FATTORI PREDITTIVI E PROGNOSTICI NEI GLIOMI MALIGNI

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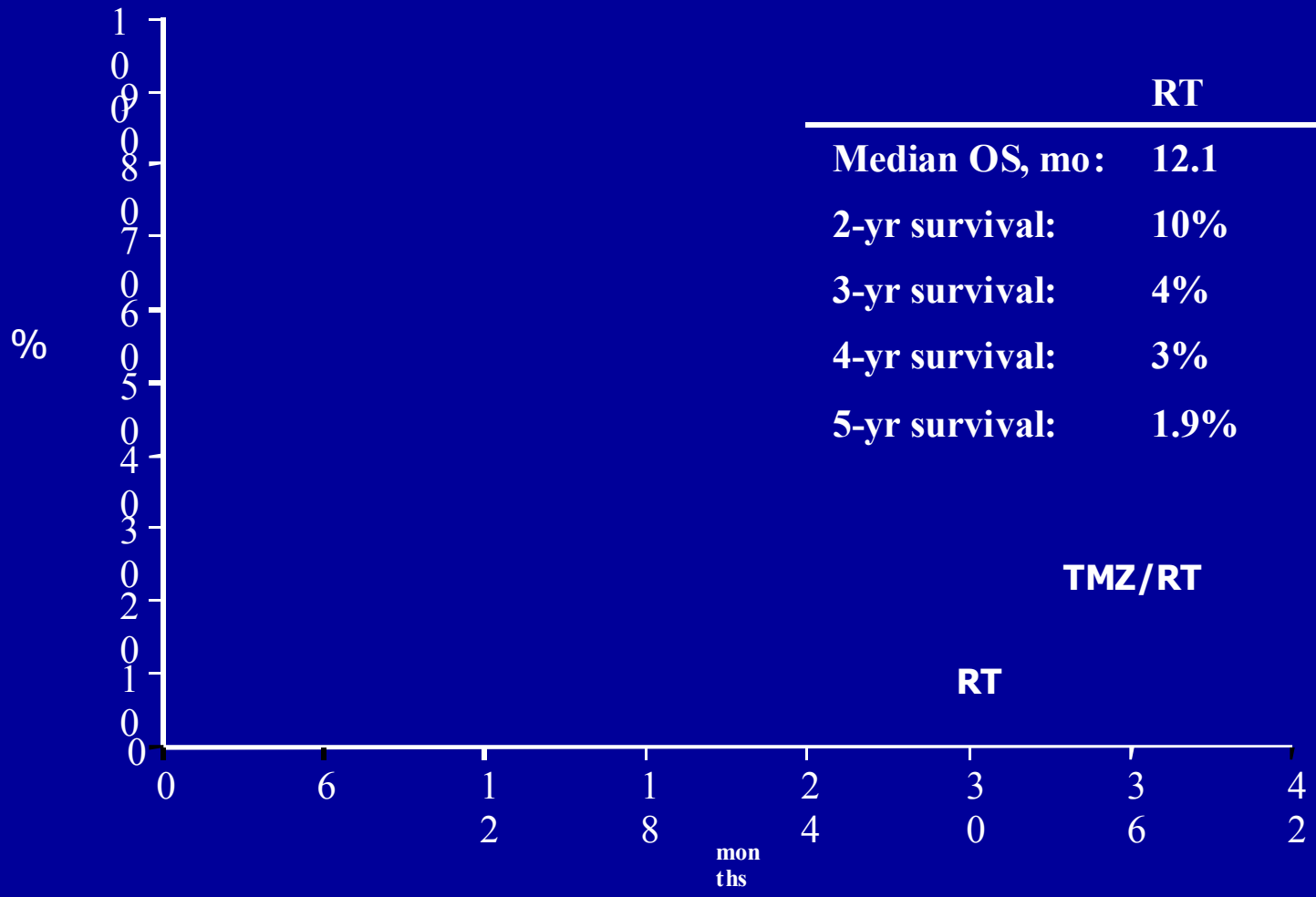
GBM: benefit from RT-TMZ



	RT	TMZ/RT
Median OS, mo:	12.1	14.6
2-yr survival:	10%	26%
3-yr survival:	4%	16%
4-yr survival:	3%	12%
5-yr survival:	1.9%	9%

Stupp et al, N Engl. J Med, 2005

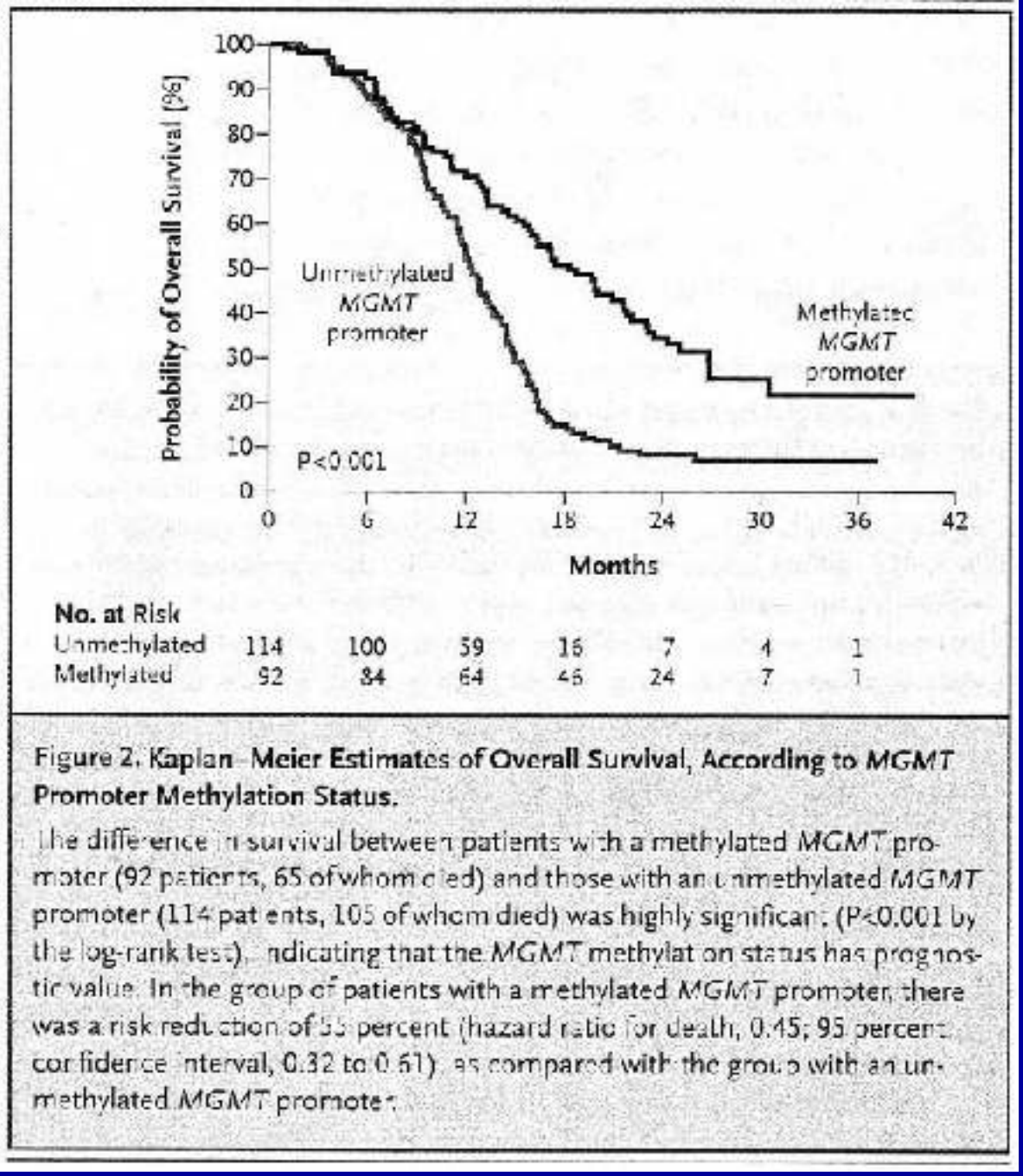
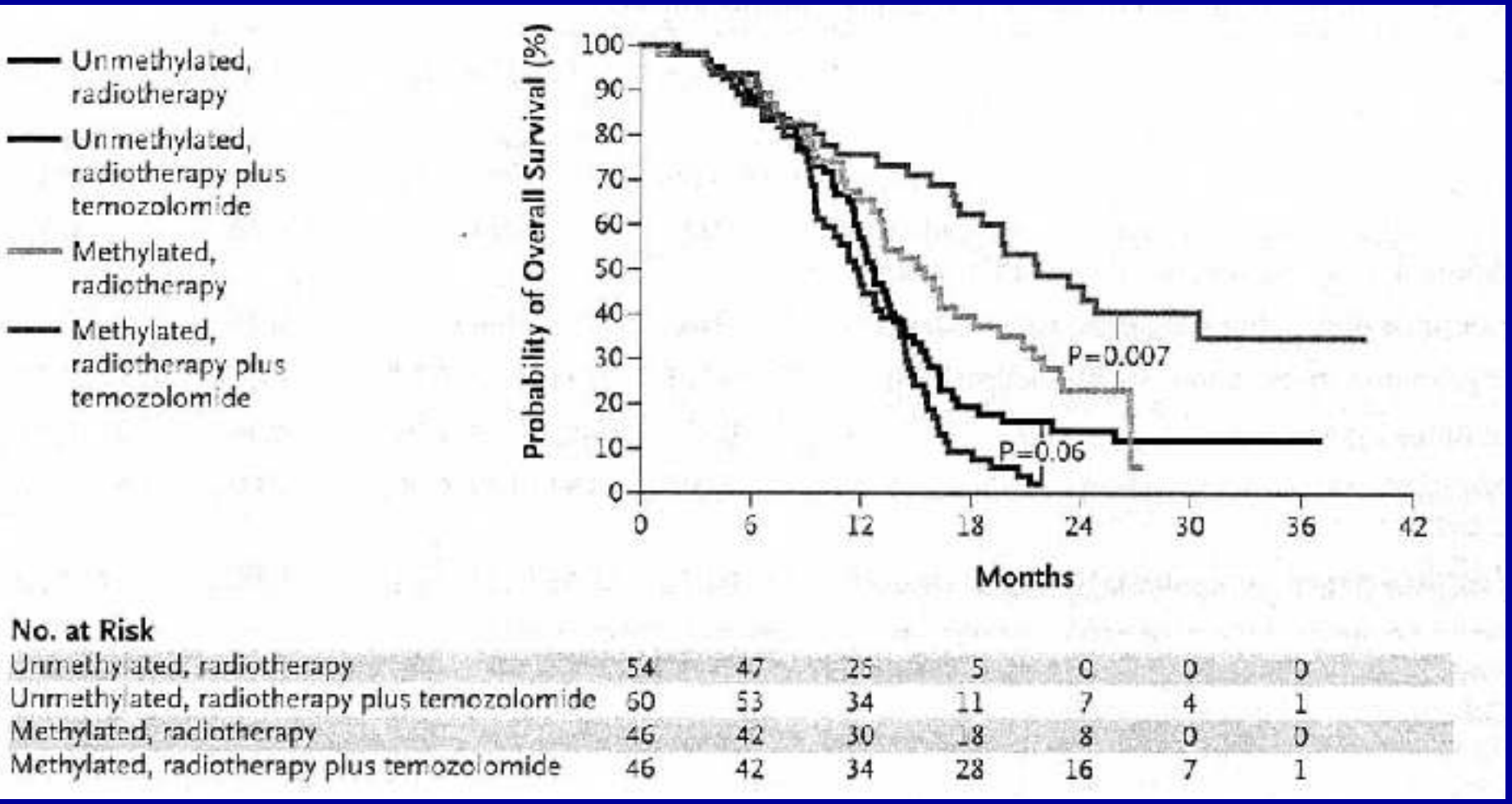


