Tumores Cerebrales

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- Tratamiento Complementario
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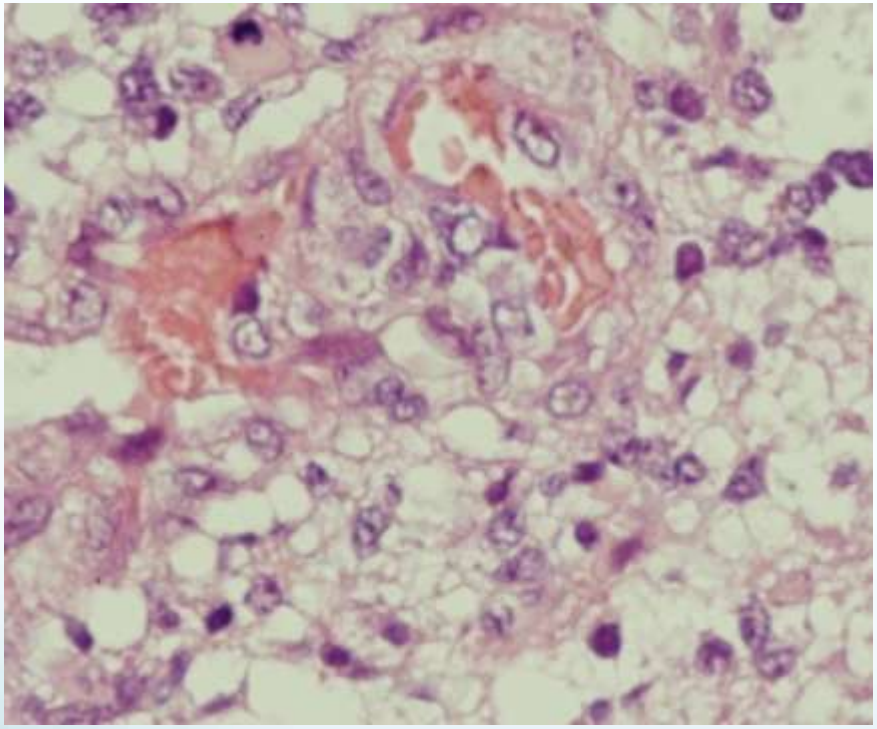
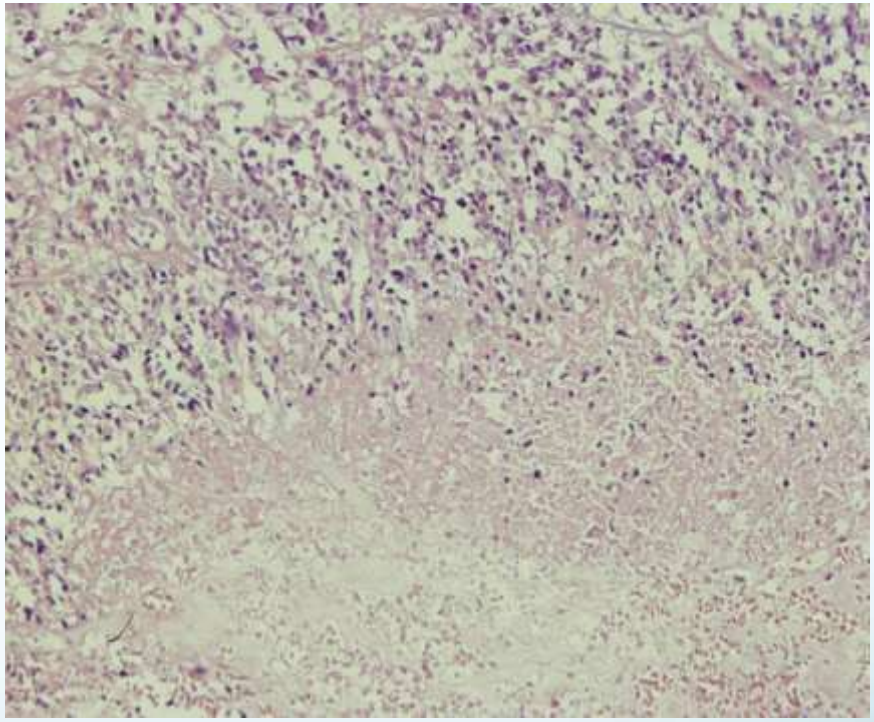
- Estrategias para mejorar el tratamiento estándar
- Tratamiento de la Recurrencia/Progresión

Glioblastoma



Proliferación Vascular



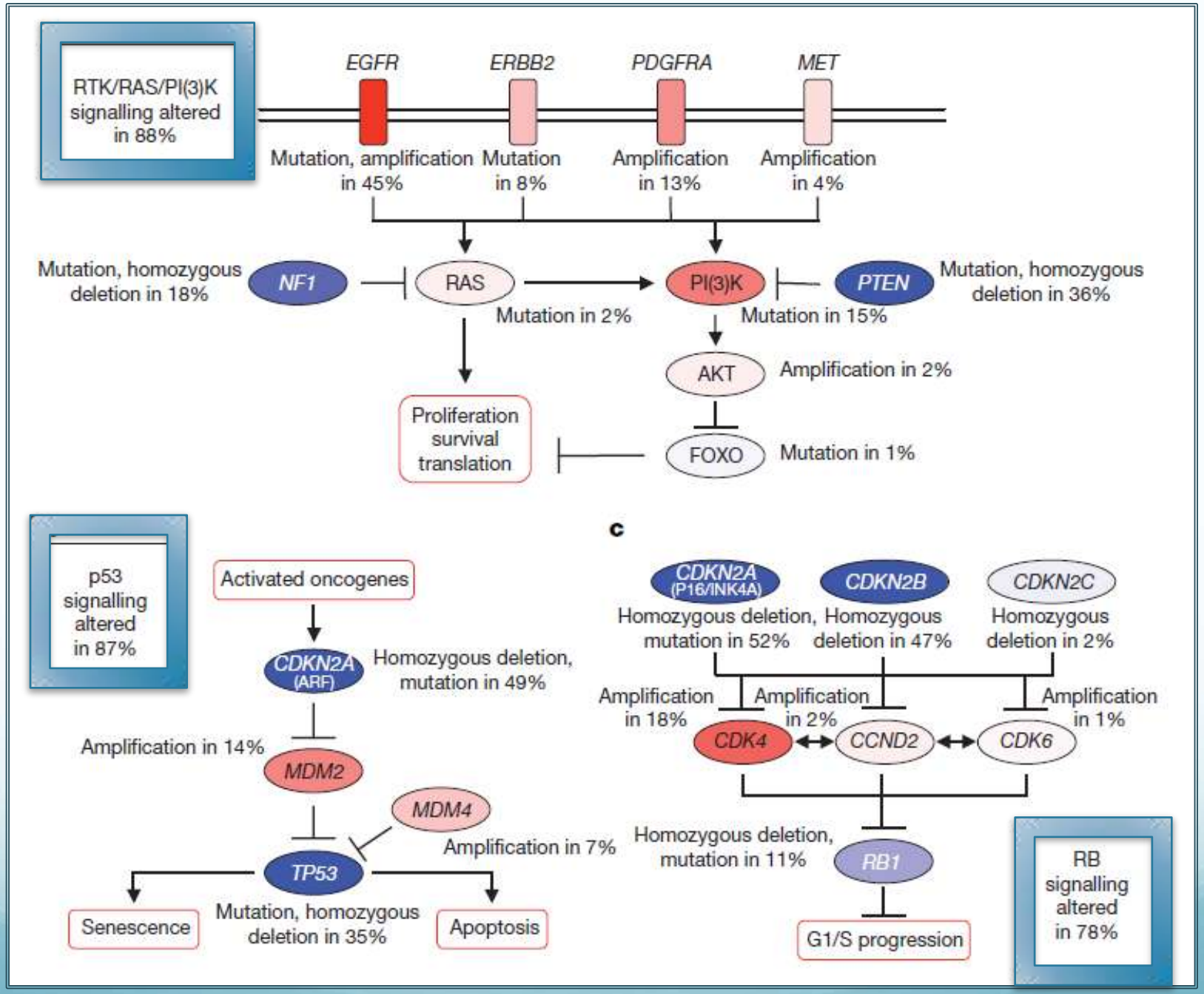
Necrosis

nature

Comprehensive genomic characterization defines human glioblastoma genes and core pathways

The Cancer Genome Atlas Research Network*

Human cancer cells typically harbour multiple chromosomal aberrations, nucleotide substitutions and epigenetic modifications that drive malignant transformation. The Cancer Genome Atlas (TCGA) pilot project aims to assess the value of large-scale multi-dimensional analysis of these molecular characteristics in human cancer and to provide the data rapidly to the research community. Here we report the interim integrative analysis of DNA copy number, gene expression and DNA methylation aberrations in 206 glioblastomas—the most common type of primary adult brain cancer—and nucleotide sequence aberrations in 91 of the 206 glioblastomas. This analysis provides new insights into the roles of *ERBB2*, *NF1* and *TP53*, uncovers frequent mutations of the phosphatidylinositol-3-OH kinase regulatory subunit gene *PIK3R1*, and provides a network view of the pathways altered in the development of glioblastoma. Furthermore, integration of mutation, DNA methylation and clinical treatment data reveals a link between *MGMT* promoter methylation and a hypermutator phenotype consequent to mismatch repair deficiency in treated glioblastomas, an observation with potential clinical implications. Together, these findings establish the feasibility and power of TCGA, demonstrating that it can rapidly expand knowledge of

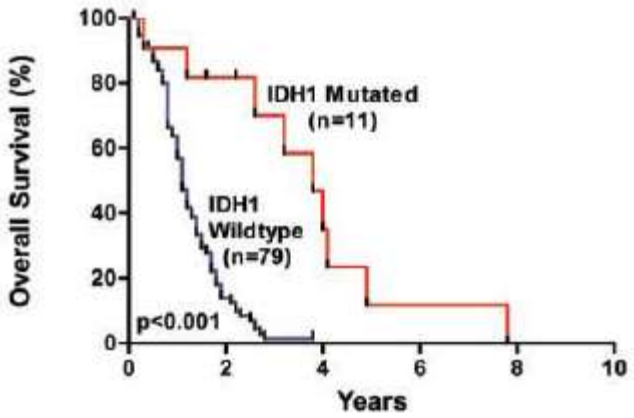

RTK/RAS/PI(3)K signalling altered in 88%
EGFR
ERBB2
PDGFRA
MET
Mutation, amplification in 45%
Mutation in 8%
Amplification in 13%
Amplification in 4%
Mutation, homozygous deletion in 18%
NF1
RAS
Mutation in 2%
PI(3)K
PTEN
Mutation in 15%
Mutation, homozygous deletion in 36%
AKT
Amplification in 2%
Proliferation survival translation
FOXO
Mutation in 1%
p53 signalling altered in 87%
Activated oncogenes
CDKN2A (ARF)
Homozygous deletion, mutation in 49%
Amplification in 14%
MDM2
MDM4
Amplification in 7%
TP53
Senescence
Mutation, homozygous deletion in 35%
Apoptosis
c
CDKN2A (P16/INK4A)
CDKN2B
CDKN2C
Homozygous deletion, mutation in 52%
Homozygous deletion in 47%
Homozygous deletion in 2%
Amplification in 18%
Amplification in 2%
Amplification in 1%
CDK4
CCND2
CDK6
Homozygous deletion, mutation in 11%
RB1
G1/S progression
RB signalling altered in 78%

Science
AAAS

An Integrated Genomic Analysis of Human Glioblastoma Multiforme

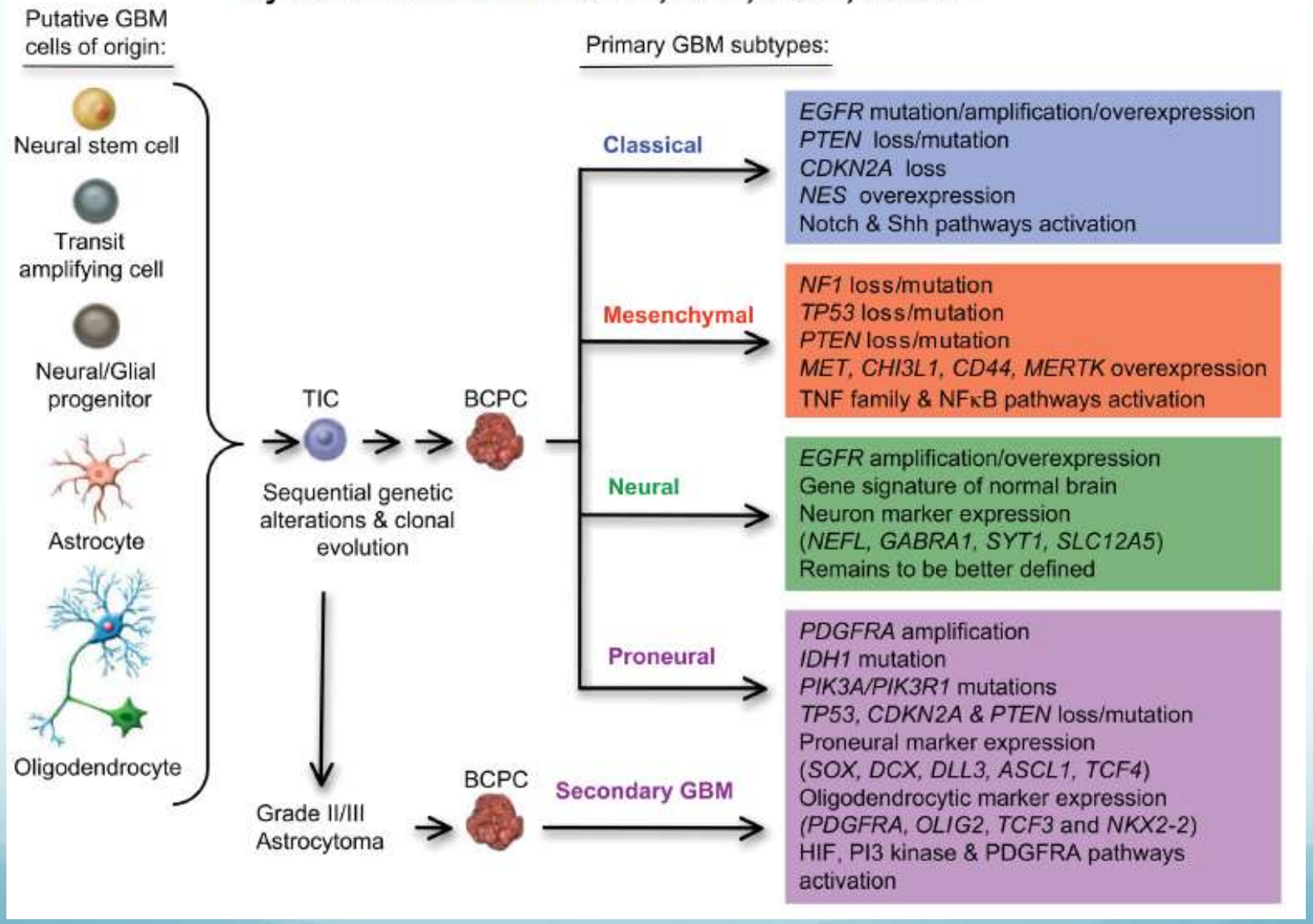
D. Williams Parsons,[1,2]* Siân Jones,[1]* Xiaosong Zhang,[1]* Jimmy Cheng-Ho Lin,[1]*

