Improvements with Risk-adapted PETHEMA Protocols in New Diagnosed Acute Promyelocytic Leukemia

Miguel A. Sanz
Chairman, Spanish PETHEMA Group
University Hospital La Fe
Valencia, Spain

7th International Symposium on Acute Promyelocytic Leukemia

Rome, Italy (September 2013)

La Fe
DEPARTAMENT DE SALUT

GENERALITAT VALENCIANA
CONSELLERIA DE SANITAT

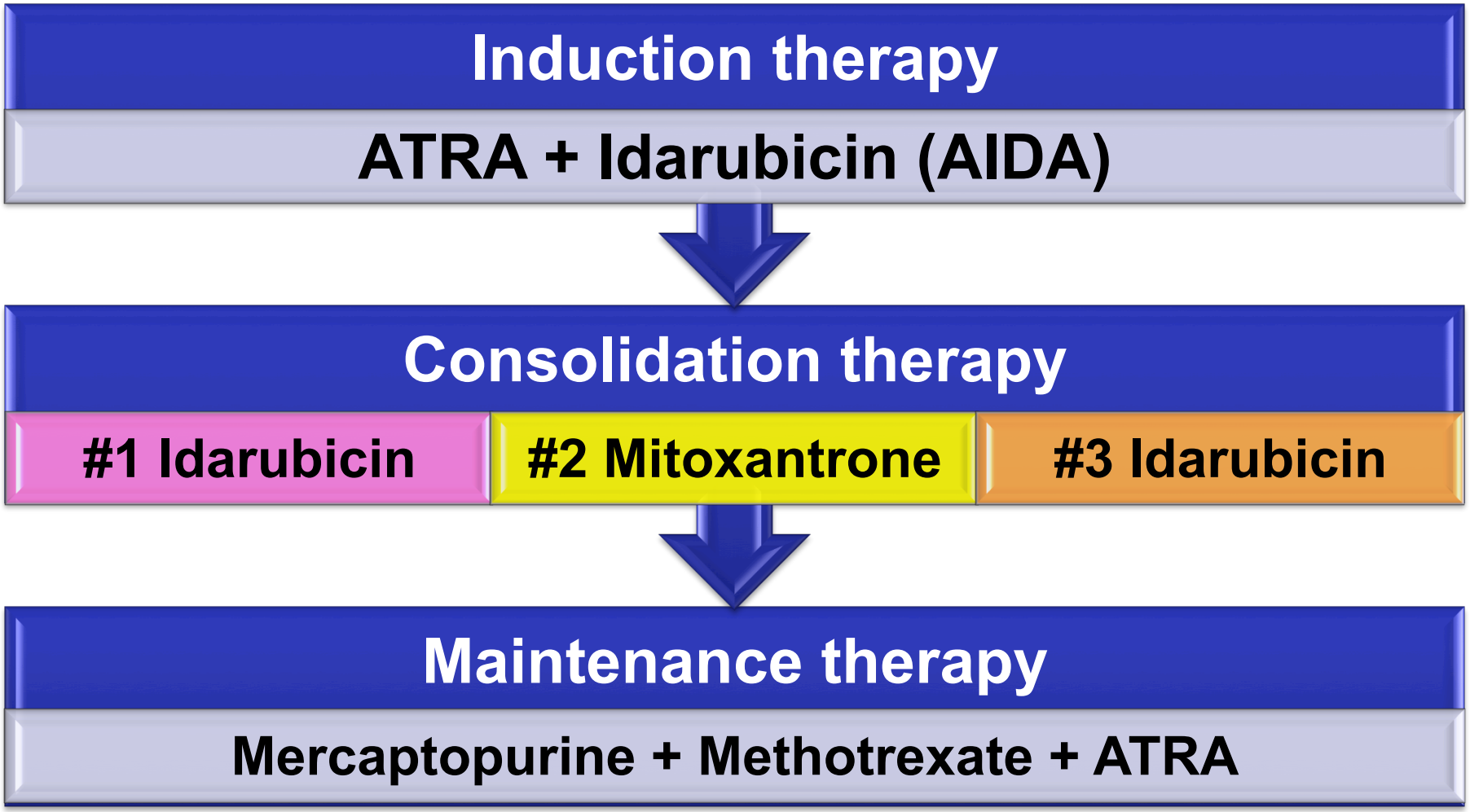
VNIVERSITAT DE VALÈNCIA

Disclosures for Miguel A. Sanz, MD, PhD

Research Support/P.I.	N/A
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Speakers Bureau	Teva Pharmaceuticals
Scientific Advisory Board	N/A

N/A = Not Applicable (no conflicts listed)
Presentation includes discussion of the following off-label use of a drug or medical device: Arsenic trioxide

The First PETHEMA Protocol (LPA96)



Adapted from the AIDA/GIMEMA (Mandelli et al., Blood 1997)

Evolving risk-adapted strategy to optimize treatment in APL (PETHEMA)

Reduction of dose intensity in elderly[1]

