REVIEW

Editorial Process: Submission:11/11/2025 Acceptance:07/08/2026 Published:07/28/2026

Prognostic Implications and Therapeutic Landscape of IDH1-Mutated AML: An Updated Review of Evidence and Indian Perspective

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Abstract

Objective: Acute myeloid leukemia (AML) is a biologically heterogeneous hematologic malignancy in which cytogenetic and molecular abnormalities critically influence prognosis and treatment decisions. Since the identification of isocitrate dehydrogenase (IDH) mutations in AML in 2009, growing evidence has highlighted their role in leukemogenesis through aberrant cellular metabolism and epigenetic dysregulation. IDH1 mutations, occurring predominantly in cytogenetically normal AML and frequently co-existing with mutations such as NPM1 and DNMT3A, have demonstrated context-dependent prognostic implications rather than uniformly adverse outcomes. **Methods:** Several studies associate IDH1 mutations with inferior clinical outcomes, including reduced remission rates, poorer overall survival, and global DNA hypermethylation, particularly in specific biological and therapeutic contexts influenced by co-mutational profiles and treatment era. **Results:** Recent therapeutic advancements have introduced selective IDH1 inhibitors targeting these mutations. Ivosidenib and Olutasidenib, have demonstrated efficacy in relapsed/refractory (r/r) AML and have received United States Food and Drug Administration (USFDA) approval for these indications. Notably, Ivosidenib has also been approved for newly diagnosed (ND) IDH1-mutated AML patients who are ineligible for intensive chemotherapy. These IDH1 inhibitors, often combined with agents like Azacitidine and Venetoclax, represent a promising shift toward personalized medicine, offering effective, less toxic alternatives for challenging AML cases, including those in elderly patients or individuals with comorbidities. **Conclusion:** This review summarizes the prognostic implications of IDH1 mutations in AML and critically examines emerging IDH1 targeted therapies, highlighting their impact on disease biology and evolving treatment algorithms.

Keywords: Myeloid Leukemia- AML- IDH inhibitors- Ivosidenib

Asian Pac J Cancer Prev, **27 (7)**, 2417-2424

Introduction

Acute Myeloid Leukemia (AML): Epidemiology and Genetic Insights

Acute myeloid leukemia (AML) has an annual incidence of approximately 2.5–3 cases per 100,000 globally, consistent with data from the Indian Council of Medical Research (ICMR) [1]. The prevalence of AML rises with age, representing less than 10% of all leukemias in children, but 80–90% of leukemias in adults over 60 years. Men are more likely to develop AML than women [2, 3].

AML is one of the most biologically and clinically diverse haematological malignancies, characterized by a poor prognosis. It results from the clonal transformation of hematopoietic precursors due to multiple gene mutations and chromosomal rearrangements. Recurrent chromosomal abnormalities serve as key diagnostic and prognostic markers, emphasizing the role of somatic mutations in AML pathogenesis. In 2009, Mardis et al. used DNA sequencing to reveal that mutations in isocitrate dehydrogenase (IDH), an enzyme vital for cellular metabolism, occur in a significant proportion of patients with normal karyotype AML [1].

IDH1 Mutations in AML: Biological and Clinical Context

IDH1 enzymes play a central role in cellular metabolism and response to oxidative stress (Figure 1).

The IDH1 isoenzyme is located in the cytoplasm, and is encoded by the IDH1 gene on chromosome 2q33 and chromosome 15q26, respectively, and primarily functions in the oxidative decarboxylation of isocitrate to α-ketoglutarate in the citric acid cycle [4]. Recurrent hotspot mutations at codon R132 confer a neomorphic enzymatic activity, leading to a gain-of-function that produces 2-hydroxyglutarate (2-HG), which competitively inhibits

