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Current and Emerging Therapies for Acute Myeloid Leukemia and Myelodysplastic Syndromes

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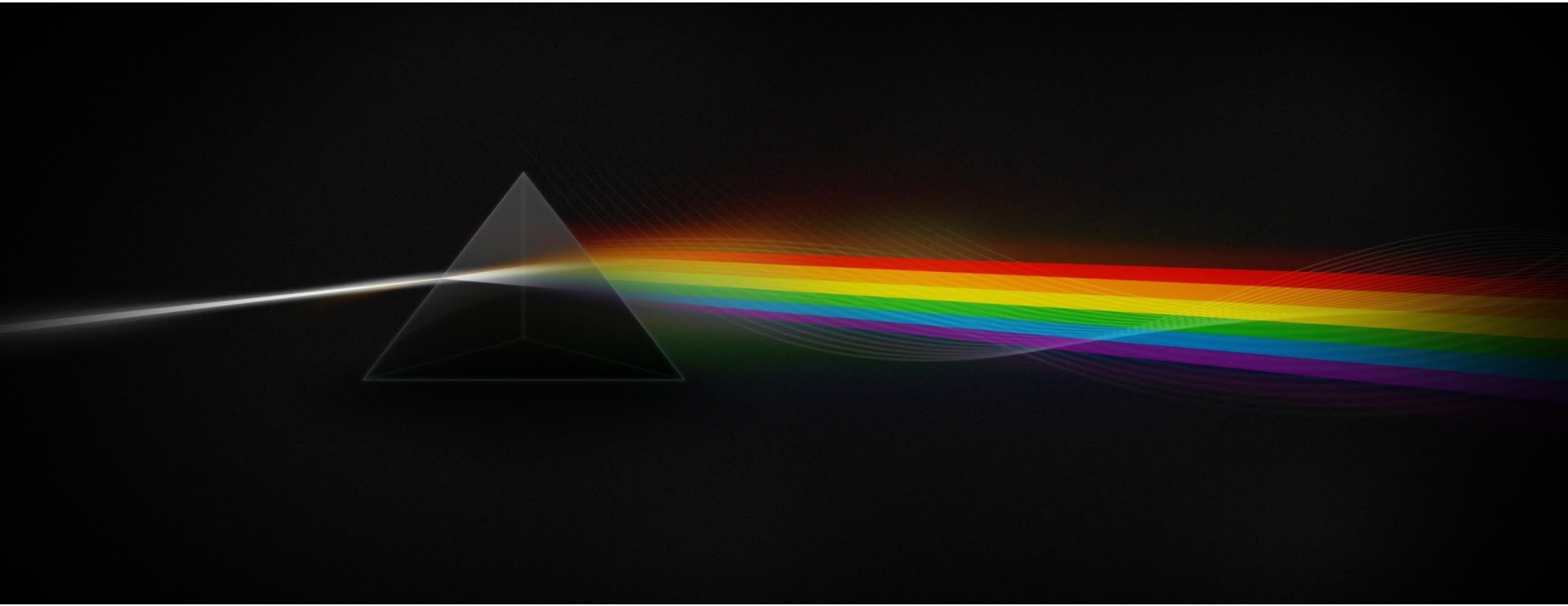
The syndrome of AML and MDS



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REVIEW ARTICLE | JULY 7, 2022

Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel

Hartmut Döhner ✉, Andrew H. Wei, Frederick R Appelbaum, Charles Craddock, Courtney D. DiNardo, Hervé Dombret, Benjamin L. Ebert, Pierre Fenaux, Lucy A. Godley, Robert P. Hasserjian, Richard A. Larson, Ross L. Levine, Yasushi Miyazaki, Dietger Niederwieser, Gert J Ossenkoppele, Christoph Röllig, Jorge Sierra, Eytan M. Stein, Martin S. Tallman, Hwei-Fang Tien, Jianxiang Wang, Agnieszka Wierzbowska, Bob Löwenberg

Leukemia www.nature.com/leu

REVIEW ARTICLE OPEN

Check for updates

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

Joseph D. Khoury[1]✉, Eric Solary[2]✉, Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52]✉

REVIEW ARTICLE | JUNE 29, 2022

International Consensus Classification of Myeloid Neoplasms and Acute Leukemia: Integrating Morphological, Clinical, and Genomic Data

Daniel A. Arber ✉, Attilio Orazi, Robert P. Hasserjian, Michael J. Borowitz, Katherine R Calvo, Hans Michael Kvasnicka, Sa A. Wang, Adam Bagg, Tiziano Barbui, Susan Branford, Carlos E. Bueso-Ramos, Jorge Cortes, Paola Dal Cin, Courtney D. DiNardo, Hervé Dombret, Eric J Duncavage, Benjamin L. Ebert, Elihu Estey, Fabio Facchetti, Kathryn Foucar, Naseema Gangat, Umberto Gianelli, Lucy A. Godley, Nicola Goekbuget, Jason R. Gotlib, Eva Hellström-Lindberg, Gabriela Hobbs, Ronald Hoffman, Elias J. Jabbour, Jean-Jacques Kiladjian, Richard A. Larson, Michelle M. Le Beau, Mignon L. Loh, Bob Löwenberg, Elizabeth A. Macintyre, Luca Malcovati, Charles G. Mullighan, Charlotte M Niemeyer, Olatoyosi Odenike, Seishi Ogawa, Alberto Orfao, Elli Papaemmanuil, Francesco Passamonti, Kimmo Porkka, Ching-Hong Pui, Jerald P Radich, Andreas Reiter, María Rozman, Martina Rudelius, Michael R Savona, Charles Schiffer, Annette Schmitt-Graeff, Akiko Shimamura, Jorge Sierra, Wendy Stock, Richard M. Stone, Martin S. Tallman, Juergen Thiele, Hwei-Fang Tien, Alexandar Tzankov, Alessandro M. Vannucchi, Paresh Vyas, Andrew H. Wei, Olga K. Weinberg, Agnieszka Wierzbowska, Mario Cazzola, Hartmut Döhner, Ayalew Tefferi

AML (WHO5) is arranged into 2 families

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.

Khoury et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022

Acute myeloid leukemia

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

Khoury et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022

International Consensus Classification (ICC) of AML

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*[b]**
• **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*)[b]**
• **AML with other rare recurring translocations**
• **AML with mutated *NPM1***
• **AML with in-frame bZIP mutated *CEBPA*[c]**
• **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*[d]**
• **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[e]**
• **AML not otherwise specified (NOS)**

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[a] **Bone marrow or peripheral blood blast count of ≥10% required, except for AML with t(9;22)(q34.1;q11.2); *BCR*::*ABL1*.**

[b] Variant rearrangements involving *RARA*, *KMT2A*, or *MECOM* should be recorded accordingly.

[c] AML with in-frame mutation in the bZIP domain of the CEBPA gene, either monoallelic or biallelic.

