Updates and Emerging Treatments in Neuro-Oncology

Ashley Ghiaseddin, MD, FAAN
Chief, Division of Neuro-Oncology
Department of Neurosurgery
University of Florida College of Medicine

UF College of Medicine
UNIVERSITY of FLORIDA

Disclosures

Alexion Pharmaceuticals
Monteris Medical Consultant
Neosoma Consultant
Novocure Advisory Board and Consultant
Servier Advisory Board and Consultant
Telix Pharmaceuticals
OnoPharma USA Advisory Board

Course Objectives

- Identify existing and emerging treatments for gliomas
- Understand challenges in glioma treatment
- Understand role of molecular profiling in gliomas for diagnosis and prognosis
- Discuss historical, current, and future directions of emerging treatments in Neuro-Oncology

Case presentation

50s 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

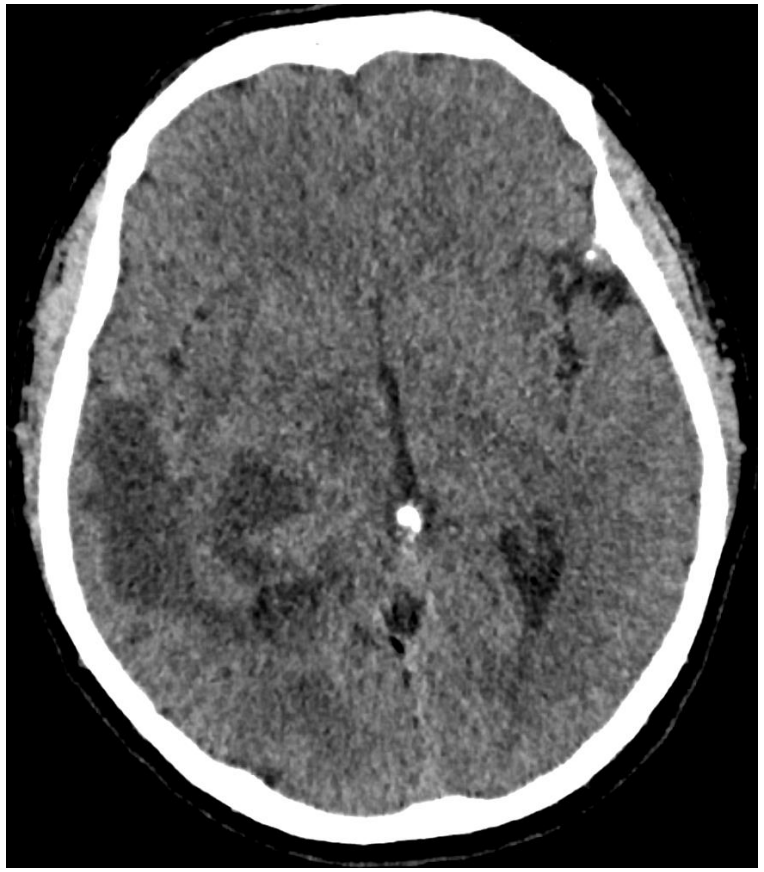
- Significant PMH Nocturnal seizures/HTN
- Social Hx Occasional EtOH
- Family Hx Hypertension and Lung Cancer

Vital signs - within normal limits

CBC w diff and CMP - unremarkable

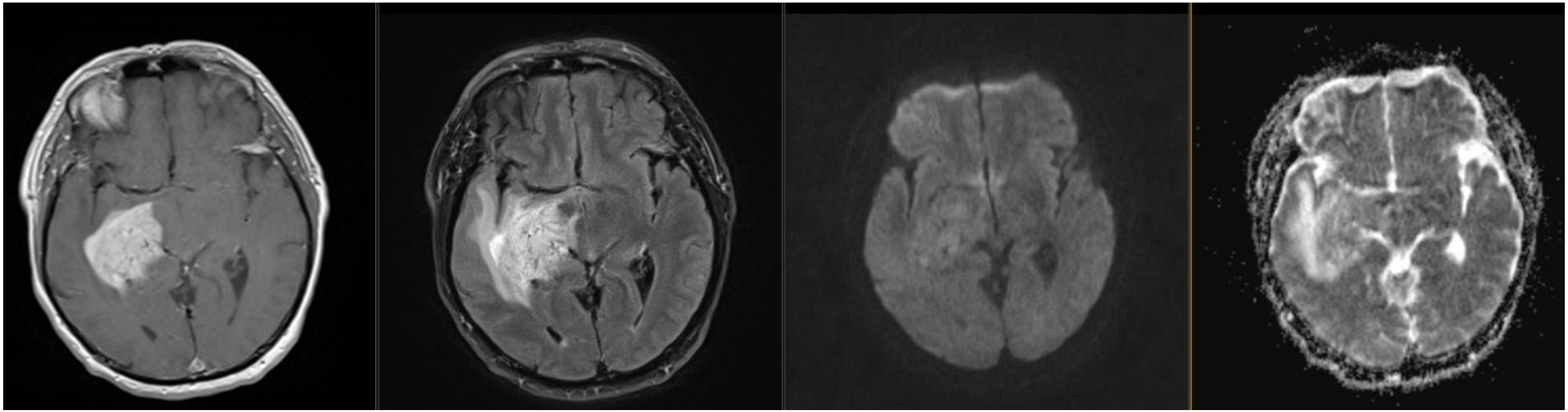
Influenza A, COVID-19, RSV – Not detected

Imaging



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

Imaging



Differential Diagnosis

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

What should we do next?

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**

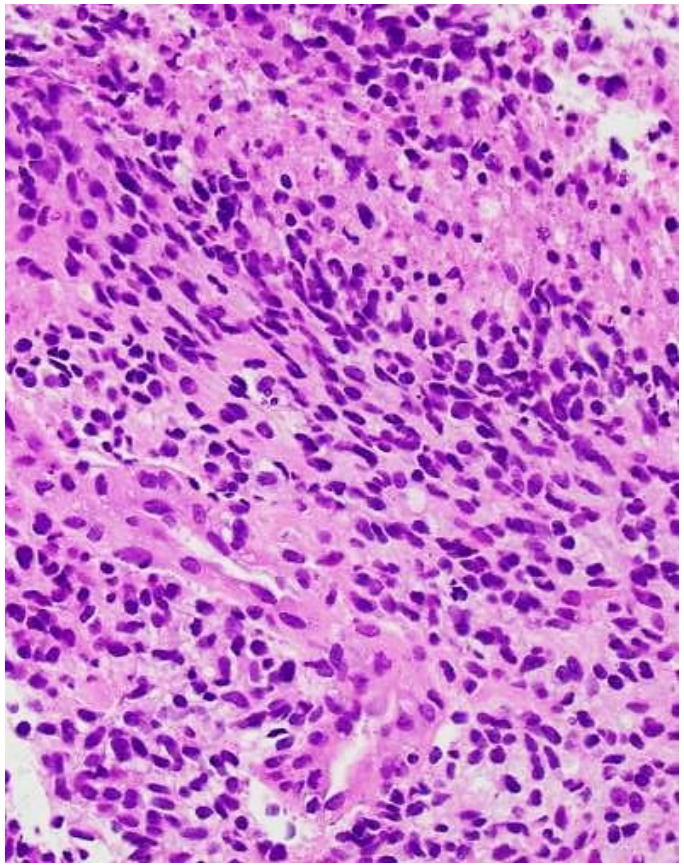
MRI Total Spine/US scrotum/Serologic workup/Ophthalmology exam - **unremarkable**

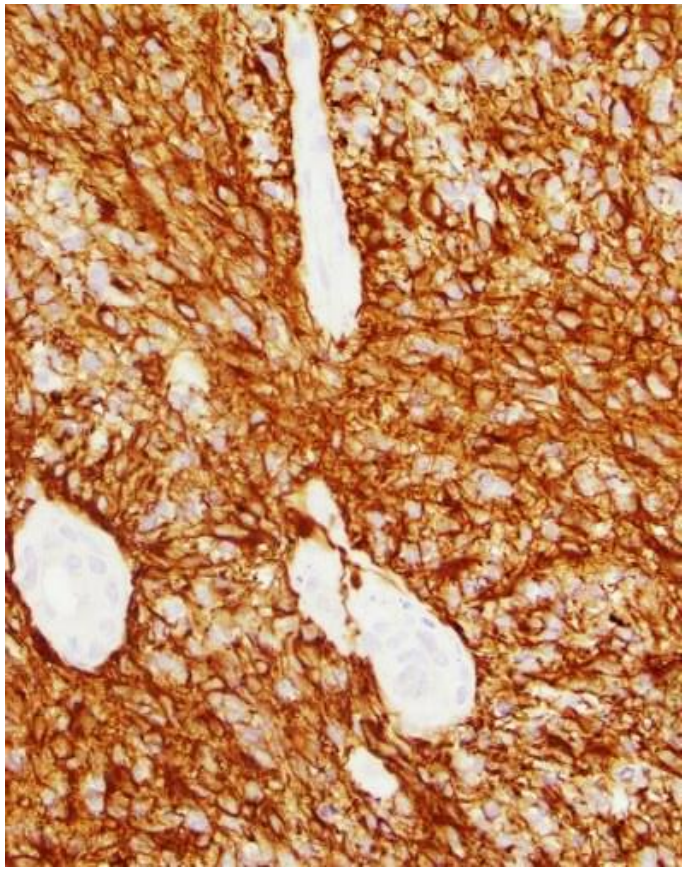
Hematopathology flow cytometry of the brain biopsy

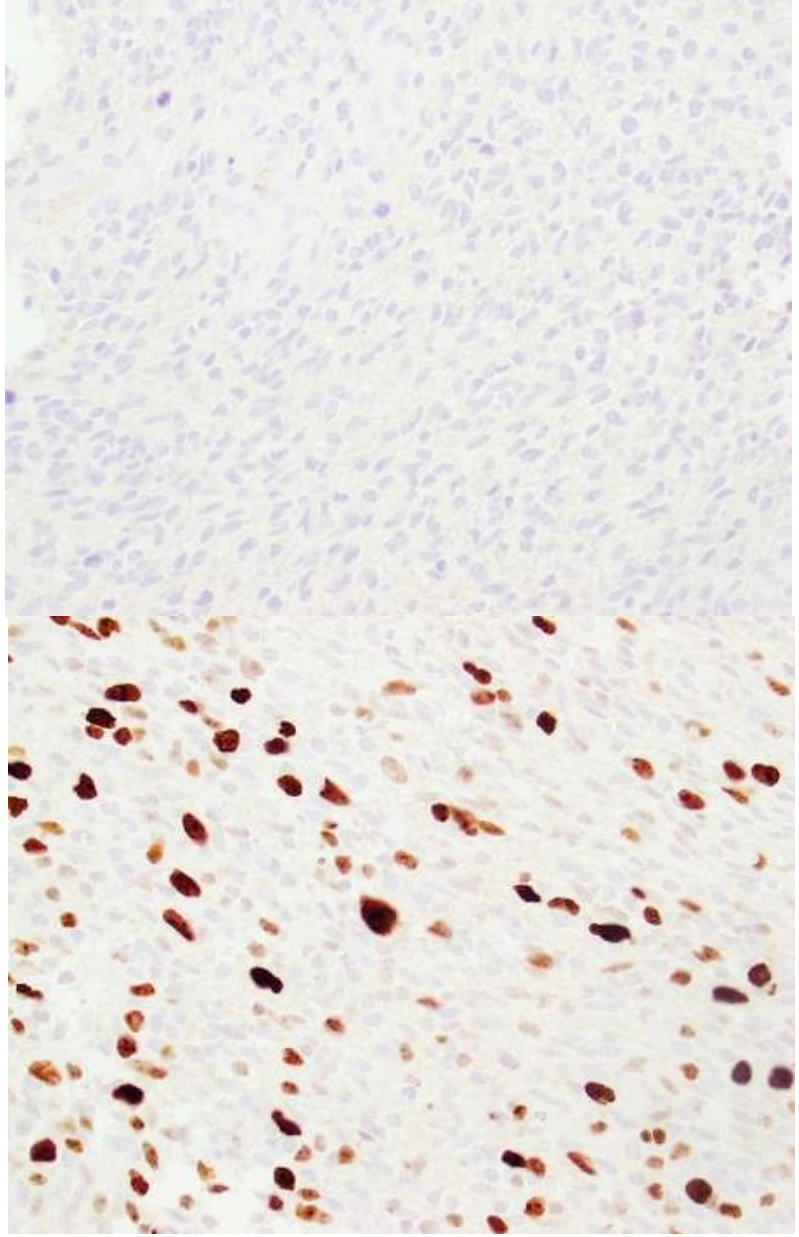
No overt evidence of clonal B-Cell or aberrant T-cell population

suggesting nonhematologic origin

Pathology







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

GFAP-positive tumor cell processes

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

Adult-type diffuse gliomas

Astrocytoma, IDH-mutant Grade 2-4

Oligodendroglioma, IDH-mutant, 1p/19q co-deletion, Grade 2-3

Glioblastoma, IDH-wildtype Grade 4

Goals of Treatment

Local Control

- Surgery, Radiation, Stereotactic Radiosurgery, Laser therapy, Tumor treating fields

