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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 *IDH1*m, 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 *IDH*m are present in the founder clone of many AML cases co-expressing other molecular aberrations.[15-17] *IDH1*m 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 leukemia, partly by promoting activation of residual leukemic stem cells. However, it enhances sensitivity to azacytidine (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 *IDH1*m 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] Lachowiez 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 *IDH1*m 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 ≥48% and/or PB blasts ≥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.

Condition	**Signs and Symptoms / clinical presentations**		**Dosage management and notes[46]**	
	Symptom Type of IDH-i Differentiation Syndrome [21,46,57]	**Presentation of IDH-i Differentiation Syndrome [21,46,57]**		
Differentiation Syndrome (DS)* **Median time to differentiation dyndrome in AGILE study: 19.5 days (3.0 - 33.0 days)[21]* *Range of IDH-i Differentiation Syndrome onset in literature: 1 - 86 days[57]*	**General**	Pyrexia, rash, rapid weight gain, bone pain	**Suspected Differentiation Syndrome**	1. Administer systemic corticosteroids (min. 3 days). Reduce the dose only after symptoms are resolved. 2. Initiate hemodynamic monitoring until symptoms resolution and at least for 3 days 3. If leukocytosis is noted, start treatment with hydroxycarbamide (see condition below)
	Laboratory	Non-infectious leukocytosis		
		Increased creatinine		
	Cardiopulmonary	Dyspnea	**Severe Symptoms (>48 hours)**	If symptoms persist despite corticosteroids, withhold ivosidenib.
		Pleural effusion		
		Hypoxia		
		Pulmonary edema		
		Pulmonary infiltrates		
		Pericardial effusion	**Improvement**	Resume ivosidenib at 500 mg/day when symptoms become moderate or less
		Pneumonia		
		Fluid overload		
	Vascular	Hypotension		
		Peripheral edema		
	Renal	Acute Renal Failure		
Leukocytosis	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
			Lack of Improvement	If leukocytosis does not improve after cytoreduction, withhold ivosidenib.
			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>5-10x10^9/L are associated with an increased risk of DS.[21] These WBC levels should probably be considered for planning cytoreduction 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	• 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 ivosidenibtreatment until QTc returns to ≤ 480 msec. Then resume at the standard dose of500 mg once daily.
Grade 3	> 500	• Monitor electrolytes and review concomitant medications • Monitor ECG every 24 hours until clinical resolution (within 30 msec of baseline or ≤ 480 msec) • IfQTc > 550 msec, consider continuous ECG monitoring, until < 500 msec.	Withhold ivosidenibuntil 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	• Emergency intervention according to clinical protocols for life-threatening arrhythmias (e.g., Torsade de Pointes).	Permanently discontinuetreatment.

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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References:

1. Shimony S, Stahl M, Stone RM. Acute Myeloid Leukemia: 2025 Update on Diagnosis, Risk-Stratification, and Management. Am J Hematol. 2025 May;100(5):860-891. Epub 2025 Feb 12. ; PMCID: PMC11966364. https://doi.org/10.1002/ajh.27625 PMid:39936576
2. SEER Data Base: Cancer Stat Facts: Leukemia" — Acute MyeloidLeukemia (AML), accessed may 11, 2063. https://doi.org/10.1016/s2152-2650(26)01985-3
3. Venditti A, Palmieri R, Maurillo L, Röllig C, Wierzbowska A, de Leeuw D, Efficace F, Curti A, Ngai LL, Tettero J, Adès L, Almeida A, Bullinger L, Dennis M, Esteve J, Ferrara F, Heuser M, Huls G, Lübbert M, Mehta P, Montesinos P, Pabst T, Récher C, Rossi G, Russell N, Sierra J, Stauder R, Vey N, Walter RB, Wang E, Nier S, Martins CG, Ossenkoppele G. Fitness assessment in acute myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood Adv. 2025 May 13;9(9):2207-2220. https://doi.org/10.1182/bloodadvances.2024013744 PMid:39913928
4. Gangat N, Dinardo CD. Newly diagnosed acute myeloid leukemia in unfit patients: 2026 treatment algorithms. Blood Cancer J. 2025 Aug 16;15(1):139. https://doi.org/10.1038/s41408-025-01346-1 PMid:40818987
5. Kantarjian HM, Short NJ, Fathi AT, Marcucci G, Ravandi F, Tallman M, Wang ES, Wei AH. Acute Myeloid Leukemia: Historical Perspective and Progress in Research and Therapy Over 5 Decades. Clin Lymphoma Myeloma Leuk. 2021 Sep;21(9):580-597. Epub 2021 May 29 https://doi.org/10.1016/j.clml.2021.05.016
6. Forsberg M, Konopleva M. AML treatment: conventional chemotherapy and emerging novel agents. Trends Pharmacol Sci. 2024 May;45(5):430-448. Epub 2024 Apr 20. https://doi.org/10.1016/j.tips.2024.03.005 PMid:38643058
7. Duployez N, Preudhomme C. The genomic landscape of acute myeloid leukemia: Redefining classifications, ontogeny, and therapeutic strategies. Semin Hematol. 2025 Jun;62(3):141-154. Epub 2025 Jun 10. https://doi.org/10.1053/j.seminhematol.2025.06.001
8. Fruchtman H, Avigan ZM, Waksal JA, Brennan N, Mascarenhas JO. Management of isocitrate dehydrogenase 1/2 mutated acute myeloid leukemia. Leukemia. 2024 May;38(5):927-935. Epub 2024 Apr 10. https://doi.org/10.1038/s41375-024-02246-2 PMid:38600315
9. Messina M, Piciocchi A, Ottone T, Paolini S, Papayannidis C, Lessi F, Fracchiolla NS, Forghieri F, Candoni A, Mengarelli A, Martelli MP, Venditti A, Carella AM, Albano F, Mancini V, Massimo B, Arena V, Sargentini V, Sciumè M, Pastore D, Todisco E, Roti G, Siragusa S, Ladetto M, Pravato S, De Bellis E, Simonetti G, Marconi G, Cerchione C, Fazi P, Vignetti M, Amadori S, Martinelli G, Voso MT. Prevalence and Prognostic Role of IDH Mutations in Acute Myeloid Leukemia: Results of the GIMEMA AML1516 Protocol. Cancers (Basel). 2022 Jun 18;14(12):3012. https://doi.org/10.3390/cancers14123012 PMid:35740677
10. Merchant SL, Culos K, Wyatt H. Ivosidenib: IDH1 Inhibitor for the Treatment of Acute Myeloid Leukemia. J Adv Pract Oncol. 2019 Jul;10(5):494-500. Epub 2019 Jul 1. https://doi.org/10.6004/jadpro.2019.10.5.7
