



Advances in Treatment for Brain Cancer

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October 2019

Disclosures



I have consulted with Novocure, Tocagen, Inovio, Regeneron, Berg Health and GW Pharma on treatments for gliomas.

Learning Objectives

(with action verbs!)

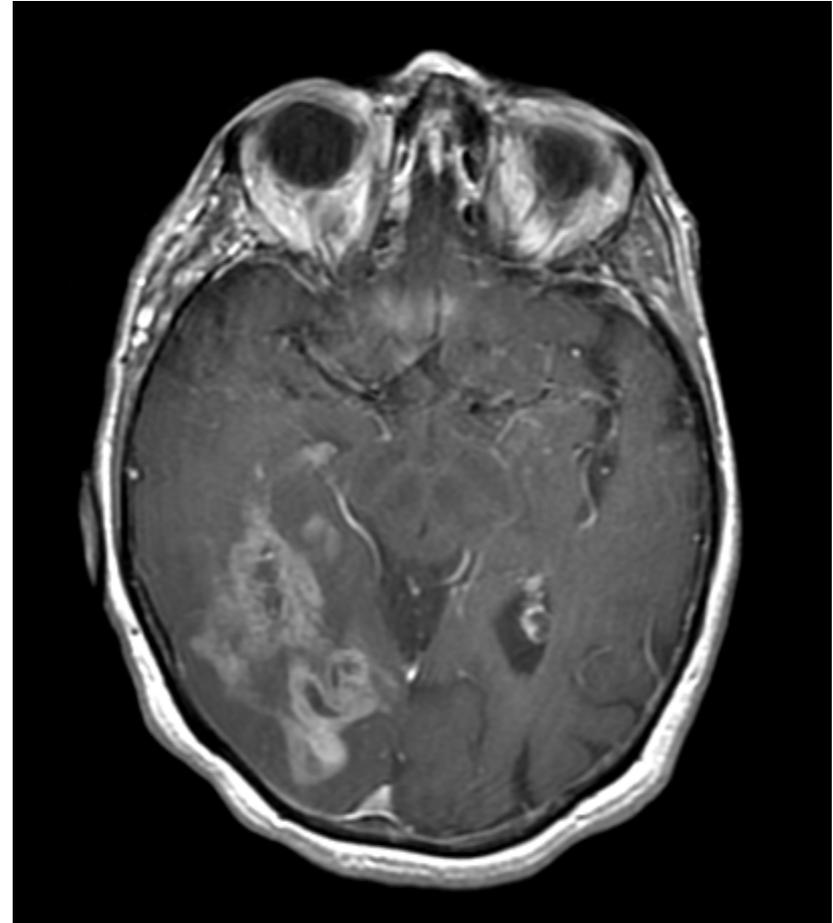


- 1) Discuss device therapy/electrical fields
- 2) Briefly update your thoughts on Polio virus in GBM
- 3) Targeted therapy in the CNS: lets talk hope!

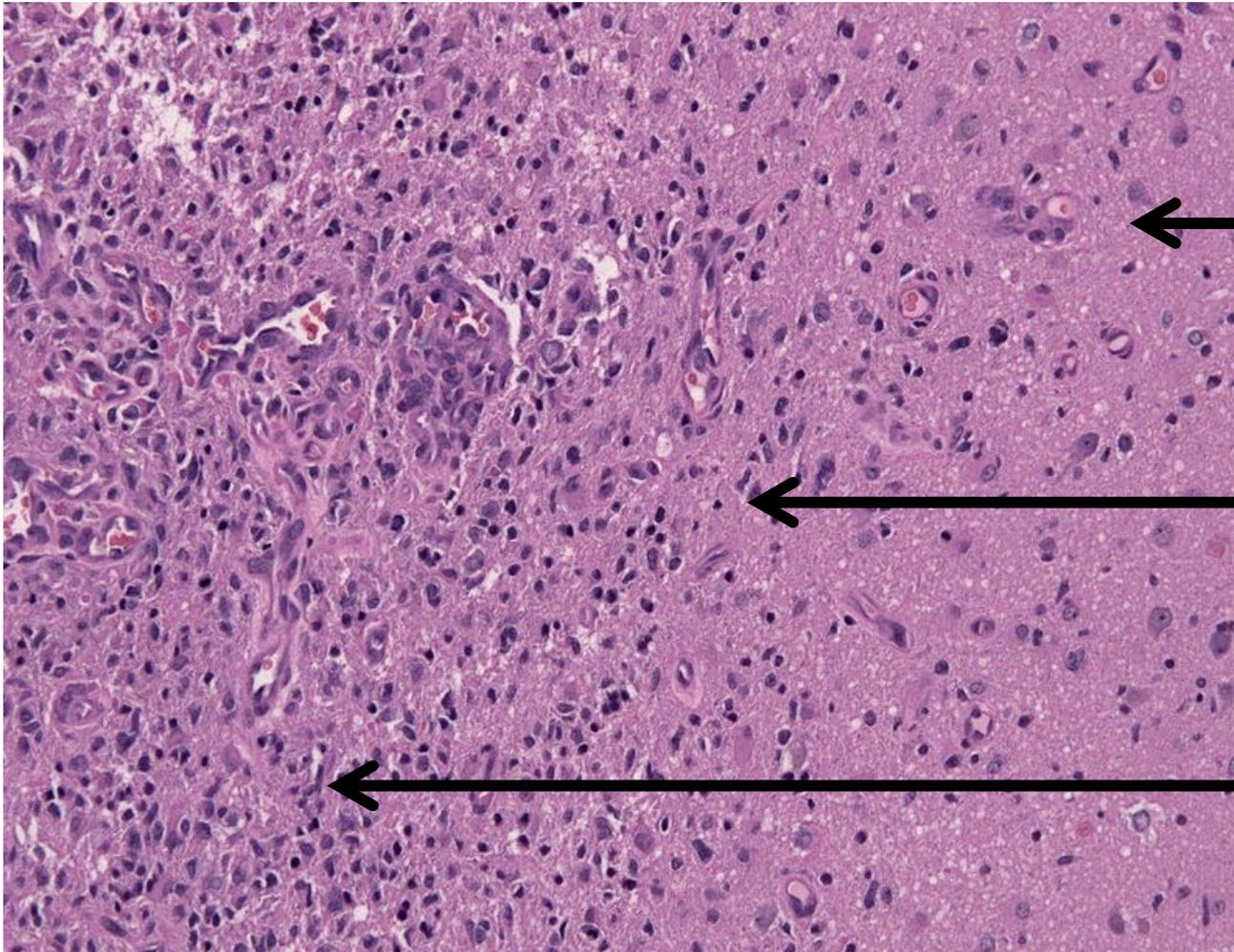
Quick Glioblastoma Review



- Most common primary brain CA
- Cancer that starts inside the brain
- Average age 64
- Median survival is increasing with each trial published, with newest major study at 24 months



Gliomas are infiltrative tumors

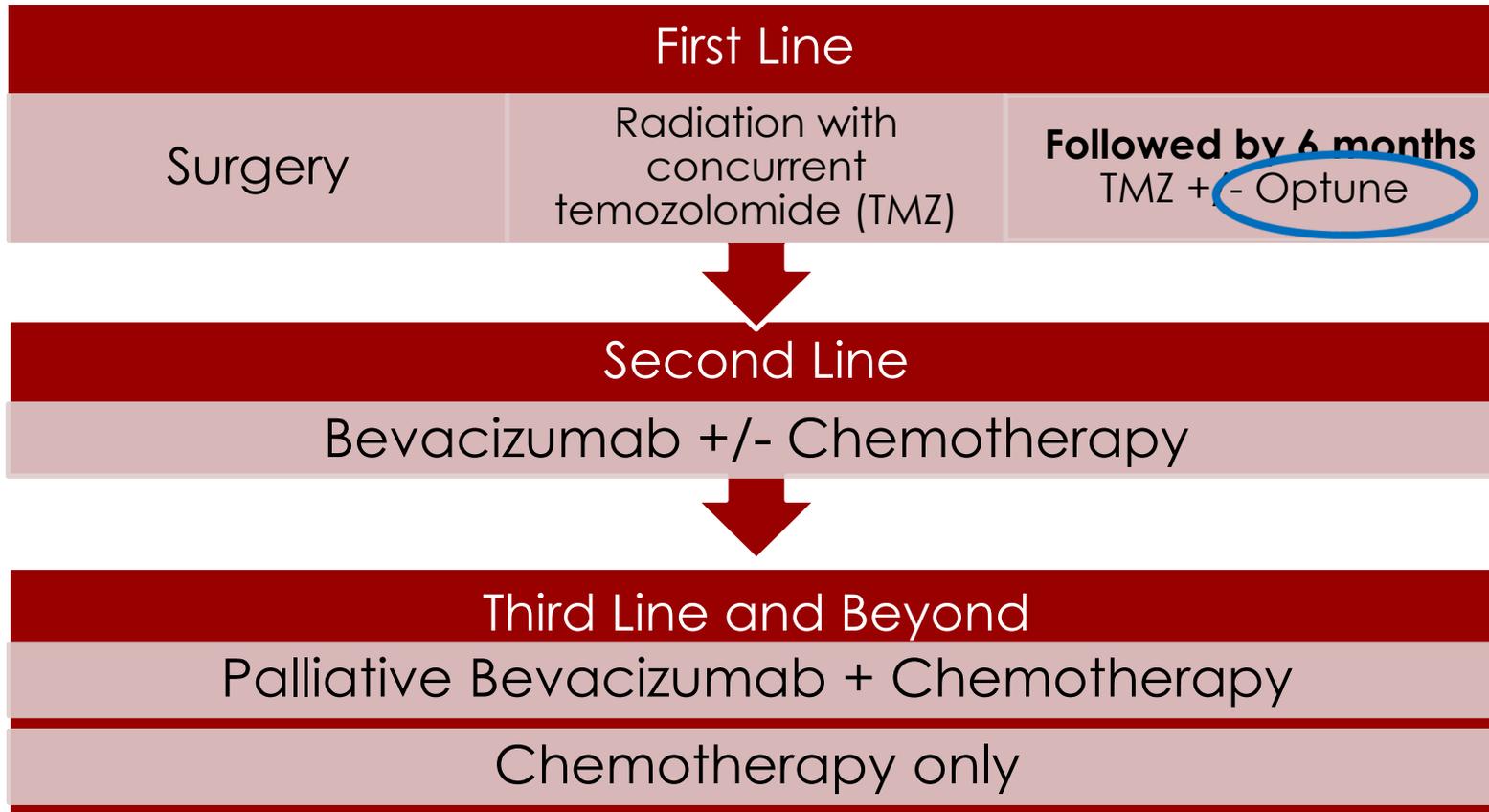


← Normal Brain

← Tumor + Normal Brain

← Predominantly Tumor

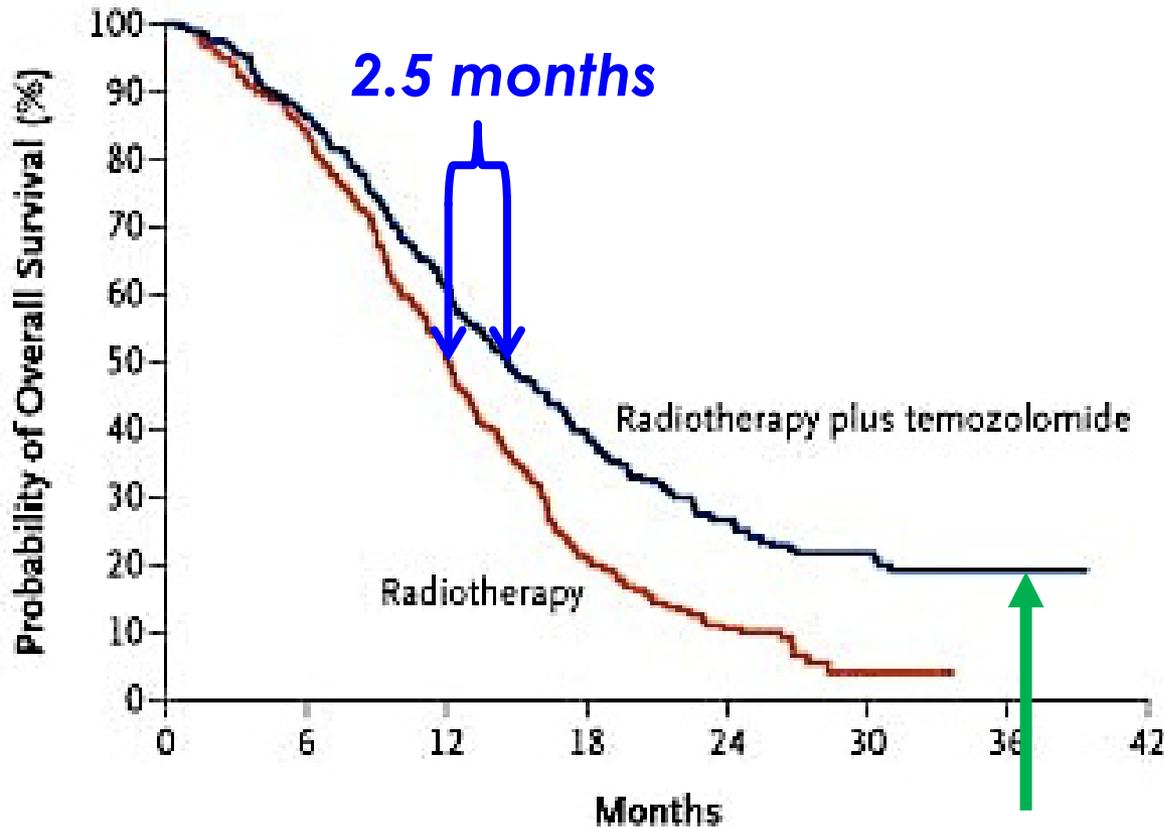
Standard Treatment Algorithm for Glioblastoma



