Clinical significance of CD56 expression in patients with *de novo* acute promyelocytic leukemia treated with the PETHEMA LPA96, LPA99 and LPA2005 protocols: an updated analysis.

Boluda B, Montesinos P, Bernal T, Vellenga E, Brunet S, González J, González M, Holowiecka A, Esteve J, Bergua J, González JD, Gil C, Tormo M, Salamero O, Manso F, Milone G, de la Serna J, Moreno MJ, Pérez-Encinas M, Krsnik I, Ribera JM, Escoda L, Lowenberg B, Sanz MA.

On behalf of the PETHEMA, HOVON, PALG, and GATLA cooperative groups

Background

Higher relapse rate reported among APL patients with CD56 expression treated with chemo plus ATRA based protocols

	Murray et al	Ferrara et al	Montesinos et al	Breccia et al
Patients (n)	12	100	651	114
CD56(+) APL (%)	-	15	11	8
Induction death (CD56(+) vs (-) APL, %)	50 vs 16*	13 vs 6	15 vs 8*	-
5y CIR (CD56(+) vs (-) APL, %)	-	-	22 vs 10*	36 vs 11*
5y OS (CD56(+) vs (-) APL, %)	↓	62 vs 86*	78 vs 84	60 vs 85*

*p<0.05

Murray et al. Journal of Clinical Oncology 1999
Ferrara et al. Journal of Clinical Oncology 2000
Montesinos et al. Blood 2011
Breccia et al. Leukemia Research 2014

Aims

To corroborate the adverse impact of CD56 expression in patients with non-secondary *de novo* APL, homogeneously treated with three consecutive multicenter PETHEMA trials, in a larger series with prolonged follow-up

