Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Advances in the Management of GBM and Other Brain Tumors

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Dana Farber/Harvard Cancer Center

Harvard Medical School

Boston, Massachusetts

Disclosures

Research Grants:

A Reason To Ride Research Fund

AstraZeneca

Five Prime Therapeutics

Immunocellular Therapeutics

Merck

Northwest Biotherapeutics

Novocure

Pfizer

Plexxicon

Vascular Biogenics

The Boston Globe

TUESDAY, JUNE 3, 2008

FKYOLATOR

Today: Sunny, some clouds. High 80-85. Low 58-63.
Tomorrow: Sun, showers, T-storms. High 79-79. Low 56-61.
High Tide: 11:22 a.m. 11:33 p.m.
Sunrise: 5:09 a.m. Sunset: 8:16 p.m.
Full Report: Page B6

Kennedy has 'successful' surgery

Rapport with pioneer surgeon leads to the senator's choice

3-hour procedure at Duke Medical Center targets tumor; doctor says goals achieved

By Stephen Smith and Carey Goldberg
GLOBE STAFF

For his brain surgery yesterday, Senator Edward M. Kennedy turned to a bold doctor known for his willingness to operate when others might not and to a treatment center at Duke University whose motto is, "There is Hope."

Massachusetts General Hospital, where Kennedy has received care until now, is as expert at treating brain tumors as Duke, cancer specialists said, but the senator was at least partly swayed by a personal connection with the charismatic Dr. Allan H. Friedman.

Duke is among the top brain tumor centers in the country in both research and care, offering a wide array of clinical trials of novel treatments.

"They have all the pieces," said Dr. John Park, head of surgical neuro-oncology at the National Institute of Neurological Disorders and Stroke. "They have excellent surgery and a wide range of experimental chemotherapies

DUKE, Page A9

'I feel like a million bucks. I think I'll do that again tomorrow.'
Senator Edward M. Kennedy

CNN politics 45 CONGRESS SUPREME COURT 2018 KEY RACES PRIMARY RESULTS

Beau Biden, son of vice president and former Delaware AG, dies at 46

By Kevin Liptak, CNN White House Producer
Updated 7:11 AM ET, Sun May 31, 2015

The Washington Post
Democracy Dies in Darkness

McCain, battling brain cancer, in Walter Reed from effects of treatment

By Washington Post on Dec 14, 2017 at 10:01 a.m.

Sen. John McCain, R-Ariz., makes his way to a meeting in Washington about the tax bill on Dec. 1. Washington Post photo by Bill O'Leary

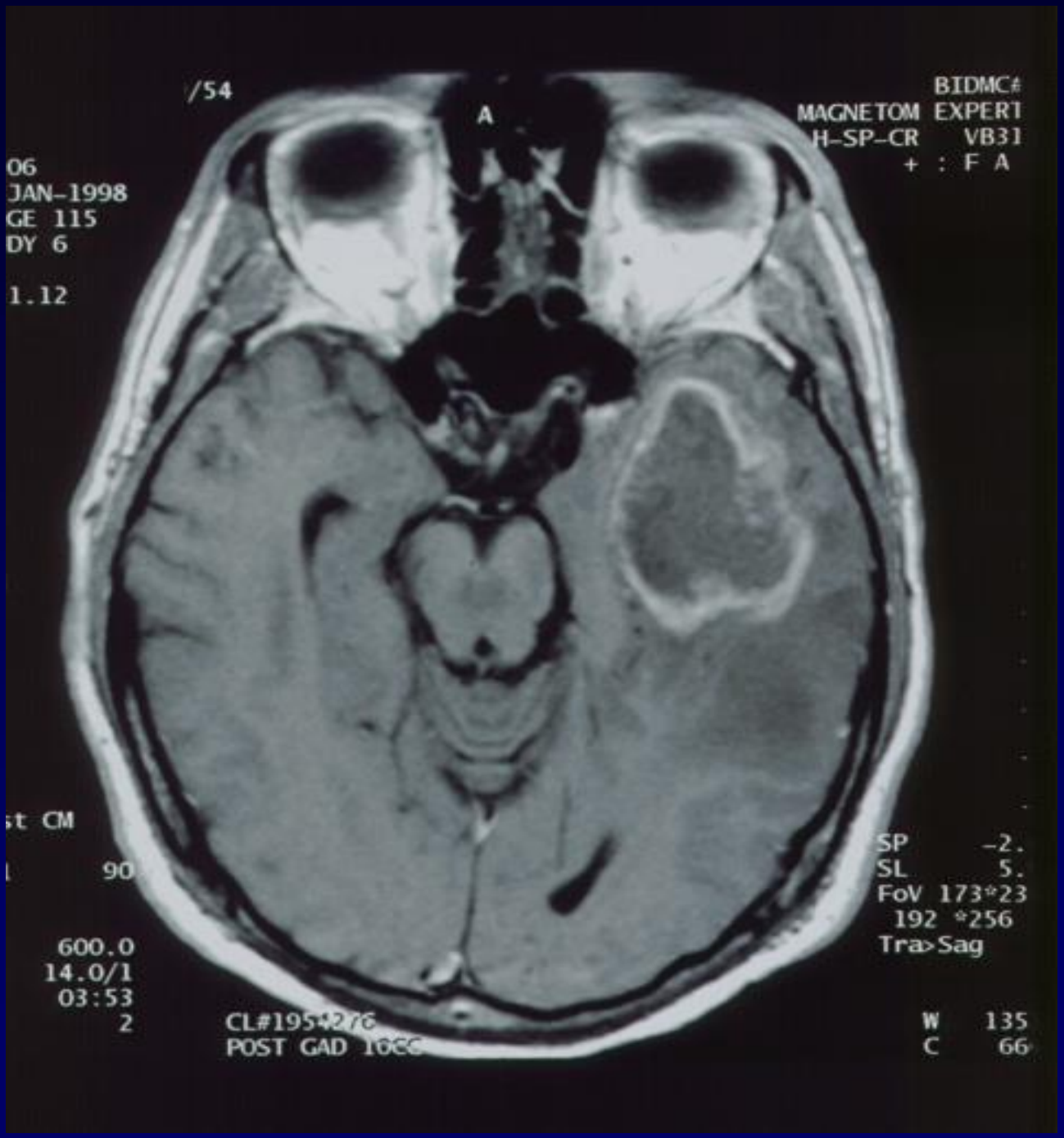
Advances in the Management of GBM and Other Brain Tumors

Objectives

- To identify recently FDA-approved therapies for malignant gliomas and other brain tumors.
- To discuss recent data on immunotherapies for malignant gliomas.
- To discuss dexamethasone interference in the management of patients with malignant gliomas.

FDA-Approved Treatments for Malignant Glioma

- June 14, 1996: Carmustine wafer for recurrent glioblastoma
- January 12, 1999: Temozolomide for anaplastic astrocytoma
- February 25, 2003: Carmustine wafer for newly diagnosed glioblastoma
- March 15, 2005: Temozolomide for newly diagnosed glioblastoma
- May 5, 2009: Bevacizumab for progressive glioblastoma (provisional approval)
- April 15, 2011: Tumor Treating Fields for recurrent glioblastoma
- October 5, 2015: Tumor Treating Fields for newly diagnosed glioblastoma
- June 6, 2017: Aminolevulinic acid hydrochloride (5-ALA HCl)
- December 5, 2017: Bevacizumab for recurrent glioblastoma (full approval)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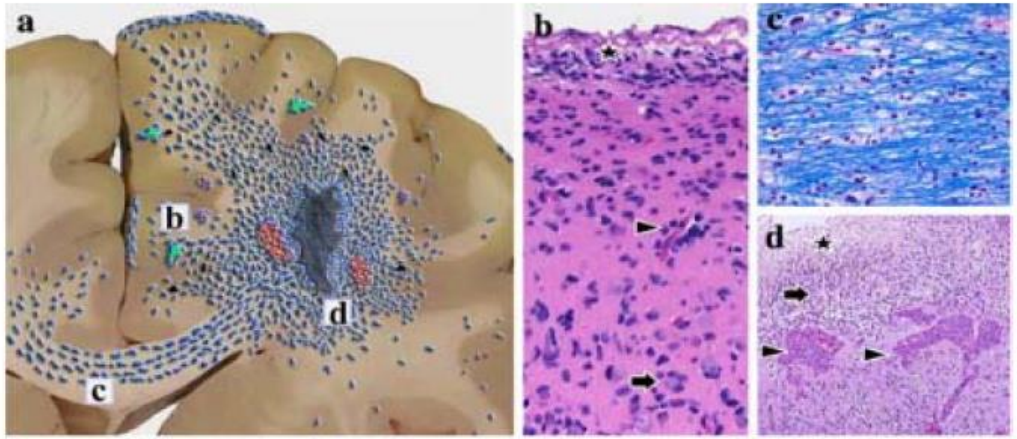
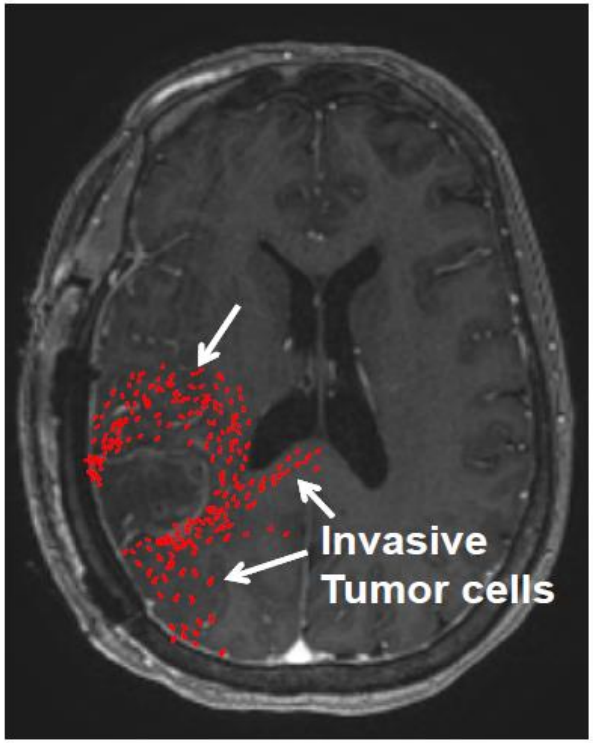
C 66

Impossible to Resect All Glioma Tumor Cells

- Invasive and infiltrative tumors
- Difficult to visualize tumor and perform maximal EOR
- Residual tumors cells outside of contrast enhancing margin
- Almost all recurrences local

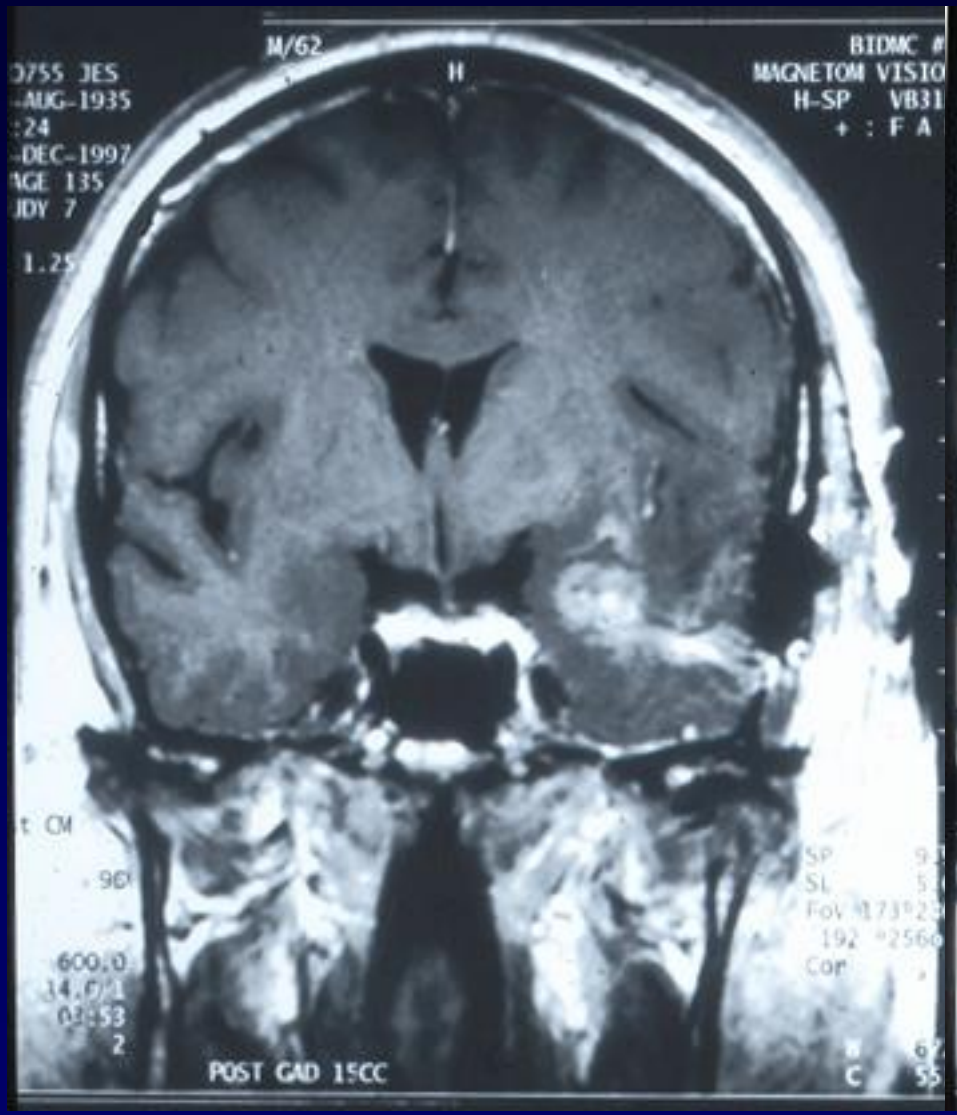


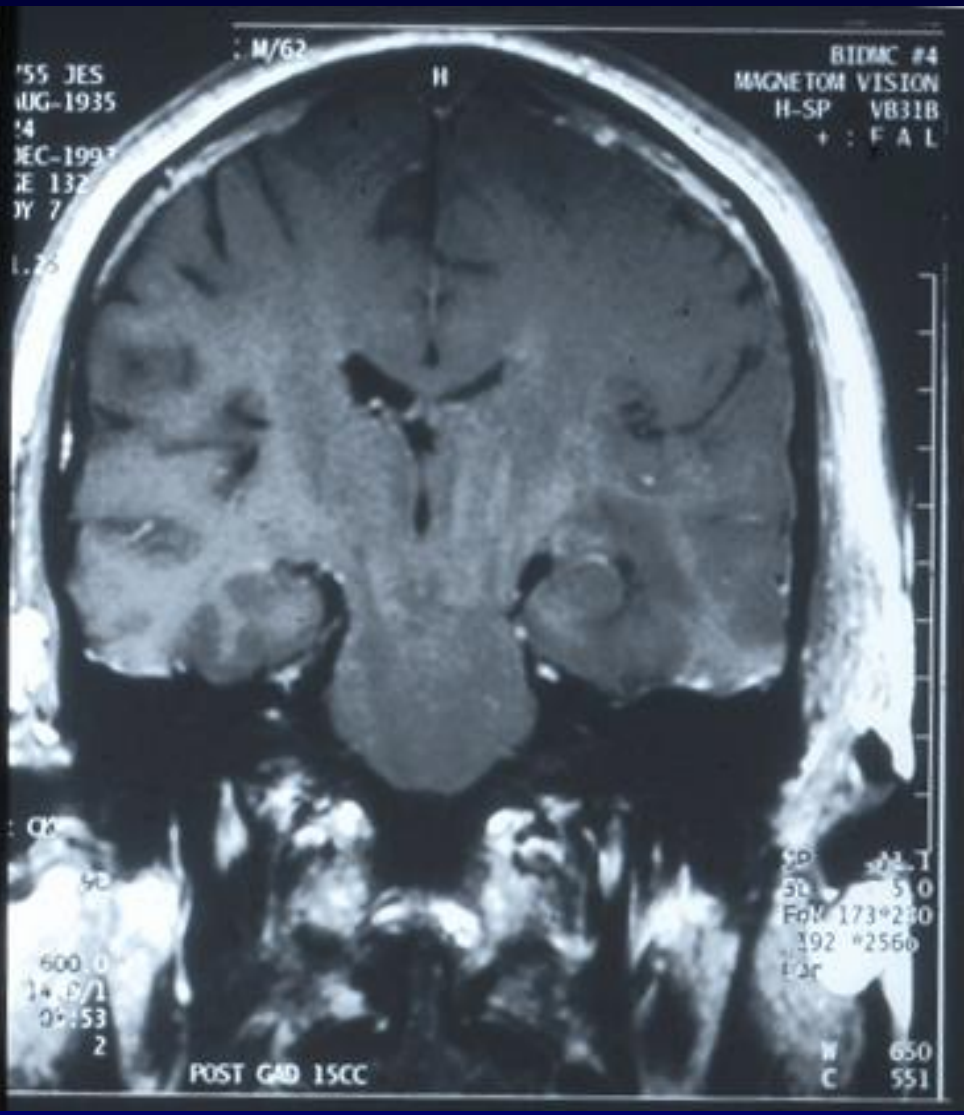


Postop MRI T1 w/Gad

Claes A et al. *Acta Neuropathol* 2007; Kelly PJ et al. *J Neurosurg* 1987.

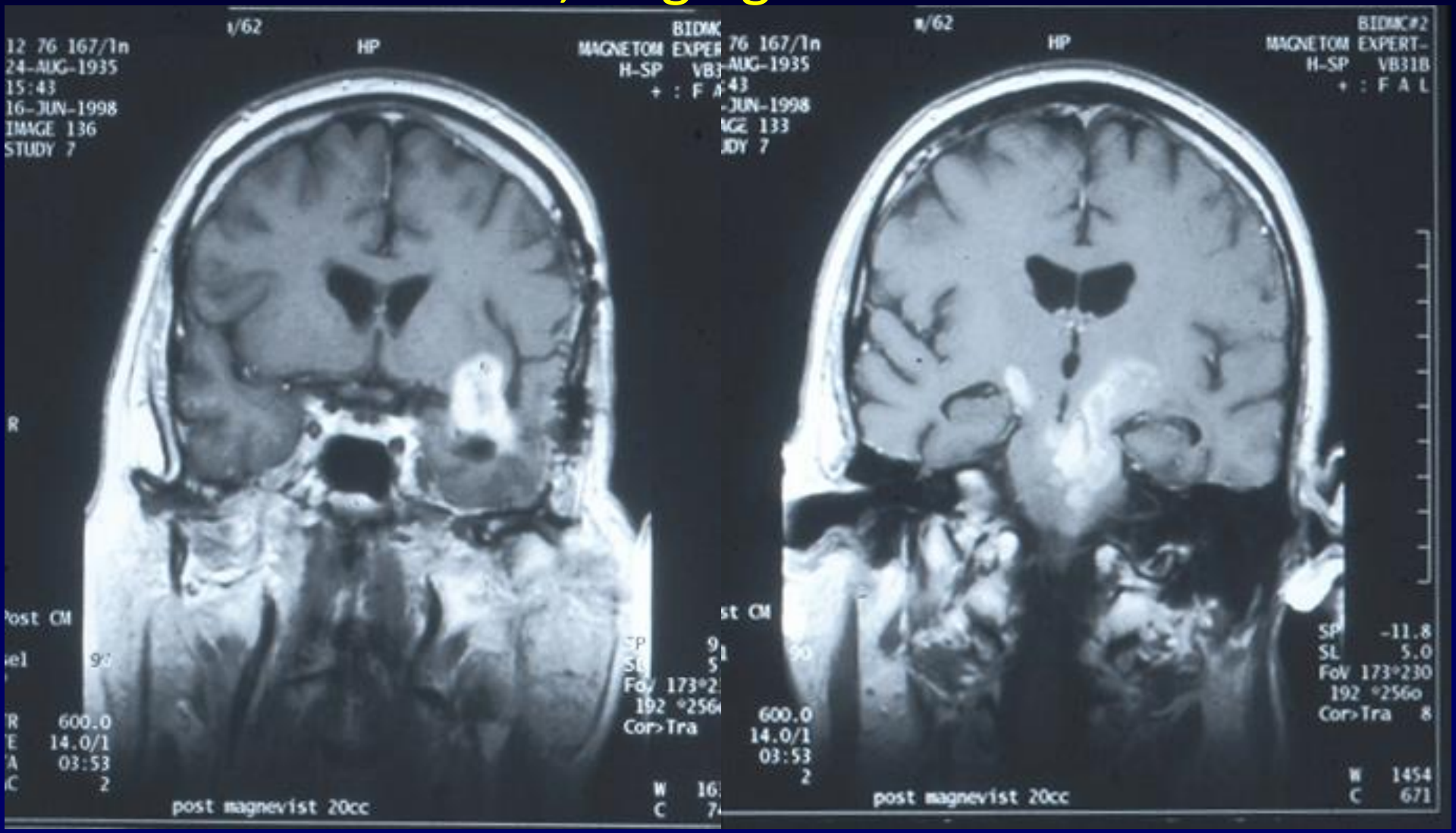
Hallmarks of Glioblastoma: Tumor Growth, Angiogenesis and Invasion





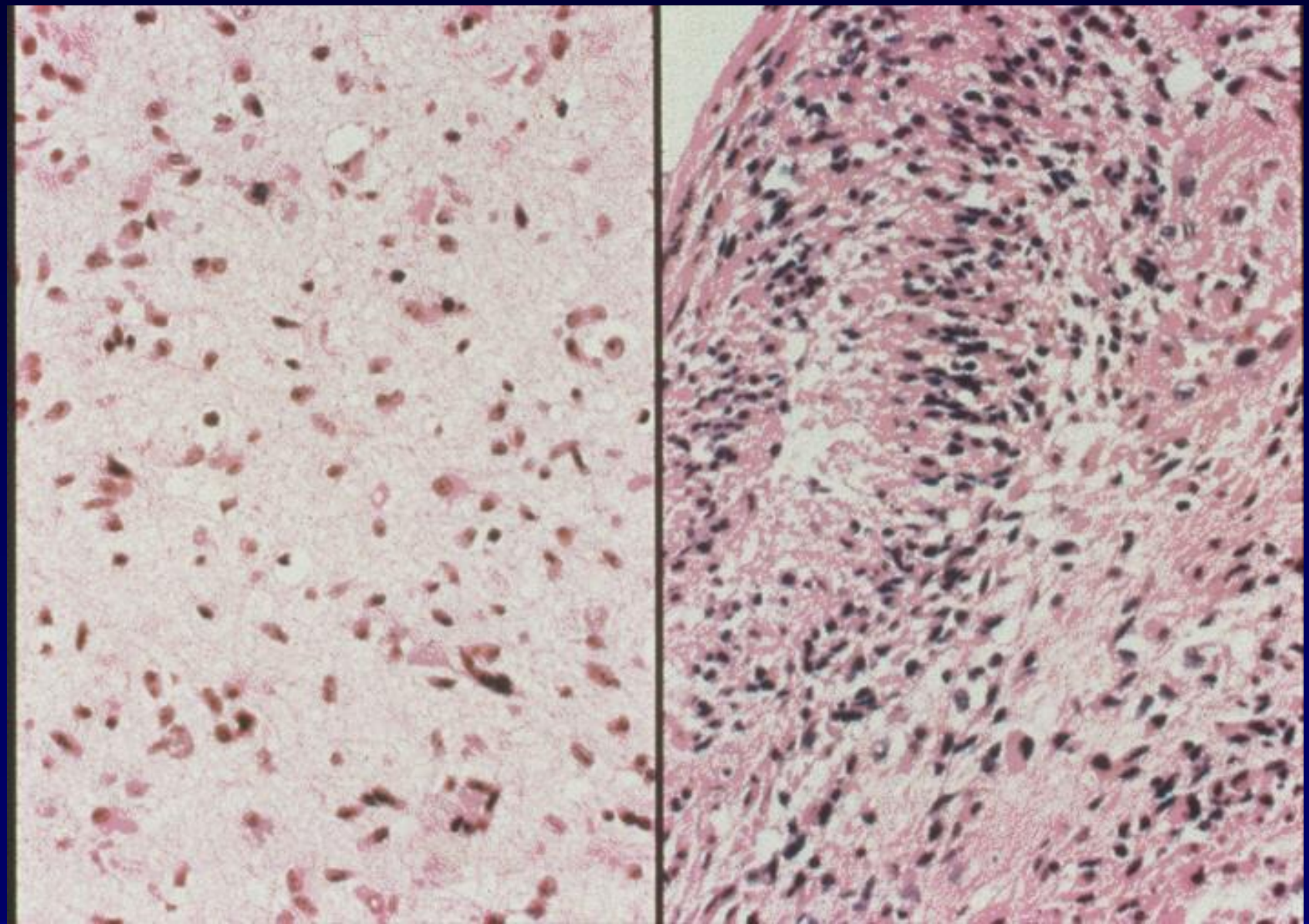
Wong ET. *J Neurooncol* 2006;77:295-296.

