



Where **Science** Becomes **Hope**

## IMMUNE THERAPY FOR GLIOMAS – A PATH FORWARD

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Comprehensive Cancer Center

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**NCI**

**Comprehensive  
Cancer Center**

A Cancer Center Designated by the  
National Cancer Institute

# DISCLOSURES

- Receiving Drug-Only support from Bristol-Myers Squibb
- Kiyatec – Advisory board
- Servier Pharmaceuticals – Advisory board

# Glioblastoma (GBM)

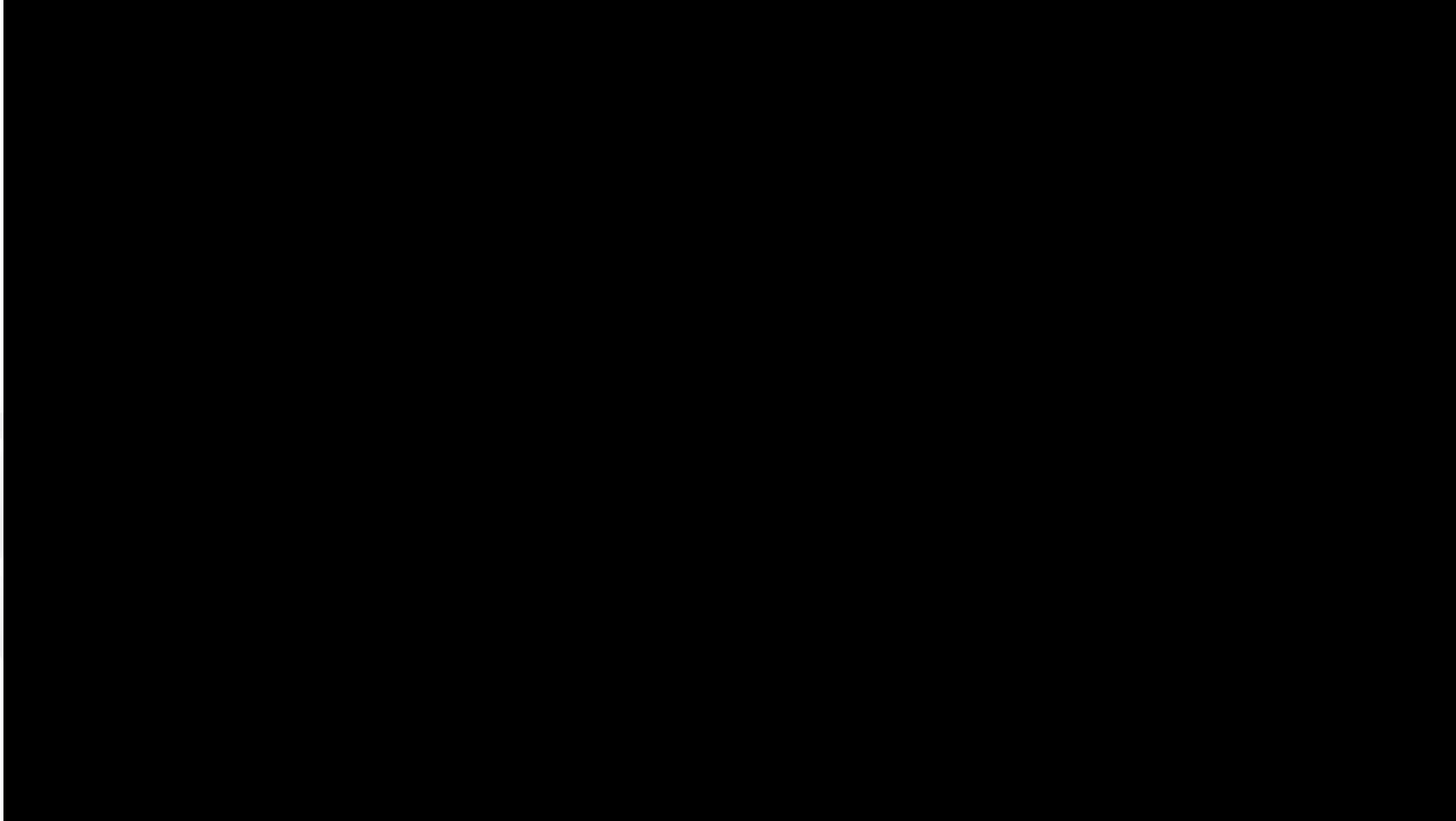
- GBM is the most aggressive and common primary malignant brain tumor in adults characterized by diffuse infiltration of the brain parenchyma
- Newly diagnosed GBM patients treated with radiation and temozolomide have a time to progression and median survival of 6.9 and 14 months respectively
- Barriers to therapy include heterogeneity of the lesions, difficulty in delivery of therapeutics past the blood brain barrier and resistance of these lesions to conventional chemotherapeutics



Stupp et al., New England Journal of Medicine, 352(10):987-996, 2005.

