Tratamiento de las LPA en 2008

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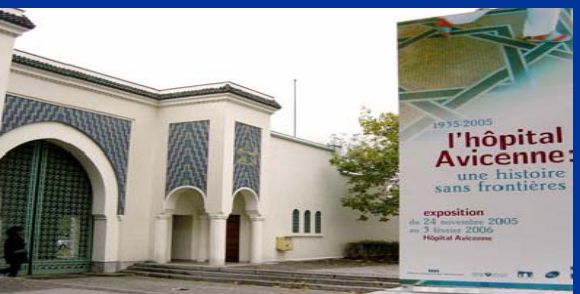


La Serena 9-08

Tratamiento de las LPA

- Fundamentos
- Preguntas actuales sobre el tratamiento de primera linea de las LPA
- Tratamiento de las recaidas

Tratamiento de las LPA

- **Fundamentos**
- Preguntas actuales sobre el tratamiento de primera linea de las LPA
- Tratamiento de las recaidas

Etiology of APL

- 10% of AML
- Incidence depending on ethnic (or environmental ?) factors
- More and more often therapy related (especially after breast carcinoma treated with topo II inhibitors)

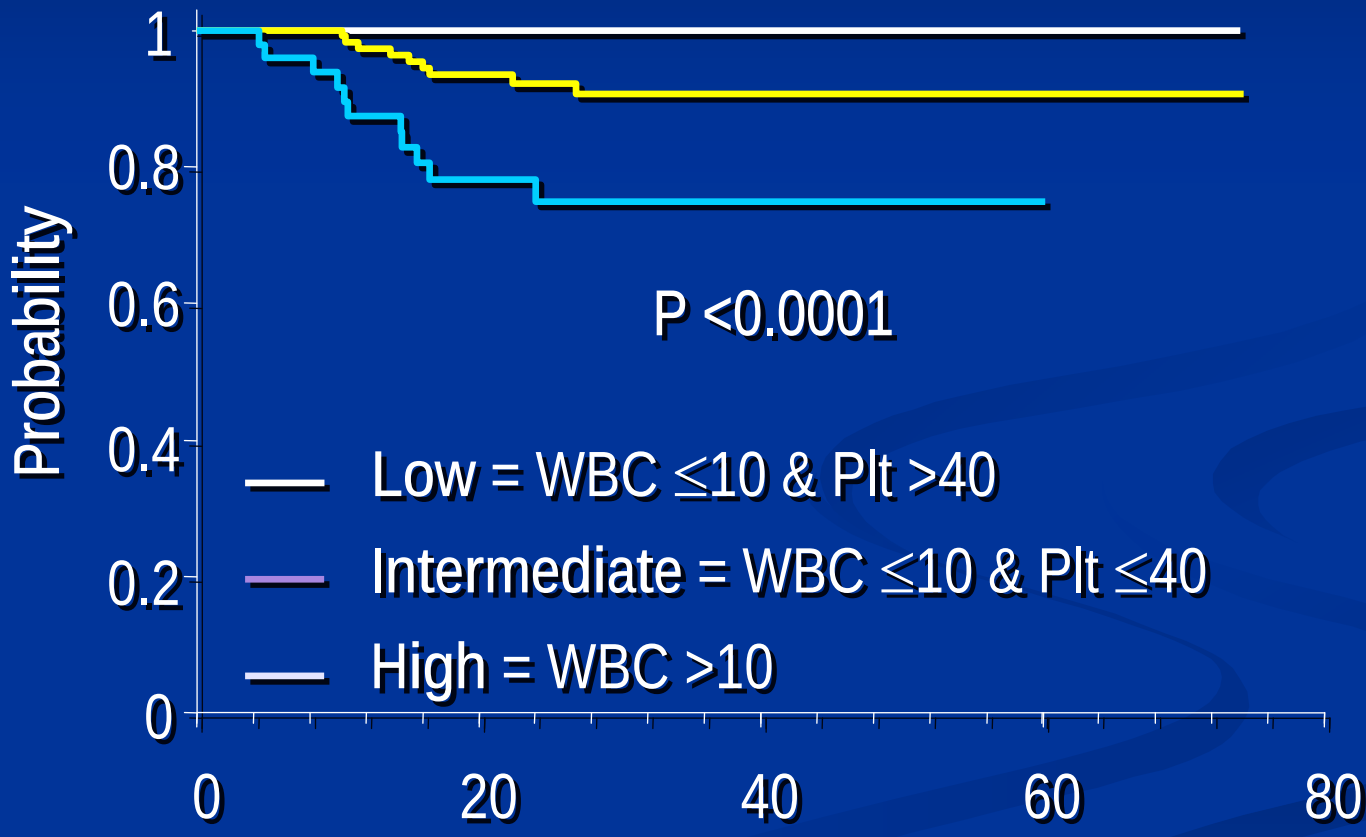
APL characteristics

- Morphology:M3, M3v
- Cytogenetics: t(15;17) (t(11;17,t(5;17) very rare)
  complex or variant translocations
- molecular biology:PML-RAR (bcr1> bcr2>bcr3)
  others (PLZF-RAR,etc very rare)
- Coagulopathy: Diffuse Intravascular Coagulation(DIC)+fibrinolysis

Prognostic factors in APL

- WBC >10000/mm3 (Sanz score)
- RT-PCR analysis after consolidation treatment (but depends on sensitivity of the assay used)
- other factors (M3v,bcr breakpoint, FLT3 ID….:generally redundant with WBC count)

Sanz's score for relapse



Sanz et al, Blood 2000

Treatment of APL

APL sensitive to

- Anthracycline+/- AraC chemotherapy
- ATRA
- Arsenic derivatives
- Gentuzumab ozogamycin

Treatment of APL before the ATRA era: chemotherapy alone

With optimal chemotherapy and treatment of DIC:

- 80% CR rate
- 50% relapses
- almost 40 % cure

ATRA followed by anthracycline based chemotherapy

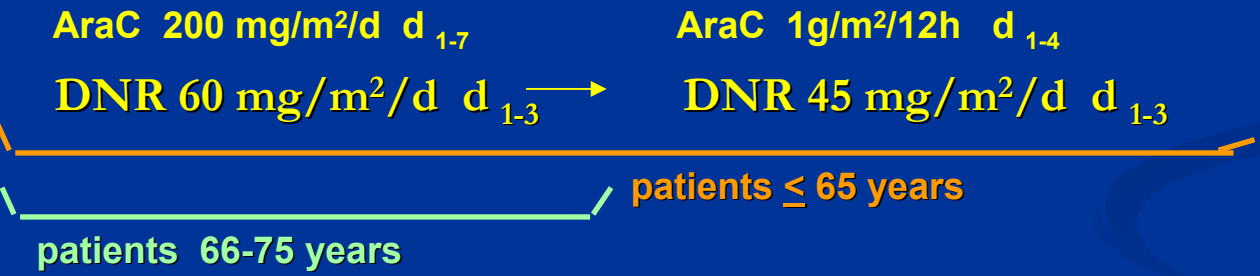
(APL 91 trial)

ATRA : 45 mg/m^2/d until CR

chemotherapy : DNR 60 mg/m^2/d d_{1-3}

AraC 200 mg/m^2/d d_{1-7}

APL 91: CONSOLIDATION TREATMENT



ATRA followed by anthracycline based chemotherapy
(APL 91 trial)

- >90 % CR rate
- 25% relapse (decrease in early relapses)
- Almost 65% cure

- However:

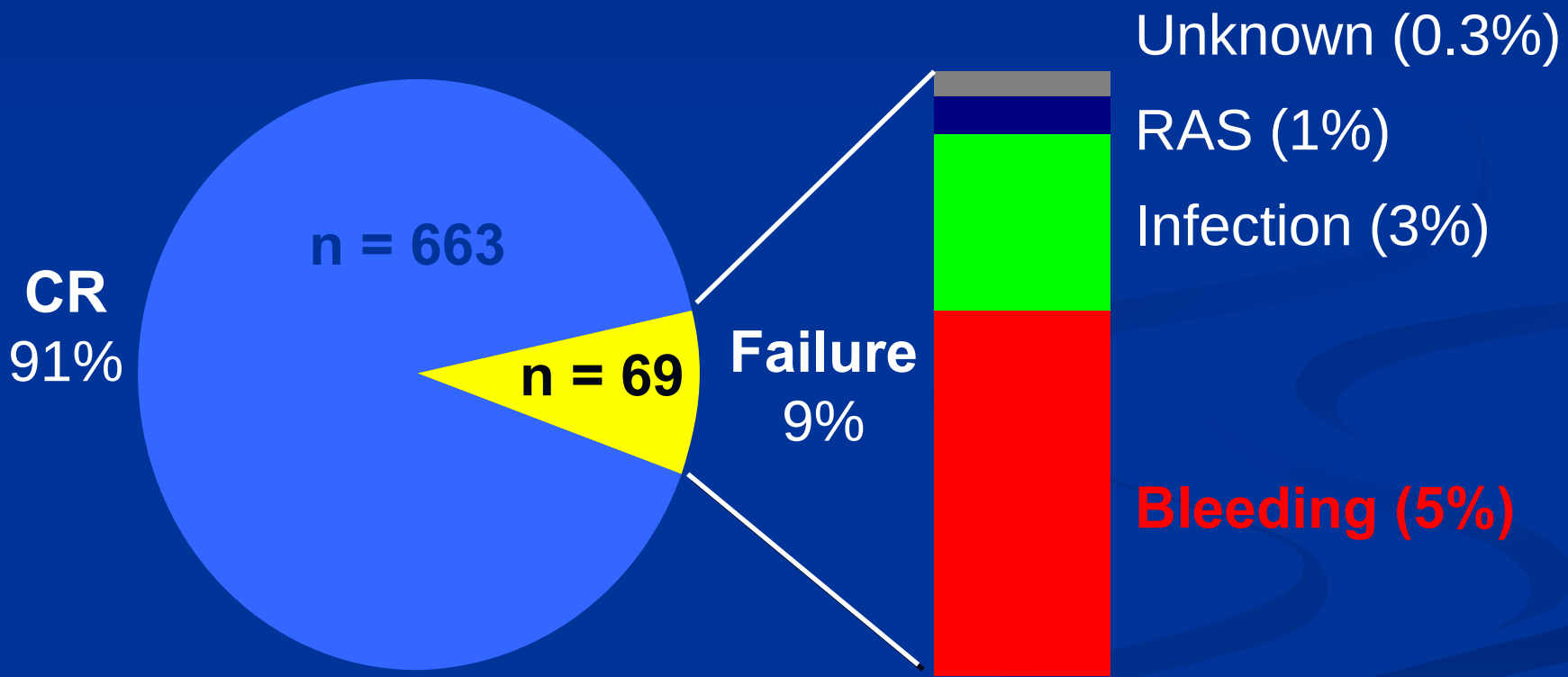
  -Almost 10% absence of CR

  -Still 25% relapses

  - intensive treatment

PETHEMA LPA96 & LPA99 Studies

Induction Response and Causes of Failure



APL 93:DEATHS IN CR

AGE	INCIDENCE
<55	4%
>65	20%

Tratamiento de las LPA

- Fundamentos
- **Preguntas actuales sobre el tratamiento de primera linea de las LPA**
- Tratamiento de las recaidas

