Glioma 2016 – State of the Art and Novel Insights

Roger Stupp, MD

Professor & Chairman
Department of Oncology & Cancer Center,
University Hospital Zurich, Switzerland
President European Organisation for
Research and Treatment of Cancer

Potential Conflict of Interest

Consutling/advisory role to

- Celgene
- Debiopharm
- Ipsen
- Merck KGaA/EMD Serono
- MSD/Merck & Co
- Novartis
- Roche/Genentech

- All honoraria to institution

Travel support received from:

- Novocure Ltd.

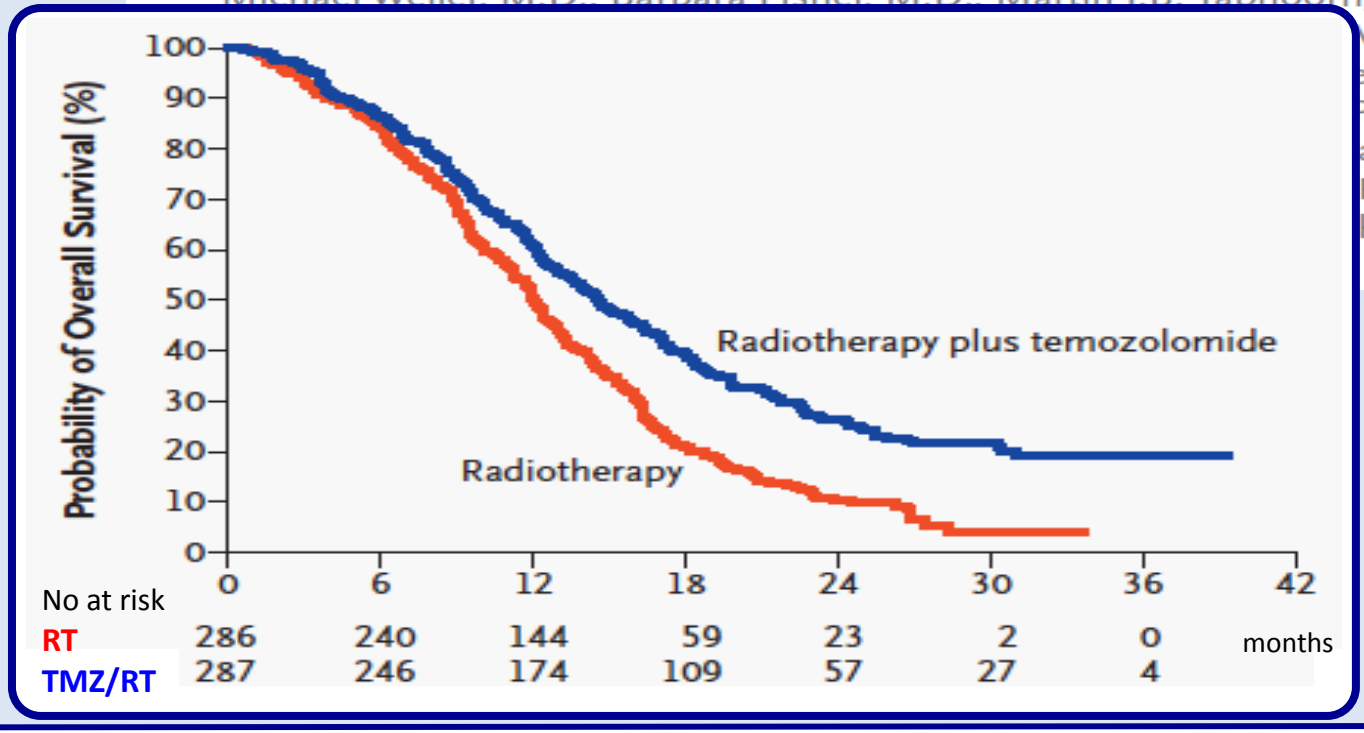
Spouse employee and stockholder of:

- Celgene

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.,
M.D.,
er, M.D.,
Ph.D.,
auer, M.D.,
Research
he National



N Engl J Med 2005;352:987-96

TMZ/RT → TMZ
Is more better ?

The impact of extended adjuvant temozolomide in newly-diagnosed glioblastoma: a secondary analysis

Presentation Society of Neuro-Oncology, Nov. 2015

DT Blumenthal, R Stupp, P Zhang, M Kim, MP Mehta, WP Mason, MJ van den Bent, M Hegi, RO Mirimanoff, G Cairncross, M Weller, M Gilbert, V Golfinopoulos, SC Erridge, J Perry, LB Nabors, KL Fink, T Mikkelsen, D Reardon, T Gorlia

How many maintenance TMZ cycles ?

History

Promising Survival for Patients With Newly Diagnosed Glioblastoma Multiforme Treated With Concomitant Radiation Plus Temozolomide Followed by Adjuvant Temozolomide

By Roger Stupp, Pierre-Yves Dietrich, Sandrine Ostermann Kraljevic, Alessia Pica, Ivan Maillard, Phillipe Maeder, Reto Meuli, Robert Janzer, Gianpaolo Pizzolato, Raymond Miralbell, François Porchet, Luca Regli, Nicolas de Tribolet, René O. Mirimanoff, and Serge Leyvraz *J Clin Oncol 20:1375-1382. © 2002*

Oncologists: 6 cycles of therapy

Procarbazine, Lomustine, and Vincristine (PCV) Chemotherapy for Anaplastic Astrocytoma: A Retrospective Review of Radiation Therapy Oncology Group Protocols Comparing Survival With Carmustine or PCV Adjuvant Chemotherapy

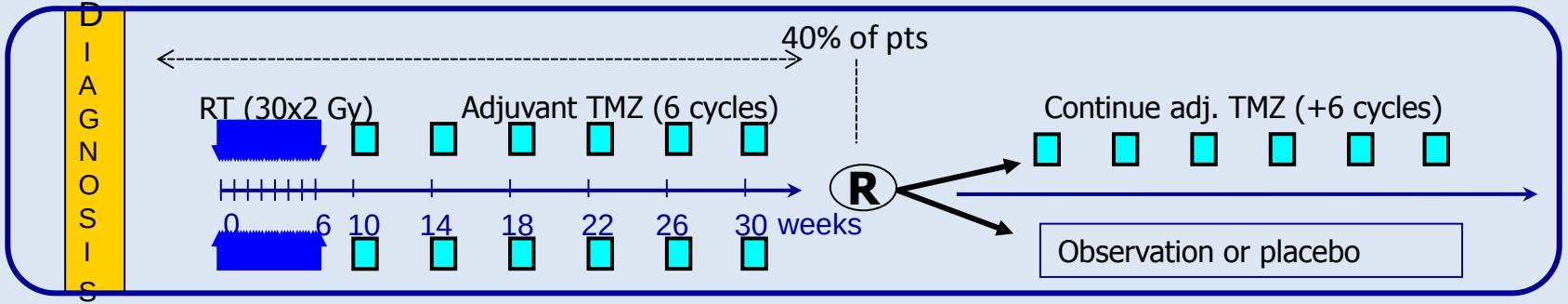
By Michael D. Prados, Charles Scott, Walter J. Curran, Jr, Diana F. Nelson, Steve Leibel, and Simon Kramer *J Clin Oncol 17:3389-3395. © 1999*

Neurologists: 1 year of therapy

- Often 12 cycles of maintenance (adjuvant)
  - USA
- Prolongation to 12 cycles in patients who continue to respond after 6 cycles
  - E.g. further reduction in residual tumor between cycle 3 and cycle 6
- Prolongation until progression
  - Treatment addiction (by patient and MD)

Value of prolonged treatment → randomized trial

Theoretical Trial Design



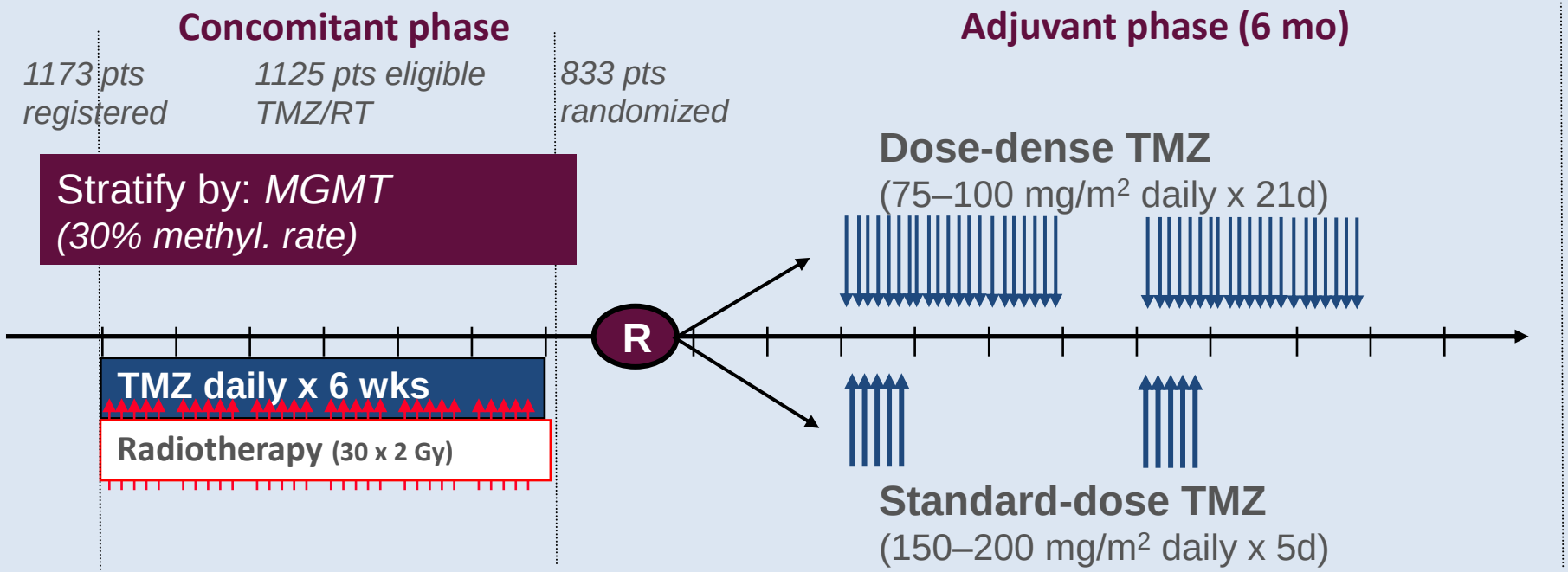
- How much benefit do you expect ?
- Feasibility (screen 1500 – 2000 pts) ?
- Value of the effort

