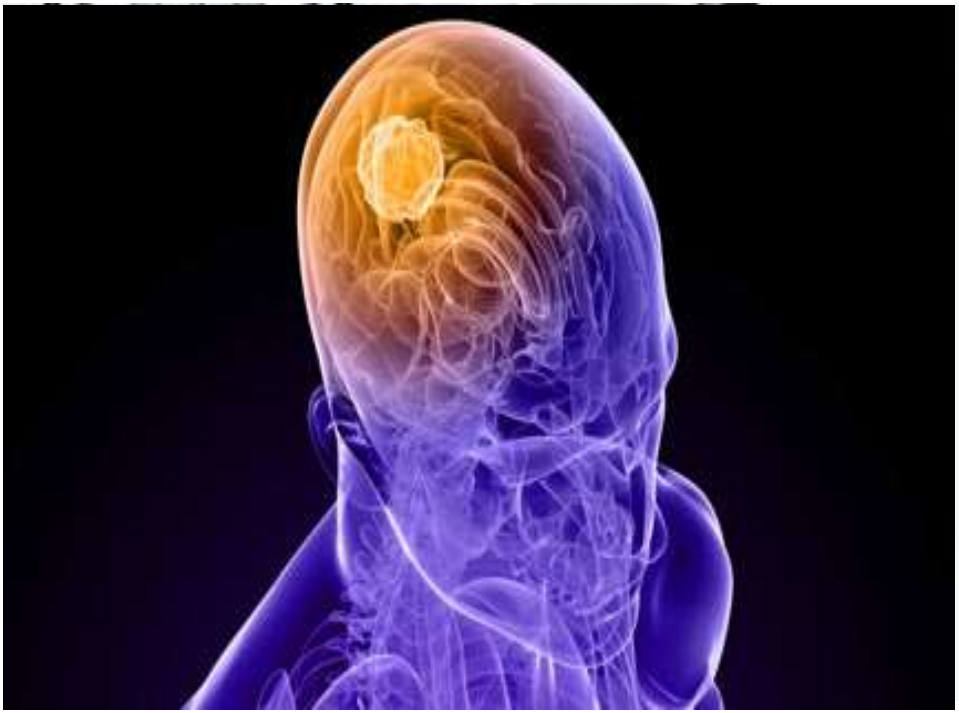
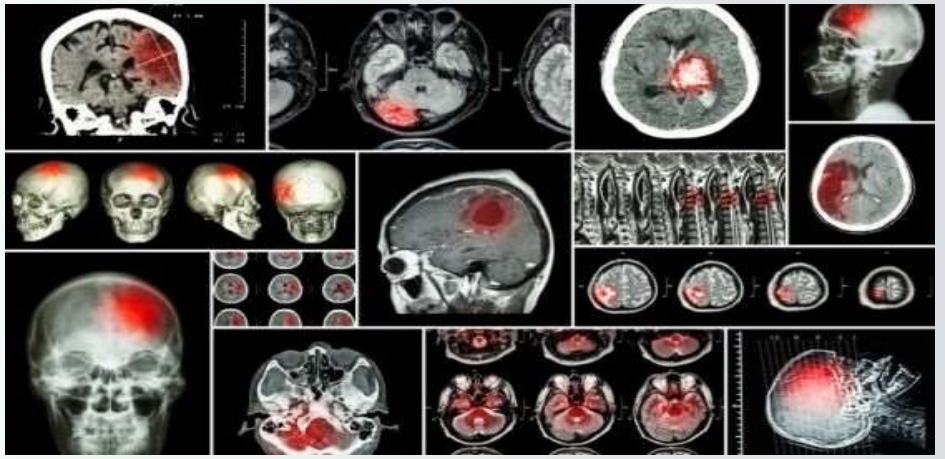




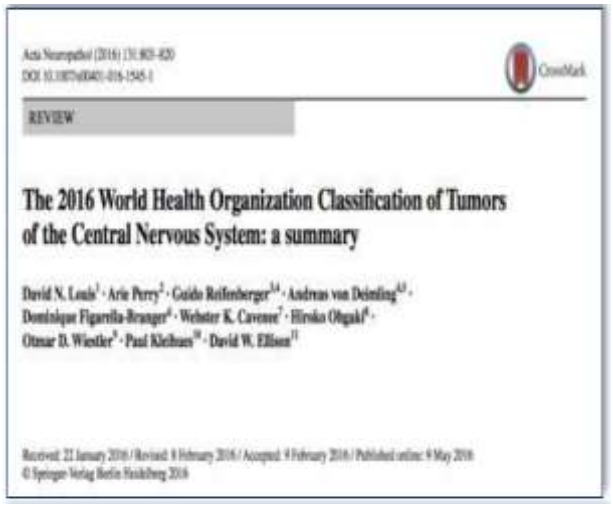
Tiziana Falbo

Oncologia Medica

I.N.I. - Grottaferrata (RM)

SISTEMA NERVOSO CENTRALE

WHO 2016 Update : «Integrated diagnosis « Histological Criteria & grade+ Molecular Markers



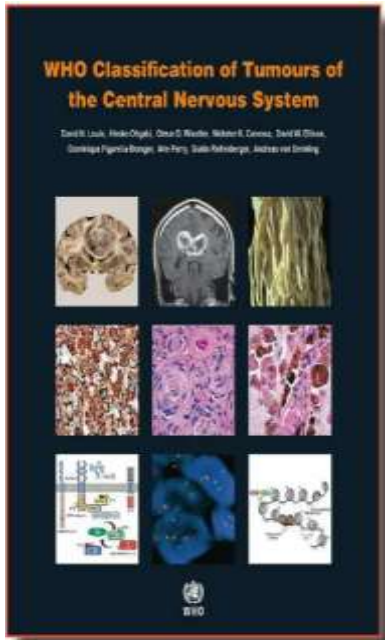
Acta Neuropathol (2016) 131:803–820
DOI 10.1007/s00401-016-1545-1

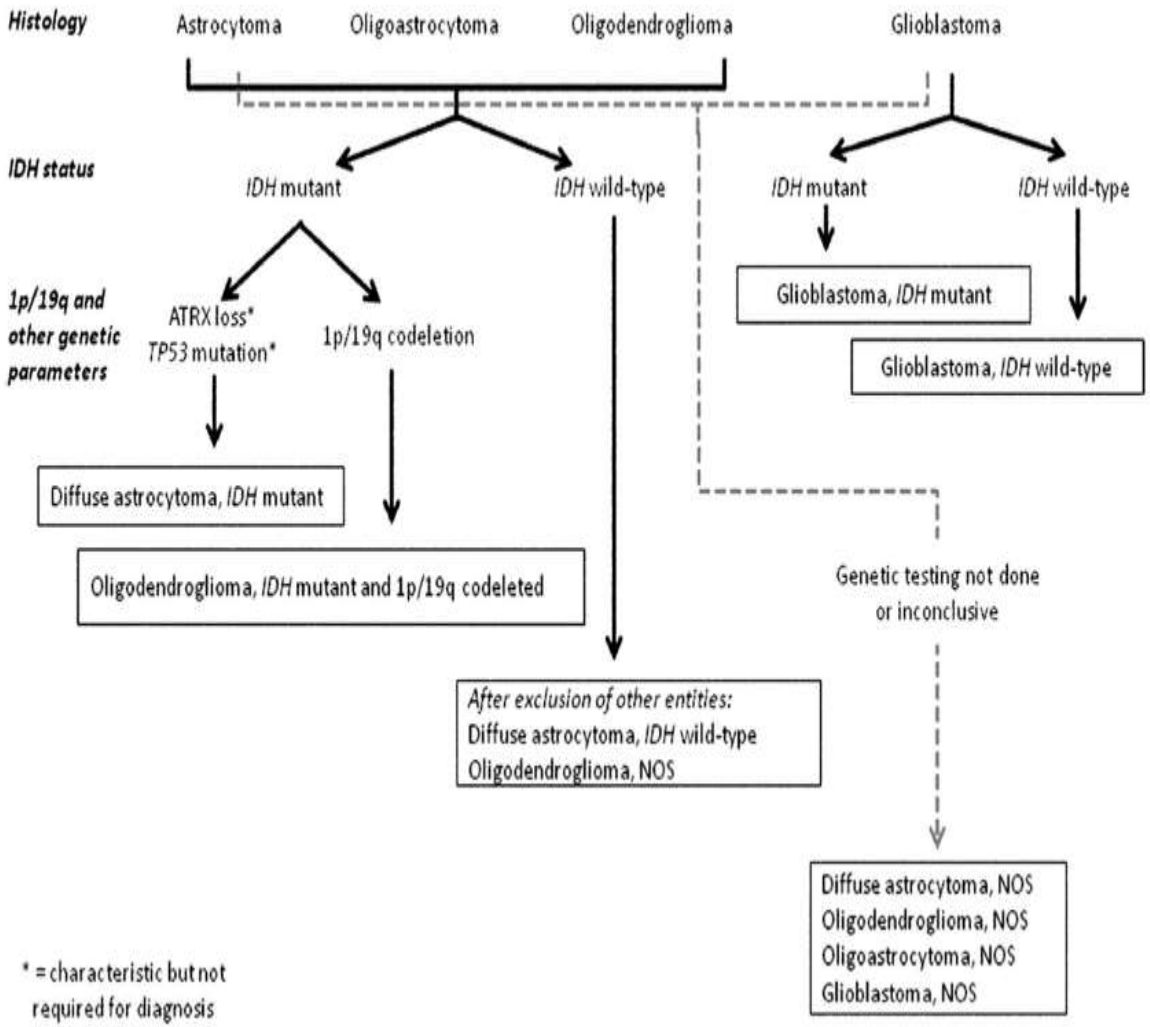
REVIEW

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

David N. Louis[1] · Arie Perry[2] · Guido Reifenberger[3,4] · Andreas von Deimling[5,6] · Dominique Figarella-Branger[8] · Webster K. Cavenee[7] · Hiroko Ohgaki[8] · Otmar D. Wiestler[9] · Paul Kleihues[10] · David W. Ellison[11]

Received: 22 January 2016 / Revised: 8 February 2016 / Accepted: 9 February 2016 / Published online: 9 May 2016





TOPICS

- Randomised phase III trial (**CCTG CE.6-EORTC 26062-22061-TROG 08.02)**
- Updated results of randomized phase II studies
- **EORTC 1410 trial INTELLANCE 2**
- **REGOMA trial**

- **Immunotherapy**
- Checkpoint Inhibitors

- New target and new subgroup in gliomas
- High-Risk low grade gliomas: comparing RTOG and EORTC criteria
- Pyrosequencing approach to detect MGMT methylation stat

