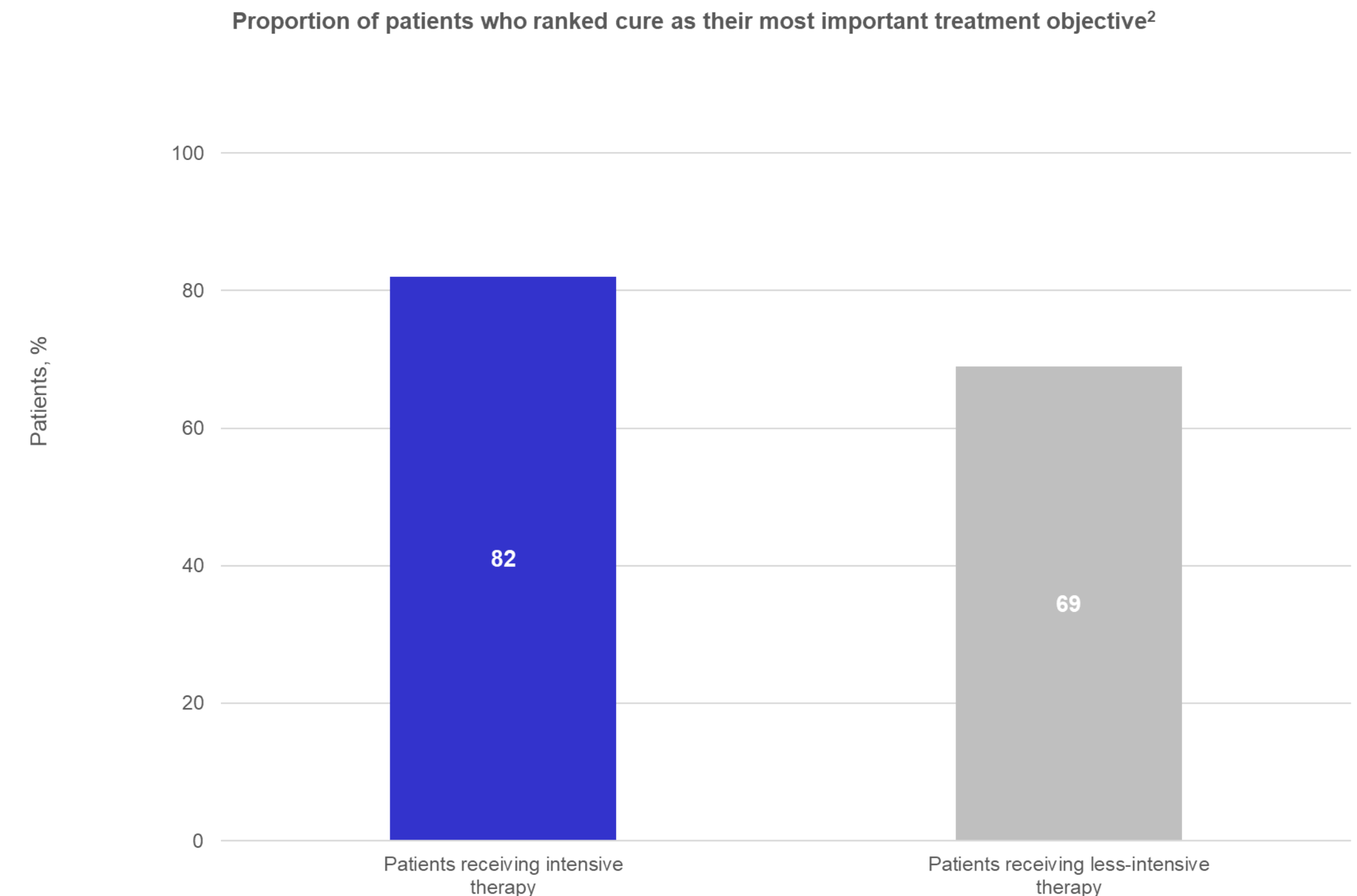


Dalla diagnosi alla malattia refrattaria nel paziente borderline per la fitness

**Adriano Venditti
Università Tor Vergata
Azienda Universitaria PTV**

Age and fitness: an individualised treatment approach?

Many patients consider cure as their main objective, independent of treatment type; their expectations may not reflect the reality of currently available treatments



Patient-reported results from a prospective, multicentre study during 2013–2017 showed that, irrespective of their treatment pathway, cure is the outcome patients with AML rank above all others.

AML, acute myeloid leukaemia.

1. Lazarevic VL. *J Intern Med*. 2021;290(2):279–93. <https://onlinelibrary.wiley.com/doi/full/10.1111/joim.13293>. © 2021 The Authors. Licensed under CC BY 4.0.

<https://creativecommons.org/licenses/by/4.0/>; 2. Sorror ML, et al. *Blood*. 2021;138(5):387–400.

Determining treatment tolerance and fitness for intensive chemotherapy in older adults with AML: A call to action

Vijaya Raj Bhatt,¹ Geoffrey L. Uy,² and Heidi D. Klepin³

¹Fred & Pamela Buffett Cancer Center, Division of Hematology-Oncology, University of Nebraska Medical Center, Omaha, NE; ²Division of Oncology, Washington University School of Medicine, St. Louis, MO; and ³Department of Internal Medicine, Section on Hematology and Oncology, Wake Forest University Health System, Winston-Salem, NC

Approaches to determining tolerance of intensive chemotherapy treatment

Approach	Characteristics	Evidence	Nature of the study
Geriatric assessment	Multidimensional assessment	Cognition, physical function, emotional health, and comorbidity burden correlate with mortality	Single-center and small multicenter prospective studies ^{3,5,7}
Ferrara criteria	Mostly age, comorbidities, and ECOG PS	Criteria-defined fitness correlates with mortality	Retrospective studies ^{10,11}
Comorbidity Index	Mostly comorbidities	Higher comorbidity burden correlates with mortality	Retrospective and prospective studies ¹²
Mortality scores* (several)	Age, performance status, laboratory data, etc	Higher score correlates with mortality	Post hoc analysis of trials and retrospective studies ^{9,13-15}

Although these are the current approaches, further evidence for validated criteria is needed

*These scoring systems do not directly measure fitness but provide the risk of early mortality associated with the use of intensive chemotherapy. AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status. Bhatt VR, et al. *Blood*. 2024;143(6):483–487.

Proposed operational criteria included in the definitions of unfitnes to intensive and non intensive chemotherapy

SIE/SIES/GITMO group: derived mainly from the definitions of comorbidities from literature

Operation criteria to define unfitnes 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 dyspnoea 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 hospitalisation, institutionalisation 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 leukaemia
9.	Any other co-morbidity that the physician judges to be incompatible with conventional intensive chemotherapy
Operation criteria to define unfitnes to non-intensive chemotherapy in AML	
1.	Refractory congestive heart failure
2.	Documented pulmonary disease with DLCO ≤65% or FEV1 ≤65%, or dyspnoea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
3.	Liver cirrhosis Child B or C or acute viral hepatitis
4.	Active infection resistant to anti-infective therapy
5.	Current mental illness requiring psychiatric hospitalisation, institutionalisation or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
6.	Uncontrolled neoplasia



Table 6: Quality of life (QoL) and social support

No.	Quality of life (QoL) and social support	LoE	GoR	LoA
18	Social support should be offered to all patients regardless of treatment intensity and throughout the entire therapeutic process.	III	C	100%
19	In the absence of a caregiver, patients' social support should be intensified when considering any therapeutic intervention.	IV	D	96%
20	Treatment selection should consider the impact of any given therapy on patient's QoL and preferences.	IV	D	85%
21	Integration of early palliative care during diagnosis should be considered standard of care to improve the QoL and patients' care in those receiving intensive chemotherapy.	II	B	65%

