Neuro-Oncology: Updates in Glioma Management

Edward Lee, PharmD, BCOP
Neuro-oncology Clinical Pharmacy Specialist
Memorial Sloan Kettering Cancer Center

Objectives

- Discuss current management of IDH-mutant low grade gliomas and H3K27M-mutant gliomas
- Review pharmacology, efficacy, safety, and monitoring parameters of vorasidenib in IDH-mutant low-grade gliomas
- Review pharmacology, efficacy, safety, and monitoring parameters of dordaviprone in H3K27M mutant diffuse midline gliomas
- Apply the pharmacology of vorasidenib and dordaviprone to patient cases

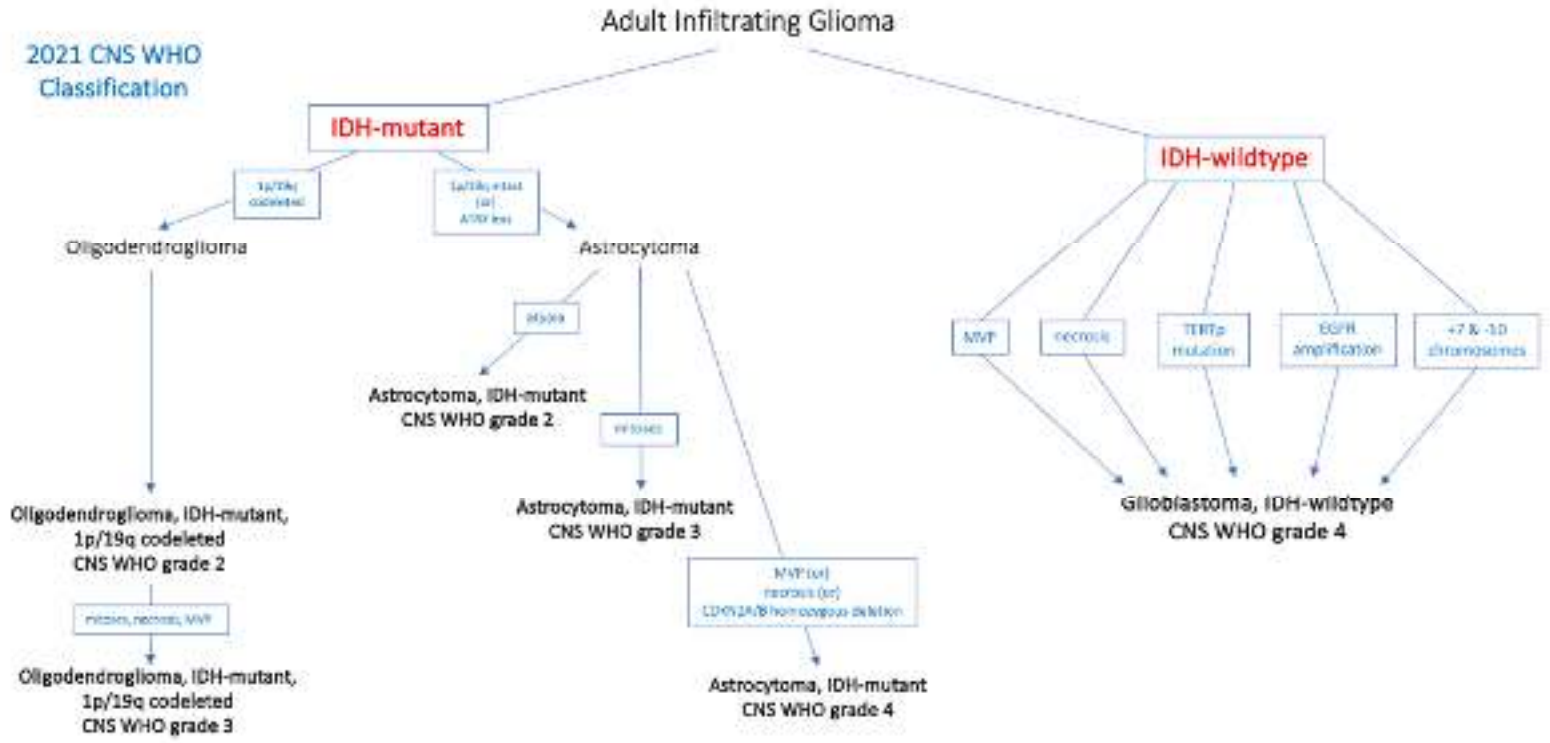
IDH-mutant Low-Grade Gliomas

Epidemiology and Clinical Presentation

- Low grade gliomas are uncommon CNS tumors
  - Estimated ~3000 new cases yearly in the United States
  - Accounts for ~20% of all gliomas
- Median age of diagnosis: 35 – 41 years
- Occur more frequently in males (~56% male predominance)
- Median overall survival: 7 to 15 years
- Observed to occur more commonly in white and non-Hispanic populations
- Generally considered **incurable**
  - Goals of treatment generally focus on halting tumor growth rather than complete eradication of tumor
- Typically present with seizures (80-90%)
  - Other common symptoms include headaches as well as cognitive and personality changes

Dhawan S, Patil CG, Chen C, Venteicher AS. Cochrane Database of Systematic Reviews 2020.

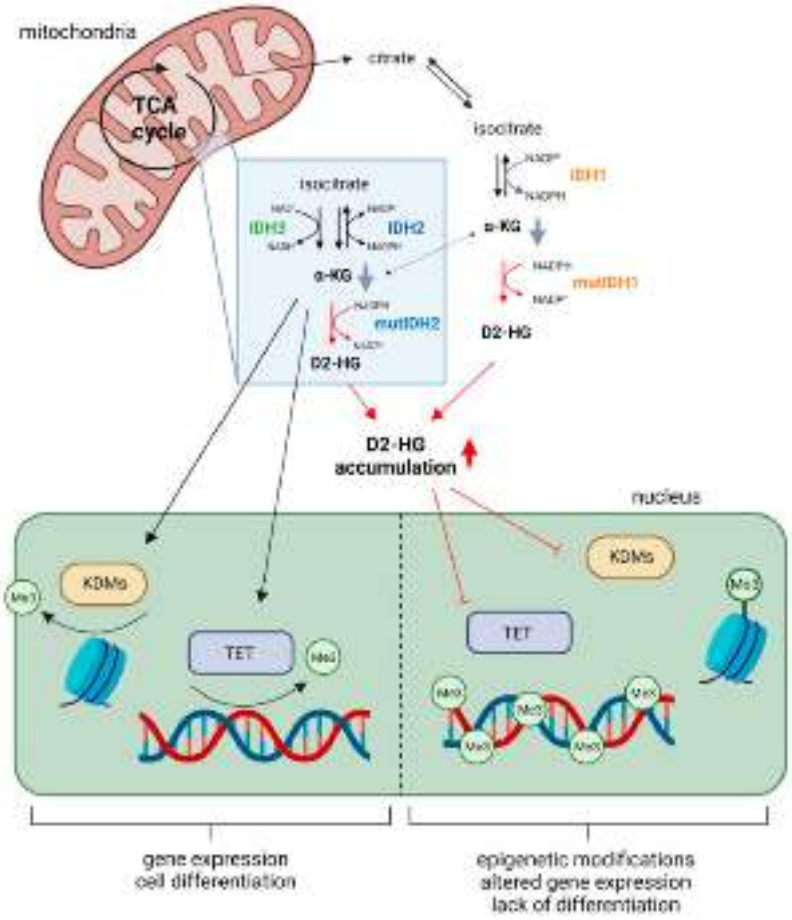
Classification



WHO classification of tumours series, 4th ed. International Agency for Research on Cancer; 2016.