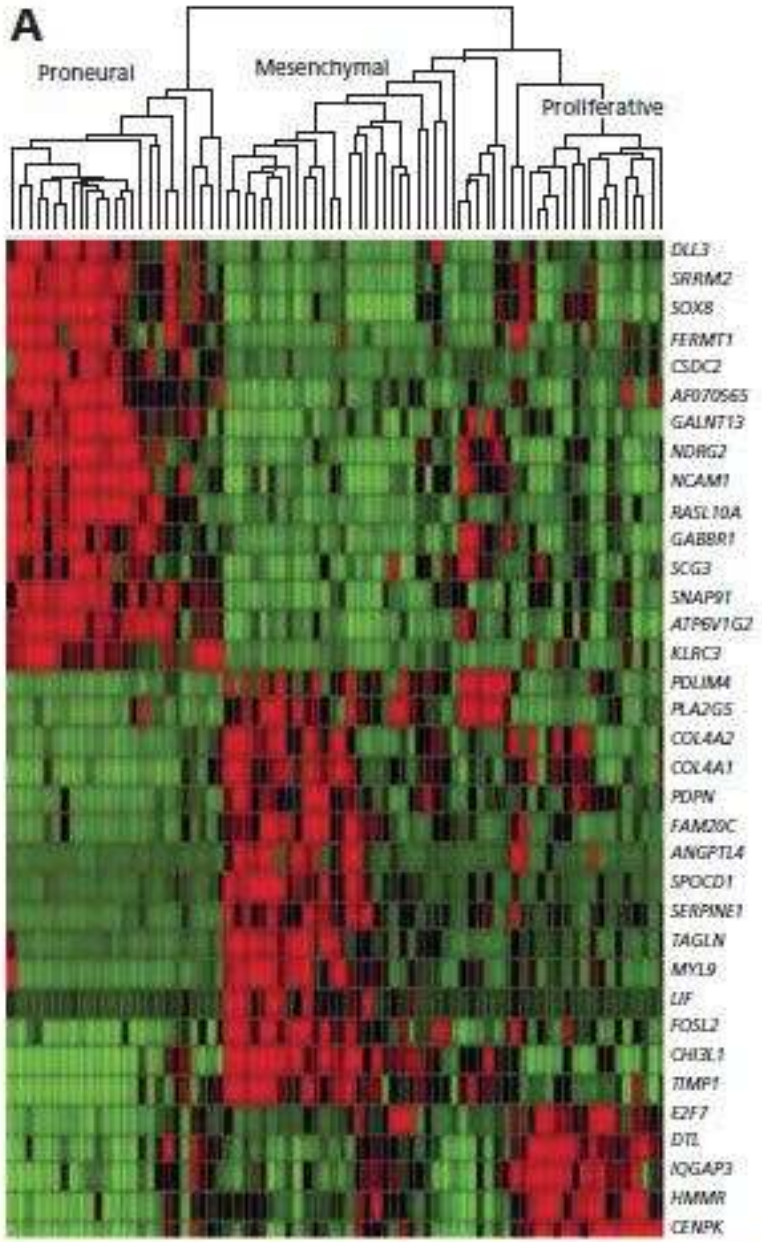
Patient ID	Patient age (years)*	Sex	Recurrent GBM†	Secondary GBM‡	Overall survival (years)§	IDH1 mutation		Mutation of TP53	Mutation of PTEN, RB1, EGFR, or NF1
						Nucleotide	Amino acid		
Br10P	30	F	No	No	2.2	G395A	R132H	Yes	No
Br11P	32	M	No	No	4.1	G395A	R132H	Yes	
Br12P	31	M	No	No	1.6	G395A	R132H	Yes	
Br104X	29	F	No	No	4.0	C394A	R132S	Yes	
Br106X	36	M	No	No	3.8	G395A	R132H	Yes	
Br122X	53	M	No	No	7.8	G395A	R132H	No	
Br123X	34	M	No	Yes	4.9	G395A	R132H	Yes	
Br237T	26	M	No	Yes	2.6	G395A	R132H	Yes	
Br211T	28	F	No	Yes	0.3	G395A	R132H	Yes	
Br27P	32	M	Yes	Yes	1.2	G395A	R132H	Yes	
Br129X	25	M	Yes	Yes	3.2	C394A	R132S	No	
Br29P	42	F	Yes	Unknown	Unknown	G395A	R132H	Yes	
IDH1 mutant patients (n=12)	33.2	67% M	25%	42%	3.8	100%	100%	83%	
IDH1 wild-type patients (n=93)	53.3	65% M	16%	1%	1.1	0%	0%	27%	

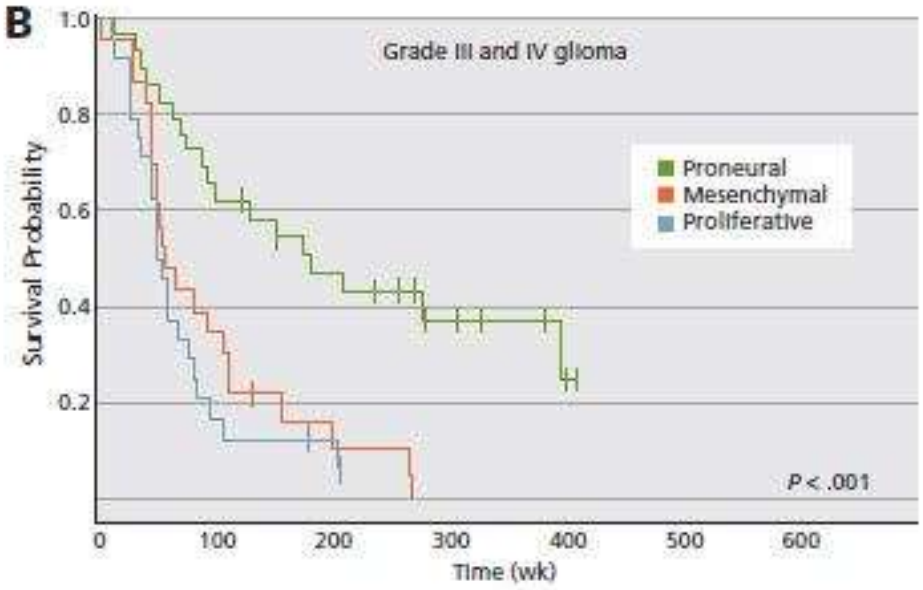


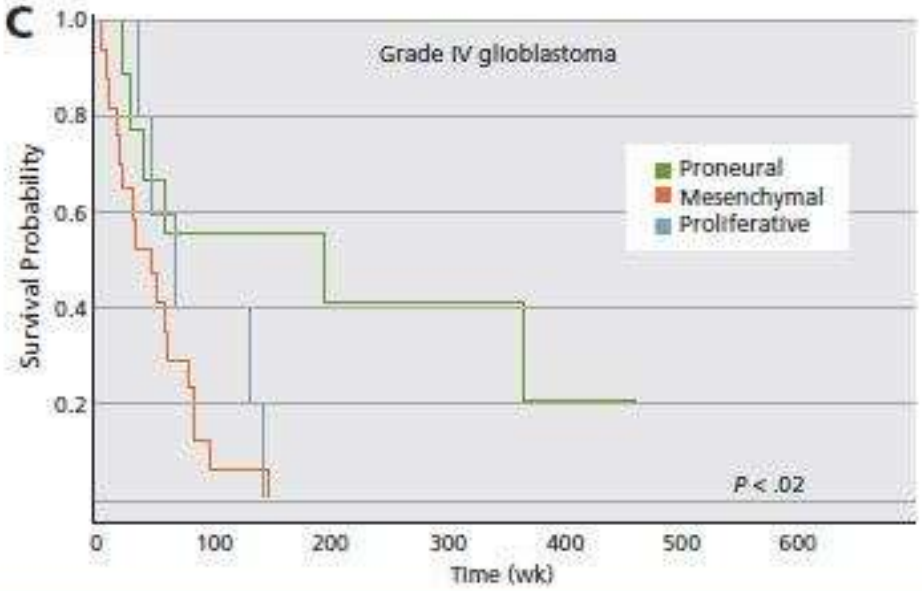
Cancer Cell
Article

Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in *PDGFRA*, *IDH1*, *EGFR*, and *NF1*







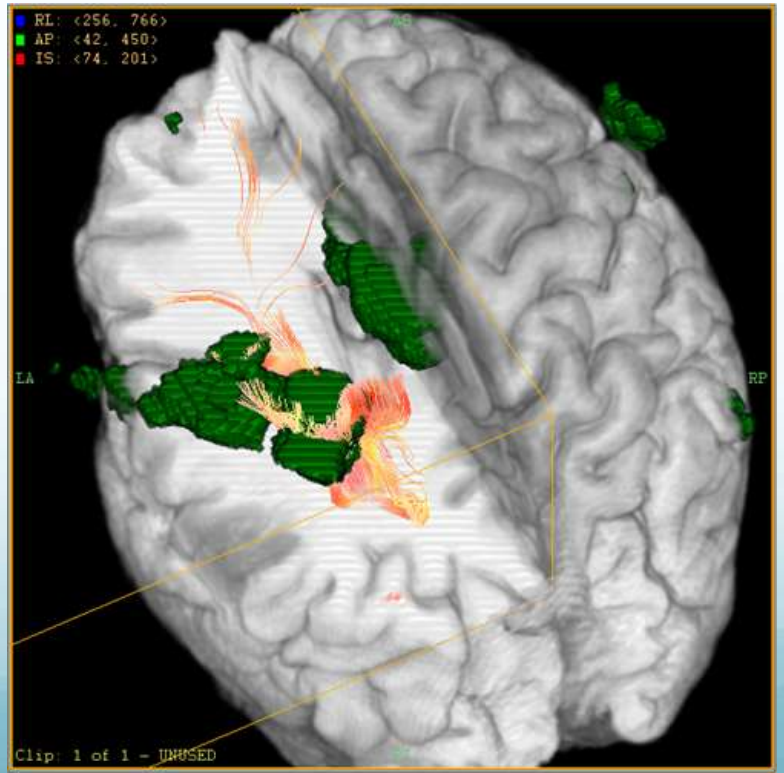


Cirugía

- La extensión de la resección es el mejor predictor de la supervivencia.
  - La resección completa es poco probable
  - OBJETIVO: RESECCIÓN LO MÁS EXTENSA POSIBLE SIN PRODUCIR SECUELAS
- Factores que influyen en la extensión de la cirugía
  - Tamaño y localización tumoral
  - Multicentralidad
  - Afectación difusa
  - Edad
  - Comorbilidad

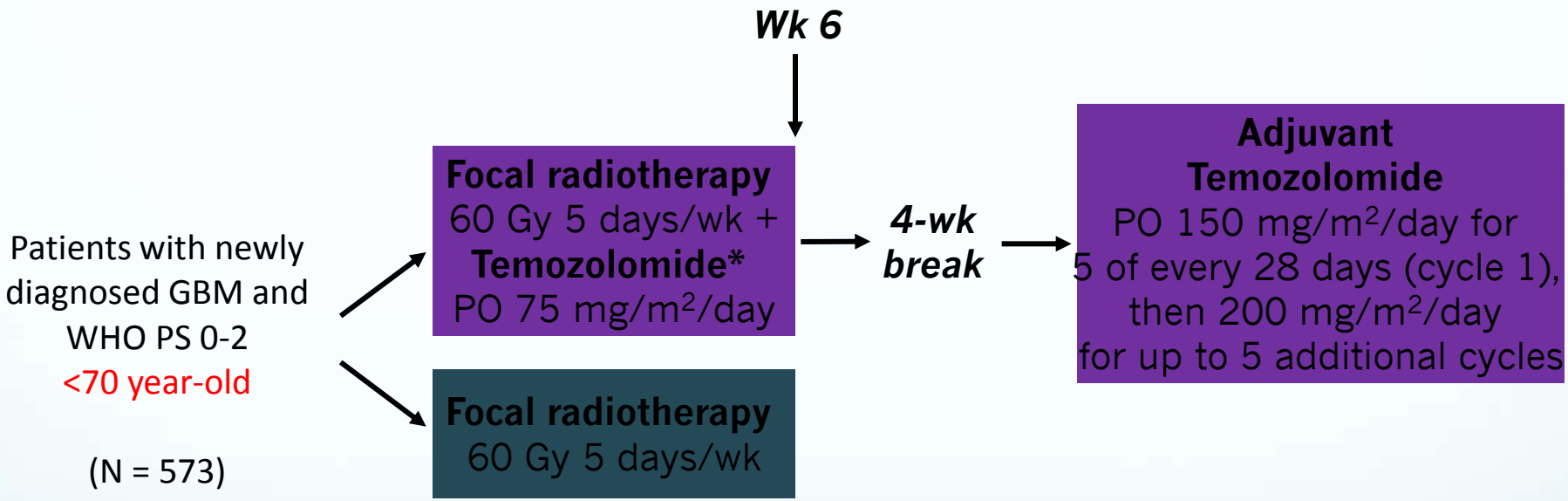
CIRUGÍA

- Mejoras en las técnicas quirúrgicas
  - Cirugía asistida por técnicas de fluorescencia
  - Monitorización intraoperatoria
  - RM funcional



Tratamiento Complementario

EORTC/NCIC Phase III Trial: Radiotherapy ± Temozolomide in Newly Diagnosed GBM



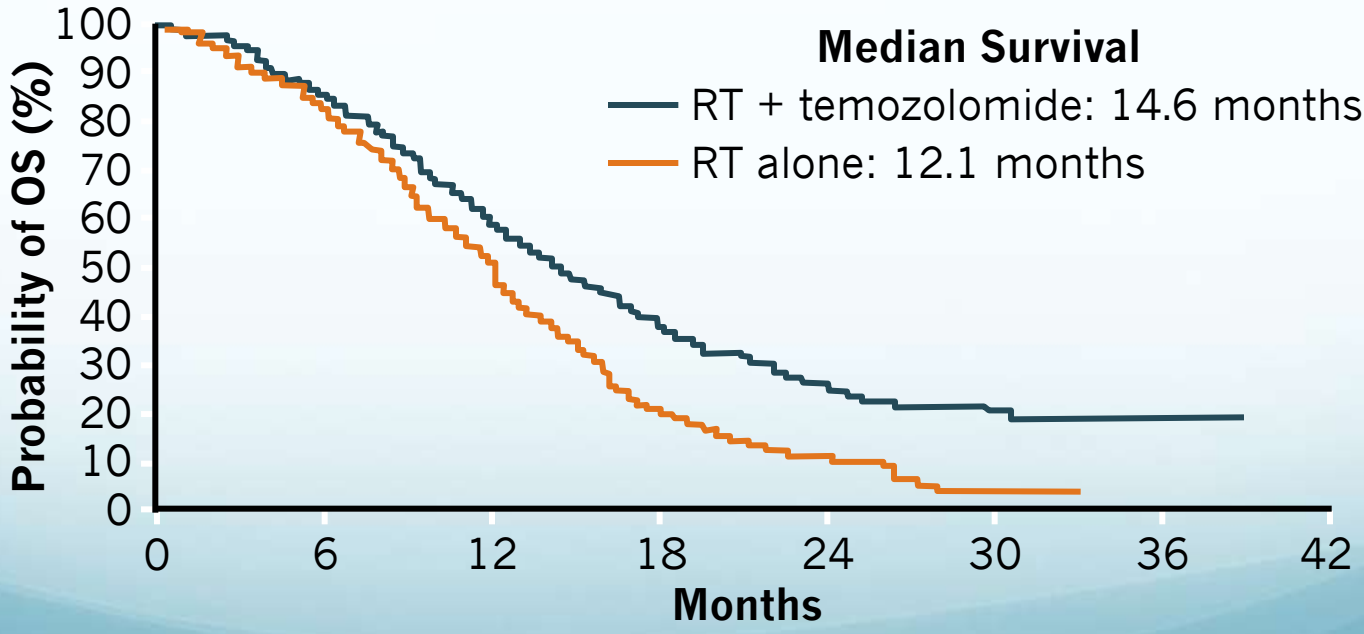
*Plus *Pneumocystic carinii* prophylaxis with pentamidine or trimethoprim-sulfamethoxazole

- **Primary endpoint: OS**
- **Secondary endpoints: PFS, safety, quality of life**

Mirimanoff RO, et al. J Clin Oncol. 2006;24:2563-2569.

