



EVOLUZIONE DELL'ALGORITMO TERAPEUTICO DEL PAZIENTE CON LAM

Dalla diagnosi alla malattia refrattaria nel paziente Fit

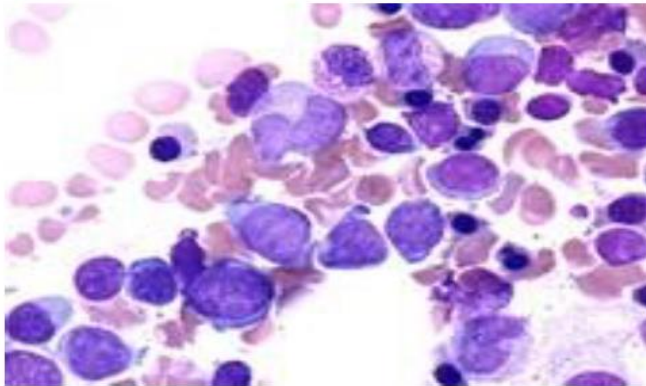
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Acute Myeloid Leukemia (AML)

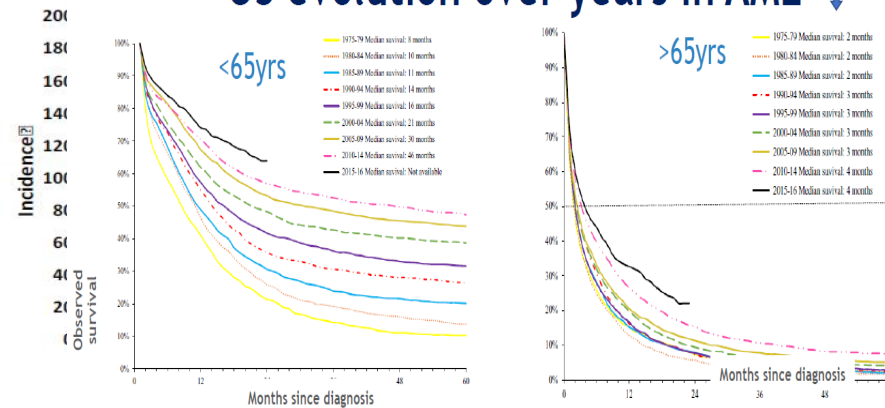
Disease of older adults (median 67-70 years)

Biologically diverse (karyotype, mutations, antigens)

Clinically aggressive disease with survival in weeks-months

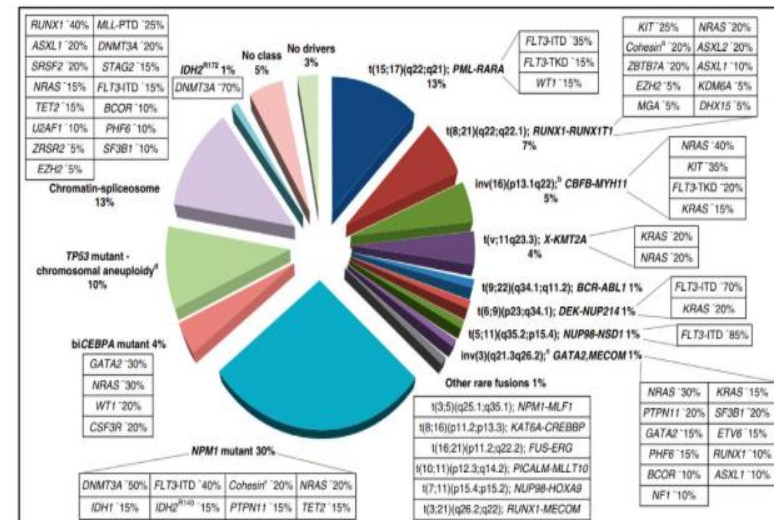


OS evolution over years in AML ↓



- Refinement of supportive care → lower ID
- More older patients treated and better selection of them
- Lower TRM
- Increased allo-transplant rate up to 70-75 yrs.
- Risk adapted treatment (ELN risk, MRD)

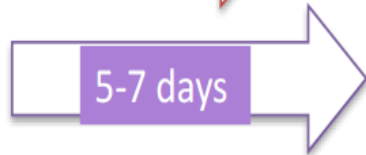
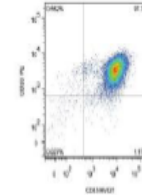
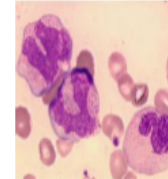
Understanding Genetic Heterogeneity and Biologic Complexity of AML Was Crucial for Development of Improved and Individualized Therapies



Ideal diagnostic workup of AML (2026)

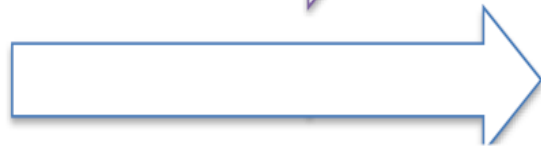
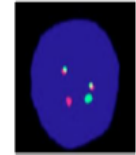


Morphology (BM, PB), Flow cytometry (CD33)



5-7 days

Conventional cytogenetics, FISH (per request), marrow IHC



Mutation results (diagnostic, actionable therapeutic target)

· *FLT3*, *IDH1*, *IDH2*, *NPM1*
· *CEBPA*, *DDX41*, *TP53*, *ASXL1*,
BCOR, *EZH2*, *RUNX1*, *SF3B1*,
SRSF2, *STAG2*, *U2AF1*, *ZRSR2*

REQUIRED (3-5 days)

· *ANKRD26*, *BCOR1*, *BRAF*, *CBL*,
CSF3R, *DNMT3A*
ETV6, *GATA2*, *JAK2*, *KIT*, *KRAS*,
NRAS, *NF1*, *PHF6*, *PPM1D*, *PTPN11*
RAD21, *SETBP1*, *TET2*, *WT1*

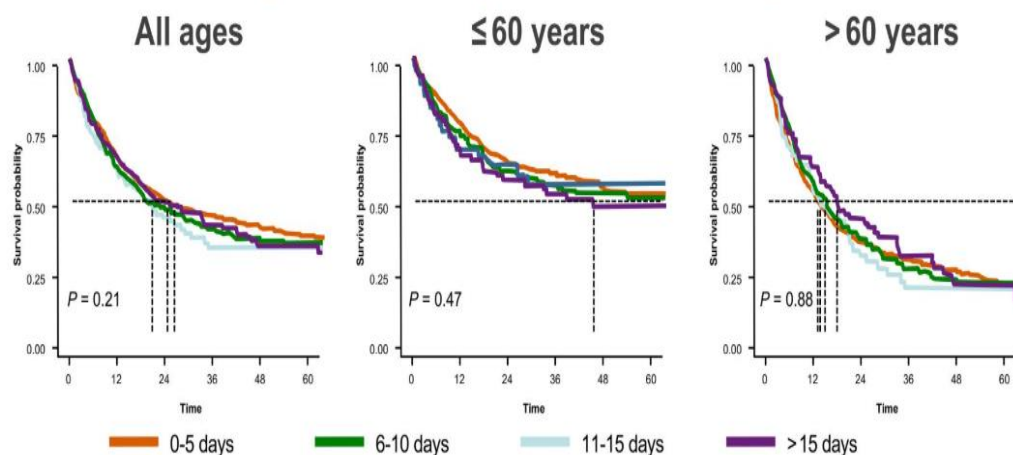
RECOMMENDED (1st cycle)

Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN

Test and procedures at diagnosis for a patients with AML

Tests and procedures	
Tests to establish the diagnosis Complete blood count and differential count* Bone marrow aspirate† Bone marrow trephine biopsy‡ Immunophenotyping by flow cytometry (see Table 5)	
Genetic analyses Cytogenetics§ Screening for gene mutations required for establishing the diagnosis and to identify actionable therapeutic targets# • FLT3, IDH1, IDH2 • NPM1 • CEBPA, DDX41, TP53; ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2 Screening for gene rearrangements** • PML::RARA, CBFB::MYH11, RUNX1::RUNX1T1, KMT2A rearrangements, BCR::ABL1, other fusion genes (if available)	Results preferably available within • 5-7 d • 3-5 d • 3-5 d • 1st cycle • 3-5 d
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	
Medical history Demographics and medical history‡‡ Detailed family history ^a Patient bleeding history ^b Analysis of comorbidities	

Time From Diagnosis to Therapy in AML: Waiting Is, in Many Cases, Totally Fine!



	Complete remission			Early death			Overall survival		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P	Hazard ratio	95% CI	P
TDT	0.990	0.974-1.007	.253	1.005	0.971-1.040	.777	1.002	0.993-1.011	.617

TDT data suggest that it may be a feasible approach to wait for genetic and other laboratory test results so that clinically stable patients are assigned the best available treatment option.

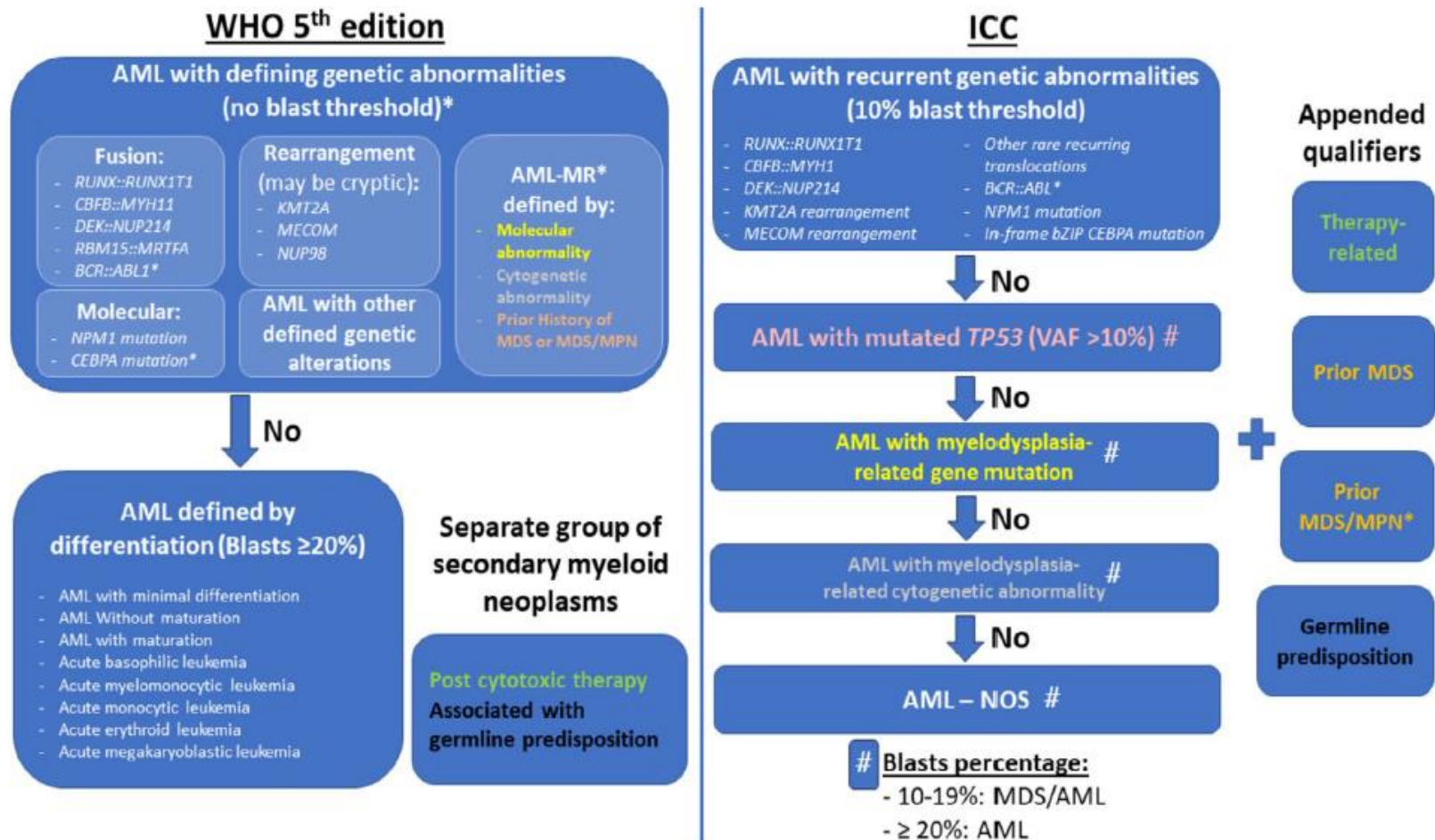


FIGURE 1 | Comparison between WHO fifth versus ICC AML definitions. * ≥ 20% blasts are required for AML definition. Colors reflect similar subgroups between classifications. AML—acute myeloid leukemia; ICC—international consensus classification; MDS—myelodysplastic syndrome; MPN—myelodysplastic neoplasm; WHO—world health organization.

- AML-defining genetic abnormalities require 10% blasts in ICC, only 'increased blasts' in WHO 5th ed.
- In WHO 5th ed, a single "AML, myelodysplasia-related" entity encompasses AML with MDS-related gene mutations, MDS-related cytogenetics and any AML progressed from MDS or MDS/MPN
 - Minor differences in MDS-related cytogenetics and MDS gene mutations
 - No entity of AML with mutated TP53 recognized in WHO 5th ed
- WHO 5th ed applies differentiation categories (FAB) to "AML-NOS"
- Overall 86% agreement between ICC and WHO AML entities
- Clinicians, researchers, and regulatory authorities need to be familiar with differences between the classifications and their implications for treatment, clinical trials, and drug approvals

ELN 2022¹

Favorable

- t(8;21)(q22;q22.1)/RUNX1::RUNX1T1
- inv(16)(p13.1;q22) or t(16;16)(p13.1;q22)/CBFB::MYH11
- Mut NPM1 w/o FLT3-ITD
- bZIP in-frame mut CEBPA

Intermediate

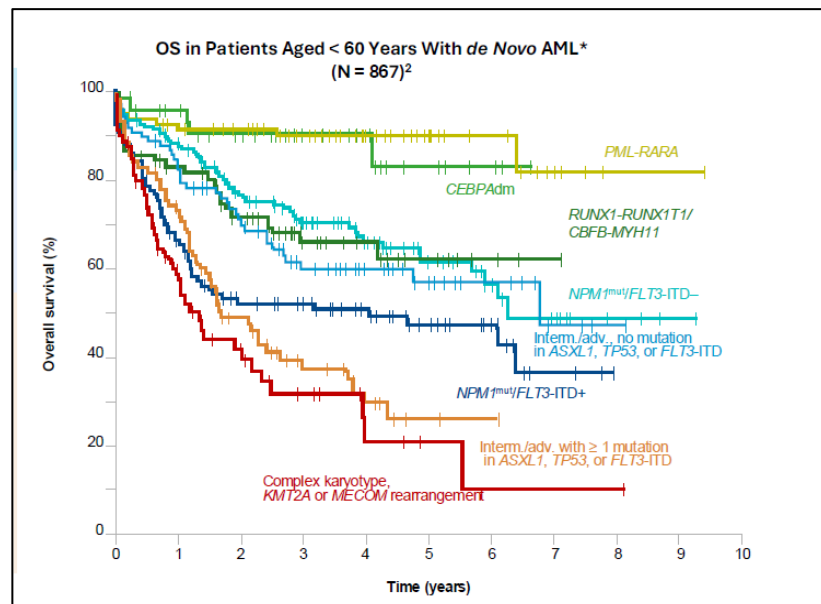
- Mut NPM1 with FLT3-ITD
- Wt NPM1 with FLT3-ITD
- t(9;11)(p21.3;q23.3)/MLL3::KMT2A
- Cytogenetic and/or molecular

Adverse

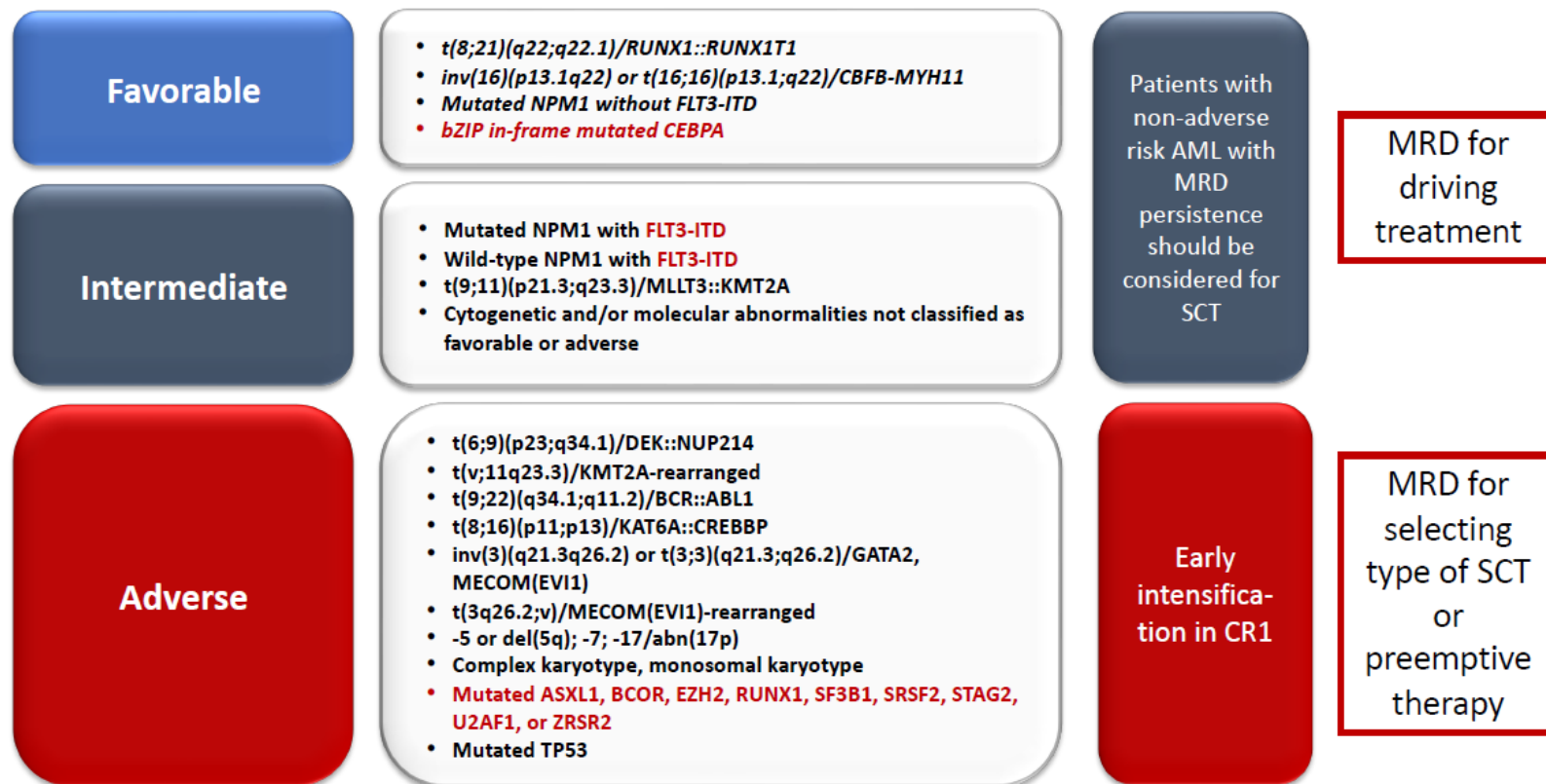
- t(6;9)(p23.3;q34.1)/DEK::NUP214
- t(v;11q23.3)/KMT2A-rearr
- t(9;22)(q34.1;q11.2)/BCR::ABL1
- t(8;16)(p11.2;p13.3)/KAT6A::CREBBP
- inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1)
- t(3q26.2;v)/MECOM(EVI1)-rearr
- -5 or del(5q); -7; -17/abn(17p)
- Complex/monosomal karyotype
- Mut ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2
- Mut TP53

However, the guidelines are largely based on intensively treated patients up to 60 years.....