Hallmarks of Glioblastoma: Tumor Growth, Angiogenesis and Invasion



Wong ET. *J Neurooncol* 2006;77:295-296.

Pseudopalisading Necrosis and Invasion are Hallmarks of Glioblastoma



VEGF mRNA is Upregulated in the Hypoxic Zone of Glioblastoma

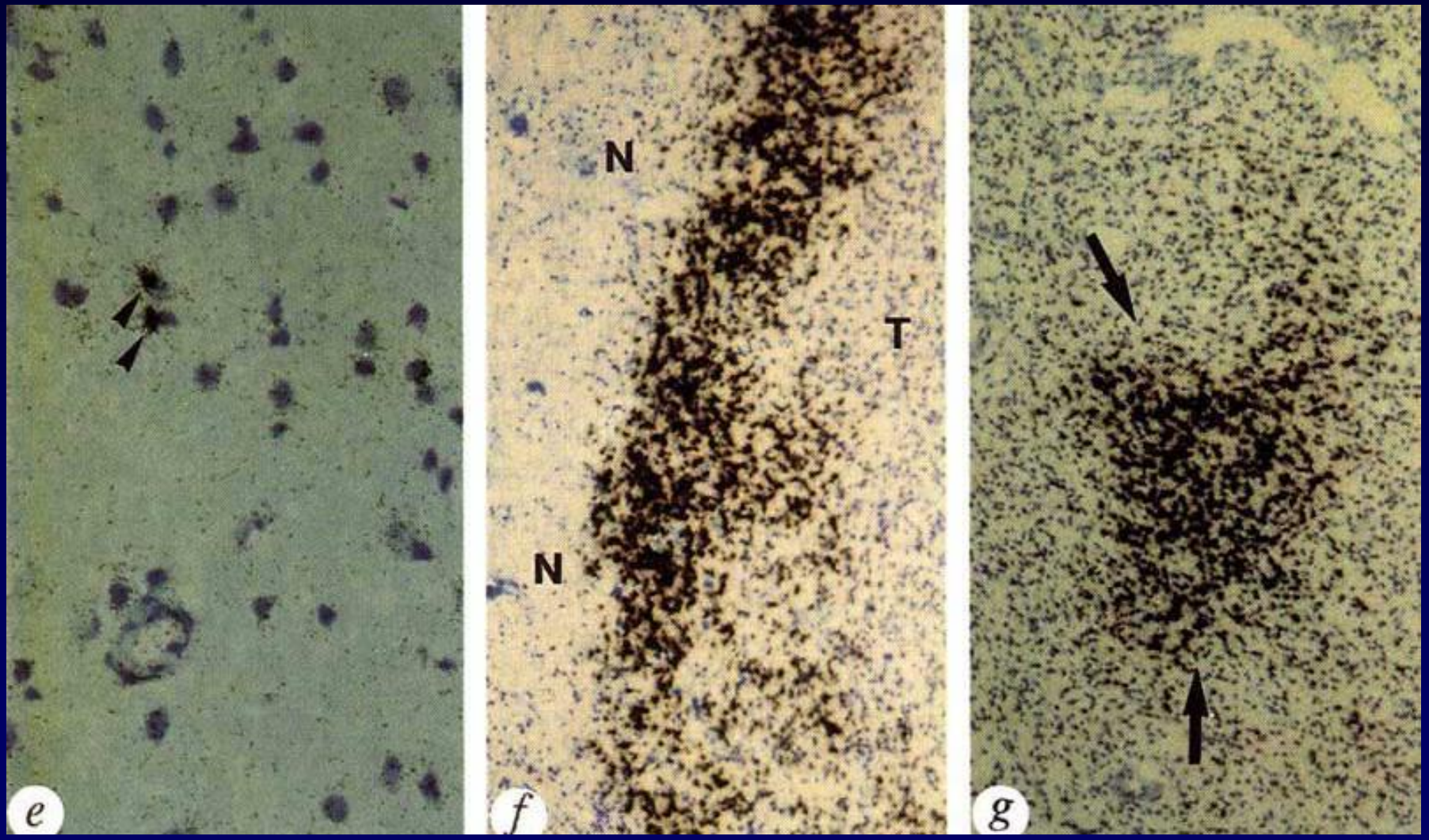


Plate KH, Breier G, Weich HA, et al. Nature 1992;359:845-848.

Bevacizumab for Newly Diagnosed Glioblastoma

1. No survival benefit in the upfront treatment of glioblastoma

PRIMARY ENDPOINTS, AVAGLIO & RTOG 0825				
	AVAGLIO		RTOG 0825	
Regimen	Bev/TMZ/RT	TMZ/RT	Bev/TMZ/RT	TMZ/RT
PFS	10.6 months	6.2 months	10.3 months	7.3 months
	HR 0.64, p<0.0001		HR 0.79, p=0.07	
OS	16.8 months	16.7 months	15.7 months	16.1 months
	HR 0.88, p=0.0987		HR 1.13, p=0.21	

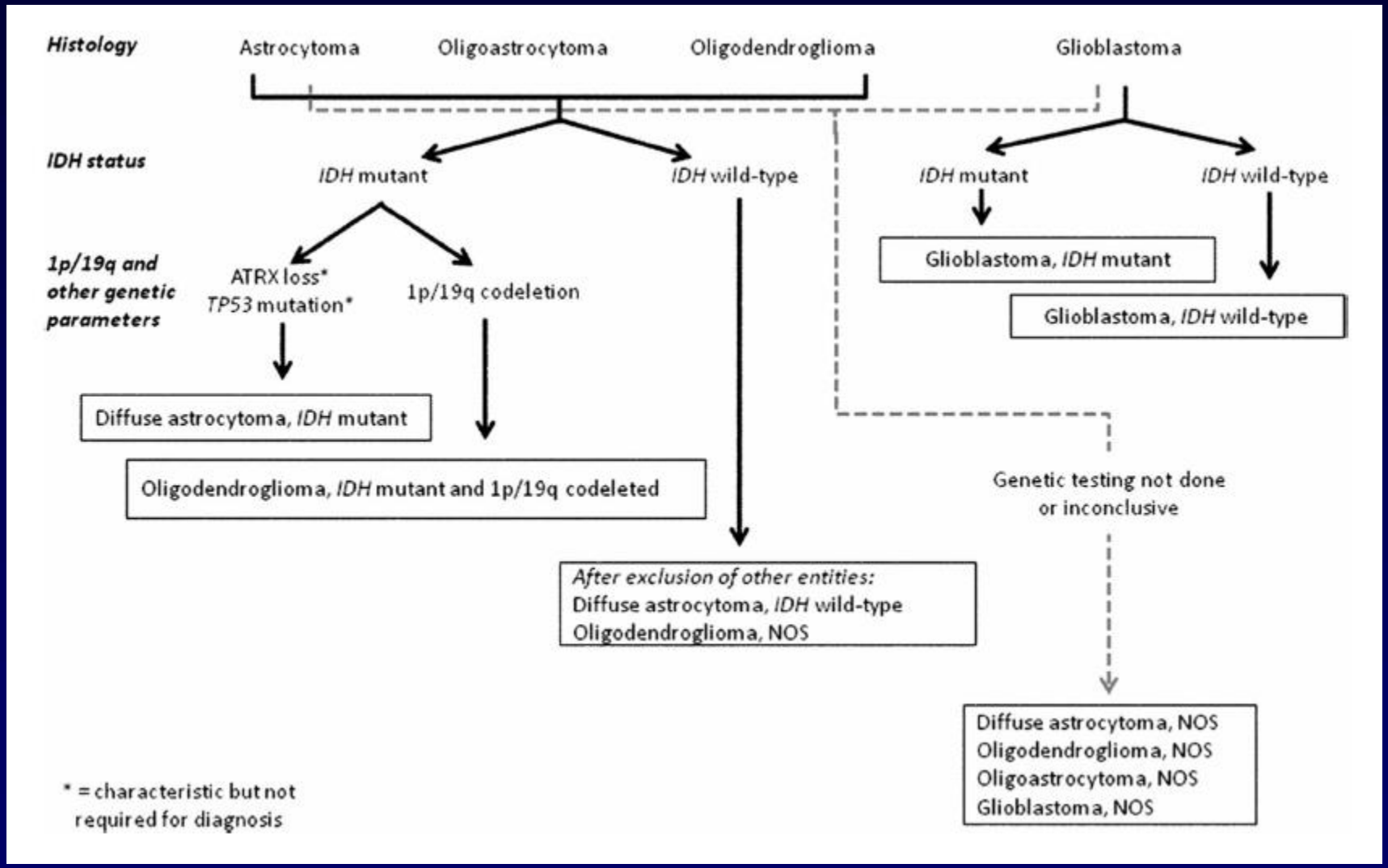
Sources: AVAglio: Wick, Abstract 2002, ASCO 2013; RTOG 0825: Gilbert, Abstract 1, ASCO 2013.

2. There may be benefit in specialized population of patients with newly diagnosed glioblastoma (i.e. large unresectable tumor, molecular genetics, etc.)

Targeted Therapies for Various Types of Common Malignancies versus Malignant Brain Tumor (www.cancer.gov/about-cancer/treatment)

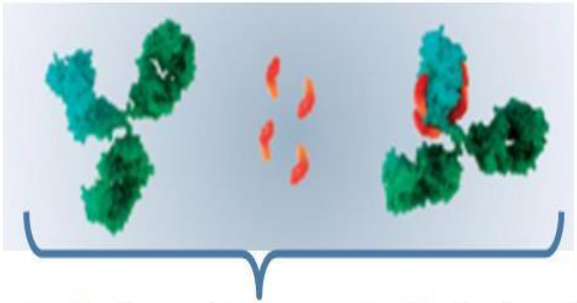
Lung Cancer	Breast Cancer	Colon Cancer	Brain Cancer
Afatinib	Abemaciclib	Bevacizumab	Bevacizumab
Bevacizumab	Ado-Trastuzumab Emtansine	Cetuximab	
Ceritinib	Everolimus	Panitumumab	
Crizotinib	Lapatinib	Regorafenib	
Dabrafenib	Neratinib	Zvi-Aflibercept	
Erlotinib	Olaparib		
Gefitinib	Palbociclib		
Osimertinib	Pertuzumab		
Trametinib	Ribociclib		
	Trastuzumab		

Updated WHO Classification for Malignant Gliomas: Incorporation of Molecular Genetics



Louis DN, Perry A, Reifenberger G, et al. *Acta Neuropathol* 2016;131:803-820.

Depatux-M (ABT-414) is a Monoclonal Antibody Drug Conjugate (ADC) Directed Against EGFR

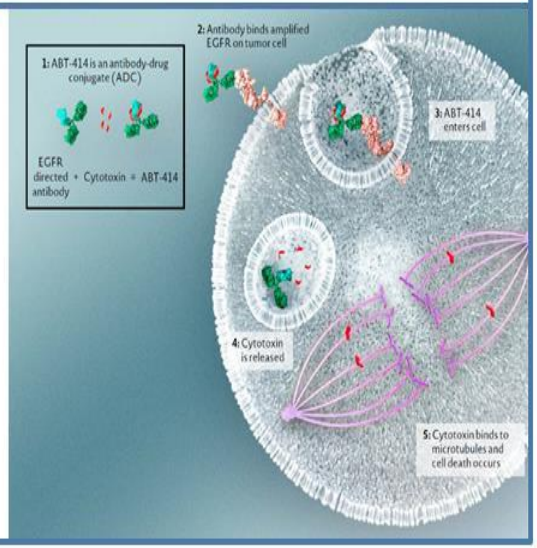


Antibody (ABT-806) + **Toxin (MMAF)** = **Antibody Drug Conjugate (Depatux-M)**

Depatux-M is an **antibody-drug conjugate (ADC)**, comprised of an antibody that ***selectively targets activated EGFR*** and a cytotoxin that is **only released inside the *tumor* cell**

REF's: Gan HK, et al. *Cancer Res.* 2012;72(12):2924–2930, Doronina SO, et al. *Bioconjug Chem.* 2006;17(1):114-124, Trail PA. *Antibodies.* 2013;2:113-129.

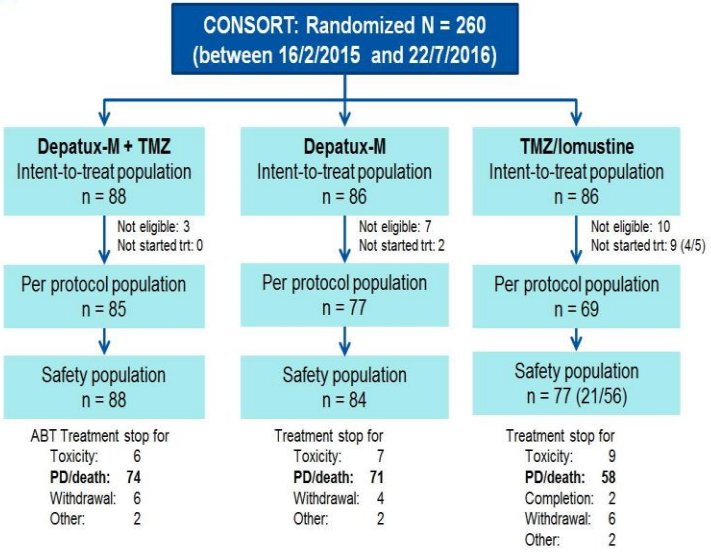
- EGFR amplification (~50% of GBM) leads to ***preferential exposure of a unique epitope*** of the EGFR protein that binds Depatux-M
- Unlike other EGFR directed therapies, there is **limited binding to EGFR in normal tissue** such as skin and other epithelial tissue.
- Depatux-M uses ***activated* EGFR** only as a target for **intracellular toxin delivery** and does not inhibit EGFR signaling; therefore, it can work in glioblastoma cells that are **resistant to classical EGFR inhibition**
- Phase I studies identified **EGFR amplification** as **biomarker for patient selection**



Disposition

Follow-up details at the time database lock (Oct 2018):

- Median follow-up for OS: 28.7 mo
- PD or died: 251
- **Died: 237 (91%)**
- Lost to follow-up: 4

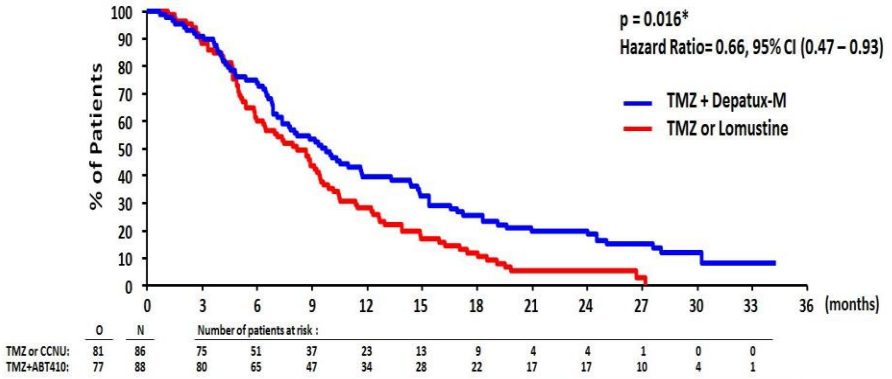


Toxicity: Hematological, Ocular

Hematology (worst grade)	TMZ+Depatux-M n = 88 n (%)		Depatux-M n = 84 n (%)		Lomustine n = 56 n (%)		Temozolomide n = 21 n (%)	
	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4
ANC	1 (1.1)				8 (14.3)	1 (1.8)	1 (4.8)	
Platelets	7 (8.0)	2 (2.3)	1 (1.2)		11 (19.6)	3 (5.4)	3 (14.3)	
WBC	2 (2.3)				9 (16.1)	2 (3.6)		

Ocular Toxicity (worst grade)	TMZ + Depatux-M n (%)	Depatux-M n (%)	Lomustine n = 56 n (%)	TMZ n = 21 n (%)
grade 0	13 (14.8)	22 (26.2)	51 (91.1)	21 (100.0)
grade 1	18 (20.5)	9 (10.7)	2 (3.6)	0
grade 2	29 (33.0)	32 (38.1)	3 (5.4)	0
grade 3	**27 (30.7)**	**20 (23.8)**	0 (0.0)	0
grade 4	**1 (1.1)**	**1 (1.2)**	0 (0.0)	0

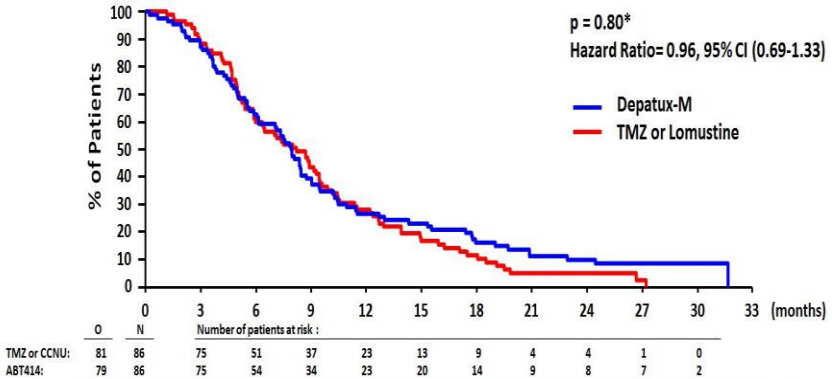
OS with 24+ months follow up:
Comparison TMZ+Depatux-M vs TMZ or Lomustine



Treatment	Patients	Observed Events	Median (95% CI) Months	% at 12 Months (95% CI)	% at 24 Months (95% CI)
TMZ or Lom	86	81	8.2 (5.9, 9.5)	28.2 (19.1, 37.9)	5.2 (1.7, 11.7)
TMZ+Depatux	88	77	9.6 (7.4, 11.8)	39.7 (29.4, 49.7)	19.8 (12.2, 28.8)

*Stratified log-rank test by stratification factors at randomization.

OS with 24+ months follow-up
Comparison of OS Depatux-M vs TMZ or Lomustine



Treatment	Patients	Observed Events	Median (95% CI) Months	% at 12 Months (95% CI)	% at 24 Months (95% CI)
TMZ or Lom	86	81	8.2 (5.9, 9.5)	28.2 (19.1, 37.9)	5.2 (1.7, 11.7)
Depatux-M	86	79	7.9 (6.1, 8.7)	26.7 (17.9, 36.4)	10.0 (4.8, 17.6)

*Stratified log-rank test by stratification factors at randomization.

