Current Therapeutic Options in Glioblastoma: Progress or *Status Quo*?

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Current Standard of Care for Newly Diagnosed Glioblastoma

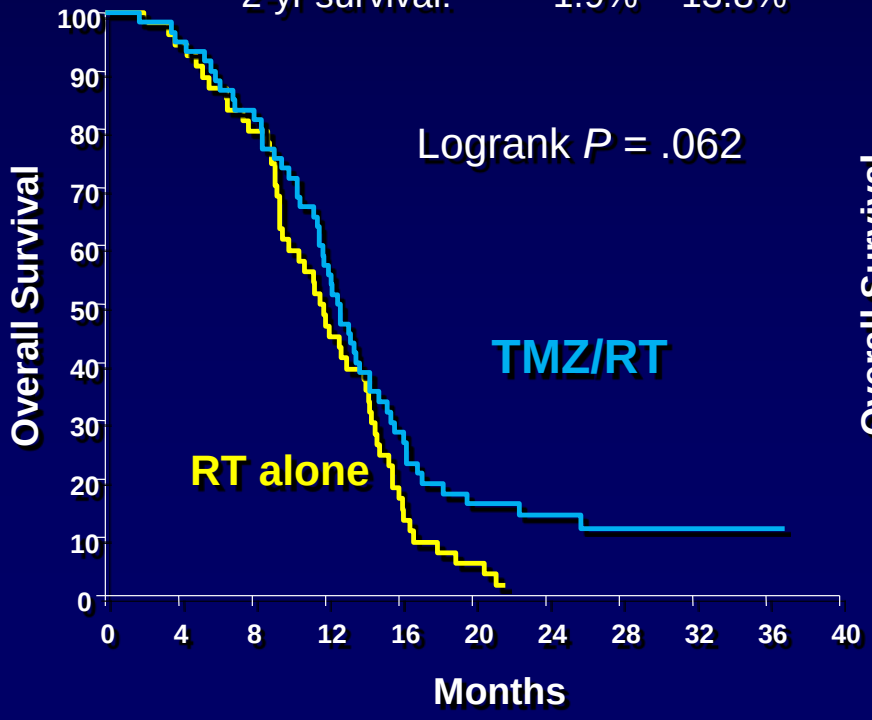
- **Maximal safe resection**
  - **No ‘level 1’ evidence**
  - **But strong supporting evidence from recent randomized controlled trials as a significant prognostic factor for OS**
  - **Allows sufficient tissue for molecular diagnostics, screening for clinical trials**
  - **Aided by advances in imaging, surgical neuronavigation, 5- ALA**

Approach to Newly Diagnosed Glioblastoma

- **Maximal safe resection**
- **60 Gy RT + concomitant/adjuvant temozolomide for appropriate patients**

