Reunión Anual
SOCIEDAD ESPAÑOLA DE
NEURORRADIOLOGÍA

20 - 22 de octubre de 2022

ZARAGOZA
Sede: Cámara de Comercio

Clínica Universidad de Navarra

S.E.N.R
Sociedad Española de Neurorradiología

Cambios radiológicos secundarios a los nuevos tratamientos en tumores del SNC

Víctor M Suárez Vega

Sección Neurorradiología

Clínica Universidad de Navarra, Campus Madrid

CONFLICTO DE INTERÉS

No conflictos de interés (desafortunadamente)

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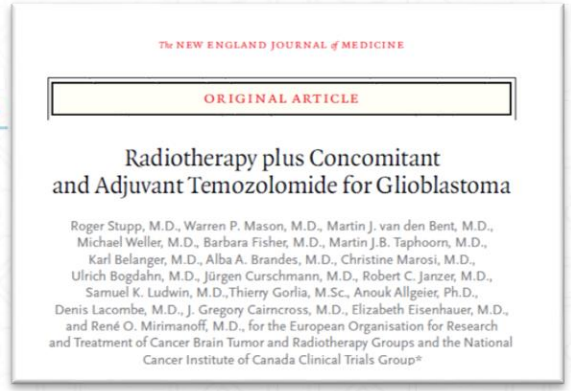
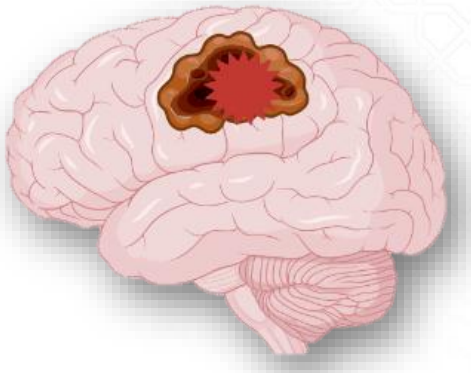

The NEW ENGLAND JOURNAL of MEDICINE

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*



PROTOCOLO STUPP

TRATAMIENTOS SEGUNDA LÍNEA

Anti-VEGF
Inmunoterapia

RANO
- **Tamaño**
- **Realce**

Pseudoprogresión

Pseudorrespuesta
iRANO
Hiperprogresión

Radionecrosis

NUEVAS TERAPIAS: CLASIFICACIÓN

TERAPIAS DE LABORATORIO (INMUNOTERAPIA)

- Tratamiento antiviral
- Terapia antiangiogénica
- Virus Oncolíticos
- “Checkpoints inhibitors”
- Vacunas antitumorales

RADIOTERAPIA (PROTONES)

TRATAMIENTO ANTIVIRAL

- Proteínas del CMV se encuentran en células GBM (20%)
- ¿CMV favorece la progression tumoral?
- Tratamiento con *Valganciclovir*
- VIGAS trial
- **Controvertido**

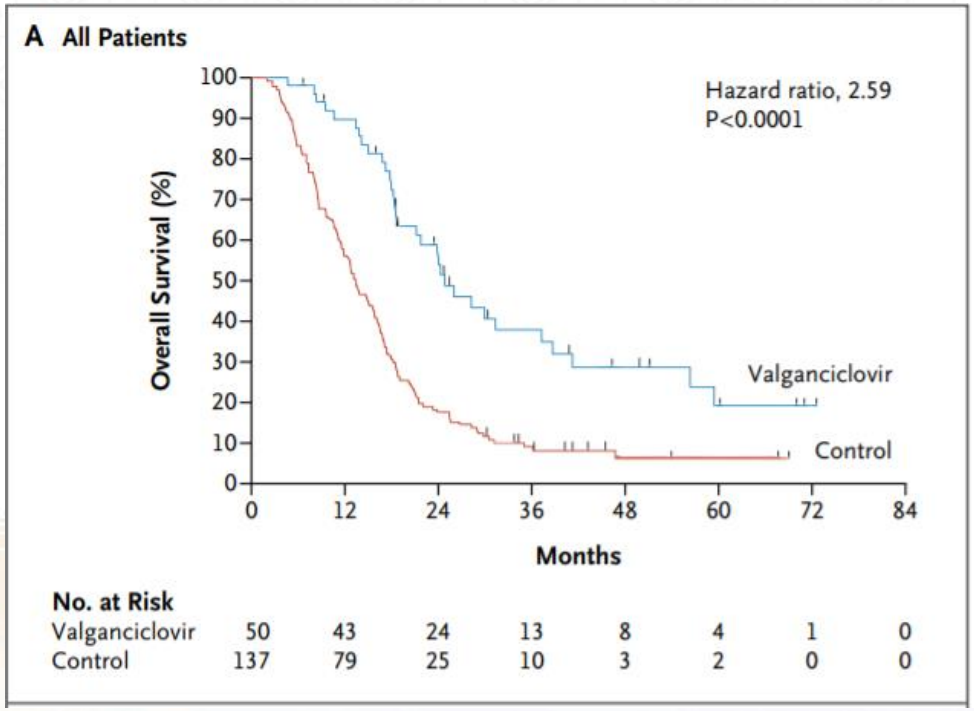


Figure 1. Kaplan–Meier Estimates of Overall Survival in Patients with Glioblastoma Receiving Antiviral Therapy against Cytomegalovirus (CMV).

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

INMUNOTERAPIAS

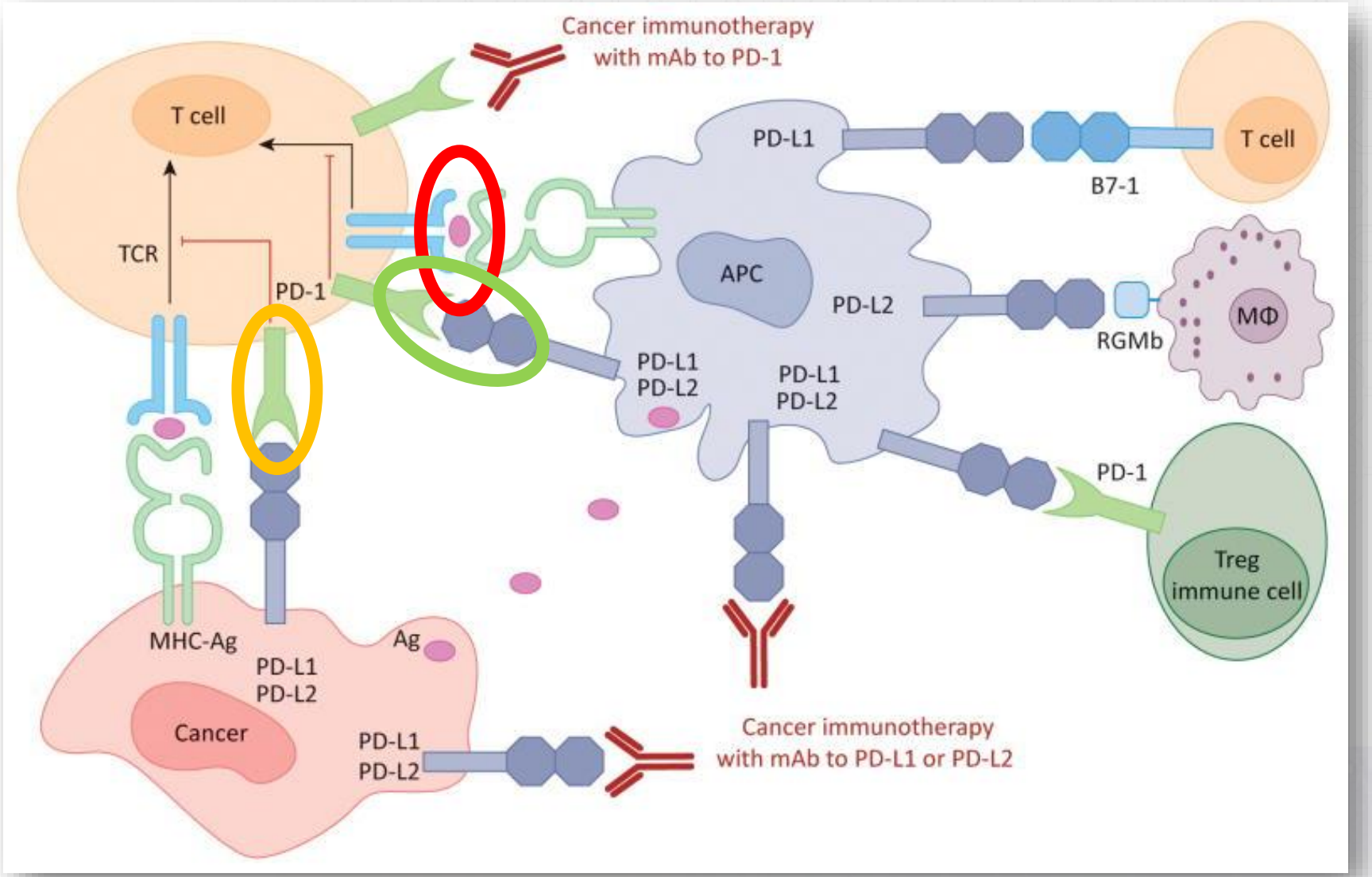
- Inhibidores de “checkpoints”
- Vacunas / Virus oncolíticos
- Conjugados AB-Fármaco
- CAR-T cells
- Inhibidores proteasa

Nivolumab
Pembrolizumab

Depatuxizumab
+ TMZ

Marizomib

INHIBIDORES DE "CHECKPOINTS"

