Management of glioblastoma: The road towards stratified cancer care

ESMO, Vienna, 29 September 2012

Michael Weller
Department of Neurology
University Hospital Zurich
Switzerland

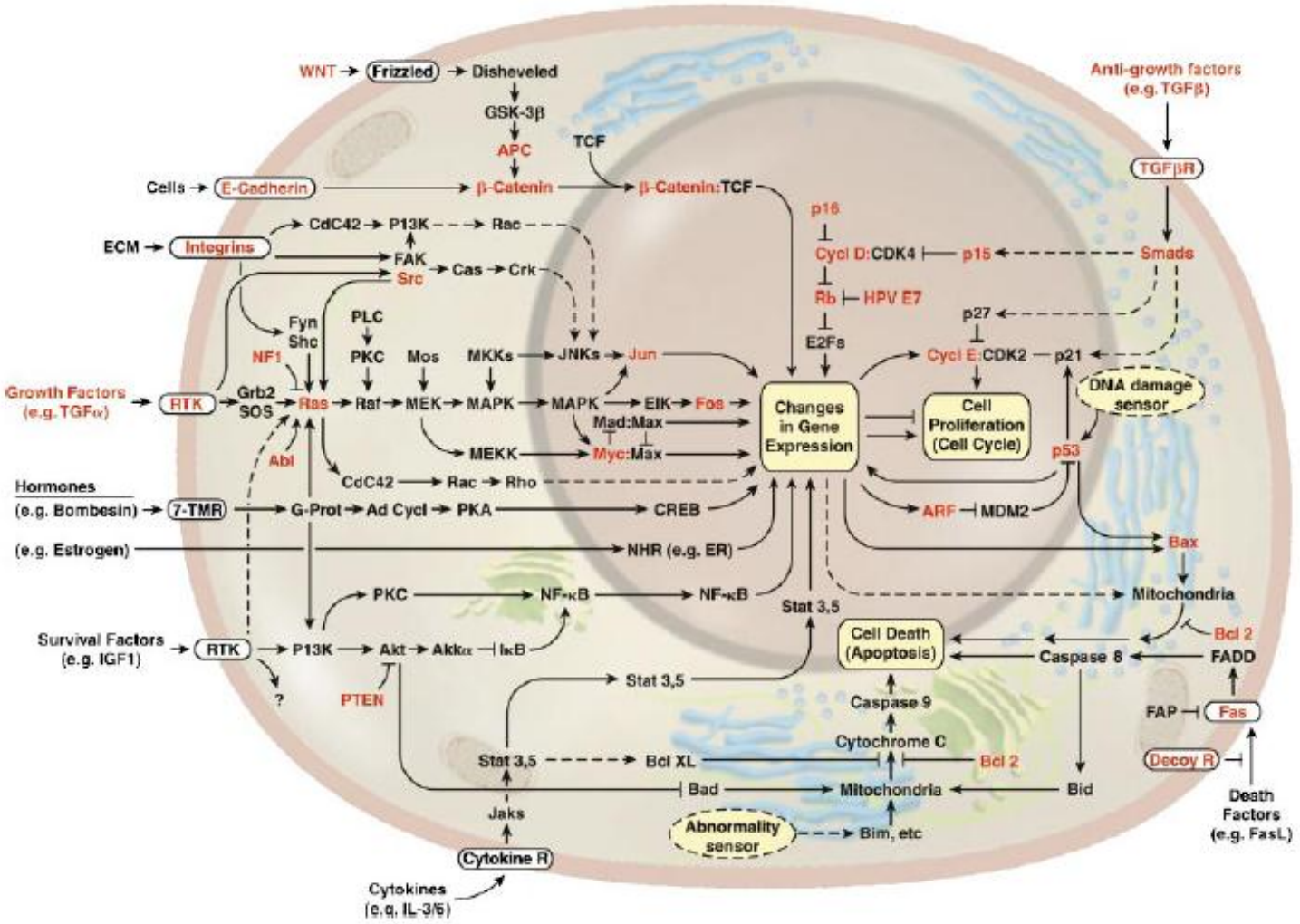
How do we select targets for intervention?

- Proliferation? Migration? Invasion?
- Understand tumor biology and interfere with tumor-related processes?
- Understand glioma biology and interfere with glioma-related processes?
- Consider genetic or expression signatures?
- Glioma targets or host targets?

Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

Douglas Hanahan* and Robert A. Weinberg†



Molecular targets of antiangiogenic therapies investigated in glioblastoma

Wick et al. Neuro-Oncology 2011;13:566-79

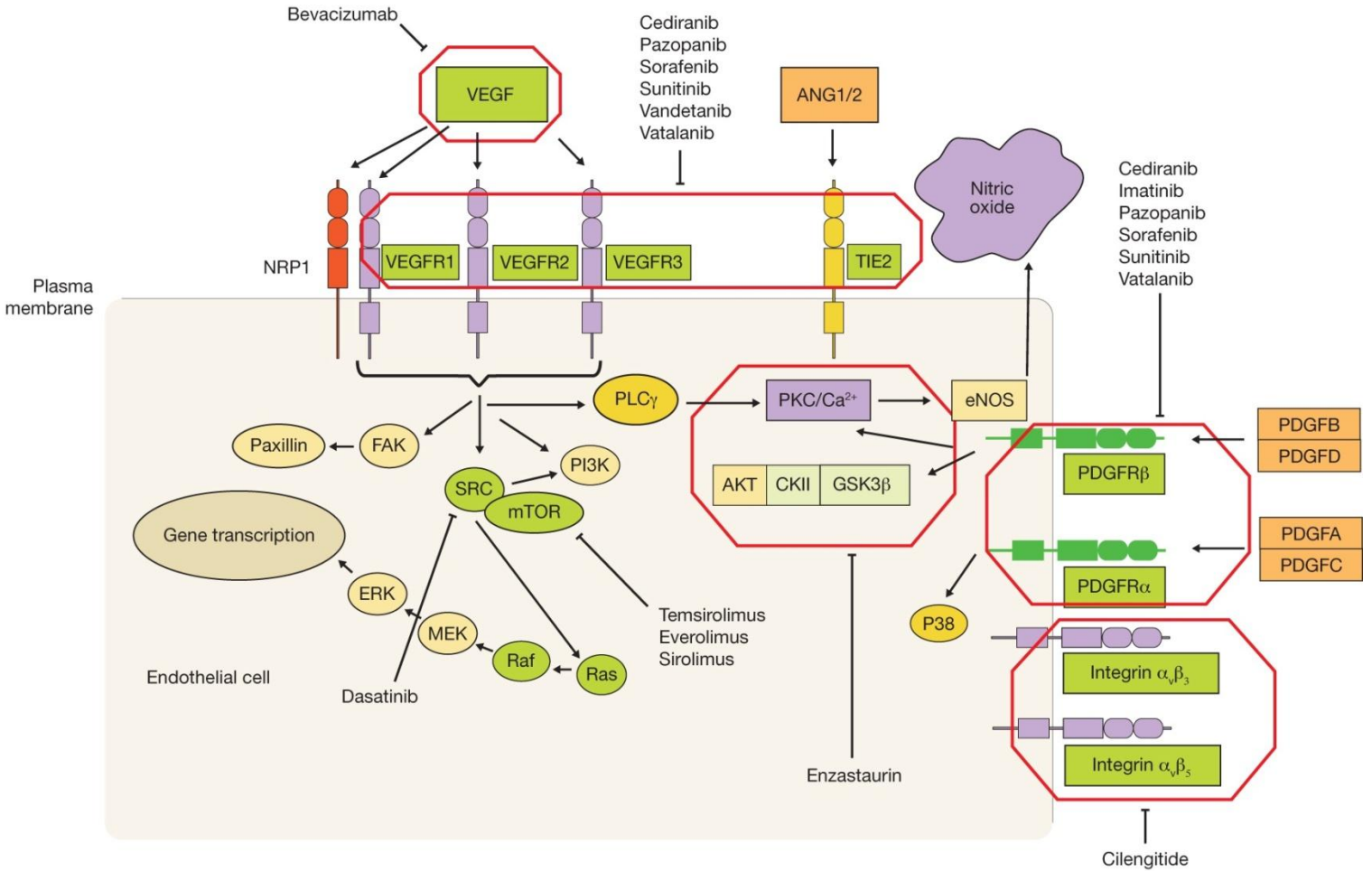


Fig. 2. Molecular targets of antiangiogenic therapies investigated in glioblastoma. ANG indicates angiopoietin; CKII indicates casein kinase II; eNOS indicates endothelial nitric oxide synthase; ERK indicates extracellular signal-regulated kinases; FAK indicates focal adhesion kinase; GSK3β indicates glycogen synthase kinase 3β; MEK indicates mitogen-activated protein kinase kinase; mTOR indicates mammalian target of rapamycin; PDGF(R) indicates platelet-derived growth factor (receptor); PI3K indicates phosphatidylinositol 3-kinase; PKC indicates protein kinase C; PLCγ indicates phopholipase Cγ; and VEGF(R) indicates vascular endothelial growth factor (receptor).

Antiangiogenic therapies for glioblastoma may not have to target proper endothelial cells

A new alternative mechanism in glioblastoma vascularization: tubular vasculogenic mimicry

Soufiane El Hallani,[1] Blandine Boisselier,[1] Florent Peglion,[1] Audrey Rousseau,[2] Carole Colin,[3] Ahmed Idbaih,[1,4] Yannick Marie,[1] Karima Mokhtari,[2] Jean-Léon Thomas,[1] Anne Eichmann,[5] Jean-Yves Delattre,[1,4] Andrew J. Maniotis[6] and Marc Sanson[1,4]

doi:10.1093/brain/awq044 Brain 2010: 133; 973–982 | 973

LETTER

doi:10.1038/nature09624

Glioblastoma stem-like cells give rise to tumour endothelium

Rong Wang[1,2,3], Kalyani Chadalavada[4], Jennifer Wilshire[5], Urszula Kowalik[1], Koos E. Hovinga[1,6], Adam G
Margaret Leversha[4], Cameron Brennan[1,3,7] & Viviane Tabar[1,2,3]

LETTER

doi:10.1038/nature09557

Tumour vascularization via endothelial differentiation of glioblastoma stem-like cells

Lucia Ricci-Vitiani[1]*, Roberto Pallini[2]*, Mauro Biffoni[1], Matilde Todaro[3], Gloria Invernici[4], Tonia Cenci[5], Giulio Maira[2], Eugenio Agostino Parati[4], Giorgio Stassi[3,6], Luigi Maria Larocca[5] & Ruggero De Maria[1,7]

Transdifferentiation of glioblastoma cells into vascular endothelial cells

Yasushi Soda[a], Tomotoshi Marumoto[a,b], Dinorah Friedmann-Morvinski[a], Mie Soda[a], Fei Liu[a], Hiroyuki Michiue[c], Sandra Pastorino[d], Meng Yang[e], Robert M. Hoffman[e,f], Santosh Kesari[d], and Inder M. Verma[a,1]

4274–4280 | PNAS | March 15, 2011 | vol. 108 | no. 11

UniversitätsSpital Zürich

Astrocyte or glial precursor cell

***TP53* mutation (≈60%)**

MGMT promoter methylation (60-70%)

***IDH-1* mutation (≈70%)**

+ 7q
+ 12p

-9p21 (*CDKN2A, p14*^{ARF})

-13q (*RB1*)

TP53 mutation (≈25%)

-10 (≈70%)
***PTEN* mutation (≈30%)**

MGMT promoter methylation (≈40%)

+ 7
+ 19
+ 20

Gene amplification (≈50%):
EGFR, *CDK4*, *MDM2*, *MDM4*, or other genes

IDH-1 mutation (≈5%)

Astrocytoma WHO grade II

- 9p21 (*CDKN2A*)
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-10q (≈70%)
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Primary glioblastoma WHO grade IV

Secondary glioblastoma WHO grade IV

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***TP53* mutation (≈60%)**

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+ 7q

-9p21

TP5

PTE

M
me

Are the genetic changes that are associated with the development of gliomas relevant for the clinial course and response to current standards of care?

Primary glioblastoma WHO grade IV

Secondary glioblastoma WHO grade IV

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TP5

PTEN

M

me

Are the genetic changes that are associated with the development of gliomas relevant for the clinial course and response to current standards of care?

No, but we could still target them specifically …

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Secondary glioblastoma WHO grade IV

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MGMT promoter methylation in malignant gliomas: ready for personalized medicine?