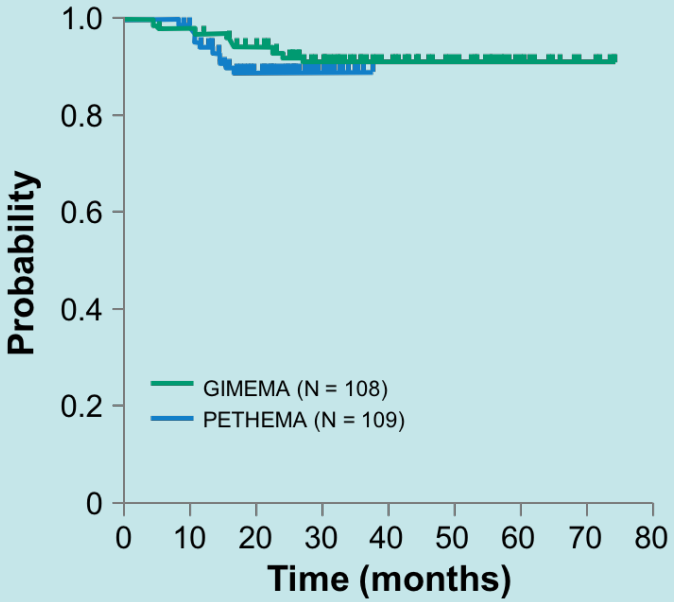
One size fits all

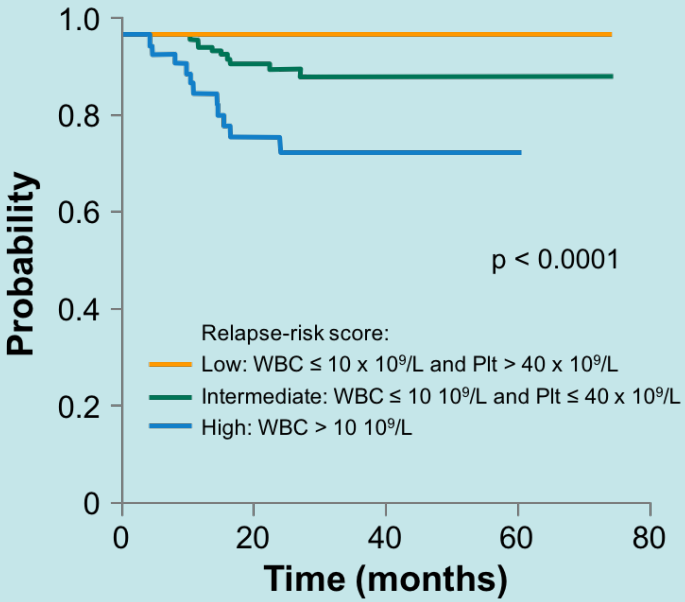
LPA96

Nov. 1996
Oct. 1999

Definition of relapse risk groups

Joint GIMEMA and PETHEMA study

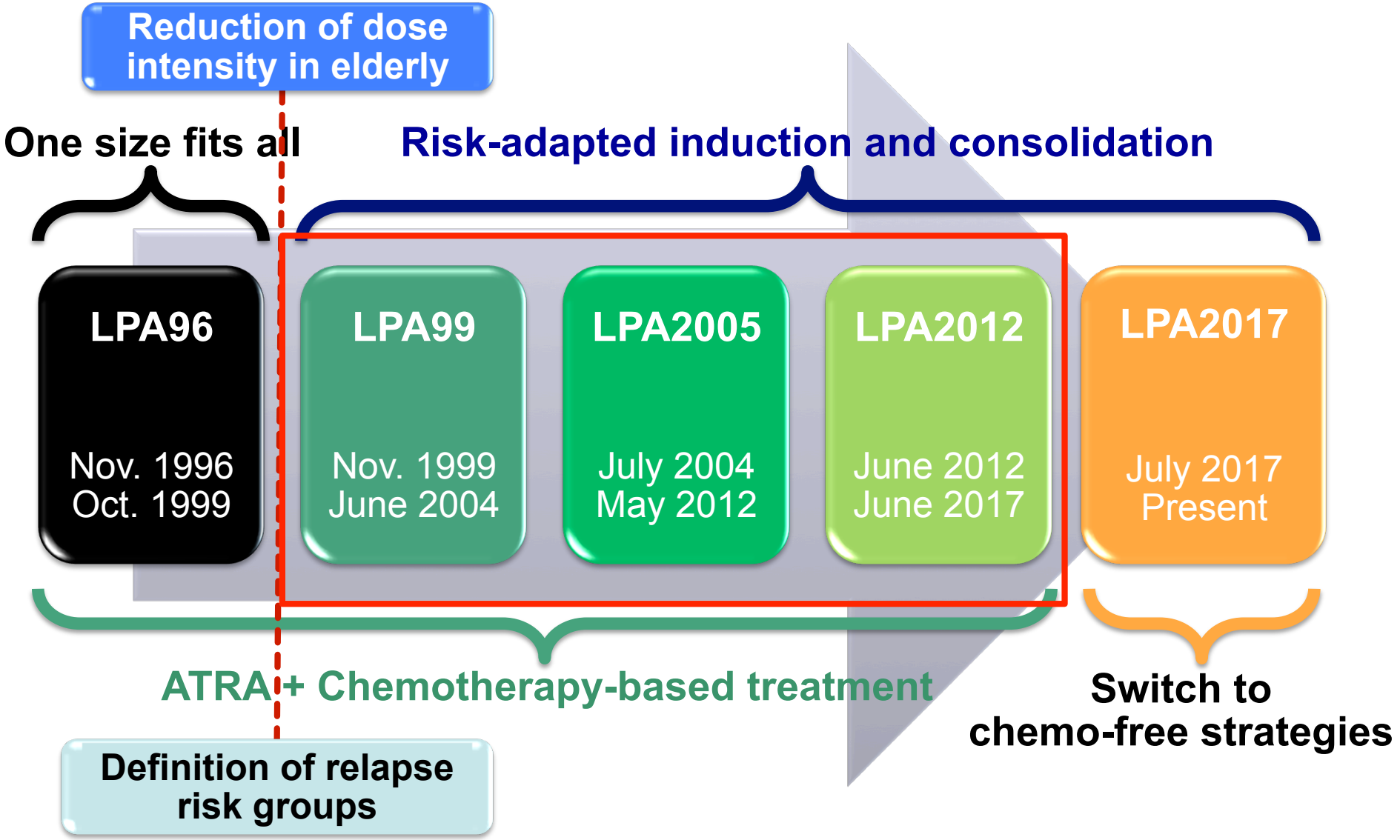




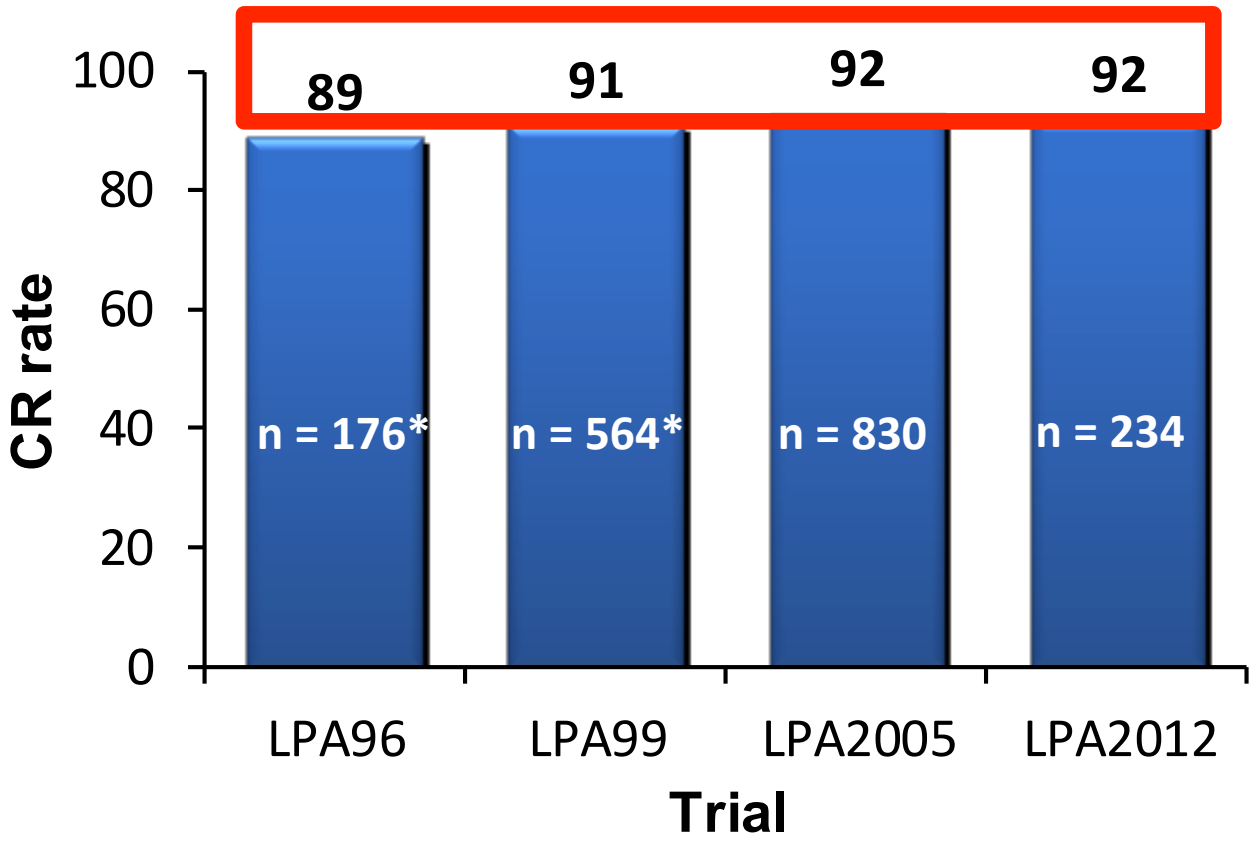
Sanz M, et al. Blood. 2000;96:1247-53.

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

Evolving risk-adapted strategy to optimize treatment in APL (PETHEMA)



Induction Therapy with AIDA
The PETHEMA experience



Learning curve?

