

Current Directions in Clinical and Preclinical Research on Myeloid Neoplasms

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Abstract

Myeloid neoplasms, including myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), have entered a precision era defined by genomic disease classification, biologically informed risk stratification, and rapidly expanding targeted therapeutics. Contemporary classification systems incorporate recurrent genetic abnormalities and unify clinical entities across bone marrow blast cell thresholds, enabling alignment of therapeutic development with molecular biology. In lower-risk MDS, erythroid maturation and telomerase inhibition have moved treatment endpoints beyond symptomatic transfusion reduction, toward durable transfusion independence and potential disease modification. In higher-risk MDS and AML, BCL-2 inhibition, next-generation hypomethylating strategies, and targeted agents against FLT3, IDH1/2, and menin-dependent transcriptional programs have redefined standards of care for specific genotypes. Parallel preclinical pipelines emphasize immunotherapies (CD47 blockade, bispecific antibodies, cellular therapies), epigenetic reprogramming, and metabolic targeting, with measurable residual disease (MRD) guiding response-adaptive sequencing. This narrative review synthesizes pivotal clinical trials, mechanistic rationale, resistance biology, and emerging translational directions expected to shape management of myeloid neoplasms through the next decade.

Key words: Myelodysplastic syndromes; acute myeloid leukemia; targeted therapy; translational research; MRD

Abbreviations

2-HG: 2-hydroxyglutarate, Allo-HSCT: Allogeneic hematopoietic stem cell transplantation, AML: Acute myeloid leukemia, AML-EB / MDS-EB: Myelodysplastic syndromes / Acute myeloid leukemia with excess blasts, AZA: Azacitidine, CAR-NK: Chimeric antigen receptor-Natural Killer, CAR-T: Chimeric antigen receptor-T cell, CCUS: Clonal cytopenia of undetermined significance, CCR: Conventional care regimens, CHIP: Clonal hematopoiesis of indeterminate potential, CMML: Chronic myelomonocytic leukemia, CR/CRh: Complete remission / Complete remission with partial hematologic recovery, EFS: Event-free survival, ESA: Erythropoiesis-stimulating

agent, Hb: Hemoglobin, HIF: Hypoxia-inducible factor, HMA: Hypomethylating agent, ICC: International Consensus Classification, IPSS-M: Molecular International Prognostic Scoring System, IPSS-R: Revised International Prognostic Scoring System, LDAC: Low-dose cytarabine, LPS: Lipopolysaccharides, LSC: Leukemic stem cell, LSD1: Lysine-specific demethylase 1, MDS: Myelodysplastic syndromes, MPN: Myeloproliferative neoplasm, MRD: Measurable (or Minimal) residual disease, NGS: Next-generation sequencing, OS: Overall survival, PCR: Polymerase chain reaction, PRO: Patient-reported outcome, PV/ET: Polycythemia vera / Essential thrombocythemia, R/R: Relapsed / Refractory, RBC: Red blood cell, RS+: Ring sideroblast-positive, TD: Transfusion-dependent, TI: Transfusion independence, t-MN: Therapy-related myeloid neoplasms, VEN: Venetoclax, WHO: World Health Organization

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INTRODUCTION

Myeloid neoplasms comprise a heterogeneous group of clonal disorders arising from hematopoietic stem and progenitor cells, characterized by dysregulated differentiation, ineffective hematopoiesis, and variable risk of leukemic transformation. For decades, diagnosis and risk assessment relied on morphology and cytogenetics. The widespread adoption of next-generation sequencing (NGS) has revealed recurrent driver mutations, clonal architectures, and targetable dependencies, shifting the field toward biologically defined entities and precision therapeutics [1,2]. The 2022 WHO and the International Consensus Classification (ICC) integrate genetic abnormalities into disease definitions and acknowledge biologic continuity across traditional blast-count boundaries (e.g., MDS/AML) [3,4].

These conceptual changes have immediate practical consequences: trial enrollment is increasingly enriched with molecularly based eligibility and response criteria, response metrics incorporate measurable residual disease (MRD), and therapeutic sequencing is shaped by genotype, fitness, and clonal dynamics.

This narrative review summarizes current directions in clinical and preclinical research on myeloid neoplasms with emphasis on (i) early clonal states and genomics-integrated risk models, (ii) practice-shaping

trials and evolving standards in lower-risk MDS, higher-risk MDS, and AML, (iii) resistance biology and rational combinations, and (iv) emerging translational platforms including immunotherapy, epigenetic and inflammatory pathway-targeting, metabolic interventions, and data-driven decision support. Key contemporary trials, representative investigational directions and related pathways discussed in this review are summarized in Figure 1 and Tables 1 and 2.

Molecular background and risk stratification

Early clonal states: CHIP and CCUS

Age-associated clonal hematopoiesis of indeterminate potential (CHIP) is defined by somatic mutations—most commonly in DNMT3A, TET2, and ASXL1—detectable in peripheral blood in individuals without cytopenias or morphologically diagnostic marrow dysplasia [5,6]. CHIP is associated with an increased risk of hematologic malignancy and cardiovascular events, linking hematologic clonal selection with systemic inflammation and vascular biology [5,7]. Clonal cytopenia of undetermined significance (CCUS) extends this concept, by coupling persistent cytopenias with clonal mutations, but without morphologic criteria for MDS. CCUS carries substantially higher risk of progression to a clinically recognizable myeloid disease

