Recent Advances in Acute Leukemias

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Learning Objectives

- Discuss recent advances in acute leukemia with a focus on AML
  - Learn about new and updated classification and prognostic systems for AML
  - Review current AML treatment paradigms
  - Discuss recently approved and emerging treatments for AML

New/Updated Classification and Prognostic Systems for AML

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

WHO 2022 Classification – 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 AML, NOS is no longer applicable.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

International Consensus Classification (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

AML with myelodysplasia-related cytogenetic abnormalities:

- 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

Arber et al, Blood 2022

Dohner et al, Blood 2022

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.

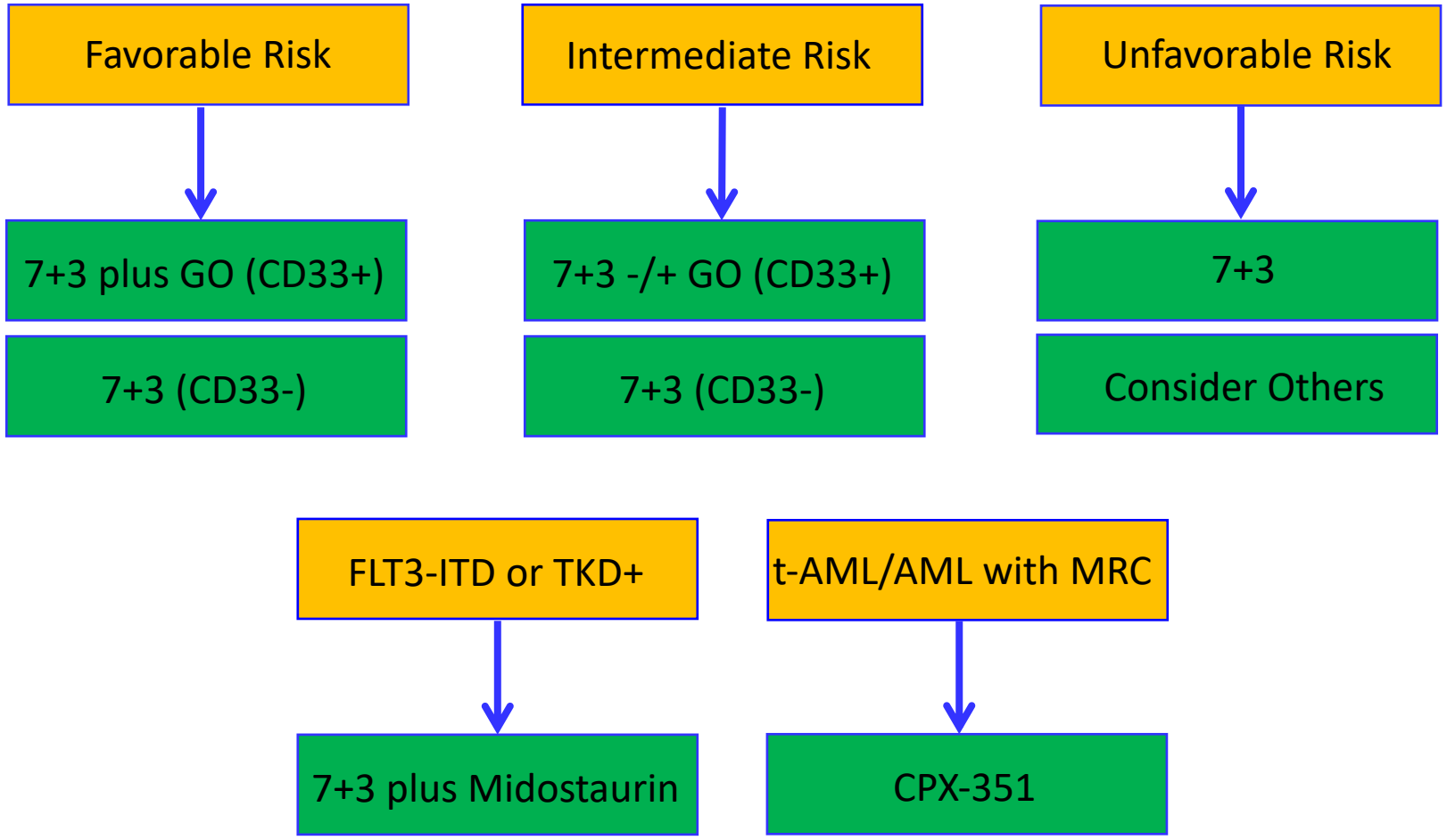
[k] *TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation); *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