P = 0.07

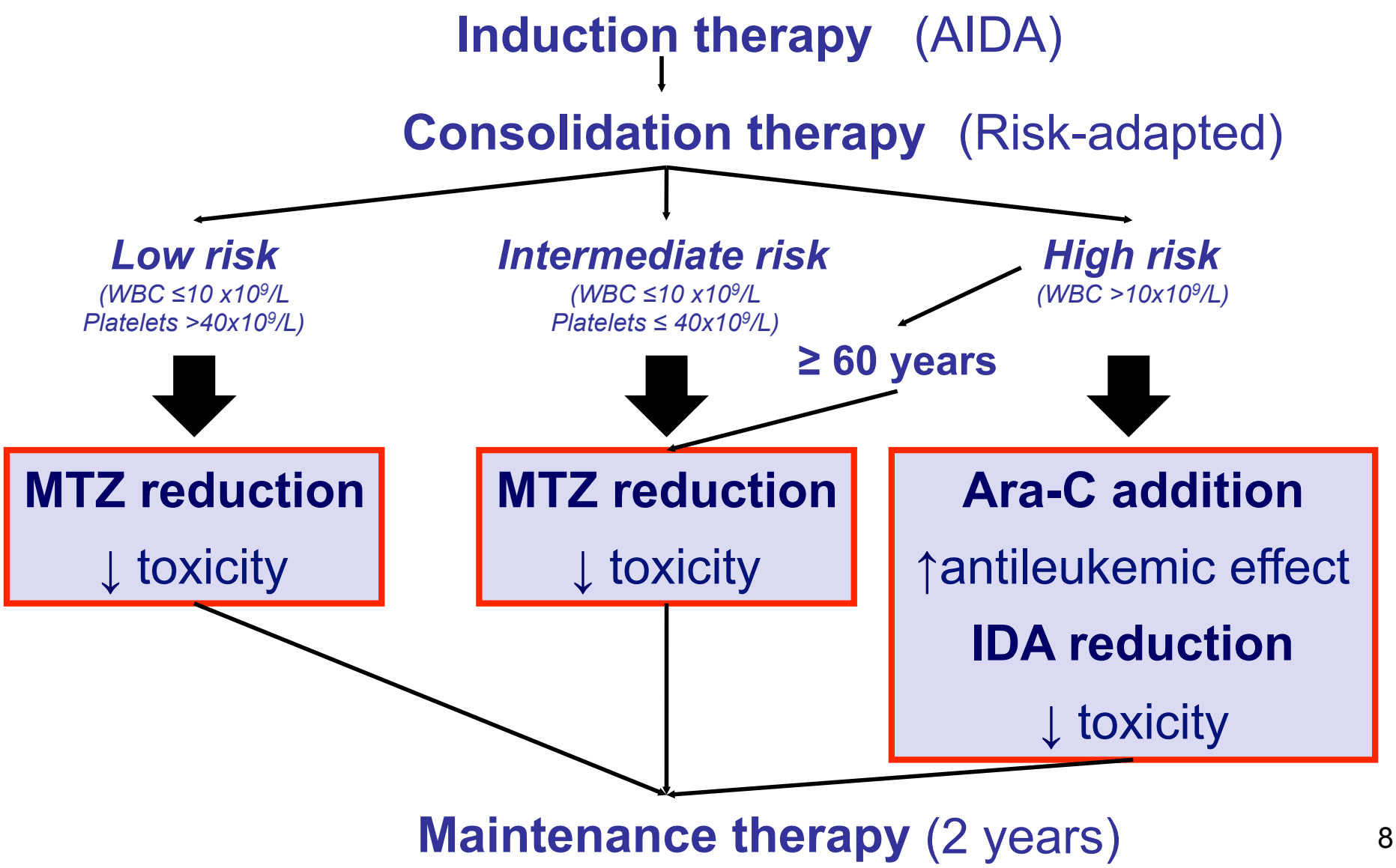
* Seven patients were assessed very early (days +18 to +36) and erroneously interpreted as resistant leukemia

PETHEMA/HOVON LPA99 trial

vs.

PETHEMA/HOVON LPA2005 trial

PETHEMA LPA2005
Changes and objectives



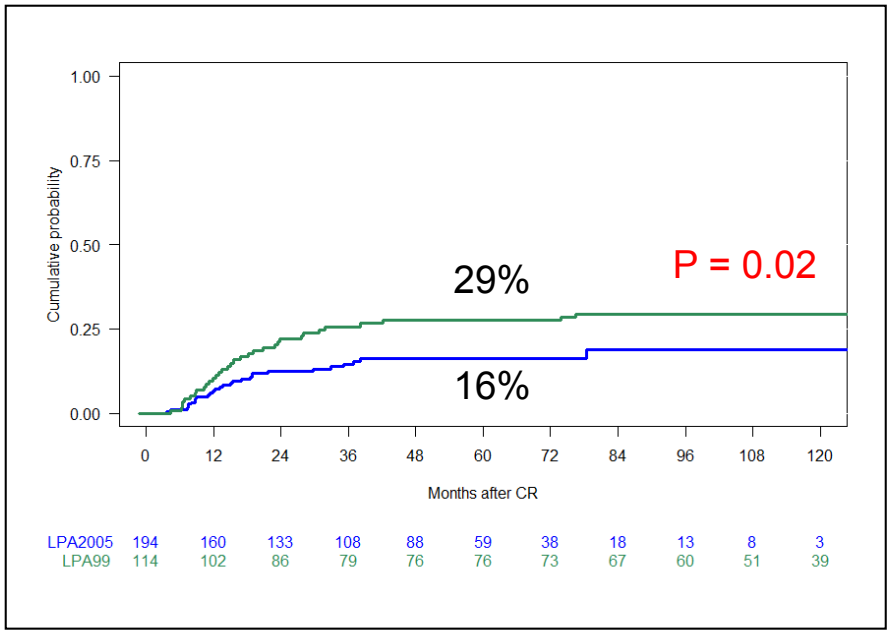
PETHEMA/HOVON LPA99 vs. LPA2005
Updated analysis

	Previous Report*	Present report
Analysis updated on	Jul 15, 2010	**Sept 15, 2017**
No. of patients	795	**1397**
FU, median (range)	40 (1 – 85)	**75 (2 – 208)**

* Sanz *et al.*, Blood 2010

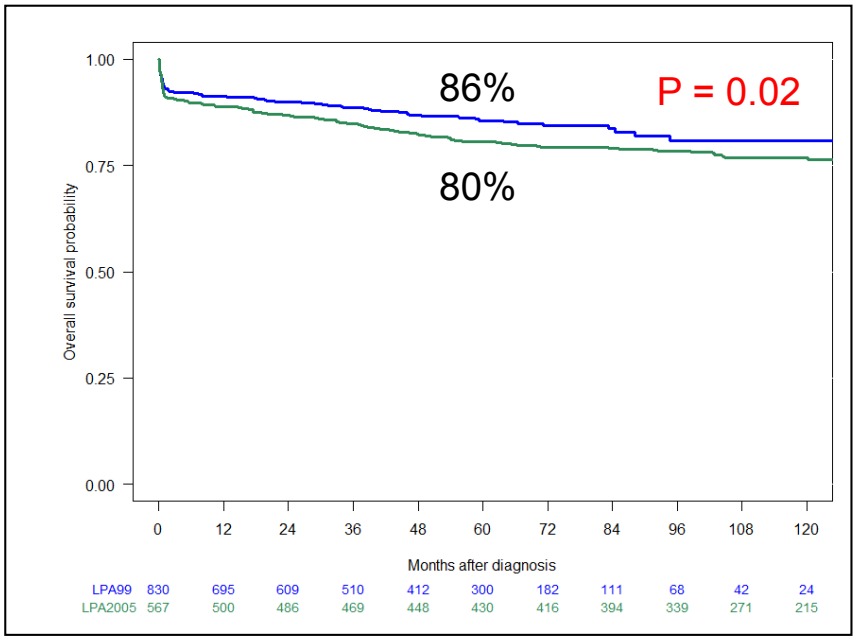
PETHEMA/HOVON LPA99 vs. LPA2005
Outcome improvements

CIR in high-risk patients



LPA2005 resulted in a **lower relapse** rate in high-risk patients

Overall survival



LPA2005 resulted in a **higher overall survival** rate

PETHEMA/HOVON LPA2005 trial

vs.