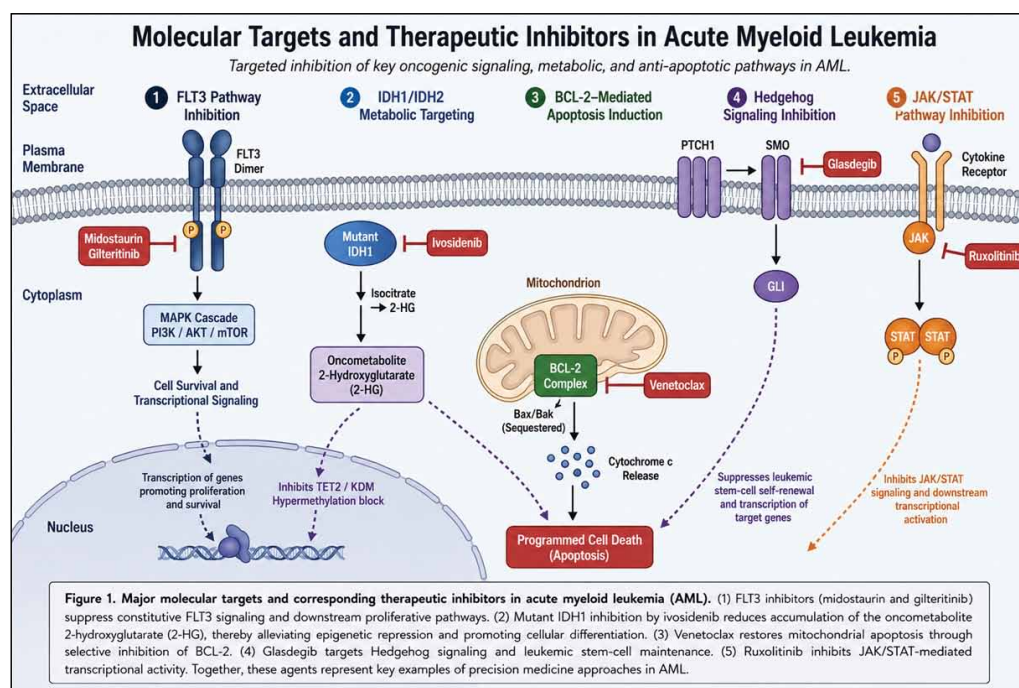


Figure 1. Major molecular targets and corresponding therapeutic inhibitors in acute myeloid leukemia.

Table 1. Pivotal phase 3 trials and selected investigational strategies in myeloid neoplasms.

Disease/ Setting	Trial (Phase)	Population	Intervention vs Control	Primary Endpoint	Key Result	Key Safety Signal	Ref
LR-MDS, TD, RS+	MEDALIST (III)	ESA-refractory	Luspatercept vs placebo	TI ≥ 8 weeks	38% vs 13%	Fatigue, GI AEs	[18]
LR-MDS, ESA-naïve	COMMANDS (III)	TD	Luspatercept vs epoetin alfa	TI + Hb↑	Superior TI & durability	Favorable safety	[19]
LR-MDS, post-ESA	IMerge (III)	TD, non-del(5q)	Imetelstat vs placebo	TI ≥ 8 weeks	40% vs 15%	Neutropenia, thrombocytopenia	[20]
HR-MDS	AZA-001 (III)	Untreated HR	Azacitidine vs CCR	OS	OS benefit	HMA-related cytopenias	[24]
HR-MDS/CMML	PANTHER (III)	Untreated HR	Pevonedistat + AZA vs AZA	EFS	NS	Manageable toxicity	[28]
ND AML (unfit)	VIALE-A (III)	Newly diagnosed	AZA + Ven vs AZA	OS	14.7 vs 9.6mo	Myelosuppression	[36]
ND AML IDH1-mut	AGILE (III)	Unfit	AZA + ivosidenib vs AZA	OS	24.0 vs 7.9 mo	Differentiation syndrome	[38]
R/R AML FLT3-mut	ADMIRAL (III)	Relapsed	Gilteritinib vs chemo	OS	OS 9.3 vs 5.6 mo	Cytopenias, QT	[40]
ND AML FLT3-ITD	QuANTUM-First (III)	Intensive	Quizartinib + "7+3" vs "7+3"	OS	31.9 vs 15.1 mo	QT prolongation	[41]
R/R AML	FF-10101 (I)	Post-FLT3i	Covalent FLT3 inhibitor	Safety	Early activity	Investigational	[42]
R/R KMT2A/NPM1	AUGMENT-101 (II)	Pretreated	Revumenib	CR/CRh	MRD-neg responses	Differentiation syndrome	[43,44]

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; CCR, conventional care regimens; CR/CRh, complete remission/complete remission with partial hematologic recovery; EFS, event-free survival; HR, higher risk; LR, lower risk; OS, overall survival; RS+, ring sideroblast-positive; TD, transfusion-dependent; TI, transfusion independence; VEN, venetoclax.

entity than CHIP, particularly when multiple mutations, high variant allele frequency, or high-risk lesions (e.g., TP53, spliceosome genes) are present [8,9]. Such pre-malignant states, like those two previously mentioned, are now central to clinical research: they enable risk modeling, biomarker discovery, and the design of early-intervention trials aimed at intercepting progression before overt neoplasia.

Genomics-integrated prognostic models

Risk stratification in MDS historically relied on IPSS-R, which uses marrow blasts, severity of cytopenias, and cytogenetics, as major prognostic parameters [10]. While clinically useful, IPSS-R does not formally incorporate somatic mutations, despite the clear prognostic significance of lesions, such as TP53, ASXL1, RUNX1, and SF3B1

mutations [11,12]. IPSS-M addresses this inadequacy, by integrating clinical variables, cytogenetics, and mutation data to redefine risk categories and improve discrimination, especially within the intermediate-risk groups, for which treatment decisions are most difficult [13]. This has catalyzed biologically-based clinical trial design, in which high-risk molecular features can drive eligibility, even at lower blast counts, and the identifiable endpoints increasingly incorporate molecular response and MRD. Beyond prognosis, somatic mutations are often not only predictive but also diagnostic: SF3B1 mutations correlate with the ring sideroblast phenotype and response to erythroid maturation strategies, whereas multi-hit TP53 defines a subset with inherent resistance to HMAs and poor outcomes with conventional approaches, including allogeneic transplantation [14,15].

