CNS Targeted Therapy: Life Beyond the Alkylators

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Objectives

1. Understand the biological basis for targeting *IDH* mutations in glioma diagnoses

2. Describe the unique mechanism of action for vorasidenib

3. Determine vorasidenib place in therapy as studied within the INDIGO Trial

Rosetta Stone

	Shorthand
central nervous system	CNS
glioblastoma	GBM
isocitrate dehydrogenase	IDH
investigating vorasidenib in glioma	INDIGO
Karnofsky performance scale	KPS
low grade glioma	LGG
mutant isocitrate dehydrogenase	mut*IDH*
procarbazine, lomustine, vincristine	PCV
response assessment in neuro-oncology	RANO
radiation therapy oncology group	RTOG
standard of care	SOC
wildtype	WT

Incidence, Survival, and Mortality

Malignant CNS tumors account for ~1% of all invasive cancer cases in the United States

- Most commonly diagnosed solid tumor in children
- Leading cause of cancer death
  - Males < 40 years
  - Females < 20 years

Gliomas are the most common malignant primary brain tumor

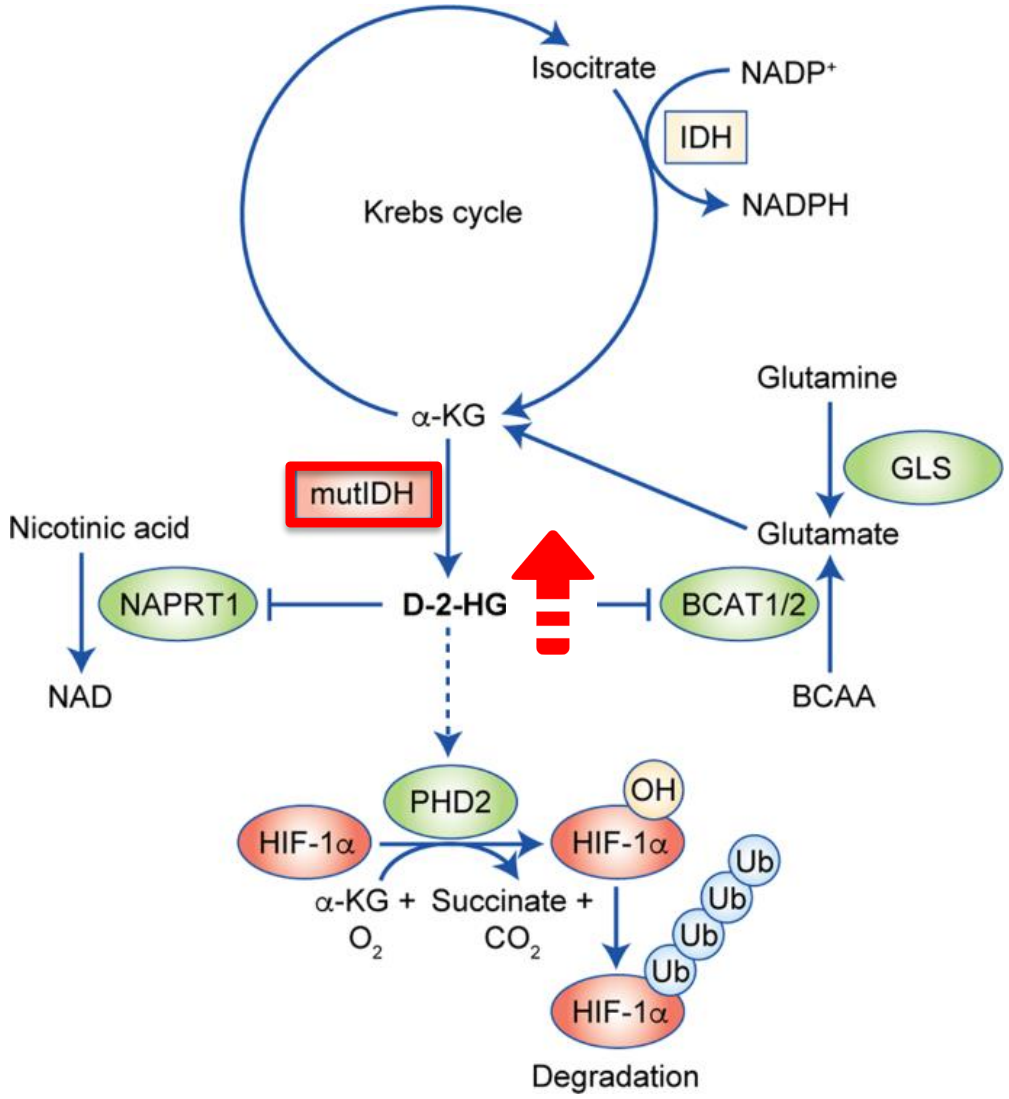
- World Health Organization categorization
  - Histology
  - Molecular features

