World Congress of Neurology

Standards of care in glioblastoma

Dubai, 30 October 2019

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Conflicts of Interest

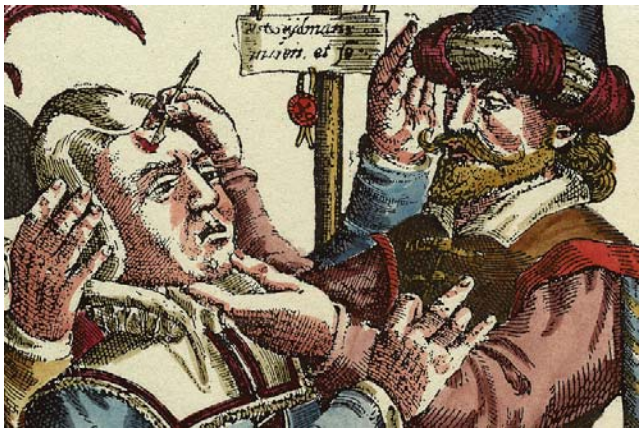
M. Weller has received research grants from Abbvie, Adastra, Dracen, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Piqur and Roche, and honoraria for lectures or advisory board participation or consulting from Abbvie, Basilea, Bristol Meyer Squibb (BMS), Celgene, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Orbus, Roche and Tocagen.

Learning objectives

- **Understand the current concepts of defining glioblastoma based on the 2016 WHO classification**
- **Understand the contributions of surgery, radiotherapy and pharmacotherapy to outcome in glioblastoma**
- **Understand the current controversies in the diagnosis and management of glioblastoma**

Key messages

- Glioblastoma is now increasingly defined based on histomorphological and on molecular genetic features
- Combined modality treatment of surgery followed by chemoradiotherapy improves outcome, but is never curative
- Novel approaches of targeted therapy and immunotherapy may provide benefit in subgroups of patients
- Standardized multidisciplinary care and focus on symptomatic treatments, e.g., of epilepsy and vascular complications, are an important aspect of a comprehensive approach to glioblastoma

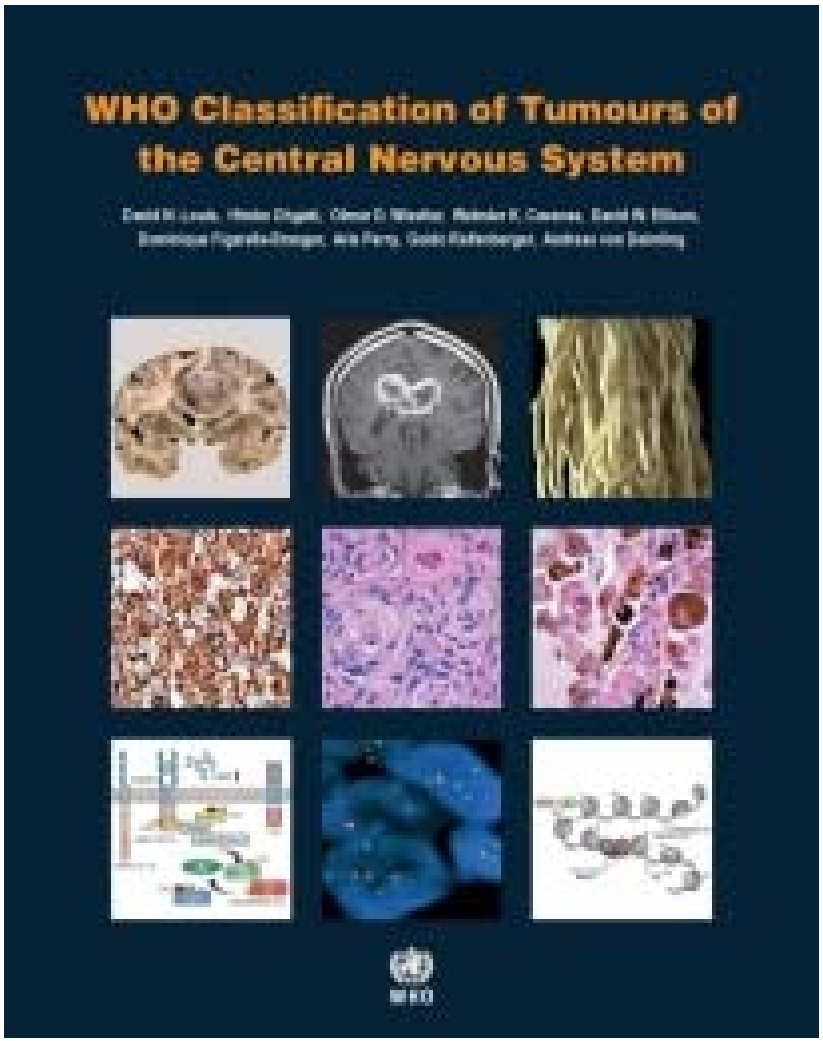


Our current standards of care are based on very few clinical trials and a lot of eminence-based medicine…

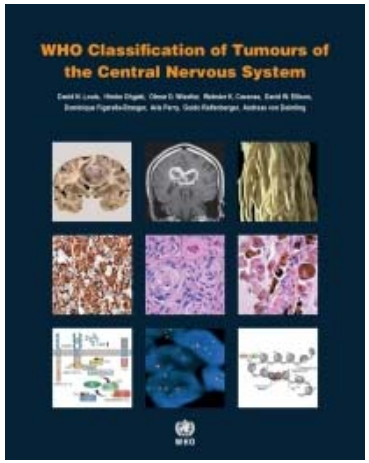
What is the “standard”?

- What the guidelines say? If so, which?
- What is approved? What is reimbursed?
- What the boss says?
- For which patients does the standard apply?
- Who changes the standard?

What is glioblastoma in 2019?

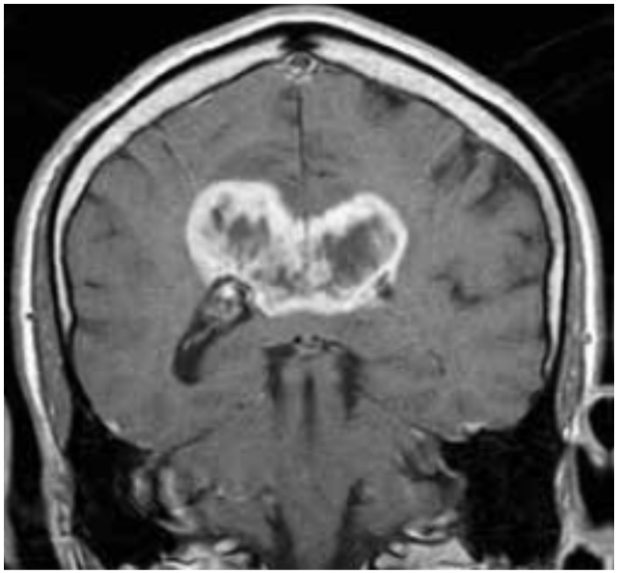


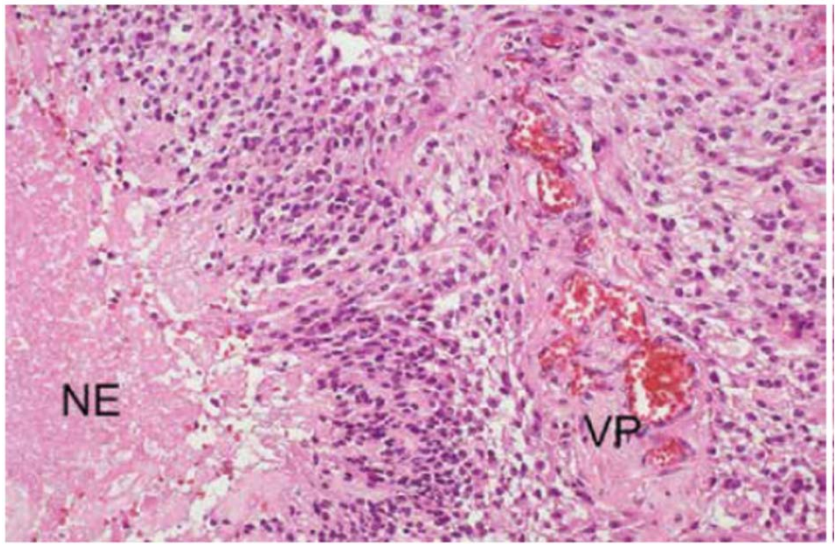
What is glioblastoma in 2019?



Definition

A high-grade glioma with predominantly astrocytic differentiation; featuring nuclear atypia, cellular pleomorphism (in most cases), mitotic activity, and typically a diffuse growth pattern, as well as microvascular proliferation and/or necrosis; without mutations in the IDH genes





What is glioblastoma in 2019?

