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BEST HOSPITALS U.S.News CANCER 2024-2025

IDH Inhibitors for Gliomas in Children

Dance Blue

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DISCLOSURES

I have nothing to disclose.

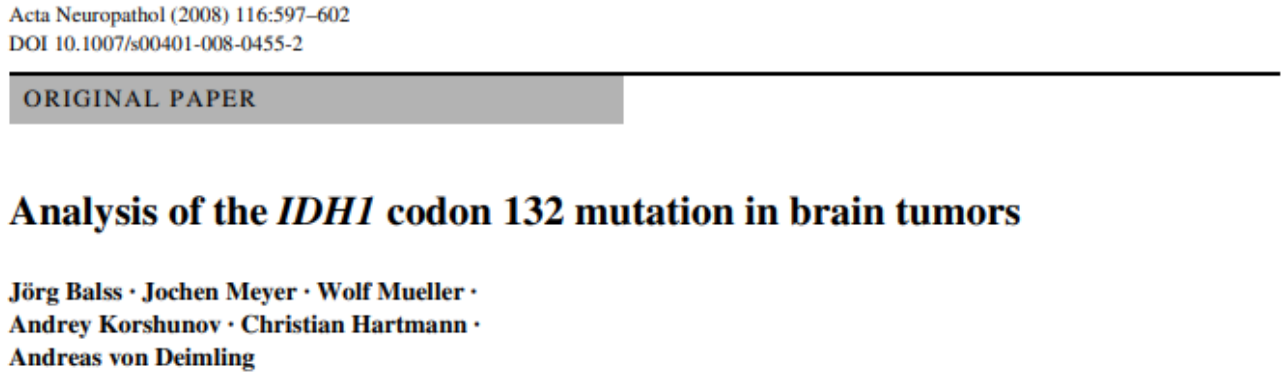
Objectives

- Review IDH mutation history
- Describe pediatric high grade glioma subtypes and role of IDH
- Discuss IDH inhibition treatment


IDH History

IDH History

- Reported in 2008
- Over 20,000 genes in 22 glioblastomas sequenced
- Common point mutation in *IDH1* in 12% of samples
  - Later studies confirmed about 80% of grade 2-3 gliomas and secondary glioblastomas carried the mutation.
- *IDH2* mutations have also been found
  - Less common (<5% of cases)
  - Mutually exclusive
- These mutations were found in more than 75% of grade 2-3 gliomas and secondary glioblastomas



Acta Neuropathol (2008) 116:597–602
DOI 10.1007/s00401-008-0455-2

ORIGINAL PAPER

Analysis of the *IDH1* codon 132 mutation in brain tumors

Jörg Balss · Jochen Meyer · Wolf Mueller · Andrey Korshunov · Christian Hartmann · Andreas von Deimling

IDH mutations

- Appear to occur at an early stage of tumorigenesis
- May affect cell determination and differentiation
- Are associated with better prognosis
- Inhibit histone and DNA demethylation, cellular differentiation, tumor microenvironment and alter epigenetic regulation