Less than 60% of patients get "standard therapy"

First Line Standard of Care:

Surgery, Concurrent Chemo-Radiation



- Increased overall survival by **2.5 months** over radiation
- Study enrolled patients **<70** (average age =64)
- Decreasing benefit with age

The tail is what got people excited

Novo-TTF/Optune Device for GB

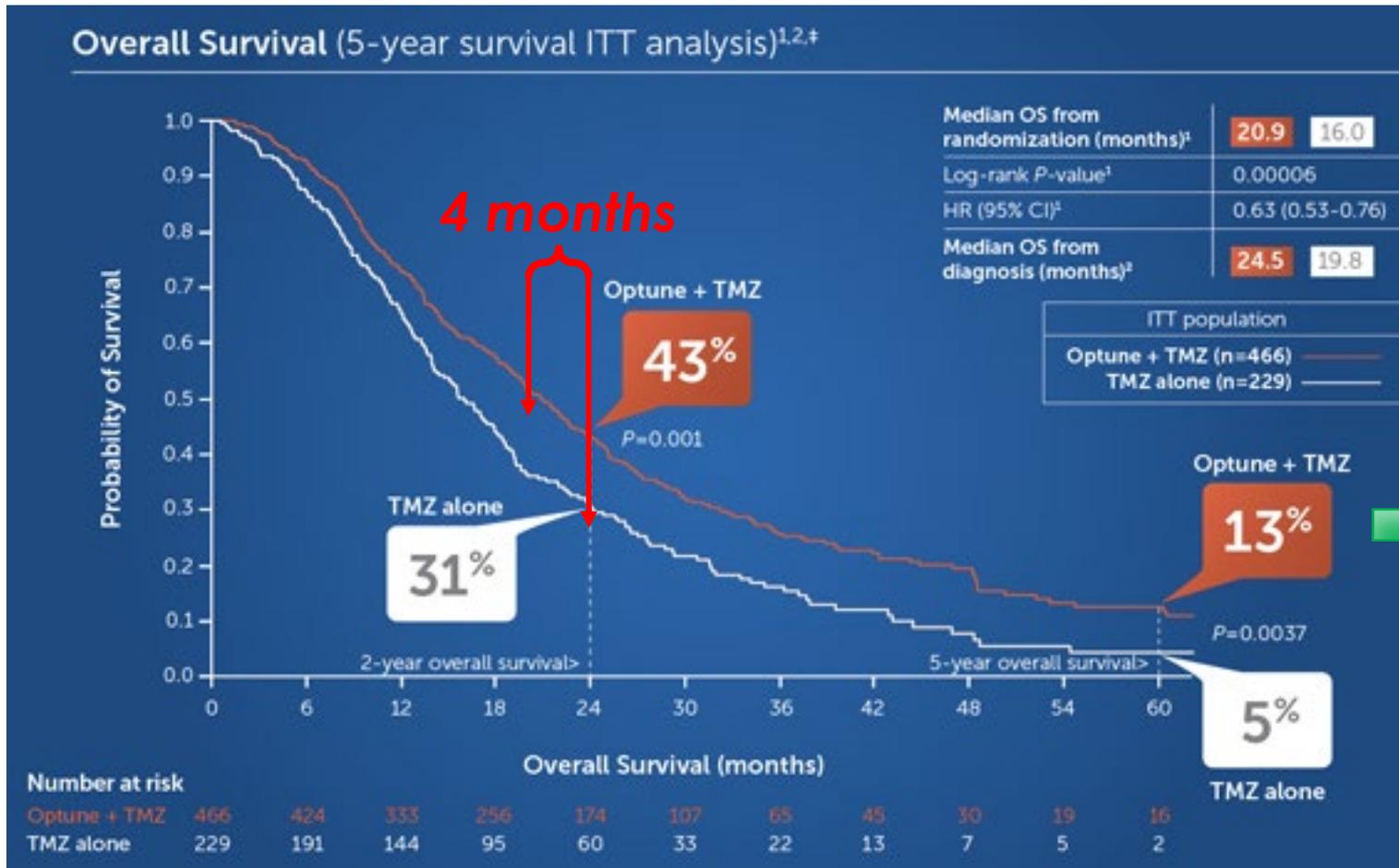


- FDA approved for newly diagnosed and recurrent GBM
- Delivers alternating low-intensity, medium frequency electrical fields
- Portable (6~~lb~~)3lb or stationary
- Approved in Europe when compared to physician's choice of traditional chemotherapy
- FDA then approved, but many US MDs did not start using it



First Line Standard of Care:

Surgery, Concurrent Chemo-Radiation, + Optune

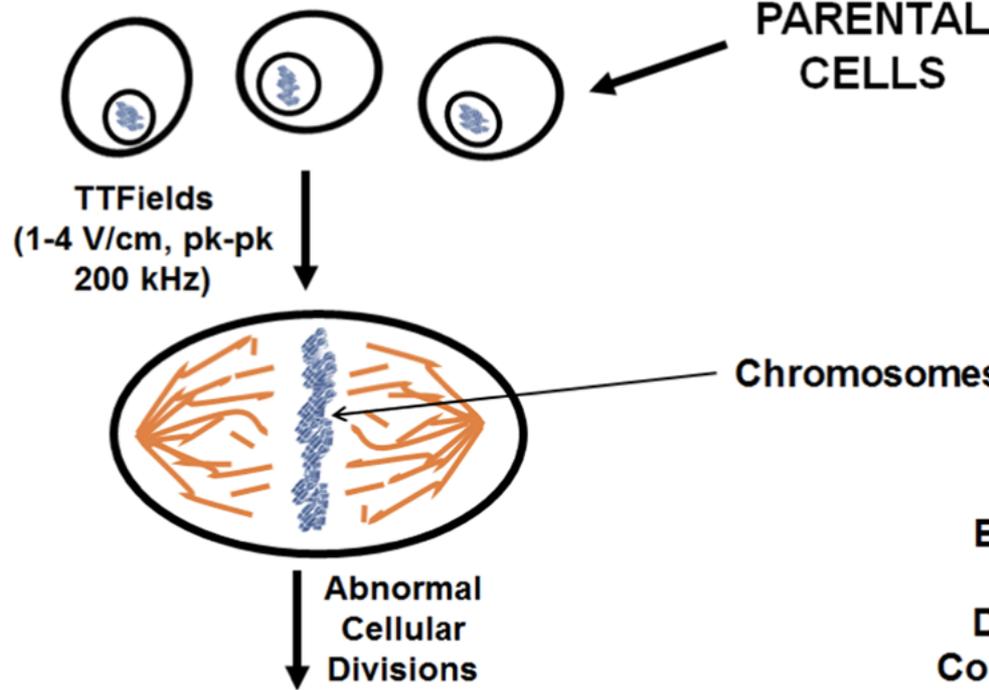


The tail is still why people are excited!

Two Possible Anti-tumor Activities

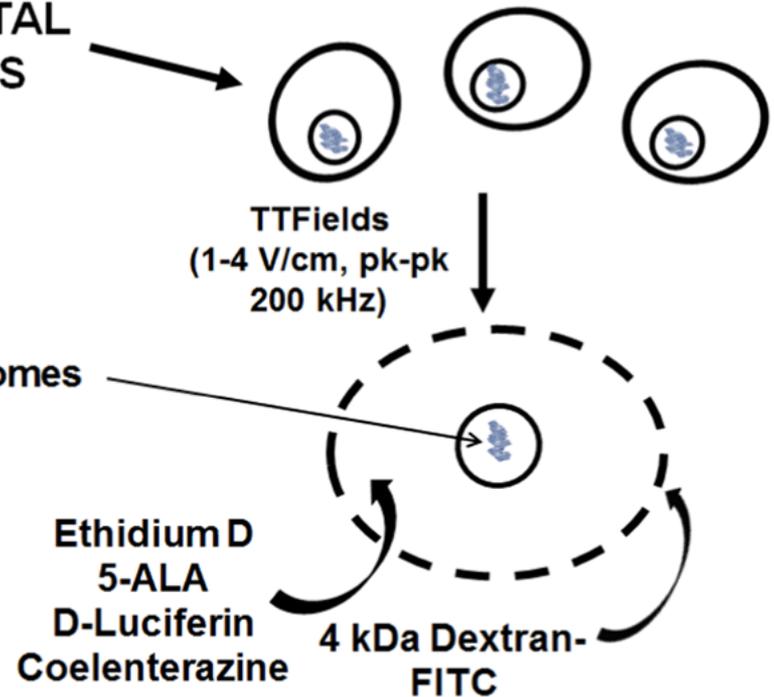


(A) Mitotic Spindle Disruption



TTFields disrupts mitotic spindles leading to abnormal cellular division and death at interphase

(B) Membrane Disruption



TTFields disrupts cellular membranes leading to greater binding to and permeability across them

Treatment Fields Thought to Disrupt Spindle Alignment

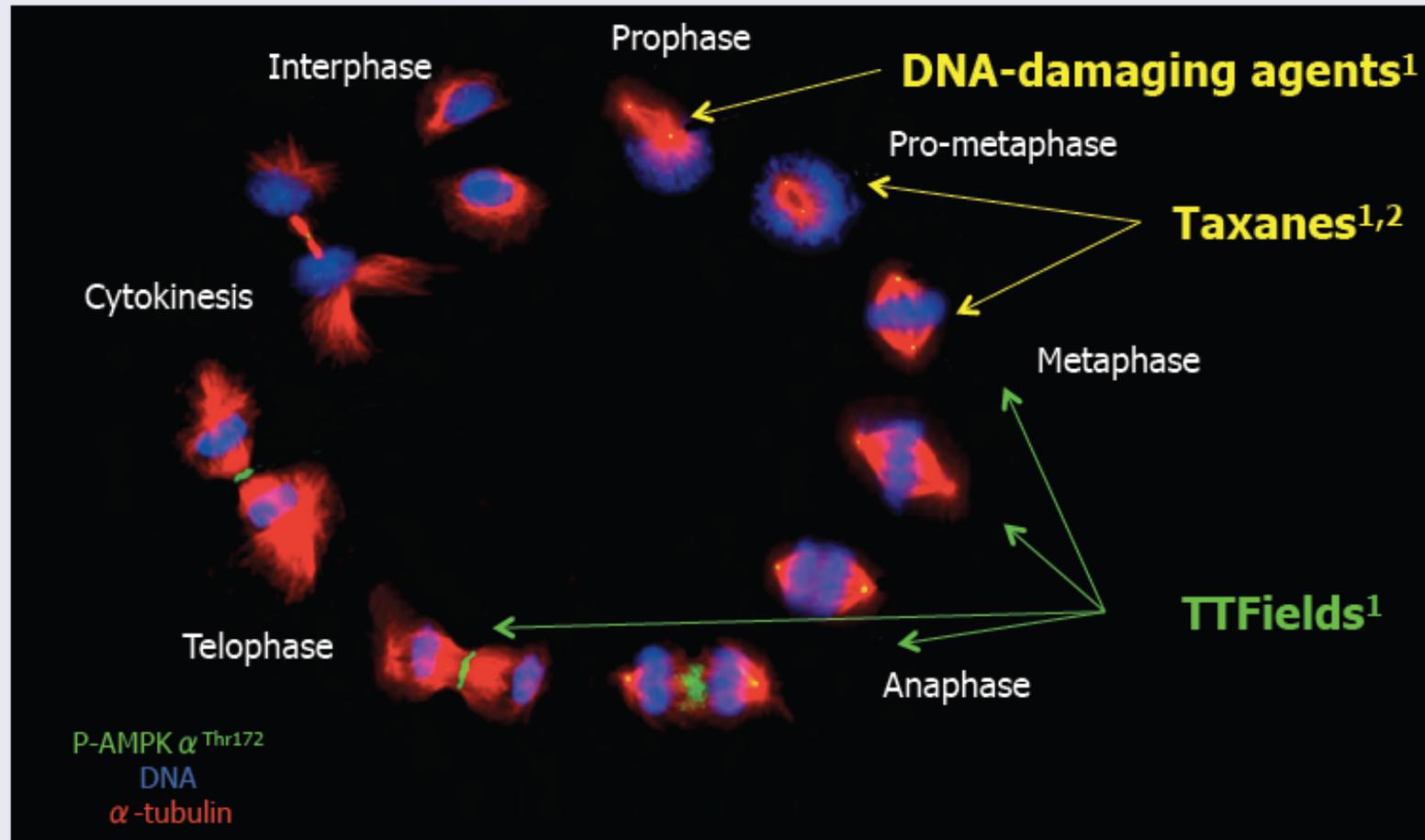
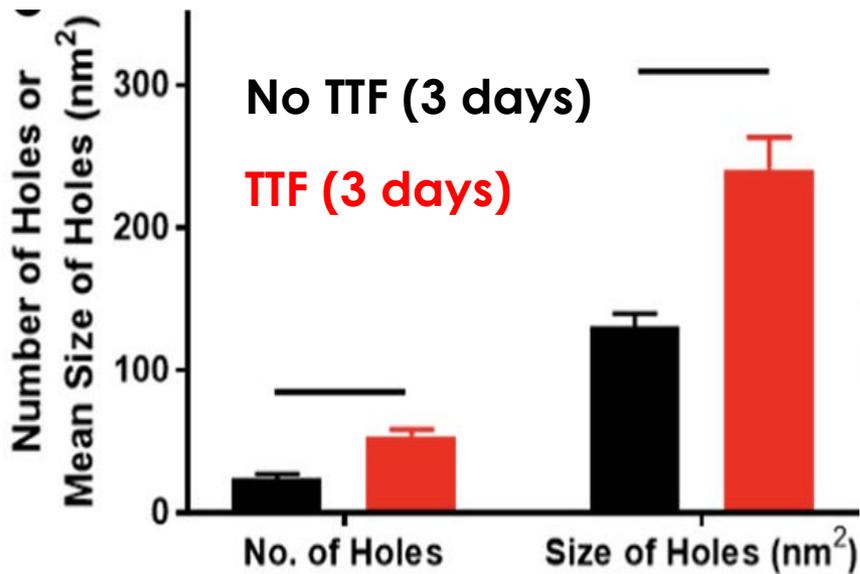
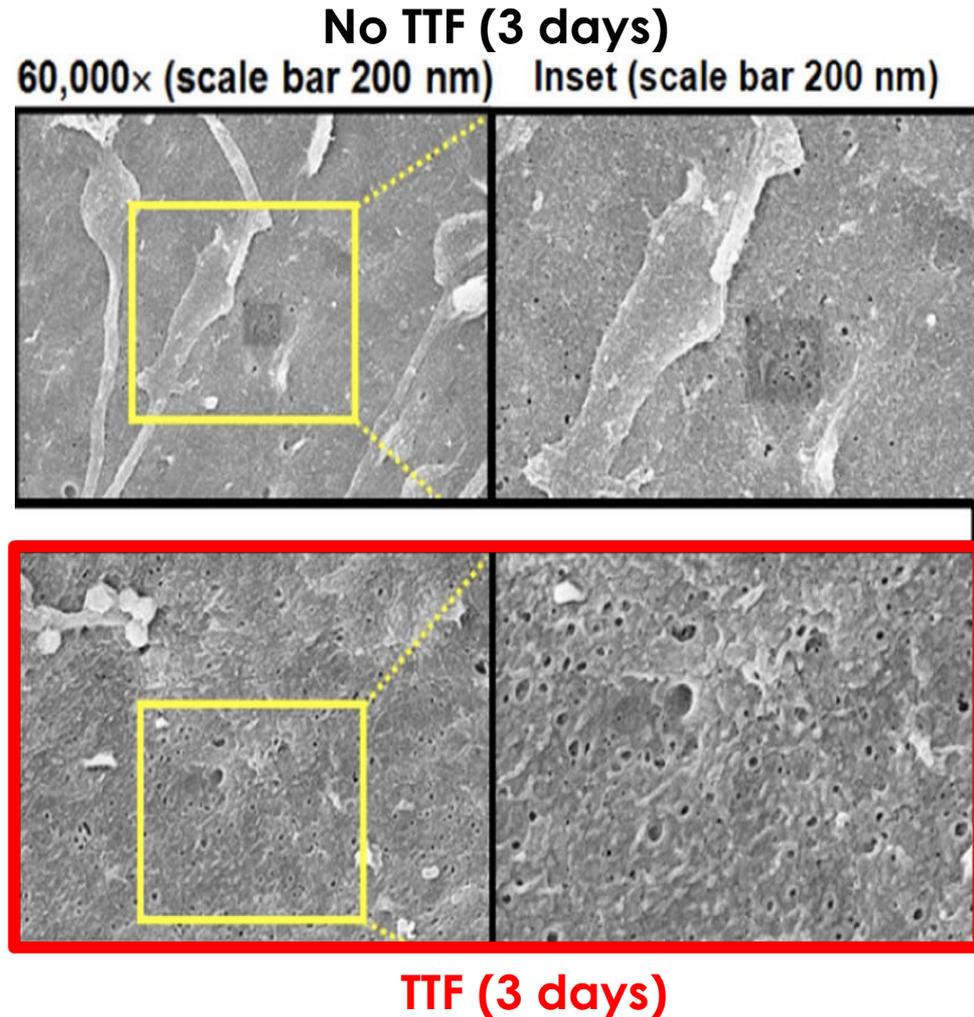