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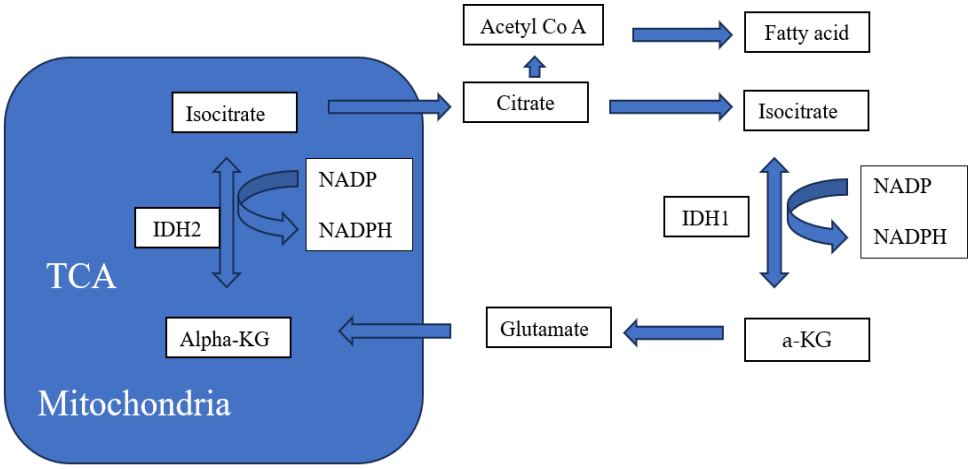

Figure 1. Role of IDH Mutation in AML. NADPH: Nicotinamide adenine dinucleotide phosphate, a-KG: alpha-ketoglutarate, IDH 1: Isocitrate dehydrogenase-1, NADP: Nicotinamide adenine dinucleotide phosphate, CoA: Co-enzyme A

α-KG-dependent reactions, including TET2-dependent DNA hydroxymethylation, histone demethylation, BCL2-dependent mitochondrial respiration, and activation of the hypoxia-inducible factor-1α (HIF-1α) pathway. The accumulation of 2-hydroxyglutarate (2-HG) disrupts cellular differentiation and promotes leukemogenesis by inducing DNA hypermethylation, aberrant gene expression, unchecked cell proliferation, and impaired myeloid differentiation.

IDH1 mutations occur in approximately 2–14% of AML cases globally, with higher prevalence in cytogenetically normal AML and older patients [5]. These mutations frequently co-occur with alterations in NPM1 and DNMT3A, reflecting a distinct clonal architecture that influences disease biology and clinical behaviour. Additionally, 15–27% of AML patients with IDH1 mutations also harbor FMS-like tyrosine kinase 3 internal tandem duplications (FLT3-ITD), further complicating the mutational landscape [6-8].

Publicly available datasets reveal significant associations between IDH1 mutations and other genetic alterations, such as NPM1 (OR=2.40, P=0.02547) and DNMT3A (OR=6.55, P=0.02531). These co-mutations impact therapeutic response and prognosis, making their identification crucial for personalized treatment strategies. A comprehensive understanding of how IDH1 mutations interact with other genetic abnormalities, including FLT3 and KRAS, further enriches our knowledge of AML's genetic heterogeneity. This mutational mapping is essential for advancing personalized medicine approaches, enabling clinicians to optimize treatment regimens and improve patient outcomes [9, 10].

Methodology of the literature review

This article is a narrative review of the published literature. A comprehensive search of PubMed, Scopus, and Embase was conducted for articles published between January 2009 and March 2025 using combinations of the terms "IDH1-mutated AML," "prognosis," "ivosidenib," "IDH inhibitors," and "targeted therapy." Approximately 150 records were identified. After removal of duplicates and title/abstract screening, 15 studies were selected based on relevance to the prognostic impact of IDH1 mutations or clinical outcomes with IDH1-directed therapies in AML. Clinical trials, large observational studies, and meta-analyses, were prioritized. Non-English publications and reports lacking clinically relevant outcome data were excluded. Owing to the narrative nature of the review, formal risk-of-bias assessment was not performed.

