Glial Tumors: Light at the End of the Tunnel?

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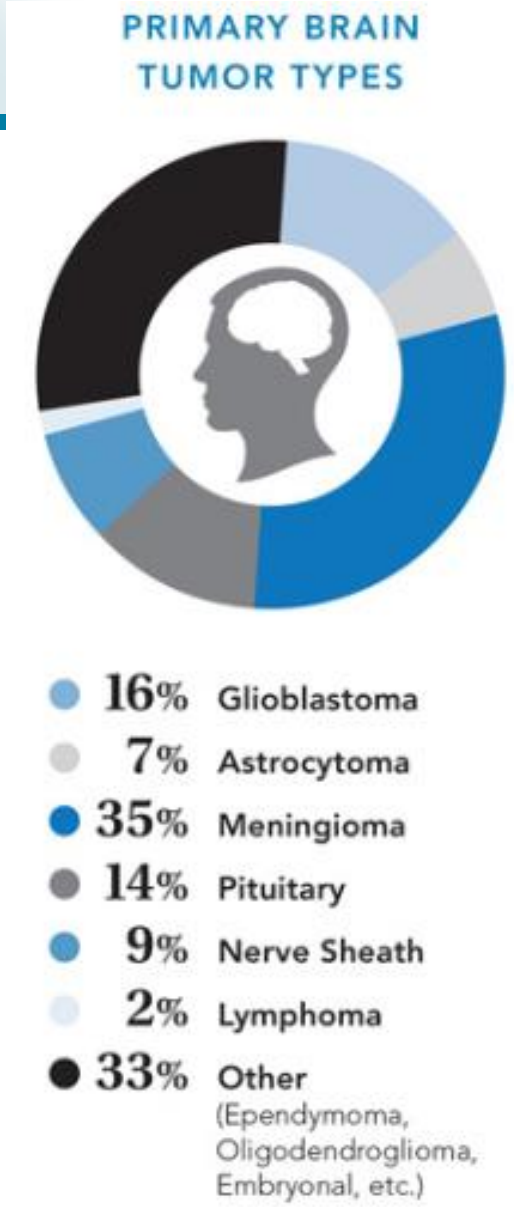
Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Malignant primary brain tumors

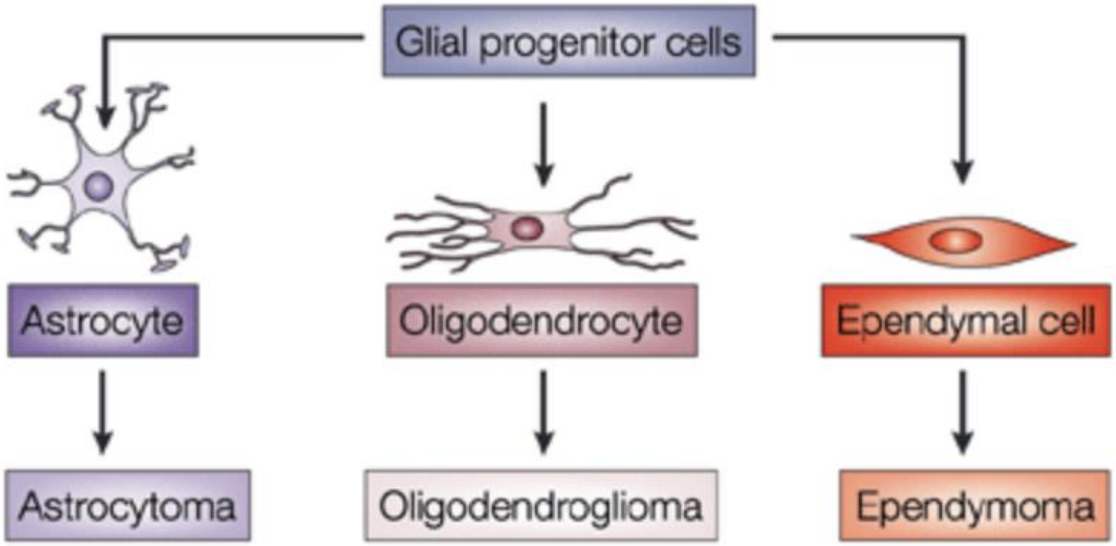
- Estimated **~ 25,130 new cases** of malignant primary brain tumors in the US for 2021.
- The 5-year relative survival rate following diagnosis of a malignant brain and other CNS tumor is ~ 23.5%
- Around 5% of patients with glioblastoma survive for a period of 3 years or more
- While the vast majority of glioma cases are sporadic, certain familial tumor syndromes increase risk including NF I, tuberous sclerosis, Turcot syndrome, Li–Fraumeni syndrome and Lynch syndrome



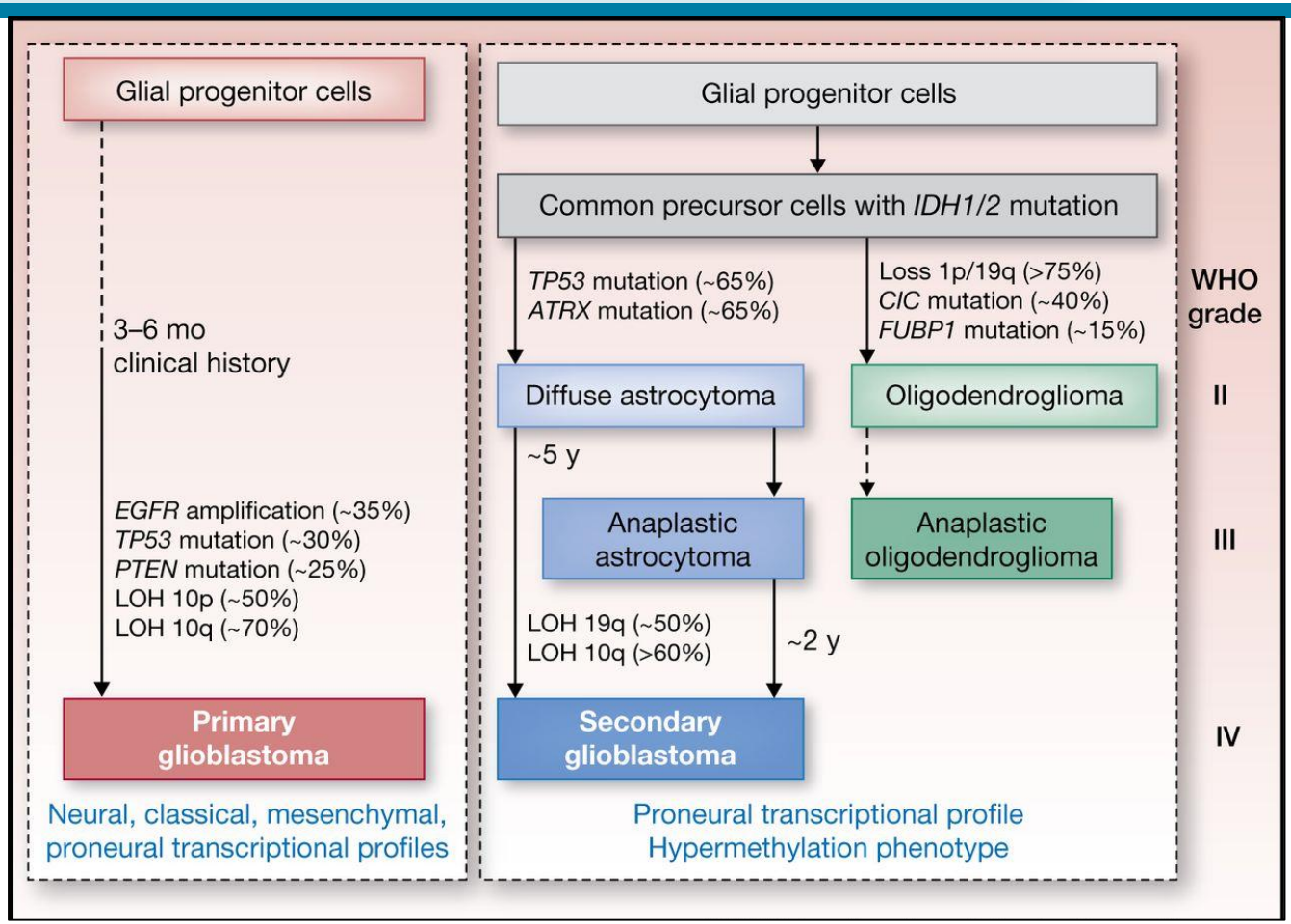
http://www.cbtrus.org/factsheet/factsheet.html

What is glioma?

