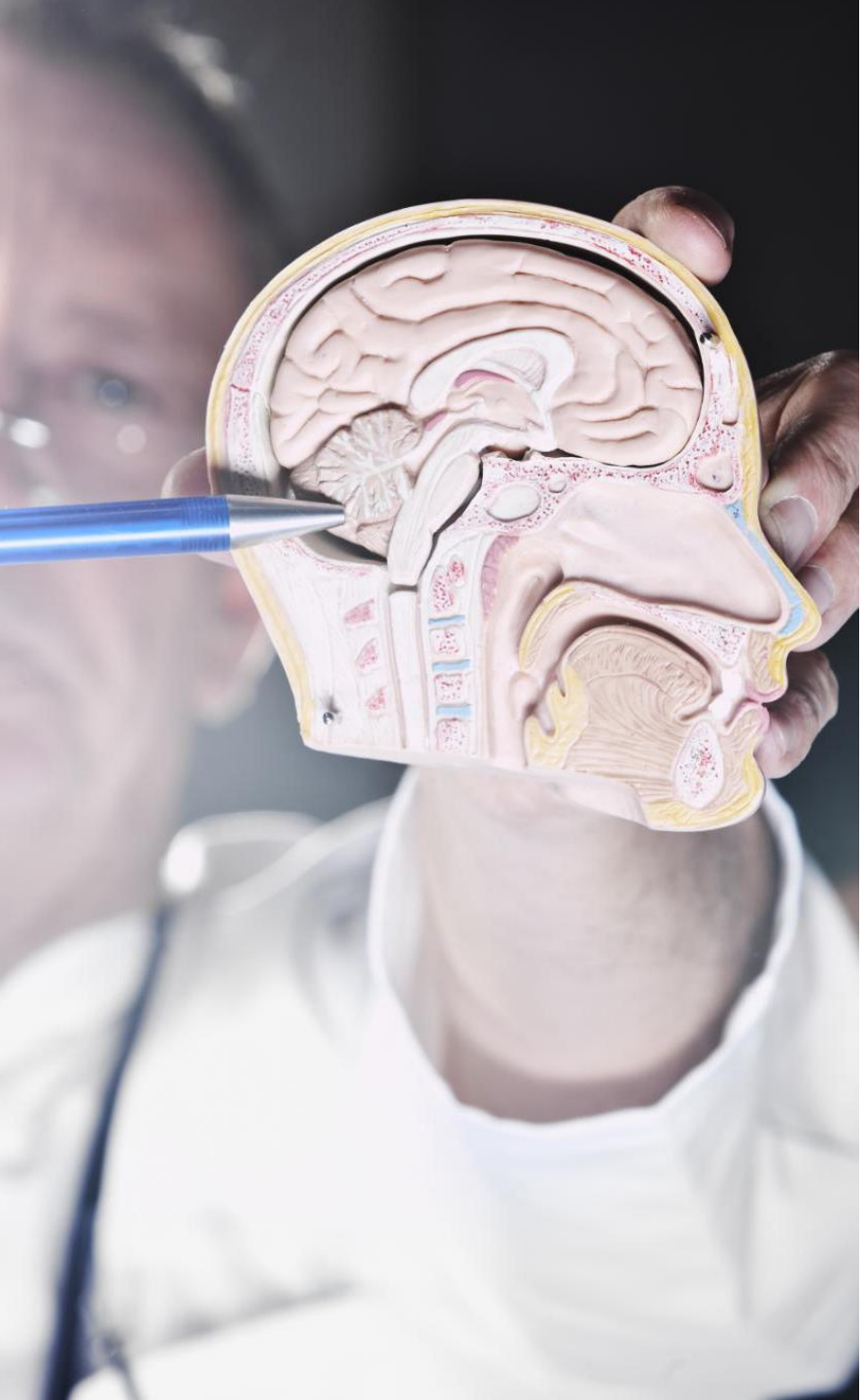
NEURO-ONCOLOGY: THE LATEST ADVANCEMENTS

Annick Desjardins, MD, FRCPC
Professor of Neurosurgery and Neurology
Director of Clinical Research

The Preston Robert Tisch Brain Tumor Center

DISCLOSURES

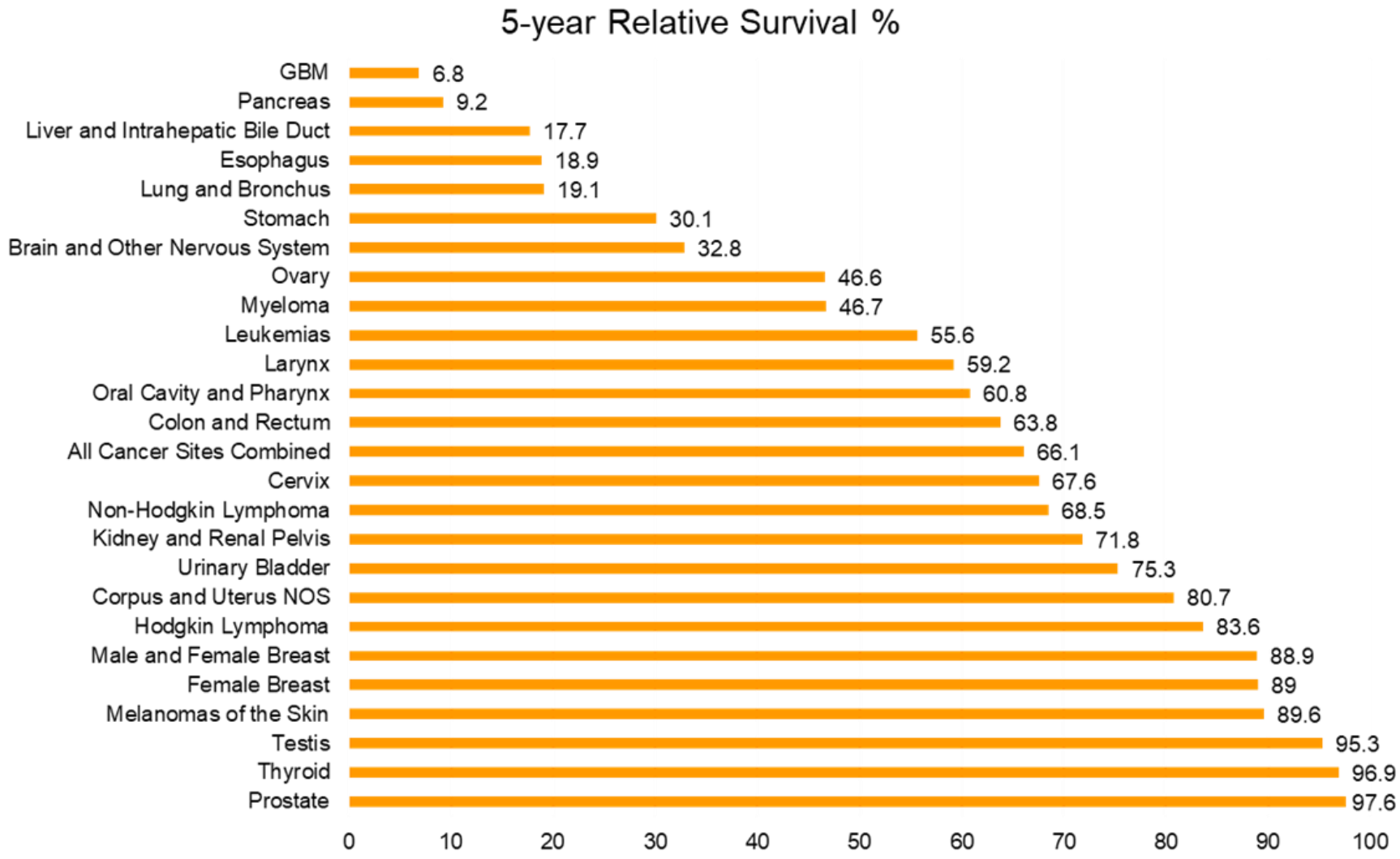
- **Consulting Fee (e.g., Advisory Board)**
  - Biodexa Pharmaceuticals PLC
  - Orbus Therapeutics, Inc
- **Contracted Research (Principal Investigators must provide information, even if received by the institution)**
  - Orbus Therapeutics, Inc
  - Biodexa Pharmaceuticals PLC
  - Exvade Bioscience Inc
- **Speakers' Bureau**
  - Chimerix Inc
- **Stock Option Holder (Individual stocks/Stock options; diversified mutual funds do not need to be disclosed)**
  - Istari Oncology



LEARNING OBJECTIVES

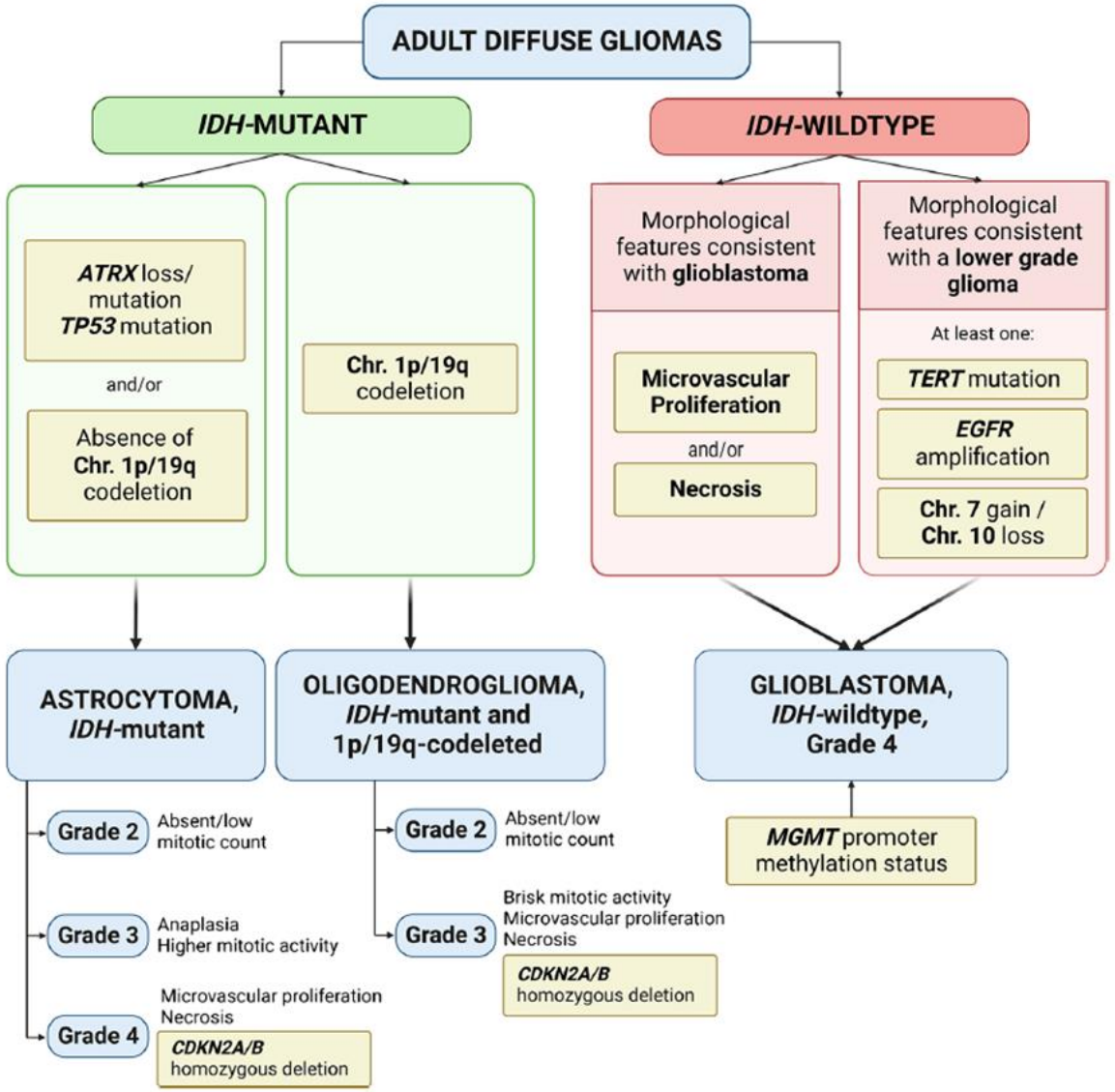
- **Identify the impact of IDH mutation on the development of the 2021 WHO Classification in Brain Tumor**
- **Describe impact of IDH directed therapy in grade 2 IDH mutated gliomas**
- **Describe standard of care for glioblastoma patients**
- **Discuss the challenges in treating primary brain tumors**

