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REVIEW ARTICLE

Menin inhibitor resistance in *KMT2A*-rearranged and *NPM1*-mutated acute myeloid leukemia

Jingxin Zhang*

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

Abstract

KMT2A-rearranged (*KMT2A*-r) and *NPM1*-mutated (*NPM1*-mut) acute myeloid leukemia (AML) share a dependency on the menin–*KMT2A* interaction. Menin inhibitors have produced clinically meaningful remissions, but primary resistance, persistent measurable residual disease (MRD), and relapse limit durability. Acquired *MEN1* drug-pocket mutations that impair inhibitor binding while preserving menin–*KMT2A* function are currently the best-established clinical mechanism of resistance. Other proposed routes—including epigenetic or signaling bypass, altered apoptotic dependence, metabolic adaptation, persistent cell states, and microenvironmental protection—are supported to varying degrees by functional preclinical studies or broader AML biology and remain incompletely validated in longitudinal patient samples. The evidence for individual mechanisms also differs between *KMT2A*-r and *NPM1*-mut AML. This review evaluates the hierarchy and subtype specificity of current evidence, distinguishes validated clinical observations from emerging concepts, and discusses biomarkers and investigational strategies for prospective evaluation. Standardized *NPM1* molecular MRD provides an established monitoring framework, whereas *KMT2A*-r molecular monitoring is more heterogeneous and often fusion- or patient-specific. Integrating validated MRD methods with research pharmacodynamic and clonal assays in prospective studies will be essential for determining which resistance mechanisms are clinically actionable.

Keywords: Acute myeloid leukemia; Menin inhibitor; *KMT2A* rearrangement; *NPM1* mutation; Drug resistance; Precision therapy

***Corresponding author:**
Jingxin Zhang
(zhangjx@zzu.edu.cn)

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1. Introduction

Acute myeloid leukemia (AML) comprises a heterogeneous group of aggressive hematologic malignancies characterized by the clonal expansion of immature myeloid cells, disruption of normal hematopoiesis, and a high risk of treatment failure and relapse.[1] Genomic classification has divided AML into biologically and clinically distinct subgroups and enabled the development of therapies directed against recurrent molecular abnormalities.[2] Nevertheless, the durability of targeted therapy is frequently limited by pre-existing clonal heterogeneity, adaptive cell-state changes, and the acquisition or selection of resistance-conferring mutations. Understanding how genetically defined AML populations escape targeted pressure is therefore necessary both for selecting patients and for designing rational combination and sequential treatment strategies.

Acute myeloid leukemia with *KMT2A* rearrangements (*KMT2A*-r) and AML with mutated *NPM1* (*NPM1*-mut) arise from different initiating genetic events but converge on a related leukemogenic transcriptional state.[3] Lysine methyltransferase 2A (KMT2A) fusion proteins recruit chromatin-associated cofactors that maintain the expression of *HOXA*-cluster genes, *MEIS1*, and other regulators of stemness and differentiation.[4] In *NPM1*-mut AML, aberrant cytoplasmic localization of mutant *NPM1* is likewise associated with persistent *HOX*/*MEIS* expression and a differentiation block.[5,6] In both settings, the chromatin adaptor menin, encoded by *MEN1*, interacts with *KMT2A* and is required to sustain critical components of the leukemic transcriptional program. This shared dependency provided the rationale for pharmacologically disrupting the menin–KMT2A interaction.[5,7]

Clinical studies of menin inhibitors have validated this therapeutic concept. Revumenib produced responses in heavily pretreated patients with *KMT2A*-r or *NPM1*-mut acute leukemia, and its subsequent regulatory development established menin inhibition as a clinically actionable strategy.[8,9] Other agents, including ziftomenib, bleximenib, and enzomenib, have expanded the class and are being investigated as monotherapies and in combination regimens.[10] Menin inhibition generally suppresses *HOXA*/*MEIS1*-associated transcription and promotes myeloid differentiation rather than inducing only rapid cytotoxicity. This mechanism can generate deep responses, but it also creates opportunities for residual leukemic populations to survive, adapt, and evolve.

The emergence of somatic *MEN1* mutations at the inhibitor-binding interface provides direct clinical evidence that menin inhibitors exert selective pressure in patients.[11] These mutations can reduce drug binding while preserving the menin–KMT2A interaction, thereby restoring chromatin occupancy and leukemogenic transcription.[12] *MEN1* drug-pocket mutations therefore represent the best-established clinical mechanism of acquired resistance. Other candidate routes—including transcriptional or epigenetic bypass, proliferative signaling, altered apoptotic dependence, metabolic adaptation, persistent leukemia cell states, and microenvironmental protection—are supported mainly by functional preclinical studies or broader AML biology. Their frequency and causal contribution in patients treated with menin inhibitors remain uncertain and may differ between *KMT2A*-r and *NPM1*-mut AML.

This review examines menin inhibitor resistance as a multilevel evolutionary process rather than a single molecular event. It first summarizes the biological basis and clinical development of menin inhibition, then evaluates on-target and target-independent resistance mechanisms, compares resistance in *KMT2A*-r and *NPM1*-mut AML, and discusses biomarkers and therapeutic strategies for preventing or overcoming treatment failure (Figure 1).

2. Biological basis of menin dependency in acute myeloid leukemia

2.1. Menin as a context-dependent transcriptional scaffold

Menin is a predominantly nuclear scaffold protein encoded by *MEN1*.[13] Unlike a kinase or histone-modifying enzyme, menin has no known catalytic activity; instead, it organizes protein complexes through an extended central cavity and several interaction surfaces. In endocrine tissues, loss-of-function alterations in *MEN1* promote tumorigenesis, supporting its canonical designation as a tumor suppressor.[14] In selected acute leukemias, however, wild-type menin is co-opted as an oncogenic cofactor.[15] The best-characterized leukemic function of menin is its direct interaction with conserved motifs in the amino-terminal region of KMT2A.[16] Menin also cooperates with lens epithelium-derived growth factor (LEDGF), which contributes chromatin-binding activity and helps stabilize *KMT2A*-containing complexes at target loci.[17] This context-dependent switch from tumor suppressor to leukemic dependency illustrates why pharmacologic inhibition can be effective without requiring a pathogenic *MEN1* alteration.

Structural and functional studies established that the menin-binding surface of KMT2A is required for leukemic transformation by KMT2A fusion proteins. Disrupting this protein-protein interaction displaces oncogenic KMT2A complexes from selected chromatin loci and suppresses the transcriptional programs that maintain self-renewal.[18] Small molecules occupy the KMT2A-binding pocket of menin and competitively prevent productive complex formation. Early compounds provided proof of principle, whereas subsequent orally bioavailable inhibitors demonstrated antileukemic activity in cell lines, primary patient samples, and xenograft models.[19,20] Because these agents target a scaffold interaction rather than an enzymatic active site, their pharmacologic effects depend on the degree to which a leukemia remains transcriptionally addicted to the menin–KMT2A complex.

