



# **Genetic basis of glioma and potential for personalised medicine**

## **Bali, Indonesia, 11 April 2010**



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**Switzerland**





# Astrocyte or glial precursor cell

**TP53 mutation (≈60%)**

**IDH-1 mutation (≈70%)**

*MGMT* promoter  
methylation (60-70%)

+ 7q  
+ 12p

**Astrocytoma  
WHO grade II**

- 9p21 (*CDKN2A*)  
- 13q (*RB1*)  
- 19q13.3

**Anaplastic astrocytoma  
WHO grade III**

- 10q (≈70%)  
*PTEN* mutation (<5%)

**Secondary glioblastoma  
WHO grade IV**

-9p21 (*CDKN2A*, *p14<sup>ARF</sup>*)  
-13q (*RB1*)

*TP53* mutation (≈25%)

-10 (≈70%)  
***PTEN* mutation (≈30%)**

*MGMT* promoter  
methylation (≈40%)

**Primary glioblastoma  
WHO grade IV**

+ 7  
+ 19  
+ 20  
**Gene amplification  
(≈50%):**  
*EGFR*, *CDK4*,  
*MDM2*, *MDM4*,  
or other genes

*IDH-1* mutation (≈5%)



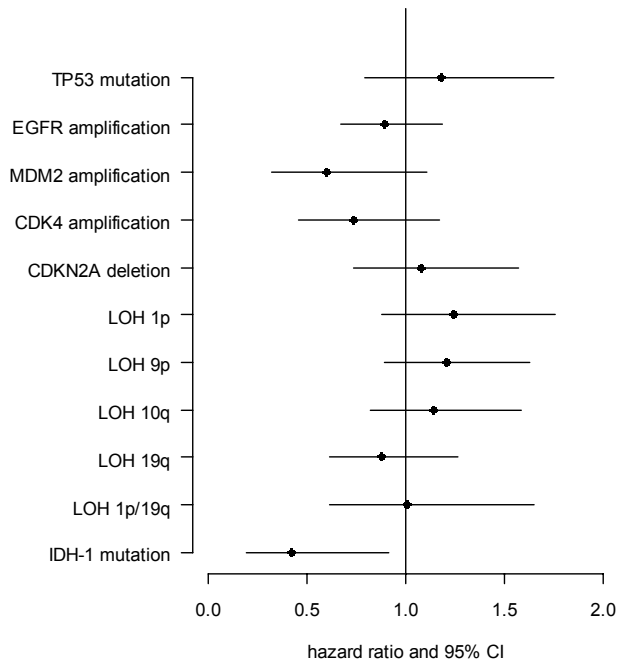
# Key questions

- Are the genetic changes that are associated with the development of gliomas relevant for the clinical course and response to treatment?
- Which molecular markers are prognostic (**independent** of therapy)?
- Which molecular markers are predictive (**dependent** of therapy)?

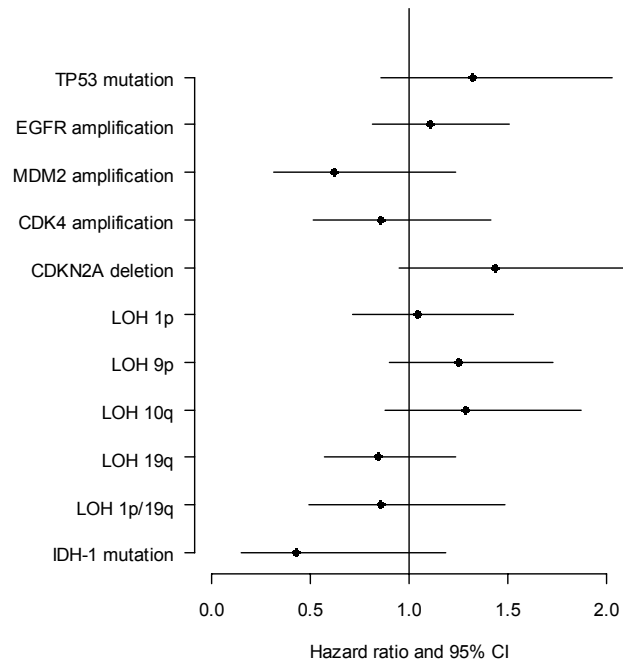
### Molecular Predictors of Progression-Free and Overall Survival in Patients With Newly Diagnosed Glioblastoma: A Prospective Translational Study of the German Glioma Network

Michael Weller, Jörg Felsberg, Christian Hartmann, Hilmar Berger, Joachim P. Steinbach, Johannes Schramm, Manfred Westphal, Gabriele Schückert, Matthias Simon, Jörg C. Tonn, Oliver Heese, Dietmar Krex, Guido Ninkovic, Torsten Pietsch, Ottmar Wiestler, Guido Reifenberger, Andreas von Deining, and Markus Loeffler

