Neuro-Oncology Debate

Grade 3 IDH-Mutated Gliomas: Is IDH Inhibitor Standard of Care

Position: Yes

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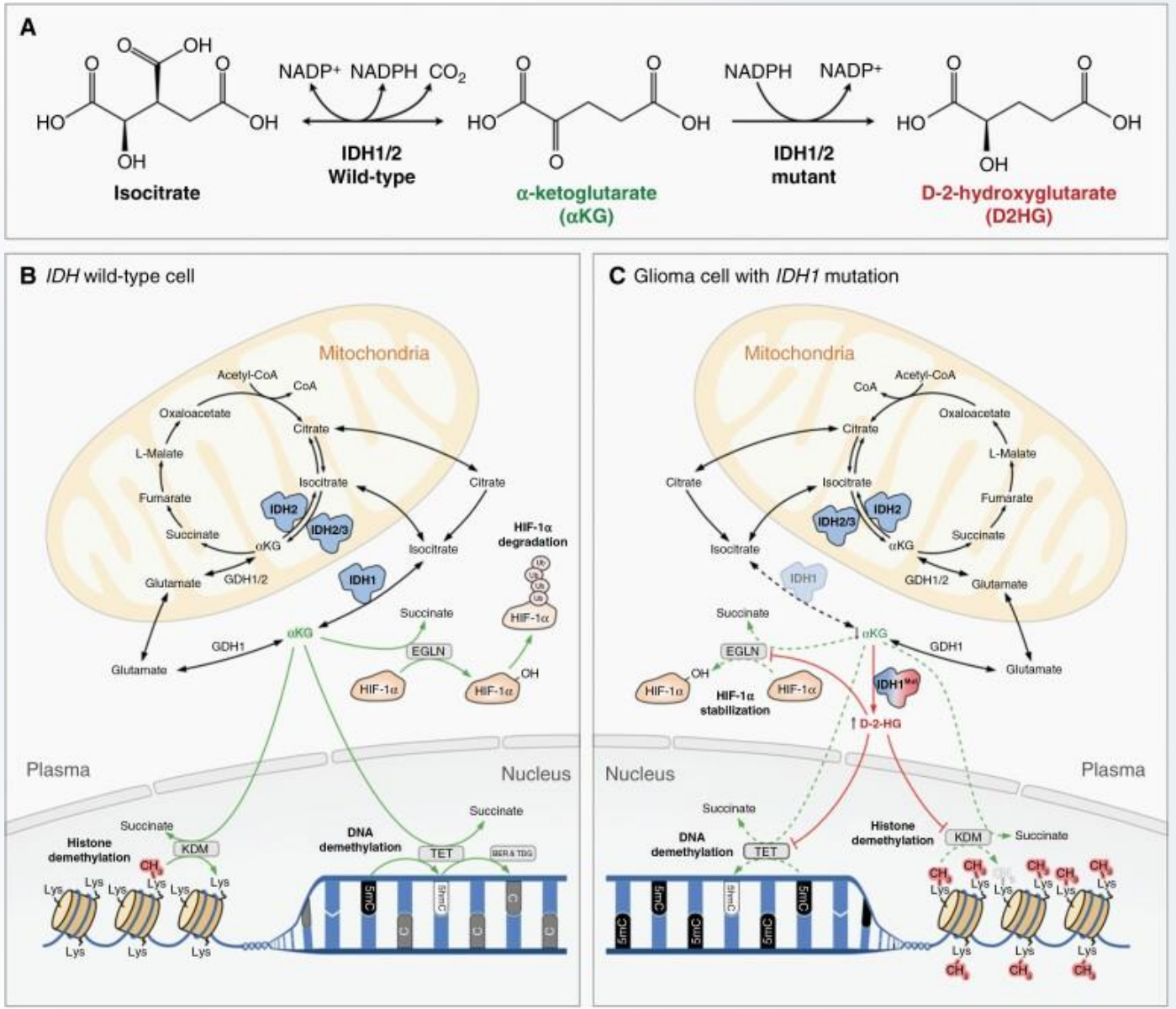
Background

- IDH Mutation Defines:
  - Astrocytomas
  - Oligodendrogliomas (with 1p/19q co-deletion)
- Deficit in TCA/Krebs Cycle
  - Catalyzes back-reaction
  - Generates oncometabolite D2HG
  - Leads to Global Hypermethylation
    - “G-CIMP” or Glioma CpG Island Methylation Phenotype
  - Early Driver of Glioma Development

