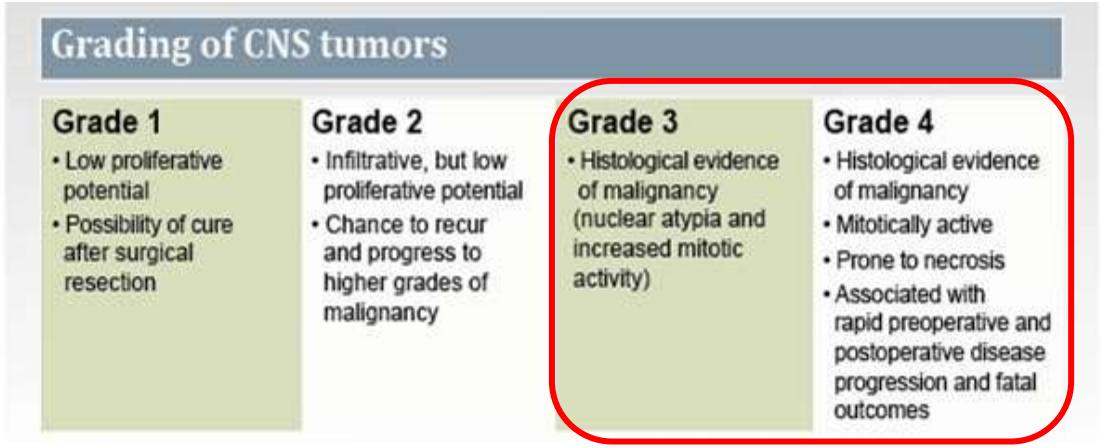
High Grade Gliomas: nuovi approcci terapeutici

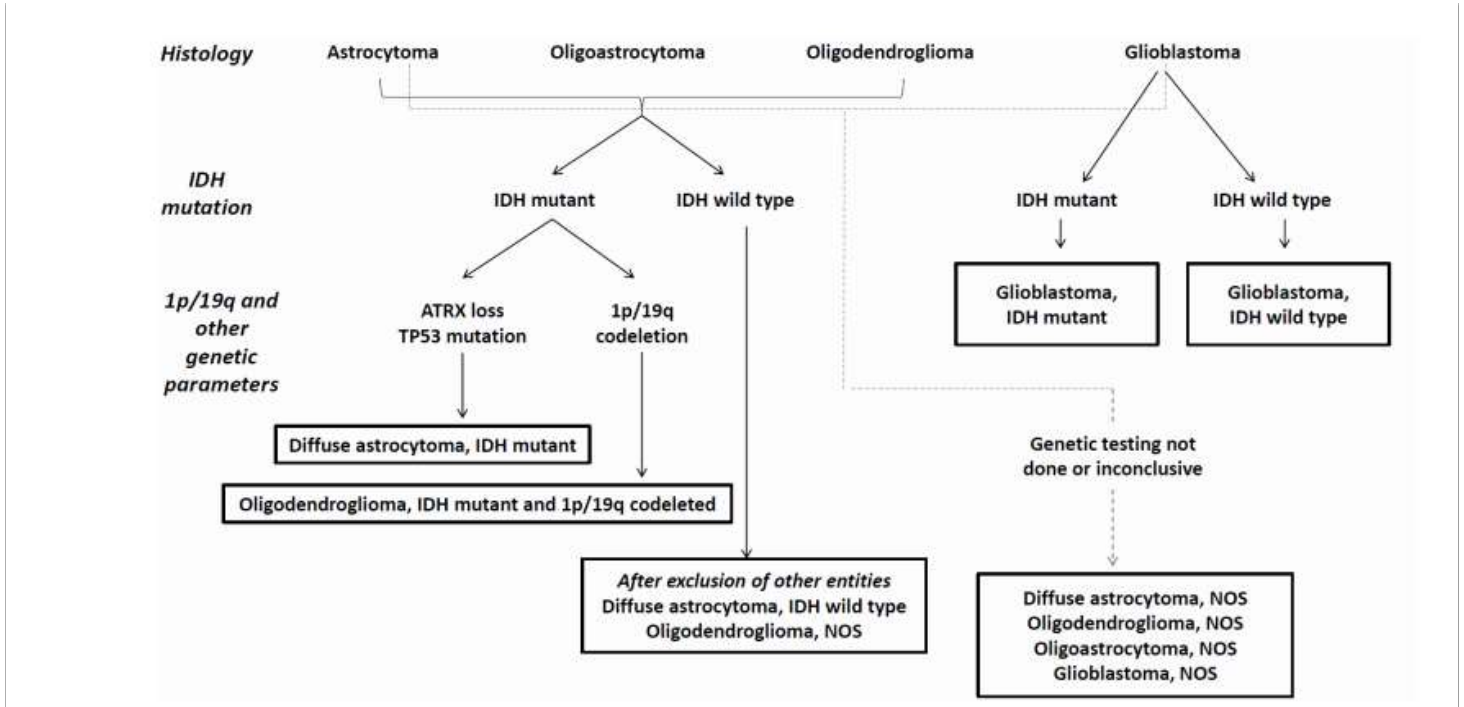
Mario Caccese, MD

Dipartimento di Oncologia Clinica e Sperimentale
Oncologia Medica 1
Istituto Oncologico Veneto-IRCCS
Padova

High Grade Gliomas



- ***Anaplastic Astrocytoma /Anaplastic Oligodendroglioma (III)***
- ***Glioblastoma (IV)***



Louis D.N. et al. Acta Neuropathol 2016

Are we going to get out of the tunnel?

Topics

Glioblastoma

- ✓ **REGOMA** (regorafenib in recurrent GBM)
- ✓ **INTELLANCE 2** (depatuxizumab-M in recurrent GBM, EGFR ampl)

Anaplastic Gliomas

- ✓ **CATNON trial** (anaplastic glioma without 1p19q codel)
- ✓ **STELLAR** (anaplastic astrocytoma - ongoing)

Precision Medicine

- Larotrectinib
- Entrectinib
- Vemurafenib

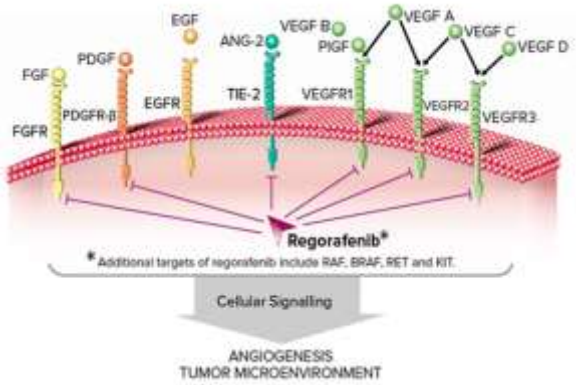
Immunotherapy

- Checkpoint inhibitors
- MMRd

THE LANCET Oncology

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



REGOMA: study design

A randomized, multicenter, controlled open-label phase II clinical trial

rGB after RT/TMZ (Stupp protocol)

- *PD by RANO criteria at least 12 weeks after completion of radiotherapy, unless the recurrence is outside the radiation field or has been histologically documented*
- *At least 1 bi-dimensionally measurable target lesion with 1 diameter of at least 10mm*
- *Histologically confirmed glioblastoma (GB)*
- *ECOG PS 0-1 (KPS≥70)*

R

1:1

Regorafenib
160mg/day (3 weeks on, 1 week off)

Lomustine
110mg/m2 day1 (every 6 weeks)

Treat until PD ***(RANO criteria)***

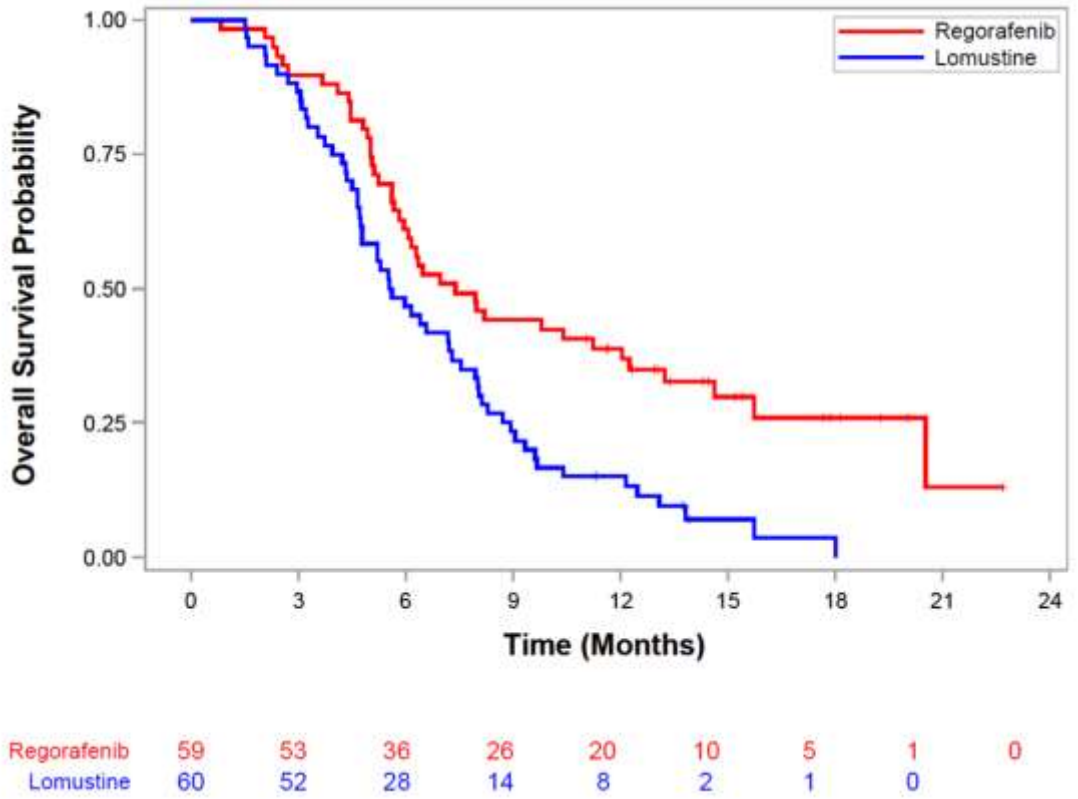
- Stratification factors: center and surgery at recurrence
- Study location: 10 centers in Italy

Lombardi G et al, Lancet Oncology 2019

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%)*
wild type	*42 (95.5%)*	*38 (100%)*

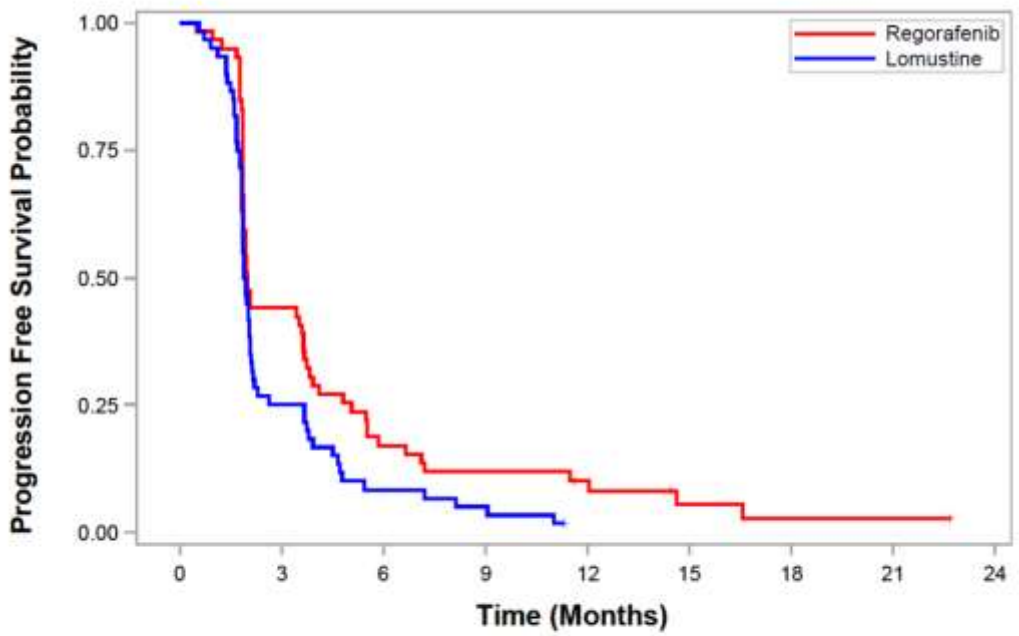
Overall Survival



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)		

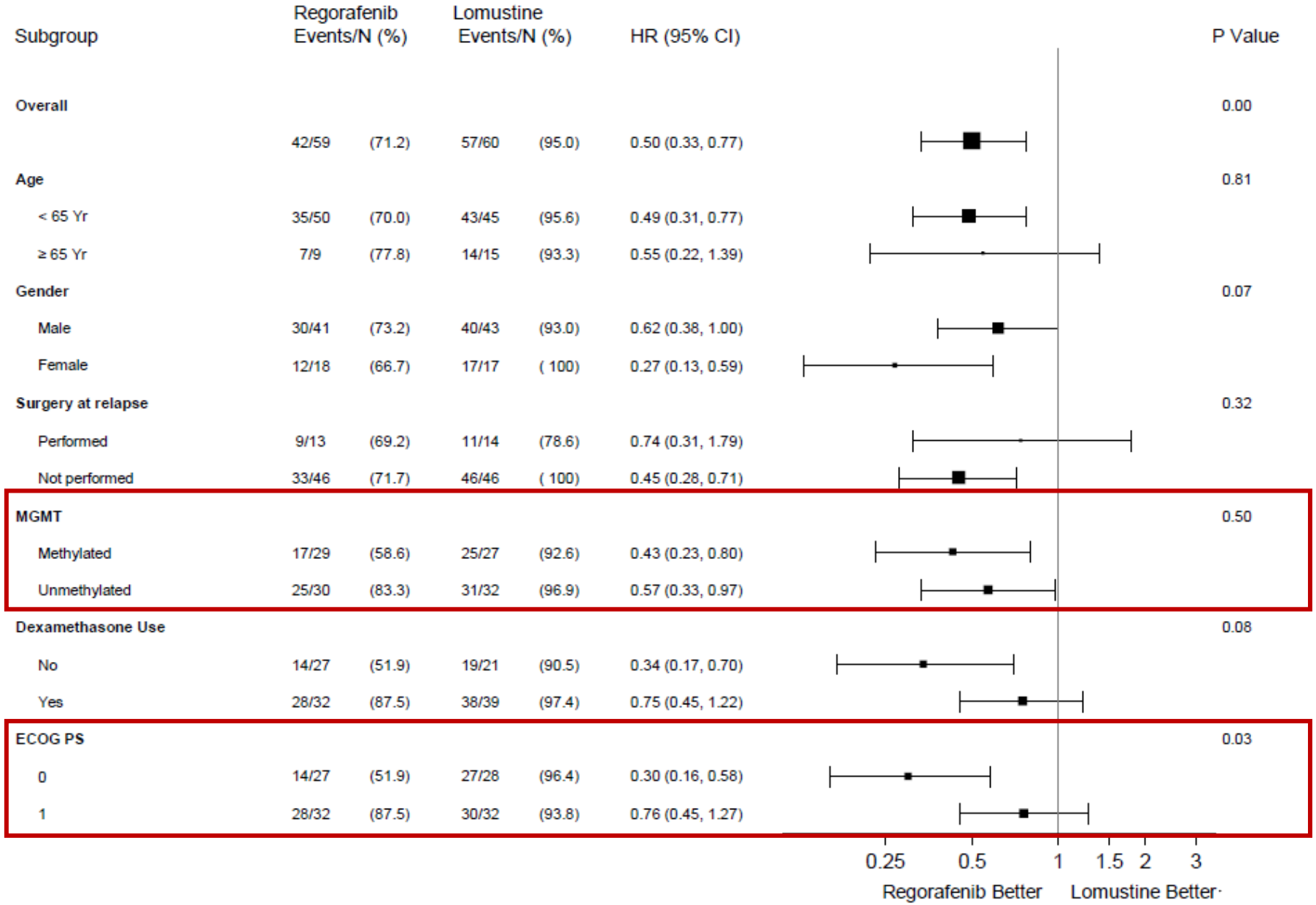
Lombardi G et al, Lancet Oncology 2019

Progression Free Survival



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%)		

Lombardi G et al, Lancet Oncology 2019



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

Response Rates

	Regorafenib	Lomustine
Complete Response	1.7%	1.8%
Partial Response	3.4%	1.8%
Objective Response Rate	**5.1%**	**3.3%**
Stable Disease	39%	17.5%
Disease Control Rate	**44.1%**	**21.1%**
Progressive Disease	55.9%	78.9%

