High Grade Gliomas:
Nuovi approcci terapeutici

Marco Filetti
Scuola di Specializzazione in Oncologia Medica
Università Sapienza-A.O. Sant'Andrea
marco.filetti@uniroma1.it

Agenda

Inibitori TKIs

- Regoma Trial

Precision Medicine

- Larotrectinib
- Entrectinib

Immunoterapia

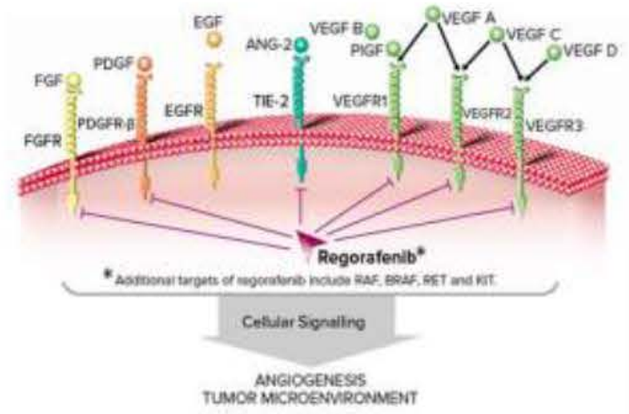
- CheckMate 143
- Pembrolizumab e MMRd

Are we going to get out of the tunnel?

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)*

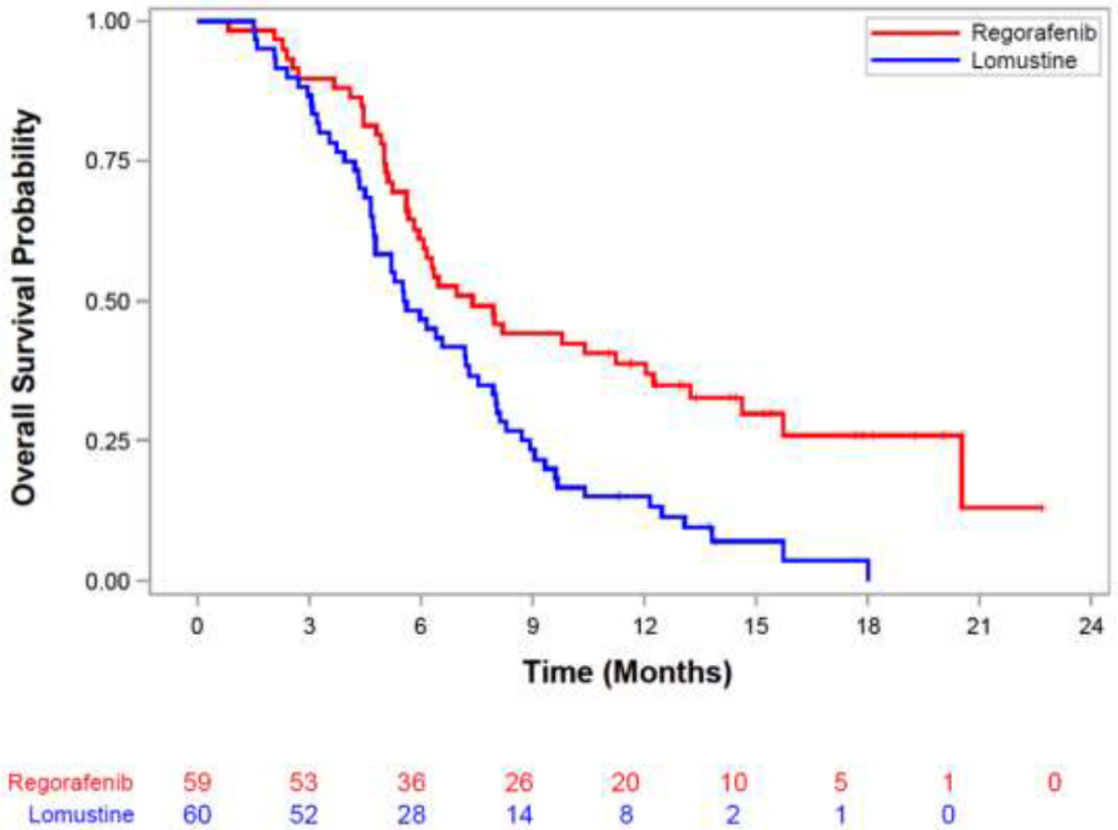
- Stratification factors: center and surgery at recurrence
- Study location: 10 centers in Italy

