UNC Lineberger Cancer Network

Presented on 1/24/24

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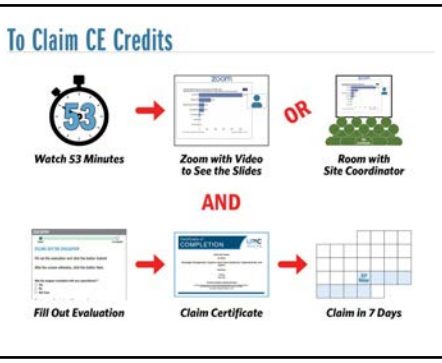

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Thank you for spreading the word!

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UNC Lineberger Cancer Network

Presented on 1/24/24

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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.

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Our Presenter

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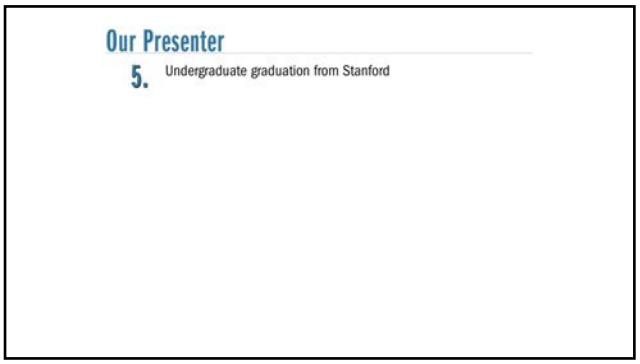
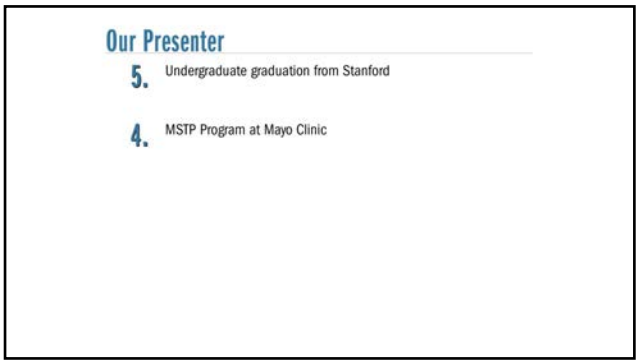

Our Presenter
5. Undergraduate graduation from Stanford

10


Our Presenter
5. Undergraduate graduation from Stanford
4. MSTP Program at Mayo Clinic

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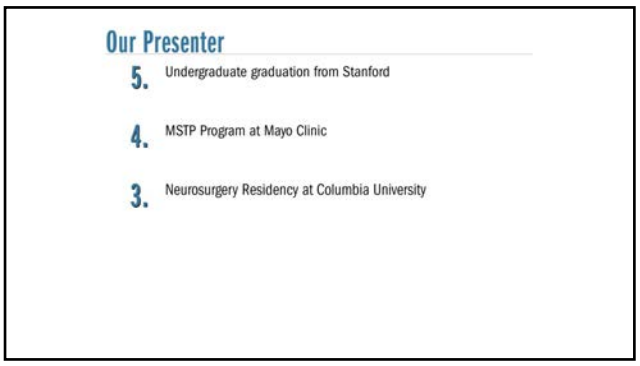
Our Presenter
5. Undergraduate graduation from Stanford
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3. Neurosurgery Residency at Columbia University

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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

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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.