2.2. Menin dependency in *KMT2A*-rearranged acute myeloid leukemia

Chromosomal rearrangements of *KMT2A* generate fusion proteins that retain the amino-terminal portion of KMT2A, including domains involved in chromatin targeting and menin binding, but lose the carboxy-terminal SET domain responsible for histone H3 lysine 4 methylation.[21] More

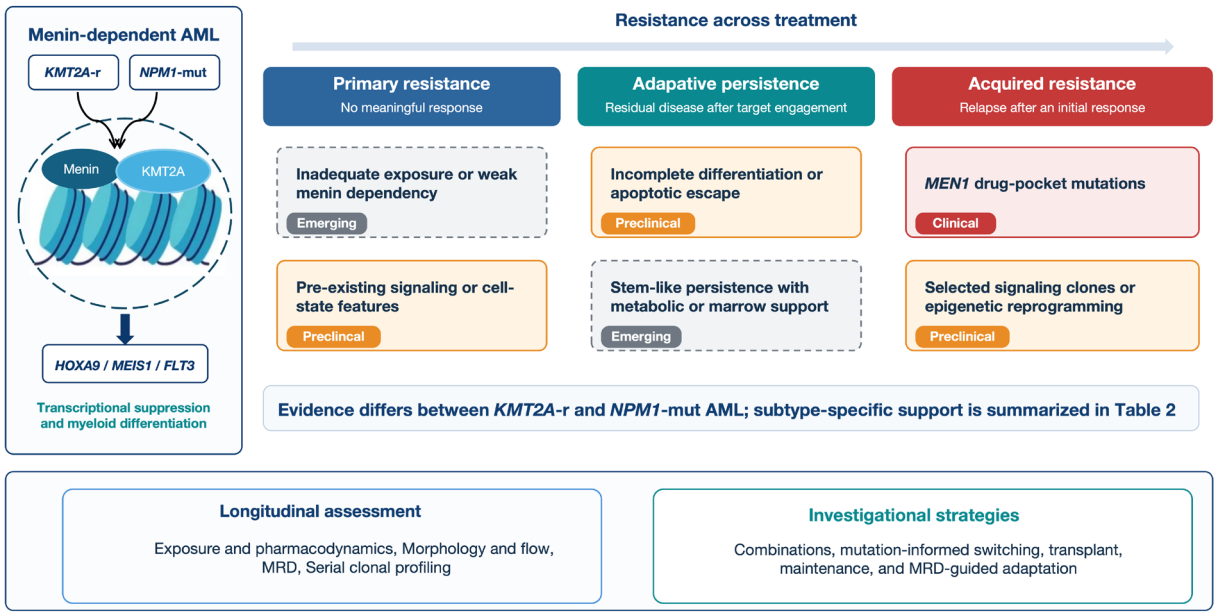


Figure 1. Temporal model of menin inhibitor resistance in *KMT2A*-rearranged (*KMT2A*-r) and *NPM1*-mutated (*NPM1*-mut) acute myeloid leukemia (AML). Menin inhibition suppresses *HOXA9*/*MEIS1*-associated transcription and promotes myeloid differentiation. Resistance may occur as primary resistance, adaptive persistence, or acquired resistance. *MEN1* drug-pocket mutations represent the best-established clinical mechanism, whereas the other mechanisms shown are supported mainly by preclinical evidence or remain incompletely validated. Evidence may differ between *KMT2A*-r and *NPM1*-mut AML. Longitudinal assessment should integrate treatment exposure, pharmacodynamic response, morphology, measurable residual disease (MRD), and clonal profiling. Resistance-directed interventions remain investigational.

than 100 KMT2A fusion partners have been described across acute leukemias. In AML, recurrent partners include *MLLT3*, *MLLT10*, *MLLT1*, and *ELL*, although their frequencies vary with age and cohort[22]; by contrast, *AFF1* is especially prominent in *KMT2A*-r acute lymphoblastic leukemia. Many AML-associated partners connect *KMT2A* fusions to transcriptional elongation or *DOT1L*-containing complexes. The resulting complexes promote productive transcriptional elongation and aberrant H3 lysine 79 methylation at leukemia-associated loci.[23] Genetic or pharmacologic disruption of *DOT1L* consequently reduces expression of critical *KMT2A* fusion targets and induces differentiation in susceptible models.[24,25]

Despite heterogeneity among fusion partners, *KMT2A*-r leukemias commonly maintain high expression of *HOXA* cluster genes and *MEIS1*, together with downstream programs that support stemness, proliferation, and impaired myeloid differentiation.[26] Menin serves as an anchoring component that facilitates occupancy of *KMT2A* fusion complexes at these developmental loci. Genetic deletion of menin or disruption of its binding to KMT2A markedly impairs transformation, demonstrating that the interaction is not merely associated with *KMT2A*-r leukemia but is functionally required for disease maintenance.[7] Preclinical menin inhibitors reproduce this effect by reducing chromatin occupancy, lowering *HOXA9* and *MEIS1* expression, promoting myeloid maturation, and suppressing leukemia propagation *in vivo*.[20,27] The strength of this dependency may nevertheless vary with the fusion partner, cellular origin, developmental stage, and cooperating lesions, providing a biological basis for heterogeneous clinical responses.

2.3. Menin dependency in *NPM1*-mutated acute myeloid leukemia

NPM1-mut AML lacks a *KMT2A* fusion but frequently exhibits a transcriptional profile resembling that of *KMT2A*-r leukemia, particularly persistent expression of *HOXA* and *HOXB* genes, *MEIS1*, and *FLT3*.[28] Mutations in *NPM1* create a new nuclear export signal and disrupt nucleolar localization, leading to cytoplasmic accumulation of mutant *NPM1*. Earlier models proposed that this redistribution indirectly prevented the physiological silencing of *HOX* genes during myeloid differentiation. Clustered Regularly Interspaced Short Palindromic Repeats-based domain screening subsequently showed that *NPM1*-mut AML cells are exceptionally dependent on the menin-binding region of wild-type *KMT2A*. Pharmacologic disruption of the menin–KMT2A interaction suppressed *HOX*, *MEIS1*, and *FLT3* expression

and induced differentiation in human and murine *NPM1*-mut AML models.[5]

More recent work indicates that mutant *NPM1* is not only a passive cytoplasmic disrupter but also participates directly in oncogenic transcription.[29] Mutant *NPM1* can associate with chromatin at active developmental genes, interact with transcriptional regulators, and contribute to multicomponent transcriptional hubs. Acute depletion of mutant *NPM1* causes rapid loss of RNA polymerase II and activating chromatin marks at target genes, followed by suppression of the leukemic program.[30,31] These findings support a model in which mutant *NPM1* and the wild-type menin–KMT2A machinery cooperate to preserve an aberrant progenitor-like transcriptional state. They also explain why genetically distinct *NPM1*-mut and *KMT2A*-r AML can respond to the same class of inhibitors. Nevertheless, the upstream driver differs: *KMT2A*-r AML is maintained by a fusion oncoprotein that physically contains the menin-binding KMT2A terminus, whereas *NPM1*-mut AML depends on wild-type *KMT2A* within a transcriptional network shaped by mutant *NPM1*.

