High-risk APL

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CONSELLERIA DE SANITAT

What is high-risk APL?

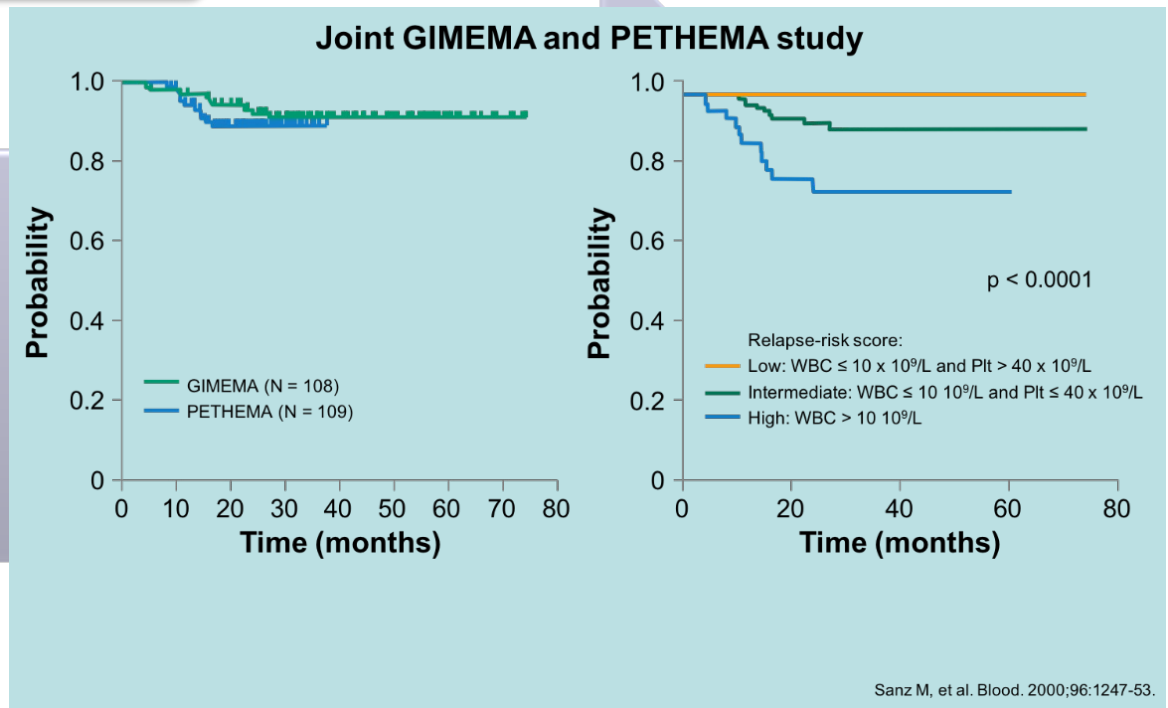
Reduction of dose intensity in elderly[1]

One size fits all

LPA96

Nov. 1996
Oct. 1999

Definition of relapse risk groups



1. Sanz M, et al. Blood. 1999;94:3015-21.

Main characteristics according to eligibility

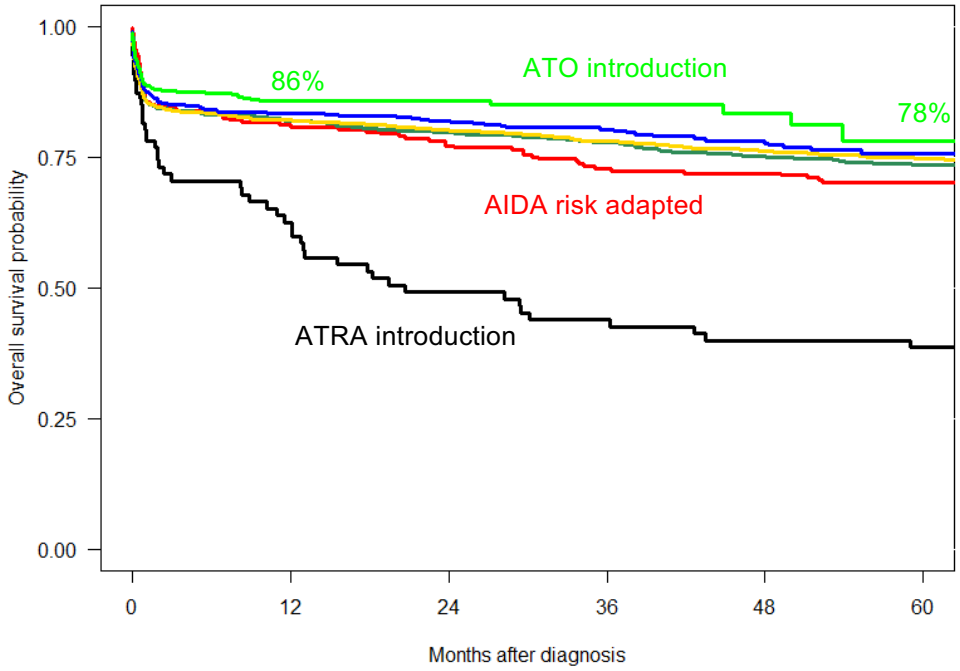
PETHEMA registry

	Overall N = 4156	Eligible N = 2740	Other protocol N = 407	Lack of data N = 360	Sec APL N = 350	Unfit N = 147	Lack of genetic N= 95	Early death N = 50	P-value
Median age, years	46	44	48	45	**58**	**58**	41	48	**<0.001**
Female (%)	50	50	48	48	55	46	51	38	0.21
ECOG 3-4 (%)	10	5	7	8	14	**81**	**36**	**34**	**<0.001**
Median WBC (10^9/L)	2.5	2.4	2.5	3.2	2.2	**8.5**	**5.1**	**16.6**	**<0.001**
Risk category[a] (%)									
Low/inter	**71**	73	66	66	74	69	69	**42**	**<0.001**
High	**29**	27	34	34	26	31	31	**58**	

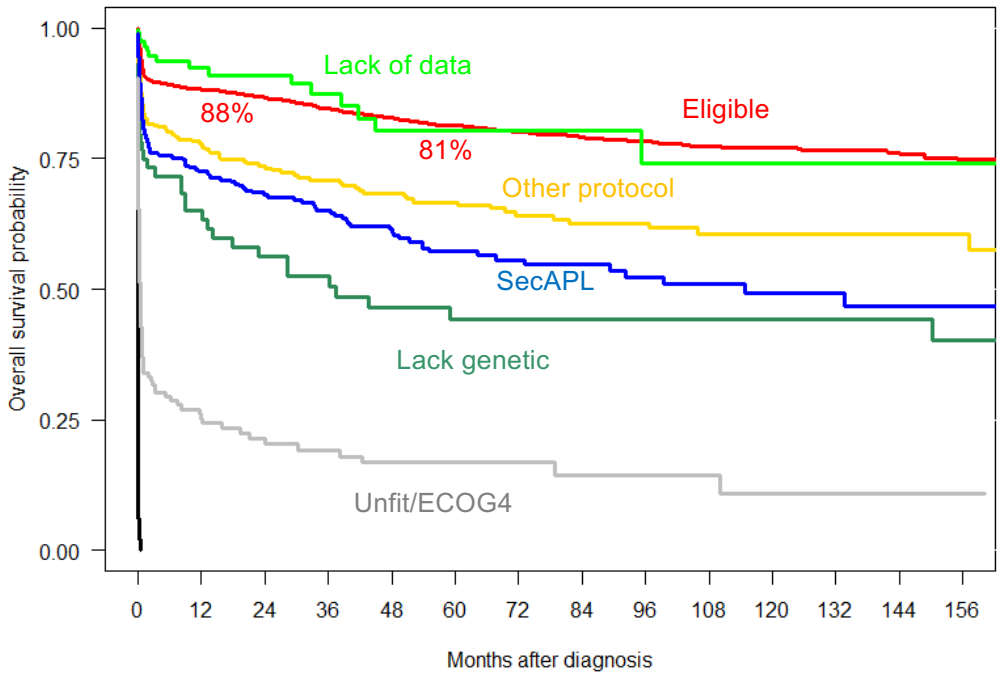
[a] Prognostic score of APL (Sanz Score): WBC < 10.0 10^9/L (low- to intermediate-risk) vs WBC ≥ 10.0 10^9/L (high-risk). BM, bone marrow; WBC, white blood cell count.
Sanz MA, et al. Blood. 2009;113:1875-91.

OS per period and eligibility

PETHEMA registry



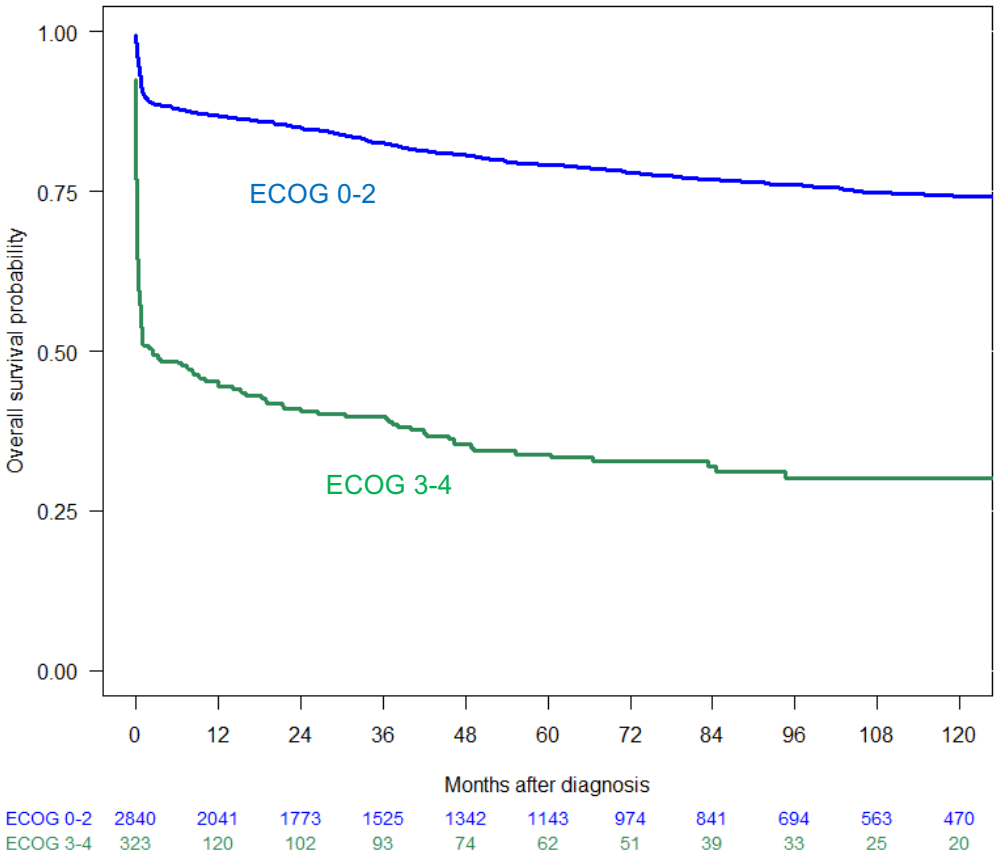
[Protocolo= 93]	89	47	37	33	30	29
[Protocolo= 96]	229	184	176	164	160	155
[Protocolo= 99]	811	610	589	566	535	511
[Protocolo=2005]	1554	1087	978	862	750	610
[Protocolo=2012]	758	420	348	238	175	120
[Protocolo=2017]	691	247	122	74	40	13



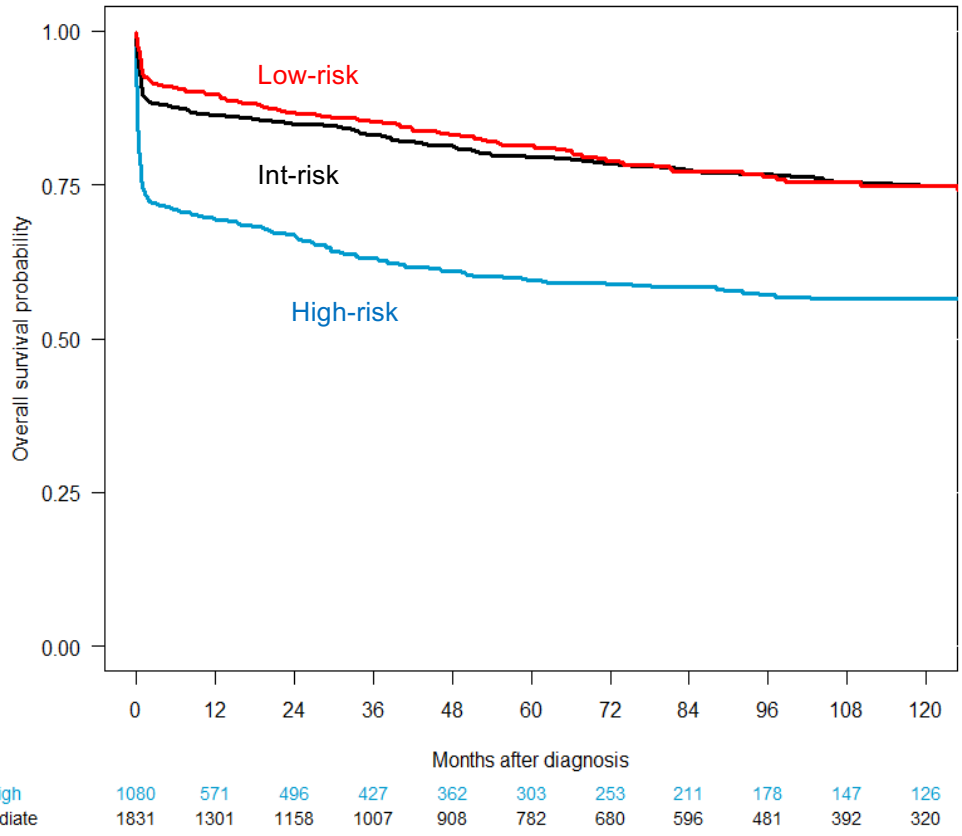
EC=earlydeath]	50	0	0	0	0	0	0	0	0	0	0	0	0	0
SEC=Elegible]	2738	2065	1813	1581	1392	1186	1013	883	717	588	487	385	283	196
EC=lackdata]	350	72	58	42	33	30	23	17	12	11	10	10	9	8
EC=lackgenetic]	93	38	30	27	21	19	19	19	19	16	14	13	11	10
C=otherthерapy]	404	205	176	143	123	112	95	78	70	55	52	41	33	20
C=secundaria]	350	187	153	128	108	81	63	51	43	31	23	21	16	12
PASEC=unfit]	147	28	20	16	13	10	8	5	4	4	3	1	1	1

