

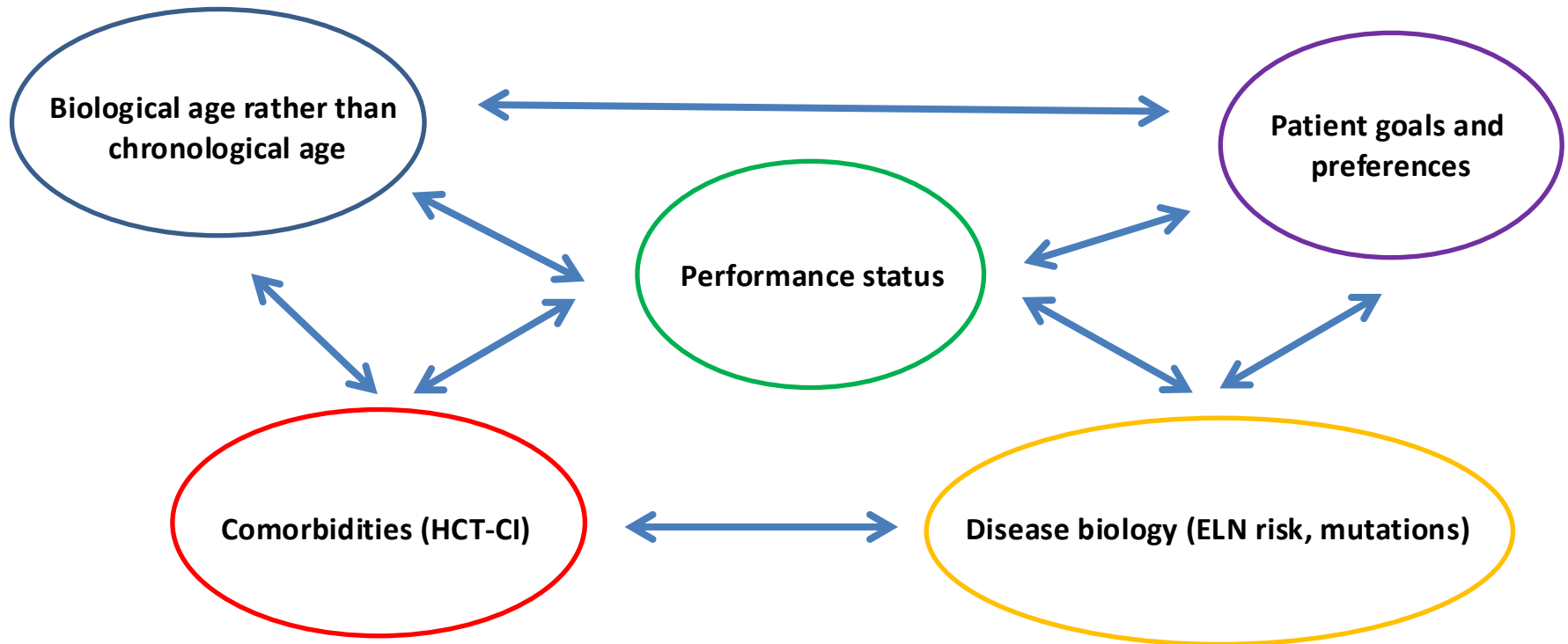


Dati a supporto del trattamento intensivo nel paziente borderline

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Navigating the Gray Zone in Elderly AML Patients

Borderline elderly patients often lie in a “gray zone” between efficacy and tolerability, where the decision depends on:



In borderline elderly AML patients, the challenge is balancing the curative potential of intensive therapy against the risk of treatment-related harm

Defining Fitness in AML: Key Principles for Treatment Decision-Making

Statement	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 considered “fit for” a specific treatment strategy.	IV	A	92%
3	Eligibility for intensive chemotherapy does not necessarily entail eligibility for allo-SCT.	IV	B	84%
4	Ineligibility for intensive treatment does not exclude eligibility for allo-SCT after achieving CR following nonintensive treatment.	IV	B	81%
5	For mitigating disease-related symptoms, antileukemic therapy should be considered even with unattainable curative intent.	IV	C	88%

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%

Integrating Fitness, Genomics, and Timing to Optimize Treatment Selection in AML

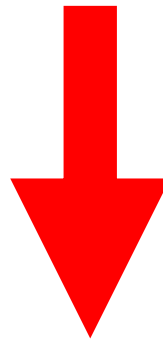
Statement	Recommendations: influence of fitness and disease genetics (sic) on treatment choice	LoE	GoR	LoA
10	Treatment decision should rely on patient- (fitness) and disease-related (genetic) features as well as patient preferences.	I	A	100%
11	Patients unfit for active therapy should be tested for mutations that could be susceptible to targeted monotherapy before being considered for supportive therapy alone.	IV	C	88%
12	Adverse genetic/cytogenetic profiles are not a contraindication to IC, in older, fit patients.	IV	B	69%
13	Psychiatric comorbidities that may interfere with patient compliance to therapies should be carefully evaluated before treatment initiation.	V	C	100%

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%

Treatment Selection in Borderline-Fit AML Patients: Intensive vs Less-Intensive Therapy

Intensive chemotherapy

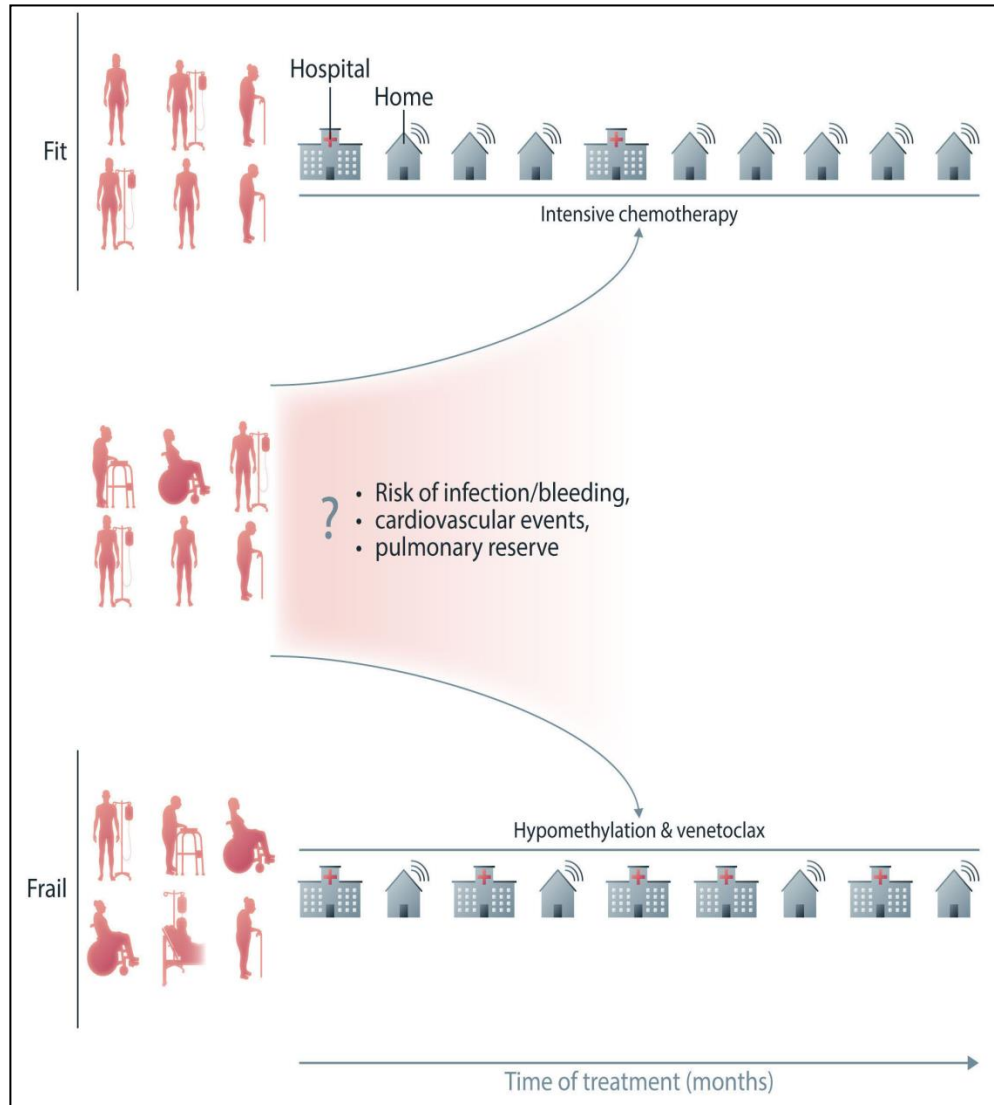
- Biological risk (low, intermediate)
- Rapid and deep remissions
- Higher probability of MRD-negative remission
- Fixed-duration treatment approach
- Earlier eligibility for HSCT
- Lower risk of post-hsct relapse
- Durable treatment-free remissions
- No long-term treatment exposure
- No cumulative toxicity after chemotherapy
- Avoidance of continuous therapy and long-term drug interactions
- Clear consolidation strategy