Temozolomide: Standard of Care in GBM

- First adjuvant systemic chemotherapy to show significant promise in GBM
  - Phase III study (N = 573): 2-year OS rate improved from 10.4% with RT alone to 26.5% with temozolomide



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

Table 3. Overall and Progression-free Survival According to Treatment Group.*

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
	value (95% CI)	
Median overall survival (mo)	12.1 (11.2–13.0)	14.6 (13.2–16.8)
Overall survival (%)		
At 6 months	84.2 (80.0–88.5)	86.3 (82.3–90.3)
At 12 months	50.6 (44.7–56.4)	61.1 (55.4–66.7)
At 18 months	20.9 (16.2–26.6)	39.4 (33.8–45.1)
At 24 months	10.4 (6.8–14.1)	26.5 (21.2–31.7)
Median progression-free survival (mo)	5.0 (4.2–5.5)	6.9 (5.8–8.2)
Progression-free survival (%)		
At 6 months	36.4 (30.8–41.9)	53.9 (48.1–59.6)
At 12 months	9.1 (5.8–12.4)	26.9 (21.8–32.1)
At 18 months	3.9 (1.6–6.1)	18.4 (13.9–22.9)
At 24 months	1.5 (0.1–3.0)	10.7 (7.0–14.3)

Resultados a largo plazo

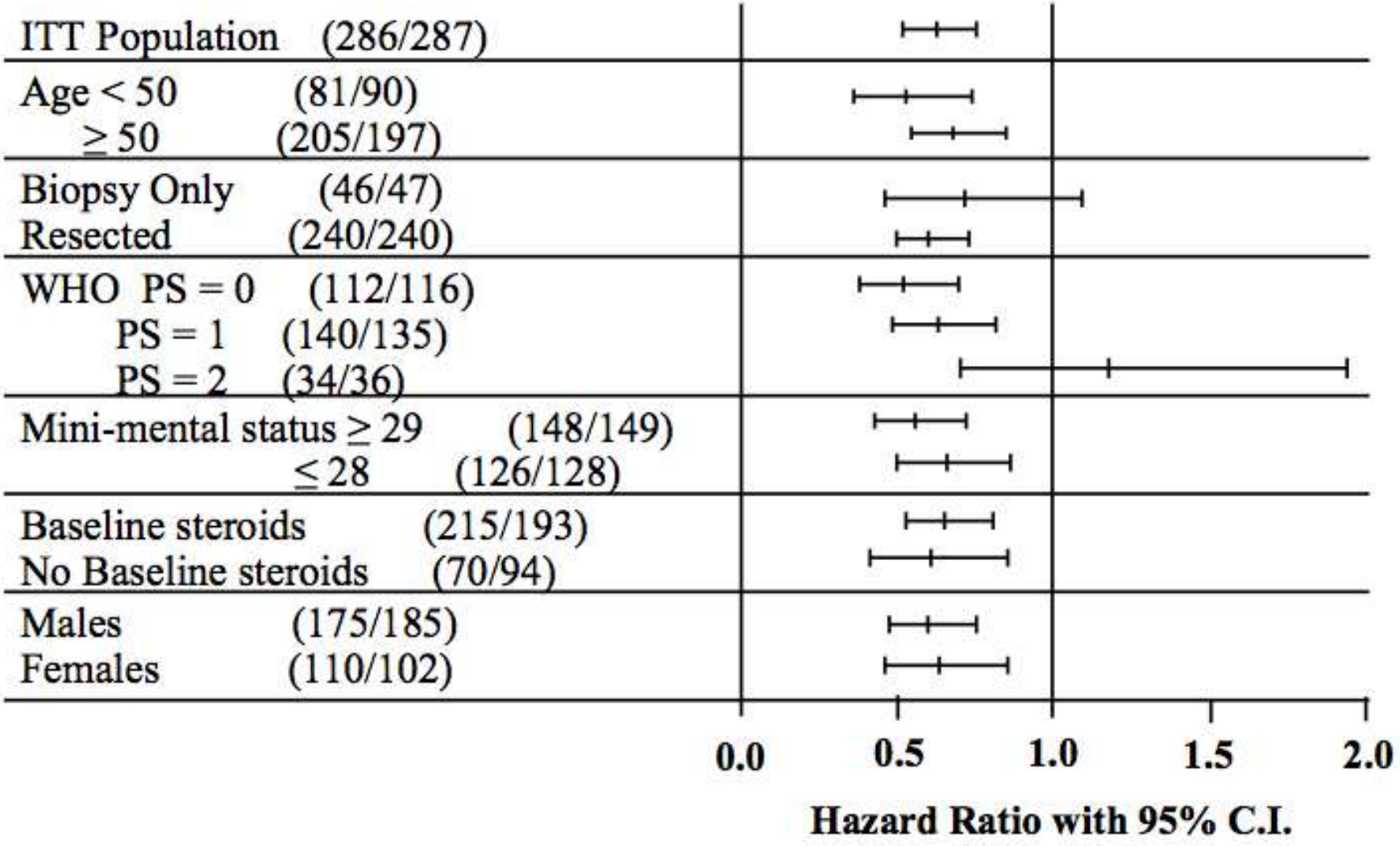
Aumento significativo de SG

- 2 años → 27 vs11%
- 5 años→10 vs 2 %

- Beneficio en todos los subgrupos

EC EORTC/NCIC 22981/26981

Analísis multivariante. Cox proportional-hazard models



Factores Pronósticos

EC EORTC/NCIC 22981/26981

Resultados por factores clínicos (SG)

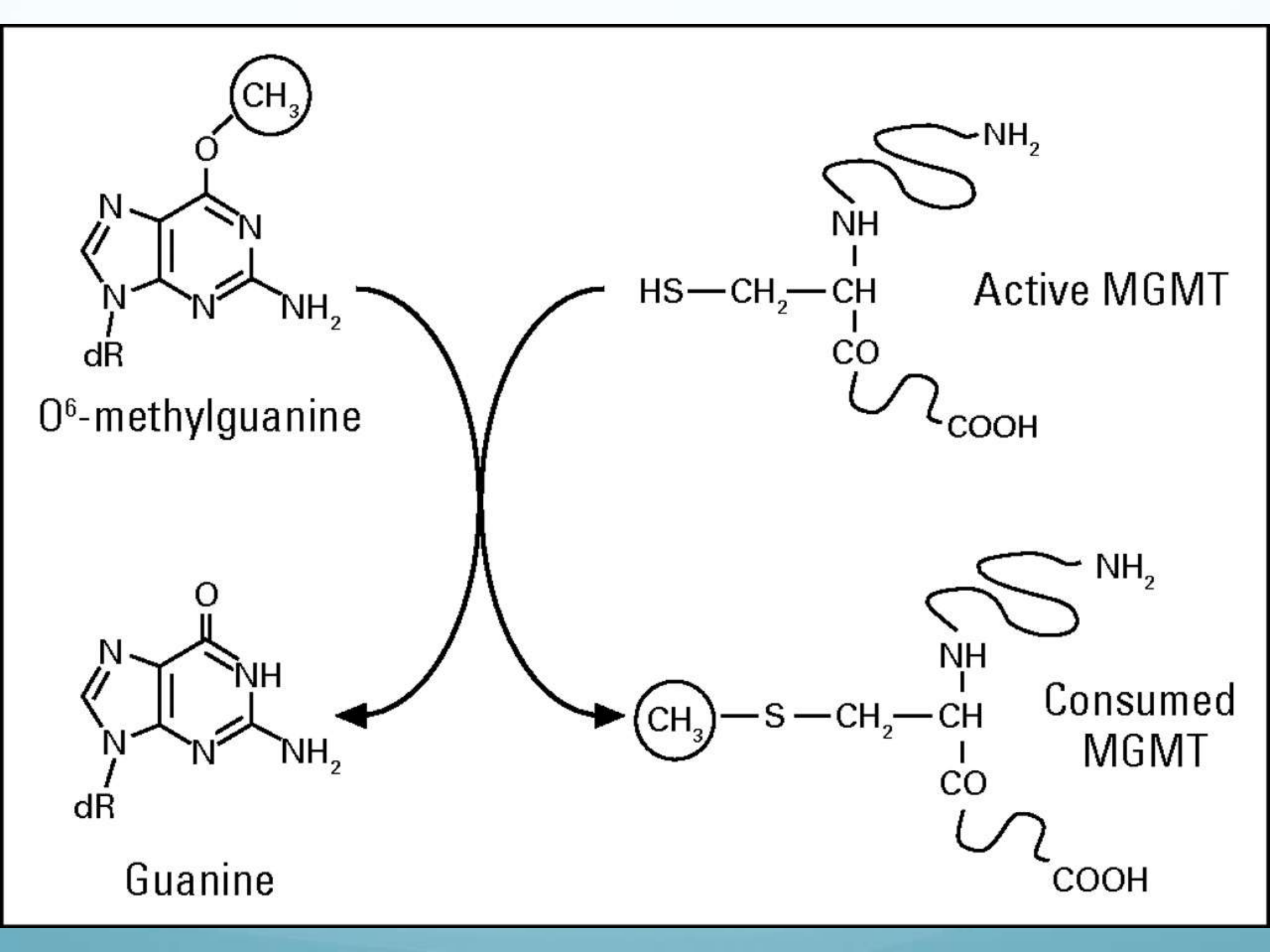
Supplemental Table 1. Subset Analysis of Median Overall Survival by Prognostic Factors

		Median survival, months	
Characteristic	**Number patients**	**RT**	**TMZ/RT**
Age			
< 50	172	13.2	17.4*
≥ 50	401	11.9	13.6*
Gender			
Male	360	11.4	14.1*
Female	213	12.8	16.3*
Prior Surgery			
Resection	480	12.9	15.8*
Biopsy Only	93	7.9	9.4
WHO performance status			
0	223	13.3	17.4*
1	277	11.9	14.0*
2	73	10.5	9.9
Baseline Steroids			
Yes	408	11.0	13.5*
No	164	16.2	19.7†

*$P < .001$
†$P = .005$
WHO = World Health Organization

MGMT
Metil-Guanina-O-Metiltransferasa

- Enzima fundamental en la reparación del daño inducido al DNA por fármacos alquilantes
- La metilación del promotor induce silenciamiento en su expresión y es un acontecimiento frecuente en gliomas
- Pérdida de expresión:
  - →Quimiosendibilidad
- Expresión normal:
  - →Quimioresistencia


CH3
O
N
N
N
N
NH2
dR
O6-methylguanine
NH2
NH
HS—CH2—CH
CO
COOH
Active MGMT
O
N
NH
N
N
NH2
dR
Guanine
NH2
NH
CH3—S—CH2—CH
CO
COOH
Consumed MGMT