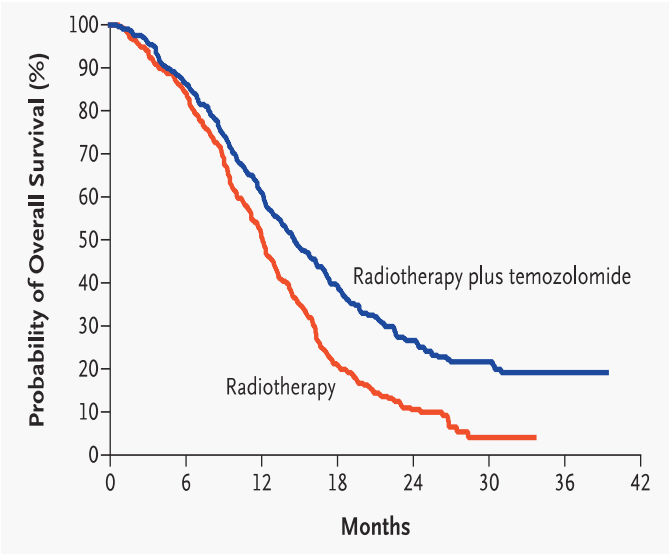
The NEW ENGLAND JOURNAL of MEDICINE

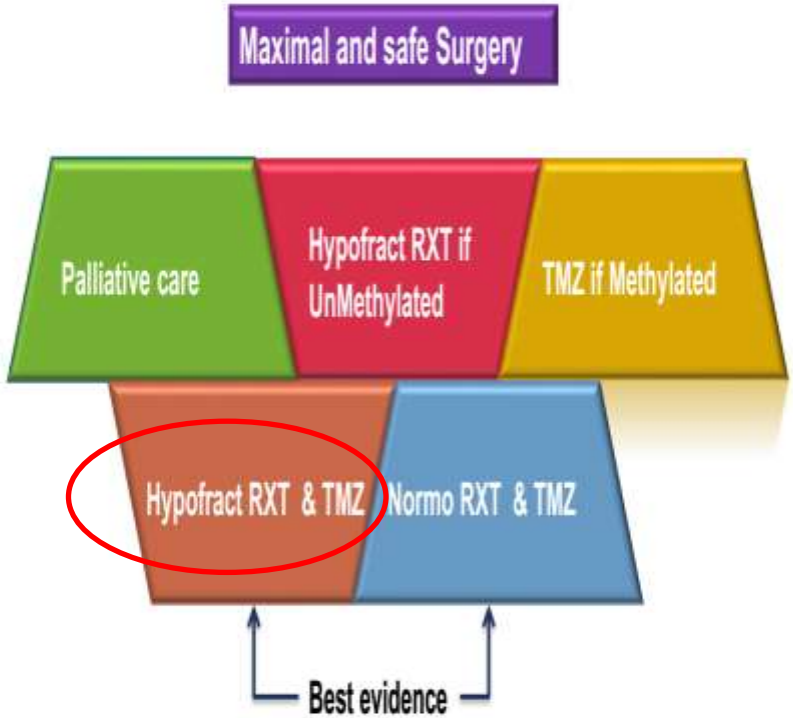
ORIGINAL ARTICLE

Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma

James R. Perry, M.D., Normand Laperriere, M.D.,

TREATMENT OPTIONS FOR ELDERLY (&FRAGILE?) PATIENTS





Age, years (number of patients)	Hazard ratio	p Value
<50 (171)	0.5	0.001
50–60 (220)	0.63	<0.05
61–65 (114)	0.64	0.096
66–70 (83)	0.78	0.340

Efficacy in elderly pts?
mOS significantly lower: 6 months

Roa W 2004; Stupp R 2005; Malsmtrom A 2012; Wick W 2012; Perry JR 2017; Weller M 2017

CCTG CE.6 -EORTC 26062-22061 Study

Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma

James R. Perry, M.D., Normand Laperriere, M.D.,

562 Patients underwent randomization

Patients ≥65 years old with newly diagnosed GBM

RANDOMIZE

→ ARM 1: Radiotherapy (RT)

40 Gy in 15 fractions over 3 weeks

→ ARM 2: Radiotherapy (RT) + Temozolomide (TMZ)

RT - 40 Gy in 15 fractions over 3 weeks

TMZ – 75 mg/m² po daily, from the first to the last day of RT

4 wks. after last RT dose

TMZ – 150-200 mg/m² on days 1-5 of each 28-day-long cycle, until PD to a maximum of 12 cycles

Disease assessment at 4 wks. after the last RT dose and then every 3 months

Disease Progression

Survival Follow-up

Primary
- Overall Survival

Secondary
- PFS
- AEs
- Quality of life
- Translational studies
  - MGMT Status (Mandatory)
  - Others planned

Planned Sample Size: 560

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CCTG CE.6 - EORTC 26062-22061

Overall Survival

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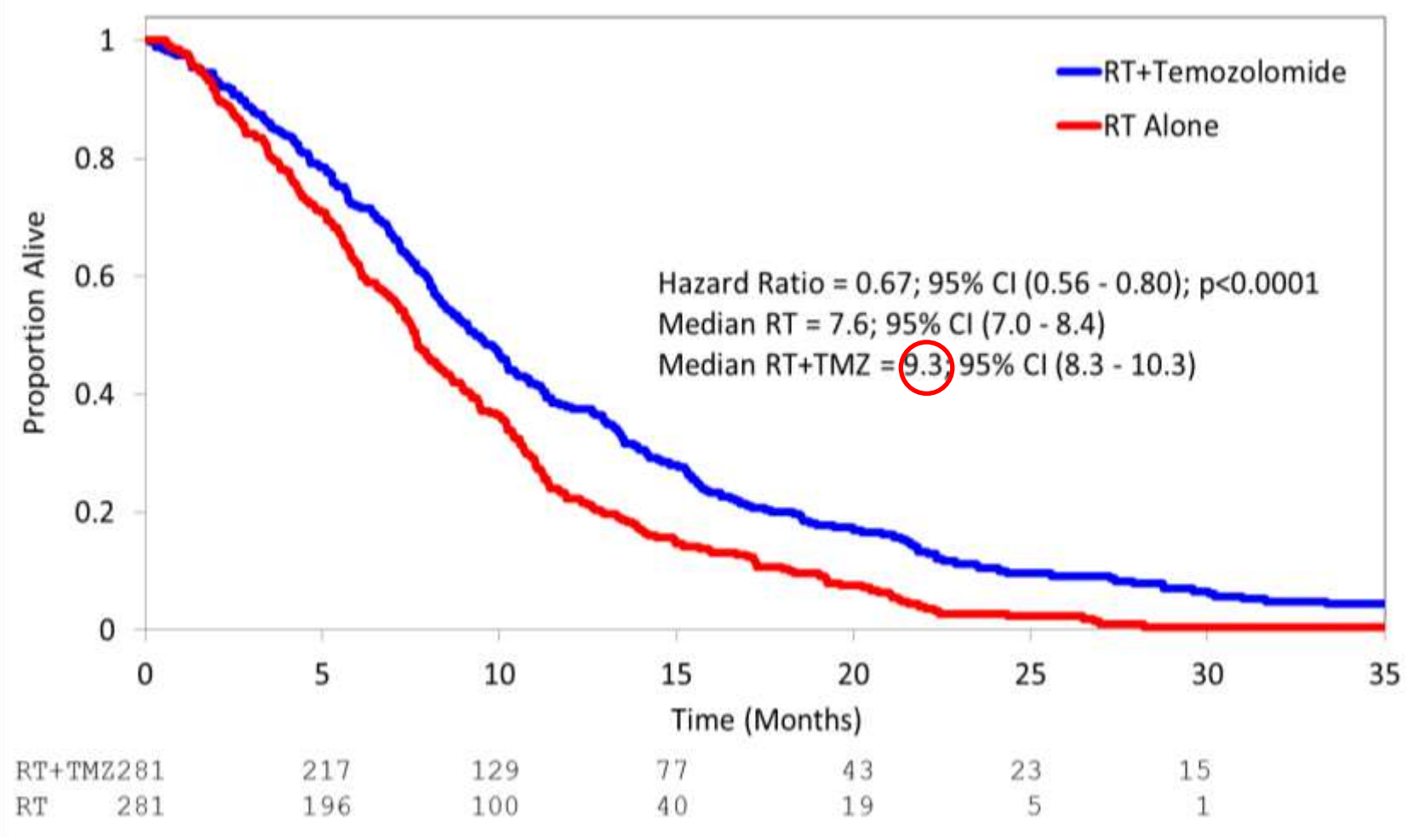
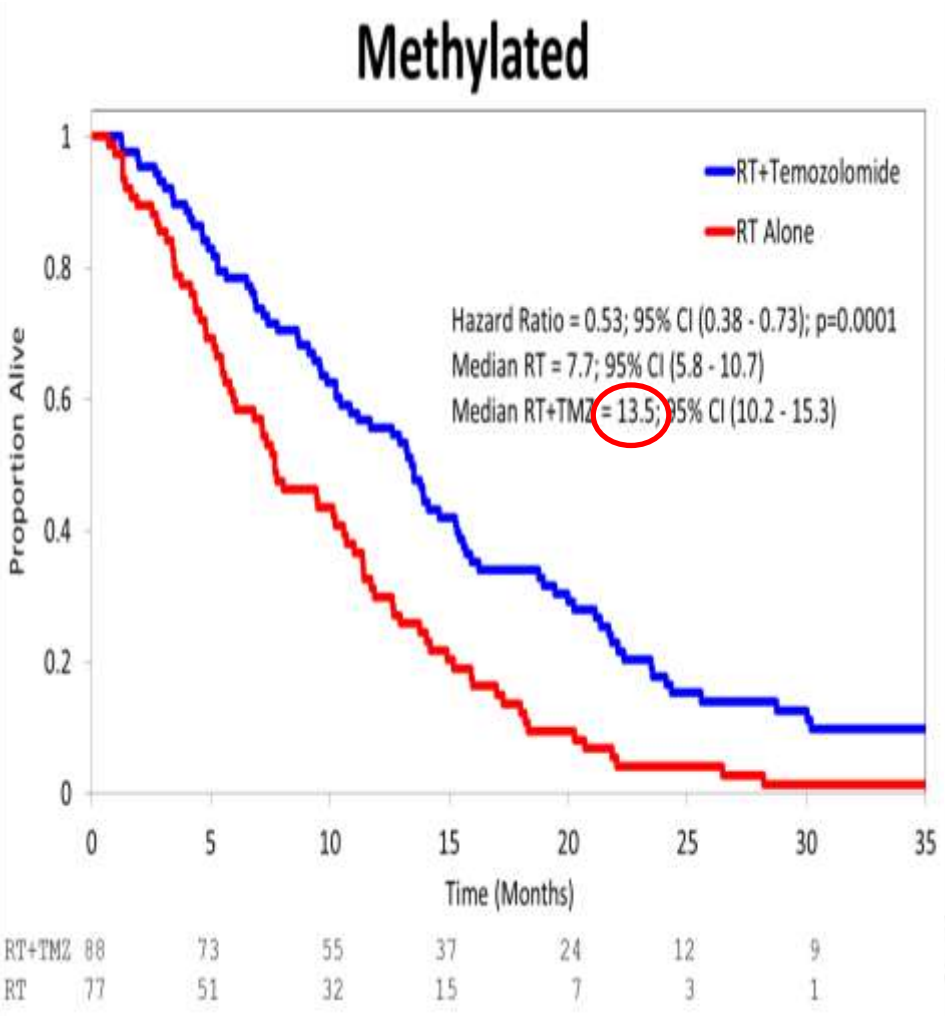
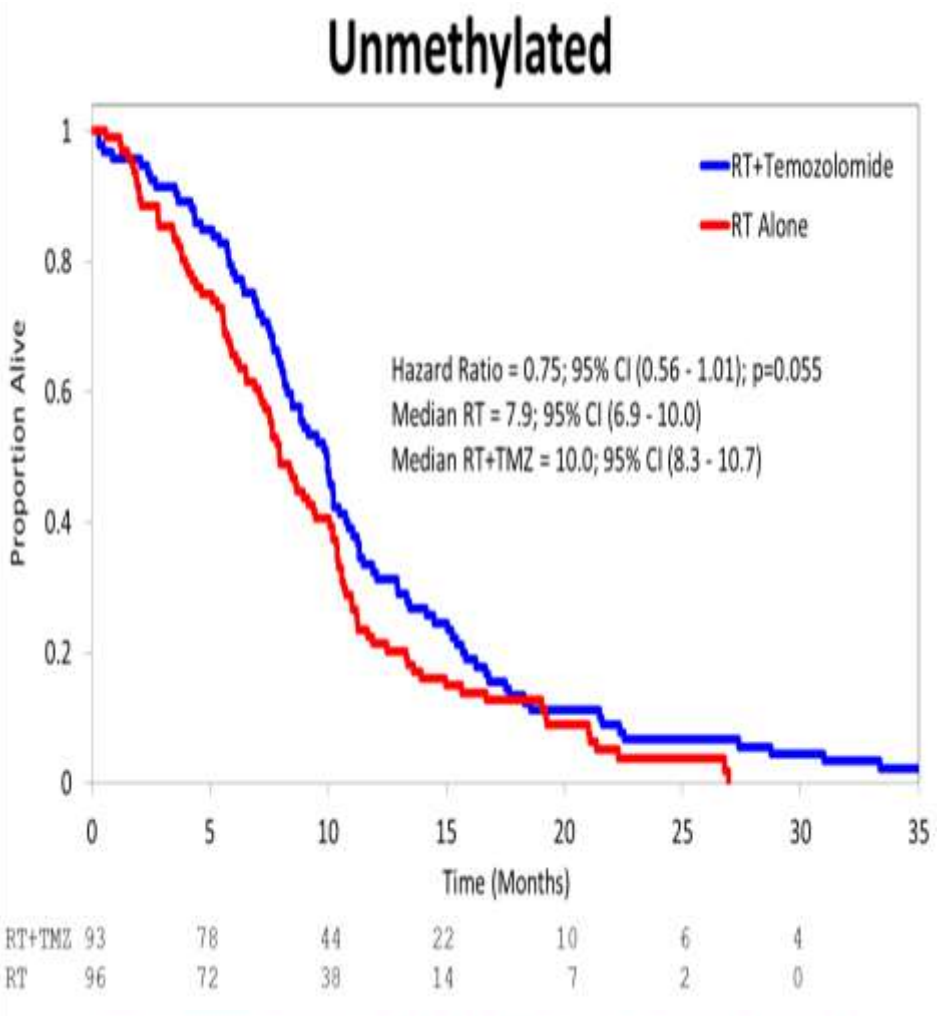