Figure 2. Kaplan–Meier Estimates of Overall Survival, According to *MGMT* Promoter Methylation Status.

The difference in survival between patients with a methylated *MGMT* promoter (92 patients, 65 of whom died) and those with an unmethylated *MGMT* promoter (114 patients, 105 of whom died) was highly significant (P<0.001 by the log-rank test), indicating that the *MGMT* methylation status has prognostic value. In the group of patients with a methylated *MGMT* promoter, there was a risk reduction of 55 percent (hazard ratio for death, 0.45; 95 percent confidence interval, 0.32 to 0.61) as compared with the group with an unmethylated *MGMT* promoter.

Hegi et al, N Engl J Med, 2005



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

Hegi et al, N Engl J Med, 2005

Overall survival for patients with a methylated MGMT promoter

Treatment	RT meth	RT+TMZ meth
Median Survival	15.3 mos	23.4 mos
2-year OS (%)	23.9	48.9
3-year OS (%)	7.8	27.7
4-year OS (%)	5.2	22.1
Hazard ratio	0.51 [0.33 – 0.81] *P* = 0.04	

Stupp et al, Lancet Oncol, 2009

Overall survival for patients with an unmethylated MGMT promoter

Treatment	RT unmeth	RT+TMZ unmeth
Median Survival	11.8 mos	12.6 mos
2-year OS (%)	1.9	14.8
3-year OS (%)	0.0	11.1
4-year OS (%)	0.0	11.1
Hazard ratio	0.66 [0.45 – 0.97] $P = 0.035$	

Stupp et al, Lancet Oncol, 2009

Issues/controversies on MGMT

- Is the predictive significance related to temozolomide only?
- Is the predictive significance maintained in the recurrent setting?
- Do changes in MGMT occur between newly diagnosed and recurrent GBM?
- Which is the role of MGMT in the elderly?

Why to treat with Stupp regimen patients with unmethylated MGMT

- To date, effective alternatives are lacking
- There is a little advantage in the combining arm (RT+tmz) in comparison to RT alone
- There are still some concerns in the definition of Met versus unmetMGMT patients (whic is the cut-off in PCR?)

Prognostic Impact of O^6-Methylguanine-DNA Methyltransferase Silencing in Patients With Recurrent Glioblastoma Multiforme Who Undergo Surgery and Carmustine Wafer Implantation

