Vorasidenib

- Low-grade IDH-mutant gliomas: from standard post-surgical treatments to novel IDH inhibitors
- Unlocking new horizons: advances in treating IDH-mutant, 1p/19q-codeleted oligodendrogliomas
- Advances in IDH-mutant glioma management: IDH inhibitors, clinical implications of INDIGO trial, and future perspectives
- INDIGO and Beyond: Approaching Vorasidenib With Cautious Optimism
- Unlocking therapeutic synergy: IDH inhibitors and immunotherapy combination in preclinical and clinical IDH mutant glioma models - A systematic review
- Incorporating Targeted Therapy Into Neuro-Oncology Practice
- Toxicological insights and safety considerations of vorasidenib in grade 2 astrocytoma and oligodendroglioma
- Contemporary Patterns of Care for Low-Grade Glioma in Australia and New Zealand

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Vorasidenib (AG-881) is an orally available, brain-penetrant second-generation dual IDH1-mutant inhibitor and IDH2-mutant inhibitor. Vorasidenib (AG-881) exhibits nanomolar inhibition of D-2-Hydroxyglutarate (D-2-HG), and the IC50 ranges of 0.04~22 nM against IDH1 R132C, IDH1 R132G, IDH1 R132H and IDH1 R132S and 7~14 nM against IDH2 R140Q and 130 nM against IDH2 R172K

In a double-blind, phase 3 trial, Mellinghoff et al. randomly assigned patients with residual or recurrent grade 2 IDH-mutant glioma who had undergone no previous treatment other than surgery to receive either oral vorasidenib (40 mg once daily) or matched placebo in 28-day cycles. The primary endpoint was imaging-based progression-free survival according to a blinded assessment by an independent review committee. The key secondary endpoint was the time for the next anticancer intervention. Crossover to vorasidenib from placebo was permitted on confirmation of imaging-based disease progression. Safety was also assessed.

A total of 331 patients were assigned to receive vorasidenib (168 patients) or placebo (163 patients). At a median follow-up of 14.2 months, 226 patients (68.3%) were continuing to receive vorasidenib or a placebo. Progression-free survival was significantly improved in the vorasidenib group as compared with the placebo group (median progression-free survival, 27.7 months vs. 11.1 months; hazard ratio for disease progression or death, 0.39; 95% confidence interval [CI], 0.27 to 0.56; P<0.001). The time to the next intervention was significantly improved in the vorasidenib group as compared with the placebo group (hazard ratio, 0.26; 95% CI, 0.15 to 0.43; P<0.001). Adverse events of grade 3 or higher occurred in 22.8% of the patients who received vorasidenib and in 13.5% of those who received a placebo. An increased alanine aminotransferase level of grade 3 or higher occurred in 9.6% of the patients who received vorasidenib and in no patients who received placebo

In patients with grade 2 IDH-mutant glioma, vorasidenib significantly improved progression-free survival and delayed the time to the next intervention. (Funded by Servier; INDIGO ClinicalTrials.gov number, NCT04164901.). [1)]

According to the phase III INDIGO trial, vorasidenib, an IDH1/2 inhibitor, significantly benefited adults with IDH1/2-mutant low-grade gliomas, reducing progression risk and delaying the need for chemoradiotherapy. Meanwhile, in a pediatric low-grade glioma cohort of FIREFLY-1, a phase II trial, robust responses to the type II pan-RAF inhibitor tovorafenib were seen [2)]

