

REVIEW ARTICLE

Therapeutic strategies in the post-venetoclax era of acute myeloid leukemia

Huan Zhang, Shijie Zhang, and Jingxin Zhang* 

Aging Decoding and Regeneration Institute, School of Life Sciences, Zhengzhou University, Zhengzhou, Henan, China

Abstract

The therapeutic landscape of acute myeloid leukemia (AML) has changed substantially over the past decade with the incorporation of molecularly targeted agents, lower-intensity venetoclax-based regimens, and increasingly refined genetic risk stratification. Among these advances, the combination of venetoclax with hypomethylating agents has become a pivotal treatment backbone for older or medically unfit patients with newly diagnosed AML, producing higher remission rates and longer survival than hypomethylating-agent monotherapy. However, venetoclax-based therapy is not curative for most patients. Primary resistance, incomplete eradication of leukemia stem and progenitor populations, lineage-associated drug tolerance, clonal evolution, and short survival after relapse have revealed major limitations of this approach. These challenges define the emerging post-venetoclax era of AML therapy. In this setting, treatment development is shifting from empiric intensification toward rational, biomarker-guided strategies that combine venetoclax-based backbones with targeted inhibitors of FLT3, IDH1/2, menin-dependent transcriptional programs, and other disease-specific vulnerabilities. At the same time, adverse-risk entities such as TP53-mutated AML continue to show limited benefit from venetoclax-based therapy, underscoring the need for alternative therapeutic frameworks. This review summarizes the clinical impact of venetoclax-based therapy, the biological and clinical mechanisms underlying treatment failure, and emerging strategies designed to improve outcomes after or beyond venetoclax exposure. We particularly highlight molecularly guided triplet regimens, menin inhibition, salvage approaches after hypomethylating-agent/venetoclax failure, measurable residual disease-guided treatment adaptation, and unresolved challenges in trial design, toxicity management, and patient selection. Understanding AML therapy through the lens of the post-venetoclax era may provide a practical framework for integrating targeted agents into precision treatment algorithms.

*Corresponding author:

Jingxin Zhang
(zhangjx@zzu.edu.cn)

Citation: Zhang H, Zhang S, Zhang J. Therapeutic strategies in the post-venetoclax era of acute myeloid leukemia. *Cancer Plus*. doi: 10.36922/CP026320047

Received: August 5, 2026

Revised: September 20, 2026

Accepted: September 29, 2026

Published online: October 13, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Keywords: Acute myeloid leukemia; Venetoclax; Hypomethylating agents; Triplet therapy; Targeted therapy; Menin inhibitors

1. Introduction

Acute myeloid leukemia (AML) is a biologically heterogeneous hematologic malignancy characterized by clonal expansion of immature myeloid progenitors, impaired differentiation, and variable sensitivity to therapy.¹ For decades, intensive cytarabine-

and anthracycline-based induction chemotherapy represented the central therapeutic platform for medically fit adults, whereas older patients or those with significant comorbidities were commonly treated with lower-intensity approaches such as hypomethylating agents or low-dose cytarabine.^{2,3} Although this historical framework remains relevant, it has become increasingly insufficient for a disease now defined by recurrent genetic lesions, measurable residual disease dynamics, clonal evolution, and patient-specific tolerance to therapy.² Contemporary AML management therefore requires a therapeutic model that integrates disease biology, treatment intensity, molecular targetability, and resistance risk.

The development of venetoclax-based lower-intensity therapy has been one of the most important advances in AML treatment. Venetoclax is a selective inhibitor of the anti-apoptotic protein BCL-2 and acts by lowering the apoptotic threshold of leukemic cells.⁴ When combined with azacitidine, venetoclax significantly improved remission rates and overall survival compared with azacitidine alone in previously untreated patients with AML who were ineligible for intensive chemotherapy.⁵ The phase III VIALE-A trial established azacitidine plus venetoclax as a major standard-of-care regimen in this patient population, demonstrating that targeted modulation of mitochondrial apoptosis could be successfully incorporated into a lower-intensity clinical strategy.⁵ This changed not only the treatment of older or unfit patients, but also the conceptual framework of AML therapy by positioning venetoclax as a backbone upon which additional targeted agents could be layered.

However, the success of venetoclax-based therapy has also exposed a new set of clinical problems. A substantial fraction of patients fail to achieve durable remission, and most responders ultimately relapse.^{5,6} Outcomes after failure of hypomethylating-agent/venetoclax therapy are poor, and optimal salvage strategies remain undefined.⁷ In this context, the term “post-venetoclax era” should not be understood narrowly as the sequence of therapies administered after venetoclax failure. Rather, it describes a broader therapeutic phase in AML, in which venetoclax exposure has become common, resistance patterns are increasingly recognized, and new treatment strategies must account for prior BCL-2 inhibition, molecular evolution, and residual clonal architecture.

Despite the clinical success of venetoclax-based therapy, primary resistance and relapse remain common and represent major barriers to durable disease control.⁸ Resistance is biologically heterogeneous and may involve altered apoptotic dependence, lineage plasticity, activation of proliferative signaling pathways, metabolic

adaptation, and clonal evolution. These mechanisms can reduce sustained reliance on BCL-2 and allow resistant subpopulations to persist or expand under treatment pressure. Importantly, the clinical implications of resistance extend beyond treatment failure itself, because the molecular and phenotypic landscape at relapse may differ substantially from that observed at diagnosis. This provides a strong rationale for repeat molecular assessment and for the development of resistance-adapted therapeutic strategies, which are discussed in detail in subsequent sections.

The therapeutic response to these limitations is increasingly shifting toward molecularly guided combination strategies. Rather than relying on uniform treatment intensification, current approaches seek to integrate genotype-directed agents with established venetoclax-based backbones according to the dominant biological driver of each AML subtype. This framework has supported the development of FLT3-, IDH-, and menin-directed combinations, although the maturity of clinical evidence differs substantially across these approaches. Some targeted agents are already approved in defined molecular and disease settings, whereas many venetoclax-based triplet regimens remain investigational and are supported primarily by early-phase studies.⁹ This distinction between established therapy and emerging combinations is increasingly important in defining treatment strategies in the post-venetoclax era.

Among emerging targeted approaches, menin inhibition is particularly relevant to the post-venetoclax era. KMT2A-rearranged and NPM1-mutated AML are characterized by aberrant transcriptional programs involving HOXA/MEIS1 and menin-KMT2A-dependent leukemogenic circuitry.^{10,11} Menin inhibitors such as revumenib and ziftomenib have demonstrated clinical activity in relapsed or refractory genetically defined AML subsets, providing a new therapeutic class that may be integrated into both salvage and frontline combination settings.^{10,11} Their development illustrates how AML therapy is increasingly moving beyond broad cytotoxic or epigenetic approaches toward genotype-directed disruption of transcriptional dependencies.

At the same time, important therapeutic gaps remain in biologically adverse AML subsets. TP53-mutated AML is a particularly prominent example, as initial responses to venetoclax-containing therapy frequently fail to translate into durable remission or prolonged survival.¹² This contrasts with several molecularly defined AML subsets in which targeted therapies have increasingly expanded treatment options. The persistent poor outcomes of TP53-mutated and other adverse-risk AML therefore highlight

the limitations of simply intensifying venetoclax-based therapy and underscore the need for alternative treatment paradigms.

In this review, we discuss therapeutic strategies in the post-venetoclax era of AML. We first summarize the clinical role of hypomethylating-agent/venetoclax therapy and its limitations as a new treatment backbone. We then examine the biological and clinical mechanisms of venetoclax resistance, with emphasis on lineage plasticity, apoptotic rewiring, signaling pathway activation, clonal evolution, and adverse-risk genotypes. Next, we review

emerging molecularly guided triplet strategies, treatment options after venetoclax failure, the expanding role of menin inhibitors, and persistent unmet needs in TP53-mutated and other high-risk AML subsets. Finally, we consider how measurable residual disease, adaptive trial designs, and integrated molecular monitoring may guide the next generation of AML treatment algorithms (Figure 1).

1.1. Literature search strategy

In this narrative review, relevant literature was identified primarily through searches of PubMed/MEDLINE using

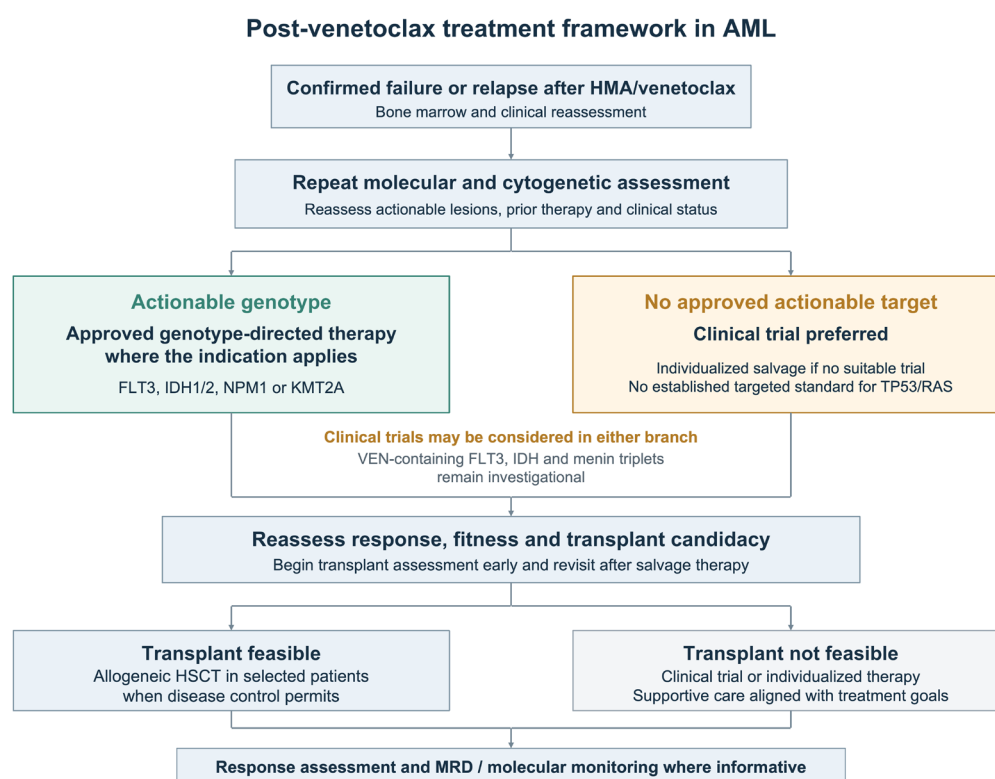


Figure 1. Proposed treatment framework after hypomethylating agent plus venetoclax failure in acute myeloid leukemia. Following confirmation of refractory disease or relapse, repeat molecular and cytogenetic assessment guides consideration of approved genotype-directed therapy, where the relevant indication applies, or clinical-trial enrollment. Clinical trials should be considered in either branch; venetoclax-containing FLT3-, IDH-, and menin-directed triplets remain investigational. In the absence of a suitable trial, salvage therapy is individualized according to disease biology, prior treatment exposure, patient fitness, and treatment goals. Transplant assessment should begin early and be revisited after salvage therapy, with allogeneic hematopoietic stem cell transplantation considered in selected patients when disease control and fitness permit. Response assessment and measurable residual disease or molecular monitoring inform subsequent management where appropriate. This framework represents a proposed clinical approach rather than a validated treatment algorithm, and approval in relapsed or refractory disease does not establish efficacy specifically after HMA/venetoclax failure. Menin inhibitor indications: Revumenib is FDA-approved for relapsed or refractory acute leukemia with a KMT2A translocation in patients aged ≥ 1 year, and for relapsed or refractory AML with a susceptible NPM1 mutation in patients aged ≥ 1 year who have no satisfactory alternative treatment options. Ziftomenib is FDA-approved for adults with relapsed or refractory AML with a susceptible NPM1 mutation who have no satisfactory alternative treatment options. Abbreviations: AML: Acute myeloid leukemia; FDA: U.S. Food and Drug Administration; HMA: Hypomethylating agent; HSCT: Hematopoietic stem cell transplantation; MRD: Measurable residual disease; VEN: Venetoclax.