2.4. Pharmacodynamic consequences of menin inhibition

Menin inhibition initiates a coordinated transcriptional and phenotypic response rather than acting solely as an acute cytotoxic insult. Displacement of menin–KMT2A complexes from chromatin is followed by reduced expression of *HOXA9*, *MEIS1*, *PBX3*, *FLT3*, and other context-dependent targets.[32] Loss of this self-renewal program permits reactivation of myeloid differentiation, reflected by morphologic maturation and increased expression of differentiation-associated surface markers. Proliferation slows, clonogenic capacity declines, and apoptosis may occur after a delay. In *NPM1*-mut models, menin inhibition can also reduce *BCL2* expression and increase susceptibility to venetoclax, linking transcriptional differentiation to mitochondrial apoptotic priming.[33]

This pharmacodynamic sequence has two implications for resistance. First, leukemia cells may escape treatment by restoring *HOX*/*MEIS*-centered transcription even when the original menin-dependent complex is inhibited. Second, cells may remain viable during the interval between transcriptional suppression and terminal differentiation or apoptosis, creating an opportunity for signaling, metabolic, or antiapoptotic adaptations. Thus, the biological basis of therapeutic response also defines the major routes through which resistance can emerge.

3. Clinical landscape of menin inhibitors

3.1. Development of the menin inhibitor class

The clinical development of menin inhibitors has progressed from first-in-human proof of concept to regulatory approval. Revumenib is approved by the US Food and Drug Administration for adult and pediatric patients aged at least one year with relapsed or refractory acute leukemia harboring a *KMT2A* translocation and for relapsed or refractory AML with a susceptible *NPM1* mutation in patients aged at least one year who have no satisfactory alternative treatment options.[34,35] Ziftomenib is approved for adults with relapsed or refractory AML harboring a susceptible *NPM1* mutation who have no satisfactory alternative treatment options.[36,37] These approvals establish revumenib and ziftomenib as the currently approved members of the class, although their labeled populations are not identical. Bleximenib and enzomenib remain investigational.[38,39] Bleximenib is being evaluated in combination programs, including a randomized phase III study with intensive induction, consolidation, and maintenance in newly diagnosed *NPM1*-mut or *KMT2A*-r AML (NCT07223814), whereas enzomenib remains in earlier-phase clinical development. Development status should be interpreted as a dated snapshot because trial phases and recruitment status continue to evolve.

3.2. Clinical activity in *KMT2A*-rearranged and *NPM1*-mutated leukemia

In the registration-enabling phase II *KMT2A*-r cohort of AUGMENT-101, 94 patients with relapsed or refractory *KMT2A*-r acute leukemia received revumenib. At the protocol-defined interim analysis with a July 24, 2023 data cutoff, 57 patients had centrally confirmed *KMT2A* rearrangement, adequate follow-up, and met the efficacy-evaluable criteria. The primary endpoint—complete remission or complete remission with partial hematologic recovery (CR + CRh)—was achieved in 13 of 57 patients (22.8%; 95% confidence interval [CI], 12.7–35.8).[9] Because the cohort included AML, acute lymphoblastic leukemia, and mixed-phenotype acute leukemia, these results should not be interpreted as an AML-only response estimate. Some responding patients proceeded to allogeneic transplantation, supporting revumenib as a potential bridge to consolidation in selected patients.

In the published registration-enabling phase II cohort of KOMET-001, 92 adults with relapsed or refractory *NPM1*-mutated AML received ziftomenib 600 mg once daily. At the October 28, 2024 data cutoff, the primary endpoint of CR + CRh was achieved in 20 of 92 patients (21.7%, reported as 22%; 95% CI, 14–32), and the protocol-defined overall response rate was 33%. Measurable residual disease

(MRD) negativity was observed in 61% of evaluable patients who achieved CR or CRh, rather than in 61% of the entire treated cohort. The median overall-response duration was 4.6 months (95% CI, 2.8–7.4).[36] Later regulatory analyses used a larger pooled population and should be reported separately rather than combined with the published phase II denominator. These data establish that pharmacologic menin dependence is clinically actionable, but they also show that only a minority of unselected patients achieve conventional complete remission with hematologic recovery and that many responses are not durable.

Cross-trial numerical comparisons require caution. The studies differed in eligibility criteria, age distribution, leukemia lineage, prior venetoclax exposure, previous transplantation, molecular composition, response-evaluable populations, follow-up duration, and definitions used for composite response. Moreover, differentiation therapy can produce delayed responses and morphologic changes that are not captured fully by early cytoreduction-based assessments. The most defensible interpretation is therefore that both revumenib and ziftomenib have validated the target, while the relative efficacy of individual agents and the optimal sequence between them remain unresolved.

3.3. Safety and pharmacodynamic manifestations

The safety profile of menin inhibitors reflects both conventional treatment toxicity and their differentiation-based mechanism. Differentiation syndrome is a clinically important class effect characterized by combinations of fever, weight gain, edema, pulmonary infiltrates, hypoxia, hypotension, renal dysfunction, or rapidly rising leukocyte counts. It requires early recognition, corticosteroid treatment, cytoreduction when indicated, and temporary interruption of the menin inhibitor in severe cases. In the pivotal studies, differentiation syndrome was generally manageable, but grade 3 or higher events occurred and can be life-threatening.[9,36]

Corrected QT interval prolongation is particularly relevant to revumenib and necessitates electrocardiographic and electrolyte monitoring, attention to interacting drugs, and dose modification according to prescribing guidance. Myelosuppression, infection, febrile neutropenia, anemia, and thrombocytopenia are also frequent in relapsed or refractory AML, although attribution is complicated by active leukemia and prior therapies. Ziftomenib produced differentiation syndrome in approximately one quarter of patients in its pivotal cohort, while clinically significant corrected QT prolongation was less prominent than in early revumenib experience.[36] These distinctions may influence agent selection, but they should not yet be interpreted as evidence that one compound universally has a superior therapeutic index.

3.4. Clinical patterns of treatment failure

Clinical resistance to menin inhibition is heterogeneous.[40,41] Primary resistance describes failure to achieve a meaningful leukemia response despite adequate drug exposure. Adaptive persistence refers to partial blast reduction or differentiation without eradication of the disease-propagating population, often manifested by persistent MRD. Acquired resistance denotes renewed leukemia expansion after an initial response, whereas post-transplant relapse after menin inhibitor bridging or maintenance represents a distinct evolutionary setting shaped by both drug and immune selection.[42] These categories may overlap within a single patient and cannot be assigned from morphology alone. In the present review, primary resistance denotes failure to achieve a meaningful response despite adequate exposure; adaptive persistence denotes survival of a residual disease-propagating population despite target engagement or differentiation; and acquired resistance denotes renewed expansion after an initial response through a selected genetic or nongenetic state. Longitudinal assessment of exposure, pharmacodynamic response, morphology, MRD, and clonal evolution is required to distinguish these patterns.

