Leucemia acuta mieloide ricaduta/refrattaria

Adriano Venditti
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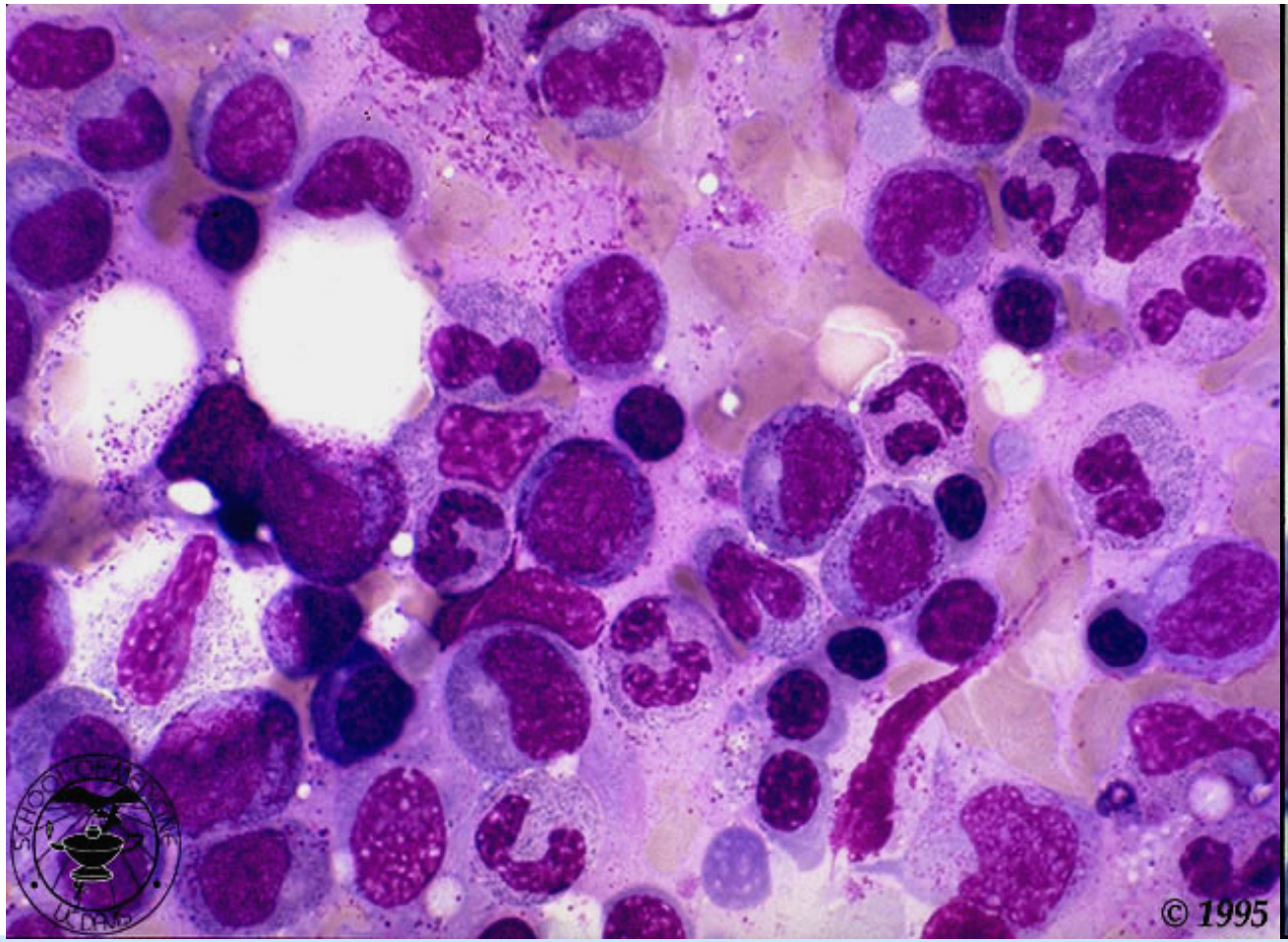
fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

Con il patrocinio di
UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

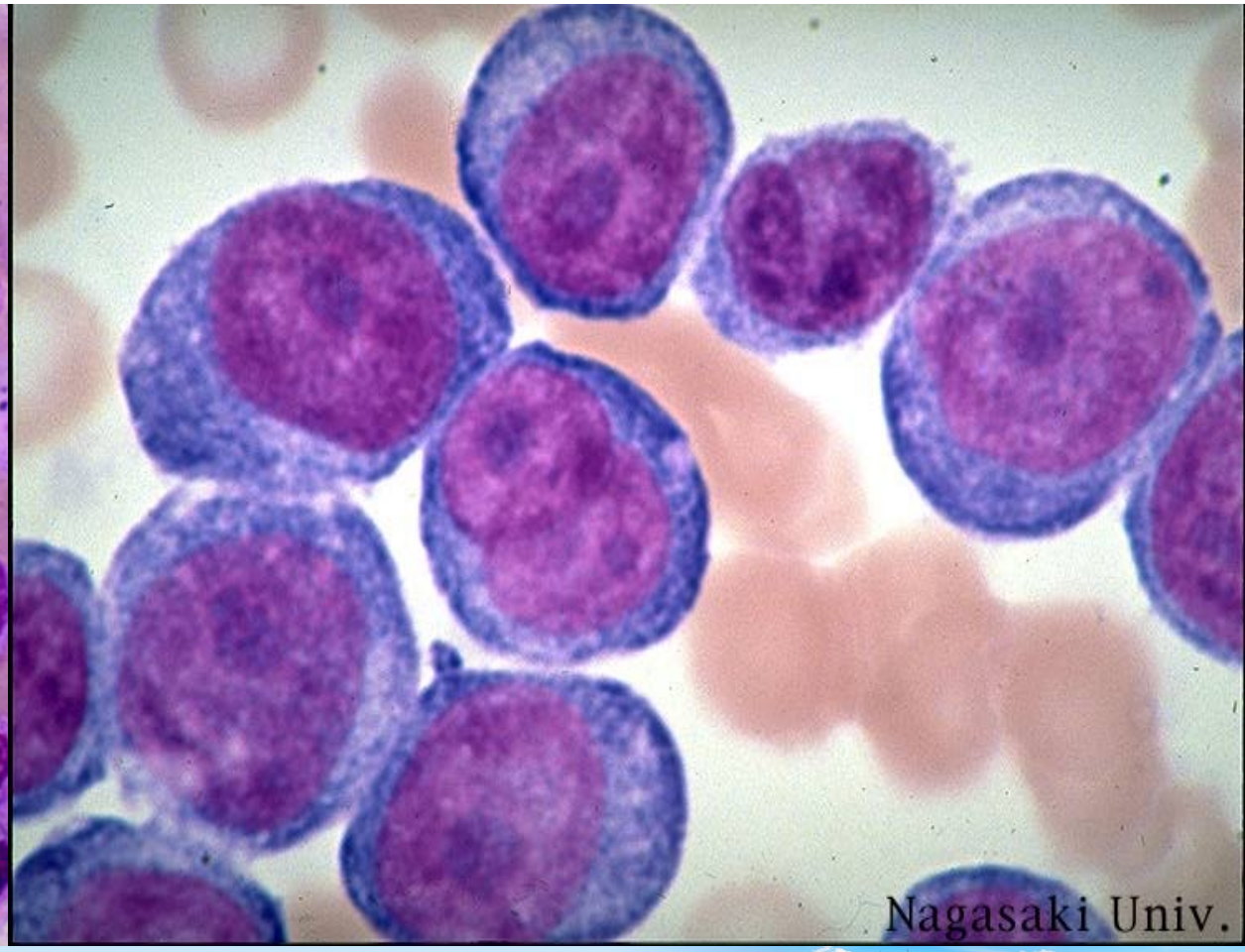
LE CURE PALLIATIVE PRECOCI IN
EMATO-ONCOLOGIA:
la nuova risposta ai bisogni di pazienti e caregivers