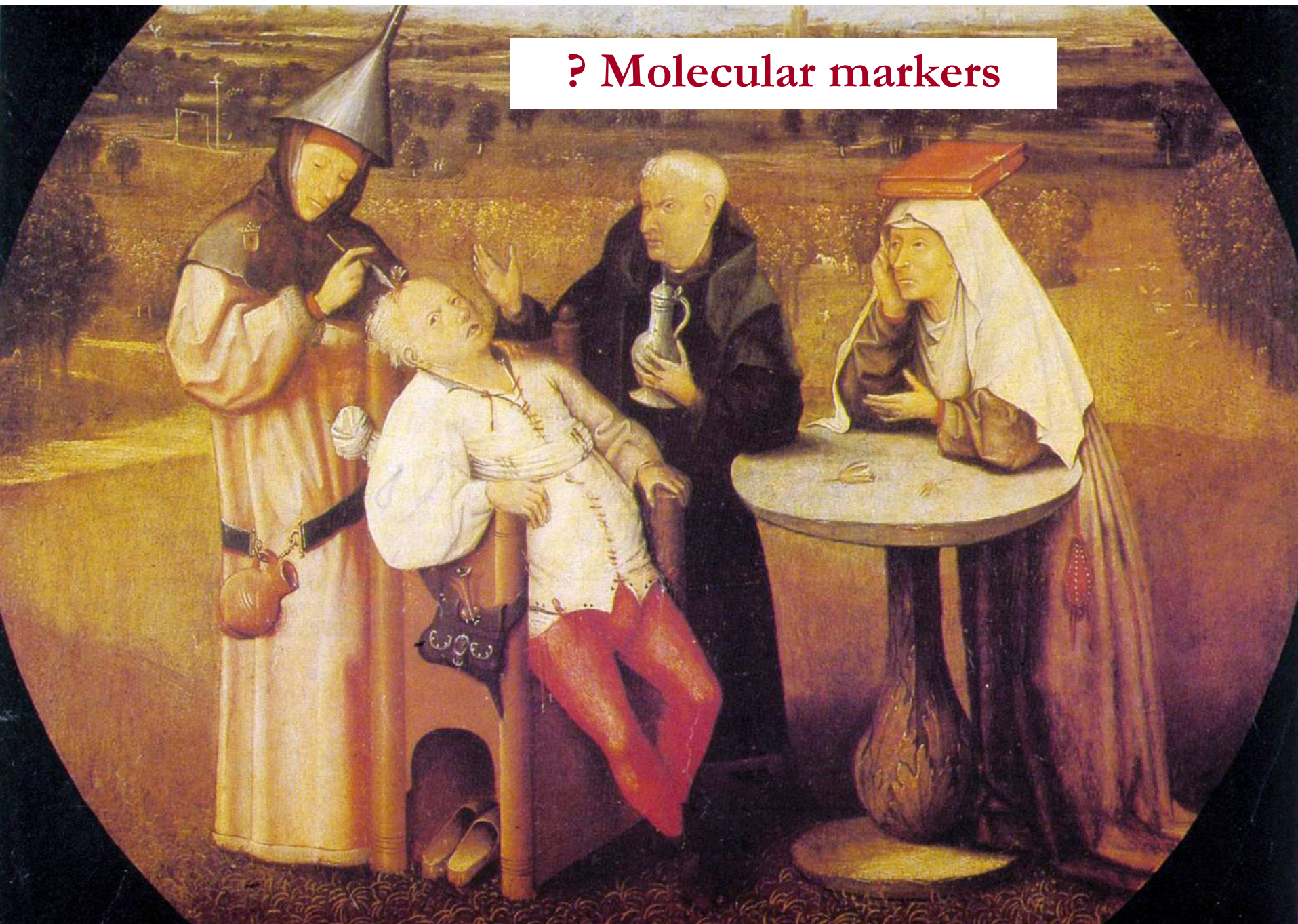
Molecular genetic markers - PFS



Molecular genetic markers - OS



# ? Molecular markers





# **Molecular markers for clinical decision making should.....**

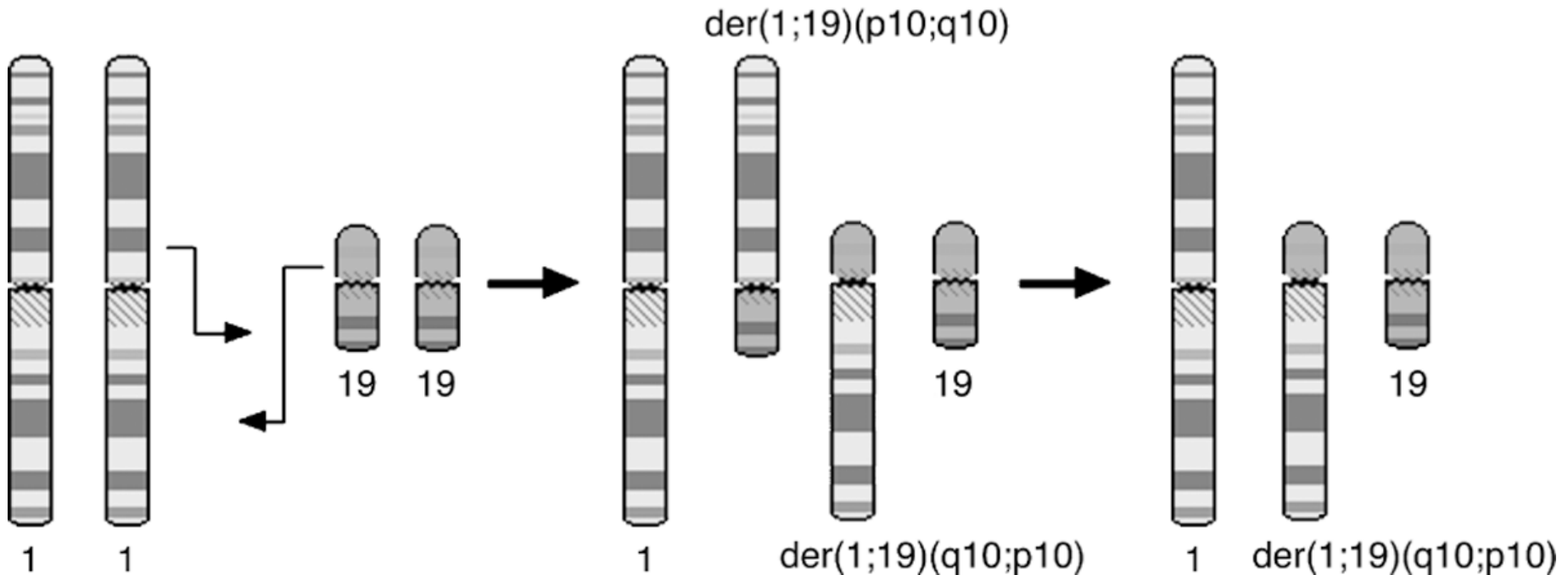
- **allow prognostic estimates**
- **complement histologic diagnoses**
