Sound Check

Start Time

Contact UNCLCN

Questions, Feedback, Technical Support:

Phone:
(919) 445-1000

Email:
unclcn@unc.edu

Website:
unclcn.org

Poll Everywhere for Q&A
pollev.com/unclcn

Upcoming Live Webinars
learn.unclcn.org/live

Self-Paced, Online Courses
learn.unclcn.org/spoc

Co-provided with *UNC Health*

1

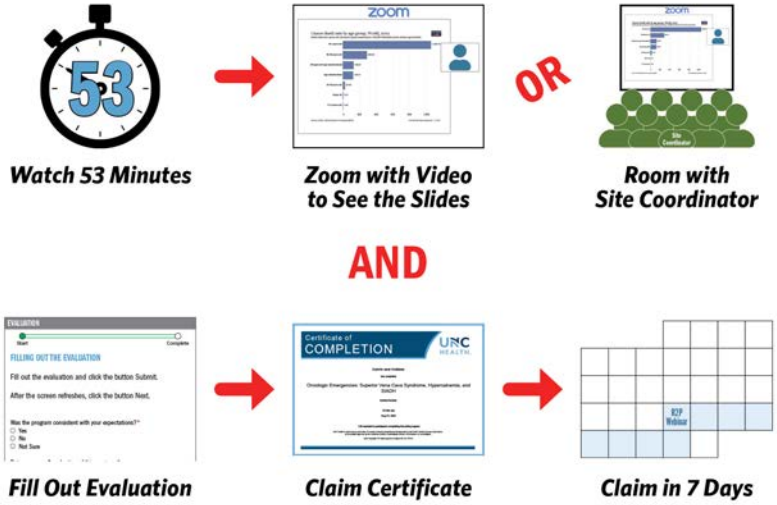
Poll Everywhere

Join by Web

1. Go to **PollEv.com**
2. Enter **UNCLCN**
3. Respond to activity

2

To Claim CE Credits



Watch 53 Minutes

Zoom with Video to See the Slides

Room with Site Coordinator

Fill Out Evaluation

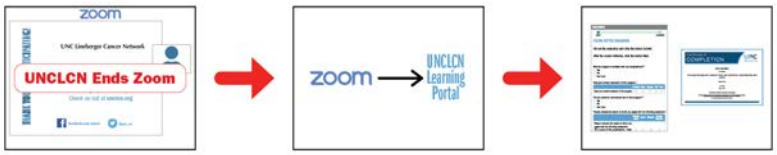
Claim Certificate

Claim in 7 Days

3

After the Webinar

Please wait for UNCLCN to end the Zoom video.



UNCLCN Ends Zoom

Zoom Sends Data to Learning Portal

Claiming CE Credit Is Open

4

Free Continuing Education Credits

Live Webinars

Only at the Day and Time Indicated learn.unclcn.org

PATIENT CENTERED CARE
CME NCPD/CNE ACPE ASRT CTR
2nd Wednesday Jan–Oct
1st Wednesday Nov–Dec
12 pm – 1 pm

ADVANCED PRACTICE PROVIDER
CME NCPD/CNE
3rd Wednesday Jan–Oct
2nd Wednesday Nov–Dec
4 pm – 5 pm

RESEARCH TO PRACTICE
CME NCPD/CNE ACPE ASRT CTR
4th Wednesday Jan–Oct
3rd Wednesday Nov–Dec
12 pm – 1 pm

SOUTHEASTERN AMERICAN INDIAN CANCER HEALTH EQUITY PARTNERSHIP
CME NCPD/CNE
1st Wednesday Feb, May, Nov
12 pm – 1 pm

Self-Paced, Online Courses

Available any Day and Time learn.unclcn.org/spoc

5

Spread the Word!

Do you enjoy our webinars and feel others may benefit, too?
Help us spread the word!

Become a promoter:

Receive special emails to share within your organization!

unclcn.org/promoter

Follow our social channels:

facebook.com/unclcn unclinebergercancernetwork

linkedin.com/in/unclcn

Send questions to **unclcn@unc.edu** or **(919) 445-1000**.

Thank you for spreading the word!

6

7

Our Presenter

Dominique Higgins,
MD, PhD

Dominique Higgins, MD, PhD, is an Assistant Professor in the Department of Neurosurgery specializing in neurosurgical oncology and the treatment of brain tumors.

Dr. Higgins completed a dual MD/PhD program at Mayo Clinic College of Medicine, appeasing both his interests in medicine and research.

He went on to complete his residency training in neurosurgery at Columbia University's Neurological Institute of New York.

Dr. Higgins also completed a brain tumor fellowship at the University of Miami, with an emphasis on minimally invasive open and endoscopic surgical treatments for brain tumors.

His research focus is the treatment of malignant brain tumors, including glioblastoma.

8

Our Presenter

9

Our Presenter

5. Undergraduate graduation from Stanford

10

Our Presenter

5. Undergraduate graduation from Stanford

4. MSTP Program at Mayo Clinic

11

Our Presenter

5. Undergraduate graduation from Stanford

4. MSTP Program at Mayo Clinic

3. Neurosurgery Residency at Columbia University

12

Our Presenter

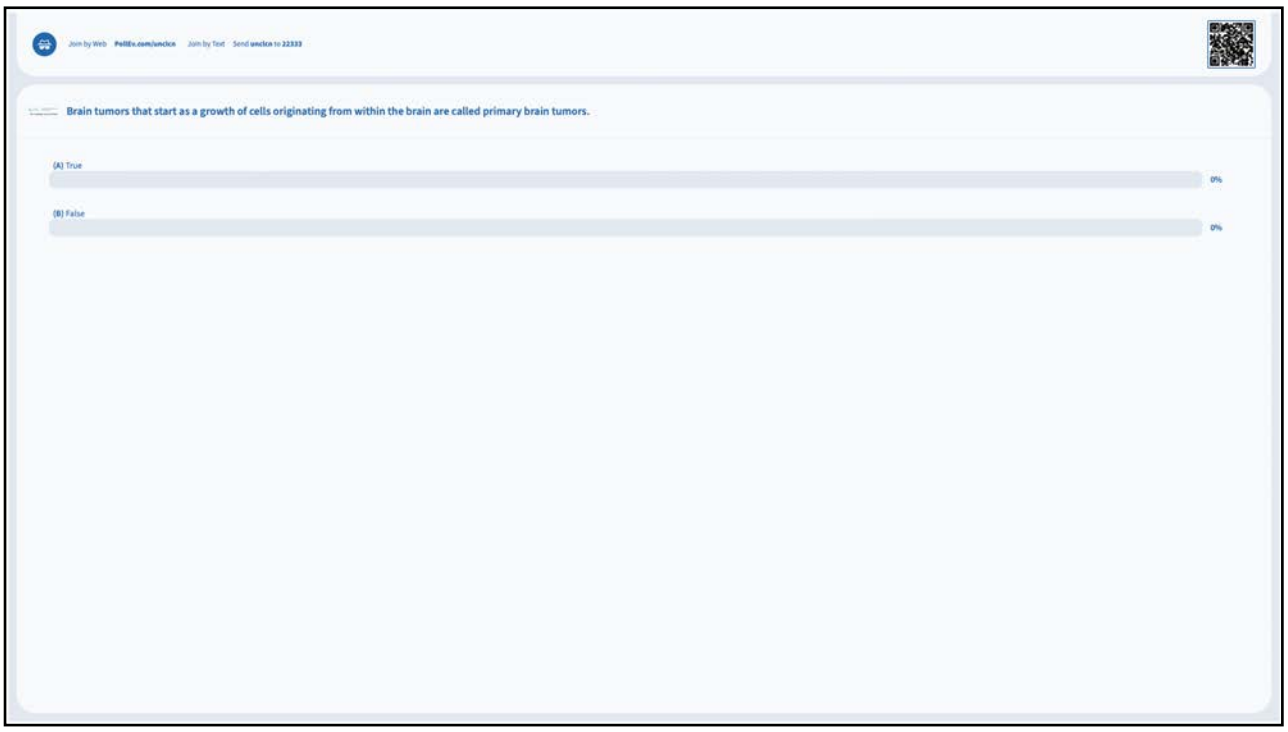
5. Undergraduate graduation from Stanford
4. MSTP Program at Mayo Clinic
3. Neurosurgery Residency at Columbia University
2. Fellowship at the University of Miami in Brain Tumor Surgery

13

Our Presenter

5. Undergraduate graduation from Stanford
4. MSTP Program at Mayo Clinic
3. Neurosurgery Residency at Columbia University
2. Fellowship at the University of Miami in Brain Tumor Surgery
1. Surgeon Scientist at UNC conducting basic and translational research with independent funding

14



15

ACCME Disclosure

This activity has been planned and implemented under the sole supervision of the Course Director, Stephanie Wheeler, PhD, MPH, in association with the UNC Office of Continuing Professional Development (CPD). The course director and CPD staff have no relevant financial relationships with ineligible companies as defined by the ACCME.

A potential conflict of interest occurs when an individual has an opportunity to affect educational content about health-care products or services of a commercial interest with which he/she has a financial relationship. The speakers and planners of this learning activity have not disclosed any relevant financial relationships with any commercial interests pertaining to this activity.

The presenter has no relevant financial relationships with ineligible companies as defined by the ACCME.