19 maggio 2023 **Roma**, Hotel Donna Camilla Savelli

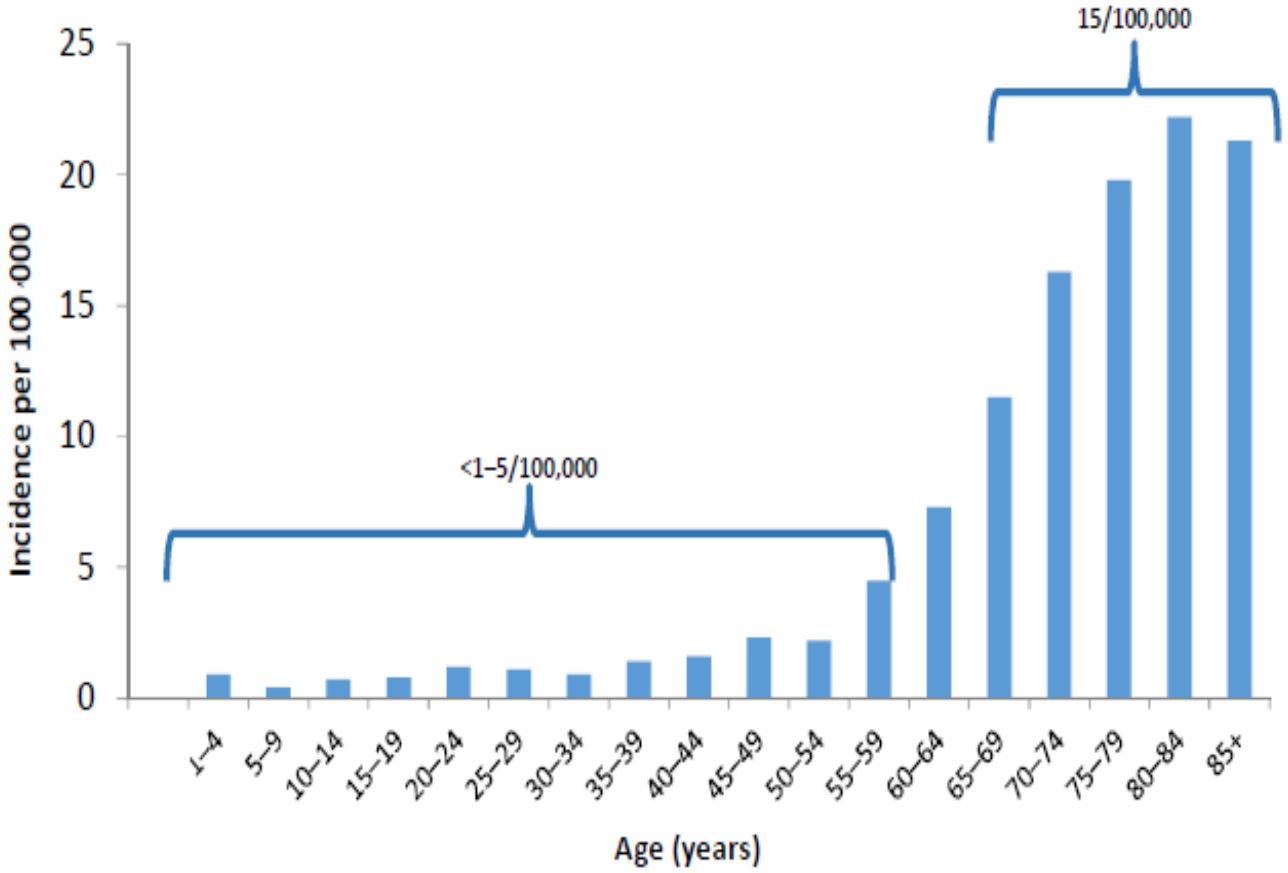
MIDOLLO NORMALE



MIDOLLO LEUCEMICO

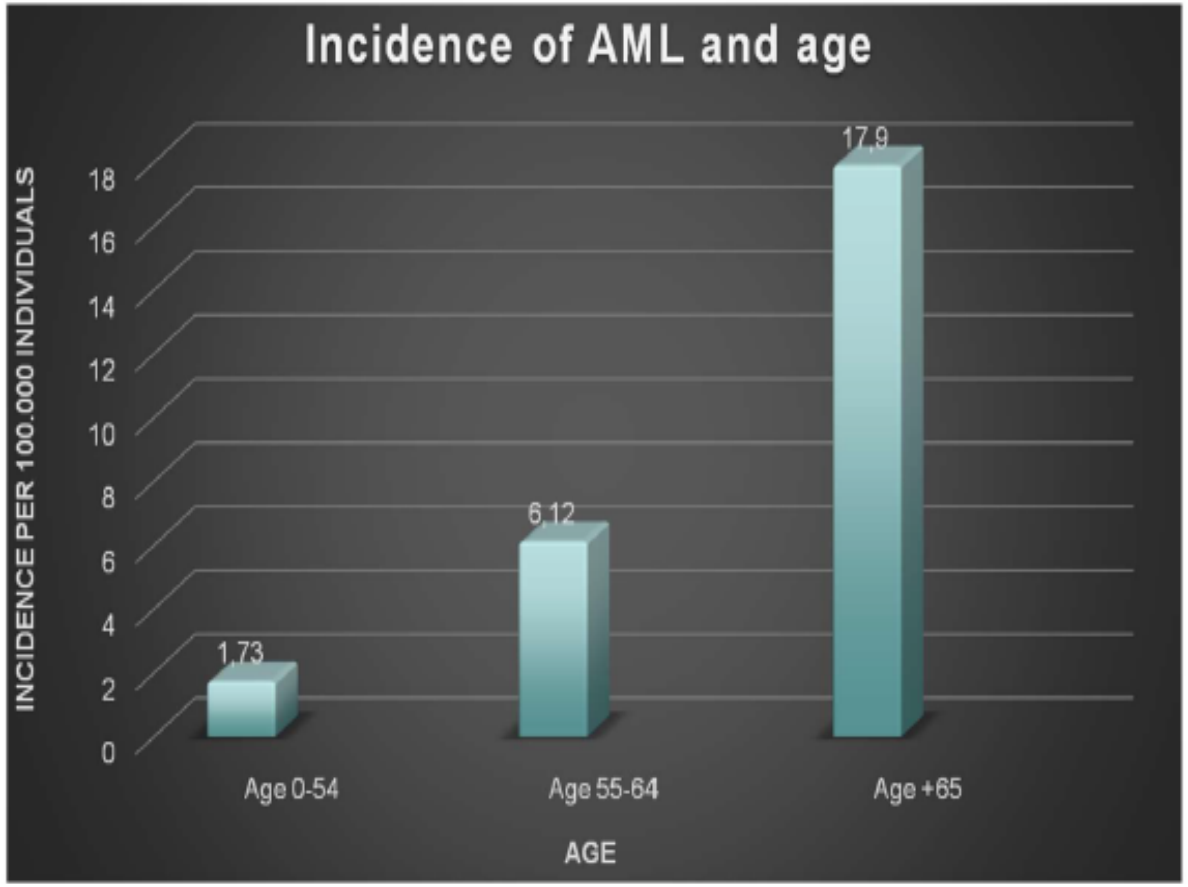


Incidence of AML increases with ageing



National Cancer Institute. SEER Cancer Statistics Review. 1975–2000.

