Clinical significance of complex karyotype at diagnosis in Patients with Acute Promyelocytic Leukemia Treated with ATRA and chemotherapy based PETHEMA trials

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[1]PETHEMA; [2]HOVON; [3]PLAG and [4]GATLA Groups.

Background and Aims

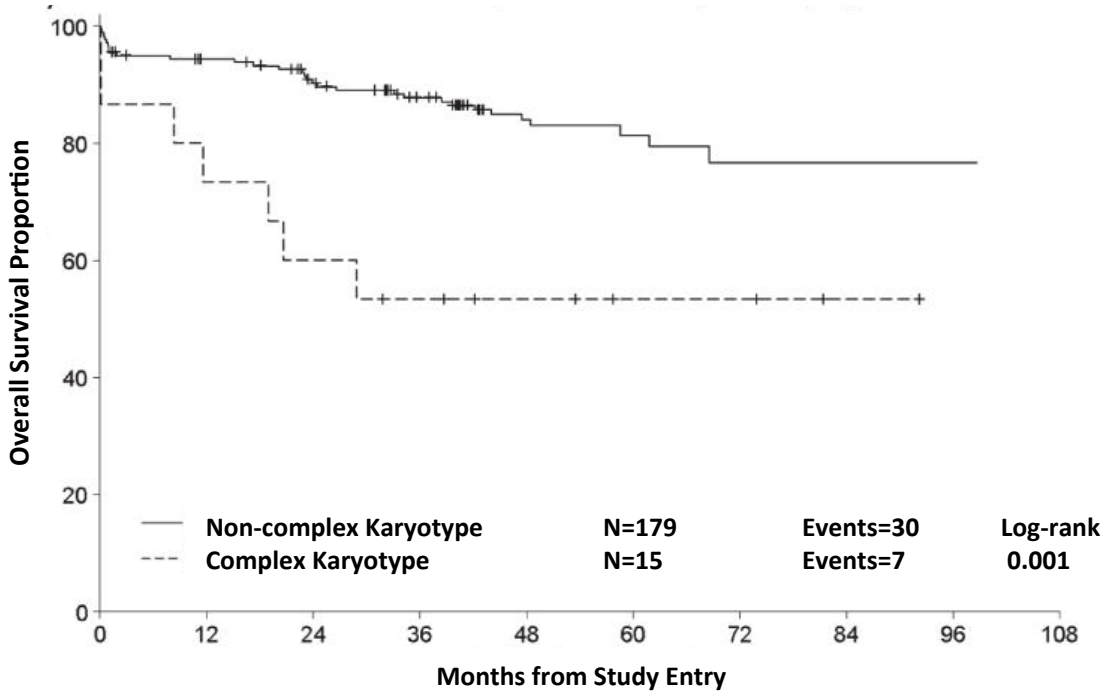
- **APL is a special case of AML in which the presence of t(15;17)/ PML-RARA predicts sensitivity to treatment with all-trans retinoic acid and arsenic trioxide.**
- **Up to 30 percent of APL patients will have chromosomal abnormalities in addition to conventional t(15;17) [1-10].**
- **The majority of studies have not shown a prognostic impact of ACA in APL patients treated with ATRA and chemotherapy-based front-line therapies [3–7, 9].**

ACA, Additional chromosomal abnormalities; APL, Acute promyelocytic leukemia; AML, Acute myeloid leukemia; ATO, Arsenic trioxide; ATRA, All-trans retinoic acid.

[1] Schoch C. Br J Haematol 1996; 94:493. [2] Hiorns LR, et al. Br J Haematol 1997; 96:314. [3] Slack JL, J Clin Oncol 1997;15:1786. [4] De Botton S, Br J Haematol 2000; 111:801. [5] Hernandez JM. Haematologica. 2001;86:807. [6] Cervera J . Haematologica. 2010;95:424. [7] Ono T. Haematologica 2011;96:174. [8] Wienick PH. Med Oncol 2012;29:2095. [9] Lou Y. Leuk Res 2013 ;37:1451. [10.] Poire X. Leuk Lymphoma 2014;55:1523.

Two studies showed an adverse outcome after ATO + ATRA front-line

- Higher relapse rate among patients with ACA[1].
- Lower CR and OS in patients with complex karyotype (i.e, 2 or more ACA)[2].



ACA, Additional chromosomal abnormalities; ATO, Arsenic trioxide; ATRA, All-trans retinoic acid. CR, Complete remission; OS, Overall survival.

[1] Lu J, et al. Zhonghua Yi Xue Za Zhi. 2008. 19;88(32):2254. [2.] Poire X. Leuk Lymphoma 2014;55:1523.

Aims

- We aim to further investigate whether a complex karyotype could be related with a higher relapse incidence in APL patients treated with PETHEMA trials.

APL, Acute promyelocytic leukemia.

Patients and methods

- Between 1996 and 2012, 1559 consecutive adult and pediatric patients were enrolled in the PETHEMA LPA 96, 99 and 2005 trials from the PETHEMA, HOVON, GATLA, and PALG groups.
- All patients with *de novo* genetic diagnosis of PML/RARa APL.
- Cytogenetic analyses in bone marrow samples at diagnosis were performed in local laboratories.
- Cytogenetic reports were available in 1128 patients (72%).