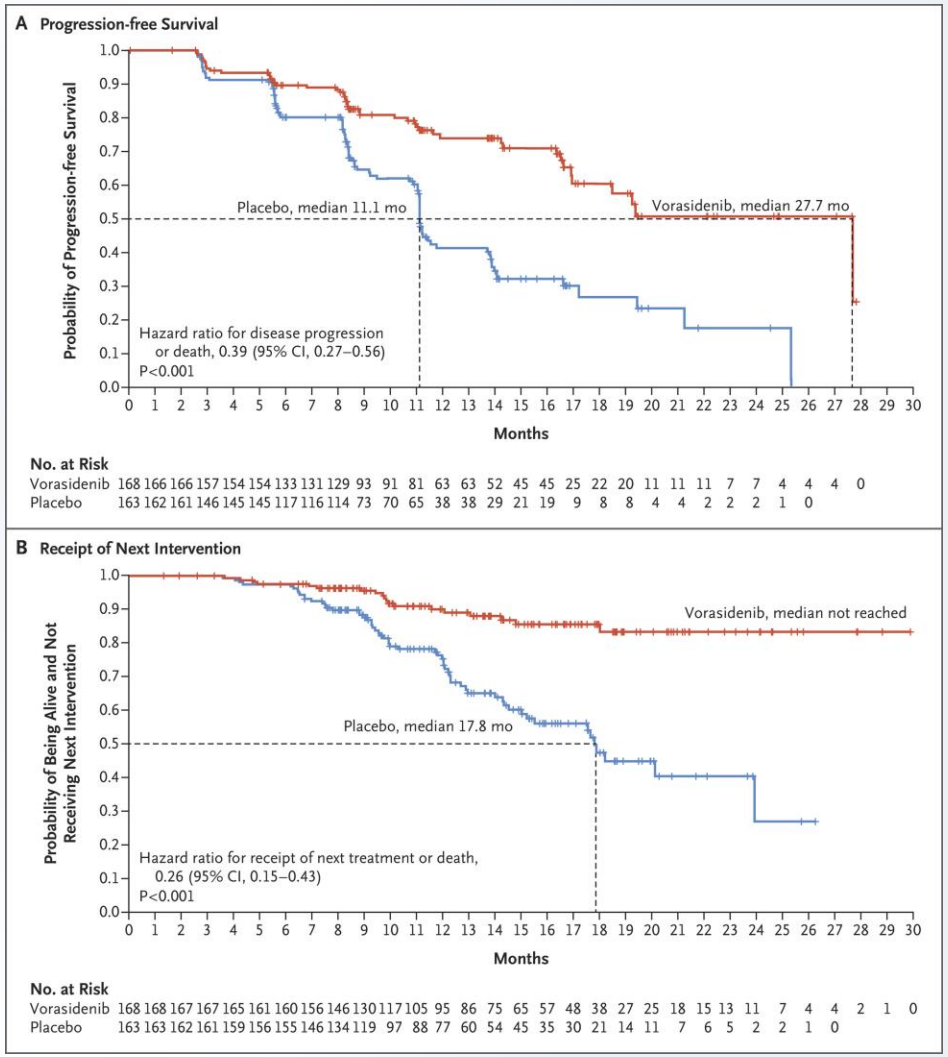


Miller et al. (2020) Neurooncol. PMID: 36239925

INDIGO Trial Shows Efficacy of Vorasidenib in Grade 2 Gliomas

Vorasidenib: Brain-Penetrant IDH1/2 Inhibitor

- INDIGO Trial in 2023 led to FDA approval in 2024 for low-grade (Grade 2) IDH mutated gliomas
- Updated data from ASCO 2026:
  - Median Progression-Free Survival: **44.1 months**
  - Time to Next Intervention: **median not reached**
  - Objective Response Rate:
    - 20.8% showing gradual or durable improvement
    - 72.6% showing stable disease
  - Seizure reduction (new finding): 72% reduction



Mellinghoff et al. (2023) *NEJM* (PMID: 37272516); Cloughesy et al. (2026) *JCO* (DOI: 10.1200/JCO.2026.44.16_suppl>2010)

Why Not Vorasidenib for Grade 3 Astrocytomas

Give me the shot,
Give me the pill,
Give me the cure,
Now what you've done to my world.
-Guy Picciotto (not an oncologist)

Getty Images

But wait, the FDA only approved it for grade 2 gliomas!
-Sensible Oncologists (like Dr. Donovan)

