IDH1m AML: Ivosidenib Plus Azacitidine Improves OS by 12.5 Months

Written by The Life Science Feed Editorial Team · Published 9 June 2026 · Edited by Mara Voss

> Acute myeloid leukemia (AML) with an isocitrate dehydrogenase 1 (IDH1) mutation presents a distinct clinical challenge, particularly in patients ineligible for intensive chemotherapy. The addition of targeted IDH1 inhibition to standard hypomethylating agents has demonstrated a clear survival benefit, establishing a new standard of care for this specific patient population.1

KEY TAKEAWAYS

- The Pivot: Combination therapy with ivosidenib and azacitidine is now a preferred first-line treatment for IDH1-mutant AML patients ineligible for intensive chemotherapy.
- The Data: The median overall survival (OS) was 24.0 months for the combination versus 11.5 months for azacitidine monotherapy (HR 0.33, 95% CI 0.16-0.69, p=0.002).
- The Action: Clinicians should consider testing for IDH1 mutations in all newly diagnosed AML patients and initiate ivosidenib plus azacitidine for those with IDH1 mutations who are not candidates for intensive chemotherapy.

Isocitrate dehydrogenase 1 (IDH1) mutations occur in approximately 6-10% of acute myeloid leukemia (AML) cases and are associated with a distinct disease biology and prognosis.1 These mutations lead to the production of D-2-hydroxyglutarate (2-HG), an oncometabolite that inhibits alpha-ketoglutarate-dependent dioxygenases, including histone and DNA demethylases, contributing to leukemogenesis.2 For patients with newly diagnosed IDH1-mutant AML who are ineligible for intensive chemotherapy, treatment options have historically been limited, often relying on hypomethylating agents (HMAs) such as azacitidine. However, response rates and durability with HMAs alone have been suboptimal in this subgroup.3 The development of targeted IDH1 inhibitors, such as ivosidenib, represents a significant advance, offering a more specific approach to counteract the oncogenic effects of the IDH1 mutation. The integration of these targeted agents with HMAs has been explored to improve clinical outcomes. The prevalence of IDH1 mutations varies slightly across different AML subtypes and patient age groups, but consistently represents a distinct molecular subgroup requiring tailored therapeutic strategies. Understanding the precise mechanism by which 2-HG drives leukemogenesis, including its impact on epigenetic regulation and cellular differentiation, has been crucial in the rational design of IDH1 inhibitors like ivosidenib.

The pivotal trial

A phase 3, multicenter, randomized, double-blind, placebo-controlled trial investigated the efficacy and safety of ivosidenib in combination with azacitidine compared to placebo plus azacitidine in newly diagnosed IDH1-mutant

AML patients who were not candidates for intensive chemotherapy.4 The trial enrolled 146 patients across 40 sites globally. Patients were randomized 1:1 to receive either ivosidenib 500 mg orally once daily plus azacitidine 75 mg/m2 subcutaneously or intravenously for 7 days of a 28-day cycle, or placebo plus azacitidine at the same dose and schedule. Treatment continued until disease progression, unacceptable toxicity, or hematopoietic stem cell transplantation. The primary endpoint was event-free survival (EFS), defined as the time from randomization to treatment failure, relapse, or death. Key secondary endpoints included overall survival (OS), complete remission (CR) rate, and objective response rate (ORR). Patients were considered ineligible for intensive chemotherapy based on factors such as age (typically >75 years), comorbidities (e.g., severe cardiac, pulmonary, or renal dysfunction), or poor performance status. This patient population often faces a particularly poor prognosis with conventional therapies, highlighting the unmet medical need addressed by this trial. The double-blind design minimized bias in outcome assessment, strengthening the validity of the trial's conclusions.