* Changes from ELN 2017

Dohner et al, Blood 2022

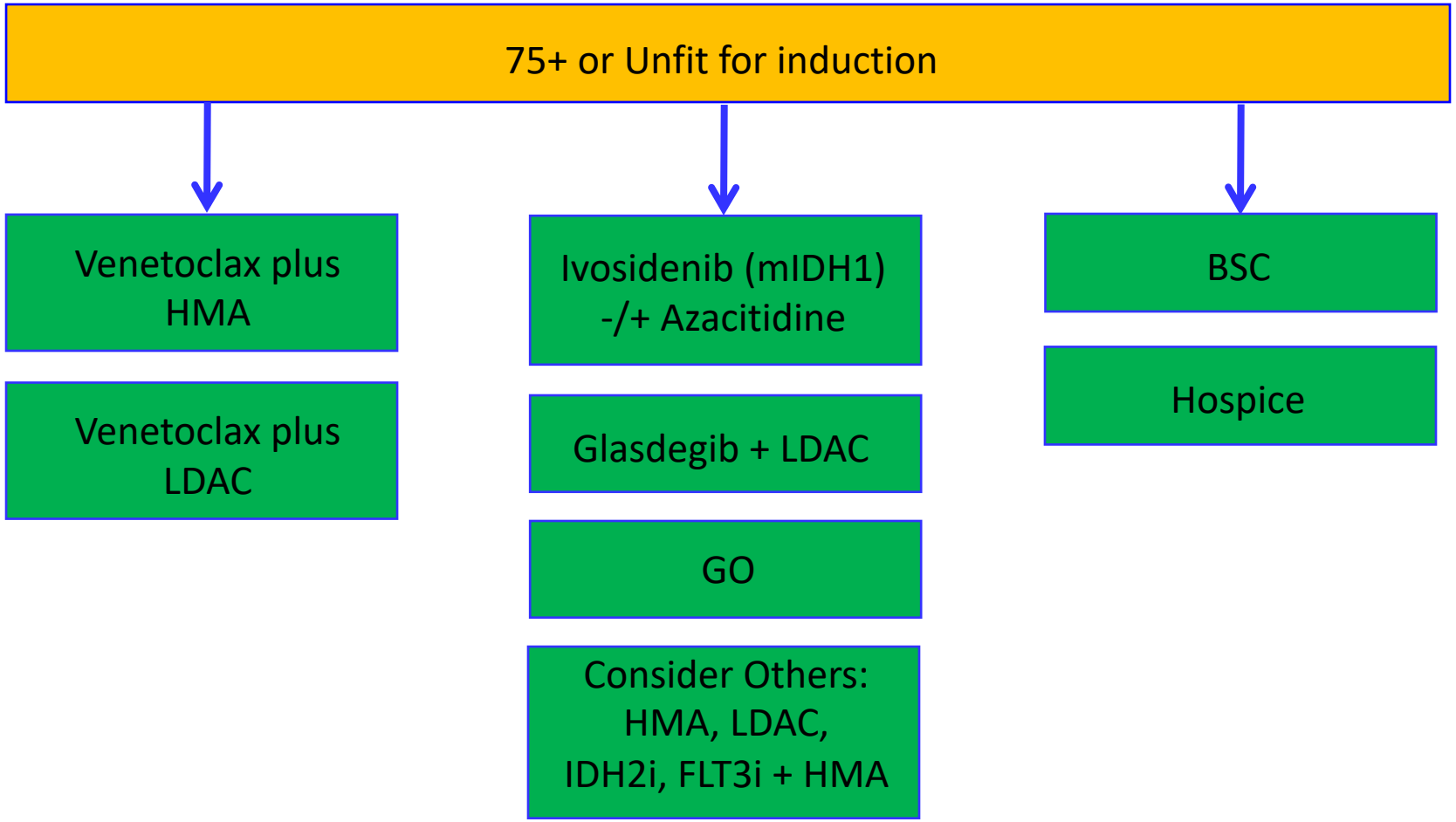
Current AML Treatment Paradigms

First-Line Treatment of Fit AML in 2022



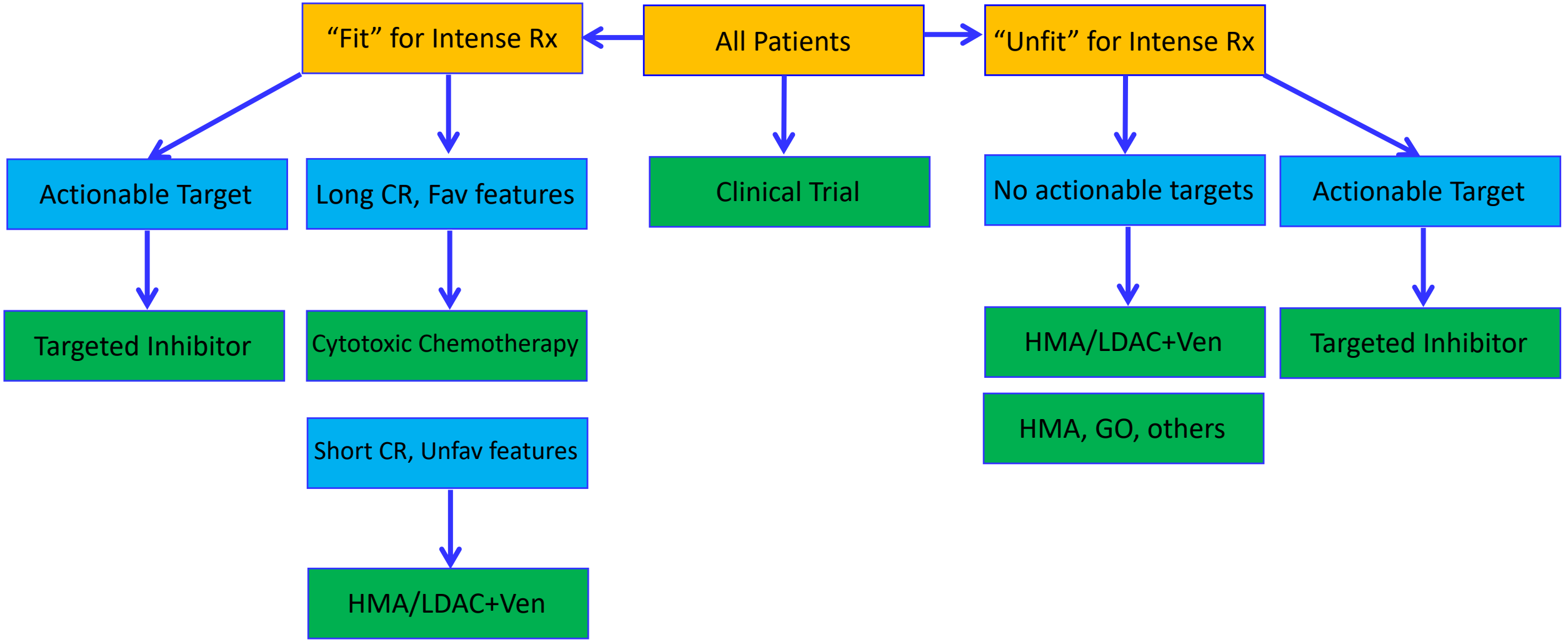
Based on NCCN guidelines, AML v2.2022

First-Line Treatment of Older/UnFit AML in 2022



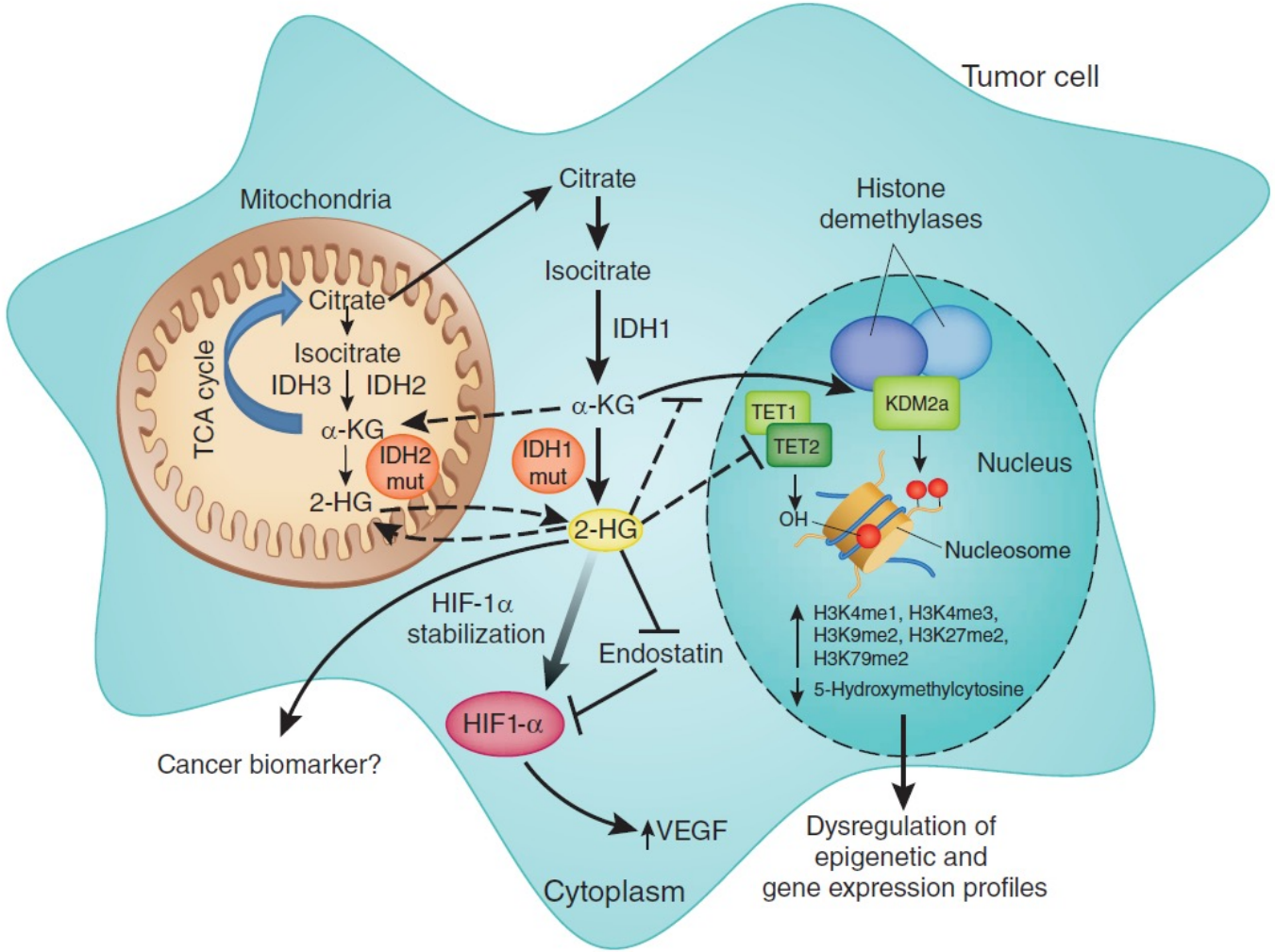
Based on NCCN guidelines, AML v2.2022

Current Options for the Treatment of r/r AML



Recently Approved Treatments for AML

Targeting Mutated IDH



- Mutation frequency = ~15-20%
- Neomorphic activity
- Cooperates with FLT3, RAS, DNMT3A mutations to drive leukemia
- **Ivosidenib** (IDH1i)
- **Enasidenib** (IDH2i)

Prensner et al, Nature Med, 2011.

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)*

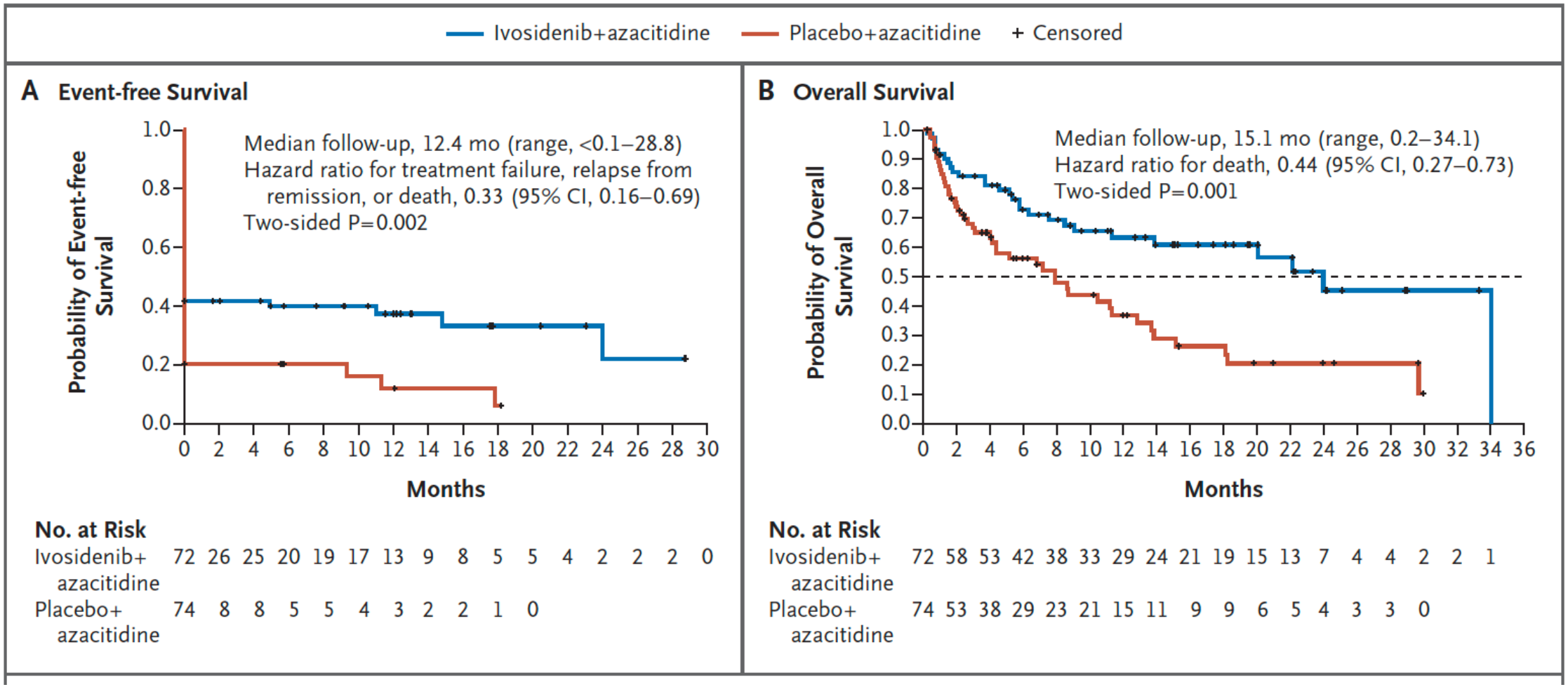
→ **Placebo** PO QD + **Azacitidine** 75 mg/m^2 SC or IV (n = 74)*

*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.