PETHEMA/HOVON LPA2012 trial

PETHEMA/HOVON LPA2012 trial

INDUCTION THERAPY

AIDA

CONSOLIDATION THERAPY

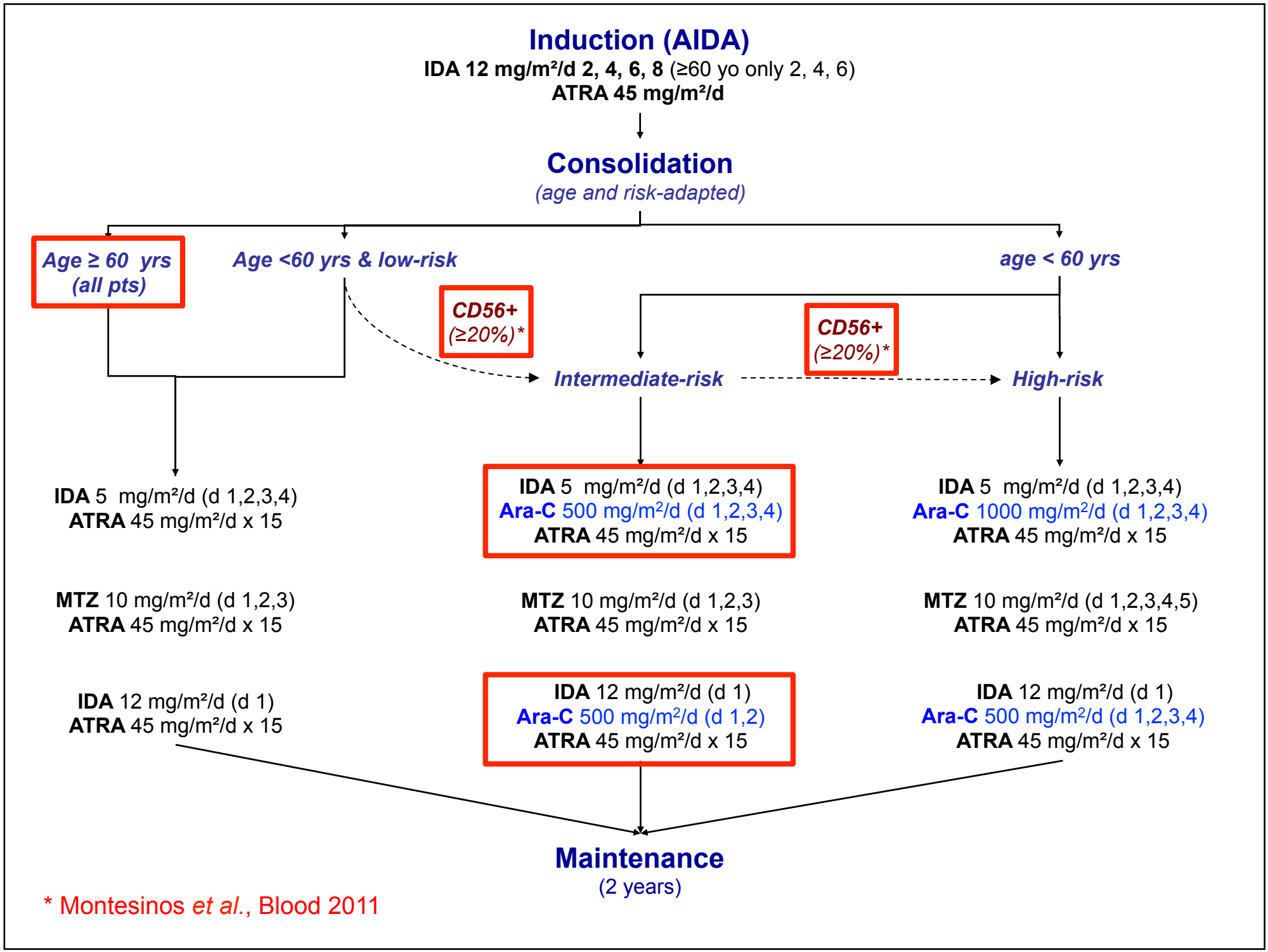
Risk-adapted consolidation

Cycle #1 Idarubicin	Cycle #2 Mitoxantrone	Cycle #3 Idarubicin

MAINTENANCE THERAPY

Adapted from LPA2005

- Extended combination of ATRA + Ida + Cytarabine to intermediate-risk group
- Dose reduction of idarubicin for elderly and intermediate-risk patients
- Risk upgrading for CD56+ patients (Montesinos *et al*. Blood 2011)

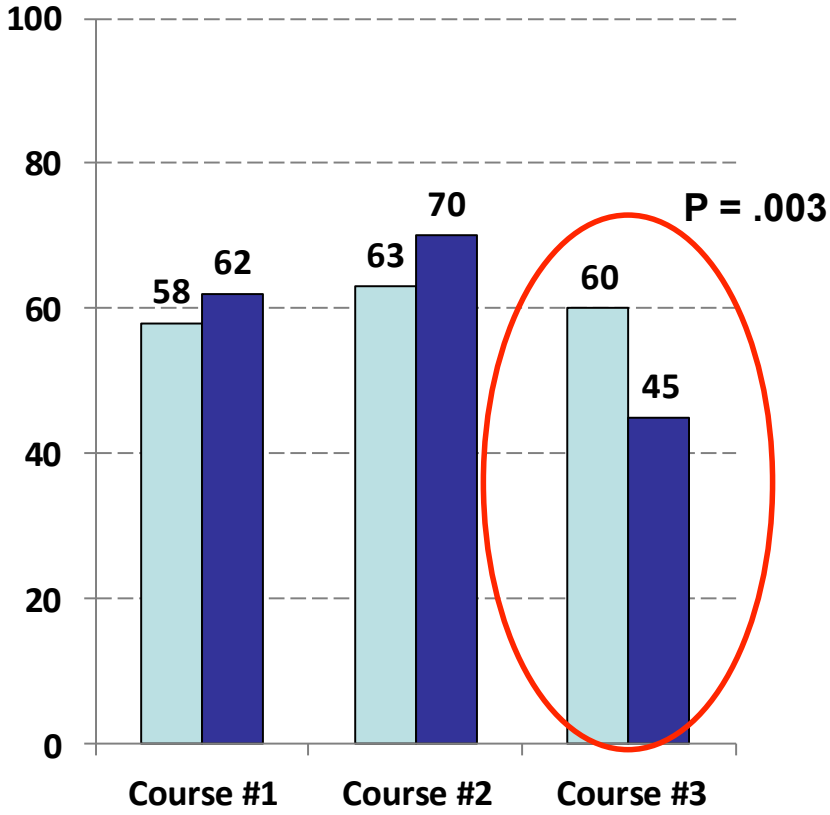

Induction (AIDA)
IDA 12 mg/m²/d 2, 4, 6, 8 (≥60 yo only 2, 4, 6)
ATRA 45 mg/m²/d
Consolidation
(age and risk-adapted)
Age ≥ 60 yrs (all pts)
Age <60 yrs & low-risk
age < 60 yrs
CD56+ (≥20%)*
CD56+ (≥20%)*
Intermediate-risk
High-risk
IDA 5 mg/m²/d (d 1,2,3,4)
ATRA 45 mg/m²/d x 15
MTZ 10 mg/m²/d (d 1,2,3)
ATRA 45 mg/m²/d x 15
IDA 12 mg/m²/d (d 1)
ATRA 45 mg/m²/d x 15
IDA 5 mg/m²/d (d 1,2,3,4)
Ara-C 500 mg/m²/d (d 1,2,3,4)
ATRA 45 mg/m²/d x 15
MTZ 10 mg/m²/d (d 1,2,3)
ATRA 45 mg/m²/d x 15
IDA 12 mg/m²/d (d 1)
Ara-C 500 mg/m²/d (d 1,2)
ATRA 45 mg/m²/d x 15
IDA 5 mg/m²/d (d 1,2,3,4)
Ara-C 1000 mg/m²/d (d 1,2,3,4)
ATRA 45 mg/m²/d x 15
MTZ 10 mg/m²/d (d 1,2,3,4,5)
ATRA 45 mg/m²/d x 15
IDA 12 mg/m²/d (d 1)
Ara-C 500 mg/m²/d (d 1,2,3,4)
ATRA 45 mg/m²/d x 15
Maintenance
(2 years)
* Montesinos et al., Blood 2011

PETHEMA/HOVON LPA2005 vs. LPA2012
Interim analysis

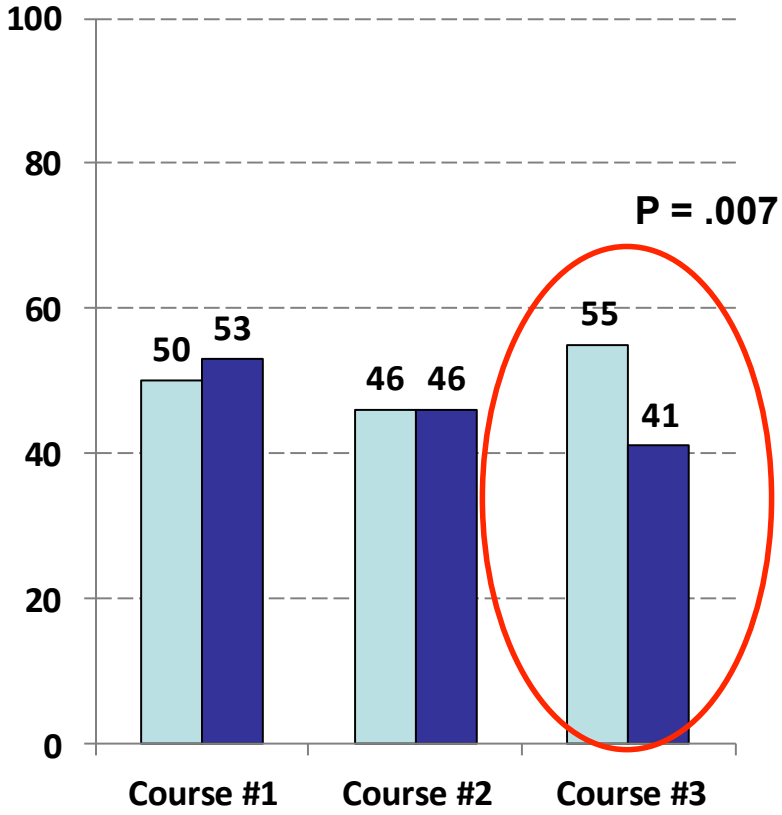
	LPA2005	LPA2012
Analysis updated on	**Sept 15, 2017**	**Sept 15, 2017**
No. of patients	830	**222**
FU, median (range)	54 (2 – 145)	**24 (1 – 60)**

