4th edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, March 26-27, 2026

Starhotels Majestic

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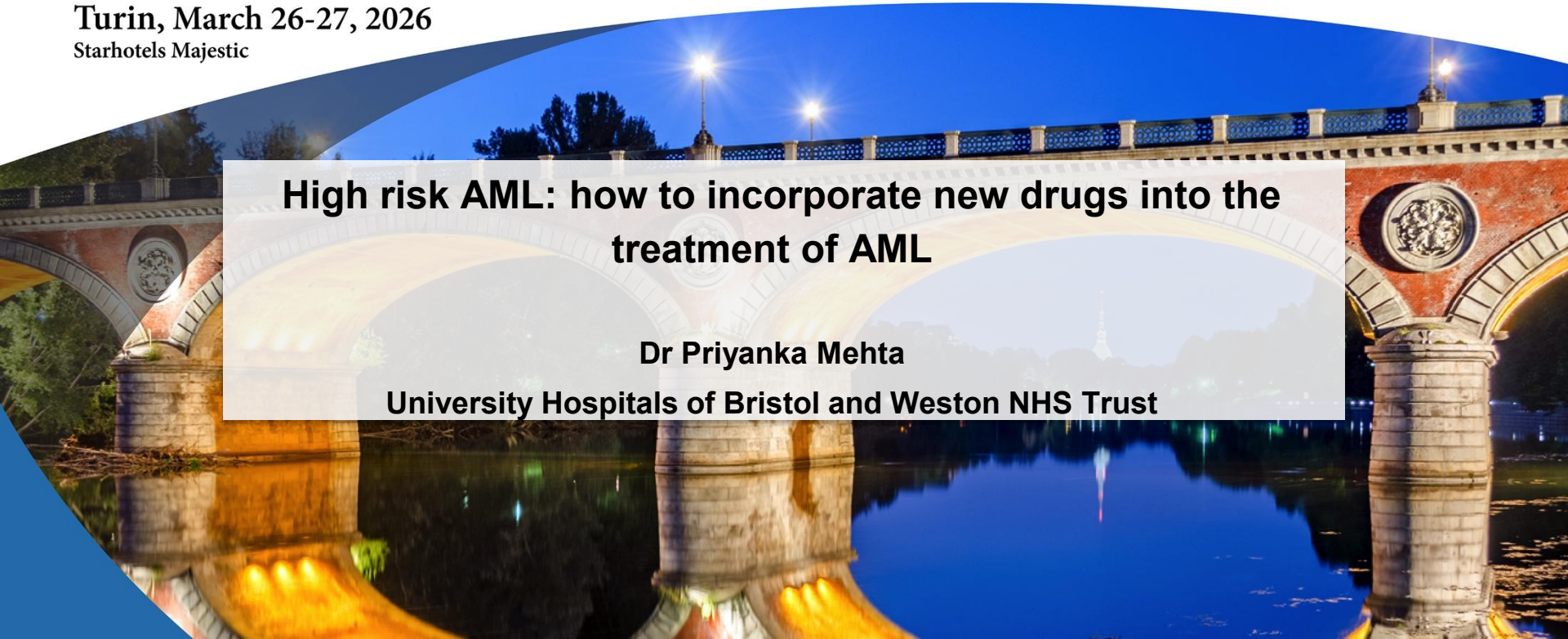

High risk AML: how to incorporate new drugs into the treatment of AML

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Disclosures of Priyanka Mehta

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					Yes		
Astellas			yes		yes		
Daiichi Sankyo			yes		yes		
Jazz Pharmaceuticals	yes		yes		yes	yes	
Pfizer					yes		
Servier					yes		
Novartis					yes		
Menarini					yes		

Topics

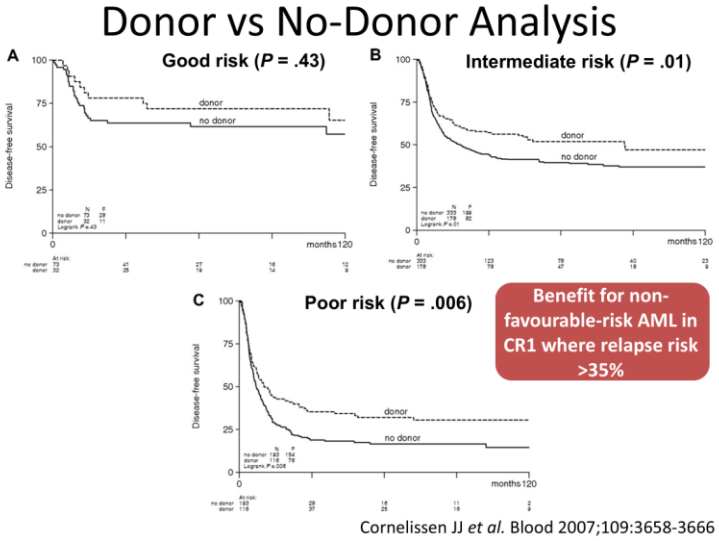
- What is high risk AML?
- New drugs in frontline treatment of fit and unfit patients
- New drugs in the relapsed AML setting
- New uses of old drugs

What is High-Risk AML?

- **Clinical Features:**
  - Older age (generally >60 years) at diagnosis.
  - Poor performance status or significant comorbidities.
  - High white blood cell count at diagnosis.

- **Genetic and Molecular Abnormalities:**
  - Certain chromosomal abnormalities such as complex karyotype (three or more chromosomal abnormalities), monosomal karyotype.
  - Specific gene mutations like TP53 mutations, FLT3-ITD with high allelic ratio, or mutations in ASXL1, RUNX1, or others.
  - Secondary AML, which arises after prior chemotherapy, radiation, or from a pre-existing blood disorder such as myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN).
- **Response to Treatment:**
  - Failure to achieve remission after initial induction chemotherapy.
  - Persistent or rising Measurable Residual Disease (MRD)
  - Early relapse after initial remission.

High risk AML patients= high risk of relapse



Cornelissen JJ *et al.* Blood 2007;109:3658-3666

Selection of patients with acute myeloid leukaemia in first complete remission for allogeneic stem cell transplantation (allo-SCT), based on relapse risk

2017 ELN Risk stratifications by genetics	MRD after cycle 2 chemotherapy	Estimated risk of relapse, based on consolidation with:		Maximal tolerated NRM prognostic scores for allo-SCT to be beneficial	
		Chemotherapy alone (%)	Allo-SCT (%)	HCT-CI score	NRM risk (%)
Favourable	Negative	25–35	15–20	N/A (<1)	5
	Positive	70–80	30–40	≤3–4	<30
Intermediate	Negative	50–60	25–30	≤2	<20
	Positive	70–80	30–40	≤3–4	<30
Adverse	N/A	>90	45–55	<5	<35

Loke J et al; Br J Haematol. 2020 Jan; 188(1): 129–146 (Döhner et al., 2017; Schuurhuis et al., 2018) and estimate of non-relapse mortality (NRM) (Sorror et al., 2014), adapted from Cornelissen and Blaise (2016).

High Risk AML fit patients: aim is to get an Allogeneic SCT

ELN 2022 AML Risk Stratification

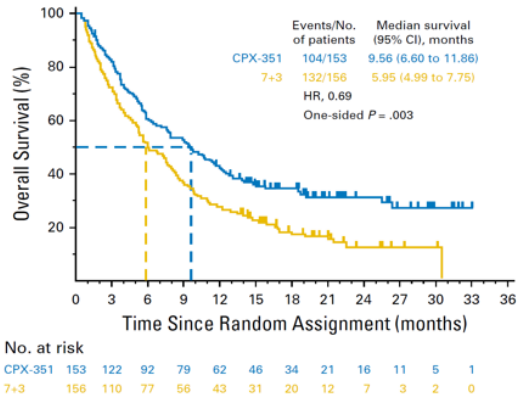
Risk category	Genetic abnormality
Favourable	t(8;21)(q22;q22.1); RUNX1::RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB::MYH11 Mutated NPM1 without FLT3-ITD bZIP in-frame mutated CEBPA
Intermediate	Mutated NPM1 with FLT3-ITD Wild type NPM1 with FLT3-ITD t(9;11)(p21.3;q23.3); MLLT3::KMT2A Cytogenetic and/or molecular abnormalities not classified as favourable or adverse
Adverse	t(6;9)(p23;q34.1); DEK::NUP214 t(v;11q23.3); KMT2A-rearranged (excluding KMT2A PTD) 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(EV11)-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

AML with MR gene mutations is now categorised in the **adverse-risk group**

Döhner H, et al. *Blood* 2022;140(12):1345–1377.