Table 2. *Signal transduction pathways, molecular targets, and therapeutic agents in myeloid neoplasms.*

Pathway / Molecular Target	Role in Pathogenesis / Mechanism	Targeted Agent(s)	Development Stage & Status	Key Myeloid Neoplasm(s)	Ref
FLT3 Signaling	Constitutive activation of FLT3 tyrosine kinase receptors drives uncontrolled cell proliferation and survival pathways.	Gilteritinib, Quizartinib, Midostaurin	FDA-approved & widely available; used in combination with intensive chemo or as monotherapy.	FLT3-mutated AML	[40,41,62]
IDH1 / IDH2 Metabolic Pathway	Neomorphic mutations result in the abnormal production of the oncometabolite 2-hydroxyglutarate (2-HG), causing global DNA hypermethylation and differentiation arrest.	Ivosidenib (IDH1), Enasidenib (IDH2), Olutasidenib (IDH1)	FDA-approved & widely available; used as targeted monotherapy or in combination regimens.	IDH1/2-mutated AML / MDS	[38,39,53,63]
BCL-2 / Apoptotic Pathway	Overexpression of anti-apoptotic B-cell lymphoma 2 (BCL-2) allows leukemia blasts to evade apoptosis and resist chemotherapy.	Venetoclax	FDA-approved & widely available; standard of care when combined with hypomethylating agents.	Acute Myeloid Leukemia (AML) (unfit for intensive therapy)	[32,33,36,69]
JAK/STAT Pathway	Aberrant JAK2/STAT signaling leads to severe cytokine hypersensitivity, constitutional symptoms, and splenomegaly via uncontrolled myeloproliferation.	Ruxolitinib, Fedratinib, Pacritinib, Momelotinib	FDA-approved & widely available across multiple myelofibrosis sub-settings.	Myelofibrosis (Primary and Post-PV/ET), Post-MPN AML	[64]
Hedgehog Signaling Pathway	Aberrant activation of Smoothened (SMO) maintains leukemia stem cell self-renewal, drives disease progression, and mediates chemotherapy resistance.	Glasdegib	FDA-approved & available; combined with low-dose cytarabine (LDAC).	Newly diagnosed AML (elderly/unfit)	[66]
KMT2A (MLL) / Menin Complex	Chromosomal rearrangements or NPM1 mutations cause dysregulated HOX gene transcription, preventing proper myeloid differentiation.	Revumenib, Ziftomenib	Advanced Clinical Development / Newly Approved (Phase II/III); highly active targeted strategy.	Relapsed/Refractory KMT2A-rearranged or NPM1-mutated AML	[43–46,65]
Spliceosome Machinery	Somatic mutations in core splicing factors (SF3B1, SRSF2, U2AF1) impair mRNA splicing of vital hematopoietic genes, altering regular differentiation.	H3B-8800, Pladienolide B derivatives	Early-phase clinical trials (Phase I/II investigational therapies); targeting RNA-splicing modulation.	MDS, CMML, AML with spliceosome mutations	[61,67,68]
Epigenetic Regulation (DNA Methylation)	Somatic hypermethylation and chromatin alterations downregulate and silence critical tumor suppressor genes.	Azacitidine, Decitabine, Oral ASTX727 (decitabine/cedazuridine)	FDA-approved & standard backbone therapy for high-risk non-intensive regimens.	HR-MDS, CMML, AML	[24,36]

Lower-risk mds: targeting ineffective erythropoiesis

Clinical goals and the ESA benchmark

Lower-risk MDS (LR-MDS) is dominated by chronic anemia and transfusion dependence, with morbidity mainly driven by cytopenias, infections, iron overload, and reduced quality of life, rather than by an imminent leukemic transformation. ESAs remain the standard first-line treatment approach for many patients with low transfusion burden and low serum levels of endogenous erythropoietin; typical response rates are about 30–40%, with median durations often lasting less than two years. Responses are less likely to be observed in patients with high baseline levels of serum erythropoietin or in those with substantial transfusion needs [16,17]. These limitations have motivated biologically targeted approaches that aim for higher response rates, longer durability, and potential disease modification.

Luspatercept: Targeting late-stage erythroid maturation

Luspatercept is an erythroid maturation agent that modulates TGF- β superfamily signaling to enhance late-stage erythropoiesis. The phase 3 MEDALIST trial was a randomized, double-blind, placebo-controlled study, enrolling transfusion-dependent LR-MDS patients with ring sideroblasts, who were refractory to, or unlikely to respond to ESAs [18]. The primary endpoint red blood cell (RBC) transfusion independence (TI) for ≥ 8 weeks during weeks 1–24—was achieved by 38% with luspatercept versus 13% with placebo, and additional benefits were observed, such as in longer TI intervals and erythroid hematologic improvement [18]. Adverse events were generally manageable; fatigue, diarrhea, and musculoskeletal symptoms were common, and discontinuation rates were relatively low. Importantly, the trial validated that targeting erythroid maturation, rather than stimulation of earlier stages of erythropoiesis can meaningfully reduce transfusion dependence in a biologically defined patient subgroup.

The COMMANDS study extended luspatercept into the frontline setting by head-to-head comparing luspatercept with epoetin alfa in ESA-naïve, transfusion-dependent LR-MDS [19]. In the primary analysis, luspatercept demonstrated superiority in the achievement of clinically meaningful transfusion independence, with hemoglobin improvement and longer response durability across relevant subgroups, including patients without ring sideroblasts, and those with low/normal

baseline serum erythropoietin levels [19]. These findings reframe first-line anemia management in lower-risk MDS patients: rather than viewing ESAs as default and luspatercept as second-line, a phenotype- and biology-informed approach can prioritize the durability of response and transfusion avoidance. Ongoing analyses focus on the identification of predictors of response (including SF3B1 mutational status), disease progression rates, and practical sequencing strategies.