16

ANCC Disclosure

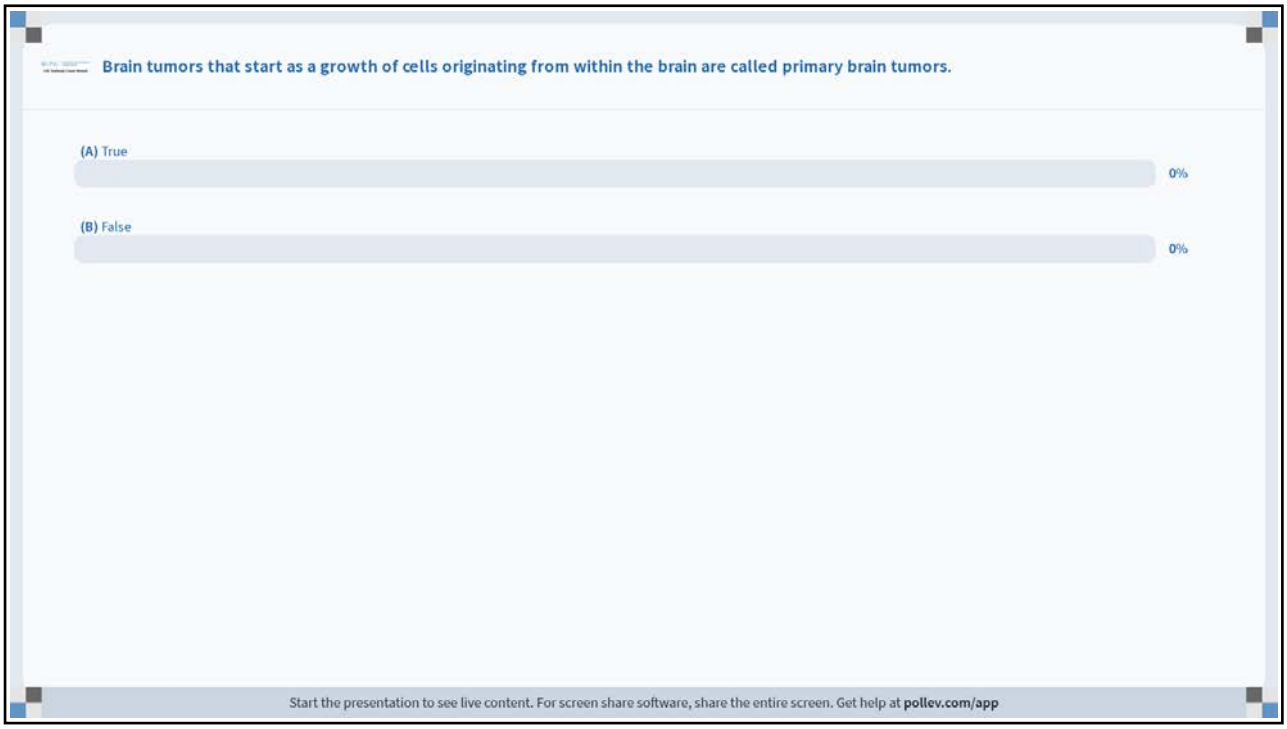
NCPD Activity #: 001-L23059
1.0 Contact Hours Provided

Relevant Financial Relationship:
No one with the ability to control content of this activity has a relevant financial relationship with an ineligible company.

Criteria for Activity Completion:
Criteria for successful completion requires attendance at the NCPD activity and submission of an evaluation within 30 days.

Approved Provider Statement:
UNC Health is approved as a provider of nursing continuing professional development by the North Carolina Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

17



18

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

UNC CANCER CARE

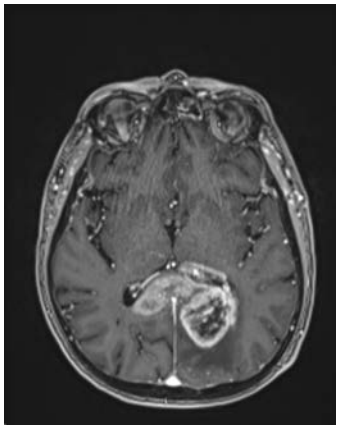
Primary Brain Tumors: Diagnosis and Management Strategies

Dominique Higgins MD, PhD
Department of Neurosurgery

19

Overview

- Classifications of Brain Tumors
- Common Presentations and Evaluation Strategies
- Treatment and Clinical trial options for malignant tumors

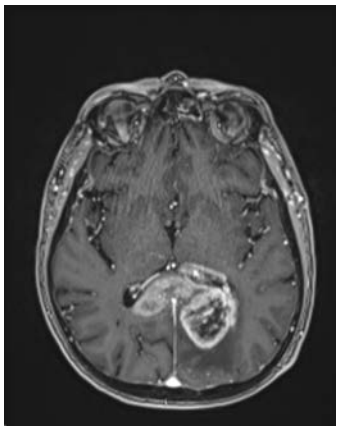


UNC LINEBERGER COMPREHENSIVE CANCER CENTER

20

Learning Objectives

1. Discuss diagnostic criteria for different brain tumors
2. Discuss the standard treatment course for these tumors
3. Discuss existing and upcoming clinical trials for treatment



UNC LINEBERGER COMPREHENSIVE CANCER CENTER

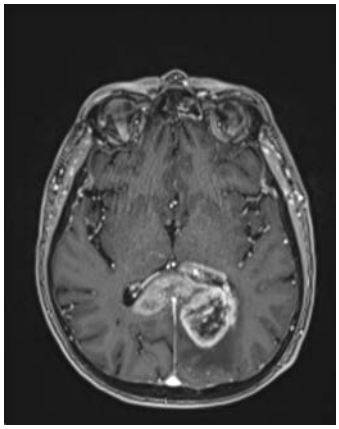
21

Classification of Brain Tumors

- Classification by tumor origin
  - Primary versus secondary/metastatic tumors
- Classification by compartment
  - Intra-axial (at or below the level of the cortex)

    -Intraparenchymal vs intraventricular
  - Extra-axial (outside of the brain, at or below the level of the skull)

    -Skull/calvarial vs dural-based vs skull base



UNC LINEBERGER COMPREHENSIVE CANCER CENTER

22

Primary Intra-axial Tumors

- Gliomas
- Ependymomas
- Intraventricular tumors

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

23

Gliomas

- Classified based on cell of origin
  - Astrocytomas, oligodendrogliomas
- WHO Grade 1-4

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

24

Gliomas: Astrocytomas

- Classified based on cell of origin
  - Astrocytomas, oligodendrogliomas
- WHO Grade 1-4
  - Grade 1 – benign
  - Grade 4 - malignant

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

25

Glioblastoma

- Grade 4 Astrocytoma
- Most common malignant primary brain tumor
- Presentation depends on location:
  - Headaches, seizures, neurologic changes (speech, weakness, confusion)

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

26

Imaging Modalities

- MRI brain with and without contrast
- Tractography
- MRI Spectroscopy
- PET CT/MRI

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

27

Glioblastoma

- Management involves maximal safe resection
  - Lesionectomy, supramaximal resection, awake surgery, functional mapping
  - Stereotactic biopsy, laser interstitial thermal therapy (LITT)
- Post-operative treatment includes fractionated radiation and concurrent temozolomide

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

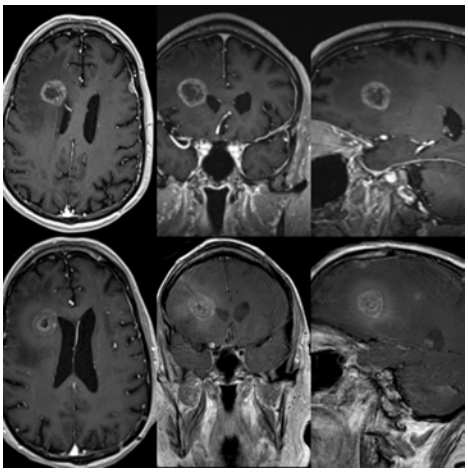
28

Operative Considerations

- Balancing visibility and tissue damage
- Asleep versus awake resections
- Tubular retractors and resection tools
- Smaller incisions and craniotomies
- Early-recovery after surgery (ERAS) protocols

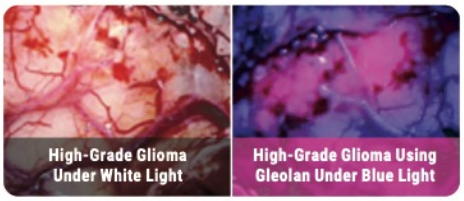
Eichberg et al. *J Neuro-Onc. June 2020*

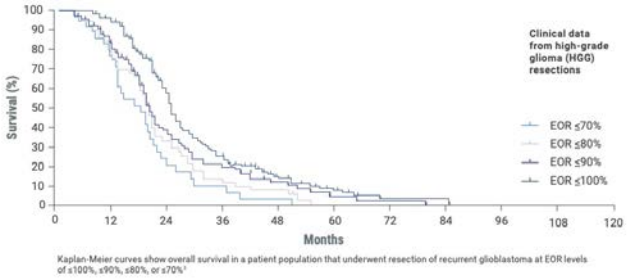
Operative Considerations – Stereotactic Robotic guided Biopsy +/- Laser Ablation



Intra-operative adjuncts

- Fluorescent guided surgery
  - Fluorescein
  - 5-ALA
- Robotic Assisted Surgeries
- Tractography
- Brachytherapy





Oppenlander ME, Wolf AB, Snyder LA, et al.

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

31

Intra-operative adjuncts

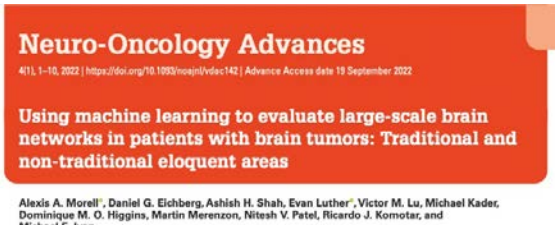
- Fluorescent guided surgery
  - Fluorescein
  - 5-ALA
- Robotic Assisted Surgeries
- Tractography
- Brachytherapy

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

32

Intra-operative adjuncts

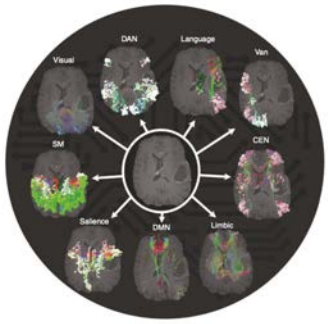
- Fluorescent guided surgery
  - Fluorescein
  - 5-ALA
- Robotic Assisted Surgeries
- Tractography
- Brachytherapy

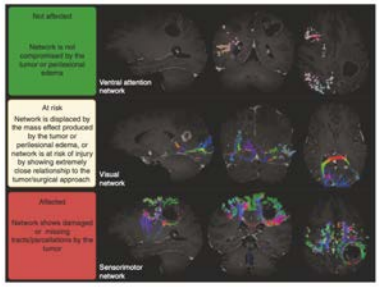

Neuro-Oncology Advances

4(1), 1–10, 2022 | https://doi.org/10.1093/noajnl/vdac142 | Advance Access date 19 September 2022

Using machine learning to evaluate large-scale brain networks in patients with brain tumors: Traditional and non-traditional eloquent areas

Alexis A. Morell, Daniel G. Eichberg, Ashish H. Shah, Evan Luther, Victor M. Lu, Michael Kader, Dominique M. O. Higgins, Martin Merenzon, Nitesh V. Patel, Ricardo J. Komotar, and Michael E. Ivan



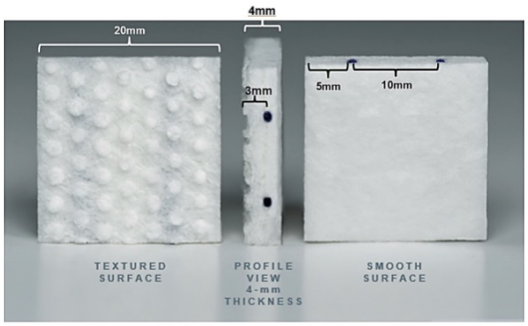


UNC LINEBERGER COMPREHENSIVE CANCER CENTER

33

Intra-operative adjuncts

- Fluorescent guided surgery
  - Fluorescein
  - 5-ALA
- Robotic Assisted Surgeries
- Tractography
- Brachytherapy



