XVI CURSO NACIONAL DE NEURORRADIOLOGÍA
Neurorradiología en la Patología Tumoral Cerebral

20-21 febrero 2020 | Madrid

S.E.N.R Sociedad Española de Neurorradiología

OPCIONES DE TRATAMIENTO EN GLIOMAS: RADIOTERAPIA Y QUIMIOTERAPIA

JUAN MANUEL SEPÚLVEDA SÁNCHEZ
ONCOLOGÍA MÉDICA
HOSPITAL UNIVERSITARIO 12 DE OCTUBRE

Outline

Molecular biology of Glioma: Is there an opportunity for targeted therapies?

Glioblastoma: Current and Emerging Treatments

Post-surgical treatment of **Grade 2 Glioma**:

RTOG 9802 Trial.

Postsurgical treatment of **Anaplastic Oligodendrogliomas**

EORTC 26951 and RTOG 9402 Trials

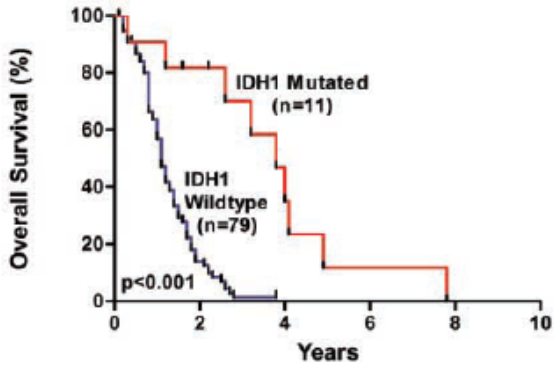
ISOCITRATE DEHYDROGENASE (IDH) MUTATIONS

An Integrated Genomic Analysis of Human Glioblastoma Multiforme

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

Science
AAAS

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	No
Br12P	31	M	No	No	1.6	G395A	R132H	Yes	No
Br104X	29	F	No	No	4.0	C394A	R132S	Yes	No
Br106X	36	M	No	No	3.8	G395A	R132H	Yes	No
Br122X	53	M	No	No	7.8	G395A	R132H	No	No
Br123X	34	M	No	Yes	4.9	G395A	R132H	Yes	No
Br237T	26	M	No	Yes	2.6	G395A	R132H	Yes	No
Br211T	28	F	No	Yes	0.3	G395A	R132H	Yes	No
Br27P	32	M	Yes	Yes	1.2	G395A	R132H	Yes	No
Br129X	25	M	Yes	Yes	3.2	C394A	R132S	No	No
Br29P	42	F	Yes	Unknown	Unknown	G395A	R132H	Yes	No
IDH1 mutant patients (n=12)	33.2	67% M	25%	42%	3.8	100%	100%	83%	0%
IDH1 wild-type patients (n=93)	53.3	65% M	16%	1%	1.1	0%	0%	27%	60%



ISOCITRATE DEHYDROGENASE 1 AND 2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

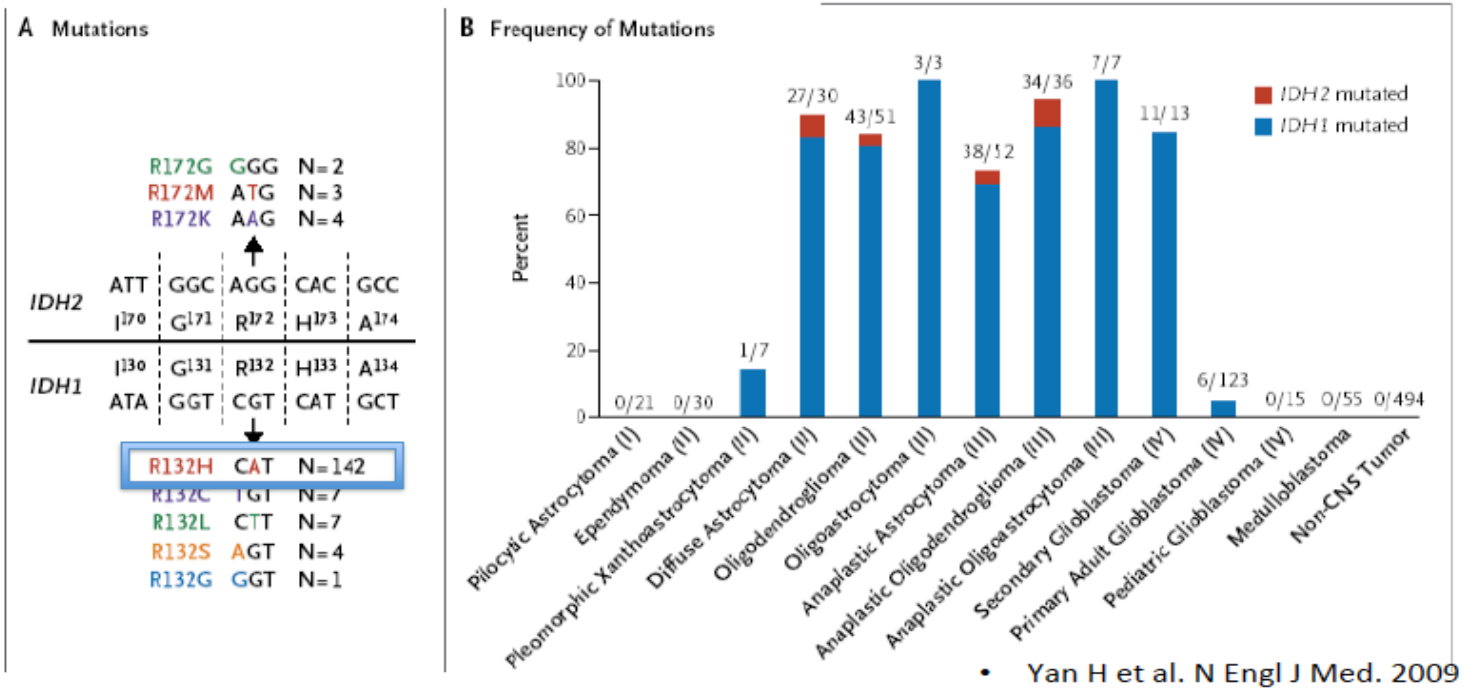
IDH1 and *IDH2* Mutations in Gliomas

Hai Yan, M.D., Ph.D., D. Williams Parsons, M.D., Ph.D., Genglin Jin, Ph.D., Roger McLendon, M.D., B. Ahmed Rasheed, Ph.D., Weishi Yuan, Ph.D., Ivan Kos, Ph.D., Ines Batinic-Haberle, Ph.D., Siân Jones, Ph.D., Gregory J. Riggins, M.D., Ph.D., Henry Friedman, M.D., Allan Friedman, M.D., David Reardon, M.D., James Herndon, Ph.D., Kenneth W. Kinzler, Ph.D., Victor E. Velculescu, M.D., Ph.D., Bert Vogelstein, M.D., and Darell D. Bigner, M.D., Ph.D.

