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Advances in the Treatment of CNS Malignancies

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Learning Objectives and Disclosures

Disclosures

- None

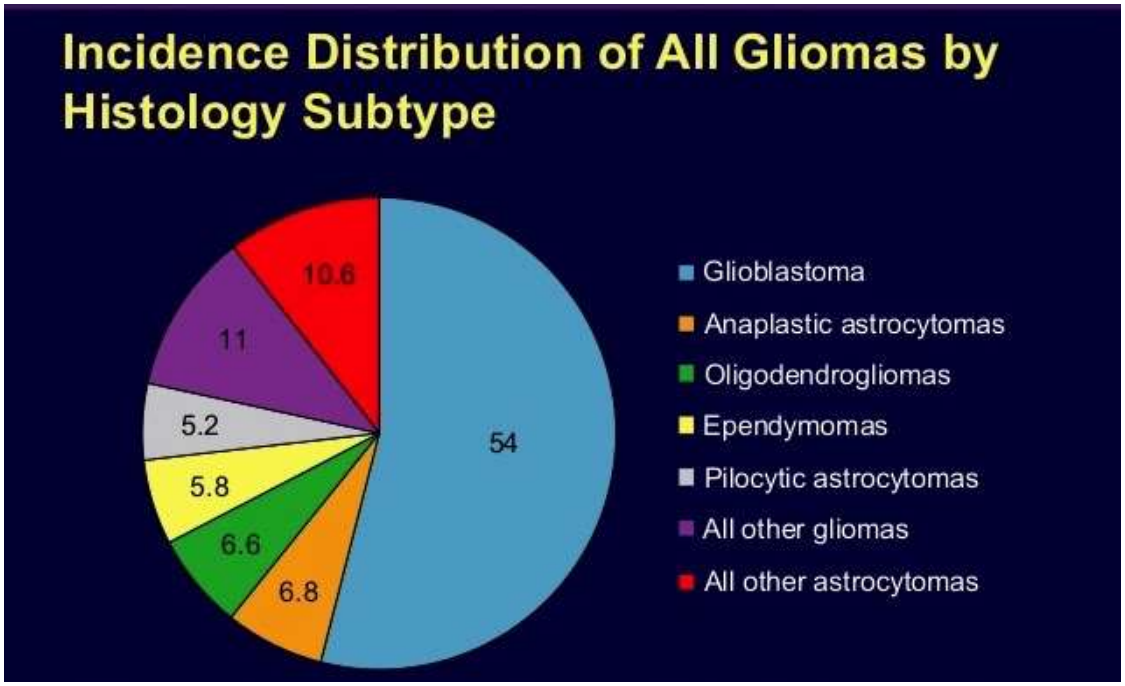
Objectives

1) Review the current standard of care for glioblastoma

2) Review results of recent clinical trials for high-grade gliomas

3) Identify emerging strategies for treatment of gliomas

Primary CNS Malignancies



Incidence of CNS tumors in US adults = 27 / 100,000 (~ 75,000 annual cases)*

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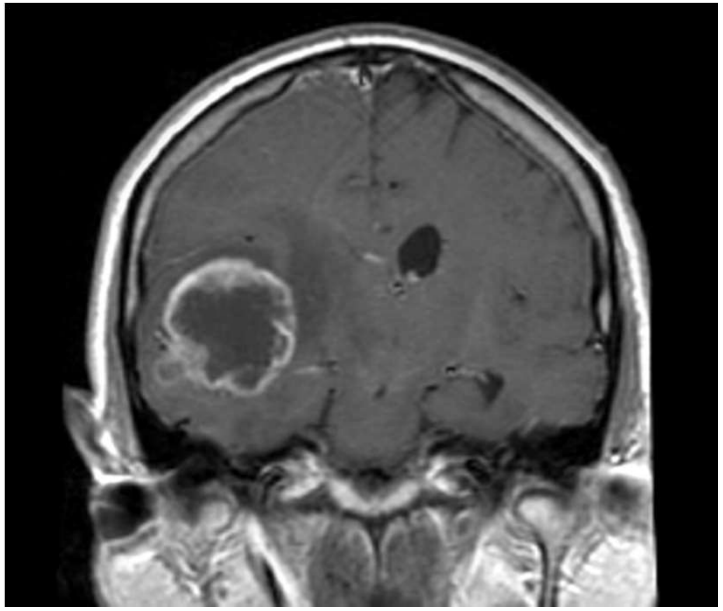
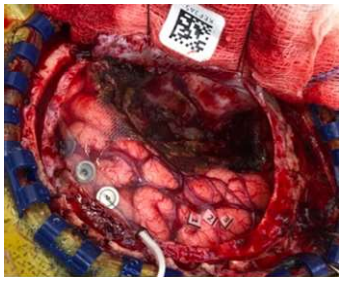
** CBTRUS 2007-2011*

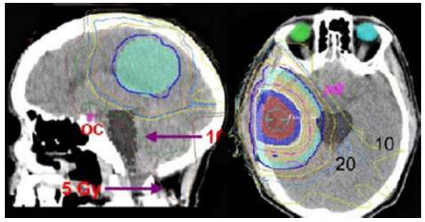
Glioblastoma (GBM)



Standard of Care:



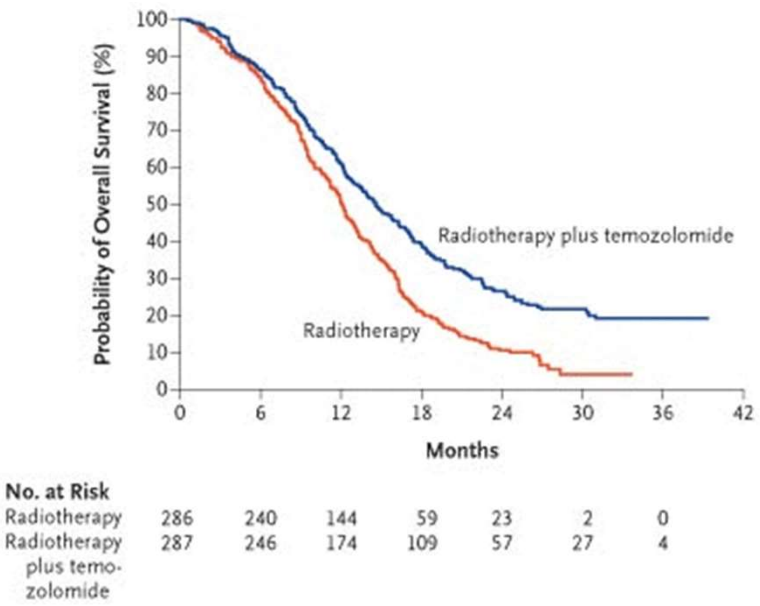
- Maximal Safe Resection



- Fractionated Radiotherapy

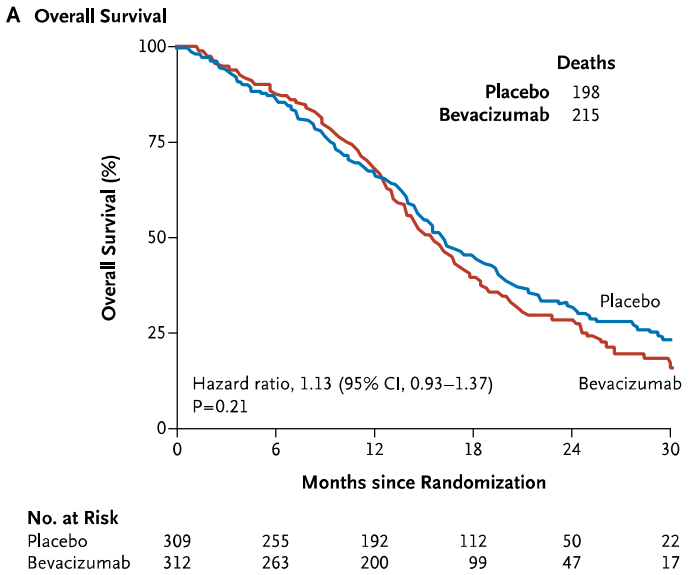
- Temozolomide Chemotherapy

GBM Survival Over The Last Two Decades



Stupp, *NEJM* 2005

Median Survival: 14.6 months



Gilbert, *NEJM* 2014

Median Survival: 16.1 months

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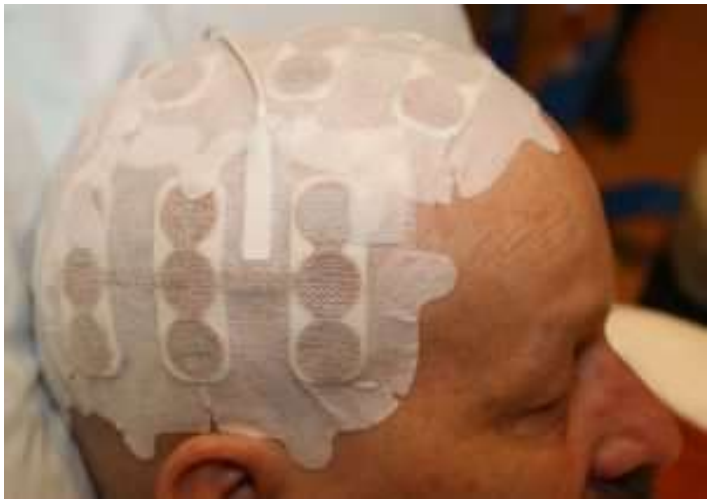
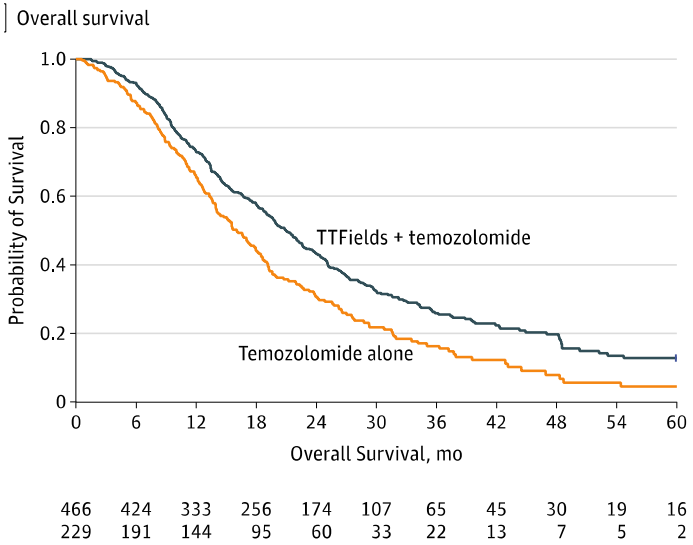
Tumor Treatment Fields for GBM

Optune:
Alternating Tumor Treatment Fields (TTF)





Stupp, *JAMA* 2017

Median Survival TMZ + TTF: 20.9 months

Median Survival TMZ Alone: 16 months

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The Role of Surgery For GBM

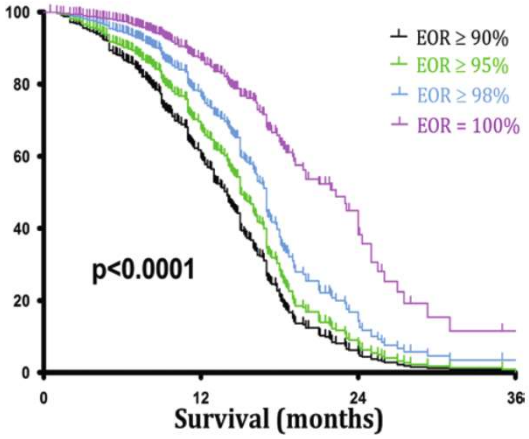
An extent of resection threshold for newly diagnosed glioblastomas

Clinical article

NADER SANAI, M.D.,[1] MEI-YIN POLLEY, PH.D.,[2] MICHAEL W. MCDERMOTT, M.D.,[1] ANDREW T. PARSA, M.D., PH.D.,[1] AND MITCHEL S. BERGER, M.D.[1]

[1]*Brain Tumor Research Center, and* [2]*Division of Biostatistics, Department of Neurological Surgery, University of California, San Francisco, California*

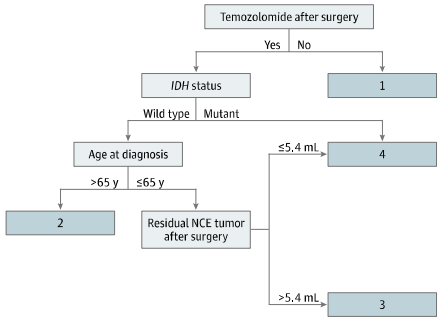
Sanai N, *J Neurosurg* (2011) 115:3-8

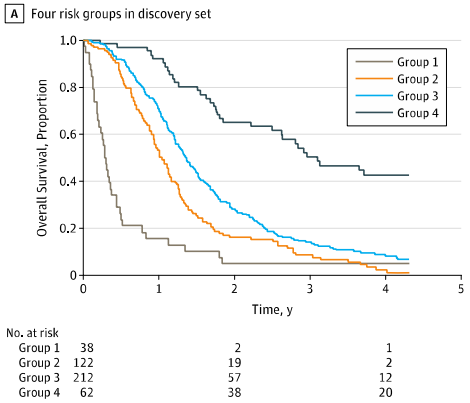


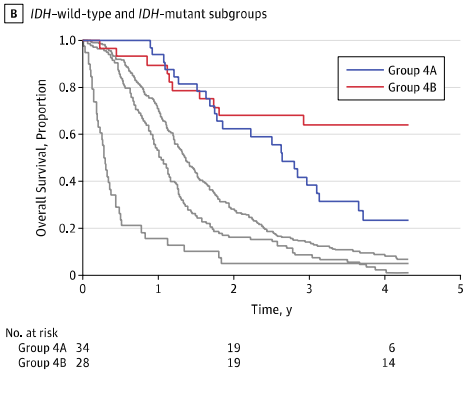
JAMA Oncology | Original Investigation

Association of Maximal Extent of Resection of Contrast-Enhanced and Non–Contrast-Enhanced Tumor With Survival Within Molecular Subgroups of Patients With Newly Diagnosed Glioblastoma

Molinaro AM, *JAMA Oncol* (2020) 6(4):496-503







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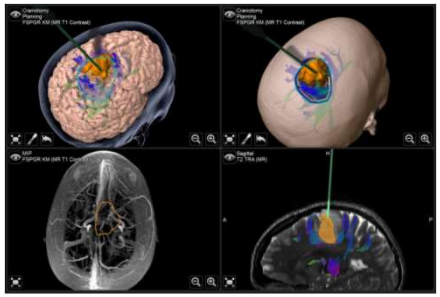
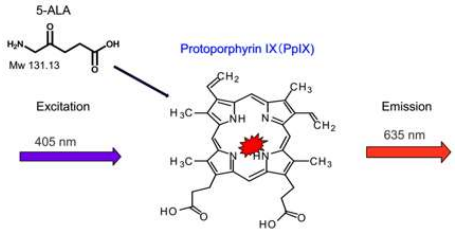
Surgical Advancements