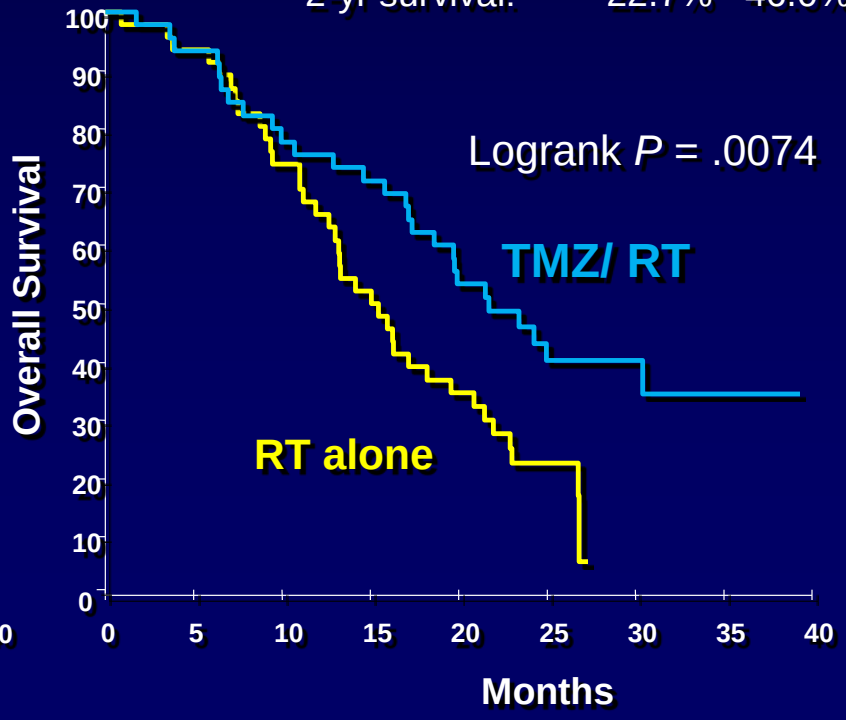
Unmethylated *MGMT*

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



Methylated *MGMT*

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



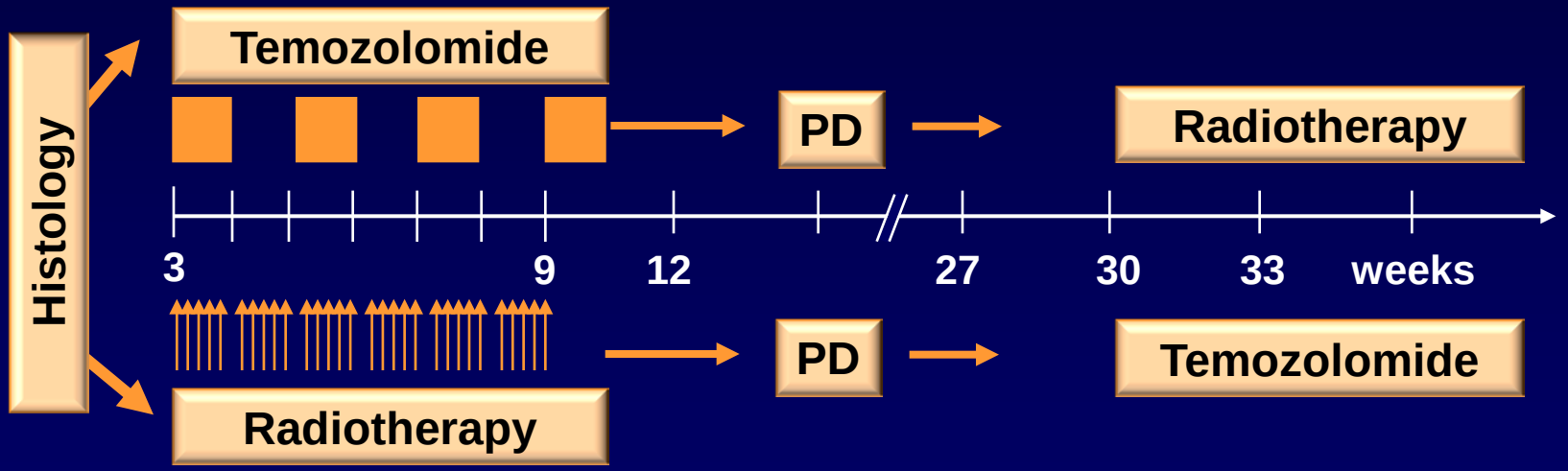
Hegi ME, et al. *N Engl J Med.* 2005;352(10):997-1003.

Radiation and Concurrent Temozolomide

- Patient selection issues for newly diagnosed patients
  - Unmethylated patients
  - Poor PS
  - Multifocal large burden of disease
  - Elderly patients
- Therapeutic issues
  - duration of adjuvant chemotherapy
  - dose/schedule of temozolomide
  - pseudoprogression

NOA-08/Methvsalem

- **Temozolomide (*one week on/one week off*) vs radiotherapy in the primary treatment of anaplastic astrocytoma and glioblastoma in elderly patients: a randomized phase III-study**