Standard of Care Radiation and Chemotherapy Can Be Deleterious

IDH Mutant Glioma patients tend to be young and in prime years

- Most diagnosed in 20s-40s: prime education/working/family age with long lifespans

Radiation Confers Risk:

- Secondary tumors, particularly treatment-refractory meningiomas
- Neurocognitive deficits are inevitable over time, can range from mild to more severe
- Treatment-related inflammation can require steroids or more aggressive interventions

Chemotherapy Confers Different and Overlapping Risk:

- Can cause fertility issues or prolonged cytopenias
- Risk of hypermutation leading to treatment-refractory glioma progression
- May also contribute to neurocognitive deficits and treatment-related inflammation

Pathology/Histochemistry is a Social Construct

Grade 2 vs Grade 3 are very subjective

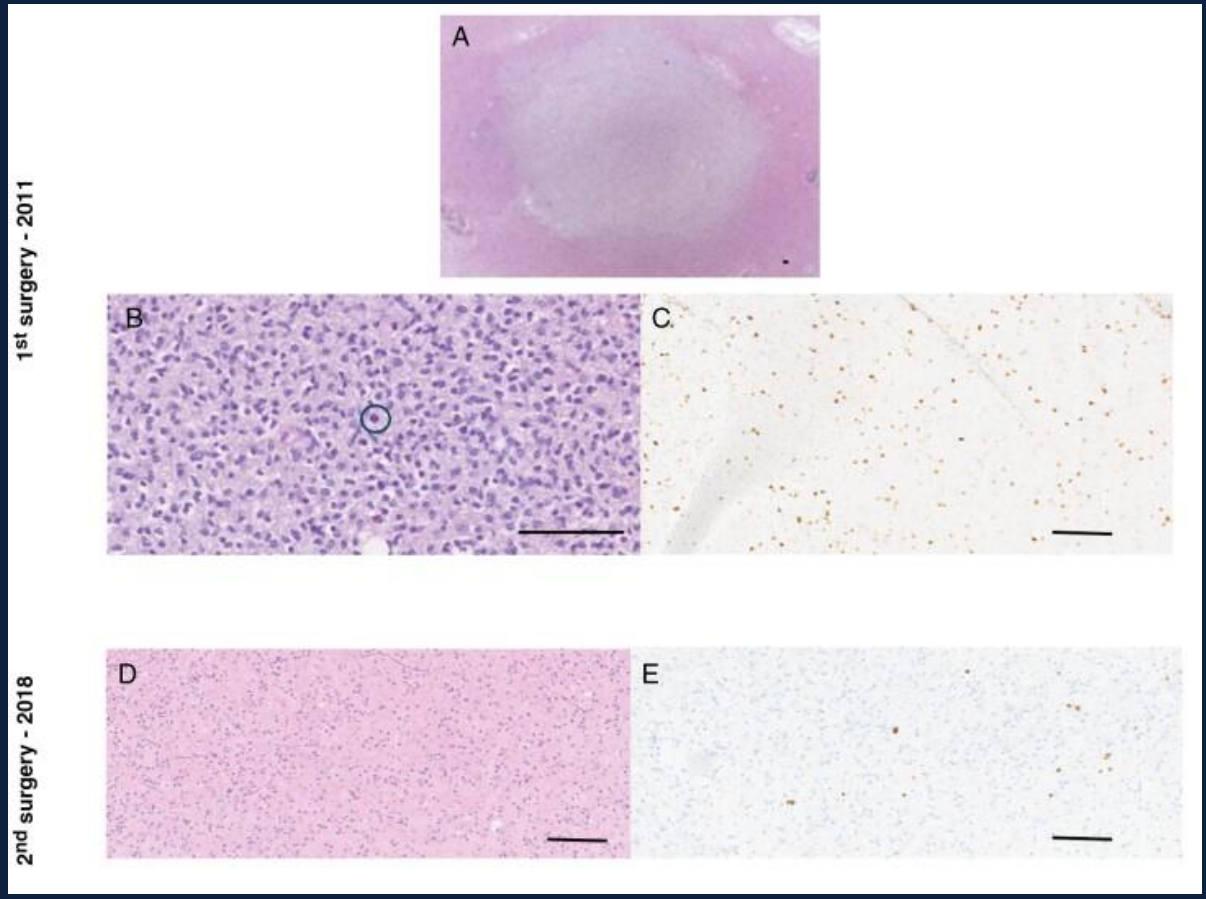
- Strong interobserver biases on histological evaluations
  - Grade 3 criteria are nebulous:
    - Anaplasia → No Standardized Definition
    - Increased mitotic activity/nuclear atypia → No Established Cutoff
    - Hypercellularity → Qualitative Evaluation
    - Mitoses per 10 High-Power Field → Quantifiable, but Subjective
    - Ki67 Index → Quantifiable, but Subjective
      (6 for oligo, 2-3 for astro)
      (But Ki67 1-6% lacks prognostic value)