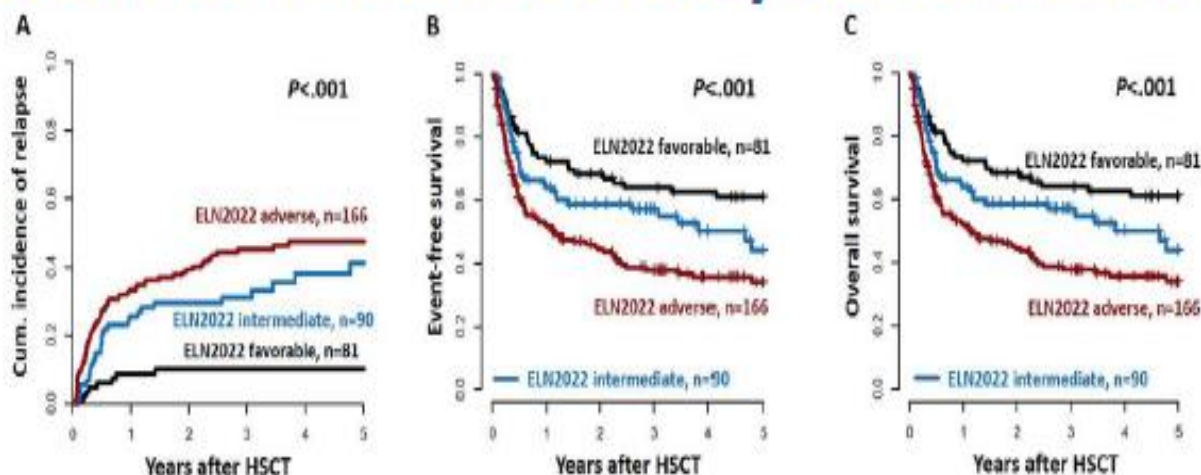
Outcomes with IC vary significantly based on the underlying cytogenetic and molecular features



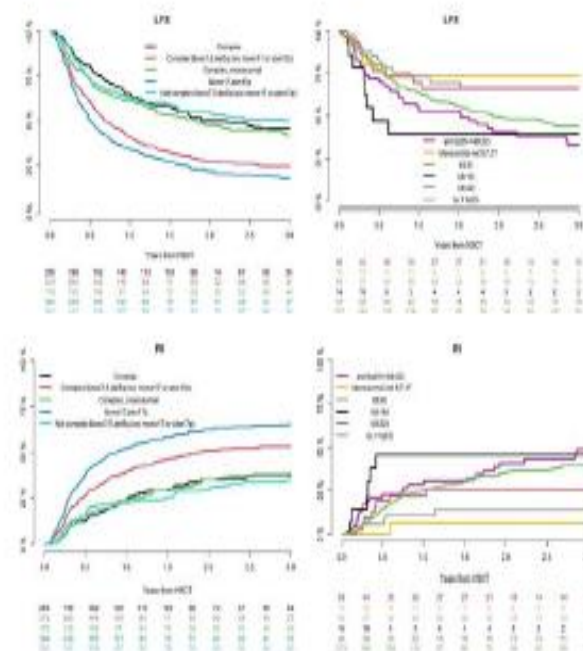
ELN2022 clinical recommendations for AML treatment



HSCT for Intermediate/Adverse Risk AML



- Transplant is the preferred strategy for non-favorable risk AML
 - widening donor options & improved GVHD prevention/treatment
 - best frontline = whatever is most likely to bridge to HSCT
- Recent EBMT retrospective registry (n=1735, median age 56) shows diverse outcomes of HSCT for ELN2022 adverse cytogenetic risk
 - cure rate ~50% for most
 - worse LFS/OS if complex karyotype or monosomal with del5q, -5, -7, or abnormal 17p
- Data on HMA/VEN vs. IC prior to HSCT to be presented at ASH 2025 (Claiborne J, et al. Sat 12/6/25 #44 9:45-10AM)



Jentzch M, et al. Blood Cancer J. 2022 Dec 19;12(12):170

Bazarbachi A, et al. Am J Hematol. 2025 Aug;100(8):1374-1386.

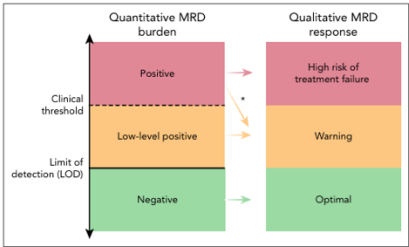
2025 update on MRD in acute myeloid leukemia:
a consensus document from the ELN-DAVID MRD
Working Party

Key updates of the revised AML MRD recommendations

1. Detailed MRD guidance is now tailored to each genetic subgroup, aligned with the ELN 2022 risk classification in adults receiving intensive chemotherapy.
2. MRD burden is categorized as negative, low-level (LL)positive, or positive. The LL-positive MRD (MRD-LL) category , defined as detectable but not clearly prognostic, has been more broadly introduced across AML subgroups and MRD technologies, including MFC.
3. A qualitative MRD response category has been newly introduced to support contextual interpretation of MRD dynamics
4. Updated tables provide distinct MRD percentage cutoffs for each assay and target, reflecting both the biological heterogeneity within AML and the technical differences of MRD assays.
5. Based on new evidence, MFC-MRD assessment is now recommended during the first year of follow-up after alloHCT, whereas (qPCR or ultrahigh-sensitivity (UHS) (NGS) MRD assessment isrecommended for 24 months after alloHCT.
6. Lower MRD cutoffs for NPM1 are now recommended, with specific distinctions between PB and BM levels.
7. FLT3 internal tandem duplication (ITD) mutation testingusing UHS-NGS is recommended after 2 cycles of CHT and before alloHCT. Based on more limited evidence, testing at EOT and during follow-up is suggested.

Table 6. Definition of MRD relapse

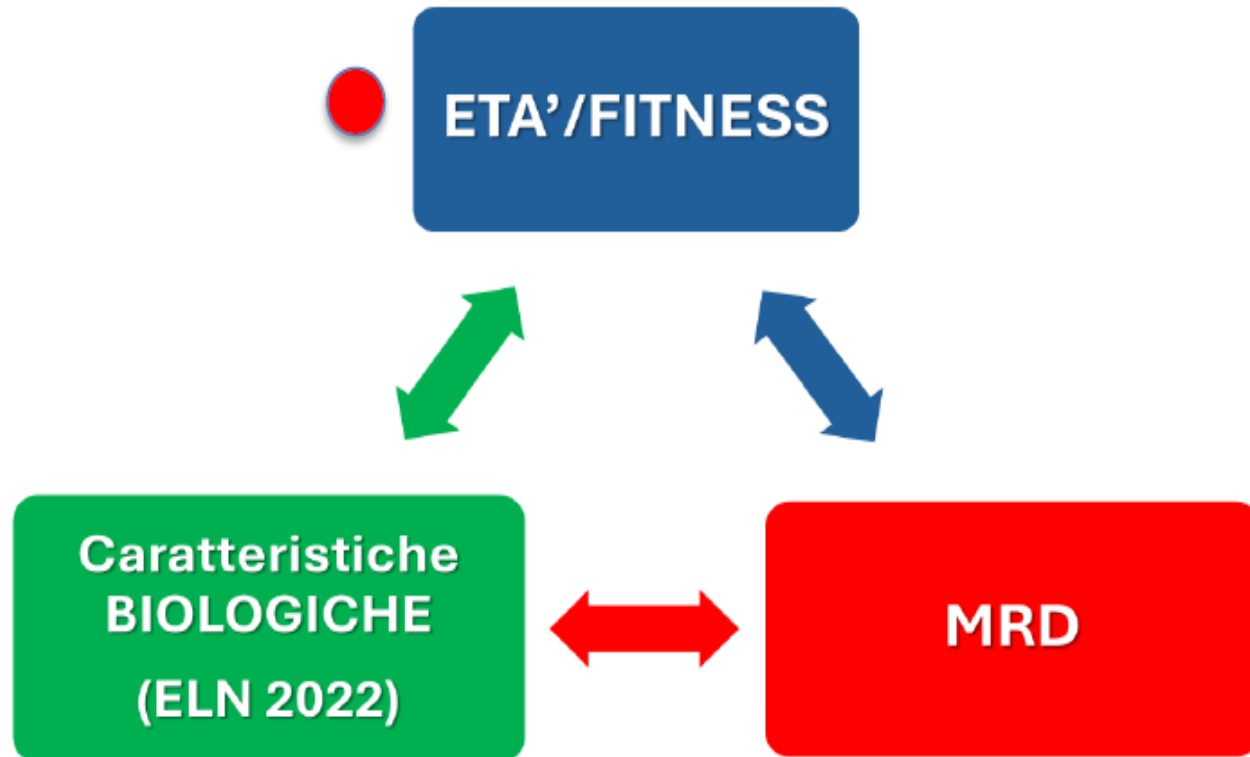
Marker	Assay	Tissue	MRD relapse definition
General definition			Conversion from undetectable to detectable MRD with the following thresholds:
NPM1	qPCR	PB	≥0.01% and detectable*,† In patients who have never tested MRD-negative, a ≥1-log ₁₀ increase from the measured nadir within the same tissue used for the nadir measurement regardless of threshold is required
NPM1	qPCR	BM	≥0.1% and detectable*,† In patients who have never tested MRD-negative, a ≥1-log ₁₀ increase from the measured nadir within the same tissue used for the nadir measurement regardless of threshold is required
RUNX1::RUNX1T1 and CBFβ::MYH11	qPCR	PB or BM	≥0.1% and detectable*,† In patients who have never tested MRD-negative, a ≥1-log ₁₀ increase from the measured nadir within the same tissue used for the nadir measurement regardless of threshold is required
PML::RARA	qPCR	BM	≥0.001% and detectable*,† In patients who have never tested MRD-negative, a ≥1-log ₁₀ increase from the measured nadir within the same tissue used for the nadir measurement regardless of threshold is required
FLT3-ITD	UHS-NGS	PB or BM	≥LOD§
Other (with LAIP/DfN)	MFC	BM	≥0.1% ,¶
Other (with gene mutation)	UHS-NGS	PB or BM	≥0.01%# In patients who have never tested MRD negative, a ≥1-log ₁₀ increase from the measured nadir within the same tissue used for the nadir measurement regardless of threshold is required



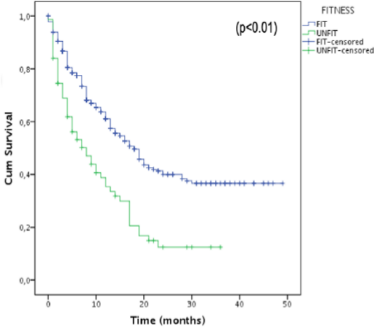
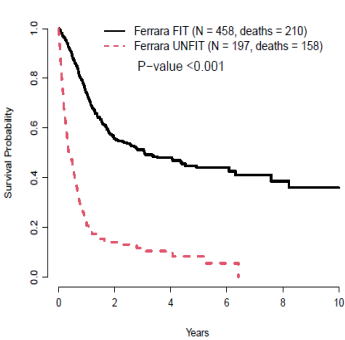
- Conventional PCR for FLT3-ITD is less useful due to insensitivity (~1%)²
- PCR-NGS is sensitive and specific for FLT3-ITD MRD (targeting exons 14-15)^{2,4}

A total of 56 recommendations were formulated, with 53 achieving a high level of consensus (≥90%). These updated guidelines represent a major step forward toward harmonizing MRD assessments in AML and enhancing its clinical utility across diverse treatment settings -

AML: FATTORI PRINCIPALI CONDIZIONANTI LA SCELTA DEL TRATTAMENTO E LA PROGNOSI



SIE/SIES/GITMO score in pts receiving IC



	28 days mortality	100 days mortality
F-Fit	7/457 (2%)	22/444 (5%)
F-Unfit	28/196 (14%)	78/185 (42%)

	28 days mortality	100 days mortality
F-Fit	10/328 (3%)	34/328 (10.4%)
F-Unfit	8/75 (10.7%)	21/75 (28%)

Criteri di Ferrara

Table 3. Operation criteria to define unfitness to intensive chemotherapy in AML	
1.	An age older than 75 years
2.	Congestive heart failure or documented cardiomyopathy with an EF ≤50%
3.	Documented pulmonary disease with DLCO ≤65% or FEV1 ≤65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
4.	On dialysis and age older than 60 years or uncontrolled renal carcinoma
5.	Liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases (> 3 times normal values) and an age older than 60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis
6.	Active infection resistant to anti-infective therapy
7.	Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
8.	ECOG performance status ≥3 not related to leukemia
9.	Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy
Abbreviations: AML, acute myeloid leukemia; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; FEV1, forced expiratory volume in 1 s.	

The criteria, suggested by Ferrara et al, are commonly incorporated into eligibility criteria and were validated in a large cohort of pts for predicting shorter-term mortality after intensive chemotherapy treatment in AML.

REVIEW ARTICLE



Fitness assessment in acute myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet

Adriano Venditti,^{1,2} Raffaele Palmieri,¹ Luca Maurillo,³ Christoph Röllig,³ Agnieszka Wierzbowska,^{4,5} David de Leeuw,⁶ Fabio Efficace,⁷ Antonio Curti,⁸ Lok Lam Ngai,⁹ Jesse Tetters,¹⁰ Lionel Adès,¹⁰ Antonio Almeida,¹⁰ Lars Bullinger,¹¹ Mike Dennis,¹² Jordi Esteve,¹³ Felcetto Ferrara,¹⁴ Michael Heuser,¹⁵ Gerwin Huls,¹⁶ Michael Lübbert,¹⁷ Priyanka Mehta,¹⁸ Pau Montesinos,¹⁹ Thomas Pabst,²⁰ Christian Récher,²¹ Giuseppe Rossi,²² Nigel Russell,²³ Jorge Sierra,²⁴ Reinhard Stauder,^{25,26} Norbert Vey,²⁷ Roland B. Walter,²⁸ Eunice Wang,²⁹ Samantha Nier,³⁰ Carolina Garcez Martins,³⁰ and Gert Ossenkoppele⁶

No.	Recommendations: general definitions	LoE	GoR	LoA
1	Fitness refers to a comprehensive evaluation of age, performance status, comorbidities, and functional capacity.	I	A	96%
2	Different fitness levels correspond to different treatment intensities. Accordingly, patients should be referred to as “fit for” a given treatment strategy.	IV	A	92%
3	Eligibility for intensive chemotherapy does not necessarily entail eligibility for AlloSCT.	IV	B	84%
4	Ineligibility for intensive treatment does not exclude eligibility for transplant after achieving CR following non-intensive treatment.	IV	B	81%
5	If mitigating disease-related symptoms is the goal, anti-leukemic therapy should be considered even when a curative intent is not attainable.	IV	C	88%

Table 2. Components of fitness

Statement	Recommendations: components of fitness	LoE	GoR	LoA
6	Age, as a single parameter, should not be considered for the definition of fitness.	II	C	92%
7	For patients aged >75 years, eligibility for IC should be evaluated carefully.	III	B	96%
8	PS plays a crucial role in the definition of fitness.	II	A	92%
9	Patient’s self-reported physical and social functioning as well QoL before illness onset, should be considered as an important parameter when evaluating fitness.	II	B	92%
LoA, level of agreement; LoE, level of evidence; GoR, grade of recommendation; IC, intensive chemotherapy; PS, performance status; QoL, quality of life.				

Table 4. Timing for fitness/genetic determination

Statement	Recommendations: timing for fitness/genetic determination	LoE	GoR	LoA
14	Because the time to treatment start does not seem to affect short- and long-term outcomes, comprehensive fitness and biological assessment should be conducted before starting therapy.	IV	B	96%
15	Fitness level attribution should be performed after appropriate supportive therapy when general condition impairments are suspected to be due to disease burden rather than preexisting conditions.	IV	B	81%
16	Fitness improvement/worsening should be assessed dynamically throughout therapy in responding and nonresponding patients to modulate treatment intensity as appropriate.	IV	B	100%
17	Biological reassessment should be performed at disease relapse to assist the choice of salvage therapy.	I	A	100%

American Society of Hematology 2025 guidelines for treating newly diagnosed acute myeloid leukemia in older adults

Mikhael A. Sekeres,¹ Ryan Mattison,² Andrew Artz,³ Maria R. Baer,⁴ Chong Chyn Chua,⁵ Roberta Demichelis-Gómez,⁶ Pamela C. Egan,⁷ Luke Fletcher,⁸ Charles Foucar,⁹ Jacqueline S. Garcia,¹⁰ Linda Gilberto,¹¹ Andres Gómez de León,¹² Jeffrey Lancet,¹³ Kah Poh Loh,¹⁴ Luca Malcovati,¹⁵ Bernard Marini,¹⁶ Uwe Platzbecker,¹⁷ Mohamed L. Sorror,¹⁸ Sara Tinsley-Vance,¹⁹ John Treitz,¹⁹ Maria Jose Oliveros,^{20,21} Sara Ibrahim,²⁰ Yetiani Roldan,²⁰ Gordon Guvatt,²⁰ and Romina Briquardello-Petersen²⁰

Inclusion criteria:

1. Newly diagnosed de novo, treatment-related, and secondary AML (ie, not relapsed or refractory AML);
2. Patients aged ≥ 55 years;
3. Patients had to have received definitive antileukemic therapy (ALT) depending on the specific question being addressed;
4. Patients were treated as part of randomized controlled trials (RCTs; which were prioritized) and nonrandomized studies (NRSs); and
5. Studies had to include ≥ 20 patients.

Exclusion criteria:

1. Acute promyelocytic leukemia;
2. Myeloid neoplasms associated with Down syndrome; and
3. Studies in which $>75\%$ of patients did not meet an eligibility criterion based on characteristics of the patients or the intervention, or in which the results were not reported separately for those who met the criteria.

Note that, compared with the 2020 American Society of Hematology (ASH) guidelines for treating newly diagnosed AML in older adults, the 2025 guidelines no longer use the terms “intensive” and “nonintensive” therapy, because the panel judged that venetoclax-based therapies were not truly “nonintensive.” Instead, the 2025 ASH guidelines have adopted the terms “conventional induction and postremission therapy” and hypomethylating agents (HMA) or low-dose cytarabine (LDAC) in combination with venetoclax.

The panel judged that, although certain studies included patients treated with either azacitidine- or decitabine-based therapy, 7-day dosing of azacitidine and 5-day dosing of decitabine are generally considered interchangeable.

