Acute Myeloid Leukemia

New Treatment paradigm

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Objectives

- De Novo Setting
- Maintenance therapy
- Post Allo-HSCT
- The Emerging horizon

PARADIGM SHIFT

Who should not receive intensive chemotherapy

Age > 75
Poor hepatic , renal Fx
Cardiac & pulmonary

Who would benefit from intensive chemotherapy

Even a ‘fit’ patient (of any age) with adverse risk might not be “appropriate” for intensive chemotherapy

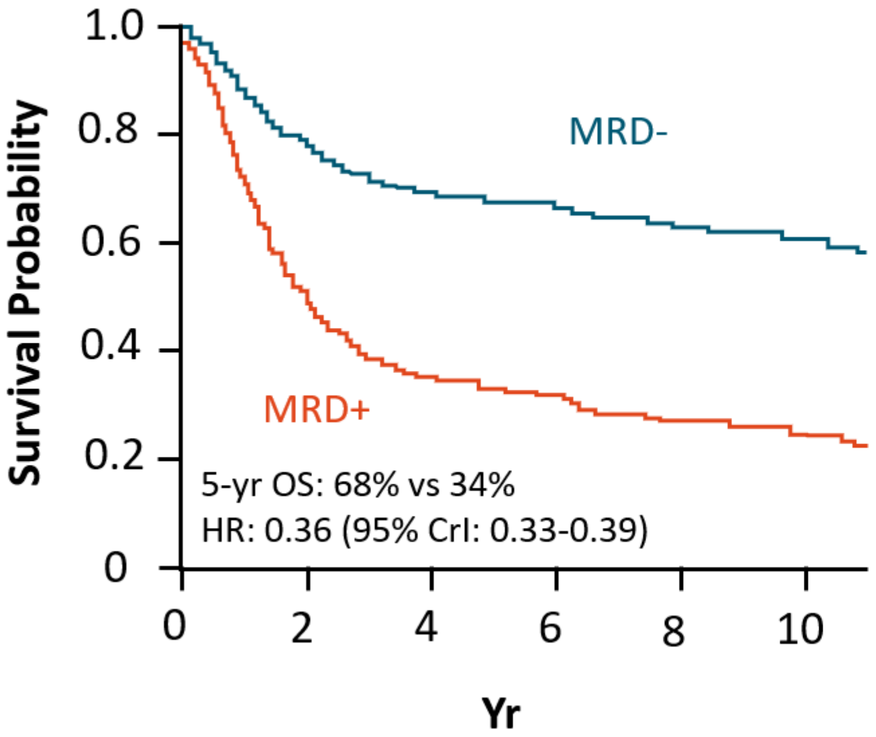
AML Risk Categorization ELN 2022

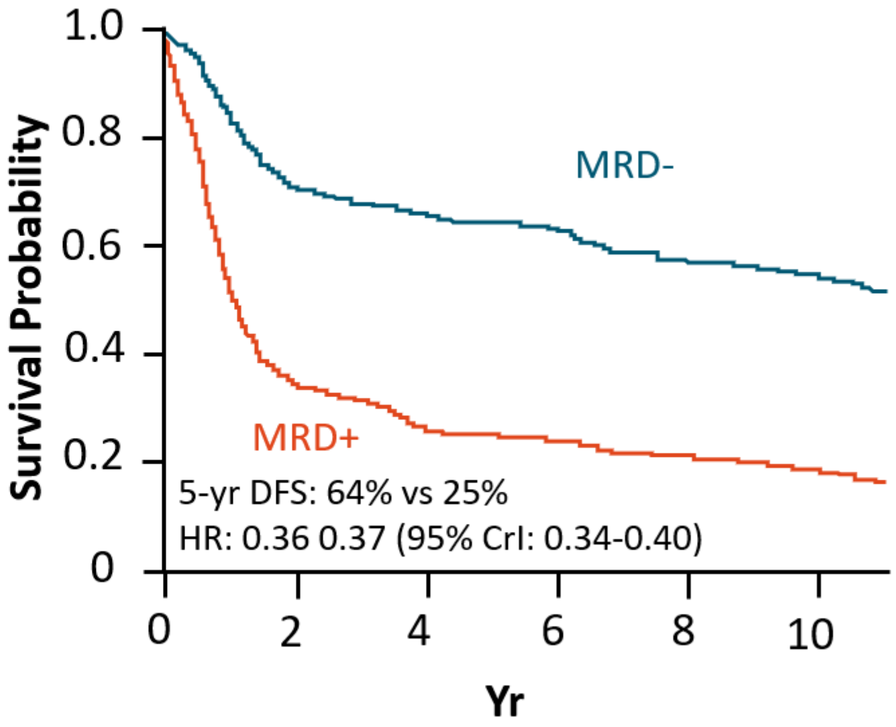
- ELN AML risk classification is based on data from intensively treated patients
- FLT3-ITD allelic ratio is no longer relevant for risk stratification

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

MRD and Survival in AML:

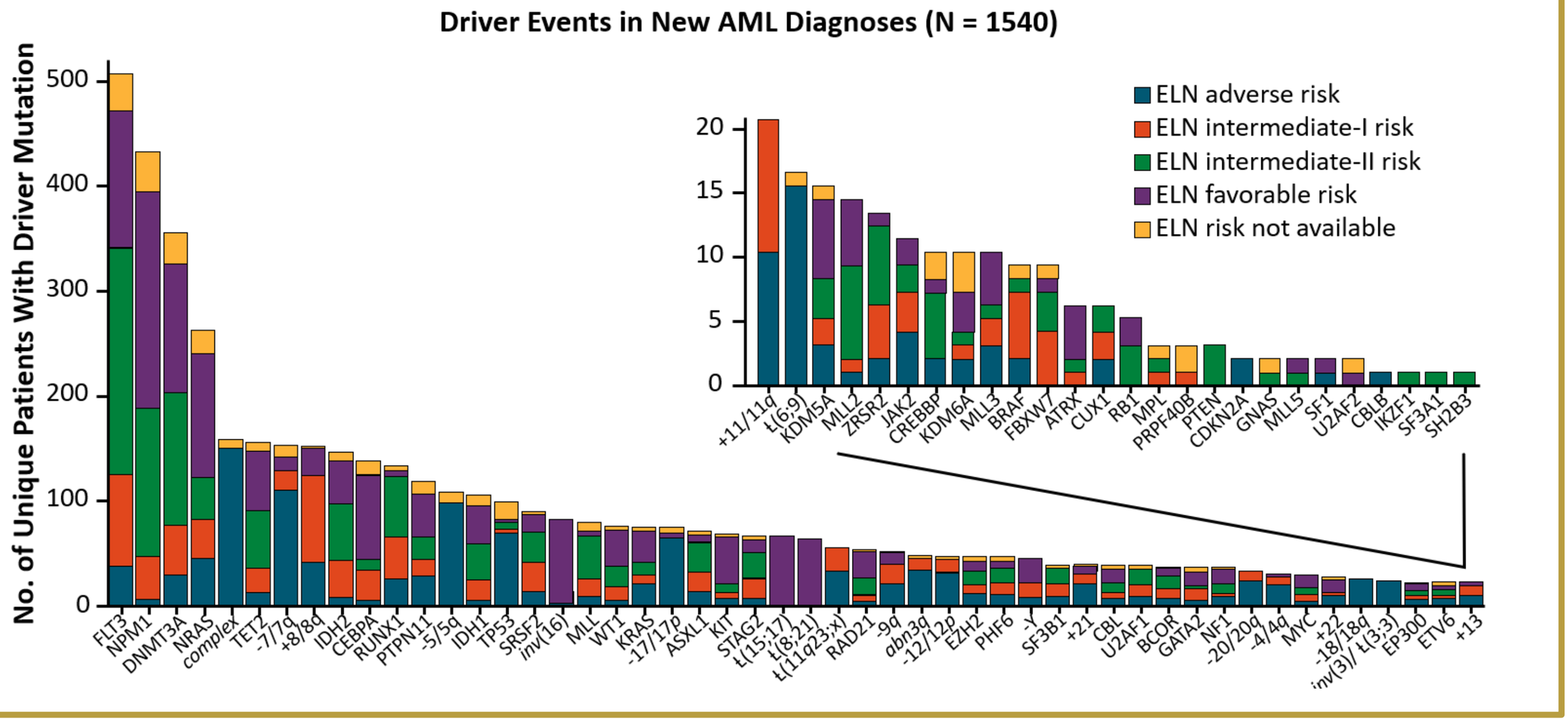
Meta-analysis of 81 Publications (N = 11,151)





Short. JAMA Oncol. 2020;6:1890.

AML Mutational Landscape



Papaemmanuil. NEJM. 2016;374:2209.

Recommended Timelines for Initial Genetic Workup

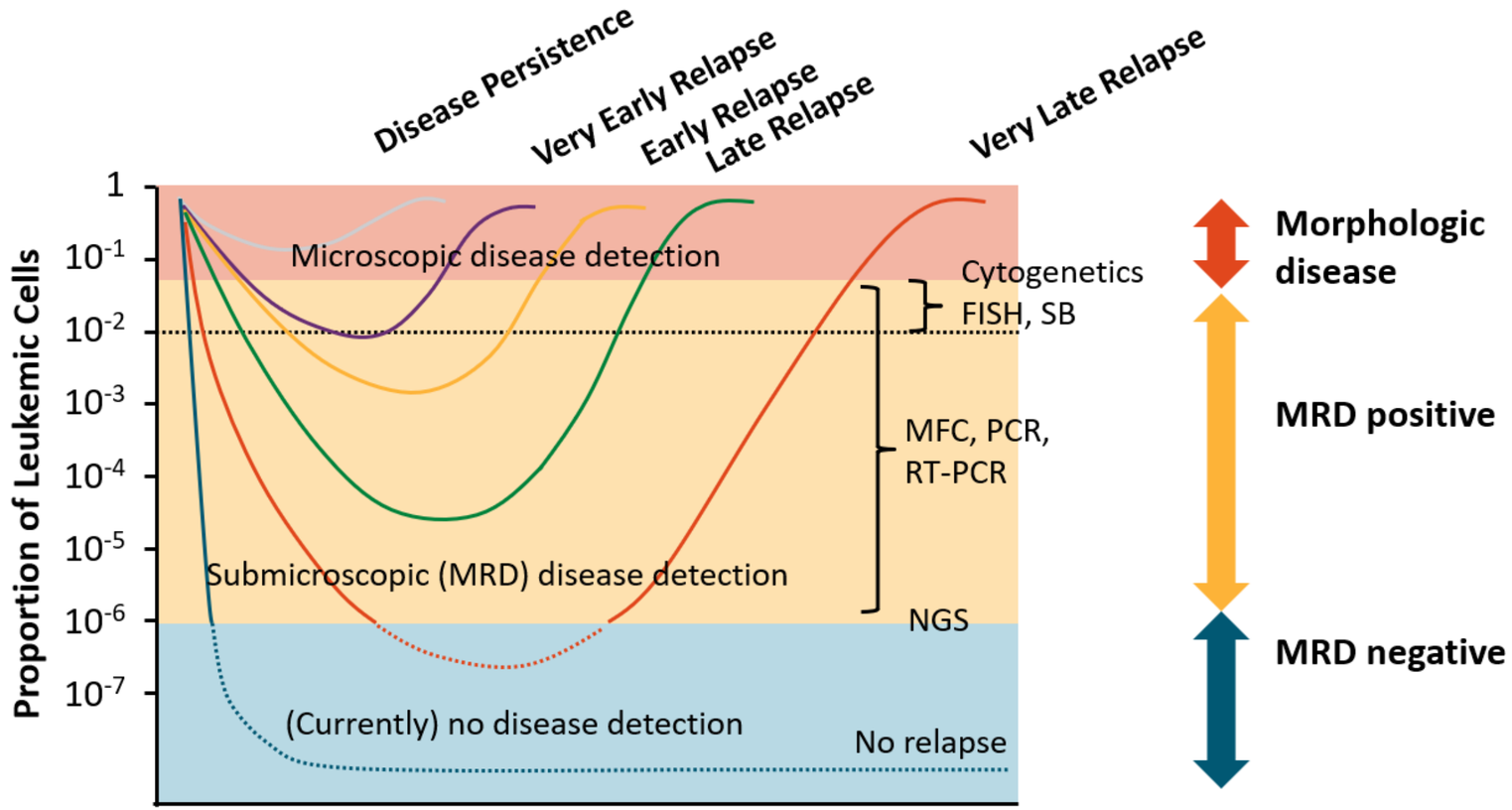
Assessment	Timing
Cytogenetics*	Results preferably obtained within 5-7 days
Screening for gene mutations including (to establish diagnosis) • *FLT3*,† *IDH1*, *IDH2* (actionable therapeutic targets) • *NPM1* • *CEBPA*,‡ *DDX41*, *TP53; ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*	Within 3-5 days Within first treatment cycle
Screening for gene rearrangements§ *PML*::*RARA*, *CBFB*::*MYH11*, *RUNX1*::*RUNX1T1*, *KMT2A*::R, *BCR*::*ABL1*, other fusion genes (if available)	Within 3-5 days
Additional genes recommended to test at diagnosis *ANKRD26*, *BCORL1*, *BRAF*, *CBL*, *CSF3R*, *DNMT3A*, *ETV6*, *GATA2*, *JAK2*, *KIT*, *KRAS*, *NRAS*, *NF1*, *PHF6*, *PPM1D*, *PTPN11*, *RAD21*, *SETBP1*, *TET2*, *WT1*	Information can be used to monitor disease by NGS-based MRD analyses (except mutations consistent with premalignant clonal hematopoiesis)

Döhner. Blood. 2022;140:1345.

Measurable Residual Disease

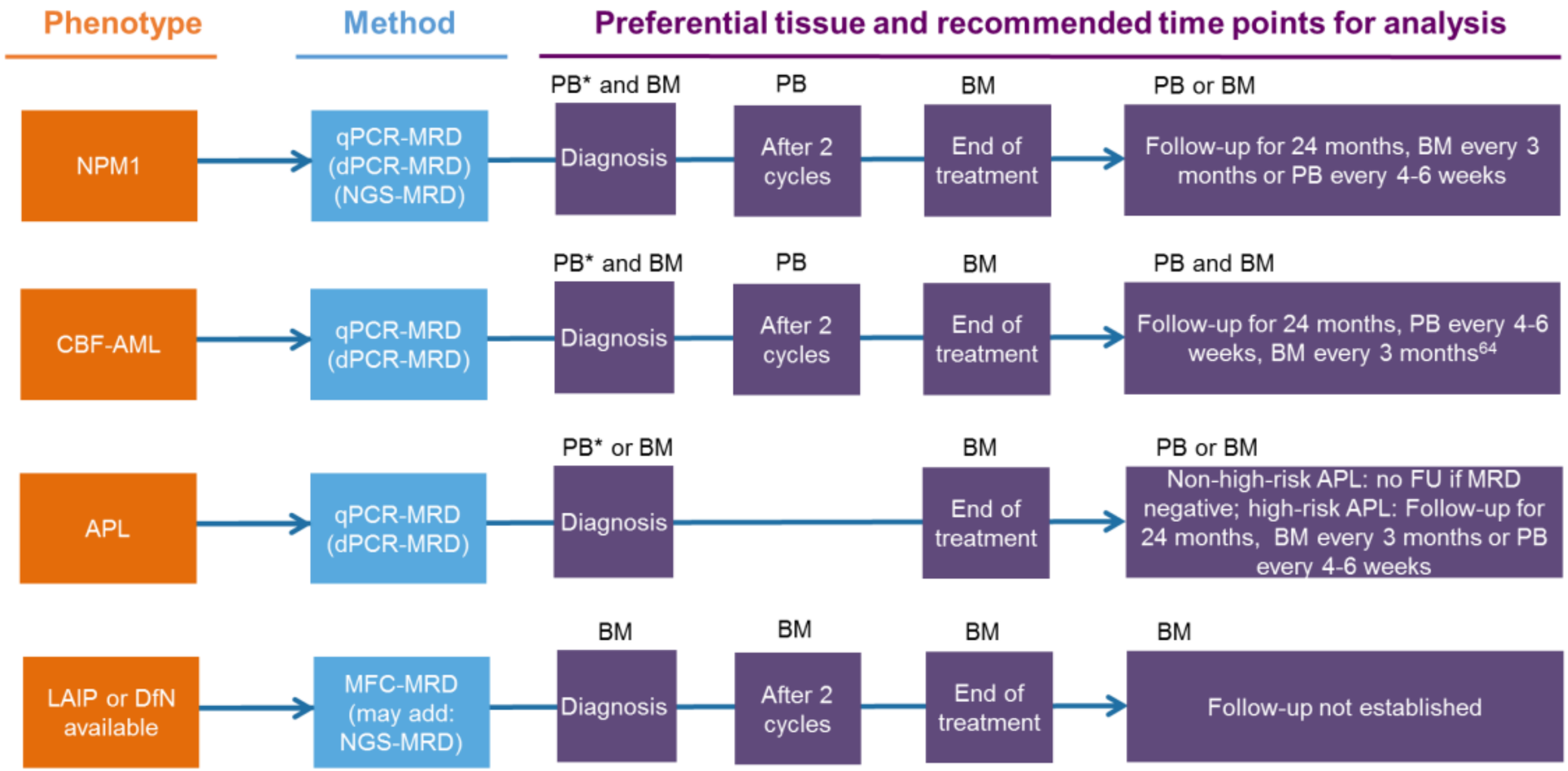
Definition

Residual leukemia not detected by morphology (<5% blasts)



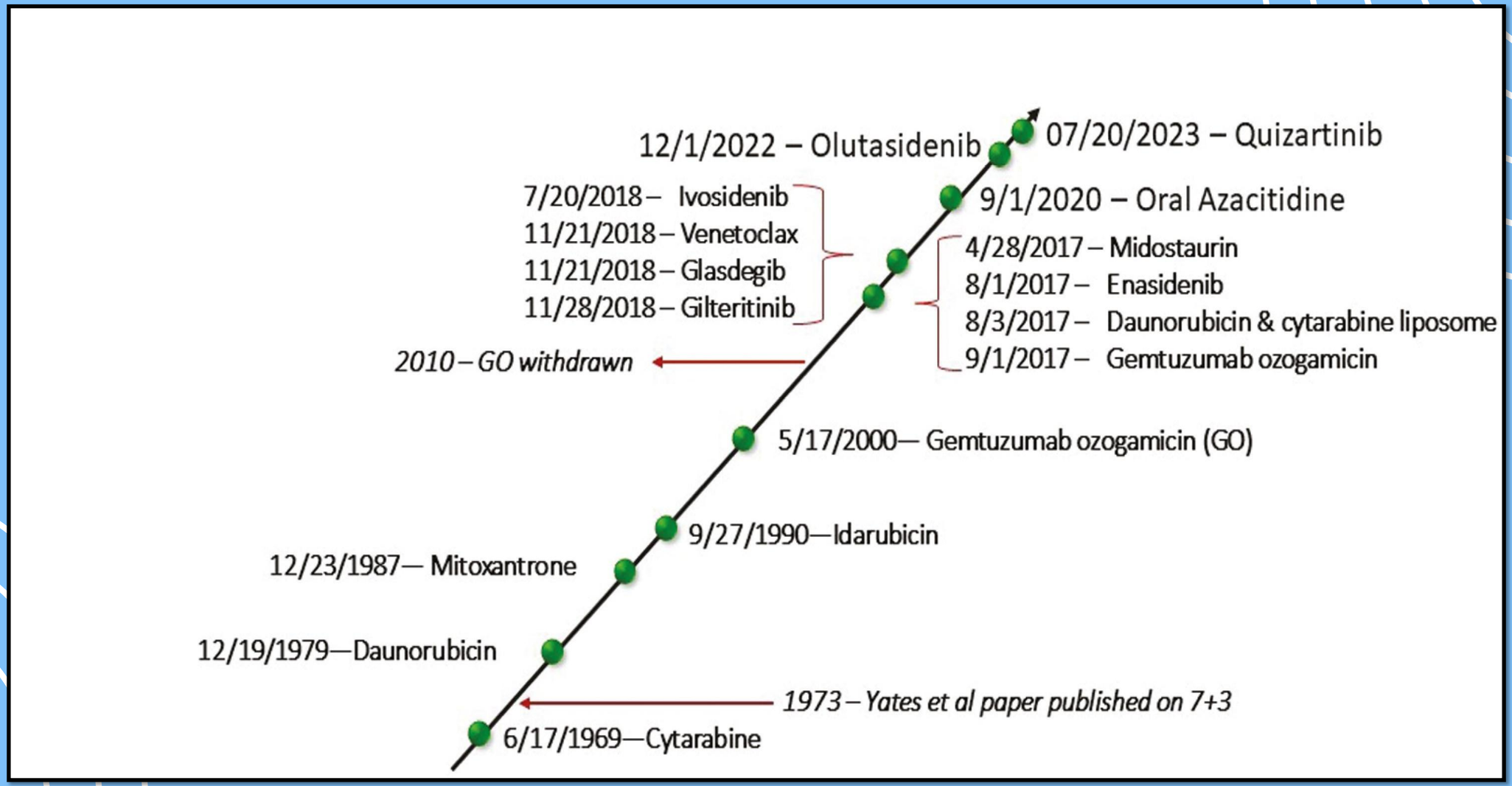
Buckley. Bone Marrow Transplant. 2013;48:630.

MRD Assessment Algorithm for Different Subtypes of AML



Heuser. Blood. 2021;Nov 1:[Epub].

