Problematiche emergenti nei trattamenti integrati

Radioterapia e Temozolomide nei tumori gliali maligni

Cristina Mantovani

Anaplastic Astrocytoma/Anaplastic Oligodendroglioma/Glioblastoma Multiforme[a]

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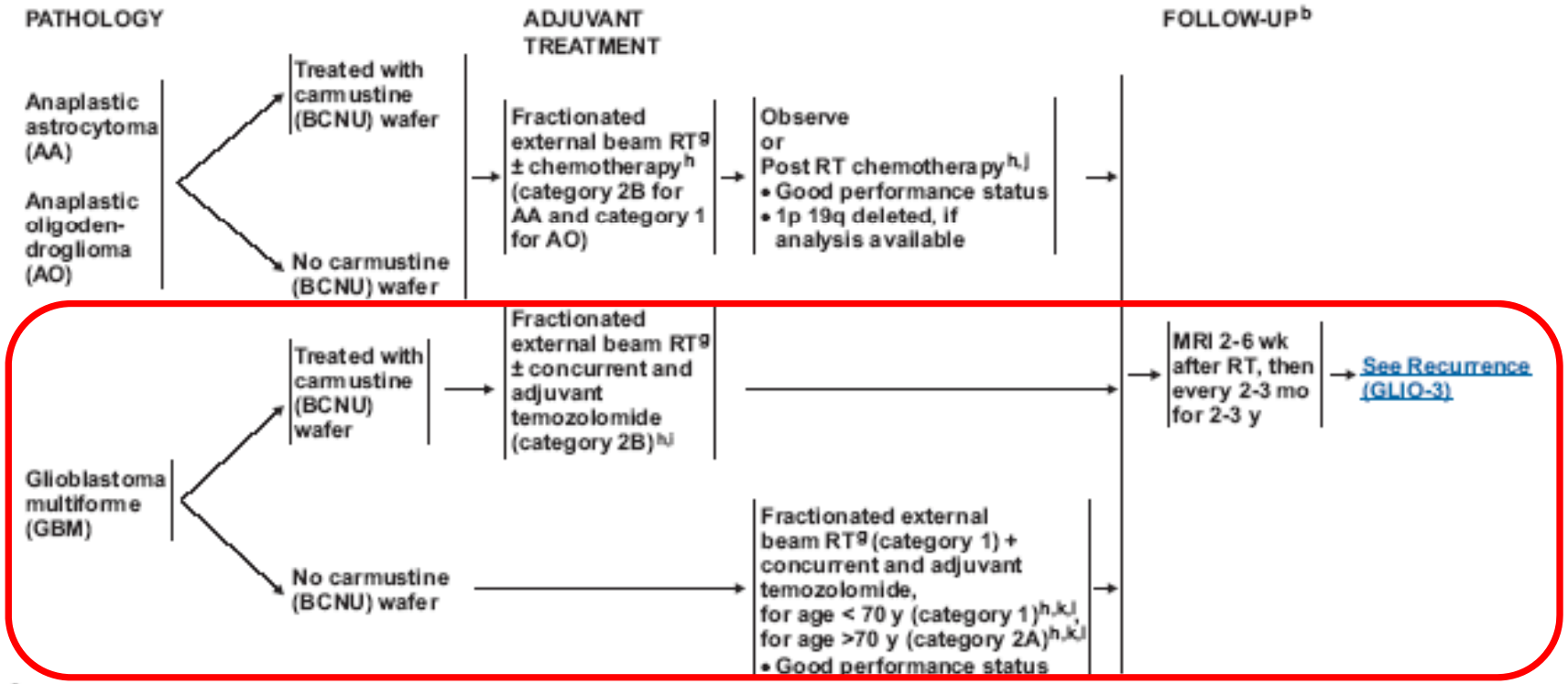

[a] This pathway also includes the classification of mixed anaplastic oligoastrocytoma.

[b] See Principles of Brain Tumor Imaging (BRAIN-A).

[g] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

[h] See Principles of Brain Tumor Chemotherapy (BRAIN-D).

[i] Combination of agents may lead to increased toxicity or radiographic changes.

[j] For AO, randomized studies show that adjuvant PCV (lomustine + procarbazine + vincristine) chemotherapy prolonged PFS (category 1). (Cairncross G, Berkey B, Shaw E, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol 2006;24(18):2707-2714 and van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organization for Research and Treatment of Cancer phase III trial. J Clin Oncol 2006;24(18):2715-2722.)

[k] Stupp R, Mason WP, van den Bent MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-996.

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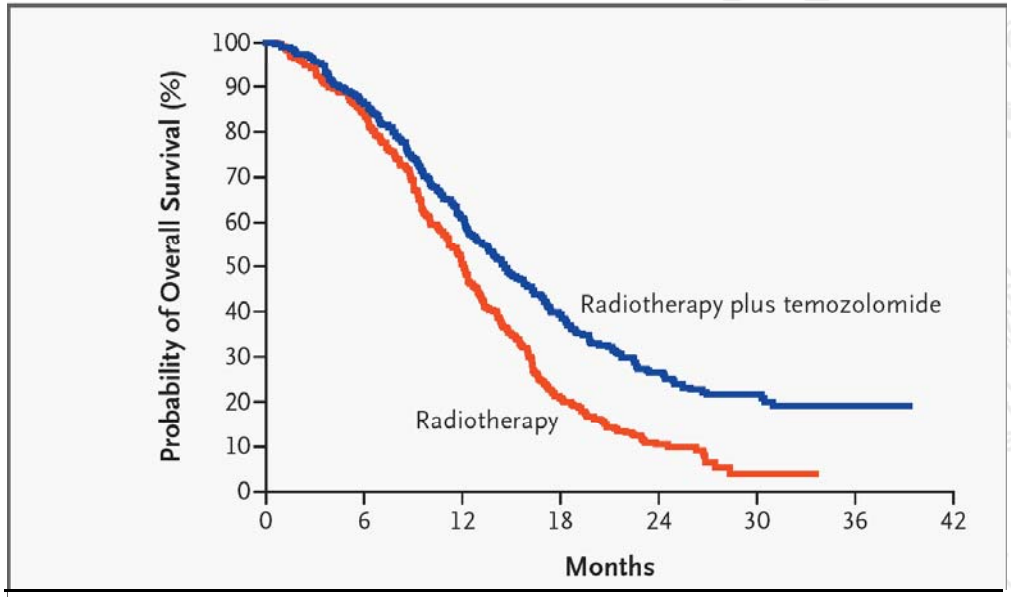
GBM: benefit from Radiotherapy and Temozolomide



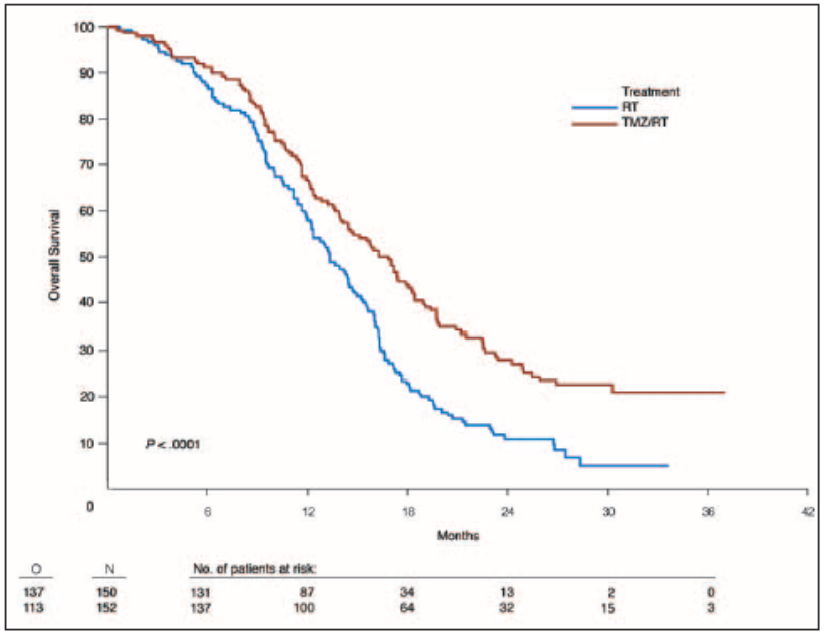
	RT	TMZ/RT
Median OS (mo)	12.1	14.6
2-yr survival	11.2%	27.3%
3-yr survival	4.3%	16.7%
4-yr survival	3.8%	12.9%
5-yr survival	1.9%	9%