APL, Acute promyelocytic leukemia;

Patients and methods

- **Between 1996 and 2012, 1559 consecutive adult and pediatric patients were enrolled in the PETHEMA LPA 96, 99 and 2005 trials[1-4] from the PETHEMA, HOVON, GATLA, and PALG groups.**
- **All patients with *de novo* genetic diagnosis of PML/RARa APL.**
- **Treatment consisted of AIDA induction followed by risk-adapted consolidation[1-4].**

APL, Acute promyelocytic leukemia;

[1] Sanz MA. Blood 1999; 94: 3015. [2.] Sanz MA. Blood 2004; 103: 1237. [3] Sanz MA. Blood. 2008;112:3130
[4.] Sanz MA. Blood 2010; 115:5137.

Patients and methods

- **Treatment consisted of [1-4]:**

➢ **<u>Induction</u> therapy with oral ATRA (45 mg/m2/d) and intravenous idarubicin (12 mg/m2/d x4 days) followed by three courses of <u>consolidation</u> with anthracycline monochemotherapy.**

  ➢ **In the PETHEMA 99 trial ATRA was added in each cycle of consolidation for intermediate and high risk patients, according to Relapse-risk score.**

  ➢ **Ara-C was added in consolidation for high-risk patients in the LPA2005 trial.**

➢ **In all trials, <u>maintenance</u> therapy consisted of intermittent ATRA and low dose chemotherapy with methotrexate and 6-mercaptopurine.**

ATRA, All-trans retinoic acid.

[1] Sanz MA. Blood 1999; 94: 3015. [2.] Sanz MA. Blood 2004; 103: 1237. [3] Sanz MA. Blood. 2008;112:3130

[4.] Sanz MA. Blood 2010; 115:5137.

Patients and methods

INDUCTION THERAPY		Relapse Risk Group	CONSOLIDATIONTION THERAPY			MAINTENANCE THERAPY (2 years)
			Course 1	Course 2	Course 3	
ATRA 45 mg/m^2/d IDA 12 mg/m^{2}d 2, 4, 6, 8	LPA96	All groups	IDA 5 mg/m^2× 4d	MTZ 10 mg/m^2× 5d	IDA 12 mg/m^2× 1d	
ATRA 45 mg/m^2/d IDA 12 mg/m^{2}d 2, 4, 6, 8	LPA99	Low	IDA 5 mg/m^2× 4d	MTZ 10 mg/m^2× 5d	IDA 12 mg/m^2× 1d	
		Intermediate High	IDA 7 mg/m^2× 4 ATRA 45 mg/m^{2}x15	MTZ 10 g/m^2× 5 ATRA 45 mg/m^{2}x15	IDA 12mg/m^2 x2d ATRA 45 mg/m^{2}x15	
ATRA 45 mg/m^2/d IDA 12 mg/m^{2}d 2, 4, 6, 8	LPA2005	Low	IDA 5 mg/m^2× 4d ATRA 45 mg/m^{2}x15	MTZ 10 mg/m^2× 5d ATRA 45 mg/m2x15	IDA 12 mg/m^2× 1d ATRA 45 mg/m2x15	
		Intermediate High	IDA 5 mg/m^2× 4d ATRA 45 mg/m^{2}x15 Ara-C (Hish risk)	MTZ 10 mg/m^2× 5d ATRA 45 mg/m^{2}x15	IDA 12 mg/m^2× 1d ATRA 45 mg/m^{2}x15 Ara-C (Hish risk)	

Treatment schedule of the LPA96, LPA99 and LPA2005 PETHEMA trials. Ara-C, cytarabine; ATRA, all-trans retinoic acid; IDA, idarubicin; MTZ, mitoxantrone.

[1] Sanz MA. Blood 1999; 94: 3015. [2.] Sanz MA. Blood 2004; 103: 1237. [3] Sanz MA. Blood. 2008;112:3130

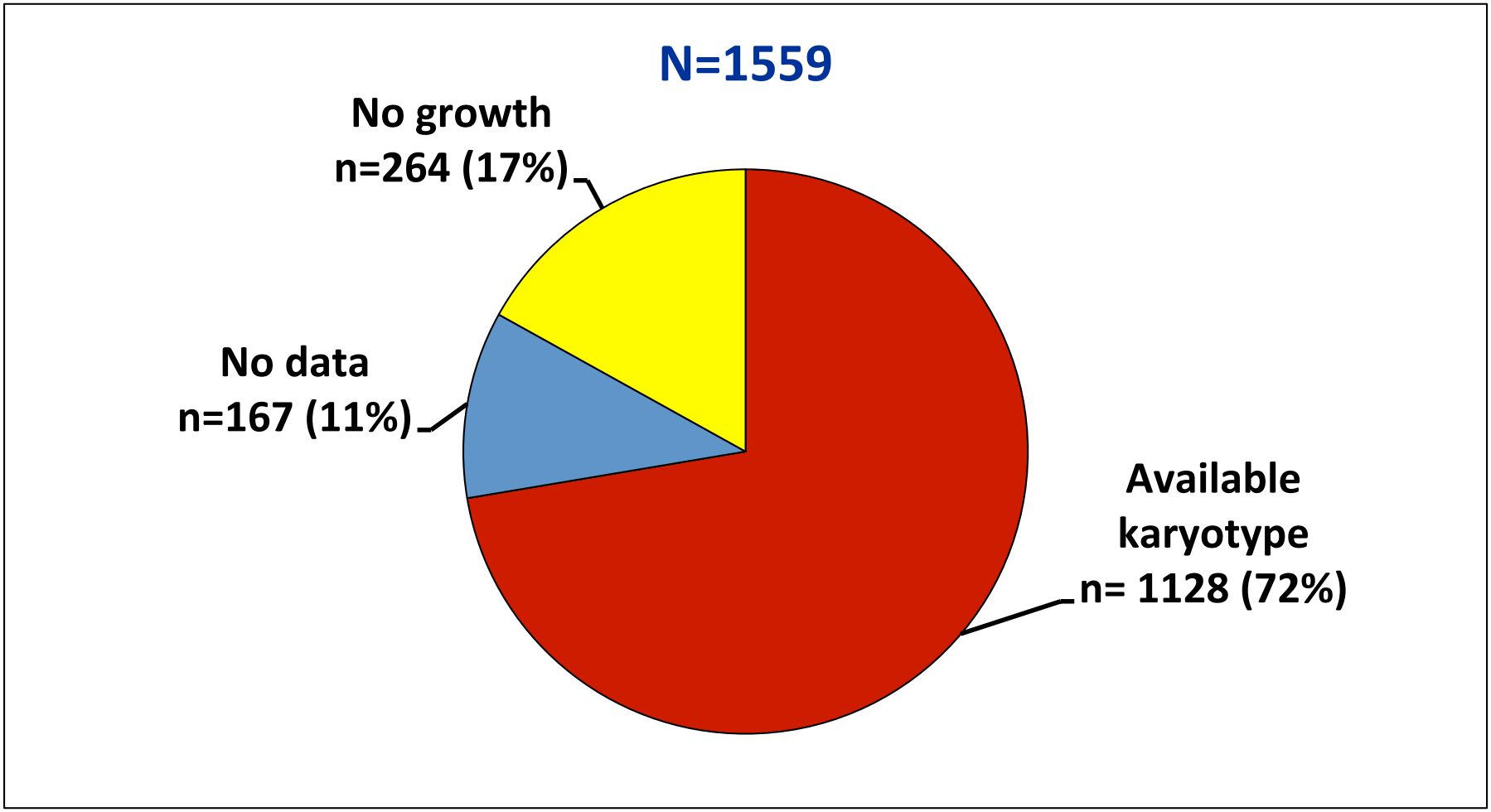
[4.] Sanz MA. Blood 2010; 115:5137.