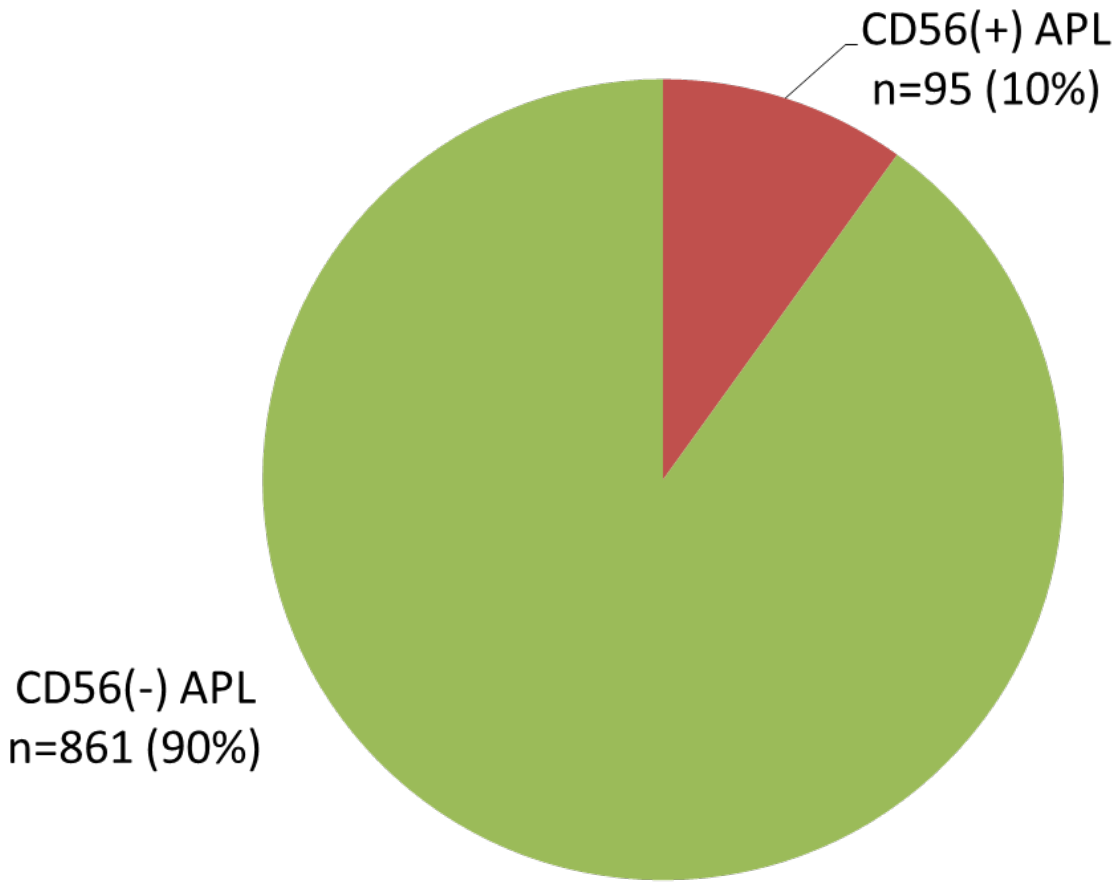
Material and Methods

- Between 1996 and 2012, 1572 consecutive adult and pediatric patients with *de novo* genetic diagnosis of PML/RARa APL were enrolled in the PETHEMA LPA96, LPA99, and LPA2005 trials
- CD56 expression was analyzed on bone marrow samples in local laboratories and was available on 956 patients (61%)
- Positivity cut-off for CD56: ≥20% of expression

Material and Methods

- Induction therapy: AIDA schedule
- Consolidation therapy:
  - LPA96 trial: 3 courses with anthracycline
  - LPA99/LPA2005 trials: risk adapted strategy