combinations of the terms “acute myeloid leukemia,” “venetoclax,” “hypomethylating agents,” “venetoclax resistance,” “FLT3,” “IDH1,” “IDH2,” “menin inhibitor,” “revumenib,” “ziftomenib,” “TP53,” “triplet therapy,” “measurable residual disease,” and “salvage therapy.” The literature search primarily covered publications from January 2018 through September 2026, with earlier landmark studies included when necessary to provide historical or mechanistic context. Priority was given to randomized clinical trials, prospective clinical studies, regulatory approval data, large retrospective cohorts, major consensus guidelines, and mechanistically relevant translational studies. Additional references were identified from the bibliographies of key publications. Because this was a narrative rather than systematic review, no formal meta-analytic or risk-of-bias assessment was performed.

2. Hypomethylating agent or venetoclax as a new therapeutic backbone

The combination of hypomethylating agents (HMAs) and venetoclax has reshaped the treatment paradigm for older or medically unfit patients with newly diagnosed AML.^{13,14} Before the venetoclax era, lower-intensity therapy with azacitidine, decitabine, or low-dose cytarabine provided modest response rates and limited survival benefit for patients who were not candidates for intensive induction chemotherapy.^{2,3} The addition of venetoclax to HMAs changed this therapeutic expectation by transforming a historically palliative approach into a remission-inducing platform. Early phase studies showed that venetoclax combined with azacitidine or decitabine produced encouraging response rates in elderly patients with AML, establishing the biological and clinical rationale for subsequent randomized evaluation.¹⁵ The phase III VIALE-A trial then demonstrated that azacitidine plus venetoclax significantly improved composite complete remission rates and overall survival compared with azacitidine alone in treatment-naïve patients who were ineligible for intensive chemotherapy.⁵ Long-term follow-up further confirmed the durability of the survival benefit and did not reveal new safety signals, supporting the regimen as a standard lower-intensity backbone in this population.¹⁶

The clinical importance of HMA/venetoclax therapy extends beyond its efficacy in older or unfit patients.¹⁷ Conceptually, this regimen introduced a new therapeutic architecture for AML: a tolerable epigenetic-apoptotic backbone that can be adapted according to disease genetics, response depth, comorbidities, and treatment goals. Venetoclax targets BCL-2-dependent survival, whereas HMAs may increase apoptotic priming and

modify transcriptional programs that sensitize leukemic cells to mitochondrial apoptosis.^{18,19} This mechanistic complementarity helps explain why the combination is substantially more active than either class alone. In clinical practice, HMA/venetoclax has therefore become not only a frontline regimen for intensive-ineligible AML, but also a reference platform for testing genotype-directed triplets and response-adapted strategies.^{19,20}

Another important contribution of HMA/venetoclax therapy is its ability to produce deep remissions in a subset of patients. In an exploratory analysis of VIALE-A, patients who achieved composite complete remission with measurable residual disease (MRD) below 10^{-3} had longer duration of remission, event-free survival, and overall survival than responding patients with persistent MRD.²¹ These findings suggest that depth of response remains clinically meaningful even in lower-intensity therapy and that MRD assessment may help refine post-remission management. However, the role of MRD in venetoclax-based treatment is still evolving. Unlike intensive chemotherapy, where MRD has been extensively incorporated into risk-adapted decision-making, the optimal timing, assay type, and clinical actionability of MRD during HMA/venetoclax therapy remain less clearly defined. This uncertainty is particularly relevant when deciding whether to continue indefinite therapy, reduce venetoclax duration, proceed to allogeneic transplantation, or intensify treatment in patients with molecular persistence.

Despite its impact, HMA/venetoclax therapy has several intrinsic limitations. First, it is not curative for most patients.²² Many patients relapse despite achieving initial remission, and survival after HMA/venetoclax failure is generally poor.^{7,23} Second, the regimen is associated with clinically relevant myelosuppression, prolonged cytopenias, infectious complications, and frequent need for dose or schedule modifications.^{24,25} These toxicities are manageable but require careful bone marrow assessment, treatment delays, venetoclax duration adjustments, and supportive care.²⁵ Real-world analyses suggest that schedule modifications can be used to manage cytopenias without necessarily compromising outcomes, but they also highlight the practical complexity of delivering this regimen outside clinical trials.^{26,27} Thus, HMA/venetoclax should not be viewed as a low-toxicity therapy simply because it is lower intensity than induction chemotherapy.

Third, the benefits of HMA/venetoclax are not uniform across AML subgroups.²⁸ Patients with *NPM1* or *IDH1/2* mutations may experience relatively favorable responses, whereas those with *TP53* mutations, complex karyotype, or signaling pathway activation often have shorter remission duration and inferior survival.^{24,29,30} This molecular

heterogeneity argues against treating HMA/venetoclax as a universal solution for intensive-ineligible AML. Instead, it should be considered a backbone whose adequacy depends on the biological context. In favorable molecular subsets, the doublet may provide meaningful disease control and serve as a bridge to transplantation in selected patients.³⁰ In adverse-risk subsets, particularly TP53-mutated AML, the doublet may increase remission rates without overcoming the fundamental biology of treatment resistance.²⁹

These limitations explain why the field is now moving beyond the initial question of whether HMA/venetoclax is superior to HMA alone. The more relevant question in the post-venetoclax era is how this backbone should be optimized, combined, discontinued, sequenced, or replaced. For some patients, optimization may involve individualized venetoclax scheduling to reduce cytopenias. For others, the key strategy may be the addition of a molecularly targeted third agent, such as a FLT3 inhibitor, IDH inhibitor, or menin inhibitor.³¹ In patients who relapse after HMA/venetoclax, prior exposure to BCL-2 inhibition must be incorporated into salvage decision-making.^{32,33} Therefore, HMA/venetoclax represents both a major therapeutic advance and the starting point for a new set of clinical challenges that define contemporary AML treatment.

3. Mechanisms of primary and acquired resistance to venetoclax

Although HMA/venetoclax therapy has substantially improved outcomes for older or intensive-ineligible patients with AML, resistance remains a major limitation.²² Resistance may be present at diagnosis, emerge under therapeutic pressure, or become clinically apparent after an initial remission.^{34,35} Importantly, venetoclax resistance is not driven by a single mechanism. Instead, it reflects convergent biological adaptations involving apoptotic rewiring, lineage-associated drug tolerance, signaling pathway activation, metabolic plasticity, leukemia stem cell persistence, and clonal evolution.^{34,36,37} Understanding these mechanisms is essential for the rational design of post-venetoclax therapeutic strategies.

A central mechanism of resistance is loss of BCL-2 dependence. Venetoclax selectively inhibits BCL-2, but AML cells can escape apoptosis by shifting survival dependence toward alternative anti-apoptotic proteins, particularly MCL-1 and BCL-XL.³⁸⁻⁴⁰ Increased MCL-1 expression or activity can reduce venetoclax sensitivity, whereas co-targeting MCL-1 or suppressing MCL-1 through upstream pathways may restore apoptotic priming in resistant AML models.^{37,41-44} These findings

provide a mechanistic rationale for combination strategies that indirectly or directly counteract MCL-1-mediated resistance. However, because MCL-1 is also essential for normal tissue homeostasis, especially in hematopoietic and cardiac contexts, therapeutic exploitation of this vulnerability requires careful attention to toxicity and therapeutic index.⁴⁵

Lineage state is another important determinant of venetoclax response. Monocytic differentiation has been associated with relative resistance to venetoclax-based therapy. Pei and colleagues⁶ showed that monocytic AML subclones exhibit reduced BCL-2 expression, increased MCL-1 dependence, and resistance to venetoclax plus azacitidine. This resistance may reflect pre-existing lineage heterogeneity or treatment-driven selection of monocytic subpopulations.⁴⁶ Clinically, this suggests that blast percentage and diagnostic genotype alone may be insufficient to predict response; the developmental state and lineage composition of leukemic cells may also influence therapeutic sensitivity. Monocytic features should therefore be viewed as a biological warning signal rather than an absolute predictor of treatment failure.^{6,47}

Genetic lesions that activate proliferative and survival signaling pathways further contribute to venetoclax resistance. FLT3-ITD, RAS pathway mutations, and PTPN11 mutations have been linked to reduced sensitivity or early relapse after venetoclax-based treatment.^{22,48} These lesions may promote alternative anti-apoptotic programs, enhance mitochondrial adaptation, and sustain leukemic proliferation despite BCL-2 inhibition. Their clinical relevance is particularly important because they provide actionable targets for rational combination therapy. The emergence or persistence of FLT3- or RAS-pathway alterations after HMA/venetoclax therapy supports repeat molecular profiling at relapse and provides a rationale for integrating kinase-directed agents into venetoclax-based regimens.

TP53-mutated AML represents a distinct resistance context.⁴⁹ Although venetoclax plus azacitidine can increase remission rates in adverse-risk AML, patients with TP53 mutations and poor-risk cytogenetics generally experience short remission duration and limited survival benefit.^{29,50-52} This indicates that initial cytorreduction does not necessarily overcome the underlying biology of genomic instability, complex karyotype, impaired apoptotic regulation, and rapid clonal adaptation. Accordingly, TP53-mutated AML should not be managed simply as a subgroup expected to benefit from venetoclax intensification. It requires dedicated therapeutic strategies and clinical trial designs that address adverse-risk biology directly.

