2025

DEBATES AND DIDACTICS in Hematology and Oncology

EMORY WINSHIP CANCER INSTITUTE
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JULY 24 - 27, 2025 • SEA ISLAND, GEORGIA

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Biomarker-Driven, Targeted-Inhibitor Therapies in Neuro-Oncology: What Are We Missing?

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Disclosures

- I have no financial disclosures
- Recently primary investigator on clinical trials supported by Merck, Bristol-Myers Squibb, and Chimerix/Jazz
- I will be discussing, and will explicitly identify:
  - FDA-approved treatments with primary CNS tumor indications
  - FDA-approved off-label treatments under investigation
  - Experimental therapies currently in clinical trials

Outline

- Assessment of Potential Targets in CNS Tumors
- Primary CNS Tumors with Inhibitor Targets:
  - IDH-Mutated Tumors
  - BRAF-Altered Tumors
- Challenges of Targeted Therapies in Primary CNS tumors
- Future Directions

Properties of Optimal Targeted Inhibition in CNS Tumors

Driver: critical to tumor initiation or maintenance

Tumor-Specific: selectively altered in tumor and not normal cells

Druggability: gene product is accessible to inhibitors

Essential for Survival: dependence on altered gene product for survival or proliferation

Low Redundancy: few compensatory pathways to develop resistance

Blood-Brain/Tumor Barrier Penetration: inhibitors effectively cross from bloodstream without excess exclusion or expulsion

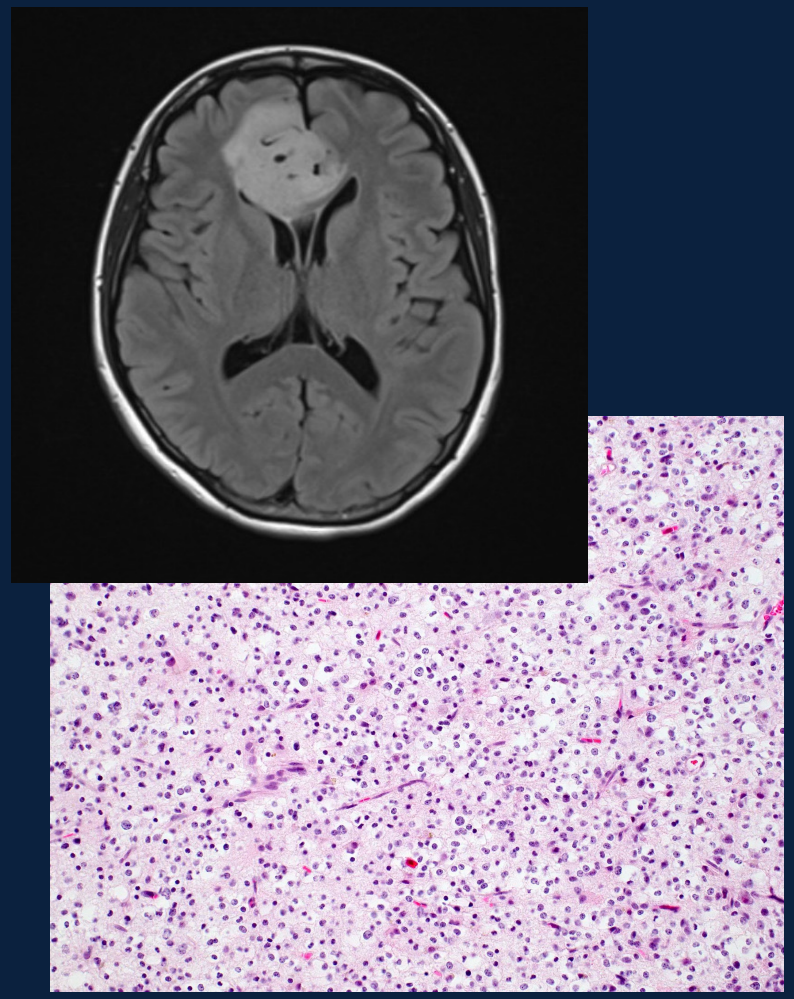
Detectable Biomarker: alteration is easily and reliably detected by molecular diagnostics

Genes of Interest for Targeted Therapies

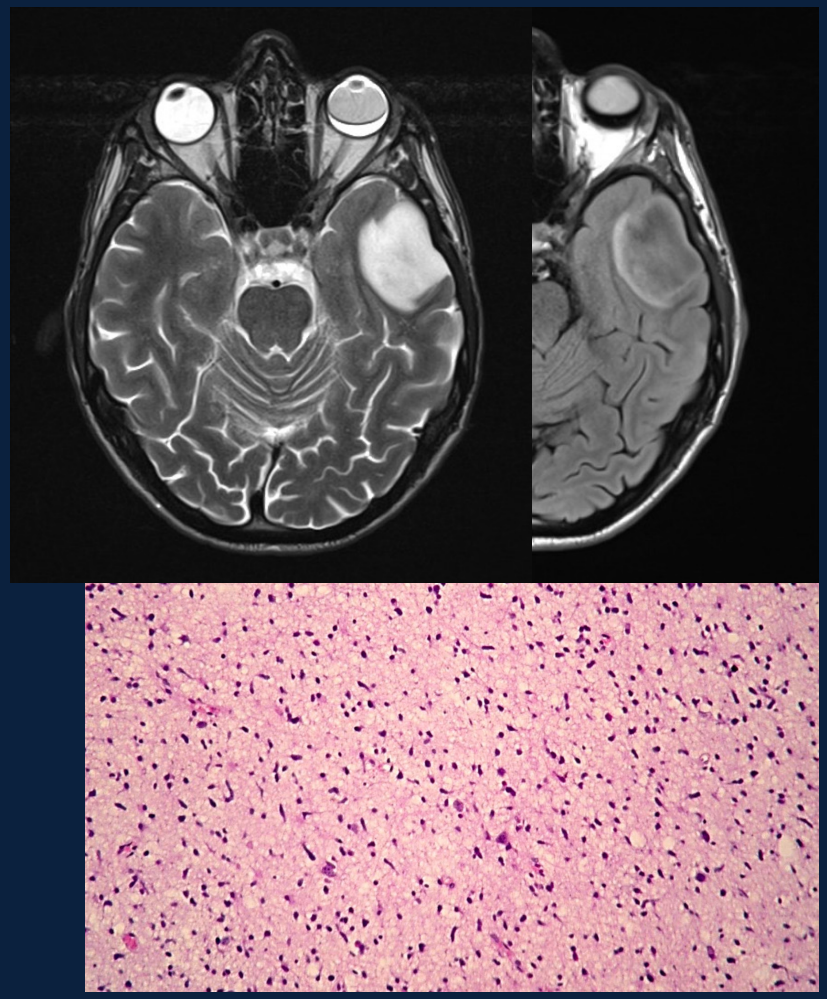
Targets	Driver	Specific	Druggable	Essential	Redundancy	BBB	Detection
IDH1/2	Yes	Low-Grade Gliomas	+ (Cytosol, Mitochond)	Yes, Early and Mid	Medium	Inhibitor dependent	IHC, NGS
BRAF V600E	Yes	Low-Grade Gliomas and Gliomaneuronal	+ (Cytosol)	Yes, Early and Mid	Medium	Inhibitor dependent	IHC, NGS
BRAF Fusion	Yes	Low-Grade Gliomas and Gliomaneuronal	+ (Cytosol)	Yes, Early and Mid	Medium	Inhibitor dependent	RNAseq
H3F3A/ EZH2	Yes	High-Grade Gliomas	+ (Nuclear)	Maybe	Low	Inhibitor dependent	IHC, NGS
NTRK Fusion	Yes	High-Grade Gliomas	+ (Cytosol)	Maybe	Medium	Inhibitor dependent	RNAseq
FGFR::TACC	Yes	High-Grade Gliomas	+ (Cytosol)	Maybe	Medium	Inhibitor dependent	RNAseq
EGFRvIII	Yes	GBM	++ (Cell Surface)	No	High	Inhibitor dependent	NGS