Michael Weller, Roger Stupp, Guido Reifenberger, Alba A. Brandes, Martin J. van den Bent, Wolfgang Wick and Monika E. Hegi

Nat. Rev. Neurol. **6**, 39–51 (2010)

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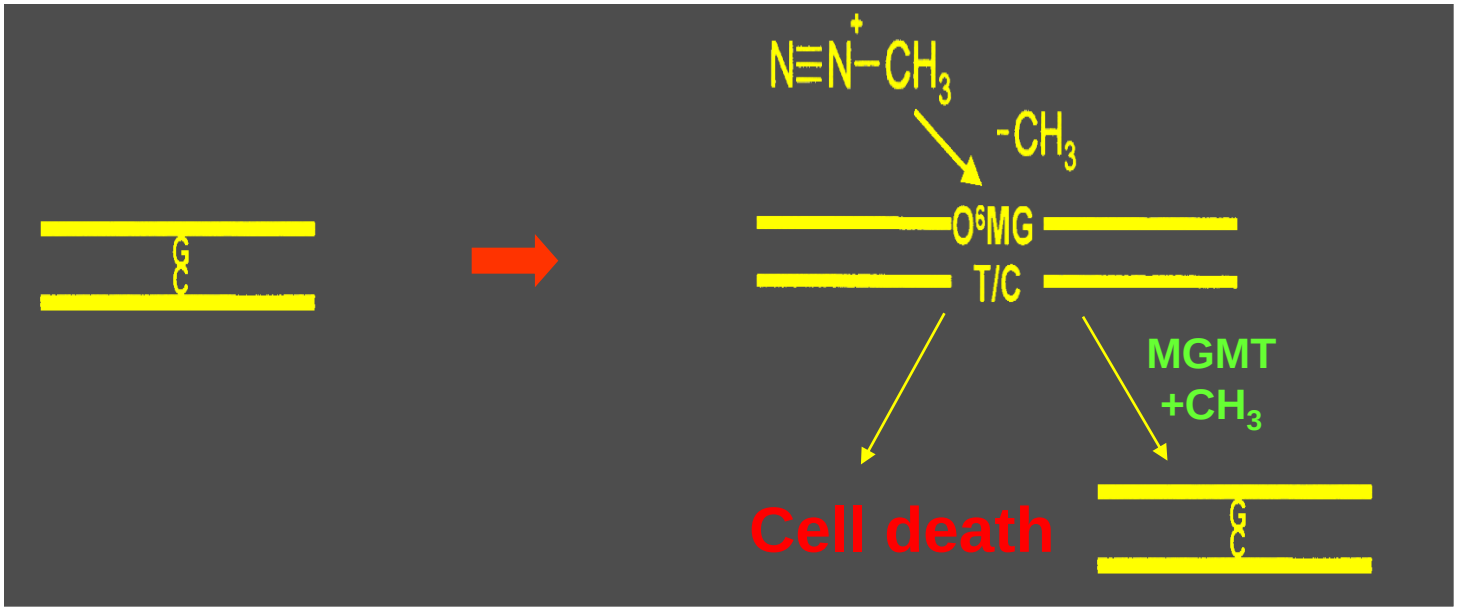
O^6-Methylguanin-methyltransferase (MGMT, AGAT), a DNA repair enzyme, counteracts the effect of alkylating agents:



MGMT promoter methylation in malignant gliomas: ready for personalized medicine?

Michael Weller, Roger Stupp, Guido Reifenberger, Alba A. Brandes, Martin J. van den Bent, Wolfgang Wick and Monika E. Hegi

Nat. Rev. Neurol. **6**, 39–51 (2010)

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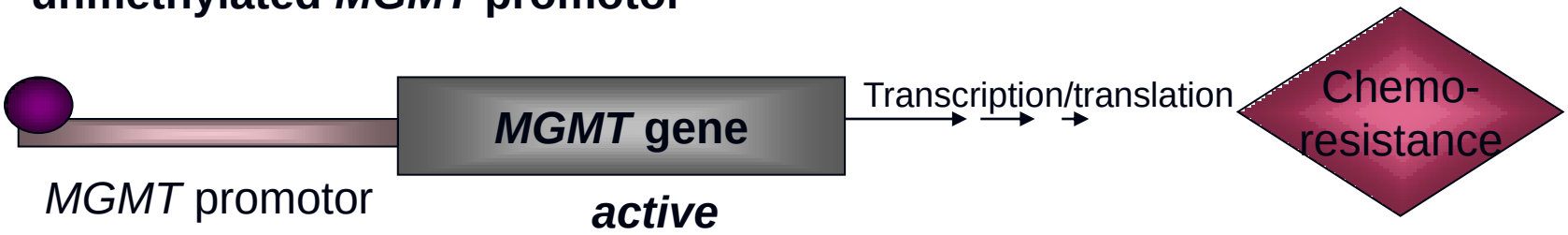
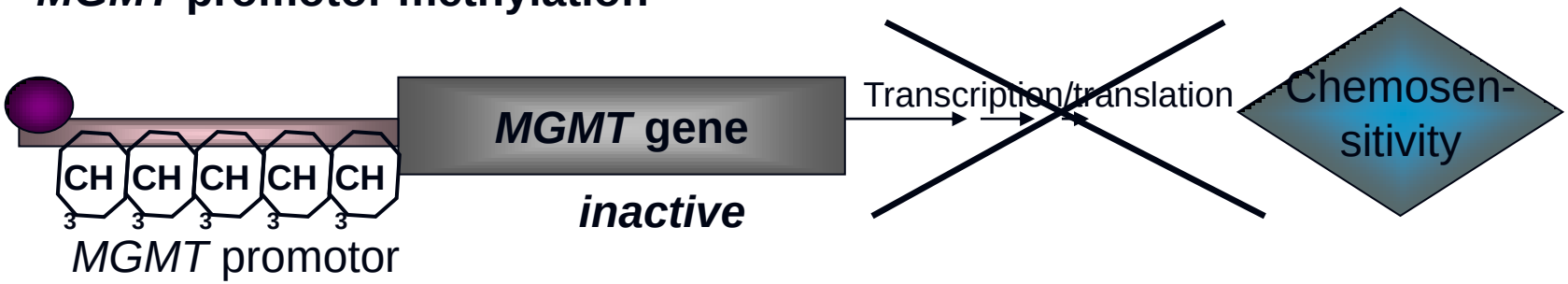
unmethylated *MGMT* promotor