Does age matter? Optimizing AML treatment in older adults

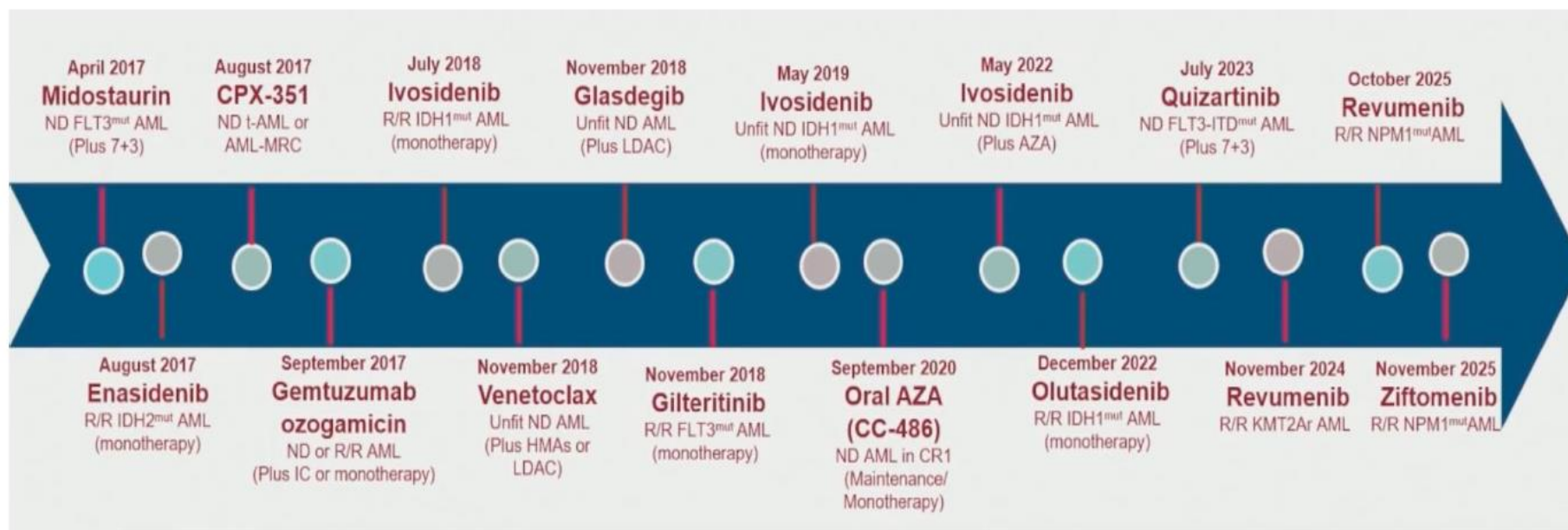
Catherine Lai² and Tara L. Lin¹

¹Division of Hematologic Malignancies, University of Kansas, Kansas City, KS; and ²Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

In total, there are 9 recommendations, summarized as follows:

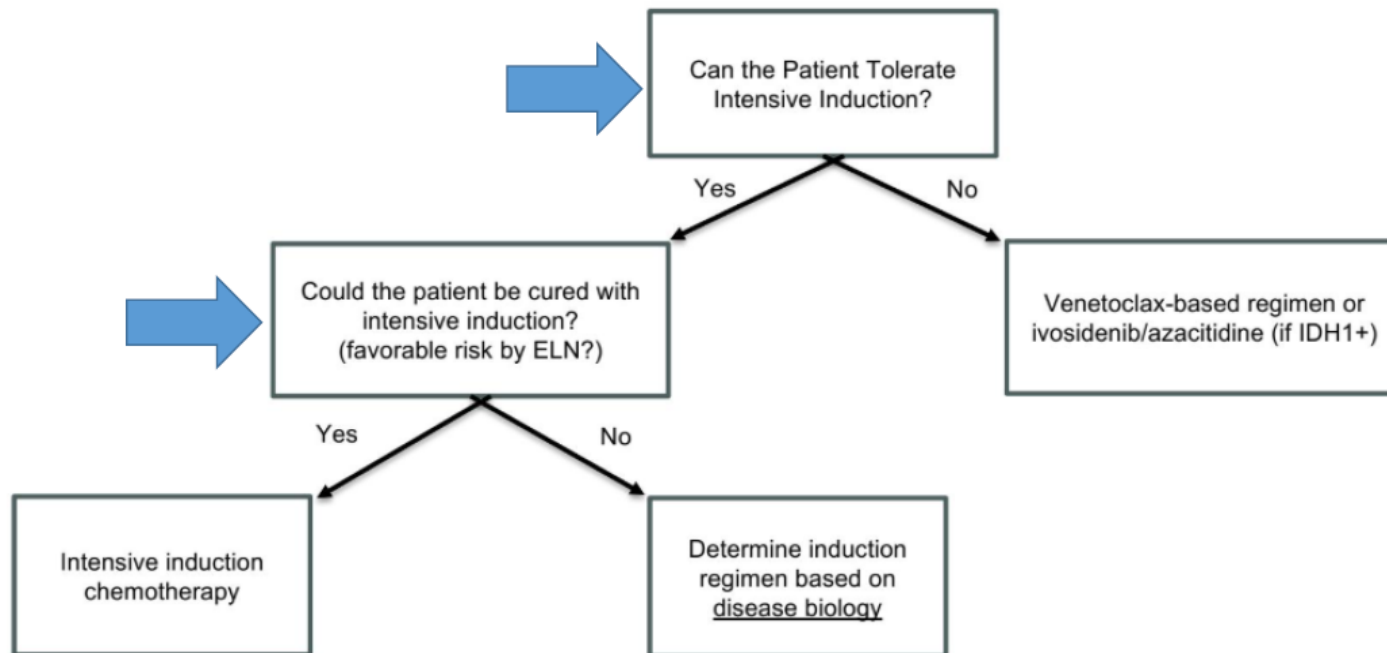
1. For newly diagnosed patients with AML able to tolerate therapy, the recommendation is for treatment over best supportive care (BSC).
2. For patients able to tolerate intensive induction, conventional chemotherapy should be given, especially in patients with favorable-risk cytogenetics. In patients with certain poor-risk molecular abnormalities, HMA- or LDAC-based treatment may be preferred.
3. For patients in remission after conventional chemotherapy and unable to undergo stem cell transplantation, postremission treatment should be given.
4. For patients unable to tolerate conventional chemotherapy, treatment with HMA plus venetoclax is preferred over HMA only. If unable to use HMA combined with venetoclax, LDAC combined with venetoclax should be used over LDAC only. Preference should be for HMA over BSC, and if using decitabine, a 5-day schedule should be preferred over 10.
5. For older adults with IDH1 mutations who are unable to tolerate conventional chemotherapy, recommendation is for azacitidine plus ivosidenib or HMA plus venetoclax. For more frail patients, recommendation is for azacitidine plus ivosidenib over azacitidine alone. For IDH2-mutated patients unable to tolerate conventional chemotherapy, the recommendation is for HMA plus venetoclax. If venetoclax is not being used, the recommendation is for azacitidine alone over azacitidine plus enasidenib.
6. For patients who receive HMA combined with venetoclax and are in remission, therapy should be continued indefinitely.
7. For FMS-like tyrosine kinase 3 (FLT3)-mutated patients who are able to tolerate conventional chemotherapy, addition of an FLT3 inhibitor is recommended.
8. For patients in remission with a high risk of relapse, recommendation is stem cell transplant if eligible and can tolerate.
9. For patients who have no further treatment options, transfusion support should be an option.

Thirteen new agents approved by FDA since 2017 for AML



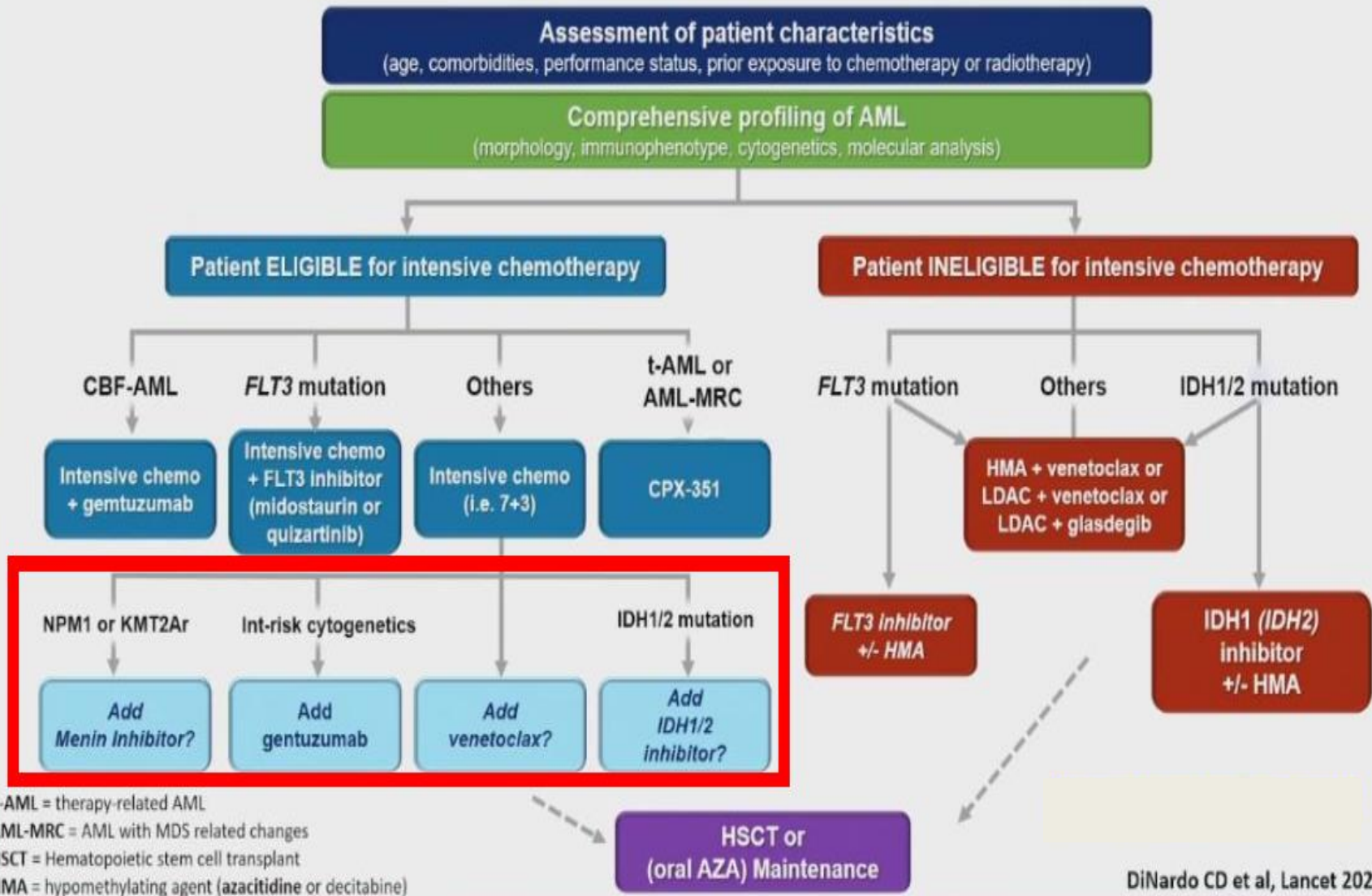
The question is not «what do we have», but «where do we place these drugs» and «what are we learning»

Two Questions To Ask When Deciding on an Induction Regimen



But.....,with multiple therapeutics emerging in recent years, the paradigm has shifted toward “**who would benefit from intensive chemotherapy**” rather than who is deemed fit.

Evolving diagnostic and treatment paradigm for Newly Dx AML

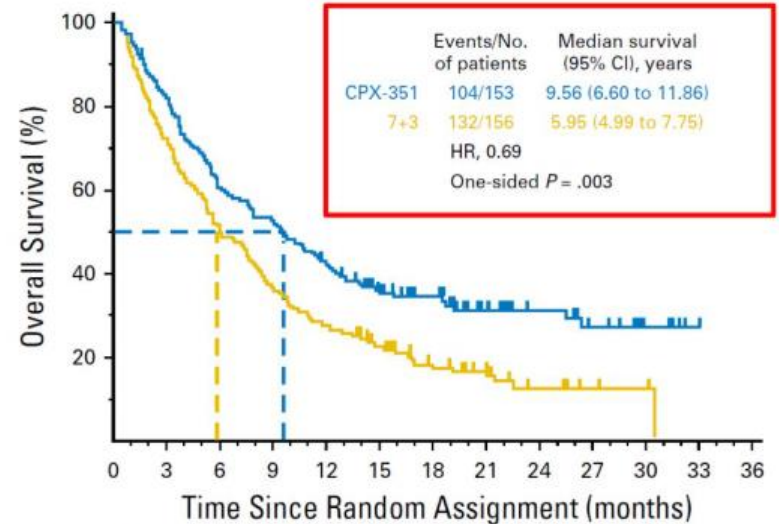
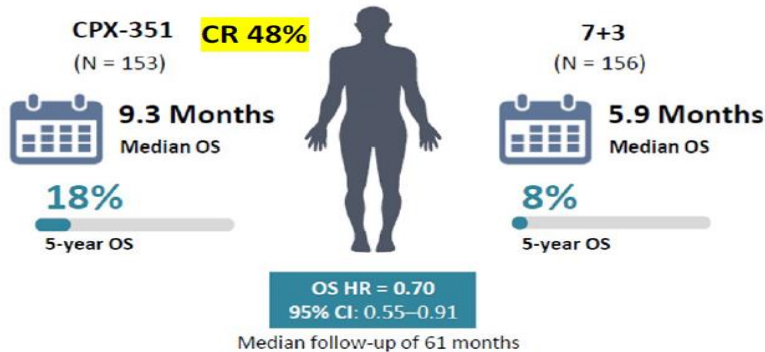


A Randomized Phase 3 Trial of CPX-351 vs 7+3 in AML-MRC/Therapy-Related AML

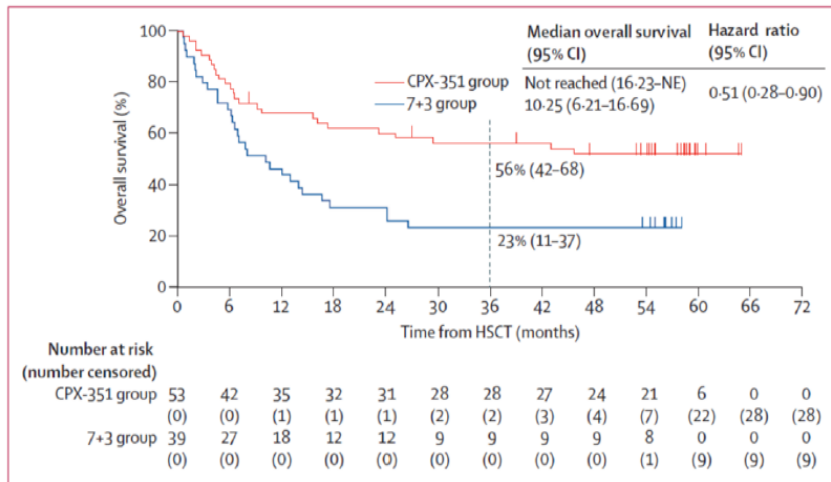


Patient Population

- ✓ 60-75 years of age
- ✓ Newly diagnosed high-risk secondary AML



Overall survival from date of HSCT: 5-year results¹



No. at risk

CPX-351	153	122	92	79	62	46	34	21	16	11	5	1
7+3	156	110	77	56	43	31	20	12	7	3	2	0

Improved median OS seen across:

- AML types (t-AML, AML-MRC)
- Age groups (60-69 yrs vs 70-75 yrs)
- After achievement of CR (w/ or w/o alloBMT)

Unclear benefit of CPX-351 in:

- Post-HMA therapy
- TP53 mutations

International real-world data corroborate clinical activity of CPX-351 in newly diagnosed AML-MRC ≥18 years

CPX-351 leads to superior outcomes compared with 7+3 in AML-MRC and represents a SOC patients aged ≥60 years & a treatment option for patients 18-60 years with AML-MRC

After a median follow-up of 60.6 months, improved median OS with CPX-351 versus 7+3 was maintained, with a HR that was very stable and consistent with the primary endpoint analysis KM-estimated survival rates were higher for CPX-351 versus 7+3 at 3 and 5 yrs

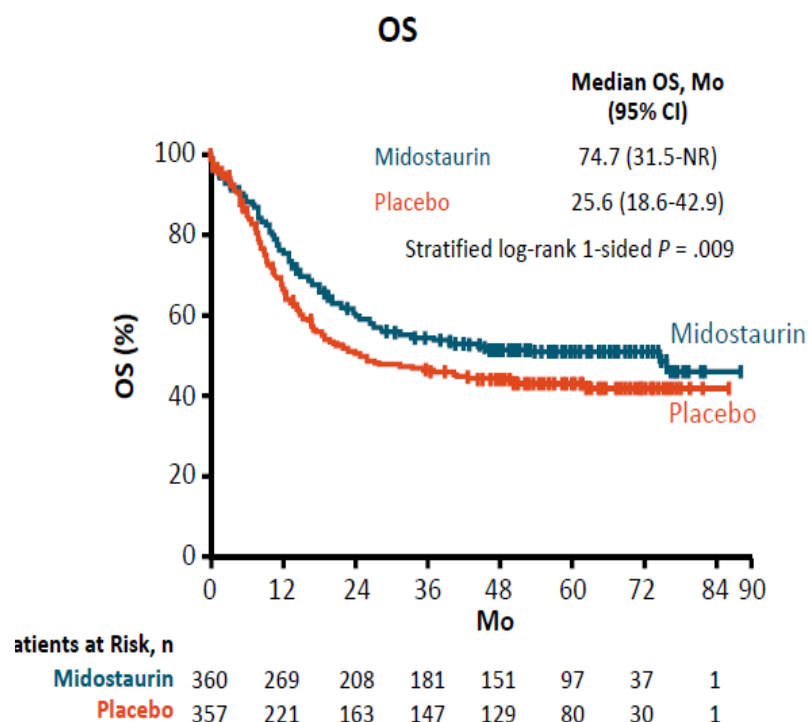
Lancet JE et al. *J Clin Oncol*. 2018;36(26):2684-2692. CPX-351 prescribing information. Jazz: 2017. Accessed May 22, 2021

Cortes JE, et al. *Leukemia*. 2019; 33(2):379-389. Heuser M, et al. *Ann Hematol*. 2021;100(5):1181-1194; Chiche E, et al. *Blood Adv*. 2021;5(1):176-184; Rautenberg C, et al. *Blood Cancer J*. 2021;11(10):164.

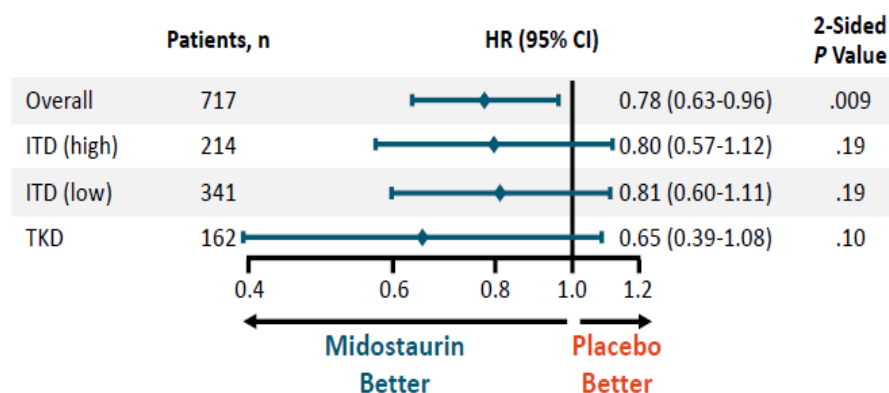
Phase III CALGB 10603 RATIFY Trial

Patients with FLT3-mutated AML received standard induction/consolidation chemotherapy plus either midostaurin or placebo. Patients in remission after consolidation entered a maintenance phase (midostaurin or placebo).