IDH Mutant (IDHm) Gliomas: A Molecularly Unifying Set of Diagnoses

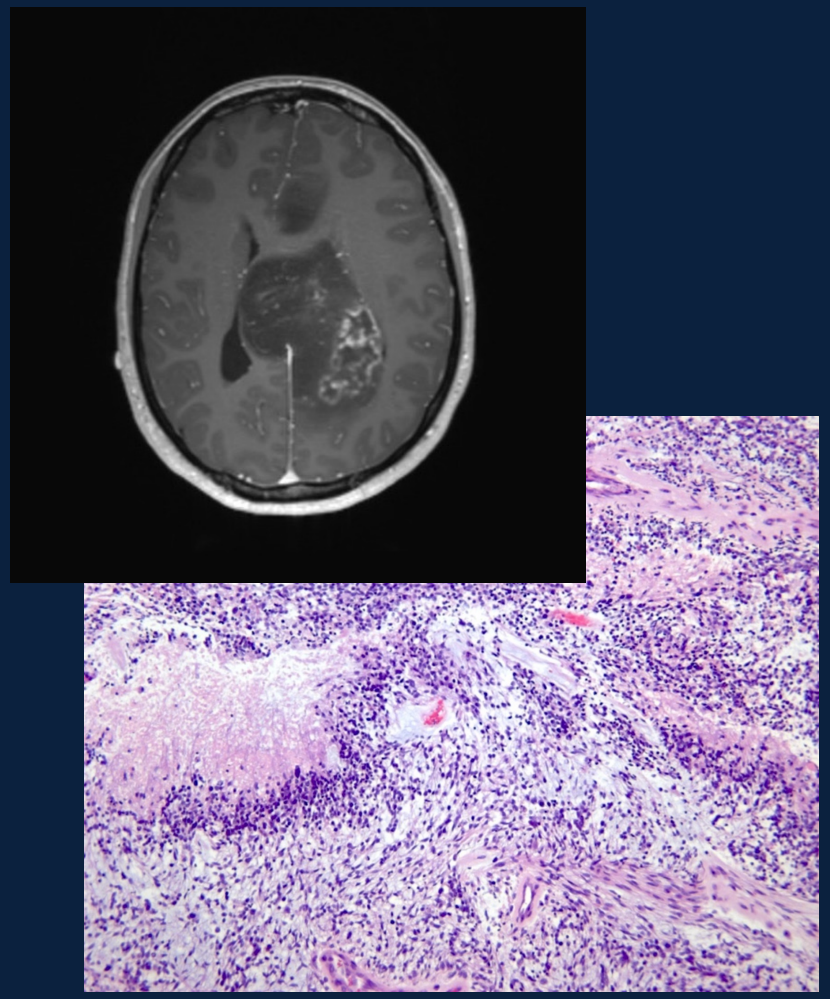
Oligodendroglioma



Astrocytoma

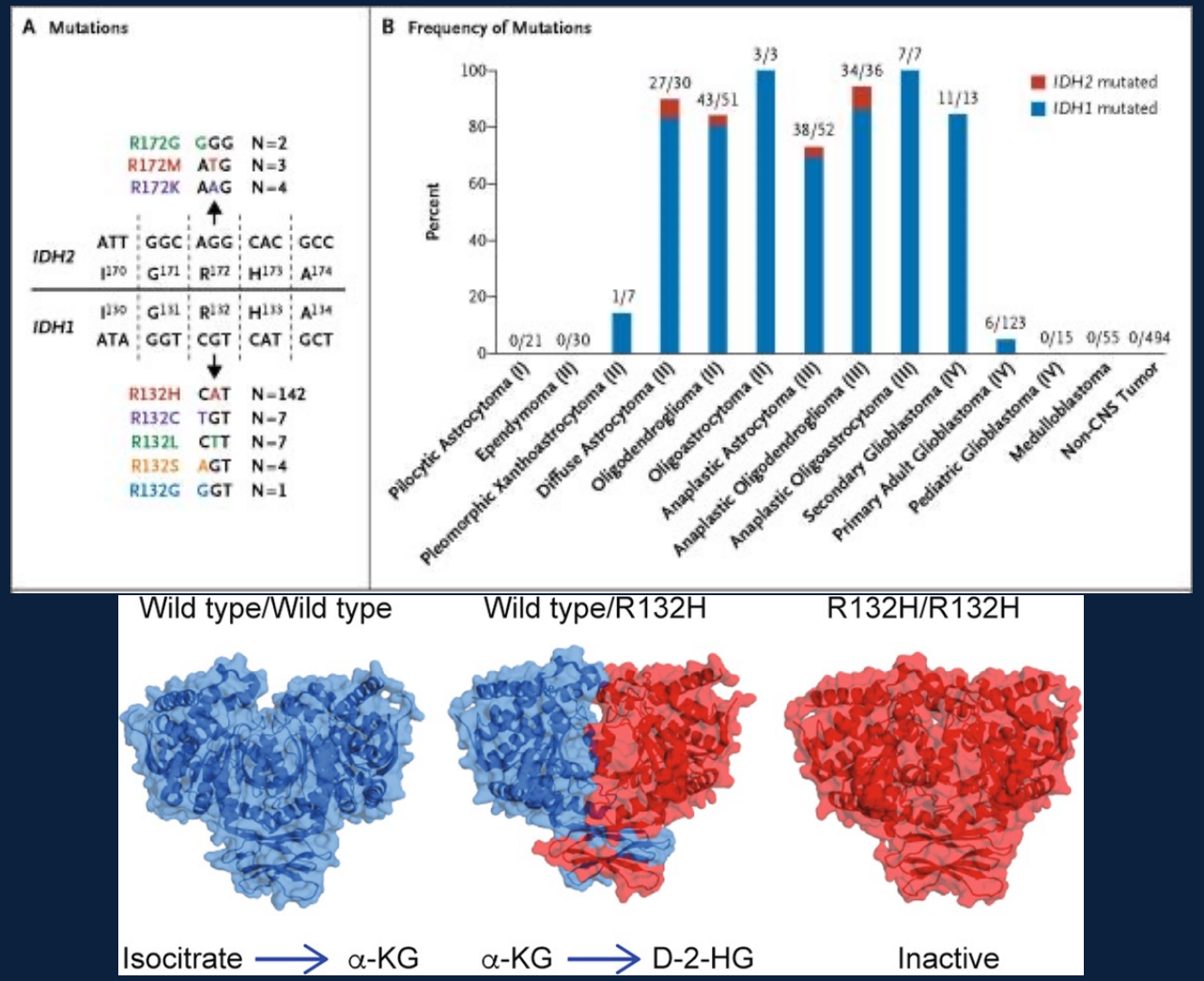


Grade 4 Astrocytoma



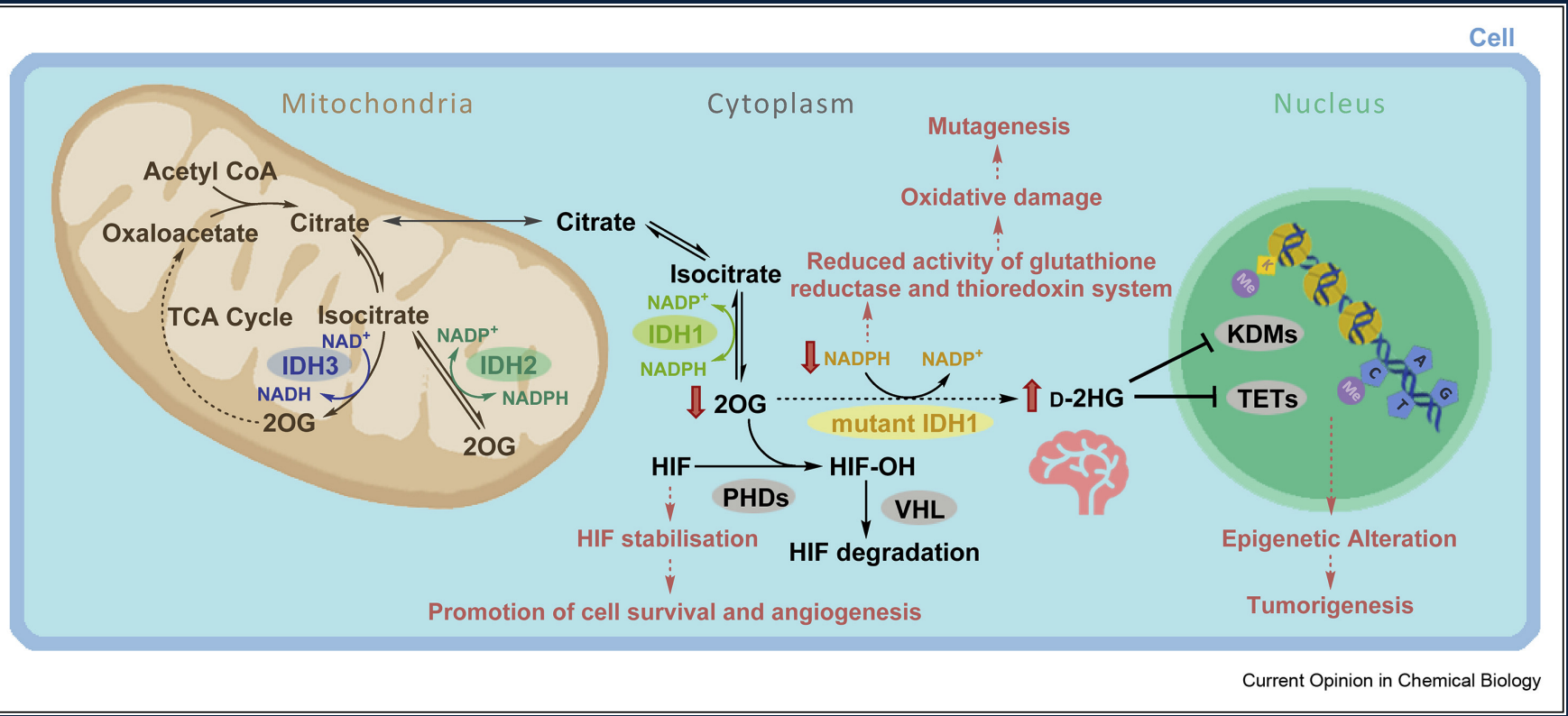
IDHm Gliomas: From Recognition to Treatment

- Discovery of IDH1 mutation in histologically grade 2/3 gliomas and secondary GBM in 2009
  - –>95% with canonical R132H mutation
- 2016 WHO criteria formally adopt IDH1/2 mutation as defining feature of astrocytoma and oligodendroglioma
  - –Eliminated category of secondary GBM



Info and Top Figure: Yan et al. (2009) *NEJM*
Info and Bottom Figure: Han et al. (2020) *Br J Cancer*