IDH

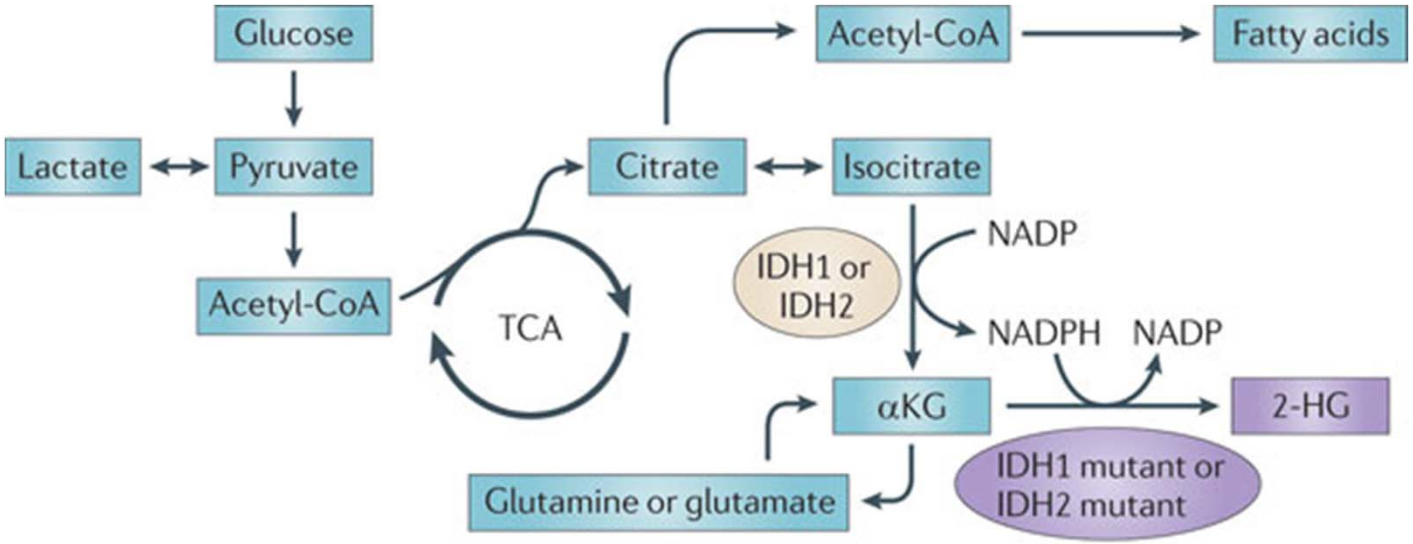
Secuencian 445 tumores SNC y 494 no-SNC

Mutaciones en 85% grado II, III y 2ºGBM



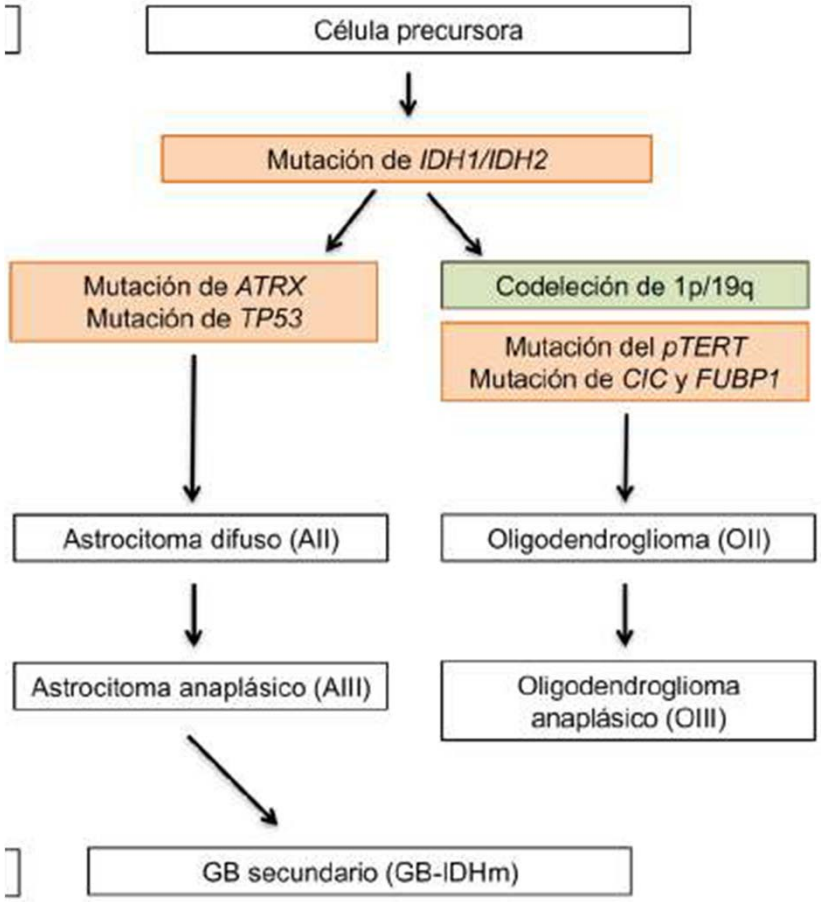
- Yan H et al. N Engl J Med. 2009

Mutations in IDH1 and IDH2



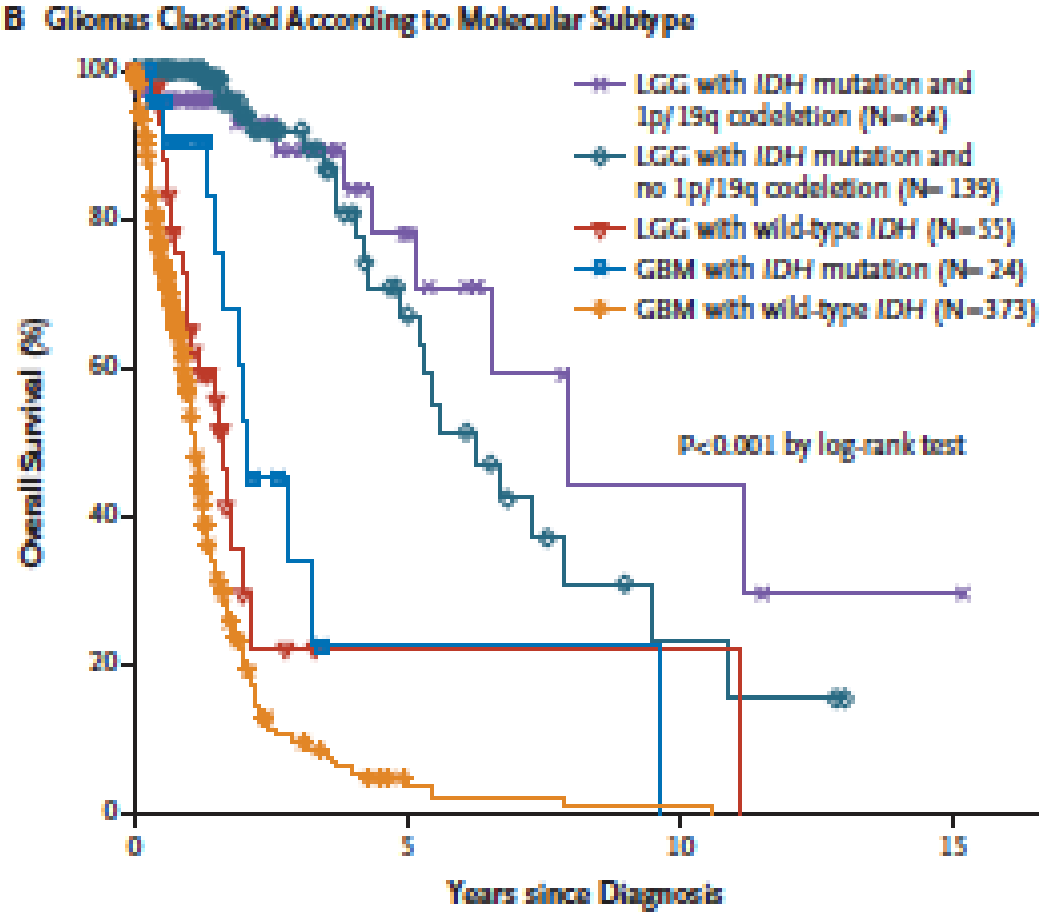
Nature Reviews | Cancer

2-Hidroxiglutarate → **Massive methilation of DNA CpG islands**
→ Damages DNA → **Genetic Instability -- >**
Chromosome losses (ej 1p19q del)