Less intensive therapy

- Continuous treatment required (no fixed-duration therapy)
- Responses often treatment-dependent
- Lower rates of MRD-negative remission
- Potentially delayed access to allogeneic transplantation
- Prolonged cytopenias
- Increased risk of infectious complications
- Frequent dose interruptions or schedule modifications
- Risk of resistance or relapse during therapy
- Limited long-term treatment-free survival
- Need for prolonged monitoring and supportive care
- Drug–drug interactions (e.g., azoles with venetoclax)
- Long-term treatment burden for patients

Does Lower-Intensity AML Therapy Really Mean More Time at Home?



- “Is ‘less intensive’ therapy really less hospitalizing?”
- “The assumption that VEN-HMA keeps patients at home may be more myth than reality.”
- “When the entire treatment journey is considered, intensive chemotherapy may actually mean more time at home, not less.”

Does Lower-Intensity AML Therapy Really Mean More Time at Home?

Retrospective study of 197 AML patients ≥65 years

Treatment groups:

- Intensive chemotherapy
- HMA + venetoclax
- HMA alone

**Early Burden
(First 30 Days)**

4

days at home
Intensive chemo

14 days HMA+VEN
12 days HMA

Time at Home

13.1

months at home
Intensive chemo

7.6 months HMA
5.5 months HMA+VEN

Overall Survival

19.9

months OS
Intensive chemo

~7 months
Lower-intensity

Avoiding upfront hospitalization does NOT necessarily mean more time at home

Promising Outcomes with Intensive Therapy in older CBF-AML Patients

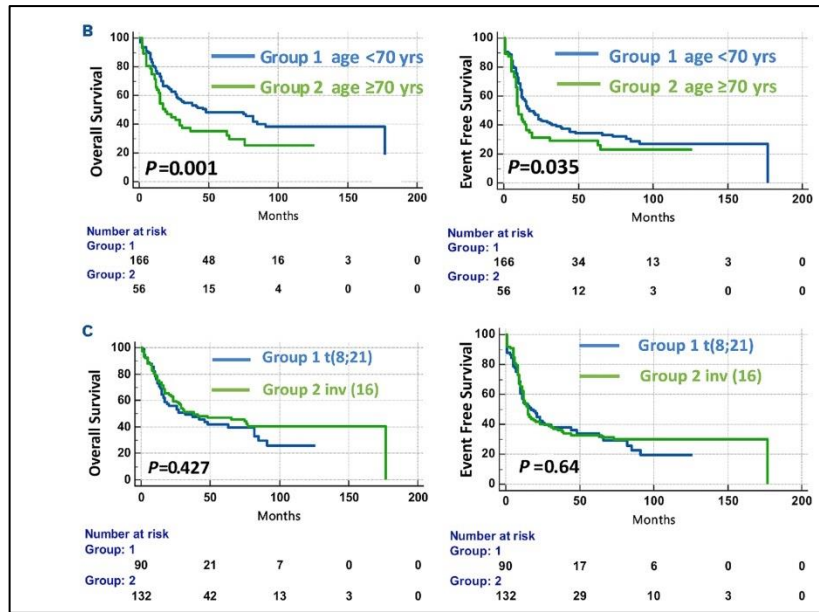
Characteristic	All patients N=229	Aged 60-69 years N=170	Aged 70-85 years N=59	P
Induction therapy, N (%)				
"3+7" regimen	100 (43.6)	76 (44.7)	24 (40.6)	0.04
"3+7" + other drugs	101 (44.2)	79 (46.4)	22 (37.2)	
No anthracycline	28 (12.2)	15 (8.9)	13 (22.2)	
Complete remission after induction, N (%)	193 (84.3)	147 (86.5)	46 (78.0)	0.204
Mortality, N (%)				
At 30 days	8 (3.5)	5 (2.9)	3 (5.1)	0.428
At 60 days	15 (6.6)	9 (5.3)	6 (10.2)	0.223
Patients in remission, N (%)	193	147	46	-
Not consolidated/only maintenance therapy after remission	24 (12.4)	15 (10.2)	9 (19.6)	-
Consolidated with 1-2 cycles	94 (48.8)	67 (45.7)	27 (58.7)	-
Consolidated with ≥3 cycles (but no transplant)	56 (29.0)	47 (32.0)	9 (19.6)	0.076
Consolidated also with auto-transplant	7 (3.6)	6 (4.0)	1 (2.1)	NA
Consolidated also with allo-transplant	12 (6.2)	12 (8.1)	0 (0.0)	NA

Intensive Treatment Outcomes in AML Patients ≥70 Years

- ~40% of patients received GO in combination with the 3+7 regimen
- CR after induction: 78%
- ~60% of patients received 1–2 consolidation cycles
- 30-day mortality: 5%
- Overall CR rate: 78%
- Only 2 treatment-related deaths after induction
- No patients underwent HSCT consolidation

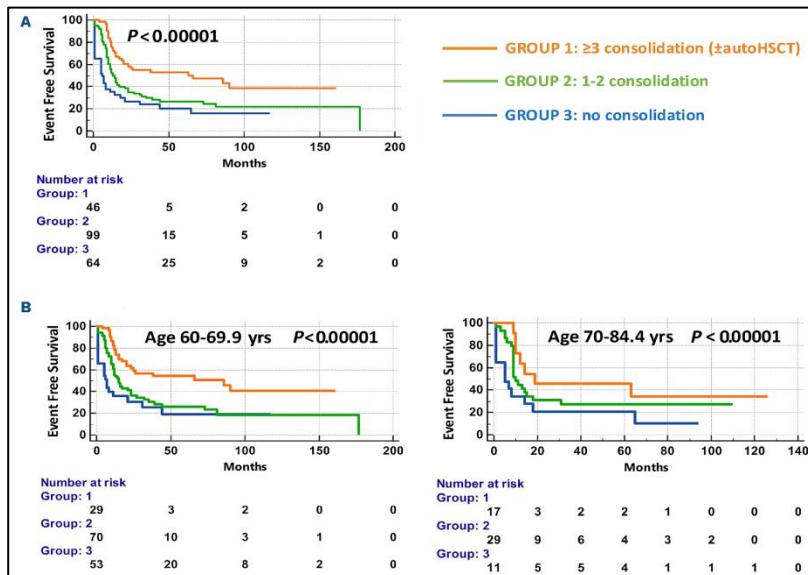
Induction therapy	Patients N (%)	CR N (%)	PR+NR+PD N (%)	Deaths N (%)	P
Patients aged 60-69.9 years					
"3+7"	76 (44.7)	65 (85.6)	9 (11.8)	2 (2.6)	-
"3+7" + other drugs	79 (46.4)	70 (88.6)	9 (11.4)	0	-
No anthracycline	15 (8.9)	12 (80.0)	3 (20.0)	0	-
Overall	170	147 (85.9)	21 (12.3)	2 (1.8)	0.4
Patients aged 70-84.4 years					
"3+7"	24 (40.6)	21 (87.6)	2 (8.3)	1 (4.1)	-
"3+7" + other drugs	22 (37.2)	18 (81.9)	3 (13.6)	1 (4.5)	-
No anthracycline	13 (22.2)	7 (53.8)	6 (45.2)	0	-
Overall	59	46 (78.0)	11 (18.7)	2 (3.3)	0.04

