

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]