- **allow individualized treatment allocation**
- **avoid unnecessary therapeutic measures and thereby ...**
- **reduce toxicity and costs**



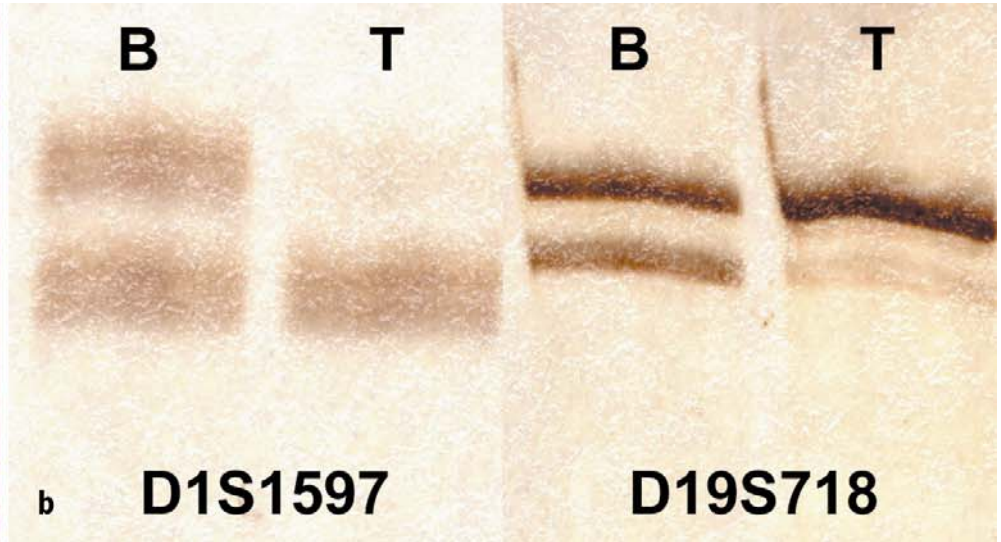
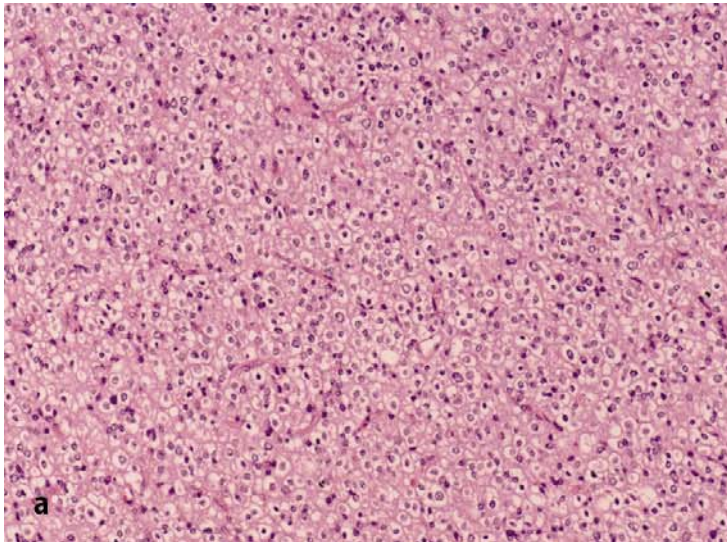
# Candidate molecular markers for clinical use in glioma therapy

