XLVIII Reunión Anual
SOCIEDAD ESPAÑOLA DE NEURORRADIOLOGÍA

S.E.N.R
Sociedad Española de Neurorradiología

COMPLICACIONES NEUROLÓGICAS DE LAS NUEVAS TERAPIAS TUMORALES

¿QUÉ DEBEMOS SABER?

Víctor M Suárez Vega

Sección Neurorradiología

Clínica Universidad de Navarra

- **Nuevas terapias tumorales**
  - Estirpe astrocítica alto grado (III y IV)
  - Estirpe oligodendroglial
  - Afectación secundaria del SN
- **Complicaciones**
  - SNC y SNP
  - Hallazgos en la imagen

- **Nuevas terapias tumorales**
  - **Estirpe astrocítica alto grado (III y IV)**
  - Estirpe oligodendroglial
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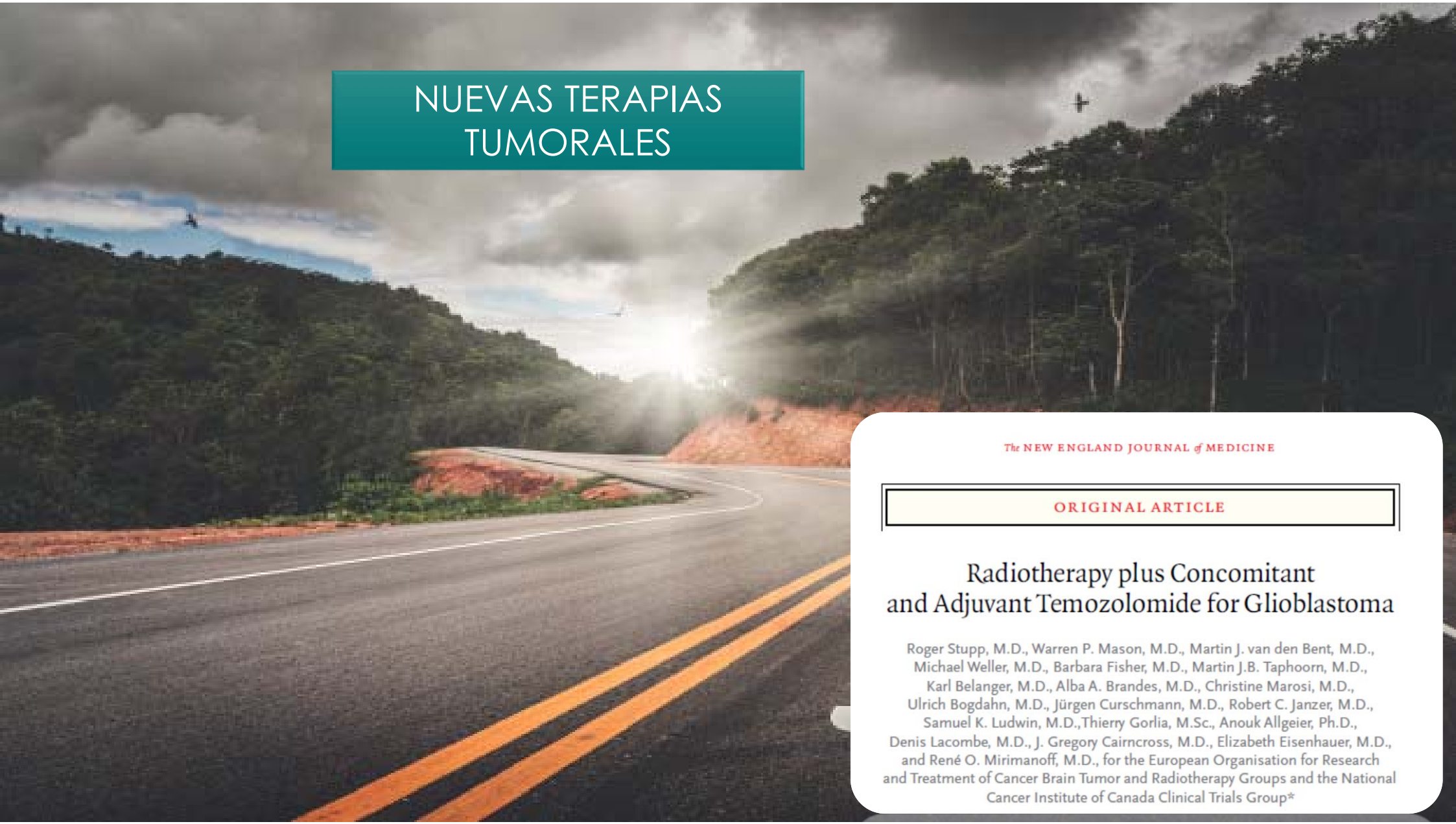
- **Complicaciones**
  - SNC y SNP
  - Hallazgos en la imagen

NUEVAS TERAPIAS TUMORALES



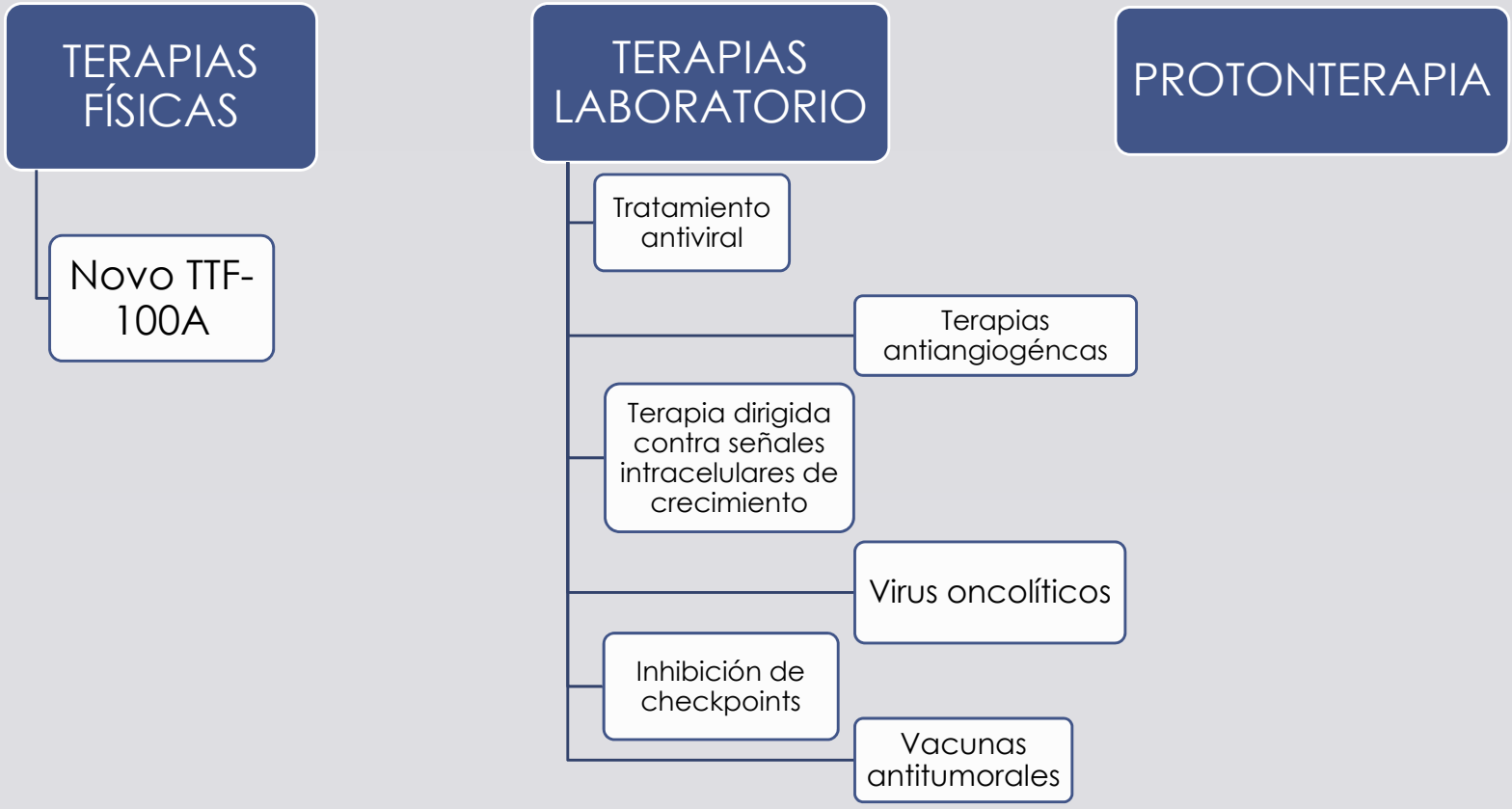
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

CLASIFICACIÓN NUEVAS TERAPIAS



TERAPIAS FÍSICAS: NOVO TTF-100A

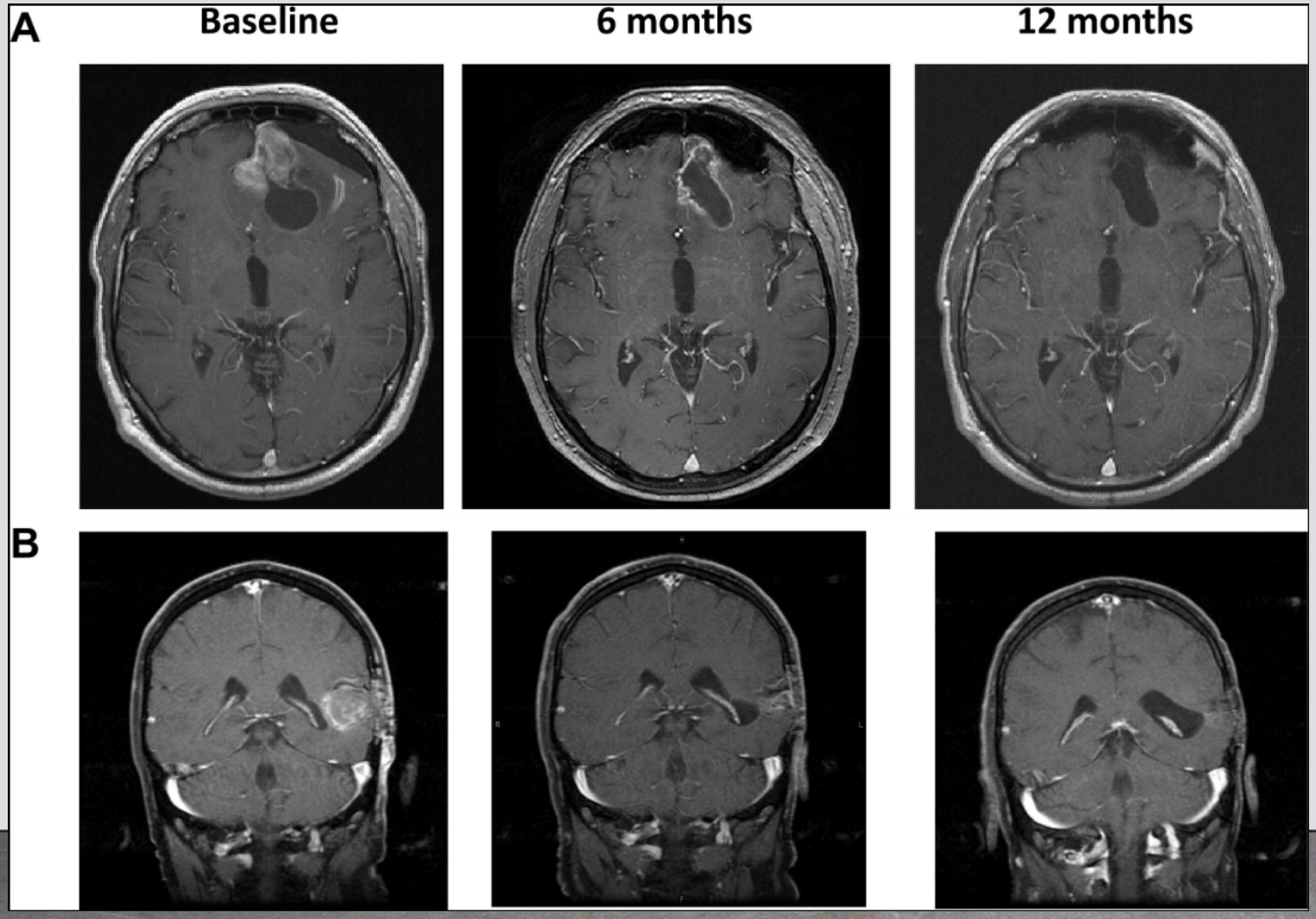
- Tumor treating fields
- Campos eléctricos de polaridad alternante
- 4 transductores en cabeza afeitada
- Al menos 18 horas al día
- 2011 FDA aprueba uso para GBM recurrente
- Efecto dielectroforético en microtúbulos del huso mitótico
- **Dermatitis**

Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma

A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew A. Kanner, MD; Santosh Kesari, MD, PhD; David M. Steinberg, PhD; Steven A. Toms, MD, FACS, MPH; Lynne P. Taylor, MD, FAAN; Frank Lieberman, MD; Antonio Silvani, MD; Karen L. Fink, MD, PhD; Gene H. Barnett, MD, MBA; Jay-Jiguang Zhu, MD, PhD; John W. Henson, MD, MBA, FAAN; Herbert H. Engelhard, MD, PhD; Thomas C. Chen, MD, PhD; David D. Tran, MD, PhD; Jan Sroubek, MD; Nam D. Tran, MD, PhD; Andreas F. Hottinger, MD, PhD; Joseph Landolfi, DO; Rajiv Desai, MD; Manuela Caroli, MD; Yvonne Kew, MD, PhD; Jerome Honnorat, MD, PhD; Ahmed Idbaih, MD, PhD; Eilon D. Kirson, MD, PhD; Uri Weinberg, MD, PhD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD

- Mayor ILP
- Mayor supervivencia global



- Primer ensayo con TTF en monoterapia
- No mejoría de supervivencia global

Stupp R, Euro J Cancer, 2012

TRATAMIENTO ANTIVIRAL

- Presencia de proteínas de CMV en células de GBM
- ¿CMV favorece progresión tumoral?
- Tratamiento *Valganciclovir*
- Ensayo VIGAS
- Evidencia dudosa

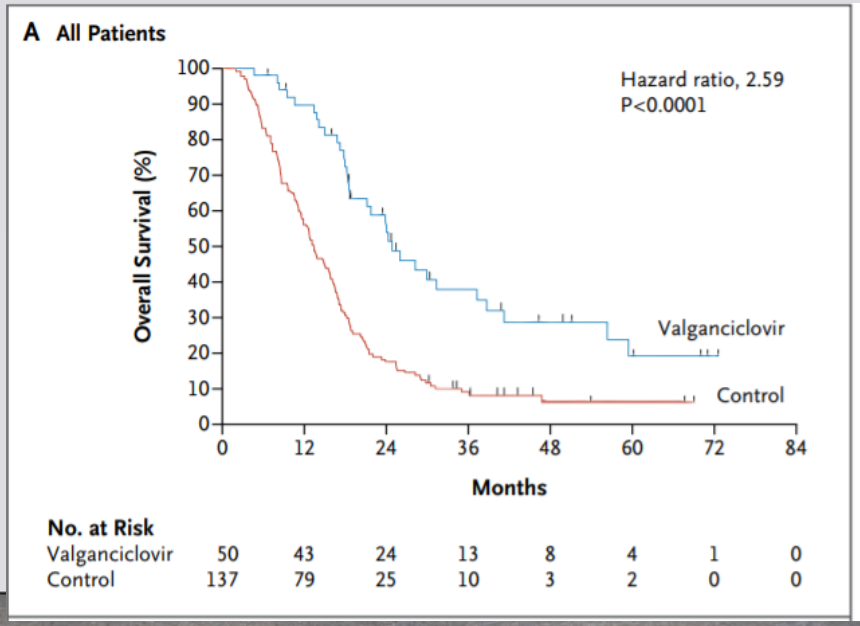


Figure 1. Kaplan–Meier Estimates of Overall Survival in Patients with Glioblastoma Receiving Antiviral Therapy against Cytomegalovirus (CMV).

Shown are estimates of overall survival for patients with glioblastoma who received valganciclovir for anti-CMV therapy and for 137 contemporary controls with glioblastoma who received similar baseline therapy. The patients receiving valganciclovir included 50 who received at least 1 dose of the drug (Panel A), 40 who received more than 6 months of therapy (Panel B), and 25 who received at least 6 months of therapy and thereafter received continuous treatment with valganciclovir (Panel C).

with a 2-year survival rate of 90% and median overall survival of 56.4 months (P<0.001) (Fig. 1C). It is unlikely that any bias in patient selection could have resulted in these high rates of survival. Our results highlight the need for a randomized

Söderberg N, N Engl J Med 2013

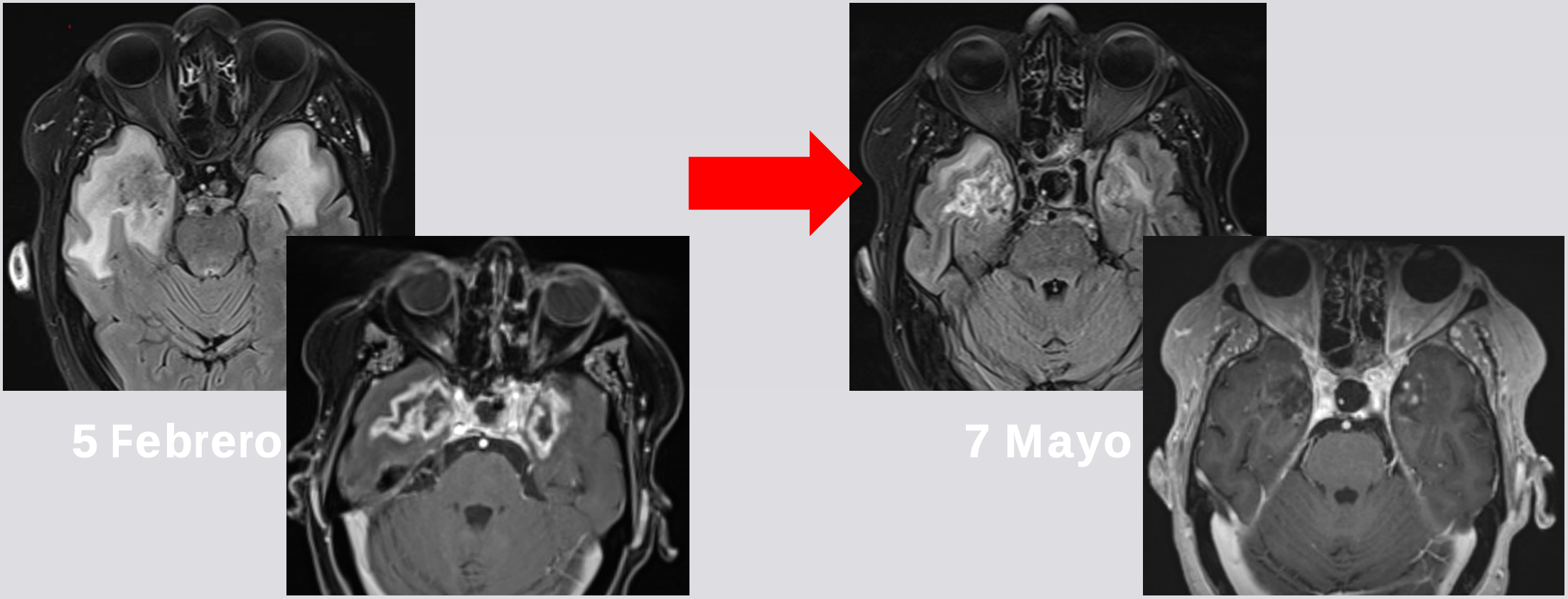
TERAPIAS ANTIANGIOGÉNICAS

- GBM tumor muy vascularizado
- Altos niveles de VEGF
- Atacar angiogénesis **efecto antitumoral**
  - Inhibe nutrición de células neoplásicas
  - Efecto tóxico directo en células que expresan VEGF
  - Normalización de la microvasculatura
- Disminución del **edema vasogénico** → mejoría clínica
- **Bevacizumab** (Avastin®) Ab monoclonal contra el VEGF
- FDA aprobación en GBM recurrente 2009
- **Cediranib** (inhibidor de la tirosín kinasa)

TERAPIAS ANTIANGIOGÉNICAS: PSEUDORESPUESTA

- Rápida disminución en realce y "tamaño" del tumor sin disminución "real" de la actividad tumoral
- Alta tasa de respuesta (34-60%)
- Puede verse tan pronto como horas tras la administración
- PLE a los 6 meses del 40%
- Efecto muy modesto sobre la supervivencia global
- Nuevo patrón de progresión

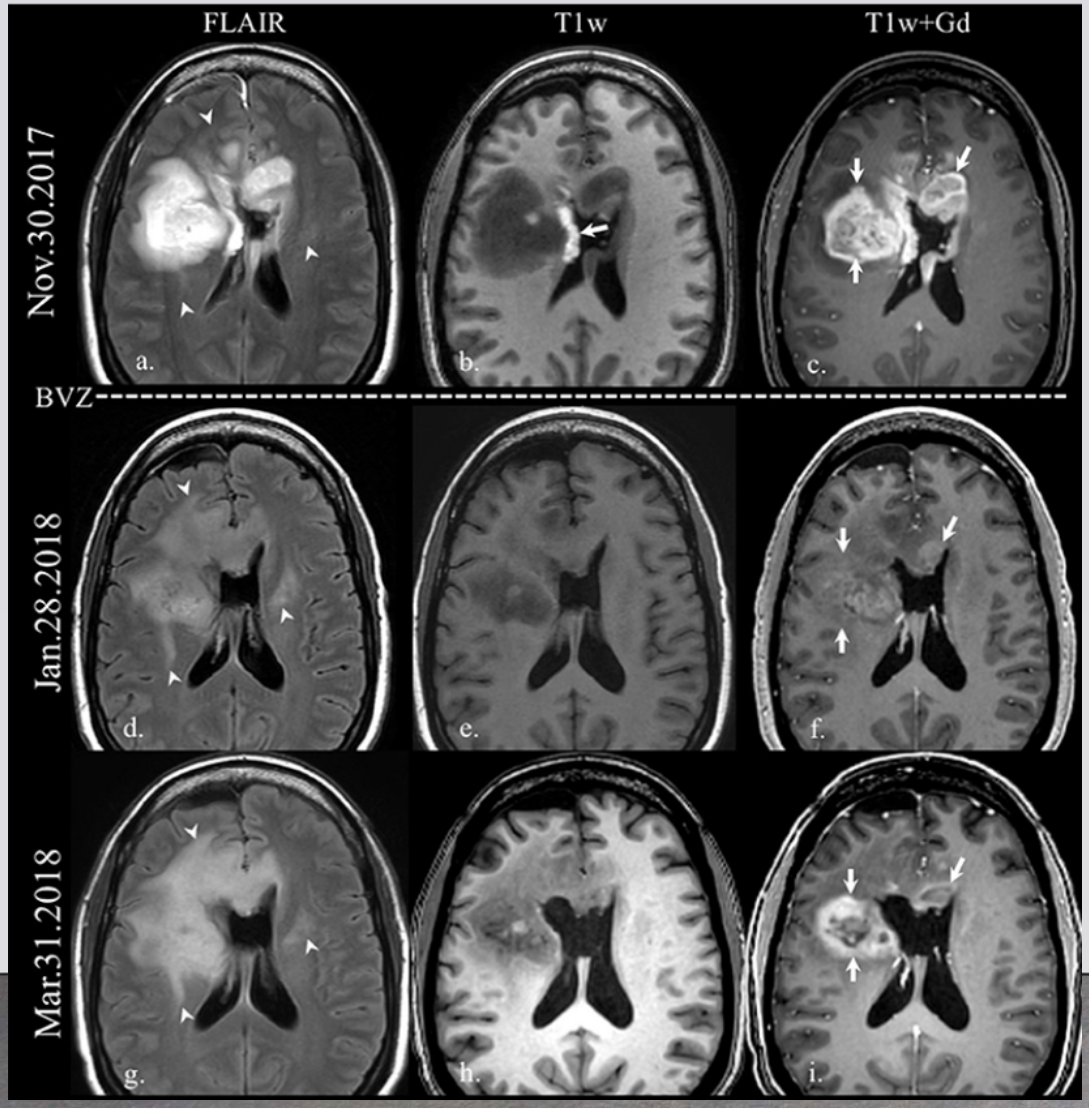
TERAPIAS ANTIANGIOGÉNICAS: PSEUDORESPUESTA