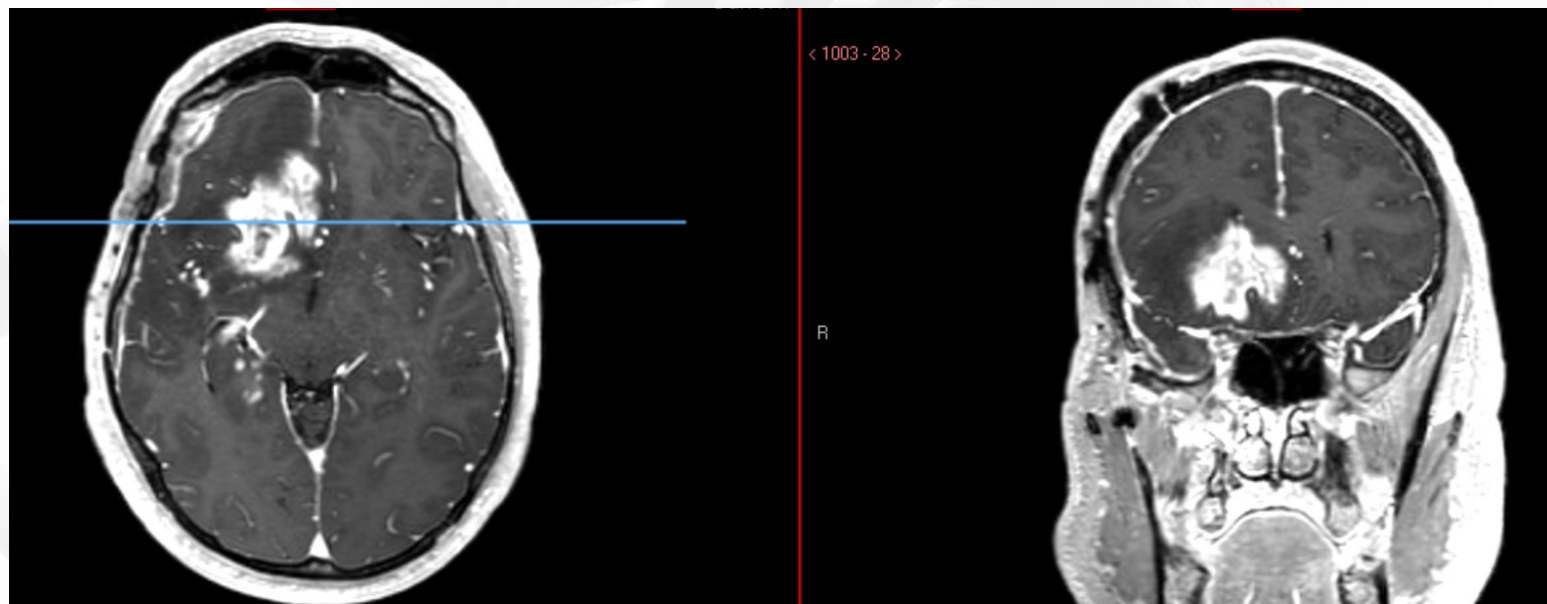


# SURGERY IS NOT ENOUGH

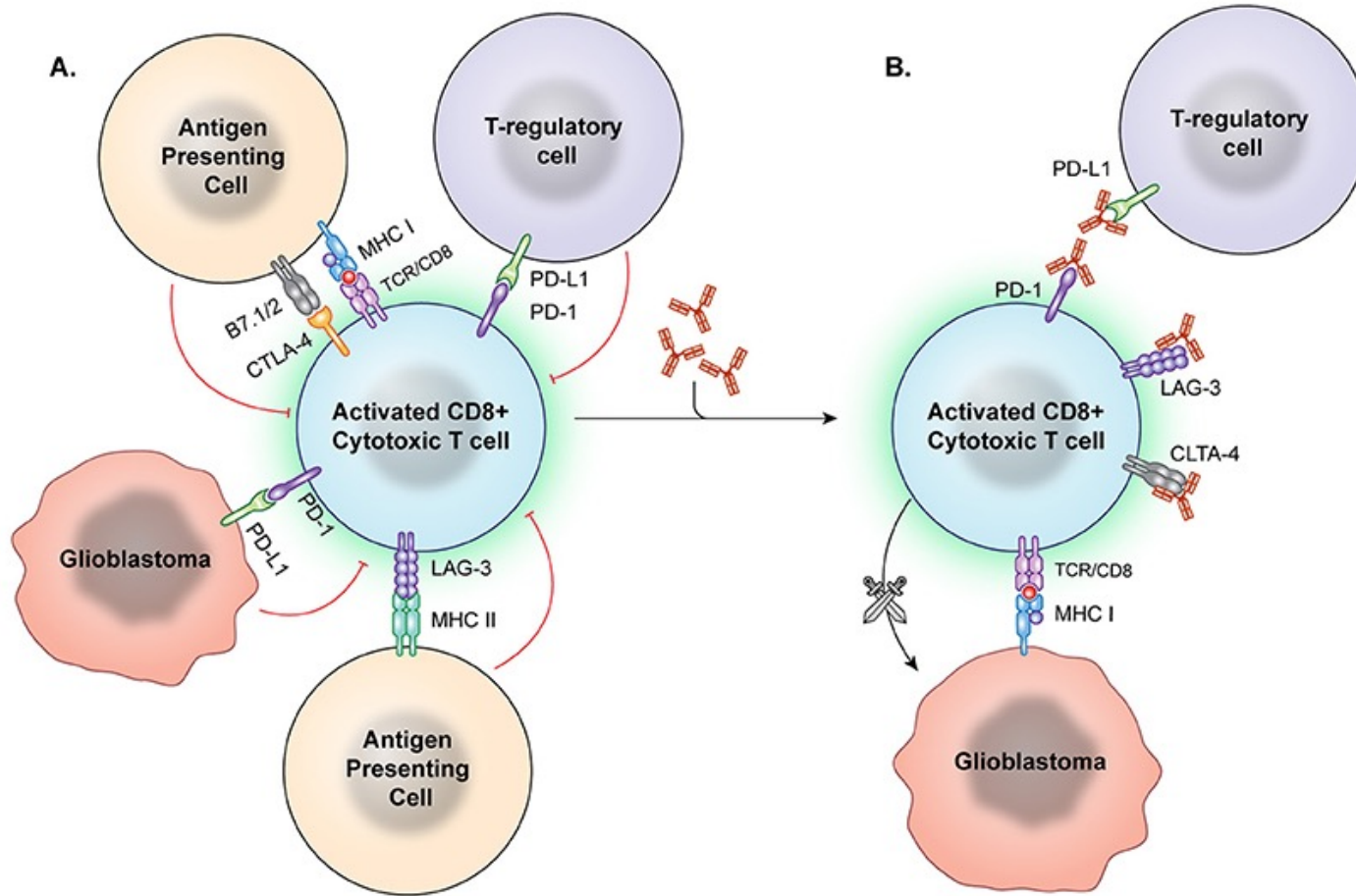




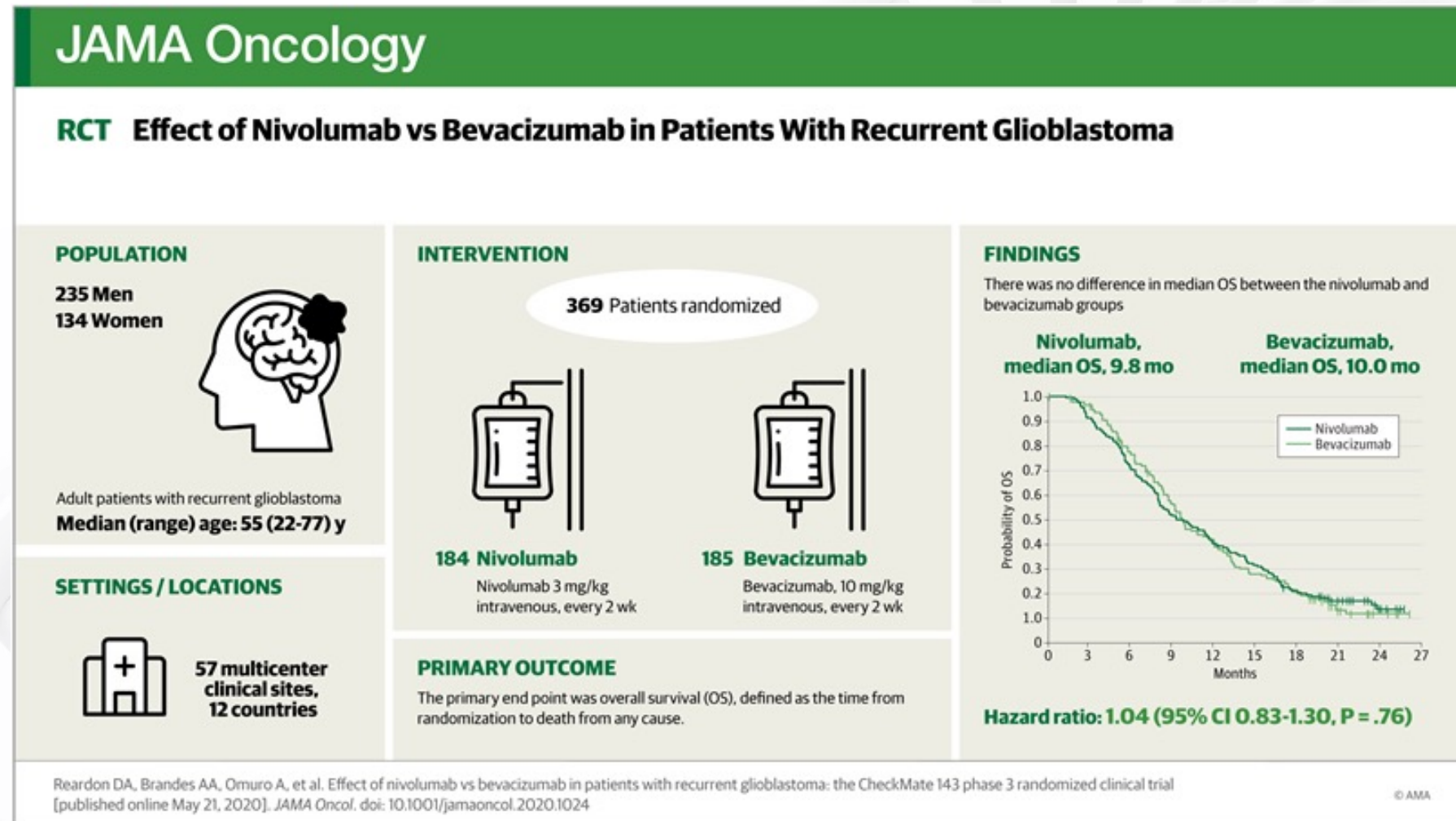