[d] **The presence of a pathogenic somatic *TP53* mutation (at a variant allele fraction of at least 10%, with or without loss of the wild-type TP53 allele) defines the entity AML with mutated *TP53*.**

[e] Cytogenetic abnormalities sufficient for the diagnosis of AML with MDS-related cytogenetic abnormalities and the absence of other AML-defining disease categories.
- Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities.
- Unbalanced clonal 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)

Distinguishing AML from MDS: a fixed blast percentage at 20% may no longer be optimal

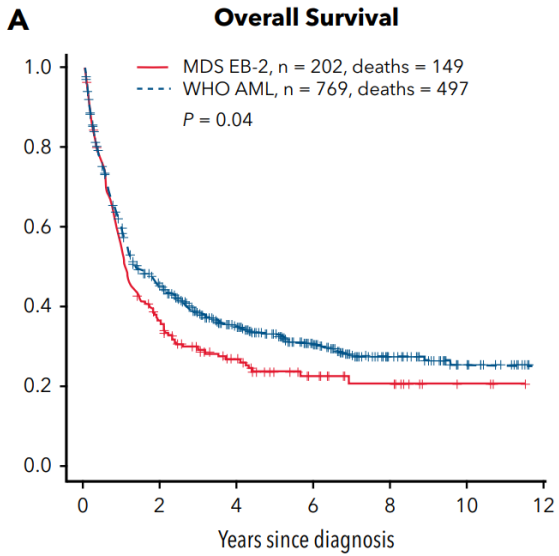


Table 2. Multivariable models

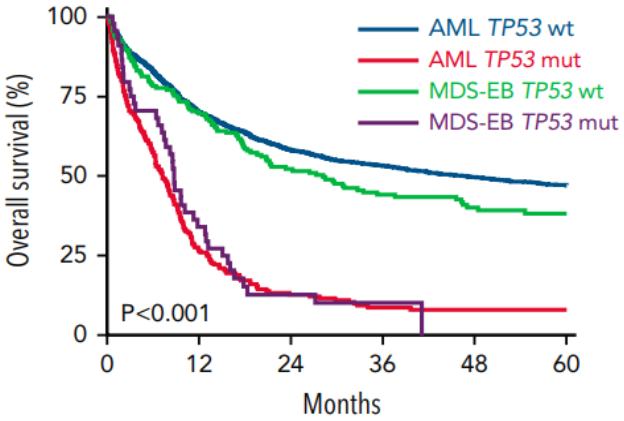
Variable	OS HR (95% CI)	EFS HR (95% CI)	CR or CRi OR (95% CI)	RFS if CR/CRi HR (95%CI)
WHO AML (ref MDS-EB2)	0.89 (0.74-1.07)	0.89 (0.75-1.06)	1.06 (0.99-1.13)	0.66 (0.53-0.83)
P	.21	.2	.11	<.001
Age (per 10 y)	1.3 (1.22-1.38)	1.19 (1.13-1.26)	0.98 (0.96-1)	1.13 (1.05-1.2)
P	<.001	<.001	.02	<.001
PS 2-4 (ref PS 0-1)	2 (1.68-2.37)	1.68 (1.42-1.99)	0.87 (0.82-0.93)	1.21 (0.96-1.51)
P	<.001	<.001	<.001	.11
ELN 2017 intermediate risk (ref favorable risk)	1.7 (1.34-2.15)	1.72 (1.38-2.14)	0.86 (0.8-0.93)	2.15 (1.67-2.76)
P	<.001	<.001	<.001	<.001
ELN 2017 adverse risk (ref favorable risk)	2.28 (1.8-2.88)	2.29 (1.84-2.85)	0.78 (0.73-0.84)	3.07 (2.35-4)
P	<.001	<.001	<.001	<.001
Secondary (ref de novo)	1.3 (1.1-1.55) *P* = 0.002	1.28 (1.08-1.5) *P* = 0.004	0.93 (0.87-0.99) *P* = 0.02	1.16 (0.93-1.43) *P* = 0.18
P	.002	.004	.02	.18
Low-intensity induction (ref high intensity)	1.3 (1.08-1.55)	1.62 (1.36-1.93)	0.7 (0.66-0.75)	1.07 (0.82-1.38)
P	.004	<.001	<.001	.63
Allogeneic HCT (ref no allogeneic HCT)	0.48 (0.39-0.6)	0.39 (0.31-0.47)	Not applicable	0.29 (0.23-0.36)
P	<.001	<.001		<.001

- After accounting for age, performance status, genetic risk, and allogeneic HCT, patients with MDS-EB2 (10-19% blasts) and AML have similar rates of survival and response to therapy, challenging the arbitrary 20% blast threshold.
- Cases with 10-19% blasts lie on the border between MDS and AML in terms of their prognosis, but also their biology

Estey E, Hasserjian RP, Döhner H. Blood 2022;139(3):323-332.

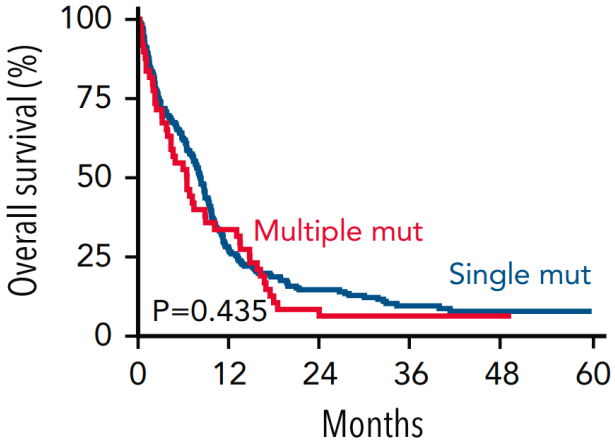
TP53 mutation in AML and MDS with excess blasts

Accumulating evidence from both a clinical and molecular perspective that AML and MDS with **mutated *TP53* represent a distinct molecular disease entity**



No. at risk:

AML *TP53* wt	1805	1255	1014	807	572	397
AML *TP53* mut	186	50	23	14	9	5
MDS-EB *TP53* wt	165	114	81	62	45	35
MDS-EB *TP53* mut	44	15	5	1	0	0

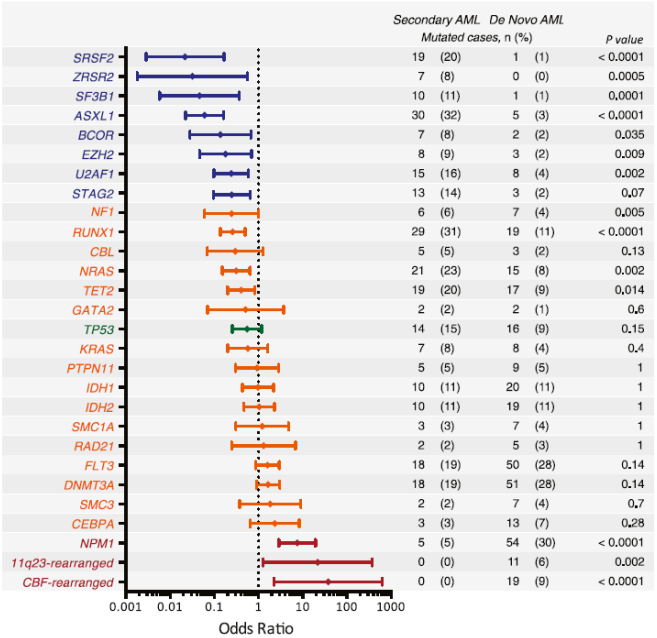


No. at risk:

Single mut	181	49	25	12	6	3
Multiple mut	49	16	3	3	3	2

Grob T, et al. Blood. 2022;139(15):2347-2354.