Systemic Control

- Chemotherapy, Targeted therapy, Immunotherapy

Why is Glioma treatment so difficult

- Infiltrate normal brain tissue
- Recurrence
- Transformation to higher grade
- Rapid growth can cause swelling, increased pressure
- Microscopic disease not found on CT/MRI

Glioblastoma WHO Grade 4

Onset

Arises in 6th-7th decades of life

De novo or transformation from lower grade

MRI findings

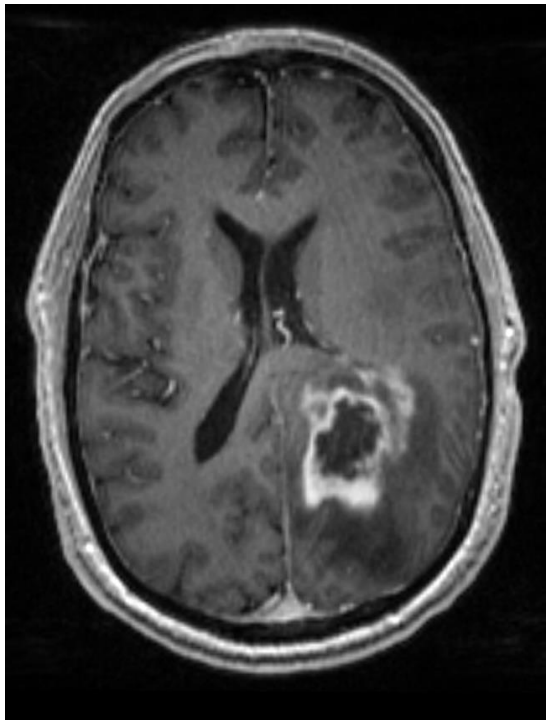
T1+c heterogeneous ring enhancement

Significant T2/FLAIR signal abnormality

non-enhancing disease

vasogenic edema

Diffuse infiltration of brain parenchyma



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 proliferation

microvascular proliferation and necrosis

Common **Molecular findings**

IDH wildtype*

TERT promoter mut

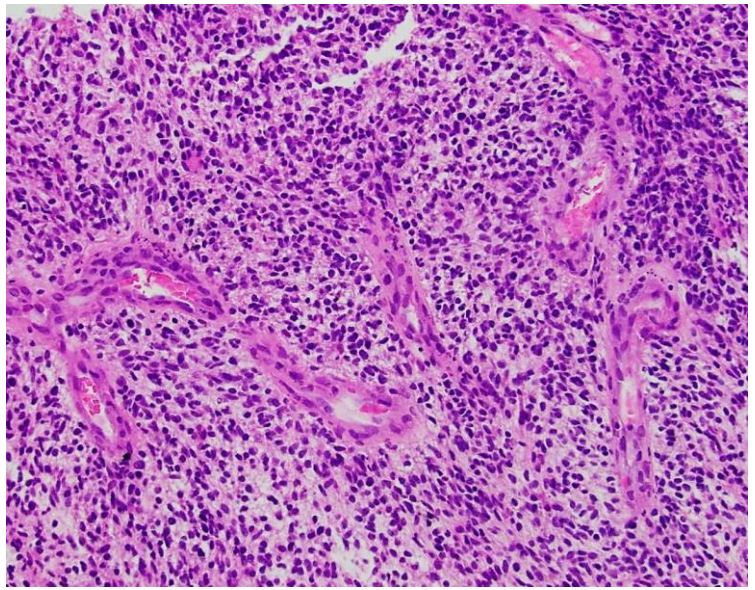
EGFR amplification

Gain of chromosome 7p/Loss of 10q

Prognosis

Overall survival 14-18 months.

Progression of tumor is common



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

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

Tissue Sampling emphasizing heterogeneity of gliomas

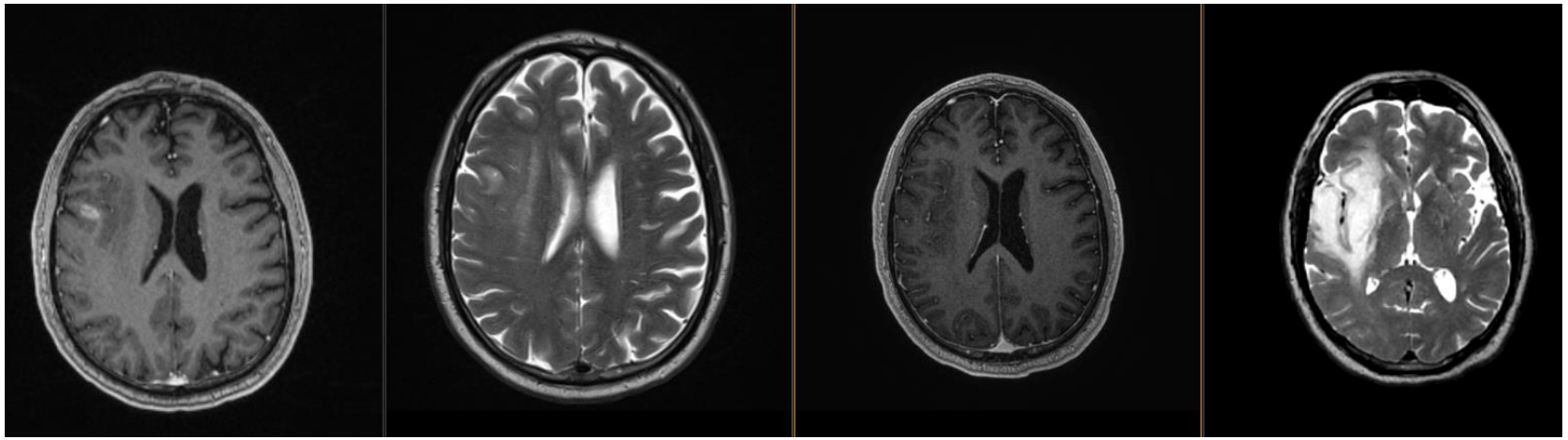
Histological analysis of MRI localized biopsies of the Enhancing and Non-Enhancing portions of Glial Tumors

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

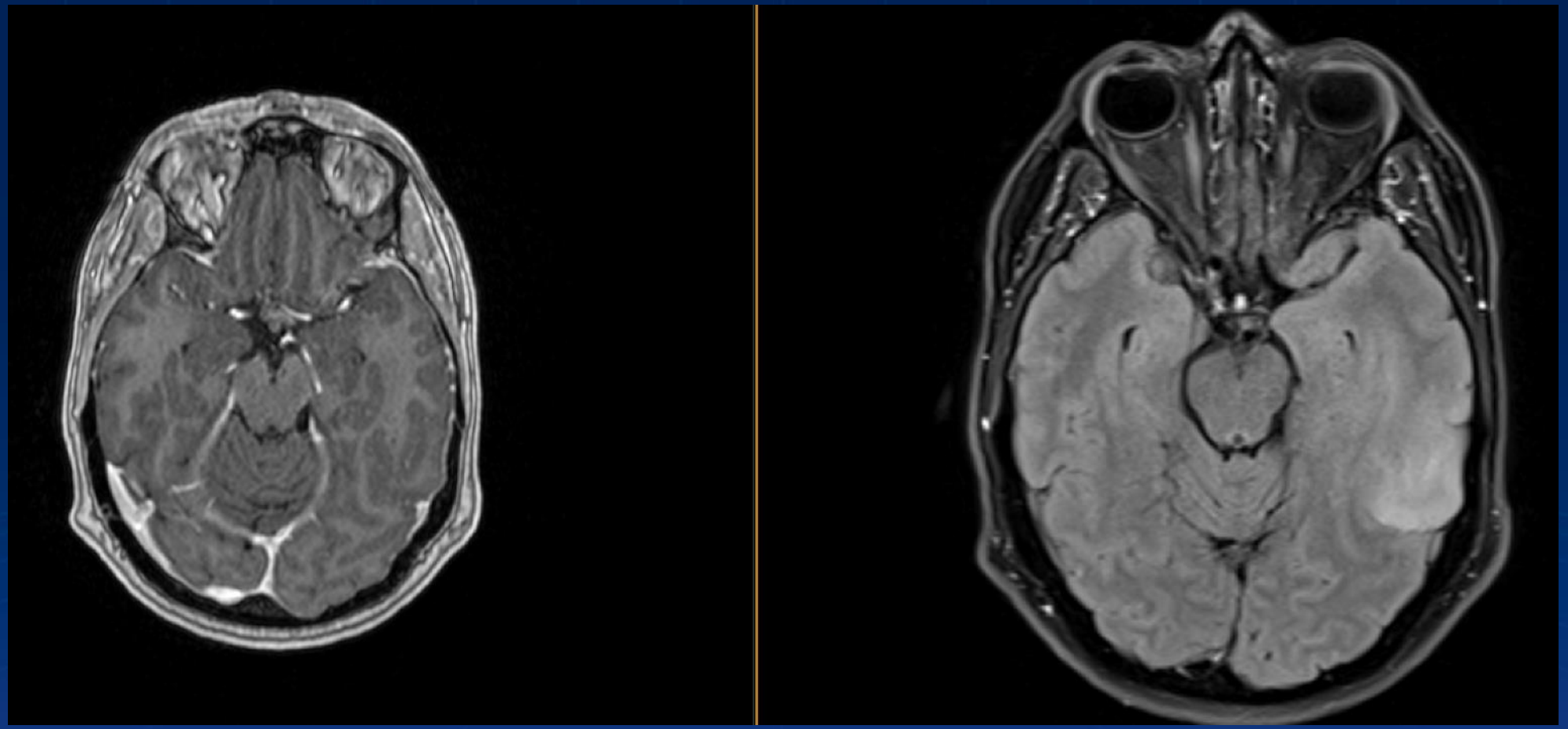


Initial path following resection of right temporal non-enhancing disease Diffuse Astrocytoma

