New Approaches and Advances in the Therapy of Gliomas

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School of Medicine

The academic core of Atrium Health

Neuro-Oncology Advances

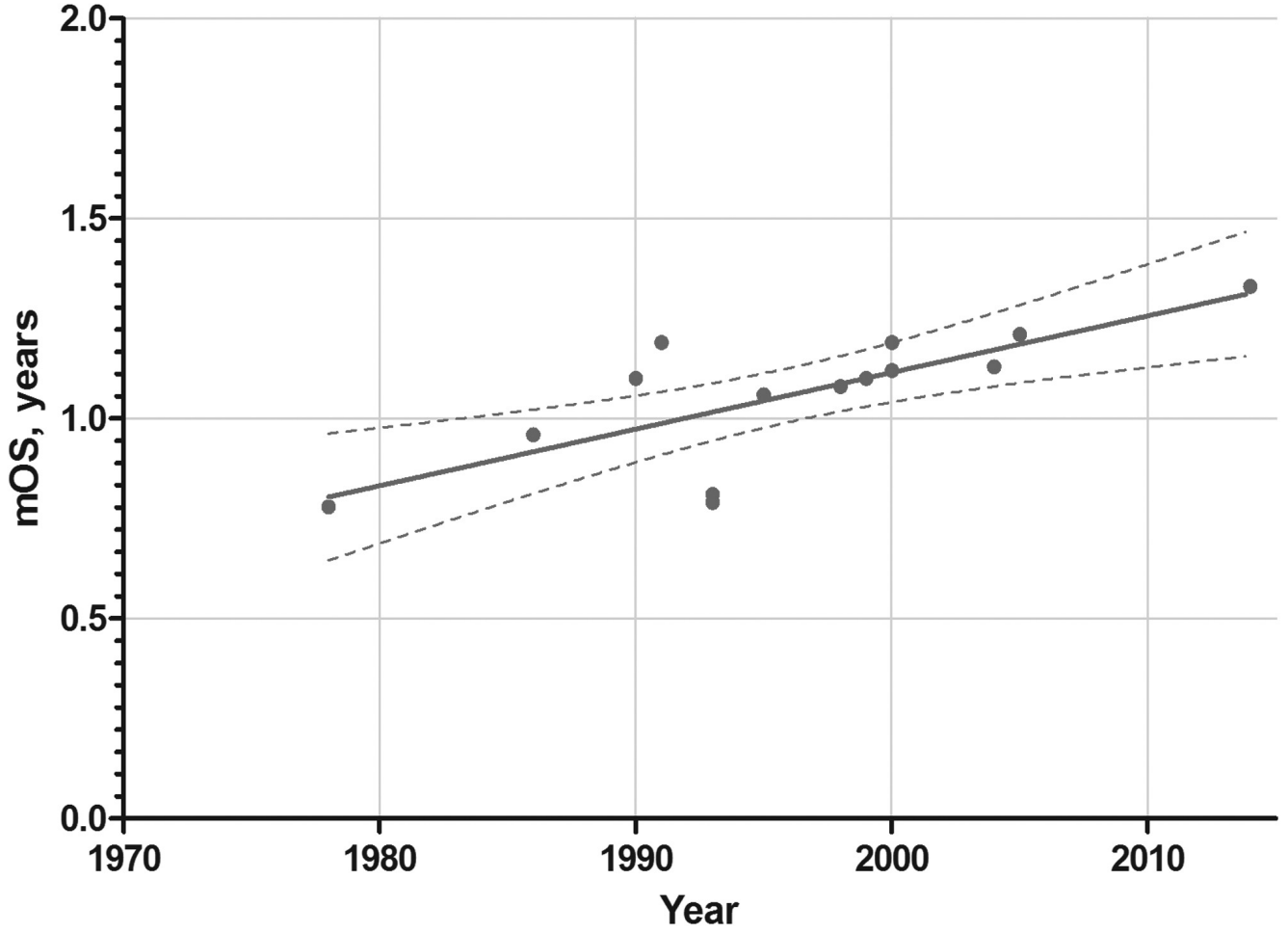
Selected Recent Negative Large Phase II/III GBM Clinical Trials

Timing	Phase	New Agent	N	mOS exp.	mOS control	MOA
New	III	Cilengitide (Centric)	545	26.3 mos	26.3 mos	αvβ3 and αvβ5 integrin inhibitor
New	III	Dose Dense TMZ (RTOG 0525)	1173	14.9	16.6	Metronomic dosing
New	III	Bevacizumab RTOG 0825	978	15.7	16.1	Monoclonal antibody against VEGF-A ligand
New	III	Bevacizumab AVAglio	921	16.8	16.7	Monoclonal antibody against VEGF-A ligand
New	III	Rindopepimut (ACT IV)	745	20.1	20.0	EGFRvIII vaccine
New	II	ICT-107	124	17.0	15.0	Autologous dendritic cell vaccine
Recurrent	III	Toca 511/5FC (Toca 5)	403	11.1	12.2	Retroviral vector with gene for cytosine deaminase
Recurrent	III	VB-111+Bev	256	6.8	7.9	Gene therapy - vascular disruption/anti-angiogenesis

(Also, Nivolumab: Checkmate 143 (rec), Checkmate 498 (n,un), Checkmate 548 (n,me))

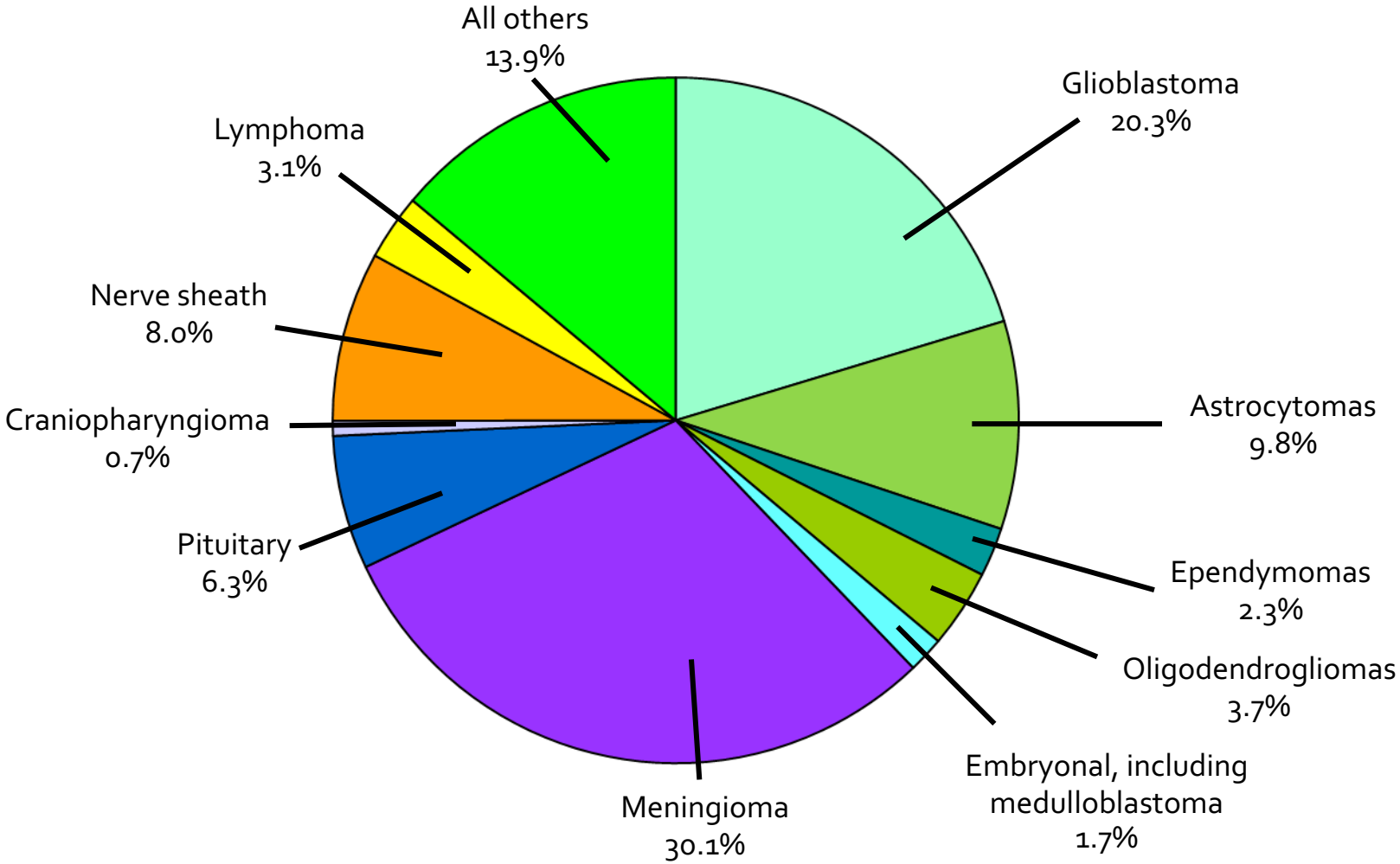
Stupp R, et al. Lancet Oncol. 2014;15:1100-8. Gilbert M, et al. J Clin Oncol. 2013;31:4085-91. Gilbert M, et al. N Engl J Med. 2014;370:699-708. Chinot O, et al. N Engl J Med. 2014;370:709-22. Weller M, et al. Lancet Oncol. 2017;18:1373-85. Wen P, et al. Clin Cancer Res. 2019;25:5799-5807. Cloughesy T, et al. Neuro Oncol. 2020;22:705-717.

Plot of Median Overall Survival (mOS) for Patients Treated with Adjuvant Chemotherapy in Phase III Clinical Trials



Levin VA, et al. Neuro Onc 2015;17:vi1-26

Distribution of All Primary Brain and CNS Tumors by Histology



CBTRUS Report, 2004-2005

CNS Tumor Speed Dating
"The Good, The Bad and The Ugly"

Only 15 minutes therefore focus on new data with therapeutic implications. No time for a review

- IDH Mutations
  - WHO Molecular Classification
  - INDIGO – ASCO Plenary Abstract #1, 2023
- Immunotherapy for Malignant Glioma
- Nibbling Around the Edges
  - Selected targetable mutations
  - Craniopharyngioma
  - Hemangioblastoma

Unique Concerns/Features That Differentiate Brain Tumors and Impact Treatment

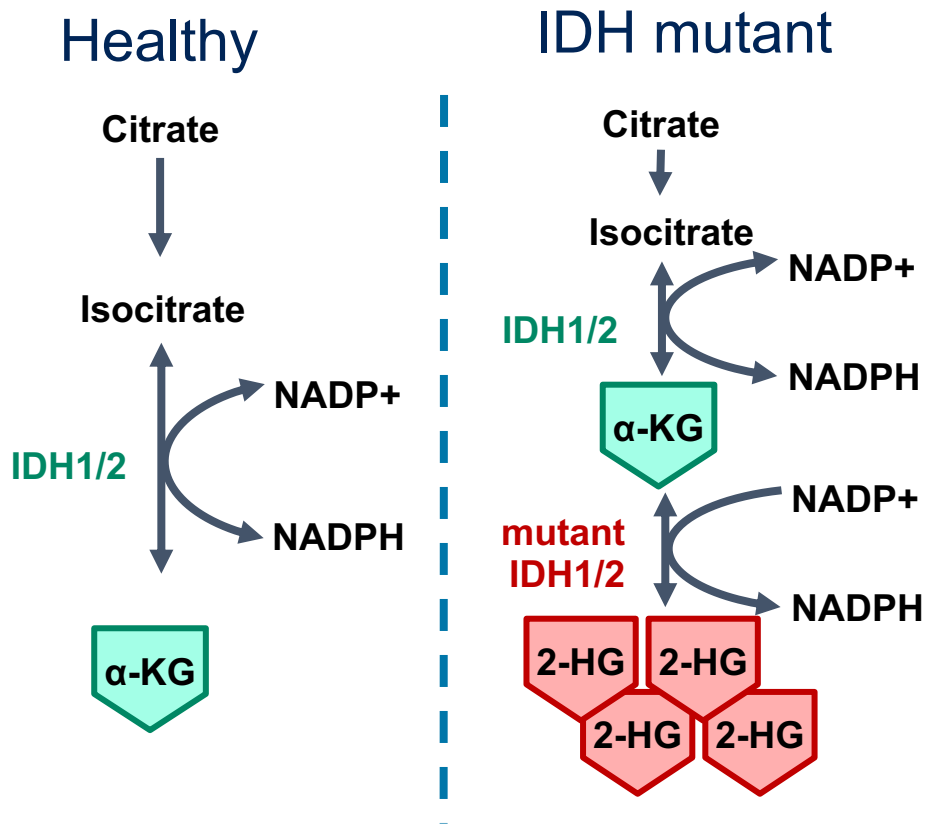
- The skull has a fixed volume
- Can be hard to measure success
  - Brain imaging studies are “estimates”
  - Steroid effects
  - Clinical deficits may be permanent
- Tumors deeply infiltrate into surrounding tissue
  - No opportunity for a “complete” resection
- The blood-brain barrier!
  - Keeps drugs out of the brain and the tumor
- Great intratumoral heterogeneity
- Immunosuppressive microenvironment
  - Few tumor specific antigens; ? Driver mutations

IDH Mutations

CLASSIFICATION AND TREATMENT IMPLICATIONS

Isocitrate dehydrogenase

- IDH1/2 hotspot mutations occur in various cancers, including diffuse gliomas[1]
- IDH1/2 mutations result in:[2]
  - Overproduction of R-2-hydroxyglutarate
  - Epigenetic dysregulation
  - Impaired cellular differentiation
  - Immunosuppressive tumor microenvironment



Competitive inhibition of α-KG-dependent enzymes

1. Dang L et al. Nature 2009;462:739–44; 2. Clark O *et al. Clin Cancer Res* 2016;22:1837–42.
IDH, isocitrate dehydrogenase; NADP(H), nicotinamide adenine dinucleotide phosphate; 2-HG, R-2-hydroxyglutarate; α-KG, alpha-ketoglutarate.