Chi-square test p-value=0.0059

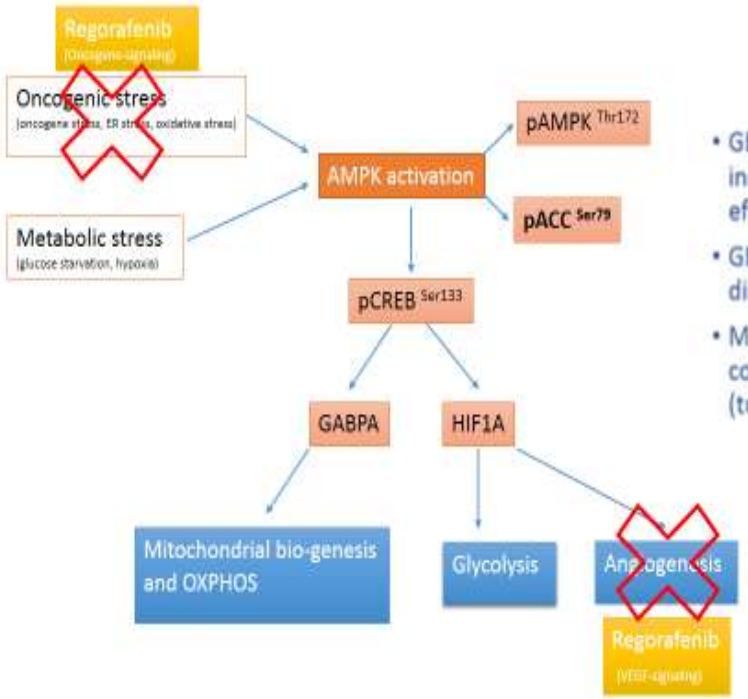
Safety

Treatment Related Adverse Event (grade 3-4)	Regorafenib	Lomustine
At least one event	**33 *(56%)***	**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%)*	-

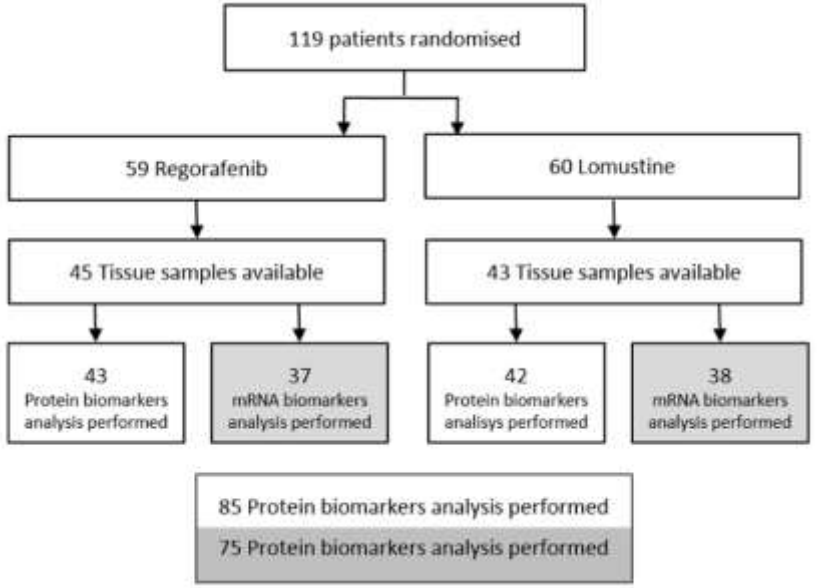
- Drug-related adverse events led to dose reductions in **17%** and **18%** of patients treated with regorafenib and lomustine, respectively
- No treatment-related death was reported

Biomarkers for predicting survival?

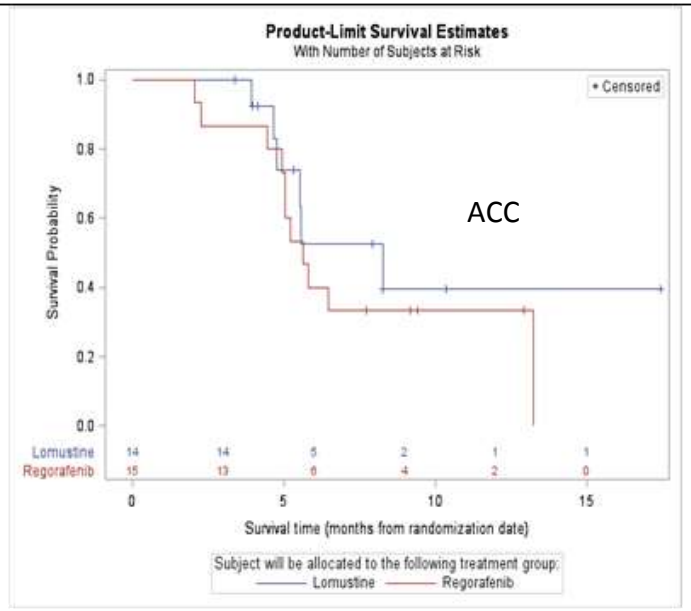
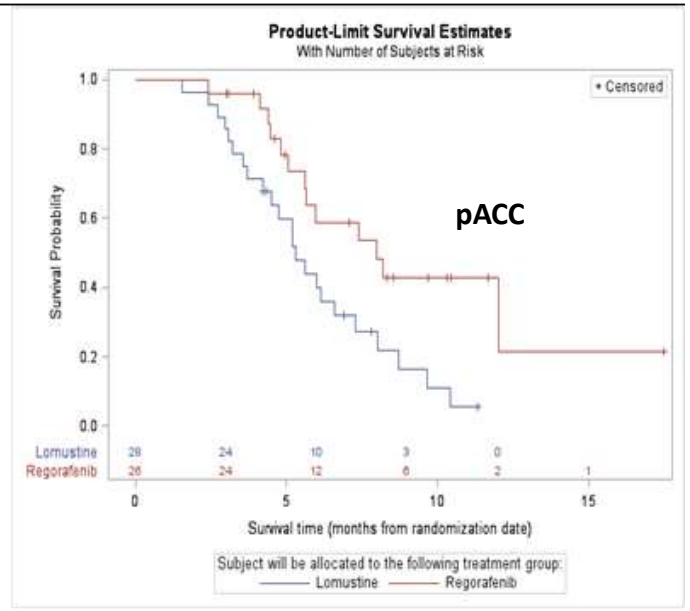
AMPK activation and response to regorafenib in relapsed GBM



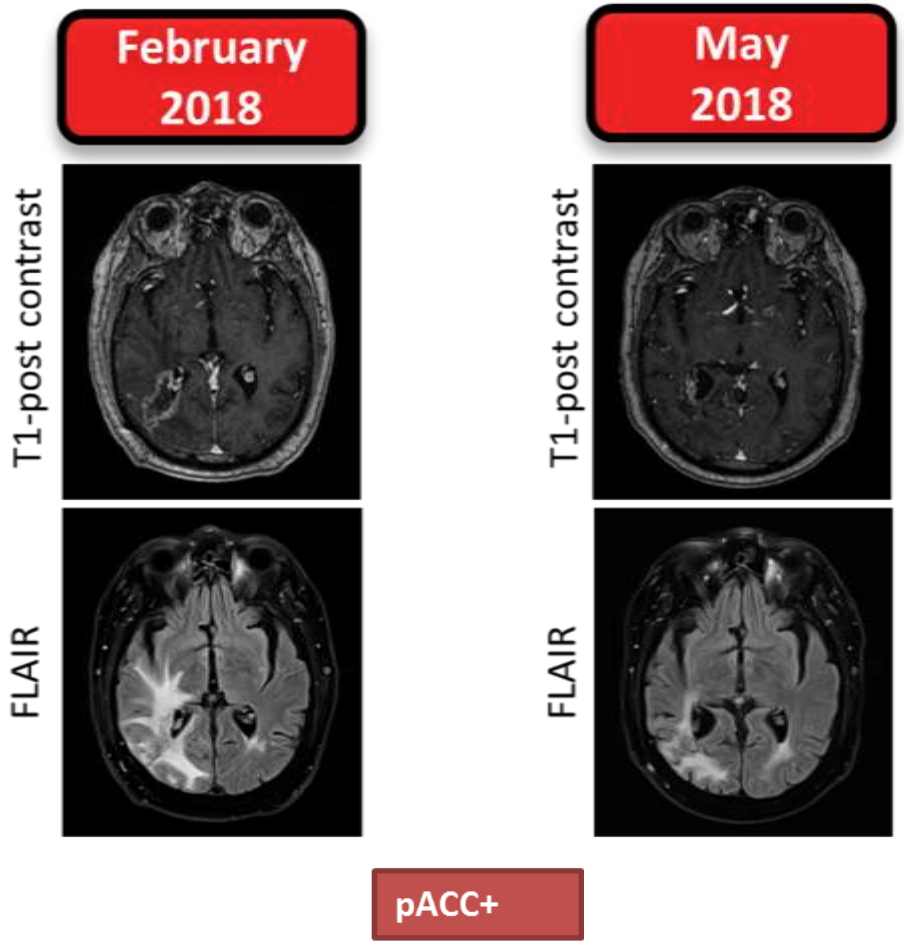
- GBM samples with AMPK activation could be more angiogenic, due to increased HIF1A levels and hence sensitive to the anti-angiogenic effects of regorafenib (indirect anti-tumor effects)
- GBM samples with AMPK activation could be more sensitive to the direct anti-tumor effects of regorafenib
- Mechanisms connecting AMPK activation to response to regorafenib could be tumor type specific, due to the dual role of AMPK in cancer (tumor suppressor versus oncogenic role)



Biomarkers for predicting survival?

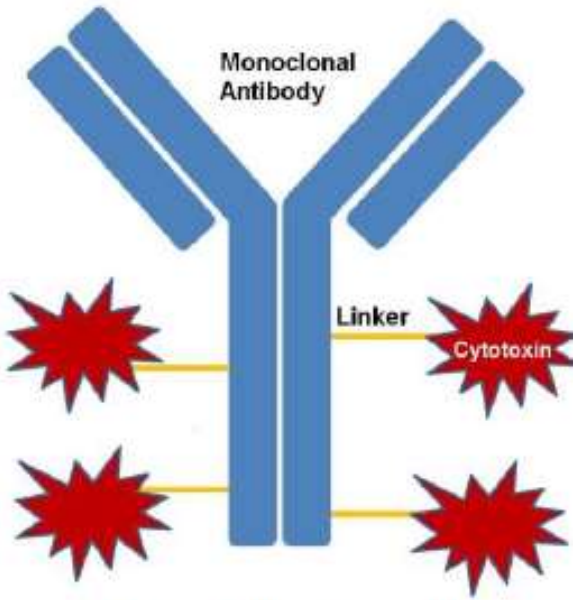
	ACC	pACC
Overall Survival		
	Log Rank test p-value= 0.4144	Log Rank test p-value= 0.0120
	HR (Reg vs Lom): 1.54 (95%CI: 0.57-4.18); mOS Rego: 5.6 months (95%CI 4.5-13.2)	HR (Reg vs Lom): 0.44 (95%CI: 0.22-0.87); mOS Rego: 8.0 months (95%CI 5.6-.)

Test for interaction p-value = 0.0419

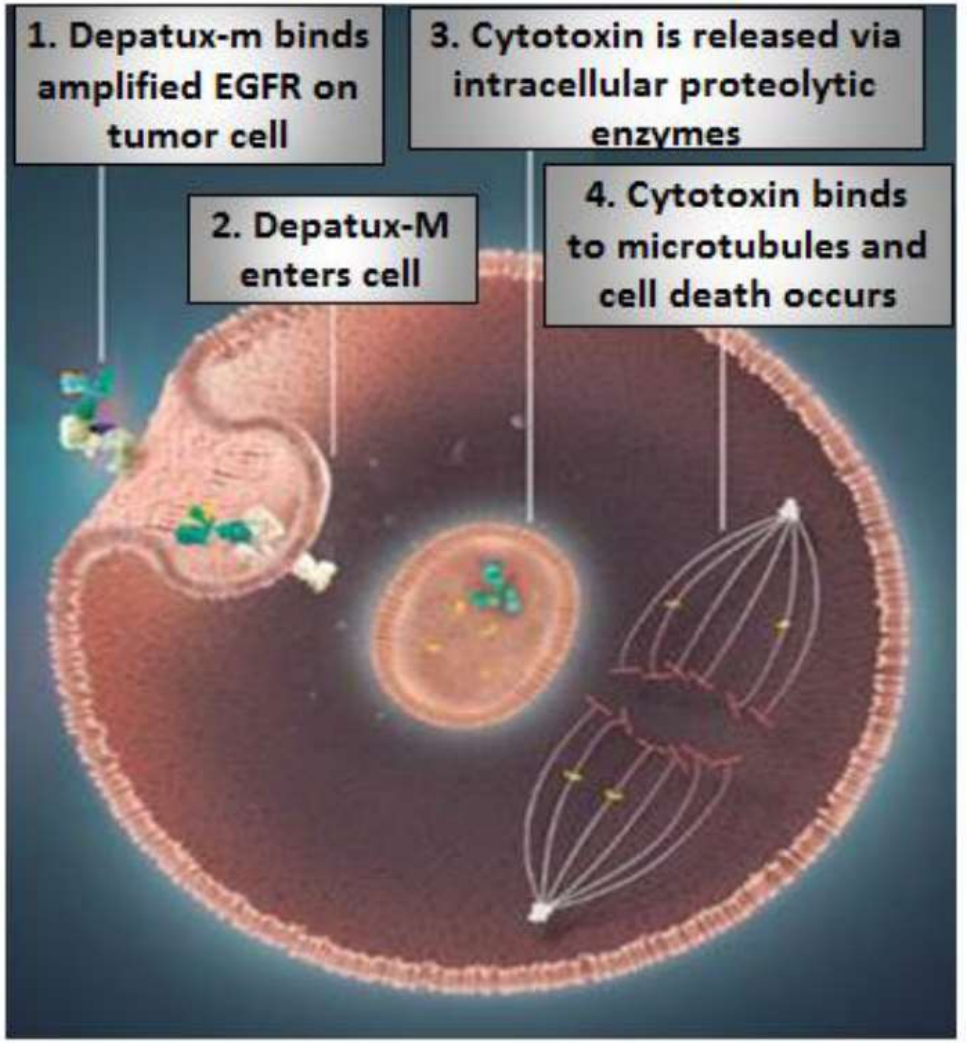


Lombardi G et al. Presented at EANO 2018

Depatuxizumab-M (ABT414)



Depatuxizumab mafodotin
(Depatux-m; ABT- 414)

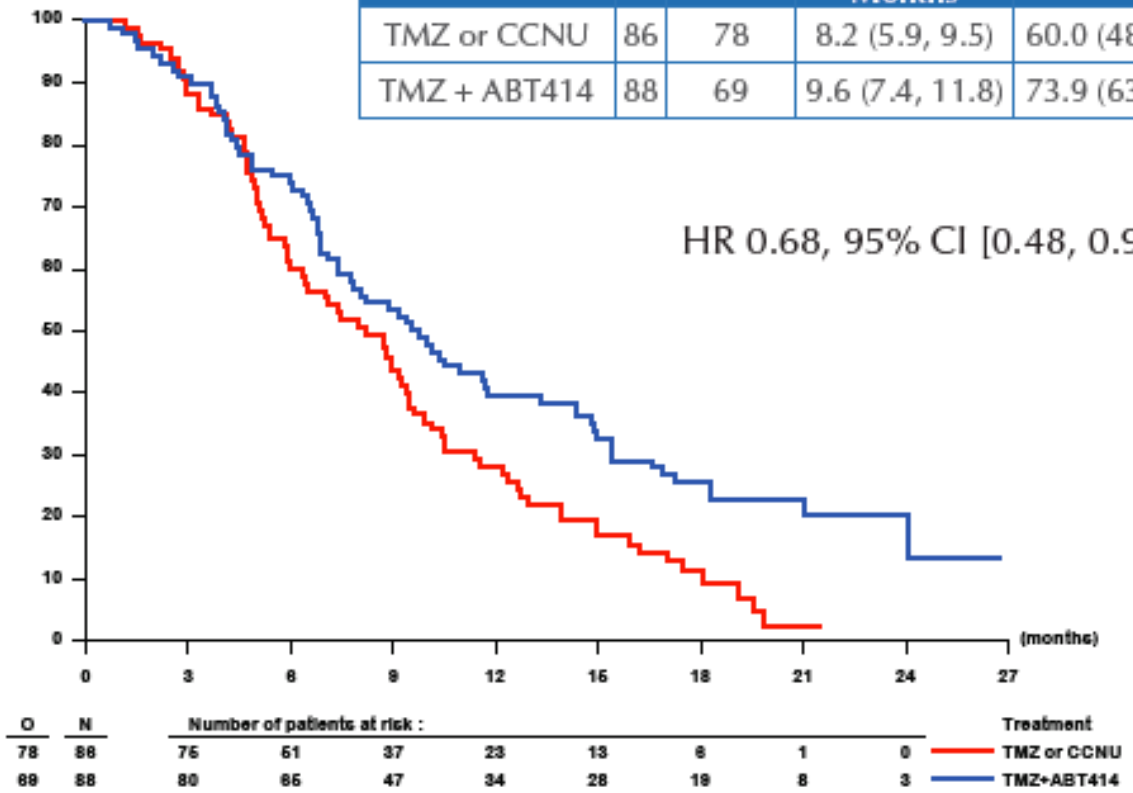


Intellance-2 (recurrent GBM)