Pooled analysis of

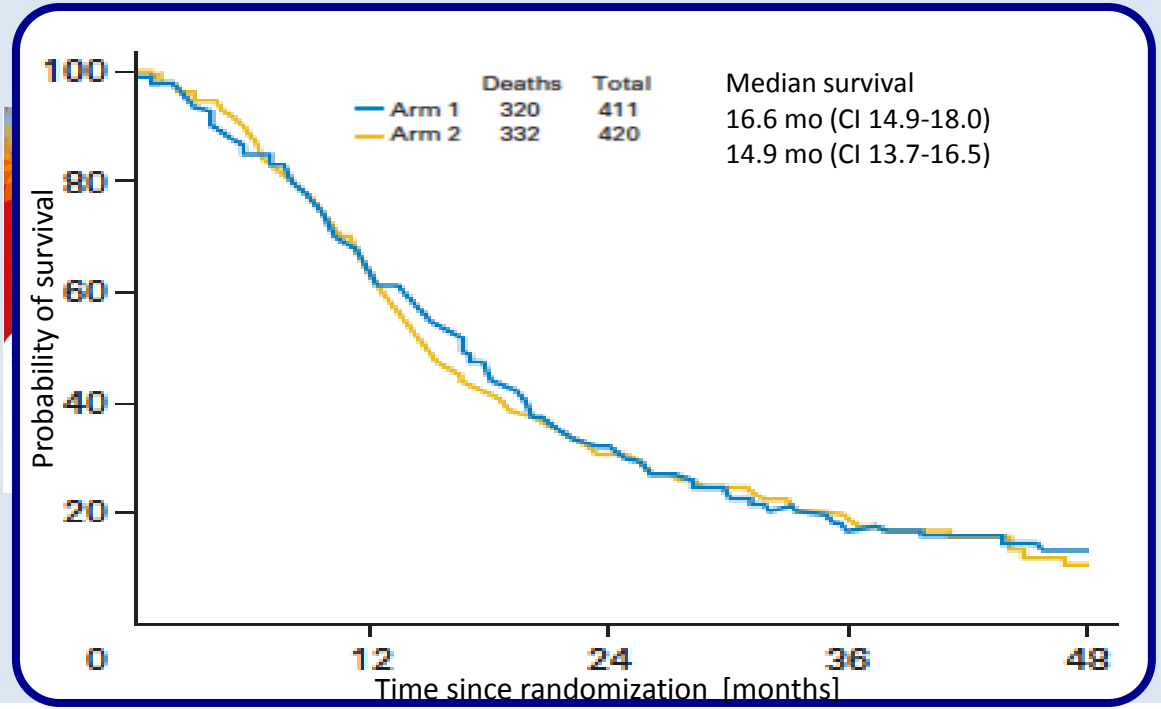
- 4 randomized trials with common treatment arms of TMZ/RT→TMZ
  - EORTC/NCIC 26981-CE.3 (n=92)
  - EORTC26071-CENTRIC (n=226)
  - EMD-CORE; }
  - RTOG 0525-Intergroup (n=228) total 546
- Patients received at least 6 cycles of adj. TMZ
  - Patients were progression-free 28 days after start of cycle 6

Alternative Dosing (dose-dense) Temozolomide (TMZ)

RTOG 0525–EORTC–NCCTG intergroup phase III study



dose-dense (dd) vs standard dose (sd) TMZ



Treatment:

- 29% pts received > 6 cycles
- No difference between European pts (6 cycles)
- US patients (-12 cycles)

Gilbert for RTOG, NCCTG & EORTC: J Clin Oncol 2013;31:4085-91.

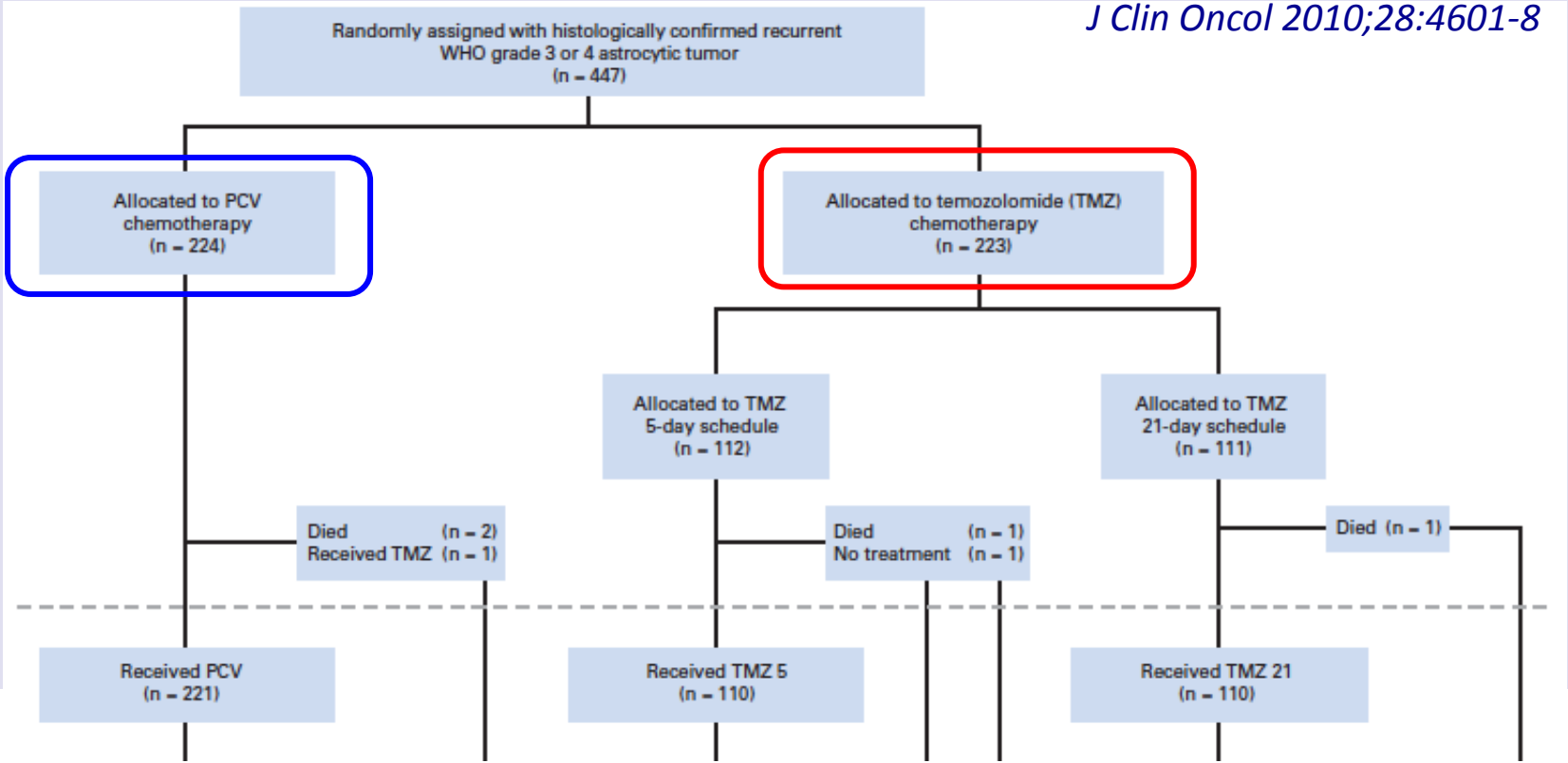
TMZ or PCV
which one is better ?

Is TMZ inferior to PCV
or is PCV inferior to TMZ ?
or
Does it matter at all ?

Temozolomide Versus Procarbazine, Lomustine, and Vincristine in Recurrent High-Grade Glioma

Michael Brada, Sally Stenning, Rhian Gabe, Lindsay C. Thompson, David Levy, Roy Rampling, Sara Erridge, Frank Saran, Rao Gattamaneni, Kirsten Hopkins, Sarah Beall, V. Peter Collins, and Siow-Ming Lee

