ACUTE PROMYELOCYTIC LEUKEMIA IN OLDER PATIENTS

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ABBVIE			X				

Background

- **Unlike other subtypes of AML, APL in older people is not resistant to current frontline drug therapy (ATRA, ATO, anthracyclines).**

- **Notwithstanding, the prognosis os the disease in the elderly is less favorable as compared to young adults**

Lo-coco F et al, BJH. 2016

Age-specific challenges in APL

- **Diagnosis can be delayed because many APL patients present with pancytopenia with few or no malignant cells seen in the peripheral blood smear**
- **Older adults are more likely to present with multi-morbidity, polypharmacy and reduced functional capacity which complicates management**
- **Only 1–3% of patients enrolled on APL trials are 70 years or over; older age persists as an exclusion criteria**

Poorer outcome in older patients with APL

- **Higher rate of early mortality**
- **Higher percentage of death in CR**

Risk stratification for early mortality in newly diagnosed acute promyelocytic leukemia: a multicenter, non-selected, retrospective cohort study

Kim et al, Front Oncol, 2024

- **313 eligible patients diagnosed between 2000 and 2021 from five academic hospitals in South Korea.**
- **The median age was 50 years (range 19-94), and 20 % of patients were over 65 years.**
- **Most patients (n=274, 87.5%) received their first dose of all-trans retinoic acid (ATRA) within 24 hours of presentation.**
- **EM occurred in 41 patients, with a cumulative incidence of 13.1%.**

Kim et al, Front Oncol, 2024

TABLE 3 Results of multivariable analysis.

Variables		HR (95% CI)	*P*
Early mortality			
Age, years	<65 ≥65	1 2.56 (1.33–4.91)	0.005
White blood cells, $\times 10^9$/L	<8.0 ≥8.0	1 3.30 (1.76–6.16)	<0.001
Timing of the first dose of ATRA administered	≤24 hours of APL presentation >24 hours of APL presentation	1 2.95 (1.39–6.28)	0.005
Post-30-day overall survival			
Age, years	<65 ≥65	1 3.23 (1.65–6.33)	<0.001
Sex	Female Male	1 2.19 (1.12–4.29)	0.022
Overall survival			
The established risk model (including age, white blood cells, and timing of the first ATRA administered)	Low Intermediate High	1 3.53 (2.08–5.99) 7.19 (3.81–13.56)	<0.001

ATRA, all trans retinoic acid; APL, acute promyelocytic leukemia; HR, hazard ratio; CI, confidence interval.

Kim et al, Front Oncol, 2024

TABLE 2 Causes of early mortality.

	Total (N=41, %)
Intracranial hemorrhage	22 (53.7)
Infection	7 (17.1)
Complications associated with APL, acute promyelocytic leukemia; differentiation syndrome	5 (12.2)
Other bleeding or thrombosis	5 (12.2)
Unknown	2 (4.9)

APL, acute promyelocytic leukemia.

Kim et al, Front Oncol, 2024

Annals of Hematology (2021) 100:2613–2619
https://doi.org/10.1007/s00277-021-04620-x

ORIGINAL ARTICLE

Risk factors for early in-hospital death in patients who developed coagulopathy during induction therapy for acute promyelocytic leukemia: a nationwide analysis in Japan

Kensuke Matsuda[1] · Taisuke Jo[2] · Kazuhiro Toyama[1] · Kumi Nakazaki[1] · Hiroki Matsui[3] · Kiyohide Fushimi[4] · Hideo Yasunaga[3] · Mineo Kurokawa[1,5]

Variable		All patients (%) (n=1115)	Elderly patients (%) (n=435)
Age, years	< 40	295 (27)	
	40–59	385 (35)	
	60–79	366 (33)	366 (84)
	≥ 80	69 (6)	69 (16)
Sex	Male	573 (51)	238 (55)
	Female	542 (49)	197 (45)
Body mass index, kg/m^2	18.5–25	617 (55)	242 (56)
	< 18.5	91 (8)	33 (8)
	25–30	300 (27)	124 (29)
	> 30	79 (7)	19 (4)
	Missing	28 (3)	17 (4)
Activities of daily living	Fit	725 (65)	242 (56)
	Unfit	281 (25)	142 (33)
	Missing	109 (10)	51 (11)
Charlson comorbidity index	2	940 (84)	341 (78)
	≥ 3	175 (16)	94 (22)
Initial volume of fresh frozen plasma per body weight, ml/kg	< 9	259 (23)	123 (28)
	9–25	572 (51)	208 (48)
	> 25	266 (24)	92 (21)
	Missing data of body weight	18 (2)	12 (3)
Conventional chemotherapy	Early initiation	521 (47)	164 (40)
	Late initiation	329 (30)	117 (28)
	Not performed	265 (24)	135 (33)
Initiation of all-trans retinoic acid	Day of admission	603 (54)	238 (55)
	One day after admission	272 (24)	103 (24)
	≥ 2 days after admission	240 (22)	94 (22)
Emergency admission		768 (69)	298 (69)
Anticoagulant therapy	None	416 (37)	178 (41)
	Recombinant human soluble thrombomodulin	458 (41)	164 (38)
	Gabexate mesilate	68 (6)	28 (6)
	Nafamostat mesilate	56 (5)	22 (5)
	Other anticoagulant agents	59 (5)	21 (5)
	> 2 anticoagulant agents	58 (5)	22 (5)

Matsuda et al, Ann Hematol, 2021

Table 2 Multivariable logistic regression analysis with generalized estimating equation for in-hospital death in all patients

