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ESMO Clinical Practice Guidelines

High Grade Glioma Clinical Case Presentation

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Disclosures

RS has served as an advisor to Roche/Genentech, Merck KGaA, MSD/Merck&Co.

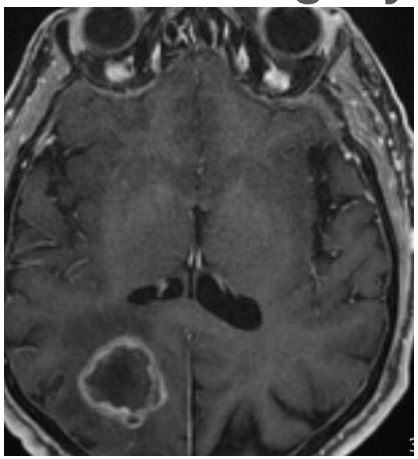
KS has received honoraria from Roche for advisory board participation.

Case 1: A 66-year-old patient with newly diagnosed glioblastoma

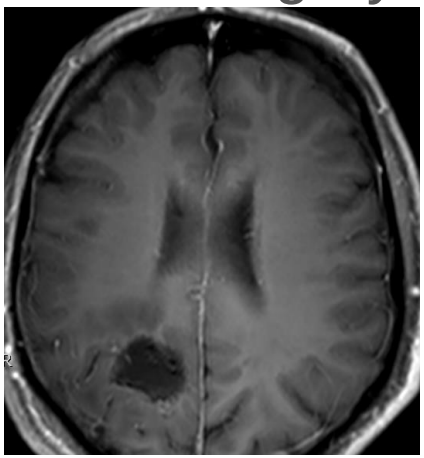
- First symptom: Generalized epileptic seizure
- Clinical condition before surgery:

  Slight hemispatial neglect to the left side, KPS 90%
- MRI

before surgery



after surgery



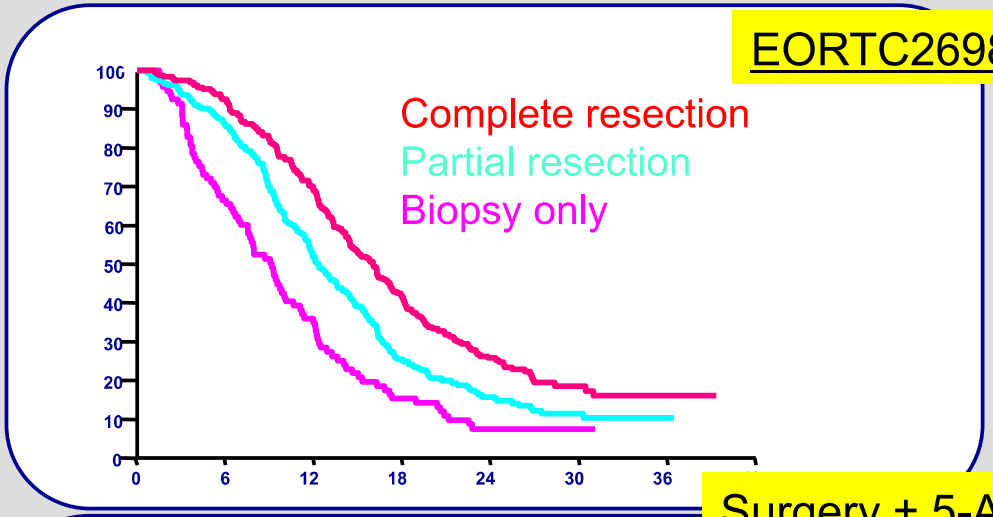
- Molecular markers:

  MGMT promoter methylated, IDH-1 not mutated

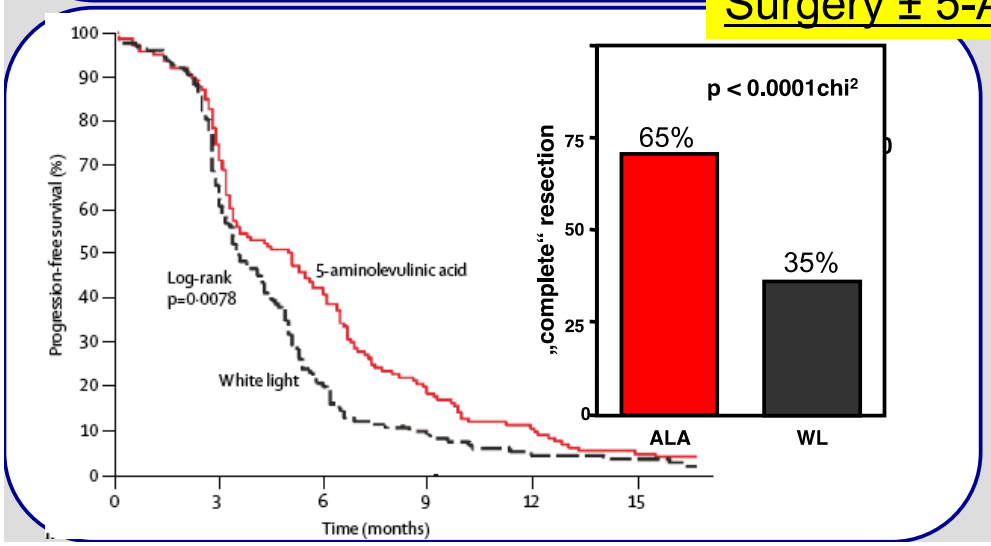
Q 1: Does the extent of surgery matter?

1. Yes - relevant for prognosis.
2. No - especially for elderly patients biopsy is sufficient

Answer 1: Yes, extent of surgery is prognostic



- Longer survival of patients after complete resection



- Improved progression-free survival after complete resection
- Higher rate of complete resection with 5-ALA
- No survival difference between 5-ALA and white-light operated pts
- Longer survival of patients with no residual tumor

Stummer et al. Lancet Oncol 2006; 7: 392–401
Stummer et al. Neuro-Oncology 2008; 10: 1025–1034

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Q 2A: Which adjuvant treatment plan do you recommend for this 66y patient with newly diagnosed glioblastoma?

1. Standard fractionated irradiation (60 Gy)
2. Hypo-fractionated radiotherapy alone (30 Gy)
3. Temozolomide alone
4. Combined radiochemotherapy with adjuvant temozolomide
5. Bevacizumab plus combined radiochemotherapy with adjuvant temozolomide
6. Best supportive care

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Answer 2A: Recommended adjuvant treatment plan for this patient

1. Standard fractionated irradiation (30 x 2 Gy)
2. Hypo-fractionated radiotherapy alone: Roa (15 x 2.66 Gy)
   Nordic (10x 3.4 Gy)

In elderly patients (cut off 60/65/70 years?):

Standard RT (60 Gy) compared with hypo-fractionated radiotherapy

- equivalent in patients >60 years (Roa et al, JCO 20054)
- inferior in patients >70 years (Nordic trial, Malmström et al, Lancet Oncol 2012)

A hypofractionated schedule should be preferred

Challenges in Elderly Cancer Patients

- 60% of all cancer occurs in patients age > 65 years
- Aging → decline in physiological reserves
  - Varies greatly between individuals
  - Signs of "fragility": weight loss, weakness, poor endurance, slowness, physical activity
- Impaired general health
  - Multiple co-morbidities
  - Polypharmacy

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Glioblastoma and Age

- Inferior prognosis of elderly patients
  - Who is elderly (> 65 yrs, > 70 yrs, > 80 yrs) ?
- Primum non nocere
  - Avoid lenghty (and toxic) therapy in elderly patients with a short survival
    --> Treatment de-escalation
    --> Search for easier therapies ?
- Different biology of elderly patients
    - e.g. TP53 mutations, LOH1p, CDKN2A/p16 deletion, EGFR amplification

(*Batchelor et al. Clin Cancer Res 2004, 10:228-233)*

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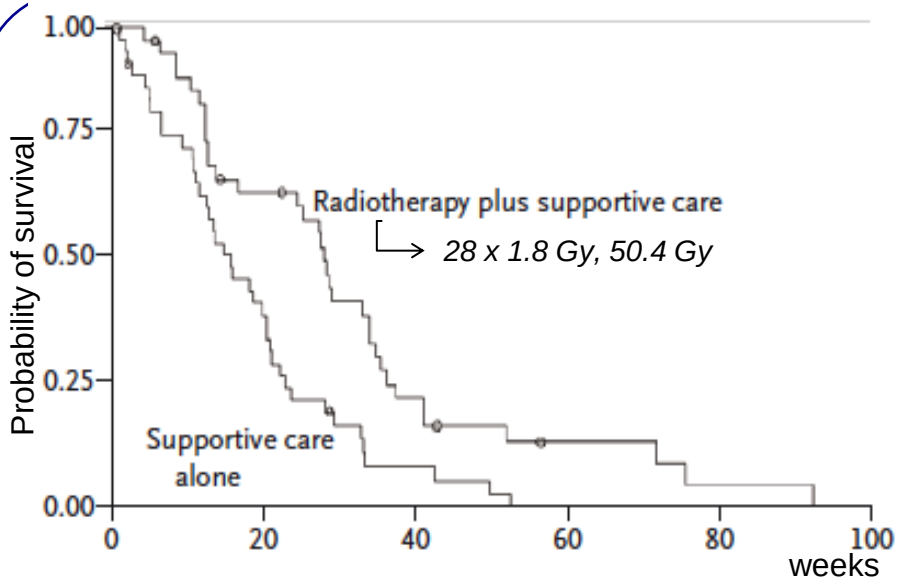
Age

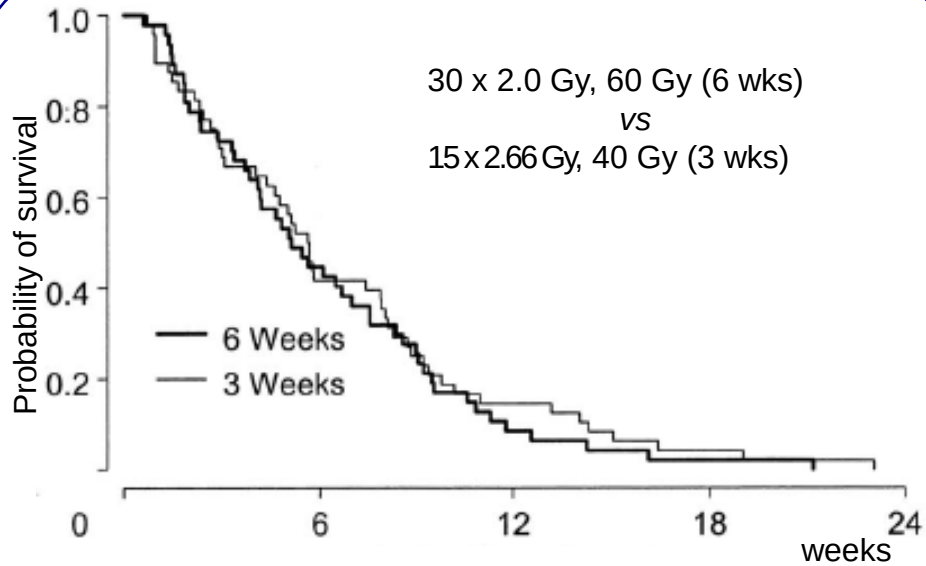
- Inferior prognosis of elderly patients
  - Who is elderly (> 65 yrs, > 70 yrs, > 80 yrs) ?

- RT improves survival also in the elderly (>70 yrs)



Keime-Guibert for ANOCEF: NEJM 2007; 15:1527-35

- Equivalent outcome with hypo-fractionated RT in elderly (>60 yrs)



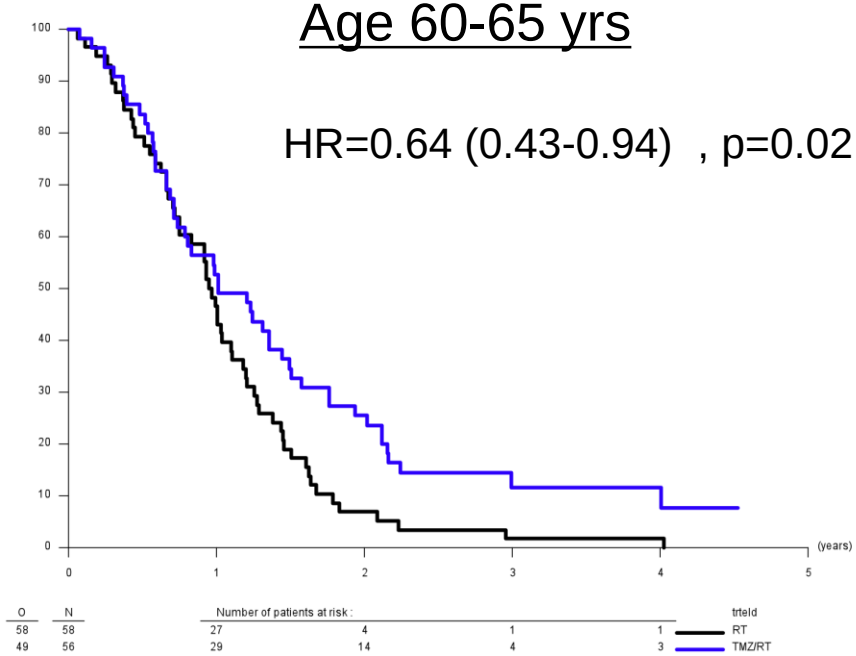
Roa et al. J Clin Oncol 2004; 22:1583-8

EORTC 26981/NCIC CE.3
Elderly Patients (60-70 yrs)

