Highlights in Central Nervous System Tumors

Giuseppe Lombardi, MD, PhD
Dipartimento di Oncologia Clinica e Sperimentale,
Oncologia Medica 1,
Istituto Oncologico Veneto-IRCCS
Padova

giuseppe.lombardi@iov.veneto.it

Topics

- **Relevant clinical trials on treatment management**
  - Gliomas (CATNON, RTOG 9802, GEINO 1401, REGOMA)
  - Meningiomas (EORTC 1320)
  - Medulloblastoma

- **Precision Medicine**
  - Larotrectinib
  - IDH inhibitor

- **Immunotherapy**
  - SurVaxM
  - Pembrolizumab in MMRd

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.*

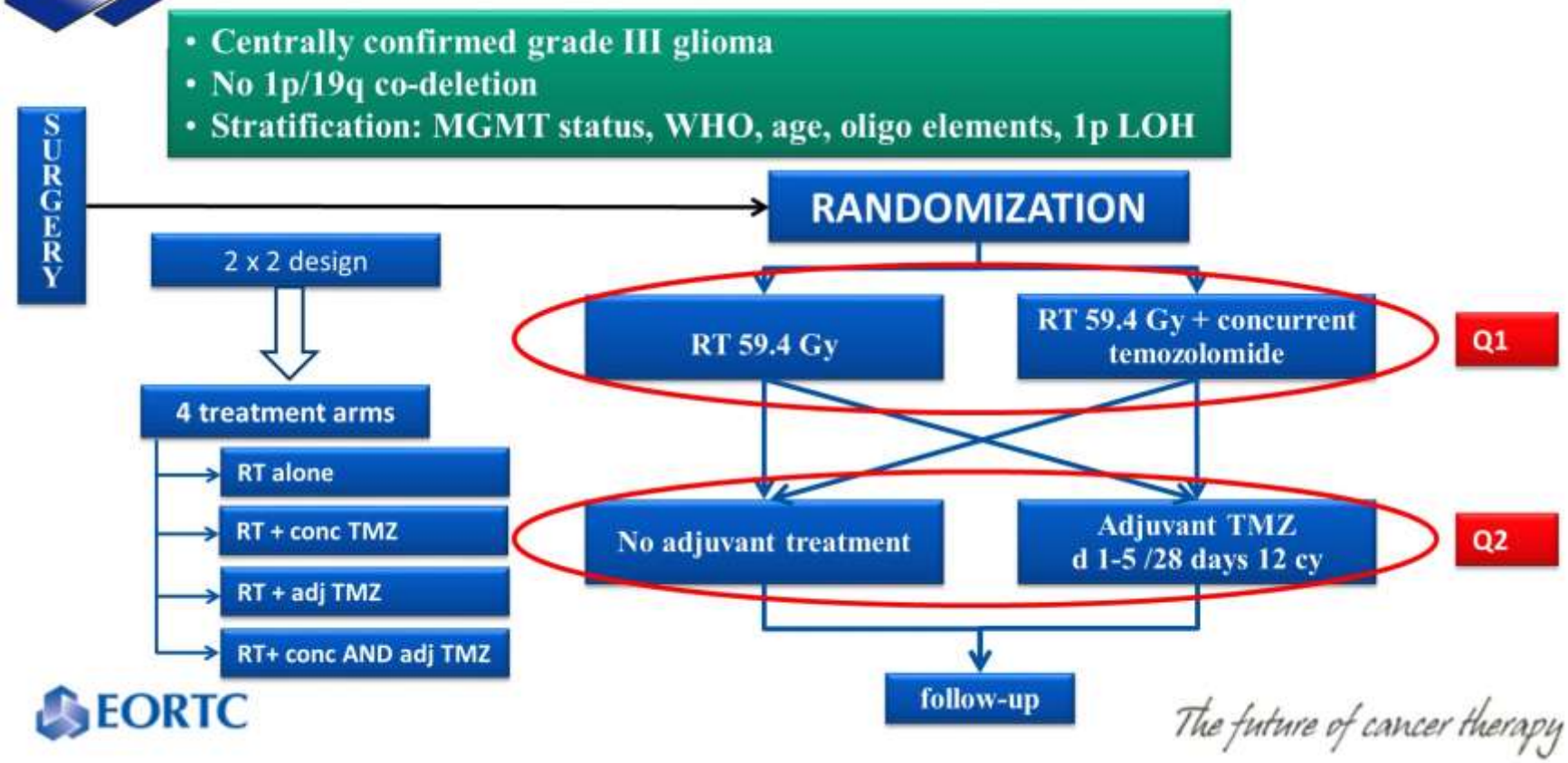
MRC Medical Research Council

COGNO COOPERATIVE TRIALS GROUP FOR NEURO-ONCOLOGY

Canadian Cancer Trials Group

Presented By Martin Van Den Bent at 2019 ASCO Annual Meeting

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



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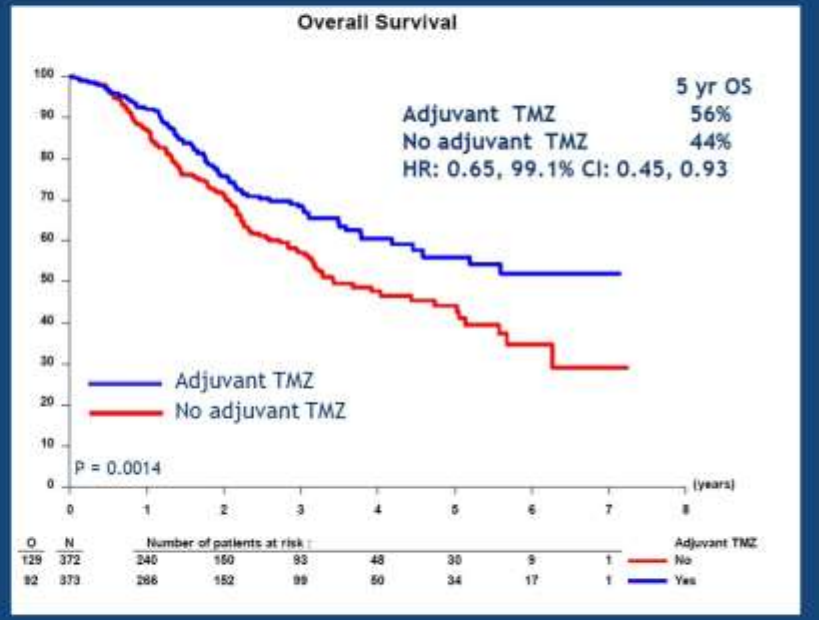
IDMC recommendation Oct 2015: release the results of the adjuvant temozolomide treatment

- Preplanned at the time 41% of the required events were observed (n = 221)
  - Occured with 745 pts randomized
  - Median follow-up: 27.4 mo (31/5/2015)

➢ Significant increase in OS after adjuvant temozolomide

  ➢ HR 0.65, 99.1% CI 0.45, 0.93



van den Bent et al, Lancet 2017;390:1645-53

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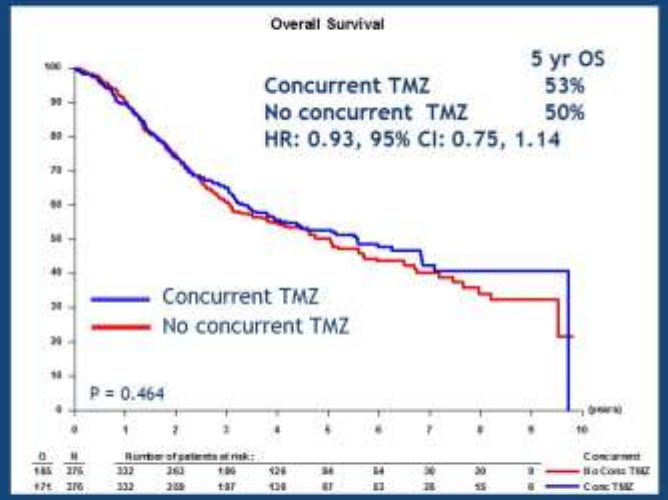
CATNON 2nd interim analysis: primary endpoint and univariate analysis

Parameter	p- value	HR	HR 99.1% CI
Concurrent TMZ	**0.7634**	**0.968**	**0.73, 1.23**
Age (>50 vs <=50%)	<.0001	3.42	2.56, 4.57
WHO PS (>0 vs 0%)	<.0001	1.53	1.15, 2.03
1p LOH (Yes vs No%)	0.2153	1.28	0.76, 2.13
Oligodendroglial elements (Yes vs No%)	0.7279	1.04	0.76, 1.44
MGMT Methylated vs Unmethylated	0.0020	0.57	0.35, 0.92
MGMT Undetermined/invalid vs unmethylated	0.0392	0.78	0.56, 1.07



Primary endpoint: OS, Cox model adjusted for stratification factors

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Distribution of the molecular parameters in the four treatment arms

	RT (n = 189)	TMZ/RT (n = 188)	RT →TMZ (n = 186)	RT/TMZ →TMZ (n = 188)	All (n = 751)
IDH status					
wildtype	50 (26.5%)	39 (20.7%)	37 (19.9%)	34 (18.1%)	160 (21.3%)
mutant	85 (45.0%)	89 (47.3%)	100 (53.8%)	94 (50.0%)	368 (49.0%)
missing	54 (28.6%)	60 (31.9%)	49 (26.3%)	60 (31.9%)	223 (29.7%)
MGMT status					
unmethylated	46 (24.3%)	46 (24.5%)	45 (24.2%)	40 (21.3%)	177 (23.6%)
methylated	98 (51.9%)	100 (53.2%)	101 (54.3%)	102 (54.3%)	401 (53.4%)
missing	45 (23.8%)	42 (22.3%)	40 (21.5%)	46 (24.5%)	173 (23.0%)

- IDH mutational rate in tumors tested for IDH: 69.6%
- MGMT promoter methylated in tumors tested for MGMT STP-S27: 69.4%

PRESENTED BY: M.J van den bent

EORTC

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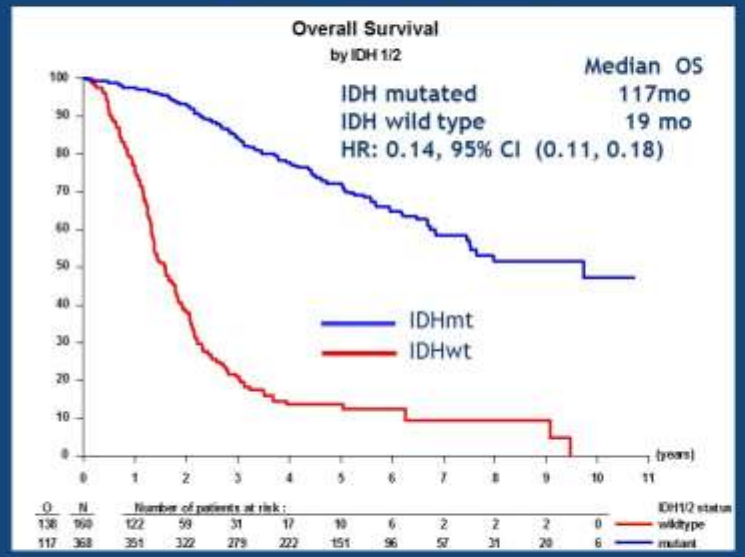
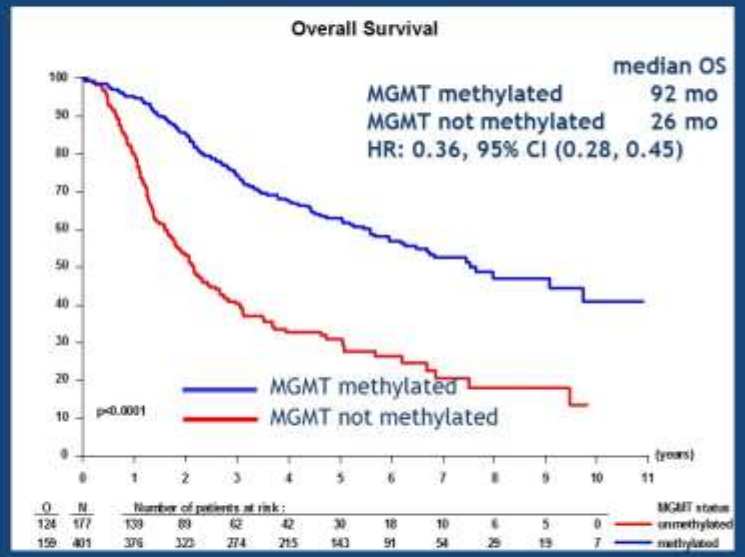
Impact of IDH, MGMT promoter on Overall Survival

IDH mutational status



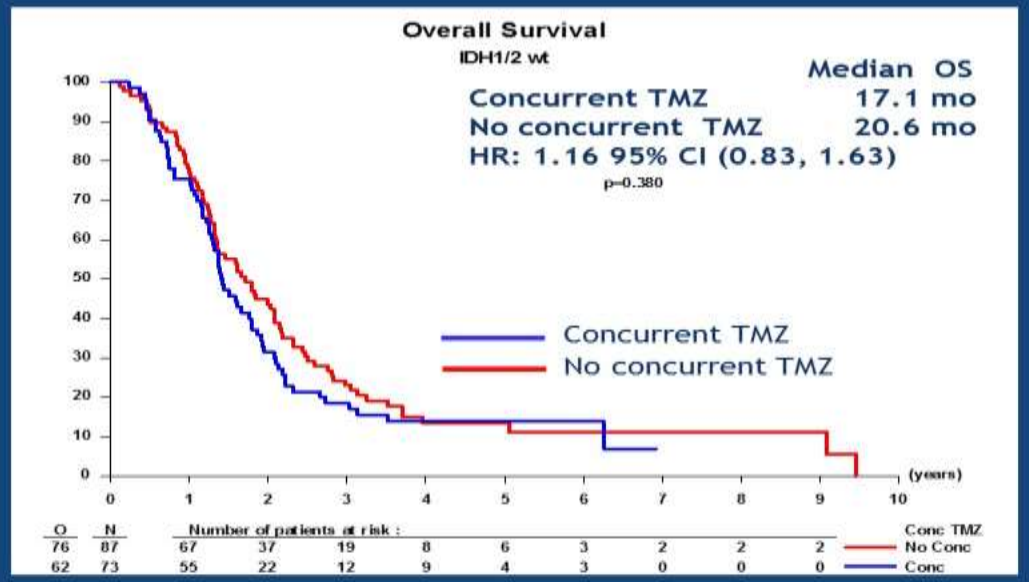
MGTM methylation status



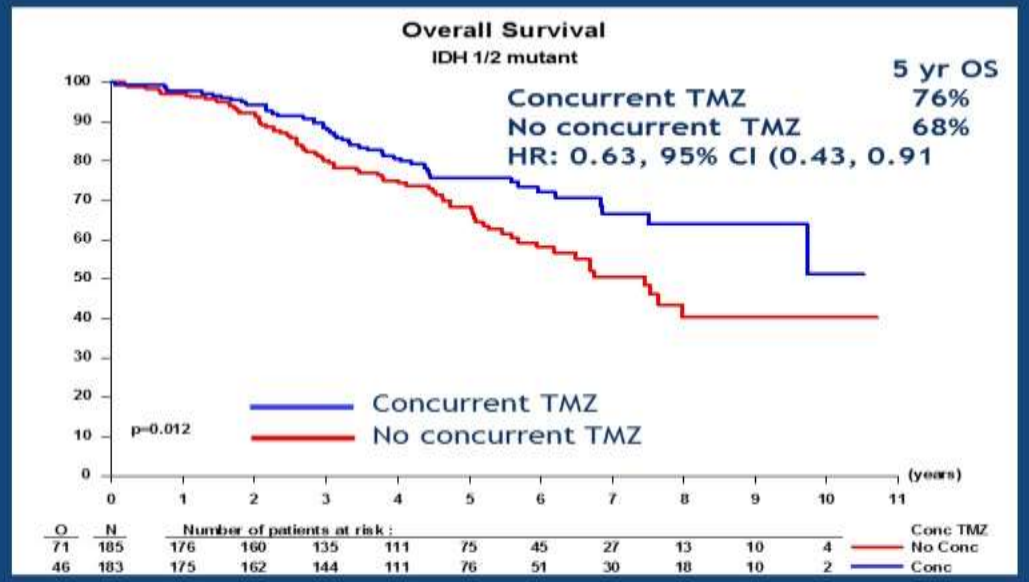
- IDH mutational status stronger correlation with outcome than MGMT promoter methylation status