A primary brain tumor that is derived from glial cells (astrocytes, oligodendrocytes, ependymal cells)

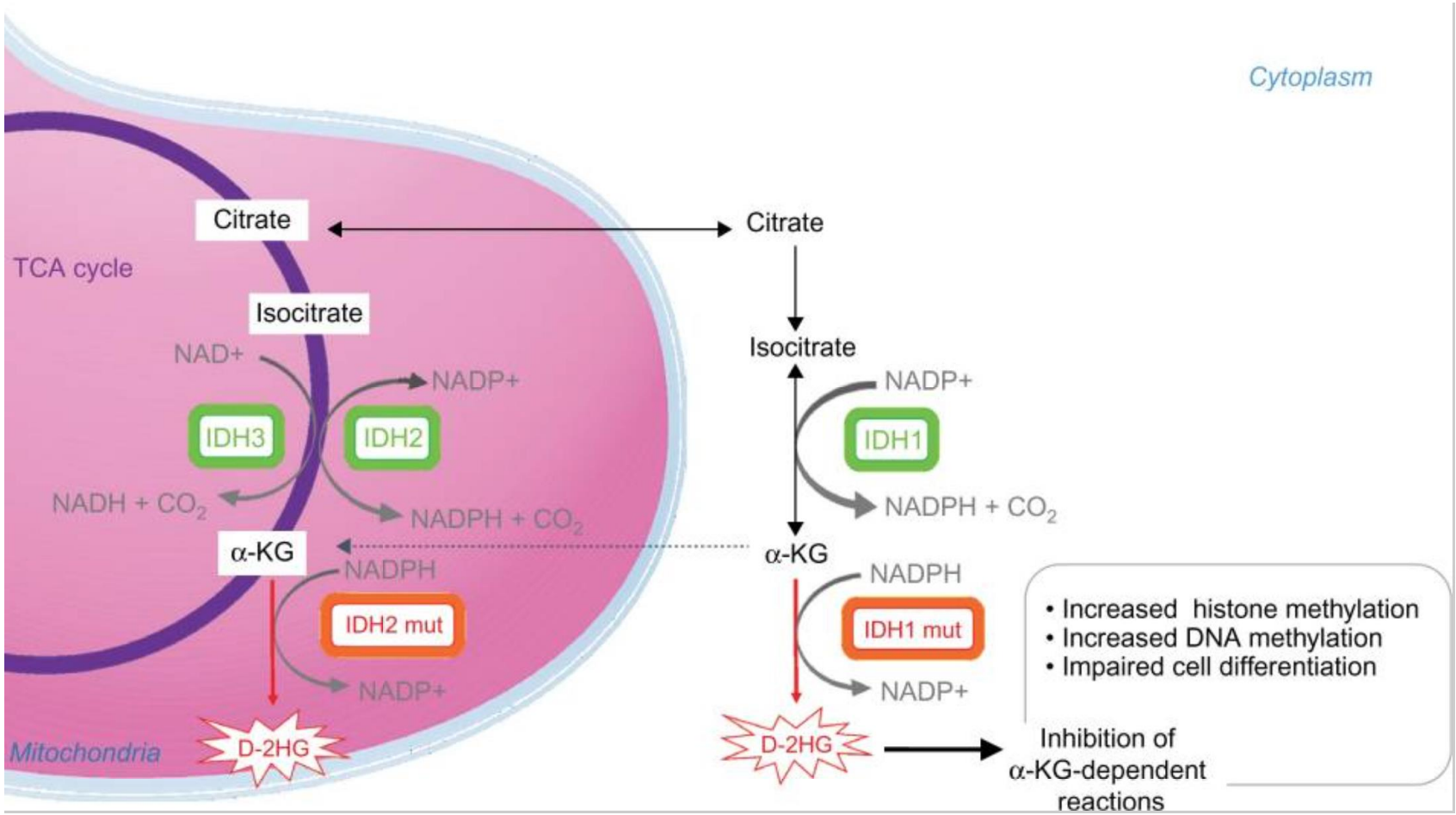


Glioma genetic alterations



Hiroko Ohgaki, and Paul Kleihues Clin Cancer Res 2013;19:764-772

IDH mutations



Mondesir et al, J Blood Med 2016

Discovery of IDH mutations in glioma

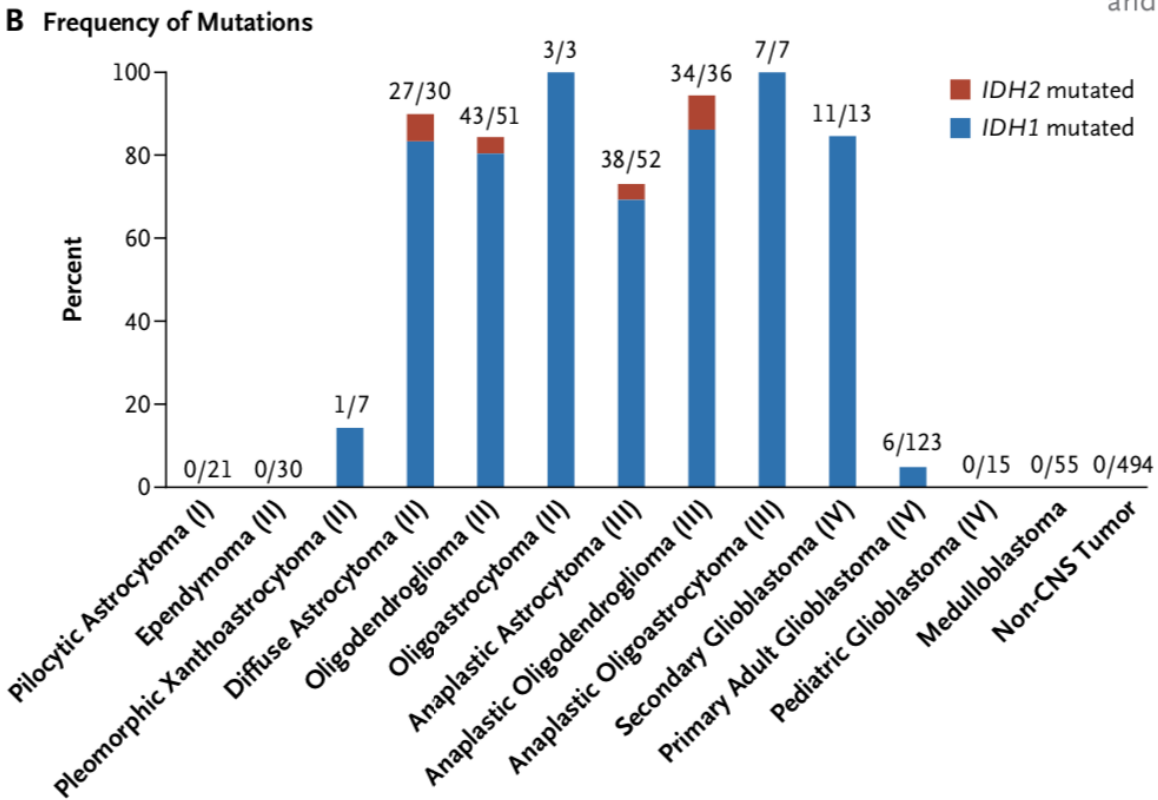
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

IDH1 and *IDH2* Mutations in Gliomas

Hai Yan, M.D., Ph.D., D. Williams Parsons, M.D., Ph.D., Genglin Jin, Ph.D., Roger McLendon, M.D., B. Ahmed Rasheed, Ph.D., Weishi Yuan, Ph.D., Ivan Kos, Ph.D., Ines Batinic-Haberle, Ph.D., Siân Jones, Ph.D., Gregory J. Riggins, M.D., Ph.D., Henry Friedman, M.D., Allan Friedman, M.D., David Reardon, M.D., James Herndon, Ph.D., Kenneth W. Kinzler, Ph.D., Victor E. Velculescu, M.D., Ph.D., Bert Vogelstein, M.D., and Darell D. Bigner, M.D., Ph.D.

N Engl J Med 2009;360:765-73.



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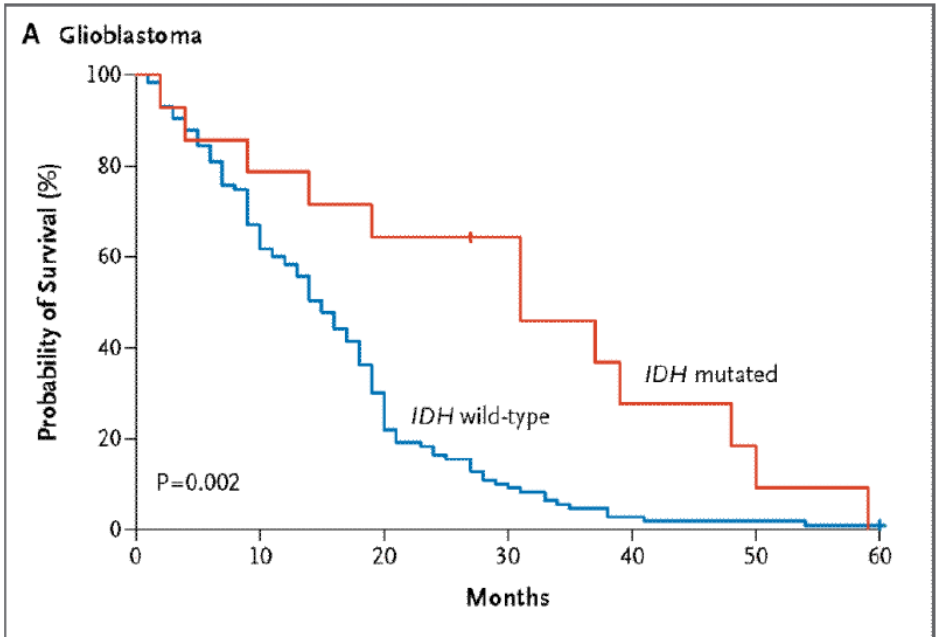
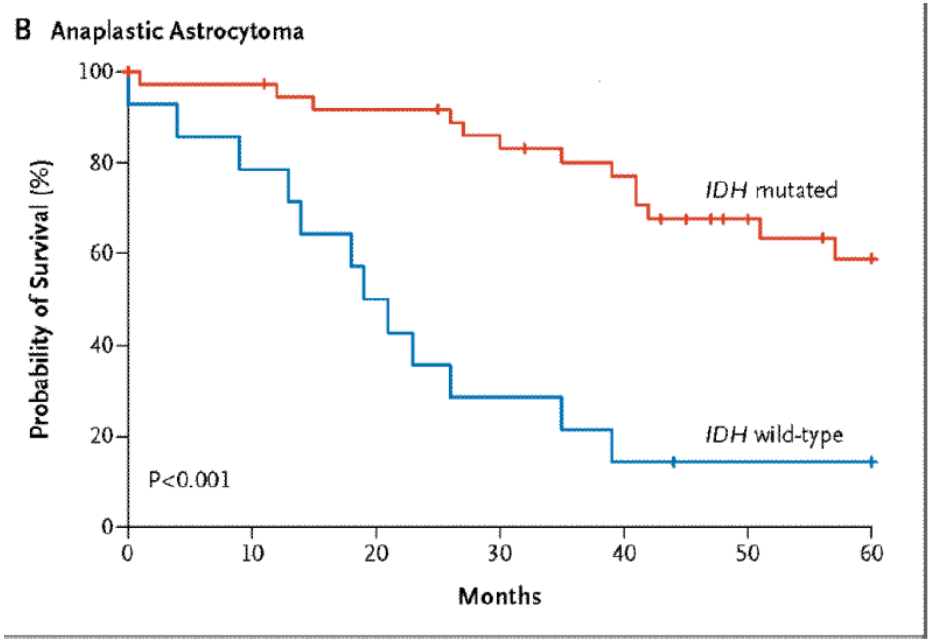


