Advances in the Treatment of CNS Malignancies

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Assistant Professor of Clinical Neurological Surgery & Neurology
February 11, 2023

Overview

1. Reclassification of pathology
2. Advances in surgery
3. Advances in radiation
4. Emerging systemic therapies

Reclassification of Pathology

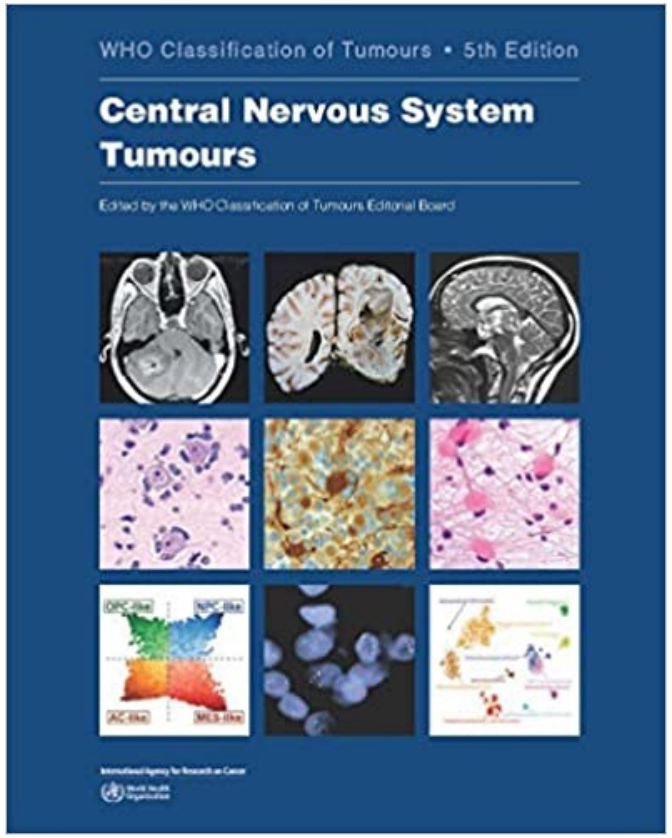
Reclassification of Pathology

WHO CNS 5 (2021)
Louis. Neuro-Onc (2021)

WHO Classification of Central Nervous System Tumors, 5th edition (2021)

Update introduces **major changes** that advance the role of molecular diagnostics in CNS classification

- Arabic rather than Roman numerals
- Molecular alterations supercede histological grading
- “Glioblastoma” no longer used for IDH-mutant tumors
- Descriptors “diffuse” and “anaplastic” no longer used



Reclassification of Pathology

Nomenclature and grading of adult-type diffuse gliomas

2016

Tumor type	Grade	IDH
Glioblastoma	IV	Mutant
		Wildtype
Anaplastic Astrocytoma	III	Mutant
		Wildtype
Diffuse Astrocytoma	II	Mutant
		Wildtype

2021

IDH	Grade	Tumor type
Mutant	4	Astrocytoma
Mutant	3	
Mutant	2	
Wildtype	4	Glioblastoma

Reclassification of Pathology

2016

Tumor type	Grade	IDH
Glioblastoma	IV	Mutant
		Wildtype
Anaplastic Astrocytoma	III	Mutant
		Wildtype
Diffuse Astrocytoma	II	Mutant
		Wildtype

Grade 4 (in the absence of microvascular proliferation or necrosis):
CDKN2A/B homozygous deletion upgrades IDH mutant

2021

IDH	Grade	Tumor type
Mutant	4	Astrocytoma
Mutant	3	
Mutant	2	
Wildtype	4	Glioblastoma

Reclassification of Pathology

2016

Tumor type	Grade	IDH
Glioblastoma	IV	Mutant
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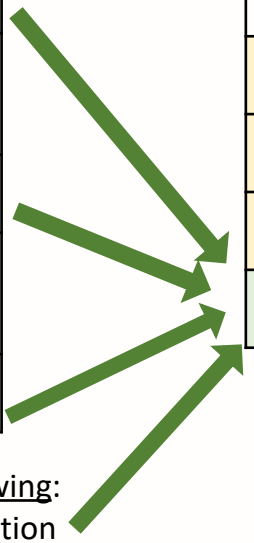
Anaplastic Astrocytoma	III	Mutant
		Wildtype
Diffuse Astrocytoma	II	Mutant
		Wildtype



Any one of the following:
TERT promoter mutation
EGFR amplification
+7/-10

2021

IDH	Grade	Tumor type
Mutant	4	Astrocytoma
Mutant	3	
Mutant	2	
Wildtype	4	Glioblastoma

Reclassification of Pathology

Ramifications:

Diagnosis requires molecular testing

- Delay time to diagnosis, challenges at local hospitals

Clinical trial enrollment

- Necessitates updates to current trials

Clinical trial protocol development moving forward

- Focus on molecular subtypes

Reclassification of Pathology

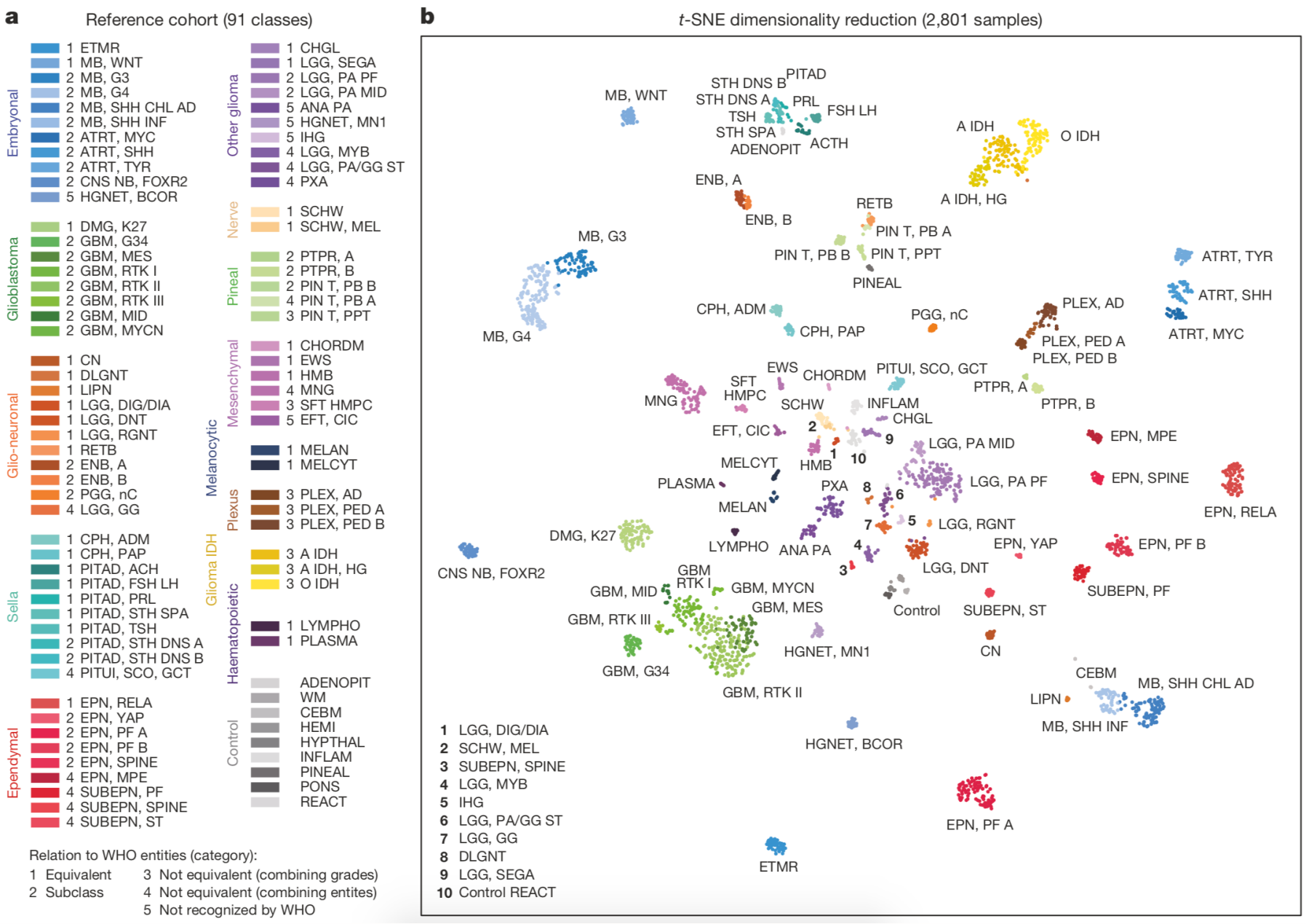
WHO CNS 5 (2021)
Louis. Neuro-Onc (2021)

Table 7 Newly Recognized Tumor Types in the 2021 WHO Classification of Tumors of the Central Nervous System

Newly Recognized Tumor Types
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
High-grade astrocytoma with piloid features
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (provisional type)
Myxoid glioneuronal tumor
Multinodular and vacuolating neuronal tumor
Supratentorial ependymoma, *YAP1* fusion-positive
Posterior fossa ependymoma, group PFA
Posterior fossa ependymoma, group PFB
Spinal ependymoma, *MYCN*-amplified
Cribriform neuroepithelial tumor (provisional type)
CNS neuroblastoma, *FOXR2*-activated
CNS tumor with *BCOR* internal tandem duplication
Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant
Intracranial mesenchymal tumor, FET-CREB fusion positive (provisional type)
CIC-rearranged sarcoma
Primary intracranial sarcoma, *DICER1*-mutant
Pituitary blastoma

Reclassification of Pathology

Von Deimling. Nature (2018)



Advances in Surgery

Surgery—5-Aminolevulinic Acid

J Neurosurg. 2021 Oct 8;1-10. doi: 10.3171/2021.5.JNS21310. Online ahead of print.