Frequency of IDH1 and IDH2 Mutations in Gliomas

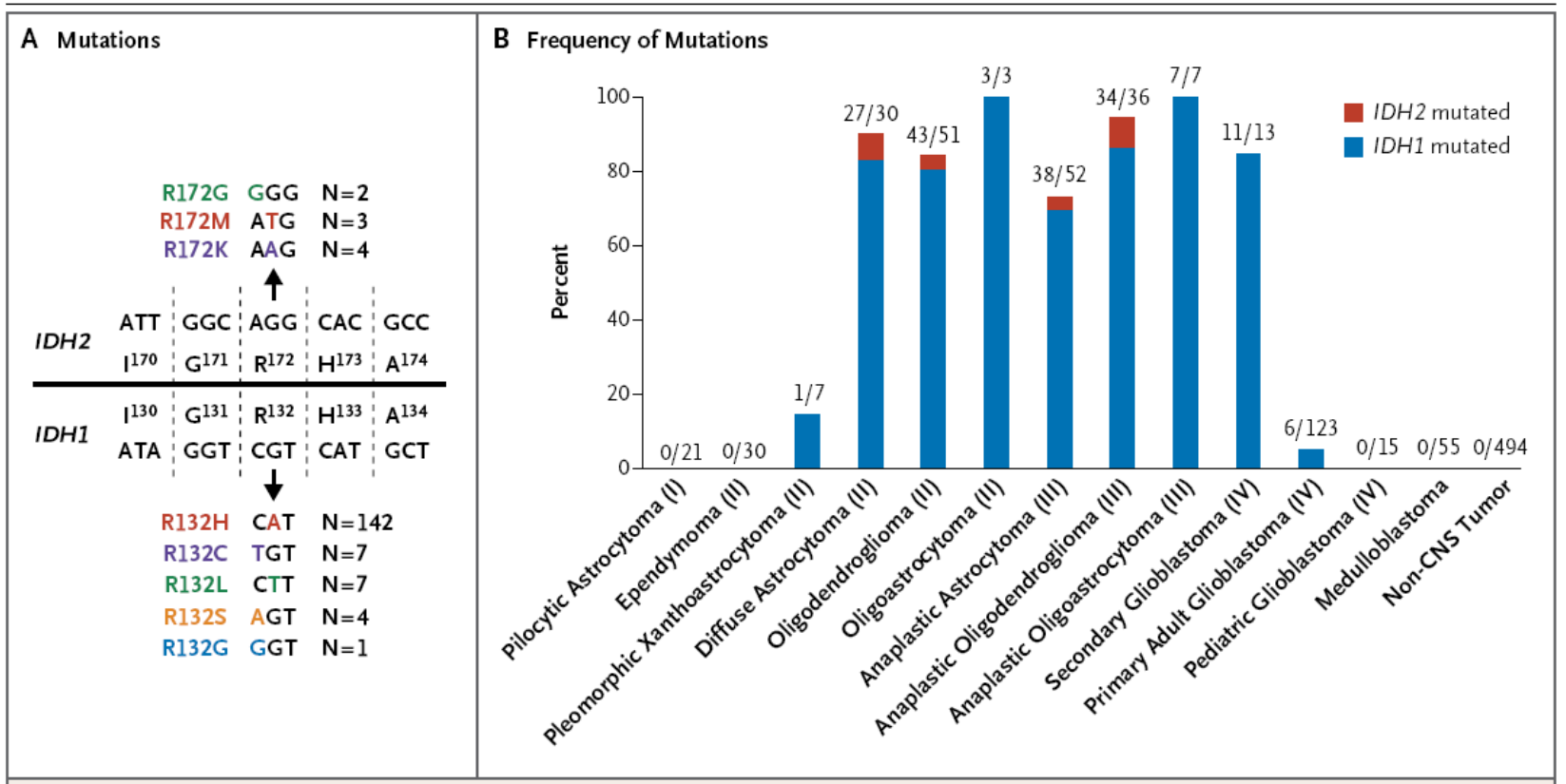


Figure 1. *IDH1* and *IDH2* Mutations in Human Gliomas.

Panel A shows mutations at codon R132 in *IDH1* and R172 in *IDH2* that were identified in human gliomas, along with the number of patients who carried each mutation. Codons 130 to 134 of *IDH1* and 170 to 174 of *IDH2* are shown. Panel B shows the number and frequency of *IDH1* and *IDH2* mutations in gliomas and other types of tumors. The roman numerals in parentheses are the tumor grades, according to histopathological and clinical criteria established by the World Health Organization. CNS denotes central nervous system.

Yan H, et al. NEJM 2009; 360:765-773

Survival and IDH Mutation

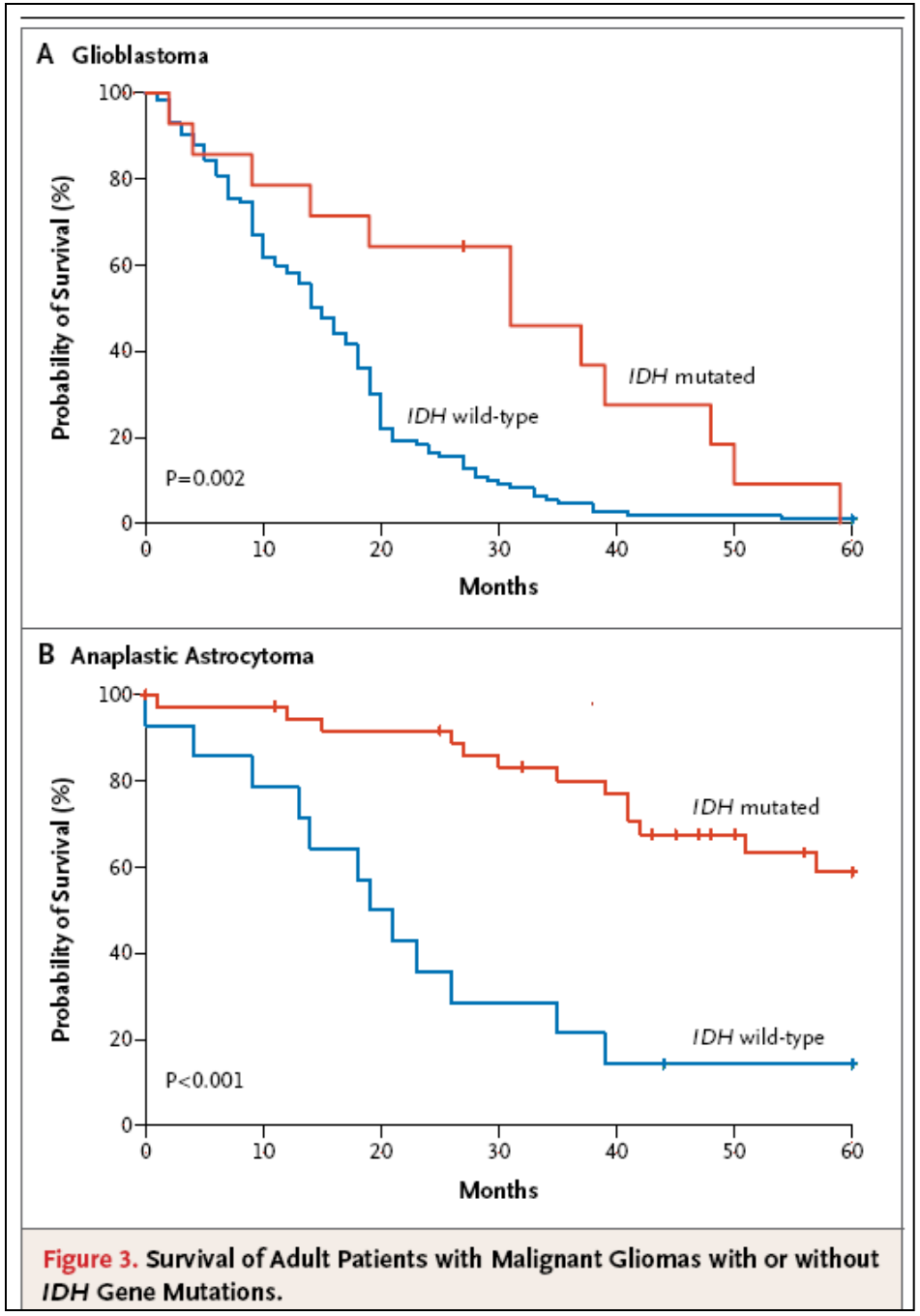


Figure 3. Survival of Adult Patients with Malignant Gliomas with or without *IDH* Gene Mutations.

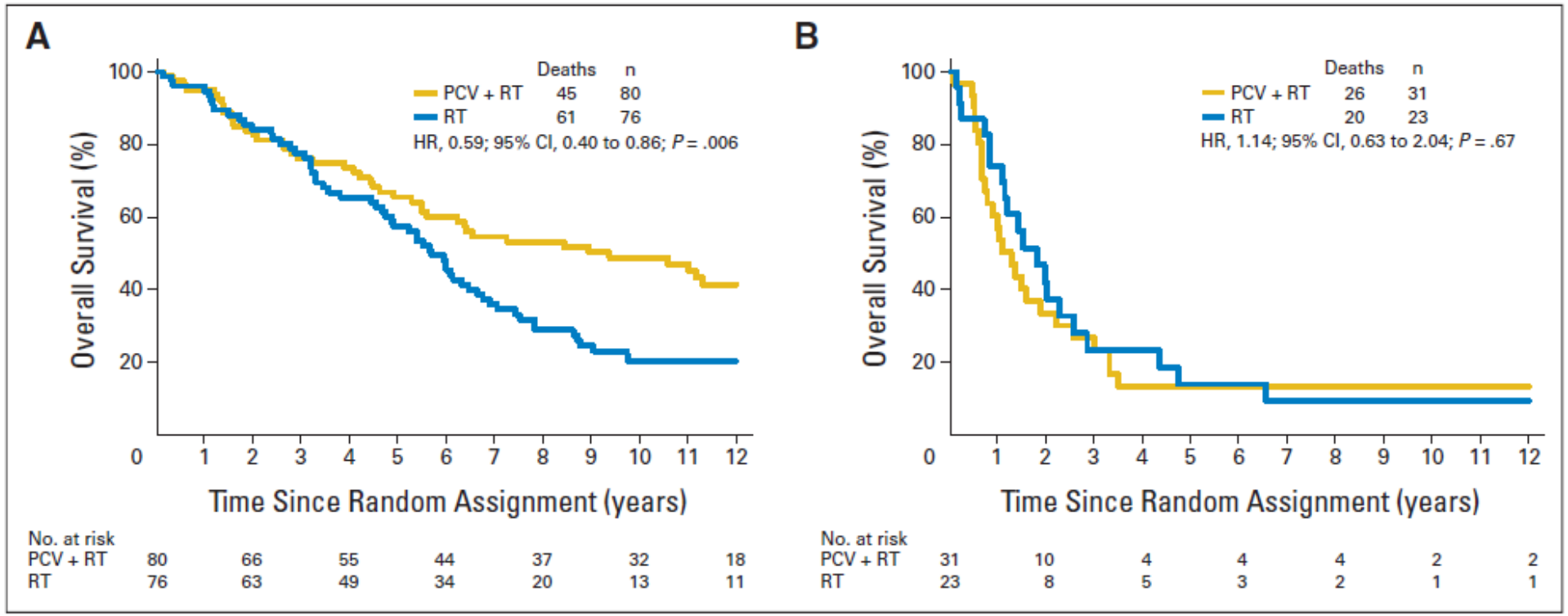
Figure 3. Survival of Adult Patients with Malignant Gliomas with or without *IDH* Gene Mutations.

For patients with glioblastomas, the median survival was 31 months for the 14 patients with mutated *IDH1* or *IDH2*, as compared with 15 months for the 115 patients with wild-type *IDH1* or *IDH2* (Panel A). For patients with anaplastic astrocytomas, the median survival was 65 months for the 38 patients with mutated *IDH1 or IDH2*, as compared with 20 months for the 14 patients with wild-type *IDH1* or *IDH2* (Panel B). Patients with both primary and secondary tumors were included in the analysis. For patients with secondary glioblastomas, survival was calculated from the date of the secondary diagnosis. Survival distributions were compared with the use of the log-rank test.

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

RTOG 9402: Impact of IDH on Survival After PCV/RT vs. RT Alone in Patients with Anaplastic Oligodendroglioma

IDH Mutant →



← **IDH Wild-Type**

Fig 1. Kaplan-Meier estimates of overall survival (OS) by treatment (procarbazine, lomustine, and vincristine [PCV] plus radiotherapy [RT] or RT) for patients with (A) *IDH*-mutated and (B) nonmutated tumors. Hazard ratio (HR) ratio for OS for those with mutated tumors was 0.59 (95% CI, 0.40 to 0.86; $P = .006$); HR for those with nonmutated tumors was 1.14 (95% CI, 0.63 to 2.04; $P = .67$).