4. Conceptual framework of menin inhibitor resistance

Menin inhibitor resistance is best understood as an evolutionary phenotype produced by several interacting layers rather than as a binary property of a leukemia clone.[43] At the pharmacologic layer, insufficient exposure, dose interruption, drug interactions, or limited tissue penetration can prevent sustained target inhibition. At the target layer, alterations in the menin drug-binding pocket can preserve the essential menin–KMT2A interaction despite therapeutic inhibitor concentrations. At the network layer, leukemia cells can reactivate *HOX*/*MEIS*-centered transcription or maintain proliferation and survival through alternative chromatin regulators, signaling pathways, metabolic programs, and antiapoptotic proteins. Finally, at the population layer, pre-existing subclones and stem-like cell states may survive the initial differentiation response and repopulate the disease.

These layers generate clinically distinct patterns.[44] Primary resistance may reflect weak baseline menin dependence, adverse co-mutations, inadequate apoptotic priming, or a cell state that cannot complete differentiation. Adaptive persistence occurs when target genes are suppressed, and blasts mature, yet a residual

leukemia-propagating compartment survives. Acquired resistance develops when treatment selects genetic or epigenetic variants that restore fitness. The same patient may move through all three states: early differentiation, molecular persistence, and later overt relapse. Resistance should therefore be classified using longitudinal evidence that integrates drug exposure, pharmacodynamic target suppression, morphology, MRD, and clonal genomics. This framework also avoids assuming that every relapse after a menin inhibitor is caused by a *MEN1* mutation.

5. On-target resistance mediated by *MEN1* alterations

The clearest validated mechanism of acquired resistance is the emergence of somatic mutations in *MEN1*. In paired clinical samples from patients treated with revumenib, recurrent substitutions arose within the menin pocket occupied by the inhibitor, particularly at residues M327, G331, and T349.[12] These variants were absent or present below routine detection before therapy and expanded during response or at relapse, consistent with drug-driven selection. Functional studies showed that the altered proteins retained sufficient interaction with KMT2A while displaying reduced inhibitor binding. As a result, menin and KMT2A complexes reoccupied chromatin, *HOXA9* and *MEIS1* expression recovered, and leukemic proliferation resumed.[12] This mechanism is analogous to gatekeeper resistance in kinase therapy, although it occurs at a protein-protein interaction surface rather than a catalytic site.

The mutational spectrum is broader than the first clinical observations suggested. Saturation base-editing screens identified both shared and compound-specific resistance substitutions. Changes at M327 and G331 impaired the activity of several chemically distinct menin inhibitors, whereas substitutions involving C334, E368, and V372 produced more selective resistance profiles.[45] Structural modeling indicates that some variants directly disrupt drug contacts, while others modify the geometry or flexibility of the binding pocket. Importantly, resistance is not predicted simply by the distance of an amino acid from the inhibitor. A substitution must diminish drug engagement without abolishing the endogenous menin–KMT2A function required by the leukemia. This functional constraint explains why recurrent resistance clusters at a limited set of permissive residues.

On-target resistance can be polyclonal. Different *MEN1* variants may emerge simultaneously in separate subclones, and their relative abundance can change with dose, treatment interruption, combination therapy, and subsequent transplantation.[46] A negative baseline assay therefore does not exclude on-target resistance: the relevant clone may be below detection, may arise de novo, or may exist in an anatomic compartment not represented by blood. Conversely, detection of a low-level *MEN1* variant during therapy does not by itself prove that it dominates clinical failure. Variant allele frequency should be interpreted alongside blast percentage, copy-number state, pharmacodynamic markers, and the behavior of founding lesions such as *NPM1* mutation or a *KMT2A* fusion.

Distinguishing class-wide from inhibitor-selective resistance has therapeutic implications. A structurally distinct inhibitor may retain biochemical activity against a compound-selective substitution, whereas variants that disrupt a conserved binding mode may confer broader cross-resistance.[47] These relationships require mutation-specific biochemical, cellular, and prospective clinical validation. Currently, detecting a *MEN1* variant does not provide a validated basis for selecting or switching between approved menin inhibitors. Resistance maps should therefore be incorporated into clinical trials of next-generation compounds and alternative approaches that target other components of the leukemogenic complex.

Serial molecular surveillance can identify on-target evolution before morphologic relapse in research settings. Error-corrected sequencing or digital assays may detect expanding *MEN1* variants at low abundance, but no standardized assay, sampling interval, or variant threshold currently defines actionable molecular resistance. *HOXA9*, *MEIS1*, and related transcriptional measurements are likewise pharmacodynamic research tools rather than validated routine biomarkers.[48] Emerging *MEN1* clones should therefore be interpreted with the founding lesion, disease burden, exposure, and clinical response and should not independently trigger treatment modification outside a prospective protocol.

6. On-target-independent resistance mechanisms

The mechanisms considered in this section lack equivalent evidentiary support. Epigenetic, signaling, and apoptotic escape have been functionally demonstrated in selected model systems but remain incompletely validated as causes of resistance in treated patients. Metabolic adaptation, persistent cell states, lineage plasticity, and microenvironmental protection are emerging or putative modifiers whose menin-specific clinical relevance is uncertain. Accordingly, these mechanisms are presented as hypotheses of decreasing clinical maturity rather than as established alternatives to *MEN1*-mediated resistance.

6.1. Epigenetic restoration of leukemic transcription

Menin inhibition is effective because it collapses a transcriptional state; resistance can therefore occur without changing menin itself. Genome-scale perturbation studies have identified Polycomb repressive complex 1.1 (PRC1.1) as an important determinant of response. Loss of the noncanonical PRC1.1 components—polycomb group ring finger 1 or BCL6 corepressor—impaired differentiation and allowed MYC-associated transcription to persist during menin inhibition.[49] In these models, resistant cells did not simply restore every canonical menin target. Instead, they substituted an alternative proliferative program that preserved leukemia fitness despite partial suppression of *HOX*/*MEIS* genes.[49] This finding broadens the definition of pathway reactivation: escape may reproduce the output of the original network without reconstructing the same chromatin complex.

Chromatin acetylation provides another adaptive route. Lysine acetyltransferase (KAT) 6A, KAT6B, and KAT7 help maintain active regulatory elements and leukemic transcriptional identity. Pharmacologic inhibition of KAT6/KAT7 has been reported to deepen responses to menin inhibitors and suppress both primary and acquired resistance in *KMT2A*-fusion leukemia models.[50] The proposed mechanism includes loss of activating histone acetylation, reduced expression of stemness-associated genes, and impaired recovery of the *KMT2A*-fusion program. These data support epigenetic combinations, but the therapeutic window will require careful definition because histone acetyltransferases also contribute to normal hematopoiesis.