Long-term survival can be achieved in a significant fraction of older patients with CBF-AML treated with intensive chemotherapy



Entire population (≥60 years)

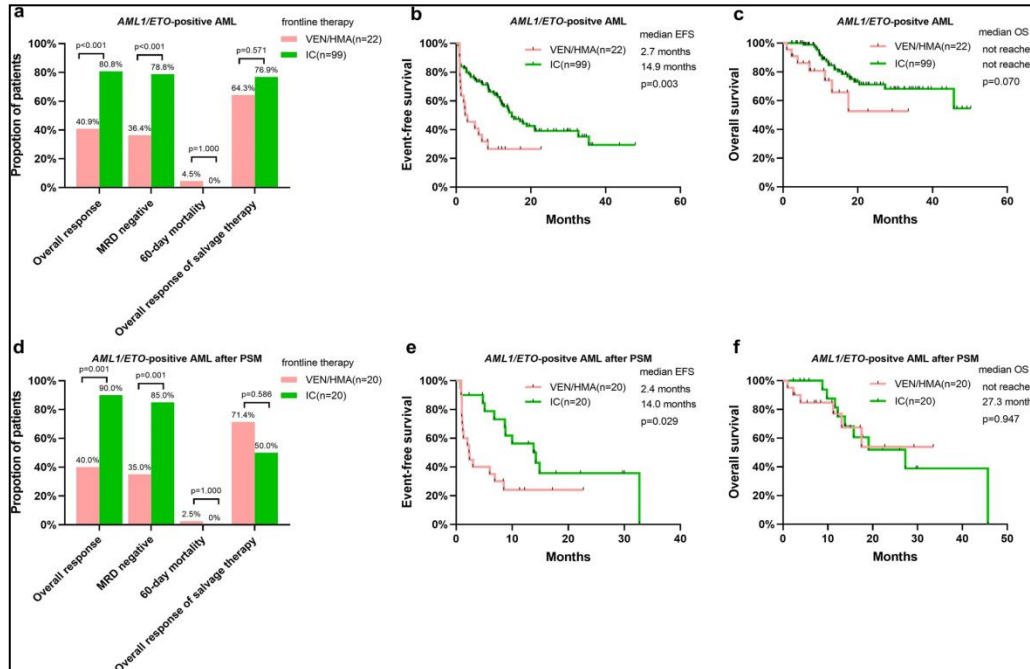
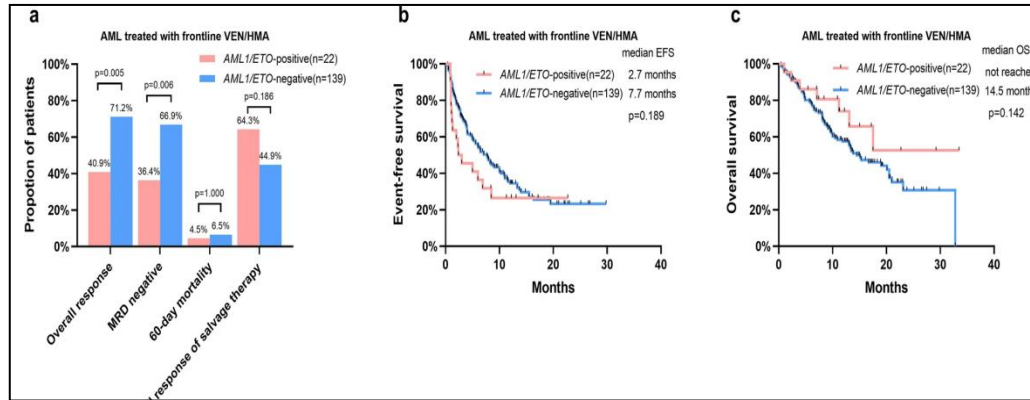
- Median follow-up: 53.5 months; 45% of patients alive at last follow-up
- 3-, 5-, and 10-year OS: 50.2%, 45.0%, and 36.7%, respectively
- No outcomes difference between inv16 and t(8;21) AML
- CR after induction (CR 84.3%) was the main determinant of survival
- Higher consolidation intensity improved EFS (5-year EFS up to 52.5% with ≥3 cycles)



≥70 years population

- Inferior survival compared with younger patients (5-year OS: 33.2% vs 48.5%; HR 1.6, $P=0.01$)
- Non-relapse mortality was comparable across age groups (27.2% in ≥70 vs 25.1% in <70 years)
- Higher leukemia-specific mortality in older patients (51.5% vs 37.5%)
- Consolidation intensity significantly influenced outcomes
- ≥3 consolidation cycles improved 5-year EFS up to ~40%

Intensive Chemotherapy Outperforms VEN/HMA in AML1/ETO AML



- AML1/ETO-positive AML showed poor response to frontline VEN + HMA (ORR 40.9% vs 71.2% in AML1/ETO-negative AML; p=0.005)
- Short EFS (2.7 months) with VEN/HMA in AML1/ETO AML
- Intensive chemotherapy demonstrated superior outcomes (ORR 80.8%, median EFS 14.9 months)
- After PSM analysis, intensive chemotherapy remained associated with significantly better outcomes than VEN/HMA
- KIT mutations predicted extremely poor response to VEN/HMA (ORR 0% vs 81.8% in KIT-WT; p=0.001)

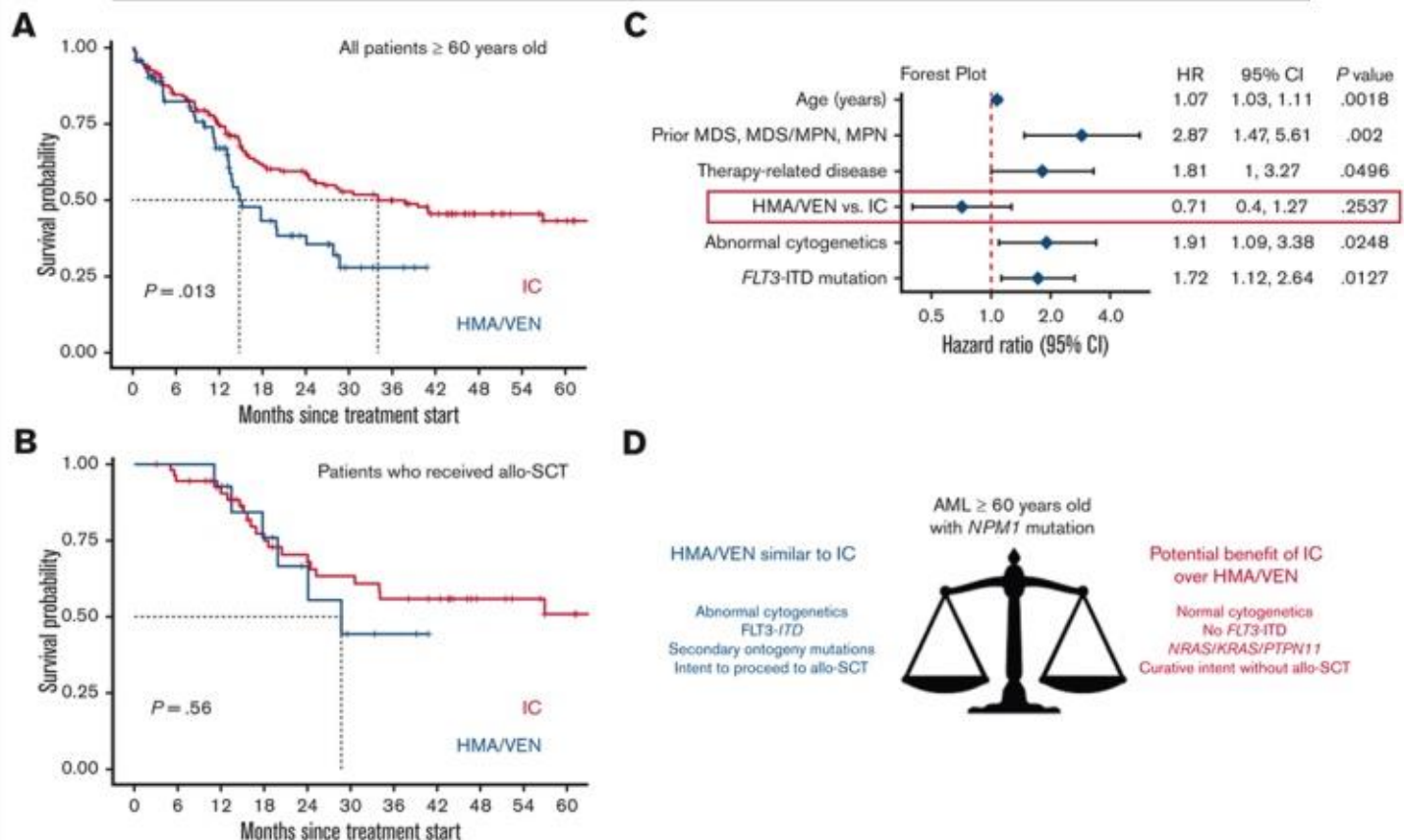
Intensive chemotherapy remains the preferred frontline strategy for AML1/ETO-positive AML