Preguntas sobre el tratamiento de primera linea de las LPAs

- cuando empezar quimioterapia ?
- como prevenir y tratar el « ATRA syndrome »?
- papel de AraC ?
- tratamiento de la coagulopatia?
- es util profilaxis del SNC?
- papel del tratamiento de mantenimiento
- papel de alo TPH
- papel de Arsenicos
- tratamiento en ninos y ancianos
- pronostico en pacientes con leucocitos muy altos
- papel de la RT-PCR

Preguntas sobre el tratamiento de primera linea de las LPAs

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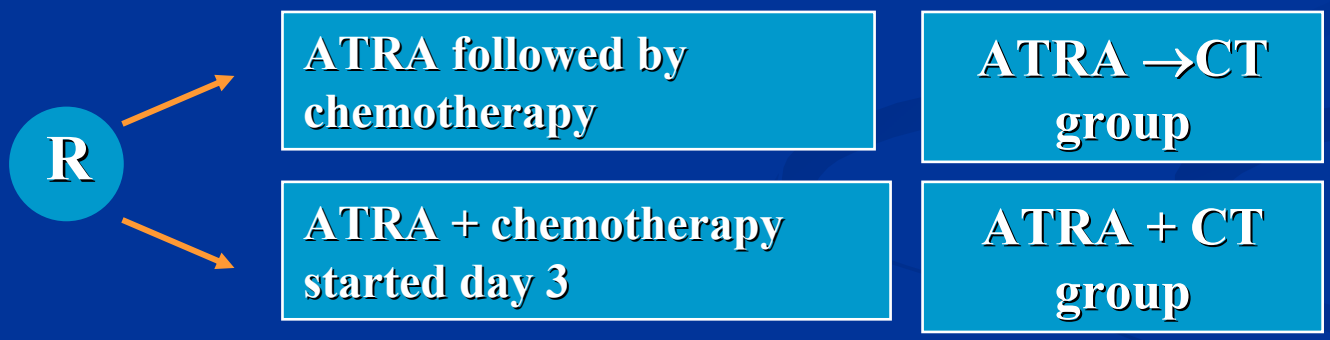
APL 93:INDUCTION TREATMENT

.

WBC ≤ 5000/mm^3 and age ≤ 65:



ATRA : 45 mg/m^2/d until CR

chemotherapy : daunorubicin (DNR) 60 mg/m^2/d d_{1-3}

AraC 200 mg/m^2/d d_{1-7}

Patients randomized for induction

	ATRA→CT	ATRA+CT	p
n	122	185	
CR (%)	93	96	0.12
Relapse at 5 years (%)	19	12	0.04
EFS at 5 years (%)	66	77	0.01
Survival at 5 years (%)	77	84	0.29

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ATRA syndrome or « leukocyte activation » syndrome (can occur after arsenic)

- 10-20% patients
- Fever
- Pleural +/- pericardial effusion
- Pulmonary infiltrates
- Weight gain
- Cardiac failure
- Renal failure
- Generally preceded by increasing WBC counts

Prophylaxis and treatment of ATRA syndrome

1)**Treatment** :high dose DXM (10mg/12H)

2)**Prophylaxis**

increasing WBC:

- Add chemotherapy+ DXM?
- Add high dose DXM only?

Incidence of ATRA syndrome according to initial randomization

(age < 66 and WBC < 5,000) (De Botton, Leukemia,2002)

	No ATRA Sd	ATRA Sd	
ATRA CT *	100 (82%)	22 (18%)	p = .026
ATRA + CT	167 (91%)	17 (9%)	

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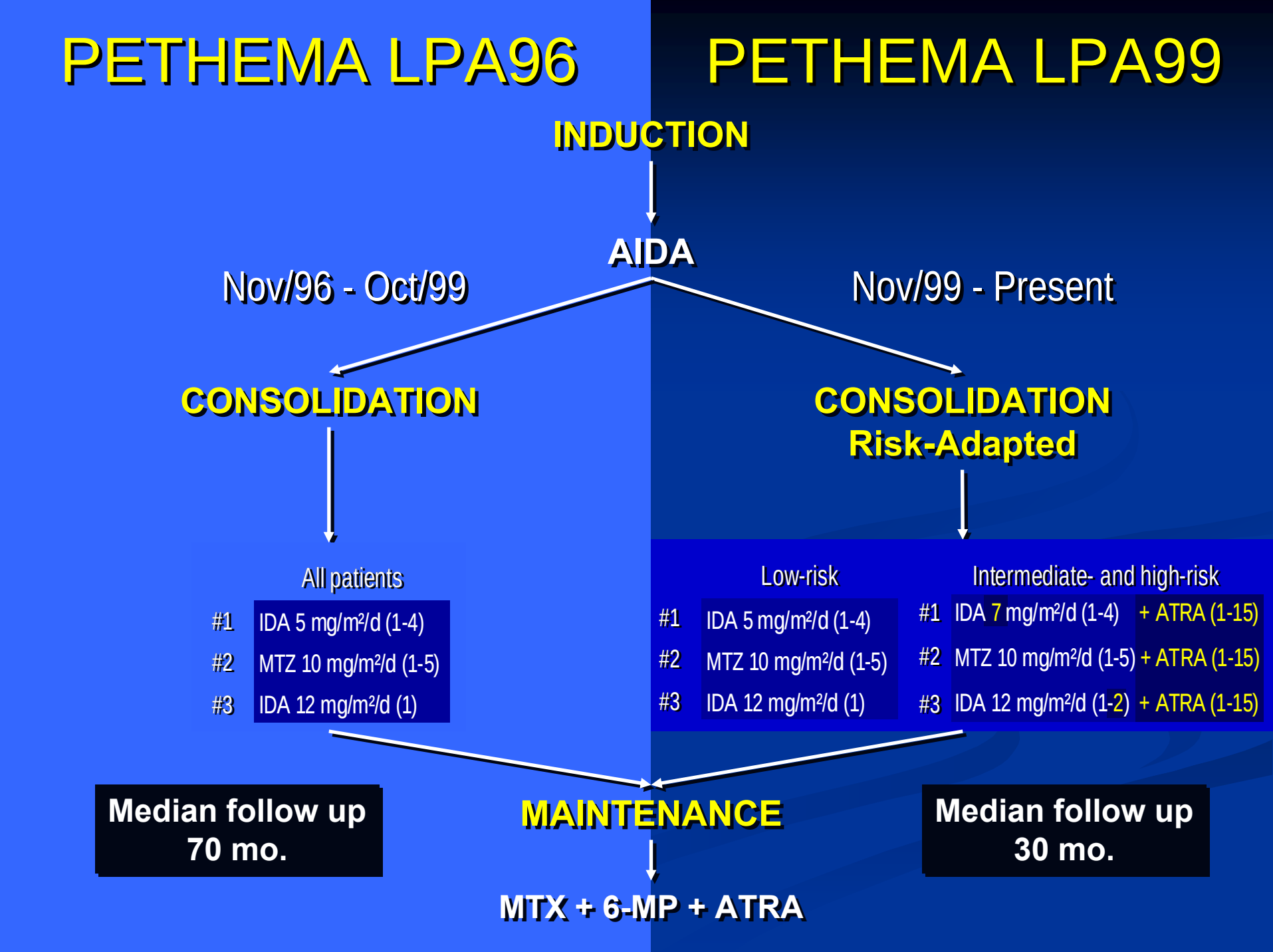

PETHEMA LPA96
PETHEMA LPA99
INDUCTION
AIDA
Nov/96 - Oct/99
Nov/99 - Present
CONSOLIDATION
CONSOLIDATION
Risk-Adapted
All patients
#1 IDA 5 mg/m²/d (1-4)
#2 MTZ 10 mg/m²/d (1-5)
#3 IDA 12 mg/m²/d (1)
Low-risk
#1 IDA 5 mg/m²/d (1-4)
#2 MTZ 10 mg/m²/d (1-5)
#3 IDA 12 mg/m²/d (1)
Intermediate- and high-risk
#1 IDA 7 mg/m²/d (1-4) + ATRA (1-15)
#2 MTZ 10 mg/m²/d (1-5) + ATRA (1-15)
#3 IDA 12 mg/m²/d (1-2) + ATRA (1-15)
Median follow up 70 mo.
MAINTENANCE
Median follow up 30 mo.
MTX + 6-MP + ATRA

PETHEMA LPA96 PETHEMA LPA99

INDUCTION

↓

AIDA

	LPA96 n = 174	LPA99 n = 441	TOTAL n = 615
CR (%)	156 (90)	403 (91)	559 (91)
Induction failure	18 (10)	38 (9)	56 (9)
Early death	*15*	*37*	*52*
Resistance	*3*	*1*	*4*

Sanz *et al*, Blood 2004

LPA96 & LPA99 Trials
Clinical and molecular relapse

	LPA96 N=156	LPA99 N=403
Molecular persistence	5	2
Molecular relapse	7	6
Clinical relapse*	16	13
	28	21
	P = 0.03	
CNS relapse	5 (5 to 49 mo)	4 (8 to 28 mo)

LPA96 & LPA99 Trials
Deaths in CR

	LPA96 N=156		LPA99 N=403	
Before consolidation	0	3	1 (81 yrs)	8
During consolidation	2 (50, 54 yrs)		4 (58, 64, 69, 72 yrs)	
After consolidation	1 (73 yrs)		3 (33, 78, 81 yrs)	

APL 2000 trial (Ades, JCO, 2006)

Patients aged <60 with WBC<10000/mm3:

Reference arm (APL 93): ATRA+DNR+ AraC+ combined maintenance (**ARA C+)**

vs

same without AraC (**ARA C -)**

Chemotherapy: AraC + vs AraC-

	n	CR rate	Leukemic resistance	2 yr cum relapse	2 yr EFS	2 yr OS
NO ARAC -	87	94%	2	11.9%	83.4%	89.9%
ARAC +	80	98%	0	3.8%	93.6%	97.4%
P value		NS		0.021	0.019	0.085

TREATMENT OF NEWLY DIAGNOSED APL : A COMPARISON BETWEEN FRENCH -BELGIAN-SWISS (APL group) AND SPANISH APPROACHES

(Blood , 2007)

L Adès, M Sanz, S Chevret, S De Botton, G Martin, E Raffoux, E Vellenga, A Guerci, M Gonzalez, A Pigneux, C Rayon, AM Stoppa, J De la Serna, T Pabst, S Meyer-Monard, R Parodi, J Bergua, F Rigal-Huguet, A Vekhoff, S Negri, N Fegueux, A Ferrant, D Bron, H Dombret, L Degos. and P Fenaux.