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

Molecular Profiling - Provide diagnostic and prognostic information

- When histology is unable to differentiate tumors
  - Reduce diagnostic interobserver heterogeneity
  - Improve accuracy of diagnosis
  - ***Increase objectivity***
- Inform clinical trial determination
  - Improve speed of eligibility determination
  - Enroll patients that more closely resemble each other
    - ***Improve reproducibility in the real-world setting***
- Identify molecular alterations within the tumor that can be potentially targeted



no clear MVP and no necrosis

mutations of EGFR and TERT promoter were identified

molecular characterization supported dx of Glioblastoma

allowed patient to enroll in newly dx clinical trial

Current Treatment Landscape in GBM

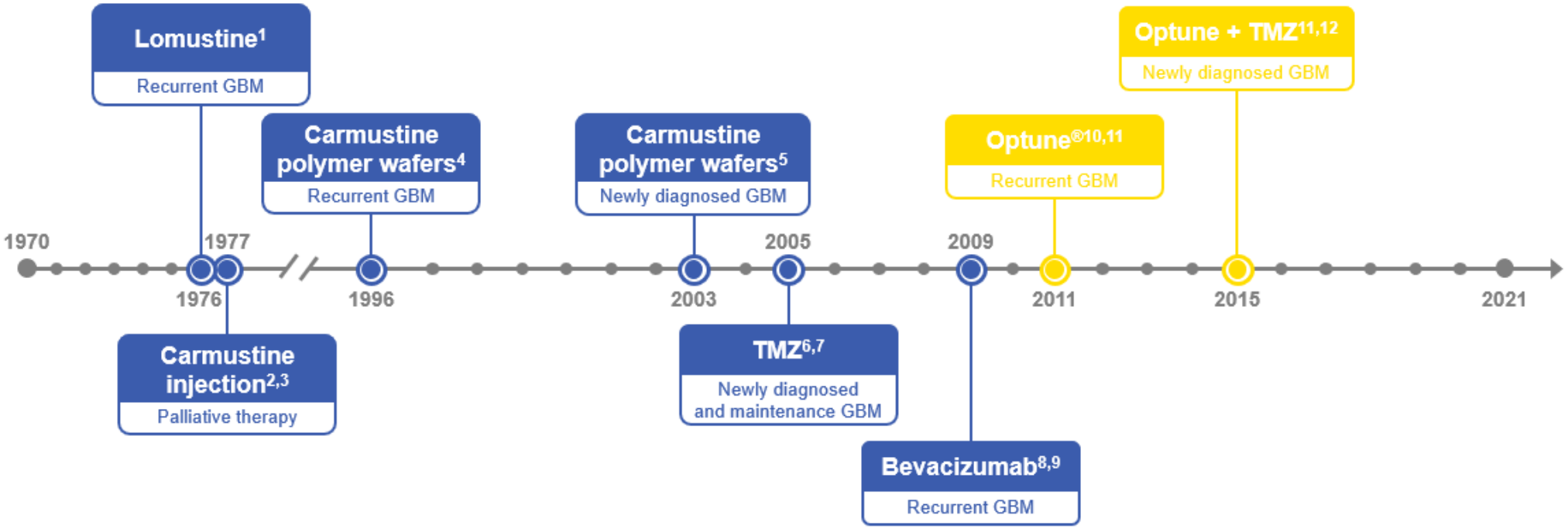
Limited success apart from Temozolomide and Tumor Treating fields in 2000s

EF-14 reported > 20 months OS

Real-world evidence (RWE) data from US registry has reported OS closer to 8 months

- Highlights criticism of strict clinical trial eligibility criteria

Timeline of approved treatments in Glioblastoma



FDA, Food and Drug Administration; GBM, glioblastoma; TMZ, temozolomide.

1. Fisher JP, Adamson DC. *Biomedicines*. 2021;9(3):324. doi:10.3390/biomedicines9030324. 2. BiCNU. Package insert. Bristol-Myers Squibb Co; 2011. 3. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed February 21, 2020. http://livertox.nih.gov/Carmustine. 4. Gliadel wafer. Package insert. Eisai Inc; 2013. 5. US Food and Drug Administration. July 8, 2003. Accessed February 21, 2020. www.accessdata.fda.gov/drugsatfda_docs/nda/2003/20-637s016_Gliadel.cfm. 6. Temodar. Package insert. Merck & Co, Inc; 2017. 7. National Cancer Institute. Accessed January 31, 2018. http://www.cancer.gov/about-cancer/treatment/drugs/fda-temozolomide. 8. Avastin. Package insert. Genentech, Inc; 2019. 9. CancerNetwork. April 1, 2005. Accessed January 31, 2018. www.cancernetwork.com/brain-tumors/temodar-approved-treating-gbm-combination-radiotherapy. 10. News release. Novocure. April 14, 2011. Accessed February 21, 2020. https://www.novocure.com/fda-approves-the-novottf-100a-system-for-the-treatment-of-recurrent-gbm/. 11. Optune. Instructions for Use. Novocure; 2019. 12. News release. Novocure. October 9, 2015. Accessed February 21, 2020. https://www.novocure.com/adding-multimedia-fda-approves-optune-in-combination-with-temozolomide-for-the-treatment-of-newly-diagnosed-glioblastoma/.

Timeline of approved treatments in Glioblastoma

1976 – Lomustine – Recurrent GBM
1977 – Carmustine injection – Palliative
1996 – Carmustine polymer wafers – Recurrent GBM
2003 – Carmustine polymer wafers – Newly Dx GBM
2005 – Temozolomide – Newly Dx GBM
2009 – Bevacizumab – Recurrent GBM
2011 – Tumor Treating Fields – Recurrent GBM
2015 – Tumor Treating Fields – Newly Dx GBM

FDA, Food and Drug Administration; GBM, glioblastoma; TMZ, temozolomide.

1. Fisher JP, Adamson DC. *Biomedicines*. 2021;9(3):324. doi:10.3390/biomedicines9030324. 2. BiCNU. Package insert. Bristol-Myers Squibb Co; 2011. 3. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed February 21, 2020. http://livertox.nih.gov/Carmustine. 4. Gliadel wafer. Package insert. Eisai Inc; 2013. 5. US Food and Drug Administration. July 8, 2003. Accessed February 21, 2020. www.accessdata.fda.gov/drugsatfda_docs/nda/2003/20-637s016_Gliadel.cfm. 6. Temodar. Package insert. Merck & Co, Inc; 2017. 7. National Cancer Institute. Accessed January 31, 2018. http://www.cancer.gov/about-cancer/treatment/drugs/fda-temozolomide. 8. Avastin. Package insert. Genentech, Inc; 2019. 9. CancerNetwork. April 1, 2005. Accessed January 31, 2018. www.cancernetwork.com/brain-tumors/temodar-approved-treating-gbm-combination-radiotherapy. 10. News release. Novocure. April 14, 2011. Accessed February 21, 2020. https://www.novocure.com/fda-approves-the-novottf-100a-system-for-the-treatment-of-recurrent-gbm/. 11. Optune. Instructions for Use. Novocure; 2019. 12. News release. Novocure. October 9, 2015. Accessed February 21, 2020. https://www.novocure.com/adding-multimedia-fda-approves-optune-in-combination-with-temozolomide-for-the-treatment-of-newly-diagnosed-glioblastoma/.

Targeted Treatment Options in Gliomas

TABLE 1. Table Summarizing Molecular Targets Responding to Therapy

Molecular Target	Agent	Activity (ORR)	Reference
Adults			
BRAFV600E	Vemurafenib	25%	19
BRAFV600E	Dabrafenib/trametinib	32% GBM; 69% LGG	18
NTRK	Larotrectinib	30%	20
FGFR mutation/FGFRTACC fusion	Erdafitinib	20.9%	21
H3K27M	Dordaviprone (ONC201)	20%	22,23
IDH	Ivosidenib, vorasidenib Olutasidenib, BAY 1436032 Safusidenib	5%-40%	24-28
Children			
TSC1/2	Everolimus	35%	29
BRAFV600E	Dabrafenib/trametinib	25%-47%	30,35
BRAF/KIAA fusion	Selumetinib	35%-40%	31
BRAF/KIAA fusion	Tovorafenib	64%[a]	
H3K27M	Dordaviprone (ONC201)		32
H3K27M	GD2 CAR-T cell	50%	33
NF1	Selumetinib	70%	34

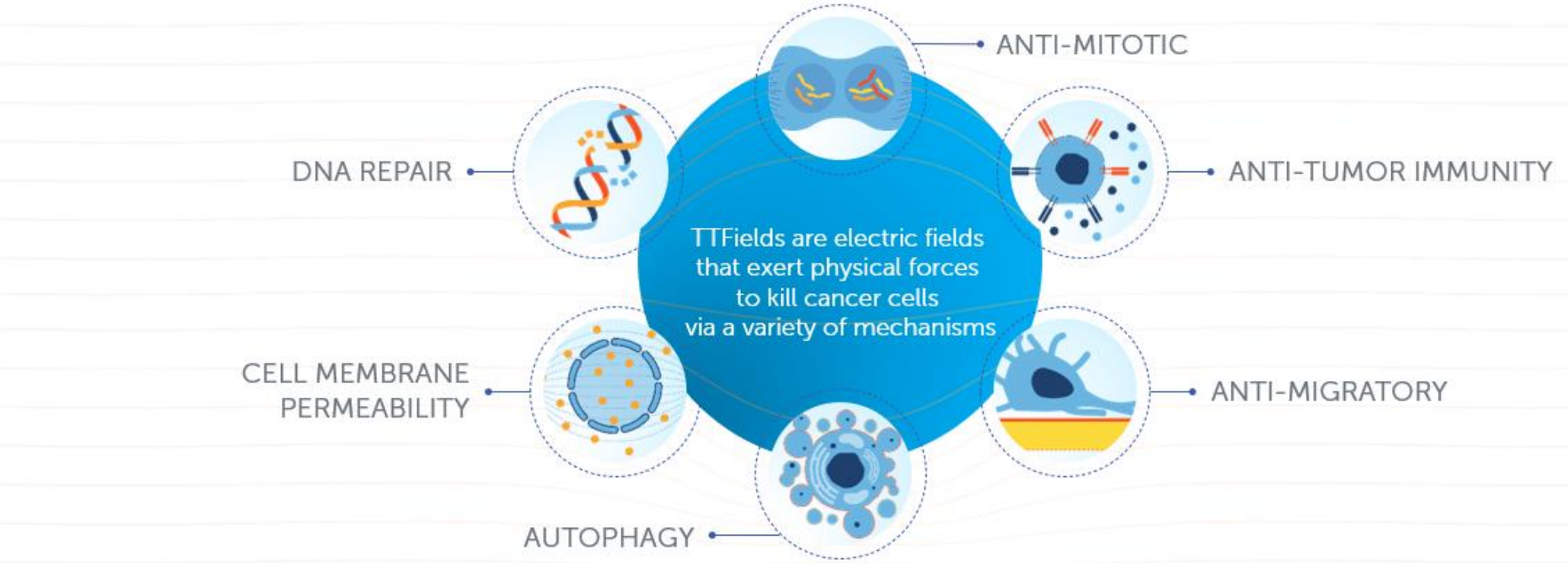
Abbreviations: CAR, chimeric antigen receptor; GBM, glioblastoma; LGG, low-grade glioma; ORR, objective response rate.
[a]Not yet published in peer review journal.

Tumor Treating Fields (TTFields)

Low intensity intermediate frequency alternating electric field therapy
Disrupt cell division/mitosis
Nerves or muscle are not stimulated
Tissue is not heated
Treatment delivery
- Application of transducer arrays (non-invasive)
- Apply to shaved scalp
- Array placement is determined using NovoTAL™
- Field intensity centered on the tumor tissue using both tumor location and patient head size

Lacouture ME. Characterization and management of dermatologic adverse events with the NovoTTF-100A System, a Novel Anti-mitotic Electric Field Device for the Treatment of Recurrent Glioblastoma. Semin Oncol. 2014

MoA of TTFields



TTFields, Tumor Treating Fields Therapy.
1. Rominiyi O et al. *Br J Cancer*. 2021;124(4):697–709; 2. Karanam NK, Story MD. *Int J Radiat Biol*. 2021;97(8):1044–1054; 3. Mun EJ et al. *Clin Cancer Res*. 2018;24(2):266–275.