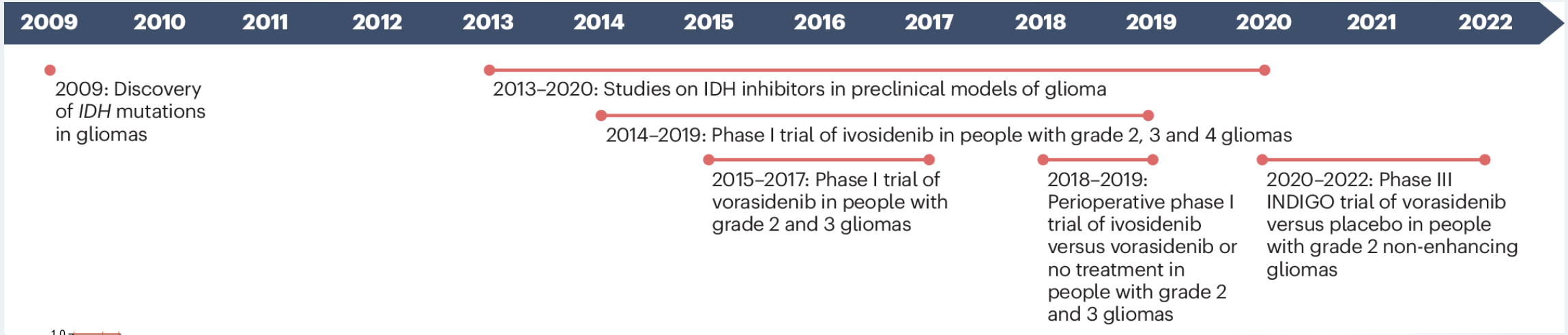
Biochemical Mechanism of Oncogenesis in IDHm

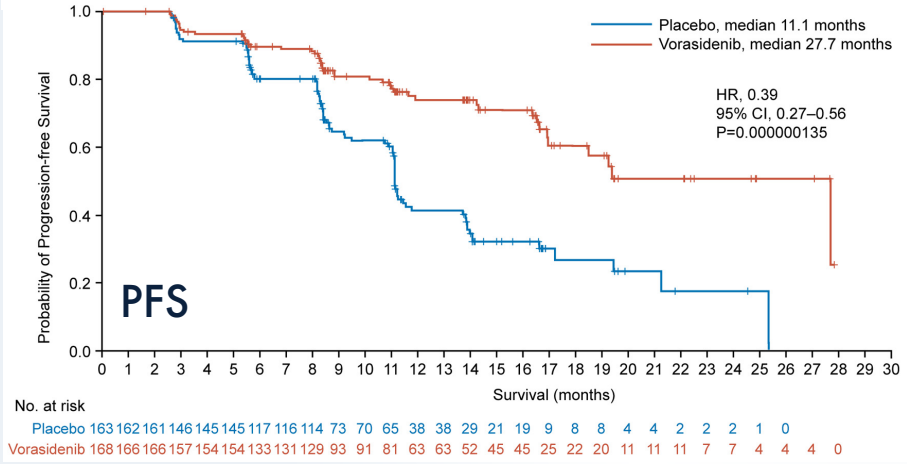


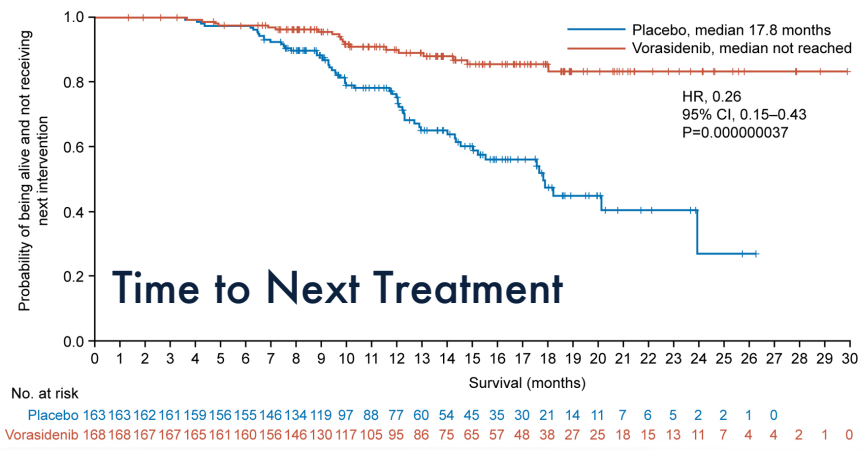
- **Metabolic**
  - –NADPH Depletion
  - –AKG Depletion
- **Epigenetic**
  - –D2HG Oncometabolite
- **Angiogenic**
  - –HIF Stabilization

Liu et al. (2020) *Curr Opin Chem Biol*

FDA Approves First Targeted Therapy for IDHm Gliomas





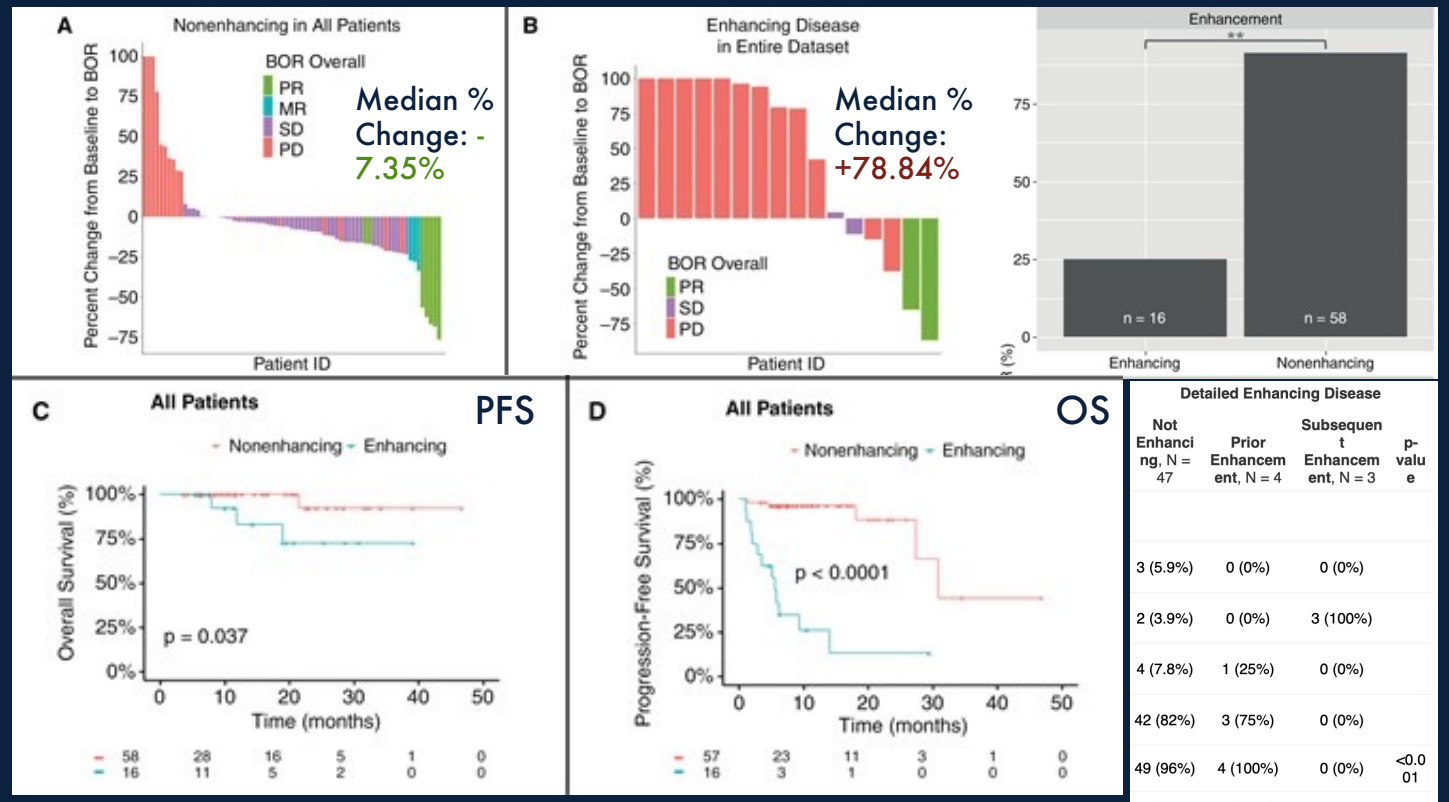


- Based on promising interim Phase 3 data, **vorasidenib** approved to treat **grade 2, non-enhancing** IDH mutant gliomas

Timeline: Rudá et al. (2024) *Nat Rev Neurol*
Kaplan-Meier: Mellinghoff et al. (2023) *NEJM*

Controversy 1: IDHm Inhibitor Use in Enhancing Gliomas

- Use in Enhancing Gliomas is currently <u>not</u> indicated:
  - —Ineffective by radiographic response, by disease control rates, and by survival outcomes
- <u>Controversy</u>: could resection of all enhancing tumor restore responsiveness to IDHm inhibitor?
  - —Small sample size suggests maybe, but more studies are needed