Siegel RL. *CA Cancer J Clin.* 2021;71:7-33

Glioma Molecular Testing

BIOMARKERS			
IDH1	CDKN2B	FUBP1	POT1
IDH2	CIC	H3F3A	PTEN
MSI	EGFR	HIST1H3B	TERT promoter
NTRK1/2/3	EGFRvIII	NF1	TP53
Tumor Mutational Burden	FGFR1	NOTCH1	TSC1
ATRX	FGFR2	PDGFRA	TSC2
BRAF	FGFR3	PIK3CA	TSC3

Metabolic Reprogramming in mut*IDH* Glioma



Han S. *British J of Cancer.* 2020;122:1580-89.

Molecular Characterization

Incidence	
Grade II	50 - 81%
Grade III	42 - 54%
Grade IV	15 - 20%

IDH1 and *IDH2* mutation

Guideline recommendation:

- Testing *required* for the workup of all gliomas

Diagnostic value:

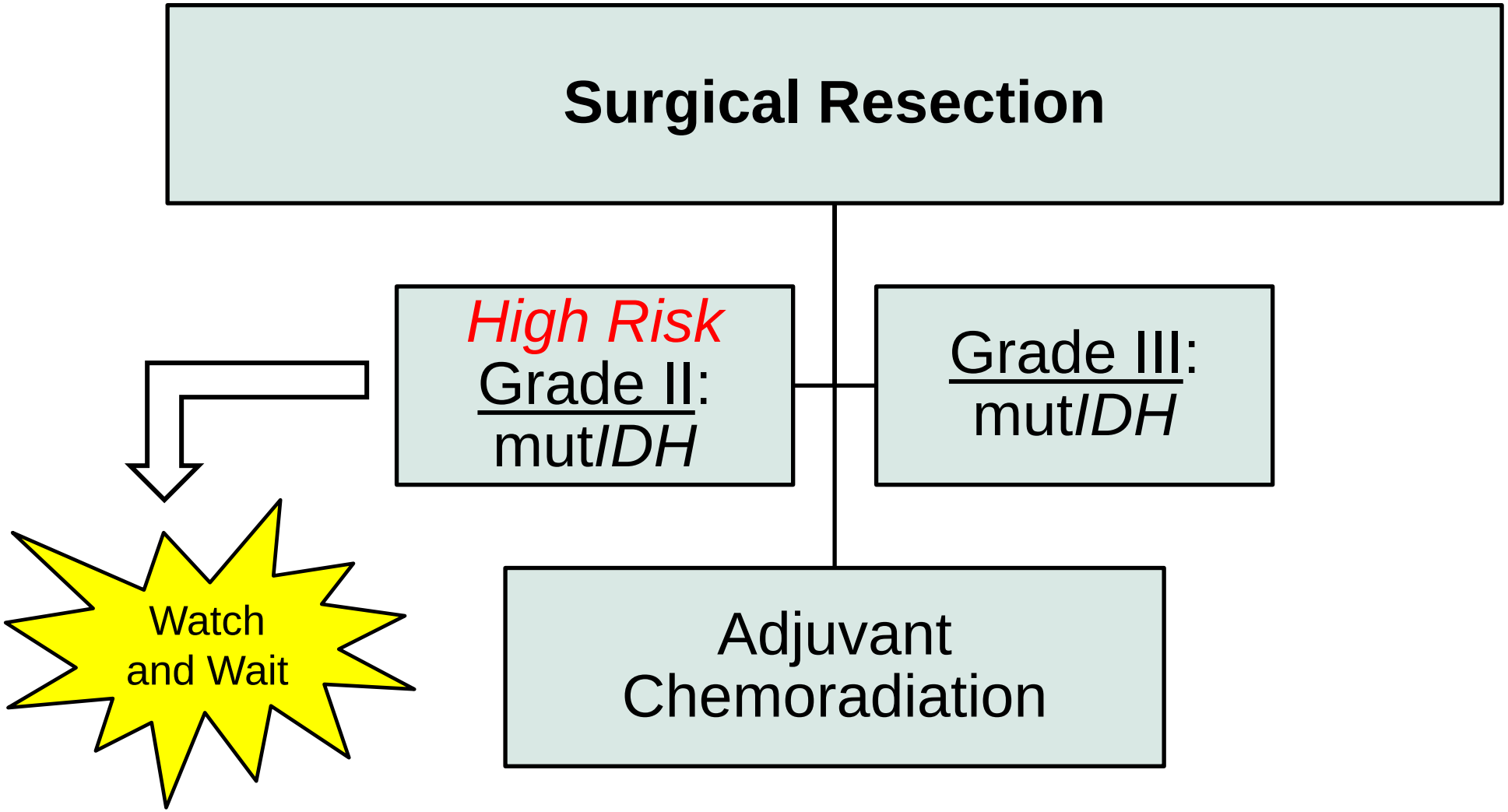
- Distinguishes lower-grade gliomas from GBM