OS per ECOG and relapse-risk score

PETHEMA registry

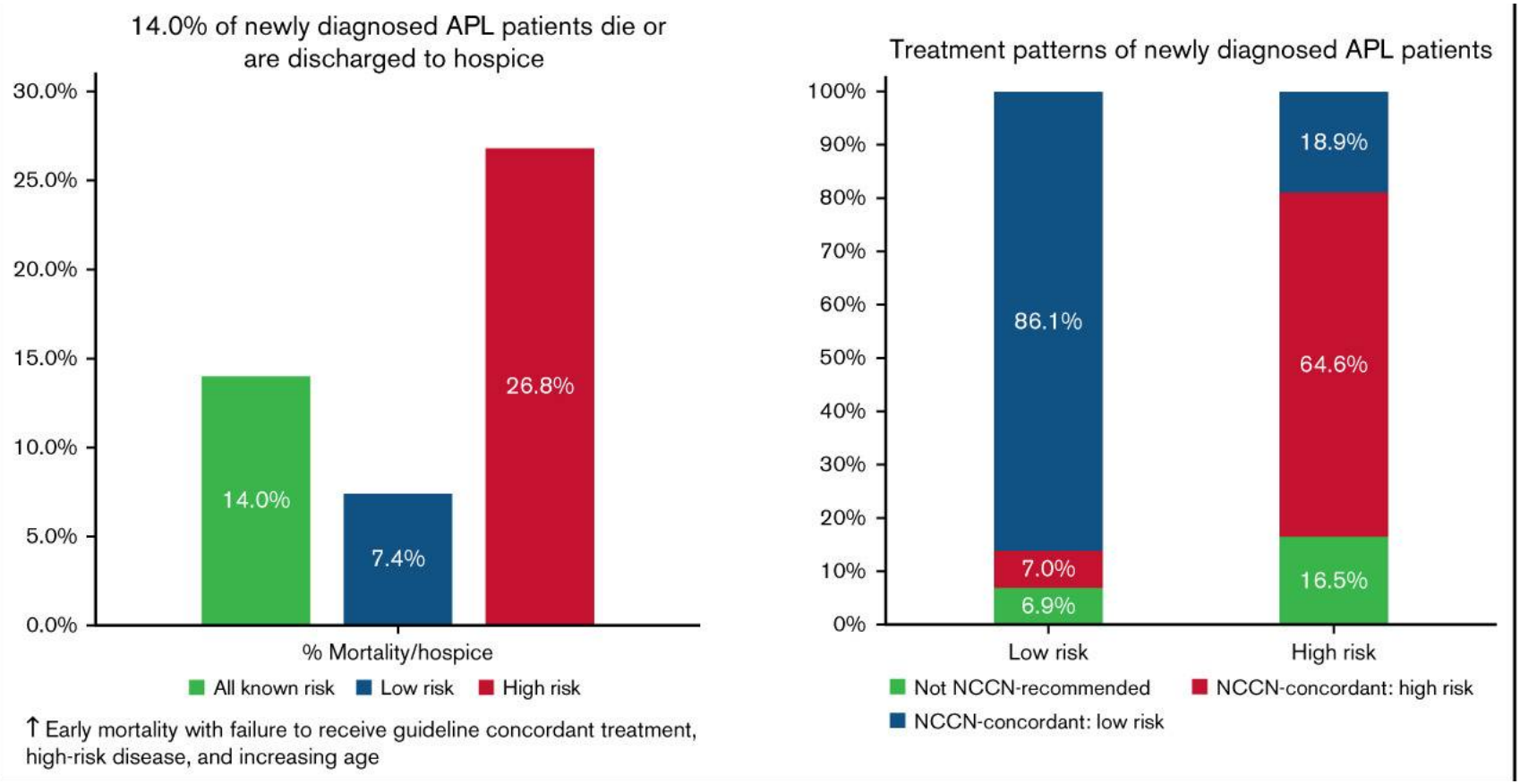


ECOG 0-2	2840	2041	1773	1525	1342	1143	974	841	694	563	470
ECOG 3-4	323	120	102	93	74	62	51	39	33	25	20



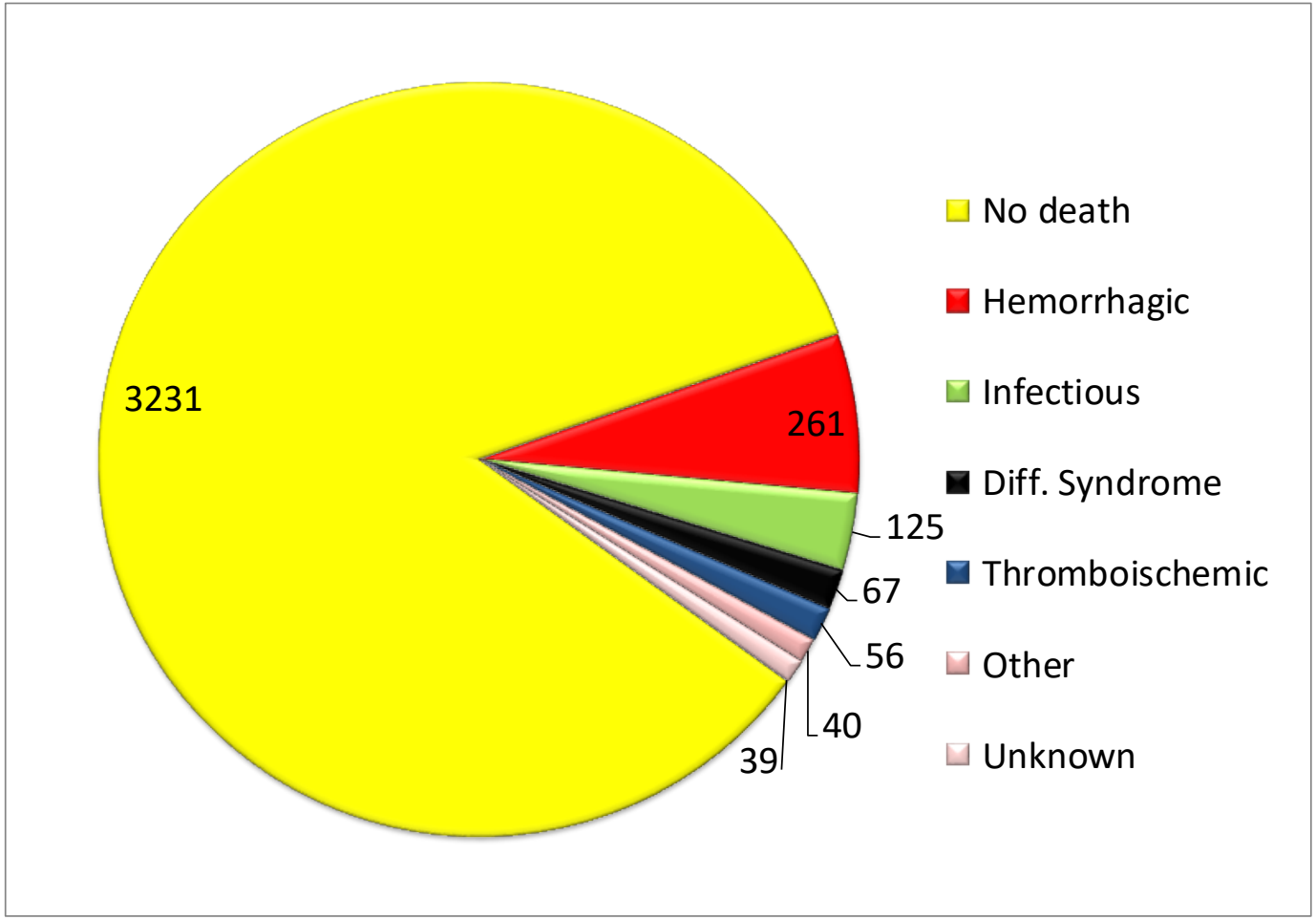
high	1080	571	496	427	362	303	253	211	178	147	126
intermediate	1831	1301	1158	1007	908	782	680	596	481	392	320
low	842	609	506	433	364	305	247	207	173	138	115

Practice patterns and real-life outcomes for patients with APL in the United States



Bewersdorf JP, Prozora S, Podoltsev NA, et al. Blood Adv. 2022 Jan 25;6(2):376-385.

Early death among 3819 patients of the PETHEMA APL registry
N=588 (15.4%)



Early death according to trial eligibility

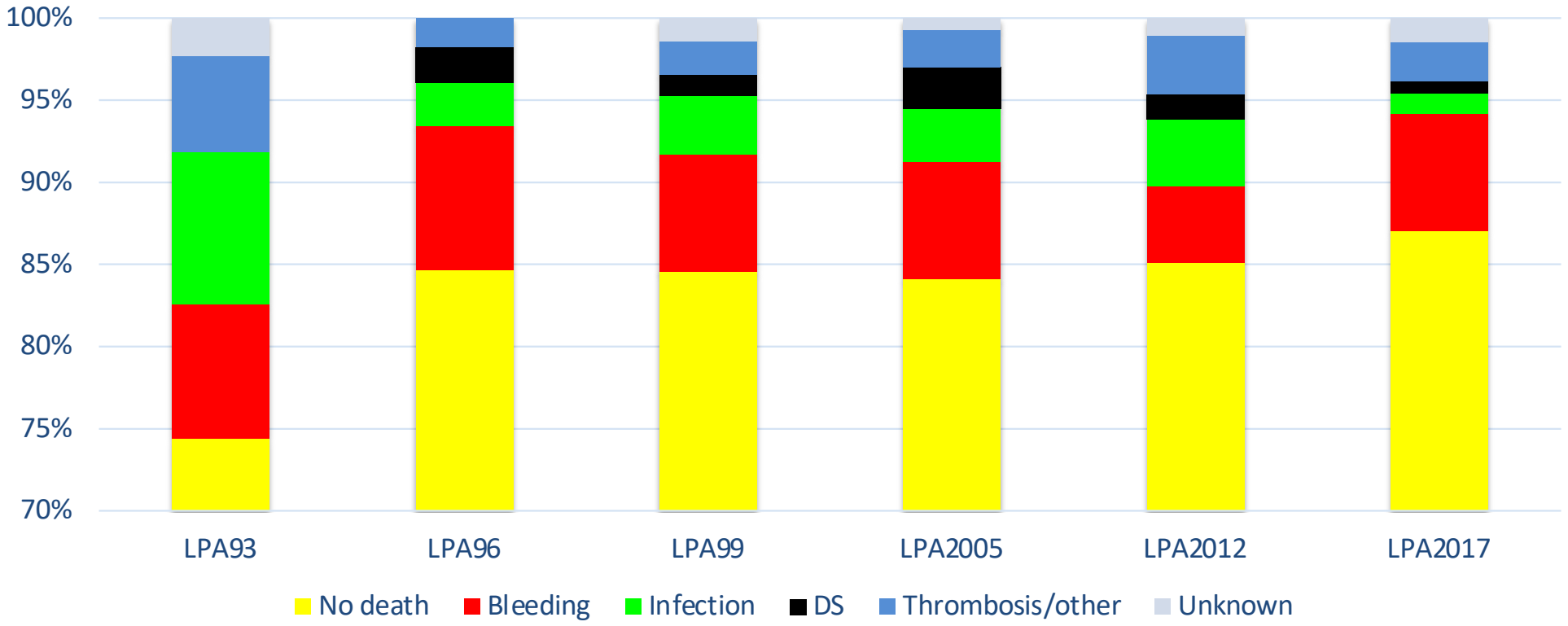
PETHEMA registry

	Eligible (n = 2740)	sAPL (n = 324)	No genetics (n = 63)	Unfit/very ED (n = 189)	p
Early death (%)	**9.9**	**23.5**	**28.6**	**78.3**	<.001
Cause of death					
Hemorrhage	**4.3**	**8.3**	**16.4**	**44.4**	
Infection	2.0	**8.3**	3.3	10.1	
DS	1.6	2.2	0.0	5.3	
Thrombosis/other	1.6	4.0	3.2	14.3	
Unknown	0.3	0.6	6.4	4.2	