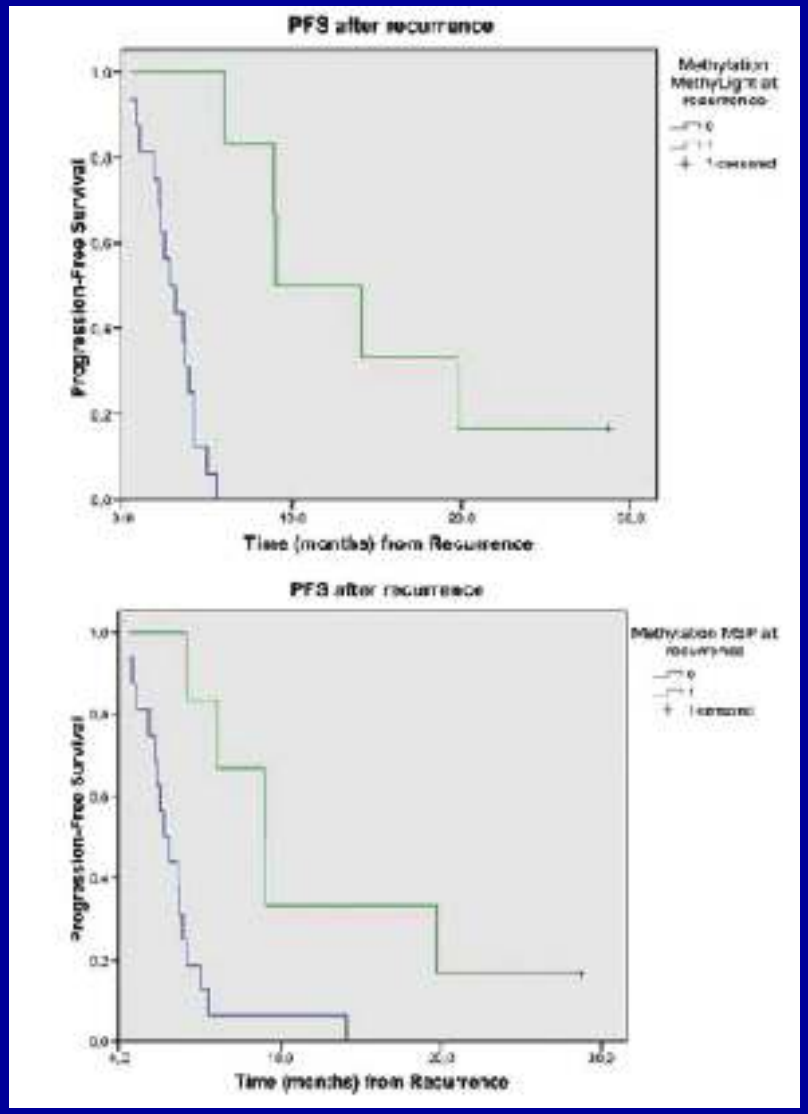
A Prospective Patient Cohort

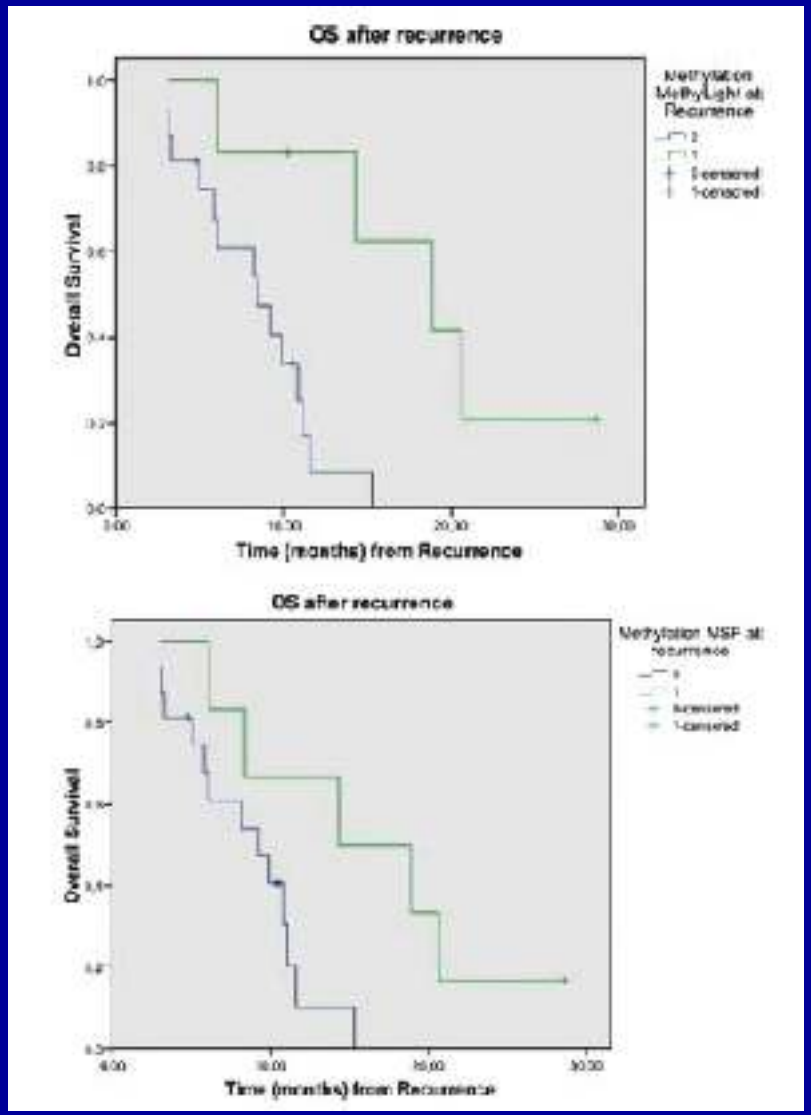
Philippe Metellus, MD[1,2]; Bema Coulibay, MD, PhD[2,3]; Isabelle Nanni, PharmD[4]; Frederic Fina, PhD[4]; Nathalie Eudes, PhD[4]; Roch Giorgi, MD, PhD[5]; Marylin Barrie, MD[1]; Olivier Chinot, MD[1,2,4]; Stephane Fuentes, MD[1]; Henry Dufour, MD[1]; L'houcine Ouafik, PhD[2,4]; and Dominique Figarella-Branger, MD, PhD[2,3]

BACKGROUND: O^6-methylguanine-DNA methyltransferase (MGMT) is a key enzyme in the DNA repair process after alkylating agent action. Epigenetic silencing of the MGMT gene by promoter methylation has been associated with longer survival in patients with newly diagnosed glioblastoma multiforme (GBM) who receive alkylating agents. In this study, the authors evaluated the prognostic value of different biomarkers in recurrent GBM and analyzed the changes in MGMT status between primary tumors and recurrent tumors.

METHODS: Twenty-two patients who had recurrent GBM and who underwent surgery with carmustine wafer implantation were enrolled prospectively between 2005 and 2007. The authors investigated the correlation between MGMT silencing in the tumor at recurrence and survival taking into account other clinically recognized prognostic factors. MGMT status was determined by using methylation-specific polymerase chain reaction analysis, a high-throughput quantitative methylation assay, and immunohistochemistry. In addition, expression analyses of human mutL homolog 1, human mutS homolog 2, and tumor necrosis factor α-induced protein 3 at recurrence were conducted with regard to their prognostic impact.

RESULTS: The median progression-free survival (PFS) and overall survival (OS) rates after recurrence were





Metellus et al, Cancer 2009

Personalized Medicine and Imaging

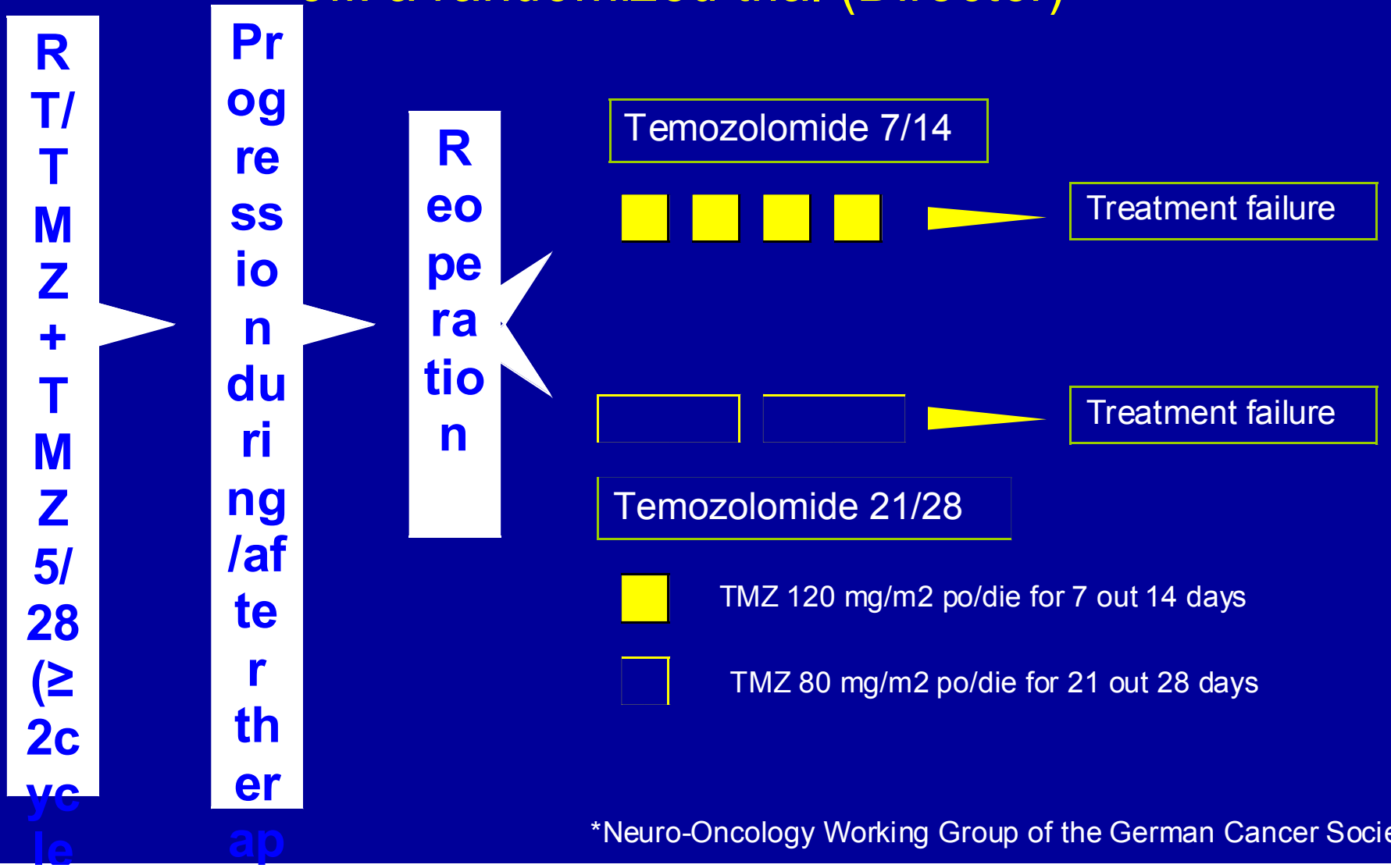
Clinical Cancer Research

MGMT Promoter Methylation Is a Strong Prognostic Biomarker for Benefit from Dose-Intensified Temozolomide Rechallenge in Progressive Glioblastoma: The DIRECTOR Trial

Michael Weller[1], Ghazaleh Tabatabai[1], Bärbel Kästner[2], Jörg Felsberg[3], Joachim P. Steinbach[4], Antje Wick[5], Oliver Schnell[6], Peter Hau[7], Ulrich Herrlinger[8], Michael C. Sabel[9], Hans-Georg Wirsching[1], Ralf Ketter[10], Oliver Bähr[4], Michael Platten[5], Jörg C. Tonn[6], Uwe Schlegel[11], Christine Marosi[12], Roland Goldbrunner[13], Roger Stupp[14], Krisztian Homicsko[14], Josef Pichler[15], Guido Nikkhah[16], Jürgen Meixensberger[17], Peter Vajkoczy[18], Spyros Kollias[19], Johannes Hüsing[2], Guido Reifenberger[3], and Wolfgang Wick[5] for the DIRECTOR Study Group

Cancer Res; 1–8. ©2015 AACR.

Dose-intensified rechallenge with temozolomide, 1 week on / 1 week off versus 3 weeks on / 1 week off: a randomized trial (Director)*