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)

HR 0.68, 95% CI [0.48, 0.95], p = 0.024



Van Den Bent M, ASCO 2018

Intellance2 - Safety

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

Ocular toxicity is reversible if quickly recognized: careful monitoring

ABT- 414 (Depatux-M) – Newly Diagnosed Glioblastoma (M13-813)

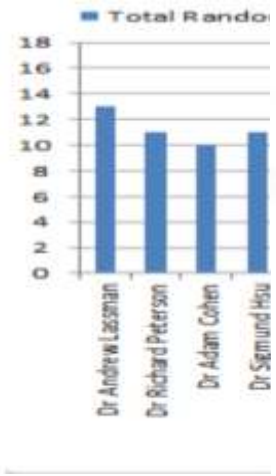
Patient populatio

Histologically confir
de novo GBM (prima
or gliosarcoma

Tumor demonstrat
EGFR amplificatio

Chemoradiation therap
within 7 weeks
of diagnosis

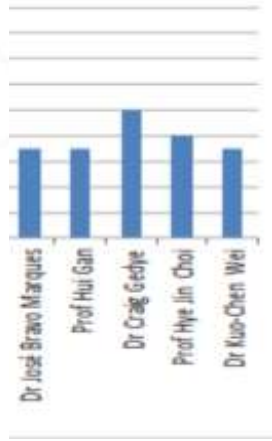
Karnofsky performance
≥70



Endpoints

objectives
ession-free survival (PFS) in
IIb
ll survival (OS) in phase III

ry objectives
n phase III
GFRvIII subgroup)
EGFRvIII subgroup)
to deterioration in:
Symptoms
Cognitive performance



No Survival benefit at the interim analysis!

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 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

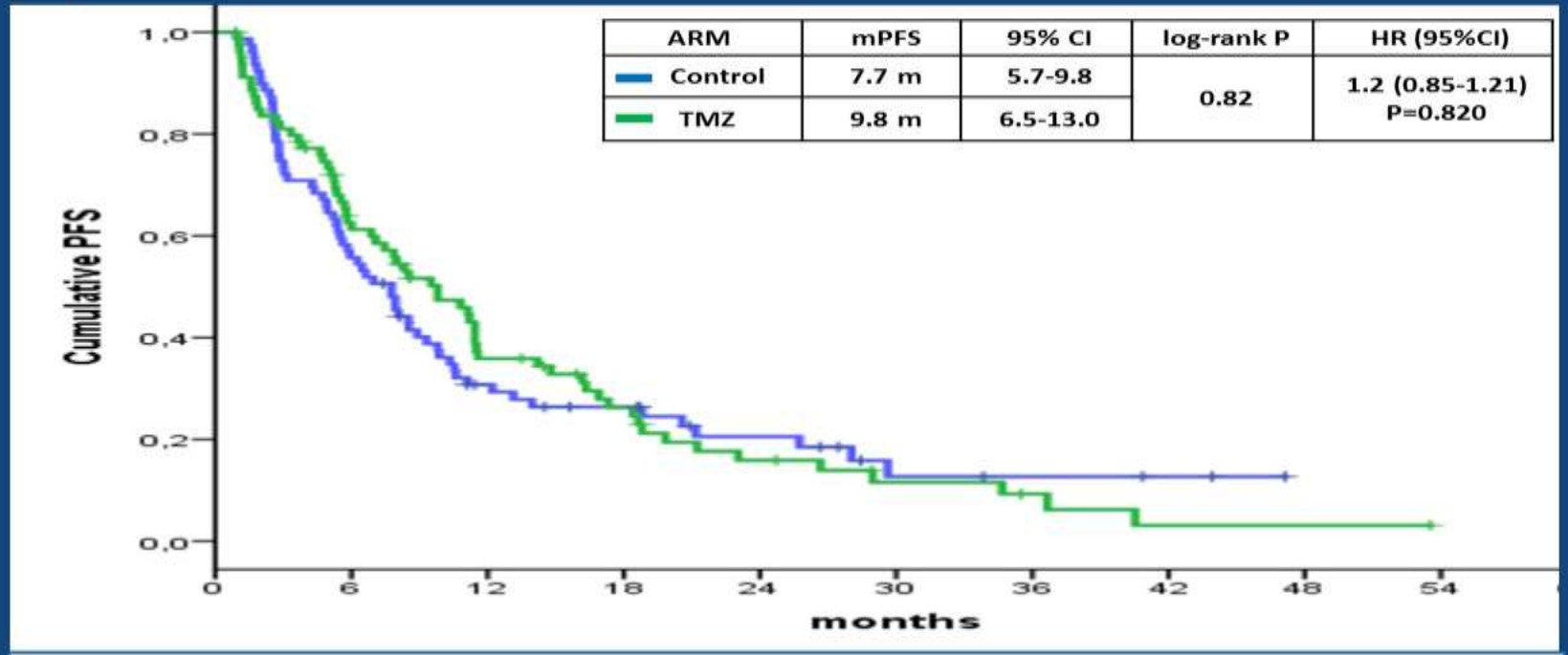
DXM and TMZ doses= the same as cycle 6
Clinical evaluation, H and B every 28 days
MRI every 3 months until DP

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

PFS by treatment arm

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

Conclusions

- This is the only successful prospective randomized trial comparing 6 to 12 cycles of adjuvant TMZ in GBM.
- We did not detect significant differences either in 6m-PFS or median PFS.
- Limitation: the study was not comparative.
  - BUT: it took 4 years for 20 centers to screen 166 patients with SD after the first 6 cycles.
  - In theory, other statistical designs may be possible but they are surely not practically feasible.
- **We conclude that patients who stop TMZ after 6 cycles can have long periods of stability without treatment, thereby avoiding added toxicity and the extra cost of further cycles of TMZ.**
- Studies of TERT promoter mutations, proteins related to TMZ resistance, subgroup outcomes, and final OS are ongoing.

Anaplastic Gliomas

EORTC

The future of cancer therapy

Second interim and 1st molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q codeletion

M J van den Bent, S Erridge, M A Vogelbaum, AK Nowak, M Sanson, A A Brandes, W Wick, P M Clement, J F Baurain, W Mason, H Wheeler, M Weller, K Aldape, P Wesseling, J M Kros, C M S Tesileanu, V Golfinopoulos, T Gorlia, B G Baumert, P French

on behalf of the EORTC Brain Tumor Group and partners

NOA Neuroonkologische Arbeitsgemeinschaft

NRG ONCOLOGY *Advancing Research. Improving Lives.*

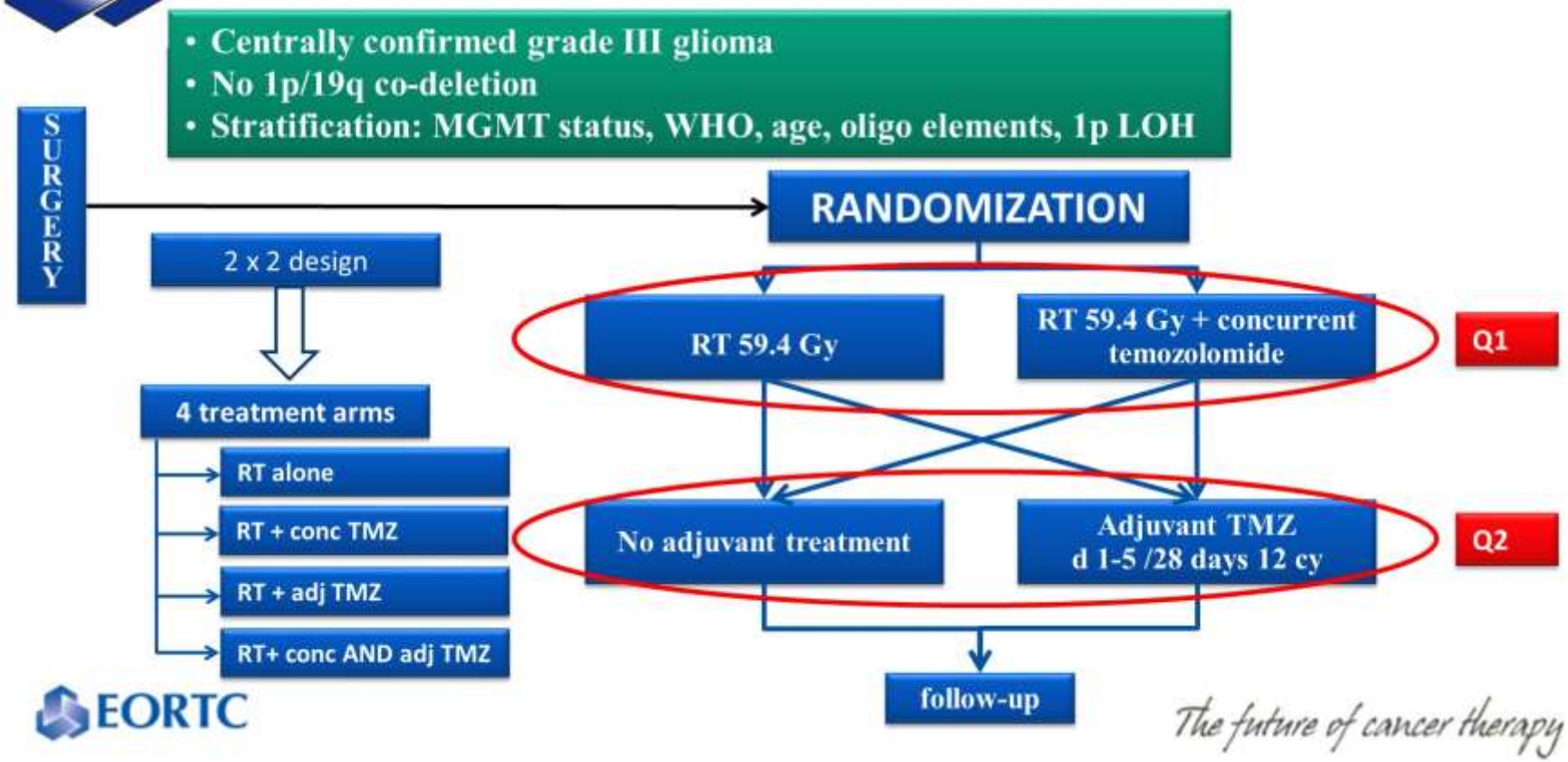
MRC Medical Research Council

COGNO COOPERATIVE TRIALS GROUP FOR NEURO-ONCOLOGY

Canadian Cancer Trials Group

Van Den Bent M, ASCO 2019

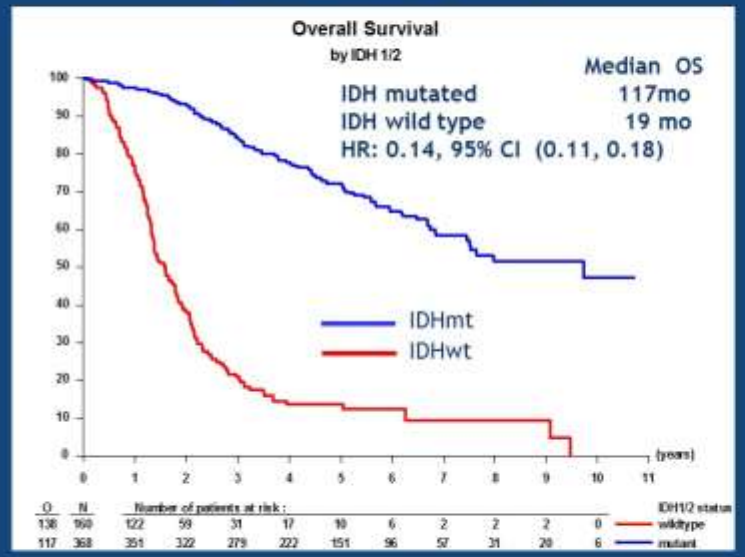
Intergroup phase III trial on concurrent and adjuvant temozolomide in non-1p/19q deleted anaplastic glioma



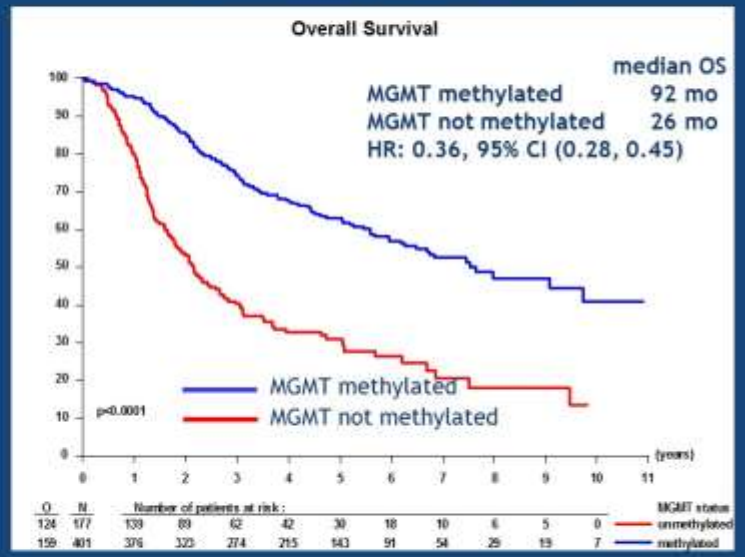
Van Den Bent M, ASCO 2019

Impact of IDH, MGMT promoter on Overall Survival

IDH mutational status



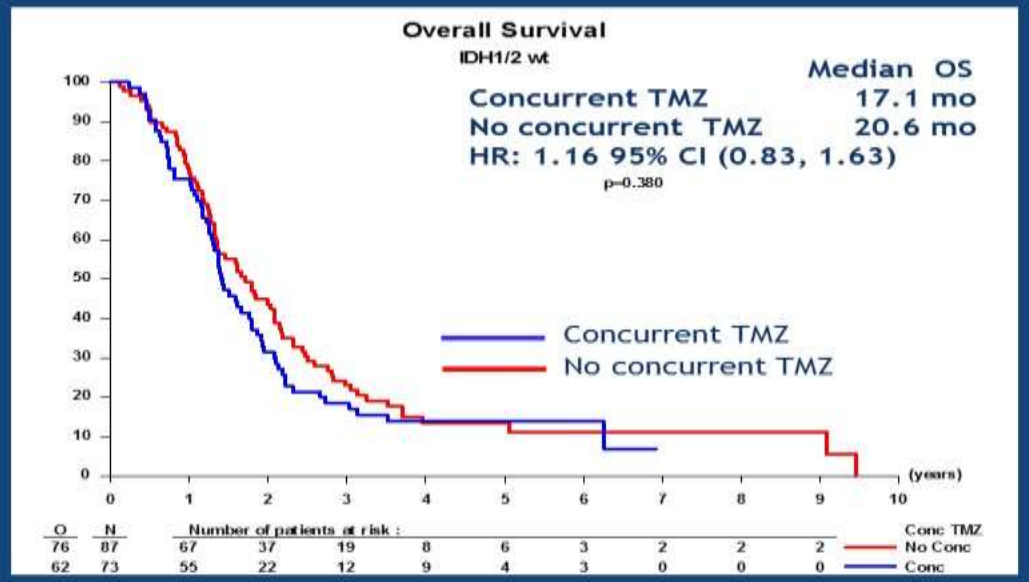
MGTM methylation status



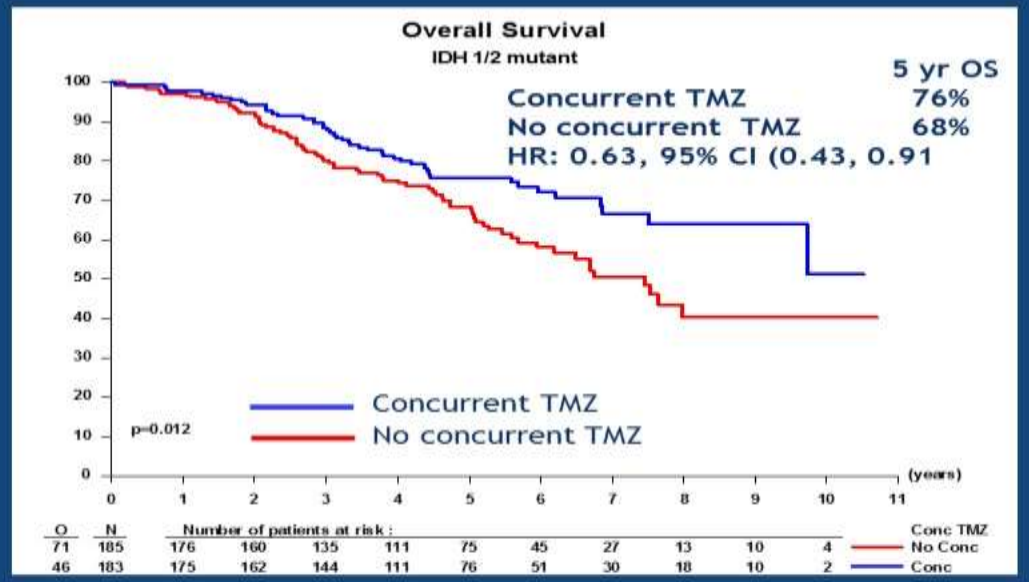
- IDH mutational status stronger correlation with outcome than MGMT promoter methylation status