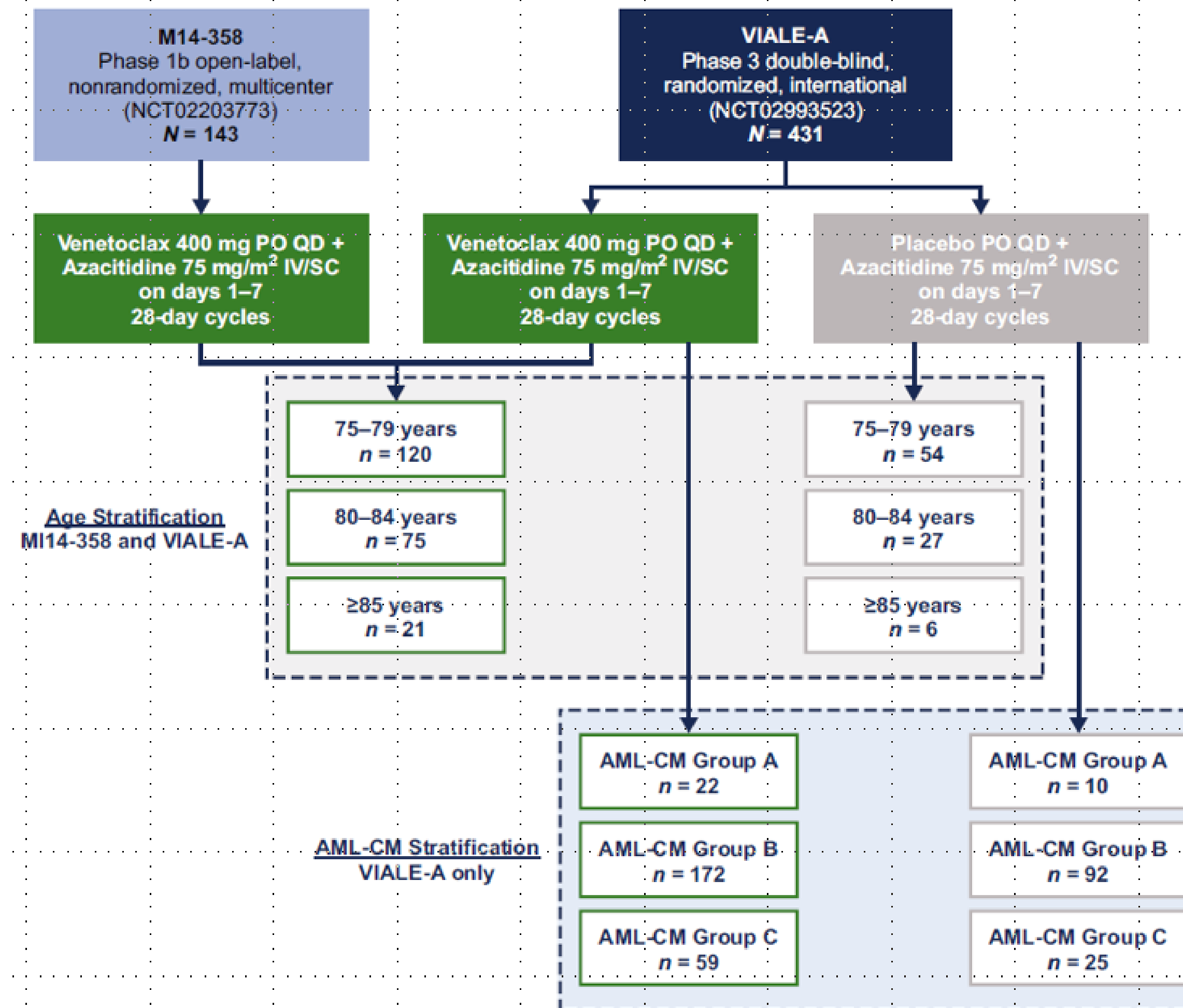
LoE, level of evidence; GoR, grade of recommendation; LoA, level of agreement

Table 4: Timing for fitness/genetic determination

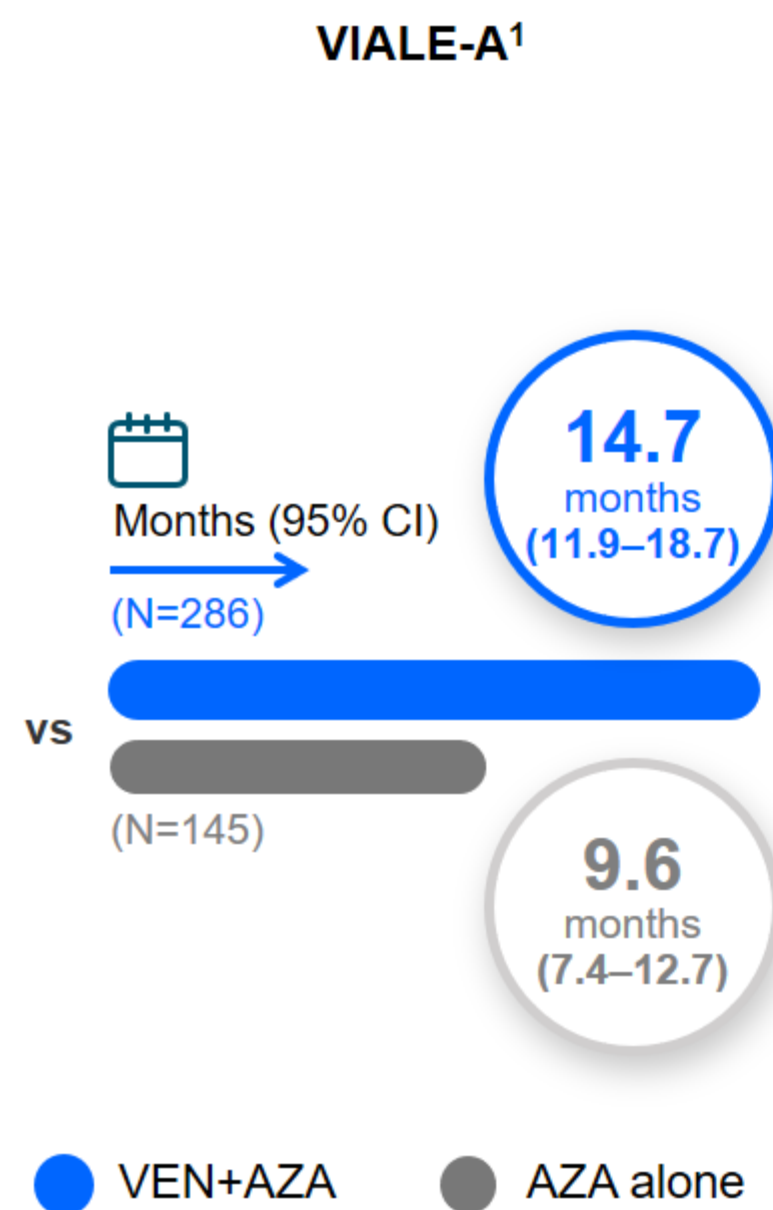
No.	Recommendations: Timing for fitness/genetic determination	LoE	GoR	LoA
14	Because the time to treatment start does not seem to affect short- and long-term outcomes, comprehensive fitness and biological assessment should be conducted before starting therapy.	IV	B	96%
15	Fitness level attribution should be performed after appropriate supportive therapy when general condition impairments are suspected to be due disease burden rather than pre-existing 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%