Timeline for approval of AML drugs

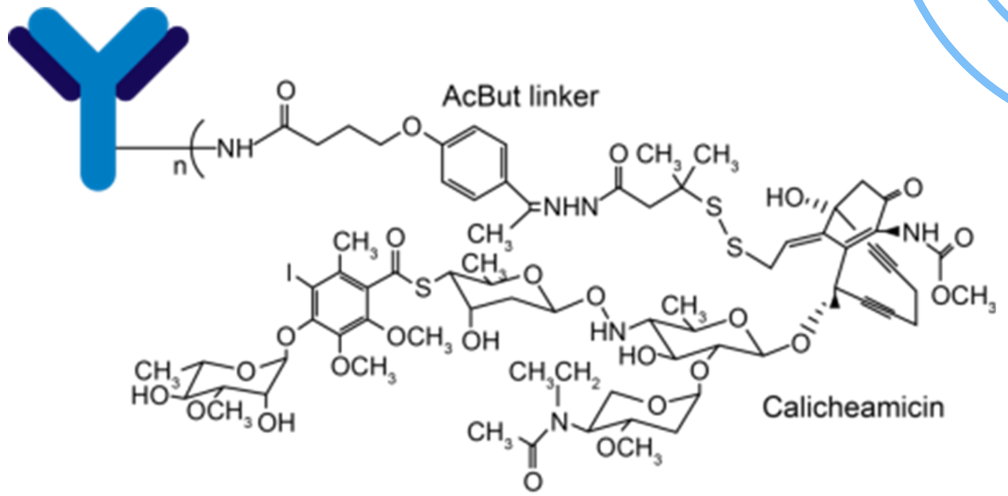


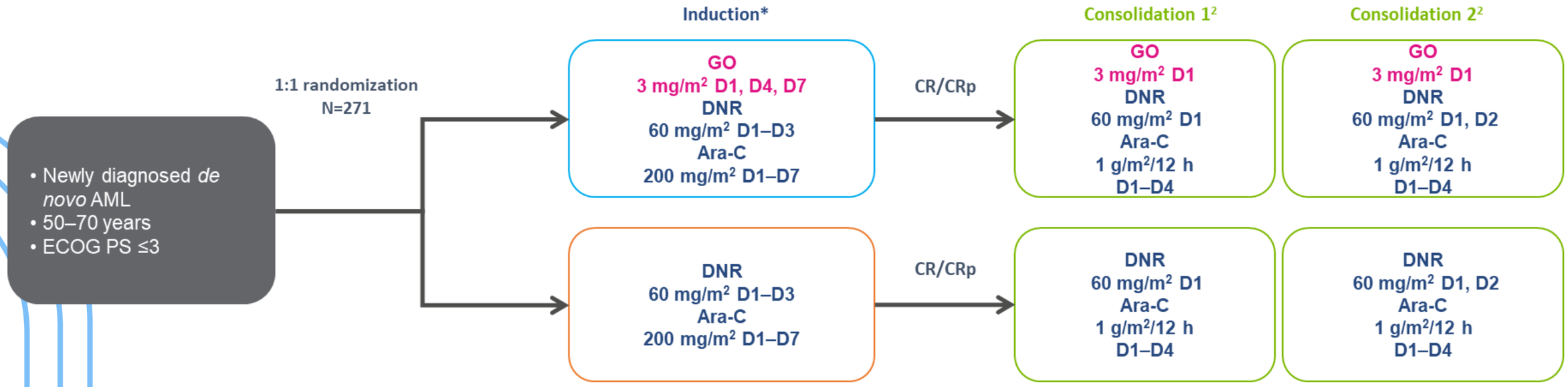
ND AML

Intensive Chemotherapy or NOT

ALFA 0701

Humanized IgG4 Anti-CD33 mAb hP67.6

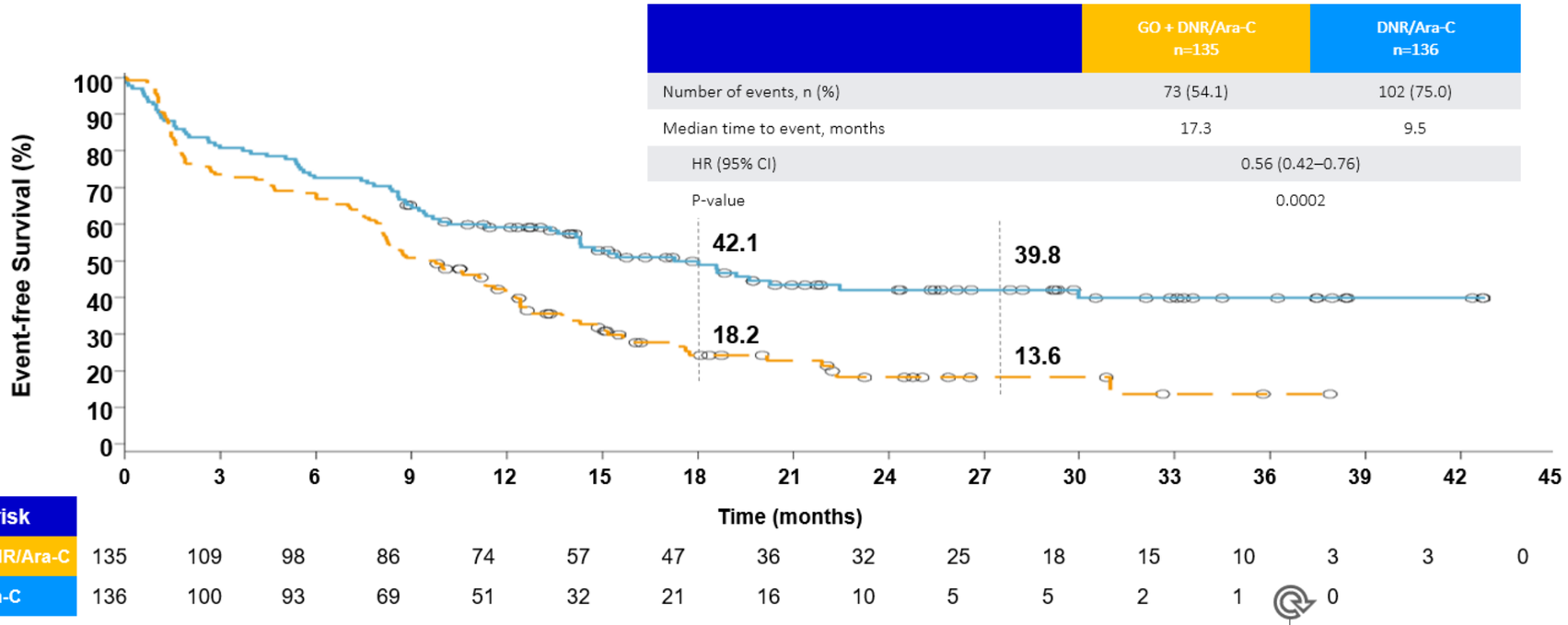




Lambert J et al. *Haematologica* 2018

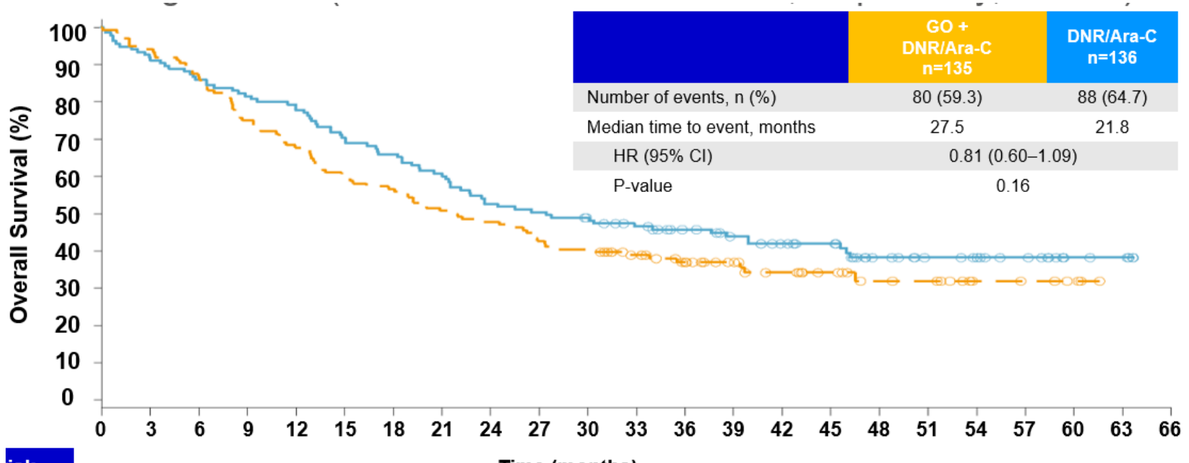
Lambert J et al. Haematologica 2018

ALFA 0701



	GO + DNR/Ara-C n=135	DNR/Ara-C n=136
Number of events, n (%)	73 (54.1)	102 (75.0)
Median time to event, months	17.3	9.5
HR (95% CI)	0.56 (0.42–0.76)	
P-value	0.0002	

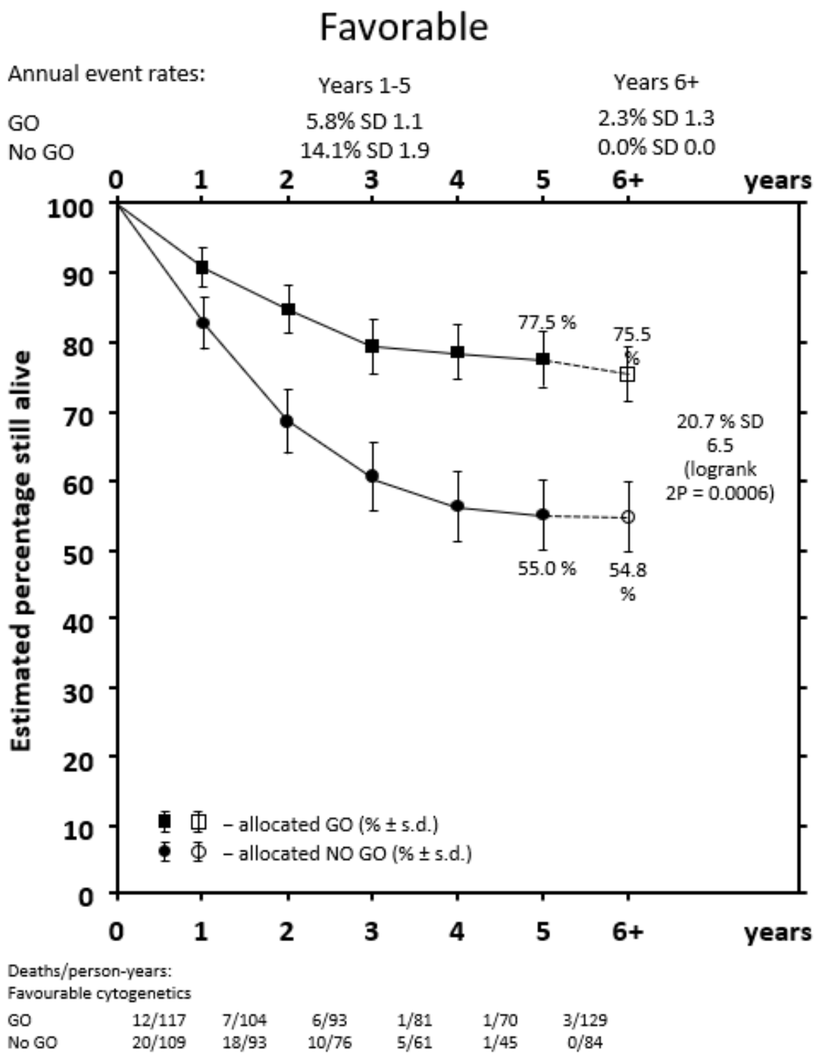
No. at risk																
GO + DNR/Ara-C	135	109	98	86	74	57	47	36	32	25	18	15	10	3	3	0
DNR/Ara-C	136	100	93	69	51	32	21	16	10	5	5	2	1	0		



	GO + DNR/Ara-C n=135	DNR/Ara-C n=136
Number of events, n (%)	80 (59.3)	88 (64.7)
Median time to event, months	27.5	21.8
HR (95% CI)	0.81 (0.60–1.09)	
P-value	0.16	

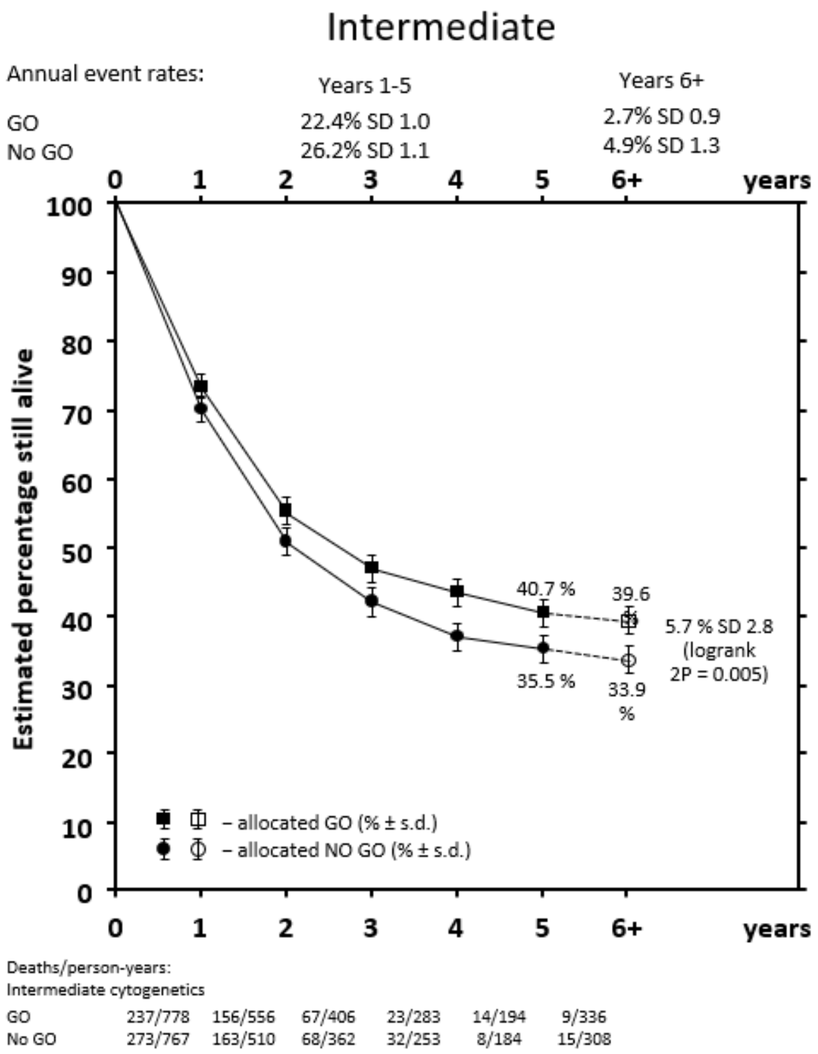
Lambert J et al. Haematologica 2018

GO Meta analysis



Deaths/person-years:
Favourable cytogenetics

GO	12/117	7/104	6/93	1/81	1/70	3/129
No GO	20/109	18/93	10/76	5/61	1/45	0/84

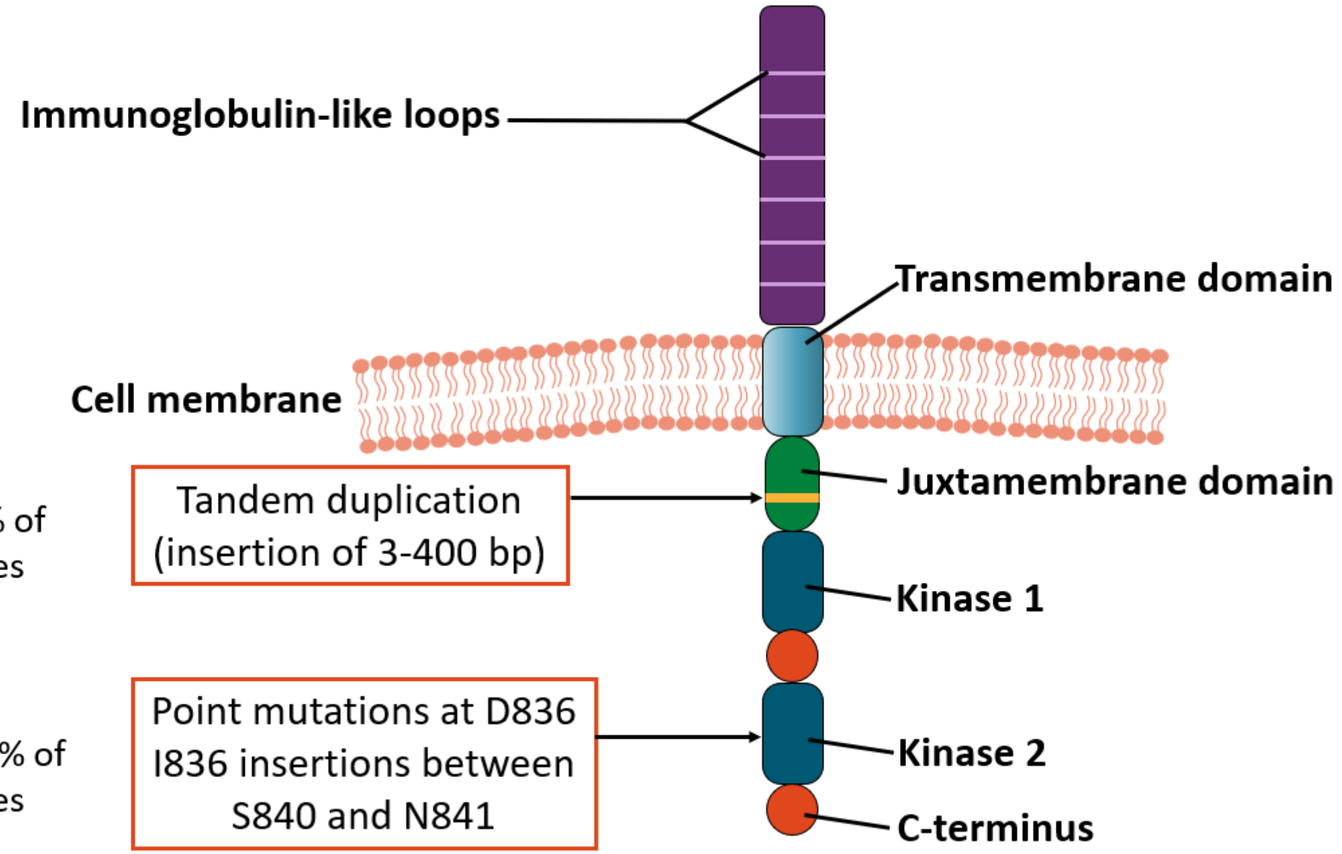


Deaths/person-years:
Intermediate cytogenetics

GO	237/778	156/556	67/406	23/283	14/194	9/336
No GO	273/767	163/510	68/362	32/253	8/184	15/308

Hills RK et al. Lancet Oncol 2014;15:986–96

Activating FLT3 Mutation

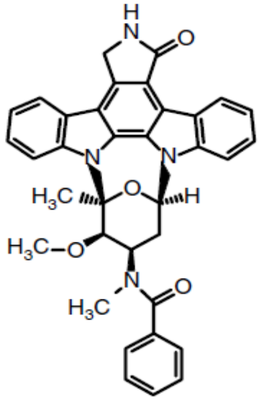


ITD Mutations ~25% of cases — Tandem duplication (insertion of 3-400 bp)

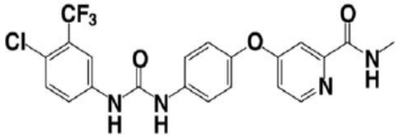
TKD Mutations 5%-10% of cases — Point mutations at D836 I836 insertions between S840 and N841

FLT3 Inhibitors

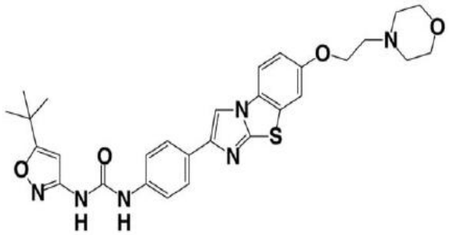
First Generation



Midostaurin

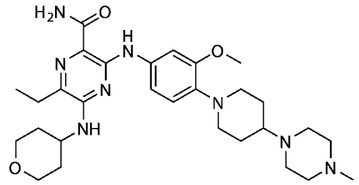


Sorafenib

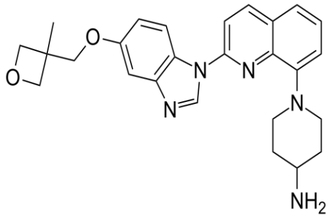


Quizartinib

Second Generation



Gilteritinib

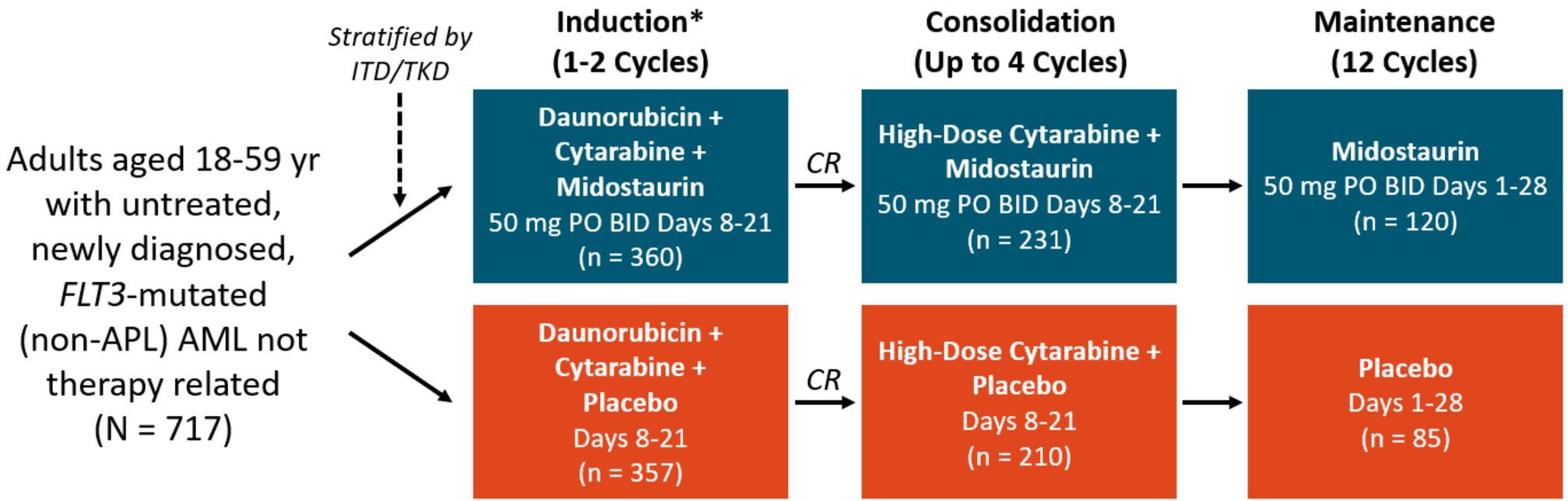


Crenolanib

- **Type I FLT3 inhibitor:** inhibits *FLT3*-ITD and TKD mutations
- **Type II FLT3 inhibitor:** inhibits only *FLT3*-ITD mutations

RATIFY

- Double-blind, placebo-controlled, randomized phase III trial



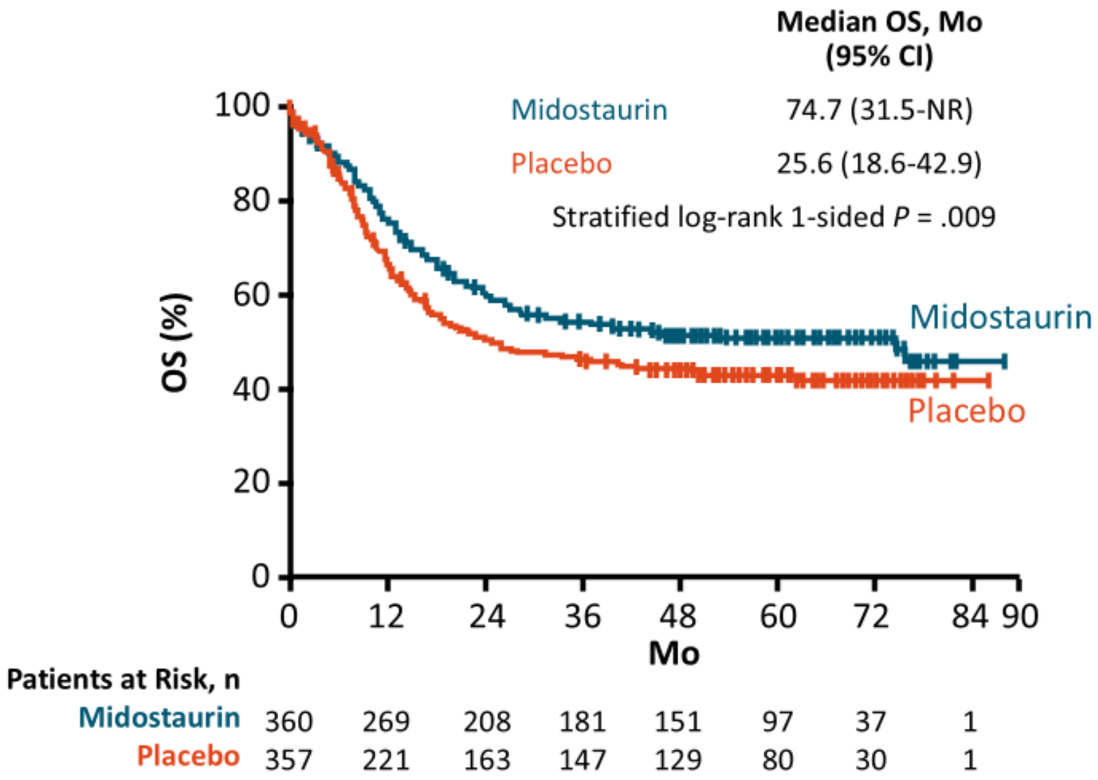
*Hydroxyurea allowed for 5 days prior to induction therapy.