MGMT
Metil-Guanina-O-Metiltransferasa

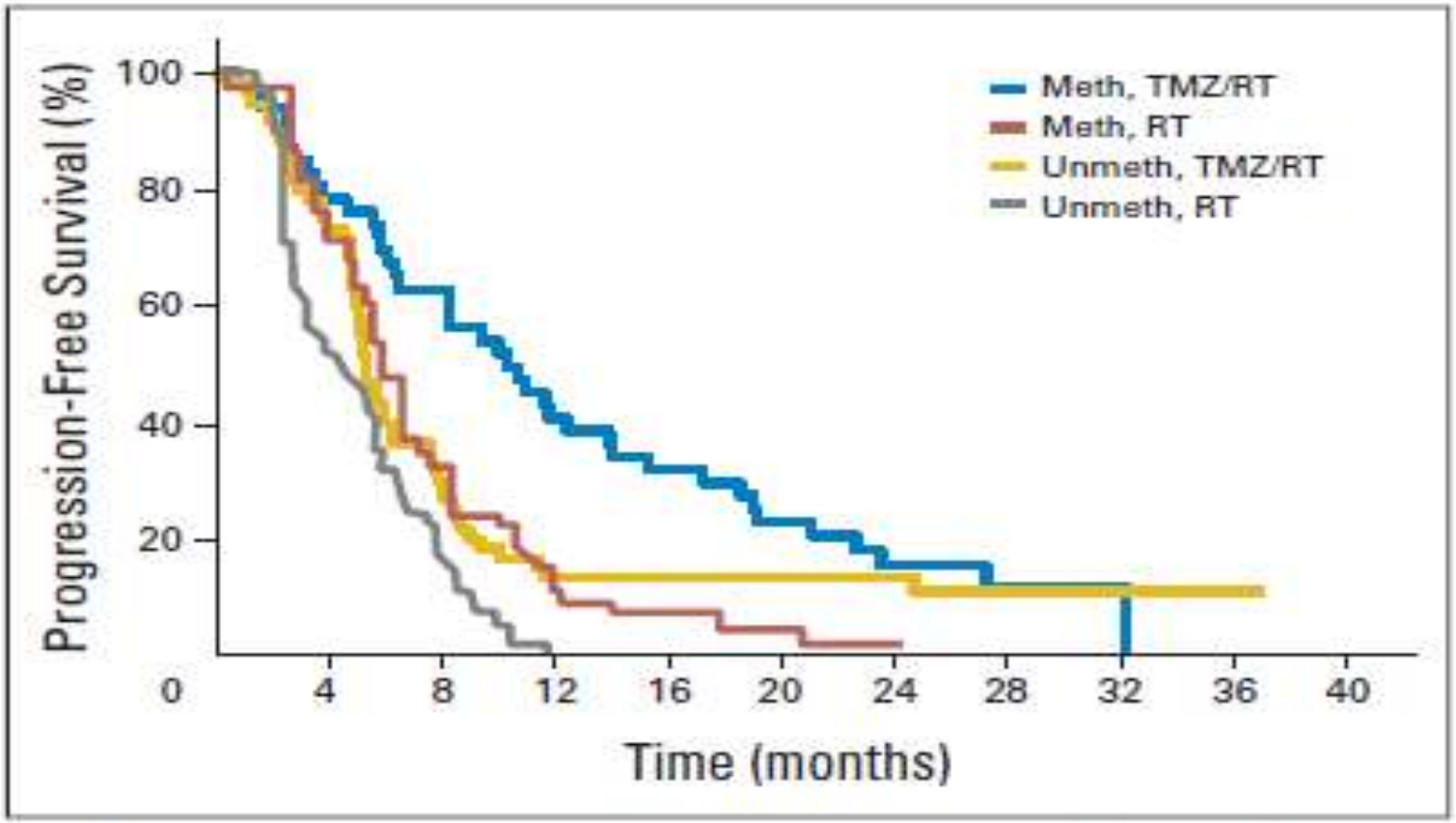
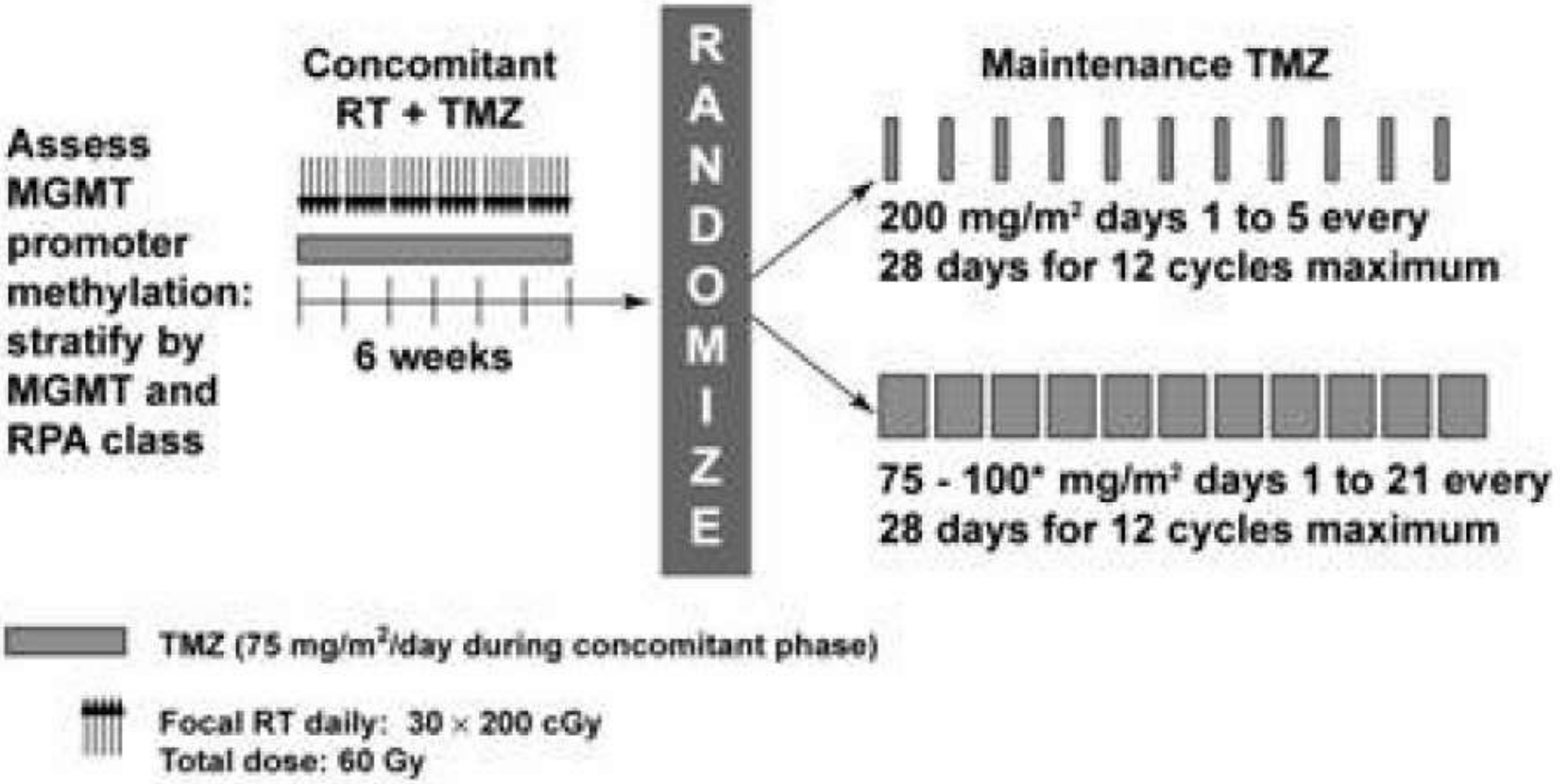


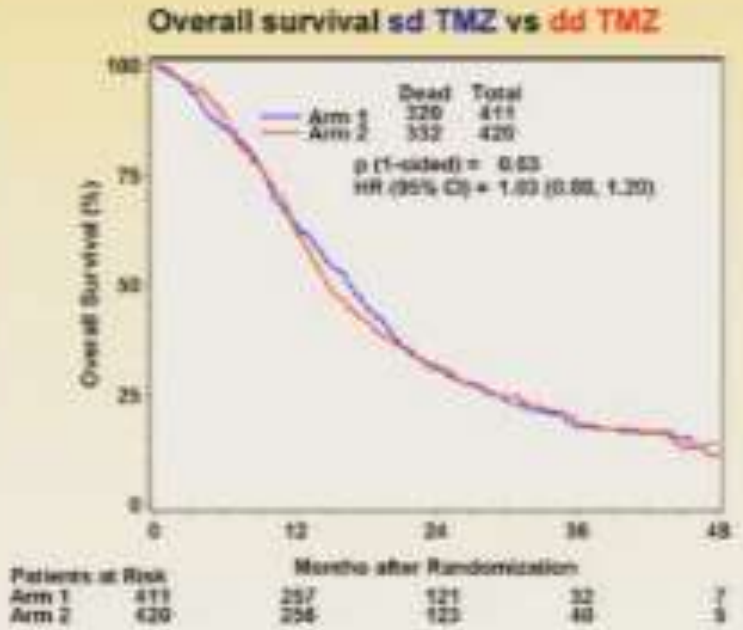
Fig 6. Kaplan-Meier estimation of progression-free survival according to randomization and O^6-methylguanine-methyltransferase promoter methylation status of the tumors. Abbreviations: Meth, methylated; Unmeth, unmethylated; TMZ, temozolomide; RT, radiotherapy. Reprinted with permission.[33]

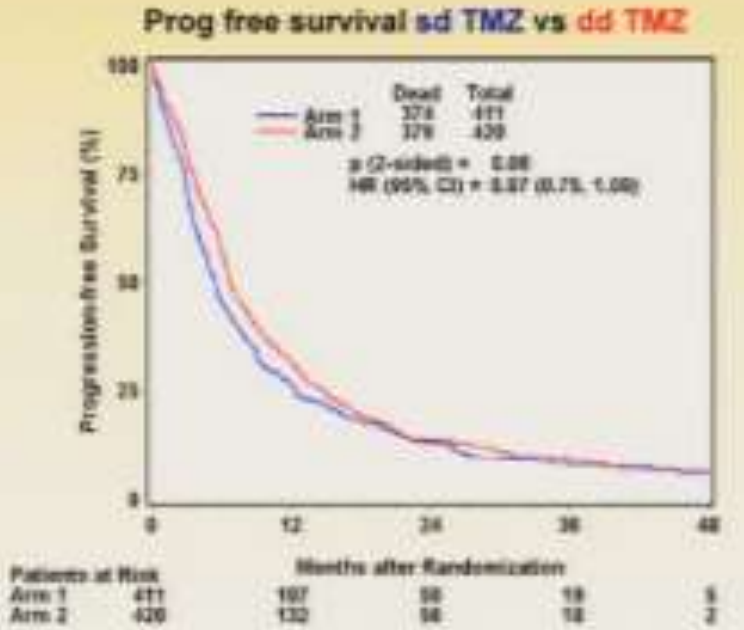
¿Optimizar el régimen de Stupp?

RTOG 0525


Assess MGMT promoter methylation: stratify by MGMT and RPA class
Concomitant RT + TMZ
6 weeks
RANDOMIZE
Maintenance TMZ
200 mg/m² days 1 to 5 every 28 days for 12 cycles maximum
75 - 100* mg/m² days 1 to 21 every 28 days for 12 cycles maximum
TMZ (75 mg/m²/day during concomitant phase)
Focal RT daily: 30 × 200 cGy
Total dose: 60 Gy

Primary Outcomes by Treatment





	Dosis estándar	Dosis densa
Mediana Supervivencia	16,6 meses	14,9 meses
Mediana SLP	5,5 meses	6,07 meses

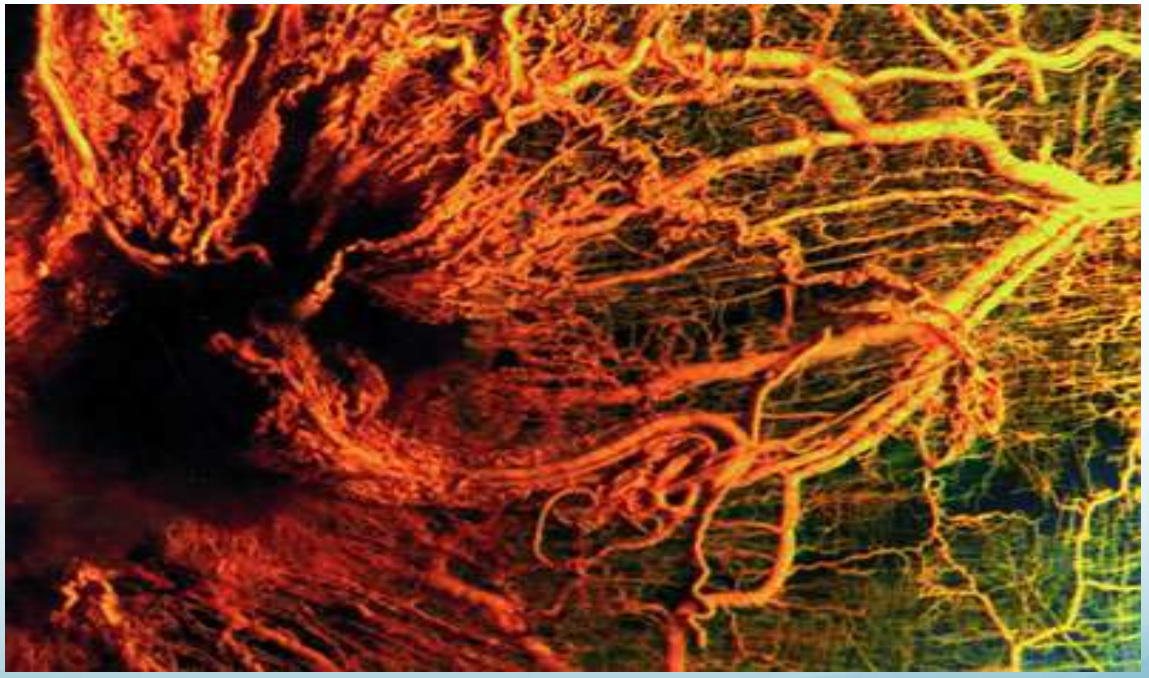
Estudio AVAglio

- Añadir bevacizumab al esquema estándar con quimiorradioterapia.

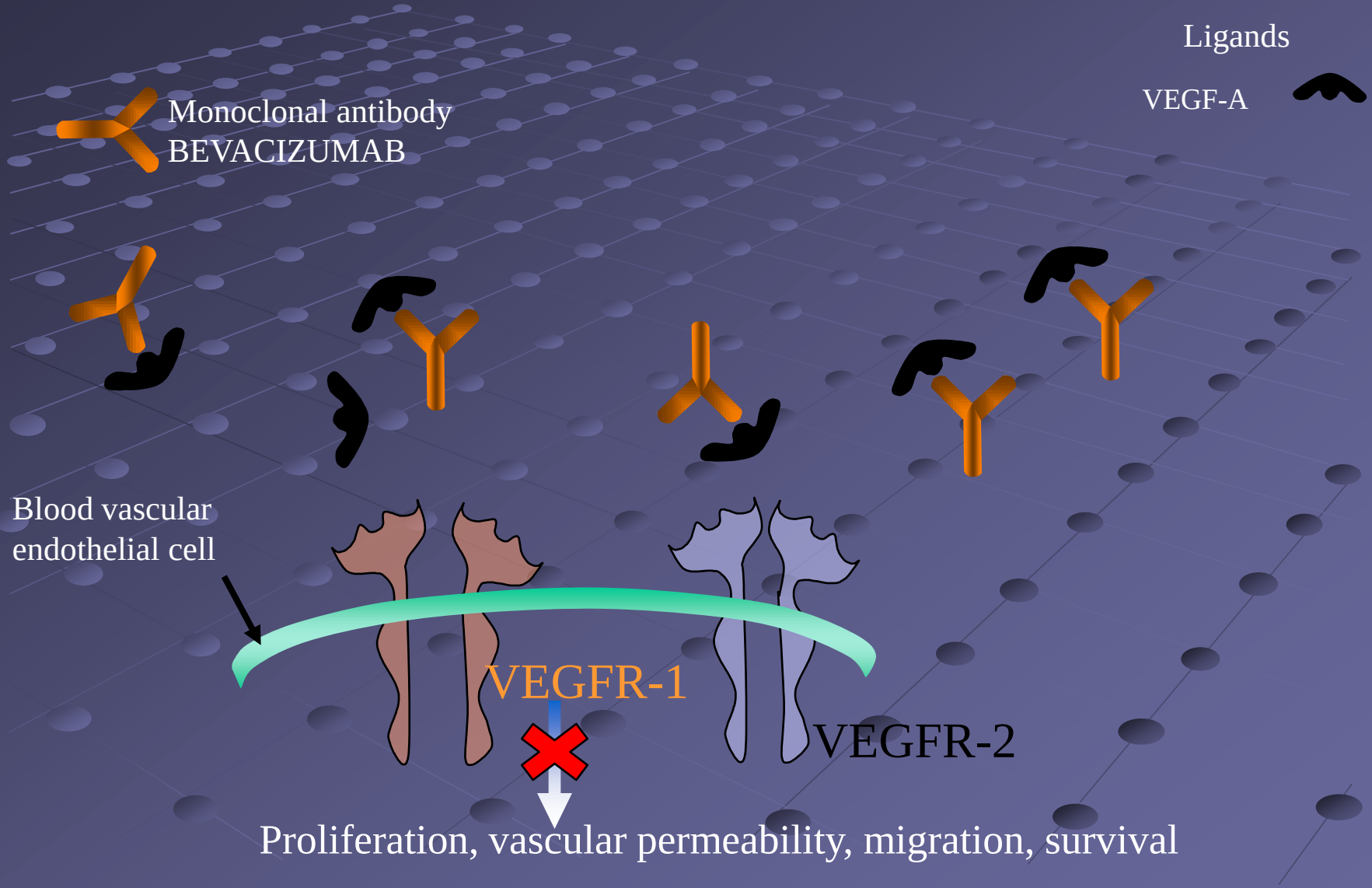
- Bevacizumab, Ac monoclonal frente a VEGF

Angiogénesis en GBM

- Angiogénesis está muy desarrollada en GBM
- Múltiples moléculas implicadas en angiogénesis están sobre-expresadas en GBM: VEGF, VEGFR, PDGFR, TGF-β, EGF