Depatux-M in Recurrent EGFR ampl Glioblastoma

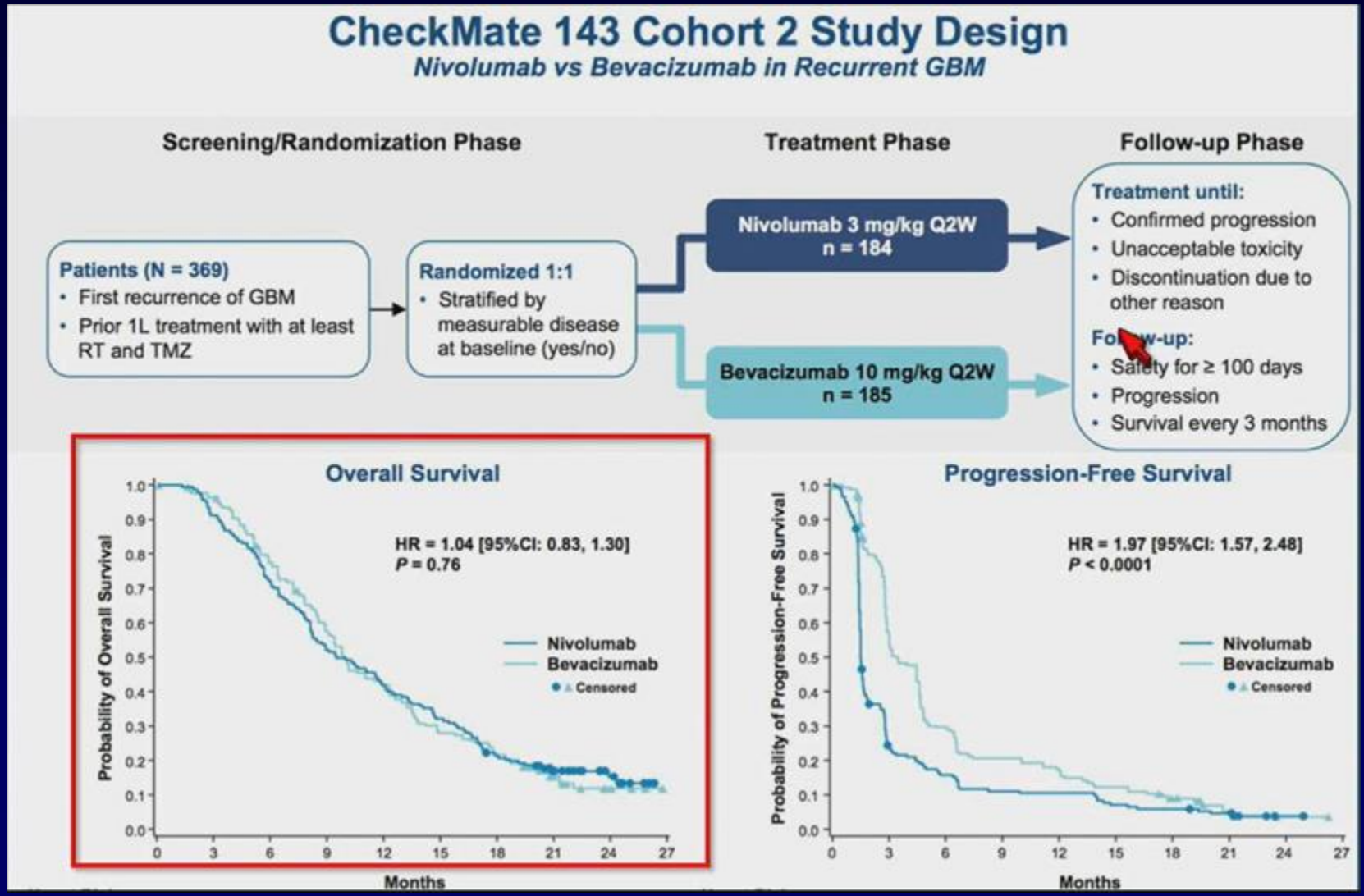
- Two phase I trial expansion cohorts demonstrated activity:
  - Depatux M monotherapy: ORR 6.8%, **6-mo PFS 29%** (n = 66)
  - Depatux M in combination with TMZ: ORR 14.3%, **6-mo PFS 25%** (n = 60)
- Dose limiting toxicity: **keratopathy**
- Two randomized trials to establish clinical activity:
  - INTELLANCE-2 study: in recurrent glioblastoma: conducted by EORTC, primary endpoint overall survival
    - Report 2017 SNO: 199 survival events
  - INTELLANCE-1 study: in newly diagnosed glioblastoma, conducted by NRG foundation

Lassman et al, *Neuro Oncol.* 2018 doi: 10.1093/neuonc/noy091. van den Bent et al, *Cancer Chemother Pharmacol.* 2017;80:1209-1217.

Checkpoint Inhibitors: Therapeutic Indications

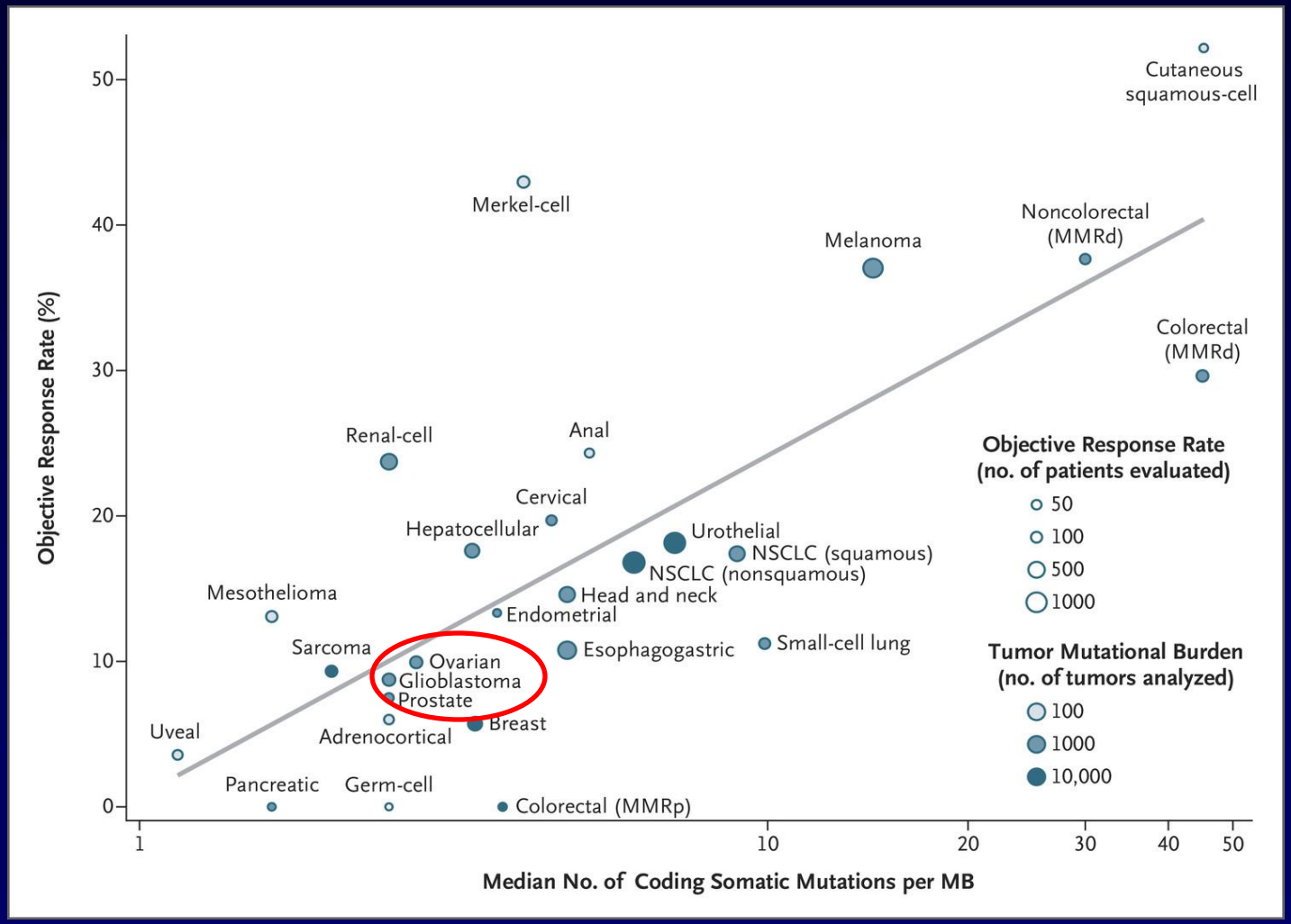
Ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab
Metastatic Melanoma	Metastatic NSCLC	Advanced Melanoma	Urothelial Cancer	Urothelial Cancer	Merkel Cell Cacrinoma
Adjuvant for Melanoma	Renal Cell Carcinoma	Metastatic NSCLC		NSCLC	Urothelial Cancer
Renal Cell Carcinoma	Hodgkin's Lymphoma	Renal Cell Carcinoma			
	Squamous H&N Cancer	Hodgkin's Lymphoma			
	Urothelial Cancer	PMBCL (Lymphoma)			
		Urothelial Cancer			
		MSI-H Cancer			
		Gastric Cancer			
		Cervical Cancer			

Nivolumab Failed to Improve Overall Survival of Patients with Recurrent Glioblastoma



Uhm J. Highlights of the Day Session 1, ASCO June 3, 2018.

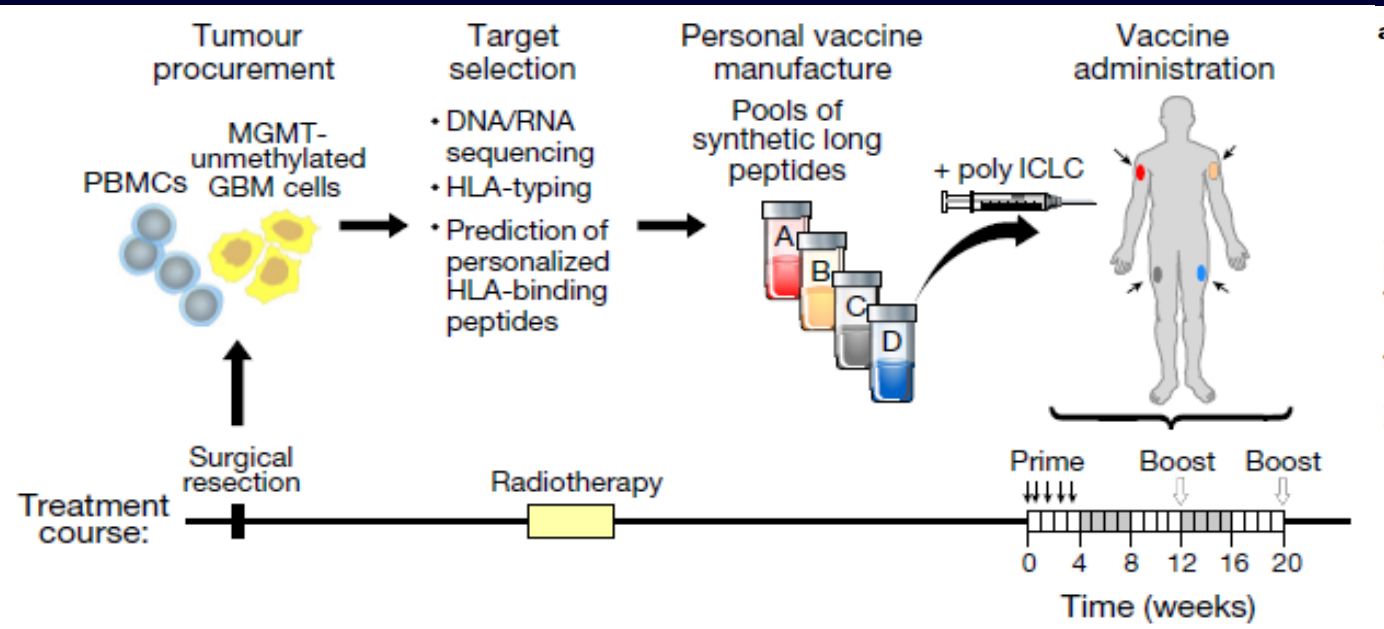
Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy in 27 Tumor Types

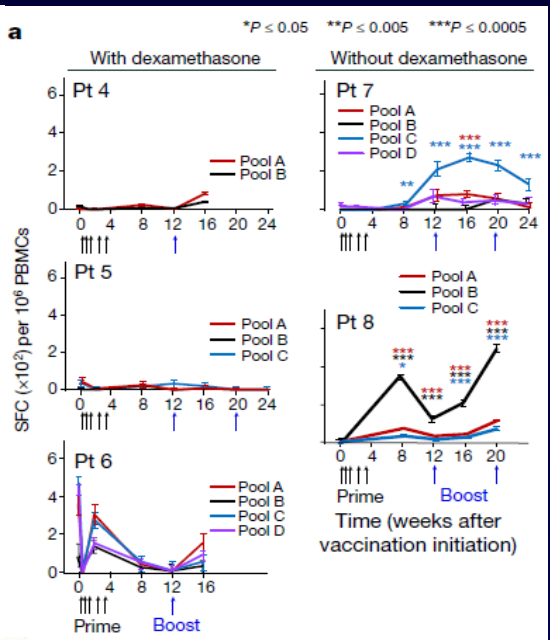


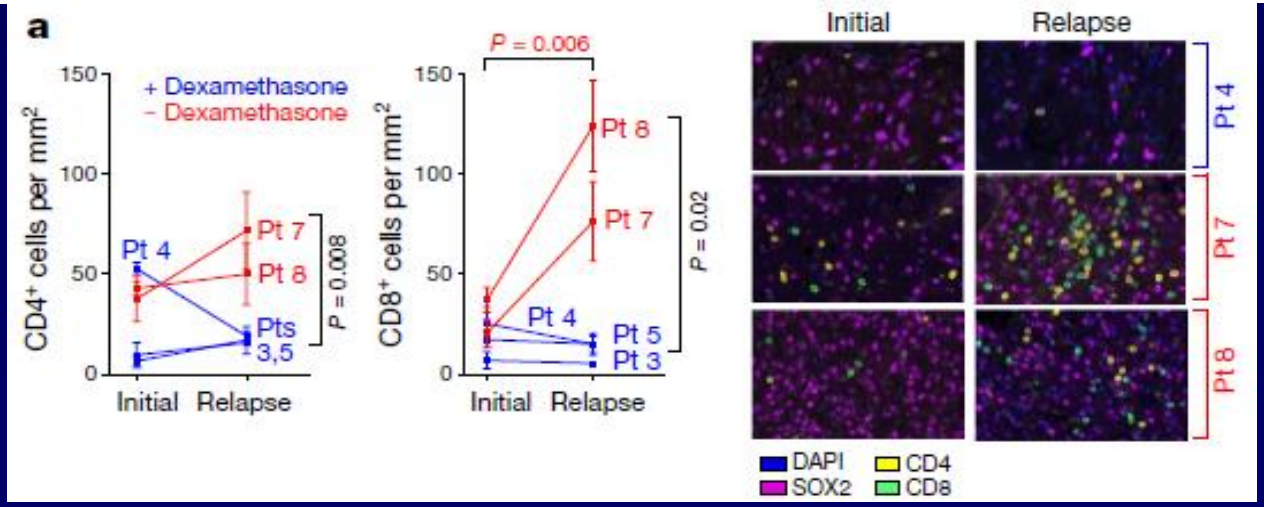
Yarchoan M et al. *N Engl J Med* 2017;377:2500-2501.

The NEW ENGLAND JOURNAL of MEDICINE

Dexamethasone Attentuates Personalized Neoantigen Vaccines in Glioblastoma





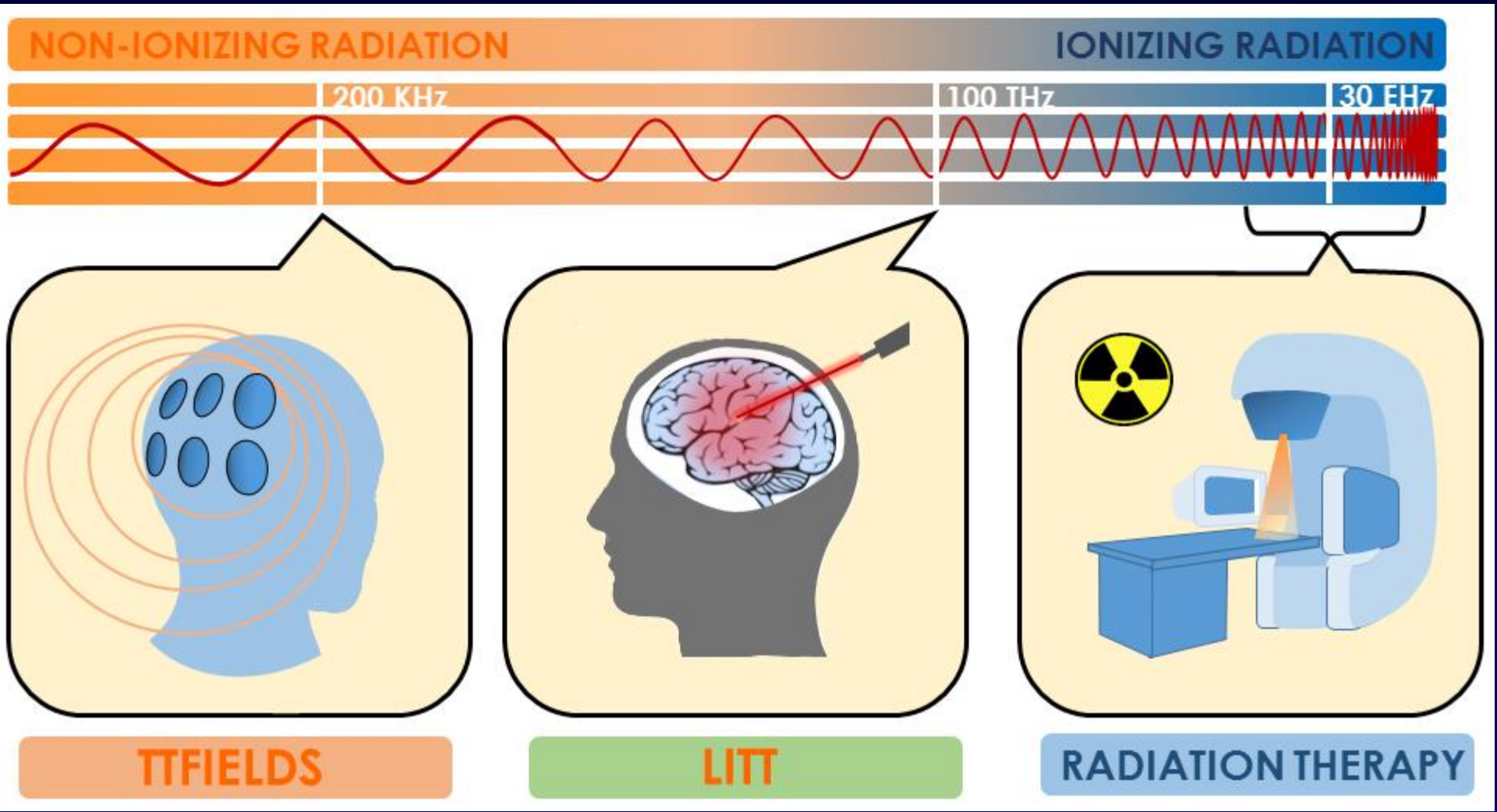


Keskin DB, Anandappa AJ, Sun J, et al. *Nature* 2019;565(5):1458-1471.

The Problem

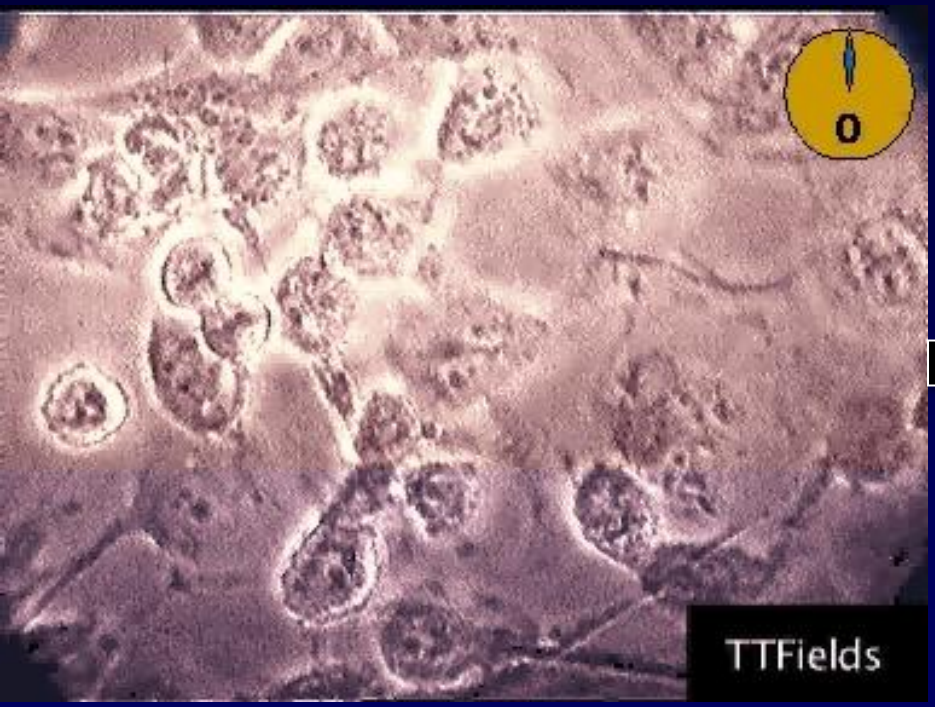
- There is no treatment that offers durable efficacy against glioblastoma growth and proliferation
- Anti-angiogenesis treatment using bevacizumab offers only temporary benefit.
- There is currently no treatment available for tumor invasion

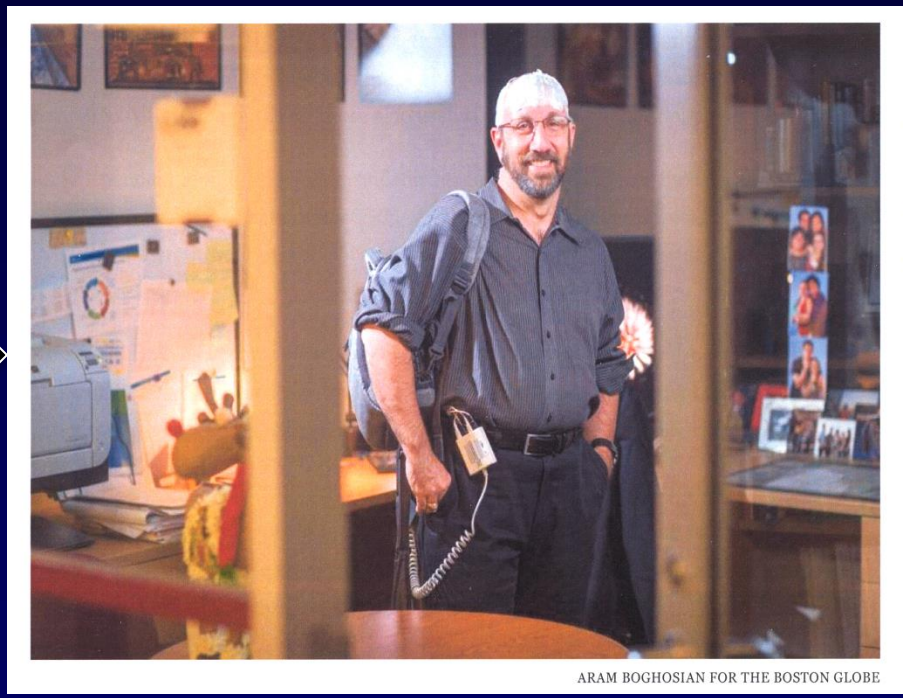
Applications of the Electromagnetic Spectrum for Brain Tumors



Swanson KD, Lok E, Wong ET. Tumor treating electric fields for glioblastoma. In Brem S and Abdullah KG (Editors): Glioblastoma, Chapter 17, pp. 213-224, 2016.