Early death according to treatment period

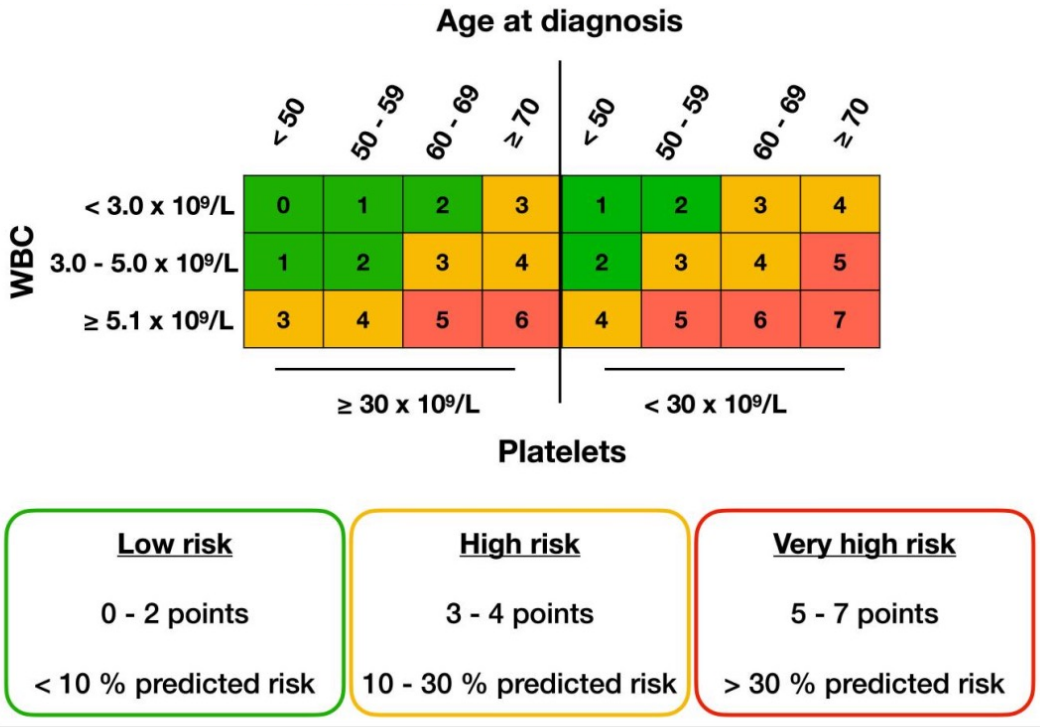
PETHEMA registry

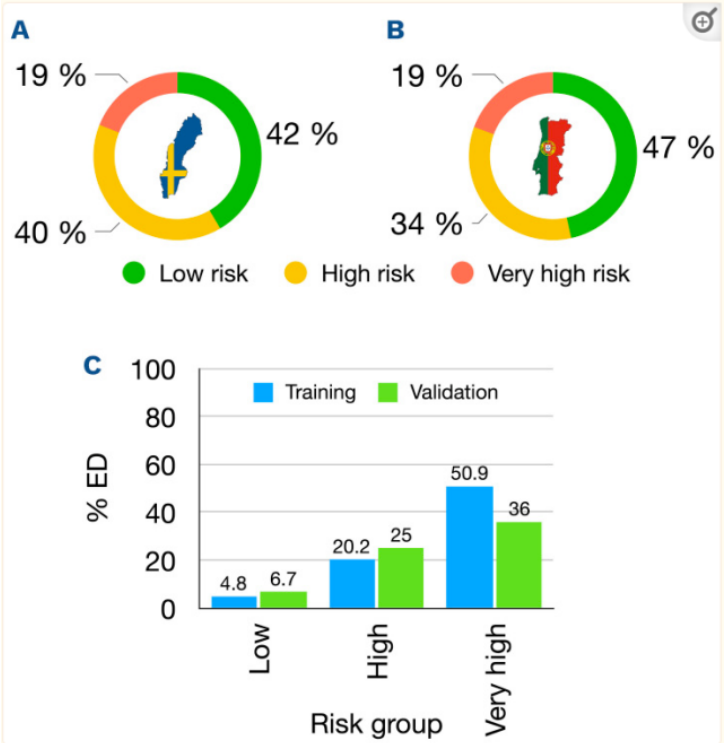
p-value = 0.008



A risk score based on real-world data to predict early death in APL

Swedish registry





Österroos A, Maia T, Eriksson A, et al. Haematologica. 2022 Jul 1;107(7):1528-1537.

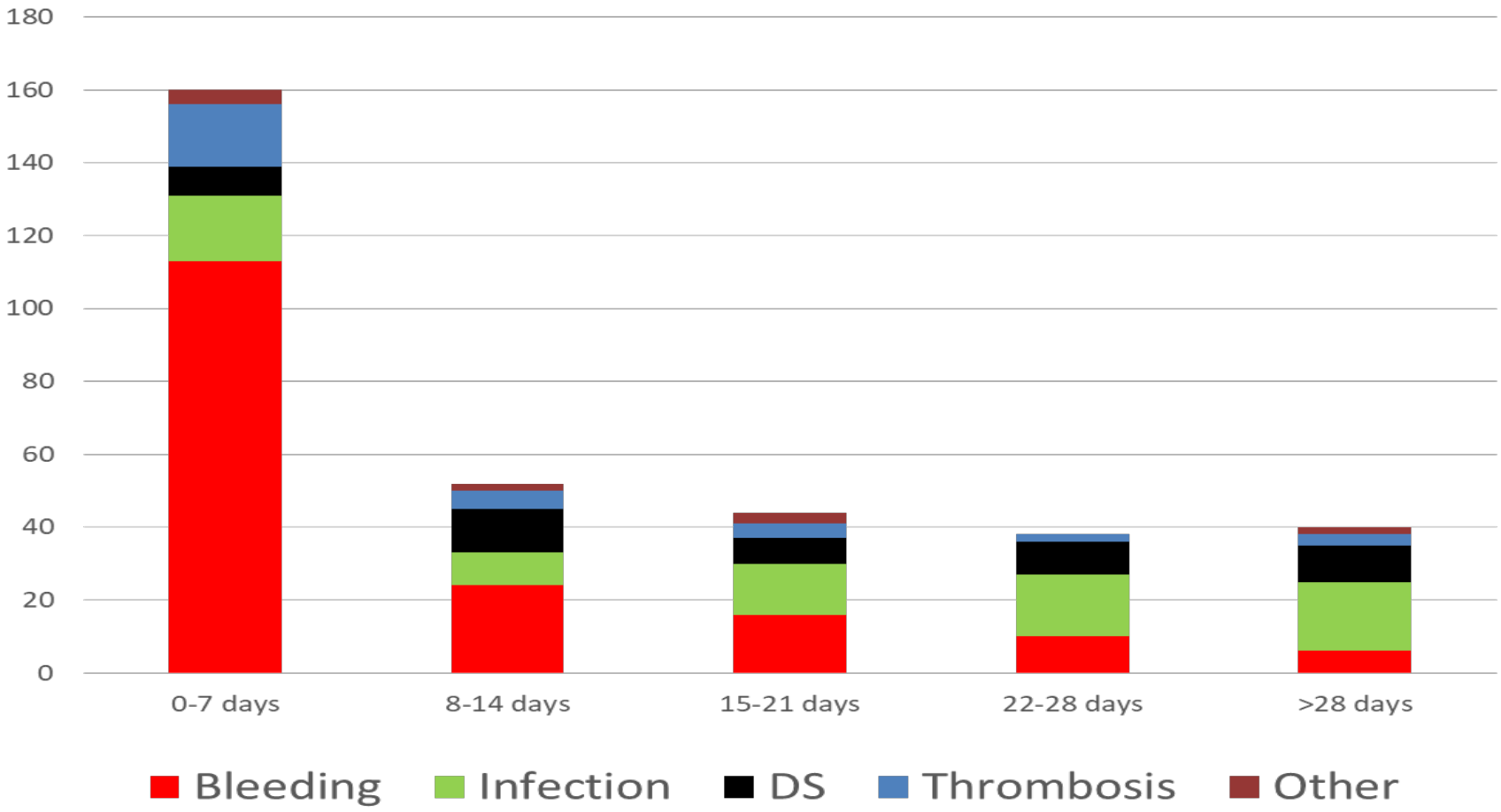
Overall ED: Multivariate análisis

PETHEMA registry

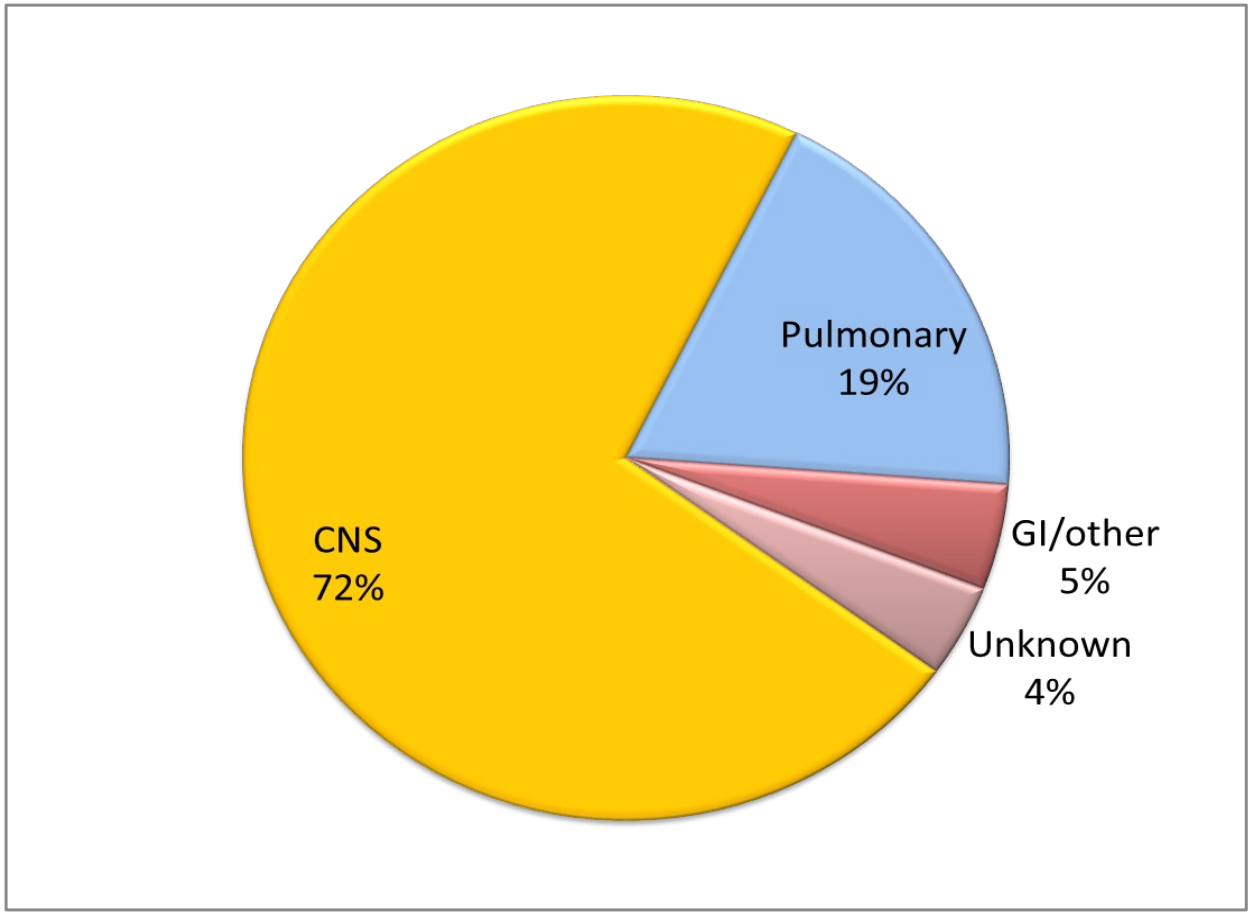
Risk factor	RR	P value
Age (per year)	1.03	<0.0001
WBC >10x10^9/L	2.1	<0.0001
ECOG (per unit)	1.9	<0.0001
LDH >ULN	1.7	0.006
Creatinine >ULN	4.2	<0.0001
Blasts in PB (per 1x10^9/L)	1.009	0.005
sAPL	1.7	0.03

Causes of death by timing

PETHEMA registry

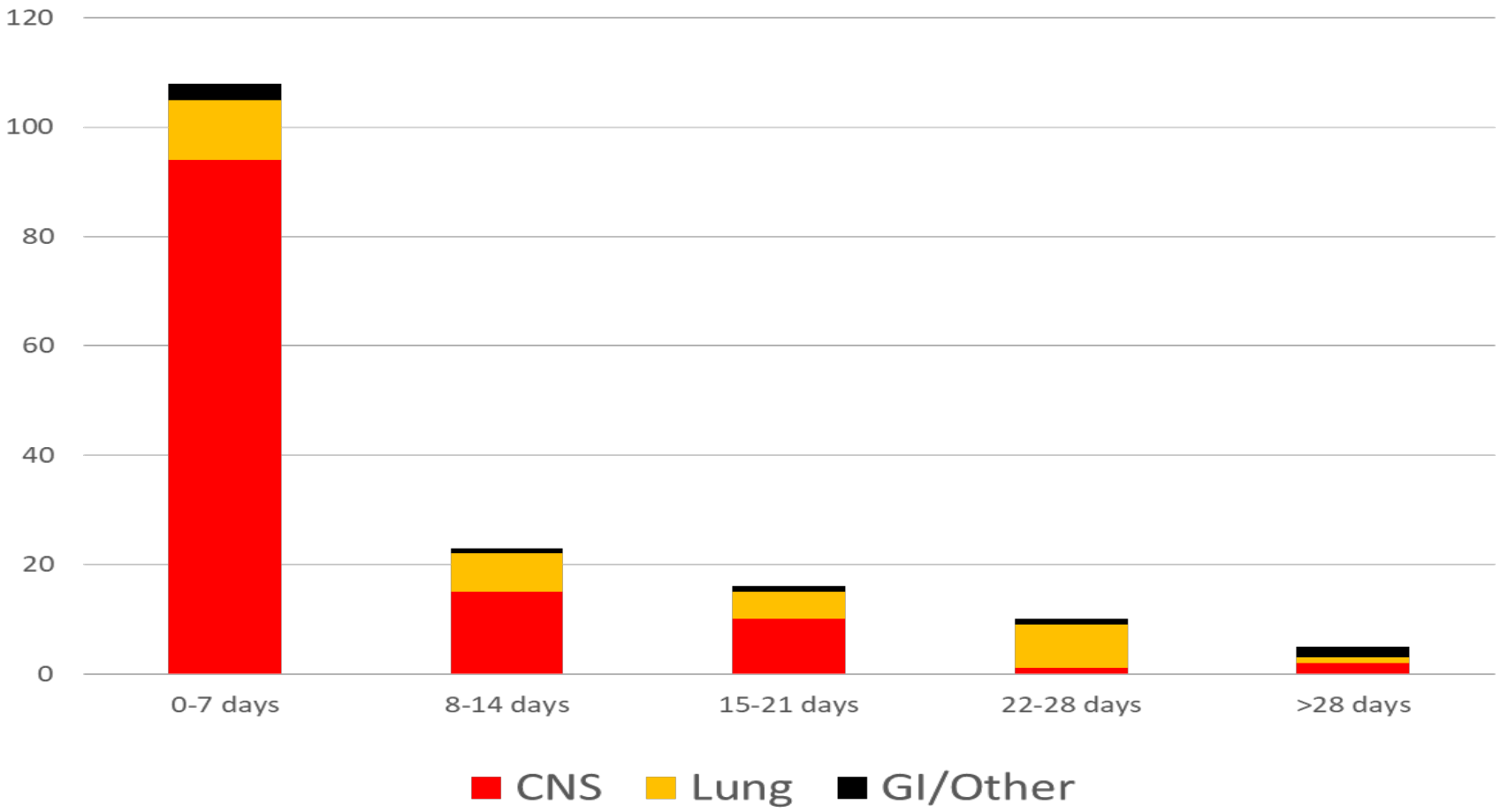


Sites of lethal bleeding
N=261 (6.8%)



Sites of fatal bleeding by timing

PETHEMA registry



Hemorrhagic ED: Multivariate análisis

PETHEMA registry

Risk factor	RR	P value
Age (per year)	1.01	0.048
WBC >10x10^9/L	2.1	0.02
ECOG (per unit)	1.8	<0.0001
Creatinine >ULN	3.1	<0.0001
Blasts in PB (per 1x10^9/L)	1.01	0.005

ELN 2019 guidelines

Appropriate setting for the management of APL

"The panel again recommends that patients with APL be managed by an experienced team in centers with documented rapid access to genetic diagnosis, a broad range of blood products, as well as ATRA, ATO, and chemotherapy".