Vorasidenib and ivosidenib inhibit mutant forms of isocitrate dehydrogenase (mIDH) and have shown preliminary clinical activity against mIDH glioma. We evaluated both agents in a perioperative phase 1 trial to explore the mechanism of action in recurrent low-grade glioma (IGG) and select a molecule for phase 3 testing. Primary end-point was concentration of D-2-hydroxyglutarate (2-HG), the metabolic product of mIDH enzymes, measured in tumor tissue from 49 patients with mIDH1-R132H nonenhancing gliomas following randomized treatment with vorasidenib (50 mg or 10 mg once daily, q.d.), ivosidenib (500 mg q.d. or 250 mg twice daily) or no treatment before surgery. Tumor 2-HG concentrations were reduced by 92.6% (95% credible interval (CrI), 76.1-97.6) and 91.1% (95% CrI, 72.0-97.0) in patients treated with vorasidenib 50 mg q.d. and ivosidenib 500 mg q.d., respectively. Both agents were well tolerated and follow-up is ongoing. In exploratory analyses, 2-HG reduction was associated with increased DNA 5-hydroxymethylcytosine, reversal of 'proneural' and 'stemness' gene expression signatures, decreased tumor cell proliferation and immune cell activation. Vorasidenib, which showed brain penetrance and more consistent 2-HG suppression than ivosidenib, was advanced to phase 3 testing in patients with mIDH LGGs. Funded by Agios Pharmaceuticals, Inc. and Servier Pharmaceuticals LLC; ClinicalTrials.gov number NCT03343197 [3)]

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computational drug repurposing strategies were employed to identify potent mIDH1- specific inhibitors from the 11,808 small molecules listed in the DrugBank repository.

Methods: Tanimoto coefficient (Tc) calculations were initially used to retrieve compounds with structurally similar scaffolds to ivosidenib. The resultant compounds were then subjected to molecular docking to discriminate the binders from the non-binders. The binding affinities and pharmacokinetic properties of the screened compounds were examined using prime Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) and QikProp algorithm, respectively. The conformational stability of these molecules was validated using 100 ns molecular dynamics simulation.

Results: Together, these processes led to the identification of three-hit molecules, namely DB12001, DB08026, and DB03346, as potential inhibitors of the mIDH1 protein. Of note, the binding free energy calculations and MD simulation studies emphasized the greater binding affinity and structural stability of the hit compounds towards the mIDH1 protein.

Conclusion: The collective evidence from our study indicates the activity of DB12001 against recurrent glioblastoma, which, in turn, highlights the accuracy of our adapted strategy. Hence, we hypothesize that the identified lead molecules could be translated for the development of mIDH1 inhibitors in the near future [4)]

Vorasidenib (AG-881) has recently been reported as a promising dual inhibitor of mutant isocitrate dehydrogenase 1 and 2 with the ability to penetrate the blood-brain barrier towards the treatment of low-grade glioma. In order to combat drug resistance and toxicity levels, this compelled us to further investigate this substance as a basis for the creation of potential selective inhibitors of mutant

isocitrate dehydrogenases 1 and 2.

Methods: By employing a wide range of computational techniques, binding moieties of AG-881 that contributed towards its selective binding to isocitrate dehydrogenase enzymes 1 and 2 were identified and subsequently used to generate pharmacophore models for the screening of potential inhibitor drugs that were further assessed by their pharmacokinetics and physicochemical properties.

Results: AG-881 was identified as the most favorable candidate for isocitrate dehydrogenase enzyme 1, exhibiting a binding free energy of -28.69 kcal/mol. ZINC93978407 was the most favorable candidatefor isocitrate dehydrogenase enzyme 2, displaying a strong binding free energy of -27.10 kcal/mol. ZINC9449923 and ZINC93978407 towards isocitrate dehydrogenase enzyme 1 and 2 showed good protein structural stability with a low radius of gyration values relative to AG-881.

Conclusion: We investigated that ZINC9449923 of isocitrate dehydrogenase enzyme 1 and ZINC 93978407 of isocitrate dehydrogenase enzyme 2 could serve as promising candidates for the treatment of lower-grade glioma as they cross the blood-brain barrier, and present with lower toxicity levels relative to AG-881 [5)]

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conducted a multicenter, open-label, phase I, dose-escalation study of vorasidenib in 93 patients with mutant IDH1/2 (mIDH1/2) solid tumors, including 52 patients with glioma that had recurred or progressed following standard therapy. Vorasidenib was administered orally, once daily, in 28-day cycles until progression or unacceptable toxicity. Enrollment is complete; this trial is registered with ClinicalTrials.gov, NCT02481154.