Antecedent history: genetic basis for secondary AML

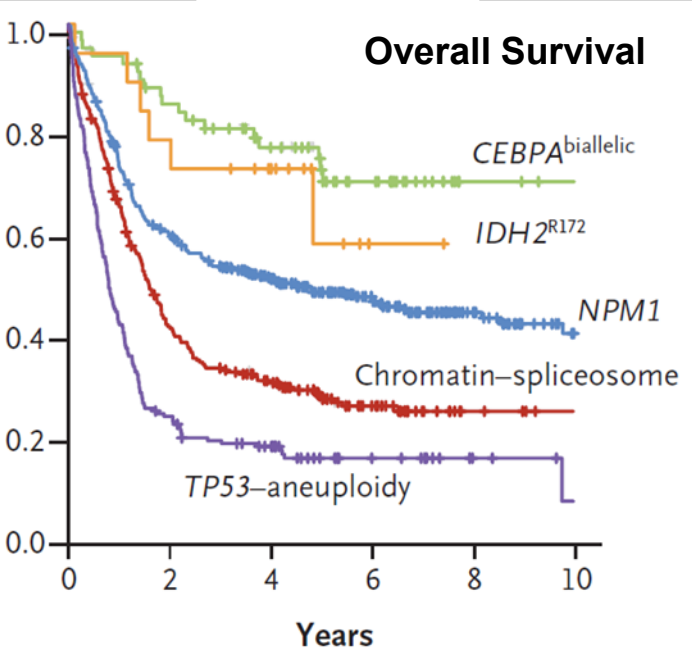


Comparison of mutational profile of 194 clinically defined s-AML or t- AML *versus* 180 *de novo* AML from the Cancer Genome Atlas

Gene mutation signature with >95% specificity for secondary type AML:

ASXL1, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*

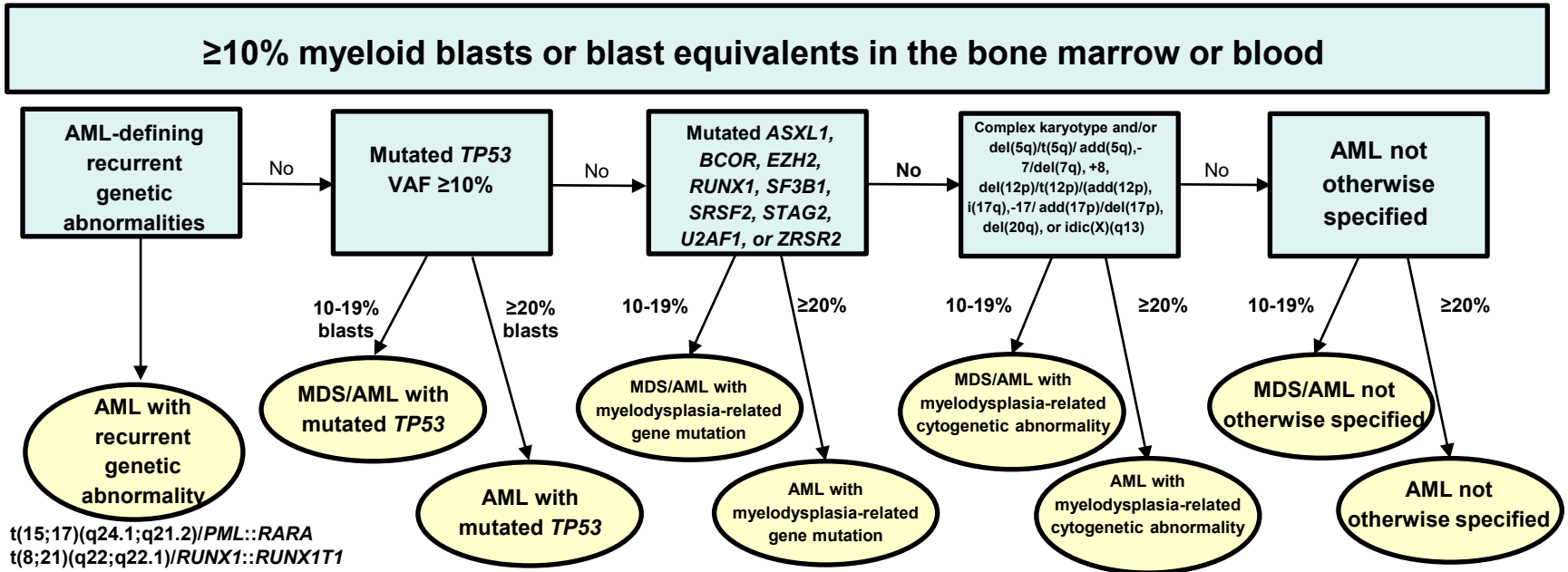
Lindsley RC, et al. Blood. 2015;125(9):1367–1376.



Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*

Papaemmanuil E, Gerstung M, et al. N Engl J Med. 2016; 374(23):2209-2221.

International Consensus Classification of AML - Hierarchy



- t(15;17)(q24.1;q21.2)/*PML*::*RARA*
- t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*
- t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*
- t(6;9)(p22.3;q34.1)/*DEK*::*NUP214*
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*::*MECOM*(*EVI1*)
- mutated *NPM1*
- in-frame bZIP mutated *CEBPA*
- t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*
- other recurrent rearrangements involving *RARA*, *KMT2A*, *MECOM*
- Other rare rearrangements