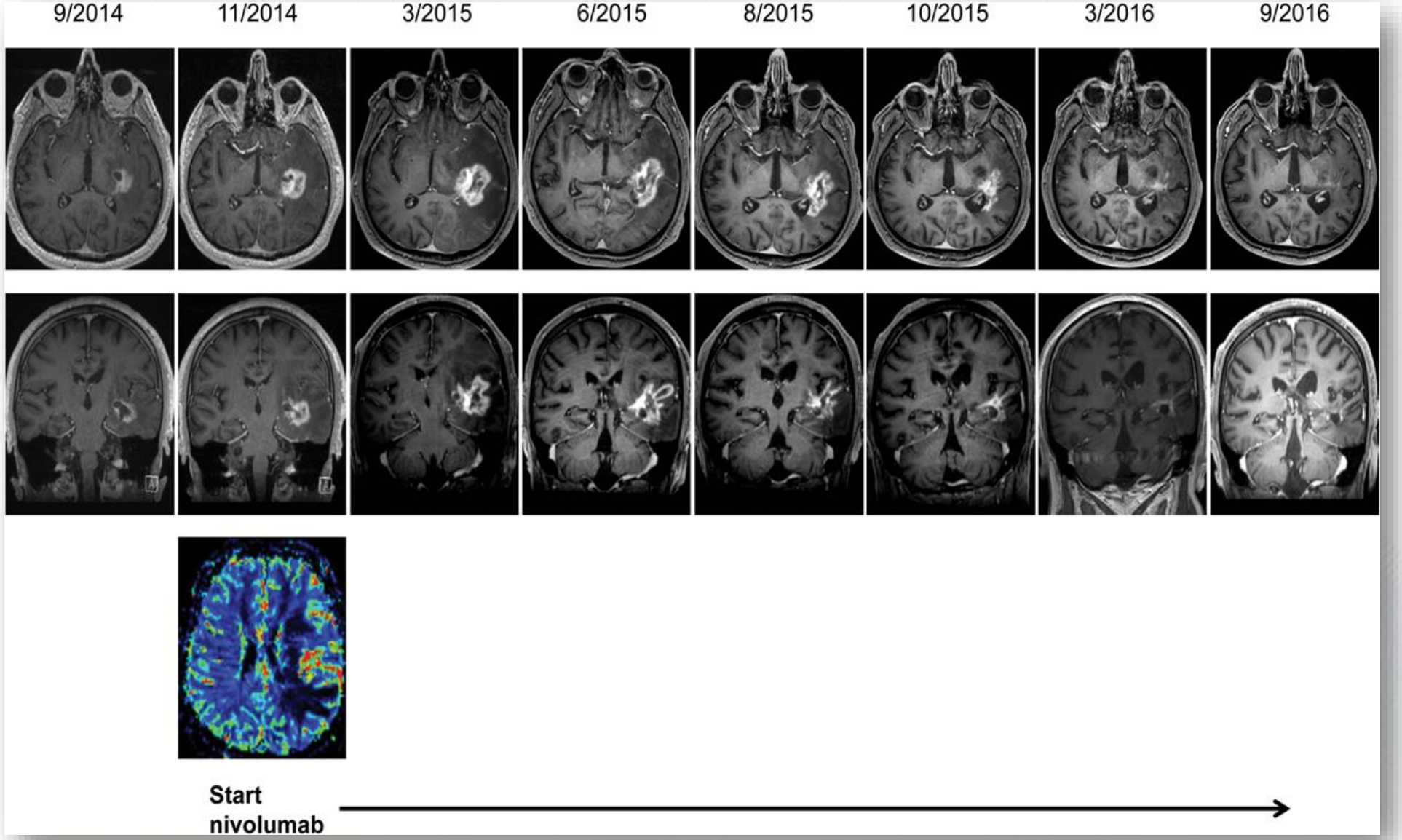


Nivolumab
Pembrolizumab

- 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

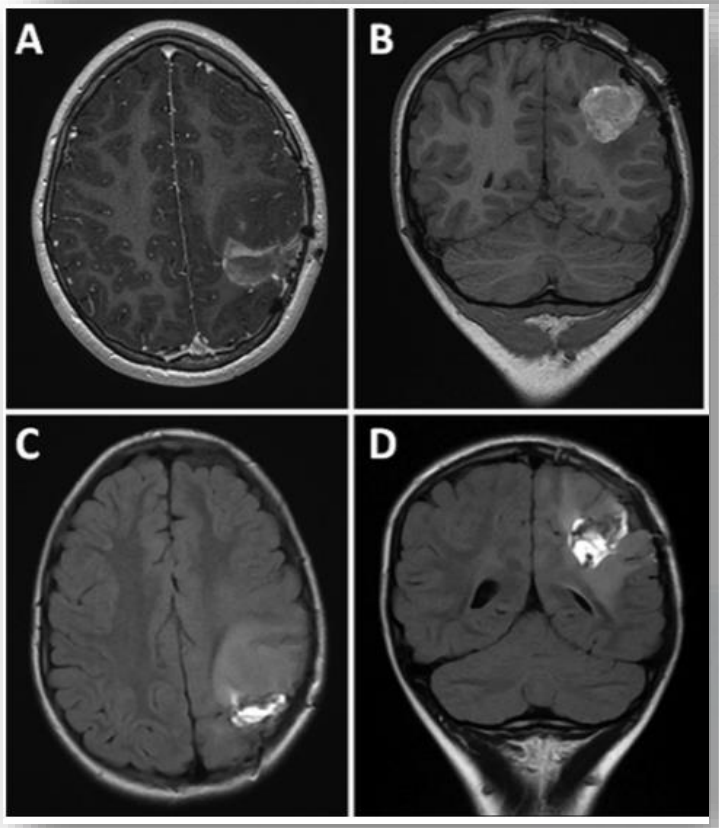
Key Considerations: RANO, irRC and iRANO

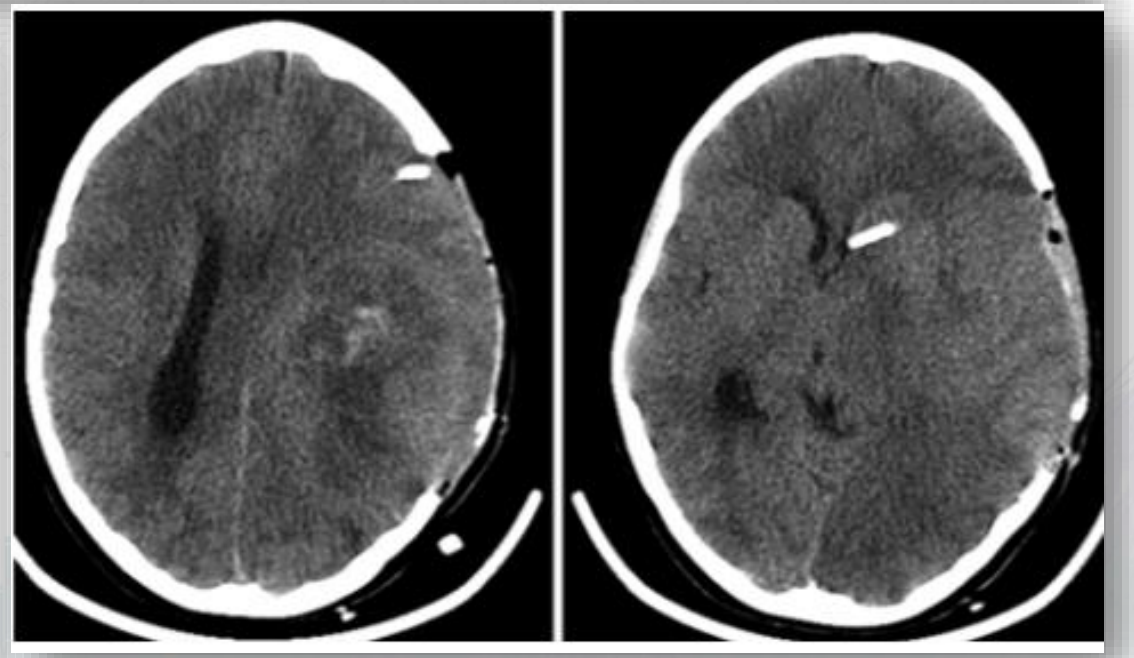
	RANO	irRC	iRANO (if ≤ 6 months after start of immunotherapy)	iRANO (if > 6 months after start of immunotherapy)
Is a repeat scan required to confirm radiographic PD for patients without significant clinical decline?	No	Yes	Yes	No
Minimal time interval for confirmation of progression for patients without significant clinical decline?	Not applicable	≥ 4 weeks	≥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]





Zhu X, J Neurosurg Pediatr, 2017

INHIBIDORES DE "CHECKPOINTS"

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

Journal of Clinical Oncology > List of Issues > Volume 37, Issue 15_suppl >

Meeting Abstract | 2019 ASCO Annual Meeting I

CENTRAL NERVOUS SYSTEM TUMORS

Hyperprogressive disease in patients with recurrent high grade gliomas treated with immune checkpoint inhibitors or other therapies.

Laura Donovan, Samuel Gedailovich, Adela Joanta-Gomez, Jessica Schulte, Teri Nguyen Kreisl, Andrew B. Lassman, ...

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

Table 1. Summary of active and completed clinical trials with OAds registered at Clinical Trials.gov.

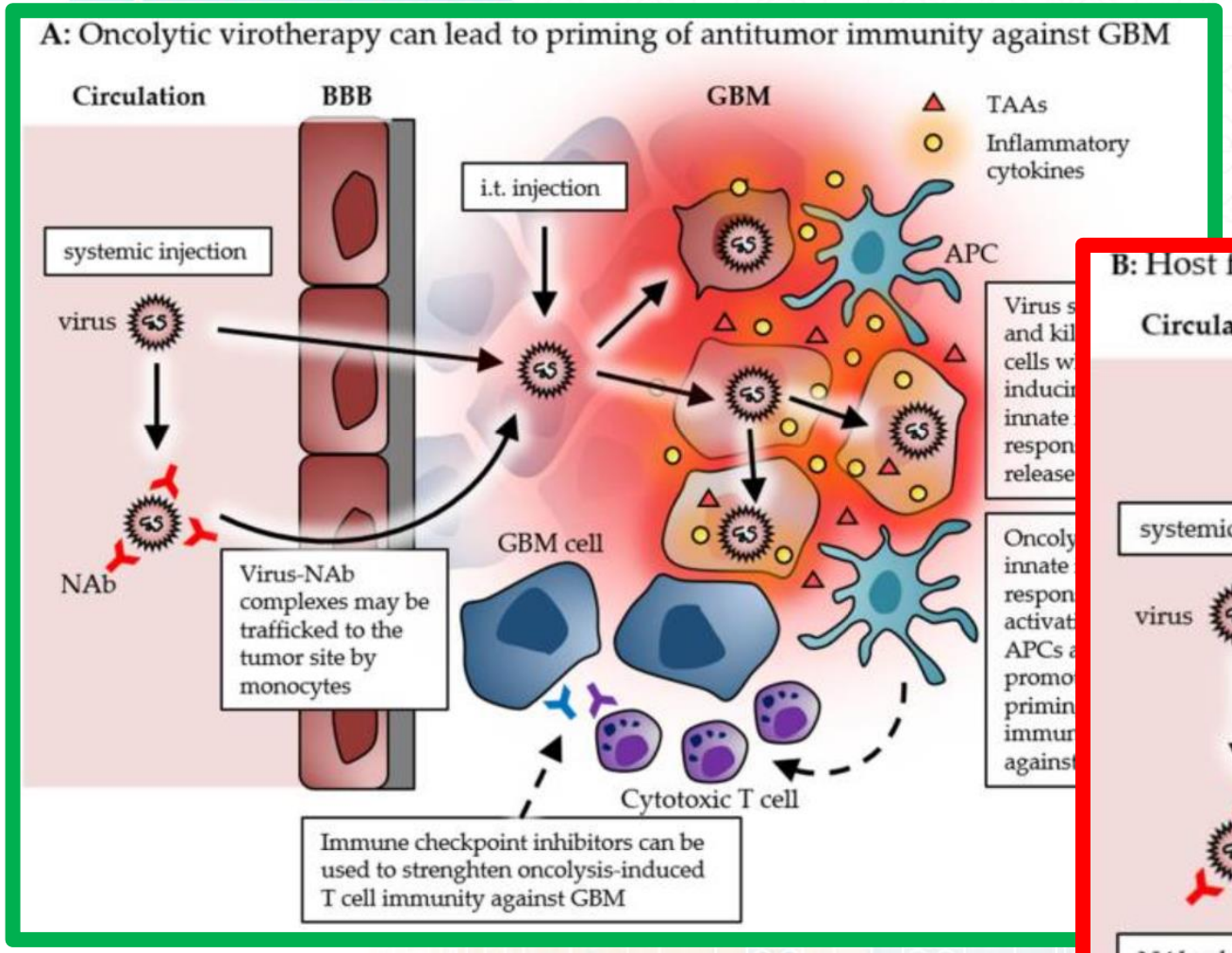
OAd	Clinical trial	Phase	Cancer	Combination	Adm
H101	NCT03790059	NA (R)	HCC	Radiofrequency ablation	IT
	NCT03780049	III (R)	HCC	FOLFOX (IV)	IV
DNX-2401	NCT03178032	I (C) (39)	DIPG	–	IT
	NCT00805376	I (C) (34)	MG	–	IT
	NCT01956734	I (C)	GBM	TMZ (oral)	IT
	NCT02197169	I (C)	GBM and GS	IFNg (IT)	IT
	NCT03896568	I (R)	AA, GBM, GS, MG	Loaded MSCs	IV
	NCT03714334	I (NR)	GBM	–	IT
	NCT02798406	II (NR)	GBM and GS	Pembrolizumab (IV)	IT
DNX-2440	NCT03714334	I (NR)	GBM	–	IT
Delta24-RGD	NCT01582516	I/II (C)	GBM	–	IT
CRAd-Survivin-pk7	NCT03072134	I (C)	MG	Loaded NSC + SoC	IT
ICOVIR-5	NCT01864759	I (C) (40)	Melanoma	–	IV
	NCT01844661	I/II (C) (41)	Recurrent/metast	Loaded MSCs (CELYVIR)	IV
OBP-301	NCT03172819	I (R)	Advanced cancers	Pembrolizumab (IV)	IT
	NCT02293850	I (R)	HCC	–	IT
	NCT04391049	I (R)	Esophagogastic	Carboplatin (IV) + paclitaxel (IV) + radiotherapy	IT
	NCT03921021	II (R)	Esophagogastric	Pembrolizumab (IV)	IT
	NCT03190824	II (NR)	Melanoma	–	IT
TILT-123	NCT04217473	I (R)	Melanoma	Monotherapy ± TIL therapy	IT
LOAd703	NCT03225989	I/II (R)	Panc, Ov, CC, BiC	SoC or GE immune-conditioning	IT
	NCT04123470	I/II (R)	Melanoma	Atezolizumab (IV)	IT
ORCA-010	NCT04097002	I/II (R)	Prostate	–	IT
CAdVEC	NCT03740256	I (R)	HER2+	Ad-specific HER2 CAR T cells (IT)	IT
CG7870	NCT00116155	I/II (C) (42)	Prostate	–	IV