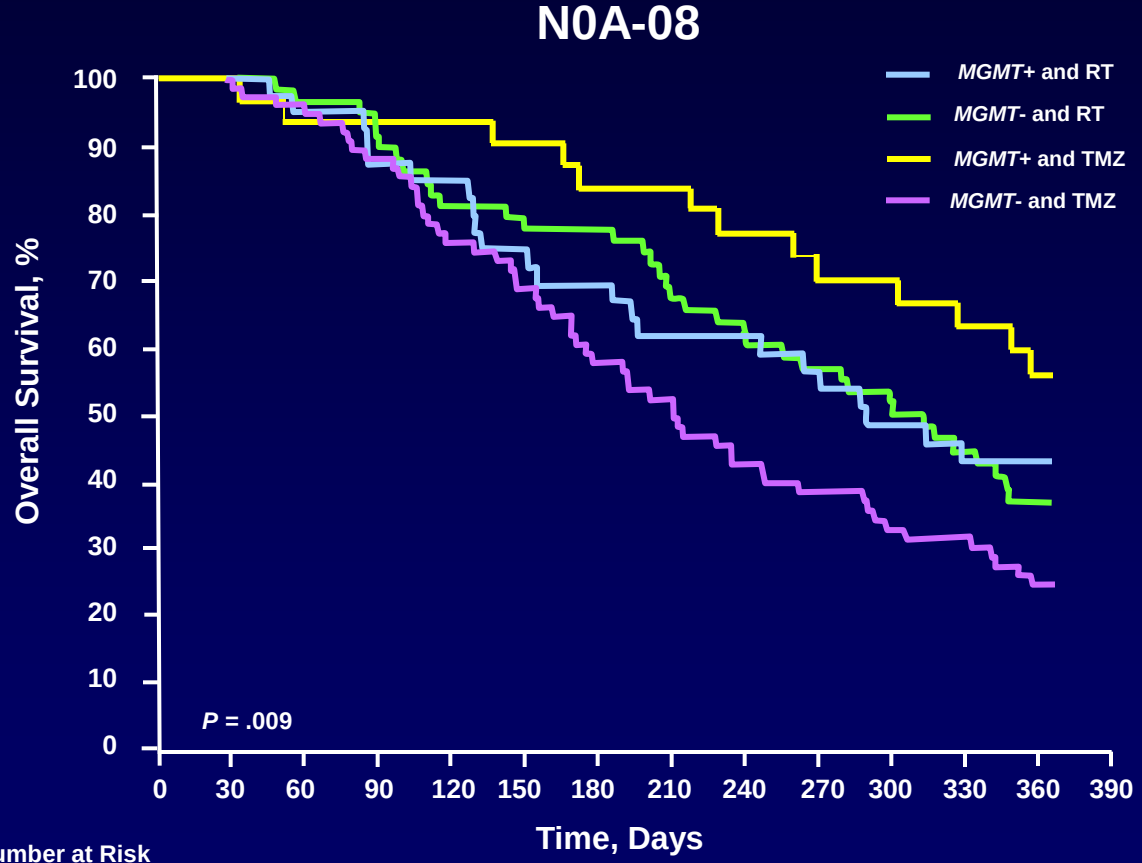
TMZ 100 mg/m^2 po/day for 7 days every 14 days until failure of therapy, to be adjusted in 25-mg steps

Focal radiotherapy daily — 30 x 1.8-2 Gy to a total 54–60 Gy

Deutsche Krebsgesellschaft e.V.
Gütesiegel A

Wick W, et al. *J Clin Oncol.* 2010;28(18s): Abstract LBA2001; Wick W, et al. *Lancet Oncol.* 2012;13(7):707-715.