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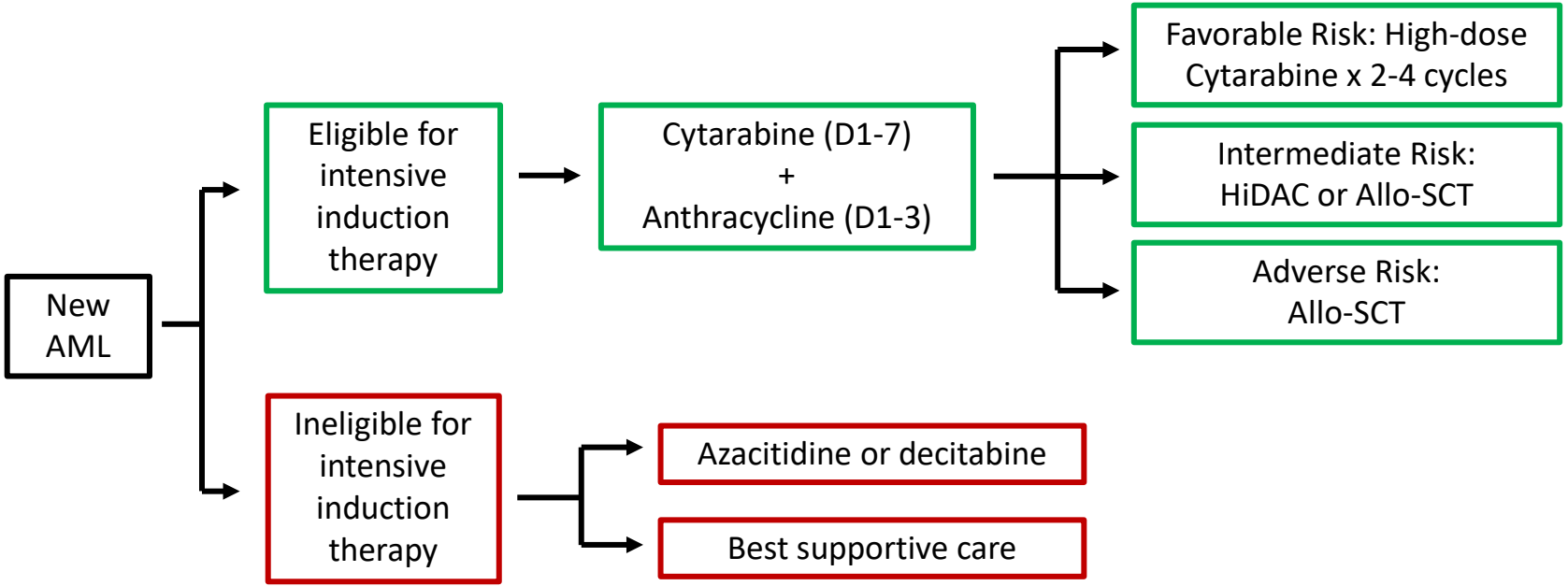
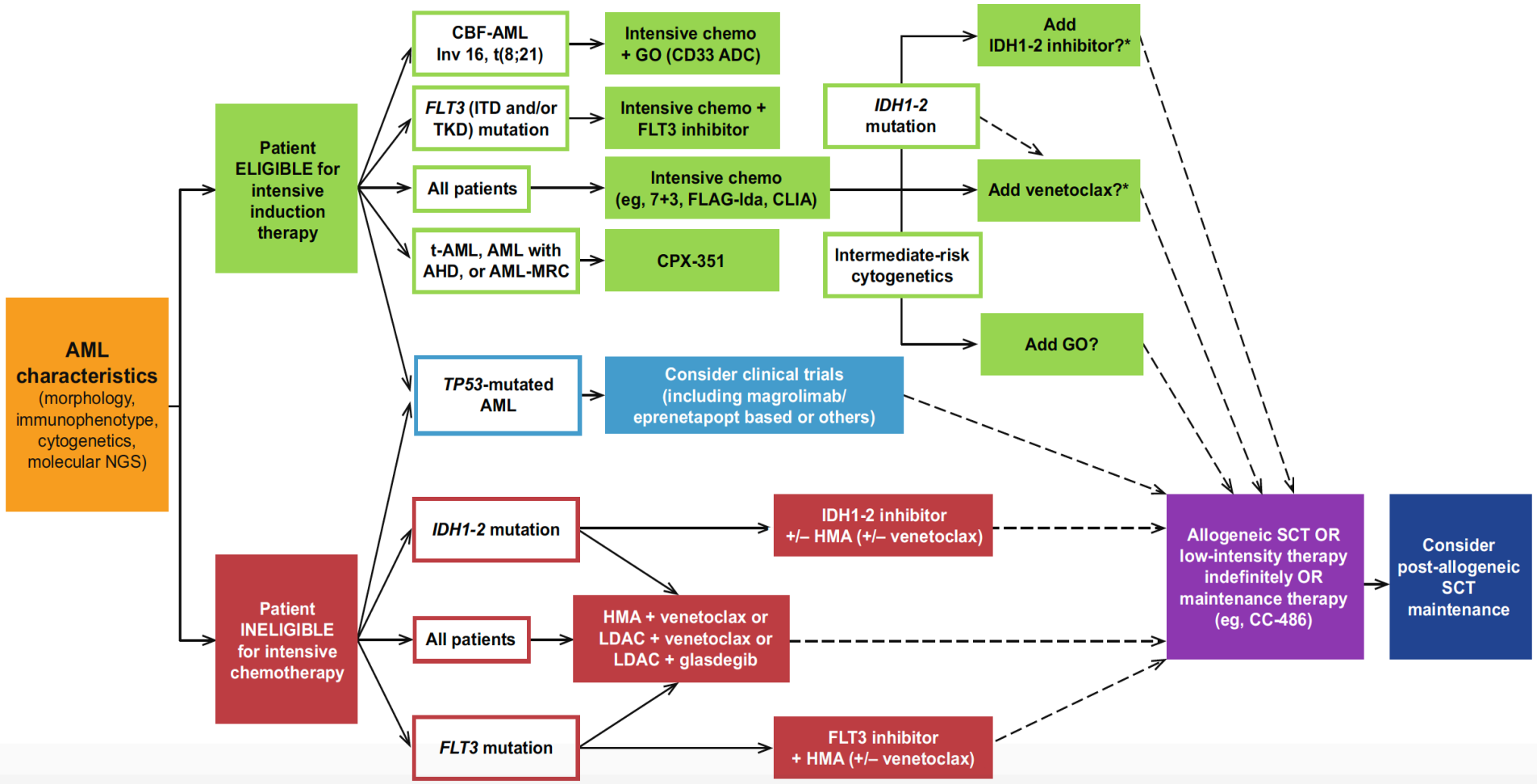
Conventional AML Treatment (pre-2020)





Daver et al, Blood Cancer J, 2020

2022 ELN risk categorization

Risk Category	Genetic Abnormality
Favorable Do not transplant	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* • Mutated *NPM1*[a] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*
Intermediate Consider transplantation	• Mutated *NPM1*[a] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse Do transplant	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • 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, monosomal karyotype • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2* • Mutated *TP53*

- The ELN AML risk classification has been developed based on data from intensively treated patients and may need modifications for patients receiving less intensive therapies
- Initial risk assignment may change during the treatment course based on the results from MRD analyses

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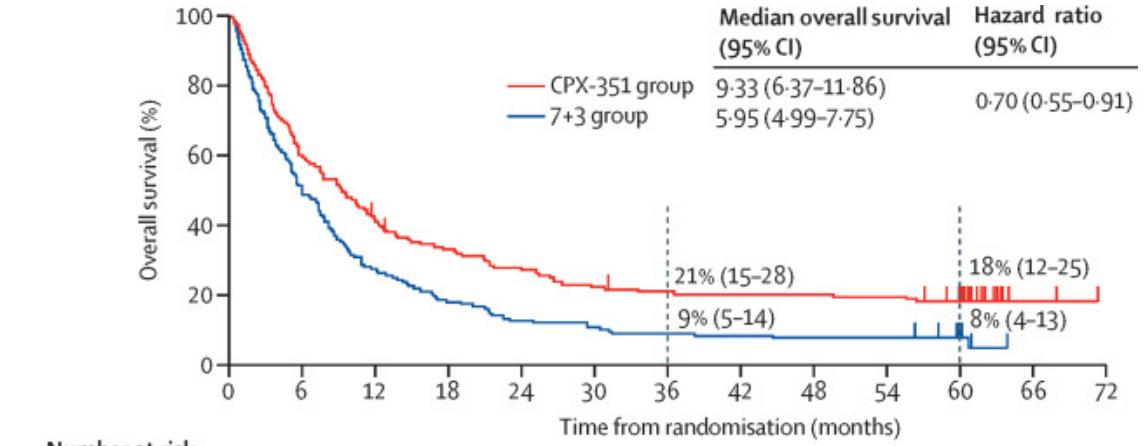
CPX-351* vs ‘7+3’ in older patients with secondary AML



Number at risk (number censored)													
CPX-351 group	153	92	62	49	40	33	30	29	29	28	22	2	0
	(0)	(0)	(1)	(2)	(2)	(2)	(3)	(3)	(3)	(3)	(7)	(27)	(29)
7+3 group	156	77	43	28	20	17	14	13	12	12	5	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(7)	(11)	(11)

Approved for “AML with myelodysplasia-related changes and therapy-related AML“

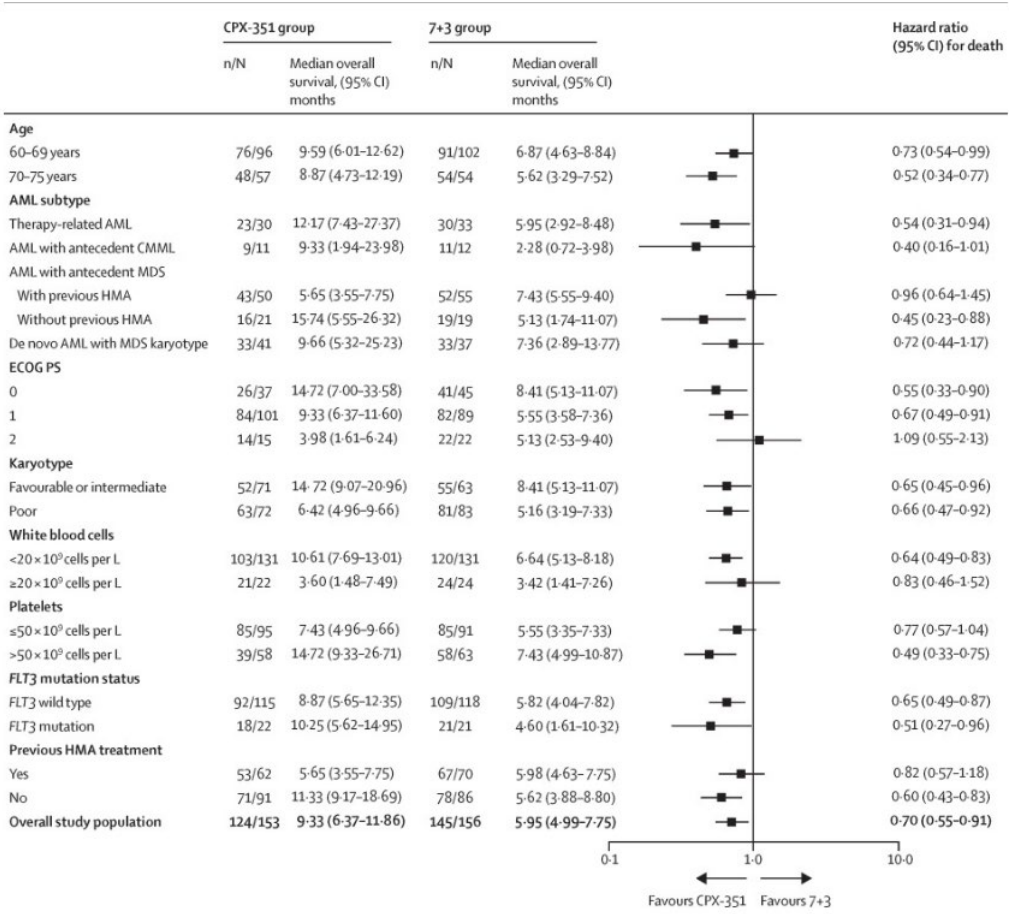
Randomized data are lacking for patients under 60 years and for AML following prior MPN.