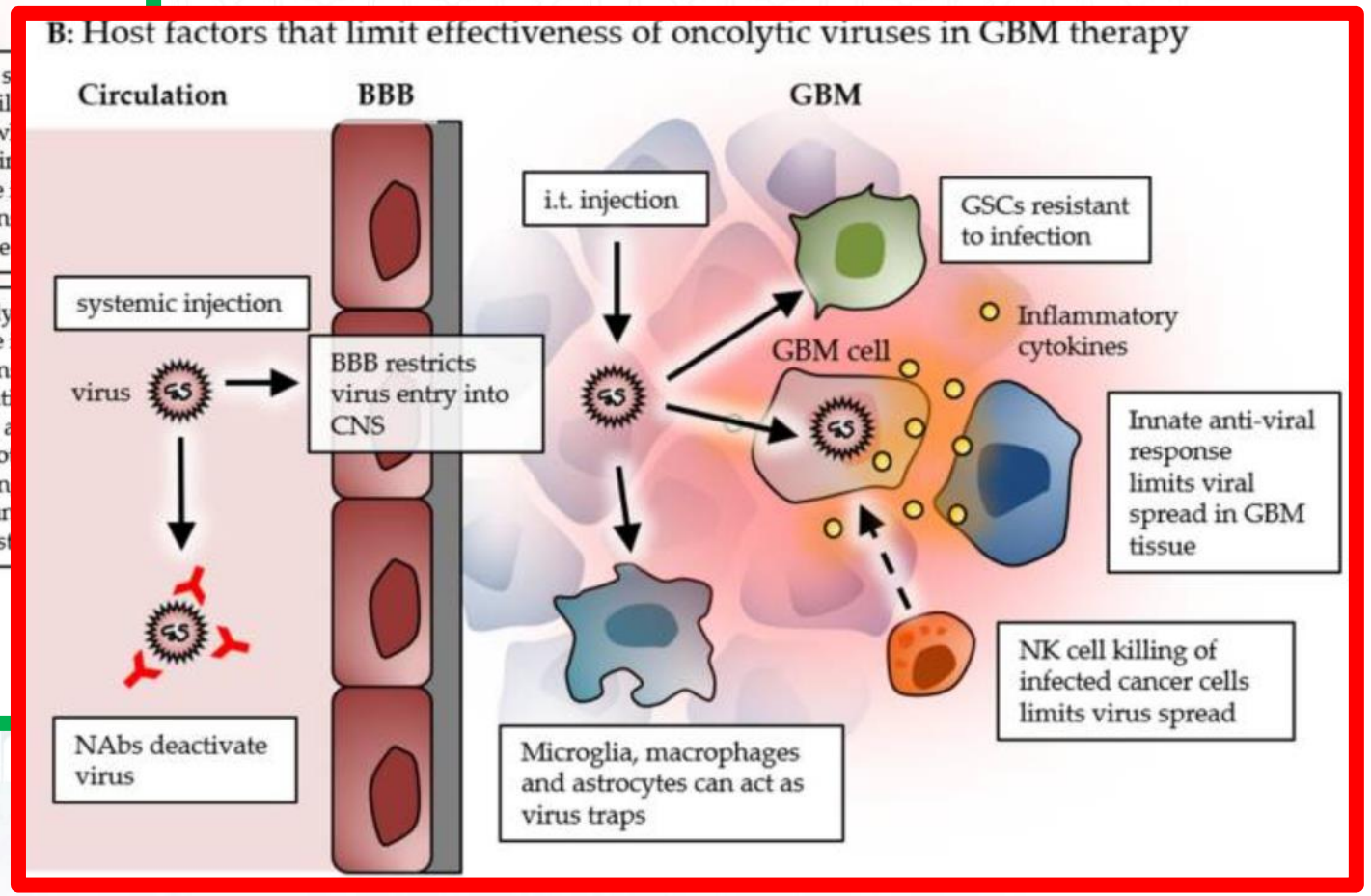
Farrera-Sal M, Clin Cancer Res, 2021

VIRUS ONCOLÍTICOS: ENSAYOS CLÍNICOS CUN

- Adenovirus
- DNX 2401 para DIPG
- DNX 2440 para GBM recidivado

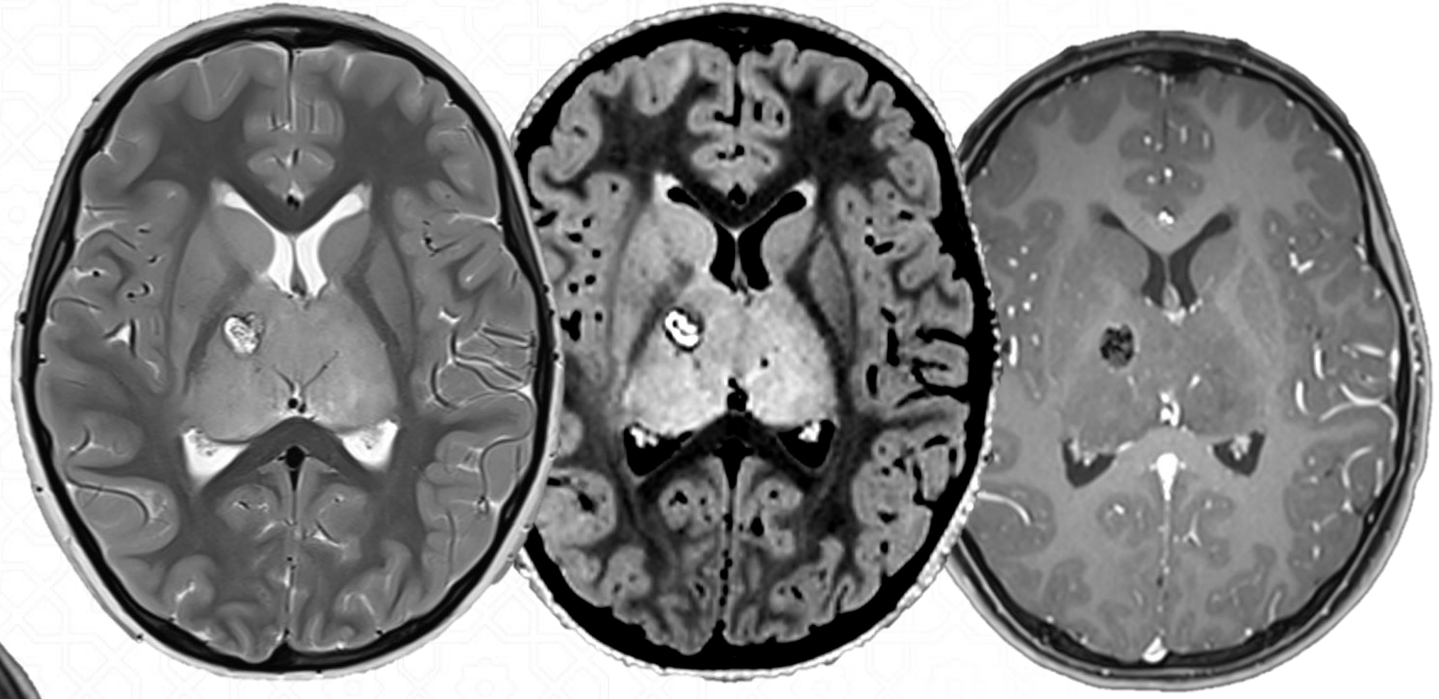
VIRUS ONCOLÍTICOS

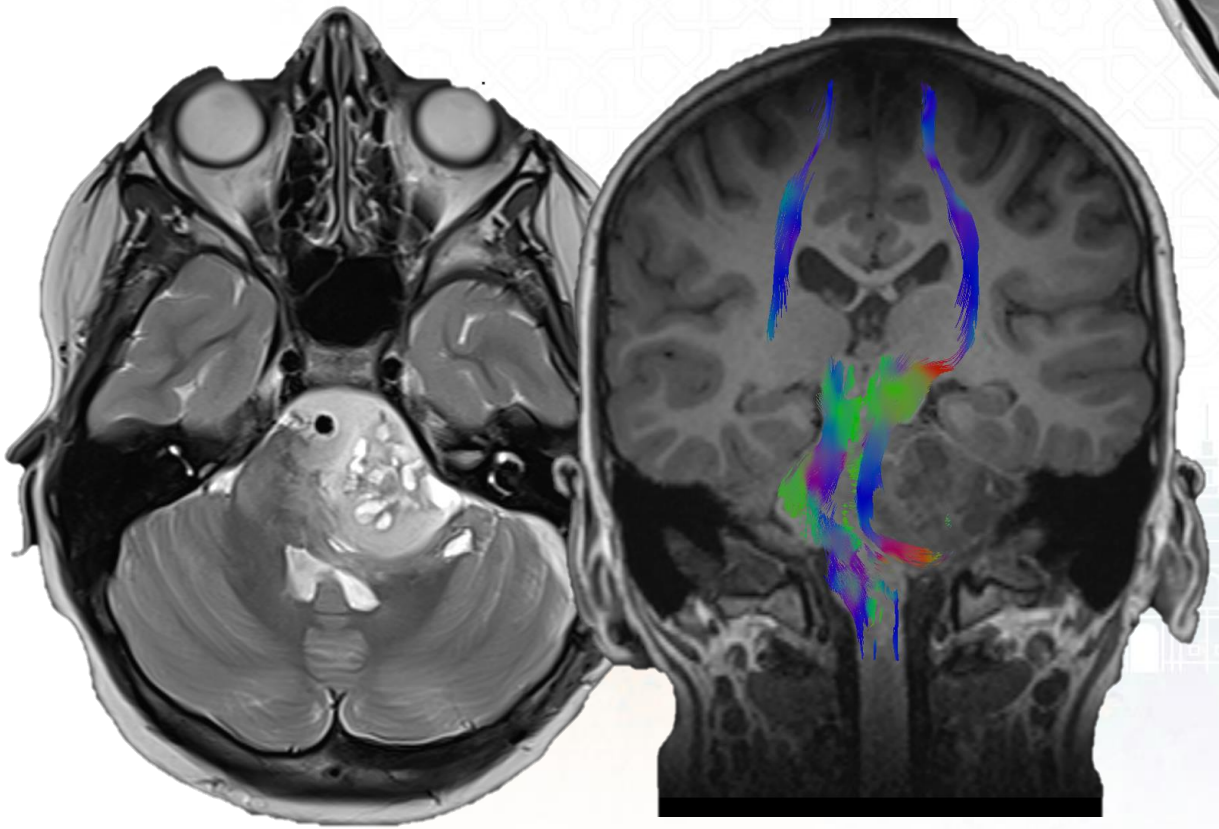


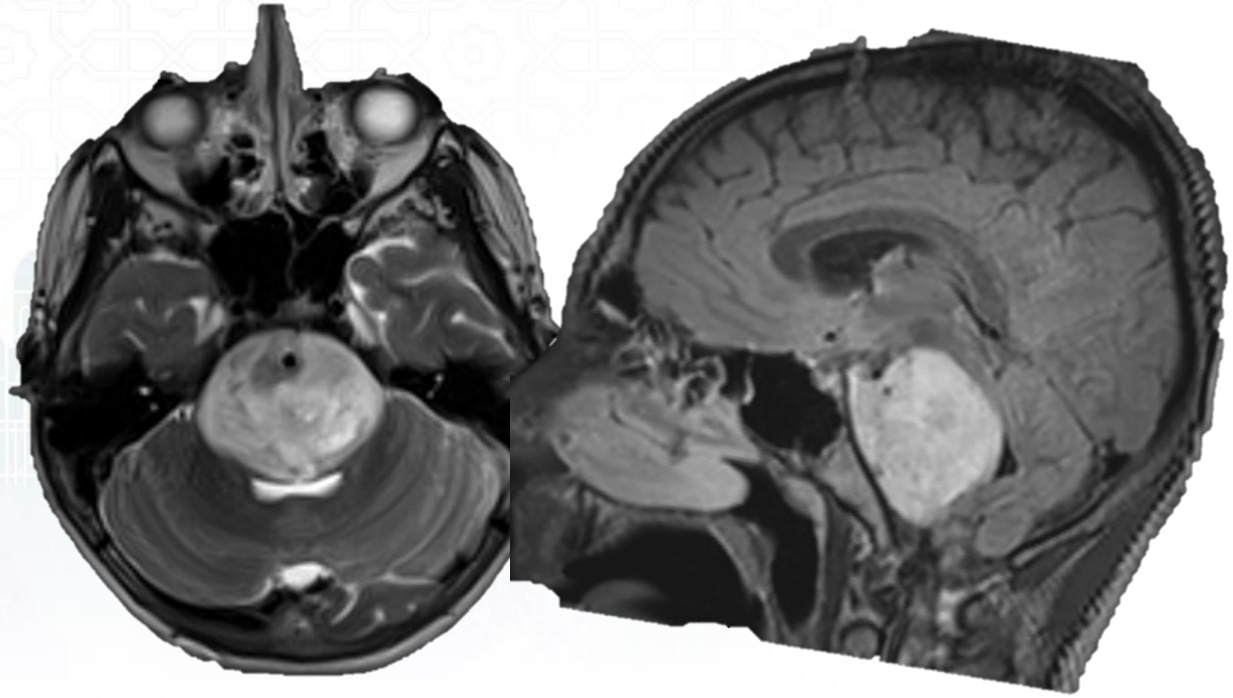


Martikainen, Cancers, 2019

Glioma difuso de línea media H3 K27-alterado (DIPG)