Prognostic Role of Idh1 Mutations in Aml

IDH1 gene mutations have been extensively studied for their critical role in AML pathogenesis. A meta-analysis of 15 studies involving 8,121 participants examined the prognostic significance of IDH1 mutations in AML. The mutation frequency ranged from 4.4% to 9.3% in AML patients overall, and from 10.9% to 16.0% in those with cytogenetically normal AML (CN-AML). Notably, six studies found that IDH1 mutations were often co-associated with Nucleophosmin 1 (NPM1) mutations, while five studies reported their presence in cases with normal cytogenetics [11].

IDH1 mutations were associated with poorer overall survival, as evidenced by a hazard ratio of 1.17 (95% CI: 1.02–1.36). In CN-AML cases, IDH1 mutations were linked to a reduced likelihood of achieving complete remission, with a risk ratio of 1.30 (95% CI: 1.04–1.63). Interestingly, while IDH1 mutations did not affect overall complete response rates in AML patients, they were signifi-cantly linked to lower remission rates specifically in CN-AML patients [11].

Recent studies also reveal that IDH1 mutations often coexist with recurring transcription factor abnormalities, including the AML1/ETO, PML/RARα, and CBFβ/MYH11 fusion proteins. This coexistence suggests a potential synergistic role of IDH1 mutations and these fusion genes in leu-kemogenesis, influencing the progression and clinical outcomes of AML with complex cytogenet-ics. Understanding this interplay may provide valuable insights into AML pathogenesis and pave the

Table 1. IDH1 Mutation Testing Recommended as Part of Multiple Guidelines

Sr. No	Guideline	Recommendation	Context
1	World Health Organization (WHO)	Recommends IDH1 mutation testing for accurate classification of AML	Used for subclassification of AML based on molecular markers.
2	National Comprehensive Cancer Network (NCCN)	Suggests IDH1 testing in ND AML patients.	Critical for targeted therapy decisions and prognosis.
3	European Leukemia Net (ELN)	Advocates IDH1 mutation assessment as part of AML risk stratification	Refines risk categories for personalized treatment.
4	College of American Pathologists (CAP)	Incorporates IDH1 testing as essential in AML diagnostic workflows	Supports molecular profiling for comprehensive care.
5	Indian Council of Medical Research (ICMR)	Recommends molecular profiling, including IDH1 mutation testing, for AML diagnosis and management.	Supports personalized treatment strategies in Indian patients.

IDH 1, Isocitrate dehydrogenase-1; AML, Acute myeloid leukemia

Table 2. Summary of Treatment Guidelines for IDH1-Mutated AML (Based on ELN and NCCN)

Aspect	NCCN Guidelines	ELN Guidelines
Molecular Testing	Recommends IDH1 mutation testing at diagnosis to guide therapy decisions.	Emphasizes IDH1 testing for molecular classification and risk stratification.
Risk Stratification	IDH1 mutations influence intermediate-risk categorization, especially with co-mutations.	IDH1-mutated AML is generally categorized as intermediate-risk. Used to guide treatment intensity.
Targeted Therapy	Ivosidenib for ND patients unfit for intensive chemotherapy, and for r/r AML. Olutasidenib approved for r/r AML.	Endorses ivosidenib as a key agent. Can be used as monotherapy or with hypomethylating agents to reduce 2-HG and promote differentiation.
Combination Therapy	Recommends ivosidenib + azacitidine for ND patients not eligible for intensive chemo improves survival with lower toxicity.	Advises combining IDH1 inhibitors with hypomethylating agents or intensive chemo to enhance outcomes when feasible.
Stem Cell Transplant	Supports allo-SCT for eligible patients post-remission.	Suggests transplant in IDH1-mutated patients with adverse features after response to therapy. Maintenance therapy for ineligible patients.
Relapsed/ Refractory AML	Ivosidenib and olutasidenib are preferred agents in r/r AML with IDH1 mutation.	Recognizes IDH1 inhibitors as essential in managing r/r AML with IDH1 mutation less toxic alternative to salvage chemo.