Mirimanoff, 2007

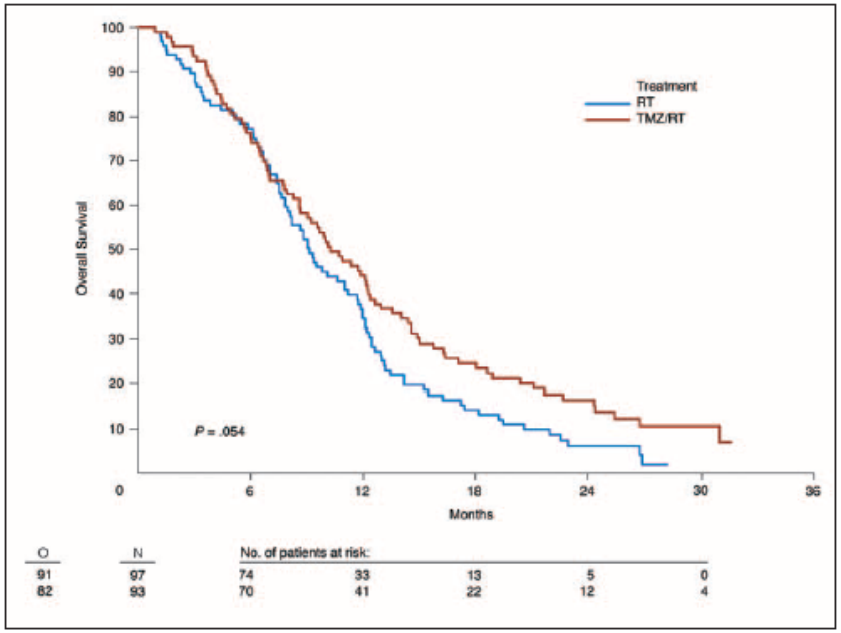
Radiotherapy and Temozolomide for newly diagnosed Glioblastoma: Recursive Partitioning Analysis of the EORTC 26981/22981-NCIC CE3 Phase III Randomized trial

In RPA class IV, the survival advantage remained significant, with median survival times of 16 *vs* 13 months, respectively, and 2-year survival rates of 28% *vs*11%, respectively (p<0.0001).

In RPA class V the survival advantage of RT/TMZ was of borderline significance (*p<0*.054).



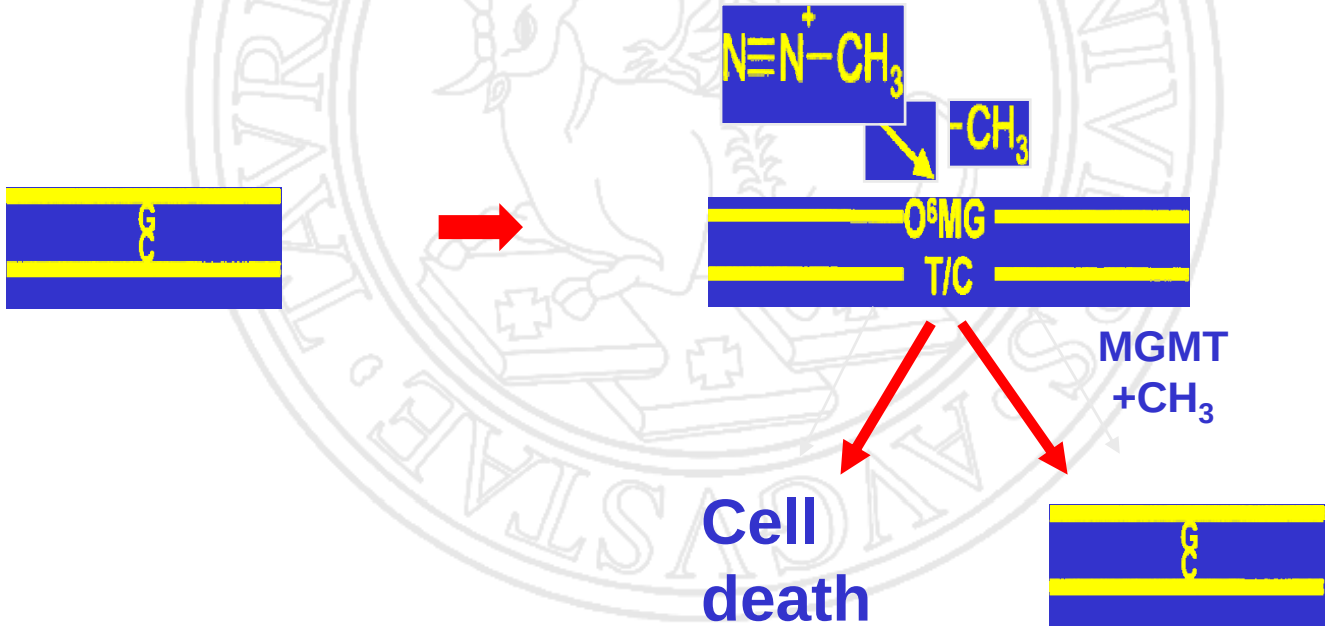
Overall survival according to the treatment in RTOG/EORTC recursive partitioning analysis (RPA) class IV.



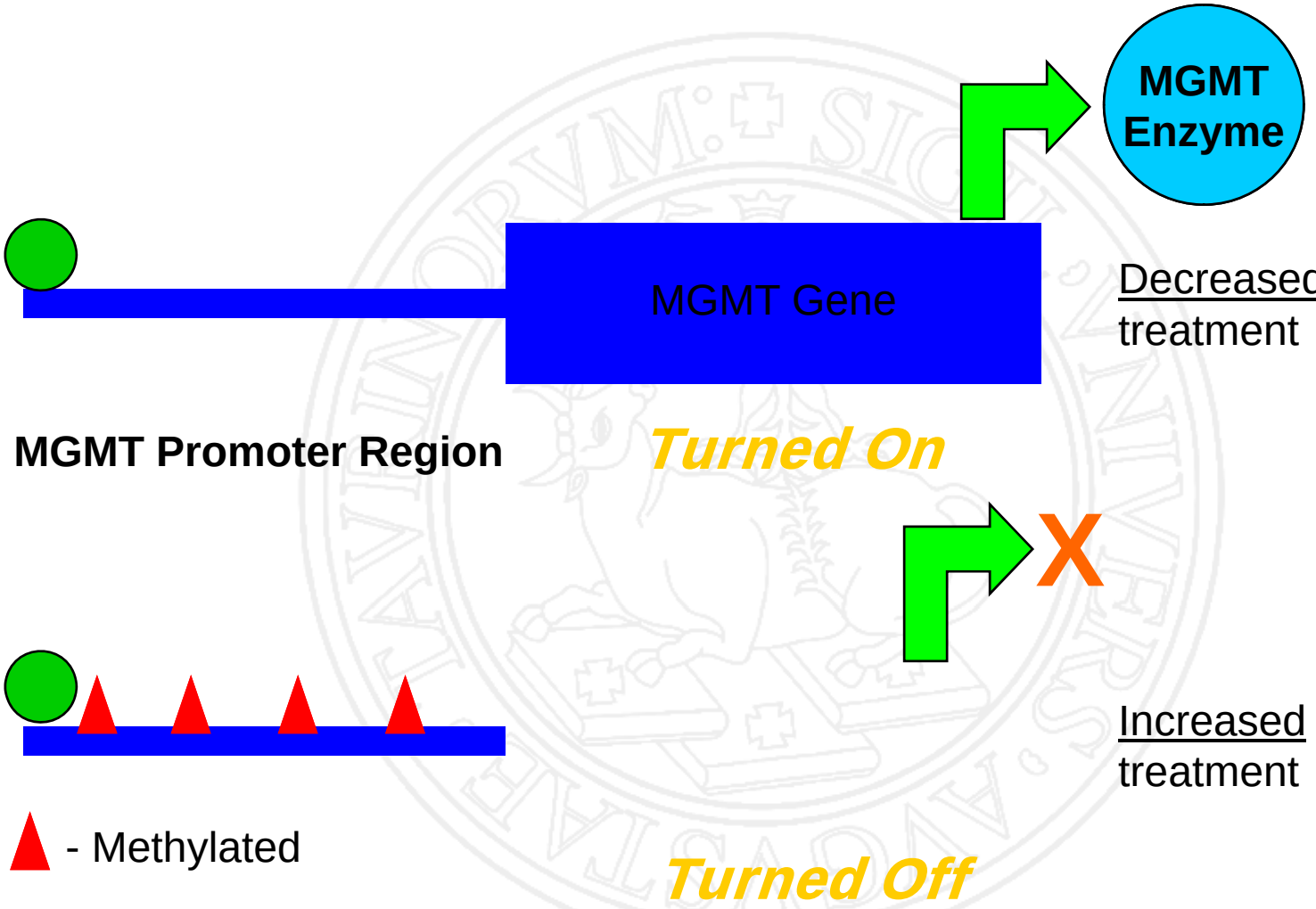
Overall survival according to the treatment in RTOG/EORTC recursive partitioning analysis (RPA) class V.