Patients and methods

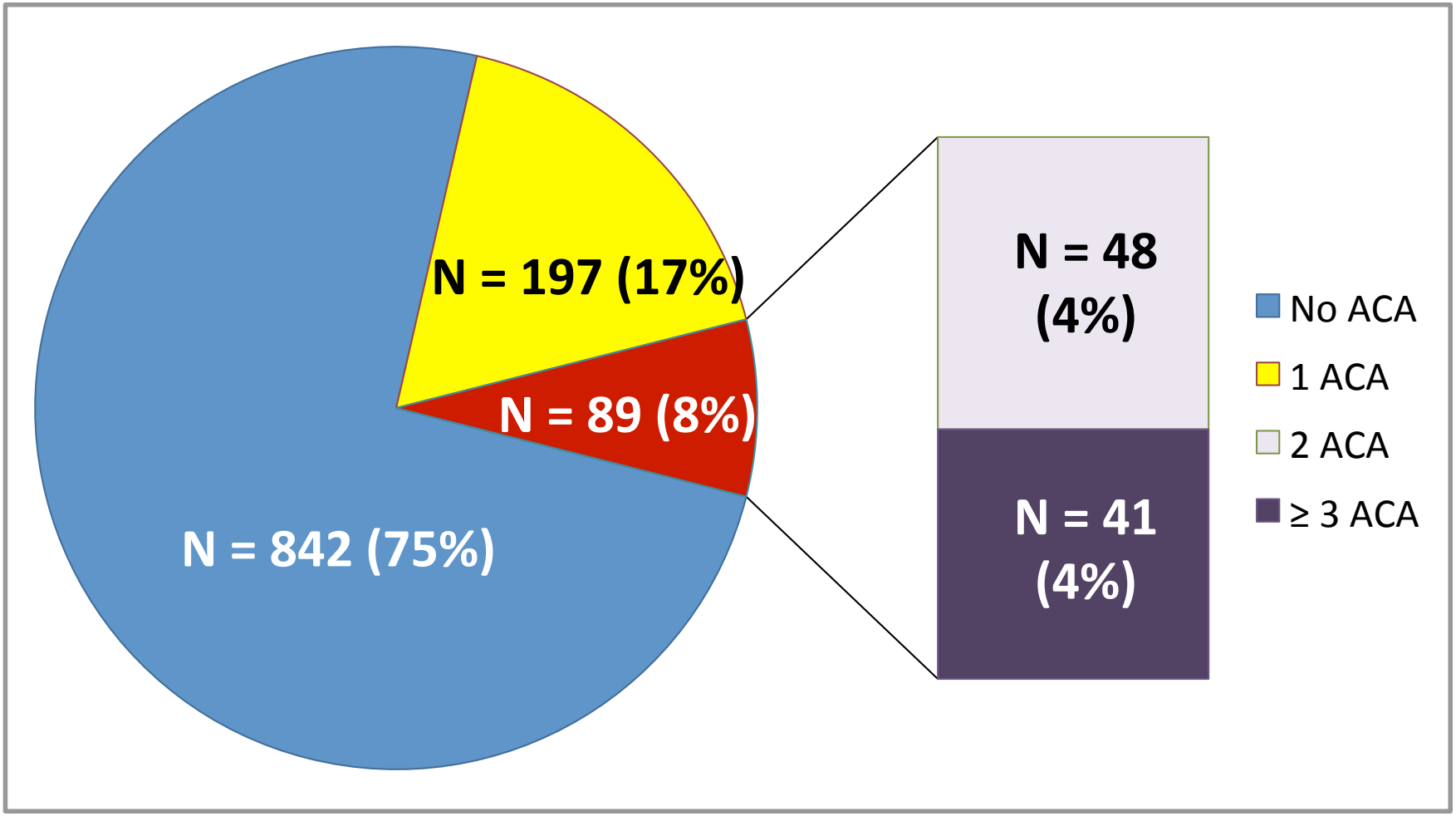
- Cytogenetic analyses in bone marrow samples at diagnosis were performed in local laboratories.
- Additional chromosomal abnormalities (ACA) were classified as follows:
  - Normal karyotype / t(15;17) alone were considered as no ACA.
  - Multiple rearrangements (i.e., triple rearrangements involving chromosome 15/17 and other) were considered as 1 ACA.
  - Abnormalities detected in FISH were considered as ACA.
- Complex karyotype: ≥2 ACA.
- Very complex karyotype: ≥3 ACA.