RATIFY: Overall Survival



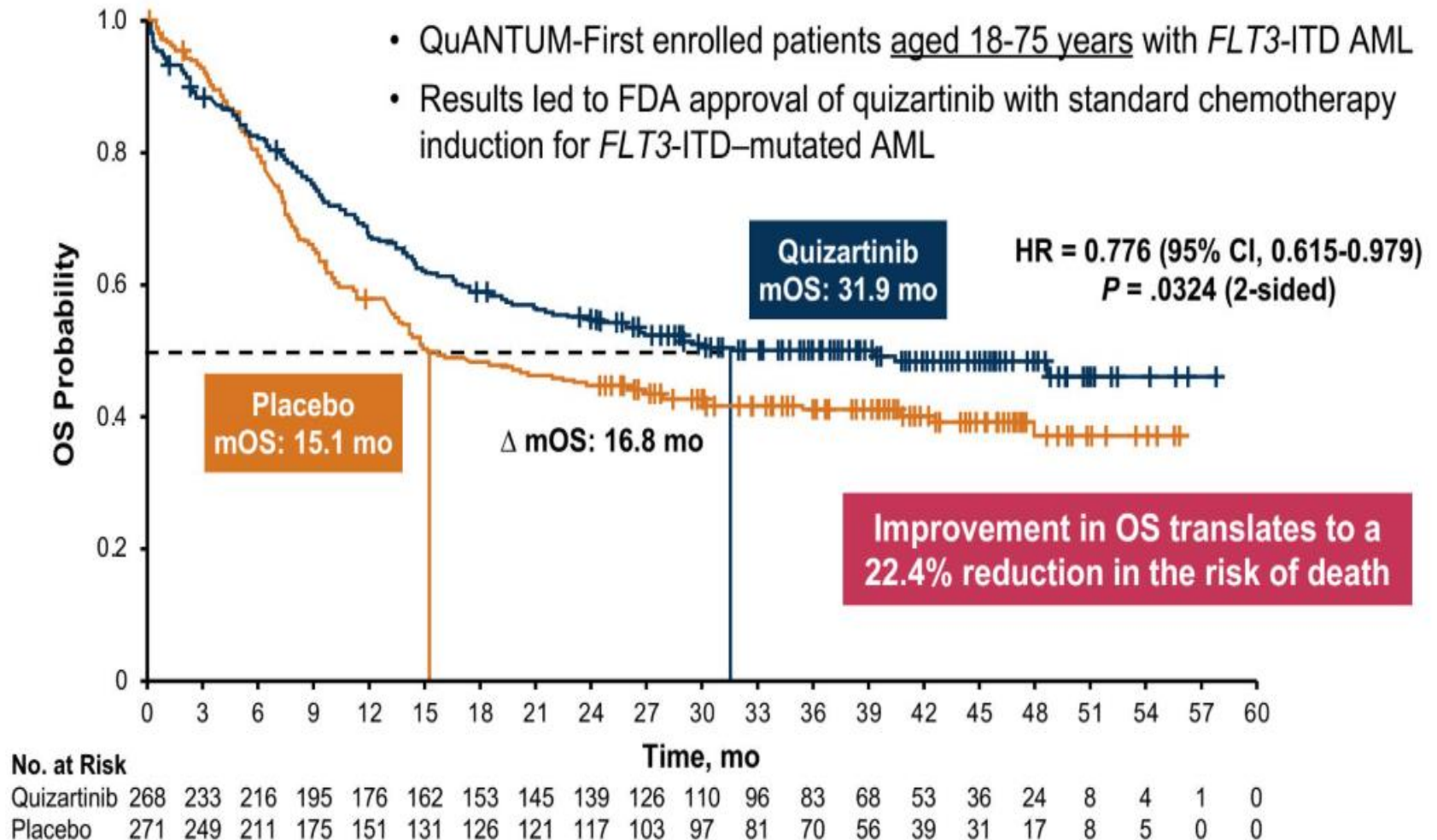
Subgroup Analysis



- 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

QuANTUM-First: Addition of Quizartinib Improves OS vs Placebo in ND FLT3-ITD+ AML

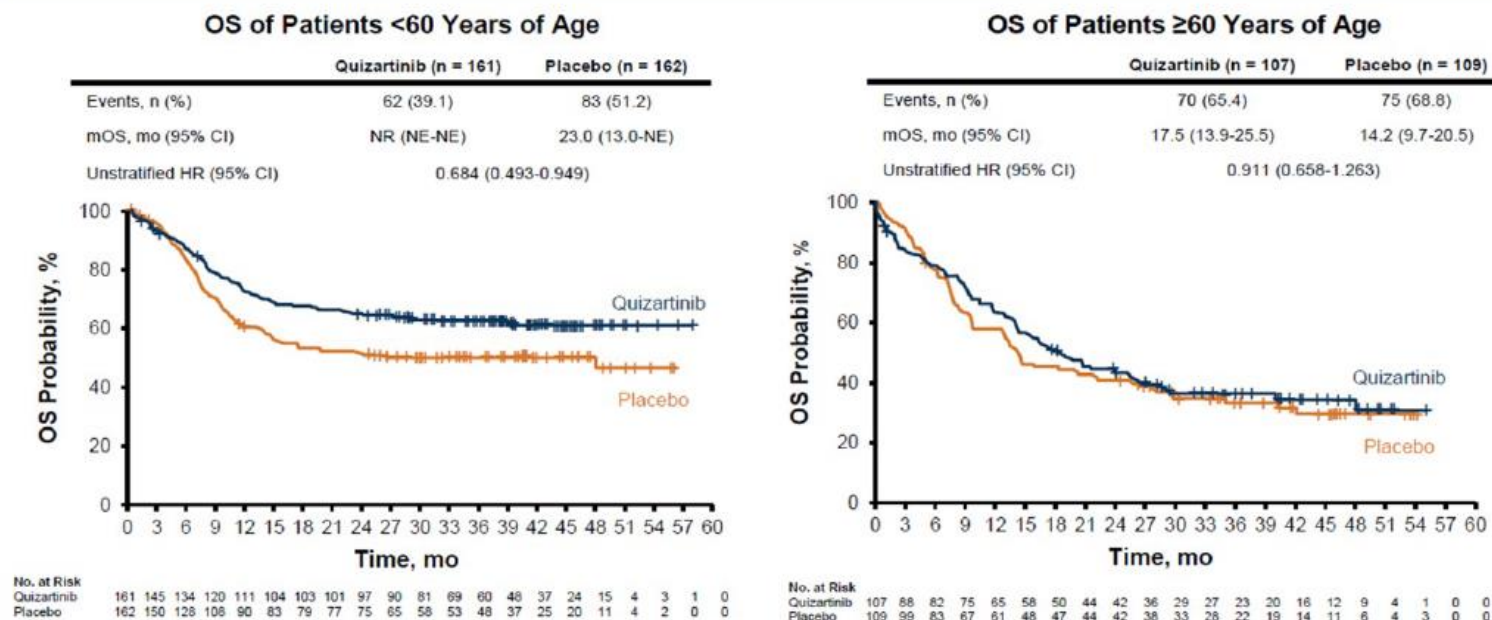
- QuANTUM-First enrolled patients aged 18-75 years with *FLT3*-ITD AML
- Results led to FDA approval of quizartinib with standard chemotherapy induction for *FLT3*-ITD-mutated AML



Erba H et al. *Lancet*. 2023;401(10388):1571-1583.

Quantum First: the primary endpoint was met, mostly in young patients

QuANTUM-First: Overall Survival by Age¹



1. Erba H et al. *Lancet*. 2023;401:1571-1583.

Elimination of MRD by *FLT3* ITD NGS MRD Assay in QuANTUM-First Trial by Treatment Course

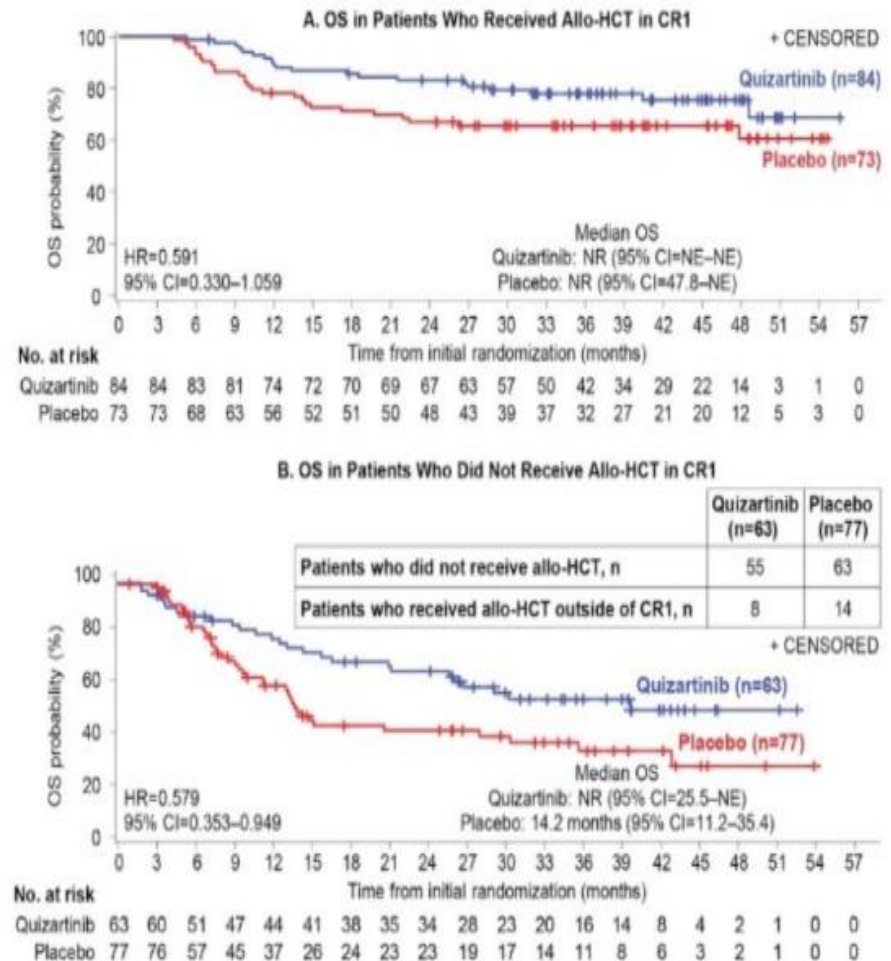
	CRc After Induction		After 2 Cycles of CTx		After Last Consolidation Cycle	
	QUIZ	PLAC	QUIZ	PLAC	QUIZ	PLAC
Patients with non-detectable MRD, %	22.8	11.9	31.7	21.7	55.8	41.2
Nominal P value	0.0122		0.0609		0.0089	

QuANTUM-First: Overall Survival in Patients Who Achieved CR by HCT Status

Patients receiving quizartinib had longer OS irrespective of alloHCT in CR1

FDA approved as maintenance monotherapy following consolidation for *FLT3*-ITD-mutated AML

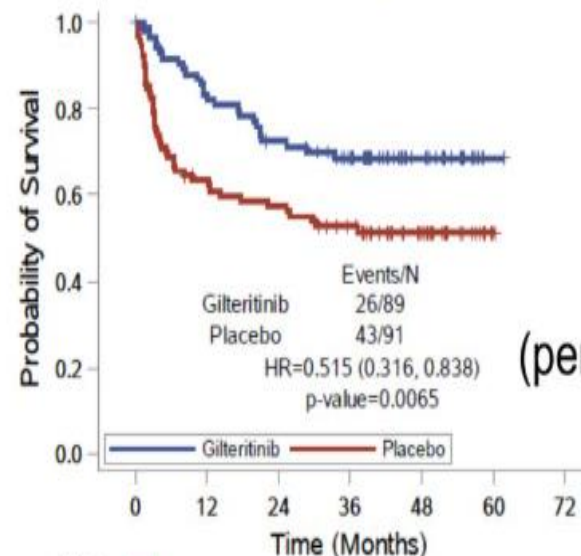
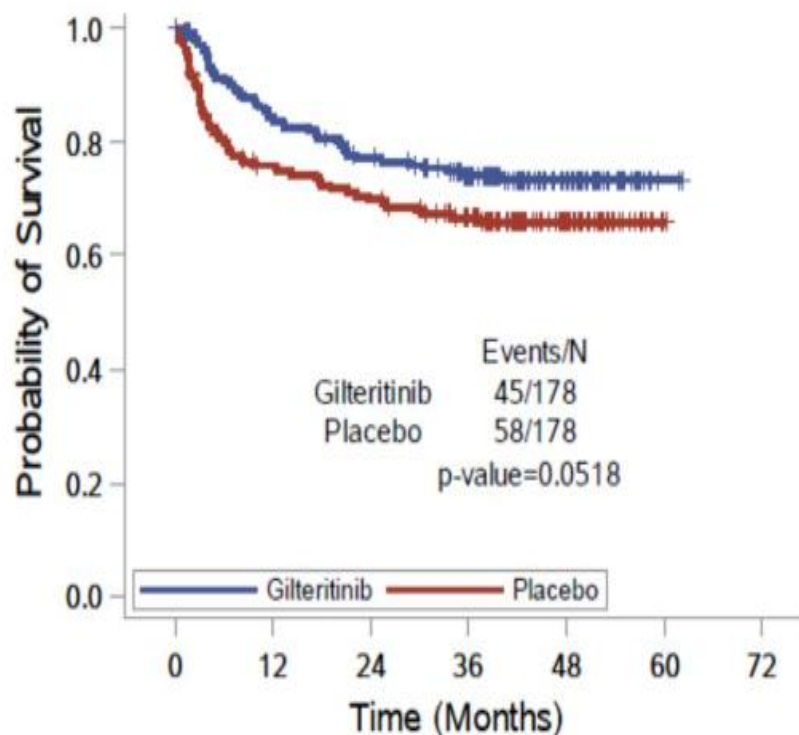
- Not indicated as maintenance monotherapy following alloHCT



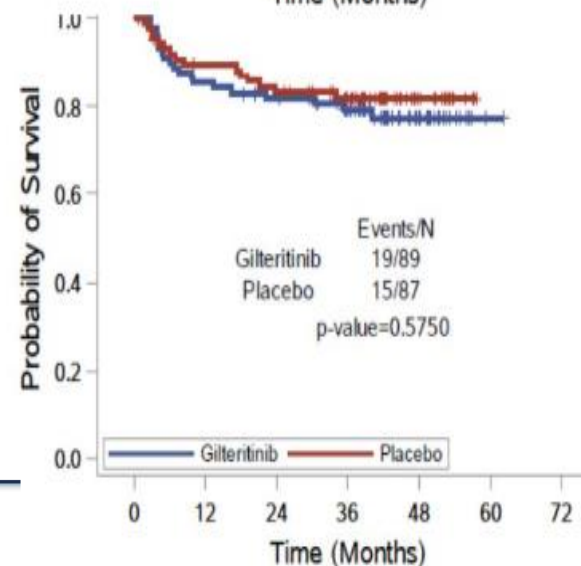
BMT-CTN 1506/MORPHO:

NGS MRD+ Had Clear Benefit With GILT Post-ASCT, NGS MRD- Did Not

Primary objective:
Relapse-free survival (RFS)
HR = 0.679 (0.459-1.005)
 $P = 0.0518$



RFS
MRD positive
(peri-transplant 50%)



RFS
MRD negative

Improvement in RFS with gilteritinib maintenance in MRD+ group

FLT3i Are Now a Standard Part of Maintenance Therapy ± HCT in AML (Patients Aged ≥18 Years)

Post-transplant

- Post-allogeneic HCT, in remission, and history of *FLT3* mutation
- Gilteritinib (*FLT3*-ITD or TKD) (preferred for *FLT3*-ITD in CR1 without MRD negativity by ultrasensitive assay pre-transplant)
- Sorafenib (*FLT3*-ITD only)
- Midostaurin (*FLT3*-ITD or -TKD)
- Quizartinib (*FLT3*-ITD only)

Patient with history of *FLT3*-ITD mutation

- Previously received FLT3i
- No allogeneic HCT is planned
- Quizartinib (*FLT3*-ITD only) (preferred for *FLT3*-ITD)
- Midostaurin (*FLT3*-ITD or TKD)

1. NCCN clinical practice guidelines in oncology. Acute myeloid leukemia. Version 2.2025.

https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. 2. Burchert A et al. *J Clin Oncol*. 2020;38:2993-3002.

ALFA-0701: GO plus 7+3 demonstrated efficacy as 1L therapy

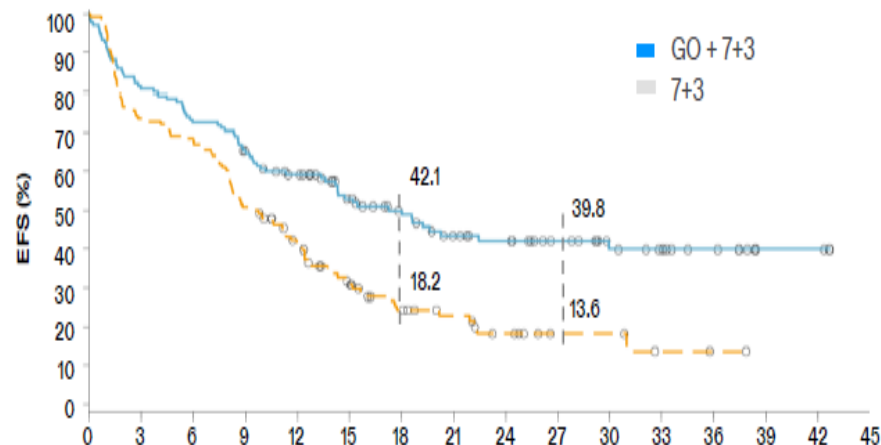
ML

EFFICACY¹

Median EFS (17.3 vs 9.5 mo; HR: 0.56 [95% CI: 0.42-0.76]; p=0.0002)

Median RFS (28.0 vs 11.4 mo; HR: 0.53 [95% CI: 0.36-0.76]; p=0.0006)

Among patients receiving GO + 7+3 vs without GO



No. at risk	Time (mo)														
GO + 7+3	135	109	98	86	74	57	47	36	32	25	18	15	10	3	0
7+3	136	100	93	69	51	32	21	16	10	5	5	2	1	0	0

Meta-Analysis (Hills, et al)

Cytogenetic Group	Estimated OS (6+ years)		Survival Benefit
	With GO	Without GO	
Favorable	75.5%	54.8%	20.7%
Intermediate	39.6%	33.9%	5.7%
Adverse	8.9%	6.7%	2.2%

GO added to intensive chemotherapy has a favorable benefit/risk ratio in those with favorable and intermediate-risk disease

OUTCOMES BY MOLECULAR SUBGROUPS

A retrospective sub-analysis evaluated the impact of molecular aberrations on outcomes with GO in non-CBF AML (N=235):²

- The EFS benefit of GO was restricted to patients in the favorable- or intermediate-risk molecular subgroups* – HR: 0.54 (95% CI: 0.30-0.98) and 0.57 (95% CI: 0.33-1.00), respectively
- Within these risk groups, EFS benefit was further limited to patients with activating signaling mutations (*FLT3*, *NRAS*, *KRAS*, *PTPN11*, *JAK2*, *RIT1*, *CBL*), which correlated with higher CD33 expression

Fractionated 3 mg/m² doses of GO in combination with 7+3 chemotherapy demonstrated robust efficacy in adult patients with newly diagnosed AML – specifically those with favorable or intermediate-risk genetic aberrations

*According to ELN 2017³ risk classification: Favorable = *RUNX1-RUNX1T1*; *CBFB-MYH11*; *NPM1* with low or no *FLT3*-ITD; biallelic *CEBPA*.

Intermediate = *NPM1* + high *FLT3*-ITD; WT *NPM1* with low or no *FLT3*-ITD and no adverse-risk lesions; *MLL3-KMT2A*; no favorable or adverse abnormalities.

1L, first-line; 7+3, DNR 60 mg/m² D1-3, Ara-C 200 mg/m² D1-7; AML, acute myeloid leukemia; Ara-C, cytarabine; CBF, core-binding factor; CI, confidence interval; DNR, daunorubicin;

EFS, event-free survival; ELN, European LeukemiaNet; GO, gemtuzumab ozogamicin; HR, hazard ratio; mo, month; RFS, relapse-free survival; WT, wild-type.

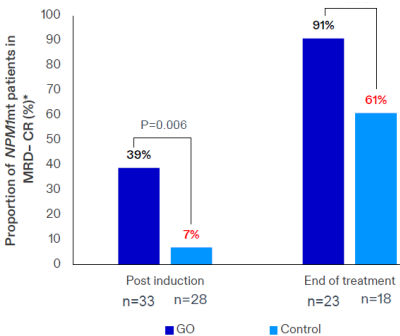
1. Lambert J, et al. *Haematologica* 2019;104:113-119. 2. Fournier E, et al. *Blood* 2020;135:542-546. 3. Döhner H, et al. *Blood* 2017;129:424-447.