Differentiation Syndrome

Clinical Characteristics of Differentiation Syndrome

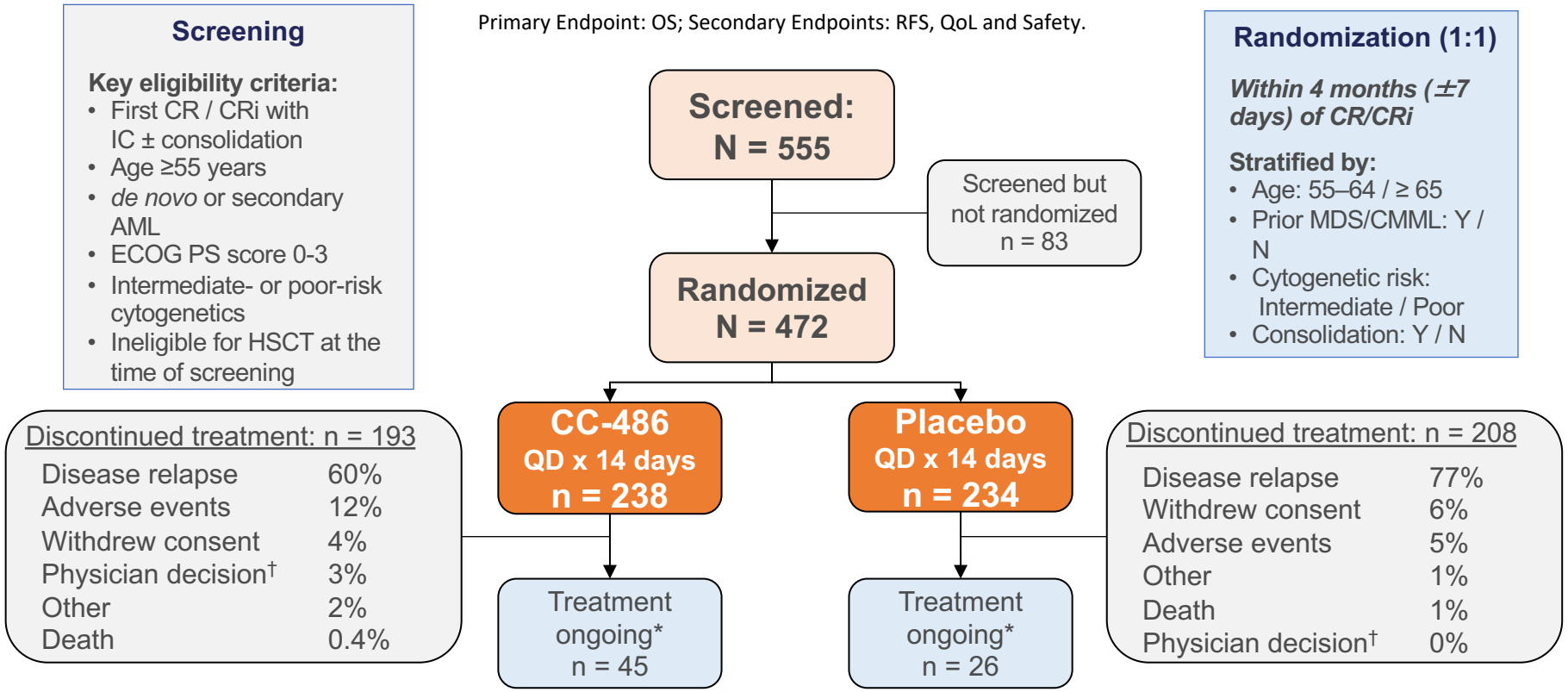
Clinical Features	Inciting Agent: ATRA/ATO	Inciting Agent: IDH inhibitor	Inciting Agent: FLT3 Inhibitor
Timing of Onset	Typically days to weeks	Variable, may occur several weeks into apparently well controlled disease	Variable (Can occur 2 wks to 2mos)
Frequency of DS	*Common, even w prophylaxis*	*Common (5-20%)*	*Uncommon*
Timing of treatment initiation	Prophylactic	Reactive	Reactive
Stop agent?	If life threatening or no response to dex	If life threatening or persistent severe complications despite steroids	If life threatening or persistent severe complications despite steroids
Impact of combinations with other differentiating agents	*Thought to confer increased risk*	*???? (yet to be studied but of concern)*	*???? (yet to be studied but of concern)*

Mainstays of treatment:
Hydroxyurea
Dexamethasone
Supportive care (O2, diuresis, Abx, etc.)

Stein et al, Blood 2017.

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

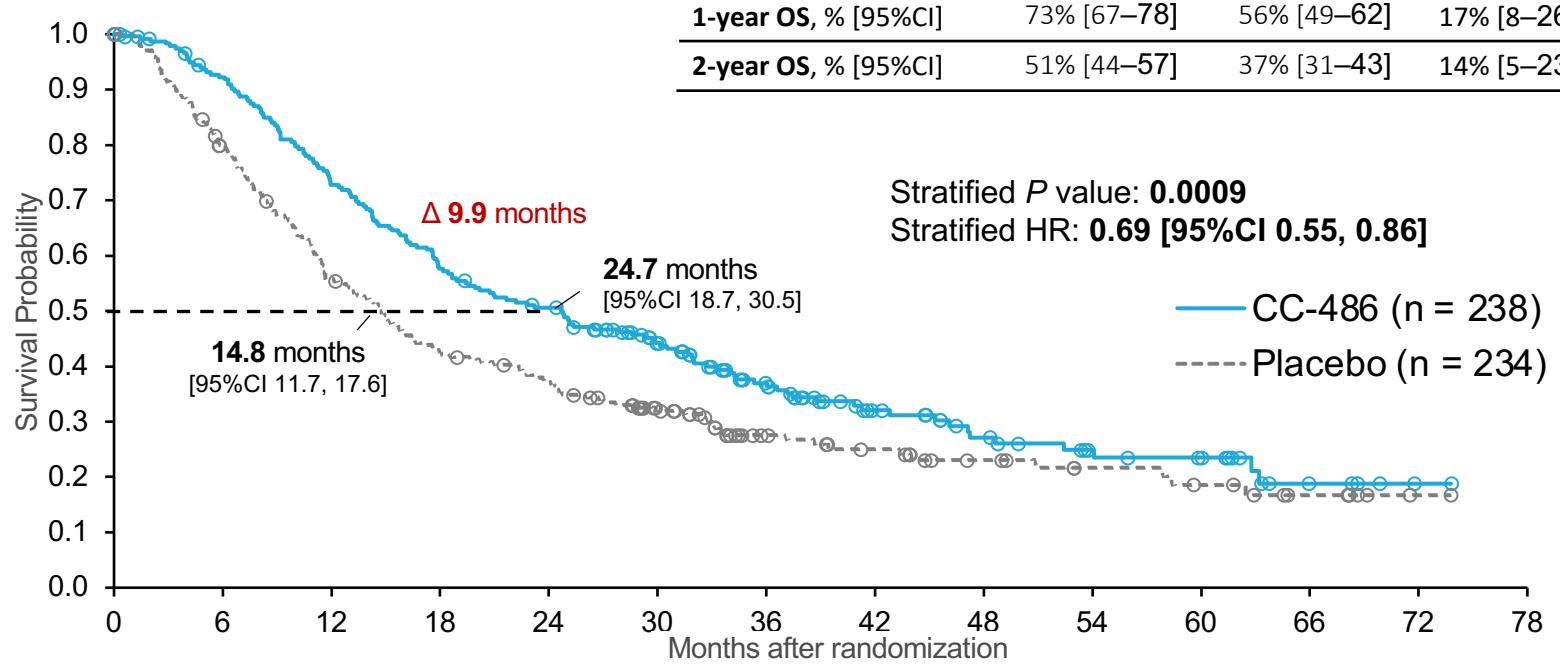
1. Dombret et al. *Blood.* 2015;126(3):291-9.
AE, adverse event; AZA, azacitidine; GI, gastrointestinal.

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]



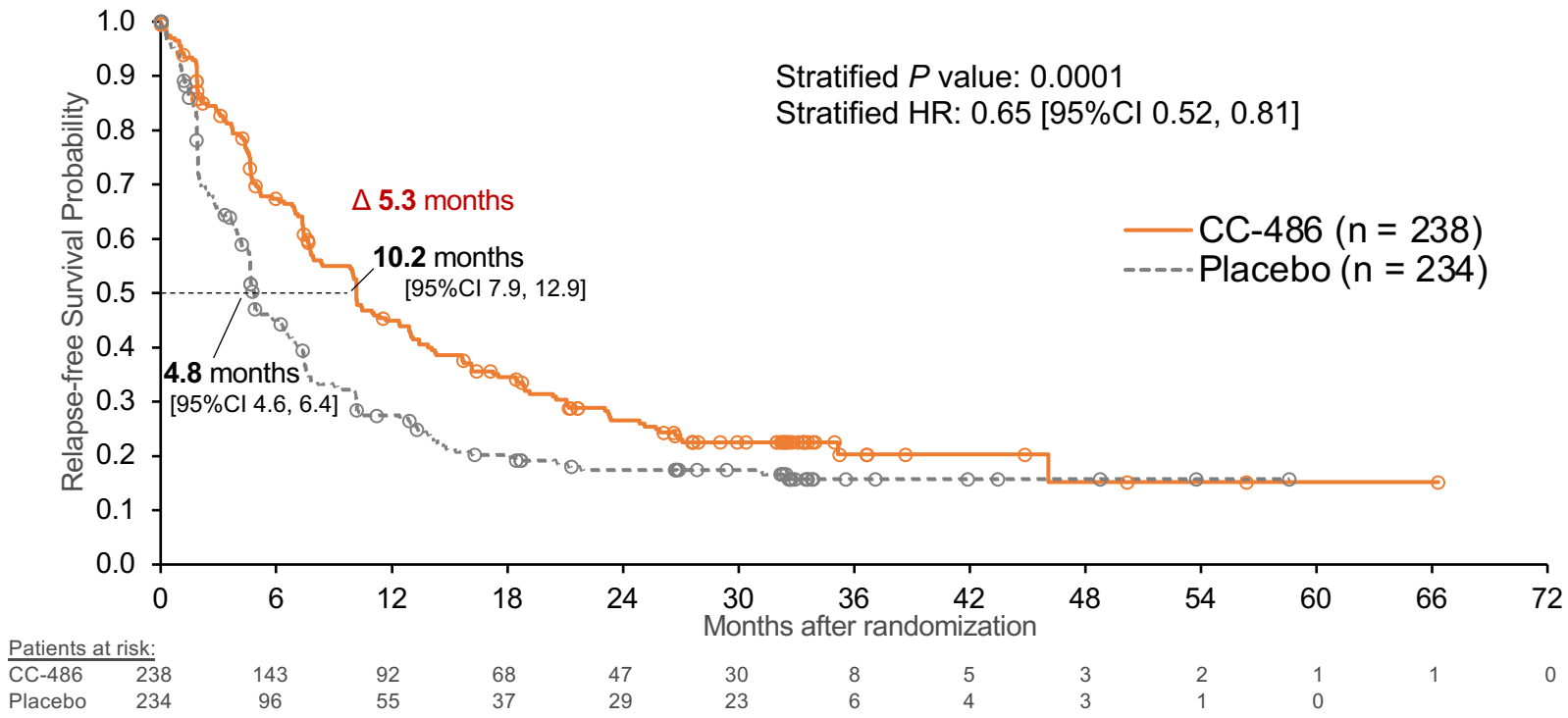
Patients at risk:

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.