Metabolic plasticity and leukemia stem cell persistence also influence venetoclax response.⁵³ Azacitidine plus venetoclax can disrupt amino acid metabolism and oxidative phosphorylation in AML stem/progenitor populations, providing a mechanistic basis for its clinical activity.⁵⁴⁻⁵⁶ However, resistant cells may maintain mitochondrial fitness through alternative metabolic programs, altered substrate utilization, or compensatory survival pathways.^{57,58} Residual stem-like compartments may therefore persist despite morphologic remission and later drive relapse.³⁶ Consistent with this concept, apoptotic dependencies within AML stem and progenitor compartments have been associated with clinical response to azacitidine/venetoclax.⁵⁹

Collectively, these mechanisms suggest that venetoclax resistance is best understood as a failure of sustained BCL-2 dependence. Some AML cells are intrinsically less dependent on BCL-2 because of lineage state or adverse genotype, whereas others acquire alternative survival programs during therapy. This concept has direct therapeutic implications. Signaling-driven resistance supports FLT3- or pathway-directed combinations; transcriptionally defined AML subsets may benefit from menin inhibitor-based strategies; and TP53-mutated AML may require non-venetoclax-centered approaches. Thus, resistance biology provides the rationale for moving from a uniform HMA/venetoclax doublet toward molecularly guided and resistance-adapted therapy.

4. Molecularly guided triplet therapy

An important consideration in the evolving post-venetoclax treatment landscape is the level of evidence supporting each therapeutic strategy. HMA/venetoclax represents an established frontline backbone for appropriately selected intensive-ineligible patients, whereas several genotype-directed agents have regulatory approval in defined molecular and disease settings.⁶⁰ In contrast, most venetoclax-based triplet regimens remain supported primarily by phase I/II or single-arm studies and should therefore be considered promising rather than established standards. This distinction is particularly important when interpreting high response rates from early-phase studies, which may not necessarily translate into improved long-term survival in randomized comparisons.

The recognition that HMA/venetoclax is an effective but incomplete therapeutic backbone has accelerated the development of molecularly guided triplet regimens in AML.^{30,31} The central rationale is not simply to intensify therapy by adding a third drug, but to match the additional agent to a dominant biological driver or resistance pathway.²² In this model, HMA/venetoclax provides a

broadly active epigenetic-apoptotic platform, whereas the third agent targets a genotype-defined dependency such as FLT3 signaling, mutant IDH-driven metabolism, or menin-dependent transcriptional addiction.^{31,61-64} This strategy is particularly relevant in the post-venetoclax era, because many of the lesions selected or enriched after venetoclax exposure are themselves therapeutically actionable.

FLT3-mutated AML provides one of the strongest examples of this approach. *FLT3*-ITD and *FLT3*-TKD mutations activate proliferative and survival signaling pathways and have been associated with inferior durability of response to HMA/venetoclax therapy.⁴⁸ These lesions may promote resistance through enhanced kinase signaling, increased MCL-1 expression, and reduced dependence on BCL-2-mediated apoptosis. Combining *FLT3* inhibition with HMA/venetoclax is therefore mechanistically attractive. Early studies of triplet therapy using an HMA, venetoclax, and an *FLT3* inhibitor showed encouraging activity in *FLT3*-mutated AML, including in relapsed or refractory settings.⁶⁵ More recently, azacitidine, venetoclax, and gilteritinib demonstrated high response rates in both newly diagnosed and relapsed or refractory *FLT3*-mutated AML, supporting the feasibility of integrating a potent *FLT3* inhibitor into a venetoclax-based lower-intensity backbone.⁶⁶ These data suggest that *FLT3*-mutated AML may be better approached through simultaneous suppression of apoptotic and kinase-dependent survival programs rather than through sequential monotherapies.

Direct comparisons between molecularly guided triplets and optimized doublets remain limited, and the available evidence should therefore be interpreted according to trial design. In *FLT3*-mutated AML, venetoclax plus azacitidine achieved a composite complete remission rate of approximately 67% and a median overall survival of 12.5 months in a pooled biomarker analysis, whereas azacitidine, venetoclax, and gilteritinib produced composite complete remission rates exceeding 90% in prospective phase II studies, with recent long-term follow-up reporting a median overall survival of approximately 29.7 months in newly diagnosed patients. However, these results are not derived from randomized head-to-head comparisons, and differences in patient selection, transplant rates, and supportive care preclude definitive conclusions regarding incremental survival benefit. Notably, the randomized LACEWING trial demonstrated that adding gilteritinib to azacitidine increased composite remission from 26.5% to 58.1% but did not improve median overall survival (8.87 vs 9.82 months), illustrating that higher remission rates do not necessarily translate into longer survival.⁶⁷ A similar distinction is evident in *IDH1*-mutated AML. The randomized AGILE trial established ivosidenib

plus azacitidine as an effective doublet, with a complete remission rate of approximately 47% and median overall survival of 24.0 months, subsequently extending to 29.3 months with longer follow-up.⁶⁸ By comparison, early-phase ivosidenib–venetoclax–azacitidine therapy produced composite complete remission rates of approximately 90%, with 63% of evaluable patients achieving MRD-negative remission and a reported median overall survival of 42 months. Although these findings suggest that triplet therapy may increase response depth, the small cohort size and non-randomized design prevent direct attribution of the apparent survival advantage to the third agent. Likewise, azacitidine, venetoclax, and revumenib achieved an overall response rate of 88.4% and a composite complete remission rate of 81.4% in older patients with newly diagnosed *NPM1*-mutated or *KMT2A*-rearranged AML, but randomized comparison with an optimized venetoclax-based doublet is still lacking. Collectively, current evidence supports the biological and clinical promise of genotype-directed triplets, but randomized studies remain necessary to determine whether deeper remission and greater molecular clearance translate into durable overall survival benefit.

Nevertheless, FLT3-directed triplets illustrate both the promise and complexity of this strategy.³¹ The addition of a FLT3 inhibitor may deepen responses and suppress early outgrowth of *FLT3*-mutant clones, but it also increases the need for careful management of myelosuppression, infections, drug-drug interactions, and dose interruptions.^{31,69} In clinical practice, the therapeutic goal is not maximal continuous exposure to all three agents, but sufficient target inhibition with tolerable marrow recovery.³¹ This is especially important for older patients, who may benefit from effective lower-intensity therapy but are also vulnerable to prolonged cytopenias. Therefore, future development of FLT3-directed triplets should focus not only on response rates, but also on duration of remission, MRD clearance, transplant feasibility, post-transplant maintenance, and optimal venetoclax scheduling.

IDH1- and *IDH2*-mutated AML represents another biologically rational setting for triplet therapy.^{31,70} *IDH* mutations produce the oncometabolite 2-hydroxyglutarate, impair differentiation, and create targetable metabolic and epigenetic dependencies. HMA/venetoclax already appears highly active in *IDH1/2*-mutated AML, with analyses from treatment-naïve cohorts showing favorable responses and survival in this molecular subgroup.⁶¹ At the same time, *IDH* inhibitors such as ivosidenib and enasidenib can induce differentiation and have established activity in *IDH*-mutated AML. The combination of ivosidenib with azacitidine improved outcomes compared with azacitidine

alone in newly diagnosed *IDH1*-mutated AML, confirming that targeted differentiation therapy can be effectively paired with epigenetic treatment.⁷¹ Building on this logic, early-phase studies of ivosidenib with venetoclax with or without azacitidine demonstrated encouraging activity and high MRD-negative remission rates in *IDH1*-mutated myeloid malignancies.⁷² These data support the concept that *IDH*-directed triplets may simultaneously target mutant metabolism, apoptotic priming, and epigenetic dysregulation.

However, *IDH*-mutated AML also raises a key question: whether every molecularly defined patient requires triplet therapy upfront.^{30,73} Because HMA/venetoclax alone can be highly effective in *IDH*-mutated AML, and because *IDH* inhibitor-based doublets also have meaningful activity, the incremental benefit of adding all three agents must be balanced against toxicity, cost, treatment burden, and sequencing flexibility.^{61,71} For some patients, triplet therapy may be most appropriate when rapid disease control, deep molecular clearance, or bridge to transplantation is desired.⁷³ For others, sequential use of HMA/venetoclax and *IDH* inhibition may preserve future options. Thus, *IDH*-mutated AML exemplifies the need to define triplet therapy not merely by feasibility, but by clinical context and measurable improvement over optimized doublet strategies.

Menin inhibitor-based triplets represent an emerging genotype-directed combination strategy for *KMT2A*-rearranged and *NPM1*-mutated AML.⁷⁴ Importantly, although menin inhibitors have now entered clinical practice as approved therapies in selected relapsed or refractory molecularly defined disease, their incorporation into frontline HMA/venetoclax triplet regimens remains investigational. Early clinical studies of azacitidine, venetoclax, and revumenib have shown high response rates in older patients with newly diagnosed *NPM1*-mutated or *KMT2A*-rearranged AML, supporting the feasibility of this approach. However, these data are derived from early-phase studies, and randomized comparisons are required to determine whether adding a menin inhibitor to an optimized HMA/venetoclax backbone improves remission durability and overall survival.

Despite the enthusiasm around triplets, several limitations must be emphasized. First, many data supporting triplet therapy come from early-phase, single-arm, or highly selected studies. Randomized comparisons against optimized doublets are needed to determine whether triplets truly improve survival rather than simply increasing remission rates.^{30,31,73} Second, toxicity is not a secondary issue. Prolonged cytopenias, infections, differentiation syndrome, QTc prolongation,

gastrointestinal toxicity, and overlapping drug interactions can substantially affect deliverability. Third, the optimal timing of triplets remains unsettled. Some patients may benefit from frontline triplet therapy, whereas others may be better served by reserving the third agent for MRD persistence, molecular relapse, or overt relapse.^{30,31} Finally, resistance to triplets will inevitably emerge, and post-triplet salvage may be even more challenging if multiple active drug classes have already been used early.³¹

Molecularly guided triplet therapy therefore represents a major step forward, but not a universal solution. Its value will depend on selecting the right patient, the right molecular target, the right treatment phase, and the right schedule. In the post-venetoclax era, the goal is not simply to add more drugs to HMA/venetoclax, but to construct rational combinations that suppress the dominant biology

of each AML subtype while preserving tolerability and future therapeutic options. A practical summary of emerging therapeutic strategies, target populations, biological rationales, and unresolved challenges in the post-venetoclax era is provided in [Table 1](#).