- **Primary endpoint:** OS (not censored for HCT)
- **Secondary endpoint:** EFS, OS (censored for HCT), DFS, HCT rate

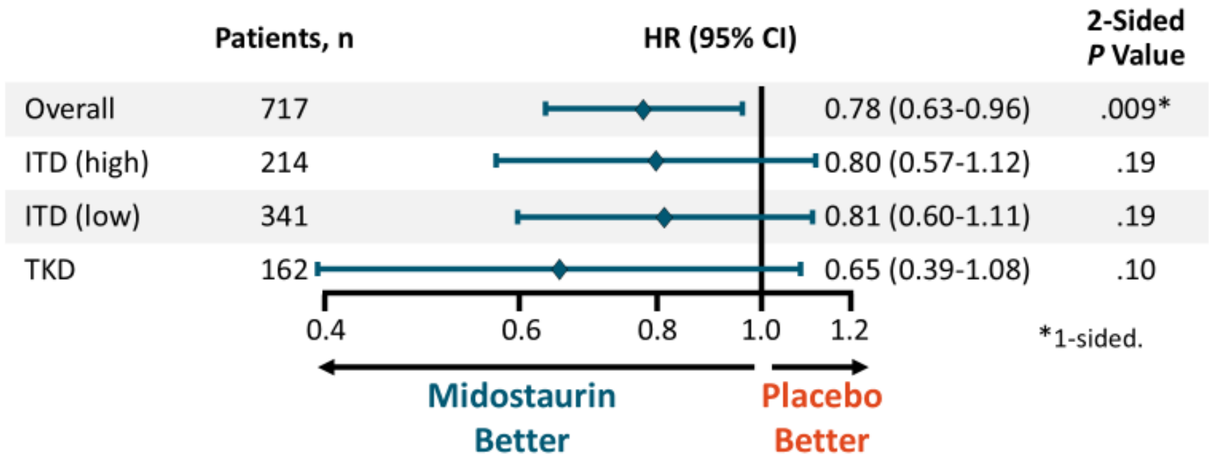
Stone NEJM 2017; 377-454

RATIFY

OS



Subgroup Analysis



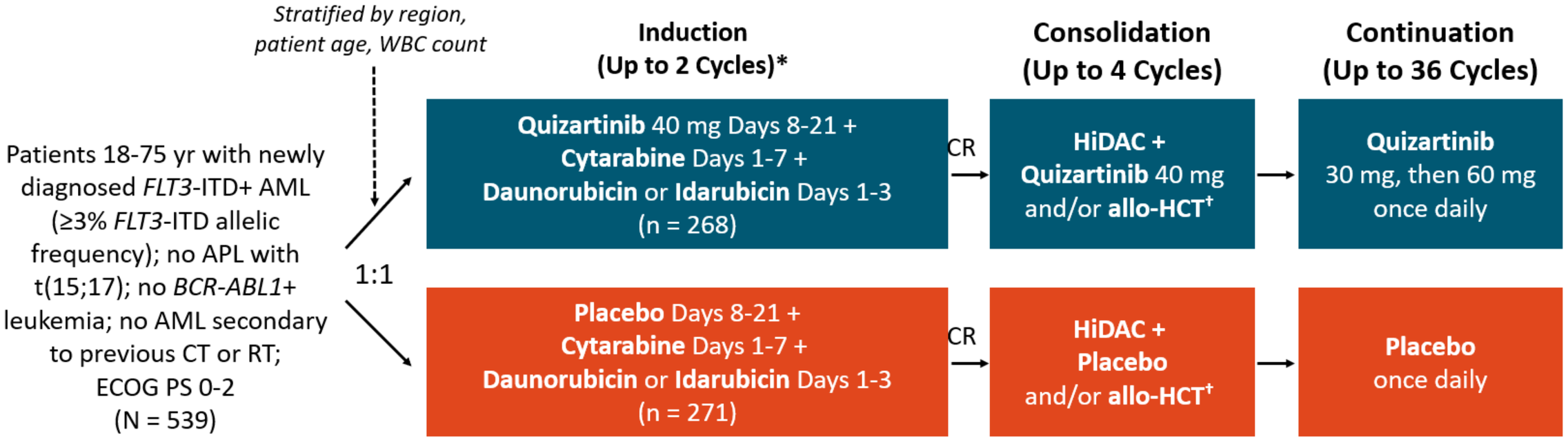
- **OS was significantly longer with midostaurin vs placebo group (HR: 0.78; *P* = .009)**
- 24.3% reduced risk of death in midostaurin arm
- At 4 yr, 63.7% were alive in midostaurin arm vs 55.7% in placebo arm

Stone NEJM 2017; 377-454

QUANTUM-First

Quizartinib + Chemotherapy in Newly Diagnosed FLT3-ITD+ AML

- Randomized, double-blind, placebo-controlled phase III trial

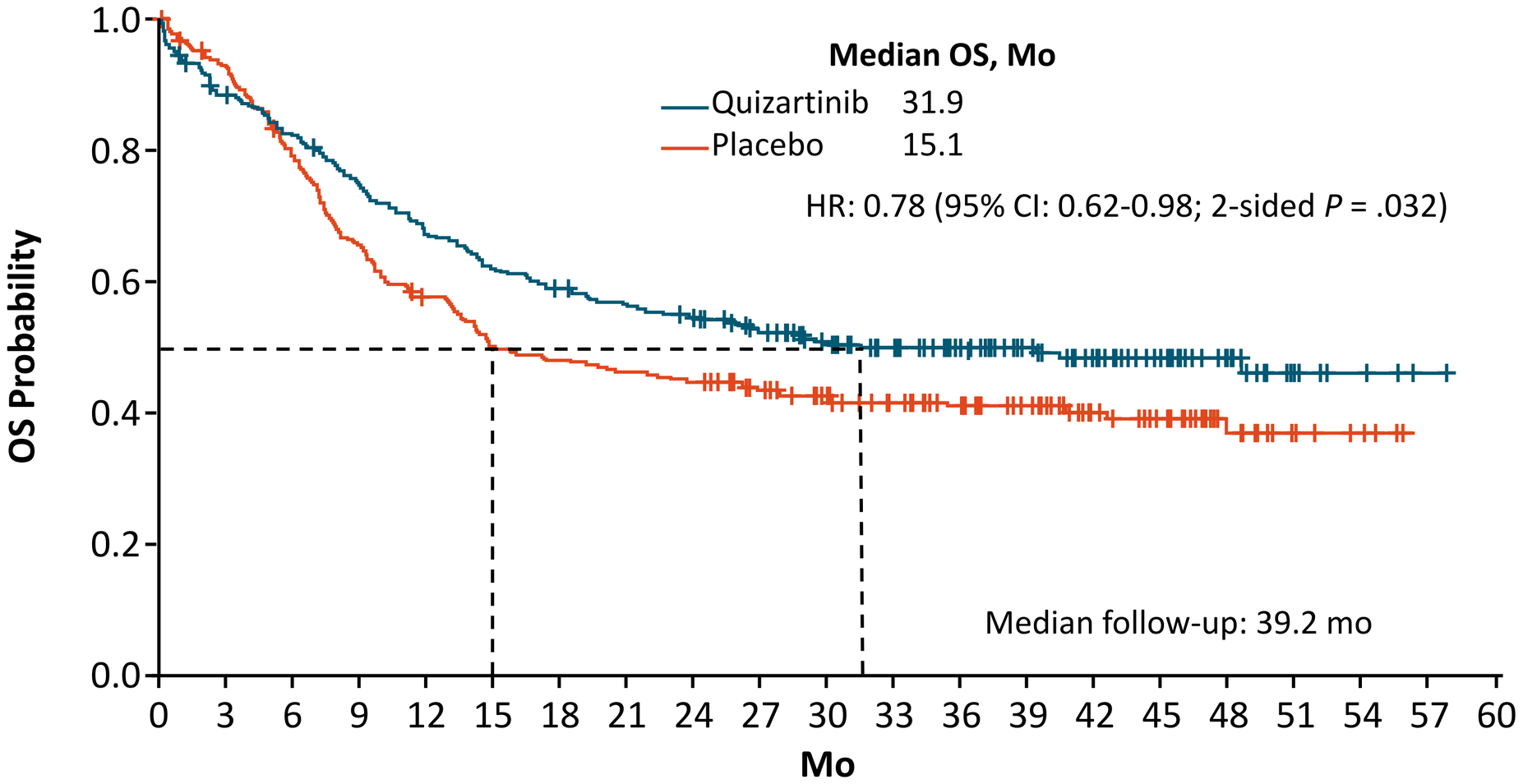


*For persistent leukemia, patients could receive second induction cycle with 7 + 3 or 5 + 2 plus quizartinib/placebo started on Day 8 or Day 6, respectively. †Per institutional policy.

- **Primary endpoint:** OS
- **Secondary endpoints:** EFS, CR/CRc, CR/CRc with *FLT3-ITD* MRD negativity (hierarchical testing), safety
- **Exploratory endpoints:** RFS, DoCR

Erba. Lancet. 2023;401:1571. Erba. EHA 2022. Abstr S100.

QuANTUM-First: OS (Primary Endpoint)



On July 20, 2023, the FDA approved quizartinib + cytarabine and anthracycline induction and cytarabine consolidation, and quizartinib maintenance monotherapy after consolidation CT for adults with newly diagnosed *FLT3-ITD+* AML

Erba. Lancet. 2023;401:1571. Erba. EHA 2022. Abstr S100. Quizartinib PI.

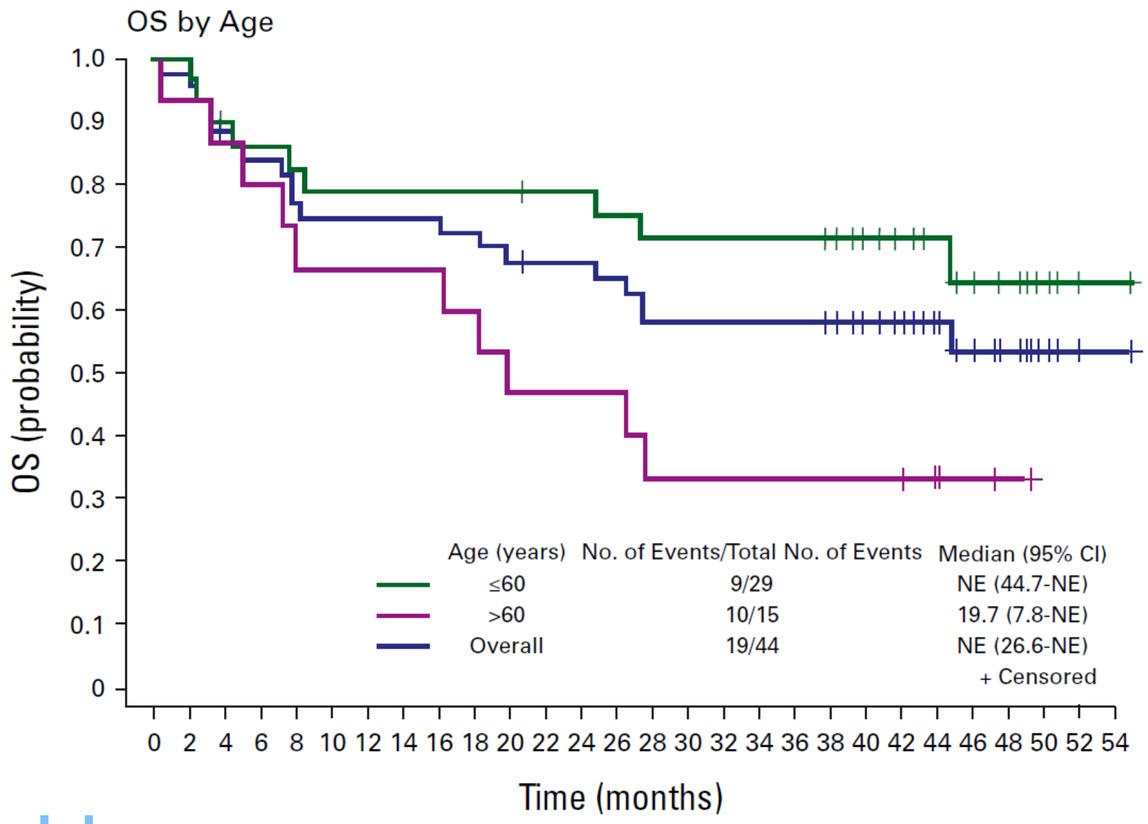
Crenolanib

Patients with newly diagnosed *FLT3*-ITD+ AML 18-75 yr of age

Crenolanib 100 mg x3/d from Days 9
Cytarabine Days 1-7 +
Daunorubicin or Idarubicin Days 1-3
(n = 44)

→ **Consolidation OR Transplant** →

Crenolanib
100 mg x3/d
For 12 months



1-, 2-, 3-Year OS, % (95% CI)			
1-year	78.9 (65.2-95.4)	66.7 (46.6-95.3)	74.6 (62.7-88.8)
2-year	78.9 (65.2-95.4)	46.7 (27.2-80.2)	67.6 (55.0-83.1)
3-year	71.4 (56.4-90.3)	33.3 (16.3-68.2)	58.0 (44.9-74.9)

J Clin Oncol. 2024 May 20;42(15):1776-1787

IDH Inhibitors

- Ivosidenib or Enasidenib
- The CR/CRi/CRp rates were 77% with ivosidenib & 74% with enasidenib
- Waiting fot the results from HOVON 150, a phase III trial evaluating the benefit of adding IDH inhibitor to 7 + 3 in fit patients with ND IDH-mutated AML

Blood 137, no. 13 (2021): 1792–1803

Wrap up

Fit patients

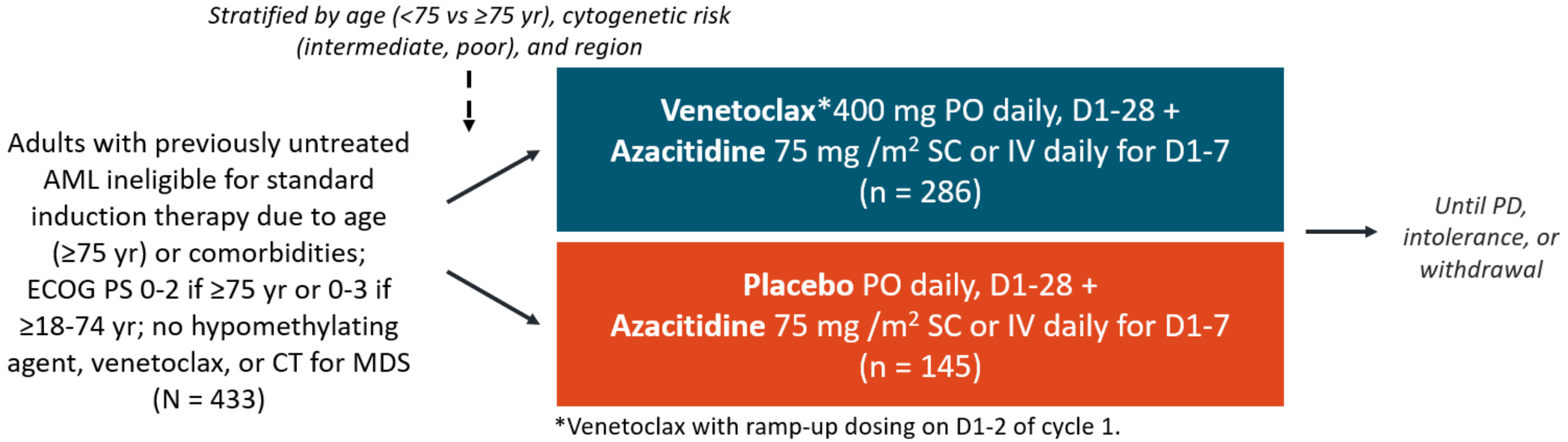
- ✓ There are two approved FLT3 inhibitors with 7 + 3 in ND *FLT3*-mutated AML
- ✓ For *FLT3*-TKD mutations, we use midostaurin
- ✓ No comparative trials between midostaurin & quizartinib (co-morbidities and specific side-effects)
- ✓ In patients who are expected to undergo chemotherapy-only consolidation without allo-SCT we favor quizartinib

- ✓ Ongoing trials
  - 7 + 3 + midostaurin vs. 7 + 3 + gilteritinib (HOVON 156)
  - 7 + 3 + midostaurin vs. 7 + 3 + crenolanib (NCT03258931)

VIALE-A

Azacitidine ± Venetoclax in Treatment-Naive AML Ineligible for Standard Induction

- Multicenter, double-blind, placebo-controlled, randomized phase III trial

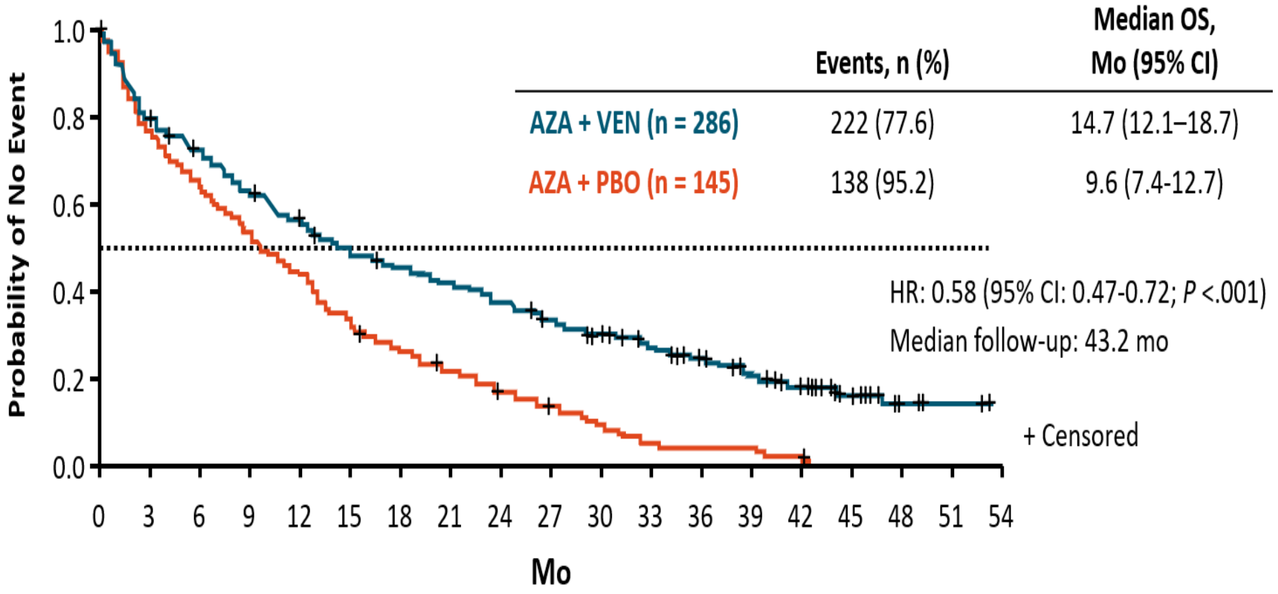


*Venetoclax with ramp-up dosing on D1-2 of cycle 1.

- **Primary endpoint:** OS (CR + CRi coprimary endpoint in EU/EU reference countries)
- **Key secondary endpoints:** CR + CRi, CR, EFS, OS by molecular subtype, MRD negativity remission rate

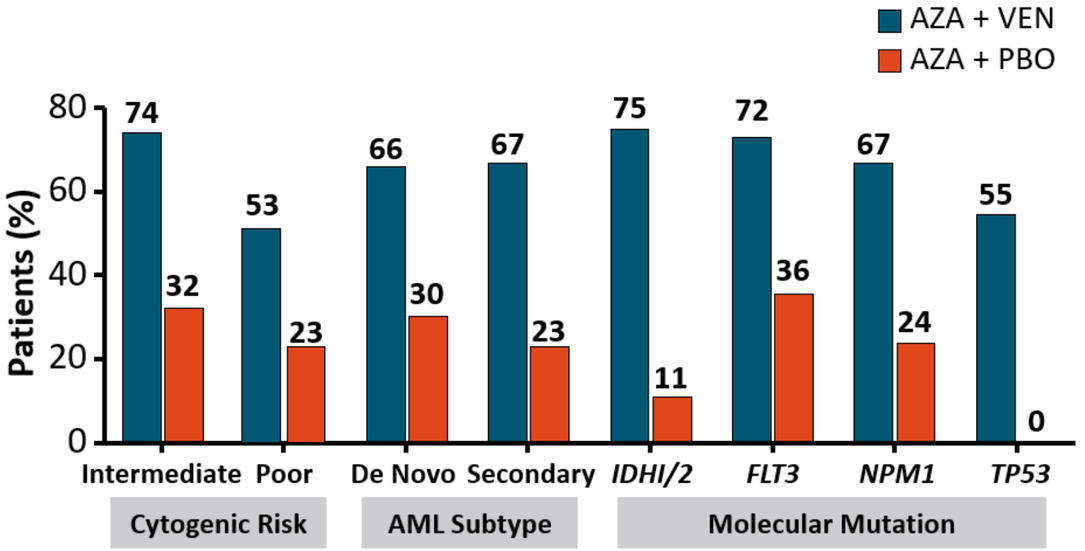
DiNardo. NEJM. 2020;383:617. Pratz. ASH 2022. Abstr 219

VIALE-A



CR rate: 36.7% vs 17.9% (*P* <.001)
CR/CRi rate: 66.4% vs 28.3% (*P* <.001)
Median time to response: 1 vs 3 cycles (*P* <.001)

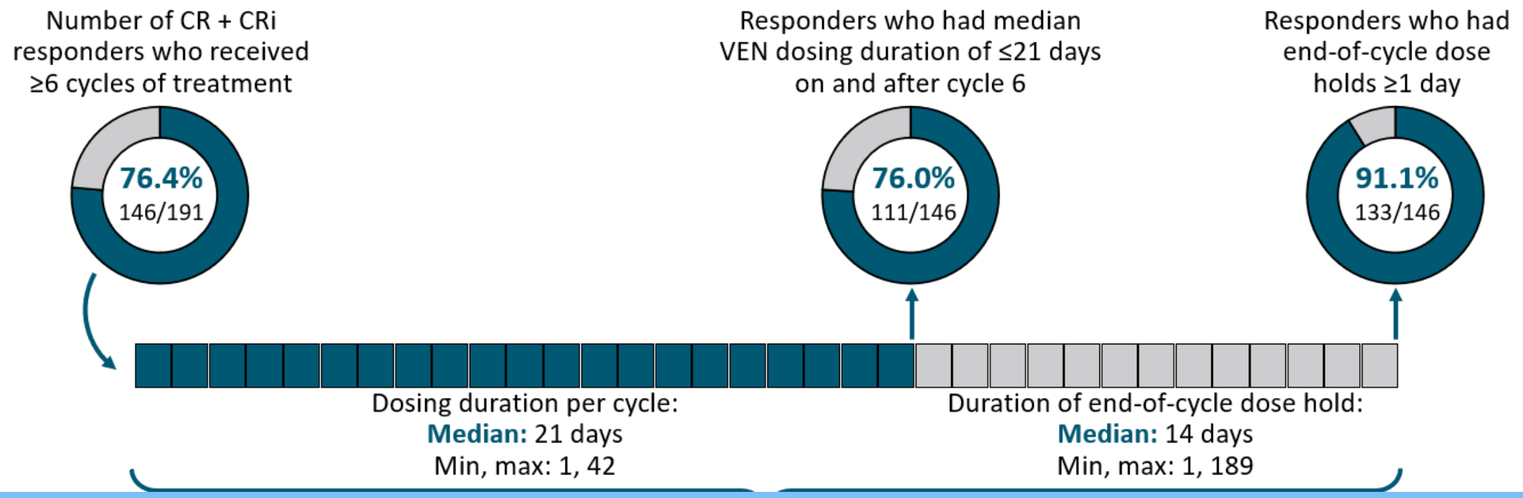
Improved Responses Occurred *Independently* of High-Risk Genomics



Erba. Lancet. 2023;401:1571. Erba. EHA 2022. Abstr S100.