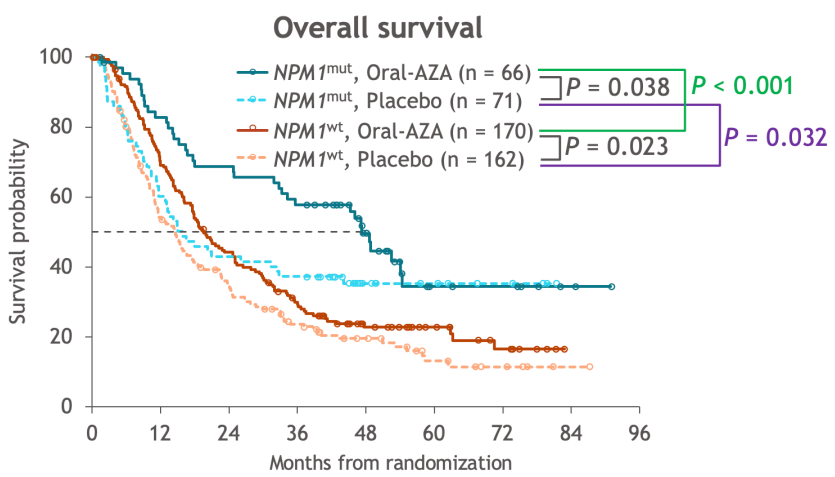
Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

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).

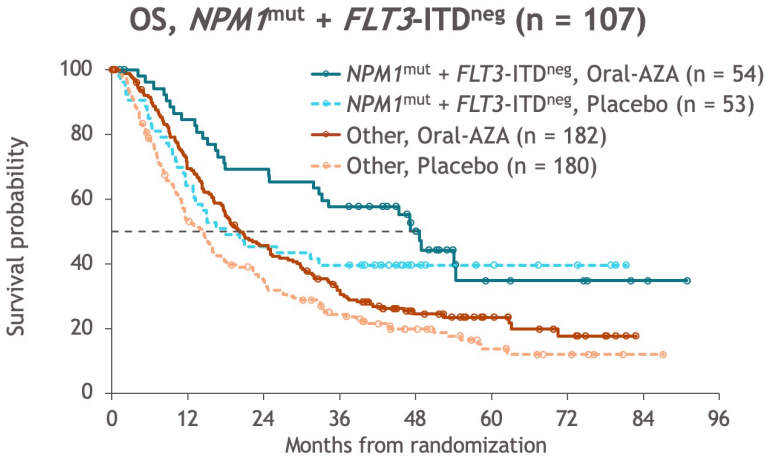
Presence of *FLT3*-ITD at Dx had a negative prognostic influence, as suggested by differences in OS results in the PBO arm

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)



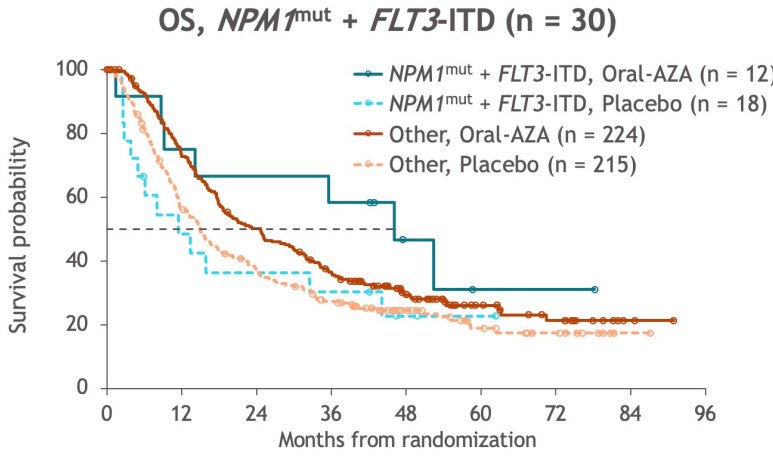
Median OS, months

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

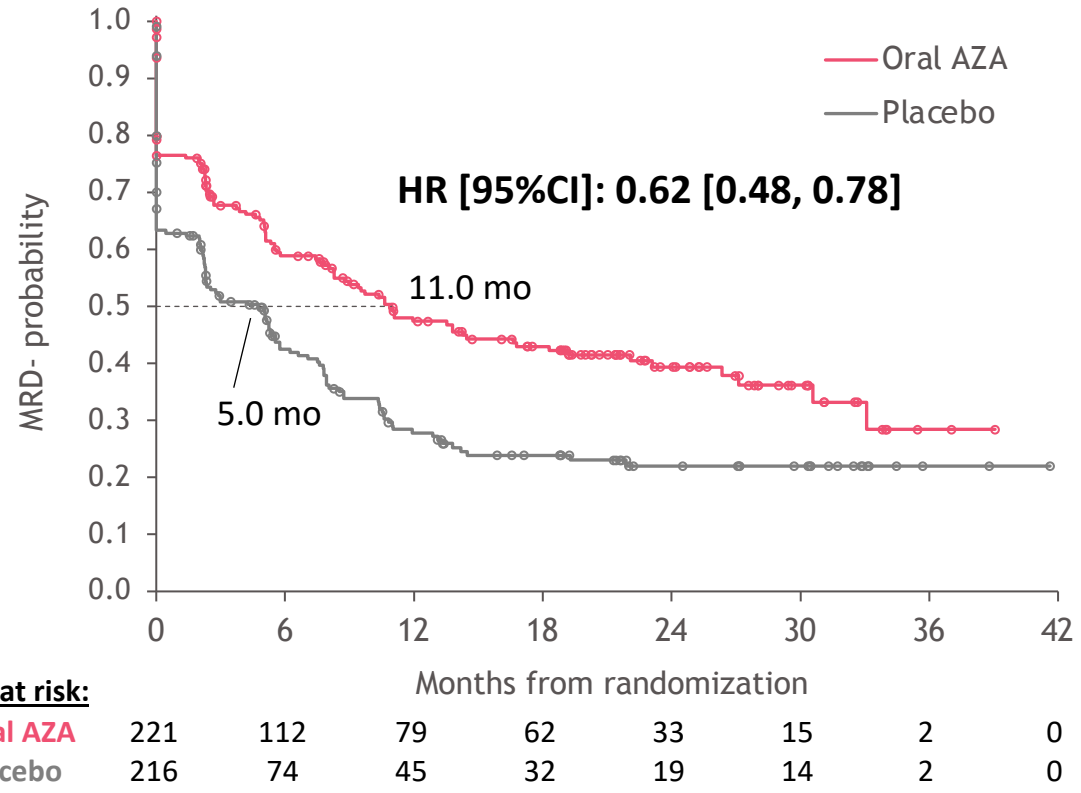
Döhner et al, EHA 2021. Abstr S131.

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



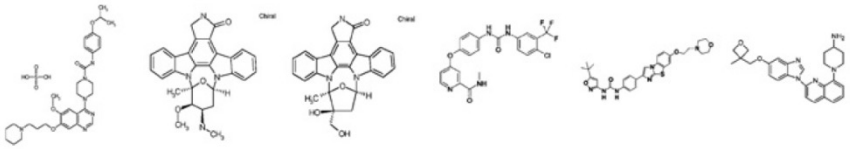
[a]Time from MRD assessment at screening.

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

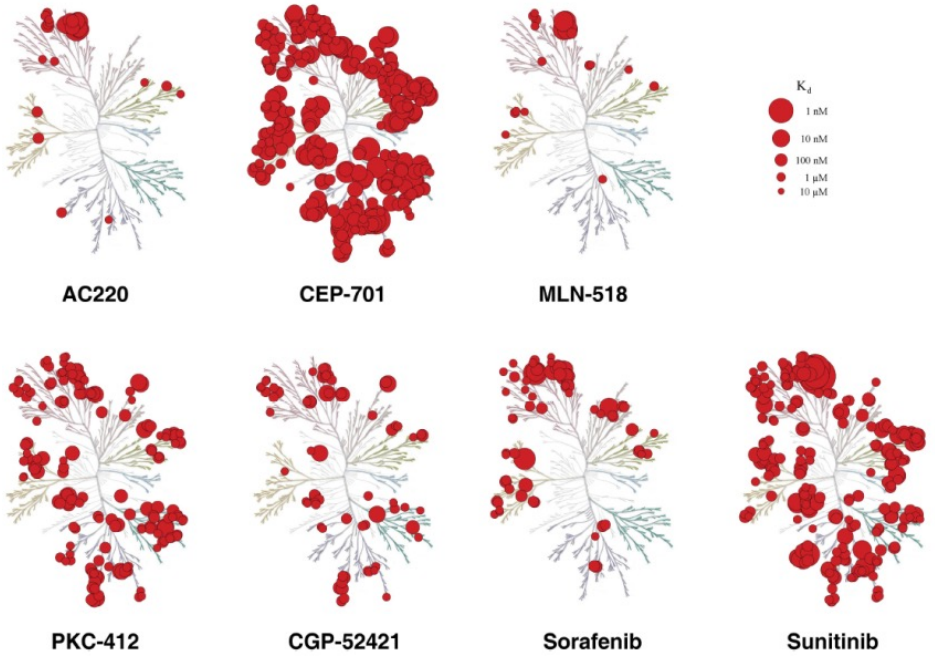
Emerging Treatments for AML

FLT3 Inhibitors Approved or In Development for AML

FLT3 inhibitors	Tandutinib	Lestaurtinib	Midostaurin	Sorafenib	Quizartinib	Crenolanib
FLT3 inhibition (IC50, nM)	220	3	<10	58	1.1	0.15
Structure						

Gilteritinib – FLT3/AXL inhibitor active against FLT3-ITD and FLT3-D835 mutations
Crenolanib – active against FLT3-ITD and FLT3-TKD mutations

Midostaurin and Gilteritinib are FDA approved.