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%)*

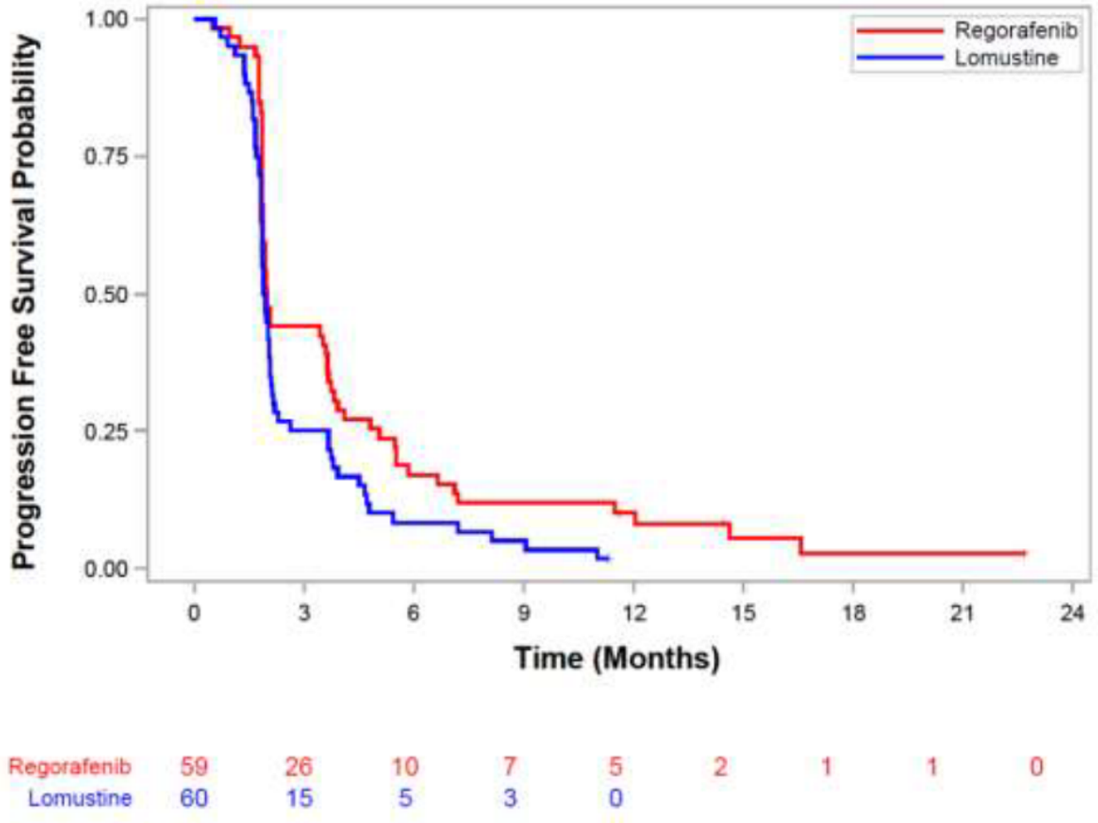
Overall Survival



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

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

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

Presented By Alexander Drilon at 2019 ASCO Annual Meeting

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.

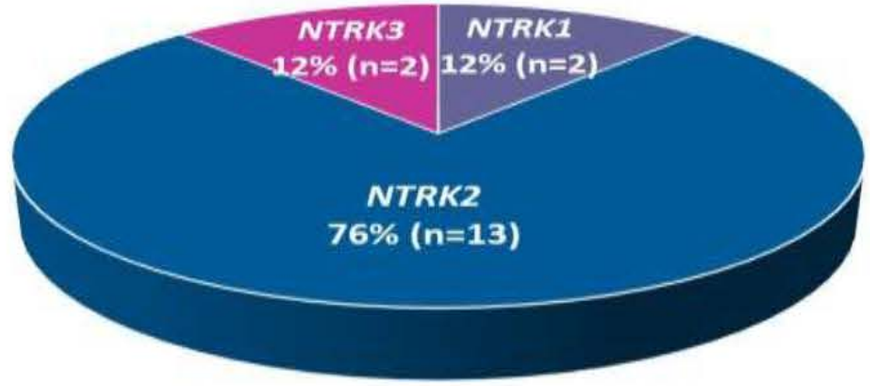
Presented By Alexander Drilon at 2019 ASCO Annual Meeting

Clinicopathologic Features: Primary CNS Tumors

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

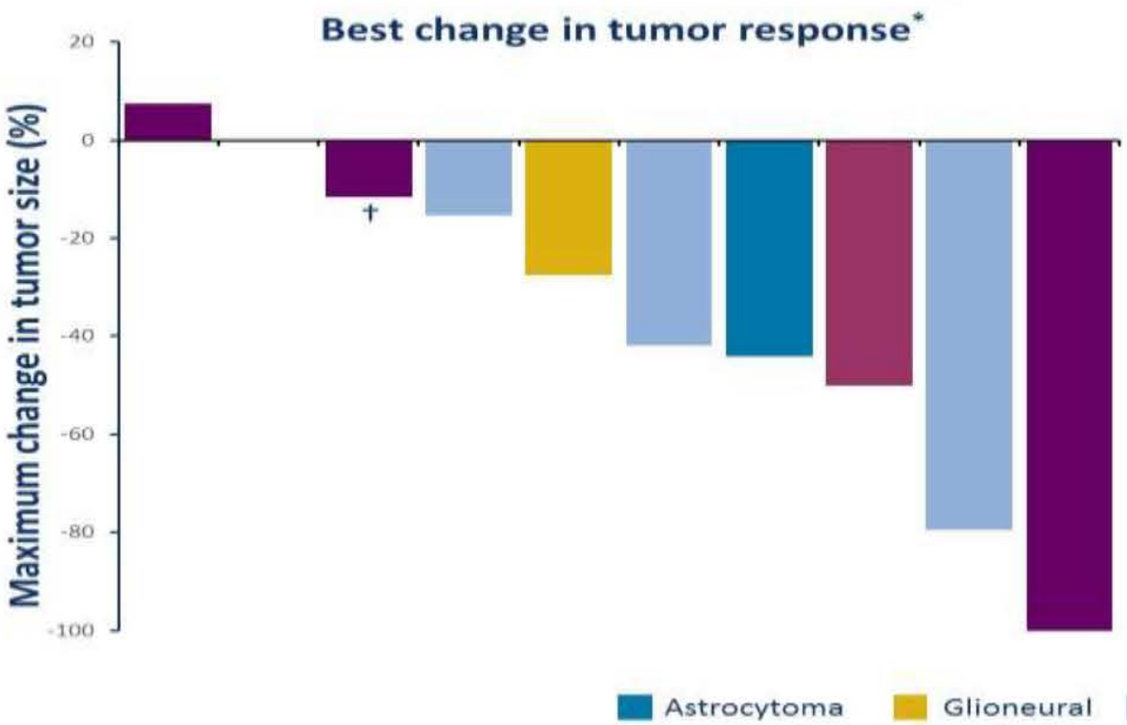
Presented By Alexander Drilon at 2019 ASCO Annual Meeting

