survival and no severe side effects** (*J Clin Oncol* 26: 2008 (May 20 suppl; abstr 2058))

our experience: nimotuzumab and radiation activity

- From January 2006 to March 2009 we treated a total of 38 consecutive children with DIPG
- The treatment - continuation of a phase 3 multicentric trial - consisted of
  - an induction therapy with weekly infusions of 150 mg/m^2 nimotuzumab for twelve weeks, concomitantly with standard radiotherapy (54 Gy) at weeks 3 to 8;
  - nimotuzumab biweekly followed until disease progression

results

- **Median PFS was 7 months, median OS 10 months thus a *little better* than literature reports and *without any side effects* correlated to nimotuzumab**
- **2 children were alive at 35, 43 months after diagnosis**

but this was not enough!

why adding vinorelbine

- **Vinorelbine is a semisynthetic vinca alkaloid that has proved active against glioma both in vitro against tumor xenografts, and in vivo**
- **Used together radiation in our previous series (2002-2006) of 12 children with DIPG it resulted in a median PFS of 6 months and median OS of 10 months with one survivor at 10 years**
- **It reportedly may also have an enhanced activity in non-small cell lung cancers that are EGFR-FISH positive**
- **and may alter receptor binding of EGF to human breast cancer cells**

J Neurooncol (2006) 80:195–201
DOI 10.1007/s11060-006-9176-3

A case of relapsing glioblast to vinorelbine

V. Biassoni · M. Casanova · F. Spreafico · L. Gandola · M. Massimino

ORIGINAL A

Diffuse Intrinsic Brainstem A Case of Therapeutic Effic

Andrea Maria Cappellano, MD, Eric Bo*
Maria T. Seixas,§ and Nasjla

(*J Pediatr Hematol Oncol* 2011;00:000–000)

Pediatr Blood Cancer 2009;53:590–593

Phase II Evaluation of Intravenous Vinorelbine (Navelbine) in Recurrent or Refractory Pediatric Malignancies: A Children's Oncology Group Study

John F. Kuttesch Jr., PhD, MD,[1]* Mark D. Krailo, PhD,[2,3] Timothy Madden, PharmD,[4] Mary Johansen, PharmD,[4] Archie Bleyer, MD[5,6] and The Children's Oncology Group[7]

Background. A Phase II trial was developed to determine the efficacy and toxicity of intravenous vinorelbine, a semi-synthetic vinca alkaloid, in children, adolescent, and young adults with recurrent or refractory solid malignancies. ***Procedures.*** Fifty patients were enrolled among three strata: soft tissue sarcomas [rhabdomyosarcoma (RMS), non-rhabdomyosarcoma, primitive neuroepithelial tumor] (20 patients); brain tumors [astrocytoma (4 patients), medulloblastoma (2 patients), other (16 patients)] (22 patients); neuroblastoma (8 patients). Vinorelbine was given weekly for 6 consecutive weeks during an 8-week interval. The response rate and toxicity profile was assessed. ***Results.*** Among the first 35 patients treated at 33.75 mg/m^2/dose, 25 experienced grades 3–4 neutropenia (75%). The dose was decreased to 30 mg/m^2/dose in the remaining 15 patients. The median age was 10 years (range, 1–25). Four responses (one complete, three partial) occurred within the soft tissue sarcoma strata (all with RMS) and two occurred in the brain tumor group (medulloblastoma and astrocytoma). The most common toxicities were hematological and neurological. ***Conclusion.*** Vinorelbine at dose of 30 mg/m^2 can be safely administered to children with recurrent or refractory solid malignancies. The study design identified vinorelbine to be active in the sarcoma category, with a response rate of 36% (4/11) among RMS patients. Pediatr Blood Cancer 2009;53: 590–593.

Key words: neuroblastoma; rhabdomyosarcoma brain tumor; sarcoma; vinorelbine

VOLUME 26 · NUMBER 26 · SEPTEMBER 10 2008
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REP

Gefitinib Versus Vinorelbine in Chemotherapy-I
Elderly Patients With Advanced Non–Small-Cell
Cancer (INVITE): A Randomized, Phase II Study

Lucio Crinò, Federico Cappuzzo, Petr Zatloukal, Martin Reck, Milos Pesek, Joyce C. Thon Hugo E.R. Ford, Fred R. Hirsch, Marileila Varella-Garcia, Serban Ghiorghiu, Emma L. D Alison A. Armour, Georgina Speake, and Michael Cullen

Conclusion
There was no statistical difference between gefitinib and vinorelbine in efficacy in chemotherapy-naïve, unselected elderly patients with advanced NSCLC, but there was better tolerability with gefitinib. Individuals who were EGFR FISH-positive benefited more from vinorelbine than from gefitinib; this unexpected finding requires further study.

Investigational New Drugs **13**: 187-193, 1995.