VIALE-A Take home message

- VEN/AZA remains an optimal approach for newly diagnosed AML not suitable for intensive therapy, irrespective of cytogenetic or molecular features at this time
  - Prolonged neutropenia compared with AZA alone
  - Early bone marrow assessment (EOC1) with VEN interruption, and shortened VEN duration for count recovery is recommended
- Responses are quick, with median time to response of 1.3 mo
  - Therapy is indefinite
  - Flow cytometry MRD–negative status predicts for improved DoR and OS



VIALE-C

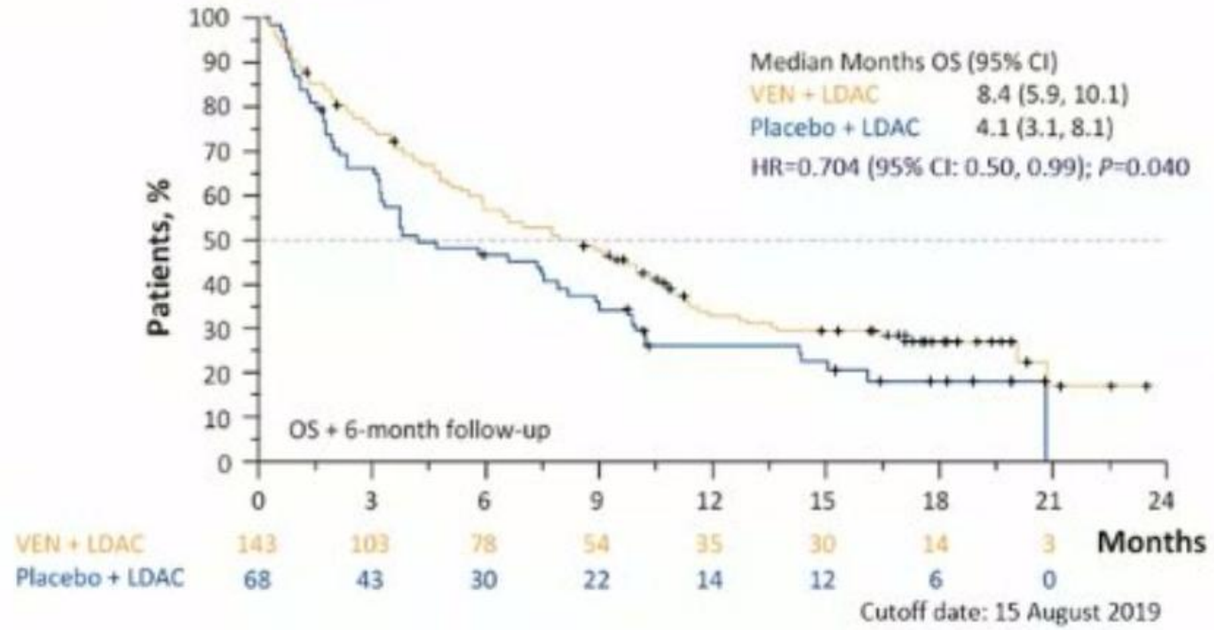
A phase 3 study of Venetoclax plus LDAC in ND Older patients with AML

With 6-months of additional follow-up, venetoclax + LDAC:

- Reduced the risk of death by 30%
- Improved CR/CRi (48% vs 13%)
- Lengthened CR duration (17 vs 8 months)
- Increased transfusion independence

Safety profile was consistent with the known AE profiles of both study drugs

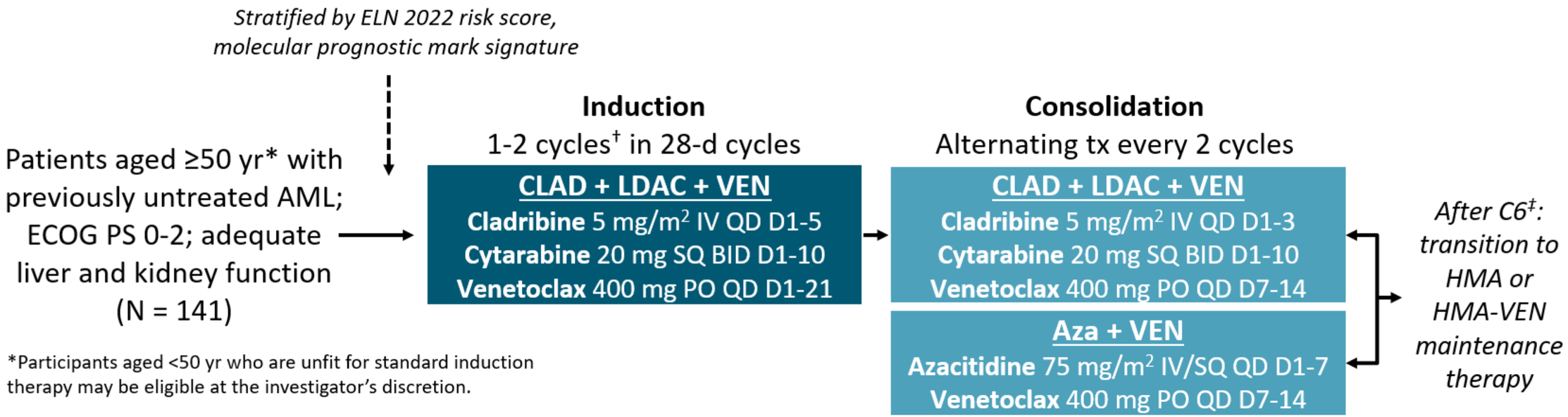
VIALE-C study confirms a clinically meaningful improvement in OS for venetoclax + LDAC with a favorable benefit-risk profile



Blood. 2020;135:2137-2145.

Venetoclax Triplets

- Single-arm, single-center, prospective phase II trial



*Participants aged <50 yr who are unfit for standard induction therapy may be eligible at the investigator's discretion.

†Patients not achieving CR or CRi after C1 may receive induction in C2. Patients not achieving CR or CRi after induction C2 may proceed to consolidation in C3 per the investigator. ‡Protocol amended to transition to HMA or HMA-VEN maintenance after C6 instead of continue consolidation therapy through C18.

- **Primary endpoint:** composite CR rate
- **Secondary endpoints:** OS, DFS, ORR, safety

Bataller. ASH 2024. Abstr 56. NCT03586609

Venetoclax Triplets

Subgroup, %	CR + CRi
All patients (N = 141)	85.8
Age, yr	
▪ <70 (n = 88)	87.5
▪ >70 (n = 53)	83.0
ELN 2022	
▪ Favorable (n = 27)	100
▪ Intermediate (n = 29)	89.7
▪ Adverse (n = 85)	80.0

Cytogenetic Subgroup, %	CR + CRi
All patients (N = 141)	85.8
RAS mut (n = 29)	82.8
TP53 mut (n = 24)	58.3
Diploid cytogenetics (n = 72)	93.1
Complex cytogenetics (n = 23)	69.6

Risk Stratification	Patient Population, n	Median OS, Mo	2-Yr OS, %	4-Yr OS, %	*P* Value
ELN 2022					
▪ Favorable	27	NA	84.2	74.9	.016 c-index .59
▪ Intermediate	29	49.8	67.3	67.3	
▪ Adverse	85	24.7	51.3	39.1	
mPRS					
▪ Favorable	86	NA	70.5	58.9	.002 c-index .62
▪ Intermediate	31	25.4	57.4	47.3	
▪ Adverse	24	10.1	32.1	32.1	

MRD Status	Patient Population, n	Median OS, Mo	2-Yr OS, %	4-Yr OS, %	*P* Value
MRD-	94	58.7	84.2	73.8	<.001
MRD+	20	15.6	52.9	31.8	

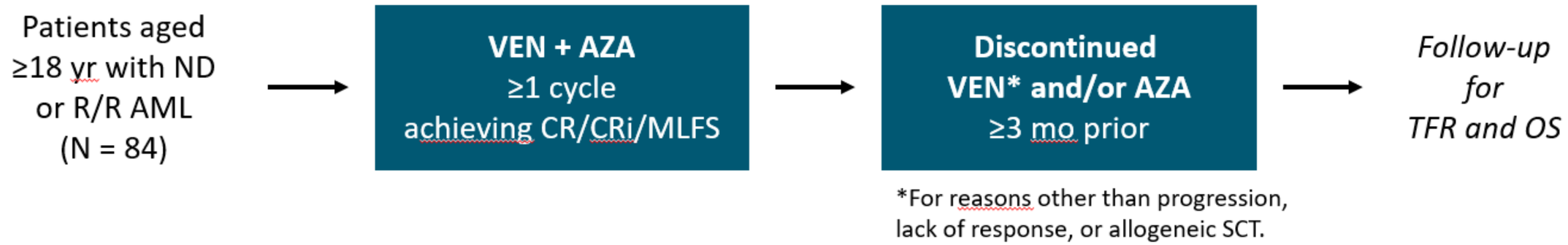
OS by HSCT	Patients, n	Median OS, Mo	2-Yr OS, %	4-Yr OS, %	*P* Value
No HSCT	63	25.4	55.2	42.5	<.001
With HSCT	62	NA	85	78.9	

Erba. Lancet. 2023;401:1571. Erba. EHA 2022. Abstr S100.

STOP-VEN

Discontinuation of Venetoclax + Azacitidine for Patients With AML in Remission

- Retrospective study of patients treated at French FILO centers and US Moffit Cancer Center between 11/2018 and 7/2023



- **Primary Endpoints**: OS, TFR (from last day of VEN)
- **Other Endpoints**: Multivariate analysis of OS and TFR by Cox regression based on disease and mutation status

Garciaz. ASH 2023. Abstr 161

STOP-VEN

Efficacy Outcomes	ND AML (n = 62)	R/R AML (n = 22)
All Patients		
Correction of cytopenias, n/N (%)	23/39 (59)	8/20 (40)
Median TFR, mo	16	10
Median OS, mo	44	19
MRD-negative Patients	**(n = 25)**	**(n = 10)**
Median OS, mo	NR	31
2-yr OS, %	80	—
VEN + AZA Rechallenged Patients	**(n = 11)**	**(n = 5)**
CR/CRi, n (%)	3 (27.3)	2 (40)

Prognostic Factor	TFR		OS	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Disease status (R/R vs ND)	0.497 (0.237-1.042)	.064	0.360 (0.165-0.783)	.010
FLT3-ITD	0.280 (0.075-1.048)	.059	0.310 (0.066-1.448)	.136
NPM1	3.095 (0.989-9.687)	.052	2.497 (0.838-7.444)	.101
IDH	0.719 (0.356-1.453)	.358	2.634 (1.196-5.797)	.016
TP53	0.700 (0.246-1.995)	.504	1.073 (0.340-3.388)	.904

Garciaz. ASH 2023. Abstr 161

STOP-VEN

- In this retrospective analysis, discontinuation of VEN + AZA treatment in responding patients with ND or R/R AML was associated with sustained responses and survival
  - Median TFR: 60 mo and 10 mo, respectively
  - Median OS: 44 mo and 19 mo, respectively
- MRD negativity was associated with sustained remission
  - Median OS in ND AML: NR
  - Median OS in R/R AML: 31 mo
- Investigators conclude that it is feasible to discontinue VEN + AZA in patients with ND AML in remission and will explore this strategy in a prospective clinical trial

Garciaz. ASH 2023. Abstr 161

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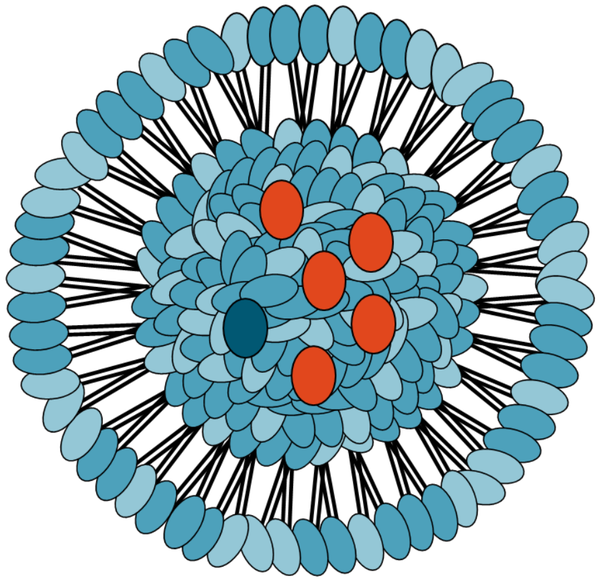
CPX-351



CPX-351 in Older Patients With Newly Diagnosed t-AML or s-AML

- Multicenter, open-label, randomized phase III trial

Stratified by age (60-69 vs 70-75 yr); AML type

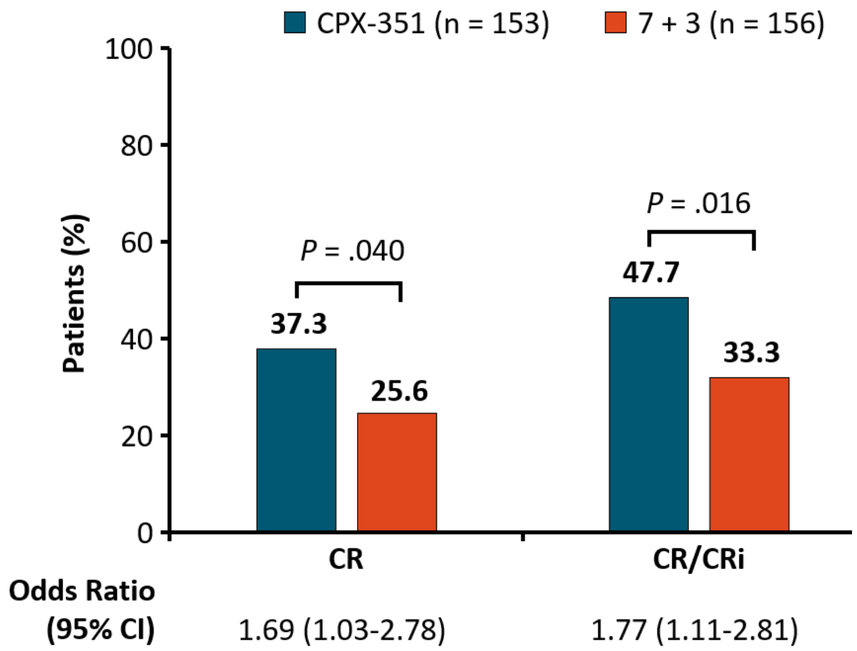
Treatment-naive patients 60-75 yr of age with t-AML or s-AML able to tolerate intensive therapy; ECOG PS 0-2 (N = 309)

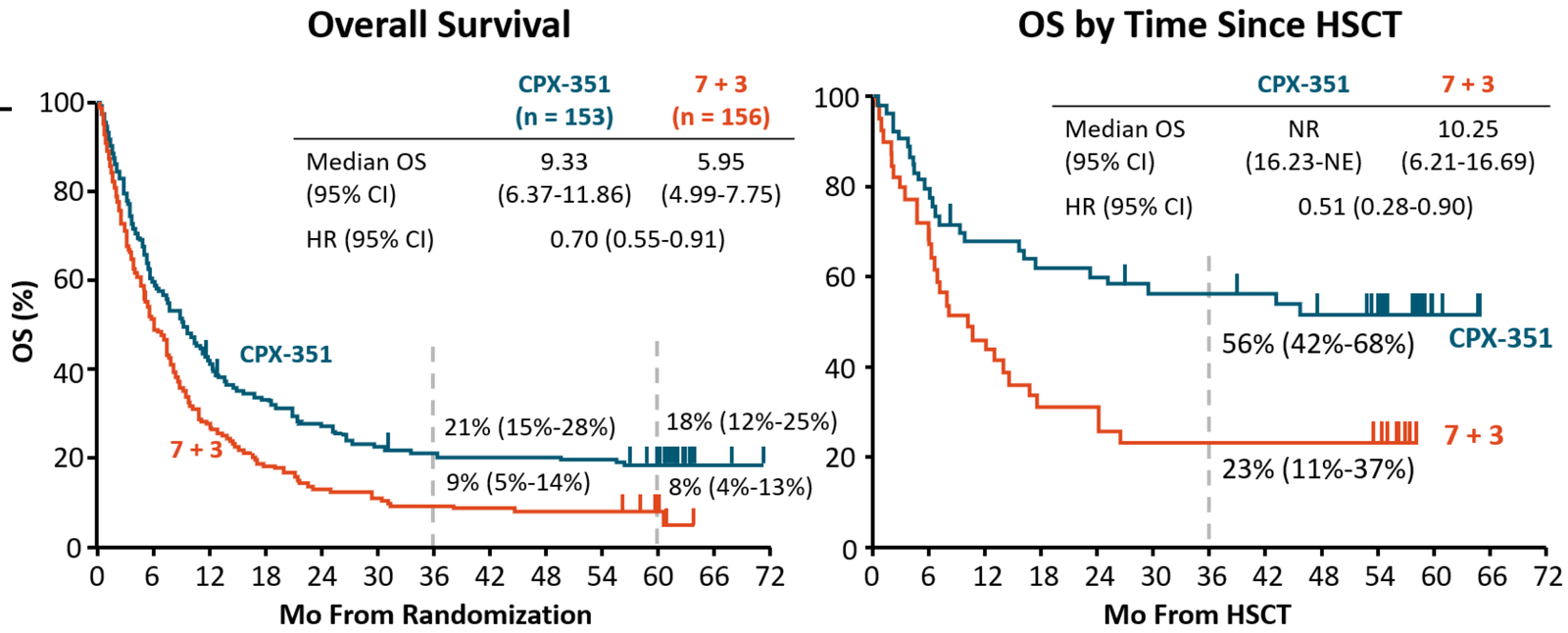
	Induction	*Subsequent Induction**	*Consolidation†*
	CPX-351 44 mg/m² daunorubicin + 100 mg/m² cytarabine liposome IV Days 1, 3, 5	**CPX-351** 44 mg/m² daunorubicin + 100 mg/m² cytarabine liposome IV Days 1, 3	**CPX-351** 29 mg/m² daunorubicin + 65 mg/m² cytarabine liposome IV Days 1, 3
	7 + 3 Regimen IV 7 days **cytarabine** 100 mg/m²/day + 3 days **daunorubicin** 60 mg/m²/day	5 days **cytarabine** 100 mg/m²/day IV + 2 days **daunorubicin** 60 mg/m²/day IV	5 days **cytarabine** 100 mg/m²/day IV + 2 days **daunorubicin** 60 mg/m²/day IV

*Subsequent induction was recommended for patients who did not achieve CR or CRi and was mandatory for patients achieving >50% reduction in percent blasts. †Postremission therapy with allogeneic hematopoietic stem cell transplant permitted either in place of or after consolidation.

Lancet. Lancet Haematol. 2021;8:e481.

CPX-351



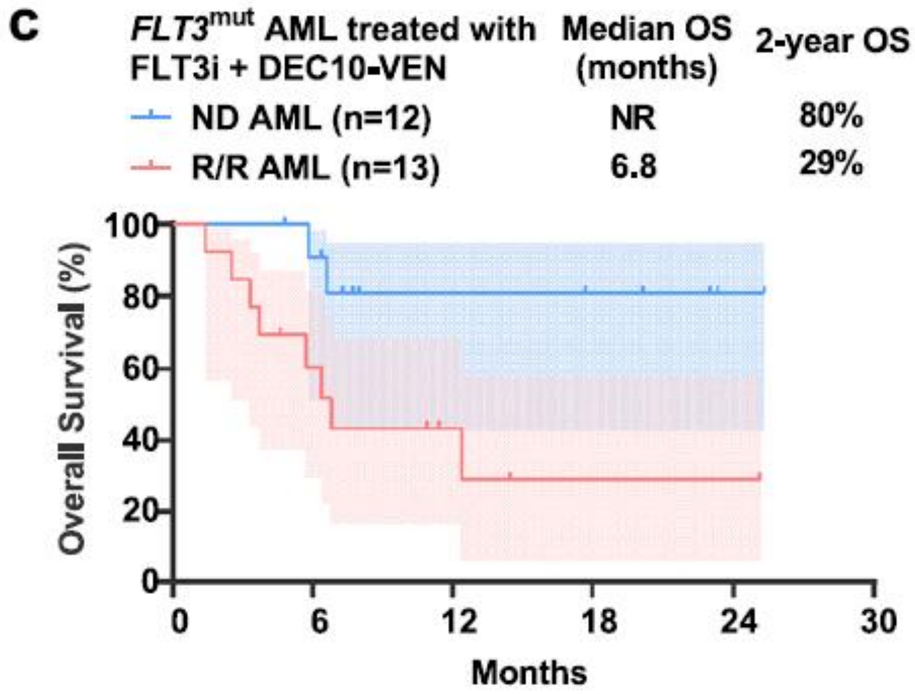


Lancet. Lancet Haematol. 2021;8:e481.

Anti FLT3 Triplets

Venetoclax + decitabine + FLT3 inhibitor

CR rates were 75% and 2-year OS was 80% among ND patients



Erba. Lancet. 2023;401:1571. Erba. EHA 2022. Abstr S100.

Anti FLT3 Triplets

Gilteritinib + Aza and Ven in FLT3-Mutated AML

Patients with R/R *FLT3*-mutated (*FLT3-ITD* or *FLT3 D835* mutations allowed), AML or high-risk MDS, or CMML; newly diagnosed *FLT3*-mutated AML unfit for intensive CT (frontline: N = 27; R/R: N = 20)

Induction

Azacitidine 75 mg/m^2 IV/SC on D1-7
+
Venetoclax* D1-28
(bone marrow on D14†)
+
Gilteritinib 80-120 mg on D1-28

*Venetoclax ramp-up during cycle 1: 100 mg on D1, 200 mg on D2, and 400 mg on D3+.
†If blasts <5% or insufficient marrow on C1D14, venetoclax held (both cohorts) and gilteritinib held (frontline only).

Consolidation (Up to 24 Cycles)

Azacitidine 75 mg/m^2 IV/SC on D1-5
+
Venetoclax 400 mg D1-7
+
Gilteritinib 80-120 mg on D1-28

- 2 cohorts: one for *FLT3*-mutated R/R AML or high-risk MDS or CMML and the other for patients with newly diagnosed *FLT3*-mutated AML unfit for intensive CT

Short. ASH 2021. Abstr 696. Short. ASH 2022. Abstr 831

Anti FLT3 Triplets

Parameter	Frontline Cohort*	R/R Cohort†
RFS, n	**27**	**14**
▪ Median, mo	NR	6.1
▪ 6 mo, %	90	50
▪ 1 yr, %	74	25
OS,‡ n	**27**	**20**
▪ Median, mo	NR	5.8
▪ 6 mo, %	96	48
▪ 1 yr, %	85	30
OS if previous HMA + Ven and/or gilterinib, n	--	**10**
▪ Median, mo	--	4.8
▪ 6 mo, %	--	22
OS if no previous HMA + Ven and/or gilterinib, n	--	10
▪ Median, mo	--	10.5
▪ 6 mo, %	--	70

*Median follow-up: 12 mo (range: 1.5-24+). †Median follow-up: 27 mo (range: 1.1-33.2+). ‡4 deaths reported: 1 patient died while in CR, 1 post HSCT (at 7 mo), and 2 post relapse (at 9.5 and 13.6 mo).

Short. ASH 2022. Abstr 831.