TCGA, Nature, 2008

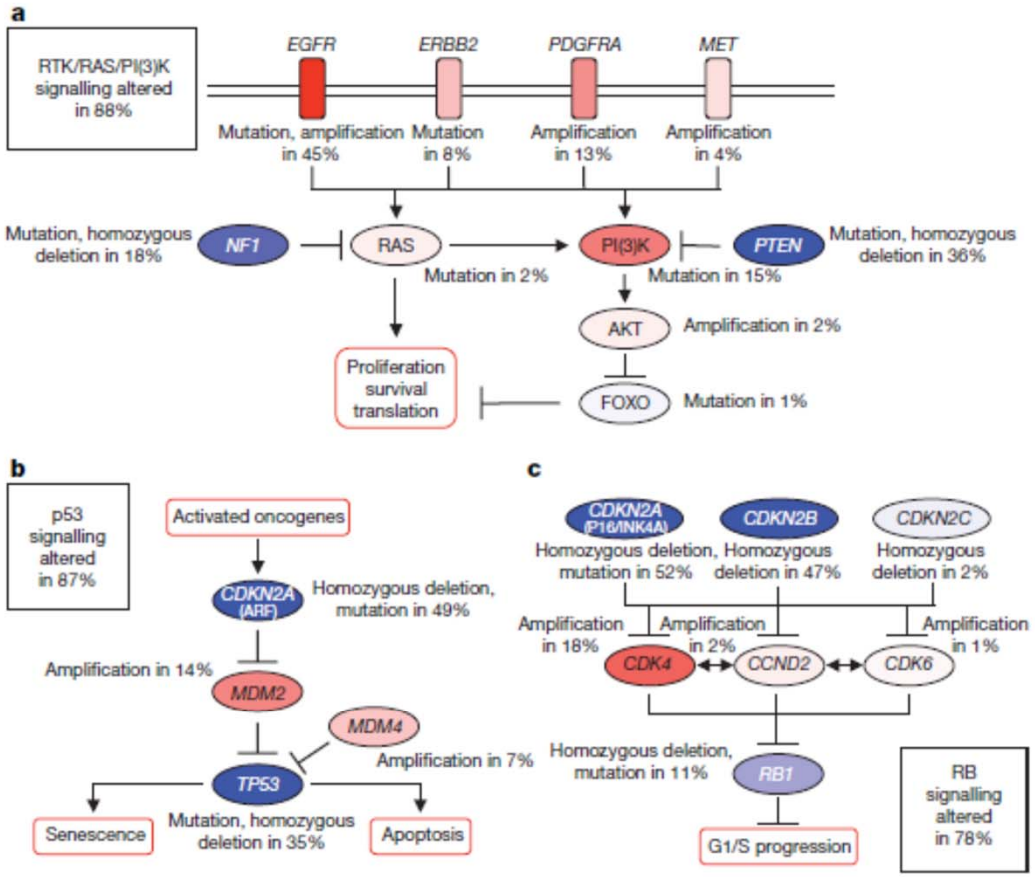


Figure 5 | Frequent genetic alterations in three critical signalling pathways. **a**–**c**, Primary sequence alterations and significant copy number changes for components of the RTK/RAS/PI(3)K (**a**), p53 (**b**) and RB (**c**) signalling pathways are shown. Red indicates activating genetic alterations, with frequently altered genes showing deeper shades of red. Conversely, blue indicates inactivating alterations, with darker shades corresponding to a higher percentage of alteration. For each altered component of a particular pathway, the nature of the alteration and the percentage of tumours affected are indicated. Boxes contain the final percentages of glioblastomas with alterations in at least one known component gene of the designated pathway.

Towards „molecular“ glioblastoma?

Acta Neuropathologica (2018) 136:805–810
https://doi.org/10.1007/s00401-018-1913-0

CORRESPONDENCE

cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV"

Daniel J. Brat[1] · Kenneth Aldape[2] · Howard Colman[3] · Eric C. Holland[4] · David N. Louis[5] · Robert B. Jenkins[6] · B. K. Kleinschmidt-DeMasters[7] · Arie Perry[8] · Guido Reifenberger[9,10] · Roger Stupp[11] · Andreas von Deimling[12,13] · Michael Weller[14]

We reached consensus that the following were the minimal molecular criteria for identifying an IDH-wildtype diffuse astrocytic glioma that, despite appearing histologically as a WHO grade II or III neoplasm, would follow an aggressive clinical course more closely resembling that of an IDH-wildtype glioblastoma:

1. *EGFR* amplification

   OR

2. Combined whole chromosome 7 gain and whole chromosome 10 loss (+ 7/– 10)

   OR

3. *TERT* promoter mutation

European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas

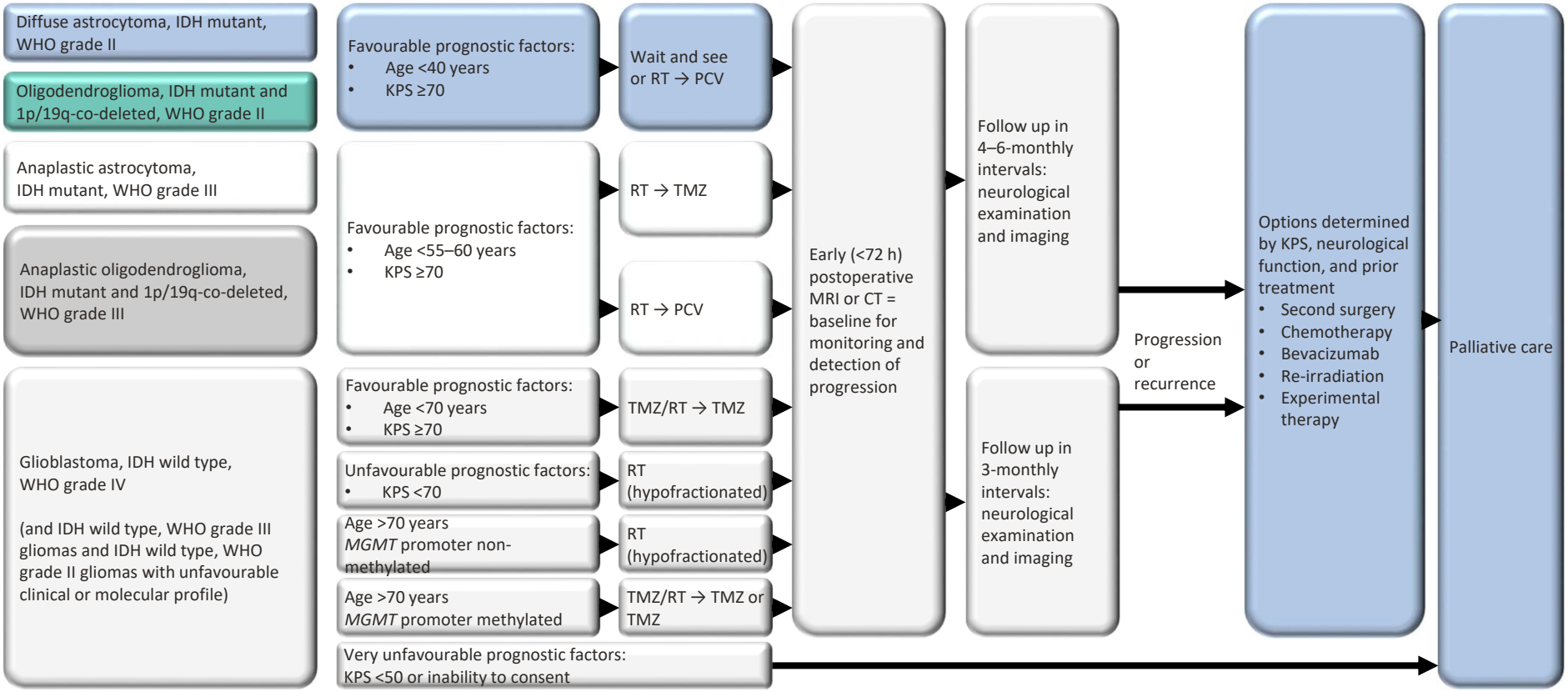
Michael Weller, Martin van den Bent, Jörg C Tonn, Roger Stupp, Matthias Preusser, Elizabeth Cohen-Jonathan-Moyal, Roger Henriksson, Emilie Le Rhun, Carmen Balana, Olivier Chinot, Martin Bendszus, Jaap C Reijneveld, Frederick Dhermain, Pim French, Christine Marosi, Colin Watts, Ingela Oberg, Geoffrey Pilkington, Brigitta G Baumert, Martin J B Taphoorn, Monika Hegi, Manfred Westphal, Guido Reifenberger, Riccardo Soffietti, Wolfgang Wick, for the European Association for Neuro-Oncology (EANO) Task Force on Gliomas

The European Association for Neuro-Oncology guideline provides recommendations for the clinical care of adult patients with astrocytic and oligodendroglial gliomas, including glioblastomas. The guideline is based on the 2016 WHO classification of tumours of the central nervous system and on scientific developments since the 2014 guideline. The recommendations focus on pathological and radiological diagnostics, and the main treatment modalities of surgery, radiotherapy, and pharmacotherapy. In this guideline we have also integrated the results from contemporary clinical trials that have changed clinical practice. The guideline aims to provide guidance for diagnostic and management decisions, while limiting unnecessary treatments and costs. The recommendations are a resource for professionals involved in the management of patients with glioma, for patients and caregivers, and for health-care providers in Europe. The implementation of this guideline requires multidisciplinary structures of care, and defined processes of diagnosis and treatment.