LoE, level of evidence; GoR, grade of recommendation; LoA, level of agreement

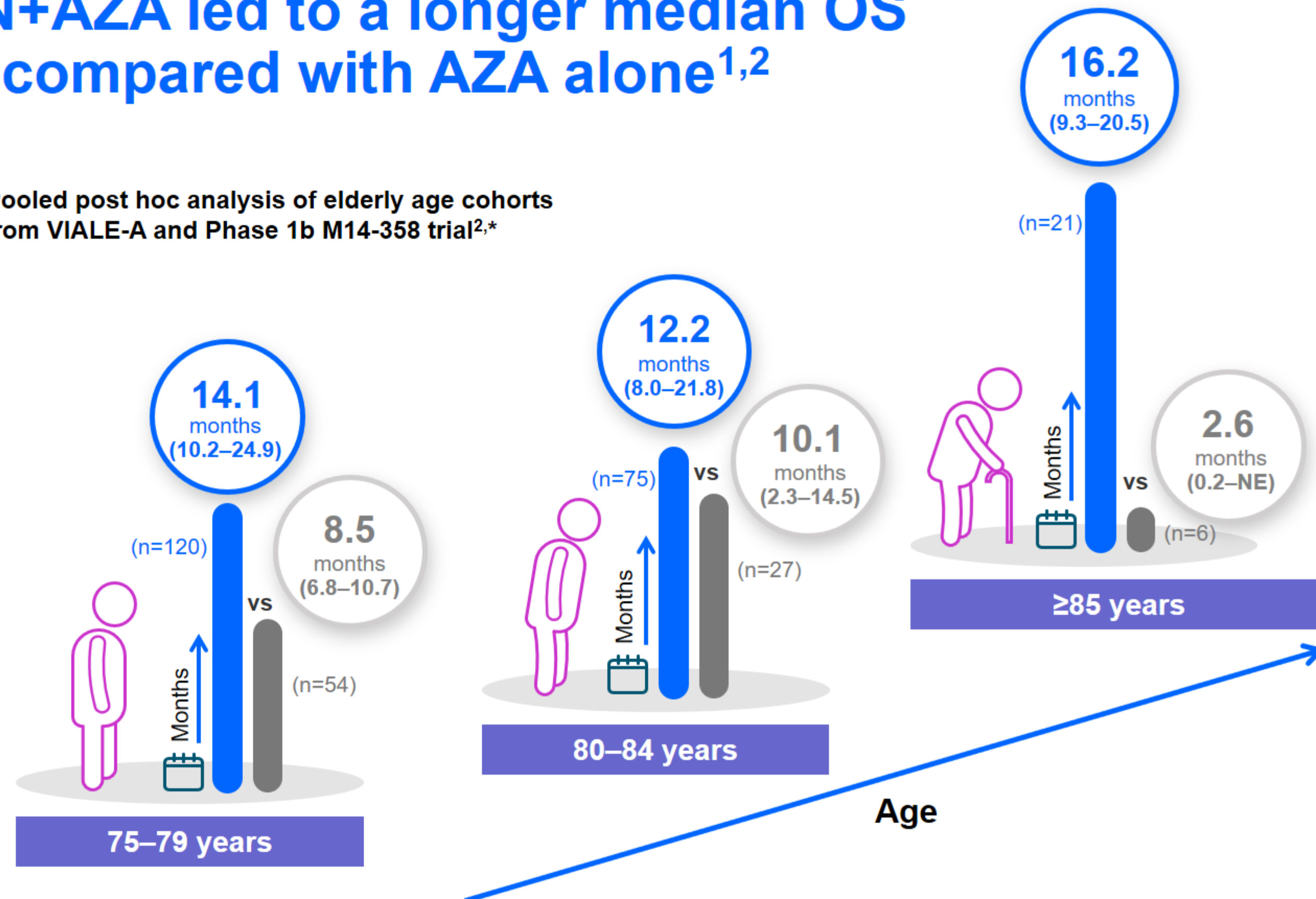
Outcomes of patients treated with VEN-AZA vs AZA alone stratified by advanced age and AML composite model



Treatment with VEN+AZA led to a longer median OS irrespective of age compared with AZA alone^{1,2}

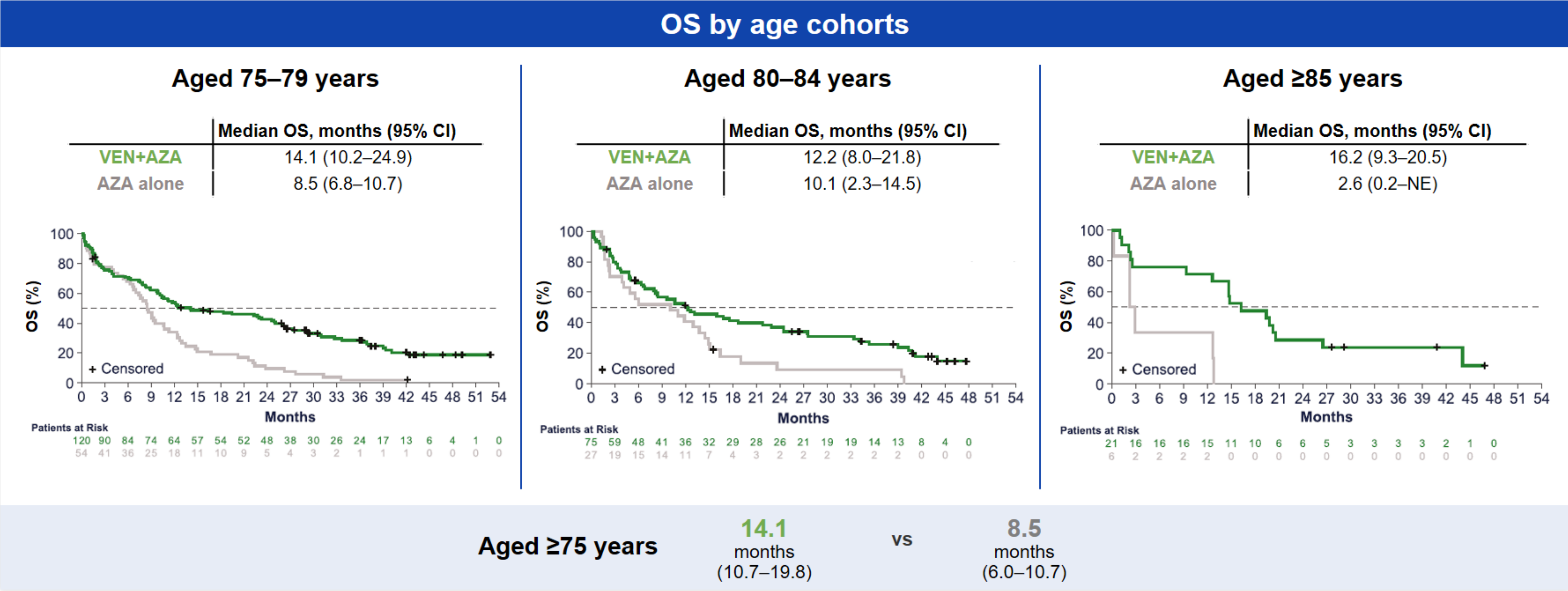


Pooled post hoc analysis of elderly age cohorts from VIALE-A and Phase 1b M14-358 trial^{2,*}



AZA, azacitidine; CI, confidence interval; NE, not estimable; OS, overall survival; VEN, venetoclax.
 1. DiNardo CD, et al. *N Engl J Med*. 2020;383(7):617–629; 2. Venditti A, et al. *Leukemia*. 2025 Nov;39(11):2697–2707

Median OS was longer with VEN+AZA versus AZA alone across age cohorts in a post hoc analysis of VIALE-A and the Phase 1b study in elderly patients*



Ferrara score, age and adverse ELN risk predict likelihood of receiving lower intensity treatment in older patients with AML in real-world clinical practice

US multicenter retrospective study assessing role of comorbidities in frontline treatment selection

Ferrara score and its components predicted likelihood of receiving lower intensity treatment*				Patient age and adverse ELN risk also predicted likelihood of receiving lower intensity treatment†			
Variable	OR	95% CI	P value	Variable	OR	95% CI	P value
Ferrara score 1-2 vs 0	4.45	2.19-9.05	<0.0001	Ferrara score 1-2 vs 0	6.06	2.60-14.11	<0.0001
CHF or EF <50%	5.88	1.48-23.36	0.01	Age at diagnosis	1.16	1.08-1.25	<0.0001
Pulmonary disease	5.35	1.79-15.98	0.003	TP53 mutation present	1.66	0.81-3.42	0.17
Active resistant infection	2.83	0.47-17.11	0.26	ELN 2017 adverse risk	2.67	1.38-5.17	0.004
ECOG ≥3	4.68	0.85-25.91	0.08	Prior myeloid malignancy	1.09	0.48-2.46	0.84
				Prior HMA therapy	0.33	0.11-0.98	0.18

*A higher Ferrara score, CHF diagnosis, and active pulmonary disease at induction predicted likelihood of Ven+HMA tx.
†Treatment decision was most influenced by Ferrara score, age, and ELN risk.