Cesium-131 seeds
Half-life 9.7 days

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

34

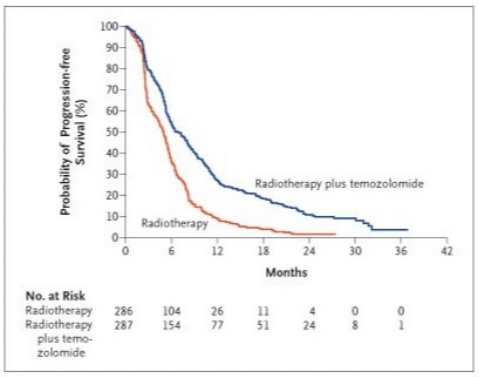
Glioblastoma

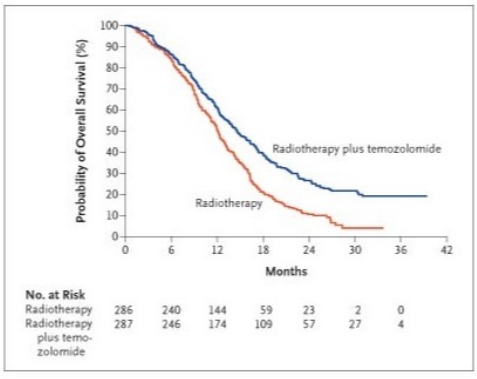
- Median survival 16 months
- Prognosis heavily dependent on tumor biology
- Key molecular changes:
  - MGMT methylation status – sensitivity to TMZ
  - Ki67 – growth rate
- Recurrence on average at 9 months

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

35

GBM Standard of Care – Concomitant Radiation/TMZ





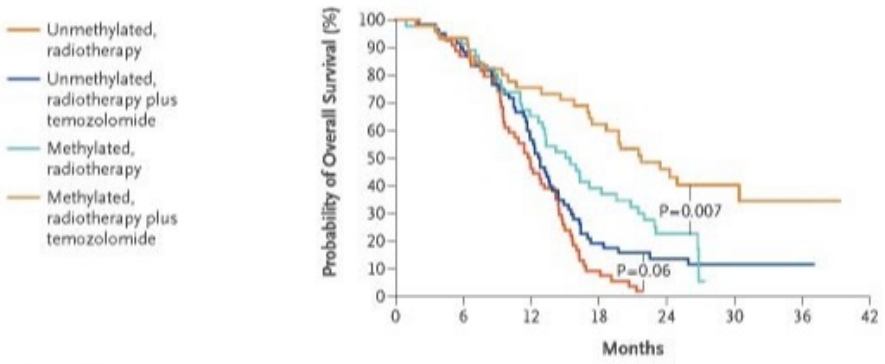
-Improved PFS from 5 to 6.9 months
-Improved overall survival from 12.1 to 14.6
-Increased 2-year survival from 10.4% to 26.5%

Stupp et al, NEJM 2005

UNC RESEARCH

36

MGMT promoter methylation



No. at Risk							
Unmethylated, radiotherapy	54	47	25	5	0	0	0
Unmethylated, radiotherapy plus temozolomide	60	53	34	11	7	4	1
Methylated, radiotherapy	46	42	30	18	8	0	0
Methylated, radiotherapy plus temozolomide	46	42	34	28	16	7	1

Hegi et al, NEJM 2005

UNC RESEARCH

37

Glioblastoma

- Clinical Trials provide promise of increasing survival
- Newly diagnosed GBM
  - Imvax IGV-001
  - Tumor treating fields
- Recurrent GBM
  - Chimeric Antigen Receptor T-cell (CAR-T) therapy
  - Focused ultrasound

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

38

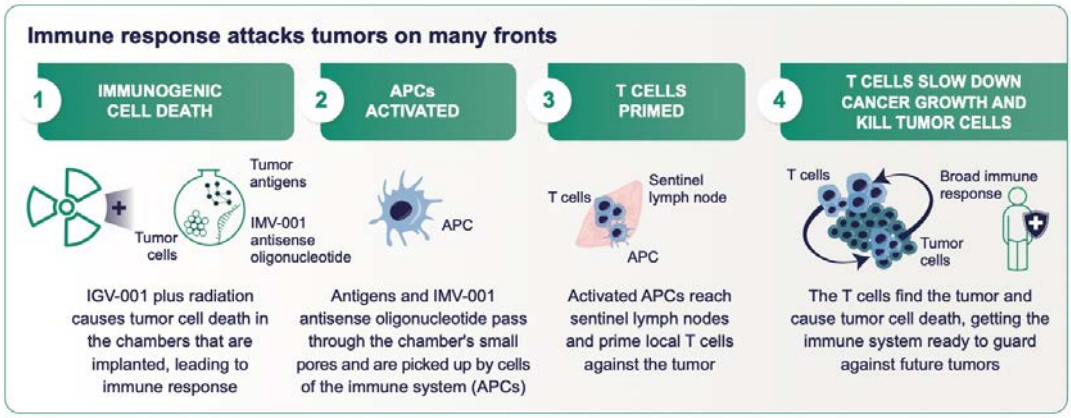
Glioblastoma

- Clinical Trials provide promise of increasing survival
- Newly diagnosed GBM
  - Imvax IGV-001
  - Tumor treating fields
- Recurrent GBM
  - Chimeric Antigen Receptor T-cell (CAR-T) therapy
  - Focused ultrasound

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

39

Glioblastoma Trials: Imvax – UNC currently enrolling



Imvax

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

40

Imvax: IGV-001 Phase 1b

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Phase Ib Clinical Trial of IGV-001 for Patients with Newly Diagnosed Glioblastoma

David W. Andrews[1,2], Kevin D. Judy[1], Charles B. Scott[3], Samantha Garcia[4], Larry A. Harshyne[1], Lawrence Kenyon[5], Kiran Talekar[6], Adam Flanders[6], Kofi-Buaku Atsina[6], Lyndon Kim[7], Nina Martinez[8], Wenyin Shi[9], Maria Werner-Wasik[9], Haisong Liu[9], Mikhail Prosniak[4], Mark Curtis[5], Rhonda Kean[4], Donald Y. Ye[1], Emily Bongiorno[4], Sami Sauma[10], Mark A. Exley[2], Kara Pigott[2], and D. Craig Hooper[1,4]

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

41

Imvax: IGV-001 Phase 1b

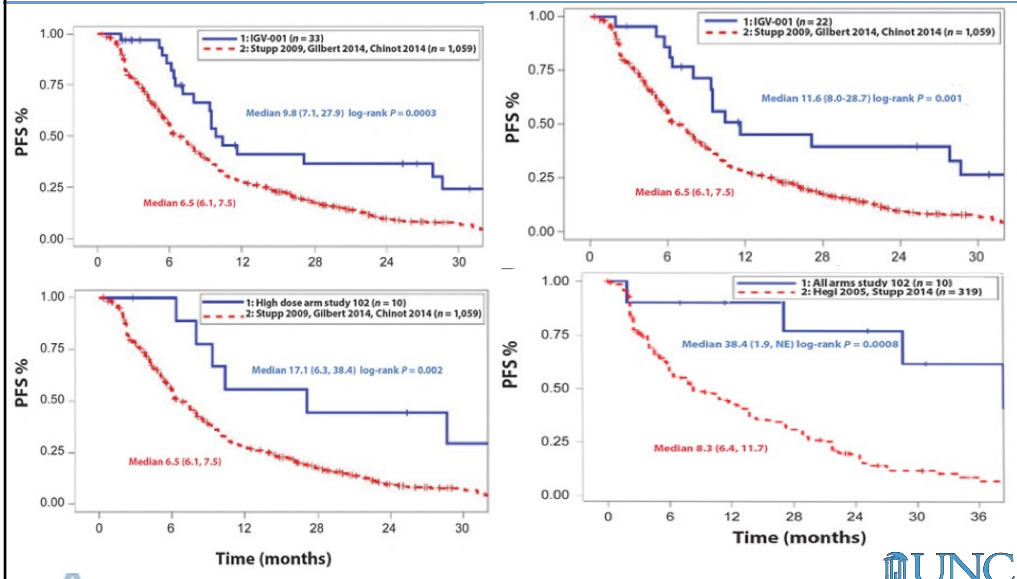
Table 1. Demographics and baseline disease characteristics.

Characteristic	IGV-001 ($n = 33$)
Sex, *n* (%)	
Male	20 (60.6)
Female	13 (39.4)
Age, y	
Mean (SD)	60.2 (10.5)
Median (range)	63 (32–77)
Extent of intracranial disease	
Single lobe	25 (76)
Multiple lobes, unihemispheric	4 (12)
Bihemispheric	4 (12)
Extent of gross resection, *n* (%)	
Total (100%)[a]	10 (30.3)
Near total (95%–99%)	7 (21.2)
Subtotal (>biopsy, <95%)	16 (48.5)
KPS, *n* (%)	
90–100	26 (78.8)
70–80	6 (18.2)
60	1 (3.0)

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

42

Imvax: IGV-001 Phase 1b

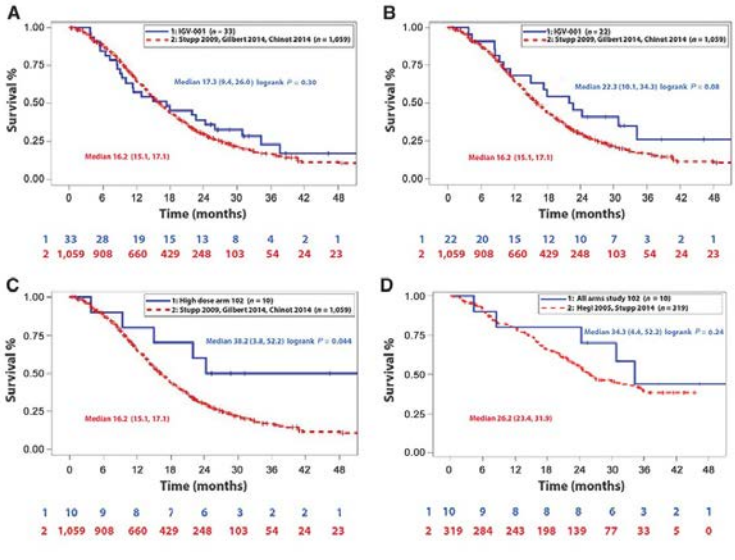


IGV treatment was associated with an increase in progression free survival

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

43

Imvax: IGV-001 Phase 1b



High dose IGV treatment was associated with an increase in overall survival

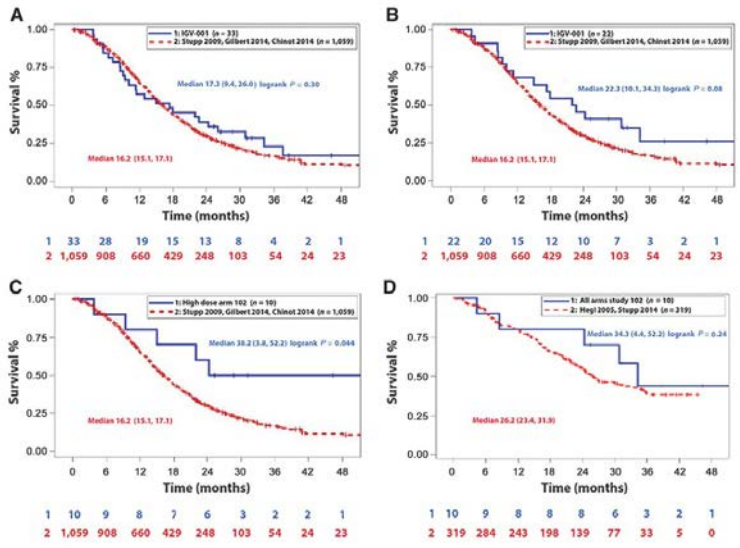
Compared to historical controls

38.2 months vs 16.2 months (p=0.044)