5 Febrero

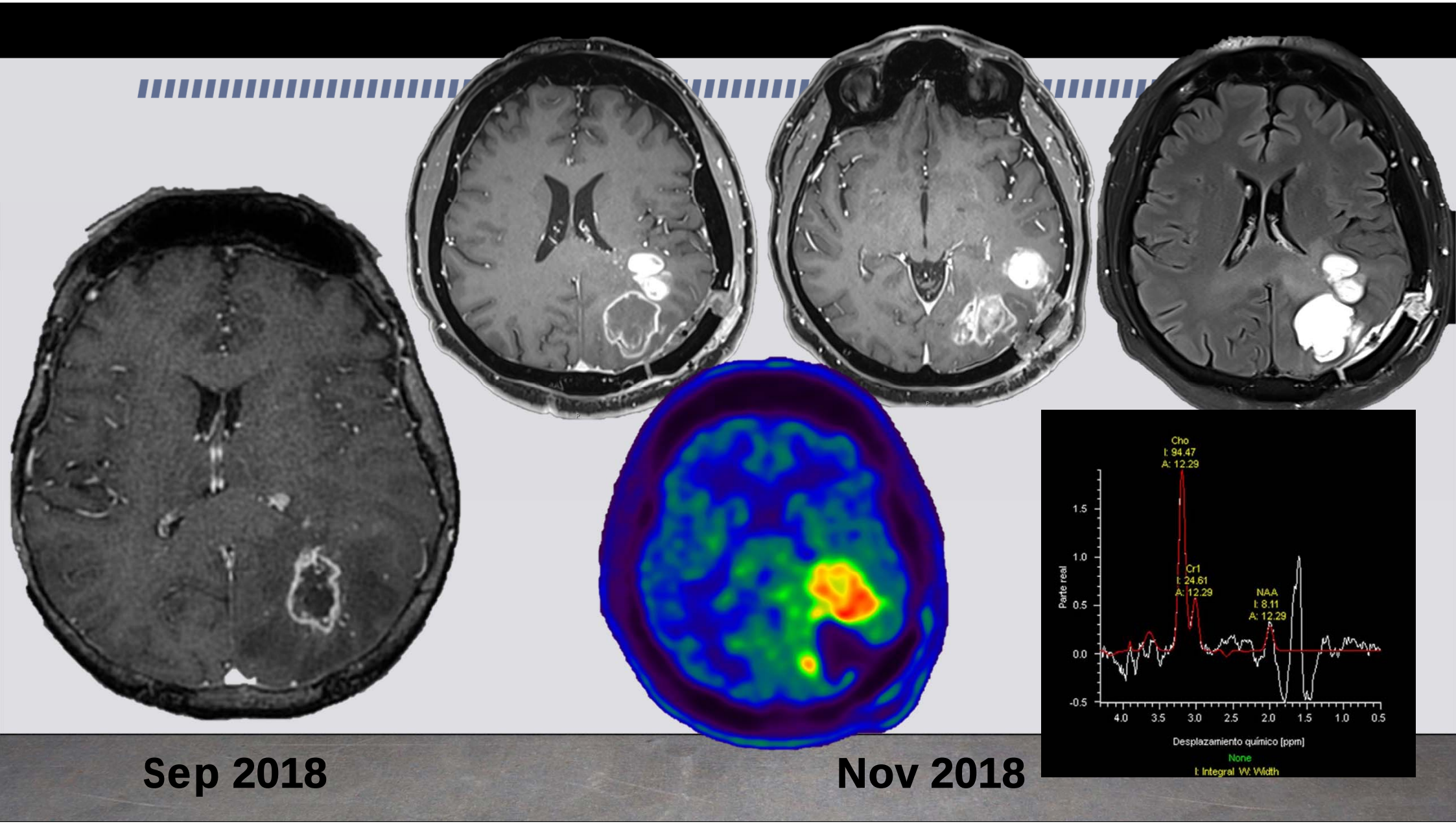
7 Mayo

TERAPIAS ANTIANGIOGÉNICAS: PSEUDORESPUESTA



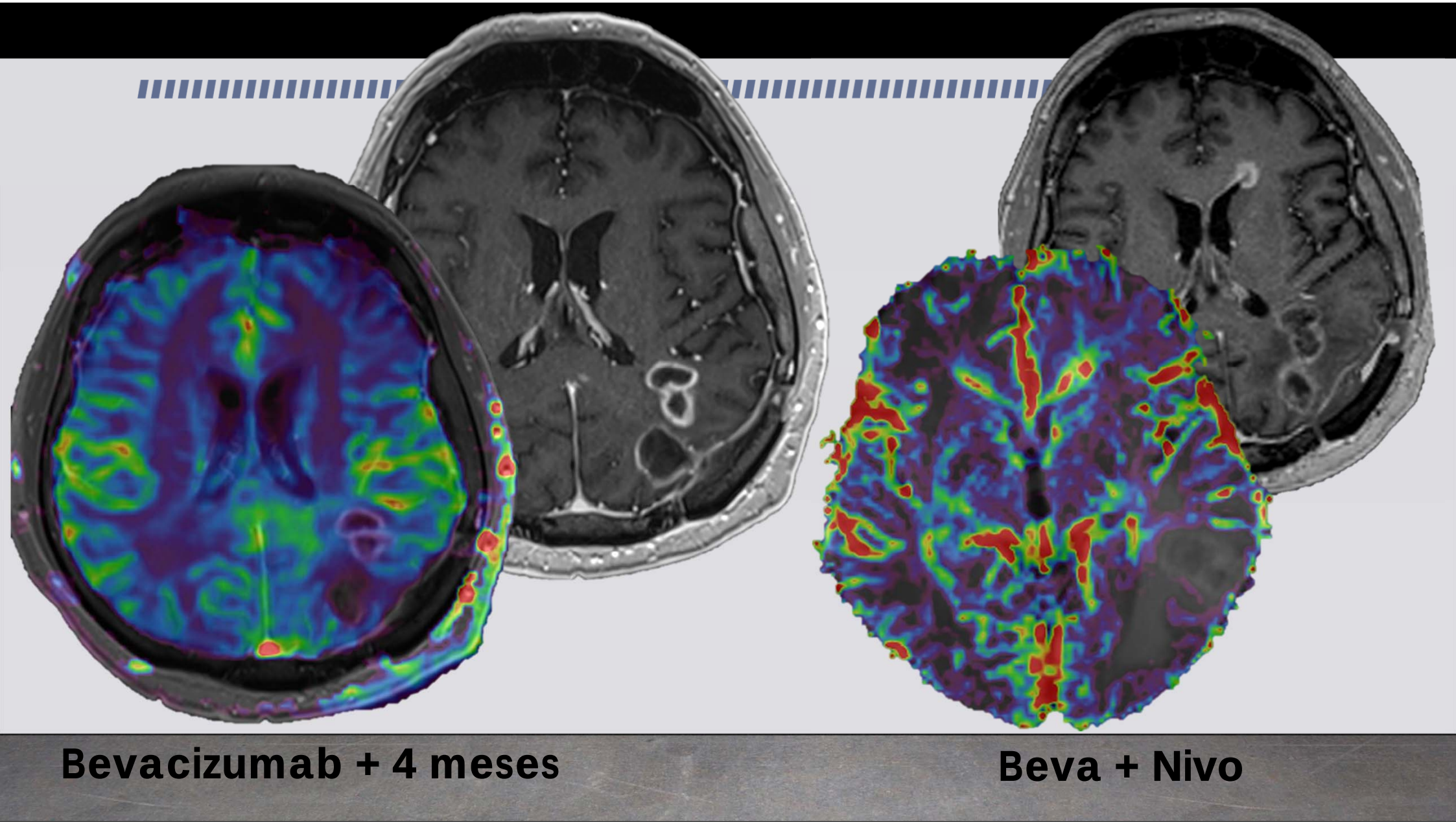
- GBM IDH wt, MGMT NOS
- Primera recidiva tras protocolo Stupp
- Gran disminución de realce de enfermedad medible
- Progresa la enfermedad no medible

Front Neurol, 2019



Sep 2018

Nov 2018


Bevacizumab + 4 meses
Beva + Nivo

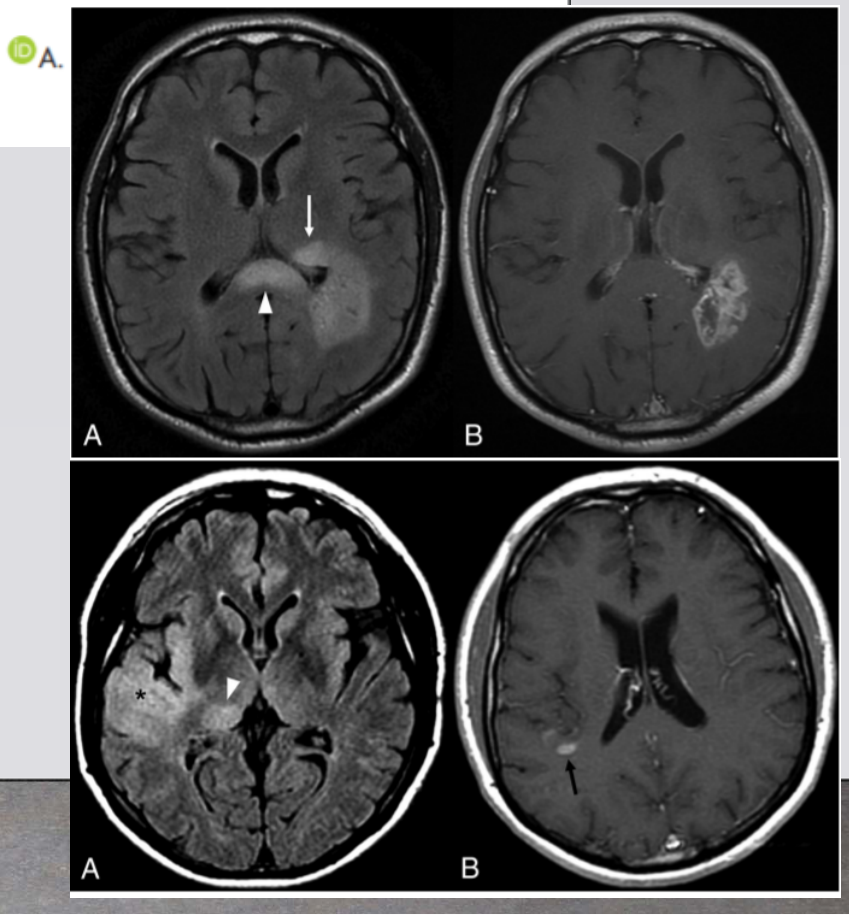
Non-contrast enhancing tumor

Non-Contrast-Enhancing Tumor: A New Frontier in Glioblastoma Research

Conventional and advanced MRI features useful for differentiating between nCET and edema

nCET	Edema
Conventional MRI features	
Gray matter involvement	Spares the gray matter
Eccentric	Relatively concentric around enhancing lesions
Relatively mild FLAIR and T2 hyperintensity	More marked FLAIR and T2 hyperintensity
Focal parenchymal expansion	More diffuse mass effect if marked edema
Advanced MRI sequences	
Relative diffusion restriction	Facilitated diffusion
Choline elevation, NAA depletion	Normal MRS findings
Elevated rCBV around CET	rCBV elevation confined to CET

Note:—rCBV indicates relative cerebral blood volume.



TERAPIAS ANTIANGIOGÉNICAS: COMPLICACIONES

- Fatiga
- Dolor de cabeza
- Hipertensión
- Tromboembolismos
- Perforación intestinal
- Hemorragia intracraneal (< 3%)
- PRESS

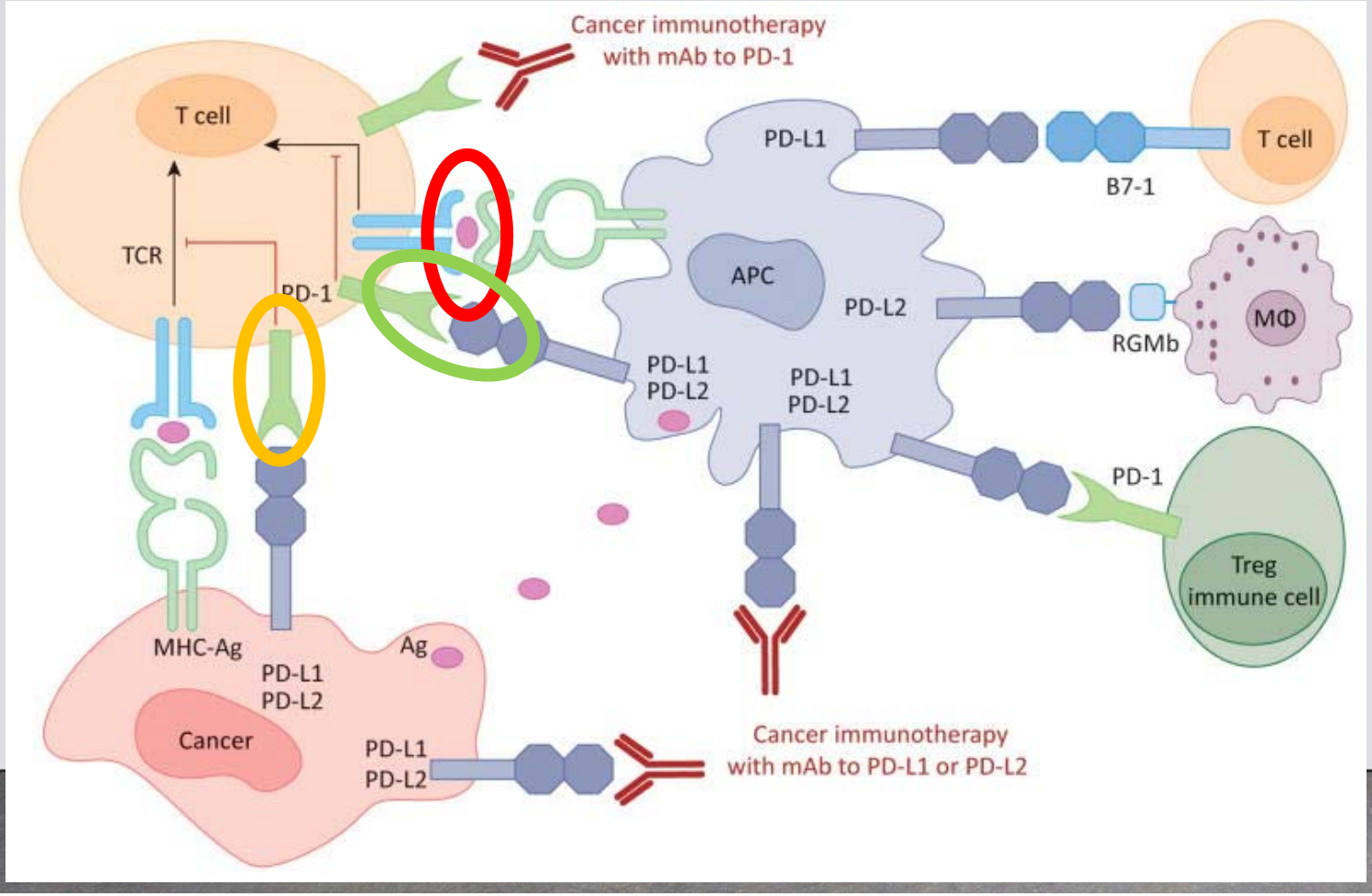
INMUNOTERAPIAS

- Inhibidores de "checkpoints" — Nivolumab, Pembrolizumab
- Vacunas / Virus oncolíticos
- Conjugados AB-Fármaco — Depatuxizumab
- CAR-T cells
- Inhibidores proteasa — Marizomib

INHIBIDORES DE "CHECKPOINTS"