2021 WHO Criteria; Blobner et al. (2025) *J Neurooncol* (PMID: 40702387)

Intratumoral Heterogeneity: Resection ≠ Residual

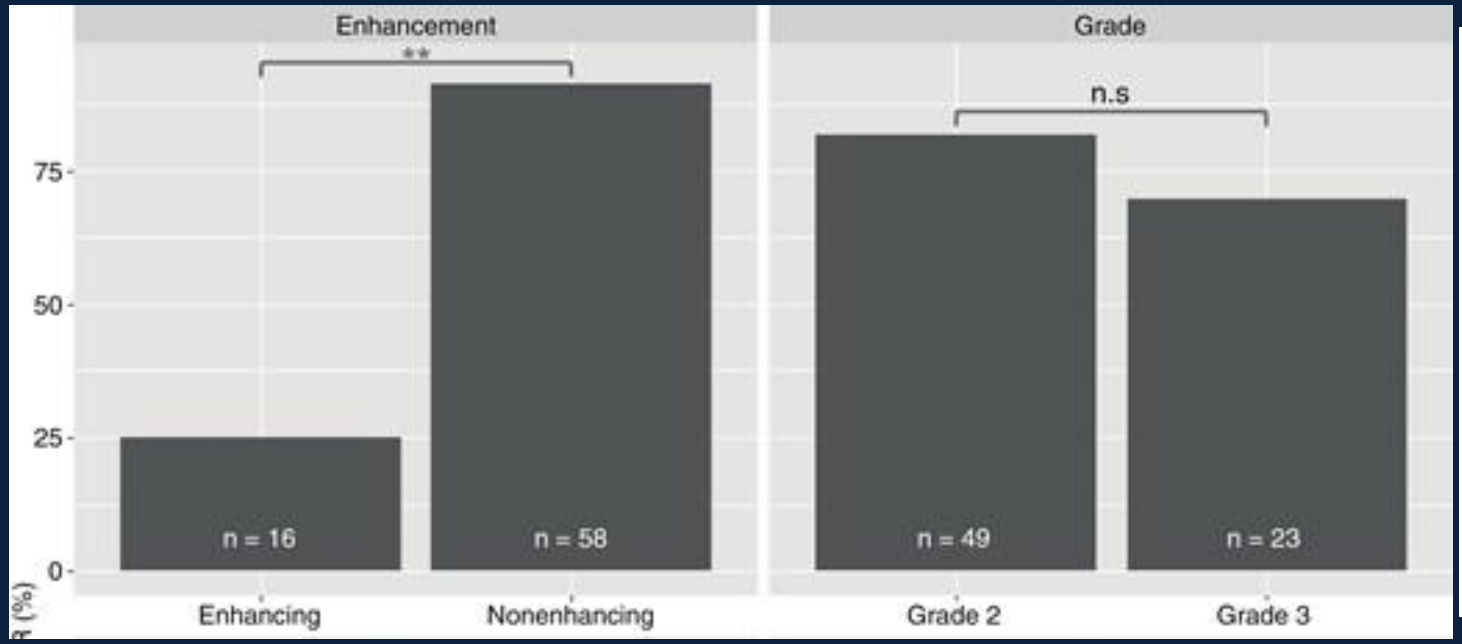
Grading based on most aggressive feature visible

- Glioma progression is a spectrum
- Resection of high-grade feature may eliminate high-grade feature
- Resected tumor does not necessarily reflect residual or microscopic tumor



Darlix et al. (2024) *Neurooncol Pract* (PMID: 39776530); Darlix et al. (2020) *Neurology* (PMID: 31969465)