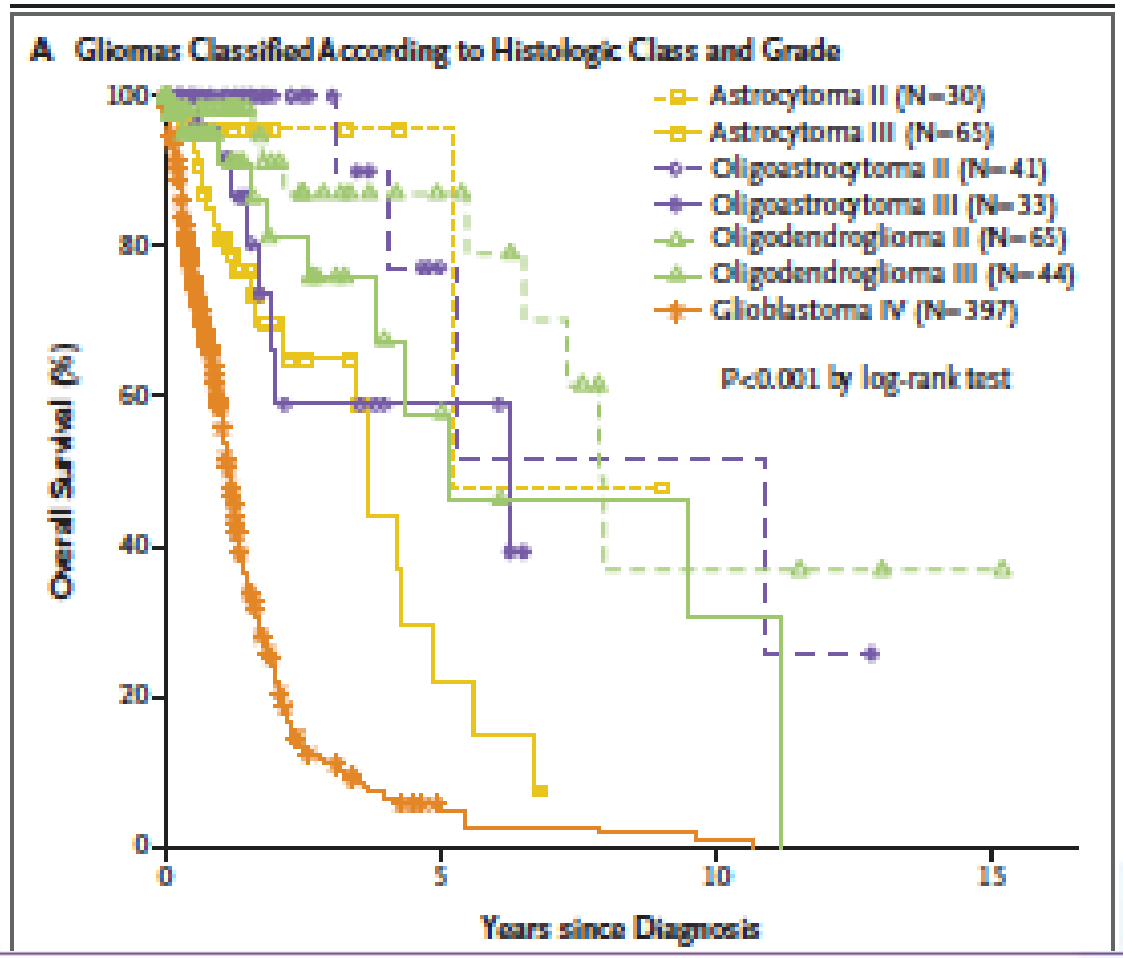


NOTE: ATRX mutations and 1p/19q codeletion are mutually exclusive events

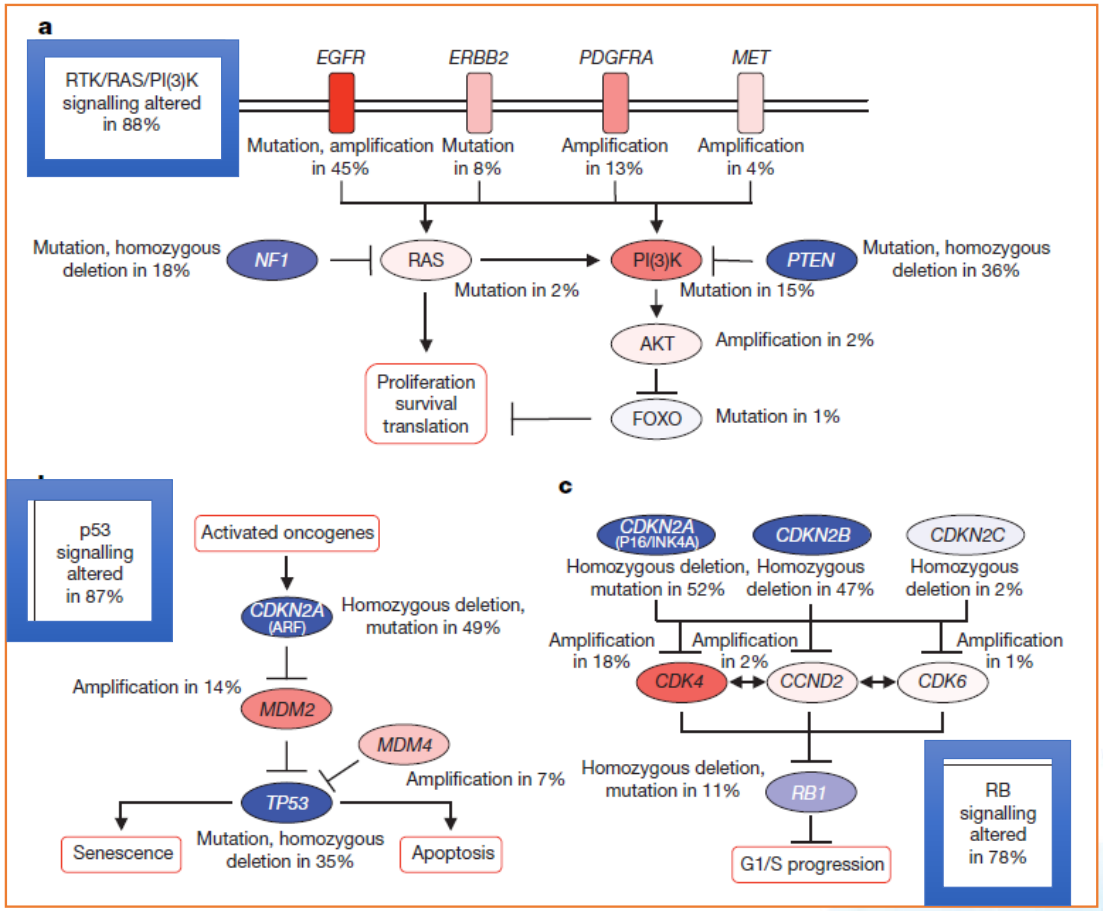
GLIOMAS CLASSIFICATION ACCORDING TO MOLECULAR SUBTYPE



GLIOMAS CLASSIFICATION ACCORDING TO HISTOLOGICAL CLASS AND GRADE

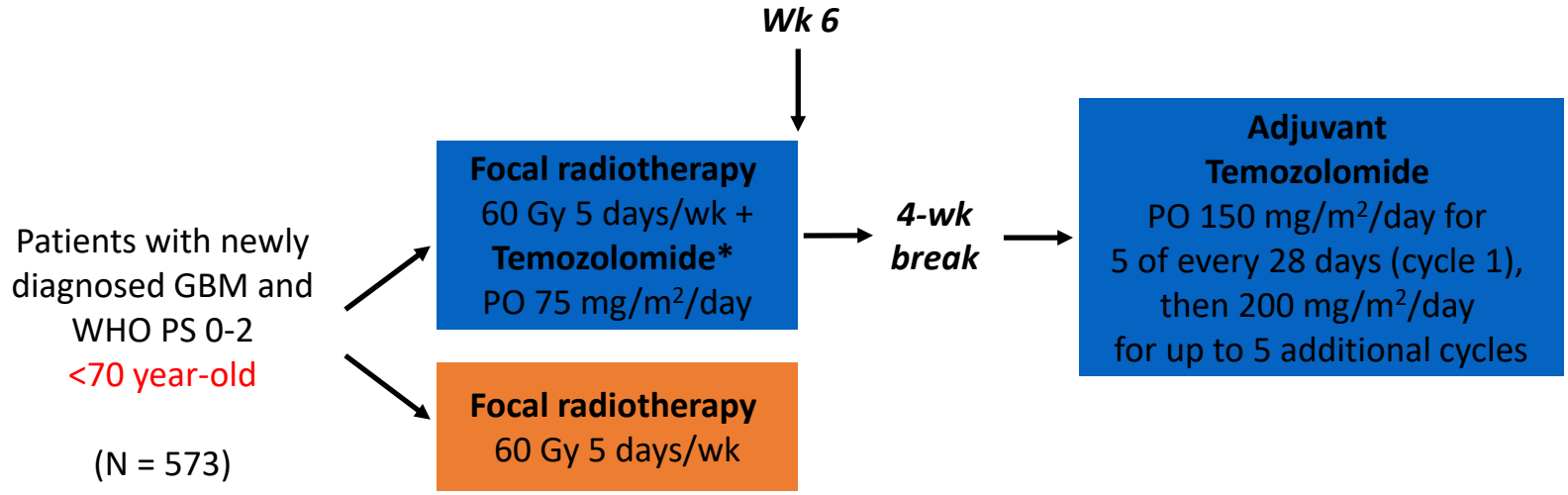


IDHwt GLIOBLASTOMA



GLIOBLASTOMA
Treatment after maximal safe resection

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



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

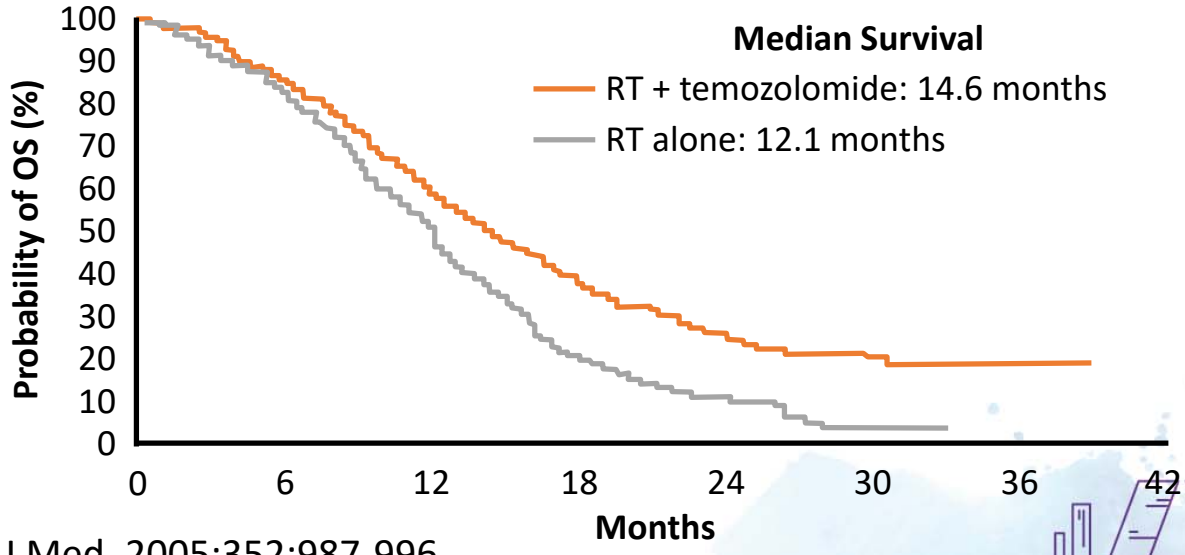
- **Primary endpoint: OS**
- **Secondary endpoints: PFS, safety, quality of life**

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)

GEINO GRUPO ESPAÑOL DE INVESTIGACIÓN EN NEUROONCOLOGÍA

Randomized clinical trial of continuation or non-continuation with 6 cycles of temozolomide after the first 6 cycles of standard first-line treatment in patients with glioblastoma. A Spanish Research Group in Neuro-oncology. Trial: GEINO 1401

Carmen Balana[1], Carlos Mesia Barroso[2], Sonia Del Barco Berron[3], Estela Pineda Losada[4], José Muñoz-Langa[5], Anna Estival[1], Ramon De las Peñas[6], Jose Fuster[7], Miguel J. Gil Gil[2], L Miguel Navarro[8], Miriam Alonso[9], Ana Herrero[10], María Ángeles Vaz Salgado[11], Sergi Peralta[12], Clara Olier[13], Pedro Pérez-Segura[14], Marta Covela Rúa[15], Cristina Carrato[16], Carolina Sanz [16], Juan Manuel Sepulveda-Sanchez[17]. On behalf of GEINO Group.

[1]Institut Catala Oncologia Badalona/Barcelona; [2]Institut Català d'Oncologia Hospital Duran i Reynals, L'Hospitalet de Llobregat/Barcelona; [3]Institut Català d'Oncologia, Girona; [4]Hospital Clinic, Barcelona; [5]Hospital Universitario La Fe, Valencia; [6] Hospital Provincial de