EJE PD-1/PD-L-1 en GBM

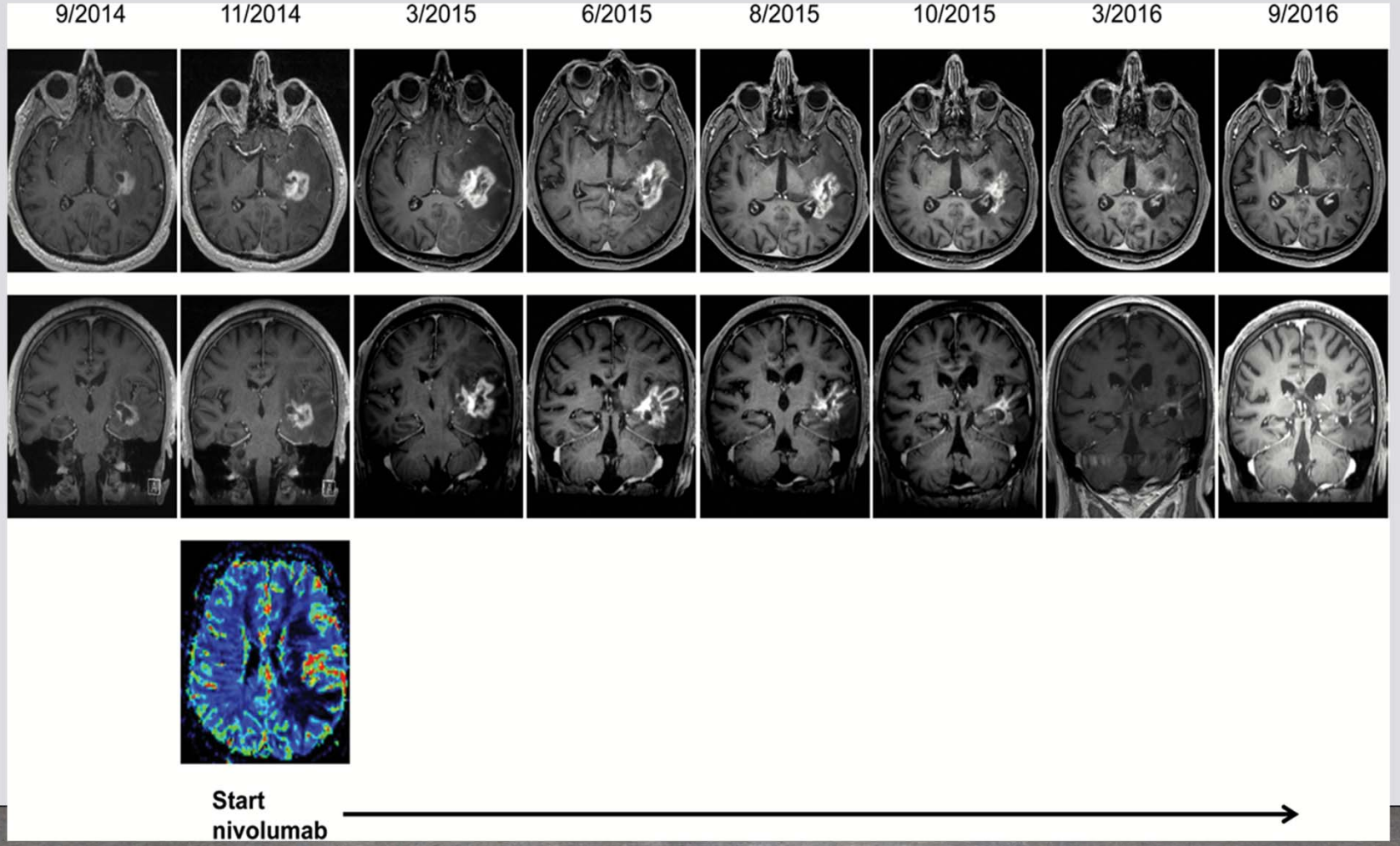
Nivolumab
Pembrolizumab



- APC presenta Ag al linfocito T y se activa
- Expresa PD-1 membrana
- PD-1/PD-L1 desactiva linfocito T

Ohaegbulam, Trends Mol Med, 2015

INHIBIDORES DE “CHECKPOINTS”



Roth P, Neuro-Oncology, 2017

INHIBIDORES DE "CHECKPOINTS"

Lancet Oncol. 2015 November ; 16(15): e534–e542. doi:10.1016/S1470-2045(15)00088-1.

Immunotherapy Response Assessment in Neuro-Oncology (iRANO): A Report of the RANO Working Group

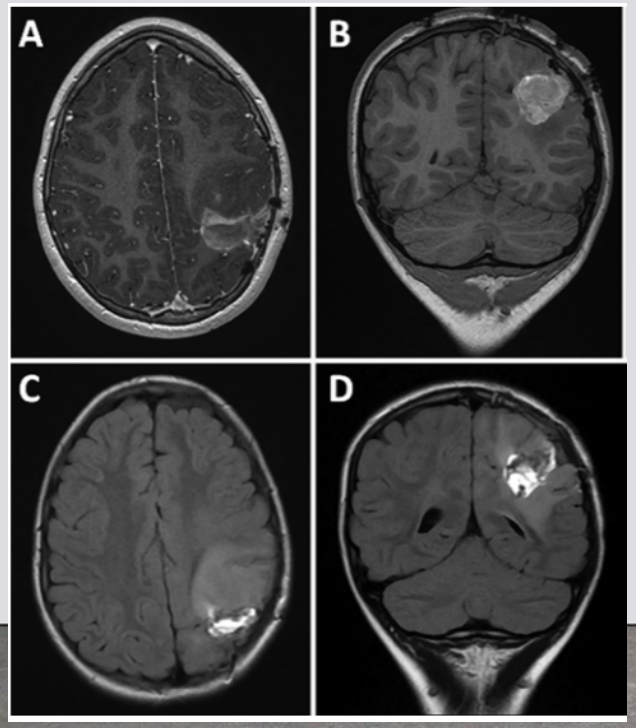
Key Considerations: RANO, irRC and iRANO

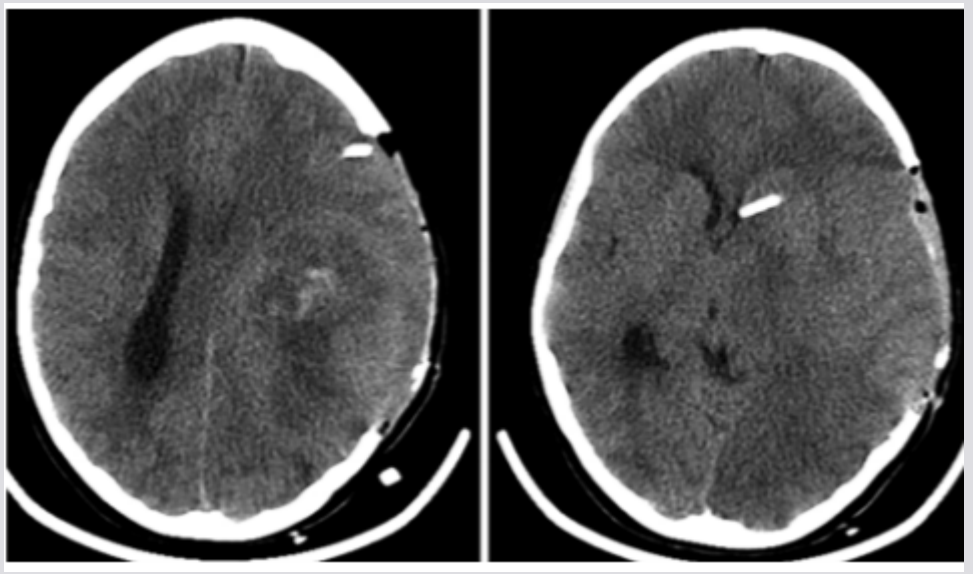
	RANO	irRC	iRANO (if ≤ 6 months after start of immunotherapy)	iRANO (if > 6 months after start of immunotherapy)
Is a repeat scan required to confirm radiographic PD for patients without significant clinical decline?	No	Yes	Yes	No
Minimal time interval for confirmation of progression for patients without significant clinical decline?	Not applicable	≥ 4 week	≥3 months	Not applicable
Is further immunotherapy treatment allowed after initial radiographic PD (if clinically stable) pending progression confirmation	Not applicable	Yes	Yes	Not applicable
Does a new lesion define PD?	Yes	No	No	Yes

INHIBIDORES DE “CHECKPOINTS”

Severe cerebral edema following nivolumab treatment for pediatric glioblastoma: case report

Xiao Zhu, BA,[1] Michael M. McDowell, MD,[1] William C. Newman, MD,[1] Gary E. Mason, MD, MS,[2] Stephanie Greene, MD,[1] and Mandeep S. Tamber, MD, PhD[1]



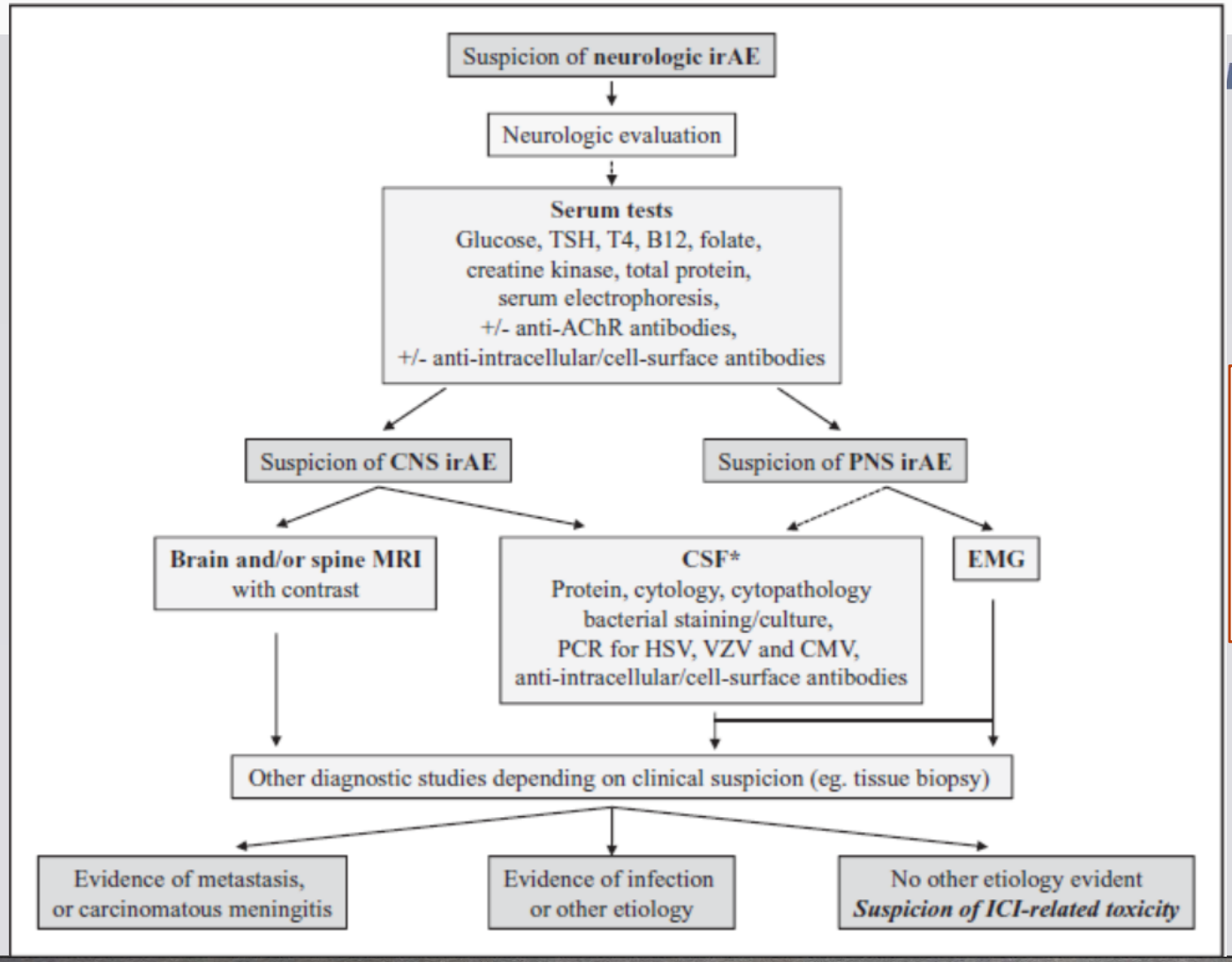


J Neurosurg Pediatr, 2017

Table 3. Selected neurologic immune-related adverse event involving the central and peripheral nervous system

Type of irAE	Suspected causing agents	Estimated frequency (%)	Selected reported cases[a] (references)	Reported onset delay after ICI initiation (weeks)	Immune-modulating treatments	Reported outcome
irAE involving the central nervous system						
Encephalitis	Nivolumab, pembrolizumab, nivolumab + ipilimumab	0.1–0.2	8 [17▪,27–30]	4–28	Corticosteroids (7/8) IVIg (1/8)	Complete recovery (6/8) Partial improvement (1/8) Death (1/8)
Aseptic meningitis	Ipilimumab	NA	3 [33–35]	1–7	Corticosteroids (3/3)	Complete recovery (3/3)
irAE involving the peripheral nervous system						
Acute immune Demyelinating Polyneuropathy	Nivolumab, pembrolizumab, ipilimumab	0.1–0.2	4 [34,61–63]	5–12	Corticosteroids (4/4) IVIg (2/4) Plasmapheresis (1/4) Tacrolimus (1/4)	Complete recovery (2/4) Death (2/4)
Chronic immune Demyelinating Polyneuropathy	Nivolumab, pembrolizumab, nivolumab + ipilimumab	NA	5 [21,61,64–66]	1–44	Corticosteroids (4/5) IVIg (4/5) Plasmapheresis (3/5) Mycophenolate mophetil (1/5)	Partial recovery (4/5) NA (1/5)
Cranial nerves neuropathie	Pembrolizumab, ipilimumab	NA	4 [19,56–58]	0.5–16	Corticosteroids (4/4) Plasmapharesis (1/4)	Complete recovery (2/4) Partial recovery (2/4)
Myasthenic syndromes	Ipilimumab, nivolumab, pembrolizumab, nivolumab + ipilimumab	0.1–0.2	8 [21,37–39,41–43]	2–6	Corticosteroids (7/8) Plasmapheresis (5/8) IVIg (5/8)	Complete recovery (1/8) Partial recovery (3/8) Death (4/8)
Myositis	Ipilimumab, nivolumab, pembrolizumab, nivolumab + ipilimumab	0.1–0.2	7 [41,49–54]	2–8	Corticosteroids (7/7) Plasmapheresis (4/7) IVIg (2/7) [illegible] (1/7) Infliximab (1/7)	Complete recovery (3/7) Partial recovery (3/7) Death (1/7)

