Vorasidenib open questions

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> Findings of: Seyve A, Ducray F. Open questions on vorasidenib. Curr Opin Oncol. 2025 Sep 12;37(6):589-594. doi: 10.1097/CCO.0000000000001193. PMID: 41029964.

Here is a detailed summary of the key "open questions" and insights from **Seyve A, Ducray F. "Open questions on vorasidenib."** ***Curr Opin Oncol.*** **2025 Sep 12;37(6):589-594. doi:10.1097/CCO.0000000000001193. PMID: 41029964** PubMed

I also add some context and commentary where relevant.

Summary & Key Findings

Purpose & Scope

The review discusses **unresolved issues** in the clinical development and optimal use of **vorasidenib** (a brain-penetrant inhibitor of mutant IDH1/2) in IDH-mutant gliomas, particularly grade 2. The authors ask: How should we time its use, how durable is benefit, how to monitor response, and whether its indication could extend to higher-grade IDH-mutant gliomas. PubMed

They frame the questions in three domains:

1. Long-term benefit / durability / endpoints
2. Optimal use in grade 2 disease
3. Extension beyond grade 2 (grade 3 / 4) and in combinations

Below is a breakdown of their main points and uncertainties.

Major Open Questions & Points of Discussion

1. Durability, endpoints, and long-term outcomes

- While vorasidenib showed efficacy in IDH-mutant grade 2 gliomas (in the INDIGO trial), its **long-term benefits** on **overall survival (OS)**, **quality of life**, and **cognition** remain uncertain. PubMed
- The authors suggest that vorasidenib may act as a **differentiation therapy** rather than a cytotoxic agent. PubMed

- There is some emerging evidence (updated INDIGO data) that vorasidenib might also help with **seizure control** in patients with IDH-mutant gliomas (in addition to tumor growth inhibition) PubMed
- For better response evaluation, **volumetric MRI** and **amino acid PET imaging** may offer advantages over conventional imaging metrics. PubMed
- However, these imaging approaches need validation as reliable surrogates, and long follow-up is required to assess if delaying standard therapies (radiotherapy, chemotherapy) via vorasidenib is safe in the long run. PubMed
- The authors caution that, before adopting vorasidenib as first-line treatment broadly, we need confirmatory trials to show that it **preserves cognition**, **maintains quality of life**, and **prolongs OS**, not just progression-free intervals. PubMed

2. Optimal use in IDH-mutant grade 2 gliomas

- One question is **timing**: Should vorasidenib be given **first-line**, or reserved until after radiotherapy/chemotherapy? The authors note that it is increasingly considered for first-line use in many patients, but how to optimally sequence it relative to standard therapies isn't settled. PubMed
- Another operational issue is **patient selection**. In some cases, the presence of **contrast enhancement** (rather than purely histologic grade) might better correlate with aggressive behavior and thus guide candidacy for vorasidenib. The authors argue that selected grade 3 IDH-mutant gliomas (showing enhancement) might benefit from vorasidenib earlier. PubMed
- They raise the possibility that in lower-risk patients, using vorasidenib may allow **deferral** of radiotherapy/chemotherapy, thereby reducing long-term neurotoxic effects. But this balance must be carefully assessed.

3. Beyond grade 2: higher-grade disease, maintenance, combinations

- The authors consider whether **grade 3 or even grade 4 IDH-mutant gliomas** (especially those with contrast enhancement) might benefit from vorasidenib, either *alone* or in **combination with standard therapies** (radiotherapy, chemotherapy). This is speculative at present. PubMed
- Ongoing trials are testing vorasidenib as **maintenance therapy** after radiochemotherapy, and in **combinations** with chemotherapy or immunotherapy; these may help define its role in higher-grade settings. PubMed
- The authors also highlight that **biomarkers** of response—or resistance—need to be developed to guide which patients may benefit most.

4. Integration with clinical trial and imaging strategies

- The need for **prospective trials with long-term follow-up** is emphasized to validate that using vorasidenib does not compromise subsequent treatments or overall survival. PubMed
- They advocate for **advanced imaging modalities** (volumetric MRI, amino acid PET) to improve sensitivity and specificity for response evaluation, especially to detect subtle growth or metabolic changes. PubMed
- Another point: given that **contrast enhancement** may better reflect disease aggression than histologic grade, imaging criteria may help refine trial inclusion or stratification.

Context, Critiques & Perspectives

- The INDIGO trial (the pivotal study for vorasidenib in grade 2 IDH-mutant gliomas) showed **marked improvements in progression-free survival** and **time to next intervention (TTNI)**. PubMed +2 PubMed +2
- However, as others have commented, criticisms include the **lack of overall survival data**, high **crossover rates** (patients on placebo switching to vorasidenib), and whether PFS is a valid surrogate in this context. mdedge.com
- Some editorial voices have questioned whether the approval of vorasidenib might have been **premature**, especially given its **high cost** and the absence of clear evidence it is superior to standard chemoradiotherapy in the long term. mdedge.com
- The authors of the review are cautious: they do not claim vorasidenib is a panacea but stress that we are still **learning how to use it optimally**, and delineating its limitations. PubMed

My Take & Implications for Research / Practice

- The review is thoughtful in mapping the landscape of unknowns and emphasizing the need for **long-term, methodologically rigorous trials**.
- In practice, adopting vorasidenib in grade 2 IDH-mutant gliomas may represent a new paradigm (differentiation therapy, delaying cytotoxic/radiation therapy), but the **tradeoffs in survival, cognition, and treatment sequencing** must be carefully weighed.
- The proposal to use **multiparametric imaging** (volumetric MRI, amino acid PET) is compelling; this may help detect earlier signs of progression or treatment effect beyond size changes alone.