*Neuro-Oncology Working Group of the German Cancer Society

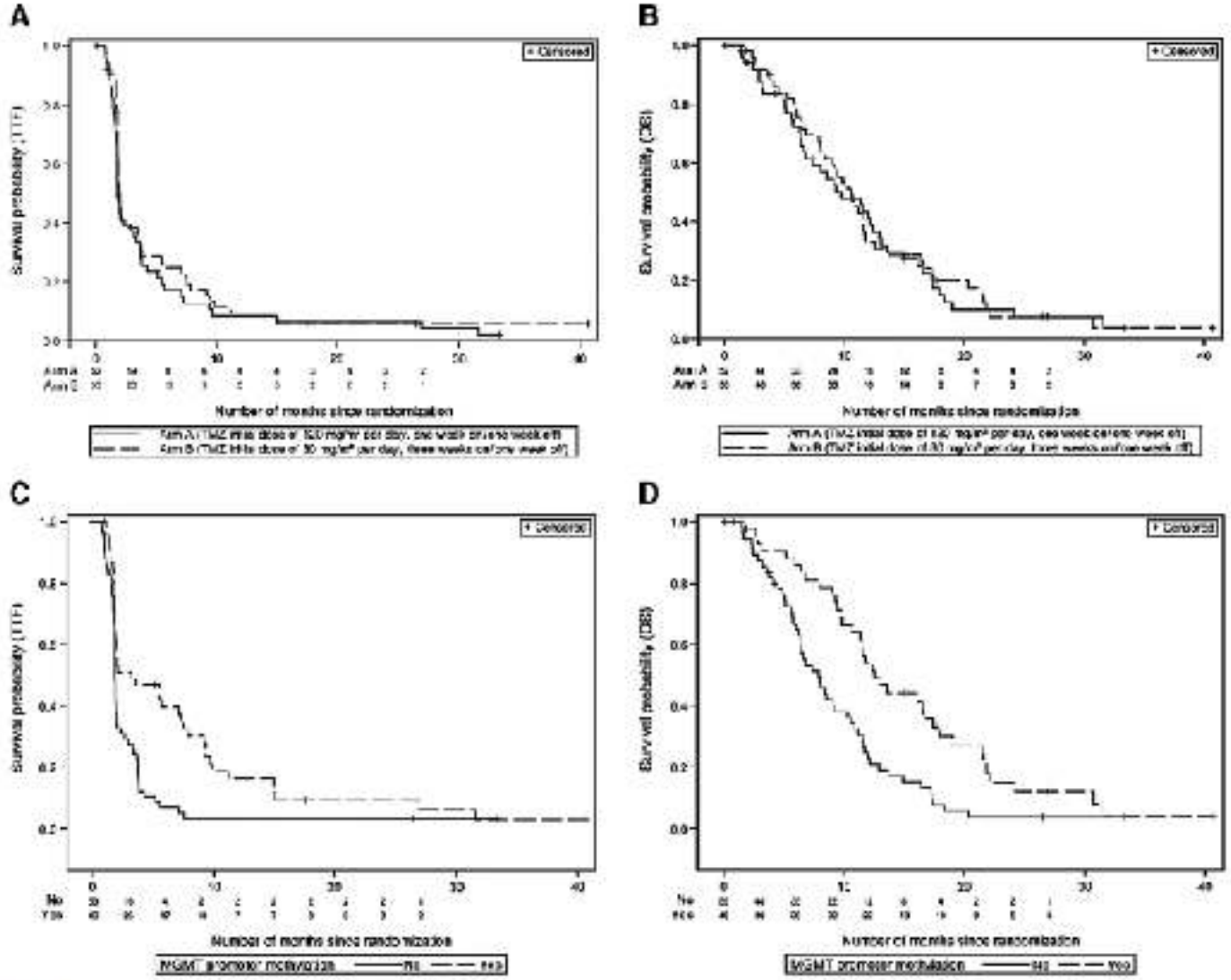


Figure 2.
Clinical outcome. TTF (A) and OS (B) in Arm A (2/36) versus Arm B (2/28). TTF (C) and OS (D) in patients without versus with MGMT promoter methylation.

CONTROVERSIES REGARDING MGMT STATUS

- Do changes in MGMT status occur between newly diagnosed and recurrent GBM ?

↓

Some studies have suggested that a proportion of patients could shift from the methylated to the unmethylated status at recurrence (*Brandes et al, 2010 ; Fiano et al, 2014*) while others had not (*Felsberg J et al. 2011*).

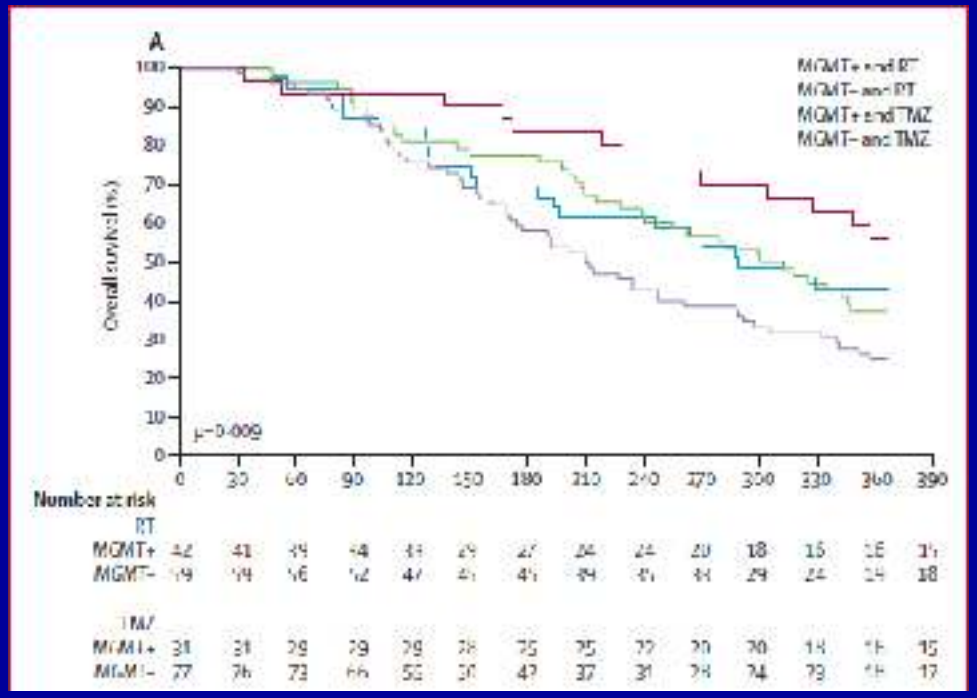
CONTROVERSIES REGARDING MGMT STATUS

- Which is the role in elderly patients ?

Table 1 Randomized Controlled Trials Designed for Elderly Patients With Newly Diagnosed Glioblastoma

Study	Patient Age (y)	Number of Evaluable Patients	Treatment	Median Survival (mo)
Nordic[47]	≥60	291	TMZ[5/21] vs RT[34] vs RT[60]	8.3 vs 7.5 vs 6.0
	>70	123	TMZ[5/28] vs RT[34] vs RT[30]	9.0 vs 7.0 vs 5.2
NOA-08[48]	>65	373	RT[50] vs TMZ[7/7]	9.6 vs 8.6
Keime-Guibert et al[34]	>70	85	RT[30] vs supportive care	6.7 vs 3.9
Roa et al[45]	>60	100	RT[40] vs RT[30]	5.1 vs 5.6

Holdoff et al, J Nat Compr Canc Netw 2013



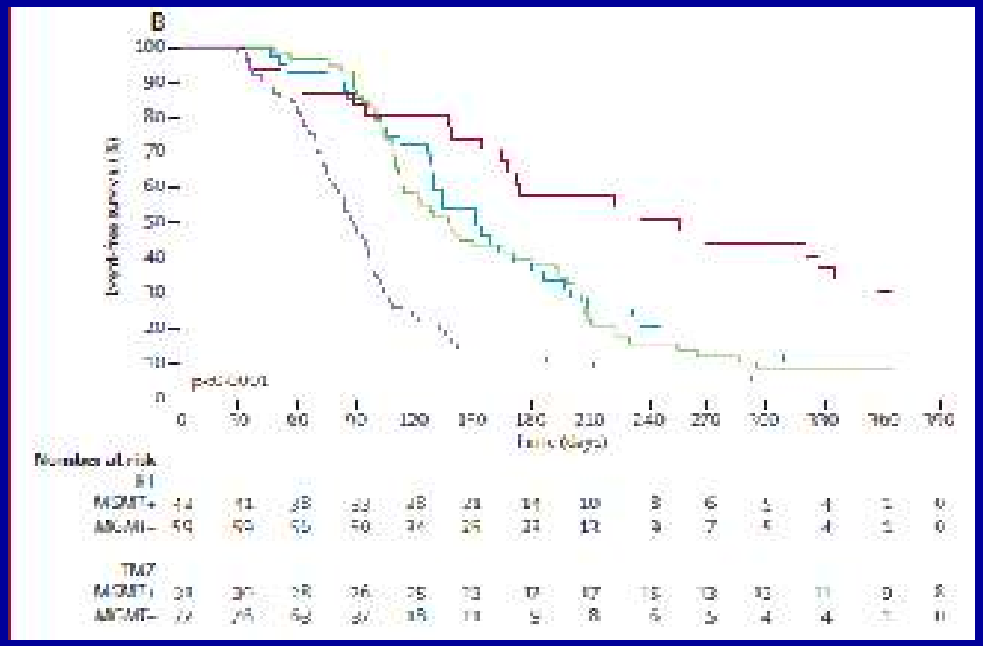
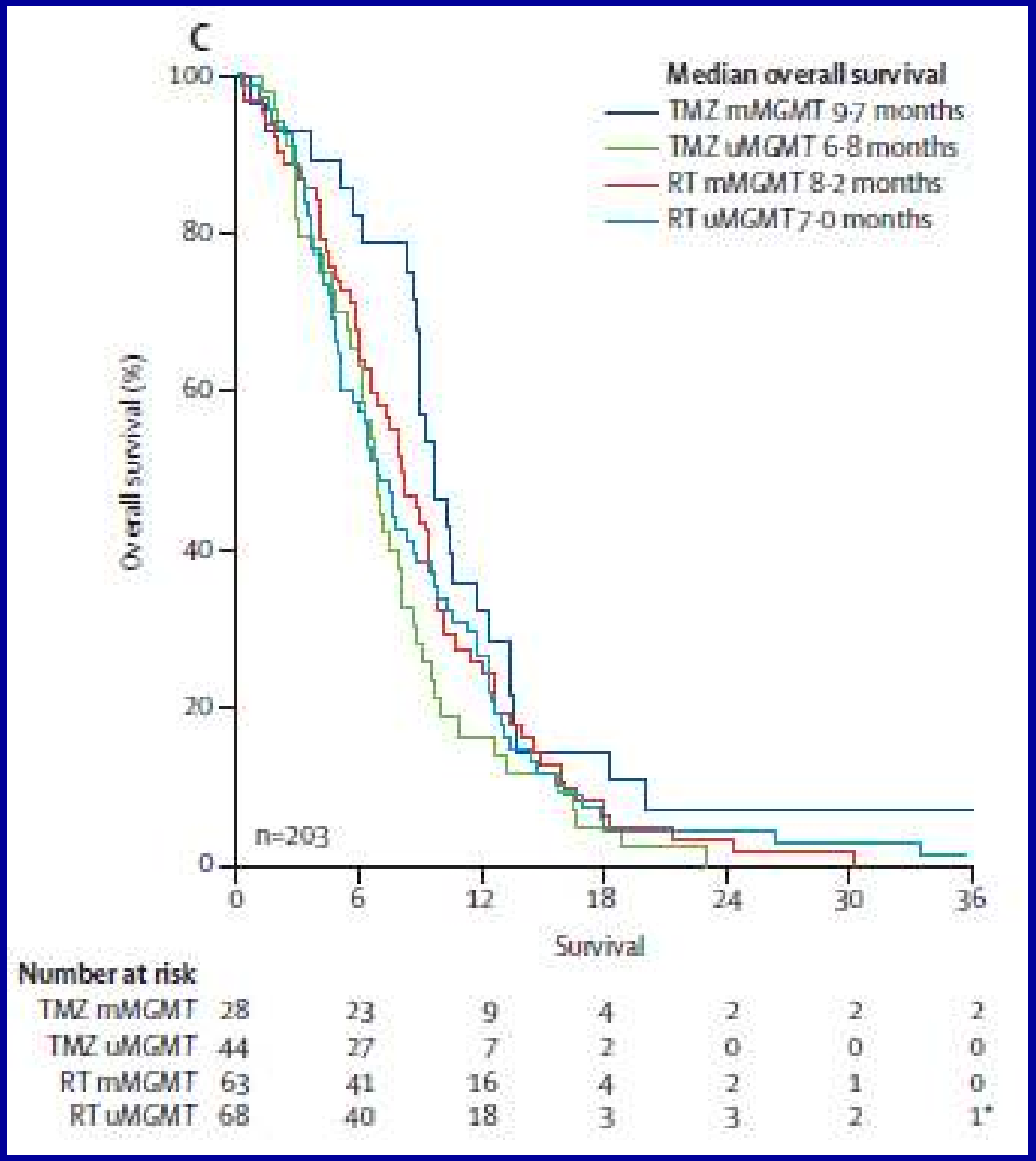


