Characteristics and outcome of elderly APL patients treated with PETHEMA protocols

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Disclosures of DAVID MARTINEZ CUADRON

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen					X		
AMGEN					X		
Pfizer						X	
Gilead					X		

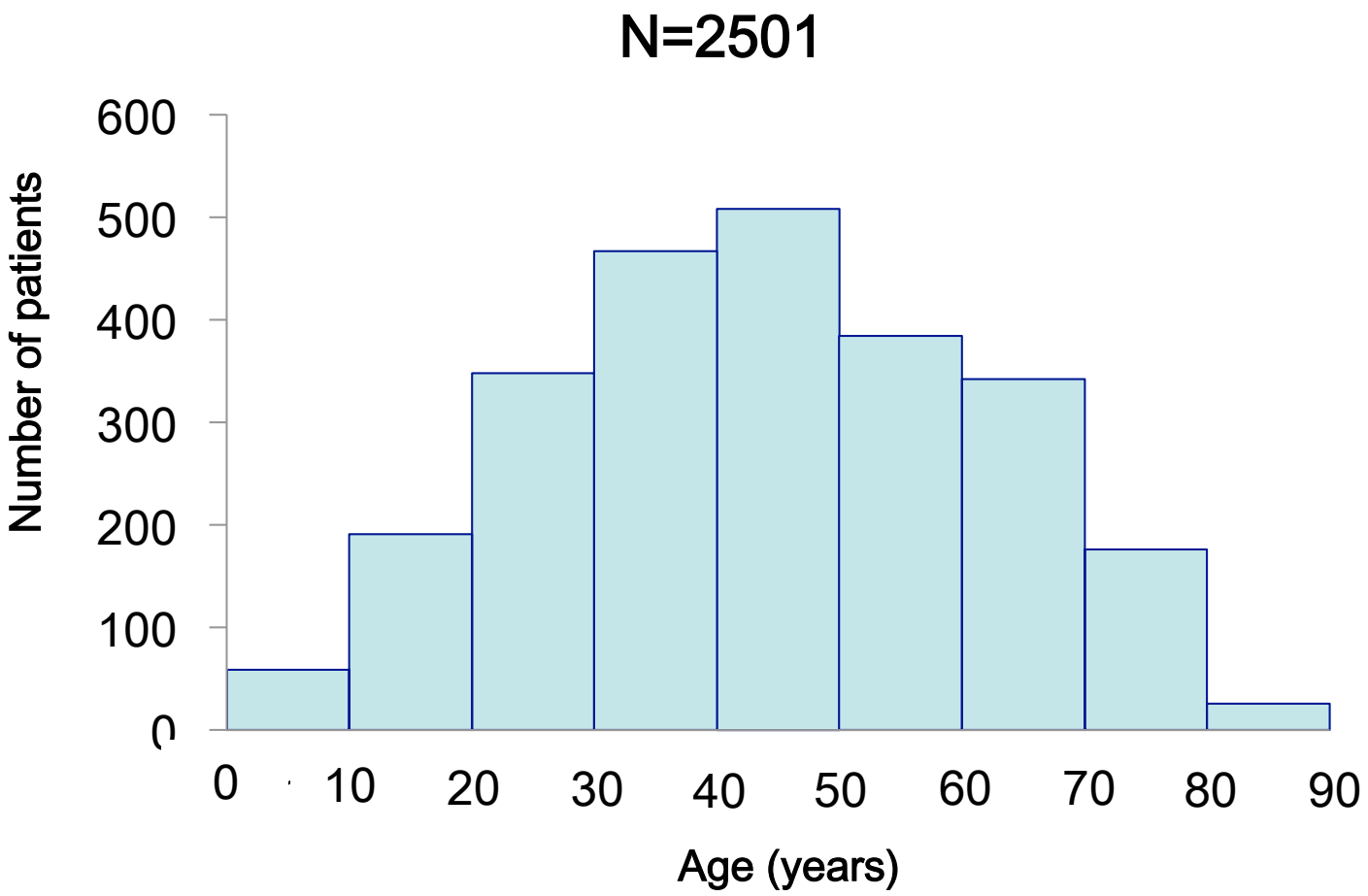
No relevant conflicts of interest to declare or Company Name(s)

Background

- Therapeutic results in patients aged more than or equal to 60 years with APL have been generally reported as being less effective compared to younger patients

- Toxicity of the treatment
  - Higher induction death rate
  - Lower tolerability and compliance in post-remission phase

PETHEMA APL registry



Main published trials in ≥ 60 years APL patients (ATRA + chemotherapy)