Imetelstat: telomerase inhibition and a disease-modifying hypothesis

Imetelstat, a first-in-class telomerase inhibitor, represents a mechanistically distinct approach that targets clonal persistence, rather than erythroid maturation alone. The multinational, randomized, double-blind, placebo-controlled phase 3 IMerge trial enrolled transfusion-dependent LR-MDS patients without del(5q), who relapsed after, were refractory to, or were ineligible for treatment with ESAs [20]. The primary endpoint of TI ≥ 8 weeks was met by 40% of imetelstat-treated patients compared with 15% of those on placebo; a clinically important subset achieved TI ≥ 24 weeks, and median TI duration approximated one year in many reports [20]. The dominant toxicities were cytopenias (notably neutropenia and thrombocytopenia), necessitating careful monitoring, dose modifications, and strategies for infection prophylaxis, where appropriate. From a translational standpoint, IMerge is a notable study, because some responders showed reductions in mutation allele burden, raising the possibility that in this patient group telomere inhibition might induce partial disease modification. Whether telomerase inhibition can consistently suppress malignant clones, while allowing recovery of effective, non-clonal hematopoiesis remains an active research question, requiring longer follow-up, clonal architecture analyses, and integration of marrow and molecular response endpoints.

Other directions in LR-MDS

Additional anemia-directed strategies include hypoxia-inducible factor (HIF) prolyl hydroxylase inhibition (e.g., roxadustat), which increases endogenous erythropoietin signaling and iron utilization, induces the formation of agents, and modulates the inflammatory marrow microenvironment [21,22]. Safety signals (including thrombotic concerns) and heterogeneous efficacy underscore the need for biomarker-driven selection and the design of a robust phase 3 validation. A

broader, unifying direction is to re-conceptualize LR-MDS as a chronic clonal disorder of aging, with inflammatory contributions (“inflammaging”), where the therapeutic aim will remain the durable transfusion independence with minimal toxicity, while delaying disease progression [7,22].

Practical sequencing and response prediction

A central clinical question is how to sequence ESAs, luspatercept, and imetelstat, in a way that maximizes survival time, free of transfusions, while concurrently minimizing cumulative toxicity and clinic burden. While ESAs remain appropriate for patients with low transfusion needs and favorable baseline serum erythropoietin levels, the COMMANDS trial results suggest that transfusion-dependent patients—particularly those with ring sideroblasts and/or SF3B1 mutations—may benefit from earlier initiation of luspatercept, to achieve longer transfusion independence and to reduce transfusion-related iron overload [19]. In contrast, imetelstat is positioned at the second or third line of treatment, for patients who have failed, are ineligible for, or are unlikely to gain benefit from ESAs, and who require a strategy with the potential for longer durability, accepting the trade-off of higher rates of cytopenias and need for monitoring [20]. From a research standpoint, predictive biomarkers for response remain an urgent need. Candidate predictors include baseline transfusion burden, serum erythropoietin, ring sideroblast status, SF3B1 mutational status, and broader co-mutation patterns that may reflect stem-cell dominance versus lineage-restricted ineffective erythropoiesis [13–23]. Another practical direction is to study “switch” or “step-up” designs (e.g., early switch from ESA to luspatercept, based on predefined non-response criteria, or escalation to imetelstat in patients with short TI duration), with endpoints that capture patient-centered benefit, such as cumulative transfused units avoided, time to achievement of a hemoglobin level above a functional threshold, and validated quality-of-life instruments.

Higher-risk mds: combination strategies and transplant bridging

Backbone therapy and unmet need

For higher-risk MDS (HR-MDS), the management objectives are to delay AML transformation, prolong survival, and, where feasible, bridge to allogeneic stem cell transplantation. Azacitidine has demonstrated survival

benefit over conventional care regimens in the pivotal AZA-001 study and remains a backbone standard for non-transplant candidates [24]. Nevertheless, responses are often transient, and outcomes after HMA failure are poor, motivating intensive research into the design of rational combinations, molecular enrichment, and MRD-guided strategies [25,26].

Venetoclax plus azacitidine: depth versus tolerability

Given the biologic overlap between HR-MDS and AML, BCL-2 inhibition with venetoclax or other similar emerging compounds has been explored in combination with azacitidine. Early phase studies in untreated HR-MDS have reported high overall response rates, with meaningful complete remission rates and the potential to bridge some patients to transplantation [27]. However, translating higher response rates into improved overall survival is sometimes challenging, because profound myelosuppression, infections, and early mortality can offset benefit in frail patients. Current clinical research, therefore, emphasizes response-adaptive scheduling (shortened venetoclax exposure or tailoring its dose), optimized supportive care, and patient selection to maximize benefit, while minimizing infection-related complications.

Pevonedistat: a phase 3 lesson in translation

Pevonedistat inhibits NEDD8-activating enzymes, disrupting cullin-RING ligase activity and inducing proteotoxic stress in malignant cells. Although earlier studies suggested synergy with azacitidine, the phase 3 PANTHER trial (pevonedistat plus azacitidine vs azacitidine alone) did not meet its primary endpoint; outcomes numerically favored the combination in some analyses but without prespecified statistical significance [28]. These results have offered a lesson: the failure of the trial to reach its primary endpoint was methodological and biologic, namely, not all “add-on” combinations succeed in heterogeneous diseases, and future programs increasingly require biomarker-defined subgroups, mechanistic correlatives, and careful endpoint selection, beyond overall response rates alone.