Variable		Odds ratio	95% confidence interval	*P*
Age, years	< 40	Reference		
	40–59	2.58	1.29–5.19	0.008
	60–79	7.66	3.89–15.10	<0.001
	≥ 80	16.83	7.41–38.21	<0.001
Sex	Male	Reference		
	Female	0.60	0.42–0.87	0.007
Body mass index, kg/m^2	18.5–25	Reference		
	< 18.5	0.78	0.40–1.52	0.458
	25–30	0.61	0.38–0.98	0.043
	> 30	1.53	0.73–3.19	0.260
Activities of daily living	Fit	Reference		
	Unfit	1.50	1.00–2.26	0.050
Charlson comorbidity index	2	Reference		
	≥ 3	1.19	0.76–1.85	0.444
Initial volume of fresh frozen plasma per body weight, ml/kg	< 9	Reference		
	9–25	1.15	0.69–1.91	0.599
	> 25	2.41	1.33–4.37	0.004
Conventional chemotherapy	Early initiation	Reference		
	Late initiation	1.38	0.88–2.18	0.161
	Not performed	2.40	1.47–3.92	<0.001
Initiation of all-trans retinoic acid	Day of admission	Reference		
	One day after admission	1.45	0.93–2.27	0.099
	≥ 2 days after admission	1.79	1.16–2.76	0.009
Emergency admission		1.29	0.87–1.91	0.211
Anticoagulant therapy	None	Reference		
	Recombinant human soluble thrombomodulin	1.46	0.94–2.25	0.091
	Gabexate mesilate	1.40	0.57–3.46	0.464
	Nafamostat mesilate	1.71	0.71–4.11	0.235
	Other anticoagulant agents	0.84	0.31–2.31	0.741
	≥ 2 anticoagulant agents	2.56	1.22–5.40	0.013

Matsuda et al, Ann Hematol, 2021

Leukemia (2003) 17, 1085–1090

www.nature.com/leu

Treatment of elderly patients (⩾60 years) with newly diagnosed acute promyelocytic leukemia. Results of the Italian multicenter group GIMEMA with ATRA and idarubicin (AIDA) protocols

F Mandelli[1], R Latagliata[1], G Avvisati[2], P Fazi[1], F Rodeghiero[3], F Leoni[4], M Gobbi[5], F Nobile[6], E Gallo[7], R Fanin[8], S Amadori[9], M Vignetti[1], G Fioritoni[10], F Ferrara[11], A Peta[12], R Giustolisi[13], G Broccia[14], MC Petti[15] and F Lo-Coco[1]
for the Italian GIMEMA Cooperative Group

Table 1 Clinical features of patients at diagnosis

Registered	169
Eligible	146
Evaluable	134
M/F	58/76
Median age (range)	65.8 years (60–75)
Median WBC (range)	1.7×10^9/l (0.3–90)
Median PLTS (range)	24×10^9/l (3–185)
PML/RARα isoform	
Long type (BCR1–2)	64
Short type (BCR3)	46
Not assessed	24

15 % deaths in CR

Table 3 Response to induction therapy according to clinical features at diagnosis

Features	*Patients (%)*	*CR (%)*	P
Age ⩽70 years	115 (86)	104 (90)	**0.001**
Age >70 years	19 (14)	12 (63)	
Males	58 (43)	48 (83)	0.25
Females	76 (57)	68 (89)	
WBC⩽3.5	90 (67)	81 (90)	
WBC>3.5⩽10	23 (17)	20 (87)	0.08
WBC>10⩽50	19 (14)	13 (68)	
WBC>50	2 (2)	2 (100)	
PLTS⩽40	101 (75)	84 (83)	**0.043**
PLTS>40	33 (25)	32 (97)	
FAB M3	127 (95)	111 (87)	0.22
FAB M3 v	7 (5)	5 (71)	
BCR1/2	64 (58)	56 (87)	0.52
BCR3	46 (42)	42 (91)	