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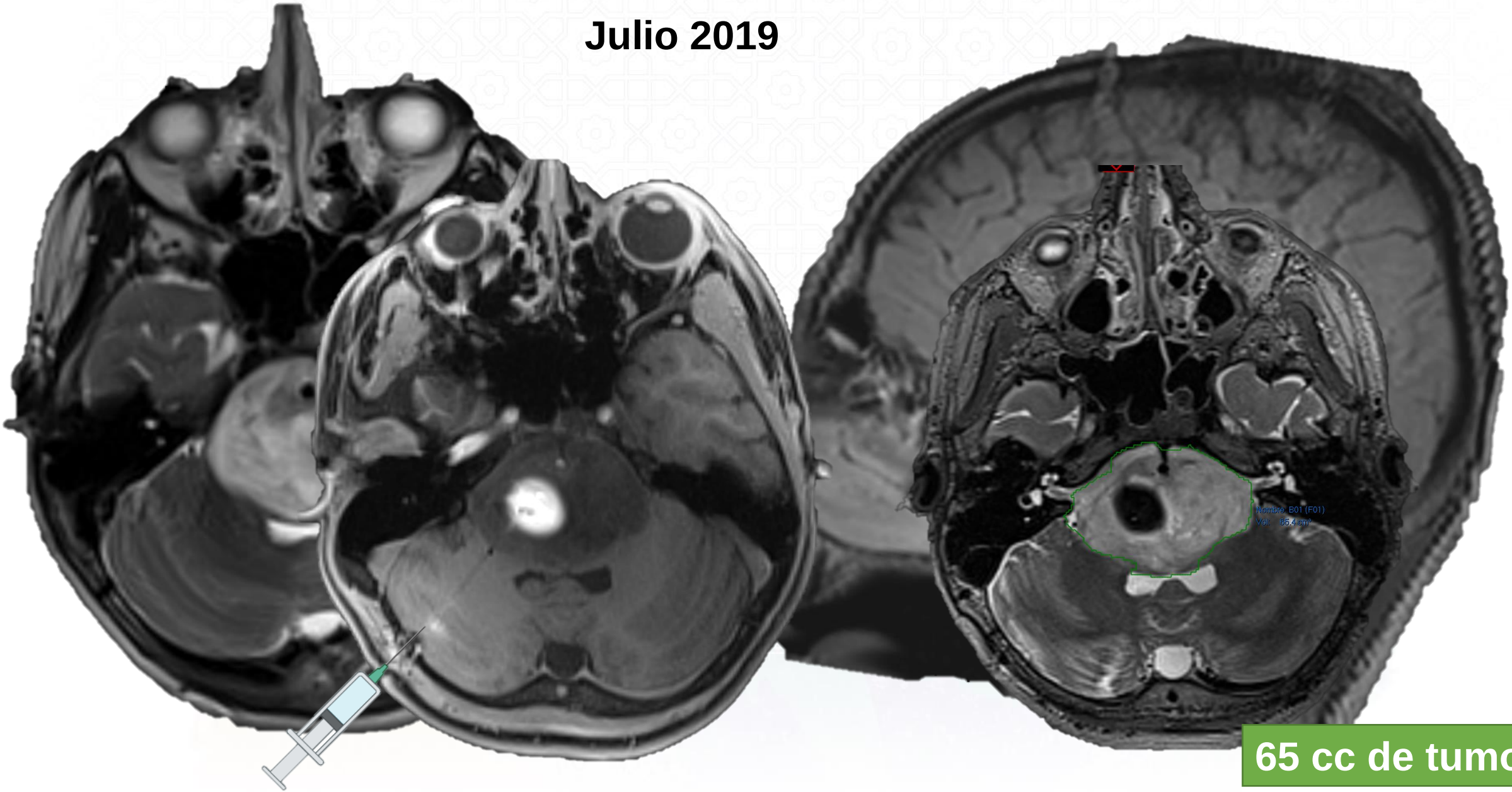
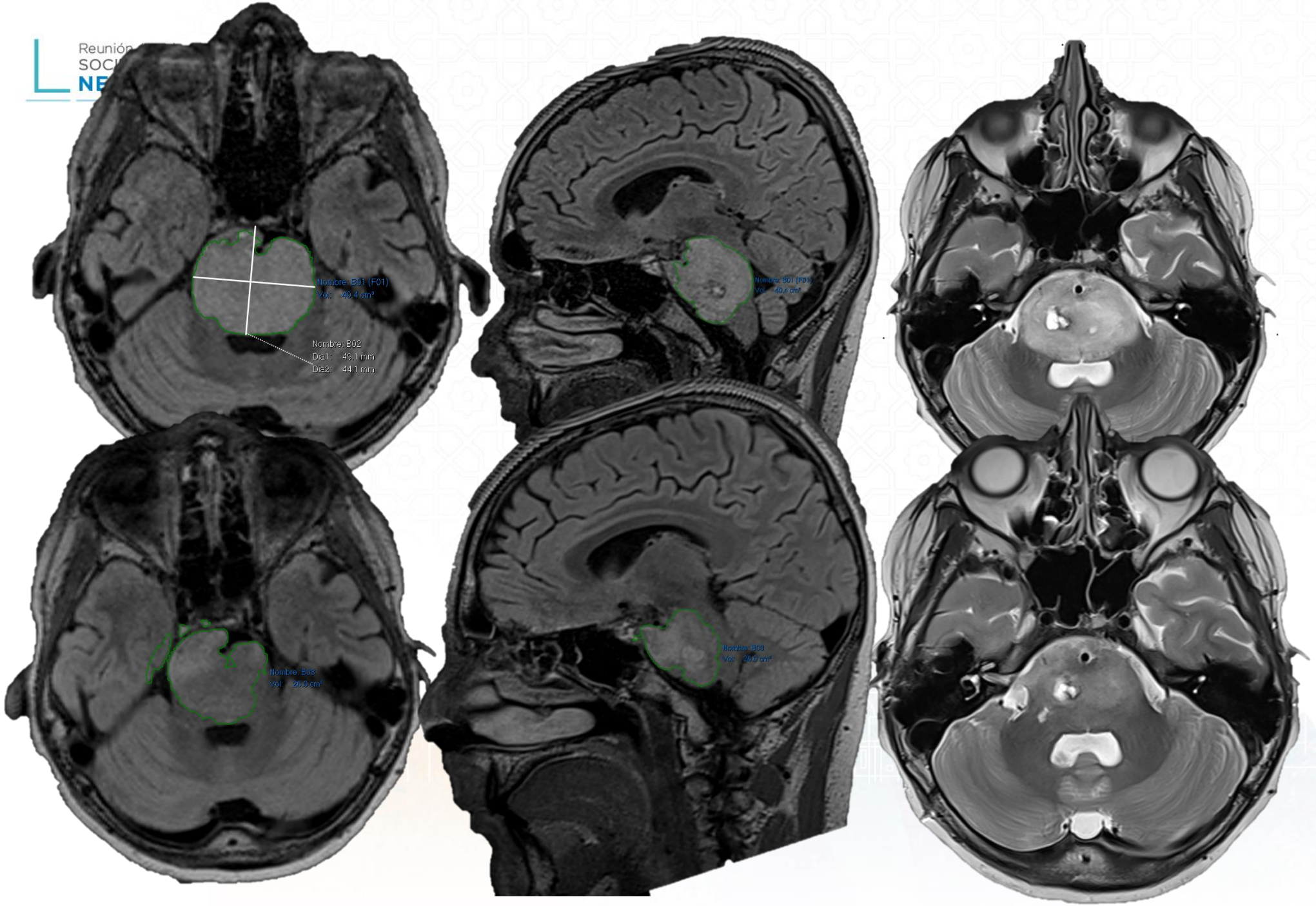
12 años DIPG H3K27M-alterado

