AML and MDS: Current Status and Future Directions

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Disclosures

For the past 12 months:

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Learning Objectives

- Discuss new and updated classification systems for AML and MDS
- Learn about new and updated prognostic systems for AML and MDS
- Review new treatment approaches for AML and MDS

New/Updated Classification Systems for AML and MDS

New/Updated Classification Systems

- 2022 Update to the WHO Classification System (WHO 2022)
- The International Consensus Classification of Myeloid Neoplasms and Acute Leukemia (ICC)
- ELN 2022 AML Recommendations

ELN 2022 Recommended Work Up

Genetic analyses	Results preferably available within
Cytogenetics[d]	• 5-7 days
Screening for gene mutations required for establishing the diagnosis and to identify actionable therapeutic targets[e]	
• *FLT3*,[f] *IDH1*, *IDH2*	• 3-5 days
• *NPM1*	• 3-5 days
• *CEBPA*,[g] *DDX41*, *TP53*; *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*	• 1st cycle
Screening for gene rearrangements[h]	
• *PML*::*RARA*, *CBFB*::*MYH11*, *RUNX1*::*RUNX1T1*, *KMT2A* rearrangements, *BCR*::*ABL1*, other fusion genes (if available)	• 3-5 days
Additional genes recommended to test at diagnosis[i]	
• *ANKRD26*, *BCORL1*, *BRAF*, *CBL*, *CSF3R*, *DNMT3A*, *ETV6*, *GATA2*, *JAK2*, *KIT*, *KRAS*, *NRAS*, *NF1*, *PHF6*, *PPM1D*, *PTPN11*, *RAD21*, *SETBP1*, *TET2*, *WT1*	

Dohner et al, Blood 2022

WHO 2022 - MDS

Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

Khoury et al, Leukemia 2022

ICC - MDS

Table 20. Myelodysplastic syndromes (MDS) and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics[b]***	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1[c]	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), -7/del(7q), abn3q26.2, or complex	*SF3B1* (≥10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1[c]	≥1	Thrombocytosis allowed	<5% BM <2% PB[d]	del(5q), with up to 1 additional, except -7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS - without dysplasia	0	≥1	0	<5% BM <2% PB[d]	-7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥10% VAF)
MDS, NOS - with single lineage dysplasia	1	≥1	0	<5% BM <2% PB[d]	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*;not meeting criteria for MDS-*SF3B1*
MDS, NOS - with multilineage dysplasia	≥2	≥1	0	<5% BM <2% PB[d]	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*,; not meeting criteria for MDS-*SF3B1*
MDS with excess blasts (MDS-EB)	Typically ≥1[c]	≥1	0	5-9% BM, 2-9% PB[d]	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1[c]	≥1	0	10-19% BM or PB[e]	Any, except AML-defining[f]	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

[a]Cytoses: Sustained white blood count ≥13 x 10^9/L, monocytosis (≥0.5 x 10^9/L and ≥10% of leukocytes), or platelets ≥450 x 10^9/L; thrombocytosis is allowed in MDS-del(5q) or in any MDS case with inv(3) or t(3;3) cytogenetic abnormality.

[b]*BCR*::*ABL1* rearrangement or any of the rearrangements associated with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions exclude a diagnosis of MDS, even in the context of cytopenia.

[c]Although dysplasia is typically present in these entities, it is not required.

[d]Although 2% PB blasts mandates classification of an MDS case as MDS-EB, the presence of 1% PB blasts confimed on two separate occasions also qualifies for MDS-EB.

[e]For pediatric patients (<18 years), the blast thresholds for MDS-EB are 5-19% in BM and 2-19% in PB, and the entity MDS/AML does not apply.

[f]AML-defining cytogenetics are listed in the AML section.

Arber et al, Blood 2022

WHO 2022 – MDS/MPNs and CHIP/CCUS

Summary Box:

- CH is recognized as a category of precursor myeloid disease state.
- CHIP and CCUS are formally defined.

Table 5. Myelodysplastic/myeloproliferative neoplasms.

Chronic myelomonocytic leukaemia
Myelodysplastic/myeloproliferative neoplasm with neutrophilia
Myelodysplastic/myeloproliferative neoplasm with *SF3B1* mutation and thrombocytosis
Myelodysplastic/myeloproliferative neoplasm, not otherwise specified

Summary Box:

- CMML diagnostic criteria undergo major revisions, including lowering the cutoff for absolute monocytosis, adopting MD-CMML and MP-CMML subtypes, and eliminating CMML-0.
- Atypical chronic myeloid leukaemia renamed MDS/MPN with neutrophilia.
- MDS/MPN with ring sideroblasts and thrombocytosis redefined based on *SF3B1* mutation and renamed MDS/MPN with *SF3B1* mutation and thrombocytosis.

Khoury et al, Leukemia 2022

ICC - CMML

Table 13. Diagnostic criteria for chronic myelomonocytic leukemia (CMML)

- Monocytosis defined as monocytes ≥0.5 x10^9/L and ≥10% of the WBC
- Cytopenia (thresholds same as MDS)[a]
- Blasts (including promonocytes) <20% of the cells in blood and bone marrow
- Presence of clonality: abnormal cytogenetics and/or presence of at least one myeloid neoplasm associated mutation of at least 10% allele frequency[b]
- In cases without evidence of clonality,
  - monocytes ≥1.0 x10^9/L and >10% of the WBC, and
  - increased blasts (including promonocytes)[c], or morphologic dysplasia, or
  - an abnormal immunophenotype consistent with CMML would be required for its diagnosis.
- Bone marrow examination with morphologic findings consistent with CMML (hypercellularity due to a myeloid proliferation often with increased monocytes), and lacking diagnostic features of acute myeloid leukemia, myeloproliferative neoplasm or other conditions associated with monocytosis[d]
- No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

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a A small proportion of cases may show only borderline or no cytopenia usually in early phase disease.

b Based on International Consensus Group Conference, Vienna, 2018.[260]

c increased blasts: ≥5% in the bone marrow and/or ≥2% in the peripheral blood.

d For cases lacking bone marrow findings of CMML, a diagnosis of clonal monocytosis of undetermined significance (CMUS) could be considered. If cytopenia is present a diagnosis of clonal cytopenia and monocytosis of undetermined significance (CCMUS) could be entertained. In these diagnostic settings, however, an alternative cause for the observed monocytosis would have to be excluded on the basis of appropriate clinicopathologic correlations.

Arber et al, Blood 2022

WHO 2022 – AML

Table 7. Acute myeloid leukaemia.

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
Acute myeloid leukaemia with *BCR*::*ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

Summary Box:

- AML is arranged into two families: AML with *defining genetic abnormalities* and AML *defined by differentiation*. AML, NOS is no longer applicable.
- Most AML with defining genetic abnormalities may be diagnosed with <20% blasts.
- AML-MR replaces the former term AML "with myelodysplasia-related changes", and its diagnostic criteria are updated. AML transformation of MDS and MDS/MPN continues to be defined under AML-MR in view of the broader unifying biologic features.
- AML with rare fusions are incorporated as subtypes under AML with *other defined genetic alterations*.
- AML with somatic *RUNX1* mutation is not recognized as a distinct disease type due to lack of sufficient unifying characteristics.

Summary Box:

- Myeloid neoplasms (MDS, MDS/MPN, and AML) *post cytotoxic therapy* (MN-pCT) require full diagnostic work up; the term replaces *therapy-related.*
- Exposure to PARP1 inhibitors is added as a qualifying criterion for MN-pCT.
- The diagnostic framework for myeloid neoplasm associated with germline predisposition is restructured along a scalable model that can accommodate future refinement and discoveries.

Khoury et al, Leukemia 2022

ICC - AML

AML and related neoplasms
AML with recurrent genetic abnormalities (requiring ≥10% blasts in BM or PB)[a]
• APL with t(15;17)(q24.1;q21.2)/*PML*::*RARA*[b]
• AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*
• AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*
• AML with t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[c]
• AML with t(6;9)(p22.3;q34.1)/*DEK*::*NUP214*
• AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*[d]
• AML with other rare recurring translocations[e]
• AML with mutated *NPM1*
• AML with in-frame bZIP mutated *CEBPA*[f]
• AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*[a]
Categories designated AML (if ≥20% blasts in BM or PB) or MDS/AML (if 10-19% blasts in BM or PB)
• AML with mutated *TP53*[g]
• AML with myelodysplasia-related gene mutations Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
• AML with myelodysplasia-related cytogenetic abnormalities[h]
• AML not otherwise specified (NOS)
Myeloid sarcoma
Myeloid proliferations related to Down Syndrome
• Transient abnormal myelopoiesis associated with Down syndrome
• Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
• Acute undifferentiated leukemia
• MPAL with t(9;22)(q34.1;q11.2)/*BCR::ABL1*
• MPAL with t(v;11q23.3)/*KMT2A* rearranged
• MPAL, B/myeloid, not otherwise specified
• MPAL, T/myeloid, not otherwise specified

Table 27. Diagnostic qualifiers that should be used following a specific MDS, AML (or MDS/AML) diagnosis*

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

*Examples: Acute myeloid leukemia with myelodysplasia-related cytogenetic abnormality, therapy-related; acute myeloid leukemia with myelodysplasia-related gene mutation, progressed from myelodysplastic syndrome; AML with myelodysplasia-related gene mutation, germline *RUNX1* mutation

**lymphoblastic leukemia/lymphoma may also be therapy-related, and that association should also be noted in the diagnosis