Hematological toxicity during consolidation in all patients

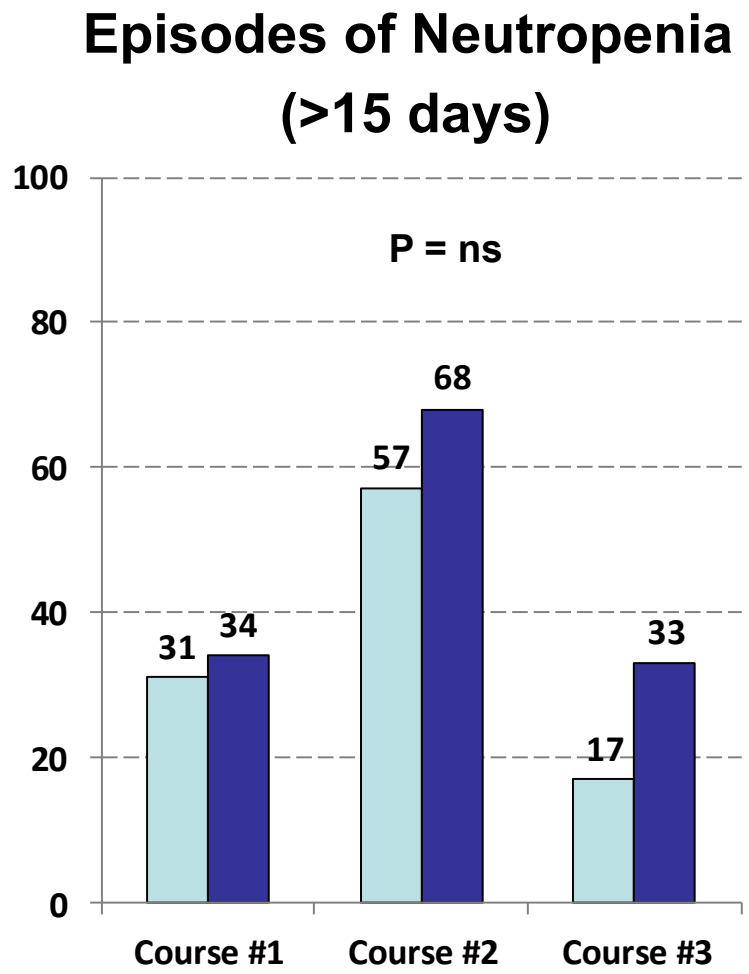
Episodes of Neutropenia (>15 days)

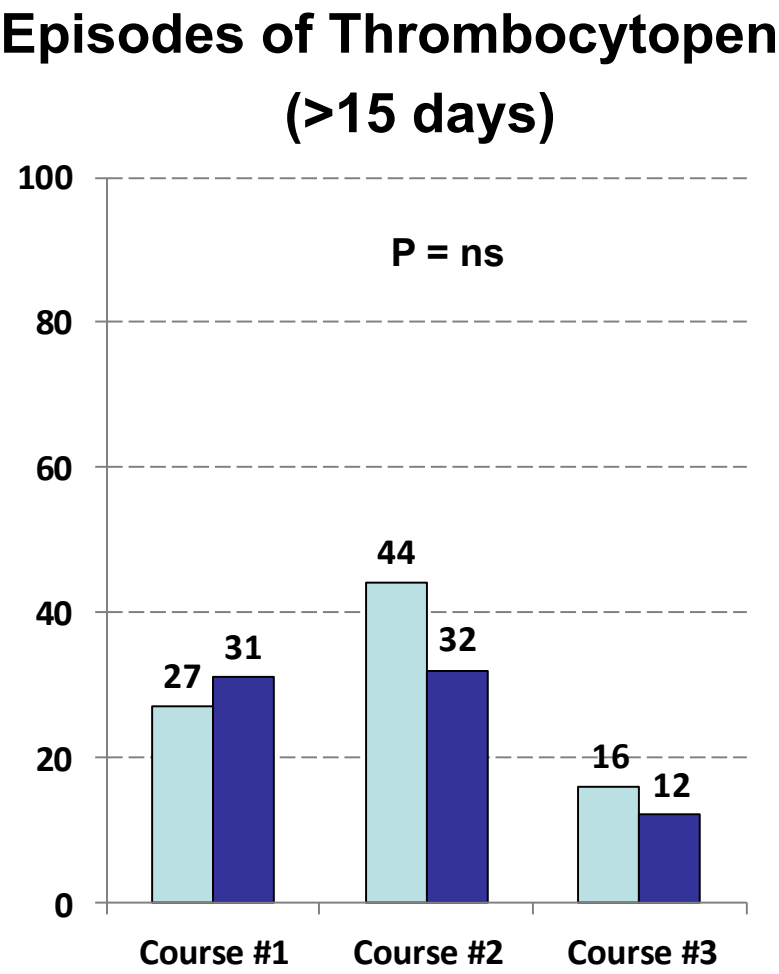


Episodes of Thrombocytopenia (>15 days)

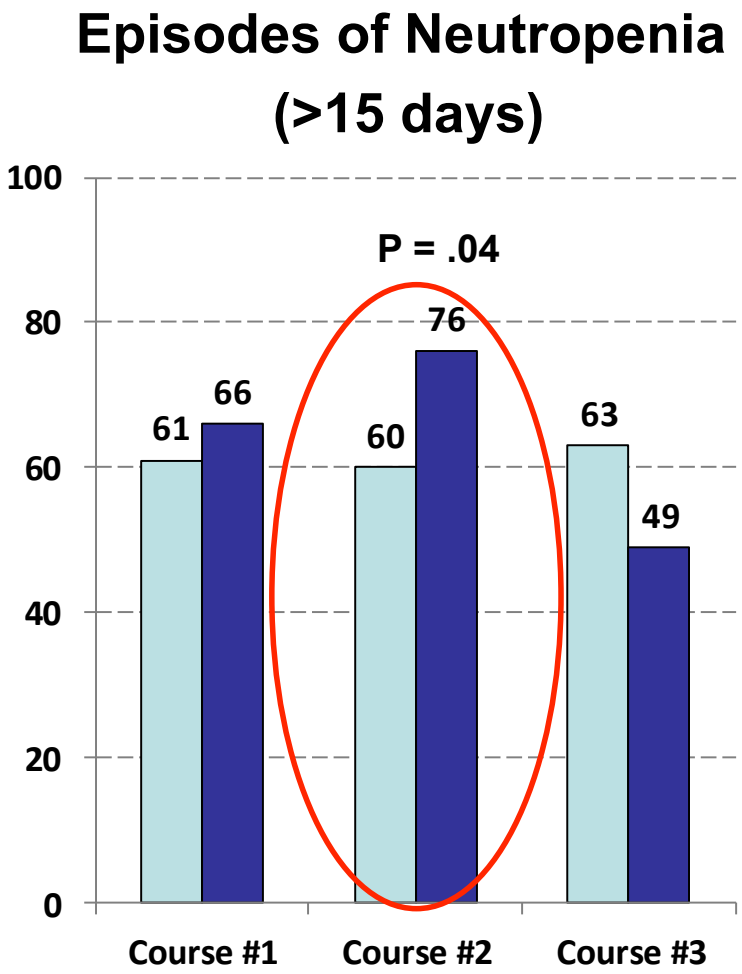


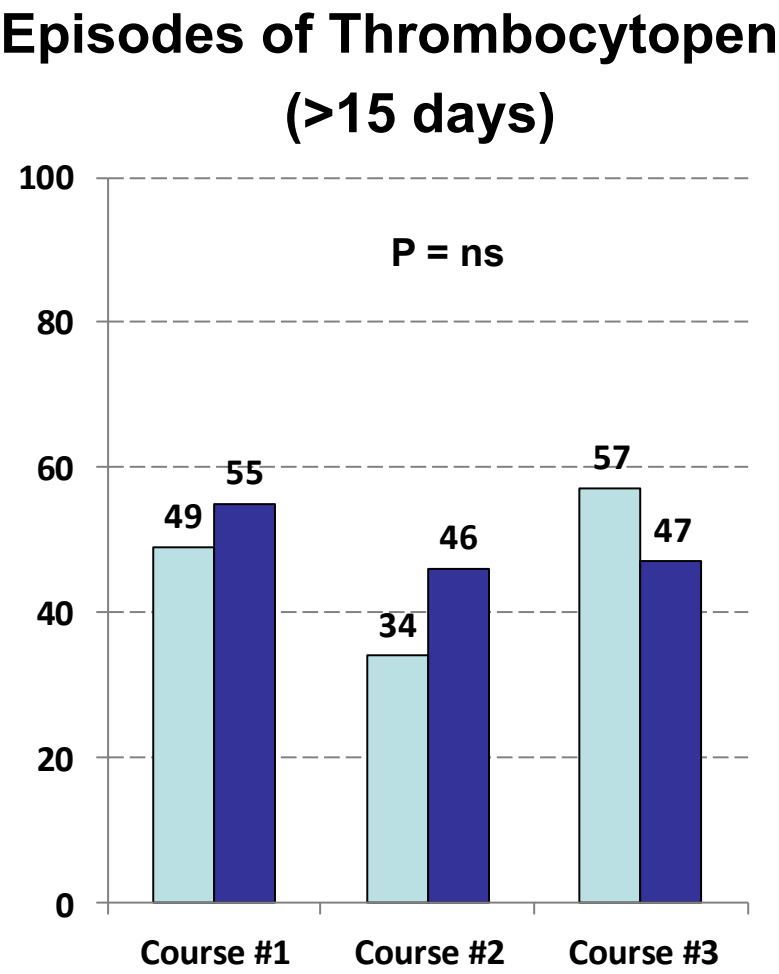
Hematological toxicity during consolidation in low-risk patients