Image modified from Vazquez-Martin A, Oliveras-Ferraros C, Mendeendez JA. *Cell Cycle*. 2009;8(15):2385-2398.*
DNA, deoxyribonucleic acid; P-AMPK, phospho-AMP-activated protein kinase.
* *Cell Cycle*, Landes Bioscience, 2009. Copyright and all rights reserved. Material from this publication has been used with the permission of Landes Bioscience.
1. Lee SX, Wong ET, Swanson KD. [SNO abstract CB-013]. *Neuro Oncol*. 2012;14(suppl 6):vi7-vi20. 2. Jordan MA, Wendell K, Gardiner S, et al. *Cancer Res*. 1996;56:816-825.

Treatment Fields May Increase Cell “Leakiness”



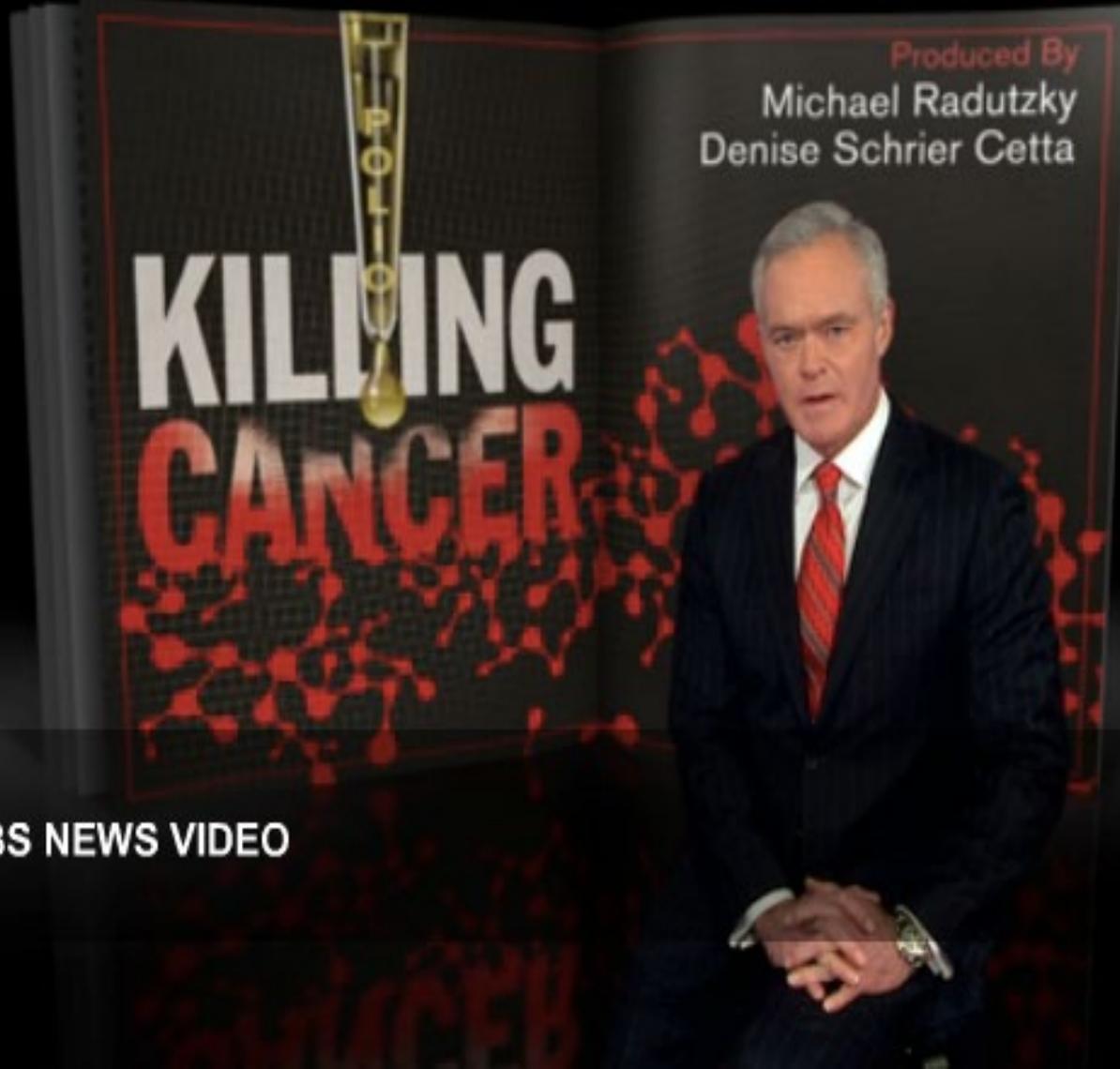
More Holes
Bigger Holes



The Polio Virus Craze: *Its back!*



60
MINUTES



PLAY CBS NEWS VIDEO

The Polio Virus Craze: *Its back!*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Recurrent Glioblastoma Treated with Recombinant Poliovirus

Annick Desjardins, M.D., Matthias Gromeier, M.D., James E. Herndon II, Ph.D., Nike Beaubier, M.D., Dani P. Bolognesi, Ph.D., Allan H. Friedman, M.D., Henry S. Friedman, M.D., Frances McSherry, M.A., Andrea M. Muscat, B.Sc., Smita Nair, Ph.D., Katherine B. Peters, M.D., Ph.D., Dina Randazzo, D.O., John H. Sampson, M.D., Ph.D., Gordana Vlahovic, M.D., William T. Harrison, M.D., Roger E. McLendon, M.D., David Ashley, M.B., B.S., Ph.D., and Darell D. Bigner, M.D., Ph.D.

ABSTRACT

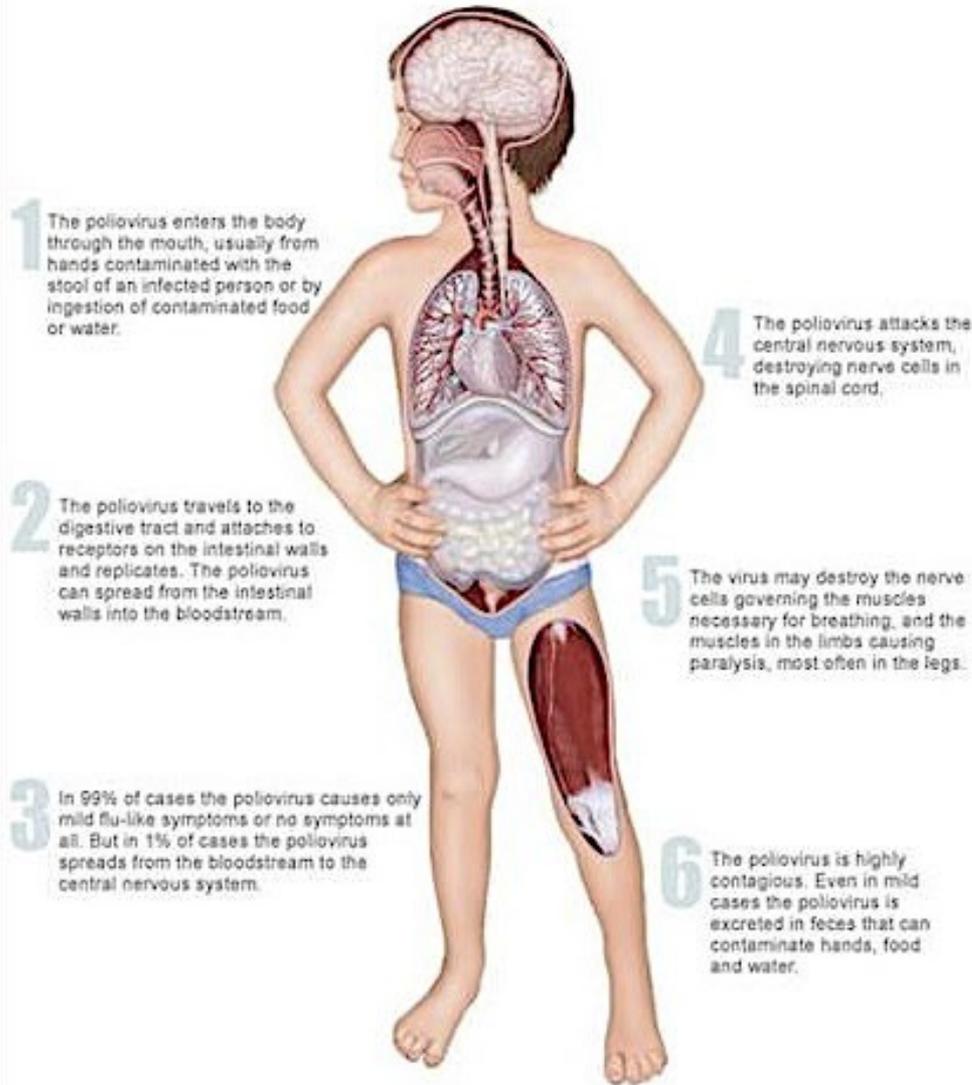
BACKGROUND

The prognosis of patients with recurrent World Health Organization (WHO) grade IV malignant glioma is dismal, and there is currently no effective therapy. We conducted a dose-finding and toxicity study in this population of patients, evaluating convection-enhanced, intratumoral delivery of the recombinant nonpathogenic polio–rhinovirus chimera (PVSRIPO). PVSRIPO recognizes the poliovirus receptor CD155, which is widely expressed in neoplastic cells of solid tumors and in major components

From the Departments of Neurosurgery (A.D., M.G., A.H.F., H.S.F., K.B.P., D.R., J.H.S., G.V., D.A., D.D.B.), Biostatistics (J.E.H., F.M.), Surgery (D.P.B., S.N.), and Pathology (W.T.H., R.E.M.) and the Preston Robert Tisch Brain Tumor Center (A.D., M.G., J.E.H., D.P.B., A.H.F., H.S.F., F.M., S.N., K.B.P., D.R., G.V., D.A., D.D.B., J.E.H., F.M., D.P.B., S.N., W.T.H., R.E.M.)