Castellon; [7]Hospital Son Espases, Palma De Mallorca; [8]Complejo Asistencial Universitario de Salamanca; [9]Hospital Universitario Virgen del Rocio, Sevilla; [10]Hospital Miguel Servet, Zaragoza; [11]Hospital Ramon y Cajal, Madrid; [12]Hospital Sant Joan de Reus, Tarragona; [13]Fundación Alcorcón, Madrid; [14]Hospital San Carlos, Madrid; [15]Hospital Lucus Augusti, Lugo; [16]Hospital Germans Trias i Pujol, Badalona/Barcelona; [17]Hospital 12 de Octubre, Madrid.

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Carmen Balana

Presented By Carmen Balana at 2019 ASCO Annual Meeting

Trial design

GEINO Grupo Español de Investigación en Neurooncología

GEINO 1401. Multi-academic-center, prospective, grant-supported

GBM
Maximal safe surgery
RxT+TMZx6cycles→SD

166 Screened:
- Confirm GBM
- *MGMT* status?
- Residual disease on MRI?

7 did not meet inclusion criteria

159 centralized R

CONTROL –stop TMZ

TMZ –continue x 6 c

DXM and TMZ doses= the same as cycle 6
Clinical evaluation, H and B every 28 days
MRI every 3 months until DP

Stratification factors: *MGMT* status and RESIDUAL DISEASE (RD) (defined as at least an enhanced lesion >10mm).
Baseline MRI max 6w before potential cycle 7

Design 2012

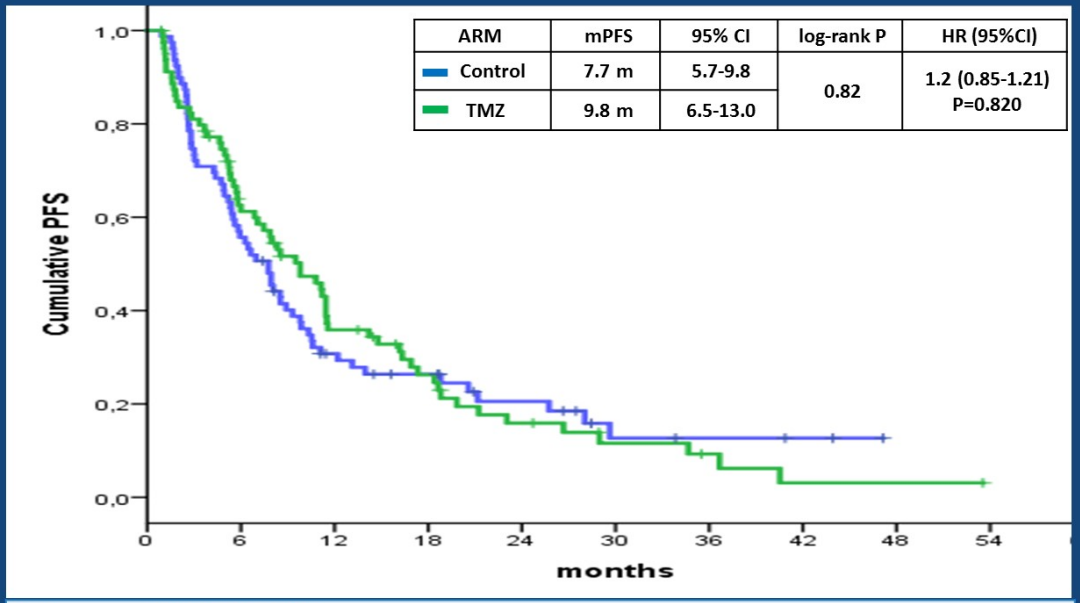
PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Carmen Balana

PFS by treatment arm

GEINO GRUPO ESPAÑOL DE INVESTIGACIÓN EN NEUROONCOLOGÍA

ARM	mPFS	95% CI	log-rank P	HR (95%CI)
Control	7.7 m	5.7-9.8	0.82	1.2 (0.85-1.21) P=0.820
TMZ	9.8 m	6.5-13.0		



ARM	Number patients at risk									
CONTROL	79	44	21	16	10	4	3	2	2	2
TMZ	80	46	25	16	9	5	3	1	1	1

From inclusion

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19 Slides are the property of the author, permission required for reuse.