	GIMEMA[1] (n = 60)	European APL group[2] (n = 129)	PETHEMA[3] (n = 104)	JALSG (n=46)[4]	German AMLCG[5] (n=56)
CR (%)	**90**	**86**	**84**	**89**	**82**
Death in CR (%)	**10**	**19**	**8**	**21**	**20**
OS (%)	**68 (5 y)**	**58 (4 y)**	**--**	**63 (10 y)**	**45 (7 y)**
DFS (%)	**65 (5 y)**	**53 (4 y)**	**79 (6 y)**	**65 (10 y)**	**48 (7 y)**
CIR (%)	**27 (5 y)**	**16 (4 y)**	**9 (6 y)**	**28 (10 y)**	**24 (7 y)**

1- Latagliata, *et al*., Br J Haematol 2011; 2- Adès, *et al*., Leukemia 2005; 3- Sanz, *et al*., Blood 2004;
4- Ono, *et al*., Cancer Sci 2012; 5- Lengfelder, *et al*., Ann Hematol 2013

Standard Therapy for elderly APL

- Since the advent of ATRA, dramatic improvements in elderly APL
- Worse therapeutic results in elderly compared to younger APL patients
- Underreported population in the context of clinical trials (oriented to fit patients)
- Do specific protocols for elderly APL patients translate into better outcomes?

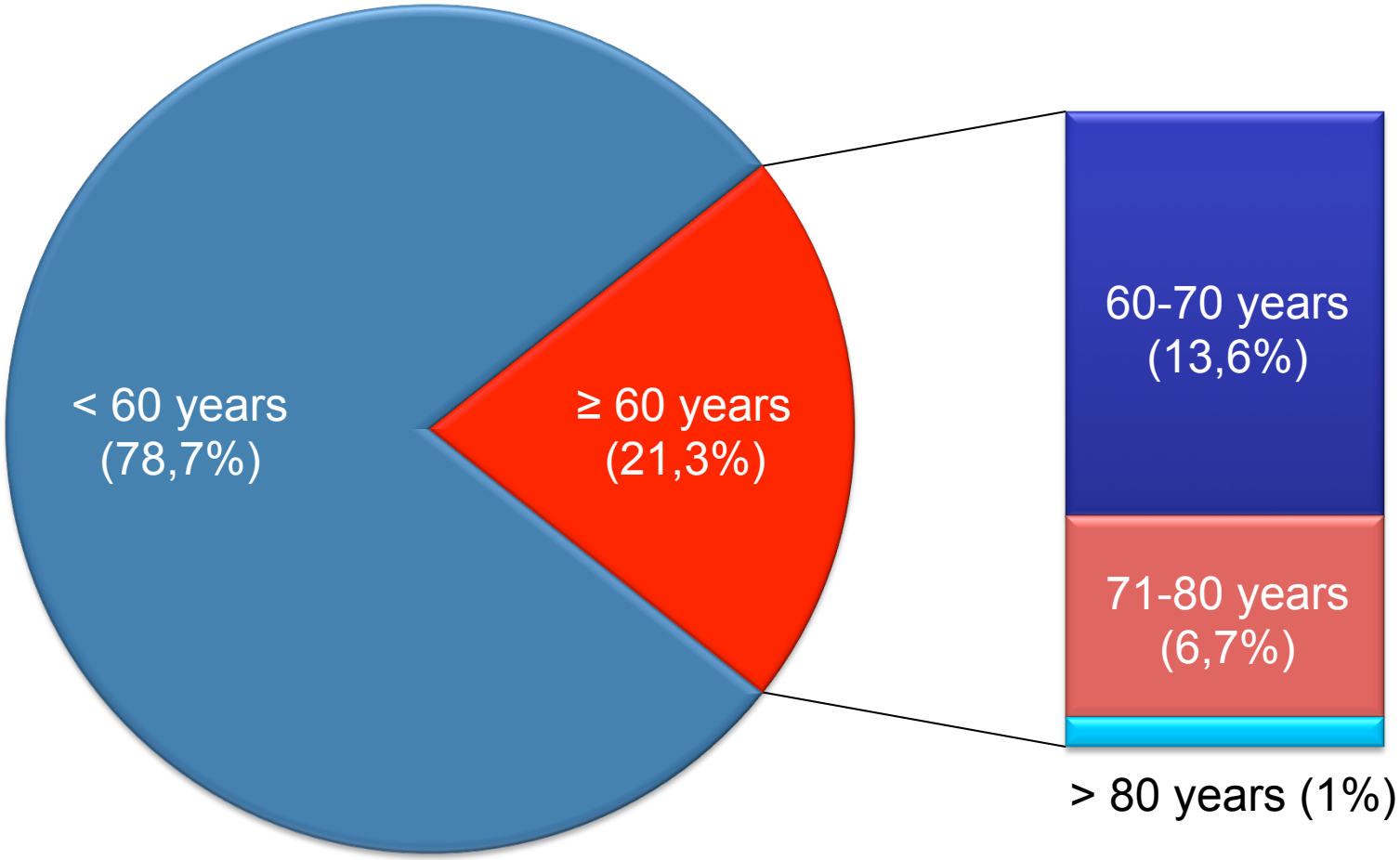
Study of outcomes of older patients included in PETHEMA trials