IDH 1, Isocitrate dehydrogenase-1; AML, Acute myeloid leukemia; ND, Newly diagnosed; r/r, Relapsed refractory; HG, Hydroxyglutarate; SCT, Stem Cell Transplant; NCCN, National Comprehensive Cancer Network; ELN, Europe-an Leukemia Net

way for targeted therapeutic strategies in patients with complex mutational profiles [12].

Guidelines from leading organizations emphasize the importance of IDH1 mutation testing in AML diagnosis, classification, and treatment (Table 1). The World Health Organization (WHO), National Comprehensive Cancer Network (NCCN), European Leukemia Net (ELN), and the Indi-an Council of Medical Research (ICMR) all advocate for integrating IDH1 mutation testing into routine clinical practice. This approach is intended to enhance patient outcomes by enabling tar-geted therapies, improving molecular subclassification, and refining risk assessment. The incorpo-ration of IDH1 mutation testing into standardized diagnostic protocols marks a significant ad-vancement in precision medicine as our understanding of these mutations continues to evolve [3].

Recent advancements have led to the development of targeted therapies for IDH1-mutated AML. Inhibitors like ivosidenib have shown promising outcomes, with clinical trials revealing objective response rates of 50% or higher in patients with relapsed / refractory (r/r) or ND IDH1-mutated AML. These treatments offer hope for improved patient outcomes and represent a significant step forward in precision medicine [12, 13].

Treatment Approaches in Idh1 Mutated Aml

Guidelines from ELN and NCCN

The treatment of IDH1-mutated AML is guided by recommendations from the ELN and NCCN. Both emphasize the integration of molecular diagnostics and targeted therapies particularly Ivo-sidenib and Olutasidenib into standard clinical practice. These guidelines as summarized below (Table 2) support a precision medicine approach, tailoring therapies to individual genetic profiles to enhance patient outcomes [14-17].

Evidence with Venetoclax based regimen in IDH1 mutated AML

Venetoclax is a selective BCL-2 inhibitor and BH3 mimetic that restores apoptosis by binding to BCL-2 and displacing pro-apoptotic proteins such as BIM, thereby activating caspases and induc-ing programmed cell death [18].

In a pooled analysis of patient-level data from Phase Ib and Phase III trials (NCT02203773, NCT02993523), Pollyea et al. evaluated Venetoclax in combination with azacitidine for patients with IDH1-mutated AML. This combination achieved a composite complete remission (CRc) rate of 66.7% and a median overall survival

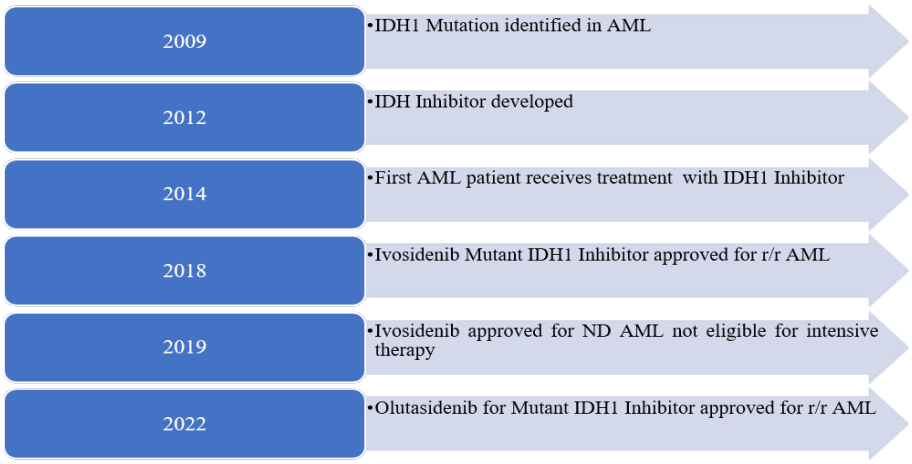

Figure 2. Timelines for Identification of Role of IDH in AML and Development of IDH1 Inhibitors. IDH 1: Isocitrate dehydrogenase-1, AML: Acute myeloid leukemia, ND: newly diagnosed, r/r: Relapsed refractory