5. Treatment after HMA/venetoclax failure

Disease progression after HMA/venetoclax therapy represents one of the most difficult clinical scenarios in contemporary AML management. Although HMA/venetoclax has improved frontline outcomes for older or intensive-ineligible patients, relapse or refractory disease after this regimen is associated with poor survival and limited therapeutic options. Retrospective studies have consistently shown that outcomes after frontline HMA/venetoclax failure are dismal, with short median survival

Table 1. Therapeutic strategies after venetoclax incorporation in AML

Strategy	Regimens / approaches	Patients	Regulatory / evidence status	Rationale	Challenges
HMA/VEN backbone	Azacitidine or decitabine + VEN	Newly diagnosed older / intensive-ineligible AML	Established therapeutic backbone	Epigenetic–apoptotic targeting	Cytopenias; relapse
FLT3/IDH triplets	HMA + VEN + FLT3 or IDH inhibitor	FLT3- or IDH-mutated AML	Promising early-phase; investigational	Targets signaling or metabolic drivers	Toxicity; scheduling; randomized validation
Menin inhibition	Revumenib	R/R <i>KMT2A</i> -translocated acute leukemia; age ≥ 1 year R/R susceptible <i>NPM1</i> -mutated AML; age ≥ 1 year*	FDA approved in the specified setting	Blocks menin-dependent transcription	Differentiation syndrome; resistance
Menin inhibition	Ziftomenib	R/R susceptible <i>NPM1</i> -mutated AML; adults only*	FDA approved in the specified setting	Blocks menin-dependent transcription	Differentiation syndrome; resistance
Menin triplets	Menin inhibitor + HMA + VEN	Newly diagnosed <i>NPM1</i> -mutated or <i>KMT2A</i> -rearranged AML	Promising early-phase; investigational	Combines transcriptional and apoptotic targeting	Randomized validation needed
Post-failure strategies	Repeat profiling; targeted salvage; HSCT; clinical trials	AML after HMA/VEN failure	Established assessment / HSCT pathways; salvage individualized	Adapts treatment to clonal evolution	Poor prognosis; no uniform salvage standard
TP53/adverse-risk therapy	Investigational immune, p53-directed or cellular approaches	TP53-mutated or other adverse-risk AML	Clinical-trial-only strategies	Addresses resistant disease biology	Limited durability; unmet need

Notes: * Both *NPM1* indications require no satisfactory alternative treatment options. Ziftomenib is not approved for *KMT2A*-rearranged disease. Approval is specific to the stated indication and does not establish efficacy after HMA/VEN failure. VEN-containing triplets remain investigational. Frontline backbones are included for context.

Abbreviations: AML: Acute myeloid leukemia; FDA: U.S. Food and Drug Administration; HMA: Hypomethylating agent; HSCT: Hematopoietic stem cell transplantation; R/R: Relapsed or refractory; VEN: Venetoclax.

and only a minority of patients able to receive effective salvage therapy.^{29,75} This has shifted the clinical question from whether venetoclax-based therapy can induce remission to how patients should be managed once this backbone fails.

The first principle after HMA/venetoclax failure is reassessment of disease biology.^{22,39} AML at relapse should not be assumed to be identical to AML at diagnosis. Prior venetoclax exposure may select for resistant subclones with altered lineage state, emergent kinase signaling, TP53-mutated dominance, RAS pathway activation, or changes in apoptotic dependence.^{38,48,76,77} Therefore, repeat cytogenetic and molecular profiling should be performed whenever feasible.^{23,76} This is particularly important because actionable lesions may emerge or expand at relapse, creating opportunities for genotype-directed salvage therapy. Conversely, loss of a previously dominant target may make continuation or reintroduction of the same targeted strategy less rational.²² In the post-venetoclax era, relapse management should therefore be guided by the current molecular architecture of the disease rather than by baseline genotype alone.

For patients with actionable mutations, targeted therapy-based salvage is often the most rational approach. FLT3-mutated relapse may be treated with a FLT3 inhibitor-containing regimen, particularly gilteritinib-based therapy, either alone or in combination depending on disease burden, prior therapy, and patient fitness.^{65,78} IDH1- or IDH2-mutated relapse may be approached with ivosidenib- or enasidenib-based strategies, especially when the mutation persists or emerges after HMA/venetoclax exposure.^{79,80} For patients with relapsed or refractory NPM1-mutated or KMT2A-translocated disease, menin inhibition has become a clinically available genotype-directed salvage option rather than solely an investigational strategy. Revumenib is FDA-approved for relapsed or refractory KMT2A-translocated acute leukemia⁸¹ and for relapsed or refractory NPM1-mutated AML in patients without satisfactory alternative treatment options,⁸² whereas ziftomenib is approved for adults with relapsed or refractory NPM1-mutated AML lacking satisfactory alternatives.⁸³ These approvals reinforce the importance of repeat molecular profiling after HMA/venetoclax failure, because identification or persistence of menin-dependent disease may directly influence treatment selection.

The role of intensive chemotherapy after HMA/venetoclax failure remains uncertain. Some younger or medically fit patients may still be considered for intensive salvage, especially if they were initially treated with HMA/venetoclax because of disease biology, physician preference, or borderline fitness rather than absolute inability to

tolerate chemotherapy. However, available retrospective data suggest that responses to intensive chemotherapy after HMA/venetoclax failure are limited.^{23,33} A recent analysis reported that only a minority of patients achieved complete remission or incomplete count recovery with intensive chemotherapy after HMA/venetoclax failure, highlighting the difficulty of rescuing disease that has already demonstrated resistance to an epigenetic-apoptotic backbone.⁷ Thus, intensive chemotherapy should not be reflexively used as a default salvage strategy. Its value is greatest when it can serve as a bridge to allogeneic hematopoietic stem cell transplantation or when no actionable targeted option is available.

Allogeneic transplantation remains the only potentially curative strategy for selected patients with relapsed or refractory AML, but its feasibility after HMA/venetoclax failure is often limited by age, comorbidities, resistant disease, and rapid clinical deterioration.^{33,84} For patients who achieve a second remission or meaningful cytoreduction with salvage therapy, transplantation should be considered early rather than delayed until repeated lines of therapy have further reduced fitness.⁸⁵ Venetoclax-based salvage therapy has been used as a bridge to transplantation in relapsed/refractory AML, and some studies suggest that venetoclax plus HMA can induce responses sufficient to proceed to allogeneic transplantation in selected patients.⁸⁵ However, this strategy is more applicable to venetoclax-naïve relapsed/refractory disease than to patients who have already failed frontline HMA/venetoclax. After true HMA/venetoclax failure, reusing the same backbone is unlikely to be effective unless a new targeted agent is added or the clinical context suggests incomplete prior exposure.⁸⁶

Clinical trial enrollment should be considered the preferred option for many patients after HMA/venetoclax failure.²³ This is especially true for patients with TP53-mutated AML, complex karyotype, RAS pathway activation, primary refractory disease, or relapse after short remission.⁸⁷ Novel approaches under investigation include menin inhibitor-based combinations, immune-directed therapies, antibody-drug conjugates, macrophage checkpoint modulation, p53-directed strategies, and rational combinations targeting apoptotic or metabolic dependencies.^{39,49,64,88} Because survival after HMA/venetoclax failure is short, referral to clinical trials should occur early, ideally at the time of molecular relapse, MRD persistence, or first evidence of inadequate response rather than only after overt clinical progression.

Overall, treatment after HMA/venetoclax failure requires a structured and biologically informed approach. The essential steps include confirming relapse or refractory disease, repeating molecular profiling, identifying

targetable lesions, assessing transplant eligibility, and prioritizing clinical trial enrollment whenever feasible. The poor outcomes observed after HMA/venetoclax failure also argue for earlier intervention before frank relapse. MRD persistence, incomplete count recovery with residual disease, or molecular expansion during therapy may provide opportunities to adapt treatment before resistant disease becomes clinically dominant. In this sense, the best strategy for post-venetoclax failure may begin before failure occurs: through molecular monitoring, response-adapted escalation, and rational incorporation of targeted agents in patients at high risk of relapse.

6. Menin inhibitors as a new therapeutic class in the post-venetoclax era

Menin inhibitors have transitioned from investigational agents to an established genotype-directed therapeutic class for selected patients with relapsed or refractory acute leukemia. Revumenib was initially approved by the U.S. Food and Drug Administration (FDA) for relapsed or refractory acute leukemia with a *KMT2A* translocation in adult and pediatric patients aged 1 year and older and subsequently received an additional indication for relapsed or refractory *NPM1*-mutated AML in patients aged 1 year and older who have no satisfactory alternative treatment options.⁸⁹ Ziftomenib has also been approved for adult patients with relapsed or refractory *NPM1*-mutated AML without satisfactory alternative treatment options.⁹⁰ These approvals establish menin inhibition as a clinically available therapeutic strategy rather than solely an emerging investigational concept in molecularly defined AML. Although menin inhibition is now an approved therapeutic strategy in selected relapsed or refractory molecularly defined disease, its incorporation into frontline HMA/venetoclax triplet regimens, MRD-directed treatment, or maintenance remains investigational.

The clinical development of revumenib provided the first major proof-of-concept that menin inhibition can produce meaningful responses in patients with *KMT2A*-rearranged or *NPM1*-mutated acute leukemia. In a first-in-human phase I trial, revumenib induced clinical responses in heavily pretreated patients with these genetic lesions, establishing menin as a tractable therapeutic target in acute leukemia.⁹¹ Subsequent clinical evaluation in relapsed or refractory *KMT2A*-rearranged acute leukemia confirmed high remission rates with a predictable safety profile, further supporting revumenib as a genotype-directed treatment option.⁹² These results are particularly important because *KMT2A*-rearranged AML is often associated with adverse clinical behavior, while relapsed *NPM1*-mutated AML can remain transcriptionally dependent on menin-associated programs despite prior therapy.

Ziftomenib has further expanded the menin inhibitor landscape. In relapsed or refractory AML, ziftomenib demonstrated clinical activity with manageable toxicity, and later data in heavily pretreated *NPM1*-mutated AML showed deep responses and a tolerable safety profile.^{93,94} Notably, differentiation syndrome has emerged as an on-target toxicity of menin inhibition, reflecting the differentiation-inducing mechanism of this therapeutic class. This toxicity is clinically manageable but requires early recognition, corticosteroids, supportive care, and treatment interruption when appropriate. Unlike conventional cytotoxic chemotherapy, menin inhibitors may produce responses through differentiation and transcriptional reprogramming rather than immediate blast clearance, which has implications for response assessment and clinical management.

The relevance of menin inhibitors to the post-venetoclax era lies in their potential to complement or overcome limitations of HMA/venetoclax therapy. *NPM1*-mutated AML frequently responds well to HMA/venetoclax, but relapse still occurs, and persistent molecular disease may identify patients at risk for subsequent progression. Menin inhibition offers a rational strategy for targeting the transcriptional dependency that remains central to *NPM1*-mutated leukemogenesis. In *KMT2A*-rearranged AML, where outcomes remain challenging and relapse risk is high, menin inhibitors may provide a targeted approach that can be integrated with HMA/venetoclax, intensive chemotherapy, or transplant-directed strategies. Early combination studies incorporating menin inhibitors with azacitidine and venetoclax suggest that frontline triplet therapy may be feasible in older patients with *NPM1*-mutated or *KMT2A*-rearranged AML.⁹⁵ However, the optimal timing of menin inhibition—frontline, MRD-directed, post-venetoclax salvage, or post-transplant maintenance—remains unsettled.