NovoTTF-100A Alternating Electric Fields Therapy for Recurrent Glioblastoma





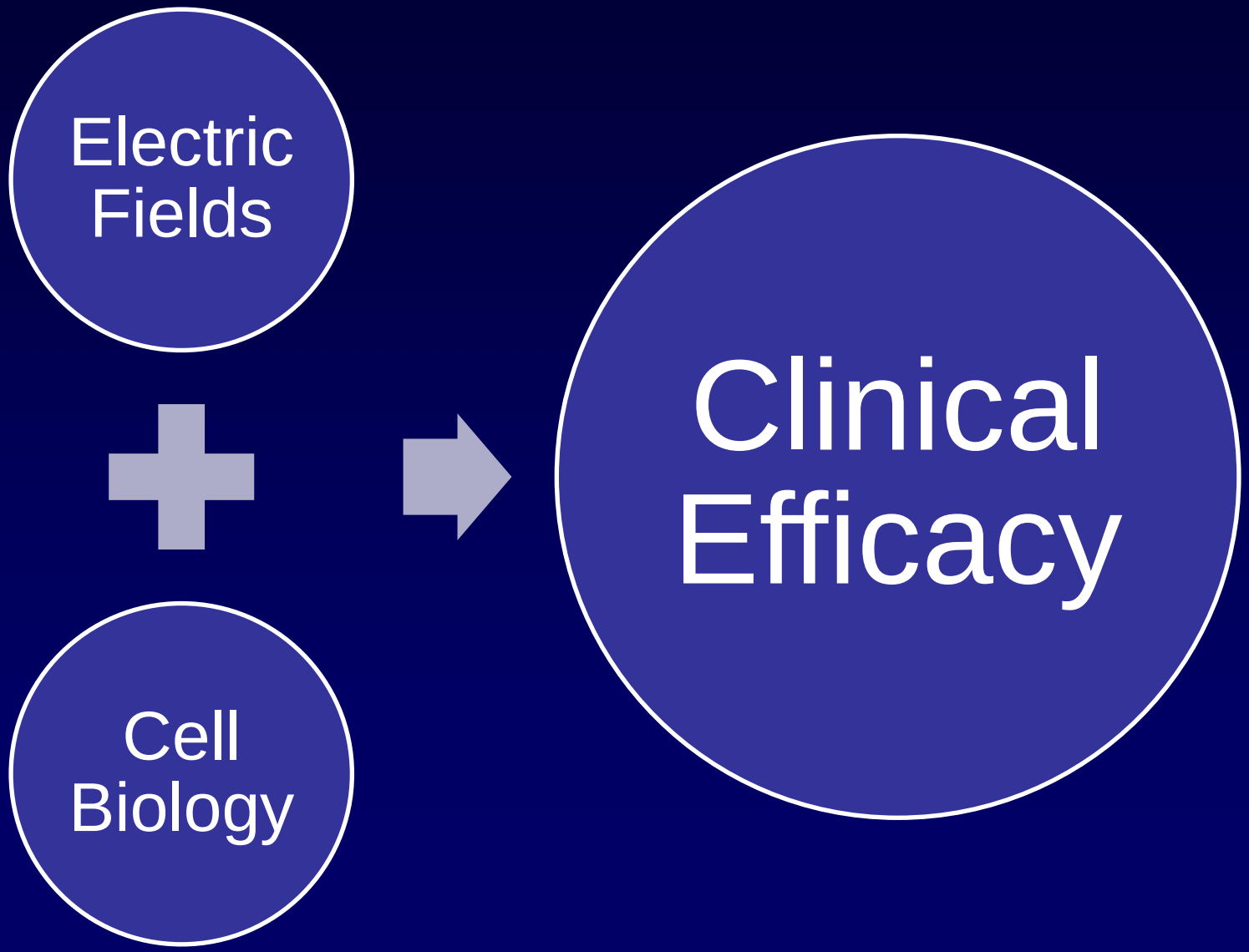
ARAM BOGHOSIAN FOR THE BOSTON GLOBE

Stupp R, Wong ET, Kanner AA, et al. *Eur J Cancer* 2012;48:2192-2202.

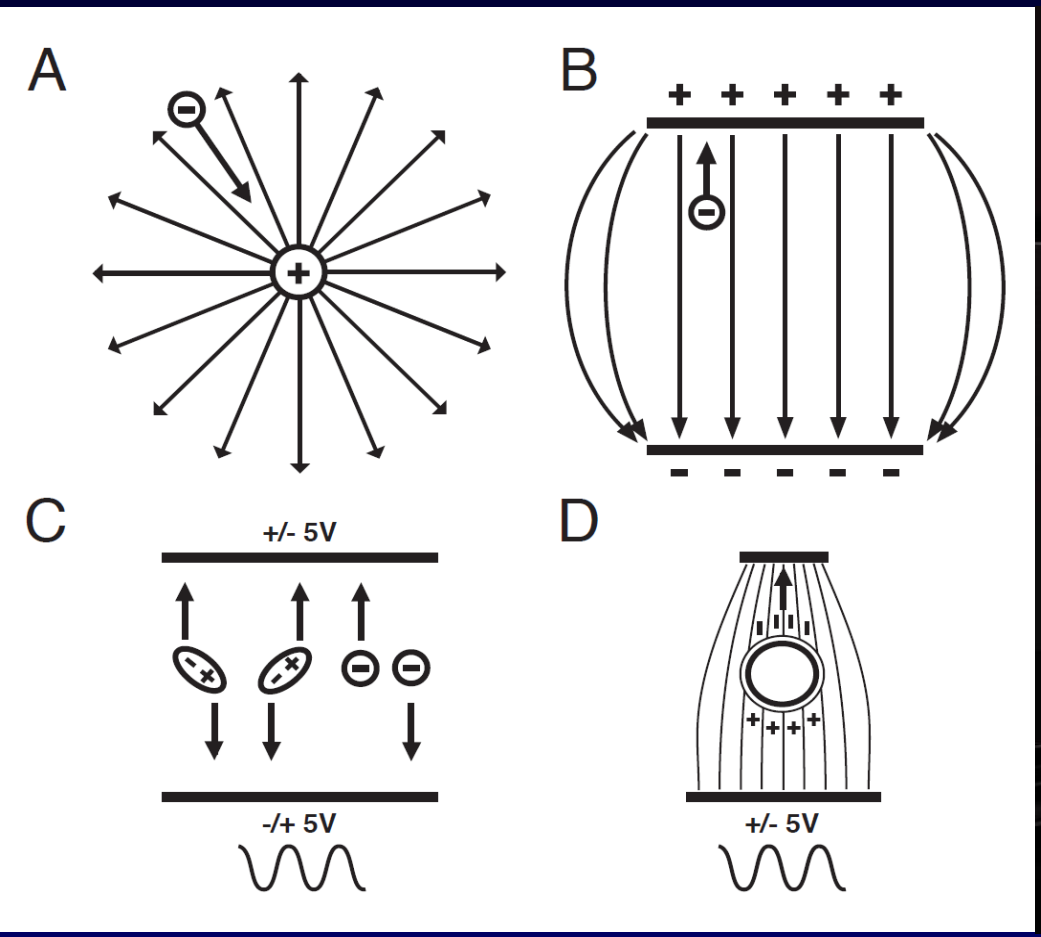
Fonkem E, Wong ET. *Exp Rev Neurother* 2012;12:895-899.

Boston Globe, December 27, 2014

Tumor Treating Fields: Mechanisms of Actions



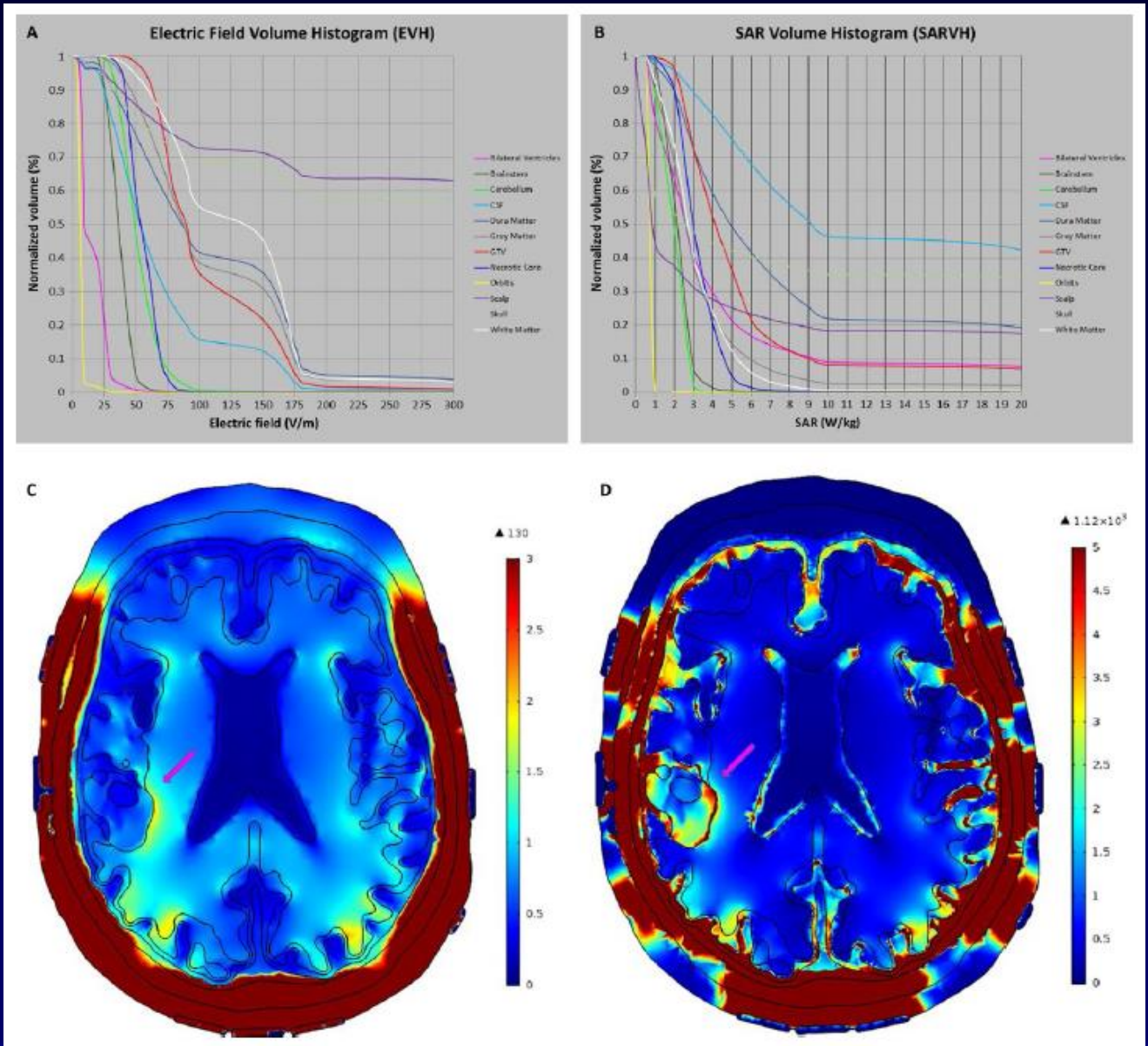
Electric Field Effect on Charges and Dipoles



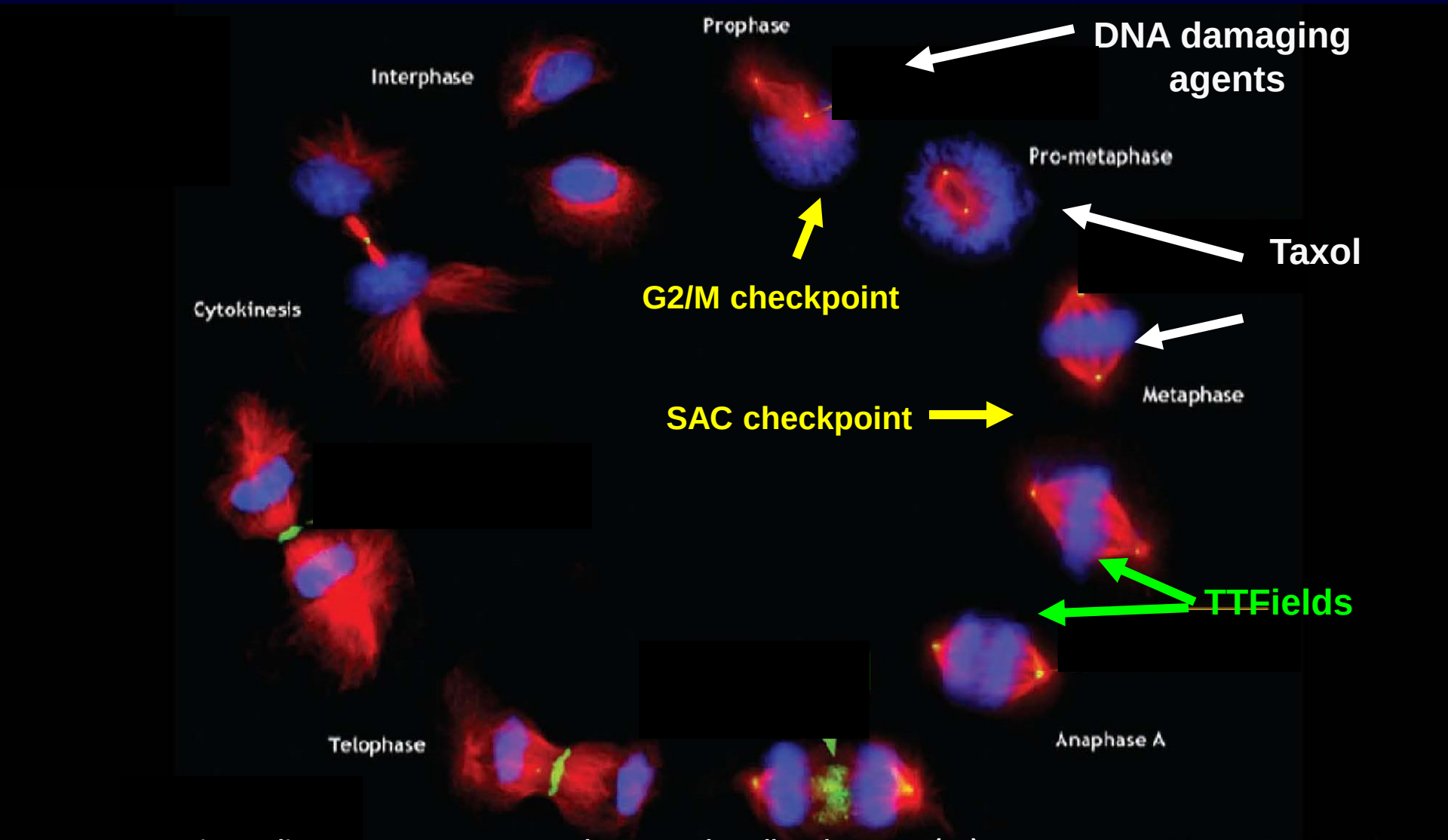
- An electric field is a potential difference in space
- Charges move and dipoles oscillate in a uniform alternating electric field

Gutin P, Wong ET. Presented at 2012 ASCO Annual Meeting Education Session; June 1-5, 2012; Chicago, IL. ASCO University website. http://meetinglibrary.asco.org/content/66664. Accessed June 26, 2013.

EVH & SARVH in Gross Tumor Volume and Other Intracranial Structures



Tumor Treating Fields Appear to Affect Cells After DNA Damaging Agents and Spindle Poisons

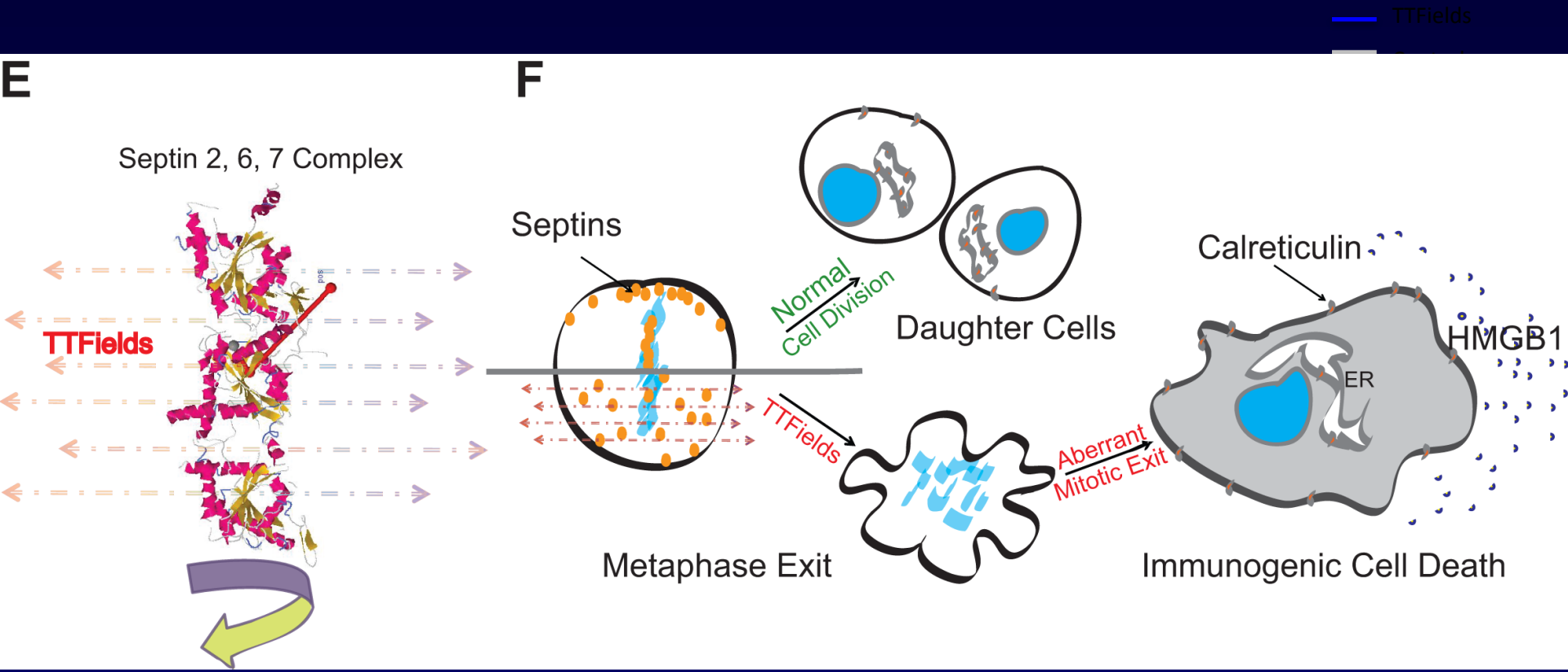


Vazquez-Martin A, Oliveras-Ferraros C, Menendez JA, et al. *Cell Cycle* 2009;8(15):2385-2398.