- The potential extension into grade 3/4 disease is intriguing but speculative; careful stratification (e.g. enhancement, molecular markers) will be key.
- From a trial design perspective, the community should aim for **OS and patient-reported outcomes**, not only PFS, and consider **biomarker-driven arms** to optimize patient selection.

Using the abstract plus contextual literature and related reviews, I can reconstruct and expand key elements that are likely present in the full text (e.g. suggested follow-up, discussion points, hypotheses). Below is an enriched reconstruction + commentary.

Likely Full-Text Structure & Additional Insights

Based on the format of *Current Opinion in Oncology* reviews and the abstract, the full text almost certainly consists of:

1. **Introduction / Background** — biology of IDH mutations, rationale for brain-penetrant IDH inhibitors, prior clinical results (e.g. INDIGO trial)
2. **Three broad domains of open questions** (as in the abstract)
    - Long-term benefit, endpoints, durability
    - Optimal use in grade 2 disease
    - Potential extension to grade 3/4 disease and combinations
3. **Discussion of imaging / biomarkers / response assessment**
4. **Challenges, caveats, and risks**
5. **Future directions** and concluding remarks

I summarize here what the full text likely contains (beyond the abstract) and fill in with what similar reviews or secondary sources report, with critical appraisal.

Expanded & Hypothesized Content + Supporting Context

Introduction / Rationale

- The authors likely begin with a brief recapitulation of the biology of IDH1/2 mutations in glioma, how mutant IDH produces the oncometabolite 2-hydroxyglutarate (2-HG), which contributes to epigenetic dysregulation, altered differentiation, and tumorigenesis.
- They would mention that vorasidenib is a **dual mutant-IDH1/2 inhibitor** designed to cross the blood–brain barrier (i.e. brain-penetrant), and that in early-phase and the INDIGO trial it showed suppression of 2-HG and efficacy in non-enhancing, residual or recurrent non–chemoradiated IDH-mutant grade 2 gliomas.

- They may mention safety and tolerability (notably transaminitis) as observed in prior studies.

Open Question Domain 1: Long-Term Benefit, Durability, Endpoints

- The authors probably elaborate on why **progression-free survival (PFS)** or **time to next intervention (TTNI)**, which were favorable in INDIGO, may not be sufficient alone to establish standard of care.
- They likely emphasize **overall survival (OS)** and **neurocognitive preservation / quality of life (QoL)** as critical endpoints, especially given the typically indolent course of grade 2 gliomas. There may be a discussion of the **crossover effect** in trials (i.e. patients in placebo arm eventually crossing to active drug) diluting OS differences.
- They could propose **imaging biomarkers** (volumetric MRI, diffusion metrics, amino acid PET [e.g. MET-PET or FET-PET]) as potential surrogates to detect subtler treatment effects or earlier progression.
- A point of debate is **treatment duration**: should vorasidenib be continued until progression (indefinitely), or stopped at some point? What is the risk of resistance or loss of efficacy on withdrawal?
- Another issue is whether long exposure to IDH inhibition could alter tumor biology such that responsiveness to later chemotherapy or radiotherapy is compromised.
- They might also discuss **seizure control** effects: updated INDIGO data suggest an ancillary benefit on seizure frequency, which is especially relevant in low-grade gliomas.
- A nuanced point: because grade 2 gliomas have long natural histories, long follow-up (5–10+ years) is needed to reliably assess outcomes; the authors likely call for extended follow-up of INDIGO and new long-term trials.

Open Question Domain 2: Optimal Use in Grade 2 Gliomas

- **Patient selection**: The authors probably debate which patients with grade 2 IDH-mutant gliomas are best suited for early vorasidenib vs “watch and wait” vs upfront radiotherapy/chemotherapy. They might propose new stratifications beyond classical “low-risk vs high-risk” models.
- **Timing / sequencing**: Should vorasidenib be given immediately after surgery in patients who do not yet require adjuvant therapy, or deferred until radiographic progression? The balance is between delaying neurotoxic therapy vs risking more aggressive disease at progression.

- **Biology vs imaging phenotype**: The authors may argue that **contrast enhancement** (even subtle) is a stronger marker of aggressiveness than histologic grade, and that some enhancing grade 2 tumors might respond differently or less well to IDH inhibition.
- They could propose hybrid strategies: resection of enhancing portions, then vorasidenib for residual non-enhancing disease.
- **Duration of treatment** and **treatment holiday strategies**: whether to consider drug pauses or de-escalation in stable disease.
- They may also consider **fertility / family planning** issues in younger patients, given prolonged therapy.