Immune checkpoint modulation and the “cold marrow” problem

Checkpoint inhibition has proven less successful in MDS than in some solid tumors, probably reflecting the existence of an immunosuppressive marrow milieu, with complex myeloid and stromal interactions. TIM-3

blockade with sabatolimab was advanced through early studies, but the pivotal development of a phase-3 study has encountered major setbacks, highlighting the difficulty of translating checkpoint concepts to MDS without combination logic, predictive biomarkers, or targeting of innate immune pathways [29,30]. Current translational efforts increasingly focus on macrophage-controlled checkpoints, bispecific antibodies, and microenvironment reprogramming, rather than simply checkpoint modulatory monotherapy.

TP53-mutant HR-MDS: the central unmet need

TP53 mutations, especially multi-hit/biallelic alterations, define a high-risk subset, characterized by genomic instability, poor HMA responsiveness, high relapse risk after transplant, and short survival [14,15]. Eprenetapopt (APR-246), designed to restore wild-type p53 conformation, generated encouraging phase 2 trial results but failed to confirm benefit in later-stage testing, emphasizing allelic context and biologic complexity [31]. Research directions include exploiting DNA damage response vulnerabilities, integrating innate immune approaches, optimizing transplant strategies, and developing maintenance regimens that target residual TP53-mutant clones. These efforts represent a defining frontier for the next generation of HR-MDS therapeutics.

Optimizing combinations and transplant pathways

In HR-MDS, venetoclax plus azacitidine is often discussed as the currently most effective regimen available, through the lens of high response rates, but the critical clinical questions are durability of response, safety, and the ability of the patient to reach transplantation in adequate clinical condition. Early phase cohorts commonly included patients with excess blasts (often MDS-EB) and demonstrated rapid cytoreduction and measurable remissions [27]. It is important to note that the results of the venetoclax plus azacitidine (Ven-Aza) combination are highly compelling; if not superior in safety and tolerability to conventional anthracycline-based intensive chemotherapy regimens. Consequently, utilizing this combination even in patients with secondary AML arising from antecedent MDS (post-MDS AML) may significantly increase the proportion of patients who can successfully achieve a deep enough remission to proceed to allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, venetoclax-driven myelosuppression may be

profound in a population that already has limited hematopoietic reserve, and infectious complications can be frequent without careful schedule optimization and application of appropriate prophylaxis. Consequently, contemporary clinical trials increasingly explore shorter venetoclax exposure per cycle (for example, 7–14 days rather than 28 days), individualized cycle length and dose intensification based on count recovery, and standardized antimicrobial prophylaxis algorithms. Translational correlates focus on apoptotic priming, BCL-2 family adaptation (e.g., upregulation of MCL-1 or BCL-xL), and clonal selection as mechanisms of resistance [32,33]. The research direction is therefore not merely “add venetoclax,” but “engineer a deliverable and affordable regimen” where depth of response is achieved without unacceptable infection-related mortality.

Outcomes after HMA failure in HR-MDS are poor, with limited effective options and frequent progression to AML [25,26]. This has driven a methodological shift: trials in the post-HMA setting increasingly prioritize endpoints, such as overall response with transfusion improvement, time to AML transformation, and event-free survival, and they incorporate molecular response and MRD where feasible. In addition, studies increasingly stratify patients by TP53 allelic state and complex karyotype, because these features clearly dominate outcomes and can dilute efficacy signals, if not balanced or enriched [14,15]. Another direction is the development of maintenance treatment strategies after the achievement of an initial response (with HMAs, targeted agents, or immunomodulatory approaches) to prolong remission and delay clonal escape, particularly for patients not proceeding to transplant.

Allo-HSCT remains the only potentially curative therapy for many HR-MDS and AML patients, but transplant benefit is tightly linked to disease biology and depth of remission at transplantation. Achieving cytoreduction with acceptable toxicity is, therefore, a core research target, and not just a secondary consideration. Trials increasingly evaluate “bridge-to-transplant” endpoints (proportion transplanted, MRD status at transplant, non-relapse mortality, and relapse-free survival), rather than response rates alone. Conditioning regimen intensity and post-transplant maintenance are also active research areas. For example, in FLT3-mutated AML, post-transplant FLT3 inhibitor maintenance treatment has demonstrated a reduction in relapse rates in multiple studies and,

therefore, the general concept that molecularly targeted maintenance may be required to suppress residual disease after transplant has clearly been formed [34,35]. Extending this paradigm to other genotypes (IDH, menin-dependent programs, TP53) is a major translational goal, although robust data still remain limited for some patient subsets.

AML: targeted therapy era and response-adaptive strategy

Venetoclax-based therapy in older/unfit AML

The phase 3 VIALE-A trial established azacitidine plus venetoclax as standard therapy for newly diagnosed AML patients ineligible for intensive chemotherapy, demonstrating improved overall survival (median 14.7 vs 9.6 months), and higher composite complete remission rates, compared with azacitidine alone [36]. The regimen's major limitation is the induction of substantial myelosuppression and an increased infection risk. Contemporary practice and research increasingly use early marrow assessment and the time interval to blood count recovery, to individualize venetoclax duration (e.g., 14–21 days rather than 28 days) and to guide cycle timing, reflecting a broader shift toward response-adaptive dosing, rather than fixed-intensity protocols [37]. Ongoing studies explore triplets (azacitidine and venetoclax, plus targeted agents) and post-remission strategies, including transplant bridging and maintenance treatment regimens.

