III Simpósio Internacional de
IMUNO-ONCOLOGIA
06 e 07 de outubro 2017 • Pullman Vila Olímpia
O FUTURO DA ONCOLOGIA

Imunoterapia em Tumores Cerebrais

O racional e as perspectivas

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Oncologista Clínica do Hospital Bp e Bp Mirante

Oncologia

A Beneficência Portuguesa de São Paulo

Potenciais conflitos de interesse

- **De acordo com a Resolução 1595 / 2000 do Conselho Federal de Medicina e com a RDC 96 / 2008 da ANVISA, declaro que:**

- **Participo de estudos clínicos patrocinados pelas empresas:**
  - Roche, Astra Zeneca, MSD

- **Participo como palestrante convidado:**
  - Jansen, Bayer, MSD

- **Patrocínio para Congressos:**
  - Roche, Bayer, Merck, GSK, Astra Zeneca

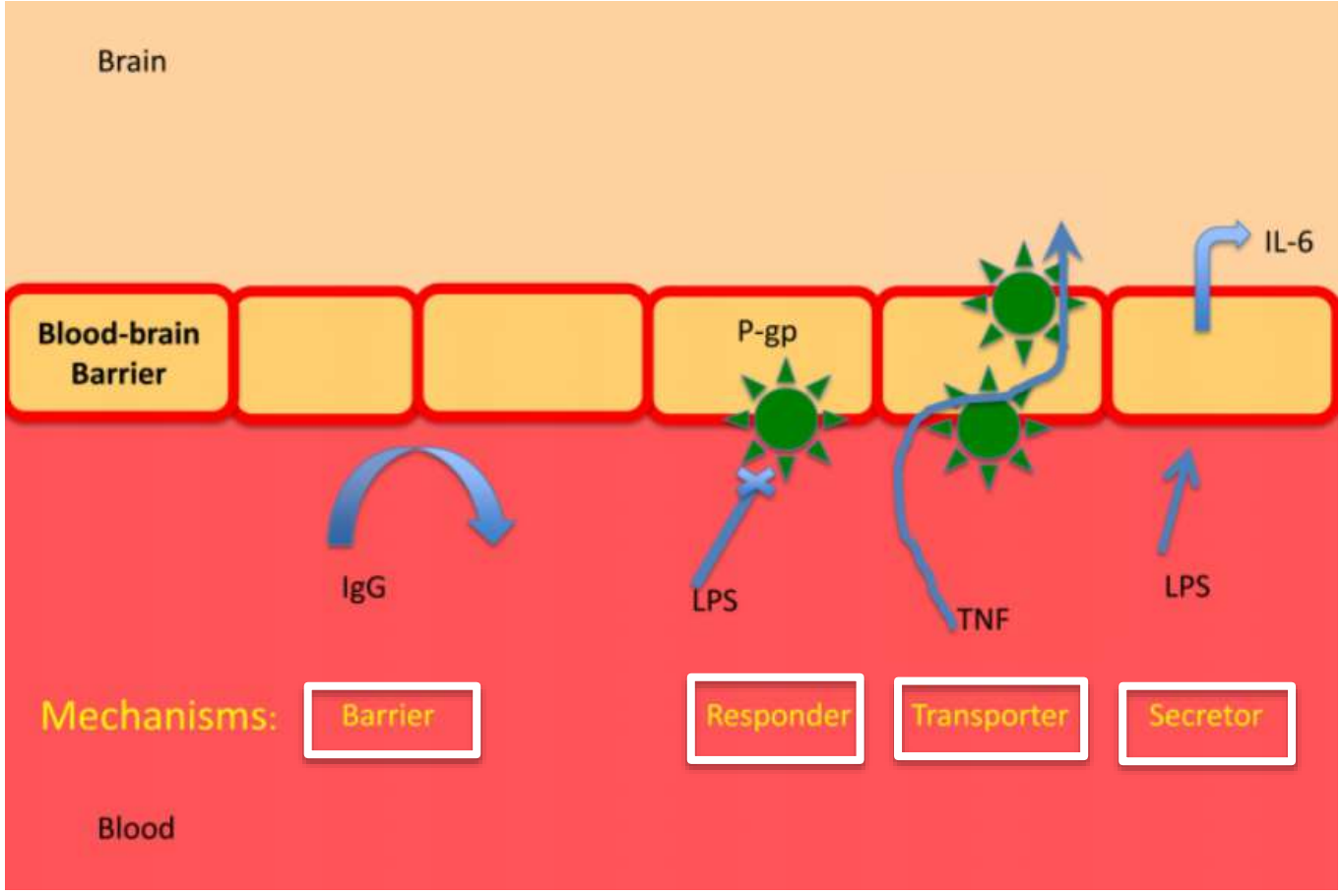
- **Não possuo ações de quaisquer destas companhias farmacêuticas.**

Neuroimunologia

- Cérebro imunologicamente privilegiado
  - Barreira hematoencefálica [1]
    - Dificuldade penetração quimioterapia e anticorpos
    - Movimentação de células do sistema imune restrito
  - Ausência de um sistema linfático desenvolvido no SNC [2,3]

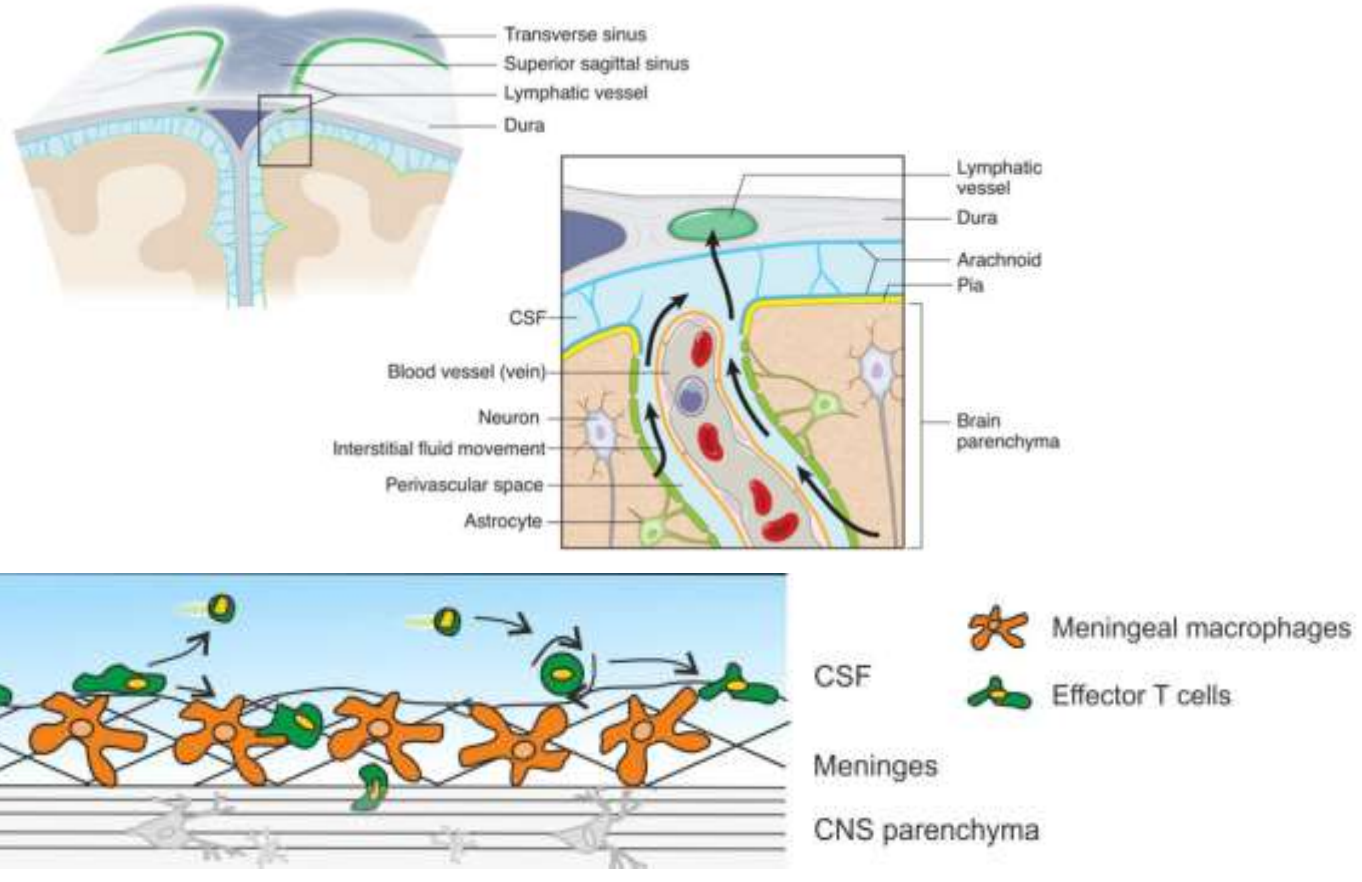
1. Banks WA, et al. J Neuroinflammation. 2012; 9:231
2. Louveau A, et al. Nature. 2015 Jul 16;523(7560):337-41
3. Schläger C., Nature 2016 Feb 18;530(7590):349-53

Barreira hematoencefálica



Banks WA, Brain Behav Immun. 2015 Feb;44:1-8

Sistema Linfático



1. Louveau A, et al. Nature 2015 Jul 16;523(7560):337-41
2. 2. Schläger C., Nature 2016 Feb 18;530(7590):349-53

Microambiente tumoral

- Downregulation S1P1 (*sphigosine-1-phosphate receptor type 1*): linfopenia e redução órgãos defesa com sequestro células T medula ossea[1]