For the European APL group and Spanish PETHEMA group

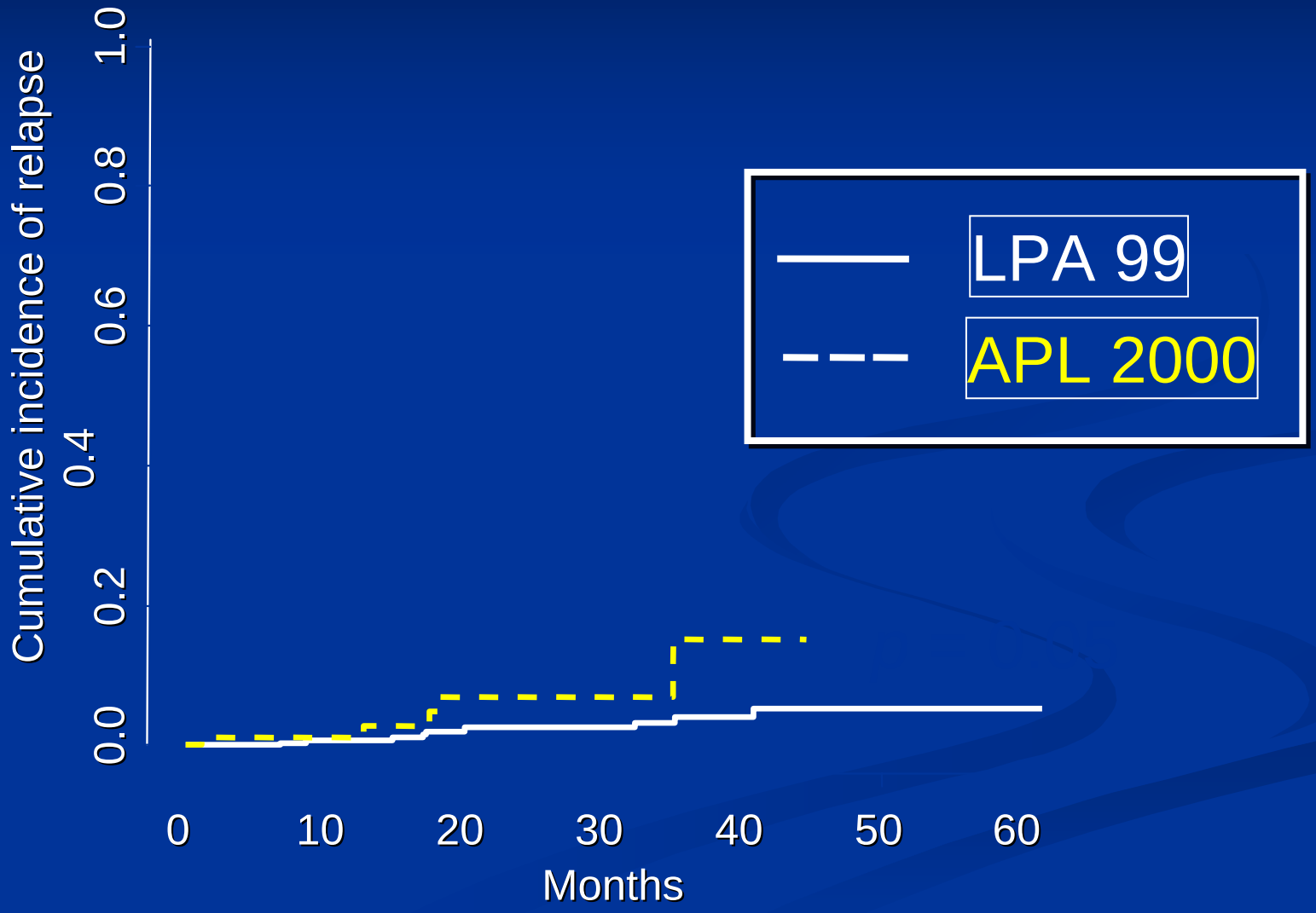
COMPARISON BETWEEN APL2000 & LPA 99

low and intermediate risk groups (WBC< 10000/mm3)

	LPA 99	APL2000	*p*
n	308	96	
CR rate	96%	99%	0.2
Cumulative incidence of Relapse	2.5%	6.9%	0.05
2-year EFS	93%	91%	0.51
2-year OS	95%	97%	0.41

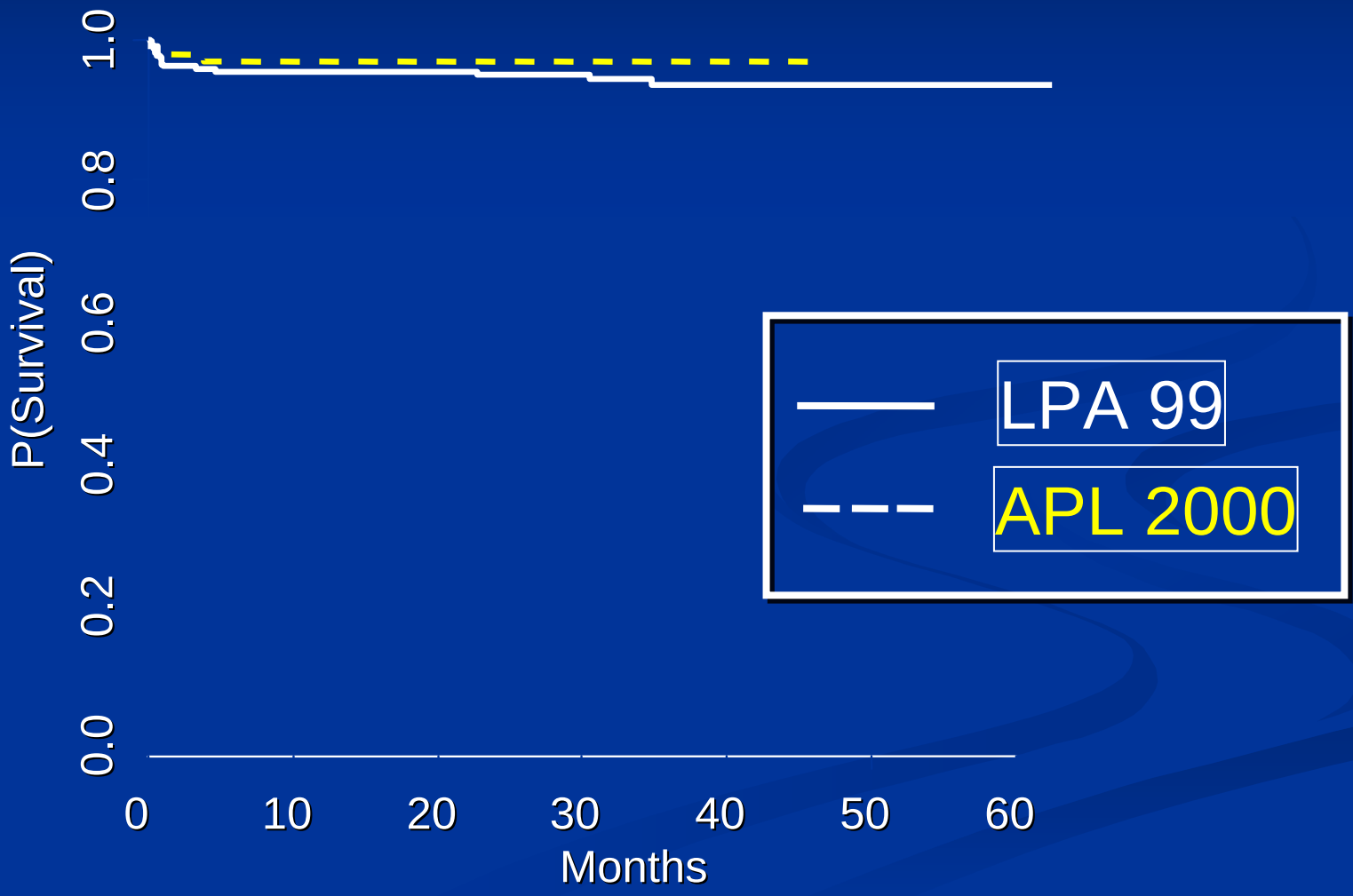
Cumulative incidence of relapse

Low and Intermediate risk group



Overall Survival

Low and Intermediate risk group



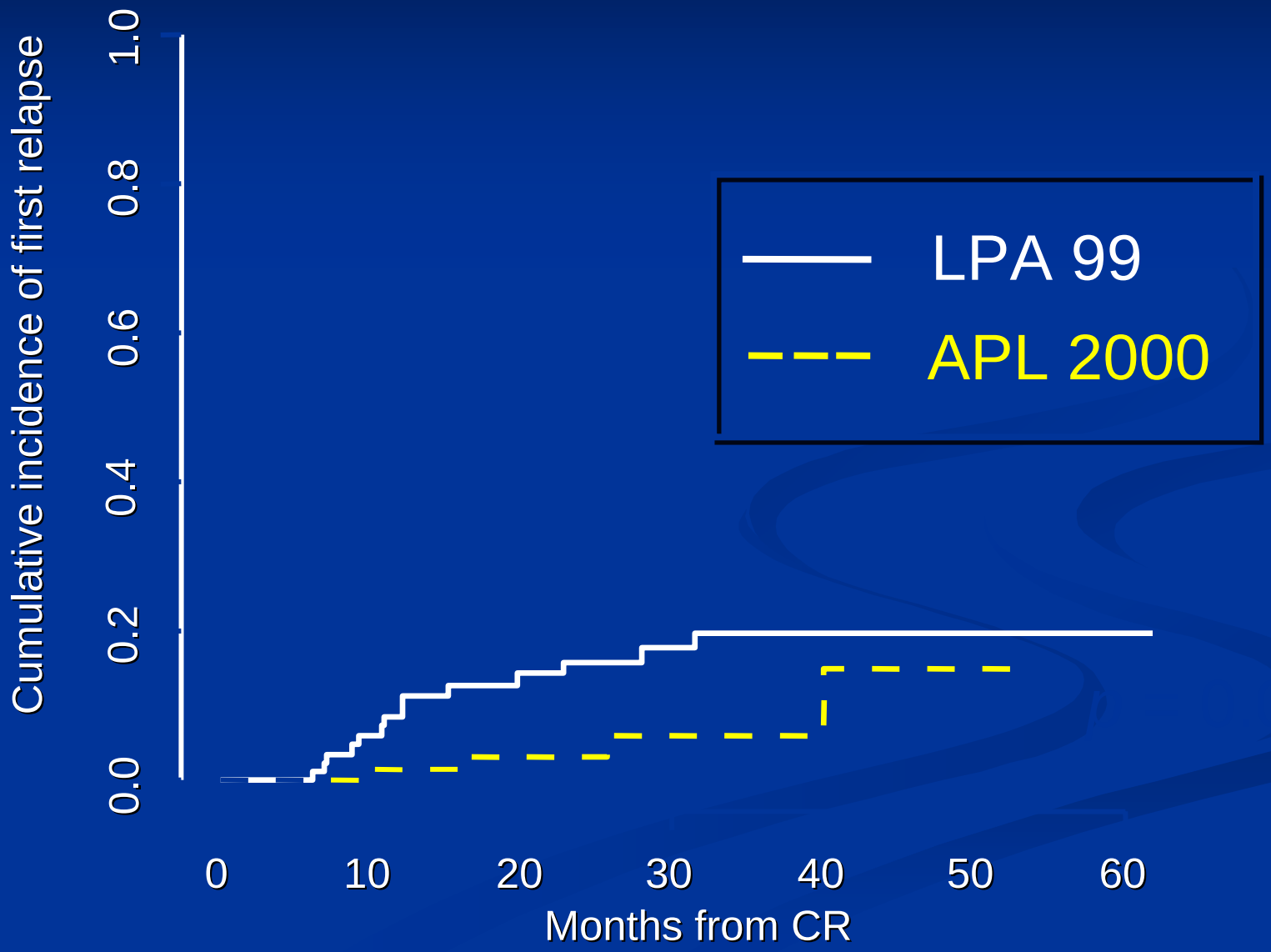
COMPARISON BETWEEN APL2000 & LPA 99

High risk group (WBC > 10000/mm3)

	LPA 99	APL2000	*p*
No patients	104	83	
CR	84	95	0.02
Cumulative incidence of Relapse	16%	3.3%	0.04
2-year DFS	69.2%	88%	0.01
2-year OS	82.4%	91%	0.05

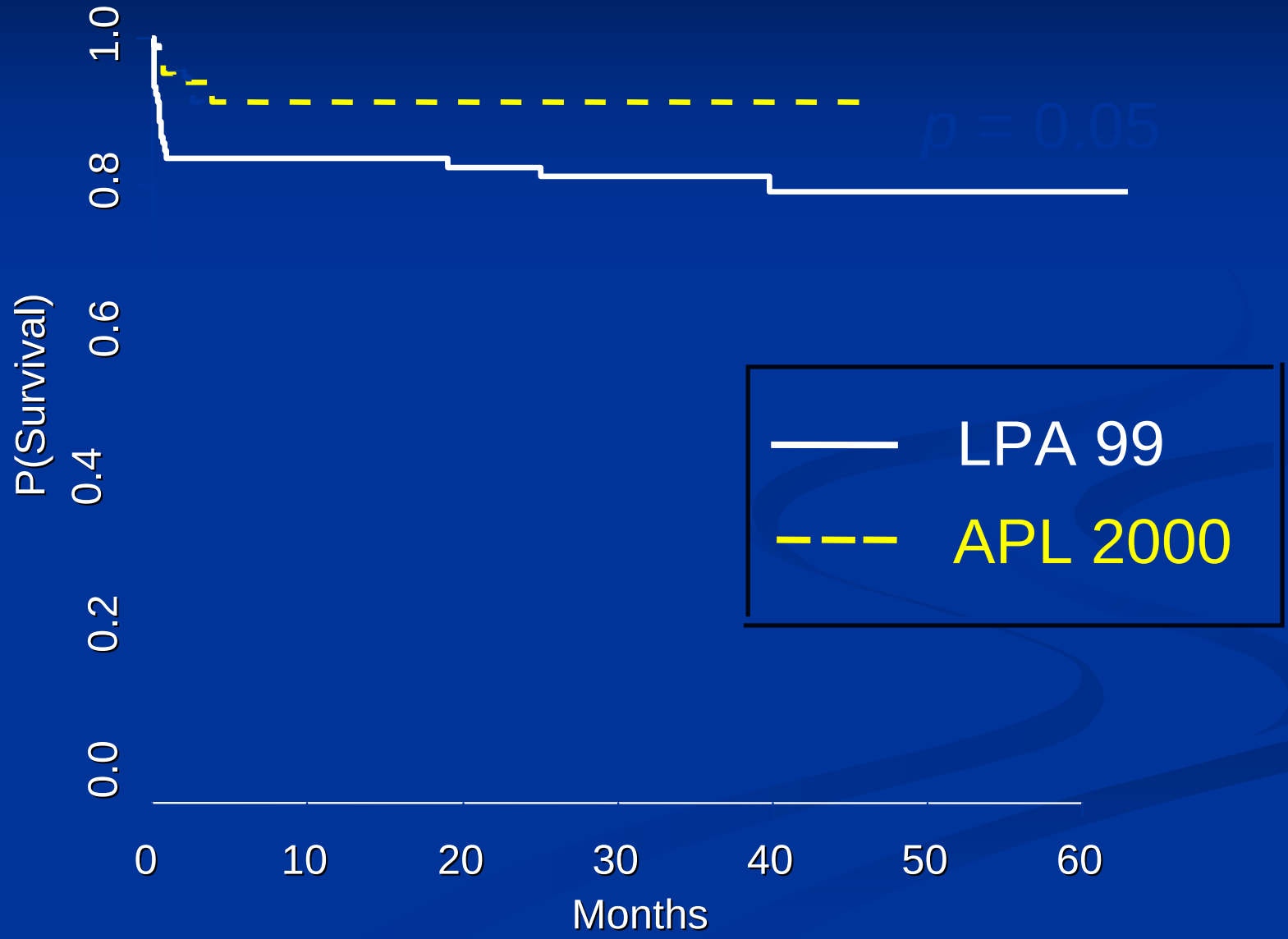
Cumulative incidence of relapse

High risk group



Overall Survival

High risk group



Conclusion (I)

- In patients with WBC < 10.000/mm^3,the current PETHEMA approach appears to yield even fewer relapses than a classical ATRA + DNR + AraC regimen, while being less myelosuppressive.

- **Reasons:**
  - Anthracyclines used ?
    - IDA and MTZ instead of DNR
  - Higher cumulative dose of anthracyclines ?
  - Consolidation ATRA for intermediate risk pts?

Conclusion (II)

- **In patients with high WBC counts, APL 2000 results yielded better EFS and survival and fewer relapses suggesting a beneficial role for AraC in this subset of patients.**
- **(or of other treatments like ATO)**

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Treatment of coagulopathy

- **Intensive platelet support (maintain plts>50000/mm3)**

- 0ther measures (heparin,antifibrinolytic agents,fibrinogen)?

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Extramedullary relapses: European and Pethema group experience (De Botton,Leukemia, 2003)

- **806 pts** included in APL91 , APL93 , PETHEMA 96 trial
- 738 (92%) CR . 174 relapses
- 14 EMD relapses =

  8% of the relapses

- EM site : CNS (n=10), skin (n=3), orbital (n=1)
- Associated bone marrow (BM) relapse (n=9)

Patients with EM relapse characterized, by

- **younger age** (p=.03)
- **higher WBC counts** (p=.007)
- No high dose AraC (p=0.03)

Outcome of EMD relapses

- 4 (29%) pts still alive after 41+ to 53+ months.
- Median survival from EMD 13 months,

Supports CNS treatment in pts with high WBC counts(>10000)
-intrathecaI MTX+ AraC
-high dose AraC?

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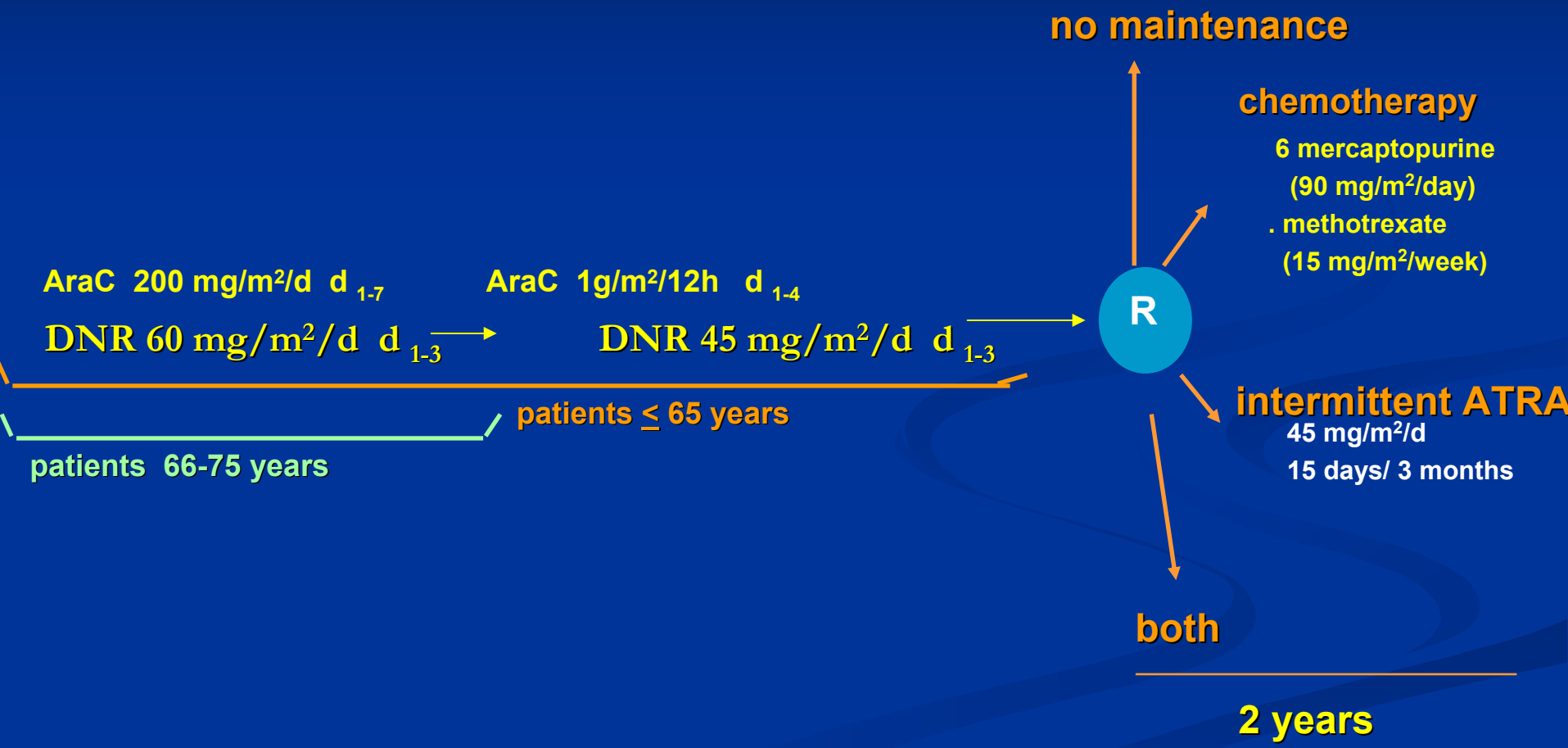
APL 93: MAINTENANCE TREATMENT