Concurrent temozolomide in IDHwt and IDHmt anaplastic astrocytoma

IDH wild type



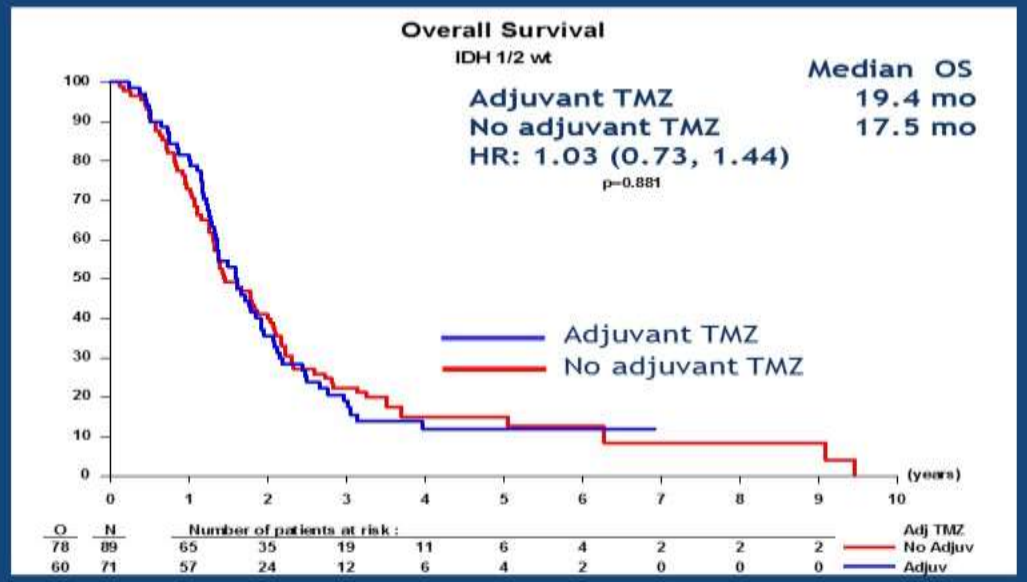
IDH mutant



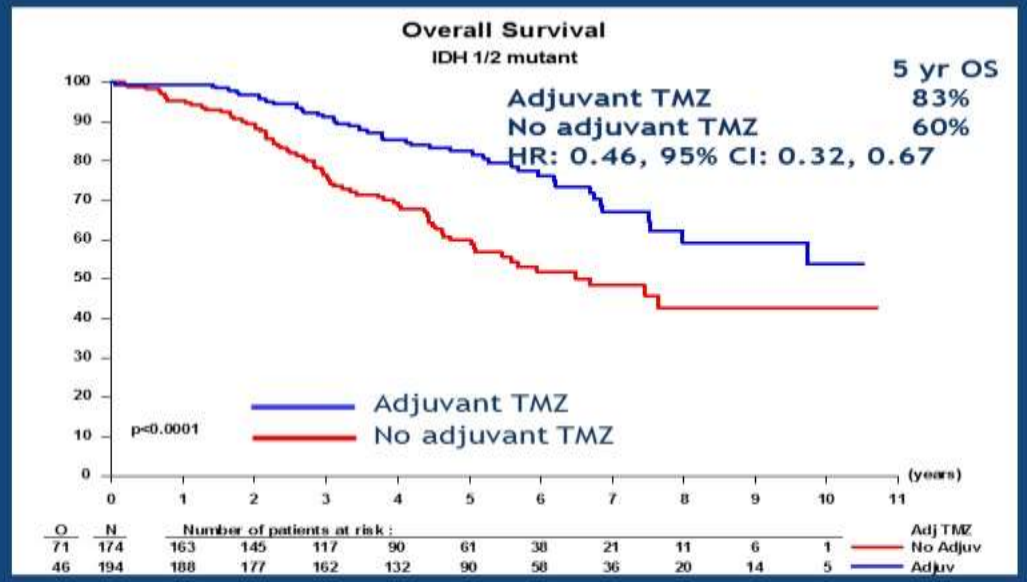
- Concurrent temozolomide improves outcome in IDH mutant anaplastic astrocytoma

Adjuvant temozolomide in IDHwt and IDHmt anaplastic astrocytoma

IDH wild type



IDH mutant



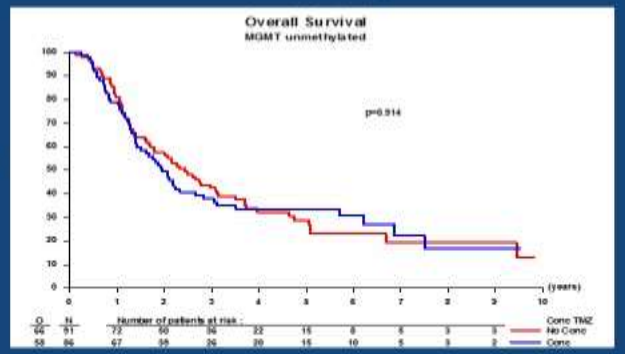
- Adjuvant temozolomide improves outcome in IDH mutant anaplastic astrocytoma

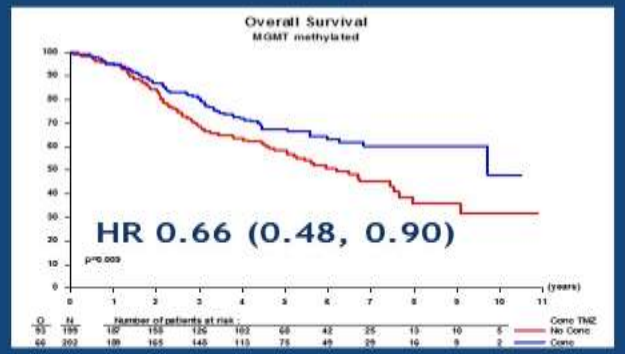
Effect of MGMT promoter status determined with methylation array

MGMT unmethylated

MGMT methylated

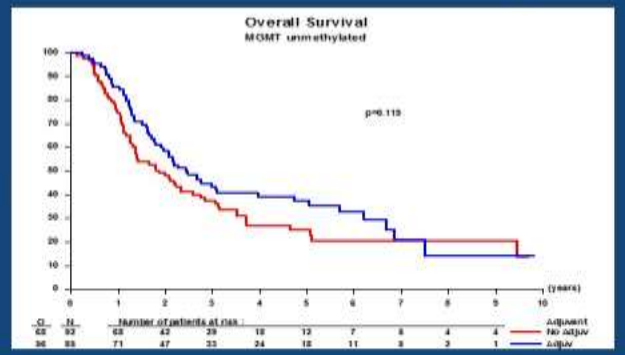
Concurrent temozolomide Question #1

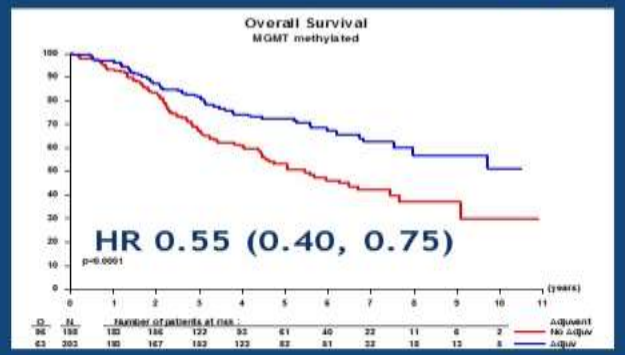




Temozolomide
No temozolomide

Adjuvant temozolomide Question #2





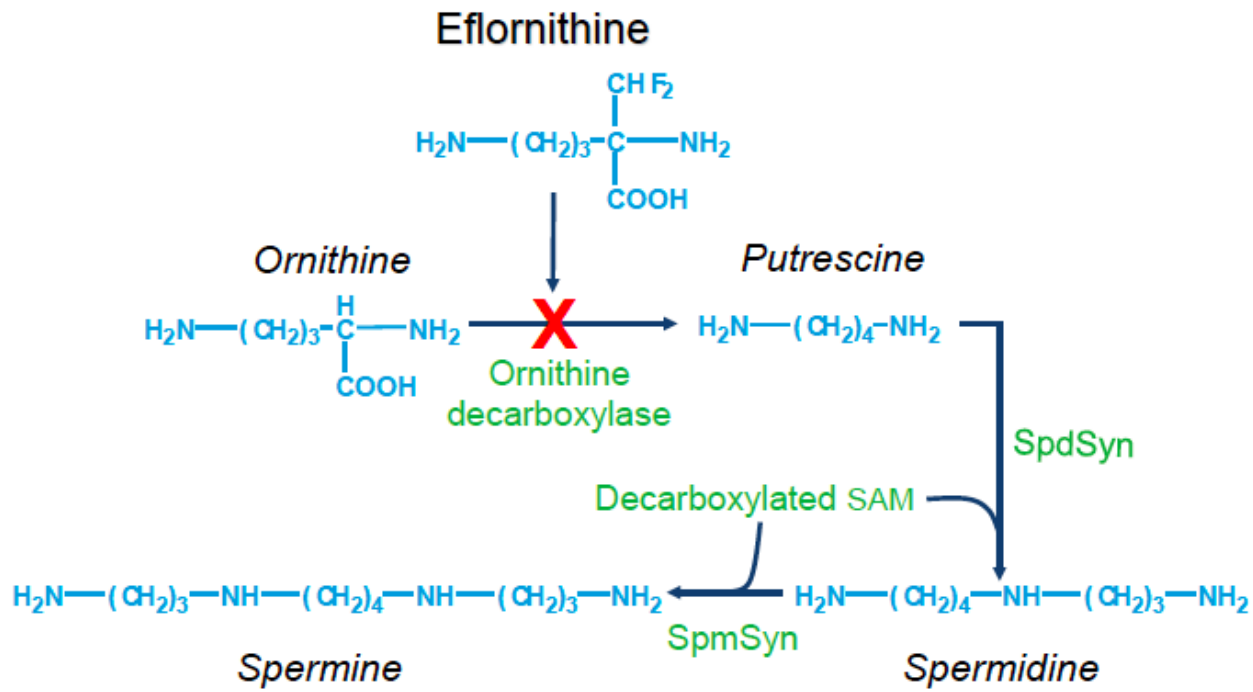
Conclusions CATNON trial at ASCO 2019

- In the entire study population, concurrent temozolomide during radiotherapy did not improve outcome
- 70% of the patients had an IDH mutated tumor, 70% of tumors showed MGMT promoter methylation
  - CATNON now to be analysed according to the WHO 2016 glioma classification
- Anaplastic astrocytoma, IDHmt benefit from adjuvant and concurrent temozolomide
  - Added value concurrent temozolomide if temozolomide is also given adjuvant appears small, but limited numbers still prevent firm conclusions
- No benefit of concurrent , adjuvant temozolomide in anaplastic astrocytoma, IDHwt
  - MGMT analysis to be reported

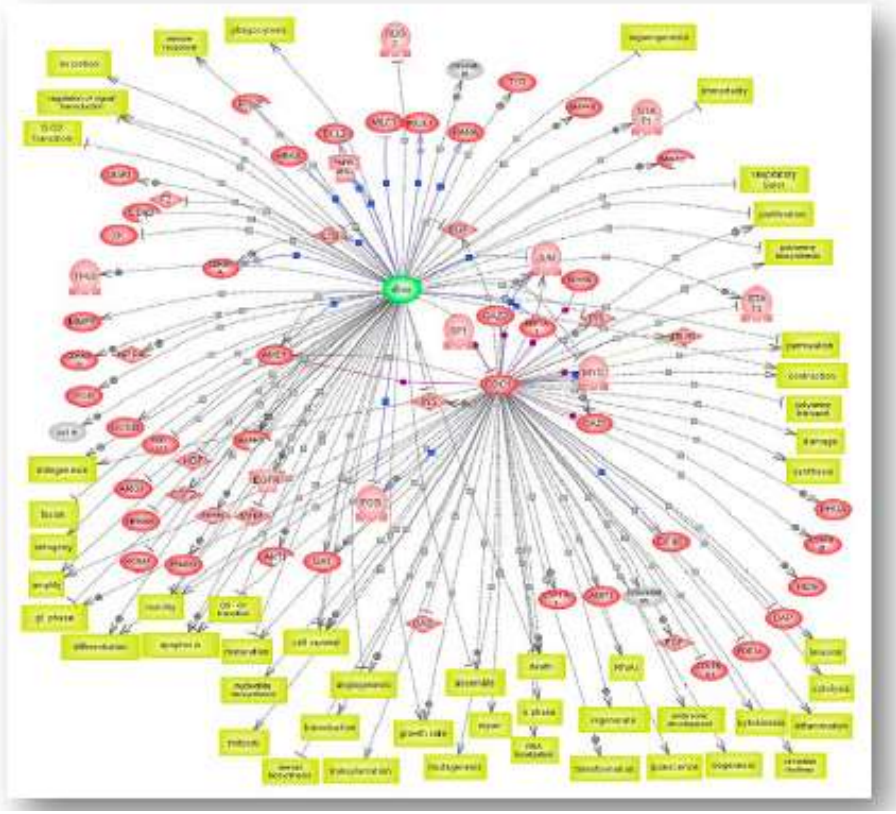
STELLAR

Orbus Therapeutics, Inc.