***MGMT* promotor methylation**



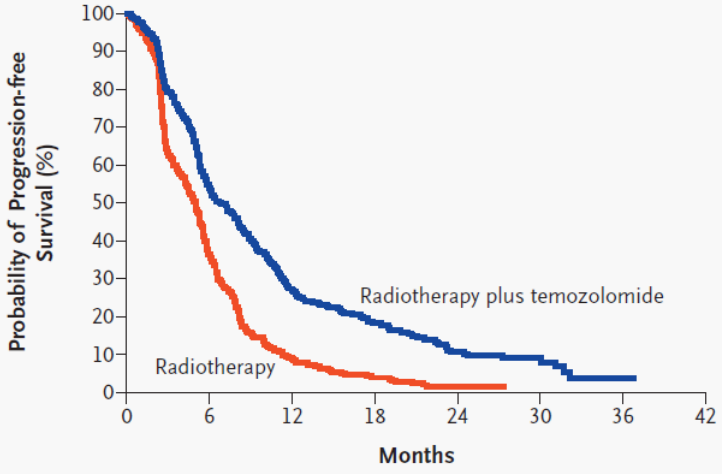
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

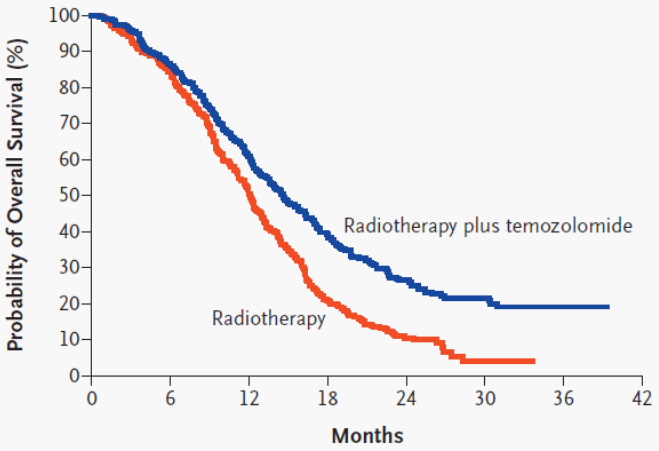
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

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



No. at Risk							
Radiotherapy	286	104	26	11	4	0	0
Radiotherapy plus temozolomide	287	154	77	51	24	8	1



No. at Risk							
Radiotherapy	286	240	144	59	23	2	0
Radiotherapy plus temozolomide	287	246	174	109	57	27	4

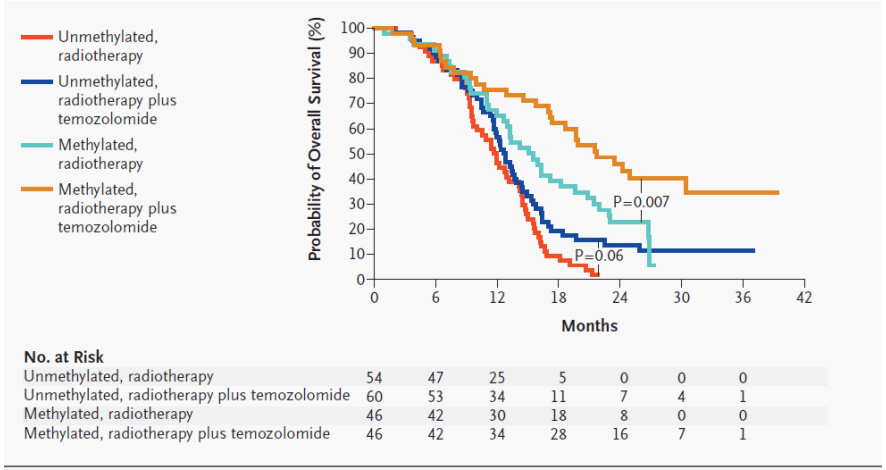
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

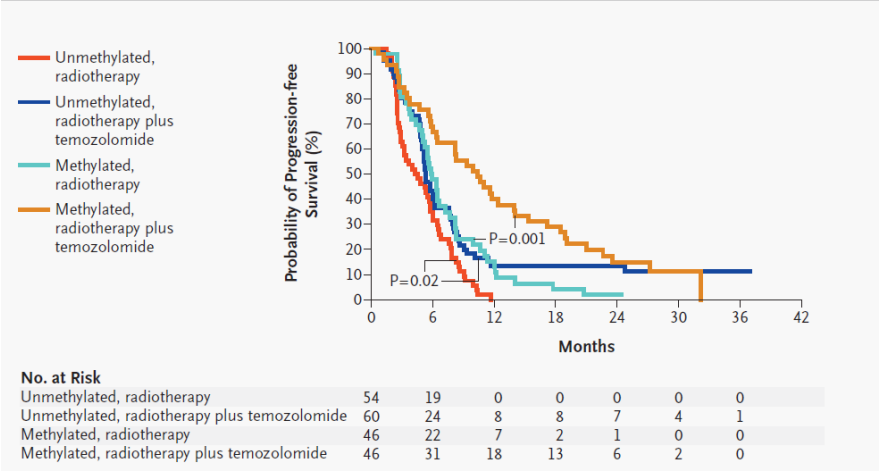
Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc., Marie-France Hamou, Nicolas de Tribolet, M.D., Michael Weller, M.D., Johan M. Kros, M.D., Johannes A. Hainfellner, M.D., Warren Mason, M.D., Luigi Mariani, M.D., Jacoline E.C. Bromberg, M.D., Peter Hau, M.D., René O. Mirimanoff, M.D., J. Gregory Cairncross, M.D., Robert C. Janzer, M.D., and Roger Stupp, M.D.

N Engl J Med 2005;352:997-1003.



No. at Risk

Unmethylated, radiotherapy	54	47	25	5	0	0	0
Unmethylated, radiotherapy plus temozolomide	60	53	34	11	7	4	1
Methylated, radiotherapy	46	42	30	18	8	0	0
Methylated, radiotherapy plus temozolomide	46	42	34	28	16	7	1