Overall Survival by MGMT status





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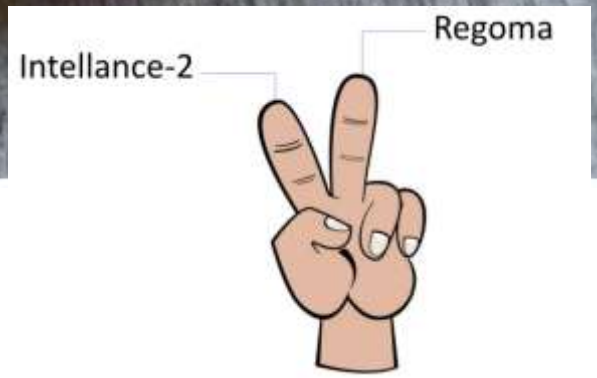
UPDATE


Regoma
Intellance-2

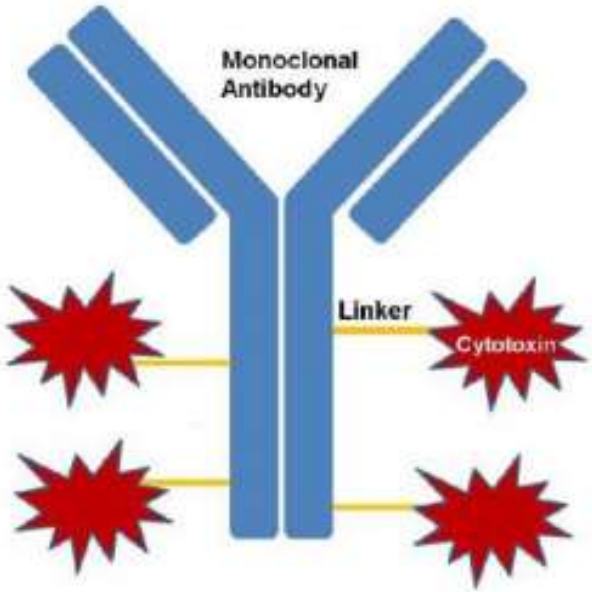
Phase 2, Randomized, Open-label (N=260)

Depatux-m ± TMZ vs Lomustine or TMZ[a]

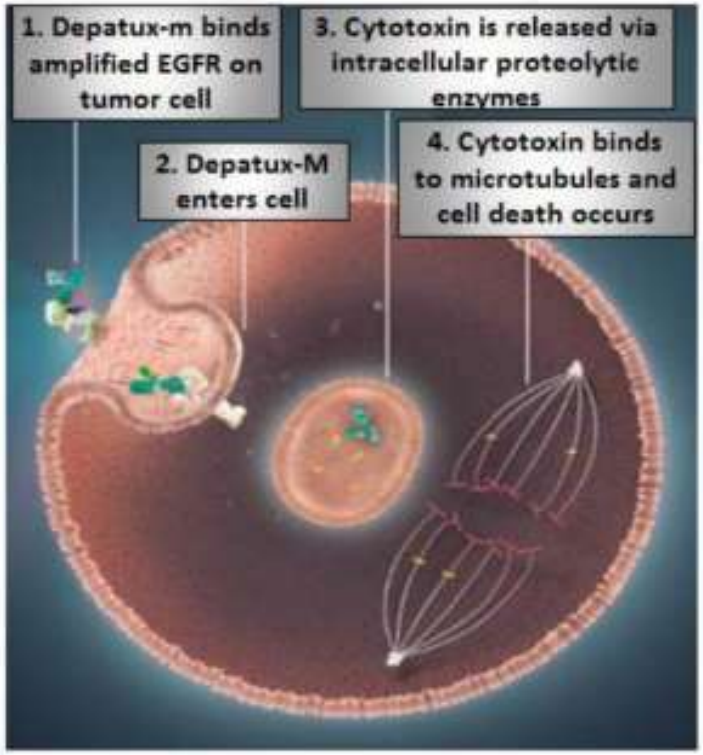
INTELLANCE-2

rGBM, EGFR+

Primary Endpoints[b]: OS

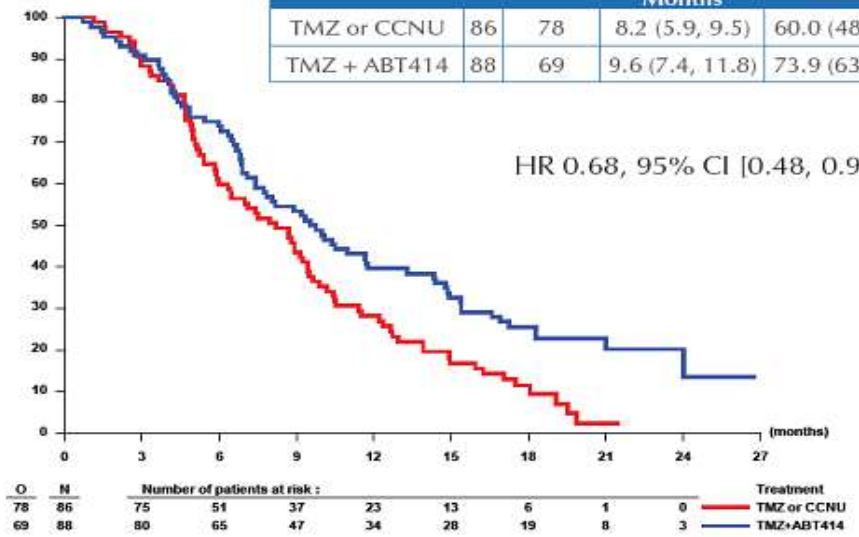


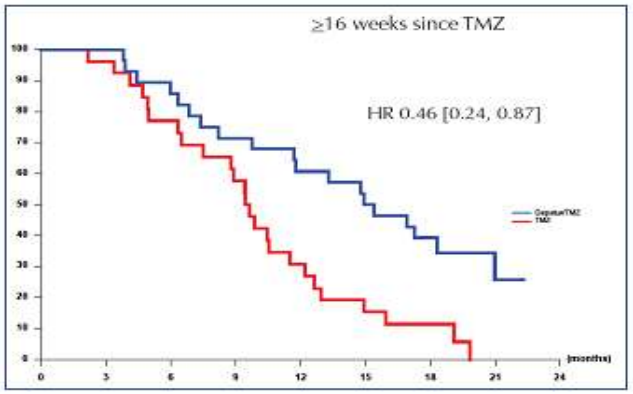
Depatuxizumab mafodotin (Depatux-m; ABT- 414)



Overall survival combination arm : improved survival

Treatment	N	Events	Median (95% CI) Months	% 6 months (95% CI)	% at 12 months (95% CI)	% at 24 months (95% CI)
TMZ or CCNU	86	78	8.2 (5.9, 9.5)	60.0 (48.8, 69.5)	28.2 (19.1, 37.9)	2.4 (0.2, 10.2)
TMZ + ABT414	88	69	9.6 (7.4, 11.8)	73.9 (63.3, 81.8)	39.7 (29.4, 49.7)	20.2 (11.9, 30.1)





Van den Bent et al, presented at ASCO 2018

Ocular toxicity (worst grade)	TMZ + Depatux-M	Depatux-M	Lomustine (n = 56)	TMZ (n = 21)
	n (%)	n (%)	n (%)	n (%)
grade 0	13 (14.8)	22 (26.2)	51 (91.1)	21 (100.0)
grade 1	18 (20.5)	9 (10.7)	2 (3.6)	0
grade 2	29 (33.0)	32 (38.1)	3 (5.4)	0
grade 3	**27 (30.7)**	**20 (23.8)**	0 (0.0)	0
grade 4	**1 (1.1)**	**1 (1.2)**	0 (0.0)	0

85%

Tossicità reversibile se prontamente riconosciuta: monitoraggio accurato

Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial

Giuseppe Lombardi, Gian Luca De Salvo, Alba Ariela Brandes, Marica Eoli, Roberta Rudà, Marina Faedi, Ivan Lolli, Andrea Pace, Bruno Daniele, Francesco Pasqualetti, Simona Rizzato, Luisa Bellu, Ardi Pambuku, Miriam Farina, Giovanna Magni, Stefano Indraccolo, Marina Paola Gardiman, Riccardo Soffietti, Vittorina Zagonel

Summary

Background Glioblastoma is a highly vascularised tumour and there are few treatment options after disease recurrence. Regorafenib is an oral multikinase inhibitor of angiogenic, stromal, and oncogenic receptor tyrosine kinases. We aimed to assess the efficacy and safety of regorafenib in the treatment of recurrent glioblastoma.