Touat, Curr Opinion Oncol, 2017



- 1/3 pacientes déficits residuales
- Desenlace fatal raro

Touat, Curr Opinion Oncol, 2017

VIRUS ONCOLÍTICOS

- Viroterapia oncolítica se basa en usar virus recombinantes oncolíticos que maten ***selectivamente*** las células "*infectadas*" de tumor
- Muerte celular por mecanismo inmunogénicos
- Antígenos asociados al tumor se liberan al microambiente
- Actúan de estímulo para la autoinmunidad antitumoral

Currently Active or Recruiting					
Adenovirus	**Virus Construct**	**Phase**	**Therapy Regimen**	**Trial No.**	**Results**
DNX-2401 + pembrolizumab	Deletion in E1A. RGD-4C fiber modification	II	IT injection followed by Pembrolizumab (IV) every 3 weeks	NCT02798406	-
DNX-2440					
CRad-S-pk7 (loaded into neural stem cells)					
HSV					
C134					
M032					
rQNestin 34.5					
G207					

Other	Virus Construct	Phase	Therapy Regimen	Trial No.	Results
Vaccinia virus TG6002 + 5-FC	TK and RR deletion Expresses cytosine deaminase	I/II	3 weekly IV infusions, followed by oral 5-FC	NCT03294486	-
Measles Virus (MV-CEA)	expresses CEA	I	injection into resection cavity and/or IT	NCT00390299	-
Poliovirus (PVSRIPO)	attenuated (Sabin) poliovirus with IRES from HRV2	I/Ib	IT via convection- enhanced delivery	NCT01491893NCT03043391	[20]
Reovirus (REOLYSIN) + sargramostim (rGM-CSF)	unmodified reovirus	I	repeated cycles of sargamostim followed by IV virus	NCT02444546	-
Toca 511 + Toca FC	described above	II/III	injection into resection cavity followed by oral Toca FC	NCT02414165	-

Completed					
Adenovirus	**Virus Construct**	**Phase**	**Therapy Regimen**	**Trial No.**	**Results**
DNX-2401 + Temozolomide	described above	I	injection in the brain parenchyma followed by temozolomide	NCT01956734	-
DNX-2401 + IFNγ	described above	I	IT injection followed by IFNγ	NCT02197169	-
DNX-2401	described above	I/II	intracerebral infusion	NCT01582516	[21]

Martikainen, Cancers, 2019

VIRUS ONCOLÍTICOS: ENSAYOS CLÍNICOS CUN

- Adenovirus
- DNX 2401 para DIPG (Fase I)
- DNX 2440 para GBM recidivado (Fase I)

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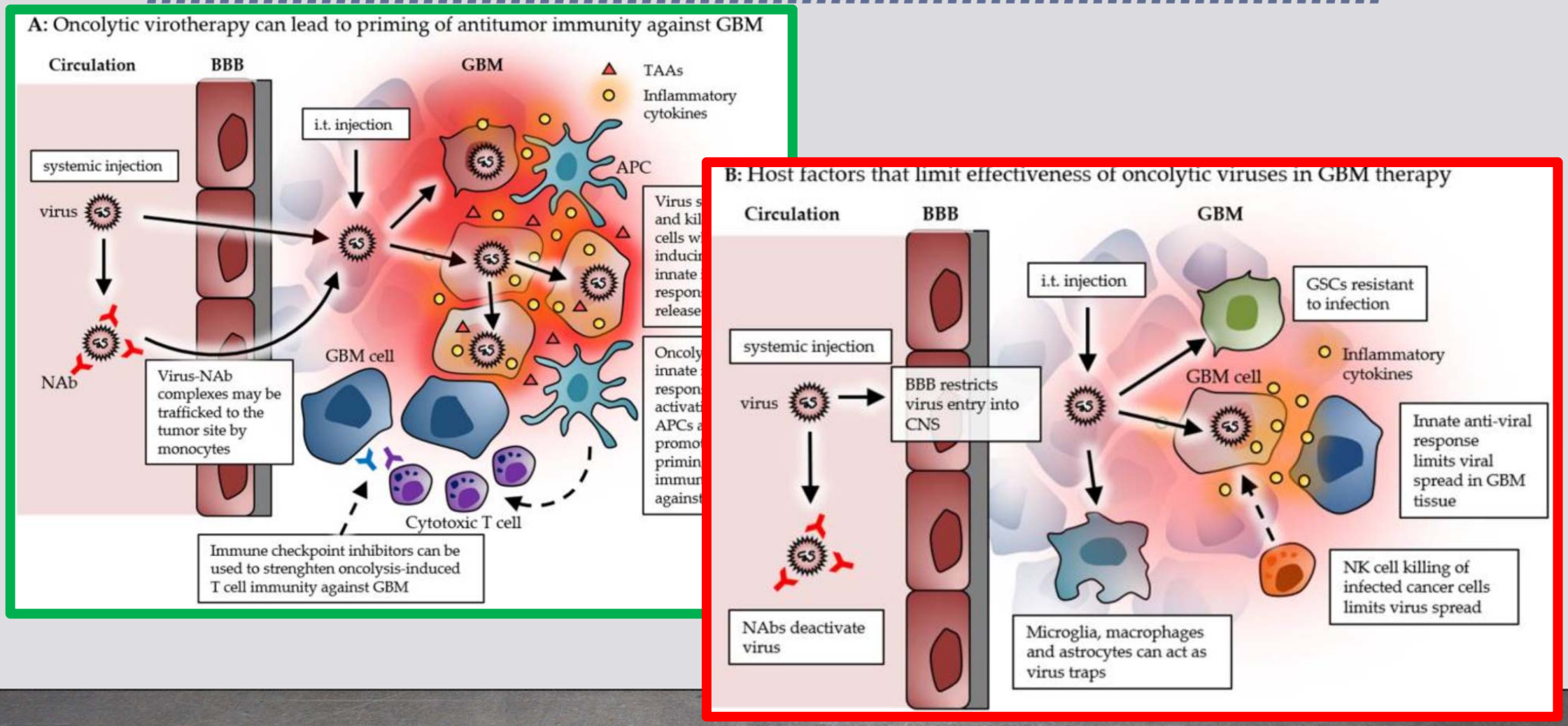
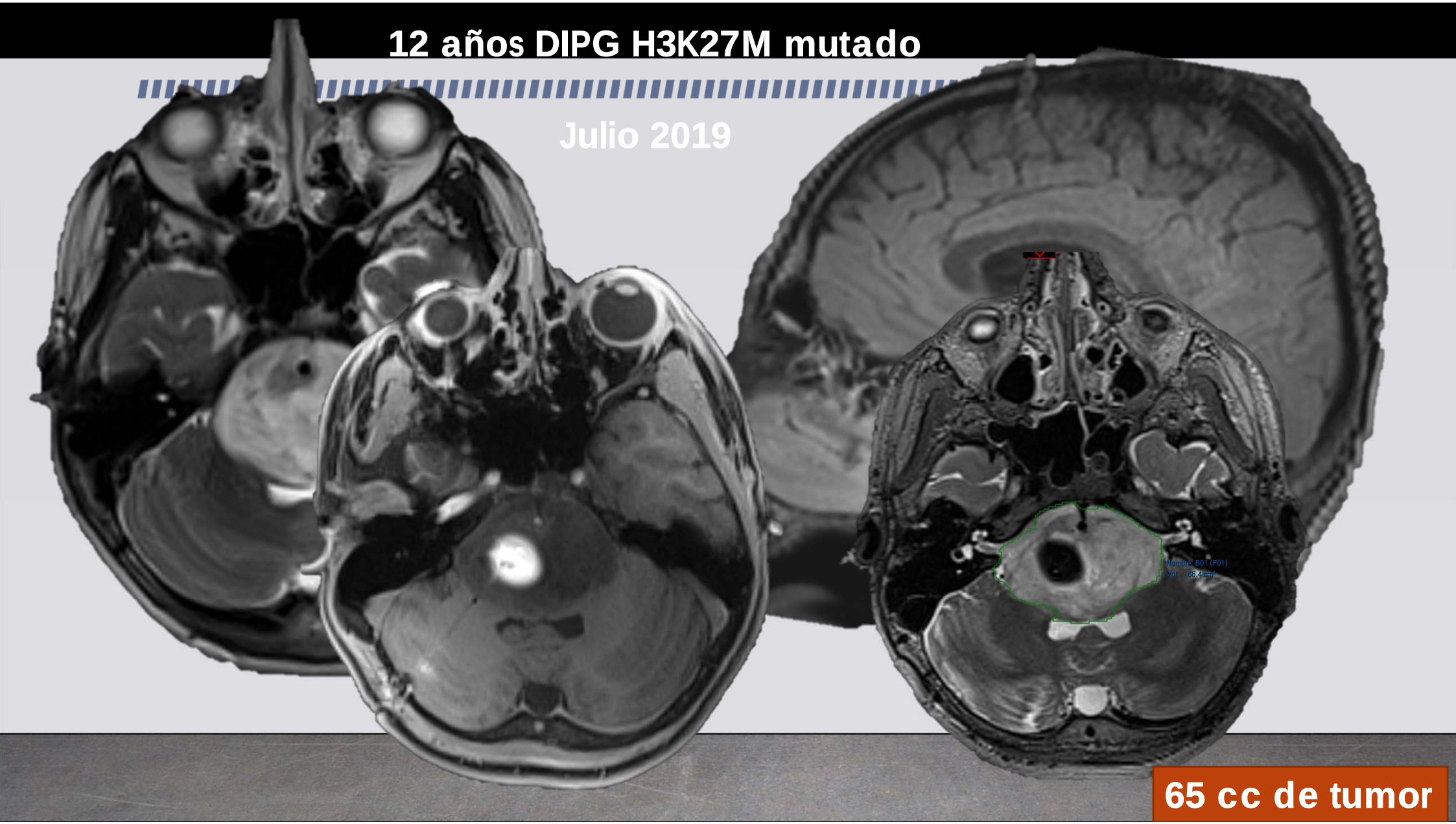
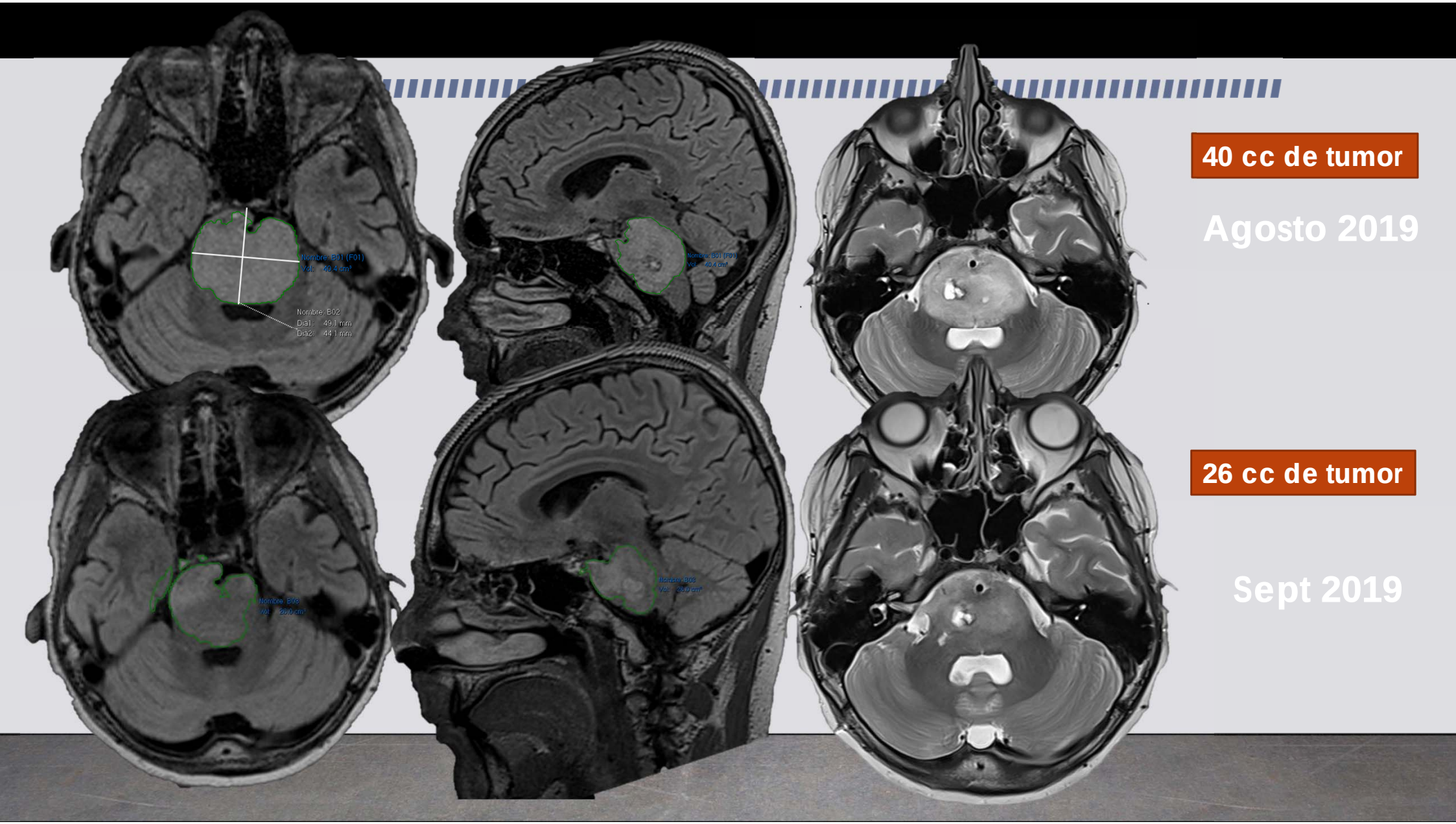
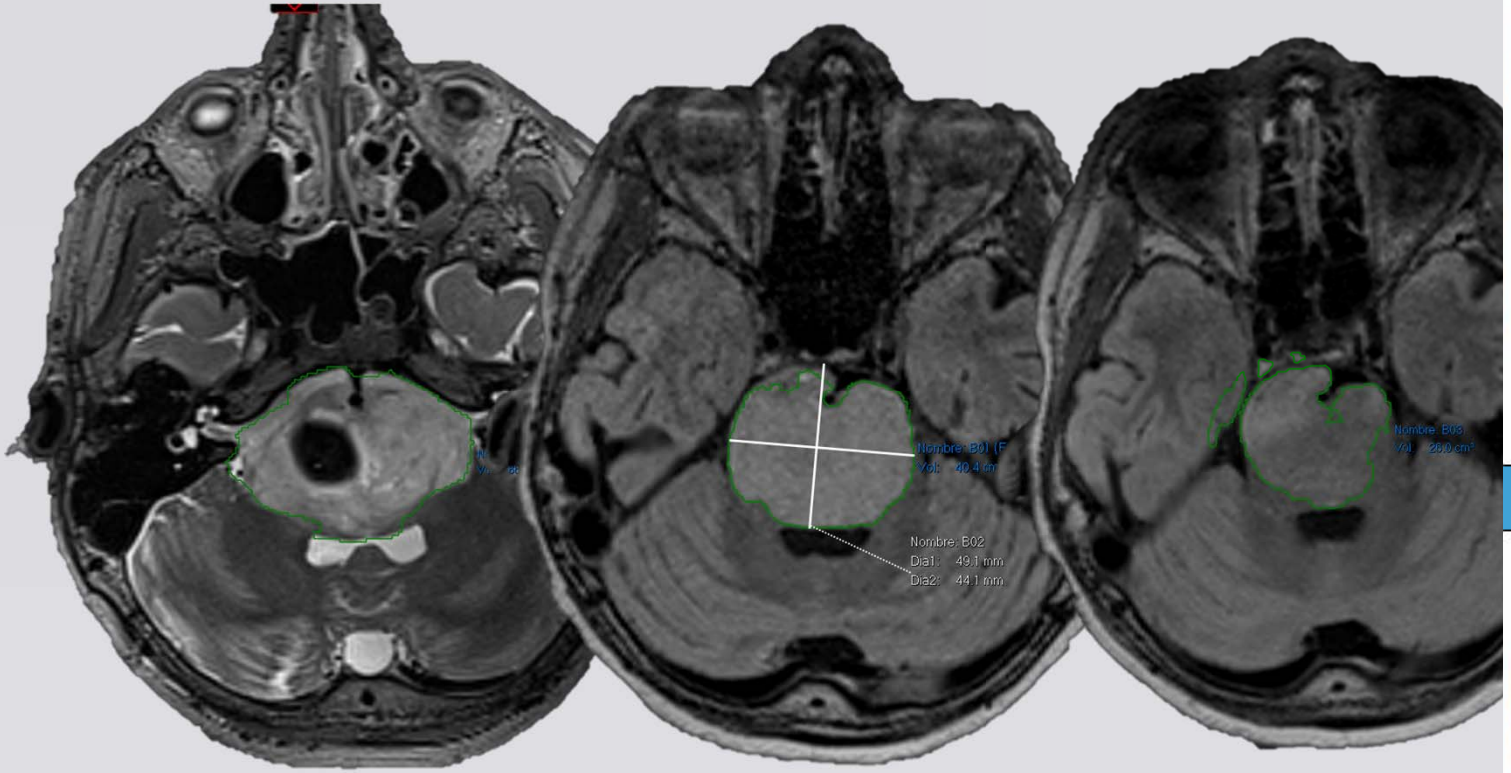
VIRUS ONCOLÍTICOS