Menendez JA et al,

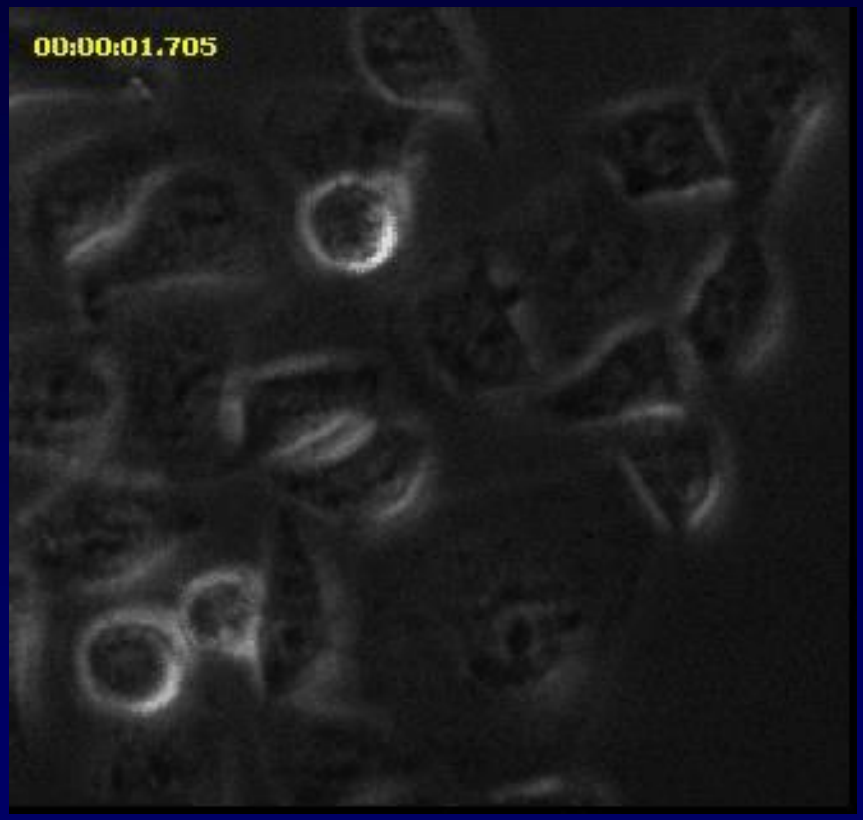
Cell Cycle 8:15, 2385; 2009

Perturbation of Septin Heterotrimers Causes Endoplasmic Reticulum Stress and Subsequent Immunogenic Cell Death

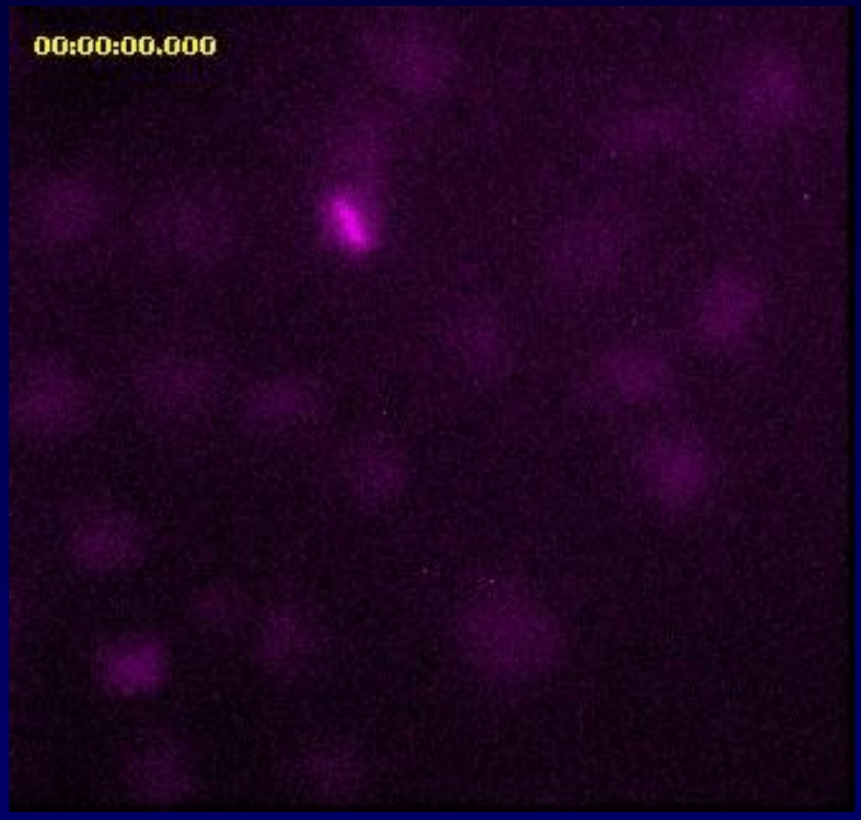


Wong ET, Lok E, Swanson KD. *Curr Treat Options Oncol* 2015;16:40.

Normal Mitosis

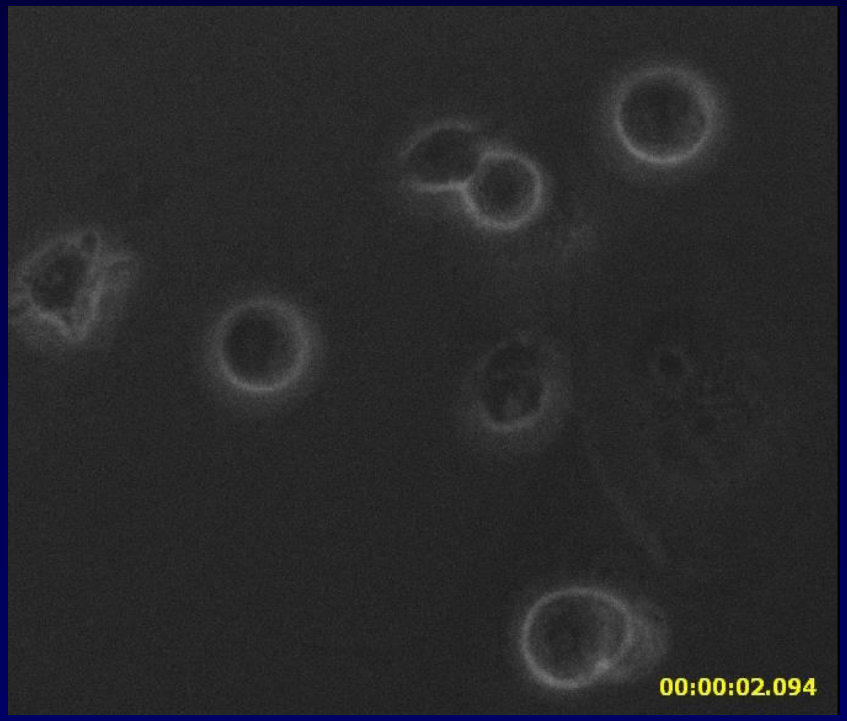


Phase Contrast

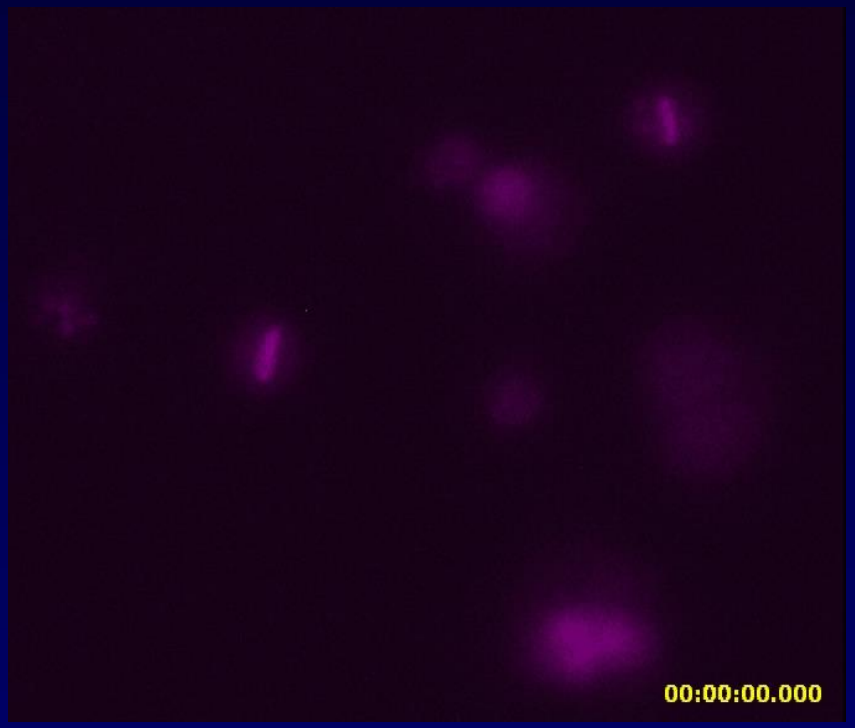


DNA (DRAQ5)

Tumor Treatment Fields Disrupt Cells During Transition from Metaphase to Anaphase

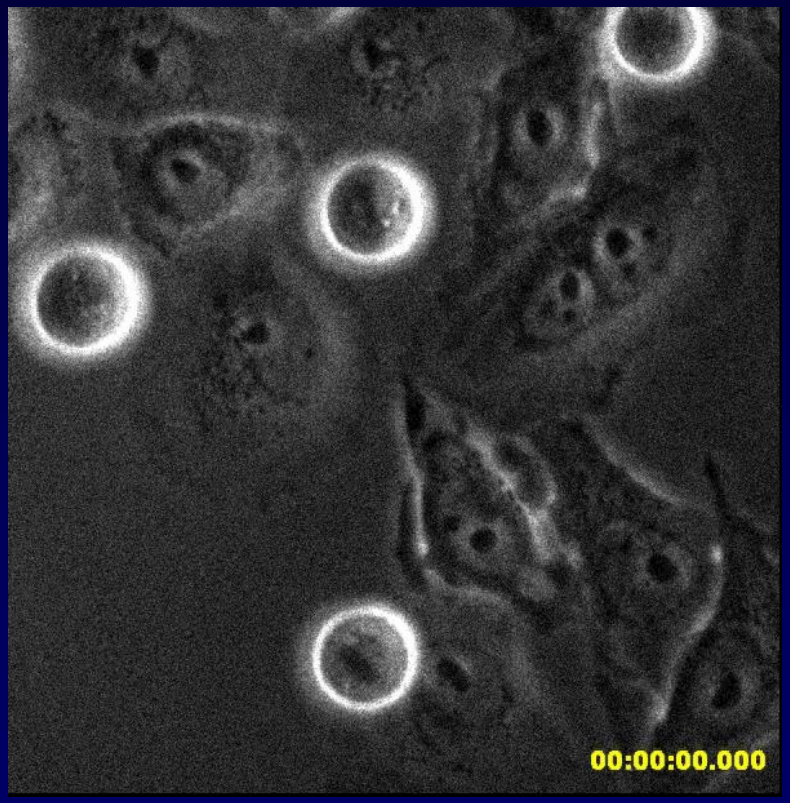


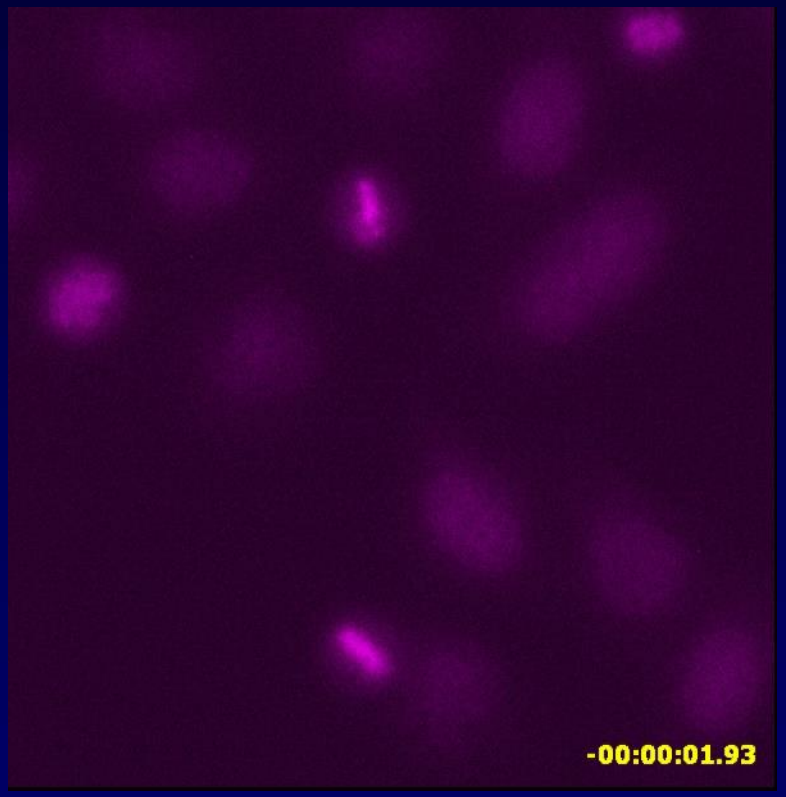
Phase Contrast



DNA (DRAQ5)

TTFields Perturb Cytokinesis

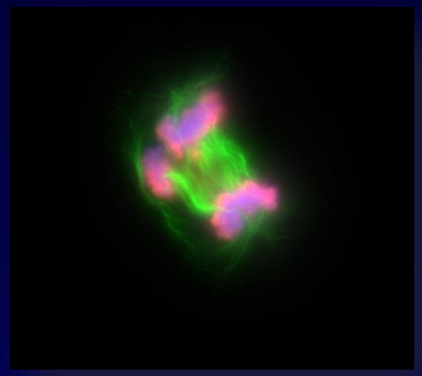


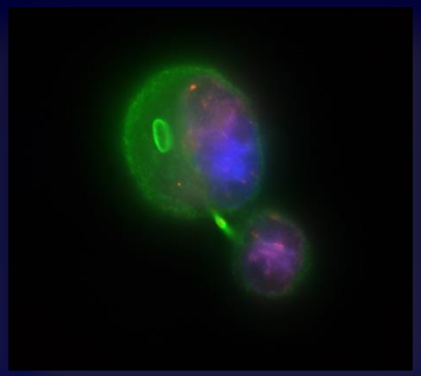


Phase Contrast

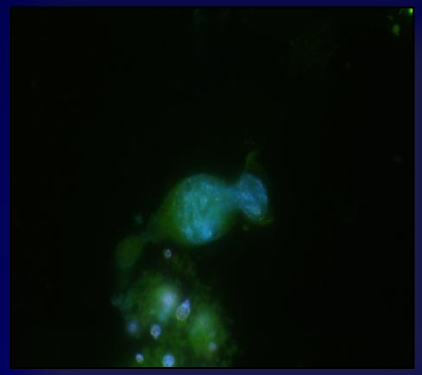
DNA (DRAQ5)

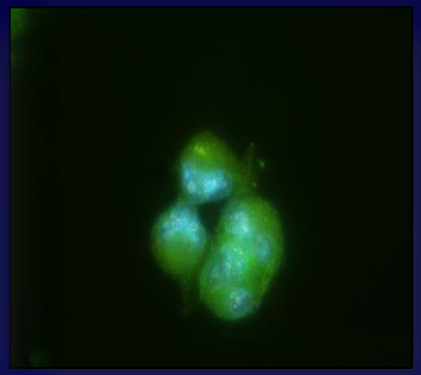
Cells Exposed to TTFields in Mitosis Exhibit Signs of Physical Perturbation in Anaphase



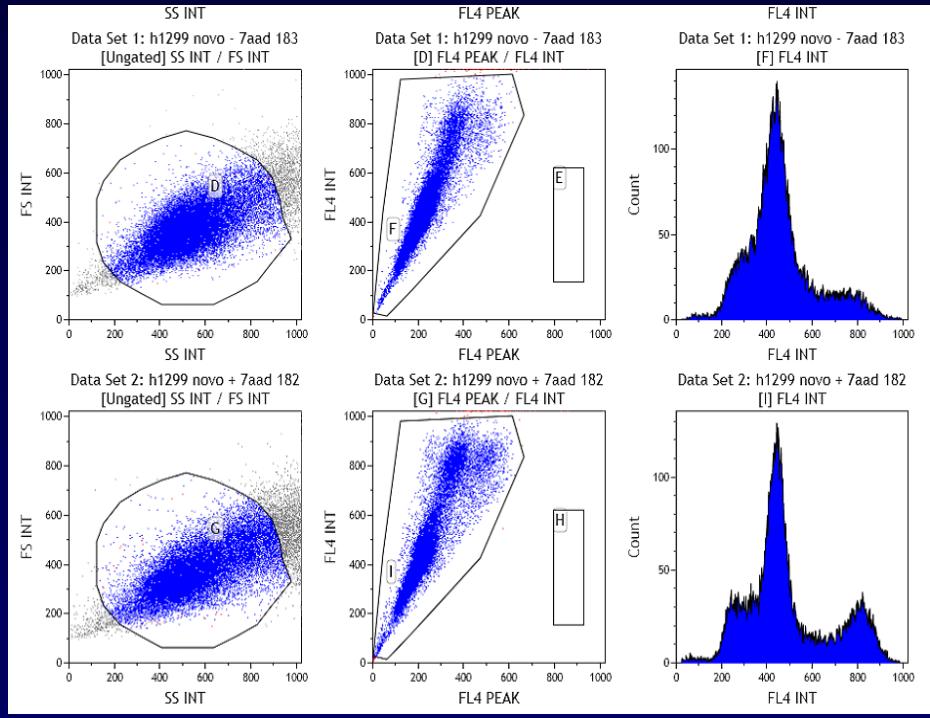


DAPI
pH3
tubulin





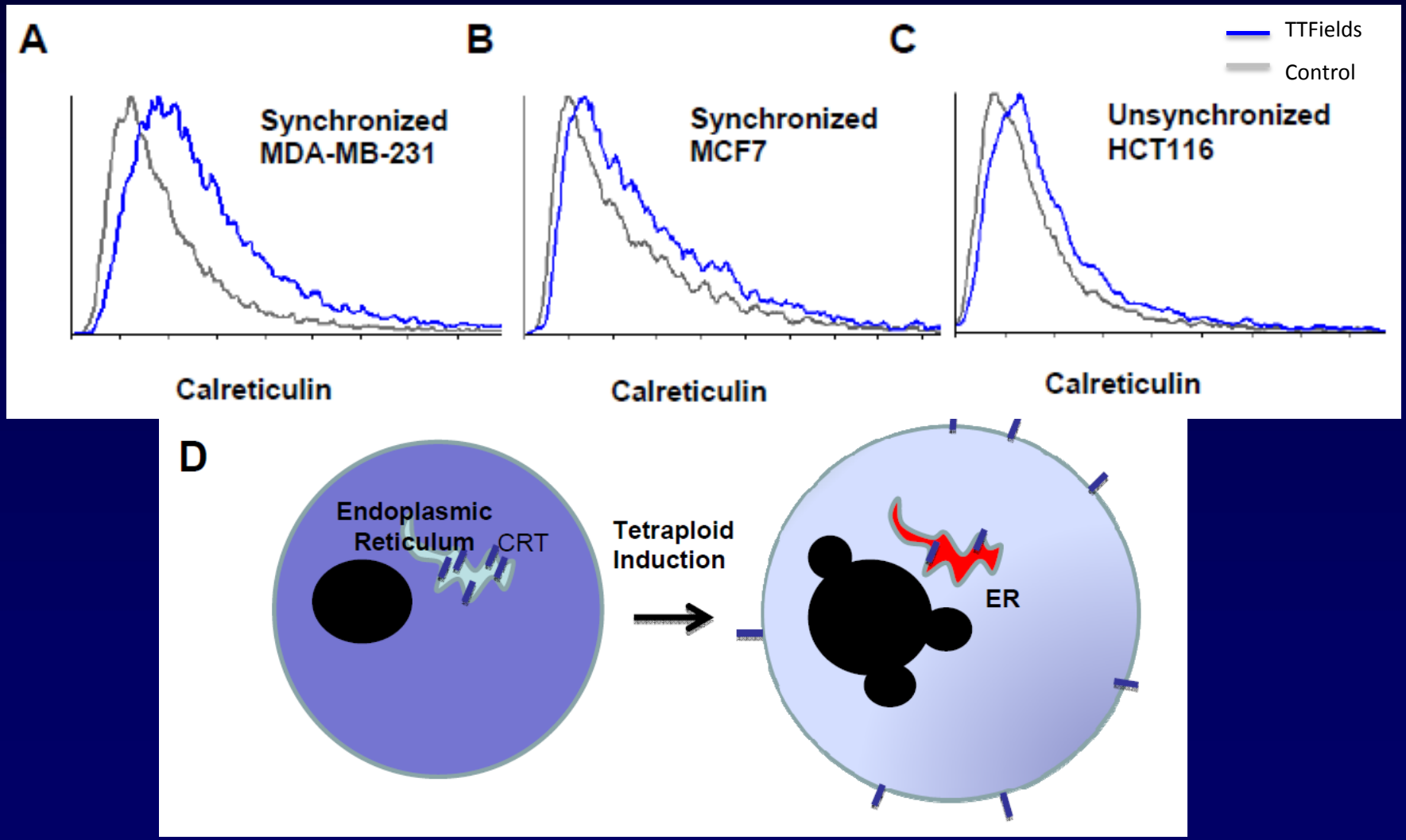
DAPI
pCenpA
BubR1



Top: Non-TTFields exposed cells
Bottom: TTFields exposed Cells

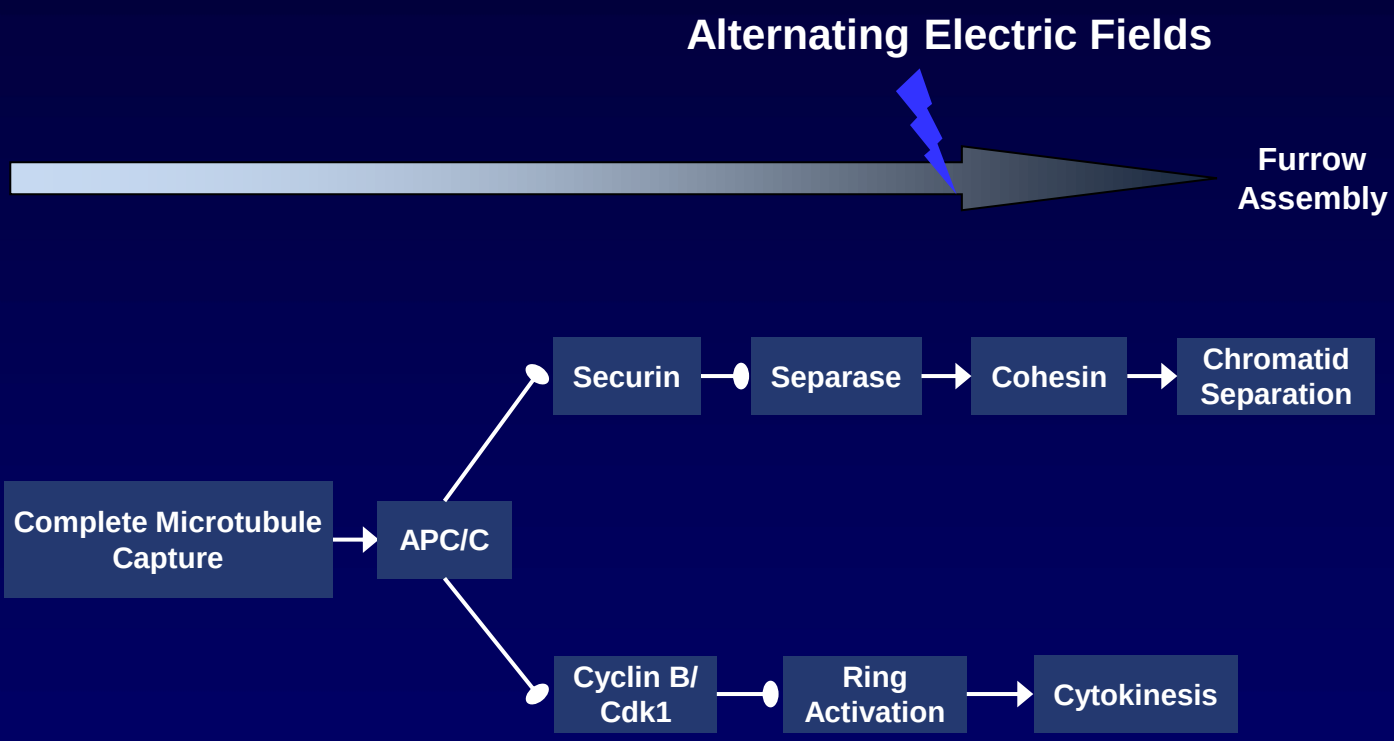
Lee SX, Wong ET, Swanson KD. *Neuro-Oncology* 2011 (CB-17).