Stupp et al. Lancet Oncol 2009
Figures unpublished

Age 60-65 yrs

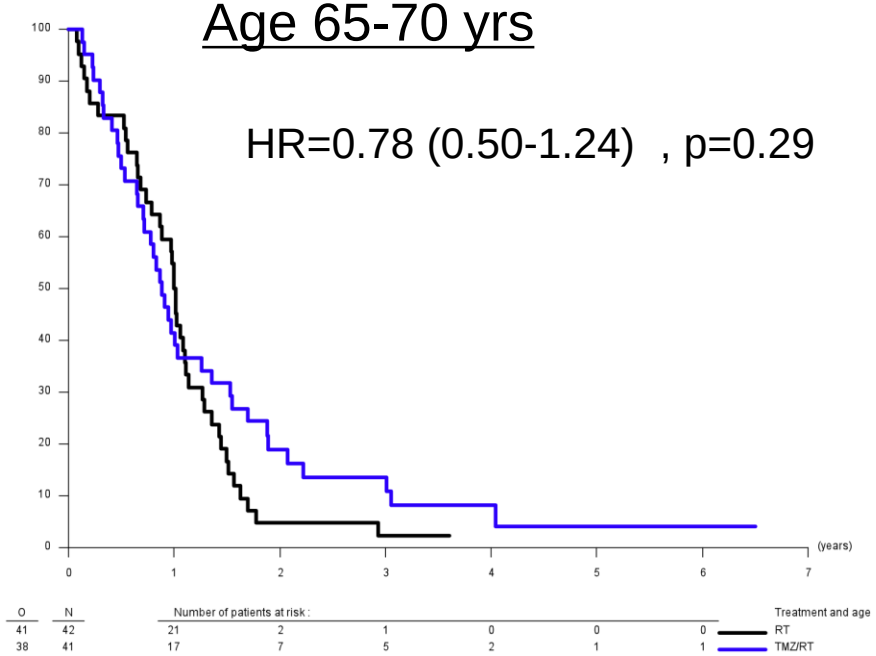
HR=0.64 (0.43-0.94) , p=0.02



	RT (95%CI)	TMZ/RT
Median	11.4 (9.0-13.3)	12.2 (8.6-17.4)
2-yr survival	8.3% (1.0-15.5)	24.2% (12.7-35.7)

Age 65-70 yrs

HR=0.78 (0.50-1.24) , p=0.29



	RT (95%CI)	TMZ/RT
Median	12.0 (9.5-13.3)	10.9 (8.7-18.4)
2-yr survival	4.9% (0.0-11.2)	17.6% (5.0-30.2)

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Answer 2A: Recommended adjuvant treatment plan for this patient

1. Standard fractionated irradiation (60 Gy)
2. Hypo-fractionated radiotherapy alone:
   Roa (15 x 2.66 Gy)
   Nordic (10x 3.4 Gy)

In elderly patients (cut off 60/65/70 years?):

Standard RT (60 Gy) compared with hypo-fractionated radiotherapy
- equivalent in patients >60 years (Roa et al, JCO 20054)
- inferior in patients >70 years (Nordic trial, Malmström et al, Lancet Oncol 2012)

A hypofractionated schedule should be preferred

But: The patient has a methylated MGMT status.

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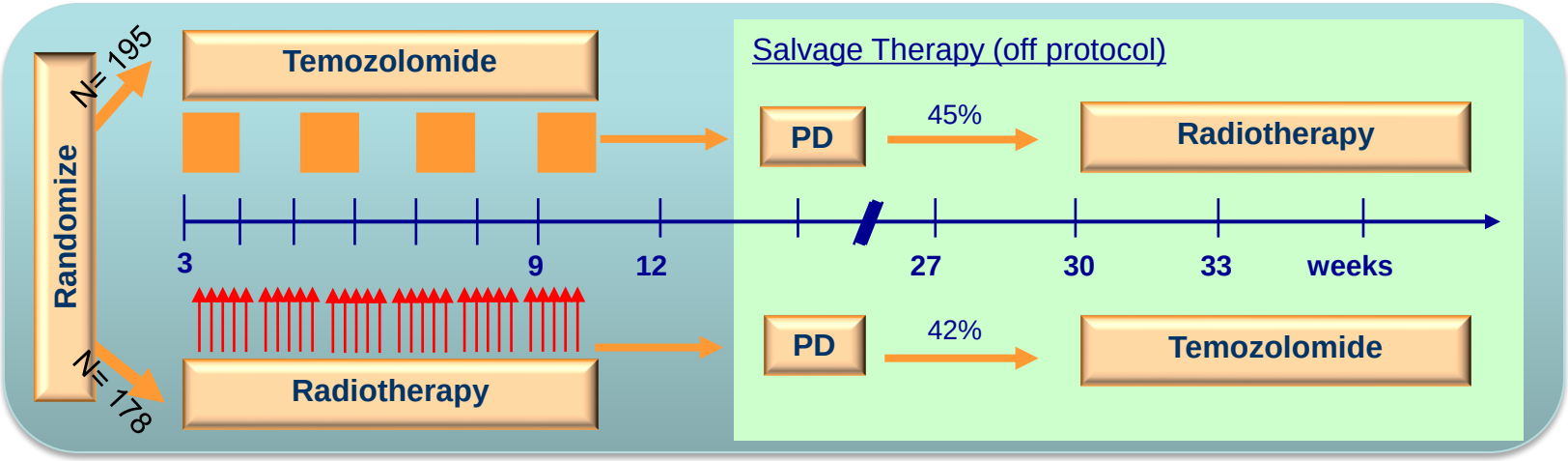
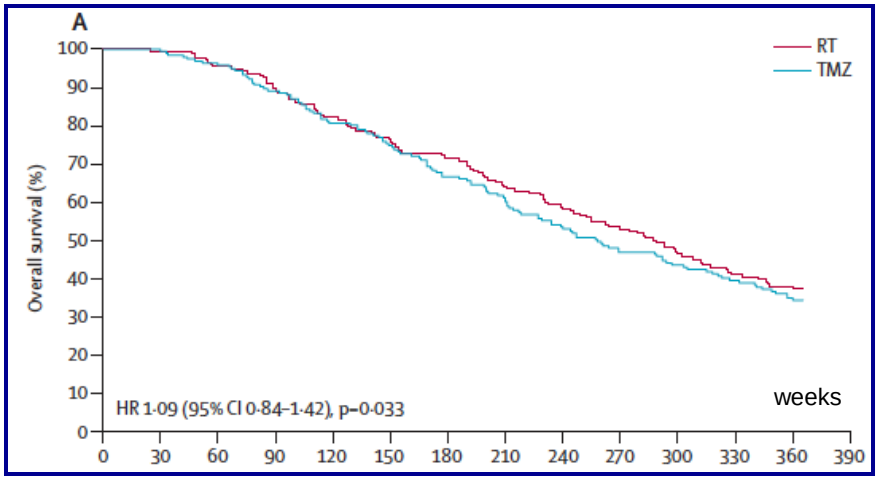
Answer 2B: Recommended adjuvant treatment plan for this patient

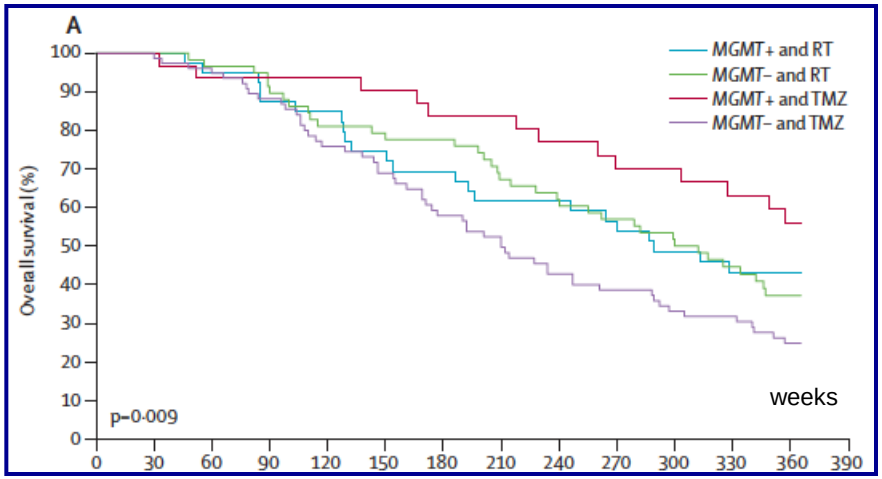
The patient is elderly and
has a methylated MGMT status.

1. Standard fractionated irradiation (60 Gy)
2. Hypo-fractionated radiotherapy alone
3. Temozolomide alone
4. Combined radiochemotherapy with adjuvant temozolomide
5. Bevacizumab plus combined radiochemotherapy with adjuvant temozolomide
6. Best supportive care

Malignant glioma in the elderly (≥65 yrs): NOA-08 randomized, phase 3 trial





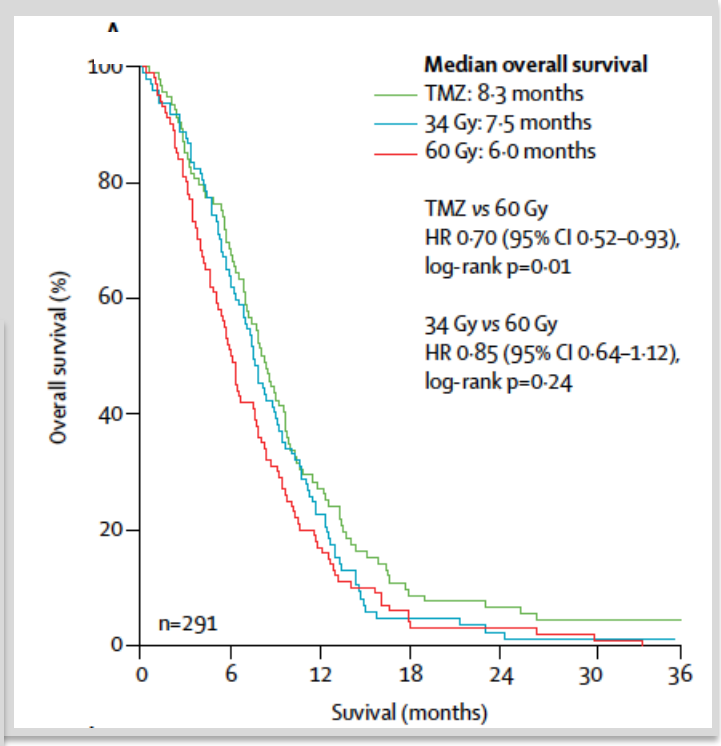


No difference in overall survival

methylated *MGMT* predicts improved survival if treated by TMZ

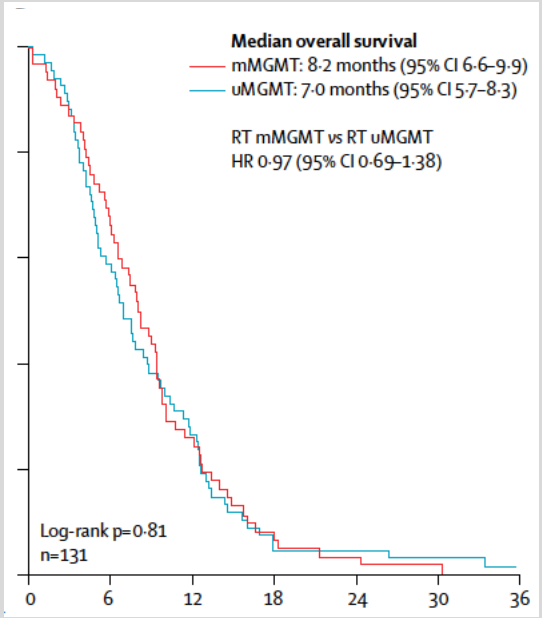
Wick et al. for NOA: Lancet Oncol 2012; 13:707-715

Comparison between RT and TMZ in elderly (>60 yrs) GBM: Nordic ph 3 trial

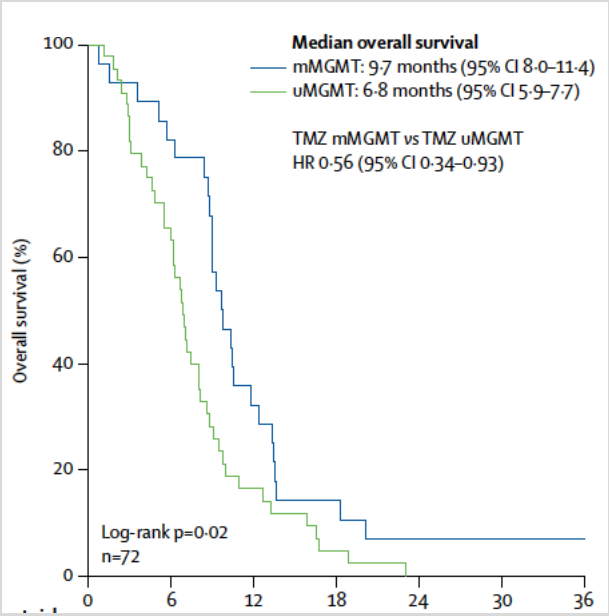


MGMT promoter methylation status in function of therapy:

Radiotherapy



TMZ



Results / Conclusions:

- Inferior outcome with RT60, in particular in pts >70 yrs
- Predictive value of MGMT when pts treated with TMZ