PRESENTED BY: Carmen Balana

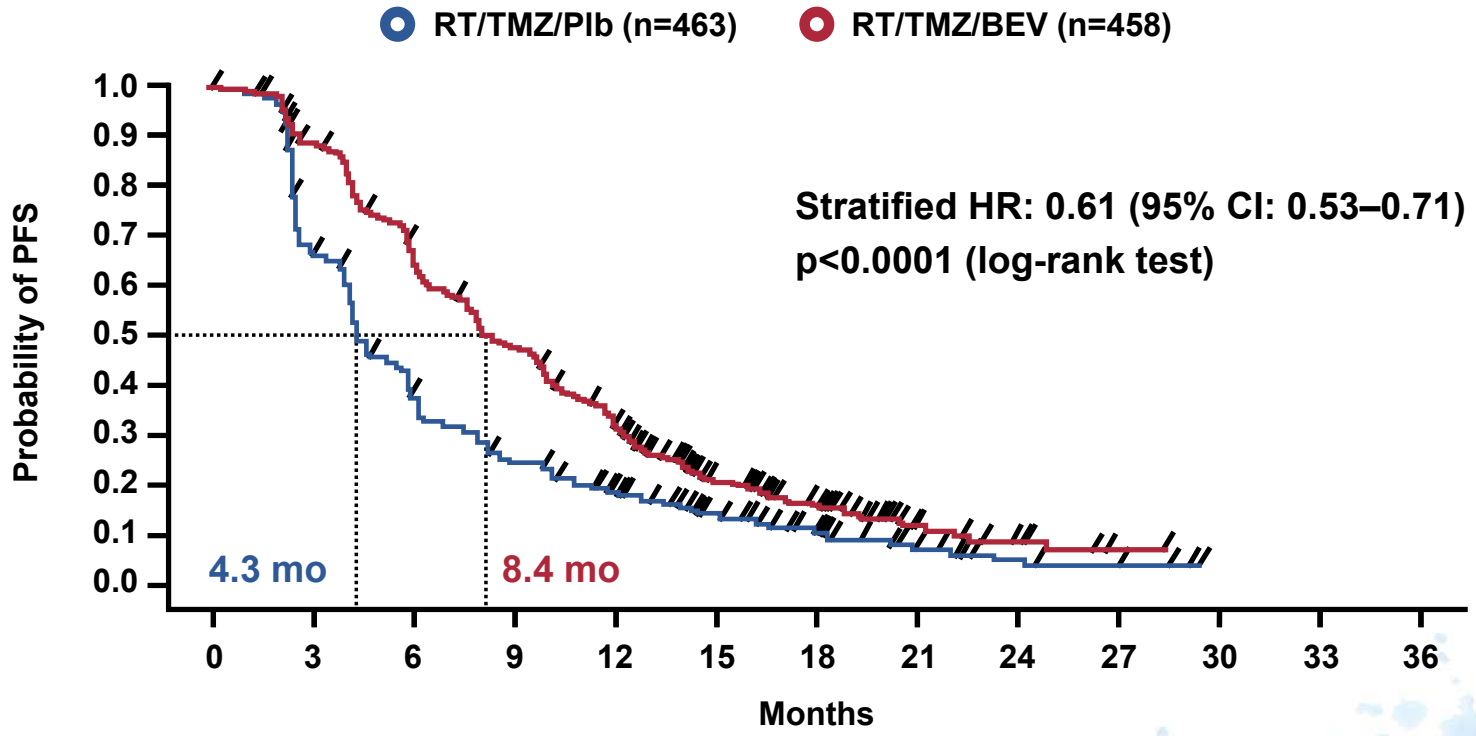
Presented By Carmen Balana at 2019 ASCO Annual Meeting

How to improve the Stupp Regimen?

AVAGLIO Trial. Adding Bevacizumab to RT/TMZ in newly diagnosed GBM

900 patients randomized to RT/TMZ + BVZ or Placebo

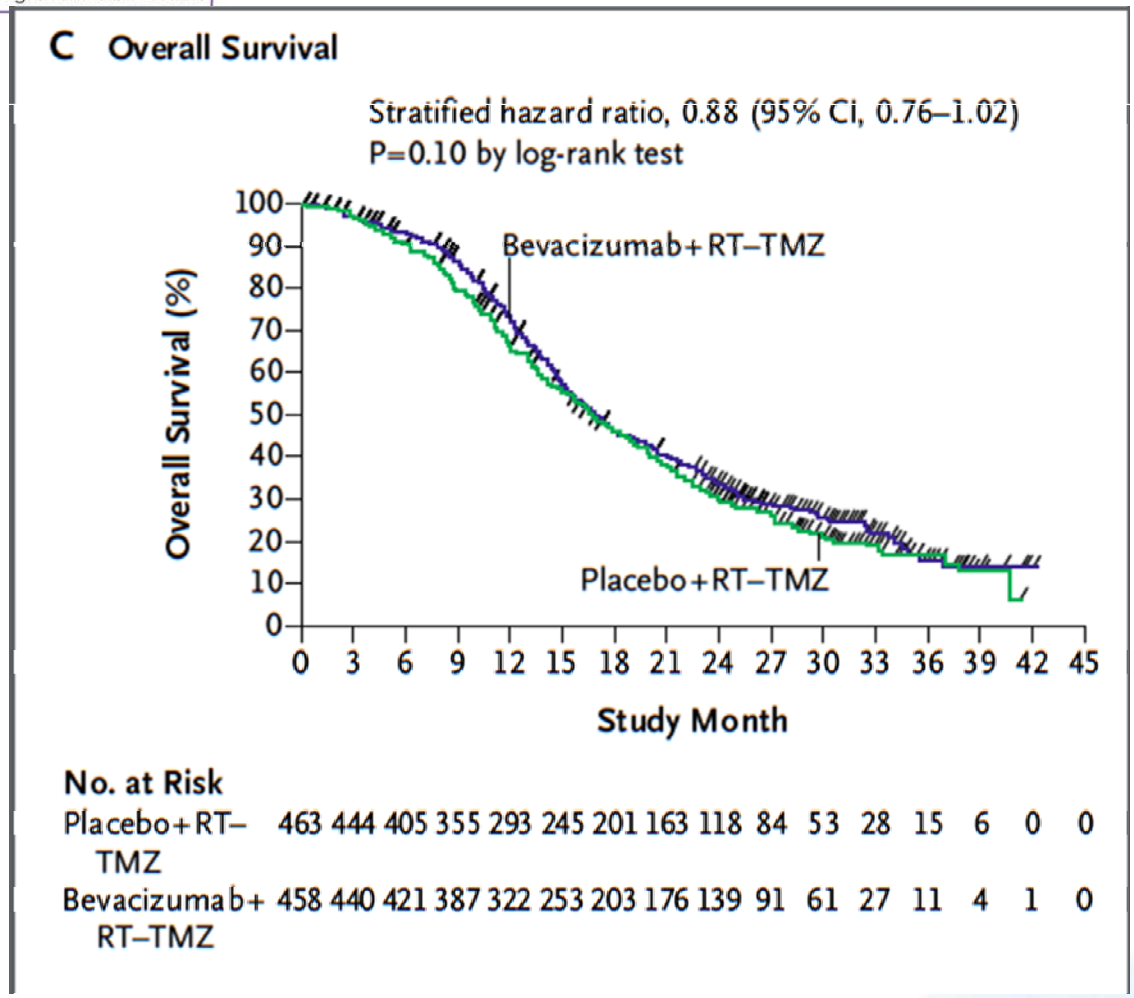
IRF-Assessed PFS (Secondary Endpoint)



Stratified HR: 0.61 (95% CI: 0.53–0.71)
p<0.0001 (log-rank test)

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

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Randomized Phase 3 Study Evaluating the Efficacy and Safety of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma: CheckMate 143

David A. Reardon,[1,a] Antonio Omuro,[2,a] Alba A. Brandes,[3] Johannes Rieger,[4,5] Antje Wick,[6] Juan Manuel Sepulveda,[7] Surasak Phuphanich,[8] Paul de Souza,[9] Manmeet S. Ahluwalia,[10] Michael Lim,[11] Gordana Vlahovic,[12,b] John Sampson[12,b]

[1]Dana-Farber Cancer Institute and Harvard University School of Medicine, Boston, MA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]AUSL-IRCCS Institute of Neurological Sciences, Bologna, Italy; [4]Klinikum der Goethe-Universität, Frankfurt, Germany; [5]University of Tübingen, Tübingen, Germany; [6]Neurology Clinic, University of Heidelberg, National Center for Tumor Diseases, Heidelberg, Germany; [7]Hospital Universitario 12 De Octubre, Madrid, Spain; [8]Cedars-Sinai Medical Center, Los Angeles, CA; [9]University of Western Sydney School of Medicine, Liverpool, Australia; [10]Cleveland Clinic, Cleveland, OH; [11]The Johns Hopkins Hospital, Baltimore, MD; [12]Duke University Medical Center, Durham, NC

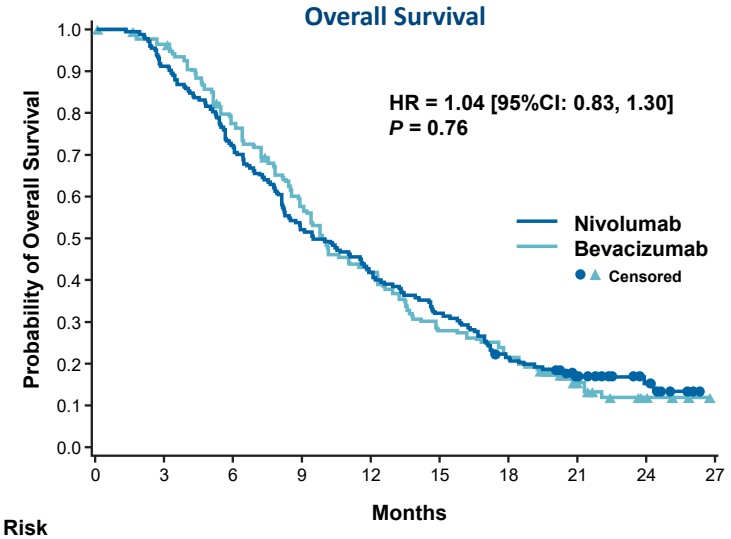
5th Quadrennial Meeting of the World Federation of Neuro-Oncology Societies
May 4-7, 2017; Zurich, Switzerland

[a] Co-first authors.
[b] Co-senior authors.