The standard arm of the registrational trial included only ‘7+3’ induction and consolidation, but no intensive intermediate-dose cytarabine-based consolidation therapy.

Lancet JE, et al. J Clin Oncol. 2018;36(26):2684-2692.

Lancet JE, et al. Haematol. 2021;8(7):e481-e491. [5-year follow-up]

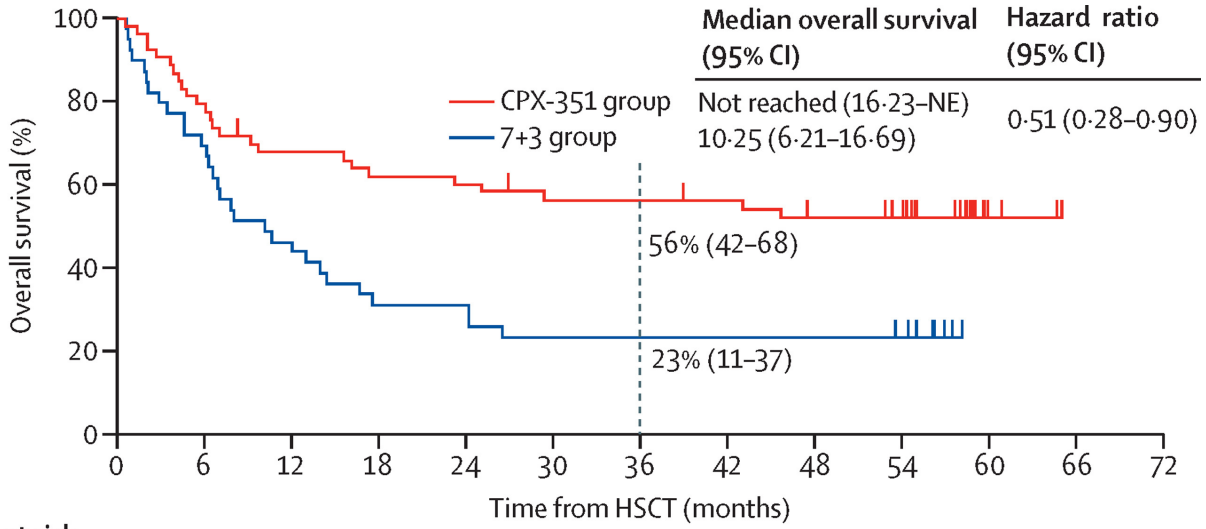
Forest plot of overall survival by baseline patient characteristics



	CPX-351 group		7+3 group		Hazard ratio (95% CI) for death
	n/N	Median overall survival, (95% CI) months	n/N	Median overall survival, (95% CI) months	
Age					
60–69 years	76/96	9·59 (6·01–12·62)	91/102	6·87 (4·63–8·84)	0·73 (0·54–0·99)
70–75 years	48/57	8·87 (4·73–12·19)	54/54	5·62 (3·29–7·52)	0·52 (0·34–0·77)
AML subtype					
Therapy-related AML	23/30	12·17 (7·43–27·37)	30/33	5·95 (2·92–8·48)	0·54 (0·31–0·94)
AML with antecedent CMML	9/11	9·33 (1·94–23·98)	11/12	2·28 (0·72–3·98)	0·40 (0·16–1·01)
AML with antecedent MDS					
With previous HMA	43/50	5·65 (3·55–7·75)	52/55	7·43 (5·55–9·40)	0·96 (0·64–1·45)
Without previous HMA	16/21	15·74 (5·55–26·32)	19/19	5·13 (1·74–11·07)	0·45 (0·23–0·88)
De novo AML with MDS karyotype	33/41	9·66 (5·32–25·23)	33/37	7·36 (2·89–13·77)	0·72 (0·44–1·17)
ECOG PS					
0	26/37	14·72 (7·00–33·58)	41/45	8·41 (5·13–11·07)	0·55 (0·33–0·90)
1	84/101	9·33 (6·37–11·60)	82/89	5·55 (3·58–7·36)	0·67 (0·49–0·91)
2	14/15	3·98 (1·61–6·24)	22/22	5·13 (2·53–9·40)	1·09 (0·55–2·13)
Karyotype					
Favourable or intermediate	52/71	14·72 (9·07–20·96)	55/63	8·41 (5·13–11·07)	0·65 (0·45–0·96)
Poor	63/72	6·42 (4·96–9·66)	81/83	5·16 (3·19–7·33)	0·66 (0·47–0·92)
White blood cells					
<20 × 10^9 cells per L	103/131	10·61 (7·69–13·01)	120/131	6·64 (5·13–8·18)	0·64 (0·49–0·83)
≥20 × 10^9 cells per L	21/22	3·60 (1·48–7·49)	24/24	3·42 (1·41–7·26)	0·83 (0·46–1·52)
Platelets					
≤50 × 10^9 cells per L	85/95	7·43 (4·96–9·66)	85/91	5·55 (3·35–7·33)	0·77 (0·57–1·04)
>50 × 10^9 cells per L	39/58	14·72 (9·33–26·71)	58/63	7·43 (4·99–10·87)	0·49 (0·33–0·75)
***FLT3* mutation status**					
FLT3 wild type	92/115	8·87 (5·65–12·35)	109/118	5·82 (4·04–7·82)	0·65 (0·49–0·87)
FLT3 mutation	18/22	10·25 (5·62–14·95)	21/21	4·60 (1·61–10·32)	0·51 (0·27–0·96)
Previous HMA treatment					
Yes	53/62	5·65 (3·55–7·75)	67/70	5·98 (4·63–7·75)	0·82 (0·57–1·18)
No	71/91	11·33 (9·17–18·69)	78/86	5·62 (3·88–8·80)	0·60 (0·43–0·83)
Overall study population	**124/153**	**9·33 (6·37–11·86)**	**145/156**	**5·95 (4·99–7·75)**	**0·70 (0·55–0·91)**

Lancet JE, et al. Haematology 2021; 8(7):e481-e491.

Overall survival from date of allogeneic transplantation



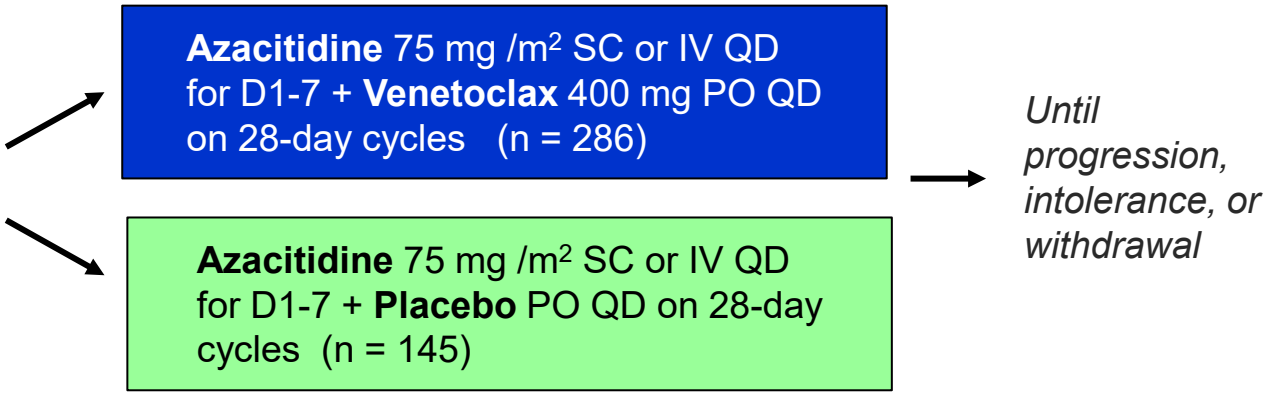
Number at risk (number censored)													
CPX-351 group	53	42	35	32	31	28	28	27	24	21	6	0	0
	(0)	(0)	(1)	(1)	(1)	(2)	(2)	(3)	(4)	(7)	(22)	(28)	(28)
7+3 group	39	27	18	12	12	9	9	9	9	8	0	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(9)	(9)	(9)

Lancet JE, et al. Haematology 2021; 8(7):e481-e491.

VIALE-A: Azacitidine + Venetoclax

- Multicenter, double-blind, placebo-controlled, randomized phase III trial for “unfit” patients

Adults with previously untreated AML ineligible for standard cytarabine/anthracycline due to age (≥ 75 yrs), ECOG PS 2-3, or comorbidities. No hypomethylating agent for antecedent hematologic disorder. (N = 431)



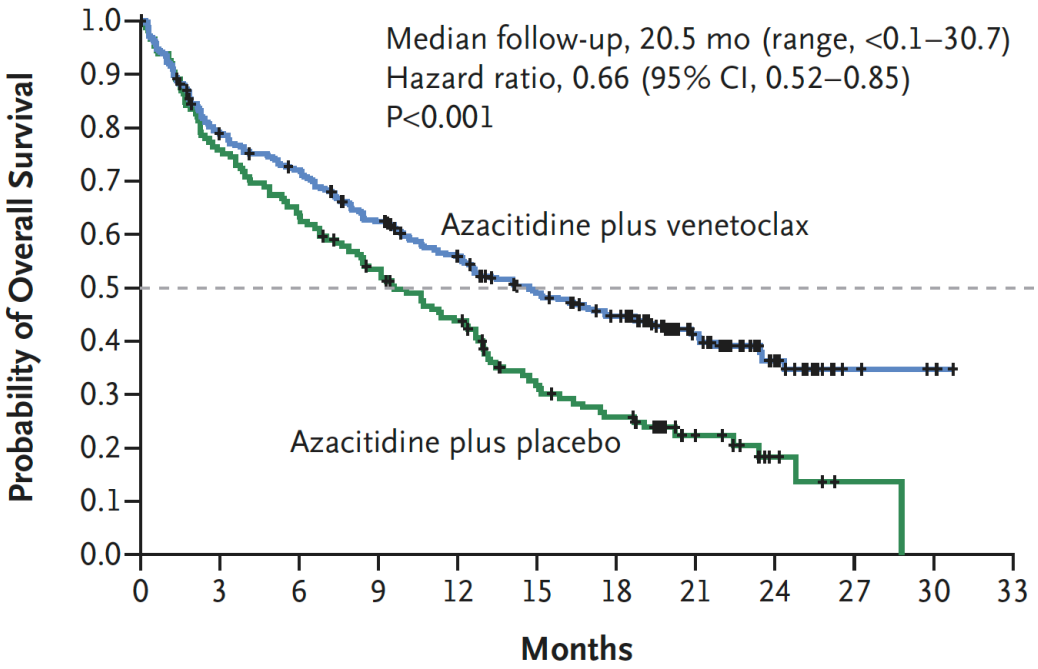
- Primary endpoints: OS, rate of CR + CRi
- Other endpoints: EFS, OS by molecular subtype, QoL, transfusion independence

DiNardo. N Engl J Med. 2020;383:617.

VIALE-A: Azacitidine + Venetoclax

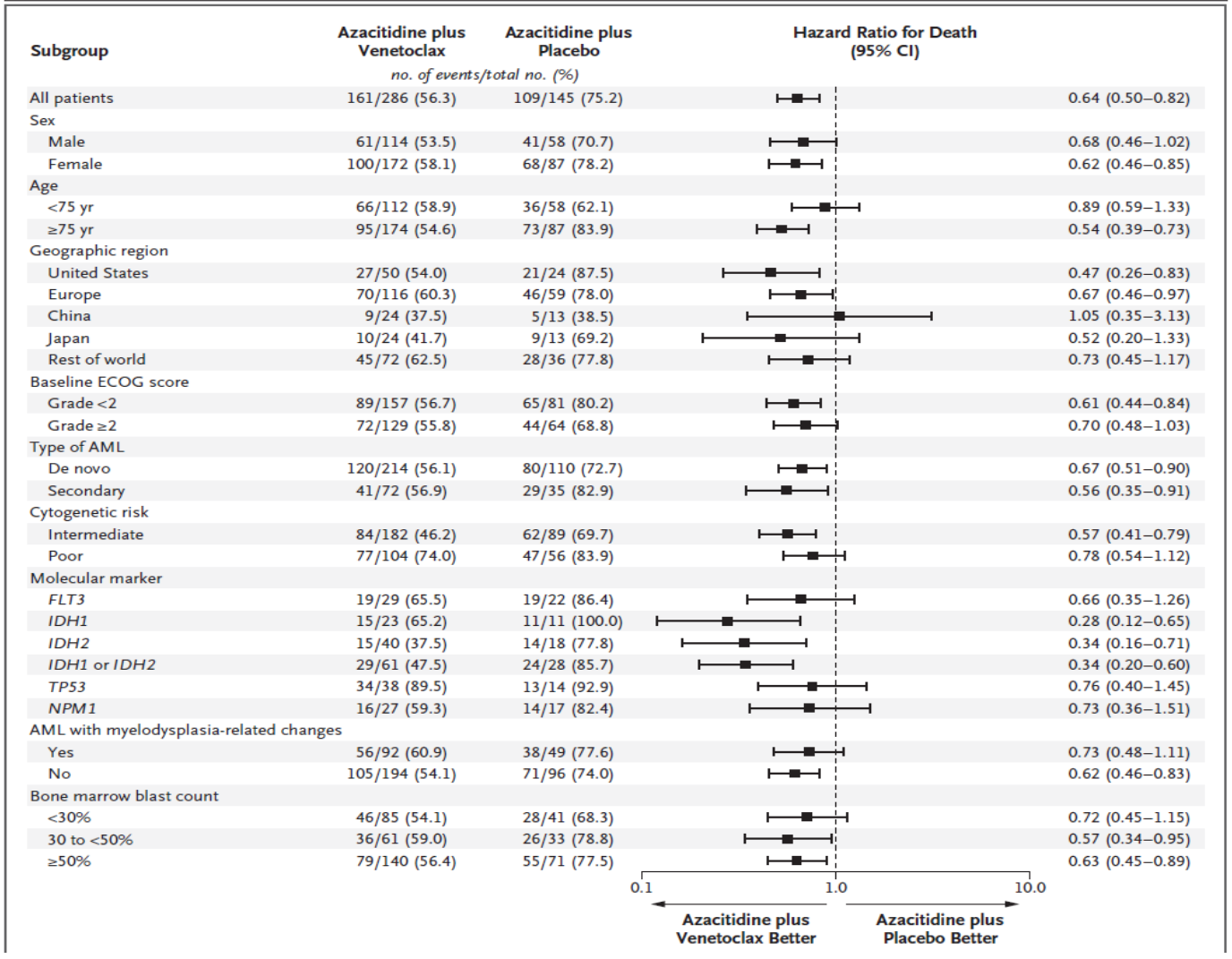
Outcome	Aza-Ven (n = 286)	Aza-Pbo (n = 145)	P-value
CR	36.7%	17.9%	<0.001
CR + CRi	66.4%	28.3%	<0.001
Median duration of response	17.5 months	13.4 months	-
Median overall survival	14.7 months	9.6 months	<0.001

