Front-line Therapy in Acute Promyelocytic Leukemia

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La Fe
DEPARTAMENT DE SALUT

Instituto de Investigación Sanitaria La Fe

GENERALITAT VALENCIANA
CONSELLERIA DE SANITAT

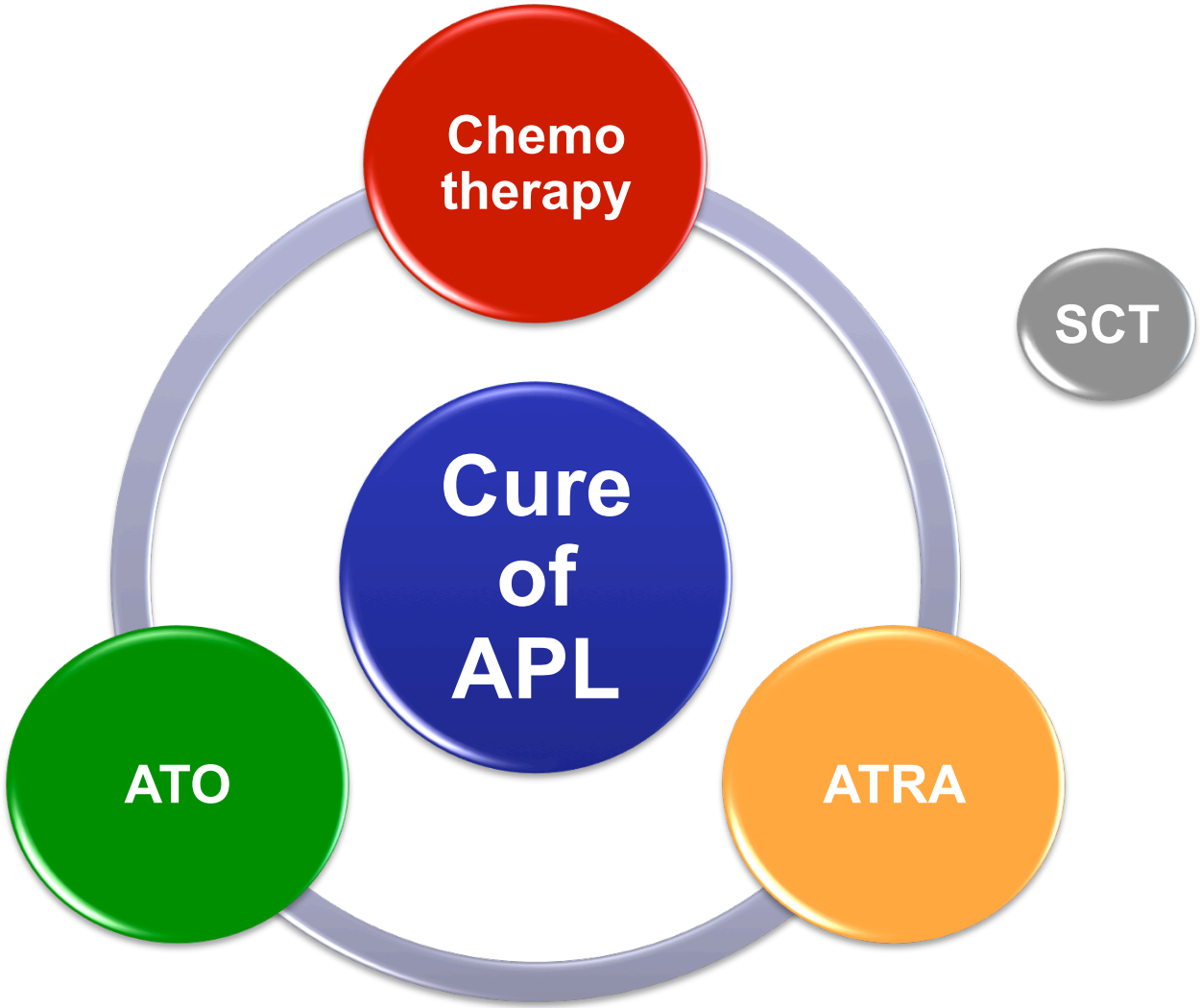
Disclosures of Pau Montesinos

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Teva	x				x	x	
Celgene	x		x		x	x	
Janssen	x				x	x	
Novartis	x				x	x	
DSI			x		x	x	
Pfizer	x				x	x	
Incyte					x	x	
Karyopharm	x					x	