Overall Survival and Progression-Free Survival

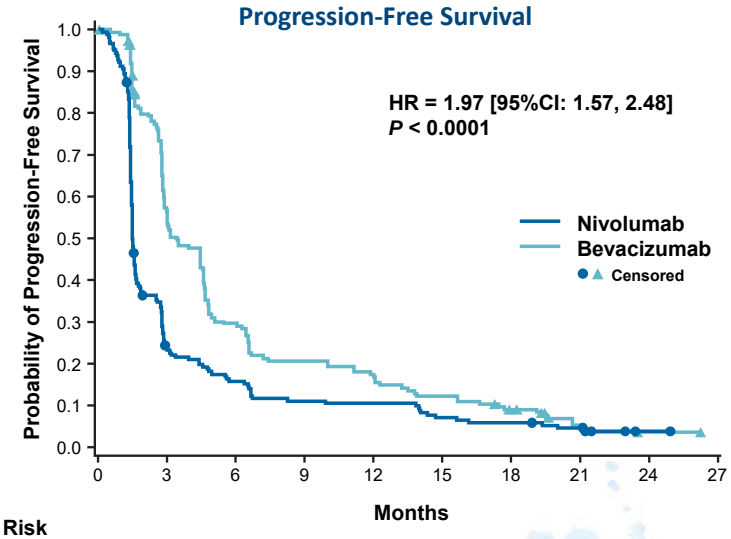
Nivolumab vs Bevacizumab in Recurrent GBM

	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], months
Nivolumab	154	9.8 [8.2, 11.8]	41.8 [34.7, 48.8]
Bevacizumab	147	10.0 [9.0, 11.8]	42.0 [34.6, 49.3]



No. at Risk										
Nivolumab	184	168	133	96	77	59	39	24	9	0
Bevacizumab	185	169	135	99	72	48	37	14	5	0

	Events, n	Median PFS [95% CI], months	12-Month PFS Rate [95% CI], months
Nivolumab	171	1.5 [1.5, 1.6]	10.5 [6.5, 15.5]
Bevacizumab	146	3.5 [2.9, 4.6]	17.4 [11.9, 23.7]

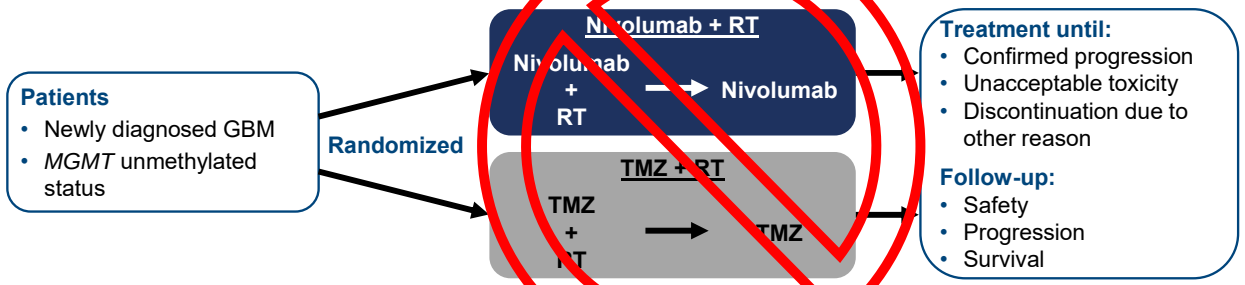


No. at Risk										
Nivolumab	184	41	27	19	18	12	10	7	1	0
Bevacizumab	185	88	46	32	27	19	12	3	1	0

HR, hazard ratio.

Clinical Trials of Nivolumab in Newly Diagnosed GBM

CheckMate 498 (NCT02617589): Nivolumab or TMZ in combination with RT in newly diagnosed patients with *MGMT*-unmethylated GBM

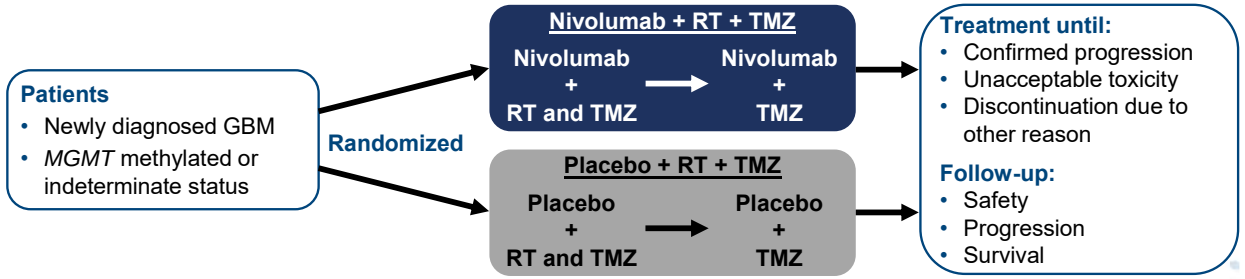


Endpoints:

Primary: OS

Secondary: PFS and 12-month OS rate

CheckMate 548 (NCT02667587): Nivolumab or placebo in combination with RT + TMZ in newly diagnosed patients with *MGMT*-methylated or indeterminate GBM

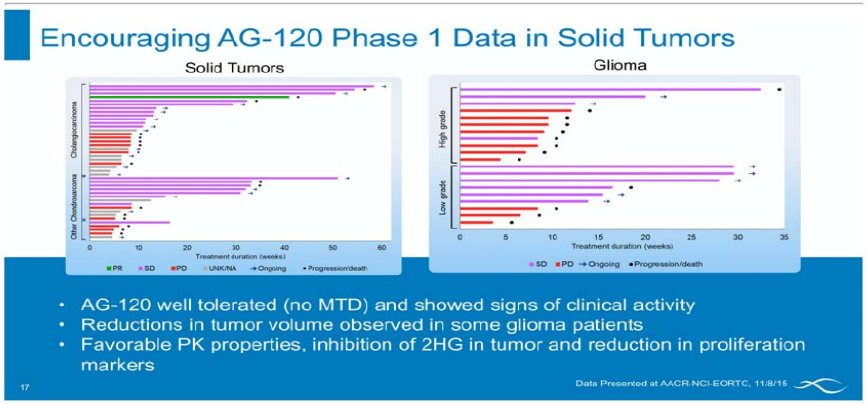


Endpoints:

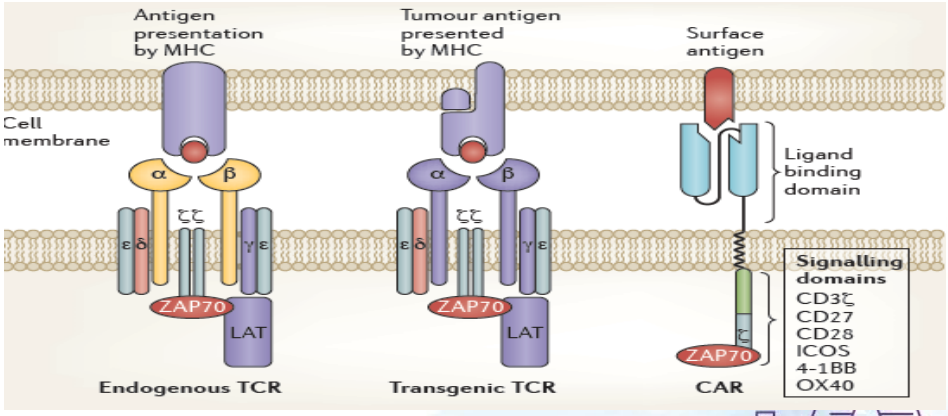
- **Primary**: OS
- **Secondary**: PFS

GBM. Future directions.