ACA, Additional chromosomal abnormalities. FISH, Fluorescence *in situ* hybridation.

Available cytogenetic report

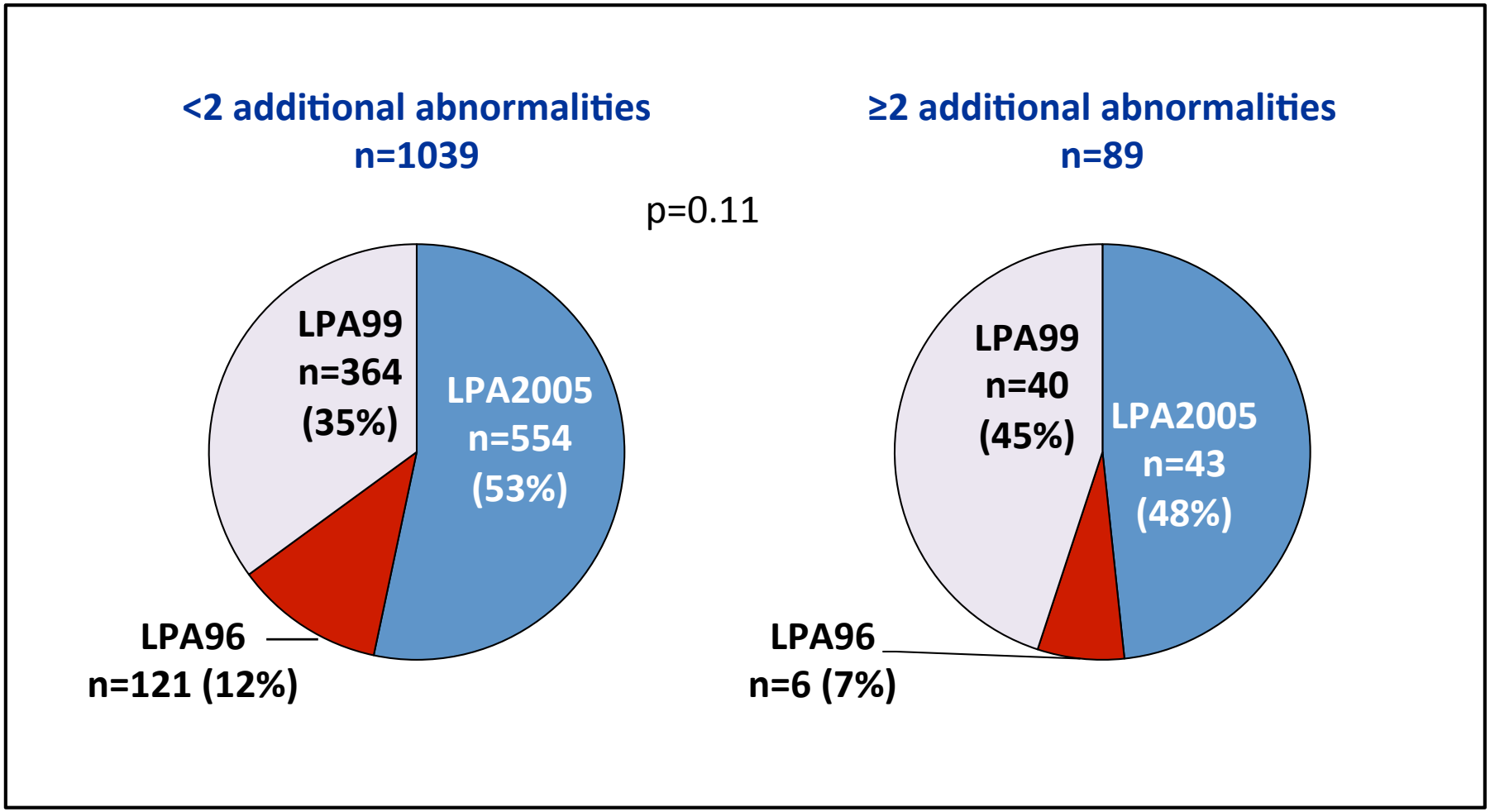


Incidence of Additional Chromosomal Abnormalities n=1128



APL, Acute promyelocytic leukemia; ACA, Additional Chromosomal Abnormalities.

Distribution of complex karyotype patients according to PETHEMA trial



APL, Acute promyelocytic leukemia.

Baseline characteristics of patients according to presence of complex karyotype

Characteristic	0-1 ACA N (%)	≥2 ACA N (%)	P-value
Overall	1039 (92)	89 (8)	
Age, years (median, range)	42 (2-84)	40 (3-78)	0.18
Male gender	531 (51)	46 (52)	0.98
WBC count ≥ 10 x 10^9/L	287 (28)	19 (21)	0.31
Platelet count ≤ 40 x 10^9/L	780 (75)	70 (79)	0.55
Relapse-risk group			0.10
Low	210 (20)	13 (15)	
Intermediate	542 (52)	57 (64)	
High	287 (28)	19 (21)	

ACA, Additional Chromosomal Abnormalities; WBC, White blood cell.