Potential reasons for overall survival not differing significantly between treatment arms

- OS can be confounded by subsequent AML therapy

ALFA-0701 MRD negativity

Post-study treatment	GO (n=135), n (%)	Control (n=136), n (%)
Patients with at least one follow-up therapy	96 (71.1)	109 (80.1)
Patients with GO as part of follow-up therapy	2 (1.5)	30 (22.1)
Patients with HSCT as part of follow-up therapy	32 (23.7)	53 (39.0)
Timing of HSCT		
In first remission for responder patients	17 (12.6)	22 (16.2)
After induction failure	2 (1.5)	9 (6.6)
After relapse	13 (9.6)	22 (16.2)



Improved efficacy outcomes in the GO arm do not appear to be driven by HSCT

ALFA-0701: GO plus 7+3 is associated with a manageable safety profile in 1L AML

SAFETY



1L

Similar proportions of patients experienced severe (Grade ≥ 3) infection across treatment arms

The addition of GO was associated with:

- Hemorrhage (Grade ≥ 3 ; 22.9% vs 9.5%)
- Thrombocytopenia (Grade ≥ 3 ; 26.0% vs 4.4%)

There was **no associated increase in early mortality**; the 30-day mortality rates were comparable between arms

VOD occurred in 4.6% vs 1.5% (with and without GO)

Summary of Deaths

Deaths, n (%)	GO + 7+3 n=131	7+3 n=137
Deaths within 30 days of initiating study treatment	5 (3.8)	3 (2.2)
Deaths during safety reporting period*	6 (4.6)	5 (3.6)
Mechanism(s) of death*		
Disease progression or relapse	2 (1.5)	2 (1.5)
Septic shock	2 (1.5)	2 (1.5)
Infection	0	1 (0.7)
Liver toxicity	1 (0.8)	0
Hemorrhage	3 (2.3)	1 (0.7)
Other	2 (1.5)	3 (2.2)

The addition of fractionated 3 mg/m² doses of GO to 7+3 was associated with higher rates of thrombocytopenia and bleeding, but similar rates of early mortality

* ≤ 28 days after the last dose of any study drug treatment. [GO: daunorubicin, cytarabine, and idarubicin (a component of salvage therapy)].

GIMEMA AML1819 TRIAL: GEMTUZUMAB OZOGAMICIN PLUS INTENSIVE CHEMOTHERAPY IMPACTS ON THE LEVEL OF POST-CONSOLIDATION MEASURABLE RESIDUAL DISEASE (MRD) IN ACUTE MYELOID LEUKEMIA

MRD by Risk Category

- Favorable Risk AML: MRD-negative: 81%
MRD-positive: 19%
- Intermediate Risk AML: MRD-negative: 63%
MRD-positive: 37%

Contextual Comparison (Historical)

- In AML1310 (no GO):MRD-negative rate post-consolidation in IR patients: 46%
- In AML1819 (with GO):MRD-negative rate in IR patients: 63%

Cross-trial comparison limitations apply

Key Takeaways

- AML1819 supports the feasibility of an MRD-oriented treatment algorithm
- GO-based regimens achieved high post-consolidation MRD negativity rates
- Ongoing follow-up will clarify the impact on long-term clinical outcomes

Real-World Efficacy and Safety of Gemtuzumab Ozogamycin (GO) and 3 + 7 regimen in fit newly diagnosed Acute Myeloid Leukemia (AML) patients. A Retrospective multicenter study of “Rete Ematologica Pugliese” (REP)

M. Dargenio^{a,*}, C. Buquicchio^b, D. Pastore^c, L. Aprile^d, L. Ciuffreda^e, G. Greco^f, M. Delia^g, V. Federico^a, MP. Fina^a, D. Seripa^a, R. Matera^a, G. Tarantini^b, A. Maggi^d, L. Melillo^e, V. Pavone^f, P. Musto^g, G. Specchia^h, N. Di Renzo^a

Characteristics	N (%)
Median age, years (range)	54.5 (25-75)
Age ≥ 60 years	11 (32)
Sex	
Male	17 (50)
Female	17 (50)
ELN 2017 risk stratification, n (%)	
Low	10 (29.4)
Intermediate	14 (41.2)
High	10 (29.4)
AML type, n (%)	
NPM1-mutated	10 (29.4)
t (8;21)	2 (5.8)
Bone marrow blast %	
Median (range)	67.5 (25-95)
White blood cells (/μL)	
Median (range)	5.63 (1-229)
Number of consolidation courses	
one	12 (35)
two	14 (41)
Allogeneic stem cell transplant	16 47

Overall Survival from diagnosis was not reached.

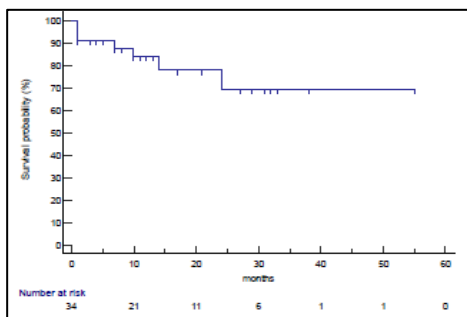
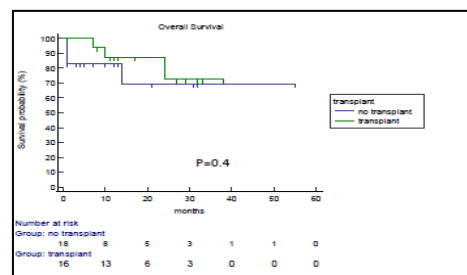
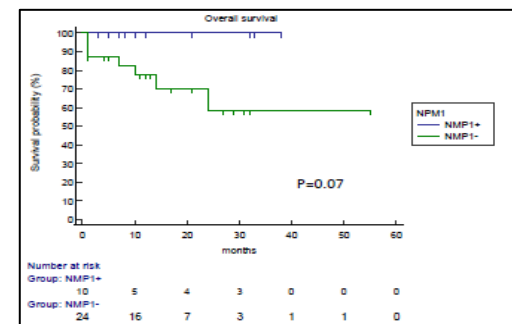


Fig. 4. Overall Survival by treatment (transplant vs no transplant)



Overall Survival according by NPM1 status

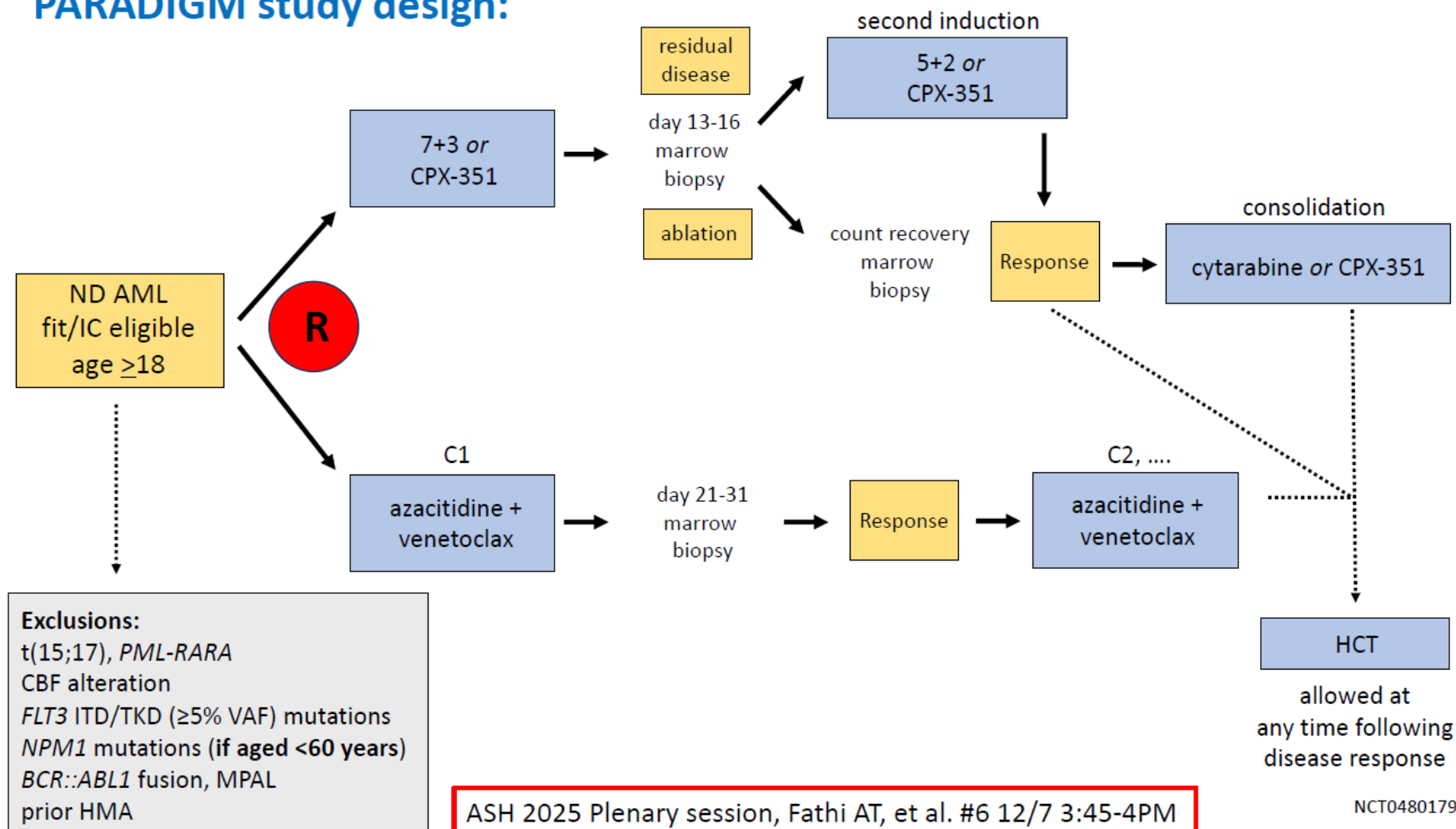


Safety.

Adverse Events	N (%)
Any grade hematological event	25 (73.5)
Any grade non hematological event	26 (76.5)
Sepsis	24 (70)
Covid 19 infection	8 (23.5)
VOD (grade 2)	3 (5.8)
Induction death	3 (5.8)

In conclusion our findings, though limited by the retrospective ,nature of the study and the small sample size, confirm in a real life setting the **efficacy and toxicity** data reported in clinical trials of com bination of GO + “3 + 7 ” . This study suggests **the feasibility of GO-based treatment given also in patients older than 60 years and as a bridge to allo-HSCT**. Moreover, fitness assessment, prophylaxis, prompt management of infectious toxicities and VOD are crucial in the man agement of this advantageous strategy for the treatment of AML.

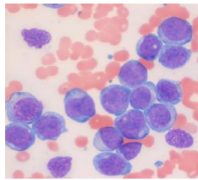
PARADIGM study design:



PARADIGM Results:

- As of 7/25/2025, 172 patients (pts) at 9 US centers were randomized to aza-ven (n=86) or IC (n=86)
- Intent-to-treat analysis:
 - ORR (OR=CR+CRh+CRi+PR+MLFS) was significantly higher in the aza-ven arm (88% vs 62%; $P<0.001$)
 - CCR (CR+CRh+CRi) was significantly higher in the aza-ven arm (81% vs 55%; $p<0.001$)
 - CR rates for aza-ven and IC were not significantly different (59% vs 50%; $p=.066$)
- Primary EFS endpoint (median follow-up 16 months):
 - 1-year EFS was 53% for the aza-ven arm and 39% for the IC arm (HR 0.61; $p=0.017$)
- Progression to HCT following response from protocol therapy differed across arms ($p=0.009$)
 - 52 (61%) pts on aza-ven arm and 34 (40%) pts on IC arm
- Grade 3/4 lung infections and sepsis occurred in 12% and 7% of aza-ven, and 15% and 11% of IC pts
- 30- and 60-day mortality rates on the aza-ven arm were both 0%, vs 3.5% and 4.7% in the IC arm, respectively

NCI Precision Medicine Initiative: MyeloMATCH



Newly diagnosed AML

AML Transcripts				
AML1	ANKRD26	PLA2	GBL	CD34
CD44	DNMT3A	FLT3	IGF1R	NRAS
DNMT3A	DNMT3A	IGF1R	IGF1R	NRAS
EP300	EP300	EP300	EP300	EP300
EP300	EP300	EP300	EP300	EP300
EP300	EP300	EP300	EP300	EP300
EP300	EP300	EP300	EP300	EP300
EP300	EP300	EP300	EP300	EP300
EP300	EP300	EP300	EP300	EP300
EP300	EP300	EP300	EP300	EP300



- Platform: Ion Torrent™ Genexus™ System
 - 45 DNA genes and 35 fusion driver genes
 - Includes 28/30 (93.3%) genes mutated with >=3% frequency in AML
 - Includes 36/50 (72%) genes mutated with >1% frequency in AML
 - Includes 779 unique fusions reported in AML
 - Can detect FLT3-ITD up to 120bp
- Can detect all genetic alterations needed for
 - WHO classification of AML, except inv 3
 - NCCN/ELN risk stratification, except inv 3

- 3-day genotyping/risk stratification
- Rational allocation to randomized trial with novel agents
 - targeted agent when present
 - genetic risk-specific if not
- Trial registration for all stages of therapy
- Correlative science in top academic labs including flow MRD and Twinstrand NGS MRI

Myelomatch “marker negative” studies

Intermediate Risk AML: MM1YA-CTG01

Newly Diagnosed, 18-59 yrs
IR AML (n=153)

7+3+Ven Aza+Ven 7+3

Study Chairs
• Sarit Assouline
• Lynn Savoie

High Risk AML: MM1YA-S01

Newly Diagnosed,
Age 18-59 years
HR AML (n=268)

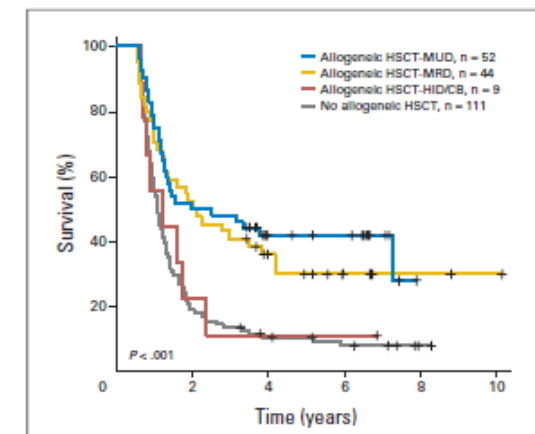
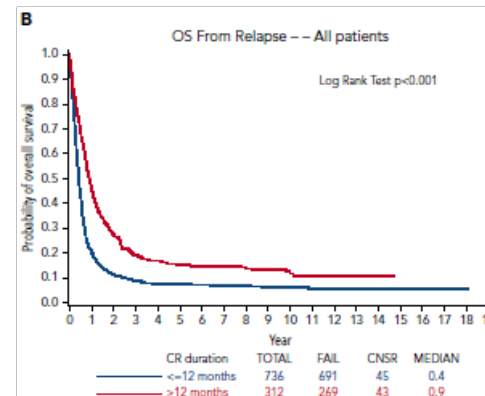
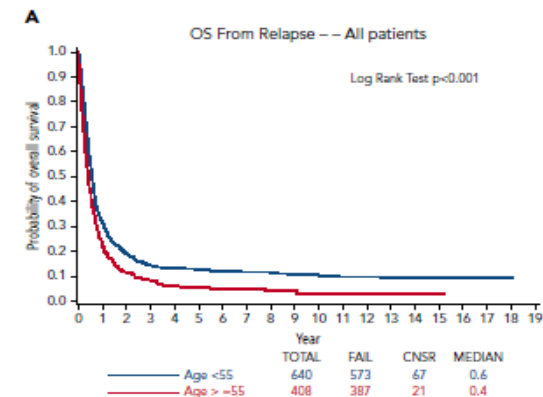
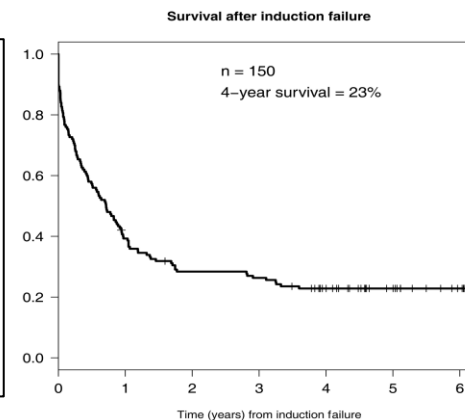
7+3 7+3+Ven Aza+Ven CPX-351 CPX-351+Ven

Study Chairs
• Paul Shami
• Tara Lin

Relapsed or refractory acute myeloid leukemia (R/R AML)

- has presented challenges for hematologists for decades.
- outcomes are consistently disappointing with median OS about 6 months and a 5-year OS rates of ~10%.
- no universally accepted standard therapy other than the enrollment into clinical trials
- 15-20% of patients demonstrate Primary Induction Failure (PIF)
- HSCT is the only reliable option with curative potential with OS in 20%–35% at 4 years.
- relapse after allo-HSCT occurs in 25%–55%

Treatment failure	
Refractory disease	No CR, CRh or CRi at the response landmark, ie, after 2 courses of intensive induction treatment or a defined landmark, eg, 180 d after commencing less-intensive therapy
Relapsed disease (after CR, CRh or CRi)	Bone marrow blasts $\geq 5\%$; or reappearance of blasts in the blood in at least 2 peripheral blood samples at least one week apart; or development of extramedullary disease



- Medical assessment
- Cytogenetic and mutational analysis
- Check availability of clinical trial



How I treat refractory and relapsed acute myeloid leukemia

Felicitas Thol,¹ Hartmut Döhner,² and Arnold Ganser¹

¹Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; and ²Department of Internal Medicine III, University of Ulm, Ulm, Germany

Table 3. FDA/EMA approvals for R/R AML

Agent	FDA/EMA approval	Age in study, y	N	ORR, %	CR, %	CRi, %	Median survival, mo	Reference
Ivosidenib	<i>IDH1</i> -mutated R/R AML/not authorized by EMA	18-89	258	42	22	9	8.8	65
Olutasidenib	<i>IDH1</i> -mutated R/R AML/not authorized by EMA	32-87	153	48	32	10	11.6	66
Enasidenib	<i>IDH2</i> -mutated R/R AML/not authorized by EMA	19-100	109	40	19	7	9.3	64
Gemtuzumab ozogamicin	CD33 ⁺ R/R AML as monotherapy/not authorized by EMA	20-87	277	26	13	13 (CRp)	4.9	97
Gilteritinib	<i>FLT3</i> -mutated R/R AML	20-84	247	54	21	26	9.3	27

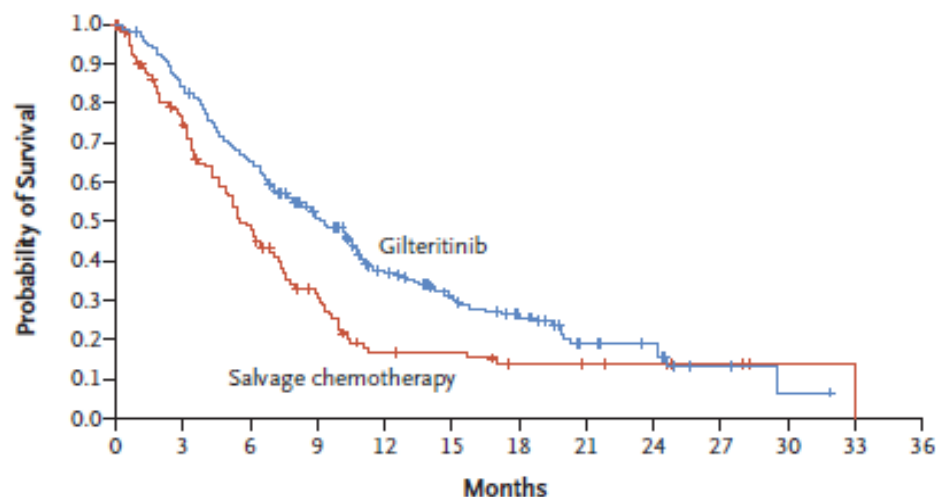
ORIGINAL ARTICLE

Gilteritinib or Chemotherapy for Relapsed or Refractory *FLT3*-Mutated AML

A.E. Perl, G. Martinelli, J.E. Cortes, A. Neubauer, E. Berman, S. Paolini, P. Montesinos, M.R. Baer, R.A. Larson, C. Ustun, F. Fabbiano, H.P. Erba, A. Di Stasi, R. Stuart, R. Olin, M. Kasner, F. Ciceri, W.-C. Chou, N. Podoltsev, C. Recher, H. Yokoyama, N. Hosono, S.-S. Yoon, J.-H. Lee, T. Pardee, A.T. Fathi, C. Liu, N. Hasabou, X. Liu, F. Bahceci, and M.L. Lewis

ADMIRAL: Gilteritinib Prolongs OS in m*FLT3* R/R AML

A Overall Survival



	Median Overall Survival (95% CI) mo
Gilteritinib	9.3 (7.7–10.7)
Salvage Chemotherapy	5.6 (4.7–7.3)
Hazard ratio for death, 0.64 (95% CI, 0.49–0.83) P<0.001	

No. at Risk

Gilteritinib	247	206	157	106	64	44	31	14	11	4	1	0	0
Salvage chemotherapy	124	84	52	29	13	12	8	7	5	3	1	0	0

The median OS in the gilteritinib group was significantly longer than that in the CHT group (9.3 mos vs. 5.6 mos; HR, 0.64; 95% [CI], 0.49 to 0.83; P<0.001).