5-YEAR SURVIVAL % BY CANCER TYPE, ALL RACES, BOTH SEXES



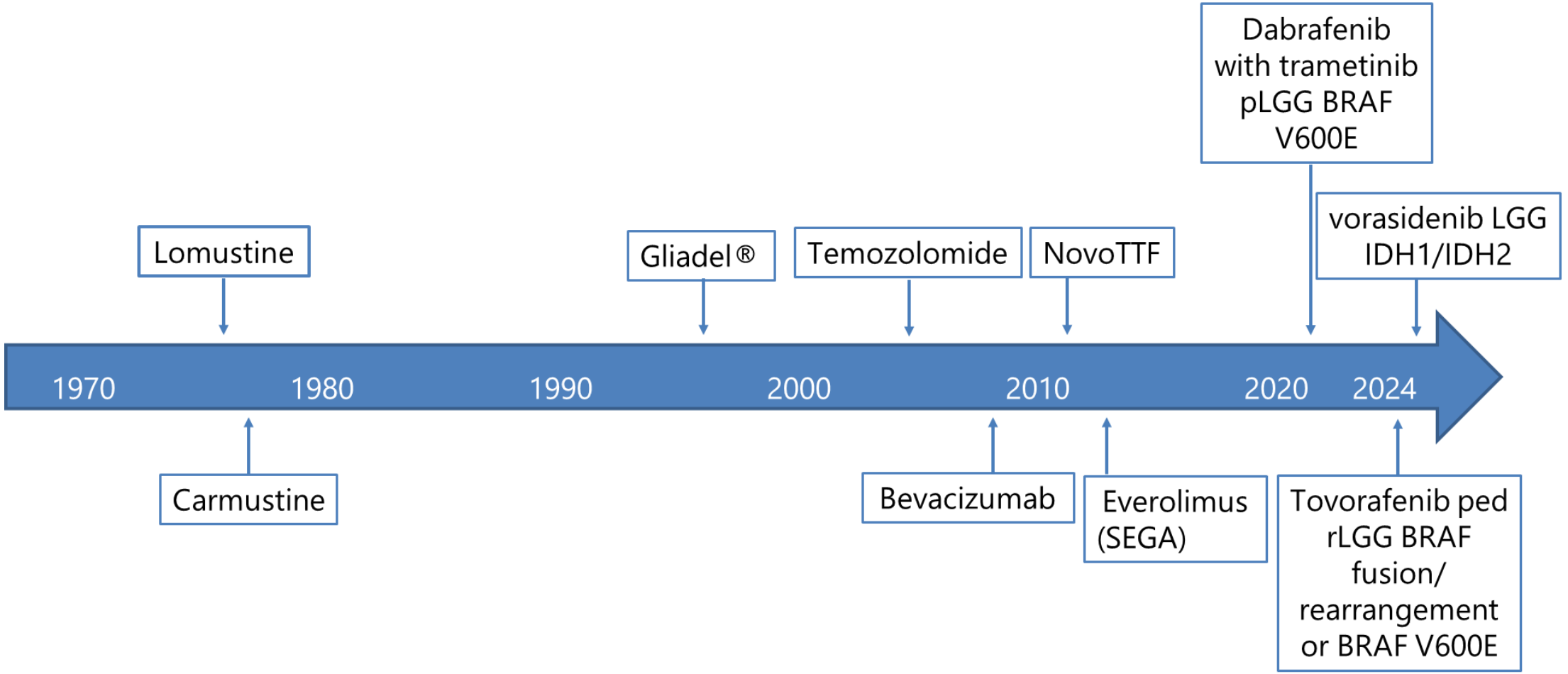
www.cdc.gov/cancer/dataviz, June 2019.
Ostrom, et al. Neur Onc 21(S5), 1–100, 2019.

2021 CLASSIFICATION IN BRAIN TUMOR

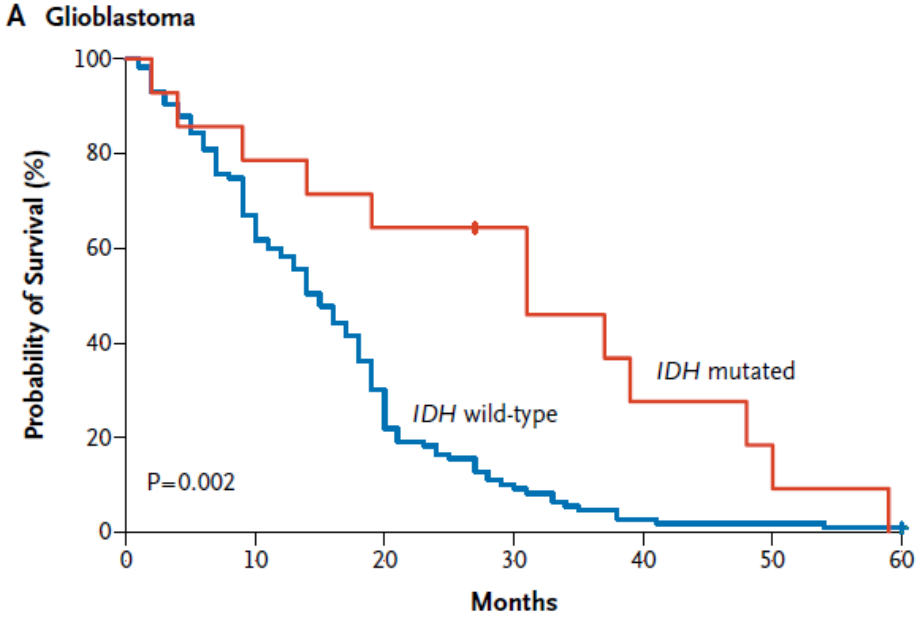


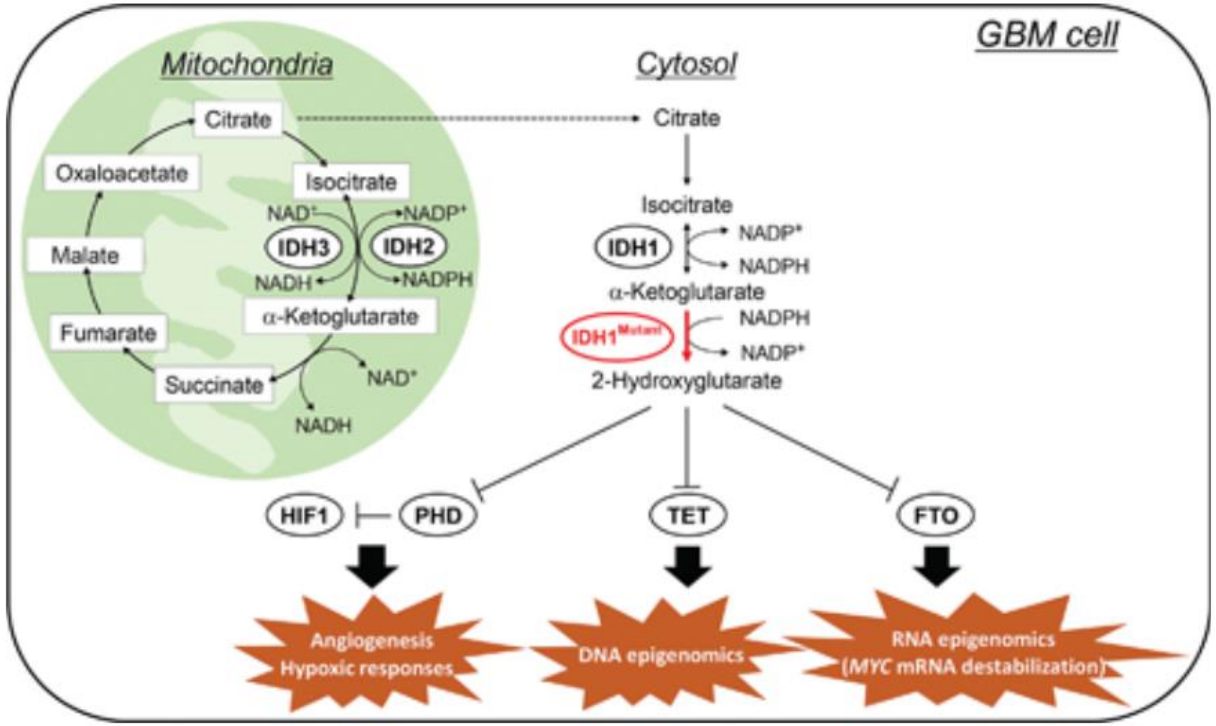
Bertero et al. Virchows Archiv 484:181–194, 2024.

FDA APPROVALS IN PRIMARY BRAIN TUMORS



1ST DESCRIPTION OF IMPACT OF IDH1 AND IDH2 MUTATIONS IN GLIOMAS – EXAMPLE IN PRIOR HISTOLOGIC DIAGNOSIS OF GLIOBLASTOMA

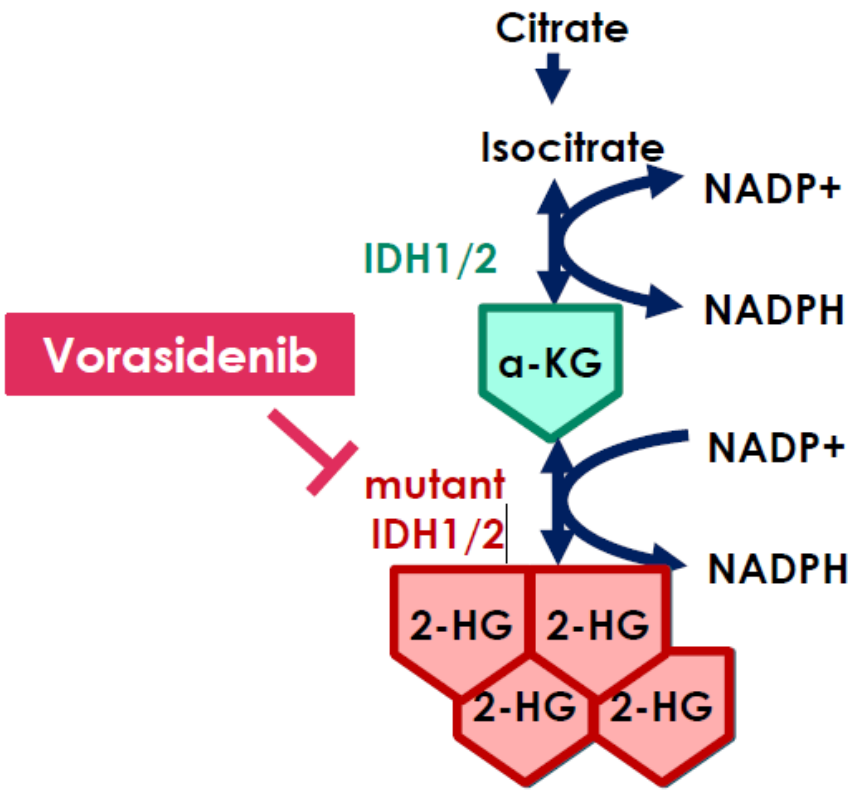




Yan H et al. N Engl J Med. 360(8):765-73, 2009.
Garrett M et al. Exon Publications; Chapter 4. PMID: 34038049.

VORASIDENIB

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



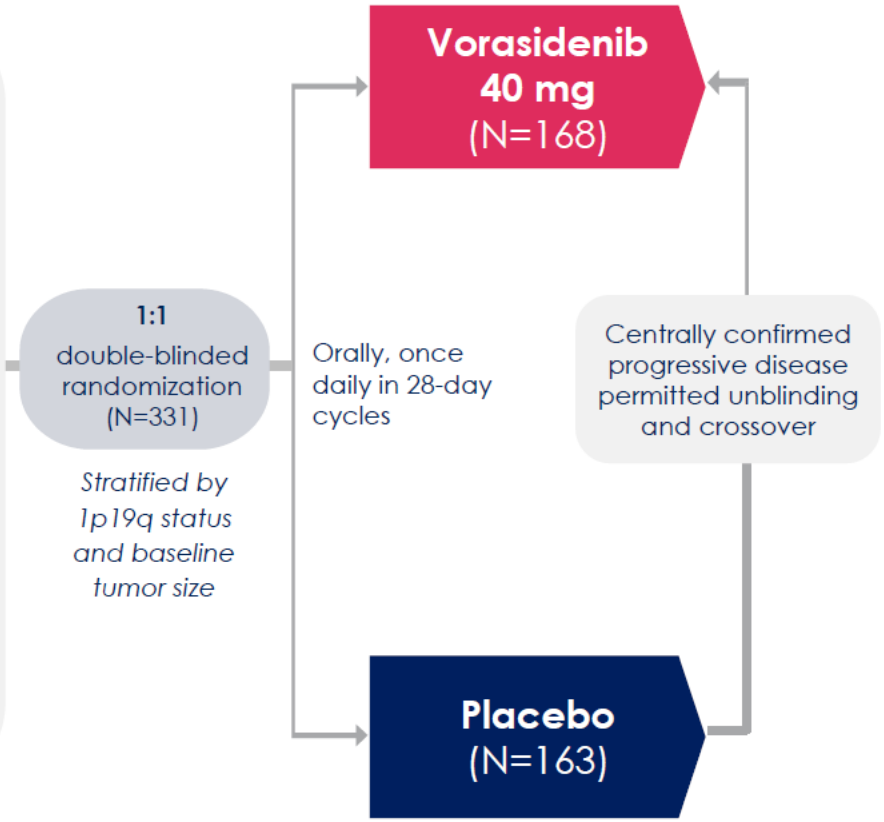
Competitive inhibition of a-KG-dependent enzymes

Mellinghoff IK et al. Nat Med 29:615–22, 2023.