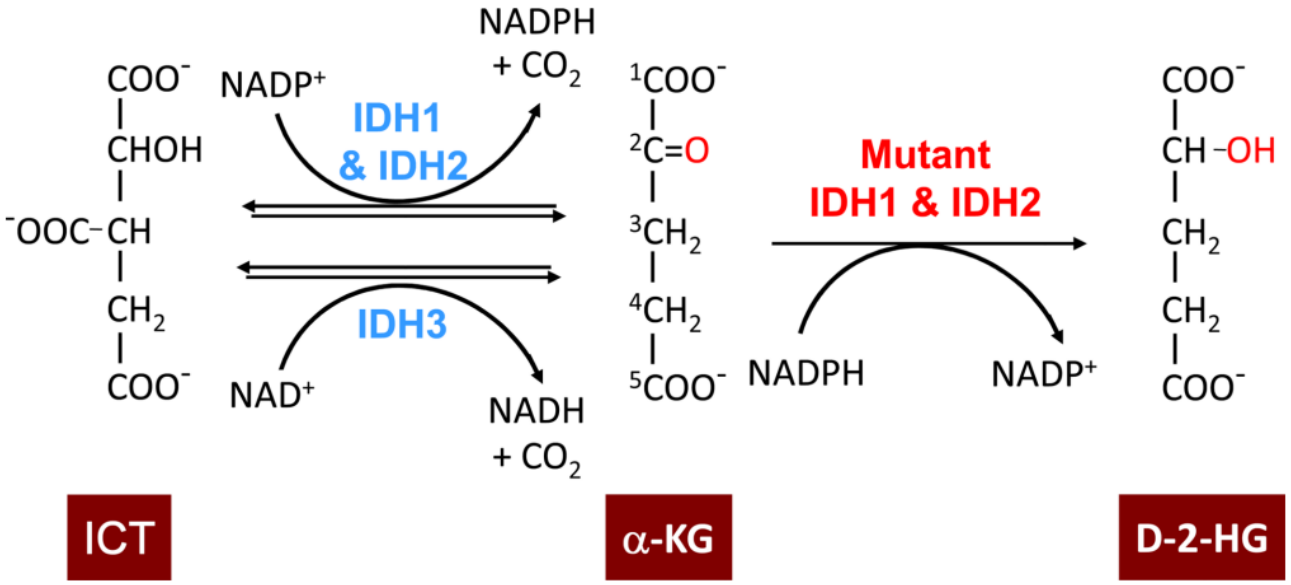


Figure 1. Chemical reactions catalyzed by the wild-type IDH enzymes and tumor-derived mutants IDH1 and IDH2
The only structural difference between α-KG and D-2-HG is the replacement of the 2-ketone group in α-KG by a hydroxyl group in 2-HG and is indicated by red color.

Yang et al, *Clin Cancer Res*, 2014.

Entire Reclassification

- 2016
  - Glioblastoma, *IDH*-wildtype
  - Glioblastoma, *IDH*-mutant
  - Diffuse astrocytoma, *IDH*-wildtype
  - Diffuse astrocytoma, *IDH*-mutant
- 2021
  - Glioblastoma: *IDH*-wildtype with either *EGFR* amplification, *TERT* promoter mutation, gain of 7 or loss of 10
  - Glioblastoma: *IDH*-mutated with loss of *CDKN2A/B*
  - Diagnosis of diffuse astrocytoma, *IDH*-mutant can be made with *ATRX* loss or *P53* loss and the absence of 1p/19q-codeletion

Acta Neuropathol (2016) 131:803–820
DOI 10.1007/s00401-016-1545-1

CrossMark

REVIEW

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

David N. Louis[1] · Arie Perry[2] · Guido Reifenberger[3,4] · Andreas von Deimling[4,5] · Dominique Figarella-Branger[6] · Webster K. Cavenee[7] · Hiroko Ohgaki[8] · Otmar D. Wiestler[9] · Paul Kleihues[10] · David W. Ellison[11]


IDH Mutations and Children

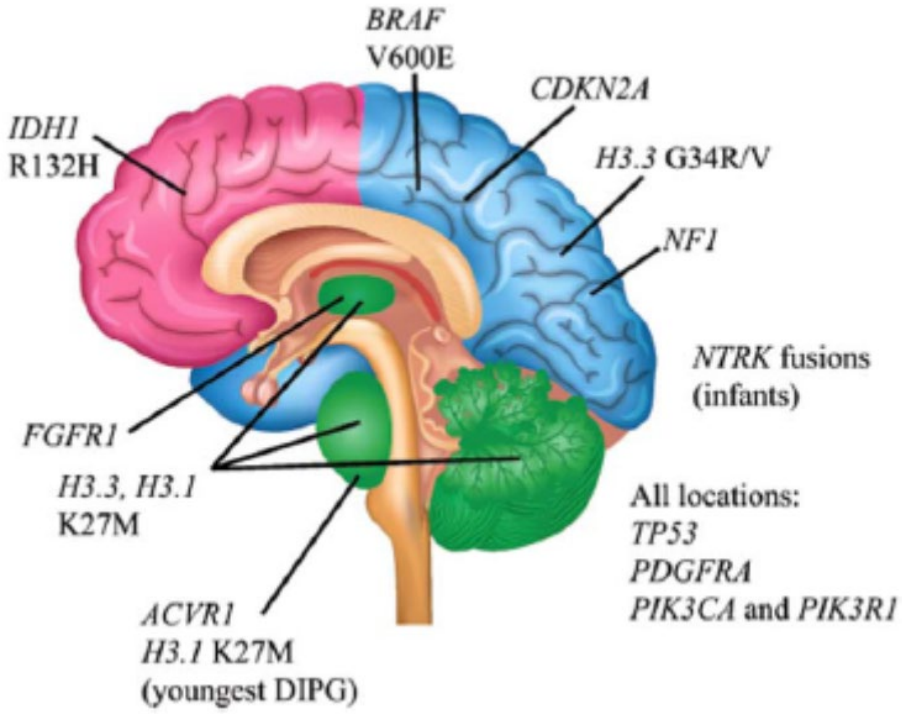
IDH mutations and Leukemia

- 227 acute myeloid leukemias: 3.5%
  - 3 with *IDH1*
  - 5 with *IDH2*
  - Seen at a higher frequency with normal karyotypes
- 288 acute lymphoblastic leukemias
  - 1 person had a mutation

Anderson et al. “IDH1 and IDH2 mutations in pediatric leukemia.” Leukemia, 2011.