Arber et al, Blood 2022

Dohner et al, Blood 2022

ICC – TP53 AML/MDS

Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation[a], or *TP53* mutation (VAF >10%) and complex karyotype often with loss of 17p[b]
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF >10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF >10%)

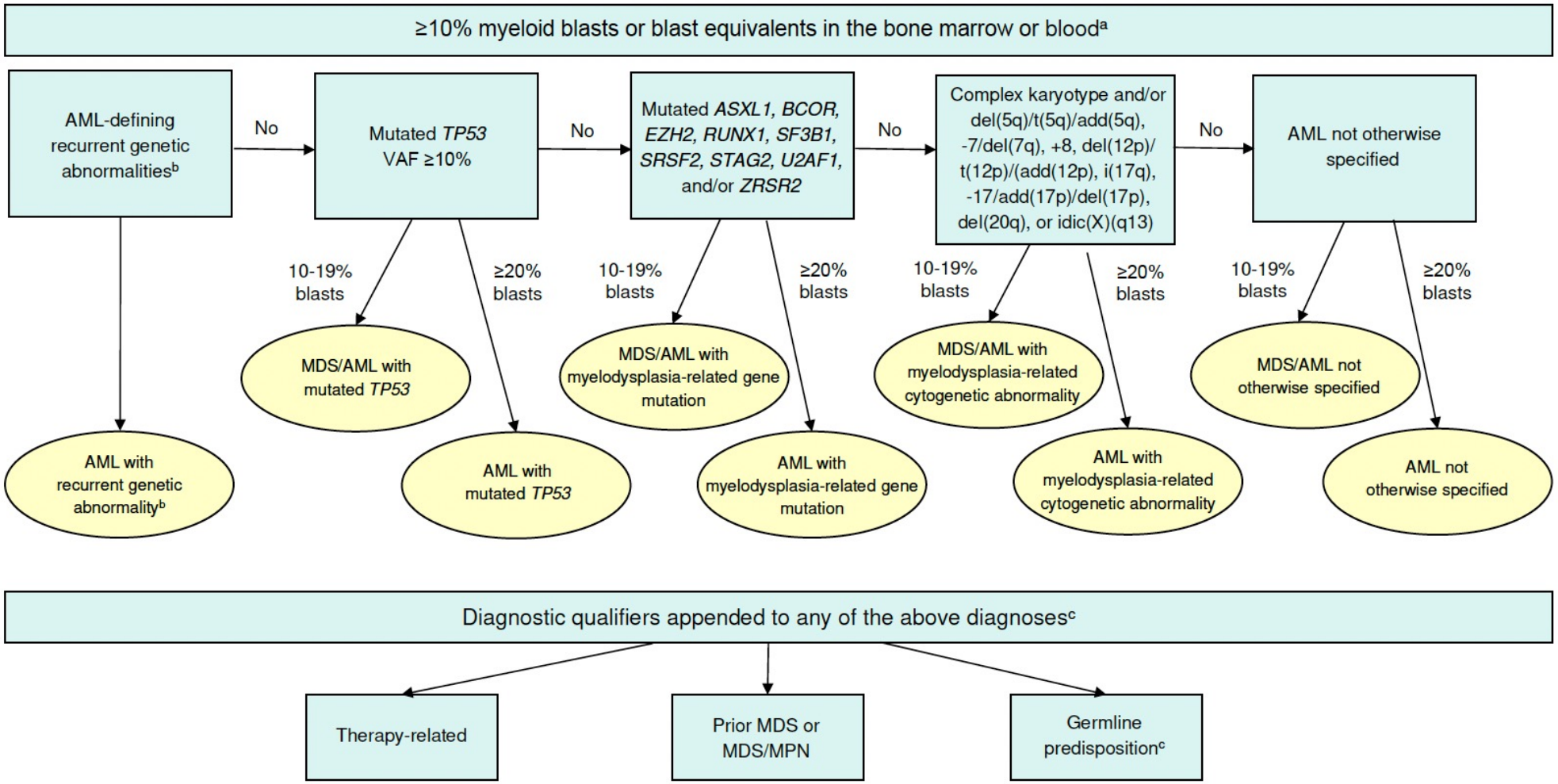
[a]Defined as two distinct *TP53* mutations (each VAF >10%) OR a single *TP53* mutation with either 1) 17p deletion on cytogenetics; 2) VAF of >50%; or 3) Copy-neutral loss of heterozygosity (LOH) at the 17p *TP53* locus.

[b]If *TP53* locus LOH information is not available

Arber et al, Blood 2022

Dohner et al, Blood 2022

ICC – AML/MDS Summary



Arber et al, Blood 2022

Dohner et al, Blood 2022

New/Updated Prognostic Systems for AML and MDS

ELN 2017 Risk Stratification

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 or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Dohner et al, Blood 2017

ELN 2022 Risk Stratification

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[b,c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[b,c] • * Mutated *NPM1*[b,d] without *FLT3*-ITD • * bZIP in-frame mutated *CEBPA*[e]
Intermediate	• * Mutated *NPM1*[b,d] with *FLT3*-ITD • * Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[b,f] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[g] • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • * t(8;16)(p11;p13)/*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,[h] monosomal karyotype[i] • * Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*[j] • Mutated *TP53*[k]

[a] Frequencies, response rates and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

[b] Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of measurable residual disease.

[c] Concurrent of *KIT* and/or *FLT3* gene mutation does not alter risk categorization.

[d] AML with *NPM1* mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.

[e] Only in-frame mutations affecting the basic leucine zipper (bZIP) region of *CEBPA*, irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.

[f] The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

[g] Excluding *KMT2A* partial tandem duplication (PTD).

[h] Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.

[i] Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).

[j] For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

[k] *TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation); *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

* Changes from ELN 2017

Dohner et al, Blood 2022

Revised International Prognostic Scoring System

	Score Value						
Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetic[e]	Very good	—	Good	—	Intermediate	Poor	Very poor
Marrow blasts (%)	≤2	—	>2-<5	—	5-10	>10	—
Hemoglobin	≥10	—	8-<10	<8	—	—	—
Platelets	≥100	50-<100	<50	—	—	—	—
ANC	≥0.8	<0.8	—	—	—	—	—

IPSS-R Risk Category (% IPSS-R pop.)*	Overall Score	Median Survival (y) in the Absence of Therapy	25% AML Progression (y) in the Absence of Therapy
VERY LOW (19)	≤1.5	8.8	Not reached
LOW (38)	>1.5-≤3.0	5.3	10.8
INT[3] (20)	>3.0-≤4.5	3	3.2
HIGH (13)	>4.5-≤6.0	1.6	1.4
VERY HIGH (10)	>6.0	0.8	0.7

Greenberg et al, Blood 2012.

International Prognostic Scoring System – Molecular

Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10^9/l	0.998 (0.997–0.999)	−0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	−0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multihit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{5q}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1$^{\alpha}$	0.92 (0.74 1.16)	−0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231

* CI denotes confidence interval; IPSS-M, International Prognostic Scoring System–Molecular; IPSS-R, International Prognostic Scoring System–Revised; ITD, internal tandem duplication; min, minimum; PTD, partial tandem duplication; and TKD tyrosine kinase domain.

† Hazard ratio is for the risk of leukemic transformation or death, adjusted for age, sex, and secondary/therapy-related versus primary myelodysplastic syndrome. Cox regression was performed for 2428 patients with available covariables and leukemia-free survival data.

‡ Model weights were derived from the logarithm of the raw hazard ratios up to three significant digits. The following formula applies: IPSS-M score = 1.15467 + $(\sum_{variables\ j} w_j x_j)/\log(2)$, where w_j denotes the weight of variable j, and x_j the value of the variable j observed in a given patient.

§ IPSS-R cytogenetic categories were as follows: 0 denotes very good, 1 good, 2 intermediate, 3 poor, and 4 very poor.

¶ *SF3B1*^{5q} is the *SF3B1* mutation in the presence of isolated del(5q) — that is, del(5q) only or with one additional aberration excluding -7/del(7q). *SF3B1*$^{\alpha}$ is the *SF3B1* mutation without comutations in *BCOR*, *BCORL1*, *RUNX1*, *NRAS*, *STAG2*, *SRSF2*, and del(5q).

‖ Nres is defined as the number of mutated genes within the following list: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, and *WT1*. The variable min(Nres,2) can therefore take the value 0, 1, or 2.

Bernard et al, NEJM Evidence 2022.