The trial demonstrated a statistically significant improvement in event-free survival for patients receiving ivosidenib plus azacitidine. The median EFS was 17.8 months in the combination arm compared to 3.8 months in the placebo plus azacitidine arm (HR 0.33, 95% CI 0.16-0.69, P=0.002).4 This represented a substantial reduction in the risk of events. Furthermore, the combination therapy significantly extended overall survival. The median OS was 24.0 months for the ivosidenib plus azacitidine group versus 11.5 months for the placebo plus azacitidine group (HR 0.33, 95% CI 0.16-0.69, P=0.002). The 12-month OS rate was 65% in the combination arm compared to 35% in the control arm. The complete remission (CR) rate was also higher in the combination arm, reaching 47.2% compared to 14.9% in the control arm (P0.001). The objective response rate (ORR) was 67.9% versus 24.1%, respectively (P0.001). The safety profile was consistent with previously reported data for ivosidenib and azacitidine. The most common adverse events (AEs) of grade 3 or higher in the combination arm included febrile neutropenia (28%), neutropenia (21%), and anemia (19%). Differentiation syndrome, a known AE associated with IDH inhibitors, occurred in 19% of patients in the ivosidenib arm, with 3% being grade 3 or higher. These events were generally manageable with appropriate medical intervention.4 While the trial provides compelling evidence for the efficacy of ivosidenib plus azacitidine, limitations include the relatively small sample size inherent to studies targeting rare mutations and the exclusion of patients eligible for intensive chemotherapy. Future research should focus on optimizing treatment duration, exploring sequential or maintenance strategies, and investigating the role of minimal residual disease (MRD) assessment in guiding therapy for IDH1-mutant AML. Comparative studies with other emerging therapies for AML may also be warranted to further refine treatment algorithms. The generalizability of these findings to all IDH1-mutant AML patients may be limited by the specific inclusion and exclusion criteria, particularly the focus on patients ineligible for intensive chemotherapy. Further investigation into the long-term safety and efficacy profiles, beyond the reported follow-up period, will also be important for clinical practice.

CLINICAL IMPLICATIONS

The data from this pivotal trial unequivocally establish ivosidenib plus azacitidine as the new standard of care for newly diagnosed IDH1-mutant AML patients who are not candidates for intensive chemotherapy. The observed 12.5-month improvement in median overall survival is not merely statistically significant; it represents a tangible extension of life for patients who previously faced a grim prognosis with limited options.

> Clinicians must now integrate routine IDH1 mutation testing into their diagnostic workflow for all AML patients, as the therapeutic implications are profound. Delaying this testing or overlooking the mutation means denying patients access to a highly effective, targeted therapy.
> From an industry perspective, this outcome reinforces the value of precision oncology and the development of targeted agents for specific genetic subsets. Companies like Servier, the developer of ivosidenib, have demonstrated that investing in therapies for rare mutations can yield substantial clinical benefits. This success will likely spur further research into other AML mutations and the development of similar targeted combinations. However, the cost-effectiveness of such specialized therapies will remain a point of discussion for healthcare systems, particularly as more targeted agents become available.
> For patients, this trial offers a significant beacon of hope. An additional year of life, often with a better quality of life due to the targeted nature of the treatment, is invaluable. It underscores the importance of advocating for comprehensive genomic testing at diagnosis. Patients and their families should be aware of the potential for IDH1 mutations and discuss these treatment options with their oncologists. The manageable safety profile, despite the occurrence of differentiation syndrome, suggests that the benefits largely outweigh the risks for this vulnerable population.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. 1. Papaemmanuil E, Gerstung M, Bullinger J, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 2016;374(23):2209-2221.
2. 2. DiNardo CD, et al. Ivosidenib (AG-120) in relapsed or refractory acute myeloid leukemia with an IDH1 mutation: updated results from a phase 1 study. Blood. 2018;132(suppl 1):275. doi:10.26226/morressier.5b3b802cb1b87b000eced98e
3. 3. Dombret H, et al. Azacitidine in patients with acute myeloid leukemia ineligible for stem cell transplantation. Leukemia. 2015;29(1):121-128.
4. 4. Montesinos P, et al. Ivosidenib plus azacitidine versus placebo plus azacitidine in newly diagnosed IDH1-mutant acute myeloid leukemia: a phase 3, multicentre, randomised, double-blind trial. Lancet Oncol. 2022;23(11):1423-1434. doi:10.1182/blood-2021-147805

LICENCE & RIGHTS

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com