Incidence of AML by age in Italy



AIRTUM Working Group – Italian Cancer Figures – Report 2015

DEFINITIONS: ELN2022

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	Patients not responding to a first cycle of 7 + 3 should be considered for a regimen containing higher doses of cytarabine
Relapsed disease (after CR, CRh or CRi)	Bone marrow blasts ≥ 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	

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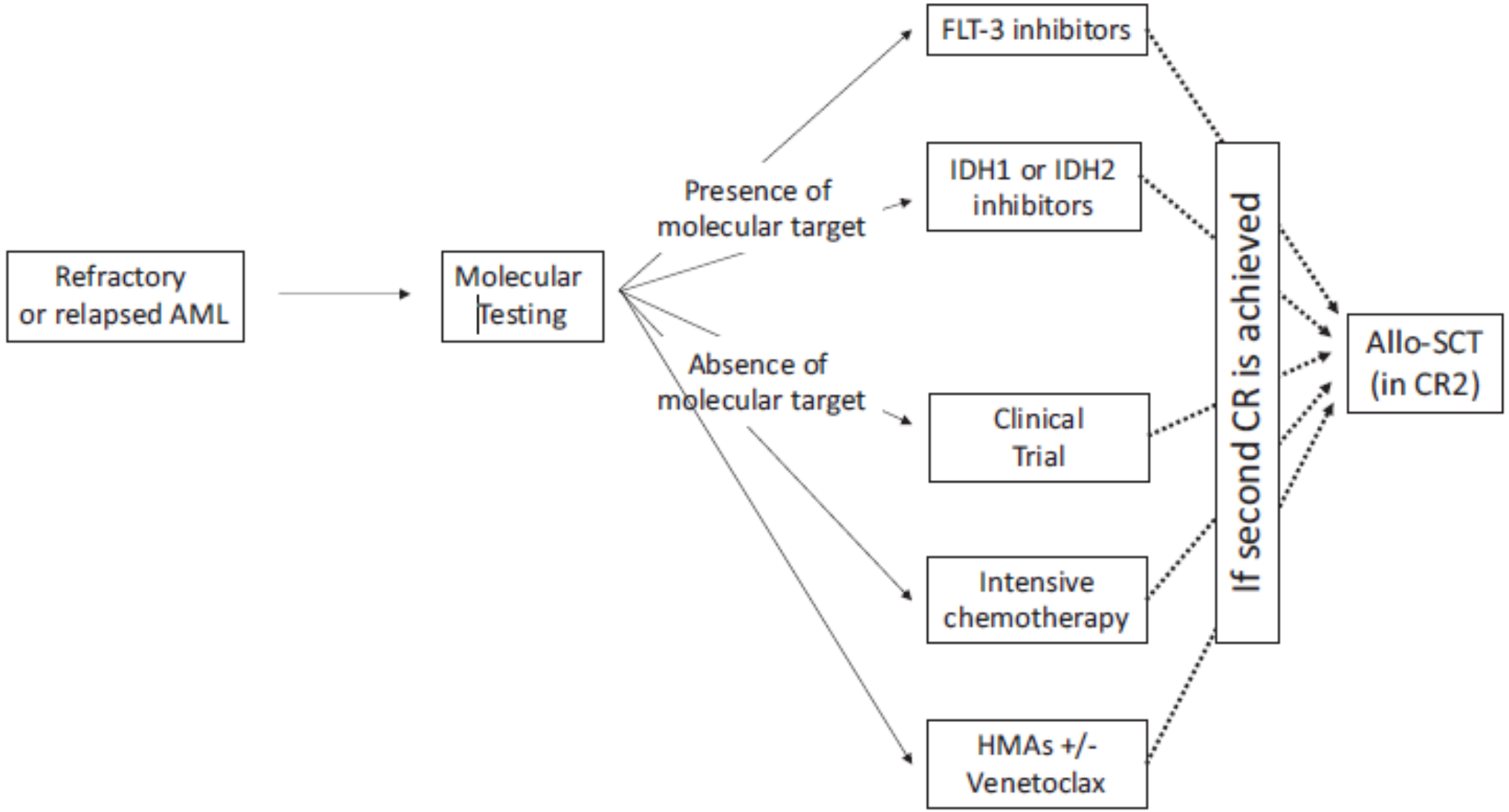
TREATMENT ALGORITHM FOR R/R AML



Isidori A, Ferrara F, COO 2021

HISTORICAL SALVAGE REGIMENS FOR FIT PTS

Year	Regimen	N	Ref/Rel	Median age (years)	CR (%)
1985	HiDAC vs. HiDAC + DXR/DNR	78	42/36	37	63 vs. 65
1988	MTZ, etoposide (ME)	61	21/20	47	43
1991	MTZ, etoposide, IDAC (MEC)	32	18/14	24	66
1993	IDA, etoposide, IDAC	97	36/61	37	43
1994	MEC ± G-CSF priming	50	6/44	43 vs. 47	54 vs. 42
1994	HiDAC vs. HiDAC + etoposide	131	–	–	31 vs. 38
1995	Etoposide, MTZ, Ara-C (EMA)	133	22/111	43	60
1998	Fludarabine, HiDAC, G-CSF (FLAG)	38	16/22	41	55
1999	HiDAC vs. HiDAC + MTZ	162	56/106	48 vs. 53	32 vs. 44
1999	EMA ± GM-CSF	192	120/72	47 vs. 46	65 vs. 59
2001	Fludarabine, HiDAC, G-CSF (FLAG)	83	44/21	47/48	37
2003	Fludarabine, HiDAC, G-CSF, IDA	46	10/36	41	52
2008	Cladribine, HiDAC, MTZ (CLAG-M)	118	78/40	45	58
2009	FLAG-IDA ± GO	71	10/61	48	29 vs. 39
2012	Clofarabine + IDAC vs. IDAC	326	171/148	67	35 vs. 18

Isidori A, Ferrara F, COO 2021

TARGETED THERAPY

Drug	Target	CR rate[a]	Overall survival (median)
Gilteritinib	FLT-3	34%	9.3 months
Ivosidenib	IDH-1	30%	8.8 months
Enasidenib	IDH-2	19.3%	9.3 months
Venetoclax	BCL-2	20.7%	1.8–7.8 months
Venetoclax + Azacitidine	BCL-2	32.3%	3.0–6.6 months