**16 MONTHS LATER**



# CHECKPOINT INHIBITION FOR GBM



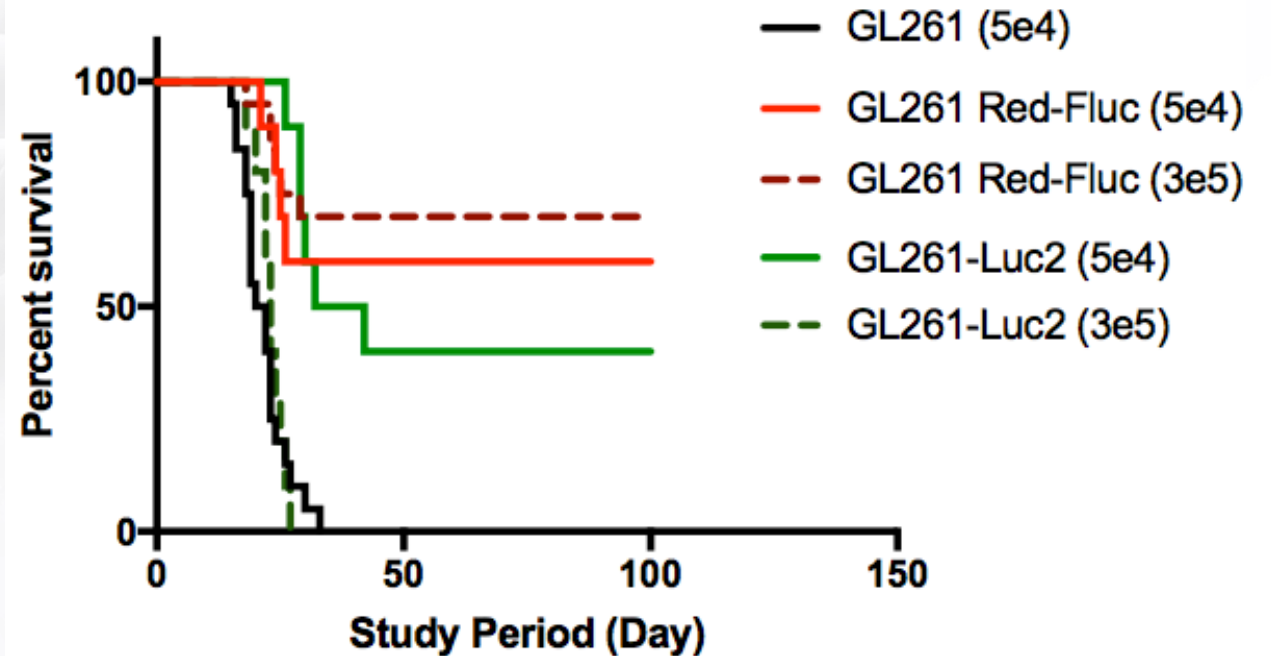
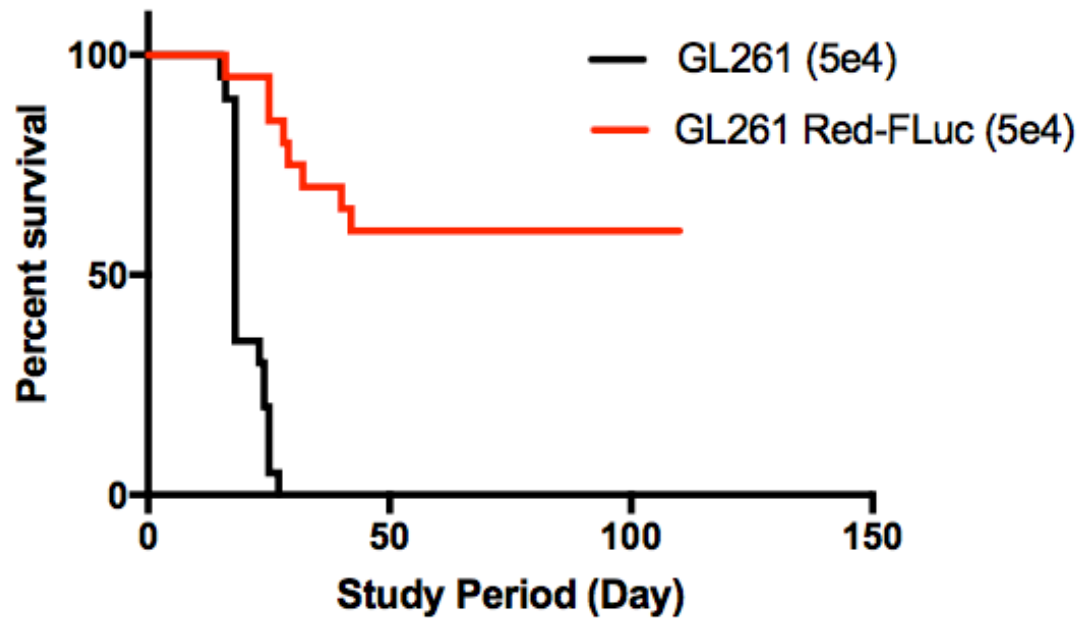
# Clinical trial failure of ICIs