Intensive Chemotherapy Still Wins in Older NPM1-Mutated AML?

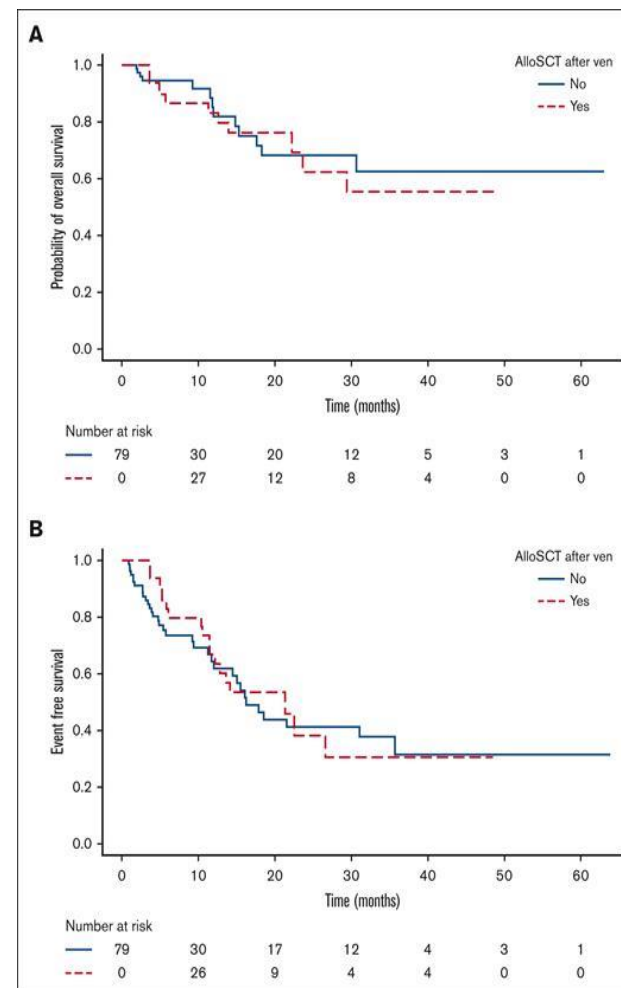
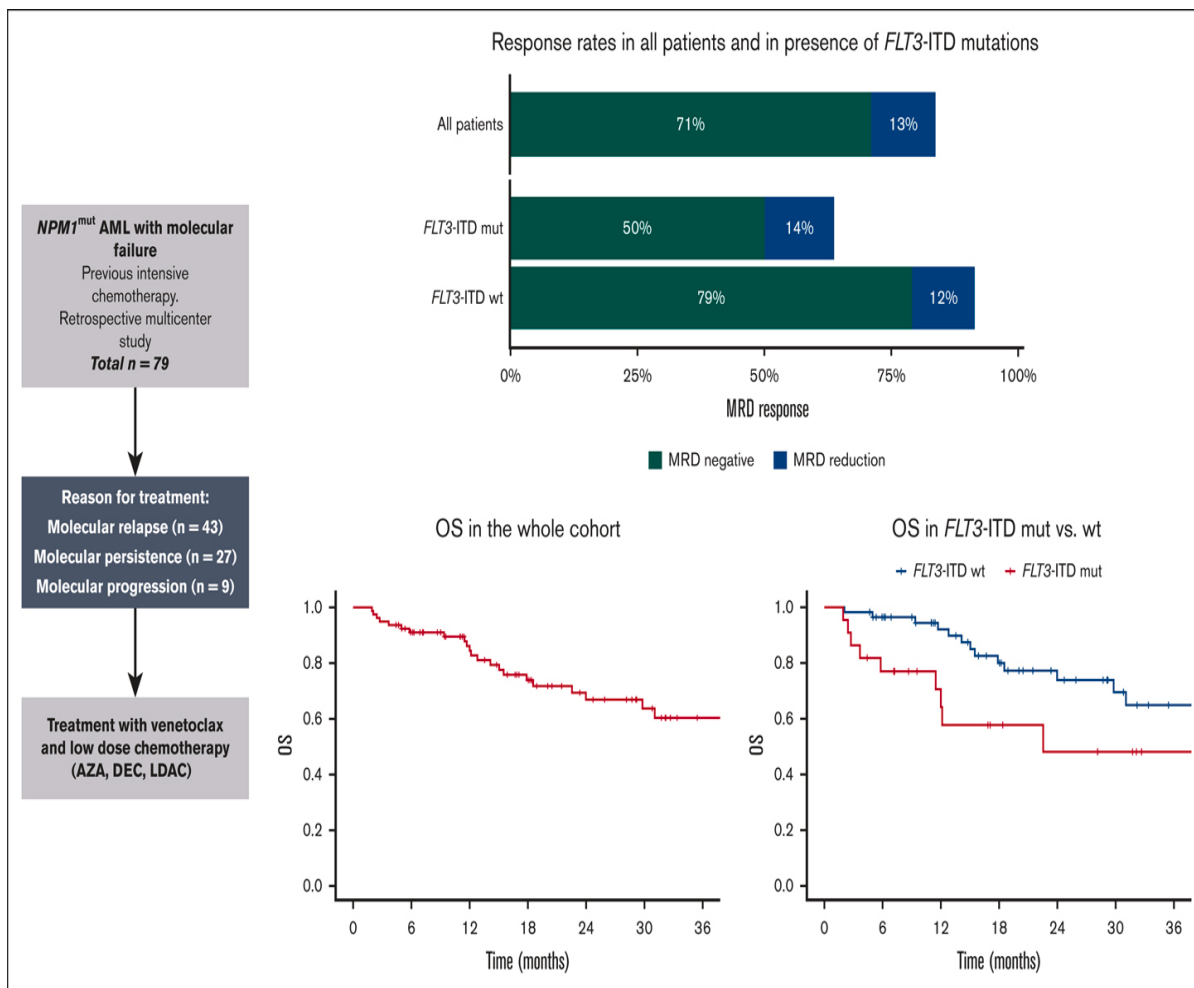
221 patients (147 treated with intensive chemotherapy [IC] and 74 with HMA + venetoclax [HMA/VEN]) age ≥ 60 years with newly diagnosed *NPM1*-mutant AML from 5 centers in United States and France included

OS superior with IC in unadjusted analysis (A) but was independent of treatment type not among allo-HCT recipients (B). Treatment type did not influence OS after adjustment for clinicopathological characteristics (C)

Patients with *NPM1*-mutant AML and normal cytogenetics, RAS pathway mutations, and no concurrent FLT3-ITD mutation (D) might benefit from treatment with intensive chemotherapy over HMA/VEN.



Venetoclax-Based Low-Intensity Therapy for Molecular Failure in NPM1-Mutated AML: A Challenge Worth Taking?



