Updates and Future Directions in Managing Glioblastoma

Ashley Ghiaseddin, MD
Clinical Associate Professor
Chief, Division of Neuro-Oncology
Preston A. Wells, Jr. Center for Brain Tumor Therapy
University of Florida, Department of Neurosurgery

Disclosures

- Served on Advisory Board for Alexion Pharmaceuticals, Servier, OnoPharma USA
- Consulting for Neosoma and Monteris Medical
- Investor in Neosoma
- Personal stock in Viatris Inc. 2022-2023
- I will be discussing novel therapies being used currently in the context of clinical trials
- I will be discussing off label use of targeted therapies in recurrent Glioblastoma

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Objectives

1. Differential diagnoses when evaluating patients Glioblastoma (GBM)
2. Describe standard treatment approaches for GBM
3. Recognize common toxicities associated with GBM

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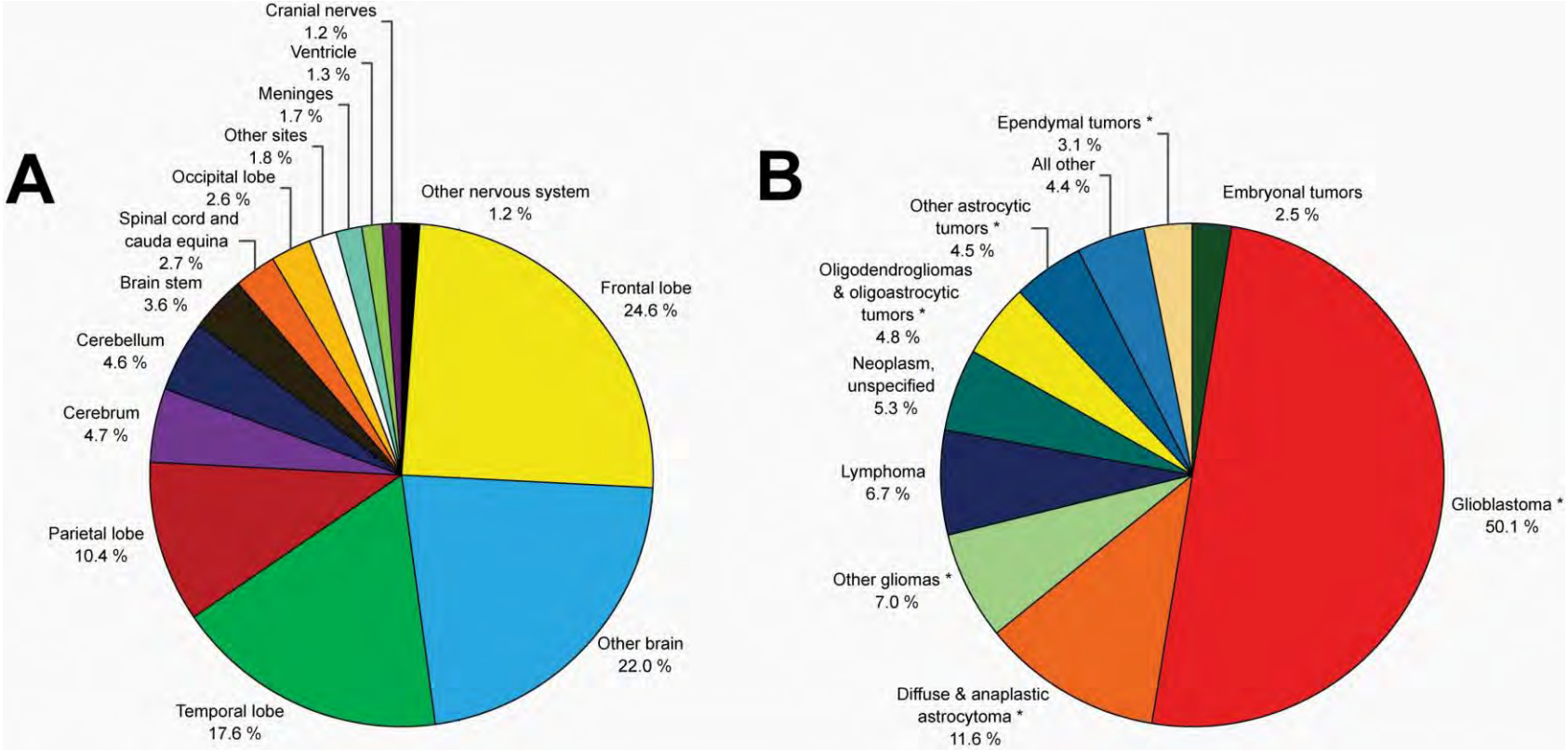
The Central Brain Tumor Registry of the United States (CBTRUS) CBTRUS Statistical Report: NPCR and SEER, 2015-2019.

Distribution of Malignant Primary Brain and other CNS Tumors (Five-Year Total=126,345; Annual Average Cases=25,269) by A) Site and B) Histopathology



a. Percentages may not add up to 100% due to rounding.
* All or some of this histopathology is included in the CBTRUS definition of gliomas, including ICD-O-3 histopathology codes 9380-9384 and, 9391-9460 (Table 2).
Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology, and End Results Program; NOS, not otherwise specified.

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Ostrom QT et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2015–2019, *Neuro-Oncology*, Volume 24, Issue Supplement_5, October 2022, Pages v1–v95

Case presentation

- 51 yo right handed M with chronic history of nocturnal seizures presented with 1 month history of diplopia with associated headache, left sided motor deficits and cognitive changes
  - Significant PMH Nocturnal seizures/HTN
  - Social Hx Occasional EtOH
  - Family Hx Hypertension and Lung Cancer
- CBC w diff and CMP - unremarkable
- Influenza A, COVID-19, RSV – Not detected

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Imaging

CT chest/abdomen/pelvis – No clear evidence of metastatic disease, No LAD

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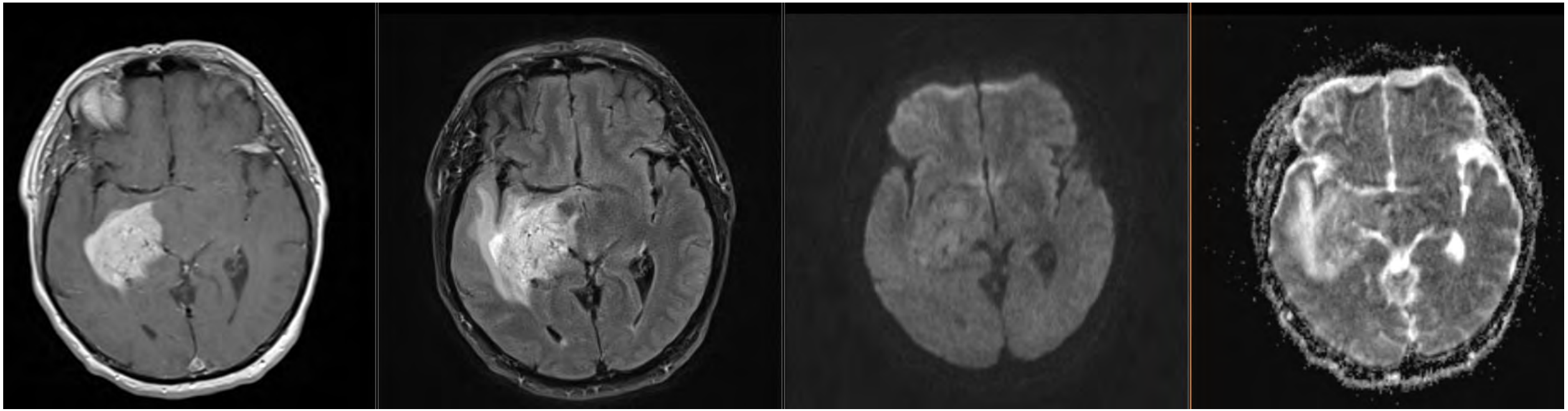
Imaging



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Differential diagnosis

a. Glioma
b. Brain Metastasis
c. Cerebral Abscess
d. Lymphoma
e. Tumefactive MS

What should we do next?

