

Review Article**Optimization of the Clinical Journey of Unfit Patients with Newly Diagnosed IDH1m Acute Myeloid Leukemia**

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Abstract. The management of acute myeloid leukemia (AML) in elderly or unfit patients has undergone a paradigm shift with the integration of molecular diagnostics and targeted therapies. Among actionable alterations, *IDH1* mutations define a biologically distinct subgroup, for which ivosidenib combined with azacitidine has recently emerged as standard of care.

However, initial clinical management remains complex. Three main themes emerged from the expert panel's discussion: all patients should be tested for *IDH1m*, with a turnaround time of 3-5 days; adequate patient monitoring during treatment is essential to detect the earliest signs of differentiation syndrome and QTc prolongation; appropriate management of concomitant therapies is required, not only for azole derivatives administered for antifungal prophylaxis, where needed.

This paper provides a comprehensive, evidence-based framework to optimize early management in unfit patients with newly diagnosed *IDH1*-mutated AML, integrating data from randomized trials, real-world studies, and updated evidence on antifungal prophylaxis and drug-drug interactions in the era of targeted therapies.

Keywords: Acute myeloid leukemia; Clinical Journey; Unfit Patients; Newly Diagnosed; *IDH1m*.

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Introduction. Acute myeloid leukemia (AML) is an aggressive hematologic malignancy that predominantly affects older adults, with a median age at diagnosis of approximately 68 years.^{1,2} The importance of a proper assessment of fitness, patient by patient, taking into account all disease- and individual-related information is crucial.³

Managing AML in unfit patients requires careful assessment of physiologic reserve, comorbidities, and functional status.⁴ In this evolving context, fitness assessment is critical. It should reflect eligibility for a specific treatment among the several available, rather than a generic binary classification of eligibility for intensive chemotherapy. Chronological age alone is insufficient to determine treatment eligibility, and a multidimensional evaluation is essential to guide therapeutic decisions.³ A new concept of “fitness” should be considered: the increasing focus on patient-centered care further underscores the importance of incorporating quality of life, patient preferences, self-reported physical and social functioning, social support, and the early integration of palliative care into the assessment framework.³

Historically, AML has been regarded as a medical emergency requiring immediate initiation of treatment due to the high risk of early mortality from infectious and hemorrhagic complications.⁵ However, this urgency-driven paradigm was developed in an era preceding the widespread use of molecular diagnostics and targeted therapies.⁶ In current clinical practice, AML is increasingly understood as a biologically heterogeneous disease, in which genomic profiling plays a central role in guiding therapeutic decisions.⁷

Mutations in the isocitrate dehydrogenase 1 (IDH1) gene occur in approximately 6-10% of AML cases and represent early leukemogenic events that impair cellular differentiation.⁸ In Italy, a retrospective GIMEMA study described an incidence higher than reported in the literature, more frequently displaying a non-complex karyotype.⁹ The development of ivosidenib (IVO), a first-in-class oral inhibitor of mutant IDH1, has transformed the therapeutic landscape of this subgroup.¹⁰⁻¹²

IDH1 mutations (IDH1m) confer a neomorphic enzymatic activity that leads to the accumulation of the oncometabolite 2-hydroxyglutarate. This metabolite disrupts α -ketoglutarate-dependent enzymatic processes, resulting in widespread epigenetic dysregulation, including DNA and histone hypermethylation. These changes ultimately lead to a block in myeloid differentiation, which is a hallmark of AML pathogenesis.^{10,13}

IDH1m are often expressed in the ancestral clone in cases of co-mutations, further highlighting the relevance

of targeted treatments for these molecular lesions.¹⁴ Recently, biological findings suggested that the underlying clonal hierarchy of IDH1m are present in the founder clone of many AML cases co-expressing other molecular aberrations.¹⁵⁻¹⁷ IDH1m was the founder clone in most of the cases co-expressing NPM1 or RTK pathway mutations, as suggested by the predominant VAF. IDH1m also occurred at high frequencies in secondary AML and AML-MR (both 9.5%) compared with MDS (1.8%) and CMML (0.8%), indicating frequent acquisition of this mutation during the transition to AML. This hypothesis was directly confirmed in a subset of patients analyzed before and after progression.¹⁵