Isidori A, Ferrara F, COO 2021

Gilteritinib: ADMIRAL trial

Key eligibility criteria

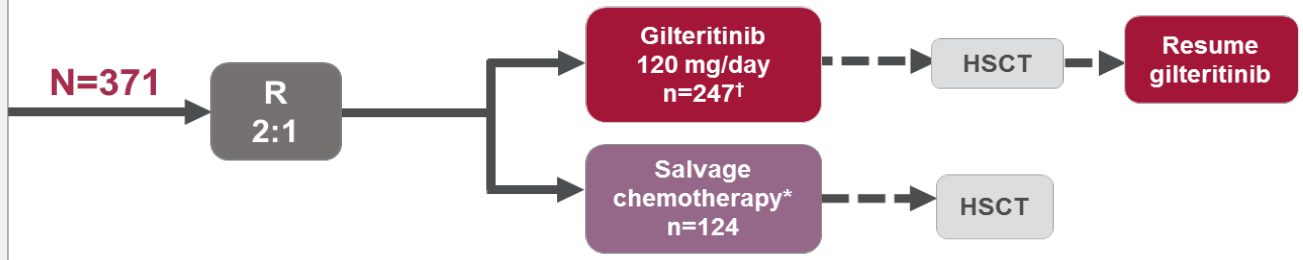
- Adults with AML refractory to, or relapsed after, first-line AML therapy ± HSCT
- *FLT3* mutation (*FLT3*-ITD, or *FLT3*-TKD D835/I836) in blood or bone marrow

Stratification factors

- Response to first-line AML therapy
  - >6 months versus ≤6 months[2]
- Preselected chemotherapy
  - High versus low intensity

Of 625 pts screened:

Between October 2015 and February 2018, 625 patients were screened and 371 were randomised in the trial



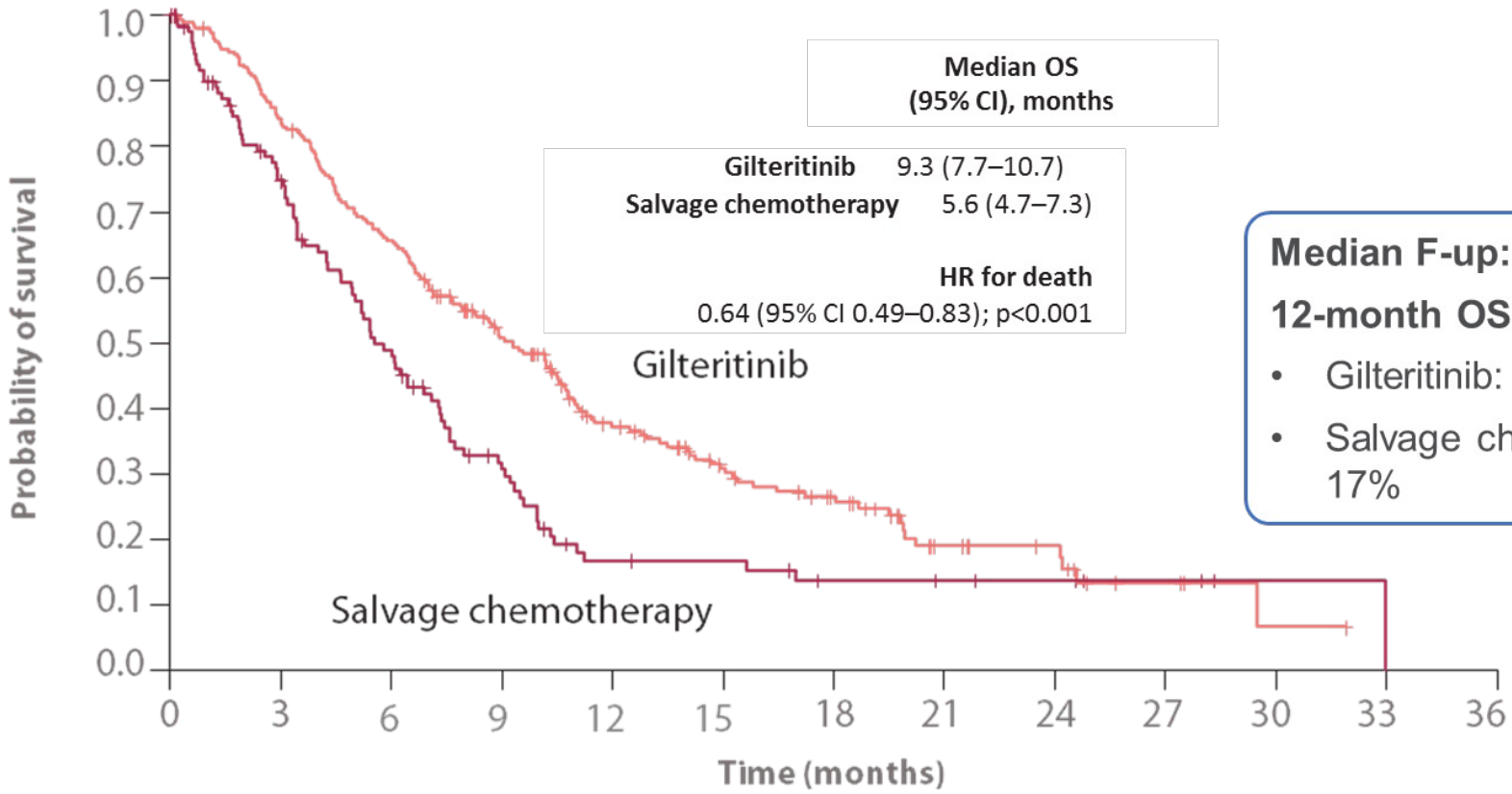
*The salvage chemotherapy regimen was selected prior to randomisation from the following options:

- **High-intensity regimens (1–2 cycles):** MEC or FLAG-IDA
- **Low-intensity regimens†:** Low-dose cytarabine or azacitidine

	Gilteritinib (N=247)	Salvage Chemotherapy (N=124)	Hazard Ratio or Risk Difference (95% CI)†
Response — no. (%)			
Complete remission	52 (21.1)	13 (10.5)	10.6 (2.8-18.4)
Complete remission or complete remission with partial hematologic recovery	84 (34.0)	19 (15.3)	18.6 (9.8-27.4)
Complete remission with partial hematologic recovery	32 (13.0)	6 (4.8)	ND
Complete remission with incomplete hematologic recovery	63 (25.5)	14 (11.3)	ND
Complete remission with incomplete platelet recovery	19 (7.7)	0 (0)	ND
Partial remission	33 (13.4)	5 (4.0)	ND
No response	66 (26.7)	43 (34.7)	ND
Composite complete remission‡	**134 (54.3)**	**27 (21.8)**	**32.5 (22.3-42.6)**
Overall response	167 (67.6)	32 (25.8)	
Median duration of remission (95% CI) — mo§	11.0 (4.6-NE)	NE (NE-NE)	NE
Time to composite complete remission — mo	2.3 ± 1.9	1.3 ± 0.5	NA
Median leukemia-free survival (95% CI) — mo	4.4 (3.6-5.2)	6.7 (2.1-8.5)	NE