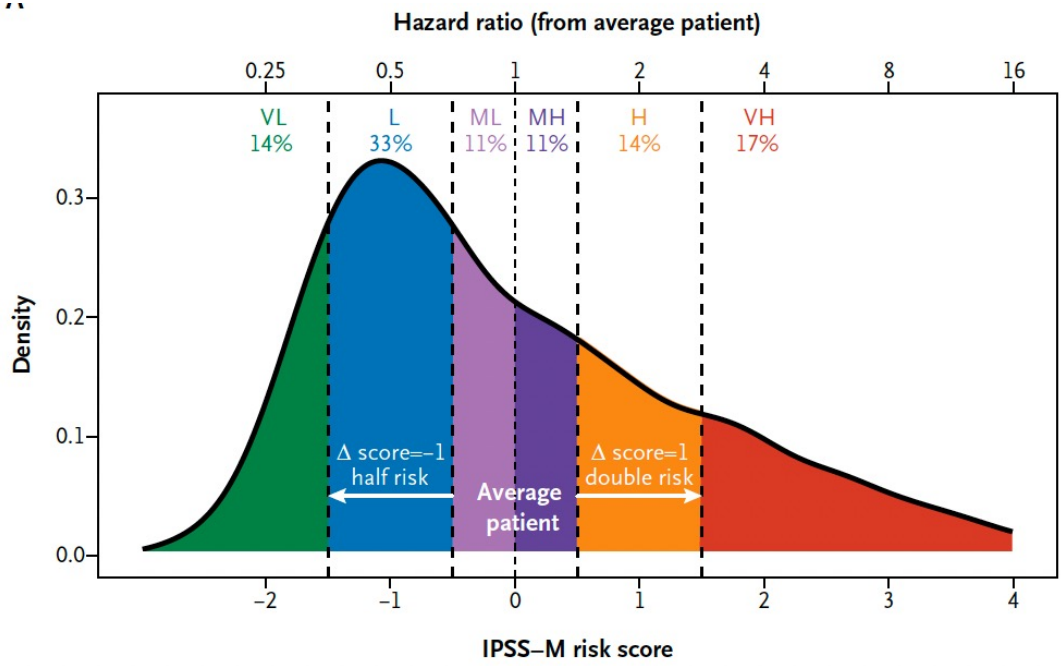
IPSS-M, Continued

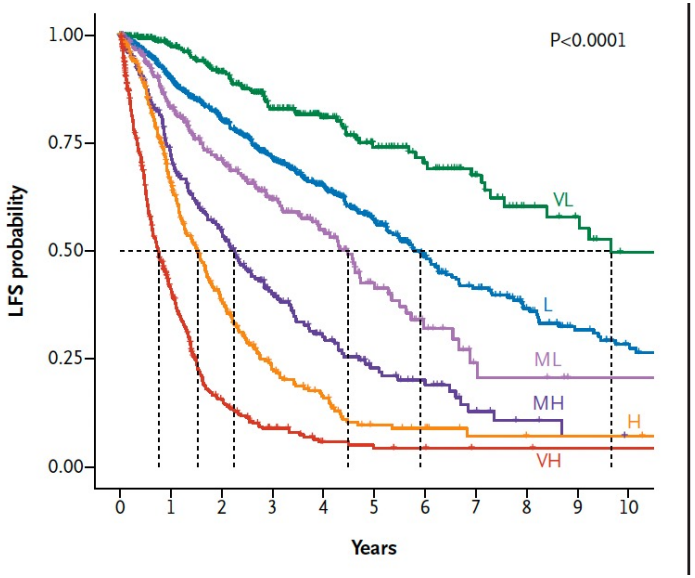
Table 2. Summary of Clinical Outcomes for 2701 Patients by IPSS-M Risk Category.*

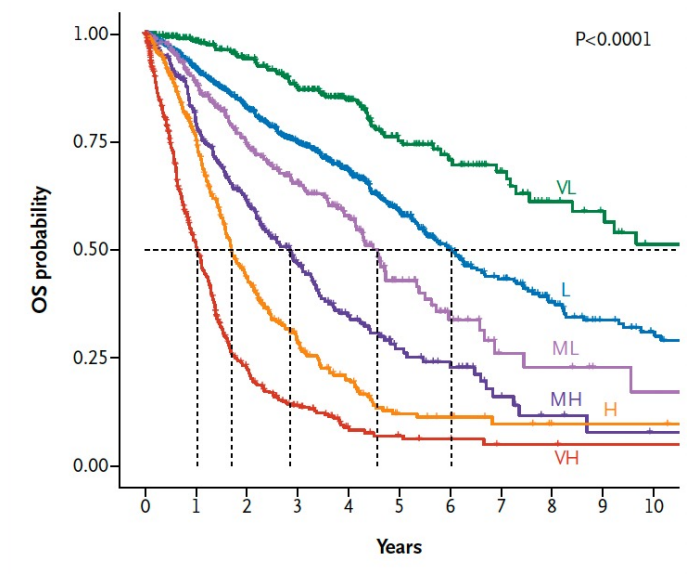
Characteristic	IPSS-M Risk Category					
	Very Low	Low	Moderate Low	Moderate High	High	Very High
Patients — No. (%)	381 (14)	889 (33)	302 (11)	281 (11)	379 (14)	469 (17)
Risk score	≤−1.5	>−1.5 to −0.5	>−0.5 to 0	>0 to 0.5	>0.5 to 1.5	>1.5
Hazard ratio (95% CI)†	0.51 (0.39–0.67)	1.0 (Reference)	1.5 (1.2–1.8)	2.5 (2.1–3.1)	3.7 (3.1–4.4)	7.1 (6.0–8.3)
Median LFS (25–75% range) — yr‡	9.7 (5.0–17.4)	5.9 (2.6–12.0)	4.5 (1.6–6.9)	2.3 (0.91–4.7)	1.5 (0.80–2.8)	0.76 (0.33–1.5)
Median OS (25–75% range) — yr	10.6 (5.1–17.4)	6.0 (3.0–12.8)	4.6 (2.0–7.4)	2.8 (1.2–5.5)	1.7 (1.0–3.4)	1.0 (0.5–1.8)
AML-t — %						
By 1 yr	0.0	1.7	4.9	9.5	14.3	28.2
By 2 yr	1.2	3.4	8.8	14.0	21.2	38.6
By 4 yr	2.8	5.1	11.4	18.9	29.2	42.8
Death without AML — %						
By 1 yr	2.2	8.5	12.0	18.0	19.3	30.6
By 2 yr	7.0	16.2	19.8	31.1	39.8	45.6
By 4 yr	15.9	29.5	33.6	51.1	54.2	51.3

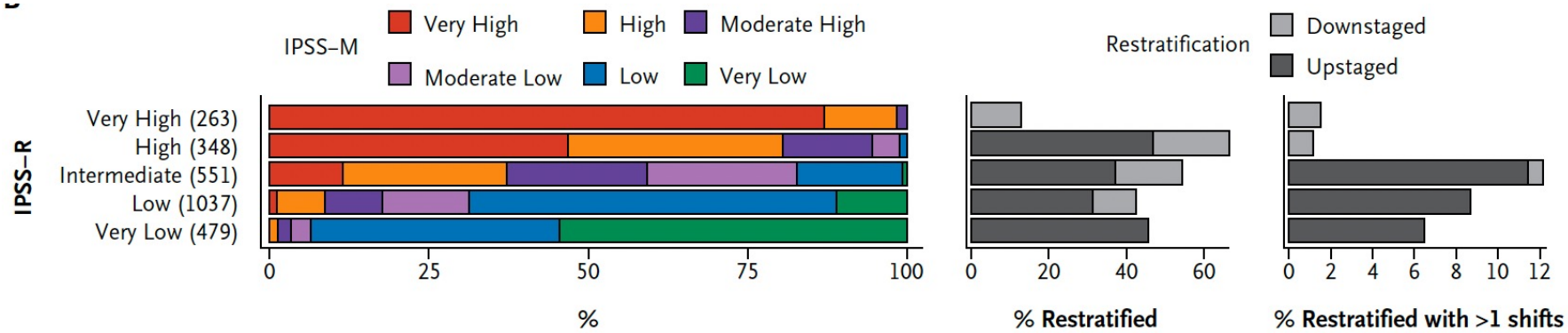
Bernard et al, NEJM Evidence 2022.