Detailed Enhancing Disease

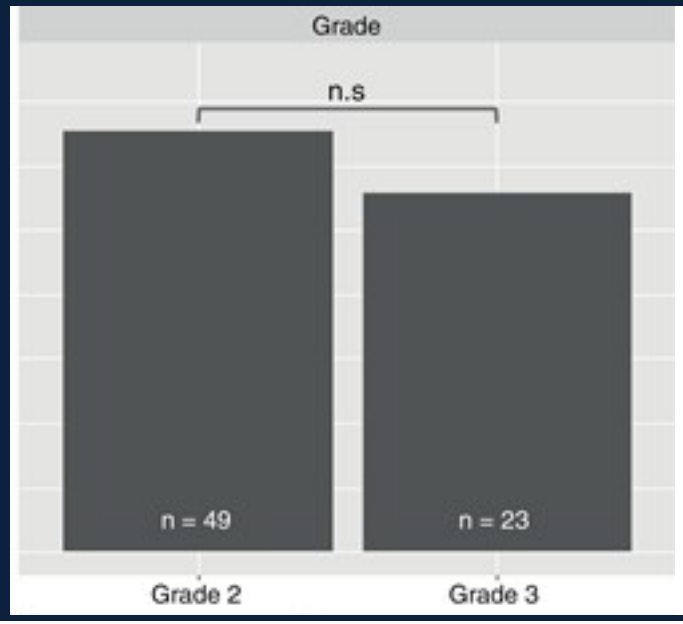
Not Enhancing, N = 47	Prior Enhancement, N = 4	Subsequent Enhancement, N = 3	p-value
3 (5.9%)	0 (0%)	0 (0%)	
2 (3.9%)	0 (0%)	3 (100%)	
4 (7.8%)	1 (25%)	0 (0%)	
42 (82%)	3 (75%)	0 (0%)	
49 (96%)	4 (100%)	0 (0%)	<0.001
7 (14%)	1 (25%)	0 (0%)	0.7

Lanman et al. (2025) *Neuro-Oncology Advances*

Controversy 2: IDHm Inhibitor in Grade 3 or 4 Gliomas

- Use in Grade 3 Gliomas is currently <u>not</u> indicated
  - —Grade 3 gliomas were part of Phase 1/2 testing but not Phase 3 (INDIGO) trial
- Pooled data suggests disease response rates are similar
  - —Rates comparable when enhancing disease is removed
- Though not indicated, insurance companies are approving in select settings
- Trials forthcoming to use in high-grade setting with standard of care

All Participants



Non-Enhancing Participants

Characteristic	Grade in All Patients: Grade 2, N = 47	Grade 3, N = 22	p-value	Grade in First-Line Ivo: Grade 2, N = 28	Grade 3, N = 4	p-value	Grade in Subsequent-Line Ivo: Grade 2, N = 19	Grade 3, N = 18	p-value[2]
BOR									
MR	2 (4.1%)	1 (4.3%)		1 (3.4%)	0 (0%)		1 (5.0%)	1 (5.6%)	
PD	9 (18%)	7 (30%)		2 (6.9%)	0 (0%)		7 (35%)	7 (39%)	
PR	4 (8.2%)	3 (13%)		4 (14%)	1 (20%)		0 (0%)	2 (11%)	
SD	34 (69%)	12 (52%)		22 (76%)	4 (80%)		12 (60%)	8 (44%)	
DCR	40 (82%)	16 (70%)	0.3	27 (93%)	5 (100%	>0.9	13 (65%)	11 (61%)	0.8
ORR	6 (12%)	4 (17%)	0.7	5 (17%)	1 (20%)	>0.9	1 (5.0%)	3 (17%)	0.3

Not yet recruiting

Vorasidenib Maintenance for IDH Mutant Astrocytoma (VIGOR)

ClinicalTrials.gov ID NCT06809322

Sponsor European Organisation for Research and Treatment of Cancer - EORTC

Information provided by European Organisation for Research and Treatment of Cancer - EORTC (Responsible Party)

Last Update Posted 2025-05-01

Recruiting

Vorasidenib in Combination With Temozolomide (TMZ) in IDH-mutant Glioma

ClinicalTrials.gov ID NCT06478212

Sponsor Institut de Recherches Internationales Servier

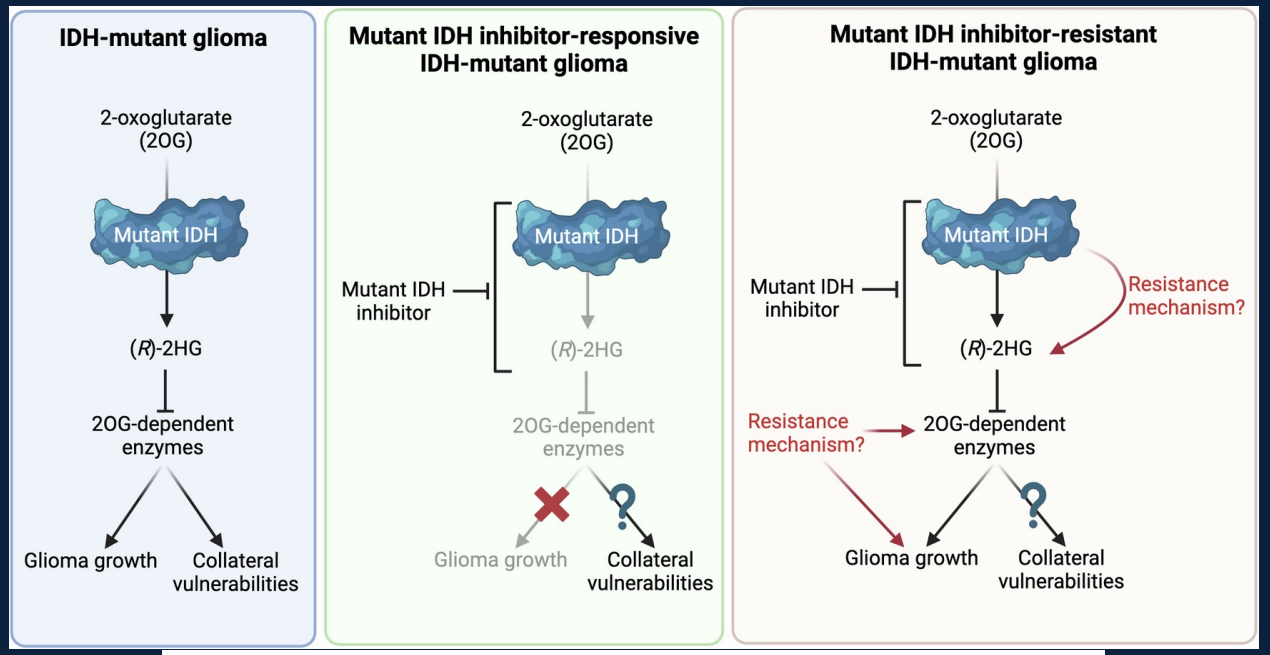
Information provided by Servier (Institut de Recherches Internationales Servier) (Responsible Party)

Last Update Posted 2025-06-05

Lanman et al. (2025) *Neuro-Oncology Advances*

Overcoming Resistance to IDHm Inhibitor

- Single inhibitor strategy could select for cells without IDHm
  - —Loss of IDHm can lead to more aggressive disease course
- Combination therapies can be considered:
  - —Toxicities have typically limited this strategy
    - +PARP inhibitor
    - +CDK inhibitor
    - +Immunotherapy
    - +Vaccine strategies



Not yet recruiting

ViCToRy: Vorasidenib in Combination With Tumor Specific Peptide Vaccine for Recurrent IDH1 Mutant Lower Grade Gliomas (ViCToRy)

ClinicalTrials.gov ID NCT05609994

Sponsor Katy Peters, MD, PhD

Information provided by Katy Peters, MD, PhD, Duke University (Responsible Party)

Last Update Posted 2025-04-16

Recruiting

Study of Vorasidenib and Pembrolizumab Combination in Recurrent or Progressive IDH-1 Mutant Glioma

ClinicalTrials.gov ID NCT05484622

Sponsor Institut de Recherches Internationales Servier

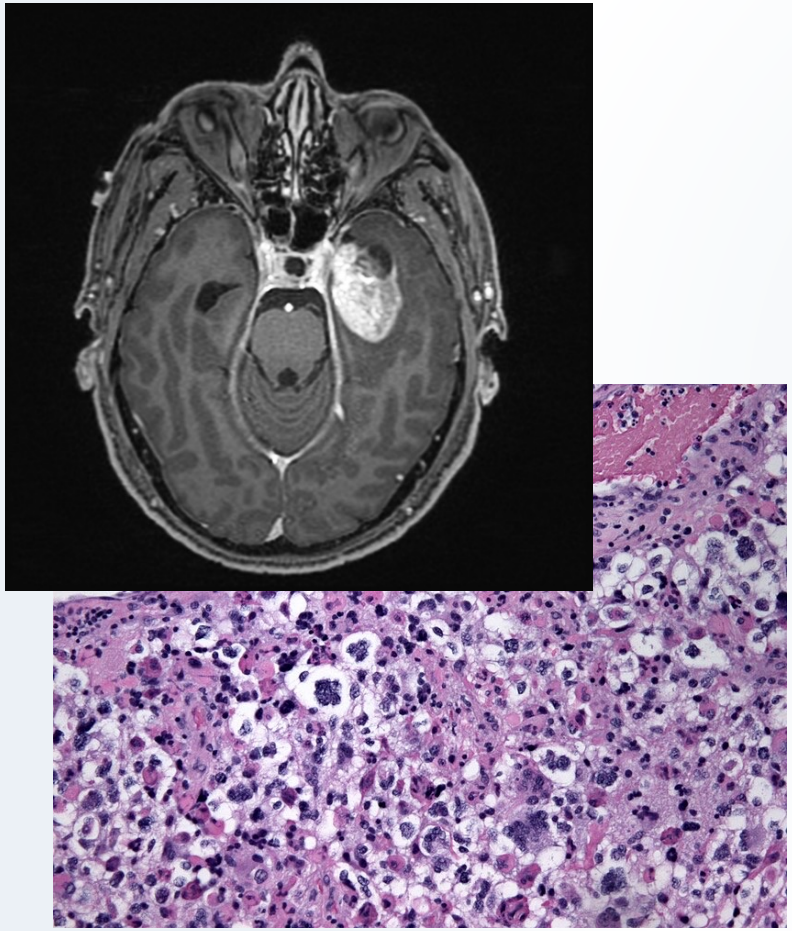
Information provided by Servier (Institut de Recherches Internationales Servier) (Responsible Party)