Sanz MA. et al, Blood 2019

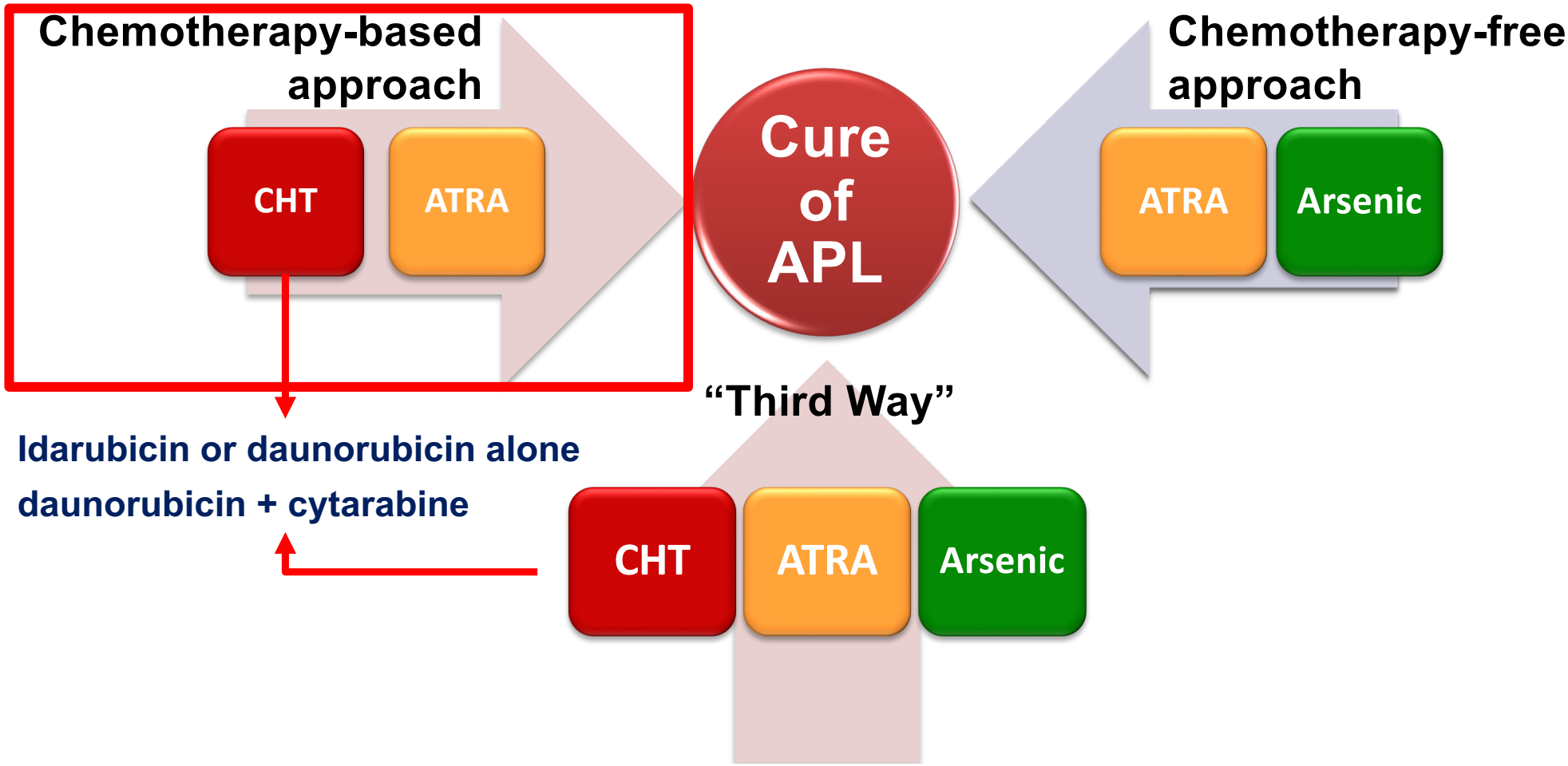
ELN 2019 guidelines
Initiation of therapy

- For non-high risk patients, starting ATO can be delayed until genetic diagnosis
- For high-risk patients:

Management of hyperleukocytosis (WBC >10 x 10^9/L) at presentation		
1.10. Cytoreductive chemotherapy should be started without delay, even if the molecular results are still pending: • For patients to be treated with ATRA plus chemotherapy, idarubicin or daunorubicin alone or combined with cytarabine should be given. • For patients to be treated with ATRA plus ATO, cytoreduction can be done with idarubicin (12 mg/m^2) or gemtuzumab ozogamicin (6-9 mg/ m^2).	IV - C	Updated
1.11. Leukapheresis should be avoided due to risk of precipitating fatal hemorrhage.	III - B	Unchanged
1.12. Prophylactic corticosteroids can be given, which may reduce the risk of APL differentiation syndrome.	IV - C	Unchanged

Sanz MA. et al, Blood 2019

Current Treatment Approaches in high-risk APL

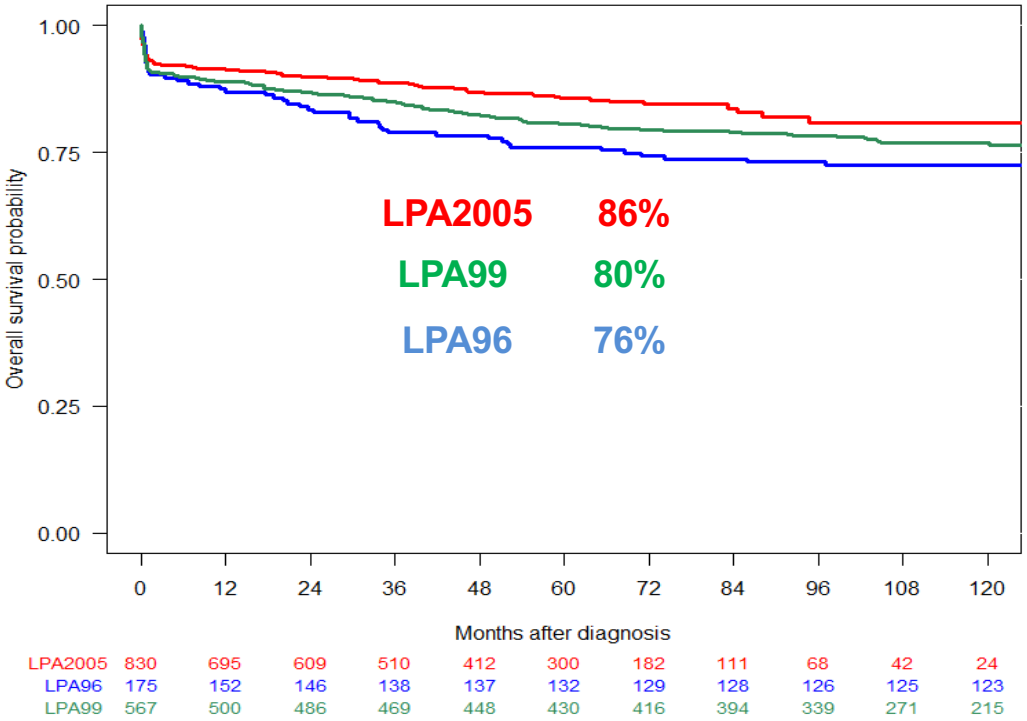


- Idarubicin or daunorubicin alone
- daunorubicin + cytarabine

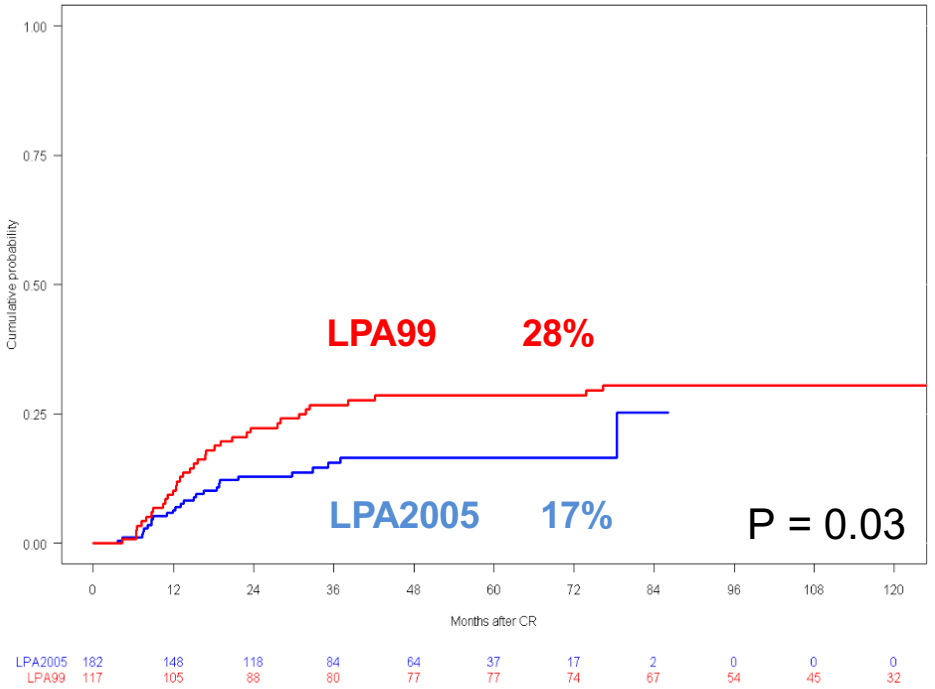
Improved outcomes at 5 years using risk-adapted trials