Eflornithine Effect on Polyamine Metabolism

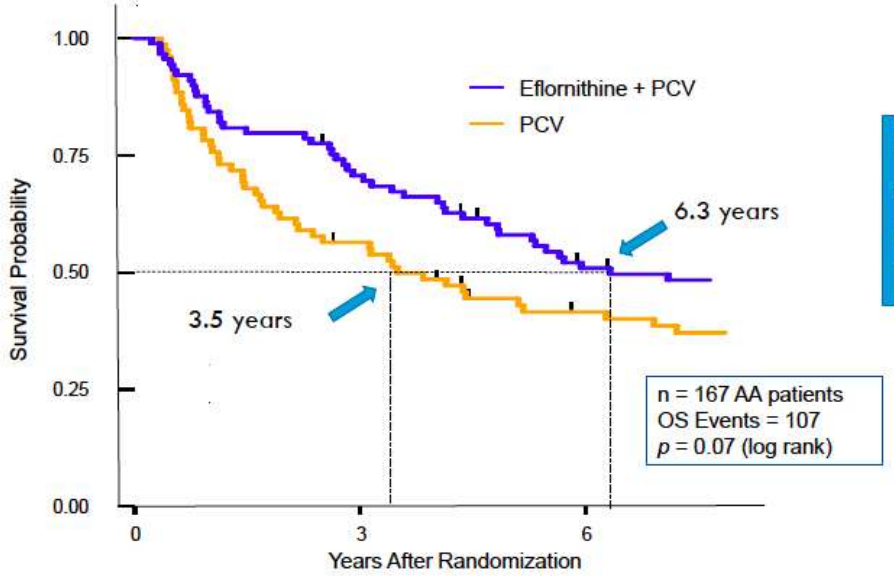


Importance of ODC as a Cancer and Glioma Target



- Constitutive elevation of ODC:
  - Associated with oncogenesis
  - Maintenance of transformed phenotype
  - ODC levels increase with malignancy grade for adenocarcinoma, glioma, and melanoma
- Proto-oncogene **ras** and **myc** downstream pathways control ODC transcription, translation and dysregulation
- Inhibition of ODC:
  - Reverts transformation of cells and reduces tumor growth
  - Cell cycle G1 arrest and accumulation of p21 and p27 CDK inhibitors and may reduce mutation rates leading to grade increase
  - Inhibits tumor cell invasion

Eflornithine Phase 3 Study in AG
Final OS Results in AA Patients



For AA patients receiving up to 12 months of eflornithine-PCV, mOS improved 2.8 years

Eflornithine Phase 3 Study in AG
Toxicity

n = 228	Toxicity Grade	Eflornithine + PCV	PCV	Delta	*p*-value
Anemia	3 & 4	8.6%	1.7%	6.9%	NS
Diarrhea	3	6.8%	0.0%	6.8%	p=0.013
Neutropenia	3 & 4	49.6%	46.1%	3.5%	NS
Leukopenia	3 & 4	39.3%	33.9%	5.4%	NS
Nausea/vomiting	3 & 4	16.3%	13.0%	3.3%	NS
Ototoxicity	3	1.7%	0.0%	1.7%	NS
Skin	3	6.8%	6.1%	0.7%	NS
Thrombocytopenia	3 & 4	33.3%	21.7%	11.6%	NS

Study Design
Eflornithine to Treat Recurrent AA Patients

Surgery ⇨ Radiation ⇨ Adjuvant
(Pathology/Dx) temozolomide

Progression/Recurrence

Randomization

Enrollment Complete
Futility Analysis

Interim Analysis

Lomustine + Eflornithine

Lomustine alone

OS Top-line Data

2016		2017				2018				2019			
3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q

Precision Medicine

Activity of Larotrectinib in TRK Fusion Cancer Patients with Brain Metastases or Primary Central Nervous System Tumors

Alexander Drilon,[1] Steven G. DuBois,[2] Anna F. Farago,[3] Birgit Geoerger,[4] Juneko E. Grilley-Olson,[5] David S. Hong,[6] Davendra Sohal,[7] Cornelis M. van Tilburg,[8] David S. Ziegler,[9] Nora C. Ku,[10] Michael C. Cox,[10] Shivani Nanda,[11] Barrett H. Childs,[11] Francois Doz[12]

1. Memorial Sloan Kettering Cancer Center, New York, NY, USA; Weill Cornell Medical College, New York, NY, USA; 2. Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA; 3. Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; 4. Gustave Roussy, Department of Pediatric and Adolescent Oncology, Université Paris-Sud, Université Paris-Saclay, Villejuif, France; 5. University of North Carolina Hospitals, Chapel Hill, NC, USA; 5. The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 7. Cleveland Clinic, Cleveland, OH, USA; 8. Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany; 9. Sydney Children's Hospital, Randwick, Australia; 10. Loxo Oncology, Inc., South San Francisco, CA, USA; 11. Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ, USA; 12. Institut Curie, University Paris Descartes, Paris, France.

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: ALEXANDER DRILON

Methods

Adult phase I trial (NCT02576431) — n=1
- Age ≥18 years
- Advanced solid tumours

Pediatric phase I/II trial (SCOUT, NCT02637687) — n=12
- Age 1 month to 21 years
- Locally advanced or metastatic solid tumours or CNS tumours

Adult/adolescent phase II basket trial (NAVIGATE, NCT02576431) — n=11
- Age ≥12 years
- Advanced solid tumours
- TRK fusion cancer

24 patients with intracranial disease

18 patients with primary CNS tumors*

6 patients with non-primary CNS tumors and brain metastases†

- CNS eligibility criteria
  - Asymptomatic and stable brain metastases
  - Primary CNS tumors§
- TRK fusion status determined by local molecular profiling

Endpoints

- **Objective response rate**
- **Intracranial response‡**

- Objective responses
  - RECIST 1.1 or RANO
  - Serial MRI/CT brain
    - required with baseline intracranial disease
- Initial larotrectinib dose
  - 100 mg or 100 mg/m^2 (maximum of 100 mg) BID

*Data cutoff: February 19, 2019. †Data cutoff date July 30, 2018. ‡In tumor for patients with brain metastases; not a formal endpoint. §SCOUT trial: neurologically stable and on stable dose of steroids.
RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors.

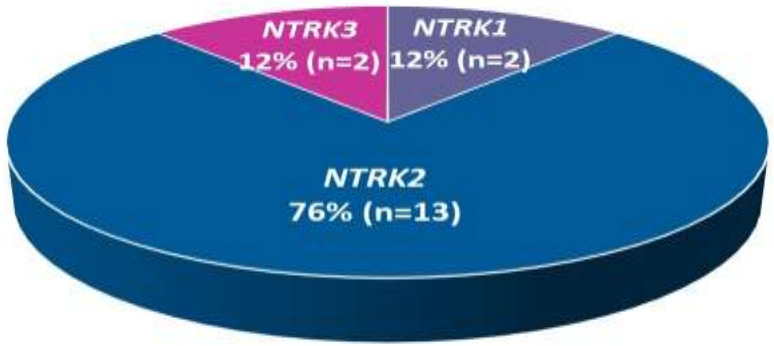
Presented By Alexander Drilon at 2019 ASCO Annual Meeting

Clinicopathologic Features: Primary CNS Tumors

Characteristic	n=18
Gender, n (%) Female Male	 10 (55%) 8 (45%)
Age, median (range) Pediatric* Adult	10 years (1–79) 14 (78%) 4 (22%)
Prior therapies, n (%) Systemic therapy Surgery or radiotherapy	 15 (83%) 13 (72%)
Number of prior systemic therapies, median (range)	1 (0–6)

Histology (n=18, investigator-reported)†		
Type	n (%)	Grade (High/Low/Unknown), n
Glioblastoma	6 (32%)	6/0/0‡
Glioma	4 (21%)	1/3/0
Glioneuronal	3 (16%)	2/0/1
Not otherwise specified	3 (16%)	1/1/1
Astrocytoma	2 (15%)	1/0/1

Fusion§



*Pediatric age range 1–16 years; adult age range 31–79 years. †Histology based on initial CRF entries. For select tumors, WHO grade, *IDH* mutation status, MGMT methylation status, and 1p/19q co-deletion status will be clarified in a future report. ‡3 cases were entered as "unknown grade"; however, these glioblastomas were assumed to be grade III. §One patient not determined.

Investigator-Assessed Efficacy of Larotrectinib in TRK Fusion-Positive Primary CNS Tumors

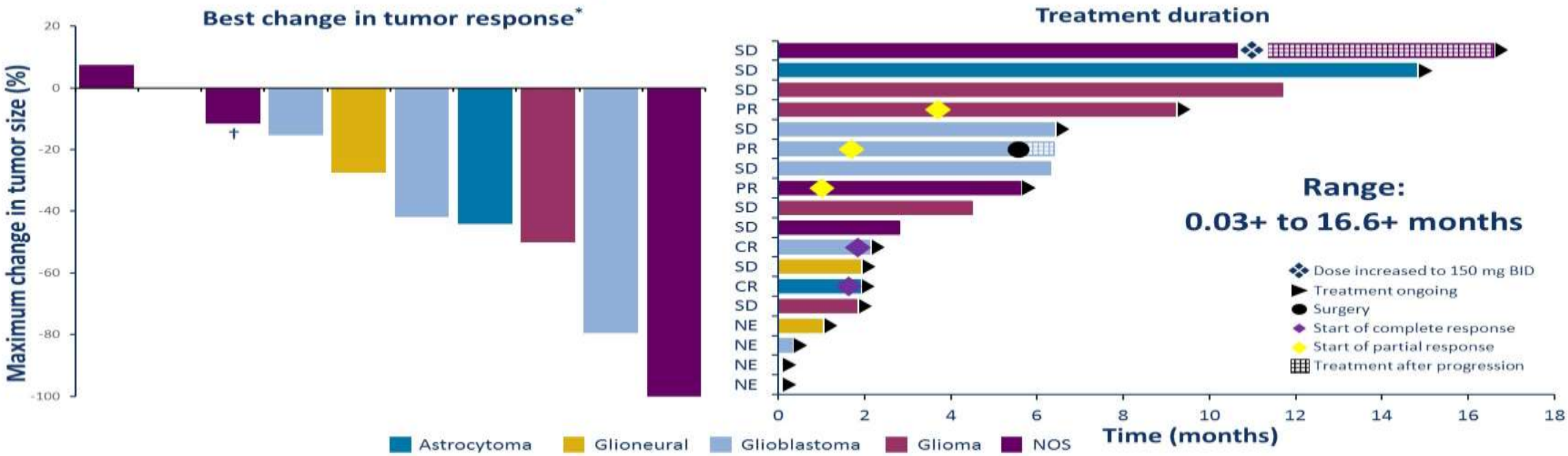
	n=14 evaluable patients
Objective response rate	36% (95% CI: 13–65)
Best overall response*, n (%)	
Complete response†	2 (14%)‡
Partial response	3 (21%)‡
Stable disease	9 (64%)
Progressive disease	0 (0%)
Disease control rate ≥ 16 weeks§, n (%)	11 (79%)
Disease control rate ≥ 24 weeks§, n (%)	10 (71%)
Progression-free survival, median**	11.0 months (95% CI: 2.8, NE)

DCR 100%

Data cutoff date February 19, 2019. *Investigator assessment based on RANO or RECIST 1.1. †Pending confirmation. ‡All responses were seen in pediatric cases (ORR 45%, n=5/11). §Disease control rate = complete response + partial response + stable disease. **In 18 patients with median follow-up of 4.4 months. CI, confidence interval; RANO, Response Assessment in Neuro-Oncology.

Presented By Alexander Drilon at 2019 ASCO Annual Meeting

Larotrectinib in TRK Fusion-Positive Primary CNS Tumors: Response and Treatment Duration



Data cutoff date February 19, 2019. Disease assessments were performed by investigators. *Tumor responses in patients with measurable disease and tumor values recorded at data cutoff, based on RANO sum of products of diameters, unless noted otherwise. †Based on RECIST 1.1 sum of longest diameter. CR, complete response; NE, not evaluable; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

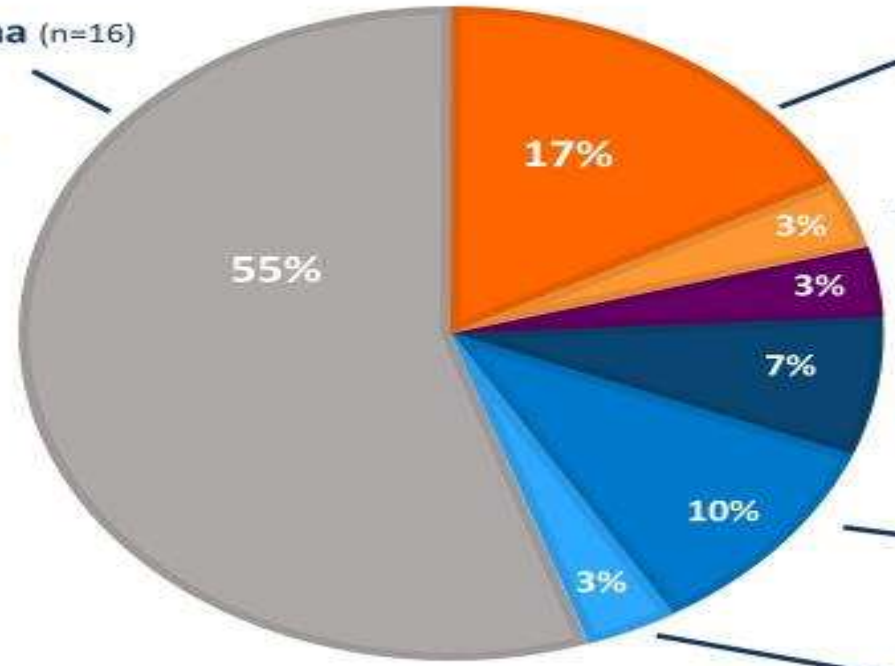
Phase 1/1B trial to assess the activity of entrectinib in children and adolescents with recurrent or refractory solid tumors including central nervous system (CNS) tumors

Authors: Giles W. Robinson[1], Amar Gajjar[1], Karen Gauvain[2], Ellen M. Basu[3], Margaret E. Macy[4], Luke Maese[5], Amit J. Sabnis[6], Jennifer Foster[7], Suzanne Shusterman[8], Janet Yoon[9], Brian Weiss[10], Mohamed S. Abdelbaki[11], Mufiza Farid-Kapadia[12], Georgina Meneses-Lorente[13], Alison Cardenas[14], Katherine E. Hutchinson[14], Guillaume Bergthold[15], Edna Chow Maneval[16], Elizabeth Fox[17], Ami V. Desai[18]

1. St. Jude Children's Research Hospital, Memphis, TN; 2. Washington University School of Medicine, St. Louis, MO; 3. Memorial Sloan Kettering Cancer Center, New York, NY; 4. Children's Hospital Colorado, Aurora, CO; 5. University of Utah/Huntsman Cancer Institute, Primary Children's Hospital, Salt Lake City, UT 6. University of California San Francisco, Benioff Children's Hospital, San Francisco, CA; 7. Texas Children's Hospital, Houston, TX; 8. Dana Farber Cancer Institute, Boston Children's Cancer and Blood Disorders Center, Boston, MA; 9. Rady Children's Hospital, San Diego, CA; 10. Cincinnati Children's Hospital Medical Center, Cincinnati, OH; 11. Nationwide Children's Hospital, Columbus, OH; 12. F. Hoffmann-La Roche Limited, Mississauga, ON, Canada; 13. Roche Products Limited, Welwyn Garden City, UK; 14. Genentech, South San Francisco, CA; 15. F. Hoffmann-La Roche, Basel, Switzerland; 16. Ignyta, Inc, San Diego, CA; 17. Children's Hospital of Philadelphia, Philadelphia, PA; 18. University of Chicago Medical Center, Chicago, IL, USA

Presented By Giles Robinson at 2019 ASCO Annual Meeting

Baseline characteristics by tumor type and target gene fusion

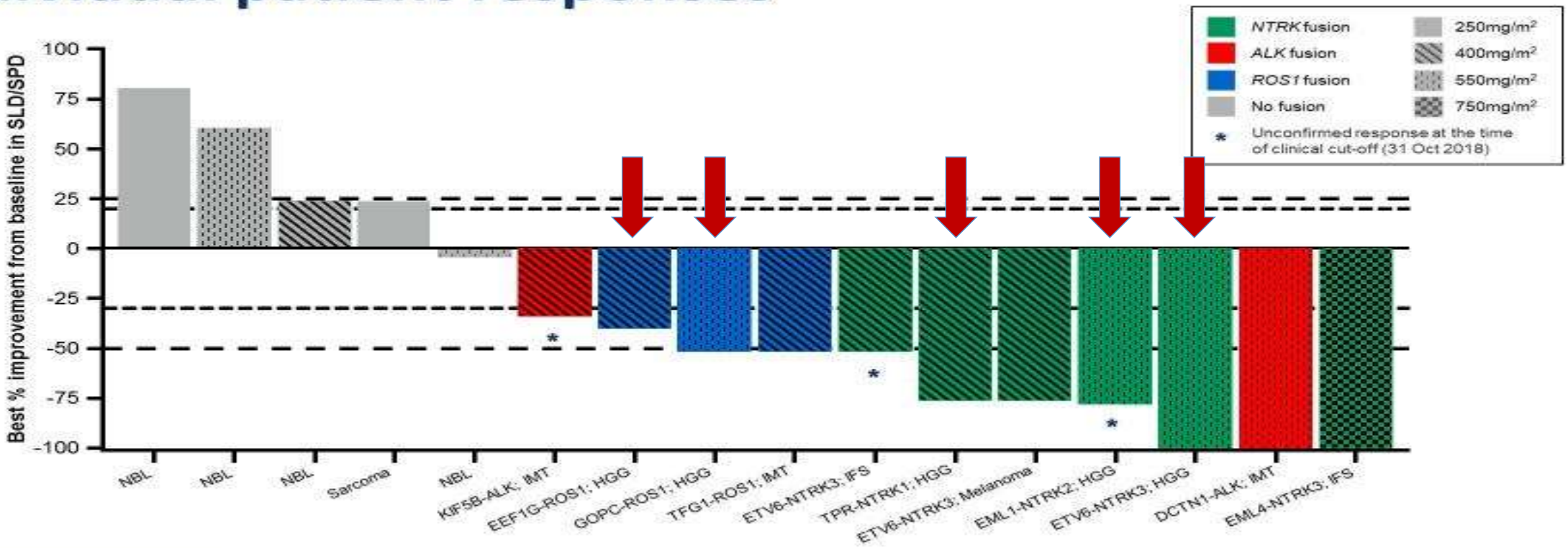


Neuroblastoma (n=16)
1 x ***ALK*** **F1174L**
15 x no *ALK/ROS1/NTRK* aberrations or unknown