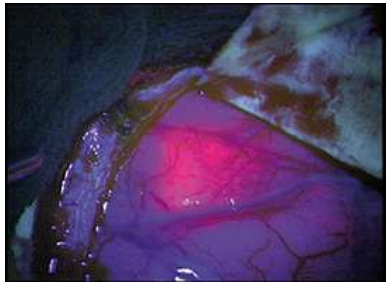
Image Guidance



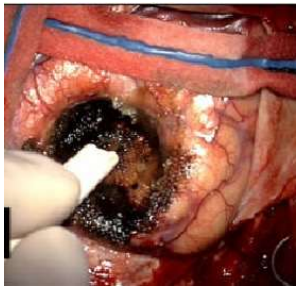
Intraoperative MRI

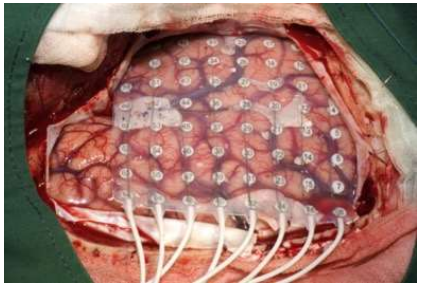
Tumor Fluorescent Dyes





Cortical Stimulation





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Immune Checkpoint Inhibition For GBM

Bristol-Myers Squibb

Press Release

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Bristol-Myers Squibb Announces Results from CheckMate -143, a Phase 3 Study of Opdivo (nivolumab) in Patients with Glioblastoma Multiforme

MONDAY, APRIL 3, [illegible] 8:47 AM EDT

FAIL

Bristol-Myers Squibb

Press Release

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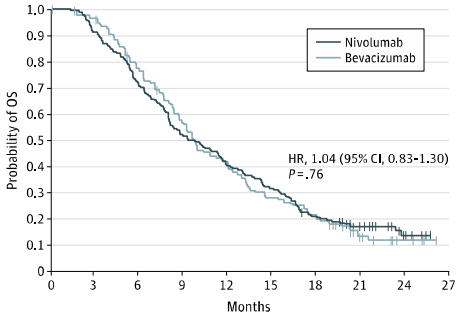
Bristol-Myers Squibb Announces Phase 3 CheckMate -498 Study Did Not Meet Primary Endpoint of Overall Survival with Opdivo (nivolumab) Plus Radiation in Patients with Newly Diagnosed MGMT-Unmethylated Glioblastoma Multiforme

CATEGORY: CORPORATE/FINANCIAL NEWS

THURSDAY, MAY 9, 2019 6:59 AM EDT

A Probability of OS by intervention

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

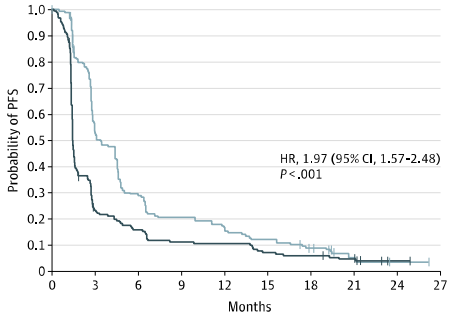


No. at risk

Nivolumab	184	168	133	96	77	59	39	24	9	0
Bevacizumab	185	169	135	99	72	48	37	14	5	0

B Probability of progression-free survival

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



No. at risk

Nivolumab	184	41	27	19	18	12	10	7	1	0
Bevacizumab	185	88	46	32	27	19	12	3	1	0

Reardon, *JAMA Oncology* 2020

On-Going

NRG BN007: Randomized Phase II/III Study of Ipilimumab and Nivolumab Versus Temozolomide for Newly Diagnosed MGMT Unmethylated GBM

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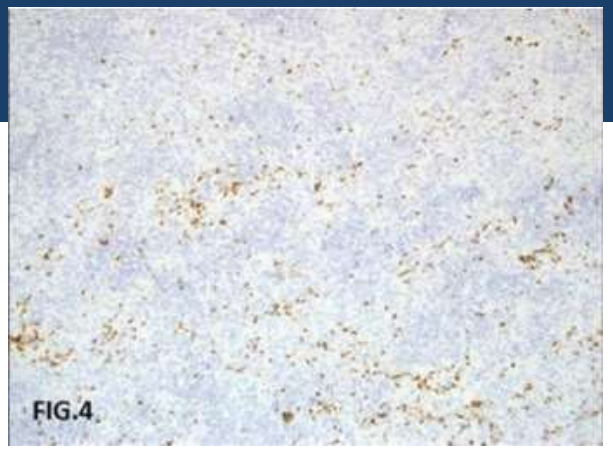
How Does GBM Differ From Other Tumors?

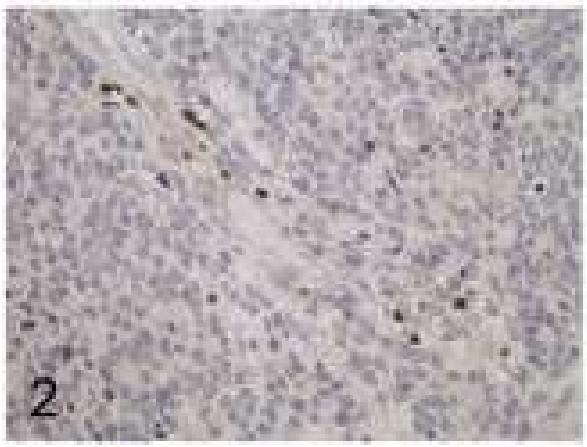
Immunotherapy Responsive CA	Glioblastoma
• Hematogenous/LN metastasis	• No extracranial metastasis
• Autoimmunization	• No direct LN drainage
• DC/Macrophage rich tissues	• Alternative antigen presentation
• High somatic mutation burden	• Low somatic mutation burden
• Driver mutations, homogenous	• Highly heterogenous tumor