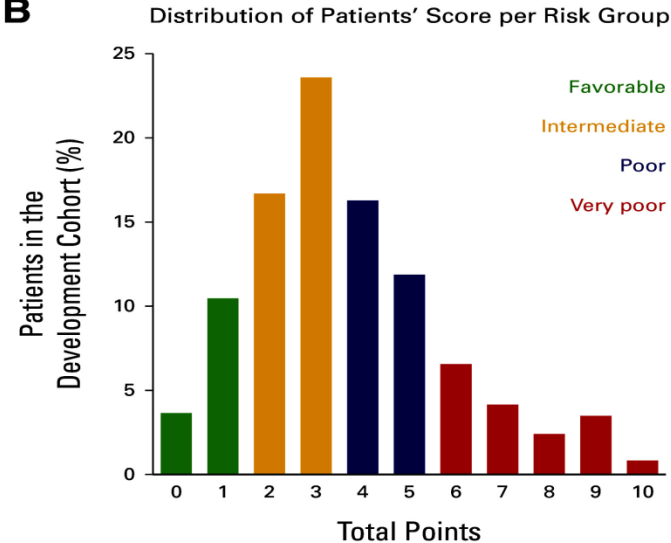
- 18 of 35 patients who did not undergo transplant became MRD negative and stopped treatment after a median of 10 months, with 2-year molecular relapse free survival of 62% from the end of treatment.
- Allogeneic transplant did not have an impact on OS ($p=0.6$) or EFS ($p=0.5$) compared with those who did not undergo transplantation.

Risk Stratification in Older Intensively Treated Patients With AML

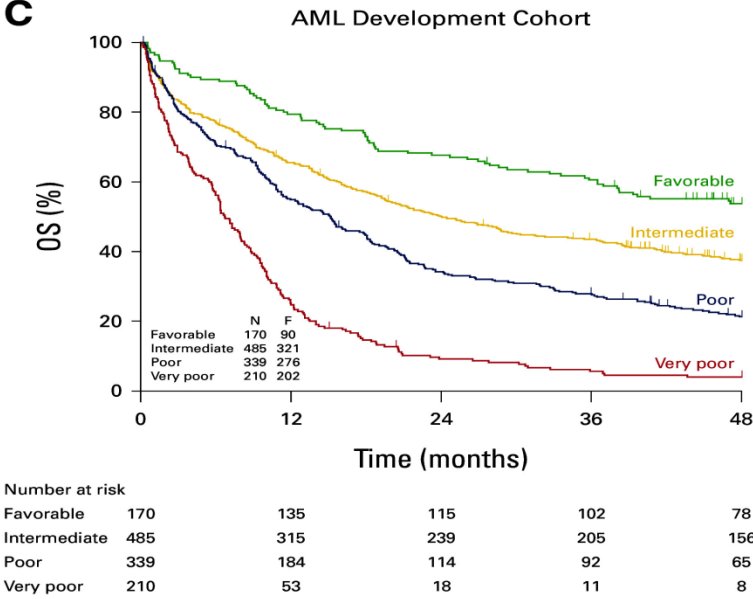
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Variable	HR	95%CI	Weight
<i>TP53</i> mutation	2.42	1.83-3.21	3
Monosomal karyotype	2.06	1.56-2.73	3
Age >65 (years)	1.50	1.31-1.72	2
<i>RUNX1</i> mutation	1.49	1.26-1.76	1
<i>FLT3</i> -ITD	1.36	1.13-1.65	1
<i>ASXL1</i> mutation	1.32	1.10-1.58	1
<i>DNMT3A</i> mutation	1.25	1.07-1.45	1
WBC >20 (10e9/L)	1.22	1.03-1.44	1
Male sex	1.15	1.00-1.32	1