NOA-08/Methvsalem: Overall Survival According to *MGMT*-Status and Treatment



Number at Risk

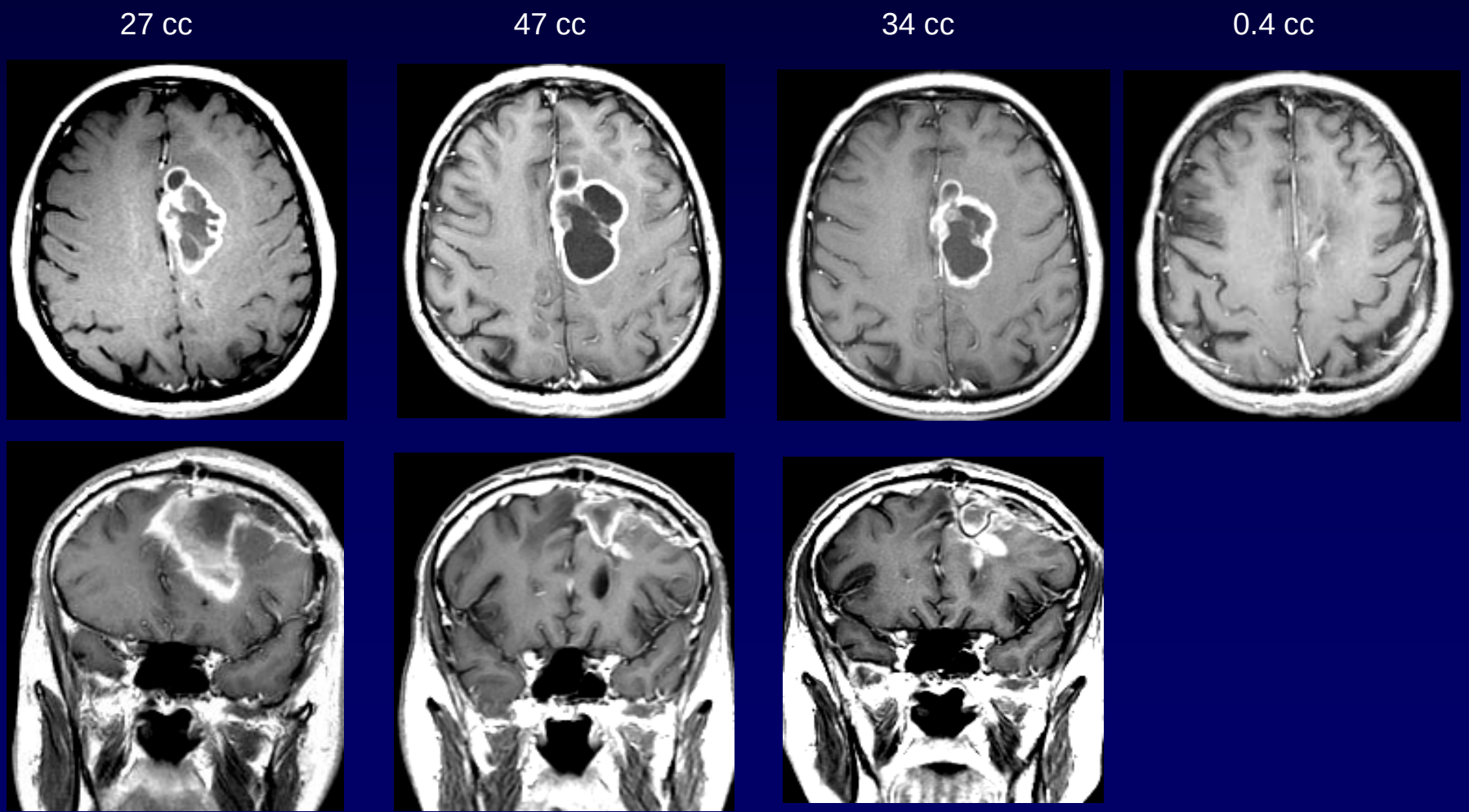
RT														
MGMT +	42	41	39	34	33	29	27	24	24	20	18	16	16	15
MGMT –	59	59	56	52	47	45	45	39	35	33	29	24	19	18
TMZ														
MGMT+	31	31	29	29	29	28	25	25	22	20	20	18	16	15
MGMT-	77	76	73	66	55	50	42	37	31	28	24	23	18	17

Wick W, et al. *Lancet Oncol.* 2012;13(7):707-715.