Julio 2019



65 cc de tumor

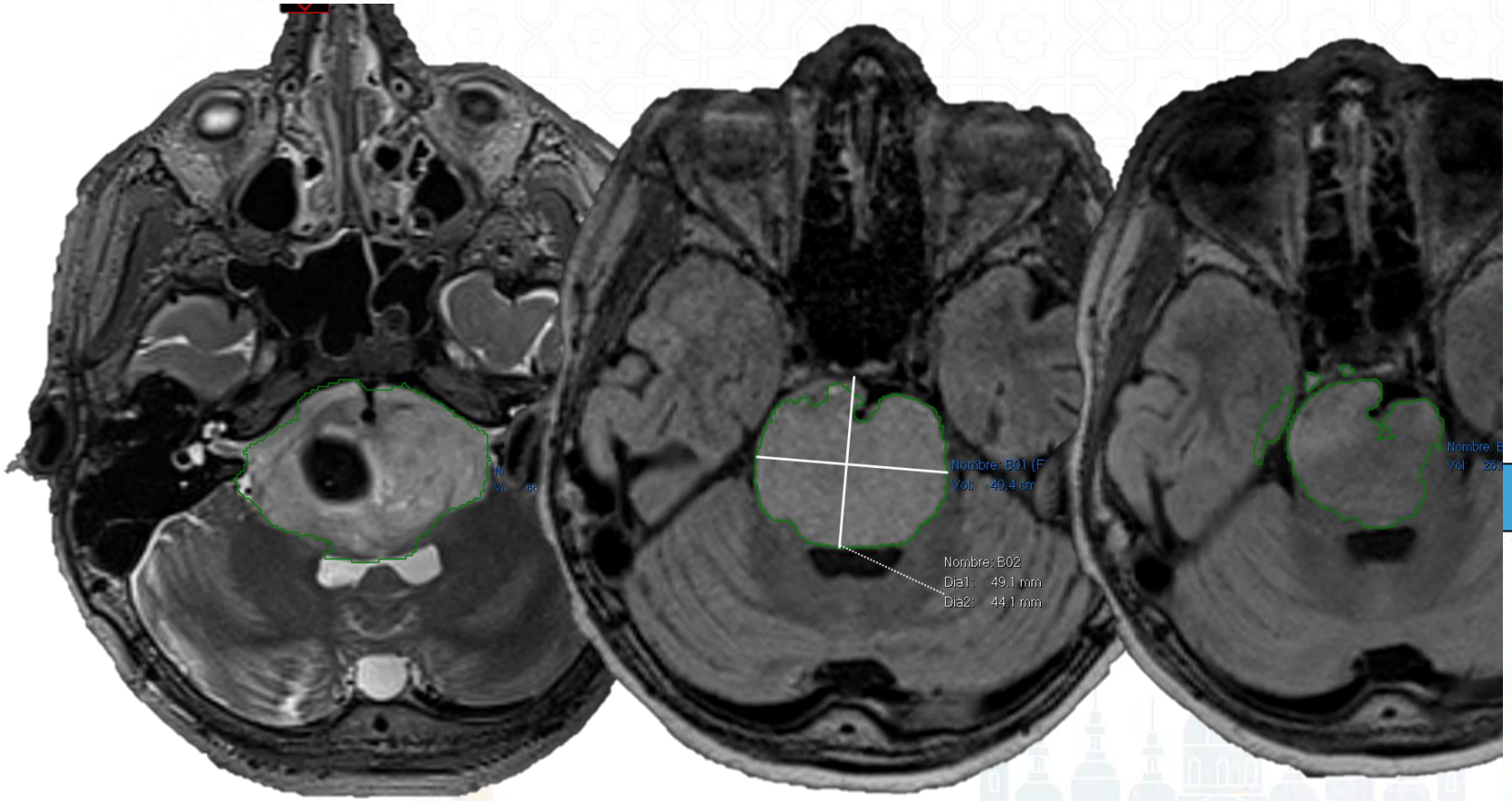


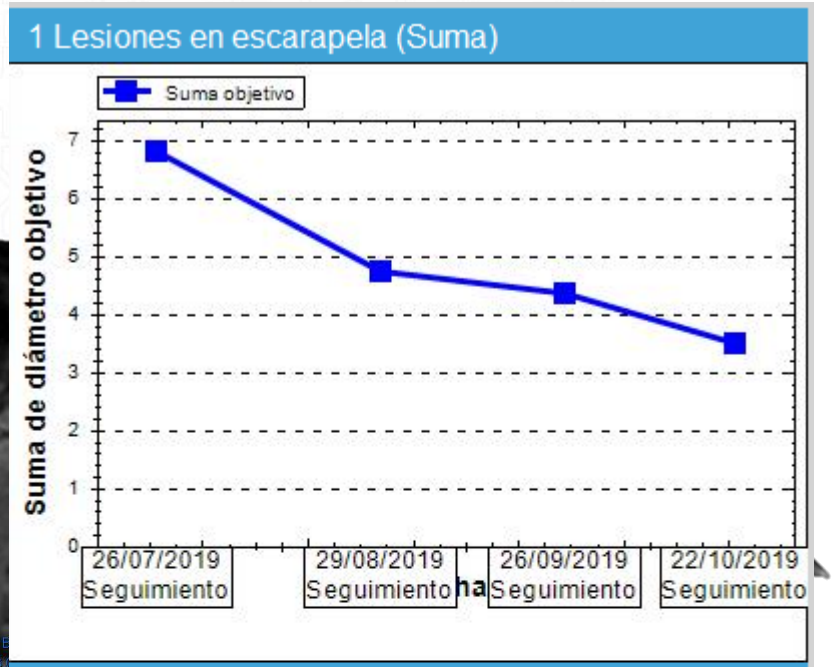
40 cc de tumor

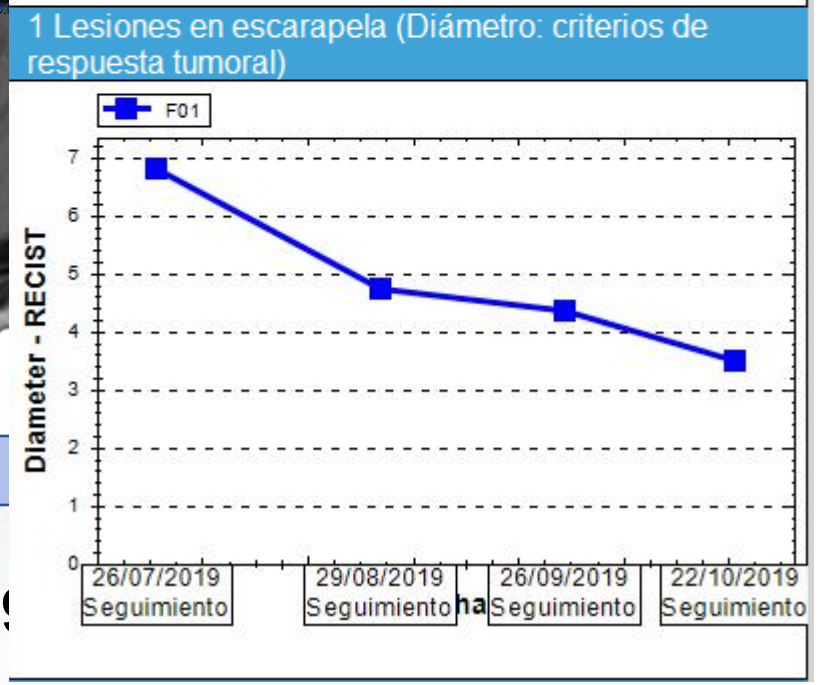
Agosto 2019

26 cc de tumor

Sept 2019







Julio 2019 **Agosto 2019** **Sept 201**

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RESEARCH SUMMARY

Oncolytic DNX-2401 Virus for Pediatric Diffuse Intrinsic Pontine Glioma

Gállego Pérez-Larraya J et al. DOI: 10.1056/NEJMoa2202028

CLINICAL PROBLEM

Diffuse intrinsic pontine glioma (DIPG) has limited treatment options and is the leading cause of brain tumor–related death in children. The oncolytic adenovirus DNX-2401 has shown promise for the treatment of recurrent malignant glioma in adults, but its safety and efficacy in pediatric patients with DIPG is unknown.

CLINICAL TRIAL

Design: A single-center, dose-escalation study examined the safety and efficacy of DNX-2401 in pediatric patients with newly diagnosed DIPG.

Intervention: 12 patients 3 to 18 years of age received a single intratumoral infusion of DNX-2401 (1×10^{10} or 5×10^{10} viral particles) through a surgically placed cannula; 11 subsequently received radiotherapy. The primary objective was to assess the safety of DNX-2401. Secondary objectives included objective response and overall survival.

RESULTS

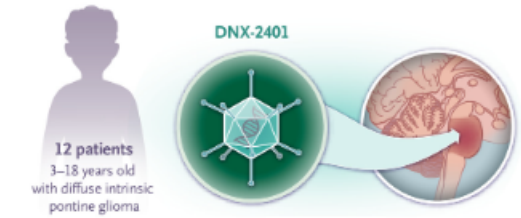
Safety: The most common adverse events were headache, neurologic deterioration, vomiting, fatigue, and fever; most were grade 1 or 2 in severity. Three serious adverse events were reported: transitory grade 3 hemiparesis, grade 3 neurologic deterioration of increased bilateral oculomotor paresis and tetraparesis, and grade 1 abdominal pain leading to hospitalization 2 months after treatment.

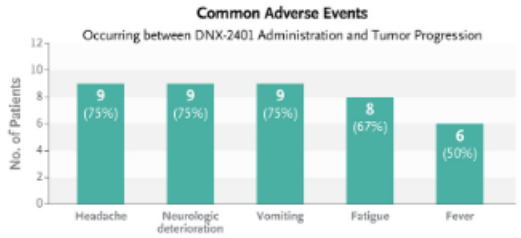
Efficacy: Reductions in tumor size were reported in 9 patients. During a median follow-up of 16.6 weeks, 3 patients had a partial response and 8 had stable disease. Median overall survival was 17.8 months; 2 patients were alive at approximately 3 years after treatment.

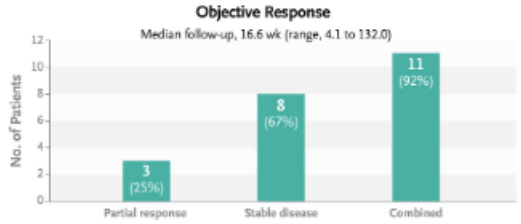
LIMITATIONS AND REMAINING QUESTIONS

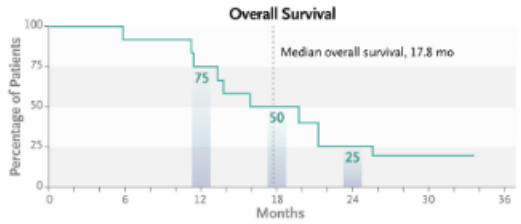
- Conclusions about survival could not be made given the small sample size and the lack of randomization.
- The relative contributions of the change in inflammatory response in the tumor and DNX-2401 oncolytic activity could not be determined.

Links: Full Article | NEJM Quick Take | Editorial









CONCLUSIONS

In pediatric DIPG, a single intratumoral infusion of the oncolytic adenovirus DNX-2401 was associated with adverse events but led to a partial response or stable disease over approximately 1.5 years in most patients.

- 12 pacientes DIPG
- Dolor cabeza, fatiga, fiebre y vómitos
- 1 hemiparesia y 1 tetraparesia
- 3 respuestas parciales
- 8 enfermedad estable

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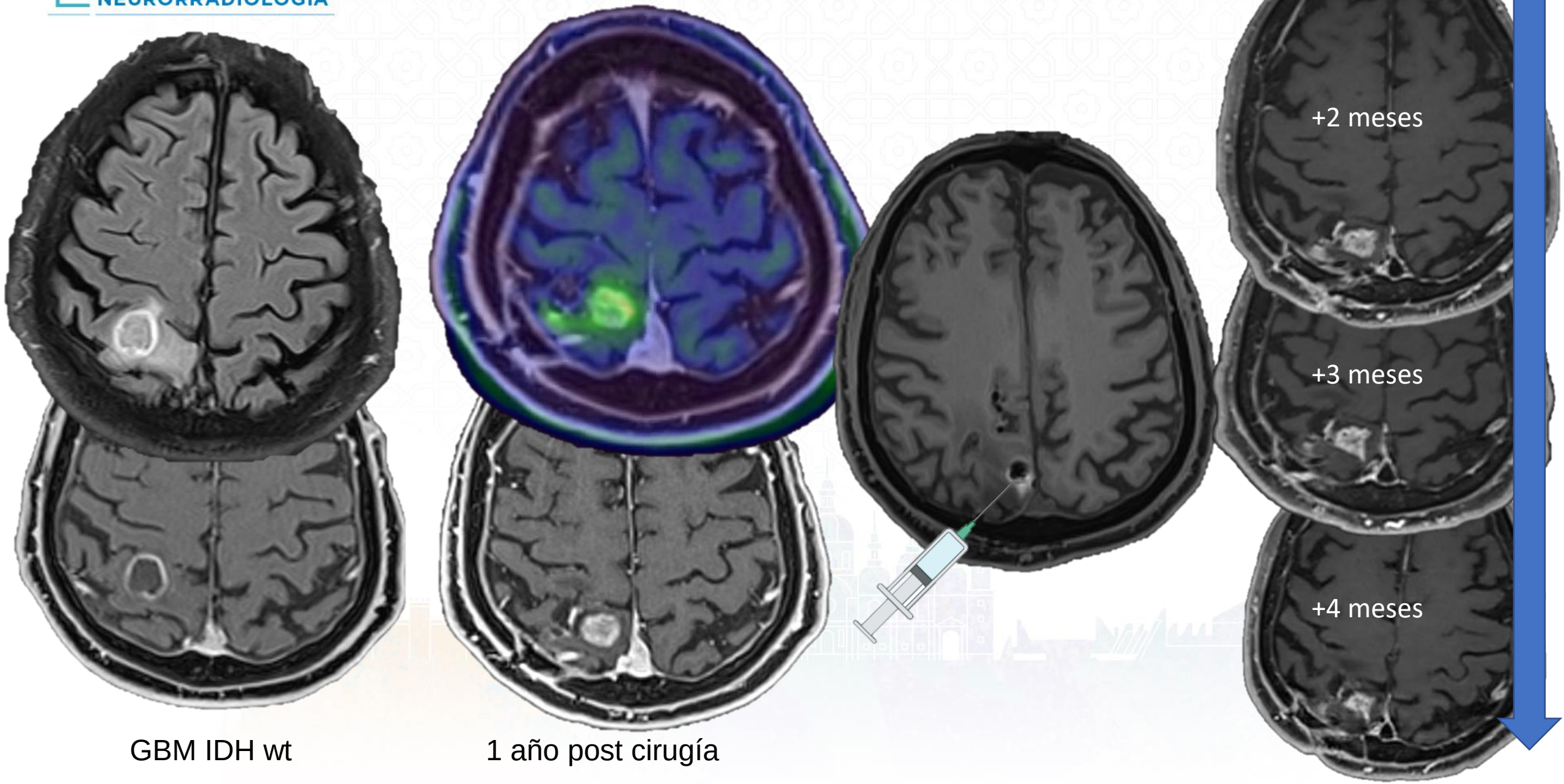
Virus oncolíticos: GBM