Tumor Induced Immunosuppression

CD_3 Staining



Melanoma



GBM

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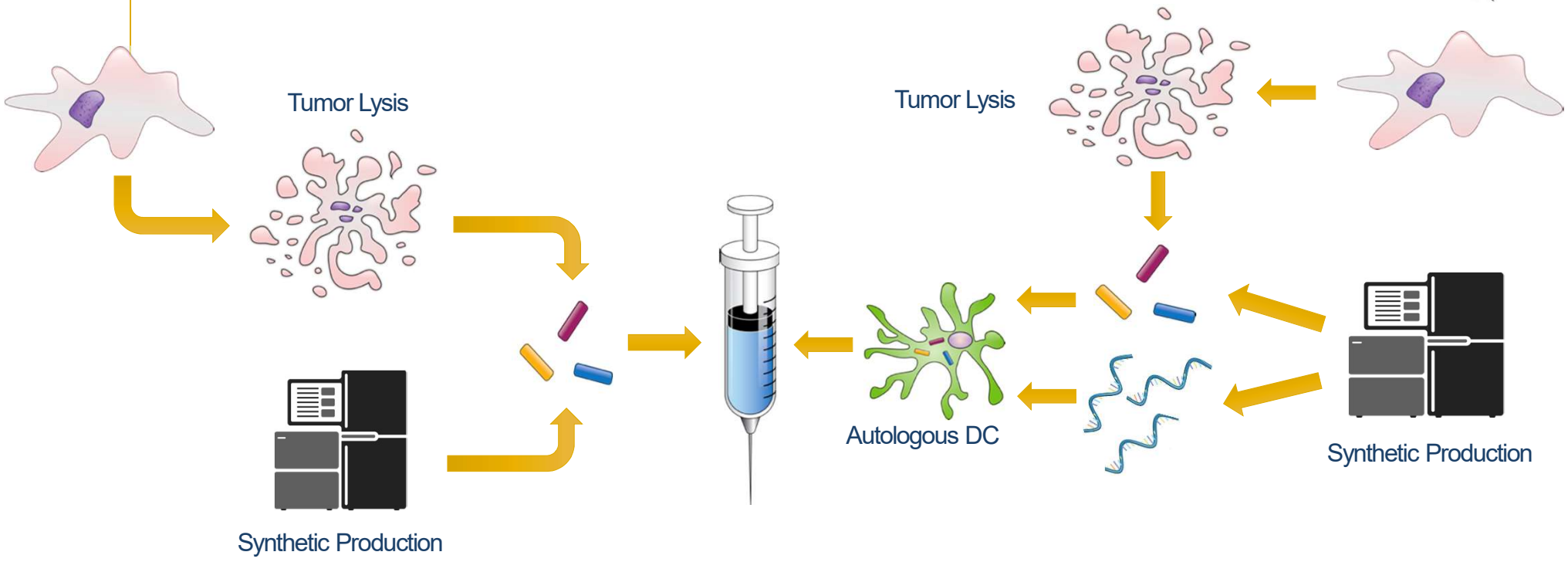
Immunosuppression in Glioblastoma

- Expression of Immune Checkpoints (Berghoff, *Neuro Oncol* 17(8):1064-75, 2015)
- Expansion of Suppressive Myeloid Cells (Chae, *Neuro Oncol* 17(7):978-91, 2015)
- Expansion of Regulatory T Cells (Fecci, *Cancer Res* 66(6):3294-302, 2006; Heimberger *Clin Cancer Res* 14(16):5166-72, 2008)
- Sequestration of $CD4^+$ Effectors (Chongsathidkiet, *Nat Med* 24(9):1459-68, 2018)
- Exhaustion of $CD8^+$ Effectors (Mohme, *Clin Cancer Res*, 24(17):4187-200, 2018)

- Immune Fingerprint is Correlated To Overall Survival (Alban, *JCI Insight* 3(21), 2018)

Anti-Tumor Vaccination



Some Active GBM Vaccine Trials

Peptide Vaccines

NCT02864368: Peptide Targets for Glioblastoma Against Novel Cytomegalovirus Antigens (PERFORMANCE).

NCT02455557: A Phase II Study of the Safety and Efficacy of SVN53-67/M57-KLH (SurVaxM) in Survivin-Positive Newly Diagnosed Glioblastoma.

NCT03149003: A Randomized, Multicenter, Phase 2 Study of DSP-7888 Dosing Emulsion in Combination With Bevacizumab Versus Bevacizumab Alone in Patients With Recurrent or Progressive Glioblastoma Following Initial Therapy. (WT1 peptide vaccine)

NCT02718443: Phase I Pilot Study in Patients With Operable Recurrent of Glioblastoma to Examine Safety, Tolerability, Immune, and Biomarker Response to the Investigational VEGFR-2 DNA Vaccine VXM01.

DC Vaccines

NCT02366728: Evaluation of Overcoming Limited Migration and Enhancing Cytomegalovirus-specific Dendritic Cell Vaccines With Adjuvant Tetanus Pre-conditioning in Patients With Newly-diagnosed Glioblastoma.

NCT02465268: A Phase II Randomized, Blinded, and Placebo-controlled Trial of CMV RNA-Pulsed Dendritic Cells With Tetanus-Diphtheria Toxoid Vaccine in Patients With Newly-Diagnosed Glioblastoma (ATTAC-II).

NCT02649582: Adjuvant Dendritic-Cell Immunotherapy Plus Temozolomide Following Surgery and Chemoradiation in Patients With Newly Diagnosed Glioblastoma (ADDIT-GLIO).

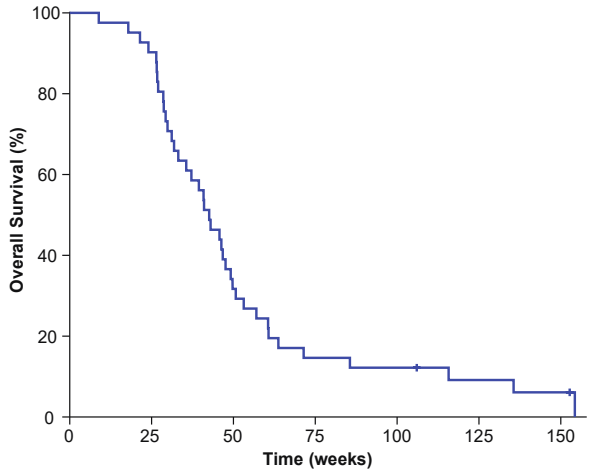
NCT01808820: Dendritic Cell (DC) Vaccine for Malignant Glioma and Glioblastoma.

NCT03400917: Autologous Dendritic Cells Loaded with Autologous Tumor Associated Antigens for Treatment of Newly Diagnosed Glioblastoma.

Phase II Single Arm Studies of HSPPC-96 For GBM

Recurrent GBM, N=41 patients

(Bloch O, *Neuro-Oncology* 16(2):274-79, 2014)



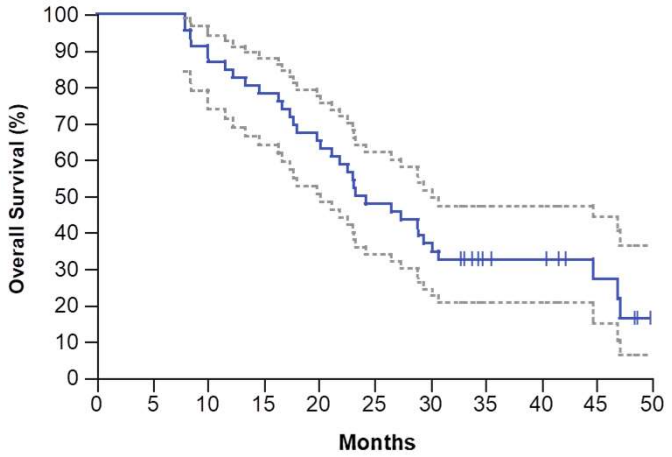
mOS = 42.6 weeks (95% CI, 34.7 – 50.5)

Phase II Results of Bevacizumab at Recurrence

- Bev alone (Friedman, *JCO* 2009): mOS - **36.8 wks**
- Bev + CPT-11 (Friedman, *JCO* 2009): mOS - **34.8 wks**

Newly Diagnosed GBM, N=46

(Bloch O, *Clin Cancer Res* 23(14):3575-84, 2017)



mOS = 23.8 months (95% CI, 19.8 – 30.2)

Phase III Results for Newly Diagnosed GBM

- RTOG 0825 (Gilbert, *NEJM 2014*): Placebo mOS – **16.1 mos**
- AVAGlio (Chinot, NEJM 2014): Placebo mOS – **16.7 mos**