High-grade glioma (n=5)	1 x *EEF1G-ROS1* 1 x *GOPC-ROS1* 1 x *TPR-NTRK1* 1 x *EML1-NTRK2* 1 x *ETV6-NTRK3*
CNS embryonal tumor (n=1)	1 x *KANK1-NTRK2*
Melanoma (n=1)	1 x *ETV6-NTRK3*
Sarcoma: IFS (n=2)	1 x *ETV6-NTRK3* 1 x *EML4-NTRK3*
Sarcoma: IMT (n=3)	1 x *DCTN1-ALK* 1 x *KIF5B-ALK* 1 x *TFG1-ROS1*
Sarcoma: synovial (n=1)	None

Data cut-off: October 31, 2018
IFS, infantile fibrosarcoma; IMT, inflammatory myofibroblastic tumor

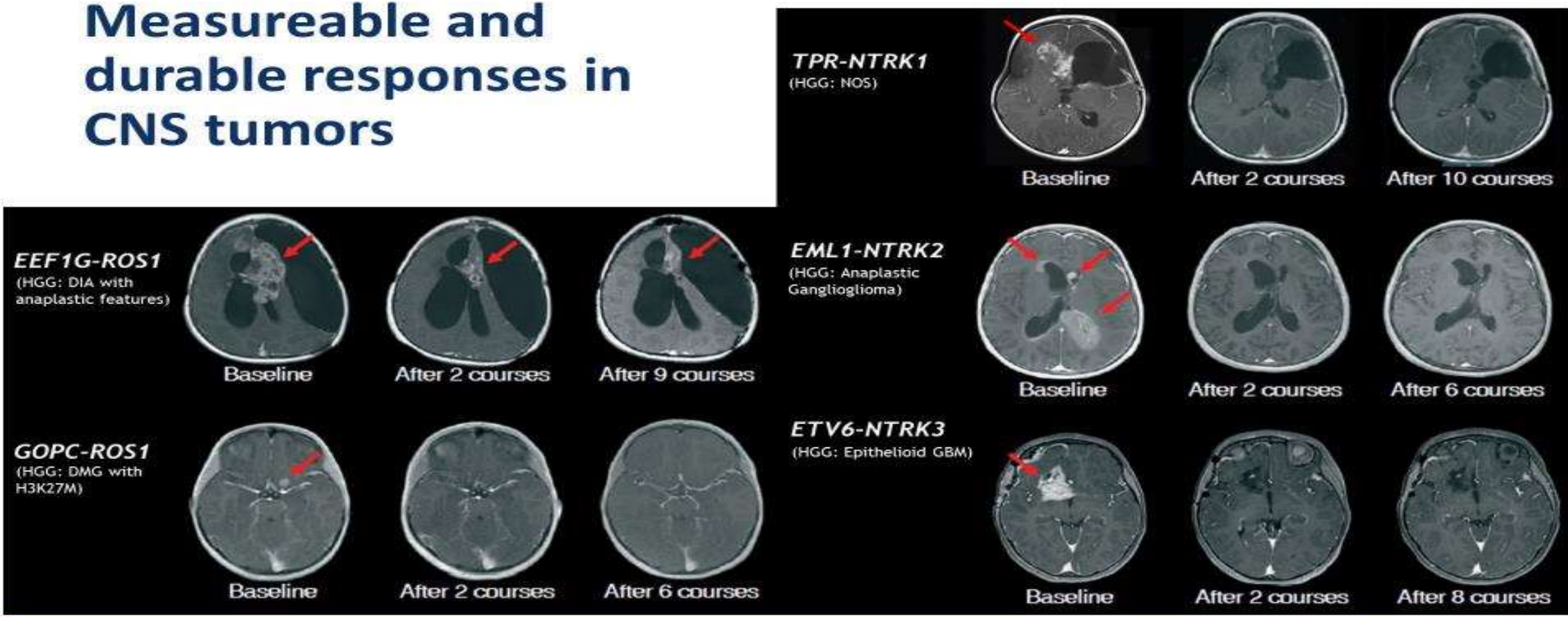
Entrectinib in pediatric solid tumors: individual patient responses



Data cut-off: October 31, 2018. Investigator assessed
Includes only patients with measureable disease at baseline and tumor assessment

Presented By Giles Robinson at 2019 ASCO Annual Meeting

Measureable and durable responses in CNS tumors



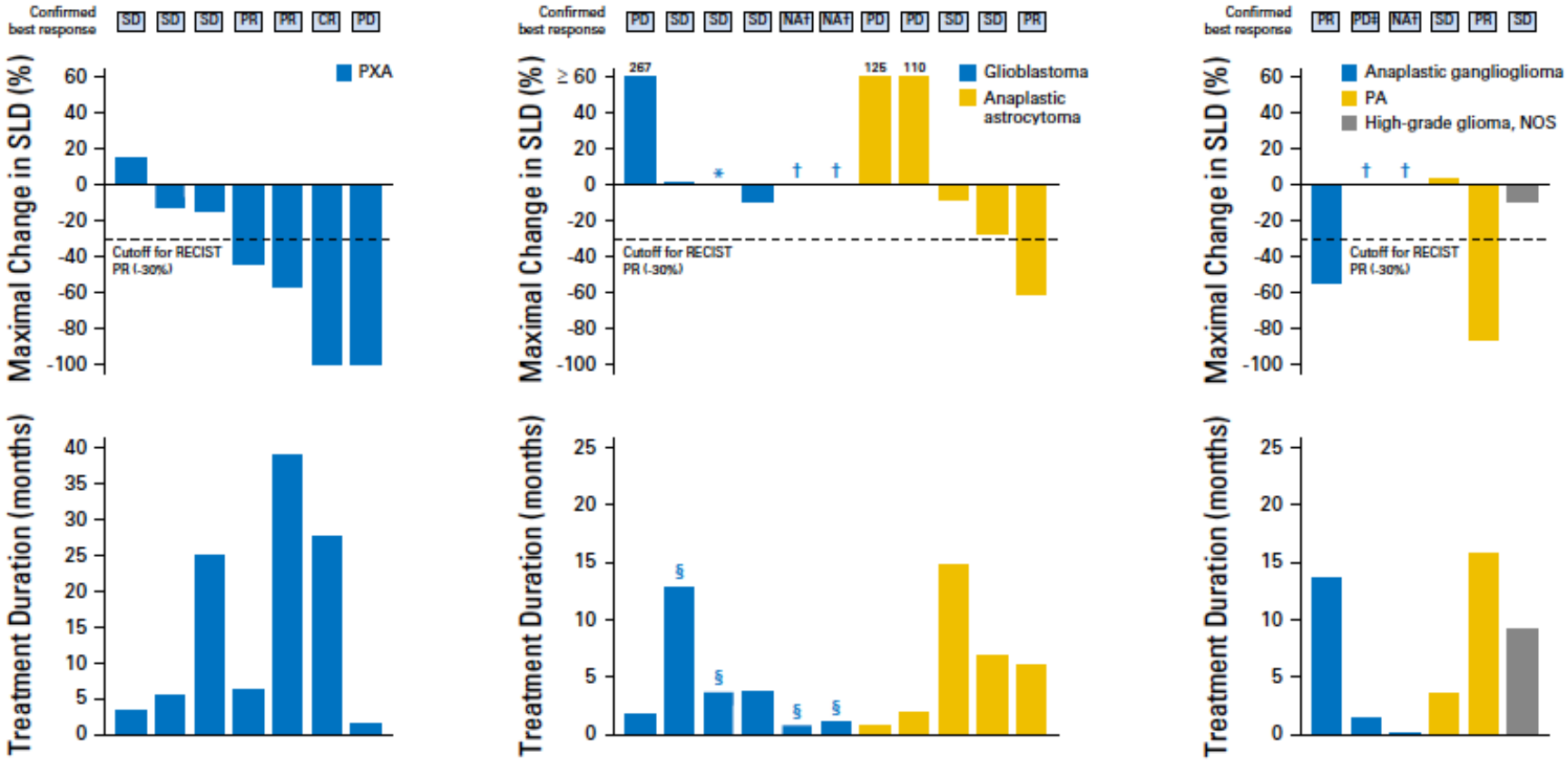
Presented By Giles Robinson at 2019 ASCO Annual Meeting

BRAF Inhibition in *BRAF*^{V600}-Mutant Gliomas: Results From the VE-BASKET Study

Thomas Kaley, Mehdi Touat, Vivek Subbiah, Antoine Hollebecque, Jordi Rodon, A. Craig Lockhart, Vicki Keedy,

BRAF ^{V600}

Xantoastrocitoma Pleomorfo	38%-100%
Ganglioglioma	18%-57%
Ganglioglioma anaplastico	50%
Astrocitoma Pilocitico	9%
High Grade Gliomas	3%

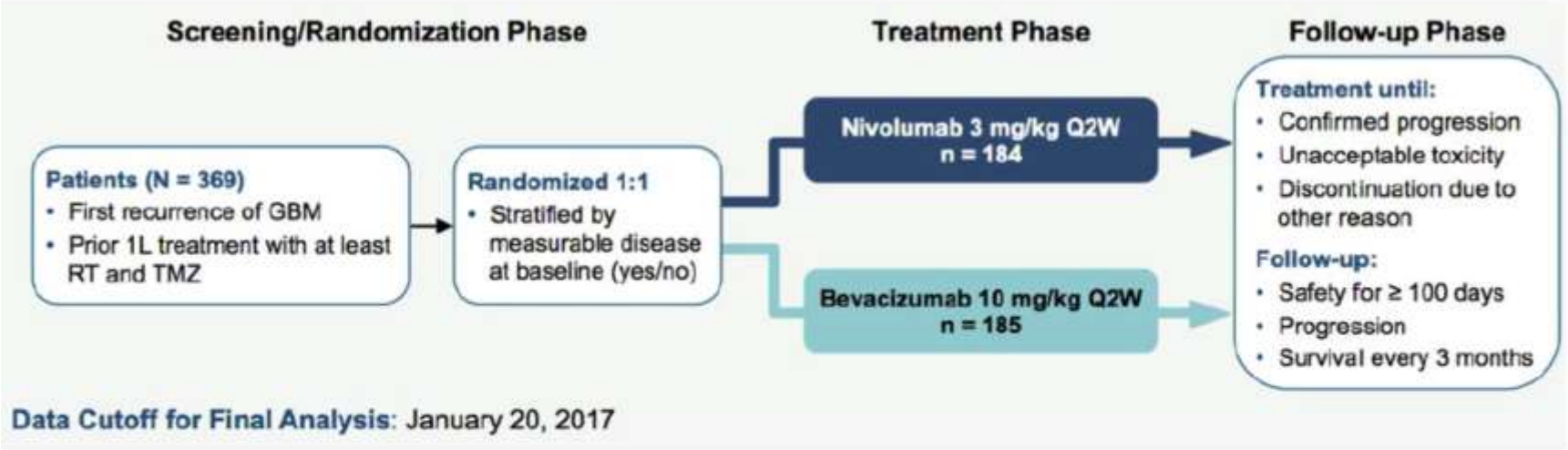


Immunotherapy

Nivolumab

CheckMate 143 Cohort 2 Study Design

Nivolumab vs Bevacizumab in Recurrent GBM



Data Cutoff for Final Analysis: January 20, 2017

Endpoints:

- **Primary**: OS in all randomized patients
- **Secondary**: investigator-assessed ORR and PFS (RANO); 12-month OS rate
- **Other key endpoints**: safety; biomarkers

Assessments:

- **Tumor**: contrast-enhanced MRI Q6W until week 13, then Q8W (RANO)
- **Safety**: CTCAE v4.0

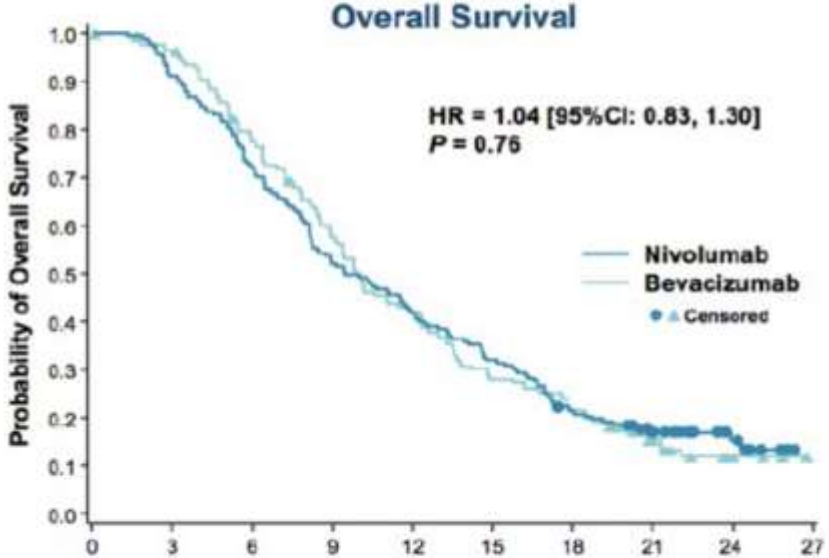
1L, first line; CTCAE, Common Terminology Criteria for Adverse Events; MRI, magnetic resonance imaging; ORR, objective response rate; PFS, progression-free survival; Q2W, every 2 weeks; Q6W, every 6 weeks; Q8W, every 8 weeks; RANO, Radiologic Assessment in Neuro-Oncology criteria.

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]

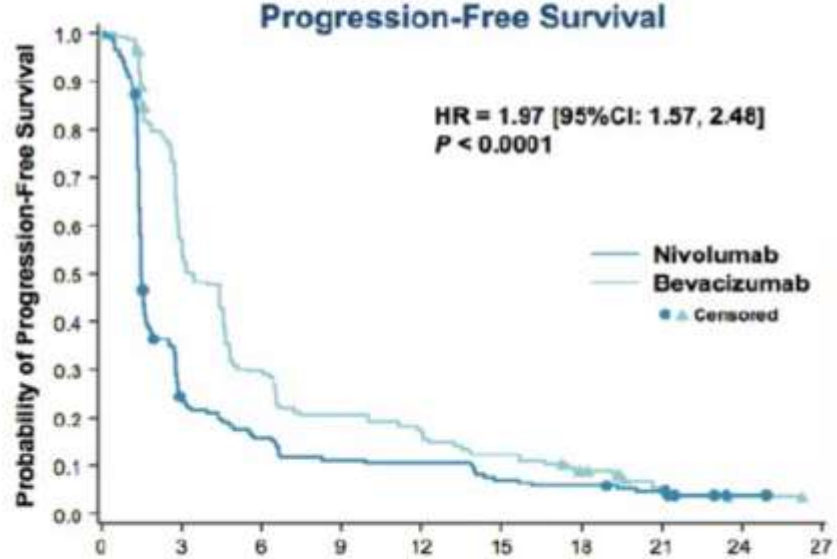
Overall Survival



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]

Progression-Free Survival



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

Response per Investigator Assessment (RANO)

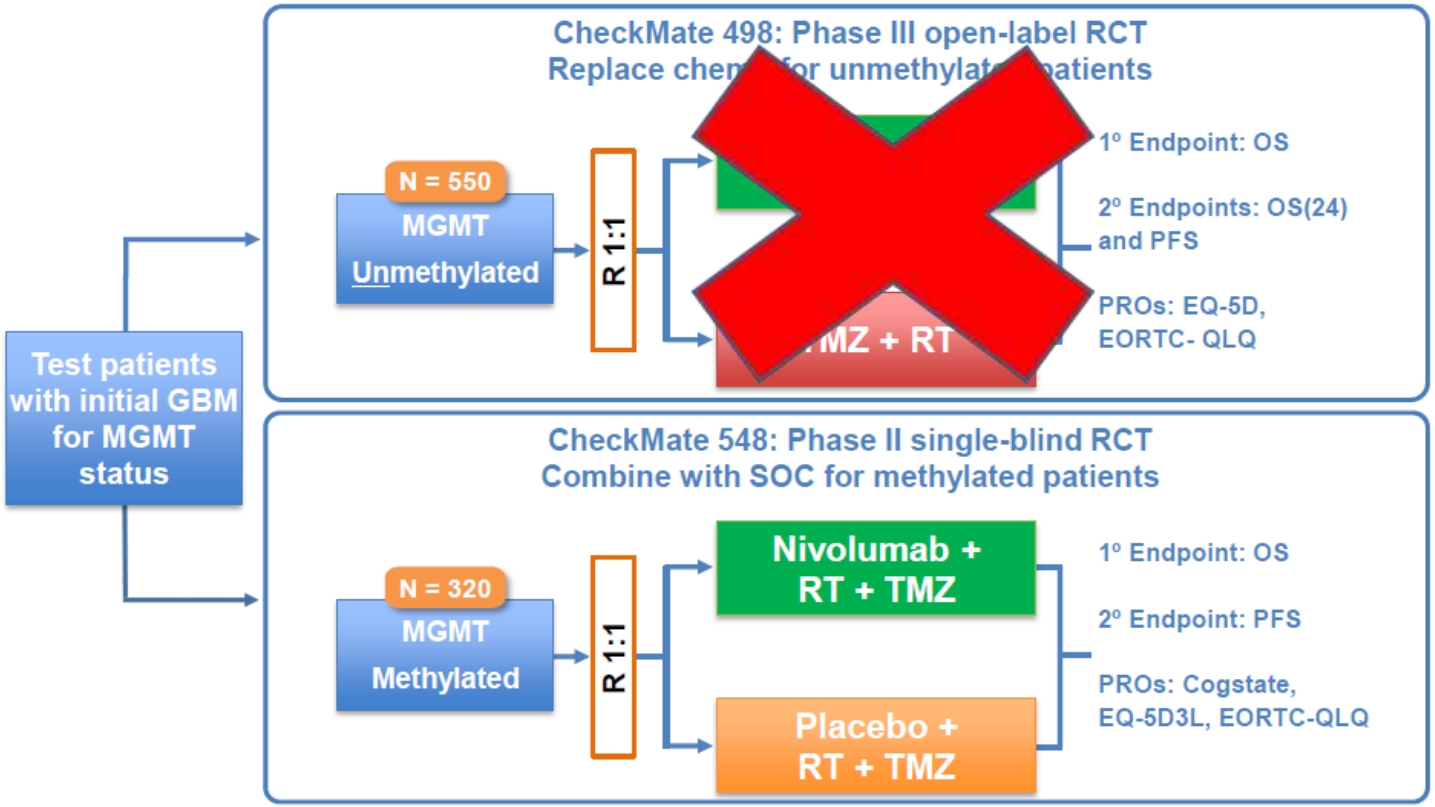
Nivolumab vs bevacizumab in recurrent GBM

	Nivolumab n = 153[a]	Bevacizumab n = 156[a]
ORR, n (%)	12 (7.8)	36 (23.1)
[95% CI]	[4.1, 13.3]	[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.