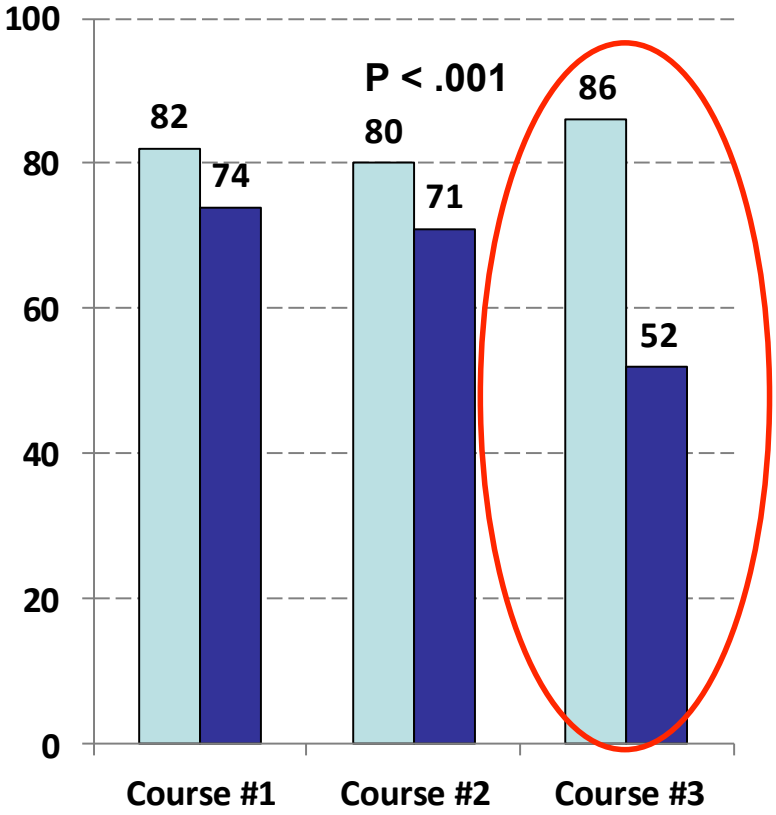
Hematological toxicity during consolidation in intermediate-risk patients



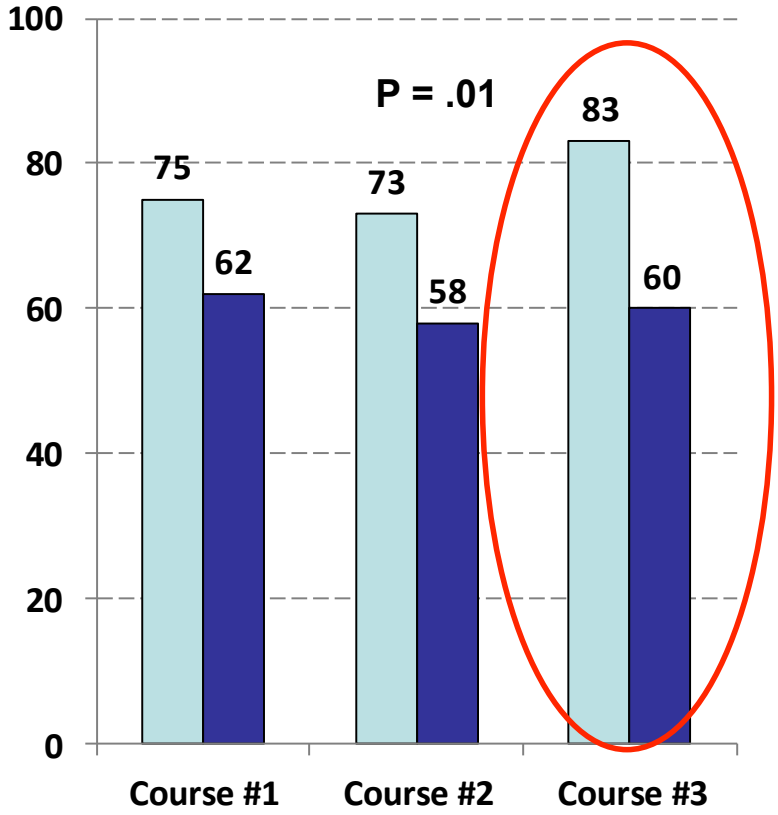


Hematological toxicity during consolidation in high-risk patients

Episodes of Neutropenia (>15 days)

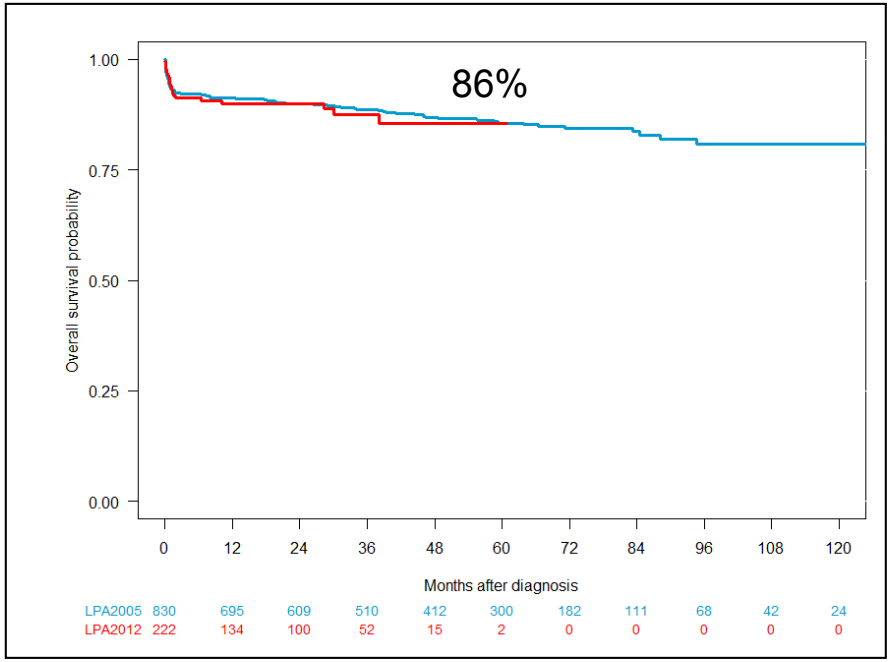


Episodes of Thrombocytopenia (>15 days)