Treating Secondary and therapy related AML: Study 301

1



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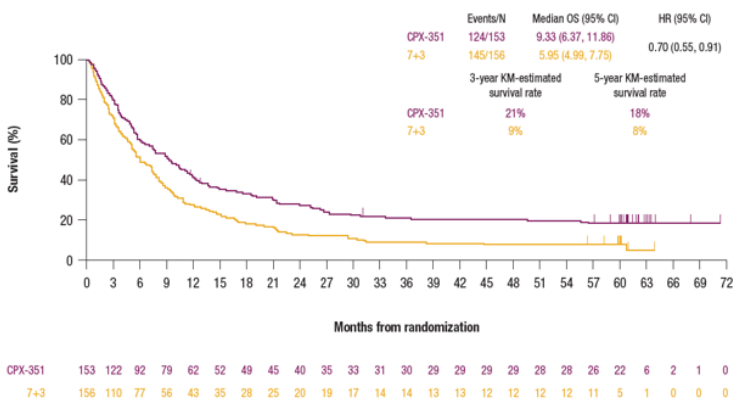
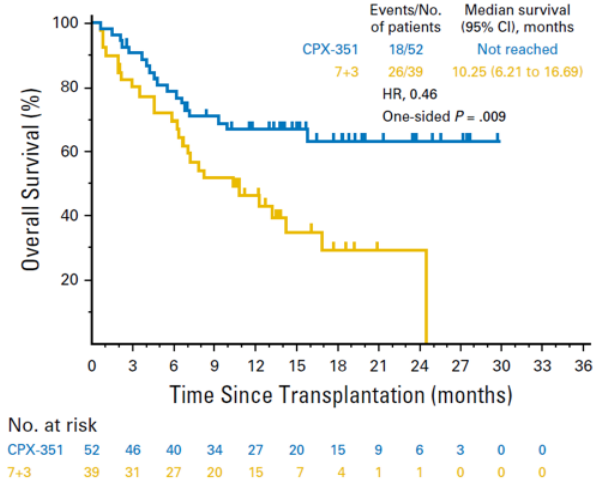


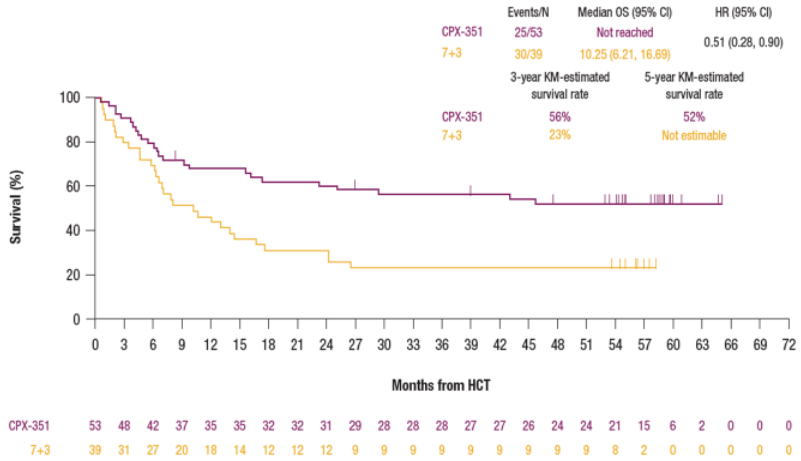
- Higher CR+CRi rate: 47.7% vs 33.3%[1]
- 31% reduction in the risk of death for patients treated with Vyxeos Liposomal vs. 3+7 (HR 0.69 [95% CI 0.52, 0.90])[1]

1.Lancet JE, *et al.* J Clin Oncol 2018;36(26):2684–2692
2.Lancet JE, *et al.* Lancet Haematol 2021;8(7):e481–e491

CR, complete remission; CRi, complete remission with incomplete neutrofil and platelet count recovery

Study 301: Post SCT survival at 2 years and 5 years

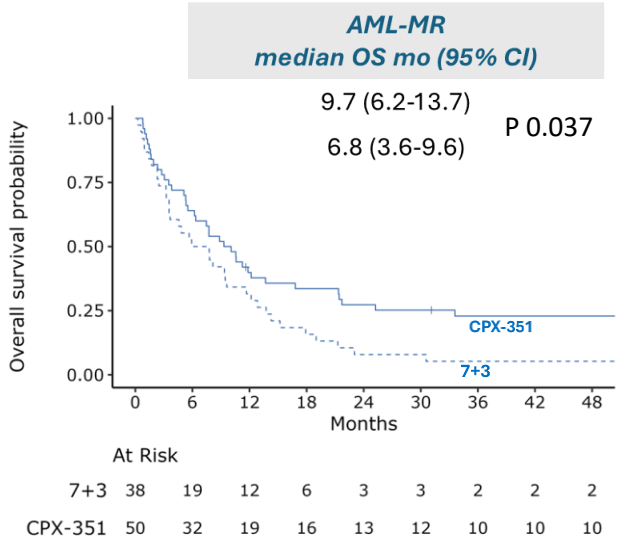


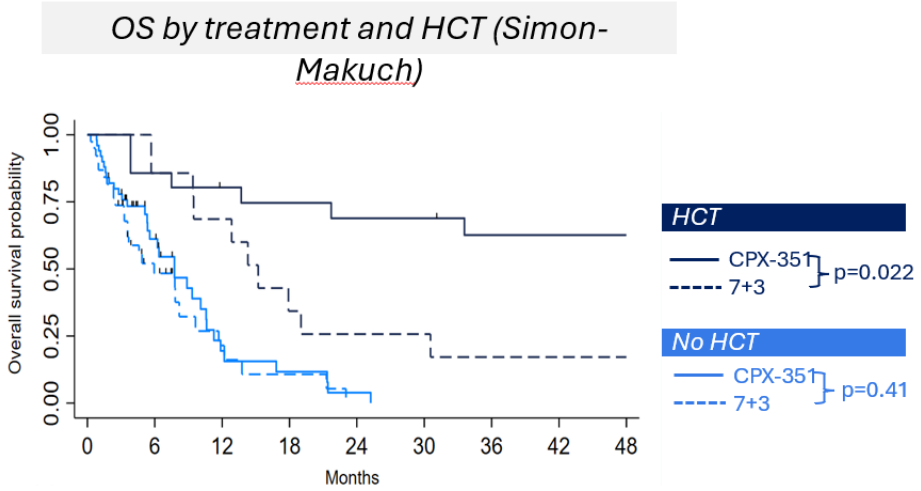


At 5 years' follow-up, the median OS landmarked from the date of HSCT was maintained above 50% at 5 years for Vyxeos Liposomal

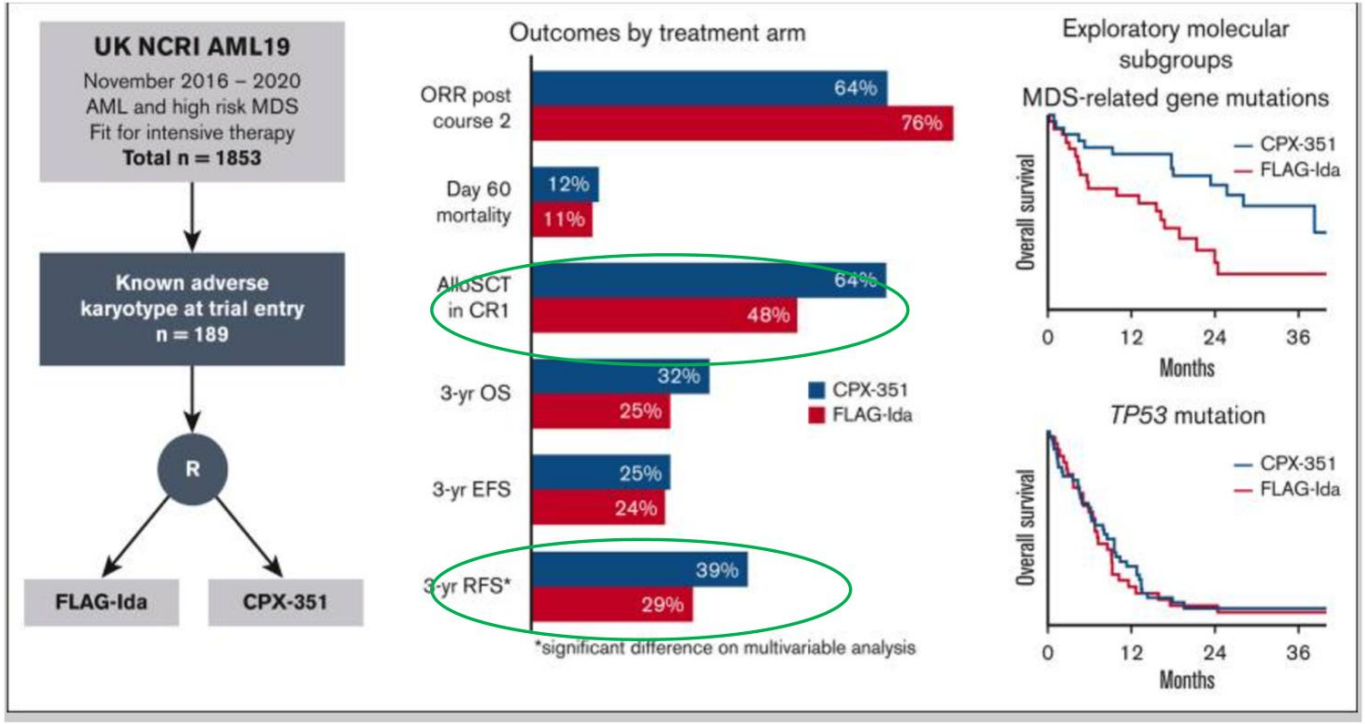
Lancet JE, *et al*. E-poster EP556. EHA25 Virtual Congress 2020

