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Articles

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

Prof Timothy F Cloughesy MD [a], Prof Martin J van den Bent MD [c], Mehdi Touat MD [d] *, Prof Deborah T Blumenthal MD [e] *, Prof Katherine B Peters MD [f], Prof Benjamin M Ellingson PhD [b], Prof Jennifer L Clarke MD MPH [g], Joe Mendez MD [h], Shlomit Yust-Katz MD [i], Liam Welsh MD PhD [j], Warren P Mason MD [k], Prof Francois Ducray MD [l], Yoshie Umemura MD [m], Prof Burt Nabors MD [n], Matthias Holdhoff MD [o], Andreas F Hottinger MD PhD [p], Prof Yoshiki Arakawa MD [q], Juan M Sepulveda MD [r], Prof Wolfgang Wick MD [s], Prof Riccardo Soffietti MD [t]...

Prof Ingo K Mellinghoff MD [ab] †

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Summary

Background

In a phase 3 trial, vorasidenib, an oral brain-penetrant inhibitor of mutant isocitrate dehydrogenase 1 and 2 (IDH1/2), resulted in improved progression-free survival (primary endpoint) and time to next intervention (key secondary endpoint) at second interim analysis,

resulting in study unblinding. We report 6 months of additional double-blind data, from second interim analysis (Sept 6, 2022) to unblinding (March 7, 2023), and the effect of vorasidenib on volumetric tumour growth rate, health-related quality of life (HRQOL), neurocognitive function, and seizure control.

Methods

INDIGO was a randomised, double-blind, placebo-controlled, phase 3 trial done in 92 hospitals in Canada, France, Germany, Israel, Italy, Japan, the Netherlands, Spain, Switzerland, the UK, and the USA. Patients aged 12 years or older with residual or recurrent grade 2 IDH1/2-mutant diffuse glioma, a Karnofsky performance-status score of 80 or higher, at least one previous surgery, and no other previous anticancer treatment were eligible. Patients were randomly assigned (1:1; stratified according to locally determined chromosome 1p/19q codeletion status and baseline tumour size) to oral vorasidenib (40 mg) or placebo once a day in continuous 28-day cycles until disease progression or unacceptable toxicity. Progression-free survival per masked independent review committee was the primary endpoint, and time to next intervention was the key secondary endpoint. Prespecified secondary endpoints included tumour growth rate (6-monthly change in tumour volume) and HRQOL (Functional Assessment of Cancer Therapy–Brain [FACT-Br]). Prespecified exploratory endpoints included neurocognitive function (cognitive performance instruments) and seizure activity (self-reported). The full analysis set was used for all efficacy analyses and included all randomly assigned patients, and the safety analysis set was used for all safety analyses and included all patients who received one or more doses of vorasidenib or placebo. The trial is registered with ClinicalTrials.gov ↗, NCT04164901 ↗. Recruitment is complete and the trial is ongoing.

Findings

Between Jan 9, 2020, and Feb 22, 2022, 331 patients were enrolled and randomly assigned to vorasidenib (n=168) or placebo (n=163). 187 (56%) patients were male, 144 (44%) were female, and 257 (78%) were White. Median follow-up was 20·1 months (IQR 15·9 to 23·8). With an additional 6 months of follow-up, median progression-free survival (not reached [95% CI 22·1 to not estimated] *vs* 11·4 months [95% CI 11·1 to 13·9]; hazard ratio [HR] 0·35 [95% CI 0·25 to 0·49]) and time to next intervention (not estimated [not estimated to not estimated] *vs* 20·1 months [17·5 to 27·1]; HR 0·25 [0·16 to 0·40]) remained substantially improved with vorasidenib versus placebo. Tumour growth rate was −1·3% (95% CI −3·2 to 0·7) with vorasidenib and 14·4% (95% CI 12·0 to 16·8) with placebo (difference 15·9% [95% CI 12·6 to 19·3]). Mean FACT-Br total scores were similar between the vorasidenib and placebo groups (158·2 [SD 26·4] and 158·8 [23·3]) at baseline and remained high (154·2 [29·8] and 153·2 [29·4]) by the end of treatment. There was no difference between vorasidenib or placebo in neurocognitive functions of verbal learning, executive function, attention, working memory, and psychomotor function from baseline through to end of treatment. The vorasidenib group had lower rates of seizures than the placebo group (18·2 seizures per person-year [95% CI 8·4 to 39·5] *vs* 51·2 seizures per person-year [22·9 to 114·8]). The most common grade 3 or worse treatment-emergent adverse events (TEAEs) in the vorasidenib and placebo groups, respectively, were increased alanine aminotransferase (17 [10%] and two [1%]), increased aspartate aminotransferase (eight [5%] and none), seizures (seven [4%]

and five [3%]), and increased γ-glutamyltransferase (five [3%] and two [1%]). Serious TEAEs occurred in 20 (12%) patients in the vorasidenib group and ten (6%) in the placebo group; the most common were seizures. There were no treatment-related deaths.