PETHEMA/HOVON/PALG/GATLA

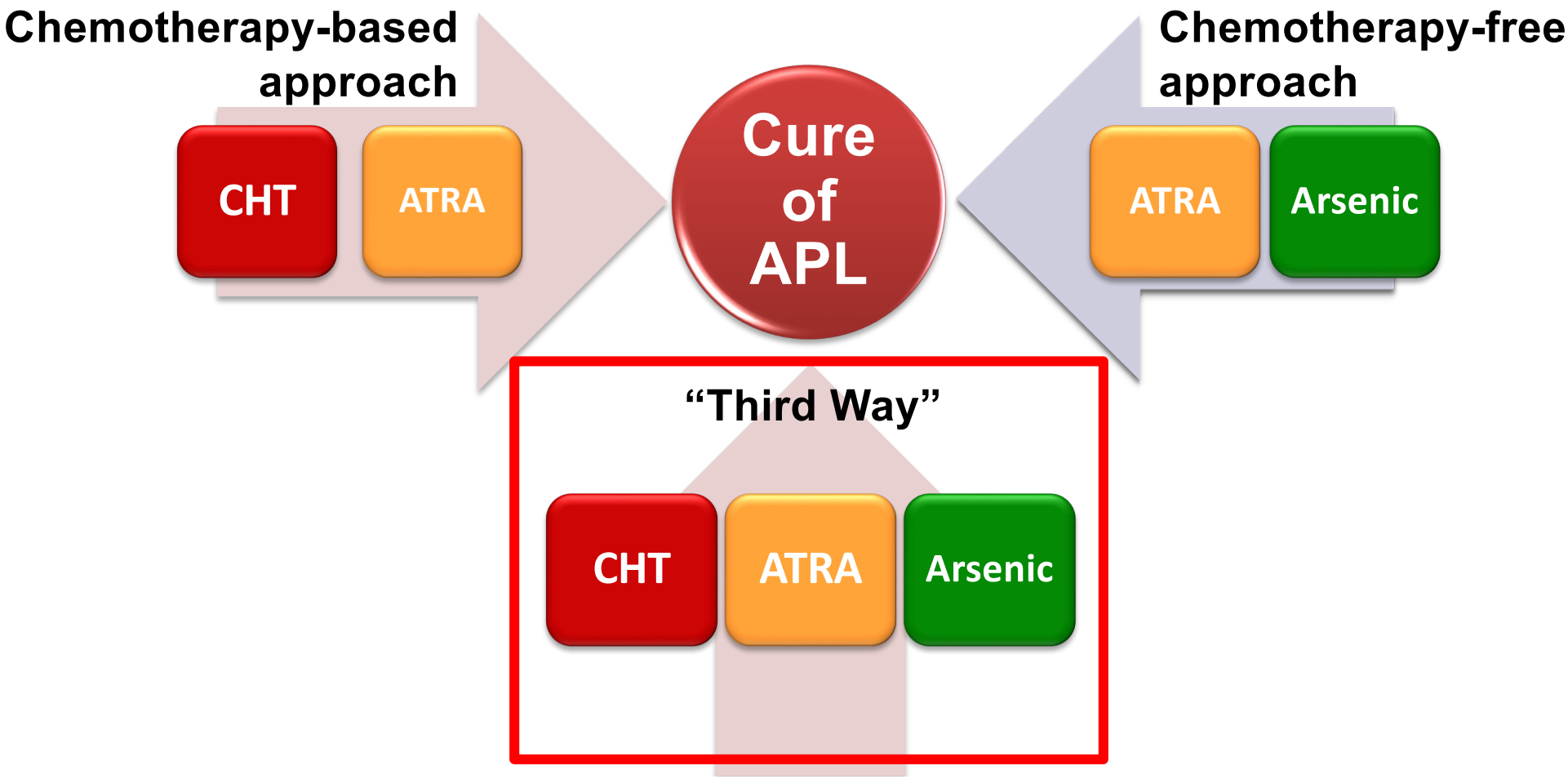
OS in all eligible patients



CIR in High-risk eligible patients



Current Treatment Approaches in high-risk APL



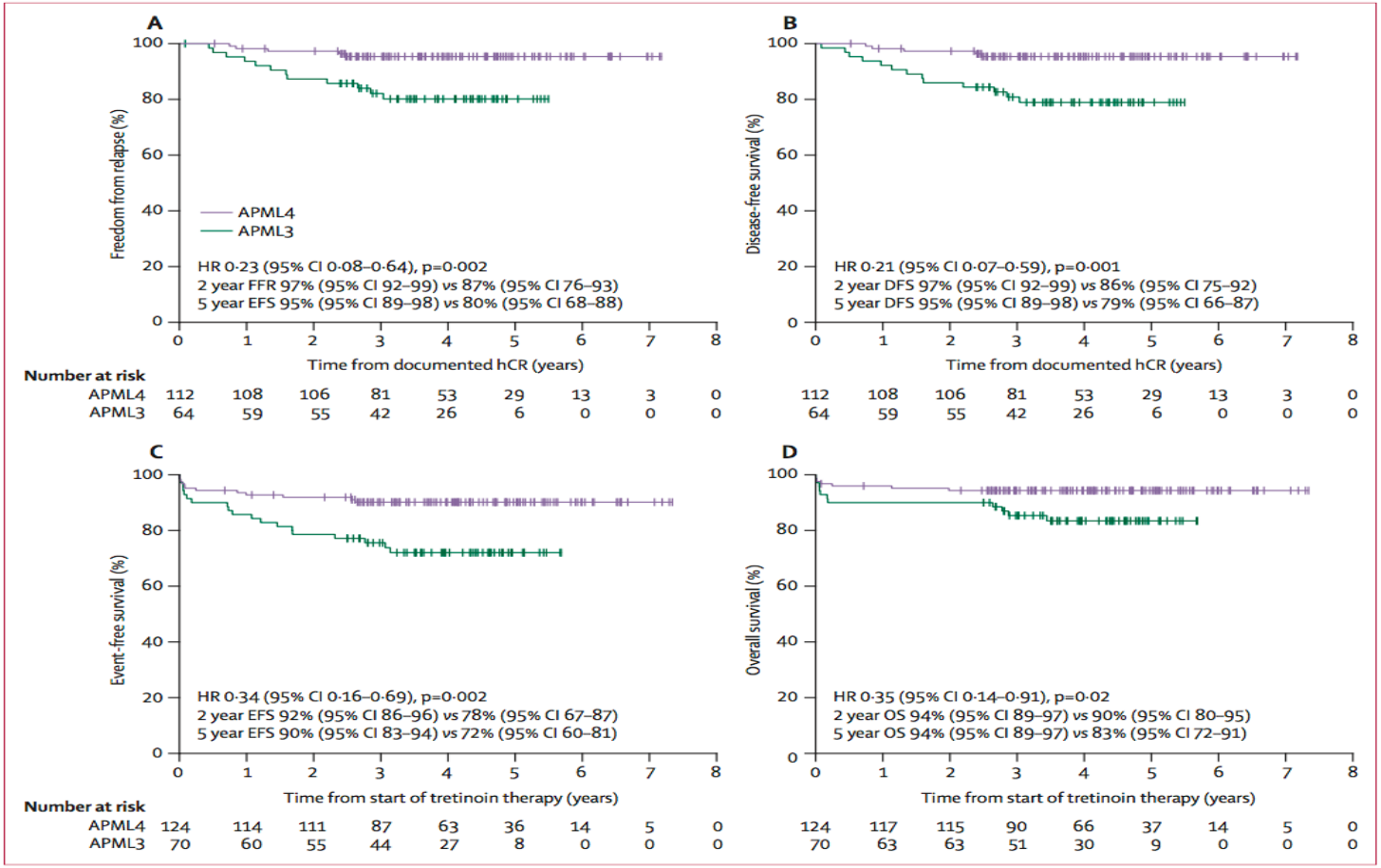
ATRA + ATO + CHT

Australasian Leukemia and Lymphoma Group

Induction
ATRA + ATO + CHT

Consolidation (2)
ATRA + ATO

Maintenance (5)
ATRA + LD-CHT



Iland HJ, et al. Lancet Haematol. 2015

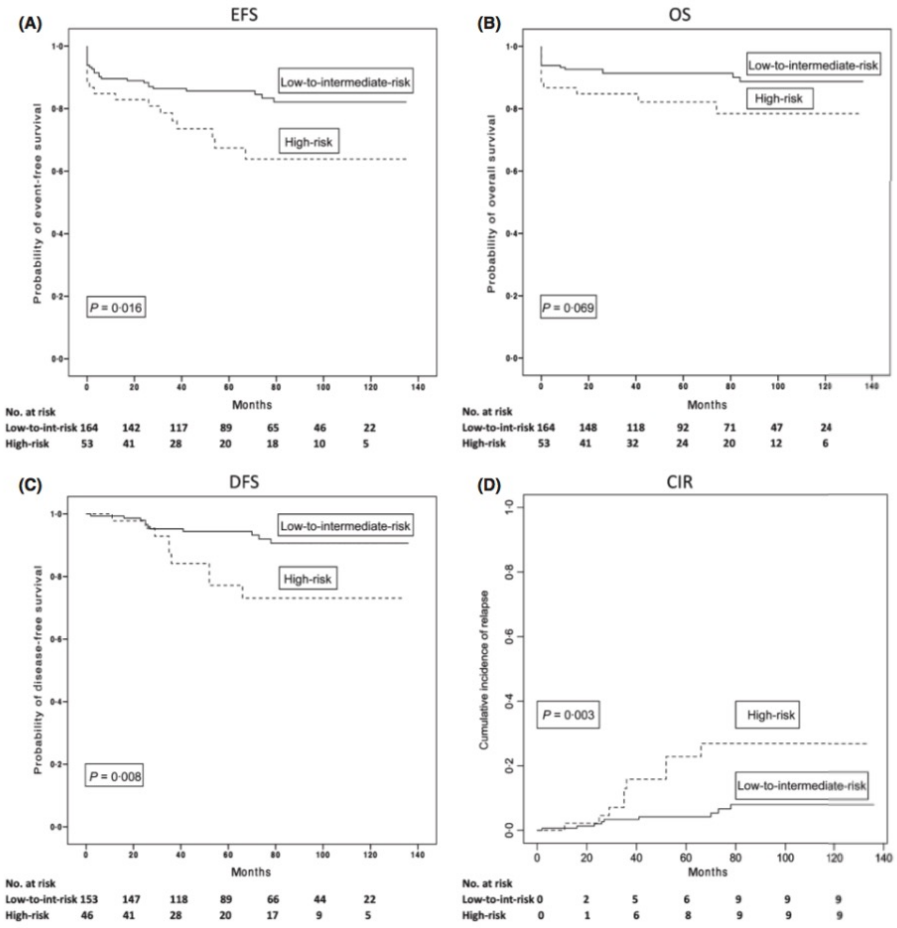
ATRA + ATO + CHT

Shanghai Group

Induction
ATRA + ATO

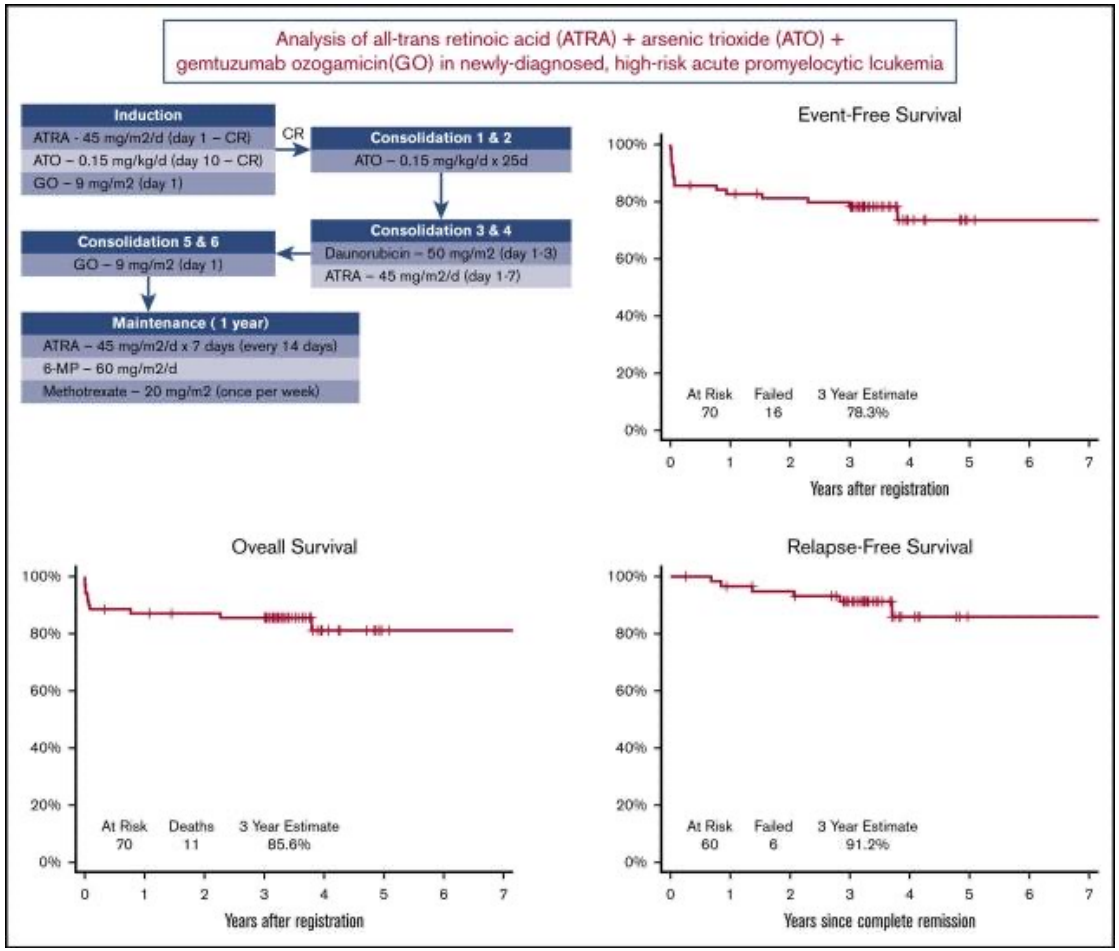
Consolidation (3)
ATRA + CHT

Maintenance (5)
ATRA, ATO & LD-CHT



Zhu H, et al. Br J Haematol. 2015

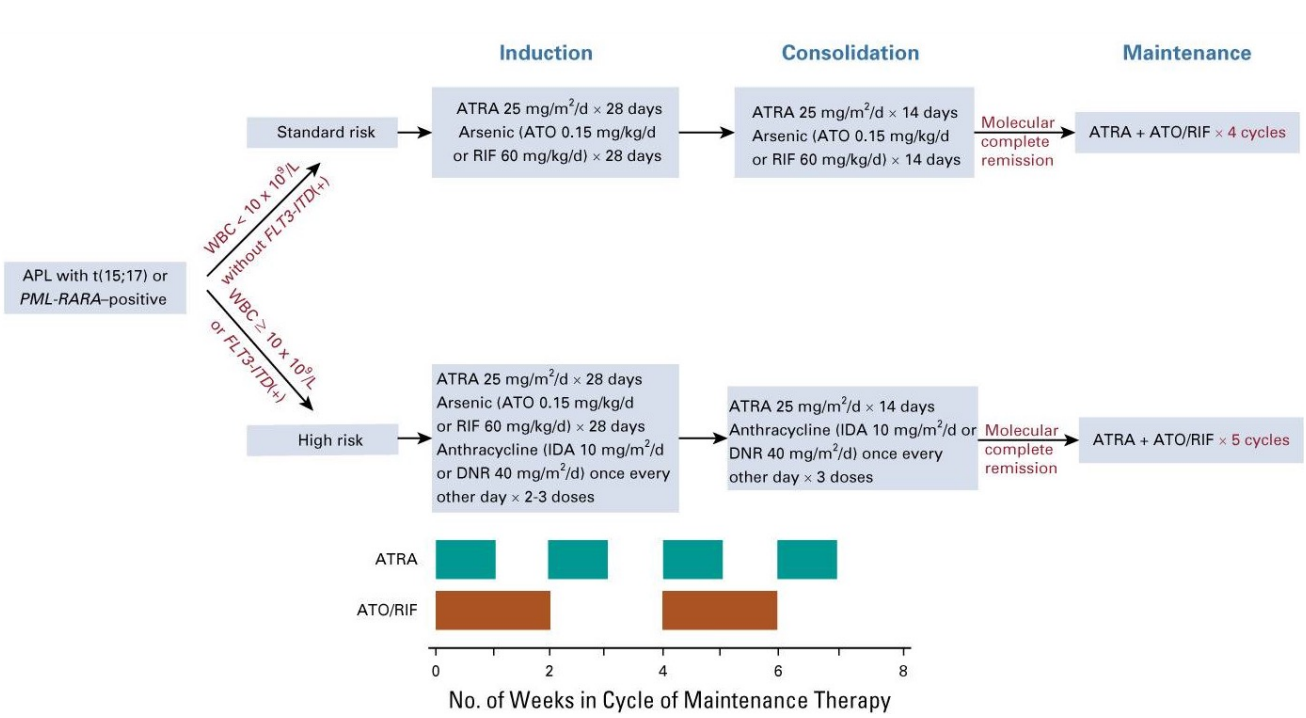
A phase 2 study of ATRA + ATO + CHT in high-risk APL (SWOG 0535)