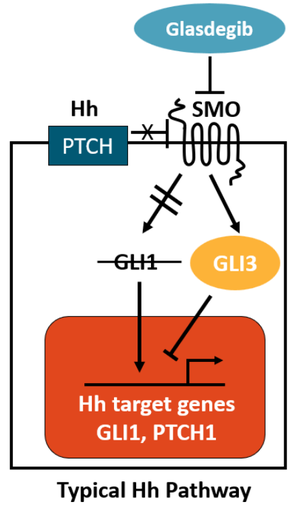
Parameter	Frontline Cohort*	R/R Cohort†
OS by *FLT3* ITD, n	**19**	**9**
▪ Median, mo	NR	8.0
▪ 6 mo, %	95	50
▪ 1 yr, %	79	--
OS by *FLT3* TKD, n	**8**	**7**
▪ Median, mo	NR	5.2
▪ 6 mo, %	100	43
▪ 1 yr, %	100	--
OS *by FLT3* ITD + TKD, n	--	**4**
▪ Median, mo	--	8.1
▪ 6 mo, %	--	50

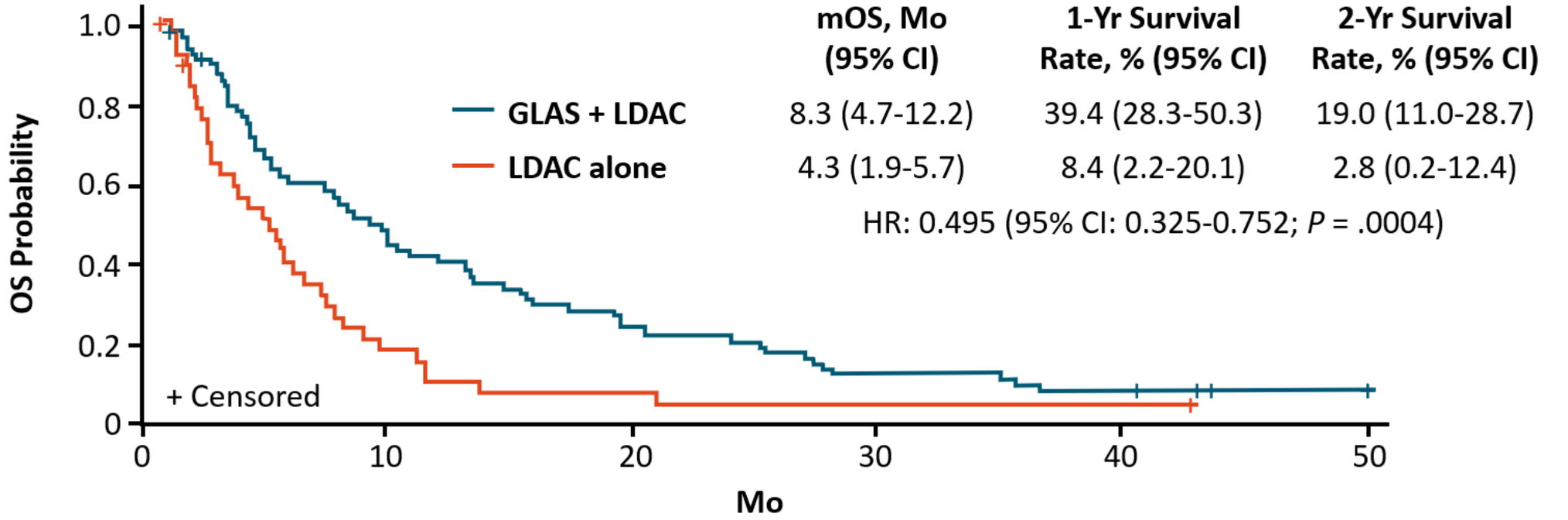
- In patients with no previous HSCT (n = 14), median OS, 6-mo OS, and 12-mo OS were NR, 100%, and 91%, respectively
- In patients with previous HSCT (n = 7), median OS, 6-mo OS, and 12-mo OS were NR, 100%, and 80%, respectively
- In patients aged <75 (n = 19), median OS, 6-mo OS, and 1-yr OS were NR, 95%, and 80%, respectively
- In patients aged ≥75 (n = 8), median OS, 6-mo OS, and 1-yr OS were NR, 100%, and 100%, respectively

Short. ASH 2021. Abstr 696. Short. ASH 2022. Abstr 831

BRIGHT AML 1003

Inhibition of Hh pathway enhanced sensitivity to chemotherapy





	mOS, Mo (95% CI)	1-Yr Survival Rate, % (95% CI)	2-Yr Survival Rate, % (95% CI)
GLAS + LDAC	8.3 (4.7-12.2)	39.4 (28.3-50.3)	19.0 (11.0-28.7)
LDAC alone	4.3 (1.9-5.7)	8.4 (2.2-20.1)	2.8 (0.2-12.4)

HR: 0.495 (95% CI: 0.325-0.752; *P* = .0004)

Fathi. Clin Cancer Res. 2019;25:6015

AGILE

Azacitidine ± Ivosidenib in Untreated IDH1-Mutated AML

- 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 (N = 146)

→ **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).

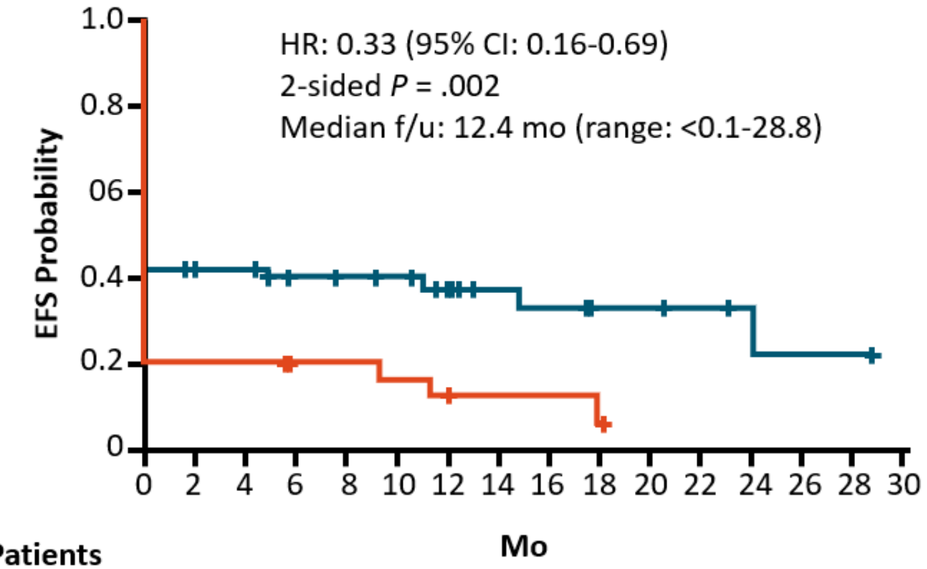
- Enrollment halted based on efficacy as of May 12, 2021 (N = 148)
- **Primary endpoint:** EFS with ~173 events (52 mo)
- **Secondary endpoints:** CRR, OS, CR + CRh rate, ORR

Montesinos. NEJM. 2022;386:1519. de Botton. ASCO 2023. Abstr 7012

AGILE

Azacitidine ± Ivosidenib in Untreated IDH1-Mutated AML

EFS[1]

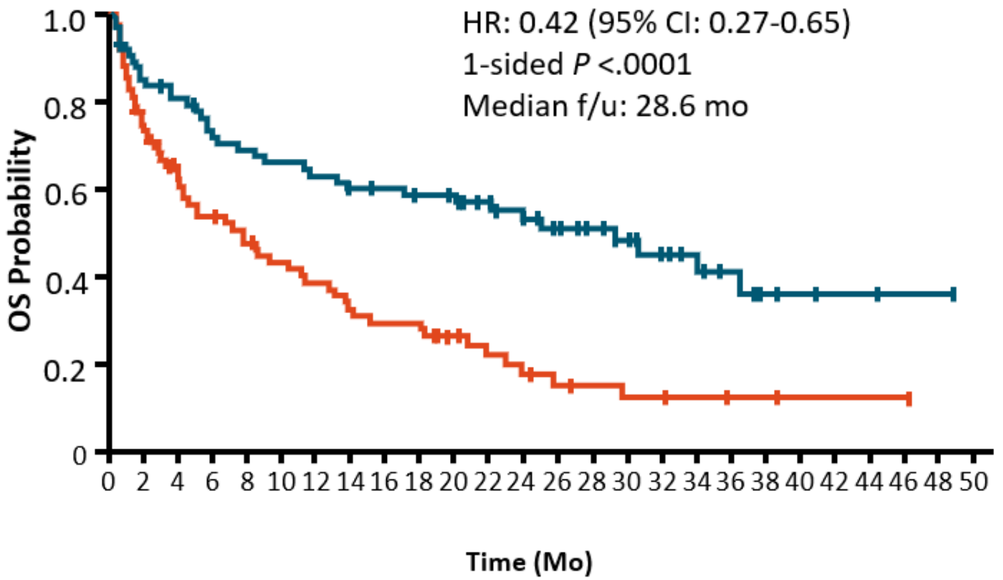


Patients at Risk, n																
IVO + AZA	72	26	25	20	19	17	13	9	8	5	5	4	2	2	2	0
PBO + AZA	74	8	8	5	5	4	3	2	2	1	0					

mEFS: .03 in both treatment arms

12-mo EFS: 37% vs 12%

OS[2]



No. at Risk																											
IVO + AZA	73	60	56	50	47	45	43	40	39	37	36	32	27	23	20	17	13	11	8	5	4	3	3	1	1	0
PBO + AZA	75	55	45	37	32	28	25	21	19	19	13	10	8	6	5	4	4	3	2	2	1	1	1	1	0	

mOS: 29.3 vs 7.9 mo

Montesinos. NEJM. 2022;386:1519. de Botton. ASCO 2023. Abstr 7012

AG221-AML-005

Clinical Trial > Lancet Oncol. 2021 Nov;22(11):1597-1608. doi: 10.1016/S1470-2045(21)00494-0. Epub 2021 Oct 18.

Enasidenib plus azacitidine versus azacitidine alone in patients with newly diagnosed, mutant-IDH2 acute myeloid leukaemia (AG221-AML-005): a single-arm, phase 1b and randomised, phase 2 trial

- 101 patients with IDH-2 mutated AML
- 2:1 Randomiazation
- CR rates were 54% versus 12% ($p < 0.0001$) in azacitidine + enasidenib versus azacitidine alone

Erba. Lancet. 2023;401:1571. Erba. EHA 2022. Abstr S100.

Wrap up

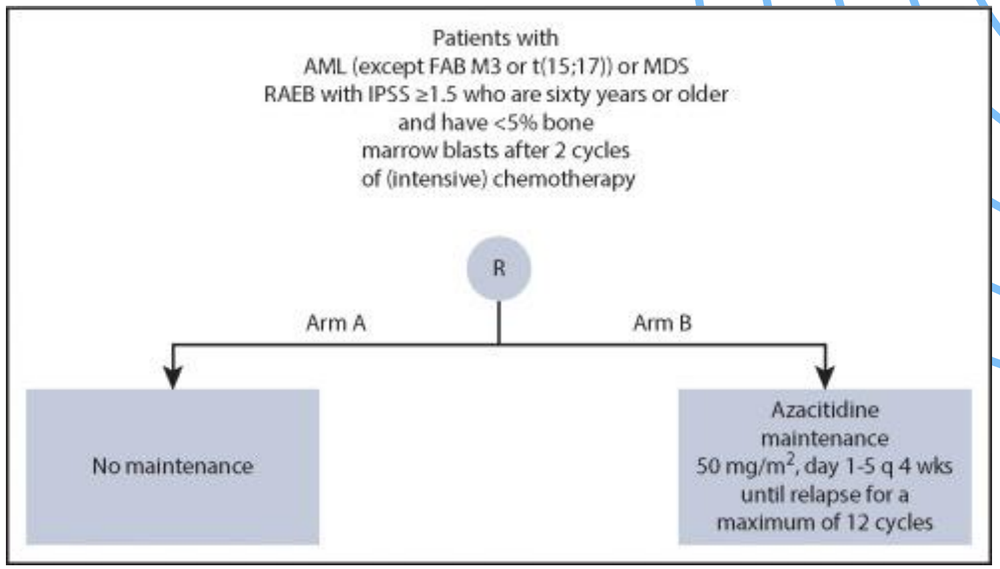
UnFit patients

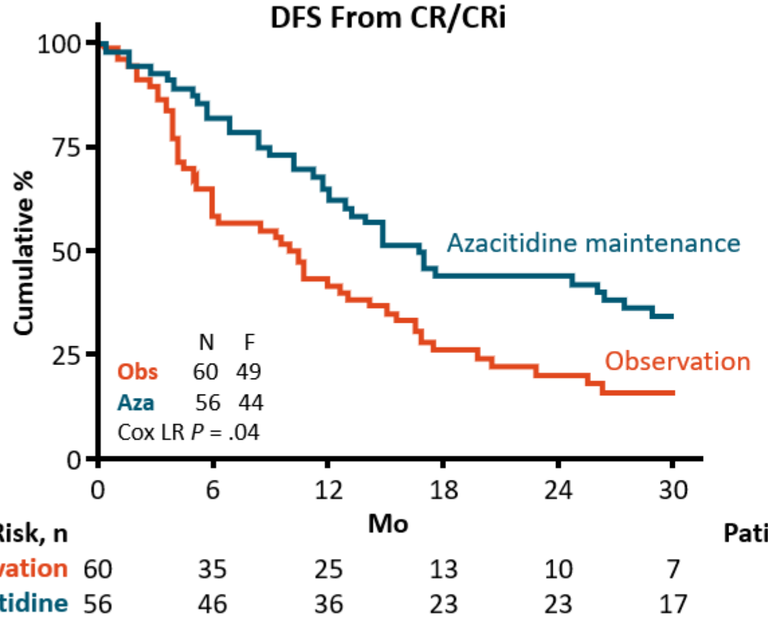
IDH Inhibitor	Indications	Key Trials
Enasidenib	▪ Adults with relapsed/refractory AML who have an *IDH2* mutation	AG221-C-001 (NCT01915498)
	▪ Adults with relapsed/refractory AML who have a susceptible *IDH1* mutation	AG120-C-001 (NCT02074839)
Ivosidenib	▪ Adults 75 yr or older or who have comorbidities that preclude use of induction chemotherapy, in combination with azacitidine or as monotherapy, for newly diagnosed AML with a susceptible *IDH1* mutation	AG120-C-009/AGILE (NCT03173248)
Olutasidenib	▪ Adults with relapsed/refractory AML with a susceptible *IDH1* mutation	Study 2102-HEM-101 (NCT02719574)

AML in remission

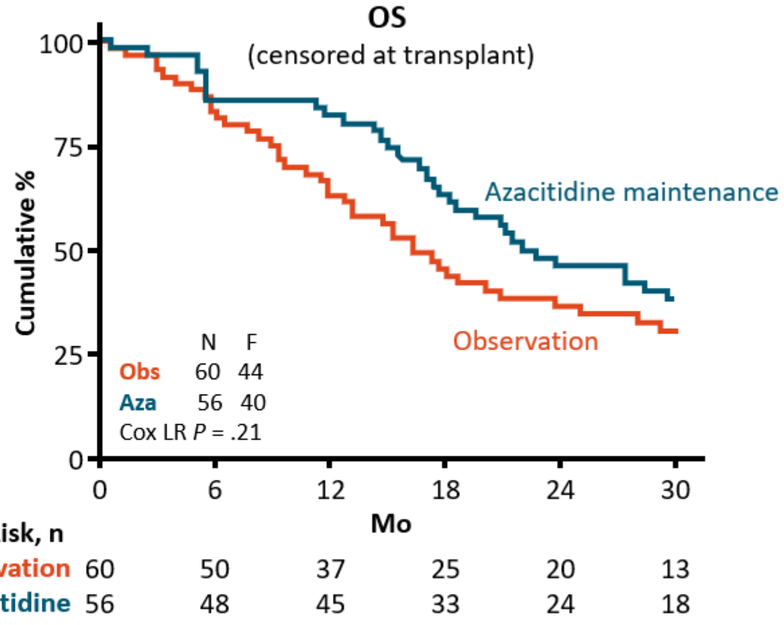
Maintenance Treatment

HOVON97





Median DFS: 15.9 vs 10.3 mo



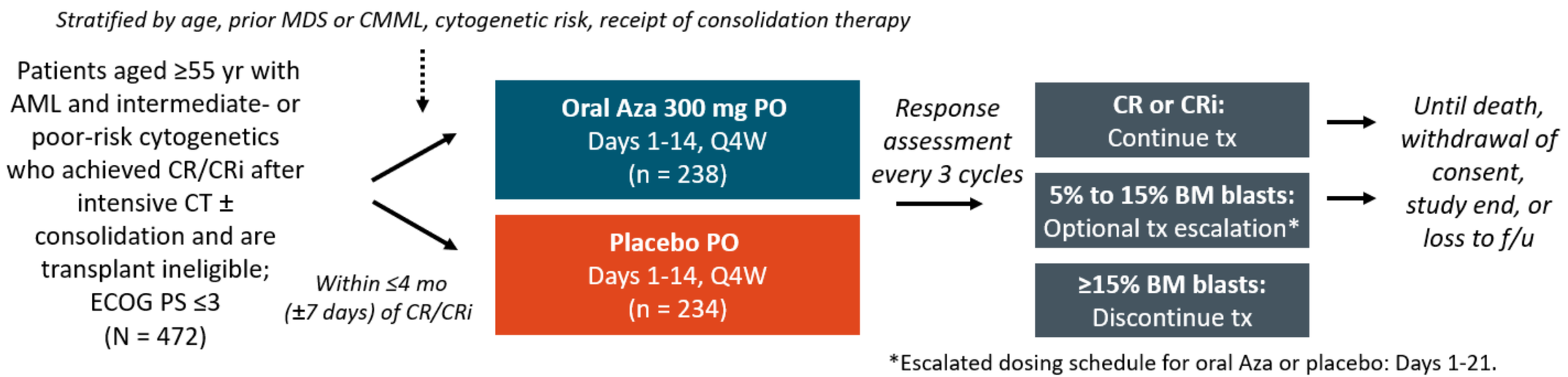
12-mo OS: 82% vs 63%

Huls. Blood. 2019;133:1457

QUAZAR 001

Oral Azacitidine in AML

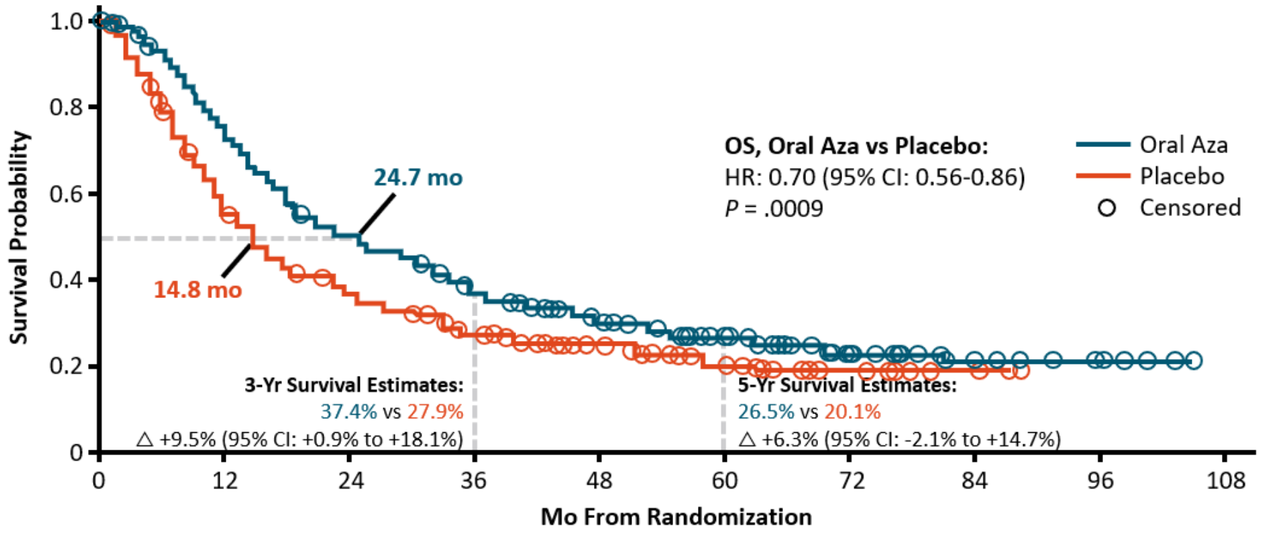
- Randomized, double-blind, placebo-controlled phase III trial