The ORR was 34.0% in the gilteritinib group and 15.3% in the CHT group.

Long-term survival is limited by the development of drug resistance mutations in persistent *FLT3*+ clones.

A review of treatment options employed in the management of Acute Myeloid Leukemia

Mohamed Zakee Mohamed Jiffry ^a, Robert Kloss ^b, Mohar Nkechi Okam ^c, Prabasha Weeraddana ^c, Dinusha Dharmaratne ^c

> Clin Lymphoma Myeloma Leuk. 2017 Nov;17(11):767-773. doi: 10.1016/j.clml.2017.06.002. Epub 2017 Jun 19.

FLAG-Ida Regimen as Bridge Therapy to Allogeneic Transplantation in Refractory/Relapsed Acute Myeloid Leukemia Patients

Mario Delia ¹, Domenico Pastore ², Paola Carluccio ², Crescenza Pasciolla ², Alessandra Ricco ², Antonella Russo Rossi ², Paola Casieri ², Anna Mestice ², Francesco Albano ², Giorgia Specchia ²

Table 3. Different chemotherapeutic regimens discussed

Regimen	Study reference			
Cytarabine + anthracycline	[25]	Phase III	667	50
Elacytarabine	[40]	Phase III	381	23
FLAG-IDA	[28]	Phase II	46	52
FLA	[30]	Phase III	405	61
FLAD	[34]	Phase II	41	53
CLAG/CLAM	[36]	Phase II	24	44
CLAG-M	[37]	Phase II	118	58
Mitoxantrone + etoposide	[31]	Phase II	61	43
MEC	[32]	Phase II	32	66
HAM	[33]	Phase II	44	36
Etoposide + cyclophosphamide	[39]	Phase II	40	42
ADE	[30]	Phase III	235	43
Vosaroxin + cytarabine	[41]	Phase III	711	30
HAA	[38]	Phase II	46	80
FLAM	[35]	Phase II	92	28

HiDAC: High dose cytarabine; FLAG-IDA: Fludarabine, cytarabine; G-CSF and idarubicin; FLA: Fludarabine and cytarabine; FLAD: Fludarabine, cytarabine and liposomal daunorubicin; CLAG: Clofarabine, cytarabine and G-CSF; CLAM: clofarabine, cytarabine and mitoxantrone; CLAG-M: clofarabine, cytarabine; G-CSF and mitoxantrone; MEC: mitoxantrone, etoposide and cytarabine; HAM: High and intermediate dose cytarabine and mitoxantrone; ADE: cytarabine, daunorubicin and etoposide; HAA: Homoharringtonine, cytarabine and aclarubicin; FLAM: Flavopiridol, cytarabine and mitoxantrone.

Intensive induction chemotherapy is often reserved for younger or fit older patients.

There are no standard guidelines regarding the optimal regimen to achieve CR prior to allogeneic HSCT. Although CR rates greater than 45% are seen with the combination of purine analogues and Ara-C, a high relapse rate greater than 40% and short remission duration (4–11 months) suggest that HSCT should be pursued as soon as CR is achieved.

Remission induction versus immediate allogeneic haematopoietic stem cell transplantation for patients with relapsed or poor responsive acute myeloid leukaemia (ASAP): a randomised, open-label, phase 3, non-inferiority trial

Matthias Stelljes*, Jan Moritz Middeke*, Gesine Bug*, Eva-Maria Wagner-Drouet, Lutz P Müller, Christoph Schmid, Stefan W Krause, Wolfgang Bethge, Edgar Jost, Uwe Platzbecker, Stefan A Klein, Jörg Schubert, Judith Niederland, Martin Kaufmann, Kerstin Schäfer-Eckart, Markus Schaich, Henning Baldauf, Friedrich Stölzel, Cathleen Petzold, Christoph Röllig, Nael Alakel, Björn Steffen, Beate Hauptrock, Christoph Schliemann, Katja Sockel, Fabian Lang, Oliver Kriege, Judith Schaffrath, Christian Reicherts, Wolfgang E Berdel, Hubert Serve, Gerhard Ehninger, Alexander H Schmidt, Martin Bornhäuser*, Jan-Henrik Mikesch*, Johannes Schetelig* on behalf of the Study Alliance Leukemia and the German Cooperative Transplant Study Group

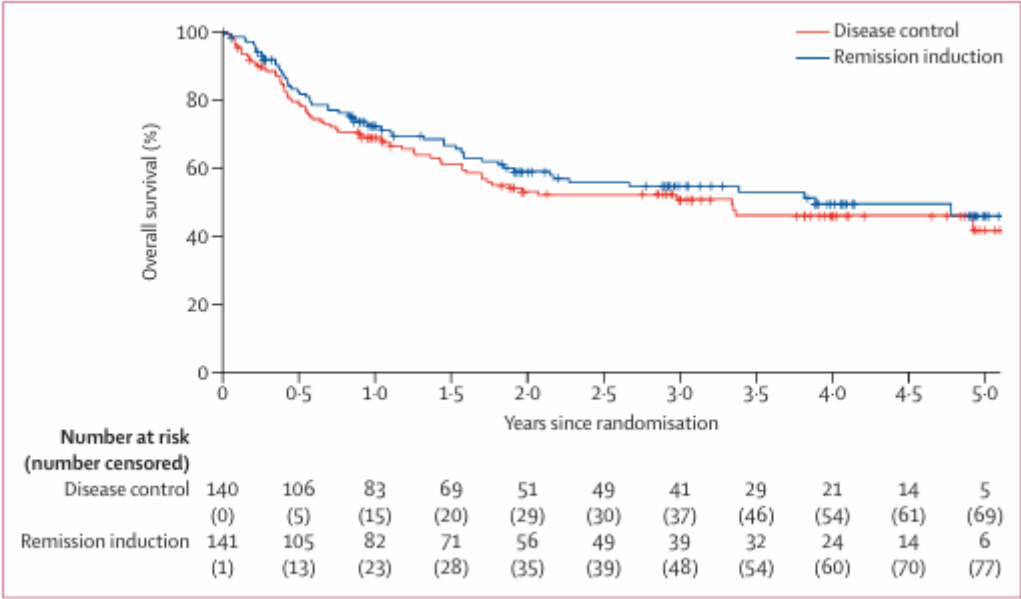
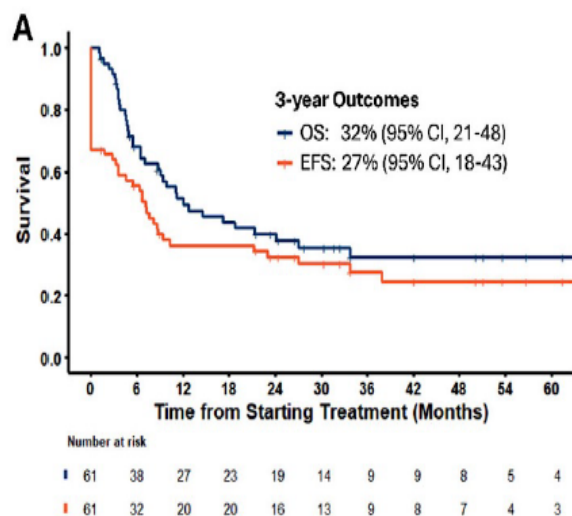


Figure 2: Overall survival from randomisation according to intention-to-treat

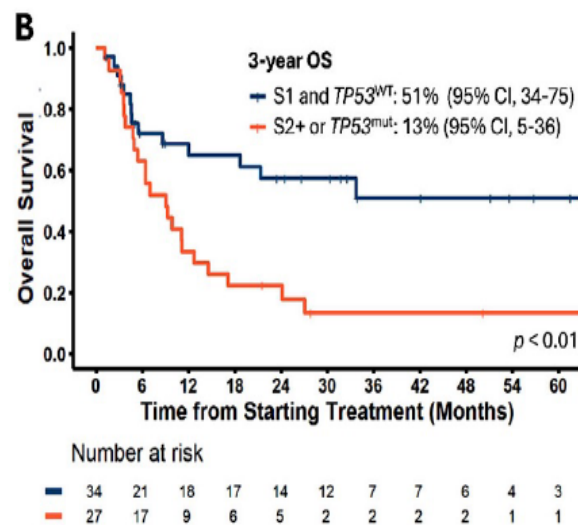
The OS was comparable between those treated with immediate alloSCT(4-yearOS of 46% [95% CI: 36%–55%]) compared with salvage therapy followed by alloSCT (4-year OS of 49% [95%CI: 39%–59%]), $p = 0.42$. Given similar OS and complete remission rates at day 56 post-alloSCT(79% vs. 83%), despite the study not meeting its primary endpoint of non-inferiority,the results suggest that immediate alloSCT may be a reasonable approach in some patients, especially if very intensive conditioning is used.

VEN-FLAG-IDA – R/R AML

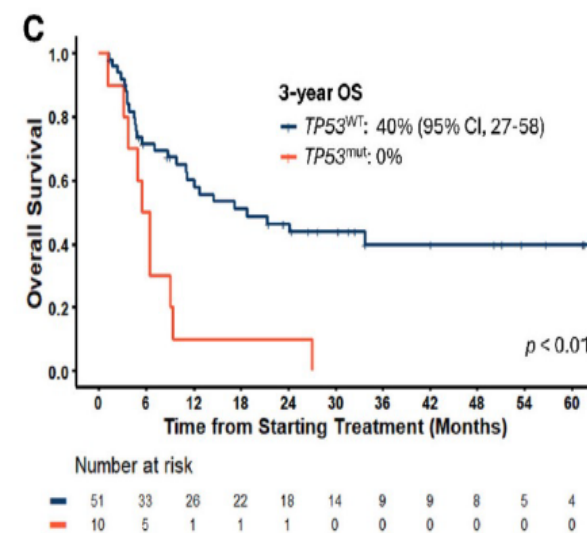
All Patients



Salvage Number/TP53 Status



$TP53^{WT}/TP53^{mut}$



- OS of first salvage $TP53$ -WT was similar to frontline therapy
- In the RR cohort, CRc=64%, and CRc=74% for first salvage $TP53$ -WT patients

Venetoclax plus hypomethylating agents as a bridge to transplant or donor lymphocyte infusion in relapsed/refractory acute myeloid leukemia

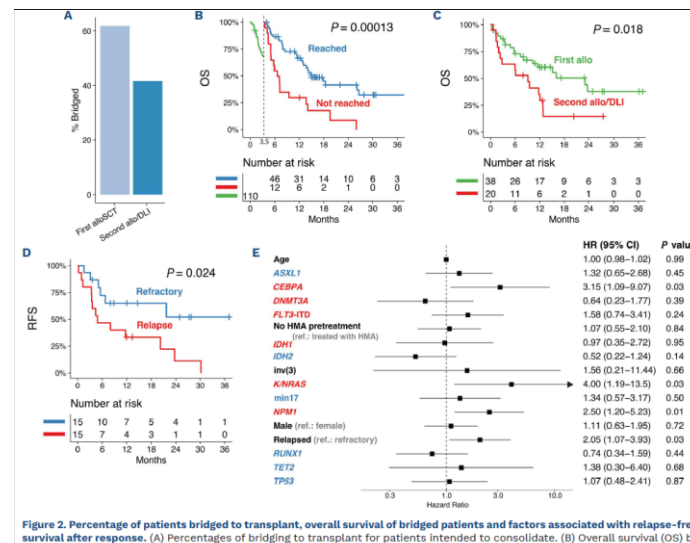
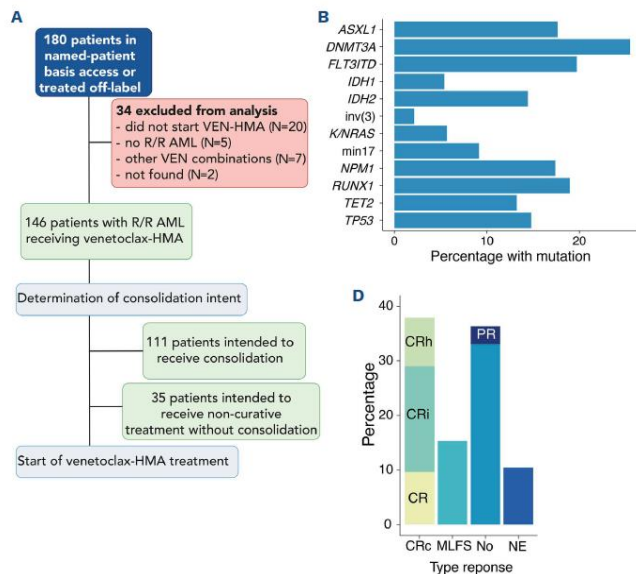


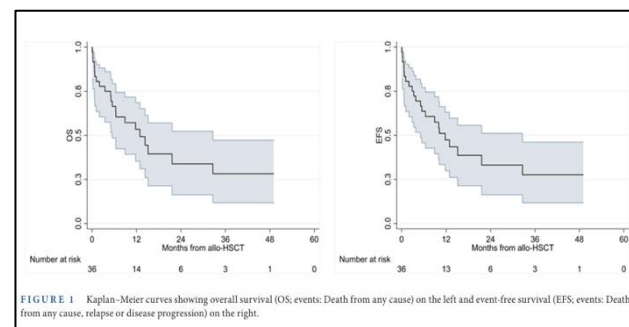
Figure 2. Percentage of patients bridged to transplant, overall survival of bridged patients and factors associated with relapse-free survival after response. (A) Percentages of bridging to transplant for patients intended to consolidate. (B) Overall survival (OS) by

Patients who achieved a response to venetoclax-HMA had a higher chance of successful bridging, with 79% of patients able to reach consolidation. In comparison, the AVALON study reported that 70% of patients received an allogeneic transplant in CRc or MLFS.7 In the VEN-DEC GITMO trial, in which newly diagnosed older patients (median age: 68.5) received venetoclax-decitabine intending to transplant, CR was reached in 69% and transplant in 57%.14 Venetoclax-HMA has high bridging rates for R/R patients achieving a response, even when compared to newly diagnosed patients.

RESEARCH LETTER

BJHaem

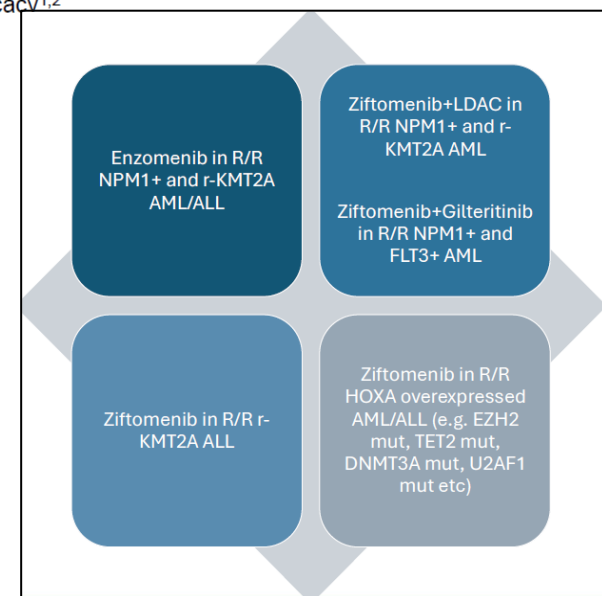
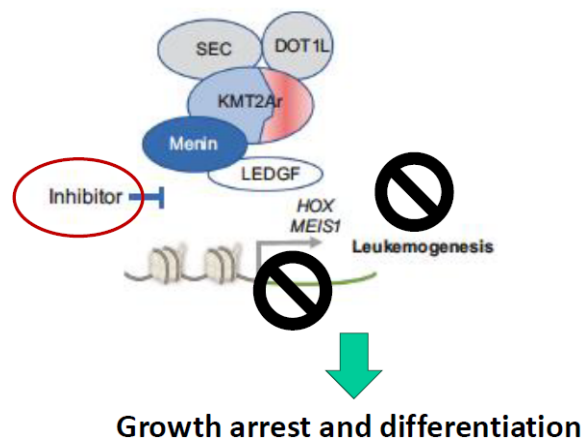
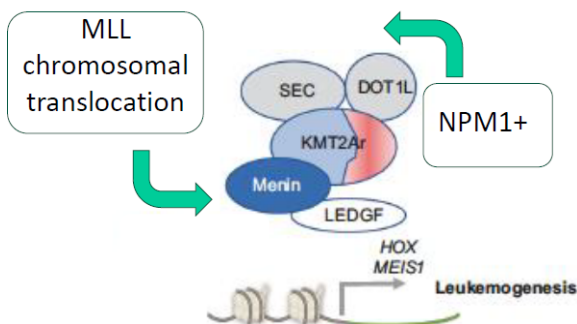
Venetoclax plus hypomethylating agents as effective bridge therapy to allogeneic stem cell transplant in relapsed/refractory acute myeloid leukaemia: A subanalysis of the AVALON study



The study provides further evidence supporting the feasibility and effectiveness of HMA- VEN as a bridge to allo- HSCT in patients with REF/REL AML. In this real- world Italian cohort, about a quarter of the REF/REL AML patients treated with HMA- VEN were able to proceed to allo- HSCT, with promising post- transplant outcomes in terms of remission, survival and manageable toxicity. Our results show that 72.2% of patients undergoing allo- HSCT after HMA- VEN achieved CR or CRi prior to transplant, consistent with previous studies reporting high CR/CRi rates in the REF/REL setting with VEN- based regimens. Post- transplant, 1- year OS, EFS, CIR and NRM were 53.4%, 47.4%, 18% and 34.2% respectively.