Perl et al, New Engl J Med 2019

Gilteritinib: ADMIRAL trial



Median F-up: 17.8 months

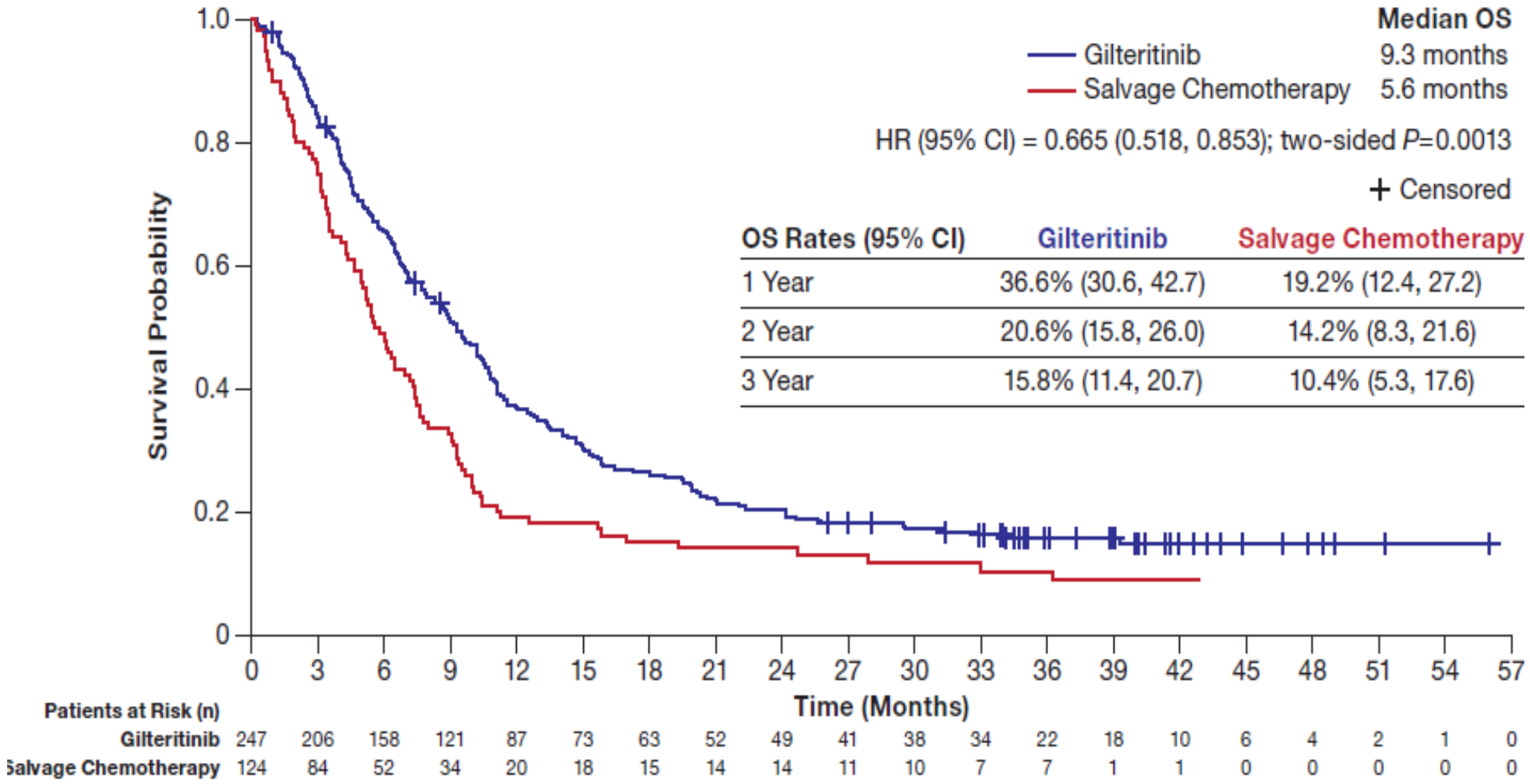
12-month OS

- Gilteritinib: 37%
- Salvage chemotherapy: 17%

Patients at risk (n)													
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

Perl et al, New Engl J Med 2019,
Smith C et al, Blood Adv 2021

ADMIRAL trial: prolonged Follow-up



OS Rates (95% CI)	Gilteritinib	Salvage Chemotherapy
1 Year	36.6% (30.6, 42.7)	19.2% (12.4, 27.2)
2 Year	20.6% (15.8, 26.0)	14.2% (8.3, 21.6)
3 Year	15.8% (11.4, 20.7)	10.4% (5.3, 17.6)

Perl et al, Blood 2022

Conclusions

- Single-agent oral gilteritinib improves response and survival compared with parenteral salvage chemotherapy in patients with *FLT3*$^{mut+}$ R/R AML
- Compared with salvage chemotherapy, gilteritinib was generally associated with lower toxicity during the first 30 days of treatment, which facilitated outpatient administration of the drug
- Gilteritinib allowed many patients (n=63) to undergo HSCT
  - The relative contribution of HSCT to the observed survival benefit from gilteritinib appears small
  - Long-term survival after HSCT appeared to be associated with restart of gilteritinib therapy
- The number of patients with *FLT3*-TKD mutations only was too small (n=31) for statistically robust conclusions in this group, however:
  - Similar CR rates (~20%) with gilteritinib therapy were observed in *FLT3*-TKD and -ITD subgroups
  - Overall survival of patients in the *FLT3*-TKD subgroup was similar to that of patients in the *FLT3*-ITD subgroup
- Findings from the ADMIRAL study have practice-changing implications that will establish a new treatment paradigm for AML

