AHFS Final Determination of Medical Acceptance: Off-label Use of Ivosidenib for Treatment of IDH Mutant Glioma

Drug: Ivosidenib

Off-label Use: Treatment of IDH Mutant Glioma

Criteria Used in Selection of Off-label Use for Review:

- Results from early phase trials, a retrospective study, and case series

Strength of Evidence: Level 3 (low strength/quality)

Grade of Recommendation: Reasonable choice (accepted, with possible conditions)

Narrative Summary:

The most common malignant primary brain tumors in adults are gliomas.[10001] The classification of these tumors has evolved with the identification of various molecular features including isocitrate dehydrogenase (IDH) mutations.[10001] In gliomas, IDH mutations are highly prevalent and confer significant improved survival as compared to IDH wild-type glioma.[10001] The standard of care for IDH mutant gliomas generally involves maximal resection (when feasible) followed by a combination of radiation and chemotherapy.[10001] However, this approach does not significantly enhance survival and can result in long-term negative outcomes (e.g., cognitive decline) impacting quality of life.[10001] Of note, transformation of low-grade glioma into a higher tumor grade is typically associated with contrast enhancement on MRI.[10003] Ivosidenib, a small molecule inhibitor that targets the IDH1 enzyme, has been evaluated as a potential treatment option in patients with non-enhancing, IDH-mutated glioma in early phase trials, a retrospective study, and a case series.

A phase 1, open-label, multicenter, dose-escalation, and dose-expansion study assessed ivosidenib therapy in 66 adult patients (41 males/25 females) with mutant IDH1 advanced solid

tumors.[10002] Twelve (18.2%) patients had a glioblastoma diagnosis and the remaining patients had a low-grade glioma (e.g., oligodendroglioma, astrocytoma, oligoastrocytoma).[10002] Of the 66 patients, 20 were enrolled in the dose escalation phase and 46 in the dose expansion phase.[10002] The escalation phase provided oral doses of ivosidenib of 100 mg twice daily or 300-, 500-, 600-, and 900-mg once daily. [10002] All patients in the dose expansion phase were administered ivosidenib 500 mg once daily. [10002] For the dose expansion phase, patients were separated into 2 cohorts based upon presence or absence of tumor contrast enhancement at enrollment. [10002] All enrolled patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and an expected survival of at least 3 months. [10002] The median age was 41 years, and the median number of prior therapies was 2. [10002] The primary objective of the study was to evaluate the safety and tolerability of ivosidenib and determine the maximum tolerated dose or recommended phase 2 dose. [10002] Secondary objectives included evaluation of dose limiting toxicities and preliminary clinical response. [10002]

The maximum tolerated dose of ivosidenib was not reached during the study and no dose limiting toxicities were noted. [10002] Most patients (95.5%) experienced at least 1 adverse event of any grade or causality. [10002] The most common adverse events (≥10%) were headache, nausea, fatigue, vomiting, seizure, diarrhea, hyperglycemia, aphasia, reduced neutrophil count, depression, hypophosphatemia, and paresthesia. [10002] Grade ≥3 adverse events were observed in 13 (19.7%) patients and included headache, hypophosphatemia, and seizure. [10002] The most common treatment-related adverse events were fatigue, reduced neutrophil count, and diarrhea. [10002] Discontinuation of ivosidenib therapy due to an adverse event did not occur; however, 8 patients experienced a dose interruption due to an event. [10002]

Local investigators assessed clinical response to therapy. [10002] The best overall response was a partial response in 1 patient, 44 patients (66.7%) experienced stable disease, and 21 patients (31.8%) had progressive disease. [10002] As of the data cutoff of January 16, 2019, patients with nonenhancing tumors had an improved median treatment duration as compared to those with enhancing tumors (18.4 vs 1.9 months). [10002] In addition, 66.7% of patients with nonenhancing tumors at baseline experienced a reduction in tumor measurements as compared to 33.3% of patients with enhancing tumors and 30 (85.7%) of the 35 patients with nonenhancing tumors had a best response of stable disease compared to 14 (45.2%) of the 31 patients with enhancing tumors. [10002] Median progression free survival was 13.6 months in the nonenhancing group and 1.4 months in the enhancing group. [10002]