Interpretation

Vorasidenib reduced tumour growth rate and improved seizure control compared with placebo, with no observed negative effects on HRQOL or neurocognition. Additional follow-up supported the robustness of progression-free survival and time to next intervention in patients with grade 2 IDH1/2-mutant diffuse glioma. These findings support the use of vorasidenib in patients with grade 2 IDH1/2-mutant gliomas who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy.

Funding

Servier.

Introduction

Malignant gliomas, which spread diffusely throughout the brain, are the most common malignant primary brain tumours in adults and cause substantial morbidity and premature death.1, 2, 3 WHO further subclassifies adult-type diffuse gliomas into glioblastomas, astrocytomas, and oligodendrogliomas according to a combination of histological findings and molecular parameters.[4]

The majority of malignant gliomas in adults younger than 50 years harbour mutations in genes encoding the isocitrate dehydrogenase 1 or 2 metabolic enzymes (IDH1/2), initially presenting as lower-grade tumours and ultimately acquiring the histological, genetic, and clinical features of highly aggressive brain tumours.1, 5, 6 Mutations in *IDH1/IDH2* occur early during glioma development, resulting in abnormal tumour cell production of 2-hydroxyglutarate, and are associated with molecular and cellular changes in the tumour caused by 2-hydroxyglutarate-mediated competitive inhibition of α-ketoglutarate-dependent enzymes.[7]

Current treatment for IDH1/2-mutant glioma includes a combination of tumour resection, radiation, and chemotherapy.[6] Although adjuvant chemoradiotherapy can result in long-term disease control, it is not curative and is associated with short-term and long-term toxicities. Radiotherapy for glioma, for instance, has been associated with neurocognitive side-effects, particularly with long follow-up.6, 8, 9 Many patients with grade 2 IDH1/2-mutant glioma therefore delay further treatment after surgery and are monitored with regular brain MRI scans and neurological evaluations. This active monitoring period is an opportunity to evaluate new therapies targeting specific vulnerabilities of IDH1/2-mutant gliomas, potentially delaying tumour progression with less treatment-associated toxicity.

Research in context

Evidence before this study

We searched PubMed with the search terms “glioma”, “isocitrate dehydrogenase”, and “phase 3” for publications before August 2023, restricting findings to randomised controlled trials. No phase 3 trials before the INDIGO trial evaluated targeted therapy in isocitrate dehydrogenase (IDH)-mutant glioma. Three pivotal trials—EORTC 22845, RTOG 9802, and EORTC 22033—defined standard care in WHO grade 2 glioma before *IDH* mutations were recognised as key molecular markers. EORTC 22845 addressed the efficacy of early radiotherapy versus deferred treatment at time of progression. Long-term follow-up showed that progression-free survival was longer in patients with early radiotherapy, but overall survival was similar between groups. The study concluded that radiotherapy could be deferred for patients with low-grade glioma who are in good condition (WHO performance status 0–2), provided they are carefully monitored. EORTC 22033 compared the effectiveness of single-modality standard radiotherapy versus temozolomide chemotherapy in patients with grade 2 glioma with at least one high-risk feature and found no difference in progression-free survival. In the RTOG 9802 trial, patients with a high-risk, low-grade glioma (subtotal resection or aged ≥40 years) were randomly assigned to postoperative radiotherapy with or without six cycles of adjuvant procarbazine, lomustine, and vincristine chemotherapy. Long-term follow-up showed that radiotherapy plus adjuvant chemotherapy improved progression-free survival and overall survival compared with radiotherapy alone. Neither trial prospectively accounted for *IDH* status, now central to diagnosis and prognosis of glioma. INDIGO showed that vorasidenib statistically significantly improved progression-free survival and time to next intervention versus placebo, with favourable safety, leading to US Food and Drug Administration approval in 2024.

Added value of this study

Our report describes the analysis of pre-planned secondary and exploratory endpoints of the INDIGO study, including volumetric tumour growth, health-related quality of life (HRQOL), neurocognitive function, and seizure frequency. We also provide 6 additional months of blinded follow-up data, allowing for updated assessment of progression-free survival, time to next intervention, and safety. Tumour volume analysis demonstrated progressive growth in the placebo group, whereas patients receiving vorasidenib showed gradual growth arrest and tumour shrinkage. We observed no negative effects of vorasidenib on HRQOL and cognitive function, with no decline compared with baseline or placebo. Patients receiving vorasidenib also had fewer seizures, particularly those with oligodendroglioma, despite seizure control being an eligibility criterion. The safety profile remained consistent, with no evidence of cumulative hepatotoxicity. These findings offer a more complete picture of vorasidenib's clinical benefit in this patient population.