Lancet Oncol 2017

Published Online
May 5, 2017
http://dx.doi.org/10.1016/
S1470-2045(17)30194-8

Clinical pathway *Glioma*
according to EANO



- **KPS, Karnofsky performance status.**

Key recommendations
according to EANO

Glioblastoma, IDH-wild-type (WHO grade IV)		
Standard of care for glioblastoma, IDH-wild-type (age <70 years, Karnofsky performance score ≥70) includes resection as feasible or biopsy followed by involved-field radiotherapy and 6 cycles of concomitant and maintenance temozolomide chemotherapy (EORTC 26981 NCIC CE.3 trial).[17]	I	A
Temozolomide is particularly active in patients with *MGMT* promoter methylation whereas its activity in patients with *MGMT* promoter-unmethylated tumours is marginal.[38]	II	B
Elderly patients not considered candidates for concomitant or maintenance temozolomide plus radiotherapy should be treated based on *MGMT* promoter methylation status (Nordic,[19] NOA-08,[20] and NCIC CE.6 EORTC 6062[21] trials) with radiotherapy (eg, 15 × 2·66 Gy) or temozolomide (5 out of 28 days).	II	B
Standards of care are not well defined at recurrence. Nitrosourea regimens, temozolomide rechallenge and, with consideration of the country-specific label, bevacizumab are pharmacological options, but an effect on overall survival remains unproven. When available, recruitment into appropriate clinical trials should be considered.	II	B

Controversies
in the management of glioblastoma

- **MGMT testing for all patients, in the elderly or not at all?**
- **Maintenance temozolomide forever?**
- **Bevacizumab for recurrent glioblastoma?**
- **Are tumor-treating fields standard of care?**

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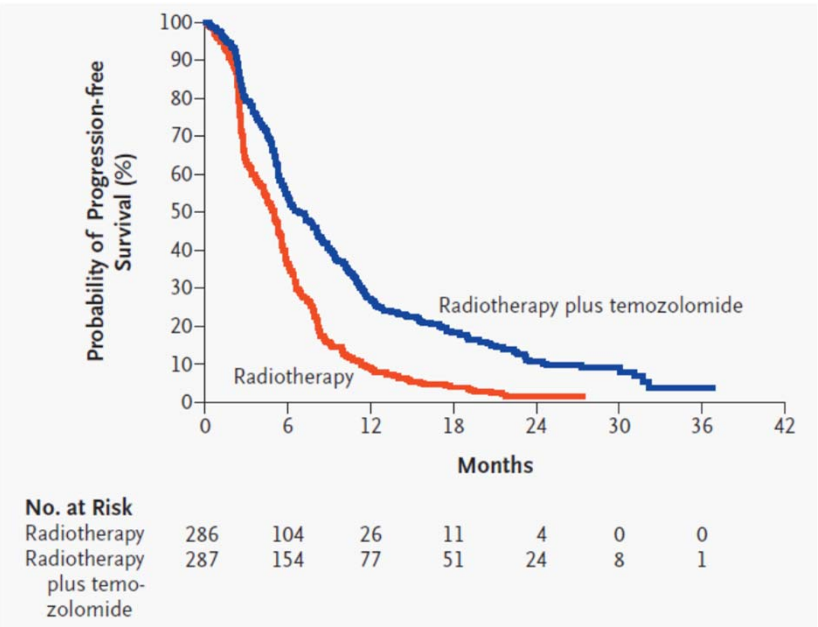
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

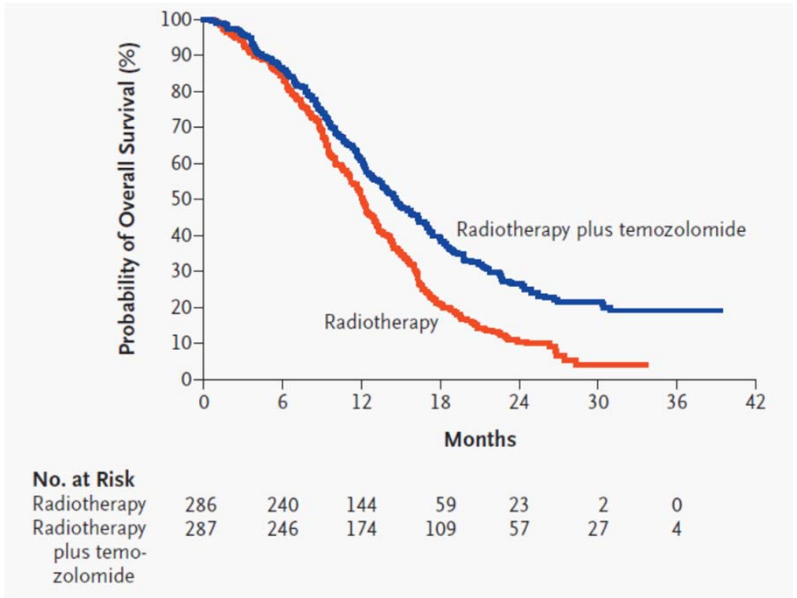
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

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

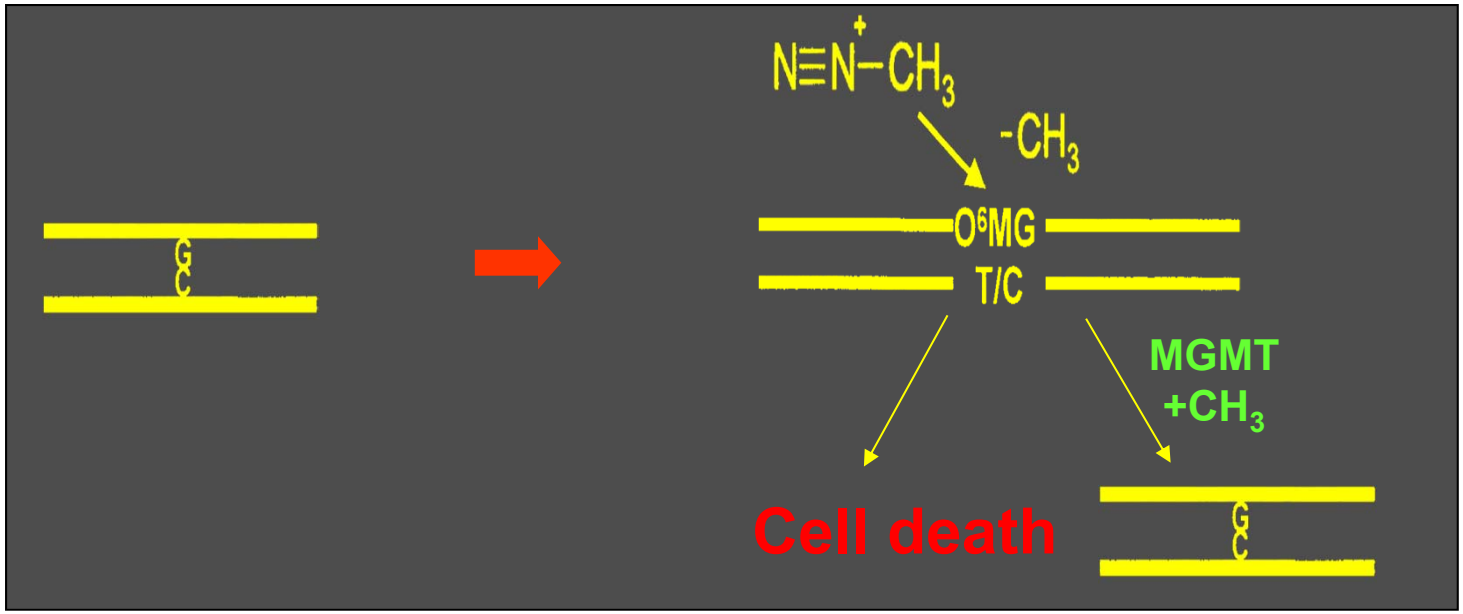
MGMT promoter methylation in malignant gliomas: ready for personalized medicine?

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)

USZ Universitäts Spital Zürich

O^6-Methylguanin-methyltransferase (MGMT, AGAT), a DNA repair protein, 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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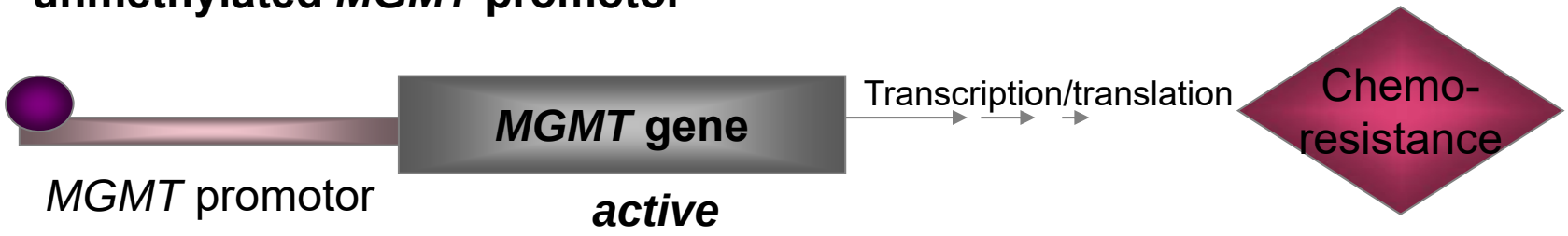
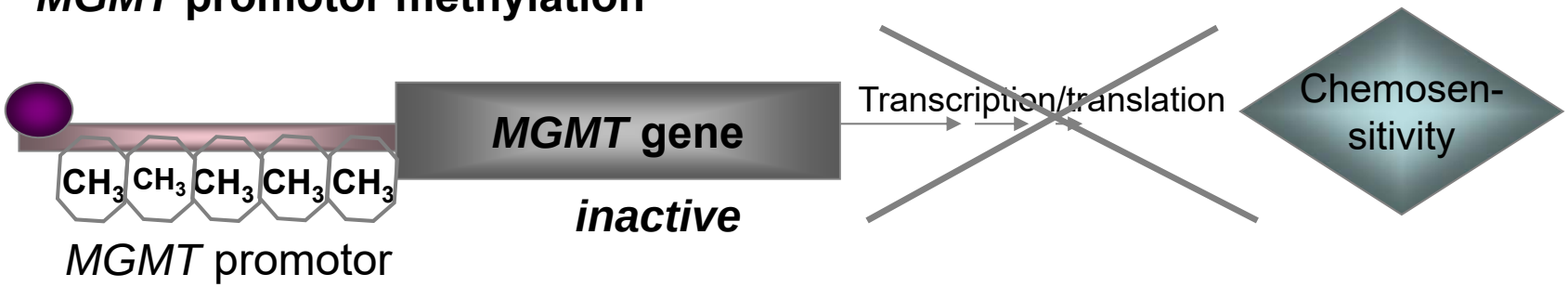
unmethylated *MGMT* promotor