Issues With Adjuvant Chemotherapy

- Standard of care = 6 months
- No benefit in either m*MGMT* or un*MGMT* with dose-dense TMZ (21/28 days, RTOG 0525)
- Many practitioners extend to 12 months or even until progression, but no evidence to support this
- Pseudoprogression can occur within the first 2 cycles of adjuvant TMZ, and even for up to 6 months or more

Pseudoprogression



"Pseudoprogression"

- **Detection of increased enhancement/edema following completion of chemoradiation**
  - **Seen in the past, even with conventional RT alone, but especially with brachytherapy and intracavitary treatment**
- **MRI at 4 wks post-RT/TMZ:**
  - ***up to 30%-50% of patients have PD by conventional criteria***
  - ***half of these are asymptomatic***
  - ***Of these, <u>up to half have resolution</u> of these changes over several months***
- **This may be more common in *MGMT*-positive pts [Brandes AA, et al. *J Clin Oncol.* 2008;26(13):2192-2197.]**
- **But no difference in rate of pseudoprogression in the AVAglio trial (unmethylated vs methylated) [Wick W, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 2002.]**
- **Thus far advanced MRI techniques, perfusion imaging, metabolic imaging not reliable enough for routine use….unmet need.**

Options for Recurrent Glioblastoma

- Re-resection
  - -to confirm presence of active disease
- Re-irradiation increasingly considered
- Systemic chemotherapy
  - TMZ rechallenge
  - Lomustine
  - Others not commonly used such as PCV, etoposide
  - No good controlled trials in the TMZ era
- VEGF-targeted therapy: bevacizumab +/- chemotherapy
- No biomarkers to assist with patient selection

Systemic Therapy Options for Recurrent Glioblastoma: The Evidence

- **2nd-line systemic therapies:**
  - **No clear standard of care**
  - **Goals of care: preservation of function, extend survival, minimize toxicities**
    - **Stable disease (SD) is a desirable outcome**
    - **6-mo PFS is the current gold standard used in neuro-oncology to judge efficacy of new agents. Standard for regulatory approval**
  - **TMZ was previously used for patients who recurred after RT-alone (pre-Stupp 2005)**
    - **5% response rate on imaging, 15% 6-mo PFS**
- **Very few studies post-2005**
  - **Lomustine (CCNU): 19% 6-mo PFS, median OS 6.1 mo**
  - **Daily temozolomide: 24% 6-mo PFS, median OS 10 mo**
  - **Bevacizumab: 30%-50% 6-mo PFS, median OS 9 mo**

Surgery, RT/TMZ: We're Now a Decade Later….Have We Improved?

- No benefit to date seen in RT/TMZ + "x" studies
- No noteworthy agents in unmethylated newly diagnosed GBM using RT + "x": huge unmet need. 60% of patients
- The recent mass funeral of upfront approaches:
  - RTOG 0525
  - RTOG 0825 (bevacizumab)
  - Avaglio (bevacizumab)
  - CENTRIC (cilengitide, integrin inhibitor, mMGMT)
  - CORE (cilengitide, uMGMT)