AML MR in Study 301





Shai Shimony et al; ASH 2024

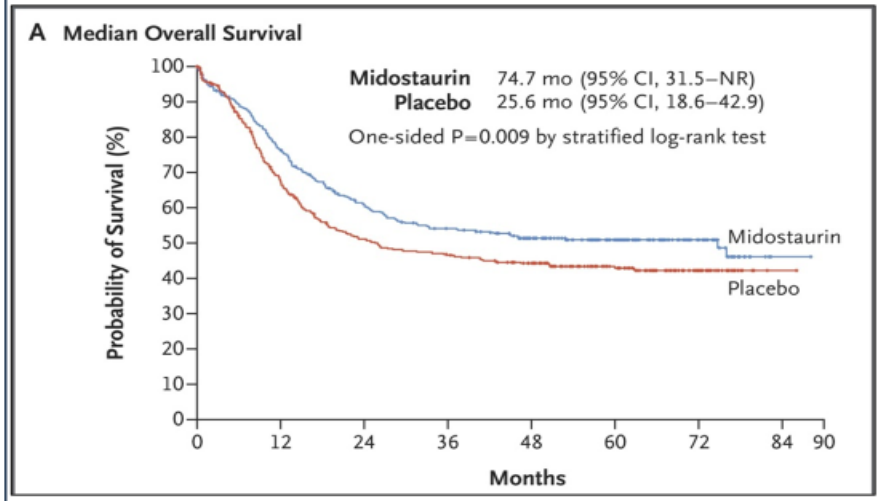


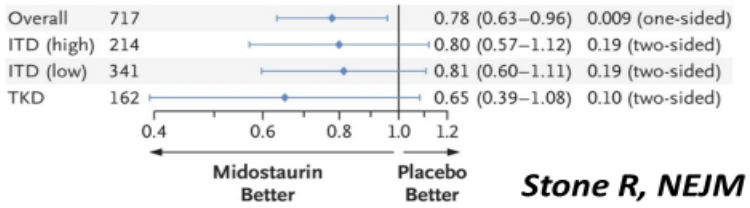
Jad Othman et al; Blood Adv; Aug 2022

RATIFY
Randomized AML Trial in FLT3 in <60 Year Olds

QuANTUM First

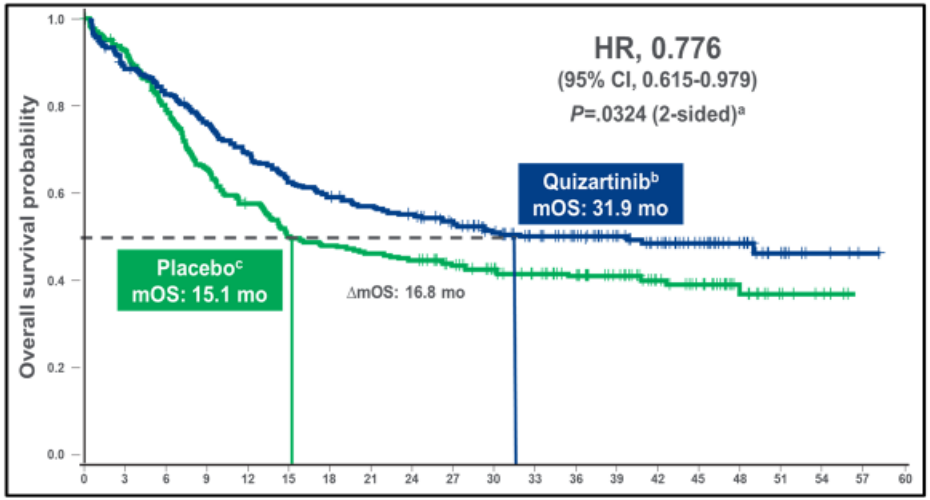
- *FLT3*+ AML, patients aged 18-60





Stone R, NEJM 2017

- *FLT3*-ITD+ AML, patients aged 18-75



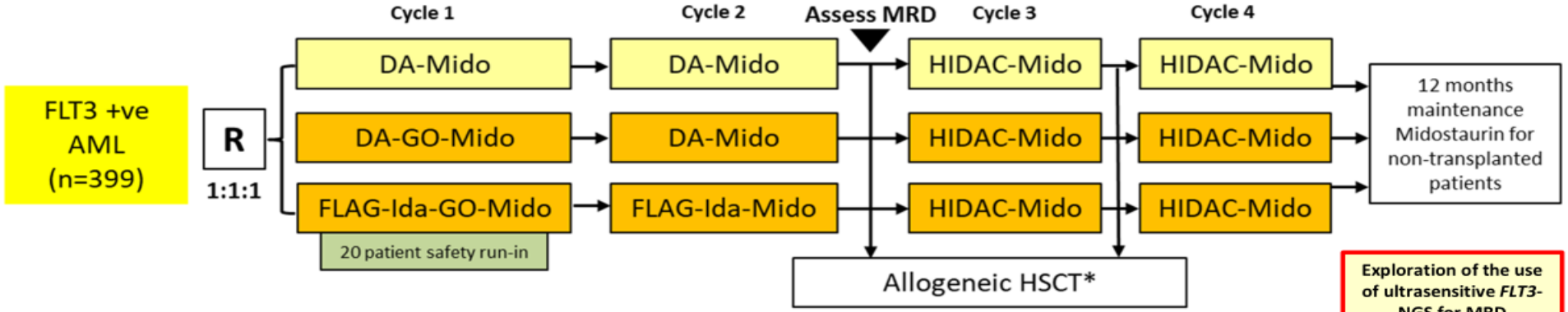
- 40% patients were aged >60yrs
- 36% CR1 transplant rate (vs 25% in RATIFY)
- Included post-BMT maintenance (up to 3yrs)

Erba H, Lancet 2023

- Newly diagnosed AML, fit to receive intensive therapy
- Age ≥16yrs (no upper limit)
- Confirmed *FLT3* ITD or TKD mutation

CANCER RESEARCH UK

CARDIFF UNIVERSITY PRIFYSGOL CAERDYDD Centre for Trials Research Canolfan Ymchwil Treialon



Exploration of the use of ultrasensitive *FLT3*-NGS for MRD monitoring

Primary Endpoint:
Event free survival

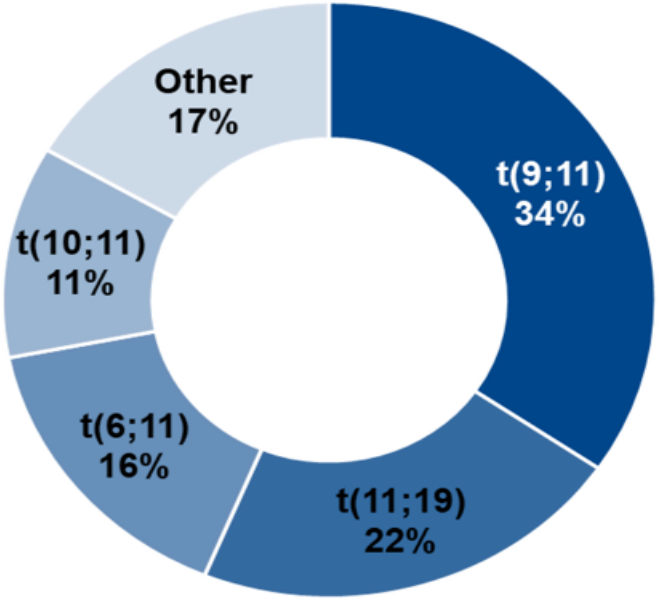
***Allogeneic haematopoietic stem cell transplant in 1st CR** recommended for:

- *FLT3+/NPM1+* with PB NPM1 qPCR+ post cycle 2
- *FLT3+/NPM1-* patients with baseline FLT3m≥5%*
- Myeloablative conditioning following cycle 2 where practical for patients ≤40-45yrs
- Reduced intensity conditioning (RIC) following cycle 3 for patients aged ≥40-45yrs