5-Aminolevulinic acid for enhanced surgical visualization of high-grade gliomas: a prospective, multicenter study

Alexander J Schupper [1], Rebecca B Baron [1], William Cheung [1], Jessica Rodriguez [1], Steven N Kalkanis [2], Muhammad O Chohan [3], Bruce J Andersen [4], Roukoz Chamoun [5], Brian V Nahed [6], Brad E Zacharia [7], Jerone Kennedy [8], Hugh D Moulding [9], Lloyd Zucker [10], Michael R Chicoine [11], Jeffrey J Olson [12], Randy L Jensen [13], Jonathan H Sherman [14], Xiangnan Zhang [1], Gabrielle Price [1], Mary Fowkes [1], Isabelle M Germano [1], Bob S Carter [6], Constantinos G Hadjipanayis [1], Raymund L Yong [1]

SCIENTIFIC REPORTS
nature research

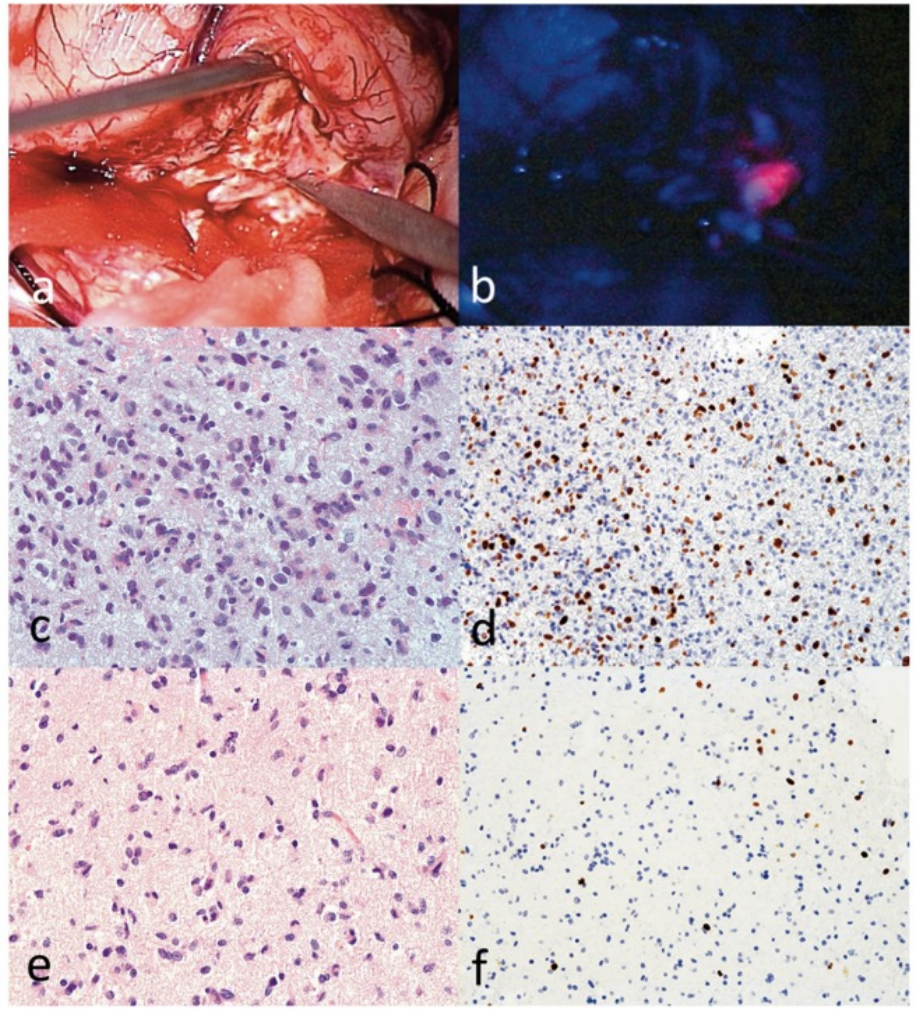
5-Aminolevulinic Acid Guided Sampling of Glioblastoma Microenvironments Identifies Pro-Survival Signaling at Infiltrative Margins

James L. Ross[3,4,7], Lee A. D. Cooper[2,5,6,7,8], Jun Kong[2,5,6,8], David Gutman[3,5,6], Merete Williams[1], Carol Tucker-Burden[1], Myles R. McCrary[6,8], Alexandros Bouras[9], Milota Kaluzova[4], William D. Dunn Jr.[2], Duc Duong[3], Constantinos G. Hadjipanayis[9] & Daniel J. Brat[1,2,5,6]

Neuro-Oncology Advances
3(1), 1–11, 2021 | doi:10.1093/noajnl/vdab047 | Advance Access date 26 March 2021

5-Aminolevulinic acid-guided resection improves the overall survival of patients with glioblastoma—a comparative cohort study of 343 patients

Asfand Baig Mirza†, Ioannis Christodoulides†, Jose Pedro Lavrador†, Anastasios Giamouriadis, Amisha Vastani, Timothy Boardman, Razna Ahmed, Irena Norman, Christopher Murphy, Sharmila Devi, Francesco Vergani, Richard Gullan, Ranjeev Bhangoo, and Keyoumars Ashkan



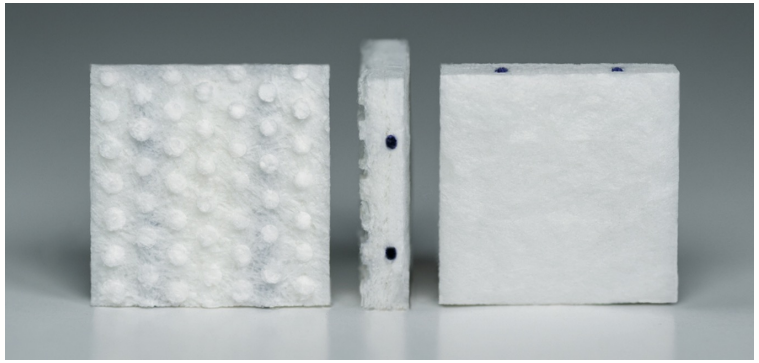
Advances in Radiation

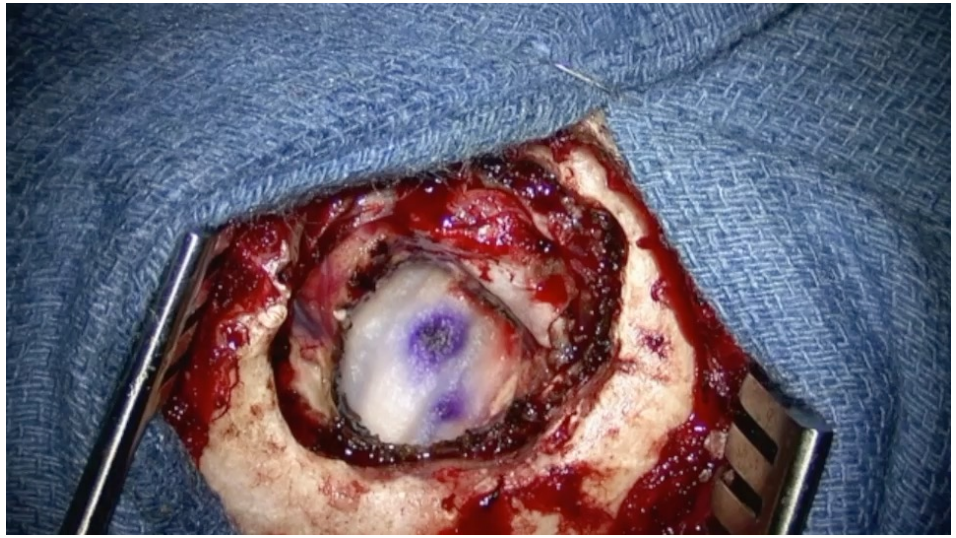
Radiation—Brachytherapy

Cesium-131 collagen carrier tile brachytherapy

FDA-cleared to deliver radiation

- Newly diagnosed malignant
- Recurrent intracranial neoplasms



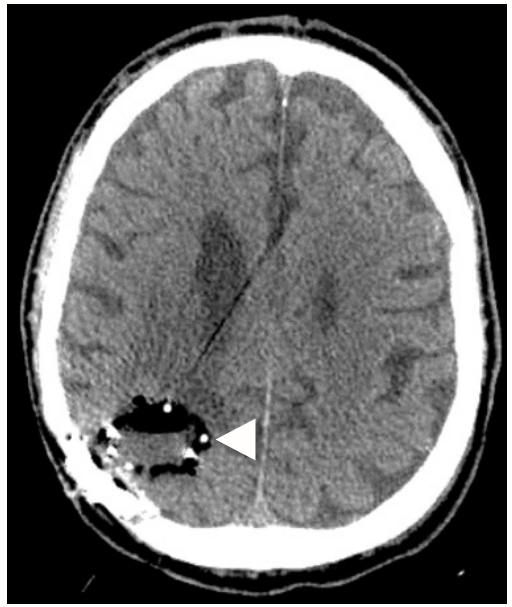


Radiation—Brachytherapy

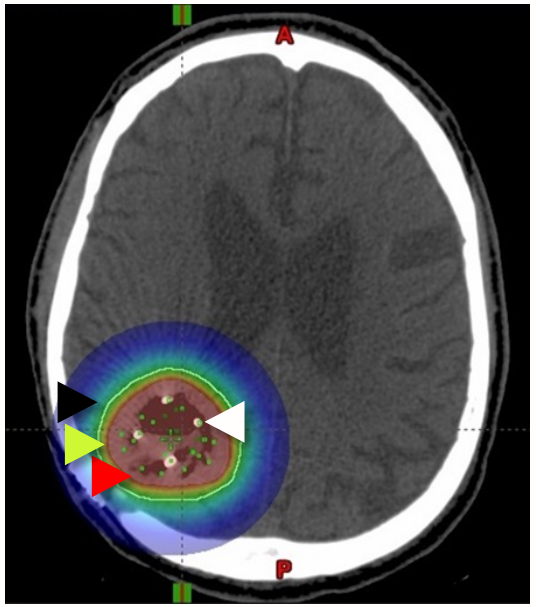
Post-Op CT

Treatment Planning Images Depict Radiation Distribution And Intensity

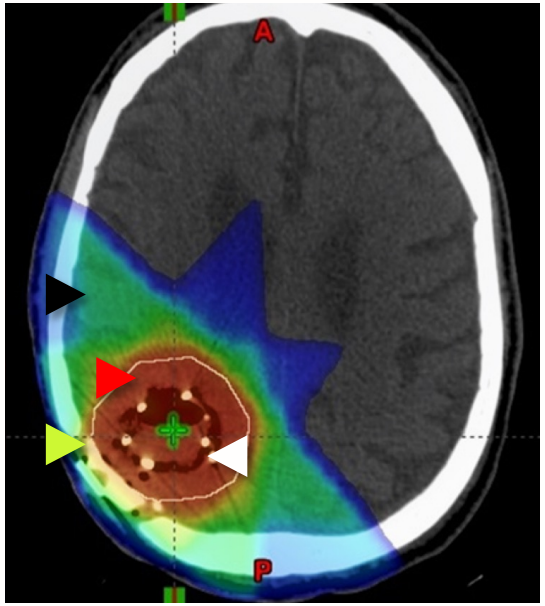
AFTER SURGERY



CESIUM-131 TILE THERAPY



INTENSITY MODULATED RADIATION THERAPY (IMRT)



Colors indicate radiation location and intensity from the 2 types of treatment.

Blue-green indicates lower radiation levels Red indicates higher levels White dots indicate radiation sources

Area of treatment intent corresponds to the continuous lighter circles

Radiation—Brachytherapy

J Neurooncol. 2022 Jul 27;1-10. doi: 10.1007/s11060-022-04101-9. Online ahead of print.