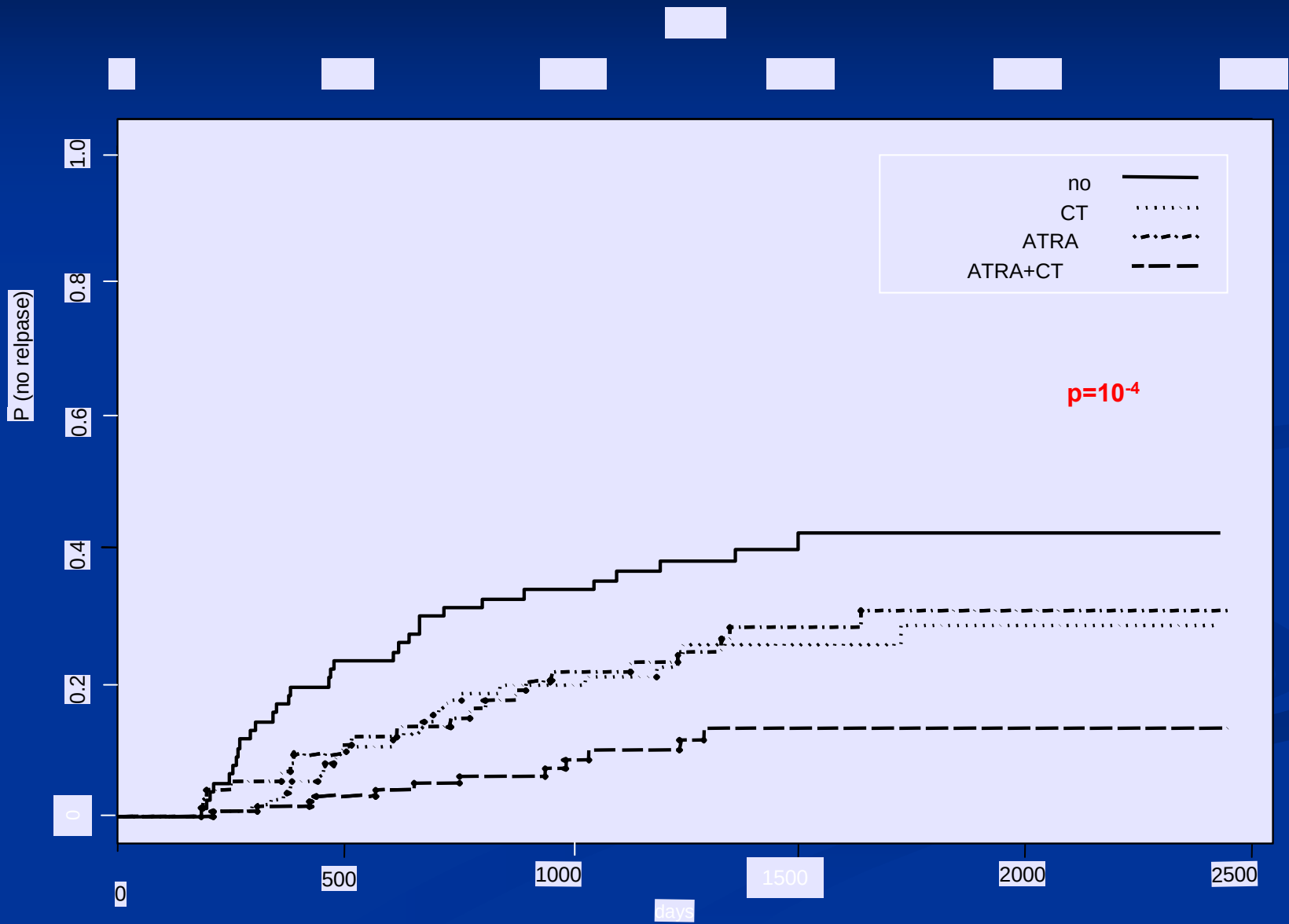


Time to relapse according to maintenance

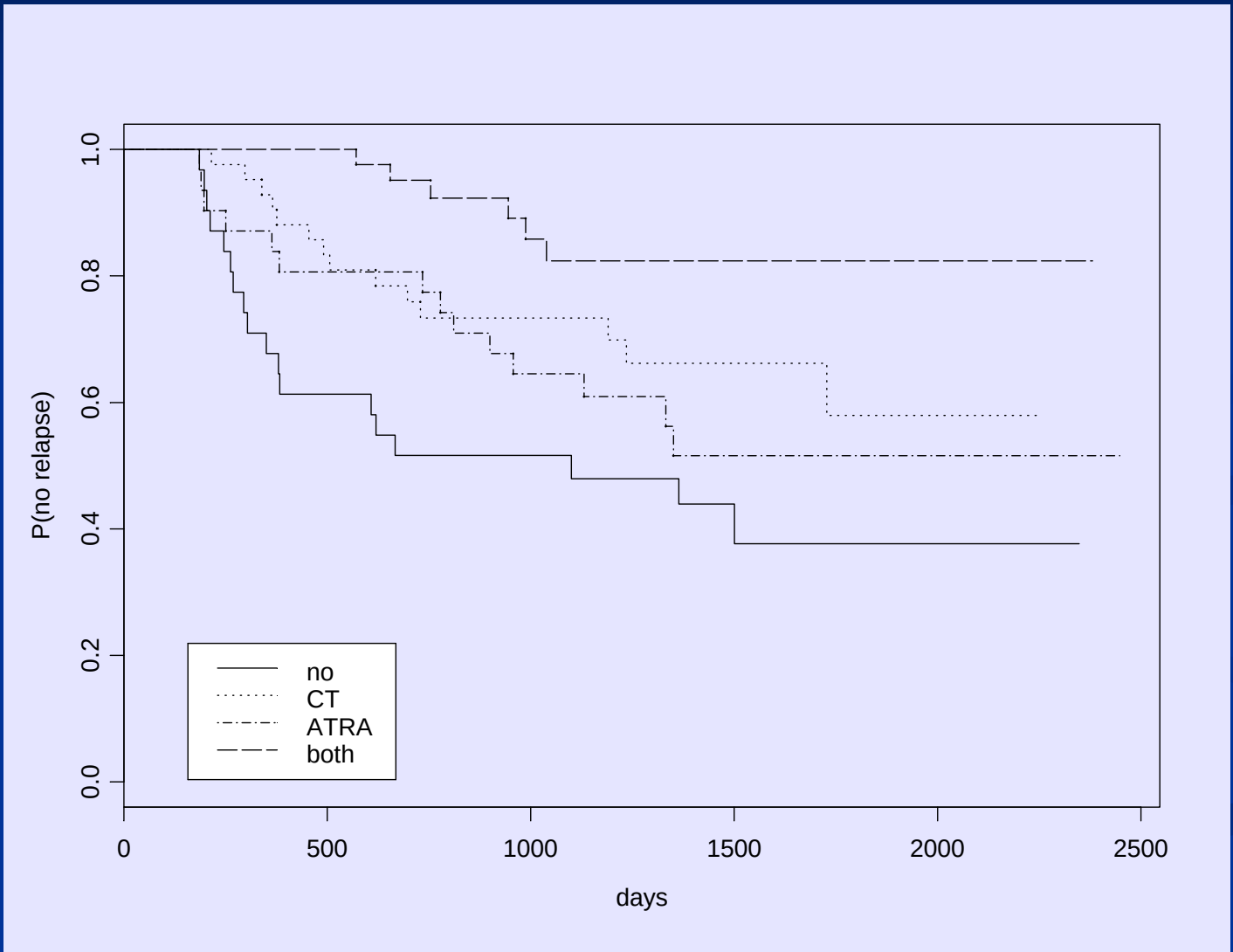
	No CT	CT	
n	155	246	
N. of relapses	57	47	
relapses at 5 years	37%	21%	$p=10^{-4}$

	No ATRA	ATRA	
n	205	196	
N. of relapses	61	43	
relapses at 5 years	34%	21%	$p=10^{-4}$

Time to relapse according to second randomization



Time to relapse according to second randomization in patients with WBC counts >5000/mm3



Duration of maintenance treatment (APL 93 trial):

46 patients < 1 year (due to side effects): 21/46 (45%) relapses

313 patients > 1 year: 49/313 (16%) relapses

Maintenance discontinuation <1 year may be deleterious

SIDE EFFECTS OF MAINTENANCE TREATMENT

. Increased Liver enzymes :

- ATRA	7%
- CT	35%
- ATRA+CT	34%

- Cytopenias with CT usual
- Pneumocystis pneumonia 3

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Allo SCT in first CR : very rarely indicated

- For patients remaining RT-PCR positive after consolidation treatment ? NO: arsenicos
- For patients with VERY high WBC counts (eg>50000/mm3) NO

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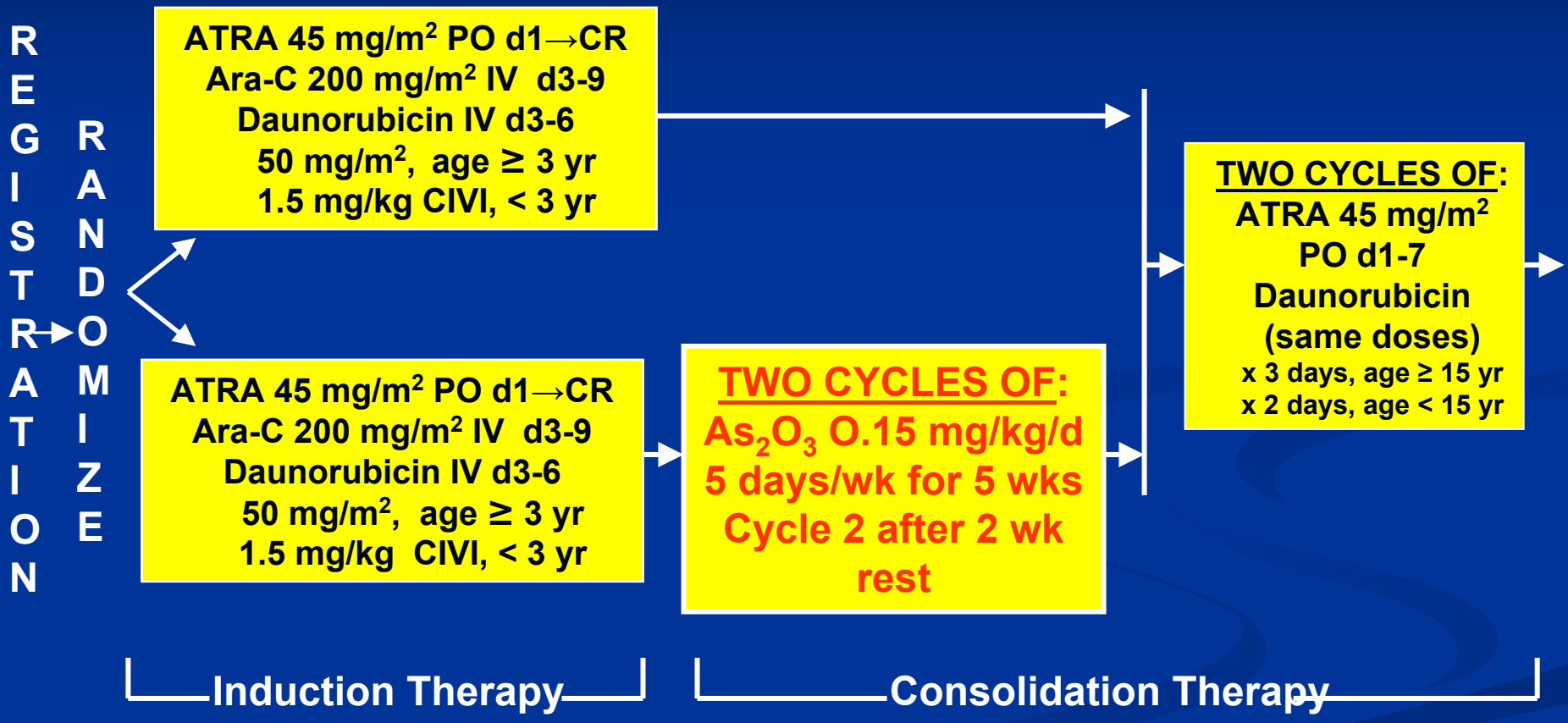
USA intergroup APL trial