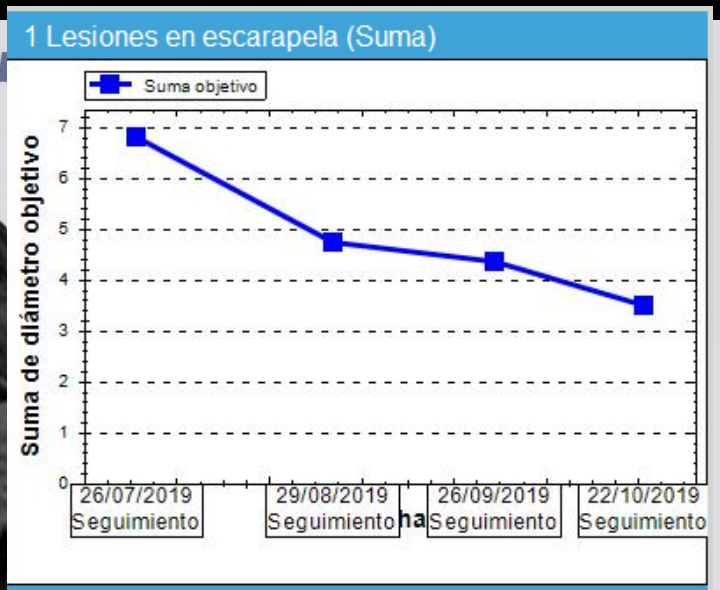


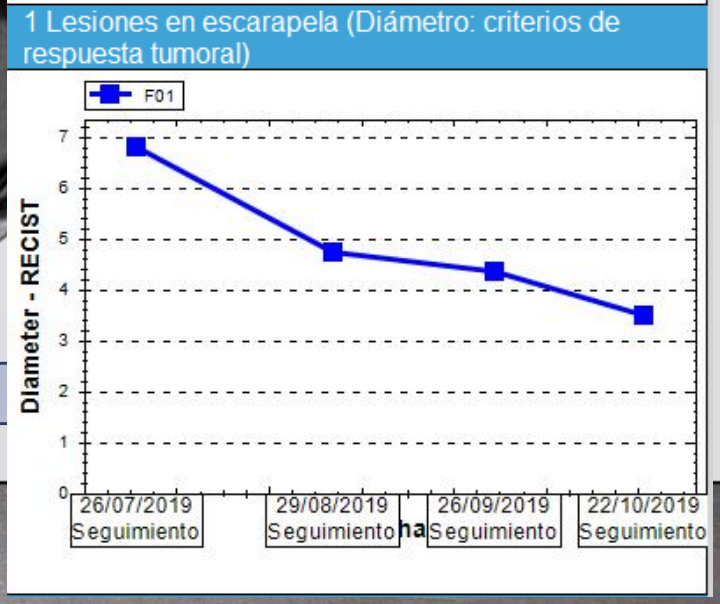
Martikainen, Cancers, 2019


12 años DIPG H3K27M mutado
Julio 2019
65 cc de tumor

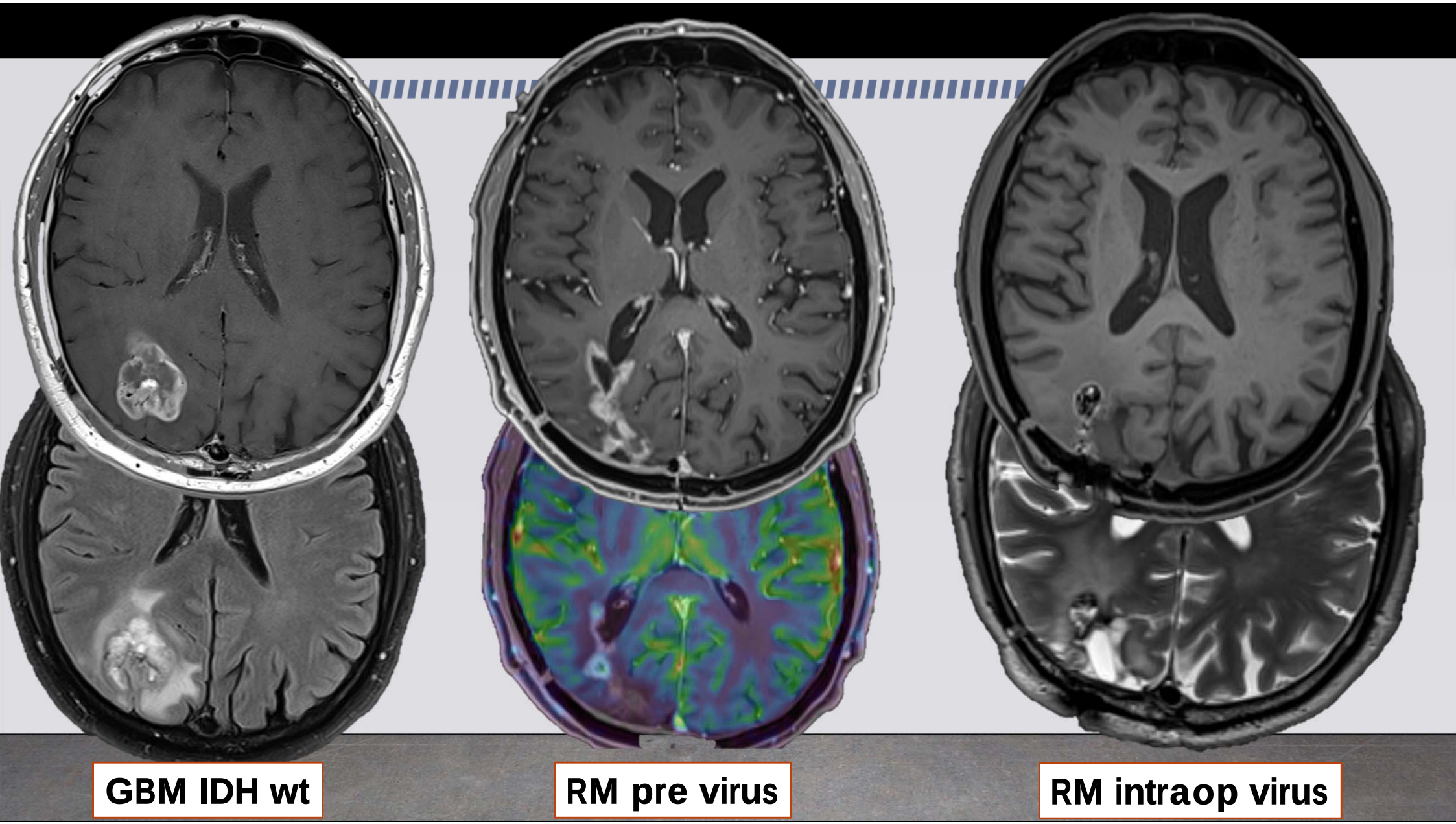

40 cc de tumor
Agosto 2019
26 cc de tumor
Sept 2019

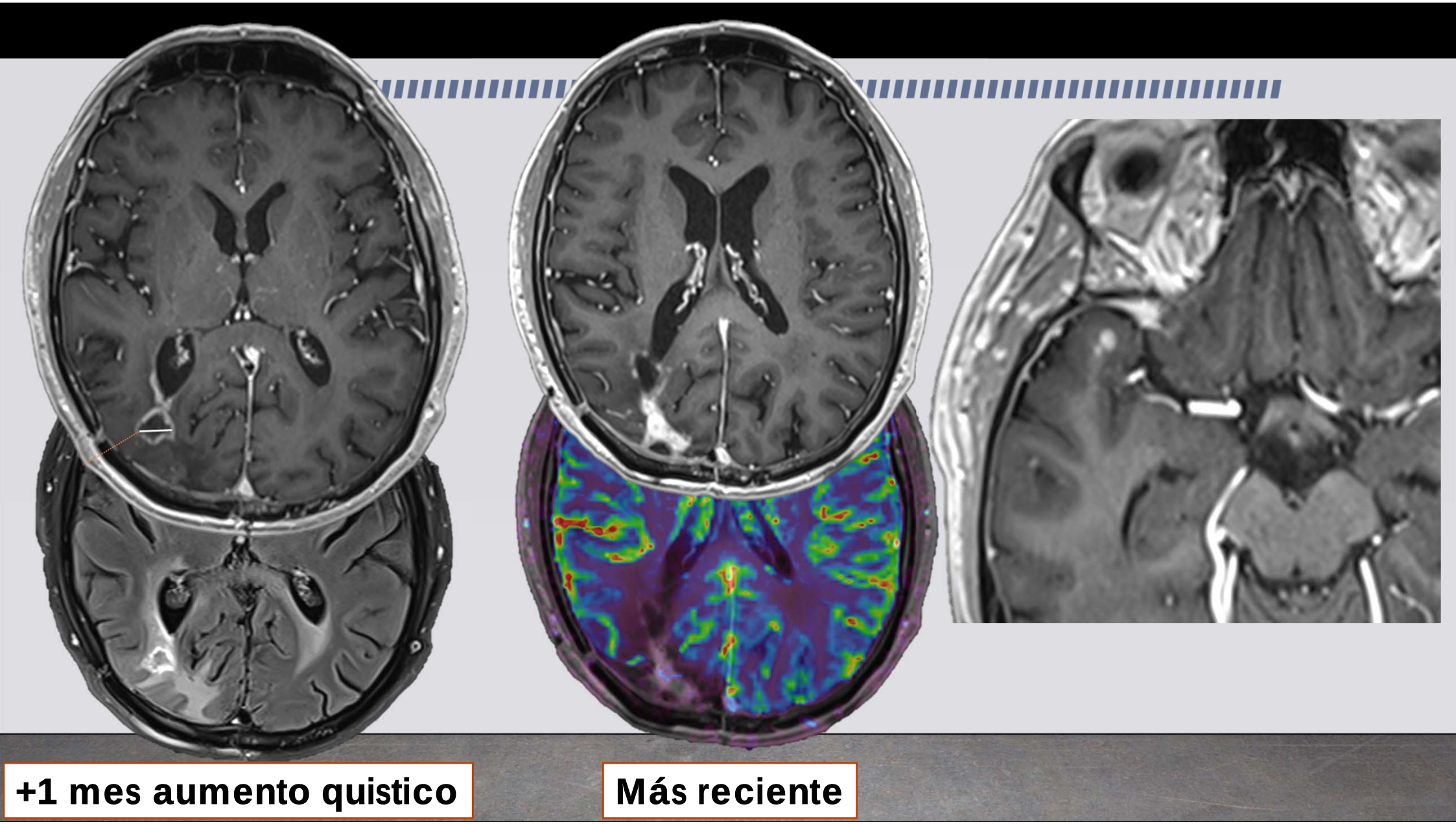






Julio 2019 **Agosto 2019** **Sept 2019**

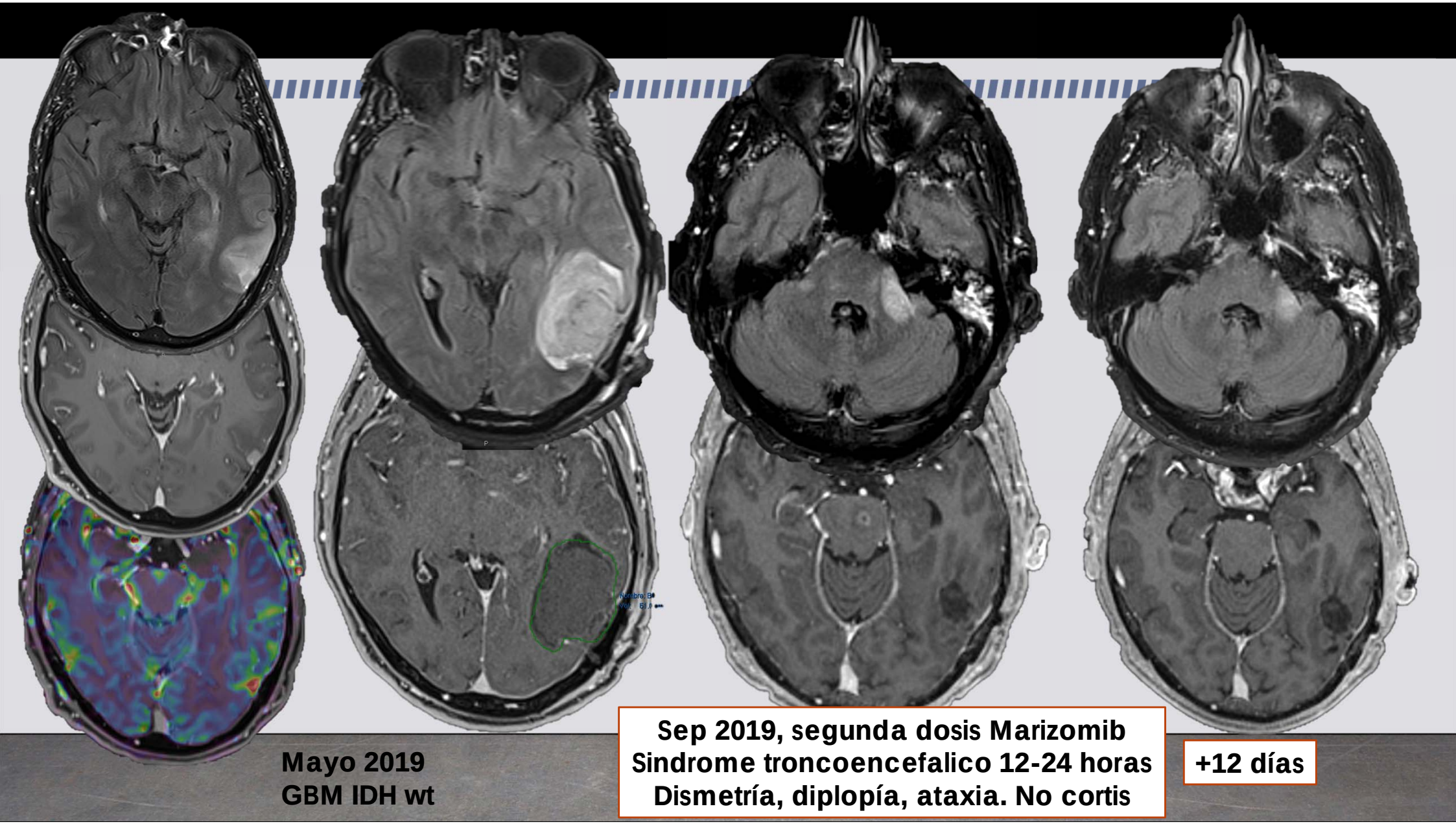

GBM IDH wt
RM pre virus
RM intraop virus


+1 mes aumento quistico
Más reciente

INHIBIDORES DEL PROTEASOMA: MARIZOMIB

- Inhibidor del proteasoma de *segunda generación*
- Salinosporamida A
- Producto marino natural
- Prometedor en el MM
- Ensayo fase III EORTC-1709-BTG

A Phase III Trial of Marizomib in Combination With Standard Temozolomide-based Radiochemotherapy Versus Standard Temozolomide-based Radiochemotherapy Alone in Patients With Newly Diagnosed Glioblastoma-FR