MGMT and resistance to alkylating agents

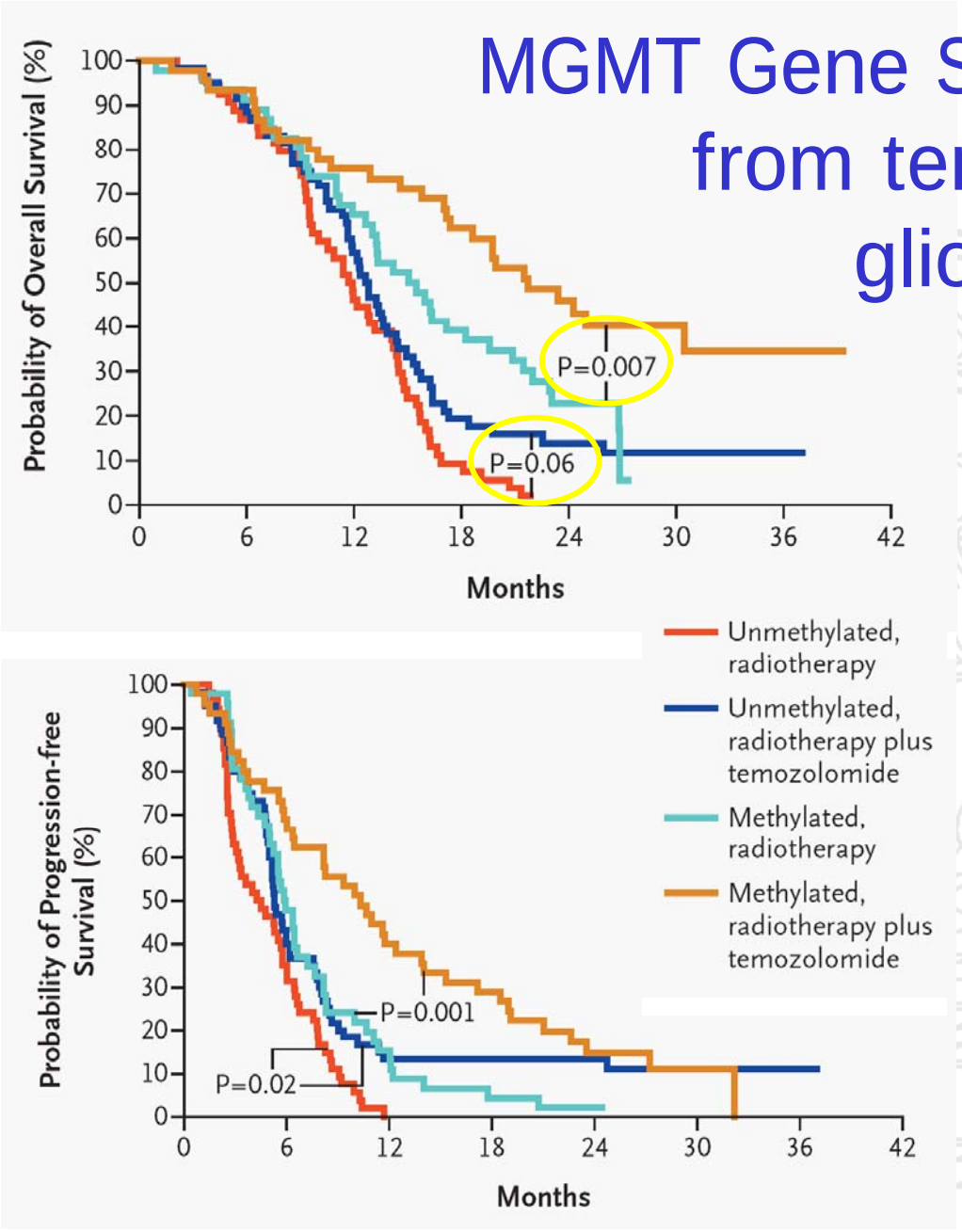
O6-methylguanine methyltransferase (MGMT, AGAT), a DNA repair enzyme, reverses DNA lesions induced by alkylating agents:



Activity of Temozolomide



MGMT Gene Silencing and benefit from temozolomide in glioblastoma



- Methylation-specific PCR was performed on 206 of 573 glioblastoma specimens; MGMT promoter methylation was detected in 92 patients

- The OS curves for TMZ and RT and for RT alone remain similar for the first nine months of follow-up → MGMT methylation is not the only factor determining outcome

Hegi et al, 2005

Overall survival for patients with a methylated MGMT promoter

Treatment	RT meth	RT+TMZ meth
2-yr OS(%)	23.9	48.9
3-yr OS(%)	7.8	27.7
4-yr OS(%)	5.2	22.1
Hazard ratio	0.51 (0.33-0.81); p=0.04	

Overall survival for patients with an unmethylated MGMT promoter

Treatment	RT unmeth	RT+TMZ unmeth
2-yr OS(%)	1.9	14.4
3-yr OS(%)	0.0	11.1
4-yr OS(%)	0.0	11.1
Hazard ratio	0.66 (0.45-0.97); p=0.035	

Strategies to modulate MGMT activity

Deplete MGMT by higher doses of real substrates such as TMZ?

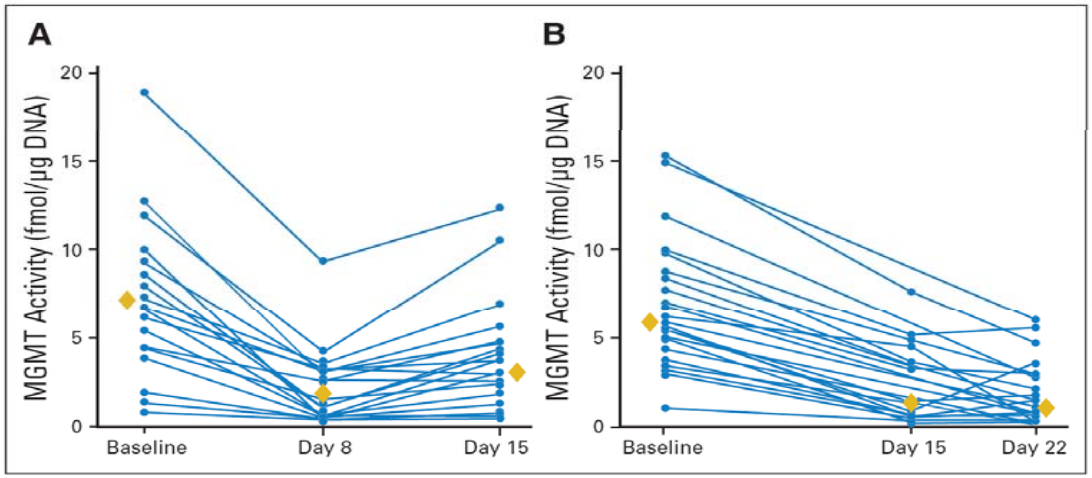
Deplete MGMT by dose-dense scheduling of TMZ or other real substrates?

Combine TMZ and other alkylators such as nitrosoureas?

Deplete MGMT activity by pseudosubstrate inhibitors?

Deplete MGMT by RNA interference?

