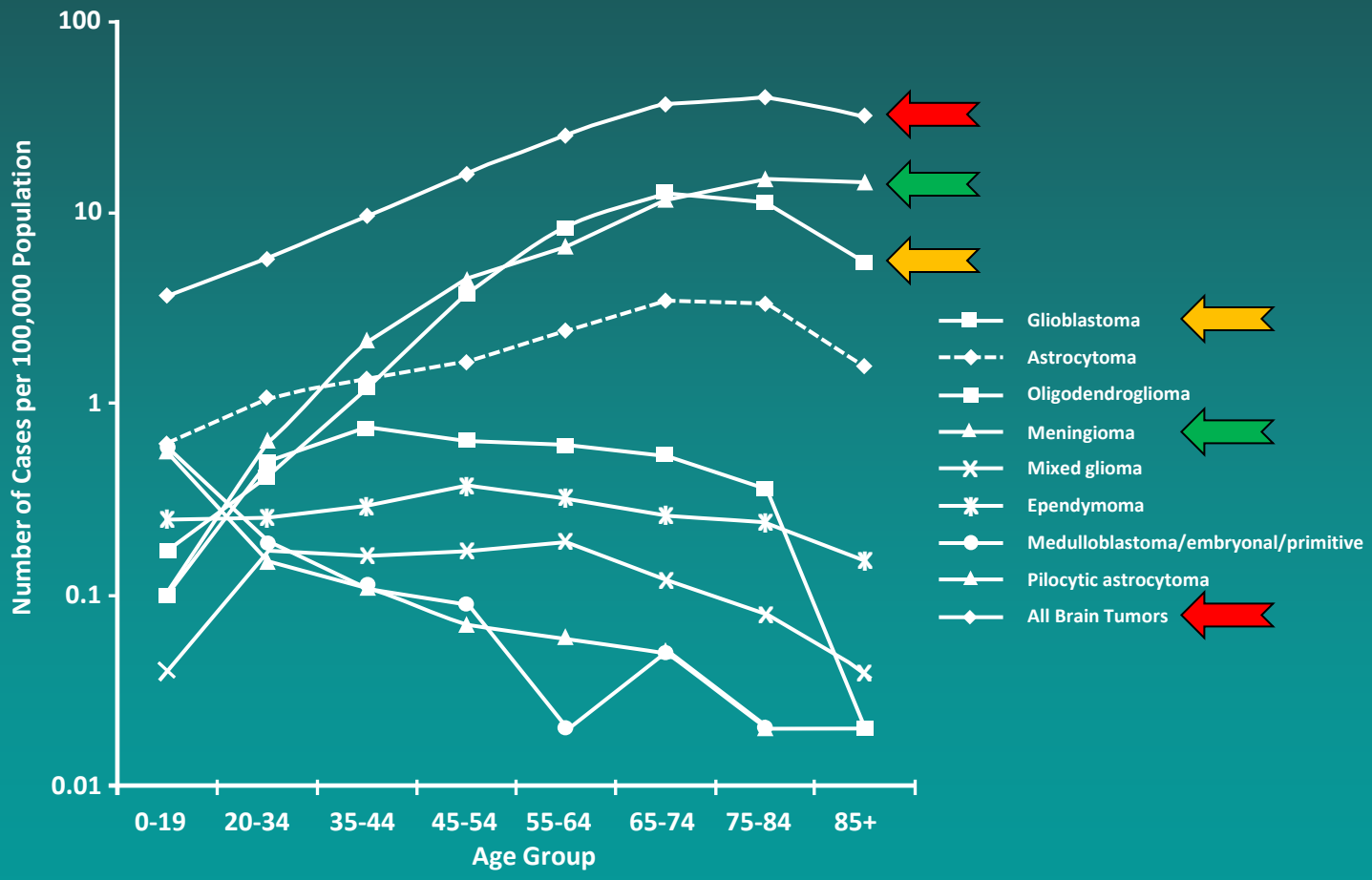
GLIOBLASTOMA: IMPROVED OUTCOMES URGENTLY NEEDED

prIME oncology

Contemporary Management of Glioblastoma

Incidence Rates of Primary Brain Tumors

Central Brain Tumor Registry of the United States, 1992-1997



Wrensch M, et al. *Neuro Oncol*. 2002;4(4):278-299.

WHO Classification

- GRADE I - "BENIGN" or low-grade
- GRADE II - "BENIGN" or low-grade (more diffuse)
- GRADE III - ANAPLASTIC (cellular atypia, etc)
- GRADE IV - MALIGNANT (necrosis, vascularity, mitoses)

Louis DN, et al. *Acta Neuropathol*. 2007;114(2):97-109.

High-Grade Malignant Gliomas

- Fibrillary astrocytomas
  - Glioblastoma (WHO grade IV)
  - *Giant-cell glioblastoma
  - Anaplastic astrocytomas (WHO grade III)
  - **Gemistocytic astrocytomas
- Oligodendrogliomas
  - Anaplastic oligodendrogliomas (or Smith classification grade C or D)
- Mixed anaplastic oligoastrocytomas
- Anaplastic mixed gangliogliomas (mixed neuronal-glial tumors)

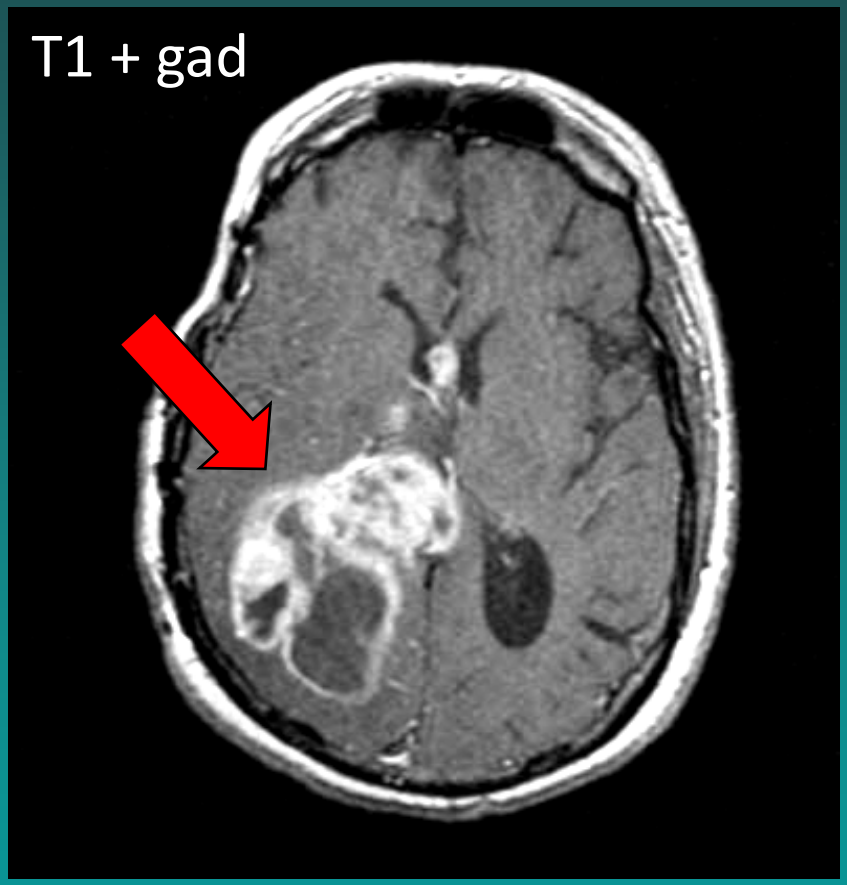
*Giant-cell glioblastoma = slower progression rate; **gemistocytic astrocytomas = grade II but acts like grade III

Stupp R, et al. *Ann Oncol*. 2010;21(Suppl.5):v190-193.

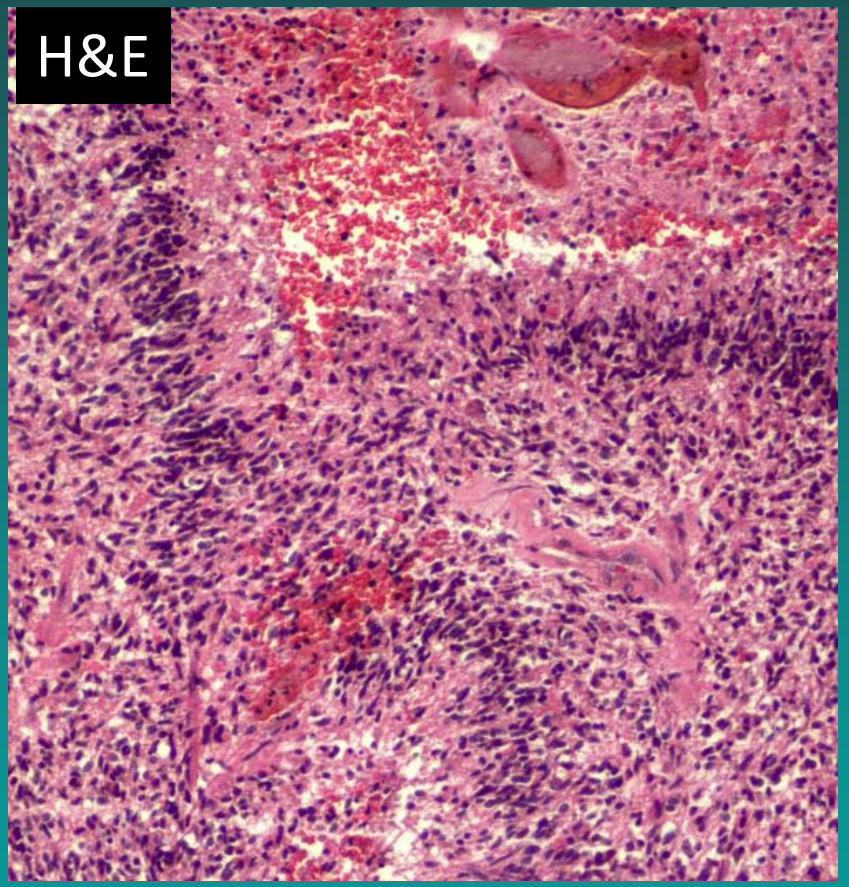
Why Is It So Difficult to Treat Malignant Gliomas?