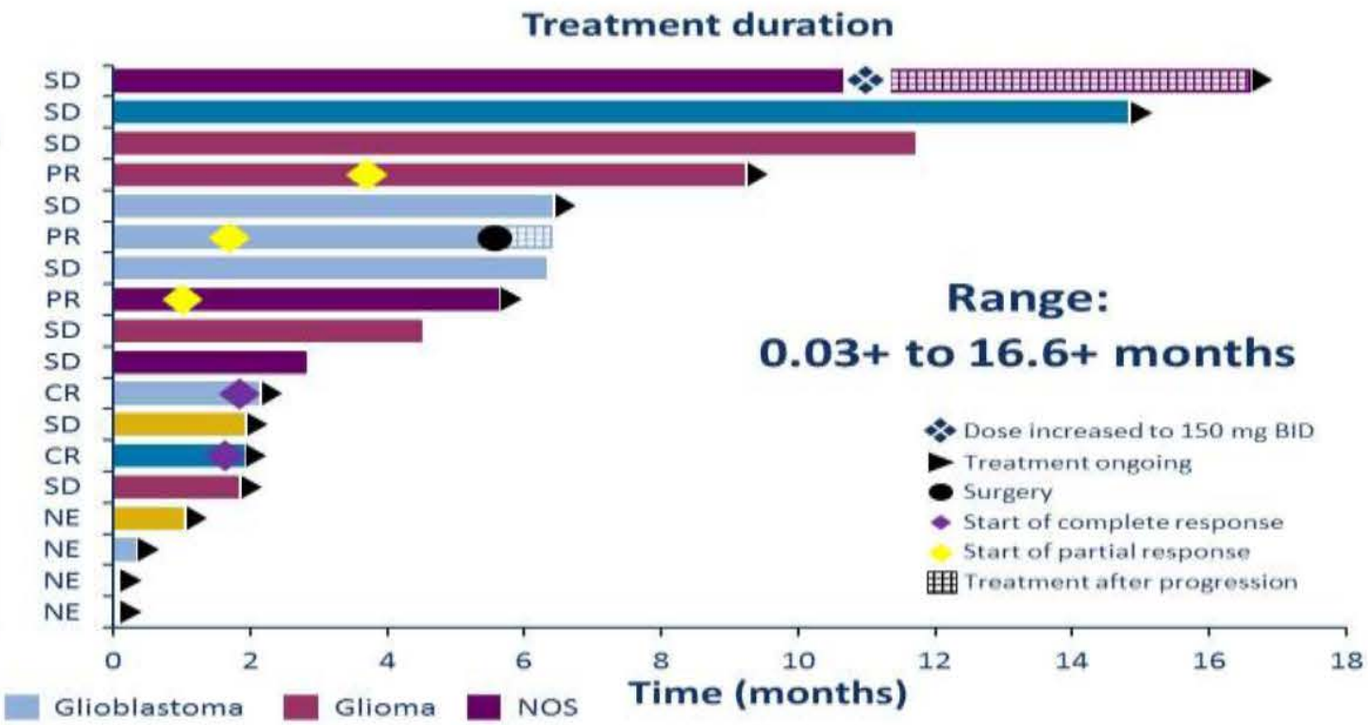
Investigator-Assessed Efficacy of Larotrectinib in TRK Fusion-Positive Primary CNS Tumors

	n=14 evaluable patients	
Objective response rate	36% (95% CI: 13–65)	
Best overall response*, n (%)		
Complete response†	2 (14%)‡	DCR 100%
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)	

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.

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





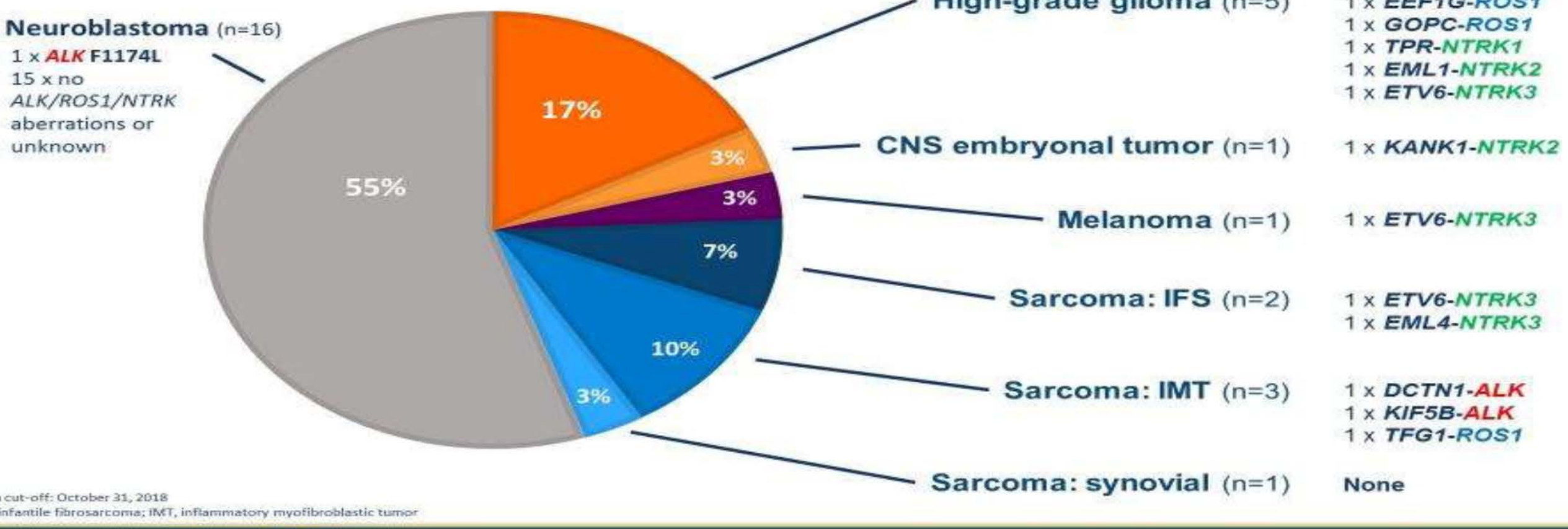
Data cutoff date February 19, 2019. Disease assessments were performed by investigators. *Tumor responses in patients with measurable disease and tumor values recorded at data cutoff, based on RANO sum of products of diameters, unless noted otherwise. †Based on RECIST 1.1 sum of longest diameter. CR, 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]