(mOS) of 15.2 months markedly superior to azacitidine monotherapy, which yielded a CRc rate of 9.1% and mOS of 2.2 months.

In comparison, the AGILE trial assessing Ivosidenib plus azacitidine in a similar population re-ported a CR/CRi rate of 62.5% and a significantly improved mOS of 29.3 months [19, 20].

However, in the absence of a direct head-on comparison between venetoclax and ivosidenib in mIDH1 AML, the relatively lower survival benefit with venetoclax based regimens combined with the prolonged cytopenias and infectious complications highlights the importance of mutation-specific therapeutic strategies [18]. However, any inference based upon the cross-trial comparison deserves caution and needs to be appreciated in light of inherent limitations of subgroup analyses and cross-trial comparisons.

Evidence with targeted IDH1 Inhibitors) in AML

The discovery of IDH1 mutations and their role in the pathogenesis of AML in 2009 marked a significant breakthrough in the molecular understanding of the disease. This paved the way for the development of targeted therapies. By 2018, the first IDH1 inhibitor ivosidenib received regulatory approval, representing a

Table 3. Results of Clinical Trials Using IDH1 Inhibitor- Ivosidenib in AML

S. No	Drug	Phase of Study	Patients Enrolled	Disease	Treatment	Outcomes	ADR
1	Ivosidenib	Phase 1	179	Refractory/ Relapsed AML	500 mg QD (starting dose)	CR-21.8% CRi/CRp-11.7 % MLFS-3% SD-38.5 % PD-8.4 %	Prolongation of QT interval -7.8 % IDH differentiation syndrome – 3.9 % Anemia – 2.2 %
2	Ivosidenib	Phase 1	34	Newly diagnosed AML with IDH1 mutation	Ivosidenib (500 mg QD)	CR-30.3% CRi/ CRp-18.2 % MLFS-3% SD-30.3 % PD-9.1 %	IDH differentiation syndrome – 9 % Prolongation of QT interval -6 % Diarrhoea – 6 % Febrile neutropenia- 6 %
3	Ivosidenib + Azacitidine	Phase 1 b	23	Newly diagnosed AML with IDH1 mutation	Ivosidenib (500 mg QD) Azacitidine (75 mg/m^2/ day for 7 day/cycle)	CR-60.9% CRi/ CRp-8.7 % MLFS-8.7 % SD-17.4 %	Neutropenia- 22 % Anemia- 13 % Thrombocytopenia- 13 % QT Prolongation -13.0 %
4	Ivosidenib + Chemotherapy (Cytarabine with either daunorubicin or idarubicin)	Phase 1	60	Newly diagnosed AML with IDH1/2 mutation	Ivosidenib (500 mg QD) + Chemotherapy (Cytarabine 200 mg/ m^2/ day for 7 days with either daunorubicin 60 mg/m^2/day for 3 days or idarubicin 12 mg/m^2/ day for 3 days,	CR-68% CRi/ CRp-8 % PR-3% MLFS-7% Treatment failure -13 %	Induction period Hypophosphatemia-16.7 % Hypokalemia – 11.7 % QT Prolongation -10.0 % Consolidation period Nausea, vomiting, hypokalemia, pyrexia, QT Prolongation, Increased ALT (2.9 %)
5	Ivosidenib + Azacitidine	Phase 3	72	Newly diagnosed AML with IDH1 mutation	Ivosidenib (500 mg QD) Azacitidine (75 mg/m^2/ day for 7 day/cycle)	CR-47% CRi/ CRp-7 % PR – 6 % MLFS-3% SD-10 % PD-3 %	Febrile neutropenia- 28 % Neutropenia- 27 % Anemia- 25 % Thrombocytopenia- 24 %