EF-11 Randomized Phase III trial

Stupp et al randomly assigned patients between 9/2006-5/2009 to receive

- TTFields monotherapy 120 patients
- Physician choice of chemotherapy 117 patients
- **Well balanced arms** with number of previous chemotherapy treatments 2 or more in approx. 80% of patients

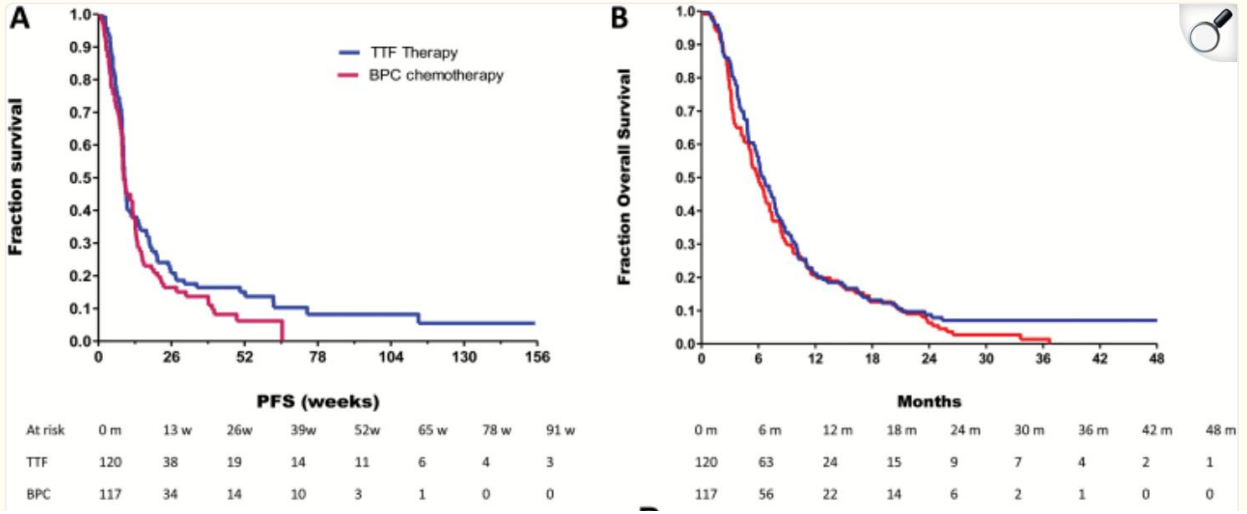
Median Survival

- TTFields alone 6.6 months
- Physician choice of chemotherapy 6 months
- P=0.27

Summary

- **No survival benefit**
- **TTFields therapy as effective as physician best choice of chemotherapy**
- Quality of life and toxicity favored TTFields arm
- **Primary toxicity in the TTField arm was mild**
- **Moderate skin rash (scalp)**

Fig. 4.



Stupp R. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomized phase III trial of a novel treatment modality. 2012
Hottinger AF. Neuro Oncol. 2016

EF-14 open-label randomized phase III trial

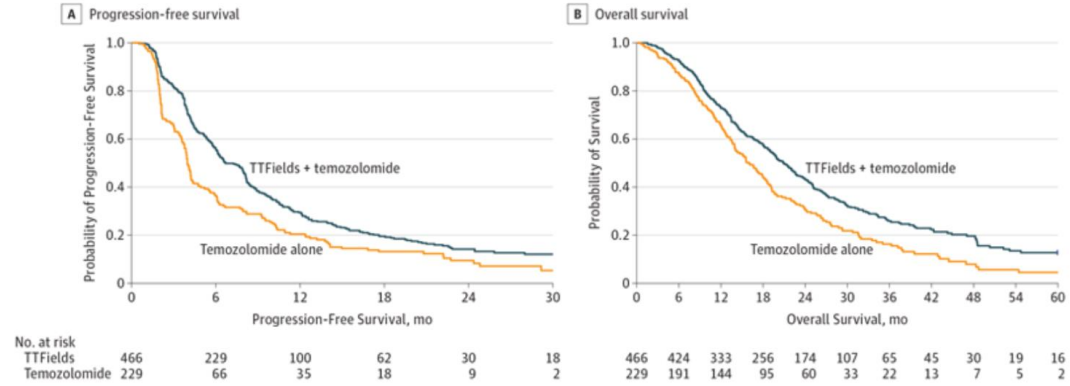
Stupp et al assessed 695 newly diagnosed GBM patient between 7/2009-11/2014 after completion of Fractionated RT with concurrent daily Temozolomide 75mg/m2

- 466 patients received TTFields plus TMZ
- 229 TMZ alone
- **Well balanced groups**
- Patients received 6-12 cycles of maintenance Temozolomide
- At progression, second line treatment given per choice of local physician
  - use of TTFields could be continued up until second progression
- Incidence/severity of adverse events comparable between the two groups
- **TTFields group**
  - higher rate of skin rash (localized to scalp)
  - higher frequency of headaches, insomnia, mild anxiety, confusion

EF-14 open-label randomized phase III trial

- Interim analysis reviewed 210 patients in TTFields/TMZ arm and 105 patients in TMZ arm
- Median OS
  - TTFields plus TMZ arm 20.5 months
  - TMZ alone arm 15.6 months
- Median PFS
  - TTFields plus TMZ arm 7.1 months
  - TMZ alone arm 4.0 months
- Percentage of patients alive at 2 years
  - TTFields plus TMZ 43%
  - TMZ alone arm 29%
  - P=0.006

Figure 2. Kaplan-Meier Survival Curves for Patients Included in the Final Analysis in the Intent-to-Treat Population



Stupp R. Maintenance therapy with Tumor-Treating Fields plus Temozolomide vs Temozolomide alone for Glioblastoma A Randomized Clinical Trial. JAMA 2015

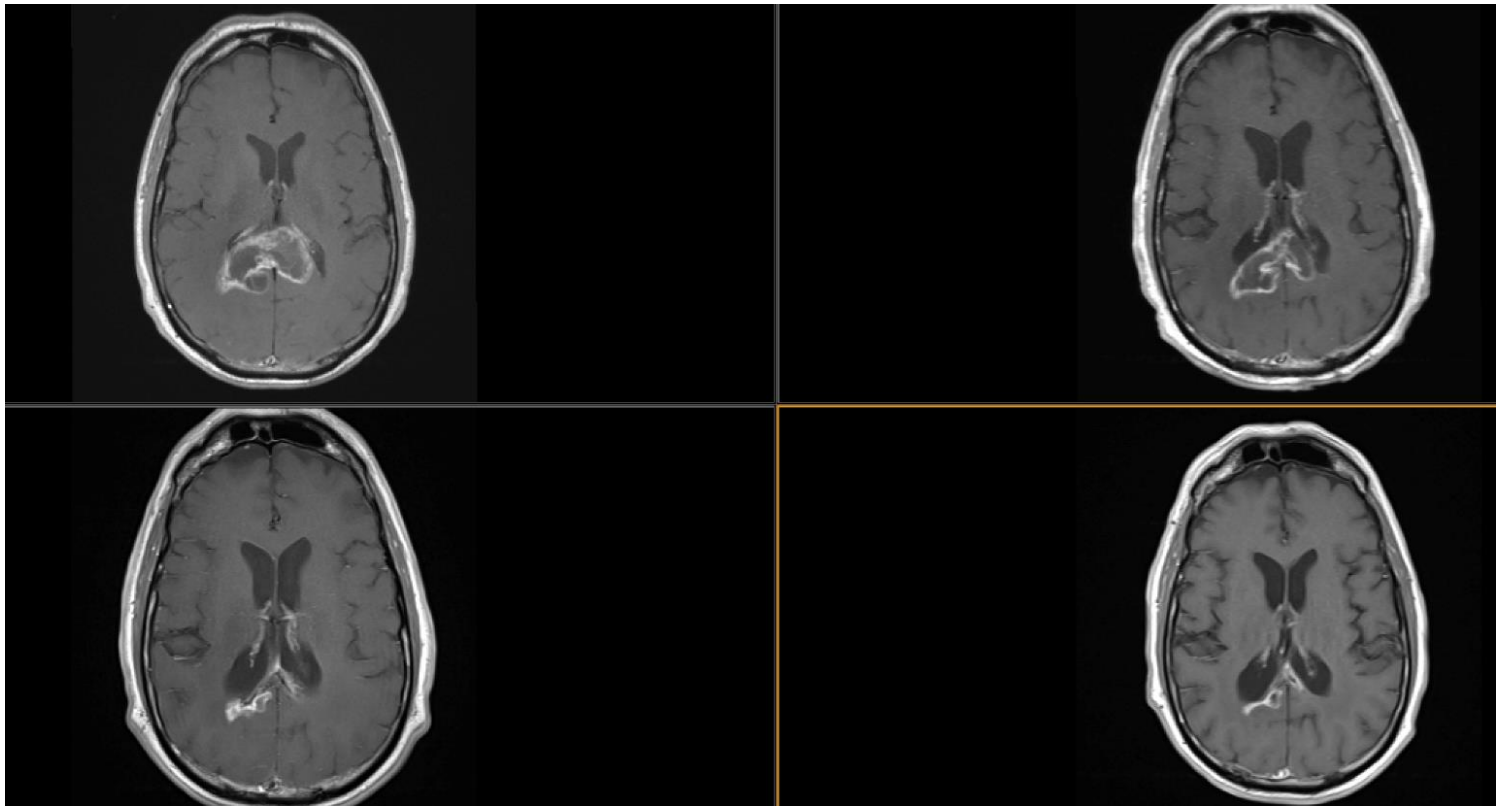
UF College of Medicine UNIVERSITY of FLORIDA

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 TTFields
    - Pembrolizumab started with C2