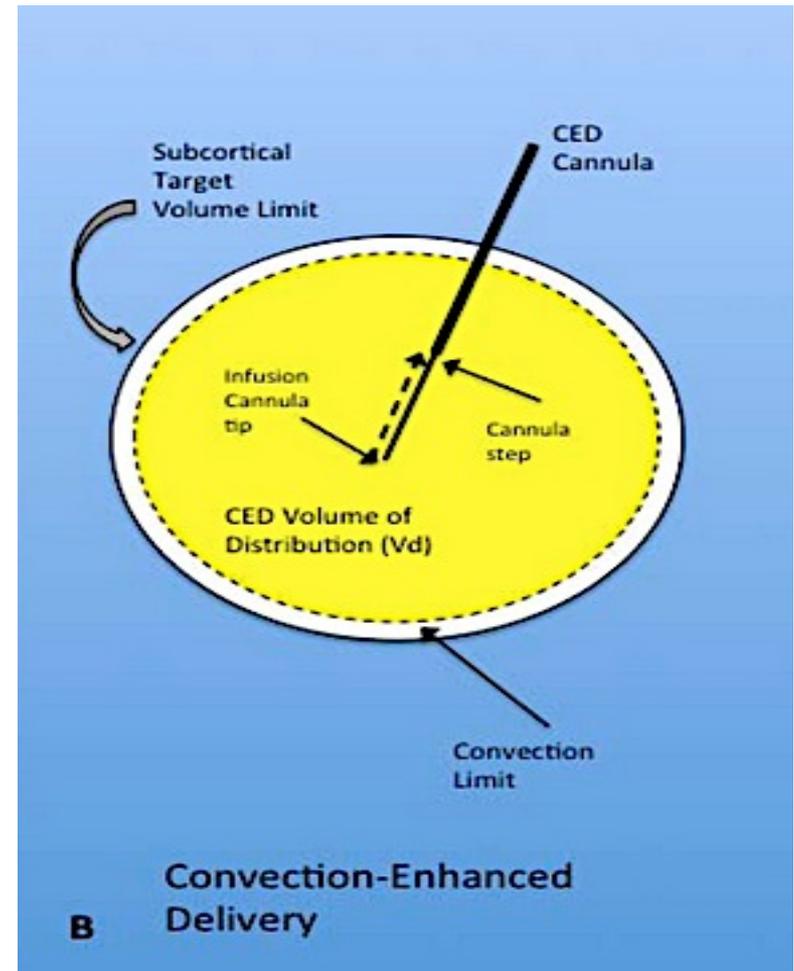
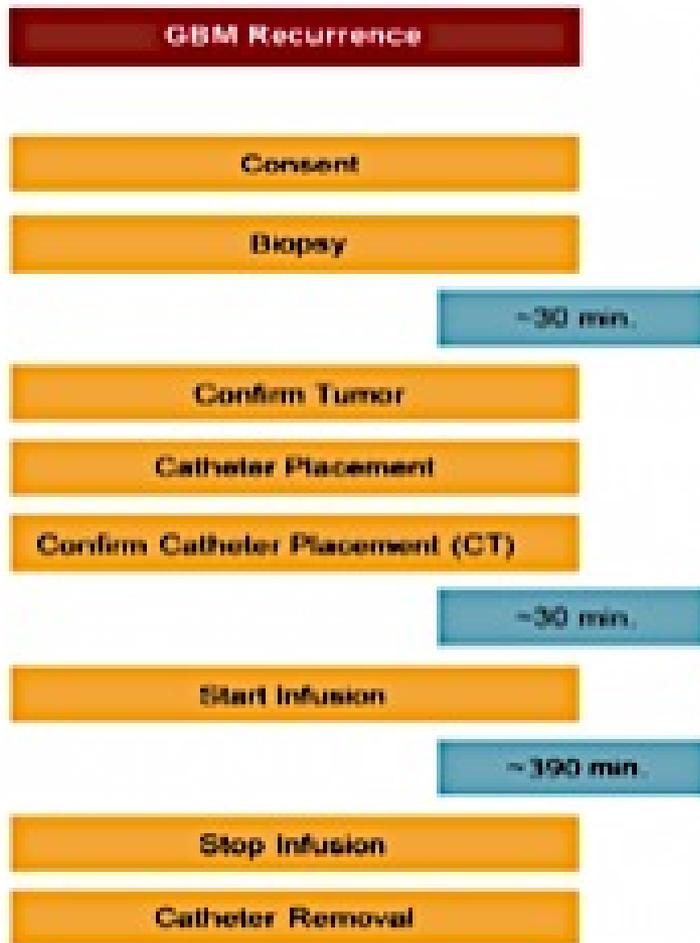
But this time, its published

Poliovirus is CNS-trophic



NecL5, the “polio receptor” is expressed in the CNS and in CNS tumors

Poliovirus spliced w Rhinovirus is CNS trophic, not CNS toxic



Convection enhanced delivery theoretically increases delivery volume

Dose-Escalation vs. Historical Controls



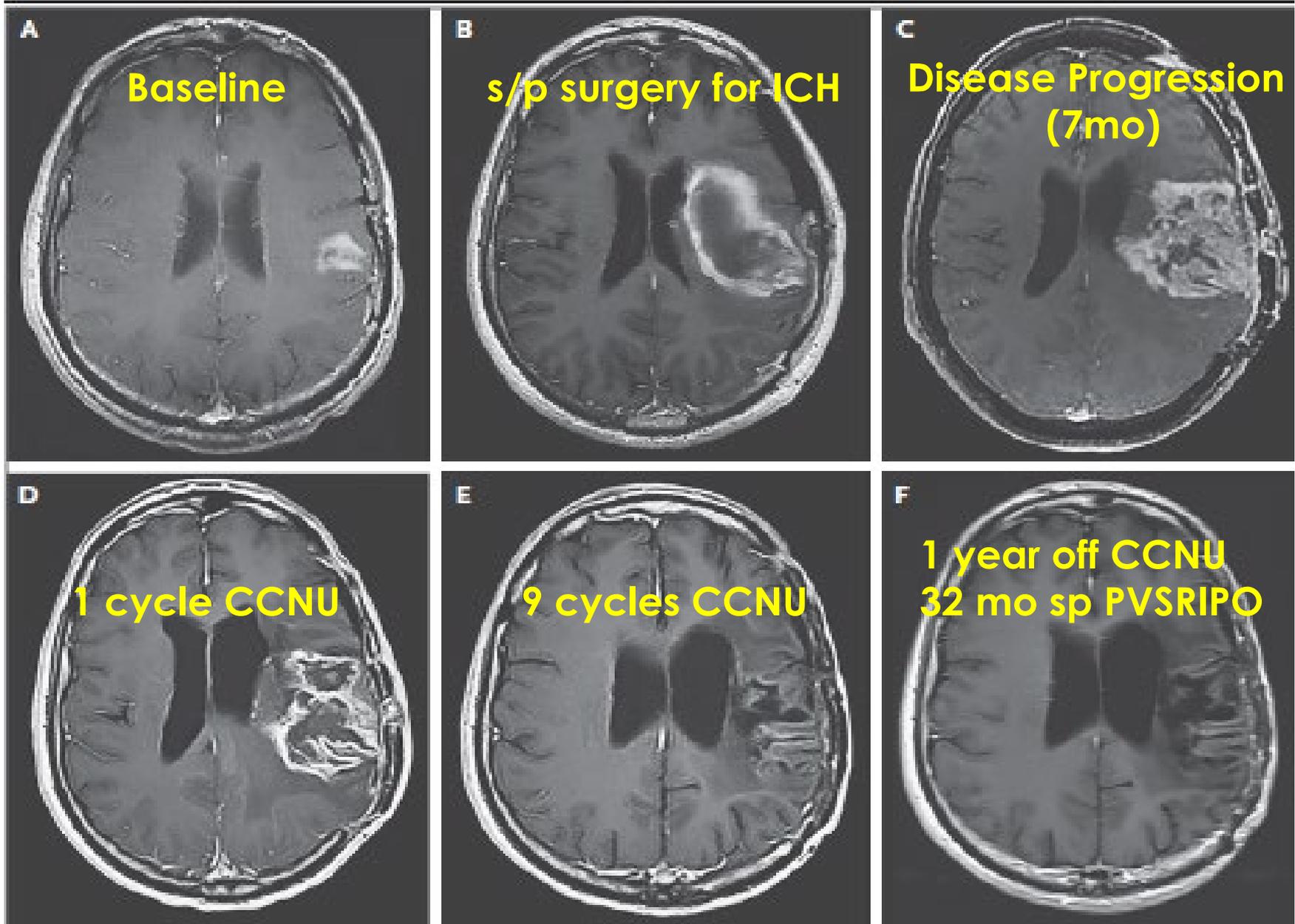
Characteristic	Patients Who Received PVSRIPO (N=61)	Historical Controls (N=104)
Sex — no. (%)		
Female	25 (41)	39 (38)
Male	36 (59)	65 (62)
Median age at PVSRIPO treatment or eligibility (range) — yr	55 (20–75)	55 (23–77)
Karnofsky performance status — no. (%)†		
100	2 (3)	8 (8)
90	42 (69)	64 (62)
80	16 (26)	30 (29)
70	1 (2)	2 (2)
Extent of maximal resection at diagnosis — no. (%)‡		
Gross total resection	47 (77)	69 (66)
Subtotal resection	14 (23)	25 (24)
Biopsy	0	10 (10)
No. of previous progressions — no. (%)		
1	45 (74)	85 (82)
2	12 (20)	11 (11)
3	2 (3)	8 (8)
4	2 (3)	0
Previous treatment failure with bevacizumab — no. (%)		
No	47 (77)	61 (59)
Yes	14 (23)	43 (41)
IDH1 R132 status at diagnosis — no. (%)‡		
Nonmutant	45 (74)	23 (22)
Mutant	7 (11)	4 (4)
Unknown	9 (15)	77 (74)

Relatively Well Tolerated

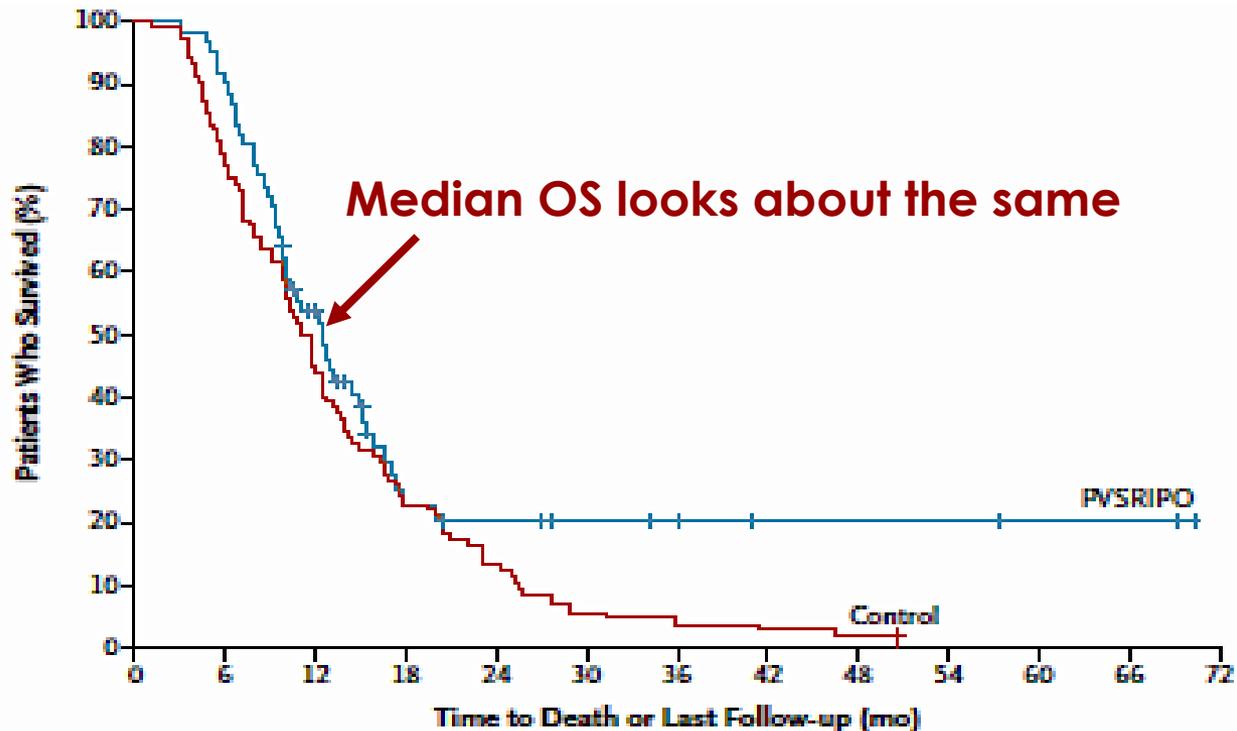


Body System and Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	<i>number of patients (percent)</i>				
Eye disorder					
Blurred vision	1 (2)	—	—	—	—
Diplopia	1 (2)	—	—	—	—
Focusing difficulty	1 (2)	—	—	—	—
Visual field cut or hemianopia	8 (15)	2 (4)	—	—	—
Gastrointestinal disorder					
Nausea	5 (10)	—	—	—	—
Vomiting	3 (6)	—	—	—	—
General disorder or administration-site condition					
Fatigue	4 (8)	2 (4)	—	—	—
Gait disturbance	4 (8)	—	1 (2)	—	—
Nervous system disorder					
Cerebral edema	—	—	—	1 (2)	—
Cognitive disturbance	12 (23)	1 (2)	—	—	—
Dysphasia	7 (13)	8 (15)	—	—	—
Dystonia	—	—	1 (2)	—	—
Facial muscle weakness	1 (2)	—	—	—	—
Headache	12 (23)	14 (27)	1 (2)	—	—
Intracranial hemorrhage	1 (2)	—	—	—	—
Paresthesia	7 (13)	—	—	—	—
Pyramidal tract syndrome†	14 (27)	8 (15)	4 (8)	—	—
Seizure	19 (37)	2 (4)	1 (2)	—	1 (2)
Psychiatric disorder					
Confusion	3 (6)	5 (10)	1 (2)	—	—
Delusions	—	—	1 (2)	—	—
Hallucinations	1 (2)	—	—	—	—
Renal and urinary disorder: urinary incontinence	1 (2)	—	—	—	—
Vascular disorder: hypertension	—	1 (2)	—	—	—
Total no. of patients with an event‡	14 (27)	23 (44)	9 (17)	0	1 (2)

Patient at Dose Level 5 with Response?