Ferrara criteria
correlated with frontline
AML treatment choice



While current clinical trials use
Ferrara criteria, Ferrara score does
not reflect all factors that influences
treatment selection in the real world



Ferrara score did not
necessarily predict
outcomes after receiving
IC vs non-IC

Common salvage regimens in patients not responding to initial induction or with relapsed disease who are candidates for intensive therapy

Gilteritinib (AML with <i>FLT3</i> mutation) Intermediate-dose cytarabine# (with or without anthracycline) FLAG-IDA** MEC CLAG-M Allogeneic HCT	Gilteritinib 120 mg PO QD d1-28, q4 wk, until disease progression Cytarabine 1000-1500 mg/m² IV over 3h q12h d1-3 (500-1000 mg/m² in patients ≥ 60y); with or without daunorubicin 60 mg/m² IV d1-3; idarubicin 8-10 mg/m² IV d3-5; or mitoxantrone 8-10 mg/m² IV d1-3 Fludarabine 30 mg/m² IV d2-6; cytarabine 1500-2000 mg/m² IV over 3h, starting 4h after fludarabine infusion, d2-6; idarubicin 10 mg/m² IV d2-4; G-CSF 5 µg/kg SC d1-5; additional G-CSF may be administered starting 7 d after end of chemotherapy until WBC count > 0.5 × 10⁹/L Consider dose reduction in patients ≥60 y: fludarabine 20 mg/m²; cytarabine 500-1000 mg/m²; idarubicin 8 mg/m² Mitoxantrone 8 mg/m² IV d1-5; etoposide 100 mg/m² IV d1-5; cytarabine 1000 mg/m² IV d1-5 Cladribine 5 mg/m² IV d1-5; cytarabine 2000 mg/m² IV d1-5 (starting 2h after cladribine infusion); mitoxantrone 10 mg/m² IV d1-3; G-CSF 300 µg SC d0-5 Consider transplantation for patients with primary refractory disease, for patients in second CR (or CRh, CRi) or with major cytoreduction but still active disease following salvage therapy. Consider second transplantation under certain conditions. Perform early HLA typing.
Salvage options if not a candidate for intensive chemotherapy	
Gilteritinib (AML with <i>FLT3</i> mutation)†† Ivosidenib (AML with <i>IDH1</i> mutation)‡‡ Enasidenib (AML with <i>IDH2</i> mutation)^a	120 mg PO QD d1-28, q4 wk, until disease progression 500 mg PO QD d1-28, q4 wk, until disease progression 100 mg PO QD d1-28, q4 wk, until disease progression

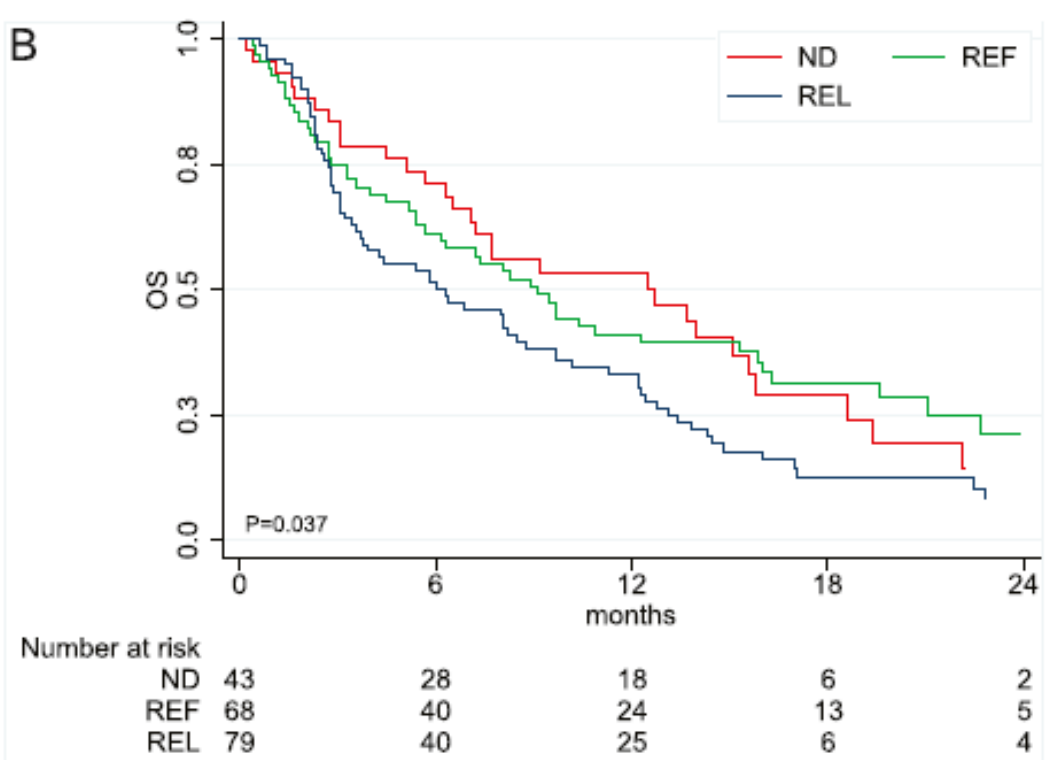
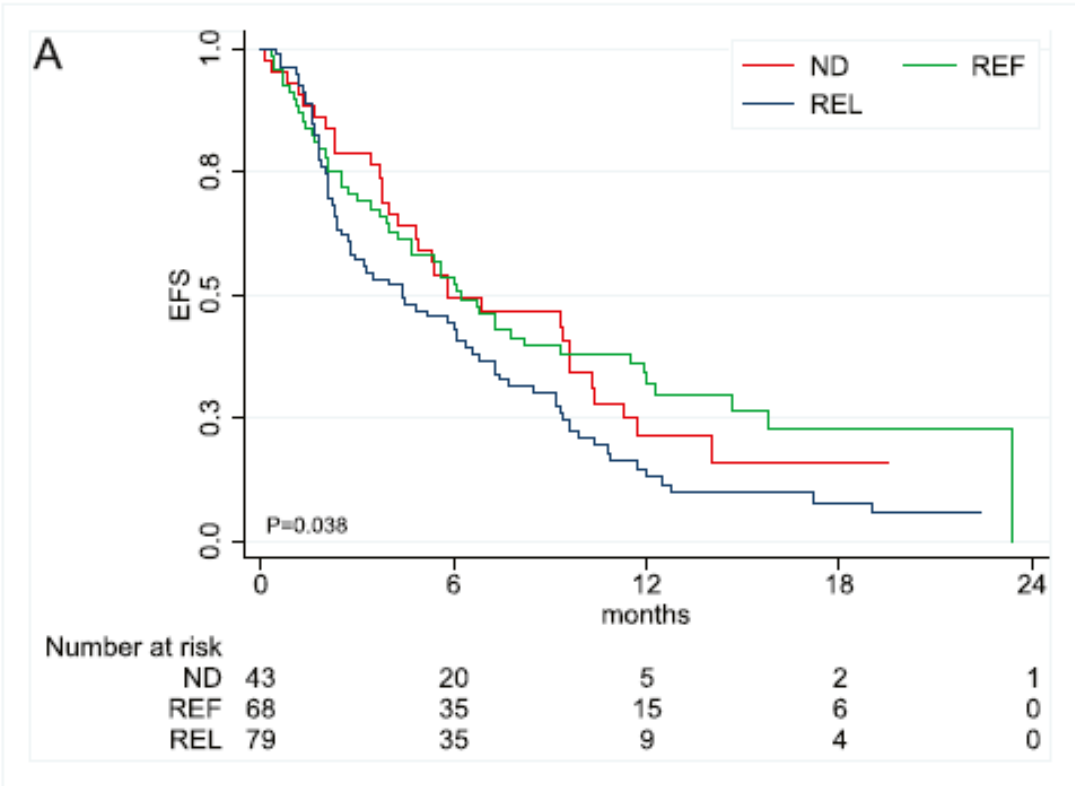
AVALON: The Italian cohort study on real-life efficacy of hypomethylating agents plus venetoclax in newly diagnosed or relapsed/refractory patients with acute myeloid leukemia