Alternative TMZ dosing regimens result in marked decrease in MGMT activity



A.MGMT activity in PBMC after treatment with temozolomide 7 days on/7days off schedule

B.MGMT activity in PBMC after treatment with temozolomide 21/28 day schedule

Dose and schedule	Average decrease in MGMT activity		
	Day 7	Day 14-15	Day 21
50 to 175 mg/m^2/day × 7 days every other week	72%	55%*	
50 to 150 mg/m^2/day × 21 days with 1 week rest		63%	73%

*After 7-day treatment free period

Tolcher et al. Br J Cancer 2003

Dose-intensity modulation: Temozolomide regimens in recurrent glioblastoma

Ref.	Treatment Schedule	RR	PFS	PFS 6 mo
Yung, 2000	Standard	5%	12.4 w	21%
Brandes,2006	3W on/1W off (75 mg/m^2, 21 days)	9%	16.1 w	30.3% (no difference for unmeth)
Wick, 2007	1W on/1W off (150mg/m^2, 7 days)	15%	24 w	43.8% (26% for unmeth)
Balmaceda, 2008	Twice daily (100mg/m^2, 9 days)	31%	17 w	
Wong, 1999	Other drugs	8%	10 w	15%

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Correlation Between O^6-Methylguanine-DNA Methyltransferase and Survival in Inoperable Newly Diagnosed Glioblastoma Patients Treated With Neoadjuvant Temozolomide

Olivier L. Chinot, Maryline Barrié, Stephane Fuentes, Nathalie Eudes, Sophie Lancelot, Philippe Metellus, Xavier Muracciole, Diane Braguer, L'Houcine Ouafik, Pierre-Marie Martin, Henry Dufour, and Dominique Figarella-Branger

- Phase II study; 30 pts (17 class V, 3 class VI) enrolled; 28 pts assessable for response

- Temozolomide 150 mg/m^2/d on days 1 to 7 and on days 15 to 21 of every 28-day cycle→ **7 days on / 7 days off**

- 25 tumor biopsy sample available for MGMT analysis: low MGMT expression was detected in 11 pts, high MGMT expression in 14 pts

Effect of MGMT Expression Status on Response

MGMT Expression	No. of Patients	PR		SD		PD	
		No. of Patients	%	No. of Patients	%	No. of Patients	%
MGMT < 35%	11	6*	55	4	36	1	9
MGMT ≥ 35%	14	1	7	3	21	10*	71

NOTE. Median expression of MGMT = 35%.
Abbreviations: MGMT, O^6-methylguanine-DNA methyltransferase; PR, partial response; SD, stable disease; PD, progressive disease.
*P = .004.

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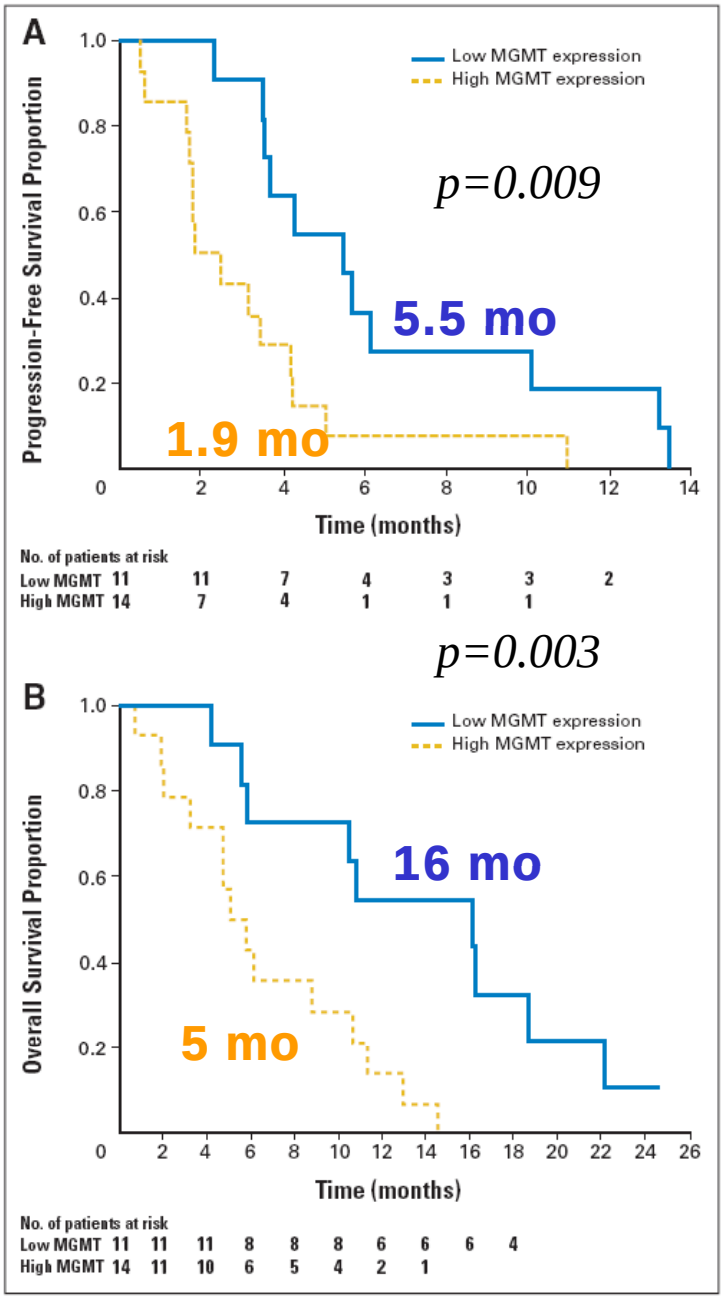
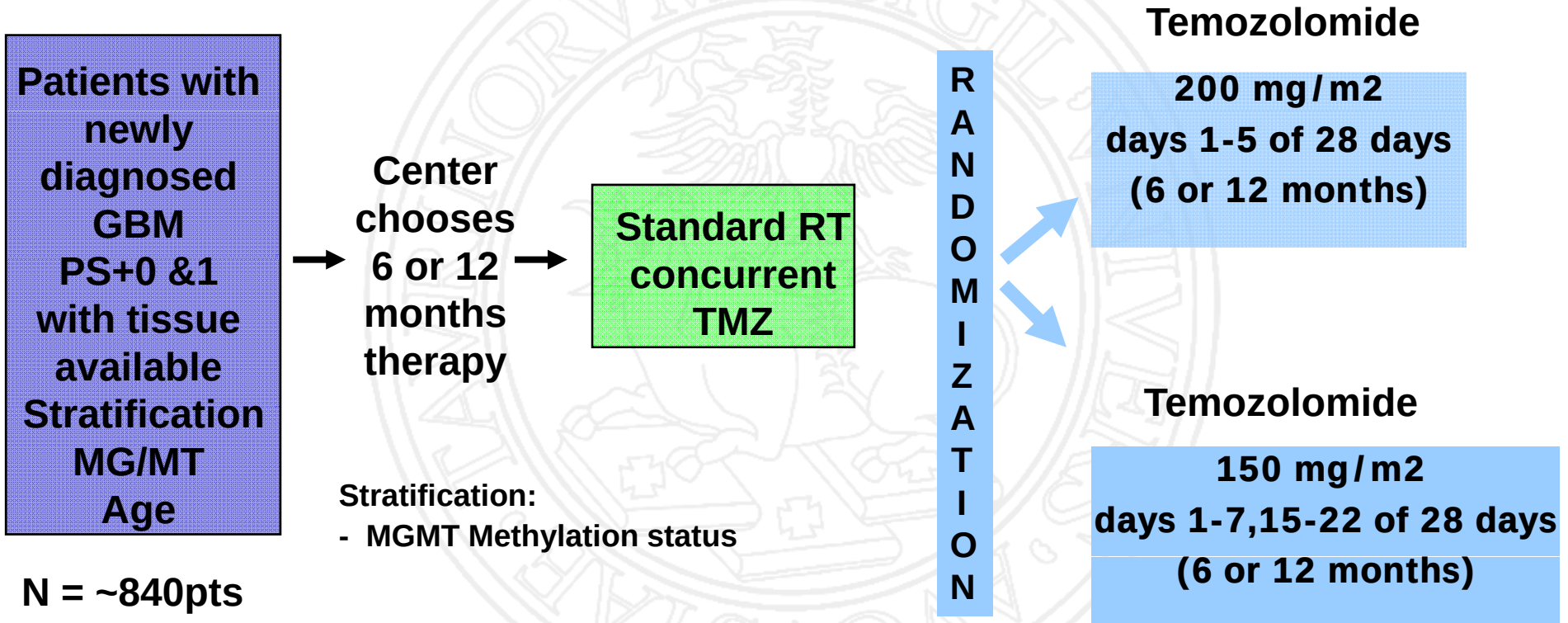