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Diagnostic workup

Stereotactic biopsy of the right thalamic tumor

Frozen section was consistent with **lymphoma**

Patient transferred to Med Onc floor with **plan for HD-MTX/RTX**

MRI Total Spine/US scrotum/Serologic workup/Ophthalmology exam - **unremarkable**

Hematopathology flow cytometry of the brain biopsy

No overt evidence of clonal B-Cell or aberrant T-cell population suggesting nonhematologic origin

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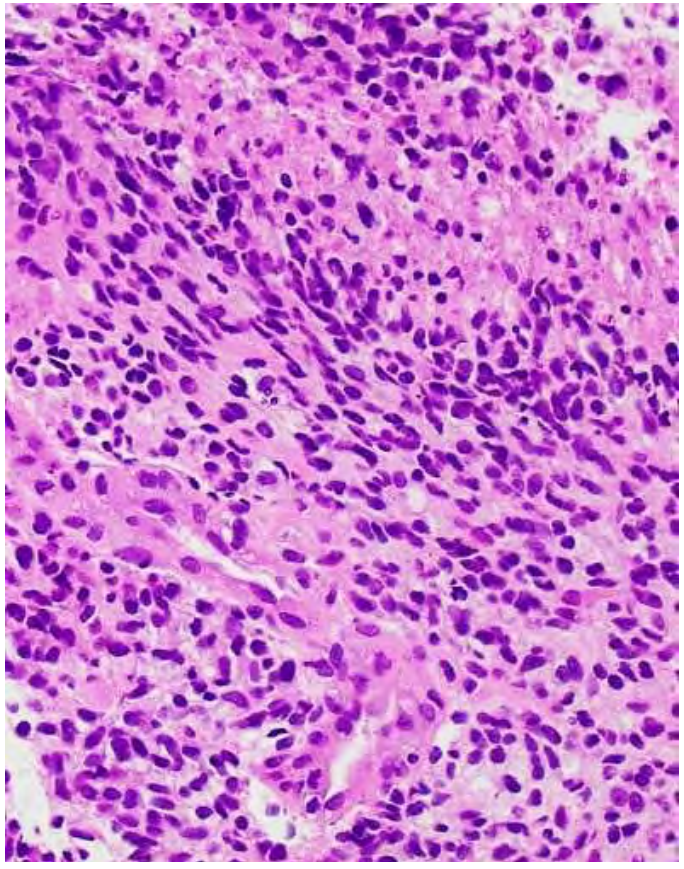
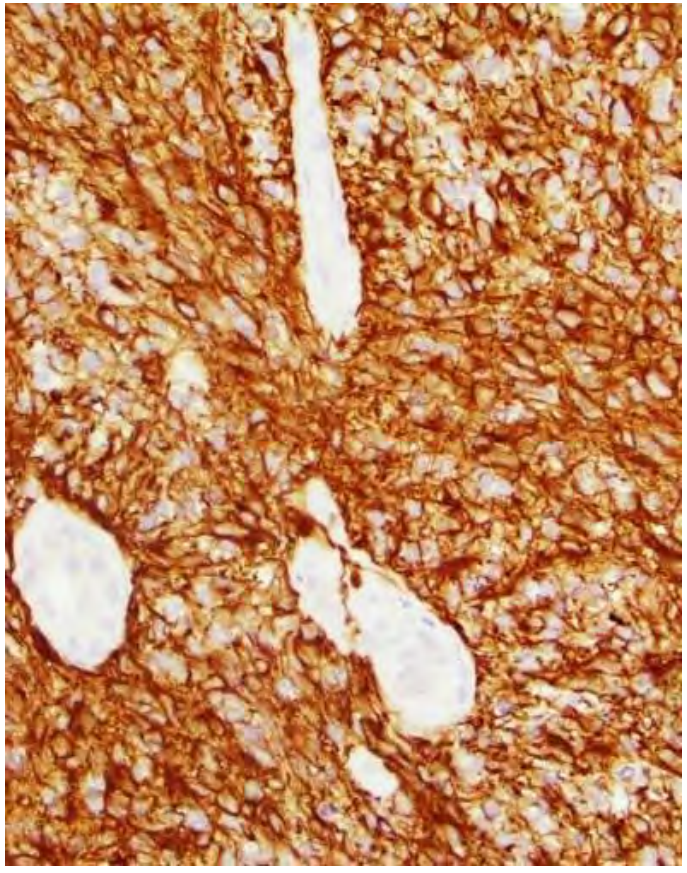
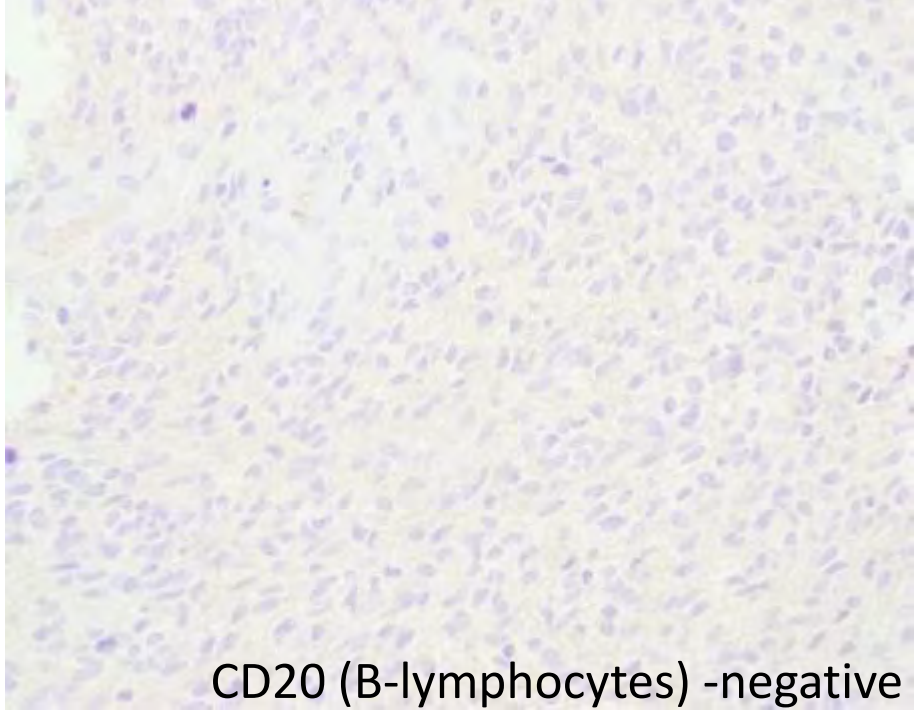
Pathology