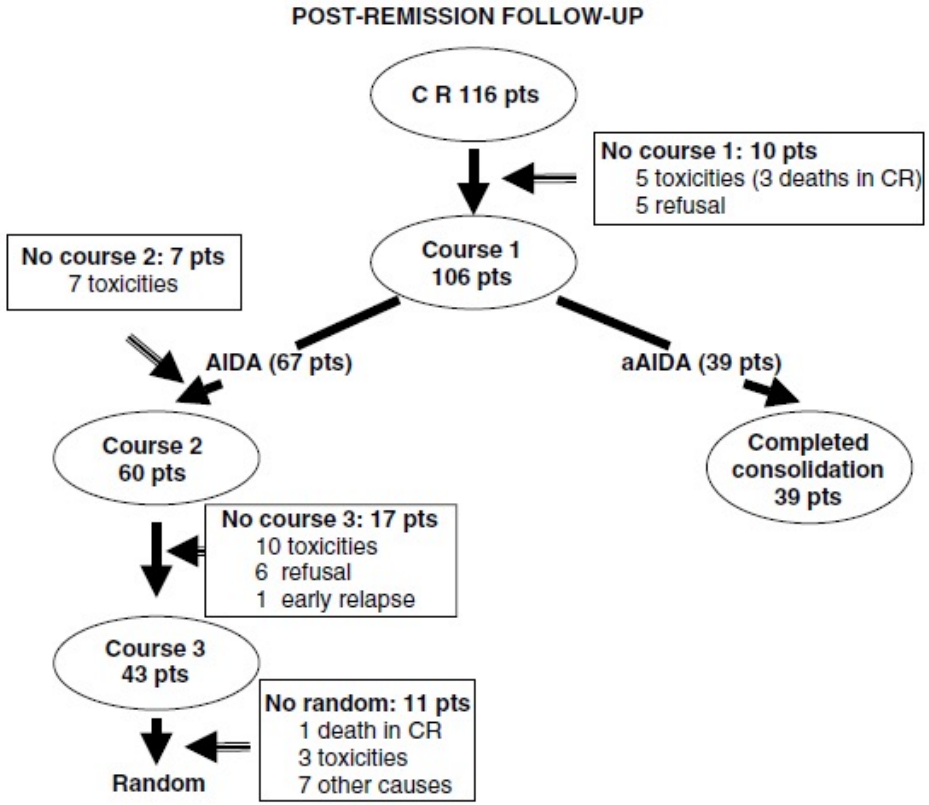
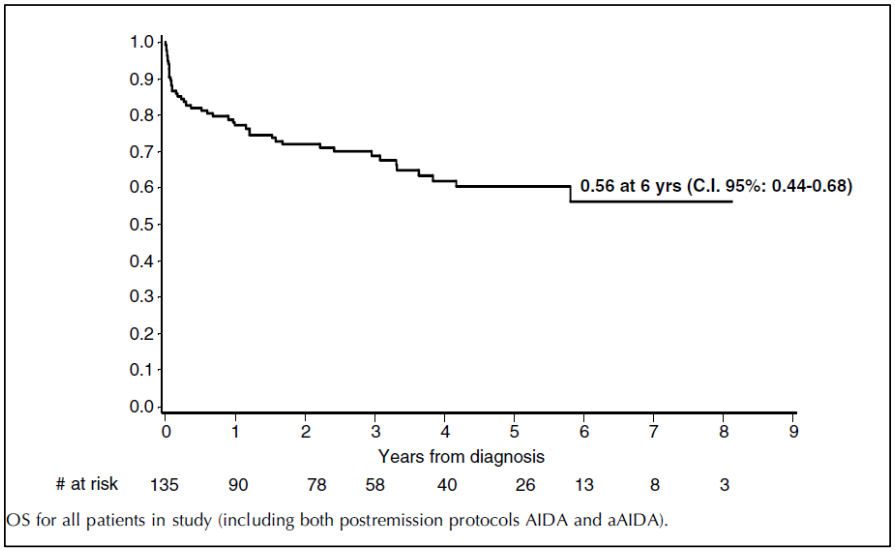


Figure 1 Flow-chart detailing postremission treatment type with patient number and withdrawals from therapy in the two different protocols AIDA and aAIDA.

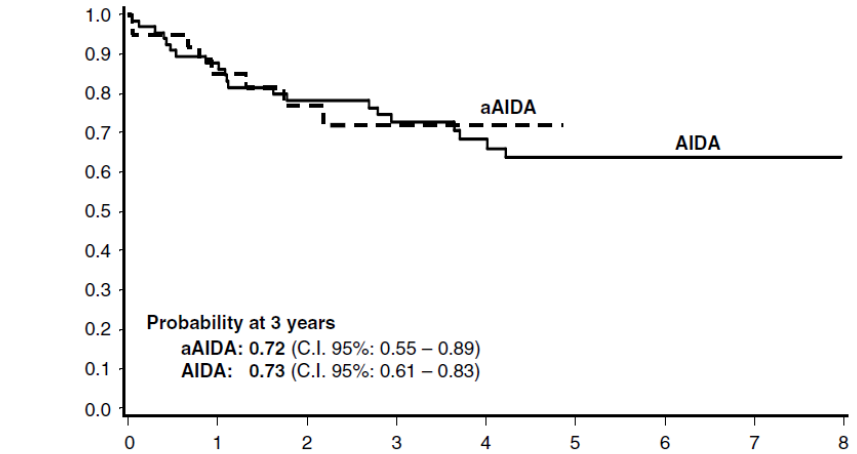
Mandelli et al, Leukemia, 2003

All patients



OS for all patients in study (including both postremission protocols AIDA and aAIDA).

Survival for patients receiving the standard AIDA or the aAIDA therapy.



15 % deaths in CR

ANTICANCER RESEARCH *30*: 967-972 (2010)

Acute Promyelocytic Leukemia in Patients Aged Over 60 Years: Multicenter Experience of 34 Consecutive Unselected Patients

FELICETTO FERRARA[1], OLIMPIA FINIZIO[1], ALFONSO D'ARCO[2], LUCIA MASTRULLO[3], NICOLA CANTORE[4] and PELLEGRINO MUSTO[5]

Table I. *Clinical and hematologic characteristics of the patients.*

Patient number	34
Median age (years)	70 (61/84)
Gender (M/F)	23/11 (68%/32%)
PS (WHO)	
0	2 (6%)
1	12 (35%)
2	16 (47%)
3	4 (12%)
M3/M3v	31/3 (91%/9%)
Cytogenetic findings	
Isolated t(15;17)	33 (97%)
t(15/17), -Y	1 (3%)
Molecular findings	
bcr1	22 (67%)
bcr2	1 (3%)
cr3	11 (30%)
Risk assessment*	
Low	12 (35%)
Intermediate	17 (50%)
High	5 (15%)
CID (Y/N)	27/7 (79%/21%)
Treated on protocol (Y/N)	23/11 (68%/32%)

Ferrara et al, 2010

Table II. *Therapeutic results*.

CR	23/34 (68%)
Resistance	0
Induction death (overall)	11/34 (32%)
Cerebral hemorrage	10/34 (29%
Infections	0
ATRA syndrome	1/34 (3%)
Early death *	6/34 (18%)
Relapse	8/23 (35%)
Second CR	6/8 (75%)

*Defined as death occurred as soon as at diagnosis or within 48 hours.