USA intergroup APL trial–
Event Free Survival at 3 Years

As_2O_3	81%
No As_2O_3	66%

$p^*=0.0007$

*Kaplan-Meier

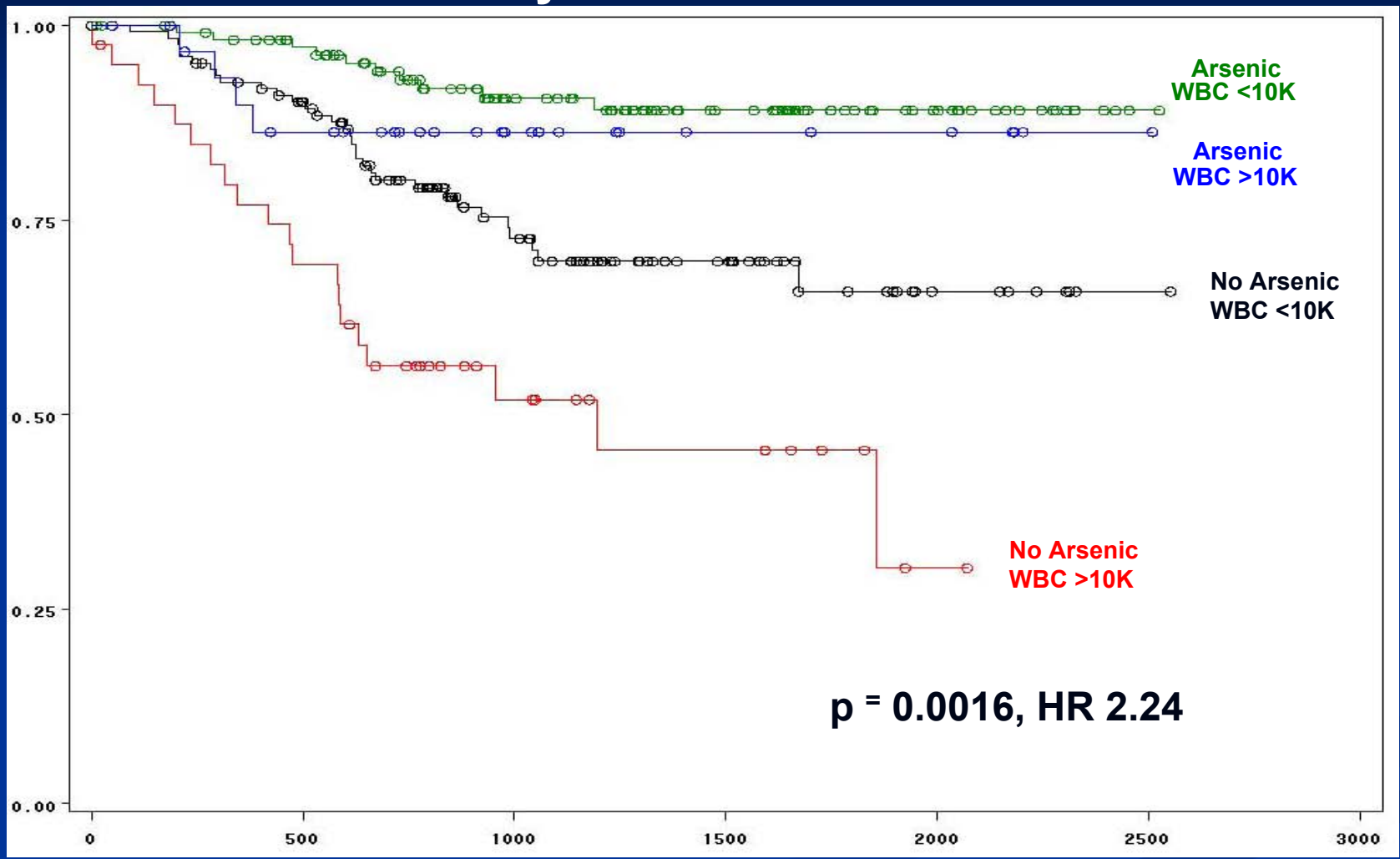
USA intergroup APL trial
Survival at 3 Years

As_2O_3	86%
No As_2O_3	79%

$p^* = 0.063$

*Kaplan-Meier

DFS By Treatment and WBC



Induction treatment of APL with ATRA and ATO (Shen,PNAS,2004,101,5328)

- **ATRAvs ATO vs ATO+ATRA followed by 9 cycles of chemotherapy** (3 DNR-AraC,3 AraC, 3 homoharringtonine-AraC)
- 61 pts; similar CR rates

- **0/20 relapses in the combined arm, vs 7/37 with monotherapy ($p<0.05$)**

Treatment of newly diagnosed APL with ATO alone (Ghavamzabeh,Ann Oncol, 2006, 17, 131)

- ATO 0.15 mg/kg/d until CR , then one consolidation course of 28 days
- 111 pts. 95 (85.6 %) CR
- Treatment Complications:
  - Leukocyte activation syndrome (10 cases,4 fatal)
- 2 year DFS 63.7%

Treatment of newly diagnosed APL with ATO alone (Mathews, Blood, 2006, 107, 2627)

- ATO 0.15 mg/kg/d until CR , then one consolidation course of 28 days, then 10 days/ month during 6 months
- 72 pts. 86% CR
- HY added in 53 pts, anthr in 8 pts
- 3 year DFS 87 %

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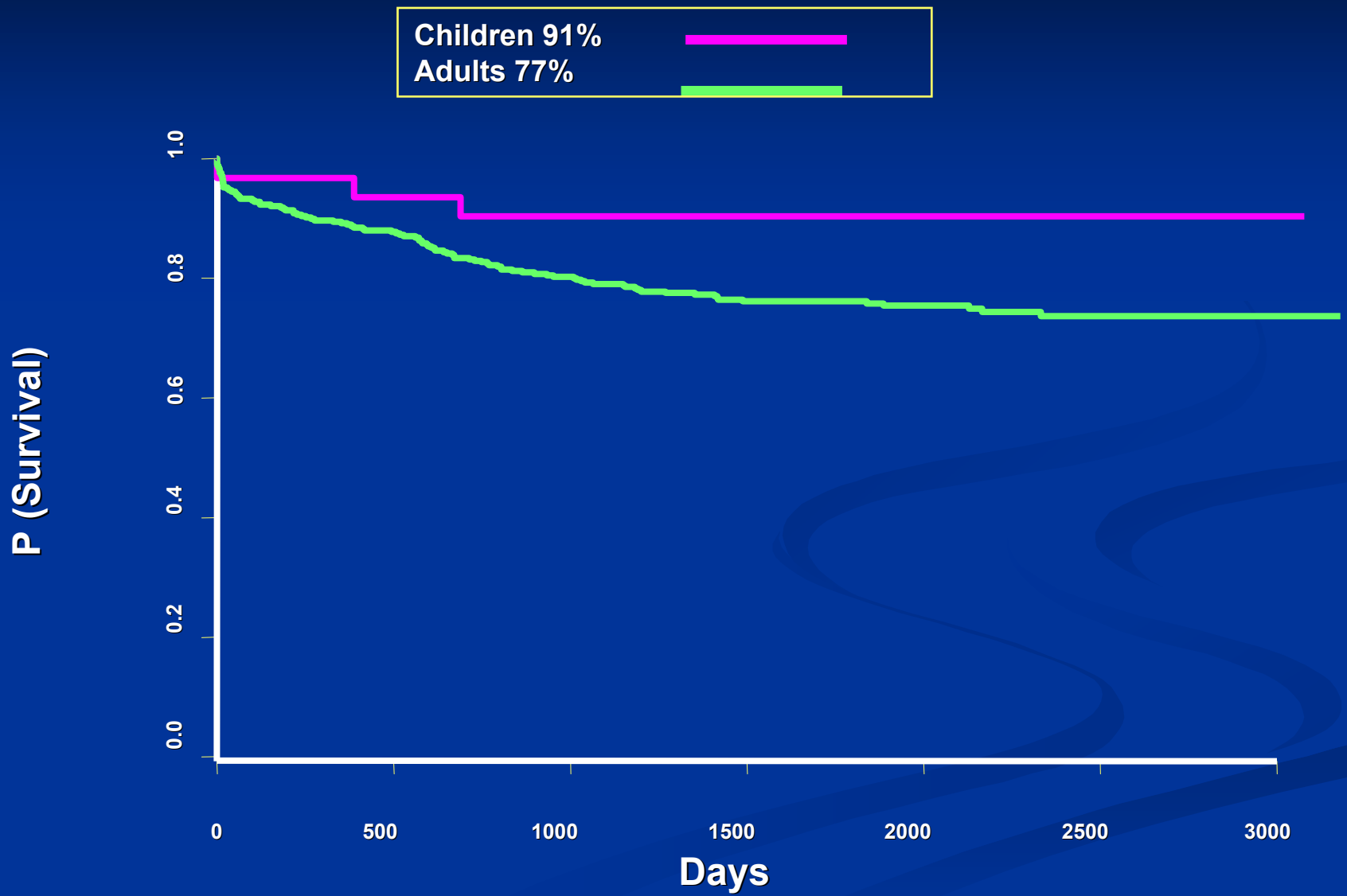
APL in children

(De Botton,JCO,2004)

- 10% of APL
- Often high WBC counts
- More relpses with ATRA+ chemo than in adults
- Concerns about:
  - Initial doses of ATRA (25 mg/m2)
  - High cumulative doses of anthracyclines

5-year OS


Children 91%
Adults 77%
P (Survival)
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
2000
2500
3000
Days

APL in the elderly

(Ades,Leukemia,2006)