- ***P53* mutations**
- ***EGFR* amplification / phosphorylation**
- **Loss of heterozygosity 1p/19q**
- ***MGMT* promoter methylation**
- **Isocitrate dehydrogenase (*IDH*) mutations**

# Combined loss of 1p and 19q resulting from an unbalanced translocation $t(1;19)(q10;p10)$



# *Loss of heterozygosity 1p/19q*



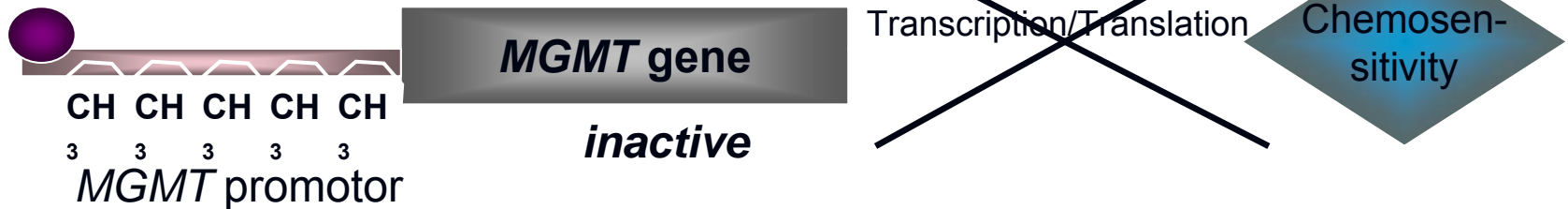
# *MGMT* promoter methylation in malignant gliomas: ready for personalized medicine?