- Multiple disordered pathways (ie, AKT, IGF, HGF, etc)
- Multiple mutated targets (ie, EGF, PDGF, VEGF, etc)
- Poor disease biomarker
- Blood brain barrier
- Limited therapeutic window
  (Central nervous system is very sensitive to insults)
- Rapid development of resistant disease

Glioblastoma (WHO IV)

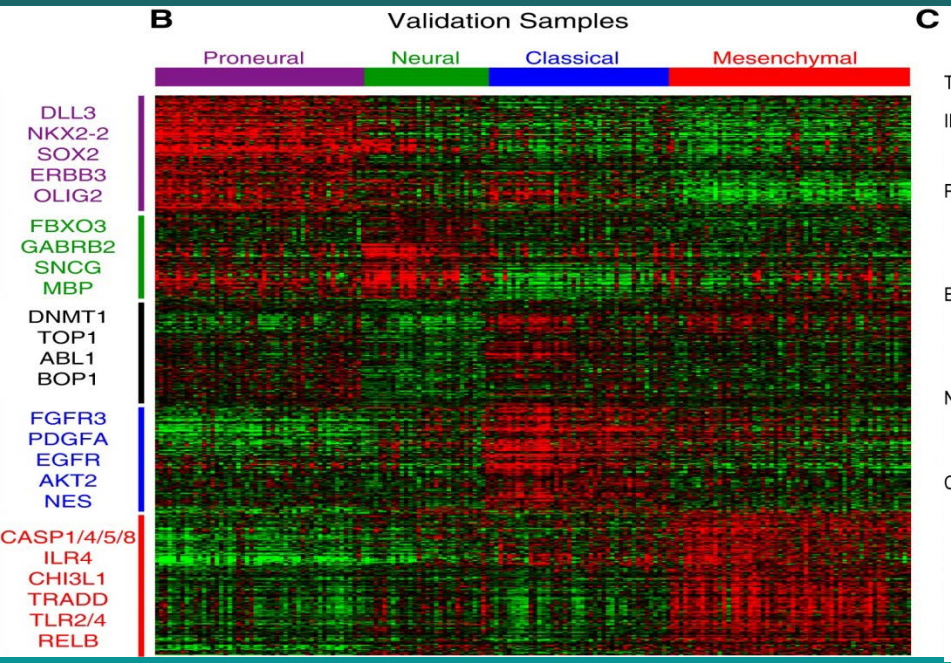


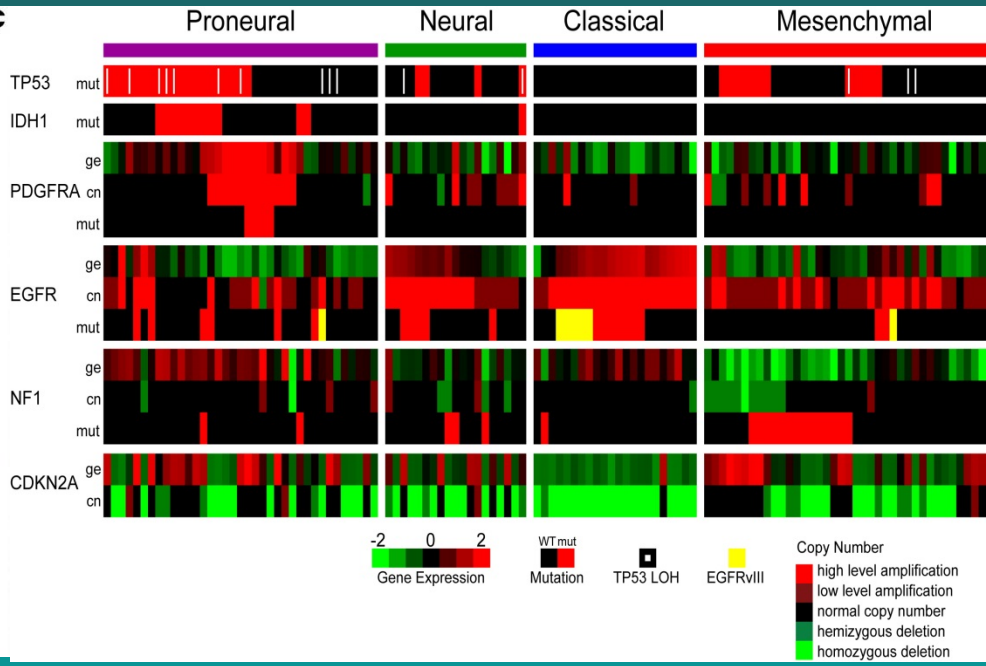
Enhancing cystic with necrosis



Enhancing cystic with necrosis
cellular, vessels, necrosis, MIB-1

At Least Four Molecular Subtypes of Glioblastomas (Secondary Glioblastomas Have Proneural Profile)



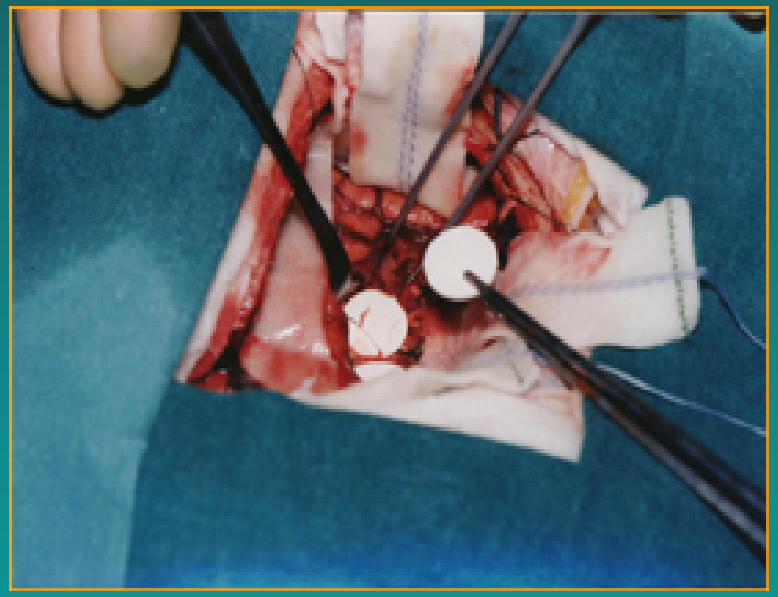


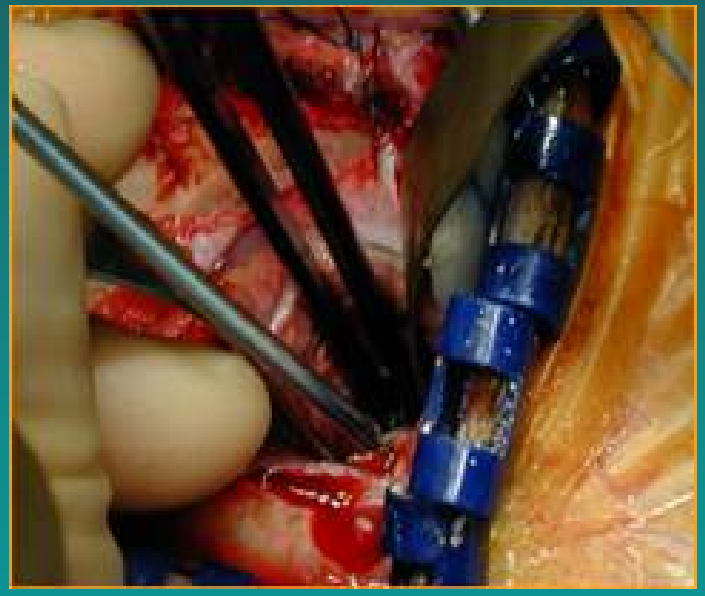
Verhaak RG, et al. *Cancer Cell.* 2010;17(1):98-110.

FDA-Approved Treatments for Malignant Glioma

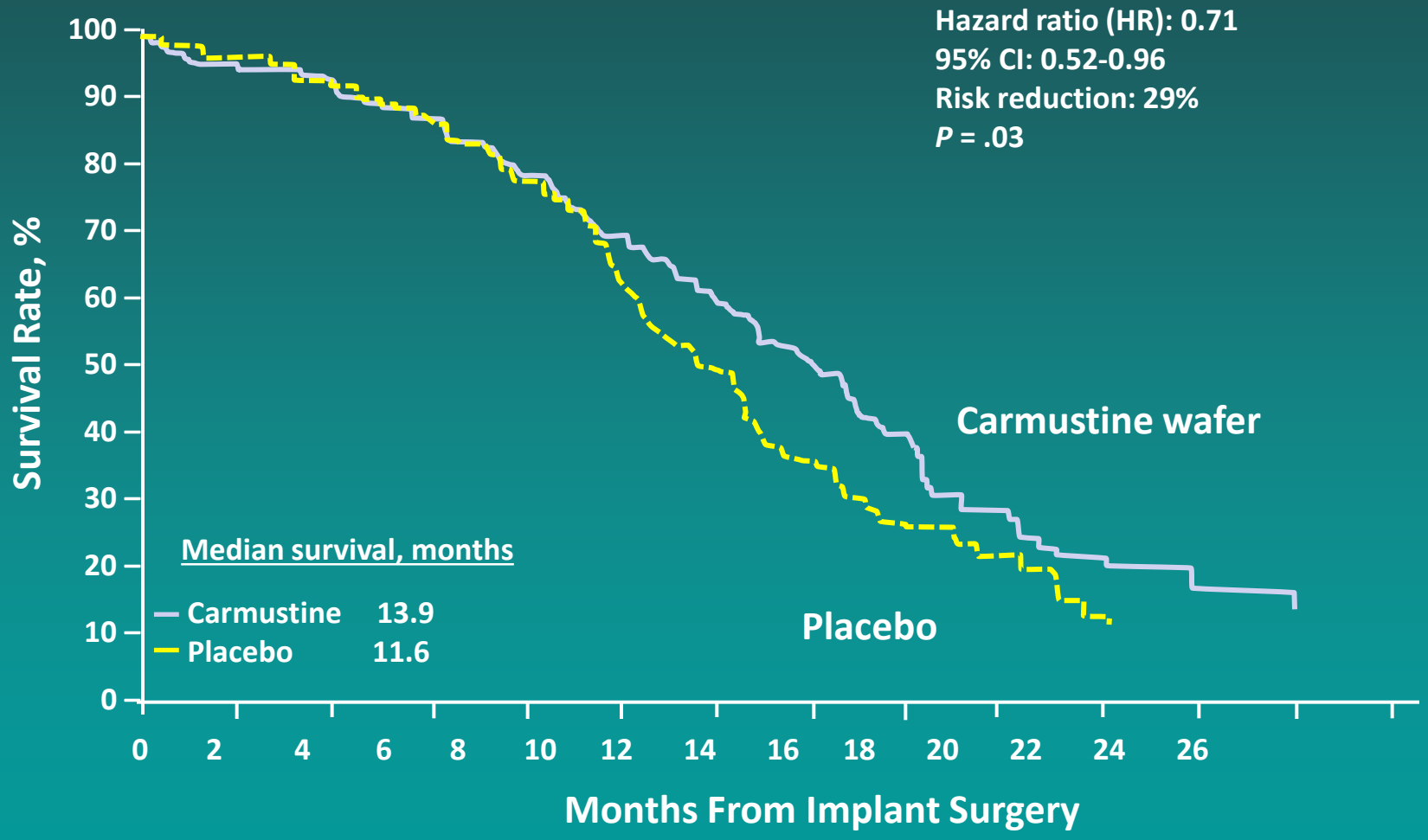
- June 14, 1996: Carmustine wafer for recurrent glioblastoma
- January 12, 1999: Temozolomide (TMZ) for anaplastic astrocytoma
- February 25, 2003: Carmustine wafer for newly-diagnosed glioblastoma
- March 15, 2005: Temozolomide for newly-diagnosed glioblastoma
- May 5, 2009: Bevacizumab (BEV) for progressive glioblastoma
- April 15, 2011: NovoTTF-100A for recurrent glioblastoma

Surgical Implantation of Chemotherapy Wafers: Carmustine





Carmustine Wafer for Newly Diagnosed Glioblastoma



Westphal M, et al. *Neuro Oncol.* 2003;5(2):79-88.