INvestigating vorasiDenIb in GliOma (NCT04164901)

Key eligibility criteria

- ≥12 years of age
- mIDH1/2* grade 2 oligodendroglioma or astrocytoma per 2016 WHO guidelines
- ≥1 prior surgery for glioma
- Measurable non-enhancing disease (≥1 target lesion measuring ≥1 cm × ≥1 cm), confirmed by BIRC
- Not in need of immediate chemotherapy or radiotherapy per investigator assessment



Endpoints included

Primary

- PFS per BIRC

Key secondary

- TTNI

Secondary

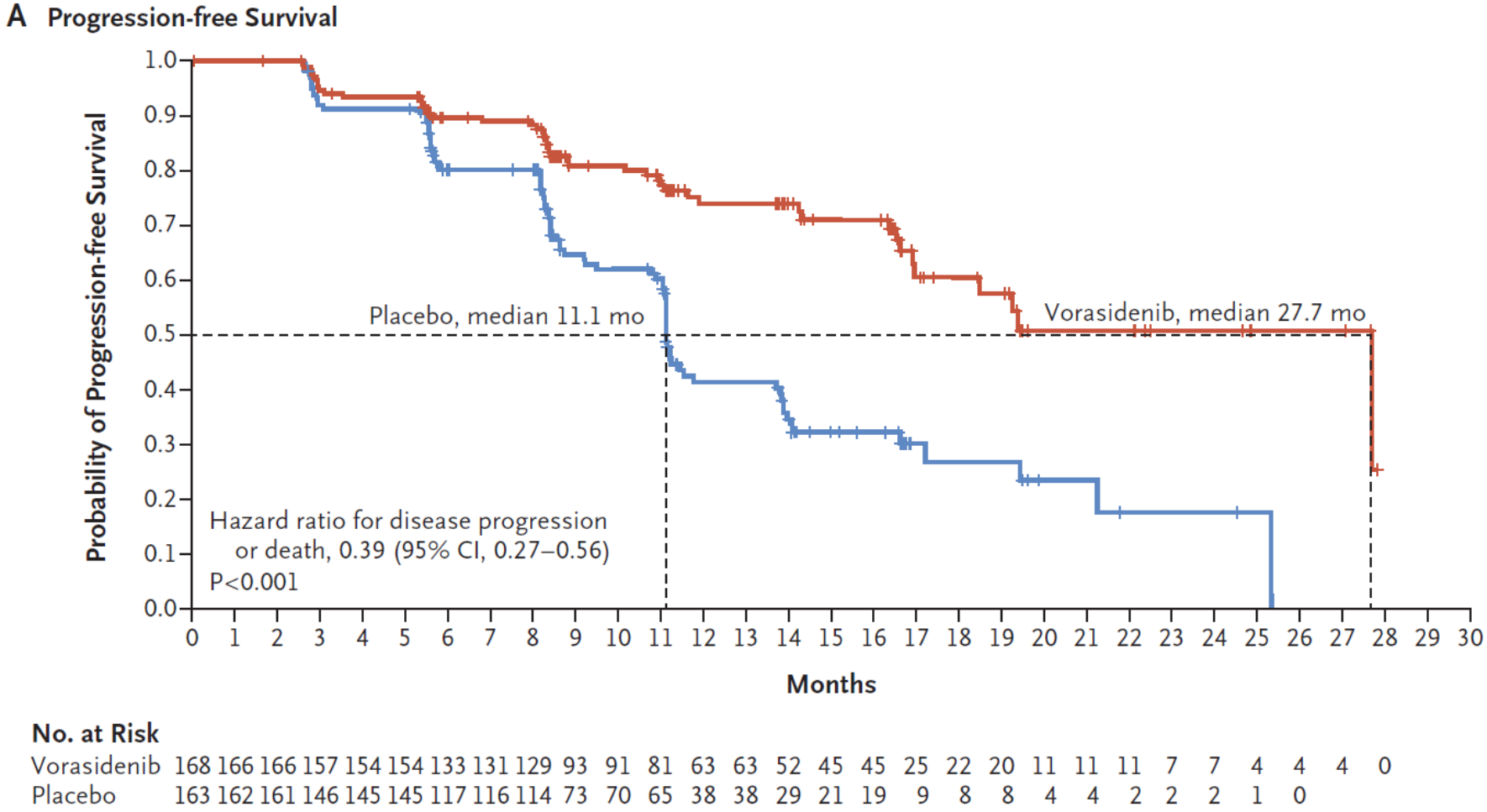
- TGR by volume
- Safety
- HRQoL (FACT-Br)

Exploratory

- Pre- and post-crossover TGR
- Pre- and post-treatment TGR
- Neurocognitive function
- Seizure activity

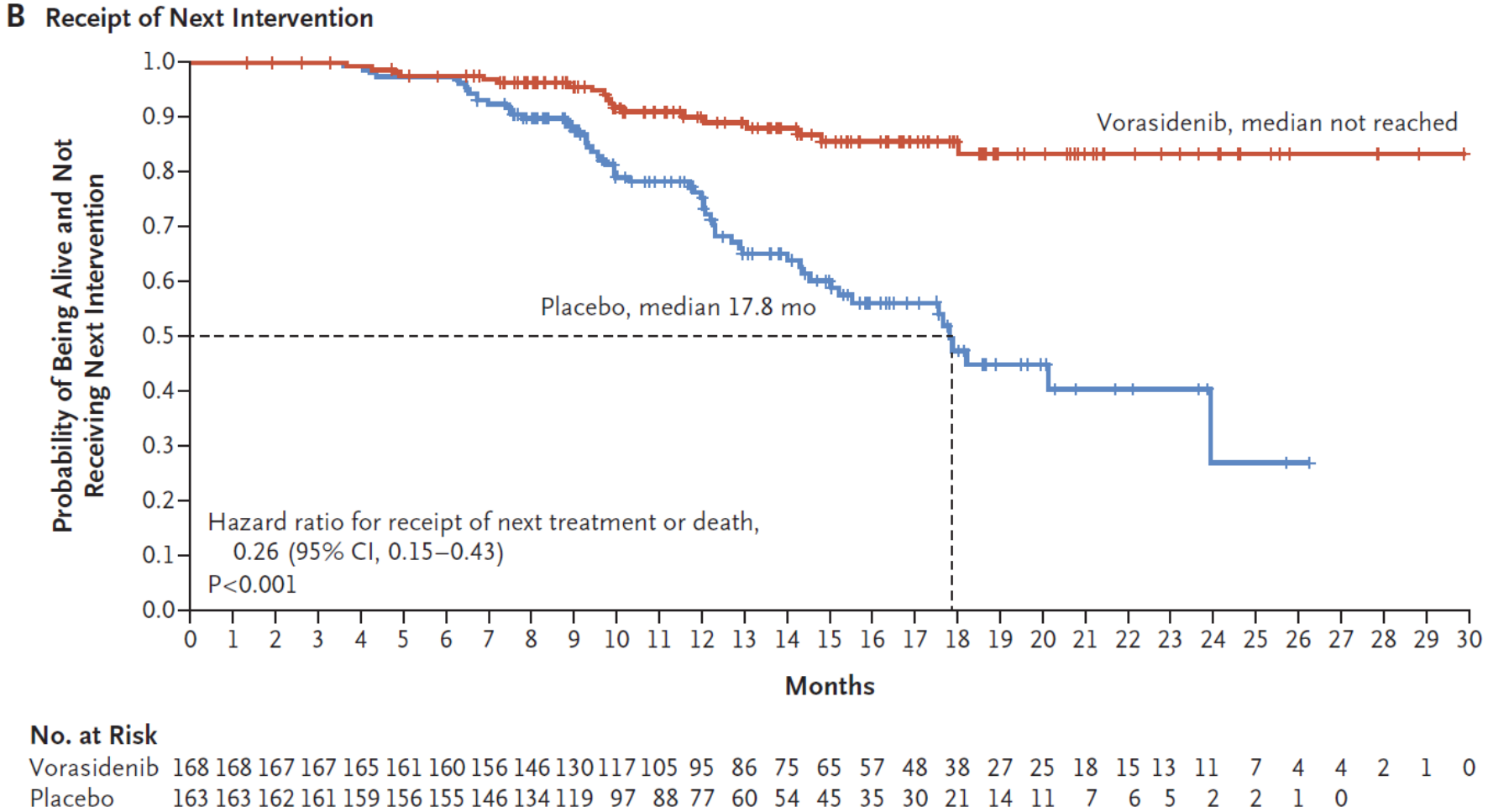
Mellinghoff IK et al. N Engl J Med. 389(7):589-601, 2023.

VORASIDENIB PROGRESSION-FREE SURVIVAL



Mellinghoff IK et al. N Engl J Med. 389(7):589-601, 2023.

VORASIDENIB TIME TO NEXT INTERVENTION



Mellinghoff IK et al. N Engl J Med. 389(7):589-601, 2023.

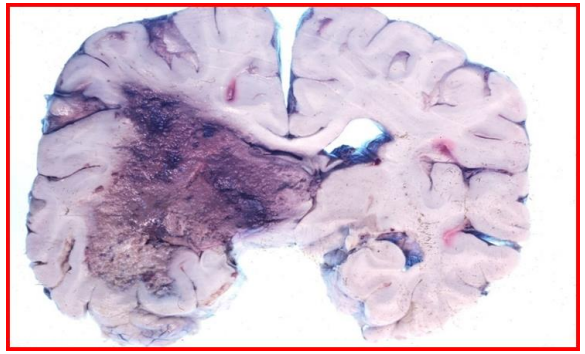
VORASIDENIB ADVERSE EVENTS

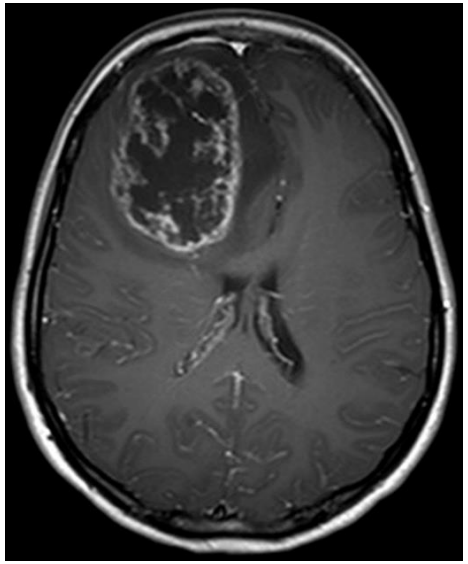
Table 2. Most Common Adverse Events (Safety Analysis Set).*

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

Mellinghoff IK et al. N Engl J Med. 389(7):589-601, 2023.

GLIOBLASTOMA

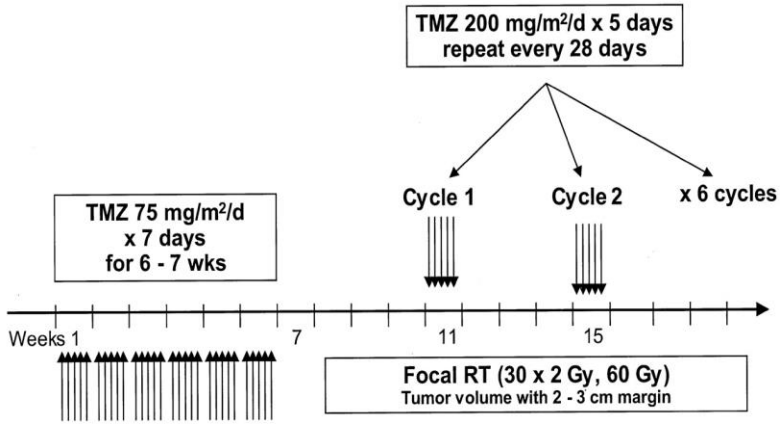


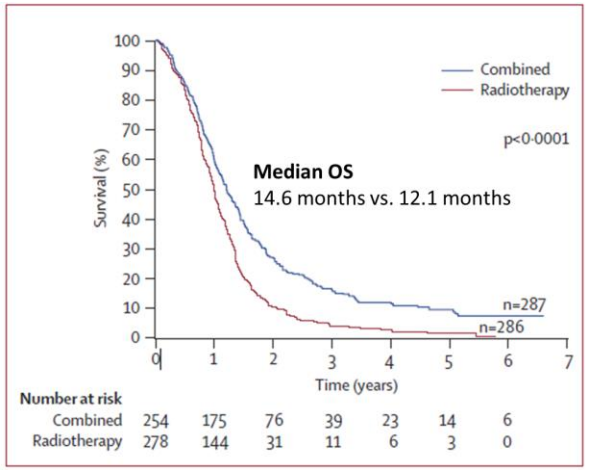


- Grade 4 malignant glioma
- Most malignant, invasive, difficult-to-treat primary brain tumor
- Frequency: most common in older adults
- Peak age: 55–65 years
- Recurrence: rapid growth
- May double every 10 days
- Median survival: ~ 14-21 months

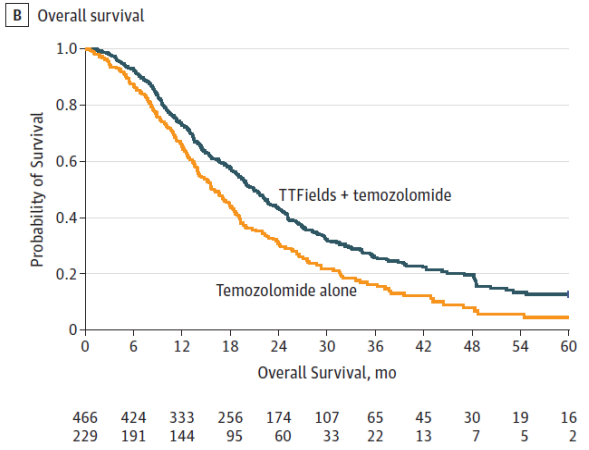
Stupp R et al. N Engl J Med. 352(10):987-96, 2005.
Stupp R et al. JAMA. 318(23):2306-2316, 2017.