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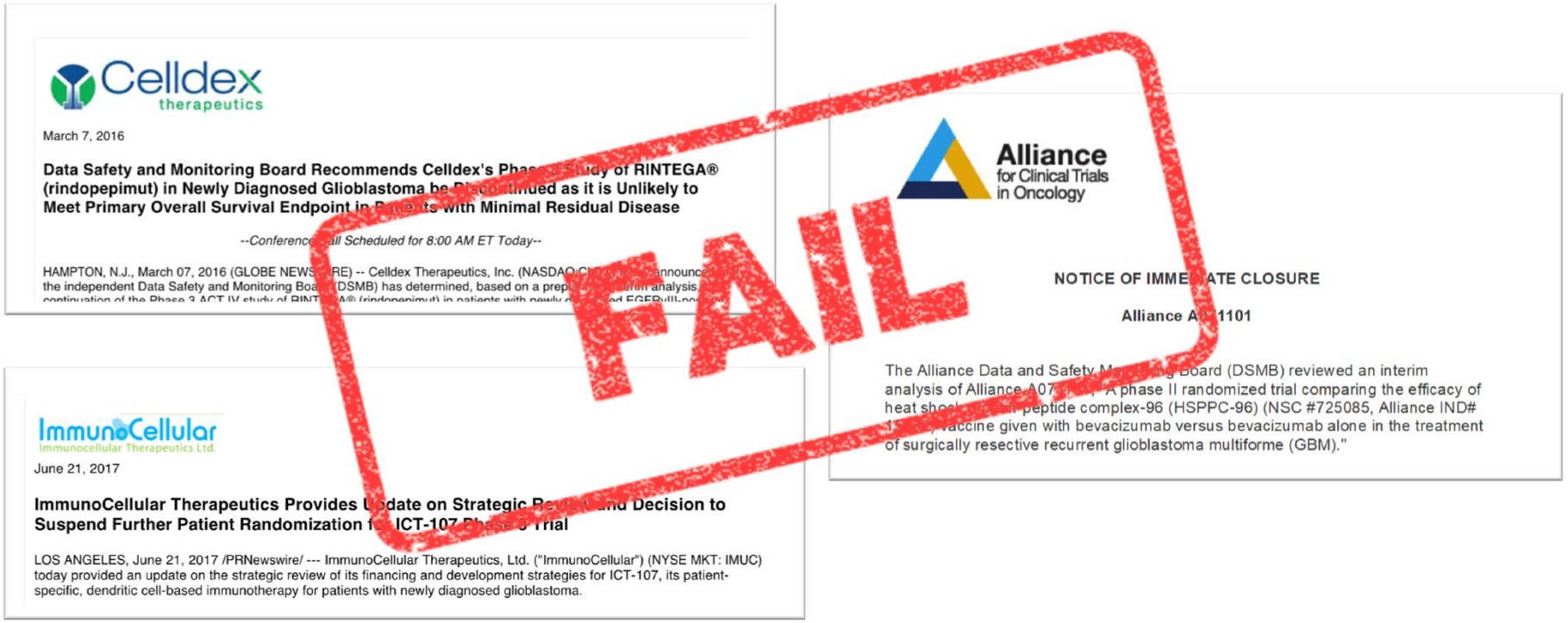
No grade 3 or 4 adverse events attributable to vaccine identified in any patient

Phase II/III Vaccine Studies for GBM



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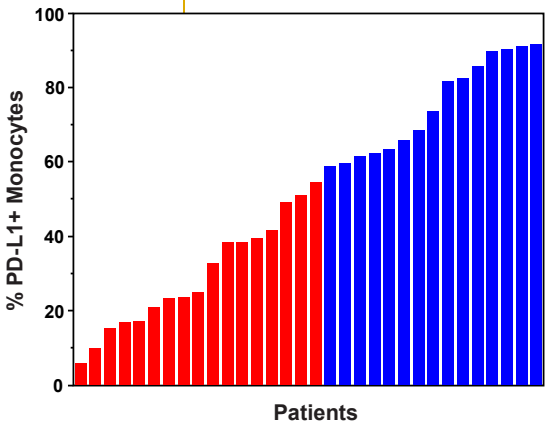
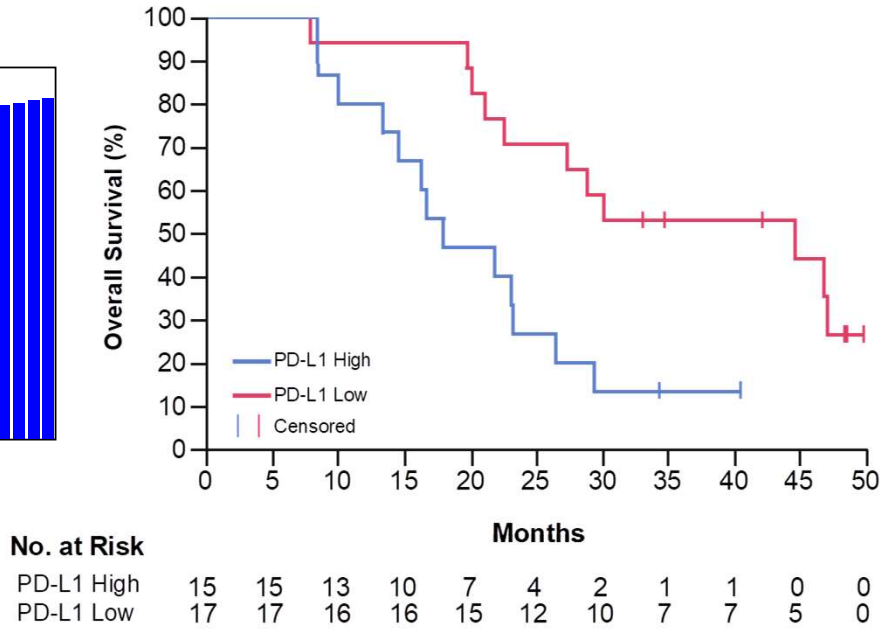
Impact of PD-L1 Expression on Survival After Vaccination





	Median OS	HR (95% CI)	p value
PD-L1 High	18.0 months	3.3 (1.4 – 8.6)	0.007
PD-L1 Low	44.7 months	reference	

Variable	Hazard Ratio (95% CI)	p value
Age (per yr)	1.06 (0.99 – 1.13)	0.08
MGMT		
methylated	reference	
unmethylated	6.3 (2.1 – 22.0)	<0.001
PD-L1		
low	reference	
high	4.0 (1.4 – 12.7)	0.008
KPS		
90-100	reference	
70-80	5.1 (1.5 – 18.0)	0.009
No. vaccinations	0.97 (0.86 – 1.08)	0.61