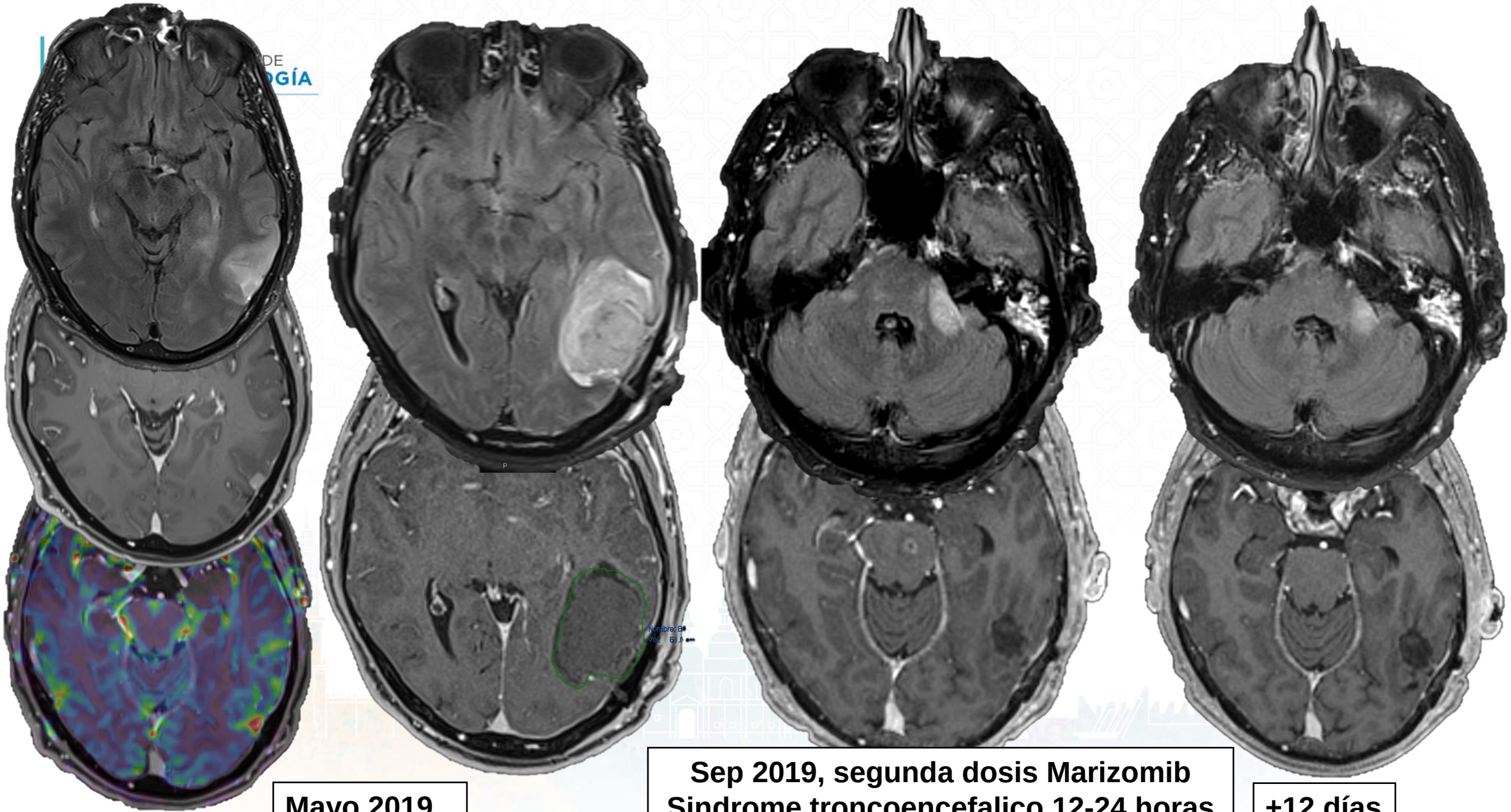
GBM IDH wt

1 año post cirugía

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

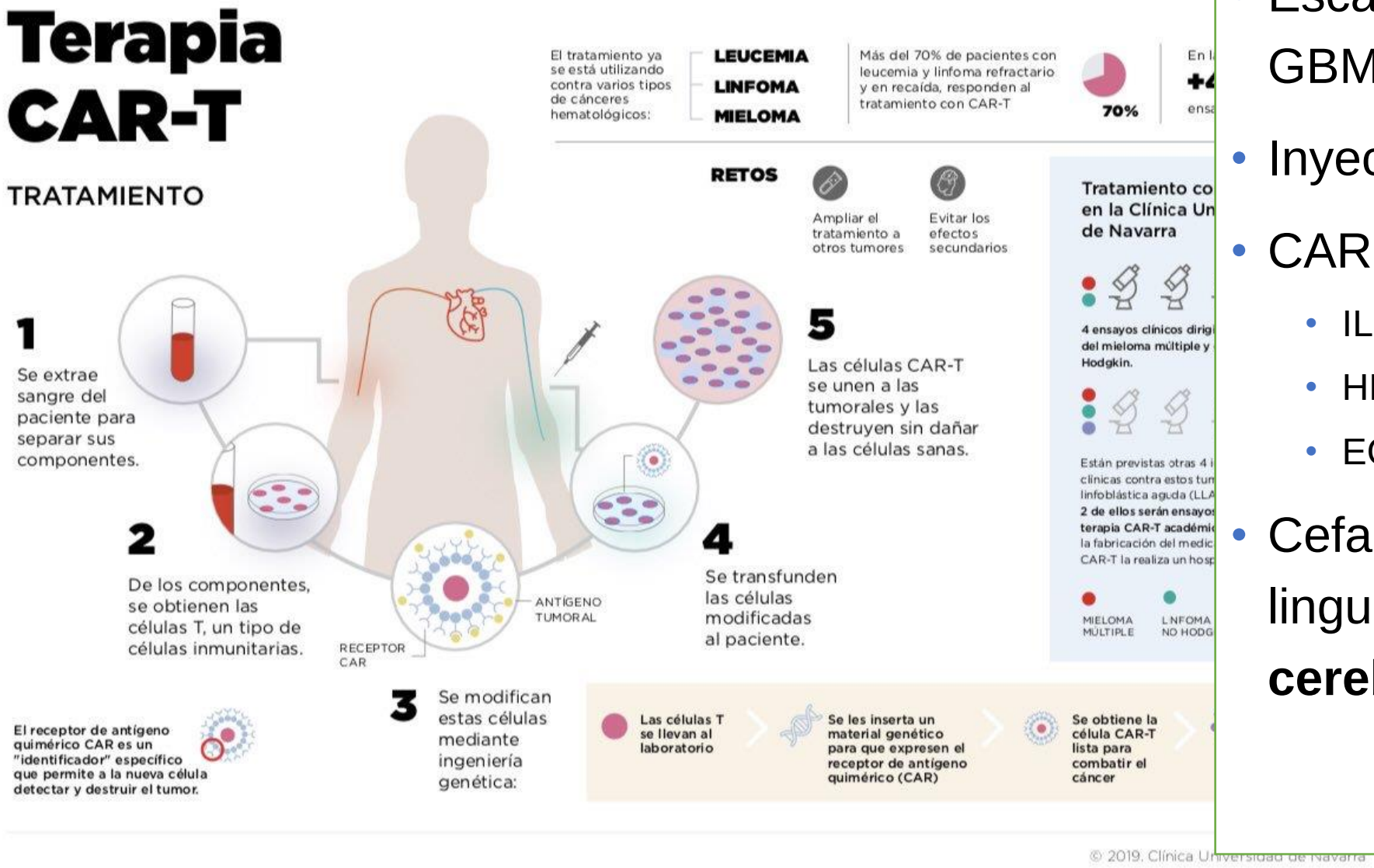


Mayo 2019
GBM IDH wt

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

+12 días

TERAPIA CAR-T

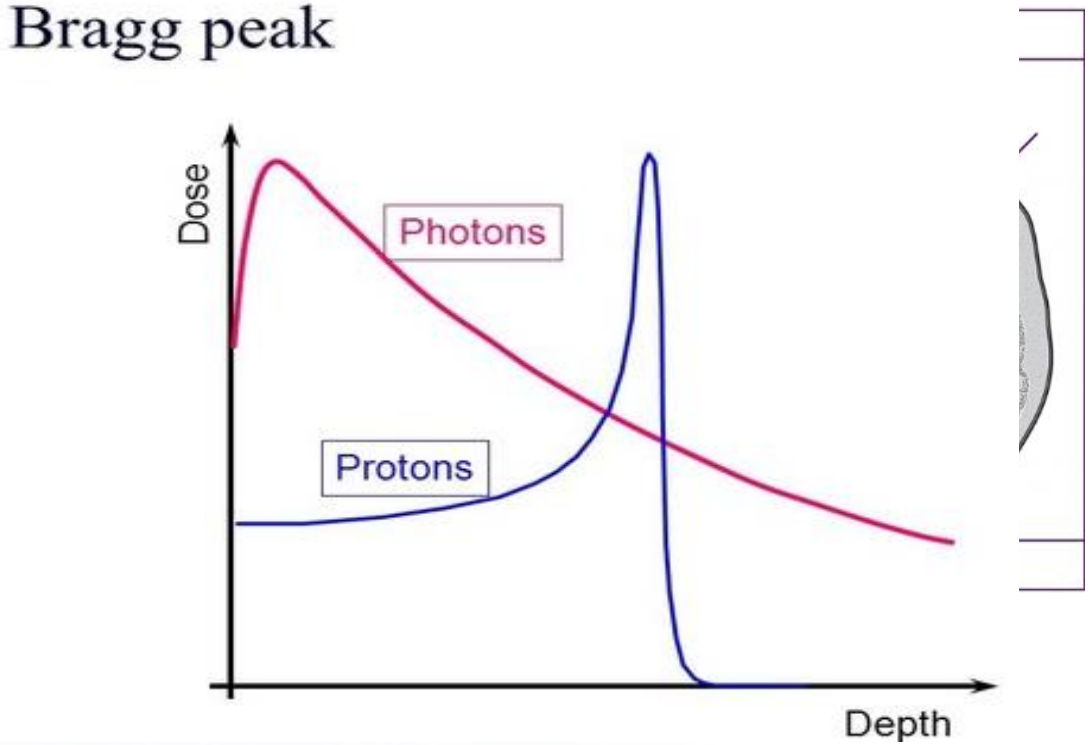


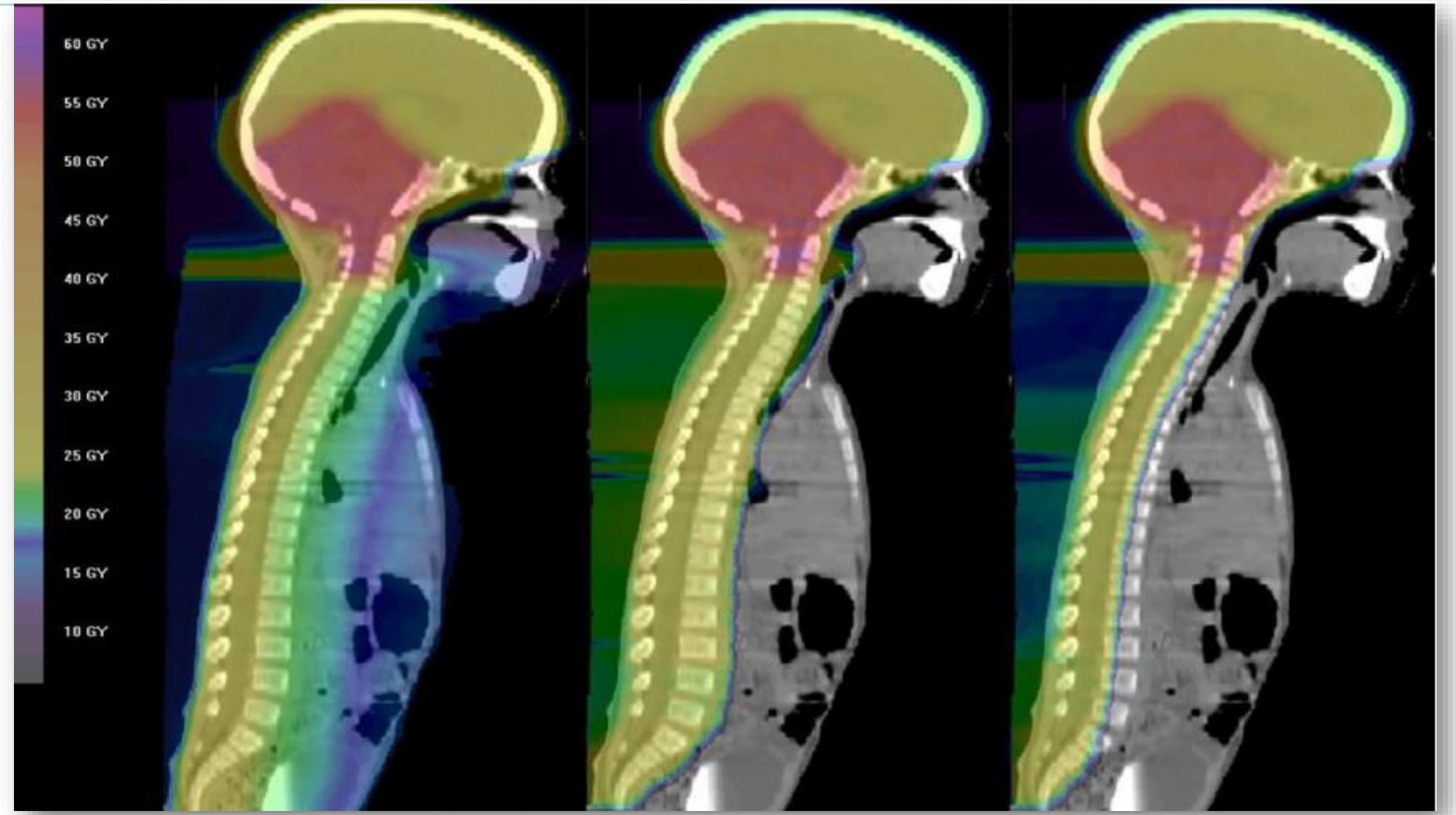
- Escasa experiencia en GBM
- Inyección periférica
- CAR targets moleculares
  - IL-13 Rα2 (N=2)
  - HER2 (N=1)
  - EGFRvIII (N=2)
- Cefalea, fatiga, desviación lingual, leucopenia, **edema cerebral** e **hidrocefalia**