RATIFY (Mido vs placebo plus chemo for FLT3-mutated AML) showed improved OS vs PBO
QUANTUM-FIRST (Quiz vs placebo plus chemo for FLT3-ITD+ AML) showed improved OS vs PBO
ADMIRAL (Gilteritinib vs SOC for R/R FLT3-mutated AML) showed improved OS vs SOC
QUANTUM-R (Quizartinib vs SOC for R/R FLT3-ITD+ AML) showed improved OS vs SOC
SORMAIN (Sorafenib vs Placebo for FLT3-ITD+ AML after allo-HCT) showed improved OS

Fathi AT, Blood, 2015.
Smith et al, Leukemia, 2015.
Kiyoi et al. Nag J Med Sci, 2015.
Zarrinkar et al. Blood, 2009.
Buchert et al, ASH 2018 Abstract #661.
Erba et al, EHA 2022.

QuANTUM-First – Quizartinib for FLT3-ITD Mutated AML

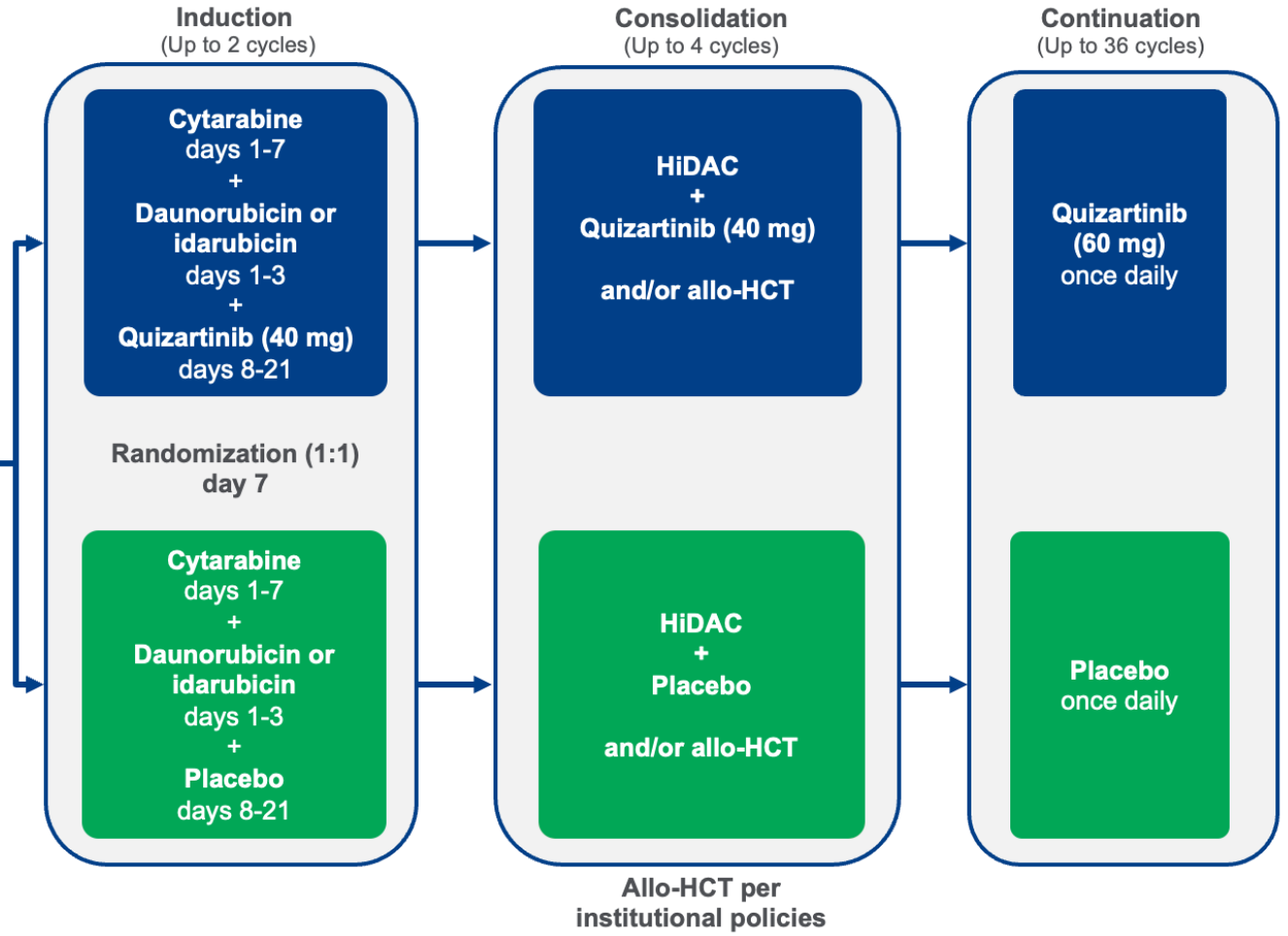
Enrollment dates: September 2016 to August 2019
Data cutoff: August 13, 2021

Stratification factors
- **Region**: NA, EU, and Asia/other regions
- **Patient age**: <60 years, ≥60 years
- **WBC**[a]: <40×10⁹/L, ≥40×10⁹/L

- Newly diagnosed *FLT3*-ITD+ AML
- 18-75 years of age
- ≥3% *FLT3*-ITD allelic frequency
- Patients begin 7+3 chemotherapy during screening

Selected endpoints
- **Primary endpoint**: OS
- **Secondary endpoints**: EFS, CR/CRc, Safety
- **Exploratory endpoints**: RFS, DoCR

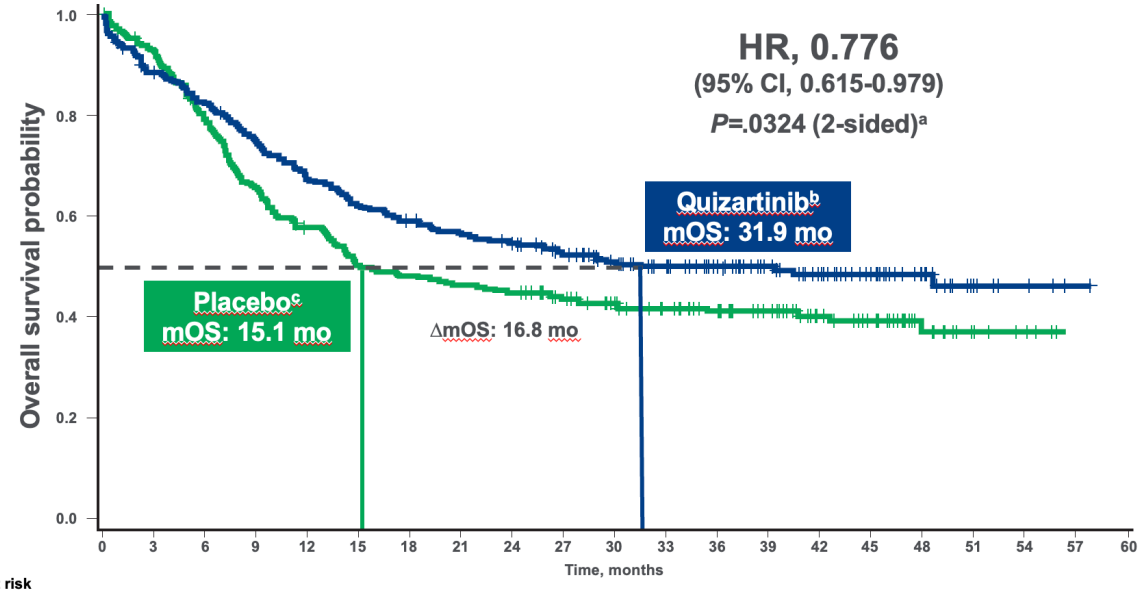
A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR and CRc.



AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; DoCR, duration of complete remission; EFS, event-free survival; EU, Europe; HiDAC, high-dose cytarabine; NA, North America, OS, overall survival; RFS, relapse-free survival; WBC, white blood cell.
[a] WBC count was measured at the time of AML diagnosis.

Erba et al, EHA 2022 Abstract # S100.

QuANTUM-First – Efficacy



HR, hazard ratio; mOS, median overall survival.
[a] *P* value was calculated using a stratified log-rank test. [b] Median follow-up time for quizartinib arm, 39.2 months. [c] Median follow-up time for placebo arm, 39.2 months.

Parameter	Quizartinib (N=268)	Placebo (N=271)
CRc		
%	71.6	64.9
95% CI	(65.8-77.0)	(58.9-70.6)
CR		
%	54.9	55.4
95% CI	(48.7-60.9)	(49.2-61.4)
CRi		
%	16.8	9.6
95% CI	(12.5-21.8)	(6.4-13.7)
Duration of CR		
Median, months	38.6	12.4
95% CI	(21.9-NE)	(8.8-22.7)

CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; IRC, independent review committee; NE, not evaluable.
[a] By end of induction by IRC.

Summary of death		
Deaths within 30 days of study drug initiation	5.7	3.4
Deaths within 60 days of study drug initiation	7.5	4.9

Erba et al, EHA 2022 Abstract # S100.

QuANTUM-First – Safety

TEAEs in ≥20% of Patients

TEAEs, %	Quizartinib (N=265)[a]		Placebo (N=268)[a]	
Hematologic adverse events	All Grades	Grade ≥3	All Grades	Grade ≥3
Febrile neutropenia	44.2	43.4	42.2	41.0
Neutropenia	20.4	18.1	10.1	8.6
Non-hematologic adverse events	All Grades	Grade ≥3	All Grades	Grade ≥3
Pyrexia	42.3	4.5	40.7	4.9
Diarrhea	37.0	3.8	35.1	3.7
Hypokalemia	35.1	18.9	35.8	16.4
Nausea	34.0	1.5	31.3	1.9
Headache	27.5	0	19.8	0.7
Rash	26.0	3.0	24.6	1.1
Vomiting	24.5	0	19.8	1.5
Stomatitis	21.5	4.5	20.9	3.0
Constipation	21.1	0.4	25.7	0

QT Prolongation and Cardiac Events

Parameter	Quizartinib (N=265)	Placebo (N=268)
QTcF interval based on central ECG data (ms), %		
New > 450 ms	34.3	17.9
New > 480 ms	7.5	2.2
New > 500 ms	2.3	0.7
QTcF increase from baseline > 30 ms	55.1	32.5
QTcF increase from baseline > 60 ms	10.1	4.9
Select cardiac events by TEAE (PT), %		
ECG QT prolonged	13.6	4.1
Cardiac arrest/ventricular fibrillation	0.8	0
Ventricular tachycardia	0.4	0.4

- Two patients (0.8%) treated with quizartinib had cardiac arrest (grade 4 [n=1], grade 5 [n=1]), with recorded ventricular fibrillation in the setting of severe hypokalemia
- One patient (0.4%) died in their sleep (PT 'death') in the quizartinib arm
- Two patients (0.8%) discontinued quizartinib due to QT prolongation

Erba et al, EHA 2022 Abstract # S100.