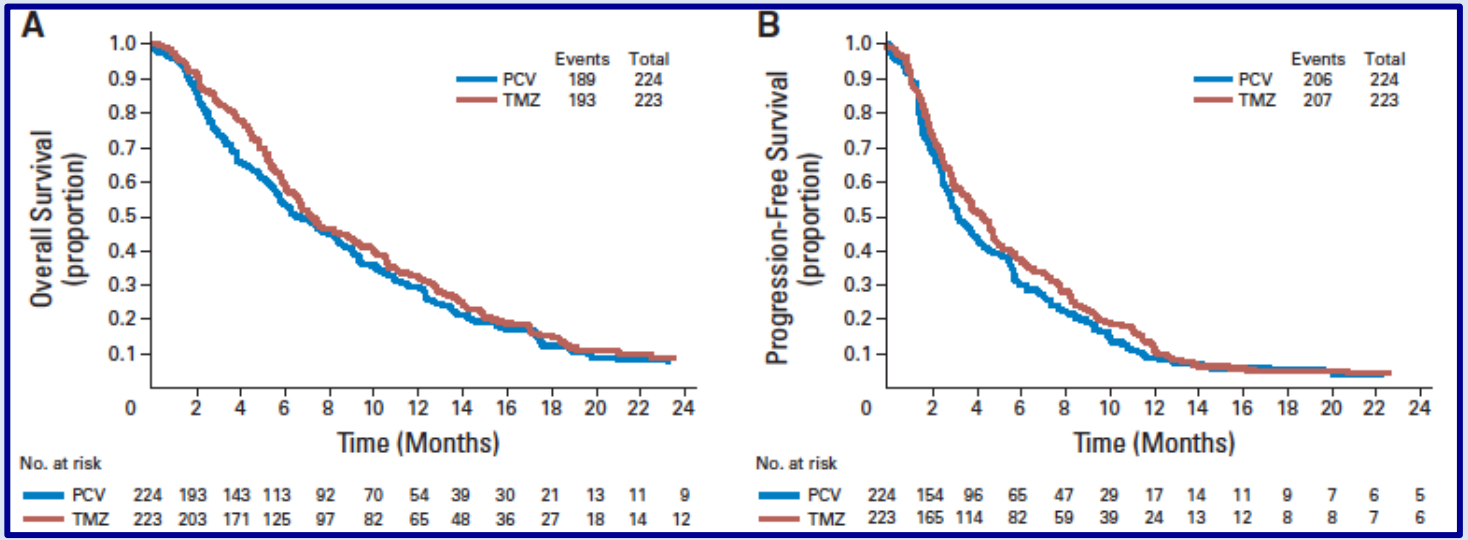
J Clin Oncol 2010;28:4601-8



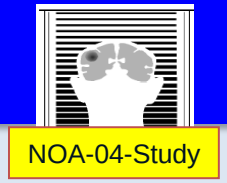
PCV vs TMZ

Brada et al:
J Clin Oncol 2010;28:4601-8

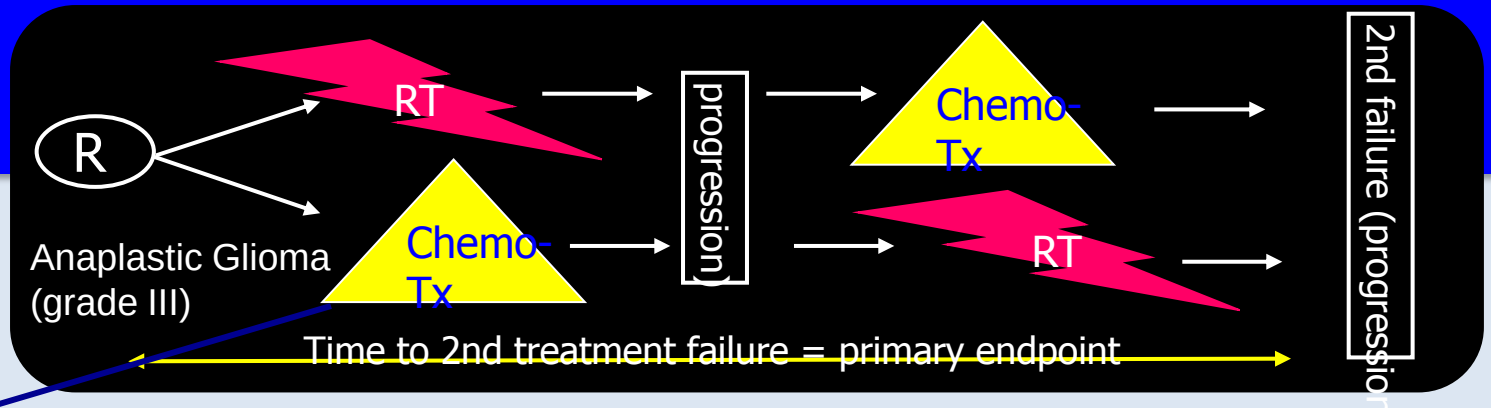
Overall Survival



Progression-free survival



NOA-04-Study



TMZ (5/28): n = 94

PCV: n= 86

NOA-04: Time to Treatment Failure

	RT (+PCV/TMZ)	PCV/TMZ (+RT)
Discontinuations, n (%) (therapy-related)	0 (0)	14 (8.9)
Median TTF, months (95% CI)	42.7+	43.8 (37.4 - NR)
Astrocytoma	32.0 (23.3 - NR)	29.4 (19.0 - NR)
Oligodendroglioma	54+	54+
Oligoastrocytoma	54+	54+
TTF 48, % (95% CI)	55.5 (46.3 - 64.7)	46.4 (36.7 - 56.1)

NR = Not reached; TTF 48 = Treatment failure rate at 48 months.

- There does not appear to be a difference in TTF between patients started on PCV (38.8 [26.3 -NR]) versus those started on TMZ (47.0 [35.7-NR])

- No difference in outcome whether TMZ or PCV

ASCO Annual '08 Meeting

Wick …& Weller
J Clin Oncol 2009; 27:5874-5880

Current Clinically Relevant

Molecular Markers *in Neuro-Oncology*

predictive

- *MGMT* promoter methylation

Esteller & Herman. NEJM 2000; 343:1350-4.
Hegi & Stupp. NEJM 2005; 2005;352:997-1003.

Prognostic & predictive

- LOH 1p/19q
  - → translocation chrs. 1;19

Cairncross & Louis. JNCI 1998 90:1473-9.
Jenkins, Cancer Res 2006; 66:9852-61

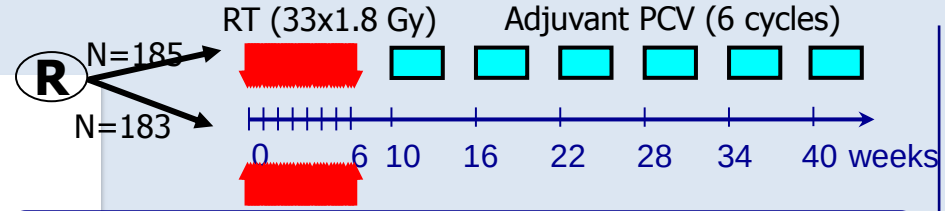
prognostic

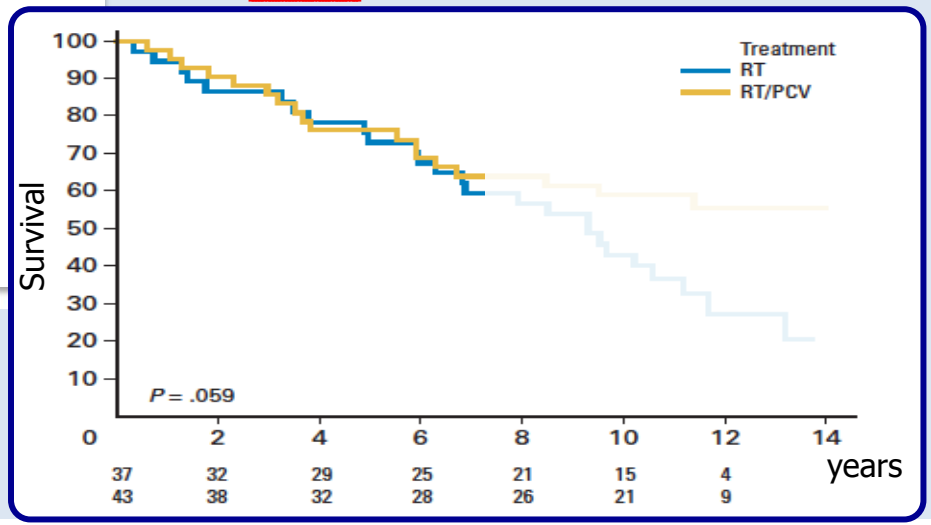
- *IDH1+IDH2* mutations

Yan& Bigner. NEJM 2009;360:765-73.
Zhao & Xiong . Science 2009.