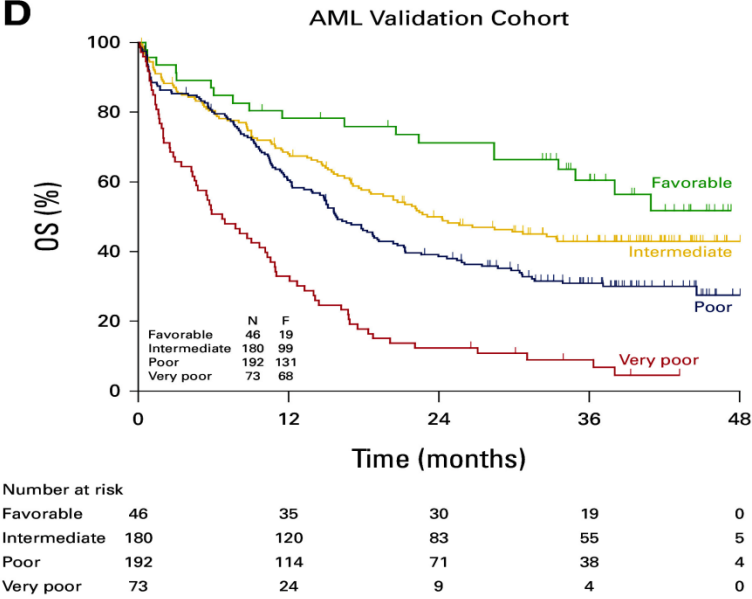
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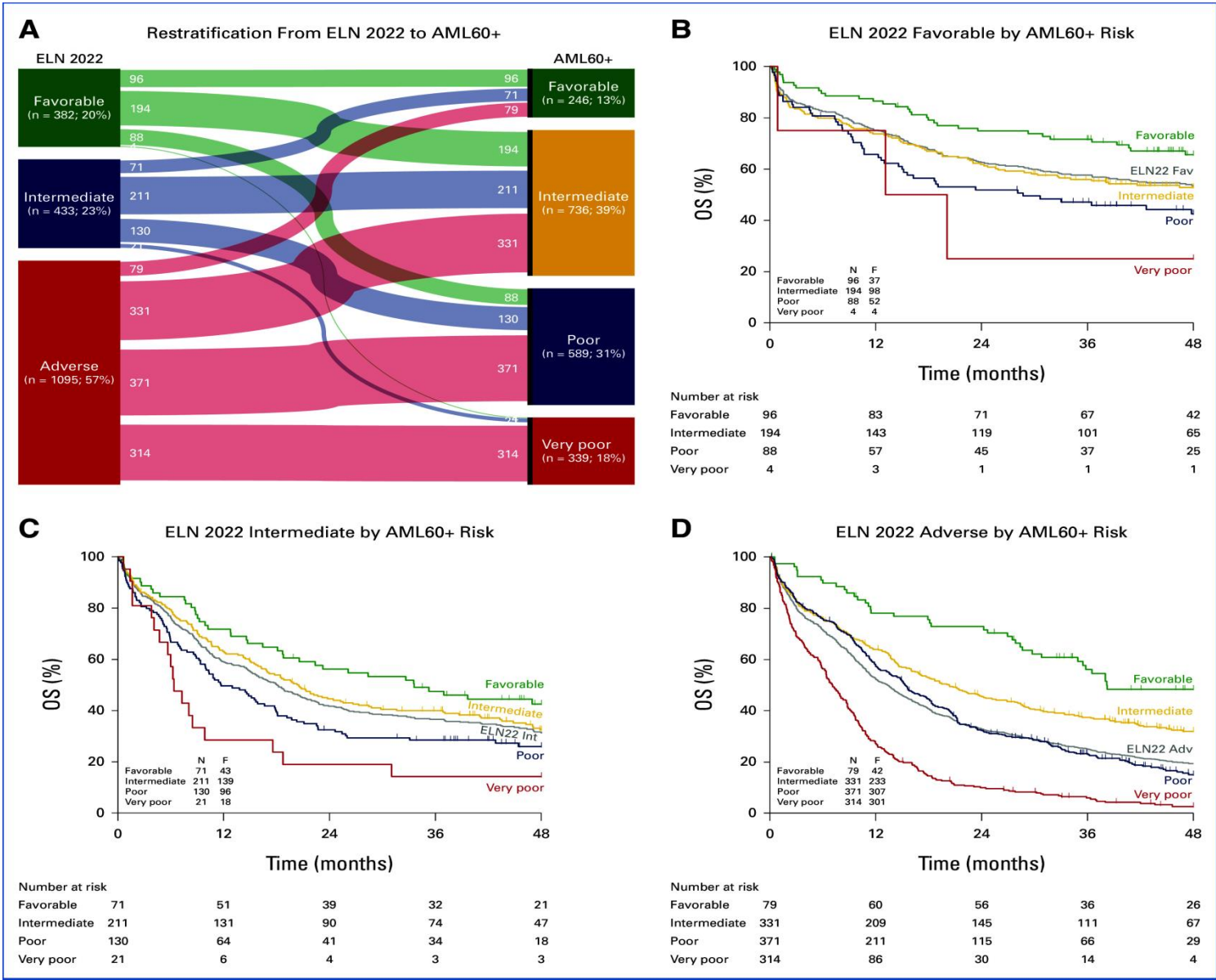
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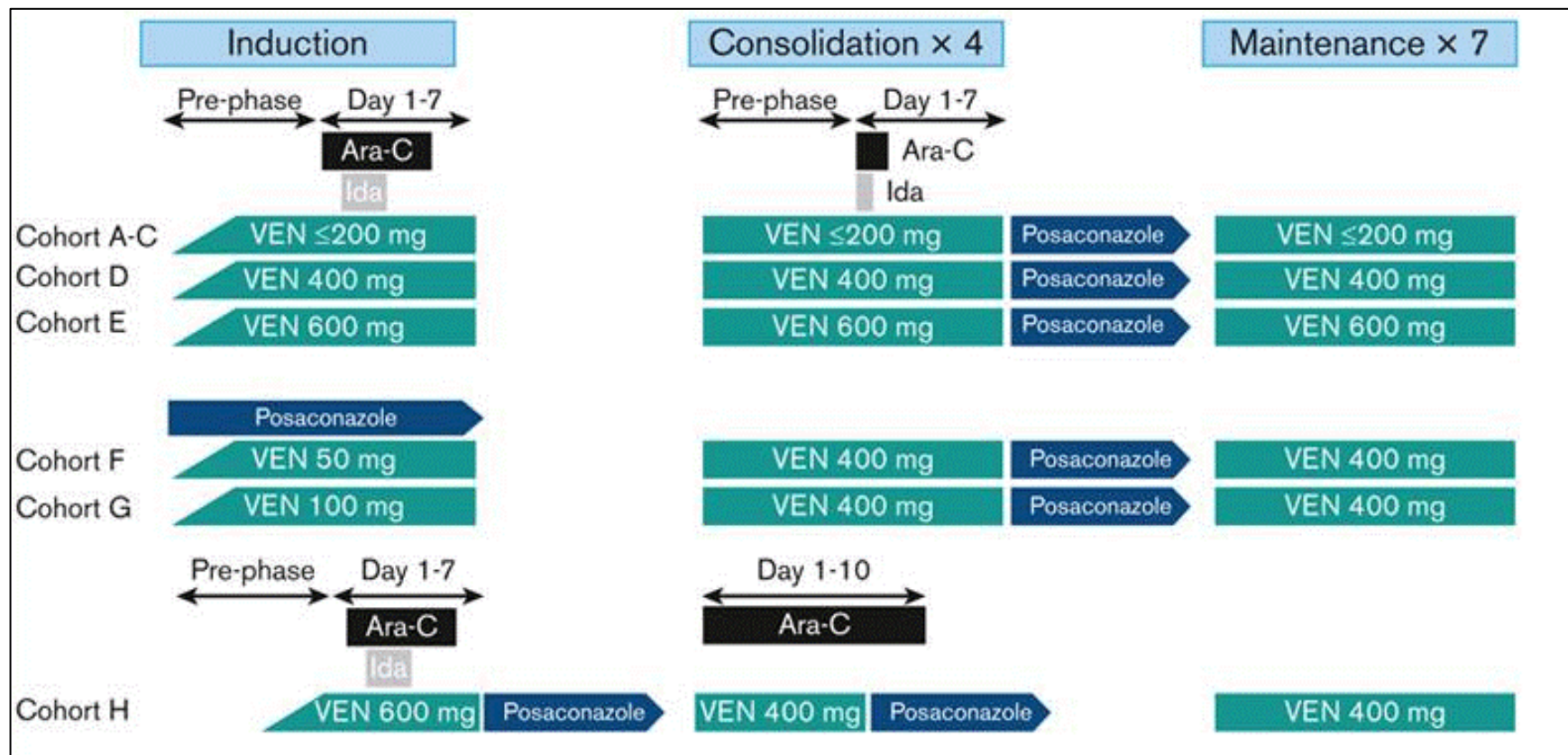


AML60+ Improves Risk Stratification Beyond ELN 2022

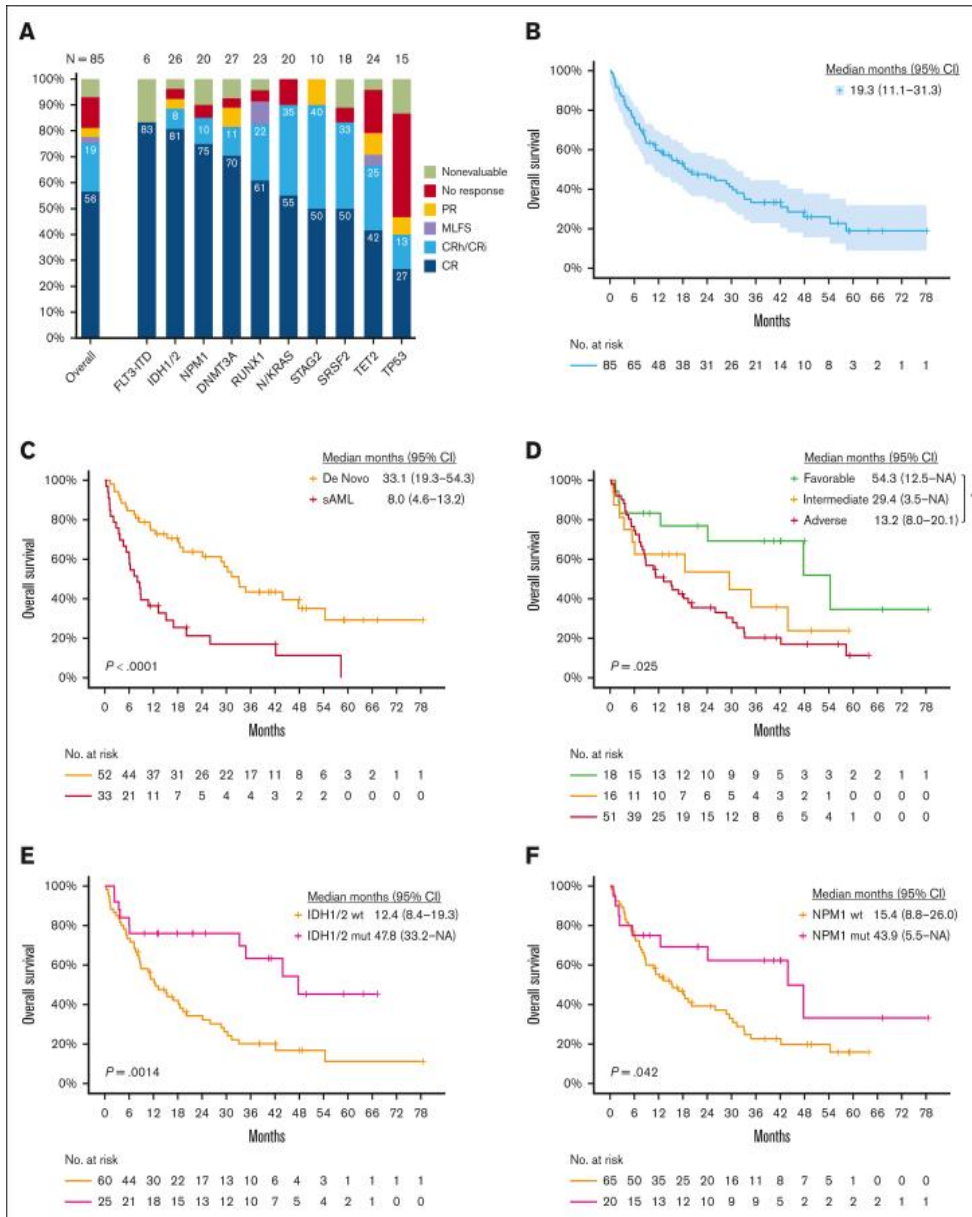


Final analysis of the phase 1b Chemotherapy and Venetoclax in Elderly AML Trial (CAVEAT study)