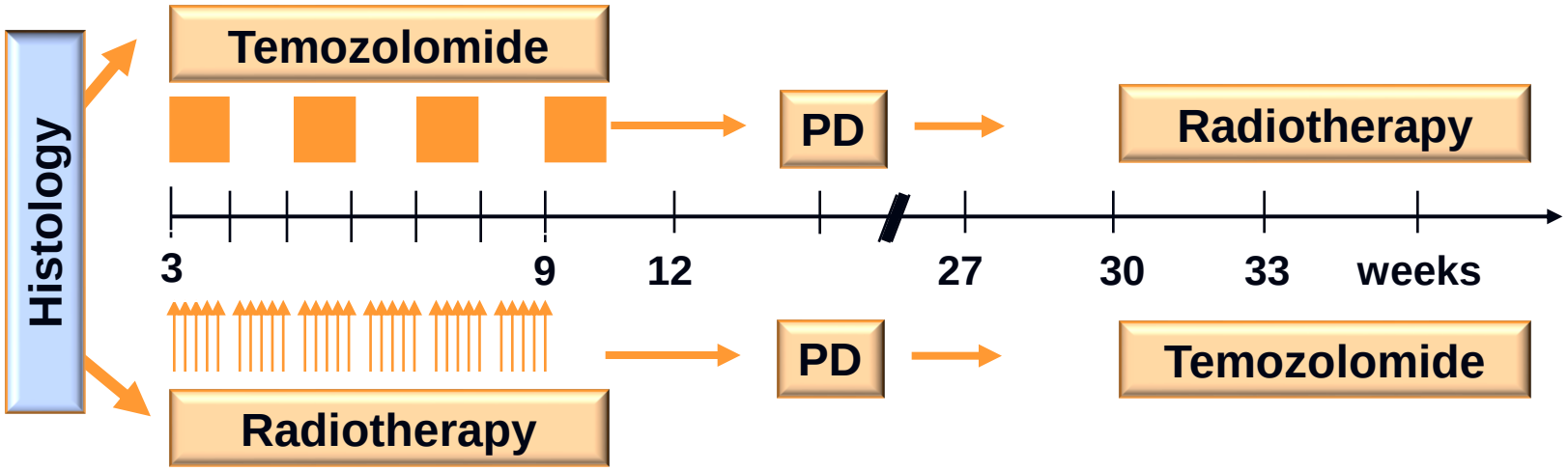


No. at Risk

Unmethylated, radiotherapy	54	19	0	0	0	0	0
Unmethylated, radiotherapy plus temozolomide	60	24	8	8	7	4	1
Methylated, radiotherapy	46	22	7	2	1	0	0
Methylated, radiotherapy plus temozolomide	46	31	18	13	6	2	0

NOA-08/Methvsalem: Design

Temozolomide *(one week on/one week off)* vs radiotherapy in the primary treatment of anaplastic astrocytoma and glioblastoma in older patients: a randomized phase III study



TMZ 100 mg/m^2 po/day for 7 days every 14 days until failure of therapy, to be adjusted in 25-mg steps

Focal radiotherapy daily — 30 x 1.8-2 Gy to a total 54–60 Gy

Deutsche Krebsgesellschaft e.V.
Gütesiegel A

TMZ is not inferior to RT

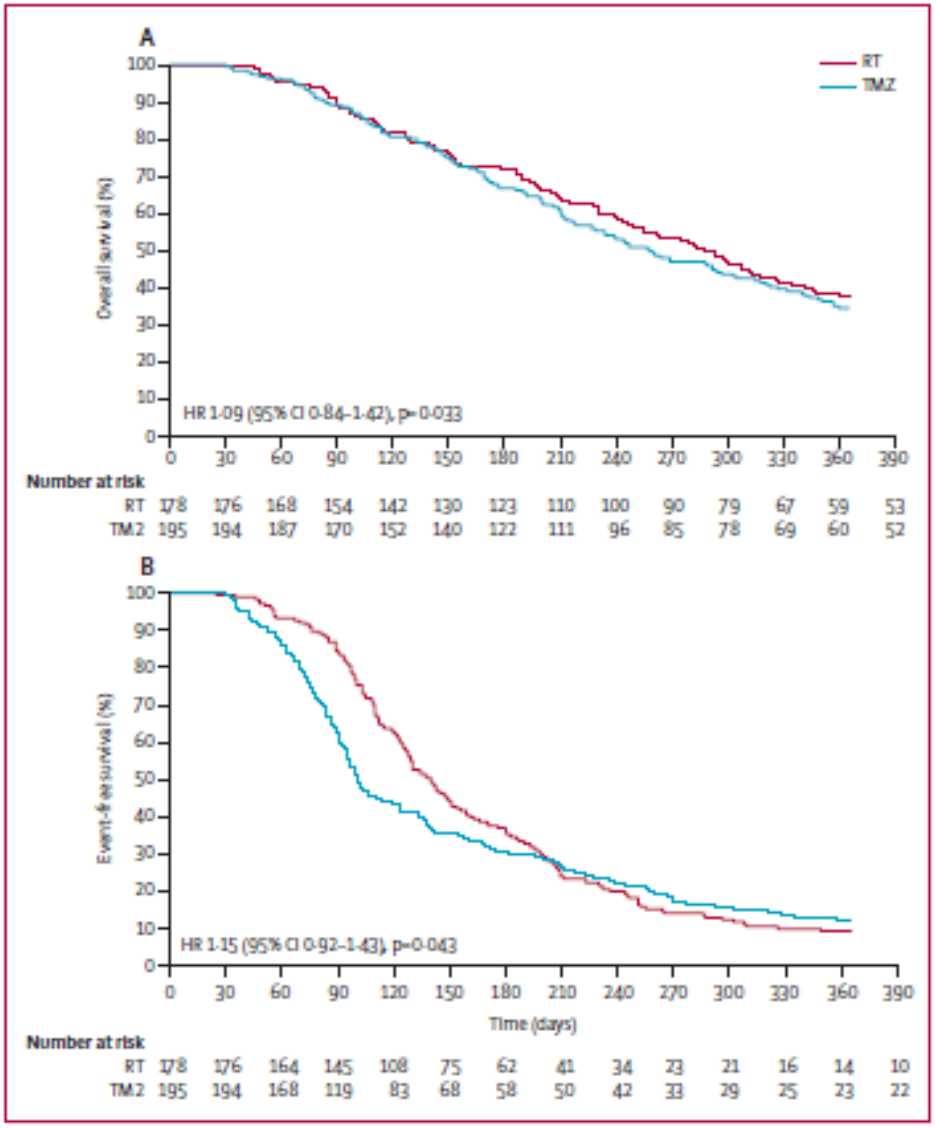


Figure 2: Kaplan-Meier analysis of overall and event-free survival
(A) Overall survival. (B) Event-free survival presented as non-proportional curves, which are deemed non-problematic in the context of non-inferiority. RT=radiotherapy. TMZ=temozolomide. HR=hazard ratio.