Unlike conventional cytotoxic therapies, IVO exerts its antileukemic activity by restoring differentiation rather than inducing direct apoptosis. IVO induces disease regression in IDH1-mutated AML but is only modestly effective as a single agent at eradicating leukemic stem cells. However, it enhances sensitivity to azacitidine (AZA), and combining the two agents shows markedly superior efficacy in preclinical models.¹⁸ This mechanism has important clinical implications, as responses are often delayed and may be associated with specific adverse event profiles, where the most notable is differentiation syndrome (DS). At the same time, this differentiation-based mechanism contributes to rapid hematologic recovery sustained over time and a reduced incidence of infectious complications compared with traditional chemotherapy.¹⁹⁻²¹

The AGILE trial is the first and only phase 3 randomized clinical trial specifically designed for IDH1m AML unfit patients, demonstrating a significant survival advantage with this regimen, with a significant event-free survival (median [m] EFS=22.9 months [7.5-NE] - median follow-up 12.4 months) and a median overall survival exceeding two years (mOS= 29.3 months, [13.2-NR]), a remarkable improvement compared with historical outcomes in this population.^{20,21} In addition, the combination is associated with higher rates of complete remission (CR), transfusion independence, and improved hematologic recovery, with long-term follow-up confirming sustained efficacy and safety profile, establishing IVO+AZA as a new standard of care for the IDH1m AML patient unfit for intensive chemotherapy.^{20,21}

Moreover, preliminary findings from the phase 3b ALIDHE (NCT05907057) study, which included the same IDH1m population as the AGILE study, seem to confirm the pivotal trial's safety and efficacy profile. thus, reproducing the benefit/risk ratio outside a rigorous randomized phase 3 study.²²

Other real-world data support the feasibility and effectiveness of ivosidenib-based regimens,^{23,24} with response and AEs rates emerging from different cohorts comparable to those encountered in the pivotal trial, and survival rates ranging from a mOS of 31.9 months to mOS not reached [NR].^{23,24} Lachowicz reported in a retrospective study conducted in the US that IVO plus hypomethylating agents (HMA) therapy improved CR rates compared with venetoclax (VEN) plus HMA (43% versus 26%). Similarly, 6-month event-free survival was higher with IVO plus HMA than with VEN plus HMA (56% versus 38%).²⁵ These advances have introduced new challenges in early clinical management, including the need to balance timely treatment initiation with comprehensive diagnostic evaluation and to address novel toxicity profiles and pharmacologic complexities, exhaustively informing the treatment decision.

The management of IDH1-mutated AML in unfit patients reflects a shift toward a biology-driven treatment paradigm. Advances in molecular diagnostics and targeted therapies have improved treatment selection and outcomes while increasing clinical complexity. The diagnostic-to-treatment interval should be considered an active phase of care, allowing integration of biological data into therapeutic decisions. Supportive care, including antifungal prophylaxis, must adapt to the evolving risk profile of targeted therapies, balancing infection prevention with potential drug interactions. In addition, the emergence of DS and other treatment-related toxicities requires prompt recognition and appropriate management to optimize patient outcomes.

This expert opinion aims to provide a comprehensive, evidence-based framework for optimizing early management in unfit patients with newly diagnosed IDH1-mutated AML, integrating data from randomized trials, real-world studies, and updated evidence on antifungal prophylaxis and drug–drug interactions in the era of targeted therapies.

Methods. This paper aims to develop pragmatic clinical considerations, based on AML specialists' experience, after screening the available literature and discussing approaches across various Hematological Centers, by reporting on three main topics following the introduction of IVO+AZA in unfit IDH1-mutated patients. Our goal would be to produce valuable scientific content in support of clinical practice about: diagnostic work-up and timing of treatment initiation, and which could be the most appropriate clinical strategies in terms of patient monitoring, response assessment, and antifungal prophylaxis in the era of targeted therapies, as well as the best management of treatment-related toxicities.