IPSS-M, Continued



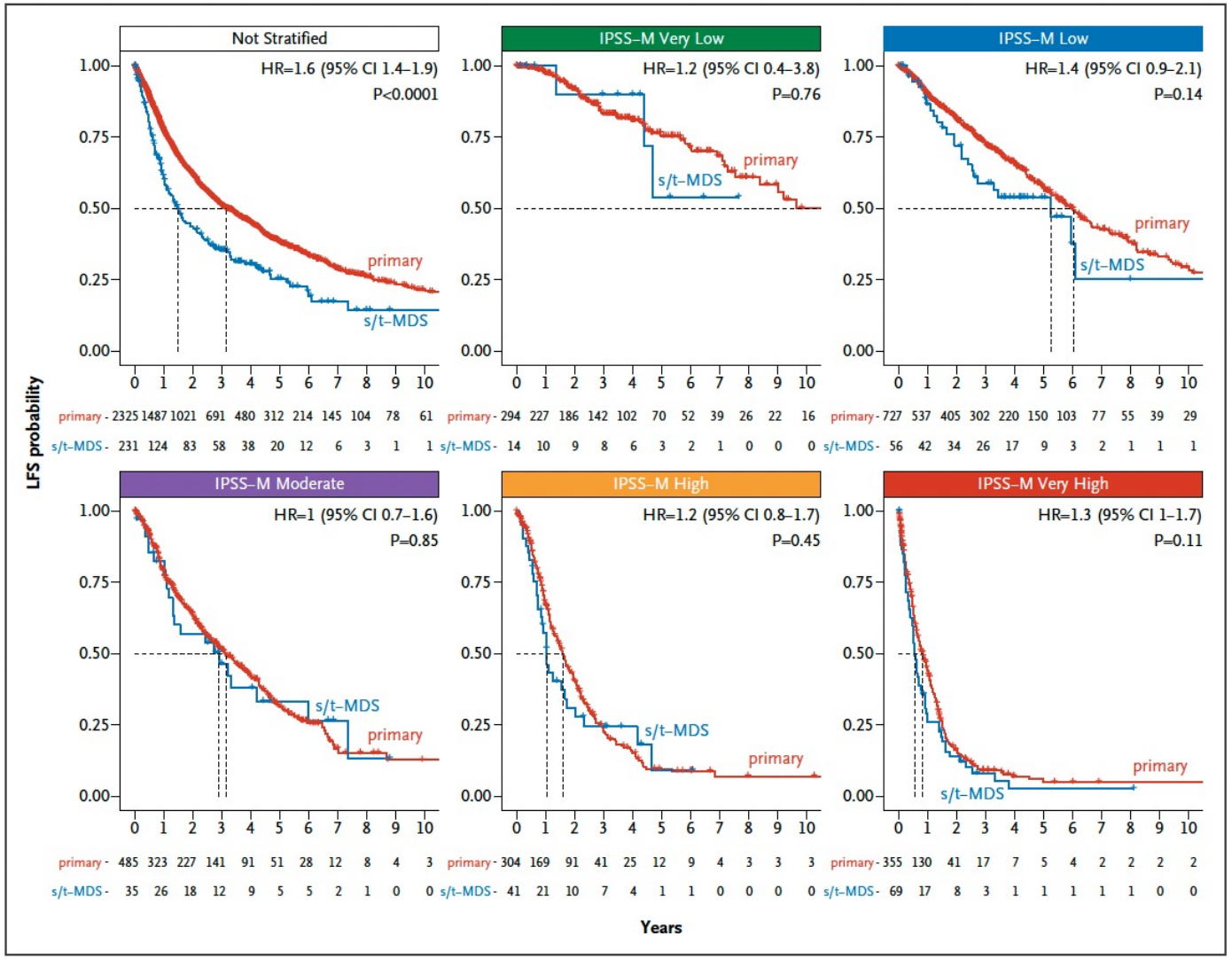






Bernard et al, NEJM Evidence 2022.

IPSS-M – Therapy-Related MDS



Bernard et al, NEJM Evidence 2022.

New Treatment Approaches for AML and MDS

AGILE: Ivosidenib+Azacitidine vs PBO+Aza for Newly Diagnosed AML with mIDH1

- Multicenter, double-blind, randomized phase III trial

Stratified by region (US/Canada vs Western Europe, Israel, and Australia vs Japan vs rest of world) and disease history (de novo vs secondary AML)

Patients with untreated AML (WHO criteria); centrally confirmed *IDH1* mutation status; ineligible for IC; ECOG PS 0-2 (planned N = 200)

→ **Ivosidenib** 500 mg PO QD + **Azacitidine** 75 mg/m^2 SC or IV (n = 72)*

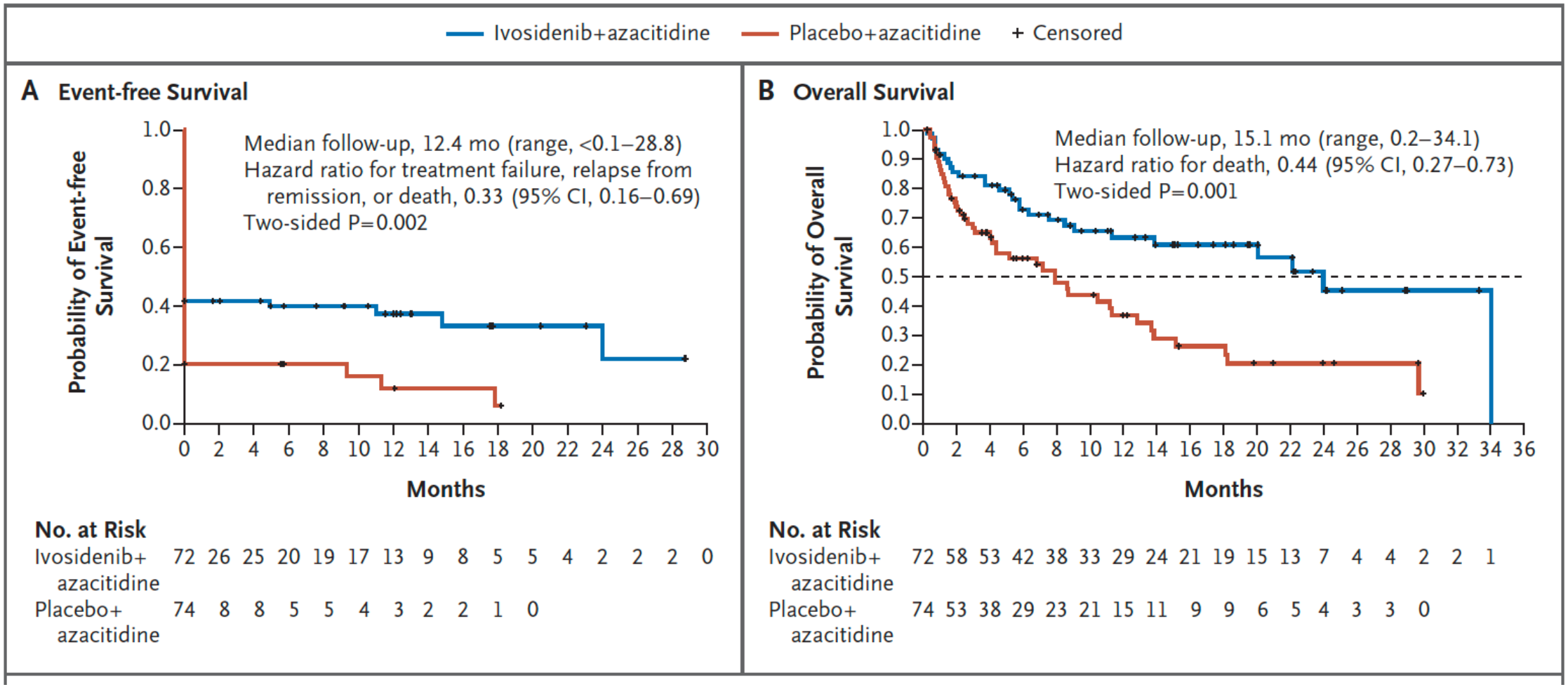
→ **Placebo** PO QD + **Azacitidine** 75 mg/m^2 SC or IV (n = 74)*

*Enrollment at time of data cutoff (May 18, 2021).

- Enrollment halted based on efficacy as of May 12, 2021 (N = 148)
- **Primary endpoint:** EFS with ~173 events (52 mo)
- **Secondary endpoints:** CRR, OS, CR + CRh rate, ORR

Montesinos et al, ASH 2021, Abstract #697.
Montesinos et al, NEJM 2022.

AGILE: OS and EFS



Montesinos et al, ASH 2021, Abstract #697.
Montesinos et al, NEJM 2022.

AGILE: Responses

Response	IVO + AZA (n = 72)		PBO + AZA (n = 74)
CR rate, n (%) [95% CI]	34 (47.2) [35.3-59.3]		11 (14.9) [7.7-25.0]
▪ OR (95% CI); *P* value		4.8 (2.2-10.5); <.0001	
▪ Median duration of CR, mo (95% CI)	NE (13.0-NE)		11.2 (3.2-NE)
▪ Median time to CR, mo (range)	4.3 (1.7-9.2)		3.8 (1.9-8.5)
CR + CRh, n (%) [95% CI]	38 (52.8) [40.7-64.7]		13 (7.6) [9.7-28.2]
▪ OR (95% CI); *P* value		5.0 (2.3-10.8); <.0001	
▪ Median duration of CR + CRh, mo (95% CI)	NE (13.0-NE)		9.2 (5.8-NE)
▪ Median time to CR + CRh, mo (range)	4.0 (1.7-8.6)		3.9 (1.9-7.2)
ORR, n (%) [95% CI]	45 (62.5) [50.3-73.6]		14 (18.9) [10.7-29.7]
▪ OR (95% CI); *P* value		7.2 (3.3-15.4); <.0001	
▪ Median duration of response, mo (95% CI)	22.1 (13.0-NE)		9.2 (6.6-14.1)
▪ Median time to response, mo (range)	2.1 (1.7-7.5)		3.7 (1.9-9.4)
m*IDH1* Clearance in BMMCs by Response, n/N (%)	**IVO + AZA (n = 43)**		**PBO + AZA (n = 34)**
CR + CRh	17/33 (51.5)		3/11 (27.3)
▪ CR	14/29 (48.3)		2/10 (20)
▪ CRh	3/4 (75)		1/1 (100)
Non-CR + CRh responders	2/4 (50)		0/2 (0)
Nonresponders	1/6 (16.7)		0/21 (0)

Montesinos et al, ASH 2021, Abstract #697.
Montesinos et al, NEJM 2022.