- Maintenance therapy: 2 years with ATRA and low dose chemotherapy with 6-MP + MTX

Results
Frequency of CD56(+) APL



Demographic and baseline characteristics

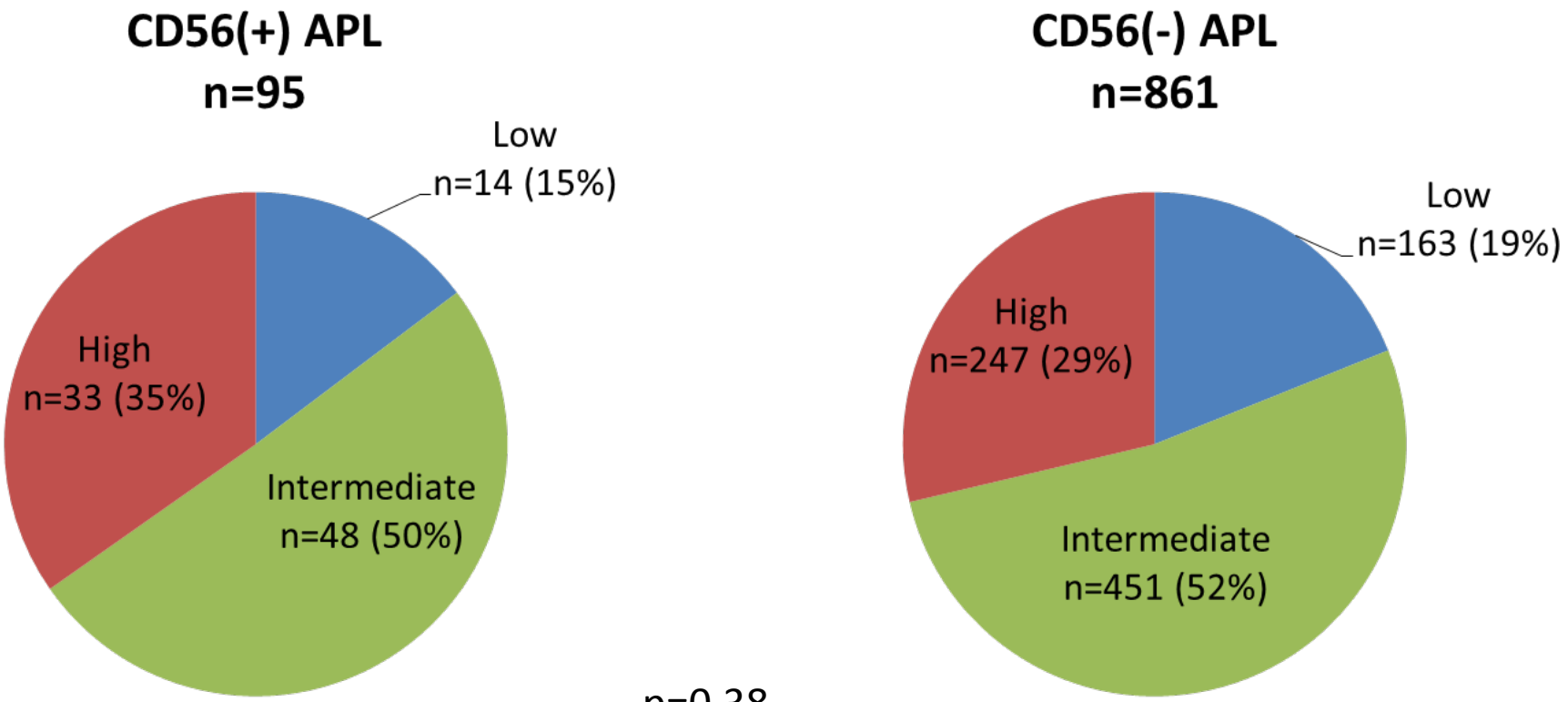
	CD56(+) APL n=95		CD56(-) APL n=861		P value
	Mean (range)	n (%)	Mean (range)	n (%)	
Age (years)	42 (5-79)		40 (2-81)		0.27
Male gender		45 (47)		455 (53)	0.38
ECOG <2		58 (67)		639 (80)	0.008
WBC count 10^9/L	3.8 (0.5-162)		2.6 (0.1-460)		0.005
Albumin levels (g/dL)	3.8 (2.1-5.7)		4 (1.7-6)		0.02
BCR3 isoform		50 (64)		291 (40)	<0.001
FLT3-ITD positive		13 (38)		68 (26)	0.22
Microgranular morphologic subtype		24 (26)		162 (19)	0.19