11. DiNardo, C. D., Stein, E. M., de Botton, S., Roboz, G. J., Altman, J. K., Mims, A. S., Swords, R., Collins, R. H., Mannis, G. N., Pollyea, D. A., Donnellan, W., Fathi, A. T., Pigneux, A., Erba, H. P., Prince, G. T., Stein, A. S., Uy, G. L., Foran, J. M., Traer, E., Stuart, R. K., … Kantarjian, H. M. (2018). Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML.The New England journal of medicine,378(25), 2386–2398. https://doi.org/10.1056/NEJMoa1716984 PMid:29860938
12. Roboz GJ, DiNardo CD, Stein EM, de Botton S, Mims AS, Prince GT, Altman JK, Arellano ML, Donnellan W, Erba HP, Mannis GN, Pollyea DA, Stein AS, Uy GL, Watts JM, Fathi AT, Kantarjian HM, Tallman MS, Choe S, Dai D, Fan B, Wang H, Zhang V, Yen KE, Kapsalis SM, Hickman D, Liu H, Agresta SV, Wu B, Attar EC, Stone RM. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. Blood. 2020 Feb 13;135(7):463-471 https://doi.org/10.1182/blood.2019002140
13. Pirozzi CJ, Yan H. The implications of IDH mutations for cancer development and therapy. Nat Rev Clin Oncol. 2021 Oct;18(10):645-661. Epub 2021 Jun 15. https://doi.org/10.1038/s41571-021-00521-0 PMid:34131315
14. Molenaar RJ, Thota S, Nagata Y, Patel B, Clemente M, Przychodzen B, Hirsh C, Viny AD, Hosano N, Bleeker FE, Meggendorfer M, Alpermann T, Shiraishi Y, Chiba K, Tanaka H, van Noorden CJ, Radivoyevitch T, Carraway HE, Makishima H, Miyano S, Sekeres MA, Ogawa S, Haferlach T, Maciejewski JP. Clinical and biological implications of ancestral and non-ancestral IDH1 and IDH2 mutations in myeloid neoplasms. Leukemia. 2015 Nov;29(11):2134-42. Epub 2015 Apr 3. https://doi.org/10.1038/leu.2015.91 PMid:25836588
15. Huber S, Goessweiner F, Walter W, Summerer I, Meggendorfer M, Ordemann R, Pohlkamp C, Kneisel N, Haferlach C, Kern W, Haferlach T, Delic S, Hoermann G. IDH1- and IDH2-mutated myeloid neoplasms: mutational pattern, clonal hierarchy, and the role in AML transformation.Blood advances,2026;10(10), 3554–3564. https://doi.org/10.1182/bloodadvances.2025019387
16. Sirenko M, Lee S, Sun Z, Chaligne R, Loghavi S, Asimomitis G, Brierley CK, Bernard E, Cai SF, Myers RM, Nadorp B, Sango J, Lallo M, Levine MF, Domenico D, Arango Ossa JE, Medina-Martinez JS, Menghrajani K, Lasry A, Mims AS, Desai H, Laganson A, Famulare C, Patel M, Lozanski G, Bolton KL, Viny AD, Roshal M, Levine RL, Papapetrou EP, Stein EM, Landau DA, Eisfeld AK, Aifantis I, Papaemmanuil E. Deconvoluting clonal and cellular architecture in IDH-mutant acute myeloid leukemia. Cell Stem Cell. 2025 Jul 3;32(7):1102-1121.e5. Epub 2025 May 22. https://doi.org/10.1016/j.stem.2025.04.012 PMid:40409258
17. Marconi G, Bandini L, Patuelli A, Robustelli V, Venturi C, Simonetti G, Nanni J, Cristiano G, Sartor C, Rondoni M, Papayannidis C, Lanza F, Ottaviani E, Curti A. Dynamics of IDH1/2 mutated clones in acute myeloid leukemia challenge their use as universal MRD markers. Blood Cancer J. 2026 Jun 30;16(1):106. https://doi.org/10.1038/s41408-026-01538-3
18. Gruber E, So J, Lewis AC, Franich R, Cole R, Martelotto LG, Rogers AJ, Vidacs E, Fraser P, Stanley K, Jones L, Trigos A, Thio N, Li J, Nicolay B, Daigle S, Tron AE, Hyer ML, Shortt J, Johnstone RW, Kats LM. Inhibition of mutant IDH1 promotes cycling of acute myeloid leukemia stem cells. Cell Rep. 2022 Aug 16;40(7):111182. https://doi.org/10.1016/j.celrep.2022.111182 PMid:35977494