Slide credit: clinicaloptions.com

AGILE: AEs

TEAEs, n (%)	IVO + AZA (n = 71)		PBO + AZA (n = 73)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	70 (98.6)	66 (93.0)	73 (100)	69 (94.5)
Any hematologic TEAE	55 (77.5)	50 (70.4)	48 (65.8)	47 (64.4)
Most common hematologic TEAEs*				
▪ Anemia	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
▪ Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
▪ Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
▪ Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)
Most common TEAEs*				
▪ Nausea	30 (42.3)	2 (3.8)	28 (38.4)	3 (4.1)
▪ Vomiting	29 (40.8)	0	19 (36.0)	1 (1.4)
▪ Diarrhea	25 (35.2)	1 (1.4)	26 (35.6)	5 (6.8)
▪ Pyrexia	24 (33.8)	1 (1.4)	29 (39.7)	2 (2.7)
▪ Constipation	19 (26.8)	0	38 (52.1)	1 (1.4)
▪ Pneumonia	17 (23.9)	16 (22.5)	23 (31.5)	21 (28.8)
Bleeding	29 (40.8)	4 (5.6)	21 (28.8)	5 (6.8)
Infections	20 (28.2)	15 (21.1)	36 (49.3)	22 (30.1)

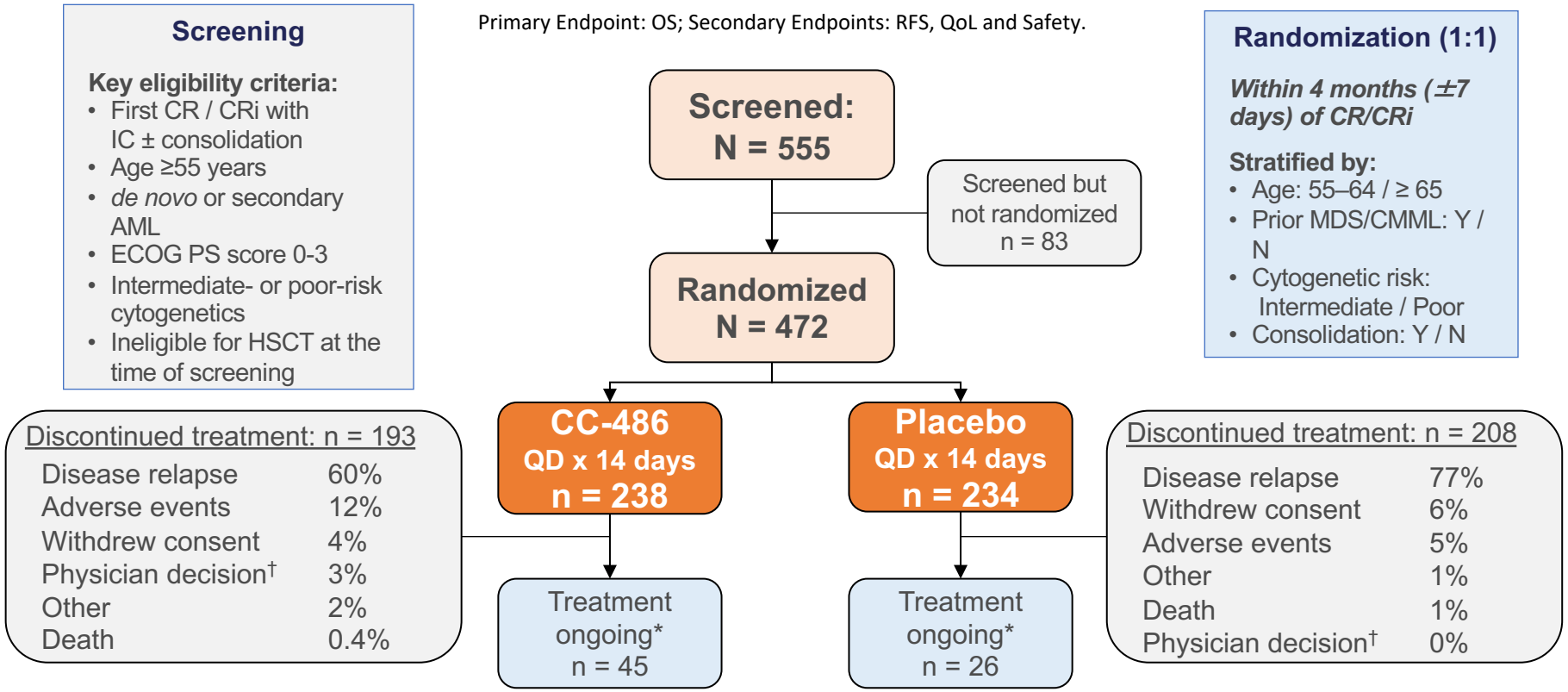
*Occurring in >20% of patients.

- AEs of special interest (IVO + AZA vs PBO + AZA):
  - Grade ≥2 differentiation syndrome: 14.1% vs 8.2%
  - Grade ≥3 QT prolongation: 9.9% vs 4.1%
- Fewer infections with IVO + AZA vs PBO + AZA (28.2% vs 49.3%)
- No treatment-related deaths

Montesinos et al, ASH 2021, Abstract #697.
Montesinos et al, NEJM 2022.

QUAZAR AML-001 Maintenance Trial
CC-486 (Oral Azacitidine)

Patient DISPOSITION / SCHEMA



*Still receiving study drug at data cutoff (July 15, 2019).
†Became eligible for hematopoietic stem cell transplant during treatment. Requirement of ANC >/= 500 and and Plt >/= 20 at the time of screening

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

QUAZAR Trial – Patient Characteristics

Table 1. Baseline Demographic and Disease Characteristics.*

Characteristic	CC-486 (N = 238)	Placebo (N = 234)	Total (N = 472)
Response after induction therapy — no. (%)			
Complete remission	187 (79)	197 (84)	384 (81)
Complete remission with incomplete blood count recovery	51 (21)	37 (16)	88 (19)
Receipt of consolidation therapy — no. (%)			
Yes	186 (78)	192 (82)	378 (80)
No	52 (22)	42 (18)	94 (20)
Median time from induction therapy to randomization (range) — mo	4.0 (1.4–8.8)	4.0 (1.3–15.1)	4.0 (1.3–15.1)
Median time from complete remission to randomization (range) — days‡	84.5 (7–154)	86.0 (7–263)	85.0 (7–263)
Median bone marrow blasts (range) — %§	2.0 (0.0–5.0)	2.0 (0.0–6.5)	2.0 (0.0–6.5)
Positive for measurable residual disease — no. (%)¶	103 (43)	116 (50)	219 (46)
Median platelet count (range) — $\times 10^{-9}$/liter§	154 (22–801)	179 (16–636)	165 (16–801)
Median absolute neutrophil count (range) — $\times 10^{-9}$/liter§	3.0 (0.3–15.9)	2.8 (0.5–9.6)	2.9 (0.3–15.9)

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

QUAZAR Trial – Safety

- Median treatment durations:
  - CC-486: 12 cycles (range 1–80)
  - Placebo: 6 cycles (range 1–73)
- CC-486 safety profile was generally consistent with that of injectable AZA[1]
- Gastrointestinal adverse events (AEs) in the CC-486 arm were most common during the first 2 treatment cycles
- Serious AEs were reported for 34% and 25% of patients in the CC-486 and placebo arms, respectively
- No treatment-related deaths

	CC-486 n = 236		Placebo n = 233	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Preferred term	n (%)			
Patients with ≥1 AE	**231 (98)**	**169 (72)**	**225 (97)**	**147 (63)**
Gastrointestinal				
Nausea	153 (65)	6 (3)	55 (24)	1 (0.4)
Vomiting	141 (60)	7 (3)	23 (10)	0
Diarrhea	119 (50)	12 (5)	50 (22)	3 (1)
Constipation	91 (39)	3 (1)	56 (24)	0
Hematologic				
Neutropenia	105 (45)	97 (41)	61 (26)	55 (24)
Thrombocytopenia	79 (34)	53 (23)	63 (27)	50 (22)
Anemia	48 (20)	33 (14)	42 (18)	30 (13)
Other				
Fatigue	70 (30)	7 (3)	45 (19)	2 (1)
Asthenia	44 (19)	2 (1)	13 (6)	1 (0.4)
Pyrexia	36 (15)	4 (2)	44 (19)	1 (0.4)
Cough	29 (12)	0	39 (17)	0

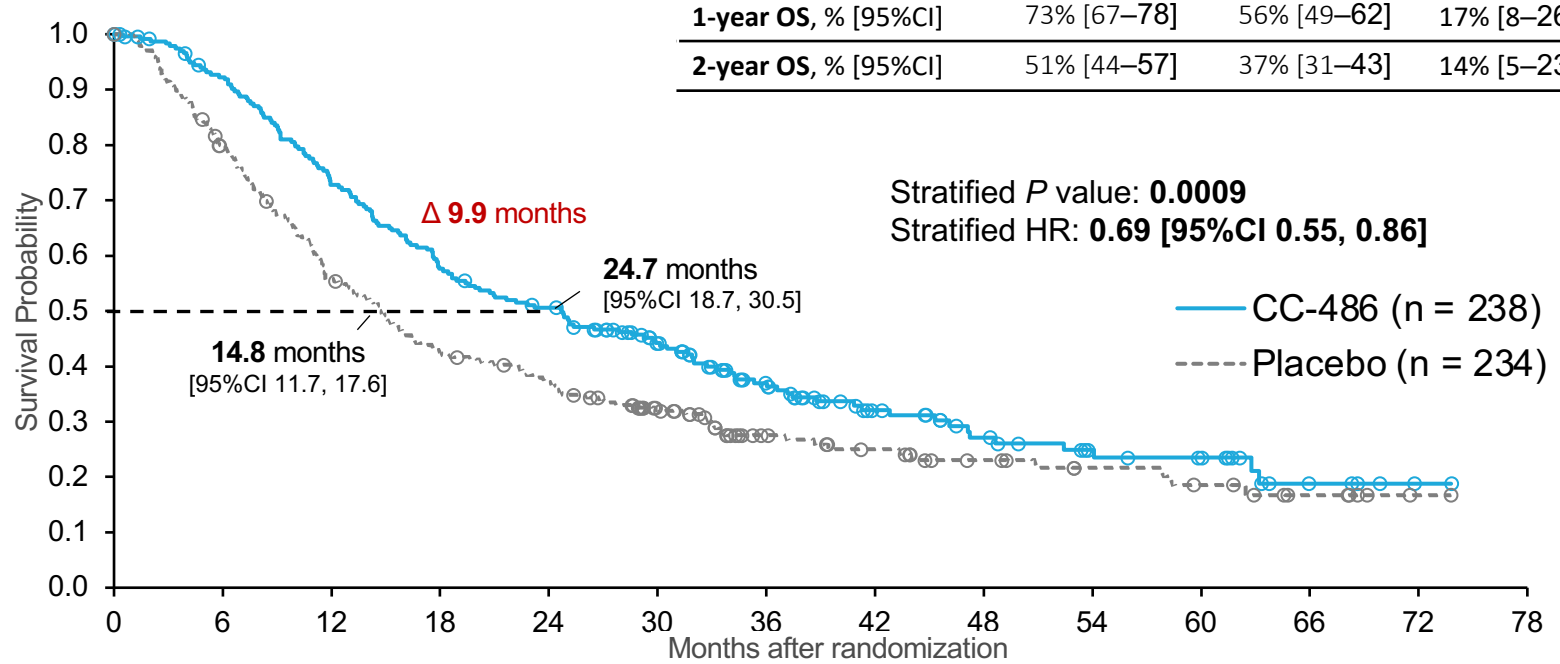
1. Dombret et al. *Blood.* 2015;126(3):291-9.
AE, adverse event; AZA, azacitidine; GI, gastrointestinal.

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

QUAZAR Trial – Primary Endpoint OS

- Median follow-up: 41.2 months

	CC-486	Placebo	Difference
1-year OS, % [95%CI]	73% [67–78]	56% [49–62]	17% [8–26]
2-year OS, % [95%CI]	51% [44–57]	37% [31–43]	14% [5–23]



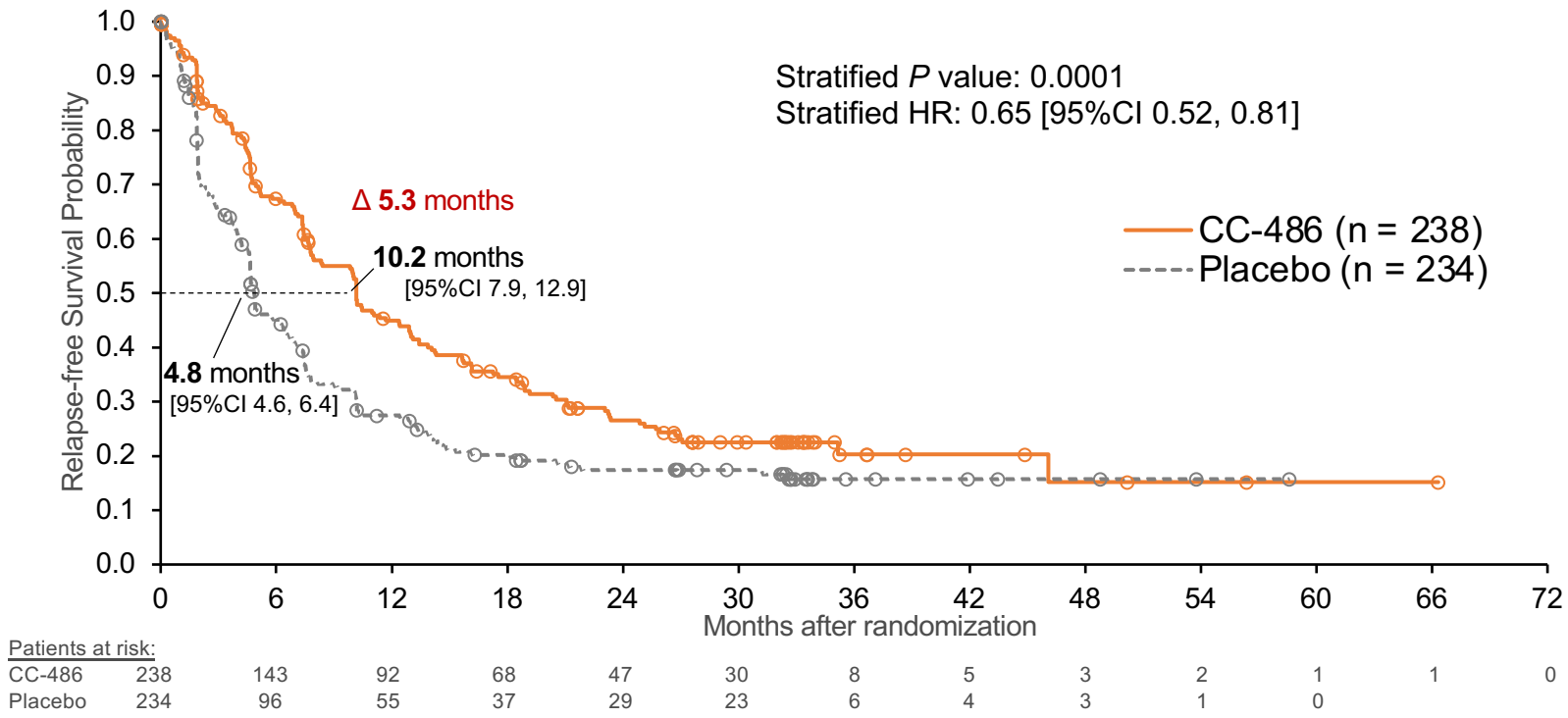
Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Data cutoff: July 15, 2019
OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 vs. placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

QUAZAR Trial – Secondary Endpoint RFS



- 1-year relapse rate was 53% in the CC-486 arm [95%CI 46, 59] and was 71% in the placebo arm [65, 77]

Data cutoff: July 15, 2019
RFS was defined as the time from randomization to relapse or death by any cause, whichever occurred first. Kaplan-Meier estimated RFS was compared for CC-486 vs. placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.

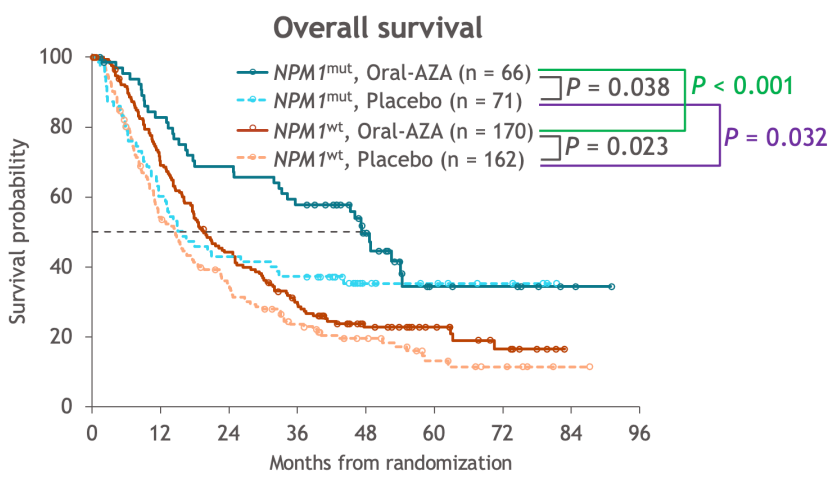
Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

QUAZAR AML-001 Trial: Effects of NPM1 and FLT3-ITD mutations

NPM1 mutational status at AML Dx was prognostic for OS and RFS, and predictive of a survival benefit for pts treated with Oral-AZA (vs. PBO).

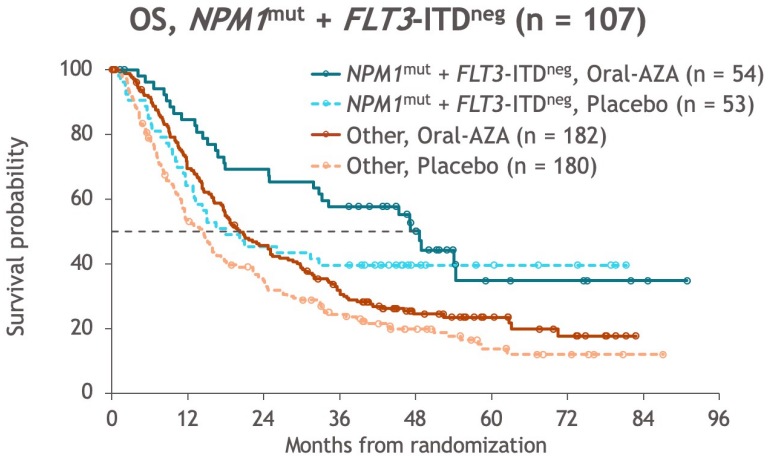
Presence of *FLT3*-ITD at Dx had a negative prognostic influence, as suggested by differences in OS results in the PBO arm

Oral-AZA prolonged OS vs. PBO in pts with *NPM1*^{mut} + *FLT3*-ITD^{neg} (48.6 vs. 18.0 mo, respectively), and in pts with both *NPM1*^{mut} + *FLT3*-ITD (46.1 vs. 11.5 mo)



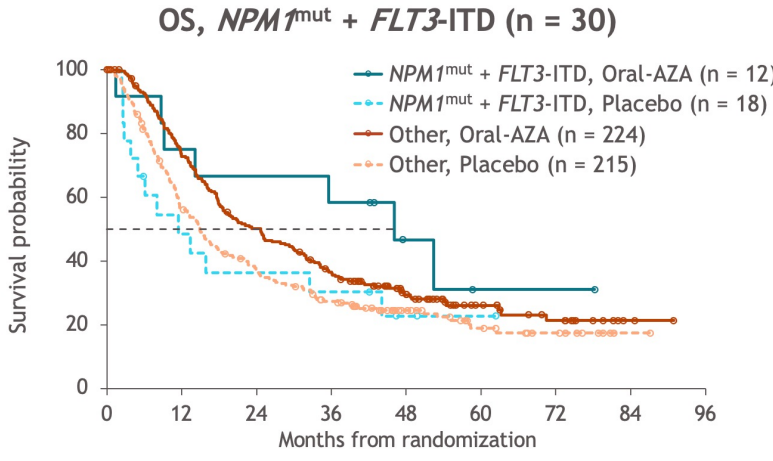
Median OS, months

NPM1^{mut}, Oral-AZA	47.2	*NPM1*^{wt}, Oral-AZA	19.6
NPM1^{mut}, Placebo	15.9	*NPM1*^{wt}, Placebo	14.6



Median OS, months

NPM1^{mut} *FLT3-ITD*^{neg}, Oral-AZA	48.6	Other, Oral-AZA	20.2
NPM1^{mut} *FLT3-ITD*^{neg}, Placebo	18.0	Other, Placebo	14.6



Median OS, months

NPM1^{mut} *FLT3*-ITD, Oral-AZA	46.1	Other, Oral-AZA	24.7
NPM1^{mut} *FLT3*-ITD, Placebo	11.5	Other, Placebo	14.9

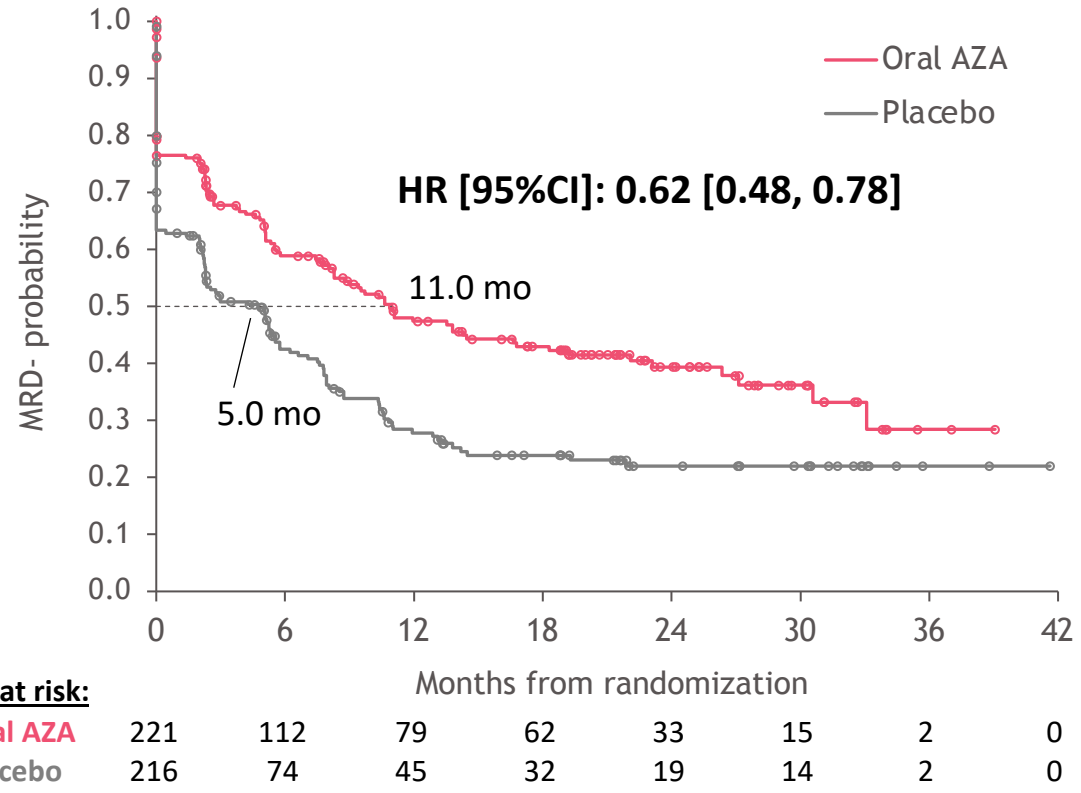
Döhner et al, EHA 2021. Abstr S131.

QUAZAR AML-001: MRD Responses

- Oral AZA was associated with a higher rate of MRD response (BL MRD+, became MRD- on-study) vs. PBO: 37% vs. 19%, respectively

MRD Response	Oral AZA	Placebo
MRD+ at screening, n	**103**	**116**
MRD responders, n/N (%)	**38/103 (37%)**	**22/116 (19%)**
Time to MRD response,[a] n/N (%)		
> 3 to ≤ 6 months	7/38 (18%)	6/22 (27%)
> 6 months	9/38 (24%)	1/22 (5%)

- The median duration of MRD negativity overall (BL MRD– and MRD responders) was extended with Oral AZA vs. PBO

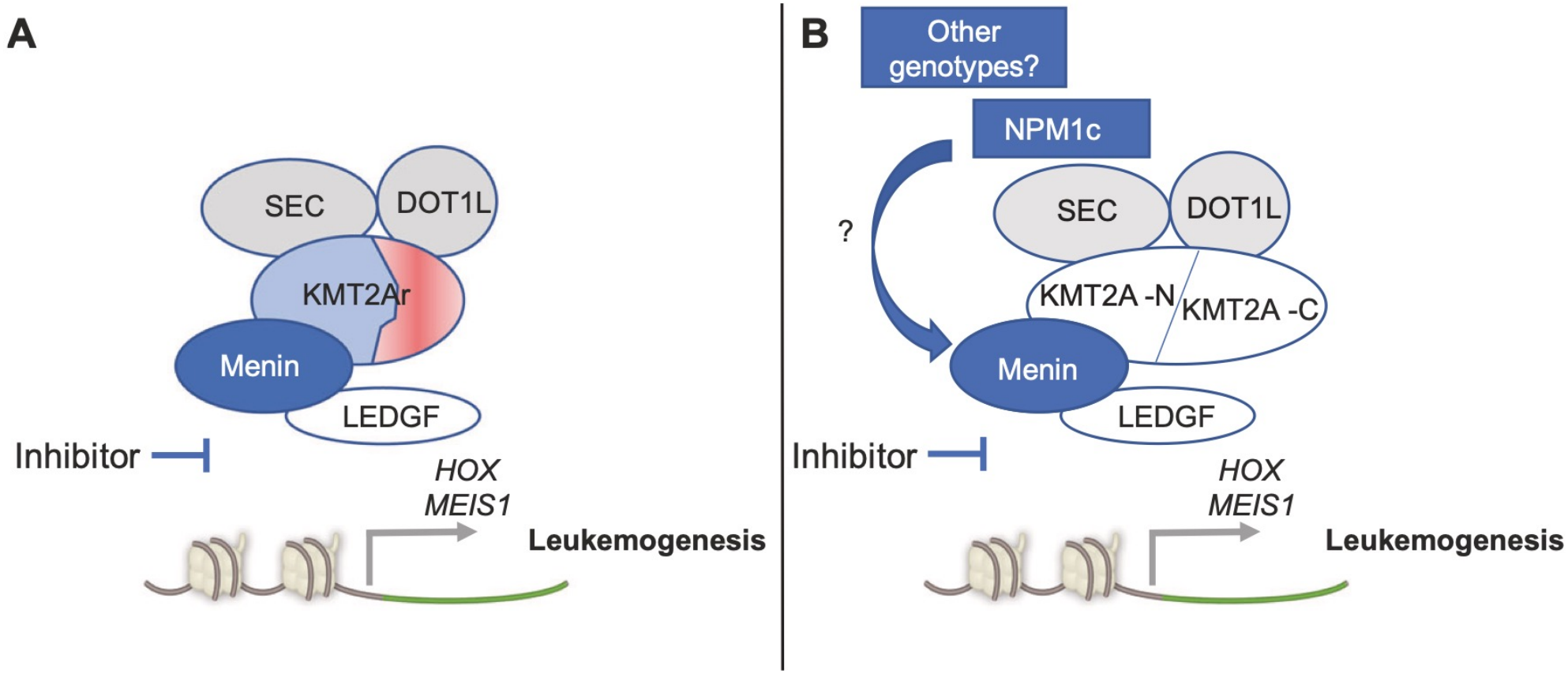


[a]Time from MRD assessment at screening.

95%CI, 95% confidence interval; AZA, azacitidine; BL, baseline; HR, hazard ratio; mo, months; MRD, measurable residual disease; PBO, placebo.

Roboz et al, ASH 2020 Abstract #692

Menin Inhibition for AML with MLL Rearrangements and NPM1c Mutations



Issa et al, Leukemia 2021.

Menin Inhibitors in Development

Table 1 Phase 1/2 clinical trials investigating menin inhibitors in refractory acute leukemias.