- To estimate the real frequency of APL elderly patients
- To analyze the clinical and biological characteristics of APL patients older than or equal to 60 years
- To analyze the outcomes for elderly patients treated with 3 consecutive multicenter PETHEMA trials

Reported patients

N = 1.823, Nov 1996-Nov 2014

Median follow-up: 70 months (range, 1-221)



Characteristics of elderly vs. younger patients

PETHEMA registry (LPA96/99/2005)

	< 60 yo n (%)	≥ 60 yo n (%)	*P*
Total number of patients	1.434 (100)	389 (100)	
WBC < 10 (x 10^9/L)	1.009 (71)	304 (79)	0.006
Platelets > 40 (x 10^9/L)	339 (24)	124 (32)	0.001
Creatinine >1,3 (mg/dL)	37 (3)	40 (11)	<0.001
Urea > 50 (mg/dL)	59 (6)	64 (25)	<0.001
Uric acid > 7 (mg/dL)	57 (5)	33 (11)	<0.001
Fibrinogen > 170 (mg/dL)	629 (48)	207 (59)	<0.001
Albumin < 3,5 (g/dL)	206 (18)	107 (35)	<0.001

Characteristics of elderly vs. younger patients

PETHEMA registry (LPA96/99/2005)

	< 60 yo n (%)	≥ 60 yo n (%)	*P*
Secondary APL	74 (5)	73 (19)	<0.001
ECOG 2-4	269 (21)	143 (41)	<0.001
No hemorrhage	259 (19)	96 (27)	0.001
Low relapse-risk	271 (19)	110 (28)	<0.001
CD2 <20%	552 (73)	166 (82)	0.014
CD34 <10%	681 (72)	193 (82)	0.002

Exclusion criteria of elderly patients for the PETHEMA protocols

November 1996 – November 2014

	n (%)
Total patients ≥ 60 years	389 (100)
Non-eligible	121 (31)
Secondary APL	73 (19)
Unfit	43 (11)
Protocol violation	5 (1)
Eligible	268 (69)

268 elderly patients (69 %) of 389 registered patients

Induction results

	< 60 yo n (%)	≥ 60 yo n (%)	*P*
Number of eligible patients	1289 (100)	268 (100)	
CR	1.206 (94)	216 (81)	<0.001
Induction death	77 (6)	52 (19)	
Hemorrhage	44 (3.4)	23 (8.6)	0.03
Infection	14 (1.1)	17 (6.3)	0.09
Diff. syndrome	10 (0.8)	7 (2.6)	0.99
Other	9 (0.7)	5 (1.8)	<0.001

Therapeutic schedule (AIDA-based)

- LPA96 → no age- nor risk-adapted
- LPA99 → no age- but risk-adapted
- LPA2005 → age- and risk-adapted

PETHEMA LPA2005 Trial
Risk- and age-adapted

All patients aged ≥ 60

INDUCTION

AIDA — **IDA 12 mg/m² d2, 4, 6, 8**

CONSOLIDATION

Low risk	Intermediate and high risk
IDA 5 mg x4 + ATRA	**IDA 7 mg x4 + ATRA**
MTZ 10 mg x3 + ATRA	**MTZ 10 mg x3 + ATRA**
IDA 12 mg x1 + ATRA	**IDA 12 mg x2 + ATRA**

MAINTENANCE

2 years

ATRA + MP + MTX

Demographic and baseline characteristics according to trial

Characteristic	LPA96/99 (n=135) Median (range)	LPA2005 (n=133) Median (range)	*P*
Age, years	68 (60-83)	67 (60-84)	.92
WBC (x 10^9/L)	1.9 (0.2-122.3)	1.5 (0.3-112.4)	.29
Platelets (x 10^9/L)	25 (2-207)	25 (2-235)	.96
Creatinine (mg/dL)	1 (0.3-2.4)	0.9 (0.5-9)	.21
Uric acid (mg/dL)	4.2 (1.2-10.1)	4.9 (1.1-10.5)	.005*
Fibrinogen (mg/dL)	175 (0-720)	210 (20-890)	.31
Albumin (g/dL)	3.7 (2.2-6)	4 (2-6)	.01*