Adverse event (≥ G3)	Aza-Ven (n = 286)	Aza-Pbo (n = 145)
Thrombo-cytopenia	45%	38%
Neutropenia	42%	28%
Febrile neutropenia	42%	19%
Infections	64%	51%



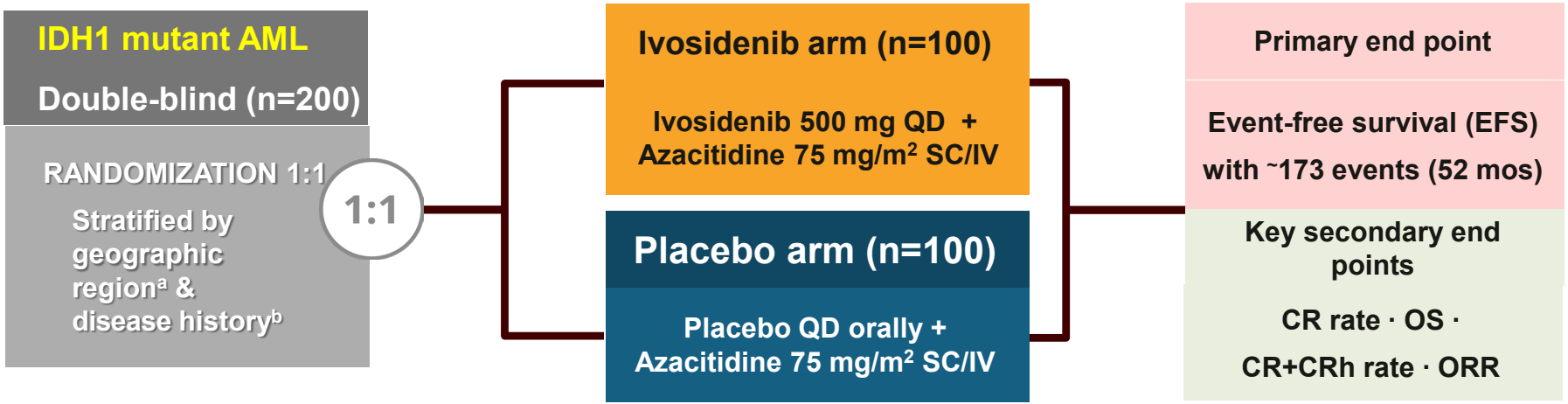
Median time to response: 1.3 months. No differences in quality of life

DiNardo. N Engl J Med. 2020; 383: 617.



DiNardo et al.
VIALE A trial.
N Engl J Med
2020; 383: 617

AGILE: Study Design and End Points

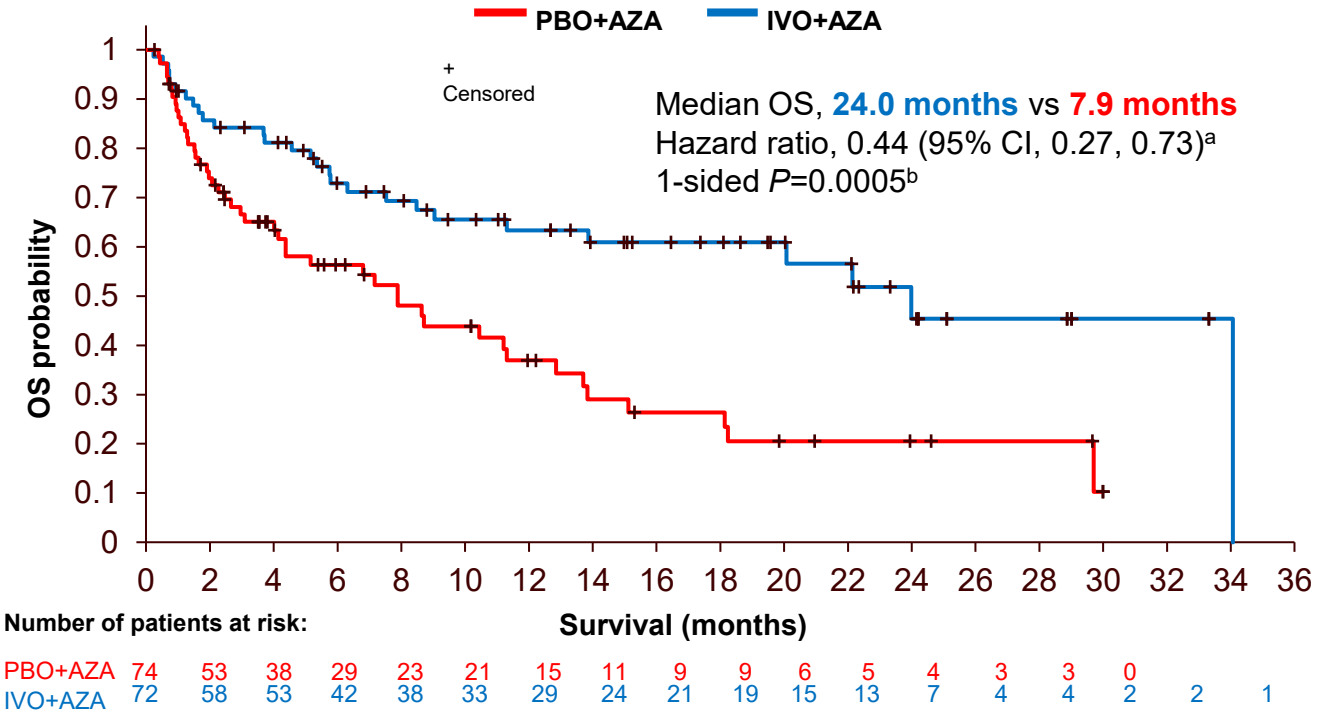


- As of the data cutoff date for this analysis (18March2021), 146 patients have been randomized (IVO+AZA, n=72; PBO+AZA, n=74).
- As of 12May2021, the IDMC recommended to halt enrollment based on a noted difference in clinical importance between the treatment groups, not related to safety.
- A total of 148 patients were enrolled at 155 active sites in 20 countries.

AT THE FOREFRONT UChicago Medicine

Goodman AM, Mohyuddin GR, Prasad V et al. N Engl J Med. 2022 Jun 30;386(26):2536.

IVO+AZA improved overall survival (OS)



- OS benefit was consistent across subgroups: de novo status, region, age, baseline ECOG PS score, sex, race, baseline cytogenetic risk status, WHO classification of AML, baseline white blood cell count, baseline percentage of bone marrow blasts.

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Goodman AM, Mohyuddin GR, Prasad V et al. N Engl J Med. 2022 Jun 30;386(26):2536.