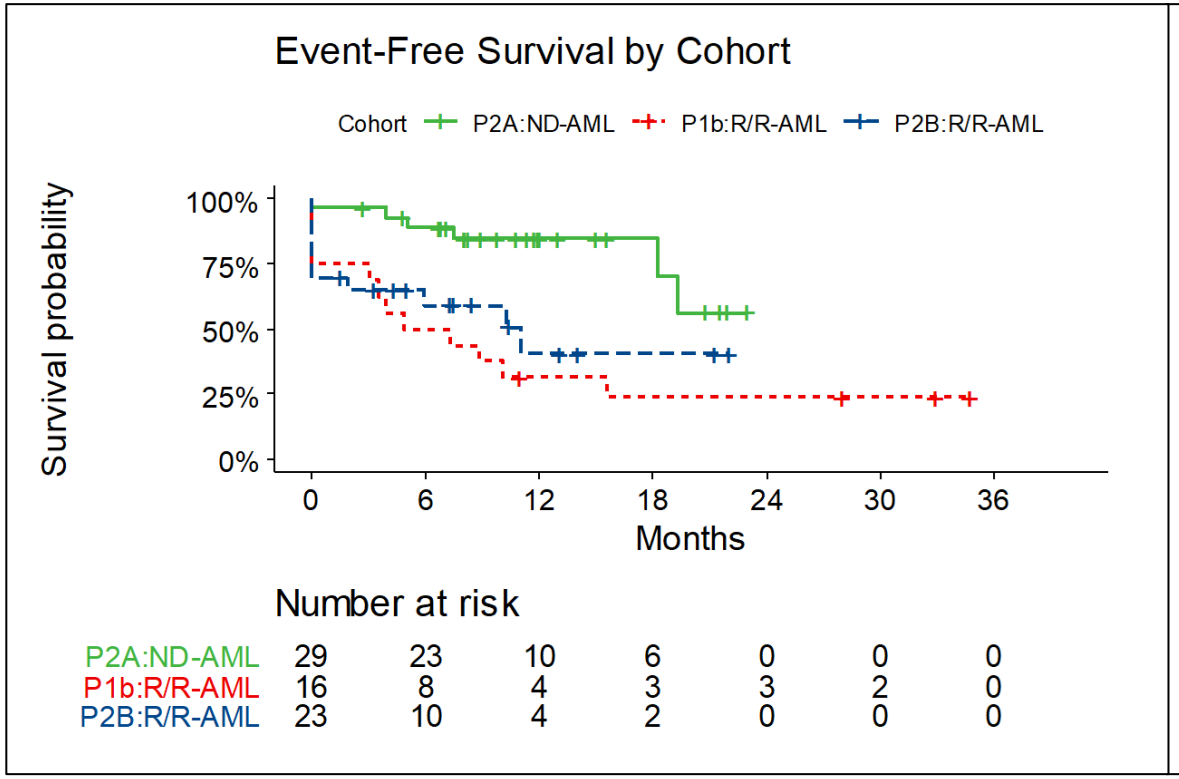
FLAG-Ida plus Venetoclax in ND and r/r AML

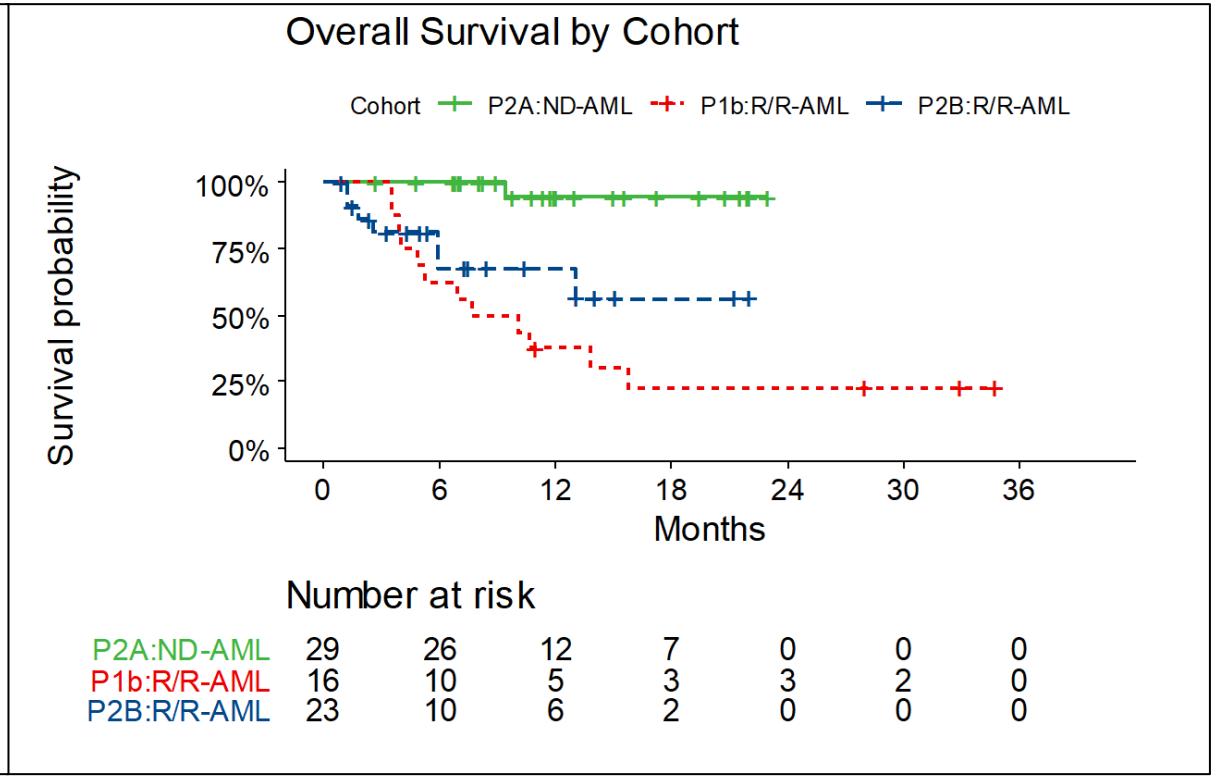
Parameter	All (N=68)	Phase 2A ND-AML (N=29)	R/R-AML (N=39)	Phase Ib R/R-AML (N=16)	Phase 2B R/R-AML (N=23)
Overall Response	56 (82%)	28 (97%)	28 (72%)	12 (75%)	16 (70%)
Composite CR	52 (76%)	26 (90%)	26 (67%)	12 (75%)	14 (61%)
CR	37	20	17	6	11
CRh	10	5	5	2	3
CRi	5	1	4	4	-
MRD negative (FC)	43 (83%)	25 (96%)	18 (69%)	7 (58%)	11 (79%)
MLFS	4	2	2	-	2
No response	12	1	11	4	7

Composite CR (CRc): Complete response + Complete response with partial hematologic recovery (CRh: ANC ≥ 500 and platelet count ≥ 50,000) + Complete response with incomplete hematologic recovery (CRi: ANC ≥ 1000 or platelet count ≥ 100,000); Morphologic Leukemia Free State (MLFS: Bone marrow blasts < 5% no hematologic recovery required); FC: Flow cytometry

DiNardo et al, JCO 2021 and ASH 2020.