***MGMT* promotor methylation**



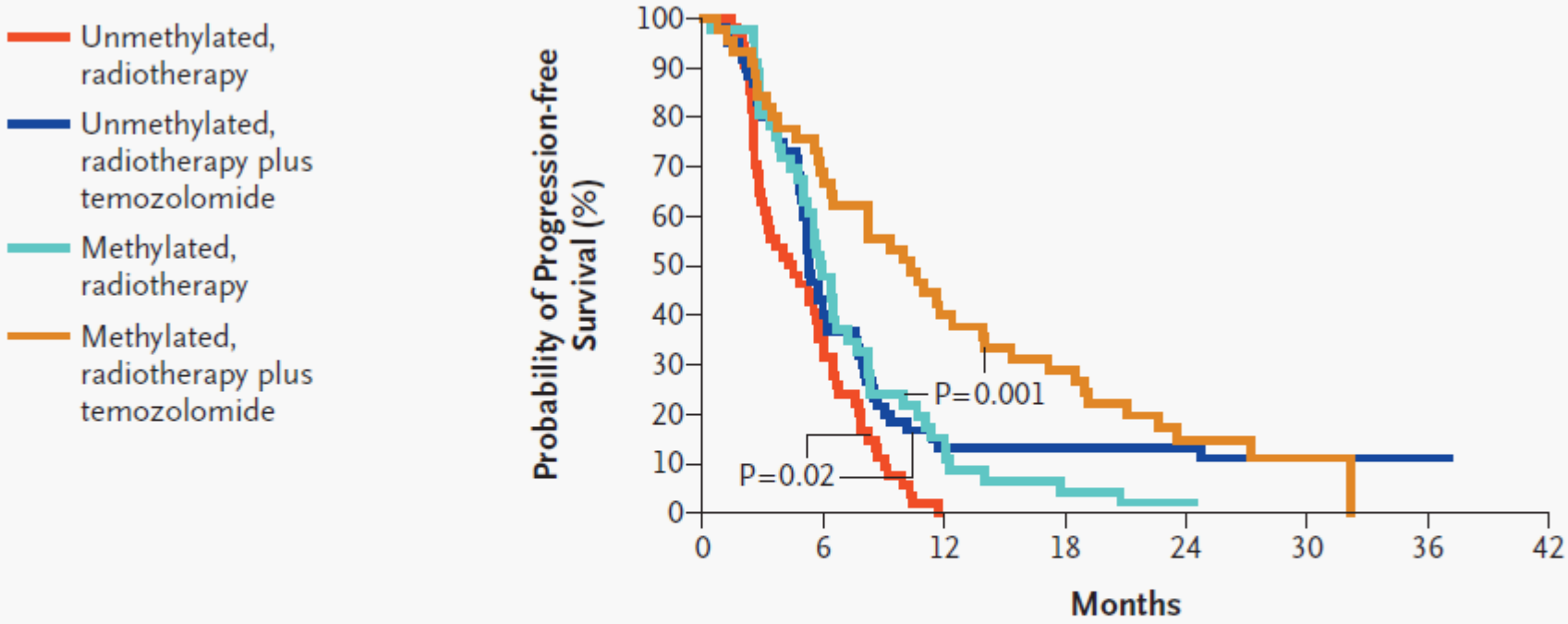
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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	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

The rationale for MGMT testing in the elderly

Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial

Wolfgang Wick, Michael Platten, Christoph Meisner, Jörg Felsberg, Ghazaleh Tabatabai, Matthias Simon, Guido Nikkhah, Kirsten Papsdorf, Joachim P Steinbach, Michael Sabel, Stephanie E Combs, Jan Vesper, Christian Braun, Jürgen Meixensberger, Ralf Ketter, Regine Mayer-Steinacker, Guido Reifenberger, Michael Weller, for the NOA-08 Study Group* of the Neuro-oncology Working Group (NOA) of the German Cancer Society

Lancet Oncol 2012; 13: 707–15

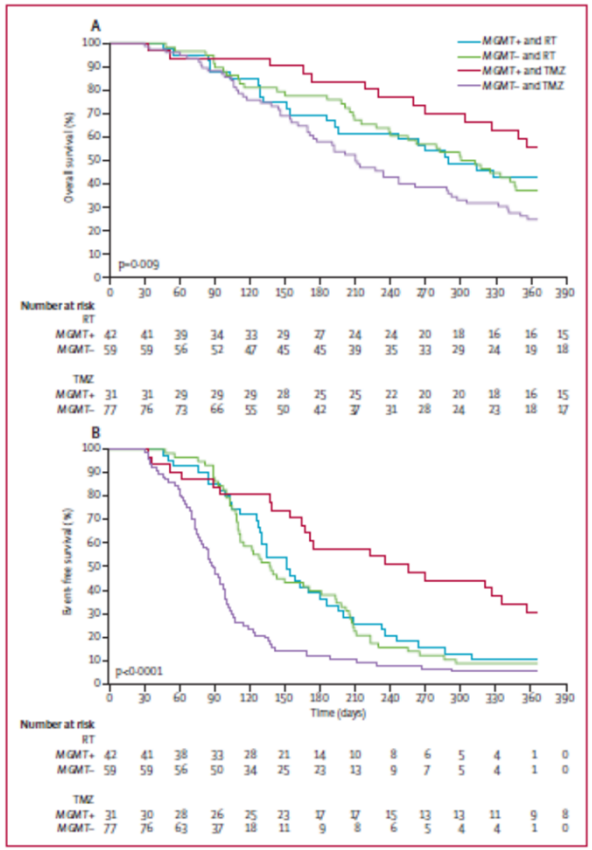
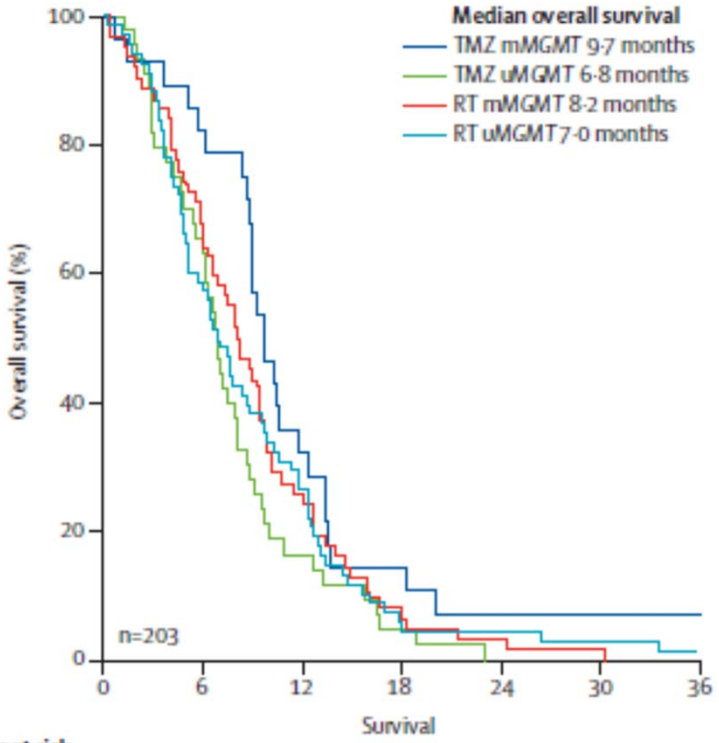


Figure 4: Kaplan-Meier analysis of overall and event-free survival in relation to MGMT promoter methylation status and treatment
(A) Overall survival. (B) Event-free survival. The p values were calculated for any significant difference in at least two of the curves. See also table 3. RT=radiotherapy. TMZ=temozolomide.

Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial

Annika Malmström, Bjørn Henning Grønberg, Christine Marosi, Roger Stupp, Didier Frappaz, Henrik Schultz, Ufuk Abacioglu, Björn Tavelin, Benoit Lhermitte, Monika E Hegi, Johan Rosell, Roger Henriksson, for the Nordic Clinical Brain Tumour Study Group (NCBTSG)

Lancet Oncol 2012; 13: 916–26



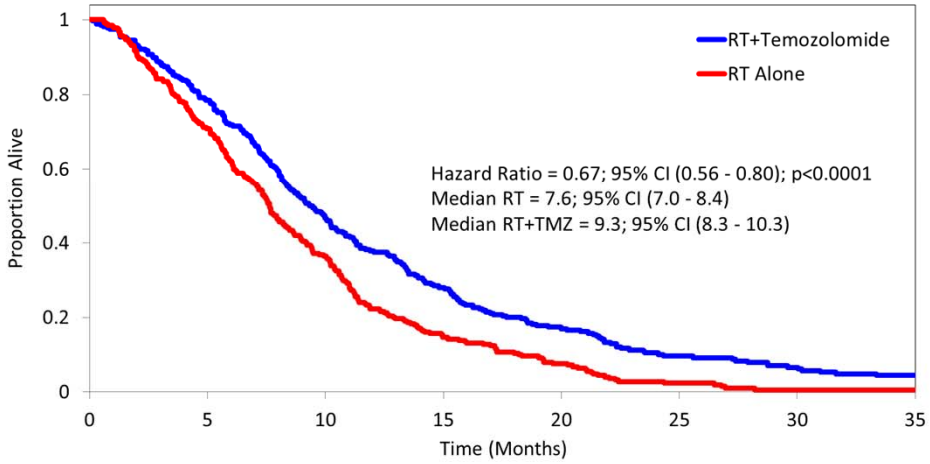
Number at risk							
TMZ mMGMT	28	23	9	4	2	2	2
TMZ uMGMT	44	27	7	2	0	0	0
RT mMGMT	63	41	16	4	2	1	0
RT uMGMT	68	40	18	3	3	2	1*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