Cairncross JG, et al. J Clin Oncol 2014; 32:783-790

CATNON: Impact of IDH Mutations on Outcome in Patients with Grade 3 Astrocytomas

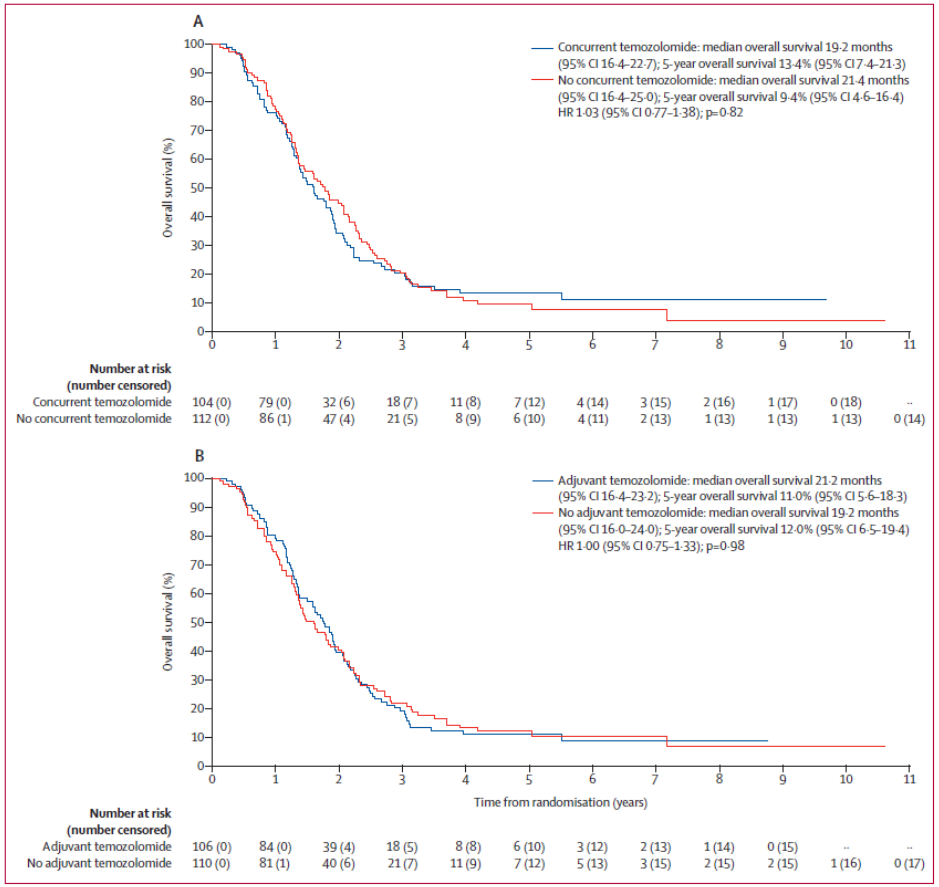


***Figure 3*: Univariable analysis of overall survival in patients with *IDH1* and *IDH2* wild-type tumours**
(A) Patients who received concurrent temozolomide versus those who did not. (B) Patients who received adjuvant temozolomide versus those who did not.

IDH Mutant →

← **IDH Wild Type**

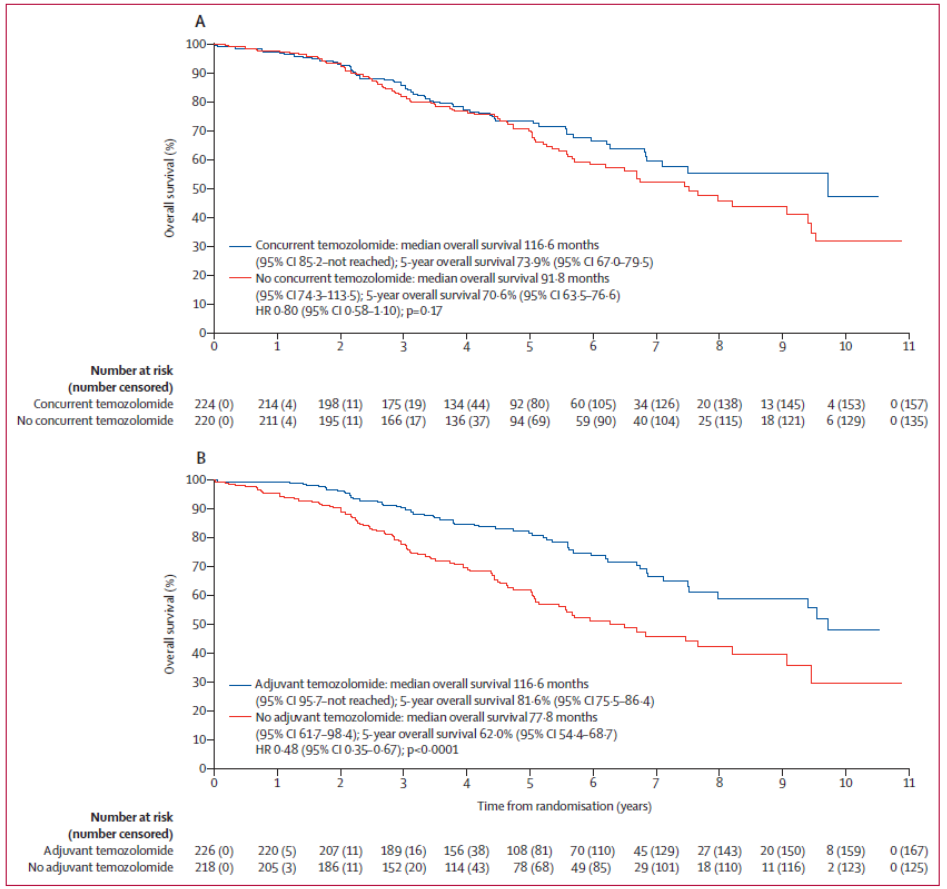
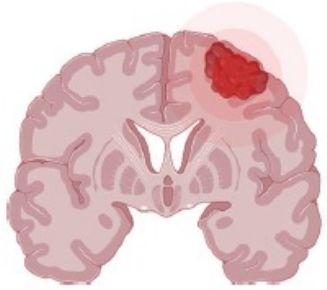


***Figure 4*: Univariable analysis of overall survival in patients with *IDH1* or *IDH2* mutant tumours**
(A) Patients who received concurrent temozolomide versus those who did not. (B) Patients who received adjuvant temozolomide versus those who did not.

Van den Bent MJ, et al. Lancet Onc. 2021: 813-823.

WHO 2021 Classification of Adult Gliomas

Figure 1. The 2021 World Health Organization Classification of Tumors of the Central Nervous System Updated Diagnosis of Adult Gliomas



IDH mutant		*IDH* wild type
Oligodendroglioma	Astrocytoma	Glioblastoma
Grade 2 1p/19q Codeletion *TERT* promoter mutation	**Grade 2** *ATRX* loss *TP53* mutation	**Grade 4** Chromosome 7 gain Chromosome 10 loss Homozygous loss *CDKN2A/2B* *TERT* promoter mutation *ATRX* retained *EGFR* amplification
Grade 3 Anaplastic features High mitotic index CDKN2A/B homozygous deletion	**Grade 3** *ATRX* loss *TP53* mutation Anaplastic features High mitotic index	
	Grade 4 *ATRX* loss *TP53* mutation *CDKN2A/B* homozygous deletion	

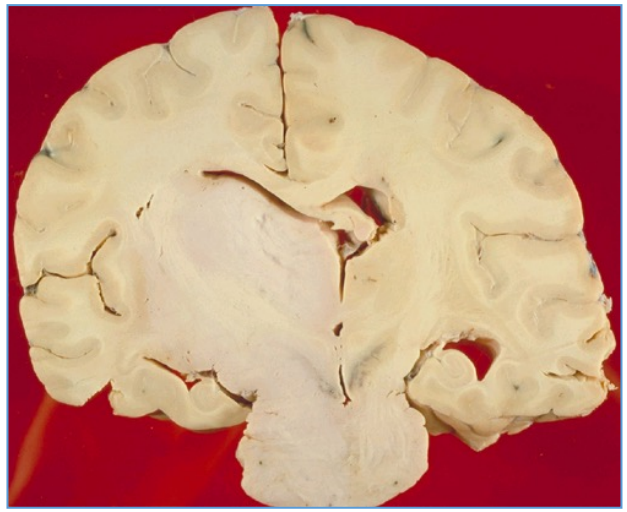
Berger T, et al. JAMA Oncol. 2022;8:1493-1501

Low Grade Gliomas

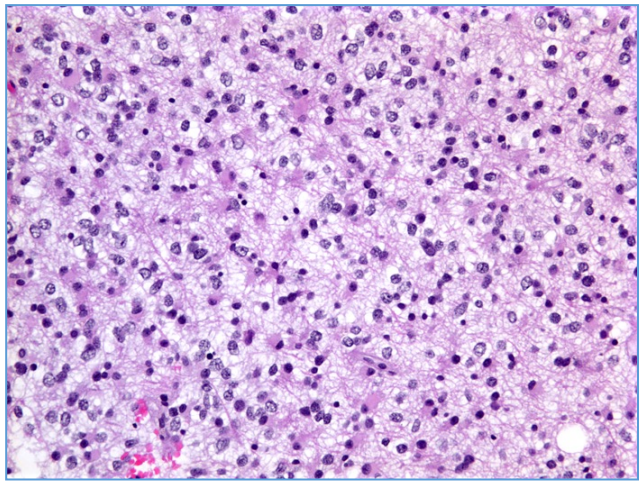
- About 4000 new diagnoses per year in this country
- Current standard of care includes partial brain radiation and chemotherapy, sometimes watch and wait. Lots of concern about long term cognitive effects of radiation
- Median age at diagnosis in 40's
  - Time of lots of life experiences: work, raising a family, caring for others (parents), fun
  - Thus, impairment in function can have huge implications for QOL broadly over a long period of time
- RTOG 9802: Median survival increased from 7 to 14 years with combination modality therapy of radiation and chemotherapy (led by Ed Shaw, Chair Rad Onc at WFSOM)
- Characterized by IDH mutations (mostly IDH1) and better outcomes with median survival of 7 to 15 years in many cases
- IDH mutations are now an essential component of diagnostic criteria (WHO 2021)

Astrocytoma = Grade II
Low Mitosis(2), Infiltrative(3), Imaging(4)

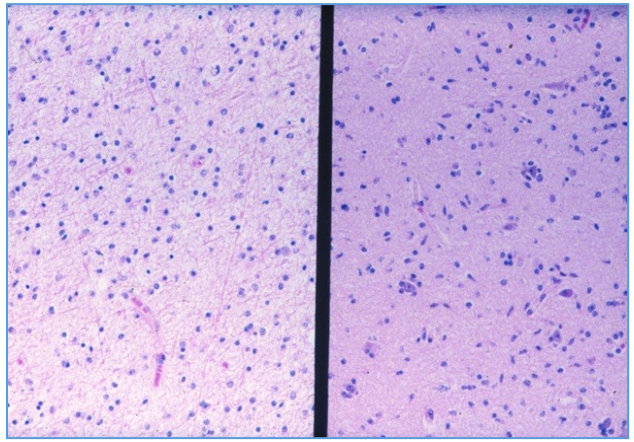
(1)



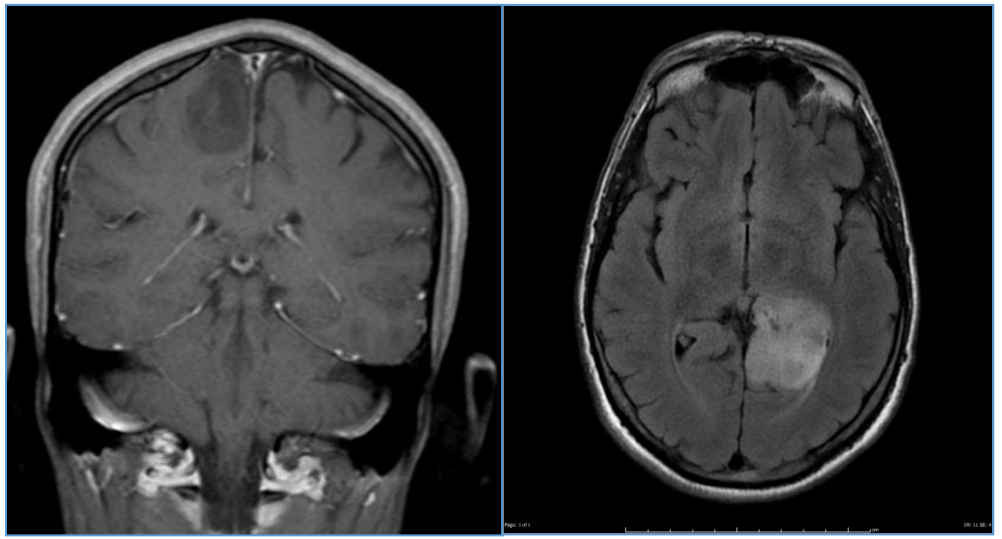
(2)



(3)