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

44

Imvax: IGV-001 Phase 1b



High dose IGV treatment was associated with an increase in overall survival

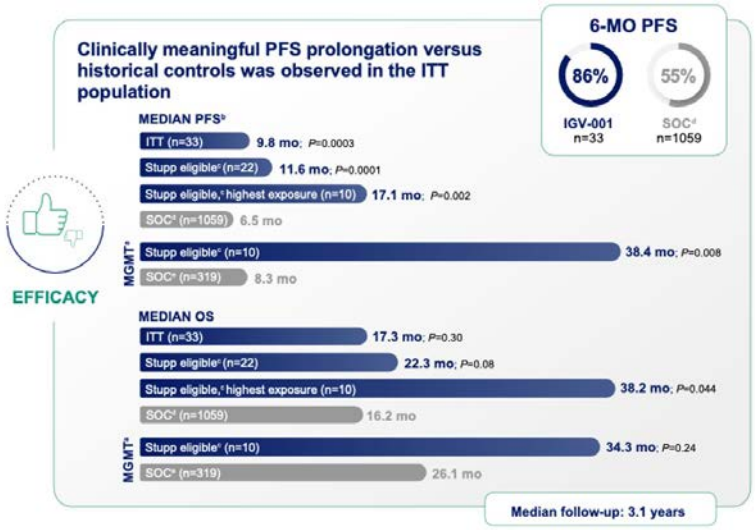
Compared to historical controls

38.2 months vs 16.2 months (p=0.044)

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

45

Imvax: IGV-001 Phase 1b



UNC LINEBERGER COMPREHENSIVE CANCER CENTER

46

Glioblastoma Trials: Imvax Phase 2b multicenter study

Protocol title

A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 2b Study to Assess the Safety and Efficacy of IGV-001, an Autologous Cell Immunotherapy With Antisense Oligonucleotide (IMV-001) Targeting IGF-1R, in Newly Diagnosed Patients With Glioblastoma

Sponsor
Imvax, Inc.

ClinicalTrials.gov identifier
NCT04485949

Protocol number
14379-201

CRITERIA

Key Inclusion Criteria

Patients who take part in the trial* must:

- Have newly diagnosed glioblastoma
- Be 18 to 70 years of age
- Have a KPS score ≥70 (unable to work but able to care for themselves overall)

Key Exclusion Criteria

Patients are not allowed to participate* in the trial if they have:

- A tumor that is on both sides of the brain
- Had previous surgery or anticancer treatment for glioblastoma
- Glioblastoma that came back
- Another cancer† while having glioblastoma or within the last 3 years that is not cured
- A weakened immune system (example: HIV, HBV, HCV) or an autoimmune disorder (example: Crohn's disease)
- Heart disease or history of heart issues

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

47

Glioblastoma Trials: Imvax – UNC currently enrolling

STUDY DESIGN

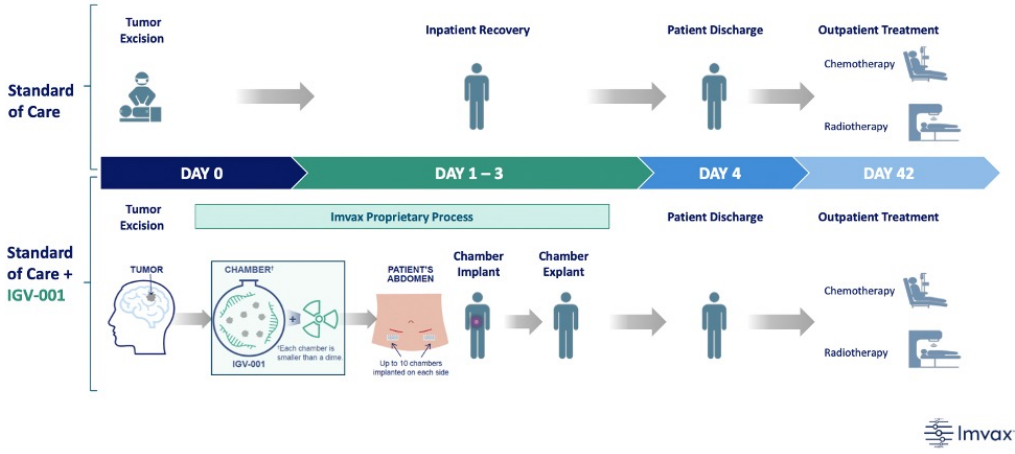
SCREENING: Patients will have screening procedures completed between Day -14 to Day -2 (up to 16 days)
RANDOMIZATION: Patients are randomly assigned 2:1 to treatment with IGV-001 or placebo
TREATMENT: Patients receive study treatment (IGV-001 or placebo) during Days 1-28
SOC TREATMENT: Patients receive usual treatment (SOC) of RT and chemotherapy (TMZ) during Weeks 7-12, then chemotherapy alone during Weeks 17-41
FOLLOW-UP: Doctors keep track of patients' health during Months 10-36

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

48

Glioblastoma Trials: Imvax – UNC currently enrolling

Currently enrolling Phase 2b trial for Newly-Diagnosed GBM



Imvax

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

49

Glioblastoma Trials: Imvax immunogenic cell death

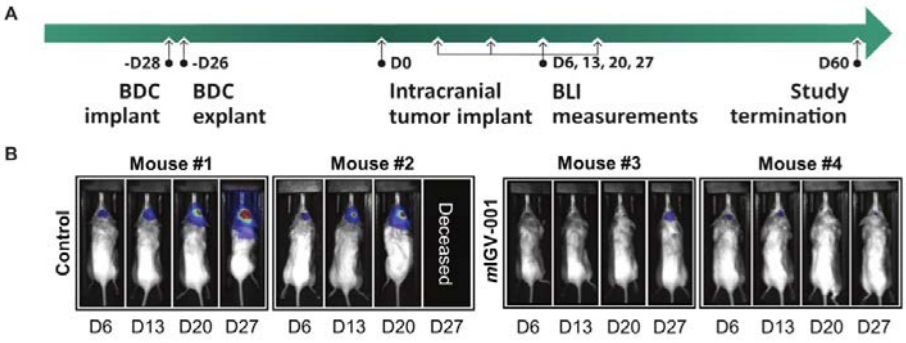
A biologic-device combination product delivering tumor-derived antigens elicits immunogenic cell death-associated immune responses against glioblastoma

Christopher Cultrara,[1] Christopher Uhl,[1] Kenneth Kirby,[1] Essam Abed Elrazaq,[1] Amelia Zellander,[1] David W Andrews,[2,3] Charles B Scott,[4] Lorenzo Galluzzi,[5,6,7] Mark A Exley,[1] Jenny Zilberberg [1]

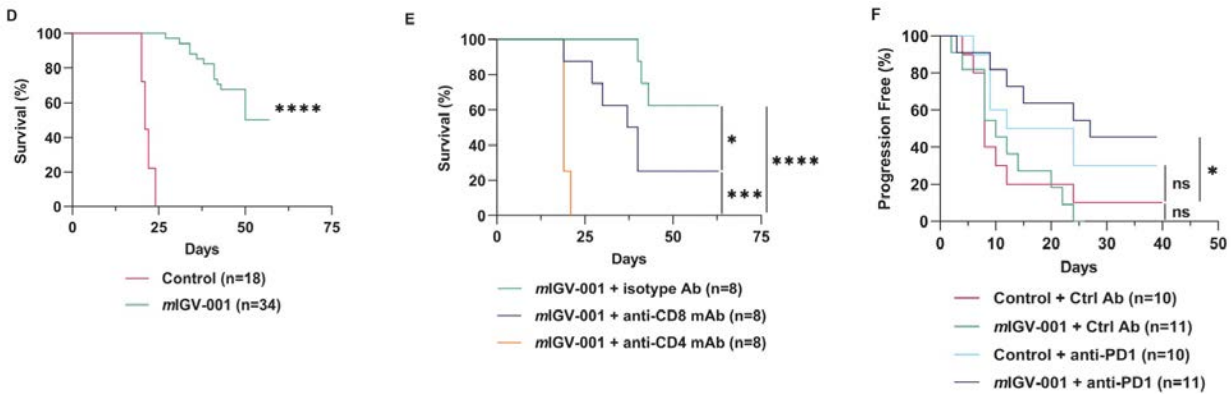
UNC LINEBERGER COMPREHENSIVE CANCER CENTER

50

Glioblastoma Trials: Imvax immunogenic cell death



Glioblastoma Trials: Imvax immunogenic cell death



Glioblastoma

- Clinical Trials provide promise of increasing survival
- Newly diagnosed GBM
  - Imvax IGV-001
  - Tumor treating fields
- Recurrent GBM
  - Chimeric Antigen Receptor T-cell (CAR-T) therapy
  - Focused ultrasound

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

53

Tumor Treating Fields (TTF)

- Low intensity, intermediate frequency, alternating electric fields
- Delivered by transducer arrays transcranially
- Requires head-shaving, 18hr/day usage
- Proposed mechanism is disruption of cell division

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

54

Tumor Treating Fields (TTF)

NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality

Roger Stupp [a,*], Eric T. Wong [b], Andrew A. Kanner [c], David Steinberg [d], Herbert Engelhard [e], Volkmar Heidecke [f], Eilon D. Kirson [g], Sophie Taillibert [h], Frank Liebermann [i], Vladimir Dbalý [j], Zvi Ram [c], J. Lee Villano [e], Nikolai Rainov [f], Uri Weinberg [g], David Schiff [k], Lara Kunschner [l], Jeffrey Raizer [m], Jerome Honnorat [n], Andrew Sloan [o], Mark Malkin [p], Joseph C. Landolfi [q], Franz Payer [r], Maximilian Mehdorn [s], Robert J. Weil [t], Susan C. Pannullo [u], Manfred Westphal [v], Martin Smrcka [w], Lawrence Chin [x], Herwig Kostron [y], Silvia Hofer [z], Jeffrey Bruce [aa], Rees Cosgrove [ab], Nina Paleologous [ac], Yoram Palti [g], Philip H. Gutin [ad]

Prior smaller single arm studies showed promise

237 recurrent GBM patients, TTF vs chemotherapy

No difference in overall survival

Stupp et al., 2012

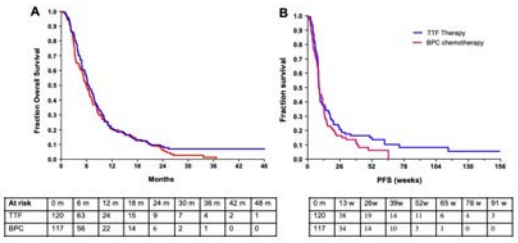
UNC LINEBERGER COMPREHENSIVE CANCER CENTER

55

Tumor Treating Fields (TTF)

NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality

Roger Stupp [a,*], Eric T. Wong [b], Andrew A. Kanner [c], David Steinberg [d], Herbert Engelhard [e], Volkmar Heidecke [f], Eilon D. Kirson [g], Sophie Taillibert [h], Frank Liebermann [i], Vladimir Dbalý [j], Zvi Ram [c], J. Lee Villano [e], Nikolai Rainov [f], Uri Weinberg [g], David Schiff [k], Lara Kunschner [l], Jeffrey Raizer [m], Jerome Honnorat [n], Andrew Sloan [o], Mark Malkin [p], Joseph C. Landolfi [q], Franz Payer [r], Maximilian Mehdorn [s], Robert J. Weil [t], Susan C. Pannullo [u], Manfred Westphal [v], Martin Smrcka [w], Lawrence Chin [x], Herwig Kostron [y], Silvia Hofer [z], Jeffrey Bruce [aa], Rees Cosgrove [ab], Nina Paleologous [ac], Yoram Palti [g], Philip H. Gutin [ad]



Prior smaller single arm studies showed promise

237 recurrent GBM patients, TTF vs chemotherapy

No difference in overall survival, but promising subanalyses

Stupp et al., 2012

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

56

Tumor Treating Fields (TTF)

JAMA | Original Investigation

Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma
A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew Kanner, MD; William Read, MD; David M. Steinberg, PhD; Benoit Lhermitte, MD; Steven Toms, MD; Ahmed Idbaih, MD; Manmeet S. Ahluwalia, MD; Karen Fink, MD, PhD; Francesco Di Meco, MD; Frank Lieberman, MD; Jay-Jiguang Zhu, MD, PhD; Giuseppe Stragliotto, MD, PhD; David D. Tran, MD, PhD; Steven Brem, MD; Andreas F. Hottinger, MD, PhD; Eilon D. Kirson, MD, PhD; Gitit Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Chae-Yong Kim, MD, PhD; Sun-Ha Paek, MD, PhD; Garth Nicholas, MD; Jordi Bruna, MD; Hal Hirte, MD; Michael Weller, MD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD

Comparison of TTF/TMZ vs TMZ alone (2009)

Interim analysis in 2015 (210 patients)

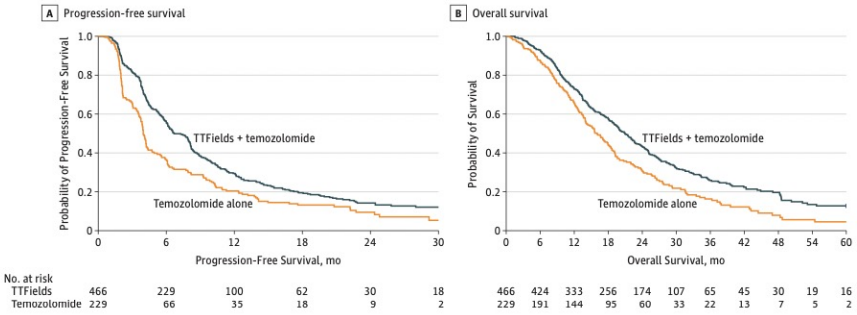
Final results in 2017 (695 patients)

Stupp et al., 2012

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

57

Tumor Treating Fields (TTF)



PFS: 6.7 months (TTF+TMZ) vs 4.0 (TMZ)

Overall survival: 20.9 months (TTF+TMZ) vs 16.0 months (TMZ)

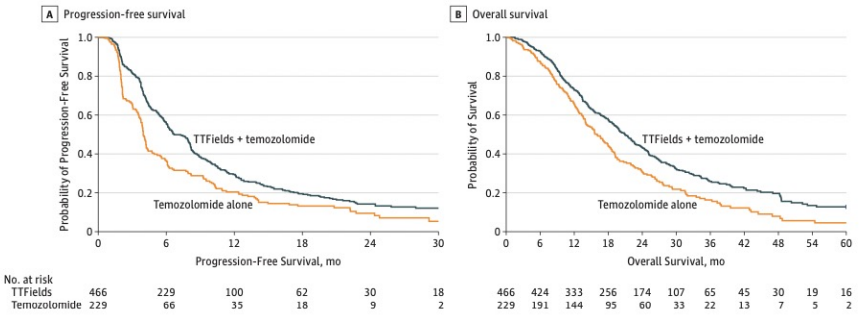
Stupp et al., 2012

Now FDA approved for treatment

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

58

Tumor Treating Fields (TTF)



PFS: 6.7 months (TTF+TMZ) vs 4.0 (TMZ)

Overall survival: 20.9 months (TTF+TMZ) vs 16.0 months (TMZ)

Stupp et al., 2012

Now FDA approved for treatment

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

59

Tumor Treating Fields (TTF): Clinical Trials

Trident Trial (“EF-32”)

Randomized study for newly diagnosed GBM patients

TTF/TMZ /Radiation vs TTF after SOC

Results pending

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

60

Glioblastoma

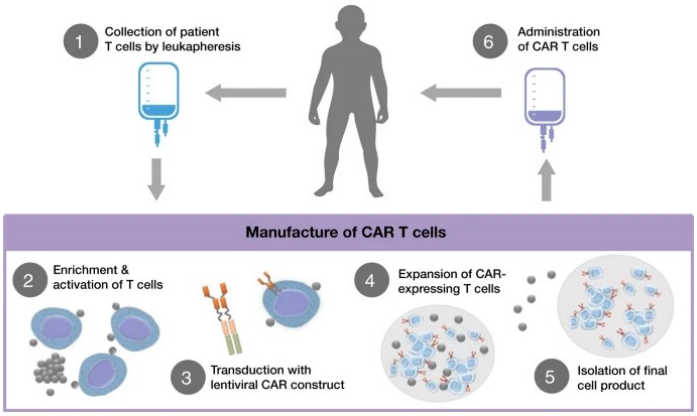
- Clinical Trials provide promise of increasing survival
- Newly diagnosed GBM
  - Imvax IGV-001
  - Tumor treating fields
- Recurrent GBM
  - Chimeric Antigen Receptor T-cell (CAR-T) therapy
  - Focused ultrasound

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

61

Chimeric Antigen Receptor T-cell (CAR-T) Therapy

- T-cells are programmed against a tumor antigen (eg. B7-H3)
- Patient blood samples are obtained to generate CAR-T cells
- CAR-T cells infused to attack tumor cells



Hucks et al, 2019

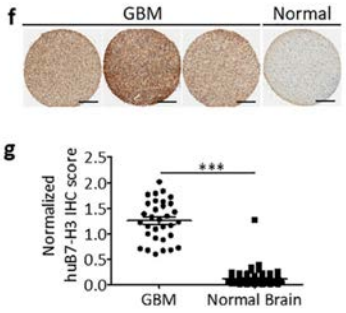
UNC LINEBERGER COMPREHENSIVE CANCER CENTER

62

Chimeric Antigen Receptor T-cell (CAR-T) Therapy

B7-H3-redirected chimeric antigen receptor T cells target glioblastoma and neurospheres

Dean Nehama [a], Natalia Di Ianni [b,d], Silvia Musio [b,d], Hongwei Du [a], Monica Patané [c], Bianca Pollo [c], Gaetano Finocchiaro [d], James J.H. Park [e], Denise E. Dunn [e], Drake S. Edwards [e,f], Jeffrey S. Damrauer [a], Hannah Hudson [a], Scott R. Floyd [e,f], Soldano Ferrone [g], Barbara Savoldo [a,h], Serena Pellegatta [b,d,**,1], Gianpietro Dotti [a,i,*,1]



B7-H3 is a member of the B7 family of immune checkpoint proteins and tumor target

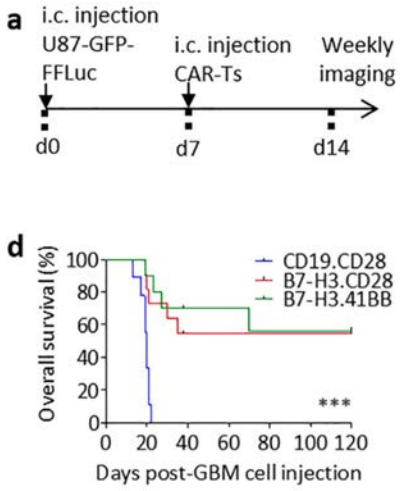
B7-H3 increased expression in GBM tissue compared with normal brain

Ebiomedicine, 2019

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

63

Chimeric Antigen Receptor T-cell (CAR-T) Therapy



B7-H3 CAR-Ts improved survival in a murine glioma model in vivo

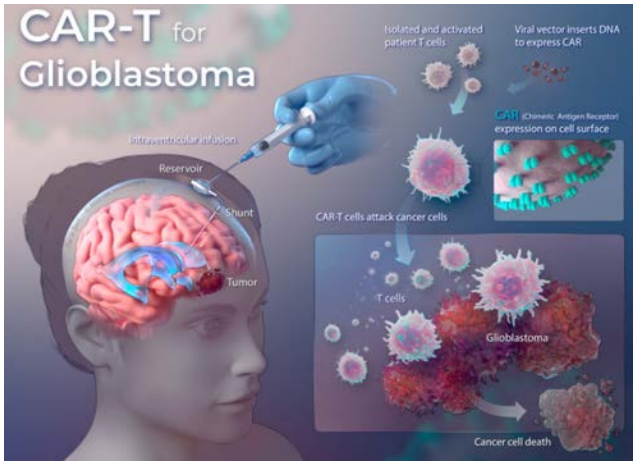
Ebiomedicine, 2019

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

64

UNC Clinical Trial: B7-H3 CAR-T Therapy for Recurrent GBM

- Phase I study underway to determine safety in recurrent GBM patients
- B7-H3 CAR-T cells injected intraventricular
- Ongoing preclinical studies aimed at enhancing survival of CAR-T cells