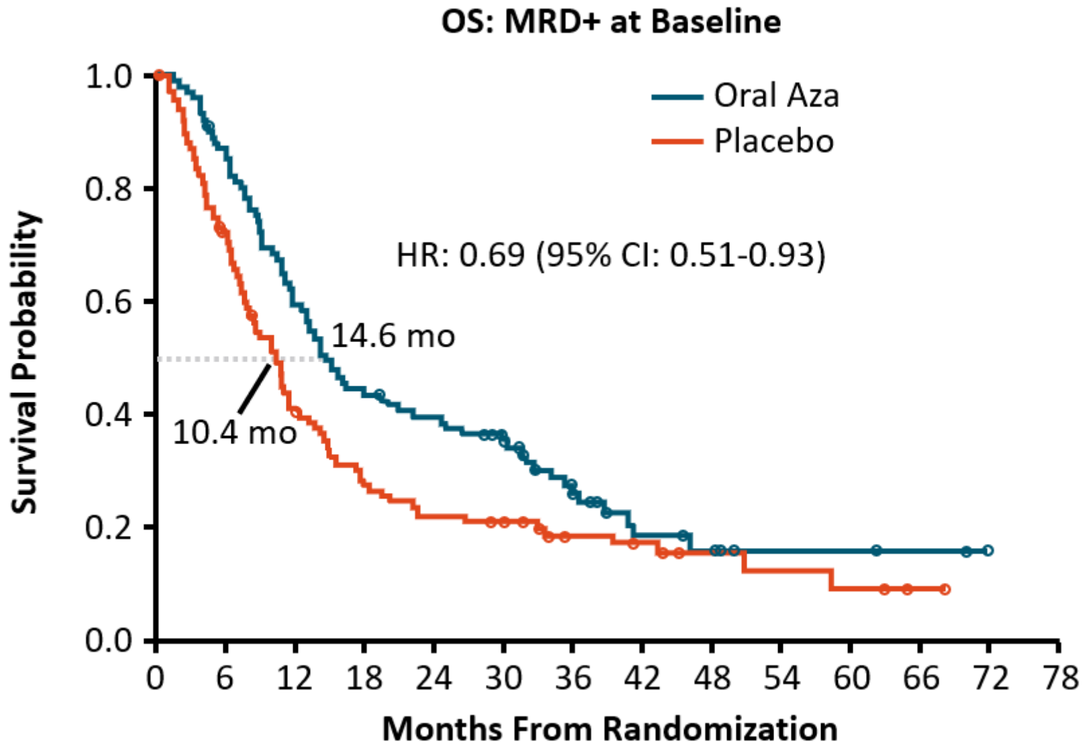


- **Primary endpoint:** OS
- **Key secondary endpoint:** RFS

Wei. Am J Hematol. 2023;98:E84. Wei. NEJM. 2020;383:2526

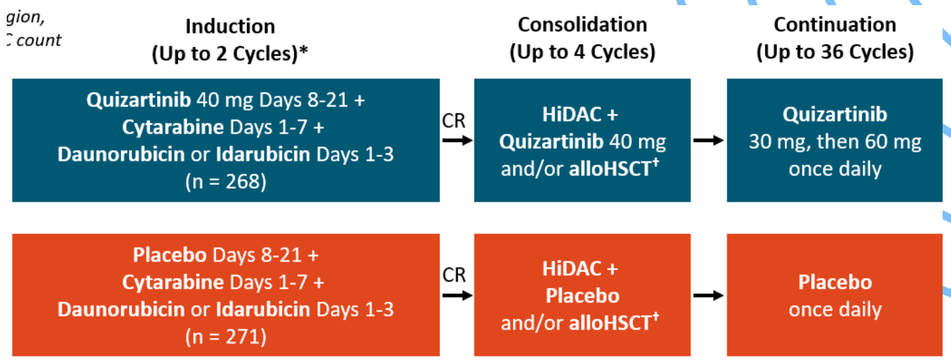
QUAZAR 001

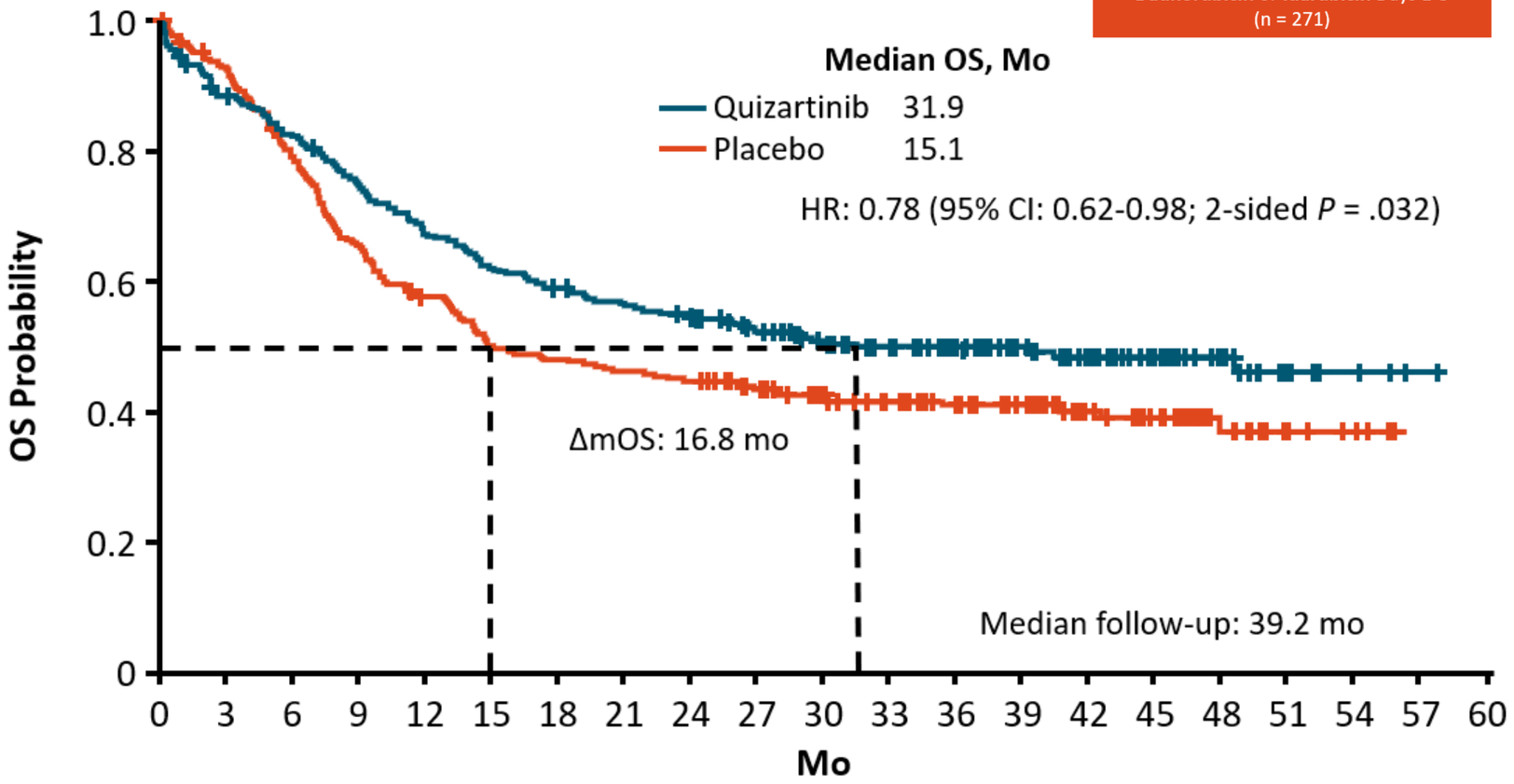




Wei. Am J Hematol. 2023;98:E84. Wei. NEJM. 2020;383:2526

QUANTUM-First





Erba. Lancet. 2023;401:1571. Erba. EHA 2022. Abstr S100

Select Ongoing Postinduction Maintenance Trials

Trial	Ph	N	Agents	Patient Population	Primary Endpoint(s)	Status
VIALE-M NCT04102020	III	112	Venetoclax + oral azacitidine vs oral azacitidine	Newly diagnosed AML in CR or CRi after induction and consolidation	DLT, RFS	Active, not recruiting
HOVON 150 AML NCT03839771	III	968	Ivosidenib or enasidenib + induction/consolidation CT, followed by ivosidenib or enasidenib maintenance	Newly diagnosed AML or MDS-EB2 with *IDH1* or *IDH2* mutation	EFS	Recruiting
HOVON 156 AML NCT04027309	III	777	Gilteritinib vs midostaurin + induction and consolidation therapy, followed by 1-yr maintenance with gilteritinib or midostaurin	Newly diagnosed AML or MDS-EB2 with *FLT3* mutations; eligible for intensive CT	EFS	Active, not recruiting
GOSSAMER NCT02927262	II	98	Gilteritinib	*FLT3*-ITD+ AML in CR1	RFS	Active, not recruiting
NCT05010772	I	125	Decitabine ± venetoclax, gilteritinib, enasidenib, or ivosidenib	AML in CR1 after consolidation/induction	Safety	Recruiting
NCT04107727	II	273	Quizartinib + CT vs placebo + CT maintenance	Untreated non–*FLT3*-ITD AML	EFS	Active, not recruiting
NCT03258931	III	510	Crenolanib vs midostaurin after induction CT and consolidation	Newly diagnosed AML with *FLT3* mutation	EFS	Recruiting

Wrap up

Maintenace Post-Induction

Patient with intermediate or adverse risk disease who meets the following criteria:

- Received intensive CT and AML is in remission
- Completed no consolidation, a recommended consolidation treatment course, or some consolidation
- No alloHSCT planned

→

Recommended maintenance therapy until PD or unacceptable toxicity:

- Oral azacitidine (category 1, preferred for age ≥55 yr)*
- Azacitidine (category 2A)
- Decitabine (category 2B)

Oral azacitidine is not intended to replace consolidation CT.

Patient with history of *FLT3*-ITD mutation:

- Received quizartinib
- No alloHSCT planned

→

FLT3 inhibitor maintenance:

- Quizartinib (*FLT3*-ITD only)

AML after HSCT

Maintenance Treatment

SORMAIN

Sorafenib Maintenance After AlloHSCT in FLT3-ITD AML

- Primary analysis of international, randomized, double-blind phase II trial

Patients with *FLT3*-ITD+ AML who underwent alloHSCT; within 60-100 days post transplant; in CHR with normal PB; ECOG PS 0/1; no GvHD grade 2-4 (N = 83*)

→ **Sorafenib** 2 x 400 mg QD† for 24 mo (n = 43)

→ **Placebo** QD† for 24 mo (n = 40)

→ ***Follow-up***

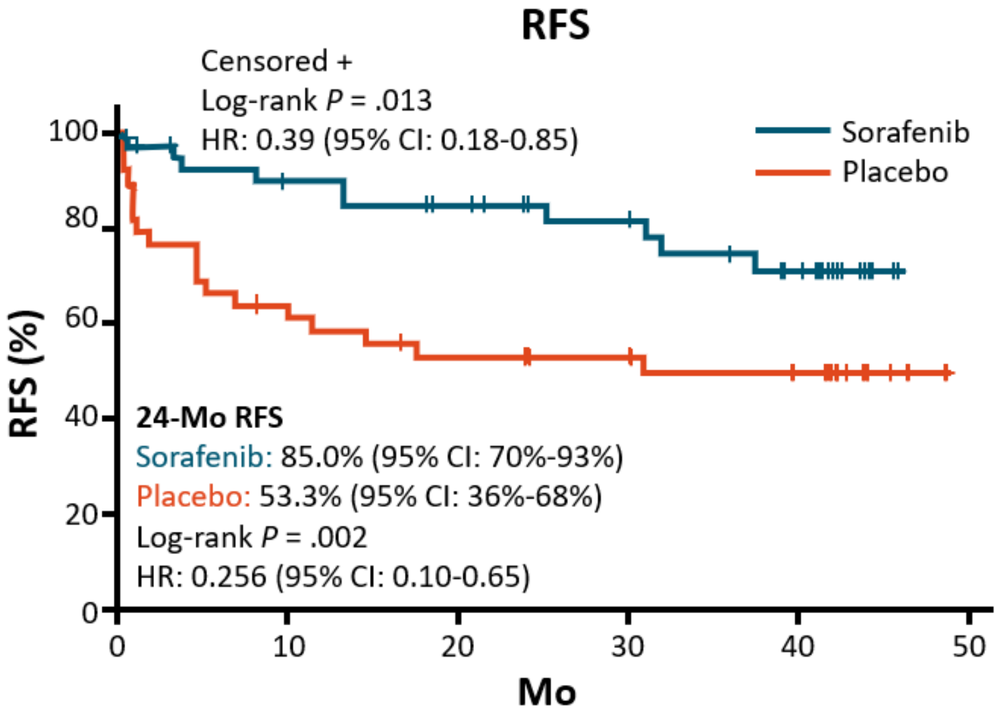
*Planned N = 184. Study ended early because of slow accrual. †Starting dose of 2 x 200 mg, increased every 14 days up to 2 x 400 mg as tolerated.

- **Primary endpoint:** RFS rate, where RFS events were death from any cause or relapse of AML
- **Secondary endpoints:** OS; RFS and OS in patients with *NPM1*-mutated vs wild-type disease; RFS and OS by *FLT3*-ITD ratio; safety; biomarker analysis

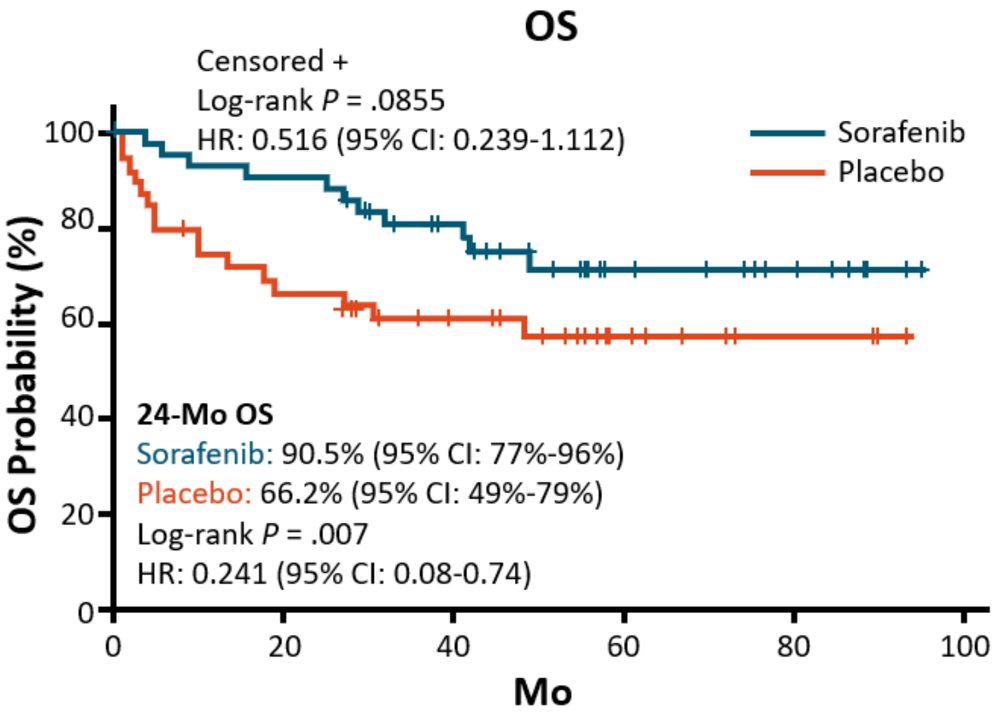
Burchert. JCO. 2020;38:2993. Burchert. ASH 2018. Abstr 661

SORMAIN

Sorafenib Maintenance After AlloHSCT in FLT3-ITD AML



- Median f/u: 41.8 mo
- mRFS (sorafenib vs placebo): NR vs 30.9



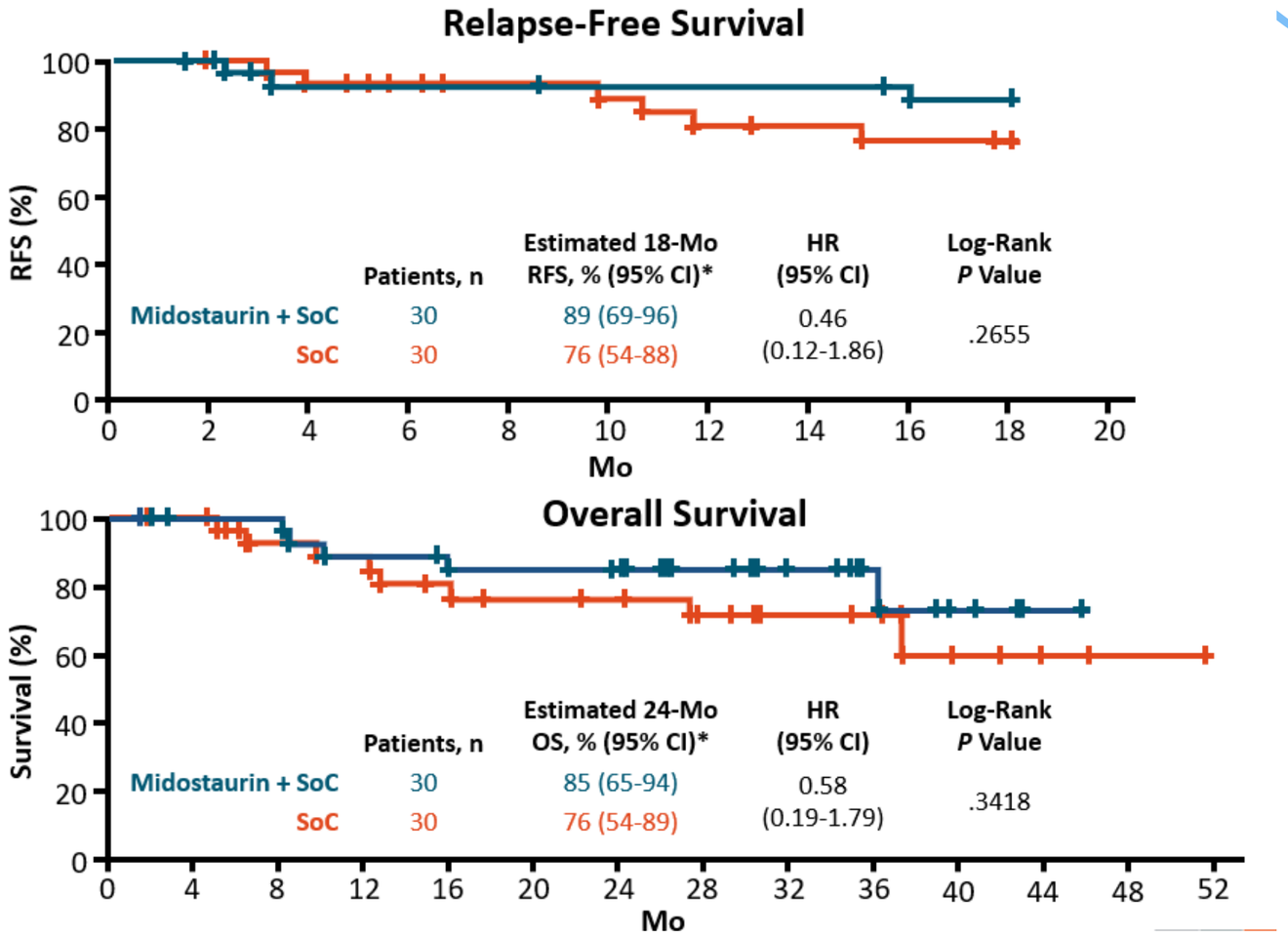
- Median f/u: 55.1 mo
- mOS NR in either treatment arm

Burchert. JCO. 2020;38:2993. Burchert. ASH 2018. Abstr 661

RADIUS

Midostaurin Maintenance After AlloHSCT in FLT3-ITD+ AML

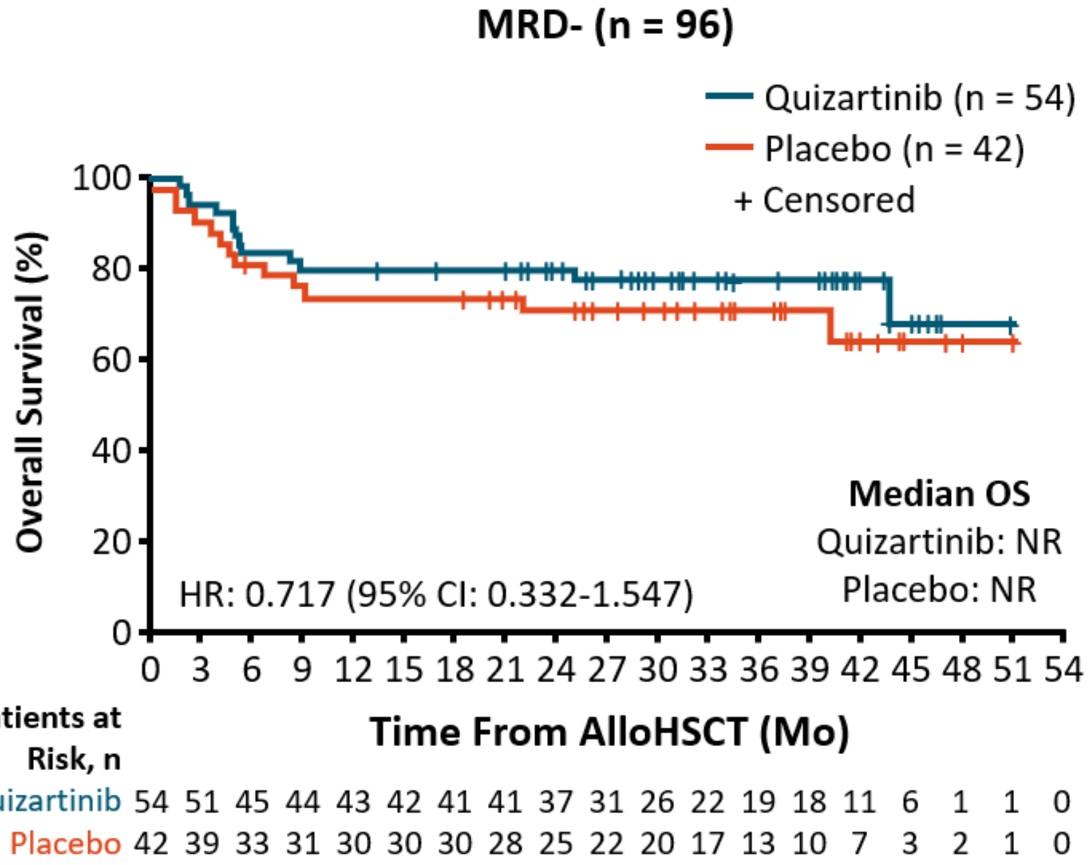
- Open-label, randomized phase II trial in adults with *FLT3*-ITD+ AML with CR1 after matched unrelated donor/matched related donor alloHSCT (N = 60)
- Comparing midostaurin + SoC vs SoC maintenance for up to 12 cycles
- **Primary endpoint:** RFS (18 mo post alloHSCT)
- **Key secondary endpoints:** OS, RFS (24 mo post alloHSCT), safety