Brain tumors as neurodevelopmental disorders

- Youngest DIPG: *ACVR1* and *H3.1* K27M
- Green: *H3 K27M*
- Blue: *H3.3 G34R/V*
  - Cortical HGGs of late adolescence
- Pink: *IDH1 R132H*
  - HGGs of late adolescence and young adulthood



Baker et al. *GLIA*, 2016.

IDH mutations and pediatric brain tumors

- Reports range from 0-17% of gliomas
- Usually in the context of *1p19q*-codeletion or *ATRX* and *TP53* mutations
- Median age of 16 years old.
- Frequency of IDH mutations similar between low-grade and high-grade gliomas

S Ryall, U Tabori & Cynthia Hawkins. *Acta Neuropathololologica Communications*, 2020.
A Mackay et al. *Cancer Cell*, Oct 2017.
KK Yeo et al. *Neuro-Oncology*, 2023.

IDH mutations and pediatric brain tumors

- Low-grade astrocytoma
  - 84% observed
  - 5-year PFS 42.9%
  - 10-year PFS 0%
  - Median overall survival of 18.9 years
  - Numerous deaths after year 10 due to progression of disease, extent of resection did not impact survival outcomes
- High-grade astrocytoma
  - 5-year PFS 36.8%
  - 5-year OS 84%

KK Yeo et al. *Neuro-Oncology*, 2023.