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

## unmethylated *MGMT* promotor

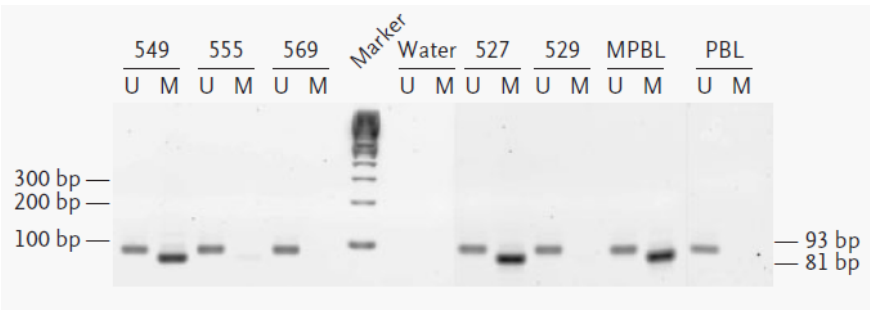


## *MGMT* promotor methylation



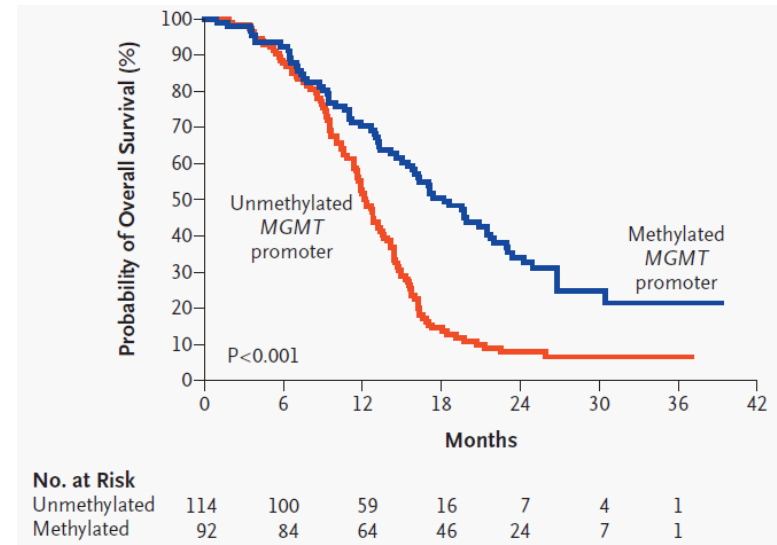
## MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Monika E. Hegl, 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.



**Figure 1. Methylation Status of the MGMT Promoter in Glioblastoma Biopsy Specimens, as Determined by a Nested Methylation-Specific PCR Assay.**

DNA from normal peripheral blood lymphocytes (PBL) was used as a control for the unmethylated MGMT promoter (U), enzymatically methylated DNA from PBL (MPBL) served as a positive control for the methylated MGMT promoter (M), and water was used as a negative control for the PCR. A 100-bp marker ladder was loaded to estimate molecular size, as shown on the left scale; the sizes of PCR products are indicated on the right scale. Glioblastoma numbers 549 and 527 contain a methylated promoter, whereas 555, 569, and 529 harbor only an unmethylated promoter. The nested PCR approach renders the analysis highly sensitive, while allowing it to retain the specificity that results in the detection of unmethylated MGMT promoter in all specimens that may also contain DNA derived from infiltrating lymphocytes, blood vessels, or contaminating normal tissue.

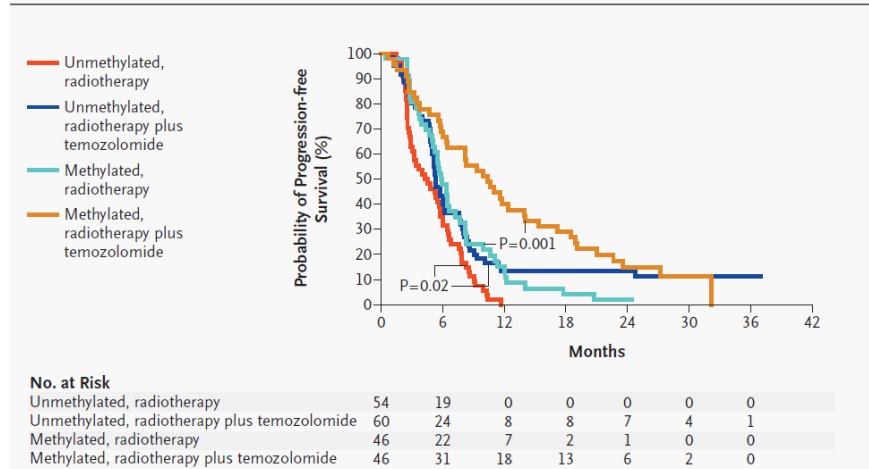
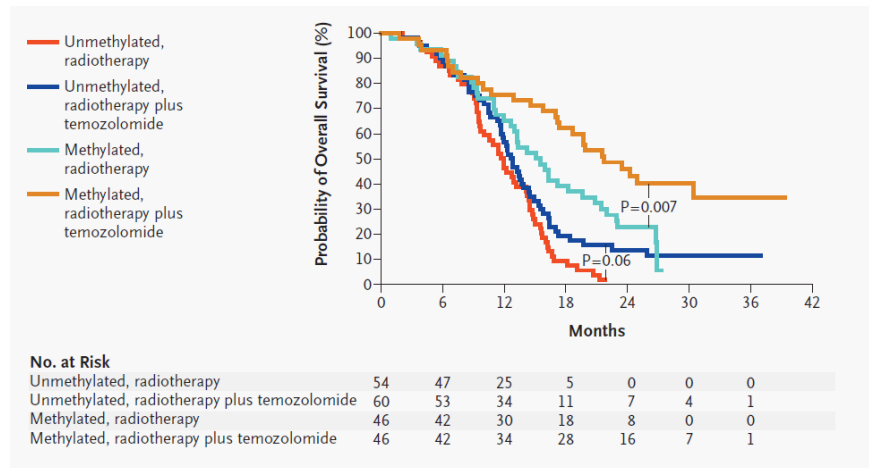