Case presentation

Presentation



Post RT, TTFields initiated

Over 6 months post TMZ/TTFields/ Pembrolizumab

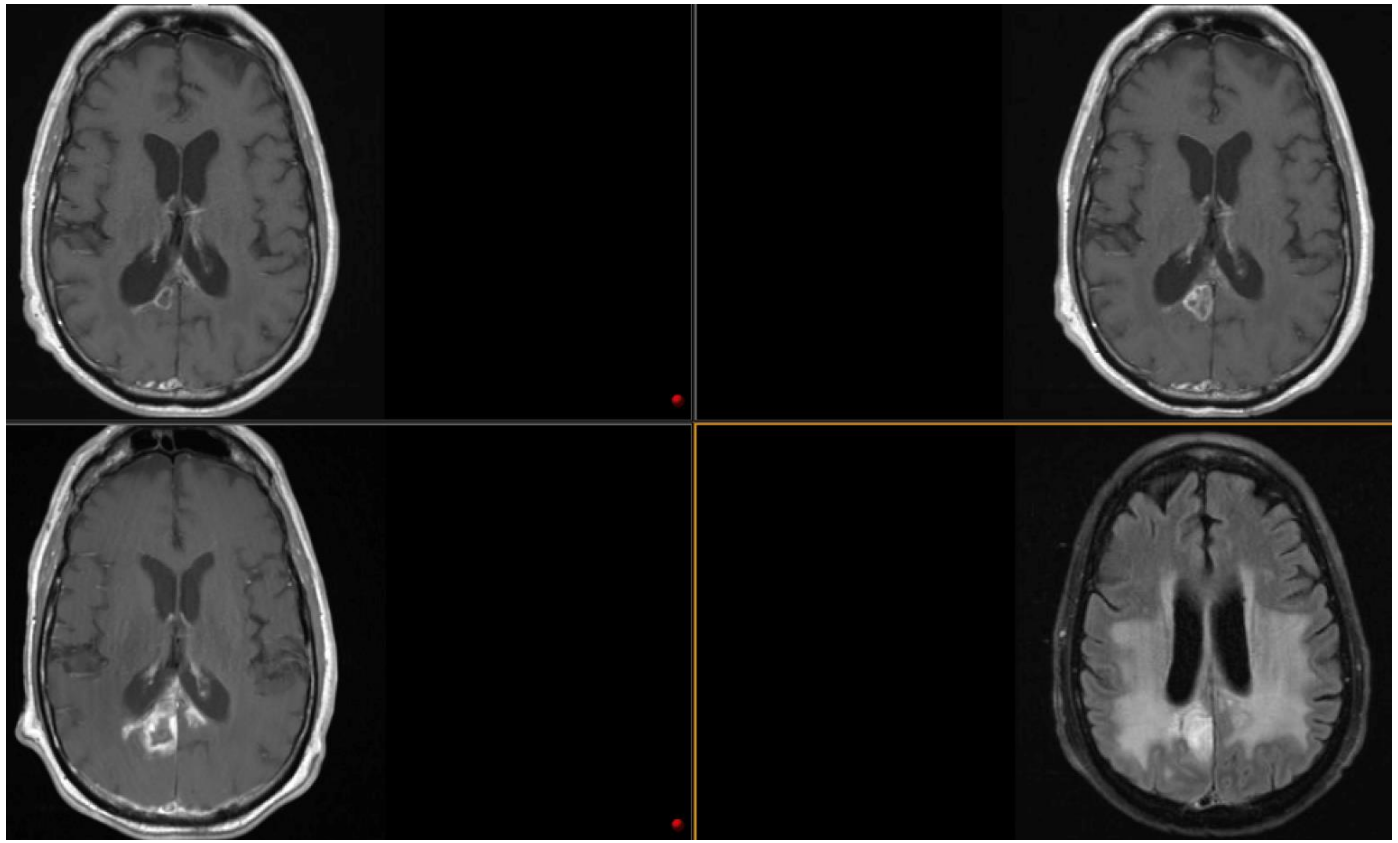
18 months post diagnosis

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

UF College of Medicine UNIVERSITY of FLORIDA

Case presentation

24 months post diagnosis



28 months post diagnosis

s/p laser ablation
Recurrent GBM
Nivolumab/Ipilimumab

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

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

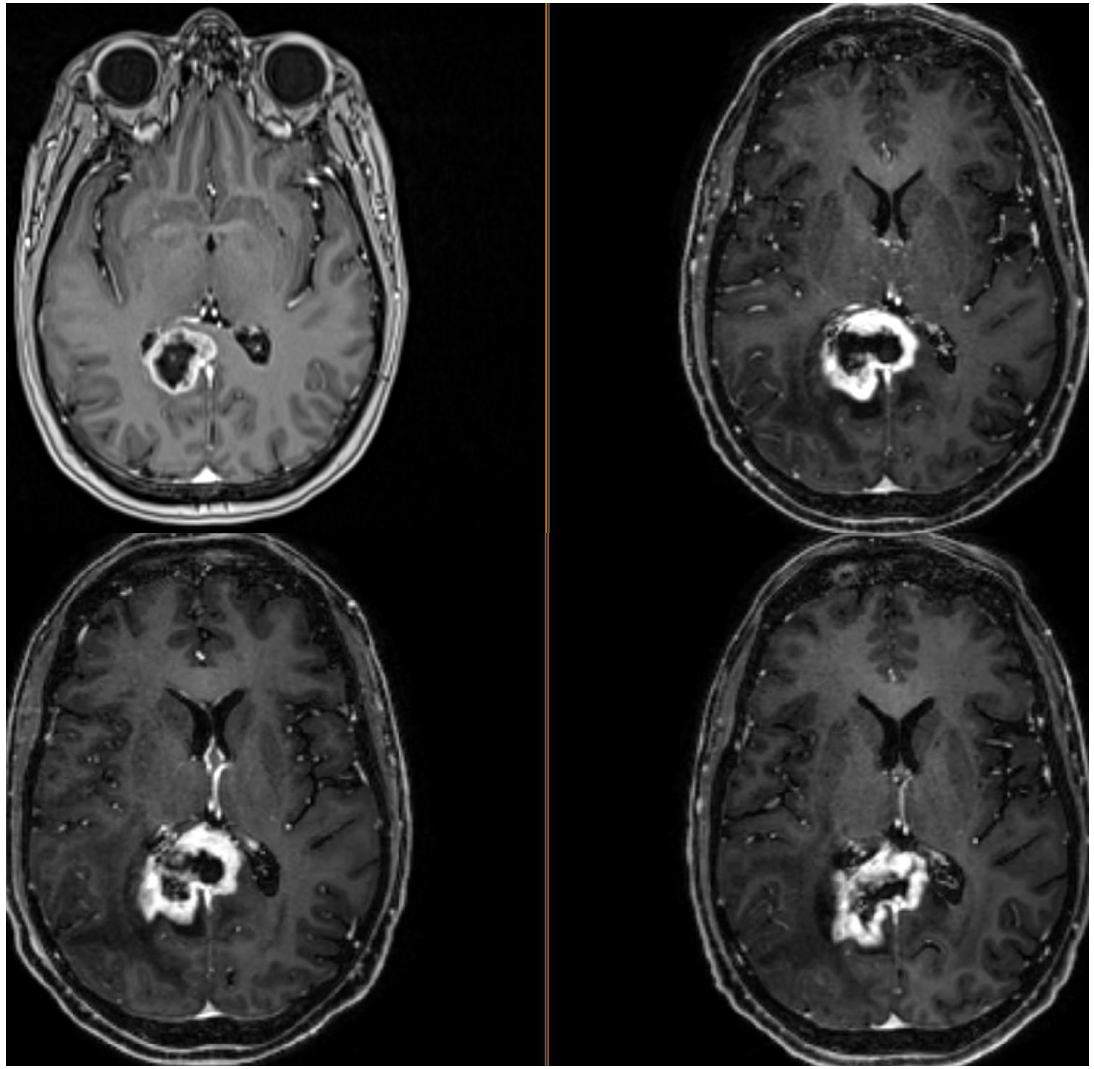
UF College of Medicine
UNIVERSITY of FLORIDA

Case presentation 2

- New onset seizure, confusion, respiratory failure, neuroimaging revealed large biparietal lesion
- Stereotactic brain biopsy with path reporting Glioblastoma WHO Grade 4; TERT mut, MGMT methylated
- Completed Fractionated RT with concurrent daily Temozolomide – post RT imaging with radiation induced inflammatory changes
- Enrolled in 2THETOP study (TTFields/5-day Temozolomide/Pembrolizumab)

Case presentation 2

Presentation



Post chemoradiation, TTFields initiated

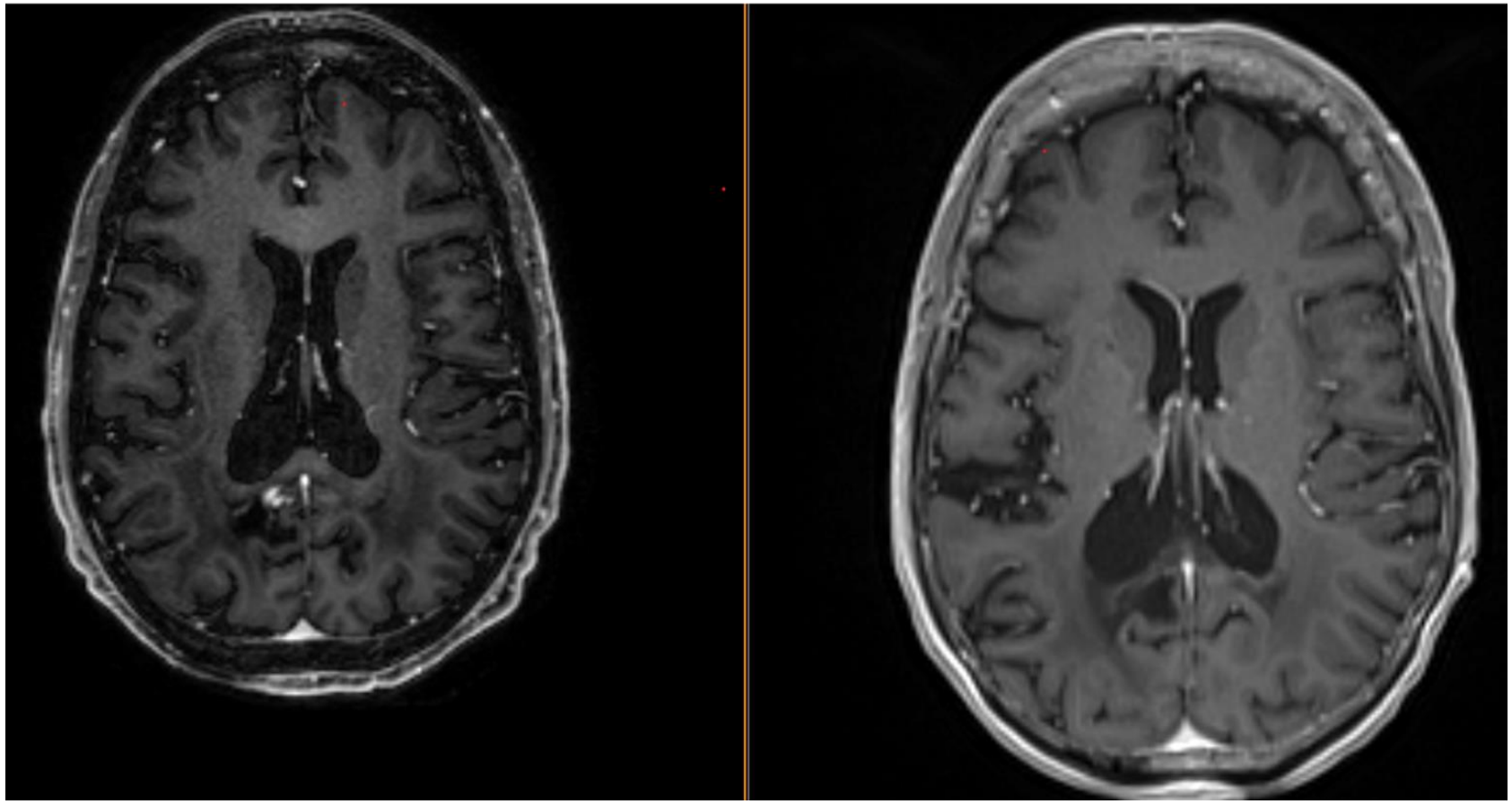
Post initiation of adjuvant treatment TTFields/TMZ/ Pemborlizumab

Post 6 months of Immunotherapy initiation

UF College of Medicine UNIVERSITY of FLORIDA

Case presentation 2

15 months post completion of adjuvant TMZ



Nearly 7 years following initial diagnosis

Final results of 2-THE-TOP: a phase 2 study of TTFields plus pembrolizumab plus maintenance temozolomide (TMZ) in patients with newly diagnosed glioblastoma (ndGBM) NCT03405792

Tran D et al. Presented at Society of Neuro-Oncology Annual Meeting November 18, 2022

TTFields induce anti-tumor immunity via type-1 interferon (T1IFN) pathways of the STING and AIM2 inflammasomes.

Chen D et al. J Clin Invest. 2022

26 GBM patients enrolled with primary endpoints as PFS versus case-matched controls of TTFields plus TMZ in the EF-14 study and immune signatures by multiomics of PBMCs and tumors. Secondary endpoints included toxicity and OS.

As of 2/16/22

Median OS was 25.2 months versus 15.9 months in controls (HR =0.382; 95% CI: 0.168-0.861; P =0.078)

Two-year OS was 57.8% (95% CI: 33.7-75.9%) versus 19.2% (95% CI: 7.0-36.0%) in controls; P =0.002.

Key Point: The triple combination demonstrated acceptable toxicity and promising efficacy in GBM. Survival and molecular data to be updated.