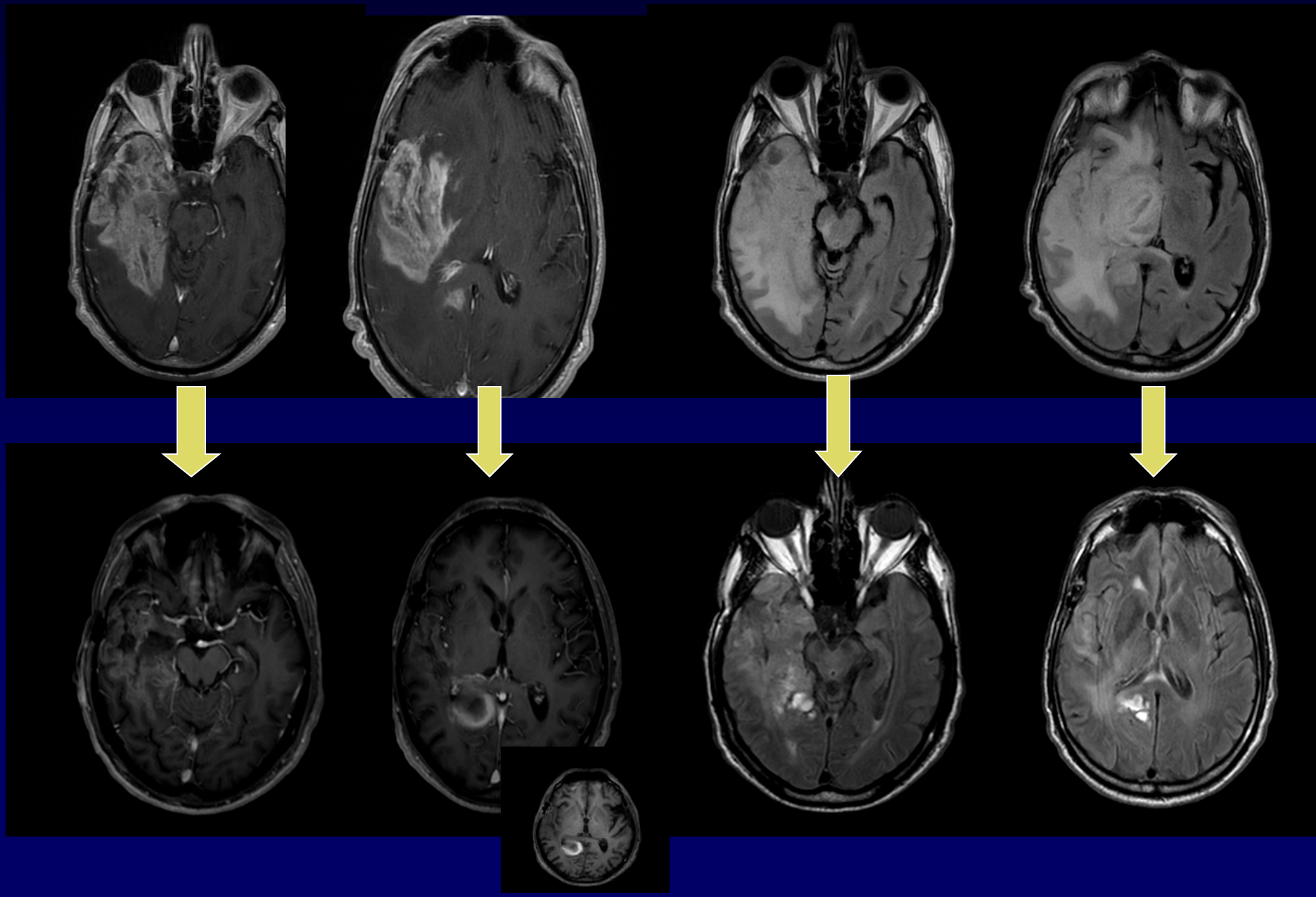
Why These Failures and Others

- **We don’t often know if the drug reaches its theoretical target and, even if it does, does it cause the anticipated downstream effect?**
- **Beyond *MGMT*, no biomarkers are helpful in GBM**
- **Not enough enriched trials**
- **Not enough trials with surgery after drug exposure**
- **Not enough trials of rationale combinations**