Demographic and baseline characteristics according to trial

Characteristic	LPA96/99 (n=135)	LPA2005 (n=133)	*P*
Female	72 (53)	70 (53)	.99
ECOG 2-3	45 (35)	35 (31)	.68
Coagulopathy	99 (73)	37 (60)	.09
Low relapse-risk	42 (31)	37 (28)	.38
CD56 <20%	63 (83)	58 (92)	.18

Induction outcome according to protocol

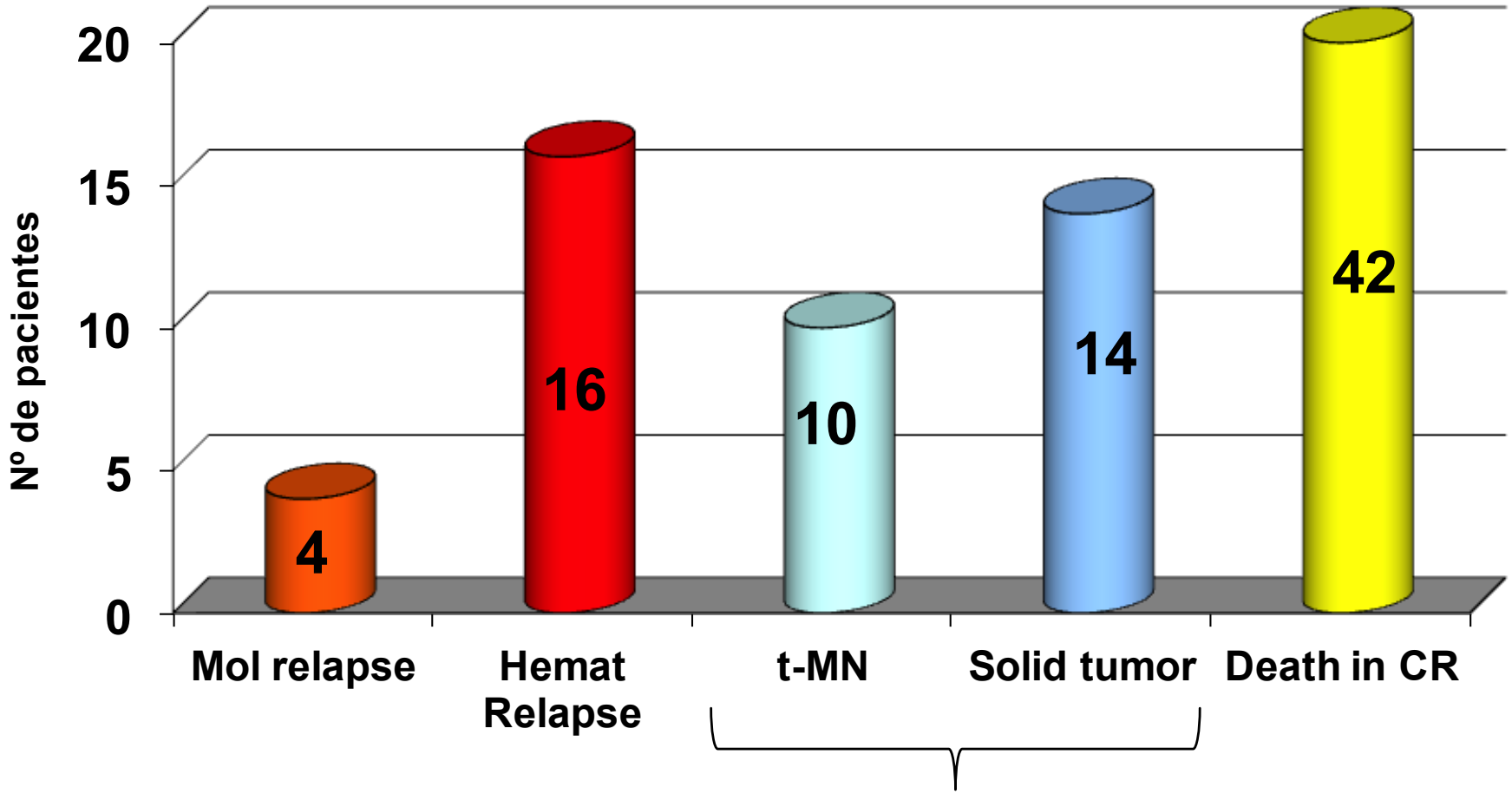
	LPA96/99 n (%)	LPA2005 n (%)	*P*
Complete remission	105 (78)	111 (83)	.31
Induction death	30 (22)	22 (17)	
Bleeding	13 (10)	10 (7)	.99
Infection	11 (8)	6 (4)	.68
Differentiation syndrome	4 (3)	3 (2)	.99
Other	2 (1)	3 (2)	.99