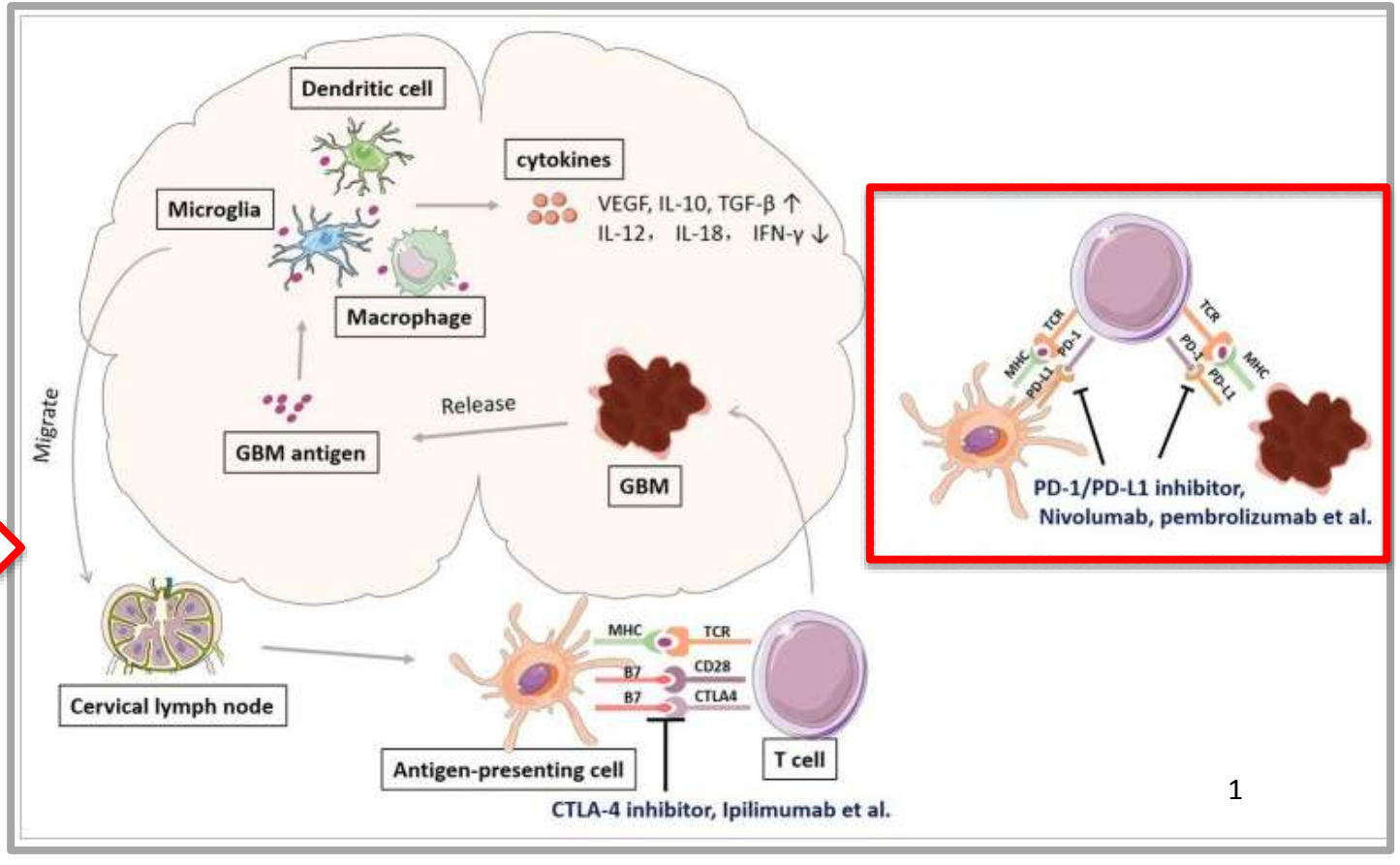
- Aumento expressão indoleamina 2,3-dioxigenase e triptofano 2,3 deoxigenase (metabolismo triptofano): depleção tripftofano e aumento catabólito kireunina > imunossupressor para céls T[2]

- Recrutamento de células T regulatórias e células supressoras mielóide-derivadas através do estímulo de citoquinas produzidos pelos macrófagos e microglia nos gliomas [3]

1. Chongsathidkiet P. et al. Neuro-oncol 18:vi88, 2016
2. Mitsuka K., et al. Neurosurgery 72(6):1031-8, 2013
3. Chang AL., et al. Cancer Res 76:5671, 2016

Microambiente tumoral

PD-1 células T circulante em pacientes com glioma[2]



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1. Huang J, et al. Front Pharmacol 8:242, 2017
2. Wei B, et al. Tumor biology 35: 2923, 2014

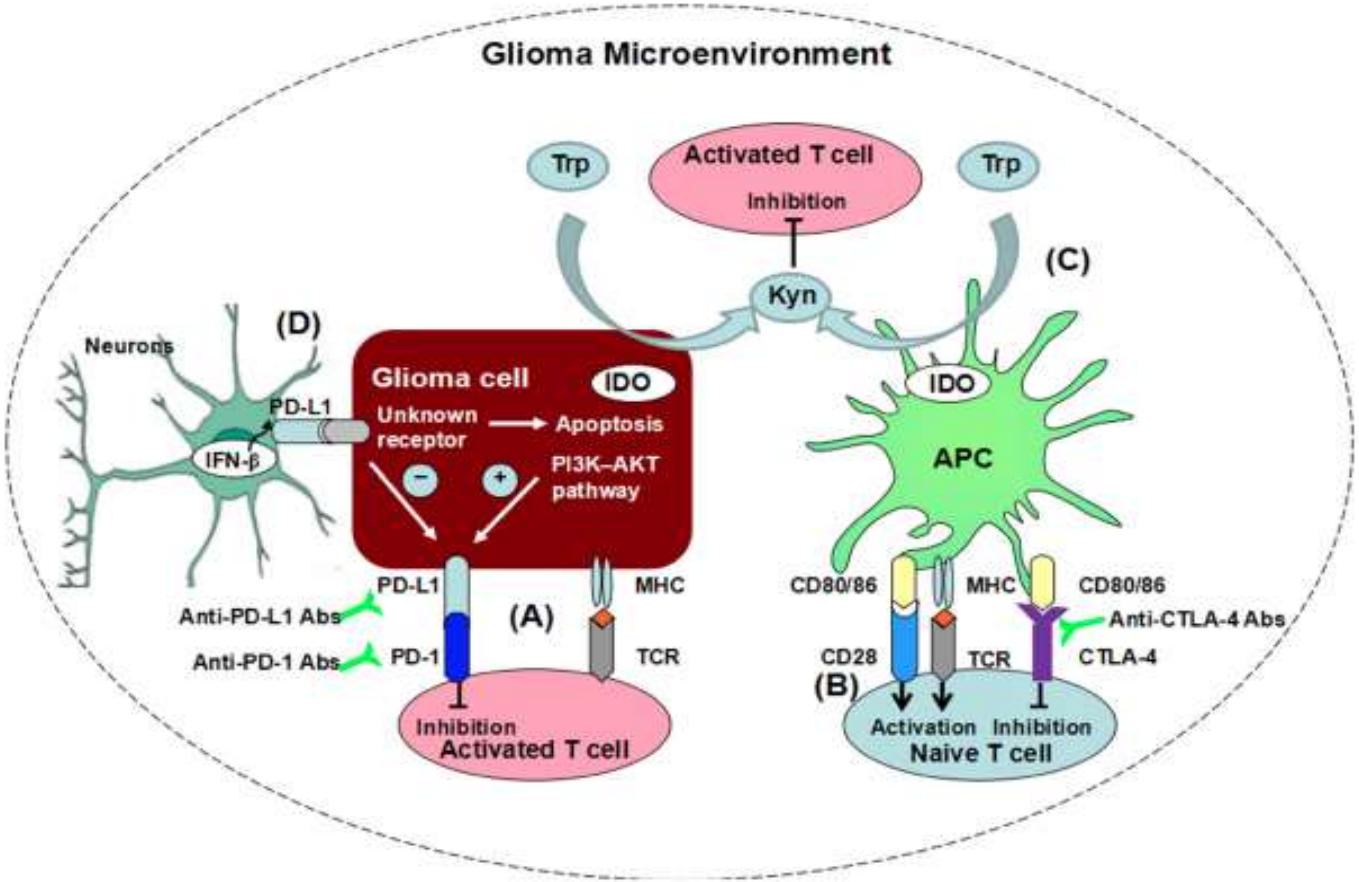


Figure 1: Immune checkpoints suppress T cell function in glioma microenvironment through differential mechanisms. **A.** The expression of PD-L1 on glioma cells is dependent on the PI3K-AKT pathway. PD-L1, upon engagement to its receptor PD-1 on T cells, inhibits activated T cell functions within the tumor microenvironment. **B.** CTLA-4 inhibits T cell activation. The co-stimulatory molecules from APCs, CD80 and CD86 bind to both stimulatory receptor CD28 and inhibitory receptor CTLA-4, yet with lower affinity to the former than to the latter. Therefore, CTLA-4 suppresses T cell activation via competitive inhibition. **C.** The maintenance, and function of T cells require adequate Trp levels, but IDO from tumor cells catabolizes Trp to numerous metabolites, such as Kyn. The decrease of Trp suppressed T cell activation. Meanwhile, the metabolites, such as Kyn can induced T cell apoptosis. **D.** In neurons surrounding glioma tissue, the expression of PD-L1 is induced by endogenous production of IFN-β. The neurons have the capability to inhibit proliferation of glioma cells and induce its apoptosis. Meanwhile, PD-L1^{-} neurons reduce the PD-L1 expression on glioma cells.

Zhang X, et al. Oncotarget 8(4): 7157, 2017

Alvos terapêuticos

- **Antígeno ideal:** expresso steam cell e se mantenha no fenótipo tumoral
  - **EGFR2:** expresso mais frequentemente nos gliomas e homogêneo, mas expresso também em tecido normal
  - **Interleucina-13 receptor α2 (IL-13Rα2):** 58% expressão GBMs, mas não essencial
  - **EGFRvIII:** presente em 30% dos GBMs; heterogêneo subclonal. Não observada em tecido normal

EGFRvIII

Epidermal growth factor receptor vIII

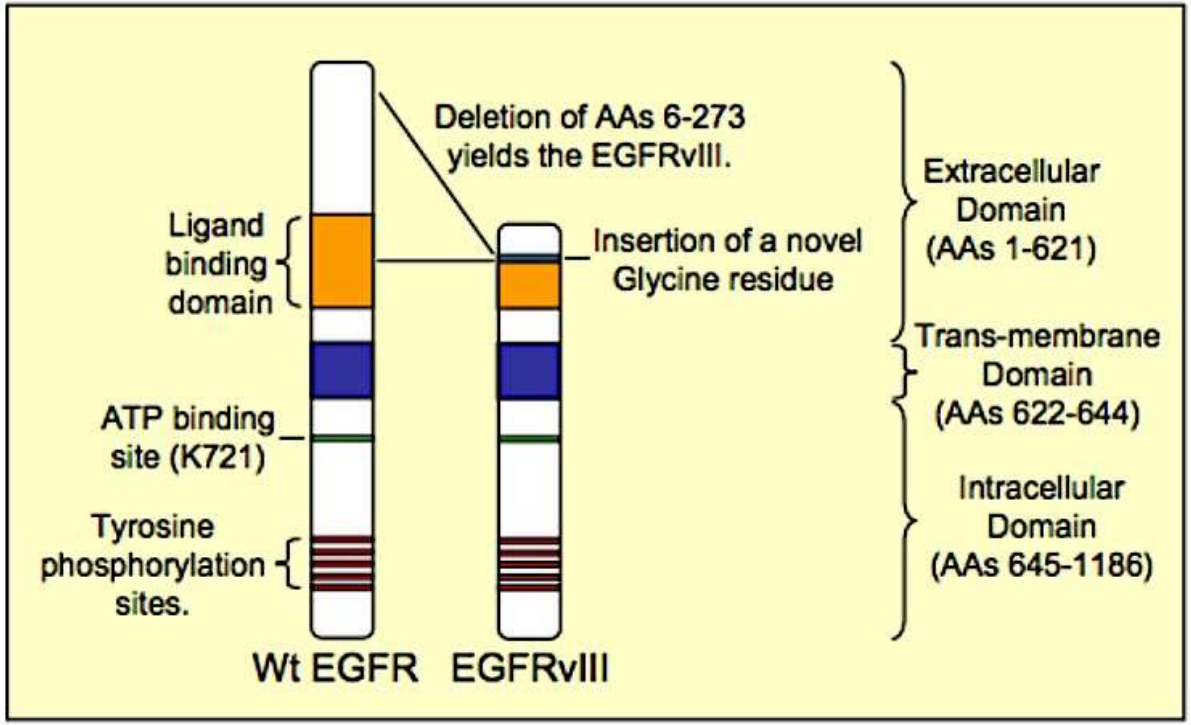


Fig. 1. Schematic of the epidermal growth factor receptor (EGFR)vIII truncation. The EGFRvIII variant receptor is characterized by a deletion of exons 2–7 of the wild type (Wt) *EGFR* gene. This results in an in-frame truncation of amino acids (AA) 6 to 273 in the extracellular domain of the full length protein, yielding a constitutively active variant receptor that can not bind ligand. The EGFRvIII also contains a novel glycine residue inserted at the fusion junction.