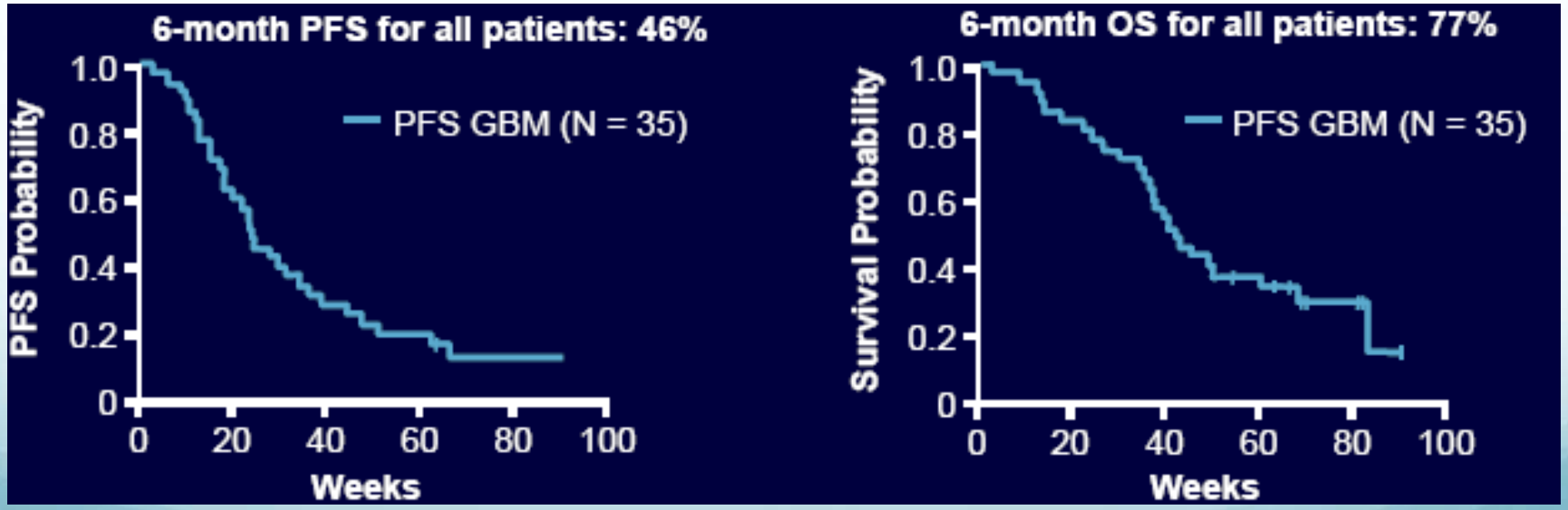


Bevacizumab– Anti-VEGF antibody



Bevacizumab. Primeros datos

- Fase II (Bevacizumab+Irinotecan)
  - N=32, gliomas grado III y IV en recaida tras RT y TMZ
  - Tasa de respuestas del 63%
  - Mediana de SLP: 20 semanas
  - Mediana SG: 10 meses

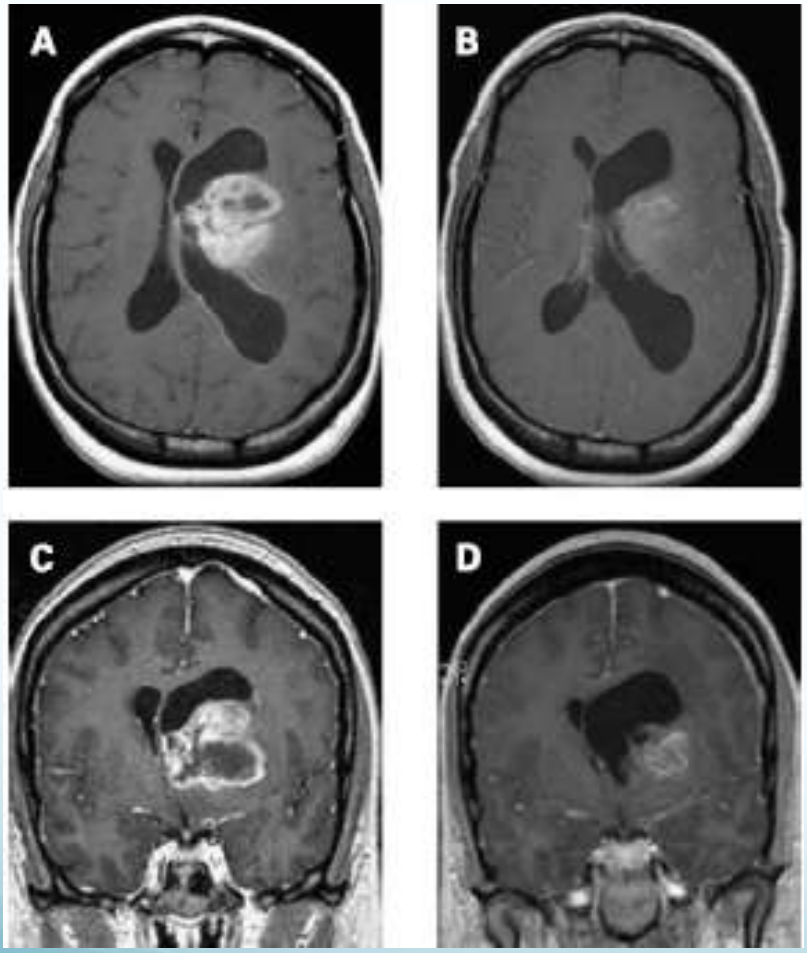


Vredenburgh JJ, et al. Clin Cancer Res 2007;13:1253–9

Bevacizumab. Primeros datos

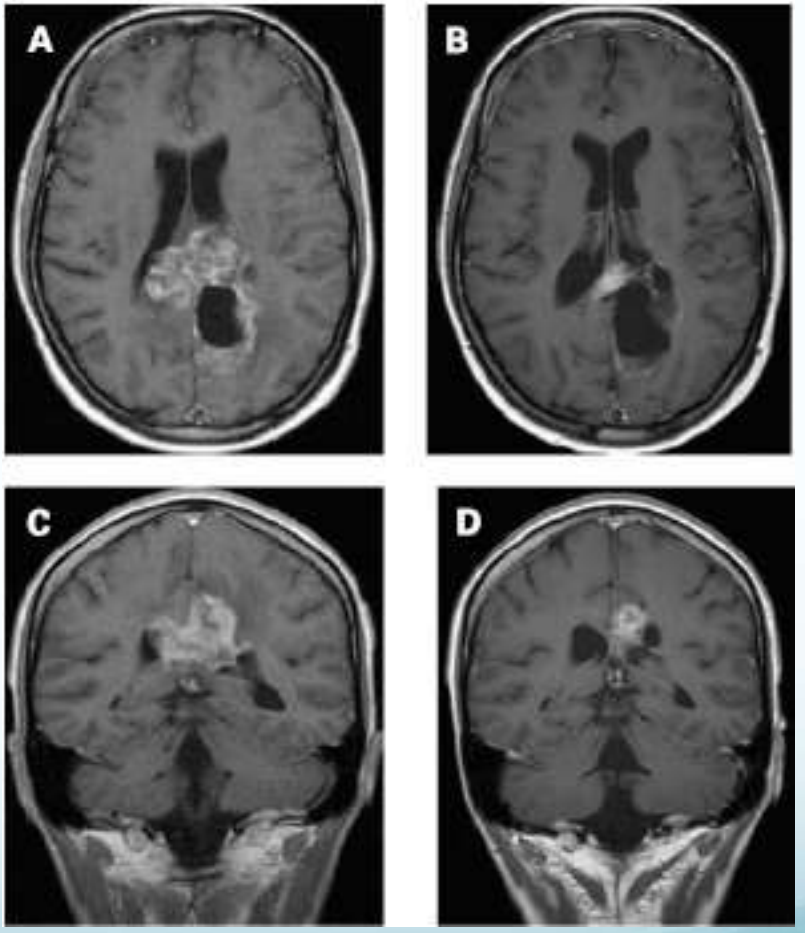
Vredenburgh JJ, et al. Clin Cancer Res 2007;13:1253–9

Bevacizumab. Primeros datos



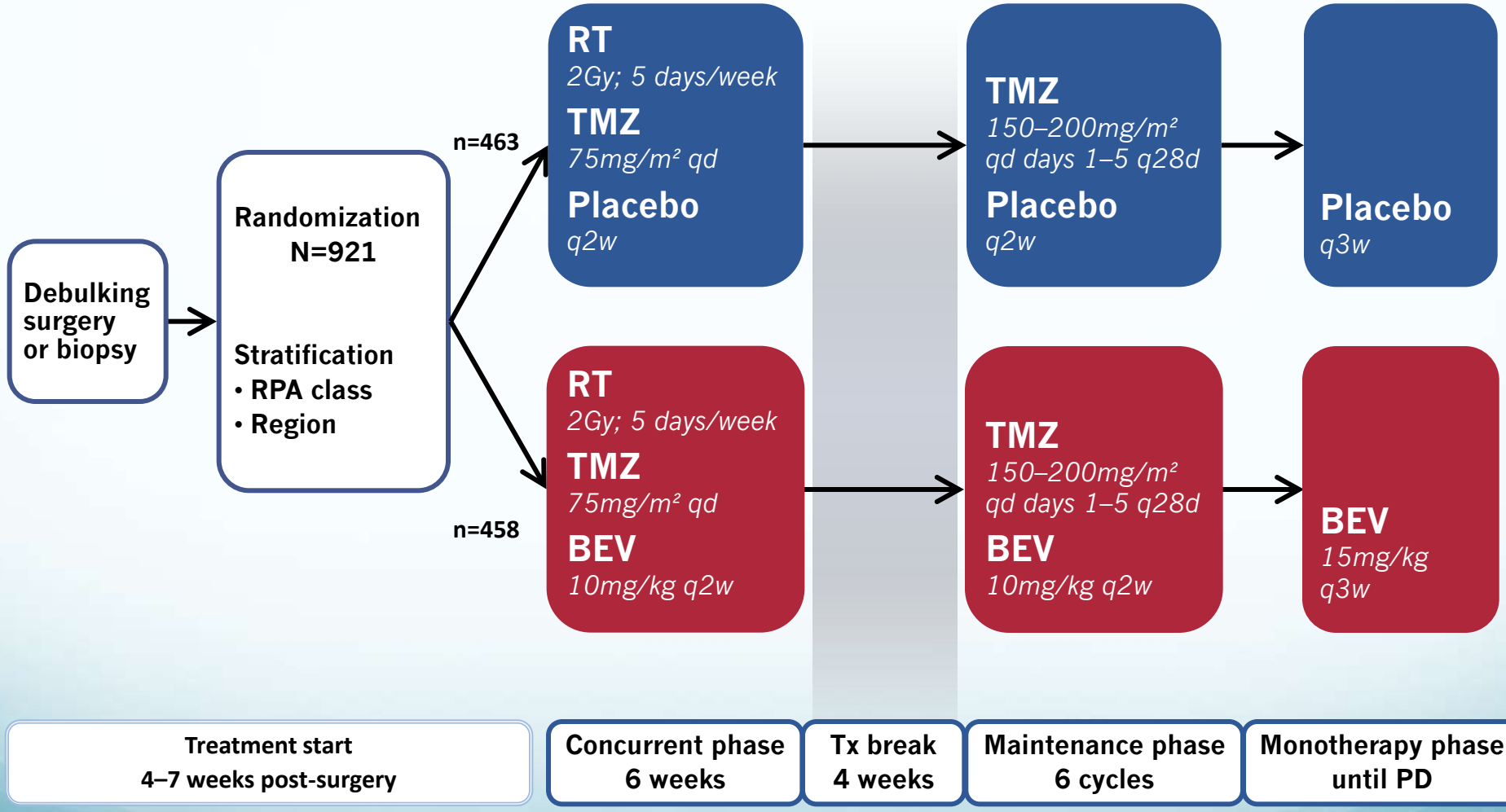
Vredenburgh JJ, et al. Clin Cancer Res 2007;13:1253–9

Bevacizumab. Primeros datos



Vredenburgh JJ, et al. Clin Cancer Res 2007;13:1253–9

AVAglio Study Design



Last patient in: March 2011

BEV = bevacizumab; PD = progressive disease; RPA = recursive partitioning analysis; RT = radiotherapy; TMZ = temozolomide; Tx = treatment; qd = daily; q28d = every 28 days; q2w = every 2 weeks; q3w = every 3 weeks

Study Objectives

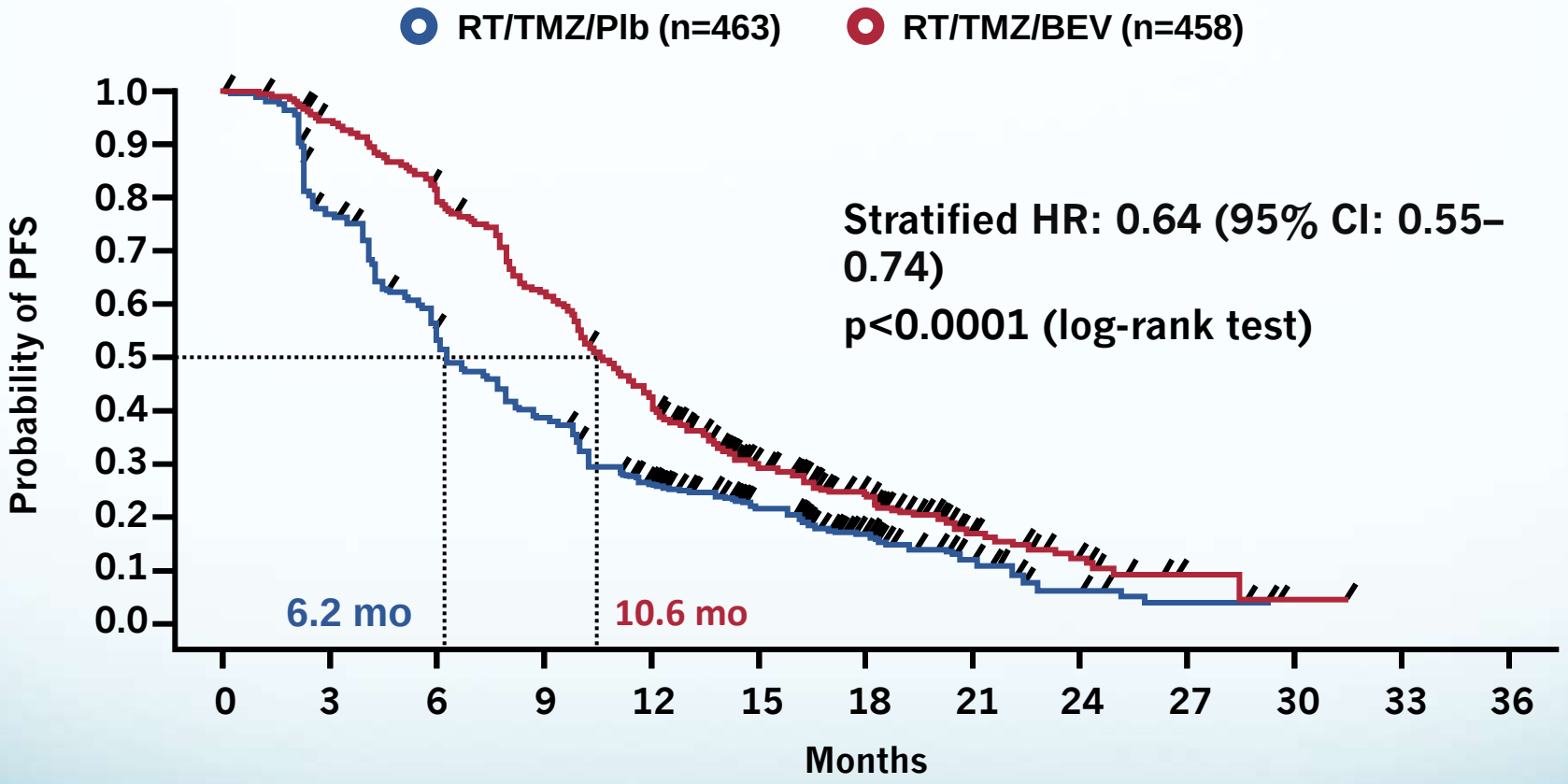
- Co-primary objectives
  - PFS (investigator assessed)
  - OS
- Secondary objectives
  - PFS (Independent Review Facility)
  - 1-year and 2-year survival rates
  - Health-related quality of life (EORTC QLQ-C30 and BN20)
  - Safety
- Exploratory objectives included
  - Karnofsky performance status
  - Use of corticosteroids