IDH inhibition: differentiation therapy via metabolic correction

Mutations in IDH1 and IDH2 produce the oncometabolite 2-hydroxyglutarate, which impairs epigenetic regulation and blocks differentiation. In the AGILE trial, azacitidine plus ivosidenib (IDH-1 inhibitor) significantly improved outcomes in newly diagnosed IDH1-mutated AML patients unfit for intensive therapy, achieving a median overall survival of 24.0 months versus 7.9 months for azacitidine plus placebo [38]. Differentiation syndrome is an important class toxicity, requiring early recognition and corticosteroid management. Enasidenib, an IDH2 inhibitor, has demonstrated activity in relapsed/refractory IDH2-mutated AML with durable responses in a subset and similar differentiation-related toxicity patterns [39]. Current research evaluates combinations of IDH inhibitors with venetoclax or HMAs, mechanisms of resistance (including clonal evolution and second-site mutations), and sequencing strategies.

FLT3 inhibition: from salvage to frontline survival improvement

FLT3 mutations, particularly FLT3-ITD, confer proliferative signaling to the leukemic cell and poor prognosis to the patient, without targeted therapy. In relapsed/refractory FLT3-mutated AML, the ADMIRAL trial showed that the FLT3-inhibitor gilteritinib improved overall survival versus salvage chemotherapy (median 9.3 vs 5.6 months), with a tolerable safety profile that supports outpatient administration and transplant bridging [40]. In the frontline intensive setting, the QuANTUM-First trial demonstrated that adding quizartinib to standard induction and consolidation improved median overall survival (31.9 vs 15.1 months) in FLT3-ITD AML, establishing potent FLT3 inhibition as a practice-changing strategy [41]. Despite these advances, resistance remains common via the presence of insensitive TKD mutations, bypass signaling, and clonal selection. Next-generation approaches include covalent FLT3 inhibitors such as FF-10101, designed to retain activity against resistant kinase conformations and to be incorporated into rational combinations [42].

Menin inhibition: targeting transcriptional dependency in KMT2A and NPM1 AML

KMT2A-rearranged and NPM1-mutated AML share a leukemogenic transcriptional program, dependent on menin–KMT2A interaction. Menin inhibitors disrupt this dependency, promoting differentiation and loss of leukemic self-renewal. In the AUGMENT-101 program, revumenib demonstrated clinically meaningful remissions in heavily pretreated KMT2A/NPM1 acute leukemias, with MRD negativity in a substantial fraction of responders and differentiation syndrome as a characteristic, manageable toxicity [43,44]. These findings represent a novel and modern differentiation therapy concept beyond APL. Ziftomenib and other menin inhibitors are currently being developed, including combinations with venetoclax and HMAs, to increase the depth and durability of response and to mitigate resistance [45,46]. Key interpretational questions include the recognition of the optimal line of therapy, establishment of the appropriate biomarkers of sensitivity, and the prevention or inhibition of potentially emerging mechanisms of acquired resistance at the menin-binding interface.

MRD, clonal dynamics, and transplantation

MRD is increasingly incorporated into AML trials and clinical practice as a crucial endpoint, because MRD

negativity correlates with relapse risk and survival across treatment intensities [47,48]. Methods for its evaluation include multiparameter flow cytometry, quantitative PCR for selected lesions, and NGS-based detection of residual clones. MRD is also being explored as a trigger for post-remission therapy escalation, transplant referral, or maintenance. In MDS, MRD assessment is more challenging, due to lower blast burden and overlap with clonal hematopoiesis, but molecular monitoring (including TP53 allele burden) is increasingly used in transplant settings and clinical research [49]. A major direction for 2025–2030 is the standardization of MRD assays, thresholds, and the establishment of appropriate timepoints, to enable MRD-guided adaptive therapy as a validated strategy rather than an investigational tool.

AML: resistance biology and rational triplets

Mechanisms of resistance to venetoclax-based therapy

Despite high initial responses, relapse after venetoclax plus HMA is common, and resistance biology has become a dominant translational research field. Mechanisms include clonal evolution with acquisition or selection of RAS/MAPK pathway mutations, upregulation of alternative anti-apoptotic proteins (MCL-1, BCL-xL), changes in mitochondrial priming, and metabolic rewiring toward oxidative phosphorylation states less sensitive to BCL-2 blockade [32,33,50]. These insights motivate rational triplets, such as venetoclax plus HMA plus a targeted inhibitor (FLT3, IDH, or menin) to address both lineage/epigenetic programs and survival signaling. However, triplets increase myelosuppression and infectious risk, reinforcing the importance of response-adaptive scheduling and supportive care as integral components of a holistic therapeutic design.

Resistance to FLT3 and IDH inhibitors

Resistance to FLT3 inhibitors arises via secondary kinase-domain mutations, activation of parallel signaling (RAS/MAPK), and stromal protection. Combination regimens aim to suppress multiple escape routes, and next-generation inhibitors (including covalent agents) attempt to maintain activity against common resistance mutations [42,51]. IDH inhibitor resistance can involve second-site IDH mutations, isoform switching (IDH1 to IDH2 or vice versa), and selection of non-IDH-driven clones, highlighting the need for serial molecular monitoring and combination strategies that prevent outgrowth of alternative clones [52,53]. In this context,

MRD and clonal tracking are not merely prognostic; they are actionable tools for early detection of escape and timely therapeutic switching.

Menin inhibitor resistance and differentiation dynamics

Menin inhibitor therapy introduces distinctive response dynamics: differentiation programs that can occur without immediate cytotoxic clearance, and differentiation syndrome can mimic infection or inflammatory relapse. Clinical research, therefore, emphasizes the need for education and standardized management pathways, including the early administration of corticosteroids and supportive care, without unnecessary discontinuation when feasible [43,44]. Resistance mechanisms include mutations that disrupt drug binding, and adaptation of transcriptional programs. Combination strategies (menin inhibitor plus venetoclax/HMA, or with kinase inhibitors in selected contexts) are being evaluated to deepen remissions and reduce the probability of resistant clone emergence [46].