Menin is an essential oncogenic cofactor for leukemogenesis driven by NPM1 mut or r-KMT2A

- Each menin inhibitor has a different chemical structure and different physiochemical properties such as polar surface area, lipophilicity, and basicity that may impact safety and efficacy^{1,2}



Modified from Issa GC et al, Leukemia 2021

Trial name (NCT)	Agent (route)	Phase 1/ 2 expansion cohorts For relapsed/refractory disease	Phase /# pts	Current status
 AUGMENT-101 (NCT04065399)	Revumenib (SNDX-5613) PO BID	(a) ALL or MPAL with <i>KMT2Ar</i> (b) AML with <i>KMT2Ar</i> ; (c) <i>NPM1</i>	Phase 1 /2 (n=186)	Ph2 <i>NPM1</i> ^{mut} <i>r-KMT2A</i> FDA approval Nov 15, 2024
 KOMET-001 (NCT04067336)	Ziftomenib (KO-539) PO QD	(a) AML with <i>KMT2Ar</i> (b) AML with <i>NPM1c</i>	Phase 1 /2 (n=199)	<i>NPM1</i> mut FDA approved in 2025
NCT04811560	Bleximenib (JNJ-75276617) PO QD	(a) AML/ALL with <i>KMT2Ar</i> (b) AML with <i>NPM1c</i>	Phase 1 (n=110)	Phase 1 (EHA 2024) Recruiting in combination with chemo
NCT04988555	Enzomenib (DSP-5336) PO QD	RR-AML/RR-ALL Ph2: <i>NPM1/KMT2Ar</i>	Phase 1/2 (n=70)	Phase 1 (EHA 2024) Recruiting
COVALENT-101 (NCT05153330)	BMF-219 PO	(a) AML/ ALL (<i>KMT2Ar</i> , <i>NPM1</i>) (b) DLBCL; (c) MM; (d) CLL/SLL	Phase 1 (n=177)	Multiple cohorts Actively enrolling

Efficacy of Menin inhibitors:
monotherapy in R/R setting

Menin inhibitor	Revumenib	Ziftomenib	Bleximenib	Enzomenib
Phase Trial	Ph 2	Ph 1b/2	Ph 1	Ph 1
Dose/frequency	163 mg bid	600 mg qd	90-100 mg bid	200-300 mg bid
KMT2Ar (n)	97	None	15	23
NPM1m (n)	83	93	14	17
CR	KMT: 15.5%; NPM1: 18.8%	NPM1: 18%	N/A	N/A
CR/CRh	KMT: 22.7%; NPM1m: 23.4%	NPM1: 35%	38%	37.5%
ORR (CRc+PR + MLFS)	KMT: 63.9%; NPM 46.9%	NPM1: 35%	47%	62.5%
MRD-neg CR/CRh	KMT: 61%; NPM: 64%	NPM1: 65%	N/A	N/A
Median DOR CR/CRh	KMT: 6.4; NPM1: 4.7 mo	NPM1: 3.7 mo	6 mo	KMT: NR; NPM1 7.0mo
Median OS (mo)	KMT: 8.0; NPM1: 4.0 mo	NPM1: 6.1 mo	N/A	N/A

Aldoss I et al EHA abstract 2025; Arellano et al EHA abstract 2025; Wang E et al JCO Nov 2025; Zeidner J et al ASH abstract 2025

Safety profile of Menin inhibitors:
monotherapy in R/R setting

Agent (# pts)	Revumenib (n=199)	Ziftomenib (n=112)	Bleximenib (n=146)	Enzomenib (n=84)
Trial	Phase 2	Phase 1b/2	Phase 1	Phase 1
DLT (Y/N)	Yes	Yes	Yes	No
DLT	QTC prolongation	DS	DS	Not reported
DS (all)	KMT2Ar:27.7%; NPM1:19%	24%	14.4% all doses	10.7%
DS (≥Gr3)	13-16%	13%	6.8%	None reported
Febr Np (≥Gr3)	34.5-38.3%	22%	19.2%	23.8%
Neutrop (≥Gr3)	29.8%	Not reported	28%	17.9%
Thromb (≥Gr3)	16.7-23.4%	20%	36%	23.8%
QTc PR (any)	25.5%-42.9%	3%	0%	1%
QTc PR (≥Gr3)	13.8-22.6%	2%	0%	1%

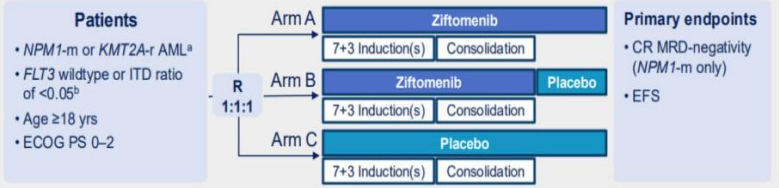
Issa GC et al JCO 2025; Wang ES et al JCO 2025; Searle E et al Blood 2024; Zeidner J et al Blood 2024

KOMET-017: Phase 3 Ziftomenib Pivotal 1L Combination Studies

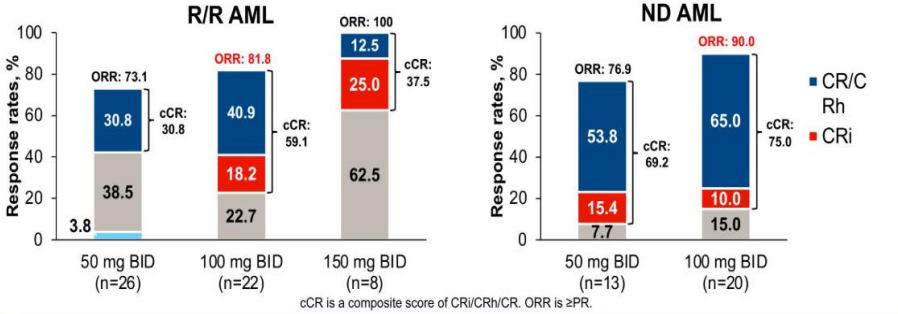
KOMET-017-NIC: Non-intensive therapy – Ziftomenib + venetoclax/azacitidine combo



KOMET-017-IC: Intensive therapy – Ziftomenib and 7+3 combo



Ph1b of Bleximenib in Combination with VEN + AZA in R/R or ND AML Efficacy



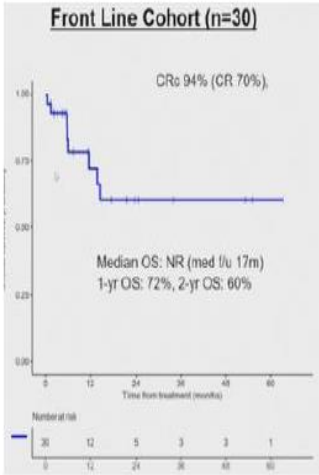
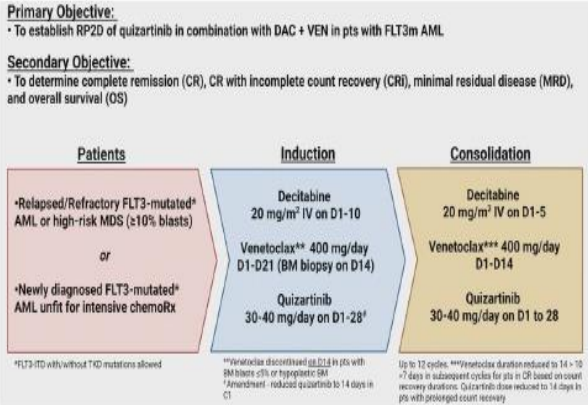
- Key observations**
- Evaluation of the data shows optimized responses with bleximenib 100 mg BID in combination with VEN/AZA
 - Response data maturing, with 6 ND pts active on treatment with the potential to deepen response
 - In pts receiving 100 mg BID, the median (range) time to first response was 23 days (18–50) in R/R and 22 days (18–57) in ND

Data cut-off date: May 7, 2025

Wei AH et al. EHA 2025. Abstract S137.

Zeidan A et al. EHA 2025. Abstract PB2573.

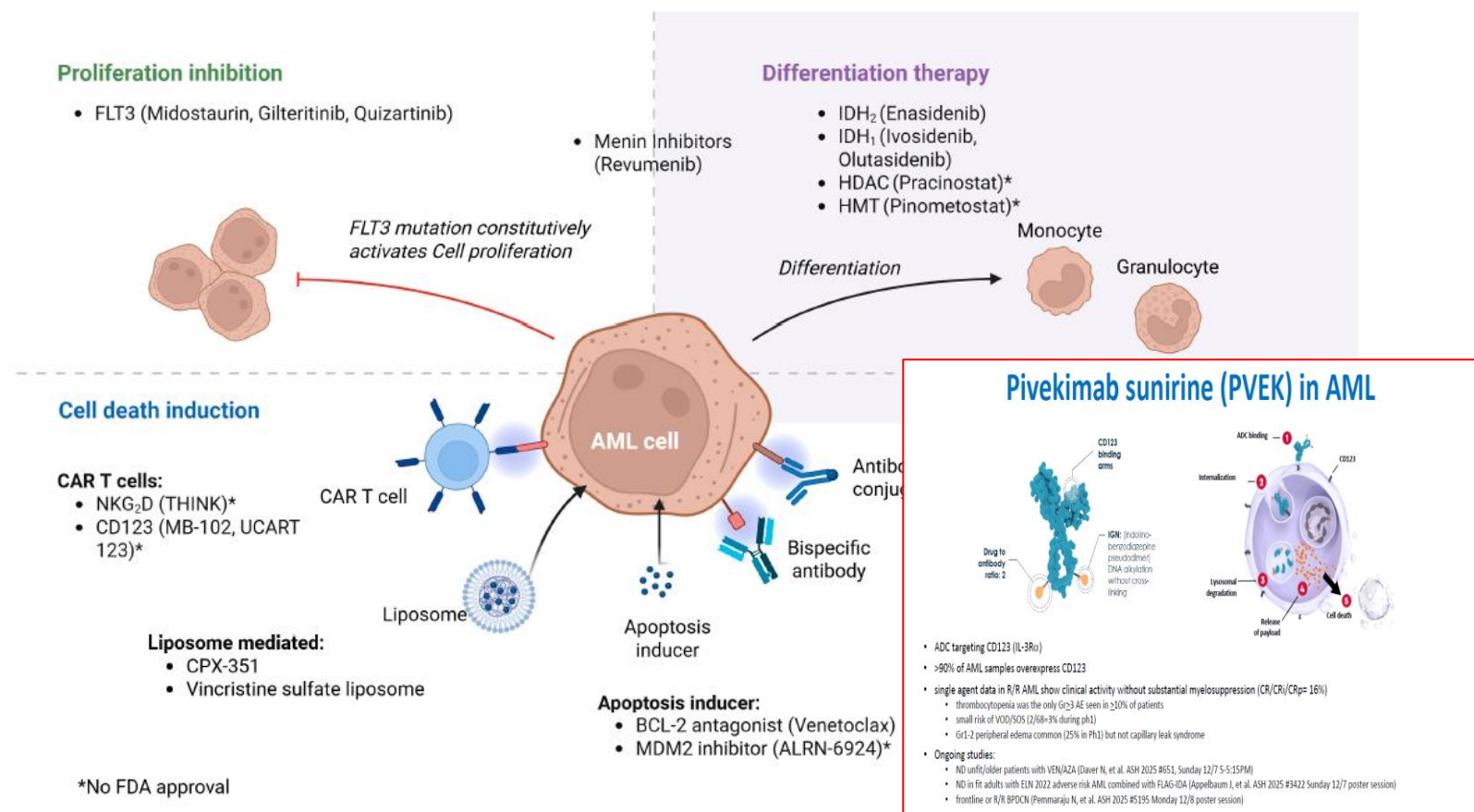
Triplet therapy: Dec+Ven+Quizartinib in FLT3m AML



Review

Evolving Paradigms in Acute Myeloid Leukemia: Personalized Approaches to Therapy Across Age and Risk Groups

Sumeet K. Yadav ^{1,*}, Utsav Joshi ², Guleid Hussein ^{1,*}, Mohamed Warsame ¹, Bolun Liu ¹, Abhash Shrestha ³, Peter Krastev ⁴, Hariprasad Reddy Korsapati ¹ and Amrit Singh ⁵



NE VEDREMO DELLE BELLE.....



Acute Myeloid Leukemia: 2025 Update on Diagnosis, Risk-Stratification, and Management

Shai Shimony | Maximilian Stahl | Richard M. Stone

Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

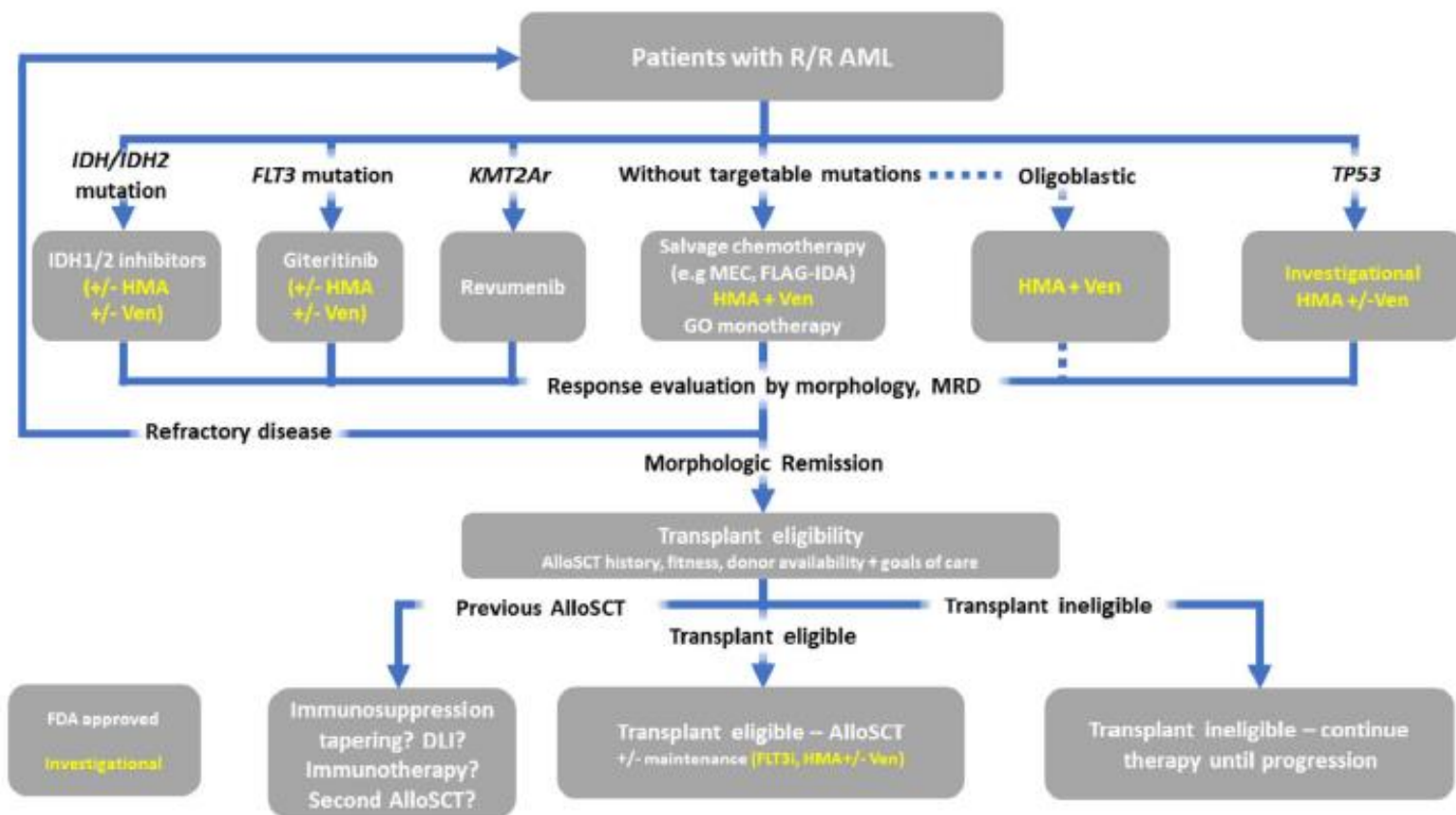


FIGURE 5 | Treatment Algorithm for patients with relapsed or refractory AML. AlloSCT—allogeneic stem cell transplantation; AML—acute myeloid leukemia; DLI—donor lymphocyte infusion; FLT3i—FLT3 inhibitors; GO—gemtuzumab ozogamycin; HMA—hypomethylating agents; IDH—isocitrate dehydrogenase; KMT2Ar—Lysine methyltransferase 2A gene (KMT2A) re-arranged; MRD—measurable residual disease; R/R—relapse or refractory; Ven—venetoclax.

CONCLUSIONS

THE PARADIGM IS CHANGED!!!!

The modern AML algorithm is moving toward personalized, dynamic, and combination-based care

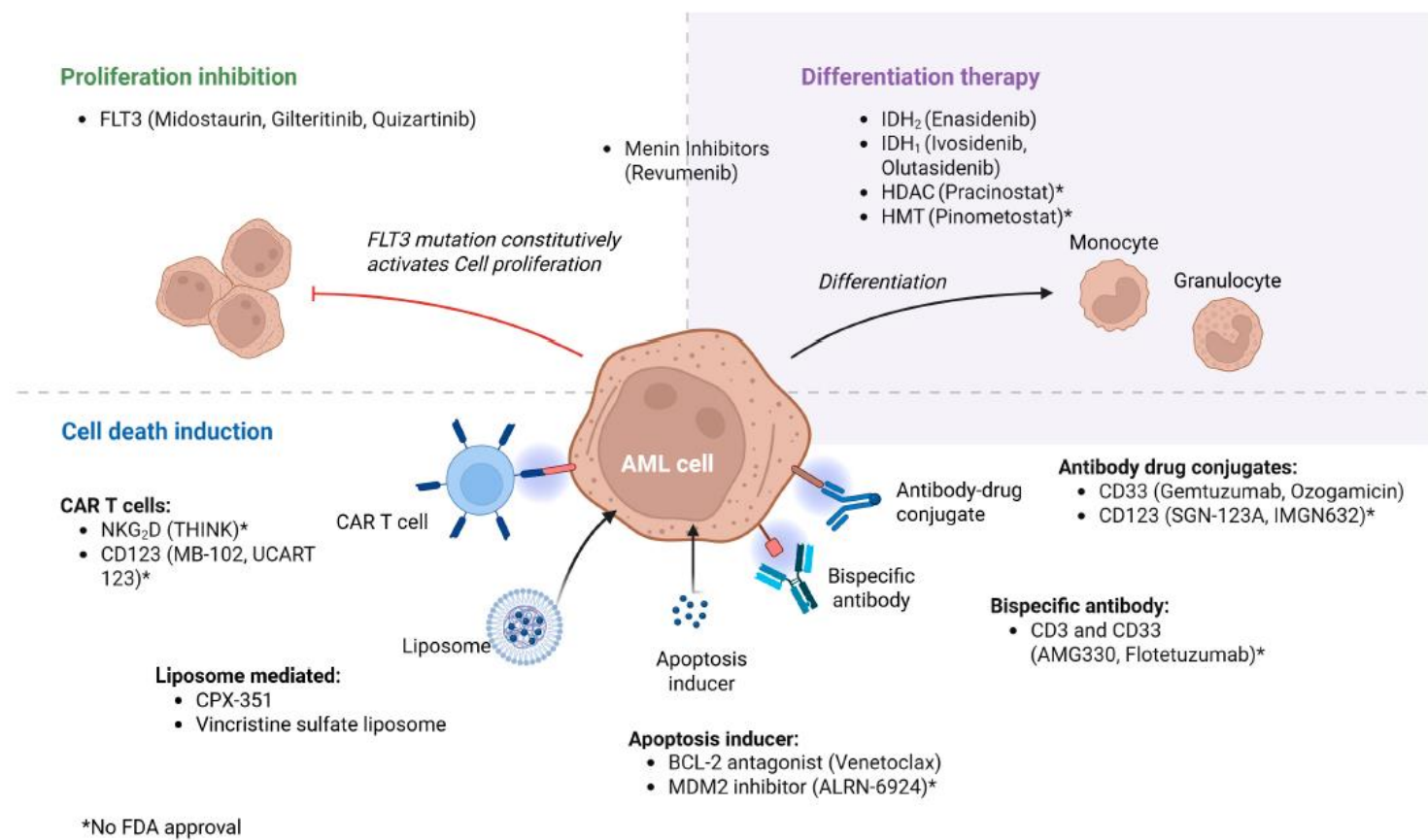
- ✓ AML treatment has shifted from a one-size-fits-all cytotoxic approach to biology-driven therapy.
- ✓ Patient fitness.....but also ” fitness for biology!!!!”
- ✓ Response goals are shifting from “any remission” to “deep and molecular remissions (MRD)”
- ✓ Triplet and sequential strategies are emerging for synergy without excessive toxicity
- ✓ Toxicity management has become a key determinant of regimen choice
- ✓ Transplant remains central, but the pathway to transplant is changing . Better front-line disease control with targeted therapies and venetoclax combinations increases the number of pts who reach transplant in remission.
- ✓ Clinical trials ...