A Phase 3, placebo-controlled study of TMZ + TTFields + pembrolizumab vs. TMZ + TTFields + placebo in newly diagnosed GBM (EF41/KEYNOTE D58)

Treatment landscape for IDH 1/2 mut Gliomas prior to 2023

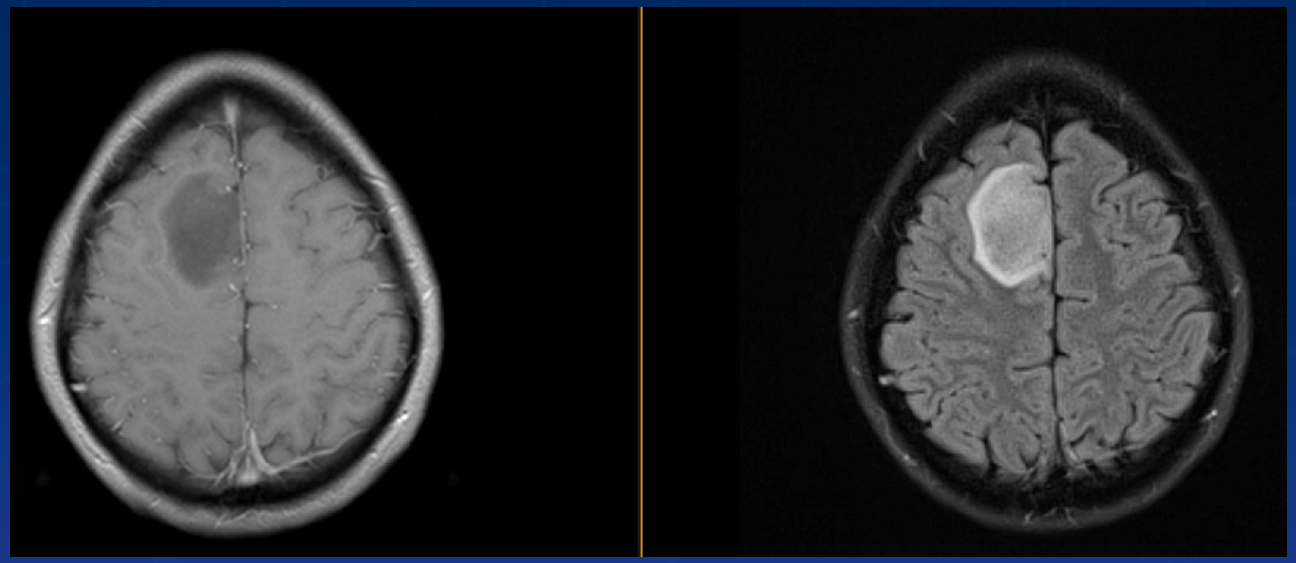
- Oligodendroglioma WHO Grade 2
  - Surgical resection followed
    - Observation*
    - Radiation followed by PCV (vs TMZ)
- Diffuse Astrocytoma WHO Grade 2
  - Surgical resection followed by
    - Observation*
    - Radiation followed by TMZ (vs PCV)

*Decision aided by certain factors such as resection status, age

Weller M et al. Nat Rev Clin Oncol 2021

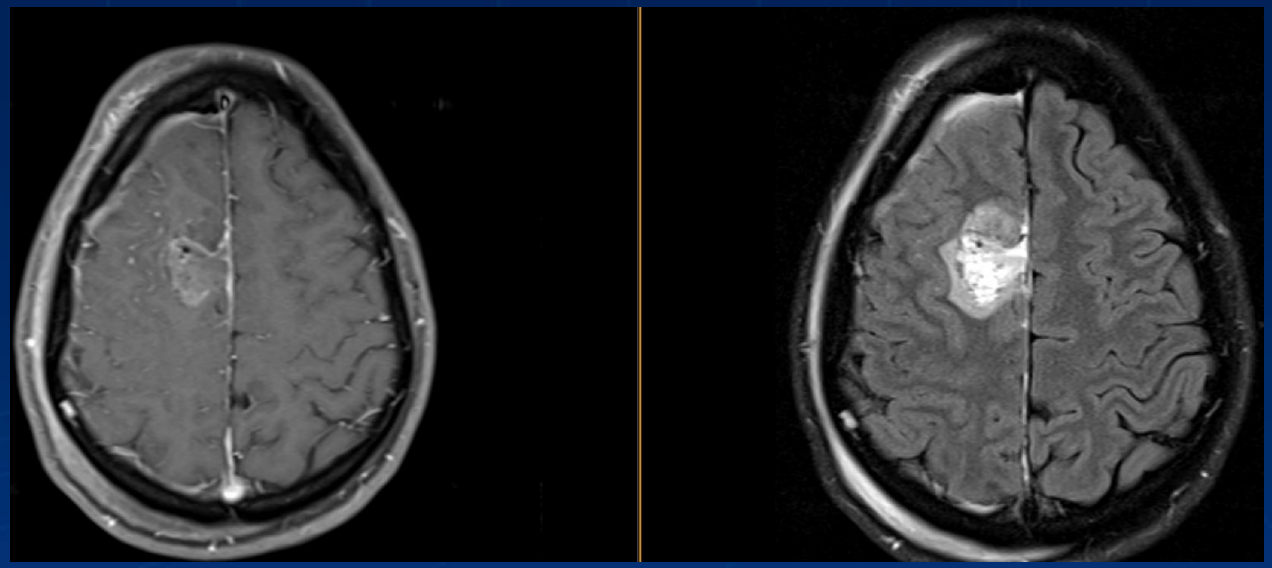
Case Presentation

- 23 yo M presented with new onset seizure activity, left facial twitching and LUE tonic-clonic activity

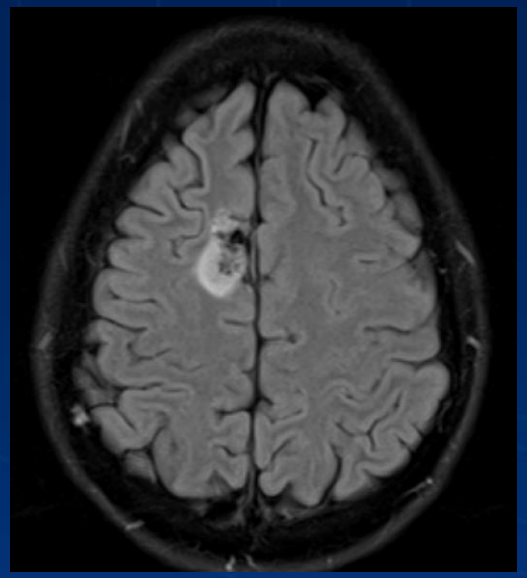


Case Presentation

Diffuse Astrocytoma IDH mut WHO Grade 2



Immediate Post-op

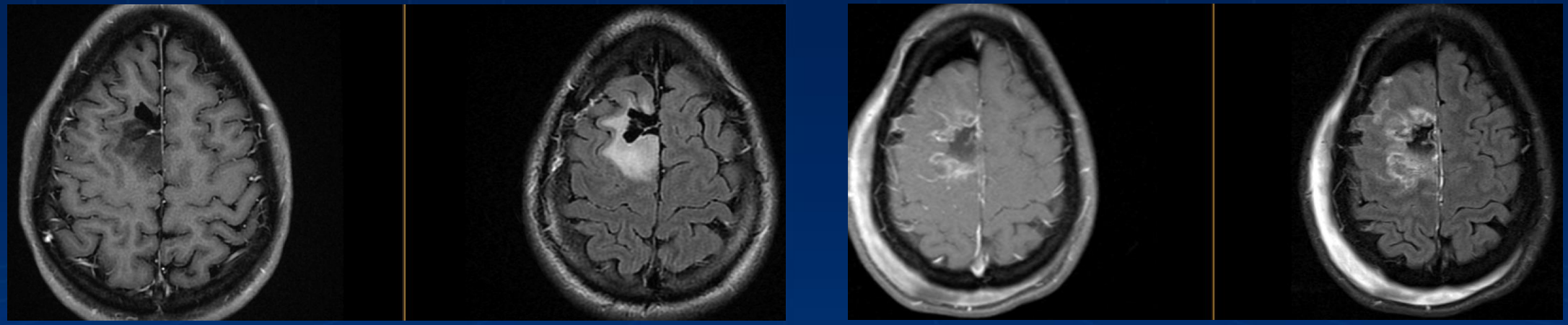


3 months post op

Tumor Board Recommendation: Observation

Case Presentation

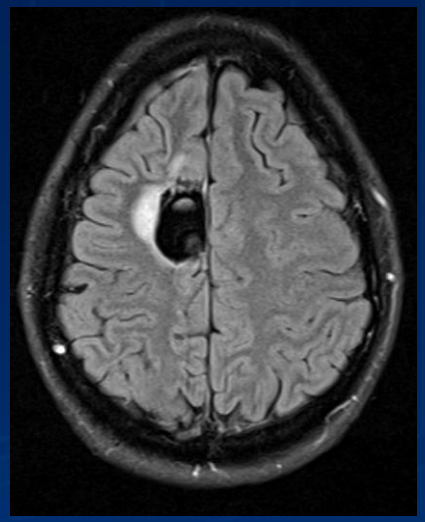
2.5 years later, MRI brain concerning for tumor progression



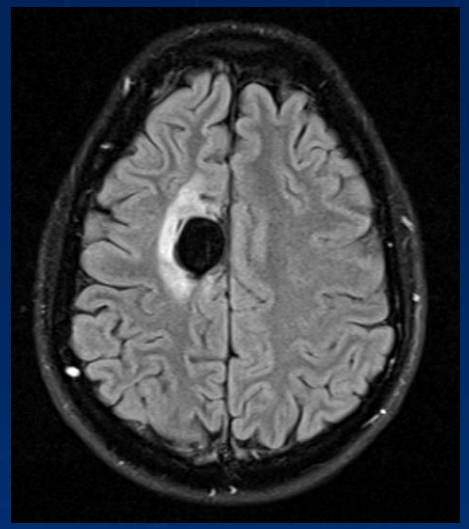
Astrocytoma IDH mutant WHO Grade 3

Tumor board recommendation: Fractionated RT with concurrent 42-day Temozolomide 75mg/m2 followed by 12 cycles of 5-day Temozolomide 150-200mg/m2