Resistance to menin inhibition is already an emerging concern. Somatic *MEN1* mutations at the revumenib-menin interface have been identified in patients with acquired resistance to menin inhibition, demonstrating that direct target-site resistance can develop under therapeutic pressure.⁹⁶ Additional resistance mechanisms may include activation of alternative transcriptional programs, persistence of cooperating mutations, or lineage adaptation. These findings indicate that menin inhibitors, like FLT3 and IDH inhibitors, are unlikely to be curative as single agents for most patients. Rational combinations will be required to deepen responses, delay resistance, and eradicate residual leukemic clones. In this regard, combining menin inhibitors with venetoclax-based therapy is attractive because it pairs transcriptional dependency disruption with apoptotic priming. Yet such combinations

must be evaluated carefully to define dose intensity, cytopenia management, differentiation syndrome risk, and the true incremental benefit over optimized doublets.

Overall, menin inhibitors have established a new genotype-directed treatment paradigm for *KMT2A*-rearranged and *NPM1*-mutated AML. The key questions now extend beyond proof of activity and include optimal sequencing, duration of therapy, management of acquired resistance, and integration with transplantation or MRD-directed treatment. Defining these issues will determine whether menin inhibition can translate high response rates into durable disease control.

7. Persistent unmet needs in *TP53*-mutated and adverse-risk AML

Despite the expanding therapeutic armamentarium in AML, *TP53*-mutated and other adverse-risk disease subsets remain poorly served by current treatment strategies. *TP53*-mutated AML is characterized by genomic instability, frequent complex karyotype, resistance to cytotoxic and lower-intensity therapies, and a high probability of early relapse. Although HMA/venetoclax can induce remissions in a subset of patients, these responses are often short-lived and do not translate into durable survival benefit.^{29,50} In a systematic review and meta-analysis of frontline therapies for *TP53*-mutated AML, outcomes remained poor across intensive chemotherapy, HMA-based therapy, and venetoclax-containing regimens, underscoring the absence of a clearly effective standard approach for this population.⁹⁷

The limited benefit of venetoclax in *TP53*-mutated AML illustrates a broader principle: improving remission rates is not equivalent to overcoming adverse disease biology. In patients with *TP53* mutations and poor-risk cytogenetics, venetoclax plus azacitidine may increase CR/CRi rates compared with azacitidine alone, but remission duration and overall survival remain limited.²⁹ Retrospective analyses have similarly suggested that venetoclax-based therapy does not fundamentally change the natural history of *TP53*-mutated AML.⁵⁰ This distinguishes *TP53*-mutated AML from molecular subsets such as *NPM1*- or *IDH*-mutated AML, where HMA/venetoclax may produce deeper and more durable responses. For *TP53*-mutated disease, the main problem is not simply insufficient apoptotic priming, but the persistence of genetically unstable clones capable of rapid adaptation after initial cyto-reduction.

Several investigational approaches have attempted to address this therapeutic gap, but results have been mixed. Eprenetapopt, a p53-reactivating agent, showed promising activity when combined with azacitidine in early-phase

studies of *TP53*-mutated myelodysplastic syndrome and AML, including responses and molecular remissions in selected patients.^{98,99} However, subsequent development has highlighted the difficulty of translating early signals into definitive survival benefit, particularly in biologically complex high-risk myeloid neoplasms. Similarly, macrophage checkpoint blockade with the anti-CD47 antibody magrolimab generated substantial interest based on early activity in *TP53*-mutated myeloid malignancies, but randomized phase III data did not confirm an overall survival advantage in *TP53*-mutated AML.¹⁰⁰ The discontinuation or failure of several promising strategies emphasizes that *TP53*-mutated AML requires rigorous randomized evaluation and cannot rely on response rate alone as a surrogate for meaningful clinical advance.

Other adverse-risk subsets also remain challenging in the post-venetoclax era. AML with complex karyotype, therapy-related disease, secondary-type mutations, RAS pathway activation, or high-risk signaling lesions may respond initially to HMA/venetoclax yet relapse rapidly.^{101,102} In some of these contexts, molecularly guided triplets may improve depth of response, but their long-term benefit remains uncertain.^{103,104} Moreover, adding more agents to venetoclax-based therapy may increase cytopenias and infection risk without fully eliminating resistant clones.^{104,105} Therefore, adverse-risk AML should not be approached with a uniform escalation strategy. Instead, treatment should be guided by a realistic assessment of disease biology, patient fitness, transplant eligibility, and the likelihood that a given regimen can produce durable disease control.

Allogeneic transplantation remains an important consideration for eligible patients with adverse-risk AML who achieve remission, but relapse after transplant is common in *TP53*-mutated disease.¹⁰⁶ This reality raises the need for better pre-transplant cyto-reduction, MRD-directed decision-making, and post-transplant maintenance approaches.¹⁰⁷ However, the optimal maintenance strategy for *TP53*-mutated AML remains undefined.¹⁰⁶ Trials incorporating novel immune therapies, antibody-based approaches, cellular therapies, synthetic lethal strategies, and agents targeting DNA damage response or mutant p53 biology are needed, but they should be designed with endpoints that capture durability, MRD clearance, and survival rather than early remission alone.¹⁰⁸

Overall, *TP53*-mutated and adverse-risk AML define the limits of the current post-venetoclax paradigm. For these patients, the field may need to move beyond simply adding targeted agents to HMA/venetoclax and instead develop treatment frameworks specifically designed

around genomic instability, clonal heterogeneity, immune resistance, and relapse prevention. The unmet need is not only for more active drugs, but for strategies capable of converting transient cyto-reduction into durable disease control.

8. Future directions

The next phase of AML therapy will require a shift from fixed treatment categories toward adaptive, biology-informed algorithms. In the post-venetoclax era, the central challenge is not only to develop more active combinations, but also to determine when venetoclax-based therapy is sufficient, when it should be intensified, when it should be discontinued, and when an alternative therapeutic framework is needed. This will require integration of baseline genetics, dynamic molecular monitoring, MRD assessment, treatment tolerance, and clonal evolution into real-time clinical decision-making.

MRD-guided treatment adaptation is likely to become increasingly important. The European LeukemiaNet (ELN) recommendations have established MRD as a clinically meaningful biomarker in AML, with applications in prognostication, response assessment, relapse prediction, and transplant decision-making.¹⁰⁹ In venetoclax-based lower-intensity therapy, MRD negativity has been associated with improved duration of remission and survival, but several practical questions remain unresolved.²¹ These include the optimal timing of MRD testing, the relative value of flow cytometry versus molecular assays, the interpretation of persistent mutations associated with clonal hematopoiesis, and the appropriate intervention for molecular persistence or molecular relapse. Future trials should incorporate MRD not only as a prognostic endpoint, but also as a trigger for therapeutic adaptation, such as adding a targeted agent, shortening or extending venetoclax exposure, proceeding to transplantation, or initiating maintenance therapy.

Another priority is optimizing treatment intensity and duration. HMA/venetoclax therapy is effective but often limited by prolonged cytopenias and infectious complications. Real-world data suggest that shorter venetoclax schedules may maintain efficacy in selected patients while improving tolerability, although prospective validation is still needed.¹¹⁰ This issue becomes even more important in triplet regimens, where prolonged myelosuppression may compromise deliverability. Future studies should therefore evaluate not only which drugs to combine, but also how to schedule them. Intermittent venetoclax dosing, response-adapted cycle modification, and genotype-specific dose adjustment may become essential components of precision therapy.

Trial design must also evolve. Traditional single-arm studies can identify promising regimens, but randomized comparisons are needed to determine whether triplets improve survival over optimized doublets. Adaptive platform trials may be particularly valuable in AML because they can assign patients to molecularly defined treatment arms, incorporate emerging biomarkers, and rapidly test combinations in biologically selected populations.¹¹¹ Such designs are especially important for smaller genomic subsets, including *KMT2A*-rearranged, *NPM1*-mutated relapsed disease, *TP53*-mutated AML, and RAS pathway-activated AML. In parallel, real-world evidence will be needed to determine whether regimens developed in specialized centers can be safely delivered to older patients with comorbidities in routine practice.

Special populations also require dedicated treatment strategies in the post-venetoclax era. In pediatric AML, experience with venetoclax-based therapy remains substantially more limited than in adults. Small retrospective and early clinical series have demonstrated the feasibility of incorporating venetoclax into frontline or salvage regimens in children and adolescents, with encouraging early remission rates, but the limited sample sizes and heterogeneous treatment backbones preclude definitive conclusions regarding long-term benefit.^{112,113} Pediatric-specific trials are therefore needed because disease biology, mutational spectra, treatment intensity, transplant use, and long-term toxicity differ substantially from those in older adults. At the opposite end of the age spectrum, frail elderly patients with multiple comorbidities represent another poorly defined population. Although azacitidine plus venetoclax remains an important option for patients considered unfit for intensive chemotherapy, frailty and comorbidity burden can substantially influence treatment delivery, tolerance, and the likelihood of receiving subsequent therapy.^{114,115} In these patients, treatment selection should incorporate functional status, comorbidity burden, infection risk, and quality-of-life goals, with greater emphasis on individualized venetoclax duration, dose modification, and supportive care rather than indiscriminate treatment intensification.

Finally, the post-venetoclax era should be defined by earlier recognition of treatment failure. Waiting for overt morphologic relapse may miss the window in which resistant clones are still therapeutically controllable. Serial molecular profiling, MRD surveillance, and early reassessment of marrow response may allow clinicians to intervene before resistant disease becomes clinically dominant. The ultimate goal is to transform AML therapy from a sequence of static regimens into an adaptive system that anticipates resistance, targets emerging vulnerabilities,

and preserves patient fitness for subsequent curative strategies.

9. Conclusions

Venetoclax combined with hypomethylating agents has transformed the management of older or intensive-ineligible patients with AML and established a new lower-intensity therapeutic backbone. However, this success has also created a new clinical landscape in which venetoclax exposure is common, resistance patterns are increasingly recognized, and outcomes after treatment failure remain poor. The post-venetoclax era therefore represents more than the management of relapse after venetoclax; it reflects a broader shift toward resistance-aware, molecularly guided, and response-adapted therapy.

Emerging strategies are beginning to address this challenge. FLT3-, IDH-, and menin-directed triplets aim to deepen responses by combining apoptotic priming with genotype-specific targeting. Menin inhibitors have introduced a new therapeutic class for *KMT2A*-rearranged and *NPM1*-mutated AML, while post-failure approaches increasingly depend on repeat molecular profiling and clinical trial enrollment. At the same time, *TP53*-mutated and adverse-risk AML continue to expose the limits of venetoclax-based treatment and highlight the need for alternative therapeutic paradigms.

Future progress will depend on selecting the right treatment backbone for the right biological context, defining when triplet therapy is truly superior to optimized doublets, and incorporating MRD and clonal monitoring into therapeutic decision-making. The goal should not be to add more agents indiscriminately, but to construct rational strategies that prolong remission, prevent resistant relapse, preserve tolerability, and ultimately improve survival. In this framework, the post-venetoclax era offers both an opportunity and a challenge: to convert the initial success of venetoclax-based therapy into durable, individualized disease control for a broader range of patients with AML.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Conceptualization: Jingxin Zhang

Visualization: Jingxin Zhang

Writing—original draft: Huan Zhang, Jingxin Zhang

Writing—review & editing: Huan Zhang, Shijie Zhang

All authors read and approved the submitted version.