A phase 1, randomized, controlled, open-label, multicenter perioperative study compared ivosidenib to vorasidenib in adult patients with recurrent, mutant IDH1-R132H, non-enhancing, oligodendroglioma or astrocytoma.[10003] In Cohort 1, patients were randomized 2:2:1 to receive ivosidenib 500 mg orally daily for 4 weeks, vorasidenib 50 mg orally daily for 4 weeks, or a control of no treatment prior to surgery. [10003] After documenting mutant IDH1 enzyme inhibition in tumors, cohort 2 was opened to test alternative dose regimens, with patients randomized 1:1 to ivosidenib 250 mg orally twice daily or vorasidenib 10 mg orally once daily. [10003] Treated

patients received 28 (+7) days of medication up to and including the day of surgery. [10003] All patients had the option to receive postoperative treatment until disease progression or unacceptable toxicity. [10003] Postoperatively, control patients were randomized 1:1 to ivosidenib 500 mg (n=3) or vorasidenib 50 mg (n=2). [10003] The median age of patients receiving ivosidenib was 37 years, and was 49 years in the vorasidenib group.[10003] The majority of patients (87.8%) in the study had grade 2 tumors.[10003] The primary endpoint was the concentration of D-2-hydroxyglutarate (2-HG; a metabolic product of mutant IDH enzymes) in surgically resected tumors. [10003] Secondary endpoints include safety and preliminary clinical activity; pharmacokinetics was also assessed. [10003]

As of April 29, 2020 (analysis cutoff date), 49 patients were randomized before surgery. [10003] All patients proceeded to surgery without unplanned delays. [10003] Overall, 24 patients received at least one dose of vorasidenib, and 25 patients received at least one dose of ivosidenib. [10003] At the time of the analysis cutoff date, 17 (70.8%) patients remained on vorasidenib treatment. [10003] Five (20.8%) patients discontinued therapy due to disease progression and 2 (8.3%) discontinued per clinician decision. [10003] Fifteen (60.0%) patients remained on ivosidenib treatment, 3 (12.0%) did not continue ivosidenib postoperatively, 6 (24.0%) discontinued therapy due to disease progression, and 1 (4.0%) discontinued due to an adverse event. [10003]

All patients experienced at least one adverse event in the study.[10003] The most common adverse events (≥20%) in the ivosidenib group were headache, anemia, diarrhea, seizure, hypocalcemia, cough, nasal congestion, hypokalemia, nausea, hyperglycemia, and insomnia. [10003] The most common adverse events (≥20%) in the vorasidenib group were nausea, headache, diarrhea, fatigue, increased alanine aminotransferase, constipation, and insomnia. [10003]

Tumor samples from 40 of 49 patients were included in the tissue analyses. [10003] The mean reduction of 2-HG concentration in tumors relative to the control group was 91.1% for ivosidenib 500 mg once daily and 92.6% for vorasidenib 50 mg once daily. [10003] The preliminary objective response rate for ivosidenib 500 mg once daily was 35.7%, with 3 subjects achieving partial responses and 2 subjects achieving a minor response, and 12.5% for ivosidenib 250 mg twice daily, with a single partial response. [10003] The preliminary objective response rate for vorasidenib 50 mg once daily was 42.9% including 2 partial responses and 4 minor responses, and 10.0% for vorasidenib 10 mg once daily, with a single minor response. [10003]

Based on the study results, vorasidenib 50 mg daily demonstrated the most consistent inhibition of mutant IDH and the greatest preliminary antitumor activity and was therefore the agent selected for further evaluation in a phase 3 study.[10003] Ivosidenib was found to possess considerably lower central nervous system penetration than vorasidenib, but reached adequate tumor concentrations to inhibit the mutant IDH in patients due to its high plasma exposure.[10003]

A retrospective study from John Hopkins Hospital (2018-2022) evaluated the use of ivosidenib 500 mg once daily in adults with radiation/chemotherapy-naïve, IDH1 mutant,

nonenhancing, radiographically active, grade 2/3 gliomas.[10004] Twelve patients (median age: 46 years; 10 males/2 females) who had undergone 116 MRI scans (71 pretreatment and 45 on-treatment) were included in the study. [10004] FLAIR-based tumor volumes, growth rates, and progression-free survival were analyzed. [10004] The median on-drug follow-up was 13.2 months. [10004]