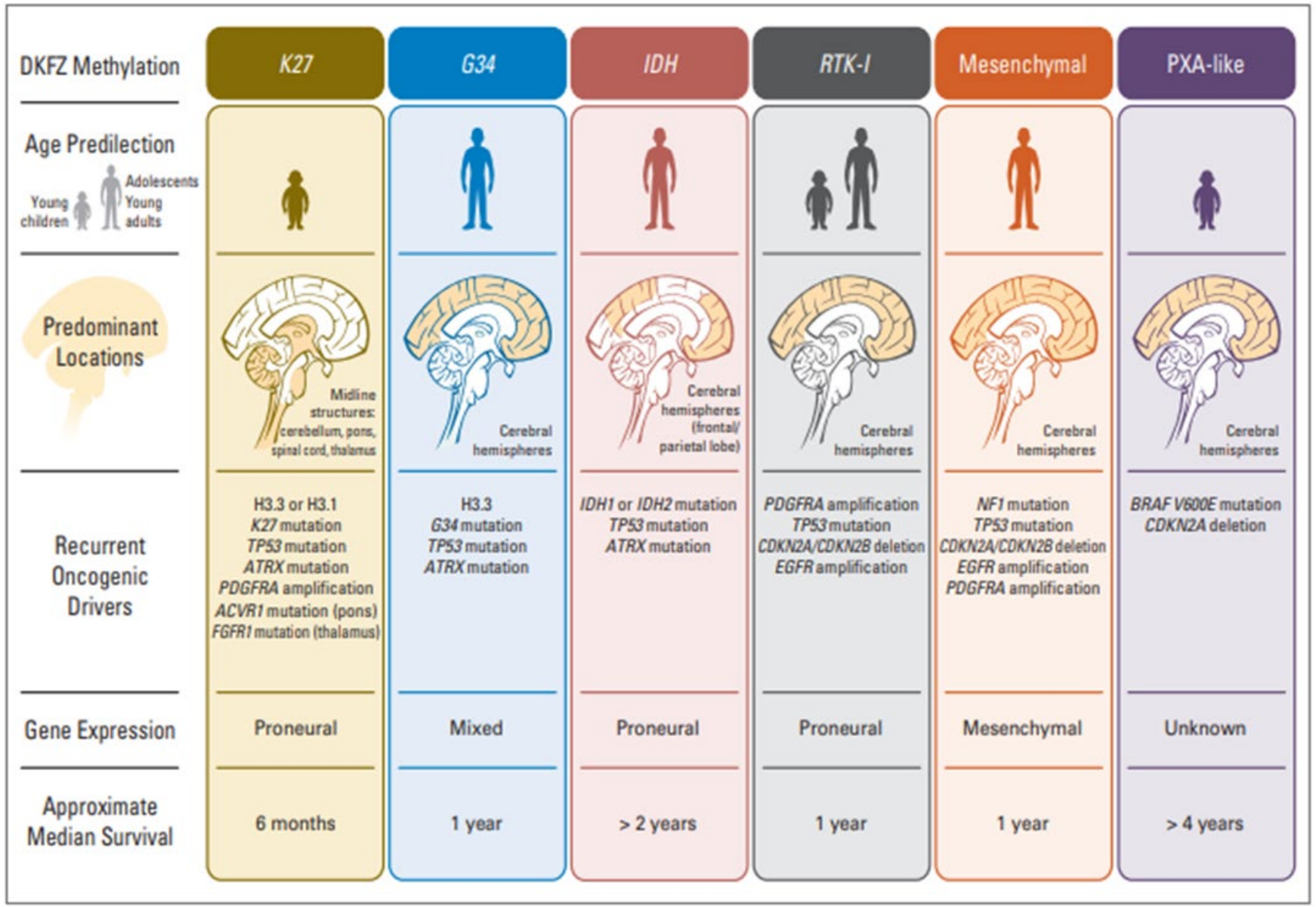


Fig 2. Subgroups of pediatric high-grade glioma that are based on German Cancer Research Center (DKFZ) methylation, age at onset, tumor location, oncogenic drives, gene expression, and median survival. IDH, isocitrate dehydrogenase; PXA, pleomorphic xanthoastrocytoma; RTK-I, receptor tyrosine kinase (subgroup 1).

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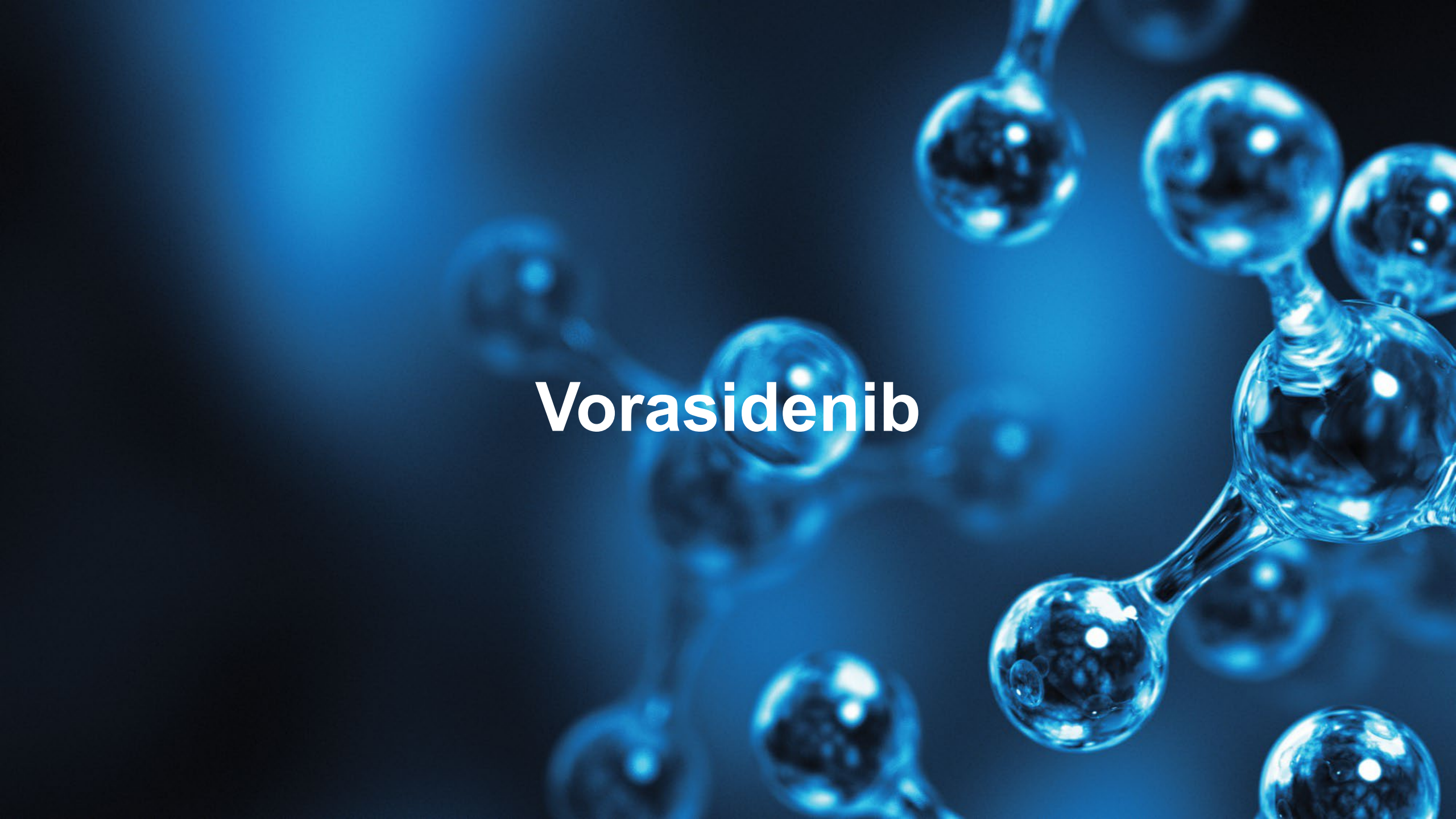
A Gajjar et al. *JCO*, Sept 2015.