Ethical approval and consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data

Not applicable.

References

1. Zhang H, Zhang J. Comprehensive omics profiling in acute myeloid leukemia: From molecular landscape to clinical translation. *Curr Proteom*. 2025;22(3):100028. doi: 10.1016/j.curpro.2025.100028
2. Zwaan CM, Tasian SK, Aplenc R, *et al*. Diagnosis and management of AML in pediatric patients: consensus recommendations from an international expert panel. *Blood*. 2026;147(14):1532-1561. doi: 10.1182/blood.2024027904
3. Döhner H, Wei AH, Appelbaum FR, *et al*. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377. doi: 10.1182/blood.2022016867
4. Konopleva M, Pollyea DA, Potluri J, *et al*. Efficacy and Biological Correlates of Response in a Phase II Study of Venetoclax Monotherapy in Patients with Acute Myelogenous Leukemia. *Cancer Discov*. 2016;6(10):1106-1117. doi: 10.1158/2159-8290.Cd-16-0313
5. DiNardo CD, Jonas BA, Pullarkat V, *et al*. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N Engl J Med*. 2020;383(7):617-629. doi: 10.1056/NEJMoa2012971
6. Pei S, Pollyea DA, Gustafson A, *et al*. Monocytic Subclones Confer Resistance to Venetoclax-Based Therapy in Patients with Acute Myeloid Leukemia. *Cancer Discov*. 2020;10(4):536-551. doi: 10.1158/2159-8290.Cd-19-0710
7. Chin KK, Valtis Y, Derkach A, *et al*. Intensive chemotherapy after hypomethylating agent and venetoclax in adult acute myeloid leukemia. *Blood Neoplasia*. 2024;1(4):100038. doi: 10.1016/j.bneo.2024.100038

8. Dhakal P, Bates M, Tomasson MH, Sutamtewagul G, Dupuy A, Bhatt VR. Acute myeloid leukemia resistant to venetoclax-based therapy: What does the future hold? *Blood Rev.* 2023;59:101036.
doi: 10.1016/j.blre.2022.101036
9. Santambrogio E, Castellino A, Audisio E, *et al.* Hypomethylating Agents and Venetoclax Based Triplets Targeting FLT3, IDH and KMT2A in Acute Myeloid Leukemia: Current Studies and Challenges of a Tailored Approach. *Cancers.* 2026;18(4):615.
doi: 10.3390/cancers18040615
10. Candoni A, Coppola G. A 2024 Update on Menin Inhibitors. A New Class of Target Agents against KMT2A-Rearranged and NPM1-Mutated Acute Myeloid Leukemia. *Hematol Rep.* 2024;16(2):244-254.
doi: 10.3390/hematolrep16020024
11. Wang ES, Erba HP, Zeidan AM, *et al.* Ziftomenib with venetoclax and azacitidine in relapsed/refractory NPM1-mutated acute myeloid leukemia. *Blood J.* 2026.
doi: 10.1182/blood.2026034043
12. Zhao P, Urrutia S. Bridging TP53-mutated myelodysplastic syndrome/acute myeloid leukemia to transplant: is venetoclax part of the answer? *Curr Opin Hematol.* 2026.
doi: 10.1097/moh.0000000000000949
13. Abaza Y, Winer ES, Murthy GSG, *et al.* Clinical outcomes of hypomethylating agents plus Venetoclax as frontline treatment in patients 75 years and older with acute myeloid leukemia: Real-world data from eight US academic centers. *Am J Hematol.* 2024;99(4):606-614.
doi: 10.1002/ajh.27231
14. Vachhani P, Flahavan EM, Xu T, *et al.* Venetoclax and Hypomethylating Agents as First-line Treatment in Newly Diagnosed Patients with AML in a Predominately Community Setting in the US. *Oncologist.* 2022;27(11):907-918.
doi: 10.1093/oncolo/oyac135
15. DiNardo CD, Pratz K, Pullarkat V, *et al.* Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood.* 2019;133(1):7-17.
doi: 10.1182/blood-2018-08-868752
16. Pratz KW, Jonas BA, Pullarkat V, *et al.* Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. *Am J Hematol.* 2024;99(4):615-624.
doi: 10.1002/ajh.27246
17. Wei AH, Loo S, Daver N. How I treat patients with AML using azacitidine and venetoclax. *Blood.* 2025;145(12):1237-1250.
doi: 10.1182/blood.2024024009
18. Tsao T, Shi YX, Kornblau S, *et al.* Concomitant inhibition of DNA methyltransferase and BCL-2 protein function synergistically induce mitochondrial apoptosis in acute myelogenous leukemia cells. *Ann Hematol.* 2012;91(12):1861-1870.
doi: 10.1007/s00277-012-1537-8
19. Mishra R, Zokaie Nikoo M, Veeraballi S, Singh A. Venetoclax and Hypomethylating Agent Combination in Myeloid Malignancies: Mechanisms of Synergy and Challenges of Resistance. *Int J Mol Sci.* 2023;25(1).
doi: 10.3390/ijms25010484
20. Fang QY, Gong XY, Li Y, *et al.* The impact of venetoclax based regimens in the preemptive of measurable residual disease in acute myeloid leukemia. *Blood Sci.* 2022;4(1):44-46.
doi: 10.1097/Bs9.0000000000000101
21. Pratz KW, Jonas BA, Pullarkat V, *et al.* Measurable Residual Disease Response and Prognosis in Treatment-Naive Acute Myeloid Leukemia With Venetoclax and Azacitidine. *J Clin Oncol.* 2022;40(8):855-865.
doi: 10.1200/JCO.21.01546
22. Chatzilygeroudi T, Karantanos T, Pappa V. Unraveling Venetoclax Resistance: Navigating the Future of HMA/Venetoclax-Refractory AML in the Molecular Era. *Cancers.* 2025;17(9):1586.
doi: 10.3390/cancers17091586
23. Jimenez-Vicente C, Arribas I, Pomares H, *et al.* Real-life outcome after failure to venetoclax and hypomethylating-based therapy for acute myeloid leukemia. *Haematologica.* 2025;110(6):1402-1406.
doi: 10.3324/haematol.2024.286589
24. Diamantidis MD. Factors affecting response and resistance to venetoclax in acute myeloid leukemia. *Front Oncol.* 2025;15:1577908.
doi: 10.3389/fonc.2025.1577908
25. Wurm S, Moritz JM, Petzer V, *et al.* Efficacy assessment following shortened venetoclax exposure in AML patients treated with venetoclax plus hypomethylating agents: a real-world, multicentric study. *Blood Cancer J.* 2025;15(1):175.
doi: 10.1038/s41408-025-01396-5
26. Vachhani P, Ma E, Xu T, *et al.* Post-remission cytopenia management in patients with AML treated with venetoclax in combination with hypomethylating agents: Pre-versus post-VIALE- A real-world experience from a predominantly US community setting. *Cancer Med.* 2023;12(17):17914-17923.
doi: 10.1002/cam4.6430

27. Vachhani P, Wolach O, Garcia JS, *et al.* Real-World Management of Patients with Newly Diagnosed Acute Myeloid Leukemia Treated with Venetoclax-Based Regimens: Results from the AML Real World Evidence (ARC) Initiative. *Blood*. 2021;138.
doi: 10.1182/blood-2021-151586
28. Shimony S, Garcia JS, Keating J, *et al.* Molecular ontogeny underlies the benefit of adding venetoclax to hypomethylating agents in newly diagnosed AML patients. *Leukemia*. 2024;38(7):1494-1500.
doi: 10.1038/s41375-024-02230-w
29. Pollyea DA, Pratz KW, Wei AH, *et al.* Outcomes in Patients with Poor-Risk Cytogenetics with or without TP53 Mutations Treated with Venetoclax and Azacitidine. *Clin Cancer Res*. 2022;28(24):5272-5279.
doi: 10.1158/1078-0432.Ccr-22-1183
30. Gangat N, Dinardo CD. Newly diagnosed acute myeloid leukemia in unfit patients: 2026 treatment algorithms. *Blood Cancer J*. 2025;15(1):139.
doi: 10.1038/s41408-025-01346-1
31. Jen WY, Lachowicz CA, Marvin-Peek J, *et al.* Optimizing lower intensity triplet therapy in acute myeloid leukemia: a practical guide. *Blood Cancer J*. 2025;16(1):6.
doi: 10.1038/s41408-025-01429-z
32. Chan OY, Walker AR. Novel therapies upon failure of HMA plus venetoclax. *Hematology*. 2023;2023(1):702-708.
doi: 10.1182/hematology.2023000456
33. Vanttinen I, Saad J, Ruokoranta T, *et al.* Drivers of clinical resistance to venetoclax and hypomethylating agents in acute myeloid leukemia and strategies for improving efficacy. *Hemasphere*. 2026;10(1):e70282.
doi: 10.1002/hem3.70282
34. Jiang W, Hong Y, Wang P, *et al.* Current Knowledge of the Integrated Stress Response in the Development and Management of Acute Myeloid Leukemia: A Novel Target with Encouraging Progress. *Drug Des Devel Ther*. 2025;19:11269-11288.
doi: 10.2147/DDDT.S573043
35. Niscola P, Catalano G, Pasqualini G, Piccioni D, Giovannini M, Noguera NI. Venetoclax and new BCL-2 inhibitors in acute myeloid leukemia. *Expert Opin Pharm*. 2025;26(16):1725-1739.
doi: 10.1080/14656566.2025.2582022
36. Waclawiczek A, Leppä AM, Renders S, *et al.* Leukemic stem cell subtypes determine venetoclax resistance and therapeutic vulnerabilities in AML. *Cell Stem Cell*. 2026;33(6):982-999.e8.
doi: 10.1016/j.stem.2026.04.012
37. Tamellini E, Frusteri C, Ferrarini I. Genes-first and phenotypes-first paths to treatment resistance in hematological malignancies. *Cell Death Dis*. 2025;16(1):819.
doi: 10.1038/s41419-025-08127-5
38. Garciaz S, Hospital MA, Collette Y, Vey N. Venetoclax Resistance in Acute Myeloid Leukemia. *Cancers*. 2024;16(6).
doi: 10.3390/cancers16061091
39. Mazzeo P, Penir SM, Shumilov E, *et al.* Clonal evolution and apoptosis resistance in myelodysplastic neoplasms and acute myeloid leukemia under treatment: insights from integrative longitudinal profiling. *Leukemia*. 2025;39(12):3026-3036.
doi: 10.1038/s41375-025-02756-7
40. Kamihara Y, Kikuchi S, Ishikawa N, *et al.* Antiapoptotic BCL2 family proteins BCL-XL and MCL1 as factors predicting resistance against venetoclax plus azacitidine for patients with newly diagnosed acute myelogenous leukemia. *PLoS ONE*. 2026;21(1):e0341461.
doi: 10.1371/journal.pone.0341461
41. Carter BZ, Mak PY, Tao WJ, *et al.* Maximal Activation of Apoptosis Signaling by Cotargeting Antiapoptotic Proteins in BH3 Mimetic-Resistant AML and AML Stem Cells. *Mol Cancer Ther*. 2022;21(6):879-889.
doi: 10.1158/1535-7163.Mct-21-0690
42. Fischer MA, Song YB, Arrate MP, *et al.* Selective inhibition of MCL1 overcomes venetoclax resistance in a murine model of myelodysplastic syndromes. *Haematologica*. 2023;108(2):522-531.
doi: 10.3324/haematol.2022.280631
43. Fleischmann M, Hansen O, Voigtländer D, *et al.* Targeting MCL-1 and MAPK overcomes venetoclax resistance in FLT3-ITD-positive AML cells harbouring activating PTPN11 (SHP-2) mutations. *Br J Haematol*. 2026;208(3):905-915.
doi: 10.1111/bjh.70344
44. Jiao CQ, Hu C, Sun MH, *et al.* Targeting METTL3 mitigates venetoclax resistance via proteasome-mediated modulation of MCL1 in acute myeloid leukemia. *Cell Death Dis*. 2025;16(1):233.
doi: 10.1038/s41419-025-07560-w
45. Vey N, Salamero O, Bajel A, *et al.* Phase 1 clinical trial of S64315, an intravenous MCL1 inhibitor, in patients with myeloid malignancies. *Leuk Lymphoma* 2026;1-8.
doi: 10.1080/10428194.2026.2699287
46. Konopleva M, DiNardo CD, Sun Y, *et al.* Analysis of Patients With Monocytic and Monocytic-Like Acute Myeloid Leukemia, Including AML-M4 and AML-M5, Treated With Venetoclax Plus Azacitidine. *Am J Hematol*. 2026;101(3):577-580.
doi: 10.1002/ajh.70161