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

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UNC LINEBERGER COMPREHENSIVE CANCER CENTER | UNC CANCER CARE

Primary Brain Tumors: Diagnosis and Management Strategies

Dominique Higgins MD, PhD
Department of Neurosurgery

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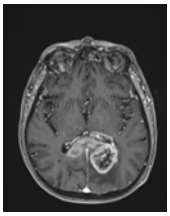
Overview

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



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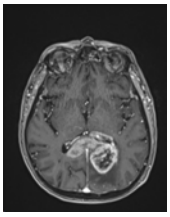
Learning Objectives

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



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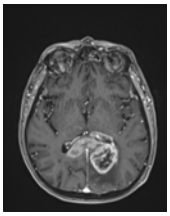
Classification of Brain Tumors

- 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



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Primary Intra-axial Tumors

- Gliomas
- Ependymomas
- Intraventricular tumors

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Gliomas

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

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Gliomas: Astrocytomas

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

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Glioblastoma

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

26

Imaging Modalities

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

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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

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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*

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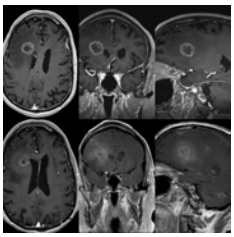
Operative Considerations – Stereotactic Robotic guided Biopsy +/- Laser Ablation



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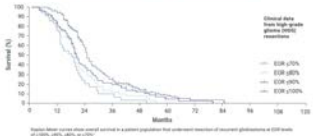
Intra-operative adjuncts

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



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

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Intra-operative adjuncts

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32

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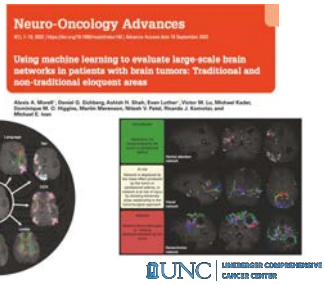

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Intra-operative adjuncts

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

Cesium-131 seeds
Half-life 9.7 days

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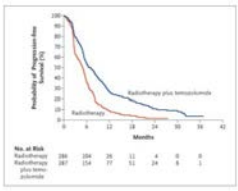
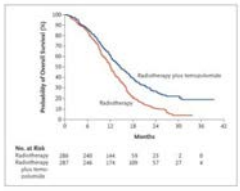
Glioblastoma

- 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

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

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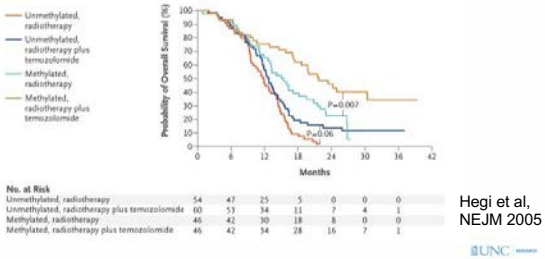
MGMT promoter methylation



Hegi et al, NEJM 2005

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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

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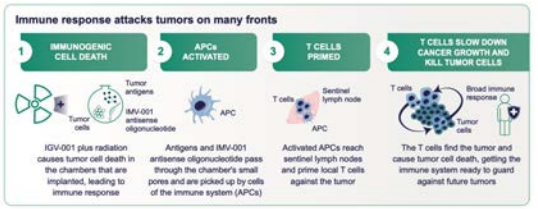
Glioblastoma Trials: Imvax – UNC currently enrolling



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[1], Samantha Garcia[4], Larry A. Harshyne[1], Lawrence Kenyon[3], 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]

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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)

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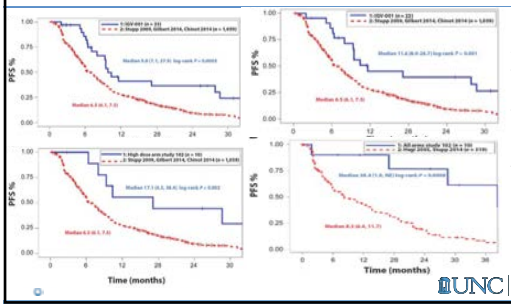
Imvax: IGV-001 Phase 1b



IGV treatment was associated with an increase in progression free survival

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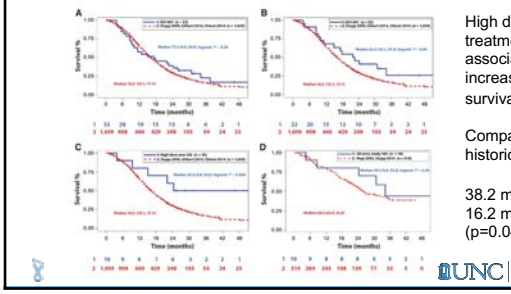
Imvax: IGV-001 Phase 1b