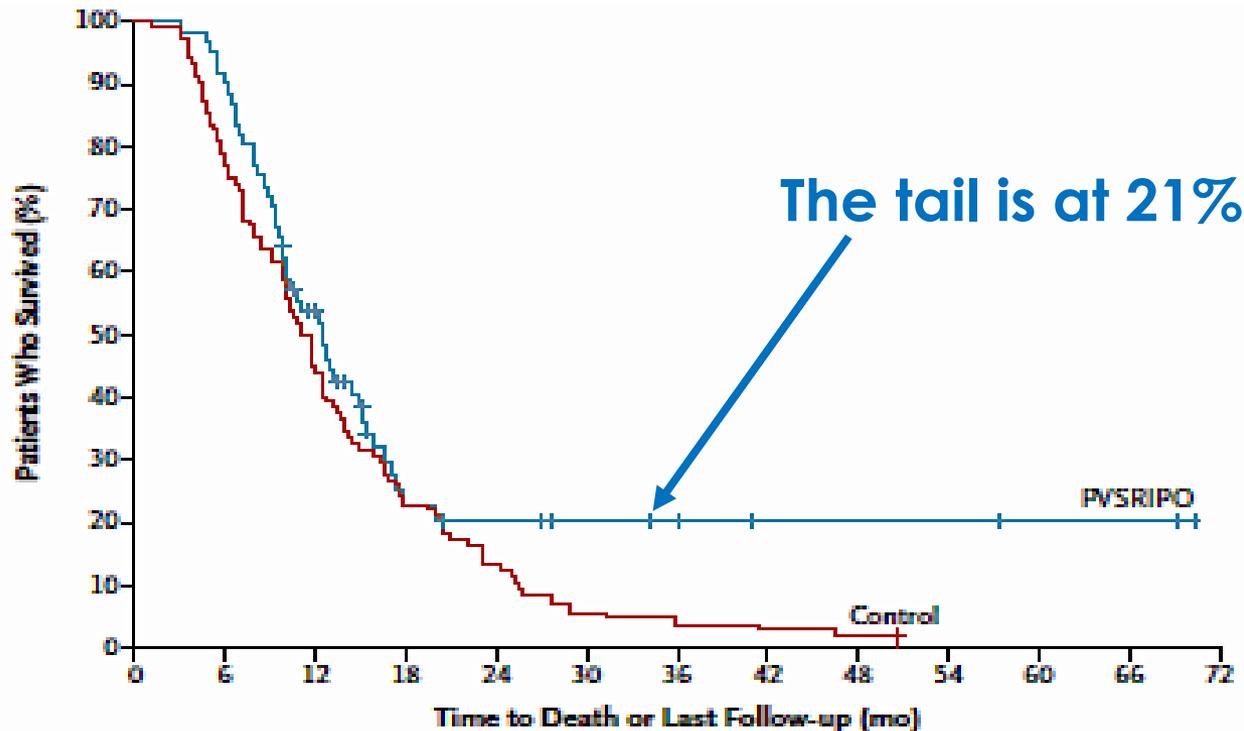
Does it Prolong Overall Survival?



No. at Risk														
PVSRIPO	61	55	29	10	8	6	5	3	3	3	2	2	-	
Control	104	80	47	24	14	6	4	3	2	-	-	-	-	

Group	Total No. of Patients	No. of Deaths	Median Survival (95% CI) mo	Survival Rate (95% CI) percent						
				6 Mo	12 Mo	18 Mo	24 Mo	36 Mo	48 Mo	60 Mo
PVSRIPO	61	44	12.5 (9.9-15.2)	90 (79-96)	54 (40-65)	23 (12-35)	21 (11-33)	21 (11-33)	21 (11-33)	21 (11-33)
Control	104	103	11.3 (9.8-12.5)	77 (68-84)	45 (36-54)	23 (16-32)	14 (8-21)	4 (1-9)	2 (<1-6)	-

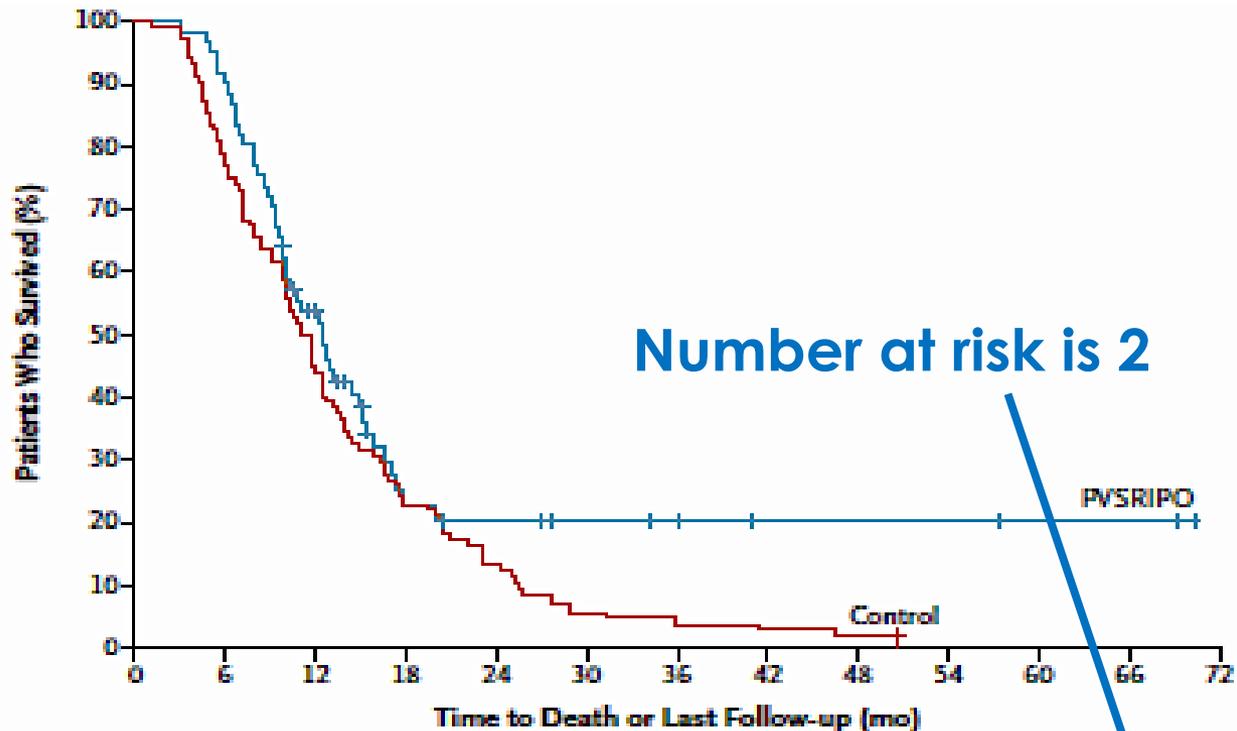
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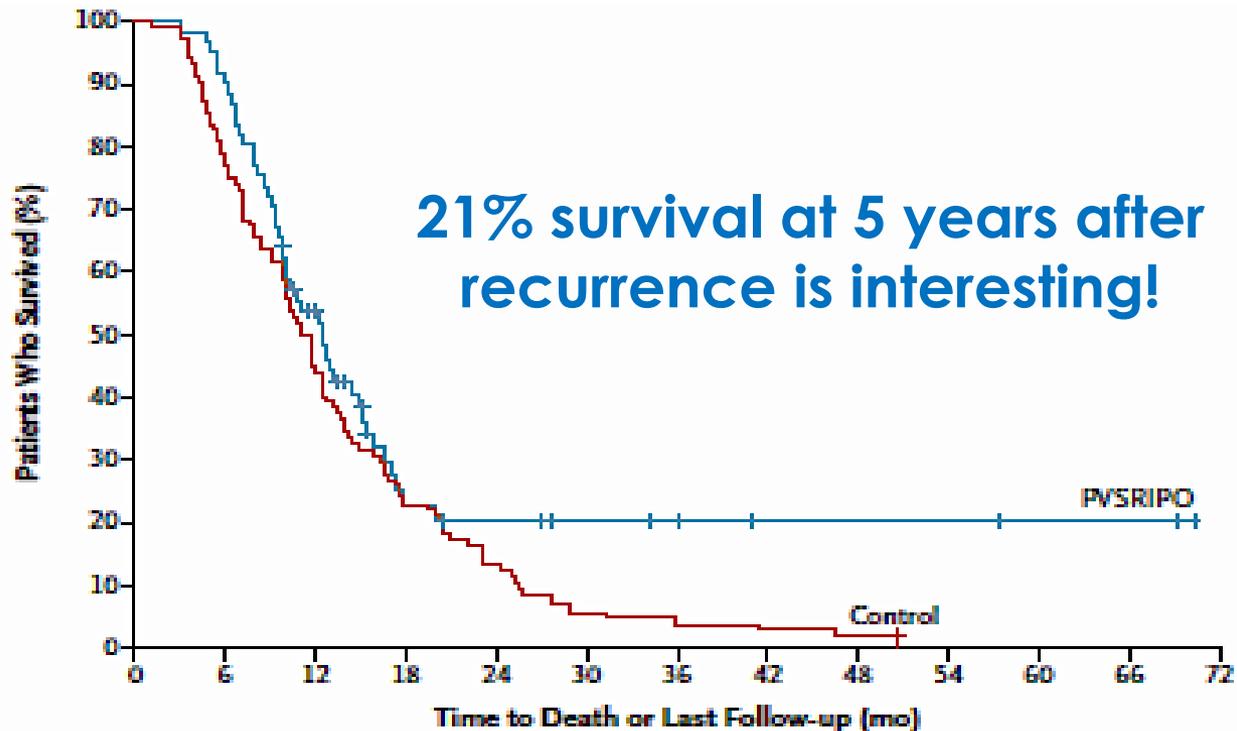
Does it Prolong Overall Survival?



No. at Risk		0	6	12	18	24	30	36	42	48	54	60	66	72
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Maybe. Further study warranted....



No. at Risk		0	6	12	18	24	30	36	42	48	54	60	66	72
PVSRIPO		61	55	29	10	8	6	5	3	3	3	2	2	—
Control		104	80	47	24	14	6	4	3	2	—	—	—	—

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Let's talk hope!