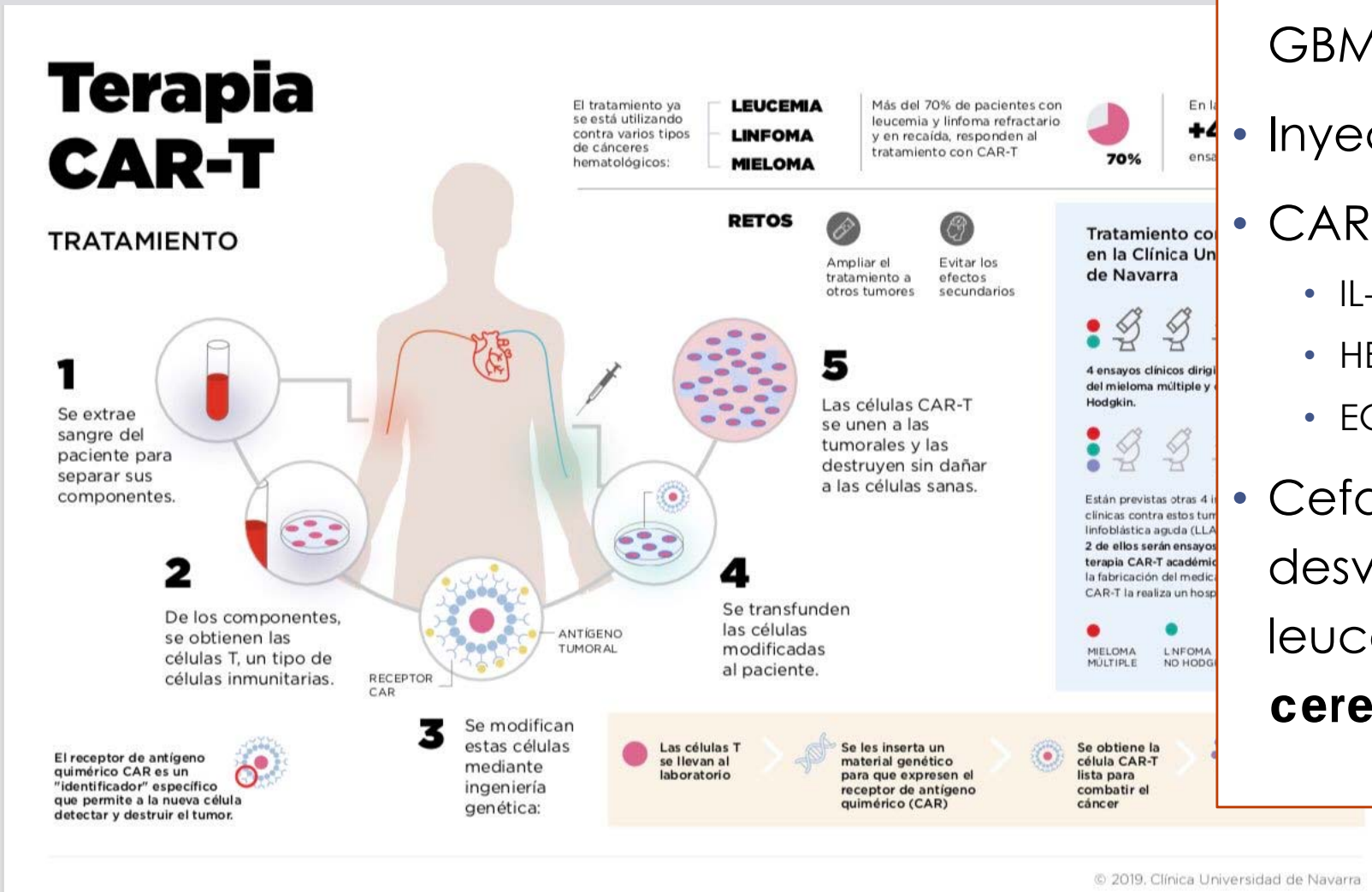


Mayo 2019
GBM IDH wt

Sep 2019, segunda dosis Marizomib
Sindrome troncoencefalico 12-24 horas
Dismetría, diplopía, ataxia. No cortis

+12 días

TERAPIA CAR-T

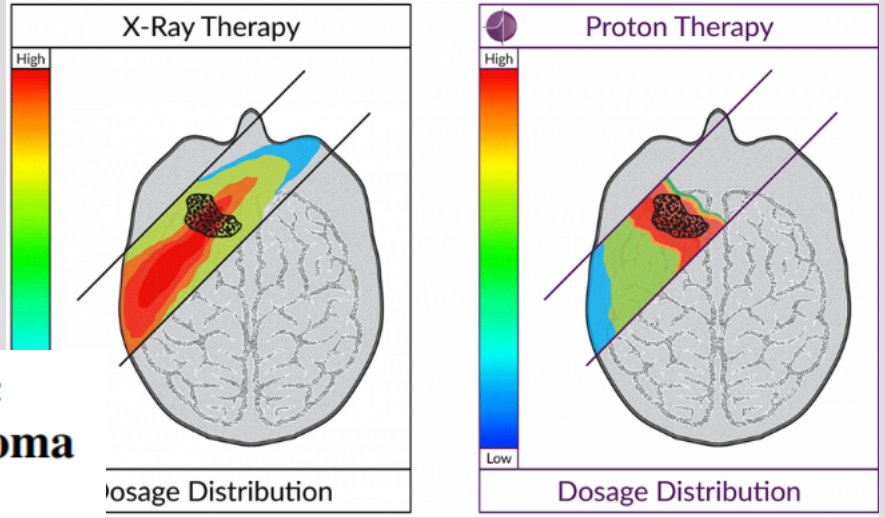


- Escasa experiencia en GBM
- Inyección periférica
- CAR targets
  - IL-13 Ra2 (N=3)
  - HER2 (N=17)
  - EGFRvIII (N=10)
- Cefalea, fatiga, desviación lingual, leucopenia, **edema cerebral** e **hidrocefalia**

Bagley, Neuro Oncol, 2018

PROTONTERAPIA

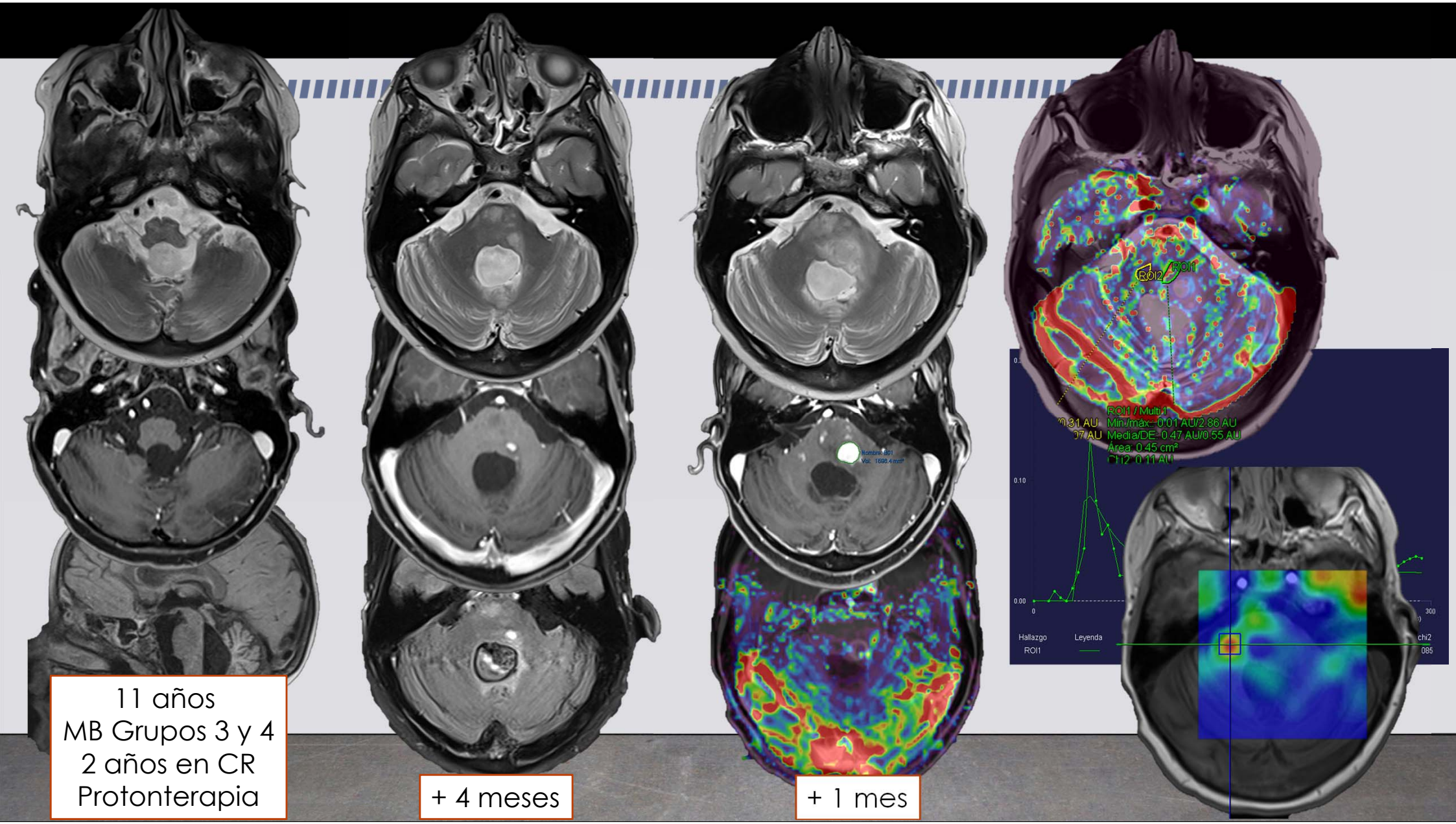
- Haz de *protones* en vez de un haz de *fotones* (radioterapia convencional)
- Permite dosis mayor focalizada en el área tumoral
- Reduciendo la dosis en áreas vecinas elocuentes en el camino del haz
- No "dosis de salida"
- Radionecrosis en bordes de isodosis