EORTC QLQ-C30 and BN20 = European Organization for Research and Treatment quality of life questionnaire core 30 and brain neoplasms 20; OS = overall survival; PFS = progression-free survival

Avaglio: Baseline Characteristics

Patients, %		RT/TMZ/Plb (n=463)	RT/TMZ/BEV (n=458)
Median age, years (range)		56.0 (18–79)	57.0 (20–84)
Gender	Male	64	62
WHO PS	0 1–2	52 48	50 50
RPA class	III IV V	16 60 23	17 57 26
MGMT status	Methylated Non-methylated Missing	26 51 23	26 49 25
Surgical status	Biopsy Partial resection Complete resection	10 48 42	13 46 41
KPS	50–80 90–100	30 70	33 67
MMSE score	<27 ≥27	24 76	24 76
Corticosteroids	On Off	45 55	41 59
EIAEDs	On Off	20 80	19 81

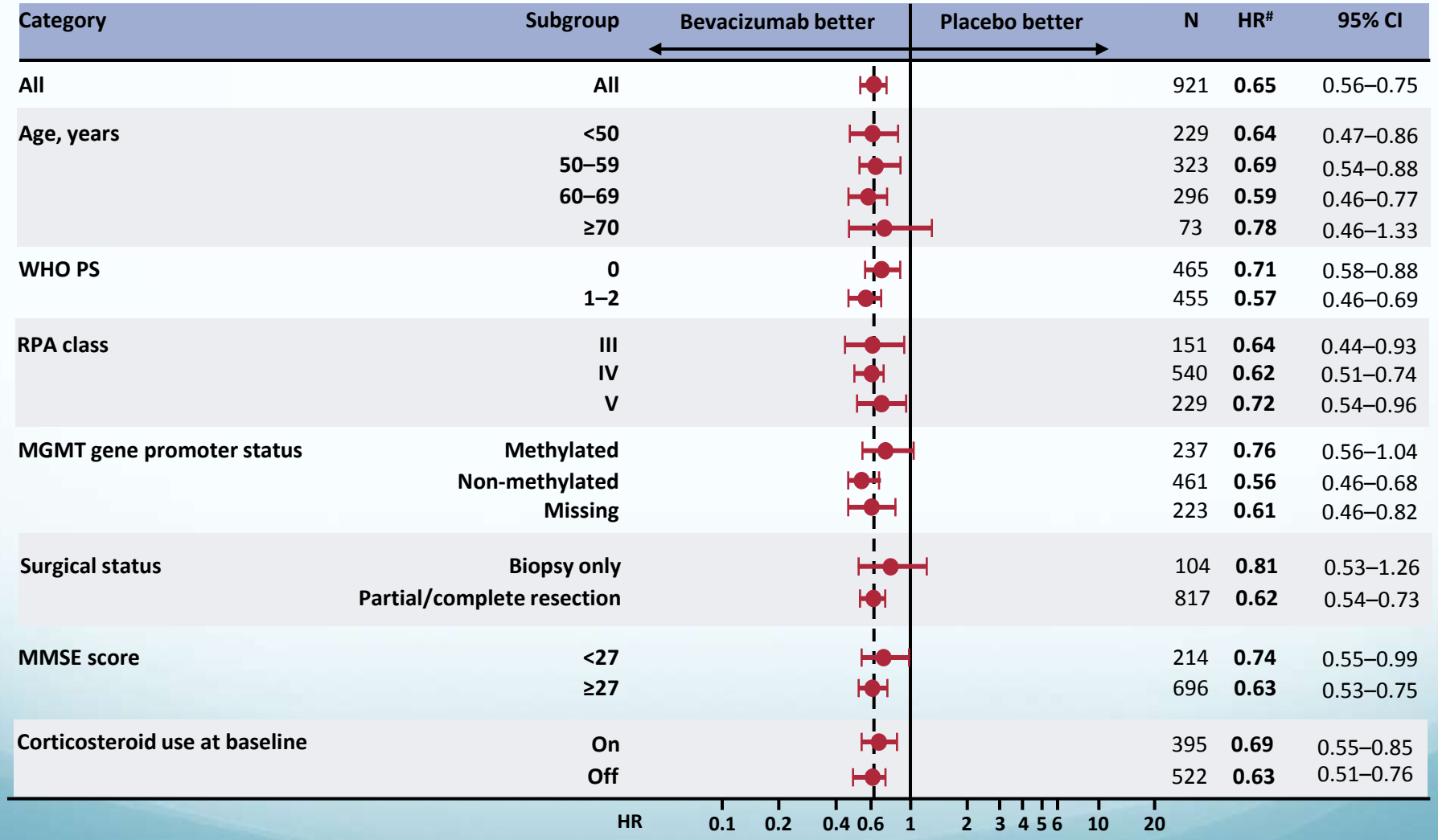
Investigator-Assessed PFS (Co-Primary Endpoint)



N at risk													
RT/TMZ/Plb	463	349	247	170	110	77	47	23	8	4	0	0	0
RT/TMZ/BEV	458	424	366	278	189	104	71	25	13	2	1	0	0

BEV = bevacizumab; CI = confidence interval; HR = hazard ratio; mo = months; PFS = progression-free survival; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Investigator-Assessed PFS: Subgroup Analyses*

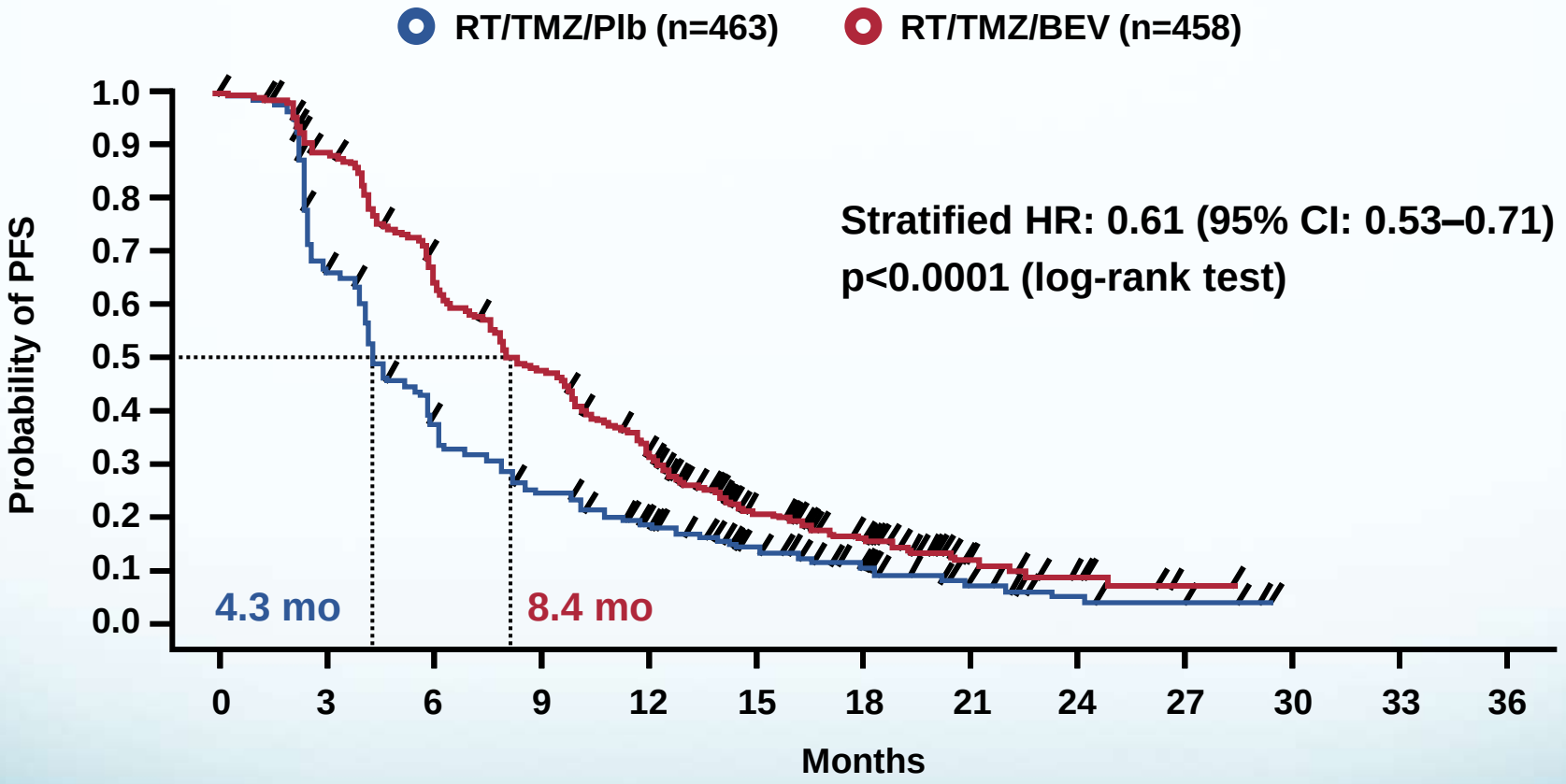


Category	Subgroup	N	HR#	95% CI
All	All	921	**0.65**	0.56–0.75
Age, years	<50	229	**0.64**	0.47–0.86
	50–59	323	**0.69**	0.54–0.88
	60–69	296	**0.59**	0.46–0.77
	≥70	73	**0.78**	0.46–1.33
WHO PS	0	465	**0.71**	0.58–0.88
	1–2	455	**0.57**	0.46–0.69
RPA class	III	151	**0.64**	0.44–0.93
	IV	540	**0.62**	0.51–0.74
	V	229	**0.72**	0.54–0.96
MGMT gene promoter status	Methylated	237	**0.76**	0.56–1.04
	Non-methylated	461	**0.56**	0.46–0.68
	Missing	223	**0.61**	0.46–0.82
Surgical status	Biopsy only	104	**0.81**	0.53–1.26
	Partial/complete resection	817	**0.62**	0.54–0.73
MMSE score	<27	214	**0.74**	0.55–0.99
	≥27	696	**0.63**	0.53–0.75
Corticosteroid use at baseline	On	395	**0.69**	0.55–0.85
	Off	522	**0.63**	0.51–0.76

*Selected subgroups only; #Unstratified analysis

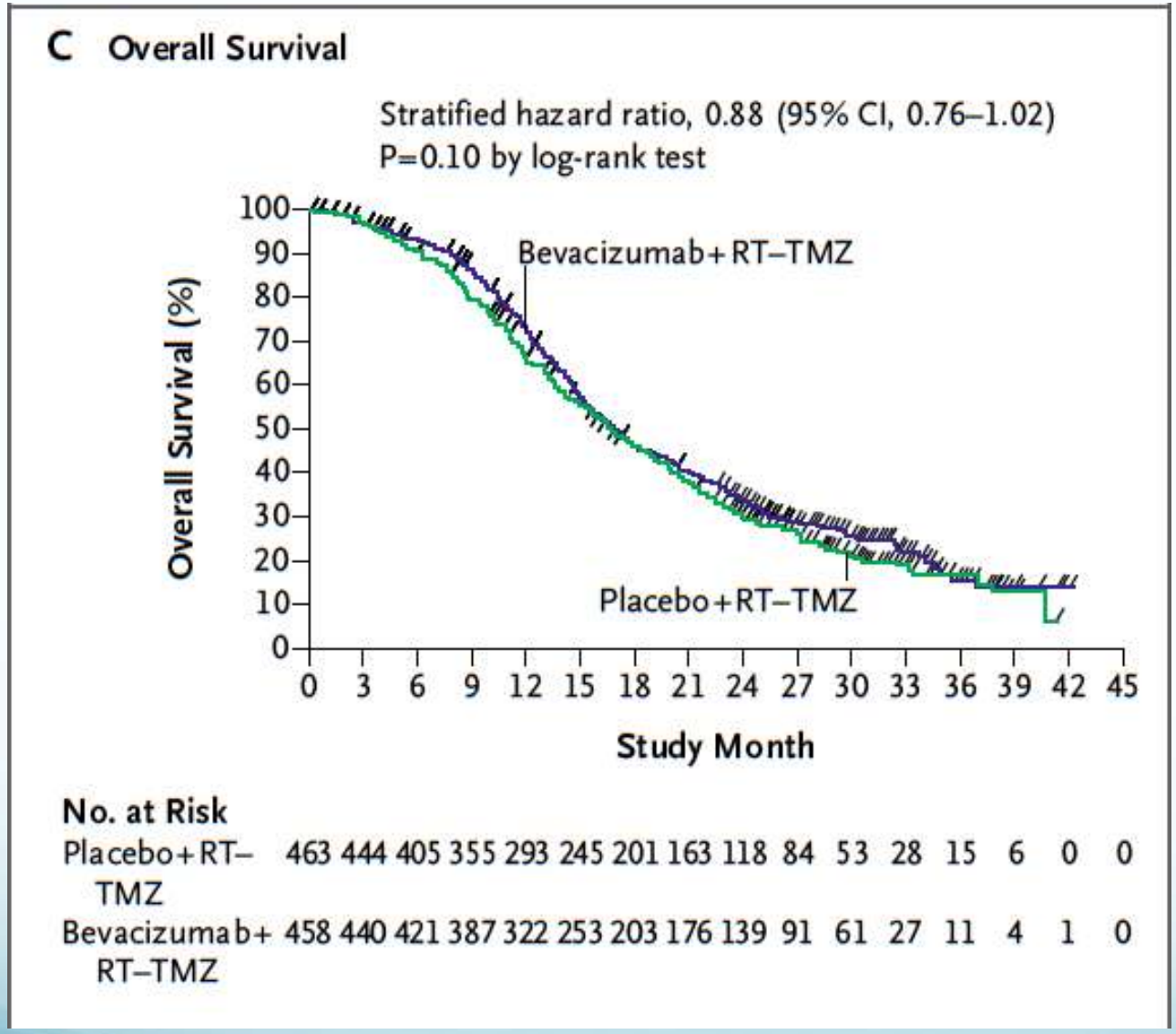
CI = confidence interval; HR = hazard ratio; MGMT = methylguanine-DNA methyltransferase; MMSE = mini-mental state examination; PFS = progression-free survival; RPA = recursive partitioning analysis; WHO PS = World Health Organization performance status