TABLE 2 Clinical response to VEN + HMA of ND, REF, and REL patients with AML

	Total		ND		REF		REL		
	(n = 190)		(n = 43)		(n = 68)		(n = 79)		p
Best response	n	(%)	n	(%)	n	(%)	n	(%)	.639
ORR	96	(50.5)	28	(65.1)	35	(51.5)	33	(41.8)	
cCR	74	(39.0)	21	(48.8)	26	(38.2)	27	(34.2)	
PR	22	(11.6)	7	(16.3)	9	(13.2)	6	(7.6)	
SD/PD ^a	70	(36.8)	11	(25.6)	24	(35.3)	35	(44.3)	
Not evaluable	24	(12.6)	4	(9.3)	9	(13.2)	11	(13.9)	
									.336
Median time to best response (months) [1Q–3Q]	2.2 [1.2–4.4]		2.8 [1.5–5.9]		1.9 [1.1–4.0]		2.3 [1.2–3.8]		.789
Median DOR (months) [95% CI]	7.6 [5.1–11.2]		10.6 [4.0–11.9]		6.8 [4.4–12.6]		8.3 [4.7–11.9]		
	Total		ND		REF		REL		
	(n = 190)		(n = 43)		(n = 68)		(n = 79)		
	n	(%)	n	(%)	N	(%)	n	(%)	
HSCT after start of combination therapy	43	(22.6)	5	(11.6)	22	(32.4)	16	(20.3)	.032

Abbreviations: 1Q, first quartile; 3Q, third quartile; cCR, composite complete remission; DOR, duration of response; HSCT, hematopoietic stem cell transplantation; ND, newly diagnosed; ORR, overall response rate; PR, partial remission; REF, primary refractory patients; REL, relapsed.

^aIncluding patients who died within 3 months of starting VEN + HMA without a disease reevaluation.



	Total		ND		REF		REL	
	(n=190)		(n=43)		(n=68)		(n=79)	
	n	(%)	n	(%)	n	(%)	n	(%)
Events	150	(79.0)	31	(72.1)	48	(70.6)	71	(89.9)
Median EFS (months) [95% CI]	5.8 [4.4 – 6.8]		5.8 [4.0 – 9.6]		6.2 [4.3 – 9.3]		4.4 [2.7 – 6.4]	

	Total		ND		REF		REL	
	(n=190)		(n=43)		(n=68)		(n=79)	
	n	(%)	n	(%)	n	(%)	n	(%)
Events	146	(76.8)	29	(67.4)	48	(70.6)	69	(87.3)
Median follow-up time (months) [95% CI]	20.9 [17.0 – 25.9]		17.3 [12.8 – 25.9]		20.7 [15.9 – 24.9]		26.1 [16.9 – NR]	
Median OS (months) [95% CI]	8.1 [6.3 – 9.7]		12.7 [6.5 – 15.6]		9.1 [5.7 – 15.3]		6.3 [3.6 – 8.8]	

A novel prognostic risk model for patients with refractory/relapsed acute myeloid leukemia receiving venetoclax plus hypomethylating agents

Rabia Shahswar¹, Razif Gabdoulline¹, Katja Krueger¹, Martin Wichmann¹, Katharina S. Götze^{2,3}, Krischan Braitsch², Manja Meggendorfer ⁴, Laura Schmalbrock ⁵, Lars Bullinger ⁵, Franziska Modemann ⁶, Walter Fiedler⁶, Juergen Krauter⁷, Stephan Kaun⁸, Susanne Rotermund⁸, Andreas Voß ⁹, Yvonne Lisa Behrens¹⁰, Anke Katharina Bergmann ¹⁰, Elisabeth Koller¹¹, Gernot Beutel ¹, Felicitas Thol ¹, Florian Heidel ¹and Michael Heuser ^{1,12}✉

Endpoint	Variables in the model	Univariate analysis			Multivariate analysis			
		HR ^a	95%CI	<i>p</i>	HR ^a	95%CI	<i>p</i>	Coefficient ^b
OS	Extramedullary AML	2.06	1.33;3.18	0.001	2.46	1.5;4.0	<0.001	0.90
	HMA pretreatment	1.63	1.15;2.31	0.006	1.9	1.3;2.8	<0.001	0.64
	<i>NF1</i> mut vs wt	2.53	1.19;5.35	0.015	2.6	1.2;5.4	0.01	0.94
	<i>PTPN11</i> mut vs wt	2.26	1.50;3.41	<0.001	2.2	1.3;4.0	0.006	0.80
	<i>FLT3</i> ^c mut vs wt	1.64	1.00;2.68	0.05	1.6	1.0;2.8	0.08	0.49
	<i>TP53</i> mut vs wt	1.49	0.96;2.29	0.073	1.5	0.94;2.3	0.09	0.39
	<i>SF3B1</i> mut vs wt	0.56	0.31;1.02	0.058	0.38	0.2;0.8	0.01	-0.98
EFS	Extramedullary AML	1.62	1.04;2.53	0.032	1.76	1.1;2.8	0.02	0.57
	HMA pretreatment	1.46	1.04;2.05	0.028	1.57	1.1;2.2	0.014	0.45
	<i>NF1</i> mut vs wt	2.74	1.43;5.22	0.002	2.25	0.95;5.3	0.06	0.81
	<i>PTPN11</i> mut vs wt	1.95	1.14;3.36	0.016	2.1	1.1;4.03	0.03	0.73
	<i>FLT3</i> ^c mut vs wt	1.97	1.25;3.11	0.003	1.82	1.1;3.04	0.02	0.6
	<i>SF3B1</i> mut vs wt	0.59	0.36;0.97	0.036	0.42	0.2;0.8	0.01	-0.87

For OS and EFS a model score value (*S*_{OS/EFS}) < 0.25 corresponds to a favorable risk, 0.25 ≤ *S*_{OS/EFS} ≤ 0.75 to an intermediate risk and *S*_{OS/EFS} > 0.75 to an adverse risk.

CI confidence interval, *EFS* event-free survival, *HMA* hypomethylating agents (i.e. azacitidine, decitabine), *HR* hazard ratio, *p* *P*-value, *OS* overall survival.