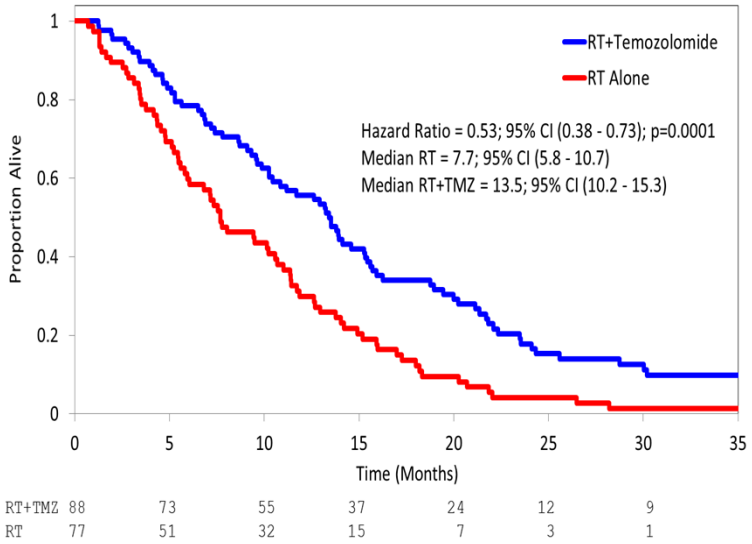
Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma

James R. Perry, M.D., Normand Laperriere, M.D., Christopher J. O'Callaghan, D.V.M., Alba A. Brandes, M.D., Johan Menten, M.D., Claire Phillips, M.B., B.S., Michael Fay, M.B., Ch.B., Ryo Nishikawa, M.D., J. Gregory Cairncross, M.D., Wilson Roa, M.D., David Osoba, M.D., John P. Rossiter, M.B., B.Ch., Arjun Sahgal, M.D., Hal Hirte, M.D., Florence Laigle-Donadey, M.D., Enrico Franceschi, M.D., Olivier Chinot, M.D., Vassilis Golfinopoulos, M.D., Laura Fariselli, M.D., Antje Wick, M.D., Loic Feuvret, M.D., Michael Back, M.B., B.S., Michael Tills, M.B., B.S., Chad Winch, M.Sc., Brigitta G. Baumert, M.D., Wolfgang Wick, M.D., Keyue Ding, Ph.D., and Warren P. Mason, M.D., for the Trial Investigators*

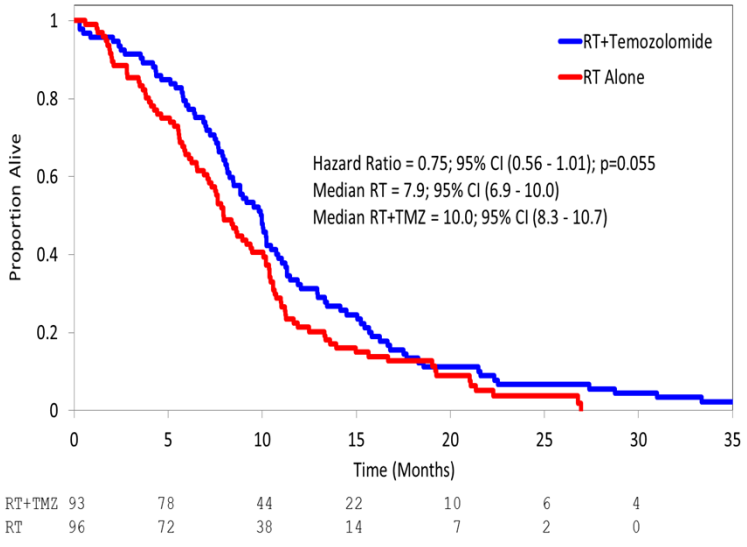


The devil is in the detail….

Methylated



Unmethylated



Controversies
in the management of glioblastoma

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- Bevacizumab for recurrent glioblastoma?
- Are tumor-treating fields standard of care?

Maintenance temozolomide: 6 cycles is enough

Limited role for extended maintenance temozolomide for newly diagnosed glioblastoma

Dorothee Gramatzki, MD
Philipp Kickingereder, MD
Bettina Hentschel, PhD
Jörg Felsberg, MD
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Gabriele Schackert, MD
Jörg-Christian Tonn, MD
Manfred Westphal, MD
Michael Sabel, MD
Uwe Schlegel, MD
Wolfgang Wick, MD
Torsten Pietsch, MD
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Michael Weller, MD

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ABSTRACT

Objective: To explore an association with survival of modifying the current standard of care for patients with newly diagnosed glioblastoma of surgery followed by radiotherapy plus concurrent and 6 cycles of maintenance temozolomide chemotherapy (TMZ/RT → TMZ) by extending TMZ beyond 6 cycles.

Methods: The German Glioma Network cohort was screened for patients with newly diagnosed glioblastoma who received TMZ/RT → TMZ and completed ≥6 cycles of maintenance chemotherapy without progression. Associations of clinical patient characteristics, molecular markers, and residual tumor determined by magnetic resonance imaging after 6 cycles of TMZ with progression-free survival (PFS) and overall survival (OS) were analyzed with the log-rank test. Multivariate analyses using the Cox proportional hazards model were performed to assess associations of prolonged TMZ use with outcome.

Results: Sixty-one of 142 identified patients received at least 7 maintenance TMZ cycles (median 11, range 7–20). Patients with extended maintenance TMZ treatment had better PFS (20.5 months, 95% confidence interval [CI] 17.7–23.3, vs 17.2 months, 95% CI 10.2–24.2, $p = 0.035$) but not OS (32.6 months, 95% CI 28.9–36.4, vs 33.2 months, 95% CI 25.3–41.0, $p = 0.126$). However, there was no significant association of prolonged TMZ chemotherapy with PFS (hazard ratio [HR] = 0.8, 95% CI 0.4–1.6, $p = 0.559$) or OS (HR = 1.6, 95% CI 0.8–3.3, $p = 0.218$) adjusted for age, extent of resection, Karnofsky performance score, presence of residual tumor, O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation status, or isocitrate dehydrogenase (*IDH*) mutation status.

Conclusion: These data may not support the practice of prolonging maintenance TMZ chemotherapy beyond 6 cycles.

Classification of evidence: This study provides Class III evidence that in patients with newly diagnosed glioblastoma, prolonged TMZ chemotherapy does not significantly increase PFS or OS.

Neurology® 2017;88:1422–1430

Neuro-Oncology
19(8), 1119–1126, 2017 | doi:10.1093/neuonc/nox025 | Advance Access date 24 March 2017

Is more better? The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma: a secondary analysis of EORTC and NRG Oncology/RTOG

Deborah T. Blumenthal, Thierry Gorlia, Mark R. Gilbert, Michelle M. Kim, L. Burt Nabors, Warren P. Mason, Monika E. Hegi, Peixin Zhang, Vassilis Golfinopoulos, James R. Perry, Do Hyun Nam, Sara C. Erridge, Benjamin W. Corn, René O Mirimanoff, Paul D. Brown, Brigitta G. Baumert, Minesh P. Mehta, Martin J. van den Bent, David A. Reardon, Michael Weller, and Roger Stupp

Abstract

Background: Radiation with concurrent and adjuvant (6 cycles) temozolomide (TMZ) is the established standard of postsurgical care for newly diagnosed glioblastoma (GBM). This regimen has been adopted with variations, including extending TMZ beyond 6 cycles. The optimal duration of maintenance therapy remains controversial.

Methods: We performed pooled analysis of individual patient data from 4 randomized trials for newly diagnosed GBM. All patients who were progression free 28 days after cycle 6 were included. The decision to continue TMZ was per local practice and standards, and at the discretion of the treating physician. Patients were grouped into those treated with 6 cycles and those who continued beyond 6 cycles. Progression-free and overall survival were compared, adjusted by age, performance status, resection extent, and *MGMT* methylation.

Results: A total of 2214 GBM patients were included in the 4 trials. Of these, 624 qualified for analysis 291 continued maintenance TMZ until progression or up to 12 cycles, while 333 discontinued TMZ after 6 cycles. Adjusted for prognostic factors, treatment with more than 6 cycles of TMZ was associated with a somewhat improved progression-free survival (hazard ratio [HR] 0.80 [0.65–0.98], $P = .03$), in particular for patients with methylated *MGMT* ($n = 342$, HR 0.65 [0.50–0.85], $P < .01$). However, overall survival was not affected by the number of TMZ cycles (HR = 0.92 [0.71–1.19], $P = .52$), including the *MGMT* methylated subgroup (HR = 0.89 [0.63–1.26], $P = .51$).

Conclusions: Continuing TMZ beyond 6 cycles was not shown to increase overall survival for newly diagnosed GBM.

Alkylating agent chemotherapy forever?

Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas

MICHAEL D. WALKER, M.D., EBEN ALEXANDER, JR., M.D.,
WILLIAM E. HUNT, M.D., COLLIN S. MACCARTY, M.D.,
M. STEPHEN MAHALEY, JR., M.D., JOHN MEALEY, JR., M.D.,
HORACE A. NORRELL, M.D., GUY OWENS, M.D.,
JOSEPH RANSOHOFF, M.D., CHARLES B. WILSON, M.D.,
EDMUND A. GEHAN, PH.D., AND THOMAS A. STRIKE, PH.D.

The Brain Tumor Study Group and the National Cancer Institute, National Institutes of Health, Bethesda, Maryland

J Neurosurg 49:333–343, 1978

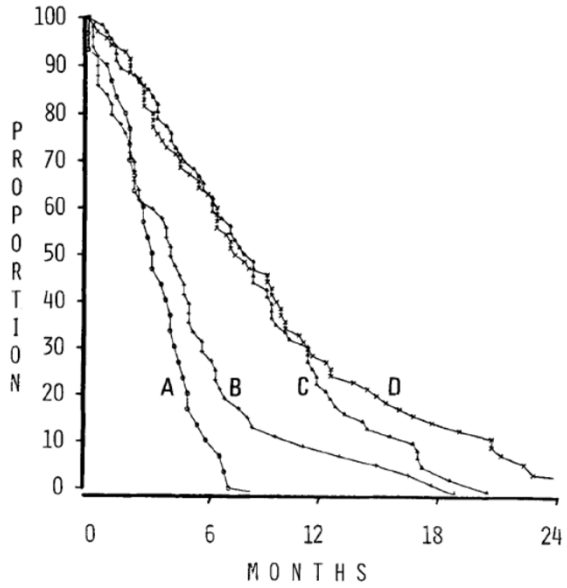


FIG. 1. Survival curves of patients who received: A) best conventional care but no radiotherapy or chemotherapy, B) BCNU, C) radiotherapy, or D) BCNU and radiotherapy.