Ferrara et al, 2010

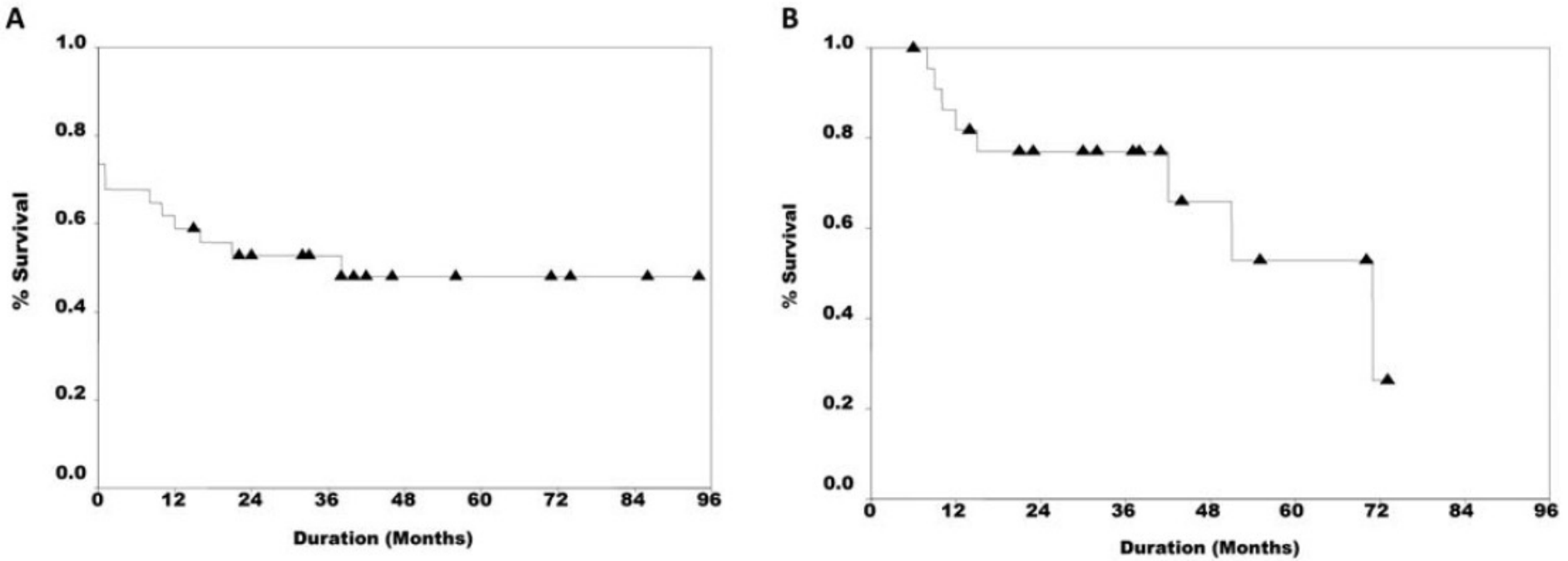
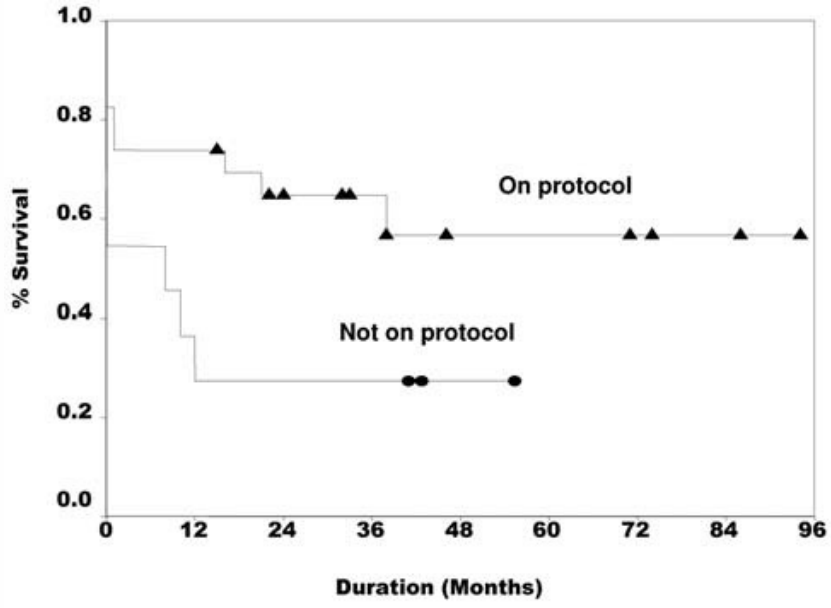


Figure 1. *Overall (A) and disease-free survival (B) of the whole patient population: median 38 months and not reached, respectively.*

Ferrara et al, 2010



Ferrara et al, 2010

Improvement of Early Death in Acute Promyelocytic Leukemia: A Population-Based Analysis

Guangda Li,[1,2] Jieya Wu,[1,2] Ruibai Li,[3] Yiming Pan,[1,2] Wei Ma,[1] Jing Xu,[1,2] Mengdie Nan,[1,2] Li Hou[1,†]