Preclinical and translational frontiers

Innate immune targeting: CD47 blockade

The CD47–SIRPα axis functions as a macrophage checkpoint, by delivering a “don’t eat me” signal to phagocytes. CD47 blockade aims to enhance macrophage-mediated clearance of malignant cells and has been investigated to enhance phagocytic signaling and immune activation [54,55]. While clinical development has been heterogeneous across programs, innate immune engagement remains a major translational direction, particularly for genomically high-risk disease, where classic cytotoxic strategies are inadequate.

Bispecific antibodies and redirected cytotoxicity

T-cell redirecting bispecific antibodies (e.g., CD123×CD3 constructs) recruit cytotoxic lymphocytes to target myeloid blasts. Early-phase studies demonstrate activity in heavily pretreated AML, with cytokine release syndrome as an important toxicity requiring standardized mitigation and monitoring [56]. Translational research focuses on improving therapeutic windows, preventing antigen escape, combining with venetoclax/HMAs to reduce tumor burden, and identifying biomarkers predictive of durable benefit.

Cellular therapy: CAR-T and CAR-NK in AML

Adoptive cellular therapies face unique constraints in AML because many of the target antigens are shared

with normal hematopoietic progenitors (e.g., CD33, CD123), and consequently raising the risk of prolonged aplasia. Strategies in development include transient CAR expression, dual-target constructs, safety switches, and use as a bridge to transplant. CAR-NK platforms may reduce cytokine toxicity and enable “off-the-shelf” manufacturing, and are being explored as a potentially safer immunotherapeutic approach [57,58].

Targeting Epigenetic Networks and Inflammatory Signaling

Epigenetic dysregulation is central to MDS/AML biology. Beyond HMAs, next-generation epigenetic strategies aim to reprogram differentiation and restore therapeutic sensitivity. LSD1 inhibition is one such approach promoting differentiation and may synergize with HMAs or venetoclax in preclinical and early clinical settings [59].

Inflammatory signaling is another emerging target. Aberrant TLR/MyD88/IRAK pathway activation has been linked to subsets of MDS/AML, particularly those with spliceosome mutations that generate IRAK4 isoforms with oncogenic signaling. IRAK4 inhibition (e.g., with emavusertib) has shown encouraging early clinical signals and represents a compelling example of targeting leukemia-intrinsic signaling and the inflammatory microenvironment simultaneously [60,61]. These directions align with the broader recognition that inflammaging and innate immune dysregulation contribute to disease maintenance and therapy resistance [7,22]. Moreover, expanding beyond these classical kinase and metabolic cascades, next-generation therapeutic strategies in Table 2 focus heavily on epigenetic reprogramming and the targeting of aberrant bone marrow inflammatory microenvironments. Simultaneously, hyperactivated innate immune signaling is emerging as a critical therapeutic vulnerability.

Also, other pathways such as FLT3 signaling, where targeting the kinase cascade with midostaurin or gilteritinib remains a cornerstone of precision care [40,62]; the IDH1/IDH2 metabolic pathway, where reversing oncometabolite-induced differentiation blocks using ivosidenib or enasidenib has yielded durable clinical remissions; the BCL-2/Apoptotic pathway, where bypassing cellular survival networks via venetoclax combinations has re-established the global standard of care in unfit acute myeloid leukemia (AML) [39,63]; the JAK/STAT pathway, where downstream cascade inhibition with ruxolitinib has transformed myelofibrosis manage-

ment [64]; and the Hedgehog signaling pathway, where stem-cell-directed targeting via glasdegib has disrupted leukemia stem cell self-renewal.

Crucial therapeutic advancements are also occurring within KMT2A (MLL)/Menin Complex chromatin-remodeling networks, where menin inhibitors like revumenib disrupt oncogenic interactions to deliver deep, minimal residual disease (MRD)-negative remissions [43,44,65]. Beyond epigenetic regulation (DNA Methylation) targeted by conventional hypomethylating agents (HMAs), next-generation epigenetic strategies aim to actively reprogram differentiation and restore therapeutic sensitivity; lysine-specific demethylase 1 (LSD1) inhibition is one such approach, promoting differentiation and showing strong potential to synergize with HMAs or venetoclax in preclinical and early clinical settings. Concurrently, targeting hyperactivated innate immune signaling and the structural components of the core spliceosome machinery (such as with the splicing modulator H3B-8800) represents a highly critical therapeutic vulnerability. Aberrant TLR/MyD88/IRAK pathway activation has been fundamentally linked to subsets of MDS/AML, particularly those harboring somatic spliceosome mutations that preferentially drive the production of oncogenic, hypermorphic IRAK4 long isoforms [67,68].

Metabolic targeting beyond IDH

AML metabolism includes dependencies in oxidative phosphorylation, amino acid utilization, and mitochondrial integrity, which intersect with apoptotic priming and venetoclax sensitivity [32,69]. Emerging metabolic strategies include N-myristoyltransferase inhibition, which disrupts membrane localization and function of signaling proteins and has demonstrated preclinical anti-leukemia activity, motivating early translational development [70]. The prevailing research theme is combination logic: metabolic stressors may sensitize leukemia cells to apoptosis-inducing regimens or overcome resistance by collapsing adaptive metabolic states.

Artificial intelligence and implementation science

As treatment options expand, the challenge shifts from drug availability to optimal selection and drug combination, treatment sequencing, and supportive care. AI-assisted decision tools are being developed to integrate genomics, MRD kinetics, comorbidities, frailty, and prior toxicity into individualized recommendations.