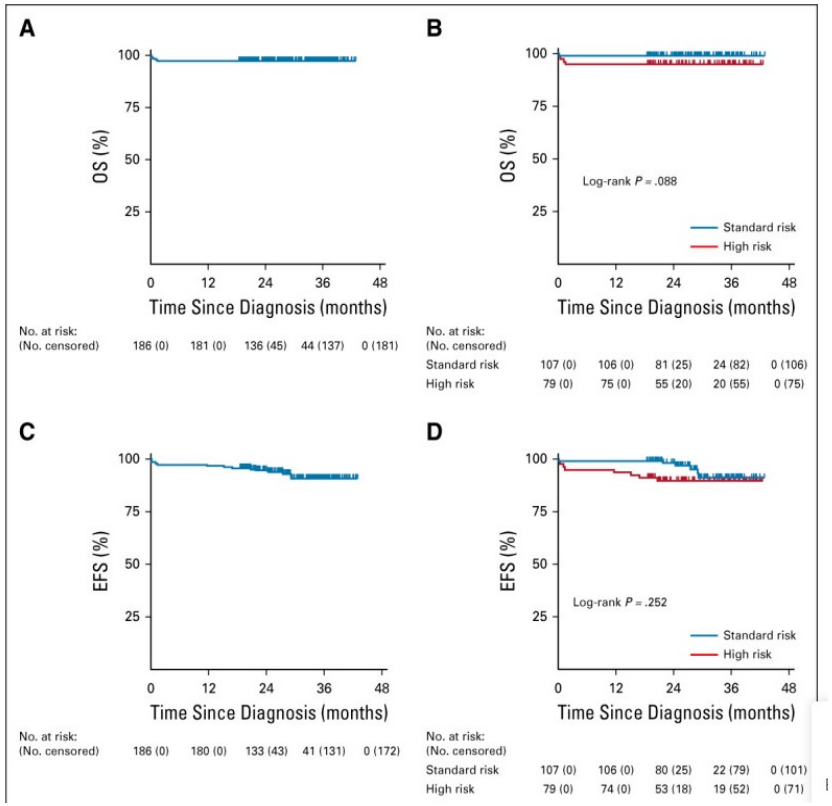


Lancet JE, Moseley AB, Coutre SE, et al. Blood Adv. 2020 Apr 28; 4(8): 1683–1689.

ATO + ATRA + CHT for High-risk Pediatric APL

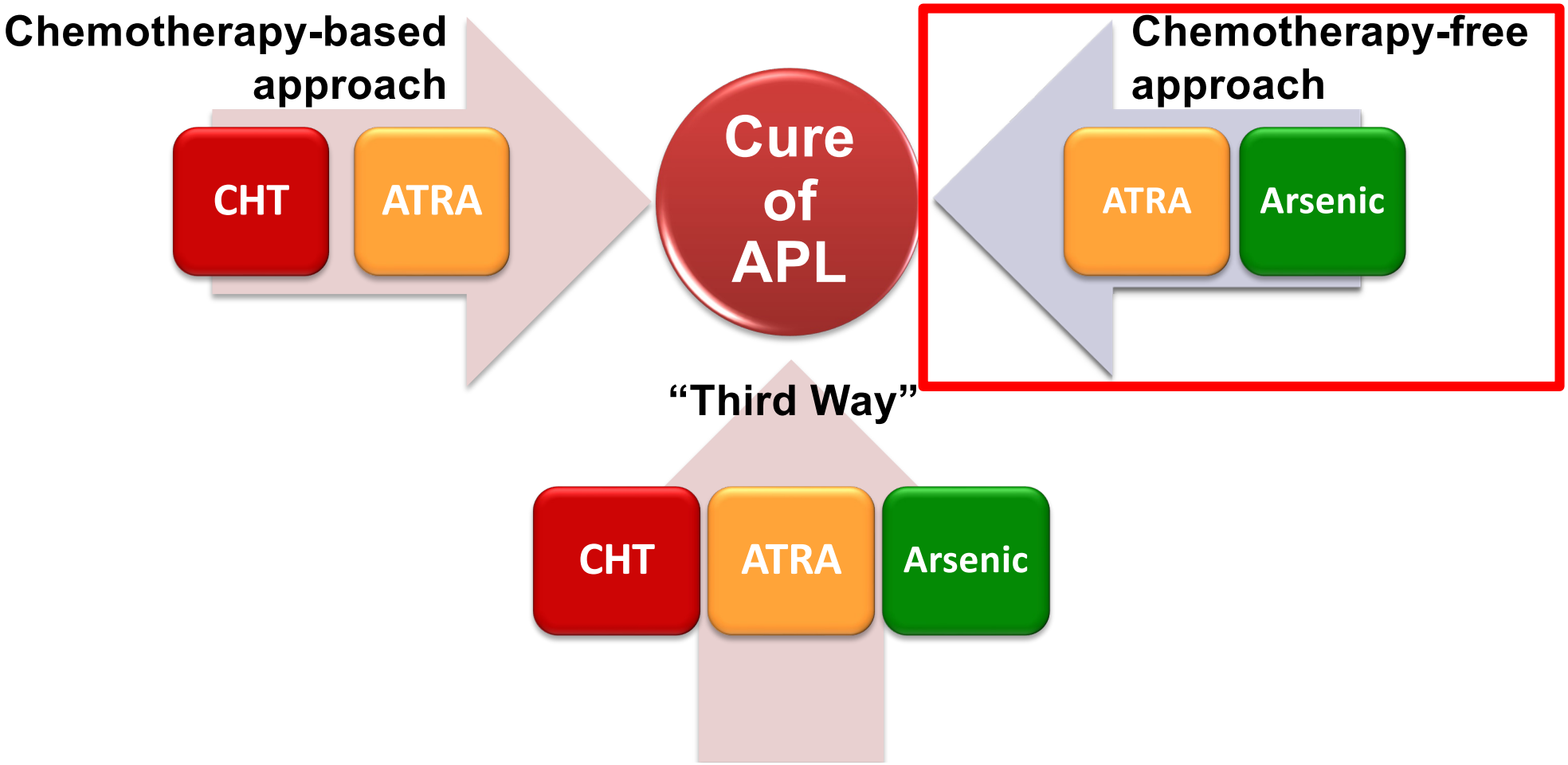
CCLG-APL2016 Study





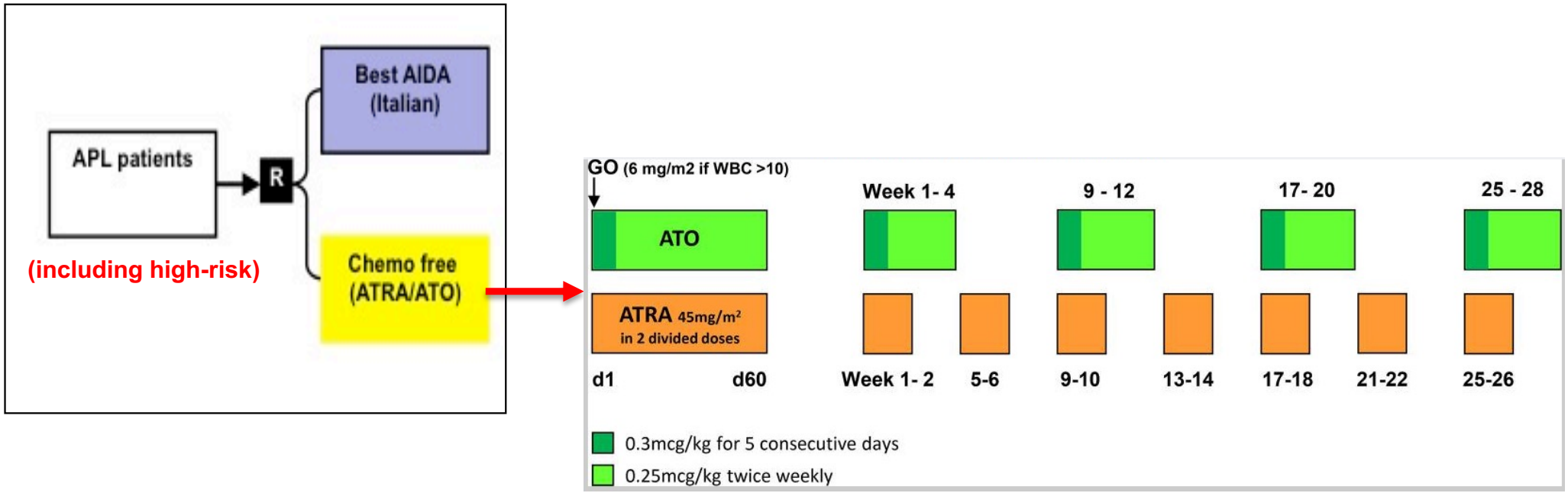
Zheng H, Jiang H, Hu S, et al. J Clin Oncol. 2021 Oct 1;39(28):3161-3170.

Current Treatment Approaches in high-risk APL



ATO + ATRA vs. AIDA

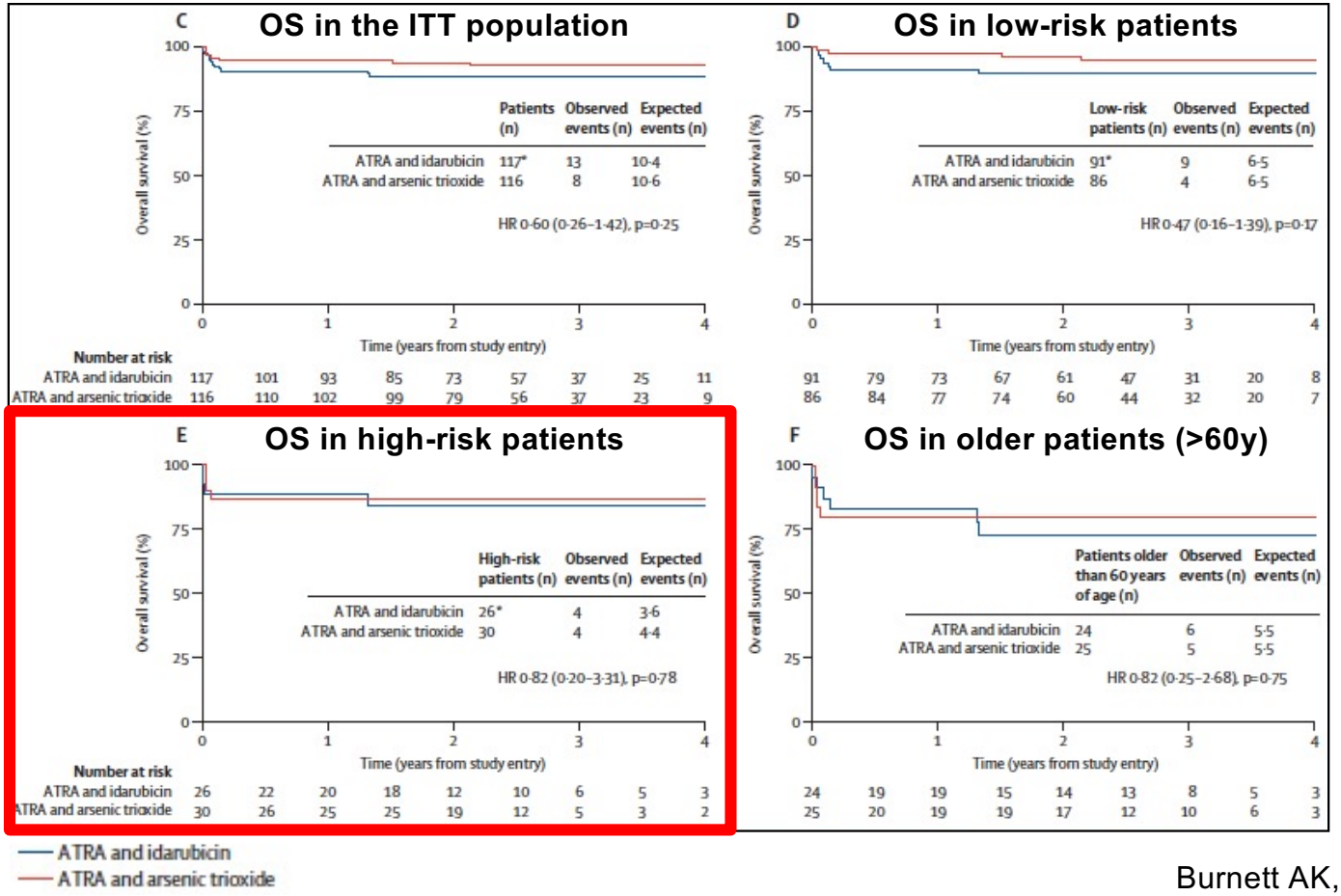
UK NCRI - AML 17 trial



Burnett AK, *et al*. Lancet Oncol 2015;16: 1295–305
Russell N, Dillon R. Front Oncol. 2020 Nov 11;10:594129.