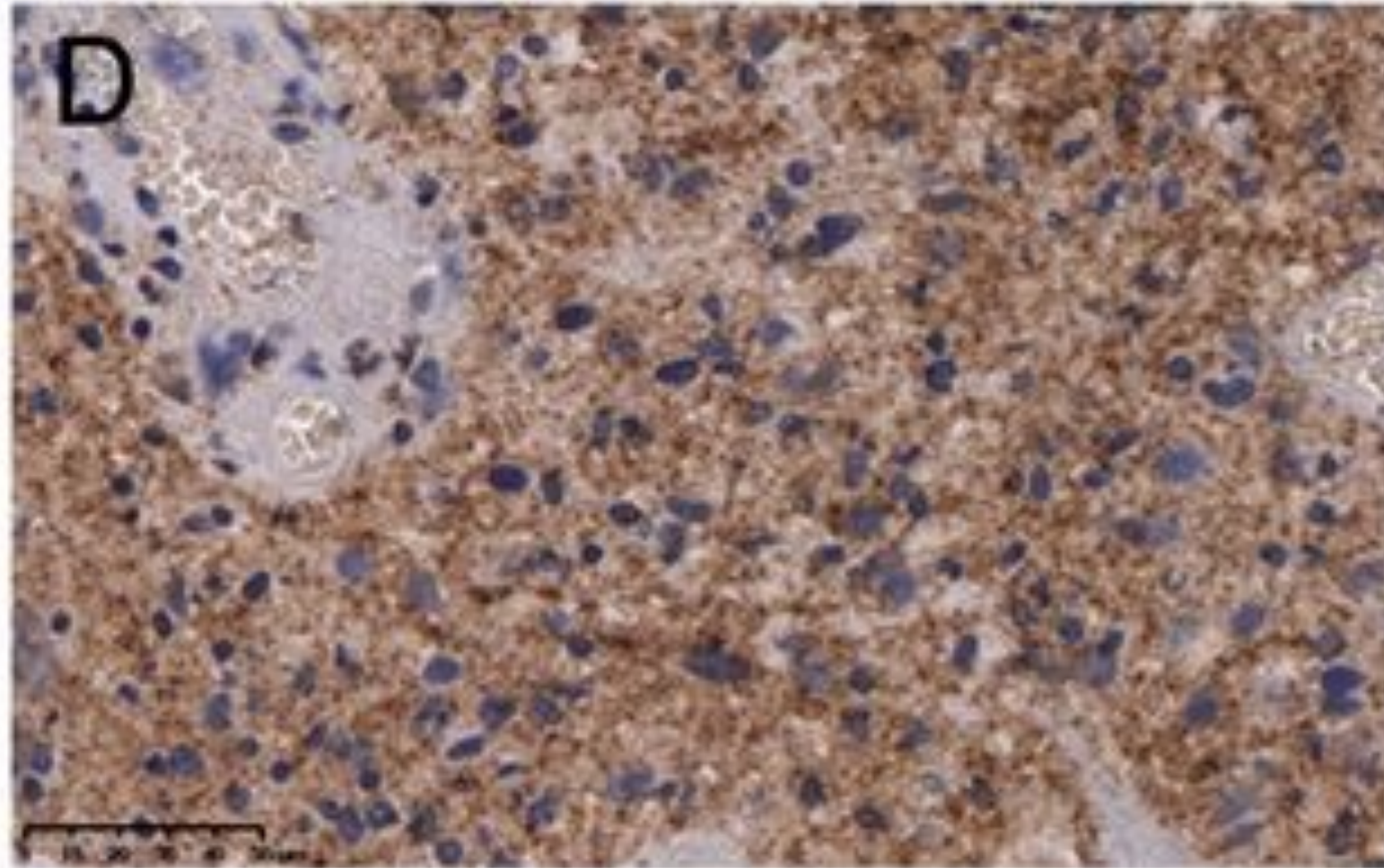
Reardon et al., JAMA Oncology, 2020



# IMPLANTED LUCIFERASE-EXPRESSING GL261 MODELS DEMONSTRATED PROLONGED SURVIVAL IN C57BL/6 MICE

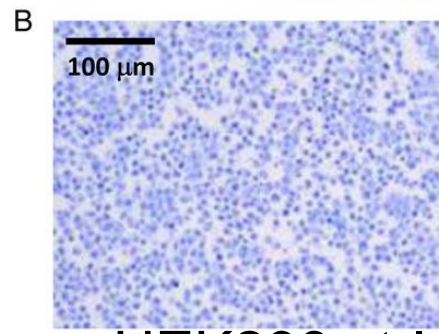
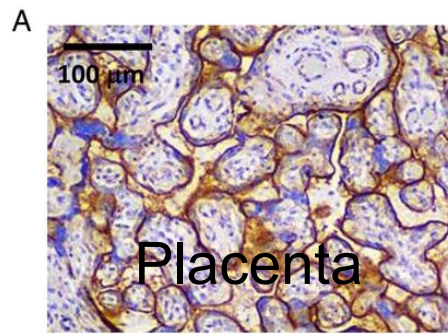