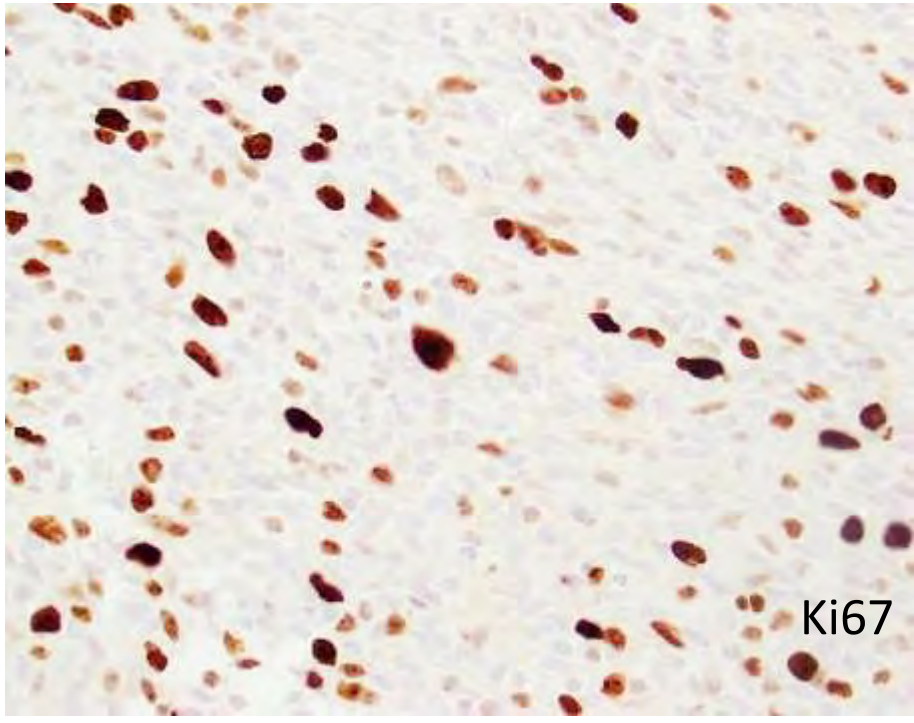
Necrosis (top, right)
Microvascular proliferation (bottom left)
Spindle shaped tumor cells



GFAP-positive tumor cell processes



CD20 (B-lymphocytes) -negative



Ki67

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Slide adapted courtesy of Anthony T. Yachnis, MD

Final Diagnosis

Next Generation Sequencing performed identified TERT mut

Final pathologic diagnosis

Glioblastoma WHO Grade 4; TERT mut

Note: Highly cellular gliomas can fluid restrict on DWI

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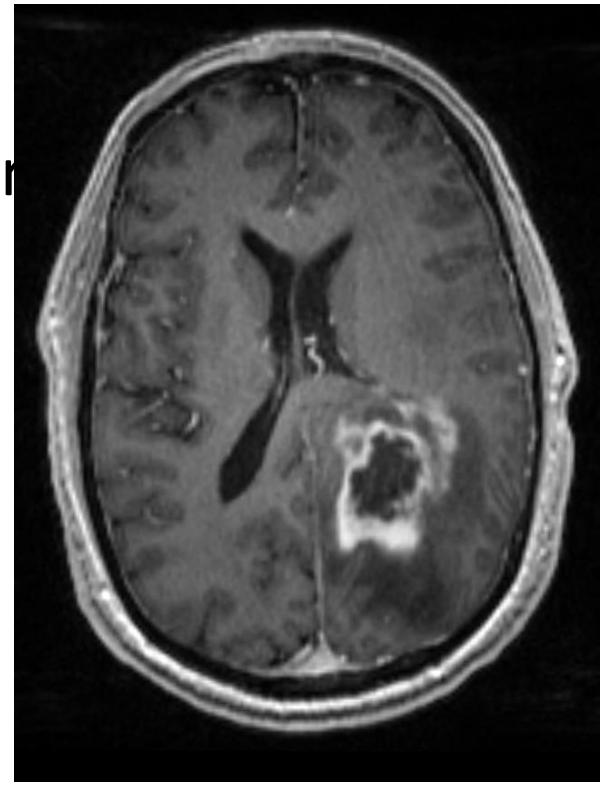
Glioblastoma WHO Grade 4

- **Onset**
  - Arises in 6th-7th decades of life
  - De novo or transformation from lower grade (ra
- **MRI findings**
  - T1+c heterogeneous ring enhancement
  - Significant T2/FLAIR signal abnormality
    - non-enhancing disease
    - vasogenic edema
- **Diffuse infiltration of brain parenchyma**



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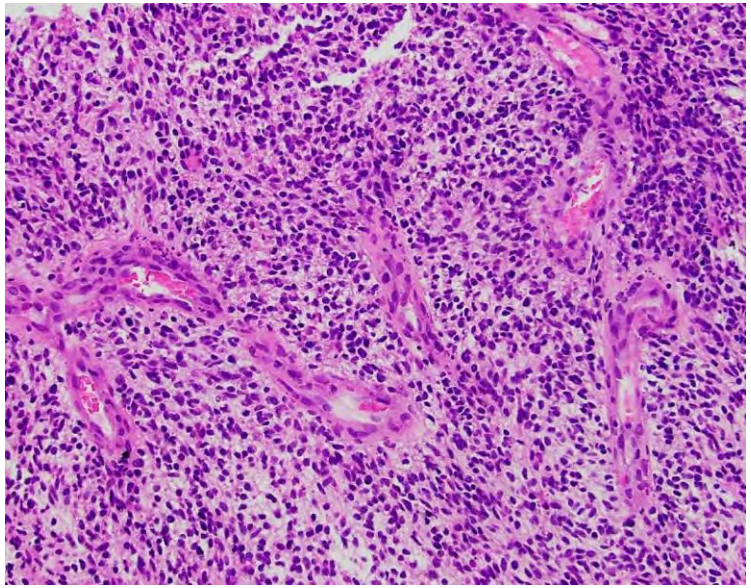
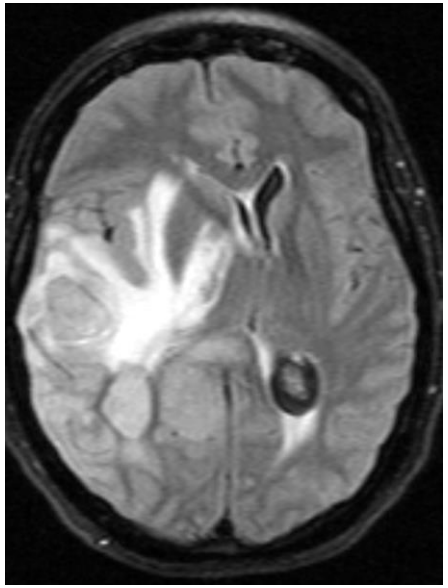
Peters KB. Introduction to CNS Tumors- Pathology, Genetics, Tumor Biology 2014
Canoll P. Primary Adult Brain Tumors, Pathology, Grading and Prognosis SNO 2014

Glioblastoma WHO Grade 4



- **Pathologic findings**
  - increased nuclear atypia and cellular proliferatio
  - **microvascular proliferation and necrosis**
- Common **Molecular findings**
  - **IDH wildtype***
    - TERT promoter mut
    - EGFR amplification
    - Gain of chromosome 7p/Loss of 10q
- **Prognosis**
  - Overall survival 14-18 months.
  - Progression of tumor is common



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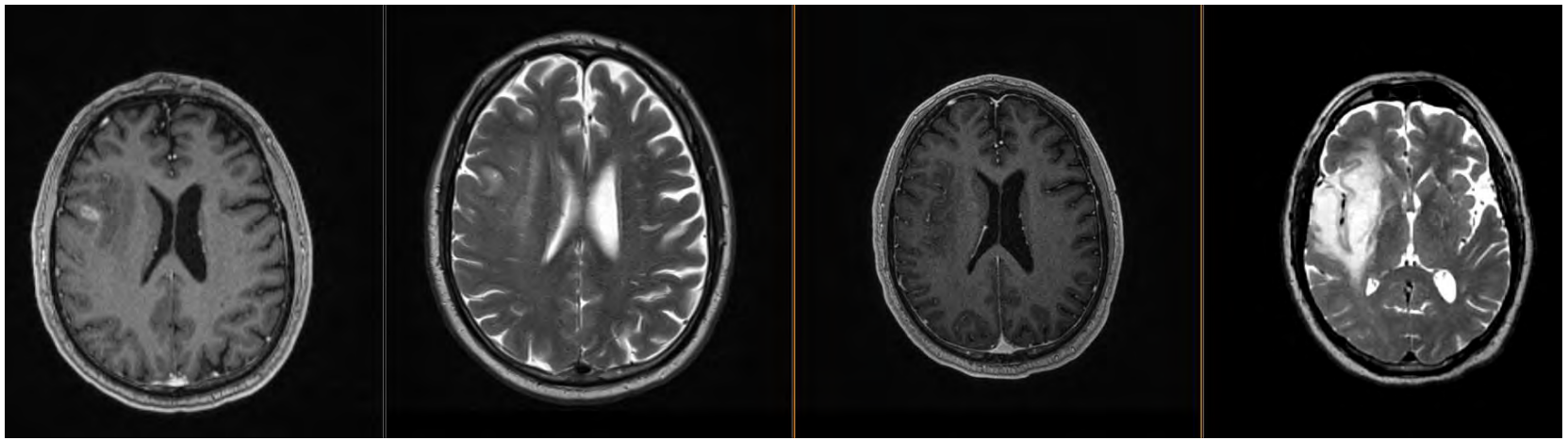
Peters KB. Introduction to CNS Tumors- Pathology, Genetics, Tumor Biology 2014
Canoll P. Primary Adult Brain Tumors, Pathology, Grading and Prognosis SNO 2014