Prognostic value:

- Associated with favorable prognosis in grade II/III glioma
- Survival benefit for patients treated with radiation or alkylating systemic therapy

NCCN: CNS Malignancies. Version1.2023. | Louis DN. *Acta Neuropath*. 2016;131:803-20

Guideline Recommended Standard of Care



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Vorasidenib (AG-881)

Mechanism of action

- Dual inhibitor of mutant *IDH1* and *IDH2* enzymes

Developed for penetration across the blood brain barrier

- Brain-to-plasma ratio (C_b:C_p): 1.33
- Tumor-to-plasma ratio (C_t:C_p): 1.25

Pre-clinical study data

- Inhibition of 2-HG production in mut*IDH* glioma tissue by >97%

Mellinghoff IK. *N Engl J Med.* 2023;389:589-601. | Konteatis Z. *ACS Med Chem Lett.* 2020;11:101-107.

INDIGO Trial: Methods

Design

- Phase III, international, double-blind, randomized
  - Vorasidenib 40 mg, oral, daily, continuous 28 day cycles
  - Matching placebo

Inclusion Criteria	Exclusion Criteria
Patients ≥ 12 years of age	Previous receipt of anti-cancer therapy
Residual or recurrent grade II oligodendroglioma or astrocytoma	<u>High-risk features</u>: Brainstem involvement Neurocognitive deficits Uncontrolled seizures
Confirmed *IDH1/2* mutant status	
KPS ≥ 80	
Asymptomatic *(no steroid requirement)*	

Mellinghoff IK. *N Engl J Med.* 2023;389:589-601.

INDIGO Trial: Endpoints

Primary end point

- Progression-free survival
  - Time from randomization to progressive disease or death from any cause
  - Assessed on imaging according to RANO-LGG criteria

Secondary end points

- Time to next intervention
- Safety

Mellinghoff IK. *N Engl J Med.* 2023;389:589-601.