UNC LINEBERGER COMPREHENSIVE CANCER CENTER

65

Glioblastoma

- Clinical Trials provide promise of increasing survival
- Newly diagnosed GBM
  - Imvax IGV-001
  - Tumor treating fields
- Recurrent GBM
  - Chimeric Antigen Receptor T-cell (CAR-T) therapy
  - Focused ultrasound

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

66

Blood brain barrier penetration

- BBB impedes delivery of therapeutics to brain tumors like GBM
- Several strategies have been employed to bypass this:
  - Ommaya reservoir
  - Convection enhanced delivery
  - Intra-arterial therapy
  - Focused ultrasound

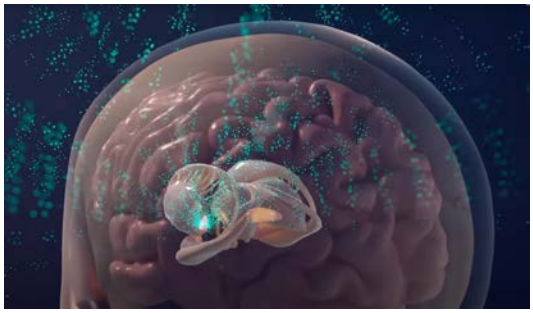
Chronic convection-enhanced delivery of topotecan for patients with recurrent glioblastoma: a first-in-patient, single-centre, single-arm, phase 1b trial

Eleonora F Spinazzi [1], Michael G Argenziano [1], Pavan S Upadhyayula [1], Matei A Banu [1], Justin A Neira [1], Dominique M O Higgins [1], Peter B Wu [2], Brianna Pereira [3], Aayushi Mahajan [1], Nelson Humala [1], Osama Al-Dalahmah [3], Wenting Zhao [4], Akshay V Save [5], Brian J A Gill [1], Deborah M Boyett [1], Tamara Marie [1], Julia L Furnari [1], Tejaswi D Sudhakar [1], Sylwia A Stopka [6], Michael S Regan [7], Vanessa Catania [7], Laura Good [1], Stergios Zacharoulis [8], Meenu Behl [9], Petros Petridis [1], Sachin Jambawalikar [9], Akiva Mintz [9], Angela Lignelli [9], Nathalie Y R Agar [10], Peter A Sims [4], Mary R Welch [11], Andrew B Lassman [11], Fabio M Iwamoto [11], Randy S D'Amico [12], Jack Grinband [13], Peter Canoll [3], Jeffrey N Bruce [14]

Lancet Oncology, 2022

Focused Ultrasound

- Microbubbles delivered intravenously and are sonicated by ultrasound waves
- Sonication results in BBB opening
- Allows increased local perfusion of drugs and immune cells



UNC Neurosurgery

Implantable Focused Ultrasound: SonoCloud

Clinical Trial > Sci Transl Med. 2016 Jun 15;8(343):343re2. doi: 10.1126/scitranslmed.aaf6086.

Clinical trial of blood–brain barrier disruption by pulsed ultrasound

Alexandre Carpentier [1], Michael Canney [2], Alexandre Vignot [2], Vincent Reina [3], Kevin Beccaria [4], Catherine Horodyckid [4], Carine Karachi [3], Delphine Leclercq [5], Cyril Lafon [6], Jean-Yves Chapelon [6], Laurent Capelle [4], Philippe Cornu [3], Marc Sanson [7], Khê Hoang-Xuan [7], Jean-Yves Delattre [7], Ahmed Idbaih [7]

- Phase 1/2a dose escalation study in recurrent GBM
- Combination of implantable focused ultrasound treatment prior to carboplatin
- Combination treatment was safe and well tolerated
- Phase 3 study in development

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

69

Gliomas: Astrocytomas

- Classified based on cell of origin
  - Astrocytomas, oligodendrogliomas
- WHO Grade 1-4
  - Grade 1 – benign
  - Grade 4 - malignant

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

70

IDH-mutant astrocytomas

- WHO Grade 2-4 Astrocytoma
- Contain mutations in the Kreb cycle enzyme isocitrate dehydrogenase (IDH)
- Results in production of oncometabolite 2-hydroxyglutarate
- Presentation depends on location:
  - Headaches, seizures, neurologic changes (speech, weakness, confusion)
- Evaluation by MRI w/wo contrast – often non-enhancing

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

71

IDH-mutant astrocytomas

- Management involves maximal safe resection
  - Lesionectomy, supramaximal resection, awake surgery, functional mapping
  - Stereotactic biopsy
  - Observation becoming less favorable
- Post-operative treatment:
  - Grade 2 low grade gliomas: chemotherapy/radiation vs observation
  - Grade 3 or 4 IDH-mutant high grade gliomas: chemotherapy/radiation

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

72

IDH-mutant astrocytomas: Novel treatments

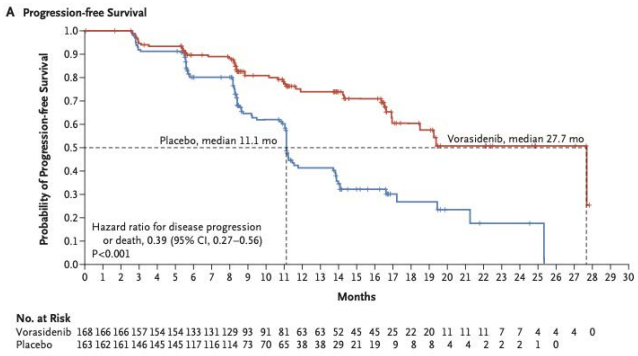
ORIGINAL ARTICLE

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., et al., for the INDIGO Trial Investigators*

- IDH inhibitor treatment in low-grade glioma improved outcomes

IDH-mutant astrocytomas: Novel treatments



- Improved PFS in treatment group vs control (27.7mo vs 11.1mo)
- Additional studies necessary to determine benefit in broader clinical contexts

Targeting metabolism in glioma

- GBM results in a shift toward cellular utilization of lipid/fatty acids - production and consumption
- Mechanisms that target metabolism are poised to be highly effective

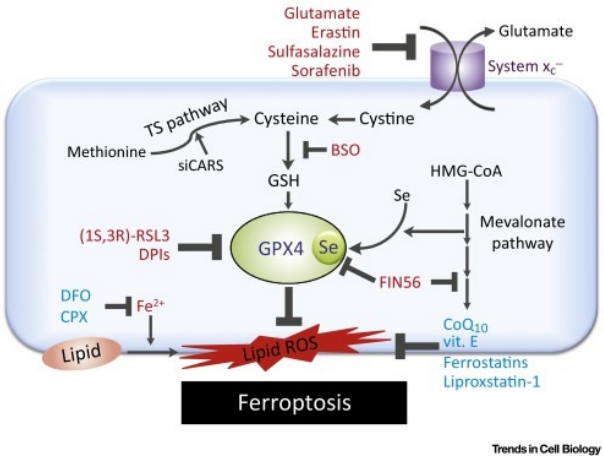
  -diagnostic and therapeutic
- Ferroptosis is a novel cell death pathway effective in resistant cancers

Ferroptosis

Regulated Cell Death

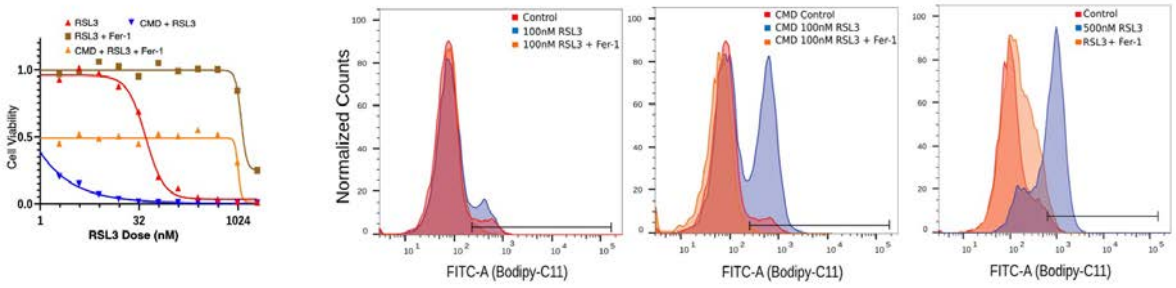
Apoptosis Necroptosis **Ferroptosis**

-Iron dependent lipid peroxidation



Sulfur-containing amino acid restriction in cancer

Dietary restriction of cysteine and methionine sensitizes gliomas to ferroptosis and induces alterations in energetic metabolism



Higgins, Upadhyayula, Mela et al. *Nature Comm 2023*

CMD = Cysteine/Methionine Deprivation
RSL3 = Ferroptosis Inducer
Ferrostatin (Fer-1) = Ferroptosis Inhibitor

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

77

Phase I study examining CMD in GBM patients

Diet initiated prior to surgery (control vs hyper-acute versus acute)

Preoperative MRI and MR spectroscopy on the day of surgery

Metabolic analysis of tissue with matching serum

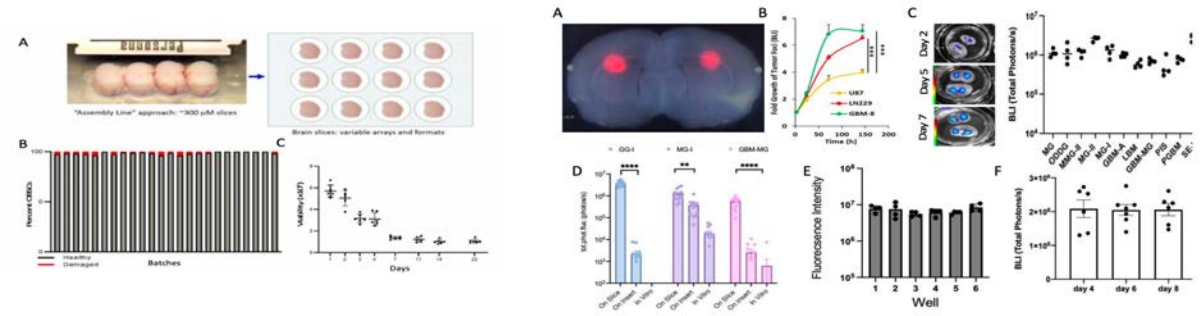
UNC LINEBERGER COMPREHENSIVE CANCER CENTER

78

Organotypic Brain Slice Culture

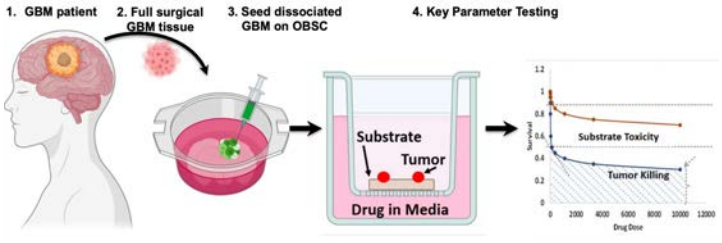
> Cell Rep Med. 2023 Jun 20;4(6):101042. doi: 10.1016/j.xcrm.2023.101042. Epub 2023 May 15.