Gan HK., et al. J Clin Neurosci 16(6):748, 2009

EGFRvIII

Epidermal growth factor receptor vIII

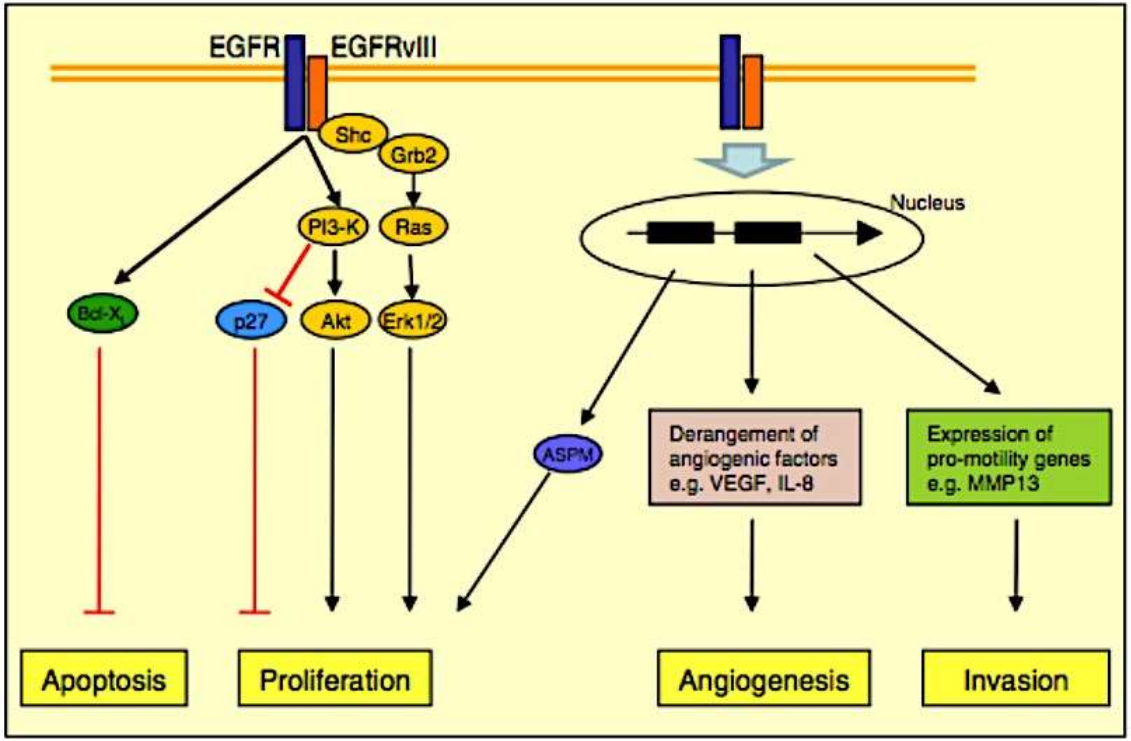


Fig. 2. The epidermal growth factor receptor (EGFR)vIII confers enhanced glioblastoma multiforme (GBM) tumourigenicity through several key mechanisms. The EGFRvIII receptor enhances cell proliferation by promoting PI3K/Akt signalling; Shc and Grb2 association and Ras activity while inhibiting cell cycle regulators such as $p27^{KIP1}$ and up-regulating abnormal spindle-like microcephaly-associated (ASPM) expression. Furthermore, EGFRvIII promotes survival in cells by increasing expression of anti-apoptotic proteins such as Bcl-X_L, and enhances angiogenesis and cell invasion by un-regulating vascular endothelial growth factor (VEGF), interleukin-8 (IL-8) and matrix metalloproteinase 13 (MMP13) expression. Red lines with blunt ends indicate inhibitory effects; black lines with arrow heads indicate stimulatory effects.

Gan HK., et al. J Clin Neurosci 16(6):748, 2009

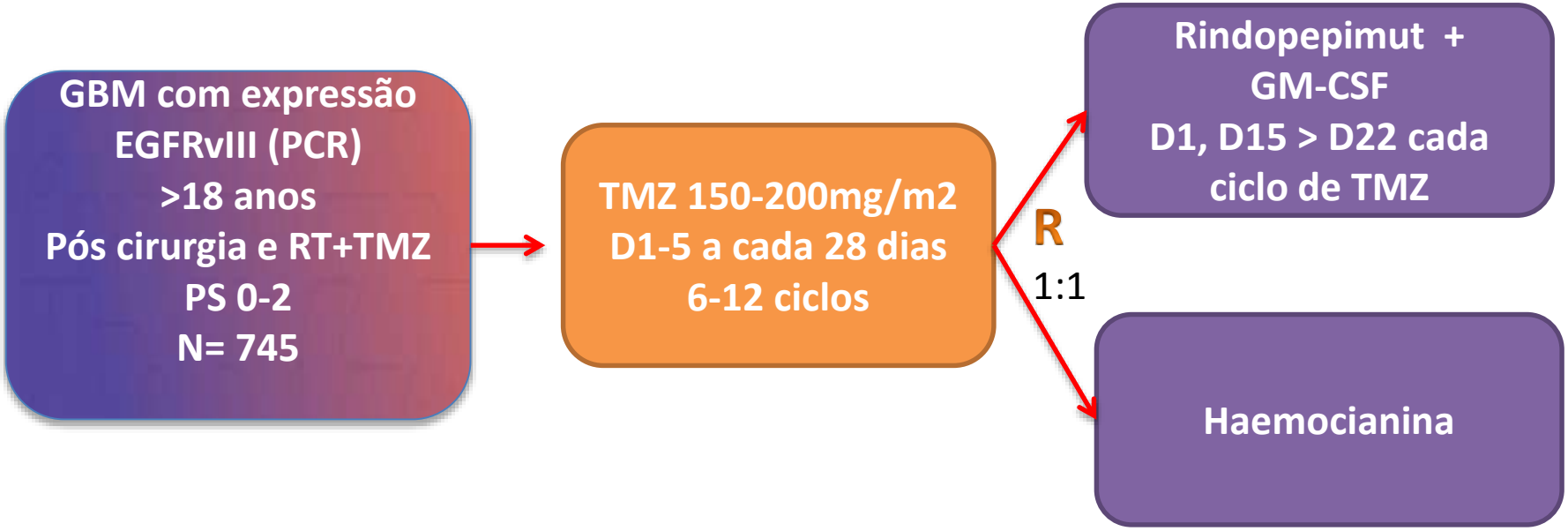
Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial

*Michael Weller, Nicholas Butowski, David D Tran, Lawrence D Recht, Michael Lim, Hal Hirte, Lynn Ashby, Laszlo Mechtler, Samuel A Goldlust, Fabio Iwamoto, Jan Drappatz, Donald M O'Rourke, Mark Wong, Mark G Hamilton, Gaetano Finocchiaro, James Perry, Wolfgang Wick, Jennifer Green, Yi He, Christopher D Turner, Michael J Yellin, Tibor Keler, Thomas A Davis, Roger Stupp, and John H Sampson, for the ACT IV trial investigators**

Weller M. et al. Lancet Oncol 18(10): 1373, 2017

ACT IV

- Fase 3, randomizado, duplo cego e multicêntrico

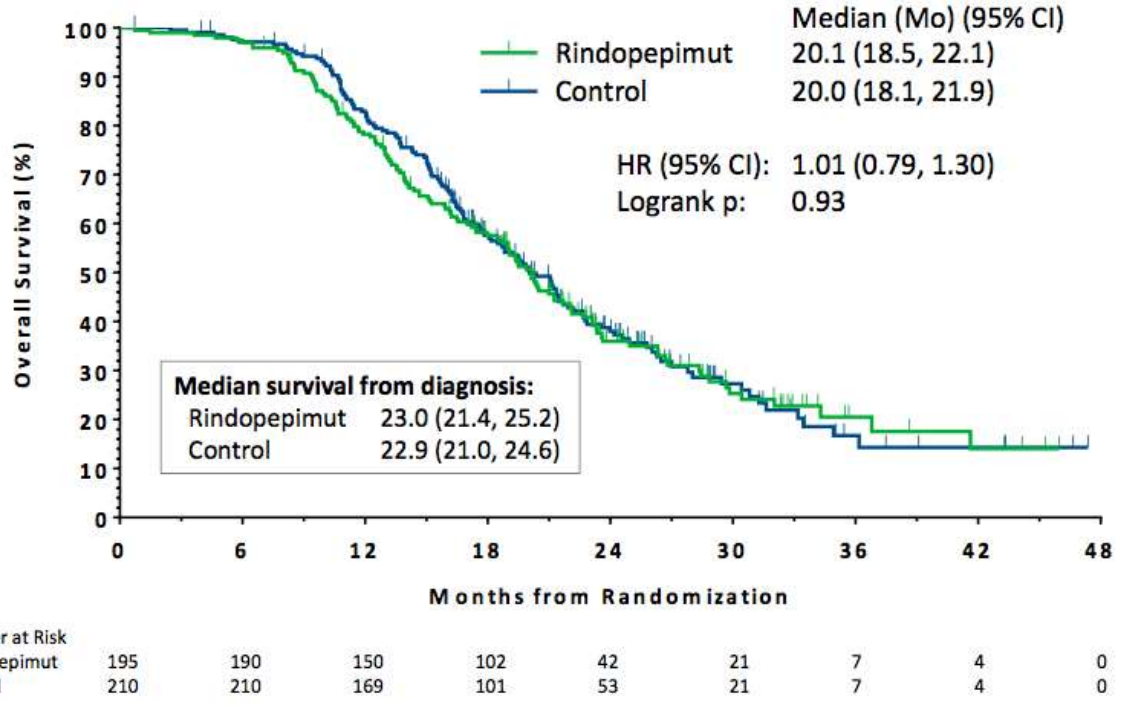


- Endpoint primário: Sobrevida Global com doença residual mínima (<2cm^2 pós RT)