## GBM PD-L1 EXPRESSION?

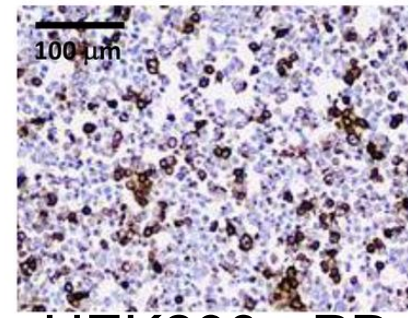


Diffuse expression reported in 88% of samples

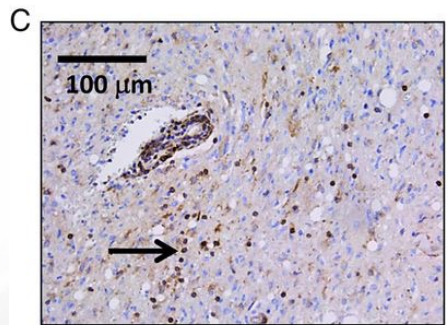




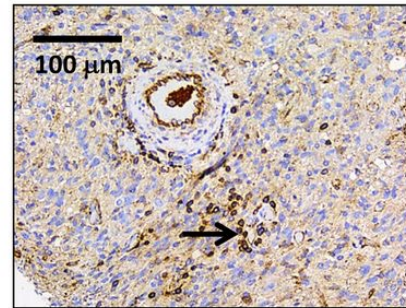
HEK293 ctrl



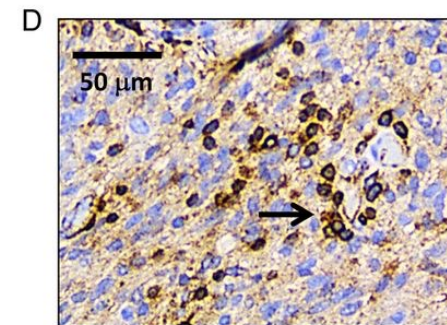
HEK293 +PD-L1



GBM TMA

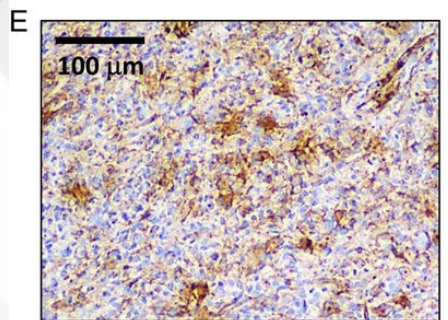


GBM TMA

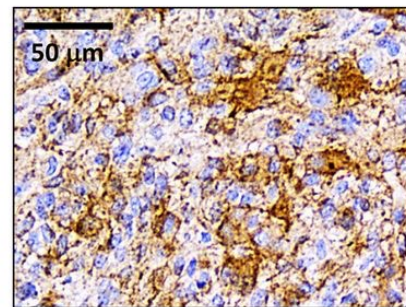


GBM TMA

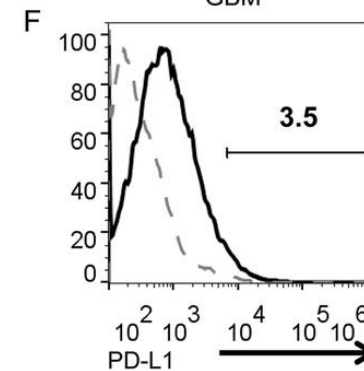
GBM



GBM TMA



GBM TMA

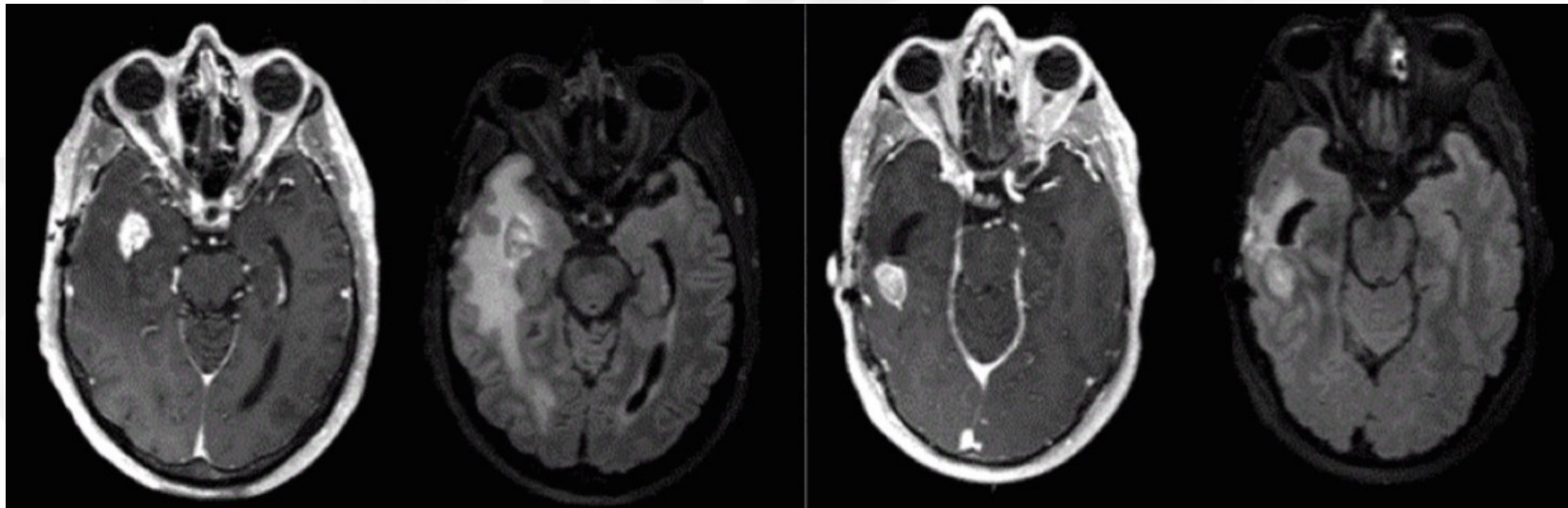


Edjah K. Nduom et al. Neuro Oncol 2015;neuonc.nov172

Neuro-Oncology

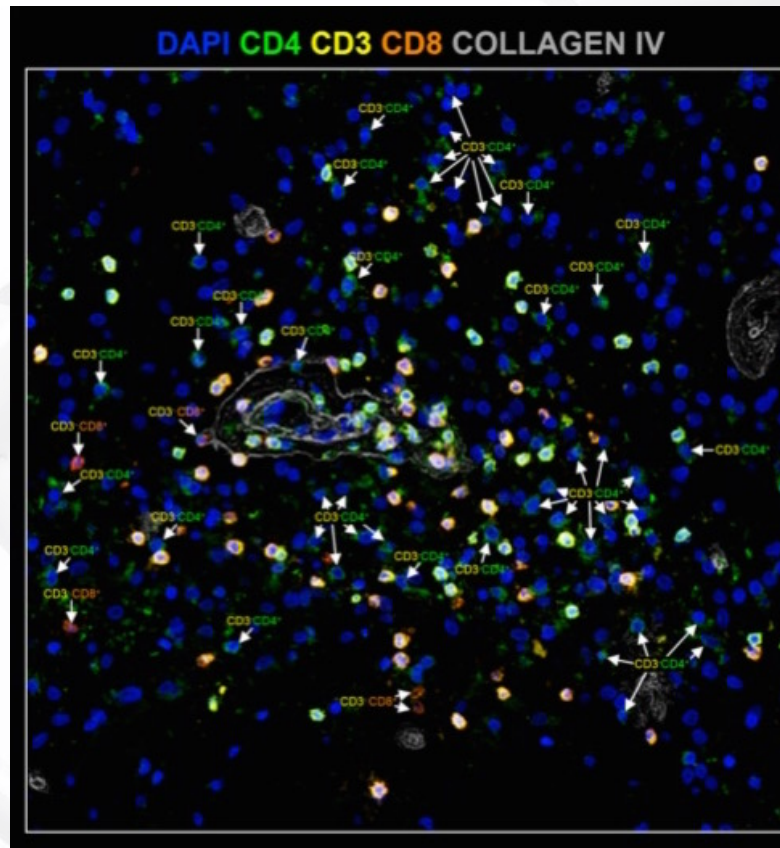


**WHICH RECURRENT LESION IS A TUMOR? NEITHER?  
BOTH? LEFT OR RIGHT?**

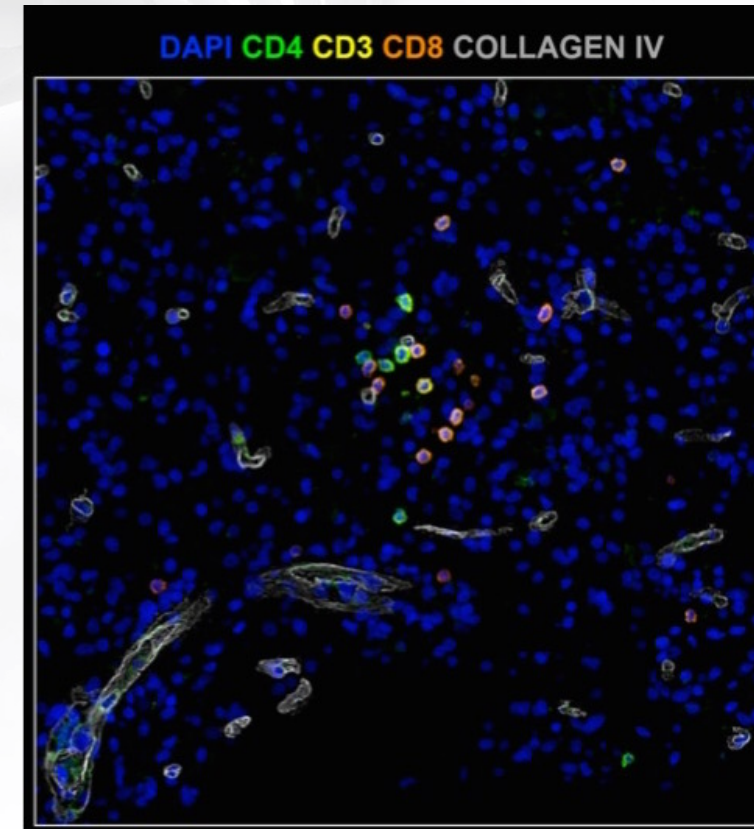


# IMMUNE RESPONSE VS NON-RESPONSE

Patient 1



Patient 2

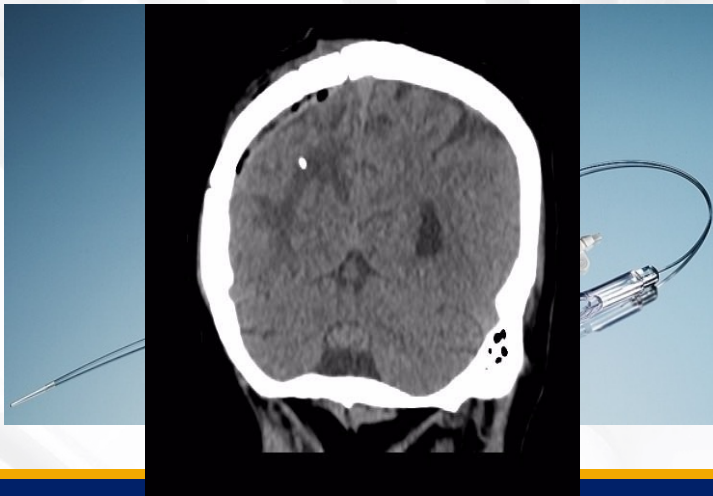




# CYTOKINE MICRODIALYSIS



Day 1



Day 3

Nivolumab

Day 8





# STUDY TIMELINE



John Lynes, MD  
Resident research  
Fellow, 2017-2018



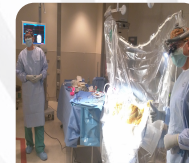
## Day 1

- Biopsy
- Lumbar drain
- Blood draw
- MD catheter placement



## Day 3

Nivolumab  
MD q6  
CSF daily  
Blood daily



## Day 8

- Resection
- Catheters removed



## FU (Day 17+)

Nivolumab  