Salvage resection plus cesium-131 brachytherapy durably controls post-SRS recurrent brain metastases

Brandon S Imber [# 1 2], Robert J Young [# 2 3], Kathryn Beal [1 2], Anne S Reiner [4], Alexandra M Giantini-Larsen [5], Jonathan T Yang [1 2], David Aramburu-Nunez [6], Gil'ad N Cohen [6], Cameron Brennan [2 5], Viviane Tabar [2 5], Nelson S Moss [7 8]

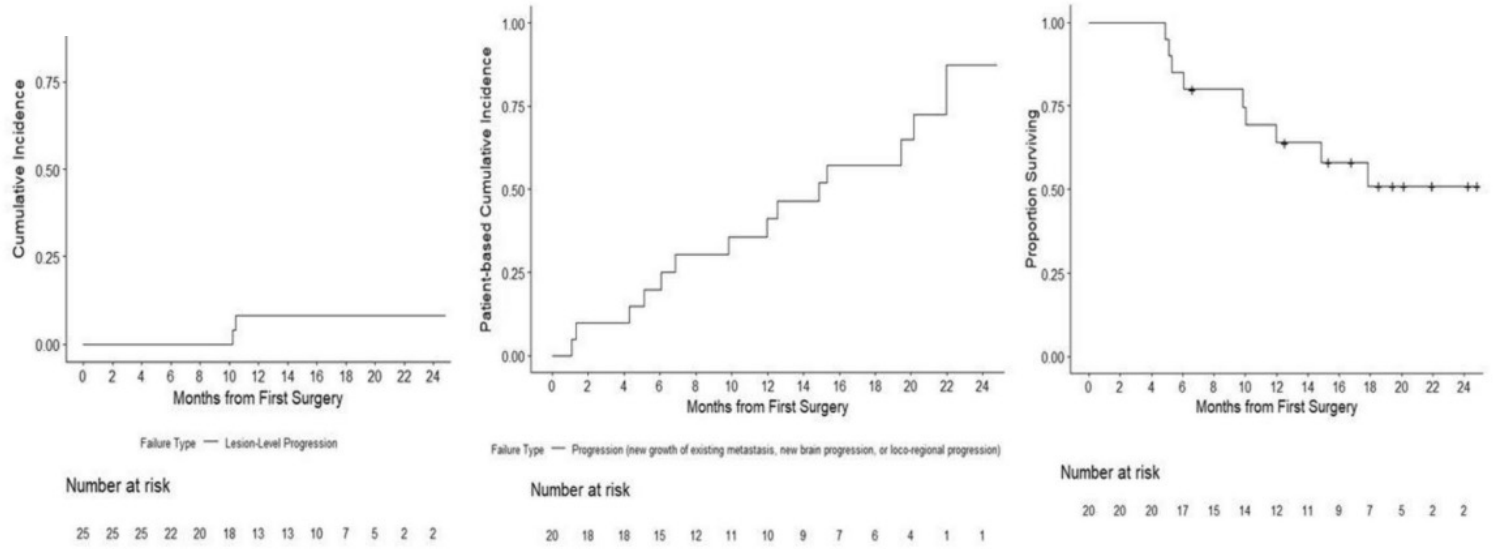


Fig. 1 Clinical outcomes. **A** cumulative incidence of local failure at the lesion level. **B** Cumulative incidence of intracranial PFS at the patient level from date of first Cs131 implant. **C** Overall survival at the patient level for the cohort from date of first Cs131 implant

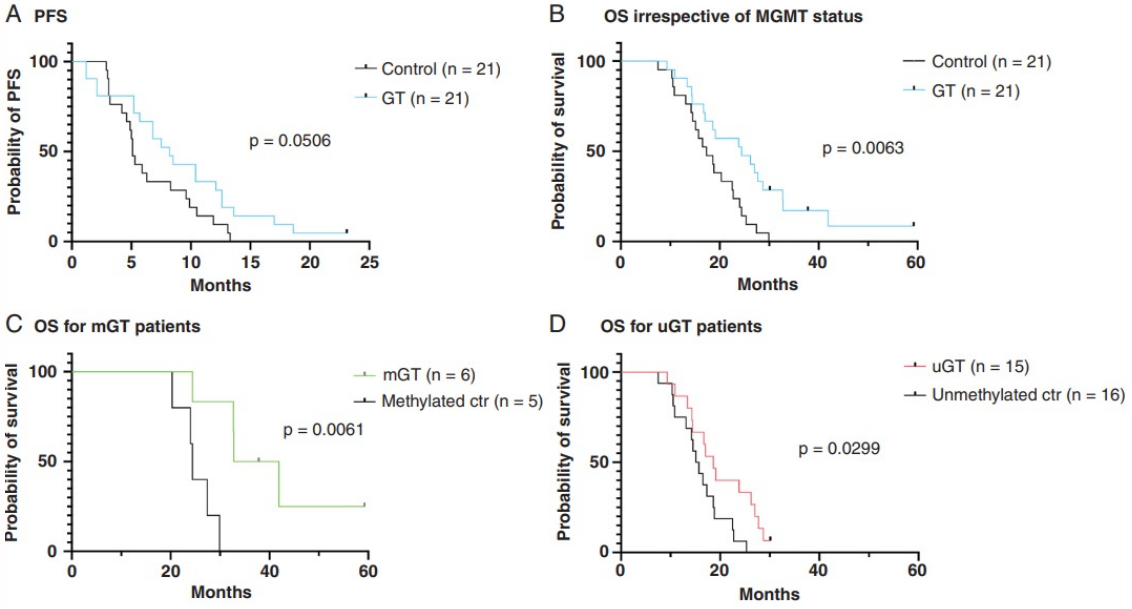
Radiation—Brachytherapy

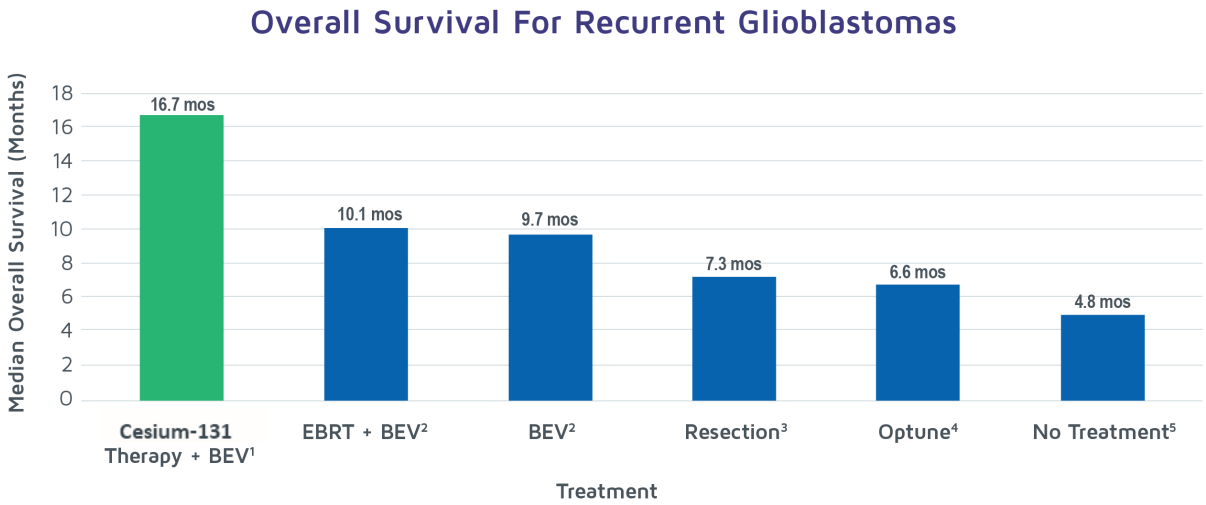
Neuro-Oncology Advances

4(1), 1–11, 2022 | https://doi.org/10.1093/noajnl/vdab185 | Advance Access date 27 December 2021

[redacted] brachytherapy in the treatment of recurrent glioblastomas

Dominic J. Gessler,* Elizabeth C. Neil, Rena Shah, Joseph Levine, James Shanks, Christopher Wilke, Margaret Reynolds, Shunqing Zhang, Can Özütemiz, Mehmet Gencturk, Mark Folkertsma, W. Robert Bell, Liam Chen, Clara Ferreira, Kathryn Dusenbery, and Clark C. Chen





Systemic Therapies

Newly-Approved & Emerging

Systemic Therapies

FDA-Approval	Drug	Condition
April 2020	Selumetinib	NF1 plexiform neurofibroma
Sept 2021	Belzutifan	VHL hemangioblastoma
July 2022	Dabrafenib/Vemurafenib	BRAF V600E mutant

Investigation	Drug	Condition
2020	Ivosidenib	IDH mutant glioma
2021	Vorasidenib	IDH mutant glioma
2021	Olaparib	IDH mutant glioma
2022	Veliparib	Glioblastoma
2021	Abemaciclib	Glioblastoma
2022	Selinexor	Glioblastoma

Systemic Therapies—FDA Approved

The NEW ENGLAND JOURNAL of MEDICINE

Selumetinib in Children with Inoperable Plexiform Neurofibromas

Andrea M. Gross, M.D., Pamela L. Wolters, Ph.D., Eva Dombi, M.D., Andrea Baldwin, P.N.P., Patricia Whitcomb, R.N., Michael J. Fisher, M.D., Brian Weiss, M.D., AeRang Kim, M.D., Ph.D., Miriam Bornhorst, M.D., Amish C. Shah, M.D., Ph.D., Staci Martin, Ph.D., Marie C. Roderick, Psy.D., et al.

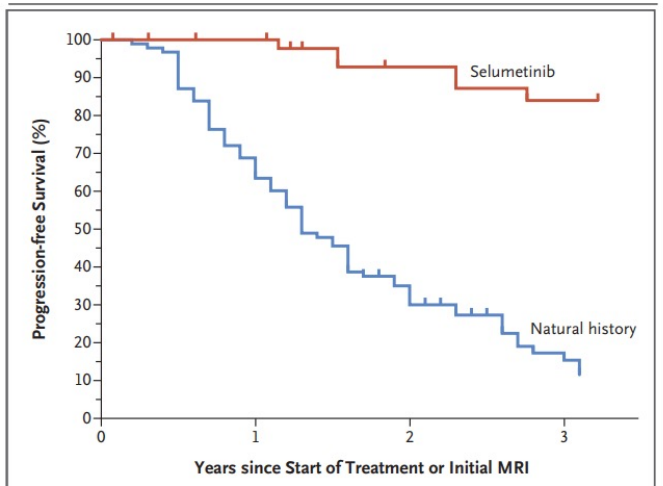
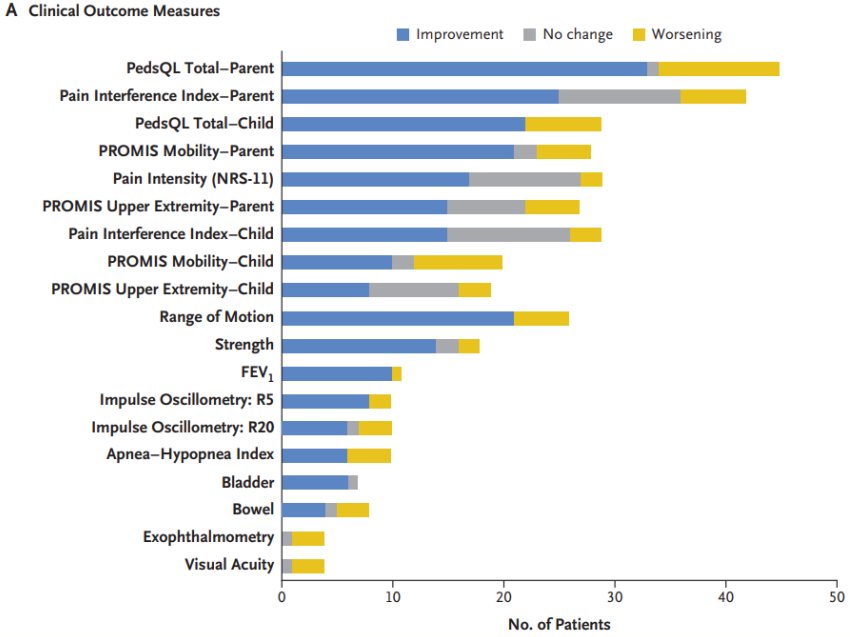
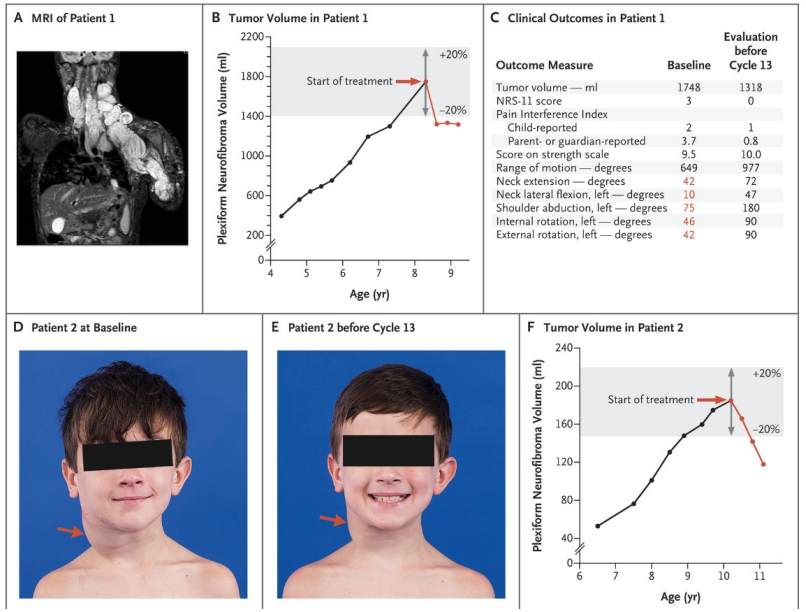


Figure 1. Target Plexiform Neurofibroma Progression–free Survival during Selumetinib Treatment as Compared with Natural History of Neurofibromatosis Type 1.