Role of IDH

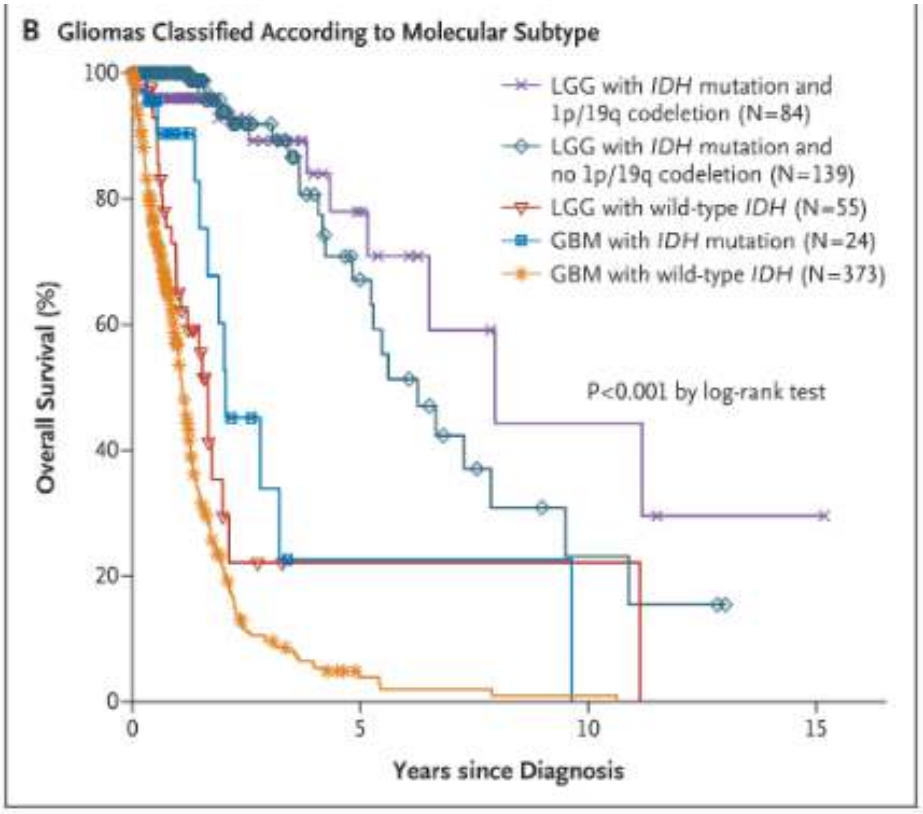
- IDH enzymes are responsible for catalyzing oxidative decarboxylation of isocitrate to alpha-ketoglutarate
- IDH mutations confer neomorphic enzymatic activity that converts alpha-ketoglutarate to D-2-hydroxyglutarate (D-2-HG or 2HG)
  - IDH changes are missense mutations
    - IDH1: **R132** and R100
    - IDH2: R172, 140
- 2-HG thought to promote oncogenic activity through multiple angles
  - Epigenetic reprogramming
  - Insulator dysfunction and oncogene activation
  - Differentiation block
  - Immune microenvironment suppression
  - DNA repair impairment



IDH: isocitrate dehydrogenase
Solomou et al. Cancers (Basel) 2023

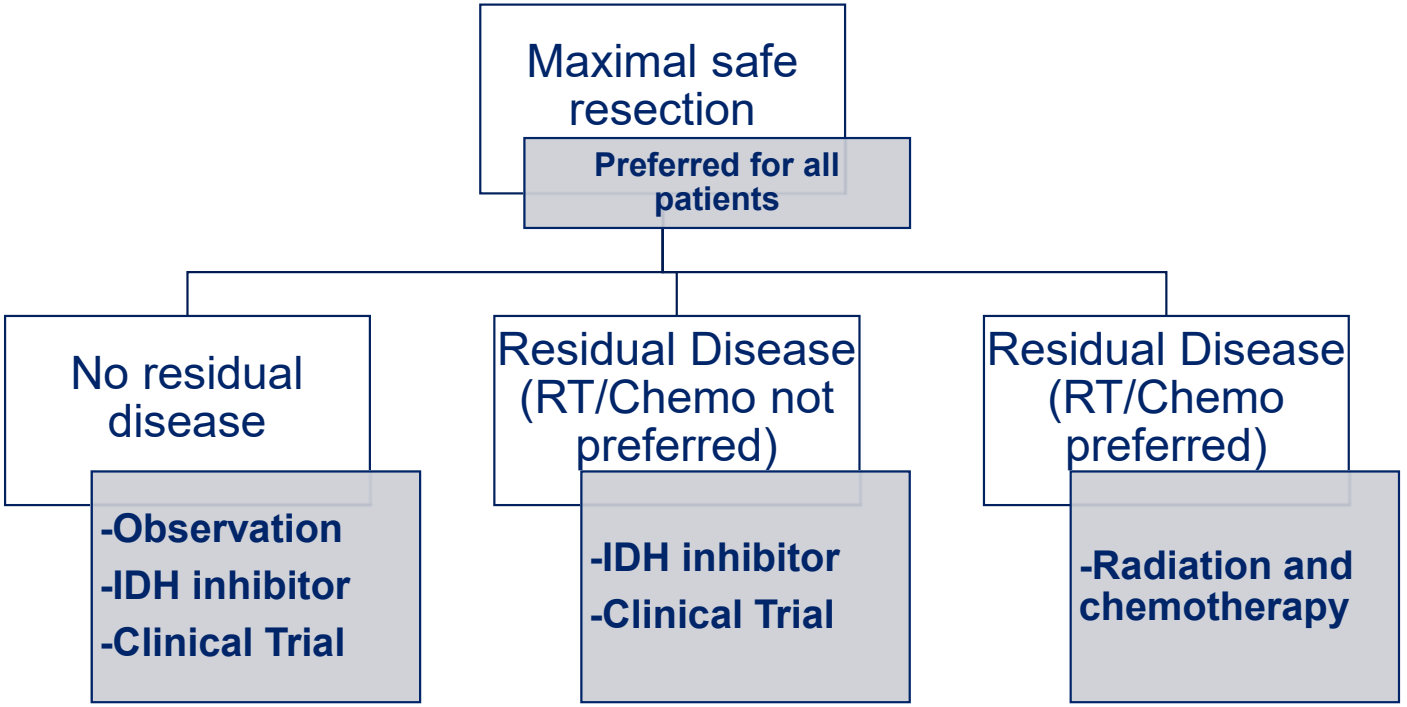
Role of IDH

- IDH mutation is the single-most powerful prognostic marker in diffuse gliomas
- Patients with lower-grade gliomas harboring an IDH mutation tend to have longer overall survival than those with tumors that express wildtype IDH



Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med. June 24, 2015.