Adjuvant Temozolomide Improves Survival in Glioblastoma

The NEW ENGLAND JOURNAL of MEDICINE

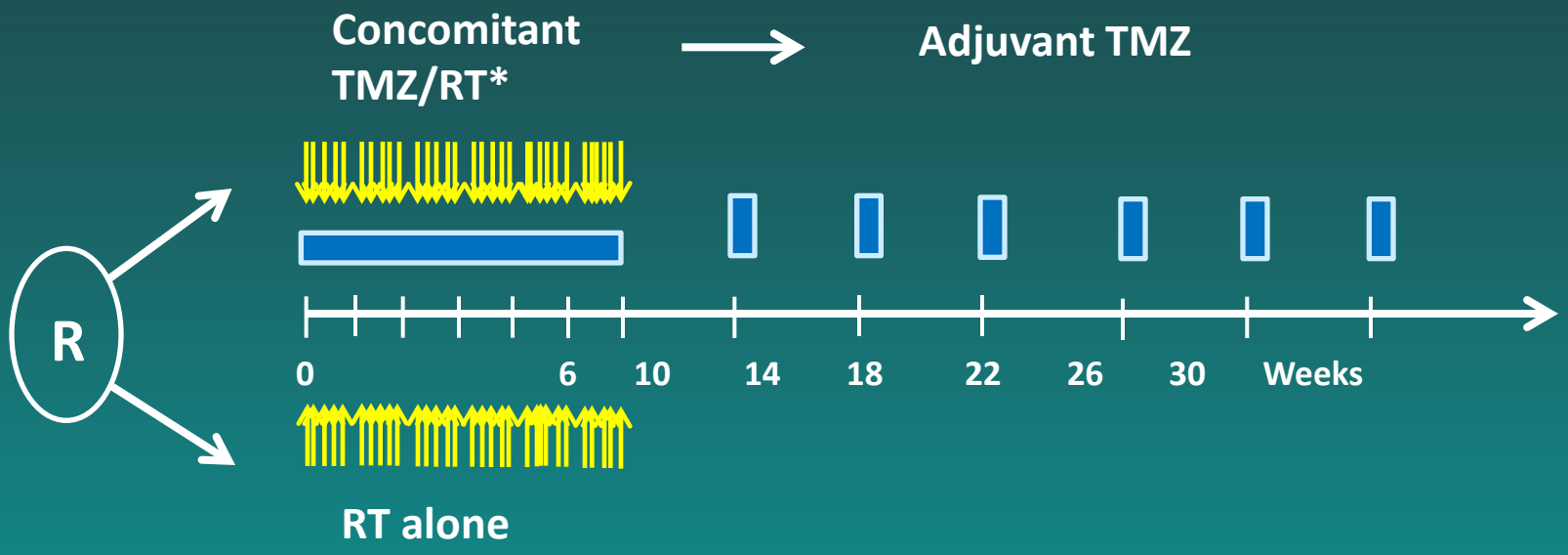
ORIGINAL ARTICLE

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*

Stupp R, et al. *N Engl J Med*. 2005;352(10):987-996.

Treatment Schema



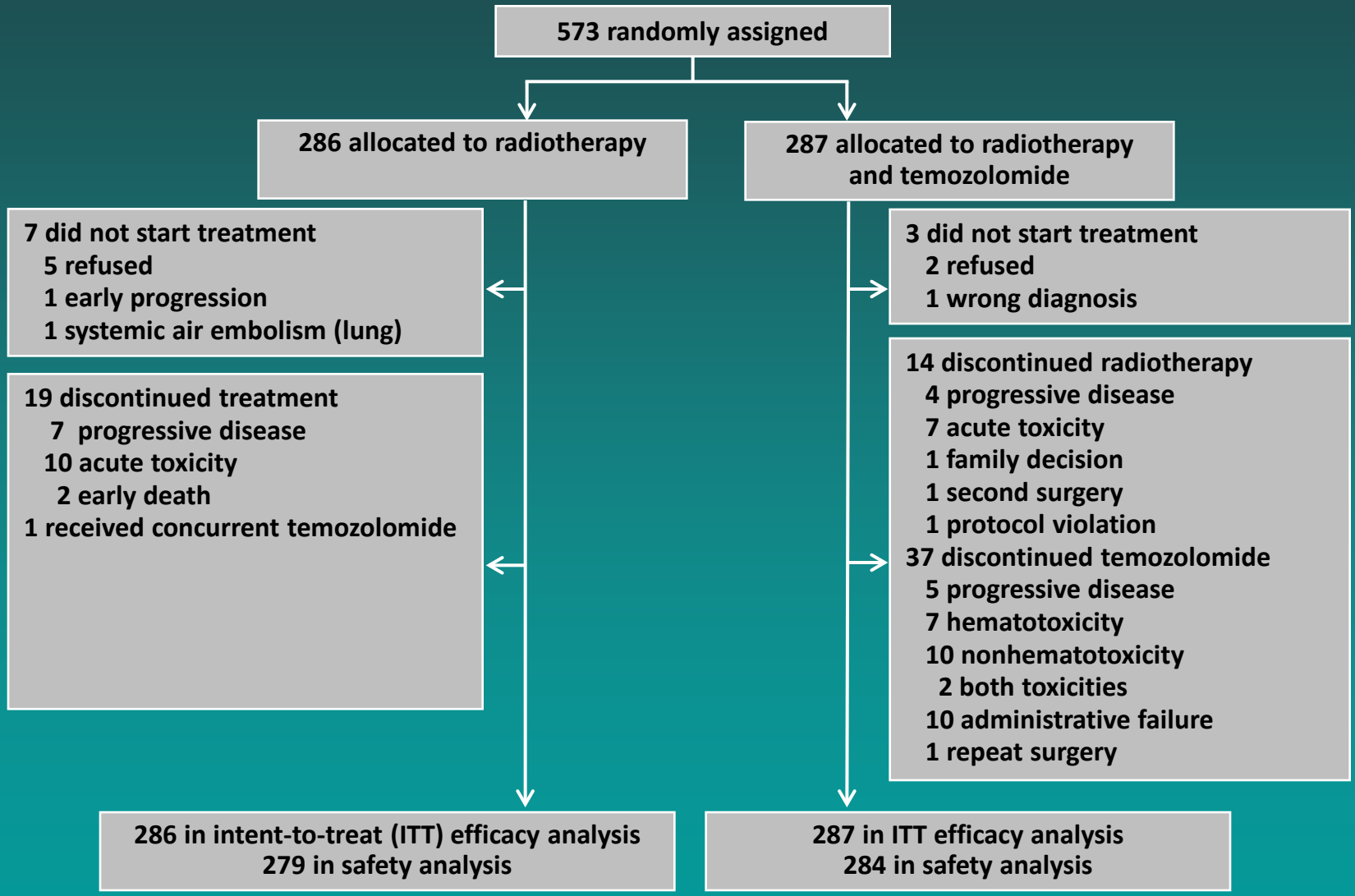
Temozolomide 75 mg/m^2 po qd for 6 weeks,
then 150 to 200 mg/m^2 po qd 1 to 5 every 28 days for 6 cycles

Focal RT daily-30 x 200 cGy
Total dose 60 Gy

***PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.**
RT, radiotherapy

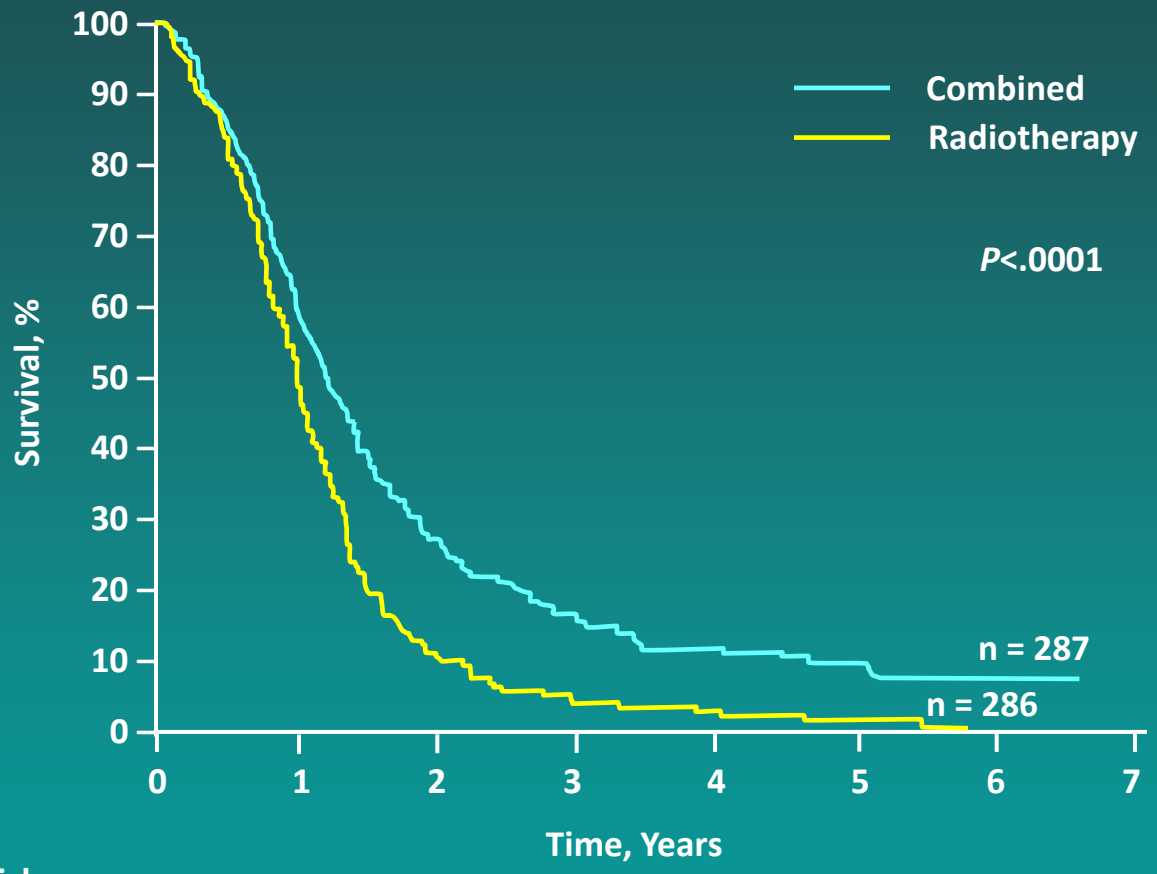
Stupp R, et al. *N Engl J Med*. 2005;352(10):987-996.

Radiotherapy and Temozolomide for Newly Diagnosed Glioblastoma



Stupp R, et al. *Lancet Oncol.* 2009;10(5):459-466.

Radiotherapy and Temozolomide for Newly Diagnosed Glioblastoma



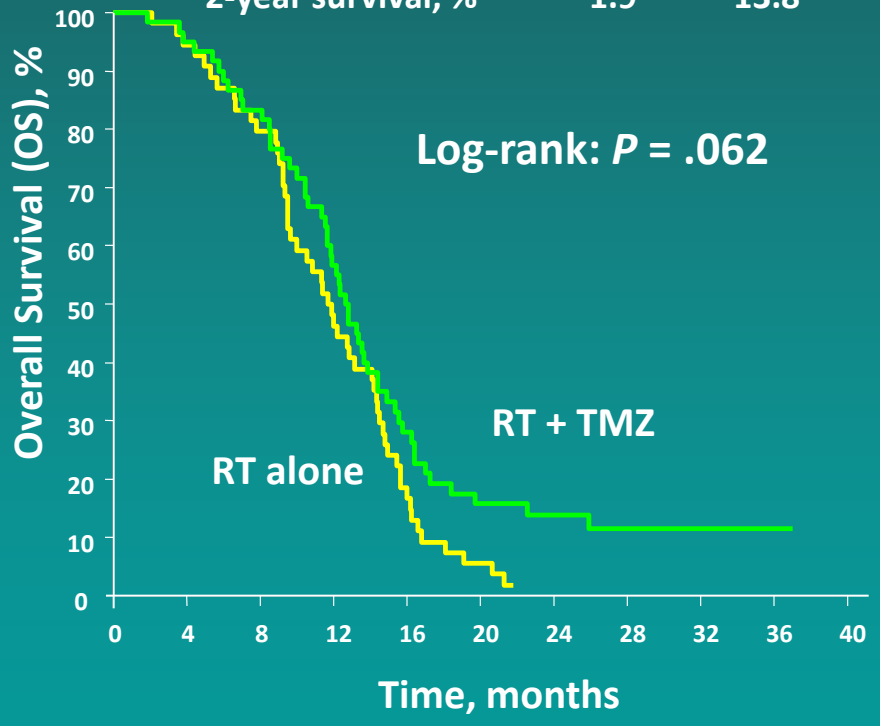
Number at risk							
Combined	254	175	76	39	23	14	6
Radiotherapy	278	144	31	11	6	3	0

Stupp R, et al. *Lancet Oncol.* 2009;10(5):459-466.