Concurrent temozolomide in IDHwt and IDHmt anaplastic astrocytoma

IDH wild type



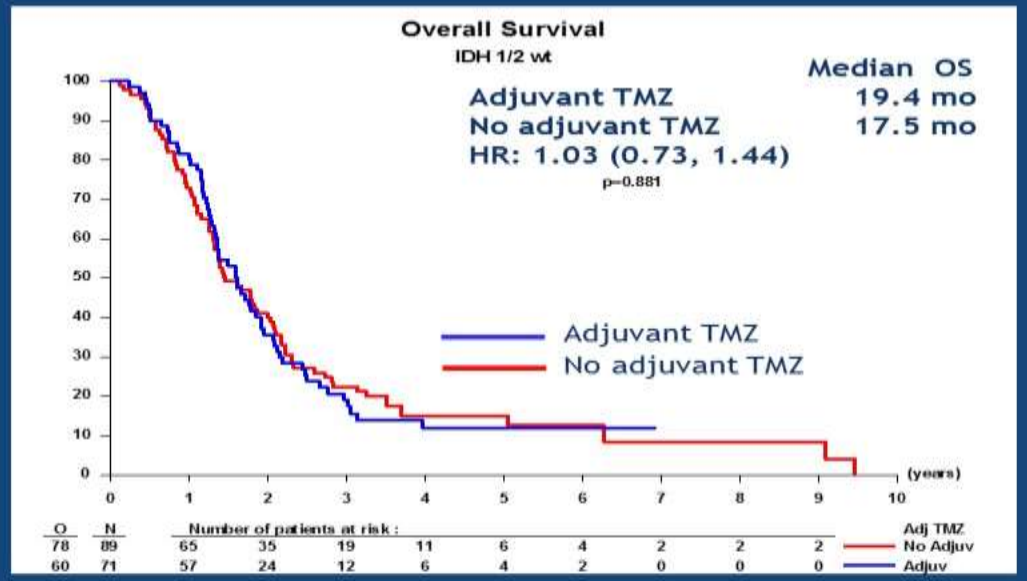
IDH mutant



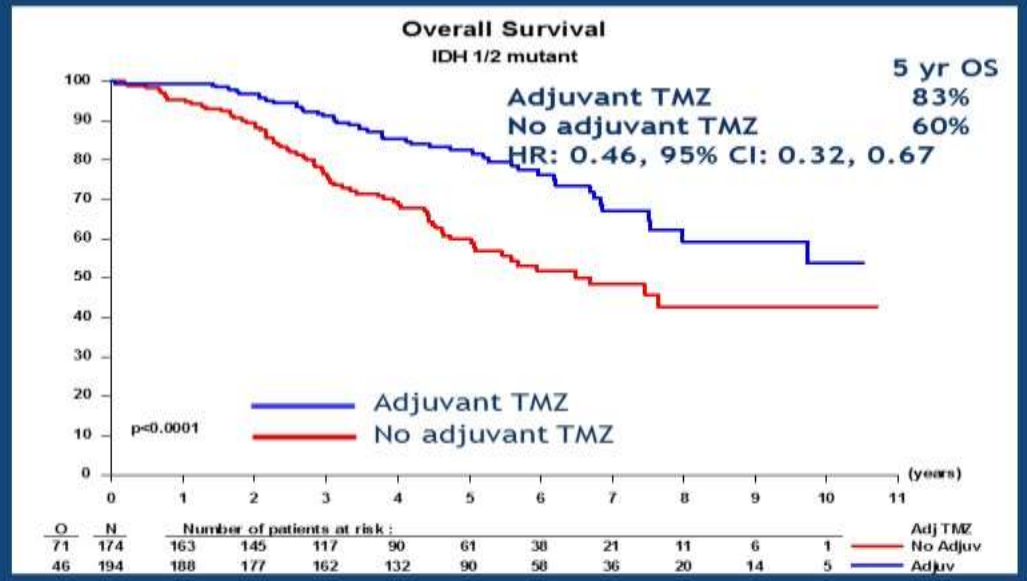
- Concurrent temozolomide improves outcome in IDH mutant anaplastic astrocytoma

Adjuvant temozolomide in IDHwt and IDHmt anaplastic astrocytoma

IDH wild type



IDH mutant



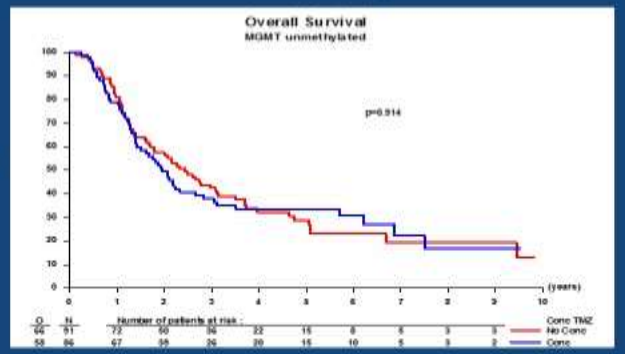
- Adjuvant temozolomide improves outcome in IDH mutant anaplastic astrocytoma

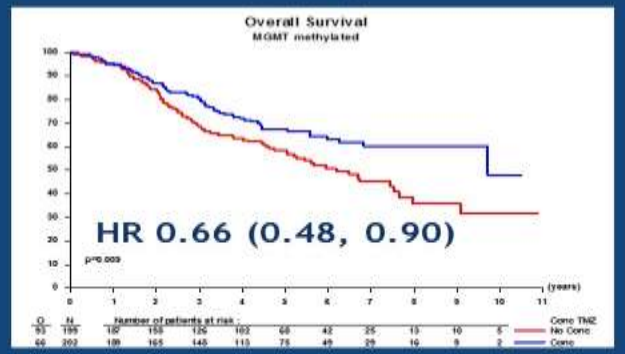
Effect of MGMT promoter status determined with methylation array

MGMT unmethylated

MGMT methylated

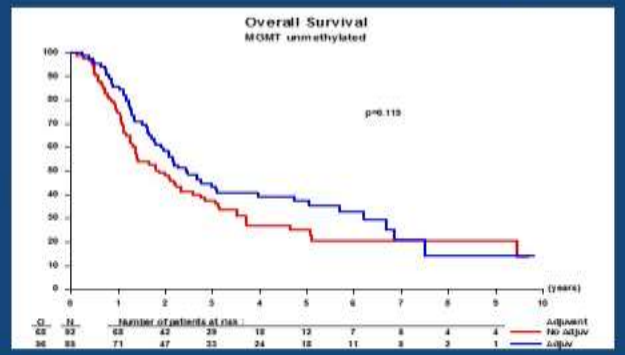
Concurrent temozolomide Question #1

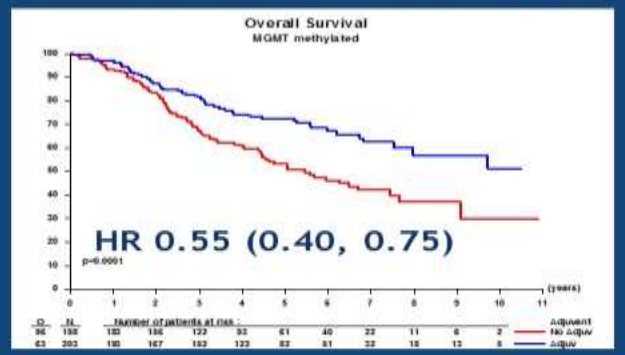




Temozolomide
No temozolomide

Adjuvant temozolomide Question #2

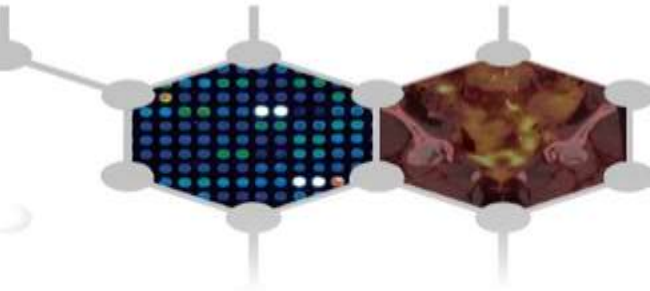




Conclusions CATNON trial at ASCO 2019

- 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

Presented By Martin Van Den Bent at 2019 ASCO Annual Meeting



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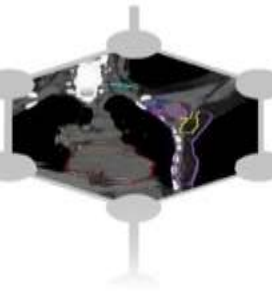


Updated predictive analysis of the WHO-defined molecular subgroups of low-grade gliomas within the high-risk treatment arms of NRG Oncology/ RTOG 9802

Erica H Bell, PhD, Minhee Won, MA, Jessica L Fleming, PhD, Aline P Becker, MD, PhD, Joe McElroy, PhD, Edward G Shaw, MD, MA, Minesh P Mehta, MD, David G Brachman, MD, Stanley Z Gertler, MD, Albert D Murtha, MD, Christopher J Schultz, MD, David Johnson, MD, Nadia N Laack, MD, Grant K Hunter, MD, Ian R Crocker, MD, Arnab Chakravarti, MD

ASCO Annual Meeting
June 3, 2019

NRG Oncology/RTOG 9802 Background

A phase III study of RT versus RT+ PCV (procarbazine, CCNU, and vincristine) in grade II gliomas

Low Risk

Age < 40
and
Grosstotal
resection

High Risk

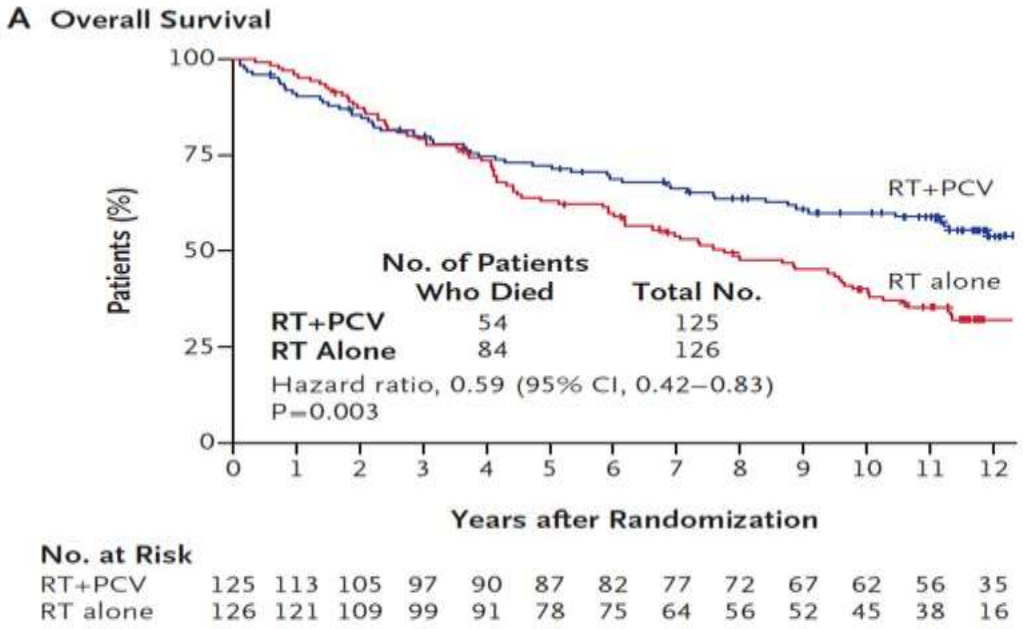
Age ≥ 40
or
Subtotal
resection/biopsy

RANDOMIZE

Arm 1 = Observe

Arm 2 = RT Alone

Arm 3 = RT → PCV



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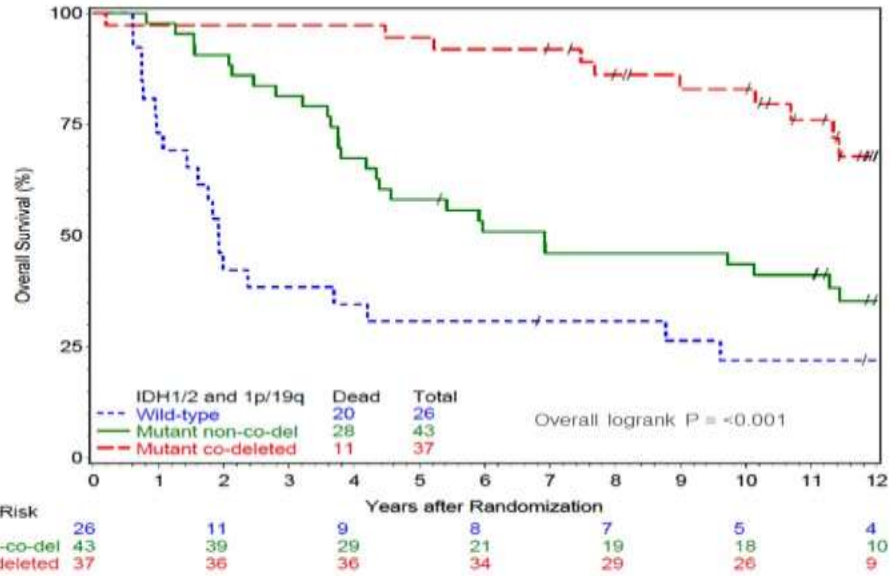
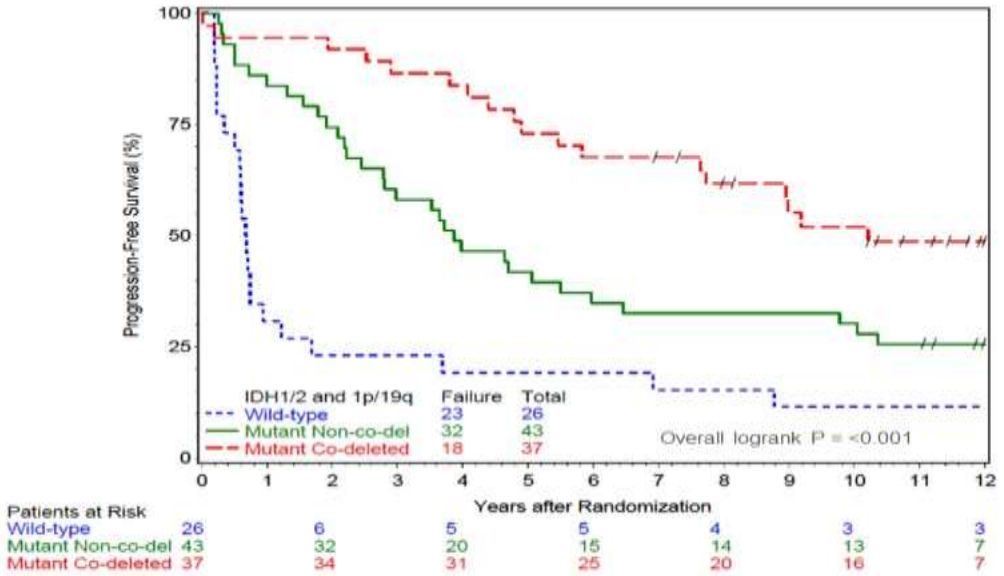
N Engl J Med 2016; 374:1344-1355