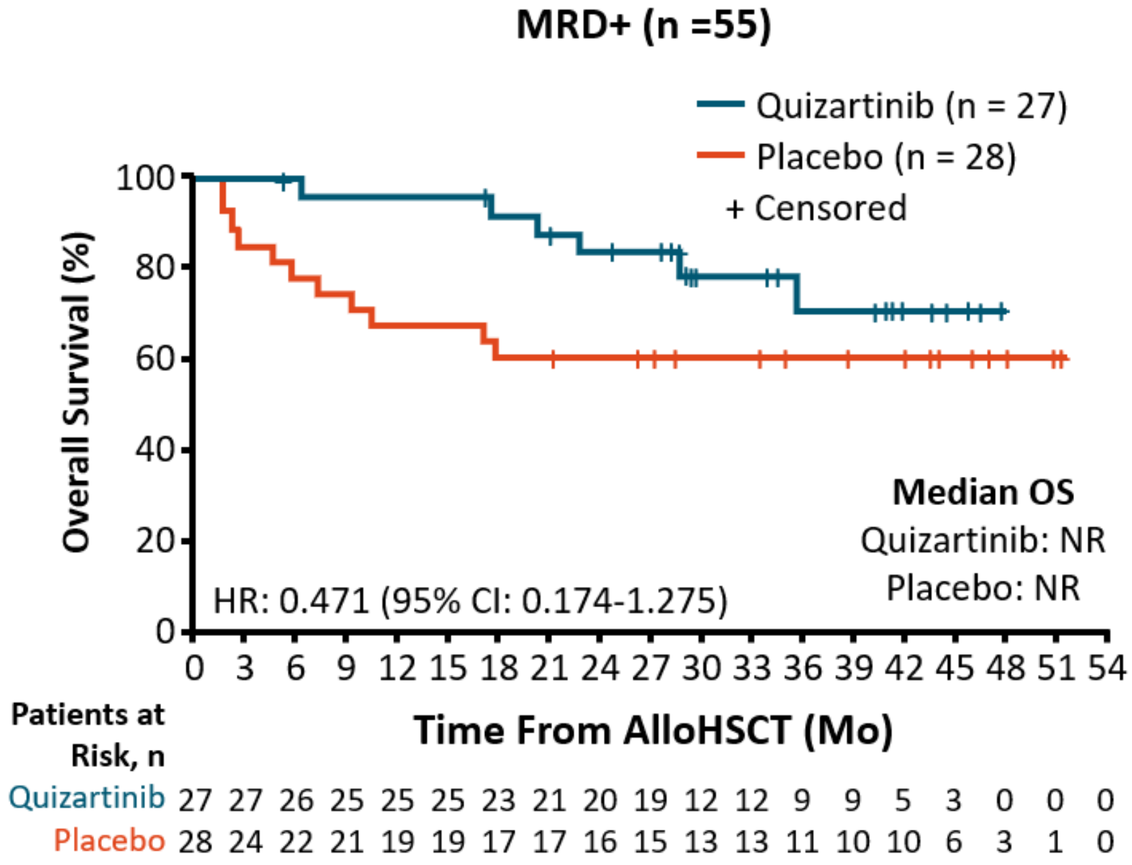


Maziarz. Bone Marrow Transplant. 2021;56:1180. NCT01883362

QUANTUM-First

Quizartinib in Patients Who Received AlloHSCT in CR1



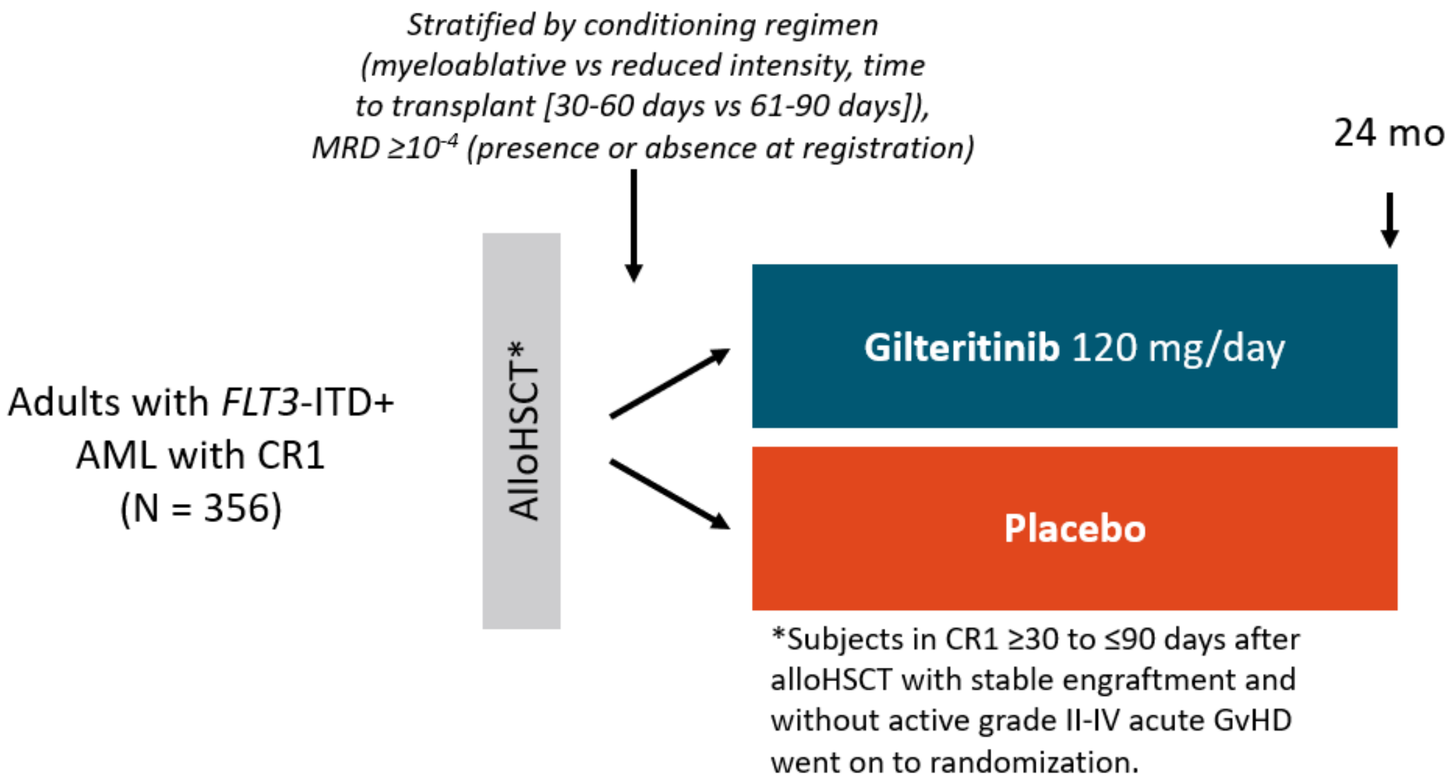


Schlenk. SOHO 2023. Abstr CT-186

MORPHO

Gilteritinib vs Placebo as Posttransplant Maintenance in FLT3-ITD+ AML

- Multicenter, randomized, double-blind, placebo-controlled phase III trial

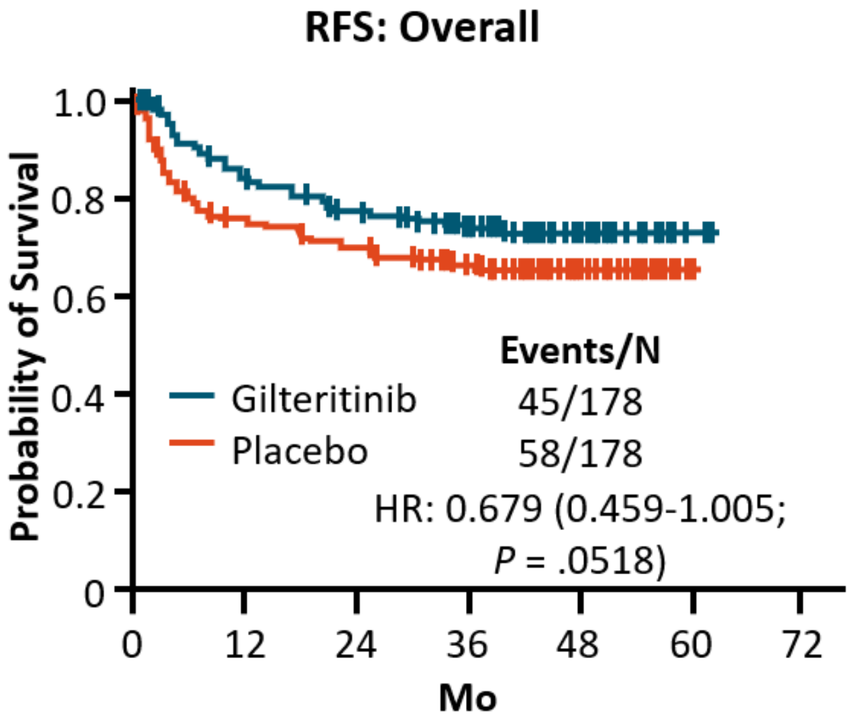


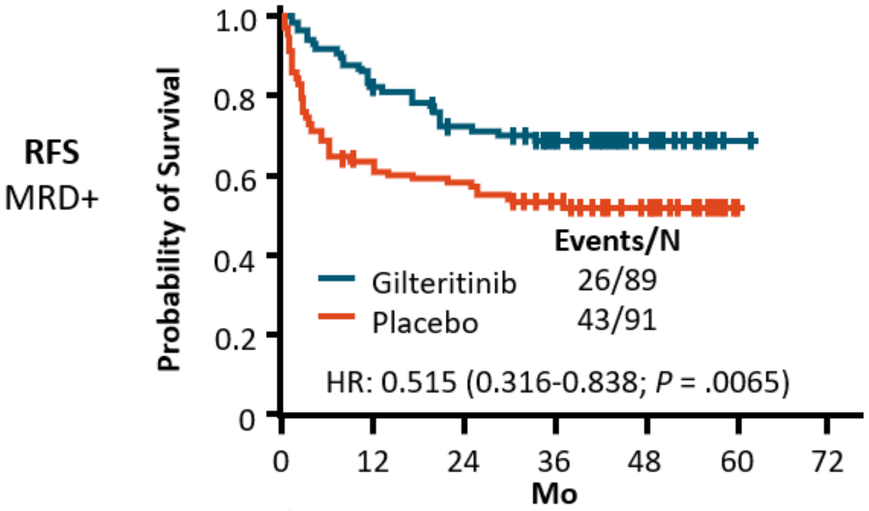
- **Primary endpoint:** RFS
- **Key secondary endpoints:** OS, EFS, GvHD incidence, safety, nonrelapse mortality
- Marrow samples for MRD analysis were collected pre transplant, pre randomization, and at 3, 6, 12, 18, and 24 mo post randomization

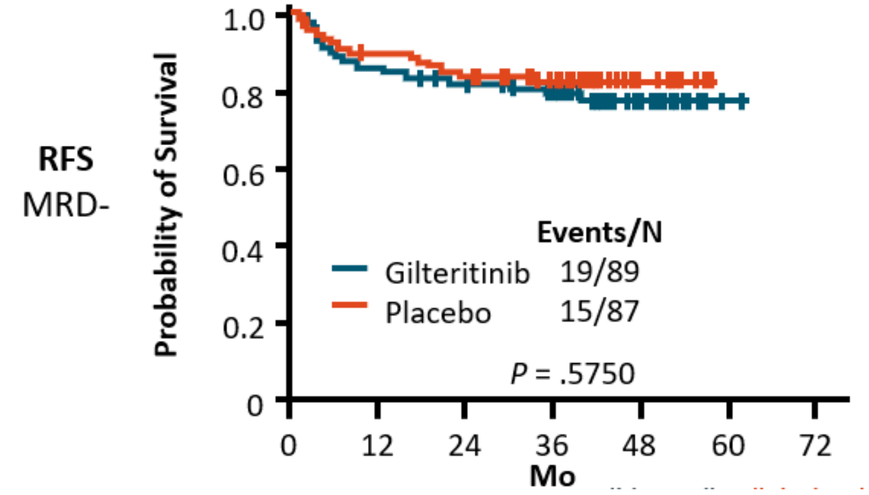
Levis. EHA 2023. Abstr LB2711. NCT02997202.

MORPHO

Gilteritinib vs Placebo as Posttransplant Maintenance in FLT3-ITD+ AML





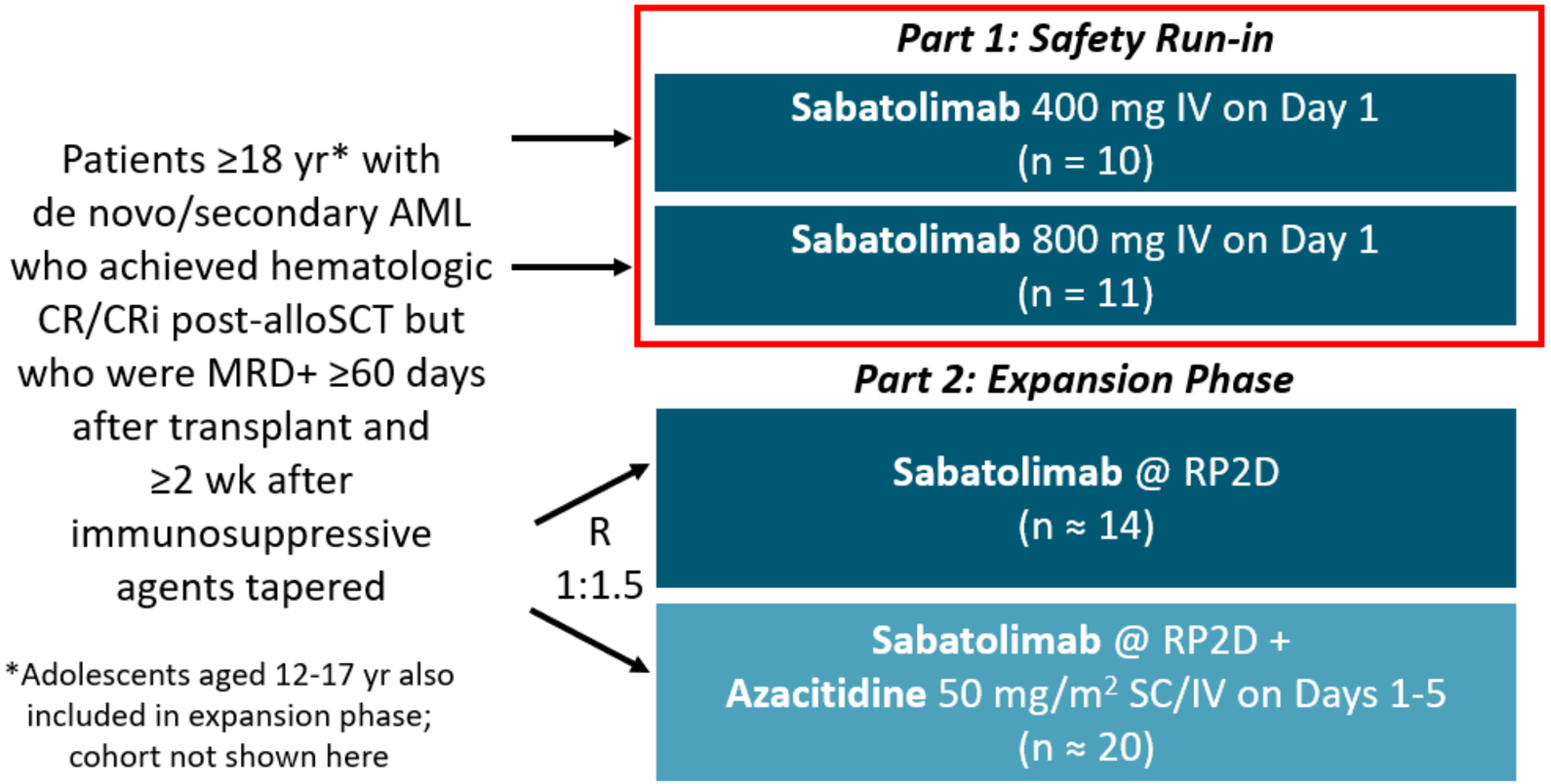


Levis. EHA 2023. Abstr LB2711. NCT02997202.

STIMULUS-AML2

novel monoclonal antibody targeting TIM-3

- Multicenter, open-label, phase Ib/II trial



- Primary endpoint for safety run-in: treatment-emergent DLTs, including acute or chronic GVHD during first 2 cycles
- Primary endpoint for safety run-in and dose expansion: no hematologic relapse after 6 cycles of therapy

Zeiser. ASH 2023. Abstr 59

STIMULUS-AML2

- 7 (33.3%) patients remain on treatment and in hematologic CR at time of data cutoff
- In sabatolimab 400 mg arm:
  - 3 of 10 patients still in CR after >1 yr on treatment
    - 2 patients had received 14 cycles, 1 had received 15 cycles
- In sabatolimab 800 mg arm:
  - 4 of 11 patients in CR
    - 1 patient had received 5 cycles, 1 had received 6 cycles, and 2 had received 7 cycles
- Preliminary efficacy appears promising
  - Longer-term follow-up of sabatolimab 400 mg cohort found 30% of patients still in CR after >1 yr on treatment
  - Data suggest onset of relapse may be delayed
- Dose-expansion cohort of sabatolimab 800 mg ± azacitidine in adults opened for enrollment in June 2023

Zeiser. ASH 2023. Abstr 59

HMA Post-HSCT Maintenance Trials

Trial	Ph	N	Agents	Patient Population	Key Results
VZ-AML-PI-0129[1] NCT00887068	III	187	Azacitidine vs supportive care	AML or MDS in CR after alloHSCT	Median RFS, yr: 2.07 vs 1.28 (*P* = .43) Median OS, yr: 2.52 vs 2.56 (*P* = .85)
CC-486-AML-002[2] NCT01835587	I/II	30	Oral azacitidine	AML or MDS	1-yr rate of relapse or PD: 21% 1-yr RPFS: 54%-72% Median OS: NR 1-yr survival: 81%-86%
ChiCTR-IIR-16008182[3]	II	220	rhG-CSF + decitabine vs no intervention	High-risk, MRD-negative AML	2-yr relapse rate: 15% vs 38.3%; HR: 0.32 (*P* <.01)
ECOG ACRIN E2906[4] NCT02085408	III	105*	Decitabine vs observation	Newly diagnosed AML in older (≥60 yr) patients; induction/consolidation, then alloHSCT followed by decitabine maintenance	4-yr OS: 42.9% 4-yr DFS: 39%
RELAZA2[5] NCT01462578	II	53	Azacitidine	MRD+ AML or MDS in CR after conventional CT or alloHSCT	12-mo RFS (MRD+): 46%

Select Ongoing Post-HSCT Maintenance Trials

Trial	Phase	N	Agents	Patient Population	Primary Endpoint(s)	Status
FLT3 Inhibitors						
NCT02400255	II	48	Crenolanib	*FLT3*-ITD+ or *FLT3*-D835+ AML	PFS	Not recruiting
IDH Inhibitors						
NCT03515512	I	23	Enasidenib	*IDH2*-mutated AML or MDS	MTD, DLT	Active, not recruiting
HMAs						
AMADEUS NCT04173533	III	324	Oral azacitidine vs placebo	AML (CR1 or CR2), secondary AML, or advanced or high-risk MDS (IPSS-R ≥3.5)	RFS	Recruiting
VIALE-T NCT04161885	III	424	Venetoclax + azacitidine + BSC vs BSC	AML (<5% BM blast after alloHSCT)	DLT, RFS	Recruiting
NCT04128501	II	125	Azacitidine + venetoclax	AML, T-cell leukemia, and mixed phenotype acute leukemia	RFS	Recruiting

Wrap up

Maintenace Post-HSCT

Patient who underwent alloHSCT and meets the following criteria:

- In remission
- History of *FLT3* mutation

→

FLT3 inhibitor maintenance:

- Sorafenib
- Midostaurin*
- Gilteritinib*
- Quizartinib (FLT3-ITD only)*

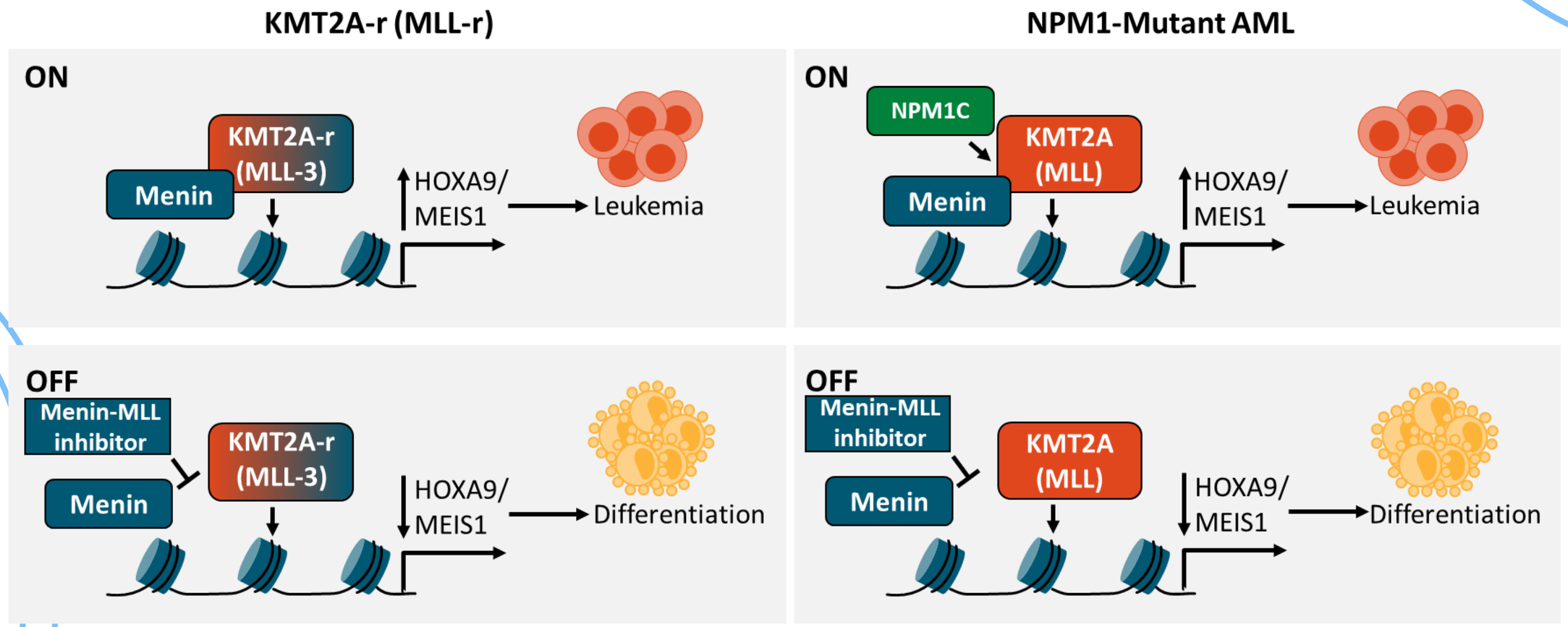
*Category 2B.

AML future

The Emerging Horizon

Menin Pathway

Menin Inhibition for MLL-Rearranged/ NPM1-Mutation AML



Borkin. Cancer Cell. 2015;27:589

AUGMENT 101

Revumenib: potent and selective oral inhibitor of the menin–KMT2A interaction

- Open-label phase I/II trial (data cutoff: July 24, 2023)

Patients ≥30 days of age with R/R *KMT2Ar* acute leukemia;* ECOG PS ≤2 or Karnofsky/Lansky score ≥50 (N = 94) → **Revumenib** 163 mg Q12H PO RP2D†‡ (28-day cycles)

*A separate cohort of patients with *NPM1*-mutant AML is still enrolling and is not described in this report. †Dose is 95 mg/m² if body weight <40 kg. ‡Plus a strong CYP3A4 inhibitor. §Lower efficacy bound of CR/CRh rate in adult evaluable population considered >10%.

- **Primary endpoint:** CR/CRh rate§
- **Secondary endpoints:** CR/CRh/CRp/CRi rate, ORR

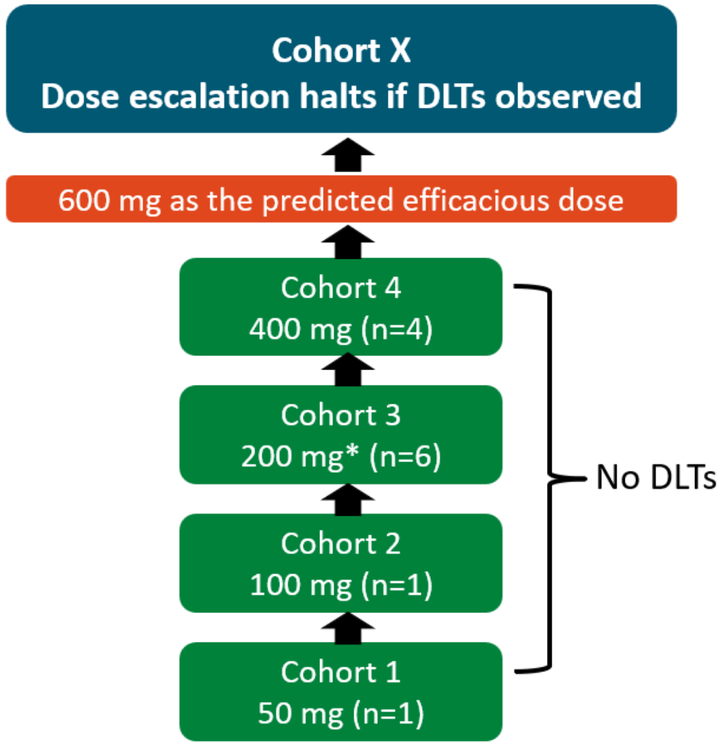
Response	Efficacy Population (n = 57)
ORR, n (%)	36 (63)
CR/CRh rate, n (%) ▪ 95% CI ▪ 1-sided *P* value	13 (23) 12.7-35.8 .0036
CR/CRh/CRp/CRi rate, n (%) ▪ 95% CI	25 (44) 30.7-57.6
MRD^{neg} status,* n/n (%) ▪ CR/CRh ▪ CR/CRh/CRp/CRi	 7/10 (70) 15/22 (68)

Parameter	Pts Achieving CR/CRh (n = 13)
Median duration of CR/CRh, mo (95% CI)	6.4 (3.4-NR)
Proceeded to HSCT, n/n (%) ▪ HSCT while in CR or CRh ▪ HSCT while in MLFS or CRp	14/36 (39) 6/14 (43) 8/14 (57)
Restarted revumenib post-HSCT, n (%)	7/14 (50)*

Aldoss. ASH 2023. Abstr LBA-5.

KOMET 001

Phase I Trial of Ziftomenib in R/R AML



*Expanded to characterize PK

Clinical activity observed in 6 patients (8 evaluable)				
Dose	**Mutational profile**	**CYP384 inhibitor**	**Prior tx, n**	**Clinical activity**
400 mg	RUNX1, SRSF2, ASXL1, TET2, STAG2, BCOR, PTPN11	Yes	3	Decreased peripheral blasts
200 mg	U2AF1, TET2, p53, DNMT3A, PTPN11	No	4	Stable disease
	NPM1, FLT3-ITD, TET2, CUX1	Yes	4	MLFS
	NPM1, DNMT3A, KMT2D	Yes	7	CR, MRD-
100 mg	SETD2, RUNX1	Yes	2	CR, MRD+
50 mg	KMT2A-r	Yes	2	Decreasing hydroxyurea requirement

- No doses discontinued due to TRAEs
- No ECG changes or interactions with azoles

- CR/CRh rate of 25%

Wang. ASH 2020. Abstr 115

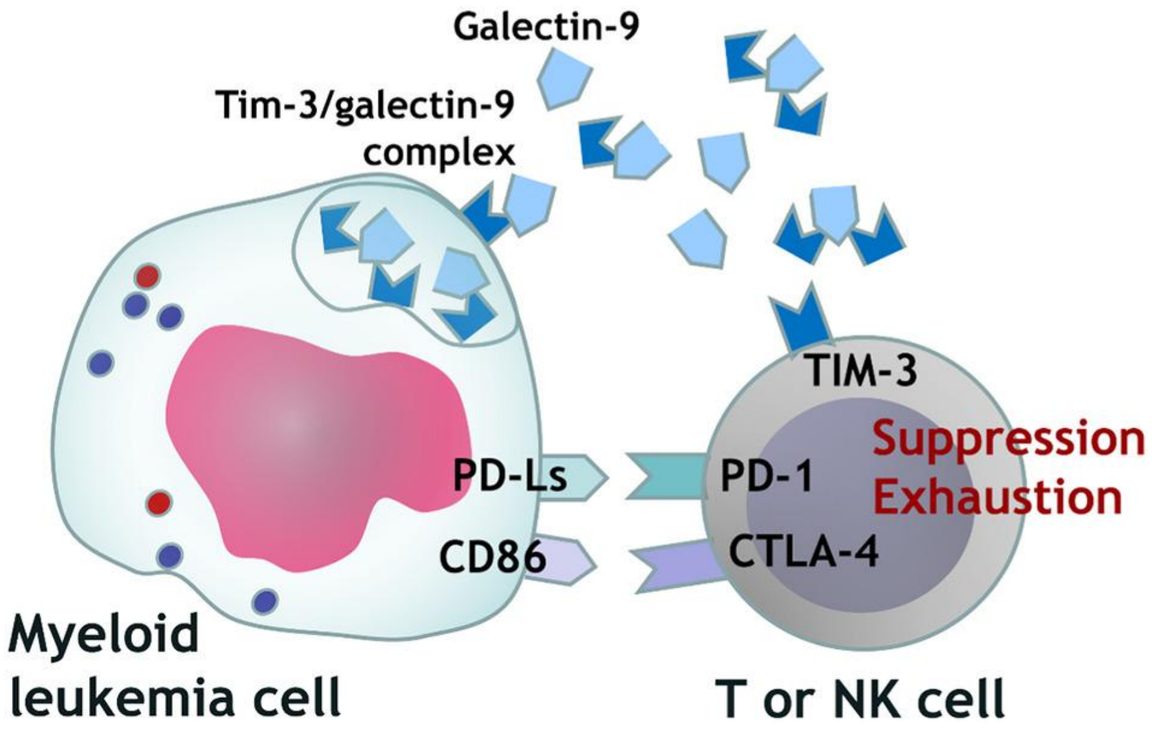
Even Newer Menin Inhibitors

TABLE 5 | Selected investigational drugs for acute myeloid leukemia.