19. Griffiths EA, Carraway HE, Chandhok NS, Prebet T. Advances in non-intensive chemotherapy treatment options for adults diagnosed with acute myeloid leukemia. Leuk Res. 2020 Apr;91:106339. Epub 2020 Feb 26. https://doi.org/10.1016/j.leukres.2020.106339 PMid:32146154
20. Montesinos P, Marchione DM, Recher C, Heuser M, Vives S, Zarzycka E, Wang J, Riva M, Calado RT, Schuh AC, Yeh SP, Tron AE, Hui J, Gianolio DA, Choe S, Patel P, De Botton S, DiNardo CD, Döhner H. Long-term results from the AGILE study of azacitidine plus ivosidenib vs placebo in newly diagnosed IDH1-mutated AML. Blood Adv. 2025 Oct 28;9(20):5177-5189. https://doi.org/10.1182/bloodadvances.2025016399
21. Montesinos P, Fathi AT, de Botton S, Stein EM, Zeidan AM, Zhu Y, Prebet T, Vigil CE, Bluemmert I, Yu X, DiNardo CD. Differentiation syndrome associated with treatment with IDH2 inhibitor enasidenib: pooled analysis from clinical trials. Blood Adv. 2024 May 28;8(10):2509-2519.. https://doi.org/10.1182/bloodadvances.2023011914 PMid:38507688
22. Vyas Paresh, Christian Recher, Hartmut Döhner, Adriano Venditti, Sam Salek, Samantha Nier, Blanca Boluda, Gaspar Aspas Requena, Raja Prince-Eladnani, Erika Borlenghi, Antonio Curti, Koen Theunissen, Alba Puyuelo, Ioana Codruta Rus, David de Leeuw, Emanuele Ammatuna, Lalit Saini, Johan Maertens, Andre Schuh, Dilza Camanho, Adam Sullivan, Anne-Marie De La Bigne, Mathilde Romagnoli, Bénédicte Cognet, Courtney DiNardo, Susana Vives. ALIDHE: An ongoing open-label phase 3b study investigating ivosidenib with azacitidine in clinical

practice in adult patients with newly diagnosed mutant isocitrate dehydrogenase 1 (mIDH1) Acute Myeloid Leukemia (AML) ineligible for intensive induction chemotherapy (IC). Blood (2025) 146 (Supplement 1): 3443. https://doi.org/10.1182/blood-2025-3443
23. Zeidner JF. Differentiating the Differentiation Syndrome Associated with IDH Inhibitors in AML. Clin Cancer Res. 2020 Aug 15;26(16):4174-4176. Epub 2020 Jun 18. https://doi.org/10.1158/1078-0432.CCR-20-1820 PMid:32554513
24. Heiblig M, Peterlin P, Morisset S, Dumas P, Sebert M, Bertoli S, Musiu P, Ravinet A, Garciaz S, Lebon D, Turlure P, Desbrosses Y, Lambert J, Cabrera Q, Bonnet S, Simand C, Laribi K, Banos A, Marçais A, Carpentier B, Daniel A, Orvain C, Cluzeau T, Ochmann M, Contejean A, Pautas C, Birsen R, Papoular B, Salanoubat C, Frayfer J, Pica G, HIEULLE J, Vallet N, Mineur A, De Botton S, Recher C, Pigneux A. Ivosidenib in refractory or relapsed IDH1-mutated Acute Myeloid Leukemia patients in real life settings: The ivoobs observational study from the French AML intergroup ALFA/filo. Blood (2025) 146 (Supplement 1): 3455. https://doi.org/10.1182/blood-2025-3455
25. Lachowiez CA, Smith BD, Ambinder AJ, Binder G, Angiolillo A, Potluri R, Papademetriou E, LeBlanc TW. Ivosidenib or venetoclax combined with hypomethylating agents in IDH1-mutated acute myeloid leukemia: a real-world study. Blood Neoplasia. 2025 Aug 4;2(4):100152. https://doi.org/10.1016/j.bneo.2025.100152
26. Moarii M, Papaemmanuil E. Classification and risk assessment in AML: integrating cytogenetics and molecular profiling. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):37-44. https://doi.org/10.1182/asheducation-2017.1.37 PMid:29222235