Effects of vinorelbine on epidermal growth factor-receptor binding of human breast cancer cell lines *in vitro*

H. Depenbrock, A. Shirvani, J. Rastetter and A.-R. Hanauske

results 1/2

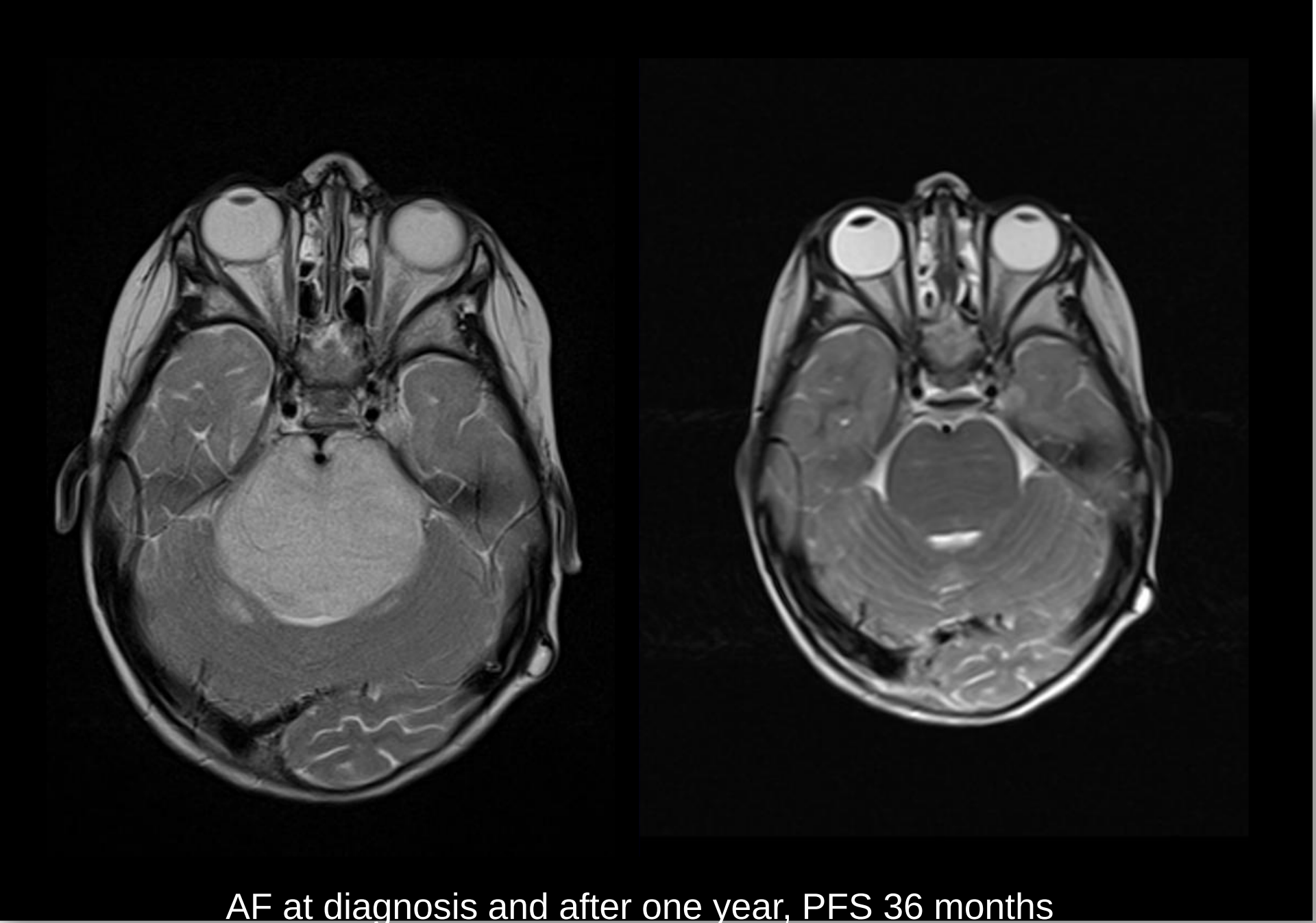
- **28/31 centrally confimed DIPG patients on 32 on treatment**
  - **3 excluded by external review because of HGG originating in medulla oblungata (2) and cerebellar peduncle (1)**
- **2 children with spinal mts at diagnosis and 1 dying after 1st radiation dose excluded from further analysis**
- **25 analysed: 15 males, 10 females**
- **Median age 7.4 years (2-17 yrs)**
- **4 biopsied**
  - **(2 diffuse astro, 2 anaplastic astro)**
- **Follow-up 5 - 44 months**

Table 8: 12-months survival status and overall survival (OS) (FAS)
*according to Kaplan-Meier method, **influenced by censored data,

results 2/2

- **18 progressed, 1 lost to follow-up with SD at 8 months**
- **3/18 dissemination, 1 locally + dissemination**
- **PFS 28% at 12 months and 17% at 24 months**
- **OS 73% at 12 months and 24% at 24 months**
- **Median PFS 8.5 months, median OS 14.6 months**