47. Zhao LP, Dumas-Rivero T, Barette L, *et al.* Prognostic significance of monocytic-like phenotype in patients with AML treated with venetoclax and azacytidine. *Blood Adv.* 2025;9(14):3556-3565.
doi: 10.1182/bloodadvances.2024015734
48. Zhang H, Nakauchi Y, Kohnke T, *et al.* Integrated analysis of patient samples identifies biomarkers for venetoclax efficacy and combination strategies in acute myeloid leukemia. *Nat Cancer.* 2020;1(8):826-839.
doi: 10.1038/s43018-020-0103-x
49. Iqbal U, Shallis RM. Mechanistic overview and suggested strategies to overcome BCL-2 inhibitor resistance in TP53-mutated acute myeloid leukemia. *Front Cell Dev Biol.* 2026;14:1779094.
doi: 10.3389/fcell.2026.1779094
50. Venugopal S, Shoukier M, Konopleva M, *et al.* Outcomes in patients with newly diagnosed TP53-mutated acute myeloid leukemia with or without venetoclax-based therapy. *Cancer.* 2021;127(19):3541-3551.
doi: 10.1002/cncr.33675
51. Brandwein J, Page D, Liew E, *et al.* A Real-World Evaluation of Frontline Treatment for Acute Myeloid Leukemia With Azacitidine Plus Venetoclax. *Clin Lymphoma Myeloma Leuk.* 2025;25(7):e435-e442.
doi: 10.1016/j.clml.2025.01.024
52. Doehner H, Pratz KW, Dinardo CD, *et al.* Genetic risk stratification and outcomes among treatment-naïve patients with AML treated with venetoclax and azacitidine. *Blood.* 2024;144(21):2211-2222.
doi: 10.1182/blood.2024024944
53. Wu X, Zhang J. Leukemia stem cell differentiation in acute myeloid leukemia: Molecular mechanisms and multi-omics insights. *Current Proteom.* 2026;23(2):100101.
doi: 10.1016/j.curpro.2026.100101
54. Pollyea DA, Stevens BM, Jones CL, *et al.* Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. *Nat Med.* 2018;24(12):1859-1866.
doi: 10.1038/s41591-018-0233-1
55. Jones CL, Stevens BM, D'Alessandro A, *et al.* Inhibition of Amino Acid Metabolism Selectively Targets Human Leukemia Stem Cells. *Cancer Cell.* 2018;34(5):724-740.e4.
doi: 10.1016/j.ccell.2018.10.005
56. Tchong M, Roma A, Ahmed N, *et al.* Very long chain fatty acid metabolism is required in acute myeloid leukemia. *Blood.* 2021;137(25):3518-3532.
doi: 10.1182/blood.2020008551
57. Han G, Cui M, Lu P, *et al.* Selective translation of nuclear mitochondrial respiratory proteins reprograms succinate metabolism in AML development and chemoresistance. *Cell Stem Cell.* 2024;31(12):1777-1793.e9.
doi: 10.1016/j.stem.2024.09.008
58. Kawano G, Ikeda R, Ishihara D, *et al.* Guanine nucleotides drive ribosome biogenesis and glycolytic reprogramming in acute myeloid leukemia stem cells. *Blood.* 2026;147(7):768-782.
doi: 10.1182/blood.2025030209
59. Waclawiczek A, Leppa AM, Renders S, *et al.* Combinatorial BCL2 Family Expression in Acute Myeloid Leukemia Stem Cells Predicts Clinical Response to Azacitidine/Venetoclax. *Cancer Discov.* 2023;13(6):1408-1427.
doi: 10.1158/2159-8290.CD-22-0939
60. Stahl M, Stone RM. HMA + venetoclax triplet regimens for the initial treatment of AML in adults- CONTRA. *Blood Adv.* 2026.
doi: 10.1182/bloodadvances.2025018556
61. Pollyea DA, DiNardo CD, Arellano ML, *et al.* Impact of Venetoclax and Azacitidine in Treatment-Naïve Patients with Acute Myeloid Leukemia and IDH1/2 Mutations. *Clin Cancer Res.* 2022;28(13):2753-2761.
doi: 10.1158/1078-0432.CCR-21-3467
62. Garciaz S, Hospital MA. FMS-Like Tyrosine Kinase 3 Inhibitors in the Treatment of Acute Myeloid Leukemia: An Update on the Emerging Evidence and Safety Profile. *Oncotargets Ther.* 2023;16:31-45.
doi: 10.2147/Ott.S236740
63. Huls G, Woolthuis CM, Schuringa JJ. Menin inhibitors in the treatment of acute myeloid leukemia. *Blood.* 2025;145(6):561-566.
doi: 10.1182/blood.2024026232
64. Ciaurro V, Sharlandjieva V, Skwarska A, *et al.* Menin inhibitor DS-1594b drives differentiation and induces synergistic lethality in combination with venetoclax in acute myeloid leukemia cells with rearranged mixed-lineage leukemia and mutated nucleophosmin-1. *Haematologica.* 2026;111(5):1610-1624.
doi: 10.3324/haematol.2024.286833
65. Maiti A, DiNardo CD, Daver NG, *et al.* Triplet therapy with venetoclax, FLT3 inhibitor and decitabine for FLT3-mutated acute myeloid leukemia. *Blood Cancer J.* 2021;11(2):25.
doi: 10.1038/s41408-021-00410-w
66. Short NJ, Daver N, Dinardo CD, *et al.* Azacitidine, Venetoclax, and Gilteritinib in Newly Diagnosed and Relapsed or Refractory FLT3-Mutated AML. *J Clin Oncol.* 2024;42(13):1499-1508.
doi: 10.1200/JCO.23.01911

67. Wang ES, Montesinos P, Minden MD, *et al.* Phase 3 trial of gilteritinib plus azacitidine vs azacitidine for newly diagnosed FLT3mut+ AML ineligible for intensive chemotherapy. *Blood*. 2022;140(17):1845-1857.
doi: 10.1182/blood.2021014586
68. Montesinos P, Marchione DM, Recher C, *et al.* Long-term results from the AGILE study of azacitidine plus ivosidenib vs placebo in newly diagnosed IDH1-mutated AML. *Blood Adv*. 2025;9(20):5177-5189.
doi: 10.1182/bloodadvances.2025016399
69. Ikeda D, Uchiyama S, Guo YM, *et al.* FLT3 inhibitor and venetoclax therapy in elderly patients with relapsed/refractory FLT3-ITD+ AML: A report of three cases. *Leuk Res Rep*. 2026;25:100591.
doi: 10.1016/j.lrr.2026.100591
70. Raimondi V, Ciotti G, Gottardi M, Ciccarese F. 2-Hydroxyglutarate in Acute Myeloid Leukemia: A Journey from Pathogenesis to Therapies. *Biomedicines*. 2022;10(6):1359.
doi: 10.3390/biomedicines10061359
71. Montesinos P, Recher C, Vives S, *et al.* Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. *N Engl J Med*. 2022;386(16):1519-1531.
doi: 10.1056/NEJMoa2117344
72. Lachowicz CA, Loghavi S, Zeng ZH, *et al.* A Phase Ib/II Study of Ivosidenib with Venetoclax ± Azacitidine in IDH1-Mutated Myeloid Malignancies. *Blood Cancer Discov*. 2023;4(4):276-293.
doi: 10.1158/2643-3230.Bcd-22-0205
73. Dinardo CD, Marvin-Peek J, Loghavi S, *et al.* Outcomes of Frontline Triplet Regimens With a Hypomethylating Agent, Venetoclax, and Isocitrate Dehydrogenase Inhibitor for Intensive Chemotherapy-Ineligible Patients With Isocitrate Dehydrogenase-Mutated AML. *J Clin Oncol*. 2025;43(24):2692-2699.
doi: 10.1200/Jco-25-00640
74. Yu H, Shi T, Zhu HH. Emerging venetoclax plus hypomethylating agent-based triplet regimens in newly diagnosed acute myeloid leukemia: updates from the 2025 ASH Annual Meeting. *Exp Hematol Oncol*. 2026;15(1).
doi: 10.1186/s40164-026-00810-3
75. Gangat N, Ilyas R, Johnson IM, *et al.* Outcome of patients with acute myeloid leukemia following failure of frontline venetoclax plus hypomethylating agent therapy. *Haematologica*. 2023;108(11):3170-3174.
doi: 10.3324/haematol.2022.282677
76. Ikoma Y, Nakamura N, Kaneda Y, *et al.* Impact of myelodysplasia-related gene mutations and residual mutations at remission in venetoclax/azacitidine for AML. *Leukemia*. 2025;39(6):1362-1367.
doi: 10.1038/s41375-025-02625-3
77. DiNardo CD, Tiong IS, Quaglieri A, *et al.* Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML. *Blood*. 2020;135(11):791-803.
doi: 10.1182/blood.2019003988
78. Perl AE, Martinelli G, Cortes JE, *et al.* Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. *N Engl J Med*. 2019;381(18):1728-1740.
doi: 10.1056/NEJMoa1902688
79. Gangat N, McCullough K, Abdelmagid M, *et al.* Molecular predictors of response and survival following IDH1/2 inhibitor monotherapy in acute myeloid leukemia. *Haematologica*. 2024;109(1):287-292.
doi: 10.3324/haematol.2023.283732
80. Zhang Y, Li J, Liang Y, *et al.* Ivosidenib in Chinese patients with relapsed or refractory isocitrate dehydrogenase 1 mutated acute myeloid leukemia: a registry study. *Blood Sci*. 2024;6(3):e00196.
doi: 10.1097/BS9.0000000000000196
81. U.S. Food and Drug Administration. *FDA approves revumenib for relapsed or refractory acute leukemia with a KMT2A translocation*. 2024. Accessed November 15, 2025. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-revumenib-relapsed-or-refractory-acute-leukemia-kmt2a-translocation>
82. U.S. Food and Drug Administration. *FDA approves revumenib for relapsed or refractory acute myeloid leukemia with a susceptible NPM1 mutation*. 2025. Accessed October 24, 2025. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-revumenib-relapsed-or-refractory-acute-myeloid-leukemia-susceptible-npm1-mutation>
83. U.S. Food and Drug Administration. *FDA approves ziftomenib for relapsed or refractory acute myeloid leukemia with a NPM1 mutation*. 2025. Accessed November 13, 2025. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ziftomenib-relapsed-or-refractory-acute-myeloid-leukemia-npm1-mutation>
84. Fanin M, Lazzarotto D, Sperotto A, *et al.* Efficacy of Venetoclax-Based Therapy Followed By Allogeneic Transplantation in Newly Diagnosed and Relapsed/Refractory AML Patients. *Blood*. 2024;144:6038-6039.
doi: 10.1182/blood-2024-205250
85. Unglaub JM, Schlenk RF, Middeke JM, *et al.* Venetoclax-based salvage therapy as a bridge to transplant is feasible and effective in patients with relapsed/refractory AML. *Blood Adv*. 2025;9(2):375-385.
doi: 10.1182/bloodadvances.2024013086