At 3 years of follow-up, the progression-free survival was 15% in the natural-history group and 84% in the selumetinib group.





Systemic Therapies—FDA Approved

The NEW ENGLAND JOURNAL of MEDICINE

Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

Eric Jonasch, M.D., Frede Donskov, M.D., Ph.D., Othon Iliopoulos, M.D., W. Kimryn Rathmell, M.D., Ph.D., Vivek K. Narayan, M.D., Benjamin L. Maughan, M.D., Stephane Oudard, M.D., Tobias Else, M.D., Jodi K. Maranchie, M.D., Sarah J. Welsh, M.D., Sanjay Thamake, Ph.D., Eric K. Park, M.D., et al., for the MK-6482-004 Investigators*

	Pancreatic lesions (n=61)	Pancreatic Neuroendocrine Tumors (n=22)	CNS Hemangioblastoma (n=50)	Retinal Hemangioblastomas (n=16)
Best Response				
CR	6 (9.8%)	3 (13.6%)	3 (6.0%)	-
PR	41 (67.2%)	17 (77.3%)	12 (24.0%)	16 (100%)
SD	13 (21.3%)	2 (9.1%)	31 (62%)	0
PD	0	0	2 (4.0%)	0
Median time to response, months	8.4 (2.5-19.1)	5.5 (2.5-16.4)	3.2 (2.3-16.6)	-
Median duration of response, months	Not Reached (2.6-22.3)	Not Reached (2.9-22.3)	Not Reached (2.6-22.3)	-

Systemic Therapies—FDA Approved

Meeting Abstract | 2022 ASCO Annual Meeting II

CENTRAL NERVOUS SYSTEM TUMORS

Primary analysis of a phase II trial of dabrafenib plus trametinib (dab + tram) in *BRAF* V600–mutant pediatric low-grade glioma (pLGG).

Eric Bouffet, Jordan Hansford, Maria Luisa Garré, Junichi Hara, Ashley Plant-Fox, Isabelle Aerts, Franco Locatelli, Jasper Van der Lugt, Ludmila Papusha, Felix Sahm, Uri Tabori, Kenneth J. Cohen, Roger J. Packer, Olaf Witt, Lali Sandalic, Ana Bento Pereira da Silva, Mark W. Russo, Darren R. Hargrave

	Dabrafenib + Trametinib (n=73)	Carboplatin + Vincristine Control (n=37)	
ORR (CR+PR)	47% (95% CI, 35-59%)	11% (95% CI, 3-25%)	OR 7.2 (95% CI, 2.3-22.4, p<0.001)
PFS	20.1 months (95% CI, 12.8-not estimable)	7.4 months (95% CI, 3.6-11.8)	HR 0.31 (95% CI, 0.17-0.55, P<0.01)
12-PFS	67%	26%	

Systemic Therapies—IDH mutation

Clinical Trial > J Clin Oncol. 2020 Oct 10;38(29):3398-3406. doi: 10.1200/JCO.19.03327. Epub 2020 Jun 12.

Ivosidenib in Isocitrate Dehydrogenase 1 – Mutated Advanced Glioma

Ingo K Mellinghoff [1], Benjamin M Ellingson [2], Mehdi Touat [3], Elizabeth Maher [4], Macarena I De La Fuente [5], Matthias Holdhoff [6], Gregory M Cote [7], Howard Burris [8], Filip Janku [9], Robert J Young [10], Raymond Huang [11], Liewen Jiang [12], Sung Choe [13], Bin Fan [14], Katharine Yen [15], Min Lu [15], Chris Bowden [16], Lori Steelman [16], Shuchi S Pandya [16], Timothy F Cloughesy [17], Patrick Y Wen [18]

	Non-Enhancing Disease (n=24)	Enhancing Disease (n=31)
PFS	13.6 mo (95% CI, 9.2-33.2)	1.4 mo (95% CI, 1.0-1.9)
Best Overall Response		
CR	0	0
PR	1 (4.2%)	0
SD	21 (87.5%)	14 (45.2%)
PD	2 (8.3%)	17 (54.8%)

Clinical Trial > Clin Cancer Res. 2021 Aug 15;27(16):4491-4499. doi: 10.1158/1078-0432.CCR-21-0611. Epub 2021 Jun 2.

Vorasidenib, a Dual Inhibitor of Mutant IDH1/2, in Recurrent or Progressive Glioma; Results of a First-in-Human Phase I Trial

Ingo K Mellinghoff [#1], Marta Penas-Prado [2], Katherine B Peters [3], Howard A Burris 3rd [4], Elizabeth A Maher [5], Filip Janku [6], Gregory M Cote [7], Macarena I de la Fuente [8], Jennifer L Clarke [9], Benjamin M Ellingson [10], Saewon Chun [11], Robert J Young [12], Hua Liu [13], Sung Choe [13], Min Lu [13], Kha Le [13], Islam Hassan [13], Lori Steelman [13], Shuchi S Pandya [13], Timothy F Cloughesy [#11], Patrick Y Wen [14]

	Non-Enhancing Disease (n=22)	Enhancing Disease (n=30)
PFS	36.8 mo (95% CI, 11.2-40.8)	3.6 mo (95% CI, 1.8-6.5)
Best Overall Response		
CR	0	0
PR	4 (18.1%)	0
SD	16 (72.7%)	17 (56.7%)
PD	2 (9.1%)	12 (40.0%)

Systemic Therapies—PARP inhibition

Meeting Abstract | 2021 ASCO Annual Meeting I

CENTRAL NERVOUS SYSTEM TUMORS

Olaparib in recurrent IDH-mutant high-grade glioma (OLAGLI).

Francois Ducray, Marc Sanson, Olivier L. Chinot, Maxime Fontanilles, Romain Rivoirard, Laure Thomas-Maisonneuve, Stephanie Cartalat, Emeline Tabouret, Alice Bonneville-Levard, Amelie Darlix, Roxana Ameli, David Meyronet, Francois Gueyffier, Laurent Remontet, Delphine Maucort-Boulch, Caroline Dehais, Jerôme Honnorat, POLA Network

	Recurrent IDH mutant gliomas (n=32)
6-PFS	11 (31%)
PFS	2.3 months
OS	15.9 months

*Did not meet primary endpoint for efficacy
PARP inhibition alone is insufficient

Systemic Therapies—PARP inhibition

Clinical Trial > Neuro Oncol. 2021 Oct 1;23(10):1736-1749. doi: 10.1093/neuonc/noab111.

A randomized phase II trial of veliparib, radiotherapy, and temozolomide in patients with unmethylated MGMT glioblastoma: the VERTU study

Hao-Wen Sim [1 2 3 4], Kerrie L McDonald [5], Zarnie Lwin [6 7], Elizabeth H Barnes [1], Mark Rosenthal [8 9], Matthew C Foote [6 10], Eng-Siew Koh [11 12 13], Michael Back [14], Helen Wheeler [15], Erik P Sulman [16 17], Michael E Buckland [18 19], Lauren Fisher [1], Robyn Leonard [1], Merryn Hall [1 20], David M Ashley [20], Sonia Yip [1], John Simes [1 4], Mustafa Khasraw [1]

	RT/Veliparib + TMZ/Veliparib (n=84)	RT/TMZ + TMZ (n=41)	
6-PFS	46%	31%	
PFS	5.7 months	4.2 months	HR 0.78 (95% CI: 0.54-1.15)
OS	12.7 months	12.8 months	HR 1.14 (95% CI 0.76-1.72)

Meeting Abstract | 2022 ASCO Annual Meeting I

CENTRAL NERVOUS SYSTEM TUMORS

Randomized phase II/III trial of veliparib or placebo in combination with adjuvant temozolomide in newly diagnosed glioblastoma (GBM) patients with MGMT promoter hypermethylation (Alliance A071102).

Jann Nagina Sarkaria, Karla V. Ballman, Sani Haider Kizilbash, Erik P. Sulman, Caterina Giannini, Sandeep H. Mashru, David Eric Piccioni, Bret Edward Buckley Friday, Jesse G. Dixon, Brian Kabat, Nadia N. Laack, Leland Hu, Priya Kumthekar, Benjamin M. Ellingson, S. Keith Anderson, Evanthia Galanis

	RT/TMZ + TMZ/Veliparib	RT/TMZ + TMZ/Placebo	(n=447)
PFS	13.2 months	12.1 months	p=0.31; HR 1.05 (0.86-1.30)
OS	28.1 months	24.8 months	p=0.15; HR 0.89 (0.71-1.11)

Systemic Therapies – CDKN2A

CTNI-47. PHASE II STUDY OF ABEMACICLIB IN RECURRENT GBM PATIENTS WITH CDKN2A/B LOSS AND INTACT RB FREE

Eudocia Lee, Alona Muzikansky, Isabel Arrillaga-Romany, Ugonma Chukwueke, Timothy Cloughesy, Howard Colman, Mariza Daras, John de Groot, Jose Mcfaline-Figueroa, Lakshmi Nayak, Robert Prins, David Reardon, Jennie Taylor, Keith Ligon, Patrick Wen

Neuro-Oncology, Volume 22, Issue Supplement_2, November 2020, Page ii53, https://doi.org/10.1093/neuonc/noaa215.213

	Abemaciclib (n=32)	
6-PFS	9.37%	95% CI 2.4-22.27%
PFS	55 days	95% CI, 49-56
OS	384 days	95% CI, 228-488

Meeting Abstract | 2021 ASCO Annual Meeting I

CENTRAL NERVOUS SYSTEM TUMORS

Preliminary results of the abemaciclib arm in the Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT): A phase II platform trial using Bayesian adaptive randomization.