STANDARD OF CARE





Radiation therapy with temozolomide vs. radiation only



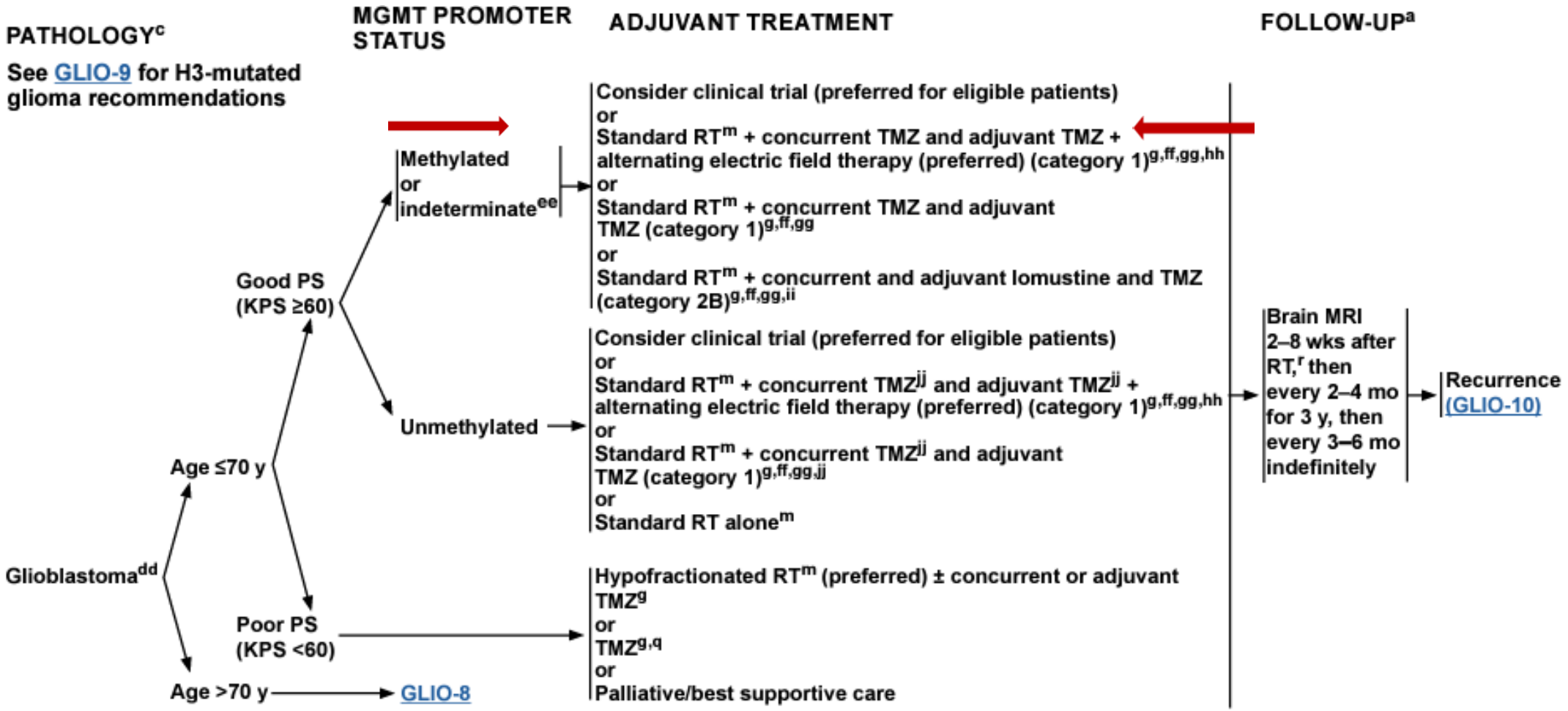
TTFields + Temozolomide vs. temozolomide only

Stupp R et al. N Engl J Med. 352(10):987-96, 2005.
Stupp R et al. JAMA. 318(23):2306-2316, 2017.

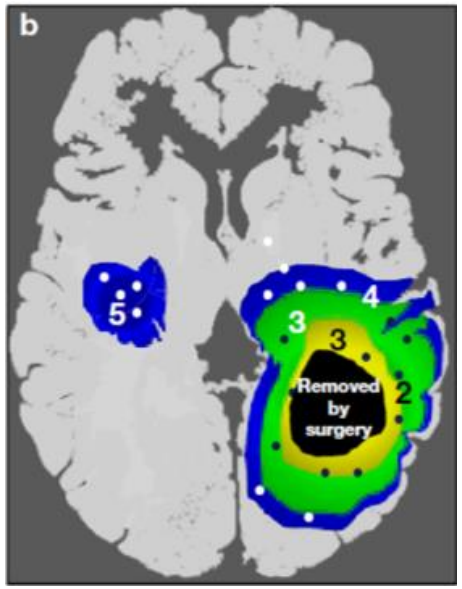
PUBLISHED TRIALS RECURRENT GLIOBLASTOMA (2005-2018)

Article	Therapy/Agent(s)	Tot. N	Survival				
			12-mo	24-mo	36-mo	60-mo	Median
Reardon 2005	Gleevec+Hydroxyurea	33	NA	NA	NA	NA	**11.3**
Vredenburgh 2007	Bevacizumab+Irinotecan	35	NA	NA	NA	NA	**9.7**
Reardon 2008	Cilengitide (500mg)	41	NA	NA	NA	NA	**6.5**
Reardon 2008	Cilengitide (2,000mg)	40	NA	NA	NA	NA	**9.9**
Quinn 2009	Gliadel+O(6)benzylguanine	52	47.0%	10.0%	NA	NA	**11.6**
Quinn 2009	TMZ+O(6)benzylguanine	34	NA	NA	NA	NA	**4.5**
Friedman 2009	Bevacizumab	85	2.4%	0.0%	0.0%	0.0%	**9.2**
Friedman 2009	Bevacizumab+Irinotecan	82	9.8%	0.0%	0.0%	0.0%	**8.7**
Kreisl 2009	Bevacizumab+Irinotecan	48	NA	NA	NA	NA	**7.1**
Park 2010	Resection	34	29.4%	8.8%	2.9%	2.9%	**NA**
Park 2010	Resection	109	23.9%	8.3%	3.7%	0.9%	**NA**
Kunwar 2010	Cintredekin Besudotox	183	NA	NA	NA	NA	**9.1**
Kunwar 2010	Gliadel	93	NA	NA	NA	NA	**8.8**
Wick 2010	Enzastaurine	174	4.6%	NA	NA	NA	**6.6**
Wick 2010	Lomustine	92	10.9%	NA	NA	NA	**7.1**
Pope 2012	Bevacizumab	97	44.3%	16.5%	NA	NA	**NA**
Stupp 2012	Tumor Treating Fields	120	20.0%	7.5%	3.3%	NA	**6.6**
Stupp 2012	Active Chemotherapy	117	18.8%	5.1%	0.9%	NA	**6.0**
Desjardins 2012	TMZ+Bevacizumab	32	31.3%	NA	NA	NA	**8.5**
Batchelor 2013	Cediranib	118	15.3%	NA	NA	NA	**8.0**
Batchelor 2013	Cediranib+Lomustine	122	16.3%	NA	NA	NA	**9.4**
Batchelor 2013	Lomustine	56	13.8%	NA	NA	NA	**9.8**
Taal 2014	Bevacizumab	50	26.0%	NA	NA	NA	**8.0**
Taal 2014	Lomustine	46	30.4%	NA	NA	NA	**8.0**
Taal 2014	Bevacizumab+Lomustine	44	45.5%	NA	NA	NA	**11.0**
Reardon 2017	Nivolumab+Ipilimumab	182	42.0%	NA	NA	NA	**9.8**
Reardon 2017	Bevacizumab	165	42.0%	NA	NA	NA	**10.0**
Duerinck 2018	Axitinib	50	NA	NA	NA	NA	**6.7**
Duerinck 2018	Axitinib+Lomustine	29	NA	NA	NA	NA	**6.3**
Omuro 2018	Nivolumab+Ipilimumab	20	30.0%	15.0%	0.0%	0.0%	**7.3**
Ghiaseddin 2018	Bevacizumab+Vorinost	40	NA	NA	NA	NA	**10.4**
Lang 2018	DNX-2401 (group A)	25	36.0%	20.0%	20.0%	NA	**NA**
Lang 2018	DNX-2401 (group B)	12	58.0%	8.0%	0.0%	0.0%	**NA**
Desjardins 2018	PVSRIPO	61	54.0%	21.0%	21.0%	21.0%	**12.5**

NCCN GUIDELINES – NEWLY DIAGNOSED GLIOBLASTOMA



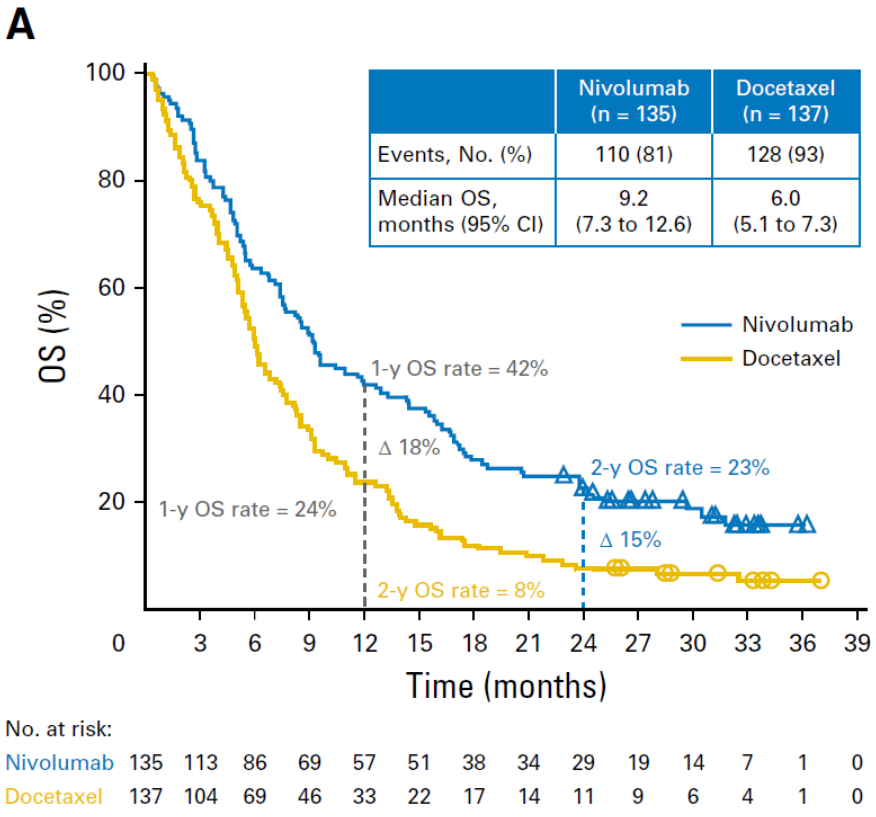
WHY IS IT SO HARD TO TREAT PRIMARY BRAIN TUMORS?



- Diffuse tumor infiltration in the brain
  - Clean margins impossible at time of resection
- Blood-brain barrier and efflux pump proteins
- Highly heterogeneous tumors
- Gliomas are generally regarded as “cold” tumors
- Tumor/treatment impact on the neurologic functioning of our patients

CHECKPOINT INHIBITORS NSCLC VS GBM

NSCLC

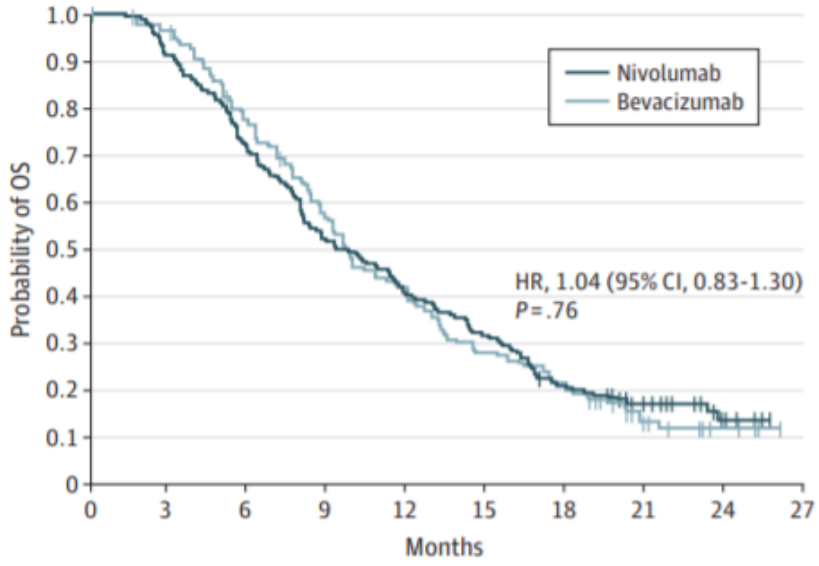


Horn L et al. J Clin Oncol 35(35):3924-3933, 2017.