***WHO 2021 classification does not allow IDH mut tumors to be classified as Glioblastoma WHO Grade 4**

Tissue Sampling emphasizing heterogeneity of gliomas

- Histological analysis of MRI localized biopsies of the Enhancing and Non-Enhancing portions of Glial Tumors
  - **Features more commonly associated with Enhancing portion**
    - Mitoses
    - Microvascular Proliferation (MVP)
    - Necrosis
  - **Increased cellular density in the Enhancing portion**

1 month later, resection of new right frontal enhancement shows MVP/necrosis thus Glioblastoma confirmed



Initial path following resection of right temporal non-enhancing disease Diffuse Astrocytoma

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Canoll P. Primary Adult Brain Tumors, Pathology, Grading and Prognosis SNO 2014
-Adapted from Gill et al. PNAS 2014

Treatment

- Newly diagnosed
  - Surgery, Radiation, Chemotherapy, Optune TTF (EF-14)
  - Clinical trials
- Recurrent
  - Clinical trials
  - Immunotherapy
  - Targeted therapy
  - Salvage Chemotherapy
  - Optune TTF (EF-11) +/_ systemic treatment
  - Laser ablation (LITT) followed by systemic treatment

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Treatment

- **Surgical Management**
  - 5-Aminolevulic acid (5-ALA) guided surgical resection
  - Laser Interstitial Thermal Therapy (LITT)
  - Focused ultrasound (FUS)
- **Radiation treatment**
  - Fractionated RT, Hypofractionated RT (Age > 70, Poor functional status)
  - Stereotactic radiosurgery (not as common for gliomas but re-irradiation using SRS at recurrence is used at some centers)
- **Chemotherapy**
  - Temozolomide (upfront)
  - Lomustine (CCNU), Carboplatin, Bevacizumab (Avastin), Etoposide
- **Targeted therapy**
  - BRAF/MEKi (Dabrafenib/Trametinib) for BRAFV600E mut
  - Regorafenib (multi kinase inhibitor – dual targeted VEGFR2-TIE2)
  - Osimertinib (EGFRvIII)

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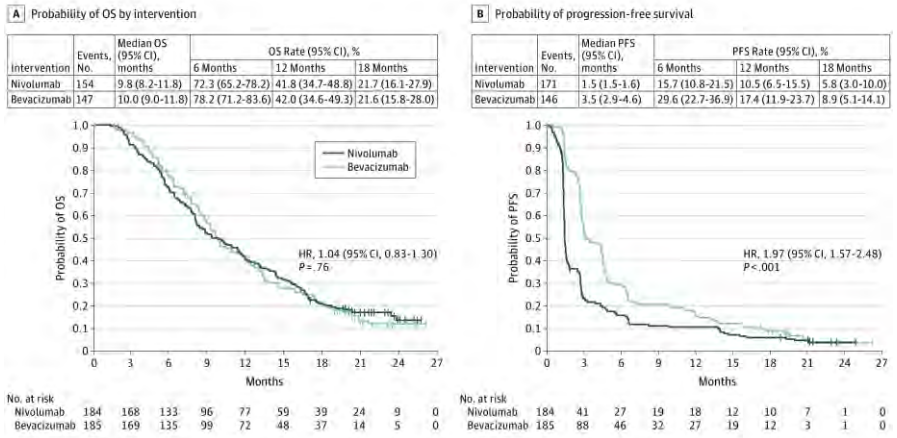
Immunotherapy

Immunotherapy limited by GBM suppressive and heterogeneous biology

CheckMate 143

- **Nivo (PD-1 inhibitor) no improved OS when compared to bev monotherapy in recurrent GBM**



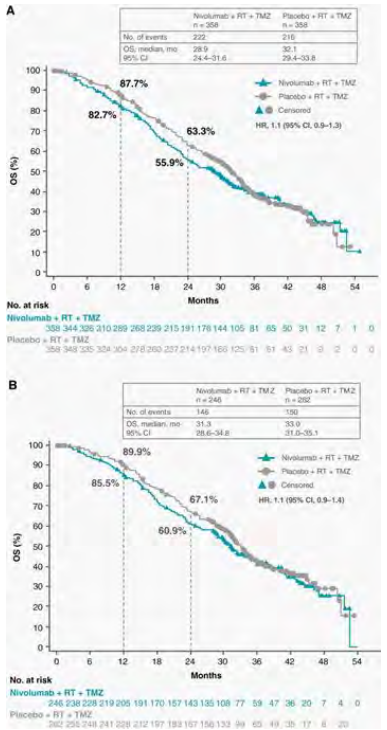
Intervention	Events, No.	Median OS (95% CI), months	OS Rate (95% CI), %		
			6 Months	12 Months	18 Months
Nivolumab	154	9.8 (8.2-11.8)	72.3 (65.2-78.2)	41.8 (34.7-48.8)	21.7 (16.1-27.9)
Bevacizumab	147	10.0 (9.0-11.8)	78.2 (71.2-83.6)	42.0 (34.6-49.3)	21.6 (15.8-28.0)

Intervention	Events, No.	Median PFS (95% CI), months	PFS Rate (95% CI), %		
			6 Months	12 Months	18 Months
Nivolumab	171	1.5 (1.5-1.6)	15.7 (10.8-21.5)	10.5 (6.5-15.5)	5.8 (3.0-10.0)
Bevacizumab	146	3.5 (2.9-4.6)	29.6 (22.7-36.9)	17.4 (11.9-23.7)	8.9 (5.1-14.1)

Reardon DA et al. Effect of Nivolumab vs Bevacizumab in Patients with Recurrent Glioblastoma. JAMA Oncol.2020

Phase III trial of RT/Temozolomide plus Nivo vs placebo (PBO) for newly diagnosed GBM patients with MGMT promoter methylation

- **Nivo (PD-1 inhibitor) no improved OS in newly diagnosed GBM patients with MGMT promoter methylated or indeterminate**



Lim M et al. Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter. Neuro Oncol. 2022

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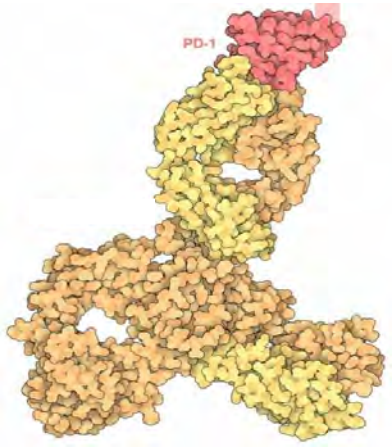
Reardon DA et al. OS10.3 Randomized Phase 3 Study Evaluating the Efficacy and Safety of Nivolumab vs Bevacizumab in Patient with Recurrent Glioblastoma: CheckMate 142. Neuro-Oncology. 2017