Updates from the ASCO Meeting 2019

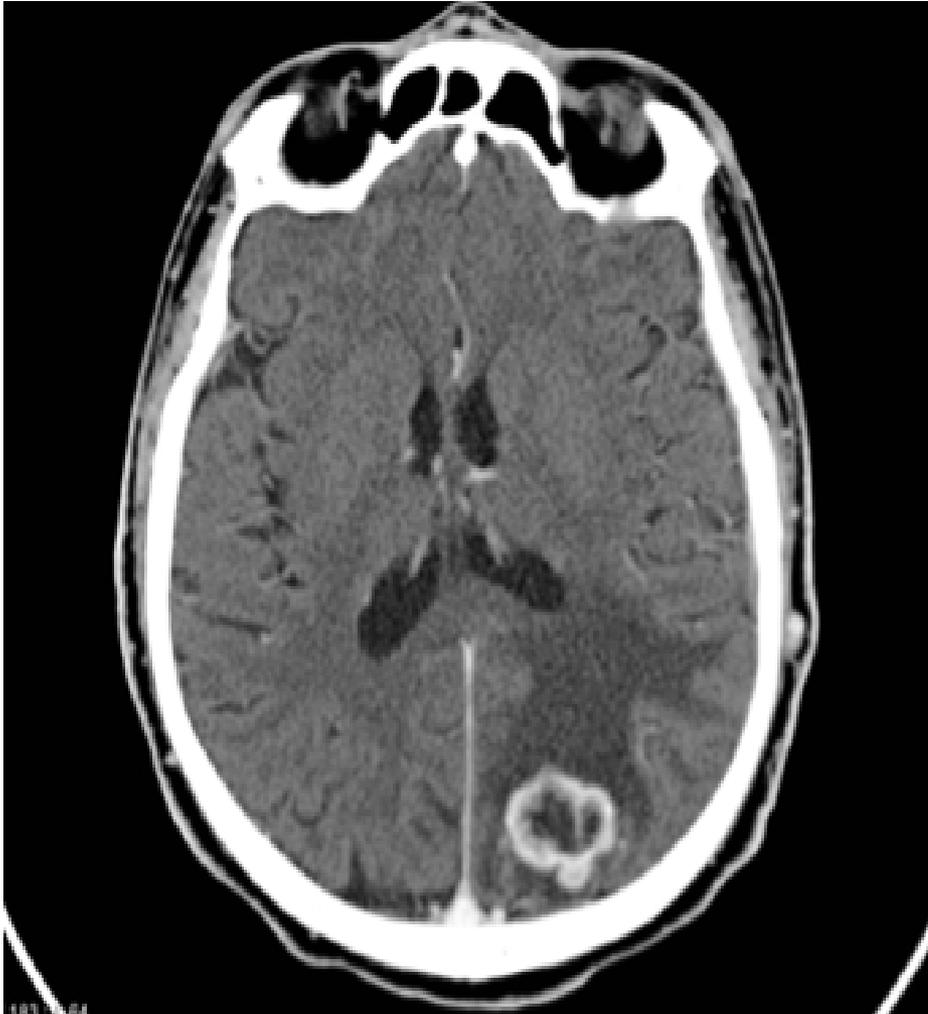
<http://kawaiibutoldfashioned.blogspot.com/2017/02/double-rainbow.html>



THE NEW ZEALAND
JOURNAL OF MEDICINE

Brain Metastases:

The most common brain tumor

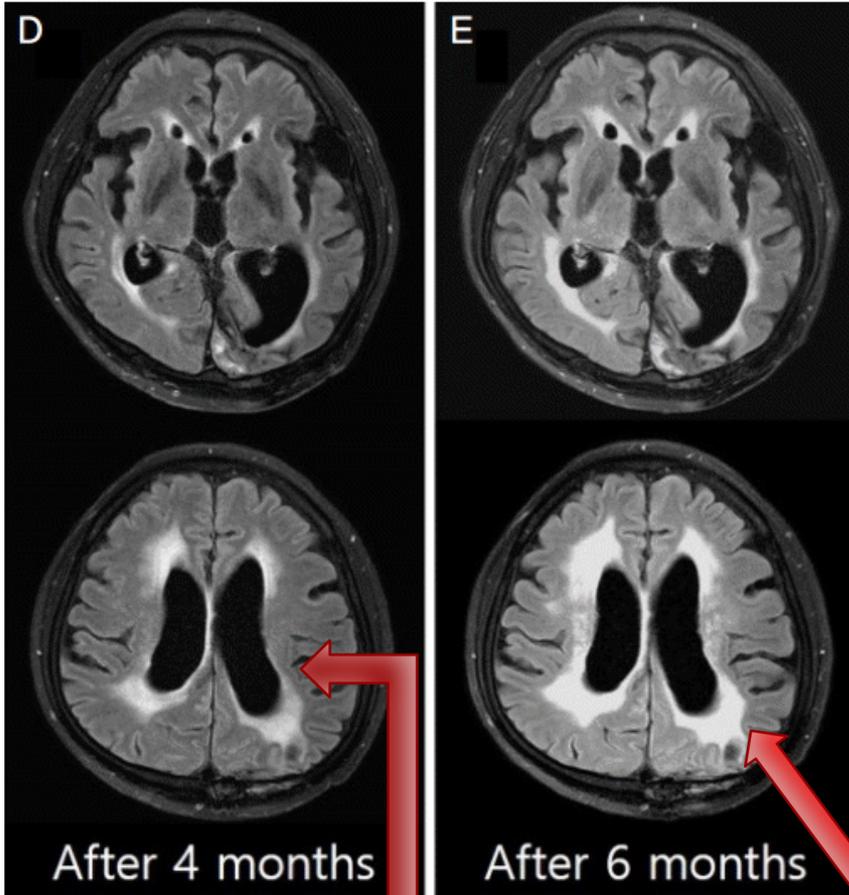


- 160-200K patients per year (25K for glioma)
- In 5-10% of patients, brain metastases are the first sign of cancer
- Up to 40% of patients some subtypes of cancers will develop brain metastases

Treating Brain Metastases



Image from jkna.org



- Surgery, focal radiation, and whole brain radiation (WBRT)
- Patients & MDs don't like WBRT!
- Leukoencephalopathy in $\geq 34\%$ at 6 months out
- New data shows oral and IV medications work in the brain!

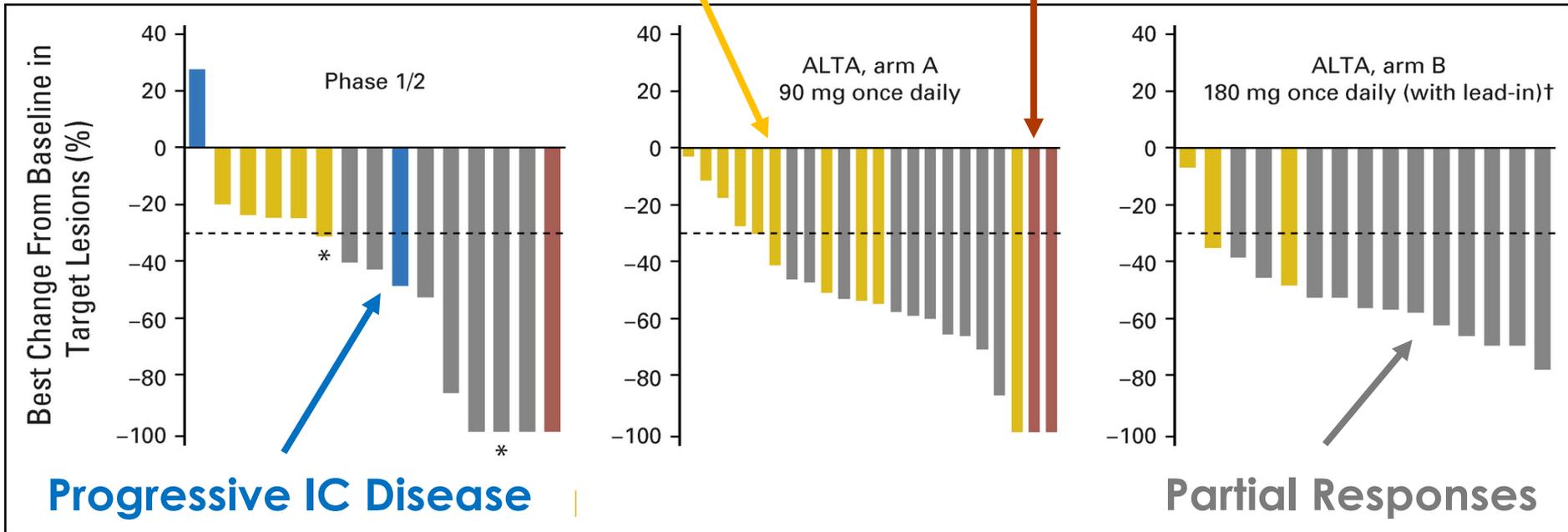
Enlarged ventricles

Changes to the white matter

3rd Generation ALK Inhibitors Give Meaningful CNS Responses

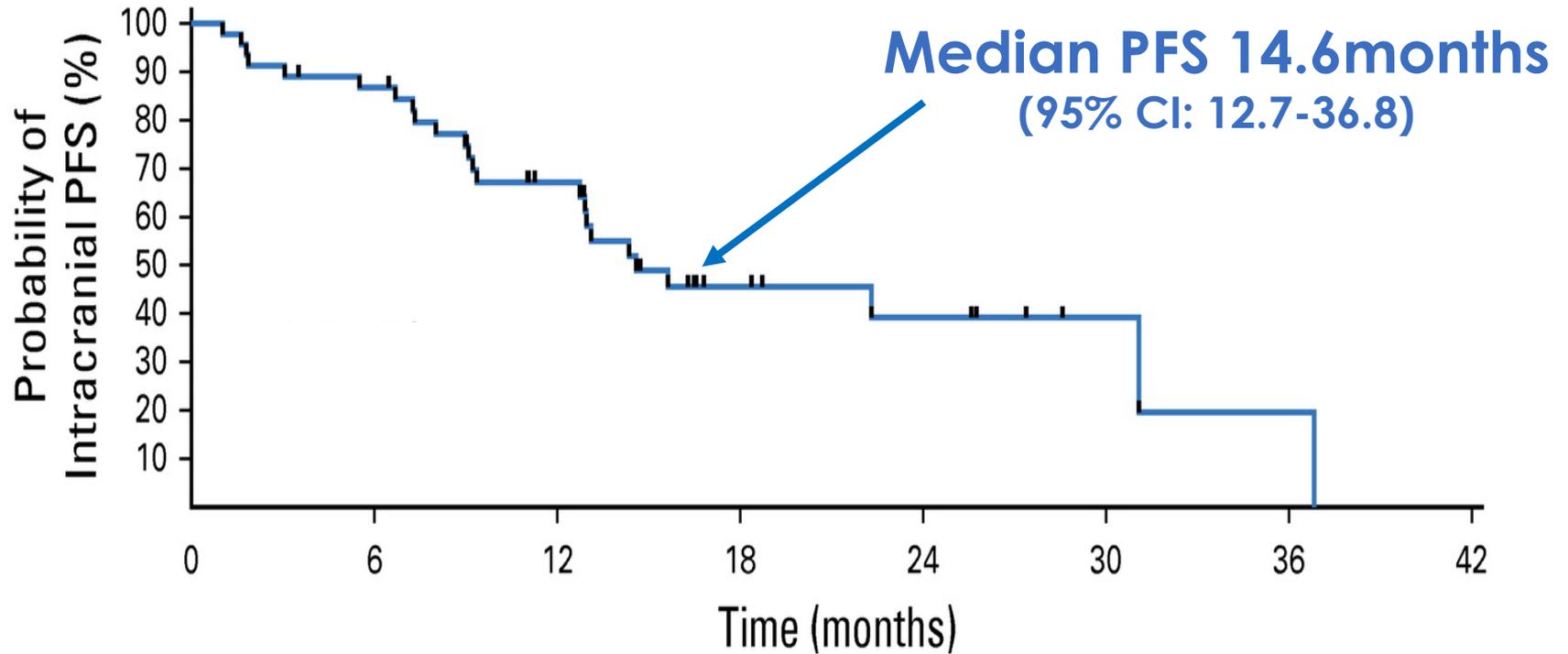


Stable Disease Complete Responses



203 patients in phase I and II trials with brigatinib (3rd Gen ALK TKI)

3rd Generation ALK Inhibitors Give Meaningful CNS Responses



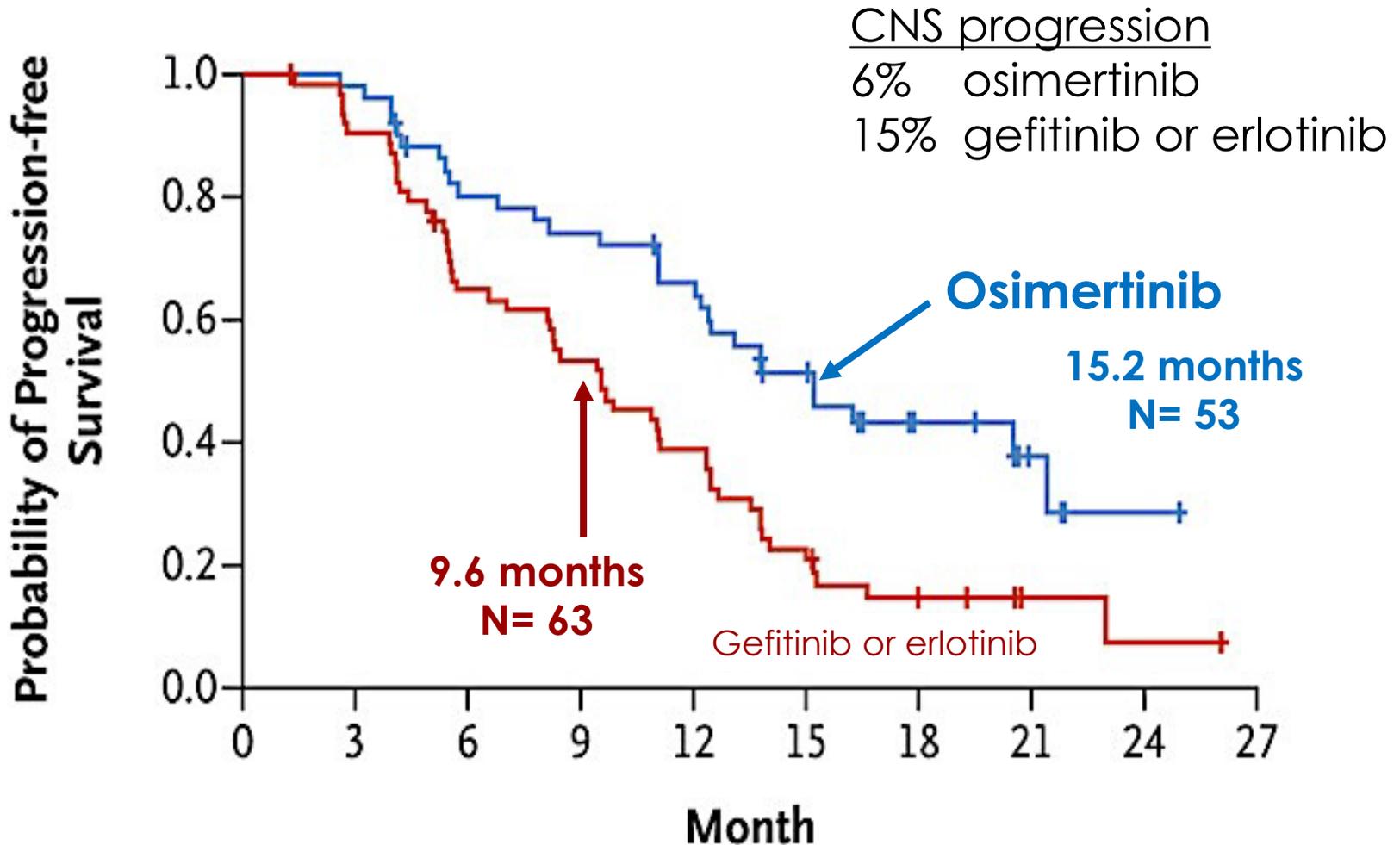
No. at risk:

All evaluable	46	37	23	9	6	2	1	0
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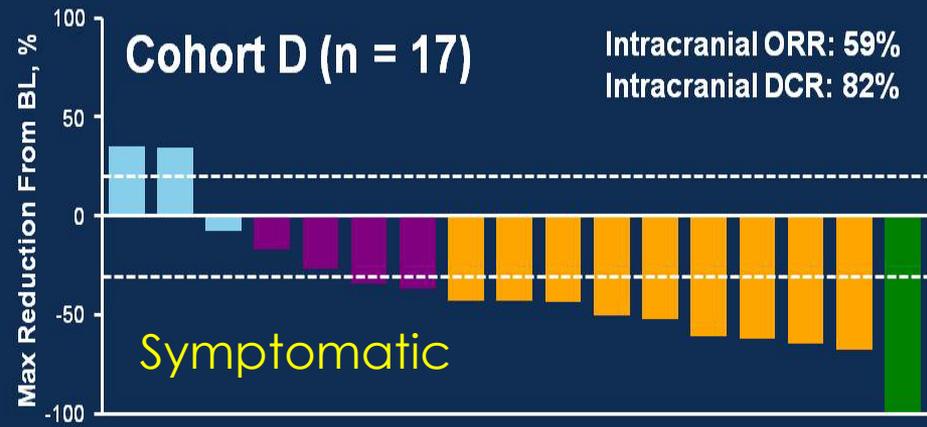
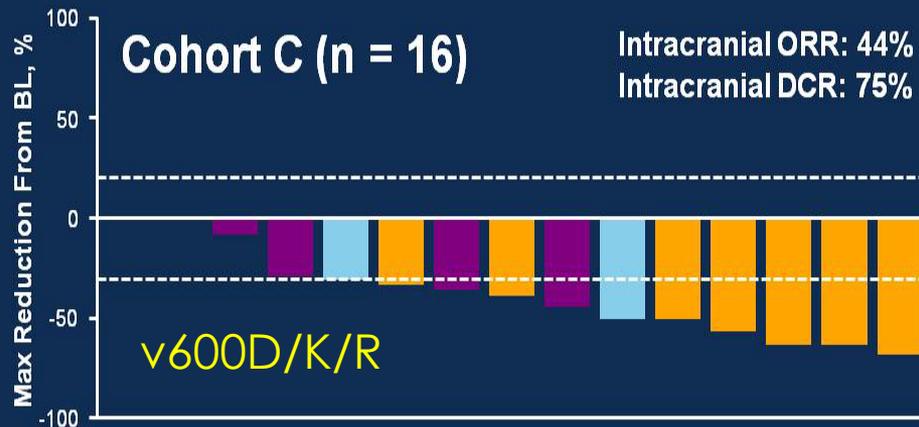
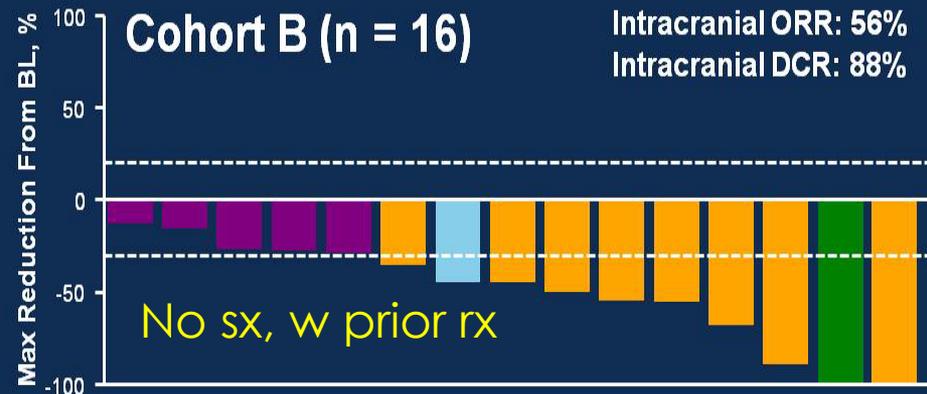
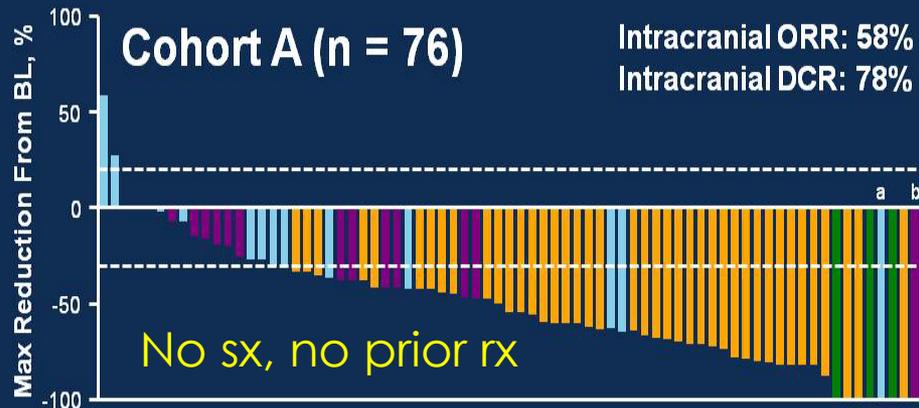
Patients in the higher dose brigantini cohort mPFS 18.4 months
And median overall survivals not met at publication!

3rd Generation EGFR TKI Improves PFS in CNS

and reduces risk of CNS as site of progression



BRAF/MEK Inhibitors Give Meaningful CNS Responses

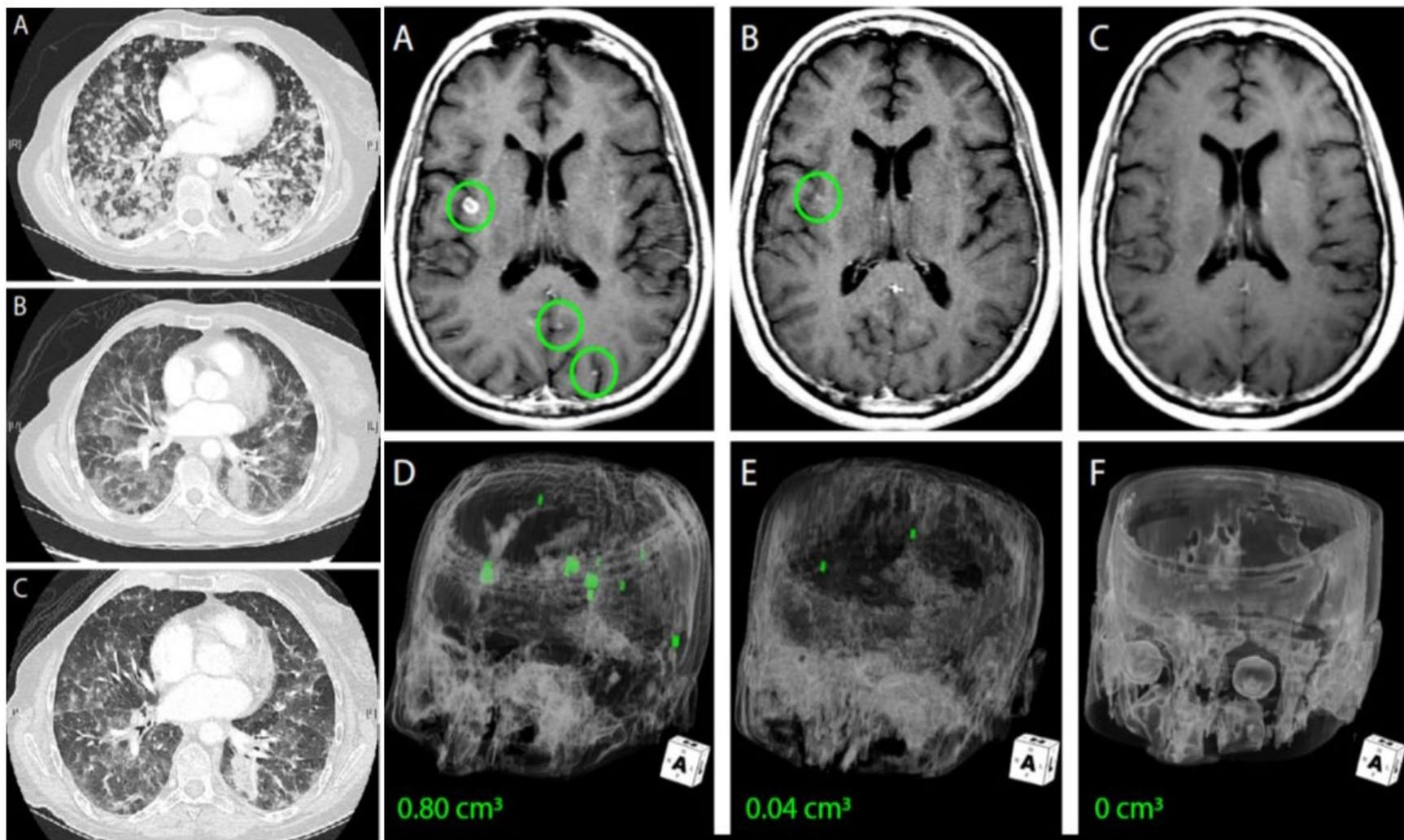


CR, complete response; SD, stable disease.

^a Patient had a CR in the target lesion, but best confirmed response was determined to be PD due to development of an unequivocal new lesion; ^b Patient had an unconfirmed CR, but best confirmed response was SD; ^c Investigator assessed; these results were supported by independent review.