Last Update Posted 2025-06-03

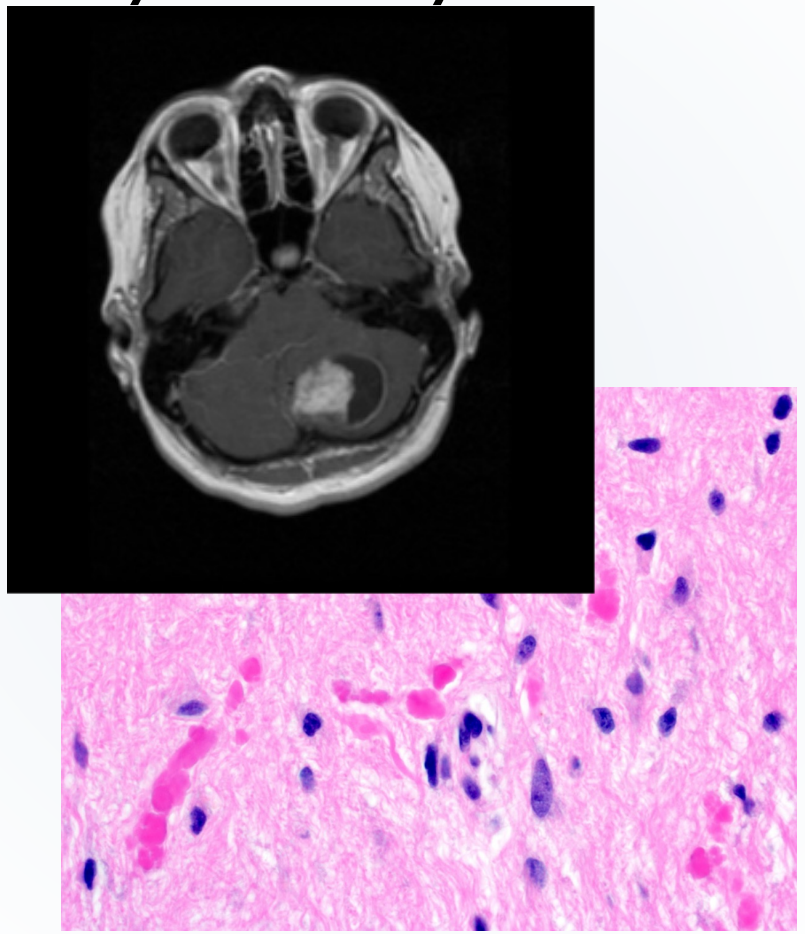
Lin et al. (2024) *NPJ Precision Oncology*

BRAF-Altered CNS Tumors: A Diverse Group of Tumors

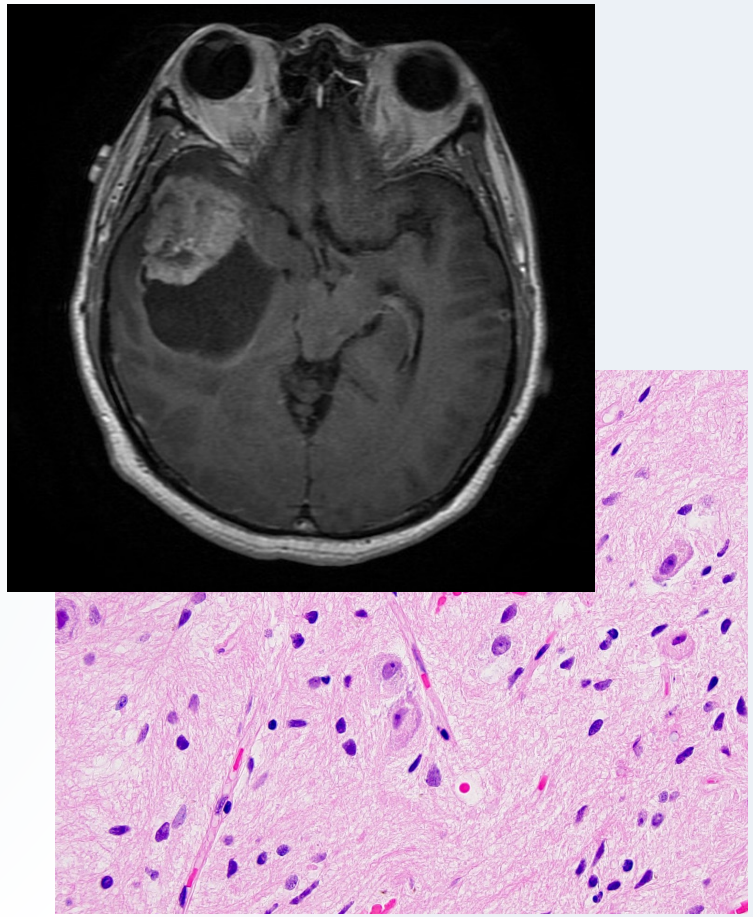
PXA



Pilocytic Astrocytoma

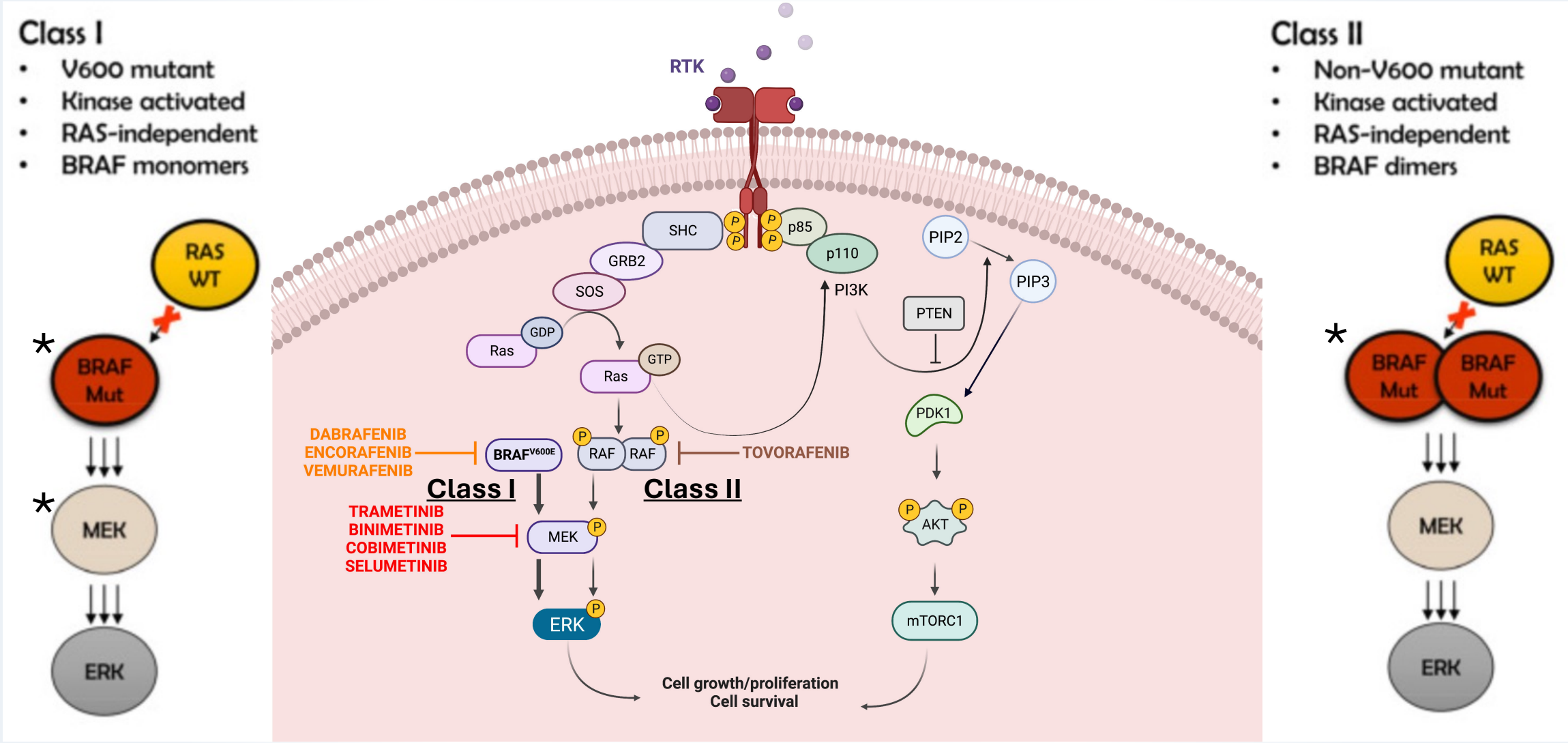


Ganglioglioma



Imaging: Radiopaedia.org.
Immunohistochemistry: PathologyOutlines.com.