Results revealed that 50% of patients experienced ≥20% tumor volume reduction on-treatment and there was a reduced absolute growth rate during ivosidenib therapy as compared to before therapy. [10004] The median time to best response was 11.2 months, and 16.8 months in patients on ivosidenib for ≥1 year. Overall, responses required 5 months to be volumetrically detectable with responses becoming most evident after almost a year of treatment. [10004] Progression-free survival at 6, 9, and 12 months was 83%, 75%, and 70%, respectively. [10004] Median progression-free survival was not reached; however, mean progression-free survival was 26.4 months. [10004] One patient reported the occurrence of fluctuating diarrhea. [10004]

The use of ivosidenib for the treatment of IDH mutant gliomas was described in a retrospective case series, occurring from August 2018 to December 2022, at the MD Anderson Cancer Center.[10005] This series included 9 patients with IDH-mutant glioma (median age: 37 years; 8 males/1 female) administered ivosidenib 500 mg daily. [10005] As of January 11, 2023, all patients administered ivosidenib were still alive, with 78% experiencing stable disease. [10005] Median progression-free survival was 3.81 months after a median follow-up 17.8 months. [10005] Patients with non-enhancing disease (n=4) had nonsignificant improvement in progression-free survival as compared to those with enhancing disease (8.28 vs. 3.81 months). [10005] Adverse events were noted in 2 patients – a single patient experienced grade 1 lethargy and another patient experienced a grade 3 surgical wound infection (unrelated to study drug). [10005]

Based on current evidence, ivosidenib for the treatment of IDH mutant glioma has Level 3 (low strength/quality) evidence supporting its use.[10002,10003,10004,10005] Currently available data include phase 1 and retrospective studies and case series.[10002,10003,10004,10005] However, based on these data, ivosidenib may have a potential role in patients with non-enhancing, IDH-mutated glioma as an alternative regimen in select patients.[10002,10003,10004,10005]

Dosage

When ivosidenib is used for the treatment of IDH mutant glioma, the usual dosage administered in clinical studies and case reports is 500 mg orally once daily.[10002,10003,10004,10005]

References:

10001. Nasany RA, de la Fuente MI. Therapies for IDH-mutant gliomas. *Curr Neurol Neurosci Rep*. 2023;23:225-33.

10002. Mellinghoff IK, Ellingson BM, Touat M, et al. Ivosidenib in isocitrate dehydrogenase 1-mutated advanced glioma. *J Clin Oncol*. 2020;38:3398-406.

10003. Mellinghoff IK, Lu M, Wen PY, et al. Vorasidenib and ivosidenib in IDH1-mutant low-grade gliomas: a randomized, perioperative phase 1 trial. *Nature Med*. 2023;29:615-22.

10004. Kamson DO, Puri S, Sang Y, et al. Impact of frontline ivosidenib on volumetric growth patterns in isocitrate dehydrogenase-mutant astrocytic and oligodendroglial tumors. *Clin Cancer Res*. 2023;29:4863-9.

10005. Lam K, Lin HY, Williford G, et al. Ivosidenib off-label use for IDH mutant gliomas: the MD Anderson Cancer Center real life experience. *J Clin Oncol*. 2023;41(16 Suppl):e14022.

Oncology Expert Committee Voting Results and Comments:

First-Round Vote:

Proposed Level of Evidence: Level 3 (Low strength/quality)

Concur with rating: 5 votes

Do not concur with rating: 2 votes

Grade of Recommendation:

Recommended use (Accepted): 0 votes

Reasonable choice (Accepted, with possible conditions): 6 votes

Not fully established (Equivocal): 1 vote

Not recommended (Unaccepted): 0 votes

Reviewer Comments on Level of Evidence and Grade of Recommendation:

A fair appraisal of ivosidenib I think at least requires some understanding of a similar compound that demonstrated phase III benefit, see June 2023 NEJM. It is not FDA approved and neither will it until at least late this year.

Given the low level of evidence and small patient populations, I selected Reasonable over Recommended. No specific subgroup in mind.