Current Treatment



Current Treatment

Study	Population	Arms	Outcomes
EORTC 22845 (2006)	Grade 2 glioma	RT up-front	PFS 5.3 years
		RT at recurrence	PFS 3.4 years
RT 9802 (2016)	High-risk low-grade gliomas	RT + PCV	OS 13.3 years
		RT alone	OS 7.8 years
EORTC 22033 (2016)	High risk low-grade gliomas	RT alone	PFS 3.8 years
		TMZ	PFS 3.2 years
CATNON (2026)	IDH mutant grade 3 astrocytoma	RT without adjTMZ	OS 6 years
		RT with adjTMZ	OS 12.5 years

Bent et al. Lancet 2005
Laack et al. Semin Radat Oncol 2016
Baumbert et al. Lancet Hemat 2016
Bent et al. Lancet Oncol 2026

Limitations with Conventional Therapy

- Radiotherapy alone prolongs time to recurrence but does not seem to have a significant effect on overall survival

- Chemotherapeutic agents that are used for low-grade gliomas present risk of toxicities and introduce risk of DNA hypermutation
  - Alkylating agents such as temozolomide and procarbazine have data to link risk of DNA hypermutation
  - DNA hypermutation may lead to an increased risk of malignant transformation of low-grade gliomas
  - Alkylating agents carry risk of secondary malignancies

- Recurrence generally will occur regardless of the type of intervention made

Claus et al. N Engl J Med 2023
Choi et al. Neuro Oncol 2018

Case

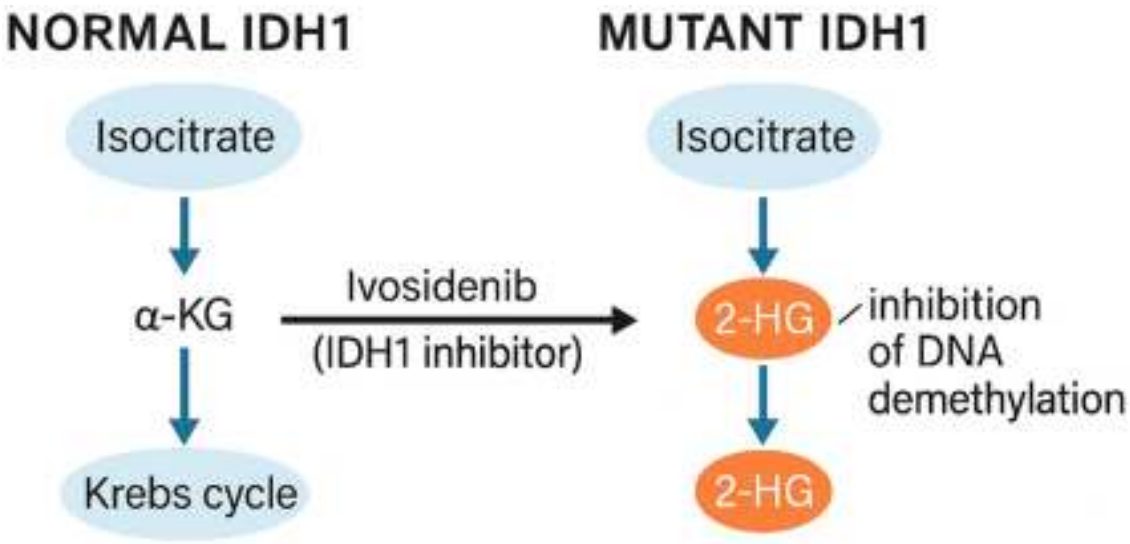
GM is a 68-year-old male with a newly diagnosed low-grade glioma. Mutational testing confirms presence of an IDH-1 mutation. Past medical history includes history of diabetes and hypertension. Current KPS is ~60 after surgery due to comorbid conditions.

After resection, there is evidence of residual disease on his post-operative imaging. While at his followup visit to discuss next steps, he states that he does not wish to take an aggressive approach to treating his tumor but is open to treatment options.

What is the most reasonable course of action to take?

A. Watch and wait
B. Consider treatment with an IDH-inhibitor
C. Strongly urge the patient to consider treatment with chemotherapy

Ivosidenib



Mechanism	IDH1 inhibitor
Usual Dosing	500mg by mouth once daily
Common Adverse Drug Reactions	**QTc prolongation**, CPK elevations, edema, nausea, diarrhea, myelosuppression Differentiation syndrome is **NOT** a concern in patients with gliomas
Pharmacist Considerations	Major substrate of CYP3A4 Should **NOT** be taken with high fat meal (may increase AUC ~25%) Off label use

Ivosidenib [package insert]. Boston, MA. Servier Pharmaceuticals Inc.; 2021
Dynarowicz et al. Pharmaceuticals. 2026

Ivosidenib in Glioma

Inclusion Criteria

- Patients 18 years or older with recurrent IDH-1 mutant glioma
- Expected life expectancy of ≥ 3 months

Ivosidenib 500mg PO once daily (N = 66)

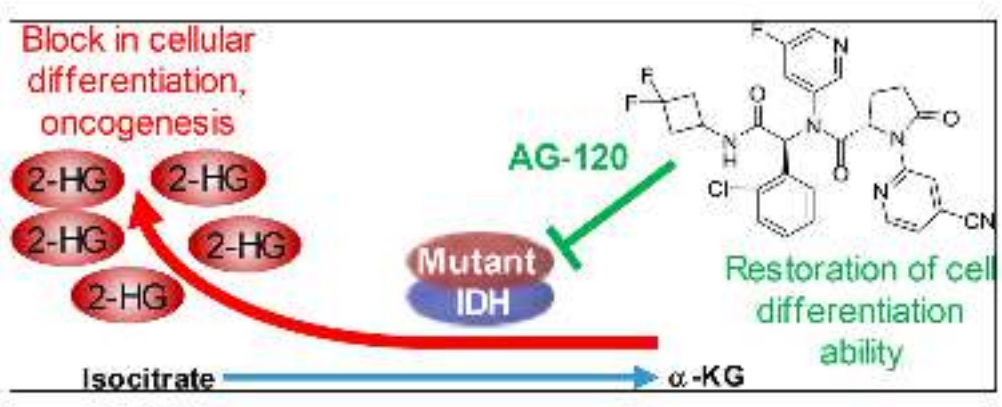
Non-enhancing disease (n = 35)
85.7% stable disease
Median PFS 13.6 months