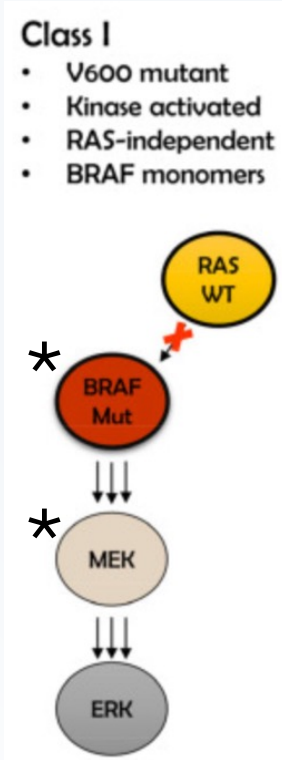
BRAF Alterations Drive Oncogenesis and are Targetable

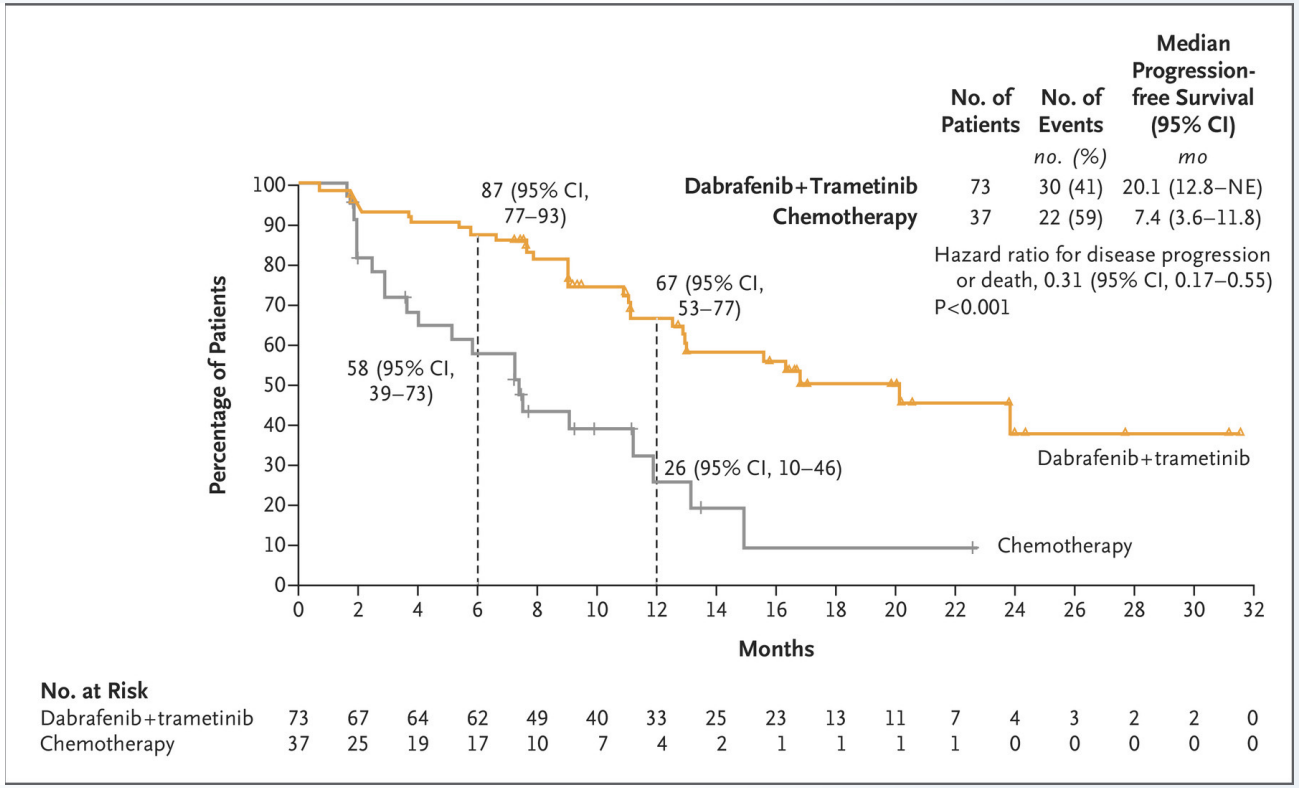


Adapted from Capogiri et al. (2023) *Front Oncol* and Smiech et al. (2020) *Genes (Basel)*

Dual RAF/MEK Inhibition for Class I (V600E) BRAF Mutations

- Study in pediatric patients (ages 1-17) without any previous treatment
  - –Vs Carboplatin/Vincristine
- Primary endpoint: overall response rate
- Toxicity (Grade ≥3)
  - –47% (dual inhibitor) vs 94% (chemotherapy)
- FDA approved dabrafenib/trametinib combination in 2023

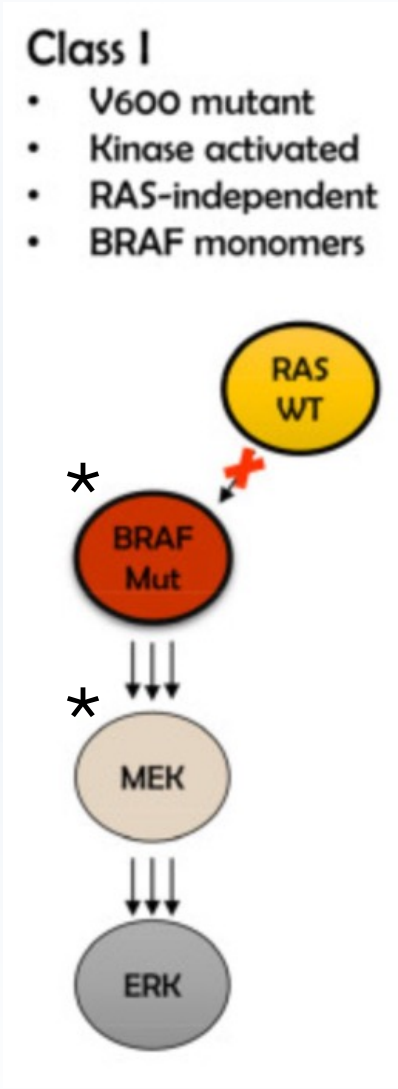


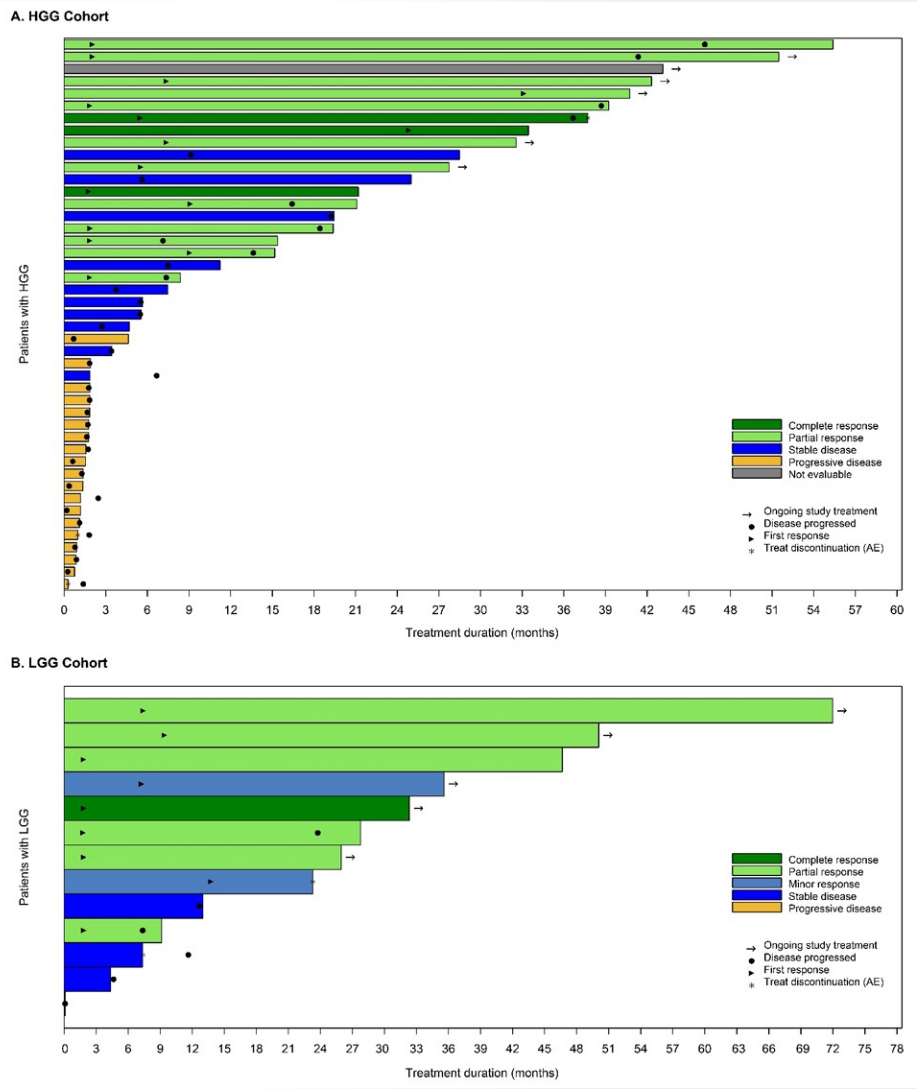


Cartoon: Smiech et al. (2020) *Genes (Basel)*
Trial: Bouffet et al. (2023) *NEJM*

Parallel BRAF/MEK Trials in Adults with BRAF Class I Mutations

- Basket trial of CNS tumors with V600E mutation for adult patients
- Primary endpoint: overall response rate
  - –Low-Grade Glioma: 69%
  - –GBM: 31%
  - –High-Grade Glioma: 33%
- Toxicity (Grade≥3) was 53% across all cohorts
  - –Primarily fatigue, neutropenia
- FDA approved for adult CNS tumors in 2022