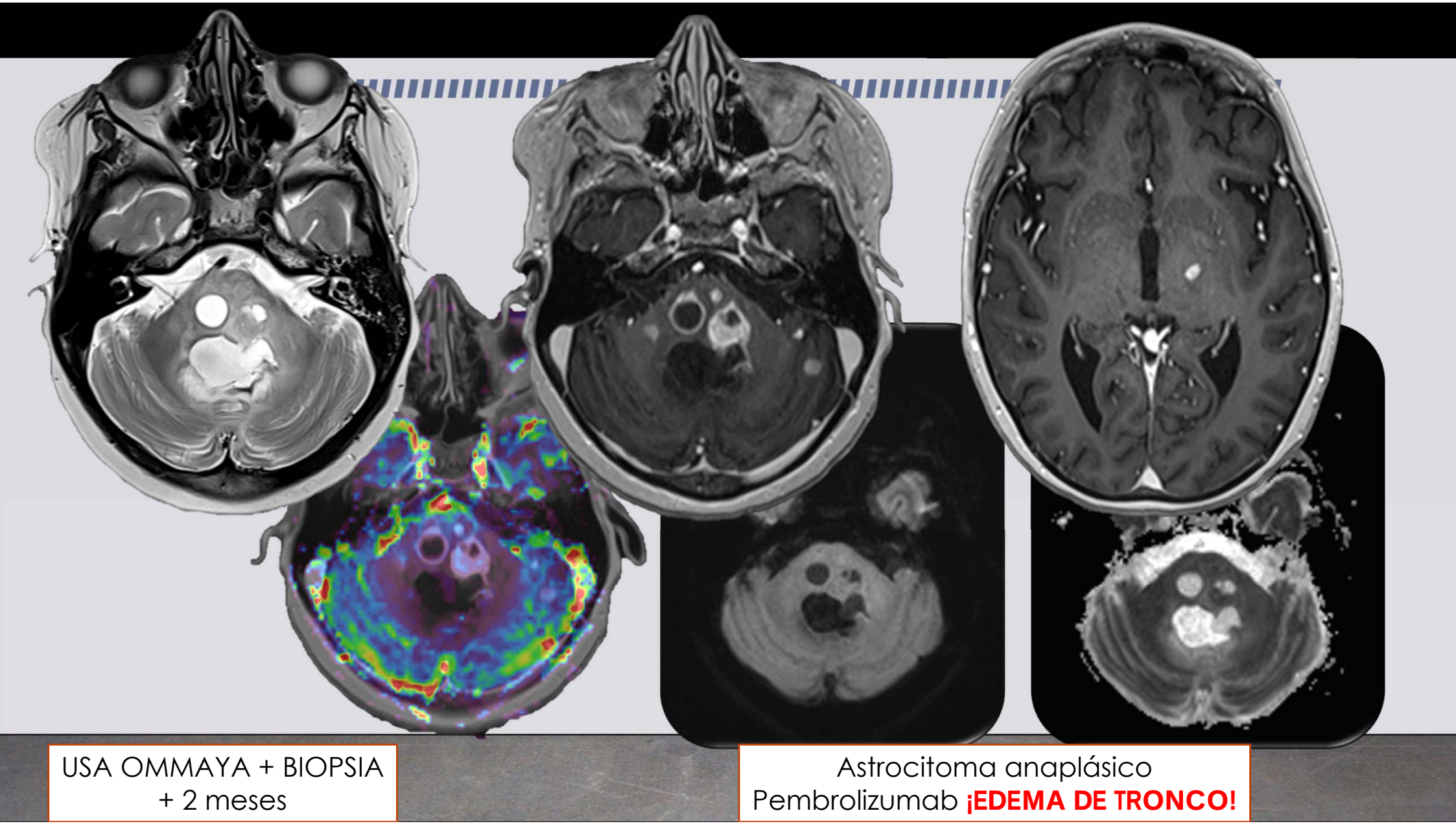


Intensity-modulated proton therapy, volumetric-modulated arc therapy, and 3D conformal radiotherapy in anaplastic astrocytoma and glioblastoma

A dosimetric comparison

S. Adeberg[1,2,3,4] · S. B. Harrabi[1,2,3] · N. Bougatf[1,2,3] · D. Bernhardt[1,3] · J. Rieber[1,2,3] · S. A. Koerber[1,2,3] ·


ROI2
ROI1
ROI1 / Multi 1
Min/max: 0.01 AU/2.86 AU
Media/DE: 0.47 AU/0.55 AU
Área: 0.45 cm²
0.10
0.00
0
300
Hallazgo
ROI1
Leyenda
11 años
MB Grupos 3 y 4
2 años en CR
Protonterapia
+ 4 meses
+ 1 mes



USA OMMAYA + BIOPSIA
+ 2 meses

Astrocitoma anaplásico
Pembrolizumab **¡EDEMA DE TRONCO!**

CONCLUSIONES

- Revisión de las nuevas terapias tumorales gliomas de alto grado
- Desde 2005, FDA solo ha aprobado 3 tratamientos para el GBM
  - Temozolamida, Bevacizumab y TTF
- Explosión de Inmunoterapia
- Combinación distintos tratamientos
- Efectos adversos de inmunoterapia son poco frecuentes pero pueden ser potencialmente mortales
- Conocer tipo de EA y tiempo de presentación (iRANO)
- Papel de Comités de tumores


MUCHAS GRACIAS
Clínica
Universidad
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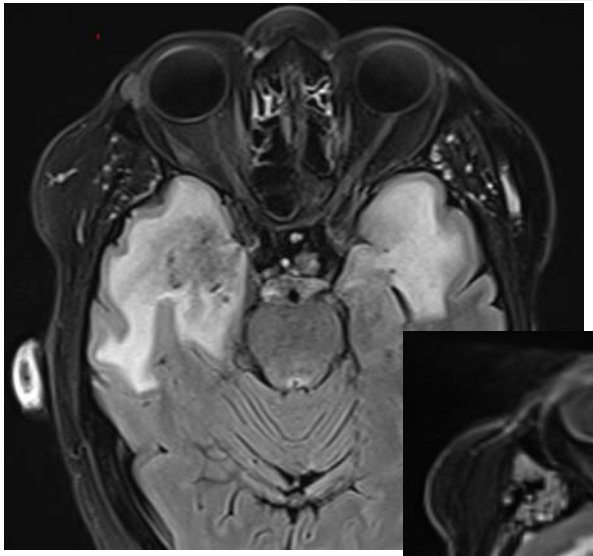
XLVIII Reunión Anual
SOCIEDAD ESPAÑOLA DE NEURORRADIOLOGÍA

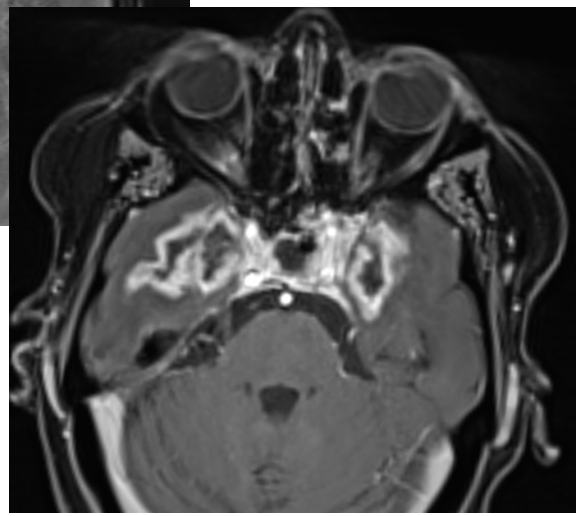
PREGUNTA 2

S.E.N.R Sociedad Española de Neurorradiología

QUINIELA

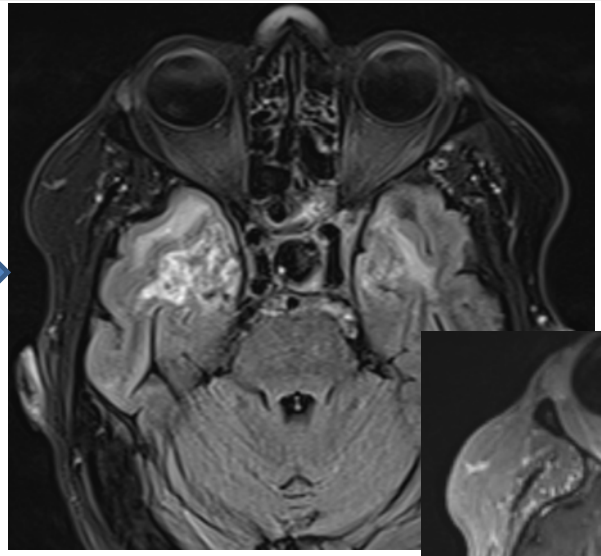
Paciente diagnosticado de radionecrosis bitemporal. ¿Qué tratamiento es más probable que haya recibido?

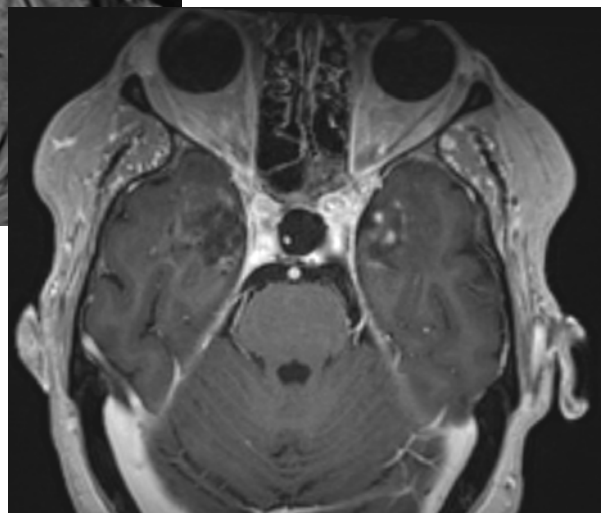




5 Febrero

¿Tratamiento?





7 Mayo

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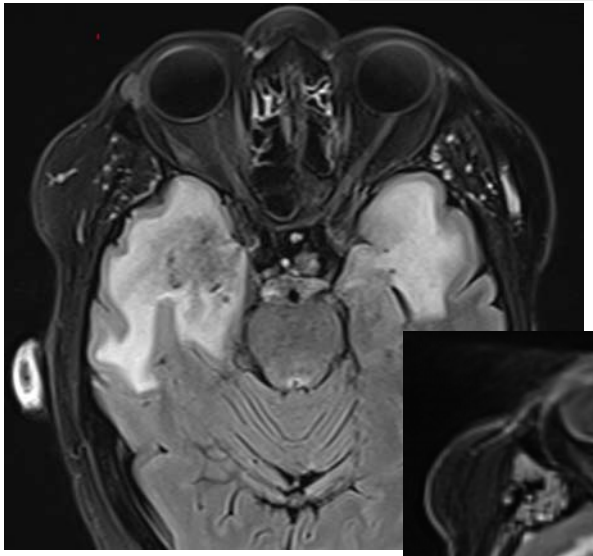
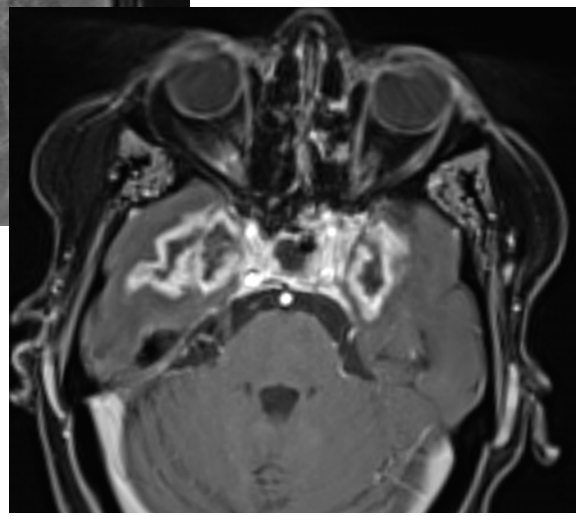
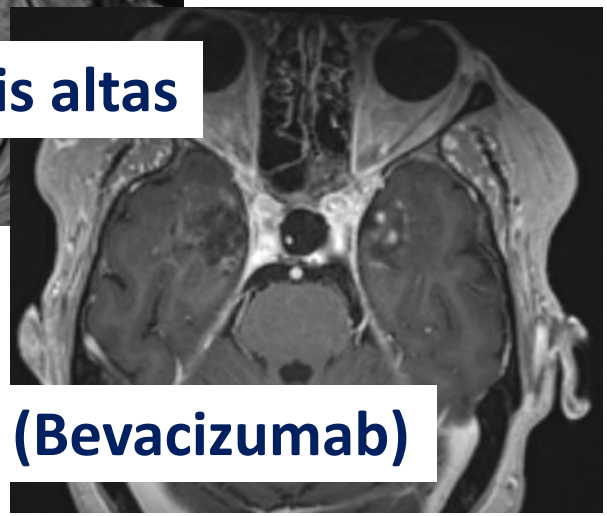


5 Febrero



¿Tratamiento?



1 Corticoides a dosis altas

X Temozolamida y Mayo

2 Antiangiogénicos (Bevacizumab)