		BSC-05 (n=42)	Milan (n=25)
12-months Survival status *	alive dead	14 (33.3 %**) 28 (66.7 %**)	12 (67.7 %**) 7 (32.3 %**)
Overall survival (months)	Median 95%-CI	9.4 7.9; 11.6	14.6 11.8; 19.2
	$p_{Log\ rank}$	0.0057	



AF at diagnosis and after one year, PFS 36 months

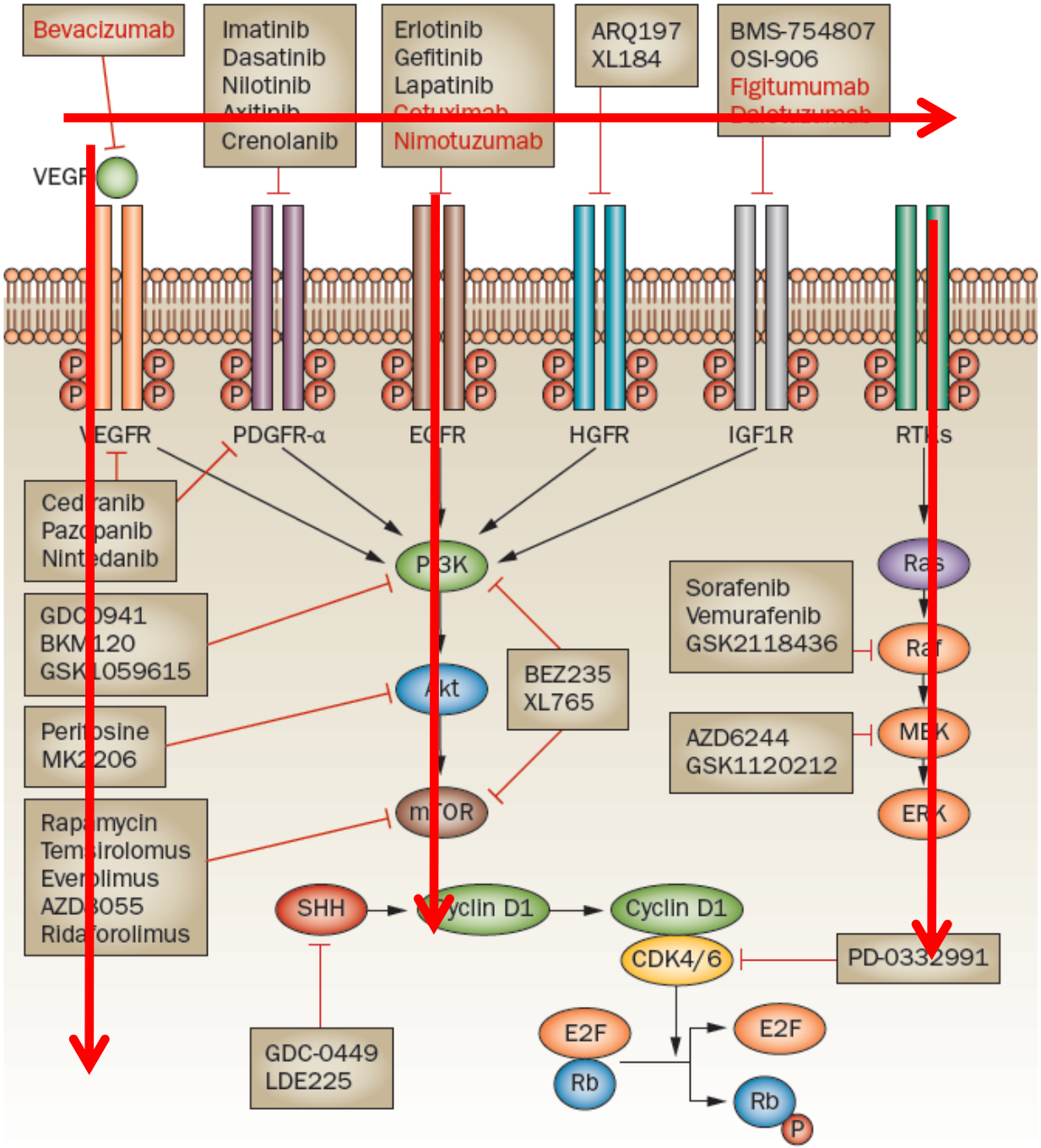
conclusions

- **The nimotuzumab/vinorelbine combination was very well tolerated, with no acute side-effects**
- **All children were treated on an outpatient basis**
- **This combination has significant differences with previous institutional and literature reported experiences**

The end (of my talk)

- **Until recently physicians have attempted to treat pediatric patients on the basis of data trials coming from adult experiences**
- **A growing body of molecular evidence now demonstrates that the prognosis and treatment of pediatric HGG require research to develop specific markers and therapies**

- The … ng
  pat… ould
  be t…
- …e… eptor
  tyro…
- ….c…
  dov…



Thank you for your attention..
and patience!!

maura.massimino@istitutotumori.mi.it

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI