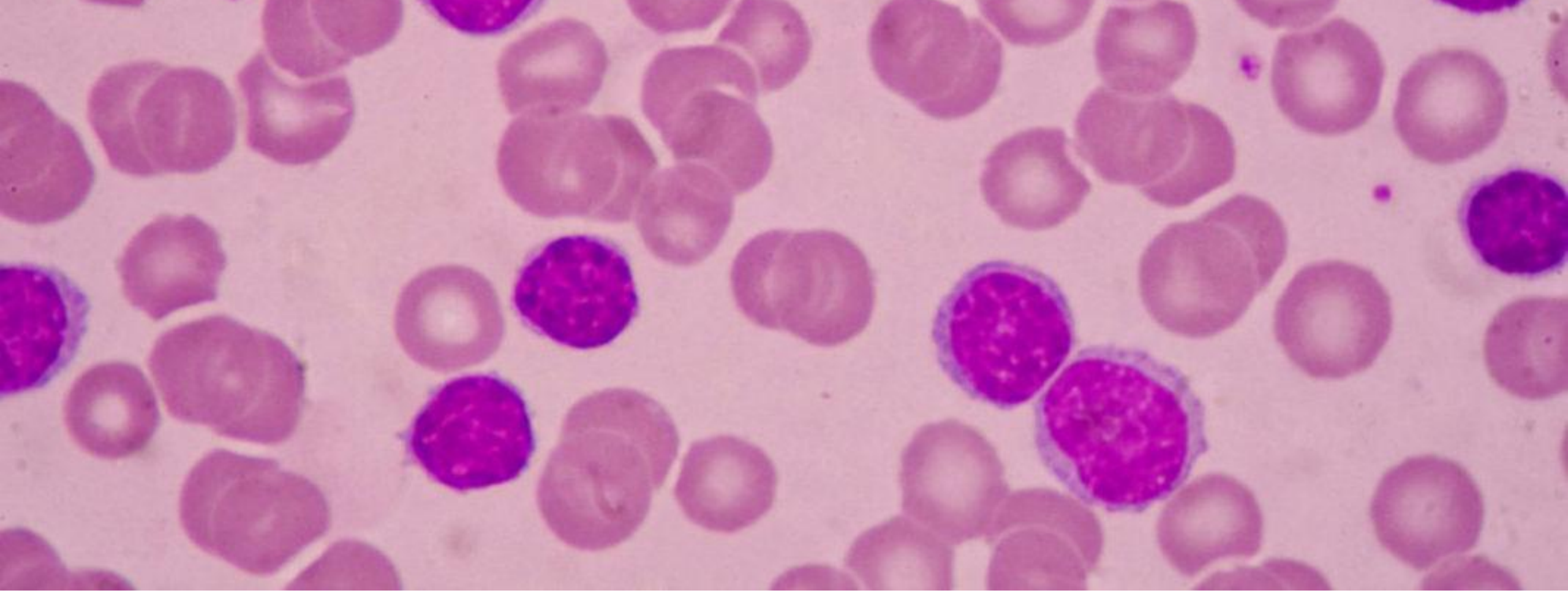

HOW I TREAT AML IN 2023

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OBJECTIVES

1. Review the updated ICC AML Classification
2. Review the new ELN 2022 Rik Stratification
3. Identify recently approved novel therapies in the treatment of AML
4. Explore suggested treatment paradigms
5. Understand the importance of MRD testing
6. Recognize ongoing clinical trials with new and combination therapies

UPDATED INTERNATIONAL CONSENSUS CLASSIFICATION

Classification of AML with percentage of blasts required for diagnosis

Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/*PML*::*RARA* ≥ 10%
APL with other *RARA* rearrangements* ≥ 10%
AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* ≥ 10%
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* ≥ 10%
AML with t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* ≥ 10%
AML with other *KMT2A* rearrangements† ≥ 10%
AML with t(6;9)(p22.3;q34.1)/*DEK*::*NUP214* ≥ 10%
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*; *MECOM*(*EVI1*) ≥ 10%
AML with other *MECOM* rearrangements‡ ≥ 10%
AML with other rare recurring translocations (see supplemental Table 5) ≥ 10%
AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*§ ≥ 20%

AML with mutated *NPM1* ≥ 10%
AML with in-frame bZIP *CEBPA* mutations ≥ 10%
AML and MDS/AML with mutated *TP53*† 10-19% (MDS/AML) and ≥ 20% (AML)
AML and MDS/AML with myelodysplasia-related gene mutations 10-19% (MDS/AML) and ≥ 20% (AML) Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
AML with myelodysplasia-related cytogenetic abnormalities 10-19% (MDS/AML) and ≥ 20% (AML) Defined by detecting a complex karyotype (≥ 3 unrelated clonal chromosomal abnormalities in the absence of other class-defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), −7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), −17/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities
AML not otherwise specified (NOS) 10-19% (MDS/AML) and ≥ 20% (AML)
Myeloid sarcoma

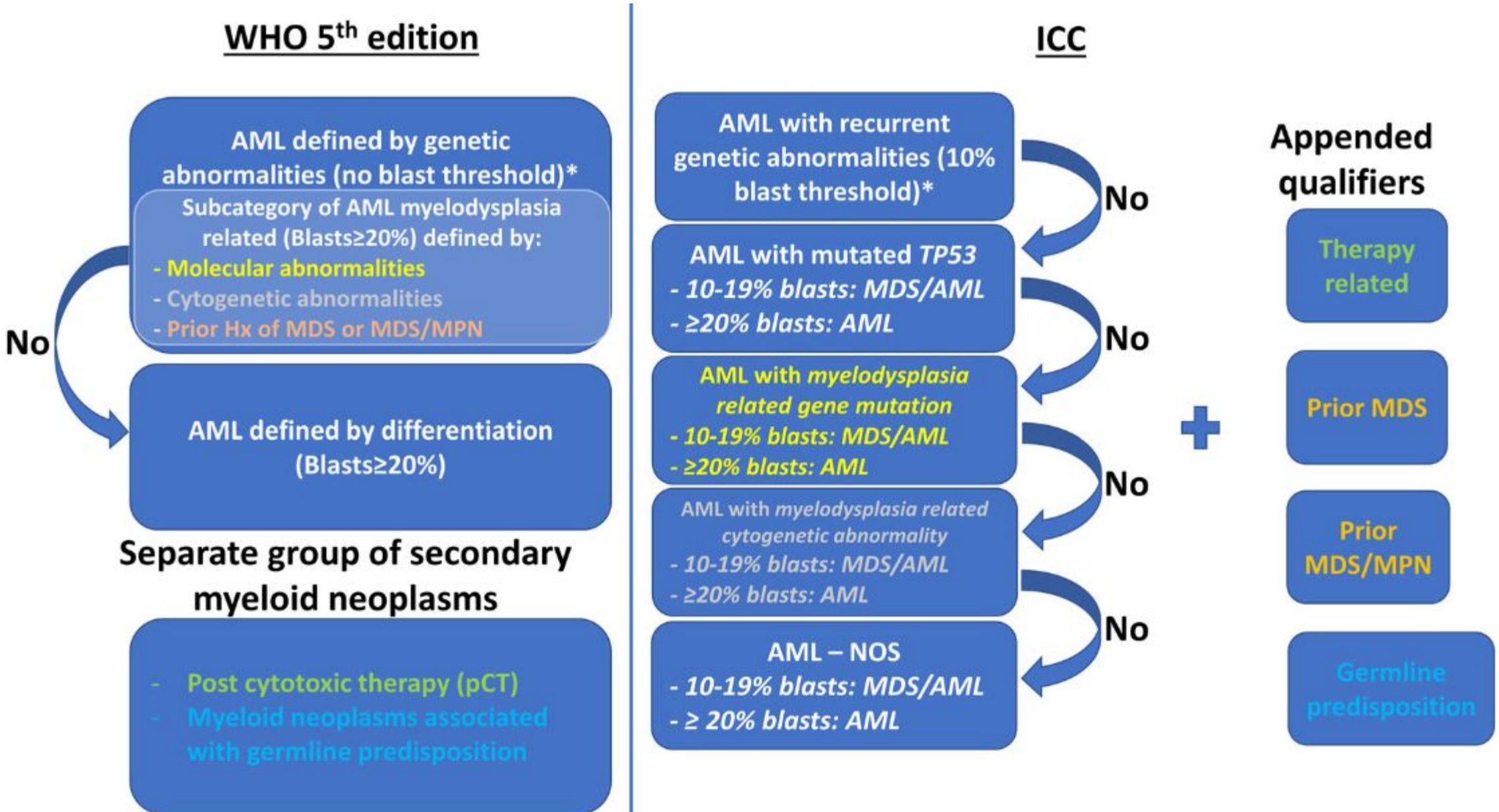
Blood (2022) 140 (11): 1200–1228.

UPDATED INTERNATIONAL CONSENSUS CLASSIFICATION

Diagnostic qualifiers that should be used following a specific AML diagnosis

Therapy-related* • prior chemotherapy, radiotherapy, immune interventions
Progressing from MDS • MDS should be confirmed by standard diagnostics
Progressing from MDS/MPN (specify) • MDS/MPN should be confirmed by standard diagnostics
Germline predisposition

Blood (2022) 140 (11): 1200–1228.



Am J Hematol. 2023;98:502–526.

ELN 2022 GENETIC RISK CLASSIFICA OSIS

Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*‡‡ • Mutated *TP53*[a]

Blood (2022) 140 (12): 1345–1377.

EVALUATION

Tests to establish the diagnosis		Additional tests and procedures
Complete blood count and differential count*		Complete physical examination[c]
Bone marrow aspirate†		Performance status (ECOG/WHO score)
Bone marrow trephine biopsy‡		Geriatric assessment[d] (optional)
Immunophenotyping by flow cytometry (see Table 5)		Biochemistry, coagulation tests[e]
Genetic analyses	Results preferably available within	Hepatitis A, B, C; HIV-1 testing; CMV, EBV, HSV, VZV
Cytogenetics§	• 5-7 d	Serum pregnancy test[f]
Screening for gene mutations required for establishing the diagnosis and to identify actionable therapeutic targets#		Eligibility assessment for allogeneic HCT (incl. HLA-typing)[g]
• *FLT3*,¶ *IDH1*, *IDH2*	• 3-5 d	Chest x-ray, 12-lead electrocardiogram, echocardiography or MUGA (on indication)
• *NPM1*	• 3-5 d	Computed tomography of the chest (on indication)[h]
• *CEBPA*,# *DDX41*, *TP53*; *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*	• 1st cycle	Lumbar puncture (on indication)[i]
Screening for gene rearrangements**		Information on oocyte and sperm cryopreservation[j]
• *PML*::*RARA*, *CBFB*::*MYH11*, *RUNX1*::*RUNX1T1*, *KMT2A* rearrangements, *BCR*::*ABL1*, other fusion genes (if available)	• 3-5 d	Biobanking[k]
Additional genes recommended to test at diagnosis††		
• *ANKRD26*, *BCORL1*, *BRAF*, *CBL*, *CSF3R*, *DNMT3A*, *ETV6*, *GATA2*, *JAK2*, *KIT*, *KRAS*, *NRAS*, *NF1*, *PHF6*, *PPM1D*, *PTPN11*, *RAD21*, *SETBP1*, *TET2*, *WT1*		

Blood (2022) 140 (12): 1345–1377.

RESPONSE ASSESSMENT (NEW DEFINITIONS)

Response	
CR*,†,‡	Bone marrow blasts < 5%; absence of circulating blasts; absence of extramedullary disease; ANC ≥ 1.0×10^9/L (1,000/μL); platelet count ≥ 100×10^9/L (100 000/μL)
CRh*,†,‡	ANC ≥ 0.5×10^9/L (500/μL) and platelet count ≥ 50×10^9/L (50 000/μL), otherwise all other CR criteria met
CRi*,†,‡	All CR criteria except for residual neutropenia < 1.0×10^9/L (1,000/μL) or thrombocytopenia < 100×10^9/L (100 000/μL)
MLFS	Bone marrow blasts < 5%; absence of circulating blasts; absence of extramedullary disease; no hematologic recovery required
PR	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pre-treatment bone marrow blast percentage by at least 50%
No response	Patients evaluable for response but not meeting the criteria for CR, CRh, CRi, MLFS or PR are categorized as having no response prior to the response landmark. Patients failing to achieve response by the designated landmark are designated as having refractory disease

Response (if including assessment of MRD)§	
CR, CRh, or CRi without MRD‡ (CR_{MRD-}, CRh_{MRD-} or CRi_{MRD-})	CR, CRh or CRi with MRD below a defined threshold for a genetic marker by qPCR, or by MFC. Response without MRD should be confirmed with a subsequent assessment at least 4 wk apart. The date of response without MRD is the first date in which the MRD was below the defined threshold Response with MRD detection at low-level (CR_{MRD-LL}) is included in this category of CR, CRh or CRi without MRD. CR_{MRD-LL} is currently only defined for *NPM1*-mutant and CBF-AML
Treatment failure	
Refractory disease	No CR, CRh or CRi at the response landmark, ie, after 2 courses of intensive induction treatment or a defined landmark, eg, 180 d after commencing less-intensive therapy
Relapsed disease (after CR, CRh or CRi)	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood in at least 2 peripheral blood samples at least one week apart; or development of extramedullary disease

Blood (2022) 140 (12): 1345–1377.

ASSESSMENT OF FITNESS

1. Age (≥75)
2. Performance status (ECOG ≥2, KPS)
3. Geriatric assessments
4. Comorbid conditions
5. Antecedent myeloid neoplasm
6. Poor-risk karyotypic abnormalities and mutational profiles

HLA Today – Free & Simple

Community providers request free HLA test kits to have on hand

DIAGNOSIS	3-4 Business Days	7-10 Business Days (from when Be The Match receives the kit)	*REFERRAL*

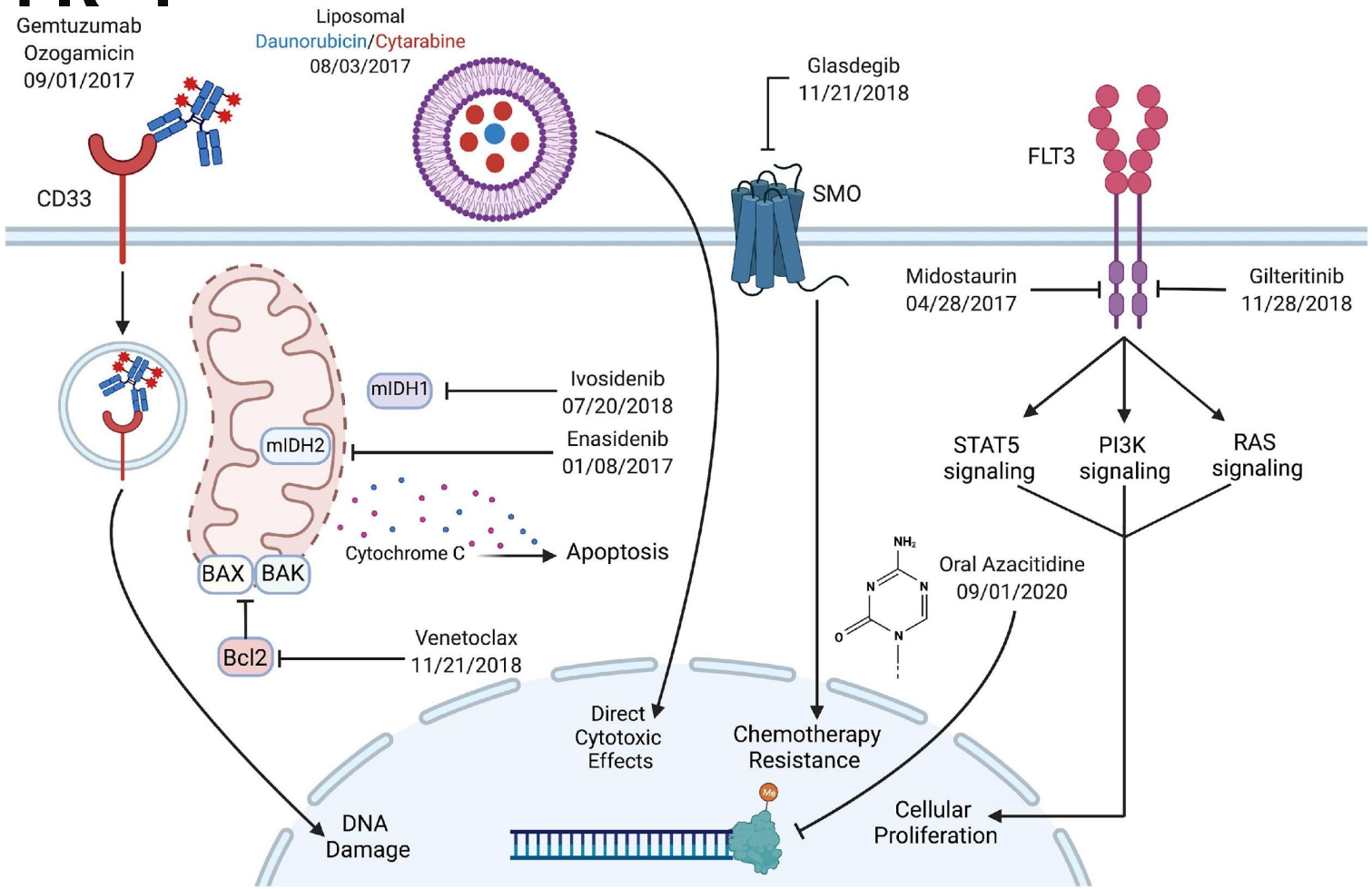
- Swabs patient using HLA kit and return kit to NMDP
- Request family typing, if needed (kits sent after patient kit received)

Completed HLA kits arrive at NMDP and swabs sent out for testing

- NMDP/BTM emails patient's unrelated donor search summary report to the provider
- Family typing results will come separately

Community providers make timely referral to transplant

NEW DRUGS INFLUENCING PRACTICE



American Society of Clinical Oncology Educational Book 42 (June 3, 2022) 568-583.

RECENT FDA APPROVALS IN NEWLY DIAGNOSED AML

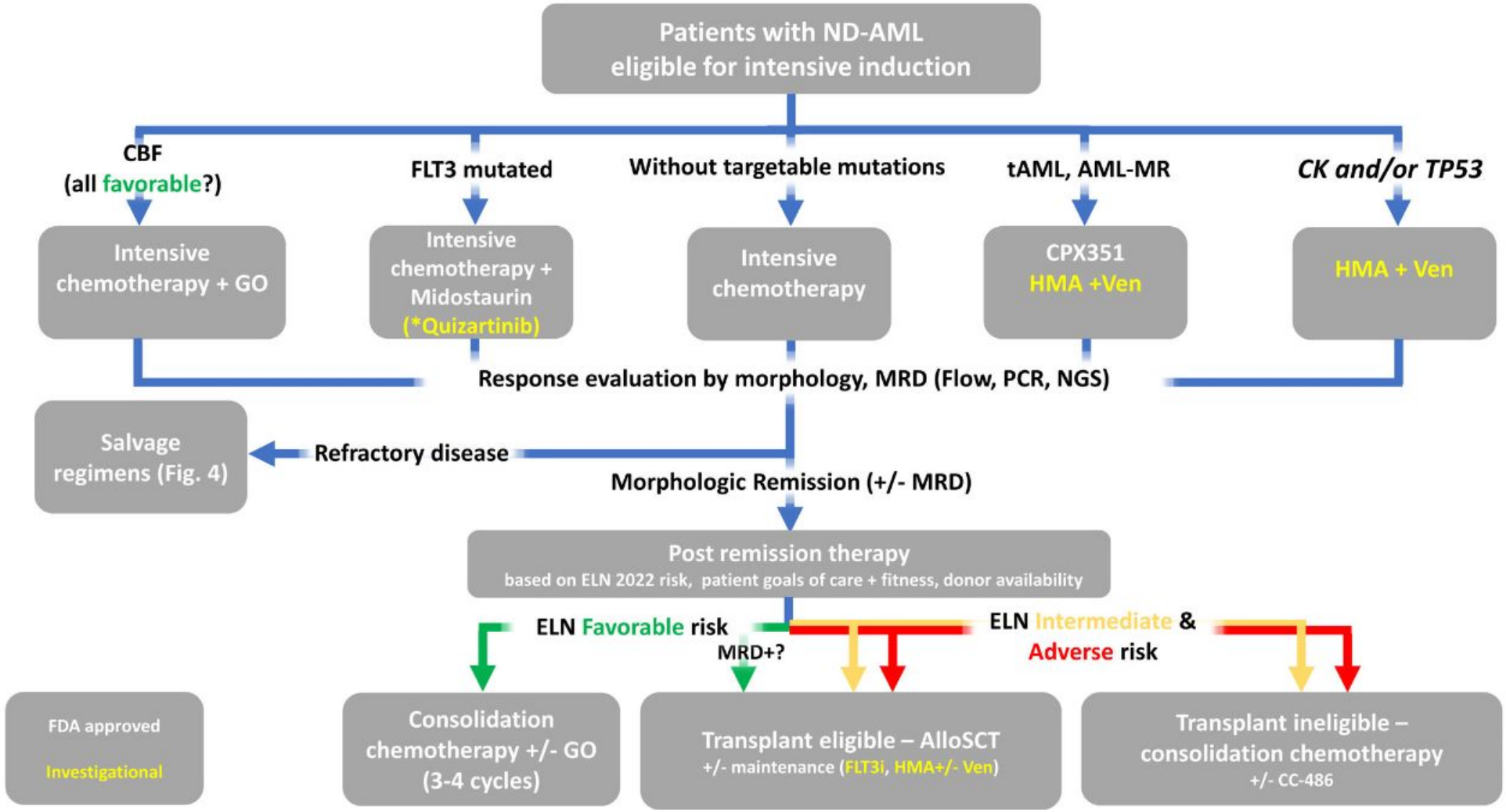
Drug/regimen	FDA approval indication	Age in study, y	N	ORR, %	CR, %	CRi, %	30-d early death, %	Survival
Midostaurin + IC	FLT3^{MUT} AML	18-59	360	—	59	N/A	4.5	51.4% at 4 y
CPX-351 liposomal daunorubicin HCl and cytarabine	tAML, AML MRC	60-75	153	47	37	10	5.9	Median, 9.6 mo
Gemtuzumab ozogamicin	Newly diagnosed adults with CD33 AML with IC	50-70	135	81	70	11 (CRp)	3.8	Median, 27.5 mo
Glasdegib + LDAC	>75 yo or unfit	76	88	27	17	10	N/A	Median, 8.8 mo
Venetoclax + HMA	New AML ≥75 y or unfit	49-91	145	67	37	30	3	Median, 17.5 mo
Venetoclax + LDAC	New AML ≥75 y or unfit	63-90	82	54	26	28	6	Median, 10.1 mo
Ivosidenib	New AML ≥75 y or unfit with IDH1^{MUT}	64-87	34	42	30	12 (CRh)	N/A	N/A
Ivosidenib + HMA (AZA)	New AML ≥75 y or unfit with IDH1^{MUT}	58-84	146	41	34	5	N/A	Median 24

On July 20, 2023, the FDA approved **quizartinib** with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML that is FLT3-ITD positive.

RECENT FDA APPROVALS FOR RELAPSED/REFRACTORY AML

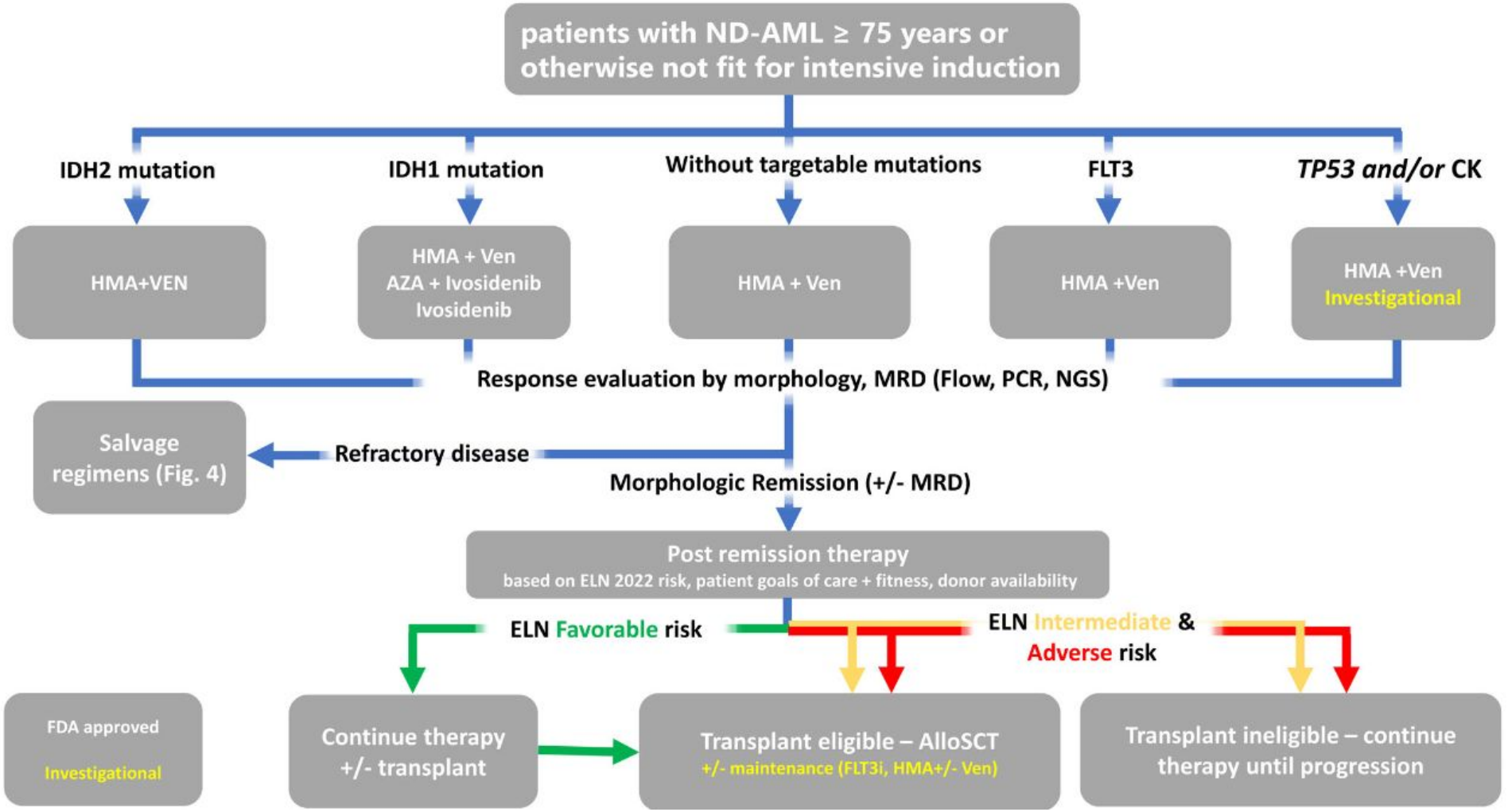
Drug/regimen	FDA approval indication	Age in study, y	N	ORR, %	CR, %	CRi, %	30-d early death, %	Survival, median no. of mo
Gemtuzumab ozogamicin	RR adults or pediatric patients ≥2 y with $CD33^{+}$ AML with IC	50-70	135	81	70	11 (CRp)	3.8	27.5
Ivosidenib	RR $IDH1^{MUT}$	18-89	258	34	22	12	7	8.8
Enasidenib mesylate	RR $IDH2^{MUT}$	19-100	214	29	20	9	5	8.8
Gilteritinib fumarate	RR $FLT3^{MUT}$	19-85	247	34	21	13 (CRh)	2	9.3
Olutasidenib	RR $IDH1^{MUT}$	≥18	147	41-46	32 (35)	2.7 (CRh)	N/A	8.7-12.1 25.9 (DOR)

ND-AML FIT FOR INTENSIVE INDUCTION



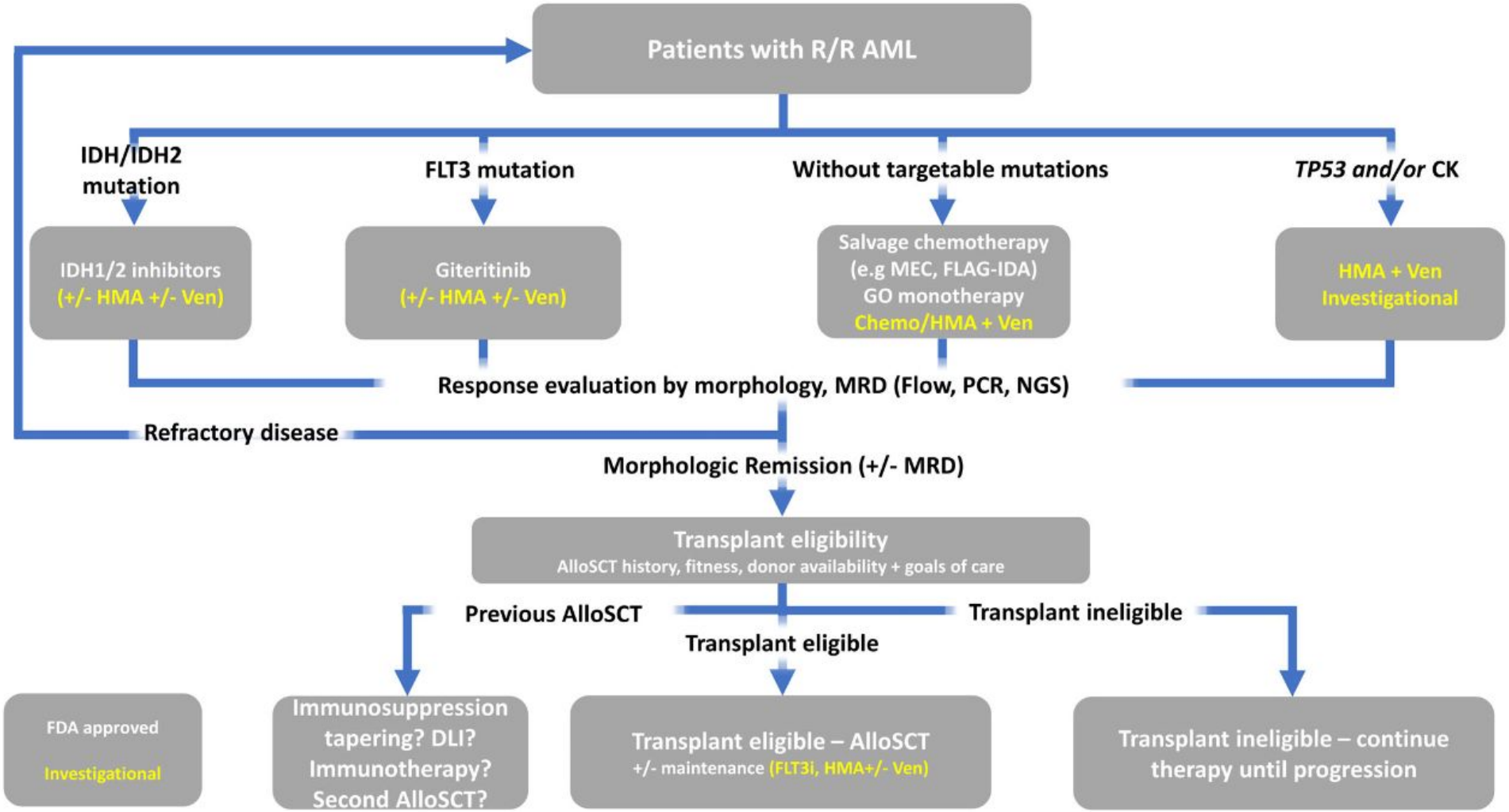
Am J Hematol. 2023;98:502–526.

ND-AML ≥75 OR UNFIT FOR INTENSIVE THERAPY



Am J Hematol. 2023;98:502–526.

CONSIDERATIONS FOR R/R AML



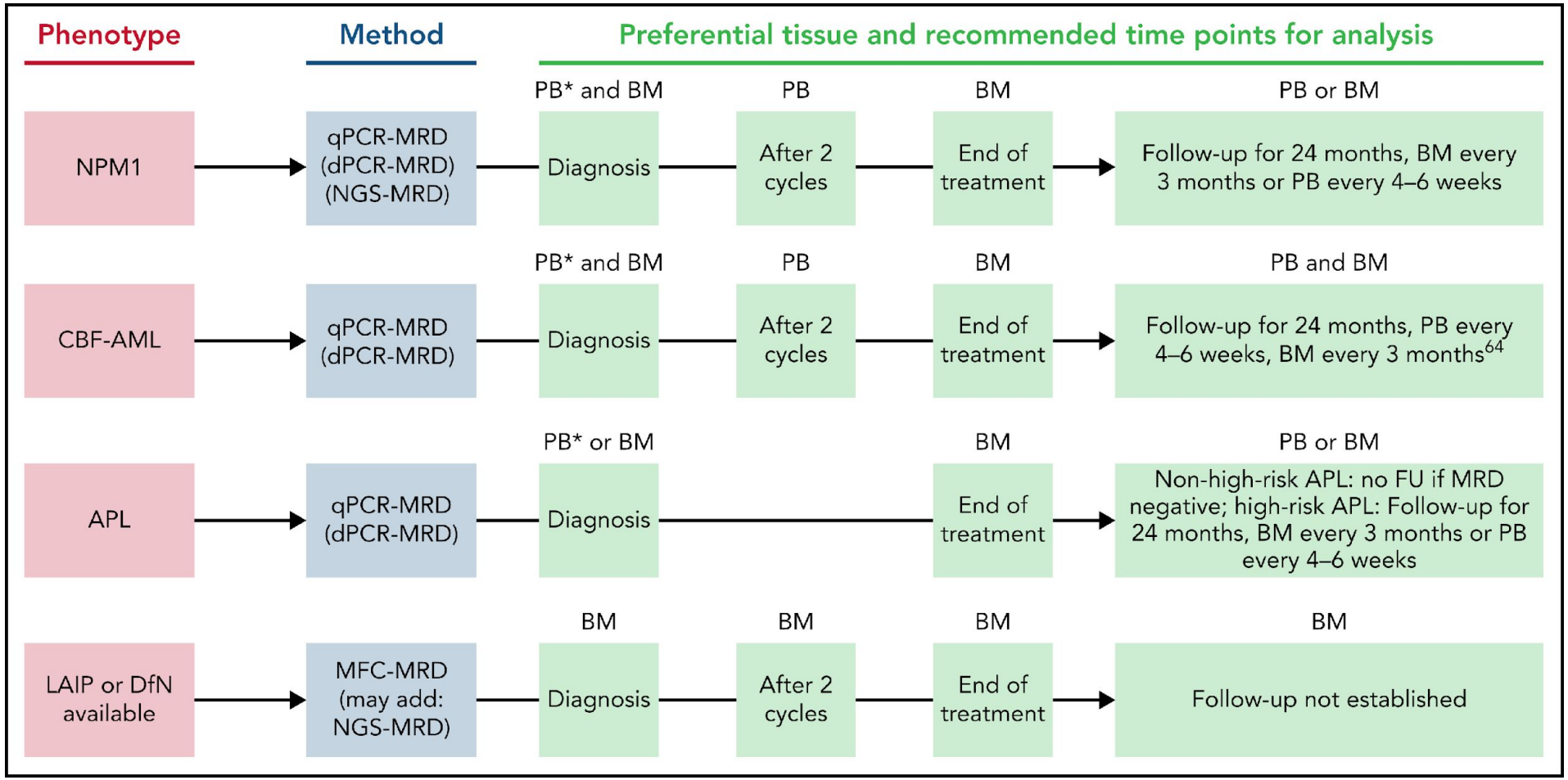
Am J Hematol. 2023;98:502–526.

MRD

MRD assessment in AML is used to:

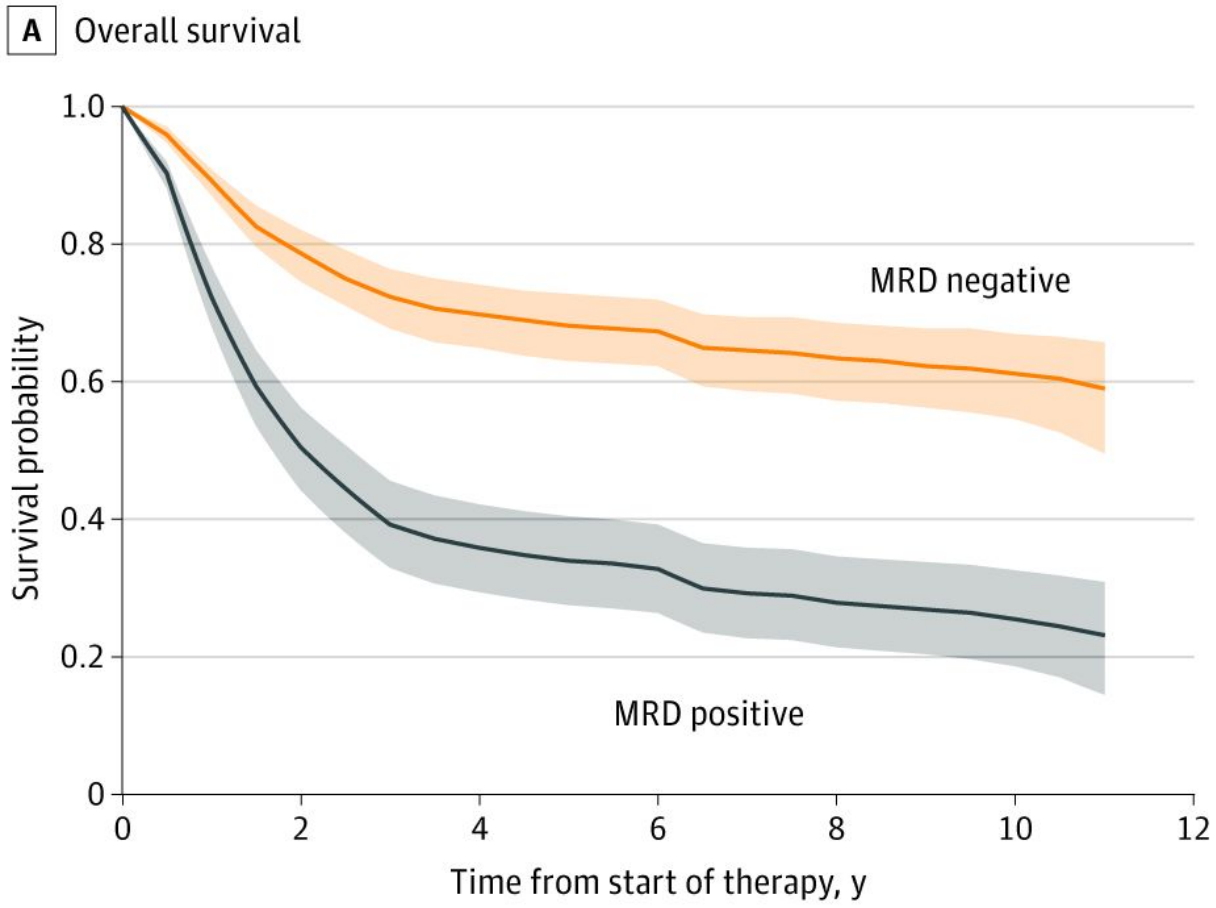
- (1) provide a quantitative methodology to establish a deeper remission status;
- (2) refine post-remission relapse risk assessment;
- (3) identify impending relapse to enable early intervention.

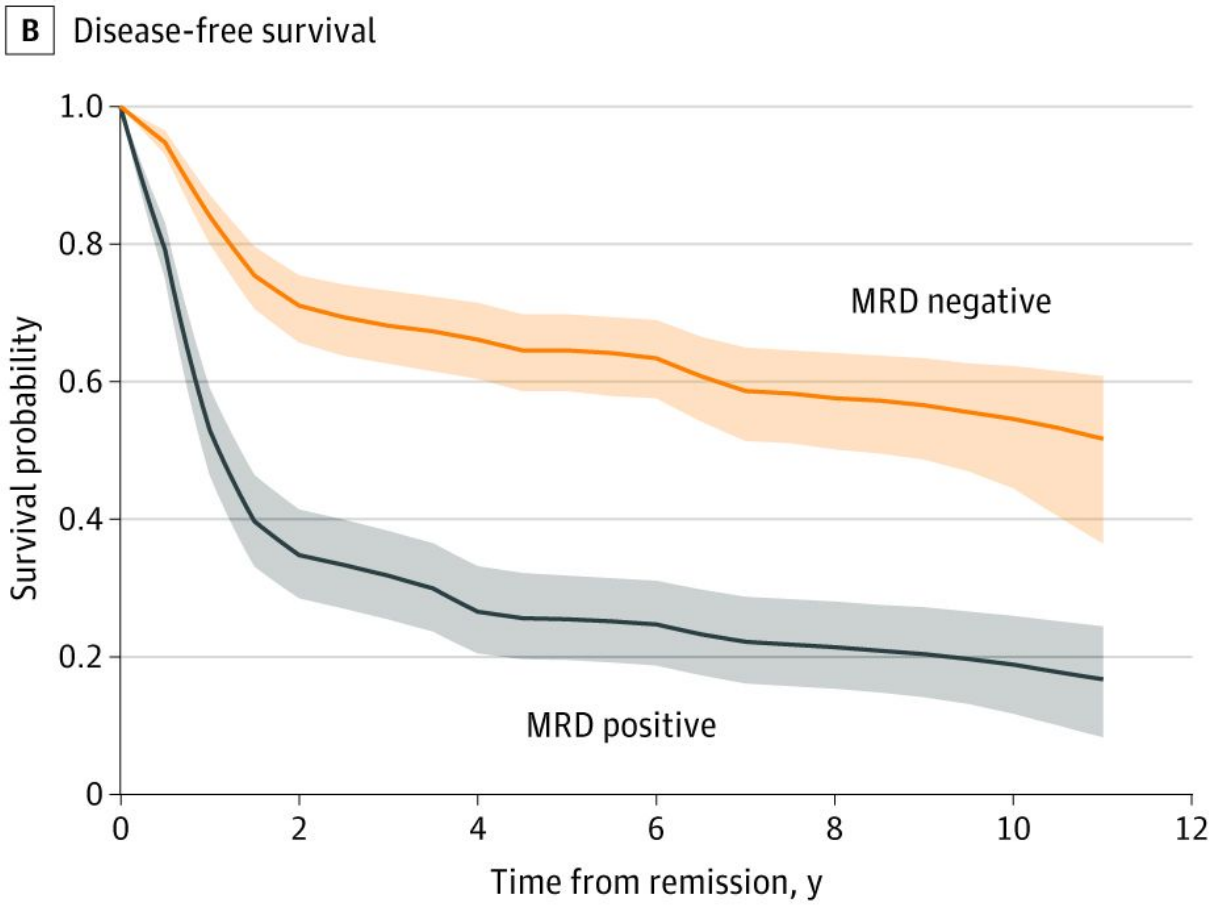
MRD ASSESSMENT ALGORITHM FOR DIFFERENT SUBTYPES OF AML



Blood (2021) 138 (26): 2753–2767.

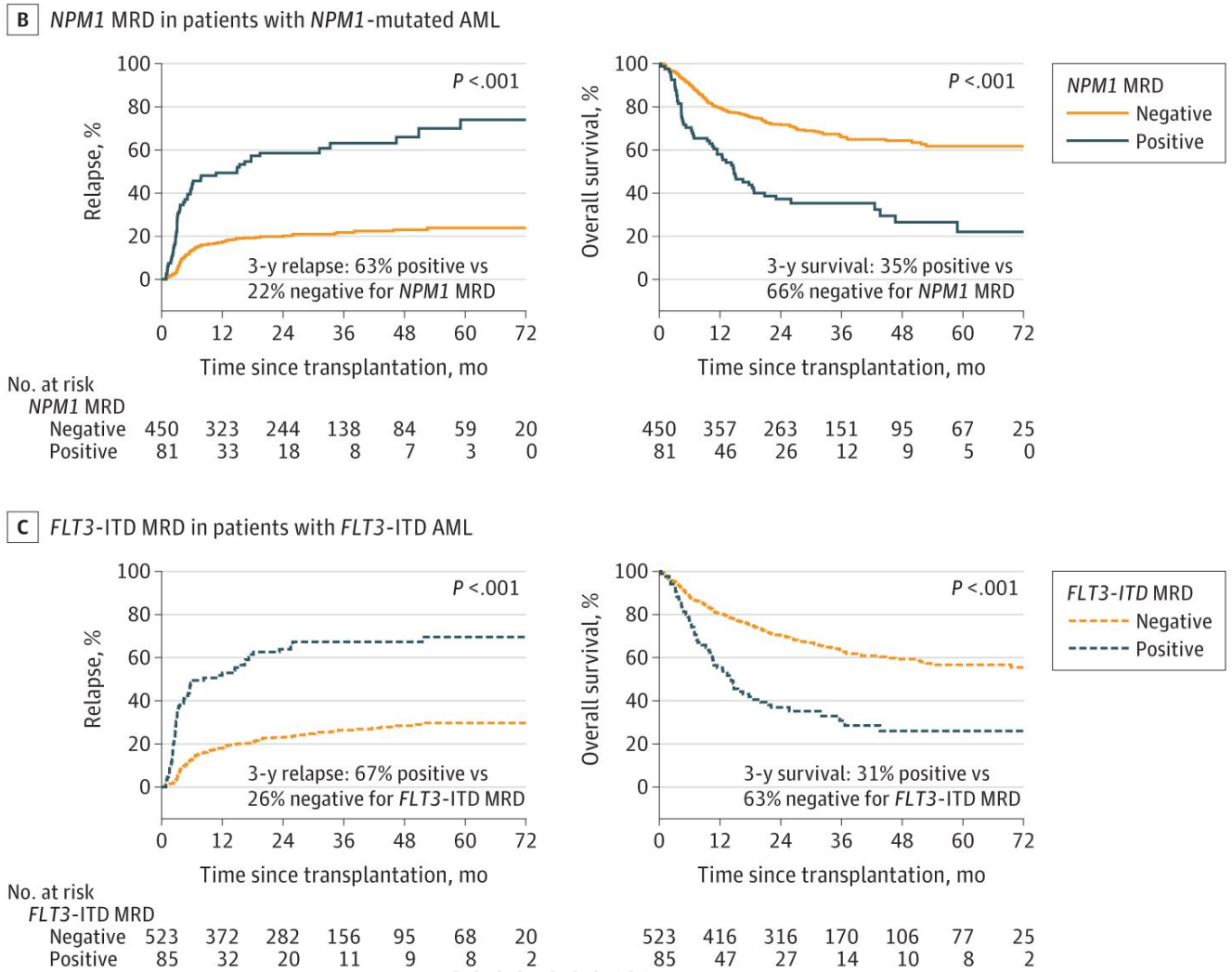
ASSOCIATION OF MRD WITH SURVIVAL OUTCOMES





JAMA Oncol. 2020;6(12):1890-1899.

IMPACT OF MRD ON HCT



JAMA. 2023;329(9):745-755.

NOVEL AGENTS FEATURED AT ASH 2022

Drug	Regimen Backbone	Indication	Mechanism
Magrolimab	AZA/VEN	ND AML	Anti-CD47 antibody
Gilteritinib	AZA/VEN	ND and R/R AML	FLT3 inhibitor
SNDX-5613 (Revumenib)	N/A	R/R AML	Menin inhibitor
KO-539 (Ziftomenib)	N/A	R/R AML	Menin inhibitor
Pivekimab sunirine (PVEK)	AZA/VEN	R/R AML	Antibody–drug conjugate targeting CD123

Drug	Indication	ORR	CRc	Notable side effects
Magrolimab	ND AML	81%	72%	Anemia, infusion reactions
Gilteritinib	ND and R/R AML	100% (ND) 70% (R/R)	92% (ND) 20% (R/R)	Infection
SNDX-5613 (Revumenib)	R/R AML	53%	38%	Differentiation syndrome
KO-539 (Ziftomenib)	R/R AML	40%	35%	Differentiation syndrome, pneumonitis
Pivekimab sunirine (PVEK)	R/R AML	45%	25%	Infusion reactions

Journal of Hematology & Oncology (2023) 16:17

KEY TAKEAWAYS

All recurrent genetic abnormalities that define specific subtypes of AML, (with the exception of AML with t(9;22)), are now considered to establish a diagnosis of AML if there are ≥10% blasts in the bone marrow or blood.

FLT3-ITD AR is no longer incorporated into ELN risk stratification. AML with FLT3-ITD is considered intermediate-risk, regardless of the NPM1 mutation status.

The treatment landscape of AML is undergoing unprecedented change, with no fewer than 9 new drug approvals since 2017.

KEY TAKEAWAYS

Our treatment paradigm has shifted away from a simple binary distinction between "curative, intensive therapy" and "palliative, lower intensity" approaches. Instead, the diversity of available therapeutic options requires a more nuanced treatment algorithm that incorporates mutation-specific targeted therapies, monoclonal antibodies, small molecules, and improved liposomal delivery of standard therapies.

MRD testing in patients with NPM1-mutated AML may be useful for risk-stratification, therapy selection, and early detection of relapse.

Clinical trials designed for chemotherapy-ineligible patients involving evaluating triplet treatments, and novel combinations of newer agents with combination chemotherapy are required.