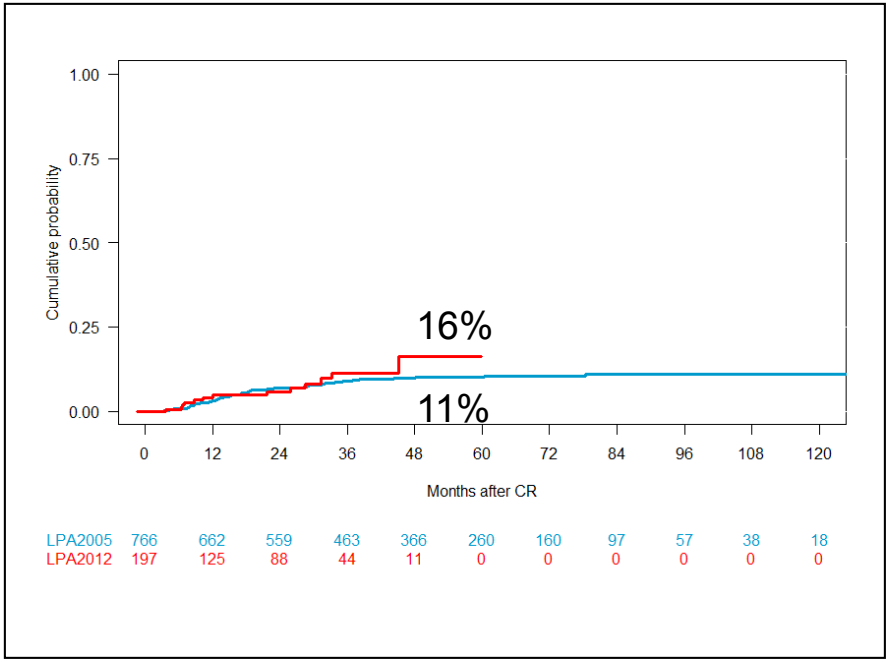


PETHEMA/HOVON LPA2012 *vs.* LPA2005
Outcome improvements

Overall survival

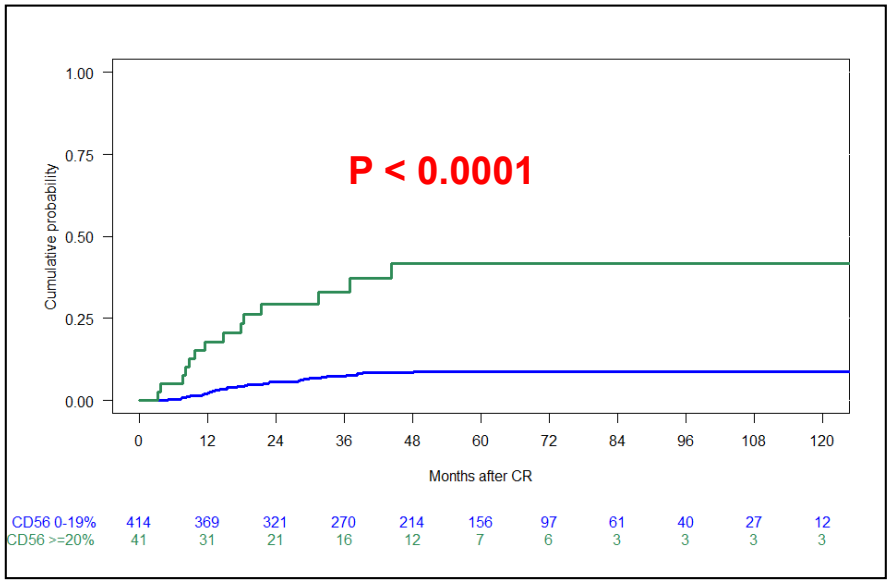


Overall CIR



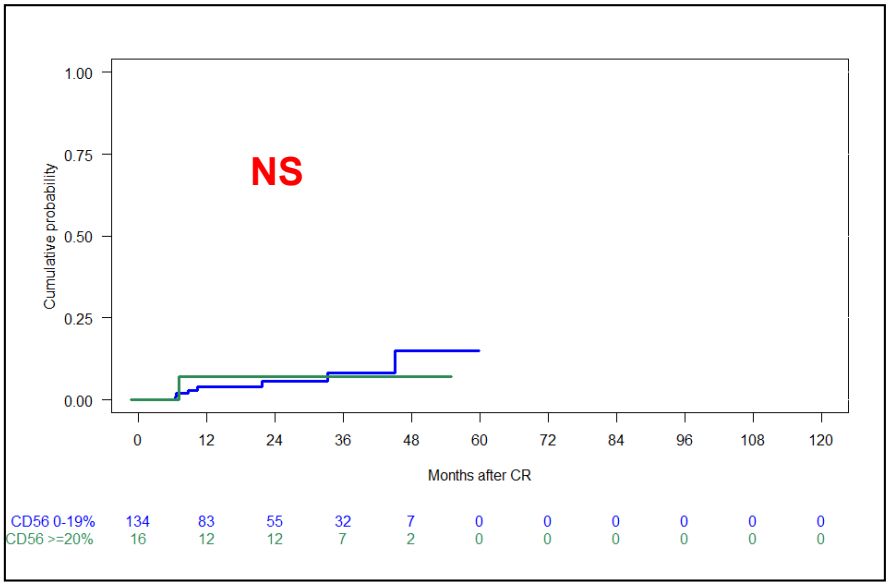
PETHEMA/HOVON LPA2012 *vs.* LPA2005
Outcome by CD56 expression