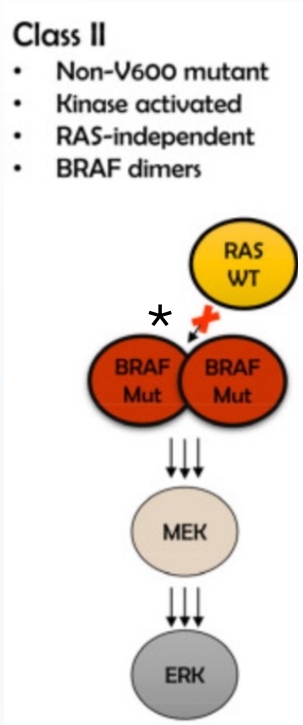


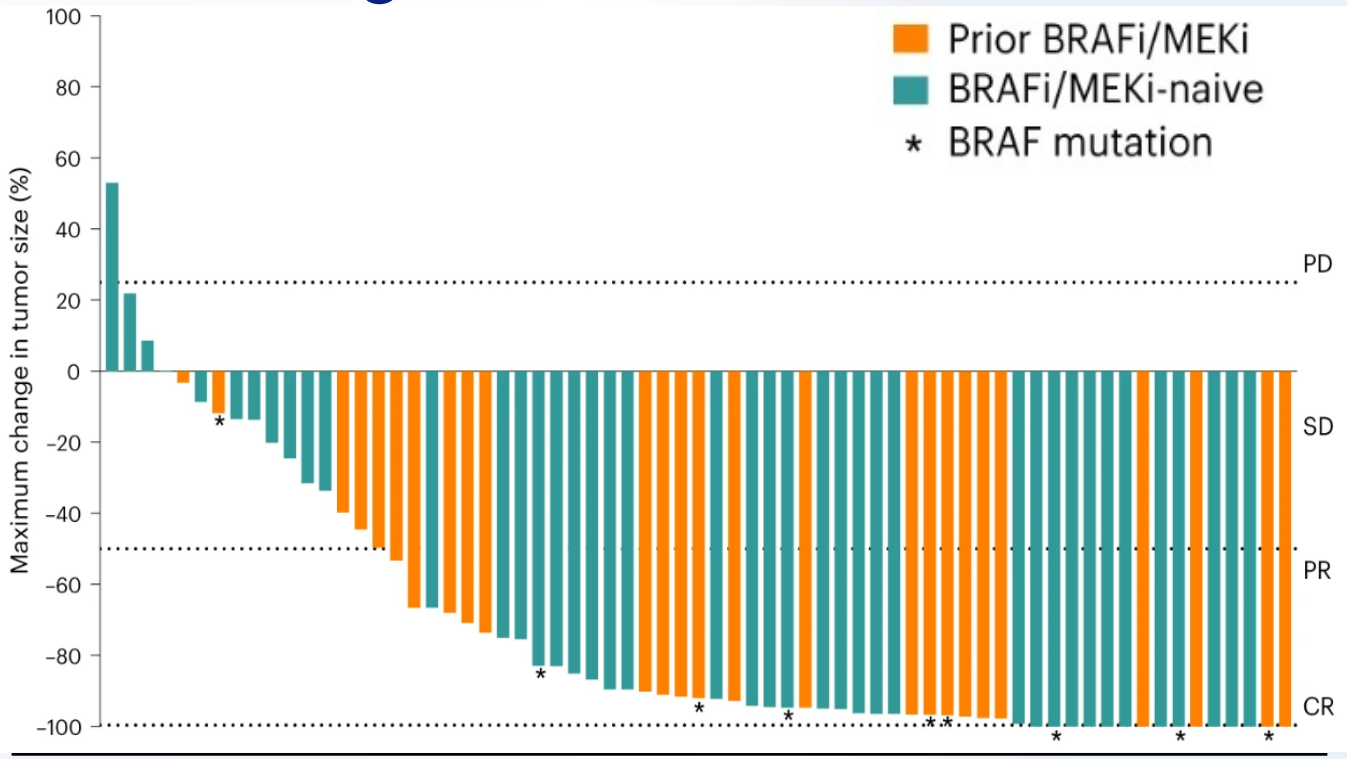


Cartoon: Smiech et al. (2020) *Genes (Basel)*
Trial: Wen et al. (2022) *Lancet*

First Class II BRAF-Inhibitor Proves Effective Against Mutant and Fusions

- Enrolled 6-month to 25-year-old patients with relapsed BRAF-altered low-grade gliomas failing ≥1 prior therapy
- Primary endpoint: overall response rate
- Toxicity Grade ≥3: 42%
  - —Primarily developmental
  - —7% tumor hemorrhage
- FDA approved in pediatric low-grade gliomas in 2024
  - —However, many insurers will approve in adult BRAF-altered CNS tumors



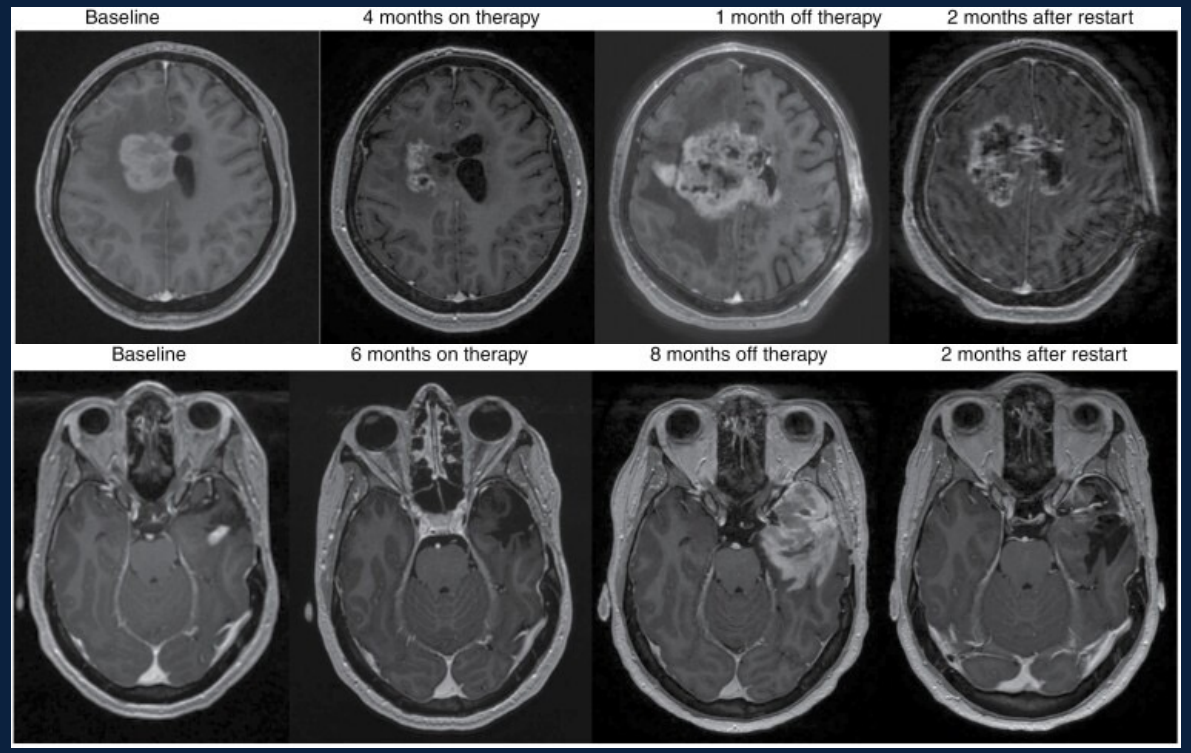


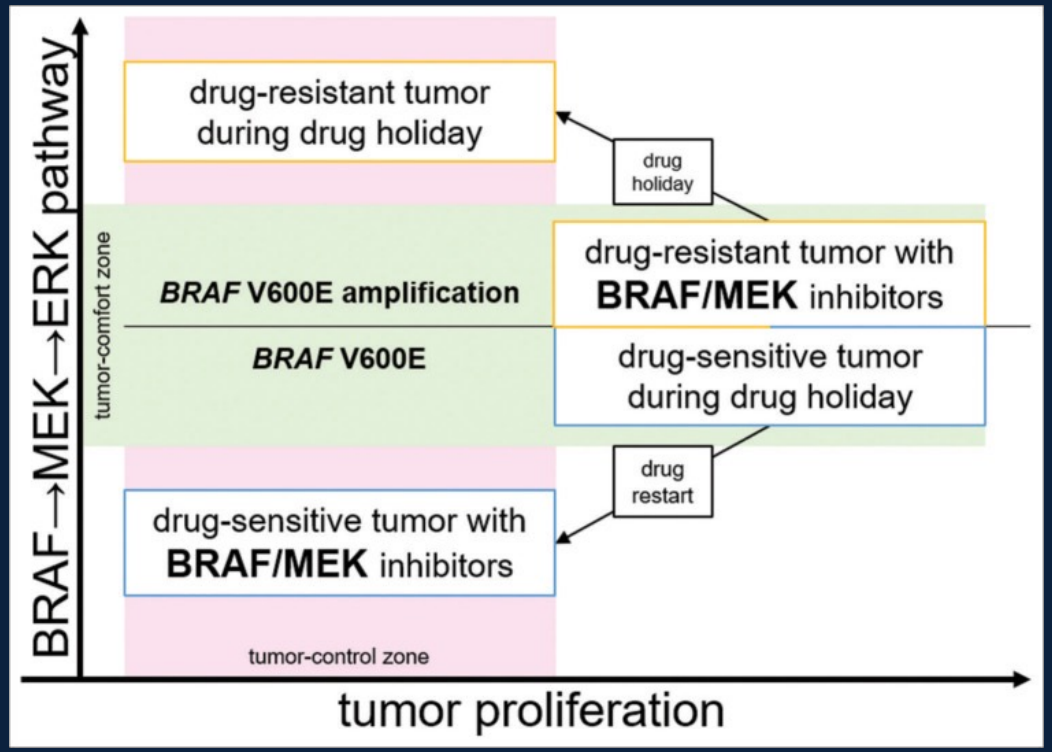
Overall response rate	RANO-HGG	RANO-LGG
BRAF fusion	41%	33%
BRAF mutation	50%	58%
Prior MAPKi	71%	51%
MAPKi naïve	61%	55%