(4)



http://neuropathology-web.org/chapter7/chapter7bGliomas.html

Current treatment approach to newly diagnosed IDH1/2-mutant glioma

No curative therapy

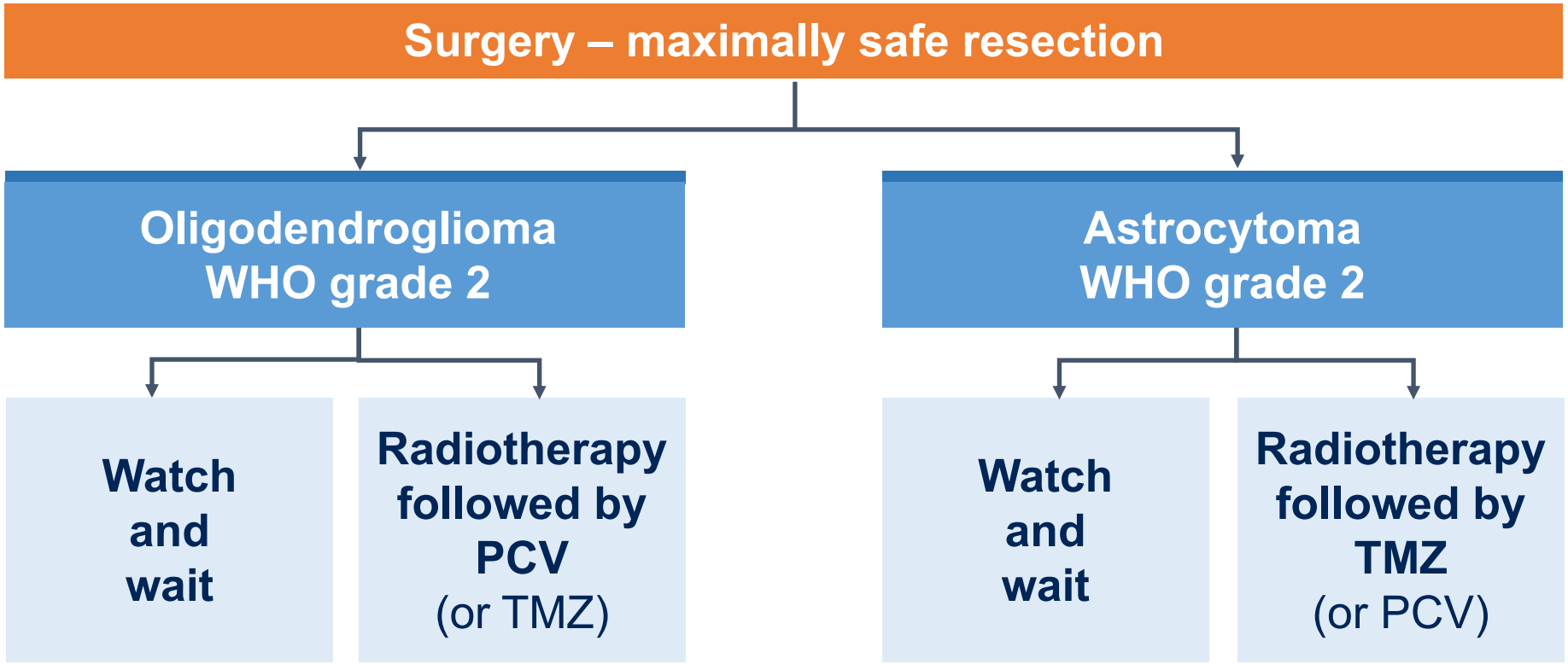
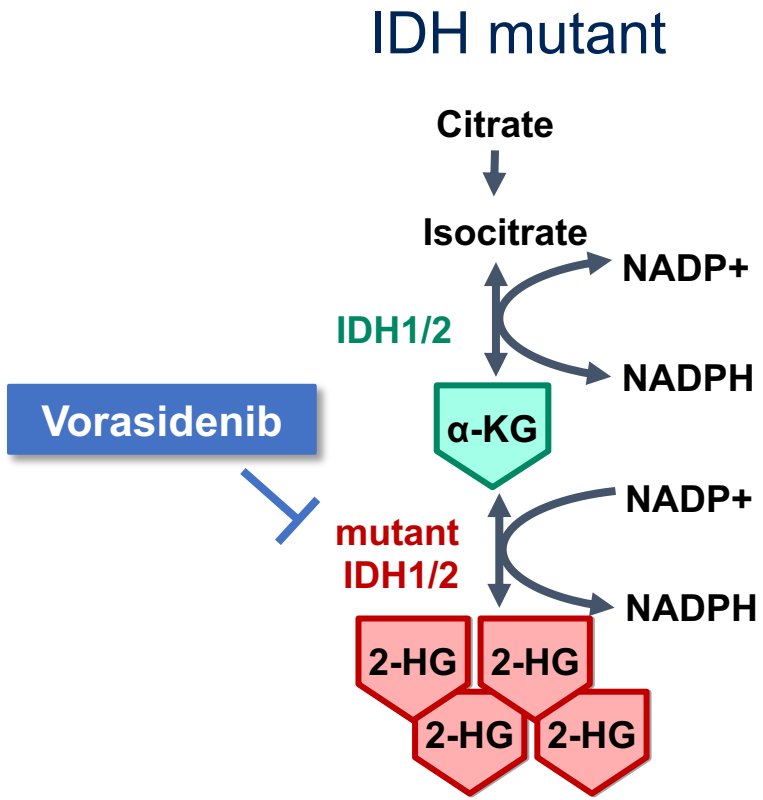


Figure modified from: Weller M *et al. Nat Rev Clin Oncol* 2021;18:170–86, with permission.
PCV, procarbazine, lomustine and vincristine; TMZ, temozolomide.

Vorasidenib

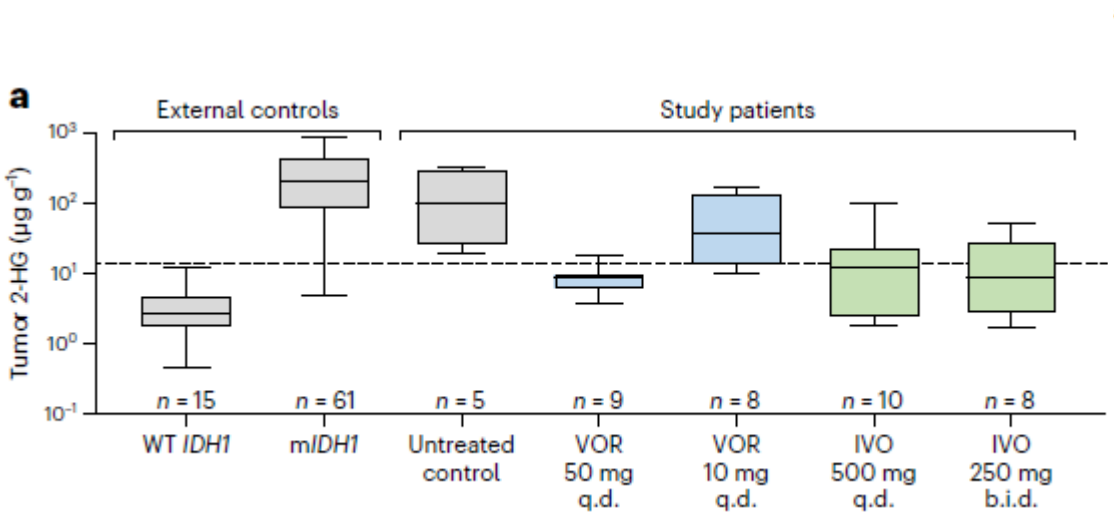
- Oral inhibitor of mutant IDH1 and IDH2[1]
- Specifically designed for brain penetrance[1]
- Reduced tumor 2-HG by >90% in resected grade 2/3 non-enhancing diffuse glioma[1]
- 2-HG reduction associated with:[2]
  - Lower tumor cell proliferation
  - Reversal of IDH1/2 mutation-associated gene expression programs
  - Increased DNA 5-hydroxy-methylcytosine
  - Increased tumor infiltrating lymphocytes

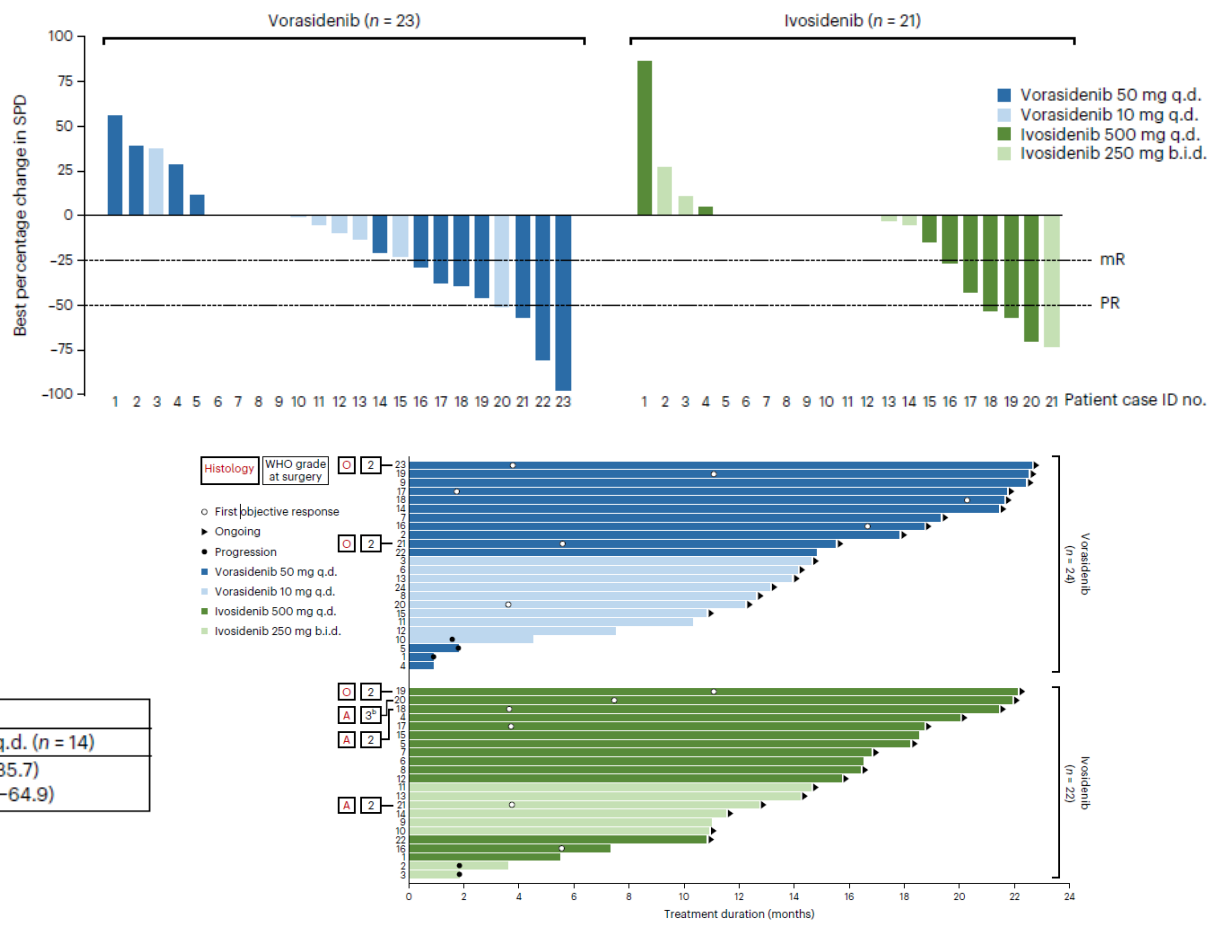


Competitive inhibition of α-KG-dependent enzymes

1. Mellinghoff I *et al. Nat Med* 2023;29:615–22; 2. Lu M et al. Presented at the American Association for Cancer Research Virtual Annual Meeting II June 22–24, 2020: abstract 2046.

Vorasidenib and Ivosidenib in IDH1-Mutant Recurrent Low-Grade Glioma: A Randomized, Perioperative Phase 1 Trial





	Vorasidenib		Ivosidenib	
	10 mg q.d. (*n* = 10)	50 mg q.d. (*n* = 14)	250 mg b.i.d. (*n* = 8)	500 mg q.d. (*n* = 14)
Objective response rate[a] — no. (%) (95% CI)	1 (10.0) (0.3–44.5)	6 (42.9) (17.7–71.1)	1 (12.5) (0.3–52.7)	5 (35.7) (12.8–64.9)

Mellinghoff IK, et al. Nature Med. 2023: 615-622.

INDIGO: INvestigating vorasiDenIb in GliOma (NCT04164901)

Key eligibility criteria

- ≥12 years of age
- IDH1/2-mutated* grade 2 oligodendroglioma or astrocytoma per WHO 2016 guidelines
- Prior surgery only
- Measurable non-enhancing disease (≥1 target lesion measuring ≥1 cm × ≥1 cm), confirmed by blinded review
- Not in need of immediate chemotherapy or radiotherapy per investigator assessment

1:1
double-blind randomization
(N=331)

Stratified by 1p19q status and baseline tumor size

Vorasidenib 40 mg (N=168)