ATO + ATRA vs. AIDA

UK NCRI - AML 17 trial

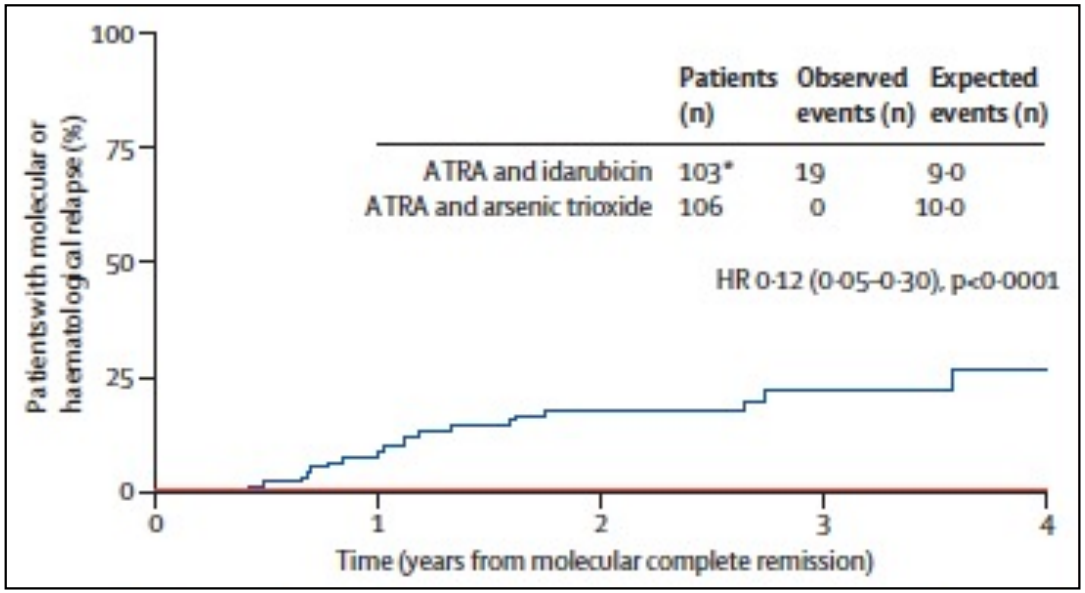


Burnett AK, *et al*. Lancet Oncol 2015

ATO + ATRA vs. AIDA

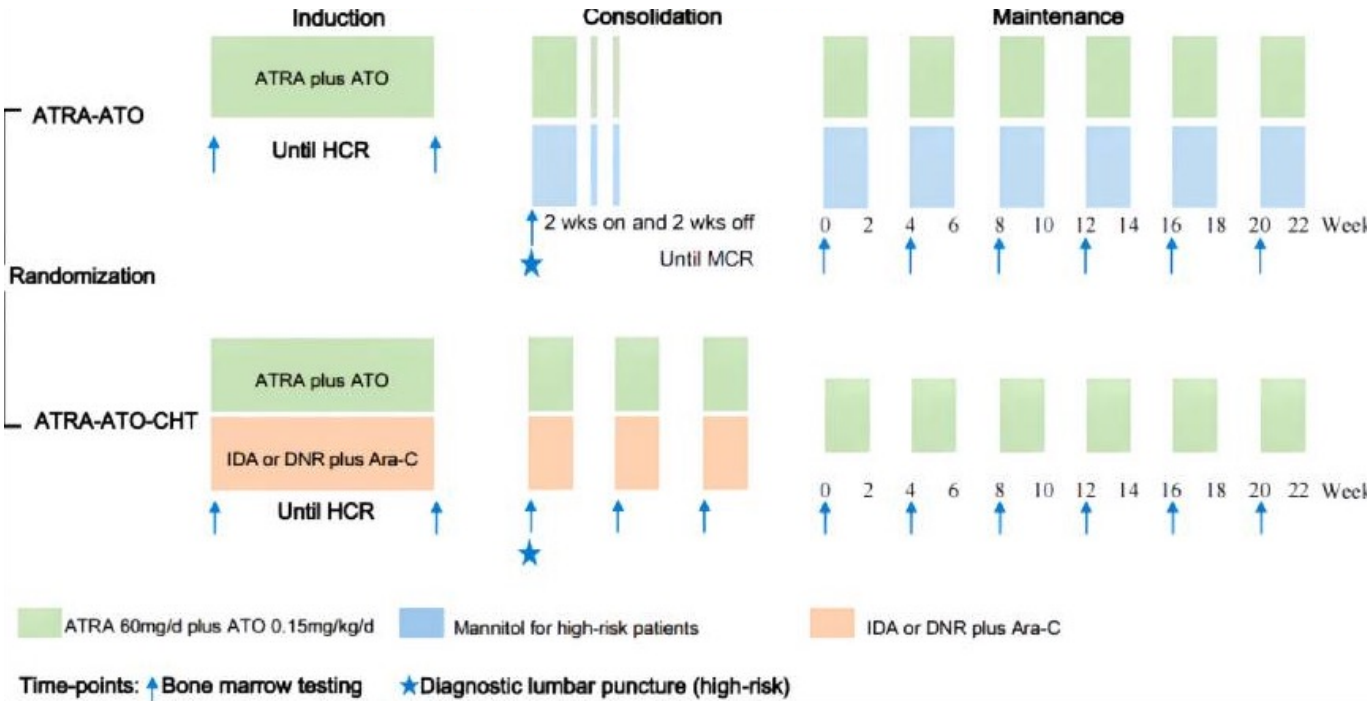
UK NCRI - AML 17 trial

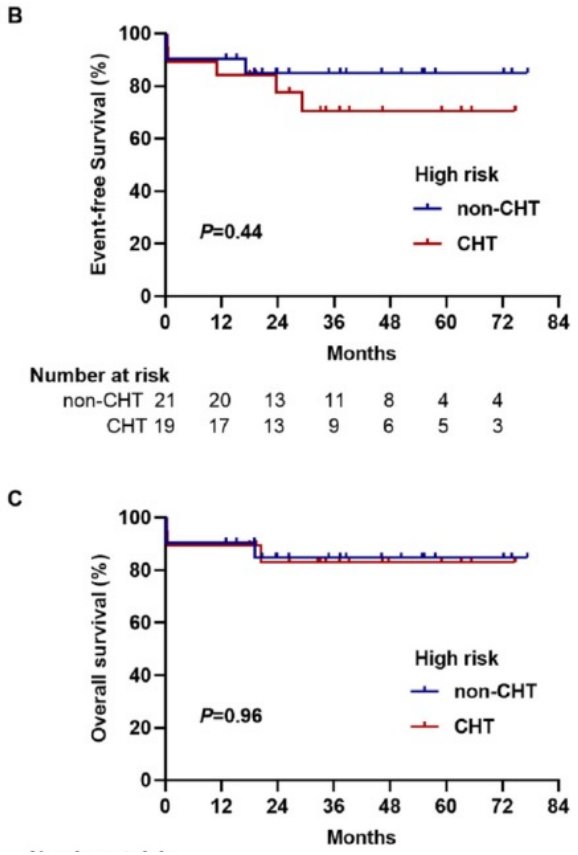
Cumulative incidence of molecular or hematological relapse



Burnett AK, et al. Lancet Oncol 2015;16: 1295–305

ATO + ATRA vs. ATO + ATRA + CHT in high-risk APL
(APL15 trial)

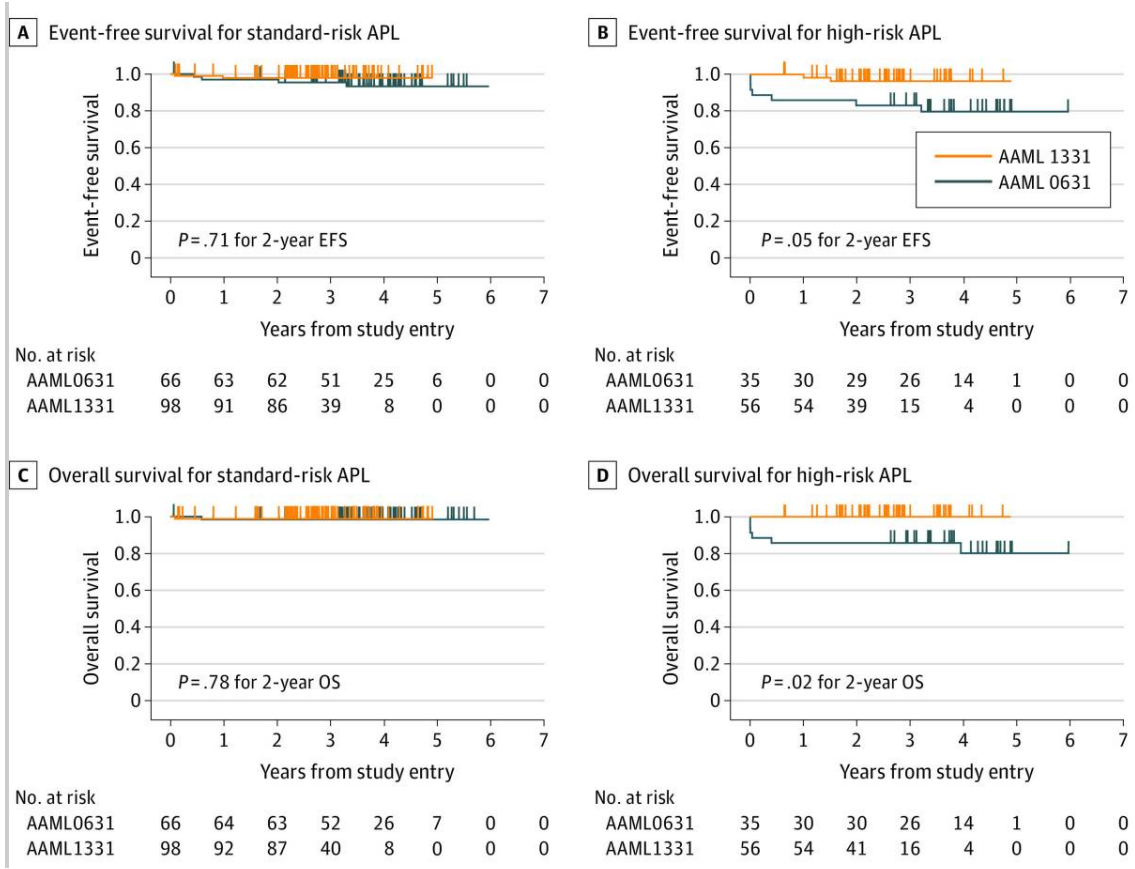




Wang HY, Gong S, Li GH, et al. Blood Cancer J. 2022 Nov 21;12(11):158.

ATO + ATRA vs. ATRA + CHT

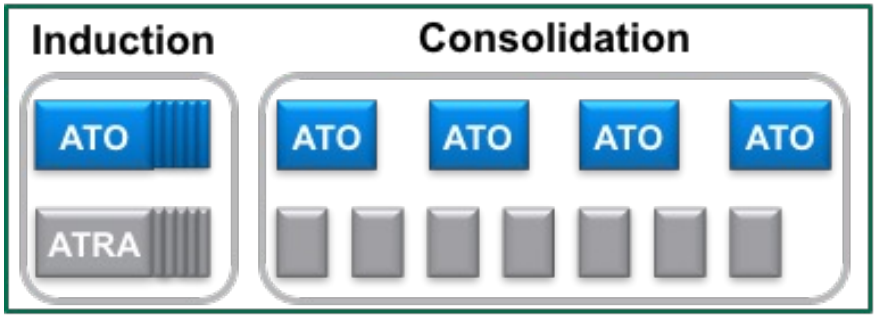
Children's Oncology Group AAML1331 Trial



Kutny MA, Alonzo TA, Abla O, et al. JAMA Oncol. 2022 Jan 1;8(1):79-87.

Current PETHEMA risk-adapted strategy in APL

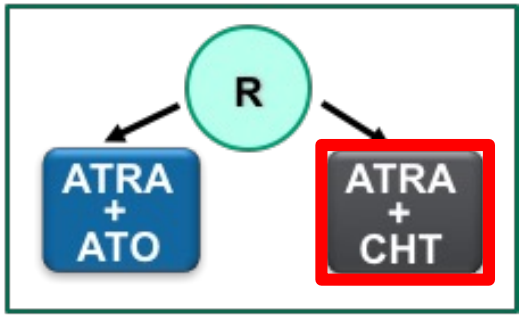
Low and intermediate risk
(WBC ≤10 x 10^9/L)



Lo-Coco F, et al. N Engl J Med. 2013;369:111-21

High risk
(WBC >10 x 10^9/L)

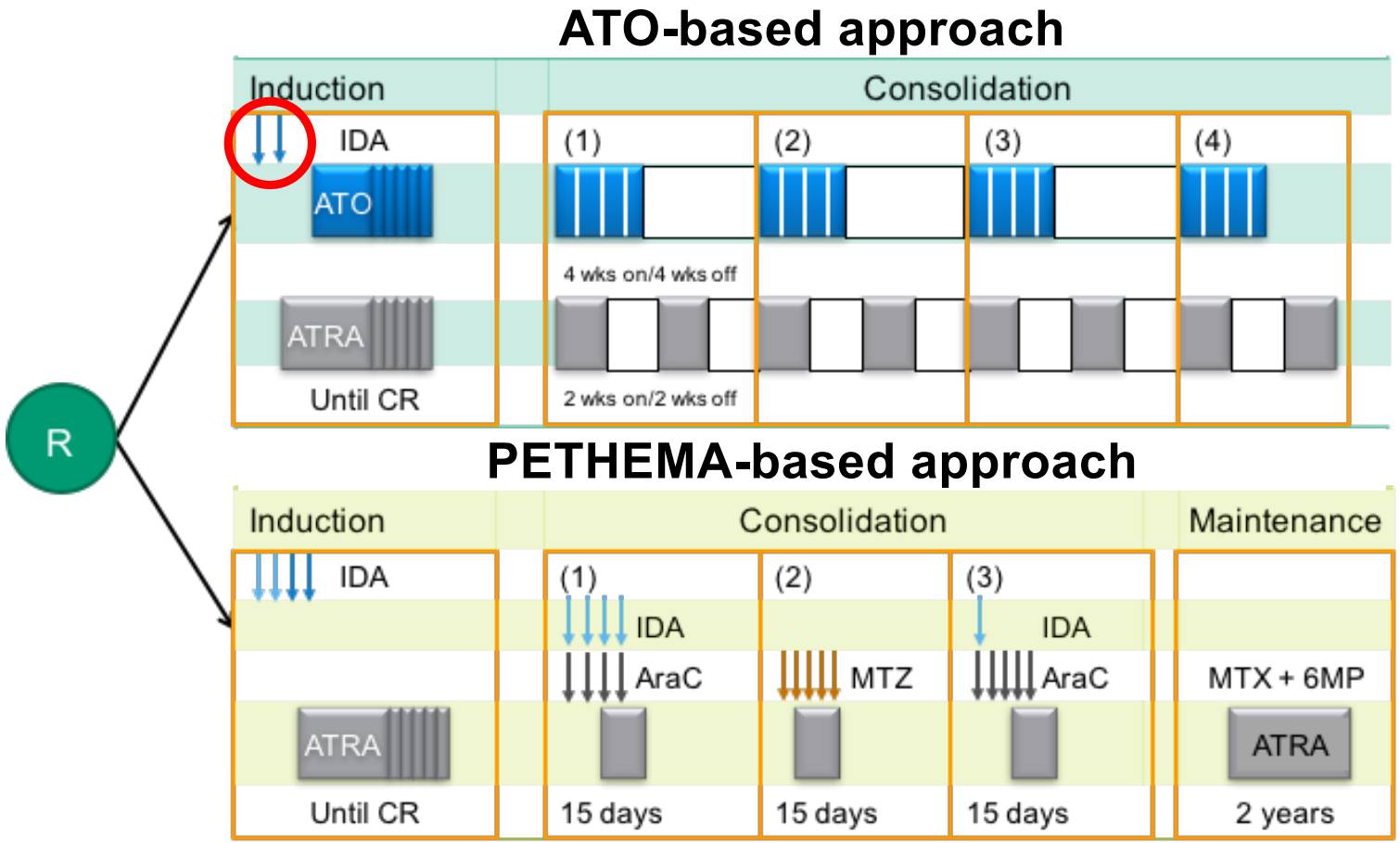
APOLLO trial
(NCT02688140)



Institutions not participating in the trial

ATO, arsenic trioxide; CHT, chemotherapy; R, randomised.