GBM

A Probability of OS by intervention

Intervention	Events, No.	Median OS (95% CI), months	OS Rate (95% CI), %		
			6 Months	12 Months	18 Months
Nivolumab	154	9.8 (8.2-11.8)	72.3 (65.2-78.2)	41.8 (34.7-48.8)	21.7 (16.1-27.9)
Bevacizumab	147	10.0 (9.0-11.8)	78.2 (71.2-83.6)	42.0 (34.6-49.3)	21.6 (15.8-28.0)



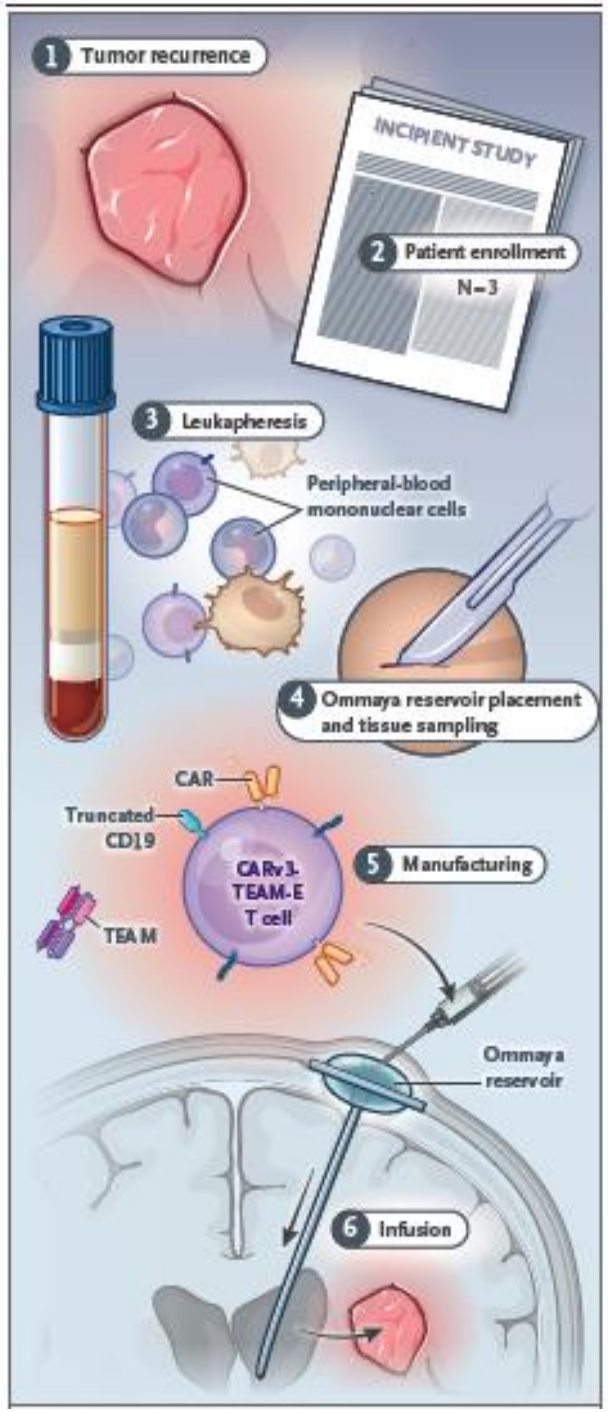
No. at risk

Nivolumab	184	168	133	96	77	59	39	24	9	0
Bevacizumab	185	169	135	99	72	48	37	14	5	0

Reardon et al. JAMA 6(7): 1003-1010, 2020.

WHY ARE CHECKPOINT INHIBITORS FAILING?

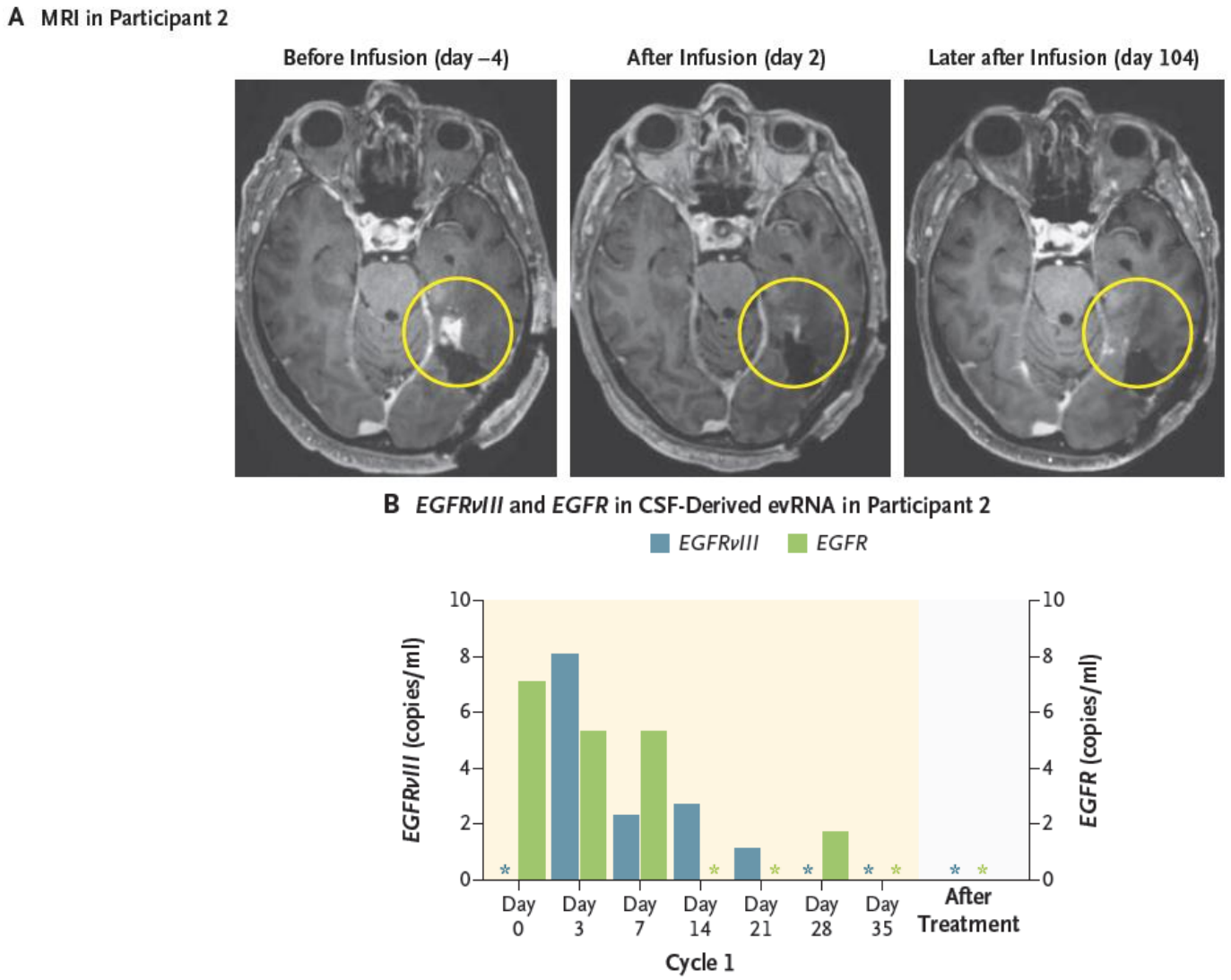
- Gliomas are generally regarded as “cold” tumors
- Intratumoral immune-activation is suppressed
- Underlying mechanisms are diverse:
  - Immuno-inhibitory function of the blood–brain barrier
  - Paucity of specific antigens (neoantigens)
  - Immunosuppressive glioma microenvironment
  - Bone marrow sequestration of immune effectors from the location of the tumor in the brain



INTRAVENTRICULAR CARV3-TEAM-E T CELLS IN RECURRENT GLIOBLASTOMA

Choi BD et al. N Engl J Med 390(14):1290-1298, 2024.

INTRAVENTRICULAR CARV3-TEAM-E T CELLS IN RECURRENT GLIOBLASTOMA



Choi BD et al. N Engl J Med 390(14):1290-1298, 2024.

LERAPOLTUREV (PREVIOUSLY PVSRIPO)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

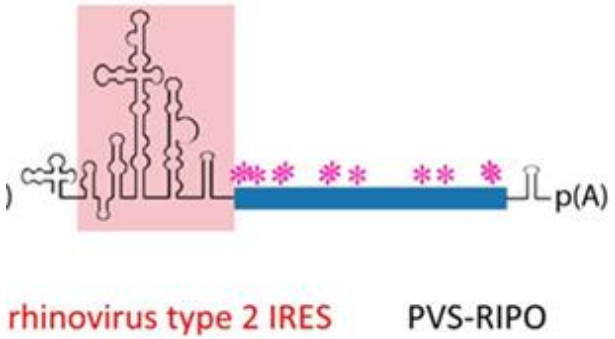
Recurrent Glioblastoma Treated with Recombinant Poliovirus

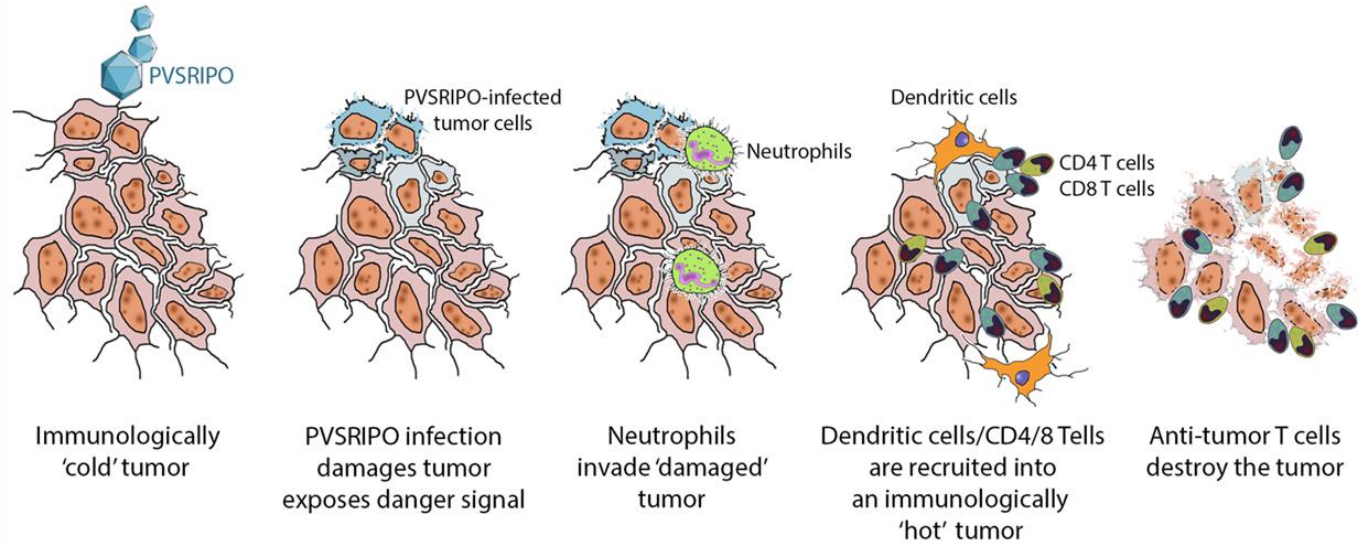
Annick Desjardins, M.D., Matthias Gromeier, M.D., James E. Herndon II, Ph.D., Nike Beaubier, M.D., Dani P. Bolognesi, Ph.D., Allan H. Friedman, M.D., Henry S. Friedman, M.D., Frances McSherry, M.A., Andrea M. Muscat, B.Sc., Smita Nair, Ph.D., Katherine B. Peters, M.D., Ph.D., Dina Randazzo, D.O., John 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.

Desjardins*, Gromeier* et al., N Engl J Med. 379(2):150-161, 2018.

LERAPOLTUREV: WHY AND HOW TO MAKE POLIO SAFE…

- Targets CD155 (poliovirus receptor)
  - Present on all solid tumor cells
- Sabin type 1 polio vaccine, where a critical piece of genetic information has been replaced
- Lerapolturev cannot harm or kill normal brain cells
- Lerapolturev is CNS-incompetent, but toxic/lethal in cancer cells
- Genetically stable





Desjardins*, Gromeier* et al., N Engl J Med. 379(2):150-161, 2018.