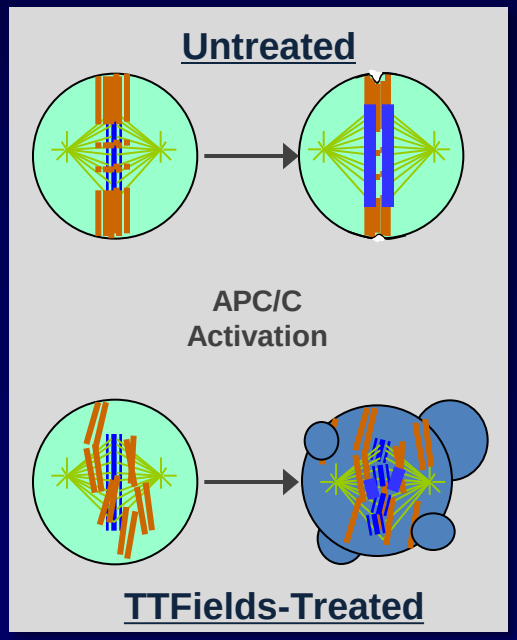
Prerequisite for Immunogenic Cell Death: Cell Cultures Treated with TTFields Exhibited Signs of Endoplasmic Reticulum Stress



Lee SX, Wong ET, Swanson KD. *Neuro-Oncology* 2012; Senovilla L, et al. *Science* 2012;337:1678-1684.

Cells Exposed to Alternating ElectricFields in Mitosis Exhibit Signs of Physical Perturbation in Anaphase



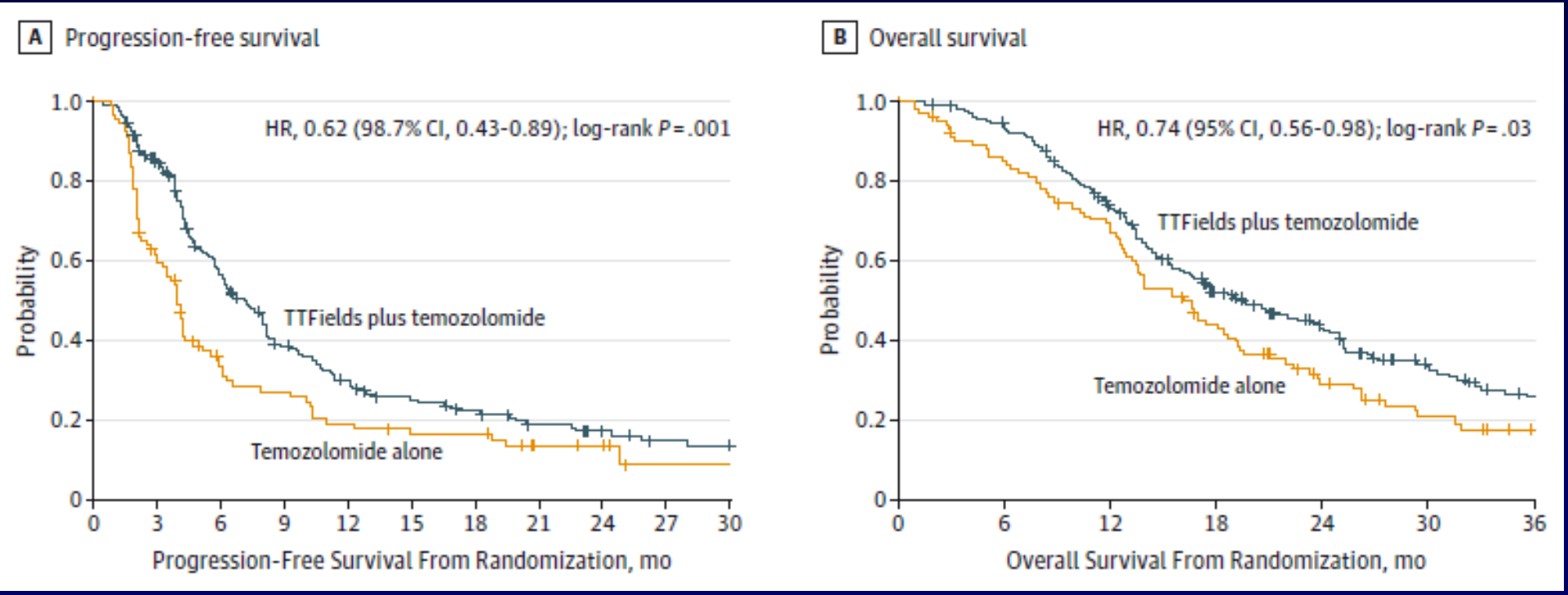


Lee SX, Tunkyi A, Wong ET, Swanson KD. [SNO abstract CB-17]. *Neuro Oncol* 2011;13(suppl 3):iii10-25.

Maintenance TTFields Added to Radiotherapy and Temozolomide Improves Survival of Glioblastoma Patients

PFS: 7.1 vs 4.0 months

OS: 20.5 vs 15.6 months

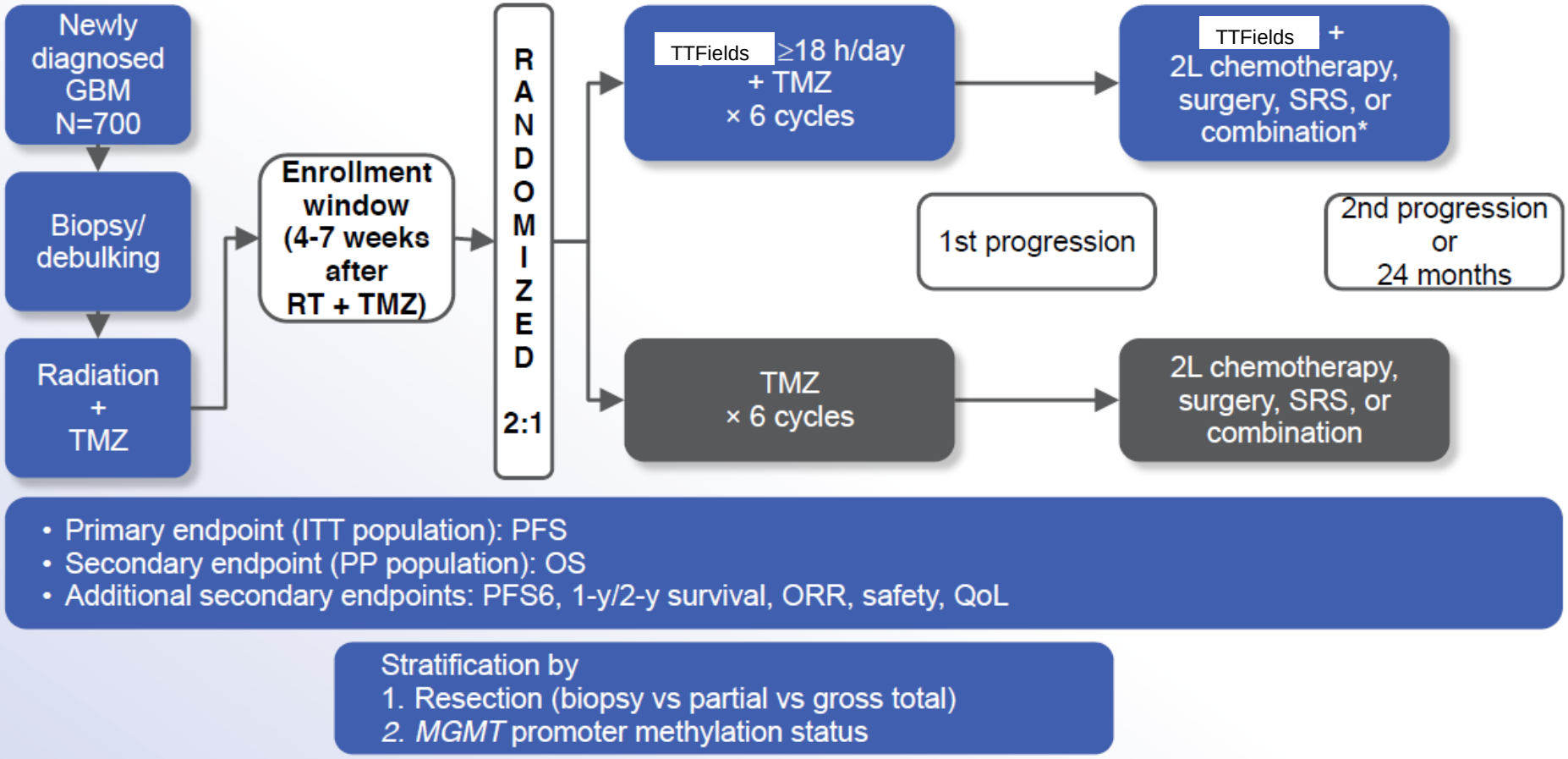


PFS: progression free survival

OS: overall survival

Stupp R, Taillibert S, Kanner AA, et al. *JAMA* 2017;314(23):2535-2543.

EF-14 Trial Design: TTFields + Temozolomide versus Temozolomide Alone



Stupp R, Tallibert S, Kanner AA, et al. *JAMA* 2015;314:2535-2543.
Stupp R, Idbaih A, Steinberg DM, et al. AACR Annual Meeting 2017, April 1-4, Washington, DC.

EF-14 5-Year Survival Analysis: Baseline Patient Characteristics are Balanced

ITT Population **Characteristics**	TTFields + TMZ (n=466)	TMZ Alone (n=229)
Median age, years (range)	56 (19-83)	57 (19-80)
Female sex, %	32	31
Median KPS (range)	90 (60-100)	90 (70-100)
Extent of resection, %		
Gross total resection	53	53
Partial resection	34	34
Biopsy	13	13
Median time from diagnosis to randomization, mo (range)	3.8 (1.7-6.2)	3.7 (1.4-6.3)
Duration of Therapy with TMZ, mo		
Median (range)	6 (0-51)	5 (0-33)
Duration of Therapy with Optune, mo		
Median (range)	8.2 (0-82)	0 (0-0)

Stupp R, Idbaih A, Steinberg DM, et al. AACR Annual Meeting 2017, April 1-4, Washington, DC.

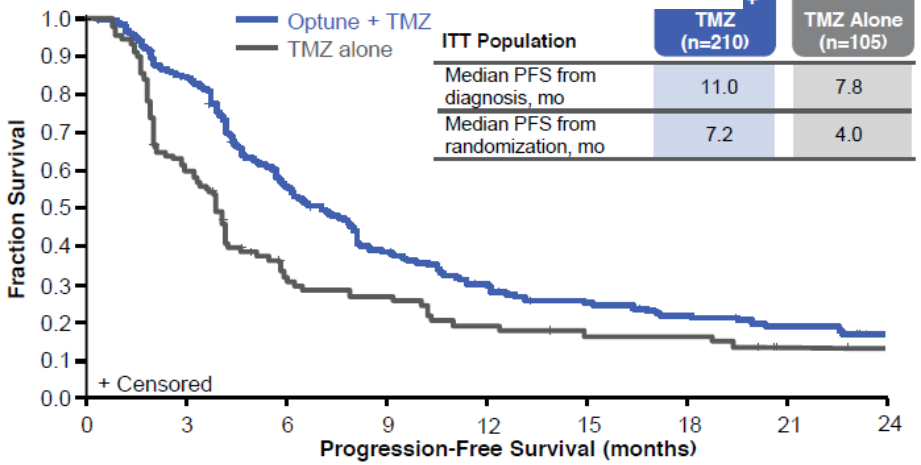
EF-14 5-Year Survival Analysis: Baseline Patient Characteristics are Balanced

ITT Population **Molecular Profiles, %**	TTFields + TMZ (n=466)	TMZ Alone (n=229)
MGMT status		
Tissue available and tested	83	81
Methylated	35	42
Unmethylated	54	51
Insufficient for testing	10	7
IDH1 R132 mutation status		
Tissue available and tested	65	65
Positive	7	5
Medications, %		
Antiepileptics	44	41
Corticosteroids	29	28
Adherence to Optune,* %	75	-

Stupp R, Idbaih A, Steinberg DM, et al. AACR Annual Meeting 2017, April 1-4, Washington, DC.

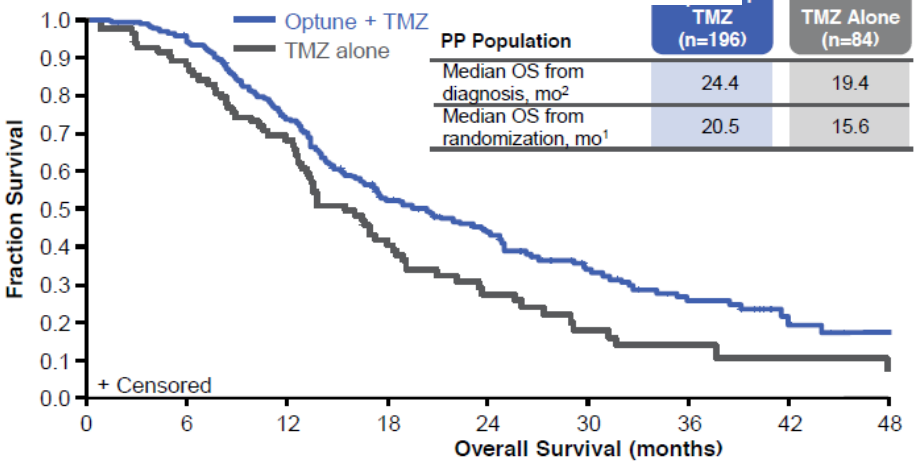
EF-14: Outcome Consistent Across Interim and 5-Year Survival Analyses

PFS Interim Analysis[1]



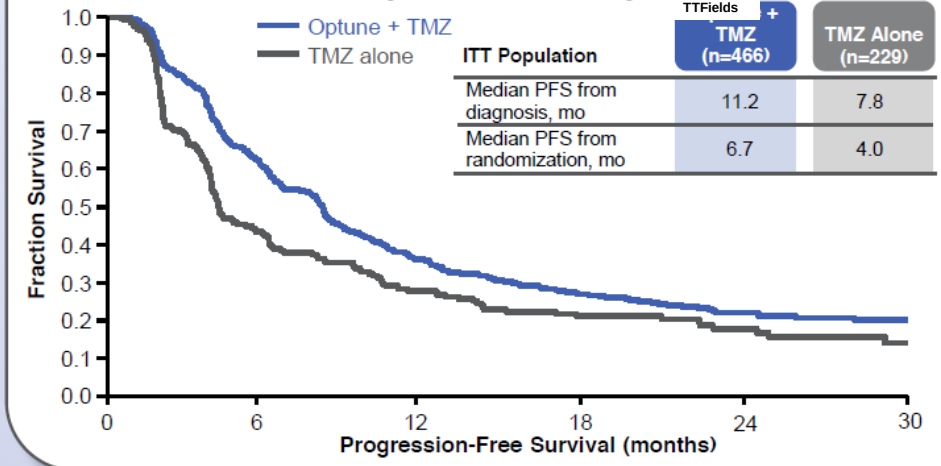
ITT Population	TTFields + TMZ (n=210)	TMZ Alone (n=105)
Median PFS from diagnosis, mo	11.0	7.8
Median PFS from randomization, mo	7.2	4.0

OS Interim Analysis[1,2]



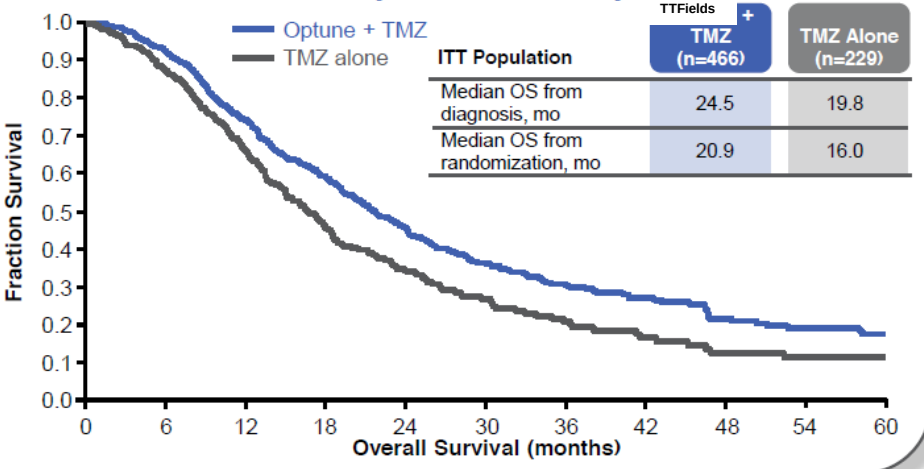
PP Population	TTFields + TMZ (n=196)	TMZ Alone (n=84)
Median OS from diagnosis, mo[2]	24.4	19.4
Median OS from randomization, mo[1]	20.5	15.6

PFS 5-year Survival Analysis[3]



ITT Population	TTFields + TMZ (n=466)	TMZ Alone (n=229)
Median PFS from diagnosis, mo	11.2	7.8
Median PFS from randomization, mo	6.7	4.0

OS 5-year Survival Analysis[3]



ITT Population	TTFields + TMZ (n=466)	TMZ Alone (n=229)
Median OS from diagnosis, mo	24.5	19.8
Median OS from randomization, mo	20.9	16.0

Stupp R, Tallibert S, Kanner AA, et al. *JAMA* 2015;314:2535-2543.
Stupp R, Idbaih A, Steinberg DM, et al. AACR Annual Meeting 2017, April 1-4, Washington, DC.

EF-14 Safety Analysis: Grade 3 or 4 Adverse Events in ≥2% of Patients

Safety Population	TTFields + TMZ (n=456) %		TMZ Alone (n=216) %	
System Organ Class	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders	9	4	9	2
Leukopenia	2	0	<1	0
Lymphopenia	3	1	3	0
Neutropenia	2	1	1	<1
Thrombocytopenia	6	3	4	1
Gastrointestinal disorders	5	<1	3	<1
General disorders and administration site conditions	9	<1	6	0
Fatigue	4	0	3	0
Asthenia	3	0	1	0
Gait disturbance	2	0	1	0
Infections and infestations	7	<1	4	1
Procedural complications	5	0	3	0
Fall	2	0	1	0
Medical device site reaction	2	0	0	0

Stupp R, Tallibert S, Kanner AA, et al. *JAMA* 2015;314:2535-2543.
Stupp R, Idbaih A, Steinberg DM, et al. AACR Annual Meeting 2017, April 1-4, Washington, DC.