Maggs L, Front Neurosci, 2021

PROTONTERAPIA

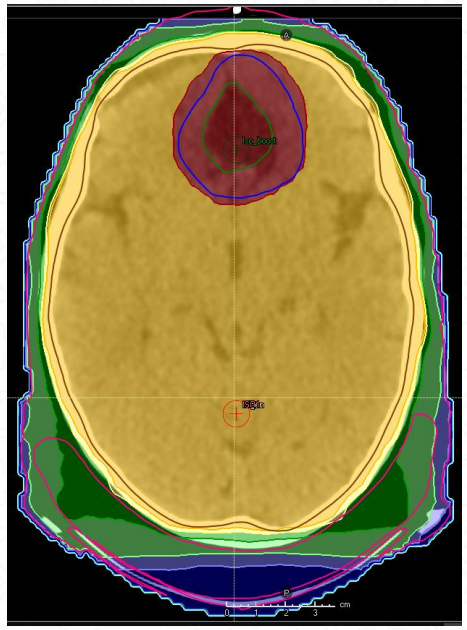
- Haz de ***protones*** en vez de un haz de *fotones* (radioterapia convencional)
- Permite dosis mayor focalizada en el área tumoral
- Reduciendo la dosis en áreas vecinas elocuentes en el camino del haz
- No “dosis de salida”
- Radionecrosis en bordes de isodosis
- **Picos de Bragg**

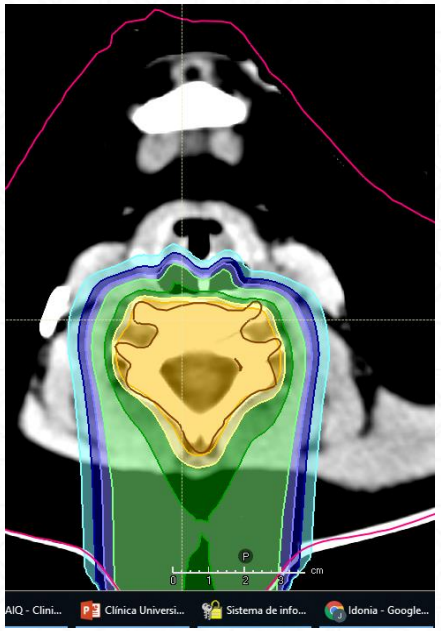


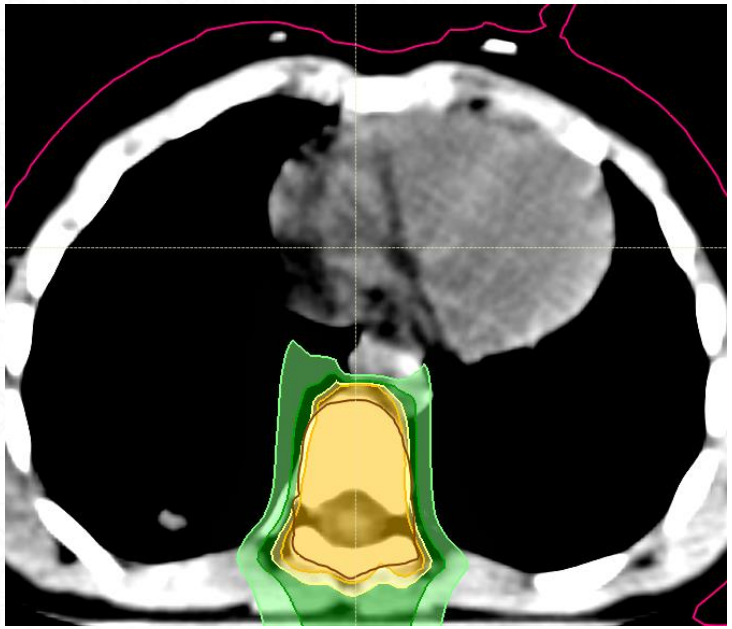


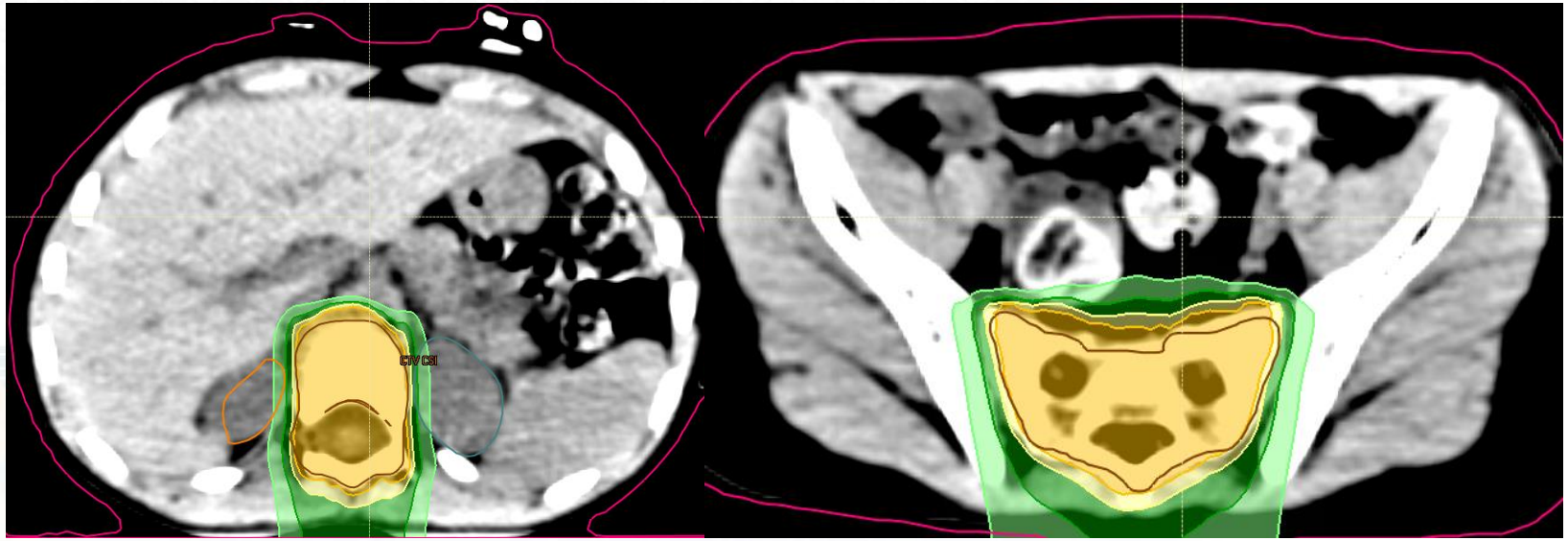
MacEwan, Advances in Rad Oncol, 2017

ATRT supratentorial
(4 años)









Cortesía Dr. Aristu, Unidad Protónterapia, CUN Madrid

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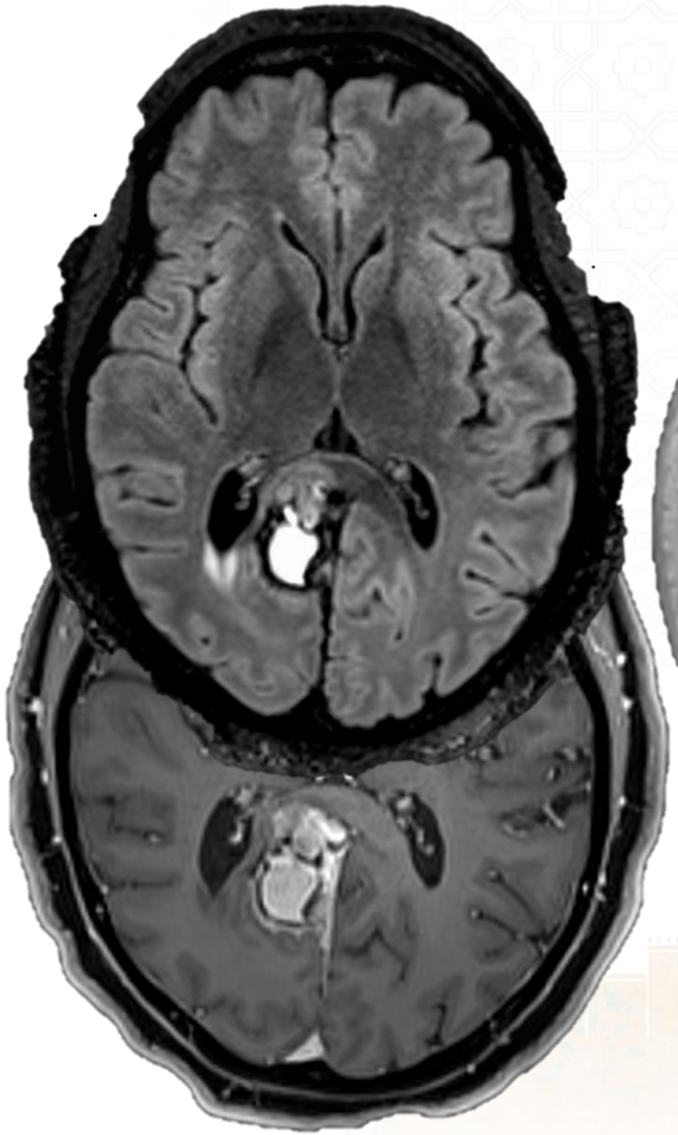
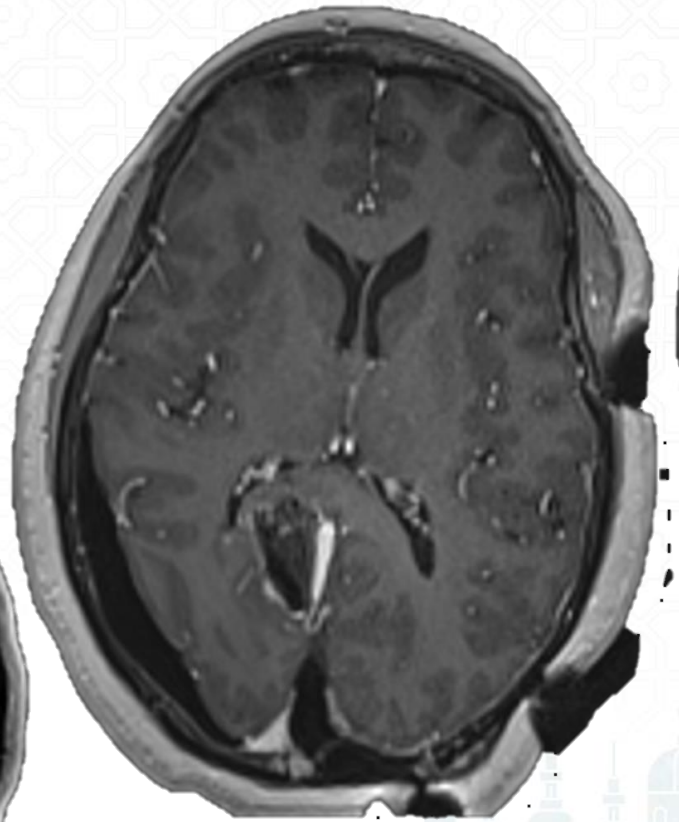
Glioblastoma IDH-wt