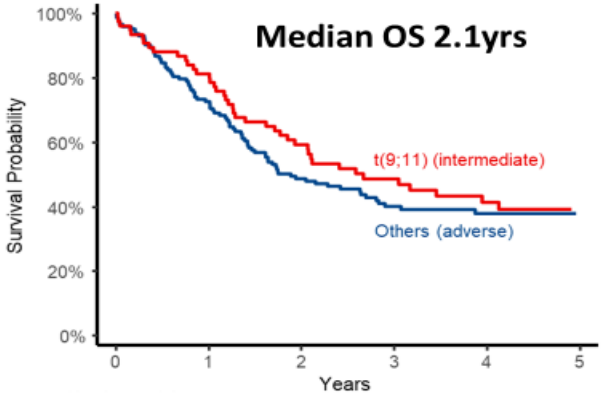
Slide courtesy Prof S Knapper

KMT2A-rearranged AML: NCRI trials experience

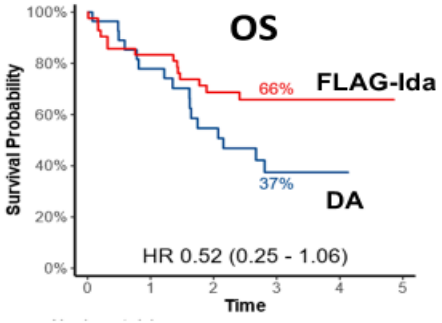
- 217 patients from AML17 & 19 trials
- Median age 41yrs (16-69)

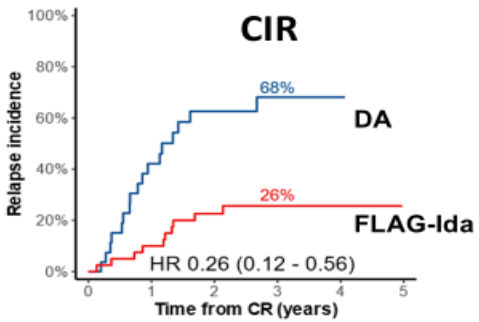


Othman. ASH 2024 (abstract 845)



AML19: FLAG-Ida vs DA (n=70)

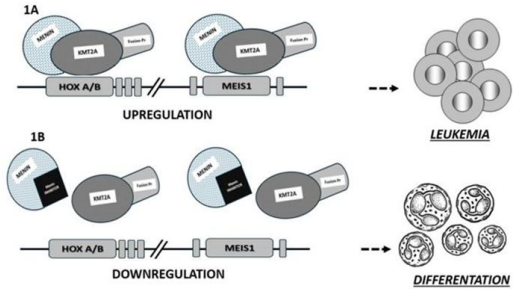




KMT2Ar AML: Combining menin inhibitors with intensive chemotherapy

Menin inhibitors in *KMT2A /NPM1*

Menin binds to KMT2A → aberrant HOX /MEIS expression → differentiation block and leukaemic transformation



1. *Issa et al; JCO, 2024*

Ziftomenib combined with intensive induction (7+3) in newly diagnosed NPM1-m or KMT2A-r acute myeloid leukemia: KOMET-007

Well tolerated

CR rates 83% with 75% MRD negativity

Amer Zeidan; ASH 2024

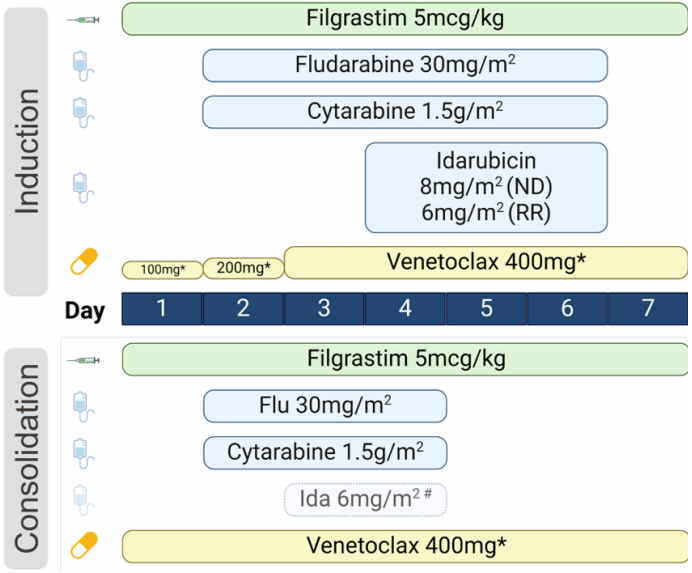
Adding venetoclax to existing regimens

Regimen	Median age in years (range)	N	CR + CRi	Median OS	Allo HSCT	Median FU
Median age >60-65:						
5+2+VEN[1]	72 (63-80)	81	75%	15.4mo	4%	41.8 mo
CLAD/LDAC/ VEN[2]	68 (57-84)	60	93%	NR	48%	22 mo
Median age ≤60:						
FLAG-Ida VEN[3]	45 (20-67)	77	95%	NR	64%	32 mo
CLIA+VEN[4]	48 (18-64)	50	94%	NR	32%	14 mo
7+3+VEN[5]	40 (18-60)	33	91%	NR	36%	11 mo
7+3+VEN[6]	59 (27-71)	34	85%	NR	29%	9.6 mo

1. Chua, Bld Adv, 2025
2. Kadia, JCO, 2022
3. DiNardo, Leukemia, 2025
4. Kadia, Lancet Haem, 2018
5. Wang, Lancet Haem, 2022
6. Mantzaris, ASH 2024

Credit: A. Wei

FLAG-Ida-Ven in frontline and R/R AML

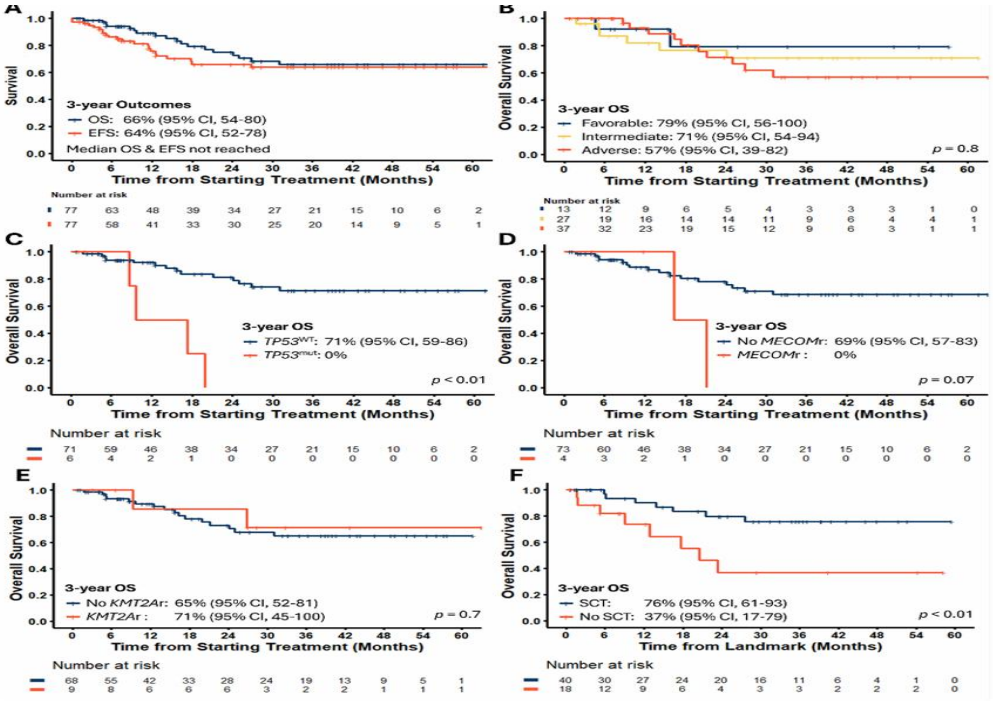


Outcome	ND Cohort				RR		
	All n = 77	Favorable n = 13	Intermediate n = 27	Adverse n = 37	All n = 61	S1 & *TP53*^{WT} n = 34	S2+ / *TP53*^{mut} n = 27
ORR, n(%)	75 (97)	13 (100)	26 (96)	36 (97)	41 (67)	27 (79)	14 (52)
CRc, n(%)	73 (95)	13 (100)	26 (96)	34 (92)	39 (64)	25 (74)	14 (52)
CR, n(%)	63 (82)	13 (100)	25 (93)	25 (68)	25 (41)	19 (56)	6 (22)
CRh, n(%)	3 (4)	0	1 (4)	2 (5)	7 (12)	4 (12)	3 (11)
CRi, n(%)	7 (9)	0	0	7 (19)	7 (12)	2 (6)	5 (19)
MLFS, n(%)	2 (3)	0	0	2 (5)	2 (3)	2 (6)	0
NR, n(%)	2 (3)	0	1 (4)	1 (3)	20 (32)	7 (21)	13 (48)
MRD Negative, n(%)	66 (90)	12 (92)	24 (92)	30 (88)	29 (74)	19 (76)	10 (71)
mOS, mo (95% CI)	NR	NR	NR	NR	12 (9–34)	NR	9 (5–15)
3y OS, %(95% CI)	66 (54–80)	79 (56–100)	71 (54–94)	57 (39–82)	32 (21–48)	51 (34–75)	13 (5–36)
mEFS, mo (95% CI)	NR	NR	NR	NR	7 (4–21)	23 (7-NE)	3 (0–8)
3y EFS, %(95% CI)	64 (52–78)	85 (67–100)	68 (50–91)	54 (38–77)	27 (18–43)	42 (27–65)	10 (3–33)