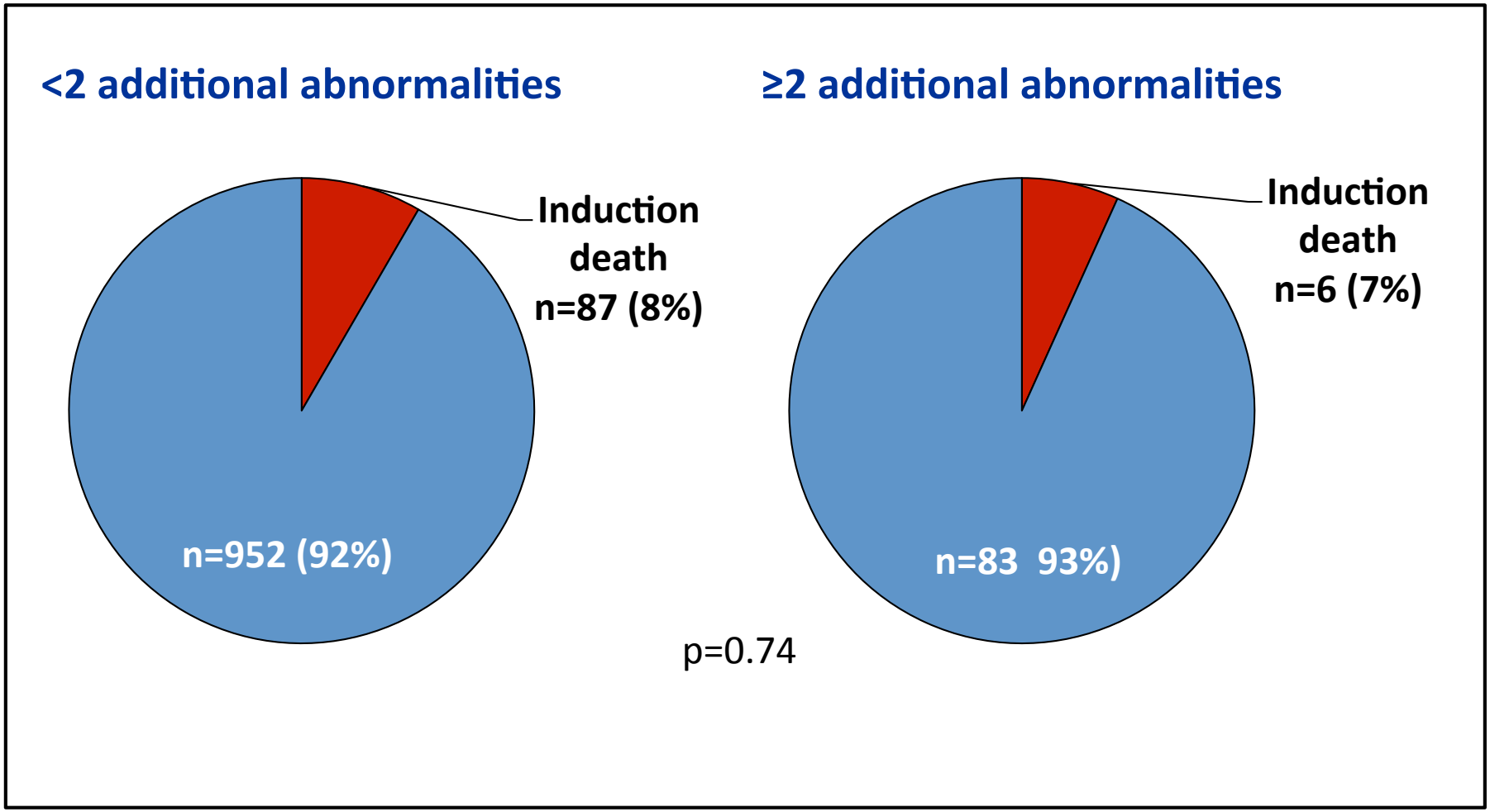
Baseline characteristics of patients according to presence of complex karyotype

Characteristic	0-1 ACA N (%)	≥2 ACA N (%)	P-value
Overall	1039 (92)	89 (8)	
Creatinine ≥ 1,3 mg/dL	36 (4)	1 (1)	0.39
ECOG <2	744 (79)	69 (82)	0.29
Albumin < 3,5 g/dL	171 (20)	10 (13)	0.21
Microgranular morphologic subtype	180 (18)	13 (15)	0.59
BCR3 isoform	355 (39)	38 (49)	0.17
CD34 + (>10%)	211 (25)	10 (14)	0.04

