How robust are the data in vorasidenib for isocitrate dehydrogenase-1 or isocitrate dehydrogenase-2 mutant low-grade glioma?

Dear Editor,

Mellinghoff *et al*.[1] conducted a double-blinded randomized study INDIGO investigating the effect of brain-penetrant vorasidenib against low-grade gliomas with mutated isocitrate dehydrogenase (IDH-1) and IDH-2. This is based on the rationale that these two enzymes with gain-of-function mutations led to the production and accumulation of oncometabolite 2-hydroxyglutarate within the local tumor microenvironment, setting off a cascade of epigenetic changes that favor glioma development and progression.[2] Typically, low-grade glioma patients are categorized as high risk for progression if they are older than 40 years of age or undergo incomplete resection of tumor. Other than resection, radiation or chemotherapy may be postponed at the time of diagnosis because the speed of progression is slow, and patients then undergo serial head magnetic resonance imaging (MRI) monitoring. The investigators took advantage of this observation period and introduced vorasidenib to delay tumor progression and prolong survival. Under blinded imaging-based independent assessment, they found that vorasidenib significantly improved progression-free survival (PFS) compared to the control population. This small molecule targeted agent also delayed time to next intervention (TTNI).

Response, PFS, and overall survival (OS) are three classic pillars of efficacy assessment in cancer clinical trials. Positive outcomes from 2 of these 3 endpoints are typically required for regulatory approval or acceptance as standard of care. Unfortunately in the glioma population, radiologic response to treatment is rarely seen on head MRI. Indeed, there were only 2 responders in the INDIGO study, and the results may be more appropriately viewed and compared to our prior experience in glioma trials. For example, the EORTC/NCIC (radiotherapy plus concomitant and adjuvant temozolomide)[3] and the EF-14 (adjuvant temozolomide with or without tumor treating fields)[4] trials for glioblastoma showed prolongation of PFS and OS, and both treatment modalities won regulatory approval in the United States accordingly. However, this was not the case for RTOG 0625 and AVAglio trials (radiotherapy and temozolomide with or without bevacizumab)[5] because they only showed prolongation of PFS but not OS, despite an apparent decrease in contrast enhancement due to pseudoresponse.

The designers of the INDIGO trial introduced the concept of TTNI as a key secondary efficacy endpoint. This is probably because, for the low-grade glioma population, lack of response and long duration of follow-up required for OS determination are major impediments to timely efficacy assessment. However, we should be cautious in asking whether TTNI is a relevant benchmark for this trial. First, prolonged PFS would lead to a delay in TTNI anyway, and therefore, these two benchmarks are not necessarily independent. Second, patients in the control group can cross over to receive vorasidenib, and their threshold for crossing over to another pill is probably lower compared to those in the experimental cohort considering additional brain surgery, radiation, or cytotoxic chemotherapy. Inertia for next intervention may, therefore, be greater among patients taking the placebo. Third, the criteria for the next intervention were not prespecified in the original protocol, and it was only introduced as a key secondary endpoint for analysis on July 20, 2021, in Amendment 3, probably after the first interim analysis and the steering committee noticed a signal. Finally, whether or not there is a difference in the number of neurologic versus radiologic progression in the two cohorts is unclear. Obviously, neurologic deficits are more serious conditions and carry a greater propensity for intervention than just observed tumor enlargement on head MRI without clinical sequela. For these reasons, TTNI is probably an inadequate secondary endpoint and the regulatory agency may need to consider mandating the sponsor to maintain careful and detailed OS follow-up, which may take decades, as the basis for approval. For example, in RTOG 9802, a randomized trial of radiotherapy plus procarbazine, vincristine for supratentorial low-grade gliomas, it took at least a decade of follow up in order to detect an OS difference.[6,7] In INDIGO however, the control group's postprogression crossover to vorasidenib may attenuate or even negate any detectable difference in OS.

Proponents of vorasidenib assert that delaying glioma progression in this younger and productive population is clinically meaningful. No one can dispute this point. However, the magnitude of delay in tumor progression is an issue. At a median follow-up of only 14 months, the investigators found a difference of 17 months in PFS between the two cohorts (28 months for vorasidenib vs. 11 months for the control). This period is only a fraction, or ≤15%, of the overall longevity of this population, which is in the order of >10 years, and the short duration may not allow them to finish college or acquire additional employable skills. Therefore, whatever measurable gain attained during this 17-month period must be discounted against the cost of this drug, which may be substantial due to the limited time for patent exclusivity

before generics compete with the manufacturer. Furthermore, INDIGO was not designed to address the neurocognitive benefit of vorasidenib treatment, and the health-related quality of life data presented in public thus far did not compared with those subjects who received standard of care radiation, chemotherapy or both.

Despite the imperfections, vorasidenib still represents a significant step forward in the management of low-grade glioma patients. The optimal use of this IDH-1/2 inhibitor alone or in combination with other treatment modalities, as well as nuances on the nonmedical impact on the patient, remains to be determined.

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Conflicts of interest

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