IDH mutations and pediatric brain tumors

- Low-grade oligodendroglioma
  - 5-year PFS 55%
  - 10-year PFS 33.2%
  - 20-year OS 100%
- High-grade oligodendroglioma
  - 2 cases
  - 1 patient had upfront treatment with RT and temozolomide. Progressed after 1.8 years and passed 4.3 years from diagnosis
  - Other patient had RT followed by PCV for 6 cycles. No evidence of disease 2.5 years from diagnosis.

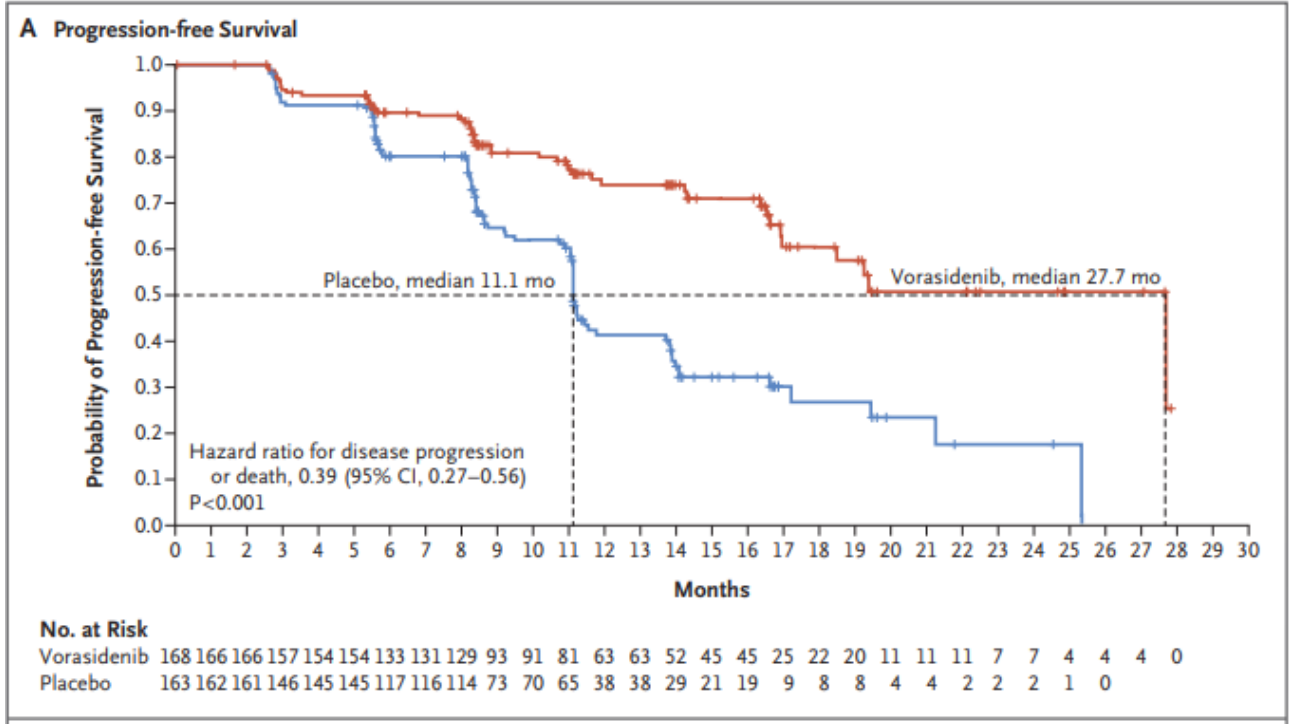
KK Yeo et al. *Neuro-Oncology*, 2023.