EF-14 Safety Analysis: Grade 3 or 4 Adverse Events in ≥2% of Patients

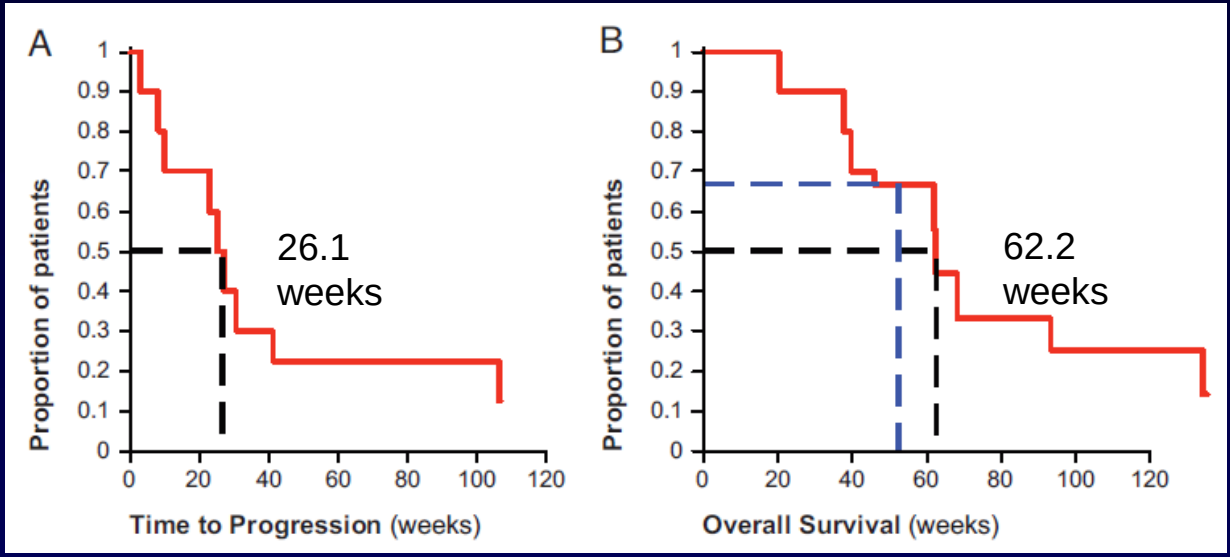
Safety Population	TTFields + TMZ (n=456) %		TMZ Alone (n=216) %	
System Organ Class	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Metabolism and nutrient disorders	2	1	5	0
Hyperglycemia	<1	1	2	0
Musculoskeletal and connective tissue disorders	4	<1	4	0
Nervous system disorders	21	3	18	2
Aphasia	2	0	1	0
Brain edema	2	<1	2	<1
Convulsion	5	1	6	<1
Headache	3	0	2	0
Hemiparesis	4	0	2	0
Neurological decompensation	2	0	1	0
Psychiatric disorders	3	1	3	0
Renal and urinary disorders	1	0	2	0
Respiratory disorders	2	4	3	2
Pulmonary embolism	<1	3	<1	2
Vascular disorders	4	0	2	0
Hypertension	2	0	<1	0

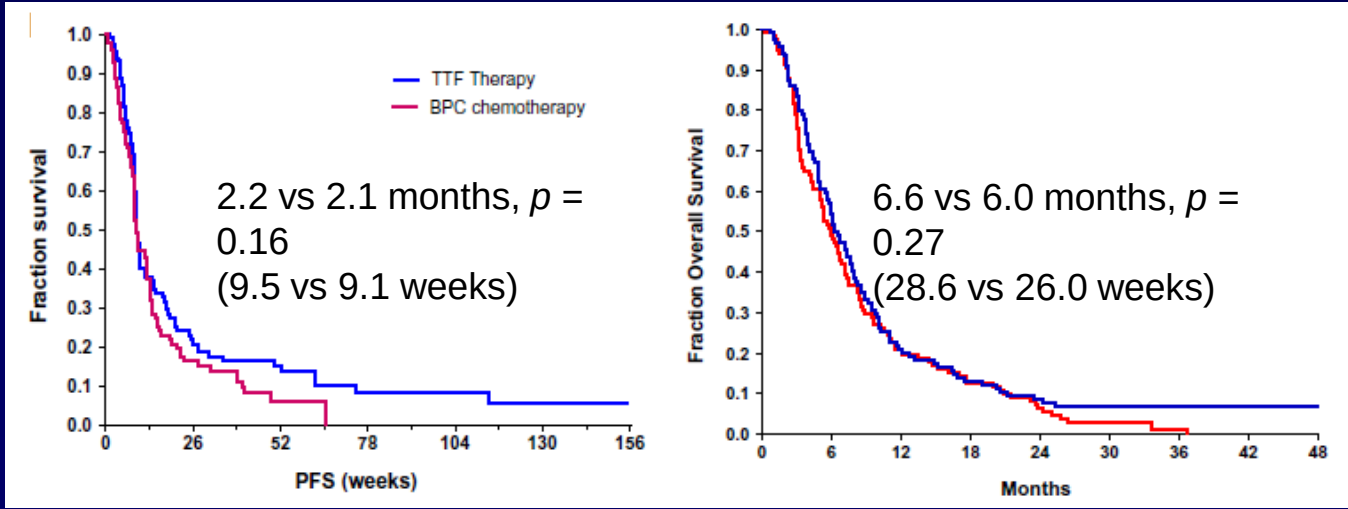
Stupp R, Tallibert S, Kanner AA, et al. *JAMA* 2015;314:2535-2543.
Stupp R, Idbaih A, Steinberg DM, et al. AACR Annual Meeting 2017, April 1-4, Washington, DC.

Tumor Treating Fields for Newly Diagnosed Glioblastoma

- TTFields plus TMZ is superior to TMZ alone in newly diagnosed glioblastoma patients
  - Side effects are similar in the two groups and consist primarily of hematologic adverse events
  - Control group did not include sham treatment

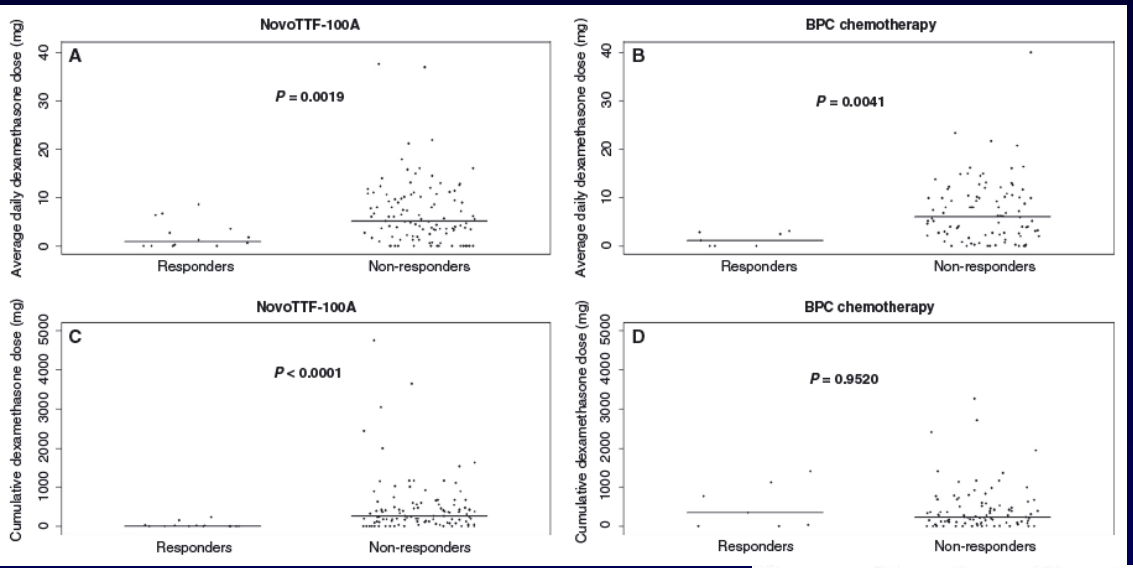
EF-11: TTFields and Chemotherapy have Comparable Efficacy in Recurrent Glioblastoma

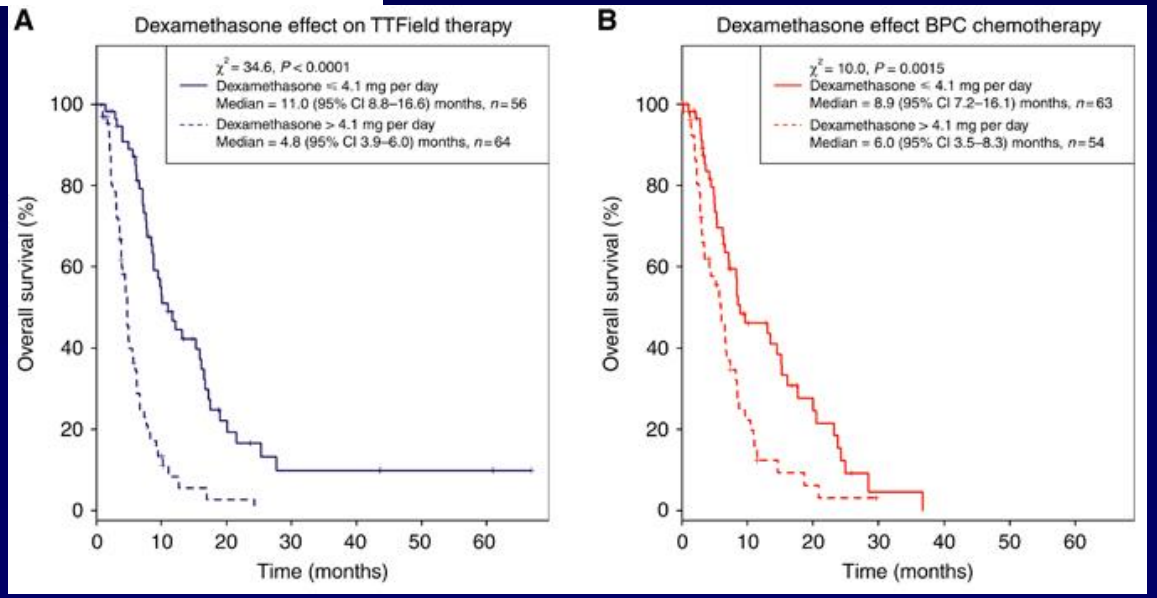




Kirson ED, Dbalý V, Tovaryš F, et al. *PNAS* 2007;104(24):10152-10157.
Stupp R, Wong ET, Kanner AA, et al. *Eur J Cancer* 2012;48(11):2192-2202.

Dexamethasone Interferes with TTFields and Chemotherapy

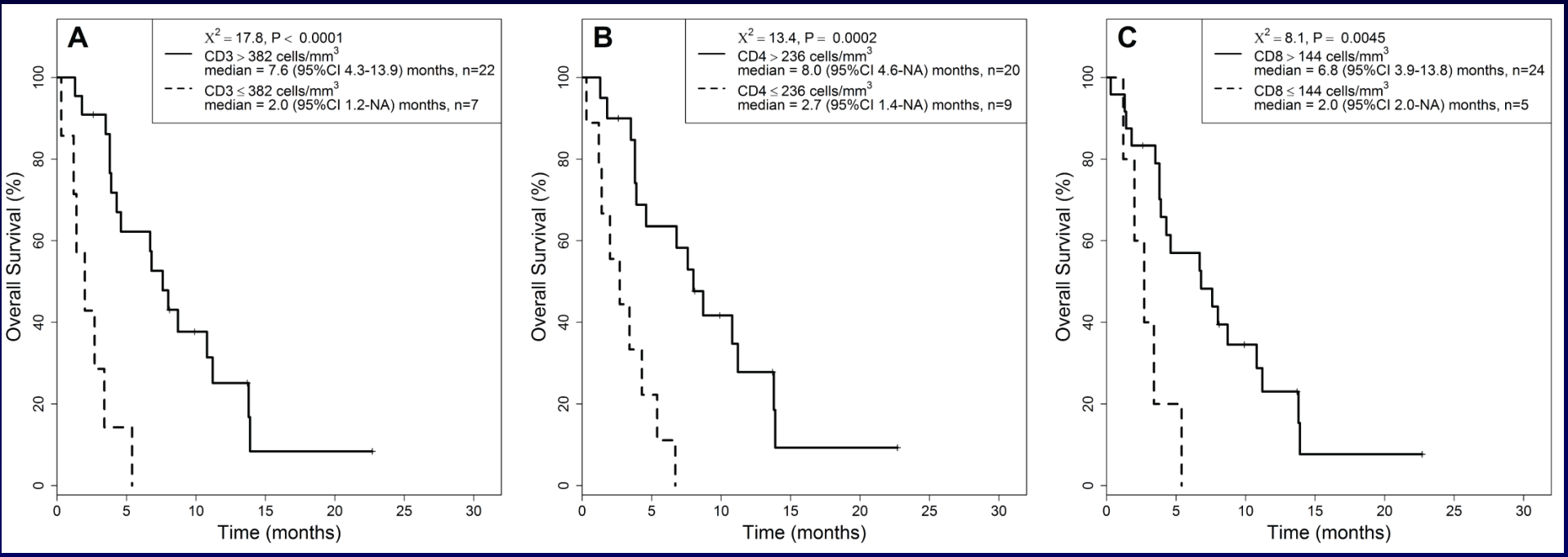




Wong ET, Lok E, Swanson KD, et al. *Cancer Med* 014;3(3):592-602.

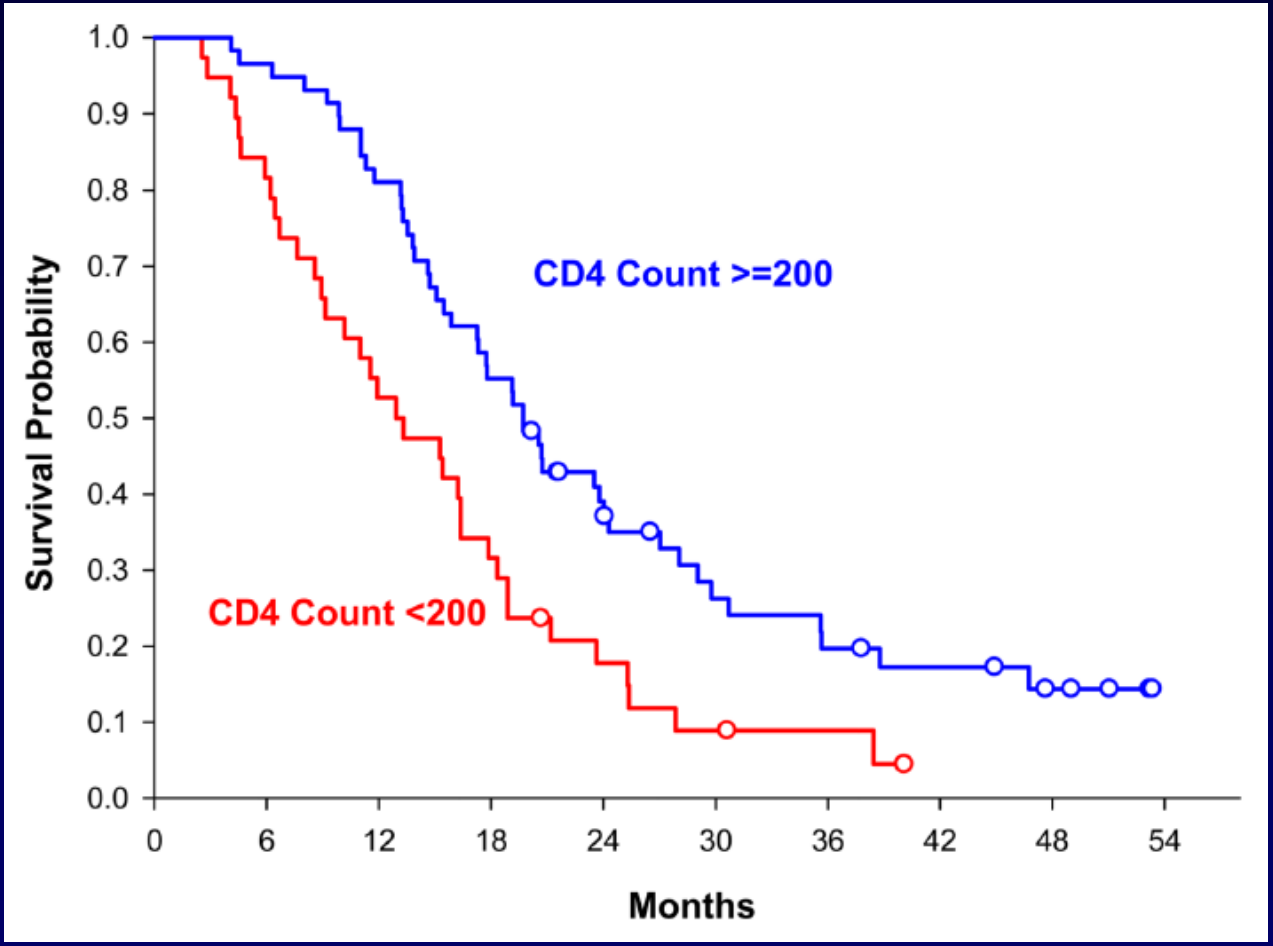
Wong ET, Lok E, Gautam S, et al. *Br J Cancer* 2015;113(23):232-241.

CD3, CD4 and CD8 Counts Influence Survival of Validation Cohort Treated with Tumor Treating Fields



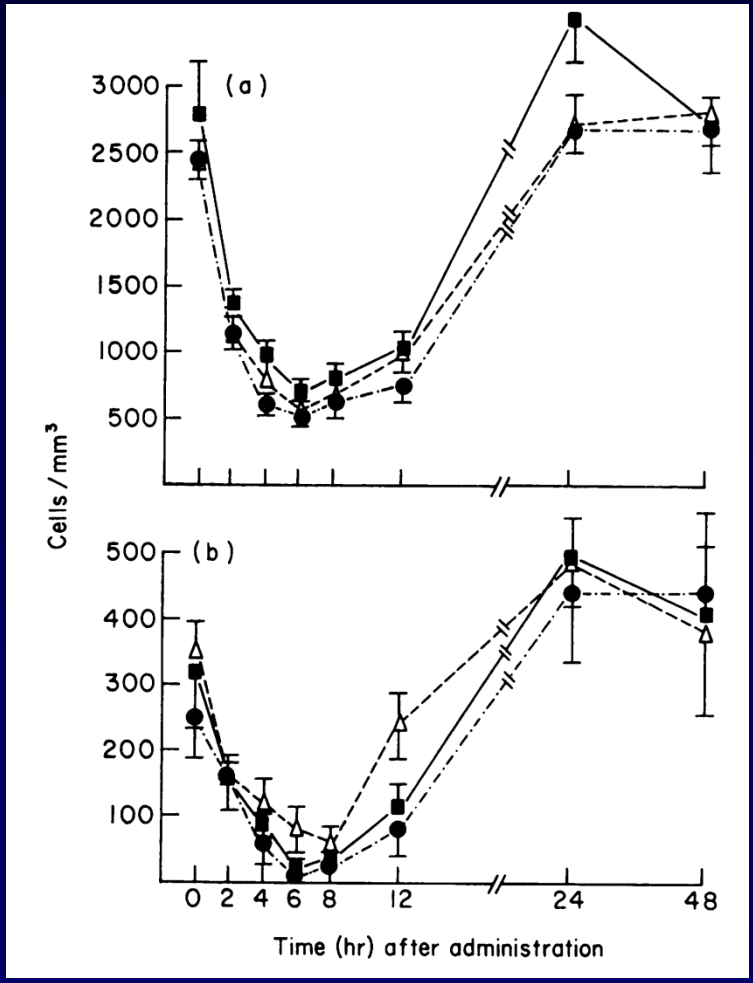
Wong ET, Lok E, Gautam S, et al. *Br J Cancer* 2015;113(23):232-241.

Absolute CD4 Lymphocyte Count is Prognostic for Newly Diagnosed Glioblastoma Patients



Grossman SA, Ye X, Lesser G, et al. *Clin Cancer Res* 2011;17:5473-5480.

Dexamethasone Affects Lymphocyte and Monocyte Count (Quantitative Effect)

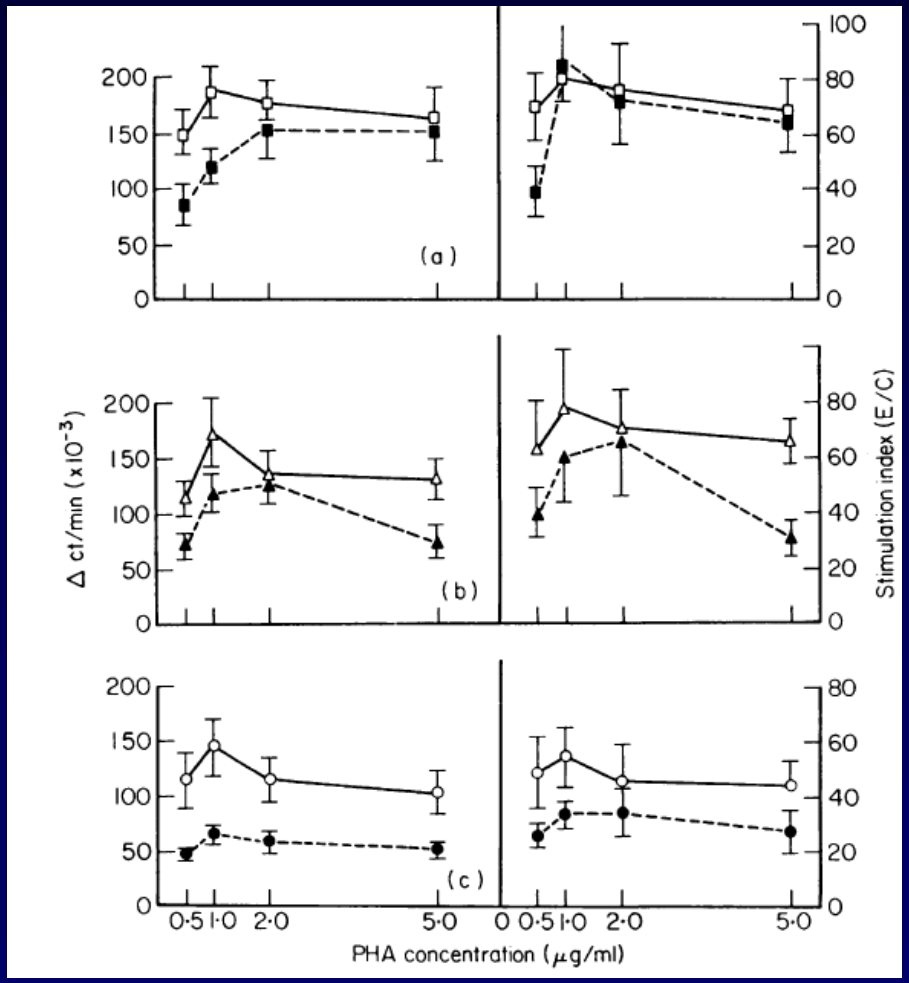


Lymphocytes

Monocytes

Fauci AS. *Clin Exp Immunol* 1976;24:54-62.