Trial: Kilburn et al. (2024) *Nat Med*
Cartoon: Smiech (2020) *Genes (Basel)*

Controversy 1: Long-Term Treatment and Drug Holidays

- Debating Point:
  - –Pro continuation: BRAF/MEK Inhibition is cytostatic and not cytotoxic
  - –Con continuation: May develop resistances and become more aggressive
  - –Pro discontinuation: toxicities, avoid developing resistances
  - –Con discontinuation: many times tumor grows back substantially





MRI Case Series: Bazer et al. (2024) *Neurooncol Pract*
Figure Case Series: Inoue et al. (2024) *Sure Neurol Int*

Controversy 2: Epithelioid Glioblastoma Treatment Sequence

- 40-50% of epithelioid GBM have BRAF V600E mutation
- Clinical behavior however is similarly aggressive as GBM
- Standard is to treat with chemoradiation with adjuvant temozolomide
  - —Early aggressive treatment has better outcomes in GBM
- Argument can be made for BRAF-directed therapies

	Typical GBM	eGBM	*P*
N	300	39	
Mean age (y)	54 ± 13	53 ± 13	.761
Age >40	248/300 (0.83)	33/39 (0.84)	
Age ≤40	52/300 (0.17)	6/39 (0.15)	
Sex ratio (male/female)	167/133 (1.26)	12/27 (0.44)	.003
Microvascular proliferation	260/300 (0.87)	16/39 (0.41)	<.001
EGFR amplification	98/263 (0.37)	10/35 (0.29)	.315
TERT mutant	176/289 (0.61)	24/36 (0.67)	.502
BRAF mutant	2/60 (0.03)	9/22 (0.41)	<.001
MGMT methylation	100/295 (0.34)	10/39 (0.26)	.302

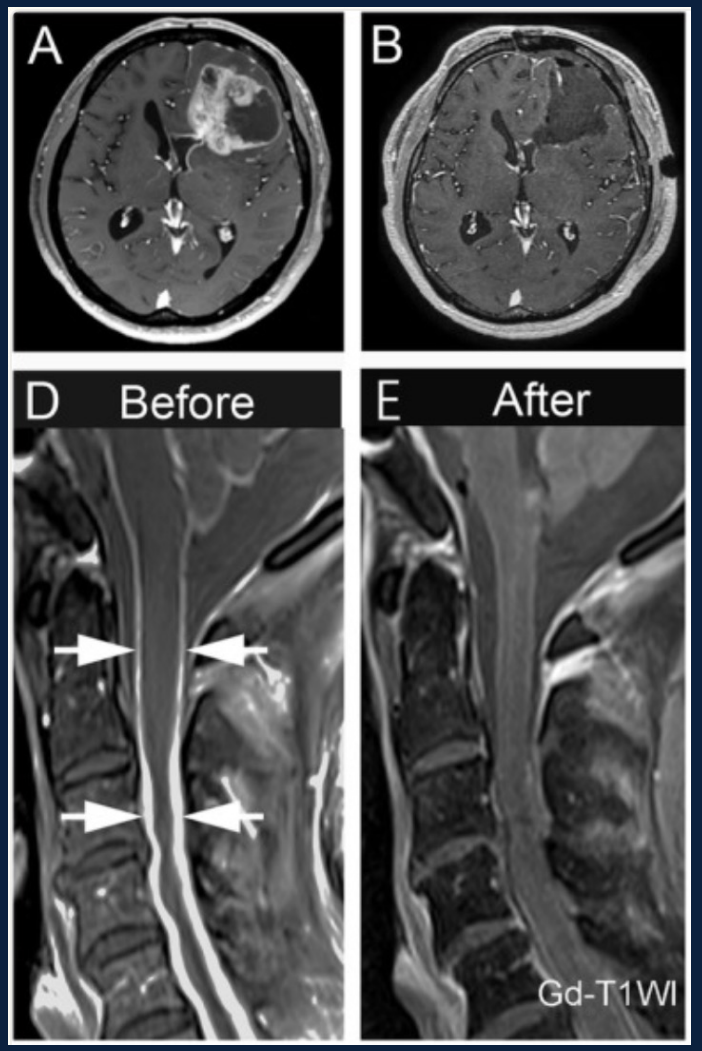
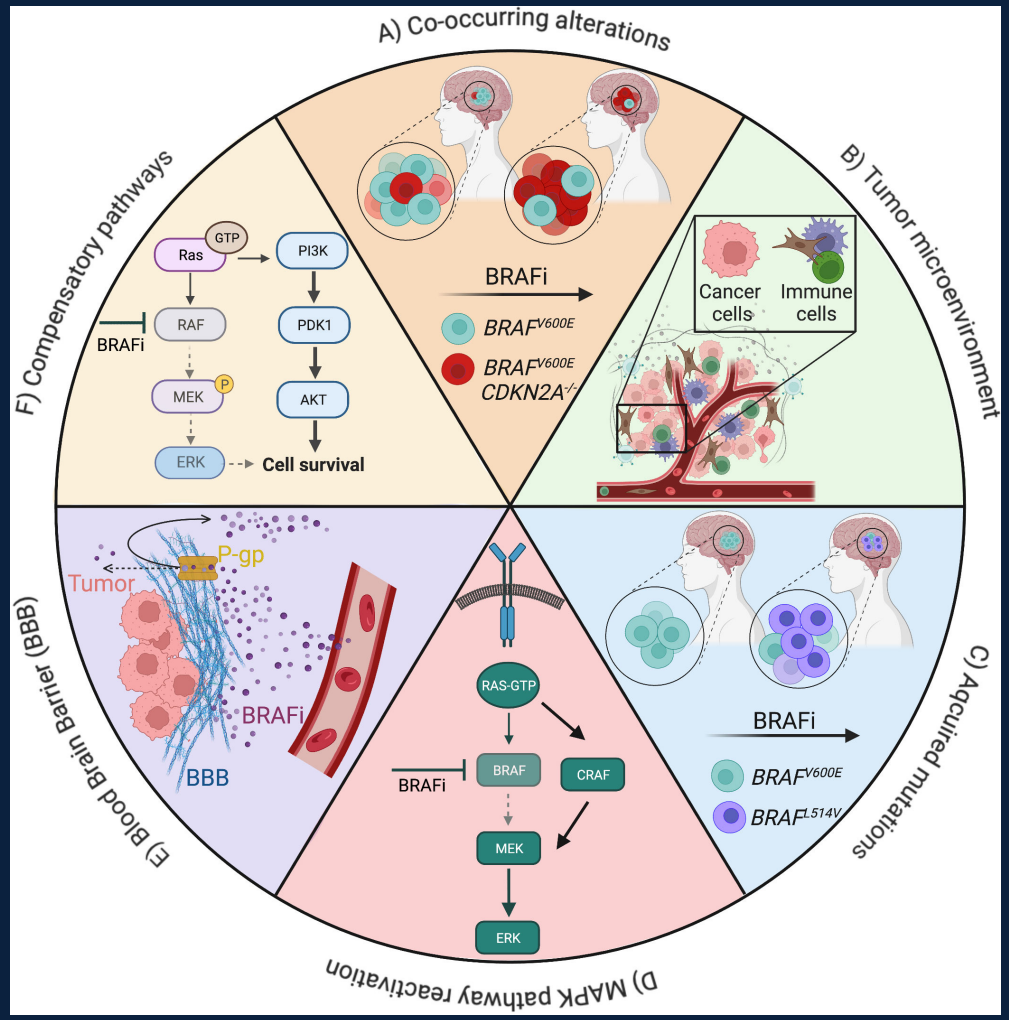


Table: Xi et al. (2024) *Int J Cancer*
Case Radiology: Kanemaru et al. (2019) *Acta Neuropathology Commun*

Overcoming Resistance to BRAF Inhibitor Therapy

- Strategies in development include:
  - Receptor tyrosine kinase and pathway inhibition
  - PI3K/AKT inhibition
  - Immunotherapeutics
  - New small molecule inhibitors



Capogiri et al. (2023) *Front Oncol*

Take-Home Points

1. FDA-Approved Targeted inhibitor therapies are emerging for CNS tumors, primarily of the lower-grade variety
2. Targeted therapies tend to be cytostatic rather than cytotoxic, and progression is not uncommon
3. Targeted inhibitors tend to perform better when used earlier and in tumors of lower grade
    - More so for IDH-directed therapies than BRAF-directed therapies
4. IDH-mutant inhibitors are only indicated for Grade 2 gliomas
    - Research into higher grades, either as mono- or combination therapy, are ongoing
5. BRAF inhibitors can be considered in any BRAF-altered CNS tumor
    - Pay attention to type of BRAF-alteration as not all agents are effective
6. Mechanisms of resistance are still unknown and being explored, and strategies to enhance or capitalize on resistances need to be developed

Q&A