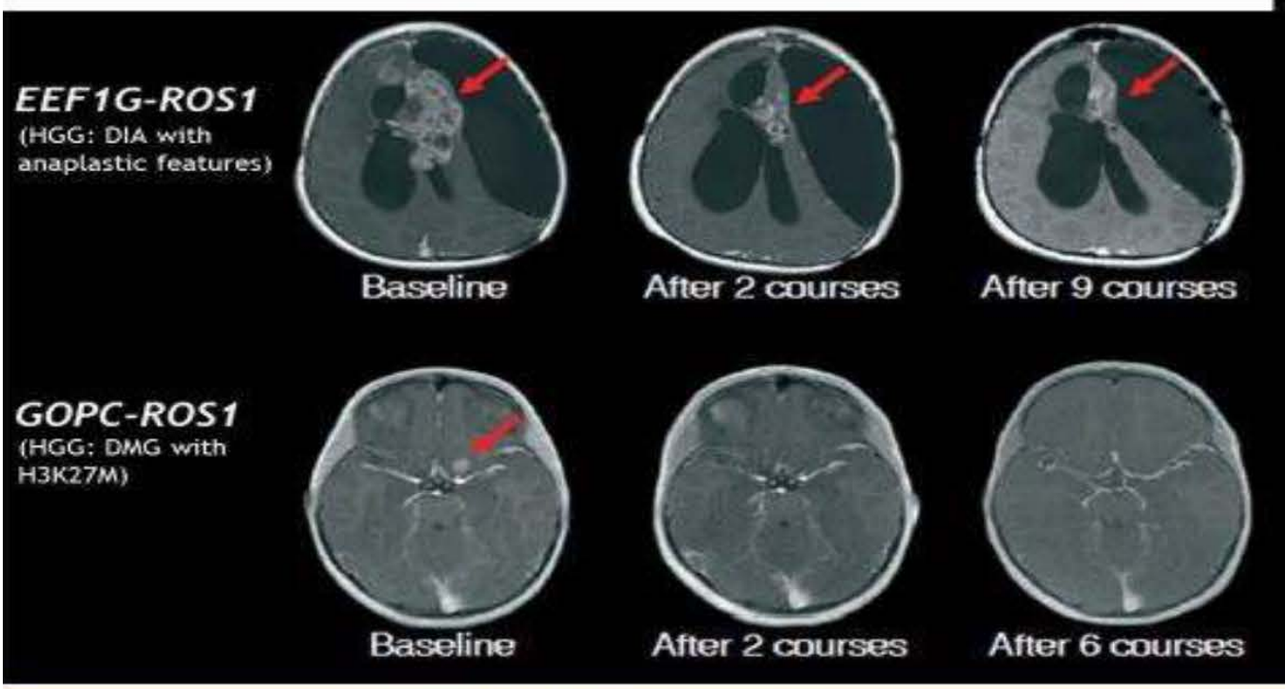
1. St. Jude Children's Research Hospital, Memphis, TN; 2. Washington University School of Medicine, St. Louis, MO; 3. Memorial Sloan Kettering Cancer Center, New York, NY; 4. Children's Hospital Colorado, Aurora, CO; 5. University of Utah/Huntsman Cancer Institute, Primary Children's Hospital, Salt Lake 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