Weller M. et al. Lancet Oncol 18(10): 1373, 2017

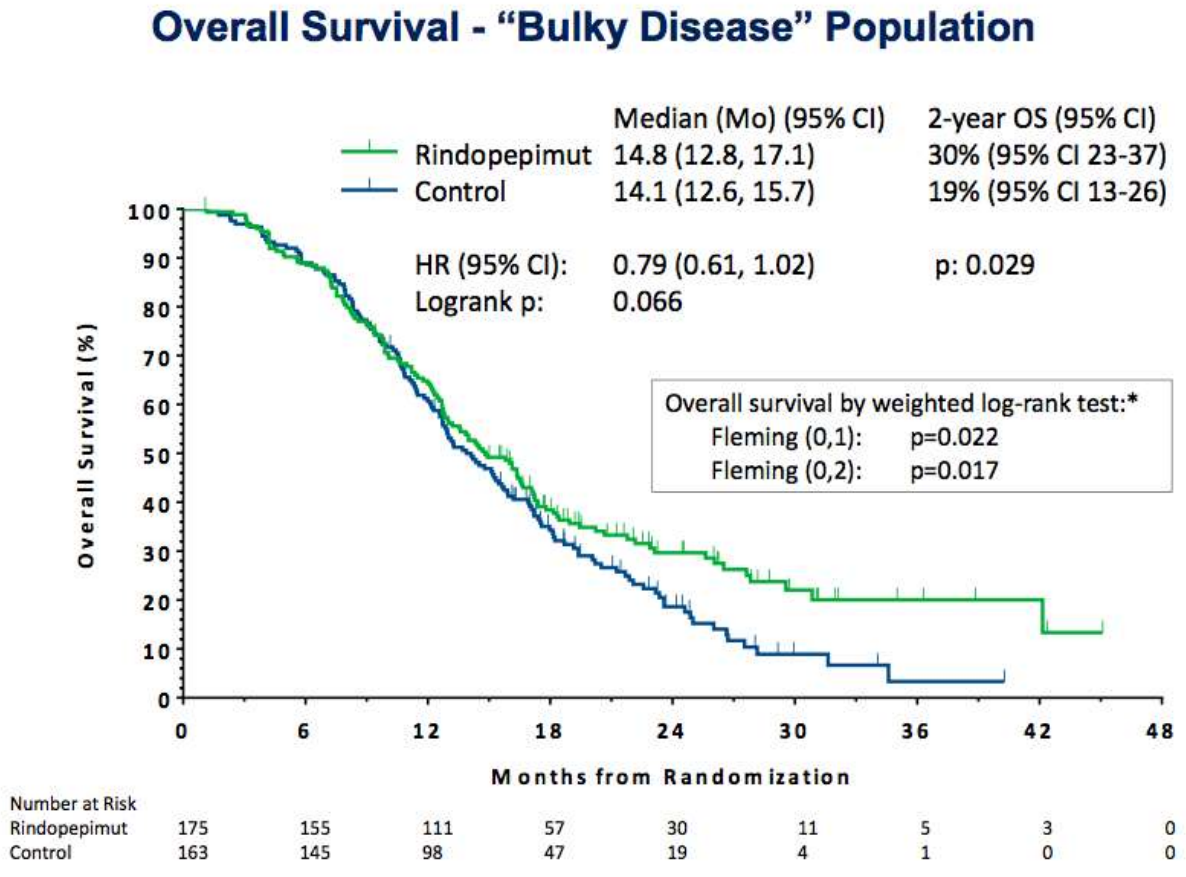
ACT IV

Primary Endpoint: Overall Survival - MRD Population



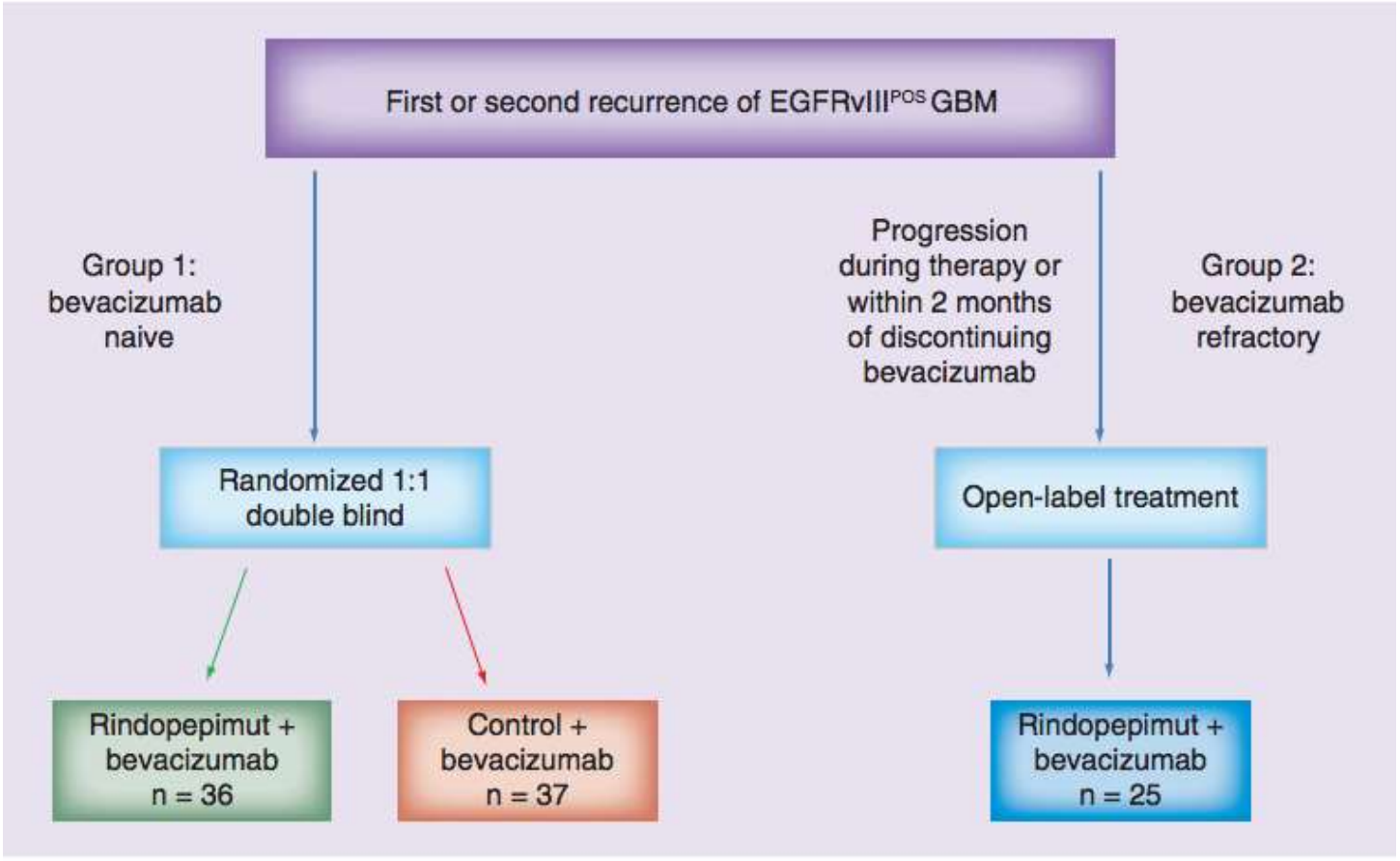
Weller M. et al. Lancet Oncol 18(10): 1373, 2017

ACT IV



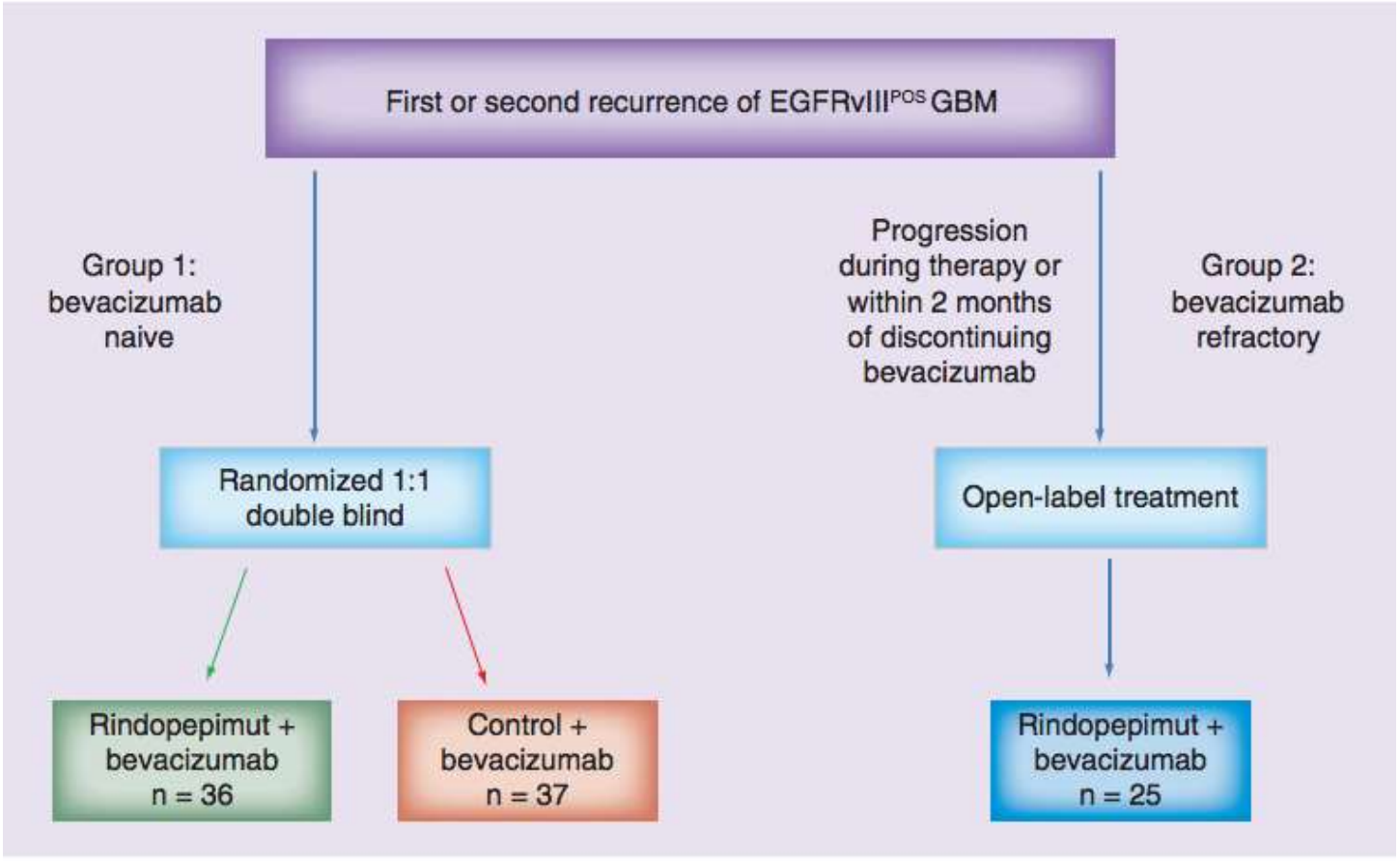
Weller M. et al. Lancet Oncol 18(10): 1373, 2017

ReACT TRIAL



Gatson NT, CNS Oncol 5(1):11, 2016

ReACT TRIAL



Gatson NT, CNS Oncol 5(1):11, 2016

ReACT TRIAL

Table 2. Comparison of studies bevacizumab use in recurrent glioblastoma.