Hematologic toxicity/Hospitalization
Second consolidation

	LPA96/99 n (%)	LPA2005 n (%)	*P*
Grade 4 neutropenia >15 days	79 (81)	50 (58)	.002
Grade 3 thrombocytopenia >15 days	68 (72)	27 (31)	.001
Hospitalization >10 days	41 (44)	21 (26)	.02

Grade 4 neutropenia: neutrophils count < 0.5 x 10^9/L; Grade 3 thrombocytopenia: platelets count < 50 x 10^9/L

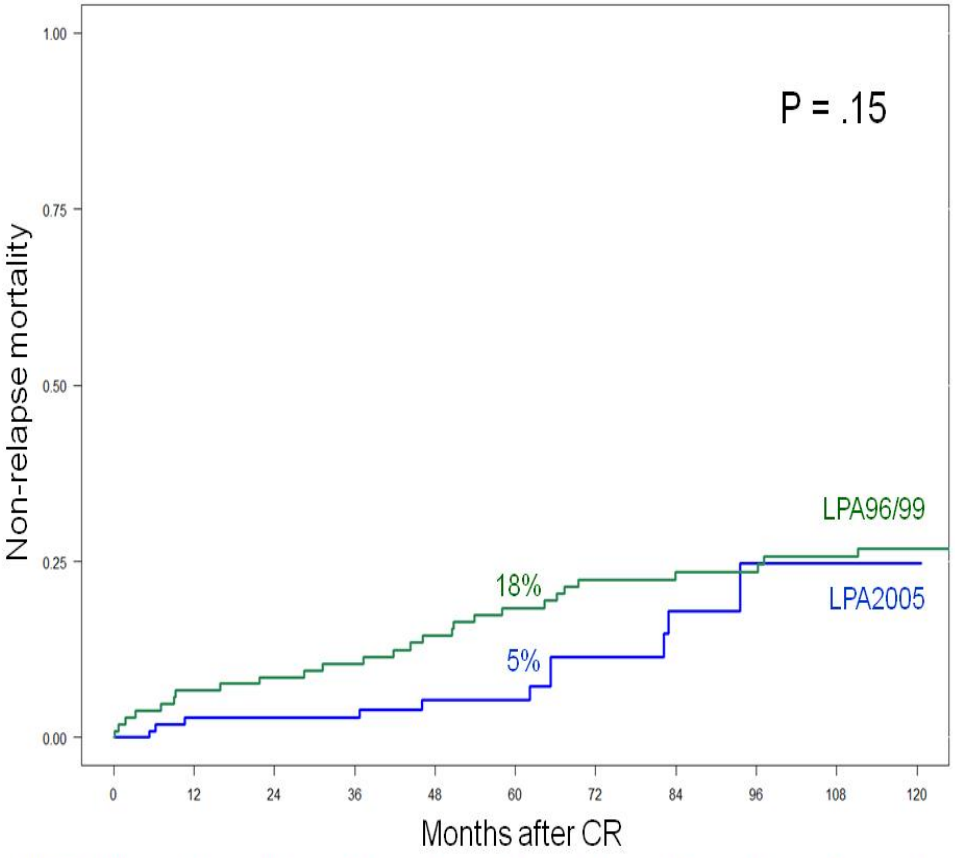
Post-remission events in elderly APL



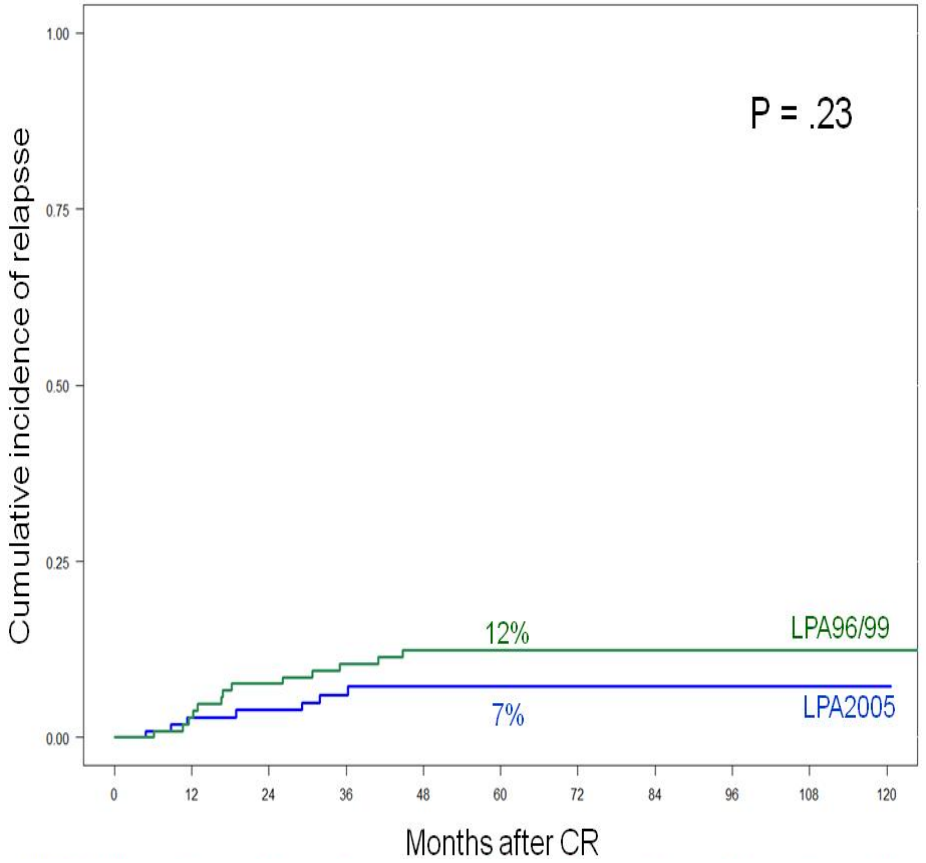
11% in ≥ 60 years vs 3% in younger
(*P*<0,001)

Non-relapse mortality & cumulative relapse according to trial (age vs. non-age adapted)