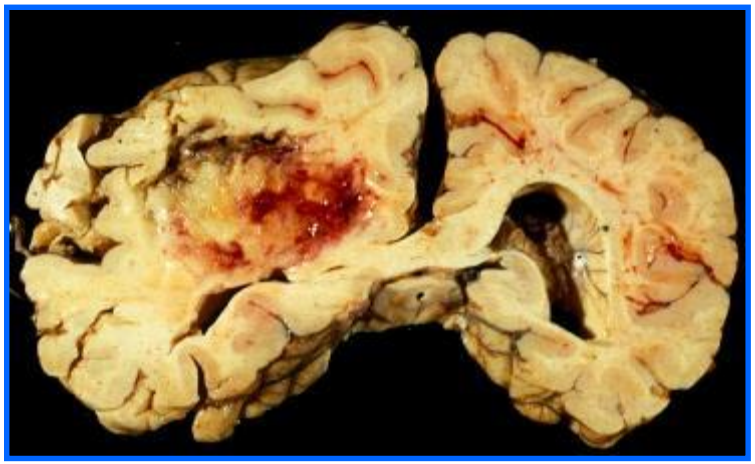


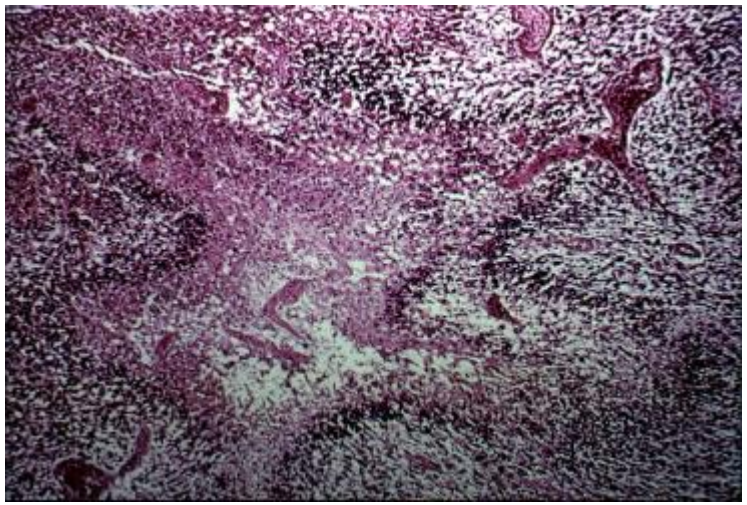
N Engl J Med 2009;360:765-73.

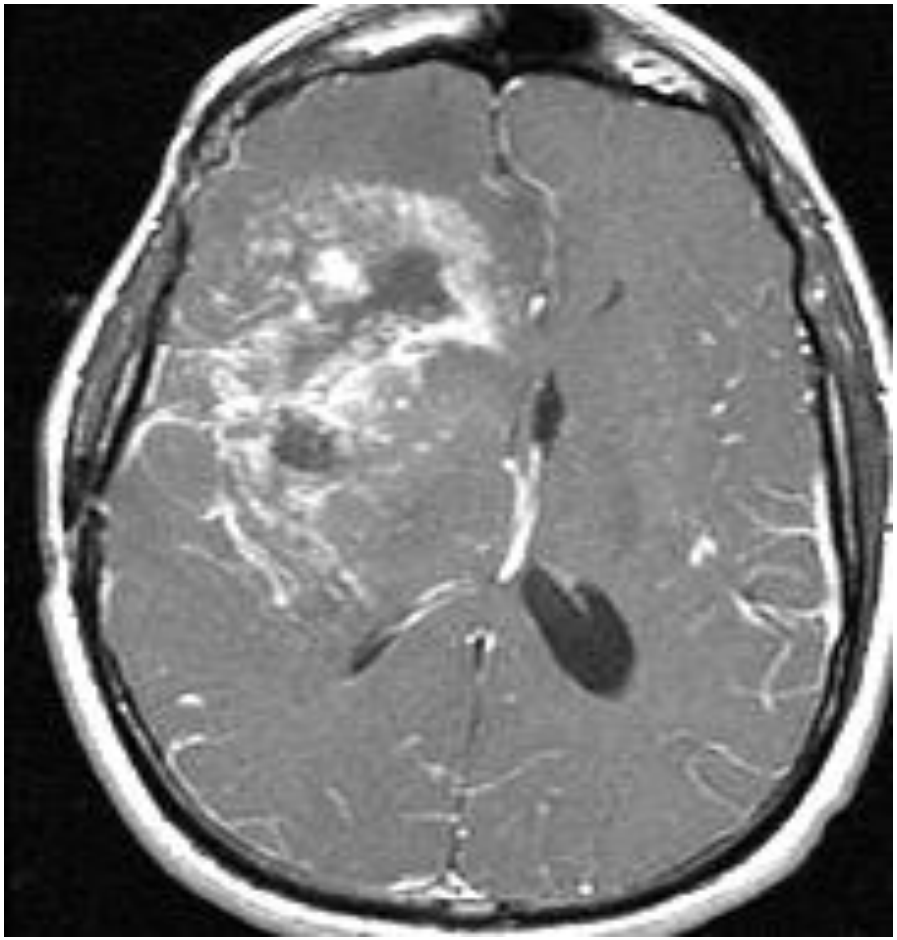
Summary Treatment IDH mutant Glioma

- Surgery (resection vs biopsy)
- Watch and wait
- Radiation
- Chemotherapy
- Clinical Trials