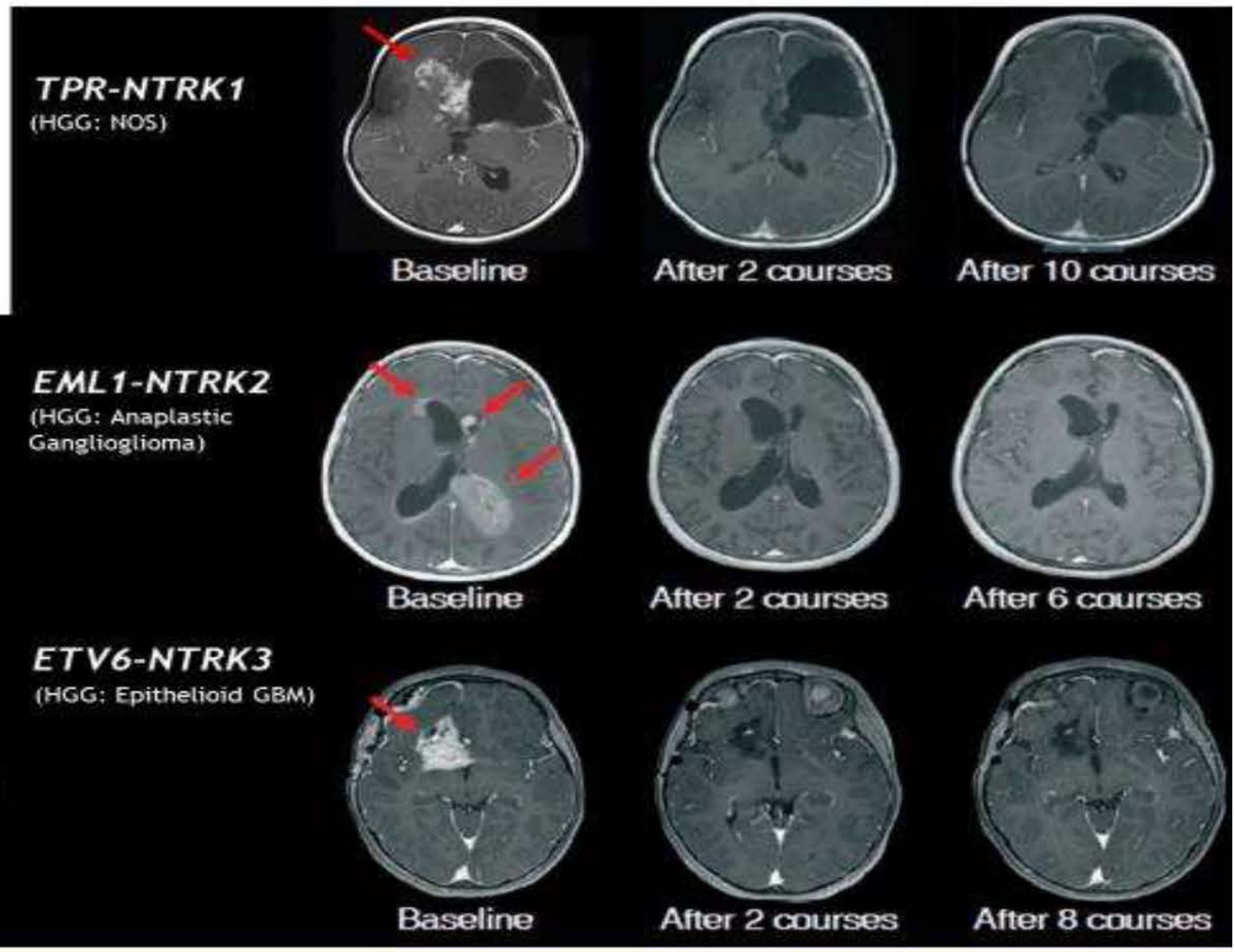
Baseline characteristics by tumor type and target gene fusion