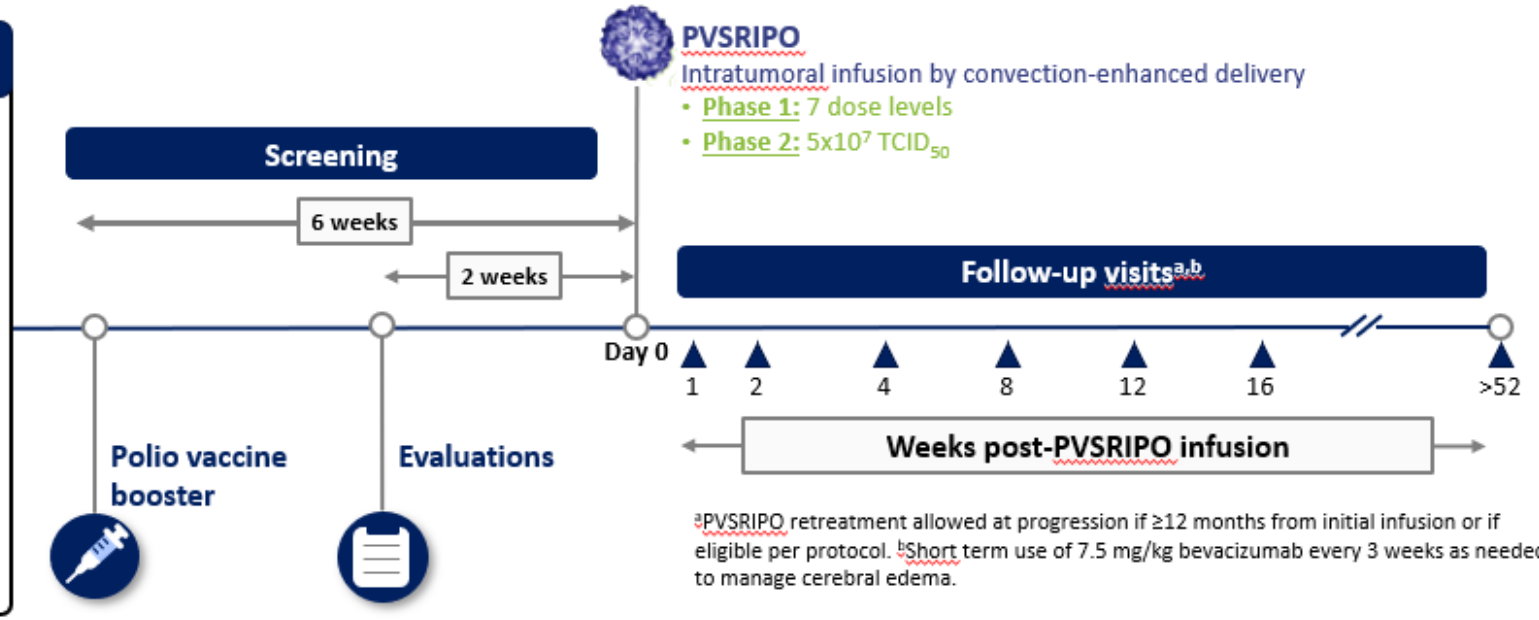
PVSRIPO MONOTHERAPY PHASE 1 AND 2 STUDY DESIGN

PVSRIPO Monotherapy

Phase 1 (NCT01491893): N=61
Phase 2 (NCT02986178): N=120

Key eligibility criteria:

- Recurrent biopsy-proven supratentorial WHO grade IV malignant glioma
- Measurable disease (≥1cm to ≤5.5 cm)
- Age ≥18 years
- KPS ≥70%



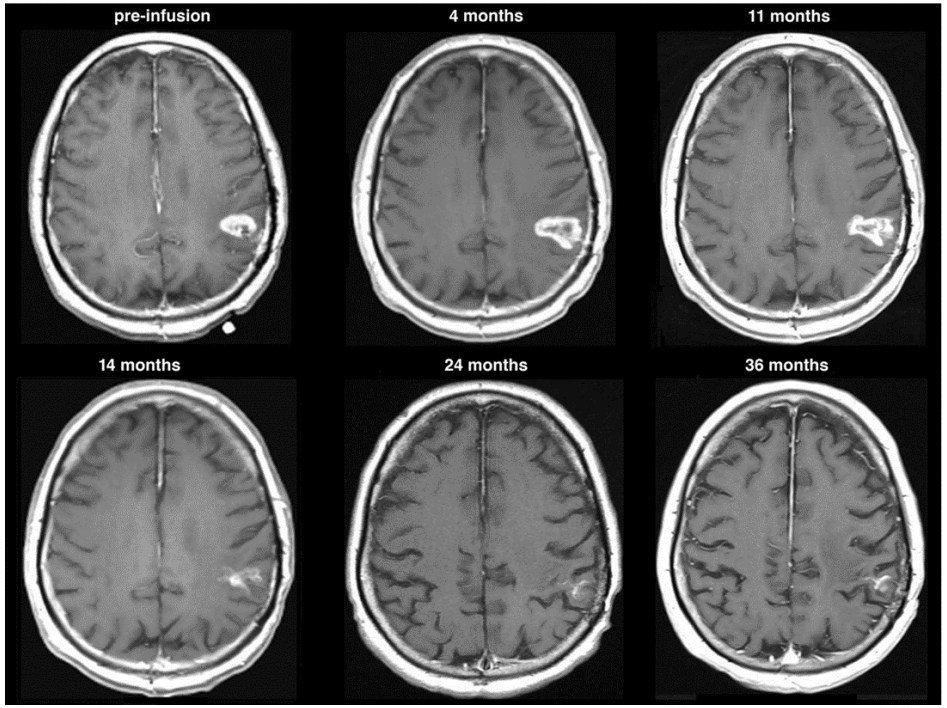
DUKE UNIVERSITY MEDICAL CENTER
MGH 1811 MASSACHUSETTS GENERAL HOSPITAL
BAPTIST MD Anderson Cancer Center
University Hospitals Cleveland Medical Center
UCSF University of California San Francisco
Dana-Farber Cancer Institute

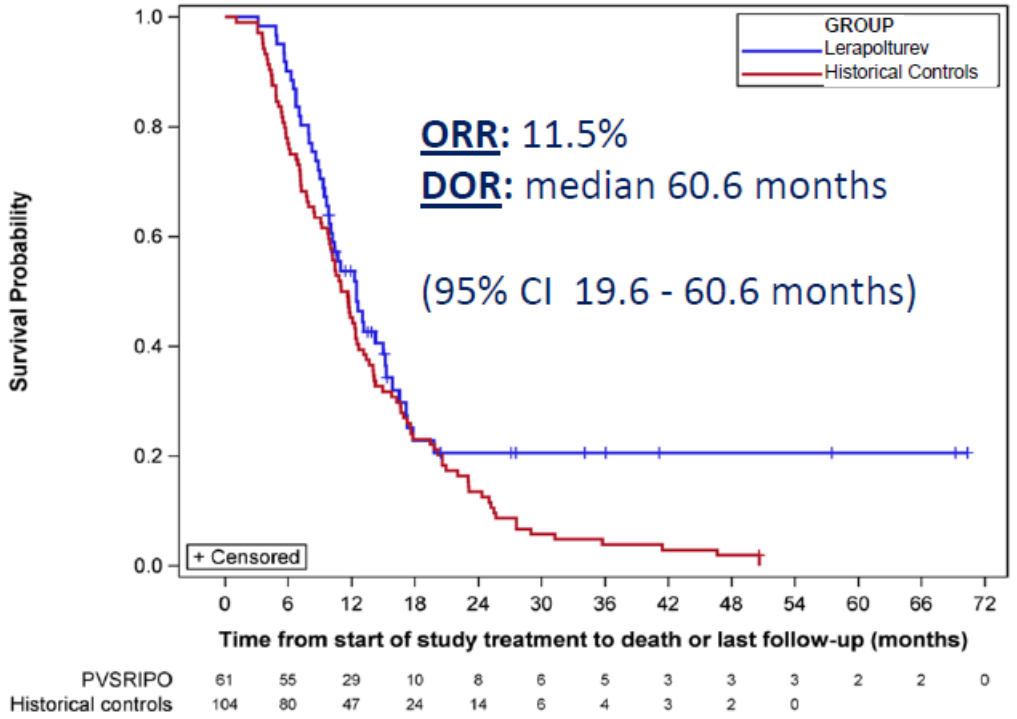
KPS, Karnofsky performance score.

Desjardins et al. Neuro-Oncol. 23(S6):vi97, 2021.

TOXICITY AND EFFICACY

- **No viral neurological toxicity (eg., encephalitis, poliomyelitis)**
- **No systemic toxicity**
- **Side effects in relation to location of tumor in the brain (close to motor strip, speech centers, etc.)**





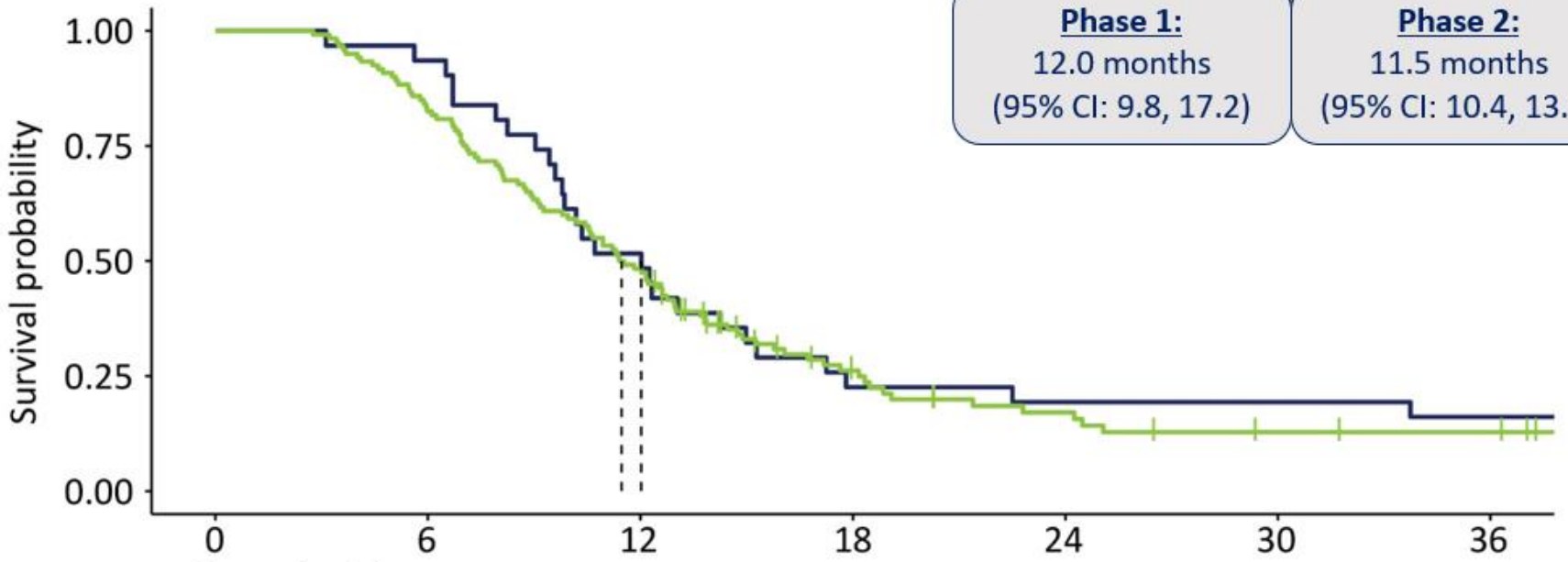
Desjardins*, Gromeier* et al., N Engl J Med. 379(2):150-161, 2018.

OVERALL SURVIVAI RESULTS WERE SIMILAR ACROSS T TWO STUDIES

PVSRIPO RP2D is 5x10^7 TCID$_{50}$/mL

Median Overall Survival

Phase 1:	**Phase 2:**
12.0 months	11.5 months
(95% CI: 9.8, 17.2)	(95% CI: 10.4, 13.0)



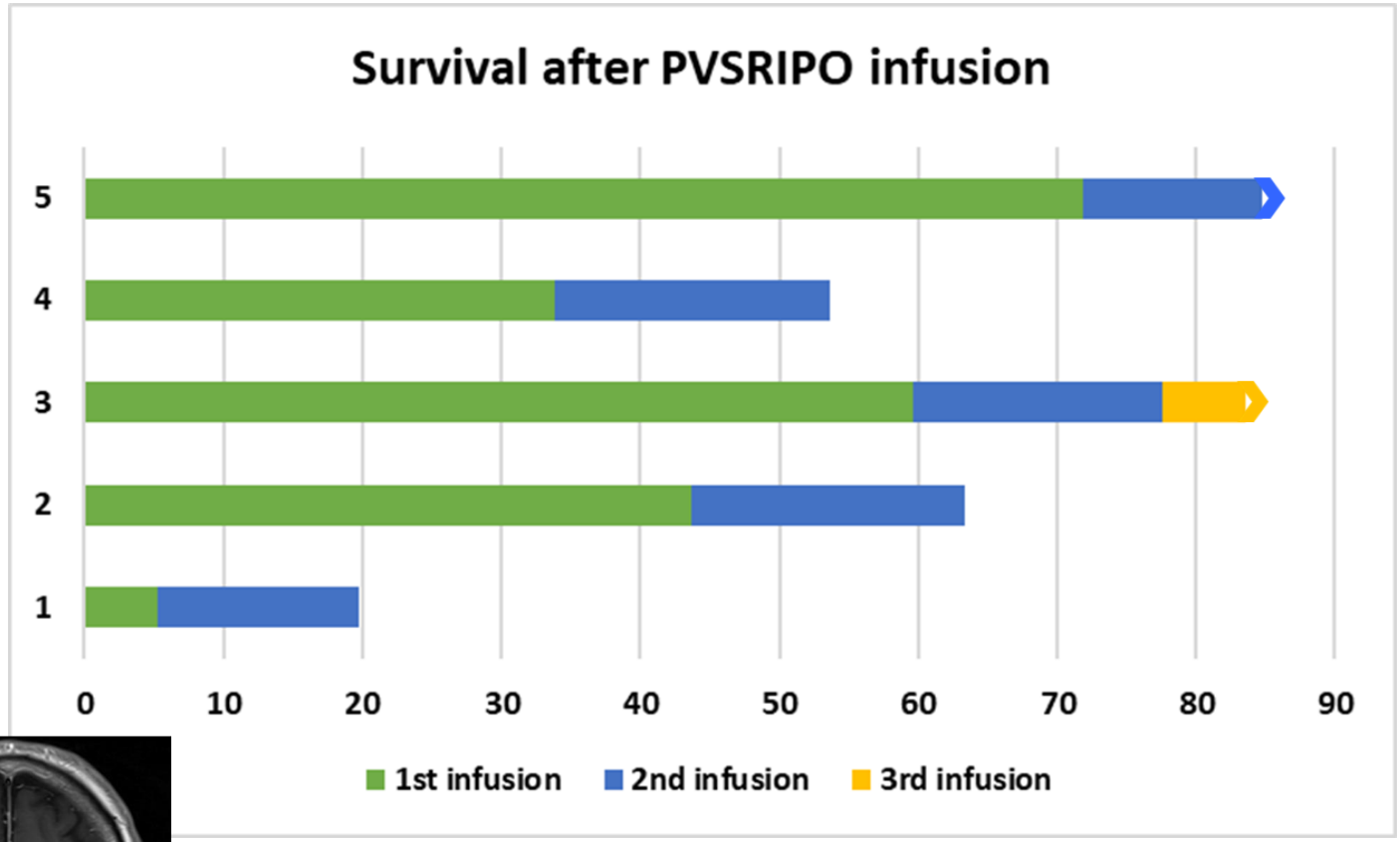
Number at risk, n (%)