Diagnostic Work-up and Timing of Treatment Initiation. The diagnostic approach to AML has evolved significantly with the integration of cytogenetic and

molecular profiling.²⁶ Current classification systems prioritize genetic abnormalities, which define disease subtypes and guide treatment selection and prognostic stratification.²⁷⁻²⁹

Although several studies in the past had not been able to identify the prognostic role of IDH1m in patients receiving intensive chemotherapy,^{9,30} the ELN2024 prognostic classifier specific for patients receiving less-intensive therapies has recently been developed, noting that IDH1m was assigned to the favorable risk class precisely within the framework of IVO+AZA therapy, thus configuring it as a predictive factor for a positive response to this therapy.²⁹ Indeed, a post hoc analysis from VIALE-A highlighted that patients with IDH1m AML and treated with VEN+AZA had an inferior survival advantage (mOS=10.2 months) compared to IDH2-mutated patients (mOS=27.5 months).³¹

In IDH1-mutated AML, rapid identification of the mutation within 3-5 days is critical for selecting appropriate targeted therapy.^{29,32}

Additionally, the concept of time from diagnosis to treatment (TdT) has been reevaluated in recent years.³³ While AML was traditionally considered a clinical emergency necessitating immediate treatment, multiple large retrospective and real-world studies have demonstrated that time-limited, purposeful delays to complete diagnostic work-up do not adversely affect clinical outcomes in patients receiving intensive chemotherapy.³³ Recently, these findings were observed also in AML patients receiving less intensive or targeted therapies across several retrospective studies, in whom disease kinetics may allow for a more deliberate and biologically informed approach.³³⁻³⁶ The trend was also observed in different subgroups, for instance, patients with an adverse risk or with hyperleukocytosis at diagnosis, when properly managed.^{37,38} Nevertheless, in the AGILE study, a positive trend in OS was also observed in patients presenting at diagnosis with high WBC.²⁰

Despite this new evidence on TdT in AML, it is crucial to ensure pragmatic facility organization (PCR, Hub&Spoke model adoption) to identify targetable mutations like IDH1m with fast turnaround times, thereby expanding available therapeutic options. This shift in perspective redefines the diagnostic-to-treatment interval as an active and critical phase of care rather than a passive delay. Morphological and immunophenotypical evaluations should be integrated with cytogenetic and genetic diagnostic workup in acute myeloid leukemia, with timelines specific to each item; e.g., for IDH1/2 and other genetic mutational markers, a 7-day or shorter turnaround (3-5 days) was identified as the ideal time length for treatment decision.

As a recap, the following considerations have been made:

In the diagnostic work-up of newly diagnosed UNFIT AML patients, it is important to obtain the result of IDH1m, ensuring a turnaround time of 3–5 days, as recommended by the 2022 ELN guidelines;²⁸ In this regard, the expert consensus emphasizes that priority should continue to be given to faster techniques such as PCR (or, if necessary, alternative methods e.g., Sanger, although it has lower sensitivity) over NGS, where NGS cannot provide results within a timeframe compatible with the therapeutic decision-making process. This approach is relevant in the context of a therapeutic decision that also takes molecular information into account, considering the possibility of targeted treatment with IVO+AZA, which demonstrated a benefit with a median OS of 29.3 months in the phase 3 AGILE study, accompanied by rapid hematologic recovery, a good tolerability profile, and a low incidence of infections in patients enrolled in the IVO+AZA arm.²⁰

1. In centers where NGS takes more than 3–4 weeks, it is recommended to use PCR or, if necessary, alternative methods (such as Sanger sequencing, although it has lower sensitivity) to avoid delays in decision-making that could be detrimental to the patient.