Glioblastoma





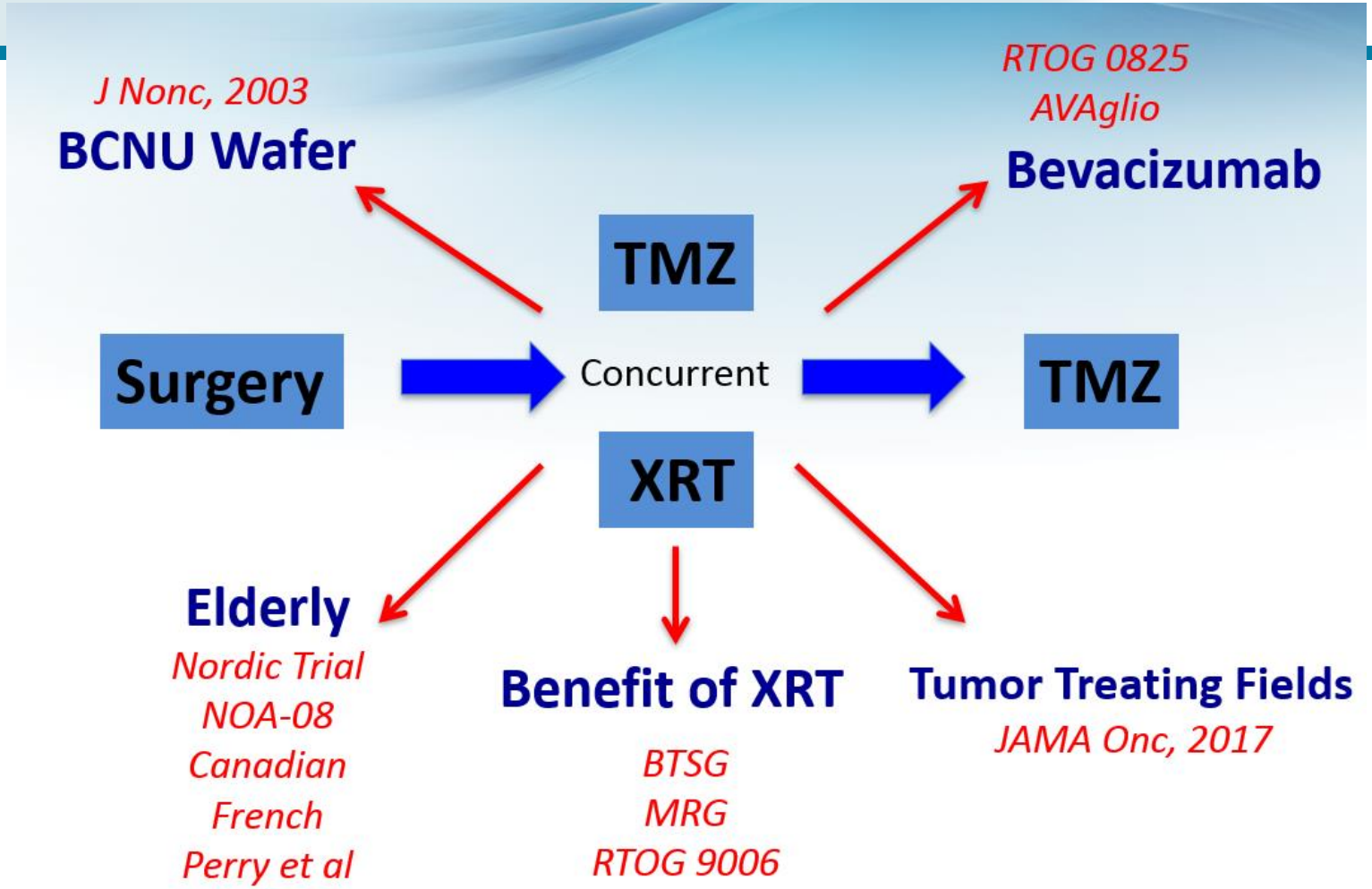


Progress Against Glioblastoma

1887	First successful surgical removal of a brain tumor	(6 months)
1970s	First promising chemotherapy for glioma (BCNU)	
1975-80	Radiation established as standard treatment for GBM	(9 months)
1980s	Gamma knife (stereotactic radiosurgery) is introduced	
2003	Chemotherapy carmustine (BCNU) “wafer”	
2005	Oral chemotherapy temozolomide receives approval	(14.6 months)
2008	Bevacizumab (Avastin) approved for recurrent GBM	
2015	Optune medical device approved for newly diagnosed GBM	(20.5 months)

ASCO http://www.CancerProgress.net

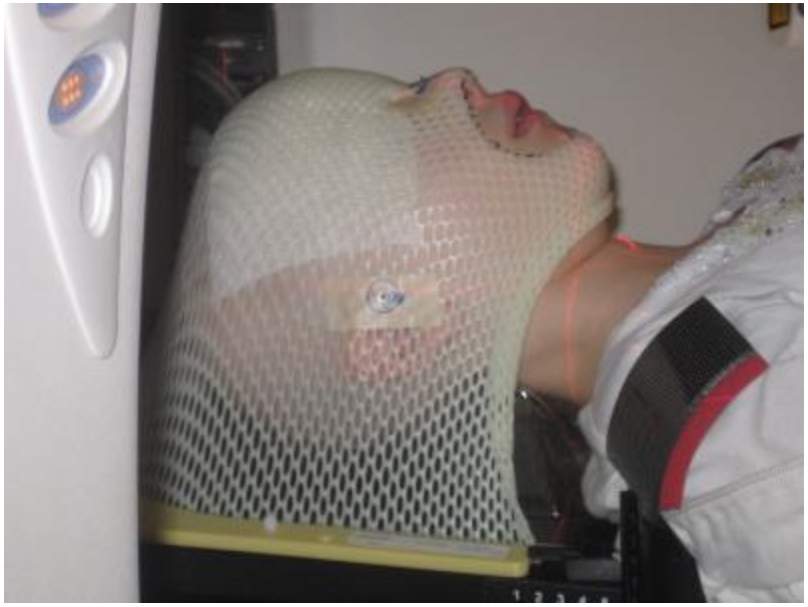
Treatment of GBM: Evidence-Based



RT for Malignant Gliomas

- WBRT more than doubles median survival
- Because most tumor recurrence is *local*, IFRT has become standard
  - recurrent high-grade glioma following WBRT develops within 2 cm of the original tumor site in 70 to 80 percent of cases
  - fewer than 10 percent are multifocal

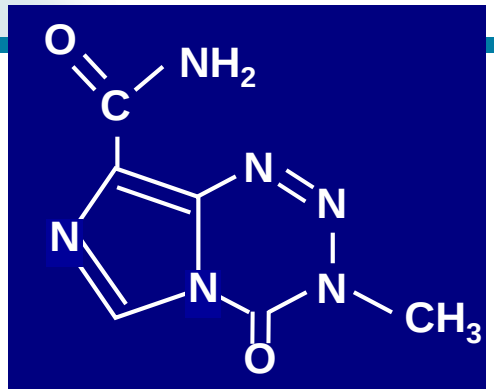
Walker MD et al. J Neurosurg 1978;49:333–343.
Walker MD et al. N Engl J Med. 1980;303(23):1323.



RT Adverse Effects

- Fatigue, alopecia, scalp irritation, nausea, headache
- Cerebral edema
- Seizures
- Radiation necrosis
- Neurocognitive decline

Temozolomide (TMZ)

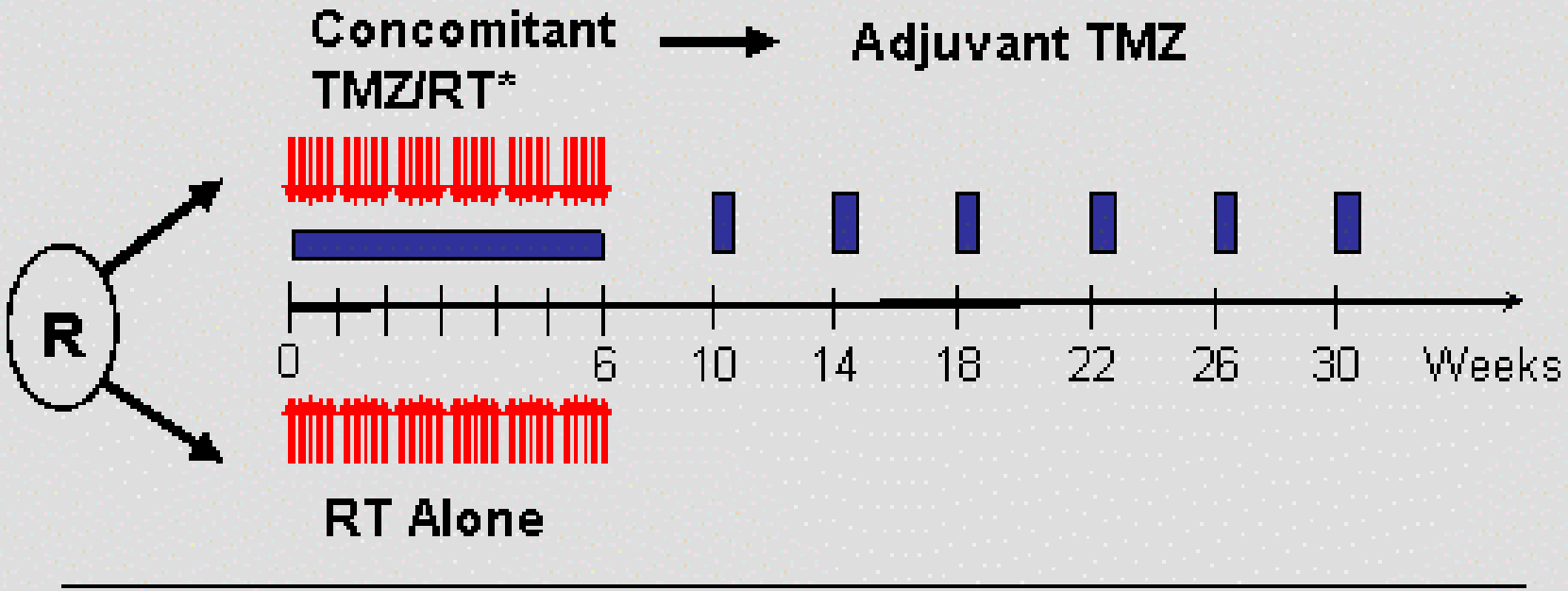


- Alkylator
- 100% orally bioavailable
- Lipid soluble, crosses BBB
- Mild side effects (<10% severe myelosuppression)
- Synergistic with RT in cell lines and animal models