Nivolumab

CheckMate 498 and CheckMate 548: Phase III Study Designs for Newly Diagnosed GBM



Trial information based on internal BMS protocol and publicly available information on clinicaltrials.gov as of May 1, 2016.

Pembrolizumab

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

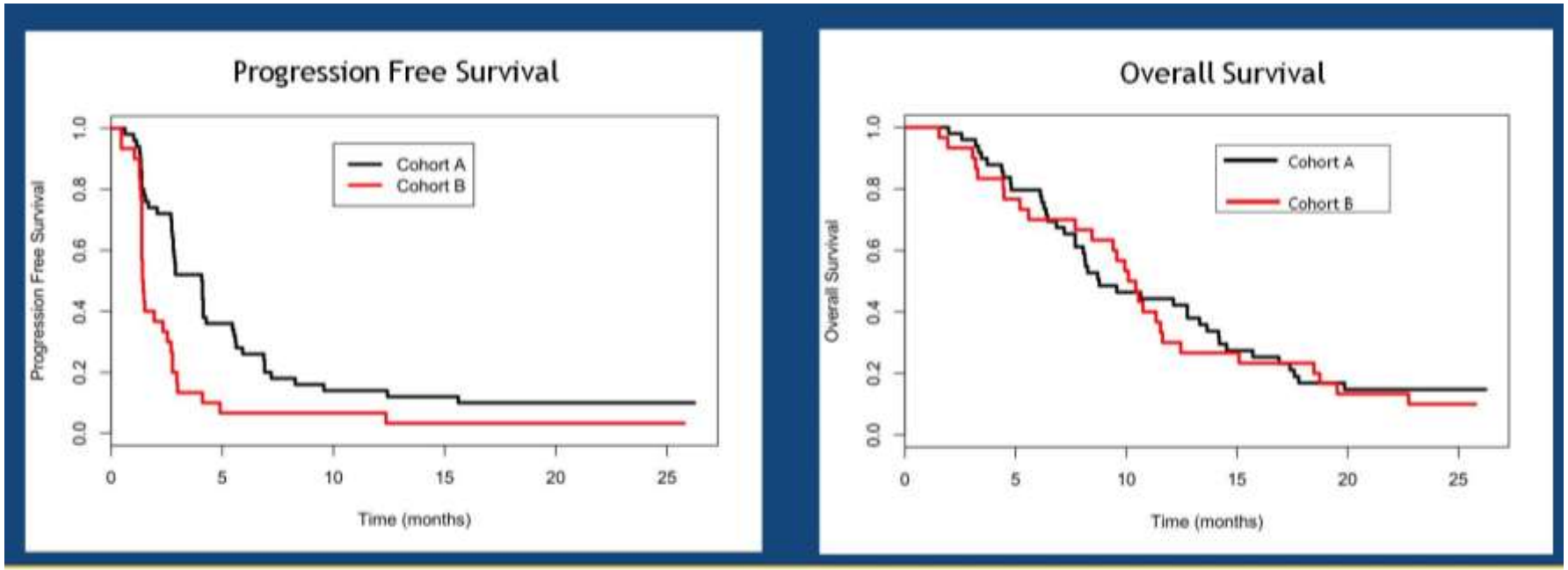
David A. Reardon,[1] Lakshmi Nayak,[1] M.D., Katherine Peters,[2] Jennifer Clarke,[3] Justin T. Jordan,[4] John de Groot,[5] Leia Nghiemphu,[6] Thomas Kaley,[7] Howard Colman,[8] Sarah C. Gaffey,[1] Victoria Caruso,[1] Myriam Bednarek Debruyne,[1] Chinmay Bhavsar,[1] Annette M. Molinaro,[3] Timothy R.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

IVY THE BEN AND CATHERINE FOUNDATION



	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, 2.5)
Median overall survival	8.78 (95% CI: 7.69, 14.17)	10.26 (95% CI: 8.45, 12.46)

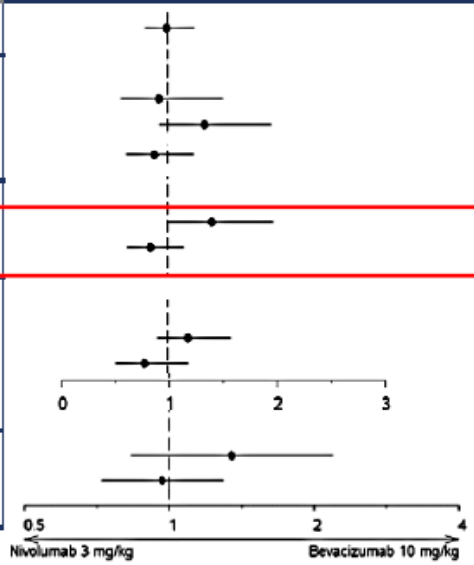
…Why?

"Corticosteroids or non-Corticosteroids, that is the question..."

Dexamethasone Use at Baseline: Poorer Survival With Nivolumab

CheckMate 143

	Patients, n		Unstratified HR [95% CI]
	Nivolumab	Bevacizumab	
All patients	184	185	0.99 [0.79, 1.24]
***MGMT* promoter status**			
Methylated	43	42	0.92 [0.56, 1.51]
Unmethylated	59	67	1.34 [0.92, 1.96]
Not reported	80	76	0.88 [0.62, 1.24]
Steroid use at baseline			
Yes	73	79	1.41 [1.01, 1.97]
No	111	106	0.84 [0.62, 1.24]
Time from initial diagnosis to recurrence			
≤12 months	108	139	1.19 [0.90, 1.56]
>12 months	76	46	0.79 [0.52, 1.19]
Tumor PD-L1			
≥1%	48	35	1.35 [0.83, 2.19]
<1%	107	114	0.97 [0.72, 1.30]



All we need is…BIOMARKERS

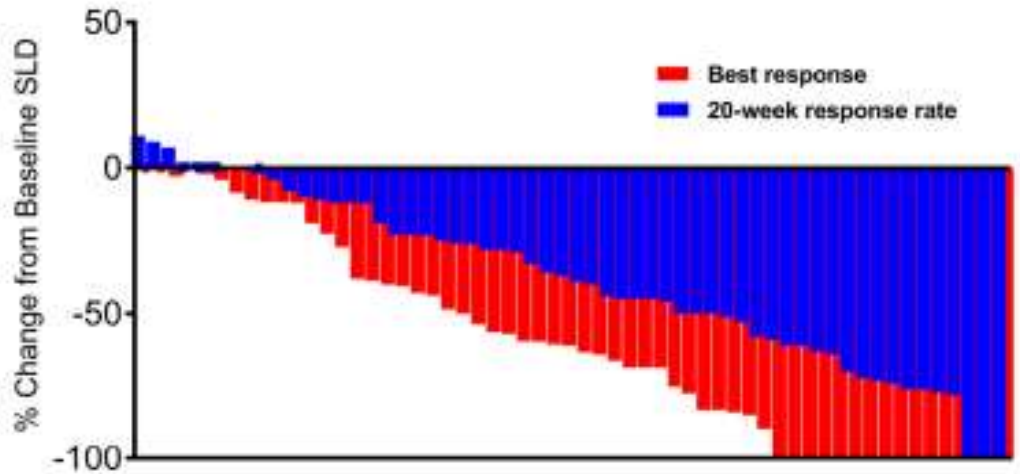
PD-L1 expression in Glioblastoma

	Newly Diagnosed Glioblastoma ($n = 117$)		Recurrent Glioblastoma ($n = 18$)	
	n	%	*n*	%
Diffuse/fibrillary PD-L1 expression				
None	18/117	15.4	5/18	27.8
≤25%	18/117	15.4	3/18	16.7
>25%, ≤50%	30/117	25.6	2/18	11.1
>50%, ≤75%	39/117	33.3	6/18	33.3
>75%	12/117	10.3	2/18	11.1
Membranous PD-L1 expression				
Positive (≥5% of tumor cells)	44/117	37.6	3/18	16.7
Negative (<5% of tumor cells)	73/117	62.4	15/18	83.3

Cite as: D. T. Le *et al.*, *Science* 10.1126/science.aan6733 (2017).

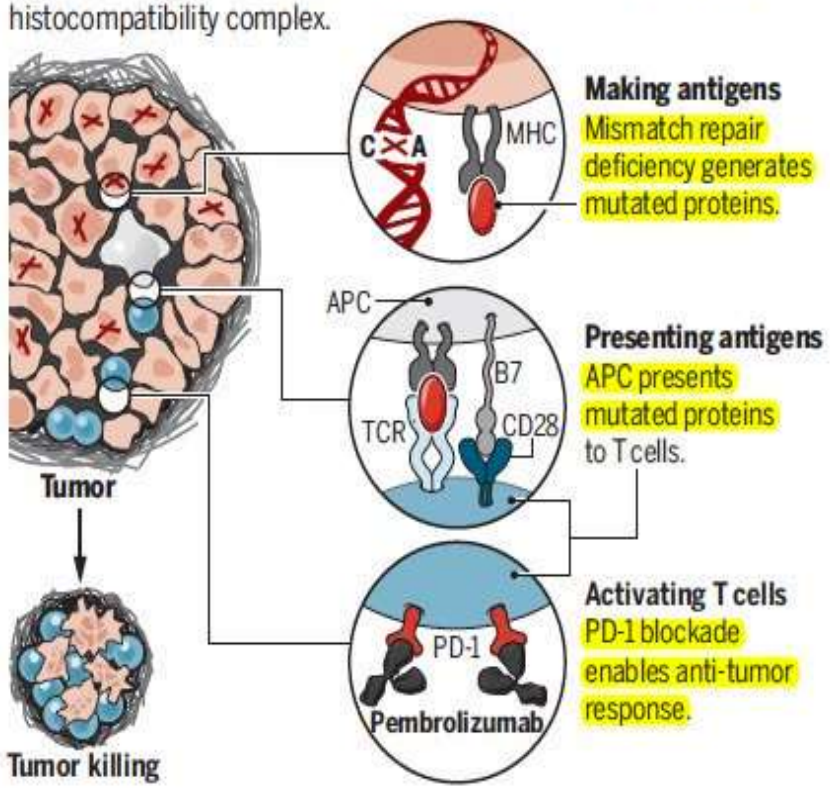
Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

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



Mutations as antigens

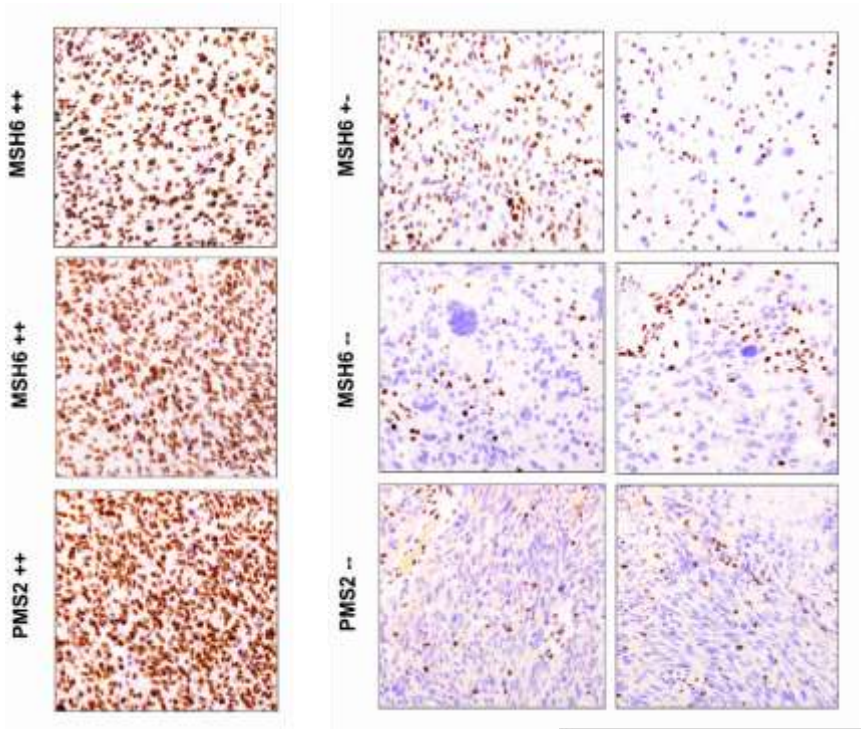
Mismatch repair deficiency in tumor cells can be used as a biomarker for immune checkpoint therapy. TCR, T cell receptor; MHC, major histocompatibility complex.



Pembrolizumab in recurrent high-grade glioma patients with mismatch repair deficiency: An observational study.