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

Measureable and durable responses in CNS tumors

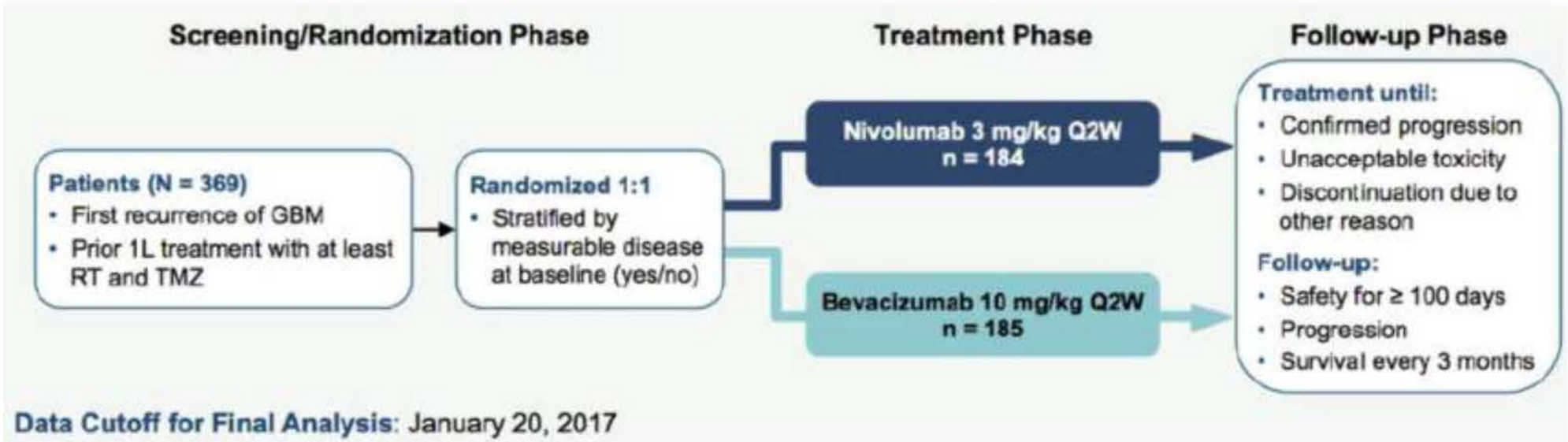




Nivolumab

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

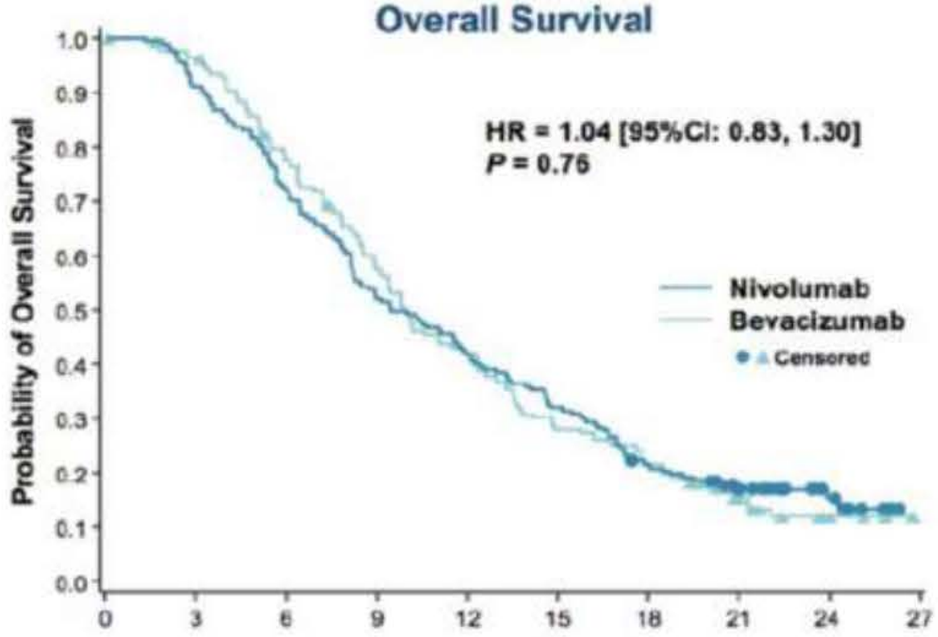
1L, first line; CTCAE, Common Terminology Criteria for Adverse Events; MRI, magnetic resonance imaging; ORR, objective response rate; PFS, progression-free survival; Q2W, every 2 weeks; Q6W, every 6 weeks; Q8W, every 8 weeks; RANO, Radiologic Assessment in Neuro-Oncology criteria.

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

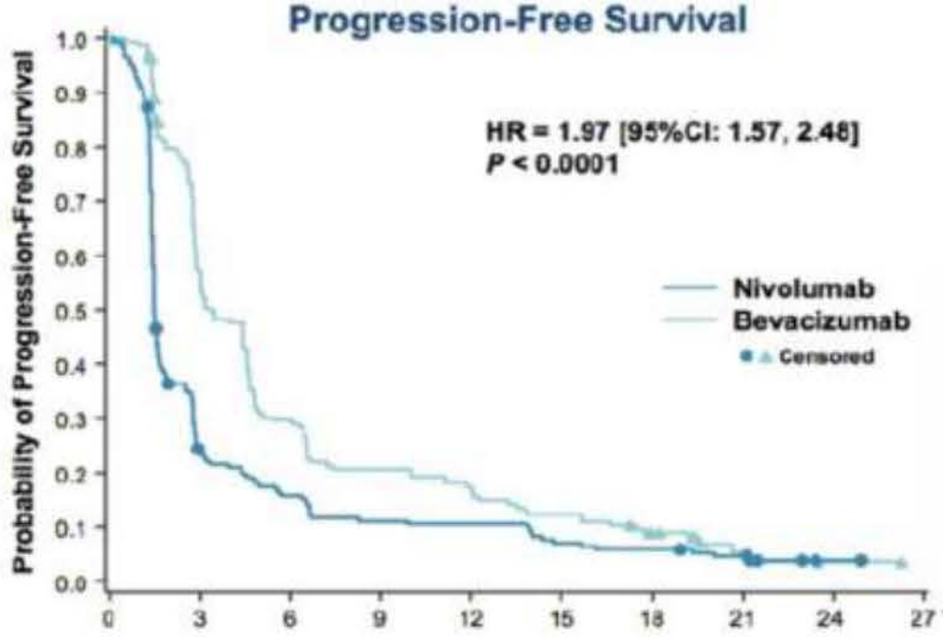


HR = 1.04 [95%CI: 0.83, 1.30]
P = 0.76

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



HR = 1.97 [95%CI: 1.57, 2.48]
P < 0.0001

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 (%) [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]

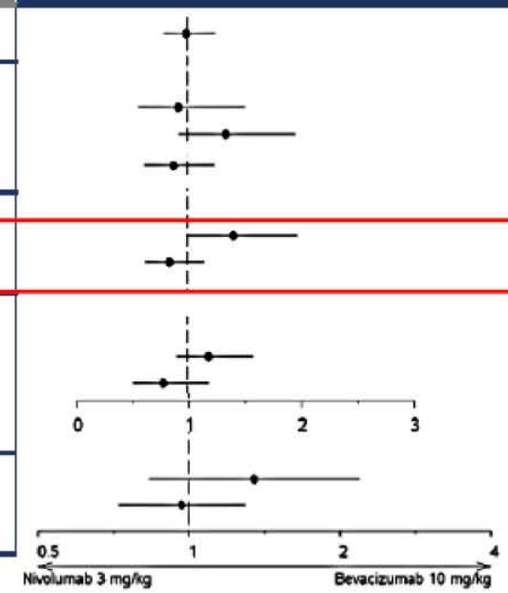
BOR, best overall response; CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response. [a]Patients evaluable for response.