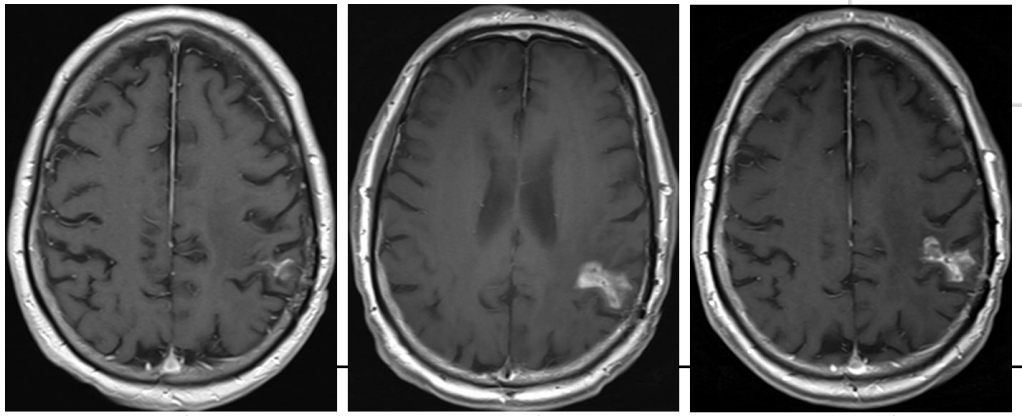
Phase 1	31 (100)	29 (94)	16 (52)	7 (23)	6 (19)	6 (19)	5 (16)
Phase 2	120 (100)	99 (82)	58 (48)	21 (18)	12 (10)	7 (6)	6 (5)

RP2D, recommended phase 2 dose; TCID$_{50}$, 50% tissue-culture infectious dose.

Desjardins et al. Neuro-Oncol. 23(S6):vi97, 2021.

WE CAN SUCCESSFULLY RETREAT PATIENTS





36 months

60 months

70 months
10 months from retreatment

Desjardins et al. J Clin Oncol. 37(15s):101s, 2019.

REPEATED POLIOVIRUS IN MELANOMA PATIENTS

Three injections; day 0, day 21 and day 42

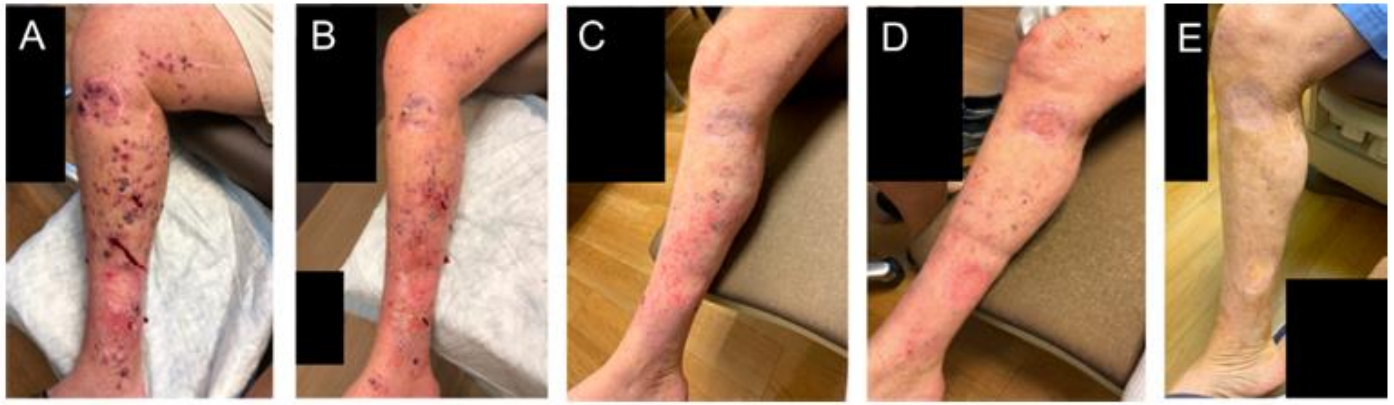
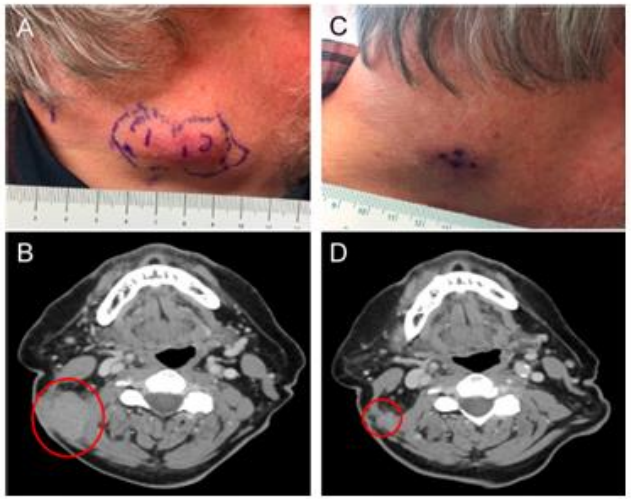


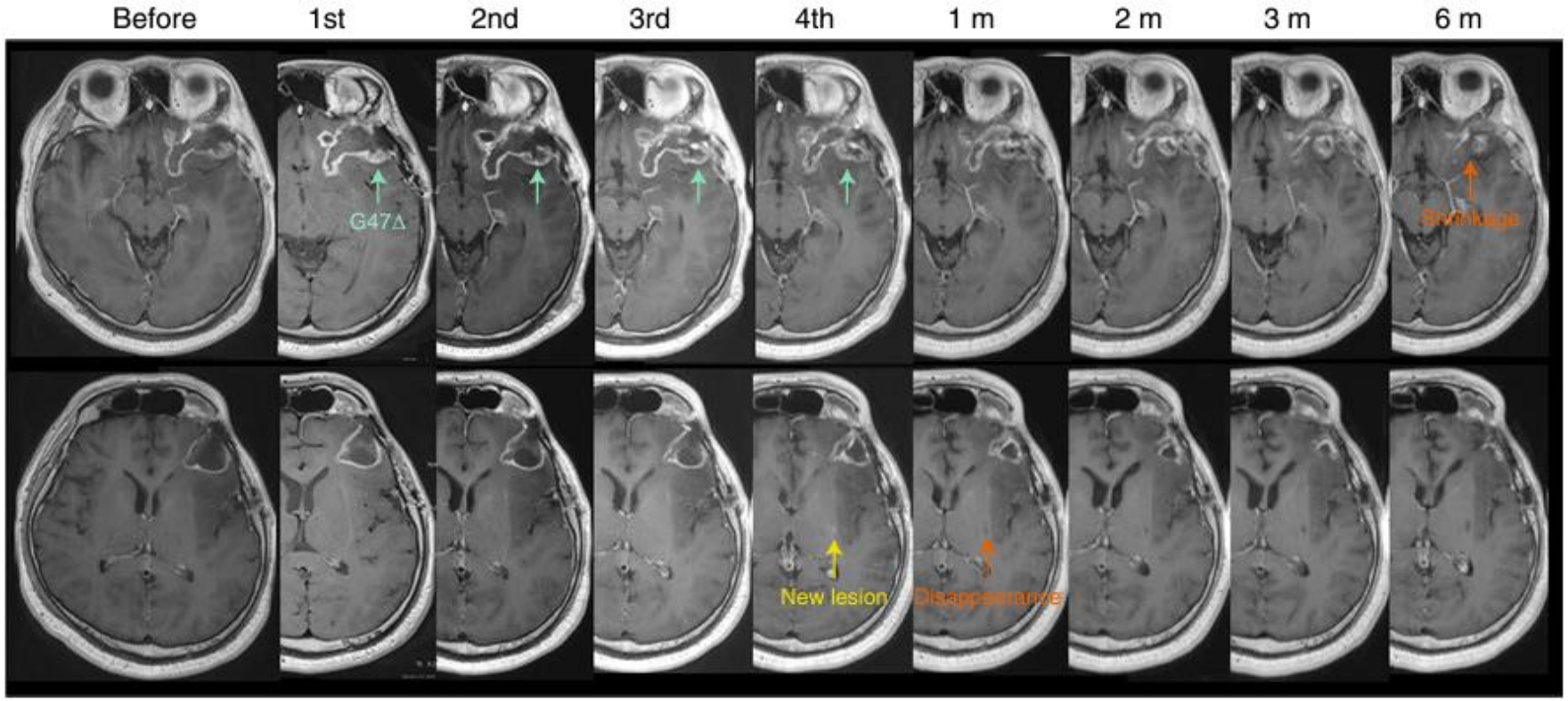
Figure 3 Patient 9 clinical photographs. (A) Pre-PVSRIPO, (B) 9 days after first PVSRIPO injection, (C) 63 days after first PVSRIPO injection, (D) 5 months after first PVSRIPO injection, and (E) 12 months after first PVSRIPO injection.

Three injections ; day 0, day 21 and day 42



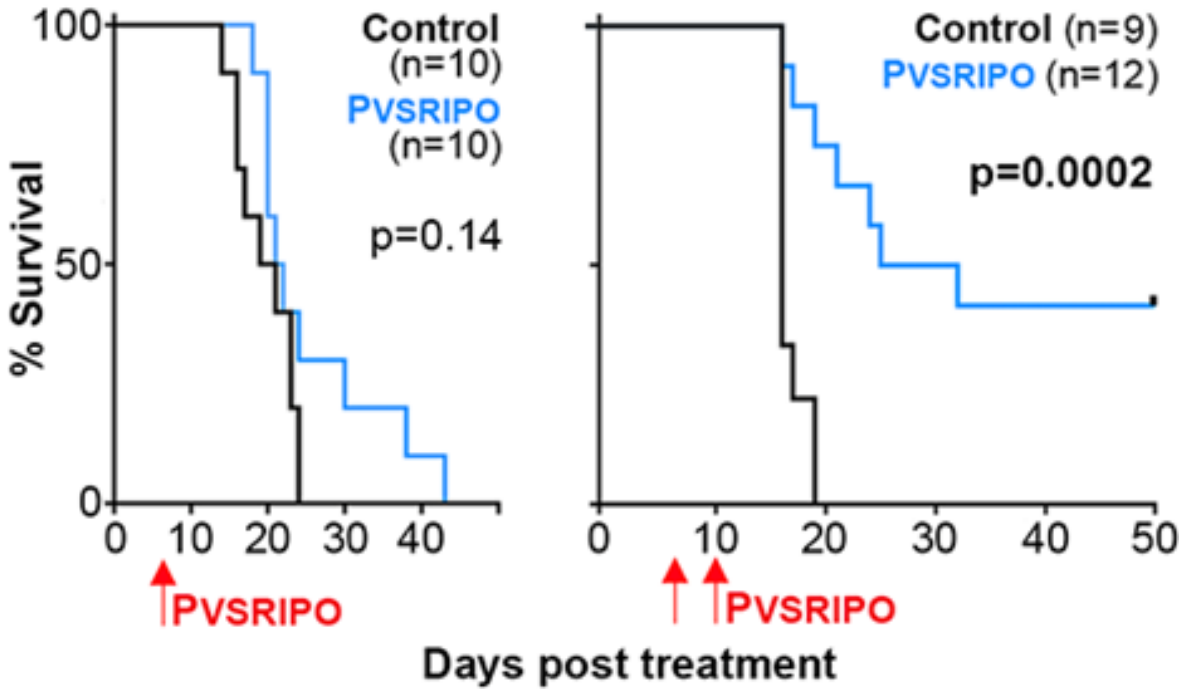
Beasley GM et al. J Immunother Cancer. 9(28(8):1630-1639, 2021.

RAPID RETREATMENT FEASIBLE – DR. TODO IN JAPAN



Todo T et al. Nat Medicine. 28(8):1630-1639, 2022.

TANDEM REPEAT INTRATUMORAL LERAPOLTUREV YIELDS SIGNIFICANTLY IMPROVED SURVIVAL IN CT2A MOUSE GLIOMA



Brown MC et al. J Immunothe Cancer. 11(4):e006463, 2023.