- 45% of pts with a low percentage of MGMT positive tumor cells did not respond, suggesting that these tumors may have other mechanisms of resistance to TMZ

- RT was completed in 91% of pts with low MGMT expression, only 64% of pts with high MGMT started RT and 43% completed RT → neoadjuvant CT may be feasible for inoperable GbI expressing low levels of MGMT without compromising RT, whereas pts with high MGMT expression are more likely to experience PD before or during RT

Chinot, et al, 2007

RTOG 0525: RTOG/NCI-C/EORTC project in GBM: Exploring the Role of Adjuvant Treatment in Relation to MGMT Status



M. Mehta (RTOG)
Roger Stupp (EORTC BTG)
Sara Erridge (EORTC ROG)

Availability of tissue mandatory!

The Temozolomide RESCUE Study: a phase II trial of continuous (28/28) dose-intense temozolomide after progression on conventional 5/28 day Temozolomide in patients with recurrent malignant glioma

- Continuous dosing and dose intensification could deplete MGMT and have an antiangiogenic activity

- Continuous dose-intense TMZ 50 mg/m2 for 28 days out of 28 for up to one year

- Phase II trial, interim analysis on 60 (out of 120) patients

- GBM pts failing during the first 3-6 mo of adjuvant therapy→ PFS at 6 mo 23%

- GBM pts failing after more than 6 mo of therapy→ PFS at 6 mo 7%

- GBM pts who recurred after stopping treatment→ PFS at 6 mo 35%

- Anaplastic Glioma pts→ PFS at 6 mo 53%

Perry, ASCO 2008

Issues to resolve … before we put all our efforts (and money) on MGMT

- How often will MGMT testing be successful in tissue from surgery for recurrent GBM?
- How often will MGMT testing be successful in tissue from surgery for recurrent GBM obtained by stereotactic biopsy?
- What is the MGMT status of glioblastomas failing TMZ?
- What is the correlation between MGMT depletion in peripheral blood cells and in tumor tissue?
- Which dose dense regimen is safer?
- Which dose-dense regimen is more effective? For nonmethylated or for methylated patients?

Cost-Effectiveness of Temozolomide for the Treatment of Newly Diagnosed Glioblastoma Multiforme

A Report From the EORTC 26981/22981 NCI-C CE3 Intergroup Study

Mean Costs Before and After Progression and Difference Between Treatment Arms

	Group RT only n = 108	Group RT + TMZ n = 110	Difference RT + TMZ-RT
	Mean (SE)	Mean (SE)	Mean (SE)
Costs before progression*	5419 (273)	18,555 (615)	13,136† (677)
Discounted costs	5414 (273)	18,545 (614)	13,131† (676)
Type of costs before progression			
Radiotherapy	3670 (66)	3663 (55)	−7 (85)
TMZ concomitant + adjuvant	not applicable	11755 (521)	—
Concomitant medication	31 (3)	378 (23)	347† (24)
Imaging	497 (39)	830 (57)	333† (69)
Visits protocol-induced	465 (15)	647 (24)	182† (28)
Hospitalizations for SAE	592 (254)	746 (177)	154 (308)
Laboratory tests	163 (11)	536 (28)	373† (31)
Costs after progression*	12563 (1711)	8810 (1058)	−3753 (2004)
Discounted costs	12395 (1680)	8637 (1030)	−3758 (1962)
Type of costs after progression			
Chemotherapy	5000 (814)	2153 (648)	−2847† (1039)
Imaging	566 (61)	568 (60)	2 (86)
Visits	273 (44)	248 (37)	−25 (57)
Hospitalizations	6255 (1278)	5333 (728)	−922 (1464)
Surgery	469 (98)	508 (110)	39 (148)
Total costs*	17,982 (1735)	27,365 (1293)	9383† (2159)
Discounted costs	17,809 (1704)	27,182 (1263)	9373† (2116)

Lamers, 2008

Cost-Effectiveness of Temozolomide for the Treatment of Newly Diagnosed Glioblastoma Multiforme

A Report From the EORTC 26981/22981 NCI-C CE3 Intergroup Study

ICER and 95% Confidence Interval (Parametric Approach)

	ICER	95% CI Fieller Method
Additional costs per life-year gained (not discounted)	37,361 (37,911)	19,544–12,3616 (19,928–12,6871)
Additional costs per progression-free life-year gained (not discounted)	34,870 (35,082)	16,839–85,633 (17,123–85,691)

ICER indicates incremental cost-effectiveness ratio; CI, confidence interval.

The presented ICER of 37.000,00 € per life-year gained are comparable to accepted first line treatment with chemotherapy

..despite the high TMZ acquisition costs concomitant and adjuvant TMZ provided also significant benefits in GBM

Lamers, 2008

Health-related quality of life in patients with glioblastoma: a randomised controlled trial

Martin J B Taphoorn, Roger Stupp, Corneel Coens, David Osoba, Rolf Kortmann, Martin J van den Bent, Warren Mason, René O Mirimanoff, Brigitta G Baumert, Elizabeth Eisenhauer, Peter Forsyth, Andrew Bottomley, for the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumour Group, EORTC Radiotherapy Group, and the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)

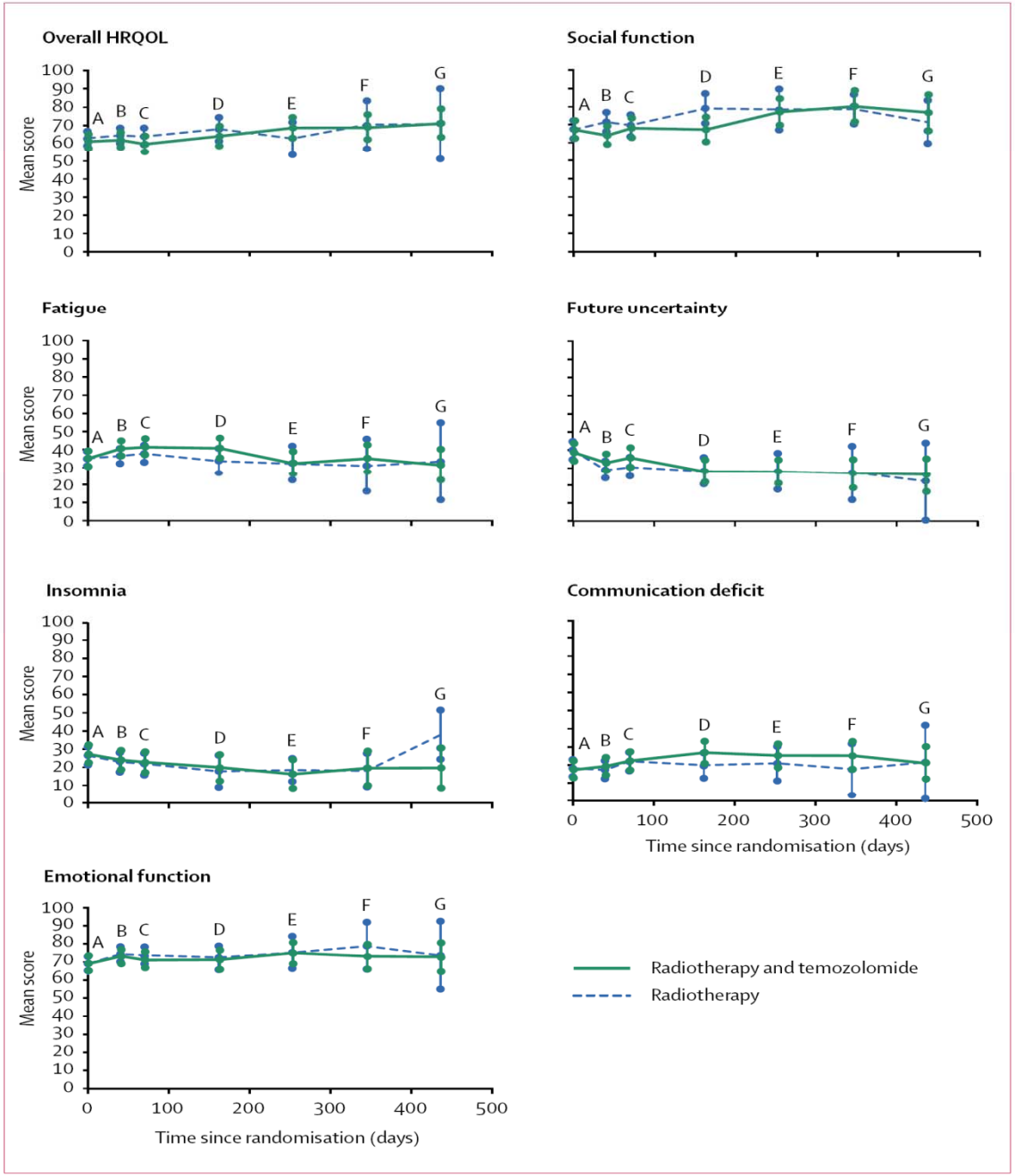
- Assessment of HRQOL at baseline, during RT at week 4, four weeks after completion of RT, at the end of the third and sixth cycle of adjuvant TMZ and every three months thereafter until PD using the EORTC quality of life questionnaire core-30 (QLQ-C30) and the EORTC brain cancer module (EORTC BN-20)