Results: Vorasidenib showed a favorable safety profile in the glioma cohort. Dose-limiting toxicities of elevated transaminases occurred at doses ≥100 mg and were reversible. The protocol-defined objective response rate per Response Assessment in Neuro-Oncology criteria for LGG in patients with nonenhancing glioma was 18% (one partial response, three minor responses). The median progression-free survival was 36.8 months [95% confidence interval (CI), 11.2-40.8] for patients with nonenhancing glioma and 3.6 months (95% CI, 1.8-6.5) for patients with enhancing glioma. Exploratory evaluation of tumor volumes in patients with nonenhancing glioma showed sustained tumor shrinkage in multiple patients.

Conclusions: Vorasidenib was well tolerated and showed preliminary antitumor activity in patients with recurrent or progressive nonenhancing mIDH LGG [6)].

A analysis proved that the dual-targeting ability of AG-881 is mediated by Val255/Val294 within the binding pockets of both mIDH1 and mIDH2 which are shown to elicit a strong intermolecular interaction, thus favoring binding affinity. The structural orientations of AG-881 within the respective hydrophobic pockets allowed favorable interactions with binding site residues which accounted for its high binding free energy of -28.69 kcal/mol and -19.89 kcal/mol towards mIDH1 and mIDH2, respectively. Interestingly, upon binding, AG-881 was found to trigger systemic alterations of mIDH1 and mIDH2 characterized by restricted residue flexibility and a reduction in exposure of residues to the solvent surface area. As a result of these structural alterations, crucial interactions of the mutant enzymes were inhibited, a phenomenon that results in a suppression of the production of oncogenic stimulator 2-HG. Findings therefore provide thorough structural and dynamic insights associated with the dual inhibitory activity of AG-881 towards glioma therapy [7)]

Mutations in isocitrate dehydrogenase 1 (IDH1mut) are reported in 70-90% of low-grade gliomas and secondary glioblastomas. IDH1mut catalyzes the reduction of α-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG), an oncometabolite which drives tumorigenesis. Inhibition of IDH1mut is therefore an emerging therapeutic approach, and inhibitors such as AG-120 and AG-881 have shown promising results in phase 1 and 2 clinical studies. However, detection of response to these therapies prior to changes in tumor growth can be challenging. The goal of this study was to identify non-invasive clinically translatable metabolic imaging biomarkers of IDH1mut inhibition that can serve to assess response. Methods: IDH1mut inhibition was confirmed using an enzyme assay and 1H- and 13C- magnetic resonance spectroscopy (MRS) were used to investigate the metabolic effects of AG-120 and AG-881 on two genetically engineered IDH1mut-expressing cell lines, NHAIDH1mut and U87IDH1mut. Results:Proton magnetic resonance spectroscopic imaging indicated a significant decrease in steady-state 2-HG following treatment, as expected. This was accompanied by a significant Proton magnetic resonance spectroscopic imaging-detectable increase in glutamate. However, other metabolites previously linked to 2-HG were not altered. 13C-MRS also showed that the steady-state changes in glutamate were associated with a modulation in the flux of glutamine to both glutamate and 2-HG. Finally, hyperpolarized 13C-MRS was used to show that the flux of α-KG to both glutamate and 2-HG was modulated by treatment. Conclusion: In this study, we identified potential 1H- and 13C-MRS-detectable biomarkers of response to IDH1mut inhibition in gliomas. Although further studies are needed to evaluate the utility of these biomarkers in vivo, we expect that in addition to a Proton magnetic resonance spectroscopic imaging-detectable drop in 2-HG, a Proton magnetic resonance spectroscopic imaging-detectable increase in glutamate, as well as a hyperpolarized 13C-MRS-detectable change in [1-13C] α-KG flux, could serve as metabolic imaging biomarkers of response to treatment [8)]

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