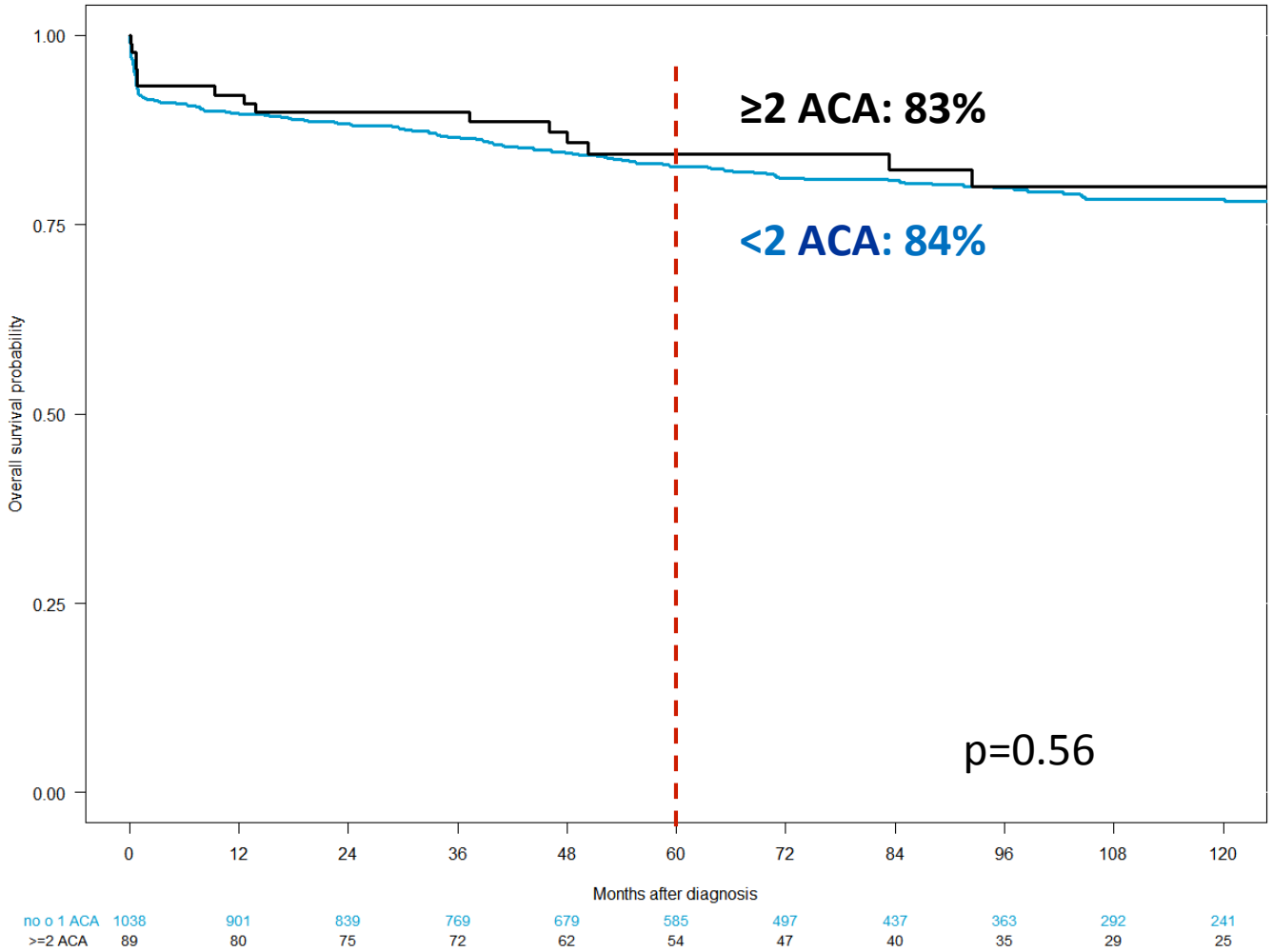
ACA, Additional Chromosomal Abnormalities; WBC, White blood cell.

The only clinical or biological characteristic associated with a complex karyotype was CD34 antigen negativity in leukemic blasts.