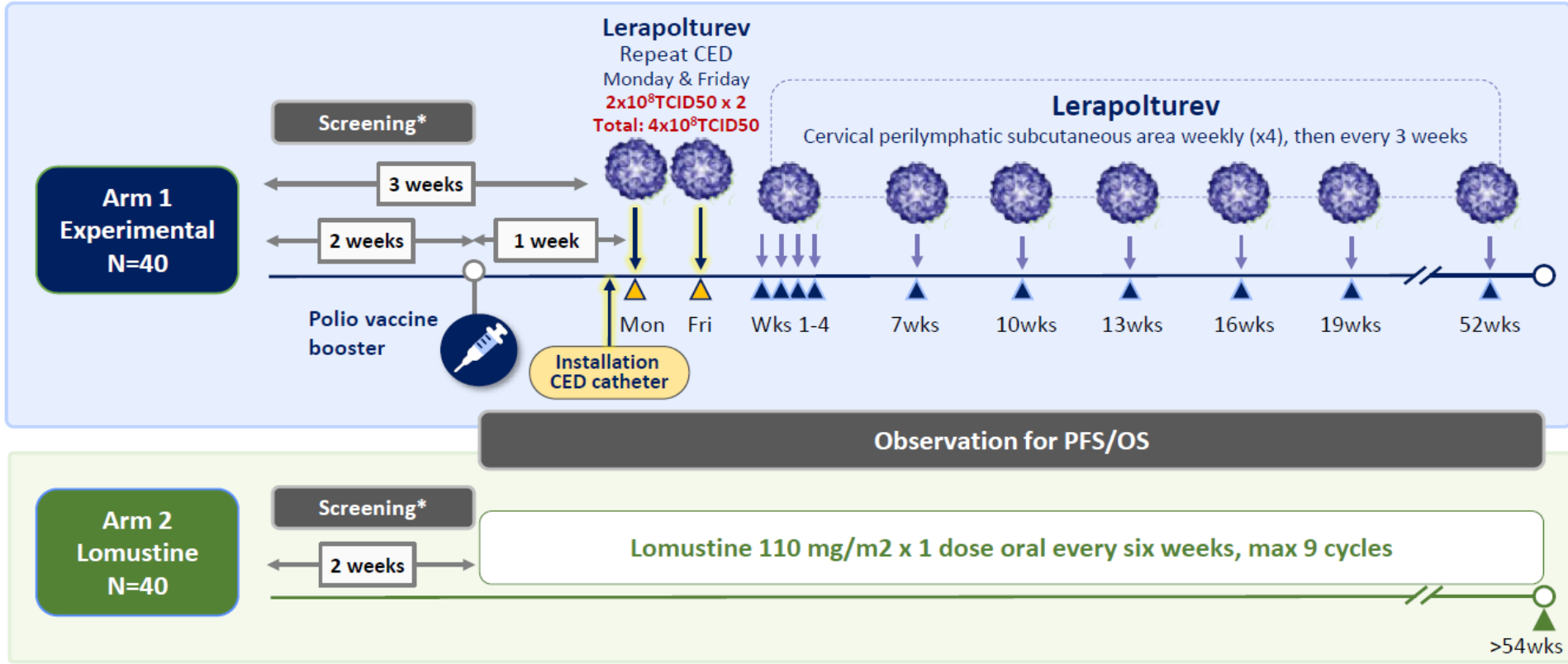
PHASE 2 TRIAL OF REPEATED CED AND CPL LERAPOLTUREV INJECTIONS VS LOMUSTINE IN RECURRENT GBM

- ✓ 2 consecutive infusions of lera via CED (Mon & Fri with same CED catheter), followed by cervical perilymphatic injections of lera every 3 weeks
- ✓ Lerapolturev is infused via CED in residual disease following maximal safe resection
- ✓ 1:1 randomization to lomustine

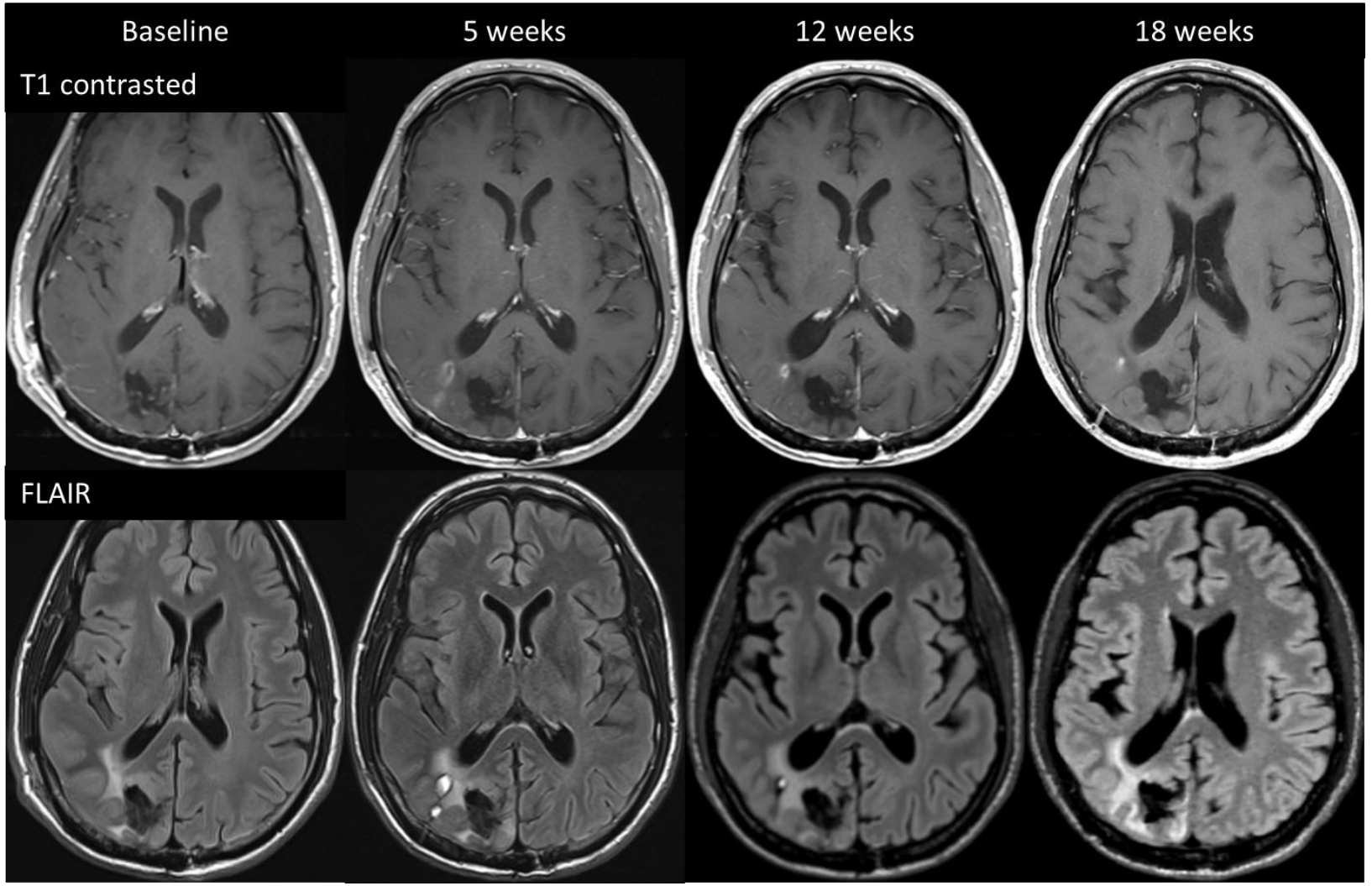
istari ONCOLOGY & Duke University School of Medicine

rGBM
Gross total resection
1:1
Randomization

**randomization at ~2 weeks post surgery*



1ST PATIENT TREATED ON THE NEW REGIMEN

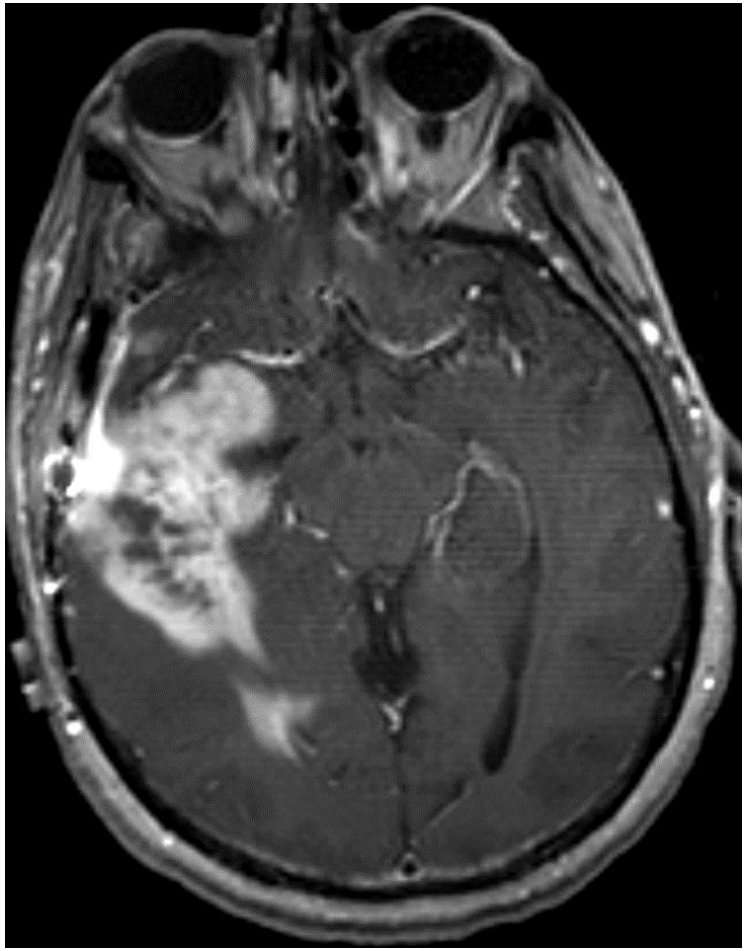


ADDITIONAL CONSIDERATIONS - PATIENT CARE DURING IMMUNOTHERAPY OR OTHER TRIALS

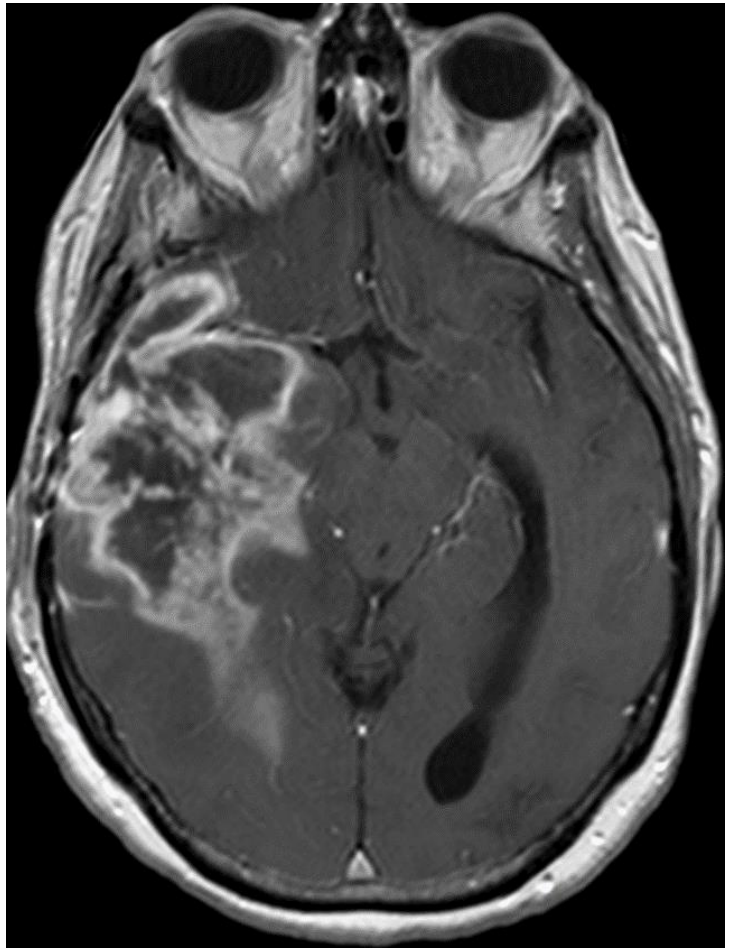
- **Headaches/Cerebral edema/Seizures**
  - **? Corticosteroids**
  - **Infusion volume/catheter placement**
- **Intracerebral hemorrhage**
  - **Platelet count ≥125 000 prior to CED catheter insertion**
  - **CT post catheter removal**
- **Pseudo-progression**
  - **Safe to start low dose bevacizumab (7.5 mg/kg IV every 3 weeks) 14 days after CED catheter removal**

Desjardins*, Gromeier* et al., N Engl J Med. 379(2):150-161, 2018.

SIGNIFICANT TUMOR BREAKDOWN



Baseline



1 month

IN CONCLUSION

- Clear unmet need for malignant glioma patients
- Malignant glioma patients and families normally decide to proceed with comfort care due to the impact of the tumor on:
  - Day-to-day functioning/independence
  - Cost to family (monetary, time, emotional)
- Each tumor progression triggers additional neurologic deficit
- Most trials only allows patients very early in their disease process
- Continued work needed in developing the optimal therapeutic
- Finally, thank you to all our patients and caregivers, the true trailblazers