MGMT Promoter Methylation Is Associated With Improved Survival in Patients Treated With RT+TMZ

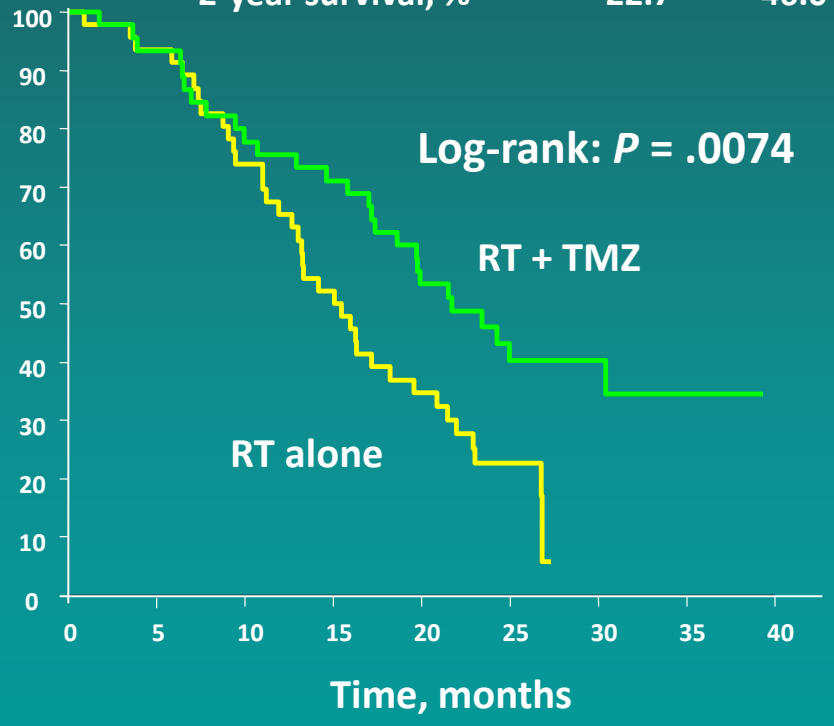
Unmethylated MGMT

	RT	RT + TMZ
Median OS, months	11.8	12.7
2-year survival, %	1.9	13.8



Methylated MGMT

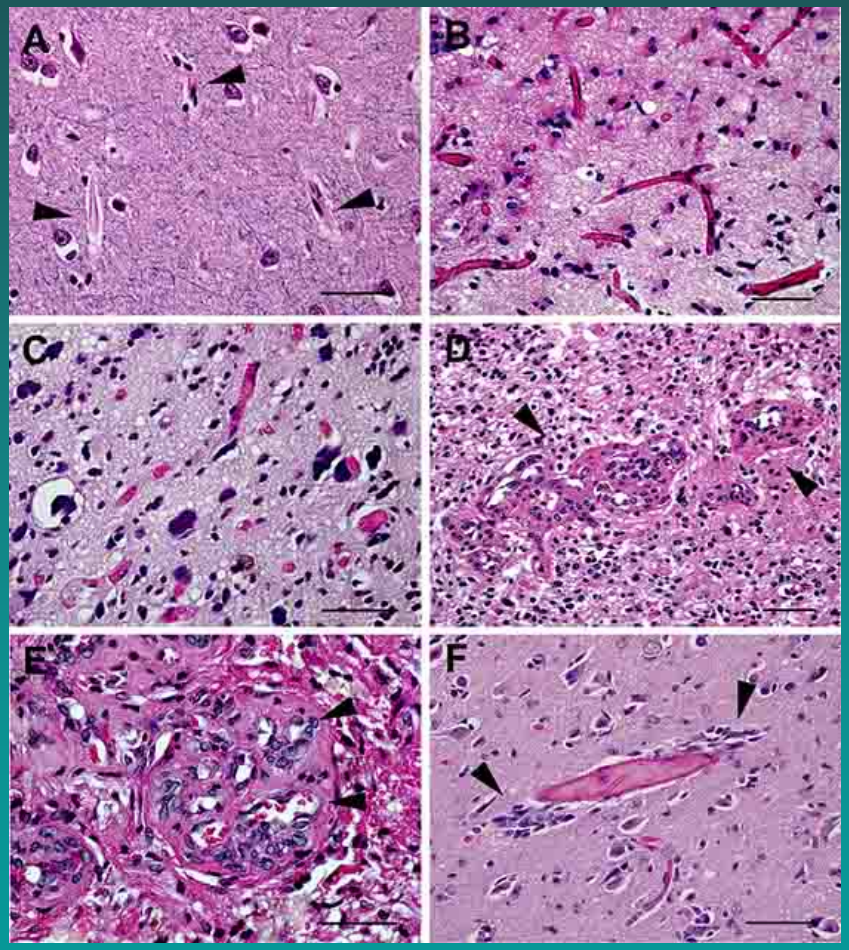
	RT	RT + TMZ
Median OS, months	15.3	21.7
2-year survival, %	22.7	46.0



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

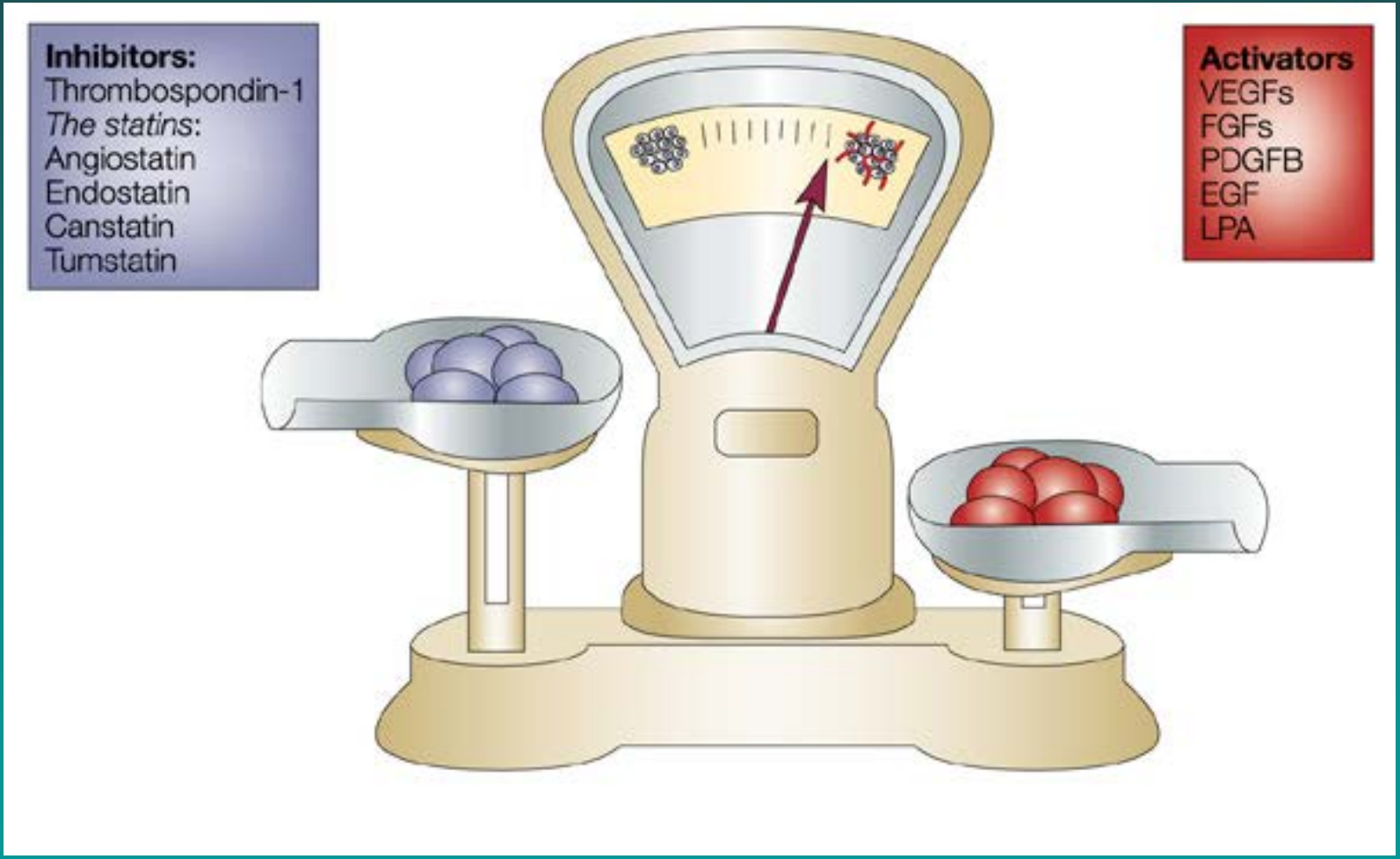
Malignant Gliomas Generate Abnormal Blood Vessels