Survival by WHO-defined Molecular Sub-groups

OS



PFS



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Predictive Value

Results

- 106 (42%) patients had tissue/quality DNA available
- **~75%** were *IDH*mut
  - 41% - *IDH*mut/non-co-deleted
  - 35% - *IDH*mut/co-deleted
  - 24% - *IDH*wt.
- ***IDH*mut/co-deleted** was **significantly** correlated with ⬆ **PFS** (P<0.001) and ⬆ **OS** (P=0.029) with the addition of PCV
- ***IDH*mut/non-co-deleted** was **significantly** correlated with ⬆ **PFS** (P=0.003) and ⬆ **OS** (P=0.013) with the addition of PCV
- ***IDH*wt** demonstrated **no significant** difference for either OS or PFS

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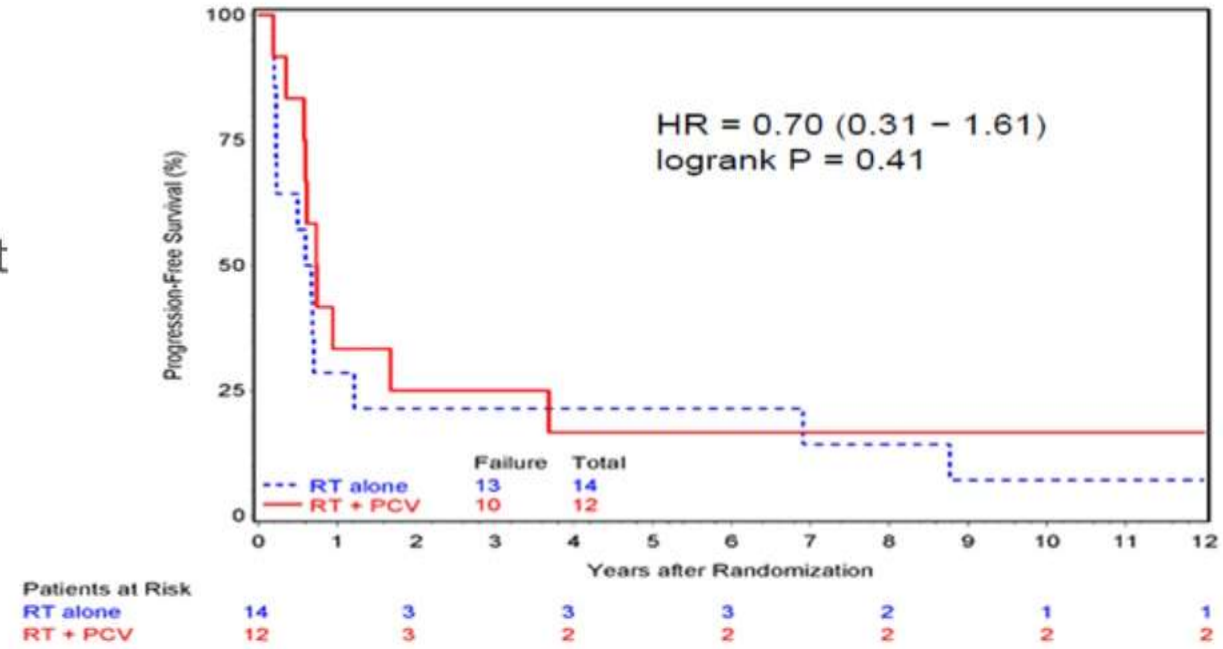
PFS by Molecular Sub-groups and Tx

IDH wt



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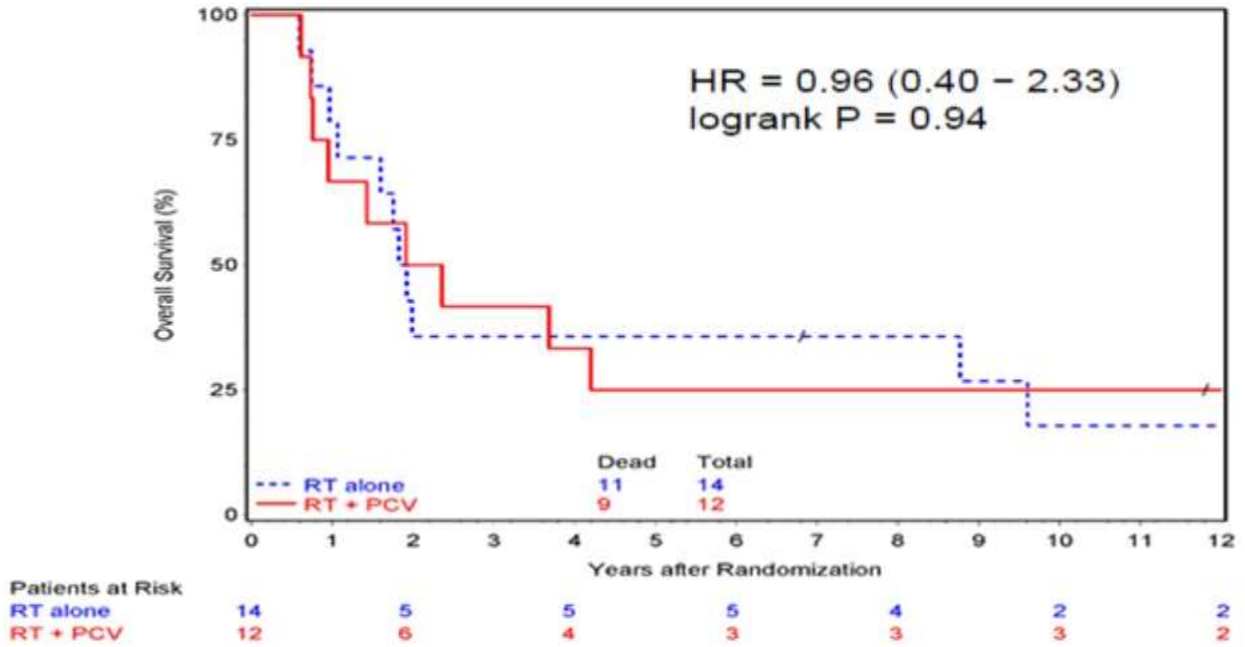
OS by Molecular Sub-groups and Tx

IDH wt



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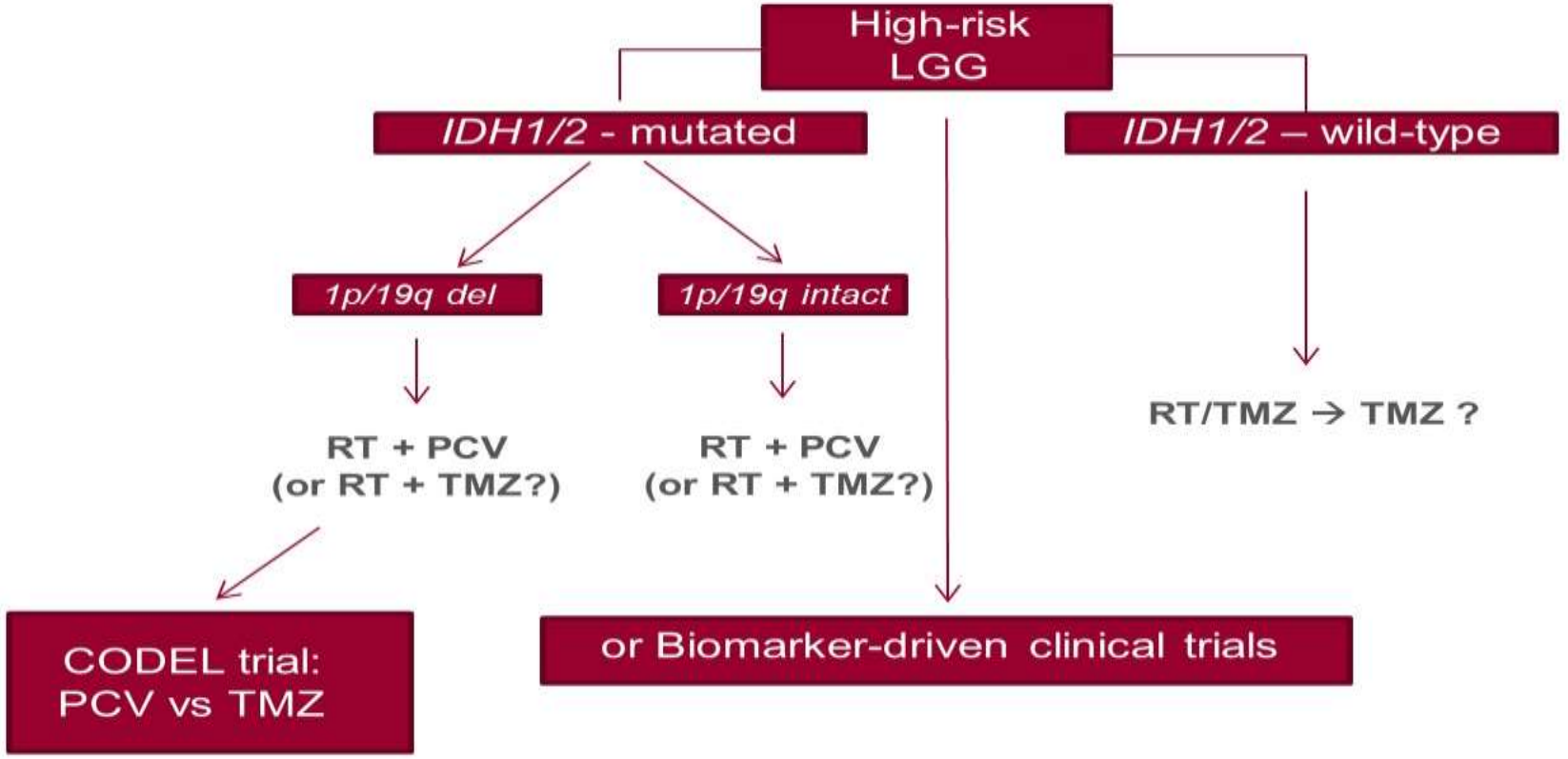
Precision Medicine for LGG Patients



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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

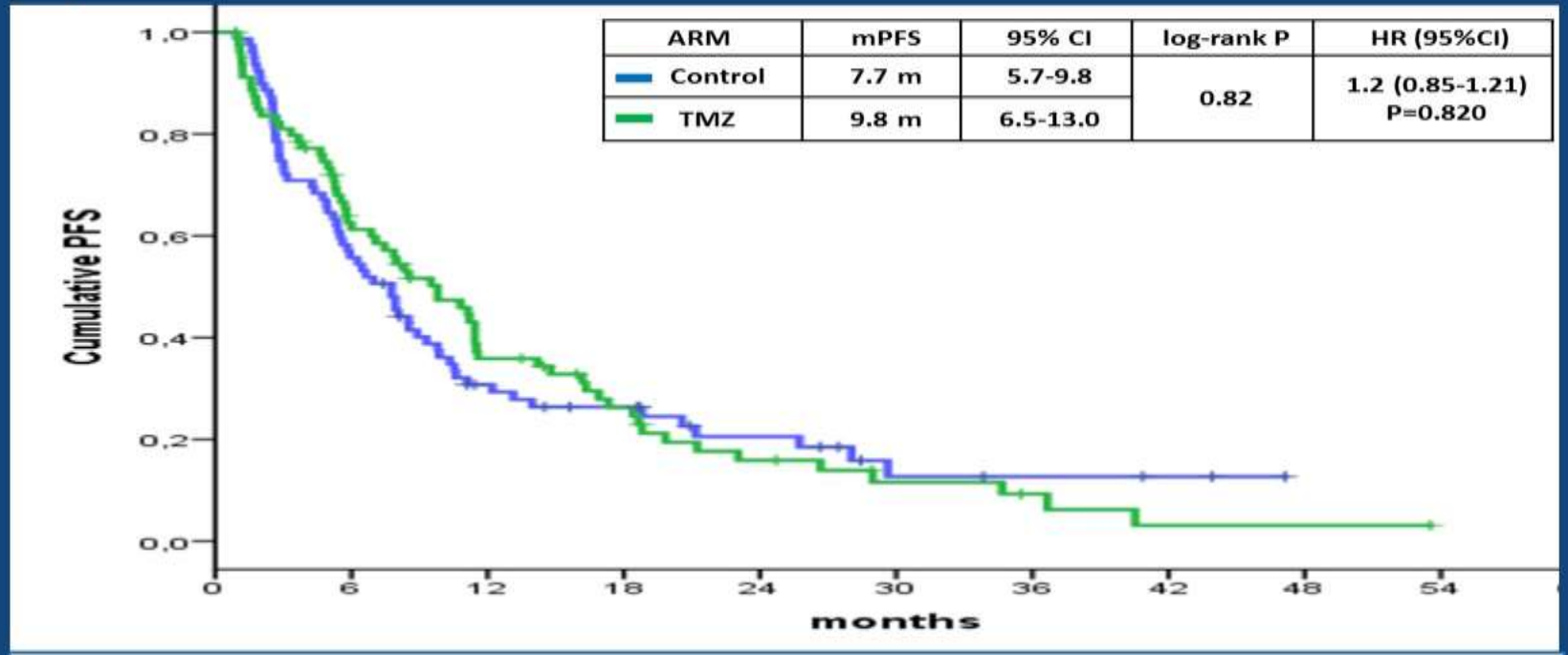
Primary endpoint: 6m-PFS

Median PFS (all pts)	ARM	6m-PFS
7.9 months 95% CI: 6.1-9.8	CONTROL	**55.7%** 95%CI 44.7-66.7
	TMZ	**62.5%** 95% CI 51.9-73.1

Median follow-up: 15.6 months
Pts with documented progression: 128/159 (80.5%)
Deaths: 92/159 (57.9%)

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

Multivariate Cox analysis of PFS

Variable		HR	95% CI	P
Treatment arm	Control	1.029	0.72-1.46	0.871
MGMT status	Met	0.606	0.41-0.88	0.009
Residual disease	No	0.655	0.45-0.94	0.023

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.