- Selection of 7 scales for primary analyses (fatigue, overall HRQOL, social function, emotional function, future uncertainty, insomnia and communication deficit)

	Radiotherapy (n=248)	Radiotherapy and temozolomide (n=242)	p	Controls*	
				Men	Women
Overall HRQOL	62·8 (1·4)	61·9 (1·5)	0·42	78·1 (21·3)	74·7 (22·2)
Fatigue	35·3 (1·6)	35·2 (1·6)	0·94	18·7 (20·7)	23·4 (22·4)
Social function	67·5 (1·9)	67·4 (1·9)	0·97	91·3 (19·3)	90·4 (19·6)
Emotional function	69·3 (1·5)	69·3 (1·5)	0·98	84·0 (19·8)	78·3 (21·9)
Future uncertainty	40·1 (1·8)	39·0 (1·8)	0·66	NA	NA
Insomnia	26·4 (1·9)	27·4 (2·1)	0·70	14·0 (24·9)	20·3 (27·5)
Communication deficit	18·6 (1·8)	17·9 (1·8)	0·79	NA	NA

Data are mean (SD). NA=not available. *Reference population.[24]

Table 3: **Mean baseline HRQOL scores by treatment group**

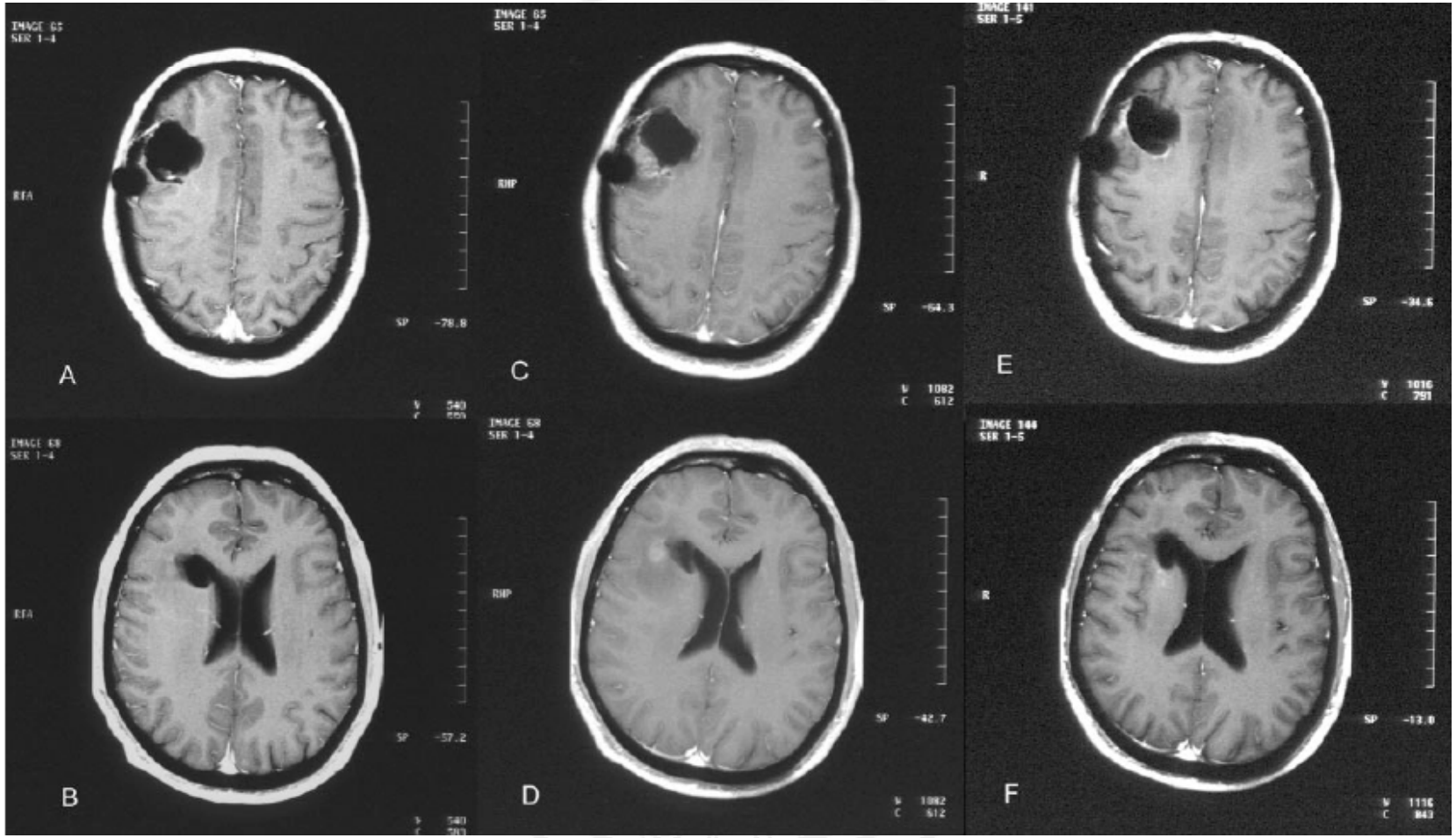


RT alone or in combination with TMZ might have no major side-effects; addition of temozolomide during and after radiotherapy for patients with newly diagnosed glioblastoma significantly improved survival without a negative effect on HRQOL

Progression or “Radiation Necrosis”?

Early Treatment-Related Neuroradiologic Findings Following Concomitant Radiotherapy and Temozolomide

Early post-RT changes may mimic tumor progression



De Wit, et al, Neurology, 2004

Studies on psPD in GBM patients treated with concurrent chemoradiation

Study	No.of pts	% of psPD	MGMT promoter status
Chamberlain, 2006	65	46.7*	Not reported
Jefferies, 2007	15	20	Not reported
Taal, 2007	85	21	Not reported
Brandes, 2008	103	31	Reported