NRM

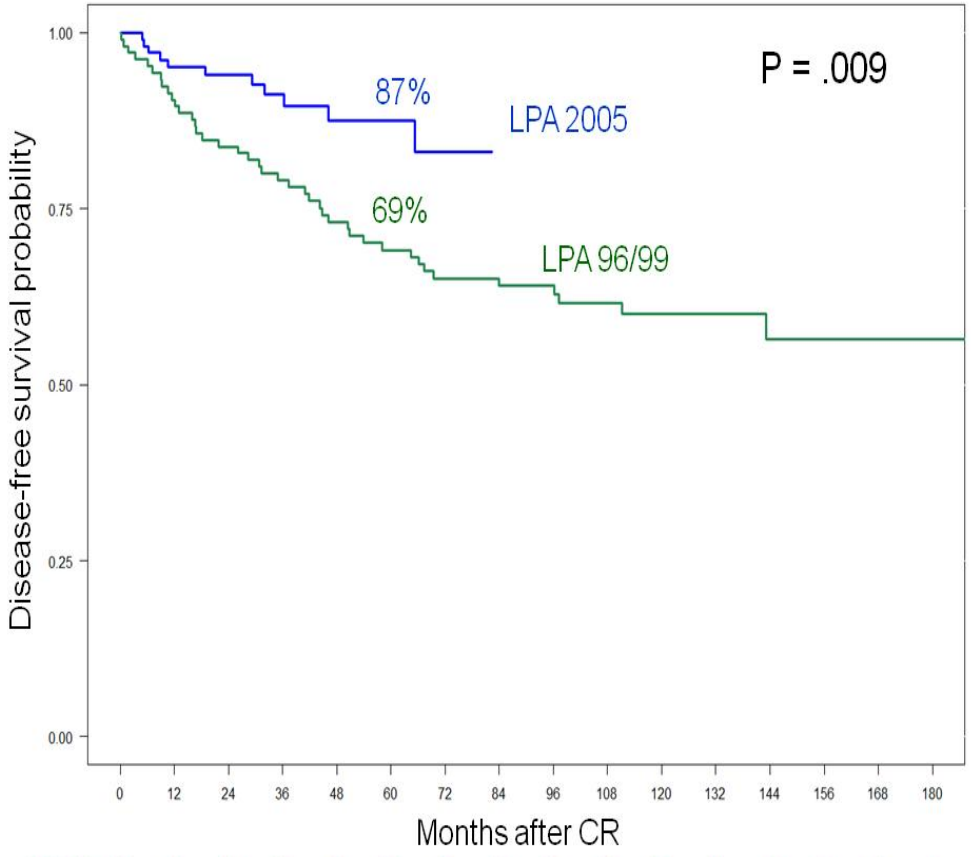


CIR

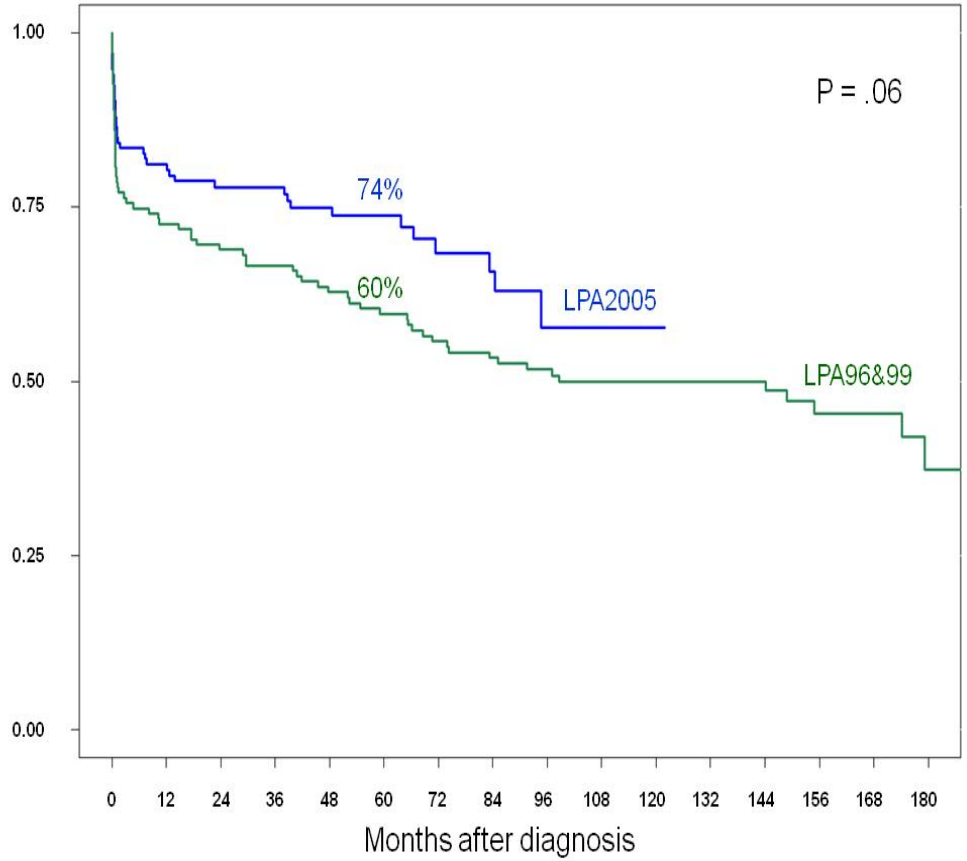


Disease-free & overall survival according to trial (age vs. non-age adapted)

DFS



OS



PETHEMA LPA2012 Trial
Age-adapted

All patients aged ≥ 60

INDUCTION

AIDA — **IDA 12 mg/m² d2, 4, 6, 8**

CONSOLIDATION

(Dose reduction)