IRF-Assessed PFS (Secondary Endpoint)



N at risk													
RT/TMZ/Plb	463	297	168	109	76	46	30	14	6	4	0	0	0
RT/TMZ/BEV	458	396	298	212	148	70	44	14	7	1	0	0	0

BEV = bevacizumab; CI = confidence interval; HR = hazard ratio; IRF = Independent Review Facility; mo = months; PFS = progression-free survival; Plb = placebo; RT = radiotherapy; TMZ = temozolomide



BEV = bevacizumab; CI = confidence interval; HR = hazard ratio; OS = overall survival; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Health-Related Quality of Life

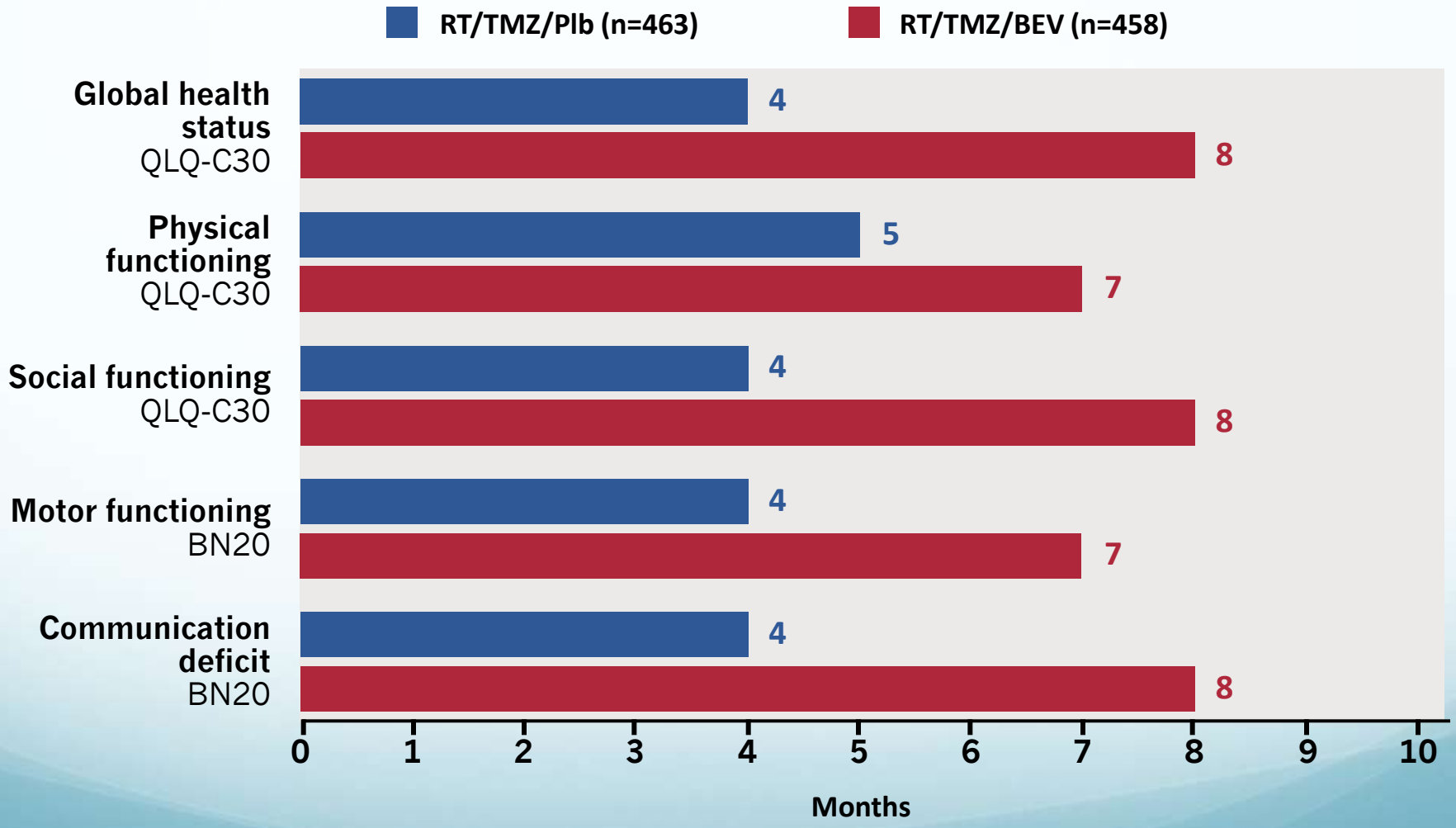
- EORTC QLQ-C30 and BN20 (brain cancer-specific), validated HRQoL instruments[1–3]

- Five domains were pre-specified as secondary analyses based on relevance and importance in glioblastoma[2,4–10]
  - Global health status
  - Physical functioning
  - Social functioning
  - Motor functioning
  - Communication deficit

[1]Aaronson 1993; [2]Osoba 1996; [3]Taphoorn 2010
[4]Bottomley, Aaronson 2007
[5]Osoba 2000; [6]Taphoorn 2005
[7]Stupp 2005; [8]Taphoorn, Bottomley 2005
[9]Klein 2001; [10]Budrukkar 2009

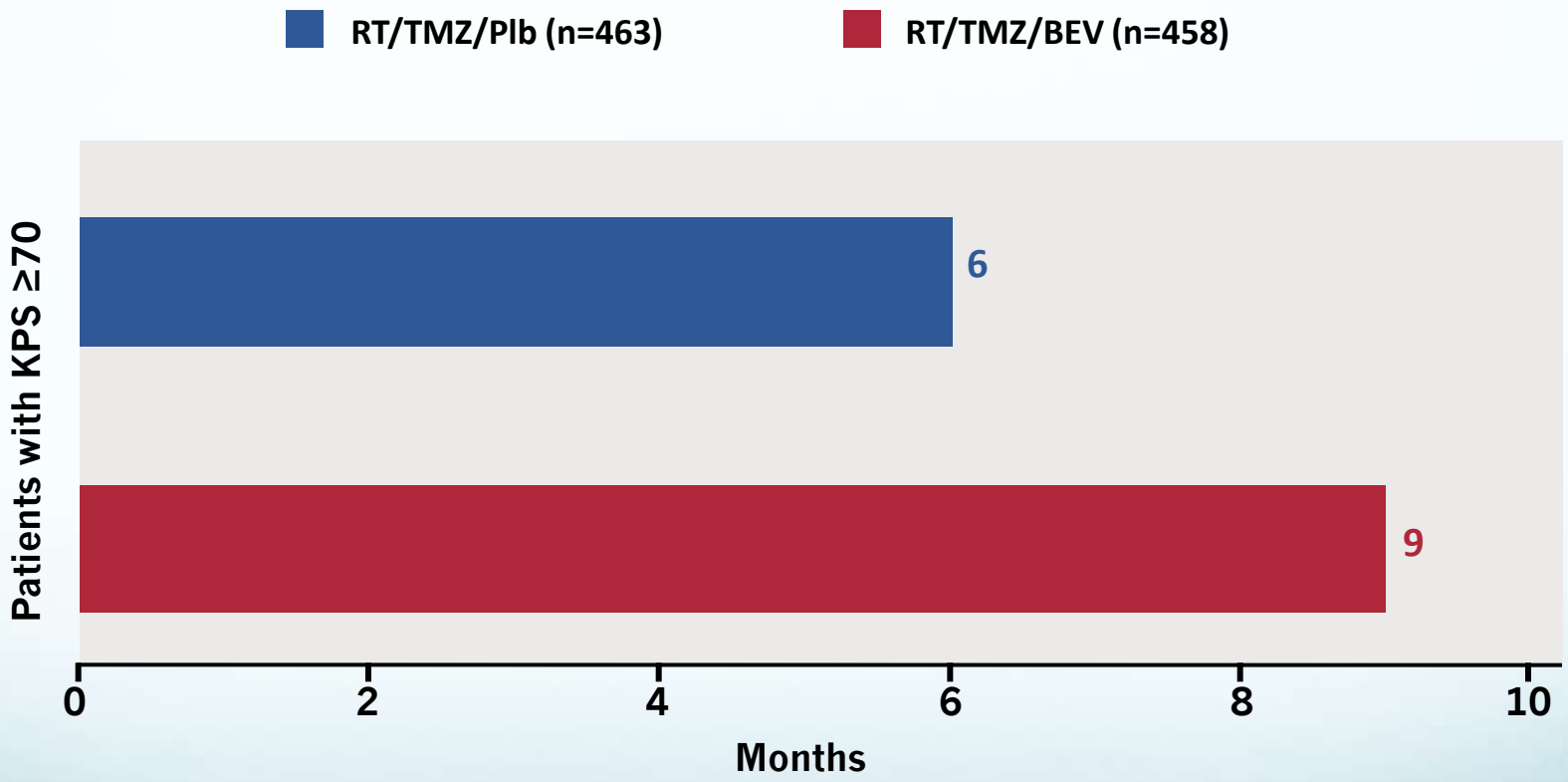
EORTC QLQ-C30 and BN20 = European Organization for Research and Treatment quality of life questionnaire core 30 and brain neoplasms 20; HRQoL = health-related quality of life

Median Duration that Patients were Stable/Improved from Baseline



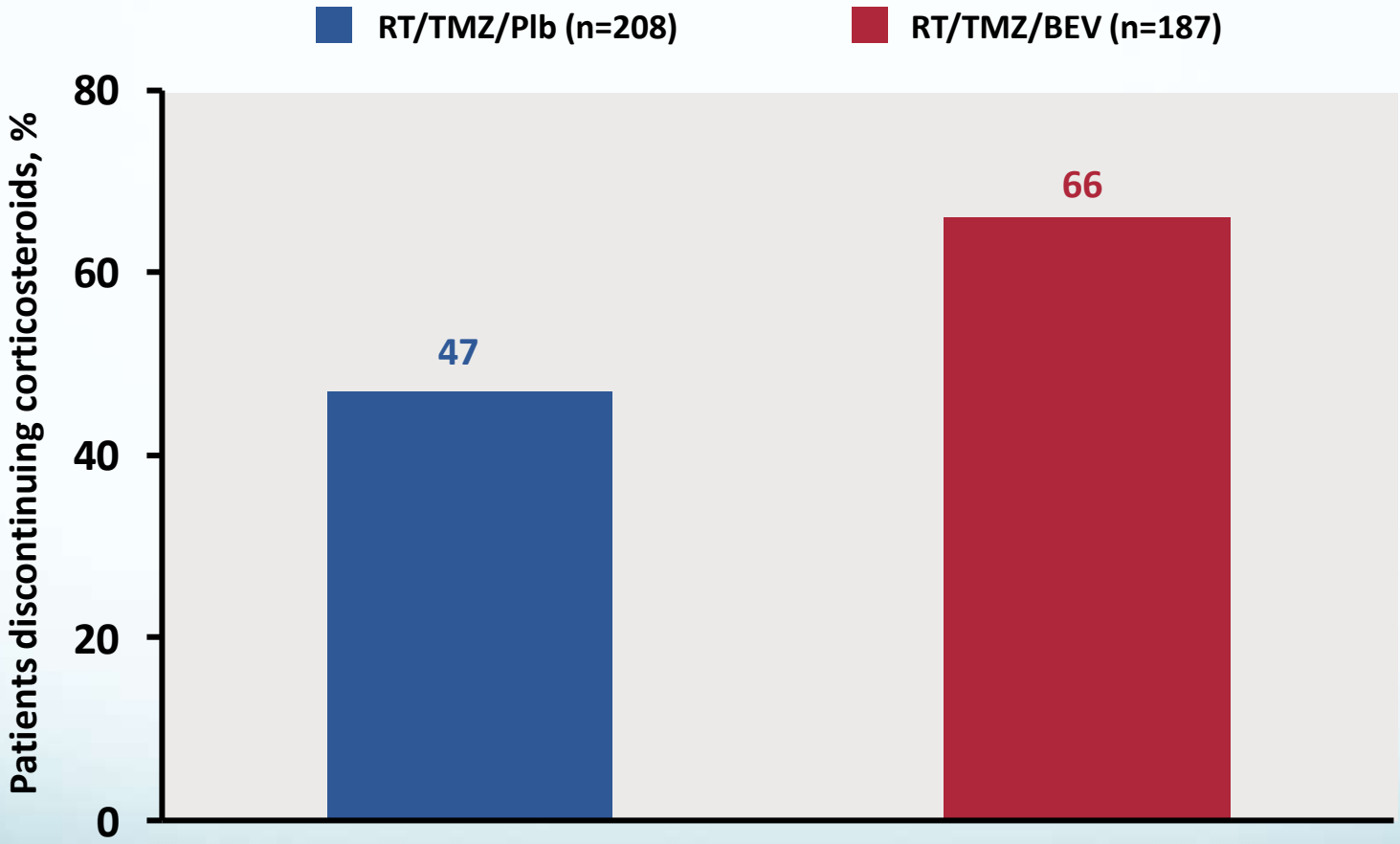
BEV = bevacizumab; BN20 = brain neoplasms 20; HRQoL = health-related quality of life; QLQ-C30 = quality of life questionnaire core 30; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Median Duration Patients Maintained a KPS ≥70