Dexamethasone Affects Lymphocyte and Monocyte Count (Qualitative Effect)



Hydrocortisone

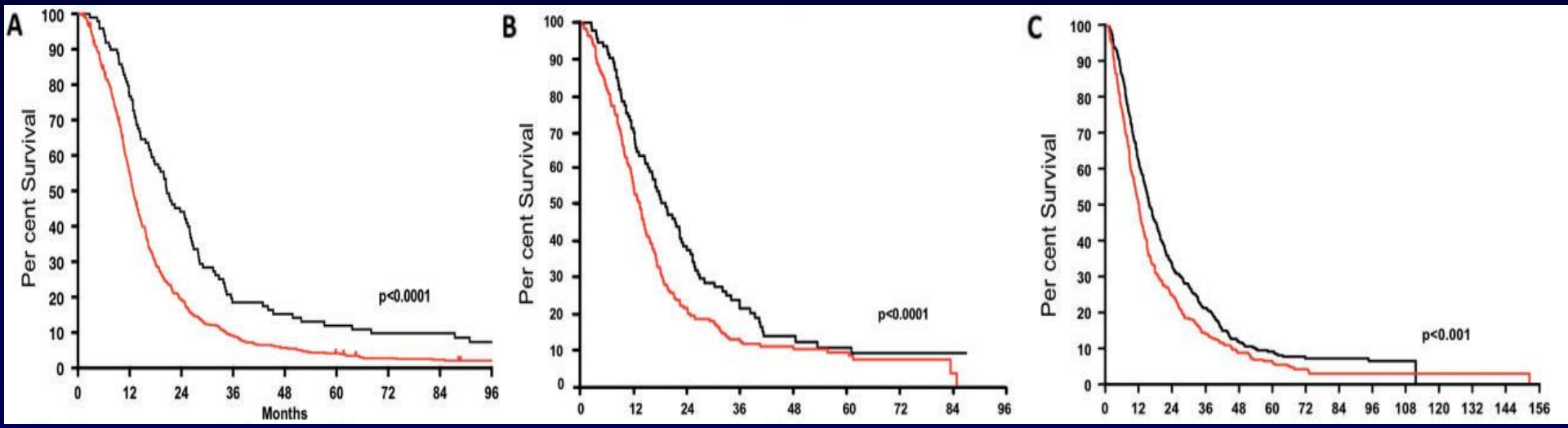
Prednisone

Dexamethasone

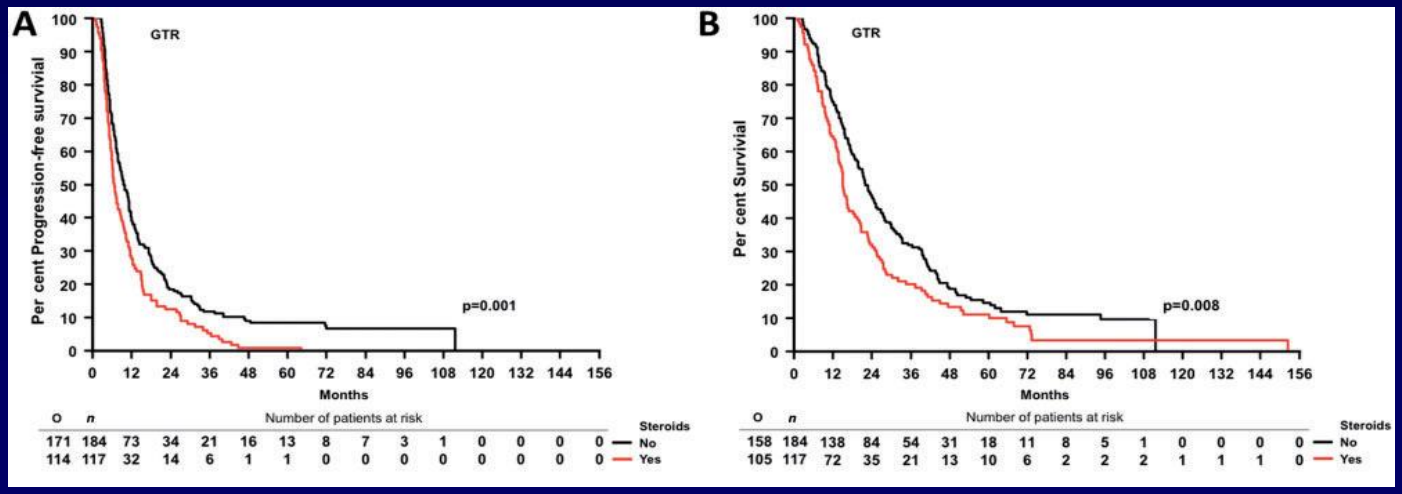
Fauci AS. *Clin Exp Immunol* 1976;24:54-62.

Dexamethasone Compromises Survival of Glioblastoma Patients

MSKCC EORTC/NCIC GGN



GGN (Gross Total Resection): PFS OS

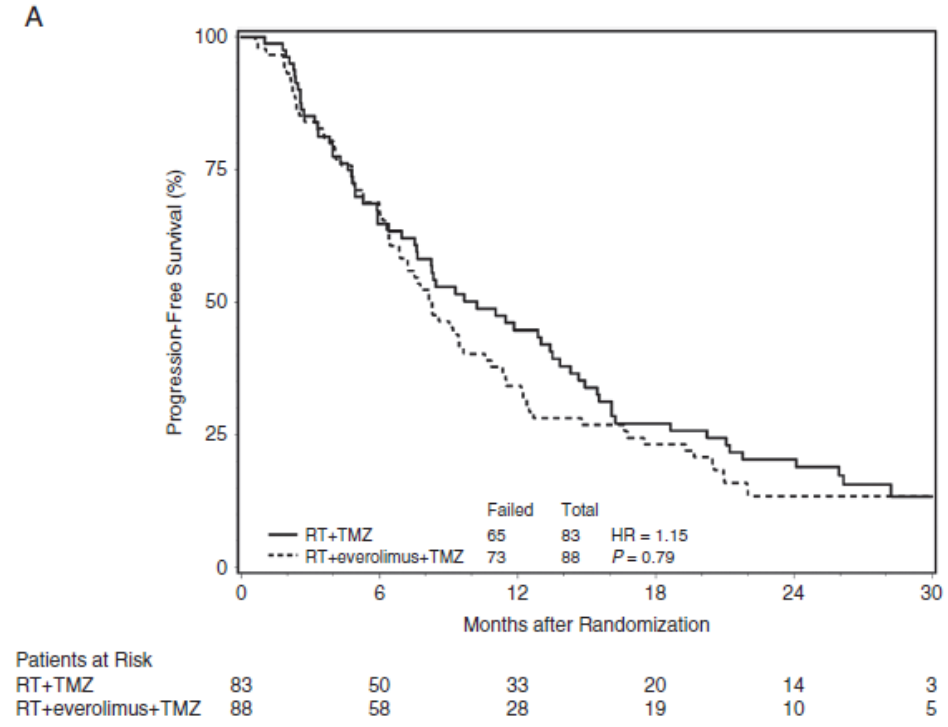


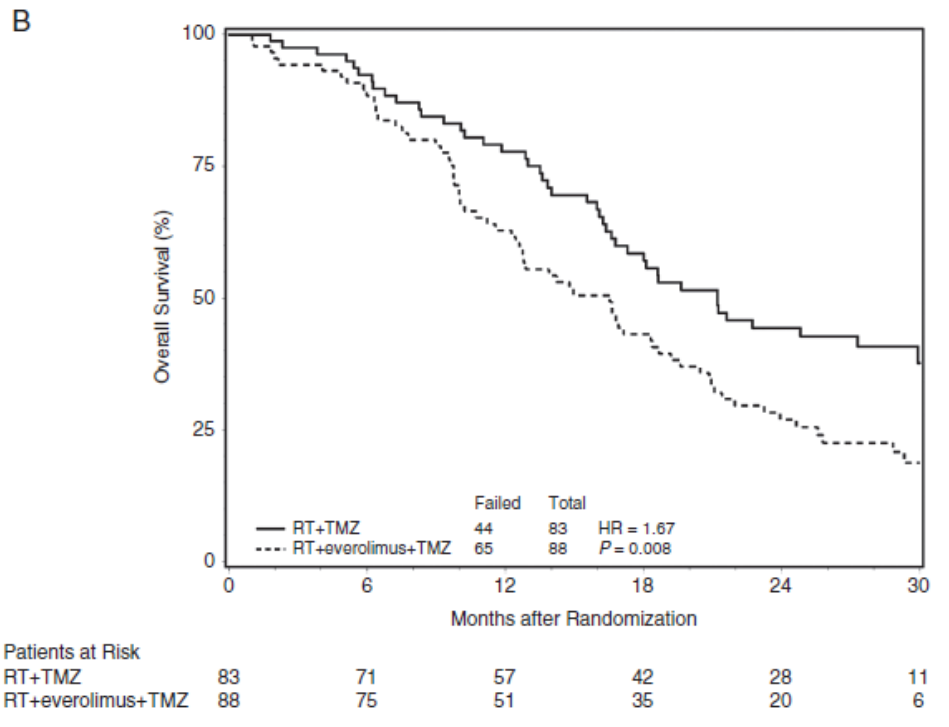
Pitter KL, Tamagno I, Alikhanyan K, et al. *Brain* 2016;139(5):1458-1471.

Immunosuppressant Everolimus Shortens Survival of Glioblastoma Patients

Progression Free Survival

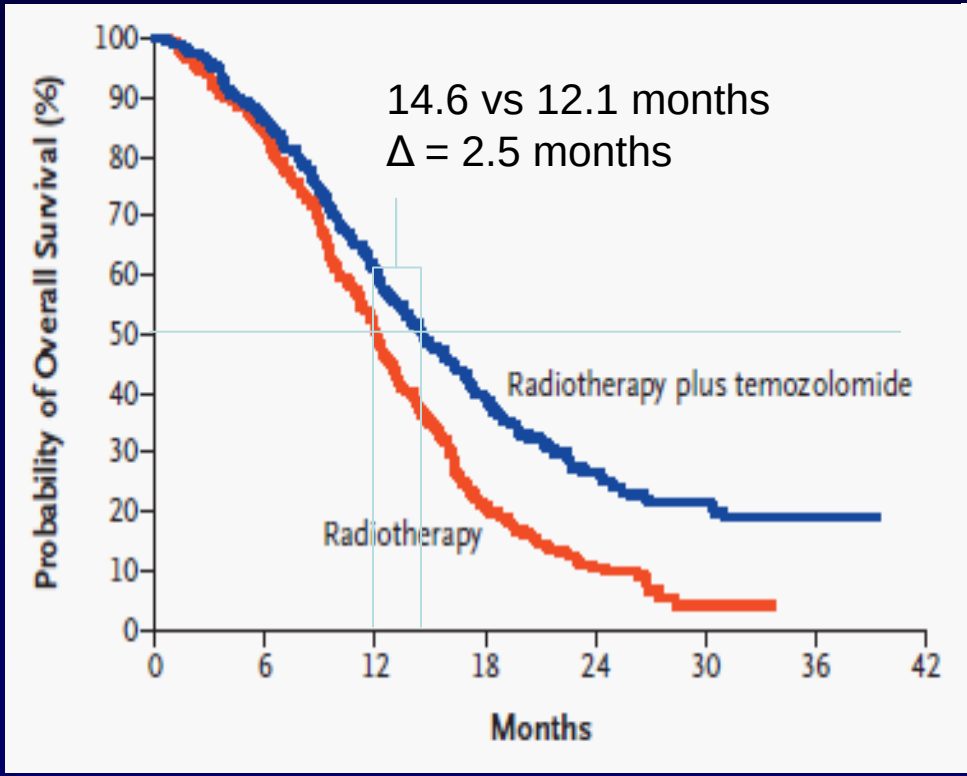
Overall Survival

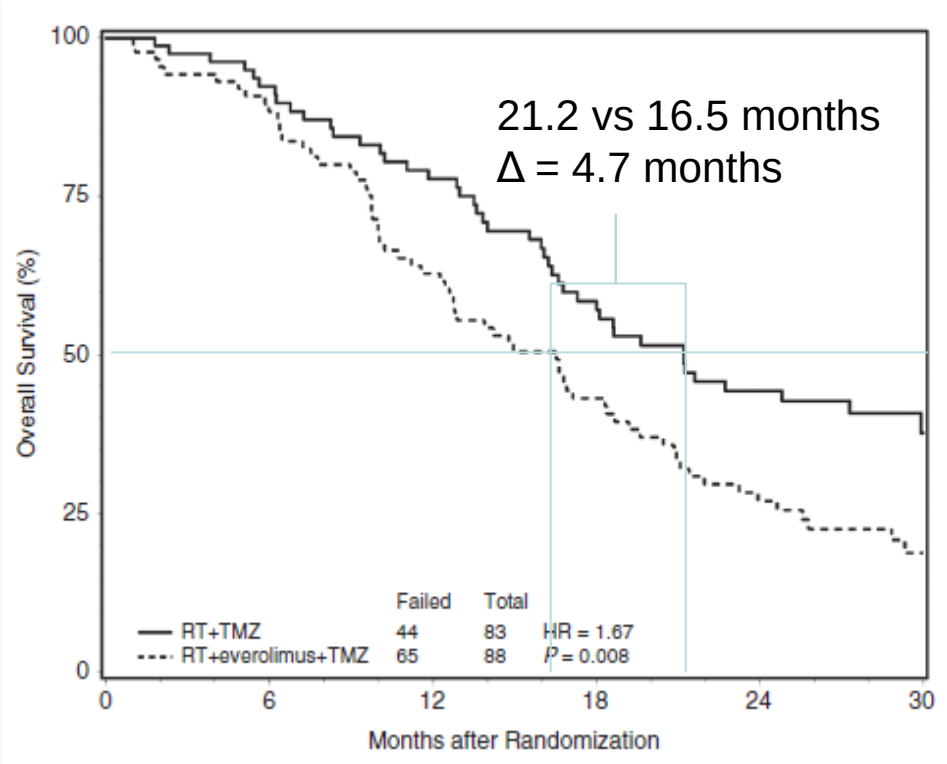




Chinnaiyan P, Won M, Wen PY, et al. *Neuro-Oncol* 2018;20(5):666-673.

Immunosuppressant Everolimus Attenuates Temzolomide Benefit During Radiotherapy





Stupp R, Mason WP, van den Bent MJ, et al. *N Engl J Med* 2005;352(10):987-996.
Chinnaiyan P, Won M, Wen PY, et al. *Neuro-Oncol* 2018;20(5):666-673.

Separate Package Inserts for Everolimus from Pharma

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFINITOR safely and effectively. See full prescribing information for AFINITOR.

AFINITOR (everolimus) tablets for oral administration
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------

AFINITOR is a kinase inhibitor indicated for the treatment of:

- postmenopausal women negative breast cancer (exemestane after failur
- adults with progressive that is unresectable, loc effectiveness of AFINI tumors have not been e
- adults with advanced re with sunitinib or sorafe
- adults with renal angio not requiring immediat treatment of renal angi objective responses in follow-up of patients is
- adults and children ≥ 3 astrocytoma (SEGA) as therapeutic interventio resection. The effective change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated. (1.5)

----------DOSAGE AND ADMINISTRATION----------

Advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC:

AFINITOR dose by approximately 50%. Subsequent dosing should be based on therapeutic drug monitoring (TDM). (2.4)

- If strong inducers of CYP3A4 are required, double the AFINITOR dose. Subsequent dosing should be based on TDM. (2.4)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZORTRESS® (everolimus) safely and effectively. See full prescribing information for ZORTRESS.

ZORTRESS (everolimus) tablets for oral use.
Initial U.S. Approval: 2010

----------DOSAGE AND ADMINISTRATION----------

- Kidney transplantation: starting oral dose of 0.75 mg twice daily as soon as possible after transplantation. (2.1)
- Liver transplantation: starting oral dose of 1.0 mg twice daily starting 30 days after transplantation. (2.2)

----------DOSAGE AND ADMINISTRATION----------

- Kidney transplantation: starting oral dose of 0.75 mg twice daily as soon as possible after transplantation. (2.1)
- Liver transplantation: starting oral dose of 1.0 mg twice daily starting 30

----------DOSAGE AND ADMINISTRATION----------

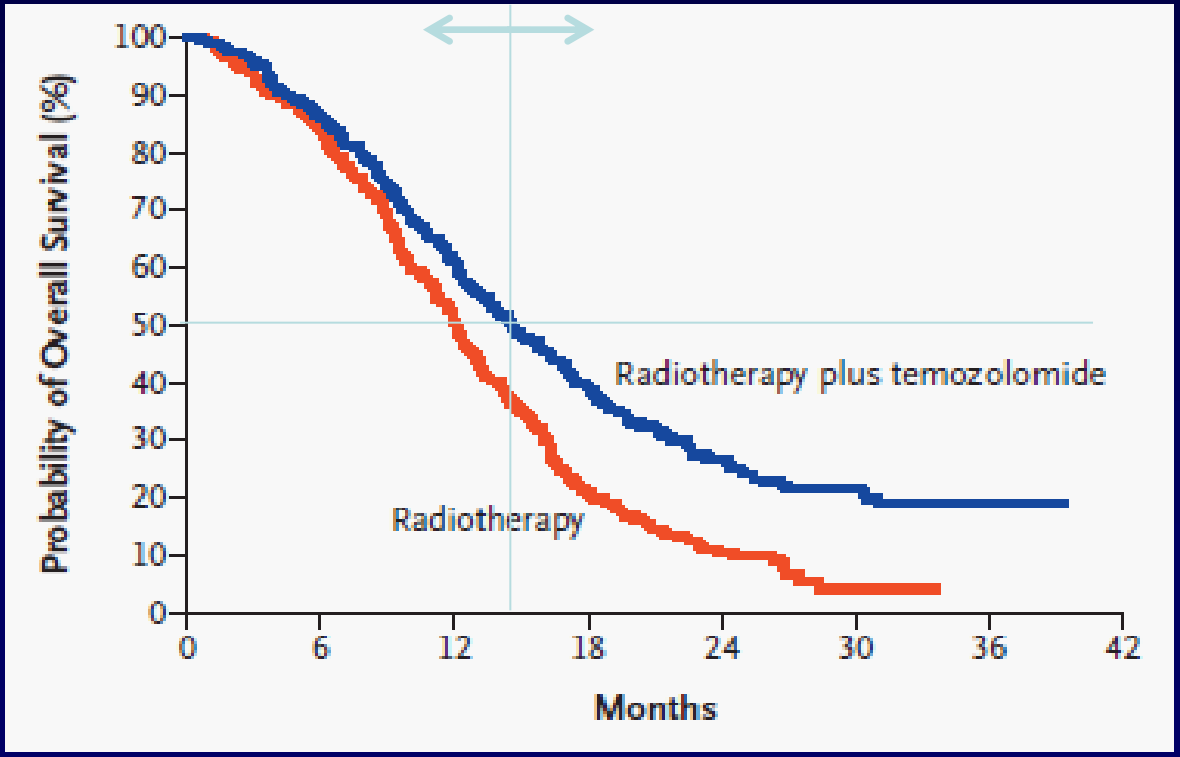
Advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC:

- 10 mg once daily with or without food. (2.1)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022334s016lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021560s006lbl.pdf

Potential Positive and Negative Factors Influencing Glioblastoma Patient Survival

IDH-1:	wild-type	mutated
MGMT:	unmethylated	methylated
TTFields:	not used	used
Dexamethasone:	used	not used
mTOR inhibitors:	used	not used



Stupp R, Mason WP, van den Bent MJ, et al. *N Engl J Med* 2005;352(10):987-996.

Update on the Management of Malignant Gliomas

- Tumor Treating Fields therapy was approved by the FDA for newly diagnosed glioblastoma patients in 2015.
- Bevacizumab received final approval by the FDA for use in recurrent glioblastoma in 2017.
- Checkpoint inhibitors offer no survival advantage to glioblastoma patients.
- Dexamethasone interferes with treatments against glioblastoma.

Clinical Trials Using Tumor Treating Fields for Brain Metastasis

Disease	Phase	Treatment	Endpoint	Status	NCT
Recurrent GBM	Pilot	TTFields + bevacizumab	PFS	Recruiting	NCT01894061
Recurrent GBM	II	TTFields + Bevacizumab	PFS	Recruiting	NCT02663271
Recurrent GBM	II	TTFields + genomic analysis to identify the genetic signature of response	ORR via RANO	Recruiting	NCT01954576
Recurrent GBM (first recurrence)	II	TTFields + bevacizumab/CCNU	AEs, PFS, OS	Pending	NCT02348255
Recurrent GBM (bevacizumab-naïve) Recurrent GBM	Pilot Pilot	TTFields + bevacizumab + SBRT TTFields	AEs Response	Recruiting Recruiting	NCT01925573 NCT02441322
Newly diagnosed unresectable GBM	II	TTFields + bevacizumab + TMZ	AEs	Recruiting	NCT02343549
Recurrent atypical and anaplastic meningioma	Pilot	TTFields	PFS	Recruiting	NCT01892397
COMET: 1-5 NSCLC brain metastases (with controlled systemic disease)	II	TTFields vs. best supportive care	Time to cerebral and distant progression	Recruiting	NCT01755624
METIS: 1-10 NSCLC brain metastases	III	TTFields vs. best supportive care	Time to cerebral progression	Recruiting	NCT02831959

Wong ET, Mehta MP, Kanner AA, Ahluwalia MS. Future directions for Tumor Treating Fields. In Wong ET (Editor): *Alternating Electric Fields Therapy in Oncology: A Practical Guide to Clinical Applications of Tumor Treating Fields*, Chapter 10, pp. 217-226, 2016.

Clinical Trials Using Tumor Treating Fields for Systemic Malignancies

Trial	Phase	Treatment	Endpoint	Status	NCT
PANOVA: Newly diagnosed advanced pancreatic	Open-label pilot	TTFields + gemcitabine with/without nab-paclitaxel	AEs	Completed	NCT01971281
INNOVATE: Recurrent ovarian carcinoma	Open-label pilot	TTFields + weekly paclitaxel	AEs	Completed	NCT02244502
STELLAR: Malignant pleural mesothelioma	II	TTFields + pemetrexed + cisplatin/ carboplatin	OS	Recruiting	NCT02397928
LUNAR: Advanced non-small cell lung cancer	III	TTFields + anti-PD1 inhibitor or paclitaxel	OS	Planning	Not available

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