Health-related quality of life evaluation in the REGOMA trial: a randomized, phase II clinical trial analyzing regorafenib activity in relapsed glioblastoma patients

Giuseppe Lombardi [1], Paola Del Bianco [2], Alba Ariela Brandes [3], Marica Eoli [4], Roberta Rudà[5], Toni Ibrahim[6], Ivan Lolli MD[7], Andrea Pace[8], Bruno Daniele[9], Francesco Pasqualetti[10], Simona Rizzato[11], Eleonora Bergo[1], Mario Caccese[1], Marta Padovan[1], Riccardo Soffietti [5], Gian Luca De Salvo[2], Vittorina Zagonel [1]

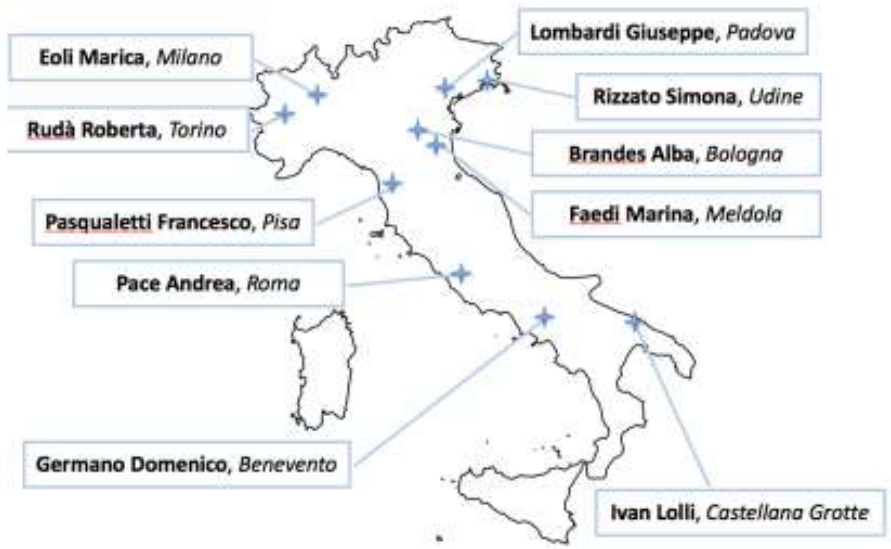
[1]Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV - IRCCS, Padova, Italy; [2]Clinical Research Unit, Veneto Institute of Oncology IOV - IRCCS, Padova, Italy; [3]Medical Oncology Department, AUSL-IRCCS Scienze Neurologiche, Bologna, Italy; [4]Molecolar Neuro-Oncology Unit, Besta Institute, Milano, Italy; [5]Department of Neuro-Oncology, University of Turin and City of Health and Science Hospital, Torino, Italy;[6]Medical Oncology Unit, IRST-IRCCS, Meldola, Italy;[7]Medical Oncology Unit-IRCCS Saverio de Bellis, Castellana Grotte, Bari, Italy; [8]Neuroncology Unit, Regina Elena Cancer Institue-IRCCS, Roma, Italy;[9] Medical Oncology Unit, A.O.G. Rummo, Benevento, Italy[10]Radiotherapy Unit, Azienda Ospedaliera Universitaria, Pisa, Italy;[11]Department of Oncology, Azienda Sanitaria - Universitaria Integrata, Udine, Italy

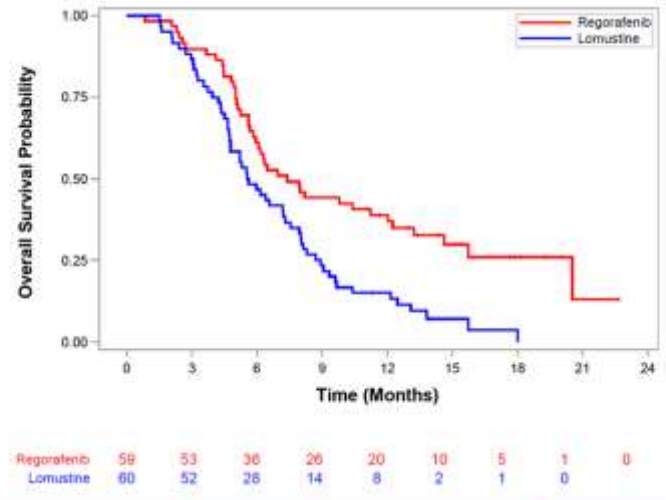
Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial

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

Acknowledgements

- **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**





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)		

Lancet Oncology 2019

Quality of Life

Methods

- ✓ HRQoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and brain module (QLQ-BN20) administered before any MRI assessments, every 8 weeks (+/- 2 weeks) until disease progression.

- ✓ Mixed-effect linear models were fitted for each of the HRQOL domain to examine the change over progression-free time within and between arms. The models included the time of questionnaire assessment, the treatment group and their interaction, as fixed effects, and a compound symmetry covariance structure for the random effects.

- ✓ Differences of at least 10 points were classified as a clinically meaningful change.

- ✓ To correct for multiple comparisons and to avoid type I error, the level of significance was set at P=0.01 (2-sided).

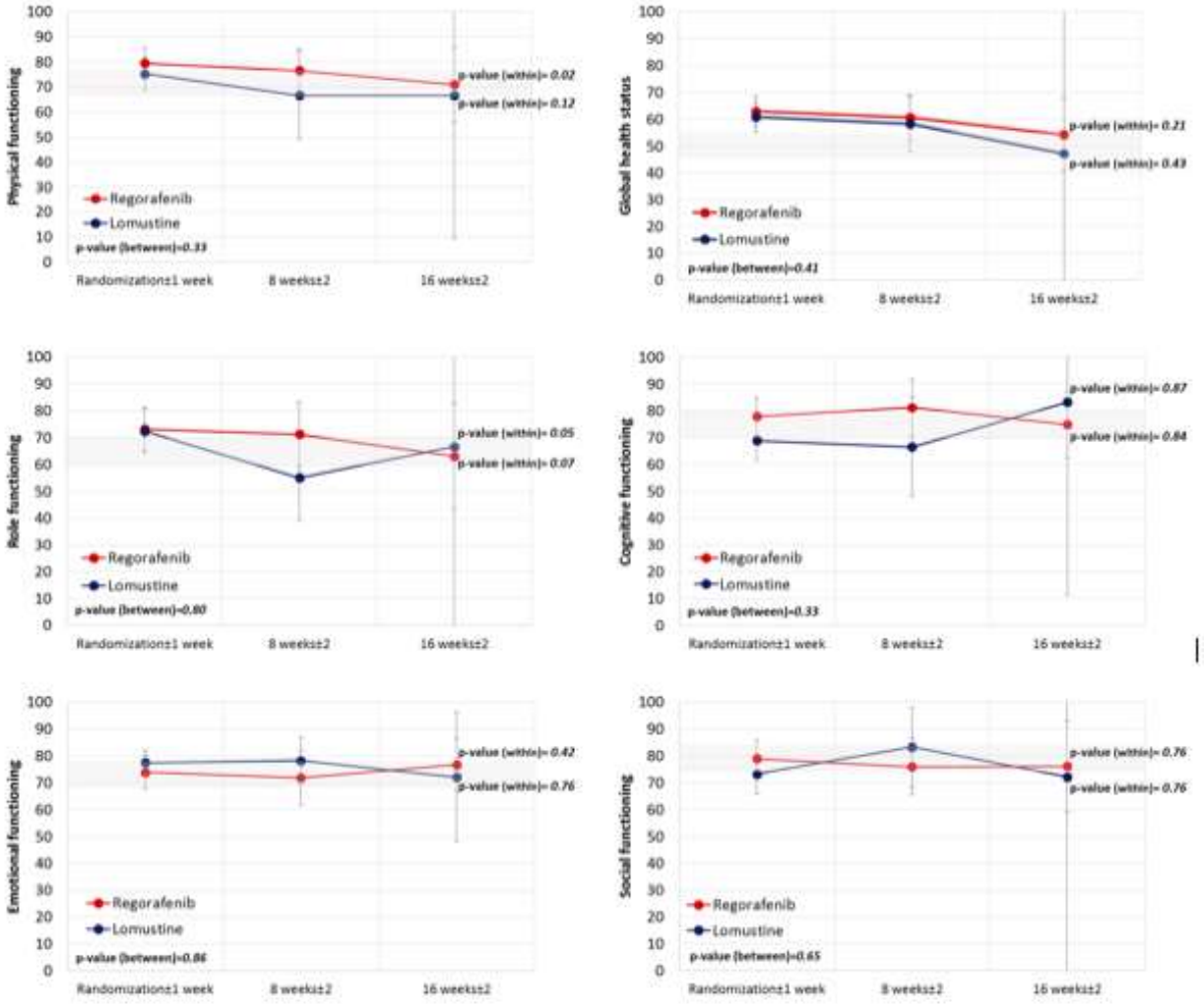
Quality of Life

Compliance

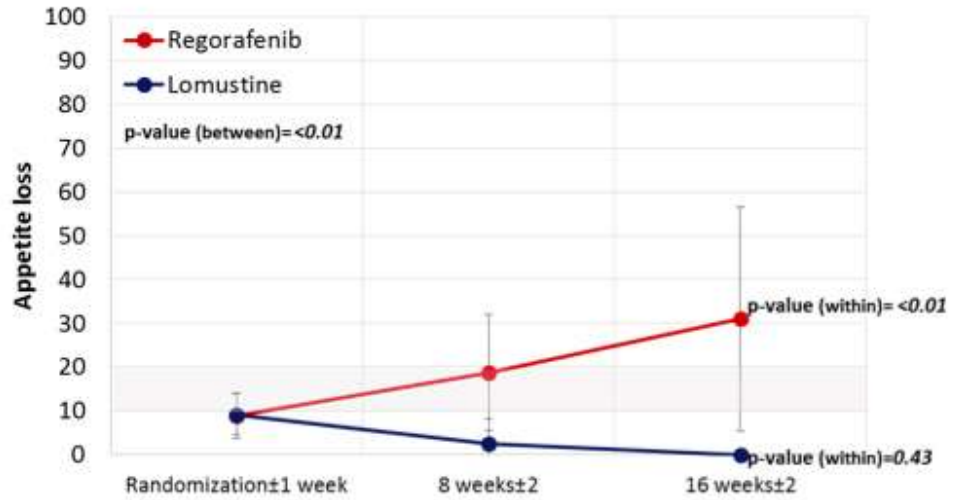
	Baseline	T1	T2	T3	T4	T5	T6	T7	T8
REGORAFENIB									
Received	56	25	14	9	6	5	3	3	3
Expected	58	25	15	11	7	6	5	5	3
% compliance	96.6%	100.0%	93.3%	81.8%	85.7%	83.3%	60.0%	60.0%	100.0%
LOMUSTINE									
Received	58	13	3	1	1	2	1	1	
Expected	59	13	4	3	2	2	1	1	
% compliance	98.3%	100.0%	75.0%	33.3%	50.0%	100.0%	100.0%	100.0%	
OVERALL									
Received	114	38	17	10	7	7	4	4	3
Expected	117	38	19	14	9	8	6	6	3
% compliance	97.4%	100.0%	89.5%	71.4%	77.8%	87.5%	66.7%	66.7%	100.0%

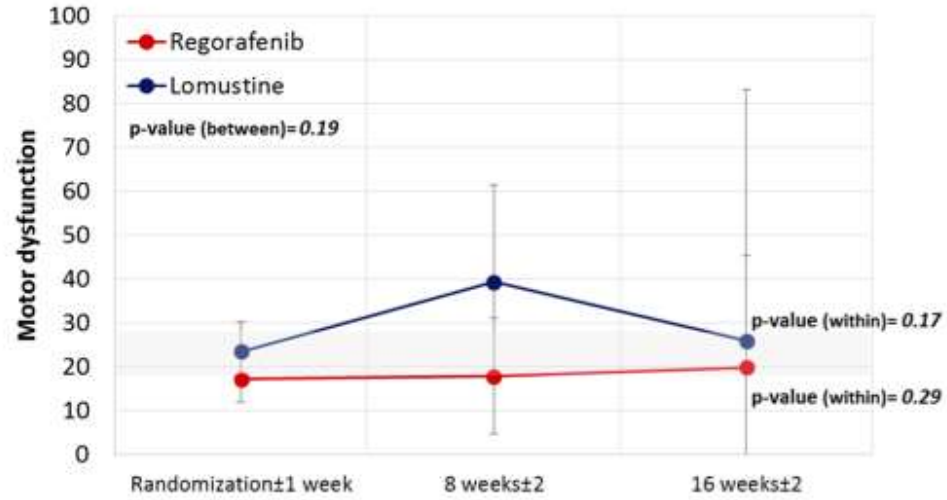
No statistically significant differences were observed in any generic or cancer specific domain during treatment in the REG and LOM arms, or between the two arms, except for the appetite loss scale which was significantly worse in PTS treated with REG (Global mean 14.7 (SD=28.6) vs 7.6 (SD=16.0); p=0.0081).

Health-related Quality of Life (HRQOL) scores over time for functional scales. Data are presented as means together with their 95% confidence interval. Higher scores represent higher levels of functioning and higher HRQOL



Health-related Quality of Life (HRQOL) scores over time for symptom scales. Data are presented as means together with their 95% confidence interval. Higher scores represent higher levels of symptomatology or problems