Figure 4: Kaplan Meier analysis of overall and event. free survival in relation to MGMT promoter methylation status and treatment

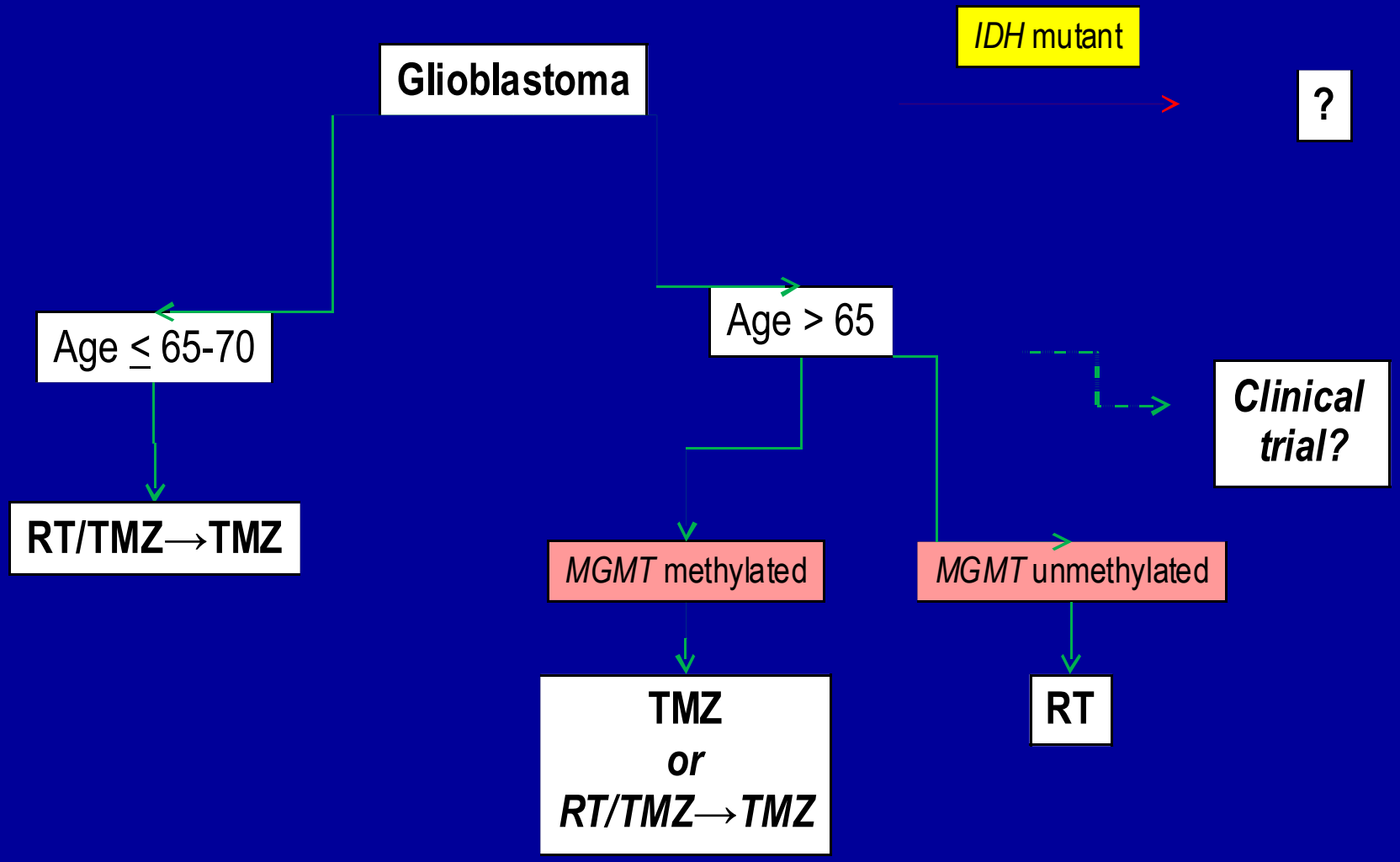
(A) Overall survival. (B) Event-free survival. The p values were calculated to any significant difference in at least two of the curves. See also table 3. RT radiotherapy. TMZ temozolomide.

Wick et al, Lancet Oncol, 2012.

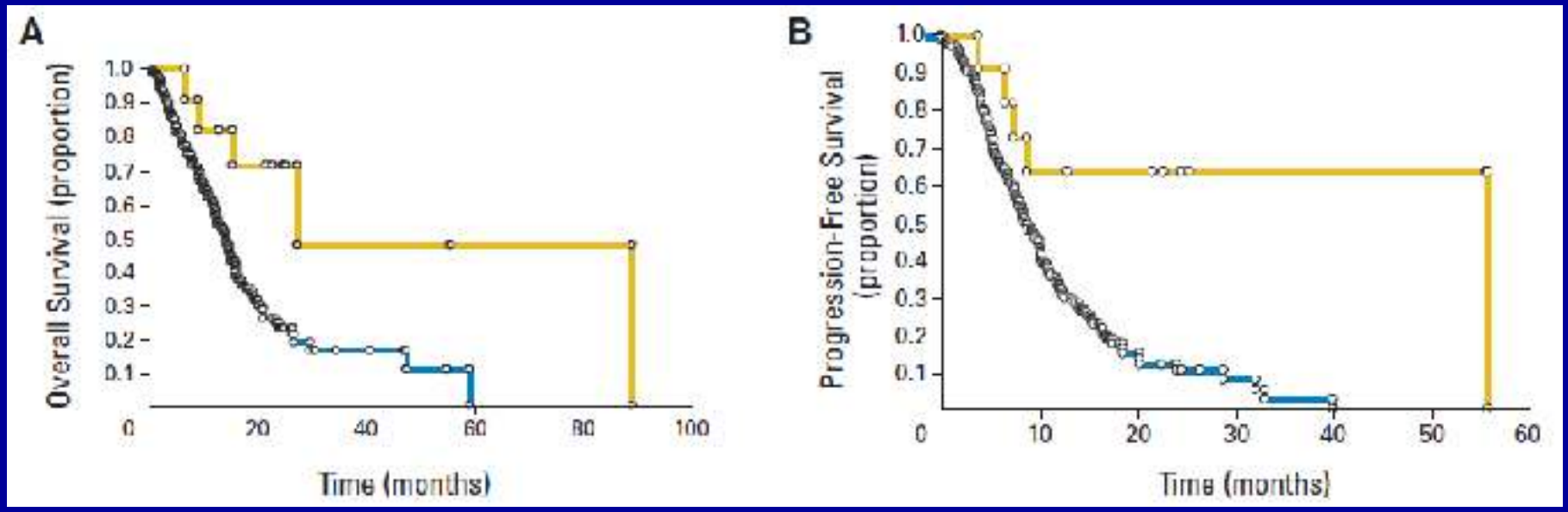


Malmström et al, Lancet Oncol, 2012.