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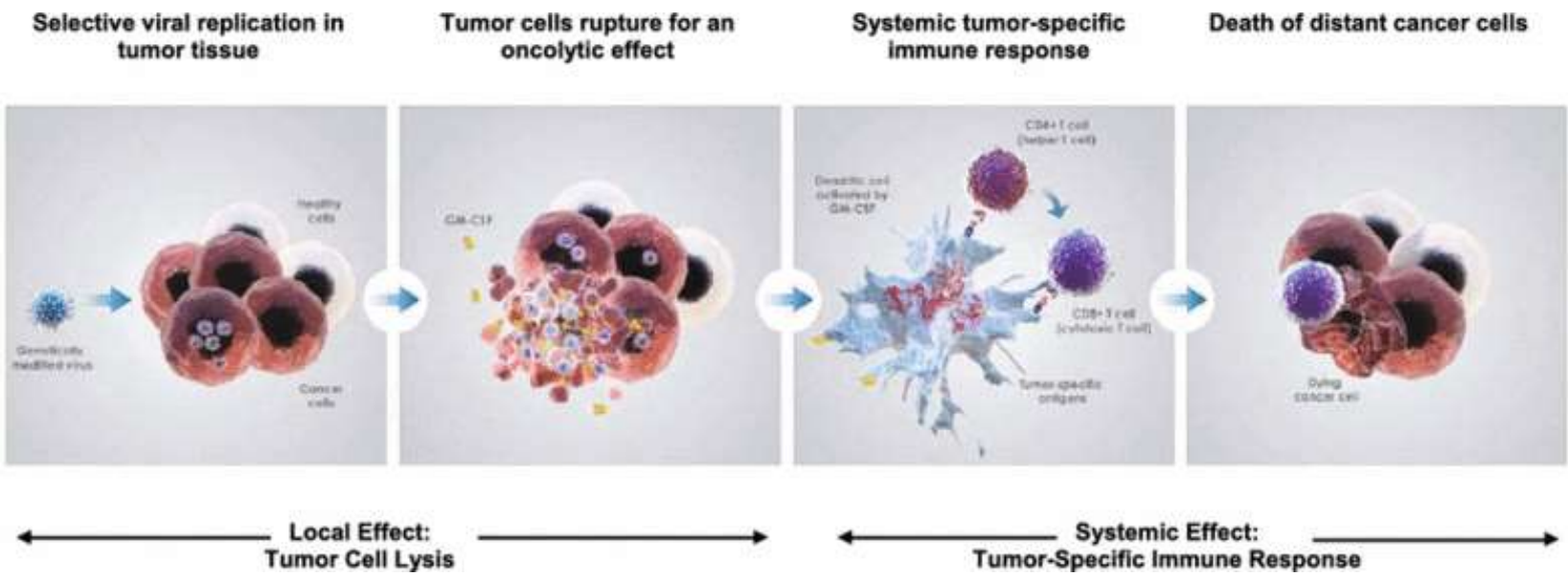
Bloch, *Clin Cancer Res* 23(14):3575-84, 2017

Combination of ICI and Vaccines

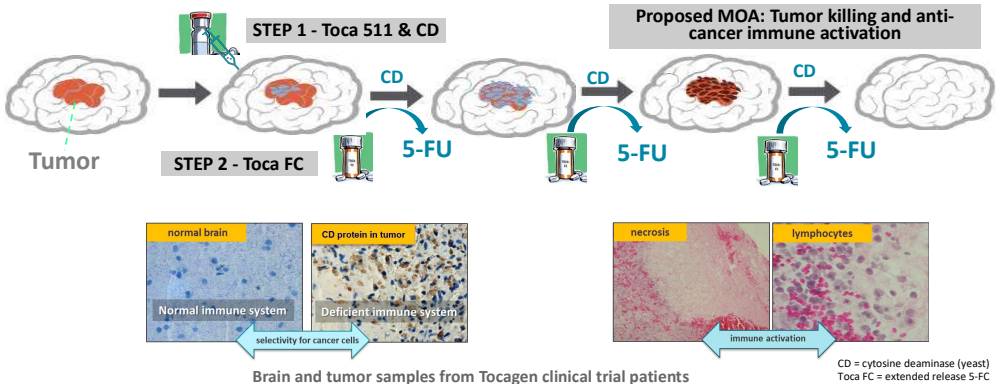
- NCT03018288: Radiation Therapy Plus Temozolomide and Pembrolizumab With and Without HSPPC-96 in Newly Diagnosed Glioblastoma (Phase II)
- NCT03665545: Pembrolizumab in Association with IMA950/Poly-ICLC for Relapsing Glioblastoma (Phase I/II)
- NCT02287428: Personalized NeoAntigen Cancer Vaccine with RT Plus Pembrolizumab for Patients with MGMT Unmethylated, Newly Diagnosed GBM (Phase I)
- NCT04201873: Pembrolizumab and a Vaccine (ATL-DC) for the Treatment of Surgically Acessible Recurrent Glioblastoma (Phase I)
- NCT03750071: VXM01 Plus Avelumab Combination Study in Progressive Glioblastoma (Phase I/II)

Oncolytic Viral Therapy



Oncolytic Virus Trials

- PSVRIPO: Poliovirus for Recurrent GBM (Phase I/II)
- Toca 511: Adenovirus + Toca-FU for Recurrent GBM (Phase III)



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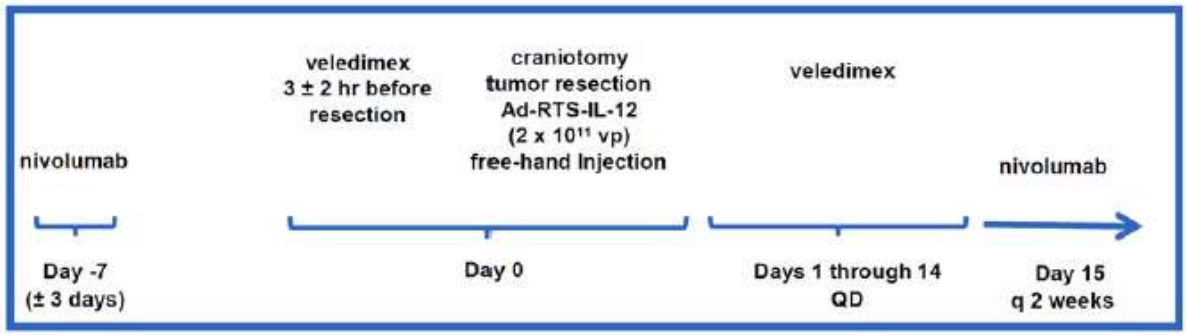
Oncolytic Virus Trials -Combination with Immune Checkpoint Inhibitors

DNX-2401(CAPTIVE): Adenovirus + Pembrolizumab for Recurrent GBM (Phase II)

Ad-RTS-hIL12: Adenovirus + Veledimex + Nivolumab for Recurrent GBM (Phase II)