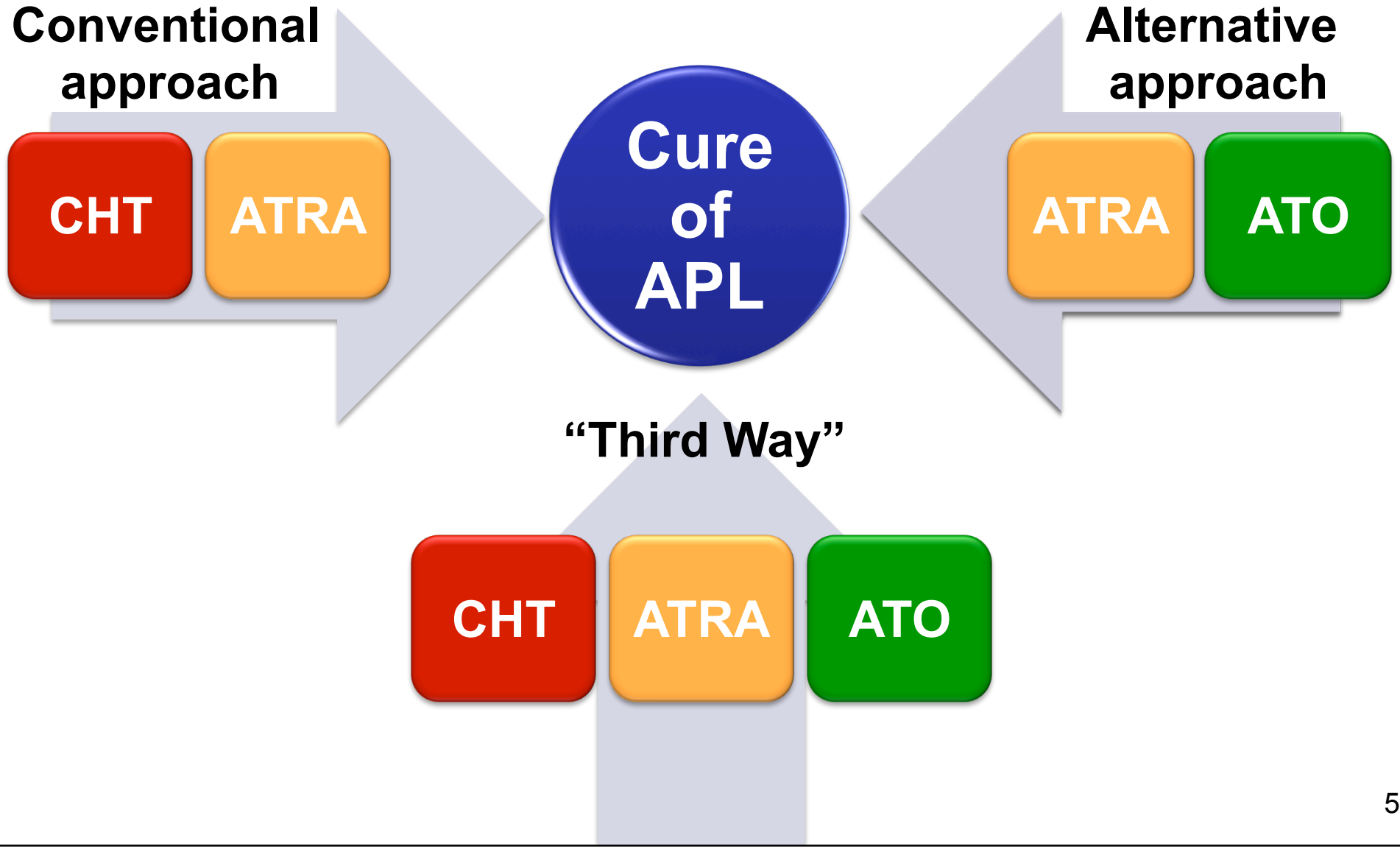
Treatment of APL
Outline

- **Current treatment options**
- **Lessons learned and controversial issues related to the main strategies**
- **Conclusions and future directions**