INDIGO Trial: Patient Characteristics

January 2020 through February 2022

– 331 patients enrolled at 77 centers in 10 countries

Key Characteristics	Vorasidenib (N = 168)	Placebo (N = 163)
Age, median (range) - yr	40.5 (21-71)	39 (16-65)
Time from initial diagnosis to randomization, mean - yr	3.3 ± 2.4	3.1 ± 2.5
Time from last surgery to randomization, median (range) - yr	2.5 (0.2-5.2)	2.2 (0.9-5.0)
Histologic subtype – no. (%) Oligodendroglioma Astrocytoma	 88 (52.4) 80 (47.6)	 84 (51.5) 79 (48.5)
IDH mutation status – no. (%) *IDH1* positive *IDH2* positive	 163 (97.0) 5 (3.0)	 152 (93.3) 11 (6.7)
Largest diameter of tumor – no. (%) ≥ 2 cm	 139 (82.7)	 137 (84.0)

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INDIGO Trial: Results

- Vorasidenib
- Placebo

Overall incidence of progression: 135/331 (40.7%)

- 47/168 (28%) *vs* 88/163 (54%)

Progression-free survival

- 27.7 mo (95% CI, 17.0 - ongoing) *vs* 11.1 mo (95% CI, 11.0 - 13.7)
- HR: 0.39 (95% CI, 0.27 - 0.56; P<0.001)

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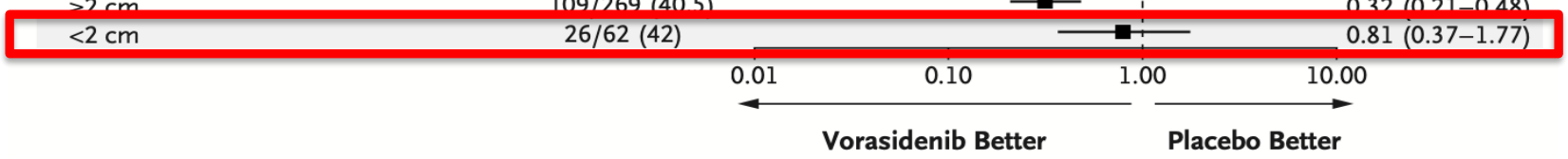
INDIGO Trial: Results

A Progression-free Survival

Subgroup	No. of Events/ Total No. of Patients (%)	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	135/331 (40.8)	0.39 (0.27–0.56)
Age		
<18 yr	0/1	NE (NE–NE)
18 to 39 yr	80/163 (49.1)	0.47 (0.29–0.75)
40 to 64 yr	53/164 (32.3)	0.32 (0.18–0.58)
≥65 yr	2/3 (67)	NE (NE–NE)
Sex		
Male	72/187 (38.5)	0.39 (0.24–0.64)
Female	63/144 (43.8)	0.41 (0.24–0.70)
Geographic region		
North America	89/193 (46.1)	0.34 (0.21–0.54)
Western Europe	31/97 (32)	0.54 (0.27–1.10)
Israel	15/41 (37)	0.45 (0.16–1.31)
Location of tumor at initial diagnosis		
Frontal lobe	92/222 (41.4)	0.47 (0.30–0.73)
Nonfrontal lobe	43/109 (39.4)	0.26 (0.14–0.50)
Time from last surgery to randomization		
<2 yr	51/130 (39.2)	0.44 (0.24–0.82)
2 to 3 yr	59/145 (40.7)	0.39 (0.23–0.66)
≥4 yr	25/56 (45)	0.28 (0.10–0.76)
No. of previous surgeries		
1	106/260 (40.8)	0.41 (0.27–0.61)
≥2	29/71 (41)	0.31 (0.14–0.68)
Chromosome 1p/19q codeletion status		
Codeleted	59/172 (34.3)	0.32 (0.18–0.57)
Non-codeleted	76/159 (47.8)	0.47 (0.29–0.75)
Longest diameter of tumor at baseline		
≥2 cm	109/269 (40.5)	0.32 (0.21–0.48)
<2 cm	26/62 (42)	0.81 (0.37–1.77)



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Time to next intervention ☑

- HR: 0.26 (95% CI, 0.15 - 0.43; P<0.001)
- Alive without next intervention at 18 mo: 85.6% *vs* 47.4%
- Alive without next intervention at 24 mo: 83.4% *vs* 27.0%

Mellinghoff IK. *N Engl J Med.* 2023;389:589-601.