Eudocia Quant Lee, Lorenzo Trippa, Geoffrey Fell, Rifaquat Rahman, Isabel Arrillaga-Romany, Mehdi Touat, Jan Drappatz, Mary Roberta Welch, Evanthia Galanis, Manmeet Singh Ahluwalia, Howard Colman, Louis B. Nabors, Jaroslaw T. Hepel, David Schiff, David M. Meredith, E. Antonio Chiocca, David A. Reardon, Keith L. Ligon, Brian Michael Alexander, Patrick Y. Wen

	RT/TMZ + Abemaciclib (n=73)	RT/TMZ + aTMZ Control (n=69)	
PFS	6.54 months	5.88 months	HR 0.67, p=0.03
	*Activated CDK4		HR 0.64, p=0.04
OS	15.5 months	15.5 months	HR 0.9, p>0.05

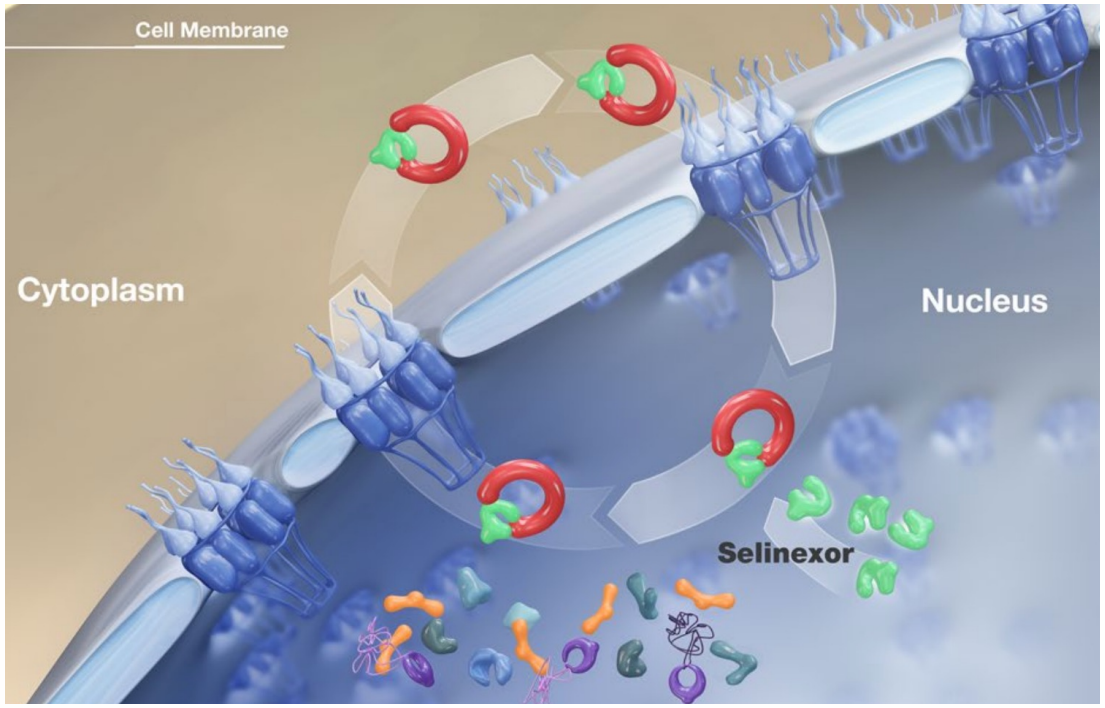
Systemic Therapies—Exportin 1

Clinical Trial > Clin Cancer Res. 2022 Feb 1;28(3):452-460. doi: 10.1158/1078-0432.CCR-21-2225. Epub 2021 Nov 2.

A Phase II Study of the Efficacy and Safety of Oral Selinexor in Recurrent Glioblastoma

Andrew B Lassman [1 2], Patrick Y Wen [3], Martin J van den Bent [4], Scott R Plotkin [5], Annemiek M E Walenkamp [6], Adam L Green [7], Kai Li [8], Christopher J Walker [8], Hua Chang [8], Sharon Tamir [8], Leah Henegar [8], Yao Shen [9], Mariano J Alvarez [9 10], Andrea Califano [2 10 11 12 13], Yosef Landesman [8], Michael G Kauffman [8], Sharon Shacham [8], Morten Mau-Sørensen [14]

	Arm B Selinexor 50mg/m2 BIW (n=24)	Arm C Selinexor 60mg BIW (n=13)	Arm D Selinexor 80mg QW (n=30)
6-PFS	10%	7.7%	17.%
PFS	1.6 months	1.9 months	1.9 months
OS	10.5 months	8.5 months	10.2 months



Systemic Therapies—Exportin 1

Clinical Trial > Clin Cancer Res. 2022 Feb 1;28(3):452-460. doi: 10.1158/1078-0432.CCR-21-2225. Epub 2021 Nov 2.

A Phase II Study of the Efficacy and Safety of Oral Selinexor in Recurrent Glioblastoma

Andrew B Lassman [1 2], Patrick Y Wen [3], Martin J van den Bent [4], Scott R Plotkin [5], Annemiek M E Walenkamp [6], Adam L Green [7], Kai Li [8], Christopher J Walker [8], Hua Chang [8], Sharon Tamir [8], Leah Henegar [8], Yao Shen [9], Mariano J Alvarez [9 10], Andrea Califano [2 10 11 12 13], Yosef Landesman [8], Michael G Kauffman [8], Sharon Shacham [8], Morten Mau-Sørensen [14]

Enrolling NOW

Phase 1/2 Trial of Selinexor and Temozolomide in Recurrent Glioblastoma [NCI Study #10505]

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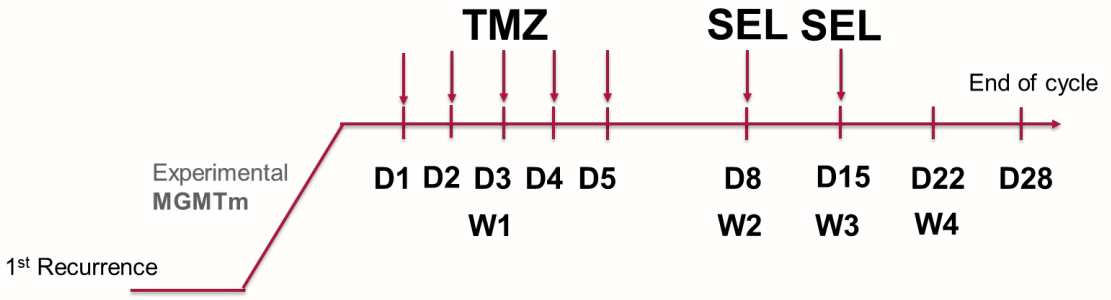
NIH NATIONAL CANCER INSTITUTE

October 17, 2022



Systemic Therapies—Immunotherapy

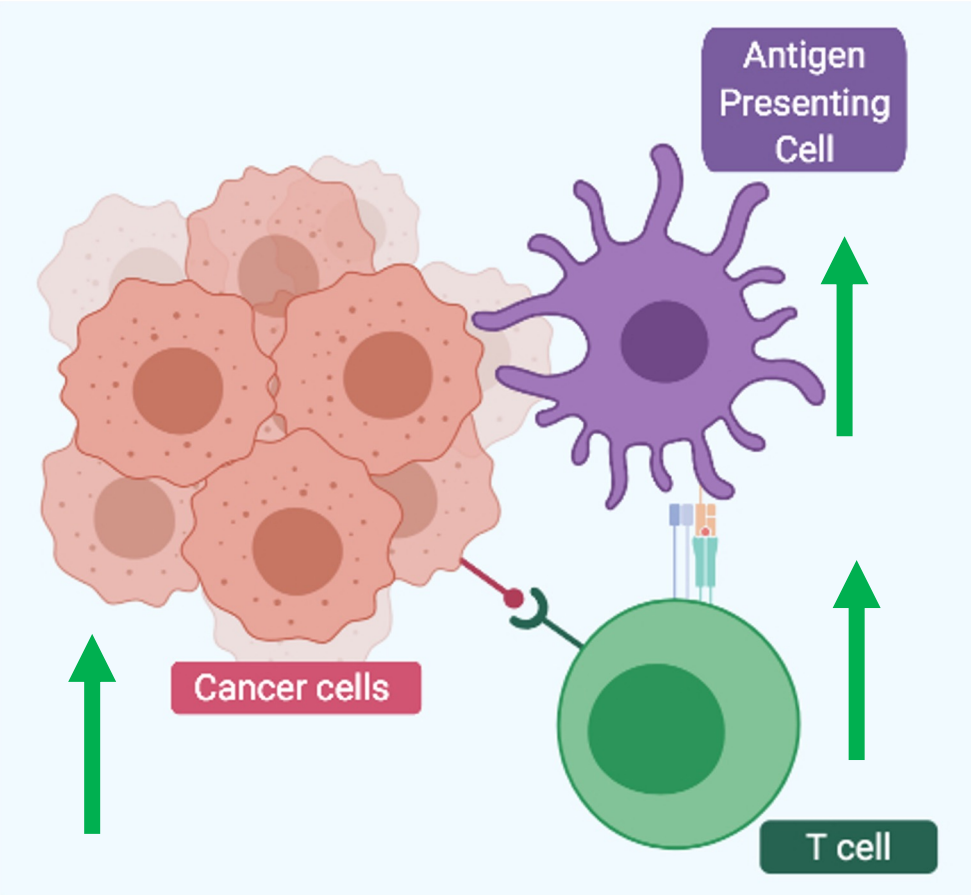
Cancer Cell
- Peptide vaccine
- Oncolytic virus

Dendritic Cell
- Vaccine

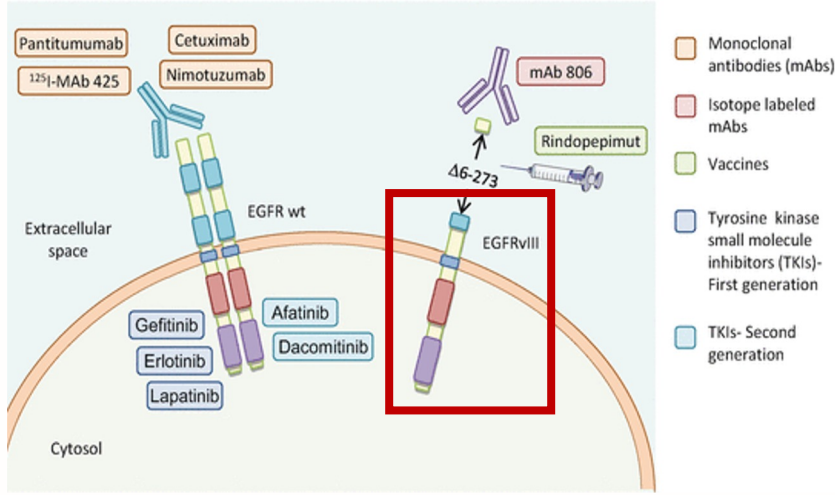
Cytotoxic T cell
- Adoptive transfer (CAR T)
- Immune checkpoint blockade