86. Saliba AN, John AJ, Kaufmann SH. Resistance to venetoclax and hypomethylating agents in acute myeloid leukemia. *Cancer Drug Resist.* 2021;4(1):125-142.
doi: 10.20517/cdr.2020.95
87. Lachowicz CA, Heiblig M, Requena GA, *et al.* Genetic and Phenotypic Correlates of Clinical Outcomes with Venetoclax in Acute Myeloid Leukemia: The GEN-PHEN-VEN Study. *Blood Cancer Discov.* 2025;6(5):437-449.
doi: 10.1158/2643-3230.Bcd-24-0256
88. Daver N, Senapati J, Kantarjian HM, *et al.* Azacitidine, Venetoclax, and Magrolimab in Newly Diagnosed and Relapsed Refractory Acute Myeloid Leukemia: Phase Ib/II Study and Correlative Analysis. *Clin Cancer Res.* 2025;31(12):2386-2398.
doi: 10.1158/1078-0432.Ccr-25-0229
89. Okeleji O, McCall D, Gibson A, *et al.* Post transplant maintenance therapy with newly FDA-approved revumenib for high-risk KMT2Ar acute leukemia. *Blood Adv.* 2025;9(8):1988-1990.
doi: 10.1182/bloodadvances.2024015527
90. Agarwal G, Tonk RK, Sangwan K. Emerging drug profile: menin inhibitors in NPM1-mutated and KM2A-rearranged acute myeloid leukemia. *Leuk Amp Lymphoma.* 2026;67(9):1860-1876.
doi: 10.1080/10428194.2026.2674818
91. Issa GC, Aldoss I, DiPersio J, *et al.* The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. *Nature.* 2023;615(7954):920-924.
doi: 10.1038/s41586-023-05812-3
92. Issa GC, Aldoss I, Thirman MJ, *et al.* Menin Inhibition With Revumenib for KMT2A-Rearranged Relapsed or Refractory Acute Leukemia (AUGMENT-101). *J Clin Oncol.* 2025;43(1):75-84.
doi: 10.1200/JCO.24.00826
93. Wang ES, Montesinos P, Foran J, *et al.* Ziftomenib in Relapsed or Refractory NPM1-Mutated AML. *J Clin Oncol.* 2025;43(31):3381-3390.
doi: 10.1200/JCO-25-01694
94. Wang ES, Issas GC, Erba HP, *et al.* Ziftomenib in relapsed or refractory acute myeloid leukaemia (KOMET-001): a multicentre, open-label, multi-cohort, phase 1 trial. *Lancet Oncol.* 2024;25(10):1310-1324.
doi: 10.1016/S1470-2045(24)00386-3
95. Zeidner JF, Lin TL, Welkie RL, *et al.* Azacitidine, Venetoclax, and Revumenib for Newly Diagnosed -Mutated or -Rearranged AML. *J Clin Oncol.* 2025;43(23):2606-2615.
doi: 10.1200/Jco-25-00914
96. Perner F, Stein EM, Wenge DV, *et al.* MEN1 mutations mediate clinical resistance to menin inhibition. *Nature.* 2023;615(7954):913-919.
doi: 10.1038/s41586-023-05755-9
97. Daver NG, Iqbal S, Renard C, *et al.* Treatment outcomes for newly diagnosed, treatment-naïve TP53-mutated acute myeloid leukemia: a systematic review and meta-analysis. *J Hematol Oncol.* 2023;16(1):19.
doi: 10.1186/s13045-023-01417-5
98. Sallman DA, DeZern AE, Garcia-Manero G, *et al.* Eprenetapopt (APR-246) and Azacitidine in TP53-Mutant Myelodysplastic Syndromes. *J Clin Oncol.* 2021;39(14):1584-1594.
doi: 10.1200/Jco.20.02341
99. Cluzeau T, Sebert M, Rahmé R, *et al.* Eprenetapopt Plus Azacitidine in TP53-Mutated Myelodysplastic Syndromes and Acute Myeloid Leukemia: A Phase II Study by the Groupe Francophone des Myélodysplasies (GFM). *J Clin Oncol.* 2021;39(14):1575-1583.
doi: 10.1200/Jco.20.02342
100. Zeidner JF, Sallman DA, Récher C, *et al.* Magrolimab plus azacitidine vs physician's choice for untreated TP53-mutated acute myeloid leukemia: the ENHANCE-2 study. *Blood.* 2025;146(5):590-600.
doi: 10.1182/blood.2024027408
101. Senapati J, Croden J, Garcia-Manero G, *et al.* Outcomes of therapy-related non-core binding factor acute myeloid leukemia with venetoclax-based therapies. *Hemasphere.* 2026;10(2):e70317.
doi: 10.1002/hem3.70317
102. Achar RK, McCormick BJ, Dworkin E, *et al.* Outcomes of patients with acute myeloid leukemia treated with intensive therapy after failure of venetoclax-inclusive, less-intensive therapy. *Leuk Res.* 2024;146:107577.
doi: 10.1016/j.leukres.2024.107577
103. Short NJ, Loghavi S, Yilmaz M, *et al.* Long-term outcomes in FLT3-mutated acute myeloid leukemia after frontline hypomethylating agent, venetoclax and a FLT3 inhibitor. *Haematologica.* 2026;111(4):1246-1253.
doi: 10.3324/haematol.2025.288553
104. Boussi L, Goldberg AD. An emerging triplet option for newly diagnosed FLT3-mutated acute myeloid leukemia. *Haematologica.* 2026;111(4):1162-1164.
doi: 10.3324/haematol.2025.289066
105. Mi R, Chen L, Wang L, *et al.* Multicenter retrospective analysis of the short-term efficacy and safety of the VAH regimen in the treatment of acute myeloid leukemia. *Leuk Res.* 2025;159:108114.
doi: 10.1016/j.leukres.2025.108114

106. Versluis J, Lindsley RC. Transplant for TP53-mutated MDS and AML: because we can or because we should? *Hematol-Am Soc Hematol Educ Program*. 2022(1):522-527.
doi: 10.1182/hematology.2022000354
107. Sallman DA, McLemore AF, Komrokji R, *et al*. Posttransplant MRD monitoring by TP53 duplex sequencing with APR-246 + azacitidine maintenance predicts outcomes. *Blood Adv*. 2026;10(4):1053-1057.
doi: 10.1182/bloodadvances.2025017742
108. Koehne G, Mushtaq MU, Muffly LS, *et al*. Remission of TP53-Mutant AML After Transplantation With Trem-Cel, a CRISPR/Cas9 Gene-Edited Allograft Lacking CD33, Followed by a Donor-Derived Anti-CD33 Chimeric Antigen Receptor T (VCAR33). *JCO Precis Oncol*. 2025;9:e2500556.
doi: 10.1200/po-25-00556
109. Heuser M, Freeman SD, Ossenkoppele GJ, *et al*. 2021 Update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party. *Blood*. 2021;138(26):2753-2767.
doi: 10.1182/blood.2021013626
110. Kanaya M, Onozawa M, Matsukawa T, *et al*. Comparable outcomes with 14-, 21-, or standard 28-day venetoclax in the first cycle of azacitidine-venetoclax in untreated acute myeloid leukemia: real-world experience from the Hokkaido Leukemia Net. *Blood Cancer J*. 2025;15(1):118.
doi: 10.1038/s41408-025-01324-7
111. Burd A, Levine RL, Ruppert AS, *et al*. Precision medicine treatment in acute myeloid leukemia using prospective genomic profiling: feasibility and preliminary efficacy of the Beat AML Master Trial. *Nat Med*. 2020;26(12):1852-1858.
doi: 10.1038/s41591-020-1089-8
112. Gibson A, Dickson S, McCall D, *et al*. Venetoclax for pediatric patients with newly diagnosed acute myeloid leukemia. *Pediatr Blood Cancer*. 2024;71(11):e31286.
doi: 10.1002/pbc.31286
113. Raj R, Catueno S, Gibson A, *et al*. FLAG-IDA plus venetoclax for children, adolescents, and young adults with newly diagnosed AML. *Blood*. 2025;146(21):2608-2611.
doi: 10.1182/blood.2025029391
114. Vigna E, Bruzzese A, Martino EA, *et al*. Clinical Utility of Frailty Scoring in Elderly Acute Myeloid Leukemia Patients Treated With Venetoclax and Hypomethylating Agents. *Eur J Haematol*. 2026;116(2):160-168.
doi: 10.1111/ejh.70058
115. Roth JA, D'Amico PG, Cappelleri JC, *et al*. Real-world treatment and utilization of venetoclax for incident acute myeloid leukemia in a Medicare population. *Future Oncol*. 2025;21(29):3811-3820.
doi: 10.1080/14796694.2025.2587568