"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]



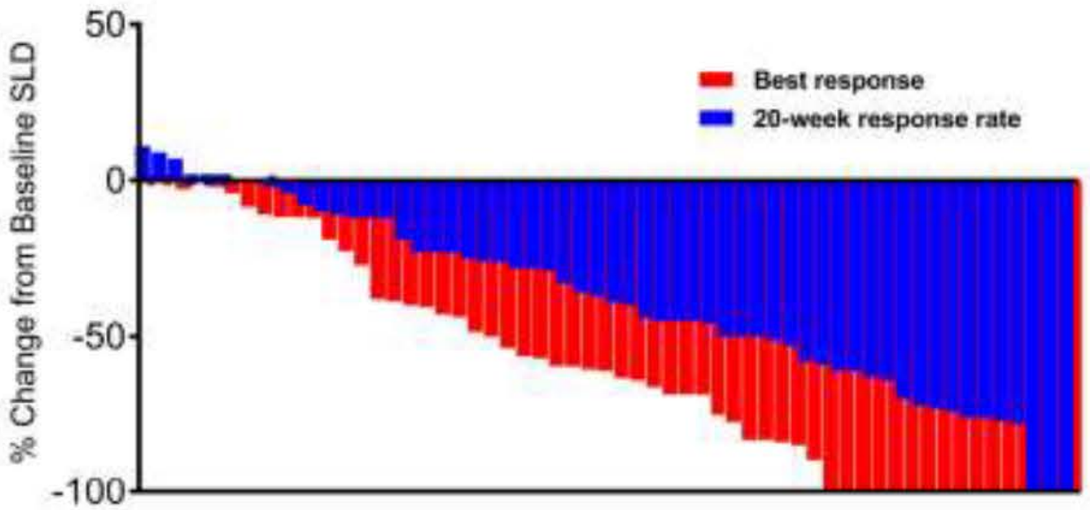
Science

REPORTS

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

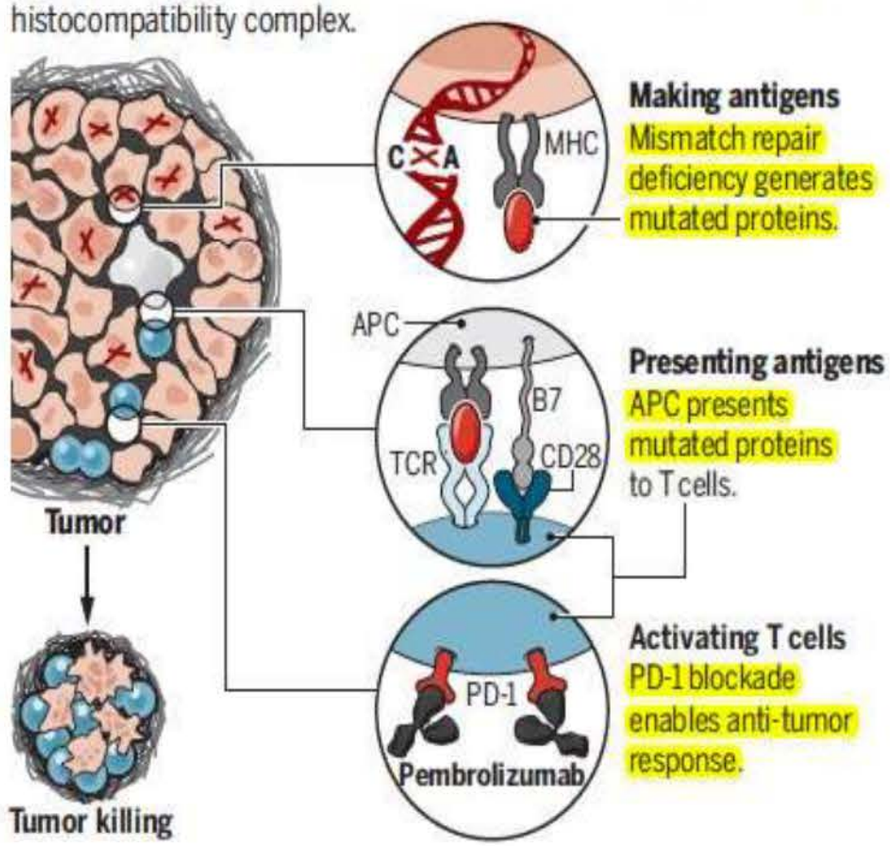
Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