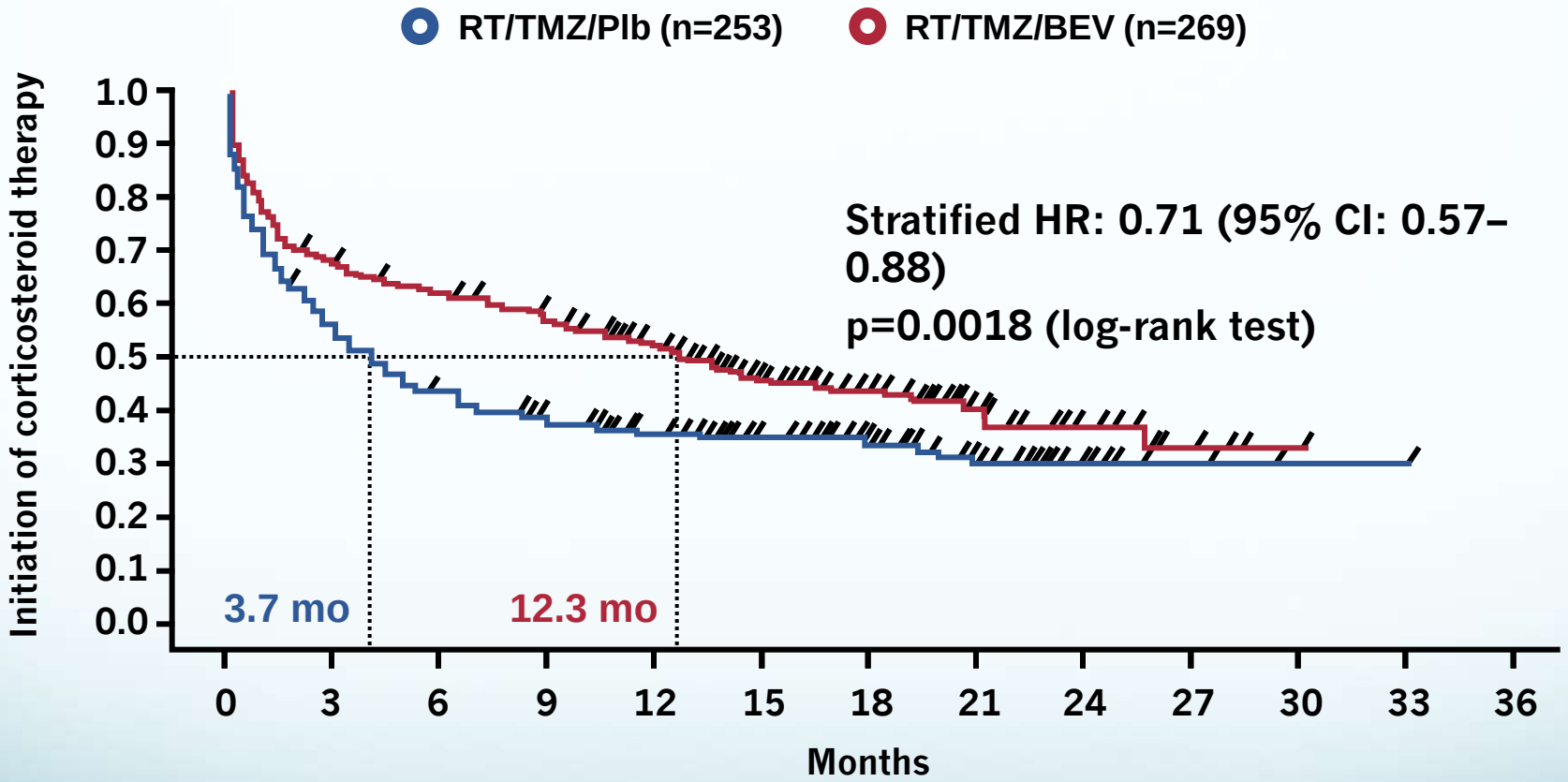
BEV = bevacizumab; KPS = Karnofsky performance status; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Corticosteroid Discontinuation* in Patients ON Steroids at Baseline



*Defined as no corticosteroid intake (0mg) for at least 5 consecutive days
BEV = bevacizumab; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Time to Steroid Initiation for Patients OFF Steroids at Baseline



N at risk													
RT/TMZ/Plb	253	133	106	88	77	56	34	17	5	2	1	0	0
RT/TMZ/BEV	269	179	163	146	125	76	47	20	11	5	0	0	0

BEV = bevacizumab; CI = confidence interval; HR = hazard ratio; mo = months; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Adverse Events of Special Interest for BEV

Patients, %	RT/TMZ/Plb (n=447)		RT/TMZ/BEV (n=464)	
	All grades	Grade ≥3	All grades	Grade ≥3
Bleeding: cerebral haemorrhage	2.2	0.7	2.6	1.5
mucocutaneous bleeding	8.9	–	26.7	0.4
other	8.1	0.4	11.6	0.6
Wound-healing complications	2.2	0.7	3.7	1.5
Arterial thromboembolic events	1.6	1.3	5.0	4.1
Venous thromboembolic events	9.6	8.1	7.8	7.3
Hypertension	13.0	2.0	37.5	10.3
Proteinuria	4.0	–	14.0	3.7
GI perforation (including GI fistula/abscess)	0.2	0.2	1.7	1.1
Abscesses and fistulae	0.4	0.4	0.6	0.6
Congestive heart failure	0.2	–	0.4	0.4
Posterior reversible encephalopathy syndrome	–	–	–	–

Safety population

BEV = bevacizumab; GI = gastrointestinal; Plb = placebo; RT = radiotherapy; TMZ = temozolomide

Conclusiones

- El estudio es positivo: alcanza su objetivo primario de SLP (reducción de riesgo 36%)
  - Reforzado por datos de calidad de vida
  - Mantenimiento de KPS
  - Menor uso de corticoides.

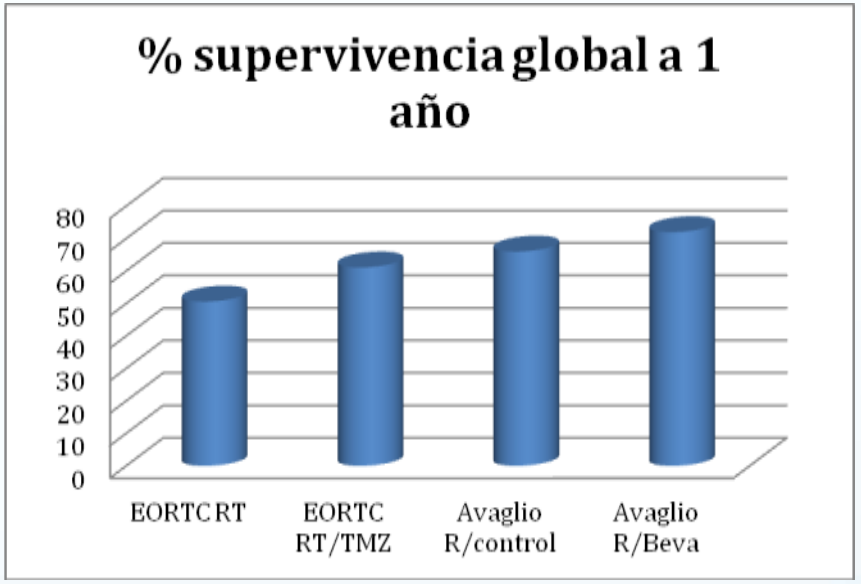
- No beneficio en SG:
  - -Cross-over
  - -¿Bevacizumab mejor en segunda línea?

Aspectos a subrayar

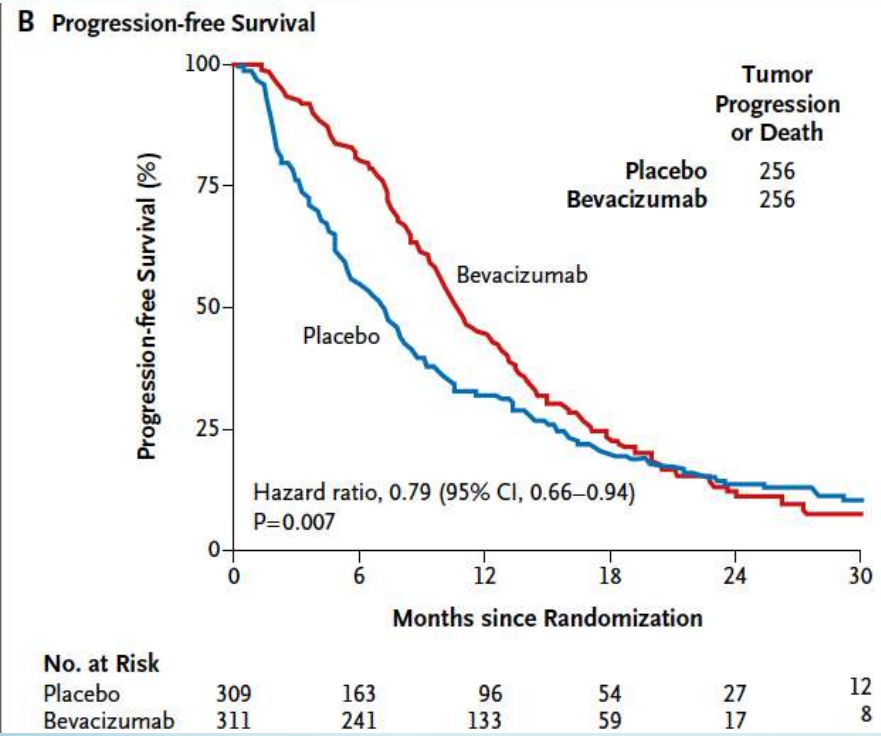
- Características de los pacientes incluidos
  - Ancianos (>70 años) fueron incluidos
  - Grupos equilibrados

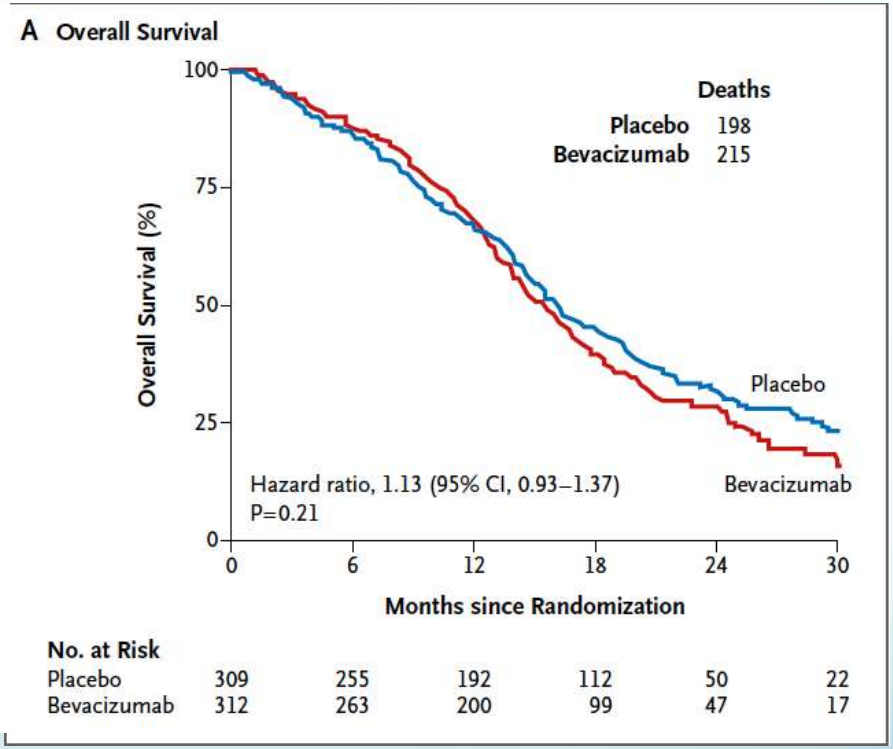
Resultados. En perspectiva

- *SUPERVIVENCIA 1 AÑO*
- *EORTC-NCIC (Stupp)*
  - *rama control 54,6%*
  - *experimental 61%*
- Avaglio
  - Control 66%
  - Experimental 72%



ESTUDIO RTOG 0825





Gilbert et al. NEJM 2014.

Tratamiento en la Progresión/Recurrencia

- Resección quirúrgica
  - Tumores localizados
  - Prolongado tiempo de supervivencia libre de progresión desde la primera cirugía
- Quimioterapia sistémica basada en estudios Fase II:
  - Bevacizumab
  - Temozolomida dosis densas
  - Nitrosureas
  - Fotemustina
  - Platinos
- Ensayos clínicos

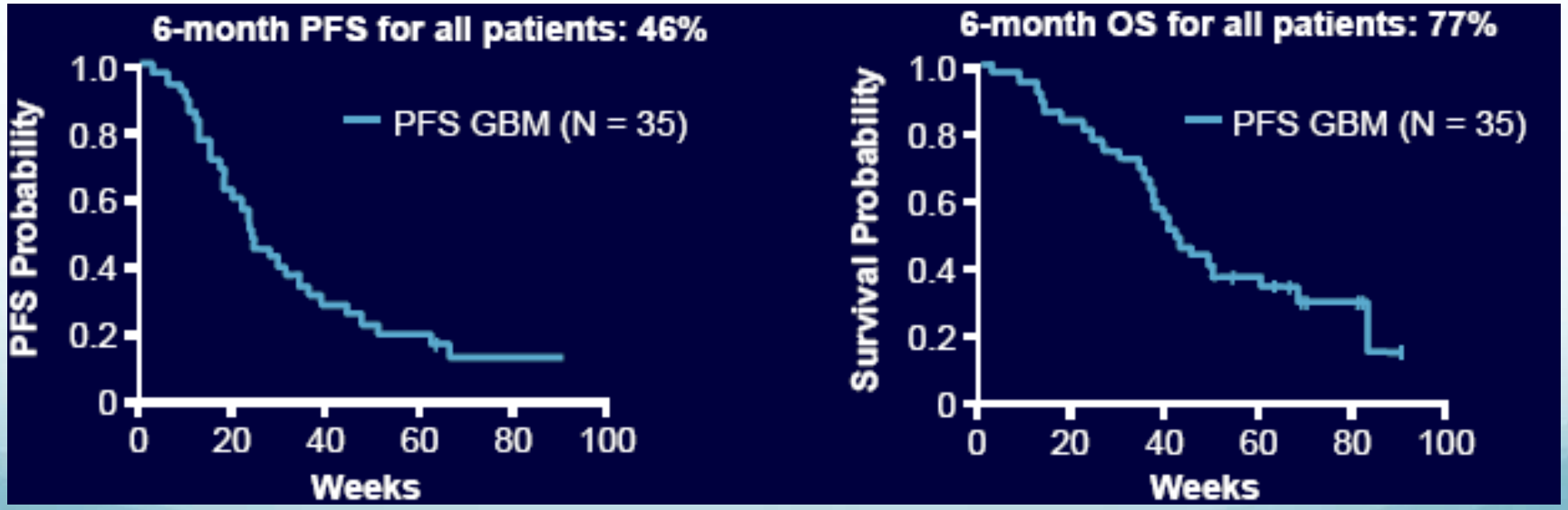
Tratamiento en la Progresión/Recurrencia

Trial	Glioblastoma Population	Response Rate, % (95% CI)	6-Mo PFS, % (95% CI)	Median OS (95% CI)
8 phase II trials (1986-1995)[1]	Recurrent (N = 225)	9 (2.9-9.1)	15 (10-19)	25 wks (21-28)
16 NCCTG trials (mainly phase II; 1980-2004)[2]	Previously treated (N = 345)	NR	9	5.0 (4.6-5.4)
12 phase II NABTC trials (1998-2002)[3]	Recurrent grade IV glioma (N = 437)	7 (4.6-9.4)	16 (12-20)	30 wks (27-33)
Lomustine control arm from phase III enzastaurin study[4]	Recurrent, intracranial (n = 92)	4.3 (0.2-8.4)	19 (10-28)	7.1 (6.0-8.8)

1. Wong FT, et al. J Clin Oncol. 1999;17:2572-2578. 2. Ballman KV, et al. Neuro Oncol. 2007;9:29-38.
3. Lamborn KR, et al. Neuro Oncol. 2008;10:162-170. 4. Fine HA, et al. ASCO 2008. Abstract 2005.

Bevacizumab. Primeros datos

- Fase II (Bevacizumab+Irinotecan)
  - N=32, gliomas grado III y IV en recaida tras RT y TMZ
  - Tasa de respuestas del 63%
  - Mediana de SLP: 20 semanas
  - Mediana SG: 10 meses



Vredenburgh JJ, et al. Clin Cancer Res 2007;13:1253–9

Conclusiones. ManejoGBM

- 1.-El tratamiento quirúrgico es fundamental. Mejor pronóstico cuanto más extensa sea la resección.
- 2.-El tratamiento estándar complementario consiste en la quimio-radioterapia basada en temozolomida. Mejora la SG en todos los subgrupos
- 3.-La metilación MGMT predice una mejor evolucion pero no sirve aún para seleccionar el tratamiento.
- 4.-Estrategias de mejora del tratamiento estándar: Por ahora fracaso de los antiangiogénicos en este conexto

Muchas gracias por su atención