Response rates and survival data by cohort and sub-group. ND: newly-diagnosed; RR: relapsed or refractory; S1 & *TP53*^{WT}: patients in first

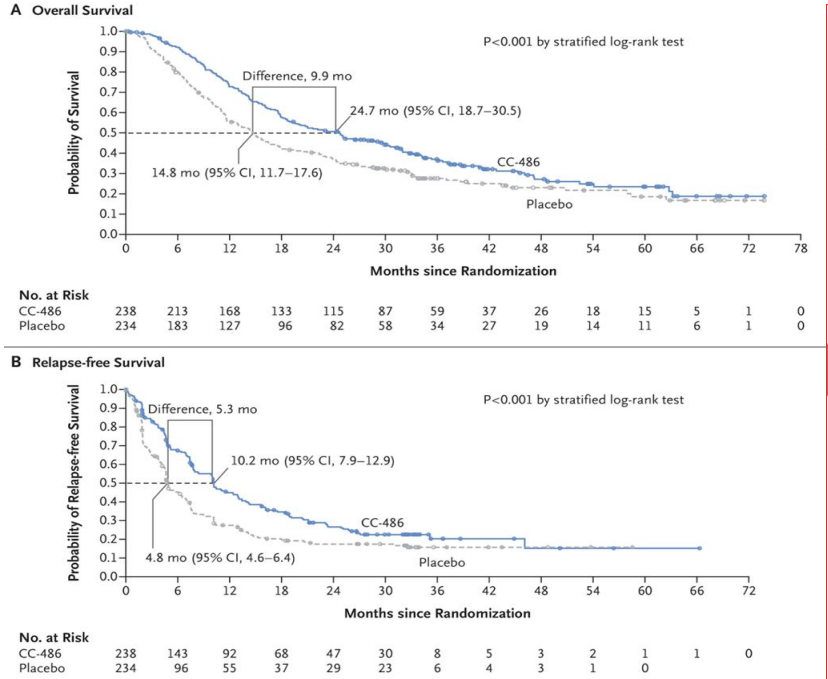
Di Nardo et al; Leukaemia 2025

FLAG-Ida-Ven in frontline: Outcomes



What about High Risk AML pts fit for intensive but cannot have a transplant?

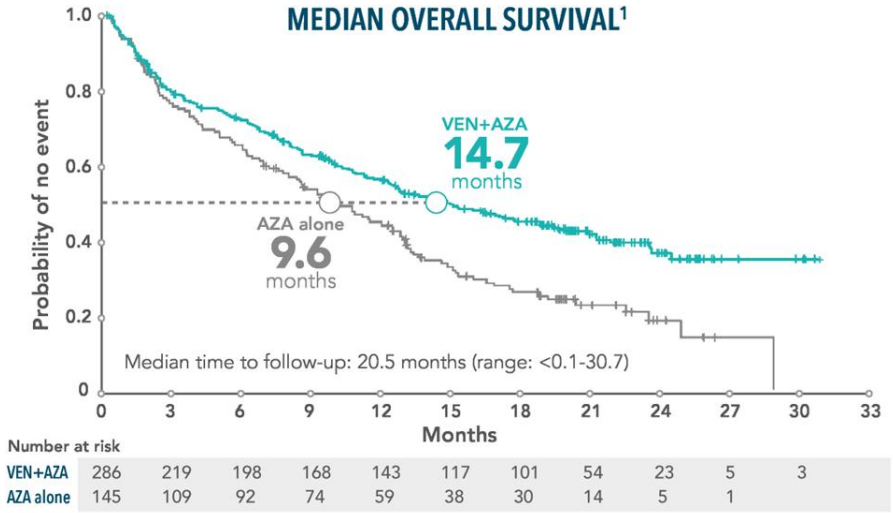
Maintenance with oral Azacitidine: QUAZAR Trial



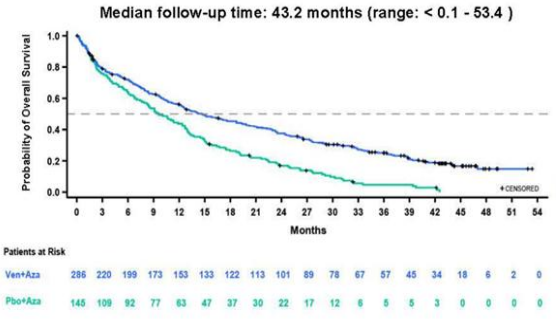
Subgroup	No. of Patients CC-486	No. of Patients Placebo	2-Yr Survival % CC-486	2-Yr Survival % Placebo	2-Yr Survival Difference (95% CI) percentage points
Overall	238	234	50.6	37.1	13.5 (4.5 to 22.5)
Age					
≥55 to <65 yr	66	68	61.3	45.1	16.2 (−0.9 to 33.4)
≥65 yr	172	166	46.7	33.9	12.8 (2.3 to 23.3)
≥75 yr	28	24	51.9	24.8	27.1 (0.7 to 53.4)
Sex					
Male	118	127	47.8	39.0	8.8 (−3.7 to 21.4)
Female	120	107	53.4	34.8	18.6 (5.7 to 31.5)
WHO AML classification					
AML with recurrent genetic abnormalities	39	46	50.0	47.0	3.0 (−18.6 to 24.5)
AML with myelodysplasia-related changes	49	42	43.5	29.8	13.8 (−6.3 to 33.8)
AML not otherwise specified	148	145	53.8	35.6	18.1 (6.8 to 29.5)
ECOG performance-status score					
0 or 1	217	217	50.9	38.0	13.0 (3.5 to 22.4)
2 or 3	21	17	47.6	25.5	22.1 (−8.2 to 52.4)
History of MDS or CMML					
Yes	22	17	66.7	31.4	35.3 (4.9 to 65.7)
No	216	217	49.0	37.5	11.5 (2.1 to 20.9)
Cytogenetic risk at induction					
Intermediate	203	203	54.1	40.4	13.6 (3.9 to 23.4)
Poor	35	31	30.3	15.5	14.8 (−5.6 to 35.2)
Consolidation after induction					
Yes	186	192	50.8	39.2	11.6 (1.4 to 21.7)
No	52	42	50.0	27.4	22.6 (3.2 to 42.0)
Consolidation cycles					
1 or 2	180	179	50.8	37.6	13.3 (2.9 to 23.7)
3	6	13	50.0	61.5	−11.5 (−59.5 to 36.4)
Response at randomization					
Complete remission	183	177	49.7	36.7	13.0 (2.7 to 23.3)
Complete remission with incomplete blood count recovery	50	44	55.1	38.6	16.5 (−3.8 to 36.8)
MRD status at randomization					
Positive	103	116	39.5	22.0	17.5 (5.3 to 29.8)
Negative	133	111	58.6	51.7	6.9 (−5.8 to 19.5)

Wei AH et al;N Engl J Med 2020

Frontline Non intensive: VIALE-A



Long term follow up of VIALE-A



	No. of events/No. of patients (%)	OS (months) median (95% CI)
Ven+Aza	222/286 (77.6)	14.7 (12.1 - 18.7)
Pbo+Aza	138/145 (95.2)	9.6 (7.4 - 12.7)

Hazard ratio: 0.58 (95% CI, 0.465 - 0.723), P < 0.001

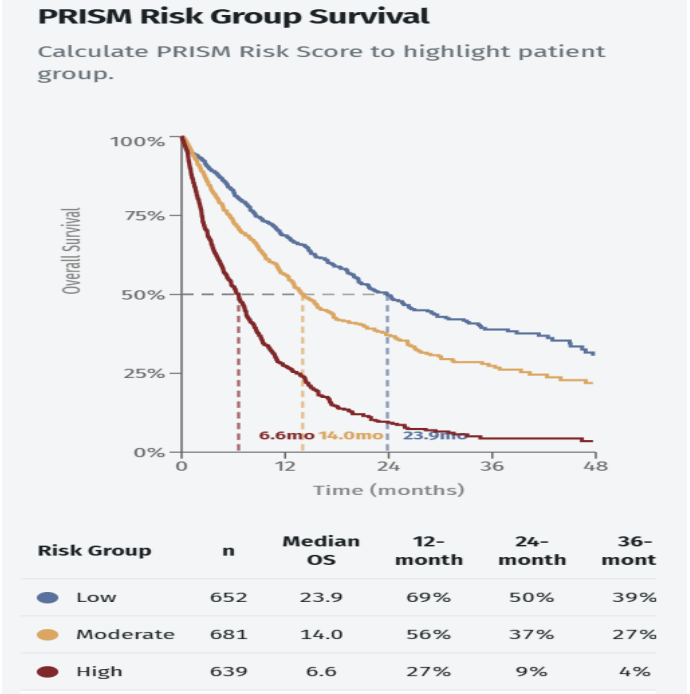
HR reduction from 0.66 (95% CI, 0.52 - 0.85) at 75% OS analysis