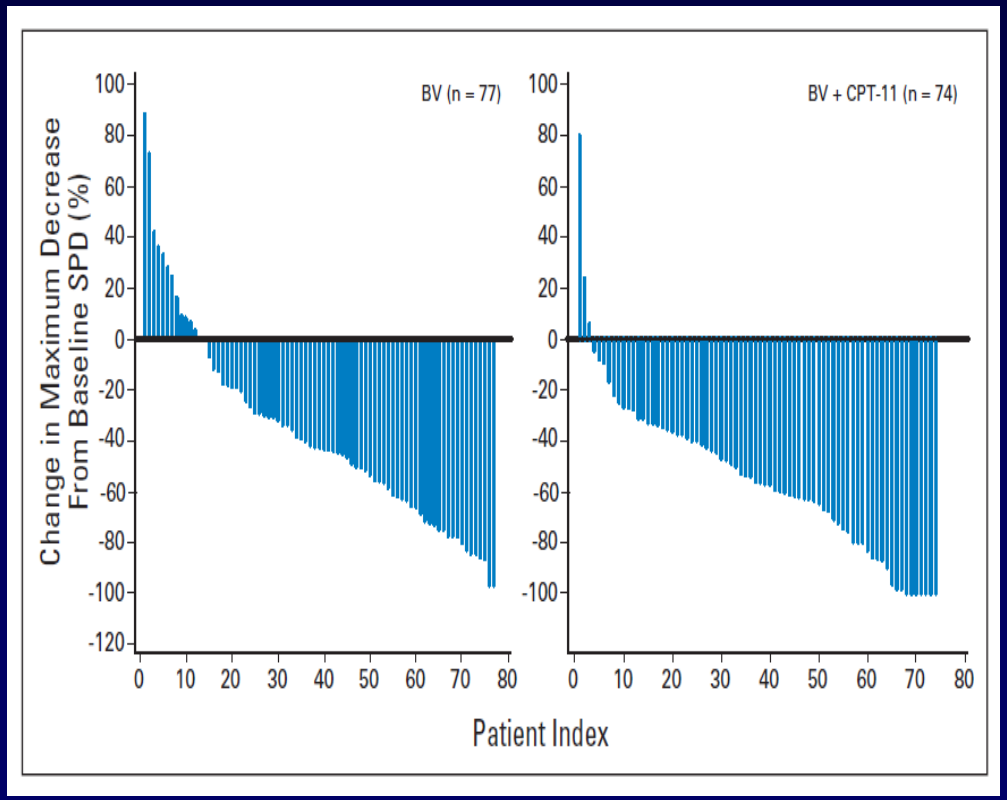
The Emergence of Bevacizumab in Neuro-oncology

- **Strong biological rationale**
  - **humanized anti-VEGF monoclonal Ab**
  - **strong VEGF upregulation and expression**
  - **VEGF drives robust angiogenesis**
- **Development in GBM delayed: fears of thrombosis and bleeding (especially ICH)**
- **2 uncontrolled trials:**
  - **Unprecedented response rates and 6-mo PFS**
- **But 2 very discouraging RCTs in newly diagnosed patients. Some PFS benefit, but conflicting data on QoL, neurocognition**

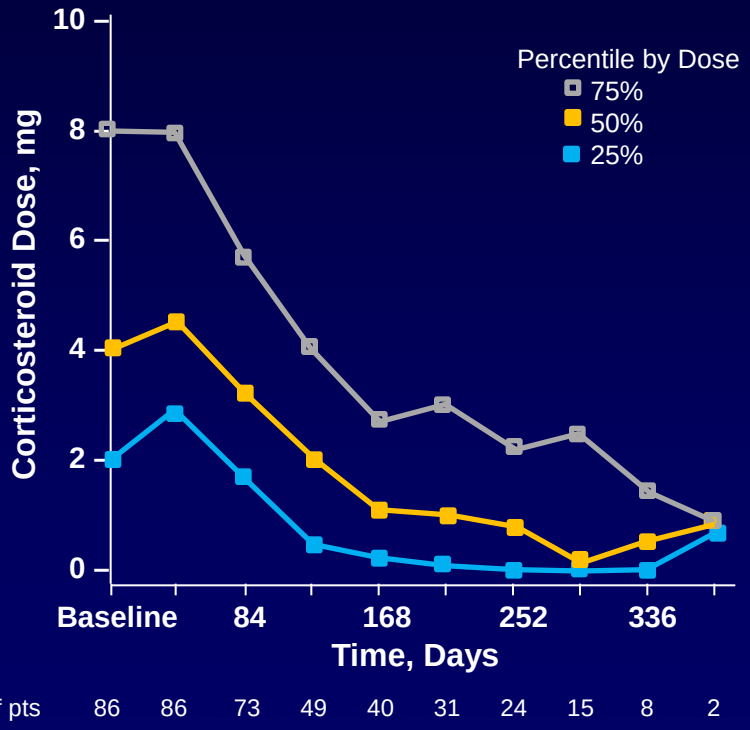
Response to 2 Doses of Bevacizumab, MRI Scans 4 Weeks Apart



Bevacizumab – Response Rate and Reductions in Dexamethasone Use



Change in Corticosteroid Dose Across Time



42-day averages of corticosteroid dose were calculated for each patient for whom data were available from baseline until disease progression or final study dose, whichever occurred first. The median (ie, 50th-percentile), 25th-percentile, and 75th-percentile doses are shown for each timepoint. The number of patients included in the analysis at each timepoint is noted below the x-axis.