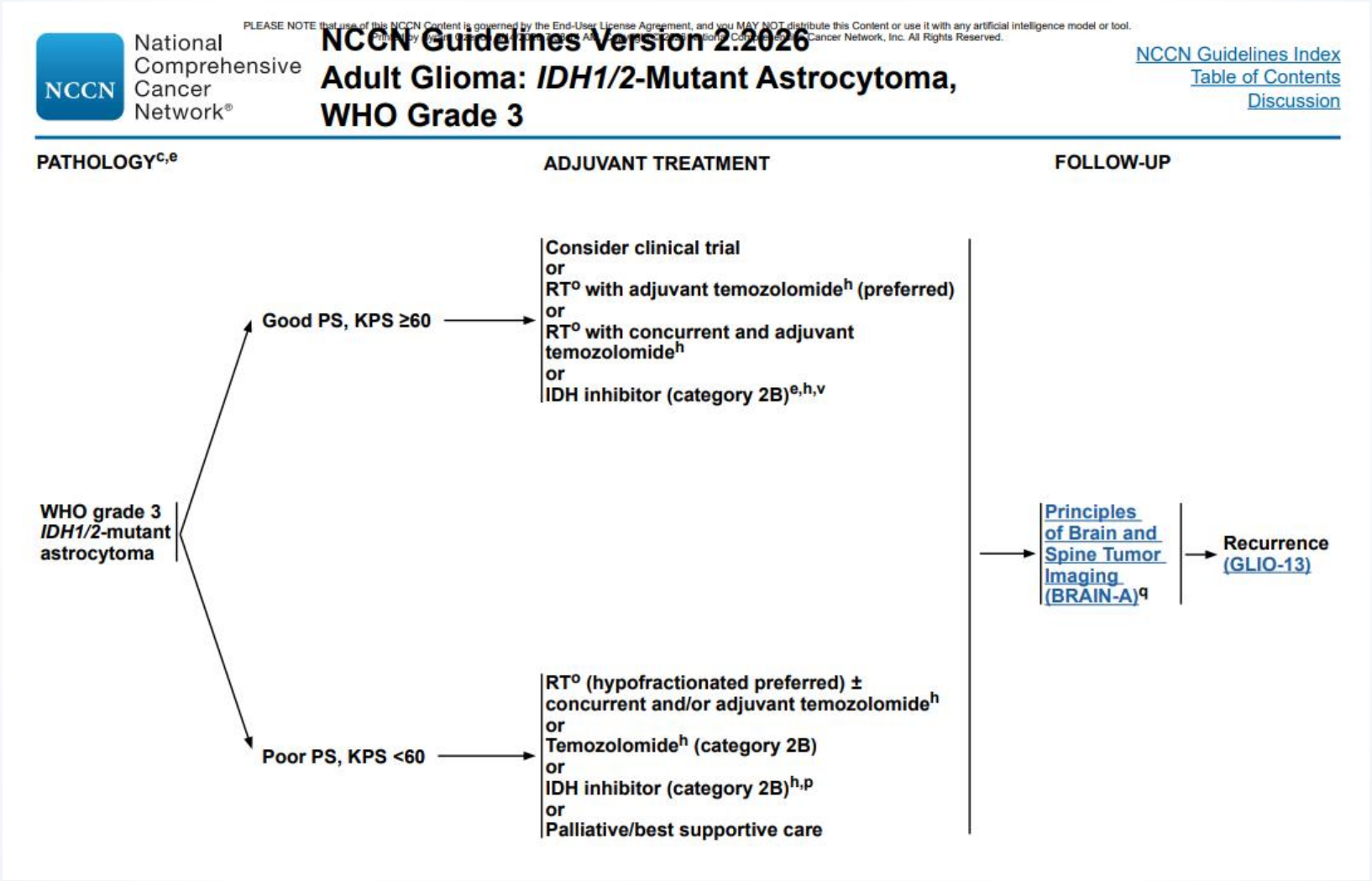
Clinical Experience with Ivosidenib Suggests Benefit in Grade 3



Characteristic	Grade in All Patients			Grade in First-Line Ivo			Grade in Subsequent-Line Ivo		
	Grade 2, N = 47	Grade 3, N = 22	p-value	Grade 2, N = 28	Grade 3, N = 4	p-value	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

Lanman et al. (2024) *Neruooncol Adv* (PMID: 39911703)

NCCN Recommends Considering in Poor KPS Patients



Same advisement in the Grade 3 Oligodendroglioma Section

https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

Summary

Benefit of IDH mutant inhibitor:

- Delays time to radiation and chemotherapy that can have long-term consequences
  - Especially in adults in prime productivity age
- Good tolerability
- Ease of administration

Though not specifically studied, evidence of potential efficacy

Histology has subjective qualities, and intratumoral heterogeneity may allow for careful selection of “better-behaving” Grade 3 gliomas

If the tumor grows on therapy, then switch over

Q&A