Methods REGOMA is a randomised, multicentre, open-label phase 2 trial done in ten centres in Italy. Eligible patients (aged ≥18 years) with histologically confirmed glioblastoma, Eastern Cooperative Oncology Group performance status 0 or 1, and documented disease progression after surgery followed by radiotherapy and temozolomide chemoradiotherapy were randomly assigned (1:1) by a web-based system, stratified by centre and surgery at recurrence (yes *vs* no), to receive regorafenib 160 mg once daily for the first 3 weeks of each 4-week cycle or lomustine 110 mg/m² once every 6 weeks until disease progression, death, unacceptable toxicity, or consent withdrawal. The primary endpoint was overall survival in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT02926222, and is currently in follow-up.

Findings Between Nov 27, 2015, and Feb 23, 2017, 124 patients were screened and 119 eligible patients were randomly assigned to receive regorafenib (n=59) or lomustine (n=60). Median follow-up was 15·4 months (IQR 13·8–18·1). At the analysis cutoff date, 99 (83%) of 119 patients had died: 42 (71%) of 59 in the regorafenib group and 57 (95%) of 60 in the lomustine group. Overall survival was significantly improved in the regorafenib group compared with the lomustine group, with a median overall survival of 7·4 months (95% CI 5·8–12·0) in the regorafenib group and 5·6 months (4·7–7·3) in the lomustine group (hazard ratio 0·50, 95% CI 0·33–0·75; log-rank p=0·0009). Grade 3–4 treatment-related adverse events occurred in 33 (56%) of 59 patients treated with regorafenib and 24 (40%) of 60 with lomustine. The most frequent grade 3 or 4 adverse events related to regorafenib were hand–foot skin reaction, increased lipase, and blood bilirubin increased (in six [10%] of 59 patients each). In the lomustine group, the most common grade 3 or 4 adverse events were decreased platelet count (eight [13%] of 60 patients), decreased lymphocyte count (eight [13%]), and neutropenia (seven [12%]). No death was considered by the investigators to be drug related.

Interpretation REGOMA showed an encouraging overall survival benefit of regorafenib in recurrent glioblastoma. This drug might be a new potential treatment for these patients and should be investigated in an adequately powered phase 3 study.

Lancet Oncol 2018

Published Online
December 3, 2018

REGOMA TRIAL

- **Vittorina Zagonel**

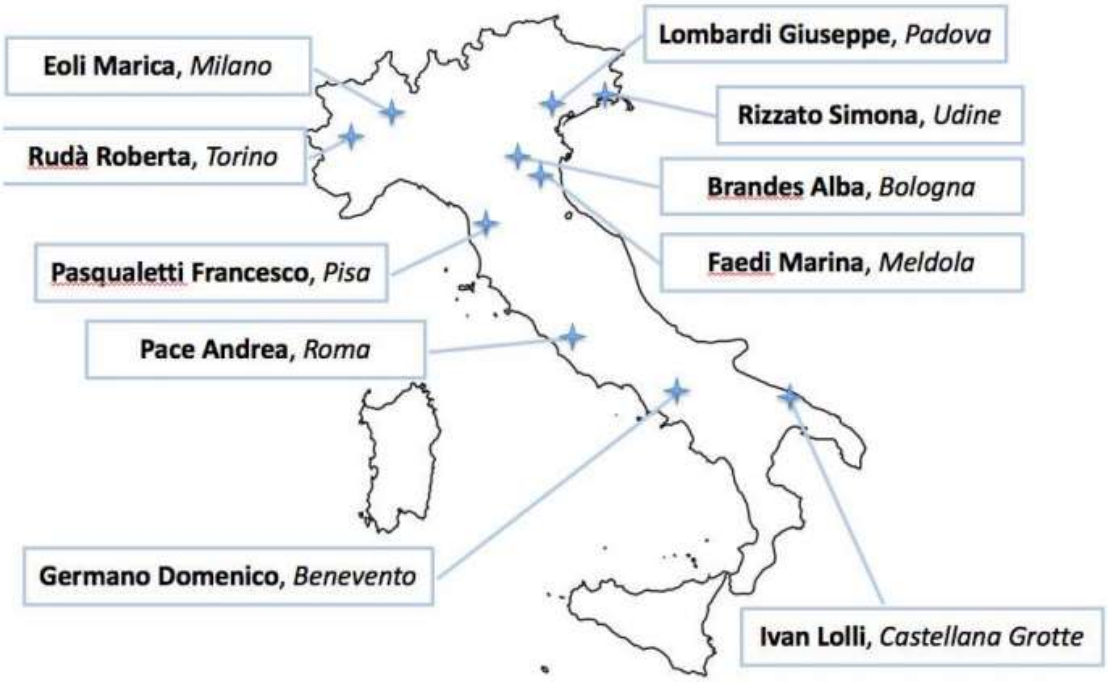
REGOMA Study Coordinator
Head of Clinical and Experimental Oncology Department, Director of Medical Oncology 1,
Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

- **Gian Luca De Salvo**

Head of *Clinical Trials and Biostatistics Unit,*
IOV-IRCCS, Padua, Italy

- **Bayer SpA**

- **Patients, Family members and Caregivers**



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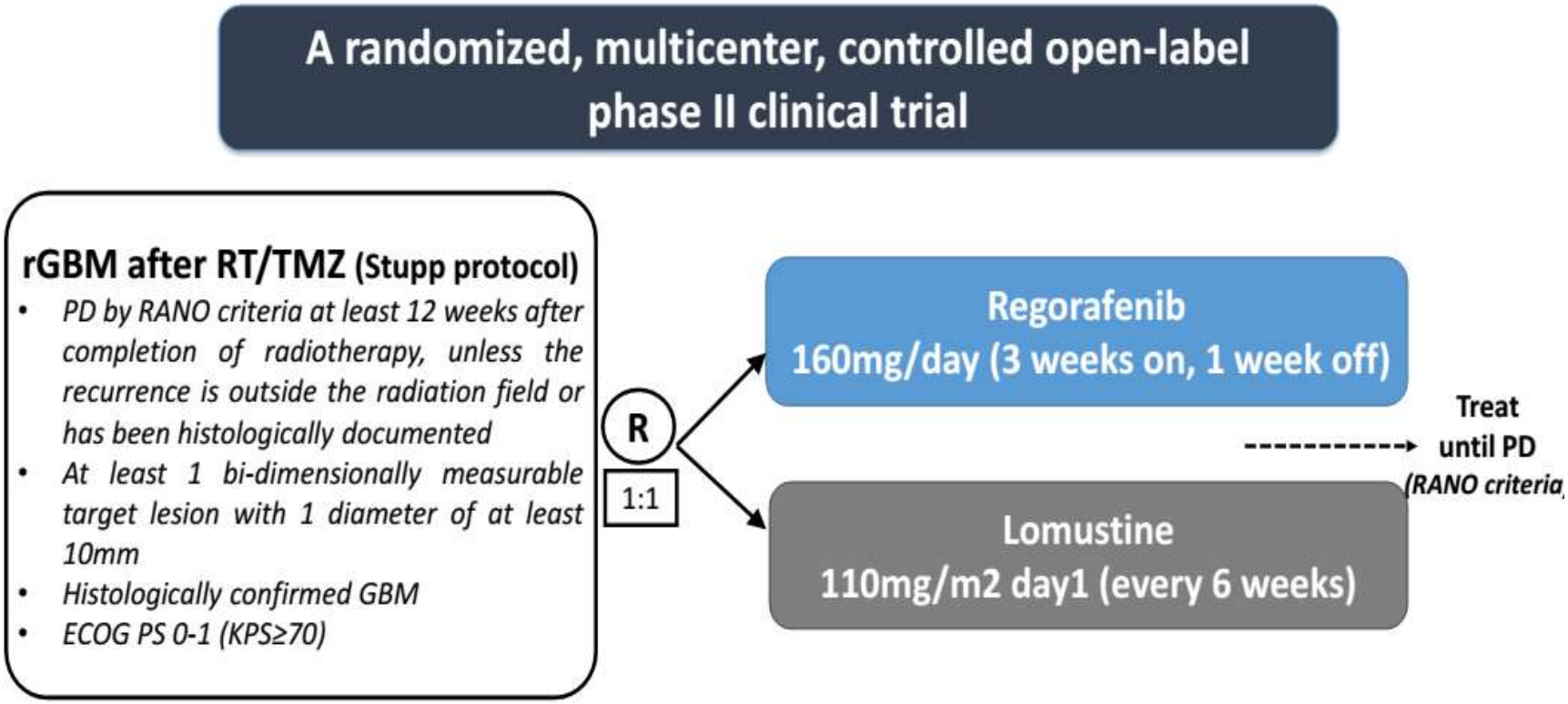
REGOMA: STUDY DESIGN



- Stratification factors: center and surgery at recurrence
- Study location: 10 centers in Italy

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OBJECTIVES OF THE STUDY

Primary Objective

- Overall Survival (OS)

Secondary Objectives

- 6-month Progression Free Survival (6m-PFS) (assessed by RANO criteria)
- Disease control rate (DCR)
- Objective Response Rate (ORR)
- Safety (assessed by CTCAE v4.0)
- Quality of Life (assessed by EORTC QoL C30 and BN-20)

Exploratory Analyses

- Analysis of angiogenic and metabolic tissue biomarkers as possible predictors of response to regorafenib

119 randomized patients from November 2015 to February 2017

	Regorafenib	Lomustine
Patients	59	60
Median age *(range)*	54.8 *(24.8-76.1)*	58.9 *(27.1-77.7)*
Gender		
male	41 *(69.5%)*	43 *(71.7%)*
female	18 *(30.5%)*	17 *(28.3%)*
ECOG PS		
0	27 *(45.8%)*	28 *(46.7%)*
1	32 *(54.2%)*	32 *(53.3%)*
Surgery at recurrence	13 *(22.0%)*	14 *(23.3%)*
Steroids at baseline	31 *(52.5%)*	37 *(61.7%)*
MGMT at diagnosis	59 (100%)	59 (98%)
methylated	28 *(47.5%)*	26 *(44.1%)*
unmethylated	31 *(52.5%)*	33 *(55.9%)*
IDH1 at diagnosis	*44 (74.5%)*	*38 (63.3%)*
mutated	*2 (4.5%)*	*0 (0%)*
unmutated	*42 (95.5%)*	*38 (100%)*