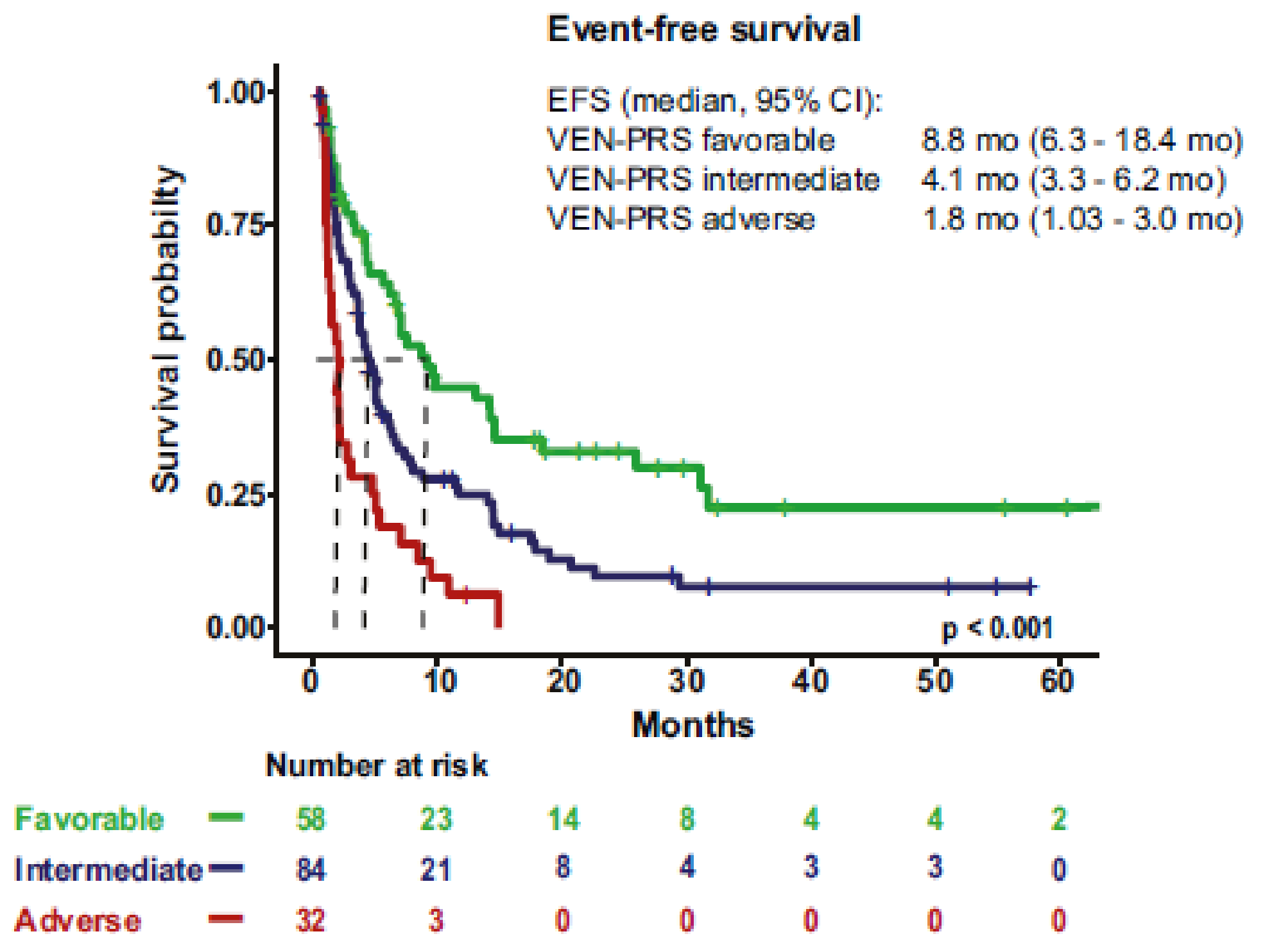
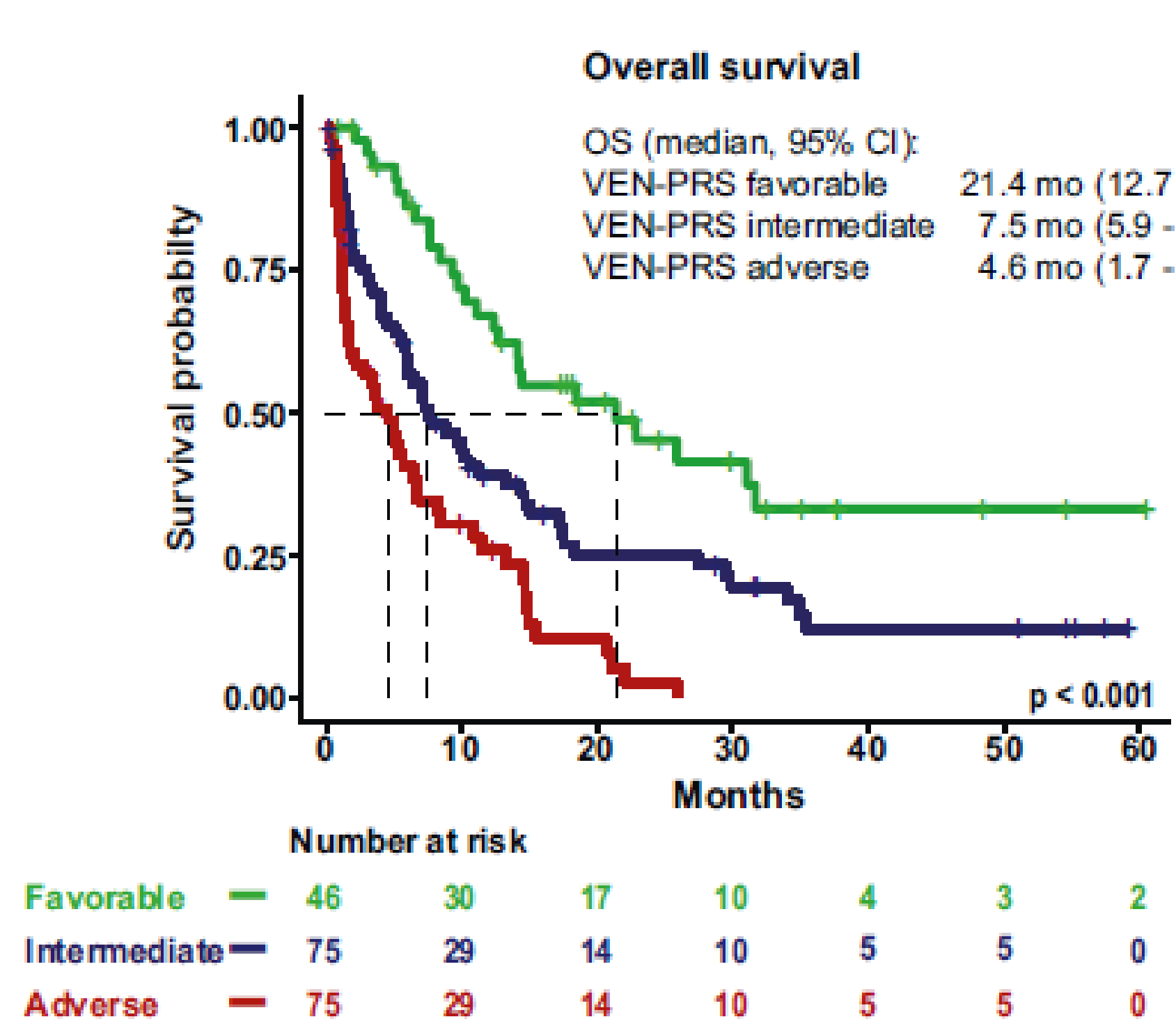
^aHazard ratios greater than or less than 1 indicate an increased or decreased risk, respectively, of an event for the categories listed.

^bThe VEN-PRS is calculated by adding coefficients of all variables that apply for each individual patient.

^cAny *FLT3* mutation. *FLT3* mutations n (%): *FLT3*-ITD: 18 (62); *FLT3*-TKD: 5 (17); atypical *FLT3*: 6 (21).

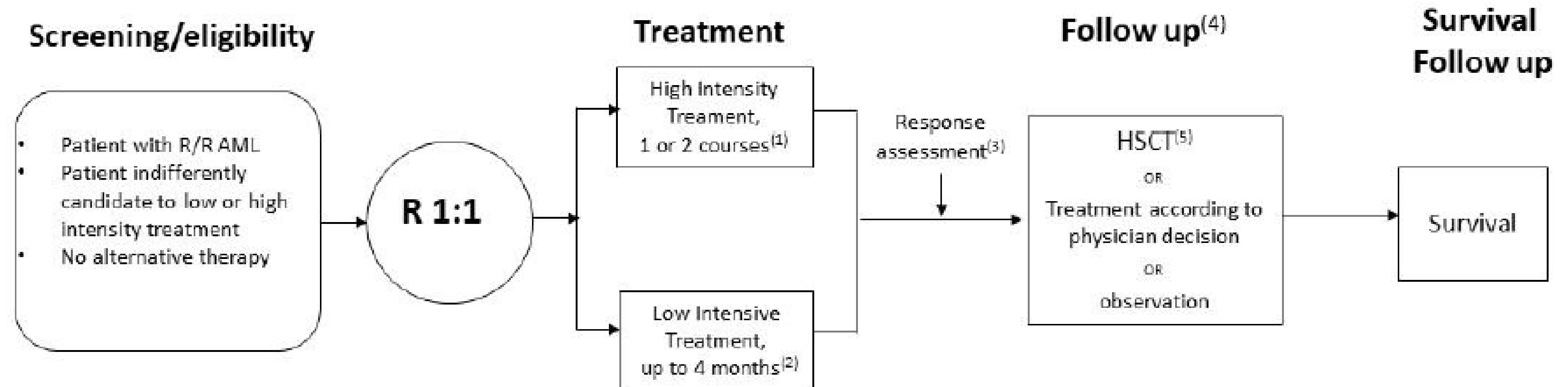
A novel prognostic risk model for patients with refractory/relapsed acute myeloid leukemia receiving venetoclax plus hypomethylating agents