Other chromatin regulators may influence sensitivity in a context-dependent manner. *DOT1L*-mediated H3K79 methylation, the super elongation complex, LEDGF, and wild-type KMT2A all participate in transcriptional maintenance in *KMT2A*-r leukemia.[51] In *NPM1*-mut AML, mutant *NPM1*-containing transcriptional hubs and wild-type *KMT2A* create a related but nonidentical dependency. Alterations that strengthen residual chromatin recruitment, stabilize enhancer-promoter contacts, or activate parallel developmental regulators could reduce the depth of menin inhibitor response. Much of this evidence remains preclinical, and a factor identified in a cell line should not be labeled a clinical resistance driver without enrichment in paired patient samples and functional confirmation. Collectively, these studies establish functional routes of reduced sensitivity in model systems—predominantly *KMT2A*-fusion models—but do not yet define their prevalence or causal contribution to clinical relapse in either *KMT2A*-r or *NPM1*-mutated AML.

6.2. Proliferative signaling through *FLT3* and rat sarcoma-mitogen-activated protein kinase pathways

KMT2A-r and *NPM1*-mut AML frequently acquire cooperating signaling lesions. *FLT3* is transcriptionally linked to the *HOX*/*MEIS* program and is commonly mutated or highly expressed in *NPM1*-mut AML.[52] Menin inhibition can reduce *FLT3* expression, but a constitutively active feline McDonough sarcoma virus-like tyrosine kinase 3 (FLT3) kinase or persistent downstream signaling may blunt the consequences of that reduction. Combined menin and FLT3 inhibition produces synergistic differentiation and leukemia control in preclinical models of *FLT3*-mutated AML.[53] These findings provide a biological rationale for prospective evaluation, particularly in *FLT3*-mutated *NPM1*-mut AML, but they do not establish that the combination prevents resistance or reverses clinically established menin inhibitor resistance.

Rat sarcoma (RAS)-mitogen-activated protein kinase (MAPK) activation is a biologically plausible bypass route.[11] Mutations in *NRAS*, *KRAS*, *PTPN11*, *NF1*, or upstream receptors can sustain proliferation in AML and may be present before therapy or selected during clonal evolution.[54] However, paired longitudinal studies have not yet established the frequency with which these lesions cause failure of menin inhibition. Historical sequencing alone is therefore insufficient to attribute resistance, and trials of RAS-, Src homology 2 domain-containing protein tyrosine phosphatase 2-, mitogen-activated protein kinase kinase-, or extracellular signal-regulated kinase-directed combinations should distinguish prevention of resistance from treatment of a documented pathway-driven relapse.

6.3. Altered mitochondrial apoptotic dependence

Transcriptional differentiation does not guarantee cell death. Menin inhibition can decrease *BCL2* expression and increase venetoclax sensitivity, providing a mechanistic basis for combination therapy.[33,55] However, AML cells can shift survival dependence from *BCL2* to *MCL1* or *BCL-XL*, increase oxidative stress defenses, or maintain a monocytic state that is intrinsically less sensitive to venetoclax. Such cells may show appropriate suppression of *HOXA9* and *MEIS1* yet remain viable. This distinction is clinically important because it separates target engagement from leukemia eradication.

Venetoclax-containing combinations may reduce survival of cells undergoing menin-driven transcriptional reprogramming. Preclinical studies demonstrate enhanced apoptosis, and early clinical combinations have reported high response rates; however, these findings do not establish BCL2-family escape as a recurrent clinical mechanism or

show that venetoclax reverses established menin inhibitor resistance.[55,56] Nevertheless, venetoclax resistance remains possible, especially after substantial prior exposure. Baseline differentiation state, BCL2-family protein balance, mitochondrial priming, and prior treatment history may determine whether adding venetoclax prevents resistance or merely adds myelosuppression. Strategies targeting *MCL1* or other apoptotic nodes are under investigation, but their hematologic and cardiac toxicities require caution.

6.4. Metabolic adaptation

Leukemia cells can also buffer transcriptional stress through metabolic rewiring. Guanine nucleotide biosynthesis has emerged as a modulator of *KMT2A* complex integrity. Blockade of inosine monophosphate dehydrogenase reduced guanine nucleotide pools, impaired the abundance or assembly of LEDGF- and menin-containing complexes, and sensitized *KMT2A*-r and *NPM1*-mut leukemia models to menin inhibition.[57] This interaction suggests that metabolic supply is not merely downstream of oncogenic transcription but can feed back on the stability of the chromatin machinery.

Other metabolic states may influence response indirectly. Leukemia stem cells can rely on amino acid metabolism, fatty-acid oxidation, and oxidative phosphorylation, but these observations arise largely from broader AML biology rather than longitudinal studies of menin inhibitor resistance.[58] Evidence that metabolic adaptation causes clinical failure of menin inhibition is currently lacking. Guanine nucleotide or other metabolic interventions should therefore be described as preclinical sensitization strategies requiring biomarker development and prospective validation, not as established resistance-directed treatments.

6.5. Stem-like persistence and cell-state plasticity

Menin inhibitors can induce conspicuous myeloid maturation while a residual immature or leukemia-propagating compartment persists.[59] Potential explanations include incomplete target suppression, survival of a transcriptional state with lower menin dependence, and failure to couple differentiation to mitochondrial apoptosis. A shift toward monocytic features may represent productive maturation, selection of a pre-existing monocytic state, or treatment-induced reprogramming; morphology alone cannot distinguish these possibilities.

Single-cell genotype-transcriptome approaches are well suited to this question because they can link founding lesions and emerging resistance alterations to cell identity across pretreatment, early-treatment, and relapse samples. Evidence of the same state before treatment would support selection, whereas appearance after target engagement could support induced plasticity. However, available data do not yet establish a reproducible stem-like or differentiation state that prospectively predicts persistence after menin inhibition, and the relative contributions of pre-existing selection and induced reprogramming remain unresolved.

Lineage plasticity may be particularly relevant to *KMT2A*-r acute leukemia, which spans myeloid, lymphoid, and mixed-phenotype disease, although systematic evidence after menin inhibition is limited. In *NPM1*-mut AML, loss of *NPM1* mutation at relapse more often suggests emergence of an ancestral or unrelated clone than phenotypic escape of the original *NPM1*-mut leukemia. These scenarios should therefore be treated as putative evolutionary routes rather than clinically validated menin-resistance mechanisms.

6.6. Bone marrow and immune microenvironment

The marrow microenvironment can supply cytokines, adhesion signals, metabolites, and antiapoptotic cues that protect AML cells from therapy. C-X-C motif chemokine ligand 12–C-X-C motif chemokine receptor 4, integrin, MAPK, and phosphoinositide 3-kinase PI3K–protein kinase B signaling provide a biological rationale for stromal support during differentiation.[60] However, direct evidence for a recurrent menin-specific microenvironmental resistance program is sparse, and the contribution of immune selection before or after transplantation remains undefined. Paired marrow and blood sampling, spatial profiling, and immune monitoring will be required to determine whether microenvironmental effects are causal resistance mechanisms or modifiers of genetically encoded persistence. The principal resistance mechanisms, their current level of evidence, candidate biomarkers, and therapeutic implications are summarized in Table 1.