ORIGINAL ARTICLE

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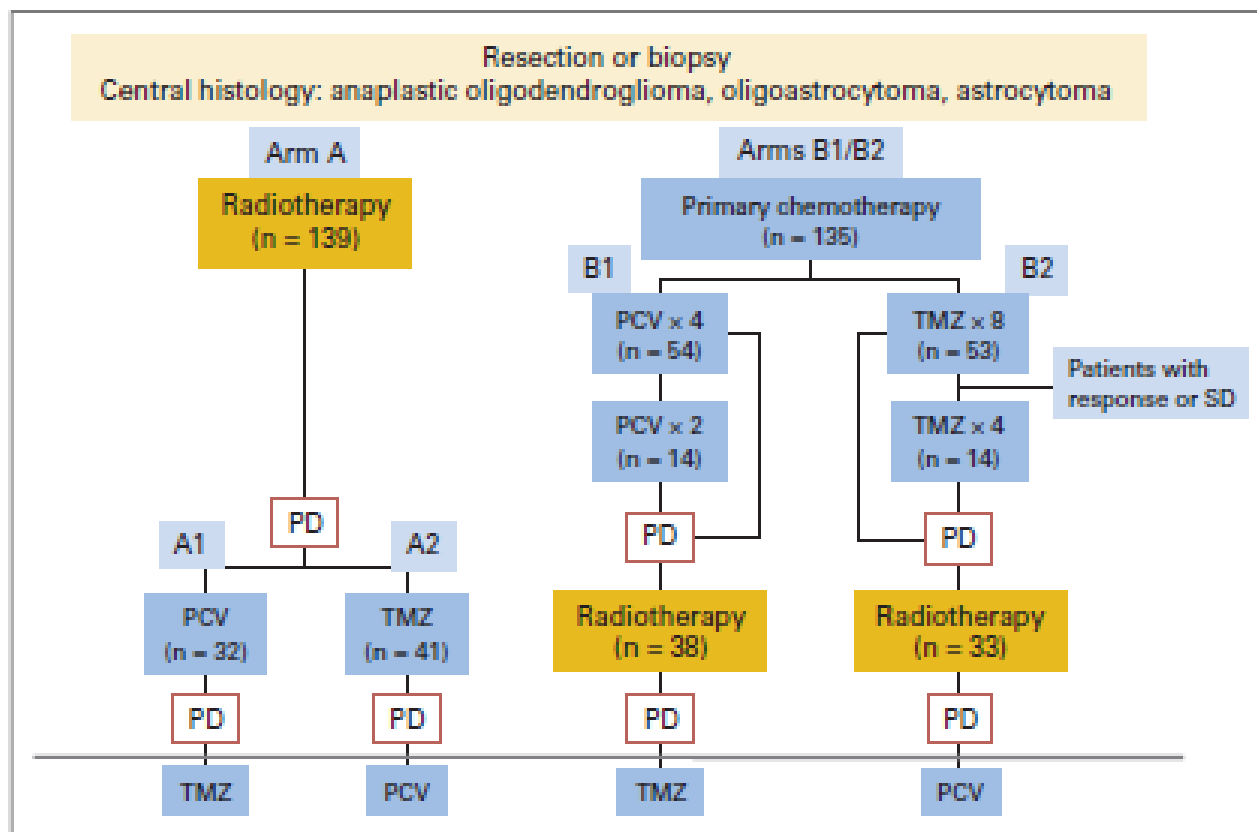




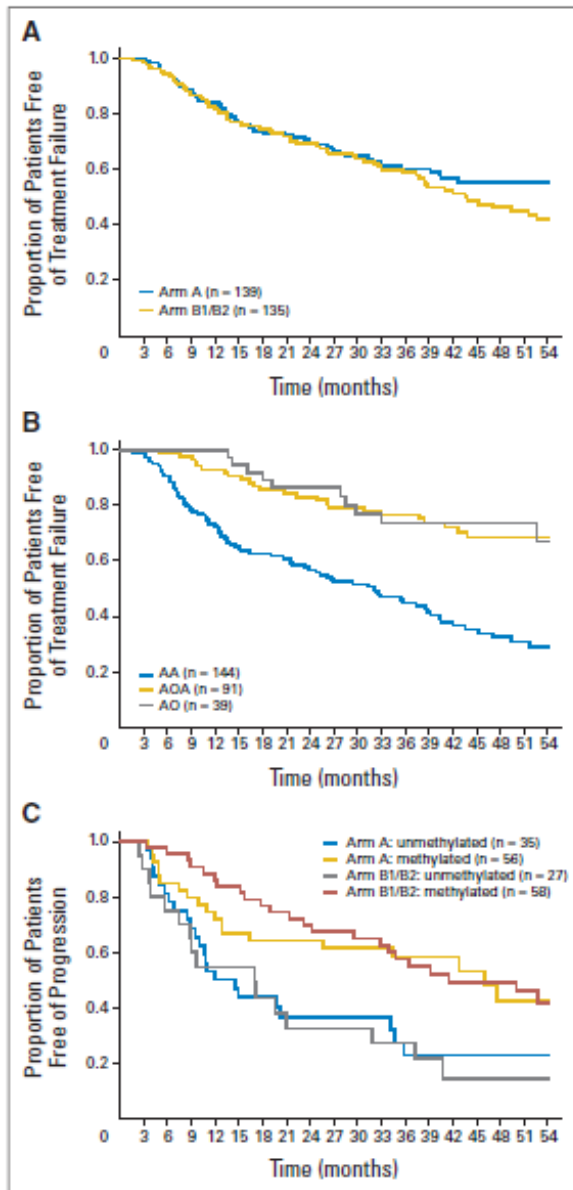
# NOA-04 Randomized Phase III Trial of Sequential Radiochemotherapy of Anaplastic Glioma With Procarbazine, Lomustine, and Vincristine or Temozolomide