When molecular results for IDH1m are not available within 5 days, it is reasonable to wait for the molecular test outcome up to about 10–14 days from the AML diagnosis (except in particular clinical situations), in light of recent real-world evidence in unfit AML patients that describes the absence of an unfavorable prognostic impact on OS, if the time between diagnosis and the start of antileukemic treatment is approximately 20–21 days.^{37,38} During this time frame, close clinical monitoring of the patient (including hematological tests) is recommended.

In patients with hyperleukocytosis at diagnosis, it is appropriate to start cytoreductive therapy (according to local practices and clinical use) regardless of the subsequent therapeutic choice, and even while awaiting molecular results, according to the recommendations of national guidelines.³⁹

Antifungal Prophylaxis and Drug-Drug Interactions.

Antifungal prophylaxis has historically been a cornerstone of supportive care in AML patients receiving intensive chemotherapy, where it has been shown to reduce invasive fungal infections and improve survival.^{40,41} However, azole antifungals inhibit cytochrome P450 3A4 (CYP3A4) and can increase plasmatic exposure to AML therapies, requiring careful dose management and patient monitoring. In this regard, IVO is primarily metabolized through the CYP3A4 pathway and also induces CYP3A4 activity, resulting in complex bidirectional drug–drug interactions.⁴² Co-administration with strong CYP3A4 inhibitors, such as azole antifungals, can increase IVO exposure, while IVO

itself may reduce plasma concentrations of concomitant medications metabolized by CYP3A4.^{43,44}

Pharmacokinetic studies and clinical analyses indicate that co-administration with azoles can significantly increase IVO exposure.^{45,46} These results primarily emerge from PK studies conducted with IVO monotherapy in healthy subjects.⁴⁶ Moreover, a recent sub-analysis of the AGILE study,⁴⁷ highlighted that in AML patients treated with IVO+AZA, the AUC of IVO at steady state (SS) was predicted through population PK modeling to increase moderately (<2-fold) when co-administered with azole antifungals compared to IVO alone; this was consistent with a trend toward increased IVO trough at SS. PK behavior differs from the IVO monotherapy PK finding and may be explained by co-administration with AZA, other co-medications, or the disease itself. Nevertheless, careful monitoring and dose adjustments in accordance with the Summary of product characteristics (SmPC) are recommended when combining IVO with CYP3A4 inhibitors or inducers.

The introduction of targeted therapies has altered the infection risk profile compared with infection rates observed with conventional therapies.^{20,48} For example, in the context of IVO+AZA therapy, this might be explained by the “differentiative” mechanism of action that translated into a rapid hematologic recovery, which generally occurred faster with IVO compared to the control arm, with median neutrophil counts rapidly increasing from baseline to Cycle 1 Day22 (C1D22) and stabilizing within the normal range from cycle 4 onward, and therefore rapidly restoring the innate immune defense.²⁰

Thus, in patients receiving less-intensive regimens with IVO, the incidence of invasive fungal infections appears lower, likely due to reduced mucosal toxicity and shorter neutropenia duration.⁴⁹

In the context of the *IDH1m* AML, in the observational IVOOBS study (NCT06377579) a reduced response rate was observed in patients receiving 250mg/die of IVO (5/6 reduced the dose due to concomitant azoles) vs those who received the recommended dose, thus questioning the role of azole prophylaxis and the complex drug–drug interaction mechanism in this multi-treated population.²⁴ However, these findings should be interpreted with caution due to the limited data available at the time of the redaction of this manuscript.

These further complexities emphasize the concept of a risk-adapted approach to antifungal prophylaxis, taking into account individual patient risk factors, treatment intensity, and potential pharmacologic interactions.⁵⁰

Considering the absence of additional prospective studies evaluating the role of azole antifungal prophylaxis in the IVO-AZA clinical setting, the following observations can be made at the state of the art:

Table 1. Azole antifungal Inhibitory activity on CYP3A4 and half-lives.