7. Shared and distinct resistance in *KMT2A*-rearranged and *NPM1*-mutated acute myeloid leukemia

The two molecular subgroups share menin dependence but are not biologically interchangeable, and the evidence for individual resistance mechanisms is asymmetric. *MEN1* pocket mutations have direct clinical and functional support across menin-dependent genotypes. By contrast, several epigenetic mechanisms have been studied predominantly in *KMT2A*-fusion models; FLT3-directed rationale is especially relevant to NPM1-mutated or *FLT3*-mutated AML; and lineage plasticity may be particularly relevant to *KMT2A*-r acute leukemia. Other proposed mechanisms remain insufficiently resolved by subtype.

Table 1. Major mechanisms of resistance to menin inhibitors in *KMT2A*-r and *NPM1*-mut AML

Mechanism	Predominant setting	Current evidence and limitations	Candidate biomarker	Research or translational implication
MEN1 pocket mutations	*KMT2A*-r and *NPM1*-mut leukemia	Paired clinical samples plus functional validation; best-established acquired mechanism	Emerging *MEN1* pocket variant with molecular or clinical progression	Define mutation-specific cross-resistance and test next-generation agents prospectively
PRC1.1 or MYC-associated bypass	Mainly *KMT2A*-fusion models	Functional preclinical evidence; prevalence in patients unknown	BCOR or PCGF1 loss; persistent MYC output	Validate in paired samples; evaluate apoptosis-directed combinations
KAT6/KAT7 chromatin adaptation	Mainly *KMT2A*-fusion models	Functional preclinical evidence; therapeutic window uncertain	Persistent acetylation or stemness program	Prospective preclinical and early-phase combination studies
FLT3 or RAS–MAPK signaling	Biologically relevant across AML; FLT3 especially relevant to *NPM1*-mut AML	Preclinical rationale and genomic plausibility; role in established menin resistance unproven	Selected signaling lesion plus pathway activity	Separate prevention trials from treatment of documented resistant disease
BCL2-family escape	Menin-dependent AML models and early combinations	Functional preclinical rationale; not a validated clinical resistance mechanism	BCL2-family balance or mitochondrial priming	Test biomarker-selected apoptosis combinations
Metabolic adaptation	Menin-dependent models and broader AML biology	Emerging preclinical concept; clinical causality lacking	Nucleotide or oxidative-metabolism signature	Develop biomarkers before clinical resistance-directed use
Stem-like persistence or plasticity	Putative across both; lineage plasticity may be greater in *KMT2A*-r disease	Menin-specific longitudinal evidence limited; selection versus induction unresolved	Persistent founding lesion within a residual cell state	Paired single-cell studies
Microenvironmental protection	Broader AML biology	Putative menin-specific modifier; direct clinical evidence sparse	Marrow versus blood discordance or spatial niche signature	Spatial and immune profiling

Abbreviations: AML: Acute myeloid leukemia; BCOR: BCL6 corepressor; FLT3: Feline McDonough sarcoma virus-like tyrosine kinase 3; KAT: Lysine acetyltransferase; *KMT2A*-r: *KMT2A*-rearranged; MAPK: Mitogen-activated protein kinase; *NPM1*-mut: *NPM1*-mutated; PCGF1: Polycomb group ring finger 1; PRC1.1: Polycomb repressive complex 1.1; RAS: Rat sarcoma.

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In *KMT2A*-r AML, the founding fusion usually remains a stable marker of clonal continuity, but molecular monitoring is not uniform across fusion partners. Recurrent fusion-transcript assays are available for selected partners, whereas other cases require patient-specific transcript or genomic-breakpoint assays with variable availability, sensitivity, and clinical validation. Adult outcome studies show substantial heterogeneity by fusion partner, co-mutation profile, age, and transplantation status.[61,62] The same variables may modify menin dependence, although current clinical cohorts are too small to define reliable fusion-specific response rates. *KMT2A*-r disease also has greater lineage plasticity than typical *NPM1*-mut AML. Monitoring should therefore retain the ability to identify lymphoid or mixed-phenotype relapse rather than focusing exclusively on myeloid markers.

In *NPM1*-mut AML, the mutant transcript provides a highly sensitive and standardized molecular marker. Persistent or recurrent *NPM1*-mut RNA after therapy strongly predicts relapse in conventional treatment settings and is well suited for evaluating the depth and kinetics of menin inhibitor response.[63–65] Co-mutations are especially important. *FLT3*-internal tandem duplication may create a targetable signaling dependency, whereas RAS-pathway mutations may support bypass. Mutations associated with clonal hematopoiesis, such as *DNMT3A*, *TET2*, or *ASXL1*, may persist during remission without proving residual *NPM1*-mut leukemia. A molecular relapse defined only by one such mutation can therefore be misleading.

The founding lesions also differ in how they behave during disease evolution (Table 2). Persistence of a *KMT2A* fusion at relapse usually supports continuity of the original leukemia. *NPM1*-mut disease can occasionally relapse as *NPM1* wild-type, reflecting selection of an ancestral clone or development of a distinct AML. In that setting, continued menin inhibition should not be assumed to remain effective. Reconfirmation of the actionable genotype at each relapse is essential for both subgroups, but it is particularly critical when the disease phenotype or molecular pattern changes.

8. Biomarkers and monitoring of resistance

A practical monitoring strategy should answer four questions: (i) Is the drug reaching and inhibiting its target? (ii) Is the leukemia showing the expected biological response? (iii) How much disease remains? (iv) Which clone is expanding? No single assay answers all four. Baseline evaluation should confirm the actionable *KMT2A* rearrangement or susceptible *NPM1* mutation, define the fusion partner where relevant, document co-mutations, and establish a repeatable disease marker whenever feasible. The monitoring plan should distinguish validated or context-dependent clinical assays from research biomarkers and should record prior venetoclax, FLT3 inhibitor, transplantation, and menin inhibitor exposure because these treatments can reshape clonal composition (Table 3).

Early assessment should first exclude inadequate exposure caused by dose interruption, organ dysfunction, or interacting medication. Serial *HOXA9*, *MEIS1*, *PBX3*, or *FLT3* expression may demonstrate target engagement in research studies but is not validated for routine treatment decisions.[66] Morphologic maturation and differentiation syndrome provide evidence of biological activity but are not surrogates for molecular clearance or durable remission, and absence of overt differentiation syndrome does not indicate absent target engagement.