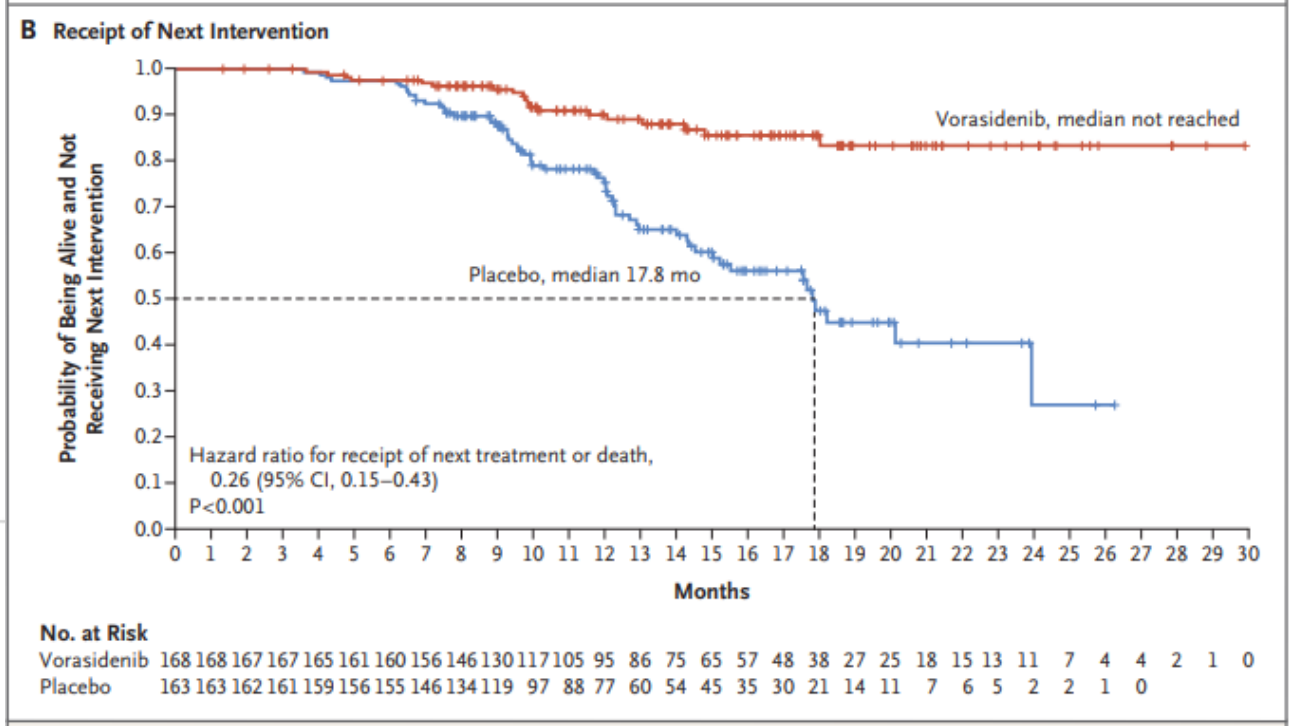
Vorasidenib



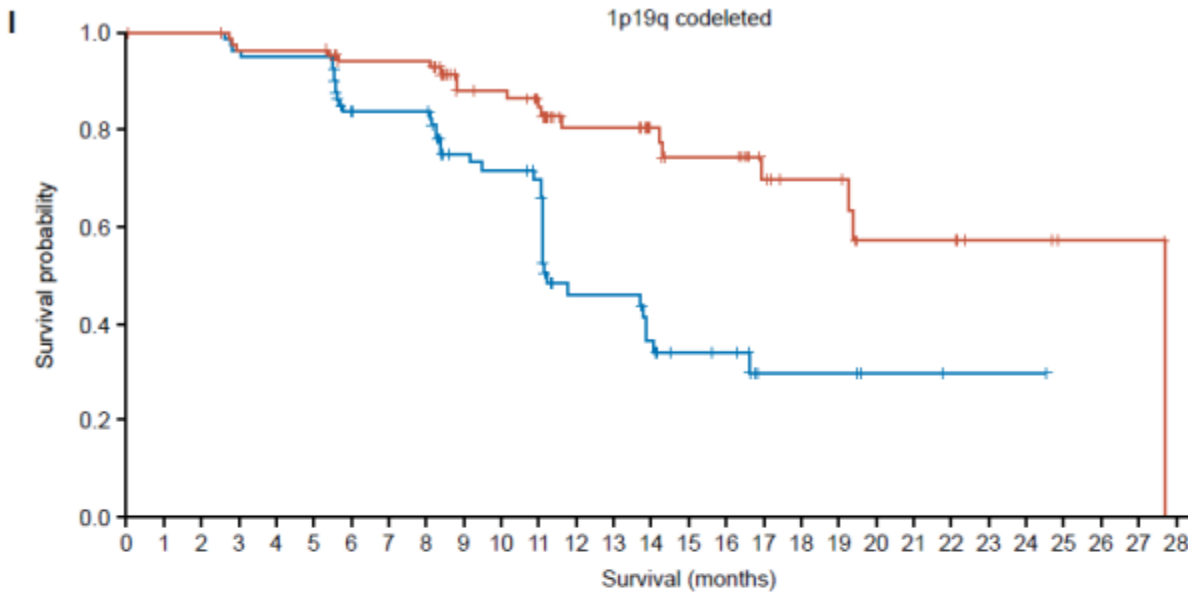
INDIGO Trial (NCT04164901)