Antifungal	Inhibitory activity on CYP3A4 ⁵¹	Half-life (Elimination/Terminal)
Fluconazole	Moderate	~110 - 115 hours
Posaconazole	Moderate to strong depending on drug levels	~30 hours
Voriconazole	Strongest	~29 hours (range 26-31 hours)
Itraconazole	Strongest	~17 hours (single dose) / 34-42 hours (repeated doses)
Isavuconazole	Low to moderate depending on drug levels	~6 hours (dose-dependent / non-linear)
Ketoconazole	Strong	~8 hours (terminal phase)

- The concomitant use of azole antifungal therapy requires a half-dose reduction of IVO due to significant pharmacokinetic interaction with CYP3A4 inhibitors (**Table 1**).⁵¹

- The ECIL guidelines indicate that, in monotherapy with ivosidenib, no antifungal prophylaxis is indicated; in combination therapy, it is advisable to administer prophylaxis at least in the first treatment cycles.^{40,52} In cases where antifungal prophylaxis is planned at diagnosis, it is reasonable to suspend prophylactic treatment upon neutrophil recovery, which has been shown to occur as early as the 1st cycle with IVO+HMA in the AGILE Study, in case the patient risk profile would allow it and provided that close clinical and microbiological monitoring is ensured. IVO treatment should then be resumed at the full dose of 500mg after 5 half-lives of the last administered azole, as reported in the SmPC (**Table 1**). In this context, it is notable that the favorable outcomes observed in the AGILE Study were achieved with a median dose intensity of 98.9% in the IVO+AZA arm.²⁰

- Also consider all concomitant therapies with other agents that could trigger drug interactions, and consequently potential adverse events.

- Where possible, local pharmacological consultation is recommended to assess better the most appropriate dosages of the polytherapy received by the UNFIT patient. In the real-world study IVOOBS, reduced efficacy at a lower dosage has been observed, a trend also consistent with other anti-leukemic therapies.²⁴

In the future, it is desirable to identify better infectious risk profiles to personalize prophylaxis in patients with AML correctly.

Monitoring Response Assessment and Monitoring Toxicities and Adverse Events. The differentiation-based mechanism of action of IVO requires reassessing traditional response evaluation practices. As mentioned before, hematologic improvement, including an increase in absolute neutrophil count, may precede morphological remission, and “delayed responses” are common.²² Indeed, in the AGILE study, the median time to CR and to 1st response in the IVO+AZA arm were 4.3 months (1.7–9.2) and 2.1 months (1.7–7.5), respectively.

Furthermore, the response landmark should be relevant for the treatment received; for example, after completion of 2 cycles of intensive therapy or 180 days after commencing less-intensive approaches.⁵³

If there is no disease progression or unacceptable toxicity, treatment should continue, as premature discontinuation may preclude delayed clinical benefit.

The duration of treatment is debatable, but we believe that, in the absence of clinical improvement, six months is an appropriate timeframe for benefits to become evident.

DS is a potentially life-threatening complication associated with therapies that induce myeloid differentiation, including IDH inhibitors.^{54,55} It is characterized by a systemic inflammatory response resulting from rapid maturation and tissue infiltration of leukemic cells.^{54,55} Clinical manifestations include fever, dyspnea, pulmonary infiltrates, pleural or pericardial effusions, hypotension, edema, and renal dysfunction.^{54,55}

The incidence of DS in patients treated with IDH inhibitors ranges from approximately 10% to 20%, with onset typically occurring within the first few weeks of therapy but potentially delayed for several months. In the AGILE study, grade 2 DS occurred in 19% and grade 3 in 4.1% of patients.^{21,56} The non-specific nature of symptoms and overlap with infection or disease progression could make AE identification challenging.²¹ Parameters or risk factors reported in the literature that could predict a DS within an IDH inhibitor are BM blasts $\geq 48\%$ and/or PB blasts $\geq 25\%$.^{23,57} Montesinos et al. 2024 also reported that higher WBC and LDH are associated with increased DS risk vs lower levels; however, they described this only for IDH2m inhibitors.