Pan-European randomized trial in high-risk APL (18-65 years old)
(APOLLO trial - NCT02688140)



International registry study in >70 years old APL

Baseline Characteristics

	CTX/ ATRA N = 260	ATO/ATRA/ ±CTX N = 177	Less intensive N = 26	P-value
Median age, years	73.5	73.6	79.6	<0.001
Median WBC (10^9/L)	2.05	1.2	2.8	<0.001
BM blasts (%)	80	70.5	82	0.006
Risk categorization[a] (%)				
Low / Intermediate	71	90	69	<0.001
High	29	10	31	

Kayser S. et al, Leukemia 2020

[a] Prognostic score of APL (Sanz Score):[1] WBC < 10.0 10^9/L (low- to intermediate-risk) vs WBC ≥ 10.0 10^9/L (high-risk)[1]. BM, bone marrow; WBC, white blood cell count. 1. Sanz MA, et al. Blood. 2009;113:1875-91.

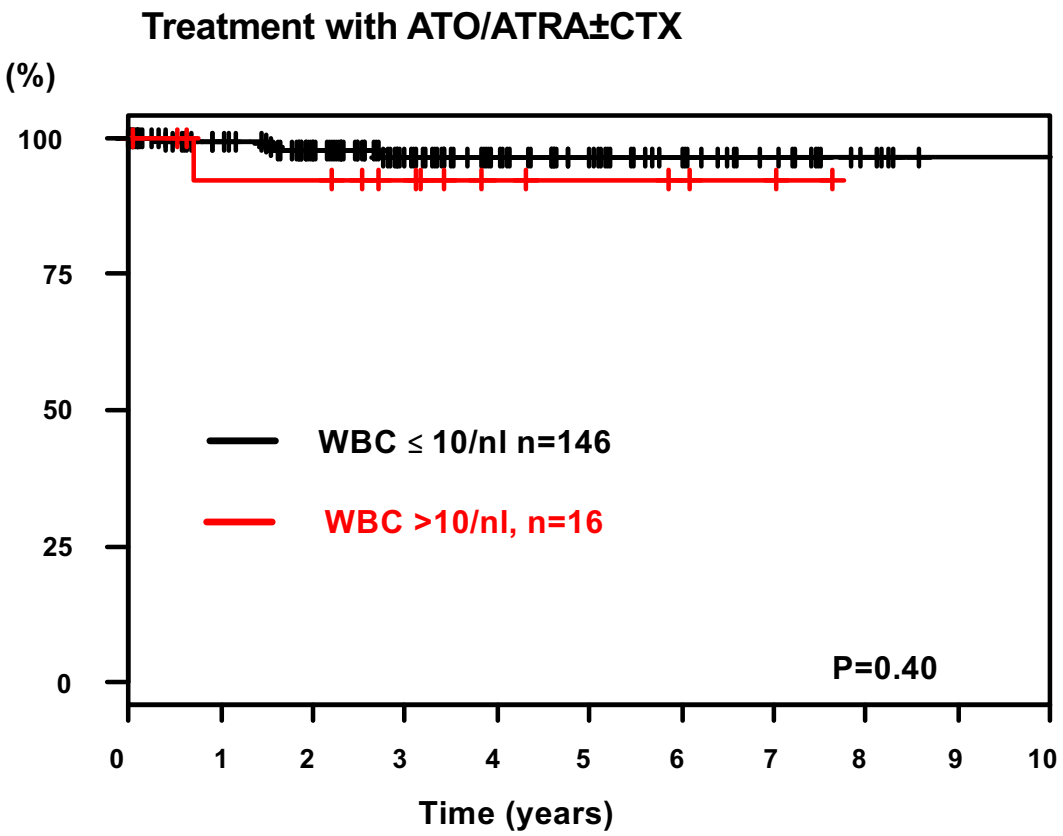
Response to Induction Therapy in >70 years old APL pts

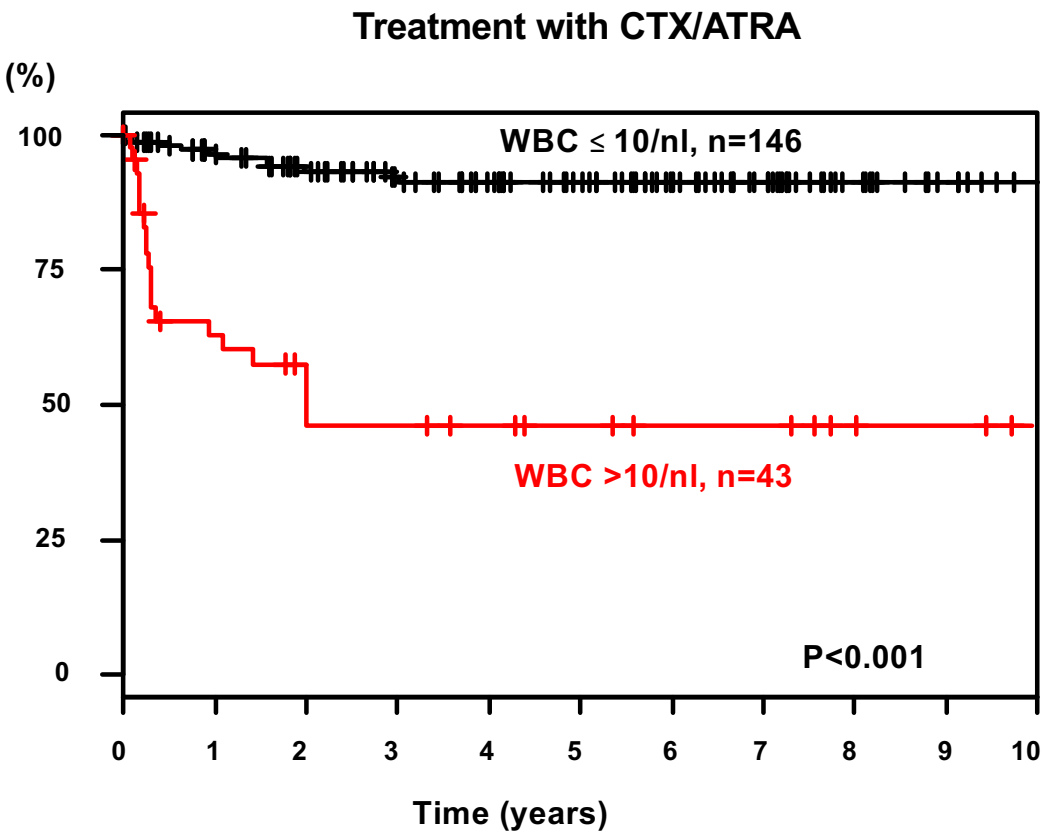
% (N)	CTX/ ATRA N = 259	ATO/ATRA/ ±CTX N = 174	Less Intensive N = 26
CR	**75** (194)	**93** (162)	**50** (13)
RD	**1** (2)	–	**4** (1)
ED*	**24** (63)	**7** (12)	**46** (12)

*** ED defined as death occurring within 43 days after treatment initiation**

Response data were available in 97% (n=459/475) patients
(missing data: CTX/ATRA, n=1; ATO/ATRA/±CTX, n=3; no treatment/unknown, n=12)
CR, complete remission; ED, early death; N, numbers; RD, refractory disease.

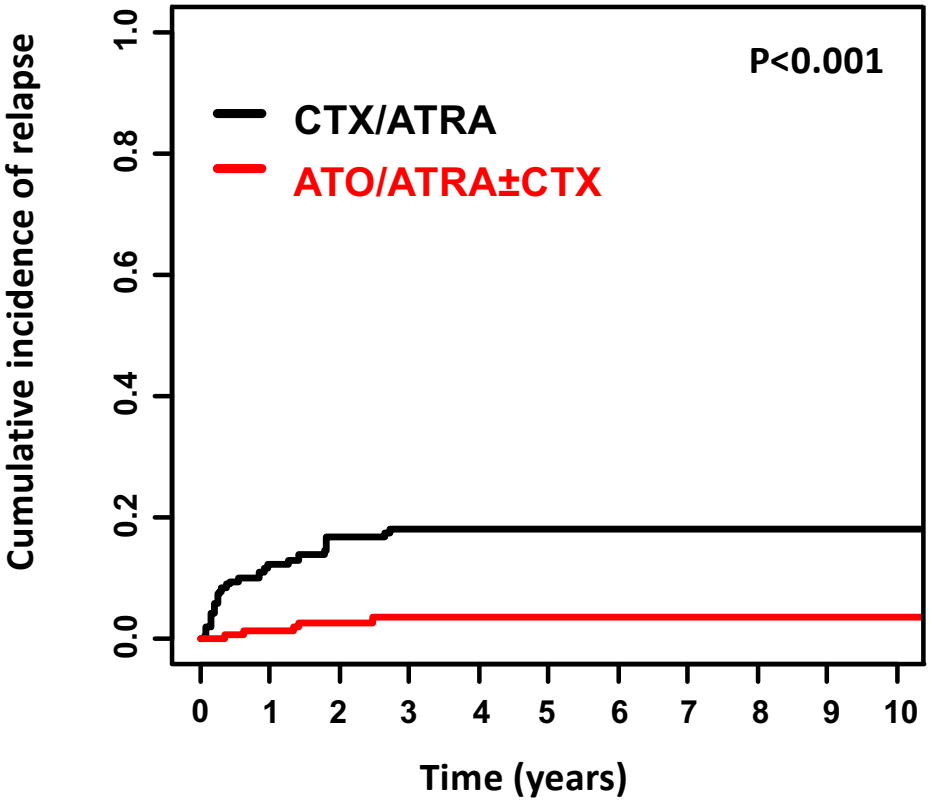
Relapse-Free Survival according to WBC Count (>70 yo)

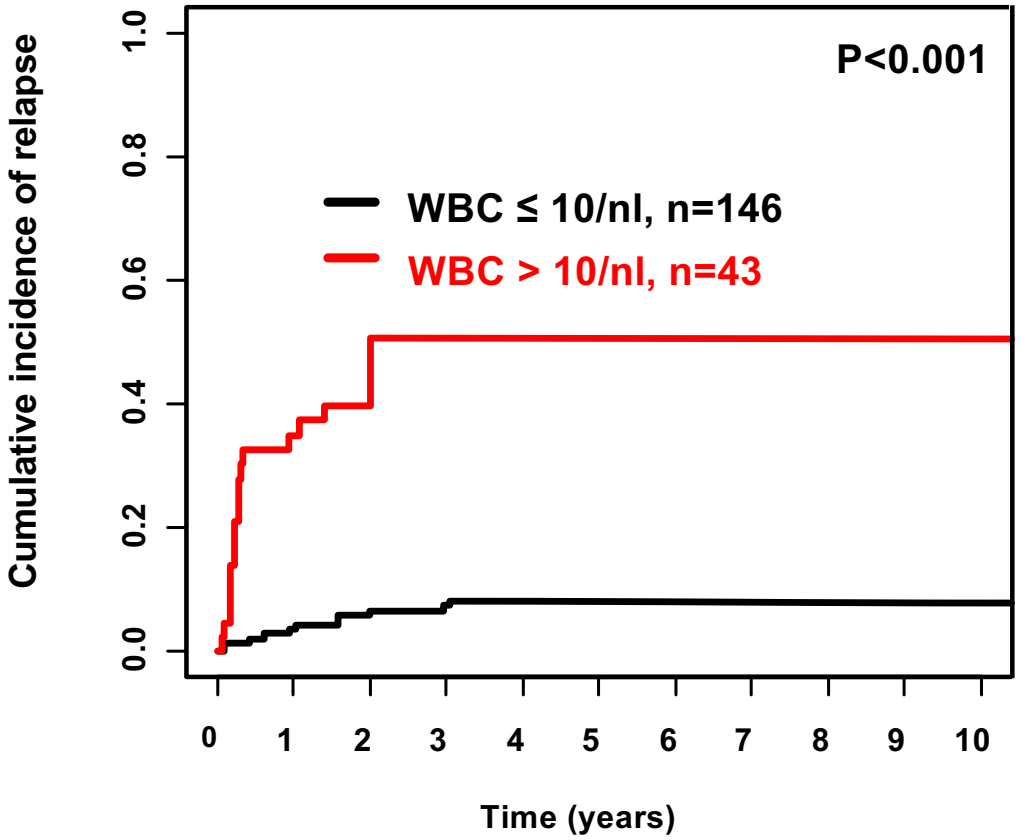




Kayser S. et al, Leukemia 2020

Cumulative Incidence of Relapse according to Treatment





Kayser S. et al, Leukemia 2020

Treatment of high-risk APL
Future directions and remaining issues

- **ATRA + ATO (+ limited CHT) could become the new standard of care**
  - **Less toxic option**
  - **Access limitations**
- Oral arsenic formulations remain a promising alternative to IV arsenic
- **Unsolved issues** in a sizable fraction of patients:
  - **Death before induction**
  - **Death during induction**
  - **Death in CR**: long-term effects of ATO not well addressed
  - **Relapse**: almost only in high-risk patients

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