NK Cell

Macrophage



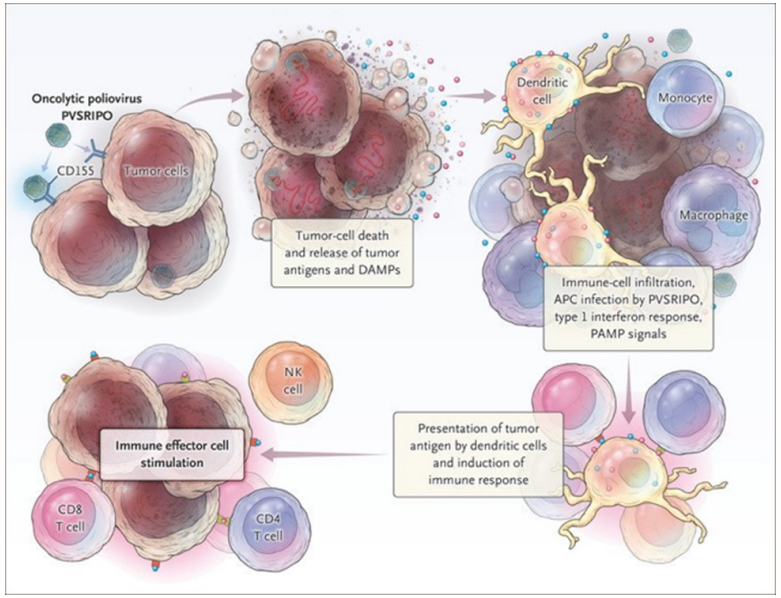
Systemic Therapies—Peptide Vaccine



Immunotherapy	Treatment	Setting	Phase	Sample Size	PFS (m)	OS (m)
ACTIVATE	Rindopepimut after RT	New	II	N=18	14.2 (vs historical control 6.4)	26.0 (vs historical control 15.2)
ACT II	Rindopepimut + TMZ vs. Rindopepimut + Dose Intense TMZ	New	II	N=22	15.2	23.6
ACT III	Rindopepimut after RT	New	II	N=65	12.3	24.6
ACT IV	Rindopepimut vs. control	New	III		--	20.0 (p=0.93) *Early termination for futility
ReACT	Rindopepimut vs. BEV	Recurrent	II	N=170	--	12.0 (vs 8.8 bevacizumab) (p=0.02)
SurVaxM	SurVaxM	New	I	N=9	17.6	86.6
SurVaxM	SurVaxM	New	II	N=63	15.5	30.5
SurVaxM + Pembro	SurVaxM + PEMBRO	Recurrent	II		--	
GlioVac	Sitoiganap vs BEV	Recurrent	II	N=84	--	10.5 *FDA recommended early termination to start Phase III study (April 2021)
IMA950		New	I	N=45	--	15.3

Systemic Therapies—Oncolytic Virus

Virus	Phase and Reference	*n* Patients	Results
Herpes	Phase I: HSV-1716 [38]	9	Two 24 moth survivors Evidence of tumor infection
	Phase Ib: HSV-1716 [39]	12	Three patients clinically stable for two years
	Phase II: HSV-1716 NCT02031965	2	No results available
	Phase I: G207 [41]	21	No toxicities
	Phase Ib: G207 [41]	6	No toxicity Evidence of tumor infection
	Phase I: G207 [42]	9	No toxicities in combination with 5 Gy
	Phase I: rQNestin34.5v2 NCT03152318	108	Recruiting
	Phase I: C134 NCT03657576	24	Recruiting
Adenovirus	Phase I: ONYX-015 [66]	24	No toxicity One patient without progression and some with regression
	Phase I: Delta-24-RGD NCT03896568	36	Recruiting
	Phase I: Delta-24-RGD NCT03178032	12	No results available
	Phase II: Delta-24-RGD NCT02798406	49	Active
	Phase I: Delta-24-RGD NCT02197169	37	No toxicities
	Phase I: Delta-24-RGD NCT01956734	31	No results available
	Phase I and II: Delta-24-RGD NCT01582516 [156]	20	Virus spread in tumor, oncolytic effect and immunostimulation 20% of >3 year survivors
	Phase I: Delta-24-RGD NCT00805376	37	12% of >95% tumor regression Evidence of immunostimulation
	Phase II Delta-24-RGD (2016-001600-40)	-	Discontinued
	Phase I: Delta-24-RGD NCT03714334	24	Recruiting
	Phase I: Delta-24-RGD NCT03072134	36	No results available
	Phase I: DNX-2440 NCT03714334	24	Recruiting
	Phase I/II: Ad-RTS-IL-12 NCT03330197	45	Recruiting



Reovirus	Phase I: Reovirus [101]	12	No toxicities
	Phase I: Reovirus NCT00528684 [102]	15	One 2 year survivor One 3 year survivor
	Phase Ib: Reovirus [100]	9	Evidence of T cell tumor infiltration and upregulation of IFN and PD-1/PD-L1 axis
	Phase I: Reovirus/Sargramostim NCT02444546	6	Active
Vaccinia	Phase I and II: TG6002 NCT03294486	78	Recruiting
Measles	Phase I: MV-CEA NCT00390299	23	No toxicities
NDV	Phase I/II: NDV-HUJ NCT01174537 [136]	14	No toxicities Complete regression in 1 patient
	Phase 0: MTH-68/H [134]	4	OS 5–9 years
	VOL-DC vaccine [135]	10	Increased OS
	Phase II: ATV-NDV vaccine [157]	23	PFS 40 weeks vs. 26 weeks
Parvovirus	H-1PV [94]	18	Enhanced immunogenicity
Poliovirus	Phase I: NCT01491893 [147]	61	No neurovirulence and increased survival rate
	Phase II: NCT02986178	122	Active
	Phase Ib: NCT03043391	12	Recruiting

Rius. Int J Molec Sci (2020)
Desjardins. NEJM (2018)

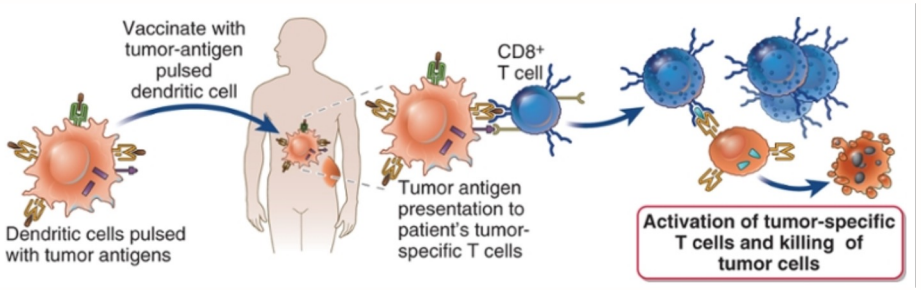
Systemic Therapies—DC Vaccine

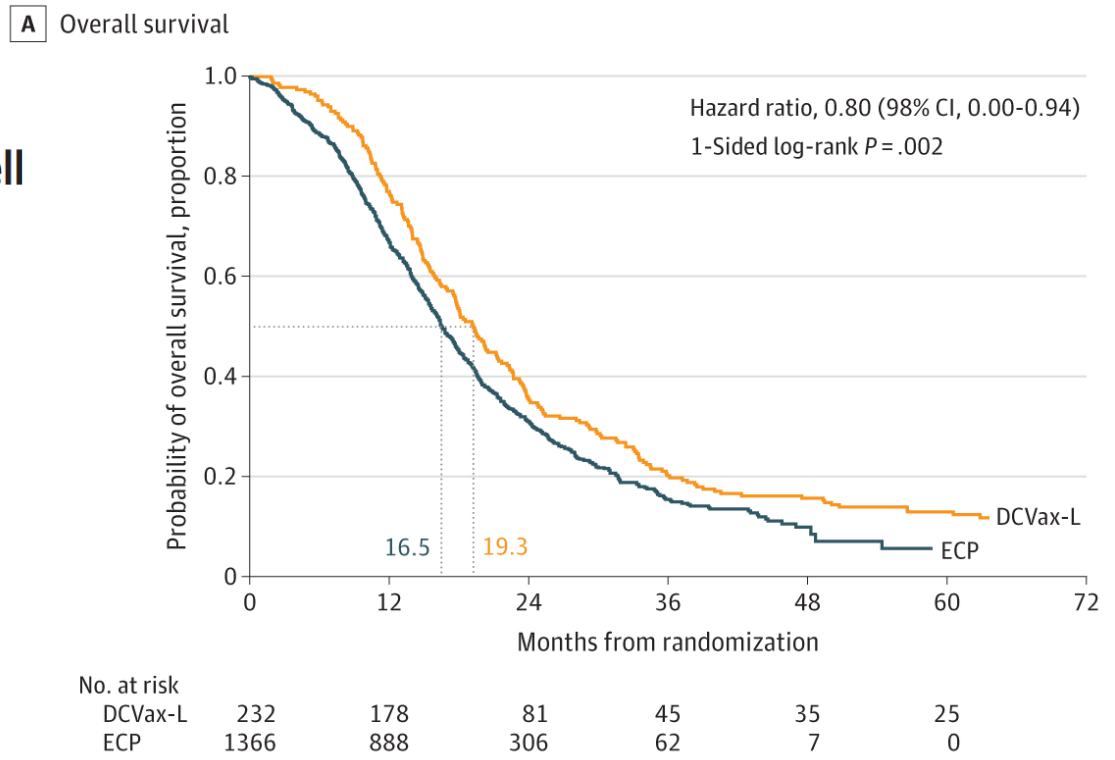
Liau. JAMA Oncol (2022)
Mulholland. Front Immun (2022)

JAMA Oncology | Original Investigation

Association of Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination With Extension of Survival Among Patients With Newly Diagnosed and Recurrent Glioblastoma

A Phase 3 Prospective Externally Controlled Cohort Trial





Systemic Therapies—DC Vaccine

Srivastava. Cancers (2019)