• Anti-Lag 3  
• MRI Monthly

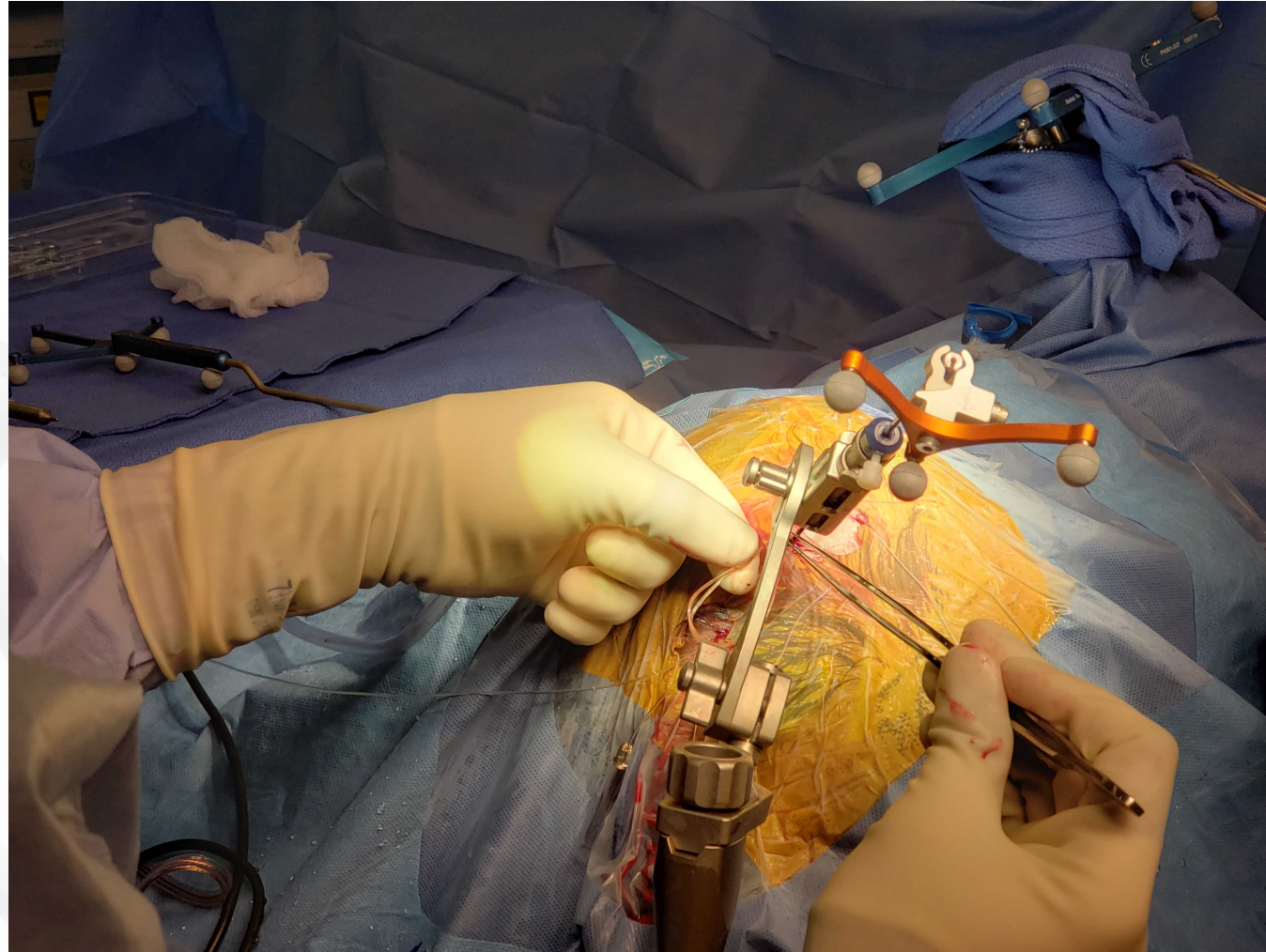
Lynes ... Nduom, *Neurosurgery*, 2018

# PASSING SLOTTED NEEDLE TO TARGET WITH STEALTH GUIDANCE





# FEEDING CATHETER INTO RIGID GUIDE





## STATUS OF TRIAL

- 23 patients enrolled
- 10 completed study procedures
- 5 failed screening/withdrew after enrollment, but before surgery
- 5 patients found to have pseudoprogression on pathology from Day 1 biopsy
- 3 withdrawn due to pharmacy issues
- No morbidity from microdialysis catheter placement

# PRELIMINARY MICRODIALYSIS PROTEOMIC RESULTS

Pathway	TUMOR_post drug2_vs_bas eline	BRAIN_postd rug2_vs_base line	CSF_8_ vs_3
Osteoarthritis Pathway	3.464	1.291	0
IL-15 Production	2.236	2.121	0
p38 MAPK Signaling	2.236	1.414	0
Cachexia Signaling Pathway	2.183	2.294	-1.667
Th1 Pathway	2	1.414	0
Role of Osteoclasts in Rheumatoid Arthritis Signaling Pathway	1.964	1.225	-0.632
Role of Tissue Factor in Cancer	1.897	1.5	-1.265
Apoptosis Signaling	1.89	1.414	0
Wound Healing Signaling Pathway	1.698	0.209	-1.387
Dendritic Cell Maturation	1.667	2	0
Necroptosis Signaling Pathway	1.633	2.121	-2
GP6 Signaling Pathway	1.633	1.89	0

# CAR T CELLS?

[Sci Transl Med](#). Author manuscript; available in PMC 2018 Jan 19.