Implications of all the available evidence

The updated results support and strengthen the initial findings from the INDIGO trial,

showing durable benefit of vorasidenib across clinical and radiographic endpoints without compromising function or quality of life. The kinetics of tumour response, with initial growth arrest and gradual tumour regression, suggest a mechanism of action distinct from that of cytotoxic therapies. Although overall survival is a secondary endpoint, it will require extended follow-up (potentially many years) given the biology of grade 2 gliomas. Ongoing follow-up and real-world data will be needed to understand the long-term effect of IDH inhibition on survival and functional outcomes.

Vorasidenib is a dual inhibitor of the IDH1/2 mutant enzymes designed to achieve enhanced brain penetration.[10] Vorasidenib showed favourable safety and preliminary antitumour activity in a phase 1 clinical trial.[11] A subsequent perioperative trial in patients with grade 2 IDH1/2-mutant glioma requiring brain tumour surgery showed that short-term treatment with vorasidenib reduced tumour 2-hydroxyglutarate levels by more than 90%.[10] The phase 3 INDIGO trial (NCT04164901 ↗) was designed to determine whether vorasidenib could delay tumour progression in patients with grade 2 IDH1/2-mutant glioma who had not yet received radiotherapy or chemotherapy and were undergoing active monitoring.

We previously reported results from the INDIGO pre-planned second interim analysis, which met the primary endpoint (imaging-based progression-free survival) and key secondary endpoint (time to next intervention).[12] Based on these results, including data as of Sept 6, 2022, INDIGO was unblinded on March 7, 2023, following the recommendation of the independent data monitoring committee.[12] All eligible patients receiving placebo were offered vorasidenib. In August 2024, the US Food and Drug Administration approved vorasidenib for the treatment of patients aged 12 years and older with grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation, following surgery.

Here, we report additional analyses investigating the effect of vorasidenib on tumour growth rate, health-related quality of life (HRQOL), neurocognitive function, and seizure control compared with placebo. We also report an additional 6 months of placebo-controlled, double-blind data, collected between the second interim analysis data cutoff on Sept 6, 2022, and trial unblinding on March 7, 2023.

Section snippets

Study design and participants

INDIGO was a randomised, double-blind, placebo-controlled, phase 3 trial conducted at 92 hospitals in Canada, France, Germany, Israel, Italy, Japan, the Netherlands, Spain, Switzerland, the UK, and the USA (appendix pp 2–5). Its design has been reported previously.[12] Briefly, patients were aged 12 years or older, had residual or recurrent grade 2 IDH1/2-mutant diffuse glioma according to WHO 2016 criteria, had at least one previous surgery for glioma, had not received any previous anticancer …

Results

Between Jan 9, 2020, and Feb 22, 2022, 331 patients were enrolled and randomly assigned to vorasidenib (n=168) or placebo (n=163). One patient in the vorasidenib group withdrew consent after random assignment and was never dosed. As of March 7, 2023, 123 (73%) of 168 patients remained in the vorasidenib group and 72 (44%) of 163 in the placebo group (appendix p 11). Baseline characteristics of randomly assigned patients were generally well balanced between groups (appendix pp 24–25). Overall, …

Discussion

To our knowledge, the phase 3 INDIGO trial represents the first prospective placebo-controlled trial for IDH1/2-mutant glioma.[7] Compared with the previously reported analysis from this trial,[12] the additional 6 months of blinded data support the robustness of previous findings of progression-free survival and time to next intervention. The HR for progression-free survival per masked independent review committee is consistent with narrower 95% CIs, highlighting the durable treatment effect of …

Declaration of interests

TFC reports grants or contracts from Roche, VBI, Merck, Novartis, BMS, and Servier via UCLA; royalties or licenses from Chimerix and Katmai; consulting fees from Katmai, the Global Coalition for Adaptive Research, Symbio, Mundipharma, Tango BlueRock, Vida Ventures, Lista Therapeutics, Stemline, Novartis, Roche, Sonalasense, Sagimet, Clinical Care Options, Ideology Health, Servier, Jubilant, Immvira, Gan & Lee, BrainStorm, Sapience, Inovio, Vigeo Therapeutics, DNATrix, Tyme, SDP, Kintara, Bayer, …

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* Contributed equally

† Co-senior authors

‡ INDIGO trial investigators listed in the appendix (p 2)

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