Malmström et al. Lancet Oncol 2012, 13:916-26

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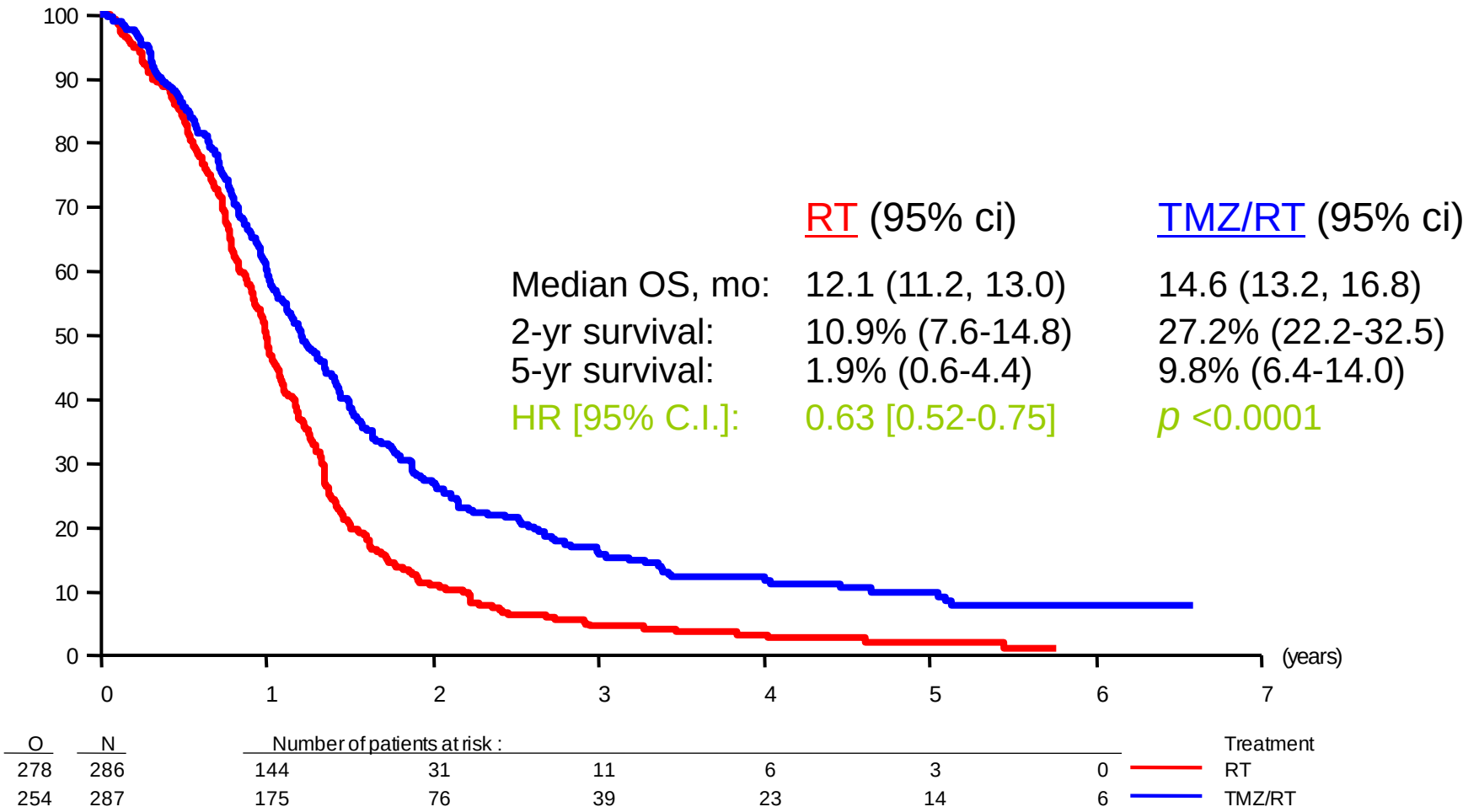
Answer 2C: Recommended adjuvant treatment plan for this patient

There is no clear cut-off for being “elderly”

Standard radiochemotherapy with adjuvant temozolomide may be considered for patients with a good performance status

Standard of care for newly diagnosed glioblastoma in “non-elderly” patients



Stupp et al. N Engl J Med 2005, 352:987-996
Stupp et al. Lancet Oncol 2009, 10:459-466

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Standard of care for newly diagnosed glioblastoma in "non-elderly" patients

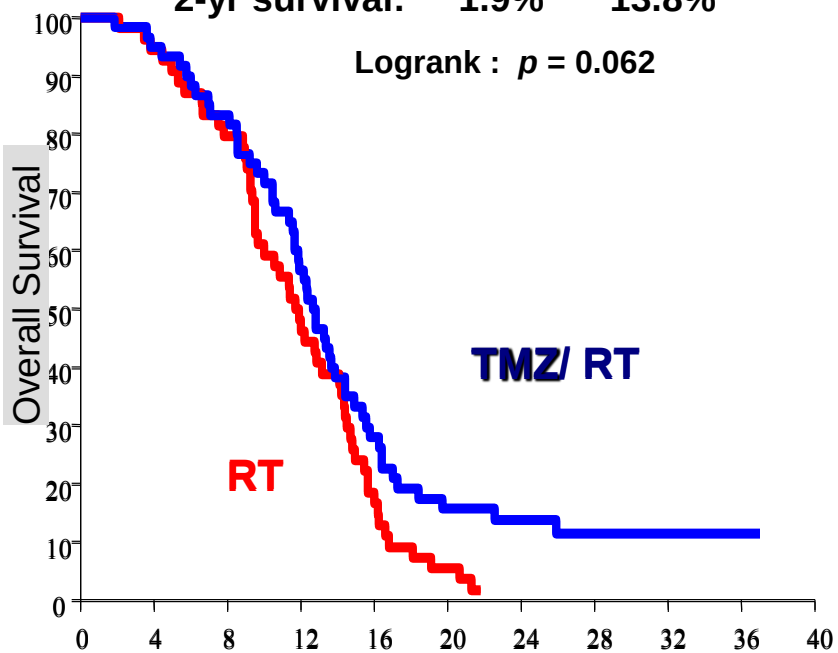
The NEW ENGLAND JOURNAL of MEDICINE
MARCH 10, 2005

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Unmethylated *MGMT*

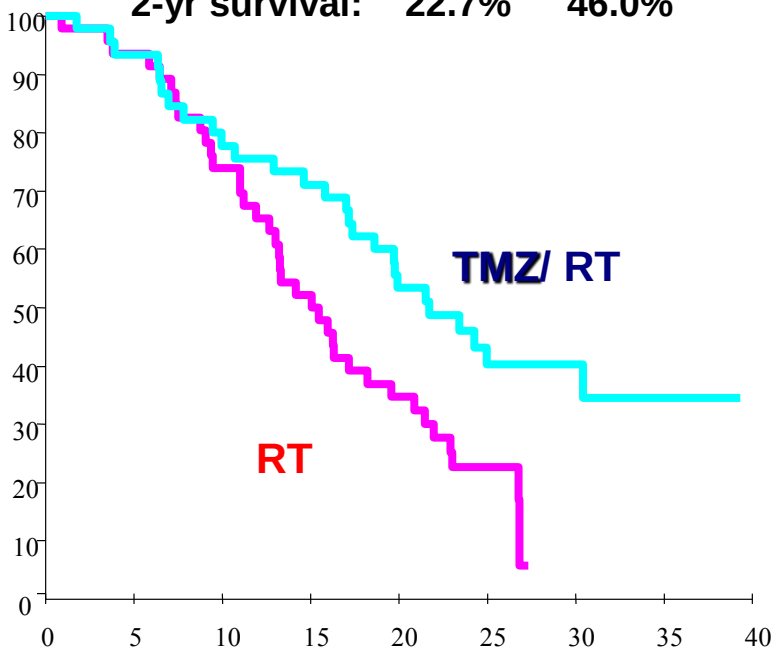
	RT	TMZ/RT
Median OS:	11.8 mo	12.7mo
2-yr survival:	1.9%	13.8%

Logrank : $p = 0.062$



Methylated *MGMT*

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



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Randomized Trials in Elderly GBM

Wick et al: ASCO 2010, Lancet Oncol 2012

- NOA-08 *(n=373 pts, 65+; med. age 72 yrs)*

R
- TMZ dose-dense (week on/week off)
- RT 54-60 Gy (30 fx)

Malmstrom et al: ASCO 2010, Lancet Oncol 2012

- Nordic *(n=342 pts, 60+; med. age 70 yrs)*

R
- TMZ standard (5/28d)
- RT 60 Gy (30 fx)
- RT hypofx 34 Gy (10 fx)

Conclusions:

- Toxicity may be increased in elderly patients
- *MGMT* predicts response
- Methylated tumors: RT alone detrimental, → TMZ
- Unmethylated tumors: TMZ alone detrimental, → RT

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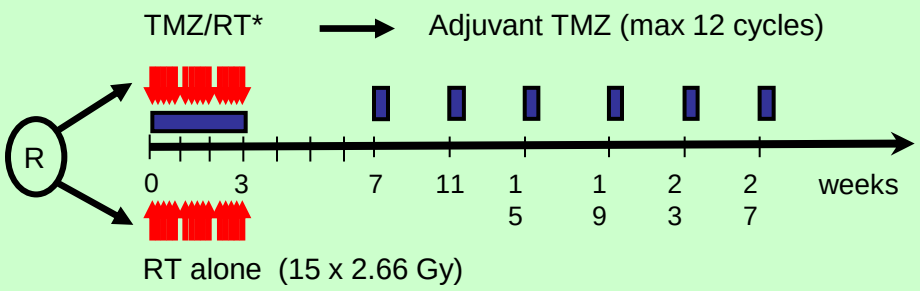
Elderly GBM patients – TMZ or RT ?

or maybe both simultaneously ?

Ongoing EORTC/NCIC Intergroup Trial (EORTC 26062-22061 / NCIC CE.6)

Inclusion Criteria / Design

- Newly diagnosed GBM
- Age ≥ 65 years
- 560 pts to be randomized
- Target hazard ratio < 0.75



- Fit elderly: TMZ/RT →TMZ (investigated up to age 70 yrs)
- Prospective trial (NCIC CE.5/EORTC) → ASCO 2015

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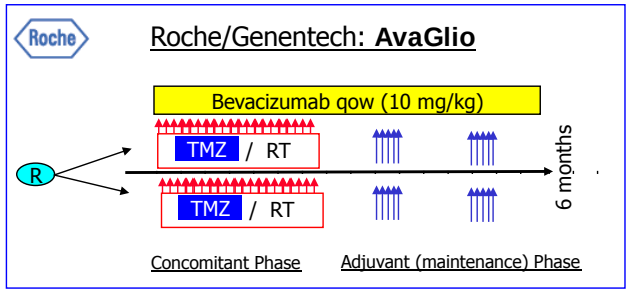
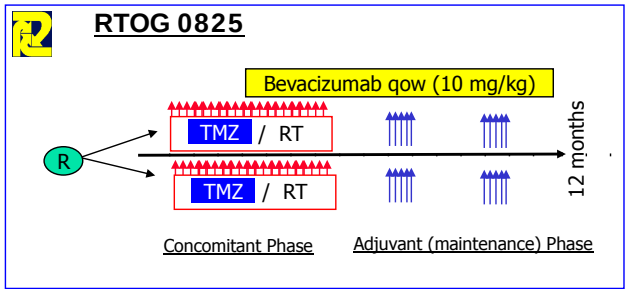
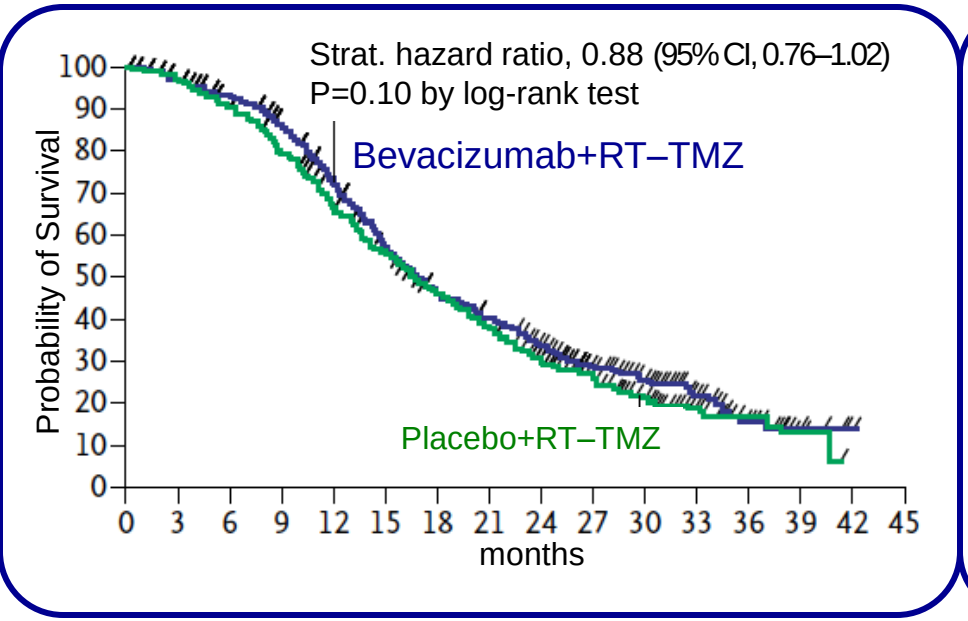
Answer 2D: Recommended adjuvant treatment plan for this patient

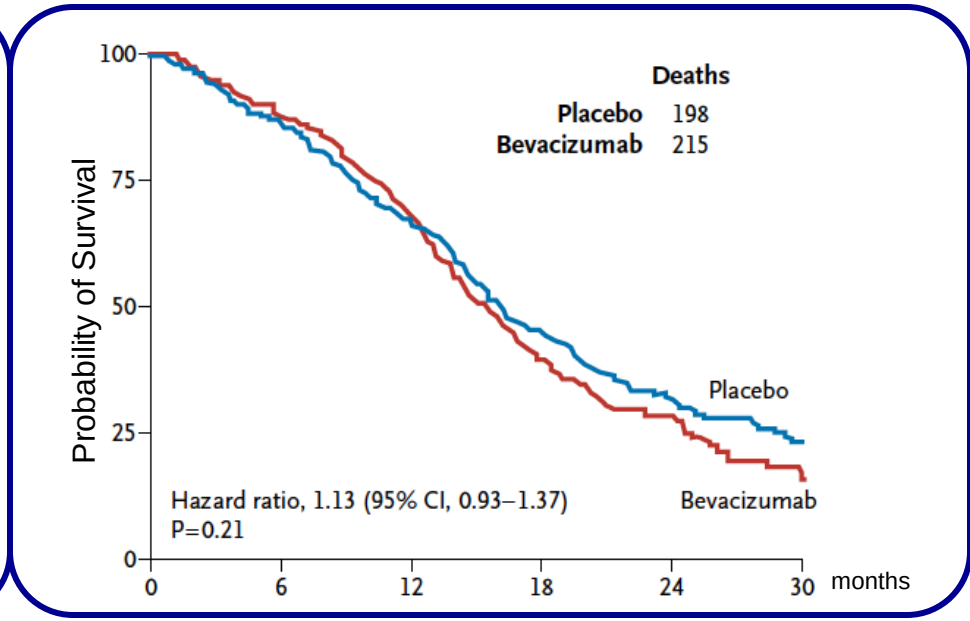
1. Standard fractionated irradiation (60 Gy)
2. Hypo-fractionated radiotherapy alone (30 Gy)
3. Temozolomide alone
4. Combined radiochemotherapy with adjuvant temozolomide
5. Bevacizumab plus combined radiochemotherapy with adjuvant temozolomide
6. Best supportive care