Prompt recognition and early initiation of corticosteroid therapy are critical for effective management and can significantly reduce mortality.⁵⁸ The median time to development of IDH inhibitor-related DS is longer than with acute promyelocytic leukemia (APL), with a median time of DS occurrence of 17 to 20 days. However, additional supportive measures, including cytoreduction with hydroxyurea and temporary therapy interruption in severe cases, may be required. Importantly, DS does not necessarily indicate treatment failure and should be managed proactively

Table 2. Identification and Management: Differentiation Syndrome and Leukocytosis.

Differentiation Syndrome (DS)*	General	Pyrexia, rash, rapid weight gain, bone pain	Suspected	<ul style="list-style-type: none"> Administer systemic corticosteroids (min. 3 days). Reduce the dose only after symptoms are resolved.
*Median time to differentiation syndrome in AGILE study: <u>19.5 days</u> (3.0 - 33.0 days) ²¹			Differentiation Syndrome	<ul style="list-style-type: none"> Initiate hemodynamic monitoring until symptoms resolution and at least for 3 days
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				<ul style="list-style-type: none"> If leukocytosis is noted, start treatment with hydroxycarbamide (see condition below)
Differentiation Syndrome (DS)*	Laboratory	Non-infectious leukocytosis	Suspected	<ul style="list-style-type: none"> Administer systemic corticosteroids (min. 3 days). Reduce the dose only after symptoms are resolved.
*Median time to differentiation syndrome in AGILE study: <u>19.5 days</u> (3.0 - 33.0 days) ²¹			Differentiation Syndrome	<ul style="list-style-type: none"> Initiate hemodynamic monitoring until symptoms resolution and at least for 3 days
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				<ul style="list-style-type: none"> If leukocytosis is noted, start treatment with hydroxycarbamide (see condition below)
Differentiation Syndrome (DS)*	Laboratory	Increased creatinine	Suspected	<ul style="list-style-type: none"> Administer systemic corticosteroids (min. 3 days). Reduce the dose only after symptoms are resolved.
*Median time to differentiation syndrome in AGILE study: <u>19.5 days</u> (3.0 - 33.0 days) ²¹			Differentiation Syndrome	<ul style="list-style-type: none"> Initiate hemodynamic monitoring until symptoms resolution and at least for 3 days
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				<ul style="list-style-type: none"> If leukocytosis is noted, start treatment with hydroxycarbamide (see condition below)
Differentiation Syndrome (DS)*	Cardiopulmonary	Dyspnea	Severe Symptoms (>48 hours)	If symptoms persist despite corticosteroids, withhold ivosidenib.
*Median time to differentiation syndrome in AGILE study: <u>19.5 days</u> (3.0 - 33.0 days) ²¹				
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				
Differentiation Syndrome (DS)*	Cardiopulmonary	Pleural effusion	Severe Symptoms (>48 hours)	If symptoms persist despite corticosteroids, withhold ivosidenib.
*Median time to differentiation syndrome in AGILE study: <u>19.5 days</u> (3.0 - 33.0 days) ²¹				
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				
Differentiation Syndrome (DS)*	Cardiopulmonary	Hypoxia	Severe Symptoms (>48 hours)	If symptoms persist despite corticosteroids, withhold ivosidenib.
*Median time to differentiation syndrome in AGILE study: <u>19.5 days</u> (3.0 - 33.0 days) ²¹				
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				
Differentiation Syndrome (DS)*	Cardiopulmonary	Pulmonary edema	Severe Symptoms (>48 hours)	If symptoms persist despite corticosteroids, withhold ivosidenib.
*Median time to differentiation syndrome in AGILE study: <u>19.5 days</u> (3.0 - 33.0 days) ²¹				
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				
Differentiation Syndrome (DS)*	Cardiopulmonary	Pulmonary infiltrates	Severe Symptoms (>48 hours)	If symptoms persist despite corticosteroids, withhold ivosidenib.
*Median time to differentiation syndrome in AGILE study: <u>19.5 days</u> (3.0 - 33.0 days) ²¹				
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				
Differentiation Syndrome (DS)*	Cardiopulmonary	Pericardial effusion	Improvement	