The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk); The hazard ratio between treatment arms were estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test; Data cutoff: 01 Dec 2021
Abbreviations: Aza, azacitidine; Pbo, placebo; Ven, venetoclax

1. Pratz KW et al. Oral Presentation 219, ASH 2022, New Orleans, USA. 2. Di Nardo CD et al. N Engl J Med. 202;387(7):617-29

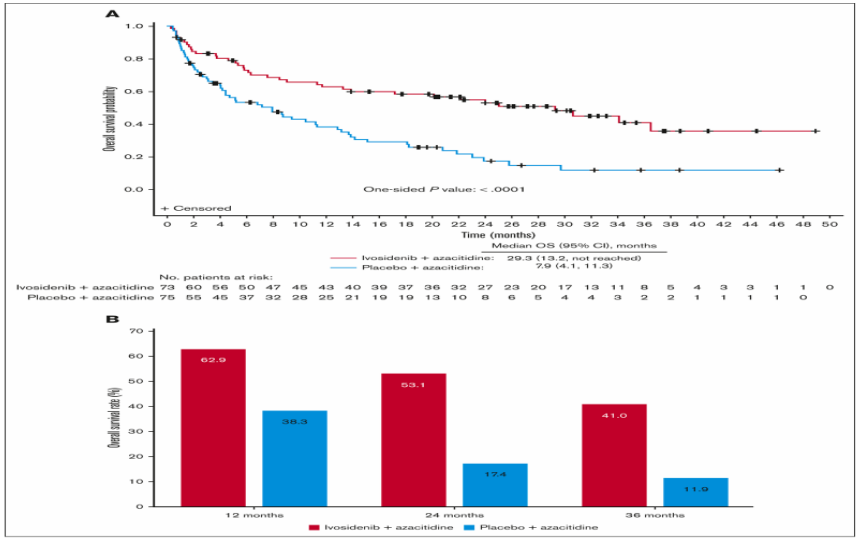
Risk stratification in non intensively treated pts: Risk calculators

Risk Category	Genetic Abnormality	Median Overall Survival (months)
Favourable	• Mutated *NPM1* (*FLT3*-ITDneg, *NRAS*wt, *KRAS*wt, *TP53*wt)	39
	• Mutated *IDH2* (*FLT3*-ITDneg, *NRAS*wt, *KRAS*wt, *TP53*wt)	37
	• Mutated *IDH1** (*TP53*wt)	29
	• Mutated *DDX41*	>24
	• Other cytogenetic and/or molecular abnormalities (*FLT3*-ITDneg, *NRAS*wt, *KRAS*wt, *TP53*wt)	23
Intermediate	• AML with myelodysplasia-related gene mutations (*FLT3*-ITDpos and/or *NRAS*mut and/or *KRAS*mut; *TP53*wt)	13
	• Other cytogenetic and molecular abnormalities (*FLT3*-ITDpos and/or *NRAS*mut and/or *KRAS*mut; *TP53*wt)	12
Adverse	• Mutated *TP53*	5-8



Ivosidenib + Aza in IDH1 mutated AML: AGILE trial

Long-term results from the AGILE study of azacitidine plus ivosidenib vs placebo in newly diagnosed IDH1-mutated AML



Pau Montesinos Blood Adv

Triplet regimens on Ven-HMA backbone for unfit AML

- Ven-Aza + Ivo/ Enasidenib for IDH1/IDH2m AML
- Oral Decitabine + Ven+ Ivo/Enasidenib
- Ven-Aza +/- Revumenib

EVOLVE-1 trial: Ivosidenib / azacitidine with venetoclax or placebo in older, unfit patients with *IDH1*-mutated AML

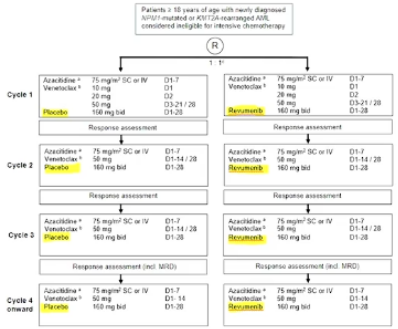
HOVON 173 AML / AMLSG 34-23 / ACT-HOV-AML-001

- Inclusion of 227 pts (3 years)
- Screening (6%): 4730 pts (assuming 20% screen failure)
- Selection +/- 150 sites committed to competitive timelines (accrual & quality data)
- Primary endpoint EFS

EVOLVE-2

Randomized study to assess revumenib in combination with azacitidine + venetoclax in adult patients with newly diagnosed NPM1-mutated or KMT2A-rearranged AML ineligible for intensive chemotherapy

HOVON 177 / AMLSG 35-24 /

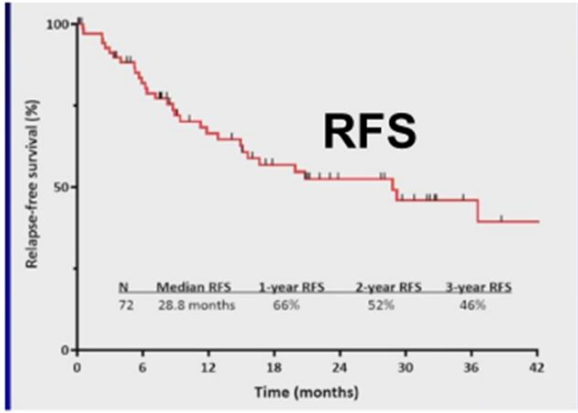


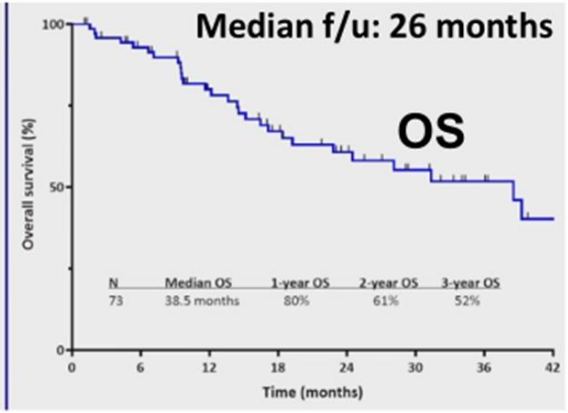
- Inclusion of 368 pts (26 months)
- Screening 3834 pts (assuming 12% NPM1-mut & 20% screen failures)
- Primary endpoint OS

Moving towards HMA/Ven/FLT3 inhibitor triplets?

- Retrospective single centre analysis of 70 FLT3-mutated patients – **median age 70** (18-88)
- HMA/Ven combined with gilteritinib (49), quizartinib (18), sorafenib (5), midostaurin (1)

Response, N (%)	N=73
CRc (CR+CRi)	68 (93)
CR	60 (82)
CRi	8 (11)
MLFS	4 (6)
ORR (CR + CRi + MLFS)	72 (99)
Early death	1 (1)





48/59 (81%) of responders flow MRD neg

Short. ASH 2024 (abstract 220)

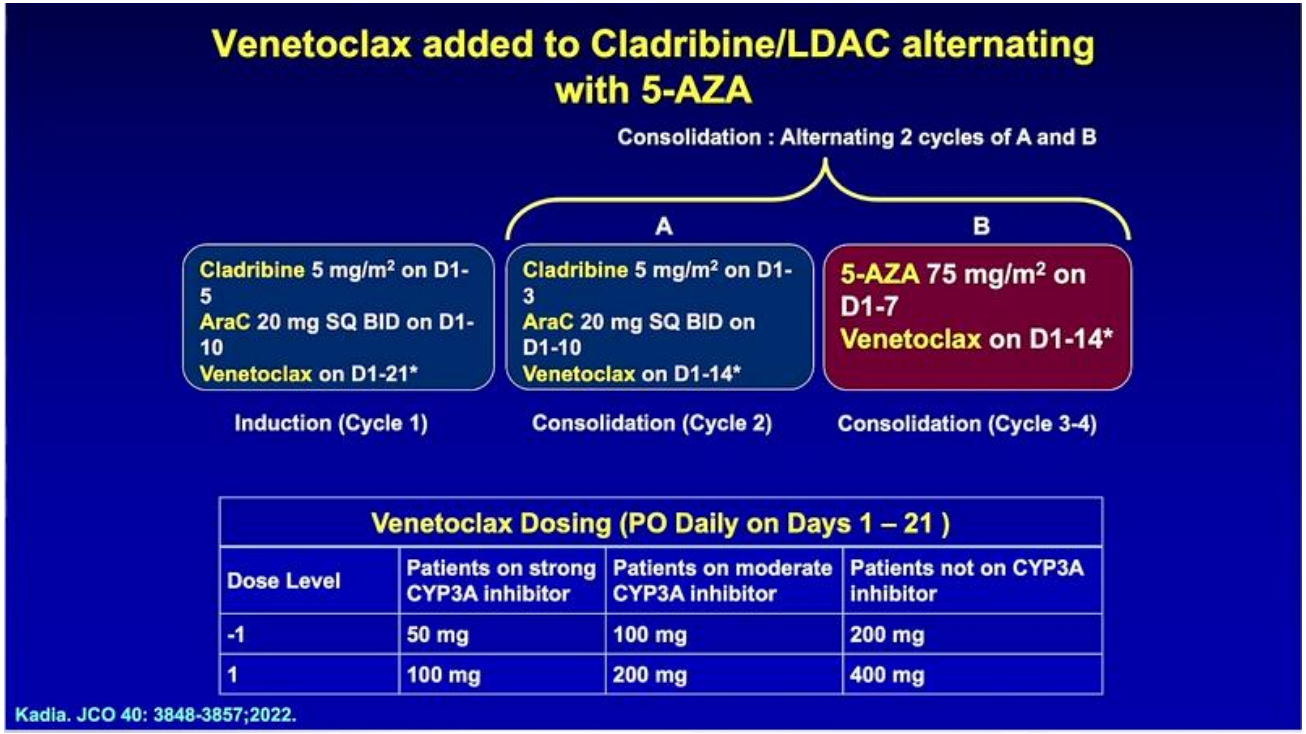
ACT
ACCELERATING CLINICAL TRIALS FOR PATIENTS