PMCID: PMC5762203

*Published in final edited form as:*

NIHMSID: NIHMS930576

[Sci Transl Med. 2017 Jul 19; 9\(399\): eaaa0984.](#)

PMID: [28724573](#)

doi: [10.1126/scitranslmed.aaa0984](#)

## A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma

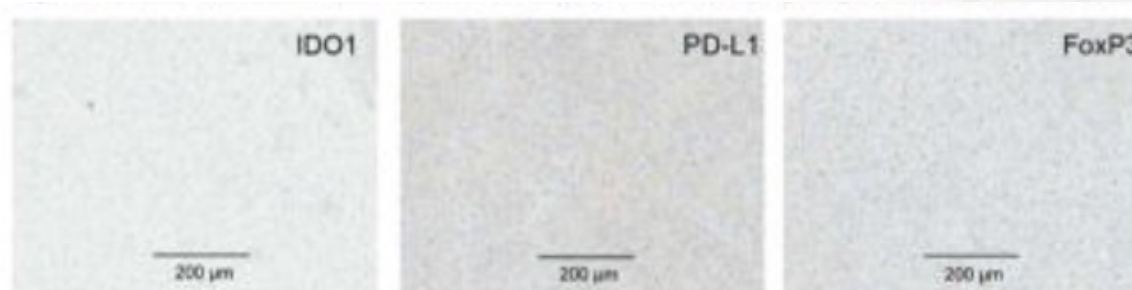
[Donald M. O'Rourke](#),<sup>1</sup> [MacLean P. Nasrallah](#),<sup>2,\*</sup> [Arati Desai](#),<sup>3,\*</sup> [Jan J. Melenhorst](#),<sup>4,\*</sup> [Keith Mansfield](#),<sup>5,\*</sup>  
[Jennifer J. D. Morrisette](#),<sup>6</sup> [Maria Martinez-Lage](#),<sup>2,†</sup> [Steven Brem](#),<sup>1</sup> [Eileen Maloney](#),<sup>1</sup> [Angela Shen](#),<sup>7</sup> [Randi Isaacs](#),<sup>5</sup>  
[Suyash Mohan](#),<sup>8</sup> [Gabriela Plesa](#),<sup>4</sup> [Simon F. Lacey](#),<sup>4</sup> [Jean-Marc Navenot](#),<sup>4</sup> [Zhaohui Zheng](#),<sup>4</sup> [Bruce L. Levine](#),<sup>4</sup>  
[Hideho Okada](#),<sup>9</sup> [Carl H. June](#),<sup>4</sup> [Jennifer L. Brogdon](#),<sup>5</sup> and [Marcela V. Maus](#)<sup>10,‡</sup>

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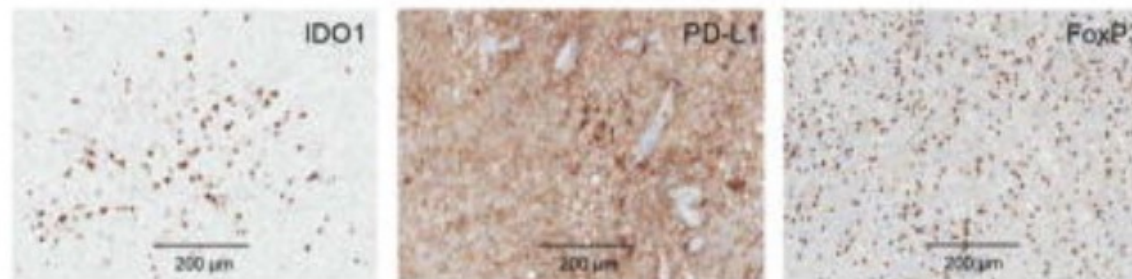
The publisher's final edited version of this article is available at [Sci Transl Med](#)



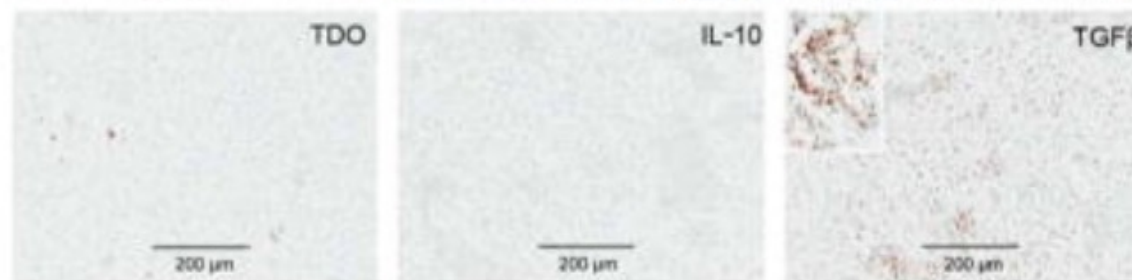
Pre



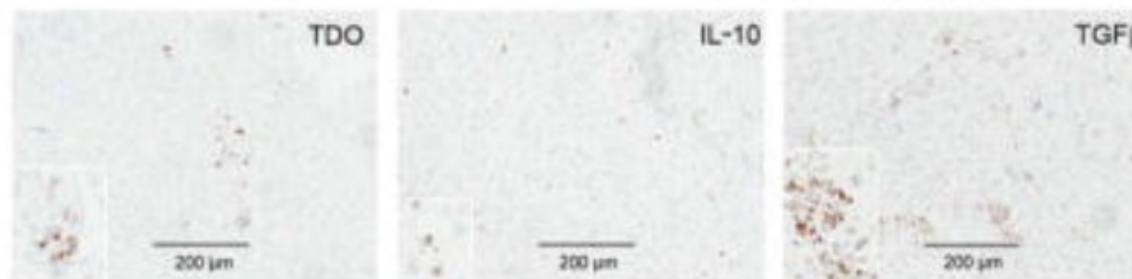
Post






Pre



Post



# Intraventricular CARv3-TEAM-E T Cells in Recurrent Glioblastoma

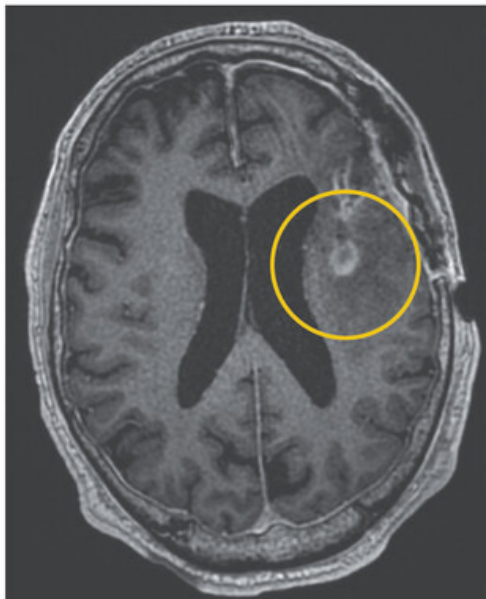
**Authors:** Bryan D. Choi, M.D., Ph.D., Elizabeth R. Gerstner, M.D., Matthew J. Frigault, M.D., Mark B. Leick, M.D. , Christopher W. Mount, M.D., Ph.D., Leonora Balaj, Ph.D., Sarah Nikiforow, M.D., Ph.D., Bob S. Carter, M.D., Ph.D. , William T. Curry, M.D., Kathleen Gallagher, Ph.D., and Marcela V. Maus, M.D., Ph.D.  [Author Info & Affiliations](#)