Normal human cortex



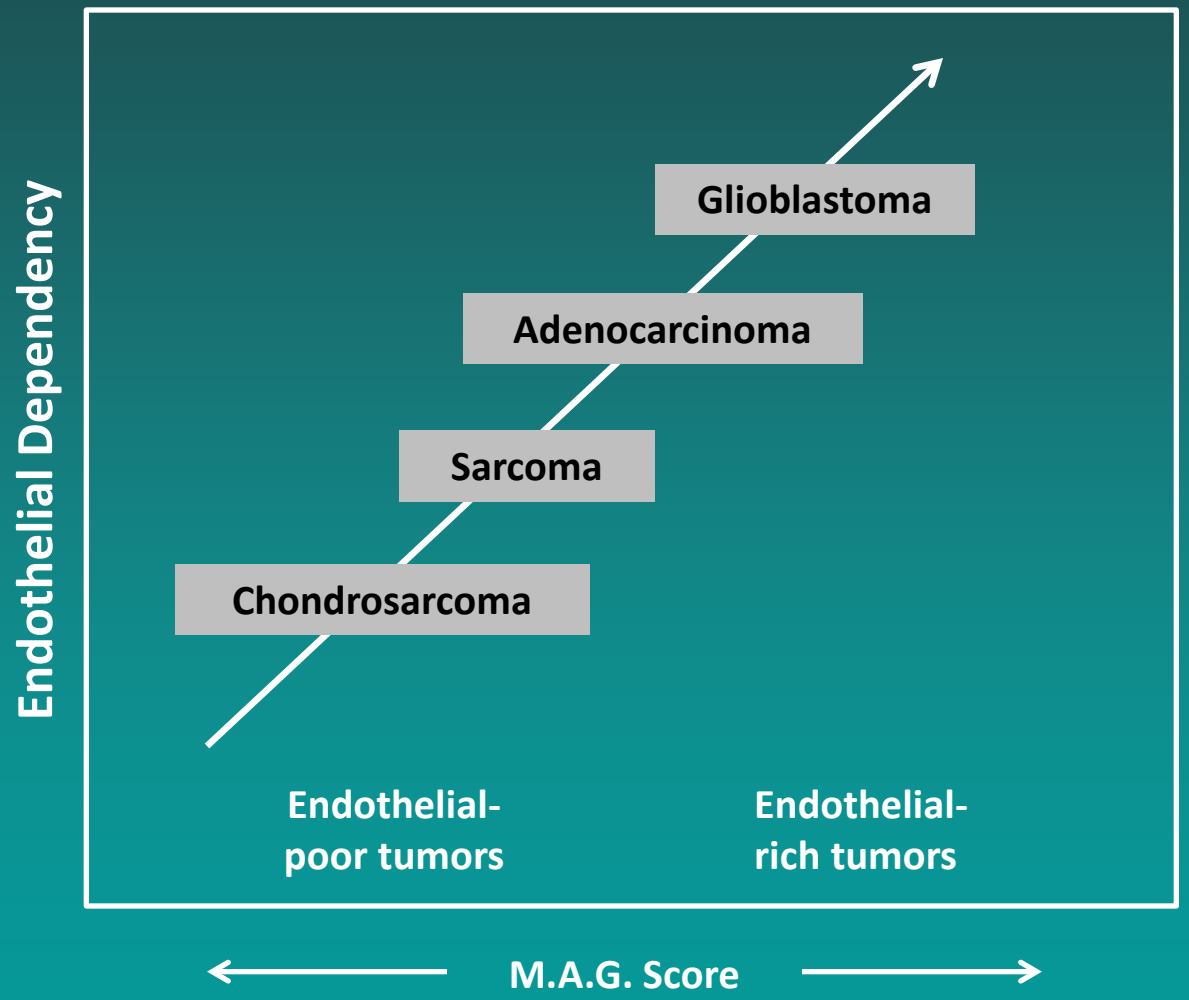
Stiver SI. *Front Biosci*. 2004;9:3105-3123.

Angiogenesis Balance



Bergers G, et al. *Nat Rev Cancer*. 2003;3(6):401-410.

Glioblastoma Has the Greatest Potential for Angiogenesis



Brem S, et al. *J Natl Cancer Inst.* 1972;48(2):347-356.

VEGF mRNA Is Upregulated in the Hypoxic Zone of Glioblastomas

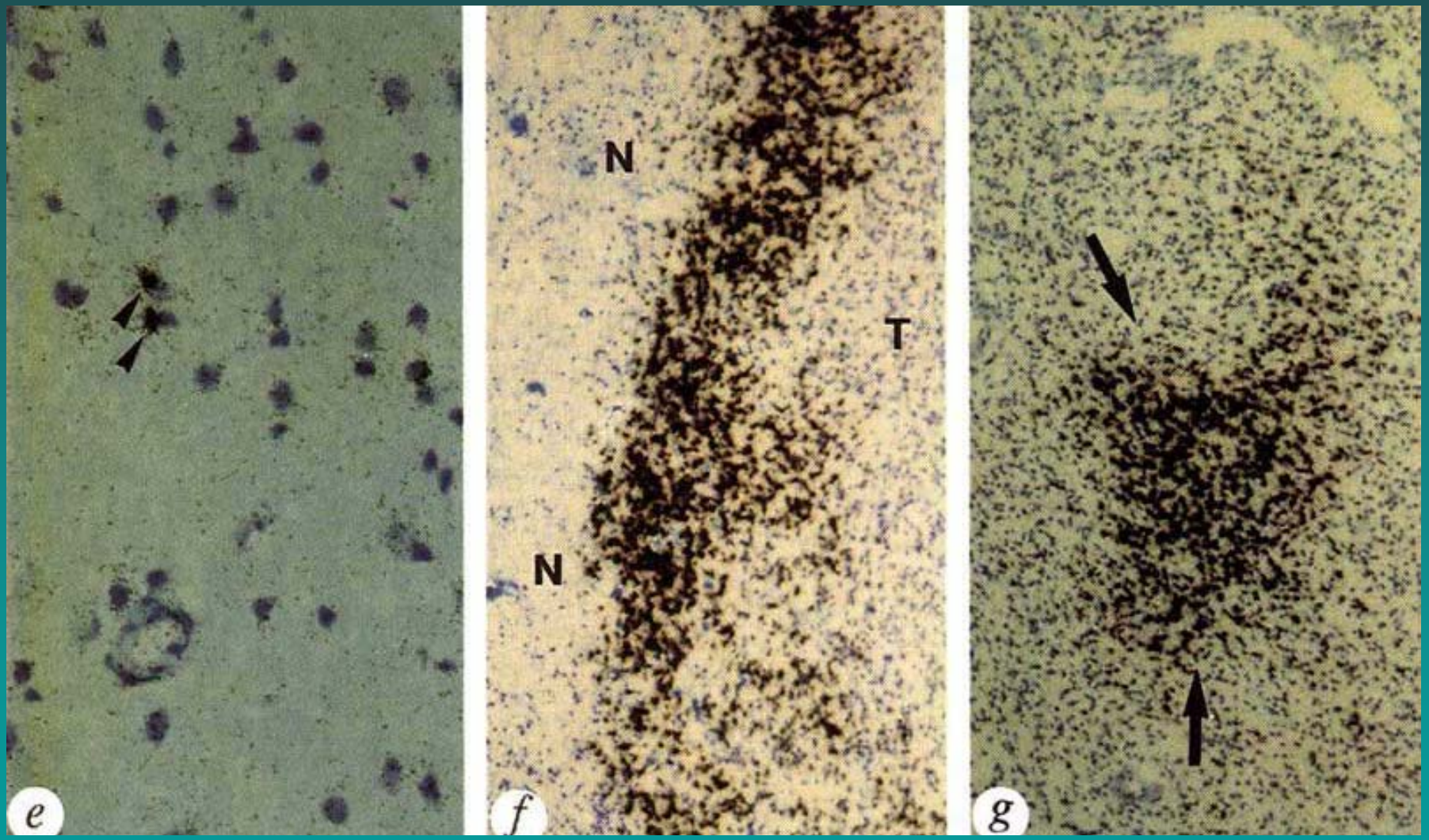


Plate KH, et al. *Nature.* 1992;359(6398):845-848.

Anti-Angiogenic Therapy in Malignant Glioma

First generation angiogenesis inhibitors:

1. Thalidomide
2. Lenalidomide
3. Penicillamine
4. Carboxyamidotriazole

Inhibitors of VEGF

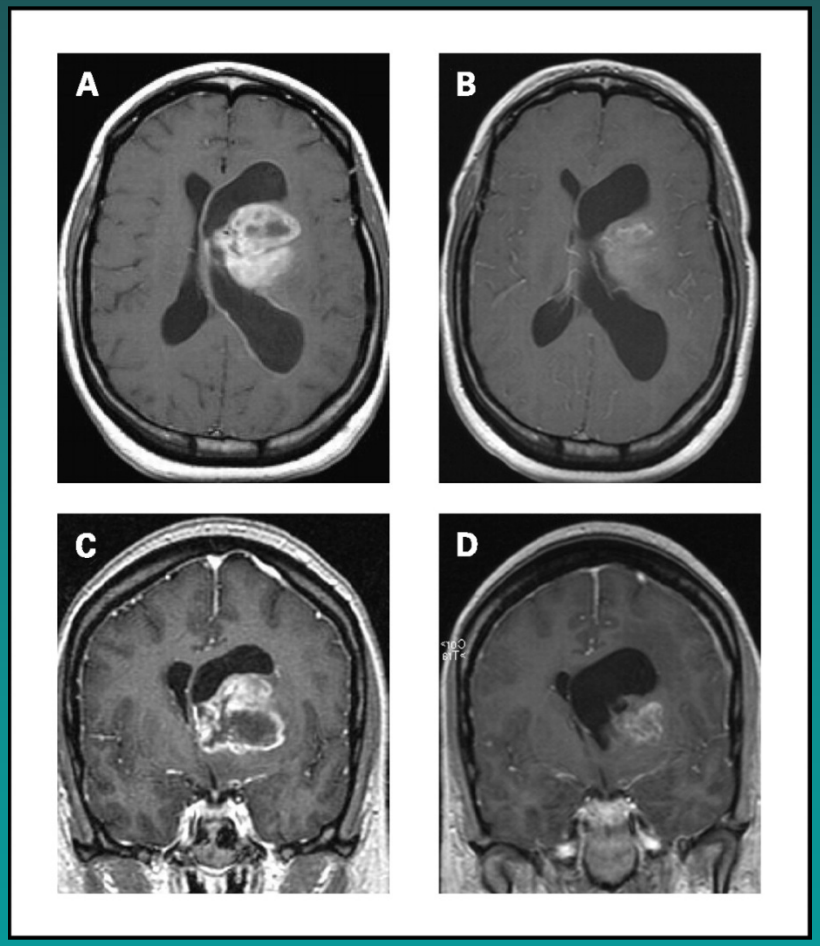
Bevacizumab

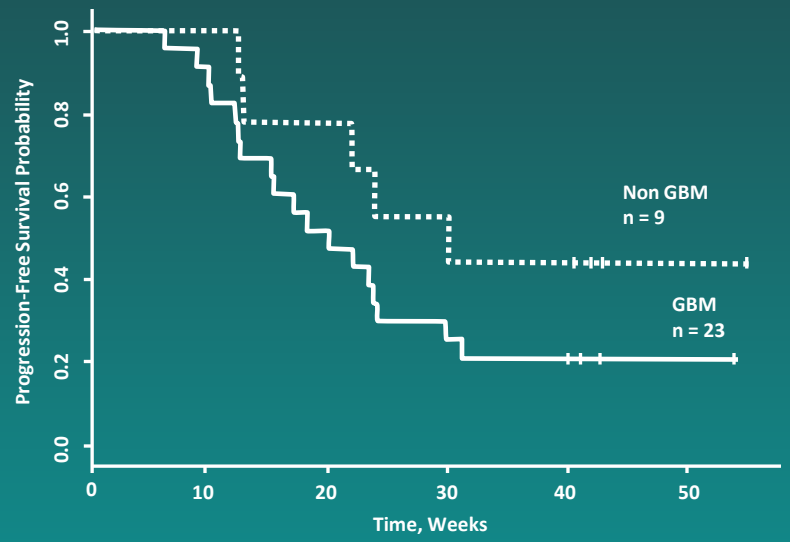
Small-molecule inhibitors of VEGRF/PDGFR/EGFR:

1. Cediranib (AZD 2171)
2. Vatalanib (PTK 787)
3. Pazopanib (GW 786034)
4. Sorafenib
5. Sunitinib
6. Vandetanib (ZD 6474)

Metronomic temozolomide

High Response Rate and Improved Progression-Free Survival (PFS) in Phase II Trial of Bevacizumab and Irinotecan