* Calculated in pts undergoing resection for images of lesion enlargment

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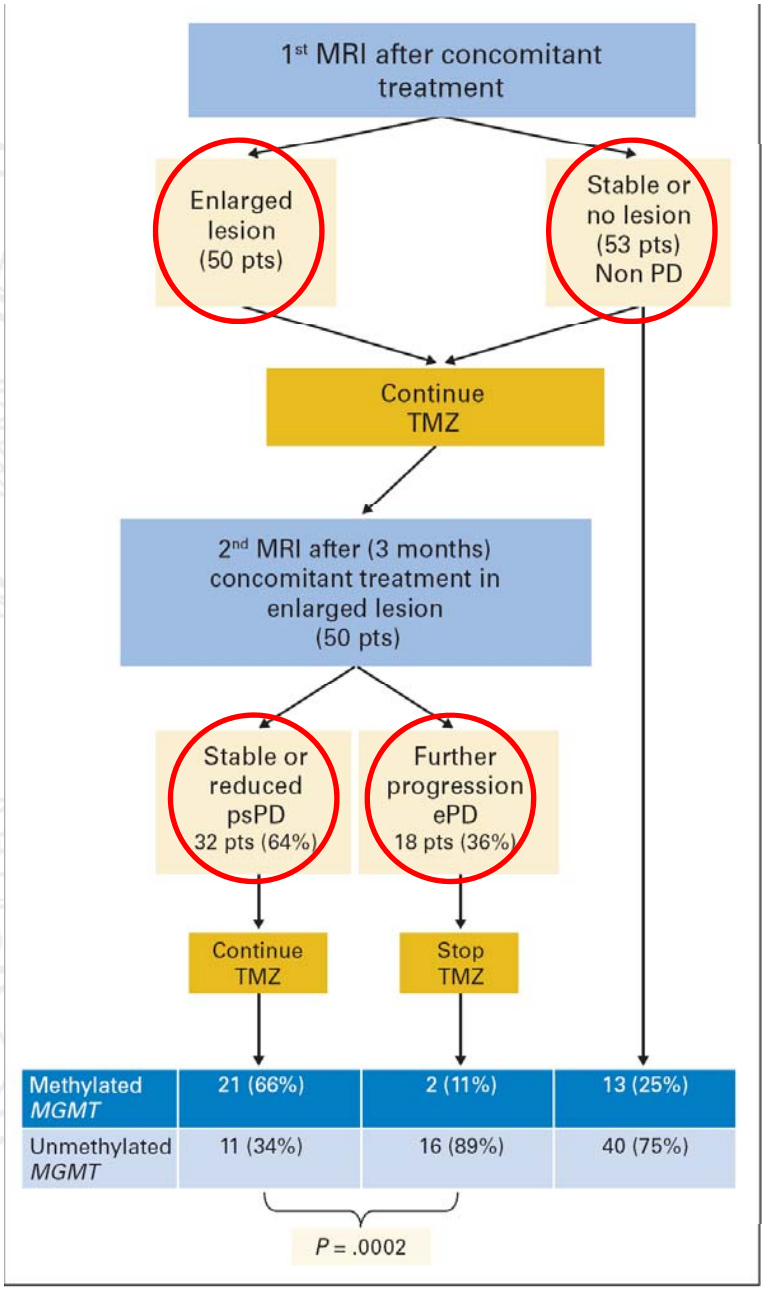
MGMT Promoter Methylation Status Can Predict the Incidence and Outcome of Pseudoprogression After Concomitant Radiochemotherapy in Newly Diagnosed Glioblastoma Patients

Alba A. Brandes, Enrico Franceschi, Alicia Tosoni, Valeria Blatt, Annalisa Pession, Giovanni Tallini, Roberta Bertorelle, Stefania Bartolini, Fabio Calbucci, Alvaro Andreoli, Giampiero Frezza, Marco Leonardi, Federica Spagnolli, and Mario Ermani

- 208 pts with GBM treated with concurrent RT-TMZ followed by 12 cycles of maintenance chemotherapy

- An analysis was made of 103 pts for whom MGMT promoter methylation status was assessable



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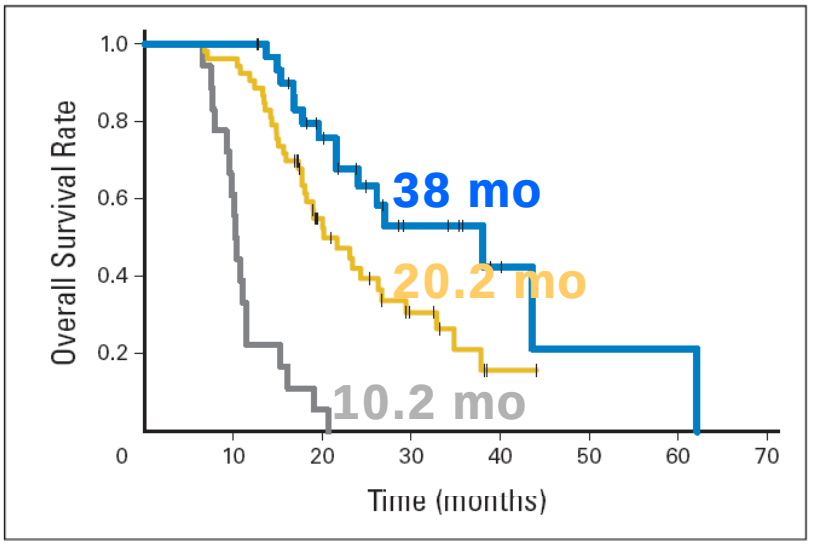
Effects of *MGMT* Promoter Methylation Status and First MRI Findings

Characteristic	TTP (months)		OS (months)	
MGMT promoter status				
Median		11.7		20.7
Methylated	P<0.0001	21.9*	P<0.0001	43.6*
Unmethylated		9.2		16.8
MRI findings				
psPD		20.7*		38*
ePD	P=0.001	5.7	P<0.0001	10.2
No PD images		11.4		20.2



Patients with pseudoprogression

Patients with early disease progression

Patients with LC

New Studies in GBM

More questions

Associazione Italiana Radioterapia Oncologica
Gruppo di Lavoro Neoplasie Cerebrali

Combining Hypofractionation with Dose escalation in High Grade Gliomas (RPA classes III and IV): Simultaneous Integrated Boost.

AIM

- Primary aims: safety, patterns of failure
- Secondary aims: OS, PFS

Associazione Italiana Radioterapia Oncologica
Gruppo di Lavoro Neoplasie Cerebrali

Simultaneous Integrated Boost (SIB) in HGG

Volume		Total dose	Dose per fraction	Fr.	Equiv D @ 2 Gy	BED (α/β= 10)
CTV_{HD}	Contrast enhanced lesion	67,5	4,5	15	81,6	97,8
CTV_{LD}	Perilesional edema	52,5	3,5	15	59,1	70,8
Standard 3dCRT		60	2	30	60	72

Higher dose Volume= CTV_{HD}	Contrast enhanced lesion on preoperative T1 weighted images
Lower dose Volume=CTV_{LD}	Perilesional edema on preoperative T2 weighted images

New Studies in GBM – more questions

What to do with poor prognosis patients?

- Elderly
- Poor performance status

– Hypofractionated RT (40Gy/15fr) as effective as standard schedule of 60 Gy

– Increasing role for temozolomide in this population

Anaplastic Astrocytoma/Anaplastic Oligodendroglioma/Glioblastoma Multiforme[a]