FLAG-Ida-Ven: EFS and OS

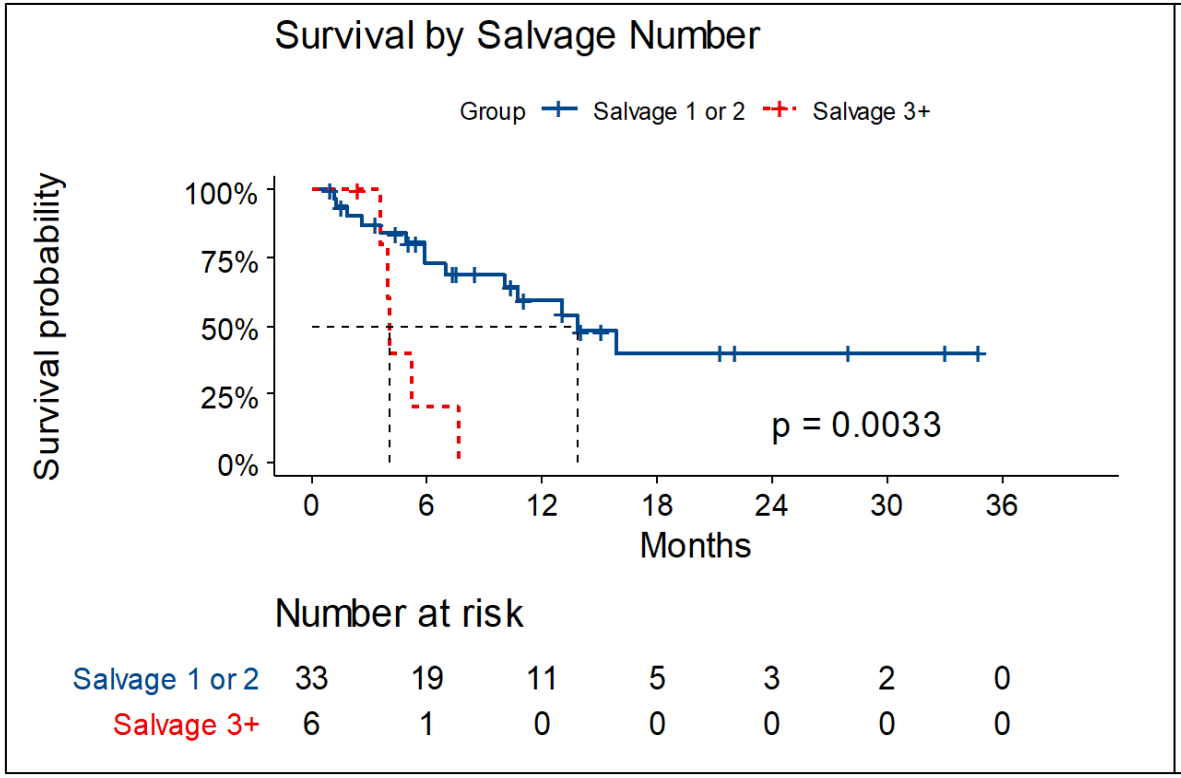


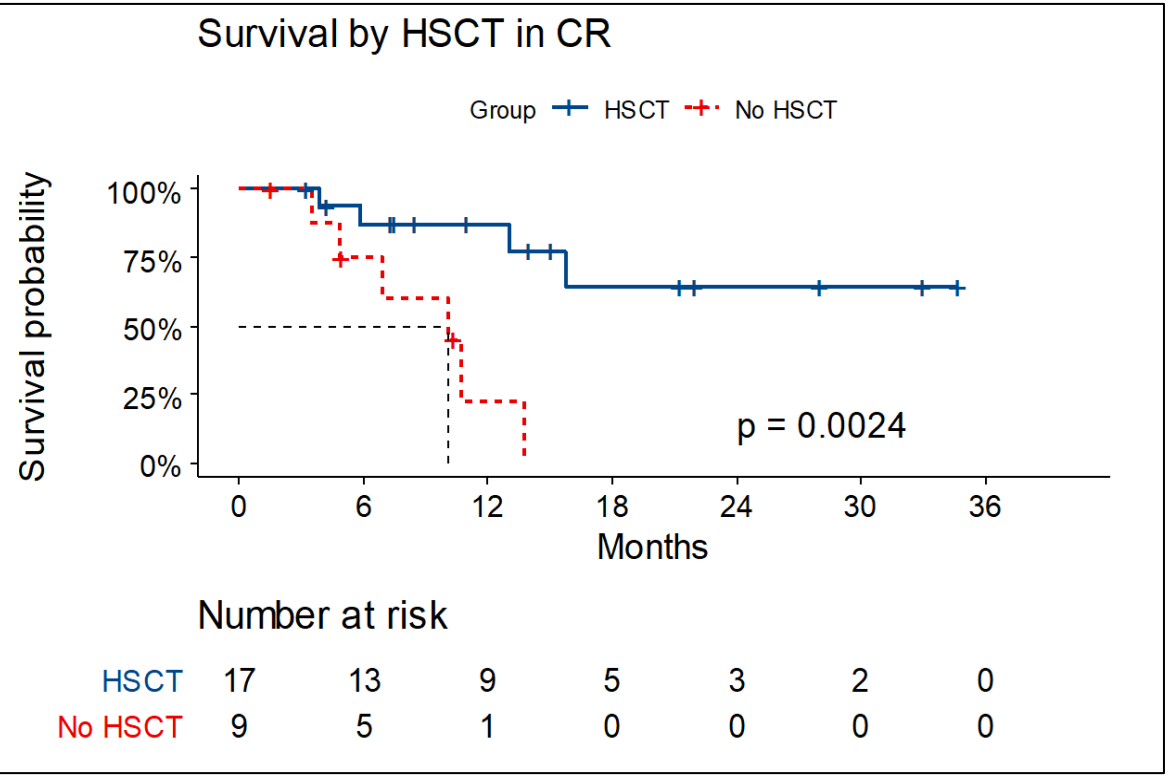


12mo OS 68% P2B

DiNardo et al, JCO 2021 and ASH 2020.

FLAG-Ida-Ven: OS by Salvage and After Allo-HCT for r/r AML

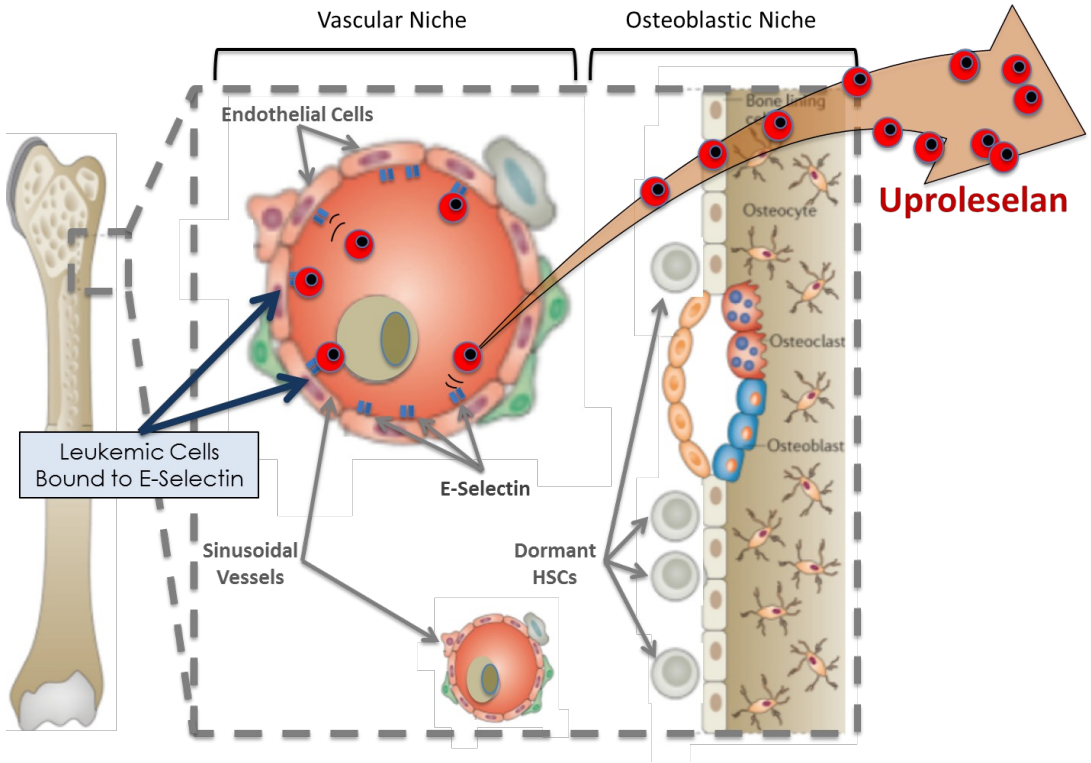




46% bridged to allo-HCT
12mo OS 87%

DiNardo et al, JCO 2021 and ASH 2020.

E-Selectin Inhibition with Uproleselan (GMI-1271) in AML



E-selectin –

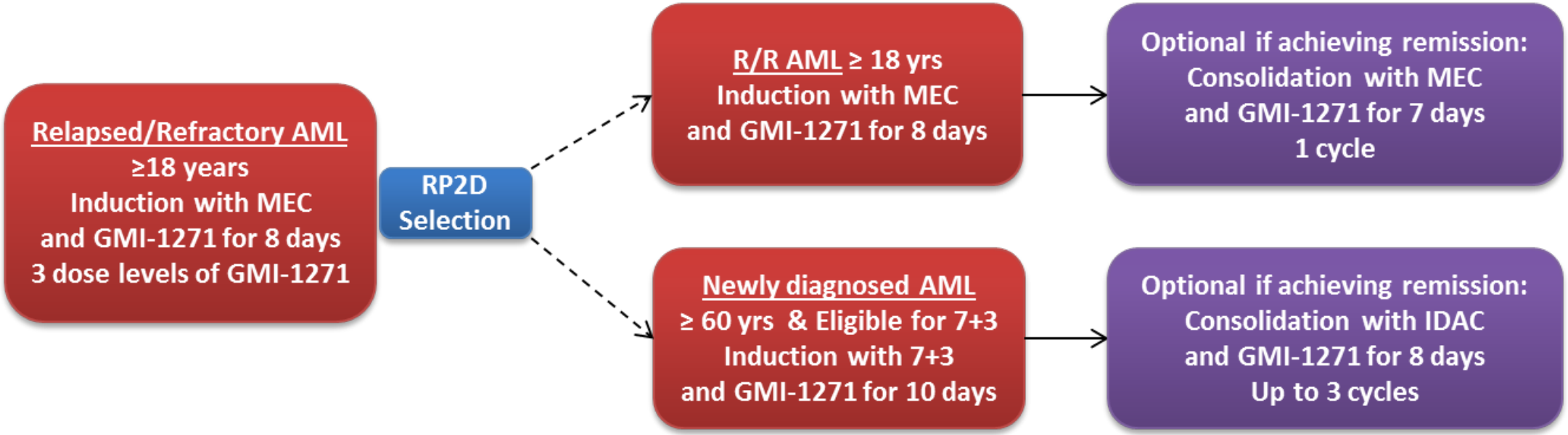
- An Adhesion molecule constitutively expressed on endothelial cells in the bone marrow microvasculature
- Binds to the E-selectin ligands (Sialyl $Le^{a/x}$) on AML cells
- Promotes environment-mediated drug resistance (EMDR) of leukemic cell

Uproleselan, an E-selectin antagonist –

- Inhibits activation of cancer survival pathways (e.g. NF-KB), disrupting EMDR within bone marrow
- Prolongs survival over chemotherapy alone in animal models
- Protects normal HSCs by enhancing quiescence and ability for self-renewal
- Reduces chemotherapy-associated mucositis

Barbier, et al, Nature Communications 2020.

Phase 1/2 Uproleselan Study Schema



DeAngelo et al, Blood 2022.