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma



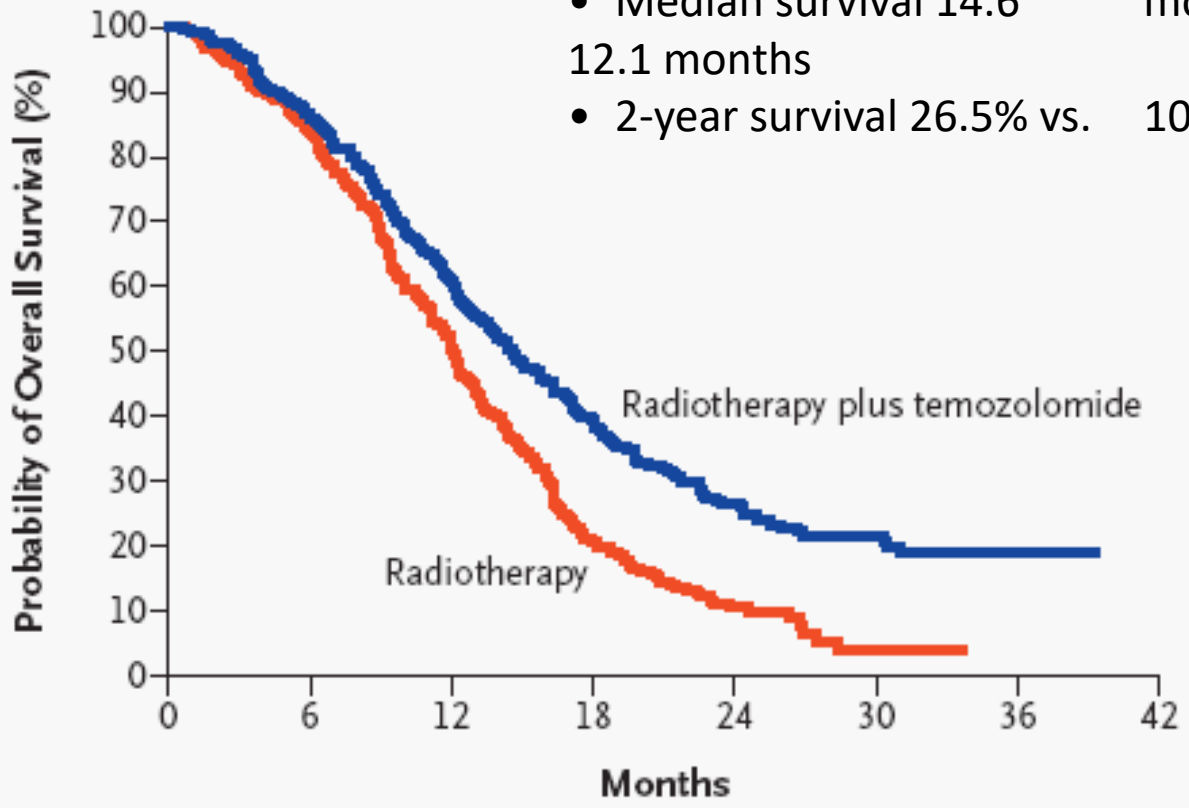
Temozolomide 75 mg/m² po qd for 6 weeks,
then 150–200 mg/m² po qd d1–5 every 28 days for 6 cycles

Focal RT daily — 30 x 200 cGy
Total dose 60 Gy

Stupp R et al. N Engl J Med 2005;352:987-96.

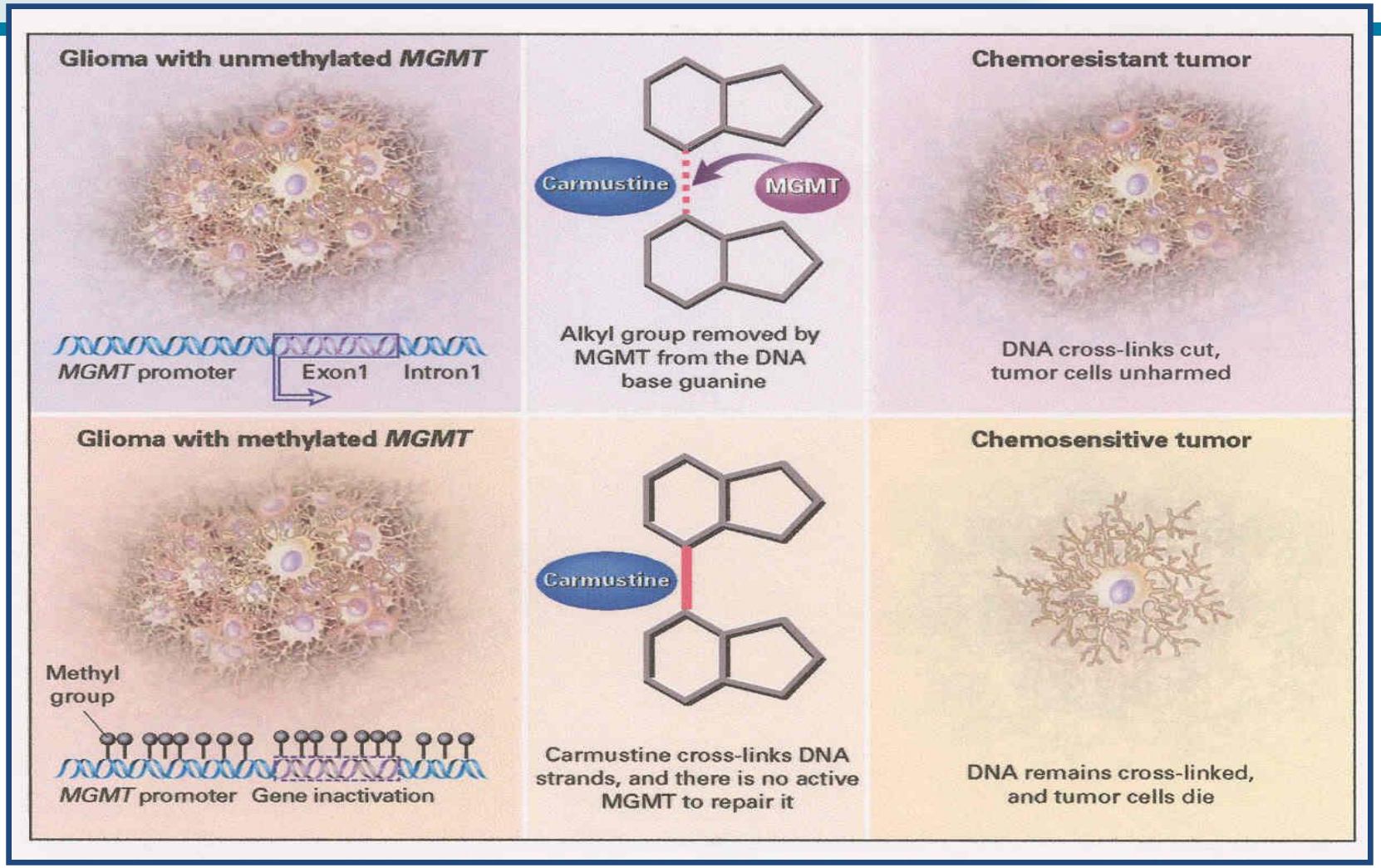
TMZ Confers a Survival Benefit

- Median survival 14.6 months vs. 12.1 months
- 2-year survival 26.5% vs. 10.4%



Stupp R et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.

Predictive and Prognostic: MGMT methylation status



Esteller, et al. *N Engl J Med* 2000; 343: 1350-1354

MGMT methylation status and temozolomide

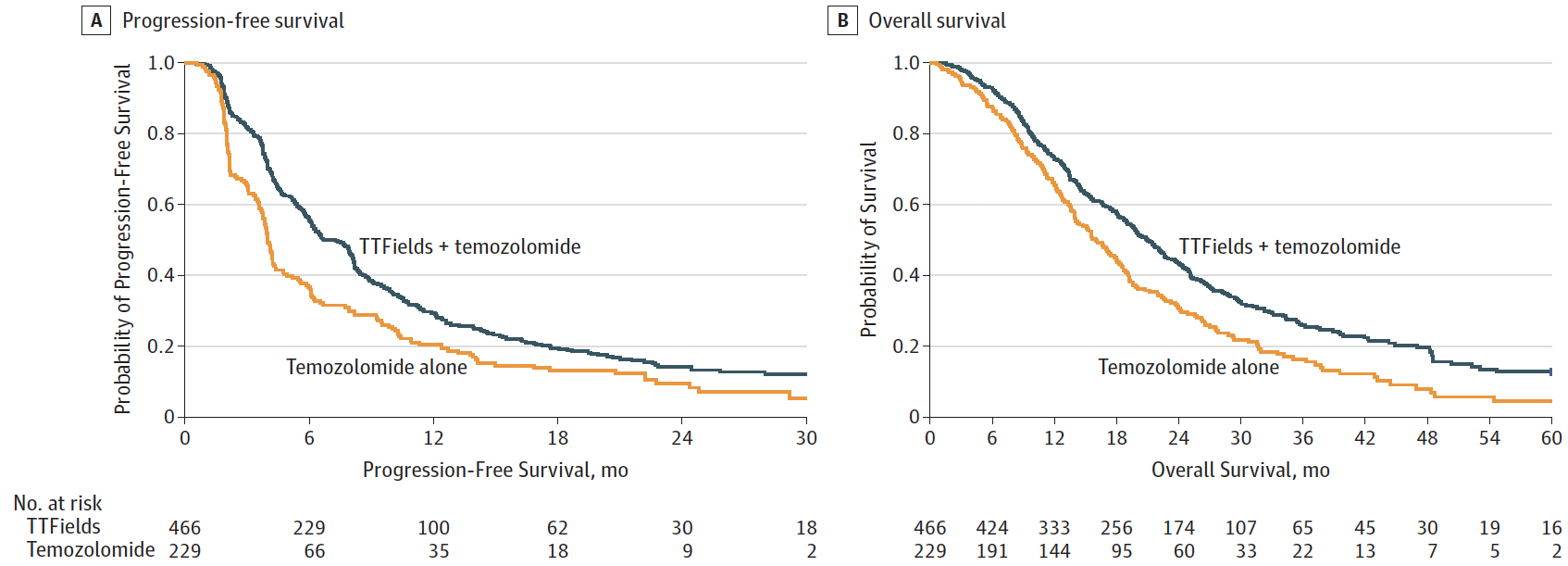
Endpoint	Patients With Methylated *MGMT* Promoter		Patients With Unmethylated *MGMT* Promoter	
	RT (n=46)	TMZ + RT (n=46)	RT (n=54)	TMZ + RT (n=60)
PFS				
Median duration, months	5.9	10.3	4.4	5.3
Rate at 6 months, %	47.8	68.9	35.2	40.0
OS				
Median duration, months	15.3	21.7	11.8	12.7
Rate at 2 years, %	22.7	46.0	<2*	13.8