- 85 patients enrolled
- Median age of 71 years (range, 63-80)
- Poor-risk disease features included:
 - ☐ 39% secondary AML
 - ☐ 60% ELN 2022 adverse risk
 - ☐ 18% *TP53* mutations

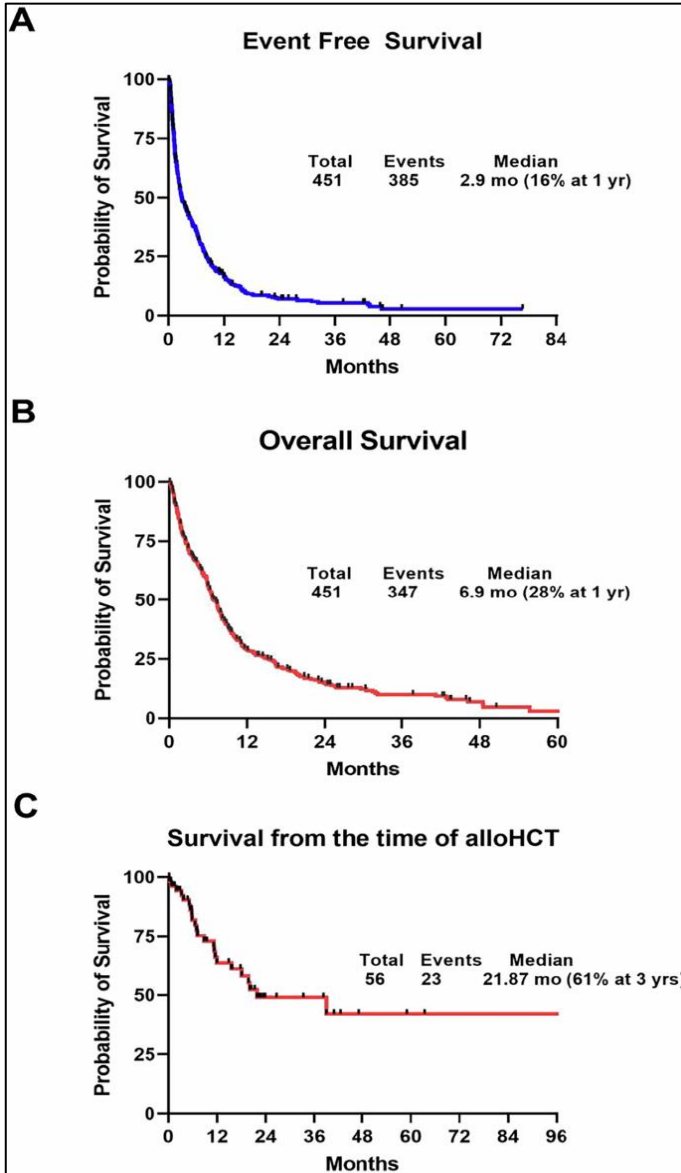


CAVEAT: A Time-Limited Venetoclax-Based Strategy Achieving Deep and Durable Responses in Older AML



- **CAVEAT redefines intensive therapy in older AML:**
VEN + modified chemo delivers 75% ORR with low early mortality (4%)
- **Outstanding efficacy in de novo AML:**
ORR 88% and median OS 33 months, highlighting a clear biologic-sensitive subgroup
- **Molecularly driven benefit:**
NPM1/IDH1/2-mutated AML shows deep, durable responses, whereas TP53 remains an unmet need
- **Time-limited therapy → meaningful TFR:**
nearly 1/3 of patients relapse-free, with median TFR ~18 months
- **Optimized consolidation (LDAC + VEN)**
mitigates myelotoxicity without compromising outcomes
→ feasible “chemo-lite” paradigm

Biology Over Therapy: No Treatment Strategy Significantly Improves Outcomes in TP53-Mutated Myeloid Neoplasms



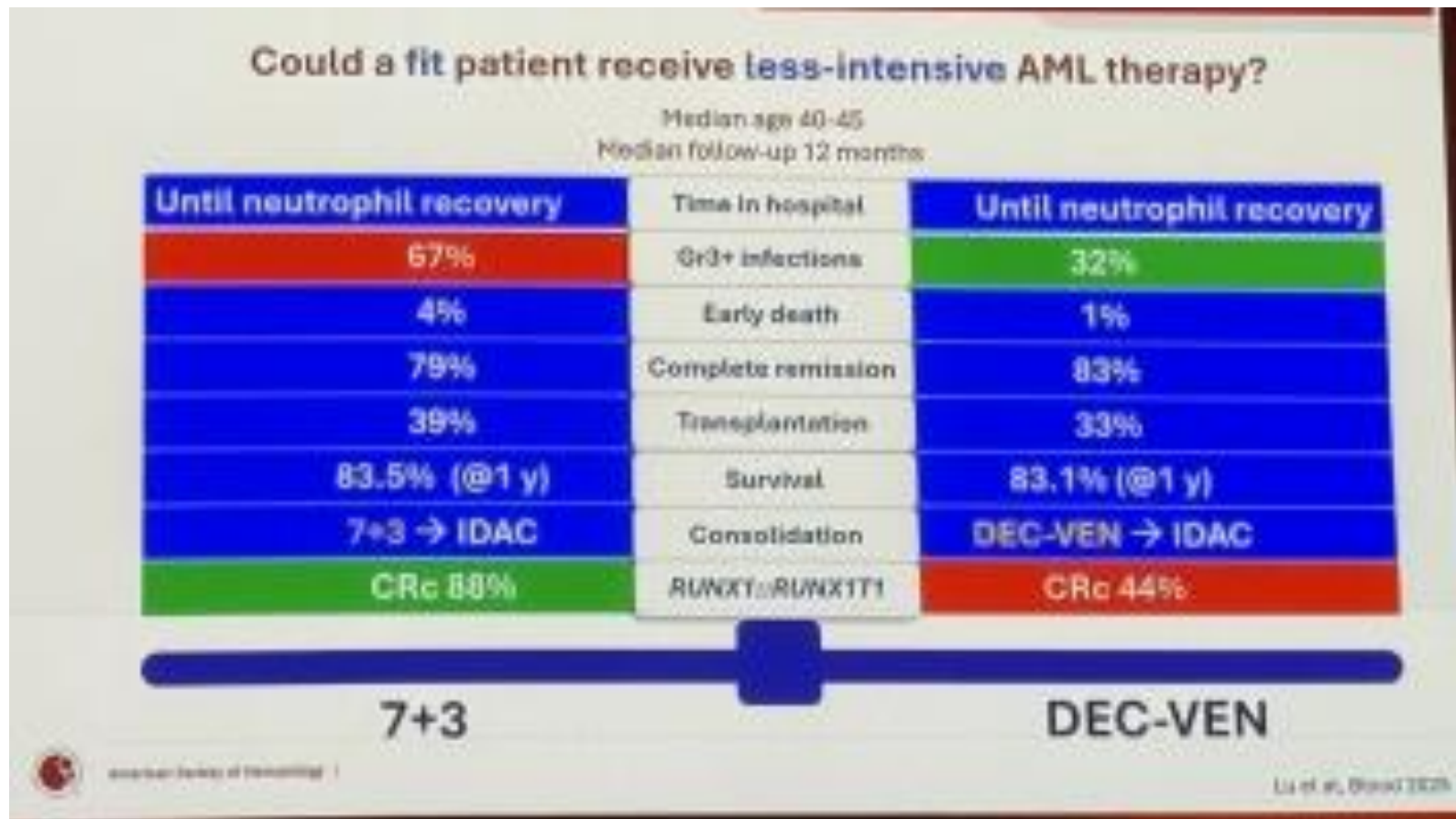
451 patients

- HMA + venetoclax: 43% (N = 193)
- Intensive chemotherapy 31% (N = 142)
- HMA-based therapy 20% (N = 88)
- Low intensity chemotherapy 6% (N = 28)