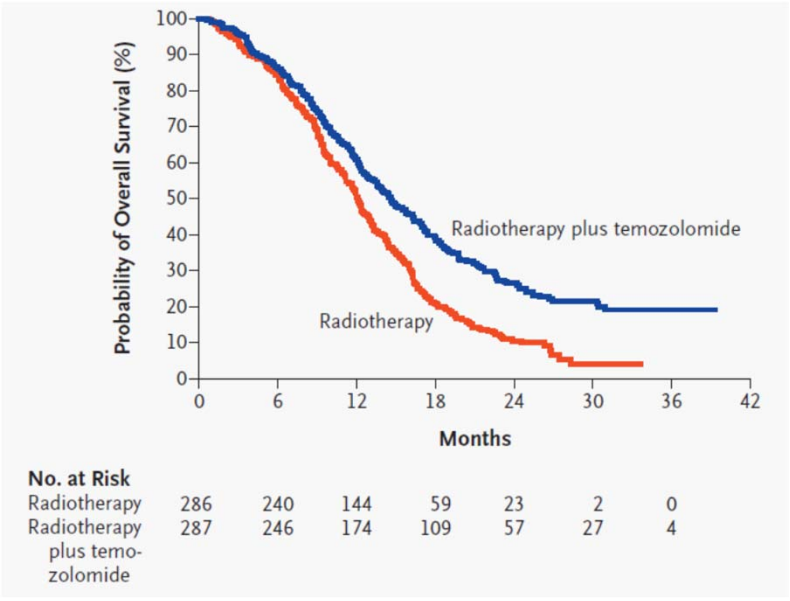
The NEW ENGLAND JOURNAL of MEDICINE

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.



Alkylating agent chemotherapy forever?

Herrlinger et al. Lancet 2019;393:678-688

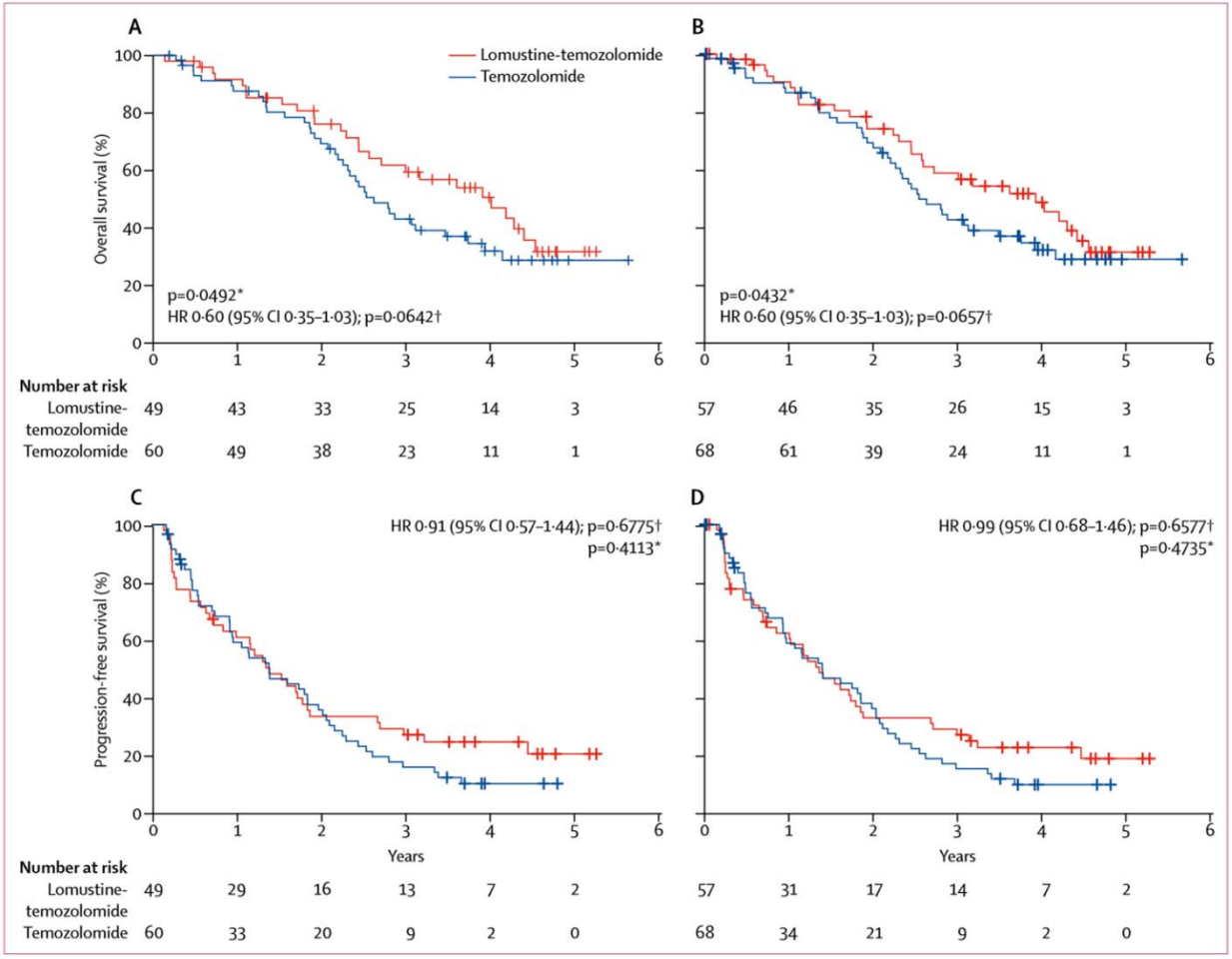


Figure 3: **Kaplan-Meier plots of overall survival and progression-free survival**

Kaplan-Meier plots of patients in both groups matched by respective centre and RPA class strata. Overall survival (A) in the modified intention-to-treat population (n=109; stratified log-rank test) and (B) in the intention-to-treat population (n=125; stratified log-rank test). Progression-free survival in the modified intention-to-treat population (C) and the intention-to-treat population (D). HR=hazard ratio. *Stratified log-rank test (primary analysis). †Multivariate Cox regression analysis.

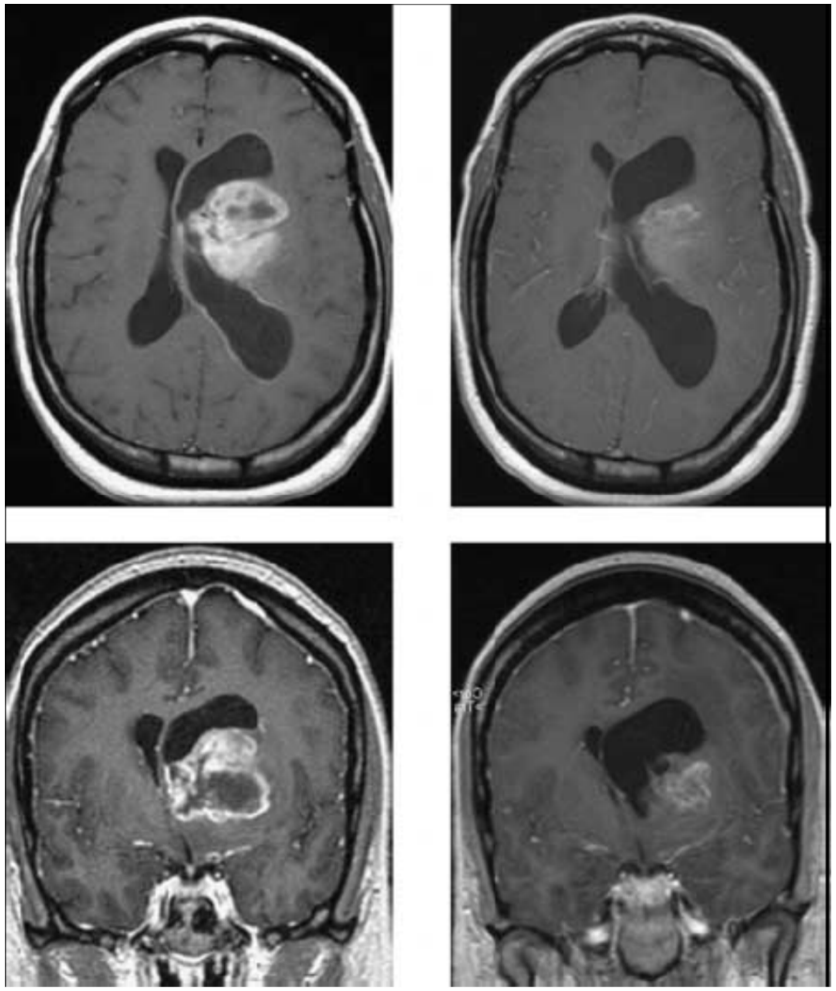
Controversies
in the management of glioblastoma

- MGMT testing for all patients, in the elderly or not at all?
- Maintenance temozolomide forever?
- Bevacizumab for recurrent glioblastoma?
- Are tumor-treating fields standard of care?