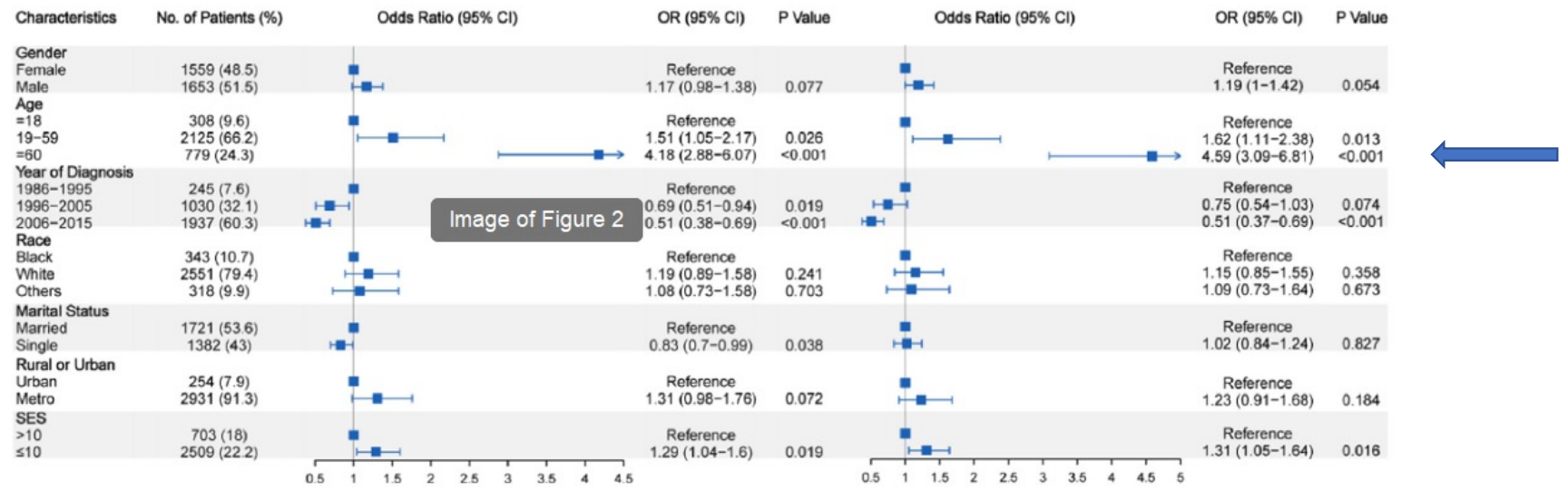
Li et al, Clin Lymphoma, Leukemia, Myeloma, 2022

Table 2 Characteristics of Early Death in APL Patients Stratified by Age.

Characteristics	Total	≤ 18			19-59			≥ 60		
		Total	Early death (%)	*P*	Total	Early death (%)	*P*	Total	Early death (%)	*P*
Total	3212	308	37 (12.0)		2125	363 (17.1)		779	283 (36.3)	
Gender				.695			.031			.860
Female	1559	155	17 (11.0)		1014	154 (15.2)		390	140 (35.9)	
Male	1653	153	20 (13.1)		1111	209 (18.8)		389	143 (36.8)	
Year of Diagnosis				.555			<.001			.028
1986–1995	245	24	4 (16.7)		157	49 (31.2)		64	23 (35.9)	
1996–2005	1030	136	18 (13.2)		671	130 (19.4)		223	97 (43.5)	
2006–2015	1937	148	15 (10.1)		1297	184 (14.2)		492	163 (33.1)	
Race				.758			.552			.642
White	2551	239	28 (11.7)		1674	290 (17.3)		638	236 (37.0)	
Black	343	39	6 (15.4)		233	34 (14.6)		71	25 (35.2)	
Others†	318	30	3 (10.0)		218	39 (17.9)		70	22 (31.4)	
Marital Status‡				.811			.035			.020
Married	1721	3	1 (33.3)		1239	232 (18.7)		479	160 (33.4)	
Divorced/single/Separate/widowed	1382	301	36 (12.0)		806	121 (15.0)		275	116 (42.2)	
Resident county‡				.100			.819			.162
Metro	2931	284	34 (12.0)		1954	330 (16.9)		693	245 (35.4)	
Nonmetro	254	21	3 (14.3)		156	28 (17.9)		77	34 (44.2)	
SES				.394			.018			.416
≤10	2509	246	32 (13.0)		1666	302 (18.1)		597	222 (37.2)	
>10	703	62	5 (8.1)		459	61 (13.3)		182	61 (33.5)	

Li et al, Clin Lymphoma, Leukemia, Myeloma, 2022

Figure 2 Risk factors of all-cause early death in APL. Univariate logistic regression analysis (left) and multivariate regression analysis (right) were performed to identify risk factors associated with all-cause early death. AbbreviationsAPL, acute promyelocytic leukemia.



Characteristics	No. of Patients (%)	Odds Ratio (95% CI)	OR (95% CI)	P Value	Odds Ratio (95% CI)	OR (95% CI)	P Value
Gender							
Female	1559 (48.5)		Reference			Reference	
Male	1653 (51.5)		1.17 (0.98–1.38)	0.077		1.19 (1–1.42)	0.054
Age							
=18	308 (9.6)		Reference			Reference	
19–59	2125 (66.2)		1.51 (1.05–2.17)	0.026		1.62 (1.11–2.38)	0.013
=60	779 (24.3)		4.18 (2.88–6.07)	<0.001		4.59 (3.09–6.81)	<0.001
Year of Diagnosis							
1986–1995	245 (7.6)		Reference			Reference	
1996–2005	1030 (32.1)		0.69 (0.51–0.94)	0.019		0.75 (0.54–1.03)	0.074
2006–2015	1937 (60.3)		0.51 (0.38–0.69)	<0.001		0.51 (0.37–0.69)	<0.001
Race							
Black	343 (10.7)		Reference			Reference	
White	2551 (79.4)		1.19 (0.89–1.58)	0.241		1.15 (0.85–1.55)	0.358
Others	318 (9.9)		1.08 (0.73–1.58)	0.703		1.09 (0.73–1.64)	0.673
Marital Status							
Married	1721 (53.6)		Reference			Reference	
Single	1382 (43)		0.83 (0.7–0.99)	0.038		1.02 (0.84–1.24)	0.827
Rural or Urban							
Urban	254 (7.9)		Reference			Reference	
Metro	2931 (91.3)		1.31 (0.98–1.76)	0.072		1.23 (0.91–1.68)	0.184
SES							
>10	703 (18)		Reference			Reference	
≤10	2509 (22.2)		1.29 (1.04–1.6)	0.019		1.31 (1.05–1.64)	0.016

Li et al, Clin Lymphoma, Leukemia, Myeloma, 2022

- These data show a still high early death rate of APL, but a decreasing trend over the past few years, which was supported by advances in the medical environment and creating awareness of APL.