Giuseppe Lombardi, Mario Caccese, Matteo Simonelli, Matteo Fassan, Marta Padovan, Pasquale Persico, Luisa Bellu, Angelo Dipasquale, Marina Paola Gardiman, Stefano Indraccolo, Vittorina Zagonel;

Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Humanitas University, Humanitas Clinical and Research Hospital-IRCCS, Pieve Emanuele, Italy; Department of Medicine (DIMED), Pathology Unit, University of Padua, Padova, Italy, Padova, Italy; Humanitas Clinical and Research Hospital-IRCCS, Rozzano, Italy; Radiotherapy Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Unità Anatomia Patologica, Azienda-Università di Padova, Padua, Italy; Immunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

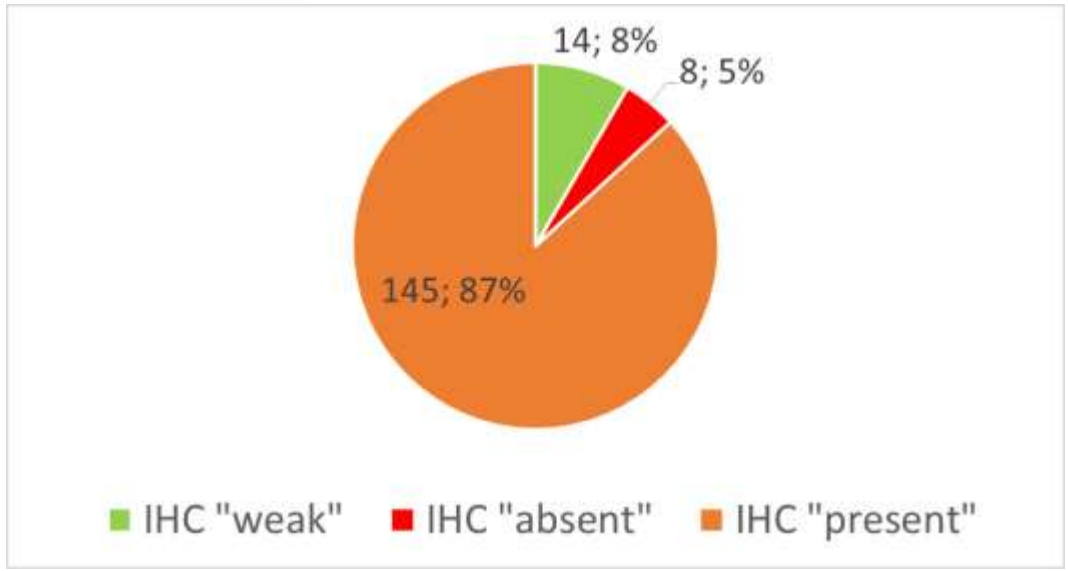


	P	OR	95% CI
Anaplastic Astrocytoma vs Glioblastoma	0.01	3.8	1.3-11.1
Recurrence vs Diagnosis	0.008	3.9	1.5-10-1
Female Pts vs Male Pts	0.03	2.7	1.07-6.7
IDHmut vs IDHwt	0.03	3.3	1.1-9.8

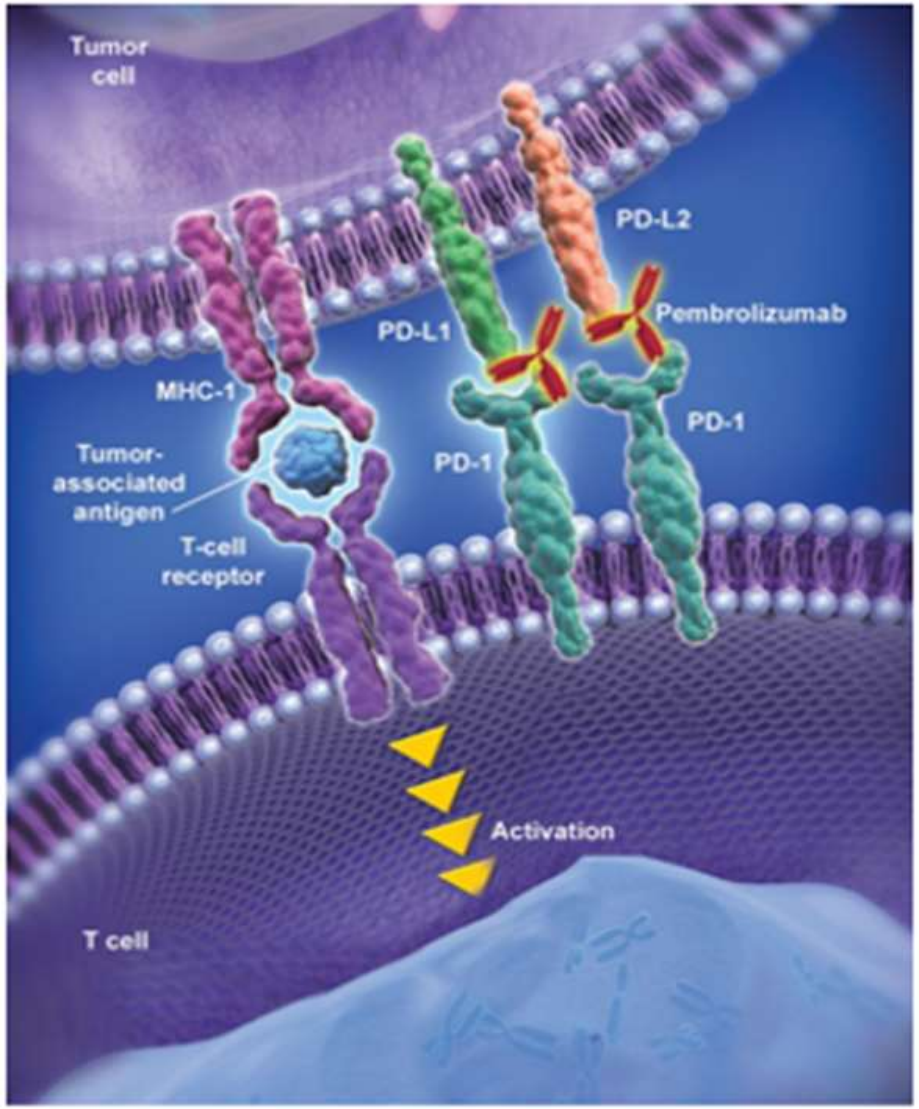
Univariate Analysis

	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



Pembrolizumab in recurrent high-grade glioma patients with mismatch repair deficiency: An observational study.

Giuseppe Lombardi, Mario Caccese, Matteo Simonelli, Matteo Fassan, Marta Padovan, Pasquale Persico, Luisa Bellu, Angelo Dipasquale, Marina Paola Gardiman, Stefano Indraccolo, Vittorina Zagonel;

Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Humanitas University, Humanitas Clinical and Research Hospital-IRCCS, Rieve Emanuele, Italy; Department of Medicine (DIMED), Pathology Unit, University of Padua, Padova, Italy, Padova, Italy; Humanitas Clinical and Research Hospital-IRCCS, Rozzano, Italy; Radiotherapy Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Unità Anatomia Patologica, Azienda Università di Padova, Padua, Italy; Immunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

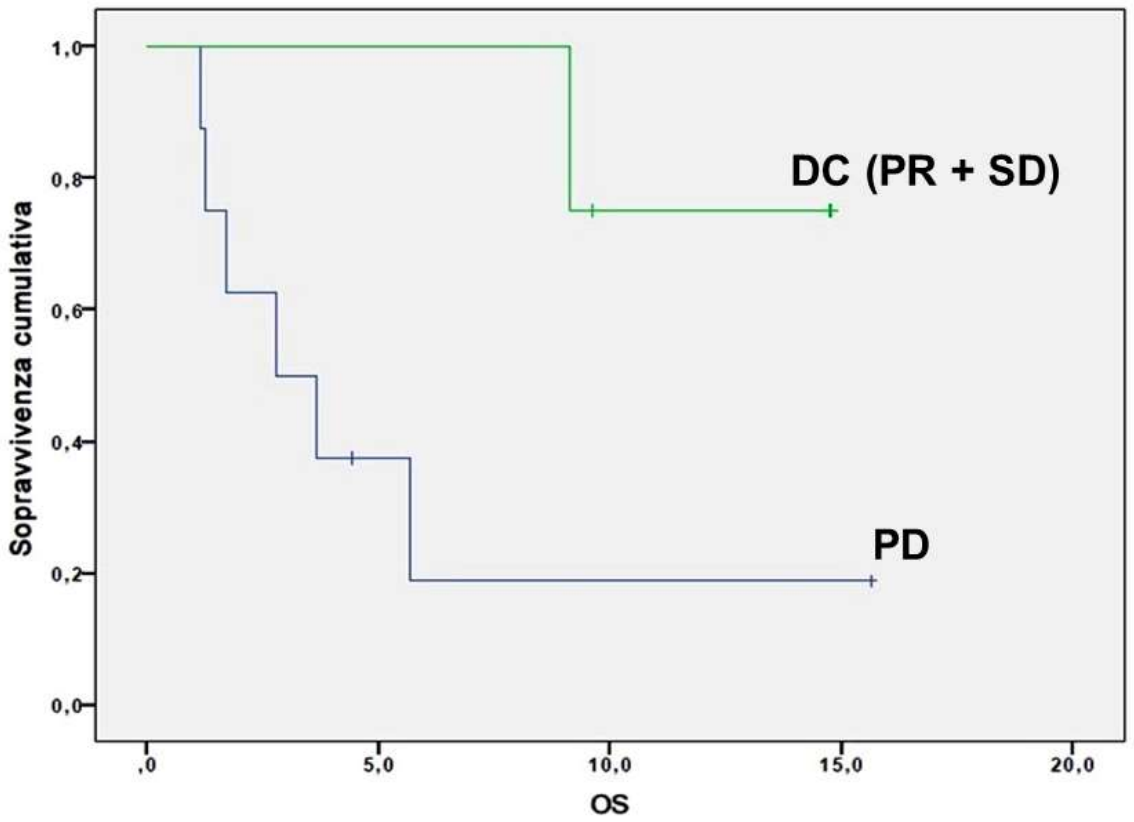
- Pembrolizumab in recurrent HGG
- ECOG PS 0-2
- Desametazone ≤4mg
- **MMR^{-} HGG** (IHC)

Baseline Patients Characteristics

Characteristics	N (%)
Patients	12
Median age	44
Histology - Anaplastic Astrocytoma - Anaplastic ODG - Glioblastoma	 5 (42) 1 (8) 6 (50)
MGMT methylation status - Metilated - Unmetilated	 8/10 (80) 2/10 (20)
IDH - Mutated - Wild-Type	 6/11 (55) 5/11 (45)
Median Previous CT lines	1 (range 1-5)
Previous RT	12 (100)

Characteristics	N (%)
Deficient protein in MMR - MSH2 - MSH6 - PMS2 - MLH1	 6 (50) 9 (75) 2 (17) 2 (17)
Deficiency in MMR - Weak Signal - Absent Signal	 8 (67) 4 (33)
Median cycles of PEM	3.5 (range 1-22)
Median DEX (mg)	1.5 (range 0-4)

Results



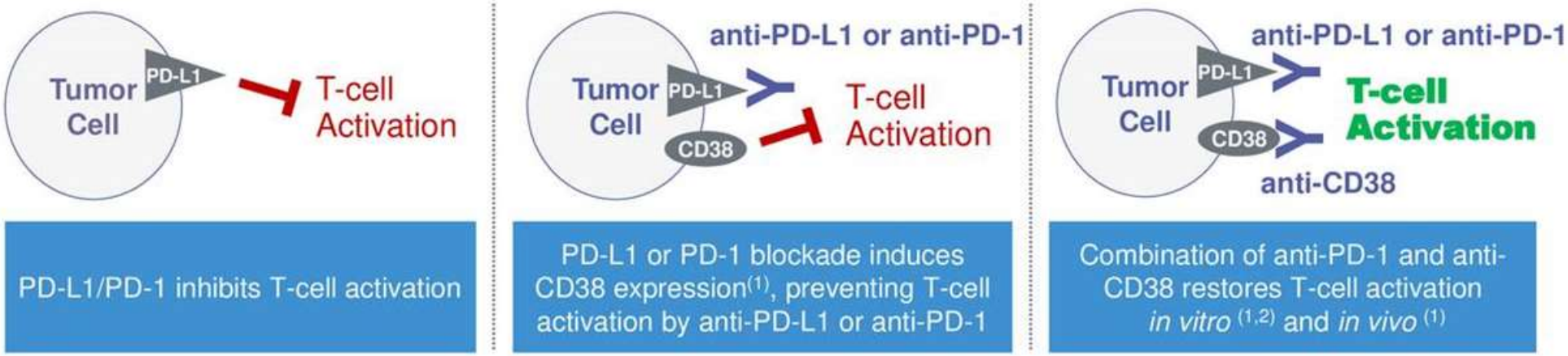
Overall Survival according to response

Response Rate according to RANO criteria	
Disease Control Rate	**33%**
- Stable Disease (SD)	*3/12*
- Partial Response (PR)	*1/12*
Progressive Disease (PD)	*67% (8/12)*

A new Horizon…ACT15377: Atezolizumab + Isatuximab

Isatuximab Targets CD38: A Second Checkpoint Inhibitor

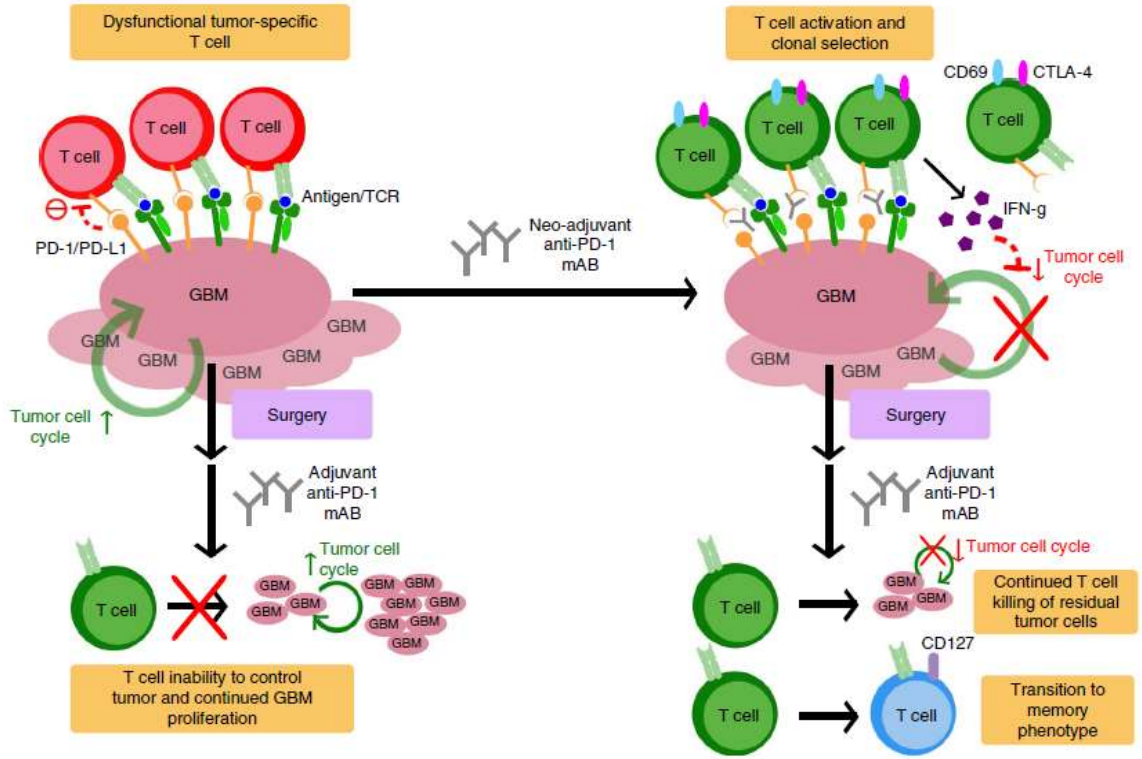
Anti-PD-1 *in vivo* resistance via CD38 upregulation on tumor cells is reversed by anti-CD38/anti-PD-1 combination[1]

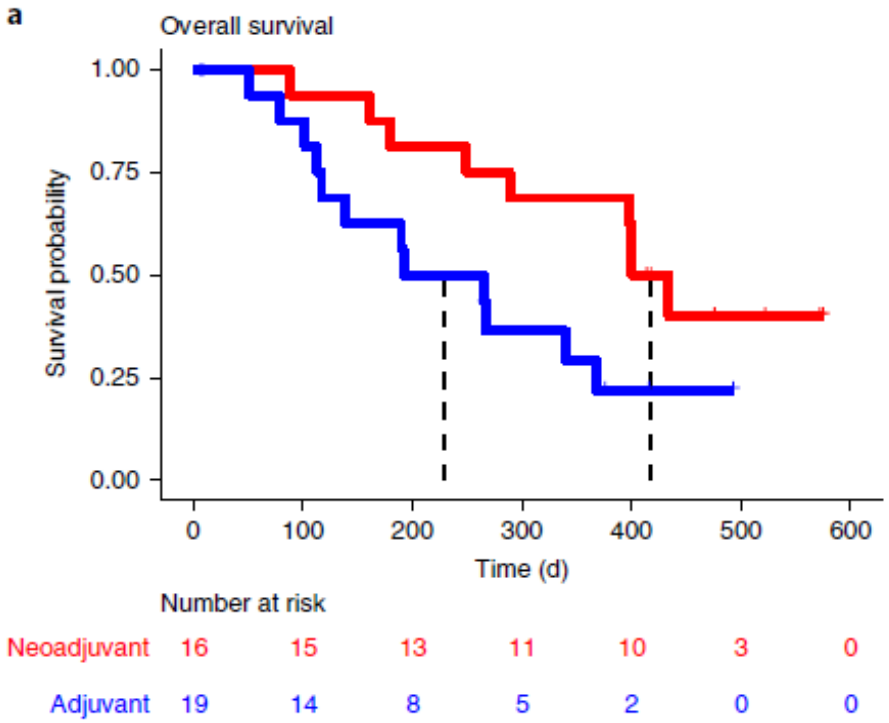


Neoadjuvant Pembrolizumab in recurrent GBM

nature medicine
FOCUS | ARTICLES
https://doi.org/10.1038/s41591-018-0337-7

Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma





mario.caccese@iov.veneto.it