HSC + PD-1 Blockade



PD-1 Inhibitor

+

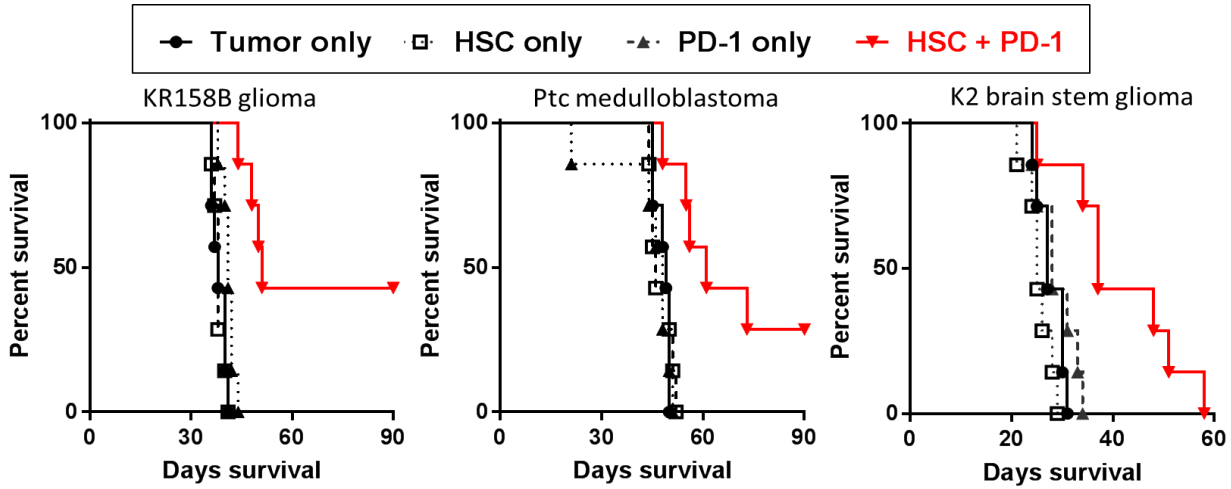
Hematopoietic Stem Cells

Tumor Microenvironment

Catherine Flores, PhD

CHAMP1ON phase 1 trial in GBM, FDA IND 21102

Clinical PIs: **Maryam Rahman, MD** and Ashley Ghiaseddin, MD



Flores et al., Nature Comm. 2018

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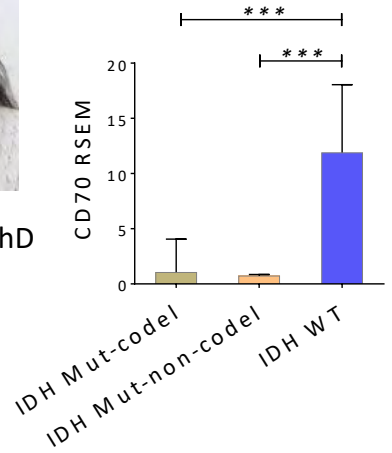
Slide adapted courtesy of Catherine Flores, PhD

CD70 is associated with poor survival in primary gliomas

Jianping Huang, MD, PhD

Linchun Jin, MD, PhD

A



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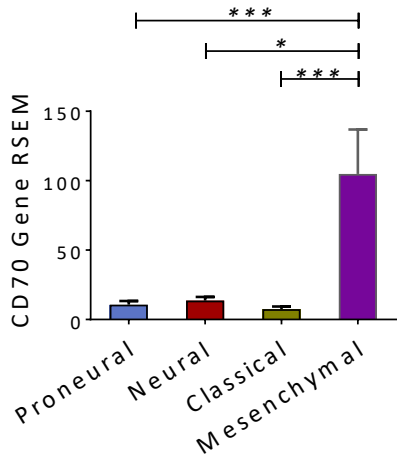

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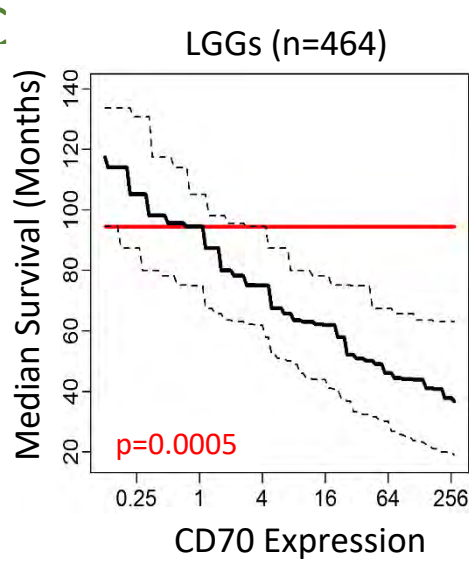

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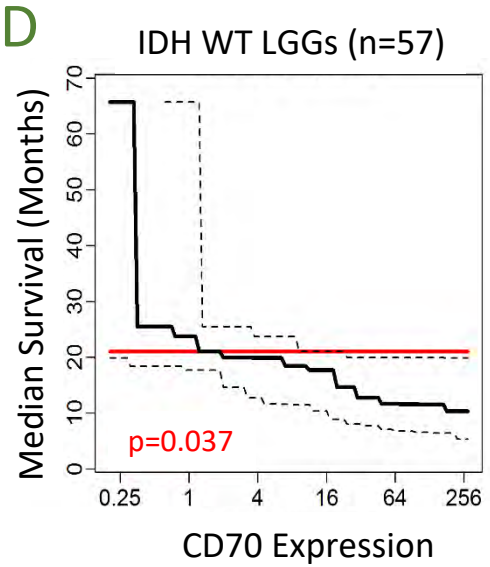

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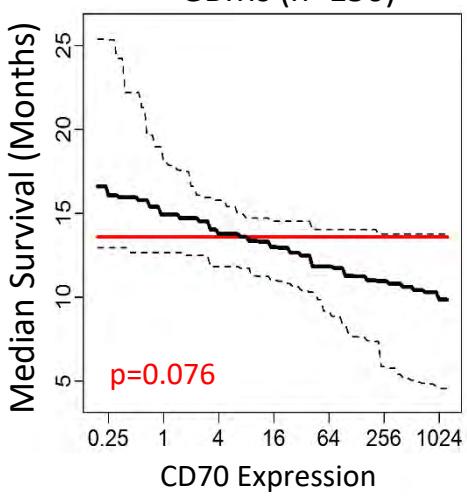

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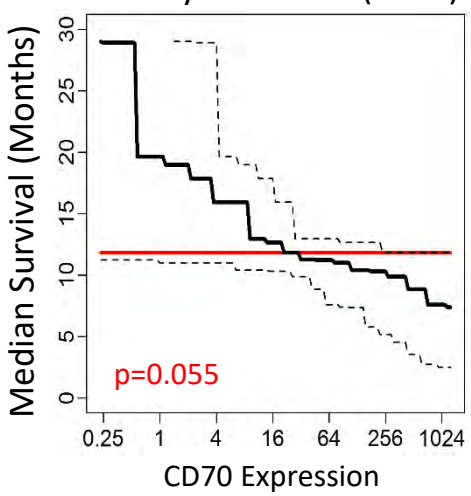