Bevacizumab first-line therapy → no improvement in overall survival









Chinot et al. Soc Neuro-Oncol 2012
Wick et al. ASCO 2013
Chinot, NEJM 2014

Gilbert et al. ASCO 2013
Chinot, NEJM 2014

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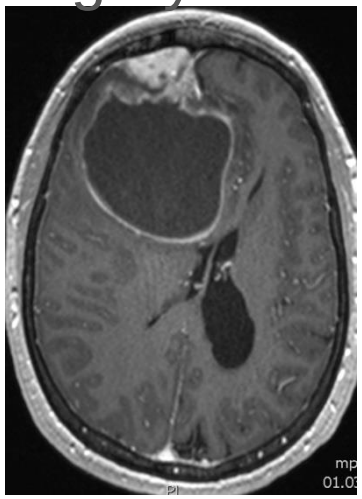
Summary
Newly diagnosed glioblastoma

1. Extent of surgery is prognostic
2. The standard therapy for newly diagnosed glioblastoma includes radiation and concomitant temozolomide (TMZ) therapy, followed by 6 cycles of maintenance temozolomide chemotherapy
3. Patients with a MGMT promotor methylation should be treated with temozolomide (+/- radiotherapy)
4. Elderly patients without a MGMT promotor methylation should receive radiation (hypofractionated schedule)
5. Bevacizumab does not prolong overall survival

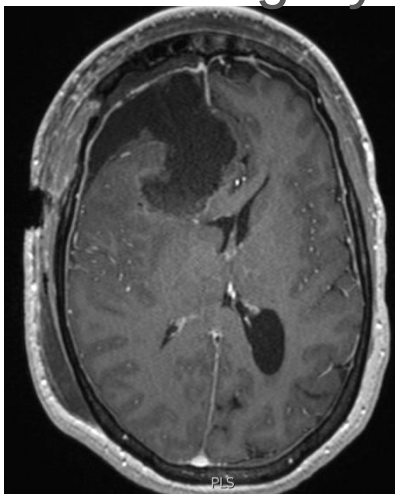
Case 2: 51-year-old patient with anaplastic oligodendroglioma

- First symptoms: Headaches, vomiting, urinary incontinence
- Clinical condition : Apathy, no further neurologic deficit, KPS 90%
- Imaging

before surgery



after surgery



- Molecular markers:

  IDH-1 mutated, LOH 1p/19q

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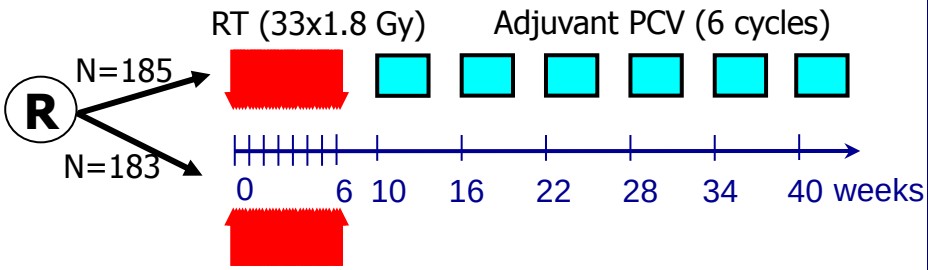
Q 3: What is your treatment of choice for anaplastic oligodendroglioma (IDH-1 mut, LOH 1p/19q)?

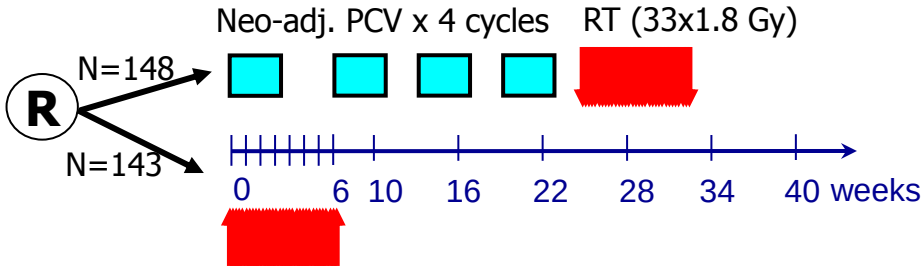
1. Radiotherapy alone
2. Radiotherapy plus PCV
3. Radiotherapy plus temozolomide
4. Temozolomide alone
5. Radiotherapy plus chemotherapy (PCV or temozolomide)

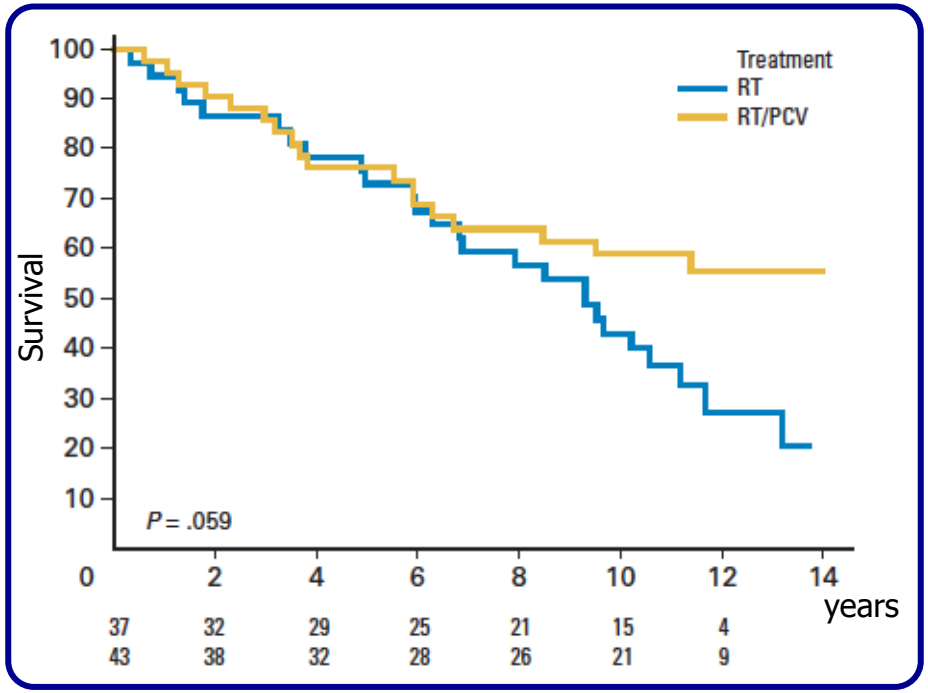
(Neo)adjuvant PCV for 1p/19q oligos: Long-term follow-up

EORTC

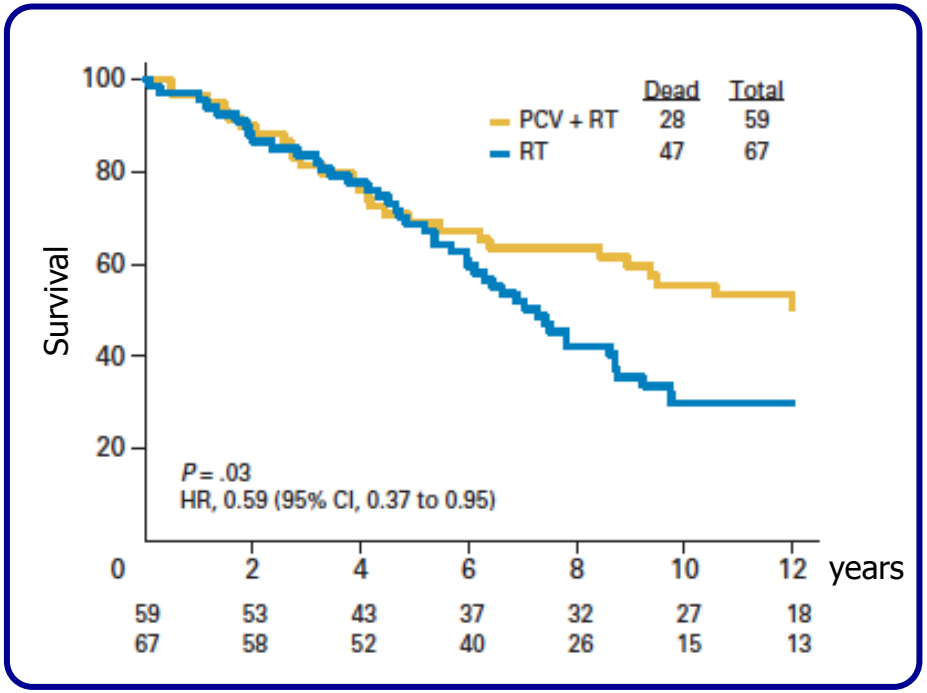
RTOG Radiation Therapy Oncology Group







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



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

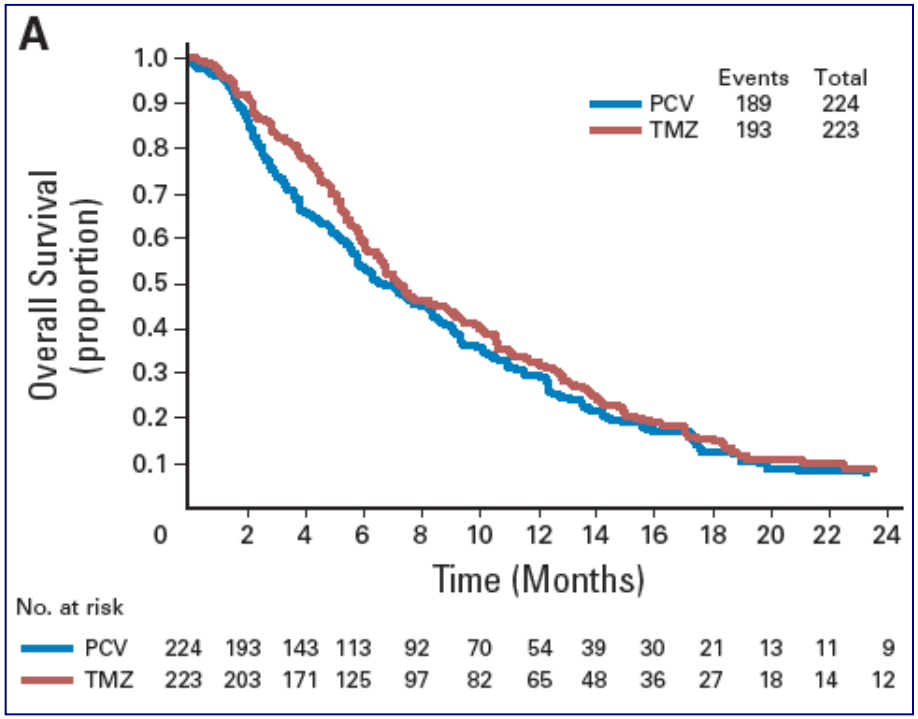
Answer 3: Treatment of choice

1. Radiotherapy alone
2. Radiotherapy plus PCV
3. Radiotherapy plus temozolomide
4. Temozolomide alone
5. Radiotherapy plus chemotherapy (PCV or temozolomide)

Chemo yes, but which chemo?