INDIGO Trial: Safety

- Vorasidenib
- Placebo

Adverse events of grade ≥3

– 38/168 (22.8%) *vs* 22/163 (13.5%)

Treatment interruption

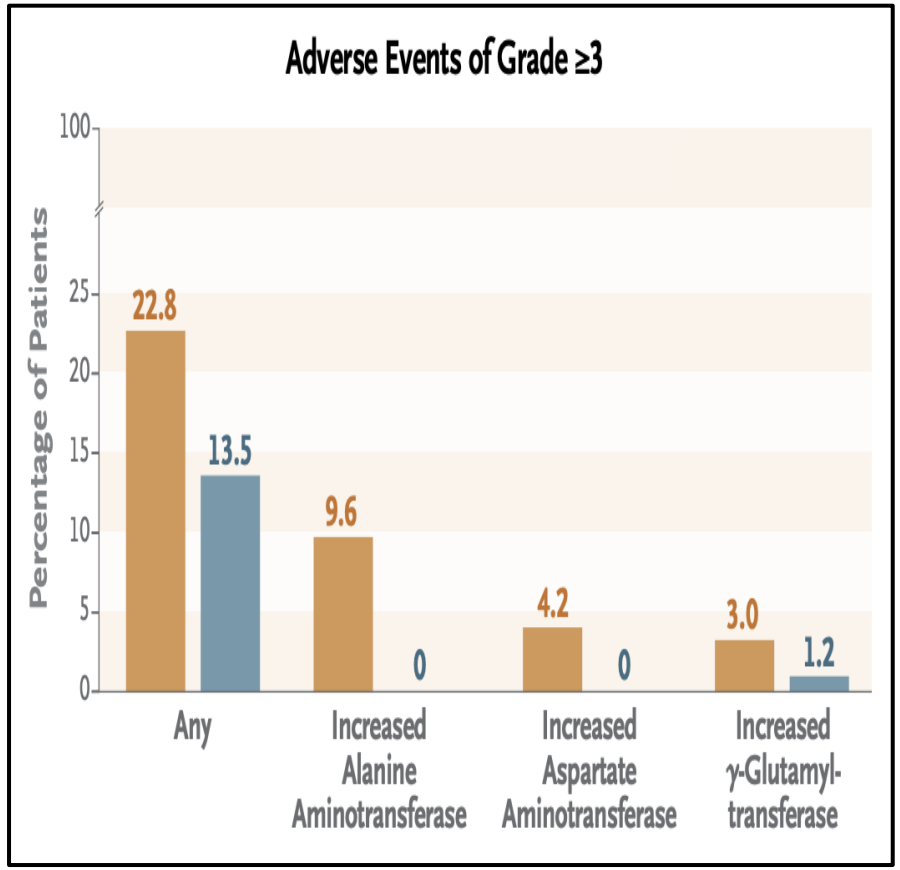
– 50/168 (29.9%) *vs* 37/163 (22.7%)

Dose reductions

– 18/168 (10.8%) *vs* 5/163 (3.1%)

Treatment discontinuation

– 6/168 (3.6%) *vs* 2/163 (1.2%)