Enhancing Disease (n = 31)
45.2% stable disease
Median PFS 1.4 months

Safety outcomes	• No major dose-limiting toxicities identified • Common ADRs included headache, nausea, fatigue, vomiting, diarrhea
Key Takeaways	**In patients with IDH-1 mutated gliomas, ivosidenib was associated with a favorable safety profile, especially in those with non-enhancing tumors**

Mellinghoff et al. J Clin Oncol 2020

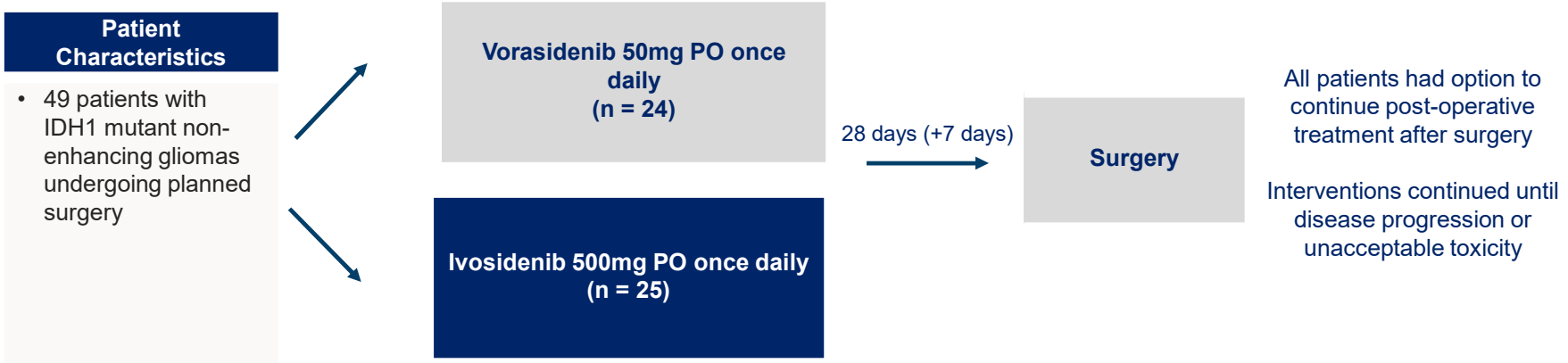
Vorasidenib



Mechanism	Dual IDH1 and IDH2 inhibitor
Usual Dosing	40mg orally once daily
Common Adverse Drug Reactions	**Hepatotoxicity,** fatigue, diarrhea, nausea, headache, myelosuppression
Pharmacist Considerations	Major substrate of CYP1A2 Vorasidenib may reduce efficacy of hormonal contraception

Vorasidenib [package insert]. Boston, MA. Servier Pharmaceuticals Inc.; 2024

Vorasidenib and Ivosidenib in IDH-1 mutant low-grade glioma



Key Outcomes	**Primary Outcome: intratumoral 2HG suppression** • Vorasidenib 92.6% suppression vs Ivosidenib 91.1% suppression **Other Key Outcomes** • Objective response rate for vorasidenib was higher than that of ivosidenib (**42.9% vs 35.7%**) • Vorasidenib showed higher tumor:plasma ratio when compared to ivosidenib • **Vorasidenib chosen as agent to pursue phase III testing**

Mellinghoff et al. Nat Med 2023

Case

After discussion, the decision is made to start GM on an IDH inhibitor. Pre-treatment workup reveals the following:

CMP:
- SCr 0.6
- AST 24
- ALT 17
- Total Bilirubin 0.3

CBC:
- WBC 3.4
- Hgb 10.2
- Plt 159,000

Other labs:
- CPK WNL
- QTc 506

Home medications
- Metformin 1000mg BID
- Lisinopril 20mg daily
- Diltiazem CR 240mg daily

Which IDH inhibitor would be preferred given the patient's characteristics?

A. Vorasidenib
B. Ivosidenib

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Which IDH inhibitor would be preferred given the patient's characteristics?

A. Vorasidenib
B. Ivosidenib

Case

GM is now planned to start vorasidenib therapy after his resection. What is an appropriate counseling point for patients starting vorasidenib?

A. Patients should avoid drinking grapefruit juice as vorasidenib is a major substrate of CYP3A4
B. Patients should avoid smoking as smoking can induce CYP1A2 and affect vorasidenib metabolism
C. Vorasidenib should be taken on an empty stomach
D. Patients should avoid acid-reducing agents as vorasidenib requires an acidic environment for absorption

INDIGO

Inclusion Criteria

- Patients 12 years or older with residual/recurrent grade 2 IDH-mutant oligodendroglioma or astrocytoma **with residual disease after surgery**
- KPS > 80
- No use of steroids for glioma management
- Considered for watch and wait

Vorasidenib 40mg PO once daily (n = 168)

Placebo (n = 163)

Outcomes	**Primary Outcome** • **Progression-free survival** **Key Secondary Outcomes** • **Time to next therapy** • **Objective response rate** • **Safety**