Clinical trial/status	Drug	Dosing	Min. age	Phase 2 expansion cohorts
AUGMENT-101	SNDX-5613	PO BID	30 d	A. ALL or MPAL with *KMT2Ar*
NCT04065399				B. AML with *KMT2Ar*
Syndax (recruiting)				C. AML with *NPM1c*
KOMET-001	KO-539	PO daily	18 yr	A. AML with *KMT2Ar*
NCT04067336				B. AML with *NPM1c*
Kura (recruiting)				
NCT04752163	DS-1594	PO BID	18 yr	A. *KMTAr* leukemia: single agent
Daiichi Sankyo (recruiting)				B. AML with *NPM1c*: single agent
				C. AML with *KMT2Ar* or *NPM1c*: in combination with azacytidine and venetoclax
				D. ALL with *KMT2Ar*: in combination with mini-HCVD
NCT04811560	JNJ-75276617	PO daily	18 yr	–
Janssen (not yet recruiting)				
Biomea Fusion (IND enabling submission)	BMF-219	PO	–	–

Status of clinical trials as of May 2021. *ALL* acute lymphoblastic leukemia, *MPAL* mixed-phenotype acute leukemia, *KMT2Ar* rearranged *Lysine Methyltransferase 2A*, *AML* acute myeloid leukemia, *NPM1c* mutation of the *Nucleophosmin 1* resulting in a cytoplasmic localization of the protein, *Min. age* minimum age for enrollement, *d* days, *yr* years, *Mini-HCVD* dose reduced combination of cyclophosphamide and dexamethasone, methotrexate, and cytarabine.

Early clinical experience:

Active in r/r AML with MLLr and NPM1c

ORR around ~50% (CR ~20-25%)

Potential AEs

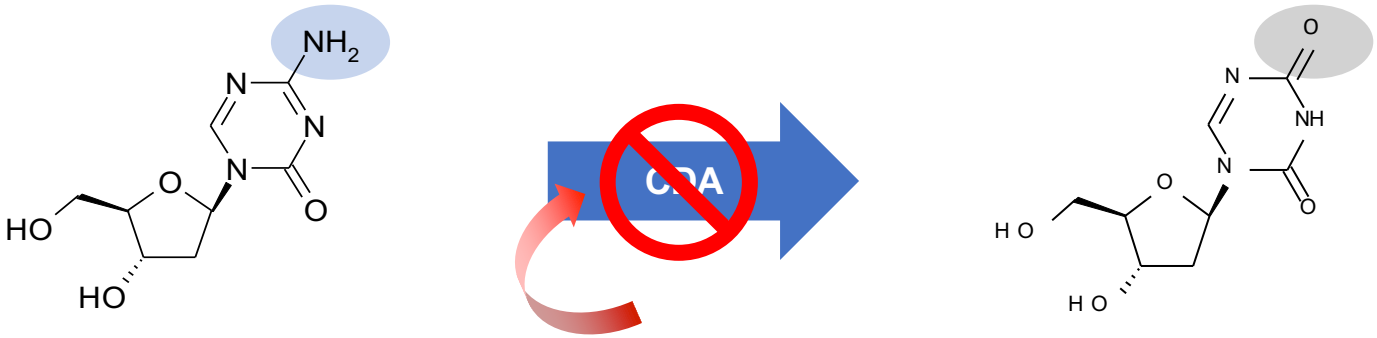
Differentiation syndrome KO-539

QTc prolongation SNDX-5613

Issa et al, Leukemia 2021.
Stein et al, ASH 2021 Abstract # 699.
Wang et al, ASH 2020 Abstract # 115.

Oral Decitabine + Cedazuridine (DEC-C)

- Current HMA treatment poses significant patient burden due to 5–7 days per month of parenteral administration in a clinic setting
- Oral bioavailability of HMAs decitabine and azacitidine is limited due to rapid degradation by CDA in the gut and liver



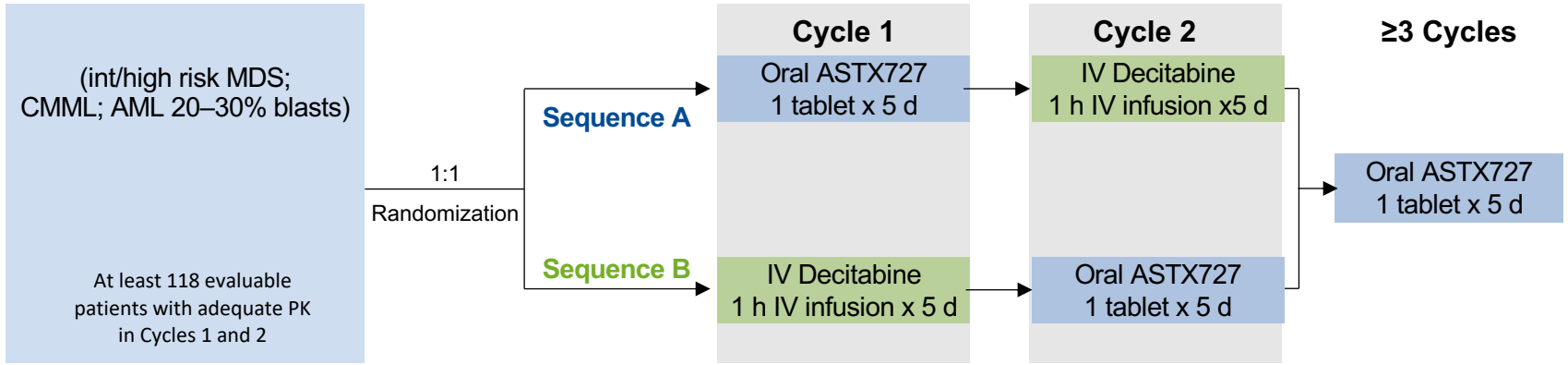
Decitabine **CDA inhibitor** **Inactive metabolite**

- Cedazuridine is a novel, potent, and safe CDA inhibitor
  - Large safety margin, with no adverse events at up to 200 mg/kg in monkeys (~2400 mg/m^2 human equivalent)

CDA, cytidine deaminase.

Savona et al. Lancet Hematogy 2019.

ASTX727-02 trial of DEC-C in MDS/CMML: Randomized Cross-Over Trial



Major entry criteria

- Candidates for IV decitabine
- ECOG PS 0–1
- Life expectancy of ≥3 months
- Adequate Organ Function
- One prior cycle of HMA is allowed

Primary endpoint

- Total 5-d decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

Secondary endpoints

- Efficacy: Response rate; Transfusion independence; duration of response; Leukemia-free and overall survival
- Safety of ASTX727
- Max LINE-1 demethylation

Garcia-Manero et al. Abstract 846 ASH 2019

ASTX727-02 Primary Endpoint: 5-day Decitabine AUC Equivalence

Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
		N	Geo. LSM	N	Geo. LSM		
Primary Analysis	Paired[1]	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7

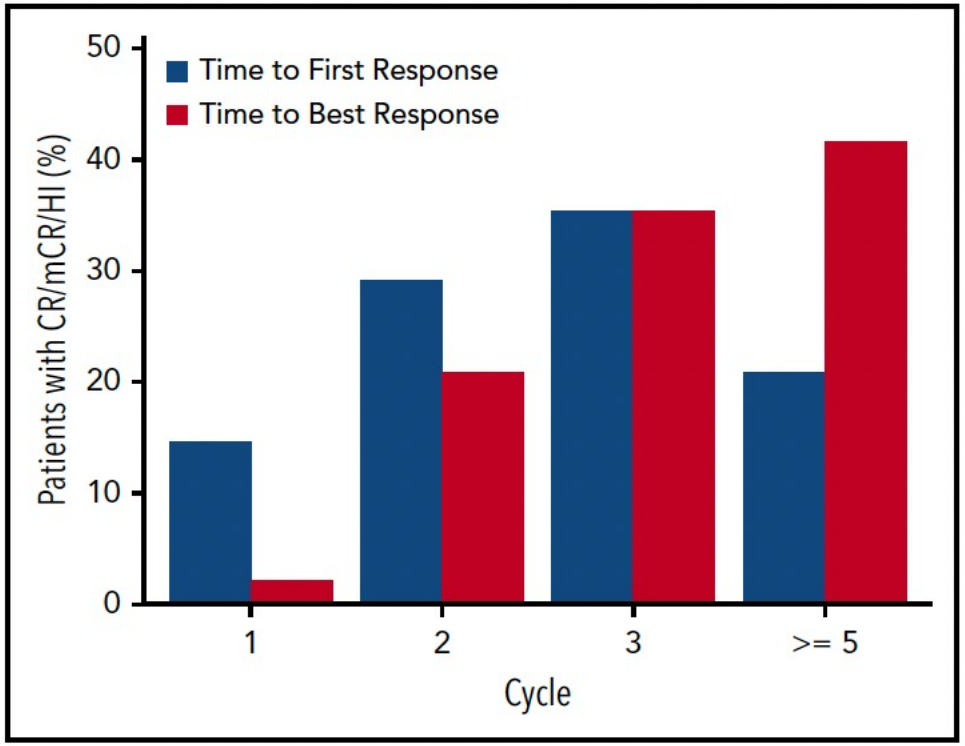
[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All Sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Garcia-Manero et al. Abstract 846 ASH 2019

ASTX727-01-B: DEC-C Responses in MDS/CMML

Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13-32
PR	0	
mCR	18 (22)	14-33
mCR with HI	6 (7)	3-16
HI	13 (16)	9-26
HI-E	8 (10)	4-19
HI-N	2 (2)	0-9
HI-P	11 (14)	7-23
Overall response* (CR + PR + mCR + HI)	48 (60)	48-71
No response	32 (40)	29-52



- Comparable safety was seen between IV decitabine and PO DEC-C

Garcia-Manero et al. Blood 2020.

Summary and Future Directions

- New classification and prognostic scoring systems have been introduced for AML and MDS
  - Implications for clinical trials design and drug development
  - Increased impact of molecular abnormalities
- It remains an exciting time for new treatments for AML and MDS
  - Standards of care are rapidly evolving
  - Clinical trials continue to advance new treatments