Wolfgang Wick, Christian Hartmann, Corinna Engel, Mandy Stoffels, Jörg Felsberg, Florian Stockhammer, Michael C. Sabel, Susanne Koepfen, Ralf Ketter, Richard Meyermann, Marion Rapp, Christof Meisner, Rolf D. Kortmann, Torsten Pietsch, Otmar D. Wiestler, Ulrike Ernemann, Michael Bamberg, Guido Reifenberger, Andreas von Deimling, and Michael Weller

*J Clin Oncol* 27:5874-5880. © 2009 by American Society of Clinical Oncology



**Fig 2.** Trial design. Patients were randomly assigned 2:1:1 to receive radiotherapy (arm A) or chemotherapy with either procarbazine, lomustine, and vincristine (PCV; arm B1) or temozolomide (TMZ; arm B2) as initial therapy. Patient numbers represent the modified intention-to-treat population. At first disease progression, patients treated initially with radiotherapy (44 patients with anaplastic astrocytoma [AA; 63% of patients with AA treated in arm A], nine patients with anaplastic oligodendrogliomas [AO; 41%], and 20 patients with anaplastic oligoastrocytoma [AOA; 43%]) crossed over to treatment with chemotherapy and were randomly assigned 1:1 to PCV (arm A1) or TMZ (arm A2). Patients who experienced disease progression after initial chemotherapy (44 patients with AA [60% of patients with AA treated in arms B1/2], six patients with AO [35%], and 21 patients with AOA [48%]) crossed over to second-line treatment with radiotherapy. SD, stable disease; PD, progressive disease.



**Fig 3.** Kaplan-Meier estimates (modified intention-to-treat analysis). Data for time to treatment failure were analyzed by (A) treatment arm and (B) tumor histology. (C) Data for progression-free survival were analyzed for treatment arm and *MGMT* promoter methylation status. AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytoma; AO, anaplastic oligodendrogliomas.

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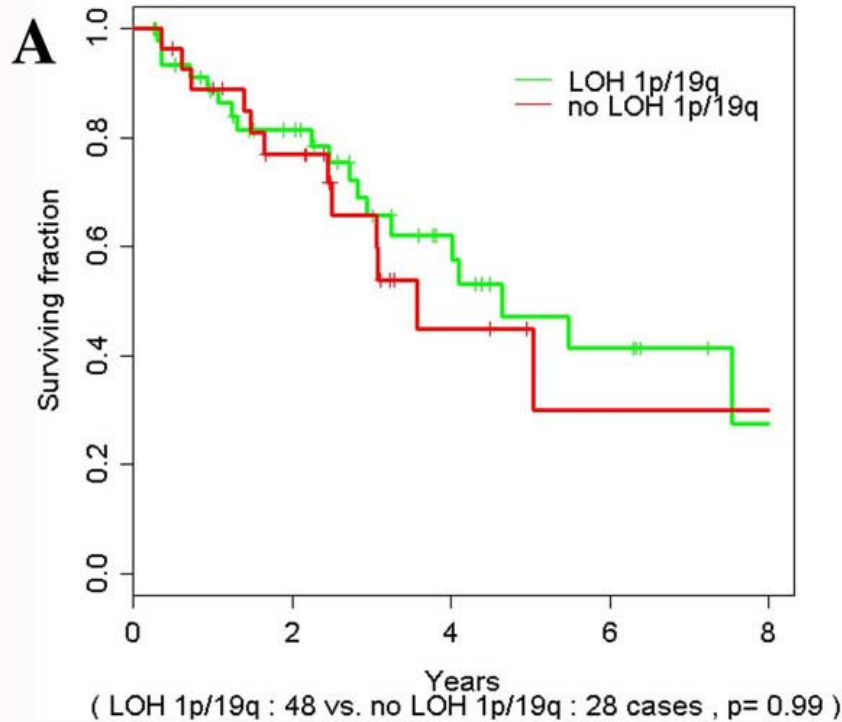
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**Table 4.** Complete Model of Major Prognostic Factors As Determined in a Multivariate Cox Regression Analysis for the Primary End Point of Time to Treatment Failure