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)

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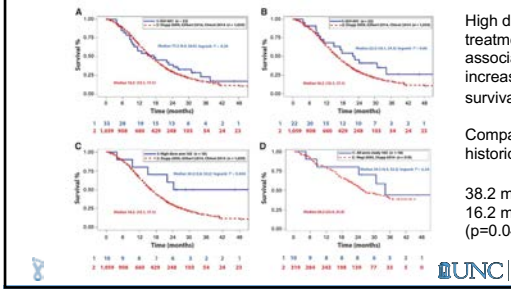
Imvax: IGV-001 Phase 1b



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38.2 months vs 16.2 months (p=0.044)

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Imvax: IGV-001 Phase 1b

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Glioblastoma Trials: Imvax Phase 2b multicenter study

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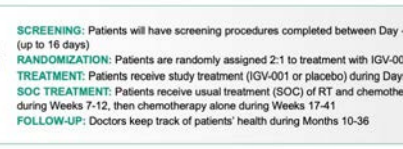
Glioblastoma Trials: Imvax – UNC currently enrolling



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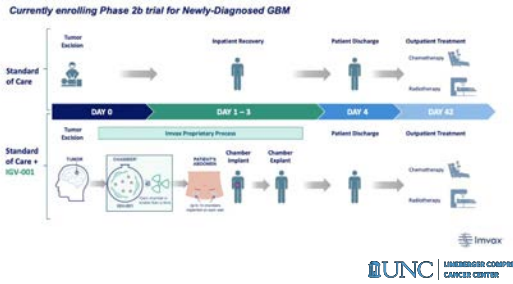
Glioblastoma Trials: Imvax – UNC currently enrolling



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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]

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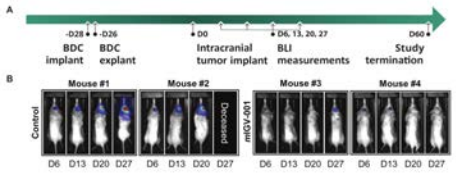
Glioblastoma Trials: Imvax immunogenic cell death



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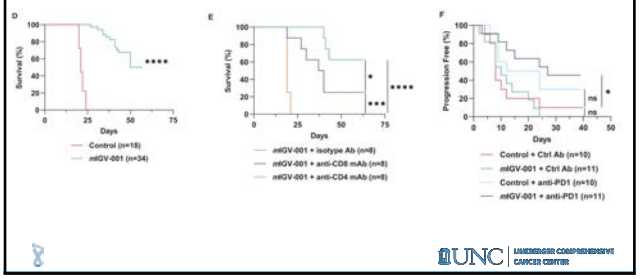
Glioblastoma Trials: Imvax immunogenic cell death



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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

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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

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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[k], J. Lee Villano[l], Nikolai Rainov[f], Uri Weinberg[g], David Schiff[h], Lara Kunschner[i], 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 Paleologos[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

Tumor Treating Fields (TTF)

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

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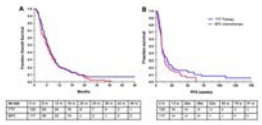


Prior smaller single arm studies showed promise

237 recurrent GBM patients, TTF vs chemotherapy

No difference in overall survival, but promising subanalyses

Stupp et al., 2012

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

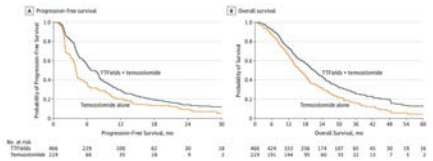
Comparison of TTF/TMZ vs TMZ alone (2009)

Interim analysis in 2015 (210 patients)

Final results in 2017 (695 patients)

Stupp et al., 2012

Tumor Treating Fields (TTF)