Friedman HS, et al. *J Clin Oncol.* 2009;27(28):4733-4740.

Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial

Walter Taal, Hendrika M Oosterkamp, Annemiek M E Walenkamp*, Hendrikus J Dubbink*, Laurens V Beerepoot, Monique C J Hanse, Jan Buter, Aafke H Honkoop, Dolf Boerman, Filip Y F de Vos, Winand N M Dinjens, Roelien H Enting, Martin J B Taphoorn, Franchette W P J van den Berkmortel, Rob L H Jansen, Dieta Brandsma, Jacoline E C Bromberg, Irene van Heuvel, René M Vernhout, Bronno van der Holt, Martin J van den Bent*

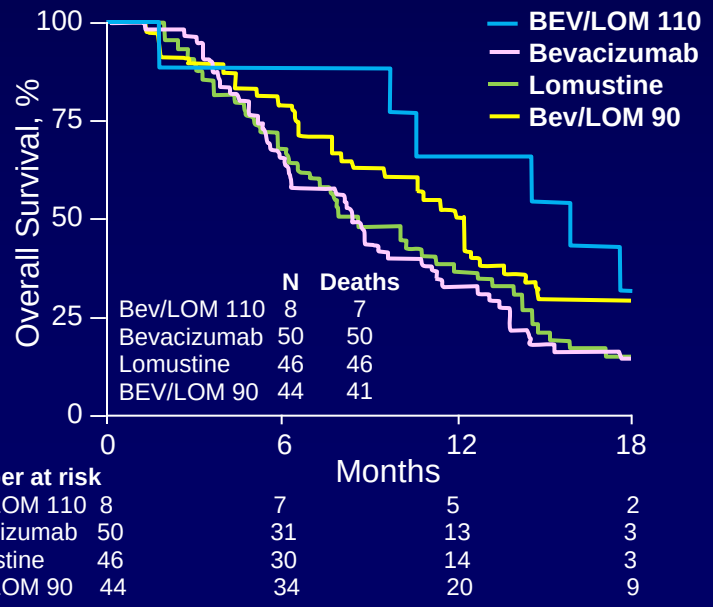
Summary

Background Treatment options for recurrent glioblastoma are scarce, with second-line chemotherapy showing only

Lancet Oncol 2014; 15: 943–53

	Bevacizumab n = 50	Lomustine n = 46	BEV/LOM 110 n = 8	BEV/LOM 90 n = 44	BEV/LOM All n = 52
Objective response rate	18/48 (38%, 24-53)	2/41 (5%, 1-17)	5/8 (63%, 24-91)	14/41 (34%, 20-51)	19/49 (39%, 25-54)
Median PFS, months	3 (3-4)	1 (1-3)	11 (1-27)	4 (3-8)	4 (3-8)
6-month PFS	16% (7-27)	13% (5-24)	50% (15-77)	41% (26-55)	42% (29-55)
Median OS, Months	8 (6-9)	8 (6-11)	16 (2-34)	11 (8-12)	12 (8-13)
12-month OS	26% (15-39)	30% (18-44)	63% (23-86)	45% (30-59)	48% (34-61)

Data are n/n evaluable (%, 95% CI), or % (95% CI). BEV/LOM 110 = bevacizumab plus lomustine 110 mg/m^2. BEV/LOM 90 = bevacizumab plus lomustine 90 mg/m^2. BEV/LOM ALL = all patients who received combination treatment of bevacizumab plus lomustine. Evaluable = number of patients evaluable for objective response.



Taal W, et al. *Lancet Oncol.* 2014;15(9):943-953.

So, What Are the Major Unmet Needs for Glioblastoma Therapy in 2014?

- Better therapies!
- In particular for unMGMT GBM
- Novel imaging to detect treatment effects versus disease progression
- Biomarkers: prognostic and predictive, especially for bevacizumab at present
- Better designed clinical trials: are drugs reaching their targets, combinations