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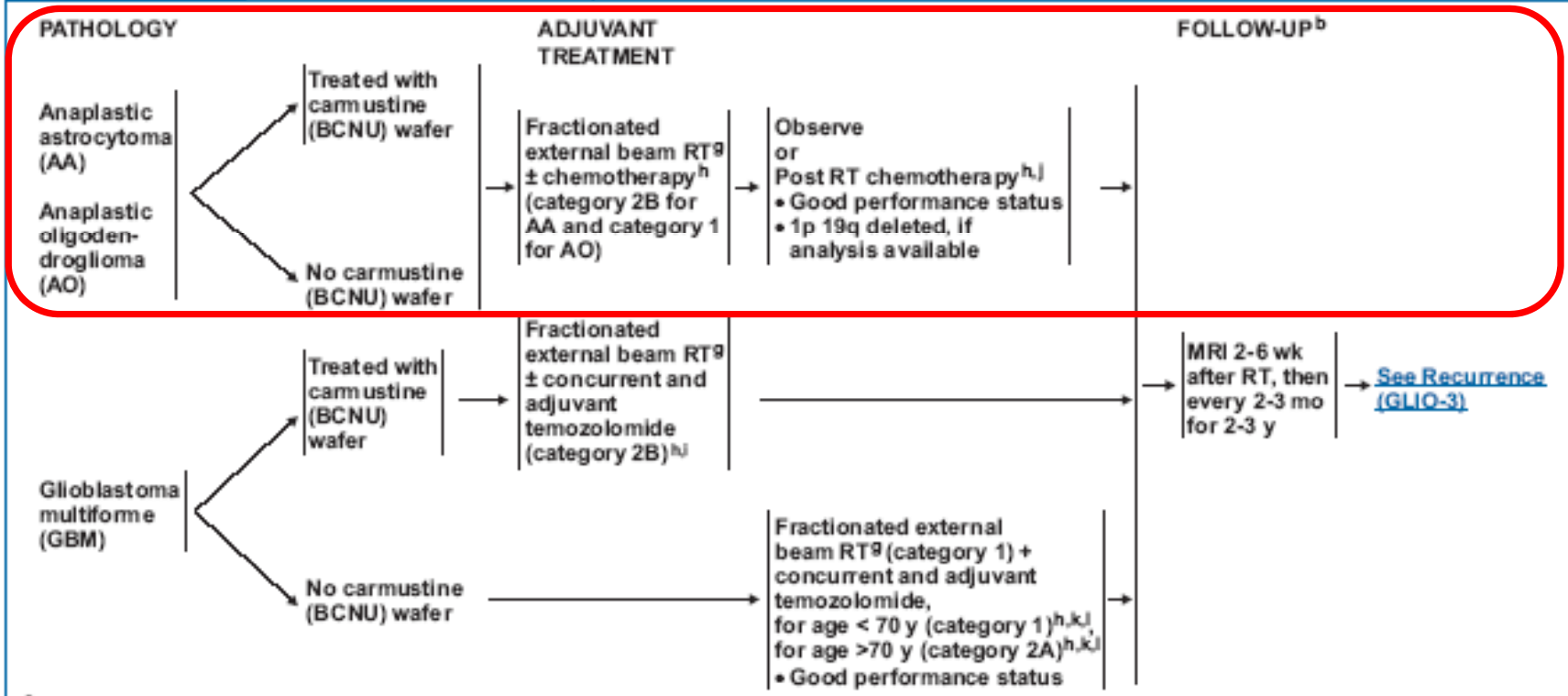

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[j] For AO, randomized studies show that adjuvant PCV (lomustine + procarbazine + vincristine) chemotherapy prolonged PFS (category 1). (Cairncross G, Berkey B, Shaw E, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol 2006;24(18):2707-2714 and van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organization for Research and Treatment of Cancer phase III trial. J Clin Oncol 2006;24(18):2715-2722.)

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

The Treatment of Anaplastic Glioma after EORTC 26981/NCI-C CE3, EORTC 26951 & RTOG 94-02

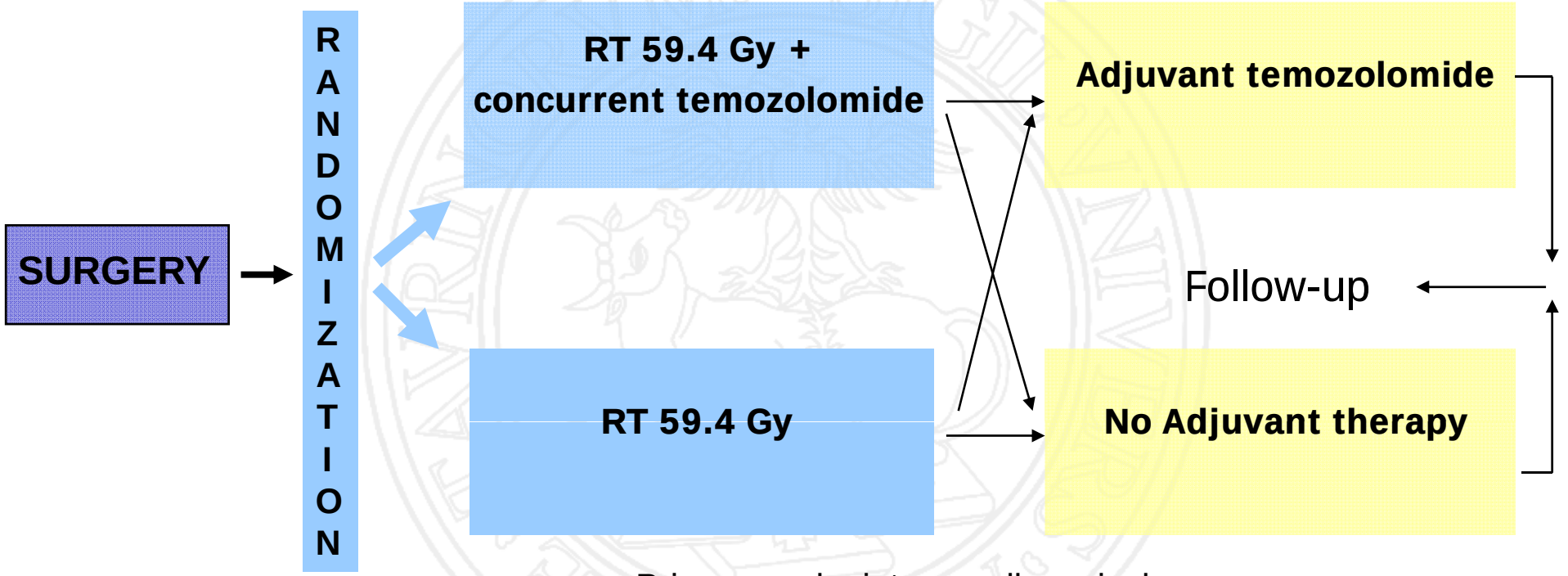
- RT with concurrent and adjuvant temozolomide is standard of care for GBM
- What do the trial results imply for the treatment of anaplastic glioma?
  - Should these patients also receive concurrent & adjuvant TMZ?
- How did trials on anaplastic oligodendroglioma affect standard of care?
  - Neither trial showed overall survival benefit of adjuvant PCV

Question To Be Answered

Does RT/TMZ provide a superior outcome in anaplastic glioma?

- Is it the concomitant part?
- Is it the adjuvant part?

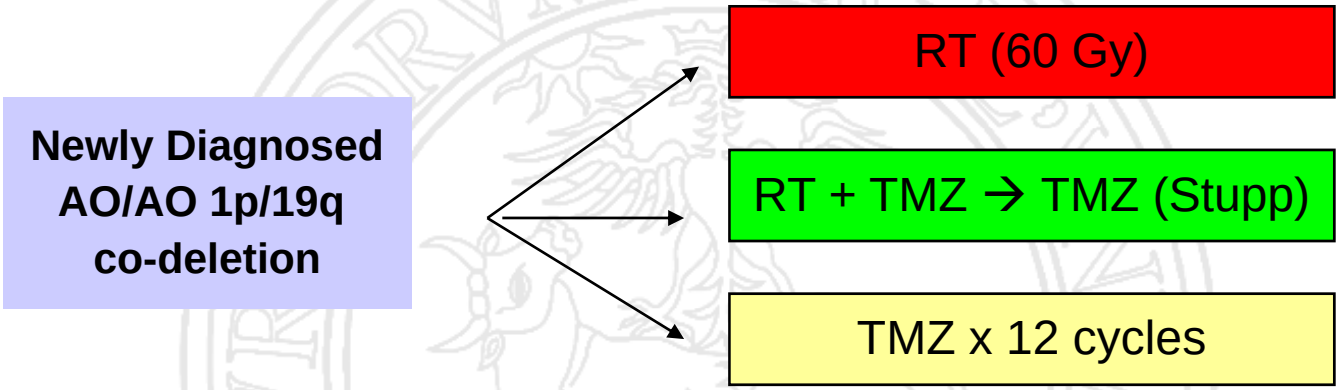
EORTC/NCI-C/RTOG study on Anaplastic Gliomas without 1p/19q loss: 2 x 2 design



- Pre-study 1p/19q testing
- Stratification:
  - Methylation status

- Primary endpoint: overall survival
- Secondary endpoints:
  - Progression-free survival
  - Quality of life
  - Neurological deterioration free survival

NCCTG NO577: Phase III Anaplastic Oligo with 1p/19q LOH



Traslational correlates

- 1p/19 traslocation
- MGMT promoter methylation
- QoL/neurocognition

Primary endpoint:
OS

Mechanisms of chemoresistance in HGGs
Future challenges

The identification of patients candidated to respond to CT by means of molecular markers (LOH1p and 19q, MGMT promoter methylation), basing on the results in anaplastic oligodendroglial tumors and glioblastomas