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

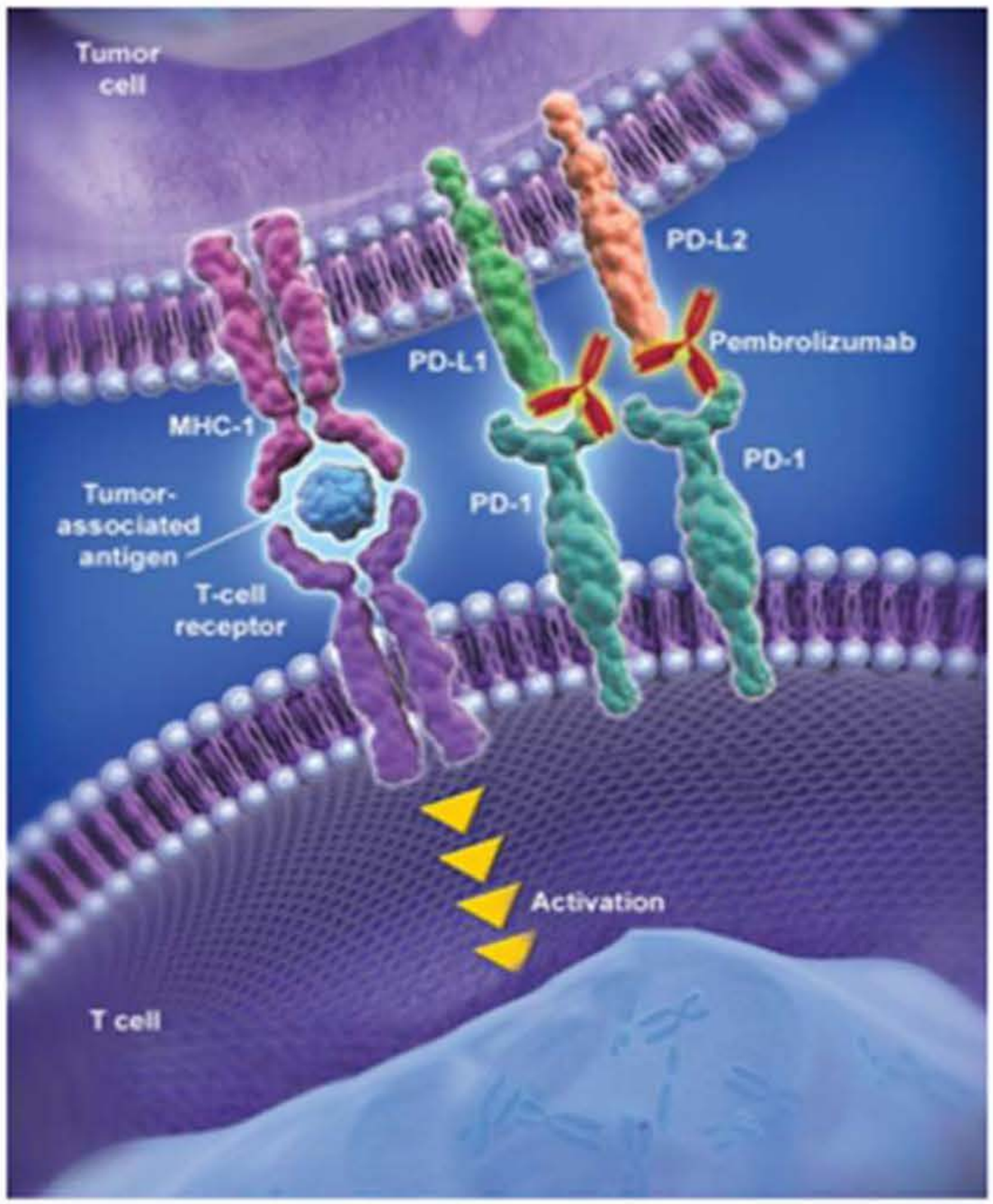
Mismatch repair deficiency in tumor cells can be used as a biomarker for immune checkpoint therapy. TCR, T cell receptor; MHC, major histocompatibility complex.



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



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

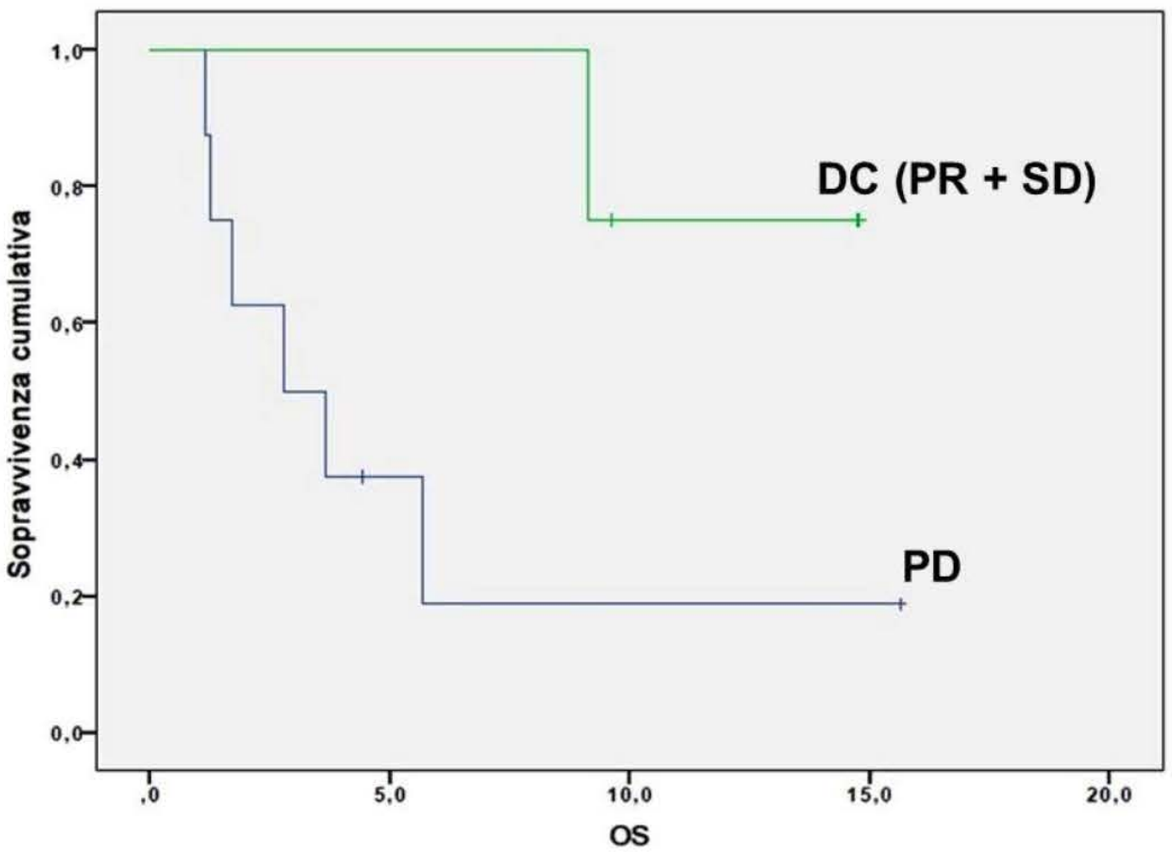
- Pembrolizumab in recurrent HGG
- ECOG PS 0-2
- Desametazone ≤4mg
- **MMR⁻ HGG** (IHC)

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)*