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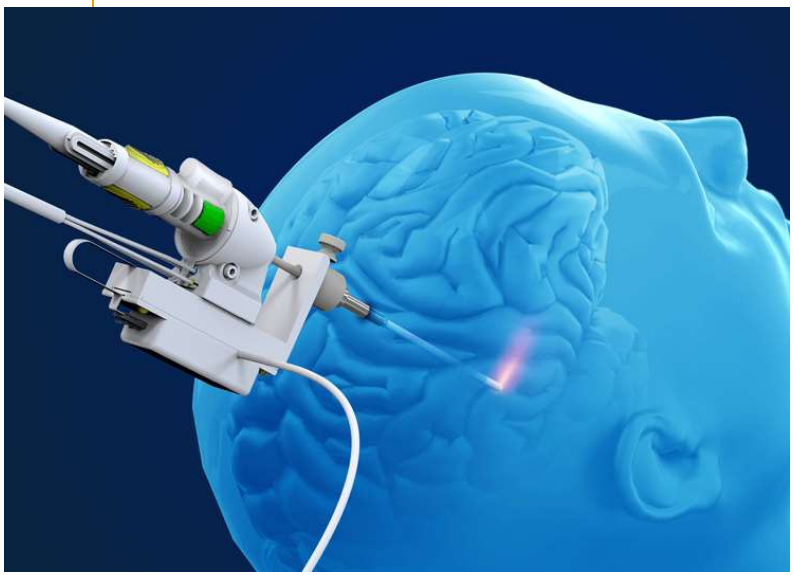
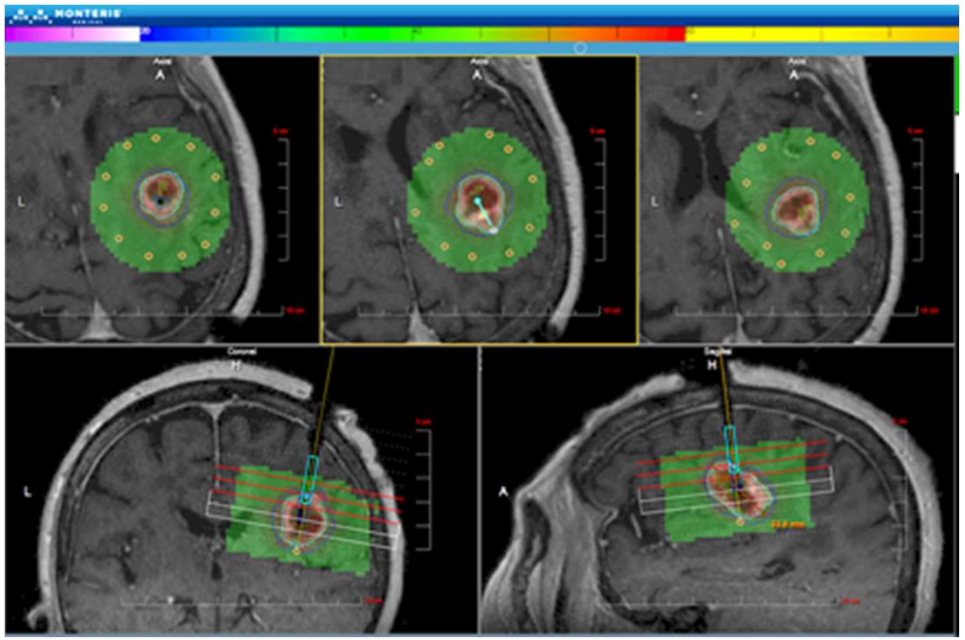
New Technologies

Surgical Advancements in Glioblastoma

- Reduce morbidity (improve quality of life)
- Attain more complete cytoreduction
- Enhance the impact of adjuvant therapy
  - BBB penetration
  - Immune activation

Laser Interstitial Thermal Therapy (LITT)





Safety of LITT

RESEARCH—HUMAN—CLINICAL STUDIES

The Role of Laser Interstitial Thermal Therapy in Surgical Neuro-Oncology: Series of 100 Consecutive Patients

Ashish H. Shah, MD
Alexa Semonche, BA
Daniel G. Eichberg, MD
Veronica Borowy, BS
Evan Luther, MD
Christopher A. Sarkiss, MD
Alexis Morell, MD
Anil K. Mahavadi, BS
Michael E. Ivan, MD, MBS
Ricardo J. Komotar, MD

BACKGROUND: Laser interstitial thermal therapy (LITT) is an adjuvant treatment for intracranial lesions that are treatment refractory or in deep or eloquent brain. Initial studies of LITT in surgical neuro-oncology are limited in size and follow-up.
OBJECTIVE: To present our series of LITT in surgical neuro-oncology to better evaluate procedural safety and outcomes.
METHODS: An exploratory cohort study of all patients receiving LITT for brain tumors by a single senior neurosurgeon at a single center between 2013 and 2018. Primary outcomes included extent of ablation (EOA), time to recurrence (TTR), local control at 1-yr follow-up, and overall survival (OS). Secondary outcomes included complication rate. Outcomes were compared by tumor subtype. Predictors of outcomes were identified.
RESULTS: A total of 91 patients underwent 100 LITT procedures; 61% remain alive with 72% local control at median 7.2 mo follow-up. Median TTR and OS were 31.9 and 16.9 mo,

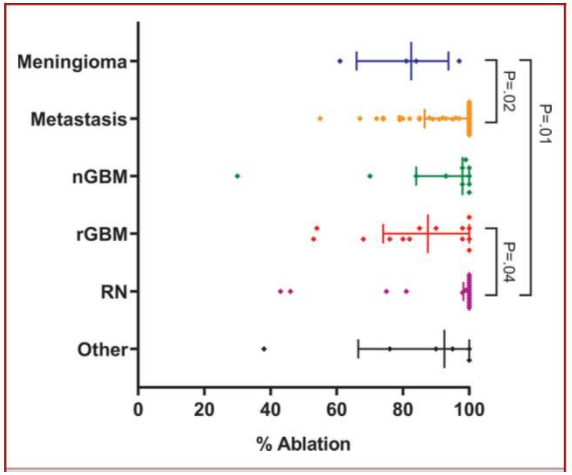
TABLE 1. Baseline Characteristics for 100 LITT Patients by Lesion Subtype

Lesion subtype	# Patients	# Cases	Mean age (years), (range)	Female sex (n, %)	Mean pre-op KPS	Mean post-op KPS	Median preoperative lesion size (cm^3), (range)
Meningioma	4	4	70 (65-82)	2, 50.0%	96	96	18.4 (10.6-78.1)
Metastasis	36	45	60 (27-75)	30, 83.0%	88	90	4.3 (0.6-28.0)
nGBM	11	11	59 (40-71)	4, 36.0%	89	90	6.8 (1.2-127.0)
rGBM	14	14	54 (29-73)	7, 50.0%	91	90	3.8 (0.5-15.8)
RN	20	20	60 (46-83)	17, 85.0%	88	91	5.9 (0.9-31.7)
Other	6	6	34 (18-49)	2, 33.3%	90	92	4.7 (0.8-23.2)
LGG	3	3	35 (25-49)	1, 33.3%	–	–	–
Pilocytic astrocytoma	1	1	35	–	–	–	–
Sarcoma	1	1	47	–	–	–	–
SEGA	1	1	18	–	–	–	–

TABLE 3. Clinical Outcomes by Subtype of Lesion Treated with LITT

Lesion subtype	Median EOA (%), (IQR)	Median length of follow-up (months), (IQR)	Recurrence, n (%)	Median time-to-recurrence (months)	Percentage local control at 1-yr follow-up	Median OS (months)	Death, n (%)	Complications (n), description
Meningioma*	82.5 (76.0-87.3)	14.8 (9.5-20.1)	1 (25.0%)	N/A	75.0	20.7	1 (25%)	1, transient
Metastasis	100.0 (88.0-100.0)	7.6 (3.4-17.2)	9 (20.0%)	55.9	77.4	16.9	17 (47%	2, post-op seizure, wound infection
nGBM	98.0 (88.5-100.0)	5.6 (1.8-25.4)	3 (27.3%)	31.9	83.3	32.3	5 (46%	–
rGBM	87.5 (77.0-99.5)	7.3 (5.6-13.5)	9 (64.3%)	5.6	24.3	7.3	12 (86%	1, wound infection
RN	100.0 (98.8-100.0)	4.4 (1.3-11.6)	5 (25.0%)	N/A	67.2	16.4	4 (30%	
Other	92.5 (79.5-98.8)	5.4 (4.0-19.7)	2 (33.3%)	12.3	80.0	24.4	0 (0%)	–

Total Complications: 3/100 (3%)



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Shah AH, *Neurosurgery*, August 2019

Efficacy of LITT for Recurrent Metastases

RESEARCH—HUMAN—CLINICAL STUDIES

Magnetic Resonance-Guided Laser Ablation Improves Local Control for Postradiosurgery Recurrence and/or Radiation Necrosis