G

CD70 tumor expression and patient survival

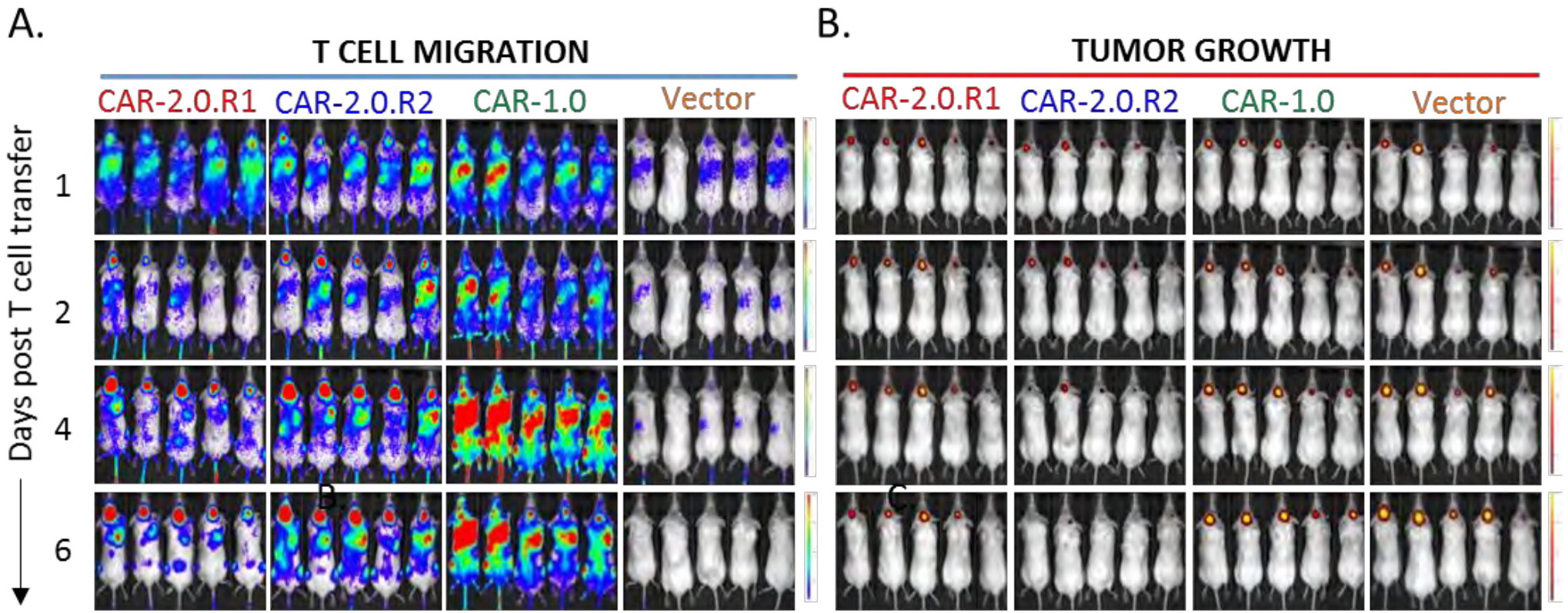
Groups	LGG	LGG-WT*	GBM	GBM-M¶
	(Months)			
CD70 ^{Low}	94.5	19.9	13.8	15.9
CD70 ^{High}	26.7	6.1	10.3	10.4
Difference	**69.8**	**13.8**	**3.5**	**5.5**

*IDH wild type LGG,
¶Mesenchymal subtype of GBM

Jin L, et al. Neuro-Oncology (2018)

Slide adapted courtesy of Jianping Huang, MD, PhD

8R-70CAR T cells efficiently treat late-stage gliomas



IMPACT: IL-8 Receptor-Modified CD70 Patient-derived Activated CAR T cell Therapy

IND#23881, NCT05353530

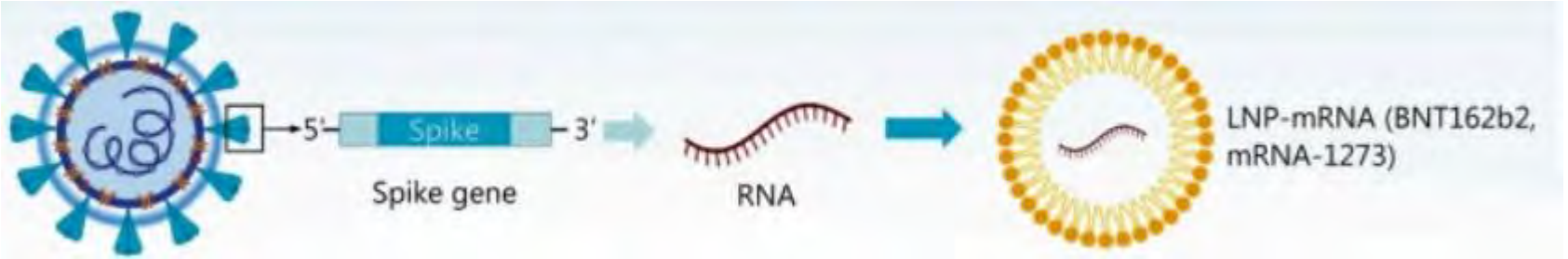
Clinical PI: Ashley Ghiaseddin, MD

Jin L, et al. Nat. Commun., *2019*

Slide adapted courtesy of Jianping Huang, MD, PhD

mRNA Vaccines

Easy and Flexible/Immunogenic/Commercializable and adaptable



Li, DD et al. *Military Med Res* **8,** 1 (2021)

Optimized for mRNA gene expression to induce adaptive immunity:

- **Modified nucleosides to silence innate immunity**
- **NP shell that is relatively inert at physiologic pH- neutral charge**
- **PEG/Cholesterol to prevent aggregation**
- **Helper lipids to prevent aggregation (100-200 nm) and mediate endosomal release**
- **Local delivery (i.m.) to induce protection over subsequent boosts**

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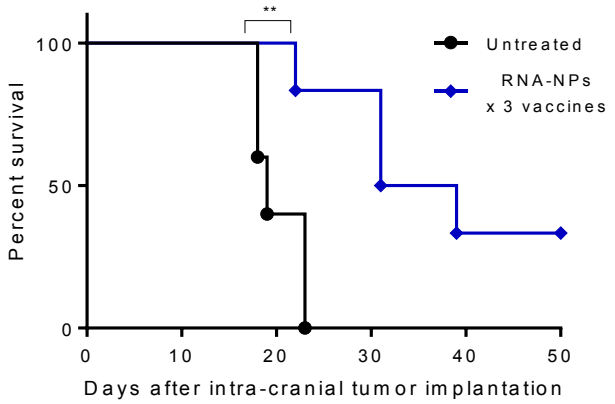
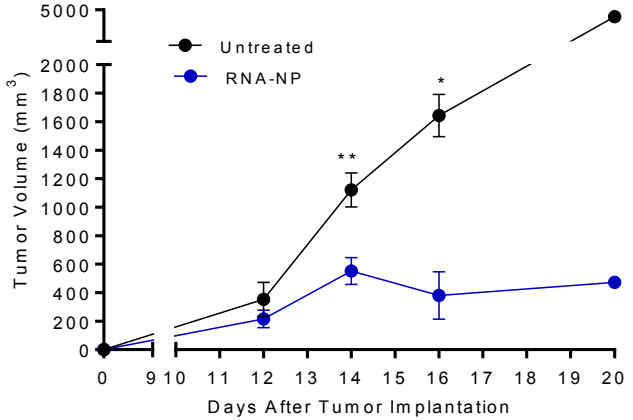
Slide adapted courtesy of Elias Sayour, MD, PhD

RNA-NPs elicit anti-tumor efficacy





Elias Sayour, MD, PhD

Sayour et al. ***OncoImmunol***. 2016. Nov 18;6(1):e1256527
Sayour et al. ***Nano Lett***. 2018 Oct 10;18(10):6195-6206

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Slide adapted courtesy of Elias Sayour, MD, PhD