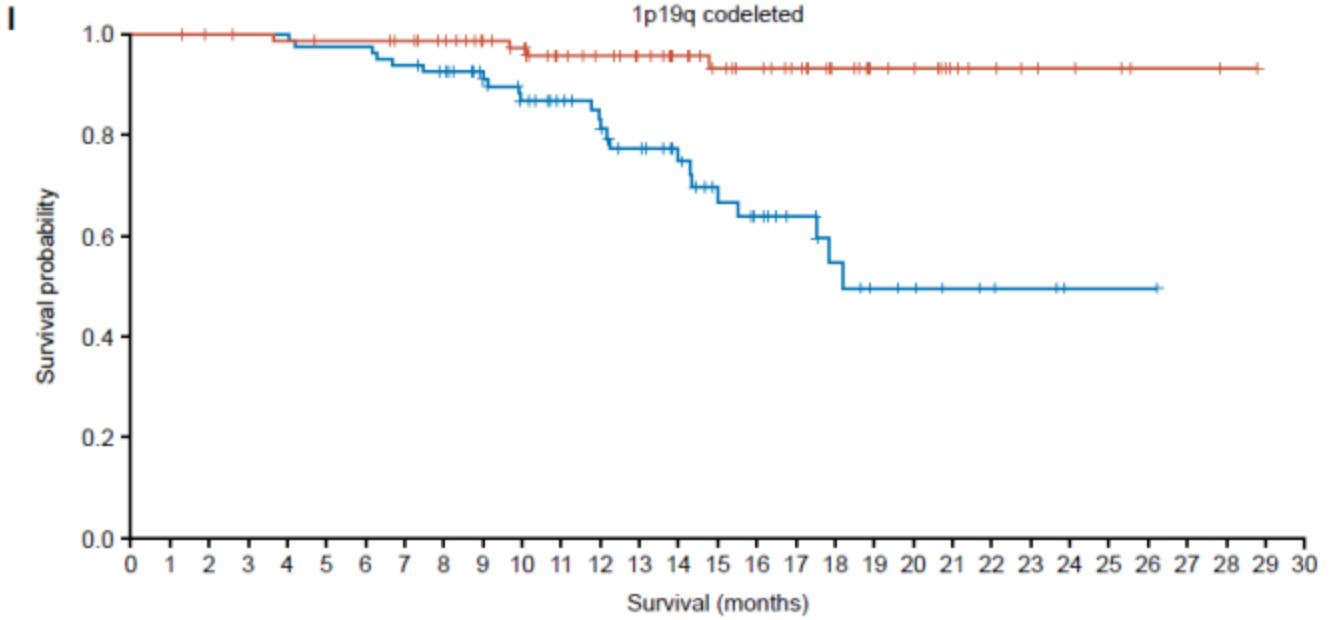
- 331 patients with residual or recurrent grade 2 IDH-mutant gliomas randomized to vorasidenib versus placebo.
- Patients 12+ years-old
- Median PFS
  - Vorasidenib: 27.7 months
  - Placebo: 11.1 months
- Time to next intervention significantly improved in the vorasidenib group.