IDH1/2 inhibitors



CAR-T cell therapy



Post-surgical treatment of Low-grade Glioma: RTOG 9802 Trial

The NEW ENGLAND JOURNAL of MEDICINE

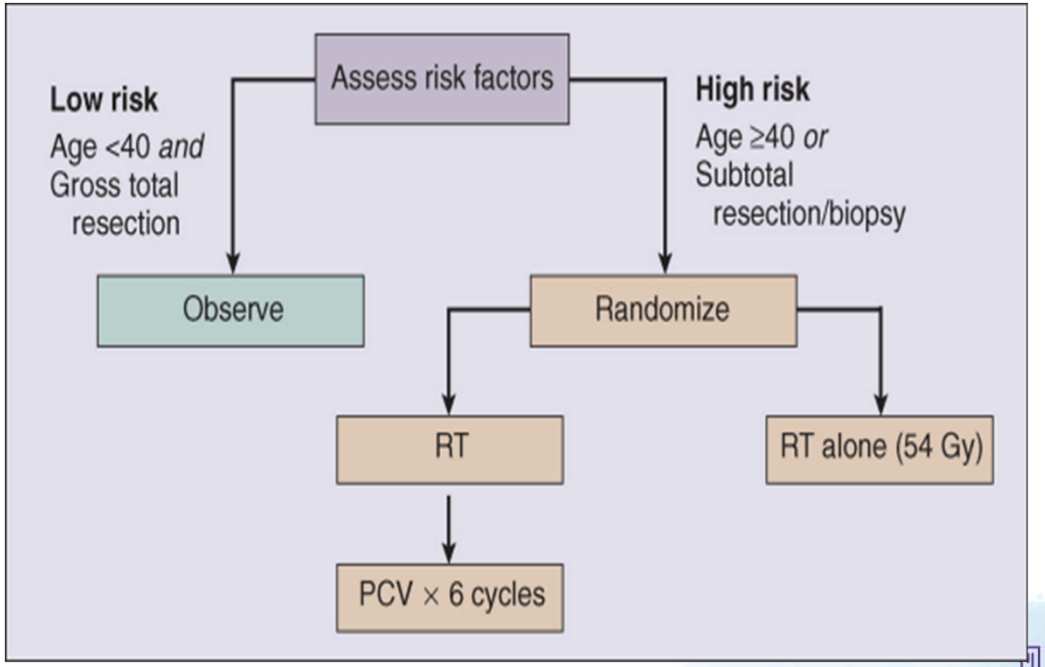
ORIGINAL ARTICLE

Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma

Jan C. Buckner, M.D., Edward G. Shaw, M.D., Stephanie L. Pugh, Ph.D., Arnab Chakravarti, M.D., Mark R. Gilbert, M.D., Geoffrey R. Barger, M.D., Stephen Coons, M.D., Peter Ricci, M.D., Dennis Bullard, M.D., Paul D. Brown, M.D., Keith Stelzer, M.D., David Brachman, M.D., John H. Suh, M.D., Christopher J. Schultz, M.D., Jean-Paul Bahary, M.D., Barbara J. Fisher, M.D., Harold Kim, M.D., Albert D. Murtha, M.D., Erica H. Bell, Ph.D., Minhee Won, M.A., Minesh P. Mehta, M.D., and Walter J. Curran, Jr., M.D.

Post-surgical treatment of Low-grade Glioma: RTOG 9802 Trial

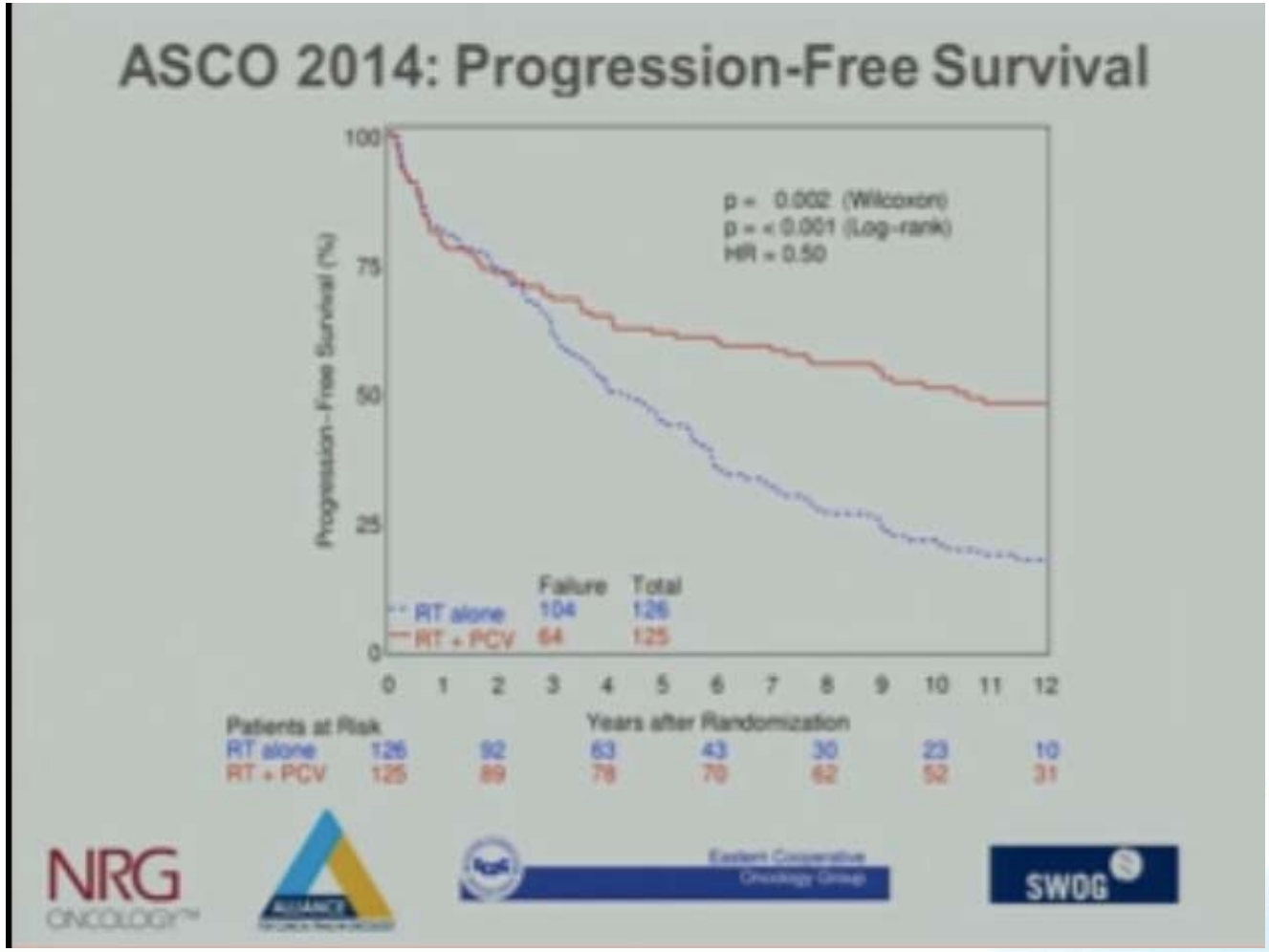
-251 patients enrolled
-Enrollment period: 1998 until 2002
-Principal Objective of the study: Overall survival



PCV: Procarbacine, Lomustine and Vincristine. 1 Cycle = 6 weeks

Table 1. Patient Characteristics

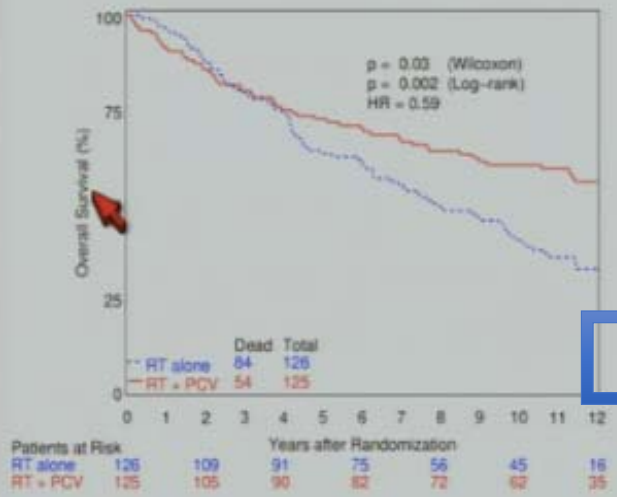
Characteristic	RT Arm No.	RT Arm %	RT + PCV Arm No.	RT + PCV Arm %
Age, years				
Median	40		41	
Range	22-79		18-82	
Median tumor size, cm	5.0		4.7	
KPS 90-100		74		75
Gross total resection		9		11
Histology				
Astrocytoma		23		29
Oligodendroglioma		45		40
Mixed astrocytoma/oligodendroglioma		32		31
Enhancement: yes		60		65