ACT-AML-902 – QUIZZICAL

- Proposed prospective UK/US randomised phase 2b study
- *FLT3*-ITD+, previously untreated, fit older adults
- HMA/Ven/Quizartinib vs DA-Quizartinib

Daiichi-Sankyo

Frontline for older AML: Clad-LDAC-ven-aza

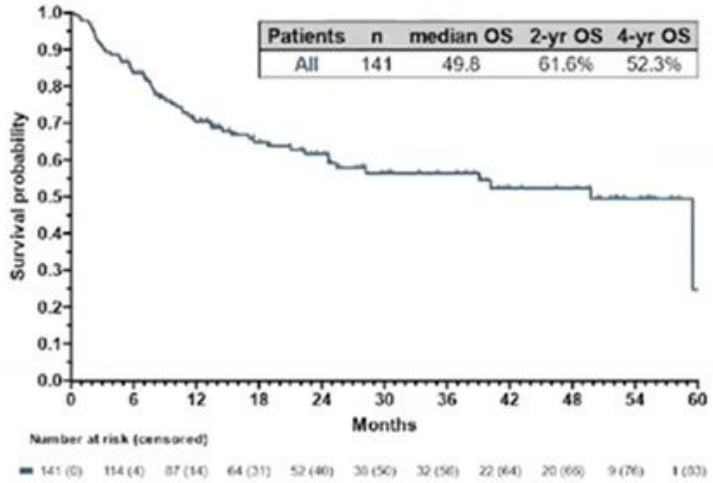


Venetoclax Dosing (PO Daily on Days 1 – 21)			
Dose Level	Patients on strong CYP3A inhibitor	Patients on moderate CYP3A inhibitor	Patients not on CYP3A inhibitor
-1	50 mg	100 mg	200 mg
1	100 mg	200 mg	400 mg

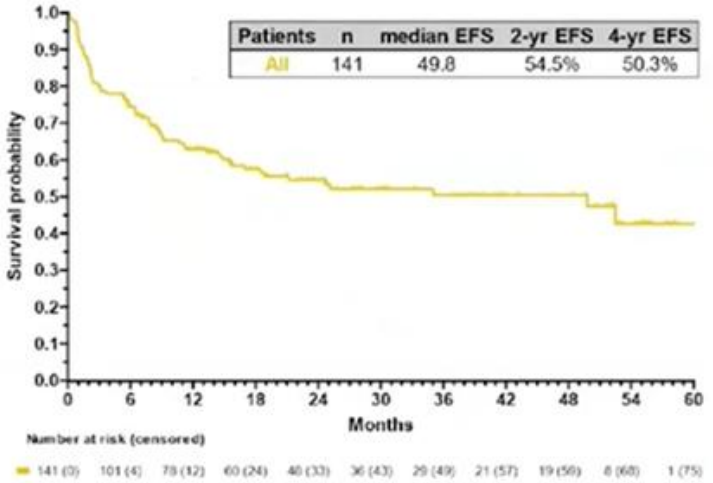
Kadia. JCO 40: 3848-3857;2022.

Median follow-up: 28 months

Overall Survival



Event-free Survival



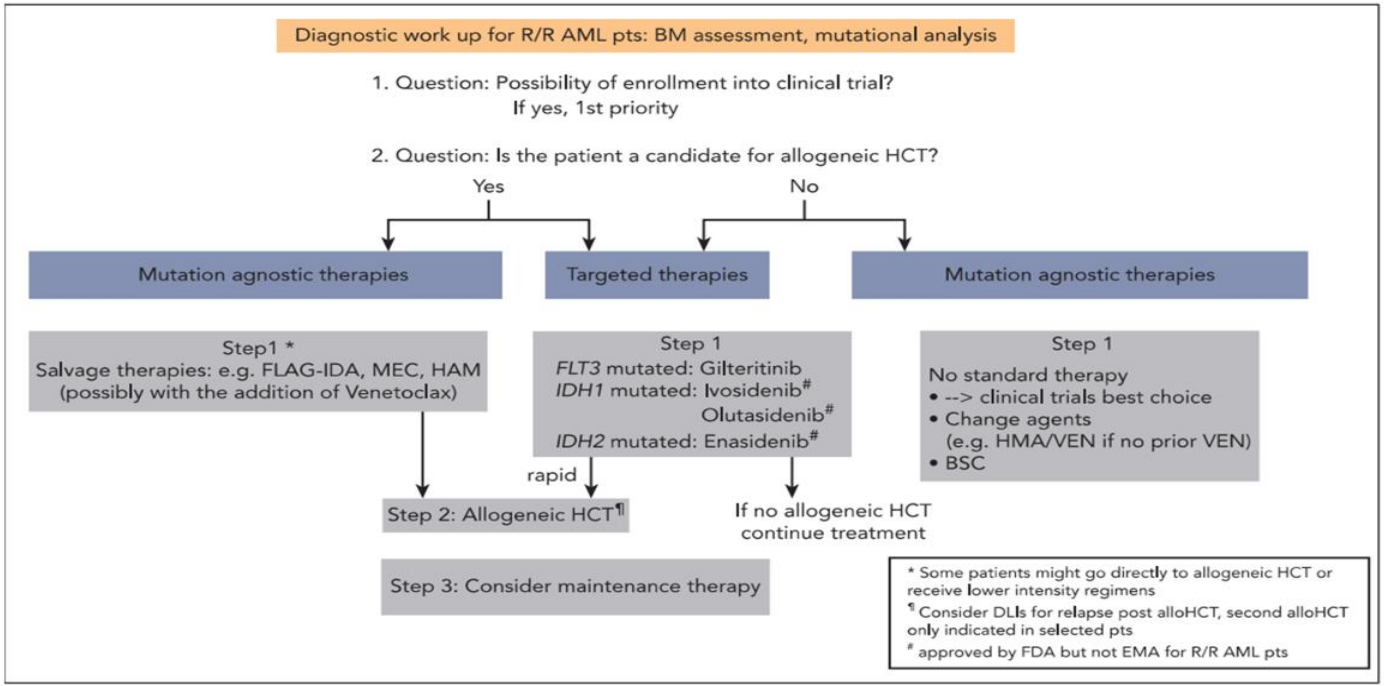
All oral non intensive: Ven+ cedazuridine + decitabine (ASCERTAIN-V trial)

TRIAL	COMPARATOR	Median OS	CR	CR + CRi
ASCERTAIN-V[1]	DEC-C+VEN (single-arm)	15.51 months (95% CI: 7.59, **NE**)	CR: 46.5% (95% CI: 36.5, 56.7)	63.4% (95% CI: 53.2, 72.7)
VIALE-A[2]	AZA+VEN vs AZA	14.7 months	38.8%	66.8%

Notes: ASCERTAIN-V has ~11 months of follow-up, compared to the ~45 months of VIALE-A follow-up.[1,2]

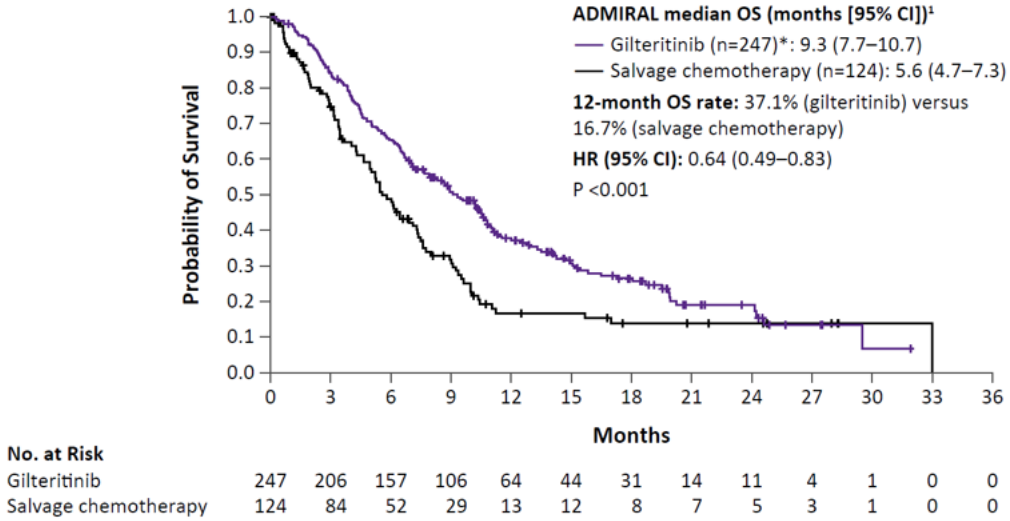
Zeidan A, Griffiths E, Dinardo C, et al. Abstract 6504. Presented at the 2025 Annual Meeting of the American Society of Clinical Oncology; May 30-June 3, 2025; Chicago, Illinois.