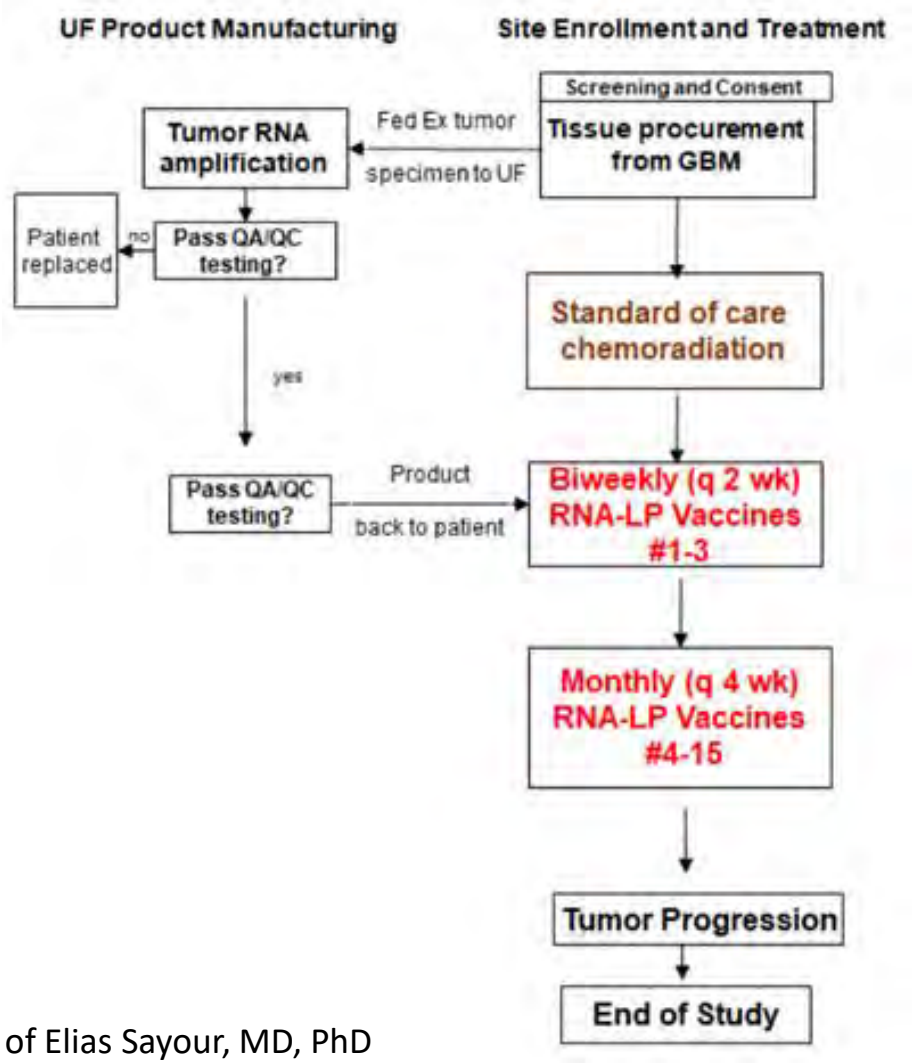
Multi-lamellar RNA-LP for glioblastoma patients

PNOC 020
A Phase I/II Study of RNA-lipid particle (RNA-LP) vaccines for Newly Diagnosed Pediatric High-Grade Gliomas (pHGG) and Adult Glioblastoma (GBM).
Sponsor: University of Florida
Collaborators: Pacific Pediatric Neuro-Oncology Consortium
University of California, San Francisco
CureSearch

Clinical PI: Ashley Ghiaseddin, MD (Stratum 1 Adult patients)
NCT04573140

Elias Sayour, MD, PhD

Follow up trials for pediatric HGG
PIs: Sabine Mueller, MD, PhD and Michael Prados, MD



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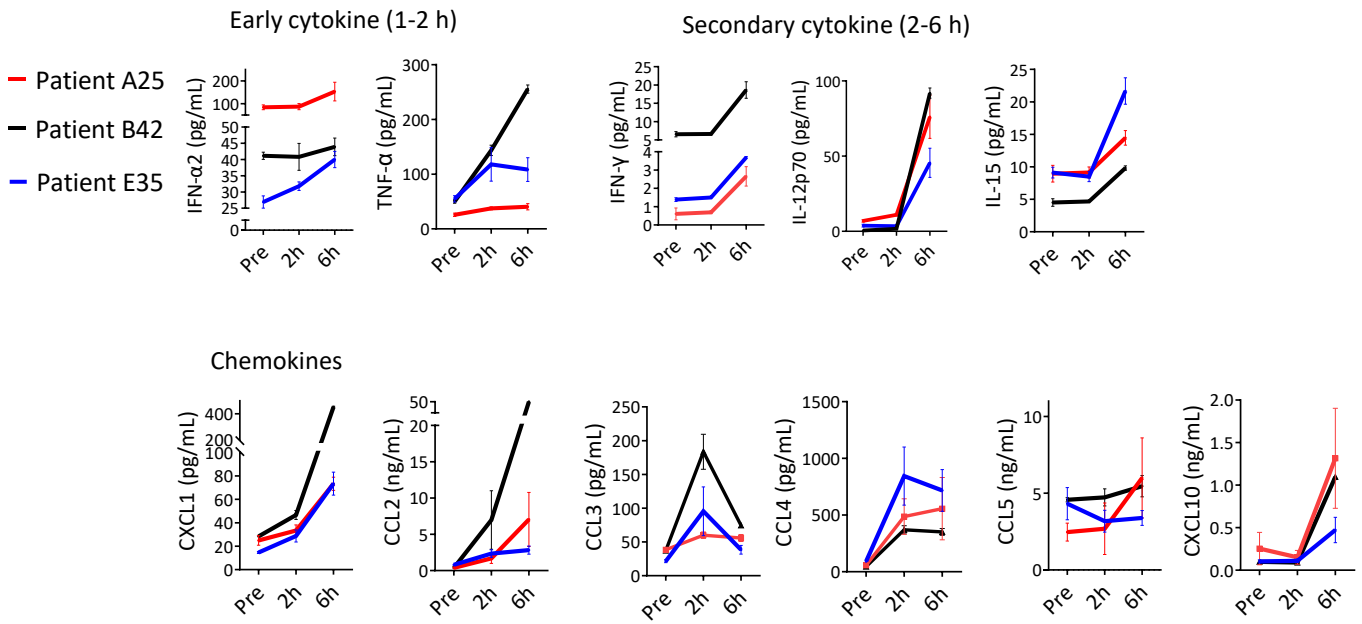
Slide adapted courtesy of Elias Sayour, MD, PhD

RNA-LPAs activate the immune system rapidly in human patients with glioblastoma



Hector Mendez-Gomez, PhD

Mendez-Gomez H et al. *medRxiv* [Preprint]. 2023.03.12.23287108

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Slide adapted courtesy of Elias Sayour, MD, PhD

Case presentation

- 67 yo right handed M with 1 month history of confusion, short term memory difficulty, and headaches
- 2019 – Present with heterogeneous enhancing mass involving the splenium of the corpus callosum
- Stereotactic brain biopsy – Glioblastoma WHO Grade 4
- Completed Fractionated RT with concurrent 42 day Temozolomide 75/m2
- Enrolled in clinical trial: 5 day Temozolomide 150-200mg/m2 plus Optune TTF
  - Pembrolizumab started with C2