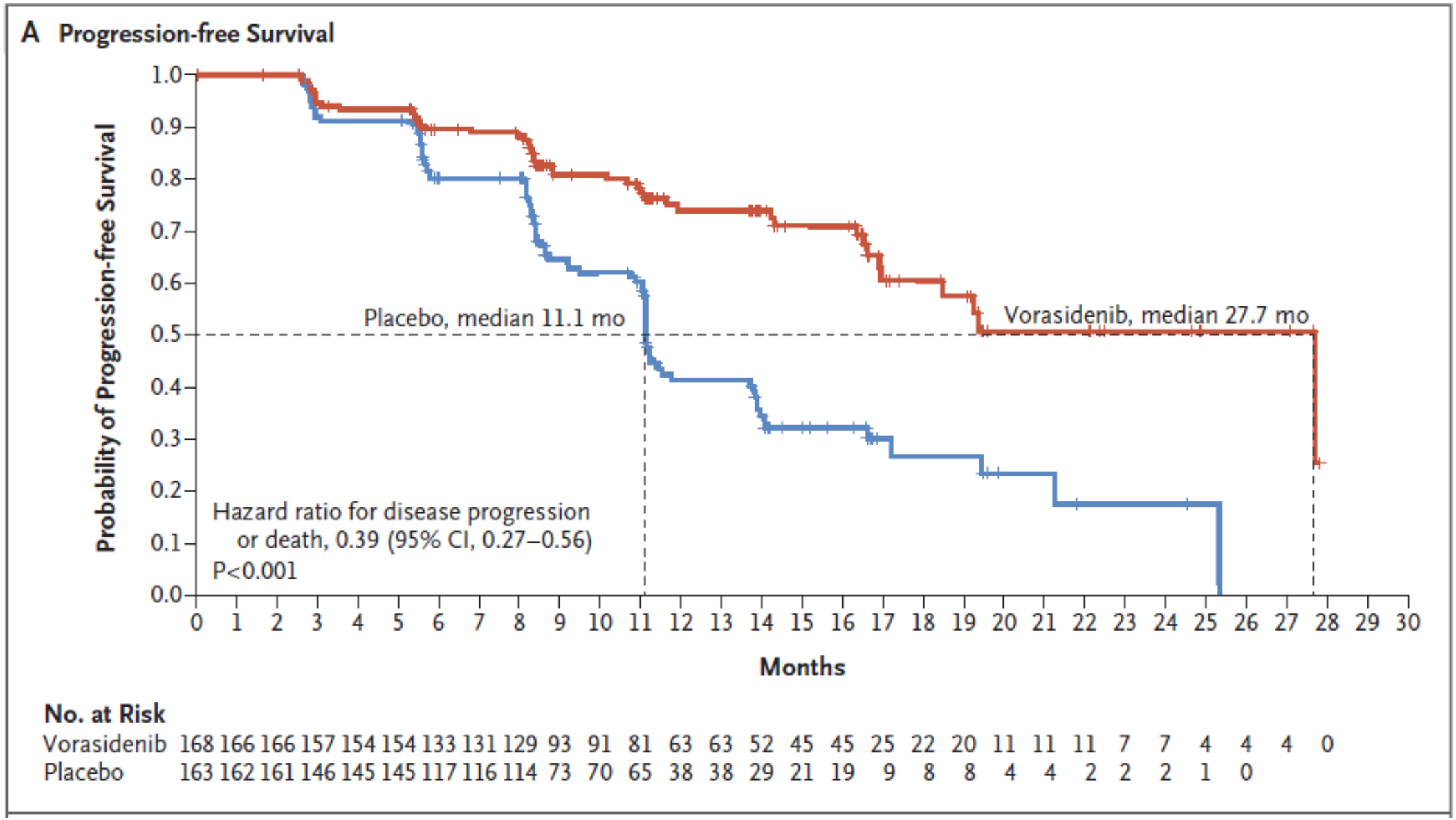
Placebo (N=163)

Orally, once daily, 28-day cycles

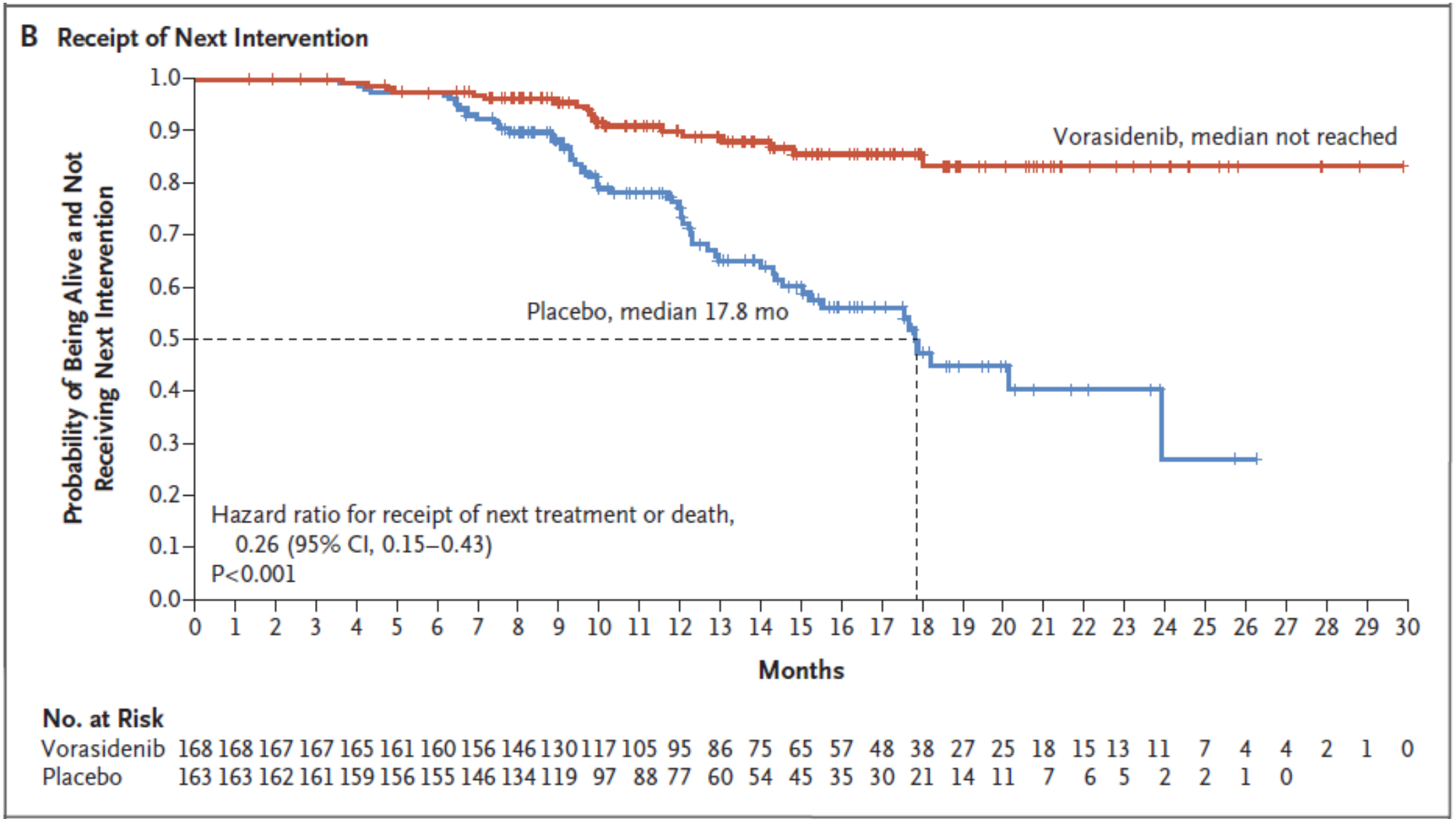
Centrally confirmed progressive disease permitted unblinding and crossover†

IDMC regularly reviewed safety and other clinical data, as well as the efficacy data following prespecified interim analyses

*Centrally confirmed using an investigational clinical trial assay, based on the Oncomine Dx Target Test and developed in partnership with Thermo Fisher Scientific Inc.;
†Real-time single BIRC reader.
IDMC, independent data monitoring committee.



Mellinghoff IK, et al. N Engl J Med. 2023: 589-601



Mellinghoff IK, et al. N Engl J Med. 2023: 589-601

Table 2. Most Common Adverse Events (Safety Analysis Set).*

Event	Vorasidenib (N=167)		Placebo (N=163)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Any adverse event	158 (94.6)	38 (22.8)	152 (93.3)	22 (13.5)
Increased alanine aminotransferase	65 (38.9)	16 (9.6)	24 (14.7)	0
Increased aspartate aminotransferase	48 (28.7)	7 (4.2)	13 (8.0)	0
Increased γ-glutamyltransferase	26 (15.6)	5 (3.0)	8 (4.9)	2 (1.2)
Coronavirus disease 2019	55 (32.9)	0	47 (28.8)	0
Fatigue	54 (32.3)	1 (0.6)	52 (31.9)	2 (1.2)
Headache	45 (26.9)	0	44 (27.0)	1 (0.6)
Diarrhea	41 (24.6)	1 (0.6)	27 (16.6)	1 (0.6)
Nausea	36 (21.6)	0	37 (22.7)	0
Dizziness	25 (15.0)	0	26 (16.0)	0
Seizure	23 (13.8)	7 (4.2)	19 (11.7)	4 (2.5)
Constipation	21 (12.6)	0	20 (12.3)	0

* The safety analysis set included all the patients who received at least one dose of vorasidenib or placebo. The individual adverse events listed are those of any grade that occurred in at least 10% of the patients in the vorasidenib group.

Mellinghoff IK, et al. N Engl J Med. 2023: 589-601

Immunotherapy of CNS Tumors

DISAPPOINTMENT THUS FAR

Late-Stage Failures With Immunotherapies in Glioblastoma

Therapeutic	Clinical Trial	Setting
Nivolumab	▪ Checkmate 143[1] ▪ Checkmate 498* ▪ Checkmate 548*	▪ Relapsed ▪ First line, unmethylated ▪ First line, methylated
Toca 511 with 5FC	▪ Cloughesy et al[2]	▪ Relapsed
VB-111	▪ GLOBE[3]	▪ Relapsed
Rindopepimut	▪ ACT IV trial[4]	▪ First line
Dendritic cell vaccine	▪ DCVax®-L phase III[5]	▪ First line
Ombipepimut-S	▪ WIZARD 201G*	▪ Relapsed

*As reported in a press release.

1. Reardon. JAMA Oncol. 2020;6:1003. 2. Cloughesy. JAMA Oncol. 2020;6:1939. 3. Cloughesy. Neuro Oncol. 2020;22:705.
4. Weller. Lancet Oncol. 2017;18:1373. 5. Tan. Clin Neuropharmacol. 2021;44:216.

Glioblastoma Has Multiple Immune Deficits: Combinations Necessary

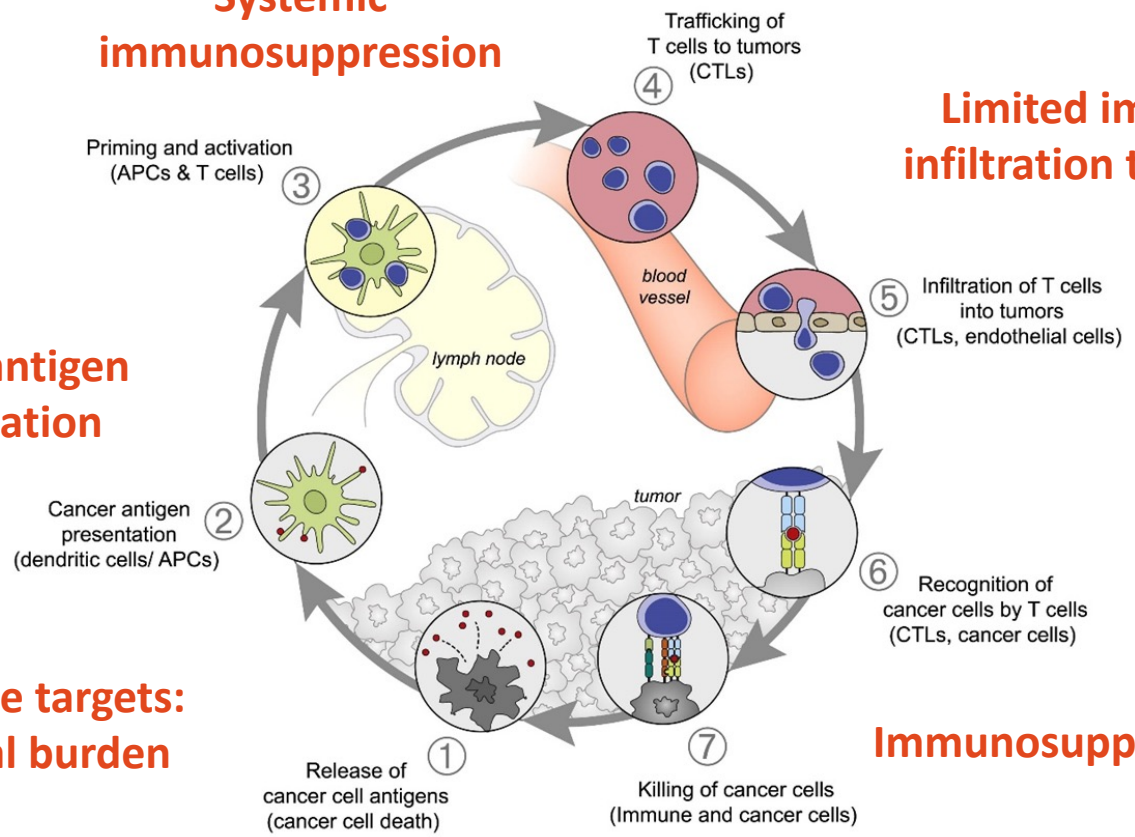
Systemic immunosuppression

Limited immune infiltration to tumor

Limited antigen presentation

Limited immune targets: low mutational burden

Immunosuppressive TME

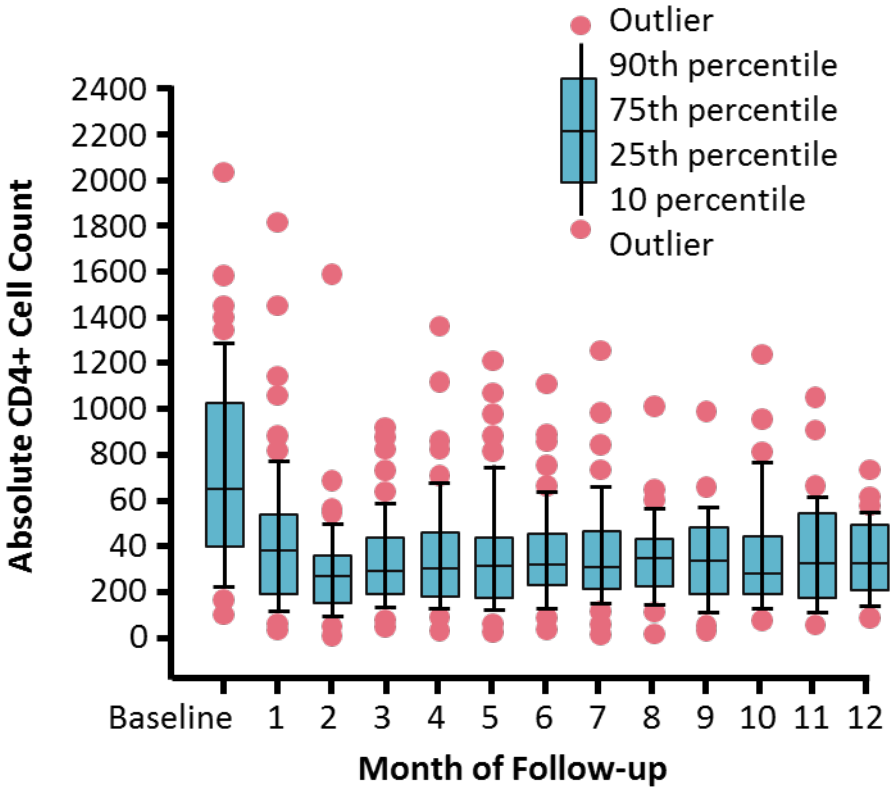


Chen. Immunity. 2013;39:1.