Disease quantification should integrate marrow morphology, flow cytometry, and an appropriate molecular assay without assuming that these measurements are interchangeable.[65] In *NPM1*-mut AML, quantitative *NPM1* molecular MRD is well established and should be interpreted using validated specimens, timepoints, and response criteria. In *KMT2A*-r AML, molecular monitoring is more heterogeneous: recurrent fusion-transcript assays are available for selected partners, whereas other cases require patient-specific fusion or genomic-breakpoint assays whose availability, sensitivity, and clinical validation vary. During menin-induced differentiation, morphologic improvement or a changing flow phenotype may precede—or occur without—clearance of the founding molecular lesion. Discordant results should therefore be reported separately and interpreted longitudinally.

At molecular persistence or relapse, broad genomic reassessment can identify clonal evolution, including changes in *FLT3* or RAS–MAPK genes.[67] Deep *MEN1* sequencing and single-cell DNA/RNA profiling are valuable research approaches for defining on-target evolution and residual cell states, but neither has a validated threshold for routine treatment modification. Their principal current value is in prospective studies using paired pretreatment, response, and relapse samples.

A composite longitudinal trajectory may ultimately prove more informative than any single baseline marker, but this concept remains investigational. Prospective studies should test whether target-gene suppression, founding-lesion MRD kinetics, *MEN1* clone evolution, and residual cell states provide independent or complementary prognostic information.[68] Until such relationships and actionable thresholds are validated, research biomarkers should not be used alone to direct treatment changes.

Table 2. Resistance mechanisms in *KMT2A*-r and *NPM1*-mut AML according to disease subtype and level of evidence

Mechanism	*KMT2A*-r AML	*NPM1*-mut AML	Evidence level and interpretation
MEN1 pocket mutations	Clinical emergence plus functional validation	Clinical emergence plus functional validation	Clinically validated acquired resistance in both; variant-specific cross-resistance remains under study
PRC1.1 or MYC-associated bypass	Functional evidence mainly in *KMT2A*-fusion models	Limited direct evidence	Predominantly preclinical; subtype generalization not established
KAT6/KAT7 adaptation	Functional evidence mainly in *KMT2A*-fusion models	Insufficient direct evidence	Preclinical candidate mechanism
FLT3 signaling	Model-dependent rationale	Especially relevant with *FLT3* mutation or high expression	Preclinical rationale; role in established clinical resistance unproven
RAS–MAPK signaling	Plausible cooperating or selected pathway	Plausible cooperating or selected pathway	Broader AML and genomic rationale; paired menin-resistance data limited
BCL2-family escape	Preclinical combination evidence	Preclinical evidence with strong biological rationale	Functional preclinical; not clinically validated as resistance
Metabolic adaptation	Preclinical evidence	Preclinical evidence	Emerging; clinical validation lacking
Stem-like persistence or plasticity	Putative; lineage plasticity may be greater	Putative; residual or monocytic states require study	Pre-existing versus induced states unresolved
Microenvironmental protection	Broader AML rationale	Broader AML rationale	Putative menin-specific modifier

Abbreviations: AML: Acute myeloid leukemia; FLT3: Feline McDonough sarcoma virus-like tyrosine kinase 3; KAT: Lysine acetyltransferase; *KMT2A*-r: *KMT2A*-rearranged; MAPK: Mitogen-activated protein kinase; *NPM1*-mut: *NPM1*-mutated; PRC1.1: Polycomb repressive complex 1.1; RAS: Rat sarcoma.

9. Investigational strategies to prevent or overcome resistance

9.1. Use menin inhibitors earlier and in rational combinations

Earlier use and rational combinations are candidate strategies for reducing the reservoir from which resistance emerges.[69] This hypothesis is biologically plausible because earlier disease may contain fewer therapy-selected clones and because complementary agents may eliminate cells that survive menin-driven differentiation. Whether either approach prevents clinical resistance requires randomized or prospectively designed studies; regimen selection should therefore follow approved indications or clinical-trial protocols rather than mechanistic rationale alone.

Azacitidine and venetoclax are a leading backbone. Menin inhibition suppresses leukemic self-renewal and can lower *BCL2*; azacitidine alters transcriptional and immune states, and venetoclax promotes mitochondrial apoptosis.[70] In a phase I study of newly diagnosed older adults with *NPM1*-mut or *KMT2A*-r AML, azacitidine, venetoclax, and revumenib produced an overall response rate of 88.4% and a composite complete remission rate of 81.4%; all assessed responders were MRD-negative by flow cytometry.[56] These results are encouraging but require confirmation with longer follow-up and randomized comparison. Prolonged cytopenias, infection, differentiation syndrome, and drug interactions may require shortened venetoclax exposure and individualized cycle timing.

Intensive chemotherapy combinations are also being explored in fit patients. Cytotoxic therapy can debulk menin-independent subclones, while menin inhibition may eradicate the transcriptionally addicted compartment and promote differentiation. The major questions are scheduling, marrow recovery, and whether continuous target suppression is necessary during chemotherapy. Trials should report molecular clearance and clonal relapse patterns, not only composite remission rates.

9.2. Match targeted partners to bypass pathways

For *FLT3*-mutated AML, combined menin and FLT3 inhibition has a strong mechanistic and preclinical rationale.[53] This rationale may be especially relevant to *NPM1*-mutated/*FLT3*-mutated AML, but clinical trials must separately determine whether the combination deepens initial response, prevents resistance, or treats resistance that has already emerged. RAS-, Src homology 2 domain-containing protein tyrosine phosphatase 2-, mitogen-activated protein kinase kinase-, or extracellular signal-regulated kinase-directed combinations are even earlier-stage concepts and require genotype-specific efficacy and tolerability studies.

Table 3. Longitudinal monitoring framework and candidate interventions for prospective evaluation during menin inhibitor therapy

Timepoint	Validated or context-dependent assessment	Investigational assessment	Interpretive limitation	Candidate intervention for prospective evaluation
Baseline	Confirm actionable genotype; broad genomic profile; establish *NPM1* MRD baseline when applicable	*HOXA9*/*MEIS1* expression; single-cell state profiling	Genotype establishes eligibility, not guaranteed menin dependence	Mechanism-informed trial stratification
Early treatment	Exposure and interactions; morphology; flow response	Serial target-gene suppression	Differentiation may alter morphology or flow without molecular clearance	Prospective exposure-correction or combination study
Best response	*NPM1* molecular MRD; flow MRD; selected *KMT2A* fusion or patient-specific assay when validated and available	Deep *MEN1* sequencing; single-cell residual-state analysis	*NPM1* and *KMT2A* molecular monitoring are not equally standardized	Trial-based consolidation or transplant evaluation
Molecular persistence or progression	Repeat founding-lesion and broad genomic assessment	Low-frequency *MEN1* kinetics; pathway-specific functional assays	No validated *MEN1* threshold for changing therapy	Prospective mutation- or pathway-directed intervention
Post-transplant	Disease-specific MRD and chimerism according to local standards	Menin-maintenance biomarkers	Maintenance efficacy and duration are undefined	Protocol-based maintenance or pre-emptive study

Abbreviation: MRD: Measurable residual disease.