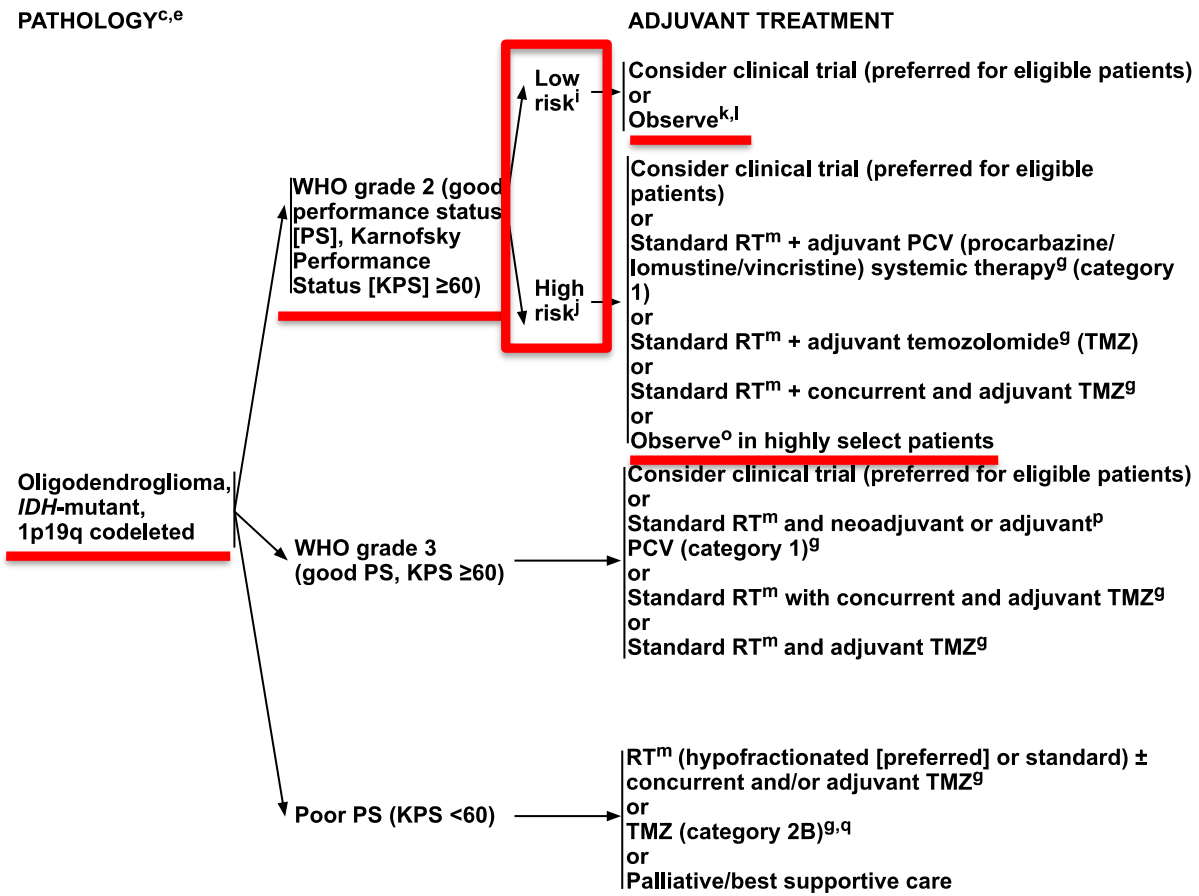
Mellinghoff IK. *N Engl J Med.* 2023;389:589-601.

Things That Make You Go Hmmm…

1. How do we dichotomize risk?
   - Inconsistencies between NCCN Guidelines and study definitions

2. Place in therapy?
   - Low risk patients?
   - High risk patients who would otherwise self-elect observation?

Adult Glioma: Oligodendroglioma (IDH-mutant, 1p19q codeleted)



[i] **Low-risk features:** ≤ 40 years and gross total resection

[j] **High-risk features:** > 40 years or subtotal resection or open stereotactic biopsy. Other high-risk factors that are sometimes taken into consideration are tumor size and neurologic deficits.

[o] **Results of RTOG 9802:** showed that there was a significant improvement in median overall survival in high-risk low-grade glioma patients treated with RT followed by PCV x 6 cycles compared with RT alone after a tissue diagnosis was made. However, this important study did not address whether all of these patients should be treated right away. Observation after diagnosis may be a reasonable option for a high-risk low-grade glioma patient who is neurologically asymptomatic or stable.