Current approach to glioblastoma patients with good prognostic clinical factors



Overall and progression-free survival in glioblastoma according to IDH1 mutation



Sanson et al, J Clin Oncol, 2009.

EGFR Mutation Variant III (EGFRvIII)

- Tumor-specific oncogene expressed in one-third of primary GBM, seldom expressed with IDH mutations but not in normal tissue
- EGFRvIII(+) cells may induce growth in EGFRvIII(-) cells via paracrine signaling, membrane-derived microvesicles, and tumor stem cells1-4
- Rindopepimut consists of EGFRvIII peptide conjugated to Keyhole Limpet Hemocyanin (KLH)
  - Generates a specific immune response against EGFRvIII-expressing GBM
  - "Off the shelf"
  - Delivered as intradermal injection of 500 µg rindopepimut with 150 µg GM-CSF as an adjuvant

EGFRvIII Linked To Poor Long Term Survival

Dataset	EGFRvIII+		EGFRvIII-	
	Median OS	3-year OS	Median OS	3-year OS
Heimberger 2005	12	<5%		
Pelloski 2007	12.7	6%		
RTOG 0525, TMZ 5/28	14.2	7%	18.2	25%
RTOG 0525, matched*	16.0	13%	22.2	36%
Lai 2010, matched*	15.2	6%		
German glioma network, all patients	11.3	8%	11.9	17%
German glioma network, matched*	17.0	17%	15.4	26%

* Matched for eligibility for Phase II rindopepimut trials (EGFRvIII+, GTR, radiation/TMZ, no progression through ~3 months post-diagnosis)

1. Inda, et al. Genes Dev. 2010:
2. Al-Nedawi, et al. Nat Cell Biol. 2008

WHO 2007: grade III gliomas

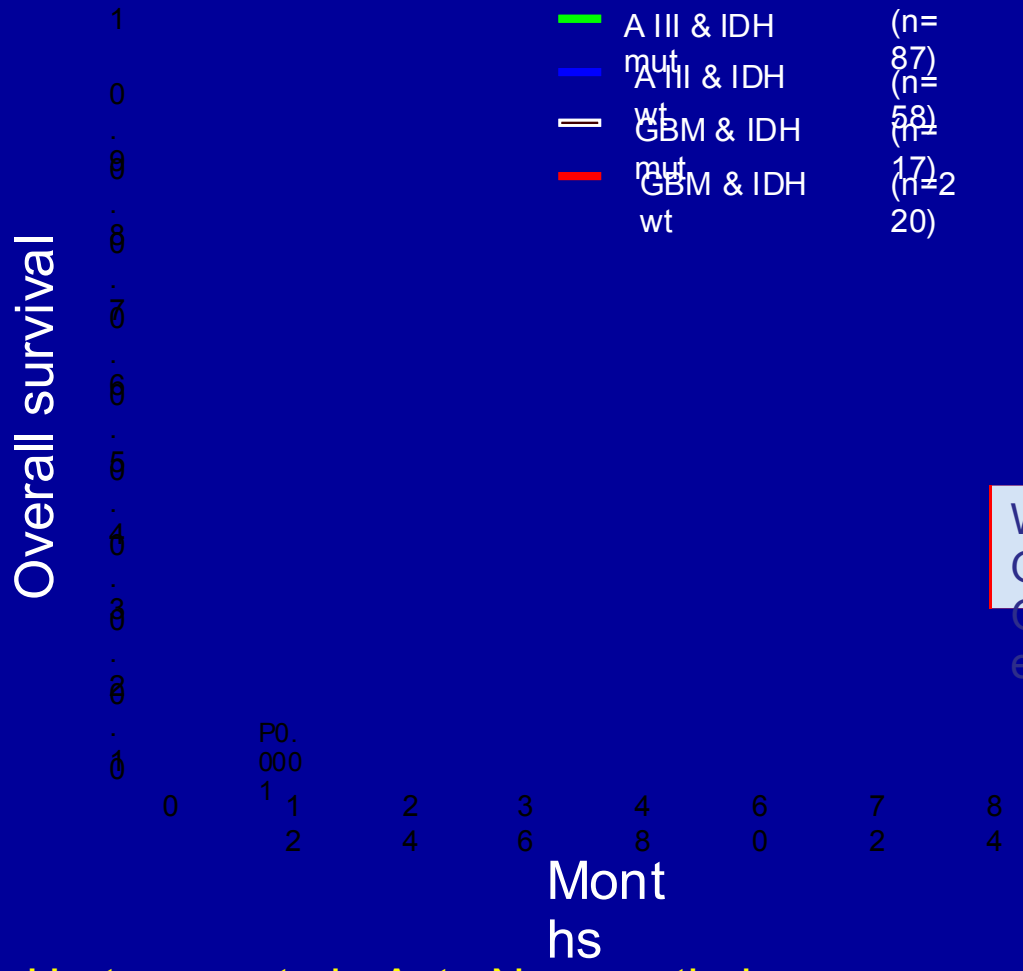
- Anaplastic oligodendroglioma
- Anaplastic oligoastrocytoma
- Anaplastic astrocytoma

Patients with *IDH1* wild type anaplastic astrocytomas exhibit worse prognosis than *IDH1*-mutated glioblastomas, and *IDH1* mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas

Christian Hartmann, Bettina Hentschel, Wolfgang Wick, David Capper, Jörg Felsberg, Matthias Simon, Manfred Westphal, Gabriele Schackert, Richard Meyermann, Torsten Pietsch, Guido Reifenberger, Michael Weller, Markus Loeffler, Andreas von Deimling

Acta Neuropathol. 2010, Volume 120, Issue 6, pp 707-718

DH: better to discriminate igh-grade glioma than WHO grade?



WHO-Grade

- Anapl. astrocytoma IDH-mut
- GBM IDH-mut
- Anapl. astrocytoma IDH-wt
- GBM IDH-wt

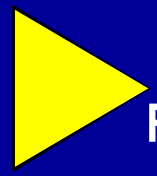
each

- MGMT meth.
- MGMT unmeth.

Hartmann et al., Acta Neuropathol 2010

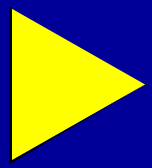
CLINICAL TRIALS ON GRADE III gliomas

RTOG phase III trial 9402 on Anaplastic Oligodendroglioma:

Arm 1: Up to 4 intensified PCV cycles  RT

Arm 2: RT

EORTC phase III trial 26951 on Anaplastic Oligodendroglioma:

Arm 1: RT  6 cycles of adjuvant standard PCV

Arm 2: RT

NOA-04 phase III on Anaplastic Oligodendroglioma

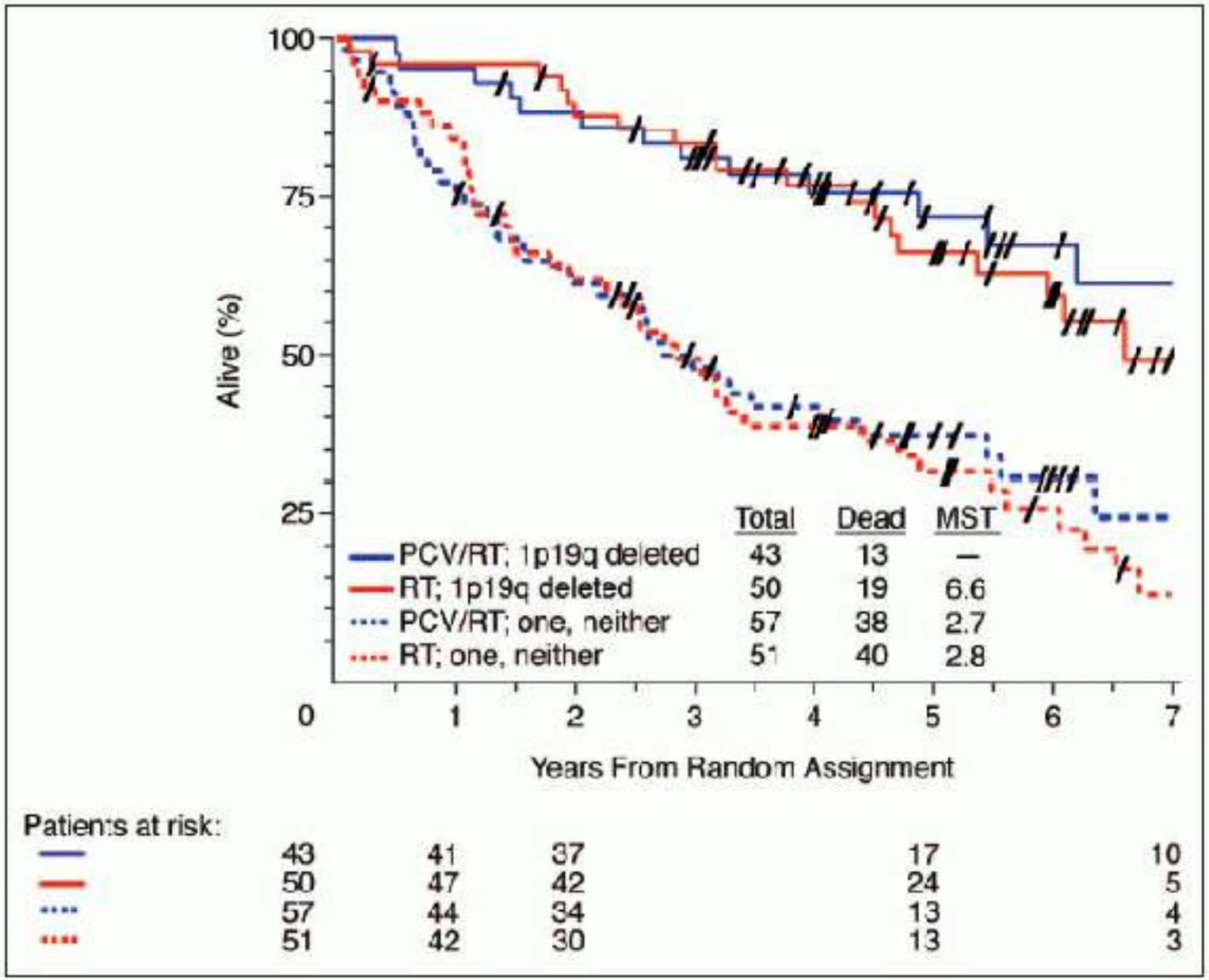


Fig 4. Kaplan-Meier estimates of overall survival by treatment and genotype. PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy; MST, median survival time.