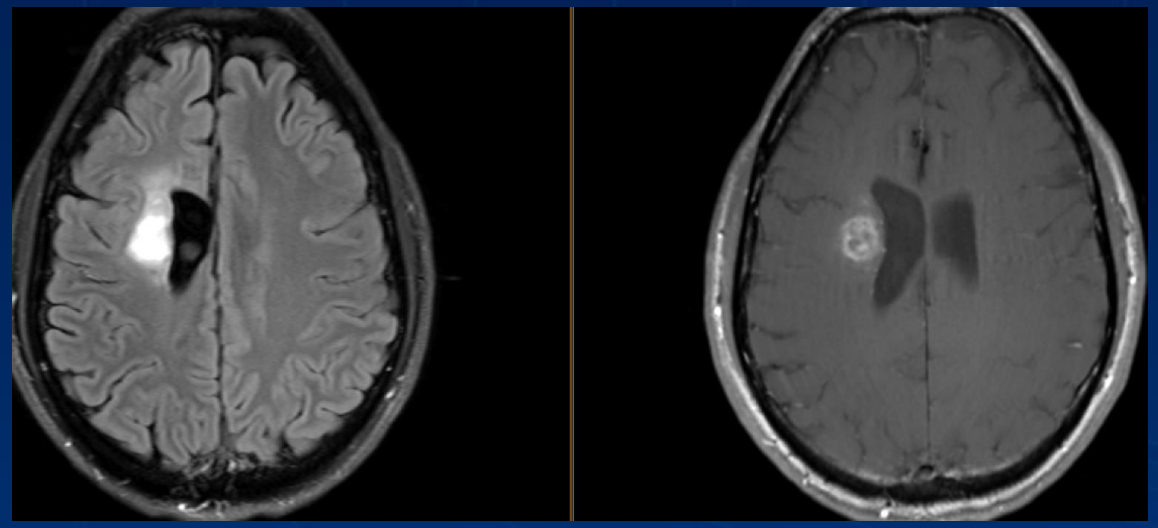
Case Presentation



Post Radiation

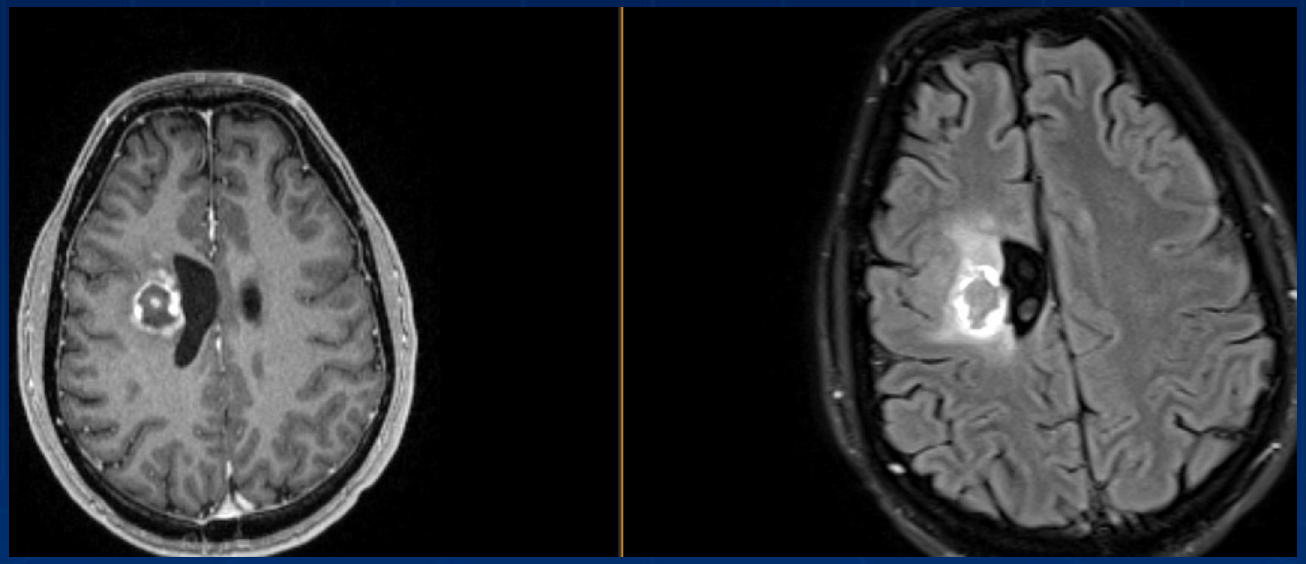


Completion of Cycle 12 of adjuvant Temozolomide



4.5 years following completion of chemotherapy

Case Presentation

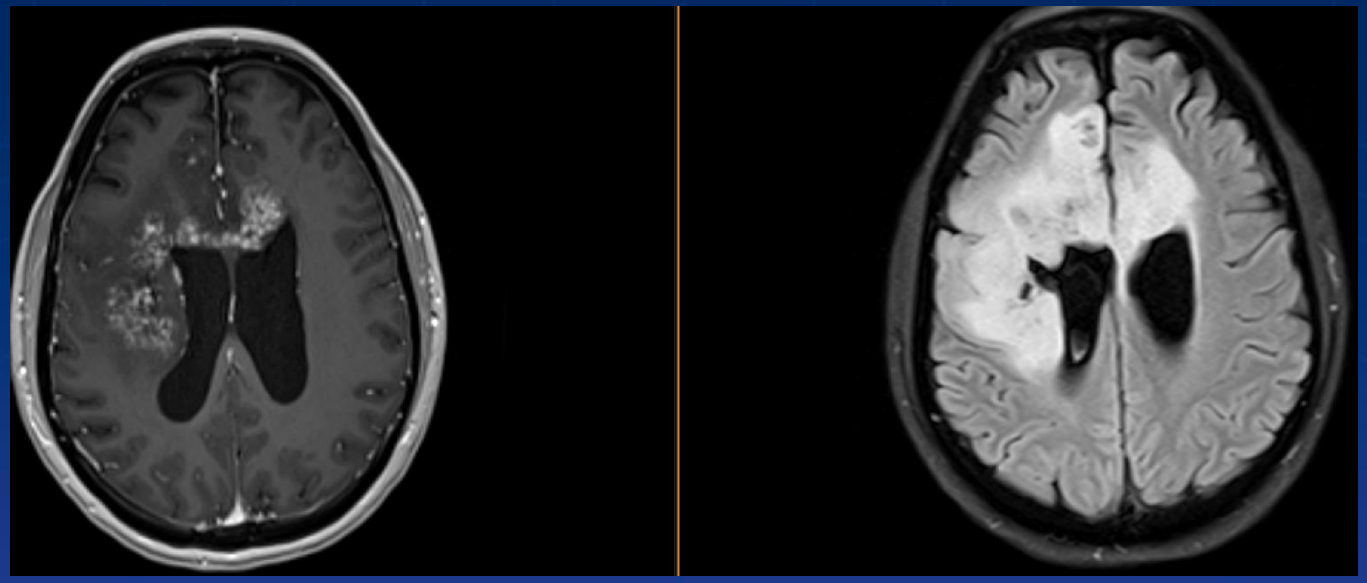


Laser interstitial thermal therapy/biopsy followed by Pembrolizumab 200mg IV every 3 weeks

Biopsy returned Astrocytoma IDH mutant WHO Grade 4

Case Presentation

- Nearly 11 years following initiation diagnosis and multiple progressions with transformation to higher grades, patient ultimately discontinued treatment and proceeded with best supportive care alone



Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

Ingo K. Mellinghoff, M.D., Martin J. van den Bent, M.D., Deborah T. Blumenthal, M.D., Mehdi Touat, M.D., Katherine B. Peters, M.D., Jennifer Clarke, M.D., M.P.H., Joe Mendez, M.D., Shlomit Yust-Katz, M.D., Liam Welsh, M.D., Ph.D., Warren P. Mason, M.D., François Ducray, M.D., Yoshie Umemura, M.D., Burt Nabors, M.D., Matthias Holdhoff, M.D., Andreas F. Hottinger, M.D., Ph.D., Yoshiki Arakawa, M.D., Juan M. Sepulveda, M.D., Wolfgang Wick, M.D., Riccardo Soffietti, M.D., James R. Perry, M.D., Pierre Giglio, M.D., Macarena de la Fuente, M.D., Elizabeth A. Maher, M.D., Steven Schoenfeld, M.S., Dan Zhao, Ph.D., Shuchi S. Pandya, M.D., Lori Steelman, M.S., Islam Hassan, M.D., Patrick Y. Wen, M.D., and Timothy F. Cloughesy, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

- Phase 3 double-blind, randomized study

Vorasidenib (IDH1/2 inhibitor) vs placebo

  - Glioma IDH 1/2 mutant WHO Grade 2 s/p resection
  - No urgent need to receive radiation or chemotherapy
- Pre-planned interim analysis
  - Vorasidenib had significant improvement in PFS and Time to next intervention (TTNI)

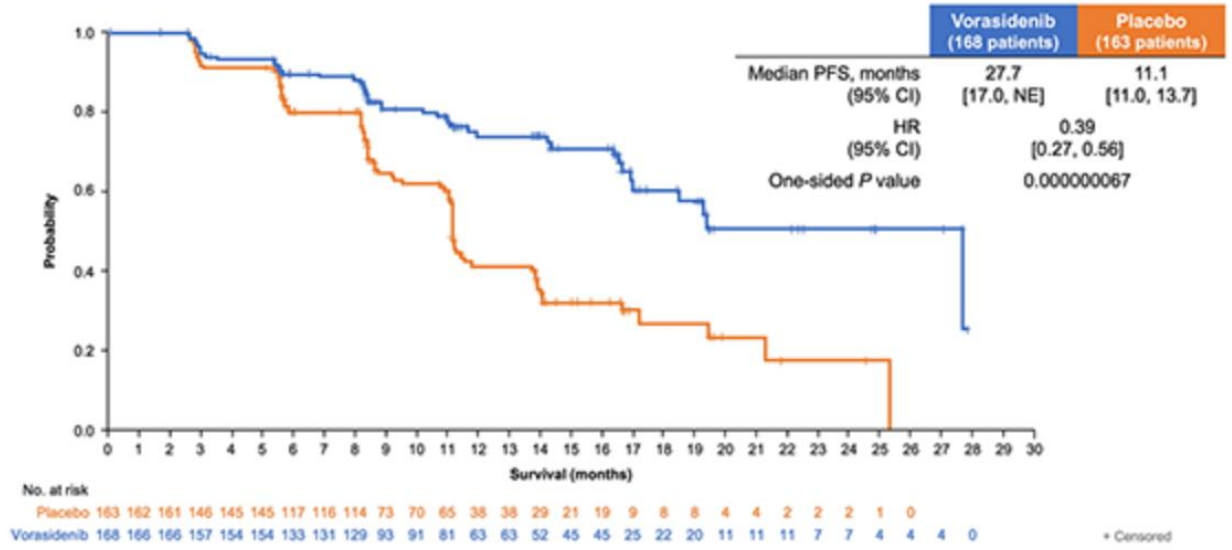
INDIGO study

- ≥12 years of age
- IDH 1/2 mut Grade 2 Oligodendrioglioma or Diffuse Astrocytoma
- Prior intervention – Surgery only
- Measurable non-enhancing disease (≥ 1 target lesion that measured ≥1cmx ≥1cm)
- Per investigator, patient not in need of urgent radiation or chemotherapy
- Enrolled from 1/2020-2/2022

Mellinghoff I et al. N Engl J Med 2023

INDIGO Study

Figure 1. Primary Endpoint of PFS per Blinded Independent Review Committee



Abbreviations: BIRC, blinded independent review committee; PFS, progression-free survival.View larger

TTNI
Vorasidenib –Not reached
Placebo – 17.8 months
P-value 0.000000019

Mellinghoff I et al. N Engl J Med 2023

Reasonable toxicity profile

Figure 2. TEAEs for Vorasidenib Versus Placebo

	Vorasidenib (167 patients)		Placebo (163 patients)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any adverse event – no. (%)	158 (94.6)	38 (22.8)	152 (93.3)	22 (13.5)
Increased alanine aminotransferase	65 (38.9)	16 (9.6)	24 (14.7)	0
Increased aspartate aminotransferase	48 (28.7)	7 (4.2)	13 (8.0)	0
Increased gamma-glutamyltransferase	26 (15.6)	5 (3.0)	8 (4.9)	2 (1.2)
COVID-19	55 (32.9)	0	47 (28.8)	0
Fatigue	54 (32.3)	1 (0.6)	52 (31.9)	2 (1.2)
Headache	45 (26.9)	0	44 (27.0)	1 (0.6)
Diarrhea	41 (24.6)	1 (0.6)	27 (16.6)	1 (0.6)
Nausea	36 (21.6)	0	37 (22.7)	0
Dizziness	25 (15.0)	0	26 (16.0)	0
Seizure	23 (13.8)	7 (4.2)	19 (11.7)	4 (2.5)
Constipation	21 (12.6)	0	20 (12.3)	0

- Treatment interruption due to TEAE:
  - Vorasidenib 29.9% (50 patients)
  - Placebo 22.7% (37 patients)
- Dose reduction due to TEAE:
  - Vorasidenib 10.8% (18 patients)
  - Placebo 3.1% (5 patients)
- No fatal TEAE

Abbreviation: TEAE, treatment-emergent adverse event.View larger

Mellinghoff I et al. N Engl J Med 2023

Changing our treatment paradigm?

- Low risk Grade 2 gliomas IDH 1/2 mutated
  - Residual disease, no urgency to start chemotherapy or radiation Give Vora
  - Gross total resection, no visible disease, observe vs Vora?
- What do we do for recurrent patients who have not had IDH inhibitors
  - Monotherapy vs combinatorial approaches
- What do we do for Grade 3 patients
  - Role for adding upfront with Chemoradiation?