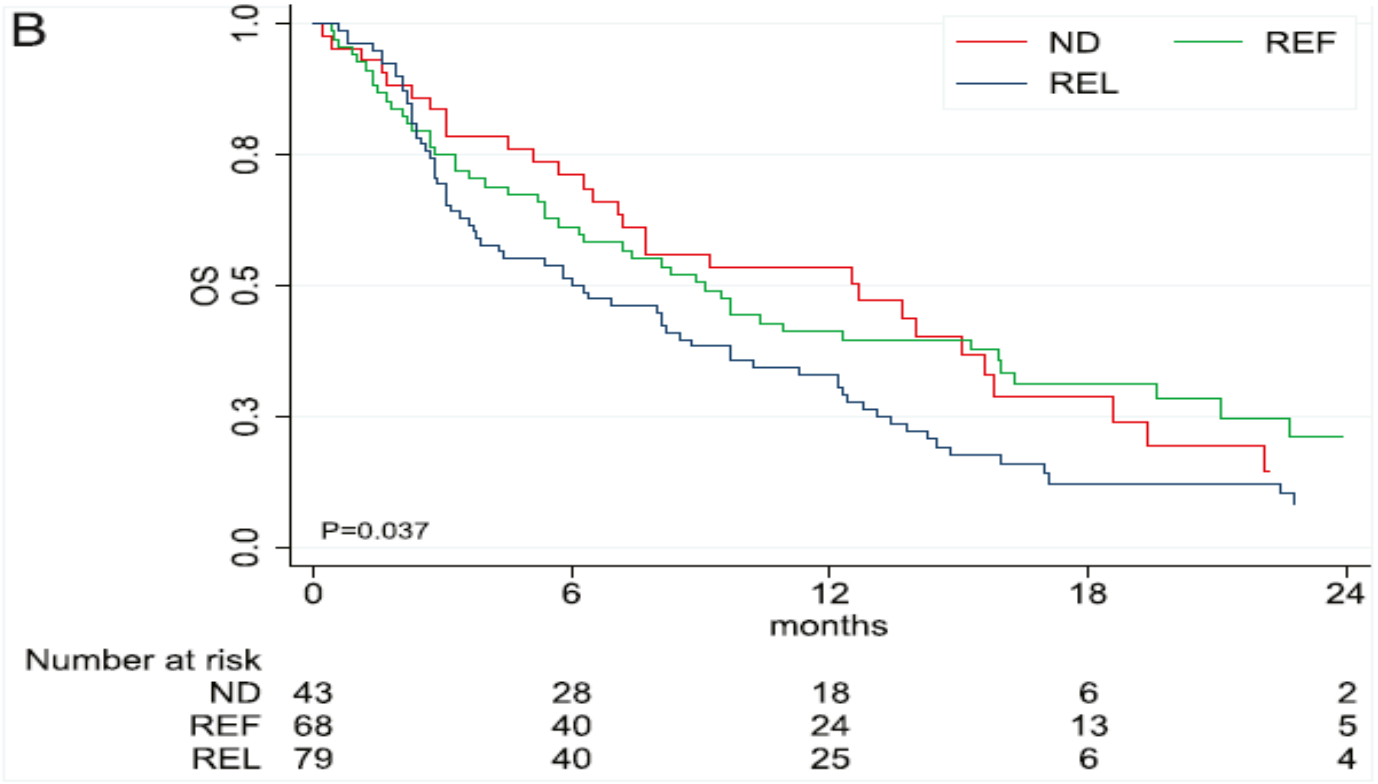
Received: 19 July 2022 | Revised: 21 October 2022 | Accepted: 29 October 2022

DOI: 10.1002/cncr.34608

ORIGINAL ARTICLE

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

Todisco E et al. Cancer. 2023;129:992–1004



	Total (n=190)		ND (n=43)		REF (n=68)		REL (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]	

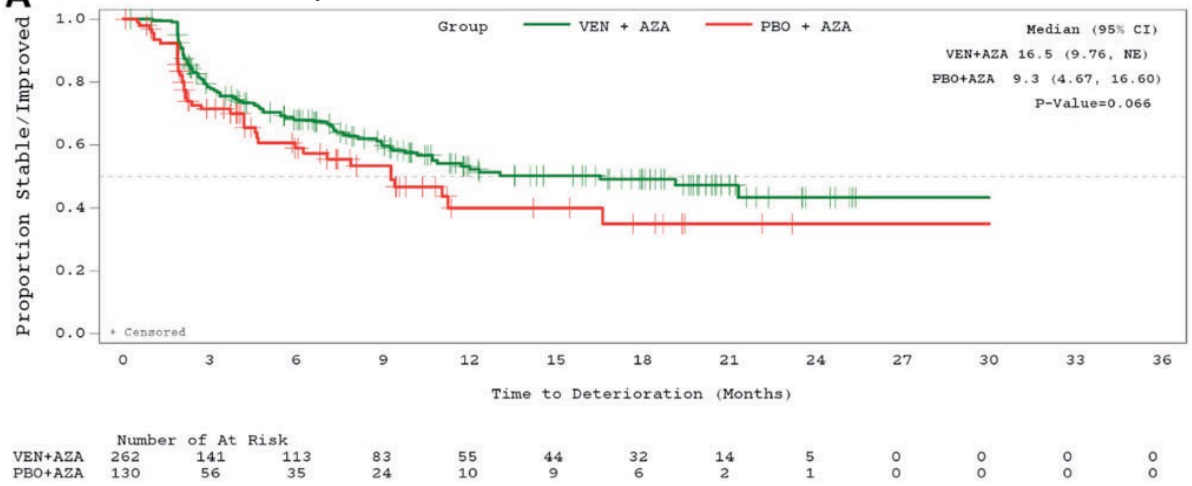
Todisco E et al. Cancer. 2023;129:992–1004

	Total (*n* = 190)		ND (*n* = 43)		REF (*n* = 68)		REL (*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]		

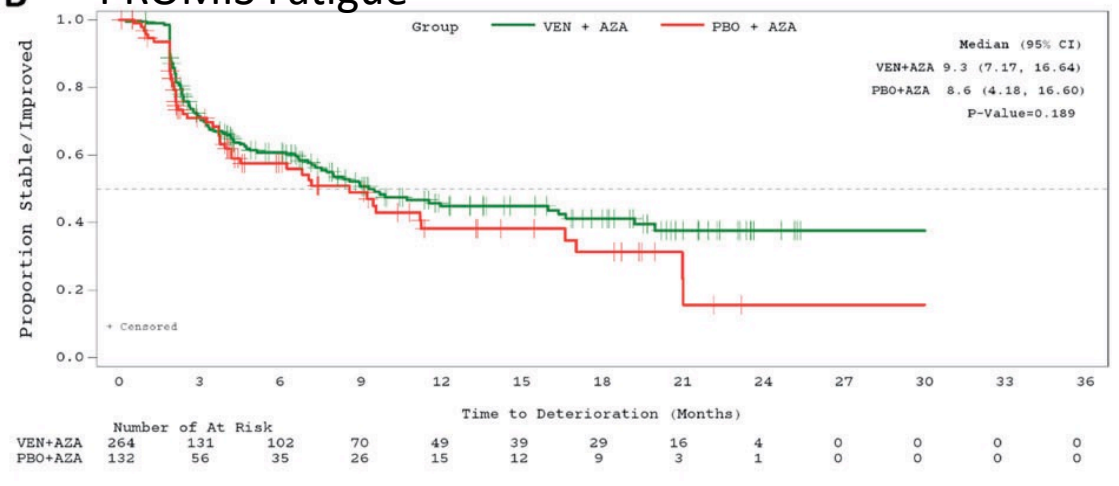
Todisco E et al. Cancer. 2023;129:992–1004