*Median time to differentiation syndrome in AGILE study: 19.5 days (3.0 - 33.0 days) ²¹				Resume ivosidenib at 500 mg/day when symptoms become moderate or less
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				
Differentiation Syndrome (DS)*				
*Median time to differentiation syndrome in AGILE study: 19.5 days (3.0 - 33.0 days) ²¹	Cardiopulmonary	Pneumonia	Improvement	Resume ivosidenib at 500 mg/day when symptoms become moderate or less
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				
Differentiation Syndrome (DS)*				
*Median time to differentiation syndrome in AGILE study: 19.5 days (3.0 - 33.0 days) ²¹	Cardiopulmonary	Fluid overload	Improvement	Resume ivosidenib at 500 mg/day when symptoms become moderate or less
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				
Differentiation Syndrome (DS)*				
*Median time to differentiation syndrome in AGILE study: 19.5 days (3.0 - 33.0 days) ²¹	Vascular	Hypotension	Improvement	Resume ivosidenib at 500 mg/day when symptoms become moderate or less
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				
Differentiation Syndrome (DS)*				
*Median time to differentiation syndrome in AGILE study: 19.5 days (3.0 - 33.0 days) ²¹	Vascular	Peripheral edema	Improvement	Resume ivosidenib at 500 mg/day when symptoms become moderate or less
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				
Differentiation Syndrome (DS)*				
*Median time to differentiation syndrome in AGILE study: 19.5 days (3.0 - 33.0 days) ²¹	Renal	Acute Renal Failure	Improvement	Resume ivosidenib at 500 mg/day when symptoms become moderate or less
Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days ⁵⁷				
Leukocytosis	White blood cell count > 25 x 10 ⁹ /L or an absolute increase > 15 x 10 ⁹ /L from baseline ⁴⁶	White blood cell count > 25 x 10 ⁹ /L or an absolute increase > 15 x 10 ⁹ /L from baseline ⁴⁶	Initiation	Start hydroxycarbamide or leukapheresis, according to standard clinical practice. Reduce the dose only after symptoms or leukocytosis are resolved
Leukocytosis	White blood cell count > 25 x 10 ⁹ /L or an absolute increase > 15 x 10 ⁹ /L from baseline ⁴⁶	White blood cell count > 25 x 10 ⁹ /L or an absolute increase > 15 x 10 ⁹ /L from baseline ⁴⁶	Lack of Improvement	If leukocytosis does not improve after cytoreduction, withhold ivosidenib.
Leukocytosis	White blood cell count > 25 x 10 ⁹ /L or an absolute increase > 15 x 10 ⁹ /L from baseline ⁴⁶	White blood cell count > 25 x 10 ⁹ /L or an absolute increase > 15 x 10 ⁹ /L from baseline ⁴⁶	Resolution	Resume ivosidenib treatment at 500 mg once daily.

without premature discontinuation of therapy (**Table 2**).⁵⁸ Therapy discontinuation is required only if the symptoms do not improve as indicated in the SmPC.

Close monitoring during the early phases of treatment is essential to detect DS, manage cytopenia, and adjust therapy as needed. It is also important to note that rapid proliferation should not be interpreted as immediate hyperleukocytosis, which requires cytoreduction according to local standards.⁴⁶

Electrocardiographic monitoring is also required due to the risk of QT interval prolongation.^{20,21}

In summary, the following considerations can be made for effective and safe monitoring of the patient:

a. It is advisable to perform a first bone marrow aspirate before the 4th cycle and again after the 4th to

evaluate CR achievement during IVO+AZA therapy. It may also be advantageous to assess the differentiating effect of IVO starting in the third week of treatment by monitoring hematologic recovery, particularly neutrophilic recovery. If there is no response, it is clinically important to continue IVO+AZA for at least 6 months, as indicated in the SmPC, given that ivosidenib has a “differentiating” mechanism of action and may therefore require slightly longer timeframes than other cytotoxic agents. In any case, continue treatment, even after CR, until progression/lack of observed clinical benefit.