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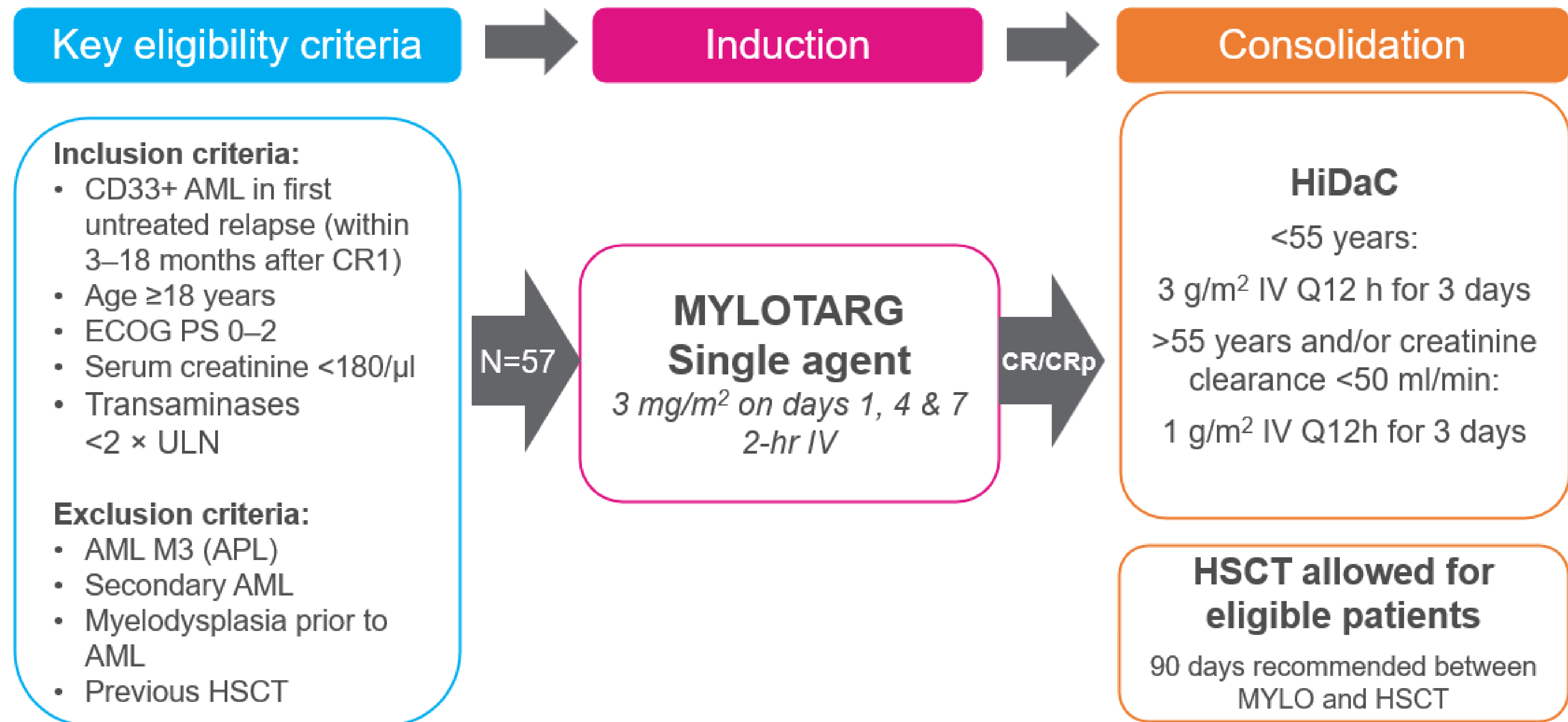


IMPACT-AML: A RANDOMIZED PRAGMATIC CLINICAL TRIAL FOR RELAPSE OR REFRACTORY ACUTE MYELOID LEUKEMIA

STUDY SCHEMA



MyloFrance-1: Study design



Response and safety (TEAEs) both assessed

MyloFrance-1:

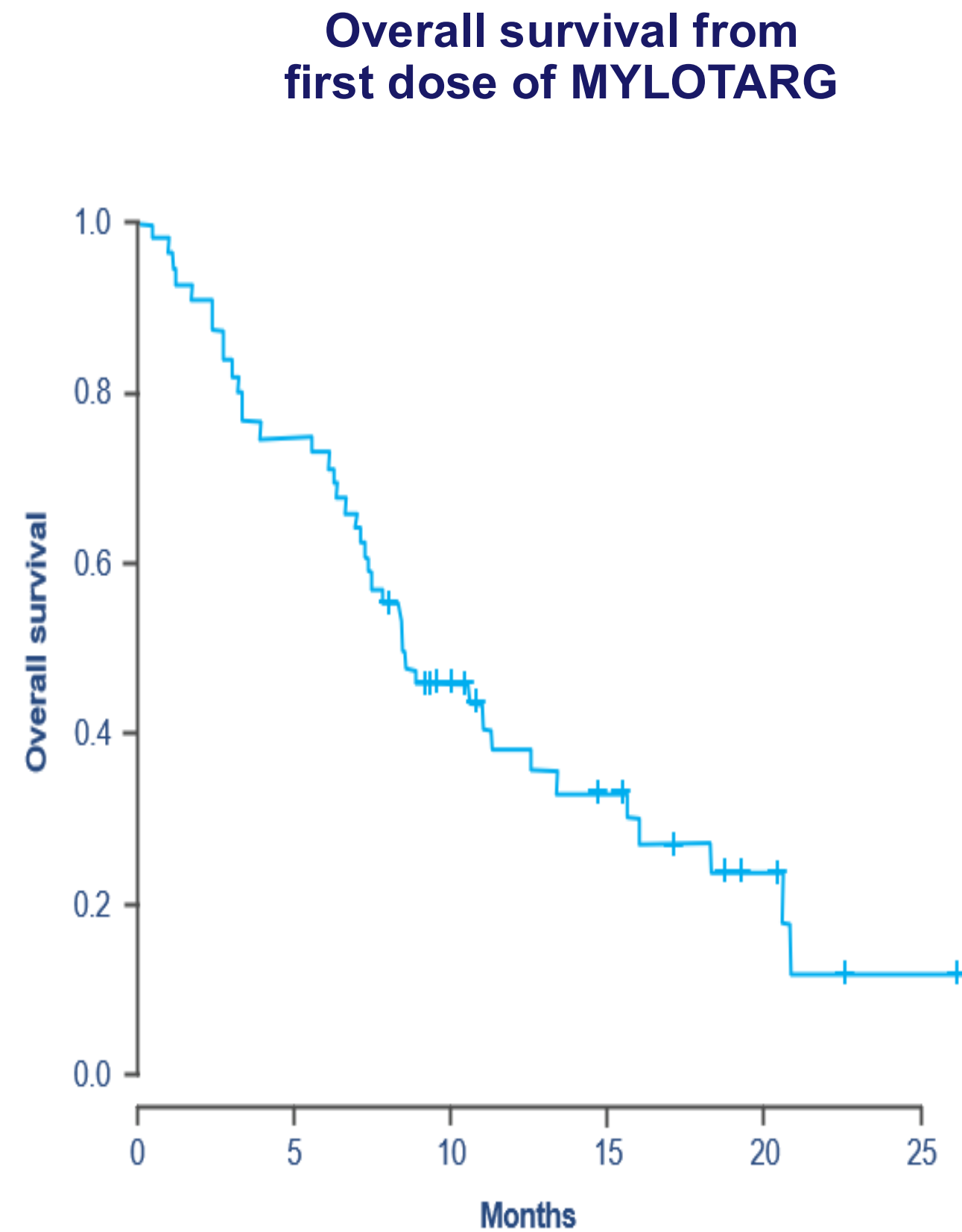
Baseline patient characteristics

Characteristics ¹	N or %
Number of patients ²	57
Age (years)	
Median ²	64
Range ²	22–80
% >60 years	61%
Duration of CR1 (months)	
Median ²	10
Cytogenetics	
Known	56/57
Favorable	0
Intermediate risk ²	44 (78%)
Poor risk ²	12 (22%)
Unknown	1