- The reduction of early death **should focus on elderly patients and people with lower SES**, specifically, early treatment, development of a detailed supportive care guideline, and to raise people's awareness of this disease is of great significance

Li et al, Clin Lymphoma, Leukemia, Myeloma, 2022

Ferrata Storti Foundation

Haematologica 2021
Volume 106(12):3100-3106

Characteristics and outcome of patients with low-/intermediate-risk acute promyelocytic leukemia treated with arsenic trioxide: an international collaborative study

Sabine Kayser,[1,2] Richard F. Schlenk,[2,3] Delphine Lebon,[4] Martin Carre,[5] Katharina S. Götze,[6] Friedrich Stölzel,[7] Ana Berceanu,[8] Kerstin Schäfer-Eckart,[9] Pierre Peterlin,[10] Yosr Hicheri,[11] Ramy Rahmé,[12] Emmanuel Raffoux,[12] Fatiha Chermat,[12] Stefan W. Krause,[13] Walter E. Aulitzky,[14] Sophie Rigaudeau,[15] Richard Noppeney,[16] Celine Berthon,[17] Martin Görner,[18] Edgar Jost,[19] Philippe Carassou,[20] Ulrich Keller,[21] Corentin Orvain,[22,23,24] Thorsten Braun,[25] Colombe Saillard,[26] Ali Arar,[27] Volker Kunzmann,[28] Mathieu Wemeau,[29] Maike de Wit,[30] Dirk Niemann,[31] Caroline Bonmati,[32] Carsten Schwänen,[33] Julie Abraham,[34] Ahmad Aljijakli,[35] Stéphanie Haiat,[36] Alwin Krämer,[37,38] Albrecht Reichle,[39] Martina Gnadler,[40] Christophe Willekens,[41,42] Karsten Spiekermann,[43] Wolfgang Hiddemann,[43] Carsten Müller-Tidow,[37] Christian Thiede,[7] Christoph Röllig,[7] Hubert Serve,[44] Martin Bornhäuser,[7] Claudia D. Baldus,[45] Eva Lengfelder,[46] Pierre Fenaux,[12] Uwe Platzbecker[1#] and Lionel Adès[12#]

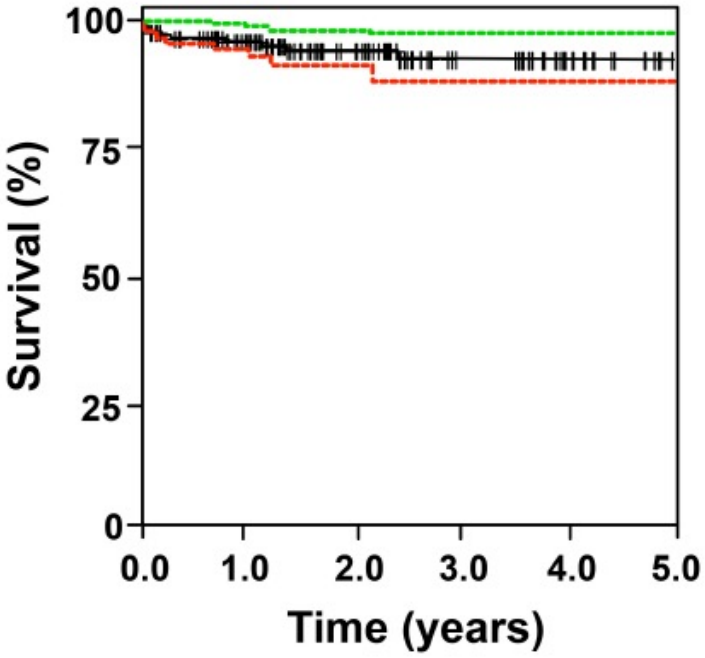


Figure 1. Kaplan Meier plot of overall survival. Green and red curves indicate upper and lower 95% confidence intervals, respectively.

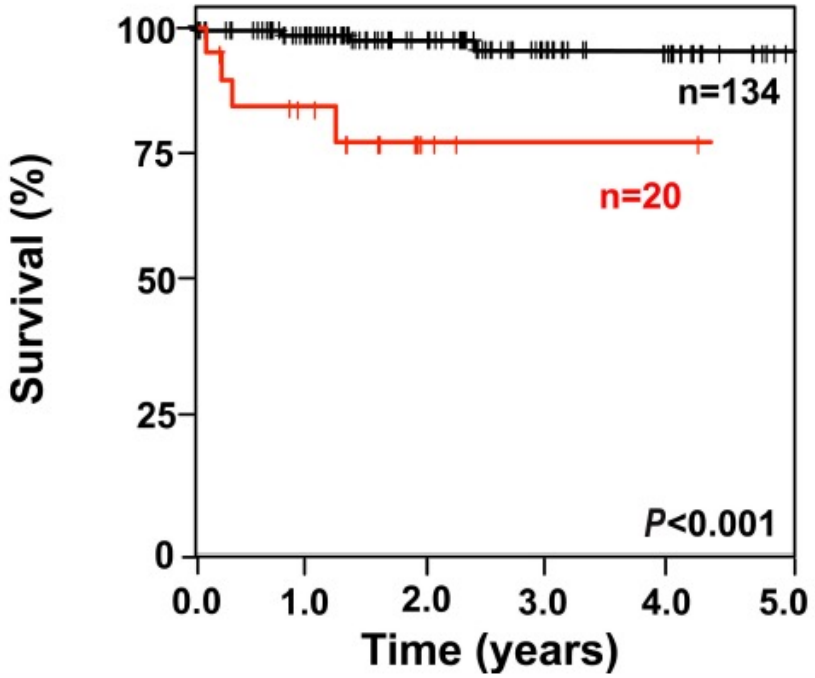


Figure 2. Kaplan Meier plot of overall survival according to age. Red curve indicates age >70 years, black curve indicates age ≤70 years.