Time to deterioration of PROs for pts on VEN+AZA vs AZA+PBO

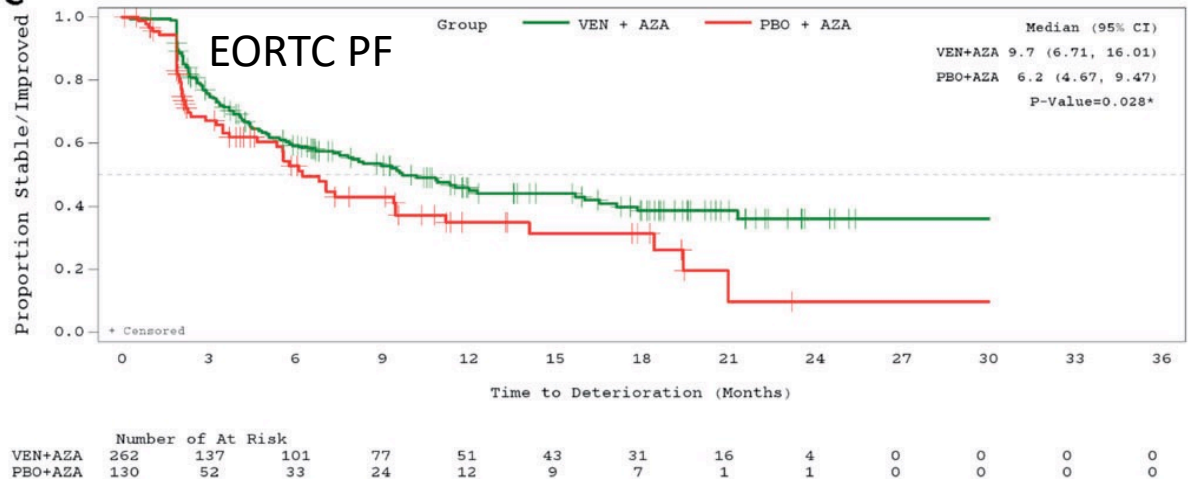
A EORTC GHS/QoL



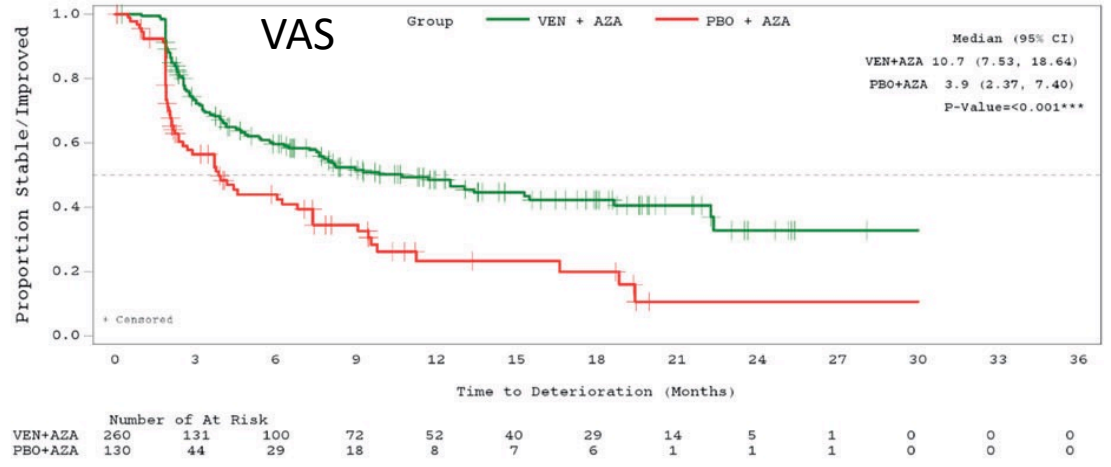
B PROMIS Fatigue



C EORTC PF



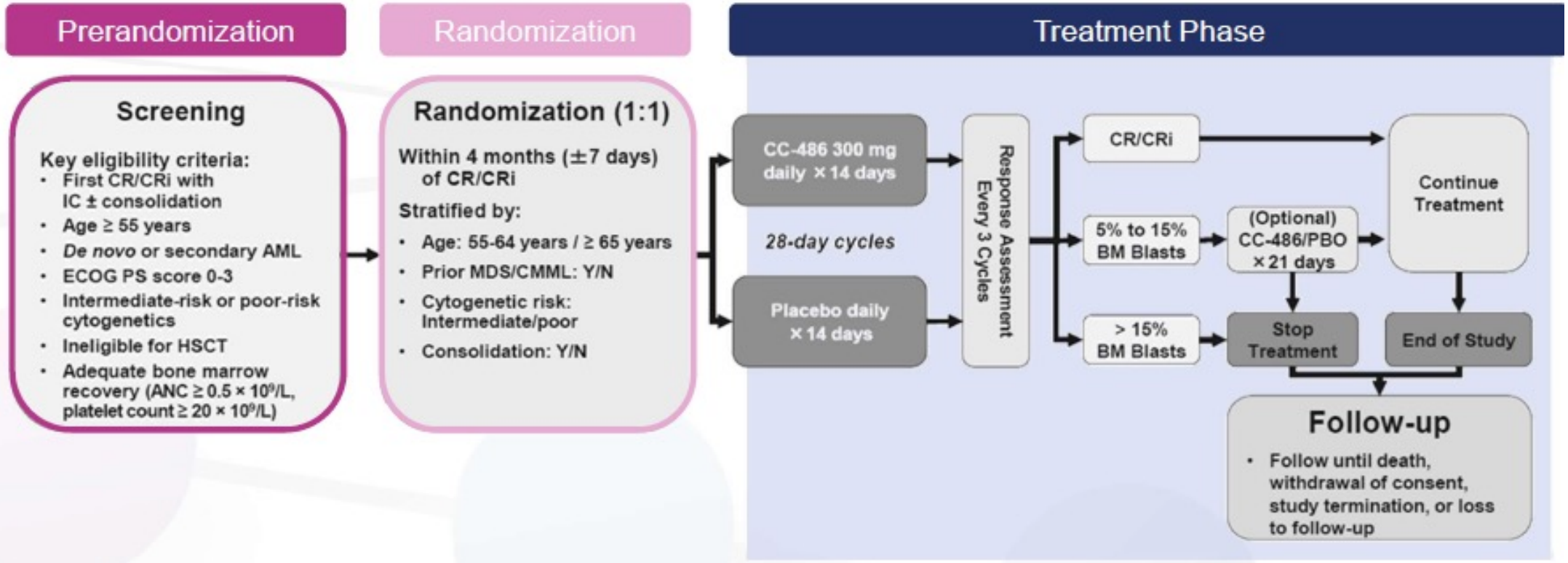
D VAS



Pratz K et al, Blood Cancer Journal (2022) 12:71

QUAZAR AML001: Study Design

- International, multicenter, placebo-controlled, double-blind, randomized, phase III study that enrolled patients from 148 sites in 23 countries (NCT01757535)



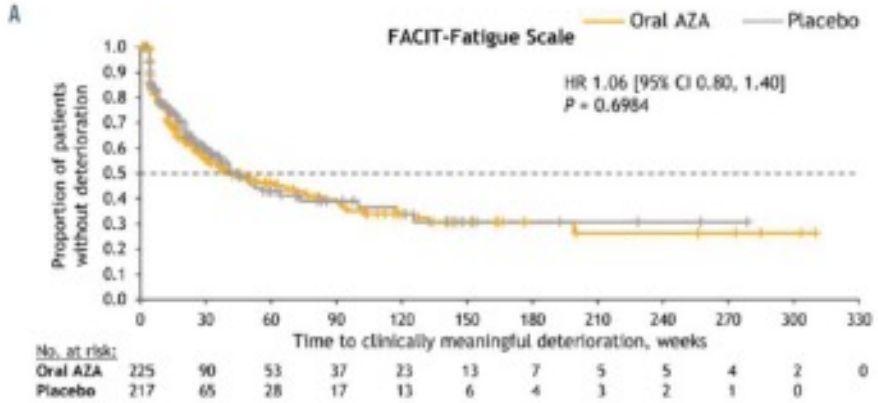
Wei et al. NEJM 2020;383:2526-2537

Fatigue and HR-QoL in QUAZAR-AML001

- **The FACIT-Fatigue Scale** is a 13-item questionnaire that measures an individual's level of fatigue during daily activities over the previous week
- **The EQ-5D-3L** includes a questionnaire that investigates 5 dimensions (mobility, self-care, pain/discomfort, usual activities, anxiety/depression) reported as absent, moderate, severe, and a visual analogue scale (VAS) that asks patients to rate their perceived HRQoL from 0-100
- Both instruments were completed on day 1 of each cycle and end-of-treatment