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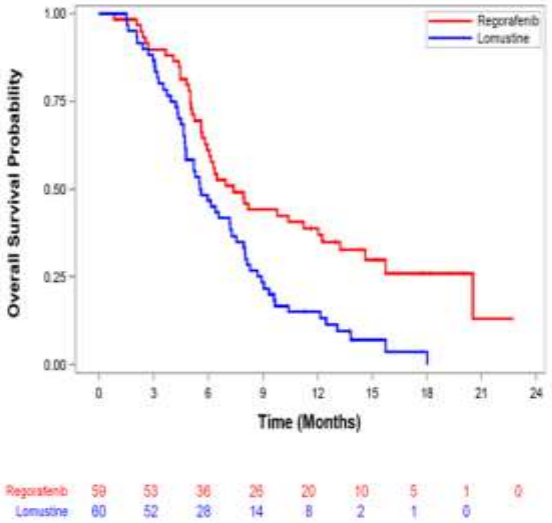
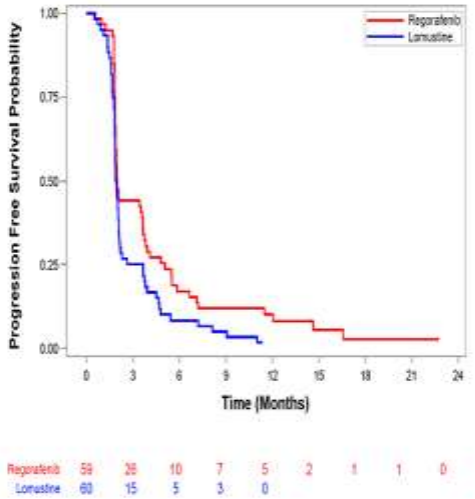
OS and PFS





Arm	Total	Failed	Median OS months (95%CI)	12-month OS (95%CI)	Log-Rank p-value	Hazard Ratio (95% CI)
Regorafenib	59	42	7.4 (5.8-12.0)	38.9% (26.6-61.0)	0.0009	0.50 (0.33-0.75)
Lomustine	60	57	5.6 (4.7-7.3)	15.0% (7.4-25.1)		

Arm	Total	Failed	Median PFS, months (95%CI)	6-month PFS (95%CI)	Log-Rank p-value	Hazard Ratio (95%CI)
Regorafenib	59	56	2.0 (1.9-3.6)	16.9% (8.7-27.5)	0.022	0.65 (0.45-0.95)
Lomustine	60	59	1.9 (1.8-2.1)	8.3% (3.1-17.0%)		

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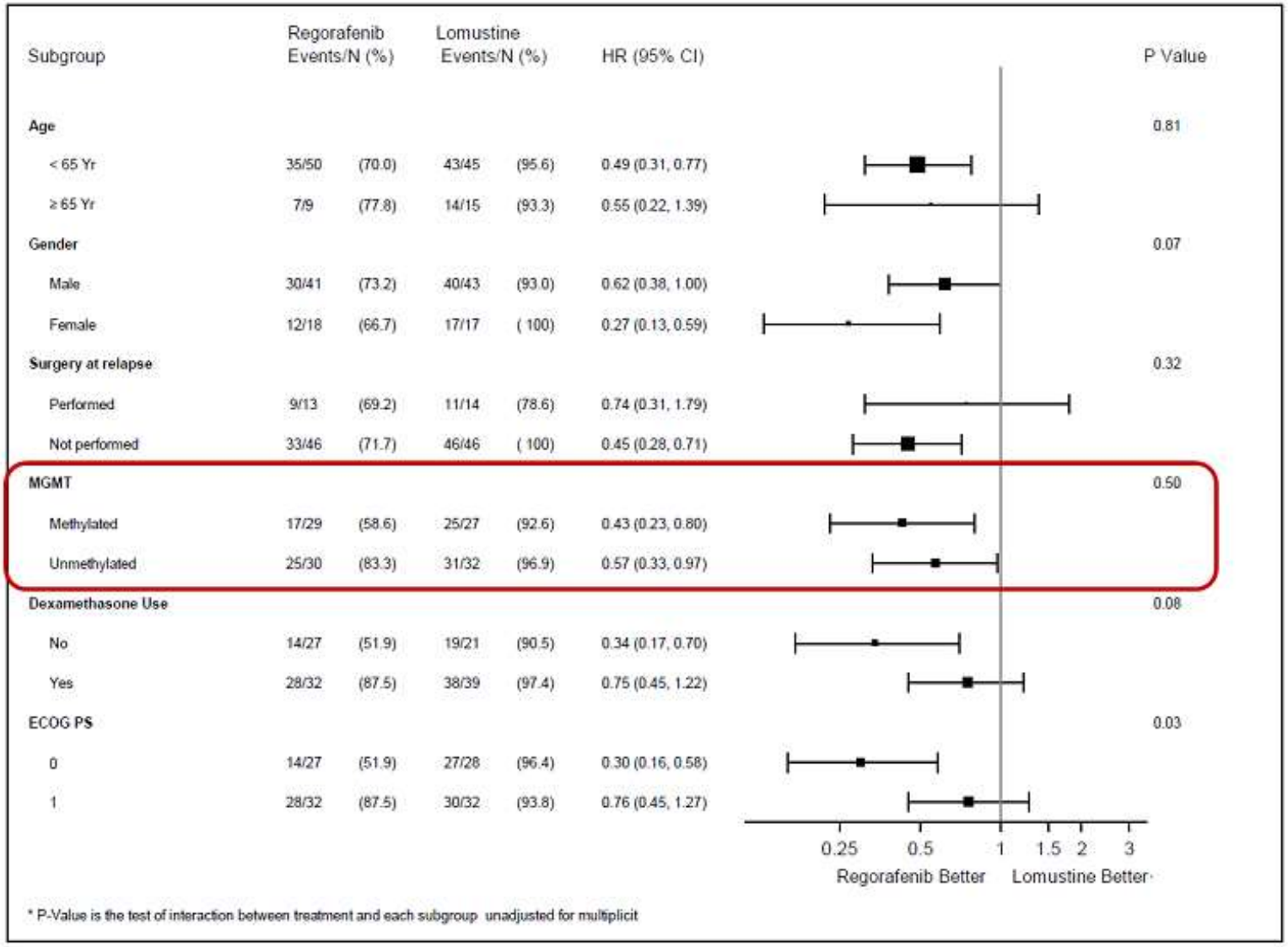

* P-Value is the test of interaction between treatment and each subgroup unadjusted for multiplicit

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RESPONSE RATES AND SAFETY

	Regorafenib	Lomustine
Complete Response	1.7%	1.8%
Partial Response	3.4%	1.8%
Objective Response Rate	**5.1%**	**3.6%**
Stable Disease	39%	17.5%
Disease Control Rate	**44.1%**	**21.1%**
Progressive Disease	55.9%	78.9%

Chi-square test p-value=0.0083

Treatment Related Adverse Event (grade 3-4)	Regorafenib	Lomustine
At least one event	**33 (55.9%)**	**24 (40.0%)**
Laboratory abnormalities		
Lymphopenia	3 (5.1%)	6 (10.0%)
Thrombocytopenia	1 (1.7%)	8 (13.3%)
Neutropenia	-	7 (11.7%)
Increased Lipase	6 (10.2%)	1 (1.7%)
Hyperbilirubinemia	6 (10.2%)	-
Hypertransaminasemia	2 (3.4%)	2 (3.3%)
GGT increase	1 (1.7%)	2 (3.3%)
Leucopenia	-	2 (3.3%)
Serum amylase increase	2 (3.4%)	-
Hypertriglyceridemia	2 (3.4%)	-
Hypokalemia	1 (1.7%)	-
Clinical Adverse Event		
Hand-foot skin reaction	6 (10.2%)	-
Fatigue	2 (3.4%)	1 (1.7%)
Rash or desquamation	3 (5.1%)	-
Constipation	2 (3.4%)	-
Hypertension	1 (1.7%)	-
Dry skin/skin alteration	1 (1.7%)	-
Diarrhea	1 (1.7%)	-

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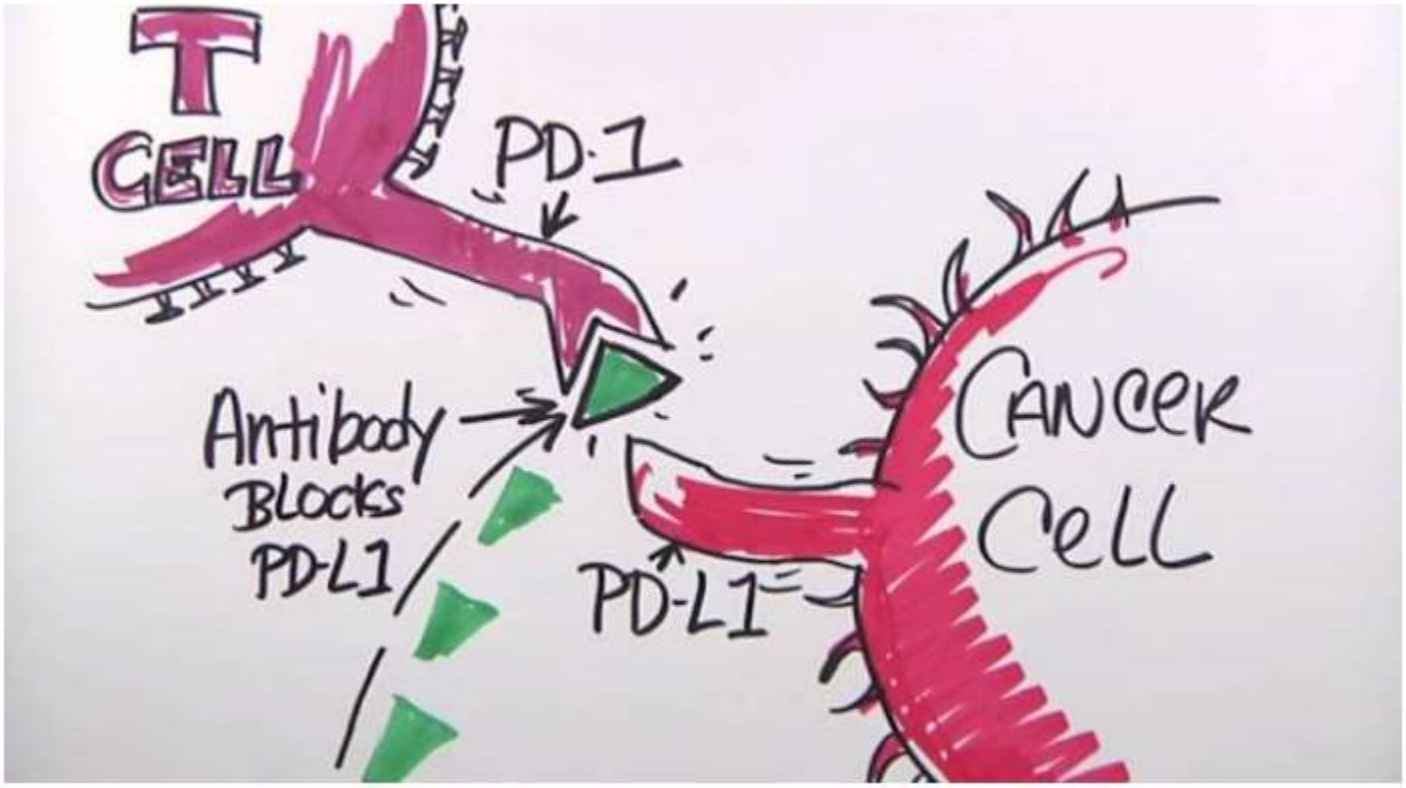
Immunotherapy checkpoint inhibitors