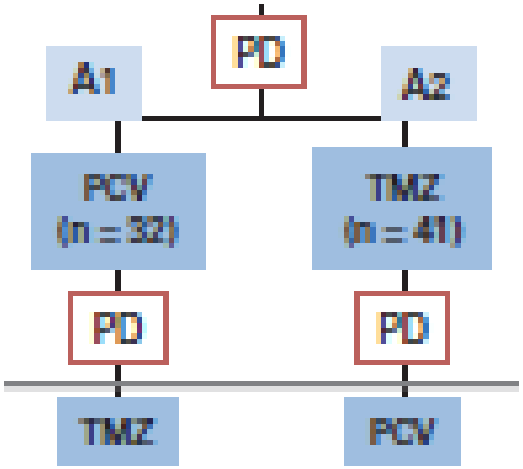
MRC Clinical Trials Unit

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



NOA -04

Wick et al.
J Clin Oncol 27:5874-5880, 2009



No difference in outcome

MRC Clinical Trials Unit

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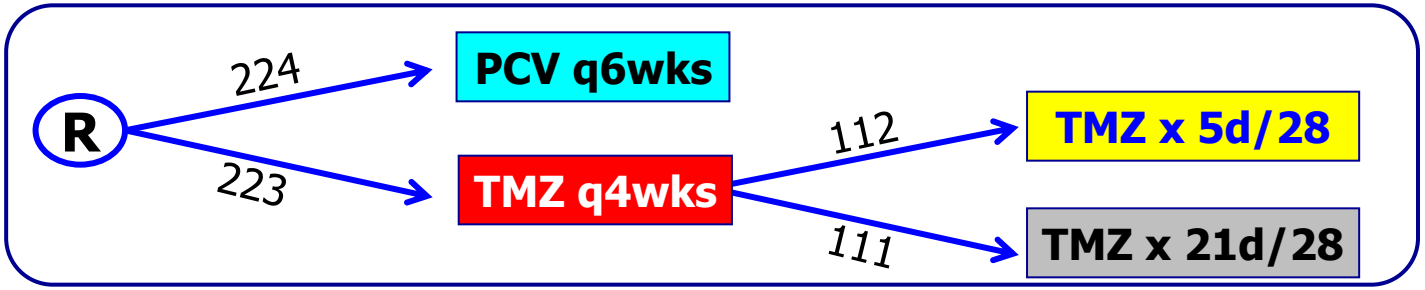
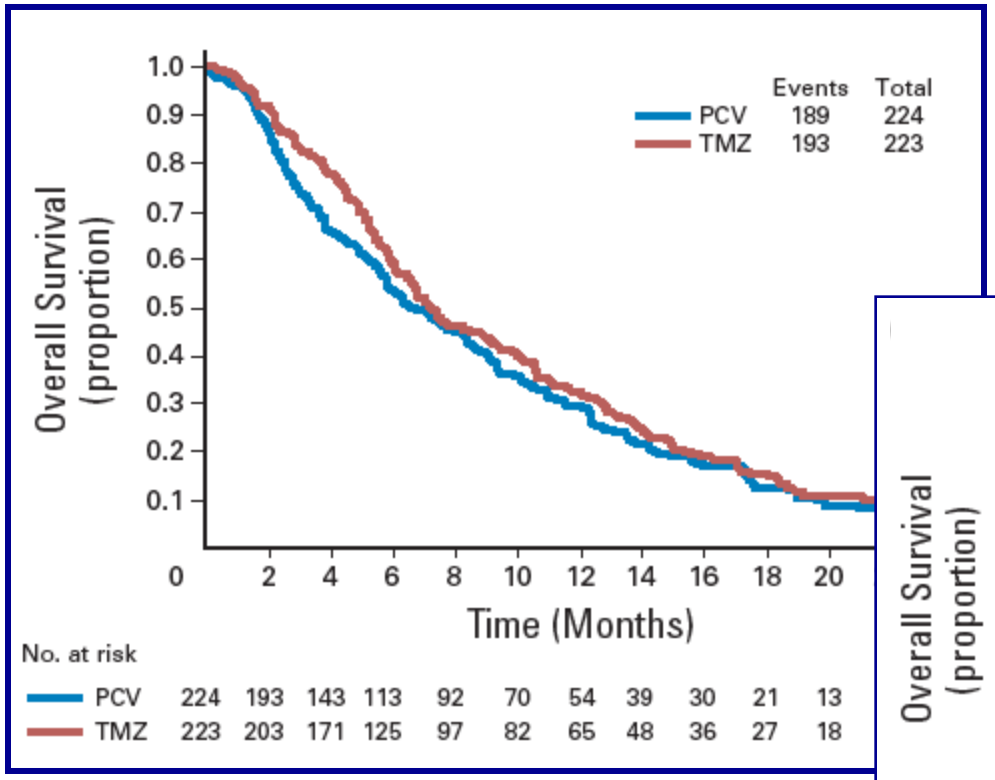
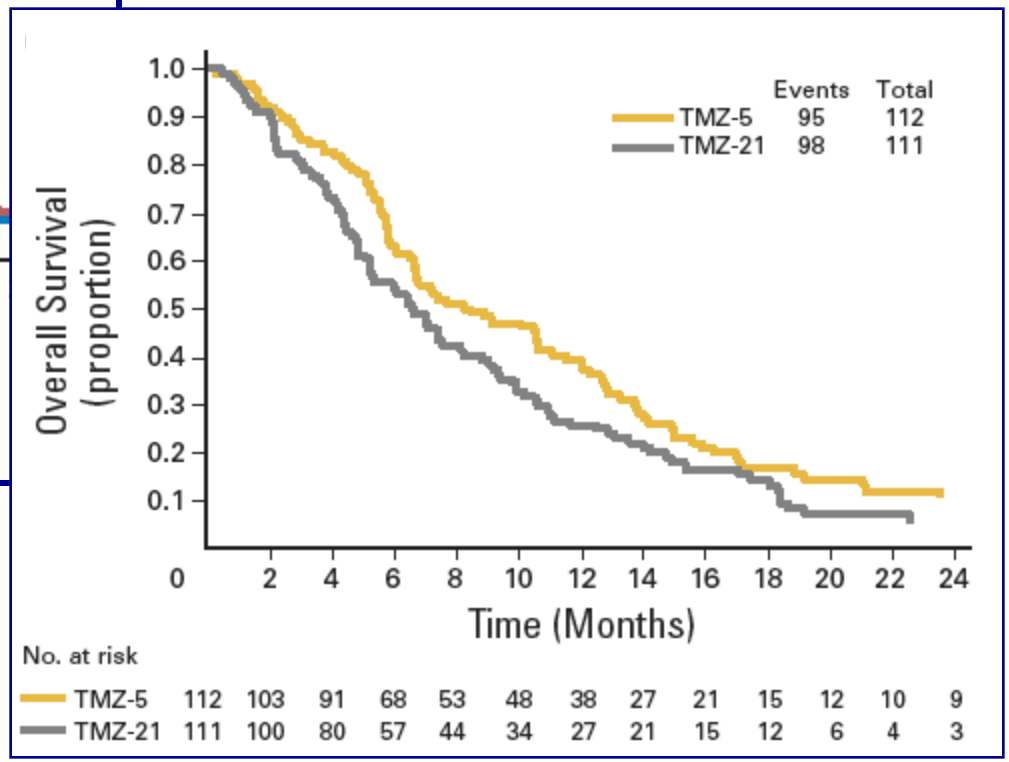




- GBM patients with recurrent disease after RT (no prior chemo)



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

Q 4: Which marker is predictive in anaplastic glioma?

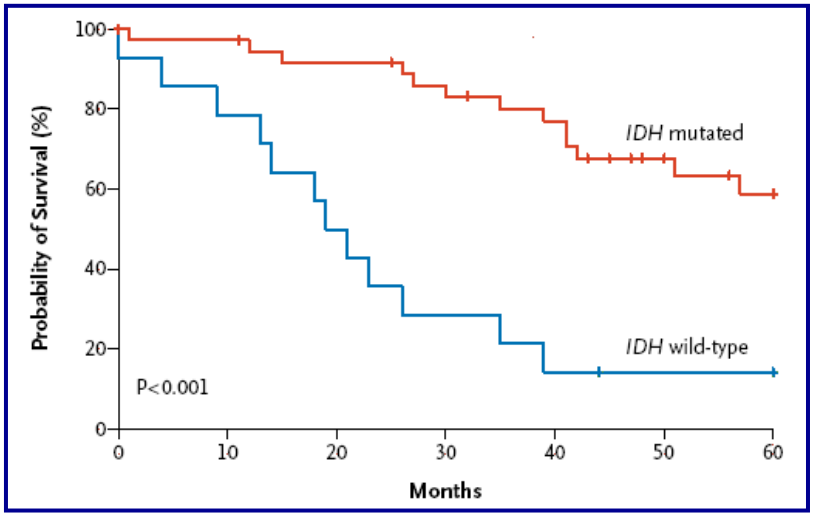
1. IDH-1
2. IDH-2
3. LOH 1p/19q

Answer 4: Predictive marker in anaplastic glioma

Prognostic

- IDH1+IDH2 mutations

Anaplastic Astrocytoma



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

- LOH 1p/19q

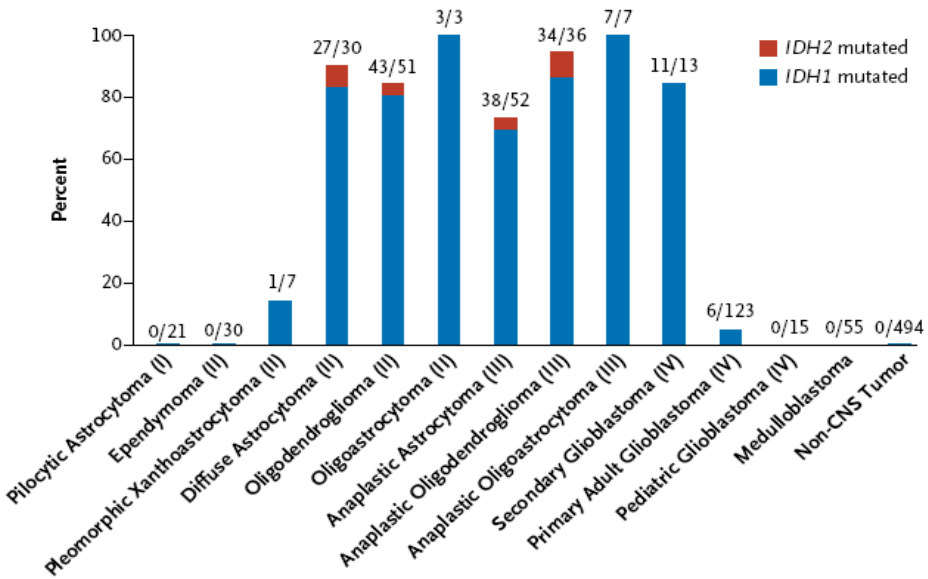
Prognostic & predictive

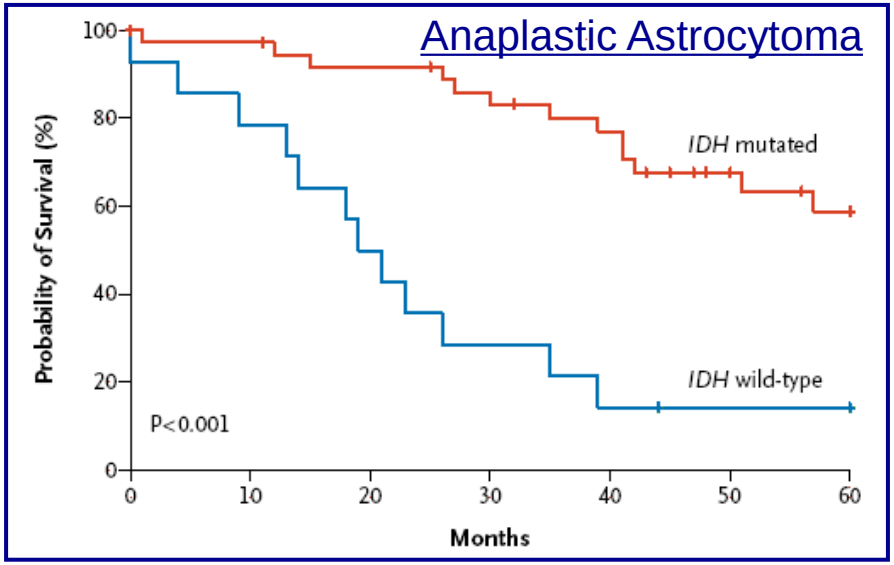
Survival benefit from early chemotherapy

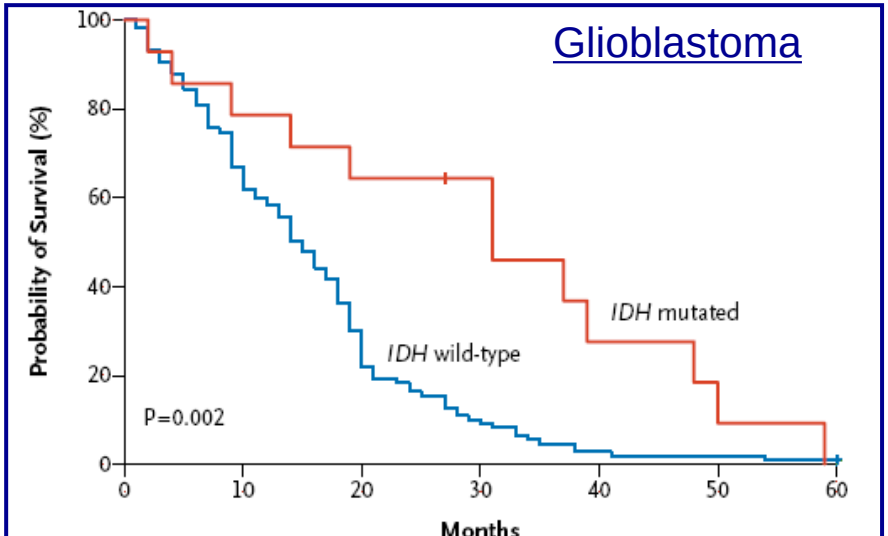
Cairncross & Louis JNCI 1998, Jenkins Cancer Res 2006
van den Bent JCO 2006/2013, Cairncross JCO 2006/2013

IDH mutations carry a more favorable prognosis

Variable frequency of *IDH* mutations







Yan, Parsons … & Bigner. NEJM 2009, 360:765-73

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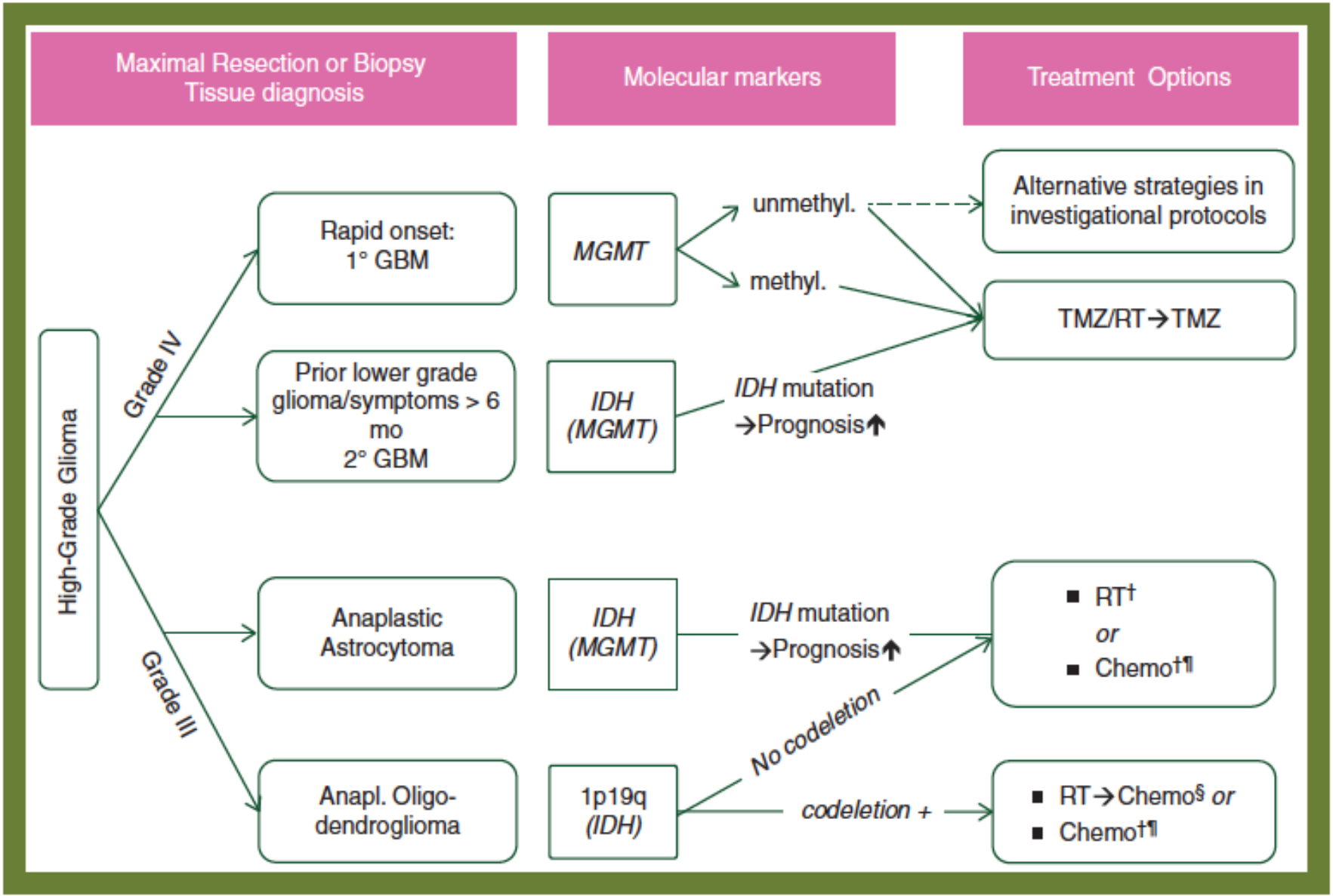
European Society for Medical Oncology

Mangement of high-grade glioma

Stupp et al. ESMO Guidelines. Ann Oncol 2014 (Sep);25 Suppl 3:iii93-iii101



Take Home Messages

- Grade III gliomas
  - IDH mutation status identifies patients with a better prognosis
  - In oligodendrogliomas, 1p/19q co-deletion is a prognostic and predictive marker.
    - Longer survival for co-deleted oligo's with (PCV-) chemotherapy given early in the course of disease (adjuvant or neo-adjuvant).
    - No benefit of adjuvant PCV in non-deleted anaplastic astrocytomas.