MGMT is a prognostic biomarker

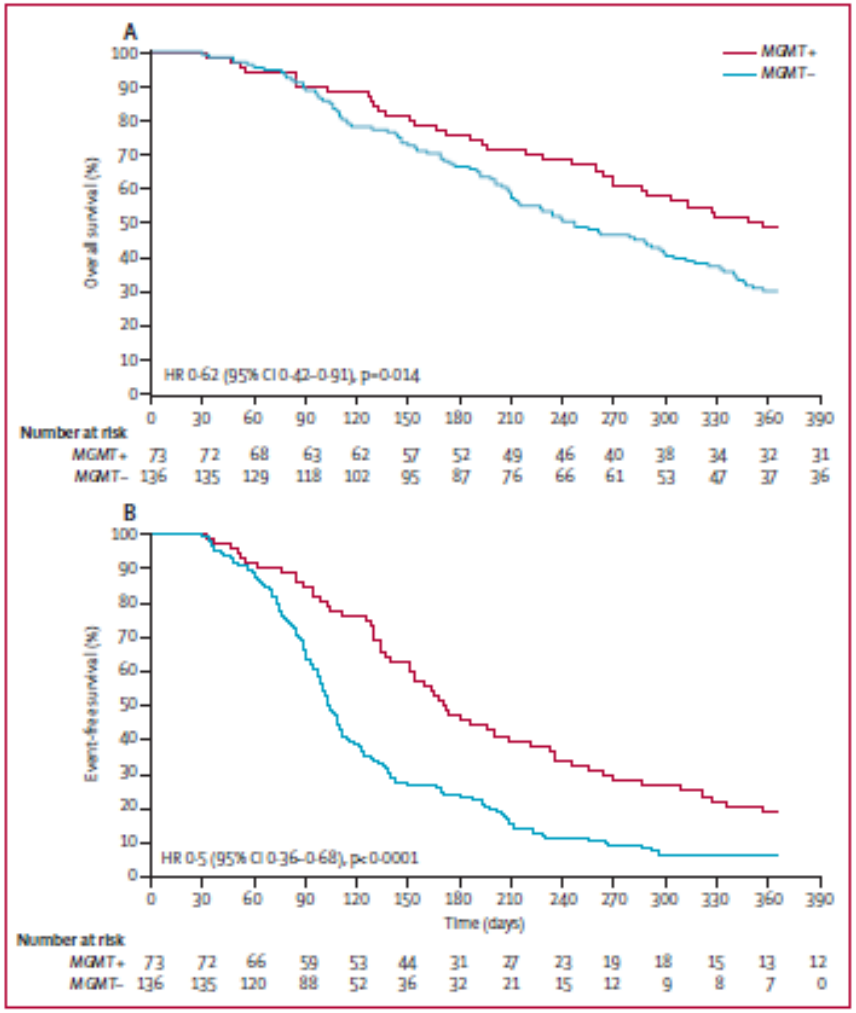


Figure 3: **Kaplan-Meier analysis of overall and event-free survival in relation to MGMT promoter methylation status**
(A) Overall survival. (B) Event-free survival. HR=hazard ratio.

MGMT is a predictive biomarker

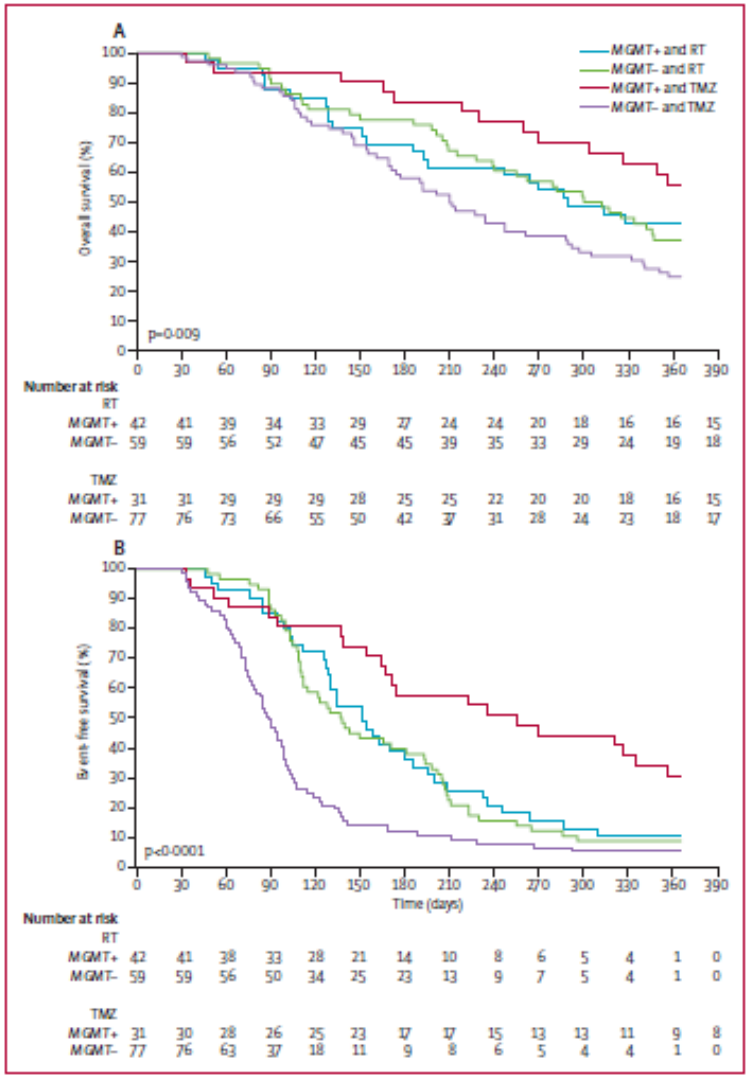


Figure 4: Kaplan-Meier analysis of overall and event-free survival in relation to *MGMT* promoter methylation status and treatment

(A) Overall survival. (B) Event-free survival. The p values were calculated for any significant difference in at least two of the curves. See also table 3. RT=radiotherapy. TMZ=temozolomide.

	Hazard ratio (95% CI)	p value
Overall survival		
Age (years)	1·02 (0·98–1·06)	0·285
Complete resection *vs* incomplete resection *vs* biopsy*	1·84 (1·44–2·35)	<0·0001
Anaplastic astrocytoma *vs* glioblastoma	0·69 (0·38–1·22)	0·201
MGMT promoter methylation†		
Temozolomide group, methylated	0·69 (0·35–1·16)	0·139
Radiotherapy group, methylated and unmethylated	1·0‡	..
Temozolomide group, unmethylated	1·34 (0·92–1·95)	0·129
Event-free survival		
Age (years)	1·01 (0·98–1·04)	0·674
Resection		
Complete resection *vs* incomplete resection *vs* biopsy*	1·29 (1·07–1·56)	0·008
Anaplastic astrocytoma *vs* glioblastoma	0·75 (0·45–1·24)	0·255
MGMT promoter methylation†		
Temozolomide group, methylated	0·53 (0·33–0·86)	0·01
Radiotherapy group, methylated and unmethylated	1·0‡	..
Temozolomide group, unmethylated	1·95 (1·41–2·69)	0·01

*Status unavailable for one patient. †Data available for 209 patients. ‡Reference.