27. Park HS. What is new in acute myeloid leukemia classification? Blood Res. 2024 Apr 15;59(1):15. https://doi.org/10.1007/s44313-024-00016-8 PMid:38616211
28. Döhner H, DiNardo CD, Appelbaum FR, Craddock C, Dombret H, Ebert BL, Fenaux P, Godley LA, Hasserjian RP, Larson RA, Levine RL, Miyazaki Y, Niederwieser D, Ossenkoppele G, Röllig C, Sierra J, Stein EM, Tallman MS, Tien HF, Wang J, Wierzbowska A, Wei AH, Löwenberg B. Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. Blood. 2024 Nov 21;144(21):2169-2173. https://doi.org/10.1182/blood.2024025409 PMid:39133932
29. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, Ebert BL, Fenaux P, Godley LA, Hasserjian RP, Larson RA, Levine RL, Miyazaki Y, Niederwieser D, Ossenkoppele G, Röllig C, Sierra J, Stein EM, Tallman MS, Tien HF, Wang J, Wierzbowska A, Löwenberg B. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. https://doi.org/10.1182/blood.2022016867
30. Kantarjian H, Borthakur G, Daver N, DiNardo CD, Issa G, Jabbour E, Kadia T, Sasaki K, Short NJ, Yilmaz M, Ravandi F. Current status and research directions in acute myeloid leukemia. Blood Cancer J. 2024 Sep 19;14(1):163. https://doi.org/10.1038/s41408-024-01143-2 PMid:39300079
31. Pratz KW, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Döhner H, Récher C, Fiedler W, Yamamoto K, Wang J, Yoon SS, Wolach O, Yeh SP, Leber B, Esteve J, Mayer J, Porkka K, Illés Á, Lemoli RM, Turgut M, Ku G, Miller C, Zhou Y, Zhang M, Chyla B, Potluri J, DiNardo CD. Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. Am J Hematol. 2024 Apr;99(4):615-624. Epub 2024 Feb 11. https://doi.org/10.1002/ajh.27246 PMid:38343151
32. Zeidan AM, DiNardo C. Deep Dive into Targeted Therapies: Understanding IDH1-Mutant AML Treatments [Podcast]. Blood Lymphat Cancer. 2025 Jul 2;15:77-83. https://doi.org/10.2147/BLCTT.S549780 PMid:40630560
33. Röllig C, Kramer M, Schliemann C, Mikesch JH, Steffen B, Krämer A, Noppeney R, Schäfer-Eckart K, Krause SW, Hänel M, Herbst R, Kunzmann V, Einsele H, Jost E, Brümmendorf TH, Scholl S, Hochhaus A, Neubauer A, Sohlbach K, Fransecky L, Kaufmann M, Niemann D, Schaich M, Frickhofen N, Kiani A, Heits F, Krümpelmann U, Kaiser U, Kullmer J, Wass M, Stölzel F, von Bonin M, Middeke JM, Thiede C, Schetelig J, Berdel WE, Ehninger G, Baldus CD, Müller-Tidow C, Platzbecker U, Serve H, Bornhäuser M. Does time from diagnosis to treatment affect the prognosis of patients with newly diagnosed acute myeloid leukemia? Blood. 2020 Aug 13;136(7):823-830. https://doi.org/10.1182/blood.2019004583
34. Rodríguez-Arbolí E. et al. TIME TO TREATMENT INITIATION AND CLINICAL OUTCOMES IN NON-INTENSIVELY TREATED ADULT ACUTE MYELOID LEUKEMIA: A PETHEMA-GPLA-ACHO-GRELAM REGISTRY. EHA library; 06/13/2025; 4159905; PF498.Last accessed on 05/05/2026 at. https://doi.org/10.1200/jco.2025.43.16_suppl.8069 PMid:42852411
35. Martelli MP, Di Renzo N, Curti A, Fracchiolla NS, Maurillo L, Caira M, Finsinger P, Gualberti G, Ferrara F, Olivieri A. Real-world treatments and clinical outcomes in unfit AML patients receiving first-line treatment or best supportive care in Italy (CURRENT study). Leuk Res Rep. 2024 Feb 23;21:100453. https://doi.org/10.1016/j.lrr.2024.100453 PMid:39035747