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Guidelines high-grade glioma
Thank you for the attention

"I'll be happy to give you innovative thinking. What are the guidelines ?"

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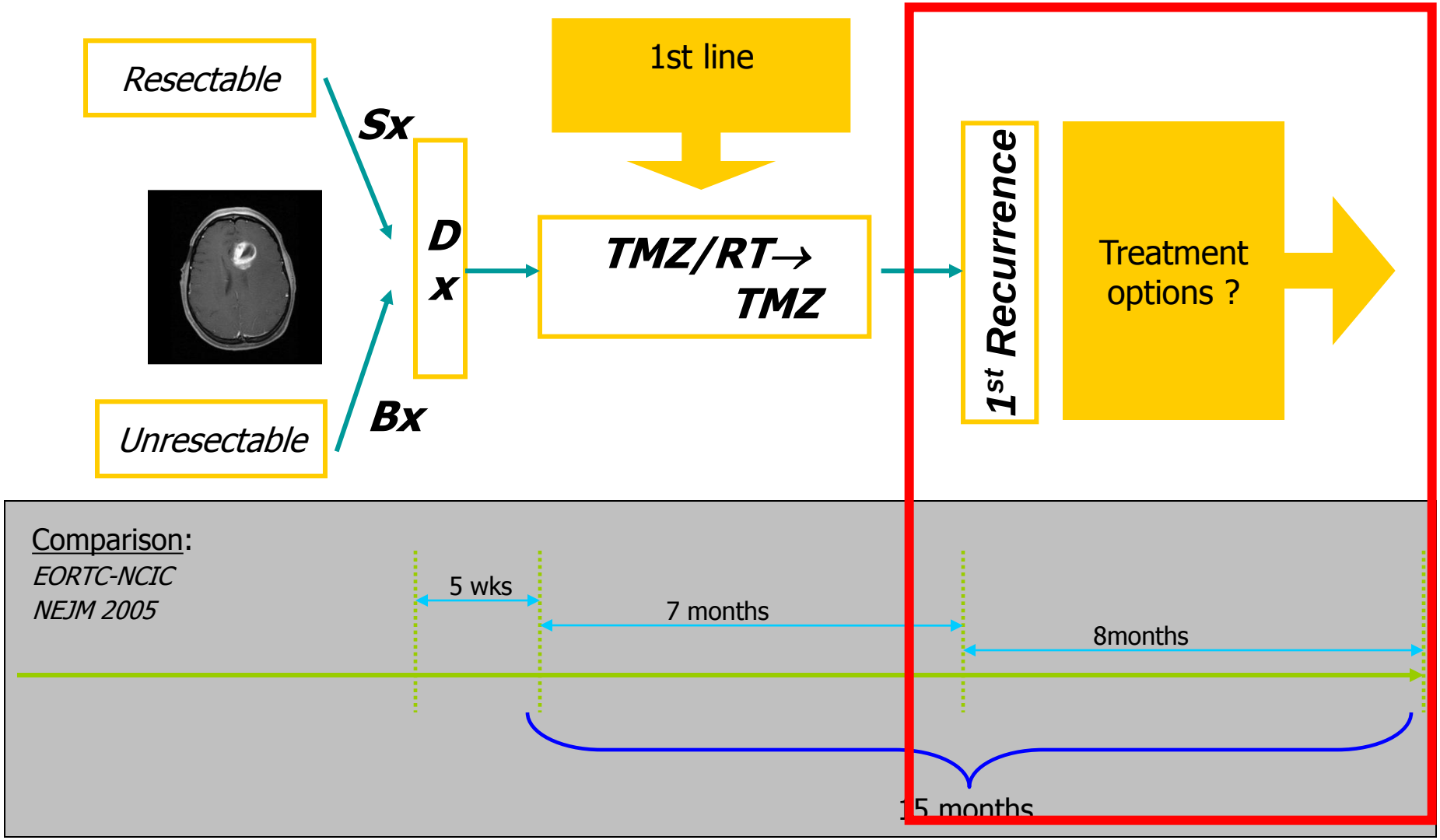
Glioma Therapy



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GBM (glioma) recurrence: Treatment options

- Repeat surgery ± Gliadel®
- Re-irradiation (experimental)
- Chemotherapy:
  - FDA/EMEA approved: Temozolomide, Carmustine, Lomustine
  - Only FDA + CH Bevacizumab (Avastin®)
  - Irinotecan (CPT11)
  - Carboplatin
  - EGFR inhibitors

Lomustine (CCNU) is an active agent (confirmed in 2009)

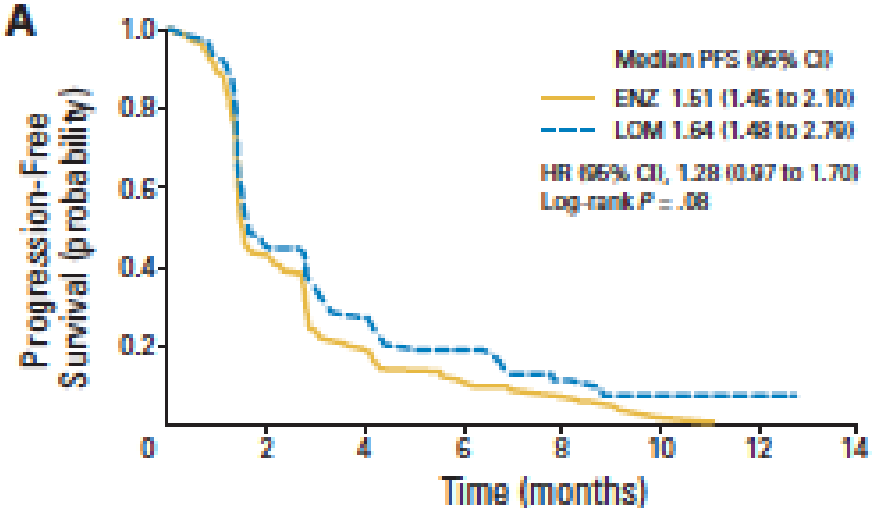
JOURNAL OF CLINICAL ONCOLOGY

2010; 28:1168-1174

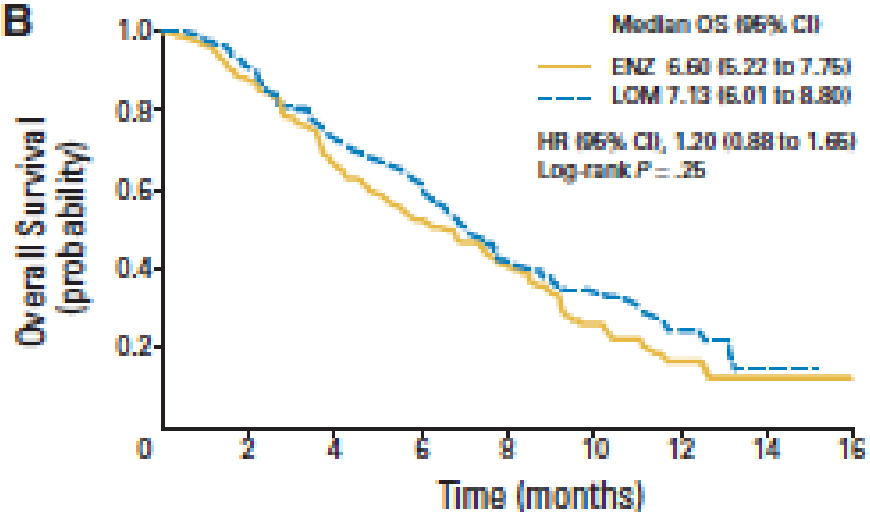
Phase III Study of Enzastaurin Compared With Lomustine in the Treatment of Recurrent Intracranial Glioblastoma

Wolfgang Wick, Vinay K. Puduvalli, Marc C. Chamberlain, Martin J. van den Bent, Antoine F. Carpentier, Lawrence M. Cher, Warren Mason, Michael Weller, Shengyan Hong, Luna Musib, Astra M. Liepa, Donald E. Thornton, and Howard A. Fine

Progression-free survival



Overall survival



	Enza		CCNU	
PFS6	11%	*vs*	19%	p=0.13
RR	2.9%	*vs*	4.3%	p=0.5

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Agents targeting VEGF or VEGFR

Agent	Type	Target(s)
Bevacizumab (Avastin®)	mAb	VEGF-A
VEGF Trap	Decoy receptor	VEGFA and VEGFB
Sorafenib (Nexavar®)	TKI	VEGFR2, VEGFR3, Raf, PDGFR, cKIT and RET
Pazopanib (Votrient®)	TKI	TKI VEGFR1, VEGFR2, VEGFR3
Cediranib (AZD2171)	TKI	VEGFR1, VEGFR2, VEGFR3, PDGFRb, cKIT
Vandetanib (ZD6474, Zactima™)	TKI	VEGFR2, EGFR, FGFR1, RET
Vatalanib (PTK787)	TKI	VEGFR1, VEGFR2

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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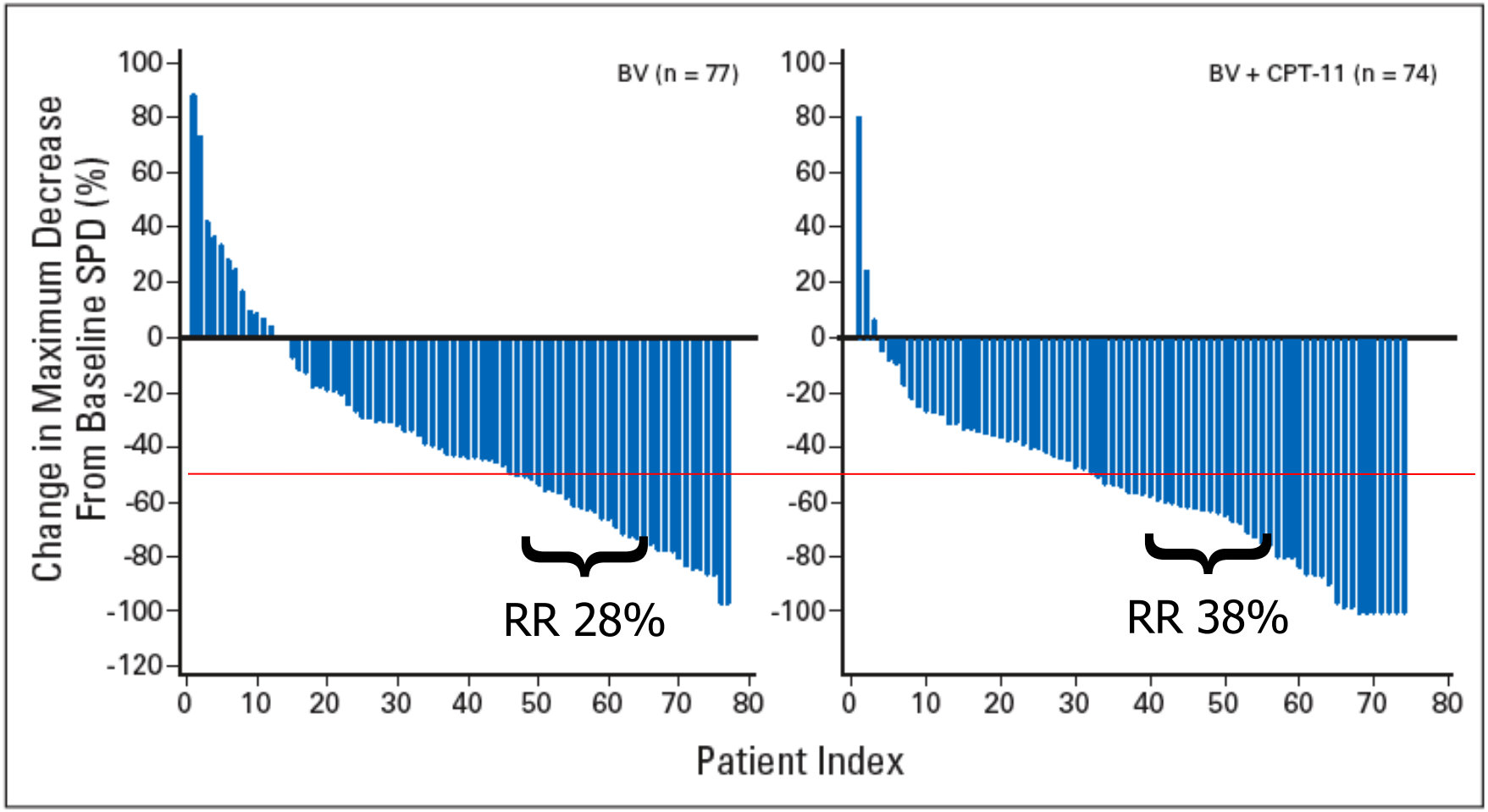
R → N=85: Bevacizumab → at PD: add CPT11