Slide credit: clinicaloptions.com

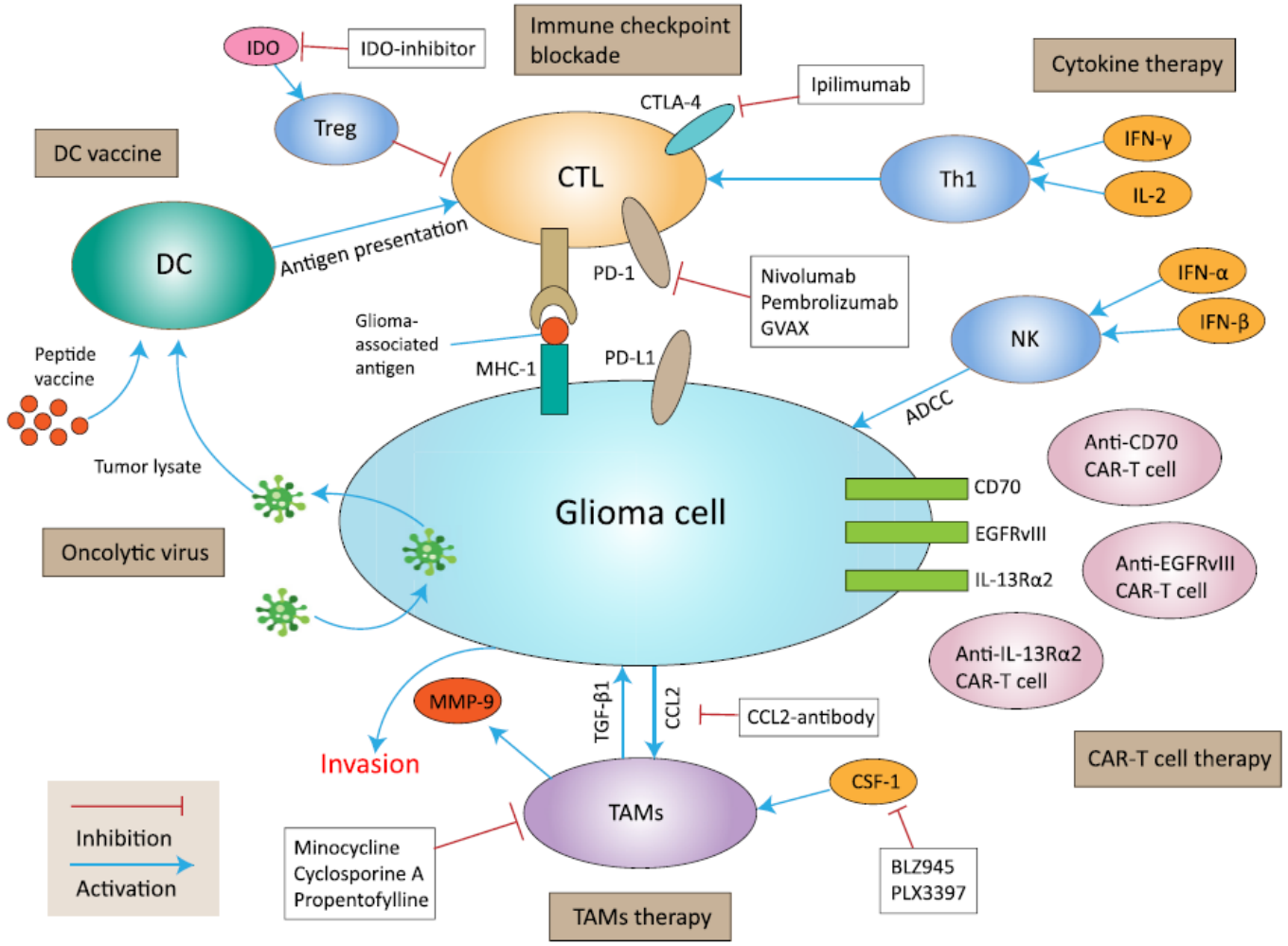
Immunosuppression In Patients with High-Grade Gliomas Treated with Radiation and TMZ

- N = 96
- Median CD4+ cell count before RT and TMZ: 664 cells/mm3
- CD4+ cell count nadir occurred 2 mos after initiating therapy; 73% had CD4+ cell counts < 300 cells/mm3, 40% had < 200 cells/mm3
- CD4+ cell counts remained low throughout the year of follow-up
- Infection risk low (2.5% rate of death from infection)



Grossman SA, Ye X, Lesser G, et al. Clin Cancer Res: 17(16); 5473-80. 2011

Current Immunotherapy Strategies for Glioma



Xu S, et al. Can Letters. 2020: 1-12.

Final results of 2-THE-TOP: a pilot phase 2 study of TTFields (Optune) plus pembrolizumab plus maintenance temozolomide (TMZ) in patients with newly diagnosed glioblastoma (ndGBM)

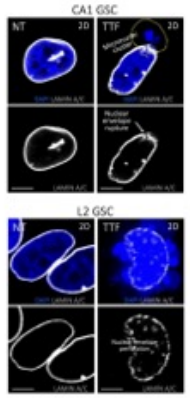
David D. Tran[1], Ashley Ghiaseddin[2], Dongjiang Chen[1], Son Le[1], Maryam Rahman[2]

[1]USC Brain Tumor Center, University of Southern California, United States; [2]University of Florida, Gainesville, Florida, United States

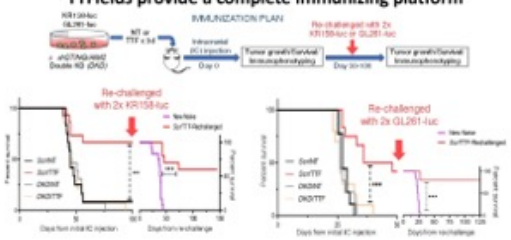
BACKGROUND

- Tumor Treating Fields (TTFields) plus maintenance TMZ is approved therapy for ndGBM[1] and are low-intensity, alternating electric fields that disrupt cellular processes critical for cancer cell viability[2–5]
- Pembrolizumab is an anti-programmed cell death protein 1 (PD-1) therapy that is approved for use in multiple cancer indications[9]
- TTFields with TMZ had been shown to elicit anti-proliferative effects and promote recruitment of immune effector cells to the tumor microenvironment with anti-PD-1 therapy potentiating the immune response to amplify therapeutic effects[4,7,10]
- TTFields has been shown to induce anti-tumor immunity via type-1 interferon pathways (T1IFN) of the STING and AIM2 inflammasomes, TTFields may synergize with immune checkpoint inhibitors to prolong survival in ndGBM patients[11]
- **Our objective is to report on the results of the 2-THE-TOP study (NCT03405792)**

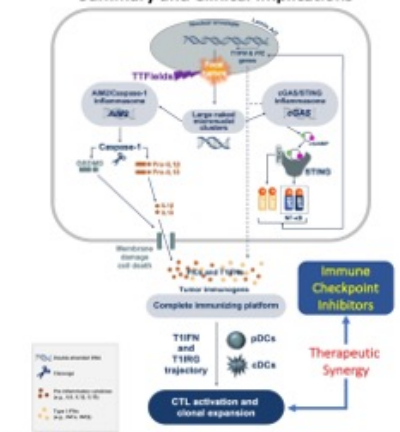
TTFields induce nuclear envelope rupture, producing micronuclei protrusions[11]



TTFields provide a complete immunizing platform

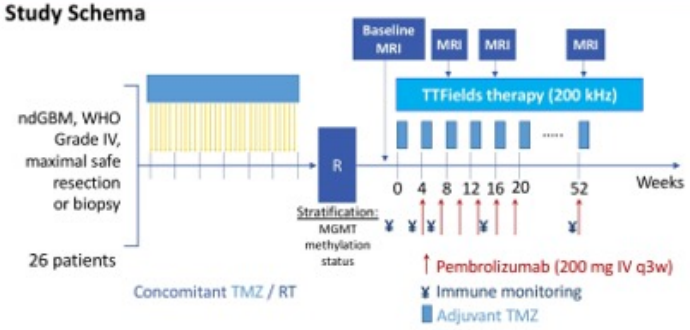


Summary and Clinical Implications



METHODS

Study Schema



Study Endpoints		
Primary	**Secondary**	**Exploratory**
• PFS compared with matched control (Phase 3 EF-14 study)	• Toxicity and tolerability of the triple therapy • OS and ORR vs historical data • Augmentation of TTFields-initiated glioma-specific immune reaction by pembrolizumab	• Metabolomic signature of immune activation by TTFields and TTFields + pembrolizumab in serum and urine • Correlation of mutation burden in primary tumor samples with response to pembrolizumab + TTFields

Inclusion criteria: (1) Histologically confirmed GBM WHO Grade IV. Resection and biopsy only allowed. (2) KPS ≥ 70%.

Exclusion criteria: (1) History of autoimmune disease. (2) Dexamethasone >4 mg/day at registration.

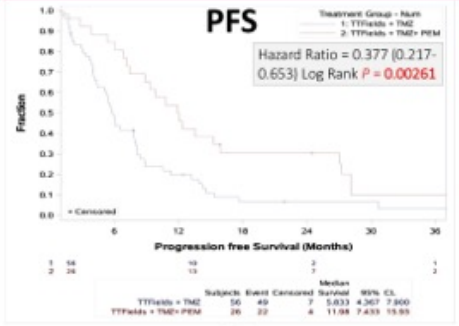
RESULTS

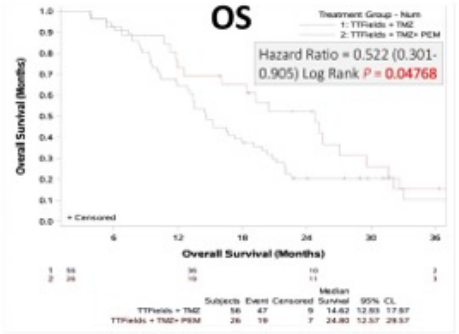
Patient characteristics of the 2-THE-TOP and control cohorts

Characteristics	EF-14 (TTFields/TMZ) (n=56)	2THETOP (TTFields/TMZ/PEM) (n=26)	p-Value
Age (Years)			
n	56	26	0.207
Mean (SD)	55.9 (12.11)	56.7 (13.28)	
Median (range)	56.5 (26-83)	60.5 (31-79)	
Sex, No. (%)			
Male	38 (68)	19 (73)	0.760
Female	18 (32)	7 (27)	
Karnofsky Performance Score			
Median (range)	80 (70-90)	80 (70-90)	1.000
Extent of Resection, No. (%)			
Biopsy	15 (27)	7 (27)	1.000
Partial Resection	14 (25)	7 (27)	
Gross Total Resection	27 (48)	12 (46)	
MGMT Methylation Status, No. (%)			
Methylated	14 (25)	7 (27)	1.000
Unmethylated	42 (75)	19 (73)	
IDH1/2 Status, No. (%)			
Positive	7 (12)	3 (12)	0.638
Negative	49 (88)	23 (88)	
Compliance in first 6 months (%)			
n	56	26	0.451
Mean (SD)	77.1 (10.53)	80.3 (10.36)	
Median (range)	80.9 (50-94)	83.2 (55-95)	

Most common serious adverse events were thromboses n=4 (15%), seizures n=3 (12%), and metabolic disturbances n=2 (8%)

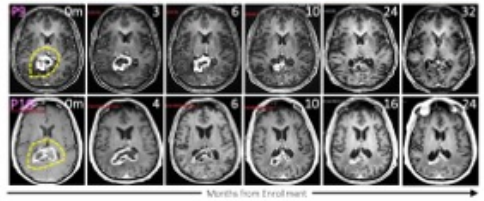
RESULTS CONT'D



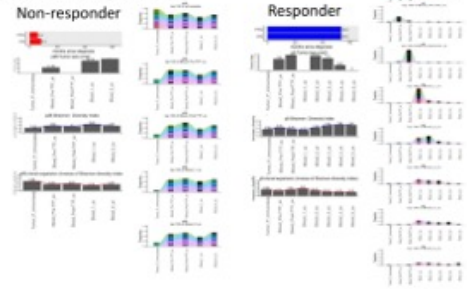


Best Response: Of the 15 subjects with measurable target lesions

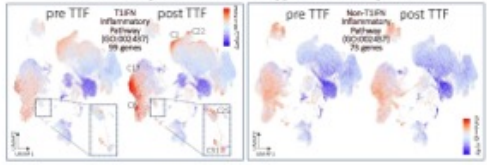
Complete response (CR) or Near CR	4 (27%)
Partial response	2 (13%)
Stable disease	8 (53%)
Progressive disease	1 (<7%)