(Neo)adjuvant PCV for 1p/19q oligos: Long-term follow-up

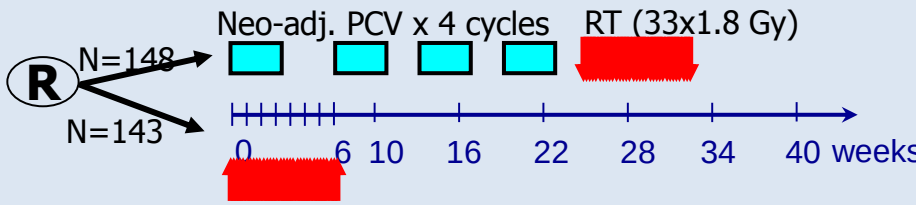
EORTC

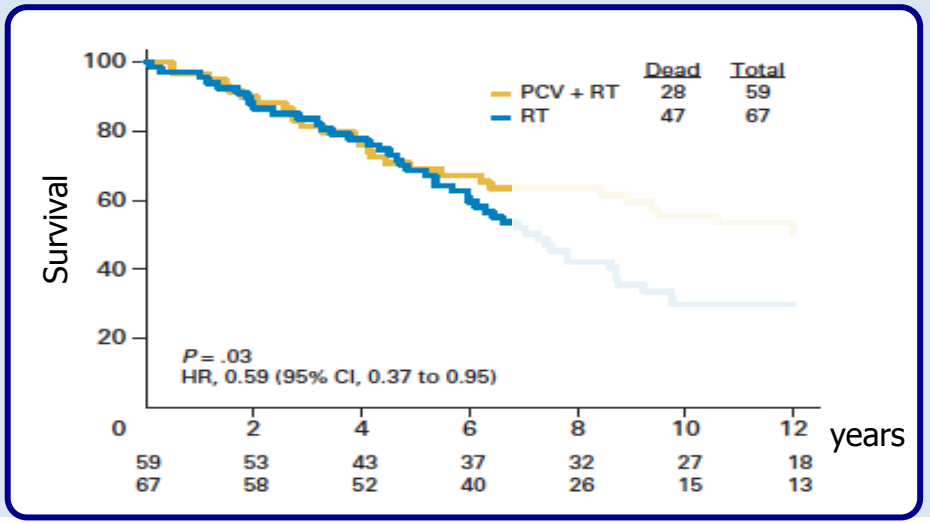




van den Bent et al.. J Clin Oncol 2006; 24:2715-22
J Clin Oncol 2013, 31:344-50

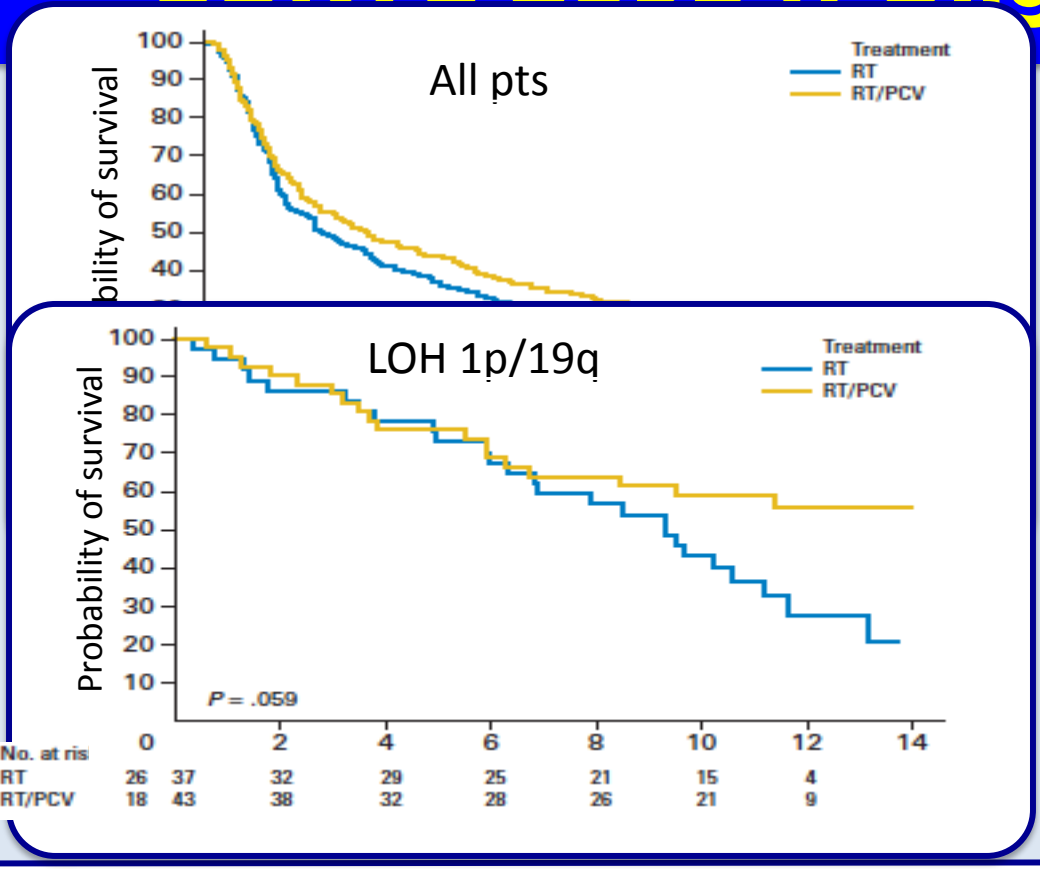
RTOG RADIATION THERAPY ONCOLOGY GROUP





Cairncross et al, J Clin Oncol 2006; 24:2707-14
J Clin Oncol 2013, 31:337-43

EORTC 26954: Oligo: RT → ±PCV



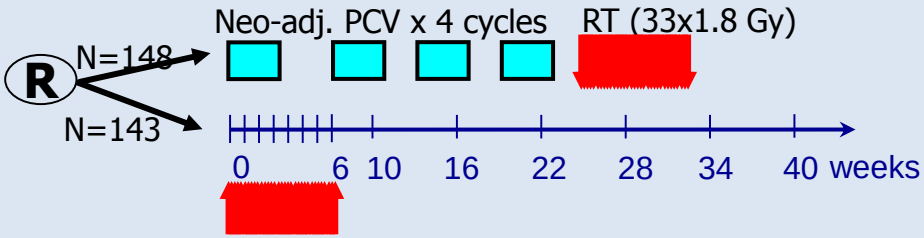
- 368 pts randomized
- After 2 years 217 pts (59%)
- After 10 yrs: 23%

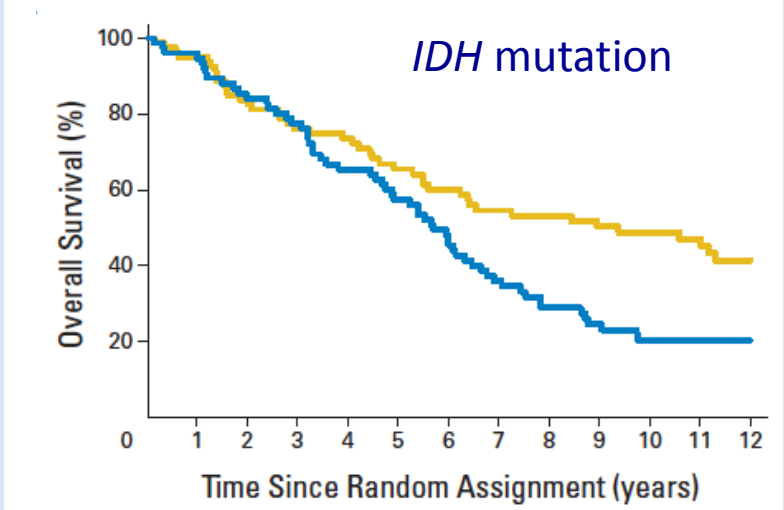
- With LOH 1p/19q: 80
  - After 10 yrs 36 pts
    - 15 RT
    - 21 RT → PCV

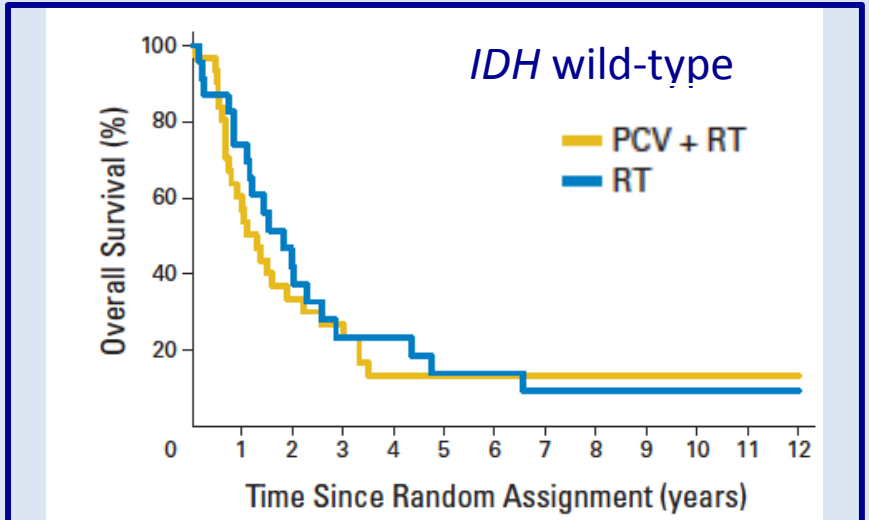
van den Bent et al. J Clin Oncol 2006; 24:2715-22
J Clin Oncol 2013, 31:344-50

RTOG 94-02: neoadj PCV

Cairncross et al for RTOG 94-02: J Clin Oncol 2014; 32:783-790







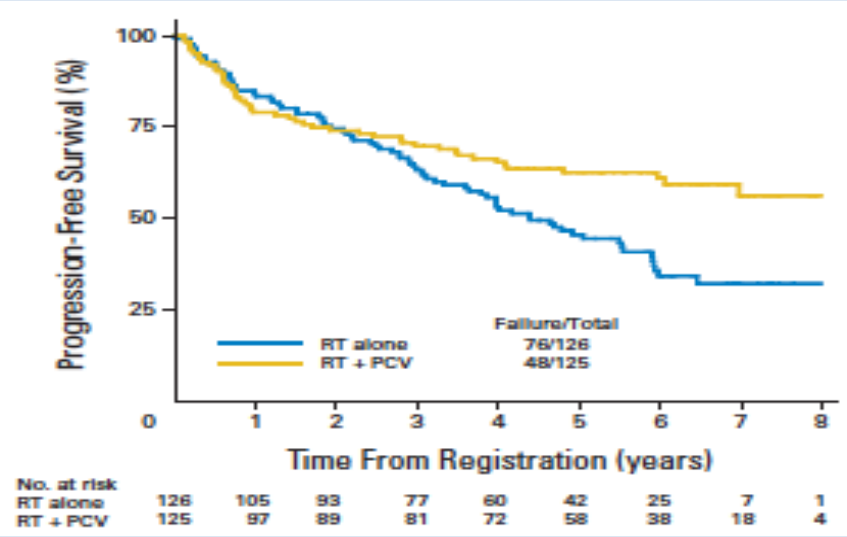
RTOG 98-02: High-risk LGG

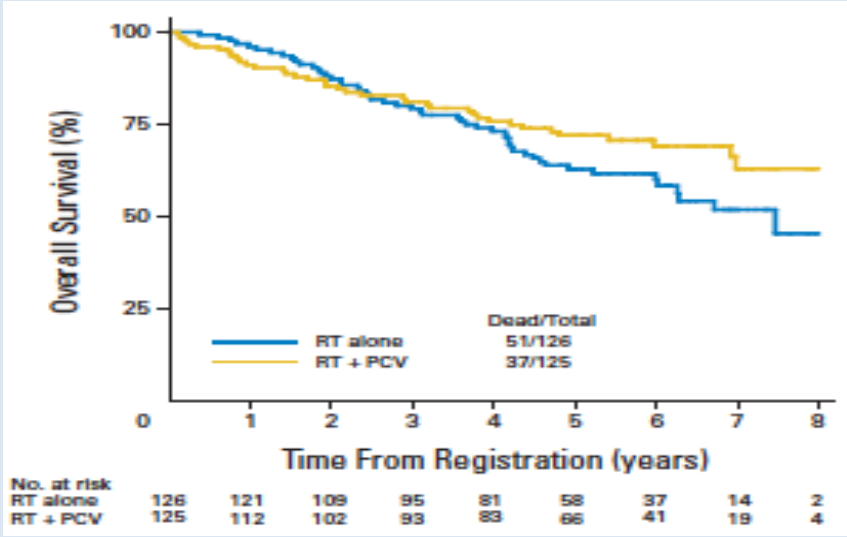
Stratify

Low-risk: Observation (n=111)

High-risk: → R → **RT + PCV** (n=125)

→ **RT alone** (n=126)





Shaw et al for RTOG-Intergroup: J Clin Oncol 2012; 30:2065-70

RTOG98-02: RT ± PCV in LGG

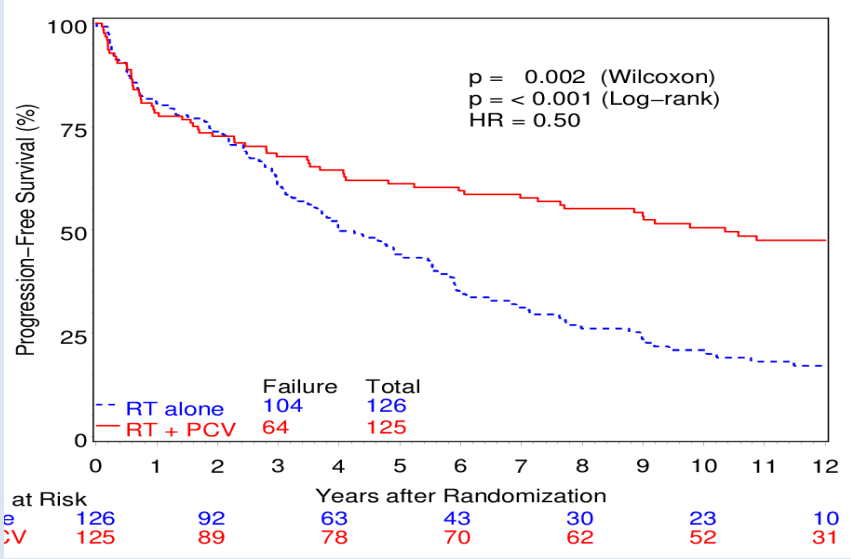
Stratify

Low-risk: Observation (n=111)