R → N=82: Bevacizumab & CPT11

Friedman et al. JCO 27: 4733-40, 2009

Waterfall plot of tumor regression



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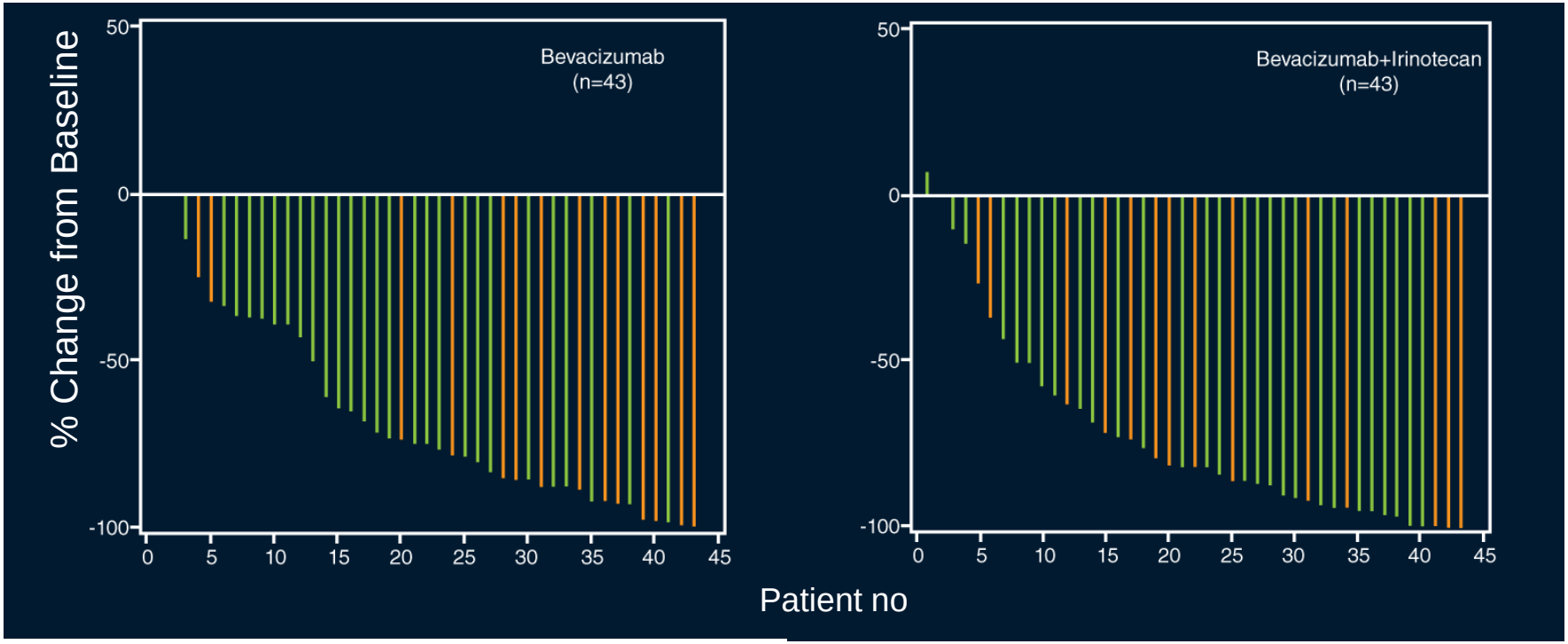
R → N=85: Bevacizumab → at PD: add CPT11
R → N=82: Bevacizumab & CPT11

Friedman et al. JCO 27: 4733-40, 2009

Corticosteroid dose



Responders are colored in orange.

Graph provided by T. Cloughesy/ ASCO 2008

JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

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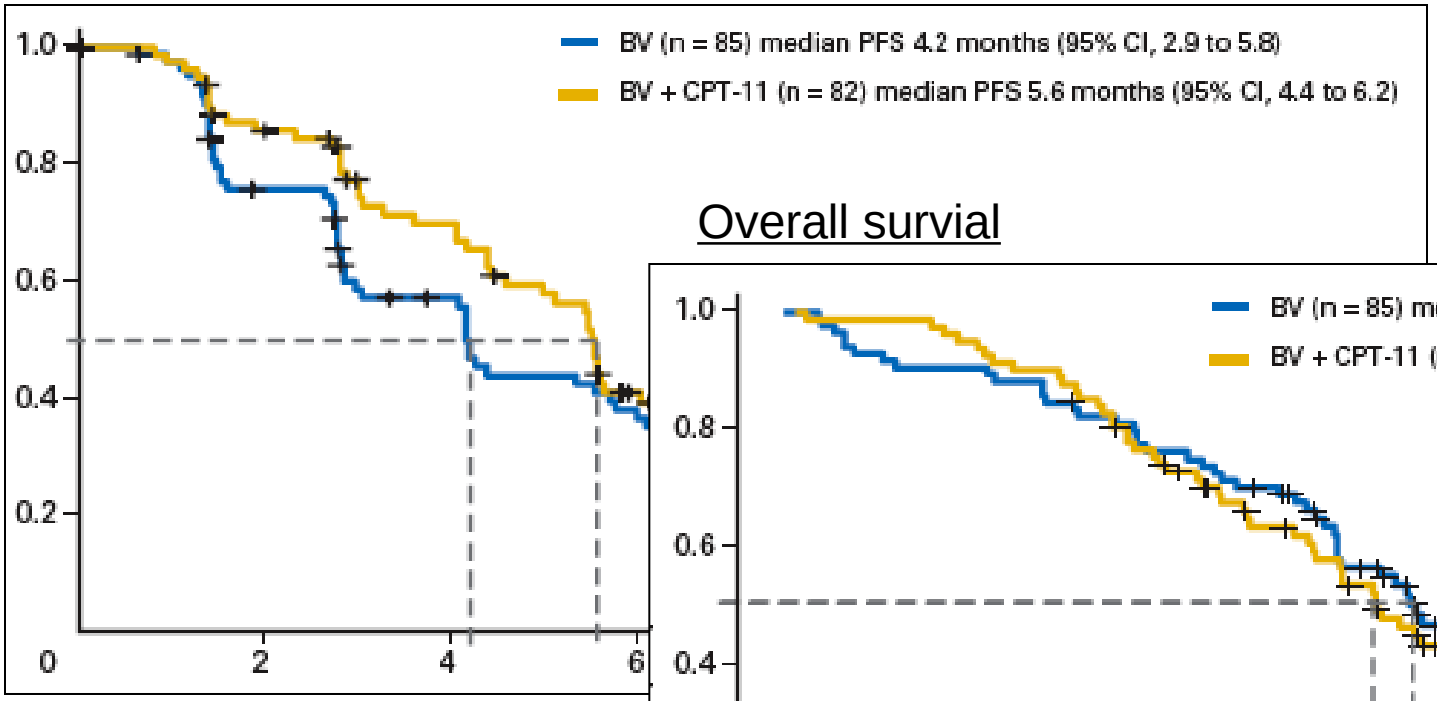
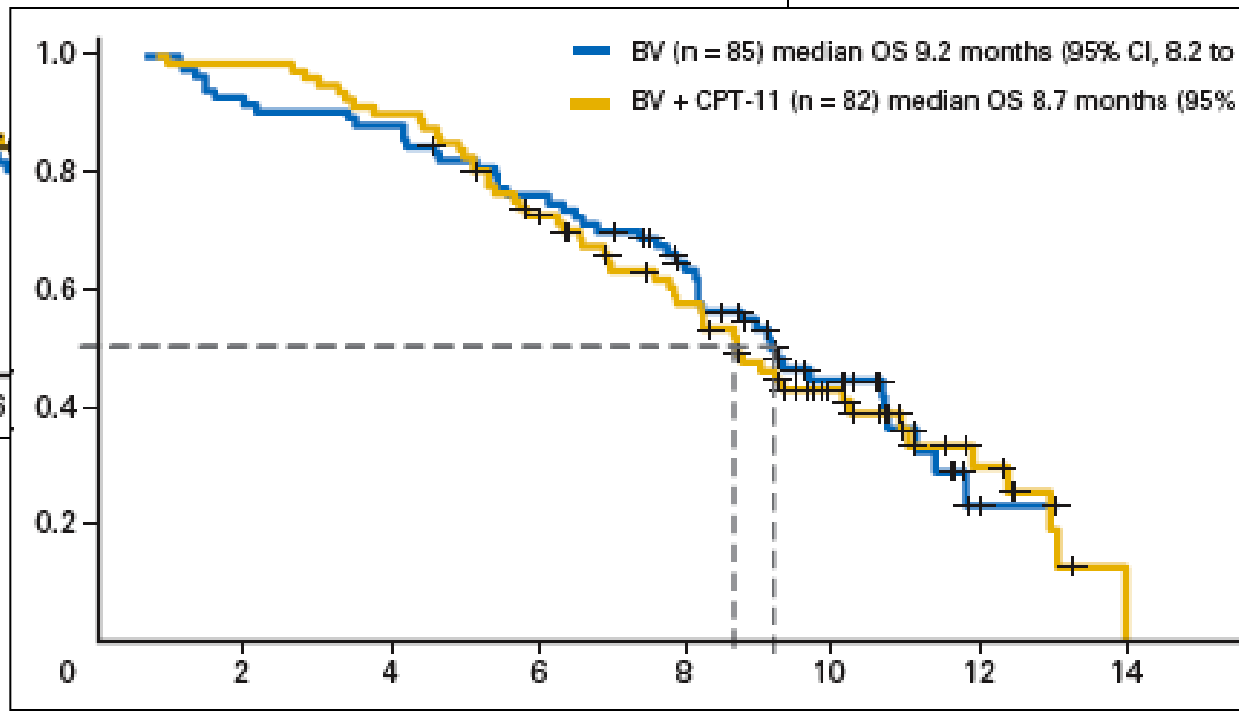
R
N=85 → Bevacizumab → at PD: add CPT11
N=82 → Bevacizumab & CPT11