Hegi, et al. *N Engl J Med. 2005;352:997-1003.*

Tumor Treating Fields

- Optune delivers Tumor Treating Fields (TTFields) to selectively disrupt mitosis in dividing cancer cells and subsequently trigger mitotic cell death

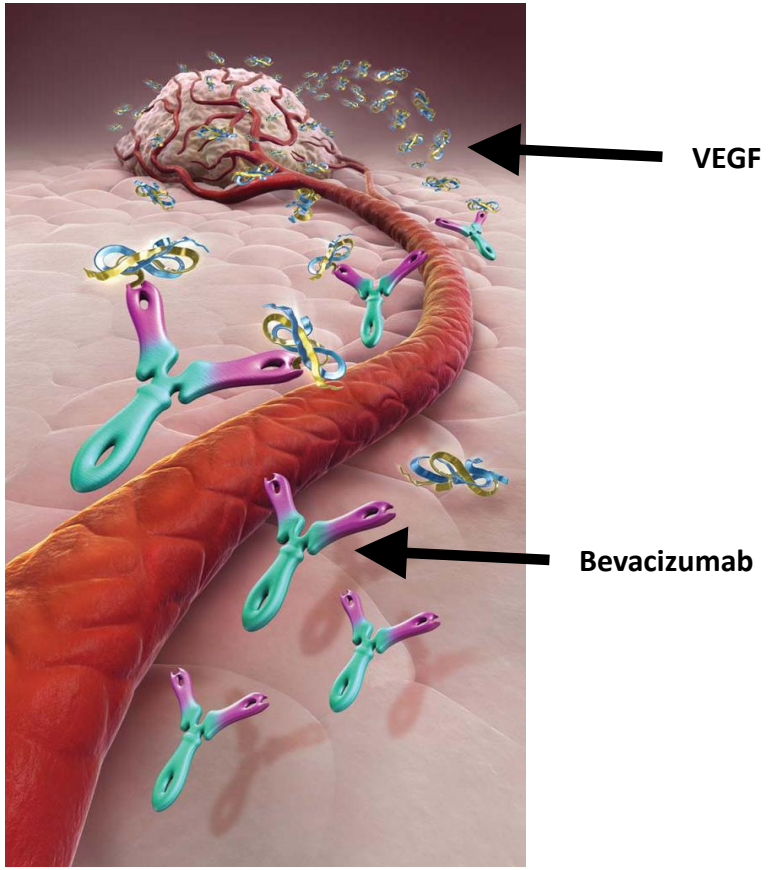
Figure 2. Kaplan-Meier Survival Curves for Patients Included in the Final Analysis in the Intent-to-Treat Population



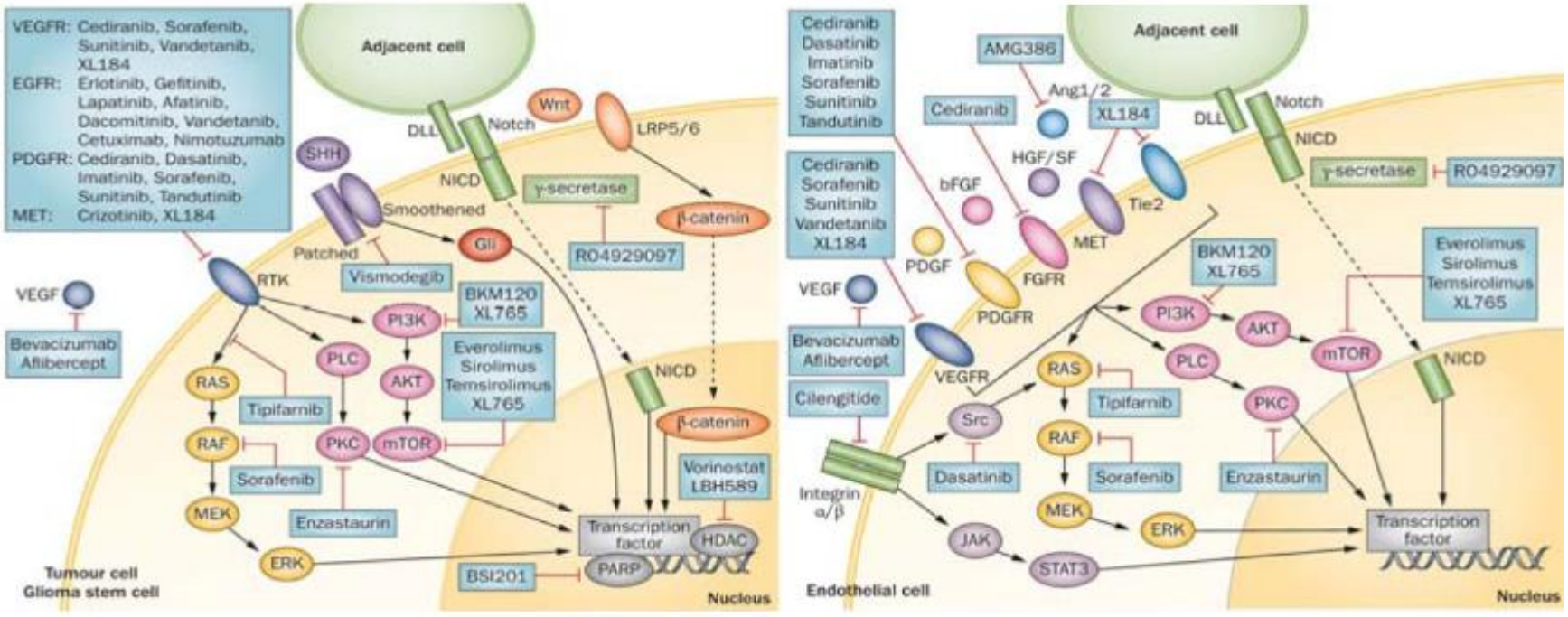
Stupp et al, **JAMA** December 19, 2017 Volume 318, Number 23

Antiangiogenesis and GBM

- VEGF is a key proangiogenic factor in GBM
- Systemic levels of VEGF receptor ligand correlate with the grade of glioma.
- Bevacizumab – humanized monoclonal antibody that targets VEGF-A
- Conditional approval in 2009
- Full approval in 2017 despite no definitive evidence of survival benefit