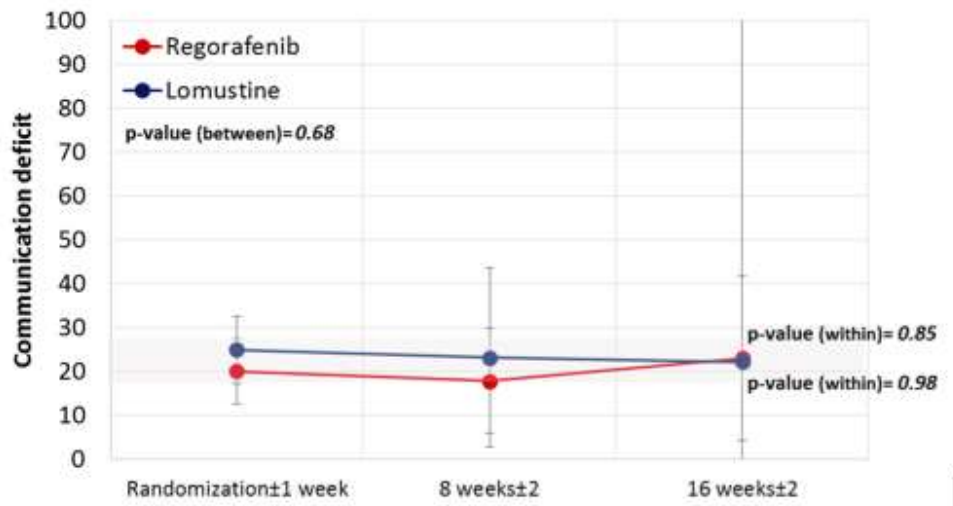
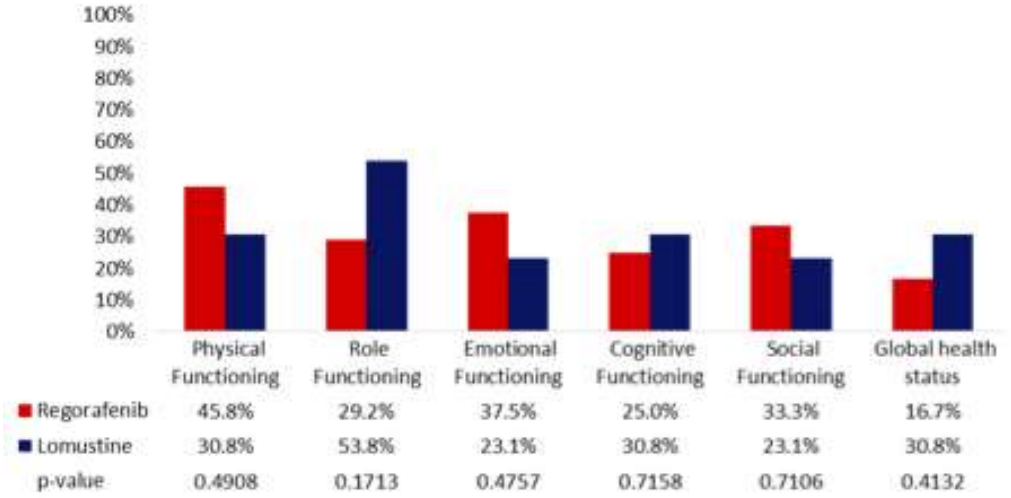
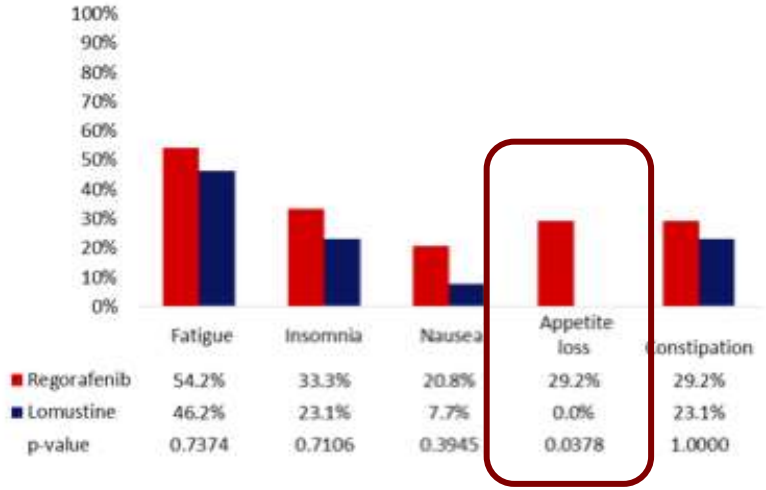
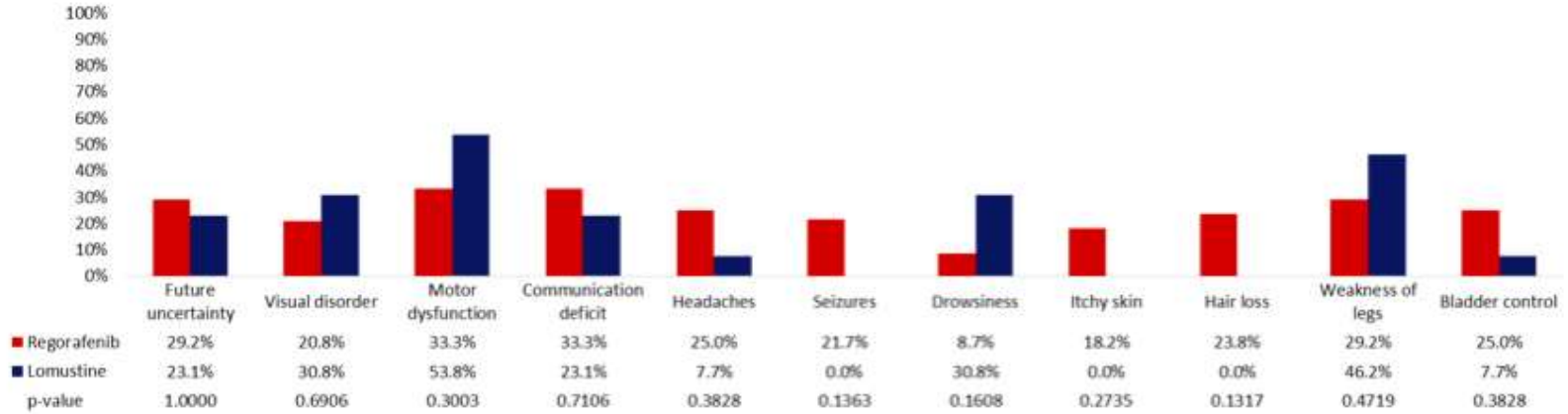


Figure 1. Proportion of patients with a clinically meaningful deterioration at first RMS assessment compared with baseline levels.







The rate of pts with a clinically meaningful worsening for appetite loss was not statistically different between the two arms (9 out of 24 and 0 out of 13 in the REG and LOM arm, respectively; p=0.02)

Trabectedin for recurrent WHO grade II or III meningioma: a randomized phase II study of the EORTC Brain Tumor Group (EORTC-1320-BTG)

Matthias Preusser*, Antonio Silvani, Emilie Le Rhun, Riccardo Soffietti , Guiseppe Lombardi, Juan Manuel Sepulveda, Petter Brandal, Ronald Beaney, Aice Bonneville-Levard, Veronique Lorgis, Elodie Vauleon, Jacoline Bromberg, Sara Erridge, Alison Cameron, Christine Marosi, Vassilis Golfinopoulos, Thierry Gorlia, Michael Weller, Wolfgang Wick

* Medical University of Vienna

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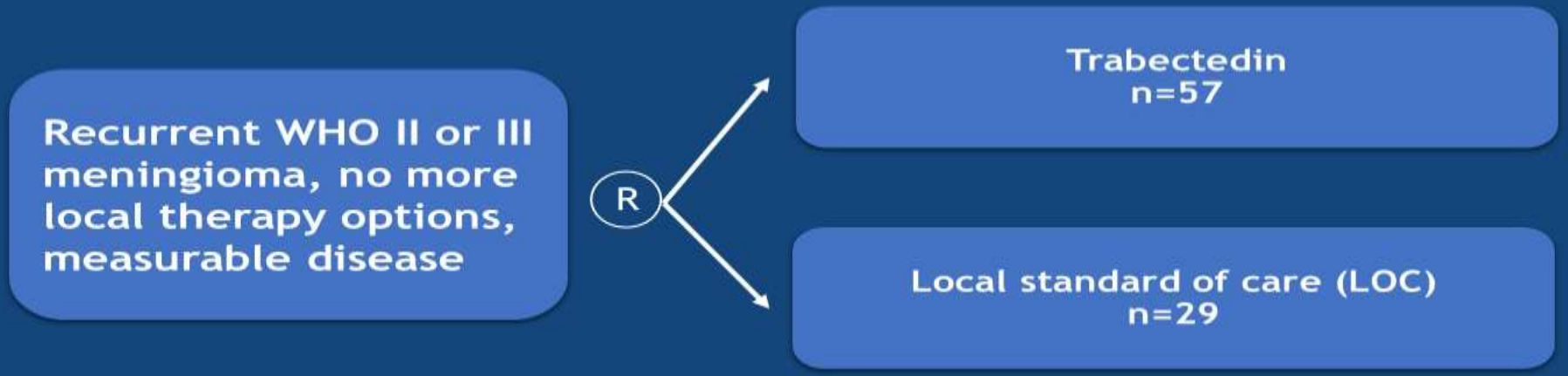
PRESENTED BY: Matthias Preusser, MD

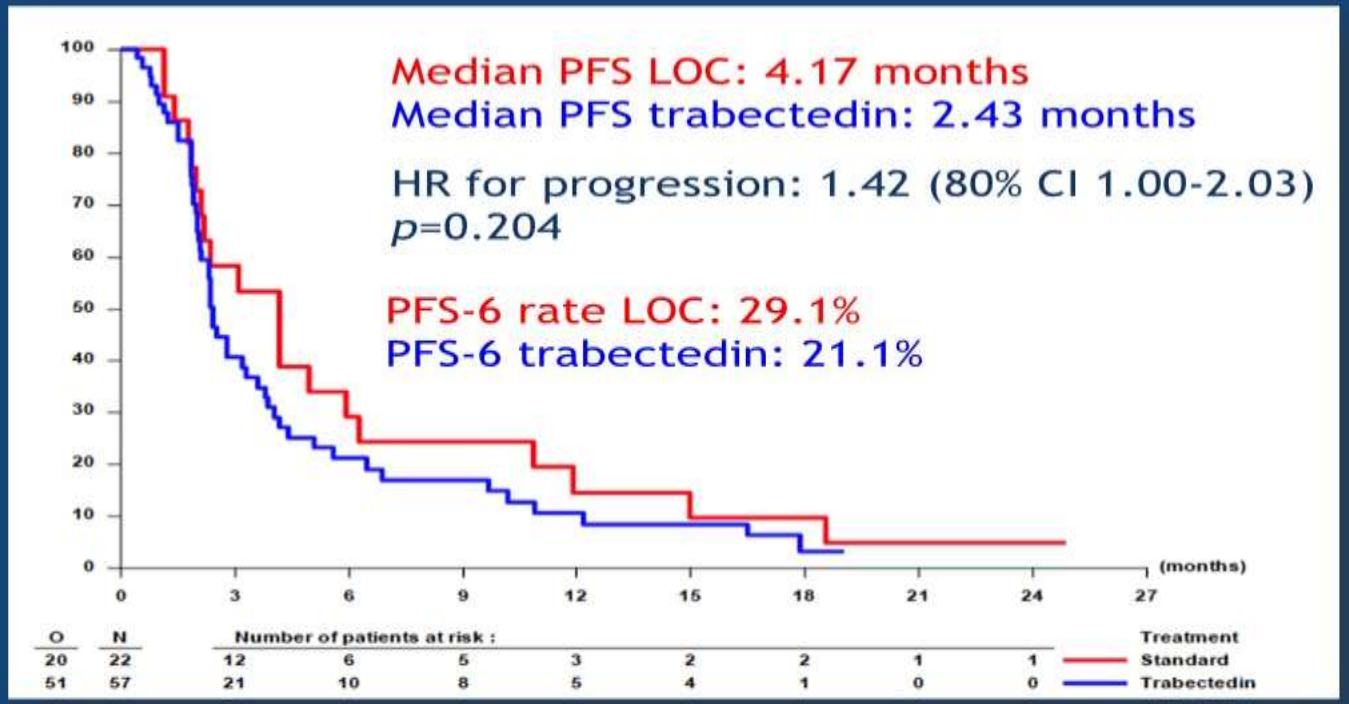
Study design



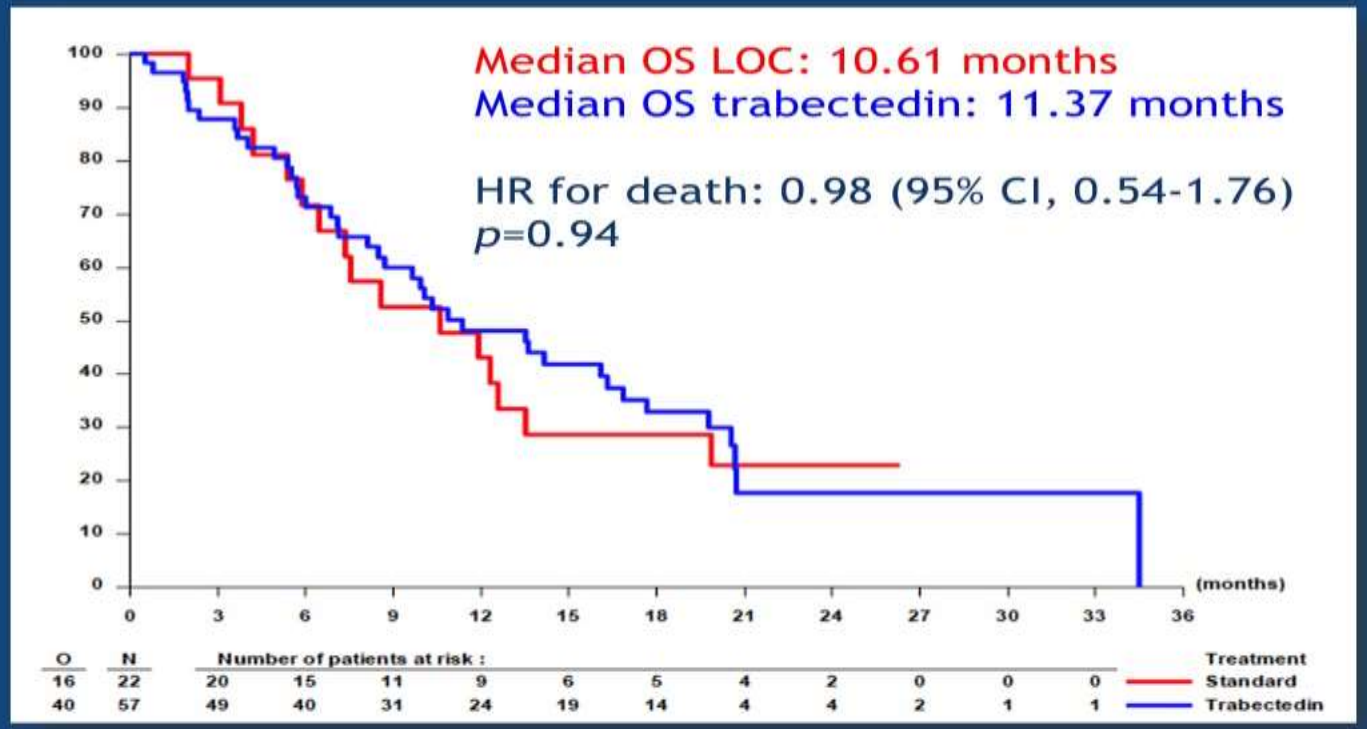
Primary endpoint: Progression-free survival (modified Macdonald criteria)

Secondary endpoints: Response rate, OS, safety, HRQoL

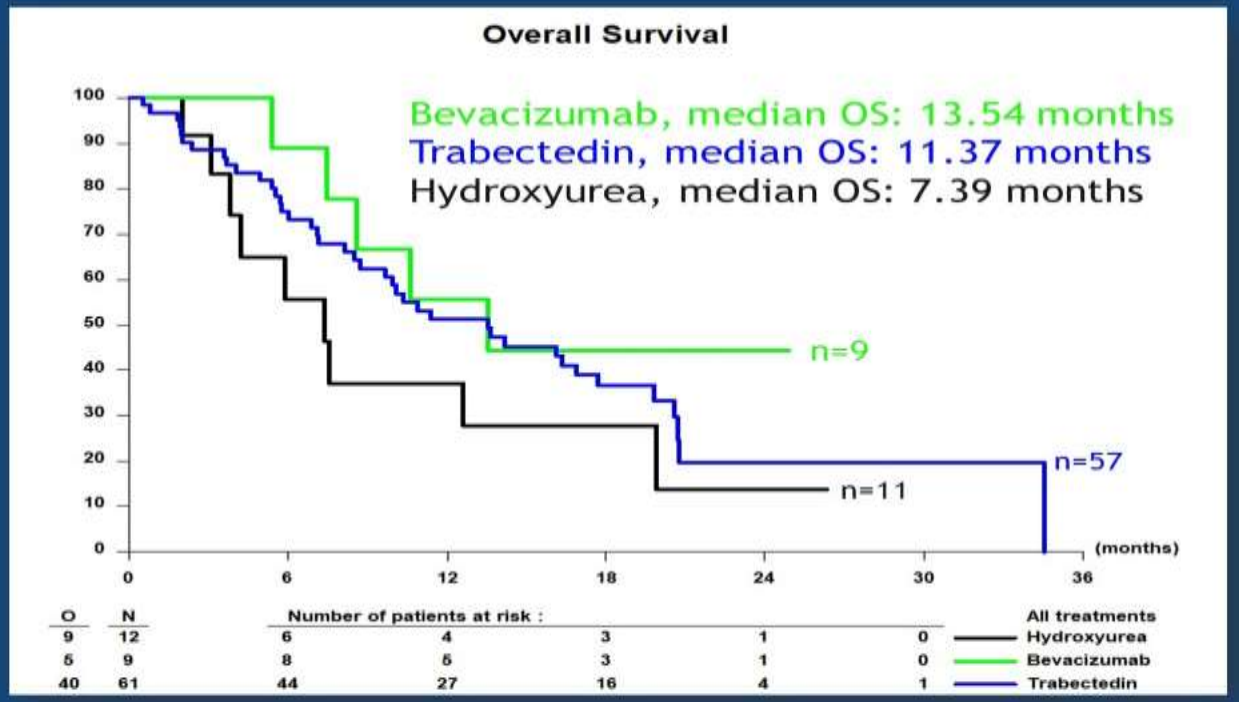
Primary endpoint: PFS



Secondary endpoint: OS



Exploratory analysis: OS by LOC treatment



Adjuvant chemotherapy improves survival in average-risk adult medulloblastoma patients: long term results