GRAZIE

Review

Evolving Paradigms in Acute Myeloid Leukemia: Personalized Approaches to Therapy Across Age and Risk Groups

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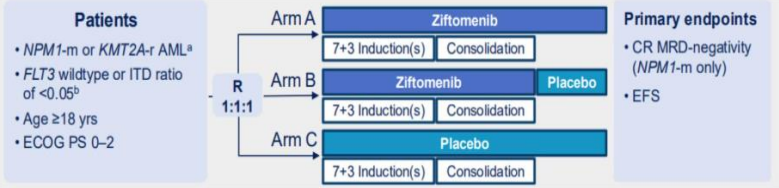
NE VEDREMO DELLE BELLE.....

KOMET-017: Phase 3 Ziftomenib Pivotal 1L Combination Studies

KOMET-017-NIC: Non-intensive therapy – Ziftomenib + venetoclax/azacitidine combo

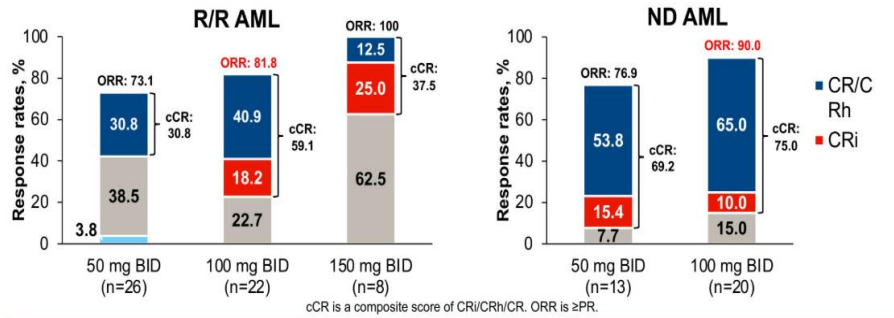


KOMET-017-IC: Intensive therapy – Ziftomenib and 7+3 combo



Zeidan A et al. EHA 2025. Abstract PB2573.

Ph1b of Bleximenib in Combination with VEN + AZA in R/R or ND AML Efficacy

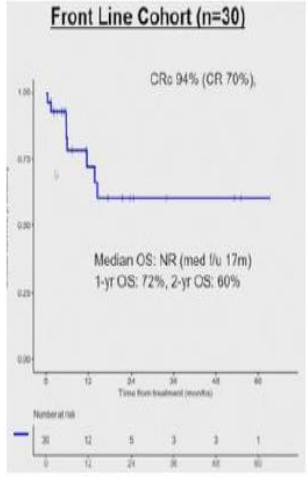
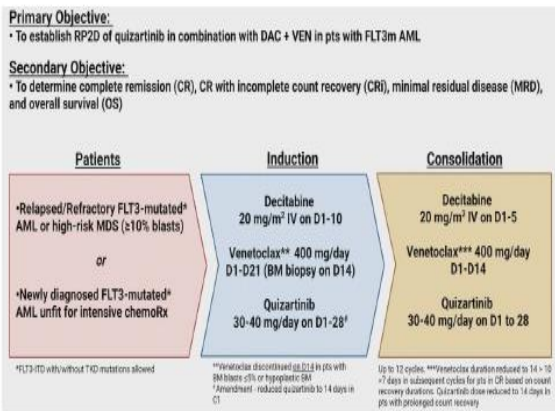


- Key observations**
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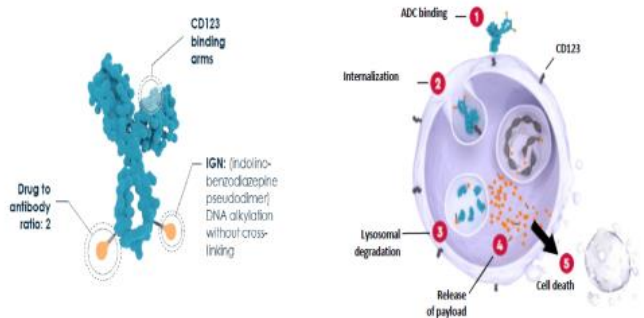
Data cut-off date: May 7, 2025

Wei AH et al. EHA 2025. Abstract S137.

Triplet therapy: Dec+Ven+Quizartinib in FLT3m AML

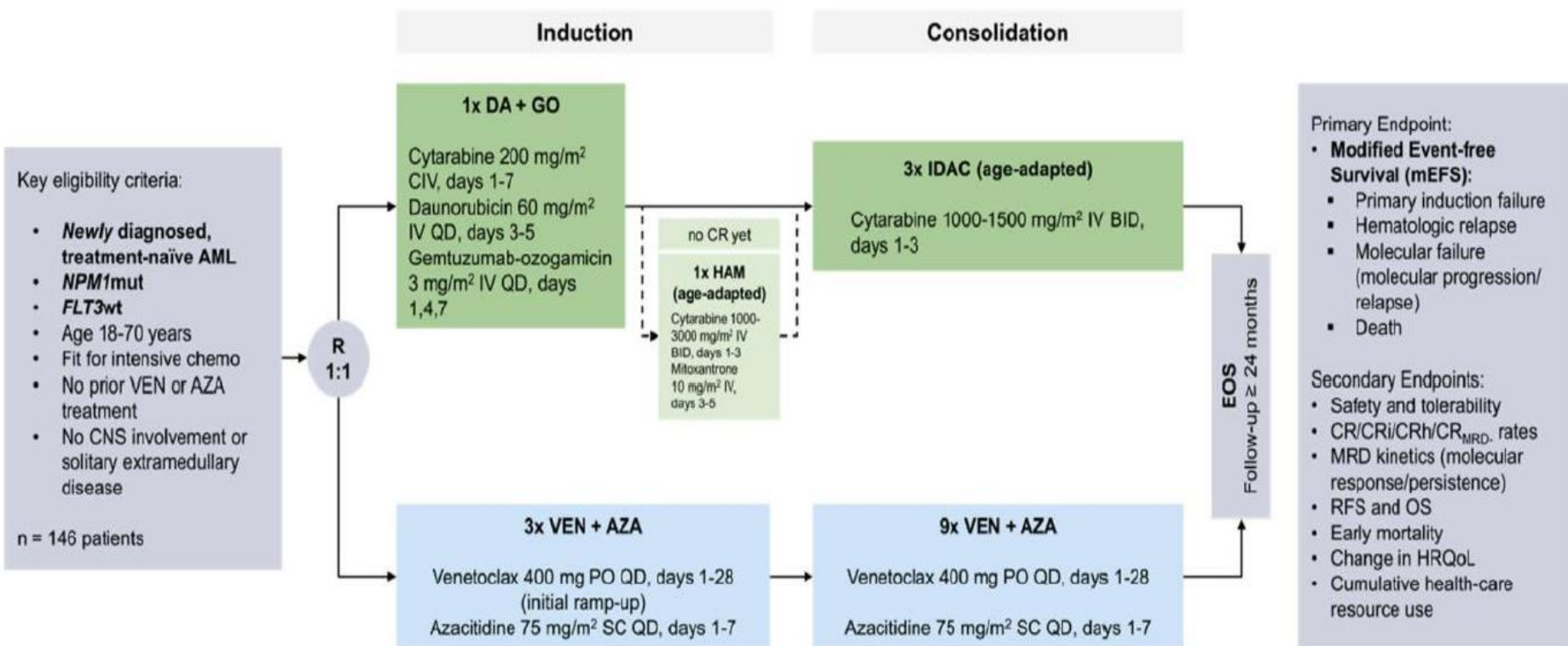


Pivekimab sunirine (PVEK) in AML



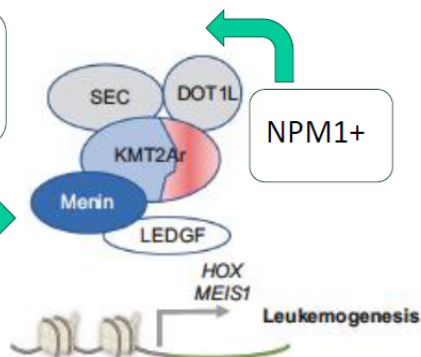
- ADC targeting CD123 (IL-3Rα)
- >90% of AML samples overexpress CD123
- single agent data in R/R AML show clinical activity without substantial myelosuppression (CR/CRI/CRp= 16%)
 - thrombocytopenia was the only Gr3 AE seen in ≥10% of patients
 - small risk of VOD/SOS (2/68=3% during Ph1)
 - Gr1-2 peripheral edema common (25% in Ph1) but not capillary leak syndrome
- Ongoing studies:
 - ND unfit/older patients with VEN/AZA (Daver N, et al. ASH 2025 #651, Sunday 12/7 5-5:15PM)
 - ND in fit adults with EUN 2022 adverse risk AML combined with FLAG-IDA (Appelbaum J, et al. ASH 2025 #3422 Sunday 12/7 poster session)
 - frontline or R/R BPCDN (Pemmaraju N, et al. ASH 2025 #5195 Monday 12/8 poster session)

VINCENT: A randomized-controlled trial evaluating venetoclax plus azacitidine versus intensive chemotherapy in patients with newly diagnosed, *NPM1*-mutated AML

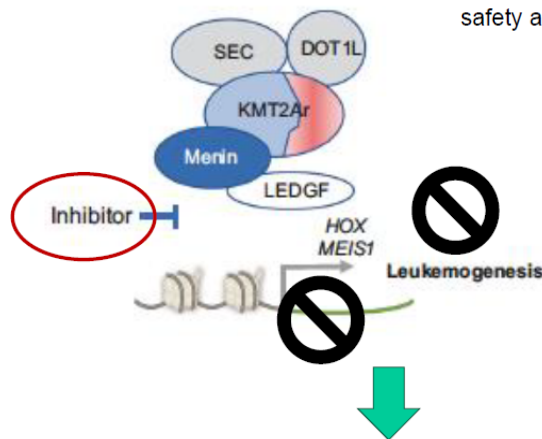


Menin is an essential oncogenic cofactor for leukemogenesis driven by NPM1 mut or r-KMT2A

MLL chromosomal translocation



- Each menin inhibitor has a different chemical structure and different physiochemical properties such as polar surface area, lipophilicity, and basicity that may impact safety and efficacy^{1,2}

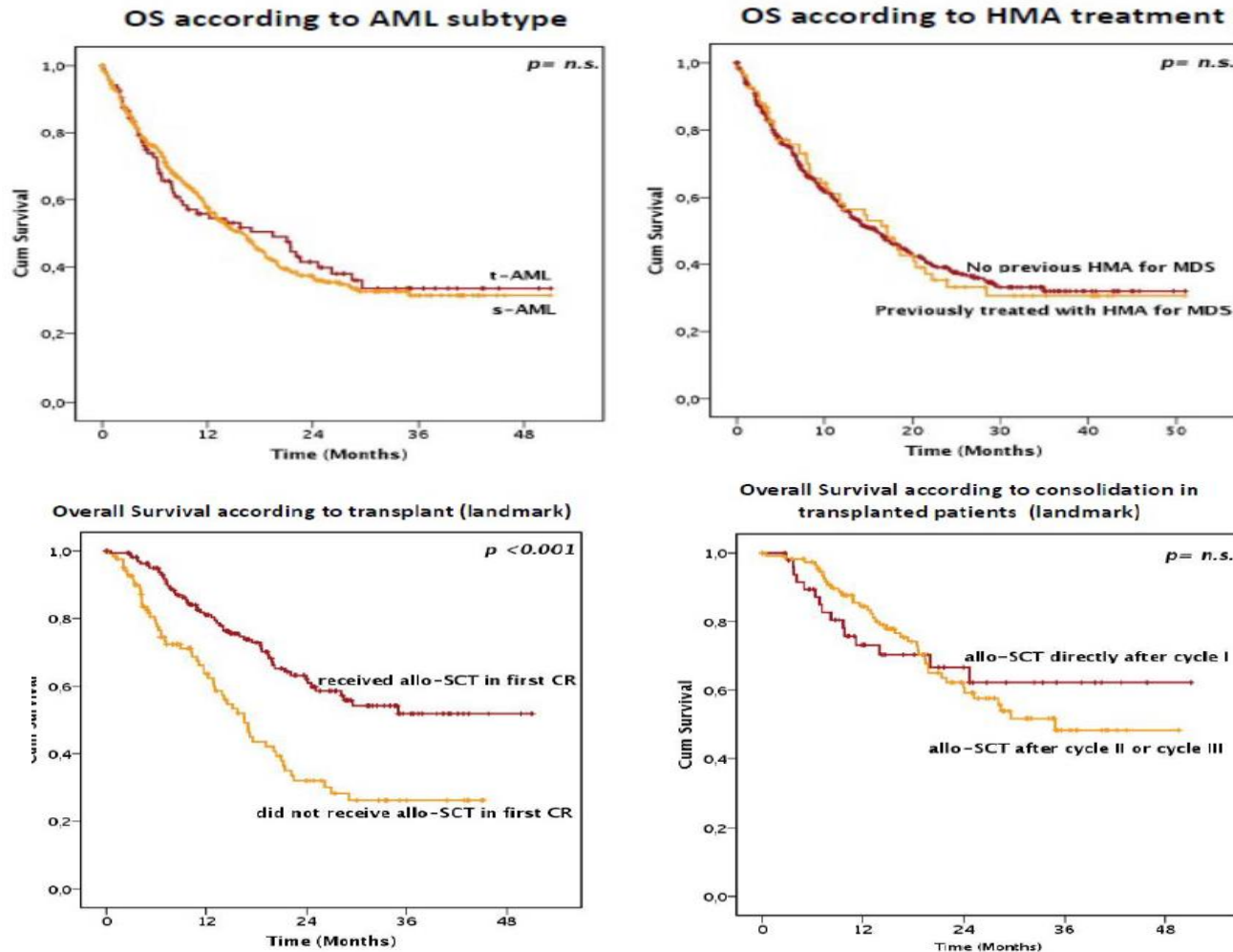


Growth arrest and differentiation

Modified from Issa GC et al, Leukemia 2021

Trial name (NCT)	Agent (route)	Phase 1/ 2 expansion cohorts For relapsed/refractory disease	Phase /# pts	Current status
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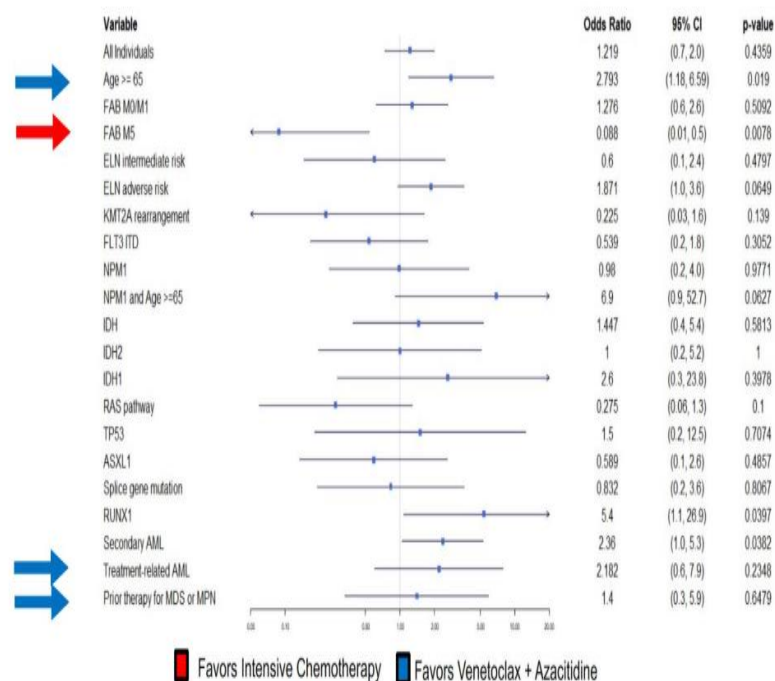
Real World Study on the Best CPX-351 Treatment Duration and Timing for Allogeneic Stem Cell Transplantation



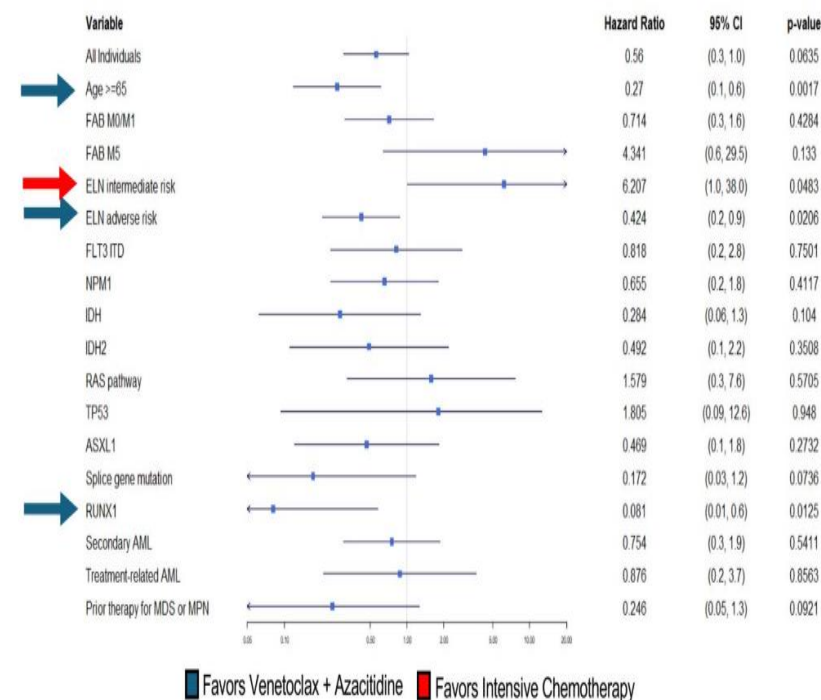
Completion of all allowed CPX- 351 cycles was beneficial only in pts not proceeding to transplant ($p < 0.05$), whereas in transplanted pts additional CPX- 351 cycles did not improve outcome. Analysis suggests that also s- AML pts with NPM1 mutations and those belonging to the ELN 2017 favorable risk category benefit from CPX- 351. In eligible pts, allo-HSCT should be performed as soon as a CR is achieved, whereas pats not undergoing transplant benefit from a complete CPX- 351 schedule.

Venetoclax and azacitidine compared with induction chemotherapy for newly diagnosed patients with acute myeloid leukemia

Venetoclax + Azacitidine Versus 7+3: Factors That Predict Response



Venetoclax + Azacitidine Versus 7+3: Factors that Predict Survival (Propensity Cohort)



Variables that favored response to ven/aza over IC included older age, secondary AML, and RUNX1 mutations. AML M5 favored response to IC over ven/aza. In the propensity matched cohort analyzing OS, older age, adverse risk, and RUNX1 mutations favored ven/ aza over IC, whereas intermediate risk favored IC over ven/aza. Pts receiving IC have improved OS compared with those receiving ven/aza. However, in a propensity-matched cohort of pts with equivalent baseline factors, there was a trend toward favorable OS for ven/aza. Specific variables, such as RUNX1 mutations,