Kayser et al, Haematologica, 2021

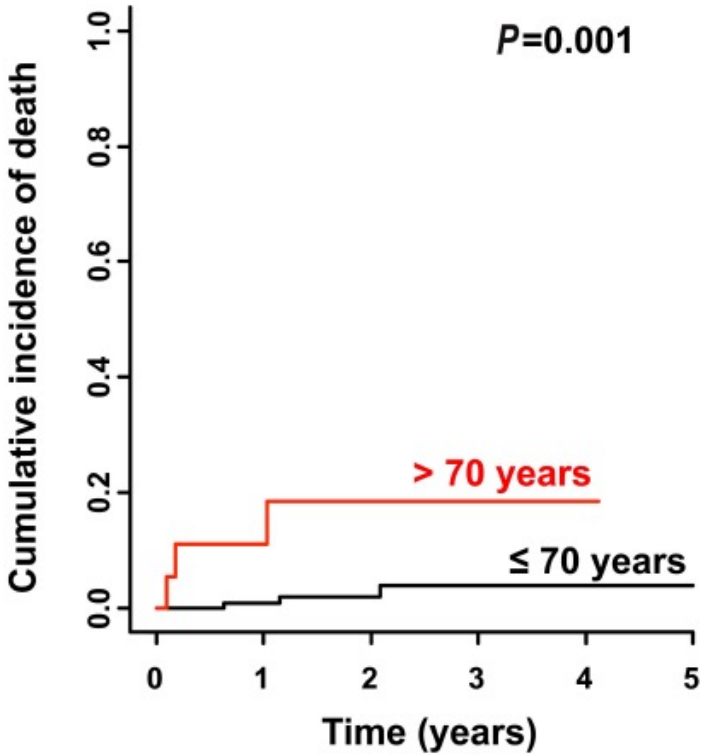


Figure 3. Cumulative incidence of death according to age.

Kayser et al, Haematologica, 2021

Leukemia (2020) 34:2333–2341
https://doi.org/10.1038/s41375-020-0758-4

ARTICLE

Acute myeloid leukemia

Outcome of older (≥70 years) APL patients frontline treated with or without arsenic trioxide—an International Collaborative Study

Sabine Kayser[1,2,3] · Ramy Rahmé[4] · David Martínez-Cuadrón[5,6] · Gabriel Ghiaur[7] · Xavier Thomas[8] · Marta Sobas[9] · Agnes Guerci-Bresler[10] · Ana Garrido[11] · Arnaud Pigneux[12] · Cristina Gil[13] · Emmanuel Raffoux[14] · Mar Tormo[15] · Norbert Vey[16] · Javier de la Serna[17] · Olga Salamero[18] · Eva Lengfelder[19] · Mark J. Levis[7] · Pierre Fenaux[4] · Miguel A. Sanz[5,6] · Uwe Platzbecker[1] · Richard F. Schlenk[3,20] · Lionel Adès[4] · Pau Montesinos[5,6]

Table 2 Response to induction therapy according to treatment strategy.

% (*N*)	CTX/ATRA *N* = 407	ATO/ATRA *N* = 26
CR	82 (332)	92 (24)
RD	0.5 (2)	–
ID	18 (73)	8 (2)

Missing data, $n = 3$ (CTX/ATRA). Percentages may not add to 100 because of rounding.

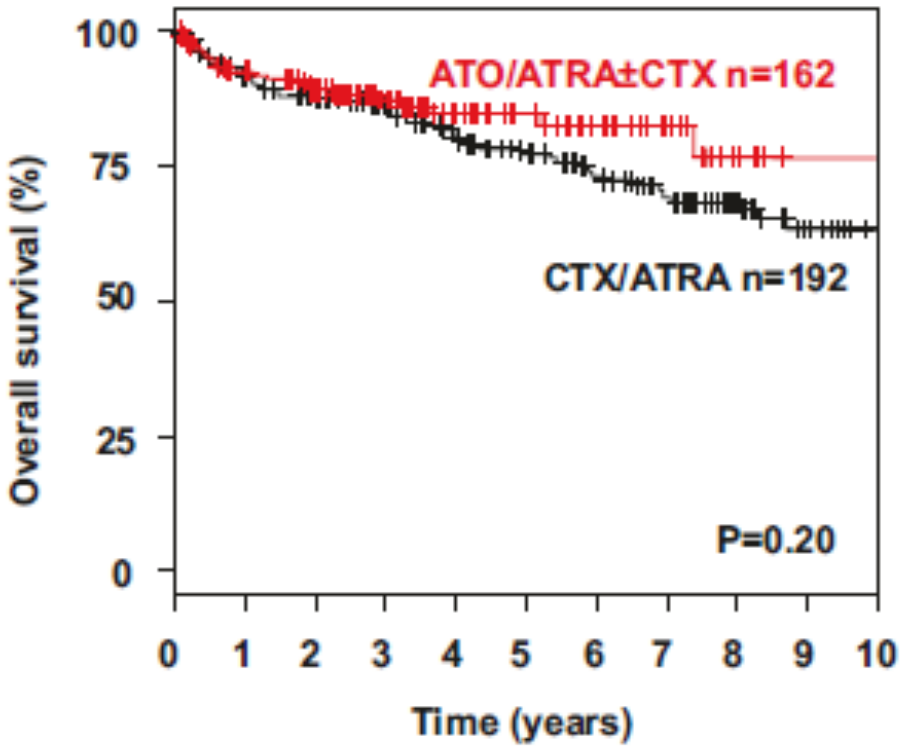
ATO arsenic trioxide, *ATRA* all-trans retinoic acid, *CR* complete remission, *CTX* chemotherapy, *ID* induction death, *N* numbers, *RD* resistant disease.