CR, Complete remission; CRi, Complete remission with incomplete haematological recovery; CRp, complete remission with platelet recovery; MLFS, Morphologic leukemia free state; SD, Stable disease; PD, Progressive disease; PR, Partial response; ECG, Electrocardiogram; IDH, Isocitrate dehydrogenase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CCR, Conventional care regimen; IDAC, Intermediate dose cytarabine; LDAC, Low dose cytarabine; BSC, Best supportive care; MDS, Melodysplastic syn-drome; NR, No response; TF, Treatment failure

major milestone in precision medicine for AML (Figure 2).

First Generation IDH1 Inhibitors

Ivosidenib (formerly AG-120) is a first-in-class, selective, oral inhibitor targeting mutant IDH1. Preclinical studies demonstrated its ability to suppress 2-hydroxyglutarate (2-HG) production and restore normal myeloid differentiation, establishing its efficacy in IDH1-mutated AML.

Second Generation IDH1 Inhibitors

Olutasidenib is the first second-generation IDH1 inhibitor approved for relapsed/refractory AML.

Clinical Evidence for the efficacy of Ivosidenib in AML

Ivosidenib was approved in 2018 for relapsed/refractory AML and in 2019 for ND AML not eligi-ble for intensive therapy. Currently, adults with r/r IDH1-mutated AML, patients with ND IDH1-mutated AML who are 75 years of age or older, or those with comorbid illnesses that prohibit in-tense chemotherapy, are eligible for Ivosidenib therapy in the United States [17].

Results of clinical trials undertaken using the IDH1 inhibitor Ivosidenib as monotherapy and com-bination therapy in AML, including details such as the phase of the clinical trial, patients enrolled, treatment doses, outcomes, and adverse drug reactions (ADRs), are summarized in Table 3 [17].

AGILE Study: Ivosidenib and Azacitidine in AML

The USFDA approved Ivosidenib for IDH1-mutated AML on July 20, 2018, shortly after the start of clinical trials. It was rapidly incorporated as a second-line, third-line, or salvage therapy. In the phase III AGILE study, the combination of Ivosidenib and azacitidine significantly improved event-free survival (EFS), response, and overall survival (OS) in patients with ND IDH1-mutated AML who were ineligible for induction chemotherapy, compared to placebo and azacitidine [19, 20].

The combination demonstrated notable improvements in health-related quality of life, transfusion independence, and side effect profiles. At a median follow-up of 12.4 months, patients treated with Ivosidenib and azacitidine had a substantially longer EFS than the placebo and azacitidine group (hazard ratio [HR] for treatment failure, relapse, or death: 0.33, 95% CI 0.16–0.69; p = 0.002). The event-free rate at 12 months was 37% for the Ivosidenib and azacitidine group versus 12% for the placebo and azacitidine group. Additionally, the median OS was 29.3 months for the treatment group, compared to 7.9 months for the control group (HR for death: 0.42, 95% CI 0.27–0.65; p <0.0001).

Regarding adverse events, bleeding incidents occurred in 41% and 29% of patients in the treatment and placebo groups, respectively. Common grade 3 or higher adverse events included neutropenia (27% vs. 16%) and febrile neutropenia (28% vs. 34%). The incidence of infections (any grade) was lower in the Ivosidenib and azacitidine group (28%) compared to the placebo group (49%). Differentiation syndrome occurred in 14% of patients treated with Ivosidenib and azacitidine, compared to 8% in the placebo group.