CIR in LPA2005



Higher relapse rate in CD56-positive patients

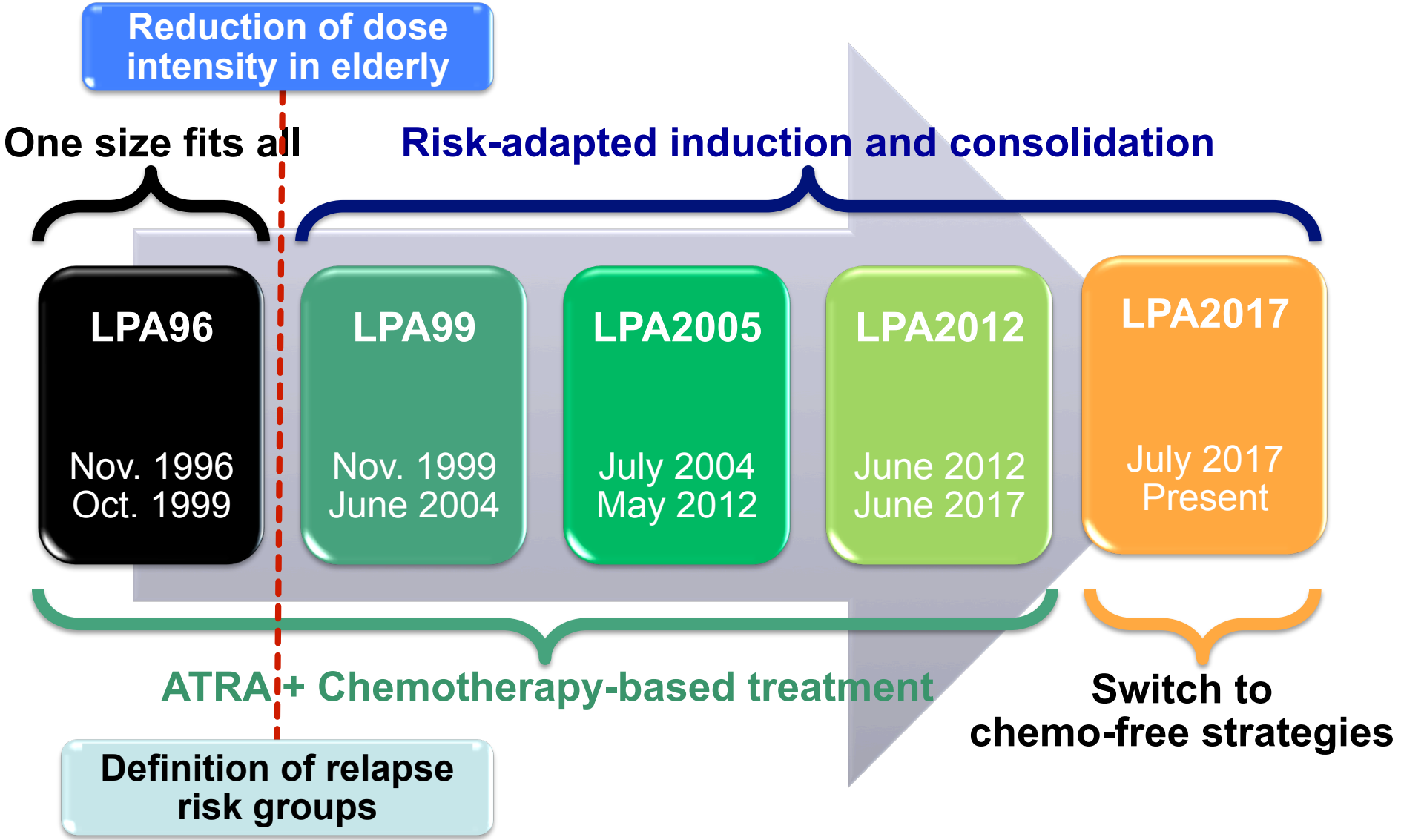
CIR in LPA2012



No differences in relapse rate by CD56 expression

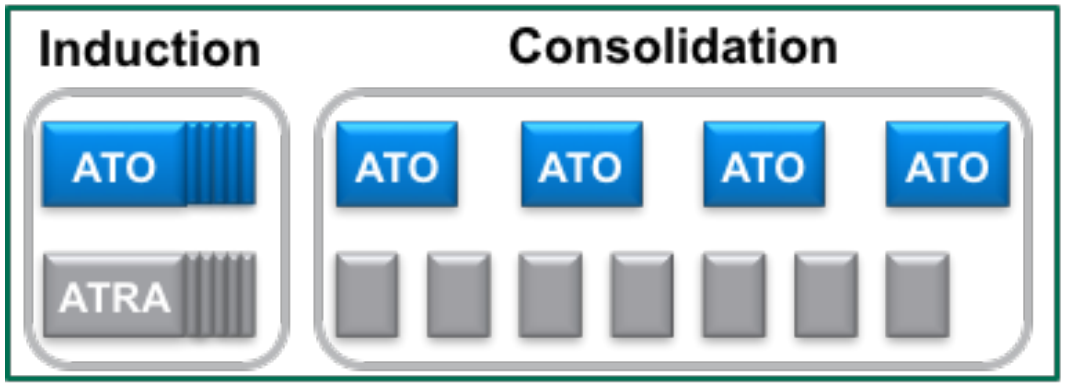
Next Step in PETHEMA

Evolving risk-adapted strategy to optimize treatment in APL (PETHEMA)

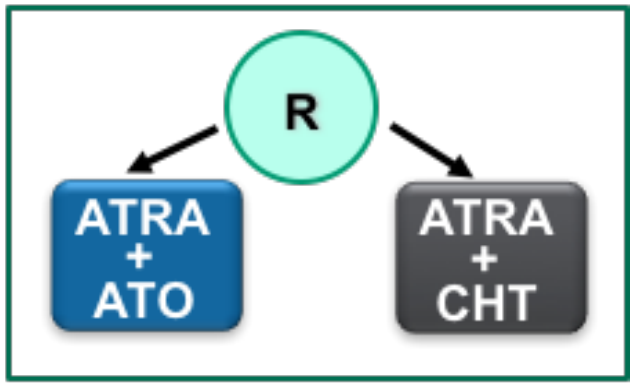


Risk-adapted strategy in APL without or with minimal use of chemotherapy (PETHEMA)

Low or intermediate risk[1]
(WBC ≤10 x 10^9/L)



High risk[2]
(WBC >10 x 10^9/L)



APOLLO trial

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

1. Lo-Coco F, et al. N Engl J Med. 2013;369:111-21
2. NCT02688140. Available from: https://clinicaltrials.gov/ct2/show/NCT02688140. Accessed October 2016.

Protocolo PETHEMA LPA2017

LPA PML/RARα positiva, de novo o secundaria
Iniciar ATRA ante sospecha

Riesgo bajo-intermedio (WBC ≤ 10 x 10^9/L) *o edad ≥ 70 años*

Inducción (ATO+ATRA)
ATRA 45 mg/m²/d VO día 1 hasta RC
ATO 0,15 mg/kg IV día 1 hasta RC

Prednisona 0,5 mg/kg VO x 14 días

Consolidación (28 semanas)

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

ATRA 45 mg/m²/d x 14 d (sem 9-10 y 13-14)
ATO 0,15 mg/kg/d lu-vi (sem 9-12)

ATRA 45 mg/m²/d x 14 d (sem 17-18 y 21-22)
ATO 0,15 mg/kg/d lu-vi (sem 17-20)

ATRA 45 mg/m²/d x 14 d (sem 25-26)
ATO 0,15 mg/kg/d lu-vi (sem 25-28)

riesgo alto (WBC > 10 x 10^9/L) *y edad < 70 años*

APOLLO trial si está disponible

Inducción (AIDA)
IDA 12 mg/m²/d días 1,3,5,7 (≥ 60 años días 1,3,5)
ATRA 45 mg/m²/d día 1 hasta RC

Prednisona 0,5 mg/kg VO x 14 días

Consolidación

Edad entre 60 y 69 años

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

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

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

Edad < 60 años

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

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

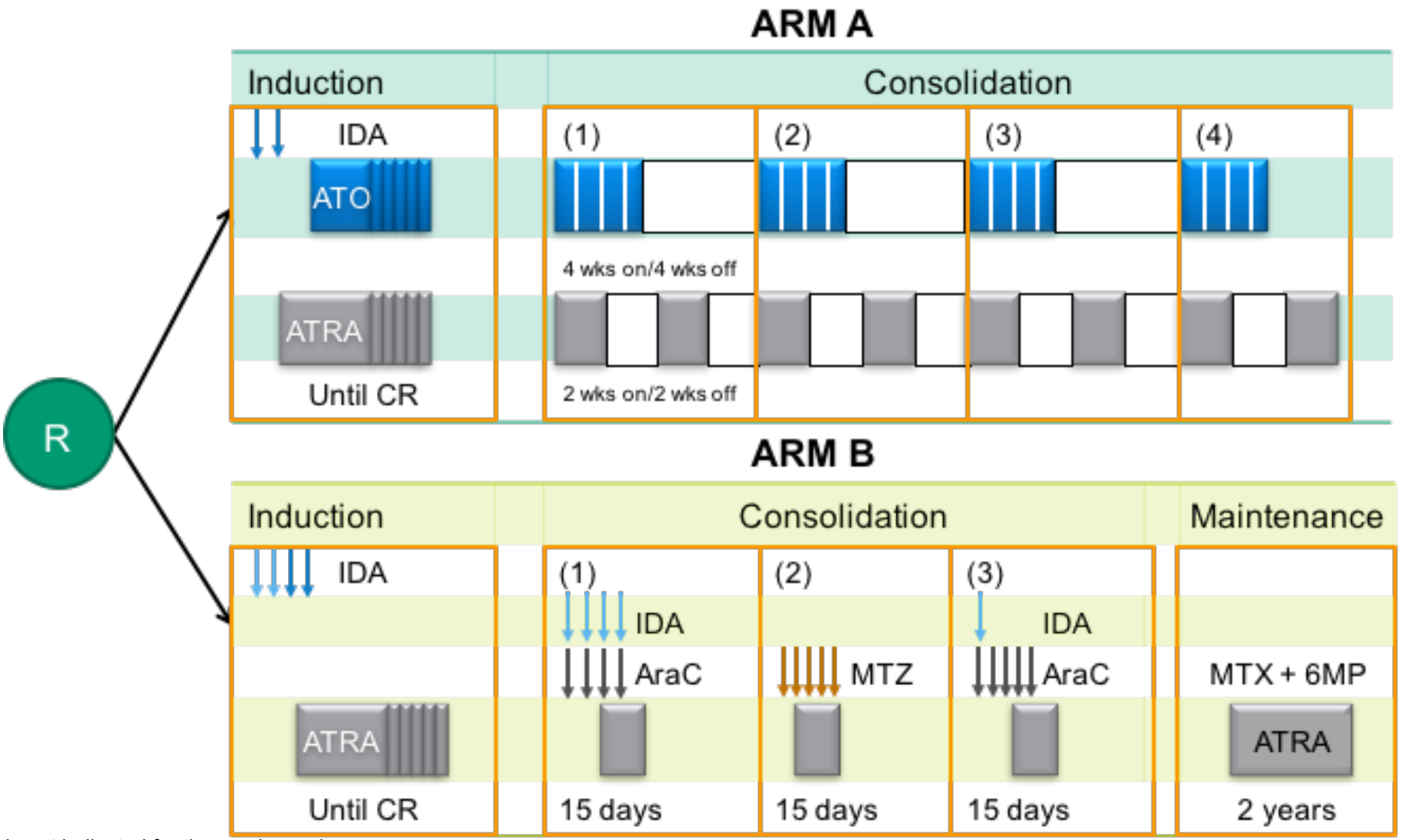
IDA 12 mg/m²/d (día 1)
Ara-C 500 mg/m²/d (días 1,2,3,4)
ATRA 45 mg/m²/d x 15

Mantenimiento (12 semanas)

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

ATRA 45 mg/m²/d x 14 d (sem 9-10)
ATO 0,15 mg/kg/d lu-vi (sem 8-12)

Pan-European randomized trial in high-risk APL (APOLLO trial - NCT02688140)



ATO is not indicated for the use in newly diagnosed high risk APL.

NCT02688140. Available from: https://clinicaltrials.gov/ct2/show/NCT02688140. Accessed October 2016.

Acknowledgements

- Participating institutions and physicians in the PETHEMA-HOVON trials

- Pau Montesinos (University Hospital La Fe, Valencia, Spain)