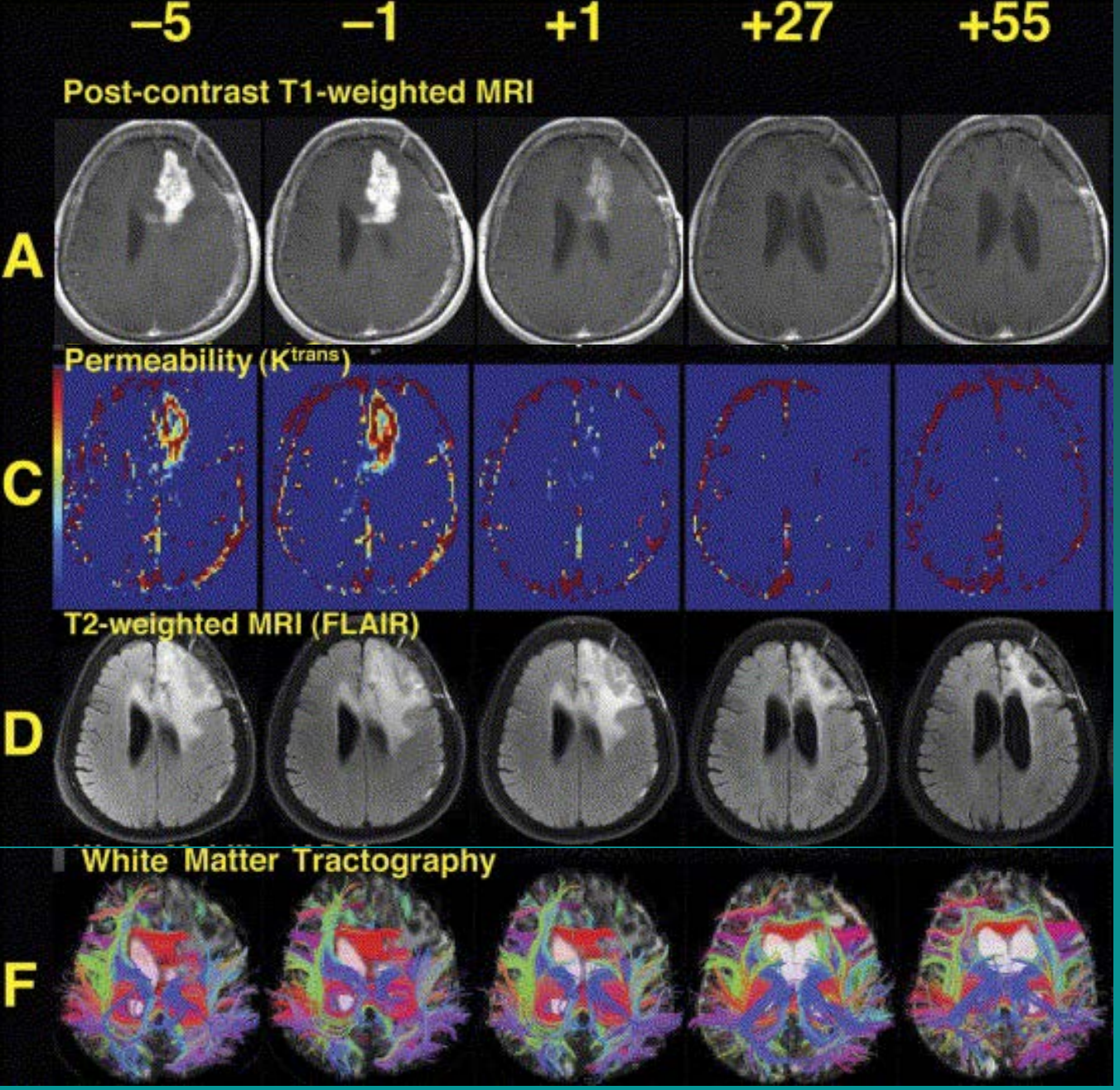
Glioblastoma (GBM)

PFS-6 (30%) = 20 weeks (9 weeks hc)

Anaplastic glioma

PFS-6 (56%) = 30 weeks (13 weeks hc)

Vredenburgh JJ, et al. *Clin Cancer Res*. 2007;13(4):1253-1259.



AZD2171 (cediranib)

(pan-VEGFR inhibitor)

Responder

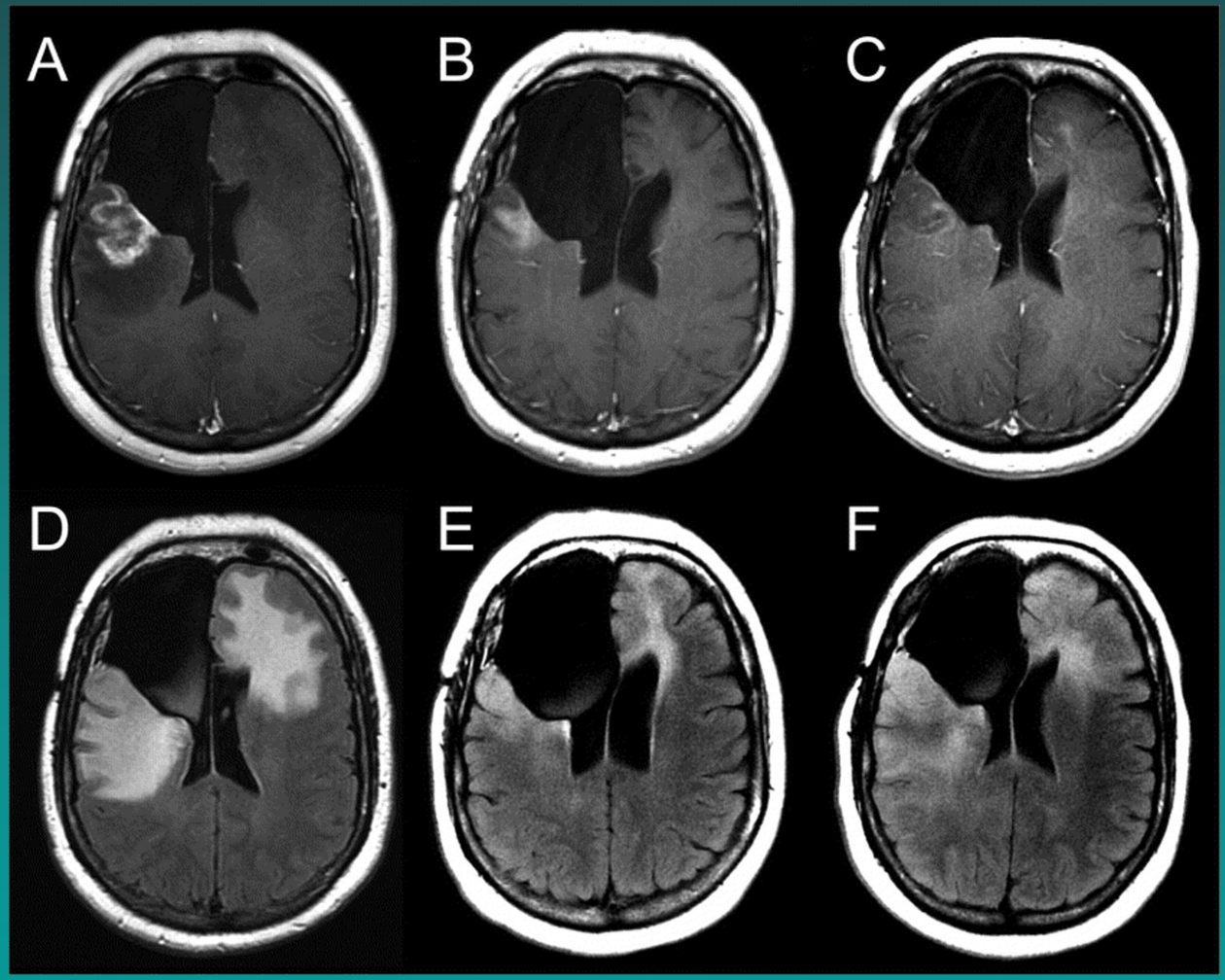
Batchelor TT, et al. *Proc Natl Acad Sci U S A.* 2013;110(47):19059-19064. Batchelor TT, et al. *J Clin Oncol*. 2013;31(26):3212-3218.

Bevacizumab Plus Irinotecan Versus Salvage Cytotoxic Chemotherapies

	PFS, 6 months	Response
Bevacizumab plus irinotecan		
Vredenburgh, et al	57%	46%
Chen, et al	47%	65%
*Friedman HS, et al	38%	50%
*Kreisl TN, et al	35%	29%
**Wong, et al - cytotoxic chemotherapy	6%	15%

Vredenburgh JJ, et al. *J Clin Oncol.* 2007;25(30):4722-4729. Chen W, et al. *J Clin Oncol.* 2007;25(30):4714-4721.
*FDA approval: Friedman HS, et al. *J Clin Oncol.* 2009;27(28):4733-4740. Kreisl TN, et al. *J Clin Oncol.* 2009;27(5):740-745.
**Wong ET, et al. *J Clin Oncol.* 1999;17(8):2572-2578.

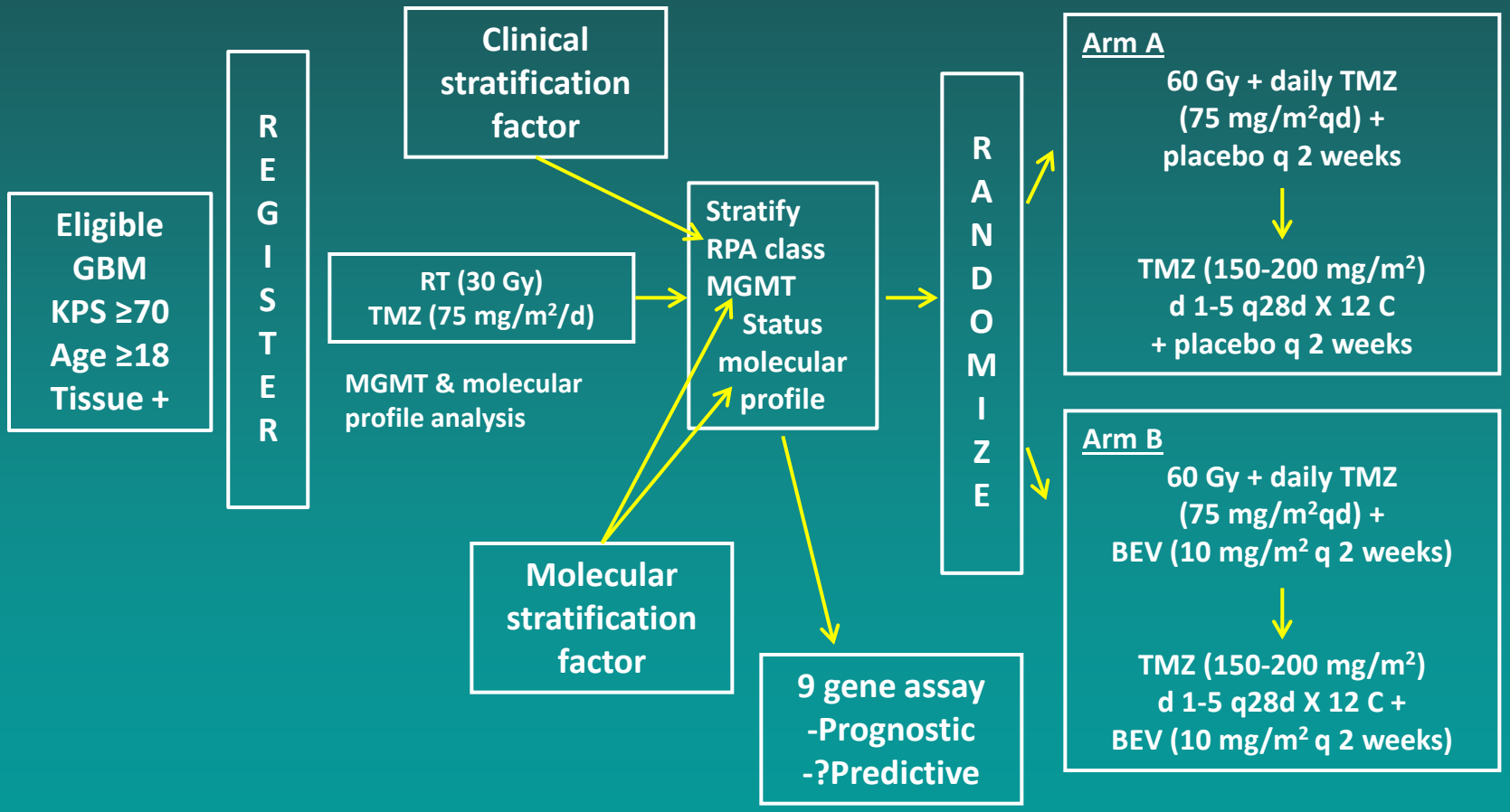
Tumor Progression During Bevacizumab Plus Irinotecan



Norden AD, et al. *Neurology.* 2008;70(10):779-787.