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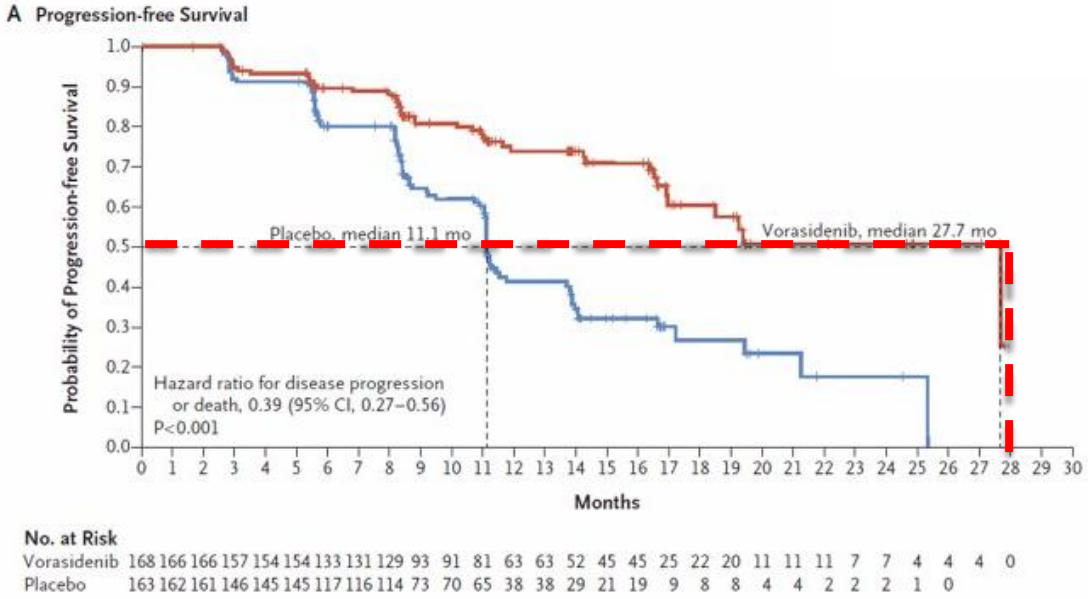
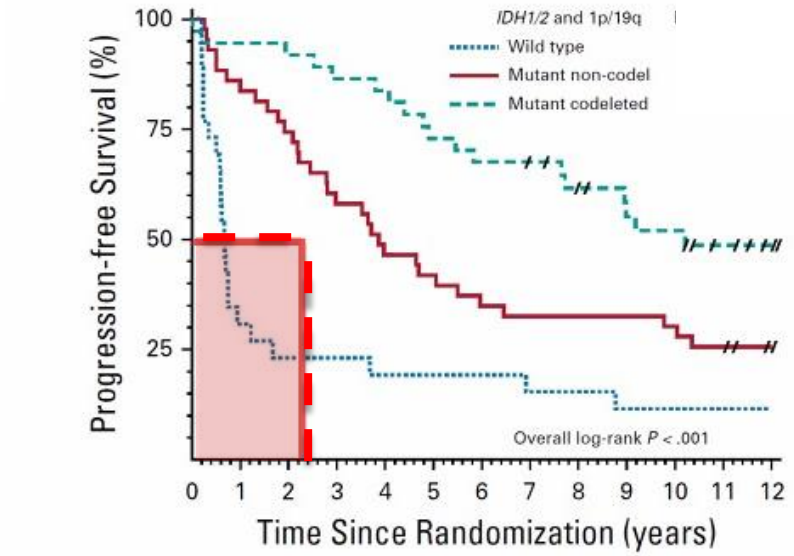
Progression Free Survival

INDIGO



RTOG 9802



No. at risk:							
Wild type	26	6	5	5	4	3	3
Mutant non-codel	43	32	20	15	14	13	7
Mutant codeleted	37	34	31	25	20	16	7

Mellinghoff IK. *N Engl J Med.* 2023;389:589-601. | Bell EH. *J Clin Oncol.* 2020;38:3407-3417.

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3. Remain to be seen
   - Combinatorial effect with SOC? Sequencing?
   - Implications on subsequent chemotherapy ± RT? 2^{O} resistance?
   - Overall survival, neurocognition, and health-related quality of life

The Takeaways

Vorasidenib demonstrated significant improvement in PFS compared with *placebo* in grade II mut*IDH* glioma

- *First new viable treatment option in over two decades
- *First molecularly targeted therapy amongst this population

Most adverse events with vorasidenib were mild

- Not associated with myelosuppression or fatigue

NCT05484622
Ongoing phase I study in combination with pembrolizumab for recurrent/persistent grade II & III mutIDH1 astrocytoma

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