Cox regression models predicting for event free survival

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age $\geq 70y$	0.95 (0.78-1.17)	0.10	-	-
Multi-hit TP53 ^{mt}	1.92 (1.47-2.51)	<0.0001	1.62 (1.11-2.39)	0.01
MDS-EB2 vs other (sAML, de novo AML, MPN-BP)	0.54 (0.39-0.76)	0.005	0.56 (0.34-0.94)	0.02
Response; CR/CRI vs other	0.30 (0.24-0.38)	<0.0001	0.31 (0.23-0.41)	<0.001
Allo-HSCT	0.27 (0.21-0.34)	<0.0001	0.32 (0.21-0.49)	<0.001
Cox regression models predicting for overall survival				
Age $\geq 70y$	1.26 (1.02-1.56)	0.02	1.34 (1.02-1.76)	0.03
Multi-hit TP53 ^{mt}	2.17 (1.62-2.90)	0.001	1.96 (1.26-3.06)	0.003
MDS-EB2 vs other (sAML, de novo AML, MPN-BP)	0.41 (0.29-0.60)	0.0003	0.45 (0.24-0.84)	0.012
Response; CR/CRI vs other	0.44 (0.35-0.56)	<0.0001	0.51 (0.38-0.68)	<0.001
Allo-HSCT	0.21 (0.17-0.27)	<0.0001	0.31 (0.19-0.49)	<0.001

Less Intensive... or Just Differently Intensive?



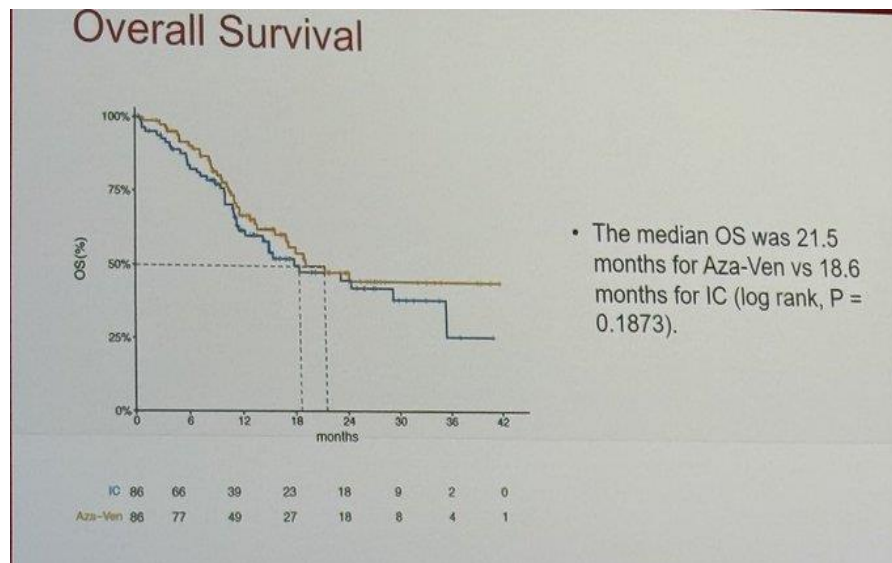
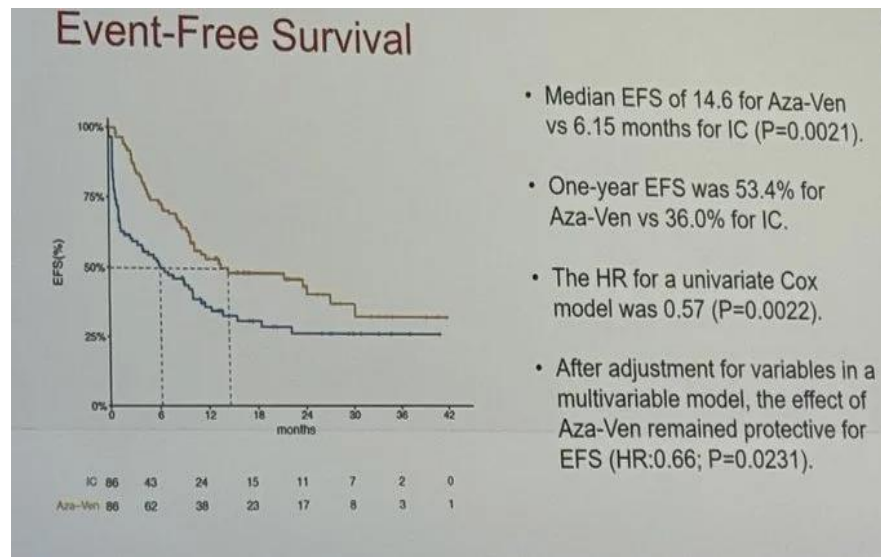
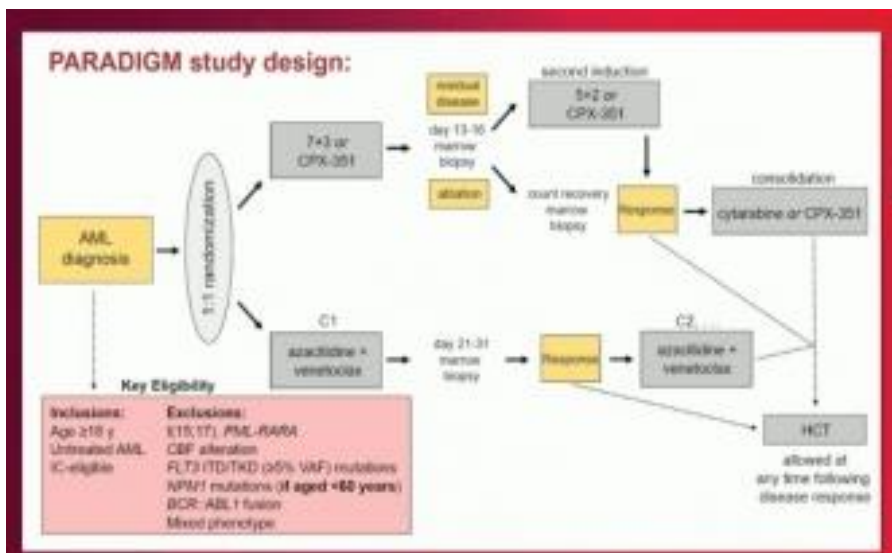
VEN-DEC showed superior CRc in:

- those with adverse risk (91% vs 42%)
- epigenetic mutations (91% vs 67%)

lower CRc in

- *RUNX1::RUNX1T1* fusion cases (44% vs 88%) than IC

Are PARADIGM Phase II Results Enough to Change AML Practice?



Aza-Ven vs IC: Practice-Changing or Premature?

Study design

Primary endpoint = EFS (not OS) → may favor aza-ven due to treatment change definitions
Open-label design → potential bias in clinical decision-making and event

Patient's features

Exclusion of favorable-risk AML (CBF, FLT3, NPM1 <60) → limits generalizability and underrepresents best IC responders
Predominance of adverse-risk patients (72%) → population inherently less sensitive to IC

Survival

Higher transplant rate in aza-ven arm (61% vs 40%) → outcomes may be driven by HCT rather than induction strategy
Short follow-up (median 16 months) → insufficient to assess long-term survival and cure

Response

No significant difference in CR rate → benefit driven by less stringent responses (MLFS)
MRD results not reported → depth and quality of remission unclear

Treatment

Heterogeneous IC arm (7+3 vs CPX-351) → potential dilution of chemotherapy efficacy
Fewer cycles delivered in IC arm → possible under-treatment

Conclusions

Borderline AML patients challenge conventional decision-making

Biology—not age—should guide treatment choice

“Less intensive” does not always mean less burden

Intensive therapy remains a valuable option in borderline patients

Depth of response and treatment-free remission are key goals

Undertreatment may be a greater risk than overtreatment