Table 3: Prognostic and predictive factors for overall and event-free survival with temozolomide on multivariate Cox's regression analysis

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***TP53* mutation (≈60%)**

MGMT promoter methylation (60-70%)

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Journal of Clinical Neuroscience 16 (2009) 748–754

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

The EGFRvIII variant in glioblastoma multiforme

Hui K. Gan [a], Andrew H. Kaye [b,c], Rodney B. Luwor [b,*]

[a] Department of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto, Canada
[b] Department of Surgery, Level 6, Clinical Sciences Building, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia
[c] Department of Neurosurgery, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia

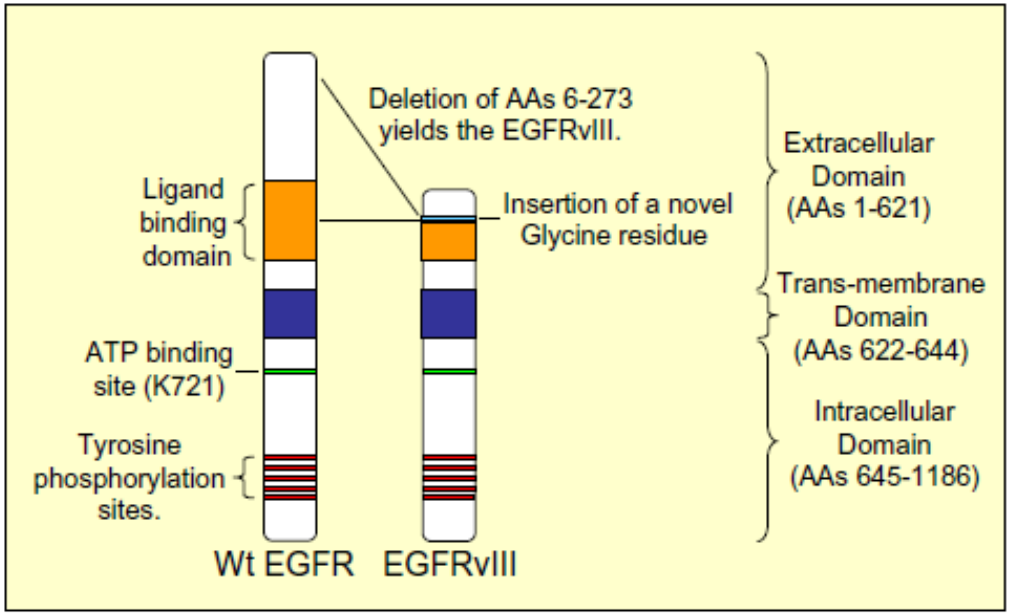

Fig. 1. Schematic of the epidermal growth factor receptor (EGFR)vIII truncation. The EGFRvIII variant receptor is characterized by a deletion of exons 2–7 of the wild type (Wt) *EGFR* gene. This results in an in-frame truncation of amino acids (AA) 6 to 273 in the extracellular domain of the full length protein, yielding a constitutively active variant receptor that can not bind ligand. The EGFRvIII also contains a novel glycine residue inserted at the fusion junction.

Immunologic Escape After Prolonged Progression-Free Survival With Epidermal Growth Factor Receptor Variant III Peptide Vaccination in Patients With Newly Diagnosed Glioblastoma

John H. Sampson, Amy B. Heimberger, Gary E. Archer, Kenneth D. Aldape, Allan H. Friedman, Henry S. Friedman, Mark R. Gilbert, James E. Herndon II, Roger E. McLendon, Duane A. Mitchell, David A. Reardon, Raymond Sawaya, Robert J. Schmittling, Weiming Shi, James J. Vredenburgh, and Darell D. Bigner

J Clin Oncol 28:4722-4729. © 2010 by American Society of Clinical Oncology

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Table 3. *EGFRvIII* Immunohistochemistry Before and After Vaccination

Before Vaccination	At Recurrence
Positive	Negative
Positive	Negative
Positive	Negative
Positive	Positive (< 1%)
Positive	Negative
Positive	Negative
Positive	Negative
Positive	Negative
Positive	Negative
Positive	Positive
Positive	Negative

NOTE. Percent negative after vaccine is 82% (95% CI, 48% to 97%) or nine of 11; binomial test $P < .001$.
Abbreviation: *EGFRvIII*, epidermal growth factor receptor variant III.