- **20% of APL aged>60**

- **CR rate (APL 93)**

< 60	94 %	difference due to
> 60	86 %	early death
> 70	85 %	rate

APL in the elderly (2)

- Relapse at 4 years
  - 26 % in pts < 60
  - 20 % in pts > 60
- Survival at 4 years
  - 79 % in pts < 60
  - 55 % in pts > 60

due to deaths in CR

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Outcome of APL with very high WBC count
(C Kelaidi, ASH 2007)

- **High** WBC count:> 10000/mm3
- **Very High** WBC counts >50000/mm3

Outcome of APL with high WBC count (APL 93)

	WBC<10	10-50	>50	P value
CR rate	94%	90%	82%	0.07
ED rate	6%	10%	18%	0.02
5 y CIR	18%	40%	59%	<0.0001
5y OS	77%	68%	36%	<0.0001

Outcome of APL with high WBC count (APL 2000)

	WBC<10	10-50	>50	P value
CR rate	95%	93%	92%	0.35
ED rate	5%	7%	8%	0.47
3 y CIR	11%	13%	24%	0.15
3 y OS	91%	88%	86%	0.25

Improvement of APL with high and very high WBC count

- For CR rate
  - Intensive platelet support
  - High dose steroids ?
- For relapse
  - Combined maintenance treatment

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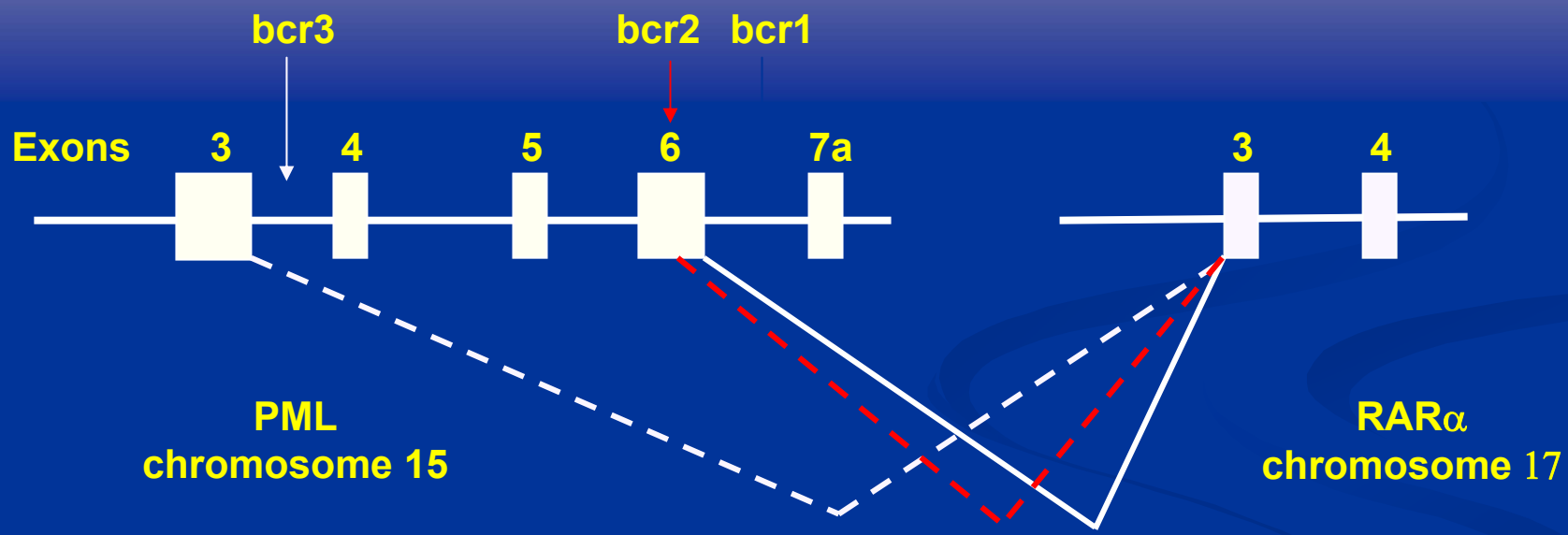
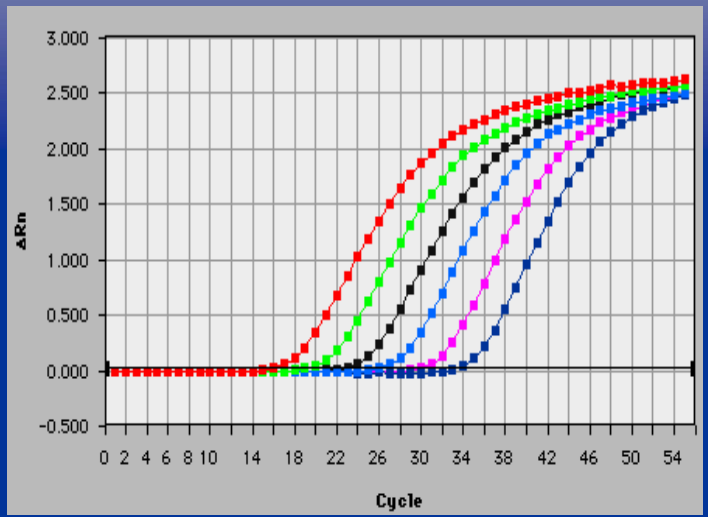
- pronostico en pacientes con leucocitos muy altos
- papel de la RT-PCR quantitativa

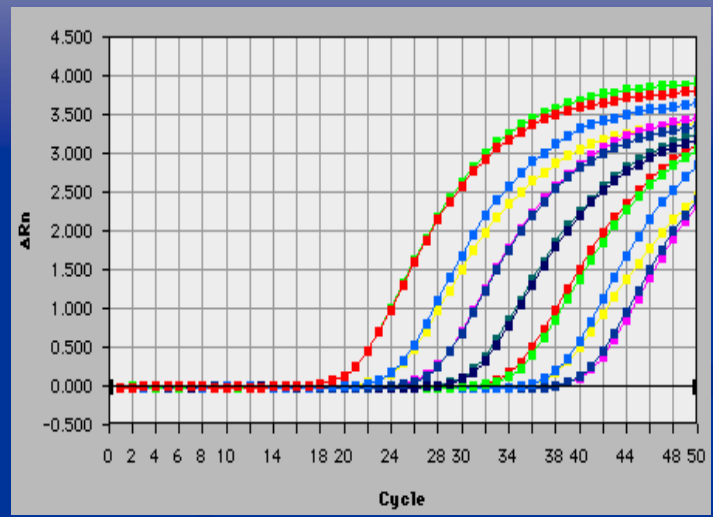
PML-RARα RQ-PCR Protocol (B Cassinat)



APL: 3 transcripts (bcr1, 2, 3)

RQ-PCR Protocol





- standards: plasmids
- reference gene: PBGD
- results: PML-RARα copy number / 104 PBGD copy number

RQ -PCR follow up (B Cassinat)

260 APL patients followed during 4 years

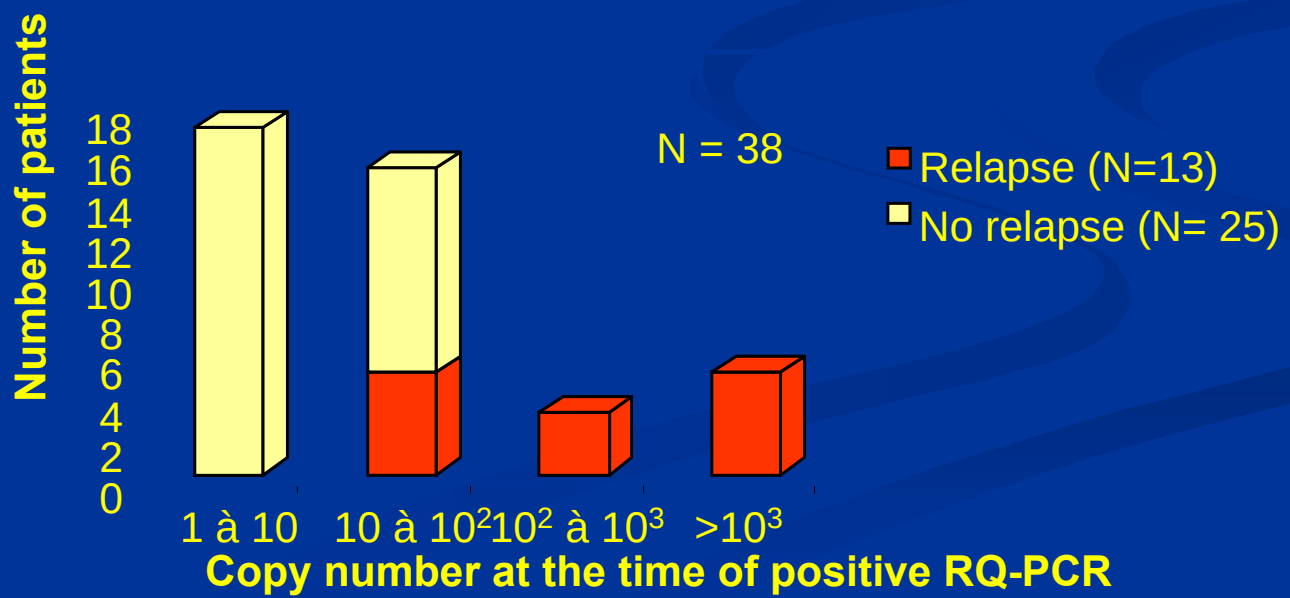
- Median follow up: 25 months (1 to 83 months)

  Median 6 samples/patient

38 patients positive at least once after negative samples

- 13 relapsed after 1 to 9 months
- 25 had not relapsed after > 12 months

Prognosis of APL patients according to level of RQ-PCR positivity



Tratamiento de las LPA

- Fundamentos
- Preguntas actuales sobre el tratamiento de primera linea de las LPA
- **Tratamiento de las recaidas**

- **TREATMENT OF RELAPSING APL WITHOUT As2O3 (European APL group experience)**

  (De Botton,JCO,2005)

- 564 patients <66 years in APL 91 and APL 93 trials :525 (93%) achieved CR.