Adjuvant PCV in Anaplastic Oligodendroglioma

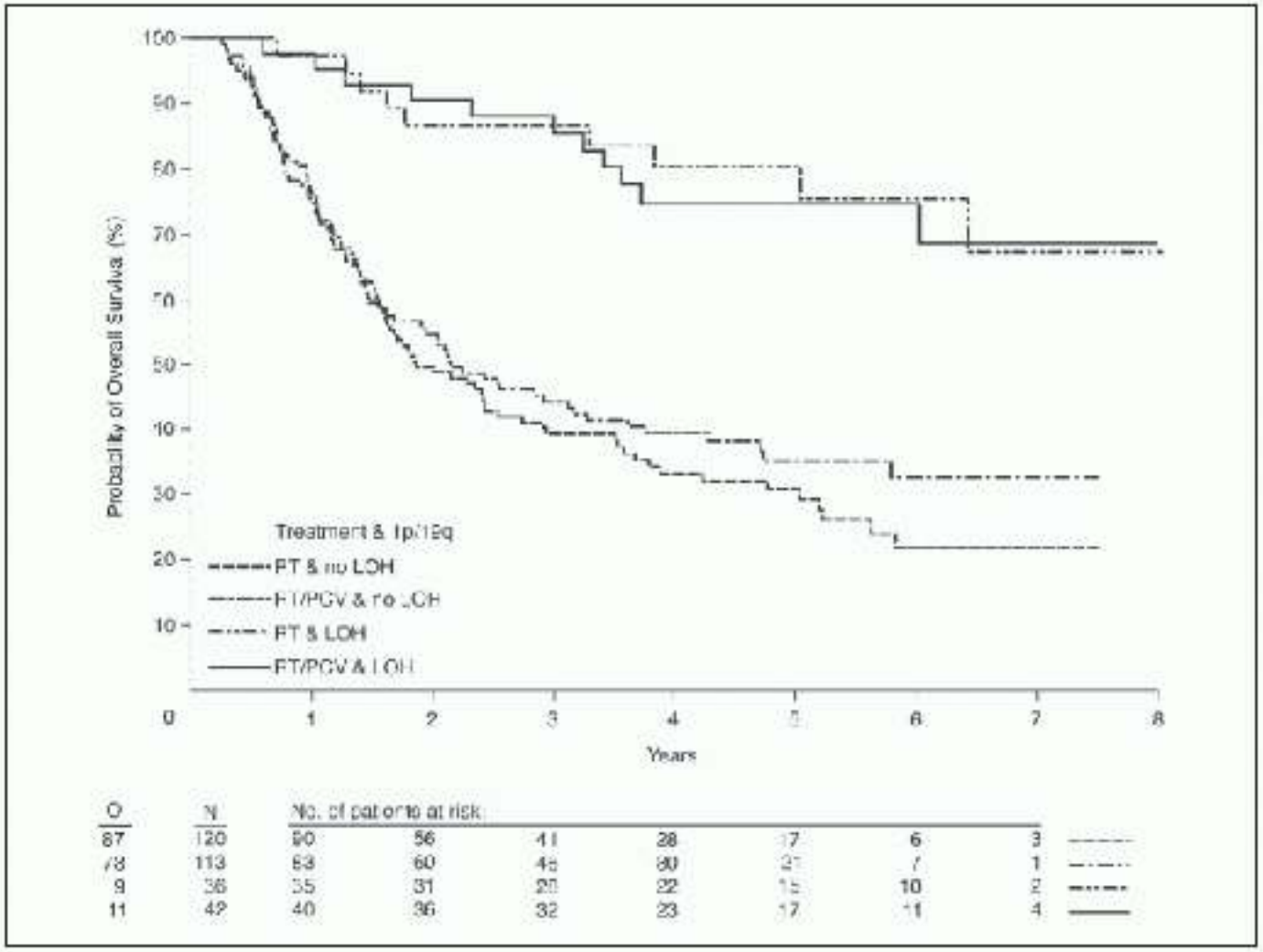


Fig 5. Overall survival in both treatment arms in the groups with and without combined 1p/19q loss. RT, radiotherapy; PCV, procarbazine, lomustine, and vincristine; LOH, loss of heterozygosity of both 1p and 19q; O, observed events; N, total number of events.

VOLUME 31 · NUMBER 3 · JANUARY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial of Chemoradiotherapy for Anaplastic Oligodendroglioma: Long-Term Results of RTOG 9402

Gregory Cairncross, Meihua Wang, Edward Shaw, Robert Jenkins, David Brachman, Jan Buckner, Karen Fink, Luis Souhami, Normand Laperriere, Walter Curran, and Minesh Mehta

VOLUME 31 · NUMBER 3 · JANUARY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951

Martin J. van den Bent, Alba A. Brandes, Martin J.B. Taphoorn, Johan M. Kros, Mathilde C.M. Kouwenhoven, Jean-Yves Delattre, Hans J.J.A. Bernsen, Marc Frenay, Cees C. Tijssen, Wolfgang Grisold, László Sipos, Roelien H. Enting, Pim J. French, Winand N.M. Dinjens, Charles J. Vecht, Anouk Allgeier, Denis Lacombe, Thierry Gorlia, and Khê Hoang-Xuan

Long-term results of RTOG 9402

2006 results

	PCV + RT	RT alone
Median survival time	4.8 yrs	4.7 yrs

…18 years after the first patient enrolled…

2012 long-term results

		PCV + RT	RT alone
Median survival time	Codeleted	14.7 yrs	7.3 yrs
	Non codel	2.6 yrs	2.7 yrs

Non codeleted tumors were grouped as follows: + 1p -19q, -1p + 19q or -1p-19q.

Cairncross et al, 2013.

Long-term results of EORTC 26951

2006 results

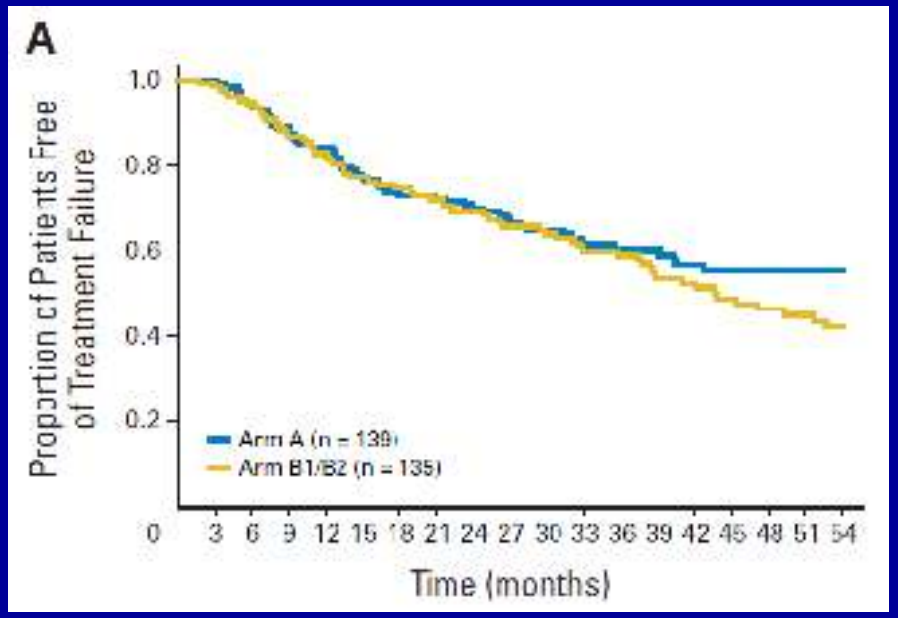
	PCV+RT	RT alone
PFS	24 mo	13 mo
OS	42 mo	31 mo