36. Molica M. Challenges and emerging therapeutic strategies for TP53-mutated acute myeloid leukemia: still disappointing findings? Expert Rev Hematol. 2025 Jan;18(1):1-4. Epub 2024 Dec 4. https://doi.org/10.1080/17474086.2024.2438241 PMid:39628102
37. Baden D, Zukunft S, Hernandez G, Wolgast N, Steinhauser S, Pohlmann A, Schliemann C, Mikesch JH, Steffen B, Sauer T, Hanoun M, Schafer-Eckart K, Krause SW, Hanel M, Einsele H, Jost E, Brummendorf TH, Scholl S, Hochhaus A, Neubauer A, Burchert A, Kaufmann M, Niemann D, Schaich M, Blau W, Kiani A, Gorner M, Kaiser U, Kullmer J, Weber T, Berdel WE, Ehninger G, Muller-Tidow C, Platzbecker U, Serve H, Bornhauser M, Rollig C, Baldus CD, Fransecky L. Time from diagnosis to treatment has no impact on survival in newly diagnosed acute myeloid leukemia treated with venetoclax-based regimens. Haematologica. 2024 Aug 1;109(8):2469-2477. https://doi.org/10.3324/haematol.2024.285225
38. Yates SJ, Weiss JJ, Sneider A, Geramita E, Murthy GSG, Badar T, Im A, Lin C, Cheng W, Abaza Y, Swaroop A, Winer ES, Litzow MR, Atallah EL, Patel AA, Shallis RM. Longer time from diagnosis to initiation of hypomethylating agents plus venetoclax for acute myeloid leukemia does not worsen survival: results from the Consortium on Myeloid Malignancies and Neoplastic Diseases (COMMAND). Haematologica. 2026 Jan 1;111(1):158-167. Epub 2025 Jul 24. https://doi.org/10.3324/haematol.2025.288085 PMid:40702896
39. Società Italiana di Ematologia. Linee guida. Leucemia acuta mieloide. Availble from: Accessed on 20 June 2026. https://doi.org/10.1007/s40619-025-01691-0 PMid:30311153
40. Pagano L, Maschmeyer G, Lamoth F, Blennow O, Xhaard A, Spadea M, Busca A, Cordonnier C, Maertens J; ECIL. Primary antifungal prophylaxis in hematological malignancies. Updated clinical practice guidelines by the European Conference on Infections in Leukemia (ECIL). Leukemia. 2025 Jul;39(7):1547-1557. Epub 2025 Apr 9. https://doi.org/10.1038/s41375-025-02586-7 PMid:40200079
41. Marchesi F, Girmenia C, Trecarichi EM, Piciocchi A, Busca A, Candoni A, Cattaneo C, Delia M, Del Principe MI, Fianchi L, Gentile G, Fracchiolla NS, Tumbarello M, Vignetti M, Venditti A, Pagano L. Antibacterial, antifungal and antiviral prophylaxis and vaccination strategies in adult patients with acute myeloid and promyelocytic leukemia: An expert panel consensus from the GIMEMA group. Blood Rev. 2026 Jun 20:101412. Epub ahead of print. https://doi.org/10.1016/j.blre.2026.101412 PMid:42350210
42. Zhang Y, Wang Z, Wang Y, Jin W, Zhang Z, Jin L, Qian J, Zheng L. CYP3A4 and CYP3A5: the crucial roles in clinical drug metabolism and the significant implications of genetic polymorphisms. PeerJ. 2024 Dec 5;12:e18636. https://doi.org/10.7717/peerj.18636
43. Azanza JR, Mensa J, Barberán J, Vázquez L, Pérez de Oteyza J, Kwon M, Yáñez L, Aguado JM, Cubillo Gracian A, Solano C, Ruiz Camps I, Fortún J, Salavert Lletí M, Gudiol C, Olave Rubio T, Solano C, García-Vidal C, Rovira Tarrats M, Suárez-Lledó Grande M, González-Sierra P, Dueñas Gutiérrez C. Recommendations on the use of azole antifungals in hematology-oncology patients. Rev Esp Quimioter. 2023 Jun;36(3):236-258. Epub 2023 Apr 5. https://doi.org/10.37201/req/013.2023 PMid:37017117