Phase II study of pembrolizumab or pembrolizumab plus bevacizumab in recurrent glioblastoma (rGBM)

David A. Reardon,[1] Lakshmi Nayak,[1] M.D., Katherine Peters,[2] Jennifer Clarke,[3] Justin T. Jordan,[4] John de Groot,[5] Leia Nghiemphu,[6] Thomas Kaley,[7] Howard Colman,[8] Sarah C. Gaffey,[1] Victoria Caruso,[1] Myriam Bednarek Debruyne,[1] Chinmay Bhavsar,[1] Annette M. Molinaro,[3] Timothy R. Smith,[9] Mariano Severgnini,[1] and Patrick Y. Wen[1]

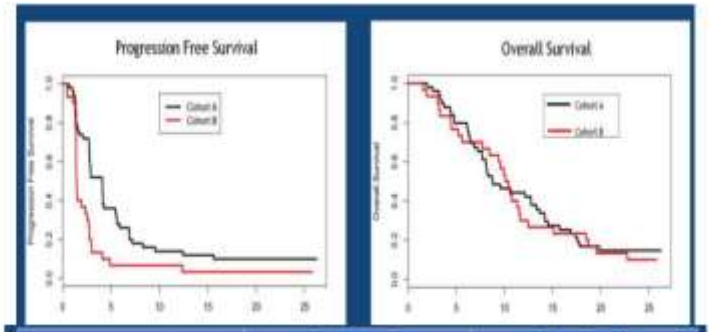
[1]Dana-Farber Cancer Institute and Harvard University School of Medicine, Boston, MA; [2]Duke University Medical Center, Durham, NC; [3]University of California, San Francisco, San Francisco, CA; [4]Massachusetts General Hospital, Boston, MA; [5]M.D. Anderson Cancer Center, Houston, TX; [6]University of California, Los Angeles, Los Angeles, CA; [7]Memorial Sloan Kettering Cancer Center, New York City, NY; [8]Huntsman Cancer Institute, Salt Lake City, UT; [9]Brigham and Women's Hospital, Boston, MA

Contact: david_reardon@dfci.harvard.edu

Supported by: The Ben and Catherine Ivy Foundation

Primary Objectives & Hypothesis

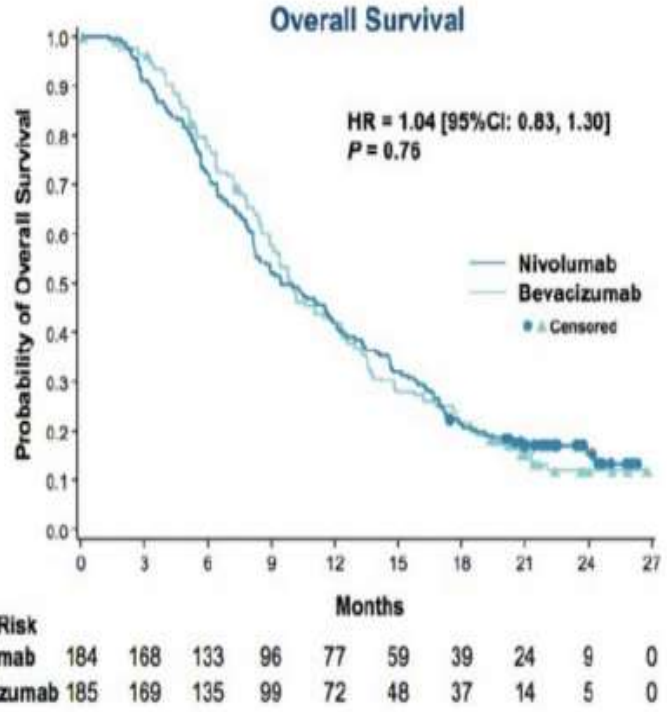
- **Objective:** To determine the RP2D/MTD of pembrolizumab when administered with bevacizumab (Cohort A) among recurrent glioblastoma patients;
- **Objective:** To evaluate the anti-tumor activity of pembrolizumab among subjects with bevacizumab-naïve recurrent glioblastoma when treated with pembrolizumab plus bevacizumab (Cohort A), and when treated with pembrolizumab monotherapy (Cohort B) as assessed by the 6-month progression-free survival (PFS-6) rate.
- ***Hypothesis:*** Administration of pembrolizumab with and without bevacizumab will be well tolerated and will result in a clinically meaningful benefit compared to the appropriate historical controls as measured by PFS-6 among subjects with bevacizumab-naive, recurrent glioblastoma.



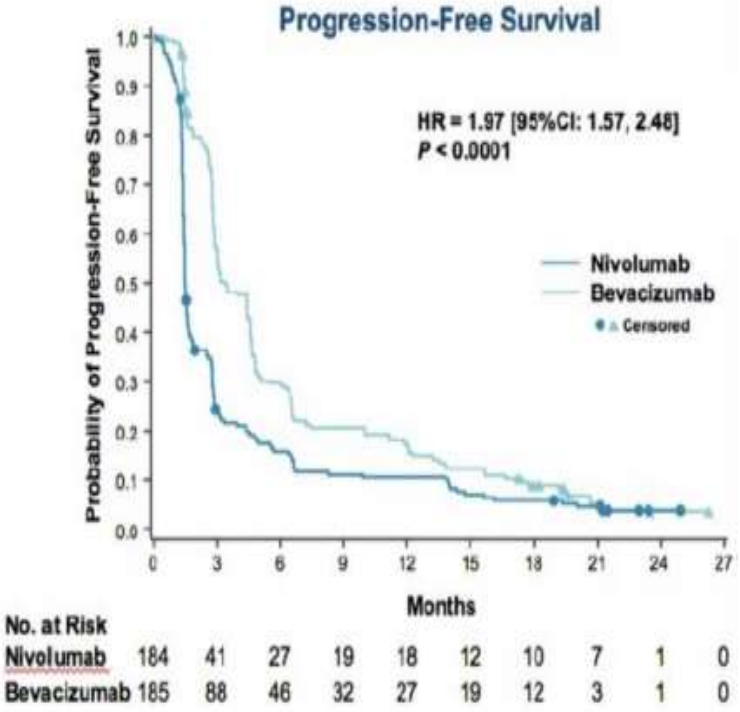
	Cohort A (n=50)	Cohort B (n=30)
Median follow-up (months)	25.2	25.8
Median progression-free survival (months)	4.09 (95% CI: 2.79, 5.52)	1.43 (95% CI: 1.38, 2.70)
Progression-free survival at 6 months (%)	26.0 (95% CI: 16.3, 41.5)	6.7 (95% CI: 1.8, 23.5)
Median overall survival	8.78 (95% CI: 7.69, 14.17)	10.26 (95% CI: 8.45, 12.46)

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 [34.8, 49.3]



	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]



Reardon DA, et al. Presented at: 5th Quadrennial World Federation of Neuro-Oncology Societies Meeting; May 4-7, 2017. Zurich, Switzerland.

Response per investigator Assessment (RANO)
Nivolumab vs bevacizumab in recurrent GBM

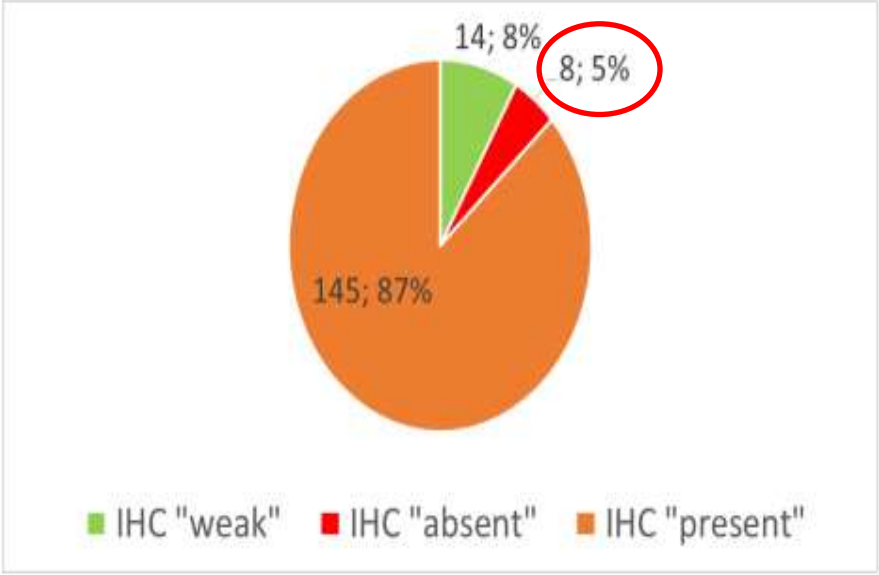
	Nivolumab n = 153[a]	Bevacizumab n = 156[a]
ORR, n (%) [95% CI]	12 (7.8) [4.1, 13.3]	36 (23.1) [16.7, 30.5]
BOR, n (%)		
CR	2 (1.3)	4 (2.6)
PR	10 (6.5)	32 (20.5)
SD	33 (21.6)	73 (46.8)
PD	107 (69.9)	26 (16.7)
Unable to determine	1 (0.7)	21 (13.5)
Not treated	1 (0.7)	16 (10.3)
Discontinued early due to toxicity	0	3 (1.9)
Other	0	2 (1.3)
Median TTR (range), months	3.0 (1.4–12.0)	1.5 (1.2–6.5)
Median DOR (range), months	11.1 (0.6–18.7)	5.3 (3.1–24.9)
PFS rate [95% CI], %		
6-months	15.7 [10.8, 21.5]	29.6 [22.7, 36.9]
12-months	10.5 [6.5, 15.5]	17.4 [11.9, 23.7]

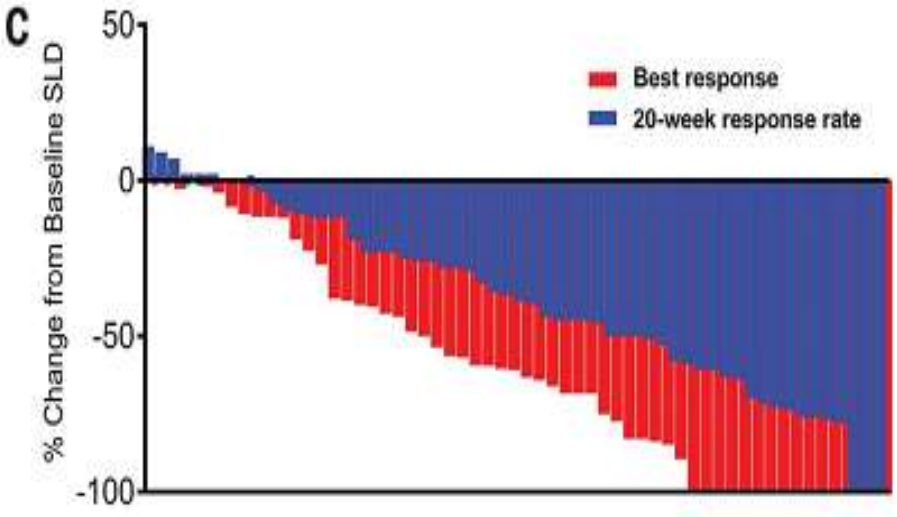
BOR, best overall response; CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response. [a]Patients evaluable for response.