The AGILE study conclusively showed that Ivosidenib and azacitidine combination therapy significantly improved OS, EFS, and complete remission rates in patients with IDH1-mutated AML who were older or ineligible for induction chemotherapy. It also demonstrated a manageable safety profile, with adverse events similar to those observed with other acute leukemia treatments. The combination therapy was associated with favorable health-related quality of life and transfusion independence rates, reinforcing its clinical benefit. The control group's performance reflected poor outcomes commonly seen with azacitidine in this patient population. Importantly, treatment discontinuations due to toxicity were minimal, further emphasizing the therapy's tolerability [19, 20].

Tolerability and Adverse Effects of Oral Ivosidenib in AML Patients

Oral Ivosidenib has demonstrated a favourable tolerability profile in both r/r and ND AML patients. Key side effects primarily include QTc prolongation and differentiation syndrome (DS), both of which are linked to rapid myeloid cell proliferation and differentiation, and are manageable with appropriate monitoring and intervention If not properly managed, these can be life-threatening. QTc prolongation occurred in 25% of r/r AML patients and 18% of ND AML patients, though no patient required permanent discontinuation of Ivosidenib. However, treatment should be discontinued if the QTc interval exceeds 500 ms or if life-threatening arrhythmias develop [21].

Minor side effects included diarrhea, nausea, abdominal pain, constipation, Guillain-Barré syndrome, and hematologic issues such as anemia, thrombocytopenia, and leukocytosis. Importantly, the combination of Ivosidenib and azacitidine can be safely administered in an outpatient setting. The safety profile of this combination is further supported by the fact that hospitalization rates due to adverse events were significantly lower compared to azacitidine monotherapy [21].

In clinical trials, 25% of ND AML patients and 19% of r/r AML patients treated with Ivosidenib developed differentiation syndrome, typically occurring between one day and three months after treatment initiation. DS symptoms included non-infectious leukocytosis, neutrophilia, fever, peripheral edema, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and elevated creatinine. Among r/r AML patients with DS, 79% recovered following treatment interruption or dose modification of Ivosidenib [21].

Real-World Evidence with ivosidenib in Idh1 mutated AML

Smith et al. (2023) compared two treatment strategies for ND AML patients with IDH1 mutations who were ineligible for intensive chemotherapy. Using data from 283 patients (182 in the Ivosidenib + Hypomethylating Agent [HMA] group, and 101 in the Venetoclax + HMA group), the study assessed Ivosidenib plus HMA versus

Venetoclax plus HMA [22].

The results showed that the Ivosidenib + HMA group achieved significantly higher complete remission (CR) + CR with incomplete count recovery (CRi) rates (63.2%) compared to the Venetoclax + HMA group (49.5%) (p=0.025). The Ivosidenib regimen also led to a quicker best response, with a median of 3.3 months compared to 4.1 months for Venetoclax (p=0.002). Furthermore, the Ivosidenib + HMA group demonstrated superior 6-month event-free survival (EFS) rates (56.0%) compared to the Venetoclax group (39.6%) (p=0.044). However, febrile neutropenia (FN) was more prevalent in the Venetoclax + HMA group (7.9%) than in the Ivosidenib + HMA group (1.6%; p=0.009). Both regimens had a similar treatment discontinuation rate of 37%.

In the absence of a head-to-head comparison between ivosidenib and venetoclax based regimens for mIDH1 AML patient management, these findings should be treated as indicative, rather than being completely conclusive, considering the limitations of a retrospective analysis.

Future directions with ivosidenib in IDH1 mutated AML

Ongoing research continues to examine Ivosidenib in combination with other agents, such as Venetoclax and Azacitidine, to further enhance survival outcomes.

The early-phase clinical trial (NCT03471260) investigated the combination of Ivosidenib with Venetoclax, with or without Azacitidine, in therapy-naïve patients with IDH1-mutated AML. The study demonstrated promising efficacy and a favorable safety profile for this combination regimen [23].