Immunophenotype findings according to CD56(+)

	CD56(+) APL n=95	CD56(-) APL n=861	P value
	n (%)	n (%)	
CD2 ≥20%	30 (41)	173 (24)	0.002
CD7 ≥20%	10 (14)	33 (5)	0.002
CD34 ≥10%	44 (50)	181 (22)	<0.001
HLA-DR ≥20%	12 (15)	47 (6)	0.004
CD117 ≥20%	69 (88)	574 (78)	0.035
CD15 ≥20%	34 (42)	187 (25)	0.001

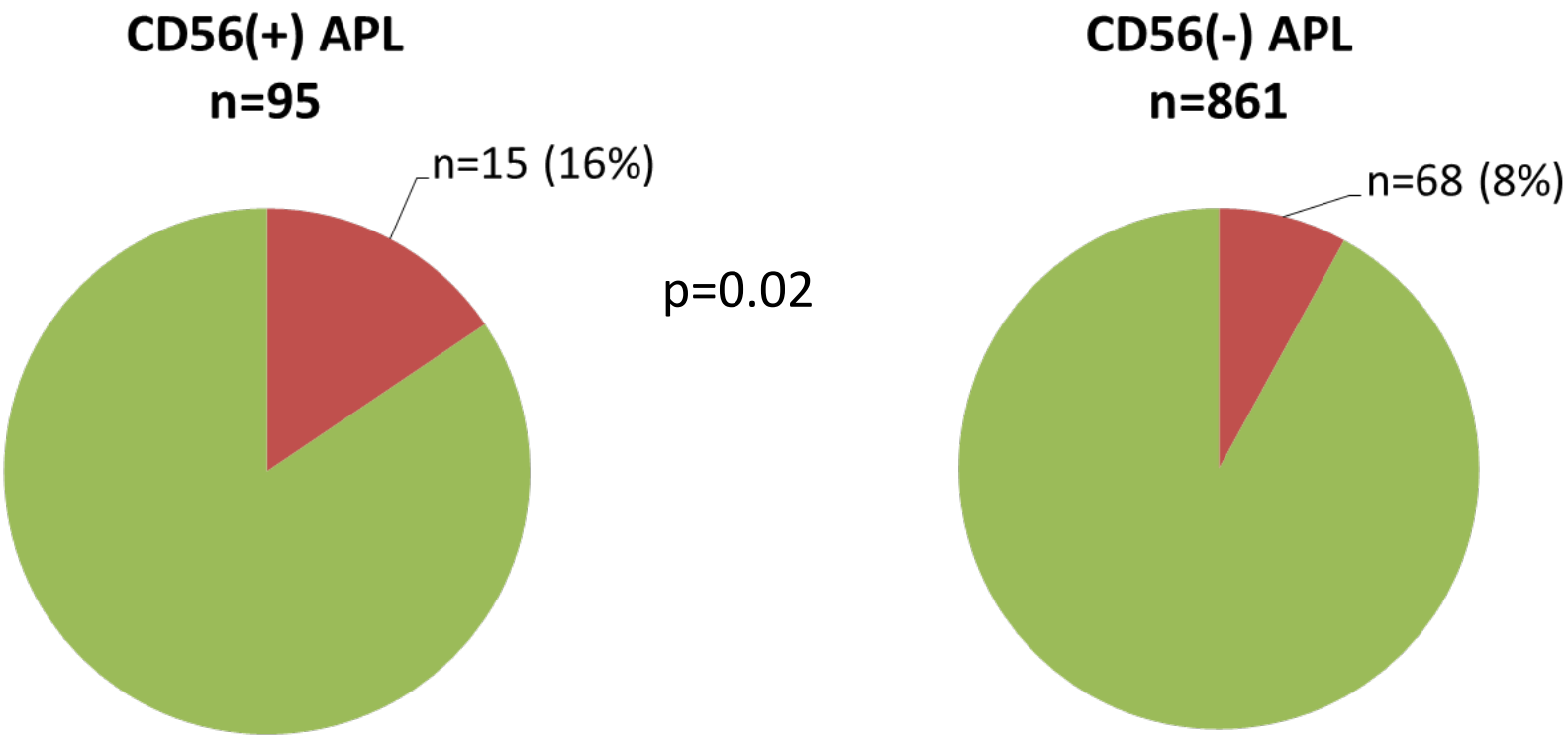
CD56(+) APL was significantly associated with the coexpression of CD2, CD34, CD7, HLA-DR, CD15, and CD117 antigens