Epigenetic partners offer a way to prevent transcriptional bypass. KAT6/KAT7 inhibition may destabilize the active chromatin state that persists after menin blockade, whereas DOT1L inhibition could suppress a complementary dependency in *KMT2A*-r leukemia.[50] Combination development should include normal progenitor assays and schedule optimization because simultaneous disruption of several transcriptional regulators may delay hematopoietic recovery. PRC1.1-deficient resistance models showed renewed sensitivity when venetoclax was added, suggesting that a genetic epigenetic lesion can create an actionable apoptotic vulnerability rather than requiring direct restoration of the missing complex.[49]

Inhibition of guanine nucleotide synthesis enhances menin inhibitor activity in preclinical models, providing a rationale for biomarker-development studies.[57] It is not yet known whether metabolic intervention can prevent or reverse resistance in patients. Clinical evaluation should therefore begin with pharmacodynamic evidence of pathway modulation and careful toxicity assessment rather than assuming a demonstrated resistance state.

9.3. Address on-target mutations with structurally informed therapy

Acquired *MEN1* mutations provide a rationale for structurally informed drug development, but mutation-guided switching is not yet clinically validated. A structurally distinct inhibitor may retain activity against a compound-selective substitution, whereas class-wide variants may not be overcome by switching.[45] Prospective trials should link recurrent substitutions to biochemical sensitivity, *ex vivo* response, pharmacokinetics, and clinical outcome before these maps are used for treatment selection.

Strategies outside the conventional binding pocket may provide broader coverage. Menin degraders, molecular glues, disruption of the KMT2A–LEDGF interaction, or targeting downstream transcriptional effectors could remain active when the pocket is altered.[71] Each approach introduces new safety issues because menin participates in endocrine tumor suppression and normal transcriptional regulation. Intermittent or leukemia-selective degradation may be preferable to complete systemic menin loss.

9.4. Use transplantation and maintenance to consolidate deep response

Allogeneic hematopoietic stem cell transplantation remains an important consolidative option for eligible patients with relapsed *KMT2A*-r or *NPM1*-mut AML.[72] Menin inhibitors can serve as a bridge by inducing remission in patients who otherwise lack a path to transplant. The decision should incorporate MRD depth, prior transplantation, comorbidity, donor availability, and the durability expected from continued drug therapy. Achieving morphologic remission without molecular clearance may still permit transplantation, but persistent

MRD identifies a higher-risk population that may benefit from additional cytoreduction or a clinical trial.[73]

Post-transplant menin inhibitor maintenance is an investigational strategy with biological rationale but unproven efficacy. Low disease burden and a potential interaction between differentiation and graft-versus-leukemia immunity support prospective evaluation[74], but the optimal start time, dose, duration, and management of cytopenias or graft-versus-host disease are undefined. Maintenance could also select *MEN1* variants if it functions as monotherapy. Prospective trials should define eligibility, MRD context, toxicity, efficacy, and patterns of clonal resistance before maintenance is incorporated into routine care.

9.5. Adapt treatment before overt relapse

Molecular progression may provide an earlier opportunity for investigation than overt morphologic relapse, but validated intervention thresholds do not yet exist. Rising *NPM1* MRD is clinically meaningful in *NPM1*-mut AML, whereas persistent *KMT2A* signal, low-frequency *MEN1* variants, and emerging signaling clones require assay- and context-specific interpretation.[75] Trials should prospectively test whether adding or switching therapy at molecular progression improves outcome; outside such protocols, these research findings should not automatically trigger a treatment change.

Adaptive trial designs are well suited to this field. Patients can begin with a common menin-containing backbone and add or switch modules according to early MRD and resistance markers.[76] Mandatory paired samples, centralized sequencing, and uniform response definitions will be essential. The aim is not maximal drug number but maximal evolutionary coverage with acceptable marrow toxicity.

10. Outstanding questions and future directions

Several questions must be resolved before menin inhibitors can reach their full potential.[77] First, the field needs validated predictors of primary resistance. Genotype alone identifies a population with possible menin dependence but does not predict which patient will achieve deep remission. Integrated measures of fusion partner, co-mutations, baseline cell state, chromatin accessibility, and mitochondrial priming may outperform any single marker.

Second, clinical resistance mechanisms must be distinguished from those generated in model systems. Saturation screens reveal what is possible, whereas paired patient samples reveal what is selected under clinically achievable exposure. International sample-sharing efforts are needed because individual trials contain few resistant cases. Standardized collection of blood and marrow at baseline, early response, best response, molecular progression, and overt relapse would permit reconstruction of evolutionary trajectories.

Third, the meaning of differentiation requires refinement. Mature cells during therapy may be terminal leukemic progeny, normal recovering hematopoiesis, or members of a persistent malignant clone; consequently, morphology, flow cytometry, and molecular clearance may be discordant. Paired single-cell genotyping, transcriptomics, and surface-protein profiling from baseline through response and relapse could determine whether a persistent state was pre-existing, selected, or induced by therapy.[78]

Fourth, optimal combinations and sequences remain unknown. Randomized studies should compare menin-containing regimens with contemporary standards and should evaluate quality of remission, duration, survival, transplantation, and late toxicity. Drug-specific resistance maps are required to determine when switching inhibitors is rational. Pharmacokinetic and pharmacodynamic modeling may identify whether continuous exposure, pulsed high exposure, or alternating combinations best suppress resistant clones.

Finally, long-term safety deserves attention as menin inhibitors move into frontline therapy and maintenance. Menin has physiological roles outside leukemia, and prolonged inhibition could have endocrine, metabolic, reproductive, or developmental consequences that are not evident in short relapsed-disease trials. Pediatric follow-up is particularly important. The successful future of the class will depend on pairing molecular precision with equally rigorous surveillance of normal tissue effects.

11. Conclusion

Menin inhibition has converted a shared transcriptional dependency in *KMT2A*-r and *NPM1*-mut AML into a clinically validated therapeutic opportunity.[79] Acquired *MEN1* drug-pocket mutations are currently the most firmly established clinical mechanism of resistance. Epigenetic and signaling bypass and altered apoptotic dependence are supported primarily by functional preclinical studies, whereas metabolic adaptation, persistent stem-like states, microenvironmental protection, and lineage plasticity remain emerging or putative contributors that require validation in paired longitudinal patient samples.

Monitoring should reflect the same hierarchy. Quantitative *NPM1* molecular MRD is comparatively

standardized, whereas *KMT2A*-r molecular monitoring is fusion- and assay-dependent. Serial target-gene expression, deep *MEN1* clone tracking, and single-cell state profiling remain investigational and should be evaluated prospectively rather than used as stand-alone triggers for treatment modification.

Earlier combinations, mutation-informed next-generation inhibitors, MRD-directed adaptation, transplantation, and post-transplant maintenance are important research strategies, but most have not been established as resistance-directed standards of care. Future trials should distinguish prevention of resistance from treatment of clinically established resistance and should incorporate uniform definitions, paired samples, and subtype-specific molecular monitoring.

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