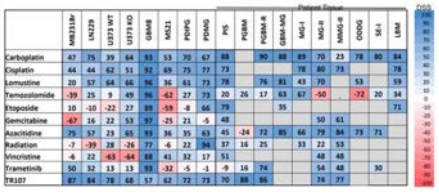
A living ex vivo platform for functional, personalized brain cancer diagnosis



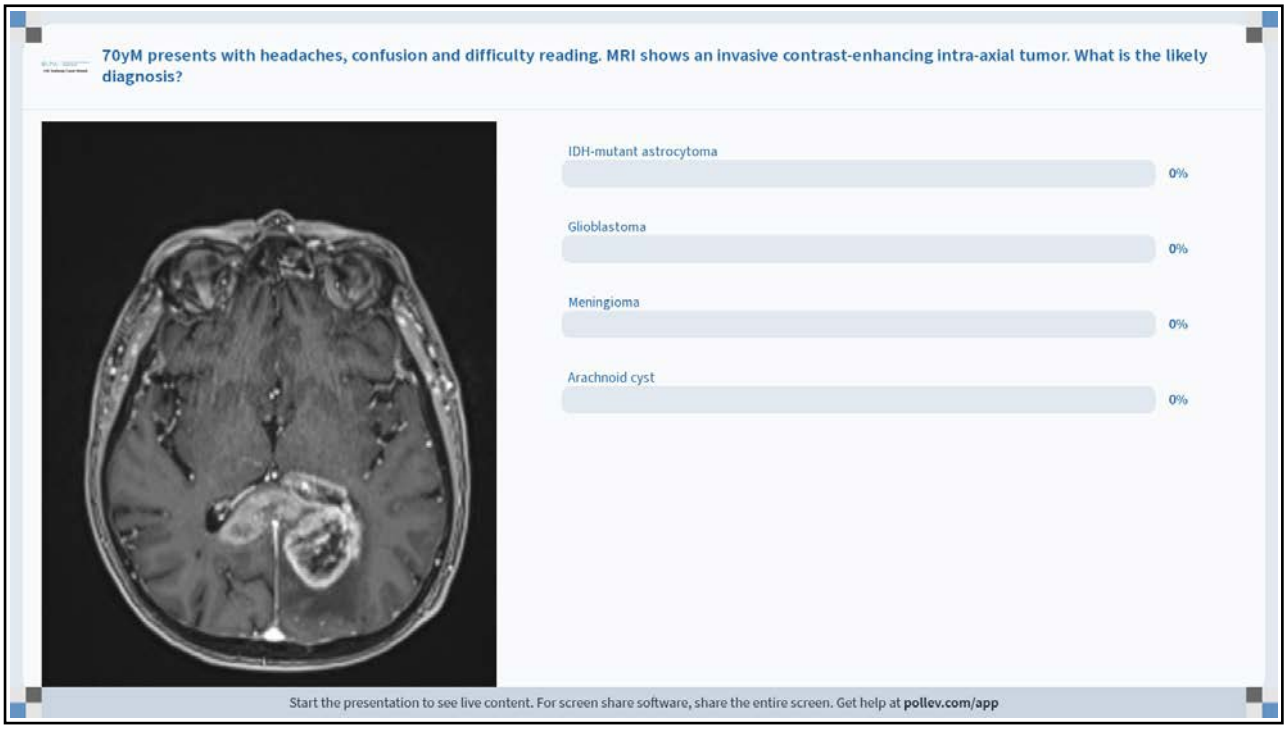
Mann et al, 2023

Glioblastoma Trials: Organotypic Brain Slice Culture

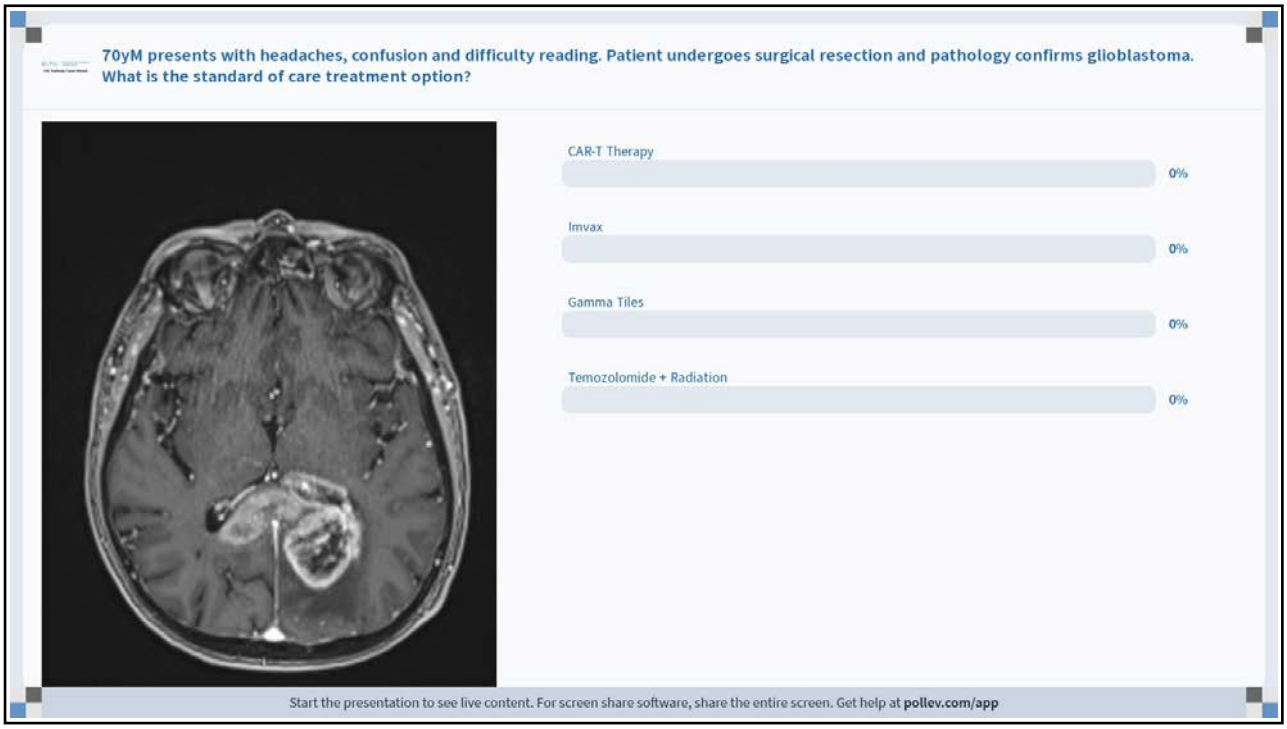




Mann et al, 2023

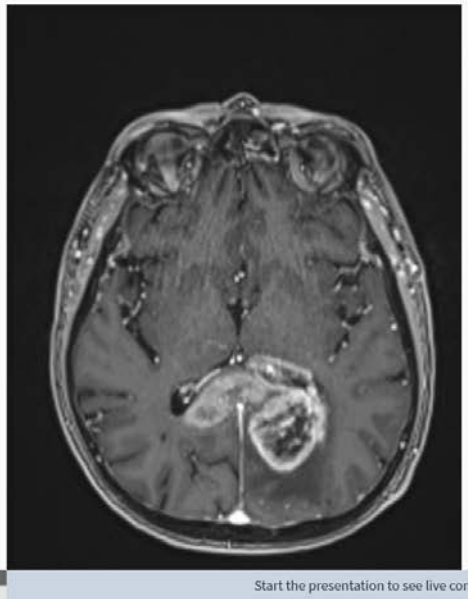

70yM presents with headaches, confusion and difficulty reading. MRI shows an invasive contrast-enhancing intra-axial tumor. What is the likely diagnosis?
IDH-mutant astrocytoma
0%
Glioblastoma
0%
Meningioma
0%
Arachnoid cyst
0%
Start the presentation to see live content. For screen share software, share the entire screen. Get help at pollev.com/app

81


70yM presents with headaches, confusion and difficulty reading. Patient undergoes surgical resection and pathology confirms glioblastoma. What is the standard of care treatment option?
CAR-T Therapy
0%
Imvax
0%
Gamma Tiles
0%
Temozolomide + Radiation
0%
Start the presentation to see live content. For screen share software, share the entire screen. Get help at pollev.com/app

82

70yM presents with headaches, confusion and difficulty reading. Patient undergoes surgical resection and pathology confirms glioblastoma. 9 months later MRI shows recurrence. What clinical trial options would be considered?



CAR-T Therapy 0%

Imvax 0%

Gamma Tiles 0%

TTF+Temozolomide + Radiation 0%

Start the presentation to see live content. For screen share software, share the entire screen. Get help at pollev.com/app