Treatment algorithm for R/R AML



Thol et al; Blood (2024) 143 (1): 11–20.

Flt3 mutated R/R AML: ADMIRAL trial



	FLT3-ITD alone	
	Gilteritinib (n=215)	Salvage chemotherapy (n=113)
Median OS, months	9.3	5.6
HR (95% CI)	0.62 (0.47–0.82)	
	FLT3-TKD alone	
	Gilteritinib (n=21)	Salvage chemotherapy (n=10)
Median OS, months	8.0	5.7
HR (95% CI)	0.69 (0.29–1.64)	

1. Perl AE, et al. *N Engl J Med* 2019;381:1728–1740.

Menin inhibitors in relapsed NPM1/ KMT2A mutated AML

Drug	Trial (ClinicalTrials.gov ID)	Phase	Regimen	Patient Population	Eligibility
Revumenib (SNDX-5613)	**AUGMENT-101 (NCT04065399)**	I/II	Revumenib monotherapy	131 Adults and children	R/R KMT2Ar AL, NPM1c AML
	AUGMENT-102 (NCT05326516)	I	-AML: Revumenib/FLA ± Revumenib/FLA -ALL/MPAL: Revumenib/Pred/VCR/ASP/DNR	30 Adults and children	R/R KMT2Ar AL, NPM1c or NUP98r AML
	(NCT05761171)	II	Revumenib/FLA, MTX	Children (recruiting)	R/R KMT2Ar ALL
	SAVE (NCT05360160)	I/II	Revumenib/ASTX727/VEN	8 Adults and children (recruiting)	R/R AML or MPAL
	BeatAML substudy (NCT03013998)	I	Revumenib/VEN/AZA	13 Adults	Newly diagnosed KMT2Ar or NPM1c AML
Ziftomenib (KO-539)	**KOMET-001 (NCT 04067336)**	I/II	Ziftomenib monotherapy	30 Adults	Phase 1a: R/R AML Phase 1b/2: KMT2Ar or NPM1c AML
	KOMET-007 (NCT05735184)	I	-Newly diagnosed AML: Ziftomenib/7 + 3 -R/R AML: ziftomenib/VEN/AZA	20 Adults	Newly diagnosed and R/R KMT2Ar or NPM1c AML
JNJ-75276617	**NCT04811560**	I	JNJ-75276617 monotherapy	58 Adults	R/R KMT2Ar AL, NPM1c AML
	NCT05453903	I	JNJ-75276617/VEN, JNJ-75276617/AZA or JNJ-75276617/VEN/AZA	Adults (recruiting)	R/R KMT2Ar AL, NPM1c AML
	NCT05521087	I	AML: JNJ-75276617/FLA ALL: JNJ-75276617/DEX/VCR/ASP	Adults and children (recruiting)	R/R KMT2Ar AL, NPM1c ALL/AML, NPM1c or NUP98r AML
BMF-219	**COVALENT-101 (NCT05153330)**	I	BMF-219 monotherapy	26 Adults	R/R AL, DLBCL or MM
DS-1594	NCT04752163	I/II	DS-1594 = AZA, VEN or mini-HCVD	17 Adults	Phase 1: R/R AL Phase 2: R/R KMT2Ar ALL/AML, NPM1c AML
DSP-5336	NCT04988555	I/II	DSP-5336 monotherapy	4 Adults	Phase 1: R/R AL Phase 2: R/R KMT2Ar ALL/AML, NPM1c AML

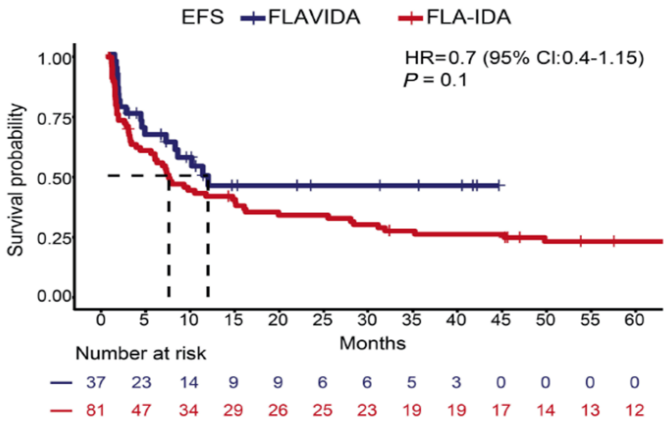
Salvage Regimens

Regimen
HiDAC+/- anthracycline (daunorubicin or idarubicin or mitoxantrone)
FLAG-Ida or FLA-Ida
Mitoxantrone, Etoposide, AraC (MEC)
Cladribine, AraC, Mitoxantrone, G-CSF (CLAG-M)
Allogeneic Transplant with active disease
Venetoclax based
FLAG-Ida plus Venetoclax
HiDAC+Mitoxantrone + Venetoclax. (HAM-Ven)
Venetoclax plus Azacitidine ORR 62% vs 42% TPC[1]

1. *Unglaub et al; Blood Adv, 2025*

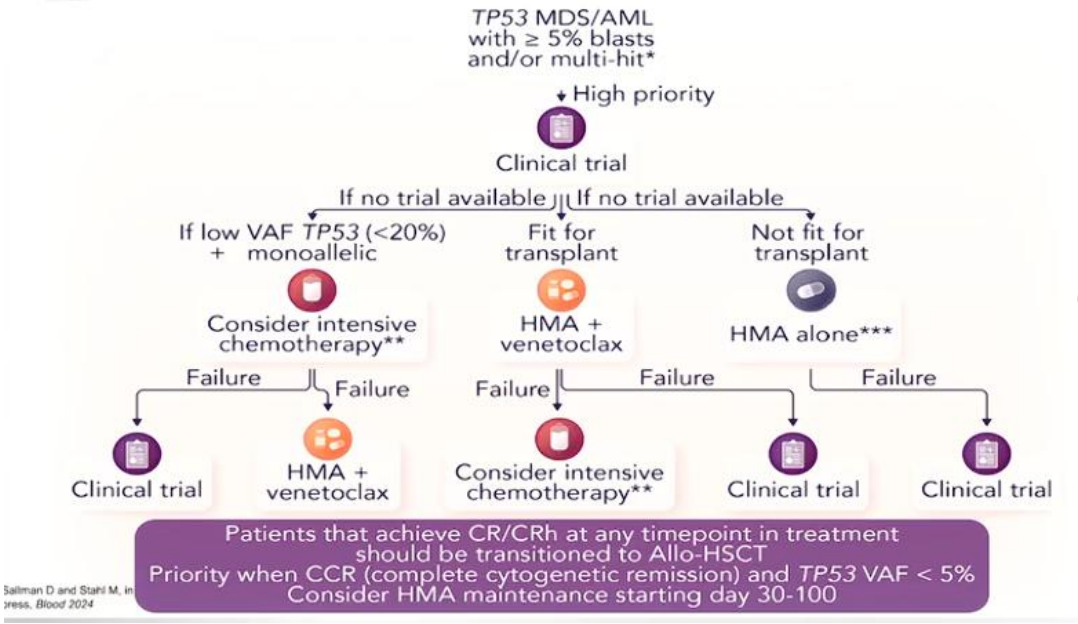
Retrospective comparison R/R patients

- ORR after 1 course: 47% FLA-Ida vs 78% FLAVIDA
- ~ 80% after either proceeded to alloHCT or DLI



Shahswar et al; Haematologica (2023)

Treatment of TP53 mutated AML



In trials/ therapeutic options:

Pivekimab Sunirine
Cusatuzumab
HMA maintenance
DLI's

Summary: New therapies in HR AML

- Identification of HR AML at diagnosis, targetable mutations and using MRD detection through treatment
- Targeted therapies may add efficacy and reduce toxicity in intensive and non intensive chemotherapy regimens
- Sequencing non intensive chemotherapy may improve outcomes in older patients
- Design of clinical trials with new therapies and participation in clinical trials is paramount

Thank you