Mellinghoff et al. NEJM 2023

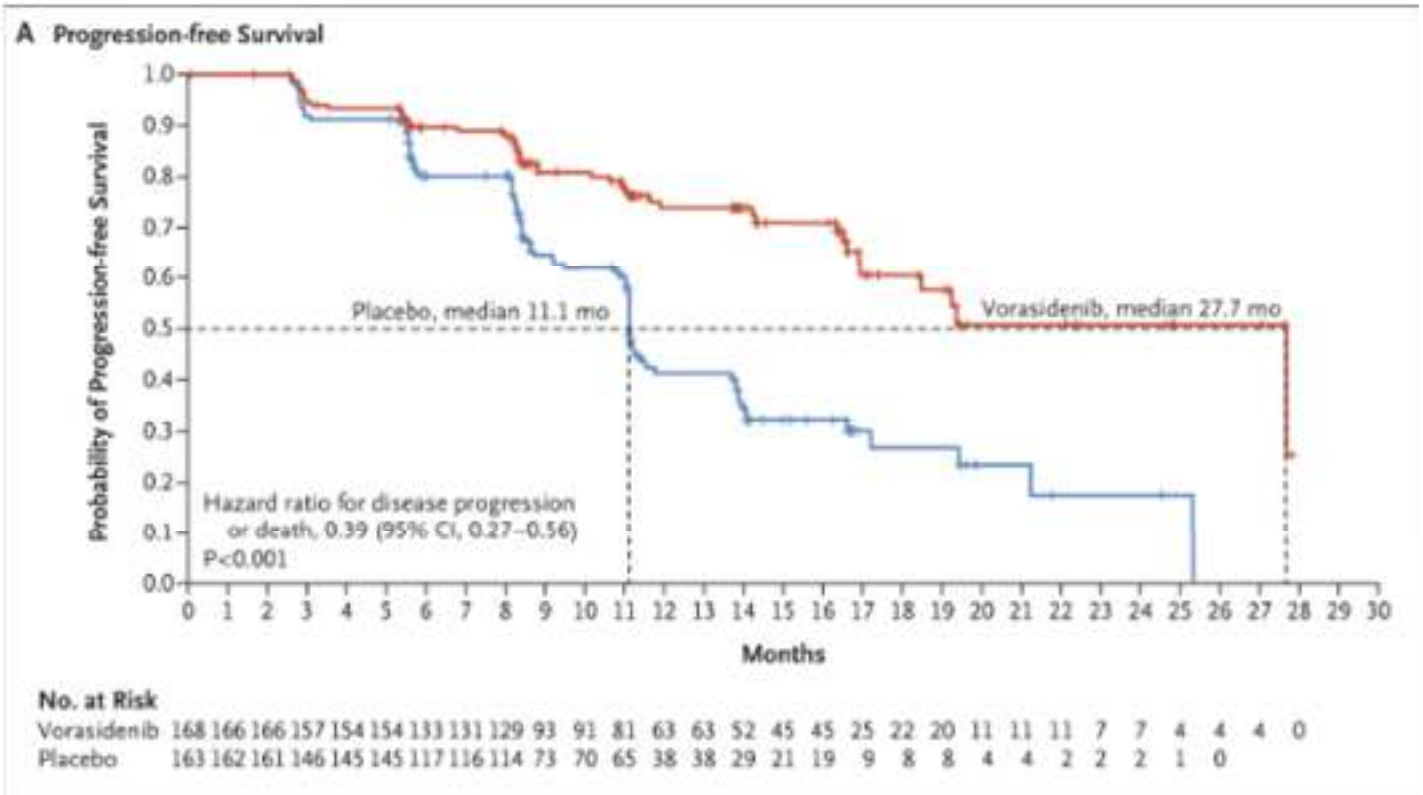
Select Patient Characteristics

Characteristic	Vorasidenib (N = 168)	Placebo (N = 163)
Age, median (range) – years	40.5 (21 – 71)	39 (16 – 65)
Male sex – no. (%)	101 (60.1)	86 (52.8)
KPS – no. (%)		
100	90 (53.6)	87 (53.4)
90 – 80	77 (45.8)	76 (46.6)
Prior lines of treatment – no. (%)		
1	126 (75.0)	134 (82.2)
≥2	42 (25.0)	29 (17.8)
Histologic Subtype – no. (%)		
Oligodendroglioma	88 (52.4)	84 (51.5)
Astrocytoma	80 (47.6)	79 (48.5)
IDH mutation Status – no. (%)		
IDH1-positive	163 (97.0)	152 (93.3)
IDH2-positive	5 (3.0)	11 (6.7)

Mellinghoff et al. NEJM 2023

INDIGO

Progression-Free Survival



Vorasidenib: **27.7 months**

Placebo: **11.1 months**

Hazard ratio: 0.39 (0.27-0.56)

Mellinghoff et al. NEJM 2023

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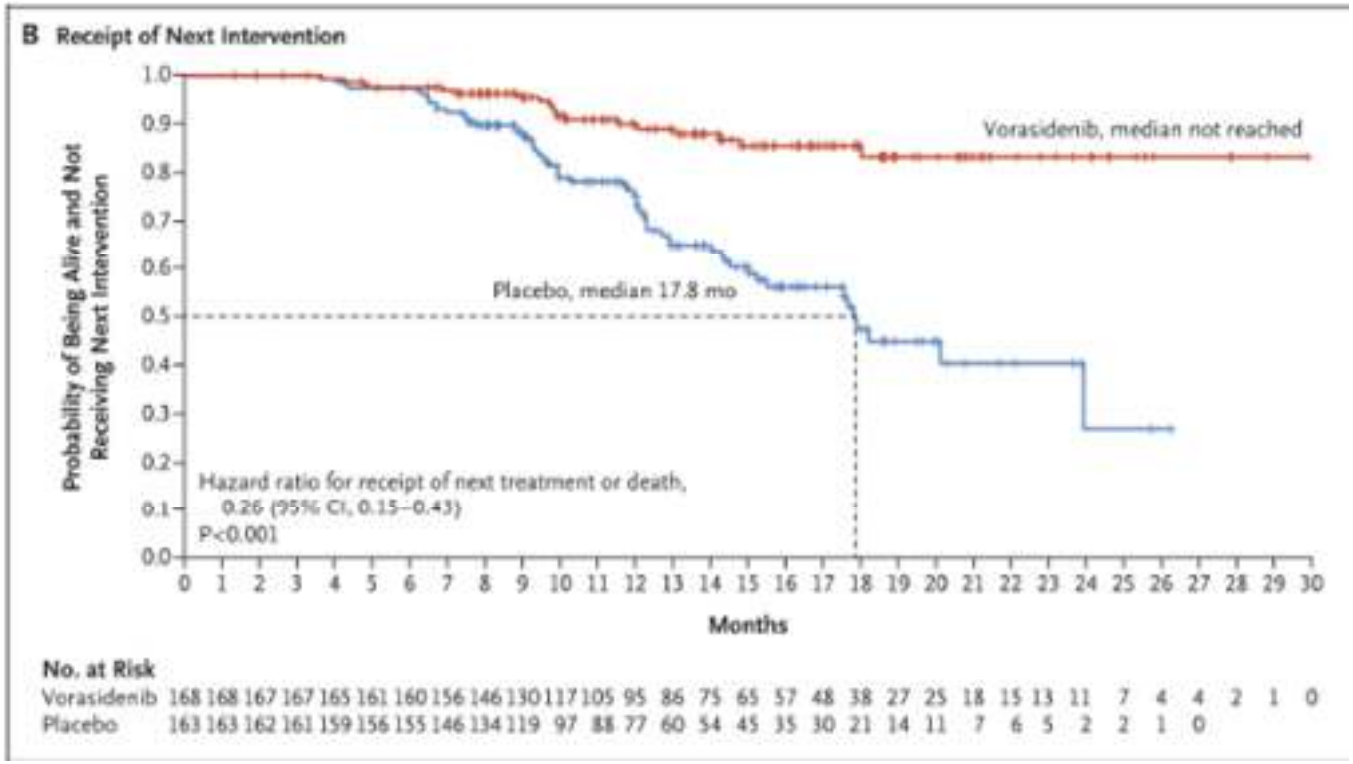
Time to Next Intervention