Early studies suggest the potential utility of AI in risk stratification and outcome prediction, but prospective validation is required before routine adoption [71,72]. Implementation research—ensuring timely molecular testing, standardized MRD workflows, infection mitigation protocols, and multidisciplinary care pathways—will be as important as pharmacologic innovation in translating trial advances into population-level outcome improvements.

Therapy-related and secondary myeloid neoplasms: a distinct translational priority

Therapy-related myeloid neoplasms (t-MN), including therapy-related MDS/AML and many secondary AMLs evolving from antecedent hematologic disorders, are enriched for adverse genetics such as TP53 mutations, complex karyotype, and epigenetic driver combinations that reflect prior genotoxic stress and clonal selection [73,74]. Clinically, these diseases have inferior responses to conventional chemotherapy and high relapse rates, making them a proving ground for biology-first strategies. Current research emphasizes the importance of early molecular identification, avoidance of ineffective cytotoxic escalation in biologically refractory subsets, and prioritization of transplant pathways when feasible. Translationally, t-MN highlights the importance of clonal evolution: relapses frequently arise from pre-existing minor clones or from CHIP-like clones that survive therapy and later acquire additional hits [75,76]. This biology supports longitudinal NGS monitoring and motivates maintenance strategies that suppress residual high-risk clones after remission or transplant. It also reinforces the need for prevention research in high-risk CHIP/CCUS populations exposed to chemotherapy or radiation, where interception could have substantial public health impact.

Patient-centered outcomes as co-primary research targets

As therapies prolong survival and shift treatment into chronic management, patient-reported outcomes (PROs) and functional measures are increasingly incorporated into trials, particularly in LR-MDS where anemia and transfusion burden drive daily well-being. Future studies should routinely measure fatigue, physical functioning, reduced in-hospital stay and transfusion-related time costs, and should report clinically meaningful hemoglobin thresholds, rather than laboratory change alone. Incorporating PROs alongside molecular

and MRD endpoints will help ensure that precision therapy improves not only survival curves but also lived experience.

CONCLUSION

Research in myeloid neoplasms is converging on a precision framework built on molecular disease definition, mechanism-native therapy, and response-adaptive clinical strategy. Classification systems that integrate genomics have moved the field beyond morphology and have enabled trials and treatment pathways centered on biologically coherent entities [3,4]. In lower-risk MDS, luspatercept validated late-stage erythroid maturation as a therapeutic lever and, in COMMANDS, demonstrated superiority over epoetin alfa, for clinically meaningful transfusion independence and durability, particularly in biologically aligned phenotypes [18,19]. Imetelstat introduced telomerase inhibition as an anemia-directed strategy, with unexpectedly durable freedom of transfusion in ESA-refractory patients, and with molecular signals that raise a credible hypothesis of partial disease modification in selected responders [20]. Together, these developments move lower-risk MDS care from just a symptom-control approach, toward a durable, biology-informed intervention.

In higher-risk MDS and AML, venetoclax-based regimens and genotype-specific targeted therapies have established a new standard: deep remissions are achievable without default reliance on intensive chemotherapy, but benefit is contingent on deliverability and safety. VIALE-A transformed outcomes in older/unfit AML, while AGILE demonstrated that molecular selection (IDH1 mutation) can yield survival gains exceeding many non-targeted approaches [36,38]. In FLT3-ITD AML, QuANTUM-First showed that potent driver suppression integrated into intensive therapy can double median overall survival, and gilteritinib remains a cornerstone in relapsed disease and transplant bridging [40,41]. Menin inhibition has opened a modern differentiation-therapy paradigm for KMT2A-rearranged and NPM1-mutated AML, with MRD negativity among responders and a distinctive, manageable toxicity profile, centered on differentiation syndrome [43,44]. Across these examples, the most practice-changing trials combine a clear biologic rationale, clinically meaningful endpoints, and feasible toxicity management, an overarching message reinforced by Table 1.

At the same time, the field has become more rigorous about what constitutes meaningful benefit. Phase

3 disappointments, such as the PANTHER trial, underscore that response rate signals are insufficient if they do not translate into survival advantage, transplant readiness, or patient-centered improvements, and they highlight the need for biomarker-enriched designs and mechanistic correlatives in heterogeneous diseases [28]. MRD has emerged as a critical integrator of biology and clinical decision-making, offering a pathway toward response-adaptive therapy intensity, transplant timing, and maintenance strategies, provided appropriate assays and decision thresholds are standardized and prospectively validated [47,48].

The largest unmet needs remain concentrated in genomically adverse and therapy-resistant subsets—most notably TP53 multi-hit MDS/AML, therapy-related myeloid neoplasms, and post-venetoclax relapse. Addressing these will likely require multi-pronged strategies that combine DNA damage response vulnerabilities, innate immune engagement, and rational combinations that prevent clonal escape rather than merely deepen initial response. Translational pipelines in innate immunity (CD47 blockade), bispecific antibodies, and cellular therapies are advancing, with the central challenge being leukemia selectivity while preserving normal hematopoiesis [54–58]. Epigenetic reprogramming, inflammatory pathway inhibition (e.g., IRAK4), and emerging metabolic strategies further diversify the research landscape and may become essential components of therapy in resistant biology [59–61,69,70].

Finally, precision medicine in myeloid neoplasms will depend as much on implementation as invention. As therapeutic options multiply, clinicians face complex sequencing decisions that must integrate genomics, MRD kinetics, frailty, infection risk, and access to transplantation. AI-supported decision tools may help operationalize this complexity, but only if they are validated prospectively and embedded within robust care pathways that ensure timely molecular testing and standardized supportive care. The next decade is therefore poised to be defined not simply by more drugs, but by coherent, biology-driven therapeutic pathways—built around early molecular diagnosis, MRD-guided adaptation, and mechanistically justified combinations—that improve survival while preserving quality of life across the spectrum of myeloid neoplasms.

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