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**B MRI in Participant 1**

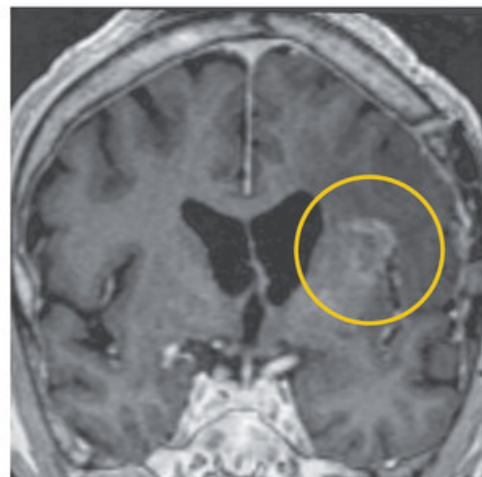
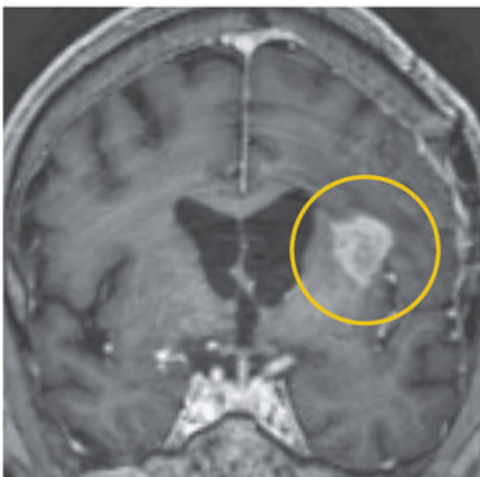
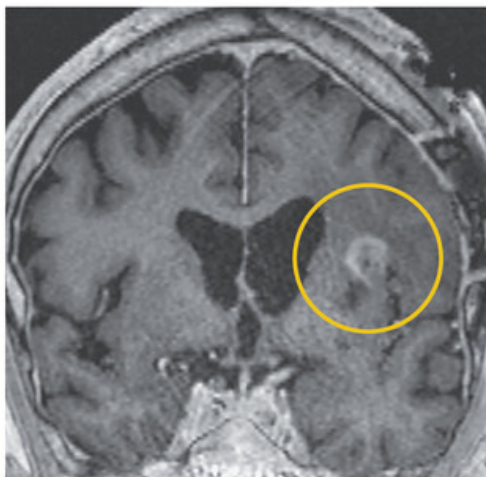
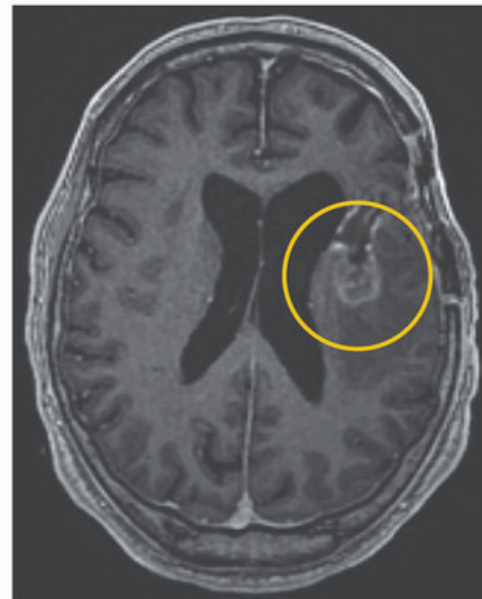
After Resection (day -40)



Before Infusion (day -6)



After Infusion (day 1)





## VERDICT ON IMMUNE THERAPY FOR GLIOBLASTOMAS

- Verdict is still out on checkpoint inhibition in GBM
- CAR T-Cells showing early promise – but no prolonged survival
- Additional biomarker-heavy studies are needed
- Combinatorial approaches may harness findings from existing studies

# **National Institutes of Health**

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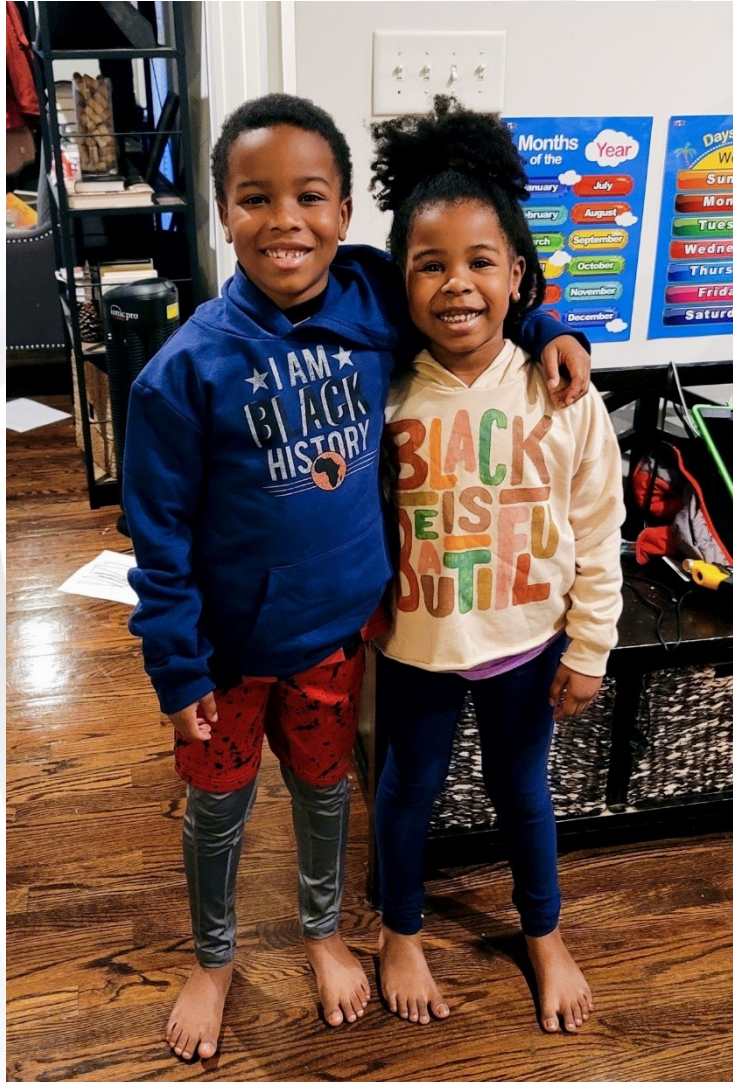
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