Giuseppe Lamberti[1], Enrico Franceschi[1], Alicia Tosoni[1], Santino Minichillo[1], Monica Di Battista[1], Alexandro Paccapelo A[1], Carmelo Sturiale[2], Maurizio Mascarin[3], Barbara Masotto[4], Lorenzo Volpin[5], Stefania Bartolini [1], Felice Giangaspero[6,7], Alba A Brandes[1]

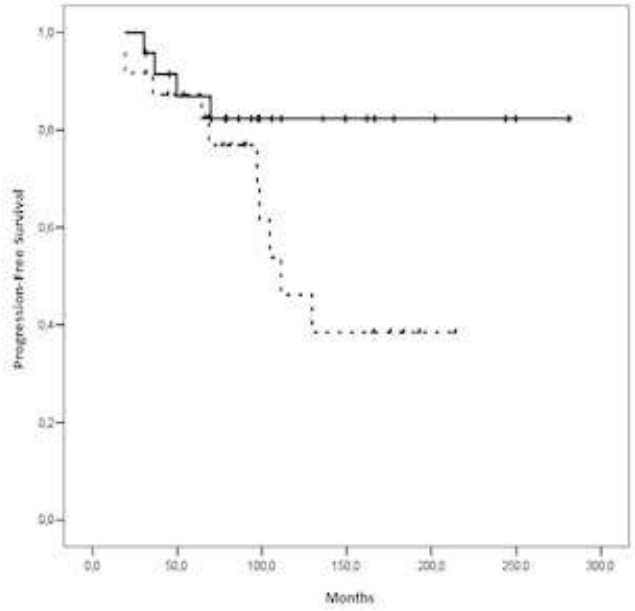
[1] Department of Medical Oncology, Bellaria Hospital, Azienda USL - IRCCS Institute of Neurological Sciences, Bologna, Italy; [2] Department of Neurosurgery, Bellaria Hospital, Azienda USL - IRCCS Institute of Neurological Sciences, Bologna, Italy; [3] Department of Pediatric Radiotherapy, CRO, Aviano, Italy; [4] Neurosurgery Department, University Hospital of Verona, Borgo Trento, Verona, Italy; [5] Department of Neuroscience and Neurosurgery, San Bortolo Hospital, Vicenza, Italy; [6] Università La Sapienza - Rome; [7] IRCCS Neuromed - Pozzilli, Rome & Pozzilli, Italy

Methods

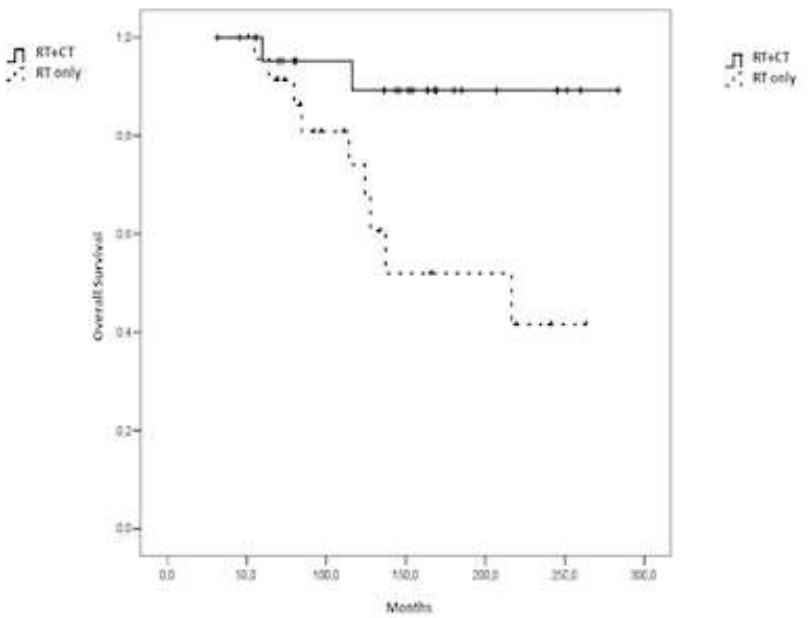
Patients ≥16 years of age, with histologically confirmed medulloblastoma and undergone adjuvant radiotherapy with or without chemotherapy were included. Average-risk was defined as postsurgical residual ≤ 1.5 cm^2 and no metastatic disease (M0) according to Chang's classification.

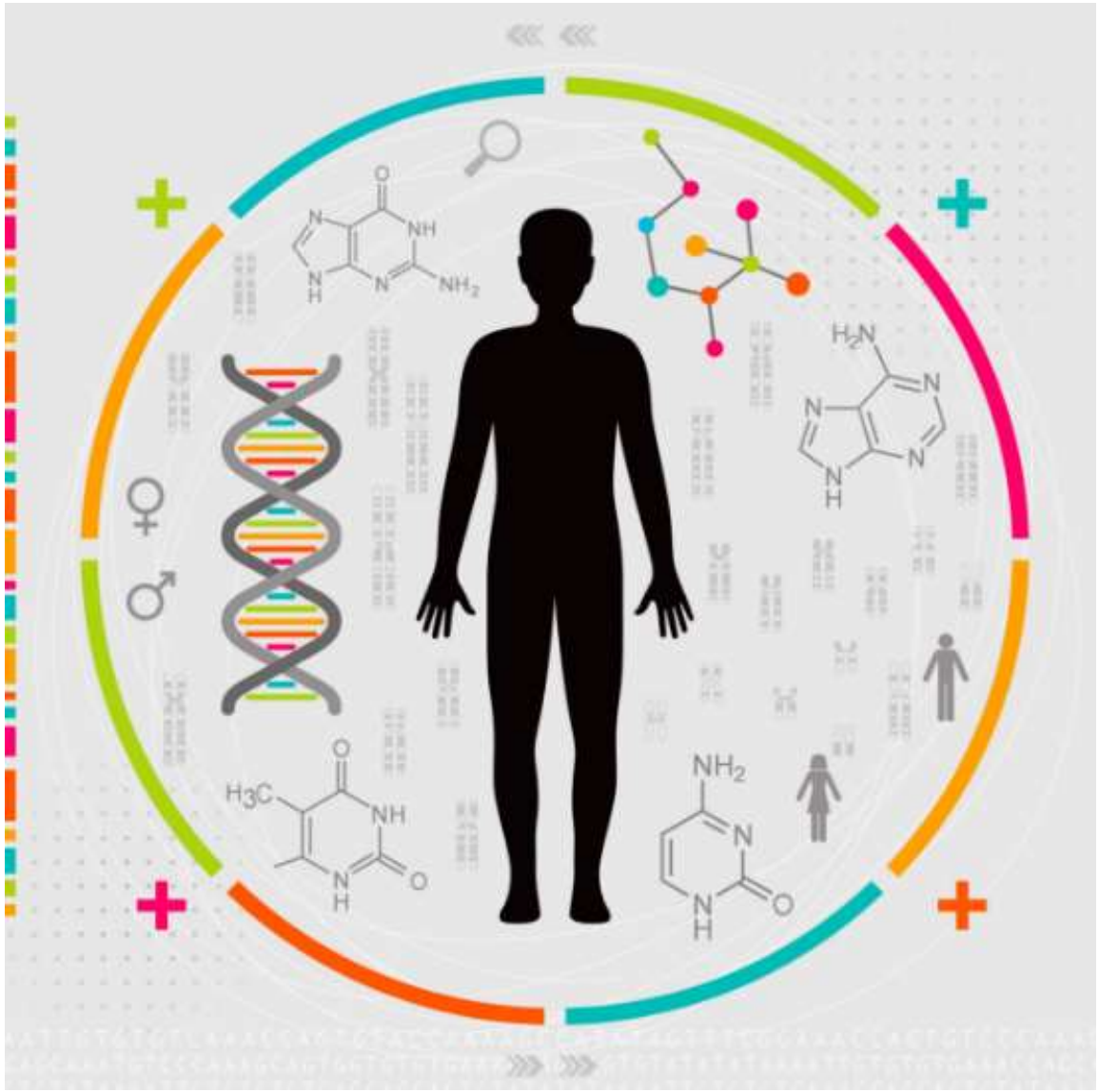
Variable	Chemotheray	No chemotherapy
Number of patients	24 (50%)	24 (50%)
Age, mean (range)	29 (16 - 61)	31 (16 - 57)
Male (%)	13 (54.2%)	13 (54.2%)
Histology subtype		
Classic	7 (29.2%)	8 (33.3%)
Desmoplastic	6 (25.0%)	9 (37.5%)
Extensive nodularity	3 (12.5%)	2 (8.3%)
Large-Cell Anaplastic	1 (4.2%)	1 (4.2%)
Unknown	7 (29.2%)	4 (16.7%)

Progression-free survival according to treatment



Overall survival according to treatment





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.

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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.

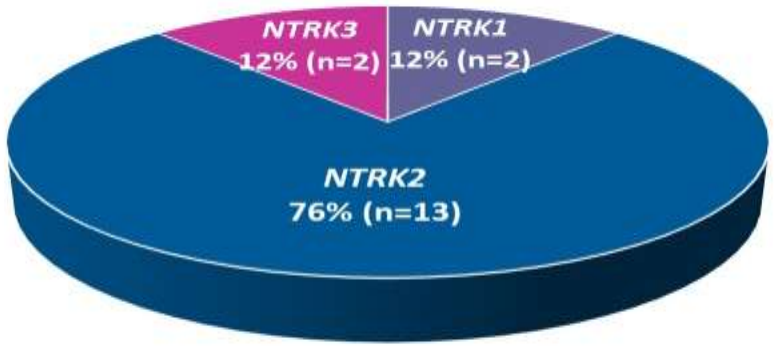
Presented By Alexander Drilon at 2019 ASCO Annual Meeting

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.

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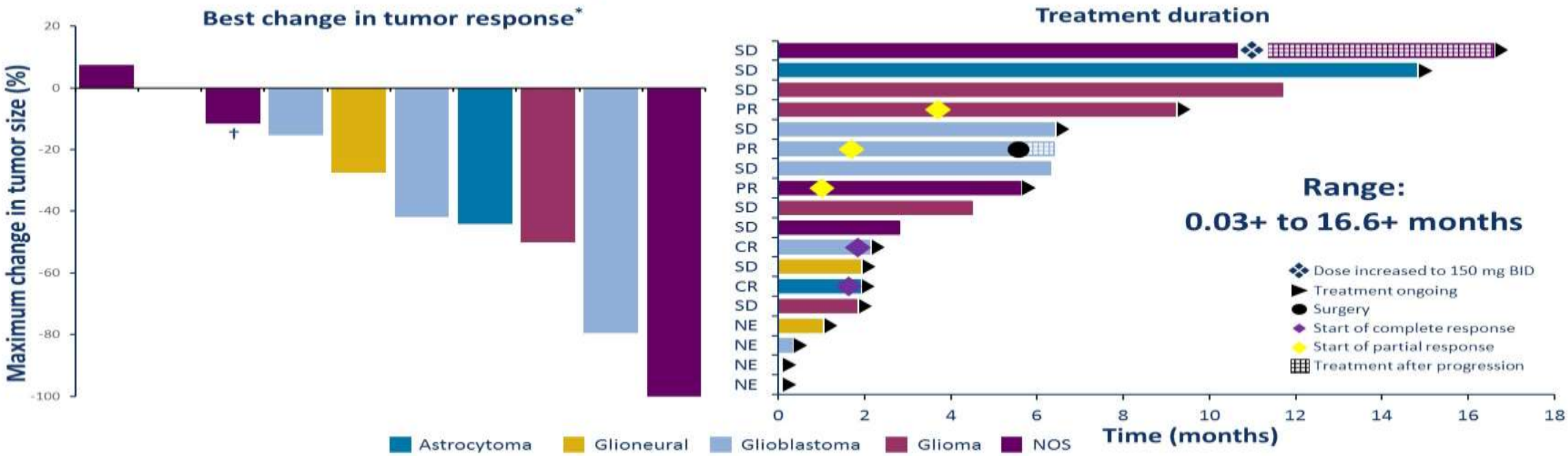
Larotrectinib in TRK Fusion-Positive Primary CNS Tumors: Response and Treatment Duration



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.