Outcomes	Bev-naive group 1		Bev-refractory group 2
	Rindo + bev	Control + bev	
Progression-free ITT, n (%)	10 (28%)	6 (16%)	Median months: 1.9
Survival at 6 months PP, n (%)	10 (30%)	4 (12%)	6-month rate: 8%
OS, median (12 months/18 months):			
– ITT	11.6 (45%/30%)	9.3 (31%/15%)	Median months: 5.6
– PP	10.9 (41%/30%)	8.5 (28%/10%)	6-month rate: 48%
ORR confirmed CR/PR, n (%):			
– ITT	9 of 30 (30%)	6 of 34 (18%)	ORR† up to 11%
– PP	9 of 29 (31%)	5 of 32 (16%)	
Discontinuation of steroids, n (%):			
– ≥2 months	8 of 18 (44%)	4 of 19 [21%]	
– Other	10 of 18 (56%)	8 of 19 [42%]	
Anti-EGFRvIII immune response†:			
– Fourfold increase over baseline (% patients)	~89%		79%
OS, median months/6 months rate (%):			
– Titers ≥1:12,800 by day 57	~20.8/95%		6.7/66%
– Titers <1:12,800 by day 57	~10.4/69%		2.8/17%

†ReACT Trial Data (for comparison). Refer to the original article for study numbers, percentages were reported in the graphic for ease in comparison. ORR included complete and/or partial responses "objective" as reported by the original article cited [Reardon D, Unpublished Data].

CR: Complete response; ITT: Intent to treat; ORR: Objective response rate; OS: Overall survival; PP: Per protocol; PR: Partial response.

Gatson NT, CNS Oncol 5(1):11, 2016

EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) AMPLIFICATION RATES OBSERVED IN SCREENING PATIENTS FOR RANDOMIZED CLINICAL TRIALS IN GLIOBLASTOMA

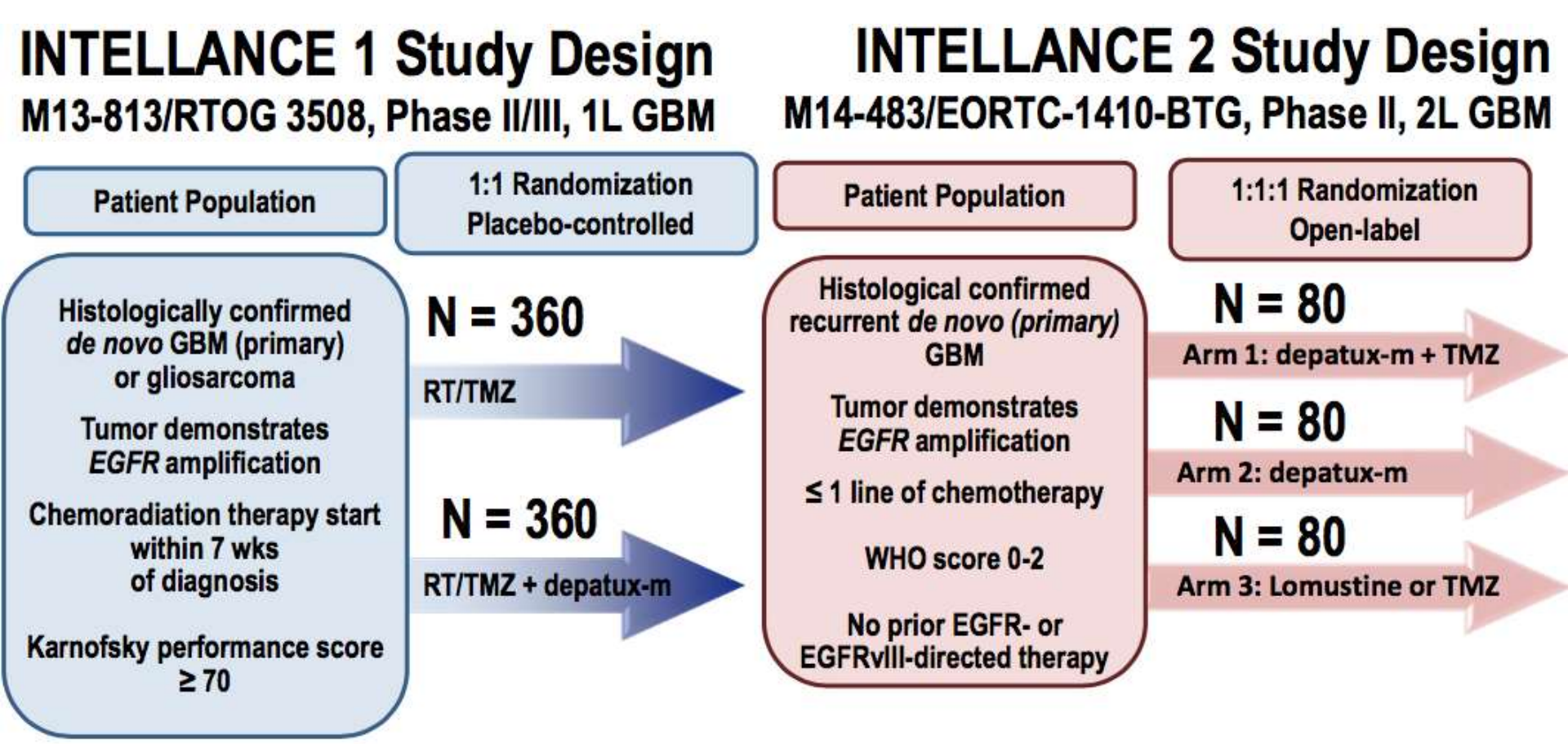
Martin J. van den Bent[1], Lisa Roberts-Rapp[2], Peter Ansell[2], James Lee[3], Jim Looman[2], Earle Bain[2], Christopher Ocampo[2], Kyle D. Holen[2], Erica J. Gomez[2], Andrew B. Lassman[4]

[1]Department of Neuro-Oncology, Erasmus MC Cancer Institute, Rotterdam, NL; [2]AbbVie Inc., North Chicago, IL, USA; [3]Abbott Molecular Inc., Des Plaines, IL, USA; [4]Department of Neurology and Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY, USA

esmo.org

Van de Bent M, et al. ESMO 2017

EGFR

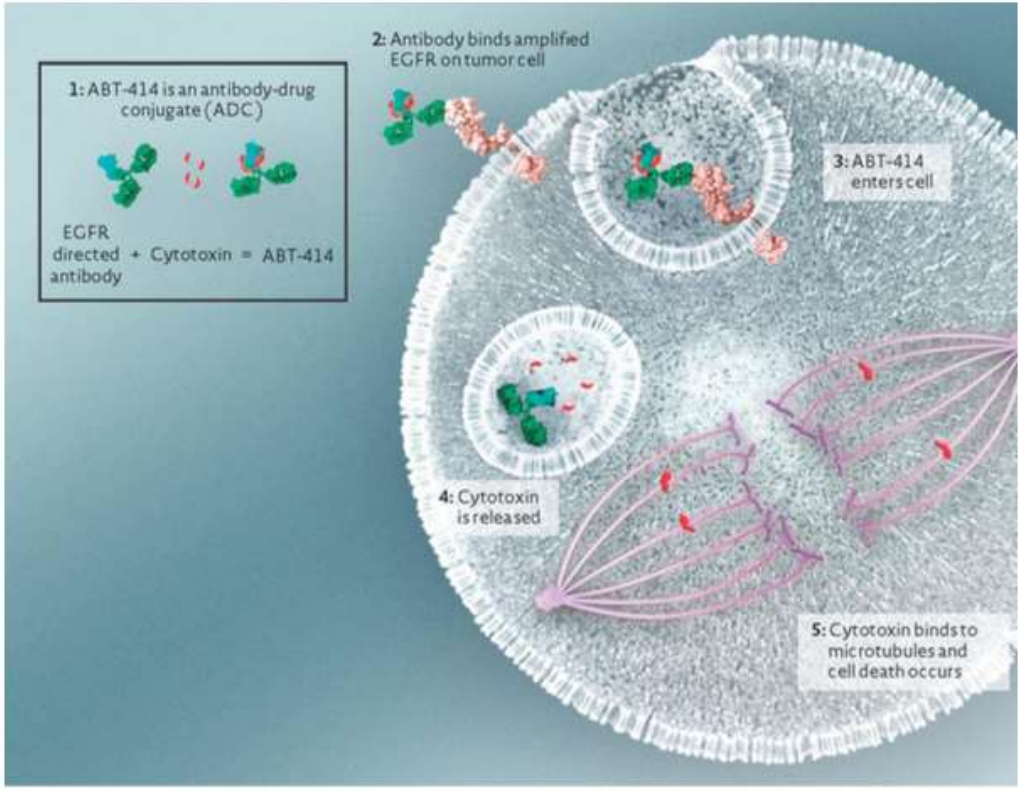


Van de Bent M, et al. ESMO 2017

EGFR

MADRID 2017 ESMO congress

Antibody-drug conjugate Depatux-M (ABT-414)



Van de Bent M, et al. ESMO 2017

EGFR

ROW	*EGFR*-amplified	Non-amplified	Total	Positive
Africa	4	5	9	44%
Americas	244	218	462	53%
Asia	70	133	203	35%
Europe	676	516	1192	57%
Middle East	22	20	42	52%
Oceania	78	104	182	43%
Total	**996**	**1094**	**2090**	**52%**

Van de Bent M, et al. ESMO 2017

EGFR

- *EGFR* amplification is present in 52% of patients with GBM
  - Largest cohort ever screened (2090 patients)
- Lower *EGFR* amplification rate in patients with GBM from Asia (35%)
- INTELLANCE 1 and INTELLANCE 2 explore the antibody-drug conjugate depatuxizumab mafodotin (depatux-m, ABT-414) in newly diagnosed and recurrent glioblastoma

Van de Bent M, et al. ESMO 2017

Vacinas Peptídeos

- **Survivina:** inibidor apoptose e regulador mitose
  - 79% dos tumores astrocíticos[1]
  - SVN53-67/M57:vacina derivada survivina[2]
  - NCT02455557 – ongoing fase 2
- **IDH1 (isocitrato desidrogenase 1)**
  - >90% GBM secundários
  - NCT02454634 – fase 1 ongoing Vacina peptideo em IDH1R132H mutado glioma grau III e IV
- **WT1 (*Wilms' tumor gene*)**
  - Aumento da expressão com aumento grau tumoral
  - Fase 1: PFS 5,2-49 meses GBM recém diagnosticado concomitante TMZ[3]
  - Fase 2: PFS 20 semanas GBM recidivado[4]

1. Kajiwara Y, et al. Cancer 97(4):1077, 2003
2. Ciesielski MJ, et al. Cancer Immunol Immunotherapy 59(8):1211,2010
3. Hashimoto N, et al. Cancer Immunol Imunother 64(6): 707, 2015
4. Izumoto S, et al. J Neurosurg 108(5): 963, 2008

Vacinas

- **Vacinas multipeptídeos:**
  - Gliovac: PFS 6 meses 100 vs 33% (N= 9 pacientes)[1]
- **Vacinas células dendríticas:**
  - APCs potentes
  - Dados preliminares sobrevida >30 meses
  - NCT02546102 – suspenso recrutamento
  - CD +CMV pp65 (ELEVATE trial)
    - Ongoing (NCT02366728)