Induction death rate

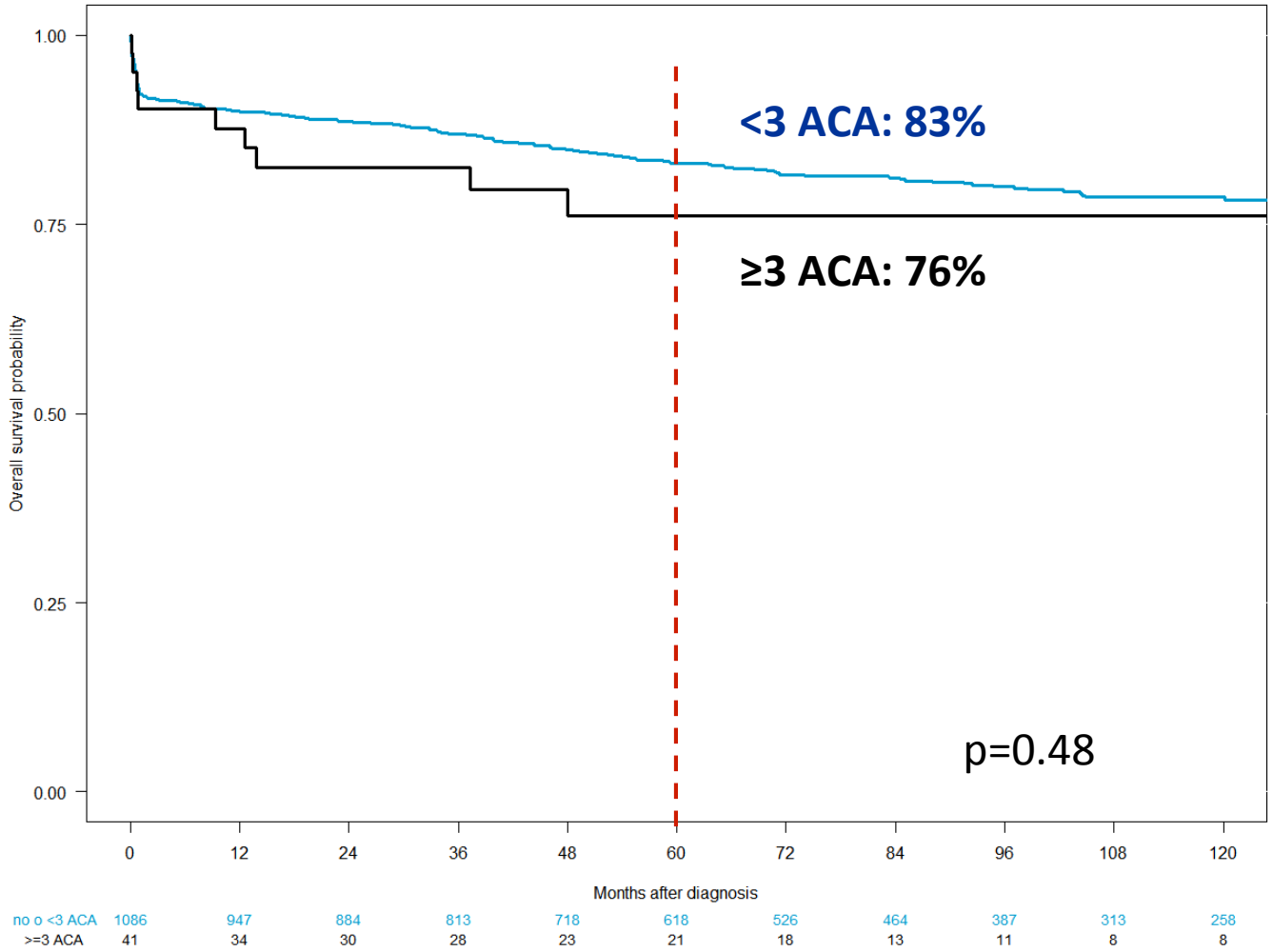


Overall survival
<2 ACA vs CK (≥2 ACA)



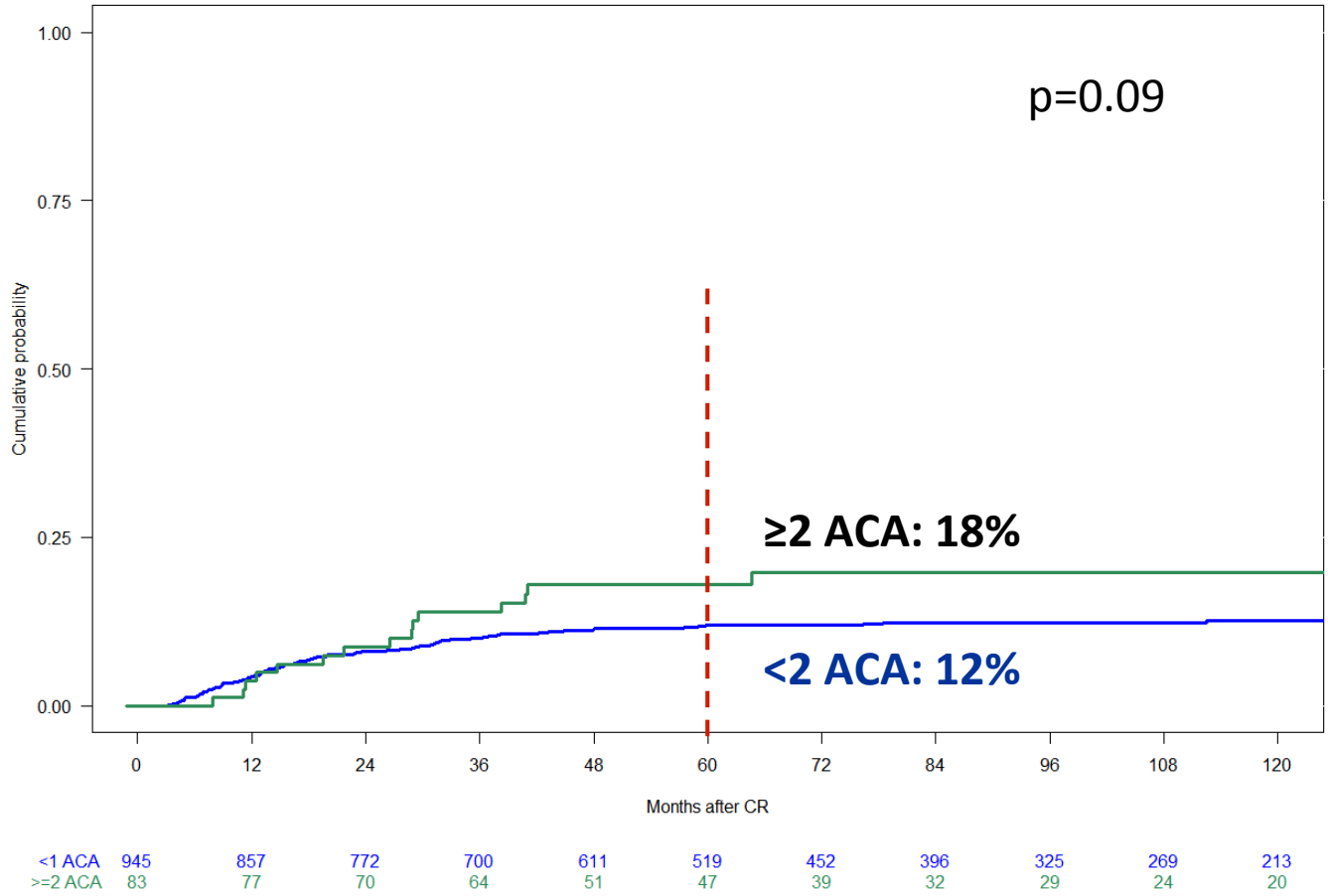
ACA, additional cytogenetic abnormalities; CK, Complex karyotype (2 or more additional abnormalities).