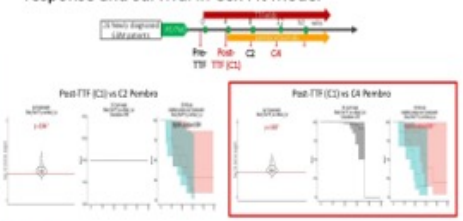
TCR Clonal Switch/Replacement is a prominent feature in responders



TTFields stimulate innate immunity via a T1IFN trajectory across multiple T1IRG+ cell types in GBM patients



Effective clonal replacement is strongly predictive of response and survival in Cox Fit Model



CONCLUSIONS

- Triple regimen of TTFields + maintenance TMZ + pembrolizumab (200 mg IV q3w) showed promising efficacy and was generally well tolerated in patients with ndGBM.
- A phase 3, double-blind, placebo-controlled study of TTFields + pembrolizumab + maintenance TMZ vs TTFields + placebo + maintenance TMZ for adult patients with ndGBM is planned

Keck Medicine of USC

USC Brain Tumor Center

ACKNOWLEDGEMENTS: Novocure GmbH

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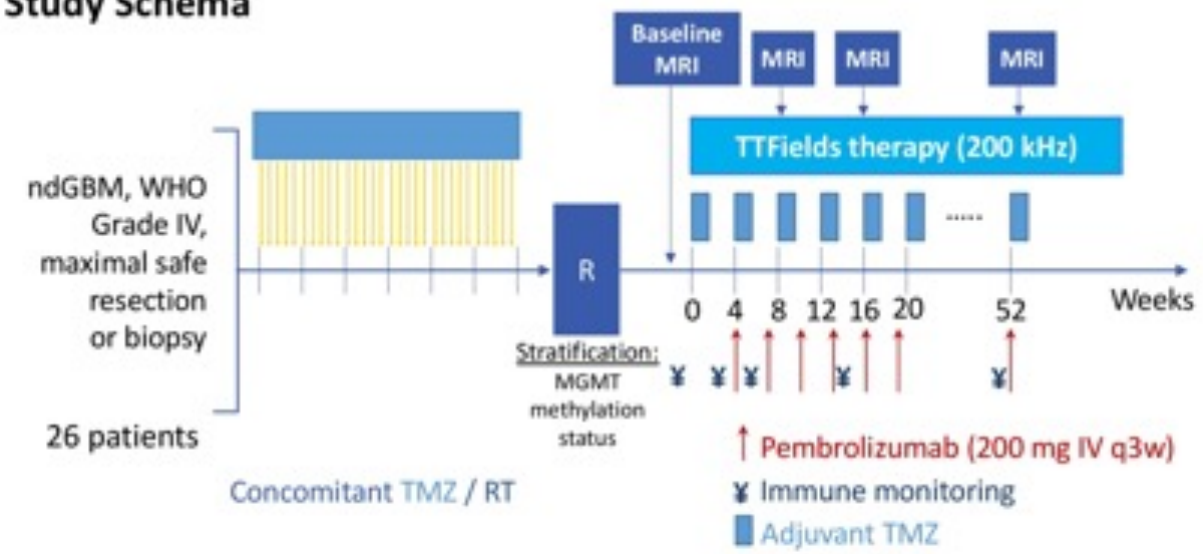
Final results of 2-THE-TOP: a pilot phase 2 study of TTFields [redacted] plus pembrolizumab plus maintenance temozolomide (TMZ) in patients with newly diagnosed glioblastoma (ndGBM)

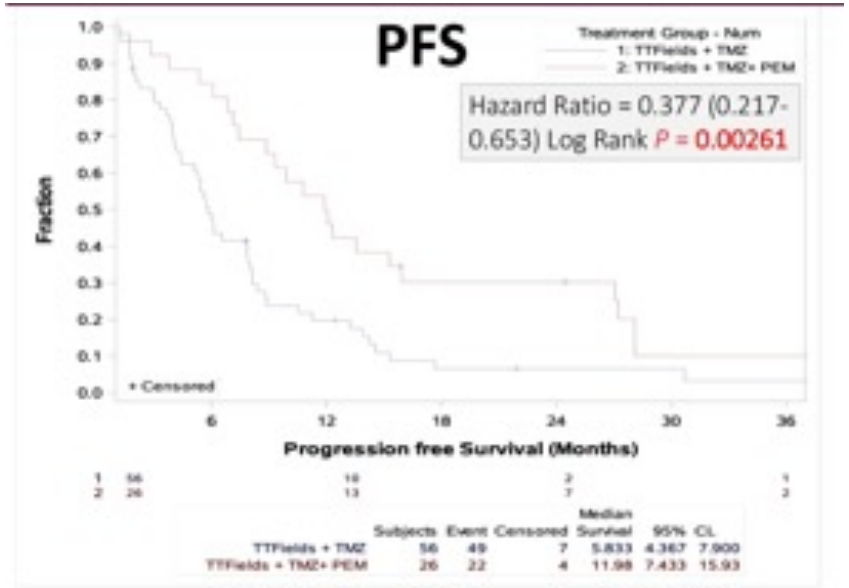
David D. Tran[1], Ashley Ghiaseddin[2], Dongjiang Chen[1], Son Le[1], Maryam Rahman[2]
[1]USC Brain Tumor Center, University of Southern California, United States; [2]University of Florida, Gainesville, Florida, United States

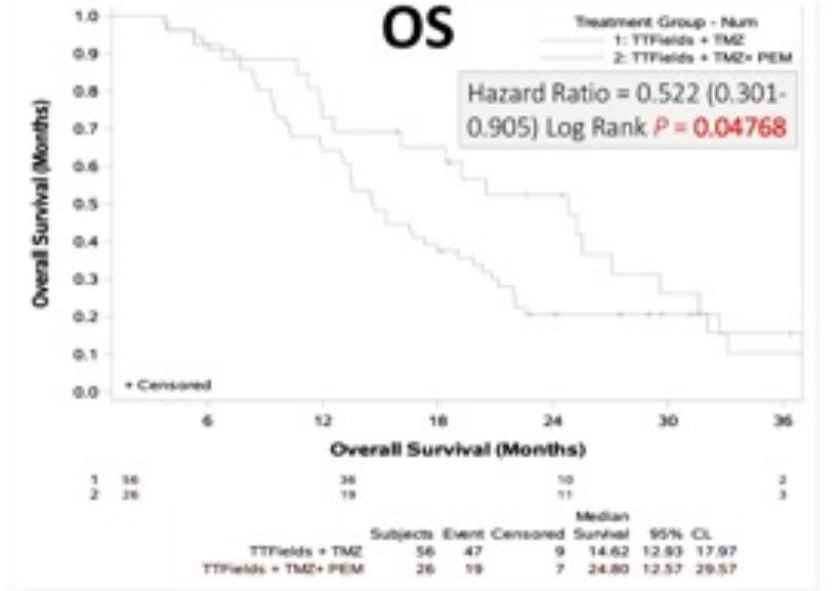
- Pembrolizumab is an anti-programmed cell death protein 1 (PD-1) therapy that is approved for use in multiple cancer indications[9]
- TTFields with TMZ had been shown to elicit anti-proliferative effects and promote recruitment of immune effector cells to the tumor microenvironment with anti-PD-1 therapy potentiating the immune response to amplify therapeutic effects[4,7,10]
- TTFields has been shown to induce anti-tumor immunity via type-1 interferon pathways (T1IFN) of the STING and AIM2 inflammasomes, TTFields may synergize with immune checkpoint inhibitors to prolong survival in ndGBM patients[11]

METHODS

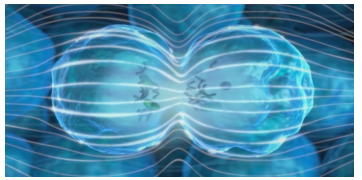
Study Schema







Tumor Treating Fields (TTF)



- Device consists of insulated transducer arrays, electric field generator, battery pack
- Generates alternating electric fields through tumor at a frequency of 200 kHz
- Antimitotic therapy:
  - Disrupted alignment of polarized tubulin subunits
  - Mitotic spindle disruption during mitosis
  - Leads to metaphase arrest, mitotic catastrophe and induced cell death
- Other mechanisms likely

Figure 3.
Second-generation (device. The complete system consists of an electric field generator (**A**), rechargeable battery pack (**B**), carrying pouch (**C**), and two pairs of disposable ceramic transducer arrays (**D**). Figure copyright

Nibbling Around the Edges

EXAMPLES OF PROGRESS IN UNCOMMON CNS TUMORS

Dabrafenib plus trametinib in patients with *BRAF*^{V600E}-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial

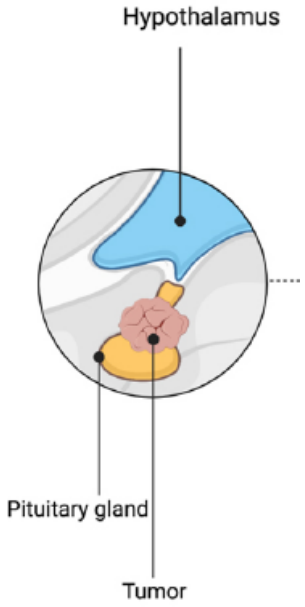
Patrick Y Wen, Alexander Stein, Martin van den Bent, Jacques De Greve, Antje Wick, Filip Y F L de Vos, Nikolas von Bubnoff, Myra E van Linde, Albert Lai, Gerald W Prager, Mario Campone, Angelica Fasolo, Jose A Lopez-Martin, Tae Min Kim, Warren P Mason, Ralf-Dieter Hofheinz, Jean-Yves Blay, Daniel C Cho, Anas Gazzah, Damien Pouessel, Jeffrey Yachnin, Aislyn Boran, Paul Burgess, Palanichamy Ilankumaran, Eduard Gasal, Vivek Subbiah

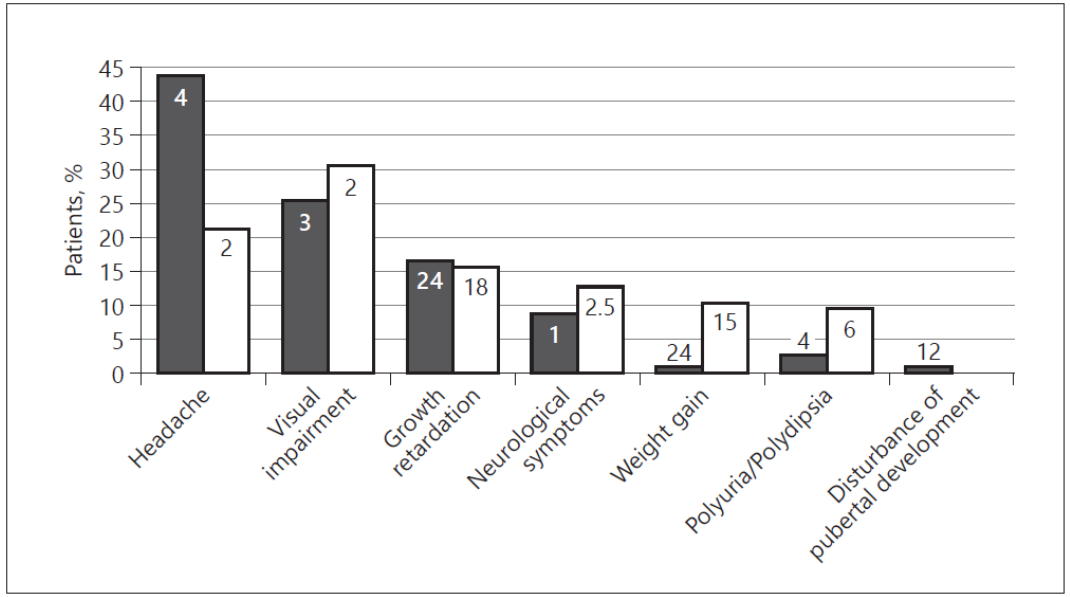
	Grade III (n=13)	Glioblastoma (n=31)	Age 18–39 years (n=22)	Age ≥40 years (n=23)
Objective response rate by investigator, % (95% CI)	38 (13·9–68·4)	32 (16·7–51·4)	50 (28·2–71·8)	17 (5·0–38·8)
Patients responding at 12 months by investigator assessment, % (95% CI)	100	67 (28·2–87·8)	89 (43·3–98·4)	50 (5·8–84·5)
Median progression-free survival by investigator, months (95% CI)	3·8 (1·7–NR)	2·8 (1·8–13·7)	18·5 (5·5–41·4)	1·7 (0·9–2·5)
Median overall survival, months (95% CI)	45·2 (6·3–NR)*	13·7 (8·4–25·6)	45·2 (17·9–NR)†	8·7 (3·7–11·7)

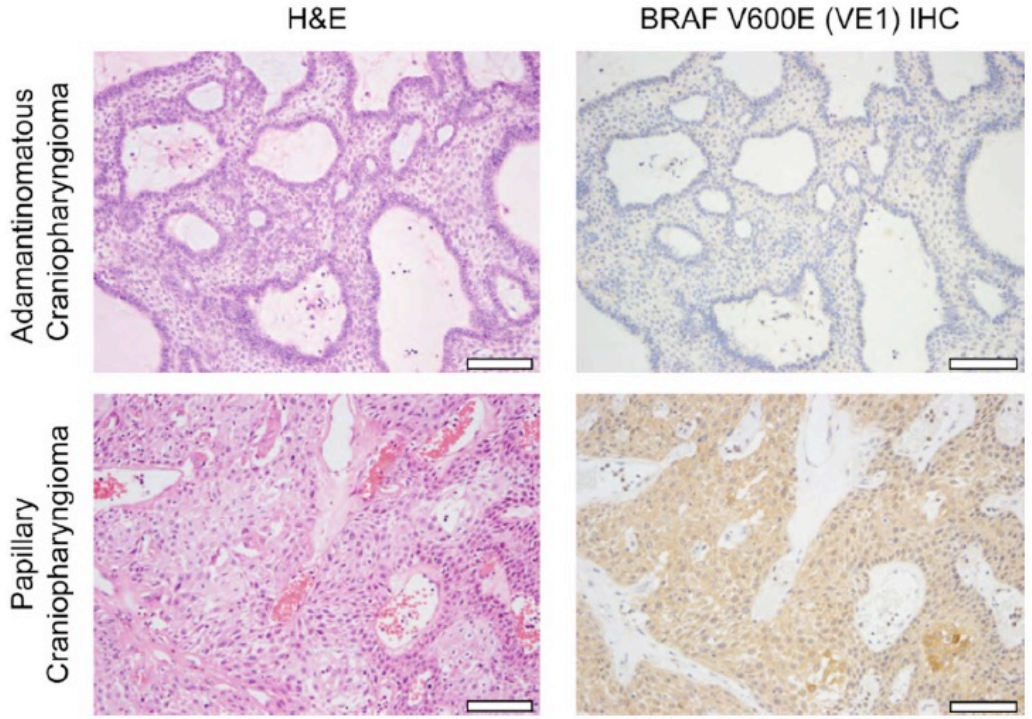
NR=not reached. *Six deaths among 13 patients. †Eight deaths among 22 patients.