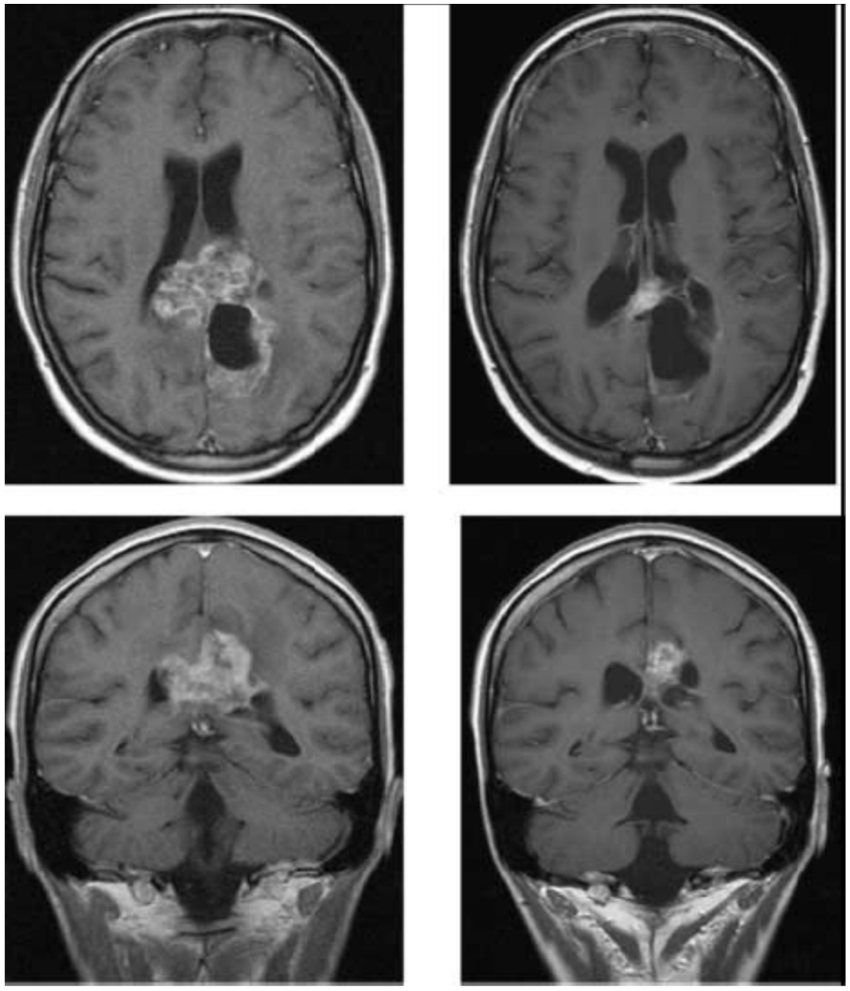
Responses to bevacizumab in recurrent glioblastoma

Clin Cancer Res 2007;13:1253-1259

GB #1



GB #2



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lomustine and Bevacizumab in Progressive Glioblastoma

Wolfgang Wick, M.D., Thierry Gorlia, Ph.D., Martin Bendszus, M.D., Martin Taphoorn, M.D., Felix Sahm, M.D., Inga Harting, M.D., Alba A. Brandes, M.D., Walter Taal, M.D., Julien Domont, M.D., Ahmed Idbaih, M.D., Mario Campone, M.D., Paul M. Clement, M.D., Roger Stupp, M.D., Michel Fabbro, M.D., Emilie Le Rhun, M.D., Francois Dubois, M.D., Michael Weller, M.D., Andreas von Deimling, M.D., Vassilis Golfinopoulos, M.D., Jacoline C. Bromberg, M.D., Michael Platten, M.D., Martin Klein, M.D., and Martin J. van den Bent, M.D.

N ENGL J MED 377;20 NEJM.ORG NOVEMBER 16, 2017

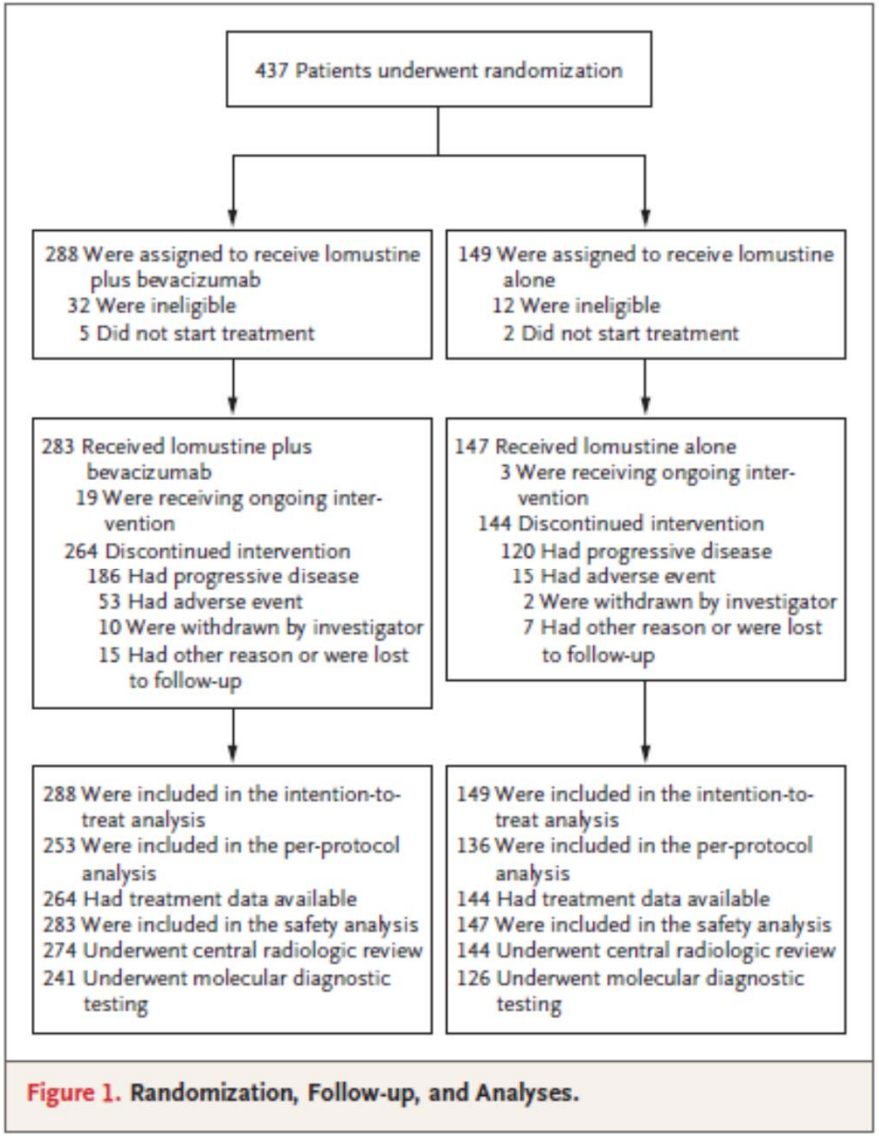


Figure 1. Randomization, Follow-up, and Analyses.

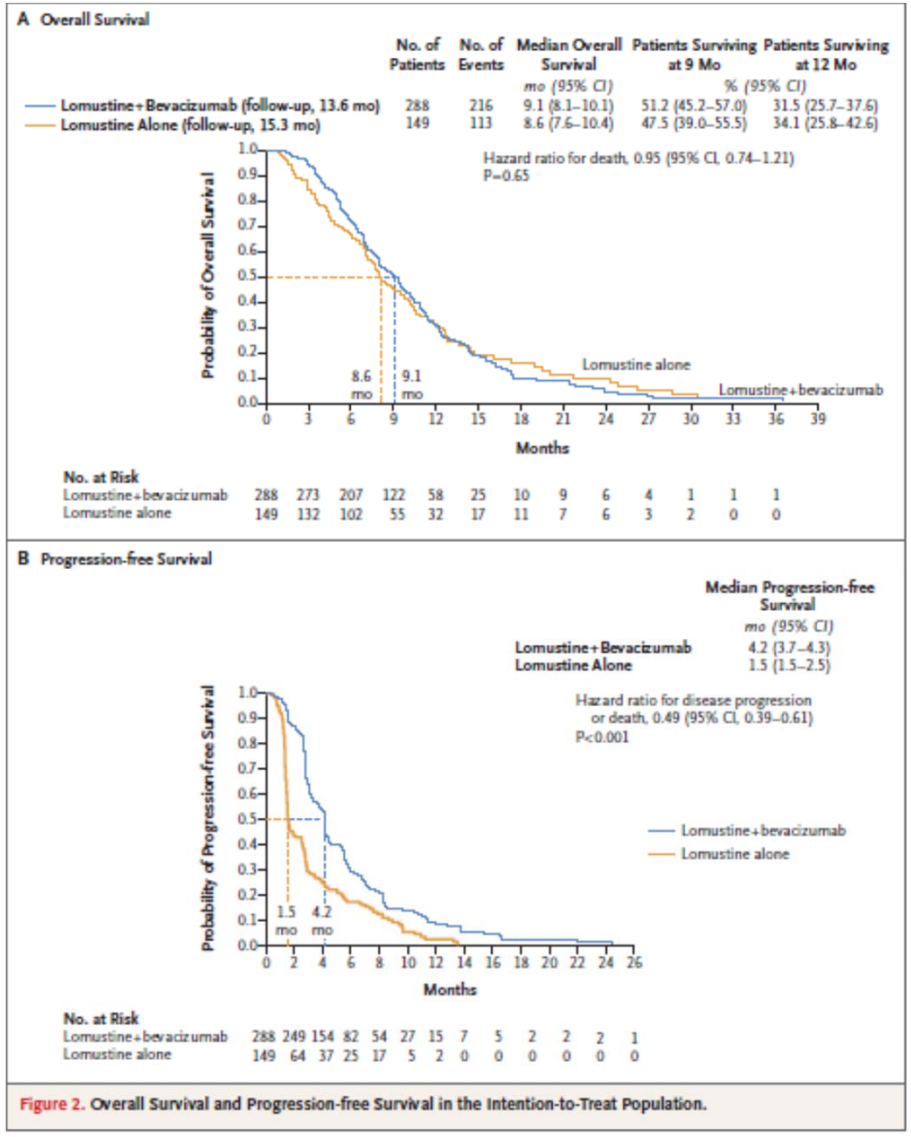


Figure 2. Overall Survival and Progression-free Survival in the Intention-to-Treat Population.