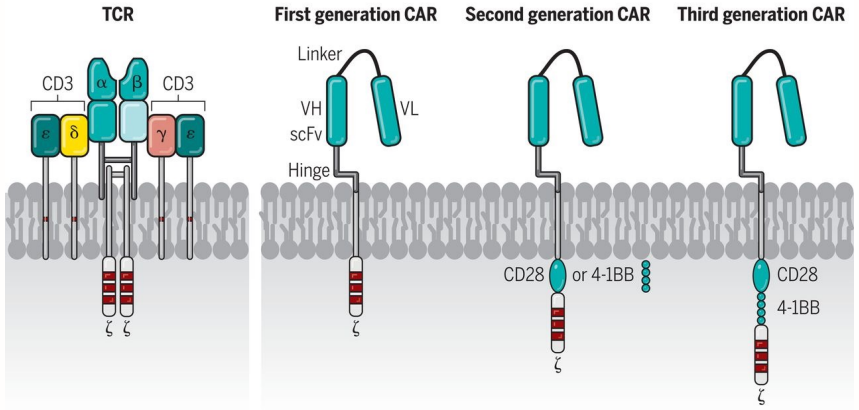
Study	Phase	Year	Patients	Antigen	Adjuvant Therapy	Clinical Efficacy	Immunologic Response
Yu et al. [183]	I	2001	7 GBM 2 AA	Autologous glioma peptides		Vaccine group: OS 455 days Control group: OS 257 days	Four out of seven patients demonstrated increased cytotoxic T cell activity; Two out of four patients who underwent re-operation showed increased infiltration of CD8+ and CD45RO+ T cells.
Kikuchi et al. [184]	I	2001	5 GBM 2 AA 1 AO	Glioma cells		Two patients had partial response	Post immunization PBMC showed reactivity against autologous glioma or U87MG cells.
Kikuchi et al. [185]	I	2004	6 GBM 2 AOA 7 AA	Glioma cells		Four patients had partial response. One patient had mixed response. Two patients with stable disease. The rest of the patients progressed.	Two out of seven patients had cytolytic activities against glioma cells post immunization.
Liau et al. [186]	I	2005	12 GBM	Tumor associated antigen		Vaccine group: PFS 19.9 months, OS 35.9 months Historical control group: PFS 8.2 months, OS 18.3 months.	Six patients developed peripheral cytotoxic tumor-specific activity. Systemic cytotoxic activity and tumor lymphocytic infiltration were associated with response.
Rutkowski et al. [187]	1	2004	10 GBM 1 PXA 1 ALL	Tumor lysate		Four out of 12 patients had partial response. Two out of six patients with complete resection had survival >35 months.	Six out of eight patients who underwent DTH skin test had a positive test after the third vaccination.
Yamanaka et al. [188]	I/II	2005	18 GBM 2 AA 2 AOA 2 AG	Tumor lysate		One partial responder and three minor responders. Vaccine group: OS 480 days Control group: OS 400 days	Presence of tumor lysate specific T cell response after vaccination was associated with longer OS.
Yu et al. [189]	I	2004	10 GBM 4 AA	Tumor lysate		Vaccine group: OS 133 weeks Matched control group: OS 30 weeks.	Eleven out of 14 patients showed evidence of cytotoxic T cell activities. Four out of nine patients studied showed cytotoxic T cells specific against tumor antigens post vaccination.
De Vleeschouwer et al. [190]	I/II	2008	56 GBM	Tumor lysate		Improved PFS in a cohort of patients who received weekly vaccination.	Nine out of 21 patients demonstrated positive DTH response post immunization.
Caruso et al. [191]	I	2004	2 GBM 3 EPM 1 AA 1 PXA	Tumor RNA		One partial responder in AA group. All GBM patients progressed on therapy.	No statistically significant cell-mediated anti-tumor responses in either an IFN-γ-producing assay or T cell proliferation assay. Modest increase in anti-tumor antibodies in two patients.
Walker et al. [192]	I	2008	9 GBM 4 AA	Irradiated glioma cells		Two partial responders in GBM group. One partial and one complete responder in AA group.	Increase in tumor T cell infiltration in three out of four patients who underwent re-operation post vaccination.
Okada et al. [193]	I	2007	6 GBM 1 AA	Tumor cell	TFG-hIL4-Neo-TK	Initial radiographic improvement, but ultimate progression of disease.	Local infiltration of CD4+ and CD8+ T cells with associated IFN-γ response to EphA2883-891.
Okada et al. [193]	I	2007	5 GBM	Tumor cell	TFG-hIL4-Neo-TK + Type I DC	All patients progressed within 10 months of vaccination.	No IFN-γ activity detected.
Prins et al. [194]	I	2010	23 GBM	Tumor lysate	Imiquimod or Poly-ICLC	Significantly increased median OS in newly diagnosed GBM compared to recurrent patients.	Patients with mesenchymal gene signatures had improved survival compared to historical data.
Ardon et al. [195]	I	2010	22 GBM 5 AA 2 PXA 1 AOA 1 AGG 1 DIPG 5 MB 4 EPM 3 ATRT	Tumor lysate	Imiquimod DC maturation ex vivo with IL-B1 and TNF-α	Six long term survivors (>24 months) in the high grade glioma group, four of which are GBM.	
Mitchell et al. [148]	I/II	2015	12 GBM	CMV pp65 RNA	Td toxoid	Median OS 18.5 months in DC only cohort. Three out of six patients in Td group still alive at >36 months.	Increased migration of DC to tumor site with Td toxoid administration. pp65-specific immune response was present for 6 months in long term survivors. pp65-specific IFN-γ response was correlated with PFS and OS.
Sampson et al. [196]	I	2009	12 GBM	EGFRvIII peptide		Vaccinated group: Median OS 22.8 months.	Increased antigen-specific T cell responses post vaccination. Positive response to pulsed peptide.
Okada et al. [197]	I/II	2011	13 GBM 5 AA 3 AO 1 AOA	IL-13Rα2, $EphA2_{883-891}$ $GP100_{209-217}$ and $YKL-40_{201-21}$	Poly-ICLC	One complete responder and one partial responder in GBM group.	Eleven out of 19 patients showed tumor-associated peptide response by ELISPOT and tetramer assay.
Phuphanich et al. [198]	I	2013	21 GBM 1 DIPG	HER2, TRP-2, gp100, MAGE-11, IL13 Rα2, and AIM-2		Median PFS newly diagnosed GBM 16.9 months Median OS newly diagnosed GBM 38.4 months	Five of 15 GBM patients had positive immune response of >0.5-fold compared to pre vaccination.
Akiyama et al. [199]	I	2012	7 GBM 1 AA 1 AO	WT-1, HER2, MAGE-A3, MAGE-A1, gp100		One patient with stable disease; eight patients with progressive disease.	Cytotoxic T cell precursors against tumor-associated peptides were detected in six evaluable cases; four patients had positive DTH tests against all peptides.
Prins et al. [200]	I	2013	Tumor lysate: 23 GBM, 5 AA TAA: 4 GBM, 2 AA	Comparison between tumor lysate and tumor associated antigens		Tumor lysate: OS 34.4 months, PFS 18.1 months TAA: OS 14.5 months, PFS 9.6 months	Increased activated NK cell population in TAA group. Post vaccination and pre vaccination T_{reg} ratio showed trend toward association with survival.

Systemic Therapies—DC Vaccine

Srivastava. Cancers (2019)

Study	Phase	Year	Patients	Antigen	Adjuvant Therapy	Clinical Efficacy	Immunologic Response
Yamanaka et al. [201]	I/II	2003	7 GBM 3 AG	Tumor lysate		Two patients with minor responses	Positive T cell-mediated immune response in two out of five tested patients. Three patients showed positive DTH
Wheeler et al. [202]	II	2008	34 GBM	Tumor lysate		Vaccine responder: OS 642 days Vaccine non-responder: OS 430 days Vaccine responders associated with improved OS and PFS.	Seventeen patients had >1.5 fold increase in lysate directed IFN-γ response post vaccination (vaccine responder)
Fadul et al. [203]	I	2011	10 GBM	Tumor lysate		Patients with high immune function measures showed improved OS trends. Four out of five patients with high immune function measures had survival >2 years.	Proportion of CD4+ and CD8+ IFN-γ producing cells showed trend of increase post vaccination.
Chang et al. [204]	I/II	2011	16 GBM 1 AA 2 MOG	Tumor cells		Vaccine group: OS 520 days Historical control: OS 380 days 37.5% 3-year survival rate, 18.8% 5-year survival rate	Increased diffuse tumor infiltration lymphocyte post vaccination. Increased CD8+ to CD4+ tumor-infiltrating lymphocyte ratio.
Cho et al. [205]	II	2012	34 GBM	Tumor lysate		Vaccine group: OS 31.9 months, PFS 8.5 months Control group: 15 months, PFS 8 months	
Laskey et al. [206]	I	2013	2 GBM 1 AOA	Tumor lysate		Two out of three patients alive >40 months.	No increase in infiltrating lymphocyte post vaccination in one studied patient. Increase in IL10 after vaccination in one studied patient.
Jie et al. [207]	II	2012	25 GBM	Tumor cells		Vaccine group: OS 17 months, PFS 11.92 months Control group: OS 10.5 months, PFS 7.75 months	Higher CD3+, CD4+, CD4+/CD8+ and NK cells levels post vaccination.
Ardon et al. [208]	I	2010	8 GBM	Tumor lysate		One patient free from progression >34 months. Three patients alive at follow up >34 months	Five out of eight patients showed increased antigen reactive T cell IFN-γ production post vaccination.
Sakai et al. [209]	I	2015	6 GBM 2 AA 1 AOA 1 OG	WT-1 antigen, tumor lysate		Median OS 26 months. One GBM patient alive > 46 months post vaccination.	Eight patients had positive DTH reactions post vaccination. Six patients demonstrated increased WT1-specific cytotoxic T lymphocytes.
Hunn et al. [210]	I	2015	14 GBM	Tumor lysate	Pretreatment with TMZ	Two patients had partial response. Two patients had prolonged progression-free survival. Median OS: 23 months.	Two patients demonstrated increased tumor-associated antigen response post vaccination.
Vik-Mo et al. [211]	I/II	2013	7 GBM	Glioma mRNA	Booster vaccines	Vaccine group: OS 759 days, PFS 694 days. Historical control group: OS 585 days, PFS 236 days.	All seven patients had tumorsphere lysate-specific lymphocyte proliferation.
Batich et al. [212]	I	2017	11 GBM	CMV pp65 mRNA with GM-CSF	Treated with TMZ	Vaccine group: OS 41.1 months; Historical control group: OS 19.2 months.	Ten out of 11 patients demonstrated increase in pp65 specific IFN-γ response. Pp65 specific CD8+ T cells increased post vaccination.
Inoges et al. [213]	II	2017	31 GBM	Tumor lysate		OS was 23.4 months, PFS was 12.7 months.	Eight patients showed increased IFN-γ production post vaccination
Liau et al. [214]	III	2018	331 GBM Dcvax-L: 232 Placebo: 99	Tumor lysate	Treated with TMZ	Intent to treat group: OS 23.1 months; 223 patients alive >30 months from surgery; 100 extended survivors of OS > 40.5 months.	
Iwami et al. [215]	I	2012	5 GBM 1 AA 2 AO	IL-13Rα2		Three patients with stable disease. One patient had mixed radiographic response.	Two out of three patients where immunologic studies can be conducted showed peptide-specific T cell activity post vaccination.

Systemic Therapies—CAR T-cell



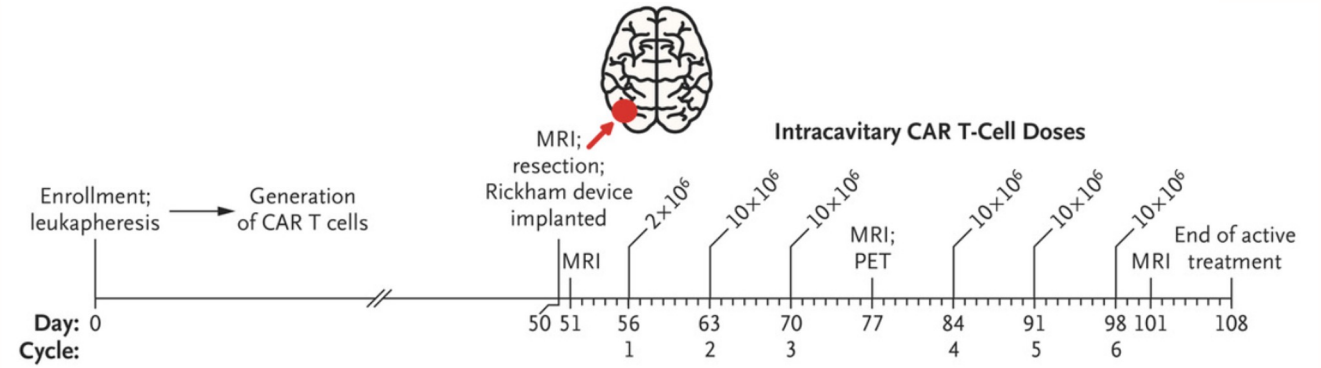
Immunotherapy	Treatment	Setting	Phase	Sample Size	PFS (m)	OS (m)
2010 (Baylor)	HER2 CAR CMV-specific CTLs (HERT-GBM)	Recurrent	I	N=16	3.5 months	11.1 months
2011 (NCI)	EGFRvIII CAR T	Recurrent	I/II	N=18	1.3 months	6.9 months
2014 (UPenn, UCSF)	EGFRvIII CAR T	Recurrent	Pilot	N=11		
2014 (City of Hope)	IL13Ra2 4-1BB-co-stimulatory CAR	Recurrent	I	N=82		
2016 (City of Hope)	HER2(EQ)BBζ/CD19t+ T cells	Recurrent	I	N=42		
2016 (Duke)	EGFRvIII CAR T (ExCeL)	New	I	N=3		
2018 (UPenn)	EGFR CAR T + PEMBRO	Recurrent	I	N=7		
2020 (City of Hope)	Chlorotoxin Tumor-Targeting Domain CAR T	Recurrent	I	N=36		
2021 (City of Hope)	IL13Ra2 CAR T +/- NIVO/IPI	Recurrent	I	N=60		
2021 (City of Hope)	IL13Ra2 CAR T for Leptomeningeal	Recurrent	I	N=30		
2022 (UNC)	B7-H3 Autologous CAR T	Recurrent	I	N=36		
2022 (Stanford)	B7-H3 CAR T	Recurrent	I	N=39		
2022 (U Florida)	IL-8R modified CD70 CAR T (IMPACT)	New	I	N=18		