Vorasidenib: **Not reached**

Placebo: **17.8 months**

Hazard ratio: 0.26 (0.15-0.43)

Select Adverse Drug Events

Event	Vorasidenib (N = 168)		Placebo (N = 163)	
	Any Grade (n, %)	Grade ≥ 3 (n, %)	Any Grade (n, %)	Grade ≥ 3 (n, %)
Increased AST	**65 (38.9)**	**16 (9.6)**	**24 (14.7)**	**0**
Increased ALT	**48 (28.7)**	**7 (4.2)**	**13 (8.0)**	**0**
Increased GGT	26 (15.6)	5 (3.0)	8 (4.9)	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
Seizure	25 (15.0)	0	26 (16.0)	0

Mellinghoff et al. NEJM 2023

Management of Liver Toxicity

Degree of Hepatotoxicity	Recommended Action
Grade 1	Continue vorasidenib at current dose
Grade 2 (AST or ALT > 3-5x ULN **without** concurrent total bilirubin > 2x ULN)	**First occurrence:** withhold vorasidenib until recovery to ≤ grade 1 or baseline If recovery occurs in **≤ 28 days**, resume vorasidenib at same dose If recovery occurs in **> 28 days**, resume vorasidenib at a reduced dose
Grade 3 (AST or ALT > 5-20x ULN **without** concurrent total bilirubin > 2x ULN)	**First occurrence:** withhold vorasidenib until recovery to ≤ grade 1 or baseline If recovery occurs in **≤ 28 days**, resume vorasidenib at reduced dose If recovery occurs in **> 28 days**, permanently discontinue vorasidenib
Grade 2 or 3 with concurrent total bilirubin > 2x ULN Or **Grade 4**	Permanently discontinue vorasidenib

Vorasidenib Dose Reduction Levels	
Usual (initial) dose	40mg once daily
First Dose reduction	20mg once daily
Second Dose Reduction	10mg once daily

Vorasidenib [package insert]. Boston, MA. Servier Pharmaceuticals Inc.; 2024

Case

GM returns to clinic four weeks after starting vorasidenib for a routine visit. Labs today are notable for **grade 2 AST and ALT elevations without any significant increases in bilirubin**. Patient confirms that he has not started any new medications or supplements and it is deemed that the hepatoxicity is most likely related to starting vorasidenib.

What is the most reasonable course of action to take?

A. Permanently discontinue vorasidenib
B. Reduce vorasidenib from 40mg daily to 20mg daily
C. Withhold vorasidenib until recovery to ≤ grade 1 or baseline
D. Continue vorasidenib at current dose and recheck labs in 2 weeks

Case

After holding drug for **6 weeks**, GM's liver enzymes are return to baseline.

What is the most reasonable course of action to take?

A. Permanently discontinue vorasidenib
B. Resume vorasidenib at a reduced dose of 20mg once daily
C. Resume vorasidenib at the initial dose of 40mg once daily
D. Consider switching vorasidenib to ivosidenib

Vorasidenib Dose Reduction Levels	
Usual (initial) dose	40mg once daily
First Dose reduction	20mg once daily
Second Dose Reduction	10mg once daily

INDIGO: Conclusions

- Vorasidenib provides significant increases in progression-free survival and delays time to next intervention in patients with IDH-mutant low-grade gliomas
- Vorasidenib is relatively well tolerated but does require close laboratory monitoring to assess for tolerability and need for dose reductions
- The role of vorasidenib in patients with no residual disease after surgery is unclear

Mellinghoff et al. NEJM 2023

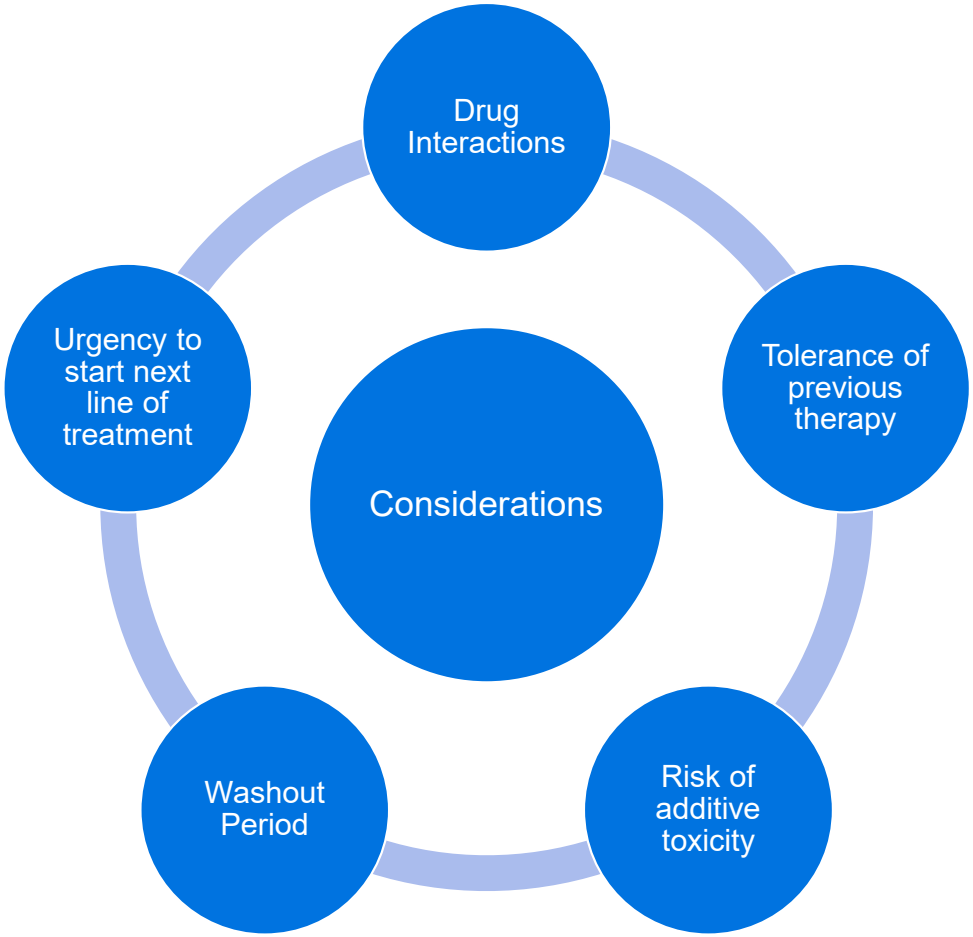
Vorasidenib and Ivosidenib Comparison

Characteristic	Ivosidenib	Vorasidenib
Mechanism of Action	IDH1 inhibitor	Dual IDH1 and IDH2 inhibitor
Adverse Drug Reactions	**QTc prolongation**, CPK elevation, fatigue, GI toxicity, myelosuppression	**Hepatotoxicity**, fatigue, GI toxicity, myelosuppression
Pharmacokinetics	Major substrate of CYP3A4 Should not be taken with high fat meal	Major substrate of CYP1A2
Clinical Commentary	Data limited to early phase trials Limited CNS penetration (brain tumor-to-plasma ratio ~0.02)	Randomized data to support use in low-grade gliomas More CNS penetration (brain tumor-to-plasma ratio 1.6)