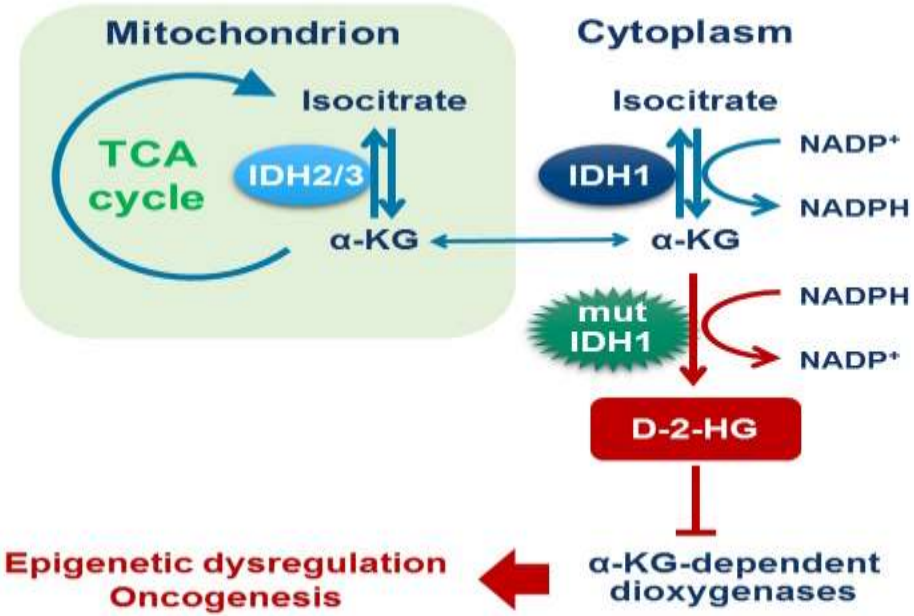
Phase I study of a brain penetrant mutant IDH1 inhibitor DS-1001b in patients with recurrent or progressive IDH1 mutant gliomas

Atsushi Natsume, MD, PhD[1], Toshihiko Wakabayashi, MD, PhD[1], Yasuji Miyakita, MD, PhD[2], Yoshitaka Narita, MD, PhD[2], Yohei Mineharu, MD, PhD[3], Yoshiki Arakawa, MD, PhD[3], Fumiyuki Yamasaki, MD, PhD[4], Kazuhiko Sugiyama, MD, PhD[4], Nobuhiro Hata, MD, PhD[5], Yoshihiro Muragaki, MD, PhD[6], Ryo Nishikawa, MD, PhD[7], Naoki Shinojima, MD, PhD[8], Toshihiro Kumabe, MD, PhD[9], Ryuta Saito, MD, PhD[10], Kazumi Ito, DVM, PhD[11], Masaya Tachibana, PhD[11], Yasuyuki Kakurai, PhD[11], Soichiro Nishijima, MS[11], Hiroshi Tsubouchi, MS[11]

[1]Nagoya University School of Medicine, Nagoya, Japan; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Kyoto University Graduate School of Medicine, Kyoto, Japan; [4]Hiroshima University Hospital, Hiroshima, Japan; [5]Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [6]Graduate School of Medicine, Tokyo Women's Medical University, Tokyo, Japan; [7]Saitama Medical University International Medical Center, Hidaka, Japan; [8]Kumamoto University Hospital, Kumamoto, Japan; [9]Kitasato University School of Medicine, Sagamihara, Japan; [10]Tohoku University Graduate School of Medicine, Sendai, Japan; [11]Daiichi Sankyo Co., Ltd., Tokyo, Japan

Isocitrate Dehydrogenase (IDH) 1 Mutations in Gliomas

- Approximately 70–80% of WHO grade II/III gliomas harbor *IDH1* mutations[1]
- Mutant IDH1 produces the oncometabolite D-2-HG, accumulation of which leads to oncogenesis and subsequent clonal expansion[2]
- In gliomas, the *IDH1* mutation is a "trunk mutation" and is considered as a promising therapeutic target
  - It occurs early in gliomagenesis[1]
  - It is ubiquitous within the tumor mass and persists throughout progression[1]



2-HG = 2-hydroxyglutarate; α-KG = alpha-ketoglutarate, IDH = isocitrate dehydrogenase; NADP+/NADPH = nicotinamide adenine dinucleotide phosphate; TCA = tricarboxylic acid.

1. Suzuki H, et al. *Nat Genet*. 2015;47:458-68.
2. Cairns RA, et al. *Cancer Discov*. 2013;3:730-41.

Safety

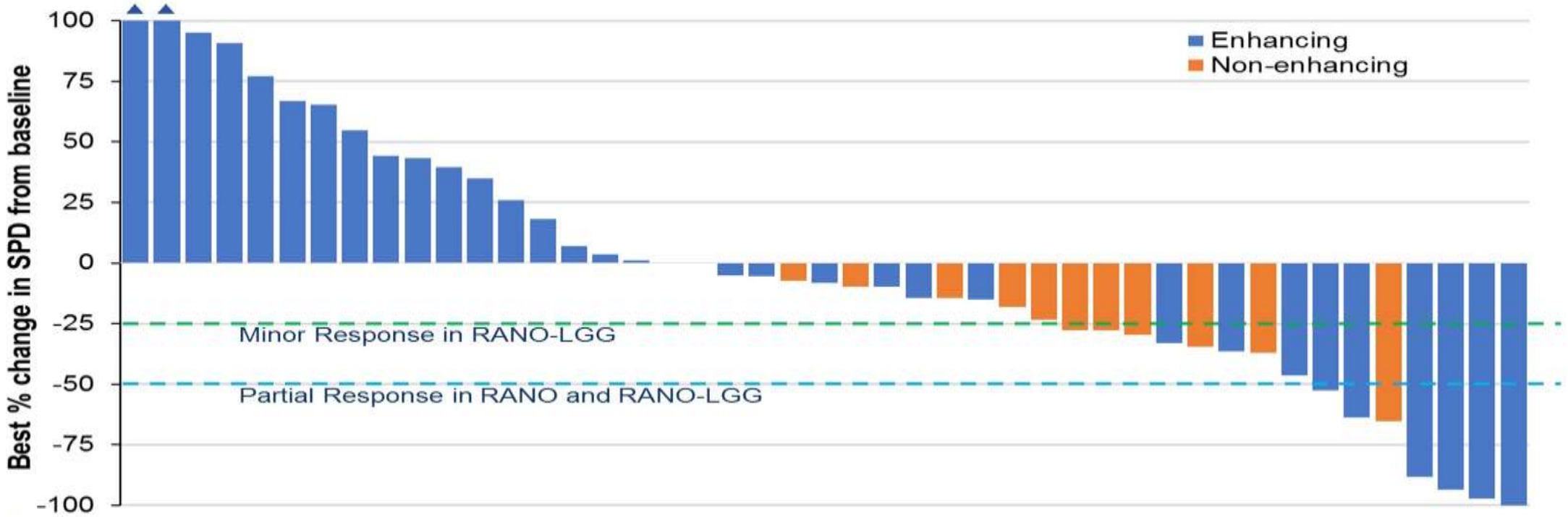
AEs occurring in ≥10% of patients, regardless of causality

Preferred Term, n (%)[a]	All Grades (N=47)	Grade ≥3 (N=47)
Skin hyperpigmentation	25 (53.2)	0
Diarrhea	22 (46.8)	2 (4.3)
Pruritus	14 (29.8)	0
Alopecia	12 (25.5)	0
Arthralgia	12 (25.5)	0
Nausea	12 (25.5)	0
Headache	10 (21.3)	0
Rash	10 (21.3)	0
Dry skin	9 (19.1)	0
Vomiting	9 (19.1)	0
Back pain	7 (14.9)	0
Neutrophil count decreased	7 (14.9)	6 (12.8)
Feces soft	6 (12.8)	0
Nasopharyngitis	6 (12.8)	0
Decreased appetite	5 (10.6)	0

- One DLT was observed at a dose of 1000 mg bid
  - Grade 3 WBC count decreased
- MTD was not reached
- No drug-related serious AEs
- 19 patients (40%) experienced at least one AE of Grade 3
  - No Grade 4 or 5 AEs were reported

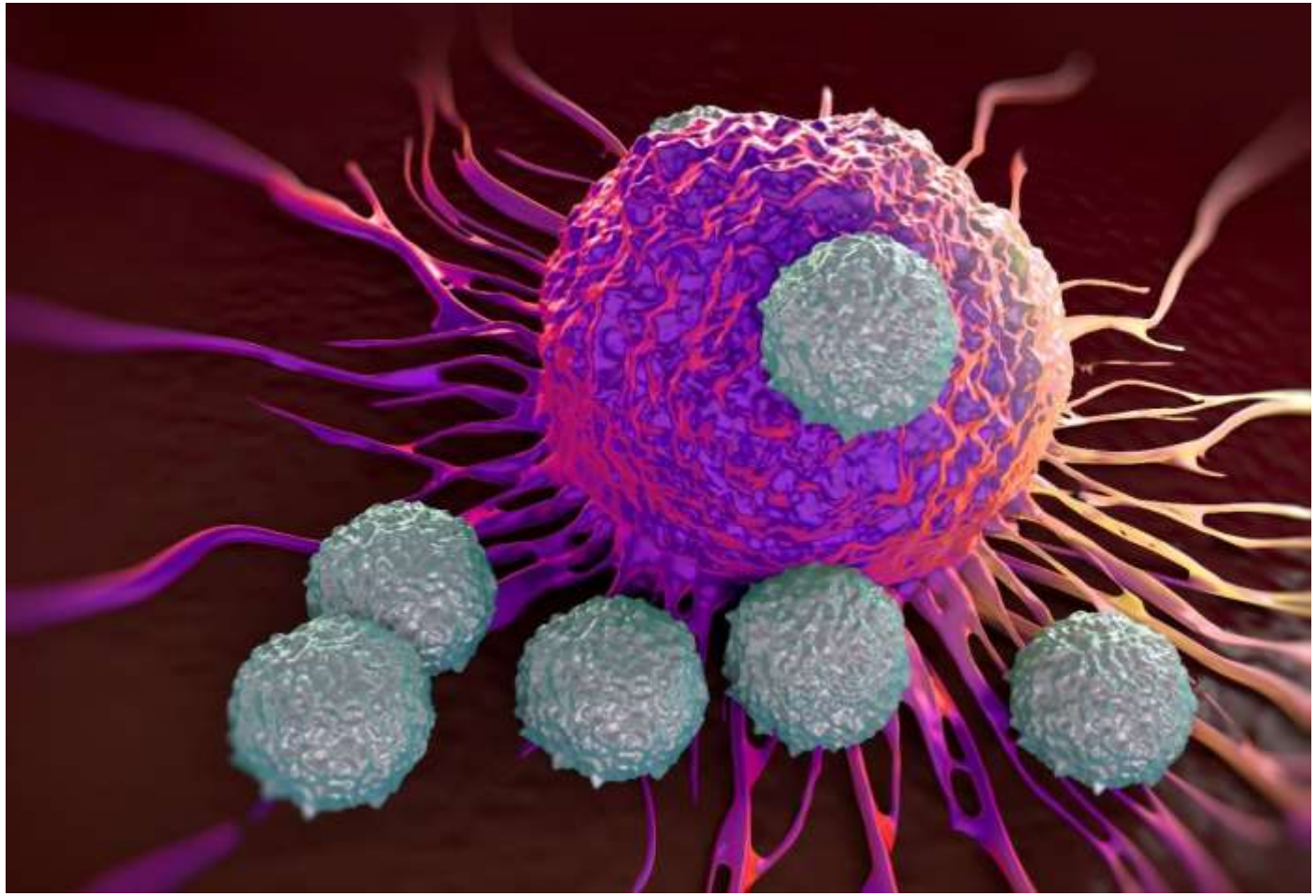
Data cutoff was on May 7, 2019.
[a] A patient was counted once if the same AE was reported more than once.
AE = adverse event; DLT = dose-limiting toxicity;
MTD = maximum tolerated dose; WBC = white blood cell.

Best Percent Change in SPD from Baseline



Data cutoff was on May 7, 2019.
Enhancing gliomas were assessed by RANO criteria, and non-enhancing gliomas were assessed by RANO-LGG criteria.
▲ These two patients showed change over 100% (188% and 155%).
LGG = low-grade gliomas; RANO = Response Assessment in Neuro-Oncology; SPD = sum of the products of perpendicular diameters.

Presented By Atsushi Natsume at 2019 ASCO Annual Meeting



Immunotherapy

SurVaxM with standard therapy in newly diagnosed glioblastoma: Phase II trial update.

Manmeet S. Ahluwalia[1], David A. Reardon[2], Ajay P Abad[6], William T. Curry[3], Eric T. Wong[4], Ahmed Belal[6], Jingxin Qiu[6], Kathleen Mogensen[5,6], Cathy Schilero[1], Alan Hutson[6], Danielle Casucci[6], Laszlo Mechtler[5,6], Erik J Uhlmann[4], Michael J Ciesielski[6,7], Robert Fenstermaker[6,7]

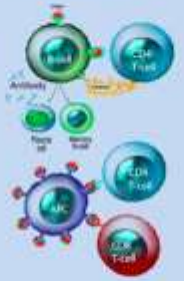
[1]Burkhardt Brain Tumor NeuroOncology Center, Neurological Institute, Taussig Center Institute, Cleveland Clinic, Cleveland, OH; [2]Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; [3]Massachusetts General Hospital, Boston, MA; [4]Beth Israel Deaconess Medical Center, Boston, MA; [5]Dent Neurologic Institute, Buffalo, NY; [6]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [7]MimiVax, LLC, Buffalo, NY

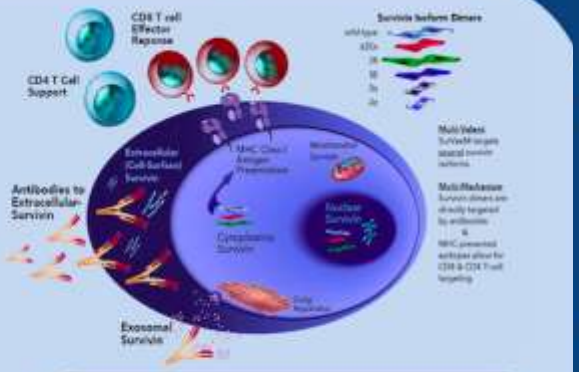
Drug – SurVaxM (DRU-2017-5947)

- Mimic of "Survivin" an Inhibitor of Apoptosis (IAP) Protein

- 15 amino acid novel, synthetic long peptide (SLP)

- High-Density Peptide Delivery conjugated to Keyhole Limpet Hemocyanin (KLH)

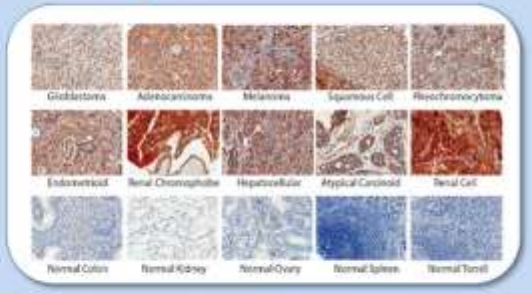




MOA

- Circumvents immune tolerance through activation of mid-affinity multi-clonal CD8 & CD4 T cells
- Multi-valent targeting of survivin in several isoforms & localizations
- Stimulates unique IgG recognition of cell surface survivin

Below, multi-clonal CD8 & CD4 T-cell epitopes contained within the 15AA SurVaxM peptide



above, immunohistochemistry of survivin expressing tumors and normal control tissues

Administration

- Cell-free subcutaneous administration
- 500µg SurVaxM in Montanide ISA 51 VG + 100µg GM-CSF,
- 1st dose after resection & chemoradiation, before adjuvant temozolomide
- 4 Biweekly doses; followed by every 12 week maintenance dosing

Trial Design

Primary Objective:

- To evaluate 6-month progression-free survival (PFS6) in patients with survivin positive newly diagnosed glioblastoma (nGBM) treated with SurVaxM and standard of care temozolomide.