Bevacizumab for Newly Diagnosed Glioblastoma

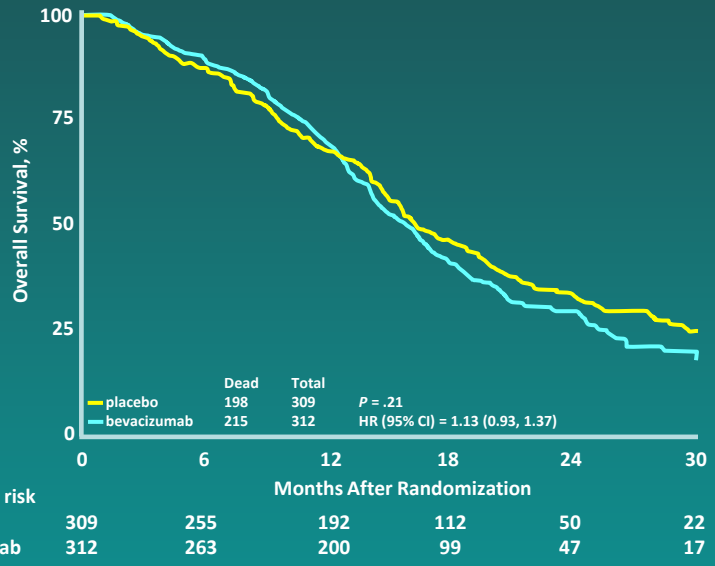
RTOG 0825: Phase III trial testing first-line treatment with bevacizumab

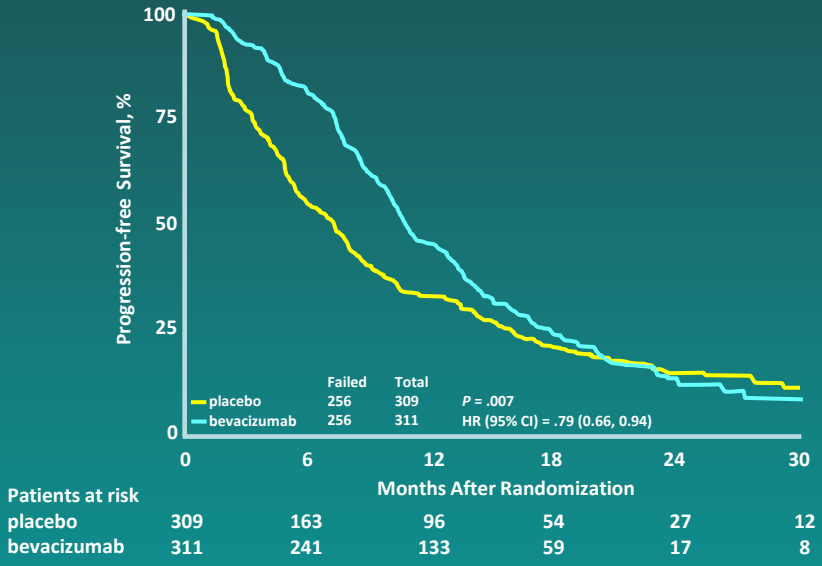


Gilbert M, et al. *J Clin Oncol*. 2013;31(suppl): Abstract 01.

Bevacizumab for Newly Diagnosed Glioblastoma

Primary outcomes by treatment





Median overall survival

Placebo: 16.1 months
Bevacizumab: 15.7 months
HR (BEV/placebo: 1.13 [95%CI: 0.93, 1.37])
P = .21

Median progression-free survival

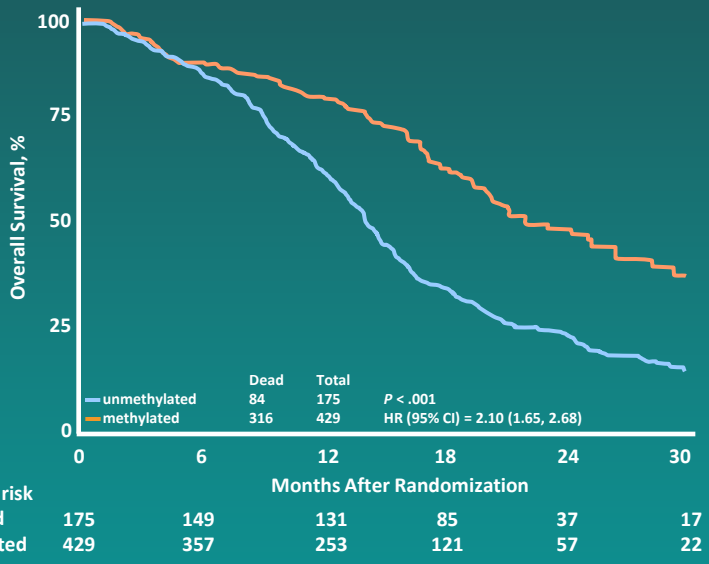
Placebo: 7.3 months
Bevacizumab: 10.7 months
HR (BEV/placebo: 0.79 [95%CI: 0.66, 0.94])
P = .007

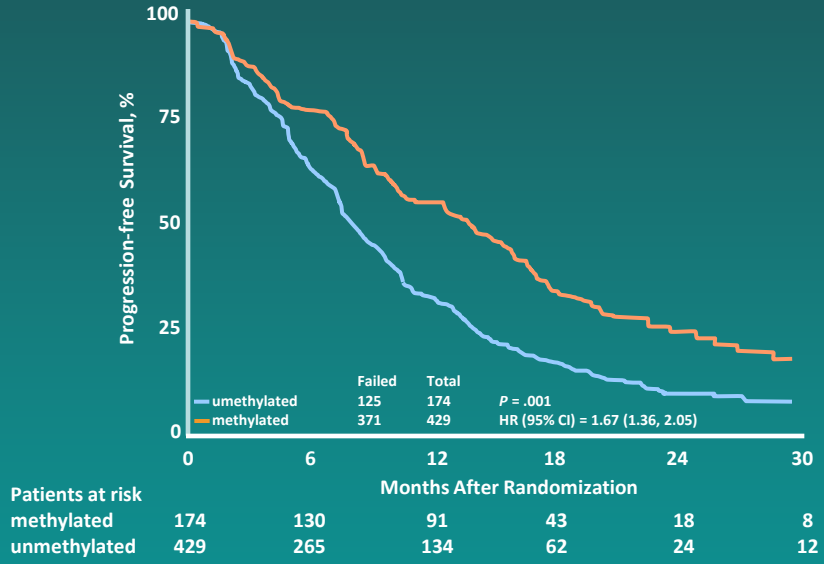
Neither OS or PFS achieved prespecified endpoints

Gilbert M, et al. *J Clin Oncol*. 2013;31(suppl): Abstract 01. Gilbert M, et al. Presented at: 2013 Scientific Meeting and Education Day of the Society for Neuro-Oncology; November 21-24, 2013; San Francisco, California: Abstract NO-046.

Bevacizumab for Newly Diagnosed Glioblastoma

Outcomes by MGMT status: Both arms pooled





Median overall survival

Methylated: 23.2 months
Unmethylated: 14.3 months
HR (unmeth/meth: 2.10 (95%CI: 1.65, 2.68)
P<.001

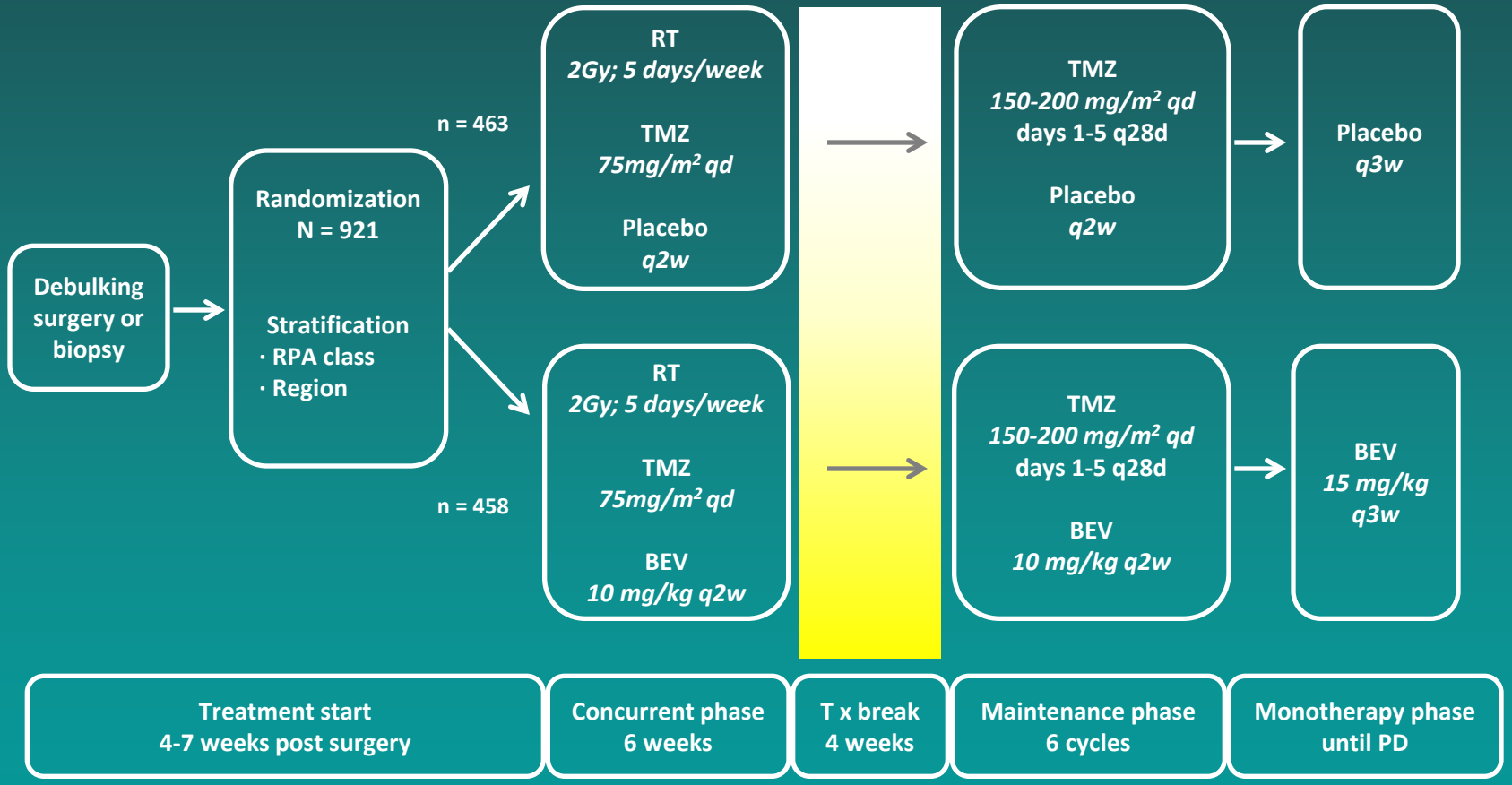
Median progression-free survival

Methylated: 14.1 months
Unmethylated: 8.2 months
HR (unmeth/meth: 1.67 (95%CI: 1.36, 2.05)
P<.001

Gilbert M, et al. *J Clin Oncol*. 2013;31(suppl): Abstract 01.