The evidence base supporting the use of this agent has multiple, significant deficiencies. However, given the context of this disease state, where there are no preferred, or strongly recommended treatment options, it is reasonable to have this agent as an option in case the more established options are contraindicated. The studies provided examine patients of this disease state in the settings of relapsed/recurrent with surgical eligibility, as well as patients that are treatment-naïve that are not surgical candidates. In the setting of relapsed/recurrent disease with surgical eligibility, the NCCN guidelines for "Central Nervous System Cancers" (Pg 20, GLIO-A) lists a number of "other recommended regimens" including: RT + adjuvant PCV or RT+ TMZ, lomustine, etc. The use of ivosidenib may fulfill a role if these treatment modalities may not be used. In the setting of treatment-naive patients that don't qualify for surgery, the NCCN guidelines for "Central Nervous System Cancers" (Pg 9 & 12, GLIO-1, GLIO-3) recommend that patients are started on a form of systemic therapy, although an exact modality is not preferred. Therefore, this agent may be considered in this setting, given the demonstration of tumor volume reduction in a portion of patients in the Kamson, et al. trial, as well as adequate safety profile.

I think an argument could be made to call this Level 2 evidence especially since we do not have a whole lot of options for glioma treatment. I think it may meet the following Level 2 requirement because of the JCO 2020 article: Evidence consists of at least one non-blind or single-blind, non-randomized clinical trial.

Ivosidenib may be useful for certain circumstances (e.g., largely recurrent disease) and patient types (those with IDH1 mutations.) The data for ivosidenib's potential benefit in patients with central nervous system cancers is largely Phase 1 clinical data or single-center experience but is growing.

The available evidence for use of Ivosidenib 500 mg daily for non-enhancing mIDH glioma was compelling with subgroup median progression free survival reported as 13.6 months plus prolonged stable disease across the evidence. However, this is viewed in light of certain limitations. First, the strength and quality were considered low for inclusion of observational/case series data, small sample sizes, confounding variables of chemotherapy and radiotherapy treatments with only phase 1 studies included with primary endpoints limited to safety, tolerability, and PKs. Vorasidenib was recognized to have better CNS penetrance and response outcomes. Grade 3 AEs resulted in treatment interruption, however, no serious AEs reported were attributable to study drugs, and no discontinuation occurred due to AEs with either vorasidenib or ivosidenib treatment, which is a promising safety profile. QoL data is lacking overall. More high-quality evidence is needed to make a formal recommendation as a reasonable choice.

Mellinghoff et al (J Clin Oncol 2020) - median PFS 13.6 months in the nonenhancing group. Best response of stable disease in 30/35 (85.7%) nonenhancing tumors; 66.7% of nonenhancing tumors had reduction in tumor measurements. No patients discontinued due to adverse effects. - As mentioned in the study by Kamson et al (Clin Cancer Res 2023), "because of the indolent clinical course and longer survival times in IDH-mutant glioma, high-level evidence for efficacy based on overall survival endpoints...are expected to take more than a decade." - Provides an alternative treatment with perhaps less negative neurocognitive effects (compared to radiation for example) for a cancer that affects a younger demographic of patients expected to survive for many years.

There were some additional comments made regarding the specific patient population for which ivosidenib may be an option, with some respondents agreeing that the appropriate patient population would be patients with non-enhancing, IDH-mutated gliomas with recurrent or progressive disease (n=4). One respondent stated that the patient population for use should be those that fit the criteria of the vorasidenib N Engl J Med 2023;389:589-601 study. Another stated that the patient population should be those with “non-enhancing, IDH-mutated glioma when currently recommended options are contraindicated or inappropriate for use.”

Consensus Vote (5 of 7 committee members returned the consensus ballot):

Proposed Level of Evidence: Level 2 (Low strength/quality)

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 0 votes

Reasonable choice (Accepted, with possible conditions): 5 votes

Not fully established (Equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Final Grade of Recommendation: Reasonable choice (Accepted, with possible conditions)

Reviewer Comments on Level of Evidence and Grade of Recommendation:

Ivosidenib is a reasonable choice as an alternative regimen for mIDH non-enhancing glioma.

While I agree with the desire to have more evidence basis, including an ideal study design, in this disease state, that is likely not going to happen. Based on the data we currently have, as illustrated in the narrative summary and the overall lack of options for these patients (some options with just as equal or less evidence), I still believe this should be a recommended choice.

Participants:

AHFS Staff Members (writing and editing): Michael Gabay PharmD, JD, BCPS

AHFS Oncology Expert Committee Members (reviewing and voting): John Villano MD, PhD; Eve Segal PharmD, BCOP; Andrew Li PharmD, BCOP; Caroline Clark MSN, APRN; Kate Taucher PharmD, BCOP; Rachel Bubik PharmD, BCOP; Chelsea Gustafson PharmD, BCOP

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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