Predictive factors?

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3*] Kellie N. Smith,[1,3*] Hao Wang,[3*] Bjarne R. Bartlett,[2,4*] Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[3] Brandon S. Luber,[3] Fay Wong,[2,4] Nilofer S. Azad,[1,3] Agnieszka A. Rucki,[1,3] Dan Laheru,[3] Ross Donehower,[3] Atif Zaheer,[5] George A. Fisher,[6] Todd S. Crocenzi,[7] James J. Lee,[8] Tim F. Greten,[9] Austin G. Duffy,[9] Kristen K. Ciombor,[10] Aleksandra D. Eyring,[11] Bao H. Lam,[11] Andrew Joe,[11] S. Peter Kang,[11] Matthias Holdhoff,[3] Ludmila Danilova,[1,3] Leslie Cope,[1,3] Christian Meyer,[3] Shibin Zhou,[1,3,4] Richard M. Goldberg,[12] Deborah K. Armstrong,[3] Katherine M. Bever,[3] Amanda N. Fader,[13] Janis Taube,[1,3] Franck Housseau,[1,3] David Spetzler,[14] Nianqing Xiao,[14] Drew M. Pardoll,[1,3] Nickolas Papadopoulos,[3,4] Kenneth W. Kinzler,[3,4] James R. Eshleman,[15] Bert Vogelstein,[1,3,4] Robert A. Anders,[1,3,15] Luis A. Diaz Jr.[1,2,3]†‡





	P	OR	95% CI
Anaplastic Astrocytoma vs Glioblastoma	0.01	3.8	1.3-11.1
Recurrence vs Diagnosis	0.008	3.9	1.5-10-1
Female Pts vs Male Pts	0.03	2.7	1.07-6.7
IDHmut vs IDHwt	0.03	3.3	1.1-9.8

Univariate Analysis

	P	OR	95% CI
Anaplastic Astrocytoma vs Glioblastoma	0.007	5.1	1.5 – 16.8
Recurrence vs Diagnosis	0.02	3.8	1.1 – 12.5

Multivariate Analysis – *Logistic Regression*

Lombardi G et al. Oral Presentation at ESMO 2018

Le *et al.*, *Science* **357**, 409–413 (2017)

Actionable targets involving FGF receptors in gliomas molecular specificities, spatial distribution clinical outcome and radiological phenotype

Anna Luisa Di Stefano, Alberto Picca, Edouard Saragoussi, Giulia Berzero, Agusti Alentorn, Mehdi Touat, Francois Ducray, Chiara Villa, Elena Trisolini, Yohann Schmitt, Ahmed Idbaih, Khe Hoang-Xuan, Jean-Yves Delattre, Anna Lasorella, Antonio Iavarone, Karima Mokhtari, Julien Savatovsky, Franck Bielle and Marc Sanson

Anna Luisa Di Stefano, MD, PhD
Neurology, Hôpital Foch, Suresnes
Experimental Neuroncology Lab, Pitié Salpétrière, Paris

Deciphering *FGFR3-TACC3*+ gliomas phenotype

Grade	Histological diagnosis	N of detected *F3T3*/No samples	N of samples tested
II	Oligodendroglioma IDH mutant and 1p19q codeleted	0/28	111
	Diffuse astrocytoma IDH mutant	0/45	
	Diffuse astrocytoma IDH wild-type	3/32	
	Diffuse astrocytoma IDH NOS	0/5	
	Pleomorphic xanthoastroyctoma	0/1	
III	Anaplastic oligodendroglioma IDH mutant and 1p19q codeleted	0/40	140
	Anaplastic astrocytoma IDH mutant	0/34	
	Anaplastic astrocytoma IDH wild-type	2/60	
	Anaplastic astrocytoma IDH NOS	0/5	
	Anaplastic ependymoma	0/1	
IV	Glioblastoma IDH mutant	0/38	861
	Glioblastoma IDH wild-type	45/699	
	Glioblastoma IDH NOS	0/117	
	Diffuse midline glioma H3 K27M mutant	0/6	
	Unclassified malignant glioma IDH wild-type	0/1	
Total		50/1112	1112

- ✓ **Variable breakpoint**

- ✓ **Retained at recurrence**
- ✓ **FGFR3 positive staining in all F3T3+**
  - Positive predictive value **56%**
  - Negative predictive value **100%**

	FGFR3+	FGFR3-	Total
F3T3 negative	19	213	232
F3T3 positive	24	0	24
Total	43	213	256

- ✓ **Recurrent histological features**

Di Stefano et al. 2015; Bielle et al. 2017; Di Stefano, in preparation

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Anna Luisa Di Stefano

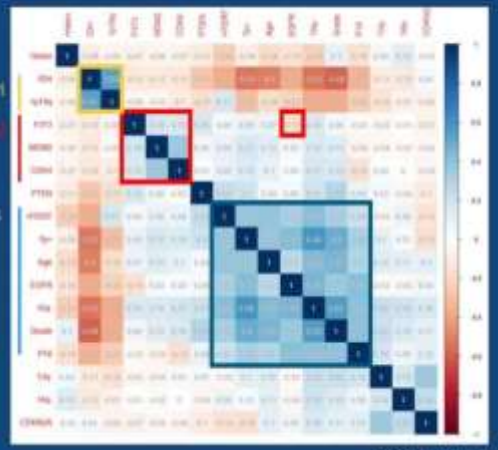
4.5%

6.4%

Activation of oxidative phosphorylation is a new pharmacologic vulnerability for tumors harboring *FGFR3-TACC3*

FGFR3-TACC3 genomic background

1112 glioma study
- Age
- Grade
- *IDH* mutations
- 1p19q codeletion
- *F3T3*
- *MDM2* amplification
- *CDK4* amplification
- *H3F3A* and *H3B* mutation
- *PTEN* homo deletion
- *CDKN2A* homo deletion
- p16 loss
- *HTERT* mutations
- 7p+
- *EGFR* amplification
- 10q-
- 13q-
- 14q-

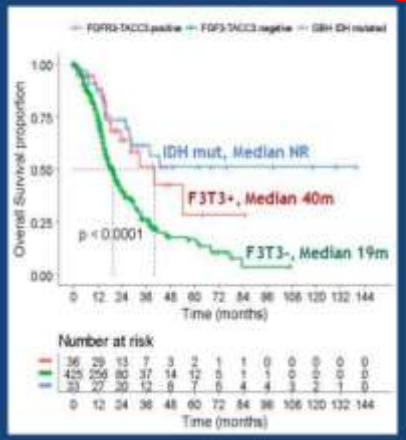


FGFR3-TACC3 cluster
- ✓ No *EGFR* amplification
- ✓ Association with 12q13.15 oncogenes

Di Stefano, in preparation

FGFR3-TACC3 prognosis

Overall Survival, GBM



Multivariate analysis, IDHwt GBM

Variables	Hazard Ratio	95% CI	P value
FGFR3-TACC3 fusion	0.34	0.18-0.62	0.001
Age at diagnosis	1.05	1.03-1.05	0.002
KPS<70	6.19	2.92-16.75	0.000
No resection at diagnosis (biopsy only)	3.46	1.80-6.66	0.000
MGMT methylated	0.49	0.31-0.77	0.002

Di Stefano, in preparation

Comparing RTOG and EORTC risk-factors in Low Grade Gliomas: who will remain standing in the ring at bell's sound?

Franceschi E[1], Mura A[1], Paccapelo A[1], Bartolini S[1], Minichillo S[1], Lanese A[1], Agati R[2], Balestrini D[3], Currà MF[1], Scafati C[1], Visani M[4], Di Battista M[1], Lombardo L[1], Genestreti G[1], Brandes AA[1]

1-Department of Medical Oncology, Bellaria Hospital, Azienda USL, Bologna; 2-Neuroradiology Department, IRCCS of Neurological Sciences, Bellaria Hospital, Bologna; 3-Department of Radiotherapy, Bellaria Hospital, Bologna; 4-Department of Pathology Bellaria Hospital, Bologna, Italy

Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study

Brigitta G Baumert*, Monika E Hegi*, Martin J van den Bent, Andreas von Deimling, Thierry Gorlia, Khê Hoang-Xuan, Alba A Brandes, Guy Kantor, Martin J B Taphoorn, Mohamed Ben Hassel, Christian Hartmann, Gail Ryan, David Capper, Johan M Kros, Sebastian Kurscheid, Wolfgang Wick, Roelien Enting, Michele Reni, Brian Thiessen, Frederic Dhermain, Jacoline E Bromberg, Loic Feuvret, Jaap C Reijneveld, Olivier Chinot, Johanna M M Gijtenbeek, John P Rossiter, Nicolas Dif, Carmen Balana, Jose Bravo-Marques, Paul M Clement, Christine Marosi, Tzahala Tzuk-Shina, Robert A Nordal, Jeremy Rees, Denis Lacombe, Warren P Mason, Roger Stupp*

EORTC risk score
- -Age >40 years
- -neurologic deficits at diagnosis
- -tumor crossing the midline
- -Astrocytoma histology
- -lesion diameter >6 cm

477 patients (2005 – 2012, median FU 48 months)

Lancet Oncol. 2016 November

ORIGINAL ARTICLE

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

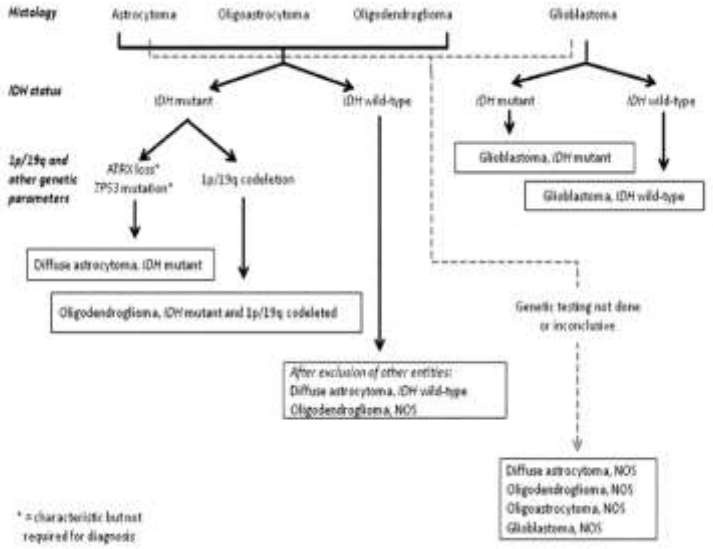
Jan C. Buckner, M.D., Edward G. Shaw, M.D., Stephanie L. Pugh, Ph.D., Arnab Chakravarti, M.D., Mark R. Gilbert, M.D., Geoffrey R. Barger, M.D., Stephen Coons, M.D., Peter Ricci, M.D., Dennis Bullard, M.D., Paul D. Brown, M.D., Keith Stelzer, M.D., David Brachman, M.D., John H. Suh, M.D., Christopher 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.