1. Taksin AL *et al. Leukemia* 2007;21:66-71; 2. US Prescribing Information 2017

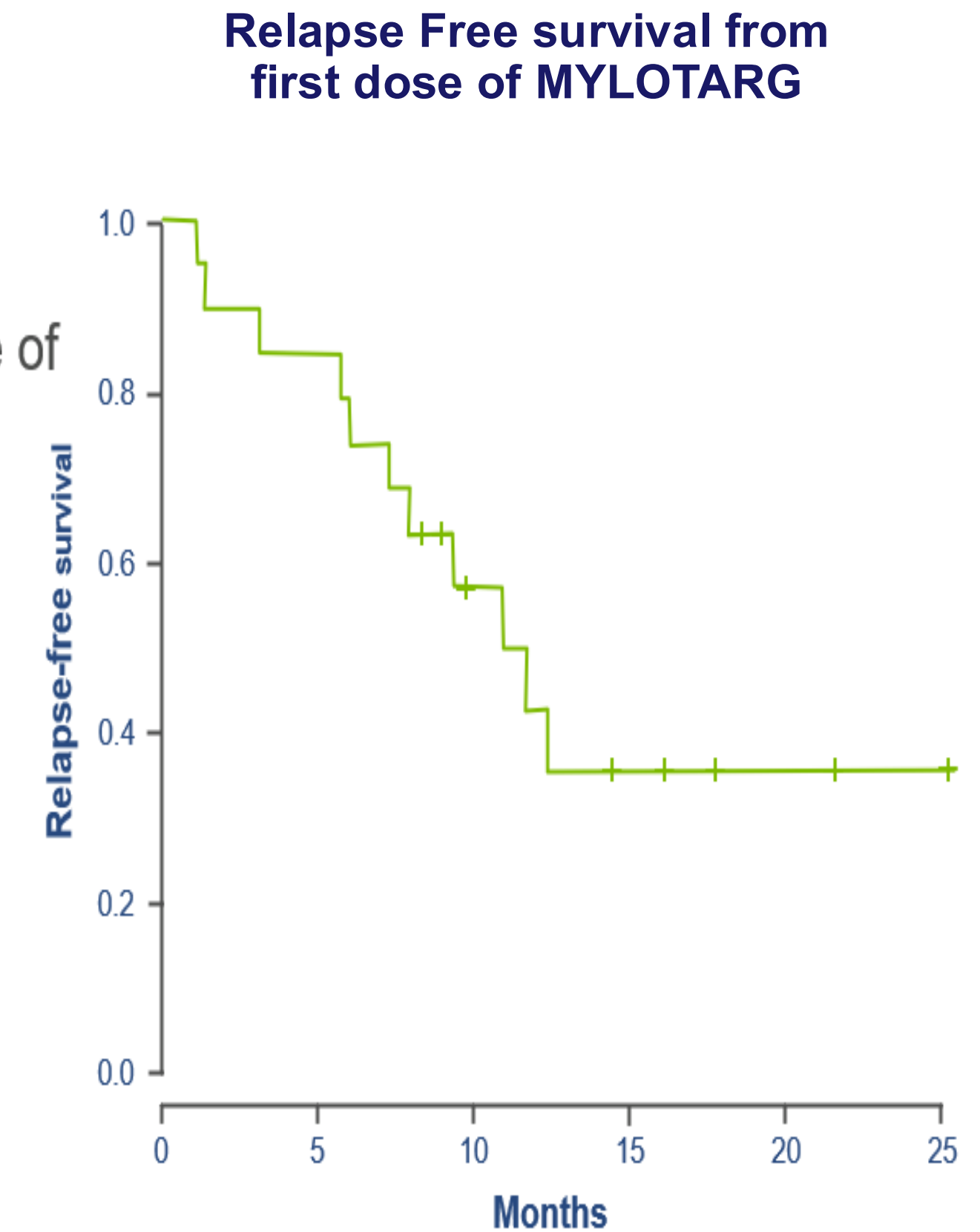
Response category	MF1 ¹ 3 mg/m ² × 3 n=57	
	n	%
OR* (CR* + CRp*)	19	33
CR*	15	26
CRp*	4	7

- Of the 57 patients enrolled, there were 40 (70.2%) deaths
- Median OS was 8.4 months
 - 8.3 months for patients aged <60 years
 - 8.9 months for patients aged >60 years (P=0.15)



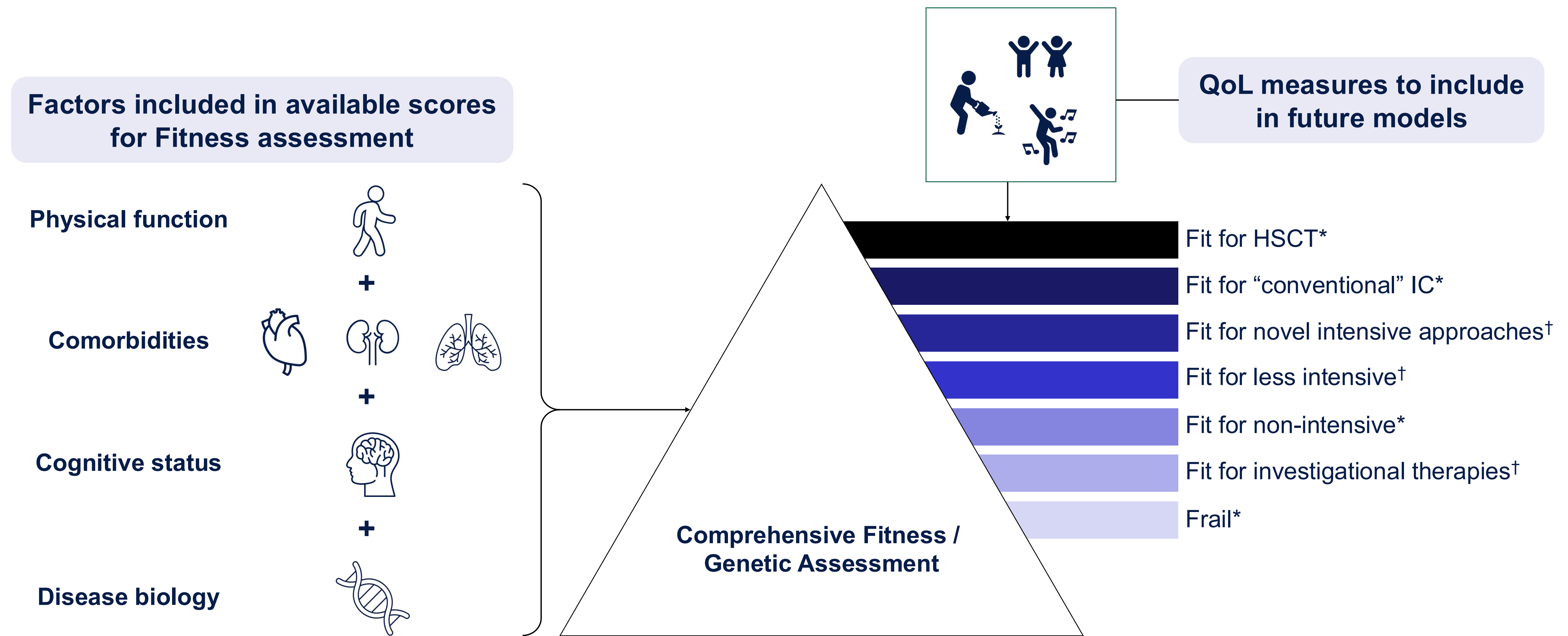
19 patients in remission

- 11 (57.9%) relapsed
- 9/11 died from leukemia
- Estimated cumulative incidence of relapse at 1 year of 57.4%
- 9/11 died from leukaemia
- Median RFS estimated at 11.0 months



Taksin AL *et al. Leukemia* 2007;21:66–71

Considering the continuous evolution of AML treatment algorithms, the concept of fitness and how to measure it also need to be updated



*Category defined by currently available Fitness Scores.

†Category not defined by currently available Fitness Scores.

AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; QoL, quality of life.