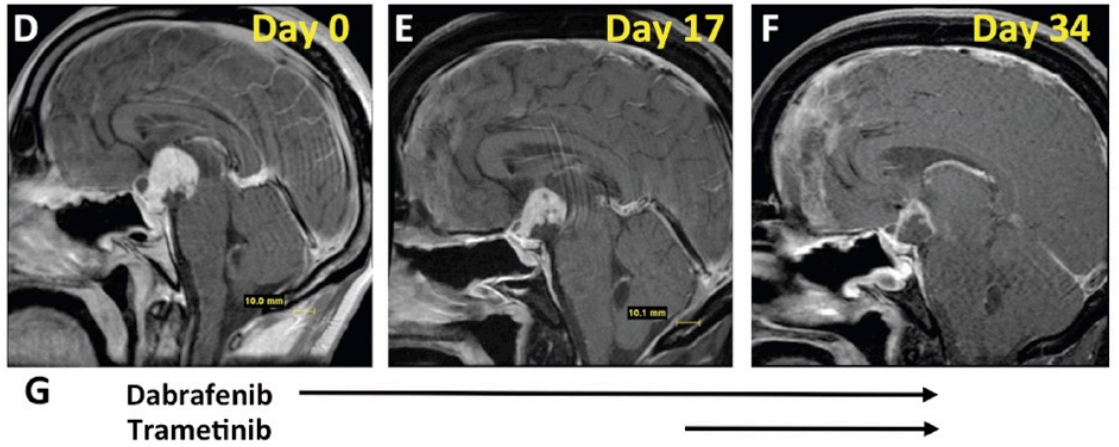
Table 3: Post-hoc subgroup analysis of the high-grade glioma cohort

Craniopharyngioma: mBRAF









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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

BRAF–MEK Inhibition in Newly Diagnosed Papillary Craniopharyngiomas

P.K. Brastianos, E. Twohy, S. Geyer, E.R. Gerstner, T.J. Kaufmann, S. Tabrizi, B. Kabat, J. Thierauf, M.W. Ruff, D.A. Bota, D.A. Reardon, A.L. Cohen, M.I. De La Fuente, G.J. Lesser, J. Campian, P.K. Agarwalla, P. Kumthekar, B. Mann, S. Vora, M. Knopp, A.J. Iafrate, W.T. Curry, Jr., D.P. Cahill, H.A. Shih, P.D. Brown, S. Santagata, F.G. Barker II, and E. Galanis

Table 2. Objective Response at 4 Months.*

Assessment	Value (N=16)
Volumetric response according to central radiologic review	
Complete or partial response — no. (%)	15 (94)
95% confidence interval	70–100
Nonresponse — no. (%)	1 (6)
Bidimensional response according to local radiologic review	
Complete or partial response — no. (%)	15 (94)
95% confidence interval	70–100
Nonresponse — no. (%)	1 (6)

* The primary end point of volumetric response was determined with the use of volumetric measurement data from the first four cycles of BRAF–MEK inhibitor combination therapy. Bidimensional measurements of lesions were used locally to assess the objective response according to modified Response Assessment in Neuro-oncology (RANO) guidelines.

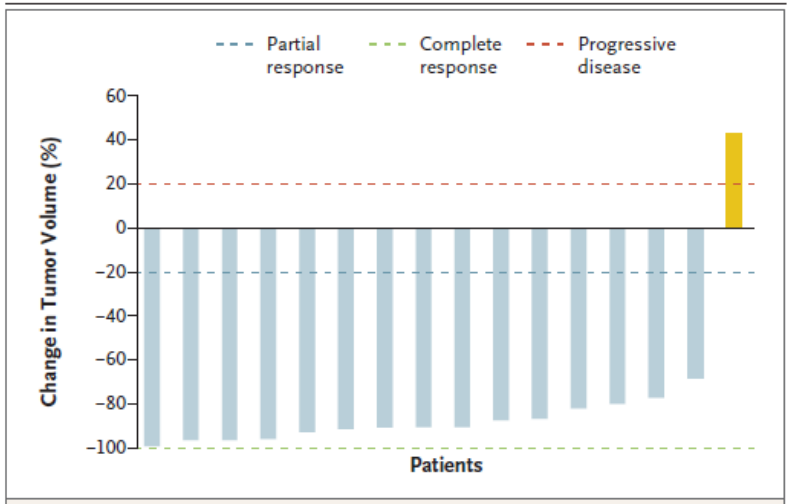
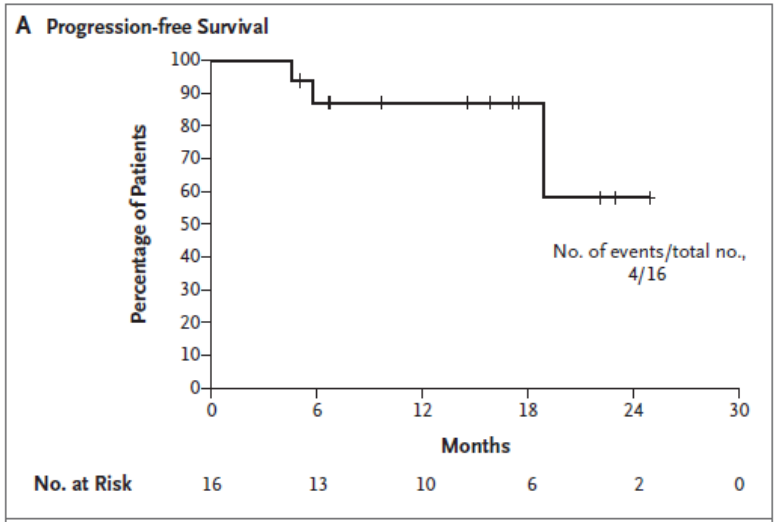
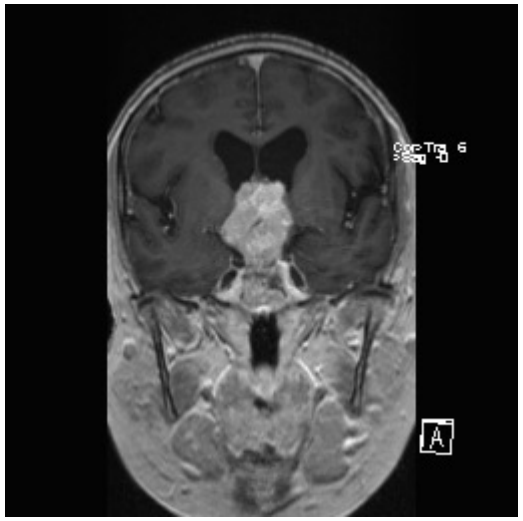


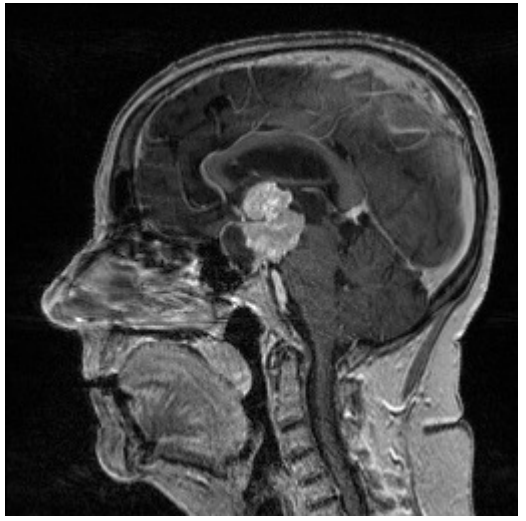
Figure 1. Change in Tumor Volume from Baseline.
The blue bars indicate the 15 patients with papillary craniopharyngiomas who had a partial response to vemurafenib–cobimetinib therapy. The yellow bar indicates 1 patient who received only 8 days of therapy before withdrawing because of toxic effects. The horizontal dashed lines indicate the corresponding measures for each type of response.



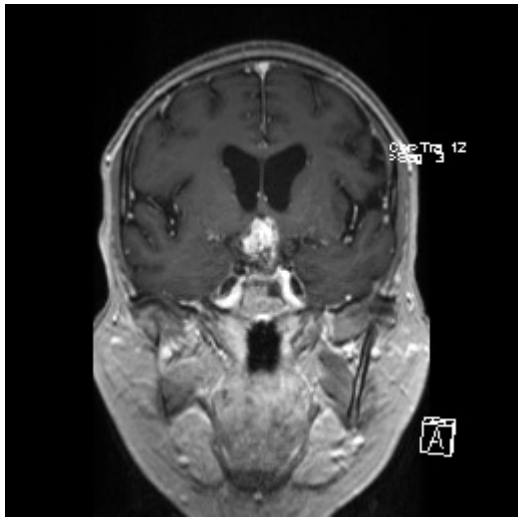
Response of a Papillary Craniopharyngioma With a BRAF V600E Mutation After 2 Months of Vem/Cobi

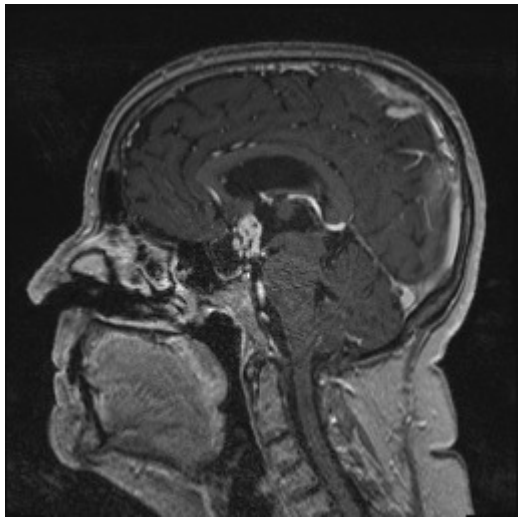
Baseline



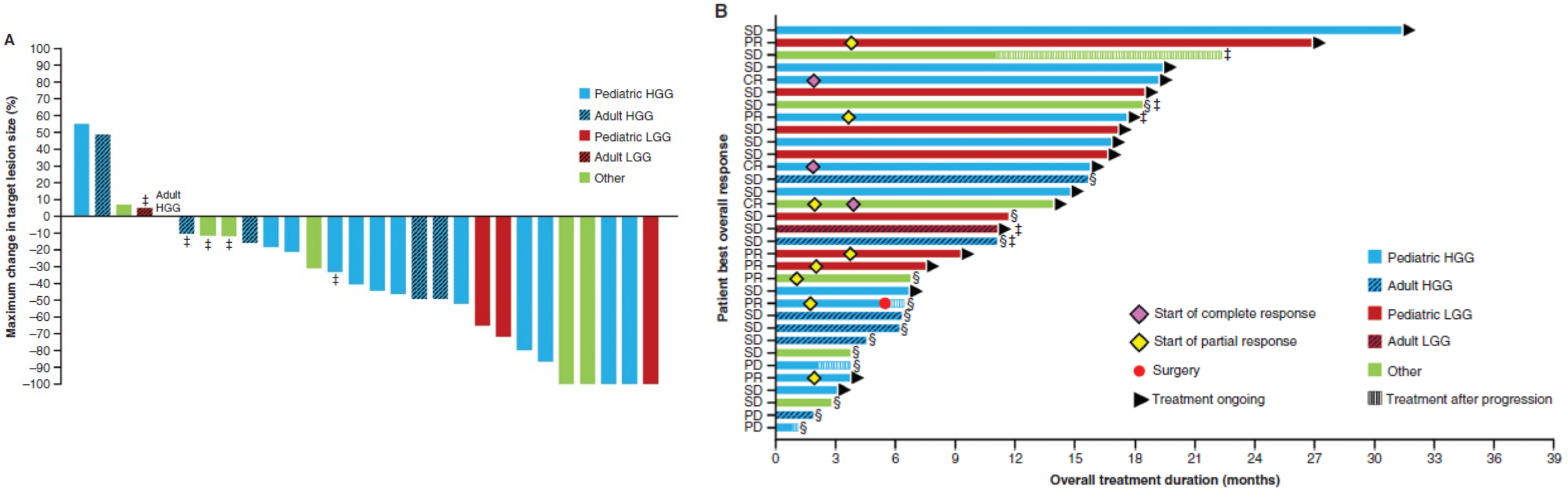


Following 2 months of Tx





Larotrectinib in TRK Fusion-Positive CNS Tumors



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BELIEVE