Additionally, the HOVON 150 study, which explored Ivosidenib in combination with conventional chemotherapy, showed improved measurable residual disease negativity, longer remission durations, and better response rates, further validating its role in induction and consolidation therapy [24].

Expert perspectives

In the management of IDH1-mutated AML, treatment choice between ivosidenib monotherapy, ivosidenib plus azacitidine, and azacitidine plus venetoclax requires careful consideration of disease biology, patient fitness, efficacy data, safety, and real-world feasibility in India. The presence of an IDH1 mutation would support the use of targeted therapy, with ivosidenib plus azacitidine emerging as the preferred frontline standard based on the AGILE trial, which demonstrated significant OS benefit and durable remissions with an acceptable safety profile. While azacitidine plus venetoclax (VIALE-A) provides high remission rates in the overall AML population, outcomes in IDH1-mutated patients are less consistent, and the regimen carries higher risks of prolonged cytopenias and infectious complications, which may be particularly challenging to manage in resource-limited Indian settings. Ivosidenib monotherapy remains a viable option for frail or elderly patients, especially those with organ impairment, prior HMA failure, or high infection risk, given its favorable tolerability and outpatient feasibility. For younger or moderately fit patients, doublet therapy with ivosidenib and azacitidine would be favored over azacitidine plus Venetoclax while balancing efficacy and safety and preserving venetoclax for potential use at relapse. Early trial data also suggest that triplet combinations (IVO+AZA+VEN) may achieve deep and durable responses, though further validation is required before routine adoption. Practical integration of ivosidenib in Indian practice requires structured monitoring for differentiation syndrome, QT prolongation, and drug–drug interactions, alongside proactive patient education. Although cost considerations remain a major determinant in India; but where affordability is not a barrier, ivosidenib-based combinations are preferred due to their lower myelosuppression, reduced transfusion needs, and greater outpatient feasibility compared with venetoclax-based regimens.

In conclusion, ivosidenib, a first-in-class targeted inhibitor of mutant IDH1, represents a major advancement in the treatment of IDH1-mutated intensive chemotherapy ineligible AML — a subtype historically associated with relatively poorer prognosis and limited treatment options.

One of Ivosidenib's most compelling advantages is its minimal myelotoxicity, in contrast to the marked bone marrow suppression commonly seen with traditional AML regimens. By reducing the risk of severe cytopenias and infections, Ivosidenib enables relatively faster hematologic recovery and earlier normalization of blood counts compared to the conventional and standard of care regimens. This not only improves patient outcomes but also reduces the need for supportive care such as transfusions and hospitalizations, thereby enhancing overall quality of life.

Clinical trials have demonstrated that Ivosidenib significantly improves OS in newly diagnosed patients ineligible for intensive chemotherapy. Its favorable safety profile and efficacy make it a valuable alternative for elderly or comorbid patients who are not candidates for aggressive treatment, effectively bridging the gap between tolerability and clinical benefit.

Though complete remission (CR) rates with IDH inhibitors may be modest compared to intensive chemotherapy, Ivosidenib delivers durable remissions and meaningful disease control. Ongoing trials and real-world evidence indicate its value across a broad spectrum of patients. By combining molecular precision with tangible clinical benefit, Ivosidenib represents a significant advancement in the therapeutic landscape of IDH1-mutated AML.

Author Contribution Statement

The authors had full access to all relevant information, meet the ICMJE criteria for authorship, were involved in the conceptualization and critical review of the manuscript, and approved the final version for submission. The authors independently developed and approved the final version of the manuscript and take full responsibility for its accuracy, integrity, and conclusions.

Acknowledgements

The authors acknowledge Renovare Healthcare Solutions for providing medical writing and editorial assistance in accordance with Good Publication Practice (GPP) guidelines.

Funding

The article processing charge was funded by Servier India Pvt. Ltd. The funder had no role in the study design, literature selection, data interpretation, manuscript development, or the decision to submit the manuscript for publication.

Conflict of Interest

None.

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