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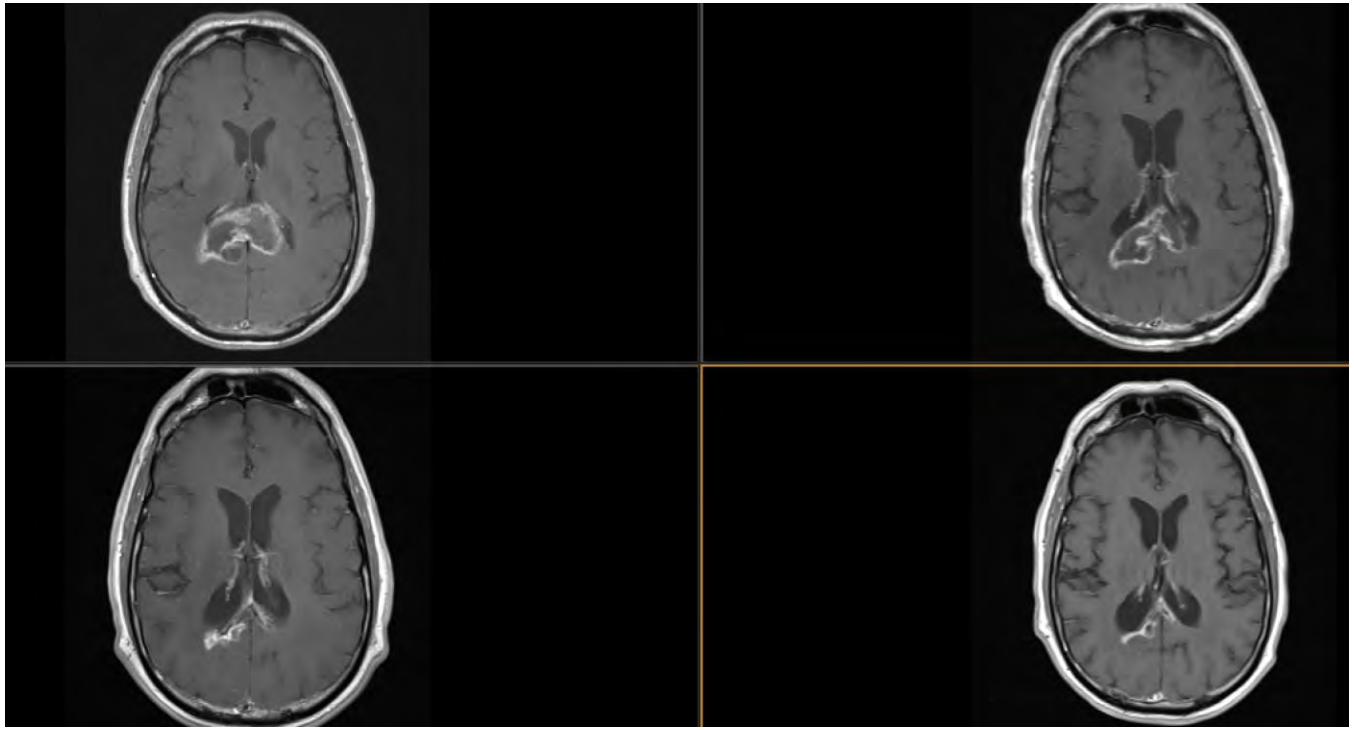
Case presentation

Presentation



Post RT, TTF started

Over 6 months post TMZ/TTF/Pembrolizumab

18 months post diagnosis

KPS 70 Intermittent HAs, Depression/Anxiety/Short term memory difficulty

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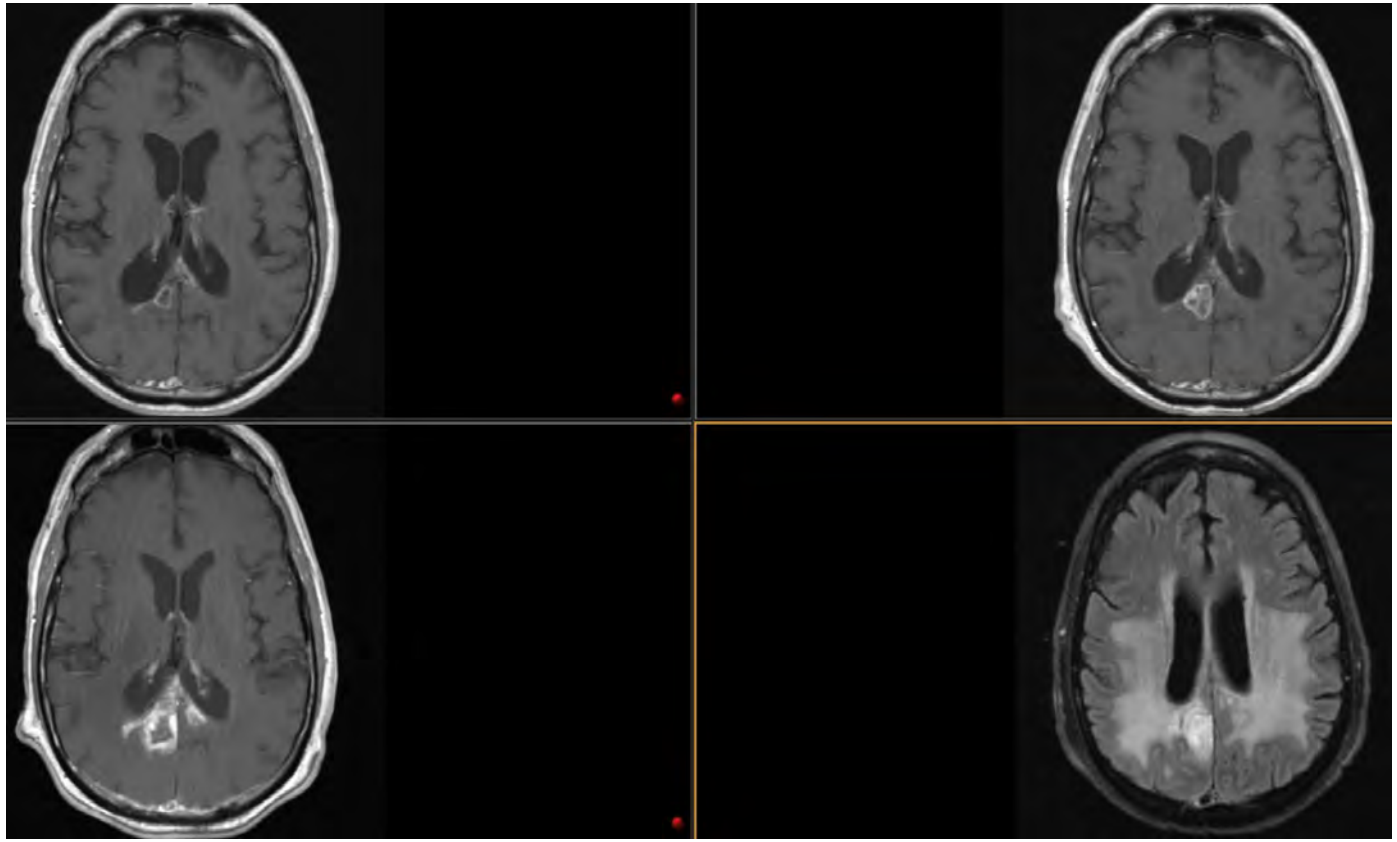
Case presentation

24 months post diagnosis



28 months post diagnosis

Status post laser ablation
Recurrent GBM
Nivolumab/Ipilimumab

37 months post diagnosis, Avastin started
Left sided hemiparesis, continued clinical decline

40 months post diagnosis, continued clinical decline, enrolled in hospice

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Toxicity of Glioblastoma treatment

- **Acute signs/symptoms of related to increased Intracranial Pressure**
  - Cerebral Edema (may include midline shift)
  - Hydrocephalus (associated Nausea/Vomiting)
  - Headaches
  - Seizures
- **Other treatment associated complications**
  - Thromboembolism
  - Myelosuppression
  - Radiation toxicity (acute/delayed effects)
  - Cognitive dysfunction
  - Fatigue
  - Mood disturbances

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BOLT STUDY

Objective : Assess the longitudinal psychosocial well-being and quality-of-life of patients with brain tumors and their caregivers;

Data collected will be used to inform quality improvement practices, future research, and lay the groundwork for future psychosocial intervention projects for brain cancer patients and caregivers

Deidre Pereira, PhD

CME Question

Glioblastoma WHO Grade 4 molecular integrated diagnosis per WHO 2021 Grading classification does not allow for IDH mutation

True

False

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