No difference in the relapse risk-score

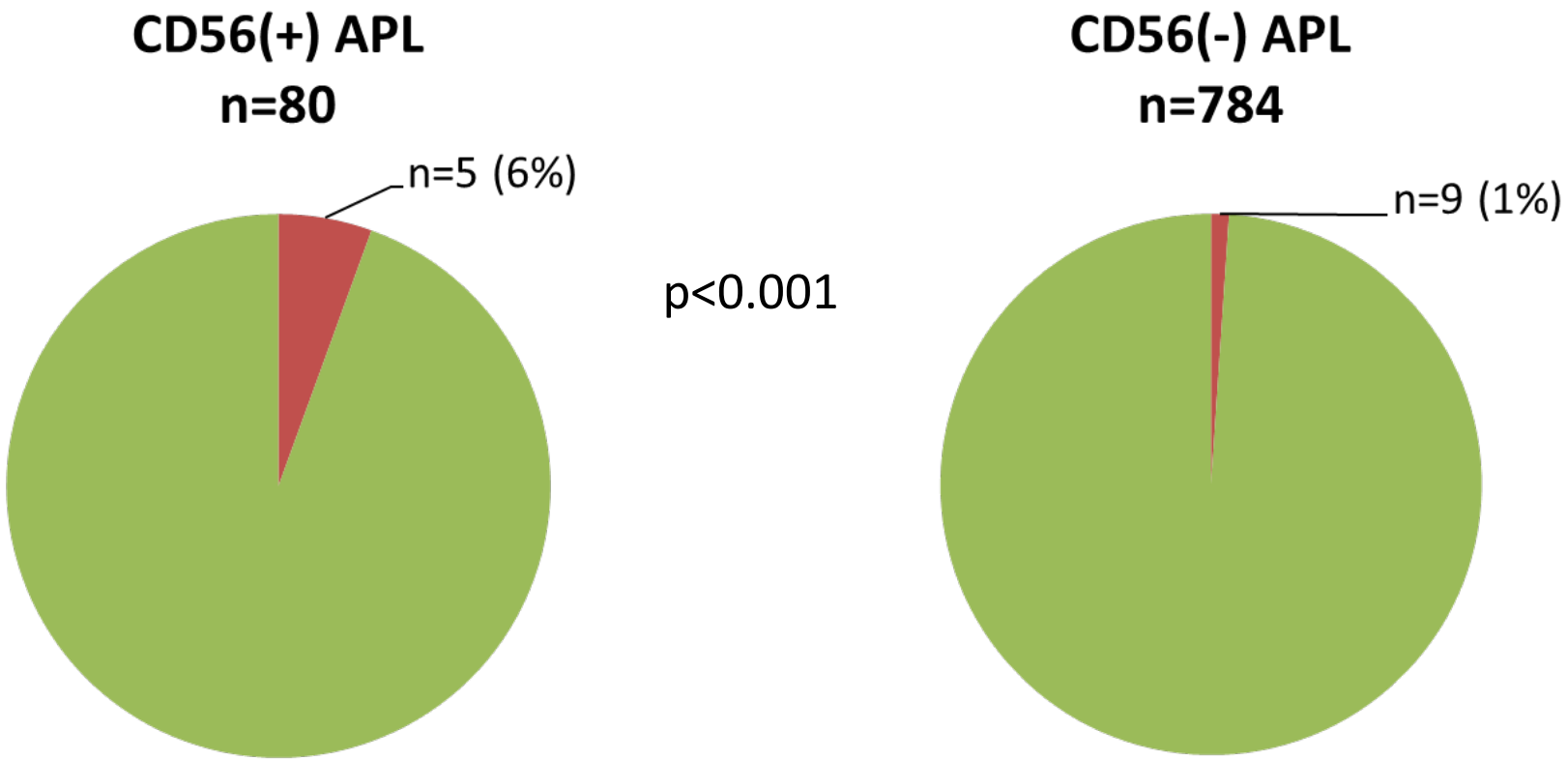


p=0.38

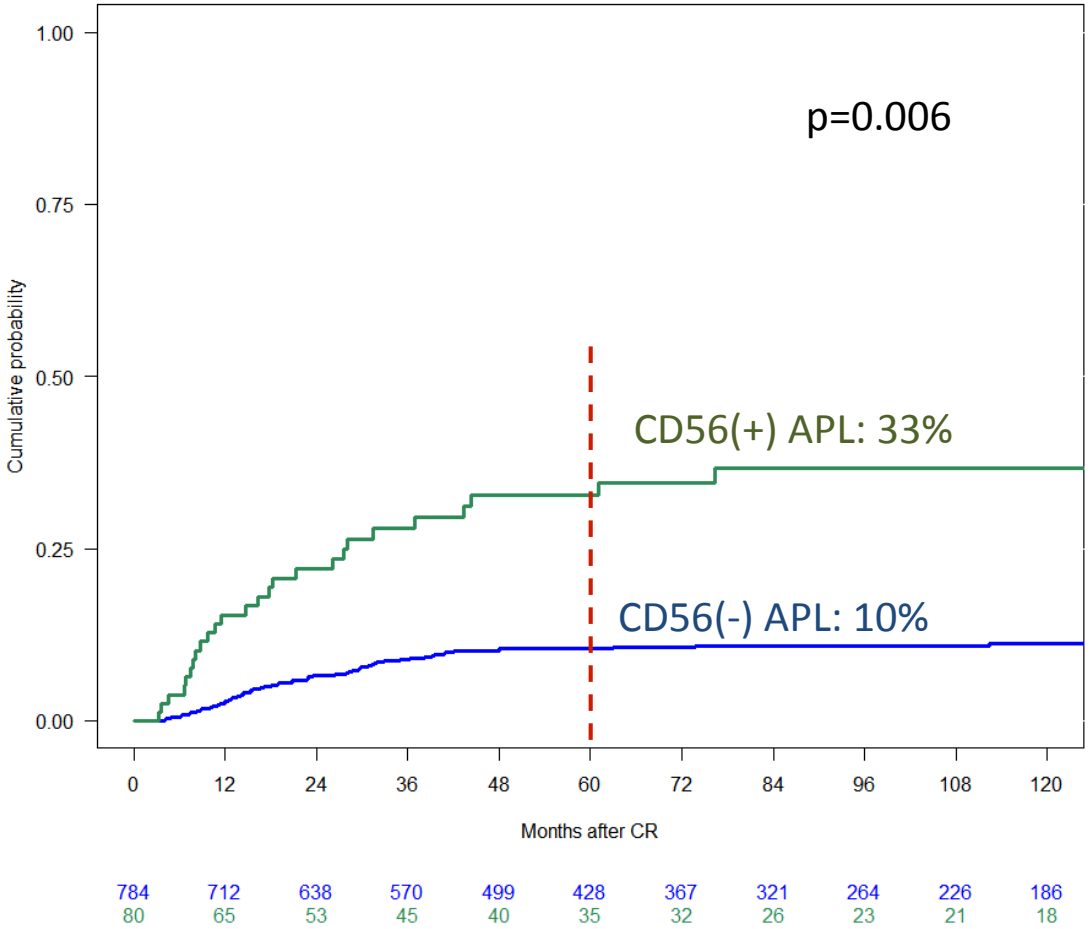
Outcome
Induction death rate



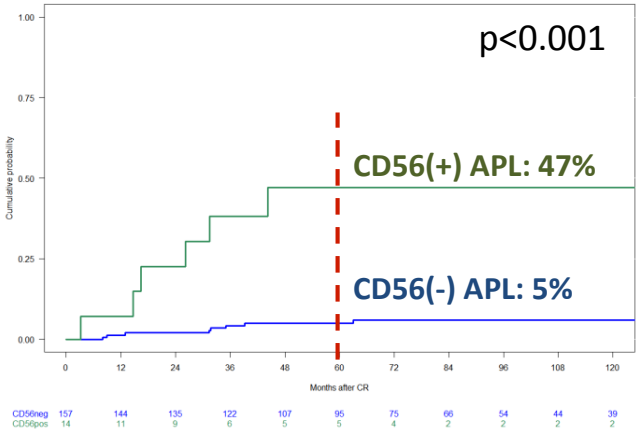
Outcome