Phase 1/2 Uproleselan Study: Responses

Outcomes, n (%)	Rel/Ref RP2D N=54	Newly Diagnosed N=25
CR/CRi	22 (41)	18 (72)
CR	19 (35)	13 (52)
ORR (CR/CRi/MLFS/PR)	27 (50)	20 (80)
Mortality, All-Cause		
30 days	1 (2)	2 (8)
60 days	5 (9)	2 (12)
Outcomes by Subgroup (CR/CRi Rate and %)		
Primary Refractory	5/17 (29)	
Relapsed (all)	18/37 (49)	
Duration of prior remission <6 mos	6/19 (32)	
Duration of prior remission ≥ 24mos	6/7 (86)	

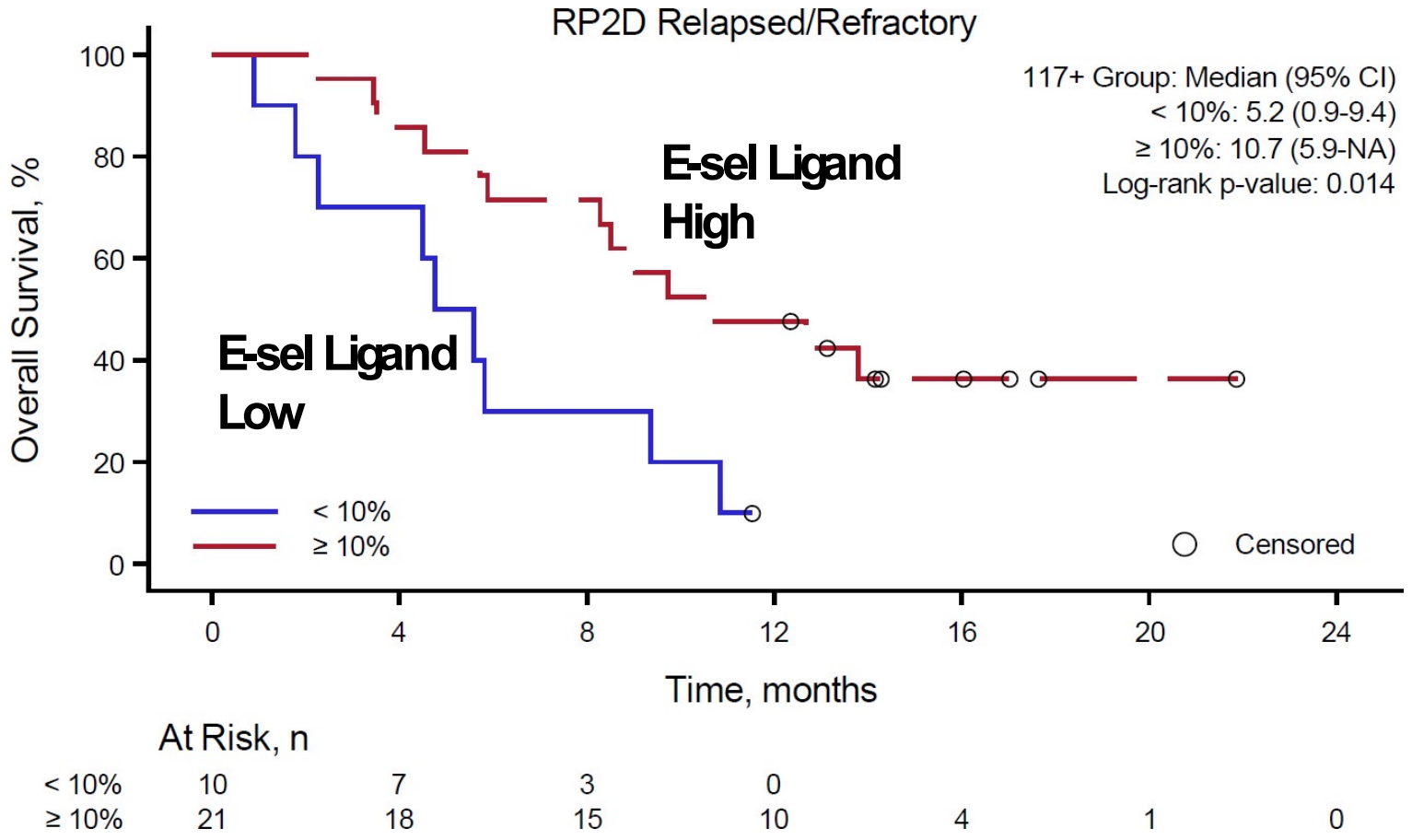
RR RP2D Cohort:
MRD Evaluable n=13
Negative 9 (69%)

G3 mucositis with Uproleselan+ MEC in rel/ref cohort ~2 %

DeAngelo et al, Blood 2022.

Phase 1/2 Uproleselan Study: OS Based on E-Selectin Ligand Expression

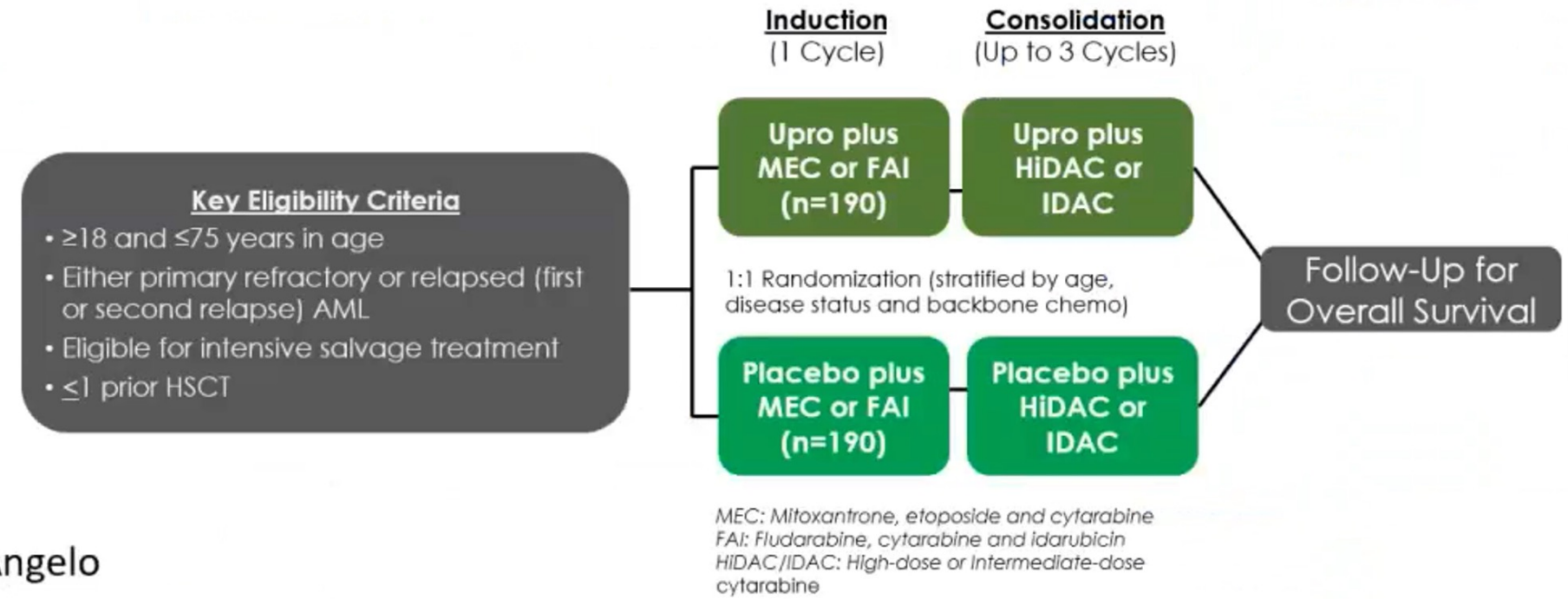
- Median OS 8.8mo
- 12mo OS:
  - All 35%
  - MRD-ve 73%



DeAngelo et al, ASH 2018.
DeAngelo et al, Blood 2022.

Phase 3 Study of Uproleselan in r/r AML

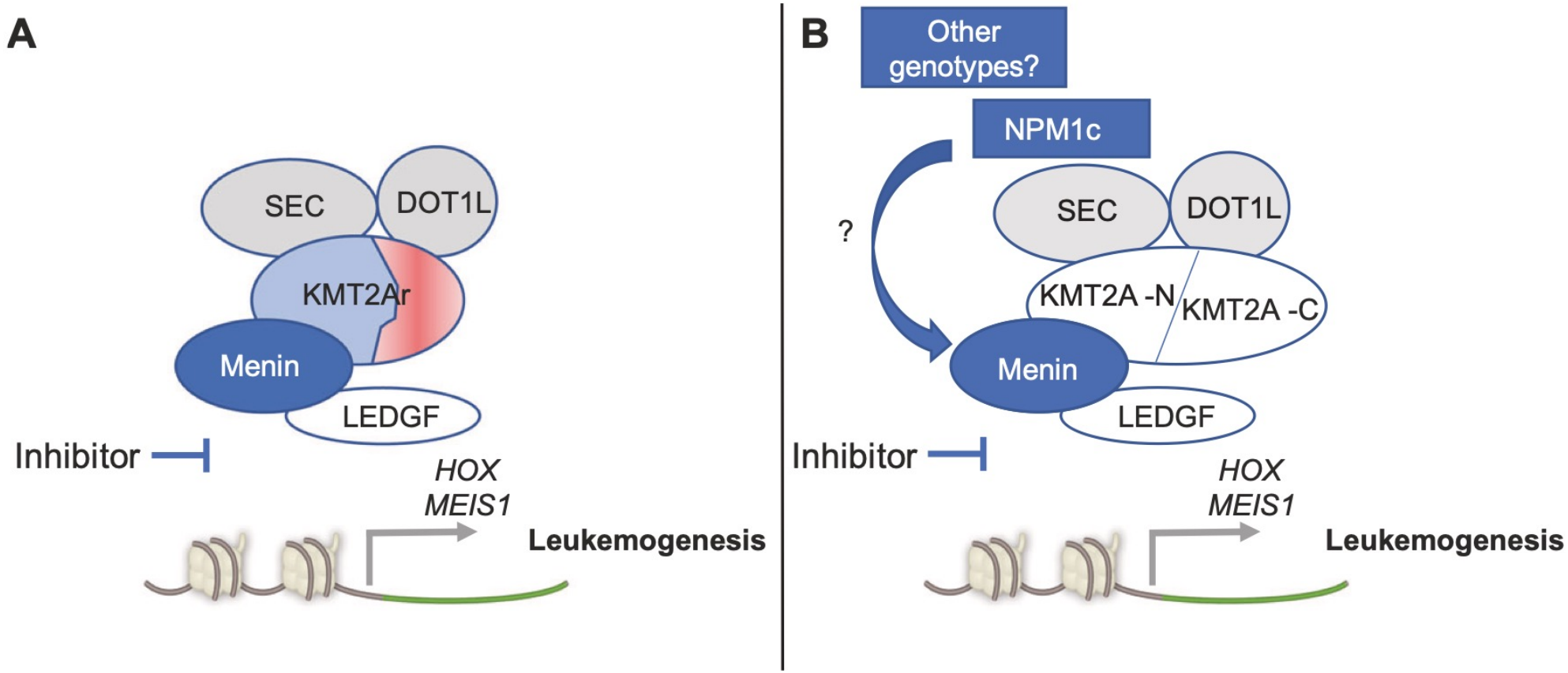
NCT#03616470



PI: DeAngelo

Primary Endpoint: OS

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.

Summary and Future Directions

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

- Questions?

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