2012 long-term results

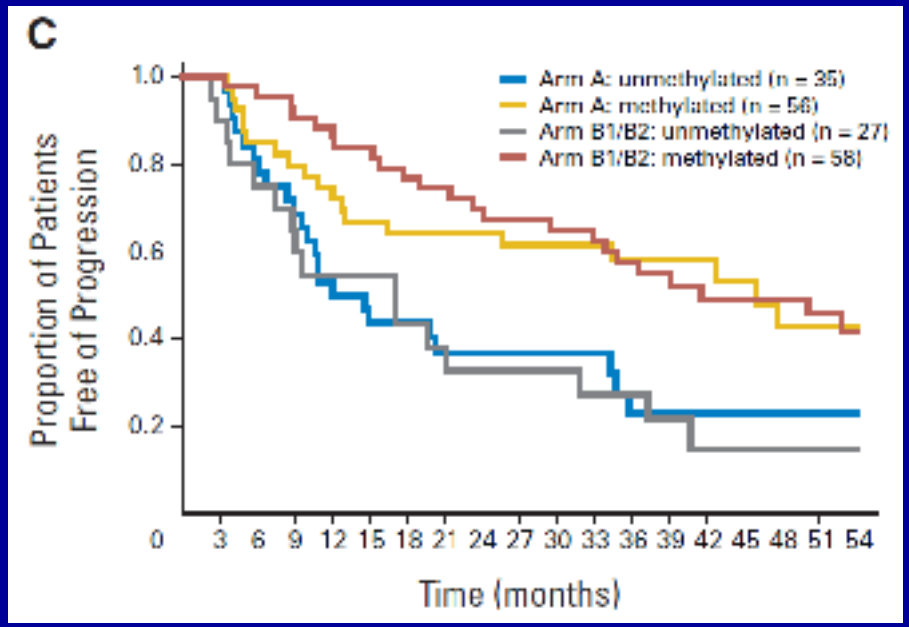
	PCV+RT	RT alone
Codeleted	NR	113 mo
Non codel	25 mo	21 mo

Conclusion: Adjuvant PCV improves OS in anaplastic oligos codeleted.
No proven benefit in *non* codeleted.

Van den Bent et al, 2013.



Initial radiotherapy or chemotherapy achieved comparable results in patients with anaplastic gliomas



Hypermethylation of the MGMT promoter was associated with prolonged PFS in the chemotherapy and radiotherapy arm

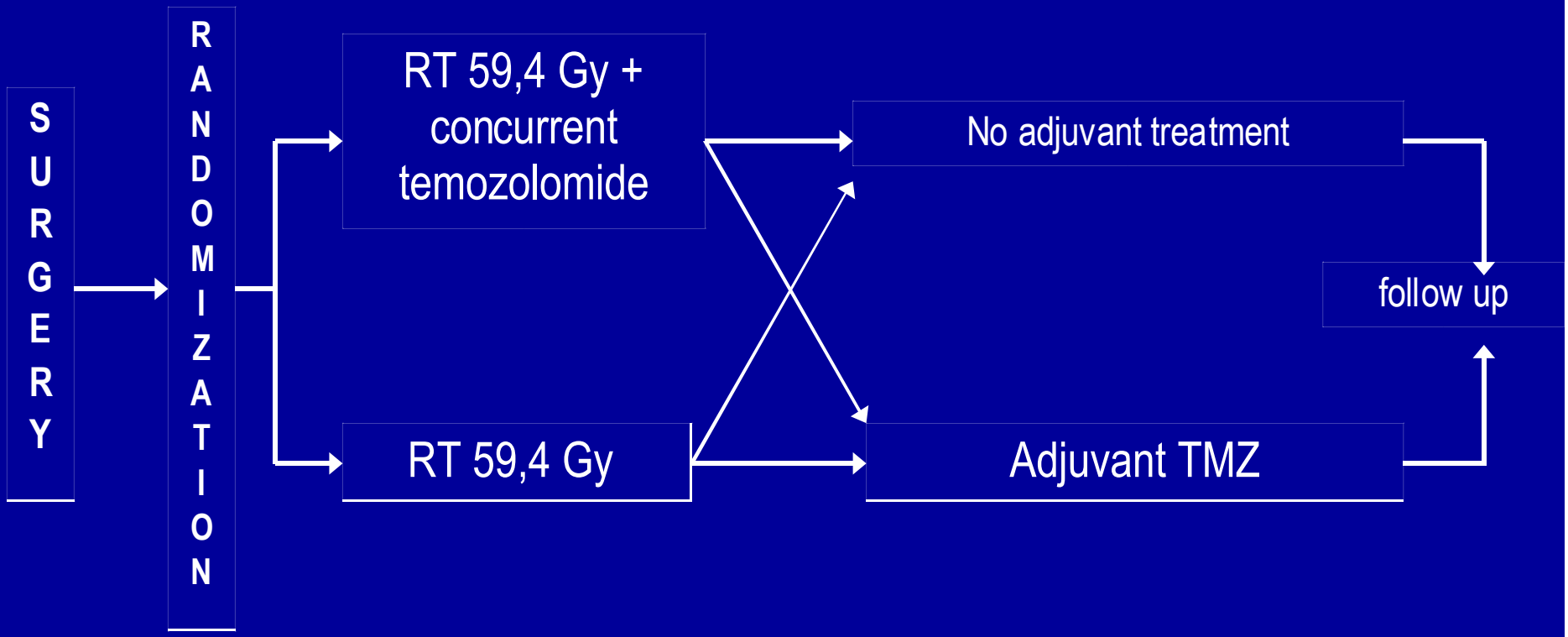
Wick et al, 2009.

Clinical trials on grade III gliomas with molecular (1p/19q) inclusion criteria

CATNON (EORTC/RTOG/NCI-C)

CODEL (NCCTG/RTOG/EORTC/NCI-C)

CATNON study on anaplastic gliomas without 1p/19q loss: 2 x 2 design



- Pre-study 1p/19q testing
- Stratification: Methylation status
- Primary endpoint: overall survival

- Secondary endpoints:
  - Progression-free survival
  - Quality of life

Anaplastic gliomas with 1p/19q loss: CODEL Study (NCCTG/RTOG/EORTC/NCI-C)

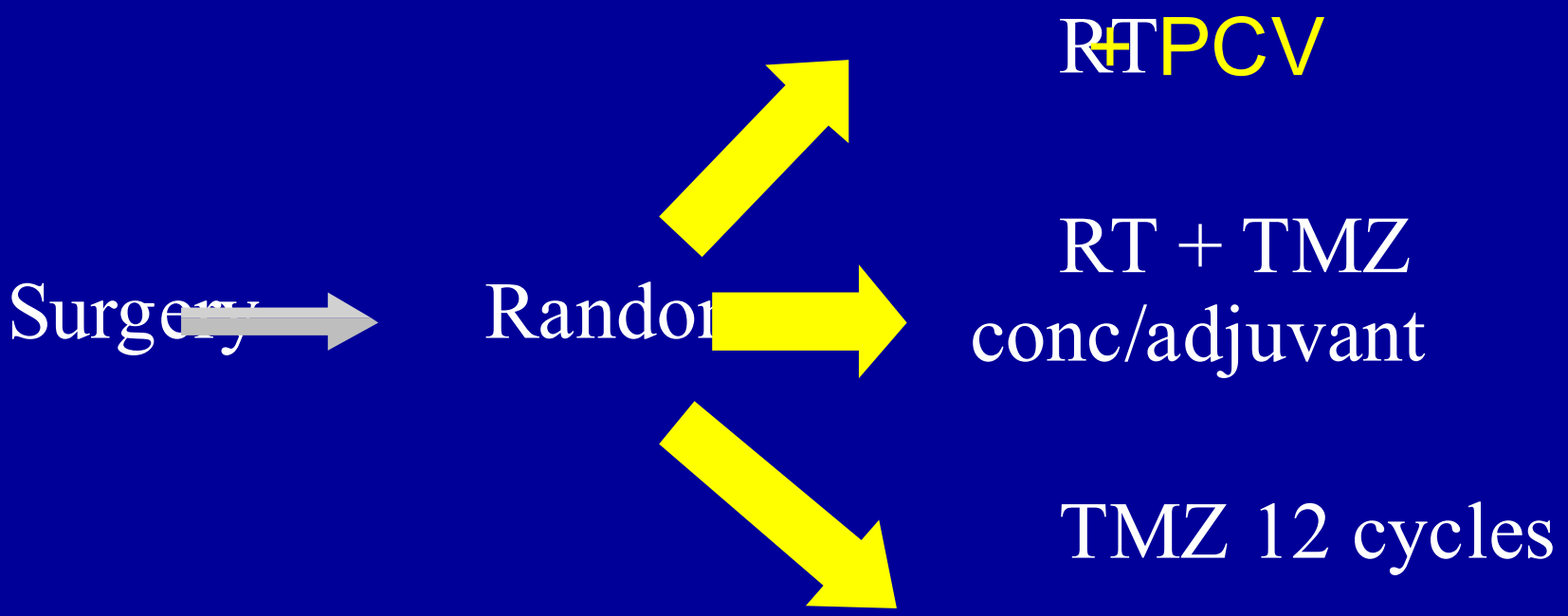


Table 1 Molecular markers with confirmed clinical relevance in gliomas

Marker	Methods	Prognostic/predictive value		
		Glioblastomas (grade IV)	Anaplastic gliomas (grade III)	Grade II gliomas
1p/19q Codeletion	PCR, FISH	None	Favorable prognostic value; predictive of response to PCV	Favorable prognostic value; probable predictive value of response to TMZ
MGMT promoter methylation	Specific PCR for methylation	Prognostic value; predictive of response to temozolomide in the elderly	Probable favorable prognostic/ predictive (to temozolomide/ PCV) value	Uncertain prognostic/predictive value
IDH 1/2 mutation	Immunohistochemistry sequencing	Favorable prognostic value	Favorable prognostic value	Favorable prognostic value