83

References

- Andrews, DW, et al. "Phase Ib Clinical Trial of IGV-001 for Patients with Newly Diagnosed Glioblastoma." *Clin Cancer Res*. 2021 Apr 1;27(7):1912-1922. doi: 10.1158/1078-0432.CCR-20-3805. Epub 2021 Jan 26. https://pubmed.ncbi.nlm.nih.gov/33500356/
- Carpentier, Alexandre, et al. "Clinical trial of blood-brain barrier disruption by pulsed ultrasound." *Sci Transl Med.*. 2016 Jun 15;8(343):343re2. doi: 10.1126/scitranslmed.aaf6086. https://pubmed.ncbi.nlm.nih.gov/27306666/
- Cultrara, Christopher, et al. "A biologic-device combination product delivering tumor-derived antigens elicits immunogenic cell death-associated immune responses against glioblastoma." *J Immunother Cancer*. 2023 Aug;11(8):e006880. doi: 10.1136/jitc-2023-006880. https://pubmed.ncbi.nlm.nih.gov/37550054/
- Eichberg, DG, et al. "Neuro-oncology practice guidelines from a high-volume surgeon at the COVID-19 epicenter," *J Neuro-Onc. June*. 2021 Mar; 85: 1–5. Published online 2020 Dec 16. doi: 10.1016/j.jocn.2020.12.012. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7834482/
- Higgins, Upadhyayula, Mela et al. "Dietary restriction of cysteine and methionine sensitizes gliomas to ferroptosis and induces alterations in energetic metabolism," *Nature Comm 2023*. Nature Communications volume 14, Article number: 1187 (2023). https://www.nature.com/articles/s41467-023-36630-w
- Mann, Breanna, et al. "A living ex vivo platform for functional, personalized brain cancer diagnosis," Cell Rep Med. . 2023 Jun 20;4(6):101042. doi: 10.1016/j.xcrm.2023.101042. Epub 2023 May 15. https://pubmed.ncbi.nlm.nih.gov/37192626/
- Mellinghoff, IK, et al. "Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma." *N Engl J Med*. 2023 Aug 17;389(7):589-601. doi: 10.1056/NEJMoa2304194. Epub 2023 Jun 4. https://pubmed.ncbi.nlm.nih.gov/37272516/
- Morell, Alexis A, et al. "Using machine learning to evaluate large-scale brain networks in patients with brain tumors: Traditional and non-traditional eloquent areas" Neuro-Oncology Advances, Volume 4, Issue 1, January-December 2022, vdac142, https://doi.org/10.1093/noajnl/vdac142. https://academic.oup.com/noa/article/4/1/vdac142/6705399
- Nehama, Dean, et al. "B7-H3-redirected chimeric antigen receptor T cells target glioblastoma and neurospheres." *EBioMedicine*. 2019 Sep:47:33-43. doi: 10.1016/j.ebiom.2019.08.030. Epub 2019 Aug 26. https://pubmed.ncbi.nlm.nih.gov/31466914/
- Oppenlander, ME, Wolf AB, Snyder LA, et al. "An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity." *J Neurosurg*. 2014 Apr;120(4):846-53. doi: 10.3171/2013.12.JNS13184. Epub 2014 Jan 31. https://pubmed.ncbi.nlm.nih.gov/24484232/
- Spinazzi, Eleonora F, et al. "Chronic convection-enhanced delivery of topotecan for patients with recurrent glioblastoma: a first-in-patient, single-centre, single-arm, phase 1b trial." *Lancet Oncology*, 23:11, P1409-1418, November 2022. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(22)00599-X/fulltext
- Stupp, Roger, et al. "NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality." *European Journal of Cancer*. Volume 48, Issue 14, September 2012, Pages 2192-2202. https://www.sciencedirect.com/science/article/pii/S0959804912003528
- Stupp, Roger, et al. "Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial." *JAMA*. 2017 Dec 19;318(23):2306-2316. doi: 10.1001/jama.2017.18718. https://pubmed.ncbi.nlm.nih.gov/29260225/

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

84

Thank you!

Dominique Higgins

higginsd@unc.edu

https://unclineberger.org/neuro/clinical-trials/

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

85

Primary Extra-axial Tumors

- Meningiomas
- Schwannomas/Neurofibromas
- Pituitary tumors

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

86

Primary Extra-axial Tumors: Meningiomas

- Most common primary brain tumor
- Arises from arachnoid cap cells
- Benign tumors (WHO Grade 1-3)
- Presentation depends on location
  - Most commonly headaches, incidental, neurologic deficits

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

87

Primary Extra-axial Tumors: Meningiomas

- Management depends on size and tumor biology
- Incidental, small, asymptomatic tumors:
  - annual MRI to monitor for changes
  - Incidental tumors, larger with growth or symptoms:
  - surgical resection versus radiation or combination
- Larger tumors
  - Surgical resection for attempted gross total
  - Post-operative radiation for higher grade pathology

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

88

Primary Extra-axial Tumors: Schwannomas

- Commonly arises from cranial nerve 8 (vestibular schwannomas)
- More rarely CN 5, 7
- Arises from nerve sheath
- Benign tumors largely
- Presentation depends on location
  - Most commonly hearing loss, vertigo, dizziness

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

89

Primary Extra-axial Tumors: Pituitary Tumors

- Benign tumors in the sella
- Non-functioning versus functioning
  - Prolactin, ACTH/cortisol, GH
- Presentation commonly headaches, vision changes (bitemporal hemianopsia), cranial neuropathies, endocrinopathies

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

90

Primary Extra-axial Tumors: Pituitary adenomas

- Management depends on type of pituitary adenoma
- Non-functioning adenomas:
  - Large tumors and symptomatic tumors recommend surgical resection
  - Otherwise annual MRI to monitor for changes

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

91

Primary Extra-axial Tumors: Pituitary adenomas

- Prolactinomas:
  - Medical therapy first line with dopamine antagonists
  - Surgery if medical failure
- Other functional adenomas:
  - Surgical resection for attempted gross total

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

92

Arachnoid Cysts

Benign Cystic lesions

Low likelihood of growth or symptoms

Rarely require intervention

Differentiate between other cystic lesions (hemangioblastoma, epidermoid, pilocytic astrocytoma, infectious lesions)

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

93

Primary Extra-axial Tumors: Schwannomas

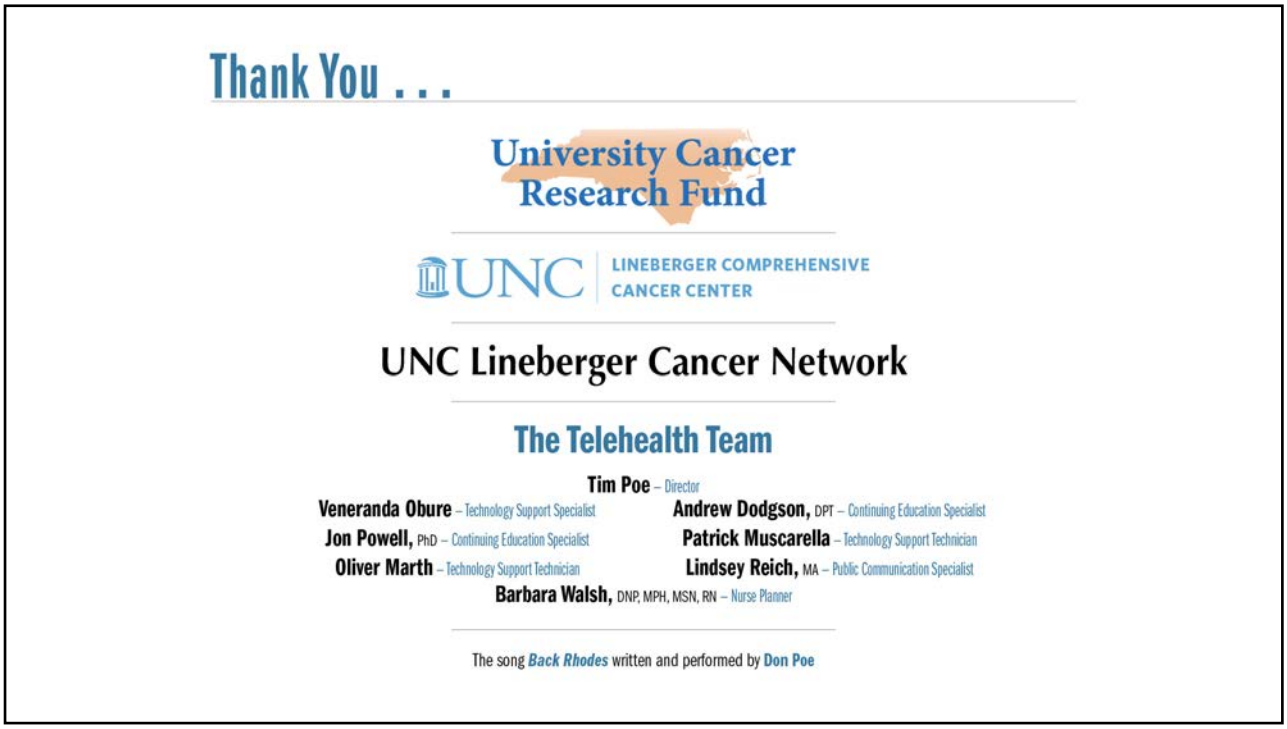
- Multiple lesions, family history, other stigmata consider genetic workup (eg. NF)
- Incidental, small, asymptomatic tumors:
  - Monitor with MRI and physical exam
  - Consider surgery, radiation versus observation
- Incidental tumors, larger with growth or symptoms:
  - surgical resection

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

94


Questions/Comments?
Nobody has responded yet.
Hang tight! Responses are coming in.
Start the presentation to see live content. For screen share software, share the entire screen. Get help at pollev.com/app

95


Thank You . . .
University Cancer Research Fund
UNC LINEBERGER COMPREHENSIVE CANCER CENTER
UNC Lineberger Cancer Network
The Telehealth Team
Tim Poe – Director
Veneranda Obure – Technology Support Specialist
Andrew Dodgson, DPT – Continuing Education Specialist
Jon Powell, PhD – Continuing Education Specialist
Patrick Muscarella – Technology Support Technician
Oliver Marth – Technology Support Technician
Lindsey Reich, MA – Public Communication Specialist
Barbara Walsh, DNP, MPH, MSN, RN – Nurse Planner
The song Back Rhodes written and performed by Don Poe

96

Upcoming Live Webinars

learn.unclcn.org

PATIENT CENTERED CARE — Live Webinar

February 14
12:00 PM

Cancer Screening in Primary Care
Noelle Robertson, MD, CAQSM

ADVANCED PRACTICE PROVIDER — Live Webinar

February 21
4:00 PM

Integrating Germline Pharmacogenomic Testing into Oncology Care
Amber Cipriani, PharmD, BCOP

RESEARCH TO PRACTICE — Live Webinar

February 28
12:00 PM

Immune (check point) Related Adverse Events
Frances Collichio, MD

97

Self-Paced, Online Courses

learn.unclcn.org/spoc

SOUTHEASTERN AMERICAN INDIAN CANCER HEALTH EQUITY PARTNERSHIP — Self-Paced, Online Course

Catawba Indian Nation & Levine Cancer Institute: Partners in Healing
Daniel R Carrizosa, MD, MS **Darcy Doege,** BSN, RN
Mellisa Wheeler, BSW, MHA

ADVANCED PRACTICE PROVIDER — Self-Paced, Online Course

Lung Cancer Screening Essentials
Jason Long, MD, MPH **Kim Shoenbill,** MD, PhD, MS
Michelle Ottersbach, MS, DNP, RN, CNL, CRCR

PATIENT CENTERED CARE — Self-Paced, Online Course

Role of Specialty Pharmacy
Sonali Acharya, PharmD

98

We Thank You for Participating Today!

UNC Lineberger Cancer Network

Ask to sign up for our monthly e-newsletter

Email: **unclcn@unc.edu**

Call: **(919) 445-1000**

Check us out at

unclcn.org *and* **learn.unclcn.org**

Look for us on these social media platforms

facebook.com/unclcn

unclinebergercancernetwork

linkedin.com/in/unclcn