b. Monitor for the onset of DS from the 1st cycle until achieving CR (especially in the outpatient setting). Any early signs/symptoms of DS that may appear later

(regardless of the number of cycles received) should not be underestimated. It is equally important to inform caregivers/patients about which signs/symptoms need attention (**Table 2**).²¹

c. In managing episodes of leukocytosis after IVO+AZA administration, which is associated with DS development, start treatment with hydroxycarbamide per institutional care standards, reducing the dose only after leukocytosis improves or resolves.^{46,59-61} Most data on WBC increases and their correlation with DS development come from studies of APL, where WBCs >5-10x10⁹/L are associated with an increased risk of DS.²¹ These WBC levels should probably be considered for planning cytorreduction also during treatment with other targeted drugs, including IVO.⁶² Only if no improvement in leukocytosis is observed after

starting treatment with hydroxycarbamide is it necessary to discontinue the administration of IVO, in accordance with the SmPC. However, we suggest careful daily monitoring of white blood cells. In any case, it is essential to clearly distinguish between "differentiation" leukocytosis and more marked leukocytosis due to disease progression (**Table 2**).

d. It is important that patients attend follow-up visits at least twice a week during the initial phases, thus not increasing the risk of missing potential DS or leukocytosis episodes.

e. Perform a careful ECG evaluation before starting treatment with IVO+AZA, at least weekly during the first 3 weeks of therapy or per cardiological assessment; subsequently, monitor at least once a month in all patients (even if QTc < 480msec) (**Table 3**).

Table 3. Clinical Management of QTc Interval Prolongation during Ivosidenib Treatment.⁴⁶

Grade 2	> 480 and ≤ 500	<ul style="list-style-type: none"> • Monitor and supplement serum electrolytes as clinically indicated • Review and adjust concomitant medications known to prolong the QTc interval. • Monitor ECG every week for 3 weeks after QTc returns to ≤ 480 msec 	Withhold ivosidenib treatment until QTc returns to ≤ 480 msec. Then resume at the standard dose of 500 mg once daily.
Grade 3	> 500	<ul style="list-style-type: none"> • Monitor electrolytes and review concomitant medications • Monitor ECG every 24 hours until clinical resolution (within 30 msec of baseline or ≤ 480 msec) • If QTc > 550 msec, consider continuous ECG monitoring, until < 500 msec. 	Withhold ivosidenib until QTc returns to within 30 msec of baseline or ≤ 480 msec. Resume ivosidenib at a reduced dose: 250 mg once daily. Note: If an alternative etiology for Grade 3 QTc prolongation is identified, the ivosidenib dose may be increased back to 500 mg once daily after resolution of the event.
Grade 4	Signs/symptoms of life-threatening ventricular arrhythmia	<ul style="list-style-type: none"> • Emergency intervention according to clinical protocols for life-threatening arrhythmias (e.g., Torsade de Pointes). 	Permanently discontinue treatment.

Conclusions. The early management of unfit patients with IDH1-mutated AML requires a comprehensive and multidisciplinary approach that integrates molecular diagnostics, targeted therapy, and individualized supportive care. Rapid identification of “druggable” genetic lesions within 3-5 days after AML diagnosis is essential for ensuring the most appropriate strategy. Time-limited, purposeful delays to complete diagnostic evaluation are justified and may improve treatment selection. Ivosidenib combined with azacitidine represents a major advance in this population, offering significant survival benefit with a manageable safety profile. Recognizing and managing DS and QTc prolongation, along with careful consideration of drug–drug interactions and antifungal prophylaxis, are critical components of care. Ultimately, embracing a biology-driven approach to AML management represents a key step toward precision medicine in hematologic malignancies.

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