RTOG criteria
- -Age >40 years and/or
- -Residual after surgery

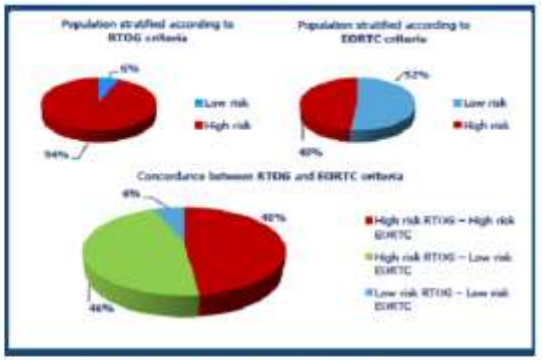
A total of 251 eligible patients were enrolled from 1998 through 2002.

N ENGL J MED 374;14 NEJM.ORG APRIL 7, 2016

Is there a concordance between RTOG and EORTC risk scores?



Population	total	
Number	50	
Median age	38 (19-69)	
gender (m/f)	30 60.0%	20 40.0%
surgery (biopsy+partial/total resection)	44 88.0%	6 12.0%
IDH (mutant/wild type)	46 92.0%	4 8.0%
Histology - astrocytoma - oligodendroglioma (1p/19q codel)	27 23	54% 46%



Concordance was 54.0% (K=0.111, P=0.086)

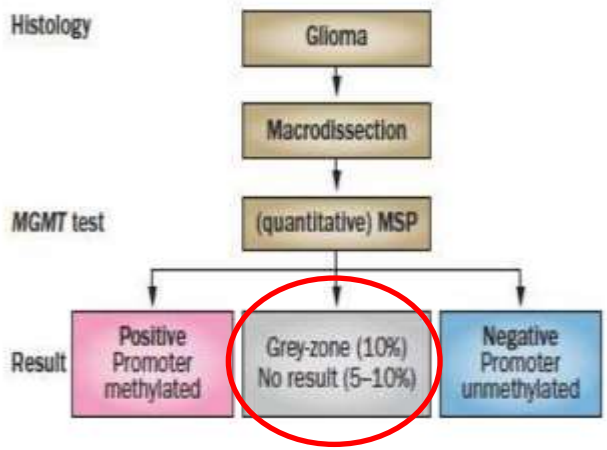
- •It is not possible to compare results of studies that include populations according to different criteria.
- •Molecular characteristics are necessary to implement these clinical risk factor criteria

A LARGE, MULTICENTER, RETROSPECTIVE STUDY TO IDENTIFY A CUT-OFF OF MGMT METHYLATION STATUS BY QUANTITATIVE PYROSEQUENCING APPROACH IN PATIENTS WITH GLIOBLASTOMA

Lombardi Giuseppe[1], Bellu L[2], Villani V[3], Rizzato S[4], Russo M[5], Carosi M[3], De Carlo Elisa[6], Biasini L[7], Gardiman MP[8], Fiduccia P[9], Pambuku A[1], Della Puppa A[10], Skrap M[11], Servadei F[12], D'Avella D[13], Carapella CM[3], Caccese M[1], Bertorelle R[8], Pace A[3], Zagonel Vittorina[1].

ADVANTAGES

- Feasible in FFPE specimens
- Yields quantitative results on MGMT methylation status and each CpG site methylation
- Reliable, reproducible, repeatable
- Overcome the problem of the «gray zone»

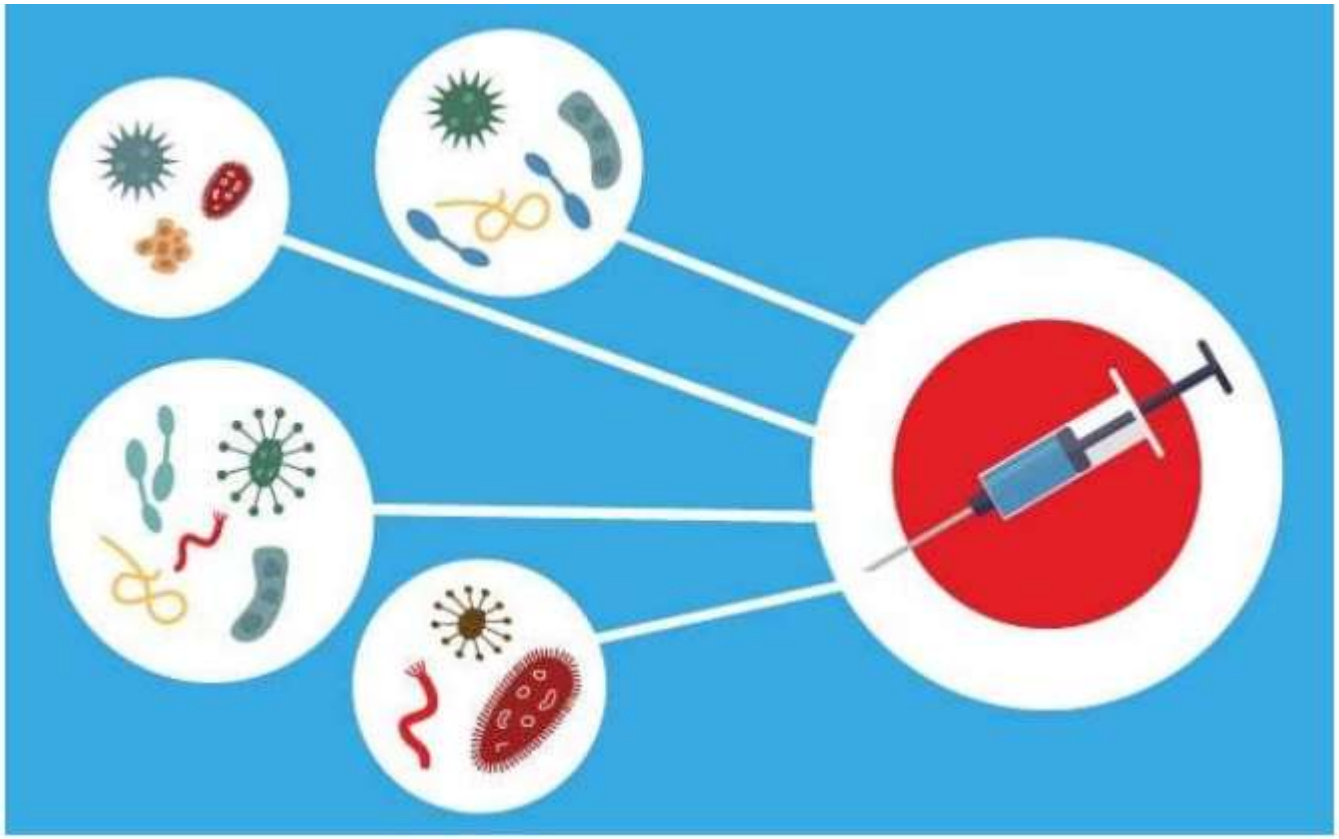


OPEN ISSUES

- A cut-off value of MGMT methylation by pyrosequencing as basis for treatment decision in still unclear
- The relative clinical relevance of the methylation status of the individual CpGs have still to be determined

Coming soon …..

Immunotherapy- vaccines



GAPVAC-101: First-in-human trial of a highly personalized peptide vaccination approach for patients with newly diagnosed glioblastoma

Wolfgang Wick, Pierre-Yves Dietrich, Sabrina Kuttruff-Coqui, Norbert Hilf, Katrin Frenzel, Arie Admon, Sjoerd H. van der Burg, Andreas von Deimling, Cécile Gouttefangeas, Judith R. Kroep, Francisco Martinez-Ricarte, Hideho Okada, Christian H. Ottensmeier, Berta Ponsati, Hans S. Poulsen, Stefan Stevanović, Ghazaleh Tabatabai, Hans-Georg Rammensee, Ugur Sahin, Harpreet Singh-Jasuja

for the *Glioma Actively Personalized Vaccine* (GAPVAC) consortium (www.gapvac.eu)

GAPVAC

UK HD

Targeting IDH1R132H in WHO grade III / IV IDH1R132H-mutated gliomas by a peptide vaccine - a Phase I safety, tolerability and immunogenicity multicenter trial (NOA-16) [a]

M. Platten[1,2,3,4], D. Schilling[3], L. Bunse[1,2,3,4], A. Wick[1], T. Bunse[2,4], D. Riehl[2,3], I. Karapangiotou-Schenkel[3], I. Harting[1], F. Sahm[1,2], A. Schmitt[1], J. Steinbach[5], A. Weyerbrock[6], J. Hense[7], M. Misch[8], D. Krex[9], S.Stevanović[10], G. Tabatabai[10], A. von Deimling[1,2], M. Schmitt[1], W. Wick[1,2,3]

[1] University Hospital Heidelberg, [2] German Cancer Research Center, [3] National Center for Tumor Diseases, [4] University Hospital Mannheim, [5] University Hospital Frankfurt, [6] University Hospital Freiburg, [7] University Hospital Essen, [8] University Hospital Berlin Charité, [9] University Hospital Dresden, [10] University Tübingen, Tübingen, Germany

a) ClinicalTrials.gov Identifier: NCT02454634

Take-home messages

- Glioma subgroups with “metabolic targets” (FGFR3-TACC3, IDH mutations)
- Checkpoint Inhibitors: low efficacy in glioblastoma (need better patient selection? TML?)
- Glioblastoma is a heterogeneous tumor: need highly personalized treatment (GAPVAC)
- Promising drugs in recurrent glioblastoma: depatux-M and regorafenib

Thanks for your attention!