44. Prakash C, Fan B, Ke A, Le K, Yang H. Physiologically based pharmacokinetic modeling and simulation to predict drug-drug interactions of ivosidenib with CYP3A perpetrators in patients with acute myeloid leukemia. Cancer Chemother Pharmacol. 2020 Nov;86(5):619-632. Epub 2020 Sep 25. https://doi.org/10.1007/s00280-020-04148-3 PMid:32978634
45. Brüggemann RJ, Alffenaar JW, Blijlevens NM, Billaud EM, Kosterink JG, Verweij PE, Burger DM. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis. 2009 May 15;48(10):1441-58. https://doi.org/10.1086/598327 PMid:19361301
46. Ivosedinib. Summary of product characteristics. https://doi.org/10.1007/978-3-642-36172-2_200037
47. Schuh Andre,Pau Montesinos,Christian Recher,Michael Heuser,Susana Vives,Ewa Zarzycka,Marta Riva,Rodrigo Calado,Su-Peng Yeh,Courtney

DiNardo,Mohammad Hossain,Jianan Hui,Diego Gianolio,Assaf Vestin,Rui Ding,Prapti Patel,Stéphane De Botton,Hartmut Döhner,Jianxiang Wang; CYP3A4 inhibitors (CYP3A4i) and myelosuppression in patients (Pts) with newly diagnosed mutant isocitrate dehydrogenase 1 (mIDH1) Acute Myeloid Leukemia (AML) in the phase 3 AGILE study. Blood2025; 146 (Supplement 1): 3440. https://doi.org/10.1182/blood-2025-3440

48. Ambinder Alexander J, Mark J. Levis, Xin Wang, Keith W. Pratz, Andrew H Matthews. The Use of Antifungal Prophylaxis Is Associated with Worse Outcomes in Patients with Newly Diagnosed AML Treated with Venetoclax/HMA: A Retrospective Analysis of Patients in the Flatiron Health Database. Blood (2024) 144 (Supplement 1): 2436. https://doi.org/10.1182/blood-2024-207062
49. Seeling C, Ganser A, Döhner H, Kühn MWM. Tailoring intensive and less-intensive treatment in acute myeloid leukemia. Semin Hematol. 2025 Jun;62(3):196-208. Epub 2025 Sep 13. https://doi.org/10.1053/j.seminhematol.2025.09.001 PMid:41093668
50. Nucci M, Maertens J. Redefining antifungal prophylaxis in acute leukaemia in the era of targeted therapies. J Antimicrob Chemother. 2026 Jan 19;81(2):dkag010. https://doi.org/10.1093/jac/dkag010 PMid:41549654
51. Bellmann R, Smuszkiewicz P. Pharmacokinetics of antifungal drugs: practical implications for optimized treatment of patients. Infection. 2017;45(6):737-779. https://doi.org/10.1007/s15010-017-1042-z PMid:28702763
52. Maschmeyer G, Bullinger L, Garcia-Vidal C, Herbrecht R, Maertens J, Menna P, Pagano L, Thiebaut-Bertrand A, Calandra T. Infectious complications of targeted drugs and biotherapies in acute leukemia. Clinical practice guidelines by the European Conference on Infections in Leukemia (ECIL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the International Immunocompromised Host Society (ICHS) and the European Leukemia Net (ELN). Leukemia. 2022 May;36(5):1215-1226. Epub 2022 Apr 2. Erratum in: Leukemia. 2022 May;36(5):1450. https://doi.org/10.1038/s41375-022-01556-7 PMid:35368047
53. Dohner Hartmut, Pau Montesinos, Susana Vives Polo, Ewa Zarzycka, Jianxiang Wang, Giambattista Bertani, Michael Heuser, Rodrigo T. Calado, Andre C. Schuh, Su-Peng Yeh, Adolfo de la Fuente Burguera, Claudio Cerchione, Scott Daigle, Jianan Hui, Shuchi Sumant Pandya, Diego A. Gianolio, Christian Recher, and Stéphane De Botton. Hematologic improvements with ivosidenib + azacitidine compared to placebo + azacitidine in patients with newly diagnosed acute myeloid leukemia. J Clin Oncol 40, 7042(2022) Volume 40, Number 16_suppl. https://doi.org/10.1200/JCO.2022.40.16_suppl.7042 PMid:42852411