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

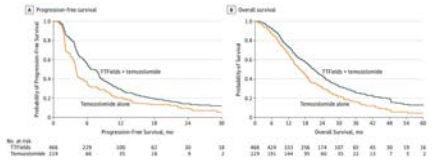
Overall survival: 20.9 months (TTF+TMZ) vs 16.0 months (TMZ)

Stupp et al., 2012

Now FDA approved for treatment

58

Tumor Treating Fields (TTF)



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

Stupp et al., 2012

Now FDA approved for treatment

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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

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Glioblastoma

- Clinical Trials provide promise of increasing survival
- Newly diagnosed GBM
  - Imvax IGV-001
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  - Focused ultrasound

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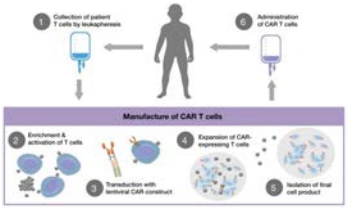
Chimeric Antigen Receptor T-cell (CAR-T) Therapy

- 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

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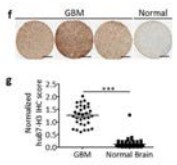
Chimeric Antigen Receptor T-cell (CAR-T) Therapy

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

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



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

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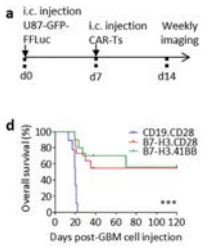
Chimeric Antigen Receptor T-cell (CAR-T) Therapy



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

Ebiomedicine, 2019

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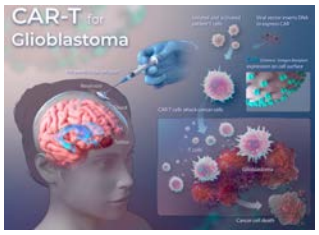
UNC Clinical Trial: B7-H3 CAR-T Therapy for Recurrent GBM

- 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



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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

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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

Lancet Oncology, 2022

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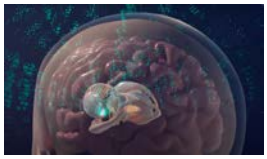
Focused Ultrasound

- 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

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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 [5], 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

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Gliomas: Astrocytomas

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

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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

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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

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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

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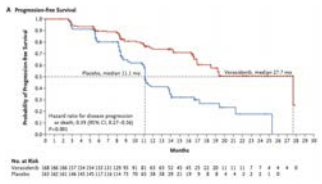
IDH-mutant astrocytomas: Novel treatments



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

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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

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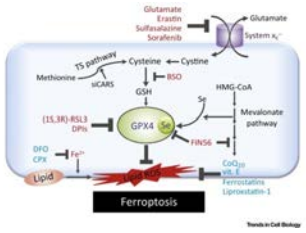
Ferroptosis

Regulated Cell Death

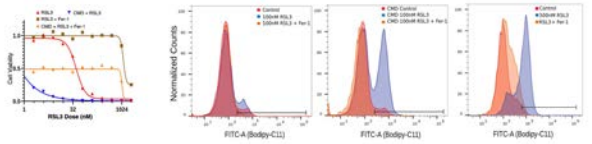
Apoptosis Necroptosis **Ferroptosis**

-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

Phase I study examining CMD in GBM patients

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

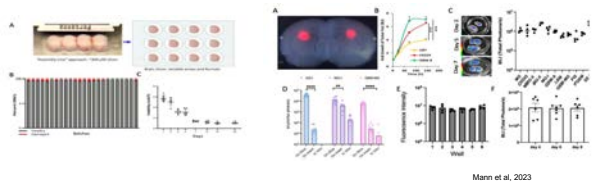
Preoperative MRI and MR spectroscopy on the day of surgery