Targeted Therapies: Complex aberrant pathways



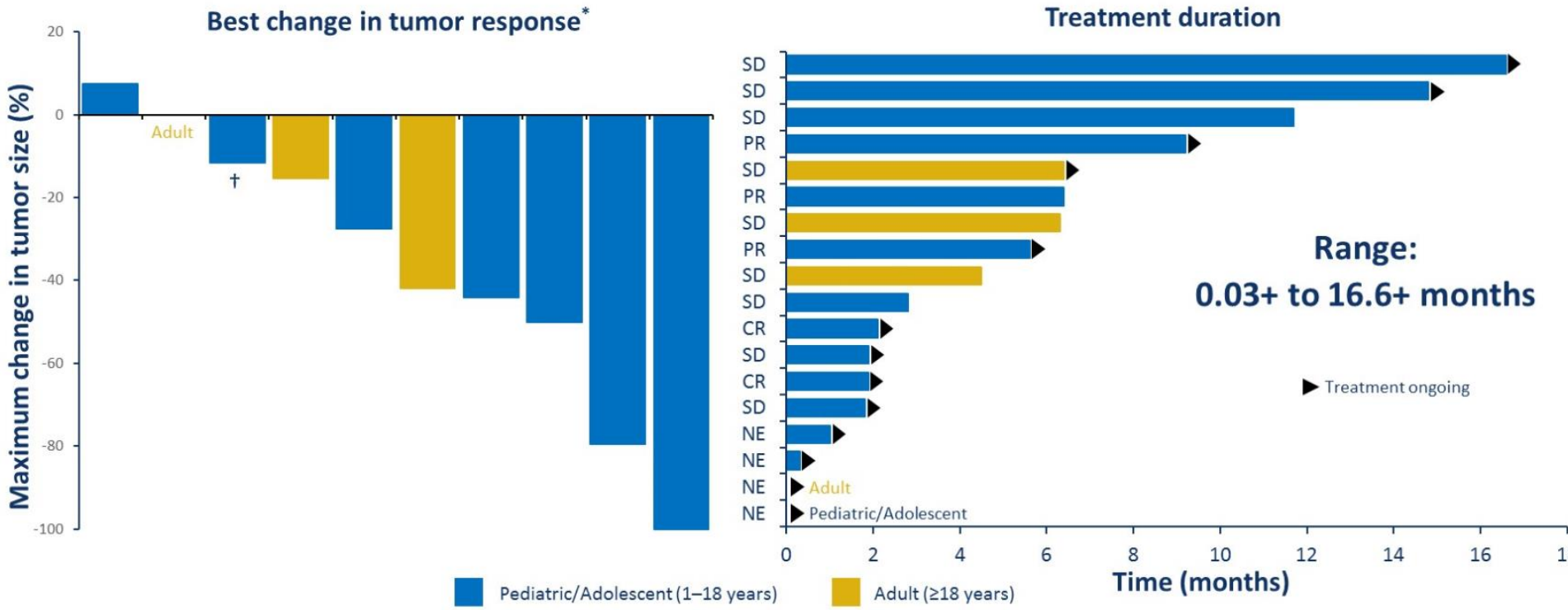
Tanaka Nat Rev Clin Oncol, 2012

Genomic alterations and example targeted therapies in glioblastoma

Gene	Alteration or target	Target frequency in glioblastoma[a] (%)	Candidate therapy (drug example)
Growth factor receptors			
EGFR	Deletion (EGFRvIII), mutation, translocation and/or amplification	55	EGFR vaccine or antibody-drug conjugate (rindopepimut, ABT-414)
KIT	Amplification, mutation	10	KIT inhibitor (imatinib)
PDGFRA	Amplification	15	PDGFR inhibitor (dasatinib)
FGFR1, FGFR3	Translocation (e.g. FGFR3-TACC3)	3	FGFR1/3 inhibitor (JNJ-42756493)
MET	Amplification, translocation	3	MET inhibitor (cabozantinib)
MAPK and PI3K/mTOR signaling pathways			
PTEN	Deletion, mutation	40	AKT inhibitor, mTOR inhibitor (voxtalisib)
PIK3CA	Amplification, mutation	10	mTOR inhibitor, PI3K inhibitor (buparlisib)
NF1	Deletion, mutation	14	MEK inhibitor (trametinib)
BRAF	Mutation (BRAF V600E)	2	BRAF inhibitor (vemurafenib), MEK inhibitor (trametinib)
Cell cycle pathways			
MDM2	Amplification	10	MDM2 inhibitor (AMG232)
TP53	Wild-type (no mutations)	60	MDM2 inhibitor (AMG232)
CDK4/6	Amplification	20	CDK4/6 inhibitor (ribociclib)
RB1	Wild-type (no mutations)	90	CDK4/6 inhibitor (ribociclib)
Others			
IDH1	Mutation	6	IDH1 inhibitor (AG120)
MYC, MYCN	Amplification	5	Bromodomain inhibitor (OTX-015)

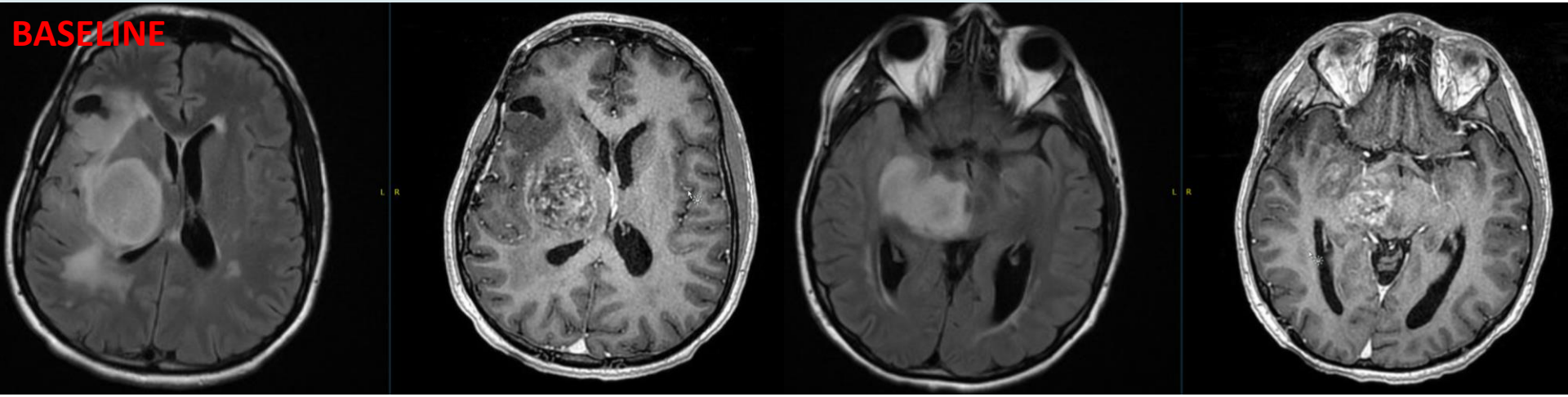
Annals of Oncology 28: 1457–1472, 2017

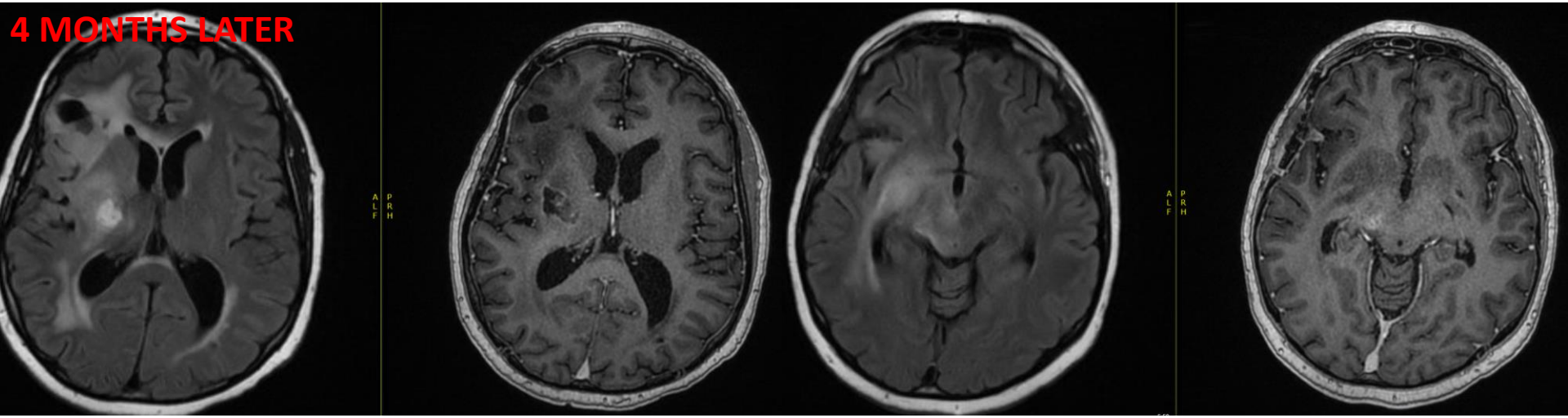
Larotrectinib in TRK Fusion-Positive Primary CNS Tumors: Response and Treatment Duration by Age Group



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.

Treatment with NTRK inhibitor





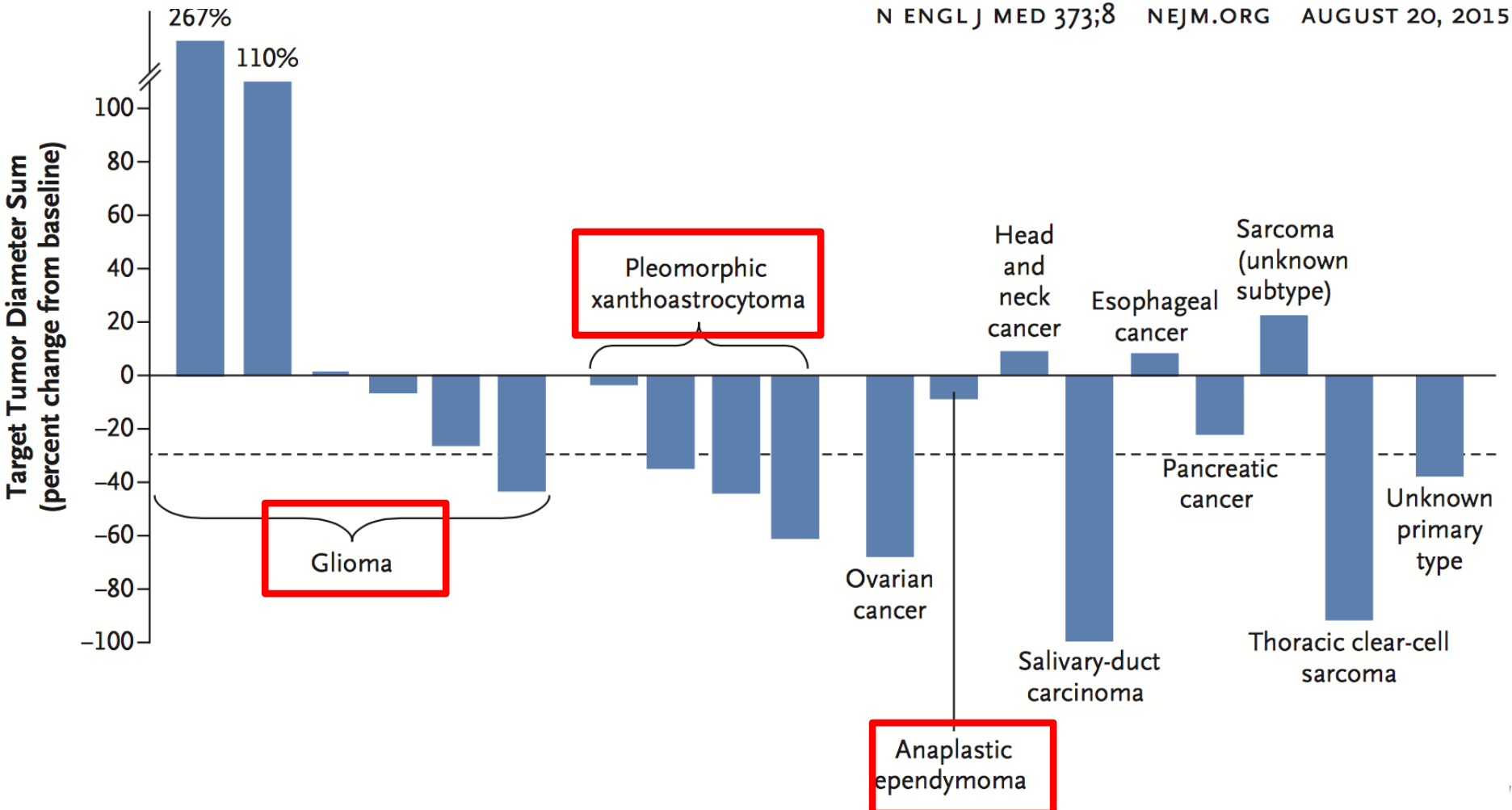
NTRK inhibitors

Larotrectinib (FDA approved in 11/2018) and **entrectinib** (FDA approval on 8/2019) can be used for the tx of adult and pedi (> 12 y/o) with solid tumors harboring NTRK gene fusions that have either progressed following treatment or have no satisfactory alternative therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