Table 3 Logistic regression model on response to induction therapy.

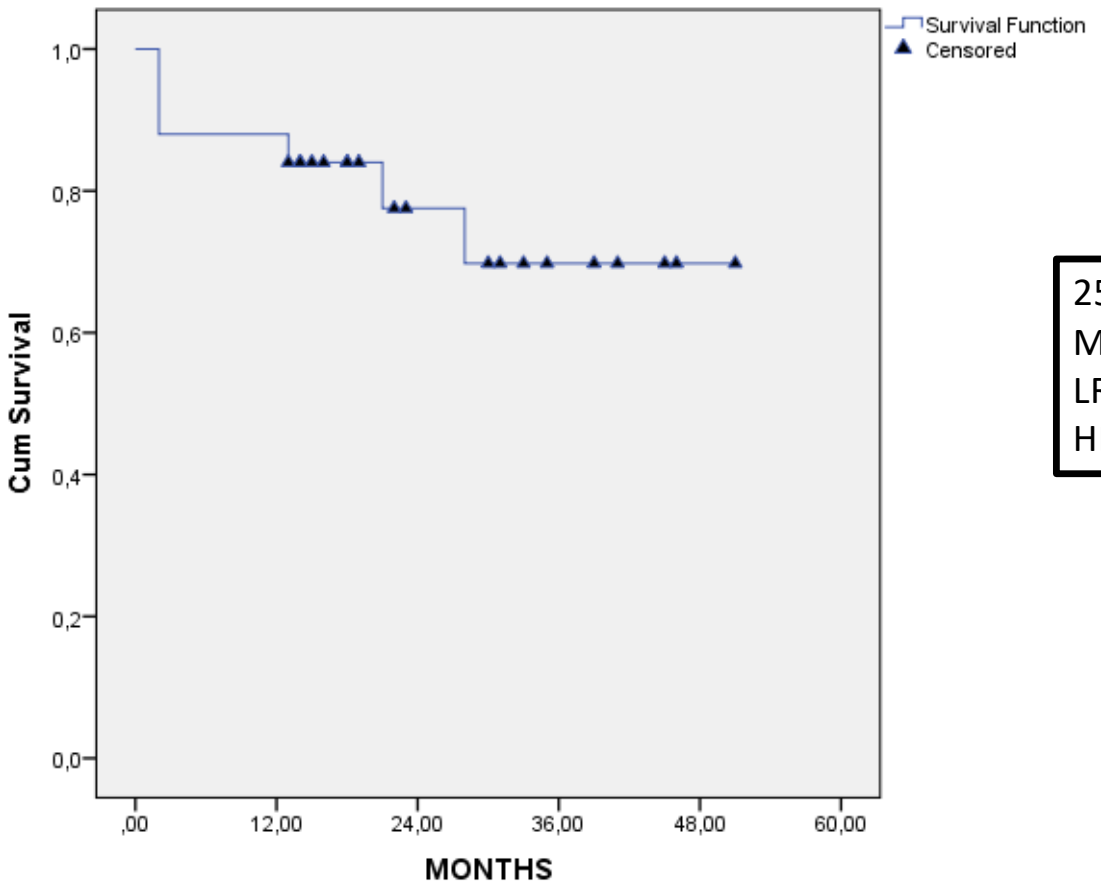
	Regression model on response to induction therapy	
	OR	*P* value
Age above 75 years	0.55	0.030
WBC ($>10 \times 10^9$/l)	0.26	<0.001
ATO/ATRA	2.21	0.30
Male gender	0.72	0.22

ATO arsenic trioxide, *ATRA* all-trans retinoic acid, *CTX* chemotherapy, *OR* odds ratio, *WBC* white blood cell count.

Kayser et al, Leukemia, 2022



Kayser et al, Leukemia, 2022



25 pts.
Median age 74 yrs.
LR: 21 (ATO-ATRA)
HR: 4 (aAIDA)

Speaker's experience

Table 2
Summary of treatment recommendations for APL from NCCN and ELN guidelines.

National Comprehensive Cancer Network (NCCN) recommendations	
WBC count ≤10,000	ATRA+ATO
WBC > 10,000	ATRA+anthracycline followed by ATO
	ATRA+anthracycline
	ATRA+GO+ATO
	In case of low LVEF: ATRA+GO+ATO
ELN recommendations	
WBC count ≤10,000	ATRA+ATO
	ATRA+anthracycline (if ATO is not available)
WBC > 10,000	ATRA+ATO with some cytoreductive chemotherapy
	ATRA+chemotherapy
	Older adults: to be treated as younger adults with some dose attenuation if in good clinical condition, ATRA+ATO can be alternatively considered

Klepin HD et al, J Ger Oncol, 2020

TAKE HOME MESSAGES

- **Available experience indicates that older adults with APL must be treated.**
- **ATRA plus ATO appear to be equally effective across the age spectrum, and cure should be the new expectation.**
- **Current challenges are to ensure rapid recognition and treatment particularly among patients above 70 who have historically often not received anti-leukemic therapy in the community due to concerns related to poor efficacy and high morbidity**
- **Minimizing early mortality with aggressive supportive care and post-remission mortality remain critical for older patients to limit the disparity in age-related outcome.**

Speaker's opinion