Low risk schedule

IDA 5 mg x4 + ATRA

MTZ 10 mg x3 + ATRA

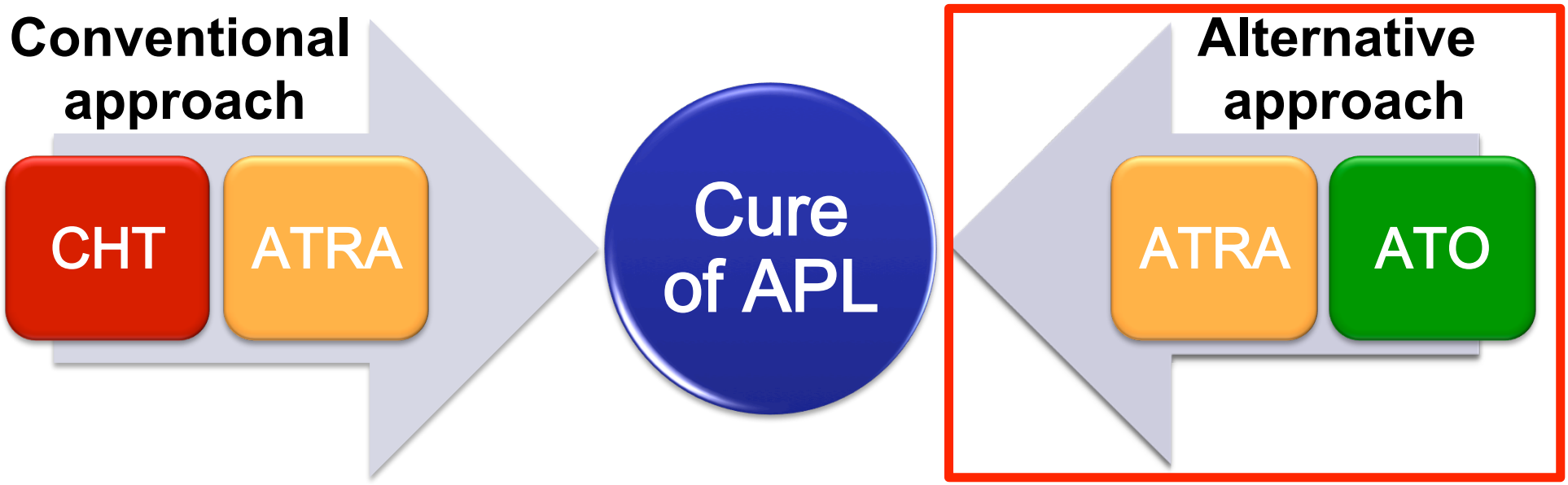
IDA 12 mg x1 + ATRA

MAINTENANCE

2 years

ATRA + MP + MTX

The next step in older patients



The main goal is to offer an optimal therapy to most of older patients

PETHEMA LPA2017 protocol

APL PML/RARα positive, *de novo* o secondary
Start ATRA if suspicions

Low-intermediate risk *(WBC ≤ 10 x 10^9/L)*
or age ≥ 70 years

Induction (ATO+ATRA)
ATRA 45 mg/m²/d VO day 1 until CR
ATO 0,15 mg/kg IV day 1 until CR
Prednisone 0,5 mg/kg VO x 14 days

Consolidation (28 weeks)

ATRA 45 mg/m²/d x 14 d (weeks 1-2 y 5-6)
ATO 0,15 mg/kg/d x 5 d (M-F) (weeks 1-4)

ATRA 45 mg/m²/d x 14 d (weeks 9-10 y 13-14)
ATO 0,15 mg/kg/d x 5 d (M-F) (weeks 9-12)

ATRA 45 mg/m²/d x 14 d (weeks 17-18 y 21-22)
ATO 0,15 mg/kg/d x 5 d (M-F) (weeks 17-20)

ATRA 45 mg/m²/d x 14 d (weeks 25-26)
ATO 0,15 mg/kg/d x 5 d (M-F) (weeks 25-28)

High risk *(WBC > 10 x 10^9/L)*
and age < 70 years

APOLLO trial if available

Induction (AIDA)
IDA 12 mg/m²/d days 1,3,5,7 (≥ 60 years: days 1,3,5)
ATRA 45 mg/m²/d day 1 until CR
Prednisone 0,5 mg/kg VO x 14 days

Consolidation

Age between 60 and 69 years

IDA 5 mg/m²/d (days 1,2,3,4)
ATRA 45 mg/m²/d x 15 d

MTZ 10 mg/m²/d (days 1,2,3)
ATRA 45 mg/m²/d x 15 d

IDA 12 mg/m²/d (day 1)
ATRA 45 mg/m²/d x 15 d

Age < 60 years

IDA 5 mg/m²/d (days 1,2,3,4)
Ara-C 1000 mg/m²/d (days 1,2,3,4)
ATRA 45 mg/m²/d x 15 d

MTZ 10 mg/m²/d (days 1,2,3,4,5)
ATRA 45 mg/m²/d x 15 d

IDA 12 mg/m²/d (day 1)
Ara-C 500 mg/m²/d (days 1,2,3,4)
ATRA 45 mg/m²/d x 15 d

Maintenance (12 weeks)

ATRA 45 mg/m²/d x 14 d (weeks 1-2 y 5-6)
ATO 0,15 mg/kg/d lu-vi (weeks 1-4)

ATRA 45 mg/m²/d x 14 d (weeks 9-10)
ATO 0,15 mg/kg/d x 5 d (M-F) (weeks 9-12)

APL in Elderly Patients: PETHEMA experience Concluding remarks

- APL is a very rare disease in elderly patients, lack of reliable information
- Due to frequent poor clinical condition and comorbidities, patients are often excluded from trials
- Induction death remains the most challenging cause of therapeutic failure (up to 20% in “eligible” patients, much more in “non-eligible”)
- “Age-adapted” AIDA-based regimens with reduced intensity appear to improve long-term outcomes