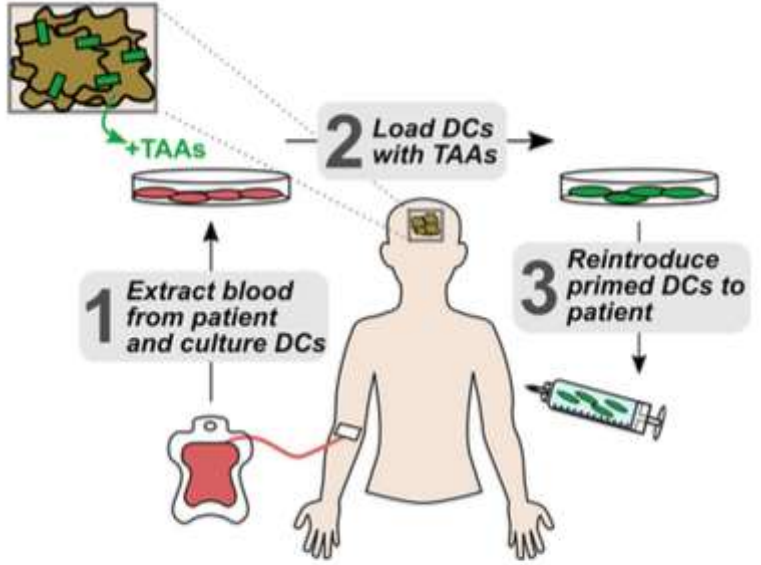


Fig 2 Schematic depicting the process of dendritic cell (DC) vaccine generation. *TAA* tumor-associated antigen

1. Schijins VE, et al. Vaccine 33(23):2690, 2015

Registration number	New/recurrent/metastatic	Therapy	Number of patients	Phase
EGFRvIII vaccine				
NCT01480479	New	Rindopepimut/GM-CSF	$n = 700$	Phase III
NCT00626015	New	EGFRvIII peptide vaccine, daclizumab	3 experimental versus 3 control	Pilot
[96]	New	DC vaccine targeting EGFRvIII antigen	$n = 12$	Phase I
[38]	New	EGFRvIII peptide vaccine	$n = 18$	Phase II
[39]	New	EGFRvIII peptide Vaccine, TMZ	$n = 22$	Phase II
[40]	New	Rindopepimut (CDX-110)	$n = 65$	Phase II
Heat-shock protein (HSP) vaccine				
NCT01814813	Recurrent	HSPPC-96 C, bevacizumab	$n = 222$	Phase II
[54]	Recurrent	HSPPC-96 vaccine	$n = 41$	Phase II
[97]	New	HSP70 vaccine	$n = 12$	Pilot
Dendritic cell (DC) vaccines				
NCT00846456	New	DC vaccine against cancer stem cells	$n = 11$	Pilot
NCT00068510	New + recurrent	C vaccine, toll-like receptor agonists	$n = 23$	Phase I
NCT00045968	New	DCVax®-L	$n = 300$	Phase III
[98]	New	DC vaccine	$n = 10$	Pilot
[99]	New	DC vaccine	$n = 8$	Pilot
[100]	New	DC vaccine	$n = 5$	Pilot
[101]	Recurrent	DC vaccine	$n = 9$	Phase I
[47]	New + recurrent	multi-epitope pulsed DC vaccine	$n = 21$	Phase I
[102]	New + recurrent	DC vaccine	$n = 17$	Phase I/II
Adoptive T-cell therapy				
NCT02209376	New + recurrent	CAR T-cells to EGFRvIII	$n = 12$	Phase I
NCT00693095	New	CMV-autologous lymphocyte transfer	$n = 12$	Phase I
NCT01109095	Recurrent	CMV-specific cytotoxic T lymphocytes	$n = 16$	Phase I
NCT01454596	Recurrent	CAR T-cells to EGFRvIII	$n = 160$	Phase I/II
NCT02208362	Recurrent + refractory	Enriched T-cells expressing IL13Ra2	$n = 44$	Phase I
[93]	Recurrent	CMV-specific T-cells	$n = 19$	Phase I

PD-1/PD-L1

- PD-1/PD-L1 expresso em HGG
- Prognóstico??
- Biomarcador?

- GBM – 135 pacientes Neuro-Biobank of Viena

Table 2. Programmed death ligand 1 expression in the Vienna retrospective glioblastoma cohort

	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

1. Berghoff A.S, et al. Neuro-Oncology 17(8), 1064, 2015

PD-1/PD-L1

	All Patients	LGA	O	MOA	E	AO	AMOA	AA	GS	GBM
Pathology										
WHO grade	I + II + III + IV	I + II	II	II	II + III	III	III	III	IV	IV
Number of patients (%)	347	26 (7.5)	19 (5.5)	8 (2.3)	2 (0.6)	9 (2.6)	4 (1.2)	33 (9.5)	13 (3.7)	233 (67.1)
Parameters										
Sex, *n* (%)										
Male	213 (61.4)	7 (26.9)	13 (68.4)	3 (37.5)	0 (0)	4 (44.4)	2 (50.0)	19 (57.6)	7 (53.8)	158 (67.8)
Female	134 (38.6)	19 (73.1)	6 (31.6)	5 (62.5)	2 (100)	5 (55.6)	2 (50.0)	14 (42.4)	6 (46.2)	75 (32.2)
Age, mean y (range)	51.9 (5–89)	39 (8–81)	45.5 (22–78)	45.1 (28–74)	14 (10–18)	48.6 (24–63)	61 (55–69)	42.4 (11–72)	55.0 (35–68)	55.6 (5–89)
PD-1/PD-L1 expression										
PD-1 on TIL, *n*/total *n* (%)										
Positive	74/235 (31.5	2/12 (16.7)	0/12 (0.0)	2/6 (33.3)	0/1 (0.0)	1/7 (14.3)	0/2 (0.0)	5/23 (21.7)	7/9 (77.8)	57/163 (35.0)
PD-L1 on tumor cells, *n*/total *n* (%)										
Positive	21/345 (6.1)	0/26 (0.0)	0/19 (0.0)	0/8 (0.0)	0/2 (0.0)	0/9 (0.0)	0/4 (0.0)	0/33 (0.0)	3/12 (25.0)	18/232 (7.8)

Garber ST, et al. Neuro Oncol 18(10): 1357, 2016.

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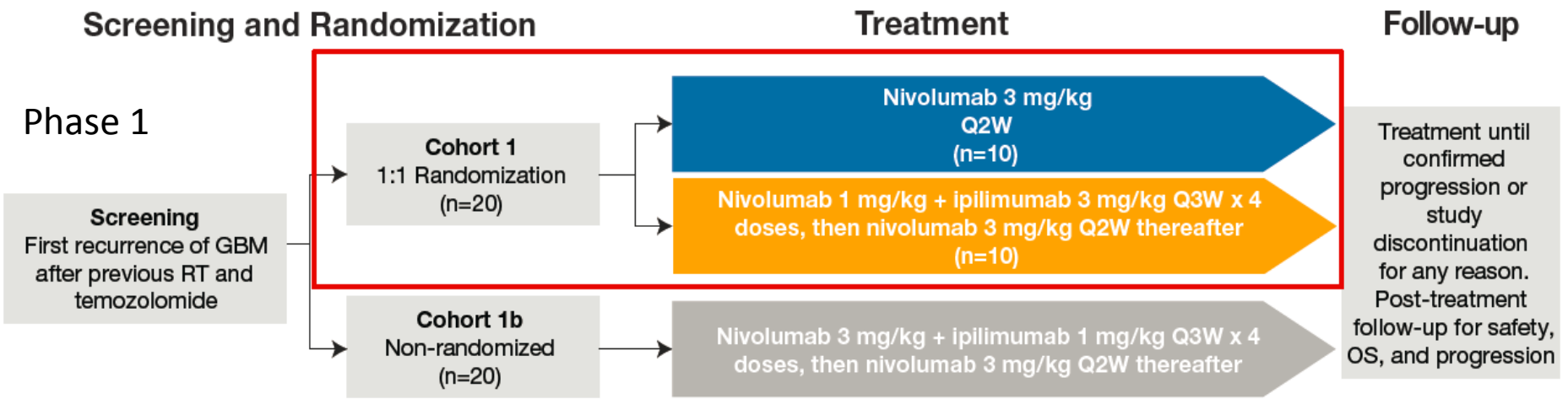

	Nivolumab 3 mg/kg (n=10)	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg (n=10)
Best overall response, n (%)[a]		
Complete response	0	0
Partial response	1 (10)	0
Stable disease	5 (50)	4 (40)
Progressive disease	3 (30)	6 (60)
Unable to determine	1 (10)	0

Sampson J, et al. SNO, 2015

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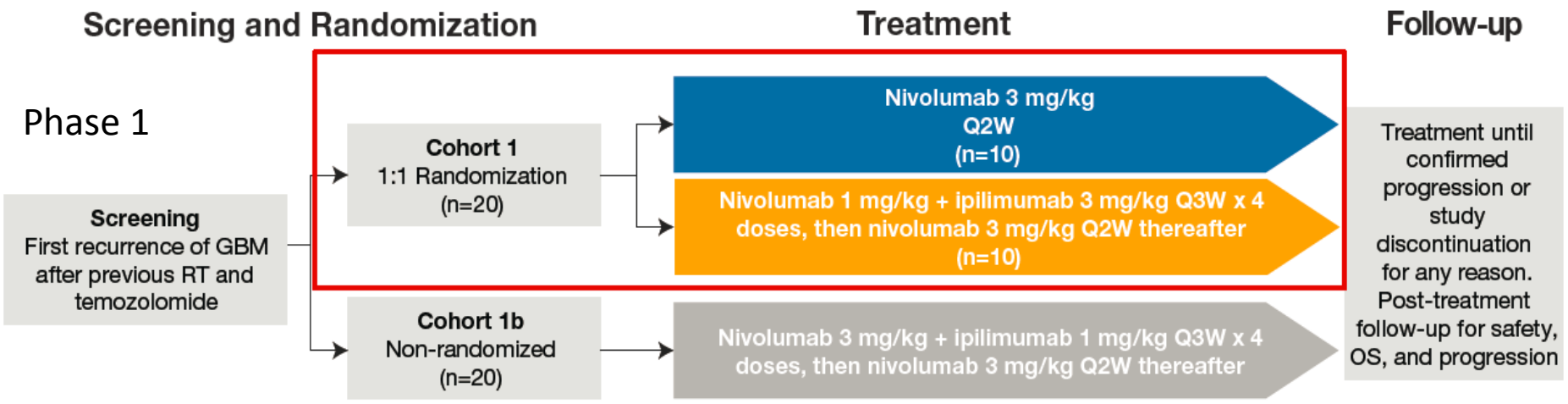

	Nivolumab 3 mg/kg (n=10)	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg (n=10)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n=20)
OS 12 months	40% (95% (CI:12-67)	30% (95%CI: 7-58)	25% (95% CI: 8-48)