Overall survival
<3 ACA vs very complex karyotype (≥3 ACA)



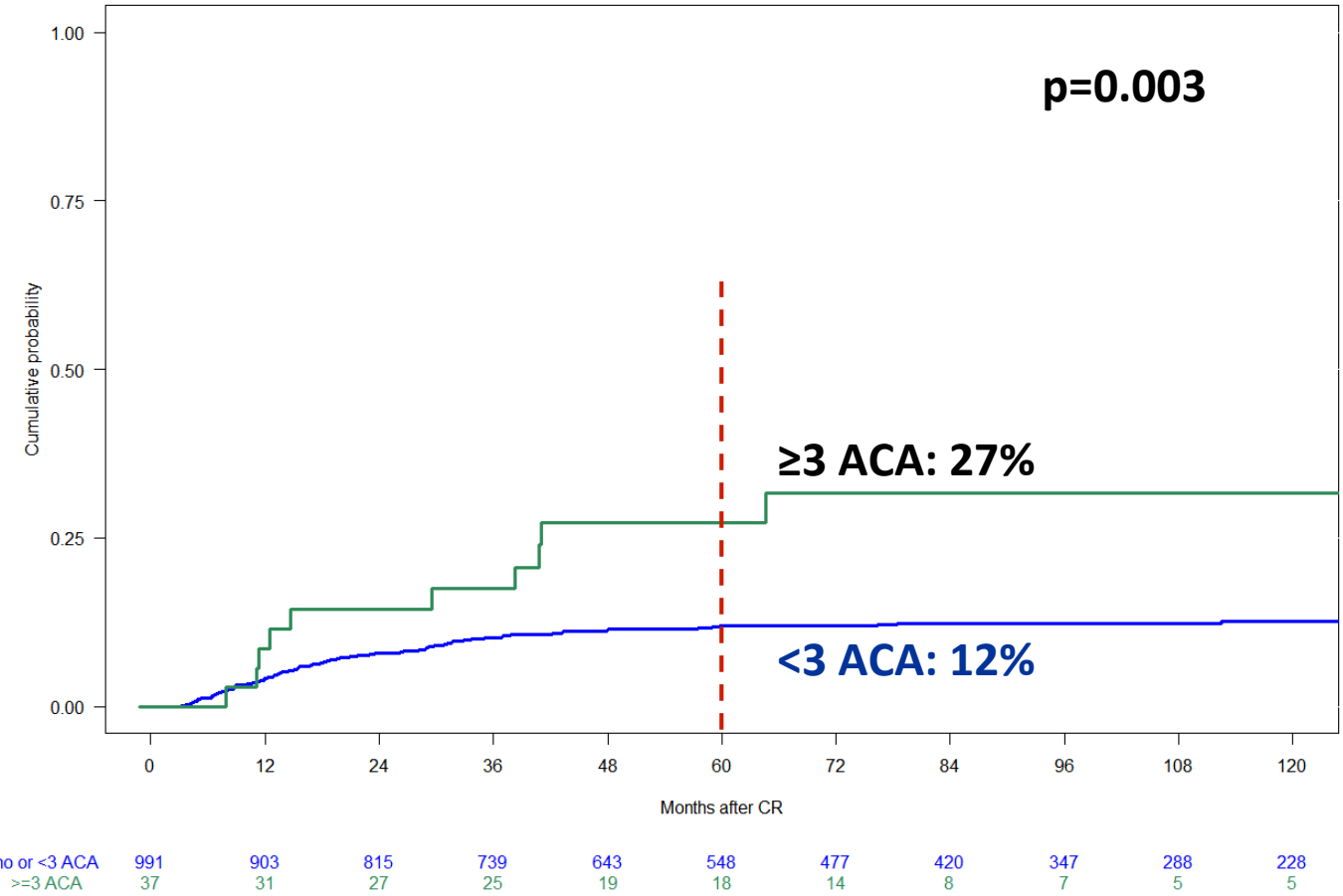
ACA, additional cytogenetic abnormalities.

Cumulative incidence of relapse
<2 ACA vs CK (≥2 ACA)



ACA, additional cytogenetic abnormalities.

Cumulative incidence of relapse
<3 ACA vs very complex karyotype (≥3 ACA)



ACA, additional cytogenetic abnormalities.

Cumulative incidence of relapse
Multivariate analysis

Variable	*P* – multivariate	HR (95% CI)
Female gender	.008	0.6 (0.4-0.9)
Higher relapse-risk group	<.0001	2.1 (1.5-2.9)
Very Complex karyotipe (≥3 ACA)	.0009	2.7 (1.5-4.9)
PETHEMA LPA96&99 trials	0.05	1.4 (1,0-2,1)

ACA, Additional Chromosomal Abnormalities.

Conclusions

- This study shows, for the first time, an increased risk of relapse among patients with very complex karyotype (at least 3 additional abnormalities) among APL patients treated with ATRA plus chemotherapy front-line regimens.
- However, this increased risk of relapse did not influence on CR and OS.
- It should be noted that only 4% of patients with an evaluable cytogenetics had a very complex karyotype.

APL, Acute promyelocytic leukemia; ATRA, All-trans retinoic acid; CR, Comlete remission; OS, Overall survival.

Acknowledgements

All the participating institutions of the PETHEMA, HOVON, GATLA and PALG groups