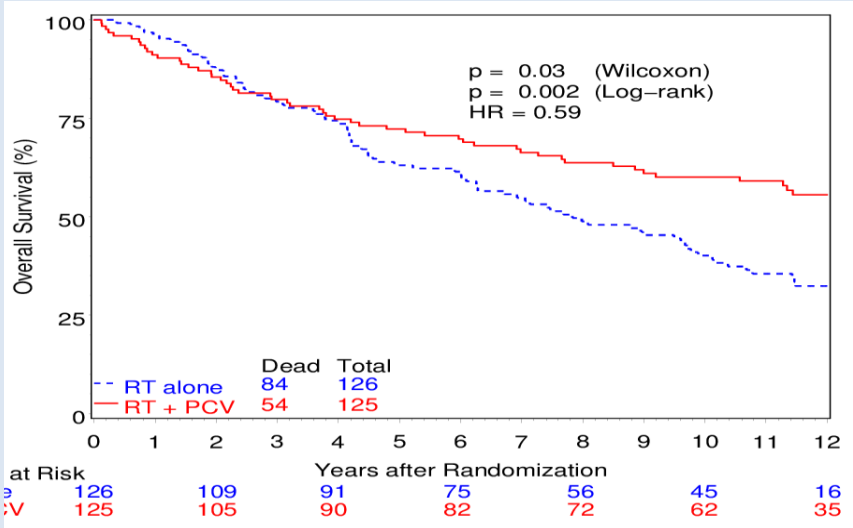
High-risk: → R → **RT + PCV** (n=125)

→ **RT alone** (n=126)

Progression-free survival



Overall survival



Buckner et al for Alliance, ECOG, RTOG & SWOG. Proc ASCO 2014

LGG: EORTC Phase III Trial

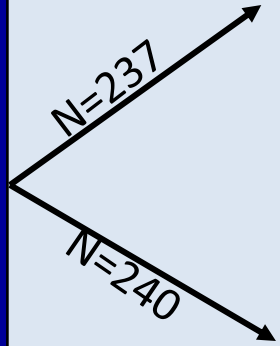
EORTC 22033-26033

Eligibility:

- Grade II glioma
- age > 40
- tumor > 5 cm
- crossing midline/unresectable
- neurological symptoms

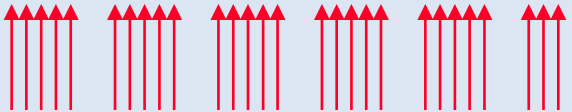
Stratification:

- Age
- Resection
- Histology (Oligo vs. Astro vs. mixed)
- 1p loss (yes/no/unknown.)
- Contrast enhancement
- Center



TEMOZOLOMIDE
75 mg/m2 x 21d / q28d x 12 cy

RADIOTHERAPY
50.4 Gy (28 x1.8 Gy)



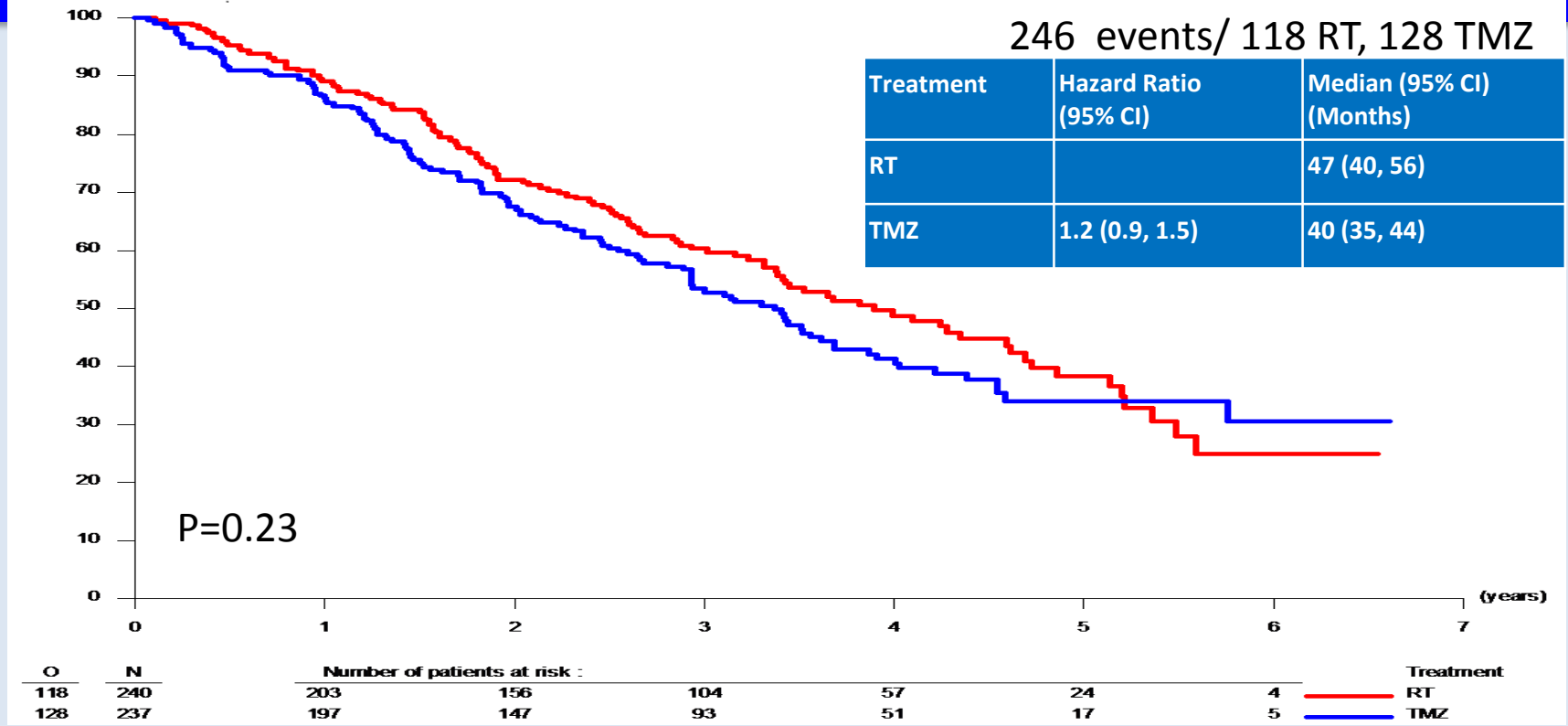
EORTC *The future of cancer therapy*

Baumert, Hegi .. Stupp. Proc ASCO 2014

Primary analysis: Progression-Free Survival

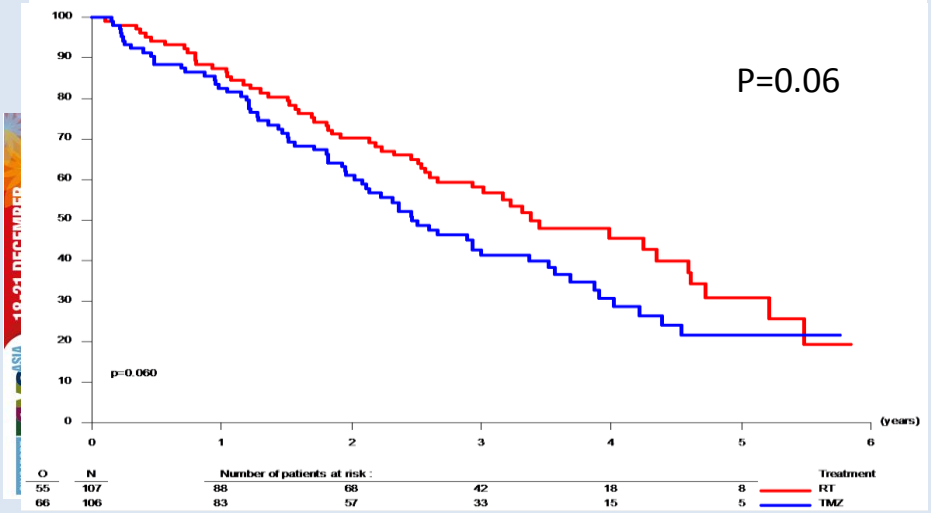
246 events/ 118 RT, 128 TMZ

Treatment	Hazard Ratio (95% CI)	Median (95% CI) (Months)
RT		47 (40, 56)
TMZ	1.2 (0.9, 1.5)	40 (35, 44)



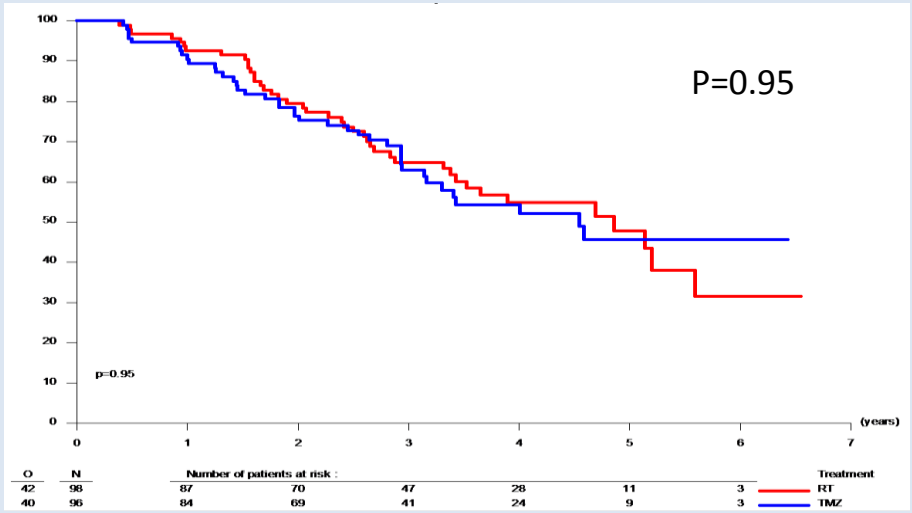
1p status: Progression-Free Survival

1p normal: n = 213; 121 events/ 55 RT, 66 TMZ



Treatment	Hazard Ratio (95% CI)	Median (95% CI) (Months)
RT		41 (32, 55)
TMZ	1.4 (1.0, 2.0)	30 (24, 40)