Central nervous system relapse



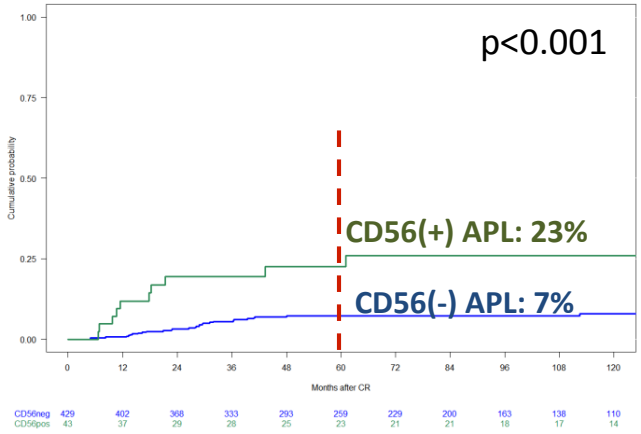
CIR according to CD56 expression
All patients



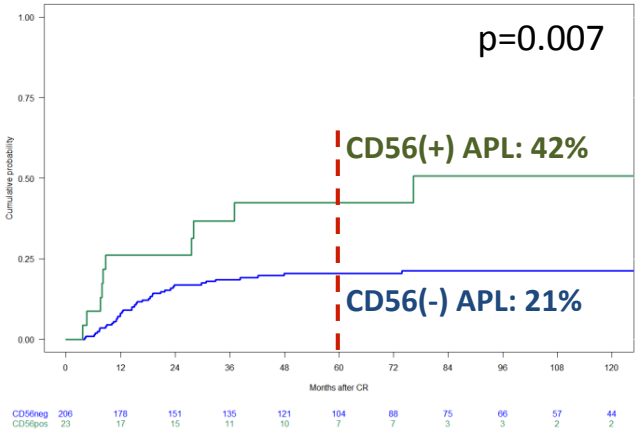
CIR according to CD56 expression
Relapse-risk score group