Treatment decisions in a world with IDH inhibitors

- Many patients with Grade 3 IDH-mutant Astrocytoma or IDH-mutant and 1p/19q co-deleted Oliogodendrogliomas live beyond 10 years
- Histological grading is subjective in IDH-mutant gliomas contributing to survival overlap between grades
- Factors that show some association with histological grade include
    - gadolinium enhancement on imaging
    - molecular findings
        - IDH-mutant Astrocytomas – *CDKN2A/B* homozygous deletion (and hemizygous deletion), *CDK4* amplification, *RB1* mutation, PI3K pathway alterations and *PDGFRA* amplification, *MYCN* amplification
        - IDH-mutant and 1p/19q co-deleted Oliogodendrogliomas – *chromosomal arm 9p loss and *CDKN2A/B* homozygous deletion, mutations in *PIK3CA* and *NOTCH1*, absence of mutation in *TERT* (less than 5% of Oligos), *PTEN* alteration, *MYC* gain

Van den Bent MJ et al. Neuro Oncol 2024

* Not well validated but suggested

Treatment decisions in a world with IDH inhibitors

- Age and patient outcome has modest association
- Most studies have shown extent of resection has decreased importance of clinical factors on prognosis
- For IDH-mutant Astrocytoma, postoperative residual disease has major association with survival
- Clinical significance of contrast enhancement is different at recurrence vs at first diagnosis
- In addition to INDIGO study, clinical trials using IDH inhibitors have shown some activity (IDH1 inhibitors Ivosidenib, Olutasidenib, Safusidenib and IDH1/2 inhibitor Vorasidenib)
    - recurrent tumors
    - enhancing tumors
    - Grade 3 tumors
- Real-world data is needed to provided much needed patient guidance when making clinical decisions

Van den Bent MJ et al. Neuro Oncol 2024

Thank you!

Real World Data

- RWE confirms support of using TTFields
- Recurrent GBM (rGBM) population
  - Registry studies PRiDE and EF-19
  - OS with TTFields in clinical practice longer than either arm of EF-11
    - PRiDE 9.6 months
    - EF-11 7.4 months
- Newly diagnosed GBM (ndGBM population)
  - TIGER study – largest prospective study (429 patients starting TTFields)
    - Median OS 19.6 months, PFS 10.2 months
    - 2-year OS rates 42.4%, 4-year OS rates 27.7%

Khagi S. The Oncologist. 2025
Bahr O. Journal of Clinical Oncology. 2024

Real World Data

Tiger Study

- Largest prospective study in ndGBM in real world practice setting
- Maintains the positive safety profile established with TTFields
- OS and PFS consistent with prior studies
- Long term survival rates in ndGBM remain promising with TTFields

Khagi S. The Oncologist. 2025
Bahr O. Journal of Clinical Oncology. 2024

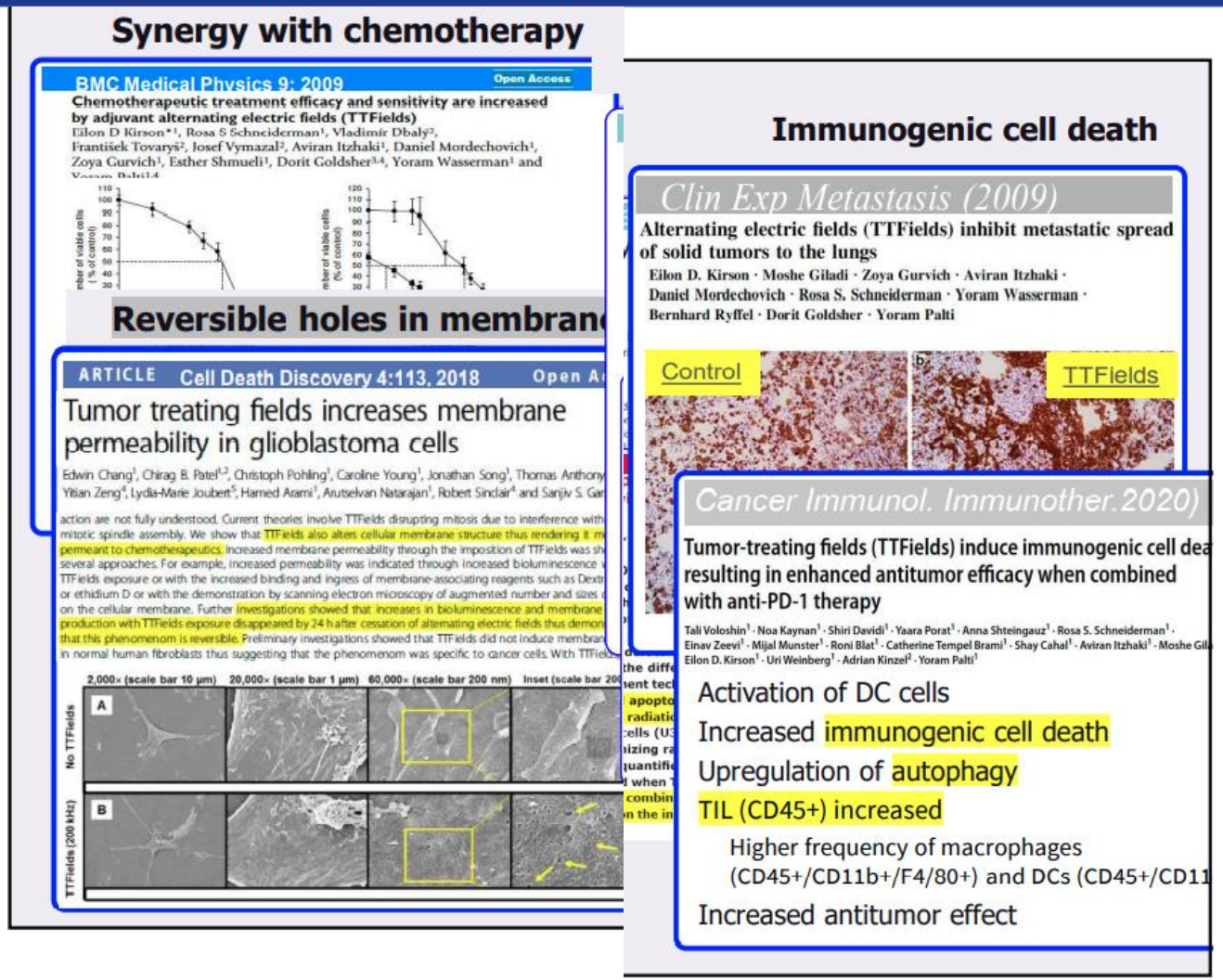
Future Directions

TaRRGET (NCT04671459) - TTFields concomitant with stereotactic radiosurgery (SRS) in the rGBM population
TRIDENT – Phase III study of TTFields concomitant with chemoradiation in ndGBM
METIS - (EF-25, NCT02831959) –Phase III study of TTFields therapy following SRS with best supportive care compared to SRS and best supportive care alone in patient with NSCLC brain mets
NCT04129515 – Phase I/II study of TTFields therapy with immune checkpoint inhibitor (ICI) Pembrolizumab for newly dx brain mets from melanoma
LUNAR (EF-24, NCT02973789) – Phase III study in with NSCLC mets progressing on or after platinum-based therapy – results reported clinical and statistically significant survival benefits for TTFields plus ICI or docetaxel (OS 13.2 months) vs ICI or docetaxel alone (OS 9.9 months)

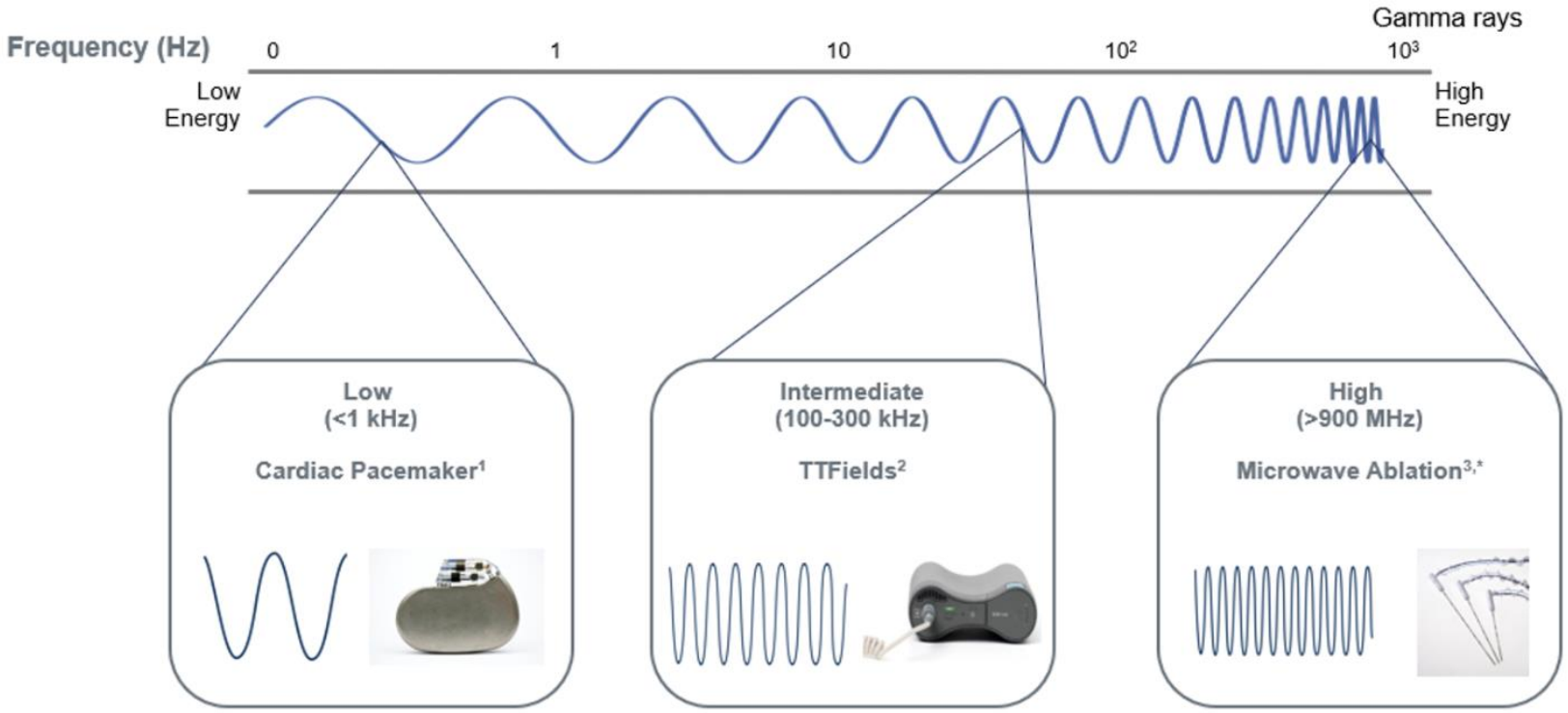
Segmentation based treatment plan compared to the current NovoTAL planning system aims to maximize therapy outcomes through enhanced transducer array layouts

Khagi S. The Oncologist. 2025

New Frontier in Cancer Care



Medical Devices that use Electric Fields



1. Seitz S. *Magnetic Resonance Imaging on Patients With Implanted Cardiac Pacemakers*. Kit Scientific Publishing; 2011. Accessed February 21, 2020. https://books.google.com/books/about/Magnetic_Resonance_Imaging_on_Patients_w.html?id=BaGKQljhc80C. 2. OptuneGio. Instructions For Use. Novocure; 2023. 3. Saldanha DF, et al. *Semin Intervent Radiol*. 2010;27(3):247-254.

UF College of Medicine
UNIVERSITY of FLORIDA