1p deleted: n=194; 82 events/ 42 RT, 40 TMZ



Treatment	Hazard Ratio (95% CI)	Median (95% CI) (Months)
RT		Not reached
TMZ	0.9 (0.6, 1.3)	74.05 (69.29, N)

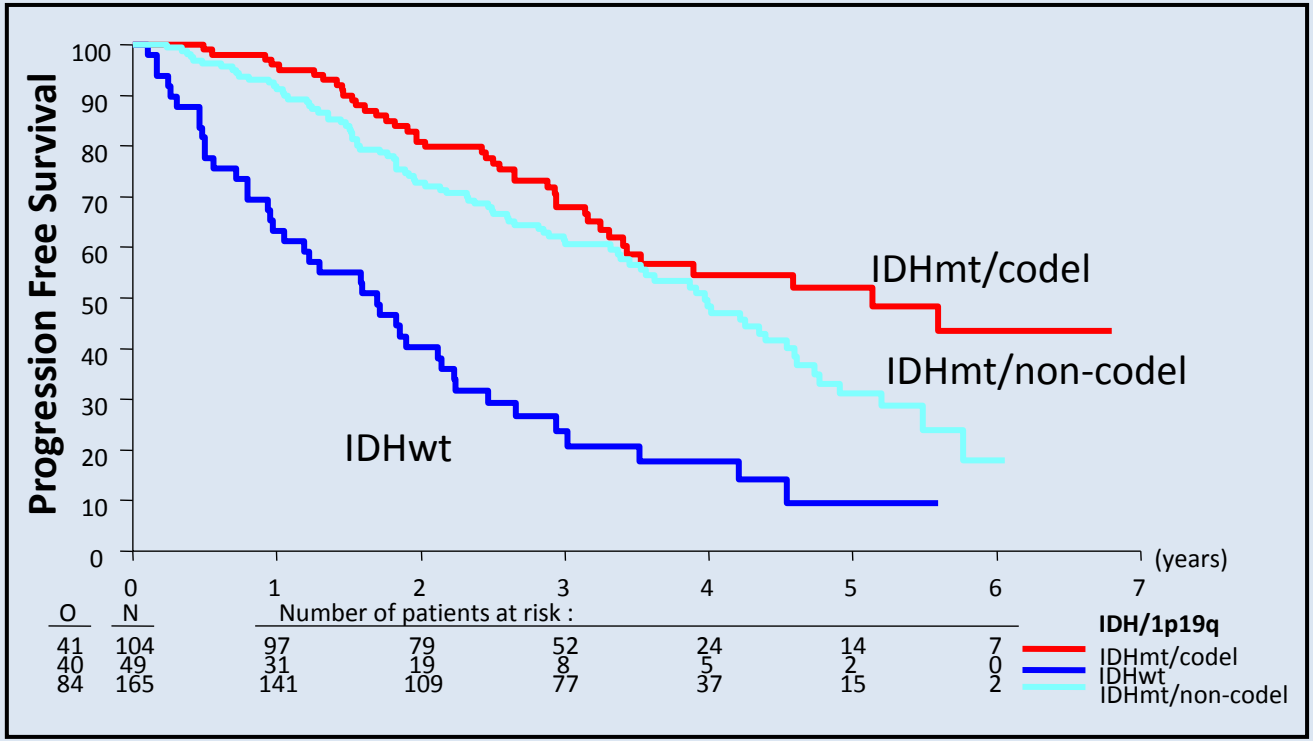
Baumert, Hegi .. Stupp. Proc ASCO 2014

EORTC 22033: Patient Characteristics

	RT N=240 (%)	TMZ N=237 (%)	Total N=477 (%)
Molecular markers			
1p			
1p deleted	98 (40.8)	97 (40.9)	195 **(40.9)**
1p normal	107 (44.6)	106 (44.7)	213 (44.7)
Missing	35 (14.6)	34 (14.3)	69 (14.5)
1p/19q status			
1p/19q codeleted	55 (22.9)	62 (26.2)	117 **(24.5)**
1p/19q non-codeleted	125 (52.1)	115 (48.5)	240 (50.3)
Missing	60 (25)	60 (25.3)	120(25.2)
***IDH 1/2* mutation status**			
IDH 1/2 mutated	164 (68.3)	163 (68.8)	327 **(68.6)**
IDH 1/2 wild-type	35 (14.6)	30 (12.7)	65 (13.6)

Baumert, Hegi .. Stupp. Proc ASCO 2015

Molecular Characteristics and Outcome



Pathogenetic Evolution of Gliomas

Neural Stem Cell / Progenitor Cell

IDH1/2 mutations (>85%)
MGMT methylation (>85%)

MGMT methylation (<50%)
TERT mutation (>80%)

EGFR amplification (40-50%)
CDKN2A homoz del (>55%)
PTEN mutation (20-30%)
NF1 mutation (8%)
CHR10 loss (80%)

TP53 mutations (>65%)
ATRX mutation (>65%)

Co-deletion 1p/19q (>75%)
TERT mutation (>60%)

Grade II

Diffuse Astrocytoma

Oligodendroglioma

TERT mutation (>80%)

Grade III

Anaplastic Astrocytoma

Anaplastic Oligodendrogl.

Grade IV

Primary GBM

Secondary GBM

Median age: 55-65 years

35-45 years

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.,

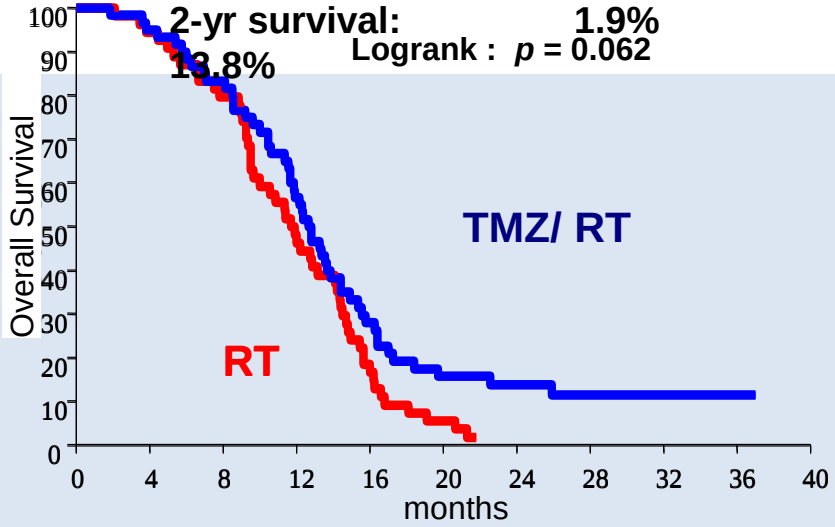
The NEW ENGLAND JOURNAL of MEDICINE

MARCH 10, 2005

Unmethylated *MGMT*

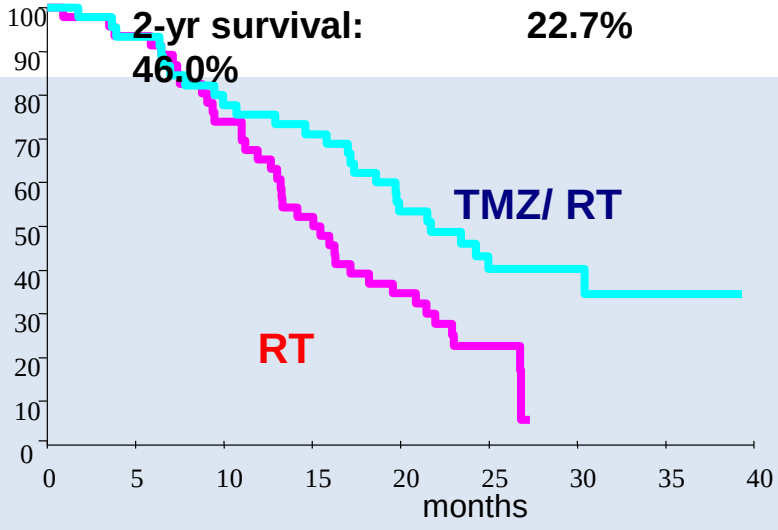
	RT	TMZ/RT
Median OS:	11.8 mo	12.7mo
2-yr survival:	1.9%	13.8%

Logrank : $p = 0.062$



Methylated *MGMT*

	RT	TMZ/RT
Median OS:	15.3 mo	21.7mo
2-yr survival:	22.7%	46.0%



EORTC The future of cancer therapy

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

Molecularly based classification

IDH wild-type

IDH mutant

1p/19q intact

- Astrocytoma
  - g-CIMP
  - *TP53* mutation
  - *ATRX* mutation
- 2º GBM
  - *CDKN2A/CDKN2B* deletion
  - Chr. 10q loss

1p/19q deleted

- Oligodendroglioma
  - g-CIMP
  - *CIC* mutation
  - *TERT* mutation

Molecularly based classification

- *MGMT* Methylated
  - → Temozolomide
- *MGMT* Non-methylated
  - → less or no benefit from alkylating agent chemo
- EGFR amplification
  - EGFRviii mutation
  - → clinical trials
- No EGFR amplification