Bevacizumab for Newly Diagnosed Glioblastoma

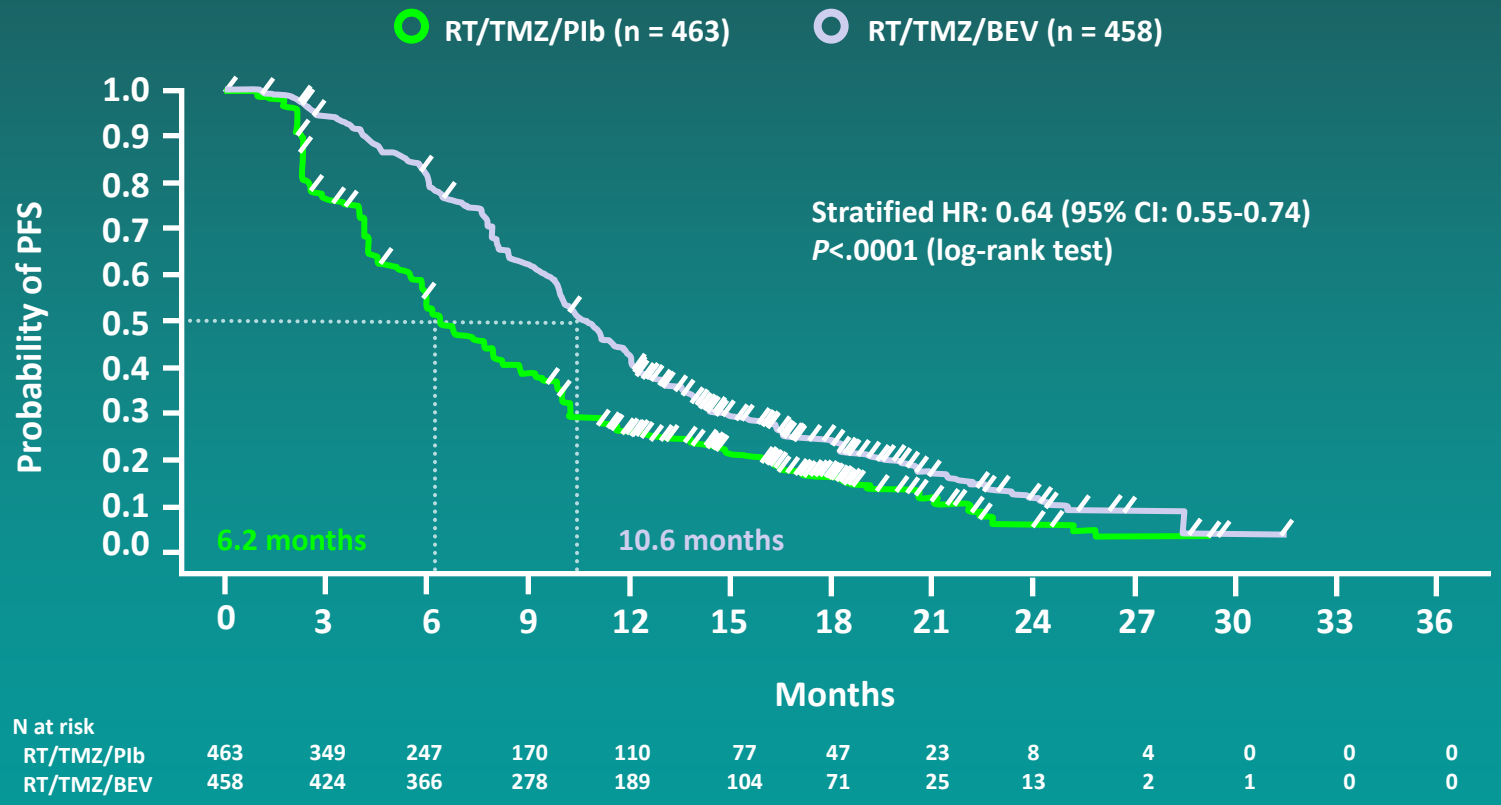
AVAglio study design



Wick W, et al. *J Clin Oncol.* 2013;31(suppl): Abstract 2002.

Bevacizumab for Newly Diagnosed Glioblastoma

AVAGlio trial: Investigator-assessed PFS (Co-primary endpoint)

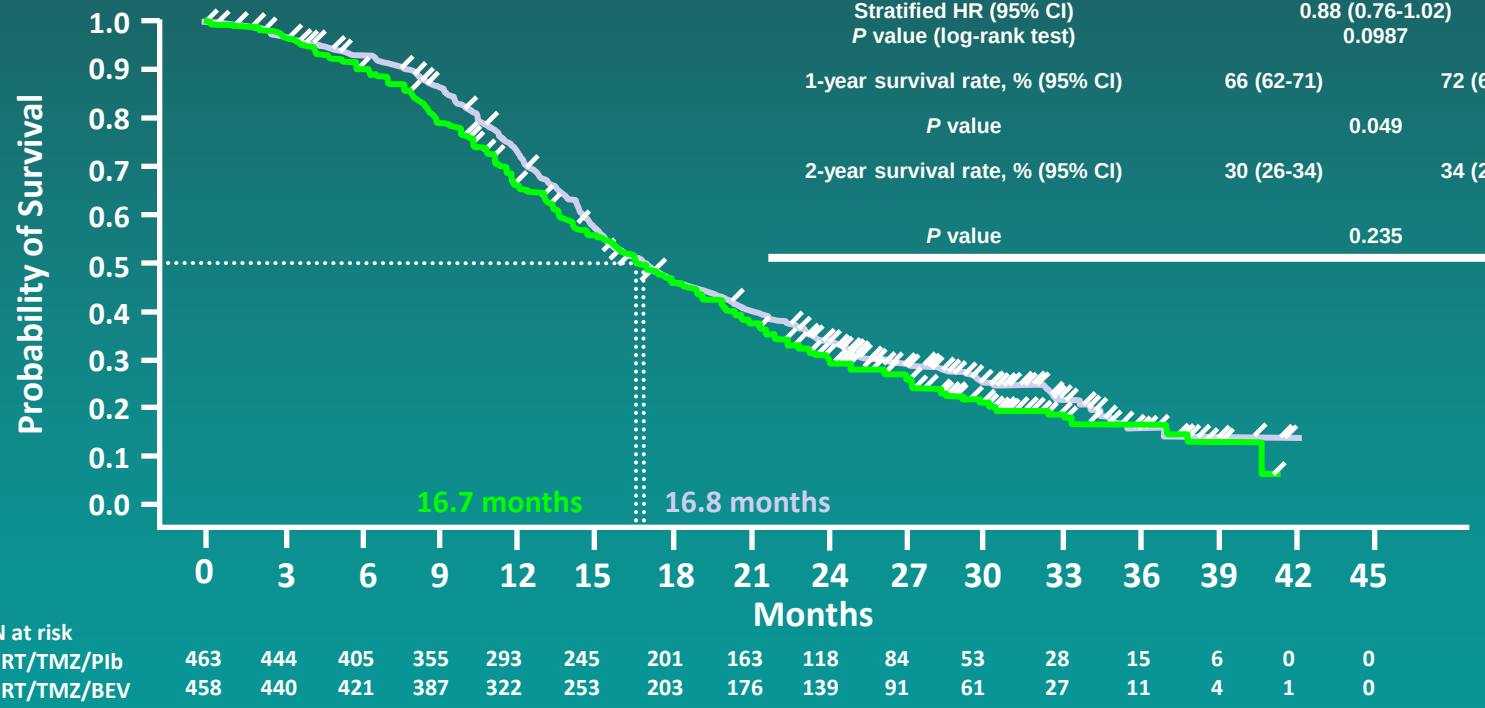


Wick W, et al. *J Clin Oncol.* 2013;31(suppl): Abstract 2002.

Bevacizumab for Newly Diagnosed Glioblastoma

Overall survival (Co-primary endpoint)

	RT/TMZ/Plb (n = 463)	RT/TMZ/BEV (n = 458)
Patients with an event, n	346	333
Stratified HR (95% CI)	0.88 (0.76-1.02)	
P value (log-rank test)	0.0987	
1-year survival rate, % (95% CI)	66 (62-71)	72 (68-77)
P value	0.049	
2-year survival rate, % (95% CI)	30 (26-34)	34 (29-38)
P value	0.235	



N at risk

RT/TMZ/Plb	463	444	405	355	293	245	201	163	118	84	53	28	15	6	0	0
RT/TMZ/BEV	458	440	421	387	322	253	203	176	139	91	61	27	11	4	1	0

Designed to achieve a HR of 0.80 (20% reduction in the risk of death) with 80% power (log-rank test, 2 sided 4% α level adjusted using O'Brien and Fleming): 683 events were required for analysis

Wick W, et al. *J Clin Oncol.* 2013;31(suppl): Abstract 2002. Chinot OL, et al. Presented at: 2013 Scientific Meeting and Education Day of the Society for Neuro-Oncology; November 21-24, 2013; San Francisco, California: Abstract NO-031.

Bevacizumab for Newly Diagnosed Glioblastoma

1. No clinical benefit in upfront treatment of glioblastoma

Primary endpoints

	RTOG 0825		AVAGLIO	
Regimen	Bevacizumab/TMZ/RT	TMZ/RT	Bevacizumab/TMZ/RT	TMZ/RT
PFS	10.3 months	7.3 months	10.6 months	6.2 months
	HR 0.79, *P* = .07		HR 0.64, *P*<.0001	
OS	15.7 months	16.1 months	16.8 months	16.7 months
	HR 1.13, *P* = .21		HR 0.88, *P* = .0987	

2. There may be benefit in specialized population of patients with newly diagnosed glioblastoma (ie, large unresectable tumor, molecular genetics, etc)

Gilbert M, et al. *J Clin Oncol*. 2013;31(suppl): Abstract 01. Wick W, et al. *J Clin Oncol.* 2013;31(suppl): Abstract 2002.

Treatment Options for Glioblastoma

Newly-diagnosed:

- Maximum safe neurosurgical resection
- Radiotherapy with concomitant temozolomide
  - Adjuvant temozolomide

At recurrence:

- Re-resection (Carmustine wafer may be used)
- Second-line chemotherapy
- NovoTTF
- Bevacizumab with or without chemotherapy
- Re-irradiation