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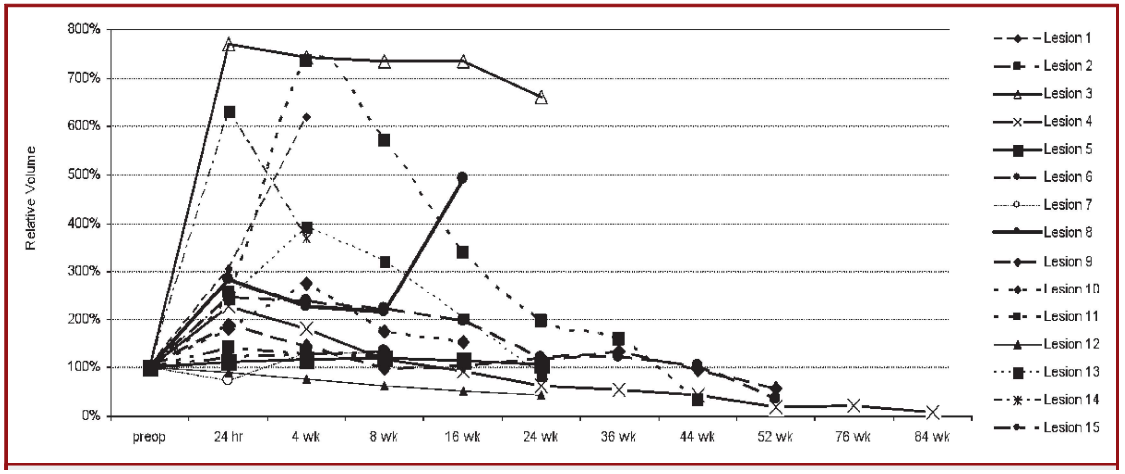
BACKGROUND: Enhancing lesions that progress after stereotactic radiosurgery are often tumor recurrence or radiation necrosis. Magnetic resonance-guided laser-induced thermal therapy (LITT) is currently being explored for minimally invasive treatment of intracranial neoplasms.
OBJECTIVE: To report the largest series to date of local control with LITT for the treatment of recurrent enhancing lesions after stereotactic radiosurgery for brain metastases.

TABLE 1. Patient Characteristics[a]

Patient	Age, y	Sex	Cancer Diagnosis[b]	Lesion Location	Prior SRS	Prior WBRT
1	72	F	NSCLC	Frontal lobe	18 Gy to 80% IDL	No
2	56	F	NSCLC	Cerebellum	27 Gy in 3 fractions	No
3	82	M	NSCLC	Frontal lobe	16 Gy to 80%	No
4	46	F	IDC	Cerebellum	20 Gy to 50% IDL	Yes
5	55	F	NSCLC	Cerebellar peduncle	20 Gy to 70% IDL	Yes
6[c]	70	M	NSCLC	Frontal lobe	20 Gy to 50% IDL	Yes
			NSCLC	Parietal lobe	18 Gy to 60% IDL	Yes
7	64	F	NSCLC	Frontal lobe	18 Gy to 50% IDL	No
8	72	F	IDC	Cerebellum	20 Gy to 80% IDL	Yes
9	73	F	NSCLC	Cerebellum	20 Gy to 45% IDL	No
10	74	M	NSCLC	Frontal lobe	18 Gy to 70% IDL	No
11	65	M	NSCLC	Temporal lobe	20 Gy to 50% IDL	No
12	64	M	NSCLC	Cerebellum	16 Gy to 50% IDL	No[d]
13	54	F	NSCLC	Cerebellum	20 Gy to 50% IDL	No
14	64	M	CA	Frontal lobe	20 Gy to 40% IDL	No



All patients with prior SRS
5 patients (36%) with prior WBRT

75% Local Control Rate

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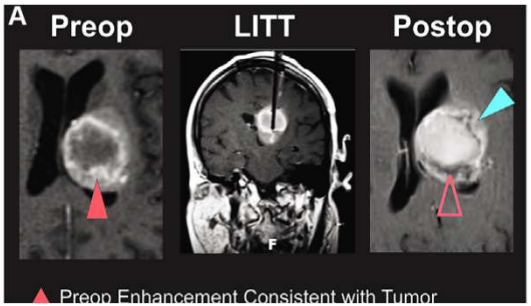
Rao MS, *Neurosurgery*, June 2014; 74(6):658-667

LITT Effect on Blood-Brain-Barrier

RESEARCH ARTICLE

Hyperthermic Laser Ablation of Recurrent Glioblastoma Leads to Temporary Disruption of the Peritumoral Blood Brain Barrier

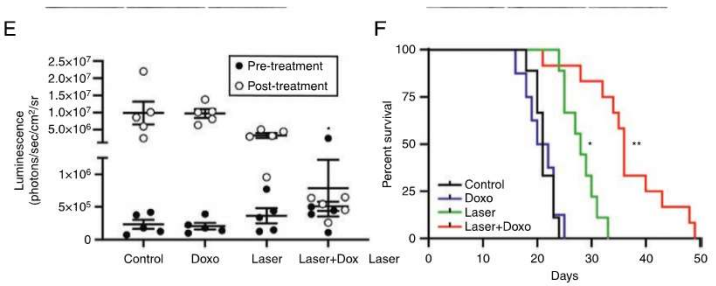
Eric C. Leuthardt[1,2,3,4,5☯*], Chong Duan[6☯], Michael J. Kim[7], Jian L. Campian[1,7], Albert H. Kim[1,2], Michelle M. Miller-Thomas[8], Joshua S. Shimony[8*], David D. Tran[9*]



Leuthardt EC, *PLoS One* (2016)

Therapeutic enhancement of blood–brain and blood–tumor barriers permeability by laser interstitial thermal therapy

Afshin Salehi[†], Mounica R. Paturu[†], Bhuvic Patel[†,●], Matthew D. Cain, Tatenda Mahlokozera, Alicia B. Yang, Tsen-Hsuan Lin, Eric C. Leuthardt, Hiroko Yano, Sheng-Kwei Song, Robyn S. Klein, Robert Schmidt, and Albert H. Kim[●]



Salehi A, *Neuro-Onc Adv* (2020) 2(1):1-12

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LITT in combination with ICI

- NCT03341806: Avelumab with Laser Interstitial Therapy for Recurrent Glioblastoma (Phase I)
- NCT03277638: Laser Interstitial Thermotherapy Combined with Checkpoint Inhibitor for Recurrent GBM (Phase I/II)
- NCT02311582: MK-3475 in Combination with MRI-guided Laser Ablation in Recurrent Malignant Gliomas (Phase I/II)

Summary

The standard of care for high-grade gliomas is surgery, radiotherapy, and temozolomide chemotherapy

- Tumor treatment fields (TTF) has been shown to have survival benefit, but compliance is challenging

GBM is a highly immunosuppressive and immunologically cold tumor

- No benefit of immune checkpoint inhibitors alone (in combination with RT and TMZ)

Anti-Tumor vaccination and oncolytic viral therapy can help boost innate immune response

- These therapies have not been individually successful in phase III trials
- Combinations of vaccine/viral therapy with immune checkpoint inhibition has promise – studies underway now

Surgical technology to increase extent of resection has reached it's limit of benefit

New surgical approaches (laser interstitial therapy) offers new biologic benefit in addition to decreased morbidity

- BBB permeability
- Immune stimulation

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Thank You

Questions