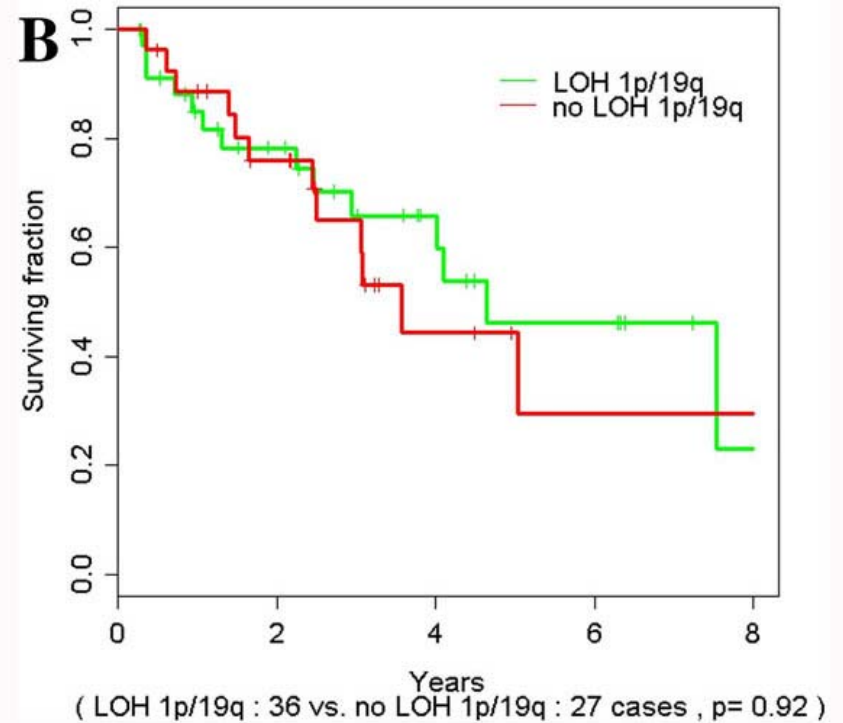
| Variable  | Hazard Ratio | 95% CI     | P     |
|---|--------------|------------|-------|
| Anaplastic astrocytoma v anaplastic oligoastrocytoma/anaplastic oligodendroglioma | 1.95         | 1.1 to 3.5 | .0237 |
| <i>IDH1</i> , wild-type v mutated   | 2.0          | 1.2 to 3.3 | .0128 |
| 1p/19q retained v 1p/19q deleted  | 1.8          | 0.9 to 3.4 | .0718 |
| <i>MGMT</i> promoter, unmethylated v methylated                                   | 1.9          | 1.1 to 3.4 | .0172 |
| Age, > 50 v ≤ 50 years  | 2.6          | 1.5 to 4.3 | .0004 |
| Extent of resection   |              |            |       |
| Incomplete v complete resection   | 1.6          | 0.9 to 3.0 |       |
| Biopsy v incomplete resection   | 2.1          | 1.1 to 4.0 | .0006 |
| Biopsy v complete resection   | 3.5          | 1.8 to 7.0 |       |

# Combined 1p/19q loss in oligodendroglial tumors: predictive or prognostic biomarker?

**Clin Cancer Res 2007;13:6933-6937**



**All tumors**



**Grade II tumors only**



# 1 p/19q

## Molecular markers for clinical decision making should.....

- **allow prognostic estimates**
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# 1p/19q

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# MGMT

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# MGMT

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# **IDH-1/2**

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# IDH-1/2

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# Molecular markers for clinical decision making

## Summary

- The **1p/19q codeletion** is predictive for response to radiotherapy and chemotherapy and thus not useful for individualized treatment
- **MGMT promoter methylation** may be predictive for response to chemotherapy in glioblastoma, but not in anaplastic gliomas where it may be predictive for either radiotherapy or chemotherapy
- **IDH-1 mutations** are probably merely prognostic



# Molecular markers for use in clinical trial design

- **Should trials for newly diagnosed glioblastoma separate or stratify for *MGMT* promoter methylation?**
- **Should 1p/19q or IDH-1 or both substitute for differential neuropathology in anaplastic glioma and low-grade glioma trials?**