Roboz G, et al. Haematologica 2021:106(12);3240-3243

A



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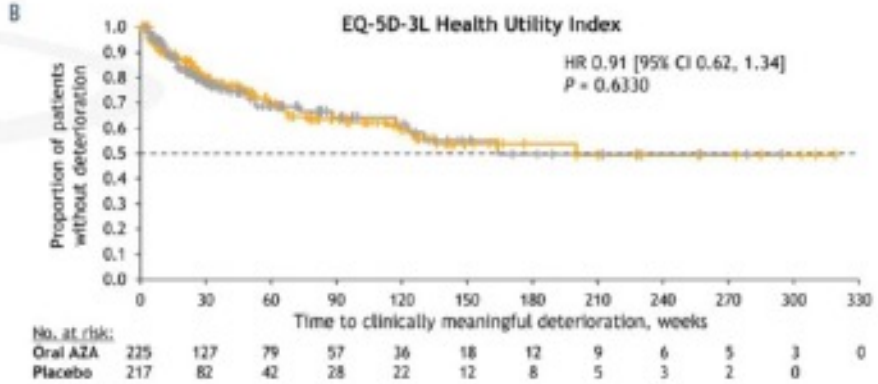

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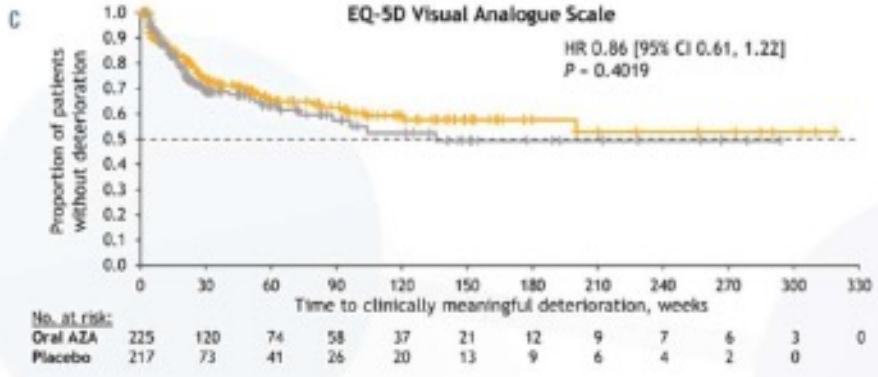
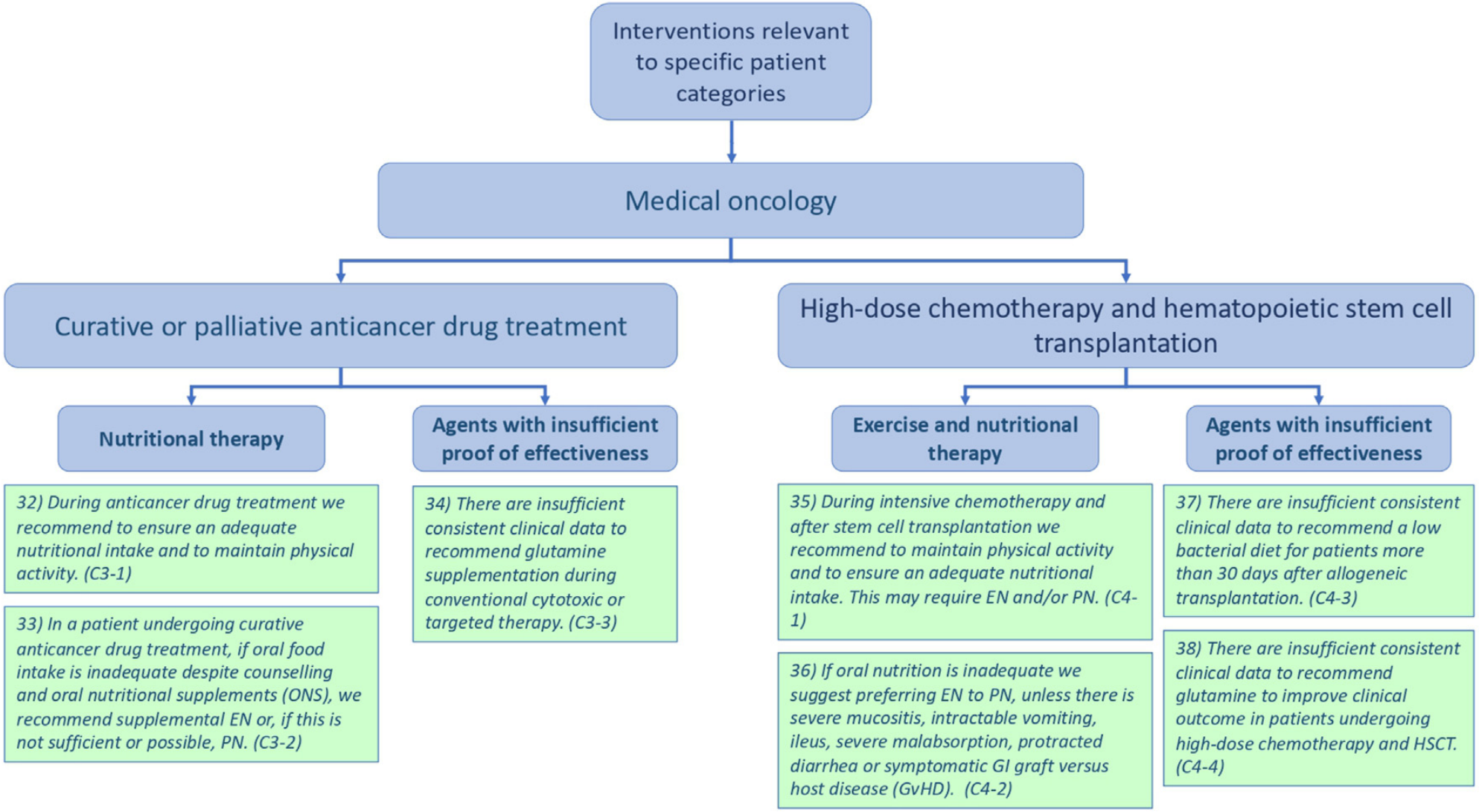


Roboz G, et al. Haematologica 2021:106(12);3240-3243

ESPEN European Society for Clinical Nutrition and Metabolism guidelines for nutrition in cancer



Muscaritoli et al Clinical Nutrition 2021