Chen Y et al. PreClin Drug Metabolism 2021

Konteatis Z et al. ACS Med Chem Lett. 2020

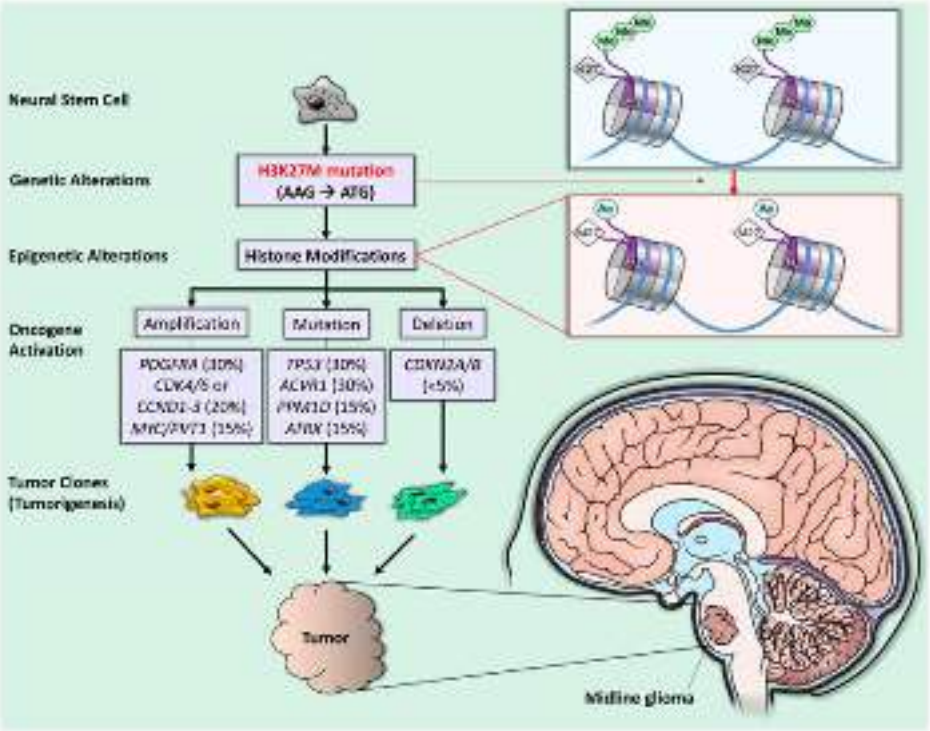
Considerations for switching from ivosidenib to vorasidenib



H3K27M-mutant Gliomas

H3K27M mutant glioma

- H3K27M mutant gliomas are a form of gliomas that arise in midline brain structures
- Histone H3 is a key protein involved in the structure of chromatin in eukaryotic cells
- Somatic missense mutation on histone H3 leads to oncogenesis through upregulation of protooncogenes and suppression of cellular differentiation
  - Lysine 27 to methionine
- Higher mortality and poorer prognosis with H3K27M glioma when compared to wildtype gliomas
- Typically present with hydrocephalus, headaches, pseudobulbar symptoms, and lower cranial neuropathies



Epidemiology

- Incidence: 0.06 per 100,000
  - Affects ~100-300 children per year in the United States
- Bimodal distribution

Characteristic	Pediatric	Adult
Age Distribution	Ages 4 – 9 Median age of diagnosis: 6 – 7 years	Median age of diagnosis: 30 – 40 years
Gender Distribution	Slight female predominance (54.7% female)	Slight male predominance (57.7% male)
Location	Pons and brainstem (65-80%)	Thalamus (~40%)

- Limited data to describe risk factors
  - Inherited cancer predisposition syndromes such as neurofibromatosis type 1 (NF-1), Li-Fraumeni syndrome, Lynch syndrome are thought to be associated

Iorgulescu JB et al. Neuro Oncol. 2022

Survival and Prognosis

- Considered the leading cause of brain tumor death in pediatric population
- Adults tend to have significantly better survival vs pediatric population

Characteristic	Pediatric	Adult
Survival	Median OS: 4-5 months	Median OS: 7.5 months

- Favorable prognostic factors in adult population
  - Older age
  - Thalamic location of tumor
  - Lower histologic grade
  - Gross total resection

Iorgulescu JB et al. Neuro Oncol. 2022

Current Treatment Landscape

- Surgical resection and radiation comprises backbone of therapy for all cases
  - Gross total resection is oftentimes not feasible given location of tumor
    - ~15% of patients are able to undergo gross total resection
    - ~15% of patients are only able to undergo biopsy
  - Radiation Dose: 54 Gy in 30 fractions

Characteristic	Pediatric	Adult
Survival without treatment	Median OS: 4-5 months	Median OS: 7.5 months
Survival with treatment	Median OS: 8-14 months	Median OS: 10-13 months

- Systemic therapies including agents like temozolomide have not shown benefit in this population

Dordavipirone (ONC201)

Mechanism	Dual Mechanism • **Mitochondrial caseinolytic proteinase P (C1pP) activation** → restoration of H3K27 trimethylation • **Dopamine D2 receptor antagonism** → inhibition of downstream pro-survival pathways and promotion of cell apoptosis
Usual Dosing	Adult: 625mg orally once weekly on **empty stomach** (no food 1 hour before, 3 hours after) Pediatric: weight-based dosing on **empty stomach** *Comes in 125mg capsules *Missed dose: if dose is missed within 2 days, may make up dose
Key Adverse Drug Reactions	**QTc prolongation**, **hypersensitivity reactions,** fatigue, headache, nausea/vomiting (consider pre-med), hepatoxicity, electrolyte imbalance, myelosuppression
Pharmacist Considerations	Major substrate of CYP3A4 Capsules may be opened and mixed with 15-30mL of liquid (must be administered within **2 hours** of preparation)

Dordaviprone [package insert]. Palo Alto, CA. Jazz Pharmaceuticals, Inc.; 2025

Case

YL is a 32-year-old female with recurrent H3K27M mutant glioma and related seizure disorder on valproic acid that presents to clinic for exploration of treatment options. After discussion with her neuro-oncologist, it is decided that she will start dordaviprone.

Which of the following is **not** a clinical consideration in patients starting this therapy?

