INDIGO trial summary

> *Findings of: Cloughesy TF, van den Bent MJ, Touat M, Blumenthal DT, Peters KB, Ellingson BM, Clarke JL, Mendez J, Yust-Katz S, Welsh L, Mason WP, Ducray F, Umemura Y, Nabors B, Holdhoff M, Hottinger AF, Arakawa Y, Sepulveda JM, Wick W, Soffietti R, Perry J, Giglio P, de la Fuente M, Maher E, Bottomley A, Tron AE, Yi D, Zhao D, Pandya SS, Steelman L, Hassan I, Wen PY, Mellinghoff IK; INDIGO trial investigators. Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2025 Oct 29:S1470-2045(25)00472-3. doi: 10.1016/S1470-2045(25)00472-3. PMID: 41175888.*

Here is an **annotated Vancouver-style summary** of the secondary and exploratory endpoint results from the INDIGO trial of Vorasidenib in grade 2 IDH1/2-mutant diffuse glioma (published by Timothy F Cloughesy et al) (Cloughesy TF, van den Bent MJ, Touat M, Blumenthal DT, Peters KB, Ellingson BM, Clarke JL, et al; INDIGO trial investigators. *Lancet Oncol.* 2025 Oct 29. doi:10.1016/S1470-2045(25)00472-3. PMID:41175888). PubMed +2 The Lancet +2

Study design & context

- INDIGO was a randomised, double-blind, placebo-controlled, phase 3 trial in patients aged ≥12 years with residual or recurrent WHO grade 2 diffuse glioma harbouring an IDH1 or IDH2 mutation, KPS ≥ 80, at least one prior surgery, and **no prior radiotherapy or chemotherapy**. PubMed +1
- Patients were randomised 1:1 to Vorasidenib 40 mg daily vs placebo, stratified by 1p/19q codeletion and baseline tumour size. PubMed
- Primary endpoint: progression-free survival (PFS) per independent review committee. Key secondary: time to next intervention (TTNI). The paper under summary reports **prespecified secondary endpoints** (tumour growth rate, health-related quality of life [HRQOL]) and **exploratory endpoints** (neurocognitive function, seizure activity). ScienceDirect +2 PubMed +2
- A total of 331 patients were randomised (168 to Vorasidenib; 163 to placebo). Median follow-up: ~20.1 months (IQR 15.9-23.8). PubMed +1

Key Findings – Secondary & Exploratory Endpoints

1. **Tumour growth rate**
    - Over 6-monthly volumetric tumour change: Vorasidenib arm had a mean tumour volume change of –1.3% (95% CI –3.2 to 0.7) vs placebo +14.4% (95% CI 12.0 to 16.8). Difference: ~15.9% (95% CI 12.6 to 19.3). PubMed +1
    - Interpretation: Vorasidenib essentially stabilized (and modestly reduced) tumour volume over 6 months, whereas placebo showed substantial tumour growth.
2. **Health-Related Quality of Life (HRQOL)**
    - Baseline mean FACT-Br (Functional Assessment of Cancer Therapy – Brain) scores: ~158.2 (SD 26.4) in Vorasidenib group vs 158.8 (SD 23.3) in placebo. At end of treatment: ~154.2 (29.8) vs 153.2 (29.4). PubMed
    - Conclusion: HRQOL remained high and comparable between arms; no detrimental effect of treatment on HRQOL.
3. **Neurocognitive function (exploratory)**
    - Assessments across domains: verbal learning, executive function, attention, working memory, psychomotor speed. No difference observed between treatment and placebo from baseline to end of treatment. PubMed +1
    - Implication: Vorasidenib did not appear to impair cognitive functioning compared to placebo in this population and timeframe.
4. **Seizure activity (exploratory)**
    - Rate of seizures per person-year: 18.2 (95% CI 8.4-39.5) in the Vorasidenib arm vs 51.2 (95% CI 22.9-114.8) in the placebo arm. PubMed +1
    - Interpretation: A markedly lower seizure rate in the Vorasidenib arm — suggesting a potential benefit on seizure control (which is clinically relevant in grade 2 glioma).
5. **Safety / Tolerability – selected serious events**
    - Grade 3 or worse treatment-emergent adverse events (TEAEs): ALT increase 10% vs 1%, AST increase 5% vs 0%, seizures 4% vs 3%, GGT increase 3% vs 1% (Vorasidenib vs placebo). PubMed
    - Serious TEAEs: 12% (Vorasidenib) vs 6% (placebo). Most common serious TEAE: seizure. No treatment-related deaths. PubMed

Interpretation & implications

- The secondary/exploratory data reinforce the primary PFS/TTNI benefit: Vorasidenib not only improved PFS and delayed next intervention, but seems to alter tumour trajectory (reduced growth rate), maintain HRQOL and cognition, and reduce seizure burden. The Lancet +1
- For patients with grade 2 IDH1/2-mutant diffuse glioma post-surgery (without prior RT/chemo) and who are in a “watch-and-wait” context or delaying further therapy, the data suggest Vorasidenib may offer meaningful benefit.
- The seizure reduction is a particularly interesting finding in neuro-oncology (especially relevant for low-grade glioma) given the impact of seizures on quality of life, driving, independence etc.
- The preservation of neurocognitive function and HRQOL is reassuring in this often long-term survivorship population.
- Safety profile appears manageable; monitoring of liver enzymes is important (as ALT/AST elevations were among the more frequent high-grade AEs).
- Given the volumetric data: the difference (~15.9% in 6-month tumour growth) suggests that the drug may shift the natural history of tumour progression (rather than just delaying progression).
- In the context of pediatric/adolescent patients (≥12 yrs included), though the median age and subgroup data may not be fully detailed here, implications for younger patients with IDH-mutant glioma (or drug delivery across the blood-brain barrier in a pediatric setting) merit further exploration (which may align with your interest in pediatric BBB/drug delivery).
- From a therapeutic strategy standpoint: this trial supports early systemic targeted therapy (IDH inhibition) in grade 2 glioma rather than waiting for conventional treatments — this could shift the paradigm.
- Limitations to note: relatively short median follow-up (~20 months), further long-term data (overall survival, late effects) are needed. Also exploratory endpoints require cautious interpretation.

Summary sentence

In summary, in the INDIGO phase 3 trial of Vorasidenib in grade 2 IDH1/2-mutant diffuse glioma, the secondary and exploratory endpoint results show a pronounced reduction in tumour growth rate, a substantial decrease in seizure frequency, and maintenance of HRQOL and neurocognitive function — supporting the benefit of early targeted IDH1/2 inhibition in this patient population.