Open Question Domain 3: Extension Beyond Grade 2, Combinations, Maintenance

- The authors likely discuss whether **grade 3 or 4 IDH-mutant gliomas** might respond to vorasidenib, especially those with non-enhancing or low-proliferative compartments.
- They may cite or mention **ongoing trials** testing vorasidenib in maintenance settings (i.e. after chemoradiotherapy) or in combination with chemotherapy, immunotherapy, or targeted agents.
- They might discuss **biomarkers of sensitivity or resistance**, e.g. the presence of co-mutations (e.g. NOTCH1) that may predict nonresponse.
- They could raise the question of whether **epigenetic or metabolic adaptation** may lead to resistance over time (e.g. activation of alternative pathways, escape via non-IDH mechanisms).
- The possibility of **combination therapy** (IDH inhibition + immunotherapy, or + radiotherapy, or + small molecule inhibitors) is probably discussed as a key next frontier.
- They may also caution on **safety in combination settings** and possible interactions (e.g. effects on DNA repair, radiosensitization, hepatic toxicity).

Discussion on Imaging, Biomarkers, and Response Assessment

- The authors likely devote a section to **ideal imaging modalities**: volumetric MRI (rather than 1D/2D diameter changes) may better capture subtle growth or shrinkage.
- They may argue for incorporation of **amino acid PET (e.g. ^18F-FET, ^11C-MET PET)** to detect metabolic changes preceding size changes.

- Advanced MRI metrics (diffusion tensor imaging, perfusion MRI) could serve as early indicators of response or microvascular changes.
- They may propose **liquid biomarkers** (e.g. plasma or CSF 2-HG, circulating tumor DNA [ctDNA] of mutant IDH) as monitoring tools, though noting technical and sensitivity limitations in brain tumors.
- They might also suggest integrating **molecular biomarkers** (e.g. co-mutations, methylation subtype, gene expression signatures) as stratifiers in trials or to predict response.

Challenges, Caveats, Risks

- The authors likely caution that **prolonged therapy** may carry cumulative toxicities (e.g. hepatic enzyme elevations).
- The possibility that **early use of vorasidenib** may reduce sensitivity to later chemotherapy or radiotherapy is a concern.
- They may note the **cost / access** issues for a long-term targeted therapy in a disease with relatively slow natural history.
- Trial design challenges: ensuring adequate power for OS endpoints, managing crossover, long follow-up, patient accrual.
- Ethical challenges in delaying standard therapies in randomized settings.
- Heterogeneity of gliomas: not all IDH-mutant gliomas are equal (co-mutations, methylation subtypes), so generalization is risky.

Future Directions & Conclusion

- The authors likely call for **prospective randomized trials** with long follow-up incorporating OS, neurocognitive, QoL endpoints, not only PFS.
- They may suggest **adaptive trial designs** or **biomarker-stratified arms**.
- Emphasis on **translational research** to identify resistance mechanisms, molecular correlates of response, and biomarkers to guide use.
- They probably reiterate that vorasidenib is already shifting the paradigm in grade 2 disease, but that many “how-to” questions remain before it can fully replace or be integrated with standard chemoradiotherapy.
- A concluding statement likely echoes the abstract: though vorasidenib is becoming widely used in grade 2 IDH-mutant gliomas, it is essential to refine how, when, and in whom it is used and explore its extension beyond grade 2.

Supporting Context from Related Reviews / Studies

Since the full text was inaccessible, additional insights come from related sources, especially the recent review **"Who will benefit from vorasidenib? Review of data from the literature and open questions"** in *Neuro-Oncology Practice*, which draws heavily on INDIGO data and aligns with many of the themes in Seyve & Ducray's review. PMC

From that review and Frontiers commentary:

- In INDIGO, **median PFS** was 27.7 months (vorasidenib) vs 11.1 months (placebo), and **time to next intervention (TTNI)** was **not reached** in the vorasidenib arm vs 17.8 months in placebo arm. Frontiers +1
- The safety profile was manageable; the most common ≥ grade 3 adverse event was **elevated alanine aminotransferase (transaminitis)**, occurring in ~9.6% of patients in the active arm. Frontiers +2 PMC +2
- Health-related quality of life (HRQOL) assessment (via instruments such as FACT-Br) did not show clinically meaningful deterioration in either arm in the shorter-term follow-up. Frontiers +2 PMC +2
- The seizure control signal is interesting: IDH mutation is associated with increased excitability (via 2-HG modulation of NMDA receptors), so IDH inhibition may reduce seizure frequency beyond tumor control. Frontiers +1
- Some authors have flagged that patient selection criteria in INDIGO were relatively narrow (non-enhancing, post-surgery residual or recurrent grade 2, no need for immediate therapy), meaning generalizability to broader patient populations is uncertain. PMC +1
- In real-world settings, whether to treat "intermediate risk" patients (neither clearly low nor high risk) remains an open debate. Frontiers +1
- The ASCO–SNO glioma guidelines (2025 update) have begun incorporating vorasidenib, but its role is not yet broadly codified. Frontiers

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