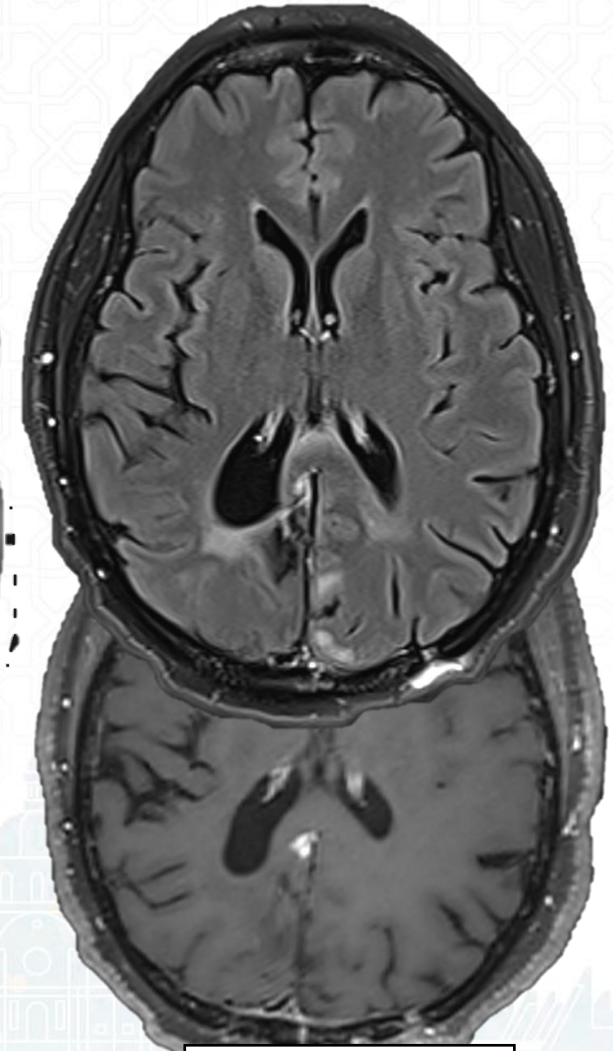


25 Enero 2021



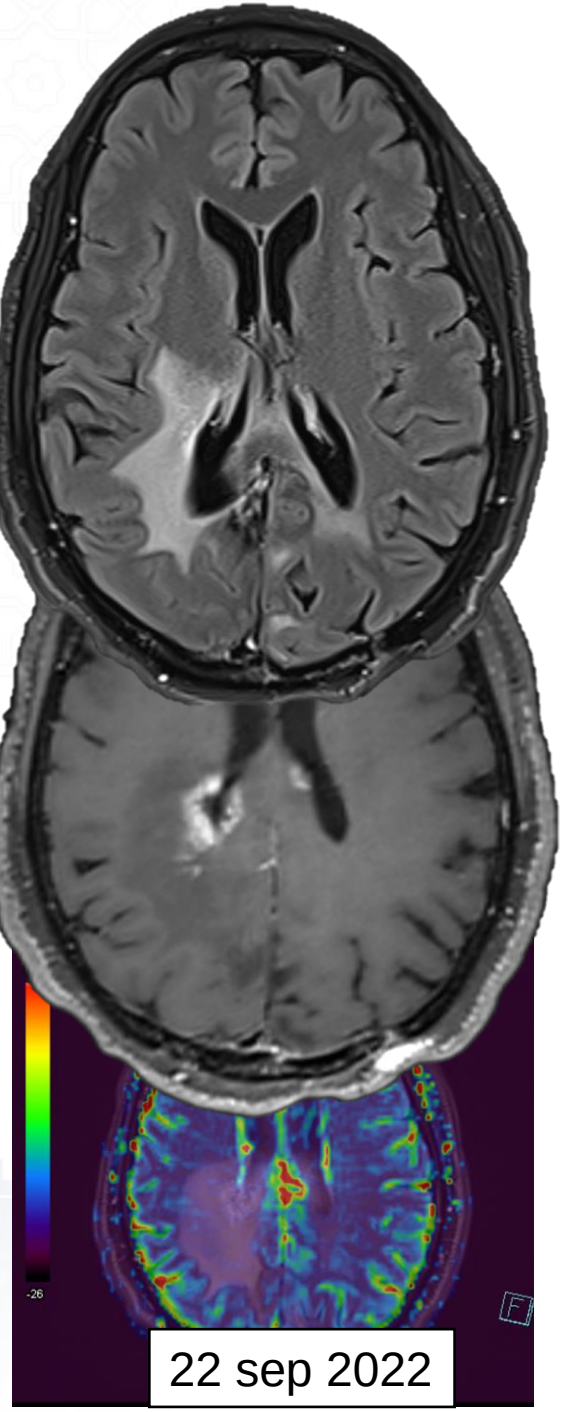
RM intraop
26 Enero 2021

2 Marzo 2021



22 junio 2022

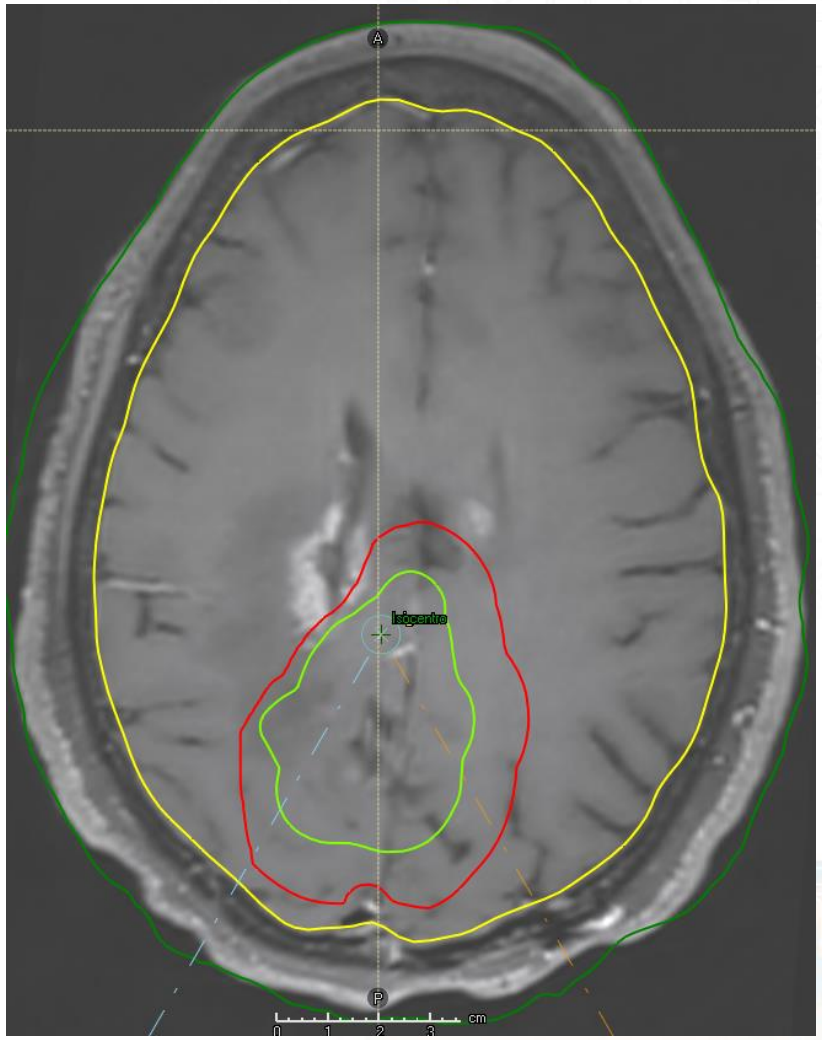
8 Abril 2021

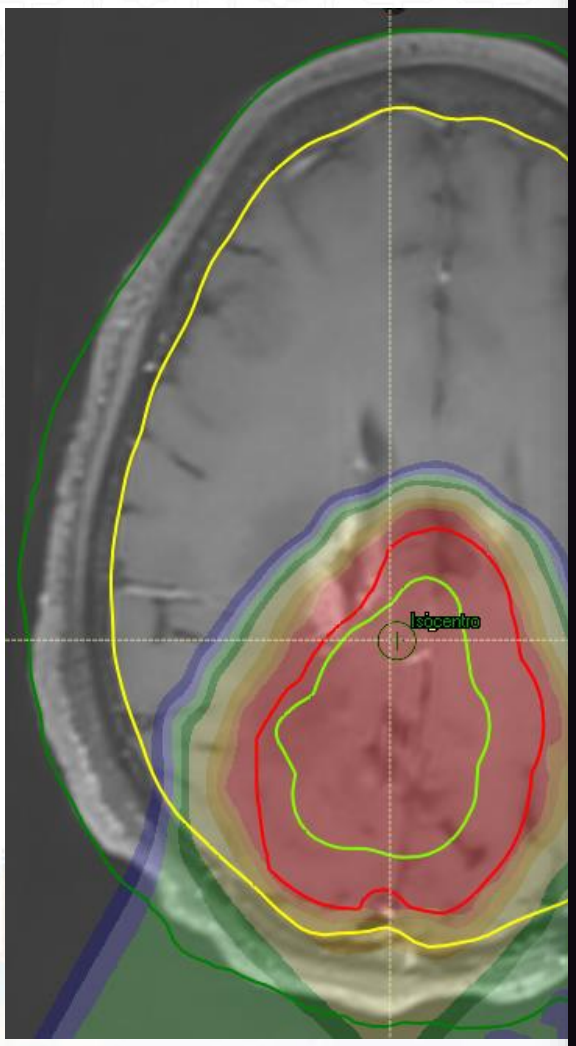


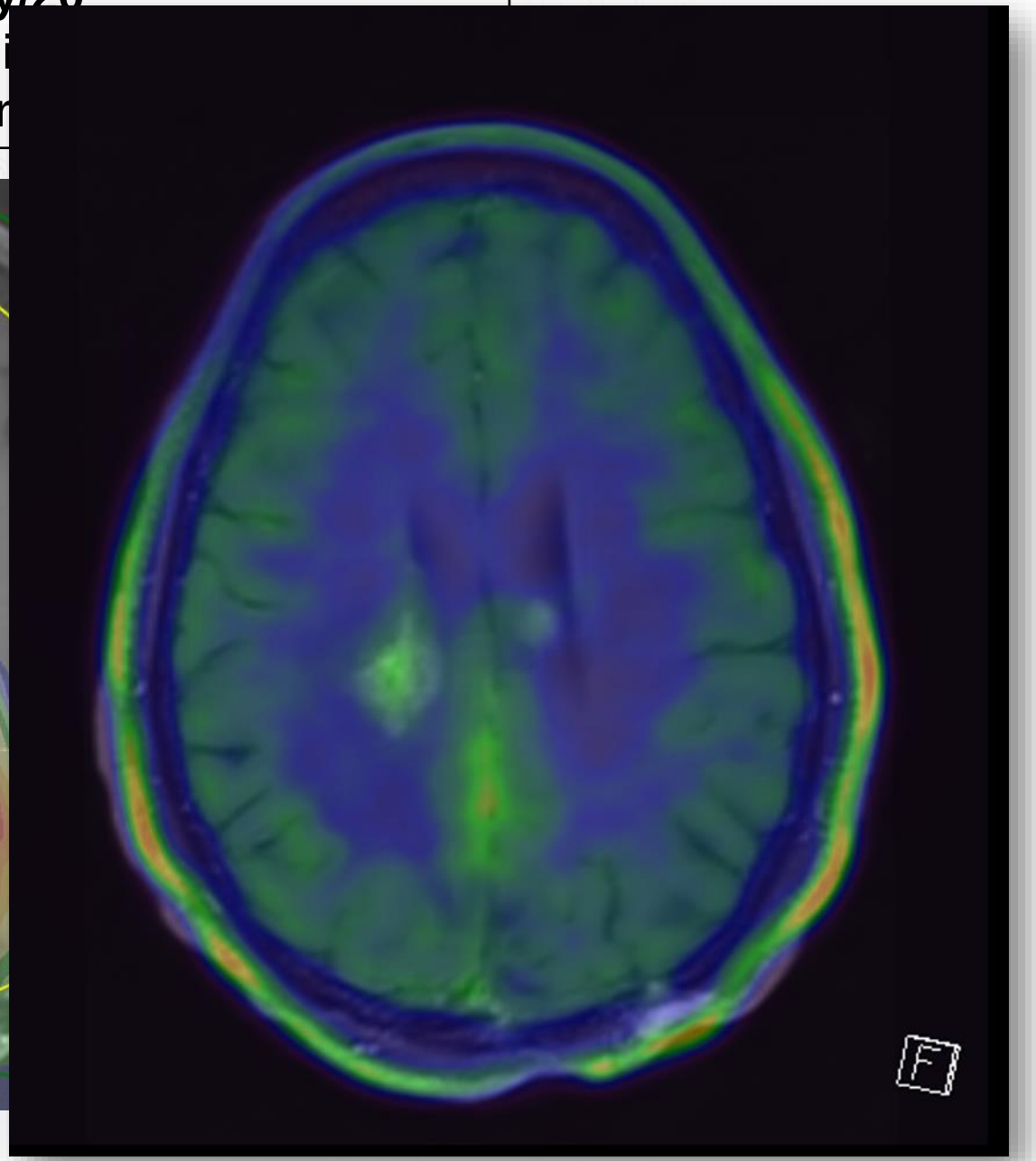
22 sep 2022

Reunión Anual
SOCIEDAD ESPAÑOLA DE
NEURORRADIOLOGÍA

60-65Gy/20
¿Recidiva o radi
Picos de Bragg en regió







Cortesía Dr. Aristu, Unidad Protónterapia, CUN Madrid

CONCLUSIONES

- Revisión de hallazgos radiológicos en los nuevos tratamientos de tumores en SNC
- Era de explosión de ***Inmunoterapia***
- Conocer los iRANO (*6 meses*)
- Protónterapia - picos de Bragg - definen el patrón de la radionecrosis

MUCHAS GRACIAS

Clínica Universidad de Navarra