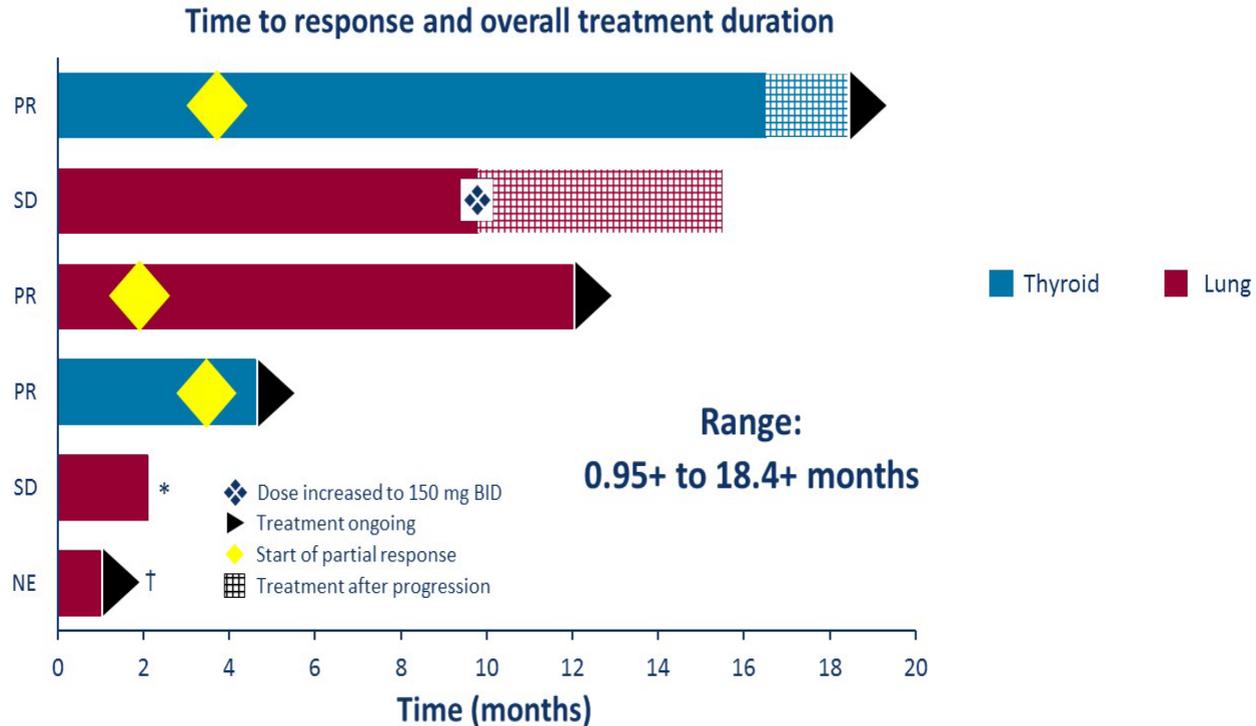
Best Confirmed IR^c: CR PR SD PD

Now, NTRK Inhibitors Give Meaningful CNS Responses



NSCLC patient on larotrectinib

NTRK Inhibitors Give Meaningful CNS Responses in Brain Mets

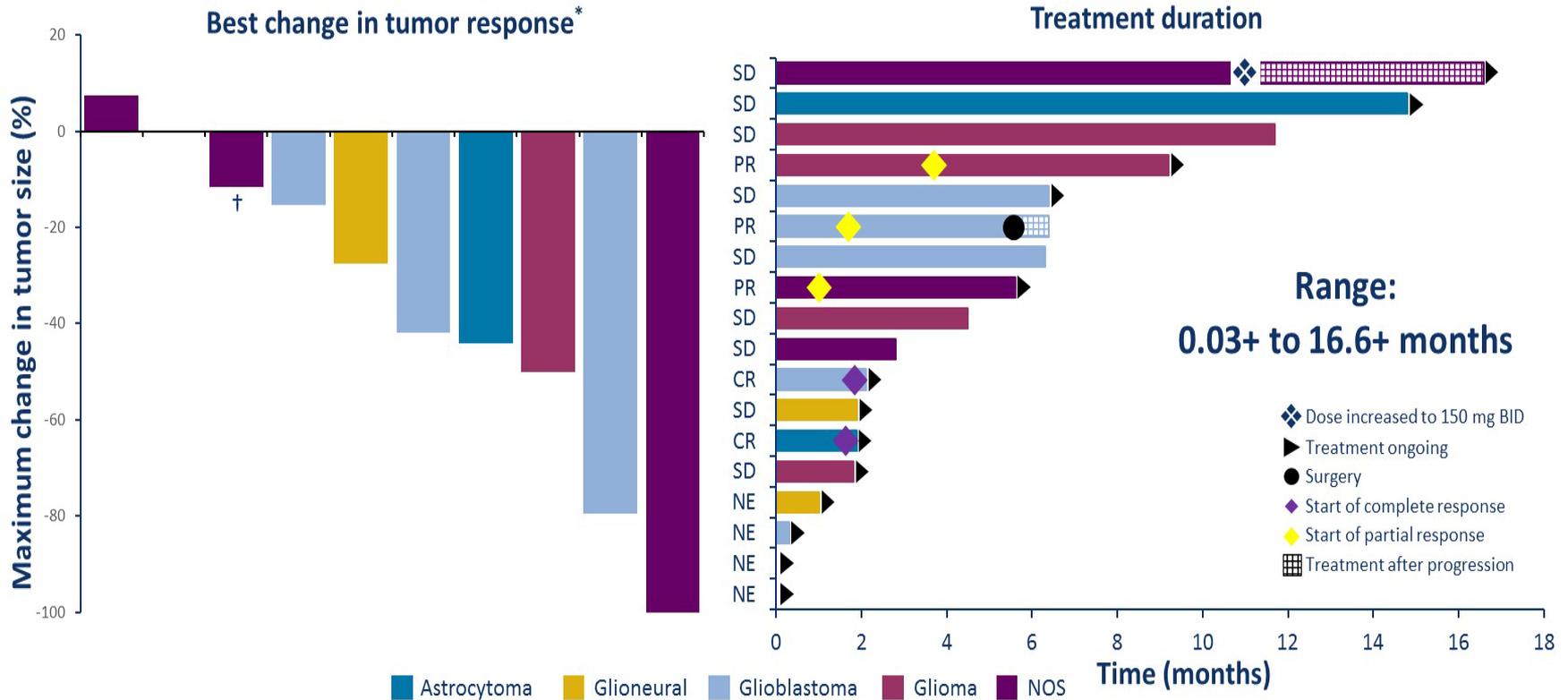


Data cutoff date July 30, 2018. Disease assessments were performed by investigators. Intracranial target tumor responses in patients with measurable disease, based on RECIST 1.1 sum of longest diameter. *Nontarget PD in asymptomatic leptomeningeal focus. †Update of this patient case presented in subsequent slide. NE, not evaluable; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Duration of response in brain metastases up to 18 months with larotrectinib



NTRK Inhibitors Give Meaningful CNS Responses in Primary Brain Tumors



Data cutoff date February 19, 2019. Disease assessments were performed by investigators. *Tumor responses in patients with measurable disease and tumor values recorded at data cutoff, based on RANO sum of products of diameters, unless noted otherwise. †Based on RECIST 1.1 sum of longest diameter. CR, complete response; NE, not evaluable; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Duration of response in pediatric primary gliomas up to 16.5 months with larotrectinib



NTRK Inhibitors Give Meaningful CNS Responses



Table 4. Intracranial efficacy in patients with baseline CNS disease^{*,†}

	<i>NTRK</i> + solid tumors (n=11)	<i>ROS1</i> + NSCLC (n=20)
ORR, % (95% CI)	54.5 (23.4–83.3)	55.0 (31.5–76.9)
Median DoR, months (95% CI)	NE (5.0–NE)	12.9 (5.6–NE)
Median PFS, months (95% CI)	14.3 (5.1–NE)	7.7 (3.8–19.3)

^{*}CNS disease at baseline determined by investigator; [†]Includes patients with both measurable and non-measurable CNS lesions at baseline.

Entrectinib

Oh, and Met Inhibitors Give Meaningful CNS Responses!



Met exon 14 skipping mutations in approx. 3-4% of NSCLC

Capmatinib is selective & potent met inhibitor

13 pts in phase 2 GEOMETRY study w brain mets at baseline (3.3 mets/pt)

54% (7/13) IC response with 4 CRs!

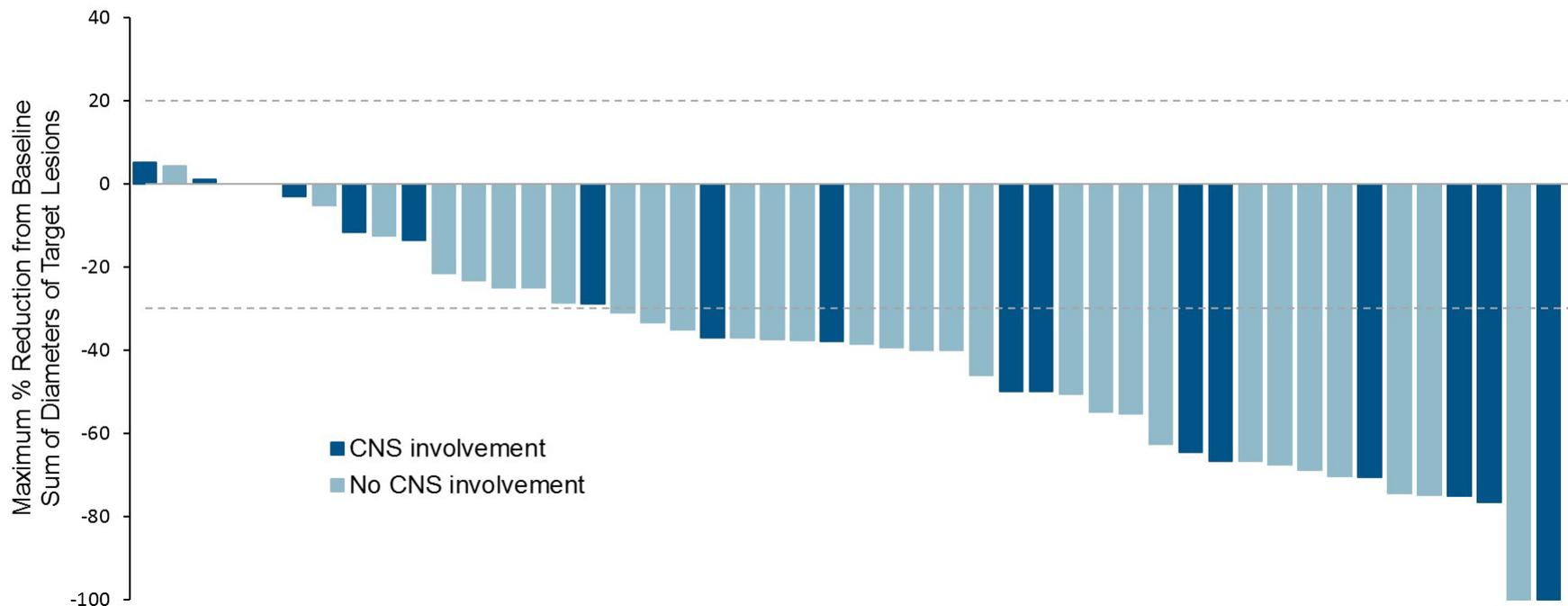
IC disease control 12/13
(I don't have DOR)



And, RET inhibition, too!



BLU-667 Starting Dose 400 mg QD

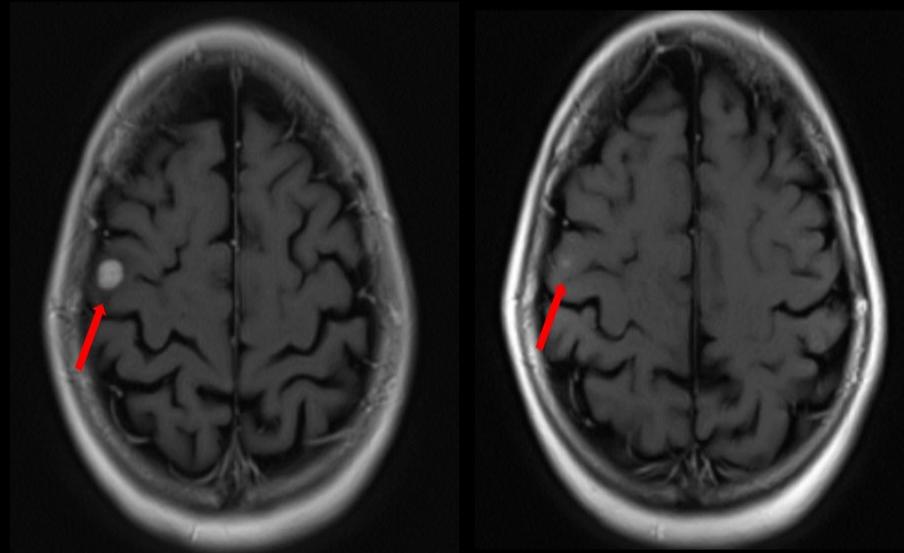


RET mutation/alterations common in advanced medullary thyroid CA

1-2% of NSCLC have RET fusions



BLU-667 is Active Against Intracranial Metastases

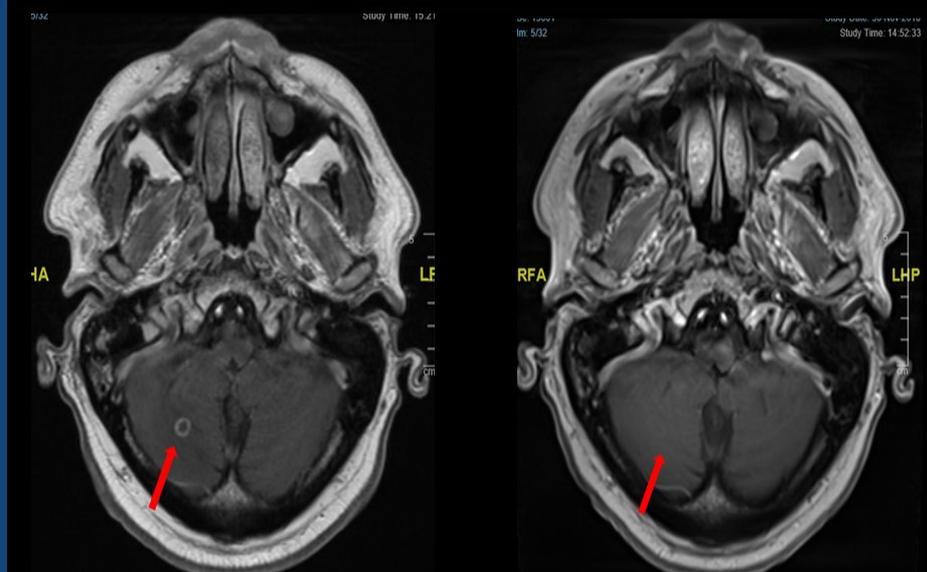


Baseline

Cycle 3, Day 1

- 52-year-old woman, RET fusion+ NSCLC, prior platinum and checkpoint inhibitor
- Near-complete resolution of previously untreated target brain metastasis after two months of BLU-667 400 mg QD
- Continues to receive treatment with ongoing confirmed PR (70% shrinkage) at ~6 months

Images courtesy of Dr. Stephen Liu, Georgetown University, Washington, D.C.



Baseline

Cycle 3, Day 1

- 59-year-old man, RET fusion+ NSCLC, prior platinum and checkpoint inhibitor
- Complete resolution of previously untreated nontarget brain metastasis after two months of BLU-667 400 mg QD
- Continues to receive treatment with ongoing confirmed PR (67% shrinkage) at ~6 months

Images courtesy Dr. P Cassier Centre Leon Berard, Lyon, FR

Learning Points



- Optune is a reasonable option for some patients, but is not without controversy
- PVSRIPO needs a bigger study (its getting one)
- Careful use of targeted therapies in CNS metastatic disease may allow deferred radiation and reduce CNS relapse.
- There are multiple drugs in the pipeline that have CNS activity, so the future is bright!