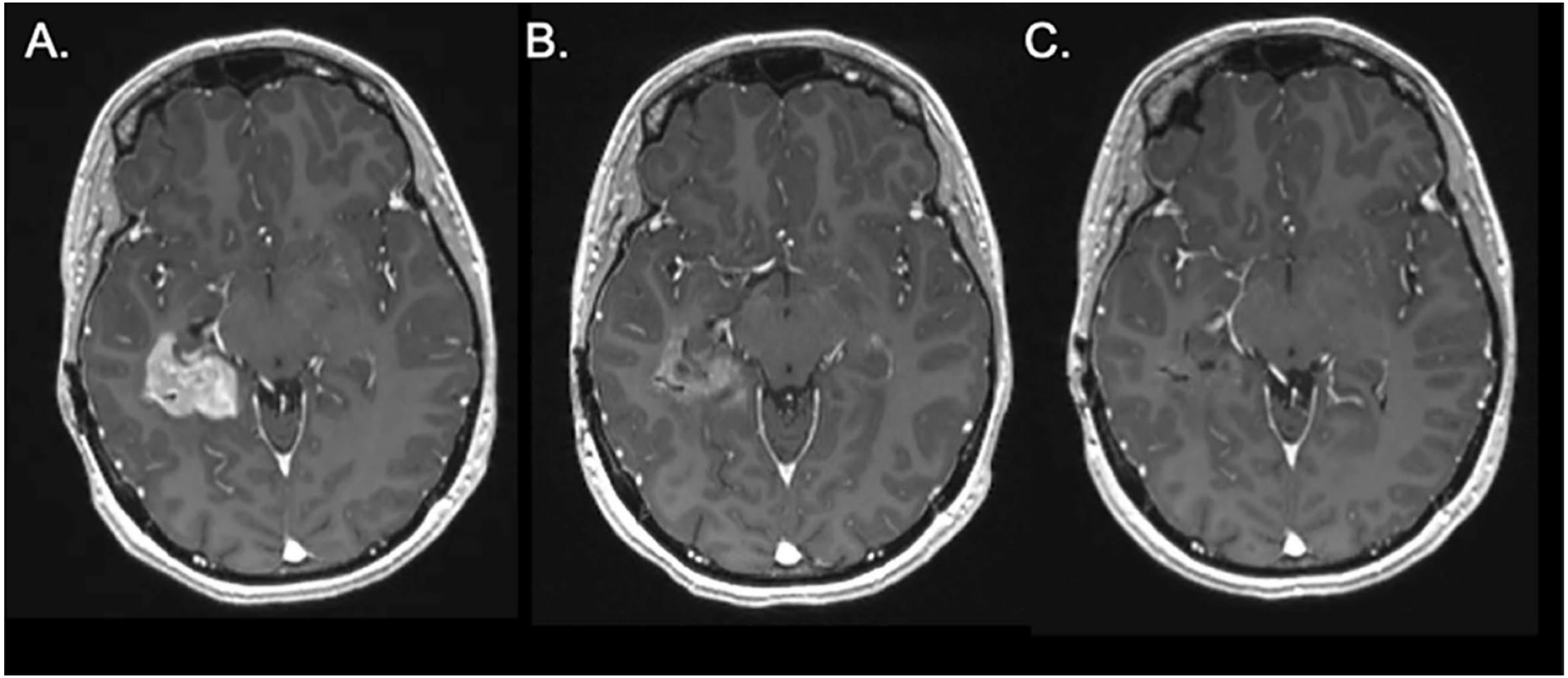
Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations



CLINICAL STUDY

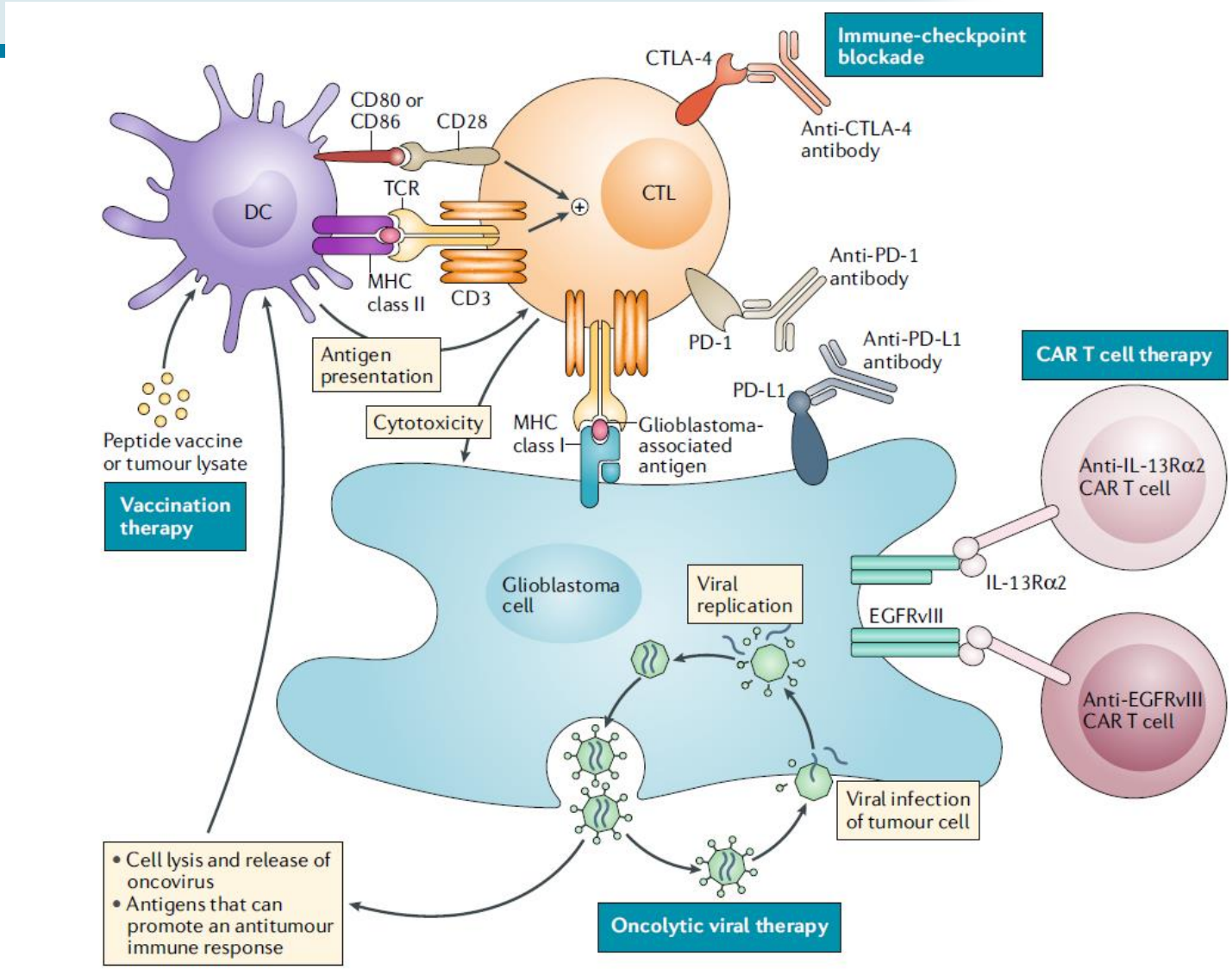
Clinical, radiological and genomic features and targeted therapy in *BRAF* V600E mutant adult glioblastoma

Mary Jane Lim-Fat[1,2,5] · Kun Wei Song[3,4] · J. Bryan Iorgulescu[6] · Brian M. Andersen[2,5] · Deborah A. Forst[3,5] · Justin T. Jordan[3,5] · Elizabeth R. Gerstner[3,5] · David A. Reardon[2] · Patrick Y. Wen[2,4] · Isabel Arrillaga-Romany[3,5]



Journal of Neuro-Oncology (2021) 152:515–522

Immunotherapy modalities under investigation for the treatment of glioblastoma



Lim et al., *Nature Reviews Clinical Oncology,* **15**, 422–442 (2018)

Questions?