Reardon DA, et al. ASCO 2016

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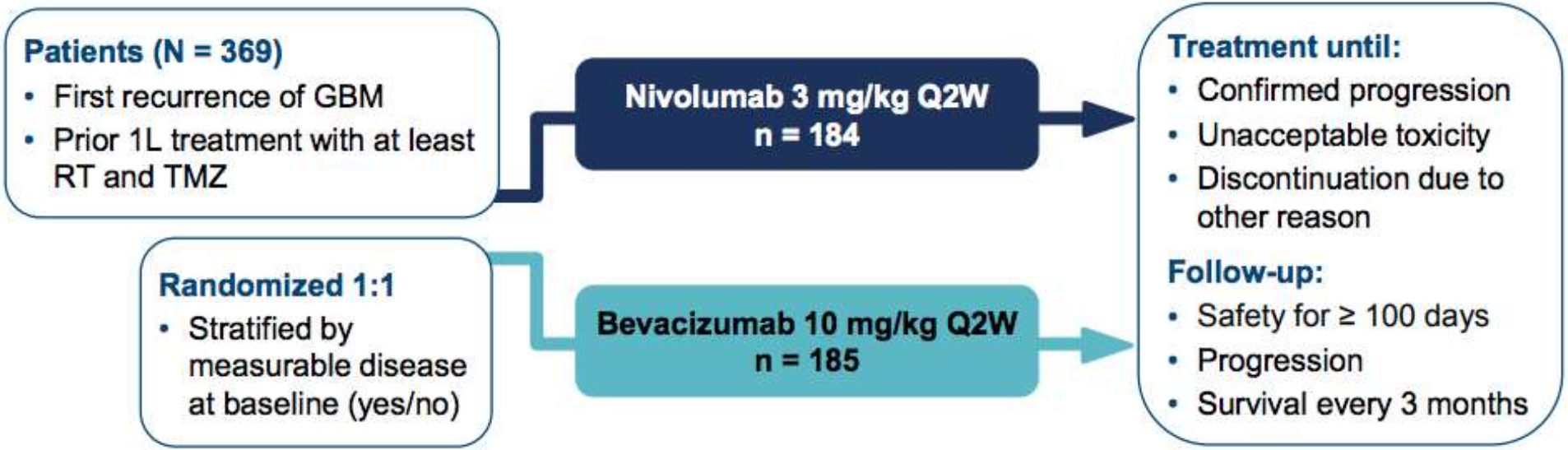
Phase 3



Reardon et al., WFNOS meeting 2017

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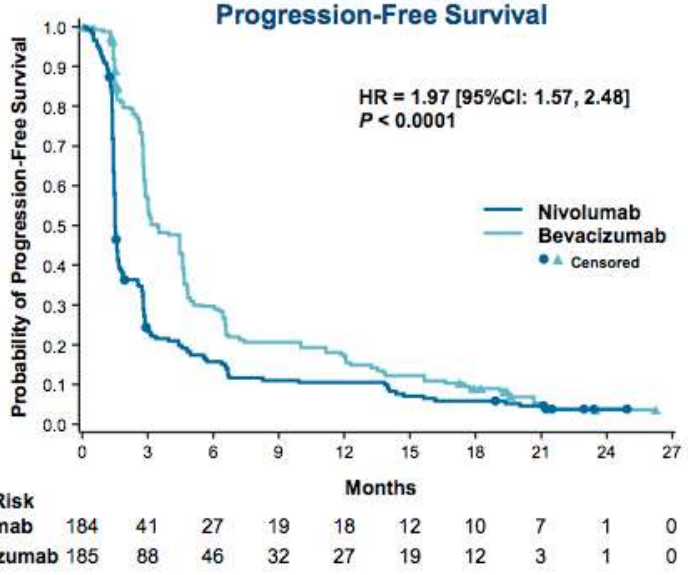
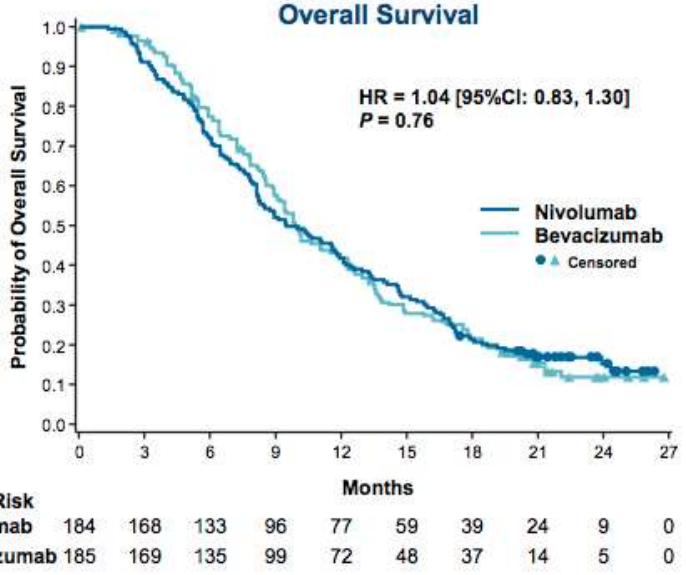
PFS

	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]



OS

	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]



Reardon et al., WFNOS meeting 2017

CHECKMATE-143

MADRID 2017 ESMO congress

Nivolumab in Combination With Radiotherapy ± Temozolomide: Updated Safety Results From CheckMate 143 in Patients With Methylated or Unmethylated Newly Diagnosed Glioblastoma

Michael Lim,[1,a] Antonio Omuro,[2,a] Gordana Vlahovic,[3] David A. Reardon,[4] Solmaz Sahebjam,[5] Timothy Cloughesy,[6] Joachim Baehring,[7] Nicholas Arthur Butowski,[8] Von Potter,[9] Ricardo Zwirtes,[9] Prashni Paliwal,[9] Michael Carleton,[9] John Sampson,[3,b] Alba A. Brandes[10,b]

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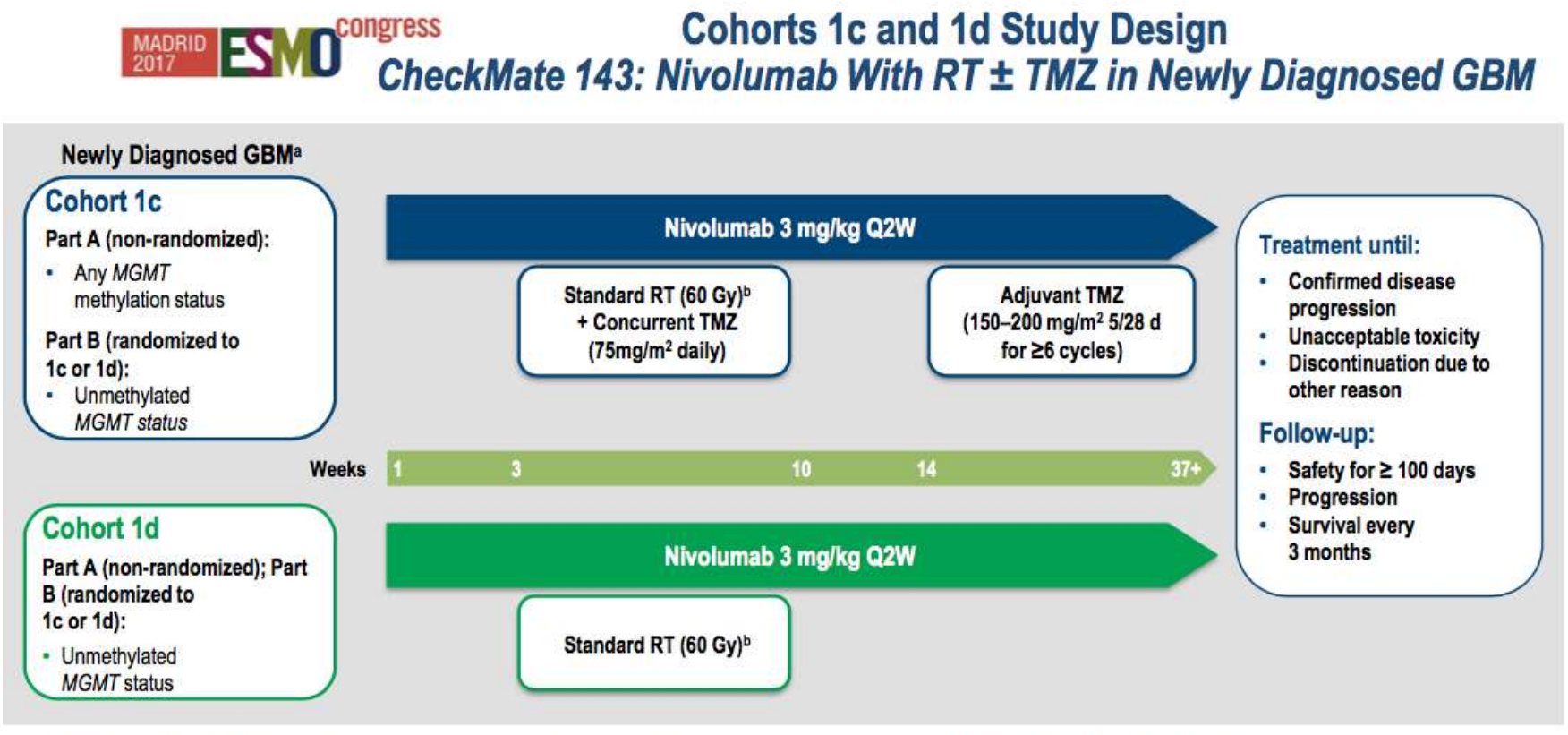
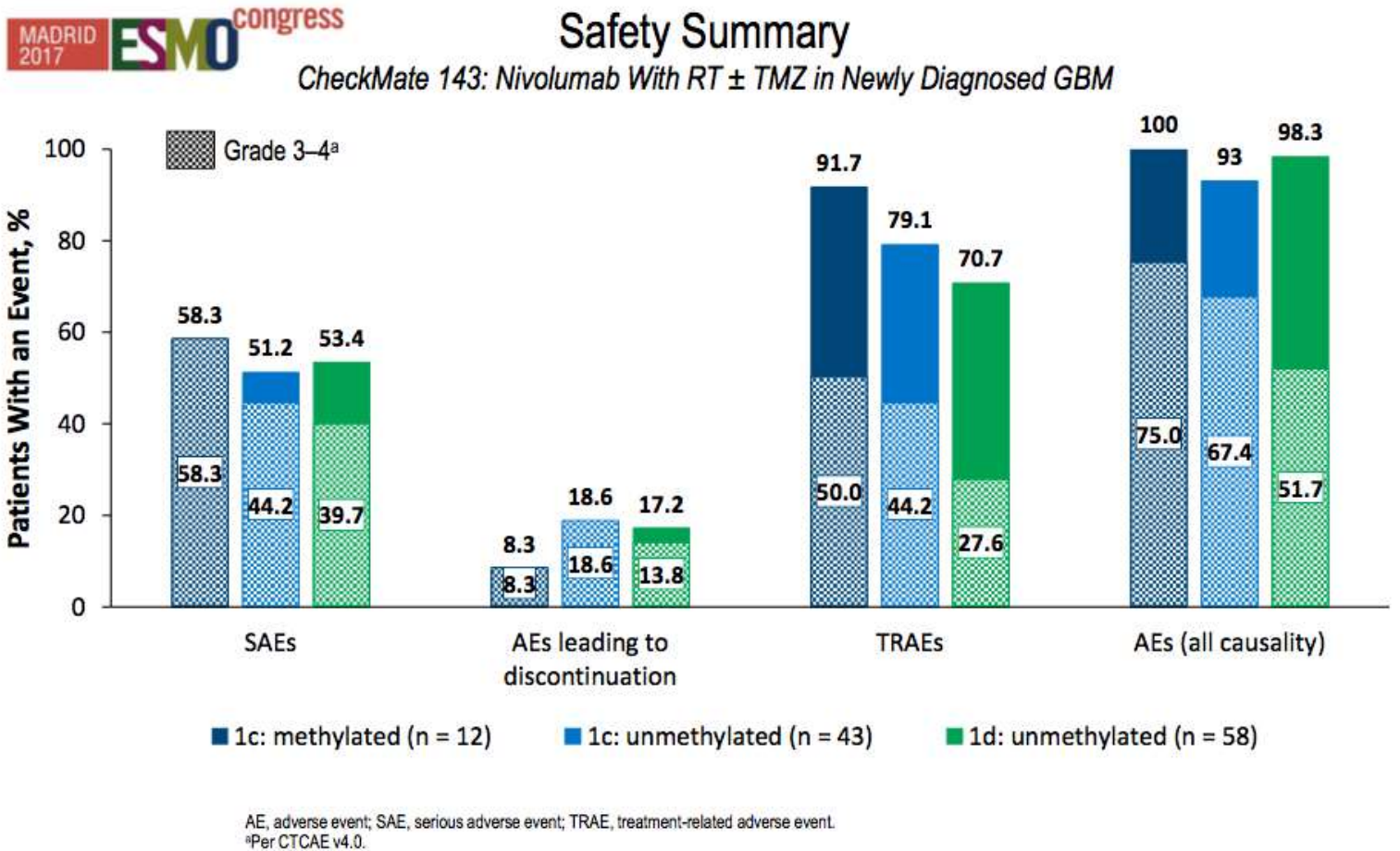
[b]Co-senior authors.