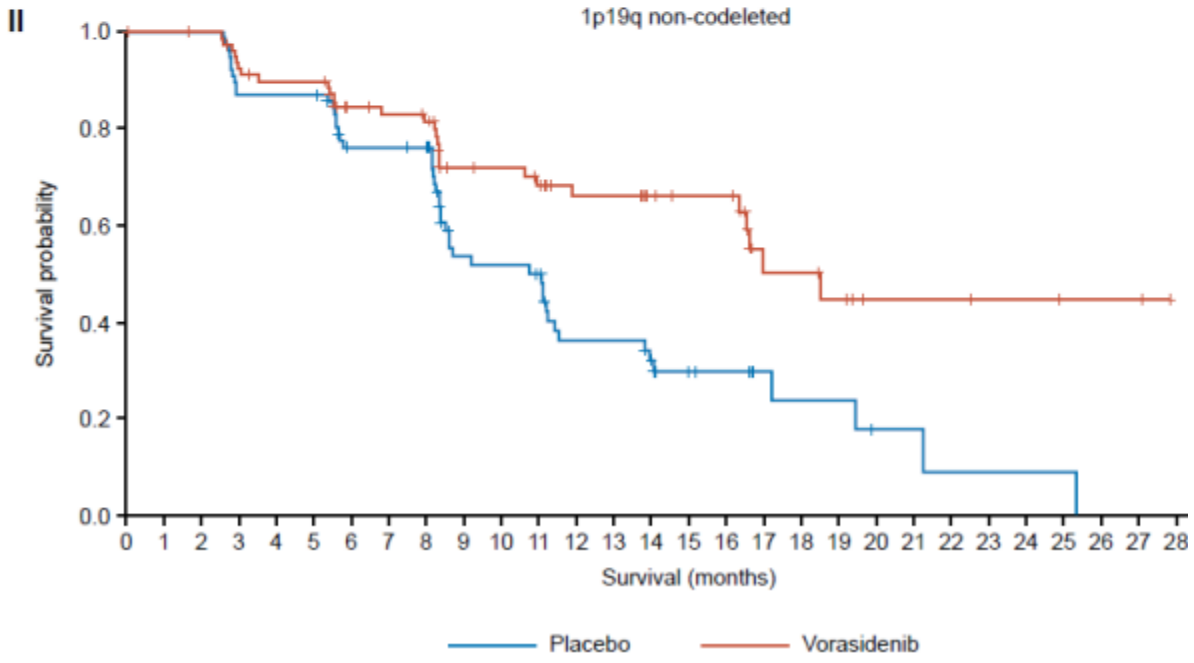


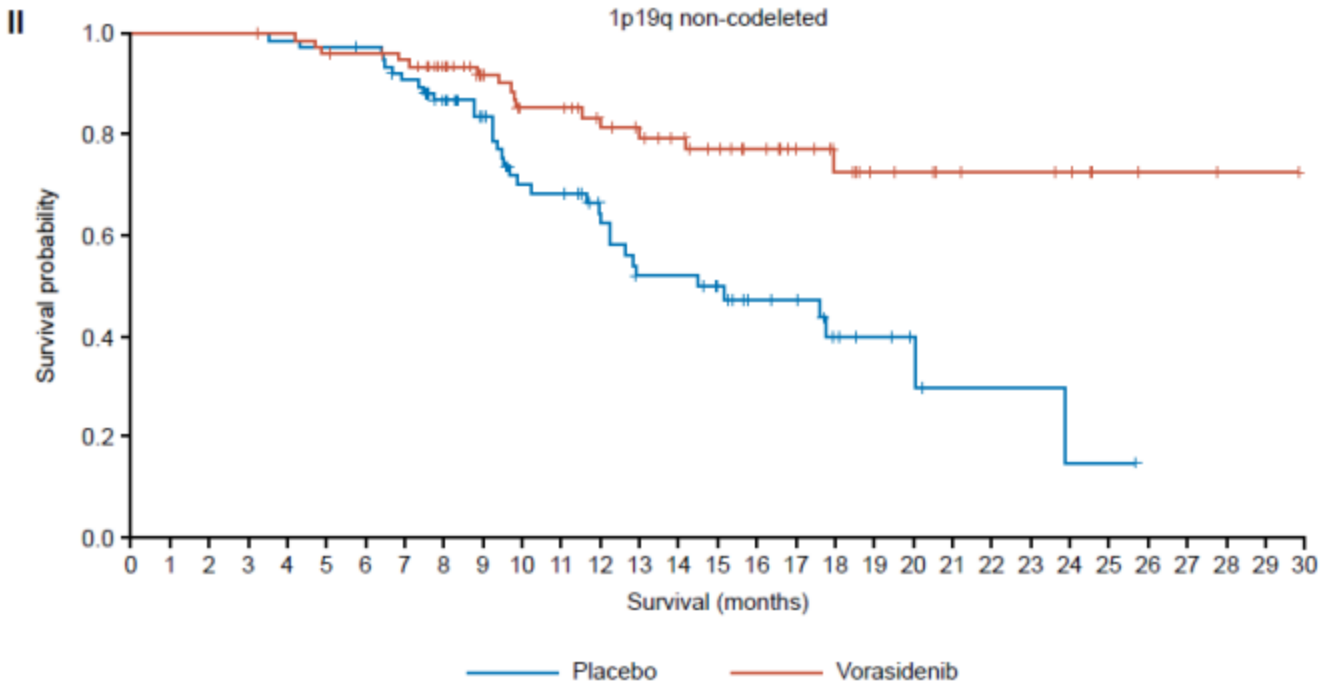


IK Mellinghoff et al. “Vorasidenib in IDH1- or IDH2-mutant low grade glioma.” *NEJM*, 2023;389:589-601.









IK Mellinghoff et al. “Voraside

INDIGO Trial (NCT04164901)

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

*

The safety analysis set included all the patients who received at least one dose of vorasidenib or placebo. The individual adverse events listed are those of any grade that occurred in at least 10% of the patients in the vorasidenib group.

IK Mellinghoff et al. “Vorasidenib in IDH1- or IDH2-mutant low grade glioma.” *NEJM*, 2023;389:589-601.

Conclusion

- Molecular profiling is more important now than ever
- Vorasidenib FDA-approved Aug 6, 2024
- The European Medicines Agency granted accelerated assessment for vorasidenib in Feb 2024. Still waiting on the European Commission
- Currently being reviewed in Canada
- Does it change progression in the long run?

“When we feel depressed we get back to the patients who had astrocytomas and look at them until our spirits rise and we are encouraged to fight against this curse of mankind.”

Percival Bailey, Douglas N Buchanan, and Paul C Bucy. *Intracranial Tumors of Infancy and Childhood* (1939), pg 560.

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