A. Patient's home medications should be screened for concomitant use of QTc-prolonging medications
B. Patient's home medications should be screened for concomitant use of medications that affect CYP3A4
C. Patient should be counseled on recognizing signs and symptoms of a hypersensitivity reaction
D. Patient's home medications should be screened for concomitant use of medications that alter gastric pH

Case

YL is a returns to clinic four weeks after starting dordaviprone.

She has been having issues tolerating her valproic acid therapy and her neuro-oncologist asks you for recommendations. What is a reasonable option?

A. Consider switching to levetiracetam
B. Consider switching to phenytoin
C. Consider switching to carbamazepine
D. Consider switching to phenobarbital

Dordaviprone in Recurrent H3K27M-Mutant Diffuse Midline Glioma

Inclusion Criteria

- Recurrent or progressive H3K27M-mutant glioma
- Age ≥ 2
- KPS ≥ 60
- Washout of at least 90 days prior to last radiation
- On stable or decreasing dosage of corticosteroids

→

Dordapivrone 625mg weekly (adults) or pediatric equivalent through clinical trial or expanded access program

→

Data Analysis (N = 50)

Outcomes	**Key Outcomes** • **Overall Response Rate** • **Median Time to Response** • **Median Duration of Response** • **Safety Outcomes**

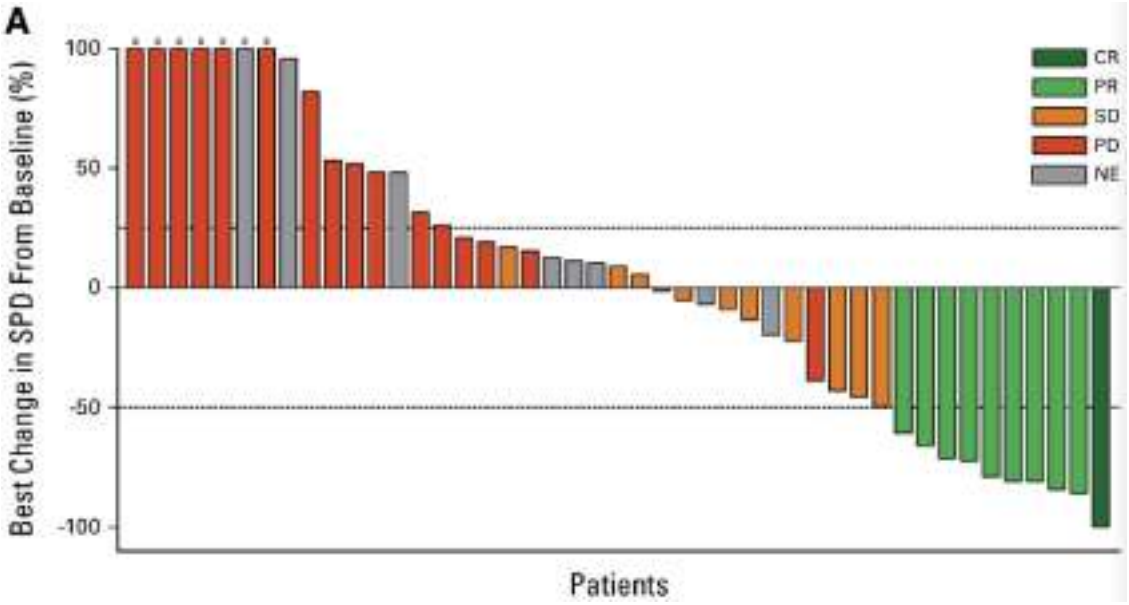
Arrillaga-Romany, et al. J Clin Oncol. 2024

Select Patient Demographics

Characteristic	All Patients (N = 50)
Age, years, median (range)	30 (8 – 70)
18 to <40, No. (%)	32 (64)
< 18, No. (%)	4 (6)
≥40, No. (%)	14 (28)
Sex, No. (%)	
Male	27 (54.0)
Female	23 (46.0)
Primary tumor location, No. (%)	
Thalamic	33 (66.0)
Other midline	17 (34.0)
Multifocal disease, No. (%)	23 (46.0)
First recurrence, No. (%)	37 (74.0)
Previous temozolomide, No. (%)	44 (88.0)
Time from recurrence, days, median (range)	20 (1-126)
Daily steroid dose (daily dexamethasone equivalent dose), mg, median (range)	1.1 (0.0-12.0)

Arrillaga-Romany, et al. J Clin Oncol. 2024

Results



Parameter	All Patients (N = 50)
Overall Response, No. (%) [95% CI]	**15 (30.0) [17.9 – 44.7]**
Complete Response	1 (2.0)
Partial Response	9 (18.0)
Stable Disease	7 (14.0)
Progressive Disease	13 (26.0)
Disease Control Rate, No. (%) [95% CI]	**22 (44.0) [30.0 – 58.7]**
Median Duration of Response	**11.2 months**
Corticosteroid Response (n = 15)	
Response rate, No. (%) [95% CI]*	7 (46.7) [21.3 to 73.4]
Time to response (months), median (range)	3.5 (1.9 – 5.6)

*Disease control rate: CR + PR + SD

*Steroid response was defined as ≥50% reduction in average daily corticosteroid dose compared with baseline with stable or improved KPS/LPS

Arrillaga-Romany, et al. J Clin Oncol. 2024

Select Adverse Effects

Event	Dordapivirone (N = 50)		
	Grades 1 – 2 (n, %)	Grade 3 (n, %)	Any Grade (n, %)
Fatigue	16 (32.0)	7 (14.0)	23 (46.0)
Nausea	17 (34.0)	1 (2.0)	23 (46.0)
Vomiting	12 (24.0)	1 (2.0)	13 (26.0)
Headache	12 (24.0)	4 (8.0)	16 (32.0)
Lymphocyte count decreased	8 (16.0)	2 (4.0)	10 (20.0)
Platelet count decreased	7 (14.0)	0 (0)	7 (14.0)
White blood cell decreased	3 (6.0)	0 (0)	3 (6.0)
ALT increased	6 (12.0)	0 (0)	6 (12.0)
AST increased	6 (12.0)	0 (0)	6 (12.0)
Rash	1 (2.0)	2 (4.0)	3 (6.0)

Arrillaga-Romany, et al. J Clin Oncol. 2024

Conclusions

- Dordapivirone exhibited durable and clinically meaningful efficacy in recurrent H3K27M-mutated gliomas
- Dordapivirone was relatively well tolerated with low rates of significant adverse drug reactions
- Data has bias toward young adult patients over pediatric patients
- Data collected was derived from a pooled analysis of trials making data difficult to extrapolate

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Edward Lee, PharmD, BCOP
Neuro-oncology Clinical Pharmacy Specialist
Memorial Sloan Kettering Cancer Center