ASCO 2014: Progression-Free Survival
Progression-Free Survival (%)
100
75
50
25
0
p = 0.002 (Wilcoxon)
p = < 0.001 (Log-rank)
HR = 0.50
Failure Total
RT alone 104 126
RT + PCV 64 125
0 1 2 3 4 5 6 7 8 9 10 11 12
Years after Randomization
Patients at Risk
RT alone 126 92 63 43 30 23 10
RT + PCV 125 89 78 70 62 52 31
NRG ONCOLOGY
ALLIANCE
Eastern Cooperative Oncology Group
SWOG

PROGRESSION FREE SURVIVAL (RTOG 9802)

	RT alone	RT + PCV
Median	4 years	10,4 years
5-year	44.1%	61.2%
10-year	20.9%	50.6%

ASCO 2014: Overall Survival



Follow-up data:

- Deaths: 138 (55%)
- Median follow up: 11.9 yrs

	RT Alone Estimate (%)	RT + PCV Estimate (%)
Median	7.8 years	13.3 years
5-year	63.1 %	72.3%
10-year	40.1%	60.1%

HR: 0.59

NRG ONCOLOGY™ ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY ECOG Eastern Cooperative Oncology Group SWOG

TREATMENT OF GRADE 3 OLIGODENDROGLIOMAS (Anaplastic)

EORTC 26951 and RTOG 9402 trials

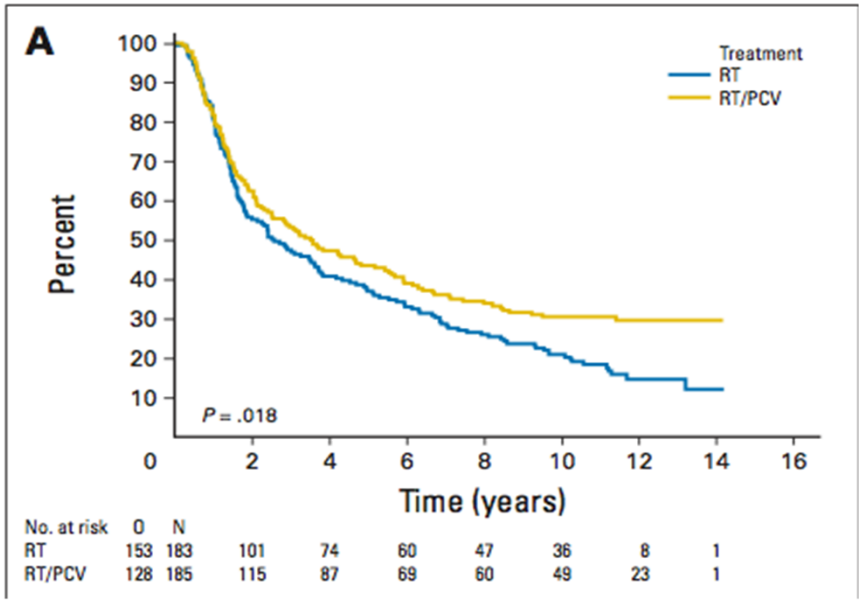
GRADE 3 OLIGODENDROGLIOMAS:
Treatment after surgery

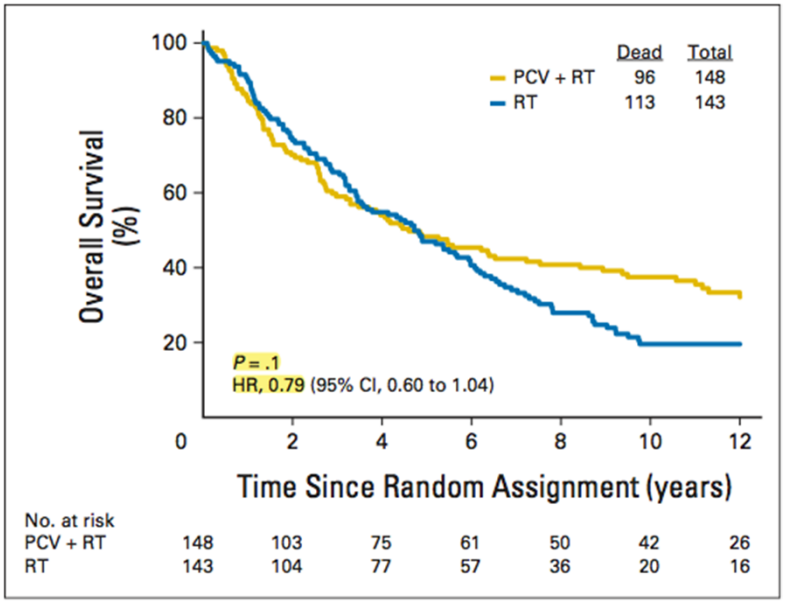
EORTC 26951	RTOG 9402
RT→ PCV x 6	**I-PCV x 4 → RT**
Vs	**VS**
RT alone	**RT alone**

Time of enrollement: >6 years

Cairncross G et al. JCO 2006; 24:2707
Van den Bent et al. JCO 2006; 24:2715

GRADE III OD. PHASE III TRIALS: OVERAL SURVIVAL





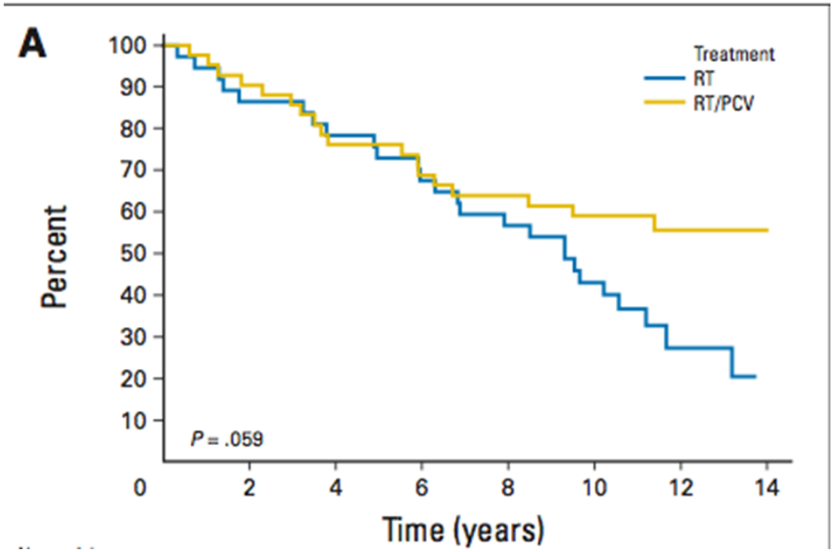
EORTC

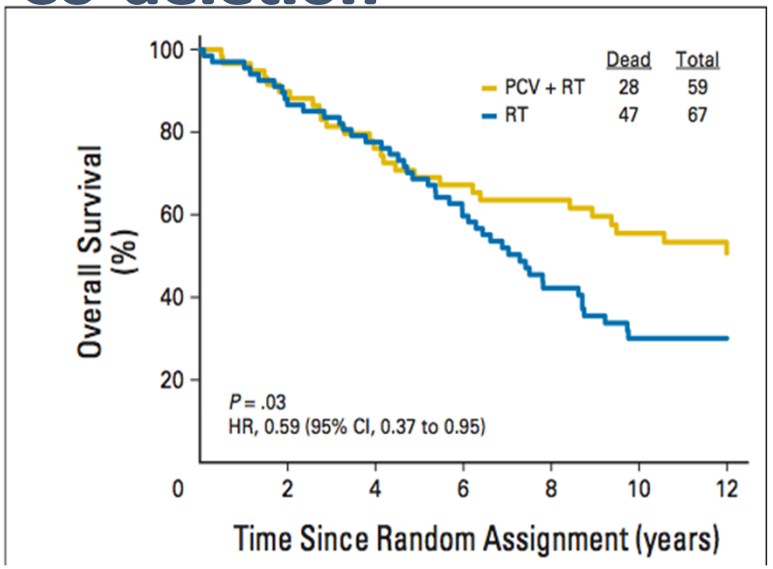
PCV + RT = 3,52 YEARS
RT = AÑOS = 2,55 YEARS
P= 0,018
HR= 0,75 (0,6-0,95)

RTOG

PCV + RT = 4,6 YEARS
RT = 4,7 YEARS
P=0,1
HR=0,79

GRADE III OD. PHASE III TRIALS: OVERAL SURVIVAL IN PATIENTS WITH 1p19q Co-deletion





EORTC

PCV + RT = NO ALCANZADA MEDIANA
RT = AÑOS = 9,33 AÑOS
HR= 0,59
P= 0,059

RTOG

PCV + RT = 14,7 AÑOS
RT = 7 AÑOS
HR= 0,58
P=0,04

Muchas gracias por su atentción