Progression-free survial



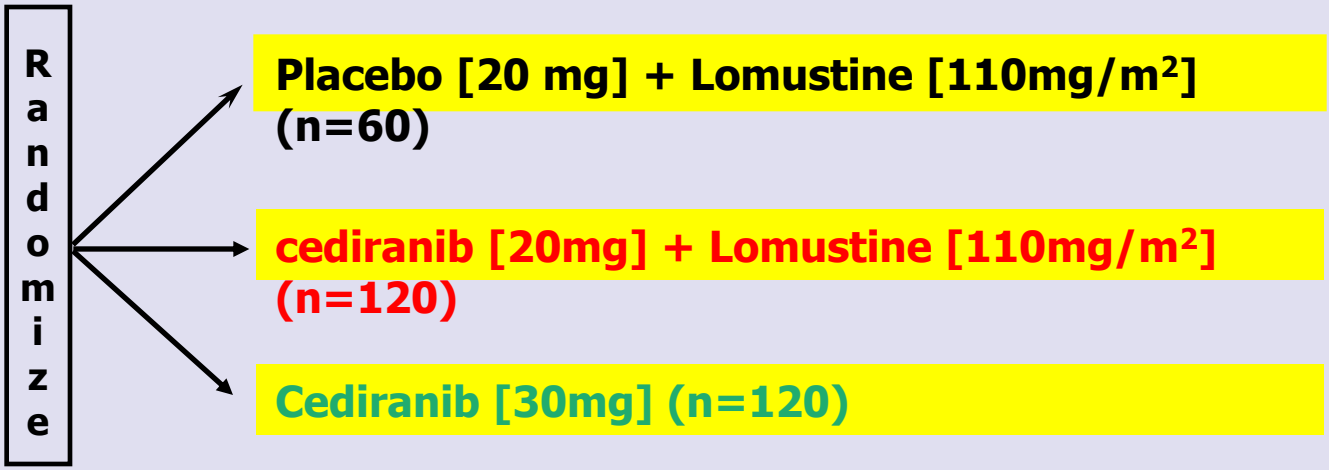
Overall survial



Friedman et al.
JCO 27: 4733-40, 2009

AstraZeneca

REGAL Study (Cediranib)
Randomized phase III in recurrent GBM



Stratified by

- age (>65)
- resection

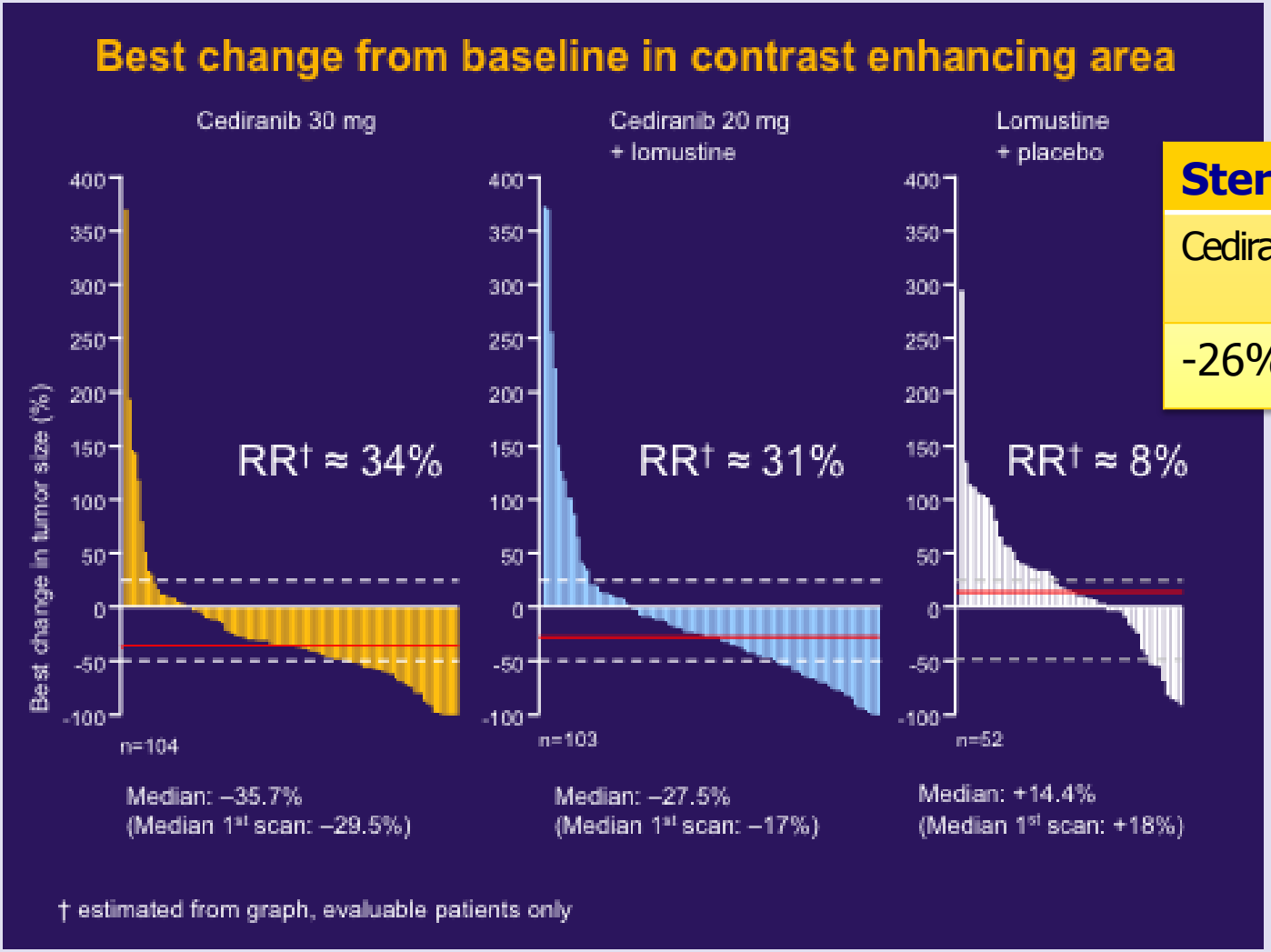
Primary endpoint:

- PFS

2° endpoints:

- OS, PFS6, RR

REGAL – Study: Responses and Steroids



Steroid use

Cediranib	Ced + CCNU	Placebo + CCNU
-26%	-23%	+5%

Batchelor et al.
ESMO 2010, LBA#7
Batchelor et al. J Clin Oncol 2013:31:3212-3218

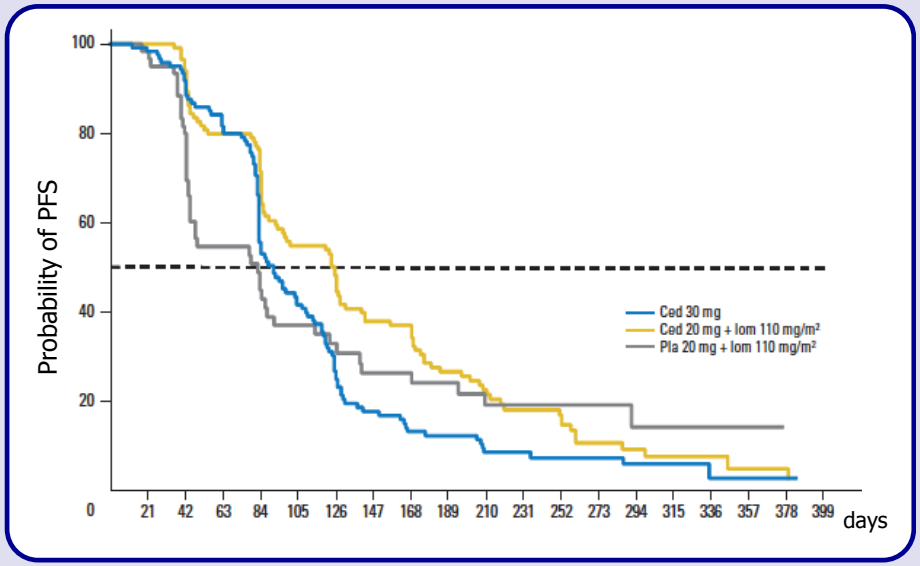
JOURNAL OF CLINICAL ONCOLOGY

2013; 31:3212-3218

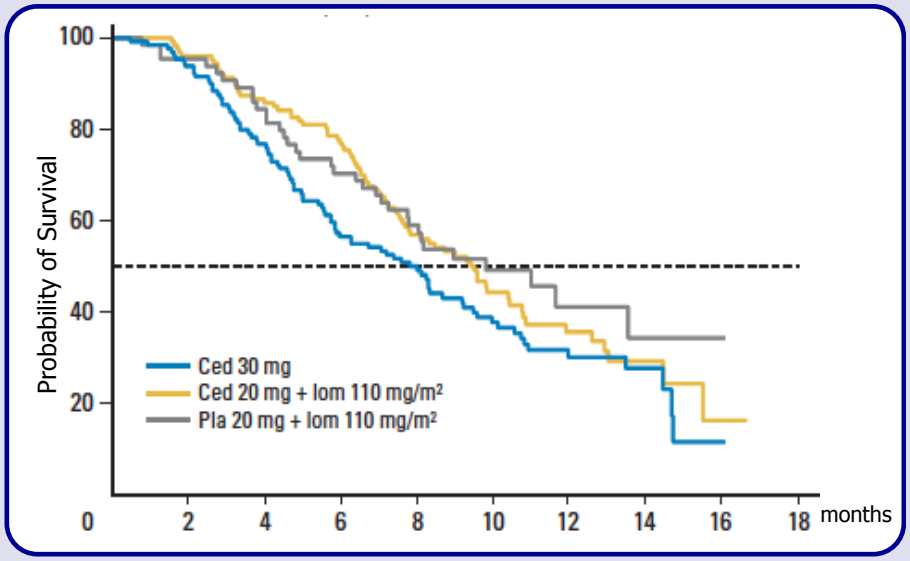
Phase III Randomized Trial Comparing the Efficacy of Cediranib As Monotherapy, and in Combination With Lomustine, Versus Lomustine Alone in Patients With Recurrent Glioblastoma

Tracy T. Batchelor, Paul Mulholland, Bart Neyns, L. Burt Nabors, Mario Campone, Antje Wick, Warren Mason, Tom Mikkelsen, Surasak Phuphanich, Lynn S. Ashby, John DeGroot, Rao Gattamaneni, Lawrence Cher, Mark Rosenthal, Franz Payer, Juliane M. Jürgensmeier, Rakesh K. Jain, A. Gregory Sorensen, John Xu, Qi Liu, and Martin van den Bent

Progression-free survival



Overall survival



	Cediranib	Ced. +CCNU	Placebo + CCNU
RR	15%	17%	9%

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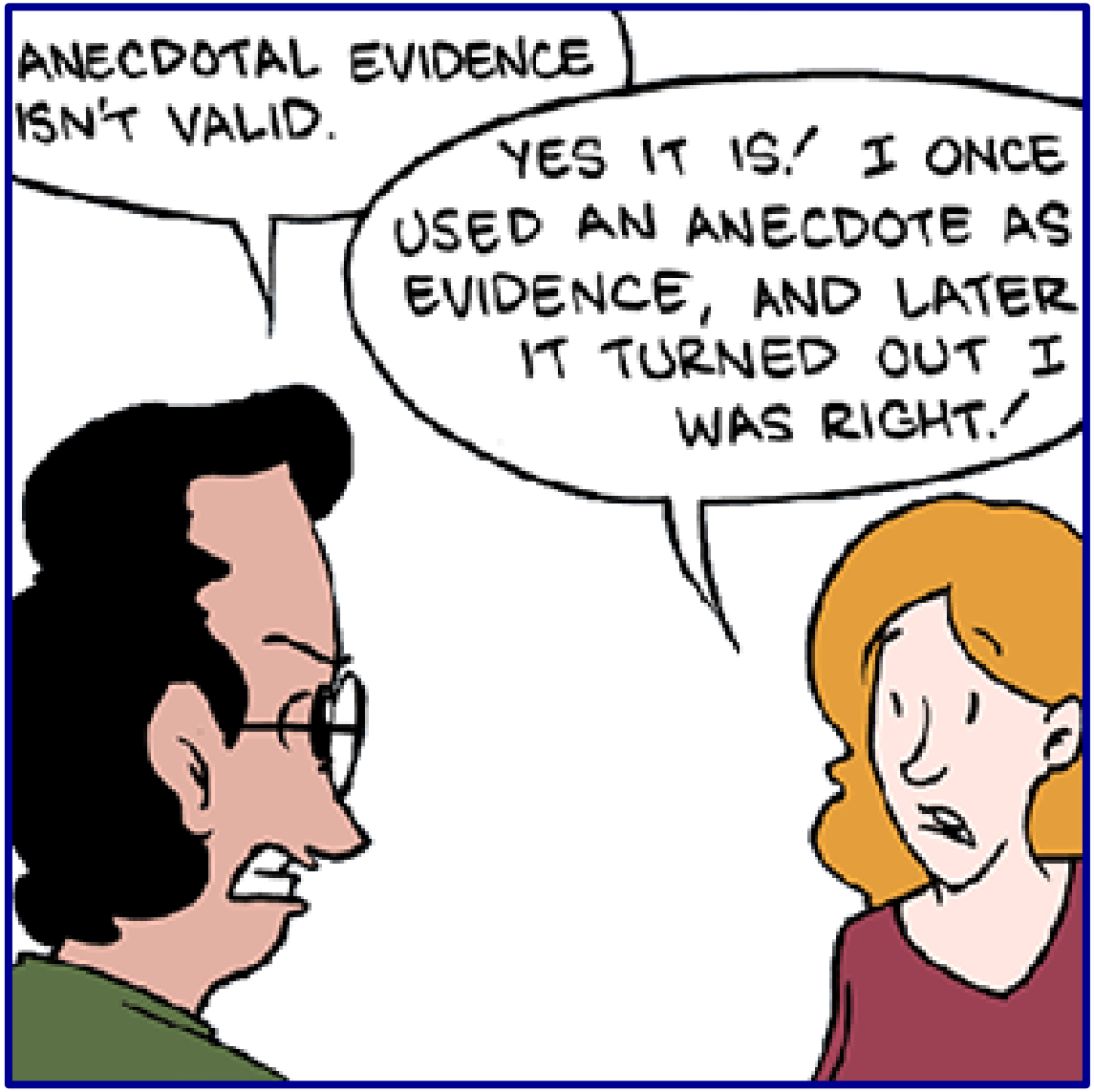
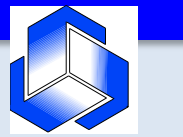
Prospective + Controlled Clinical Trials



CCNU + bevacizumab *vs* CCNU

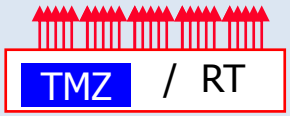
Recurrent GBM

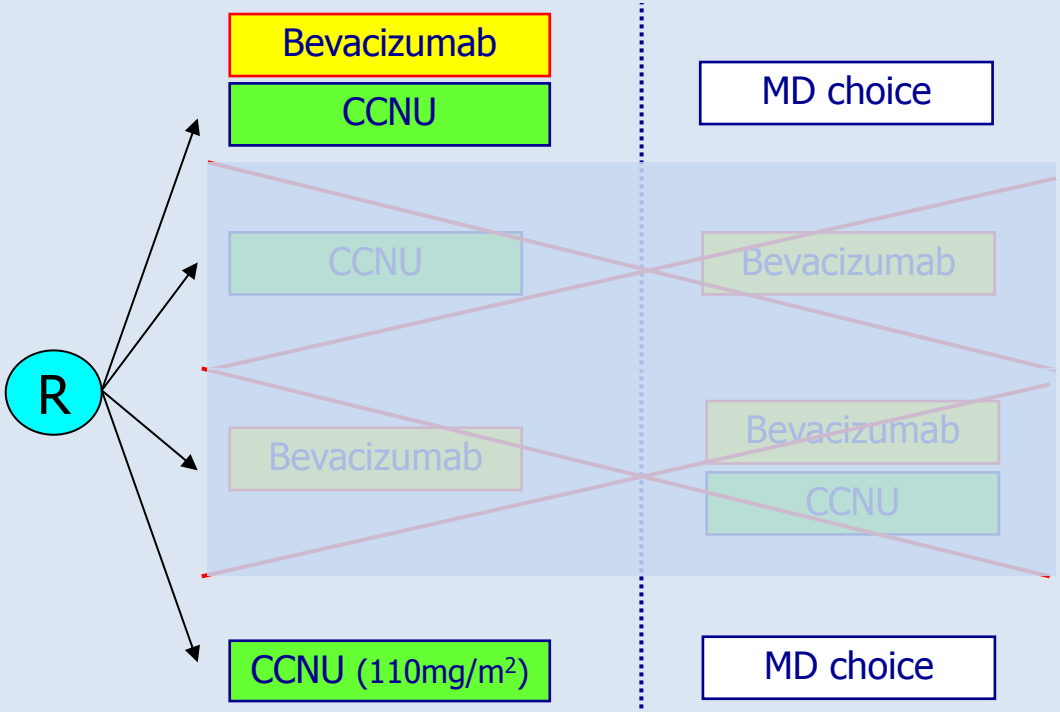


EORTC 26101

1st recurrence/ Progression

2nd recurrence/ Progression





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

Primay endpoint: Overall survival
2:1 random., > 400 pts required

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Guidelines high-grade glioma
Thank you for the attention

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