Low relapse-risk



Intermediate relapse-risk

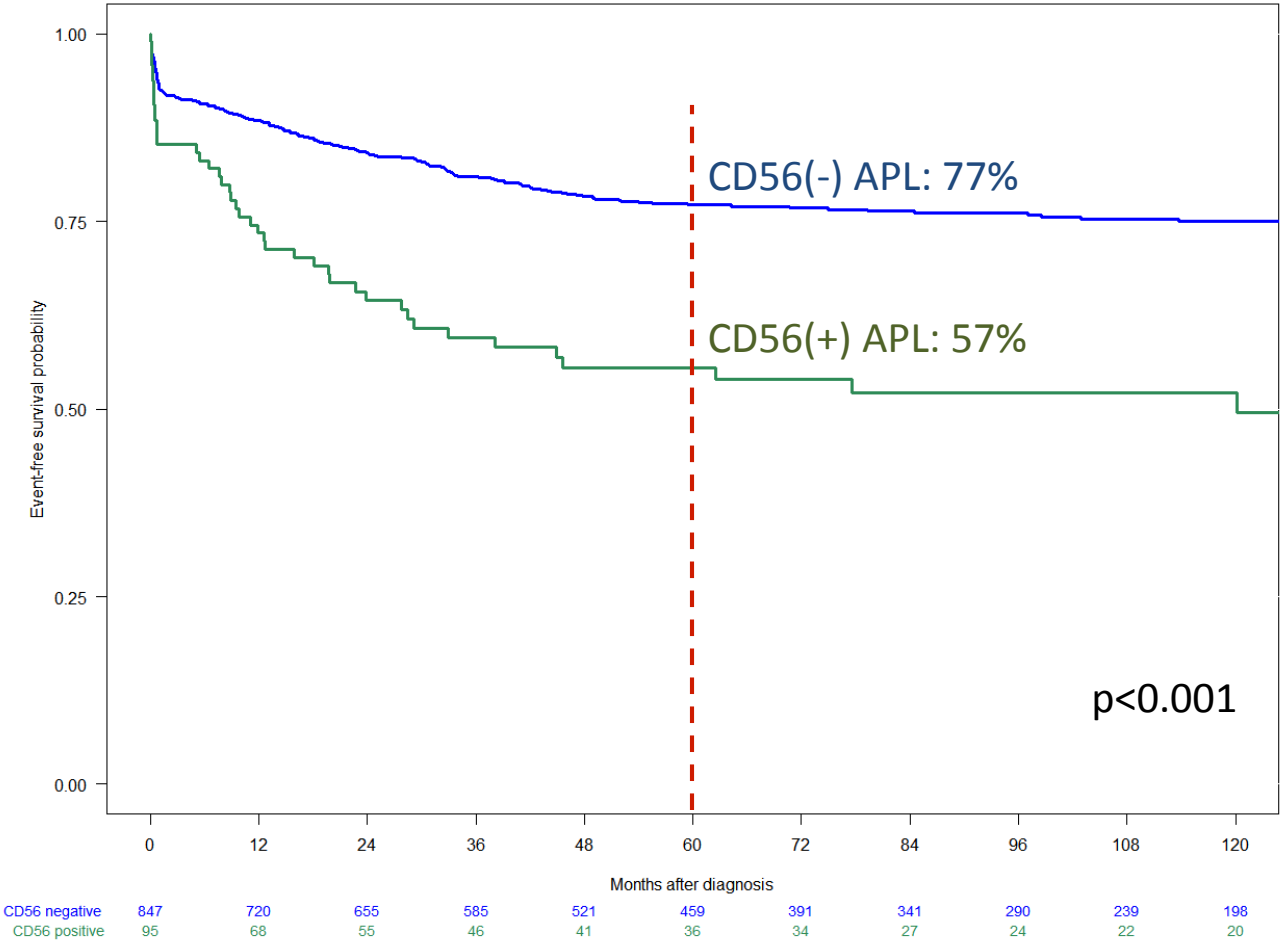


High relapse-risk

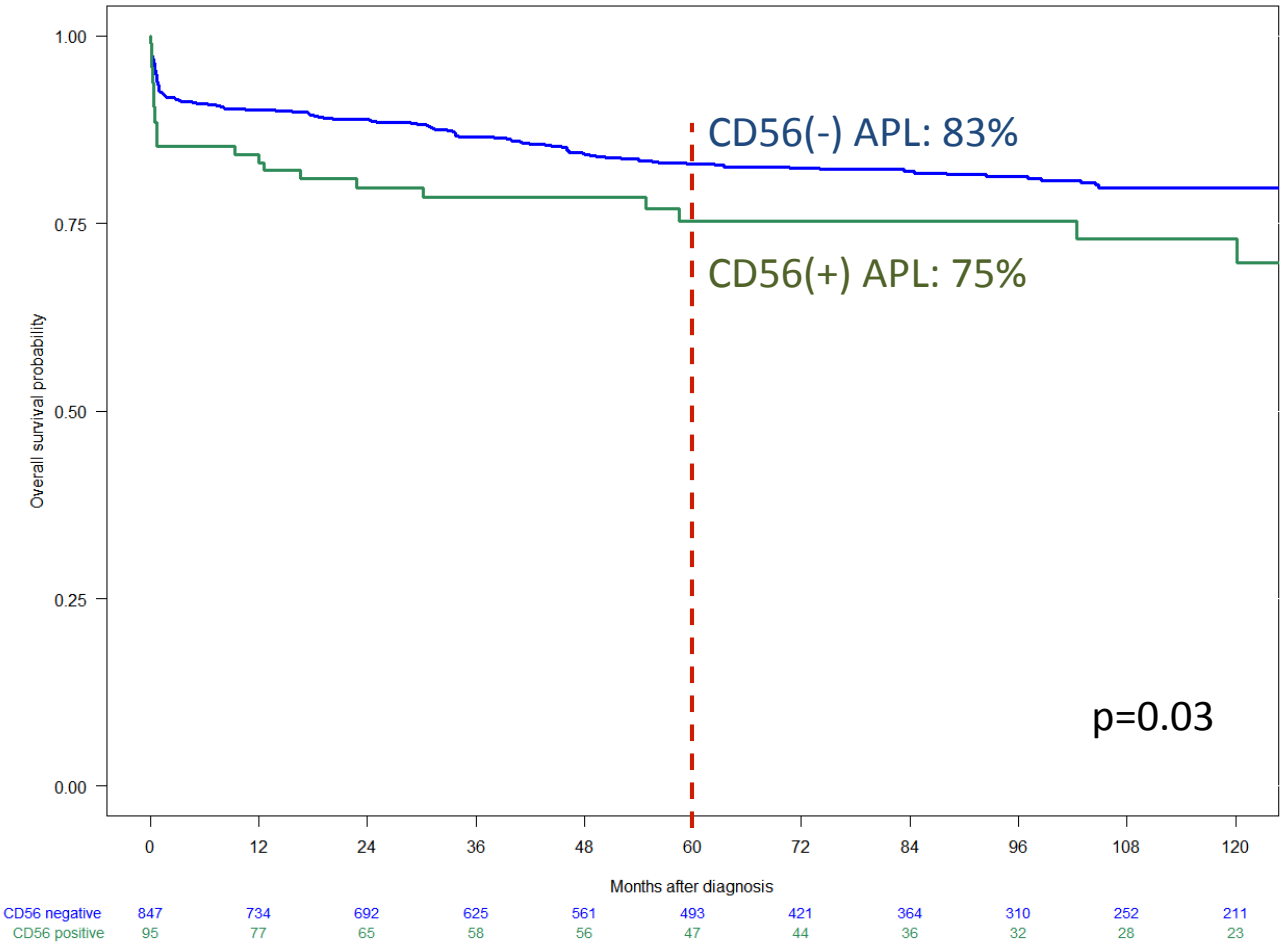
Cumulative incidence of relapse
Multivariate analysis

Risk factor	HR (IC 95%)	P value
CD56 expression ≥20%	3.9 (2.5-6.3)	<0.0001
High relapse-risk score	2 (1.4-2.9)	0.001
Female gender	0.6 (0.5-1)	0.05

Event-free survival according to CD56 expression



Overall survival according to CD56 expression



Conclusions

- This study confirms the relevance of CD56 expression as an independent adverse prognostic factor for relapse in patients with APL, treated with ATRA plus idarubicin-derived regimens
- This marker was incorporated in the AIDA-based LPA2012 trial for implementing risk-adapted consolidation in APL
- The prognostic relevance of CD56 expression under chemo-free regimens remains to be established

Aknowledgements

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