- **122 /140 (87%) relapsing patients achieved CR2**

  ATRA:8

  ATO:4

  Chemotherapy(CT):24

  ATRA+CT:98

. 47 pts received no auto or allograft: 3 year EFS of 36%

APL in CR2:Allo and auto SCT

(De Botton,JCO,2005)

	Auto SCT		Allo SCT	
		APL Study Group** (Europe)		APL Study Group** (Europe)
No. Pts		50		25
Relapse		21%(7 yrs)		8%
DFS		79%(7 yrs.)		52%
OS		60%(7 yrs.)		52%
TRM		6%		39%

Arsenic trioxyde in relapsing APL

Ref	Dosing	Nb pts	CR rate	Post induction	Long term outcome
				As_2O_3 alone (n =18)	12/18 relapses
Niu	0.15mg/kg/	47	85 %		
				As_2O_3 + CT (n =11)	2/11 relapses
Shen	0.08 mg/kg	20	80 %	variable	2 year relapse free survival : 61 %
Kwong	10 mg	8	100 %	Ida	7/8 still in CR 6 in molecular CR
Soignet	0.15 mg/kg	52	87 %	Allo (n = 9) or auto (n = 3)	11 still in CR
				As_2O_3 (n = 21)	9 still in CR
Ohnishi	0.15 mg/kg	14	78 %	As_2O_3	median CR duration : 8 months

As203 in relapsing APL: recent French experience

(X Thomas et al, Hematologica, 2006)

- 28 pts (R1=22;R>1=6) between 2002 and 2005
- Median previous CR duration 20 m (1-74)
- 24 CR, 2 early deaths, 2 leukemic resistance
- 24% grade III-IV infections, 20% APL differentiation syndrome

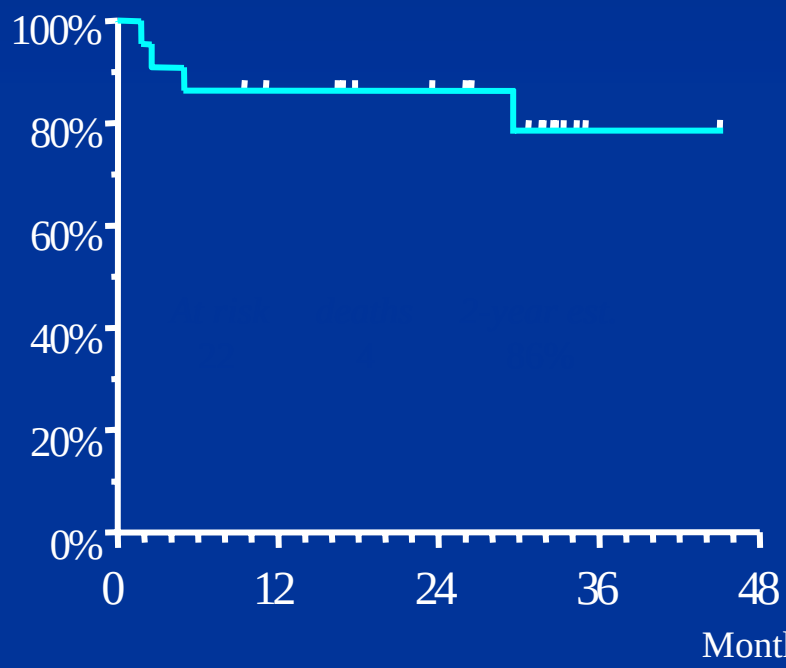
As203 in relapsing APL: recent French experience

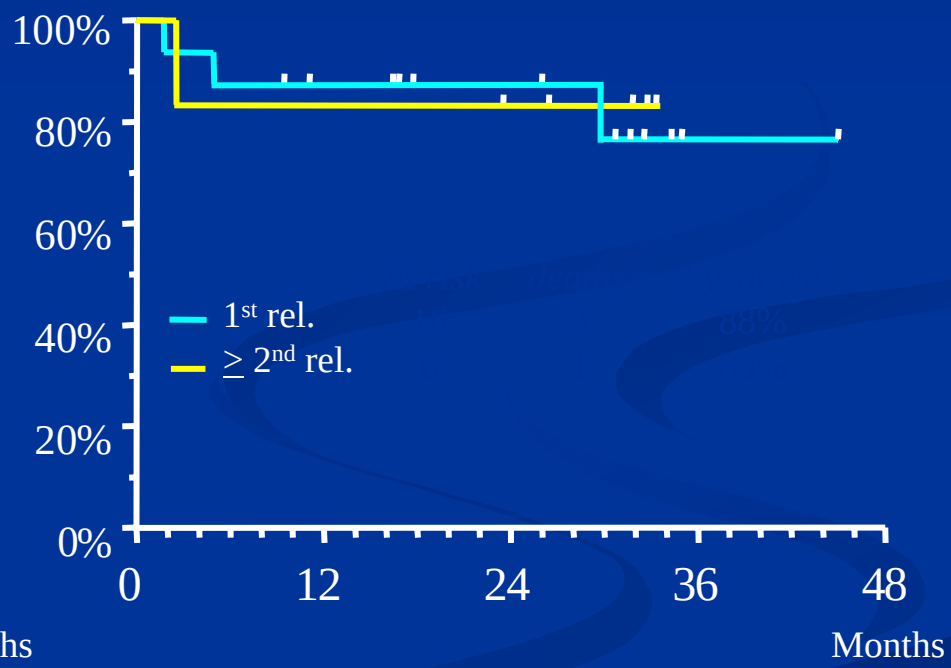
(X Thomas et al)

	With As2O3	Without As2O3
2 y LFS	84%	47%
2y OS	79%	51%
Grade III-IV infections	24%	54%

Allo SCT after ATO Salvage

Post-transplant survival (Soignet,Dombret)





Median follow-up: 30 months post SCT (range, 9.5 to 45)

Treatment of APL molecular relapse by Gentuzumab ozogamycin(GO) (Lo Coco,Blood,2004)

- 16 pts with molecular relapse (8,5,2,1)
- GO 6mg/m2 x 2 + 1
- 14 molecular CR achieved
- 7 pts still in CR (7+ to 31+ months),7 relapses after 3 to 15 months

European recommendations for APL patients in first relapse

- Induction with ATO (0.15 mg/kg, max 50 days)
- Consolidation with ATO (5 days/w for 25 doses)

donor and<40yrs:allo

no donor:Ida AraC
-if PCR neg:auto
-if PCR pos:GO,etc..

elderly pts:maintenance
ATO,ATRA
low dose CT,GO

,

APL 2006 trial:Patients<70 , WBC <10000/mm3

IDA 12 mg/m² x4

AraC 200 mg/m²

IDA 9 mg/m² x3

AraC 1 g/m² x 8

ATRA 45 mg/m²

IDA 12 mg/m² d1-d3-d5

AraC 200 mg/m²

R

IDA 12 mg/m x4ATRA day 1-15

IDA 9 mg/m² 3ATRA day1-15

MAINTENANCE : ATRA – 6MP+MTX

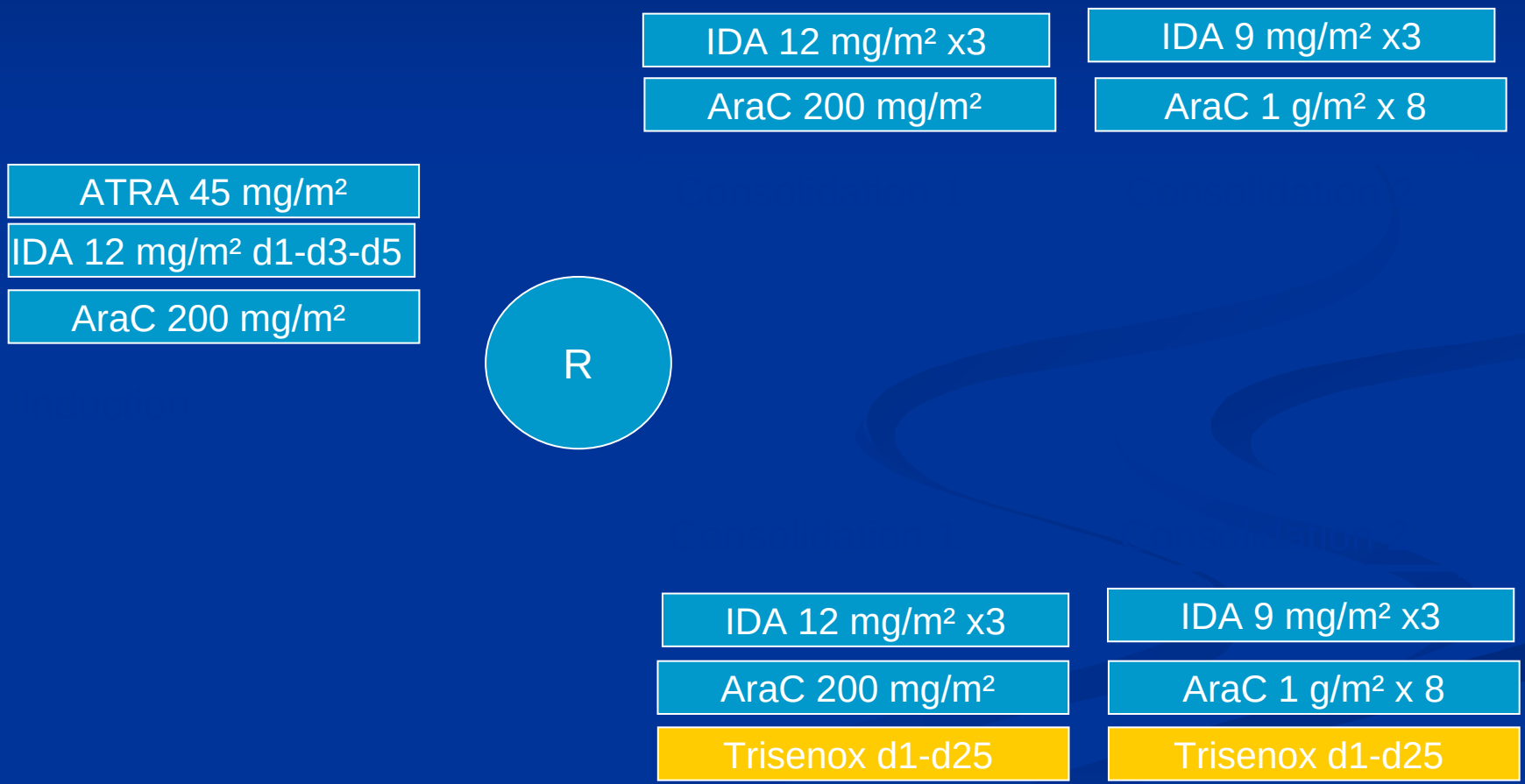
IDA 12 mg/m² x4

Trisenox d1-d25

IDA 9 mg/m² x3

Trisenox d1-d25

APL 2006 trial: Patients < 70 yrs with WBC>10000/mm3



APL 2006 trial: patients< 70 yrs,WBC<10000/mm3

ATRA 45 mg/m²

IDA 9 mg/m² d1 d3 d5

IDA 9 mg/m² d1-d3

Trisenox d1-d25

ATRA 45 mg/m² d1-d15

Trisenox d1-d25

MAINTENANCE : During the 1st year
, ATO will be added to the classical maintenance
with continuous low dose chemotherapy
and intermittent ATRA (2 years).

French Belgian Swiss APL group

- All participating centers
- Clinical trials and date management
  - L Ades
  - C Kelaidi
  - S de Botton
  - B Beve
- Minimal residual disease
  - B Cassinat
  - C Chomienne
- Biostatistics
  - C Chevret