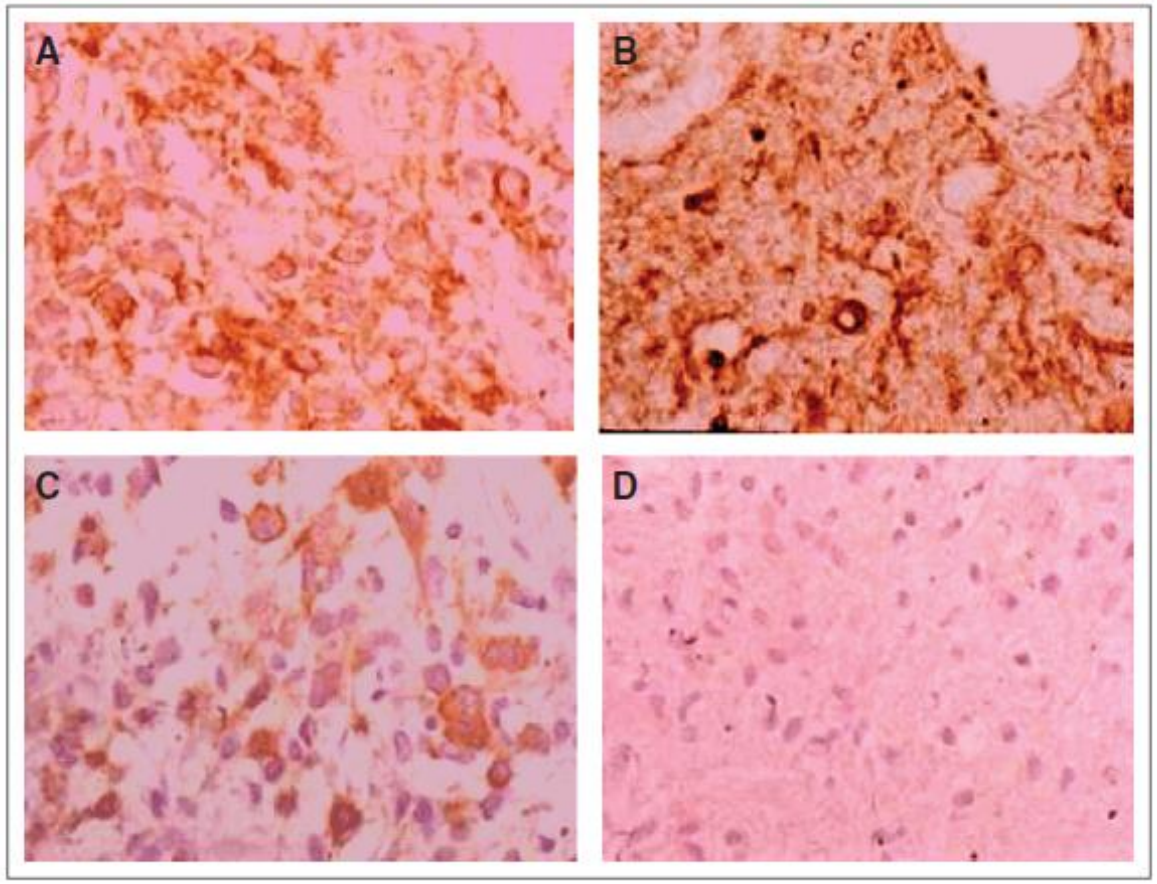

Fig 3. Epidermal growth factor receptor (EGFR) and EGFR variant III (*EGFRvIII*) immunohistochemistry of a patient with glioblastoma multiforme (GBM). Staining with (A) EGFR and (B) *EGFRvIII* before vaccine. (C) Preservation of EGFR staining but (D) specific loss of *EGFRvIII* staining at recurrence after vaccination.

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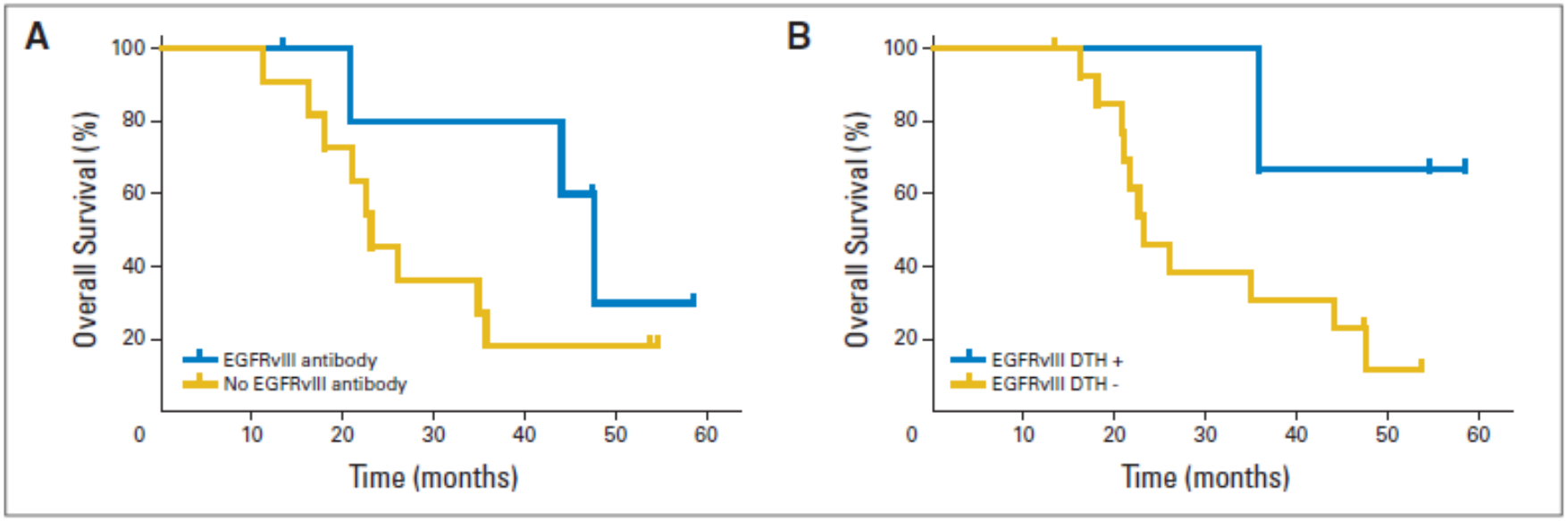
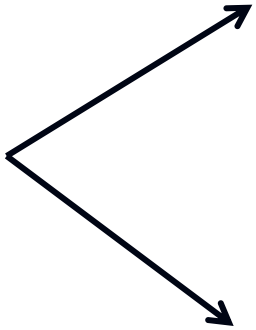


Fig 4. Immune response correlates. Overall survival (OS) from histologic diagnosis for all patients for whom serum was available to test for epidermal growth factor receptor variant III (*EGFRvIII*) –specific antibody titers (n = 14; left) and delayed-type hypersensitivity (DTH; n = 17; right). The blue line shows patients with *EGFRvIII*-specific immune responses, and the gold line shows patients without *EGFRvIII*-specific responses. Left: The median OS for the six patients who developed *EGFRvIII*-specific antibody responses was 47.7 months (95% CI, 20.8 to ∞ months). For the eight patients who did not develop antibody responses, the OS was only 22.8 months (95% CI, 21.0 to 34.9 months). After adjustment for age, Karnofsky performance status, and methylguanine methyltransferase methylation, the OS from vaccination of the patients who developed antibody responses was found to be greater (hazard ratio, 0.08; 95% CI, 0.007 to 0.93; $P = .043$). Right: The median OS for the three patients who developed DTH responses specific for PEPvIII (a 13-amino-acid peptide with an additional terminal cysteine that spans the *EGFRvIII* mutation) has not been reached at 50 months. For the 14 patients who did not develop DTH responses to PEPvIII, the OS was 23.1 months (95% CI, 21.0 to 44.1 months). Patients who developed PEPvIII DTH responses had a significantly longer OS ($P = .03$).

EORTC 26112-22115
Trial Design

- RT/TMZ completed
- EGFRvIII mutation
- Tumor ≤ 2 cm



Adjuvant TMZ/Placebo ► P Maintenance

Adjuvant TMZ/Rindopepimut ► R Maintenance

- **Double-blind vaccination**
- ***Priming*: 2 injections, 2 weeks post RT/TMZ**
- **During adjuvant TMZ: 1 injection day 22 each cycle**
- **Maintenance: 1 weekly injection**