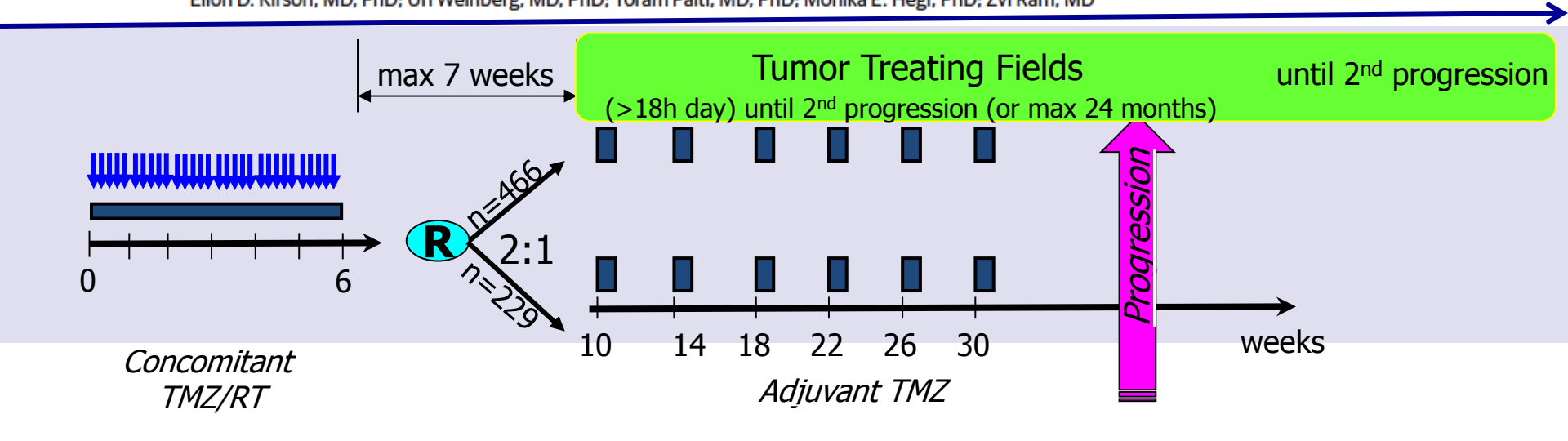
JAMA

Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma

A Randomized Clinical Trial

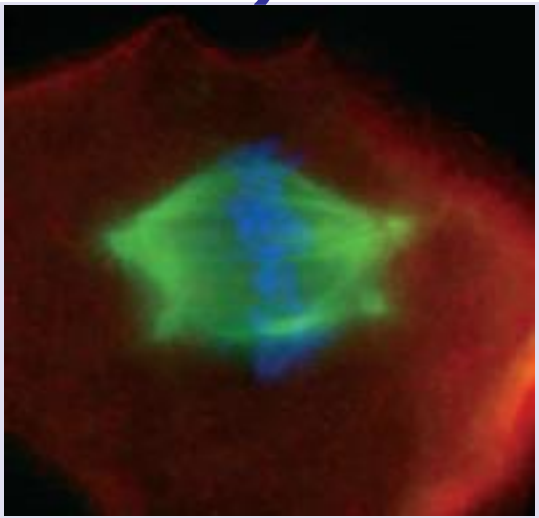
15. December 2015

Roger Stupp, MD; Sophie Taillibert, MD; Andrew A. Kanner, MD; Santosh Kesari, MD, PhD; David M. Steinberg, PhD; Steven A. Toms, MD, FACS, MPH; Lynne P. Taylor, MD, FAAN; Frank Lieberman, MD; Antonio Silvani, MD; Karen L. Fink, MD, PhD; Gene H. Barnett, MD, MBA; Jay-Jiguang Zhu, MD, PhD; John W. Henson, MD, MBA, FAAN; Herbert H. Engelhard, MD, PhD; Thomas C. Chen, MD, PhD; David D. Tran, MD, PhD; Jan Sroubek, MD; Nam D. Tran, MD, PhD; Andreas F. Hottinger, MD, PhD; Joseph Landolfi, DO; Rajiv Desai, MD; Manuela Caroli, MD; Yvonne Kew, MD, PhD; Jerome Honnorat, MD, PhD; Ahmed Idbaih, MD, PhD; Eilon D. Kirson, MD, PhD; Uri Weinberg, MD, PhD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD



TTFields: low amplitude alternating electrical fields (1-3 V/cm, 200 kHz)

- Living cells contain ion / charged molecules
  - Charged cell components can generate and be influenced by electric fields
- Generated forces will:
  - Disrupt cell division
  - Interfere with assembly of organelles, either directly or by interrupting spindle checkpoints



multipolar spindle

Kirson ED et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors Proc Natl Acad Sci USA. 2007;104(24):10152-10157

Kirson ED et al. Disruption of cancer cell replication by alternating electrical fieds. Cancer Res 64, 3288–3295, May 1, 2004

Did not meet eligibility criteria (n= 52)
Progr. disease (before random.) (n= 82)
Did not complete RT/TMZ (n= 8)
Cannot tolerate TMZ (n= 4)
Refusal of randomization (n= 53)
Did not want the device (n= 46)

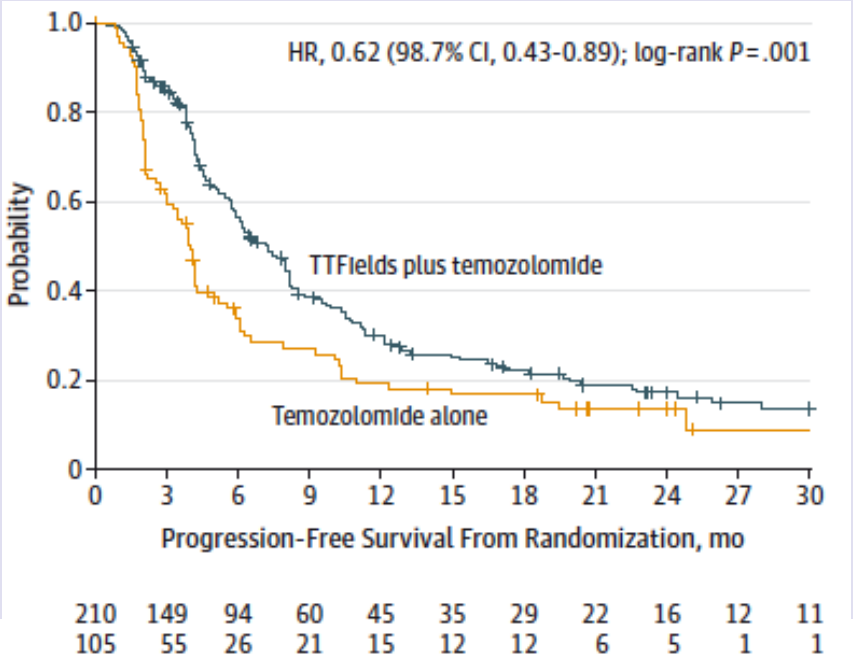
Participation in another trial (n= 20)
Travel distance to the site (n= 18)
Refused any further treatment (n= 4)
Unknown (n= 37)

Mature Data
Median f/up
38 months

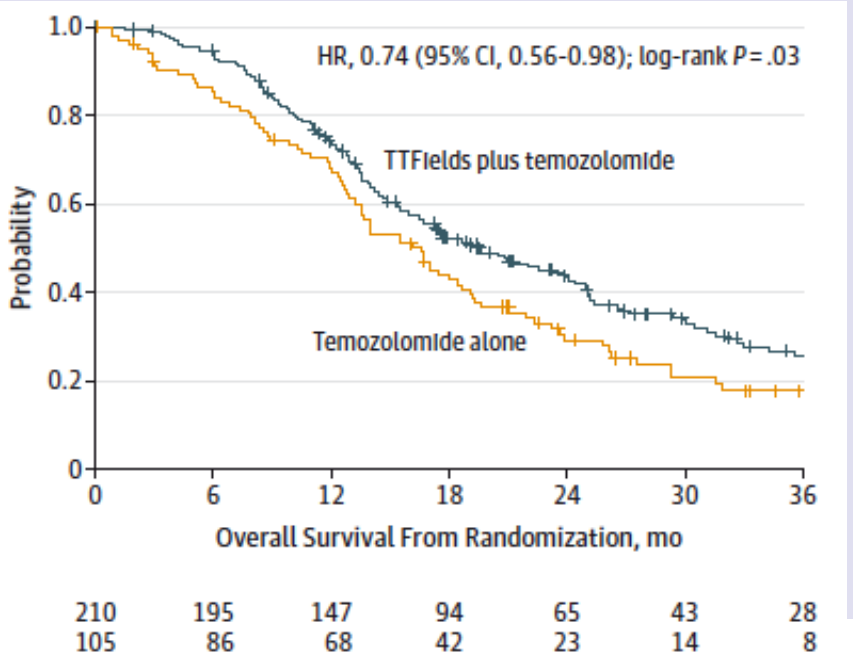
Adj. TMZ ± TTFields

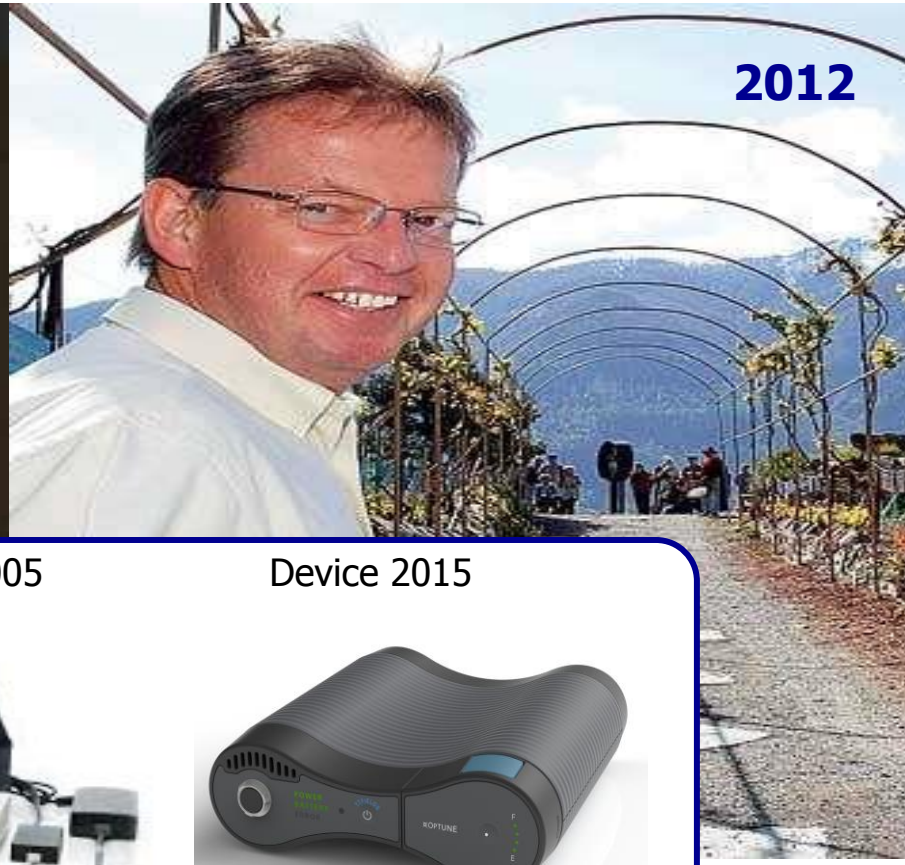
Stupp et al. JAMA. 2015 Dec 15;314(23):2535-2543