Target	Drug	Regimens	Population	Early efficacy outcomes	Selected ongoing trials
Menin	KO-539 (ziftomenib)	Monotherapy (KOMET-001) [237]	*KMT2A* rearranged or *NPM1*-mutated R/R AML	CR/CRh—25%	KOMET-007 (NCT05735184): ND-AML and R/R AML 7 + 3 + ziftomenib aza + ven + ziftomenib KOMET-008 (NCT06001788): Ziftomenib in combination with FLAG-IDA, LDAC, or gilteritinib for the treatment of patients with R/R AML
	JNJ-75276617 (bleximenib) Enzomenib	Monotherapy [236, 269]		ORR 40%–50%	As monotherapy (NCT04811560). Combination with chemotherapy (NCT05521087). Combination aza + ven (NCT05453903).

Targeting Immune Checkpoints in AML

Inhibition of T/NK Cells by Immune Checkpoints[1]



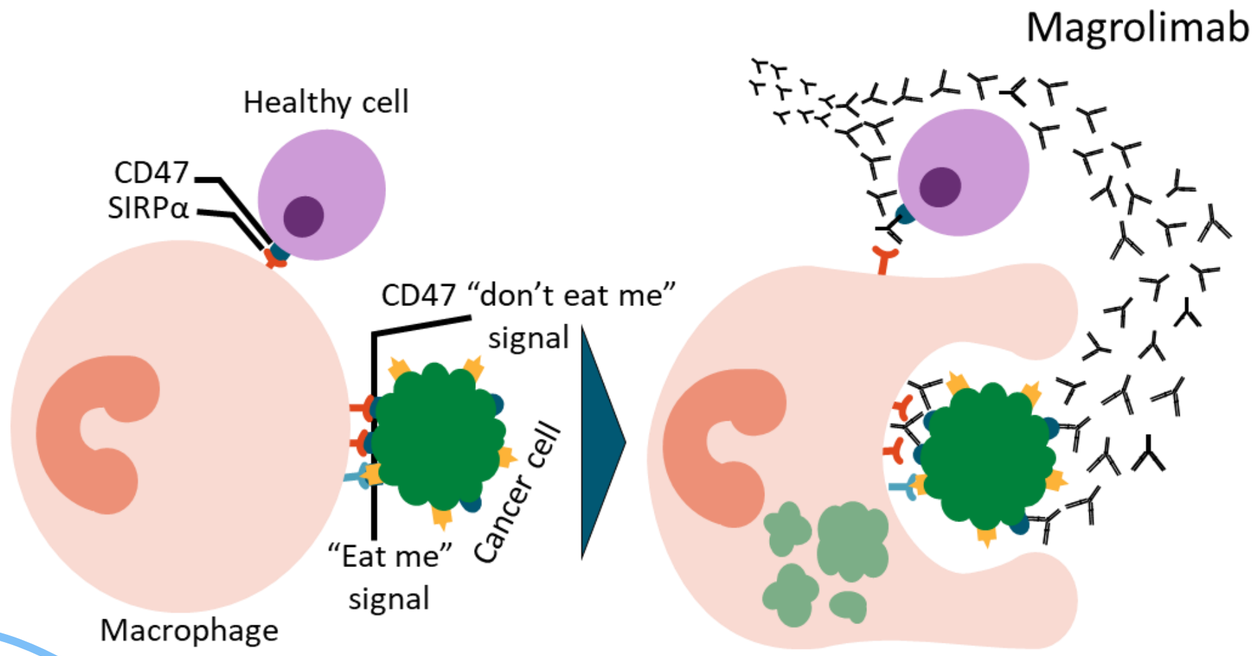
Antibodies under clinical investigation

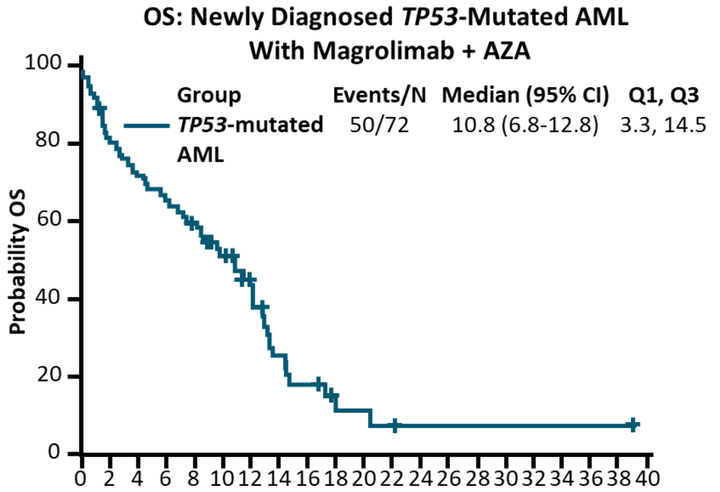
- Nivolumab (anti–PD-1)[2]
- Ipilimumab (anti–CTLA-4)[2]
- Magrolimab (anti-CD47)[3]
- Sabatolimab (anti–Tim-3)[4]

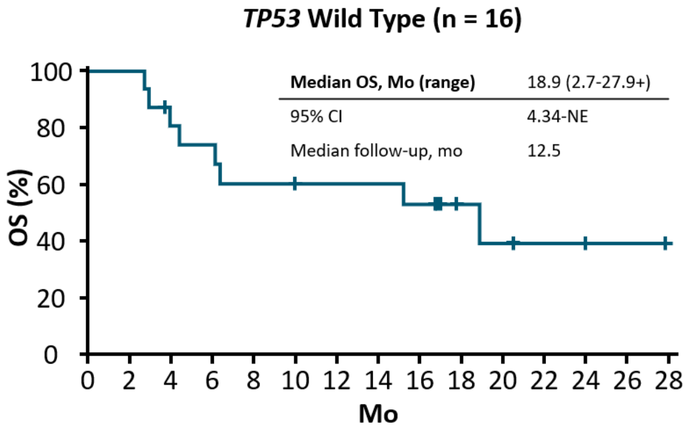
1. Kursunel. EBioMedicine. 2017;23:6. 2. Daver. ASH 2020. Abstr 1041.
3. Sallman. ASH 2020. Abstr 330. 4. Brunner. ASH 2020. Abstr 657.

ENHANCE trials

Magrolimab, an lgG4 anti-CD47 mAb eliminating tumor cells through macrophage phagocytosis







- ENHANCE trials were futile compared to Ven+Aza

Chao. Front Oncol. 2020;9:1380. Sallman. ASCO 2020. Abstr 7507. Daver. EHA. 2022. Abstr S132.

STIMULUS AML1

Anti TIM3 Ab

- Multicenter dose-escalation phase Ib

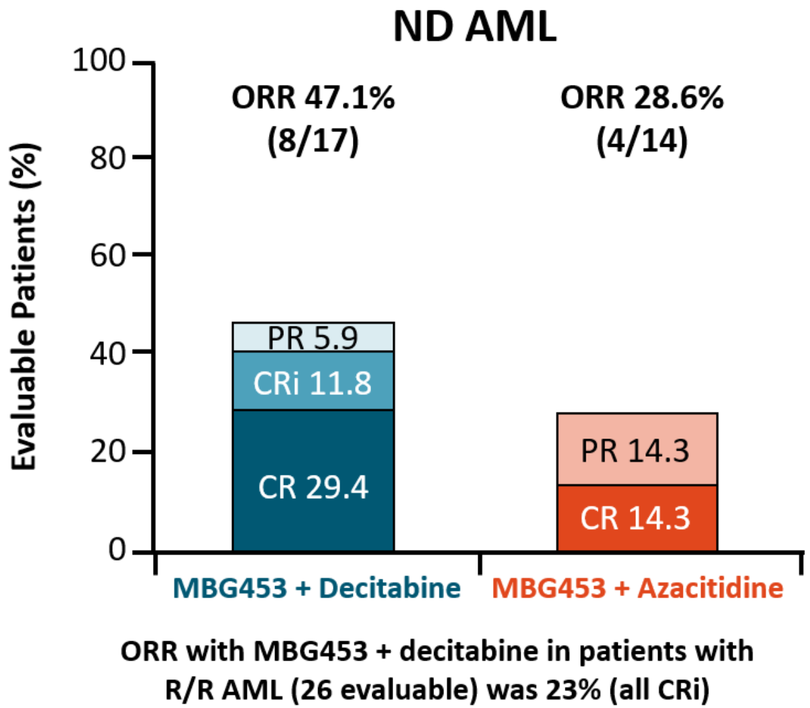
Adults with ND or R/R AML to ≥1 therapy (decitabine arm only), HMA naive, and ineligible for induction chemotherapy (N = 50)

→ **Decitabine** 20 mg/m² Days 1-5 + **MBG453*** every 28 days

→ **Azacitidine** 75 mg/m² Days 1-7 + **MBG453*** every 28 days

*Escalating doses of MBG453 were given IV at 240 or 400 mg Q2W (Days 8, 22) or 800 mg Q4W (Day 8).

- Primary endpoint: safety and tolerability
- Secondary endpoints: PK, efficacy (by IWG)



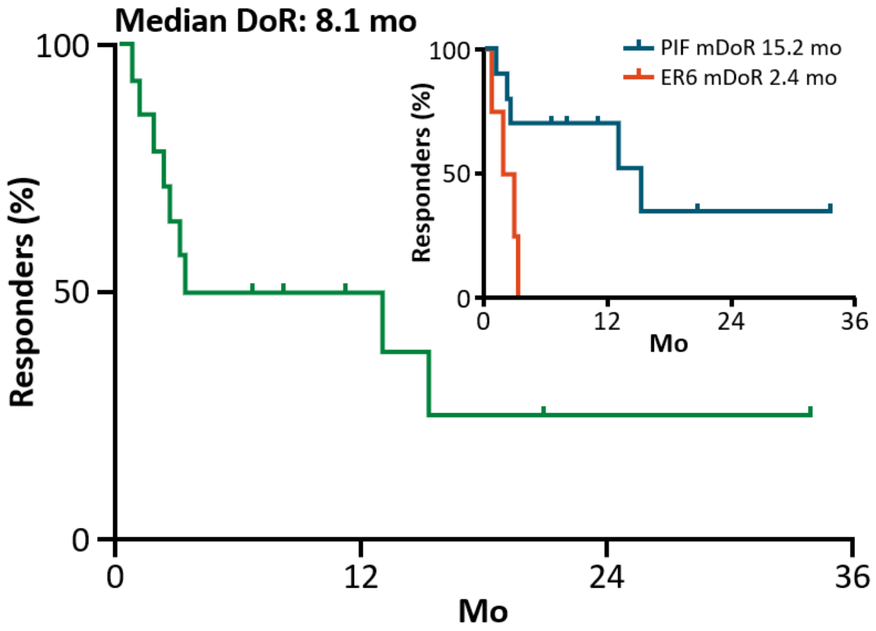
ORR with MBG453 + decitabine in patients with R/R AML (26 evaluable) was 23% (all CRi)

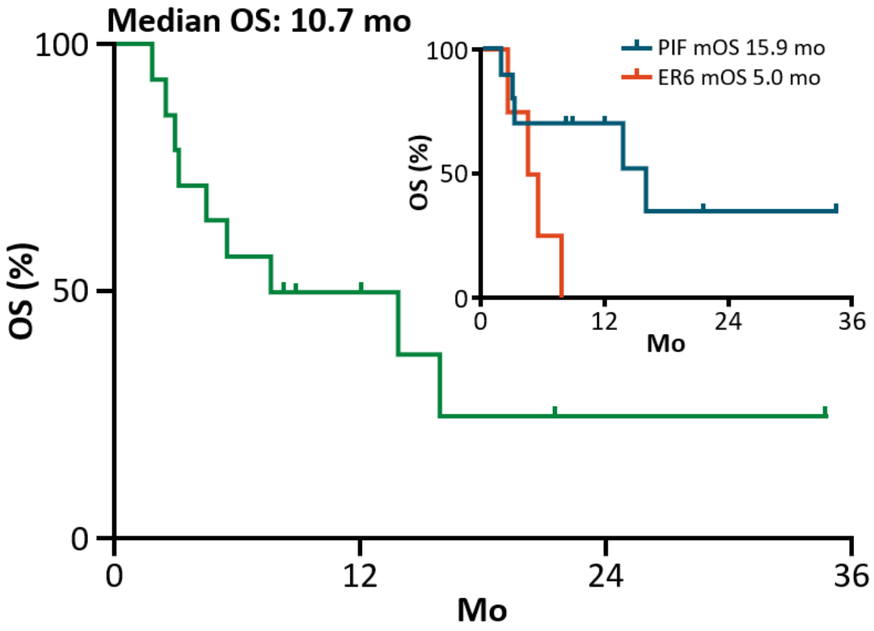
- Discontinued after STIMULUS-MDS2 failed vs. Azacitidine

Borate. EHA 2020. Abstr S185

FLUTETUZUMAB

- Bivalent, bispecific (CD3 x CD123) coengaging T-cells with a tumor-associated antigen
- Dual-affinity retargeting agent (DART)
- Engineered to redirect T-cells to kill tumor cells & recognize tumors regardless of TCR, MHC
- The complete remission (CR)/CR with partial hematological recovery (CRh) rate was 26.7%





*ER6, early relapse <6 mo; PIF, primary induction failure.

Aldoss. ASH 2020. Abstr 331

Anti CD123

Tagraxofusp

- Truncated diphtheria toxin bound to IL-3
- In combination with azacitidine + venetoclax showed a promising CR/CRi rate of 59% in ND-AML patients with adverse risk ND-AML

Pivekimab sunirine

- Antibody-drug conjugate with an indolinobenzodiazepine pseudodimer antibody drug payload
- 17% CR/CRi/CRh rate in R/R AML

- Both under investigation in phase II trials with HMA + Venetoclax

Aldoss. ASH 2020. Abstr 331

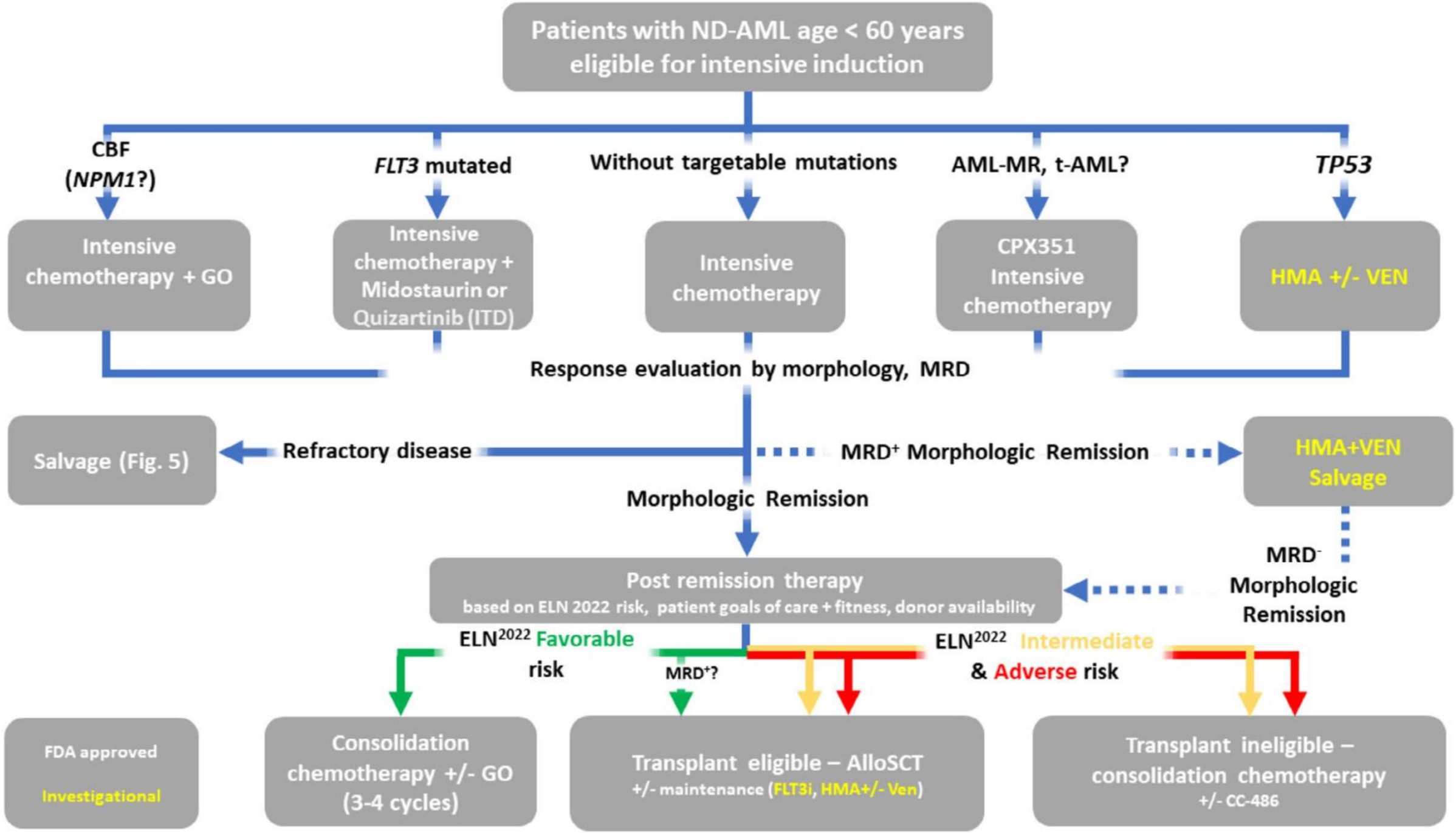
uproleselan

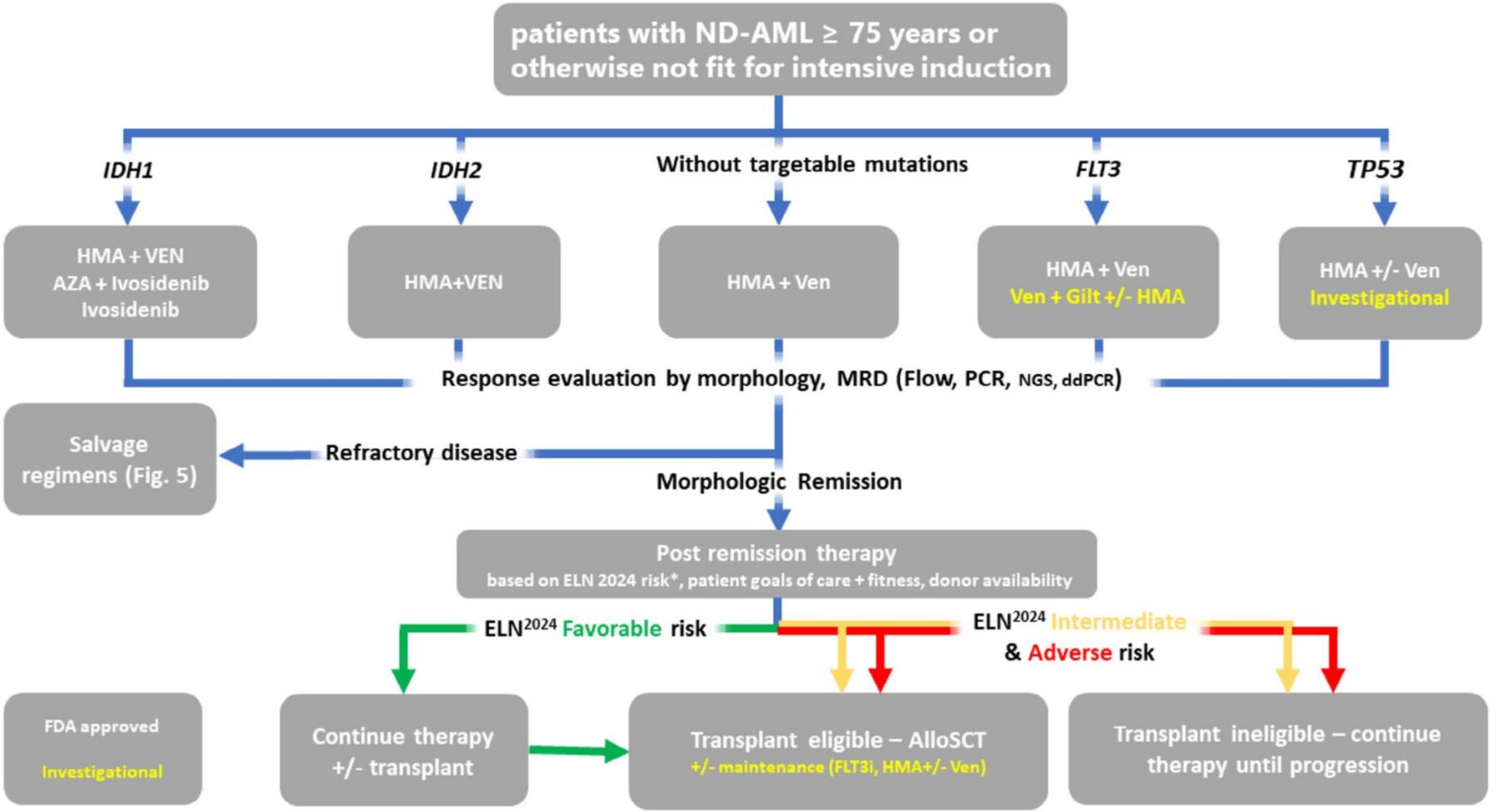
- E-Selectin Inhibitor
- Disrupts the leukemia stem cell-niche interaction
- Failed to improve OS in combination with chemotherapy in patients with R/R AML

- A phase II/III trial of chemotherapy +/-uproleselan in ND-AML older than 60 years

  (NCT03701308) has completed accrual but results are not yet available

Aldoss. ASH 2020. Abstr 331


Patients with ND-AML age < 60 years eligible for intensive induction
CBF (NPM1?)
FLT3 mutated
Without targetable mutations
AML-MR, t-AML?
TP53
Intensive chemotherapy + GO
Intensive chemotherapy + Midostaurin or Quizartinib (ITD)
Intensive chemotherapy
CPX351 Intensive chemotherapy
HMA +/- VEN
Response evaluation by morphology, MRD
Salvage (Fig. 5)
Refractory disease
MRD+ Morphologic Remission
HMA+VEN Salvage
Morphologic Remission
MRD- Morphologic Remission
Post remission therapy
based on ELN 2022 risk, patient goals of care + fitness, donor availability
ELN2022 Favorable risk
MRD+?
ELN2022 Intermediate & Adverse risk
FDA approved
Investigational
Consolidation chemotherapy +/- GO (3-4 cycles)
Transplant eligible – AlloSCT
+/- maintenance (FLT3i, HMA+/- Ven)
Transplant ineligible – consolidation chemotherapy
+/- CC-486


patients with ND-AML ≥ 75 years or otherwise not fit for intensive induction
IDH1
IDH2
Without targetable mutations
FLT3
TP53
HMA + VEN
AZA + Ivosidenib
Ivosidenib
HMA+VEN
HMA + Ven
HMA + Ven
Ven + Gilt +/- HMA
HMA +/- Ven
Investigational
Response evaluation by morphology, MRD (Flow, PCR, NGS, ddPCR)
Salvage regimens (Fig. 5)
Refractory disease
Morphologic Remission
Post remission therapy
based on ELN 2024 risk*, patient goals of care + fitness, donor availability
ELN2024 Favorable risk
ELN2024 Intermediate & Adverse risk
FDA approved
Investigational
Continue therapy +/- transplant
Transplant eligible – AlloSCT
+/- maintenance (FLT3i, HMA+/- Ven)
Transplant ineligible – continue therapy until progression

- Our knowledge about AML has expanded exponentially
- The therapeutic landscape has changed dramatically

Once a simple one-way road is now a complex labyrinth