54. Norsworthy KJ, Mulkey F, Scott EC, Ward AF, Przepiorka D, Charlab R, Dorff SE, Deisseroth A, Kazandjian D, Sridhara R, Beaver JA, Farrell AT, de Claro RA, Pazdur R. Differentiation Syndrome with Ivosidenib and Enasidenib Treatment in Patients with Relapsed or Refractory IDH-Mutated AML: A U.S. Food and Drug Administration Systematic Analysis. Clin Cancer Res. 2020 Aug 15;26(16):4280-4288. Epub 2020 May 11. https://doi.org/10.1158/1078-0432.CCR-20-0834
55. Gasparovic L, Weiler S, Higi L, Burden AM. Incidence of Differentiation Syndrome Associated with Treatment Regimens in Acute Myeloid Leukemia: A Systematic Review of the Literature. J Clin Med. 2020 Oct 18;9(10):3342. https://doi.org/10.3390/jcm9103342
56. Braitsch Krischan, Karin Huber, Andrew Berdel, Lydia Kretschmer, Adrian Gottschlich, Tim Lohmann, Kathrin Rieger, Karsten Spiekermann, Thomas Schroeder, Silke Kapp-Schwoerer, Mareike Verbeek, Florian Bassermann, Hartmut Döhner, Tim Sauer, Christoph Röllig, Jan-Henrik Mikesch, Franziska Westendorf, Lars Fransecky, Katharina S. Götze. Real-world experience with IDH inhibitors in Acute Myeloid Leukemia: A German multicenter analysis with a focus on differentiation syndrome. Blood (2025) 146 (Supplement 1): 2846. https://doi.org/10.1182/blood-2025-2846
57. Fathi AT, Stein EM, DiNardo CD, Levis MJ, Montesinos P, de Botton S. Differentiation syndrome with lower-intensity treatments for acute myeloid leukemia. Am J Hematol. 2021 Jun 1;96(6):735-746. Epub 2021 Mar 18. https://doi.org/10.1002/ajh.26142 PMid:33625753
58. Issa GC, Stein EM, DiNardo CD. How I treat acute myeloid leukemia with differentiation therapy. Blood. 2025 Mar 20;145(12):1251-1259. https://doi.org/10.1182/blood.2024024008 PMid:38976876
59. Röllig C, Ehninger G. How I treat hyperleukocytosis in acute myeloid leukemia. Blood. 2015 May 21;125(21):3246-52. Epub 2015 Mar 16. https://doi.org/10.1182/blood-2014-10-551507
60. Shallis RM, Stahl M, Wei W, Montesinos P, Lengline E, Neukirchen J, Bhatt VR, Sekeres MA, Fathi AT, Konig H, Luger S, Khan I, Roboz GJ, Cluzeau T, Martínez-Cuadron D, Raffoux E, Germing U, Umakanthan JM, Mukhereje S, Brunner AM, Miller A, McMahon CM, Ritchie EK, Rodríguez-Veiga R, Itzykson R, Boluda B, Rabian F, Tormo M, Acuña-Cruz E, Rabinovich E, Yoo B, Cano I, Podoltsev NA, Bewersdorf JP, Gore S, Zeidan AM. Patterns of care and clinical outcomes of patients with newly diagnosed acute myeloid leukemia presenting with hyperleukocytosis who do not receive intensive chemotherapy. Leuk Lymphoma. 2020 May;61(5):1220-1225. Epub 2020 Feb 26. ; PMCID: PMC8273667. https://doi.org/10.1080/10428194.2020.1728753 PMid:32100599
61. Hydroxyurea. Summary product of characteristics. https://doi.org/10.1007/978-3-642-36172-2_200037
62. Chang GA, Bey T, Stroh J, Qdaisat A, Yeung SJ. Identification and Management of Differentiation Syndrome in Emergency Settings: A Narrative Review. Cancers (Basel). 2026 Jun 1;18(11):1798. https://doi.org/10.3390/cancers18111798 PMid:42279388