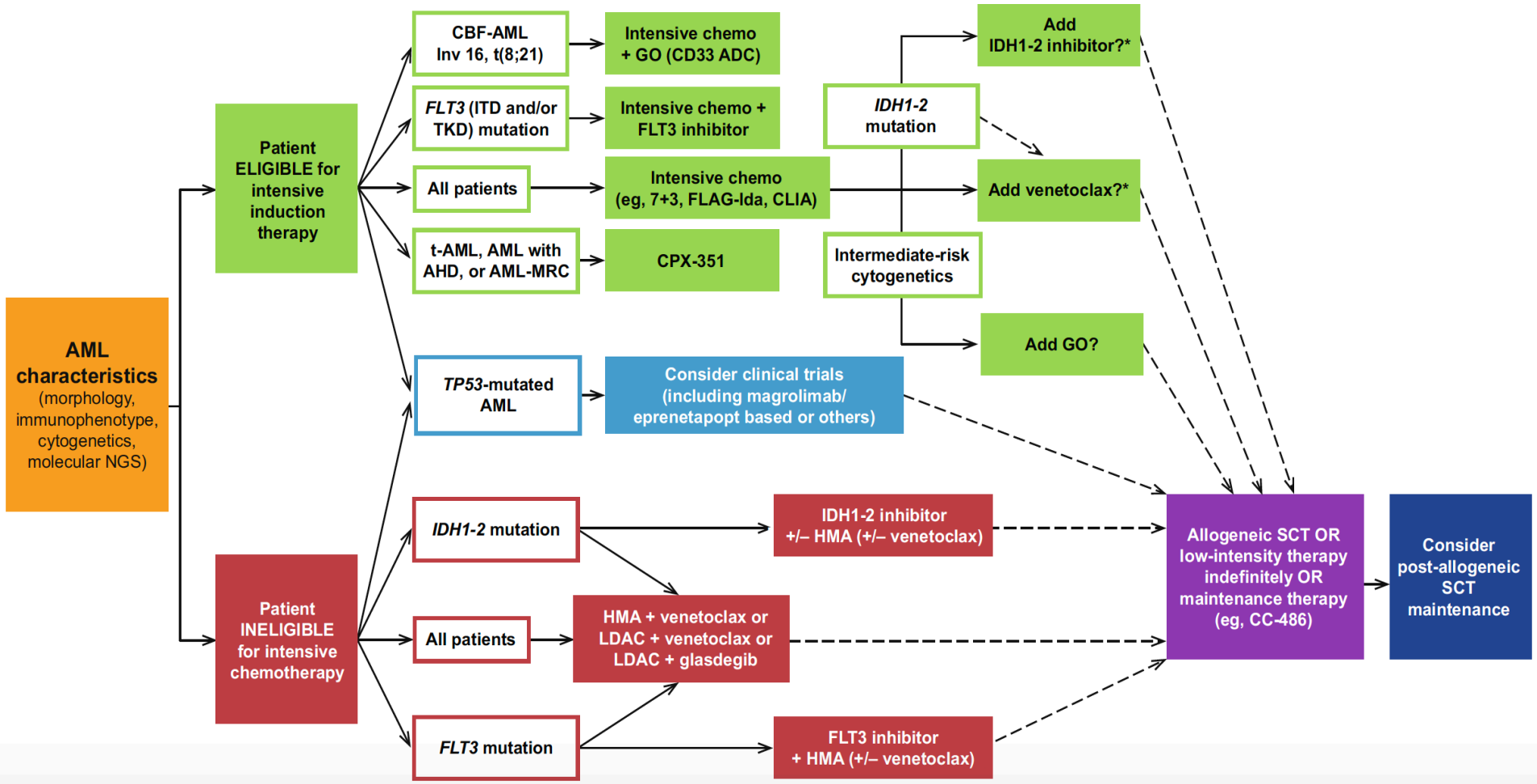
Selected treatment options for patients **not suitable for intensive chemotherapy**

Regimen	Recommended dosing
Azacitidine or decitabine+ venetoclax[a,b]	Azacitidine 75 mg/m^2 SC/IV d1-7 (alternatively d1-5 + d8-9) or decitabine 20 mg/m^2 IV d1-5; venetoclax dose ramp up: 100 mg d1, 200 mg d2, 400 mg PO QD d3-28 • Adjust venetoclax dose if concurrent strong CYP3A4 inhibitors: 10 mg on d1, 20 mg on d2, 50 mg on d3, 100 mg (or less[b]) PO QD from d4 • For venetoclax dose modifications and management of myelosuppression see Table 12
Low-dose cytarabine + venetoclax[a,b]	Cytarabine 20 mg/m^2 SC daily, d1-10; venetoclax dose ramp up: 100 mg d1, 200 mg d2, 400 mg d3, 600 mg d4-28 • Adjust venetoclax dose if concurrent strong CYP3A4 inhibitors: 10 mg d1, 20 mg d2, 50 mg d3, 100 mg (or less[b]) PO QD d4-28 • For venetoclax dose modifications and management of myelosuppression see Table 12
Azacitidine + ivosidenib (AML with *IDH1* mutation)	Azacitidine 75 mg/m^2 SC/IV d1-7 (alternatively d1-5 + d8-9); ivosidenib 500 mg PO QD d1-28; both q4weeks, until progression
Ivosidenib (AML with *IDH1* mutation)	For very frail patients, ivosidenib 500 mg PO QD d1-28 as monotherapy, until progression may be considered
Best supportive care	Including hydroxyurea; for patients who cannot tolerate any anti-leukemic therapy, or who do not wish any therapy

[a] **To reduce the risk of tumor lysis syndrome, the prophylactic use of uric acid lowering drugs, close electrolyte monitoring and cytoreduction of the WBC to <25,000/µL or even lower, for patients with high bone marrow blast burden, elevated LDH is recommended.**

[b] **In the VIALE-A and VIALE-C trials, an adjusted venetoclax dose of 50 mg was used in the presence of a strong CYP3A4 inhibitor. This venetoclax dose is supported by a pharmacokinetic study examining venetoclax in the presence of posaconazole.**

Döhner et al. BLOOD 2022



Daver et al, Blood Cancer J, 2020

Approved and *investigational* therapies for MDS and AML

- Olutasidenib (targeting IDH1) – FDA approved
- Decitabine + cedazuridine (approved for MDS) +/- venetoclax
- Oral azacitidine (CC-486) – approved for maintenance in AML
- *Magrolimab* (targeting TP53 mutant disease)
- *Sabatolimab* (anti-TIM3) – MBG453
- Azacitidine/venetoclax + gilteritinib (FLT3-mutant AML)
- *Eprenetapopt* (targets mutant TP53)
- *Pevonidostat* (NEDD8 inhibitor)

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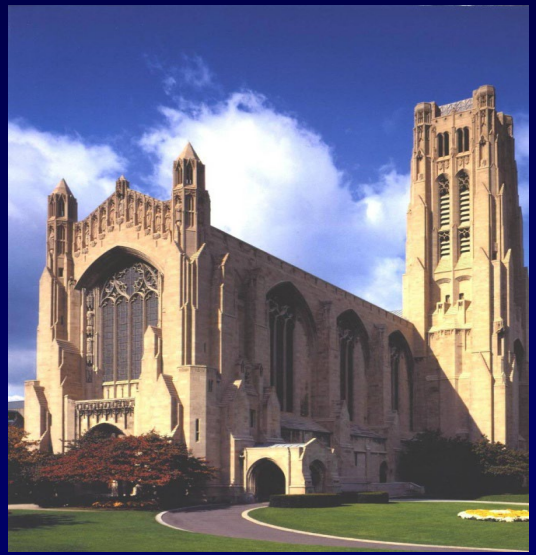

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