Controversies
in the management of glioblastoma

- MGMT testing for all patients, in the elderly or not at all?
- Maintenance temozolomide forever?
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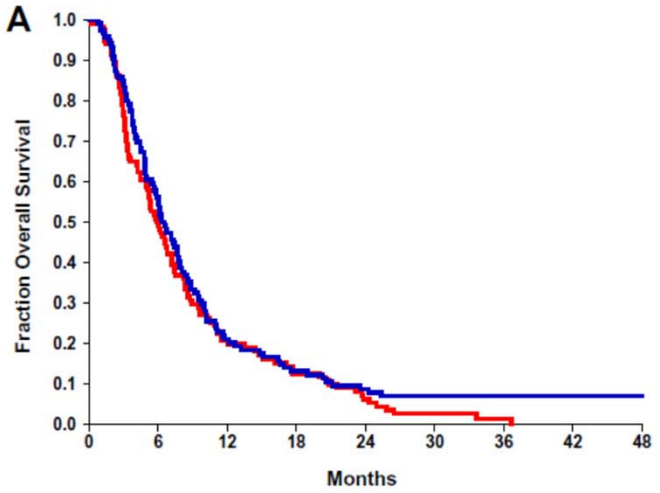
- Are tumor-treating fields standard of care?

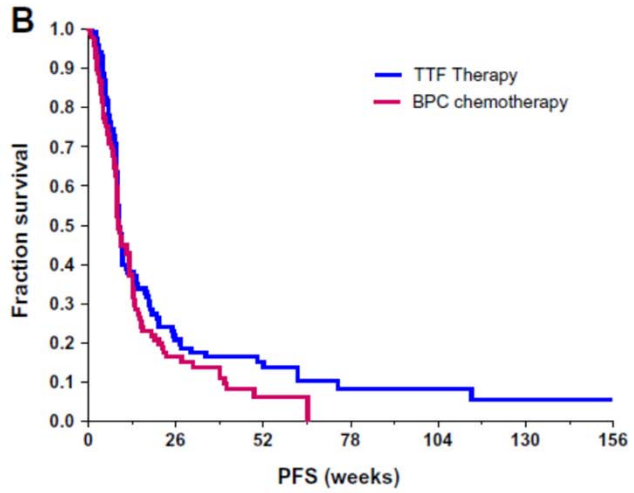
Are tumor-treating fields *standard of care*?

NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality

Roger Stupp[a,*], Eric T. Wong[b], Andrew A. Kanner[c], David Steinberg[d], Herbert Engelhard[e], Volkmar Heidecke[f], Eilon D. Kirson[g], Sophie Taillibert[h], Frank Liebermann[i], Vladimir Dbalý[j], Zvi Ram[c], J. Lee Villano[e], Nikolai Rainov[f], Uri Weinberg[g], David Schiff[k], Lara Kunschner[l], Jeffrey Raizer[m], Jerome Honnorat[n], Andrew Sloan[o], Mark Malkin[p], Joseph C. Landolfi[q], Franz Payer[r], Maximilian Mehdorn[s], Robert J. Weil[t], Susan C. Pannullo[u], Manfred Westphal[v], Martin Smrcka[w], Lawrence Chin[x], Herwig Kostron[y], Silvia Hofer[z], Jeffrey Bruce[aa], Rees Cosgrove[ab], Nina Paleologous[ac], Yoram Palti[g], Philip H. Gutin[ad]

European Journal of Cancer (2012) 48, 2192–2202





At risk	0 m	6 m	12 m	18 m	24 m	30 m	36 m	42 m	48 m
TTF	120	63	24	15	9	7	4	2	1
BPC	117	56	22	14	6	2	1	0	0

0 m	13 w	26w	39w	52w	65 w	78 w	91 w
120	38	19	14	11	6	4	3
117	34	14	10	3	1	0	0

Fig. 2. Overall survival (A) and progression free survival (B) Kaplan–Meier curves.

Are tumor-treating fields *standard of care*?

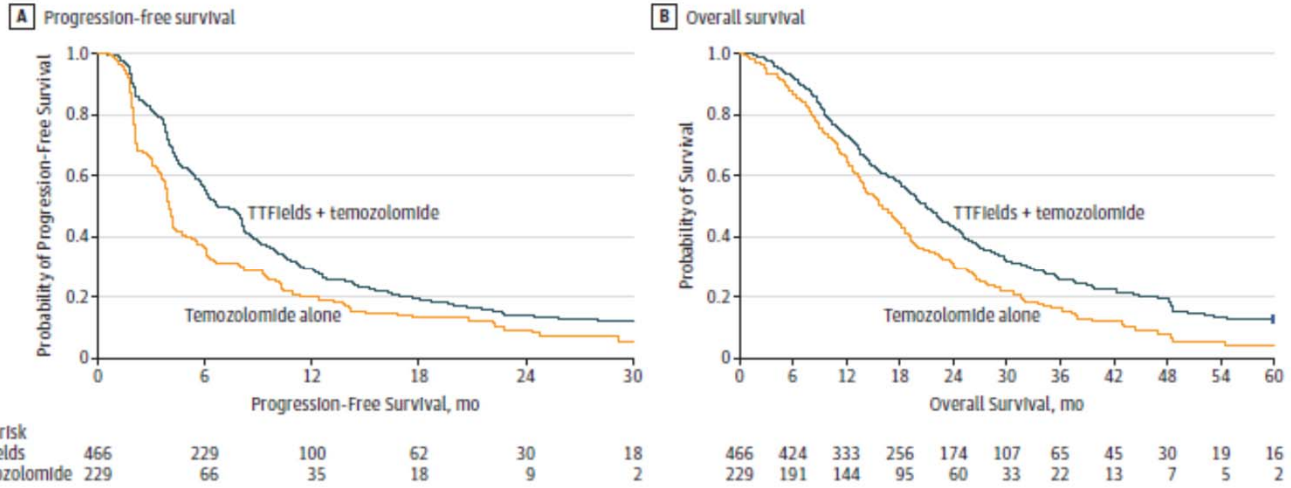
Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma

A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew Kanner, MD; William Read, MD; David M. Steinberg, PhD; Benoit Lhermitte, MD; Steven Toms, MD; Ahmed Idbaih, MD; Manmeet S. Ahluwalia, MD; Karen Fink, MD, PhD; Francesco Di Meco, MD; Frank Lieberman, MD; Jay-Jiguang Zhu, MD, PhD; Giuseppe Stragliotto, MD, PhD; David D. Tran, MD, PhD; Steven Brem, MD; Andreas F. Hottinger, MD, PhD; Eilon D. Kirson, MD, PhD; Gitit Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Chae-Yong Kim, MD, PhD; Sun-Ha Paek, MD, PhD; Garth Nicholas, MD; Jordi Bruna, MD; Hal Hirte, MD; Michael Weller, MD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD

JAMA. 2017;318(23):2306-2316

Figure 2. Kaplan-Meier Survival Curves for Patients Included in the Final Analysis in the Intent-to-Treat Population



A, Median progression-free survival from randomization for the tumor-treating fields (TTFields) plus temozolomide group was 6.7 months and was 4.0 months for the temozolomide-alone group (hazard ratio [HR], 0.63; 95% CI, 0.52-0.76; $P < .001$). B, Median survival from randomization was 20.9 for the TTFields plus temozolomide group vs 16.0 months for the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Median follow up was 44 months (range, 25-91 months) in both groups.

Some facts on TTF

TTF disrupt mitosis and are cytotoxic *in vitro* Kirson et al. Cancer Res 2004;64:3288-95, Kirson et al. Proc Natl Acad Sci U S A 2007;104:10152-7, Giladi et al. Sci Rep 2015;5:18046, Silginer et al. Cell Death Dis 2017;8:e2753

TTF do not prolong survival in recurrent glioblastoma Stupp et al. EJC 2012;48:2192-202

TTF prolong survival in newly diagnosed glioblastoma patients who have not progressed after concomitant TMZ/RT Stupp et al. JAMA 2015;314:2535-43, 2017;318:2306-16

Extensive subgroup analyses have not resulted in a clinical, imaging or molecular profile associated with benefit (or lack thereof) from TTF in newly diagnosed glioblastoma

TTF: a SWOT view

Strengths – positive phase III trial 1L, non-overlapping toxicity

Weaknesses – negative phase IIII trial 2L, no predictive biomarker, no specific imaging or pathology changes associated with response or failure, stigma, questionable commercialization strategy

Opportunities – combination, non-overlapping toxicity, expansion into other tumor entities

Threats – TTF might not work, might not be embraced by patients, relatives and HCP, might not be reimbursed, might be replaced by competing treatments

Soft standards of care in glioblastoma

- Always tell the truth, but do it in fractions…
- Check the need for steroids
- Check the need for anticonvulsants
- Watch out for treatment-related side effects
- Watch out for vascular complications: deep vein thrombosis, pulmonary embolism, haemorrhage, stroke
- Listen and watch for alternative treatment use

It is not standard of care:

- To use radiosurgery (including Gamma Knife and CyberKnife®) in the treatment of newly diagnosed or recurrent glioblastoma
- To put or maintain all patients with newly diagnosed glioblastoma on steroids during radiotherapy or even thereafter
- To put or maintain all patients with newly diagnosed glioblastoma on anti-epileptic drugs
- To withhold full-dose heparin or warfarin from glioblastoma patients with deep vein thrombosis or pulmonary embolism

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