Progression-free survival



Overall survival





Device 2005

Device 2015

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EORTC 26101

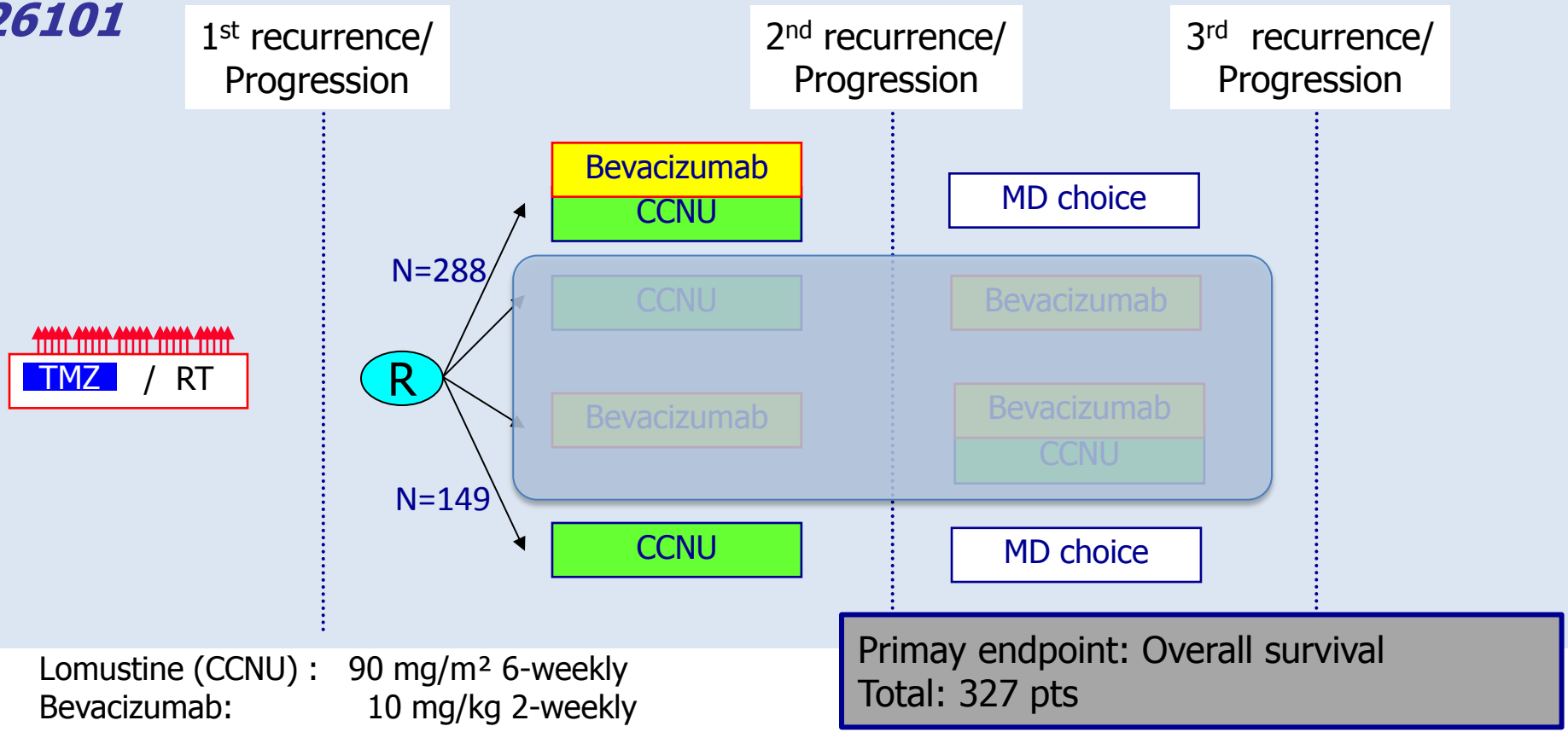
A Phase III Trial Exploring the Combination of Bevacizumab and Lomustine in Patients with First Recurrence of a Glioblastoma

W. Wick on behalf of the EORTC Brain Tumor Group, Society of Neuro-Oncology (SNO) Annual Meeting, San Antonio, 21. November 2015

CCNU ± immediate *vs* delayed bevacizumab

Recurrent GBM

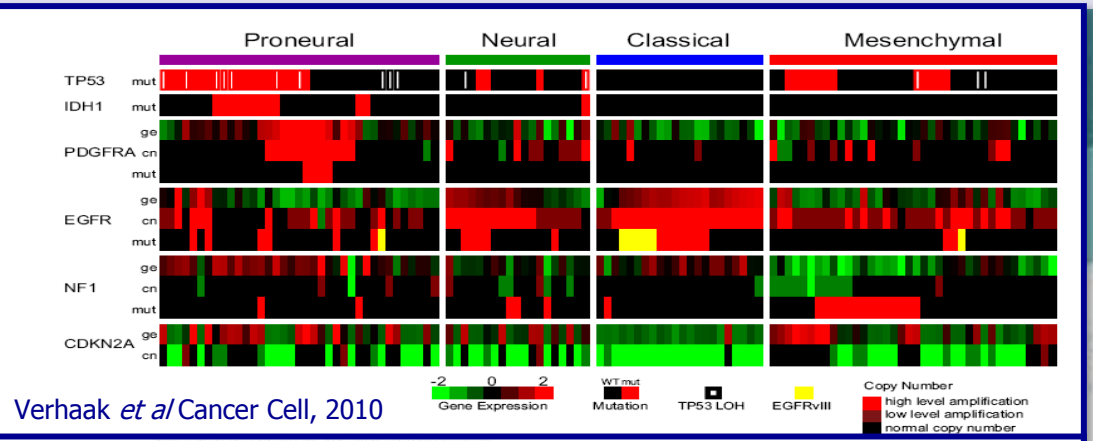
EORTC 26101



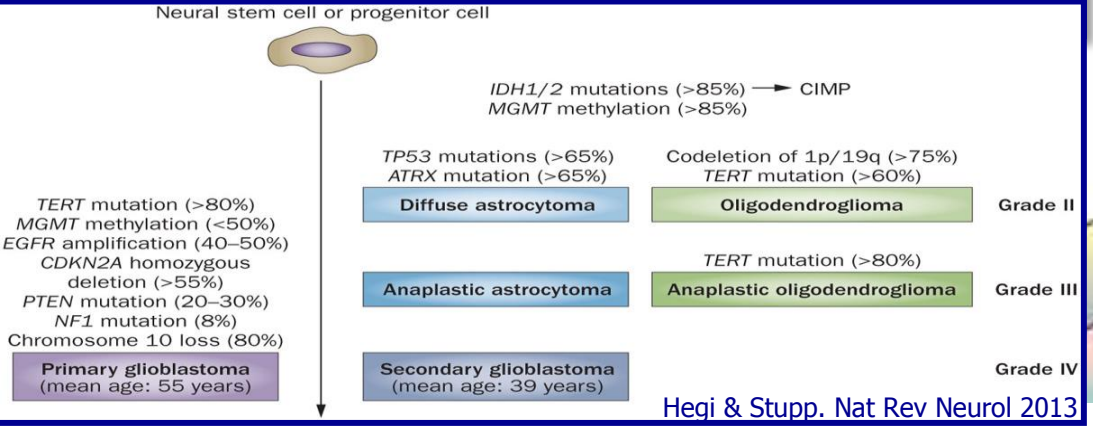
Lomustine (CCNU) : 90 mg/m² 6-weekly
Bevacizumab: 10 mg/kg 2-weekly

Primay endpoint: Overall survival
Total: 327 pts

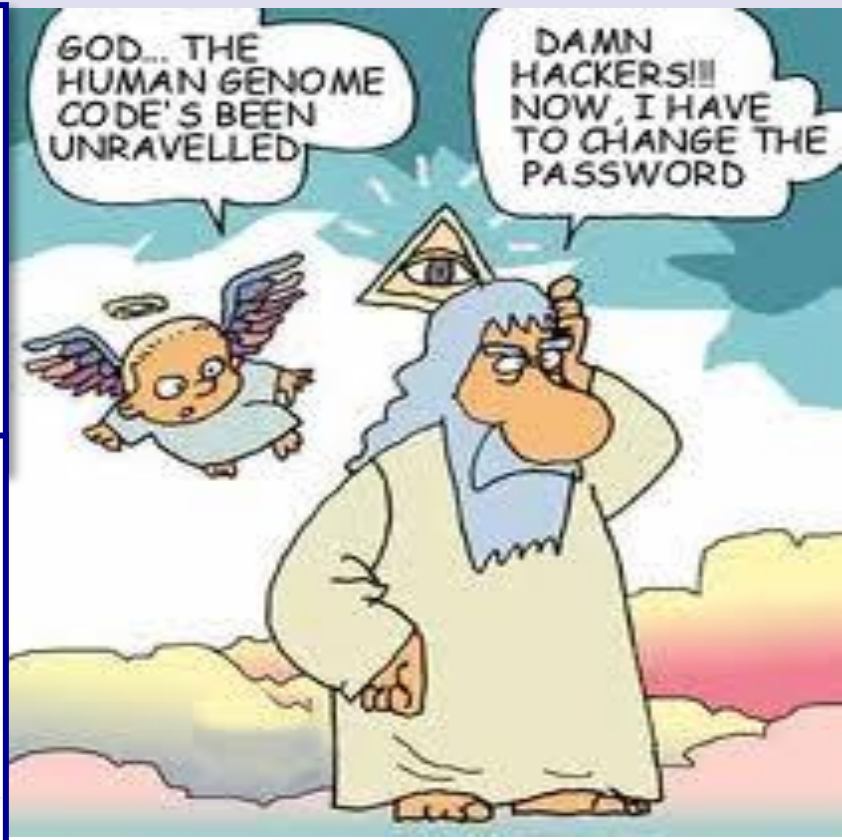
molecular understanding



Verhaak *et al* Cancer Cell, 2010



Hegi & Stupp. Nat Rev Neurol 2013



5th Quadrennial Meeting of the World Federation of Neuro-Oncology

Zurich / Switzerland, May 3 - 7, 2017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