Metabolic analysis of tissue with matching serum

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

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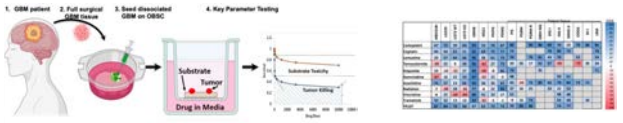
Glioblastoma Trials: Organotypic Brain Slice Culture



Mann et al, 2023

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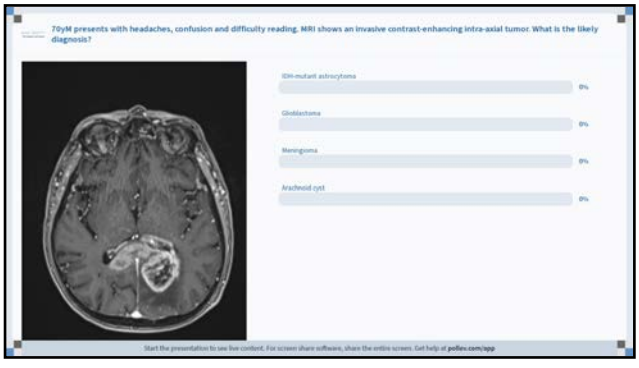

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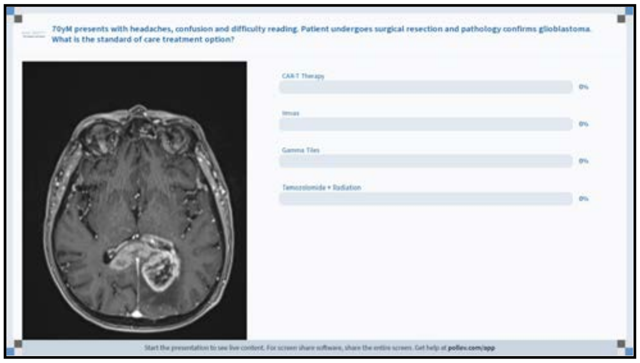

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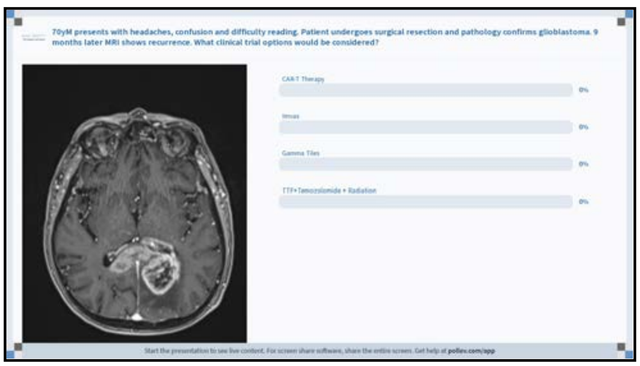

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Thank you!

Dominique Higgins

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

85

Primary Extra-axial Tumors

- Meningiomas
- Schwannomas/Neurofibromas
- Pituitary tumors

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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

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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

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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

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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

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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

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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

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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)

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

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Questions/Comments?

Nobody has responded yet.

Hang tight! Responses are coming in.

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Thank You . . .

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The song *Back Rhodes* written and performed by Don Poe

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Amber Cipriani, PharmD, BCOP
RESEARCH TO PRACTICE
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Frances Collichio, MD

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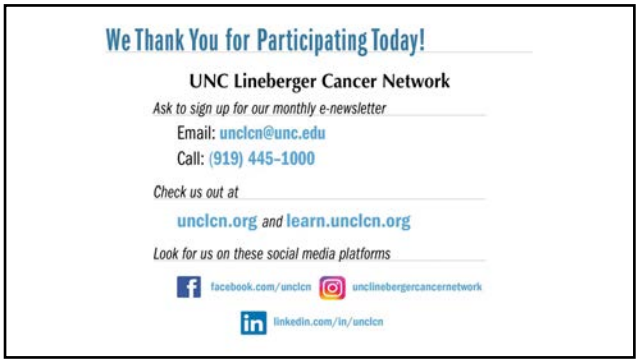
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