CHECKMATE-143



CHECKMATE-143



AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event.
[a]Per CTCAE v4.0.

CHECKMATE-143

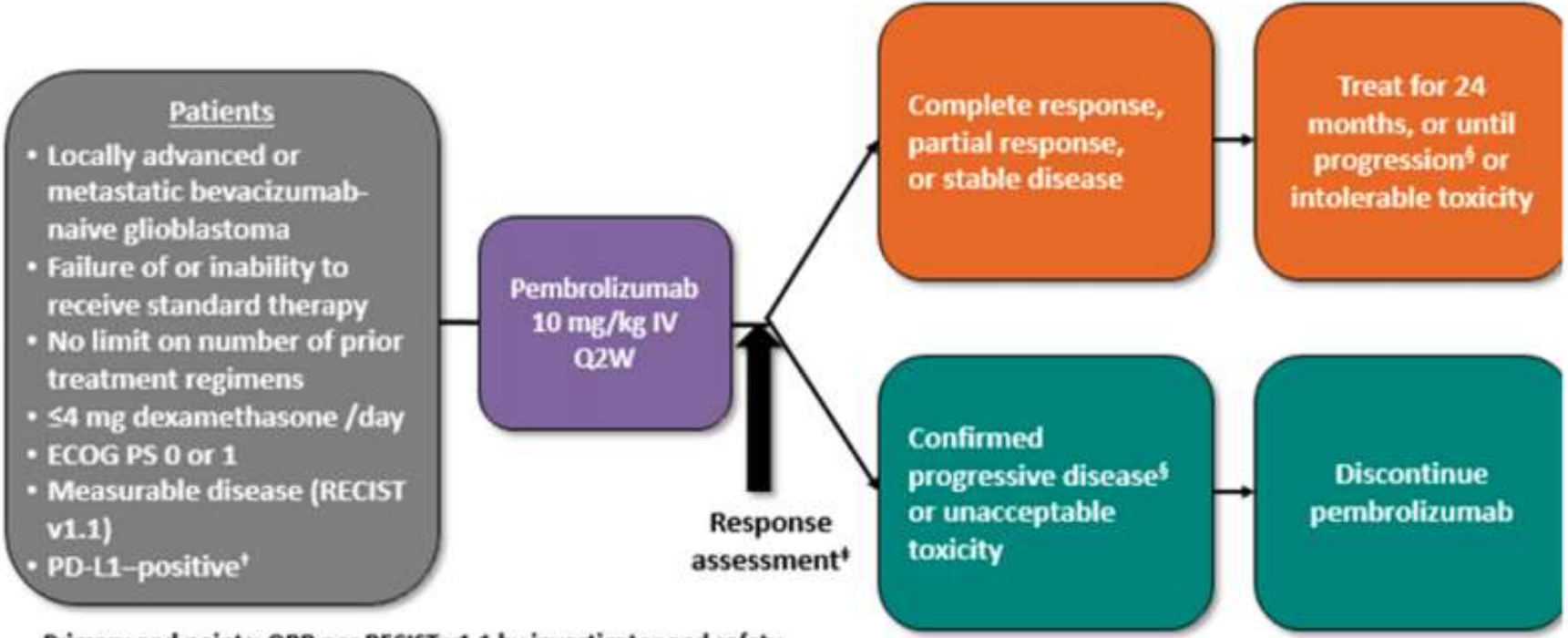
MADRID 2017 ESMO congress

Conclusions

CheckMate 143: Nivolumab With RT ± TMZ in Newly Diagnosed GBM

- Nivolumab in combination with RT ± TMZ was well tolerated, with no new safety signals
  - The use of TMZ in combination with nivolumab and RT did not lead to significant additional safety events, other than those known to occur with TMZ alone
  - The cohort not receiving TMZ did not show any significant additional immune-mediated AEs
- The incidence of grade 3–4 neurological TRAEs was relatively low (< 5%) and consistent with our previous experience in GBM
- These results suggest that nivolumab in combination with RT and nivolumab in combination with RT and TMZ are safe for further clinical evaluation in patients with newly diagnosed GBM

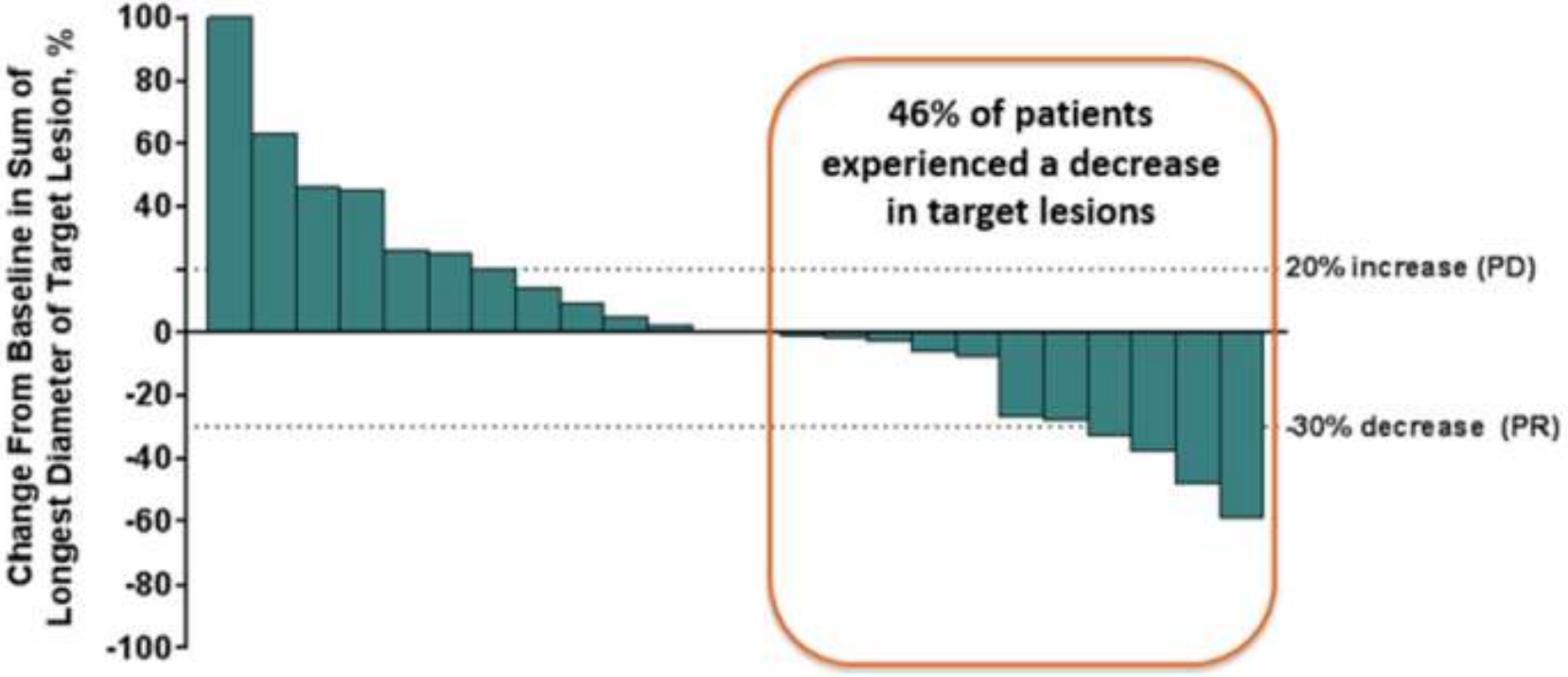
KEYNOTE 028



Primary end points: ORR per RECIST v1.1 by investigator and safety
Secondary end points: PFS, OS, duration of response
Data cutoff date: February 17, 2016

Reardon et al., SNO 2016

KEYNOTE 028



Reardon et al., SNO 2016

Immune Checkpoints Inhibitors

Target	Intervention	Clinical Trials No.	Phase	Condition
PD-1	Pidilizumab	NCT01952769	Phase I/II	Diffuse pontine glioma
	Pembrolizumab + MRI-guided laser ablation	NCT02311582	Phase I/II	Recurrent malignant glioma
	Nivolumab + DC Vaccines	NCT02529072	Phase I	Recurrent brain tumors
	Pembrolizuma + Adenovirus	NCT02798406	Phase II	Recurrent glioblastoma or gliosarcoma
	Nivolumab + FPA008	NCT02526017	Phase I	Advanced solid tumors, including glioma
	Nivolumab +Galunisertib	NCT02423343	Phase I/II	Advanced solid tumors, including glioma
	Nivolumab + anti-LAG-3 or anti-CD137	NCT02658981	Phase I	Recurrent glioblastoma
CTLA-4 & PD-1	Ipilimumab/nivolumab, or both + Temozolomide	NCT02311920	Phase I	Newly diagnosed glioblastoma or gliosarcoma
	Nivolumab ± Ipilimumab vs Bevacizumab	NCT02017717	Phase III	Recurrent glioblastoma
PD-L1	MEDI4736 ± radiotherapy vs MEDI4736 + Bevacizuma	NCT02336165	Phase II	Glioblastoma
IDO	Indoximod + Temozolomide + Bevacizumab + Radiation	NCT02052648	Phase I/II	Adult patients with primary malignant brain tumors
	Indoximod + Temozolomide + Conformal Radiation	NCT02502708	Phase I	Pediatric patients with primary malignant brain tumors

Conclusões

- SNC particularidades diferem dos demais tecidos
  - Barreira hematoencefálica/ sistema linfático/ microambiente tumoral
- Dados pouco mais robustos são em vacinas
- Fase 3 - negativos
- Imunoterapia em gliomas parece que tem alguma atividade somente em tumores de alto grau
- Respostas duráveis raras
- Clinical trials

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