Rationale for newly diagnosed glioblastoma:

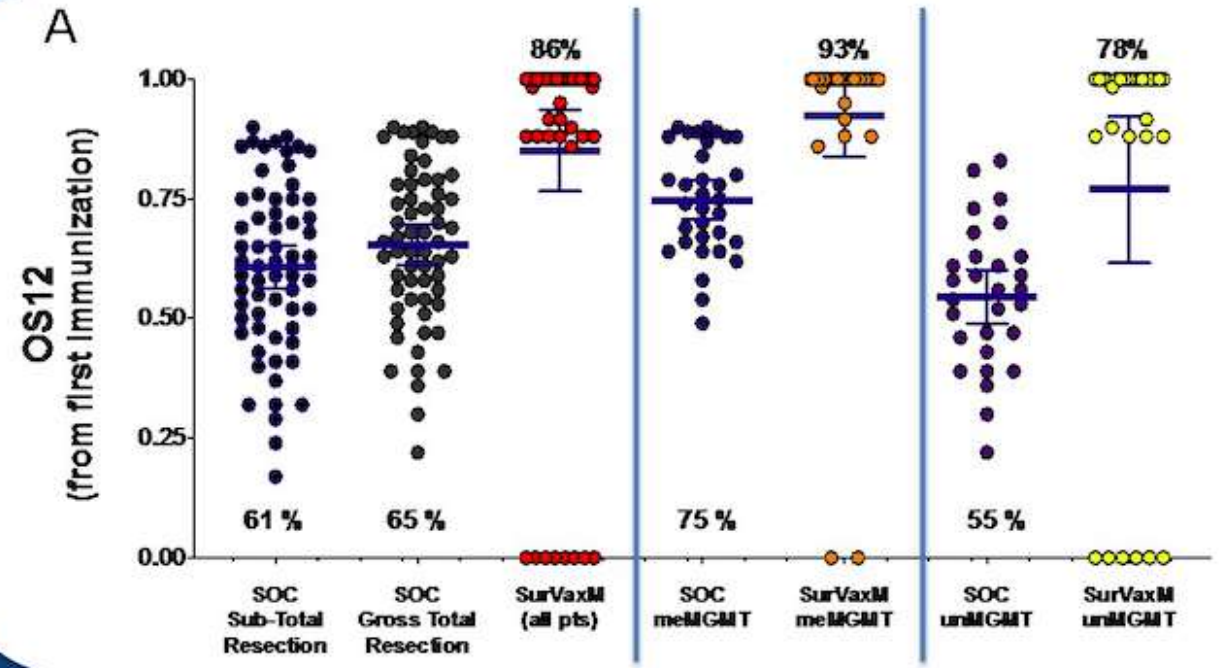
- Low immunosuppression post-tumor resection
- Window of opportunity (1 mo.) prior to adjuvant chemotherapy
- Over 90% of glioblastomas are survivin-positive

Trial Design:

- Single arm SurVaxM® (prime-boost) + adjuvant temozolomide
- Multi-center trial performed at Roswell Park, Cleveland Clinic, Dana-Farber, Mass General & Beth Israel Deaconess Hospital

measured from first immunization	mOS
SurVaxM	26.0 mos.
meMGMT	28.2 mos.
unMGMT	15.6 mos.
median follow-up	*18.7 mos.*

Historical Comparators



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

CHECKMATE 143

Patients (N = 369)
- First recurrence of GBM
- Prior 1L treatment with at least RT and TMZ

Randomized 1:1
- Stratified by measurable disease at baseline (yes/no)

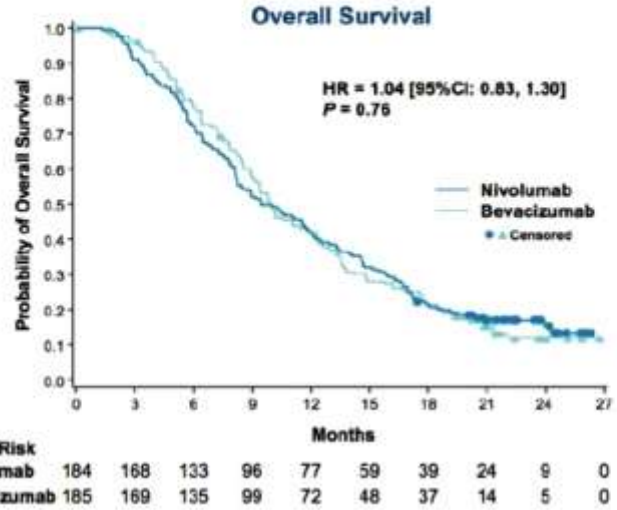
Nivolumab 3 mg/kg Q2W
n = 184

Bevacizumab 10 mg/kg Q2W
n = 185

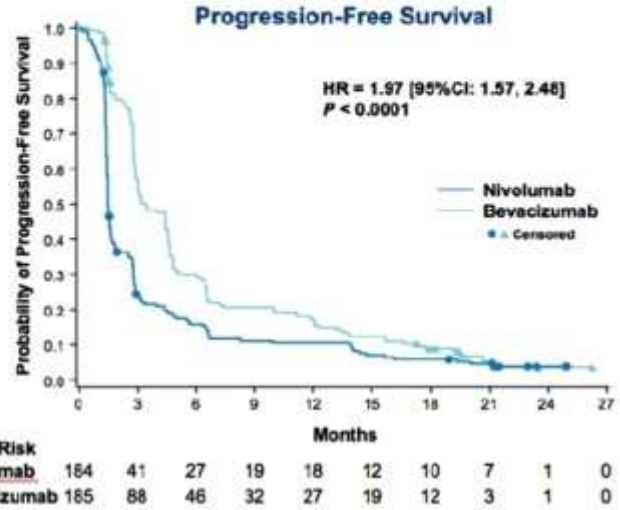
Treatment until:
- Confirmed progression
- Unacceptable toxicity
- Discontinuation due to other reason

Follow-up:
- Safety for ≥ 100 days
- Progression
- Survival every 3 months

	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]

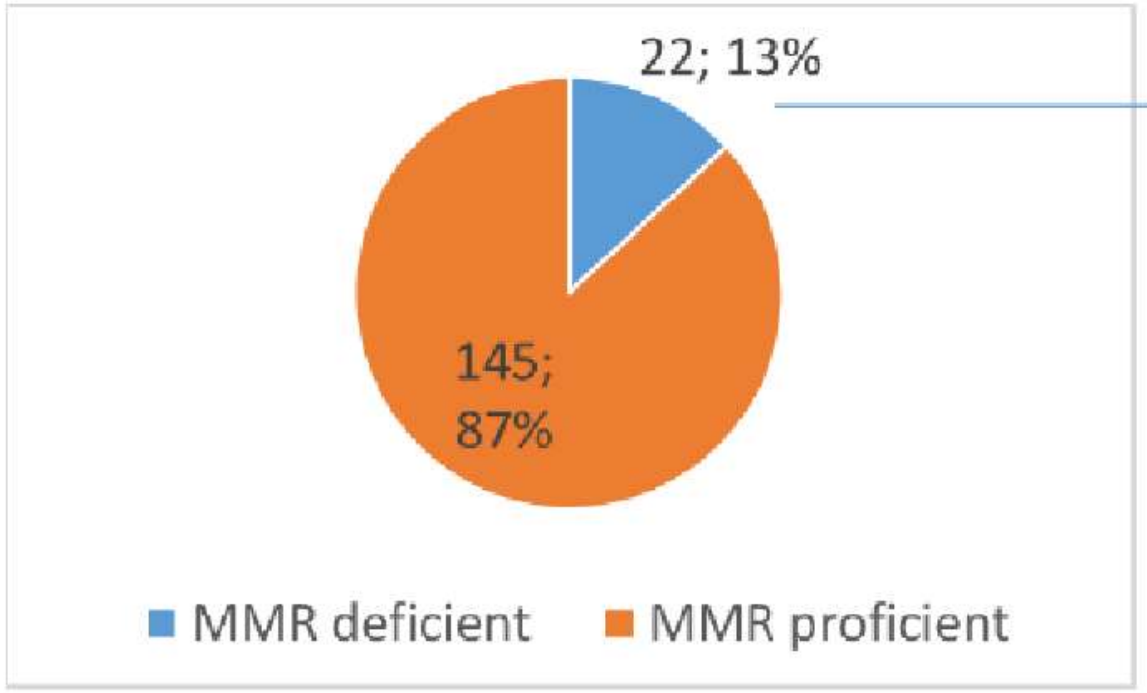


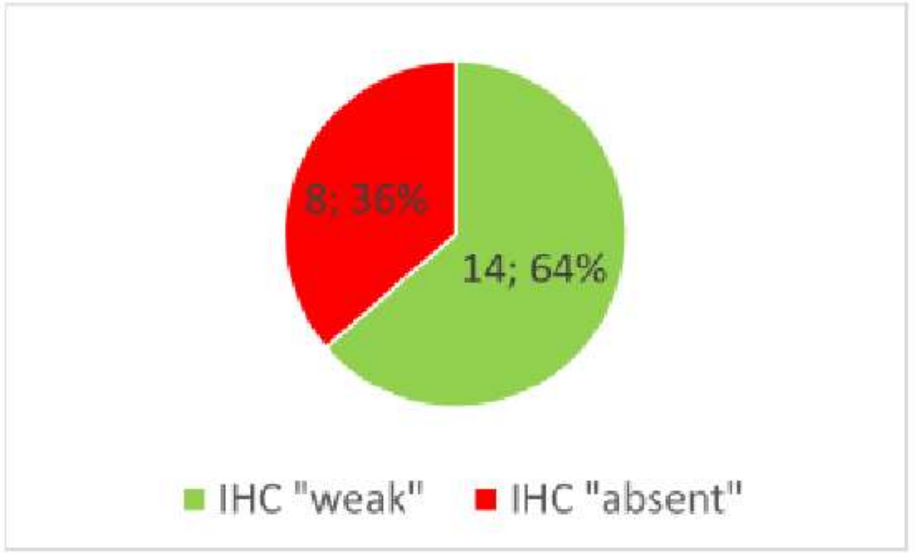
	Events, n	Median PFS [95% CI], months	12-Month PFS Rate [95% CI], months
Nivolumab	171	1.5 [1.5, 1.6]	10.5 [6.5, 15.5]
Bevacizumab	146	3.5 [2.9, 4.6]	17.4 [11.9, 23.7]

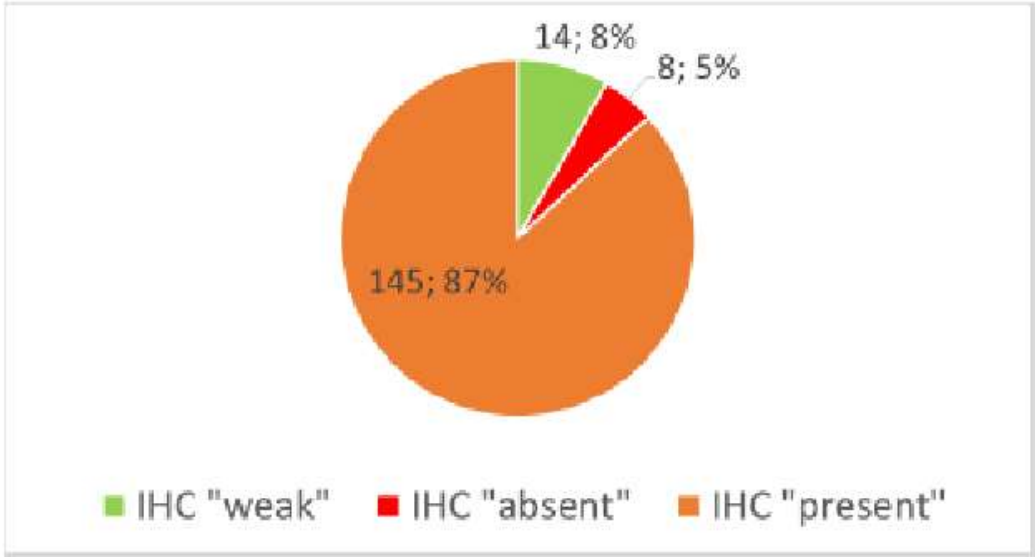


	Nivolumab n = 153[a]	Bevacizumab n = 156[a]
ORR, n (%) [95% CI]	12 (7.8) [4.1, 13.3]	36 (23.1) [16.7, 30.5]
BOR, n (%)		
CR	2 (1.3)	4 (2.6)
PR	10 (6.5)	32 (20.5)
SD	33 (21.6)	73 (46.8)
PD	107 (69.9)	26 (16.7)
Unable to determine	1 (0.7)	21 (13.5)
Not treated	1 (0.7)	16 (10.3)
Discontinued early due to 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]

MMRd in glioma patients







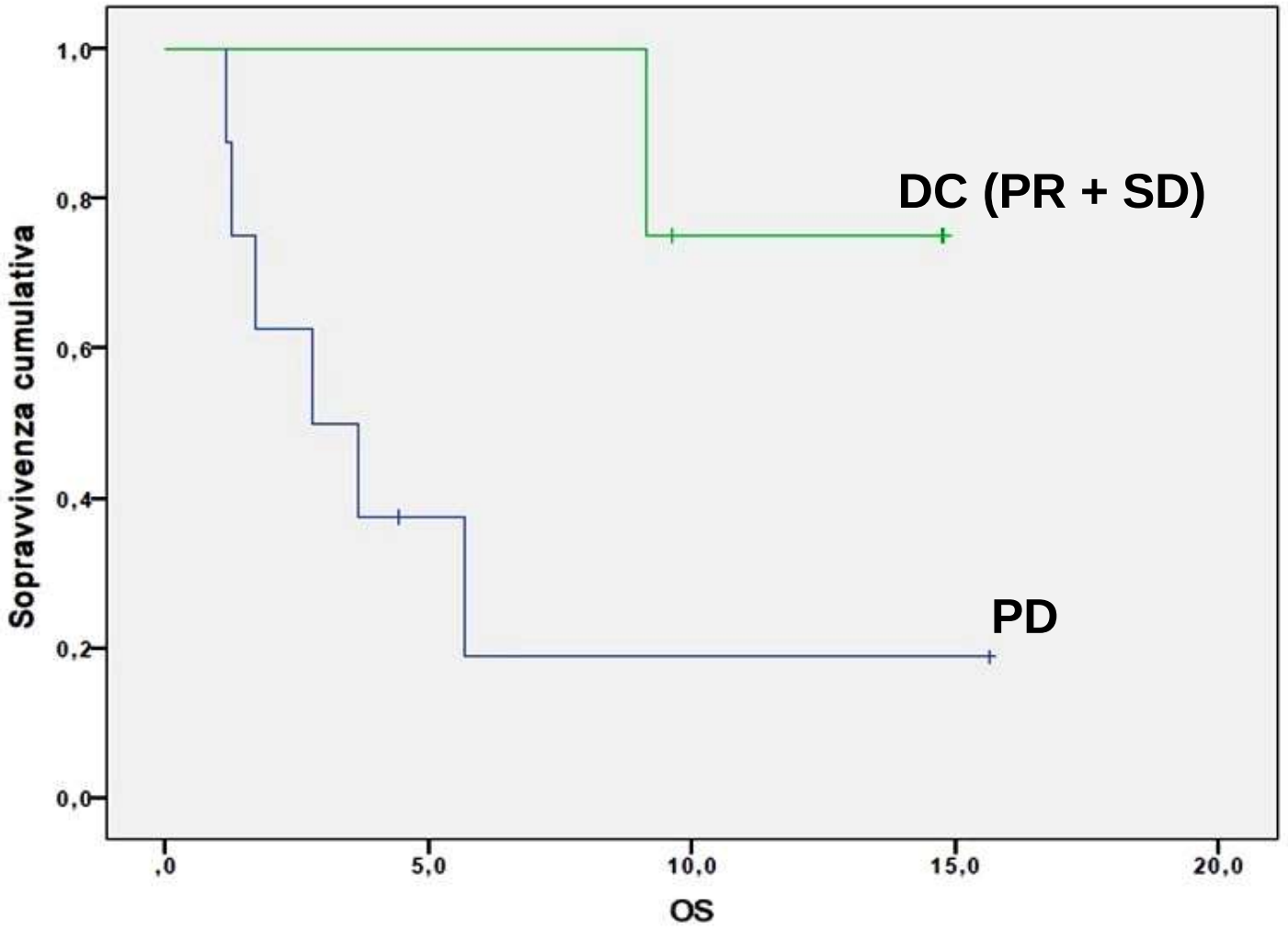
Baseline patients characteristics

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)

Baseline patients characteristics

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

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)*

Thanks for your attention

giuseppe.lombardi@iov.veneto.it