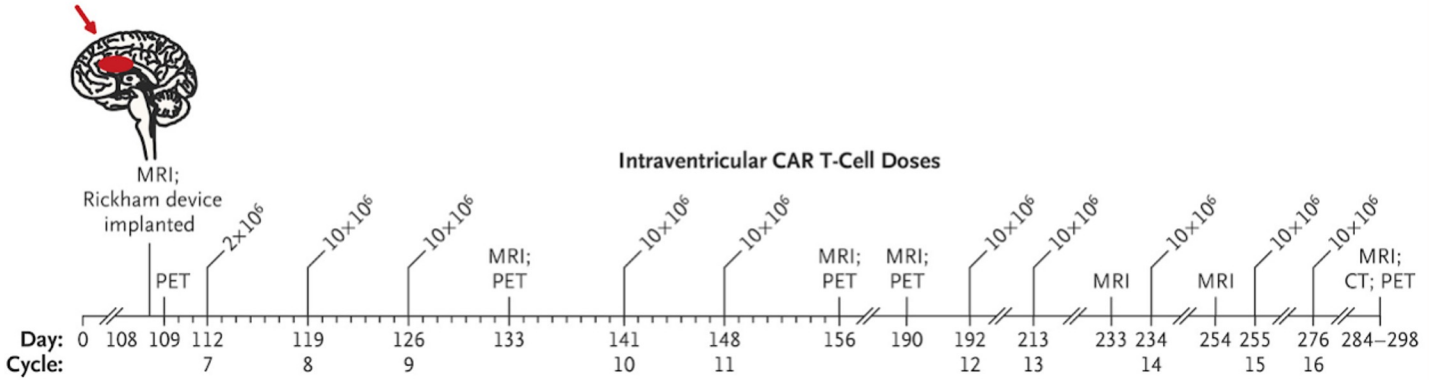
Systemic Therapies—CAR T-cell

Brown. NEJM (2016)

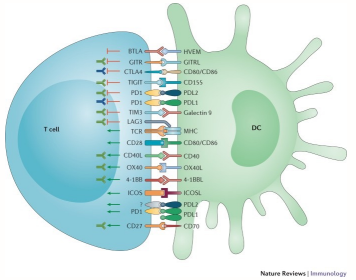
The NEW ENGLAND JOURNAL of MEDICINE

Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy





Systemic Therapies—Checkpoint Blockade



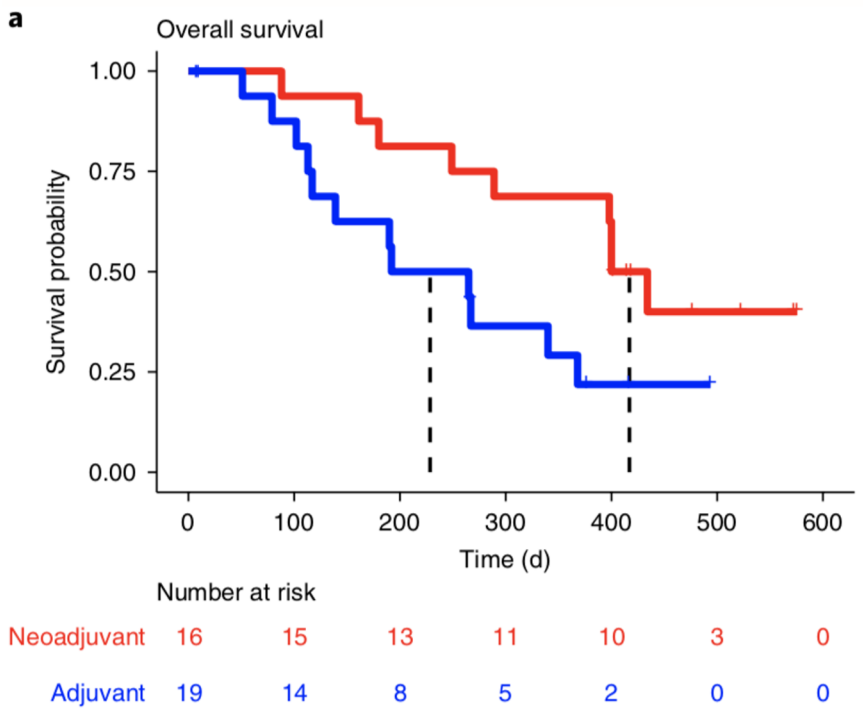
Immunotherapy	Treatment	Setting	Phase	Sample Size	ORR (%)	PFS (m)	OS (m)
Carter (2016)	IPI + BEV	Recurrent	Retrospective	N=16	31.0	--	--
Blumenthal (2016)	PEMBRO	Recurrent	Retrospective	N=10	--	--	2.6 [Range 0.4-11.6]
Chamberlain (2017)	NIVO	Recurrent	Retrospective	N=16	0.0	2.0 (95% CI 1.3-2.7)	35 (95% CI 2.8-4.2)
Omuro (2018) CheckMate 143	NIVO	Recurrent	I	N=10	11.0	1.9 (95% CI 1.3-4.6)	10.4 (95% CI 4.1-22.8)
	NIVO + IPI	Recurrent	I	N=10	0.0	1.5 (95% CI 0.5-2.8)	9.2 (95% CI3.9-12.7)
	NIVO + IPI	Recurrent	I	N=20	10.0	2.1 (95% CI 1.4-2.8)	7.3 (95% CI 4.7-12.9)
Mantica (2018)	NIVO (+ BEV)	Recurrent	Retrospective	N=37	0.0	4.6 [range 0.5-15.0]	6.5 [range 0.8-19.5]
Lukas (2018)	ATEZO	Recurrent	I	N=16	6.0	1.2 [range 0.7-10.7]	4.2 [range 1.2-18.8+]
Reardon (2020) CheckMate 143	NIVO vs. BEV	Recurrent	III	N=369	NIVO 7.8% BEV 23%	NIVO 1.5 (95% CI 1.5-1.6) BEV 3.5 (95% CI 2.9-4.6)	NIVO 9.8 (95% CI 8.2-11.8) BEV 10 (95% CI 9.0-11.8)
Cloughesy (2019)	Neoadjuvant PEMBRO	Recurrent	II	N=16		3.3	13.7
	Adjuvant PEMBRO	Recurrent	II	N=16		2.4	7.5
Schalper (2019)	Neoadjuvant NIVO	Both	II	N=29		4.1 (95% CI 2.8-5.5)	7.3 (95% CI 5.4-7.9)
CheckMate 498 (2019)	MGMTun NIVO+RT vs. RT/TMZ	New	III	N=560		--	*did not meet primary endpoint of OS
CheckMate 548 (2020)	MGMTm NIVO+RT/TMZ vs. RT/TMZ	New	III	N=693		*did not meet primary endpoint of PFS	*did not meet primary endpoint of OS

Systemic Therapies—Checkpoint Blockade

nature medicine

Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma

Timothy F. Cloughesy[1,2,3,18*], Aaron Y. Mochizuki[4,18], Joey R. Orpilla[5], Willy Hugo[6], Alexander H. Lee[2,5], Tom B. Davidson[3,4], Anthony C. Wang[5], Benjamin M. Ellingson[3,7], Julie A. Rytlewski[8], Catherine M. Sanders[8], Eric S. Kawaguchi[9], Lin Du[9], Gang Li[3,9], William H. Yong[10], Sarah C. Gaffey[11], Adam L. Cohen[12], Ingo K. Mellinghoff[13], Eudocia Q. Lee[11], David A. Reardon[11], Barbara J. O'Brien[14], Nicholas A. Butowski[15], Phioanh L. Nghiemphu[1], Jennifer L. Clarke[15], Isabel C. Arrillaga-Romany[16], Howard Colman[12], Thomas J. Kaley[13], John F. de Groot[14], Linda M. Liau[3,5], Patrick Y. Wen[11,19] and Robert M. Prins[2,3,5,17,19*]

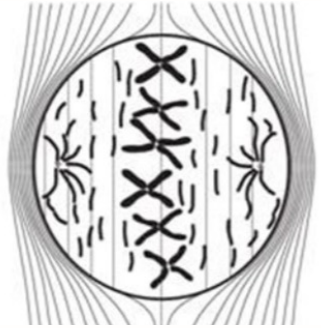


Systemic Therapies—Checkpoint Blockade

JCI The Journal of Clinical Investigation

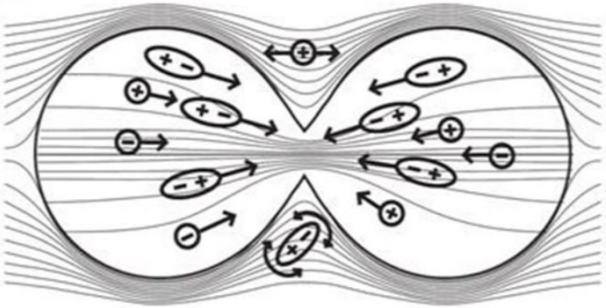
Tumor Treating Fields dually activate STING and AIM2 inflammasomes to induce adjuvant immunity in glioblastoma

Dongjiang Chen,[1] Son B. Le,[1] Tarun E. Hutchinson,[1] Anda-Alexandra Calinescu,[1] Mathew Sebastian,[2] Dan Jin,[1] Tianyi Liu,[1] Ashley Ghiaseddin,[1] Maryam Rahman,[1] and David D. Tran[1]



TTF induces immune activation

EF-41/KEYNOTE D58 *coming soon*
Phase 3 double-blind, controlled study of Tumor Treating Fields with Pembrolizumab in Newly Diagnosed Glioblastoma



Future Directions

Future Directions

Combination Therapies
- Radiation
- Laser interstitial therapy
- Tumor Treating Fields
- TIM3, IDO1
- Other immunotherapies

Breaching the blood brain barrier
- Penetration of therapies

Assessment of response/progression
- Lack adequate imaging techniques
  - Diffusion-weighted sequencing
  - Labeling dendritic cells with iron oxide/indium
  - pH via chemical exchange saturation transfer
  - PET probes
- Biomarkers (tissue, CSF, blood)

Clinical Trial Design
- Factorial design to evaluate multiple therapies at once
- Adaptive design

Thank you!

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