Mainstay of Curative Treatment for APL



Current Treatment Options in APL



Induction Therapy
Current options

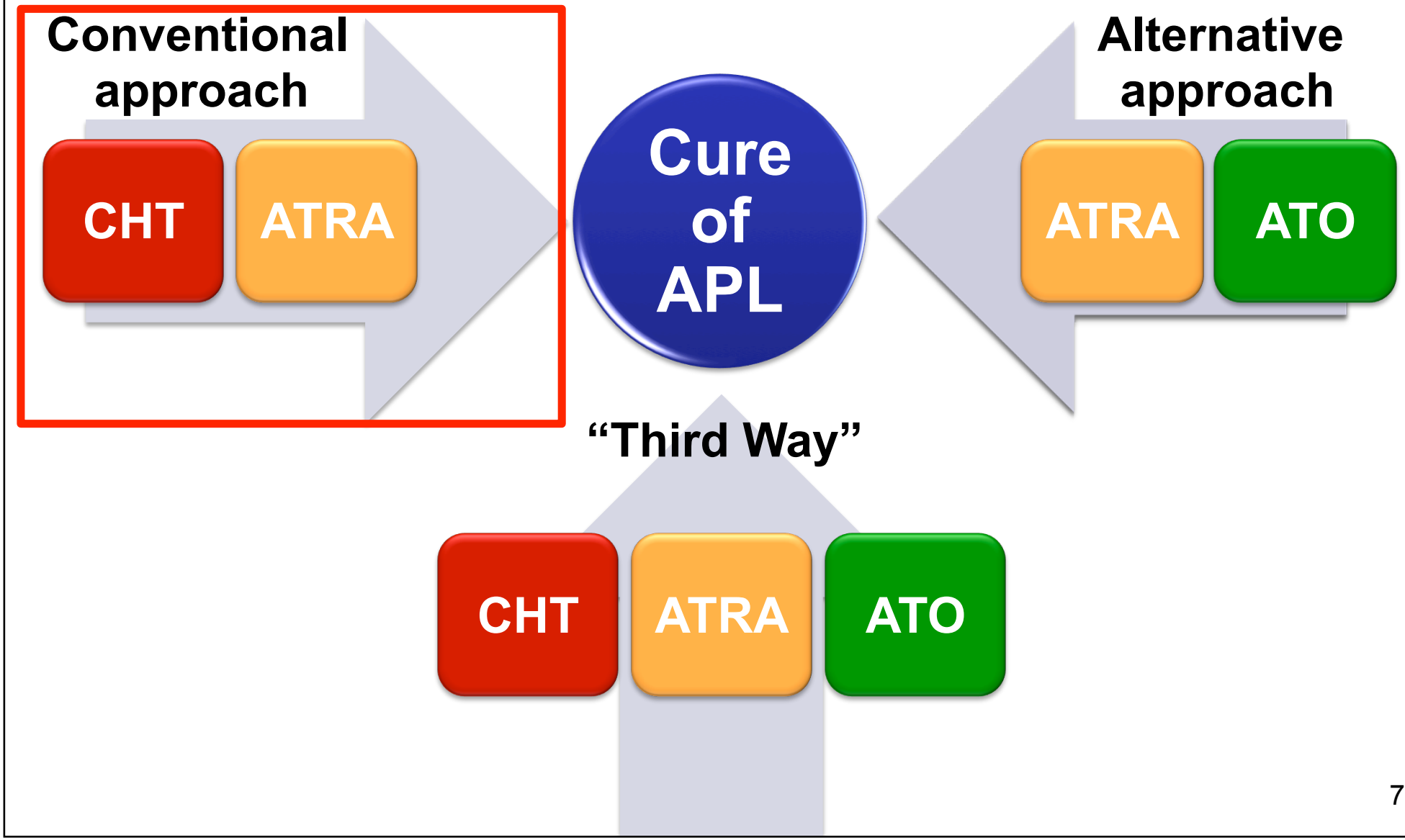
- **Once a diagnosis of APL is suspected**
  - Confirm diagnosis at the genetic level
  - Start **ATRA*** and **supportive measures** to counteract the coagulopathy with no delay

- **Once genetic diagnosis is confirmed**

1. **ATRA + anthracycline-based chemotherapy**
2. **ATRA + ATO**
3. **ATRA + ATO + CHT**

*ATRA: 45 mg/m^2/d until CR (25 mg/m^2/d for children)

Current Treatment Options in APL



Induction Therapy with ATRA + CHT
Current options

- **Once a diagnosis of APL is suspected**
  - Confirm diagnosis at the genetic level
  - Start **ATRA*** and **supportive measures** to counteract the coagulopathy with no delay

- **Once genetic diagnosis is confirmed**

1. **ATRA + anthracycline-based chemotherapy**
   - **Idarubicin (daunorubicin) alone**
   - **Daunorubicin + cytarabine**

*ATRA: 45 mg/m^2/d until CR (25 mg/m^2/d for children)

Induction Therapy with ATRA + CHT
Lessons learned and advances

- **CR rate: 90-96%**
- **ATRA + Dauno + Ara-C similar to ATRA + Ida**
- **Virtual absence of resistant leukemia**

Delayed maturation with persistence of blasts is occasionally detectable up to 40–50 days after the start of treatment

ATRA should be continued until terminal differentiation of blasts

Consolidation Therapy (ATRA + CHT)
Lessons learned and advances

- 2-3 cycles of anthracycline-based therapy
- In addition to anthracycline, cytarabine, and ATRA, can also play a role for consolidation
- Molecular remission is achievable in roughly 99%
- CIR at 5 years 11%*
- Risk-adapted consolidation is a reasonable strategy (e.g., age, CD56, and relapse risk score)

Dose reduction in older patients

*Sanz MA *et al*. Blood 2009;113:1875-91

Evolving risk-adapted strategy to optimize treatment in APL

Reduction of dose intensity in elderly[1]

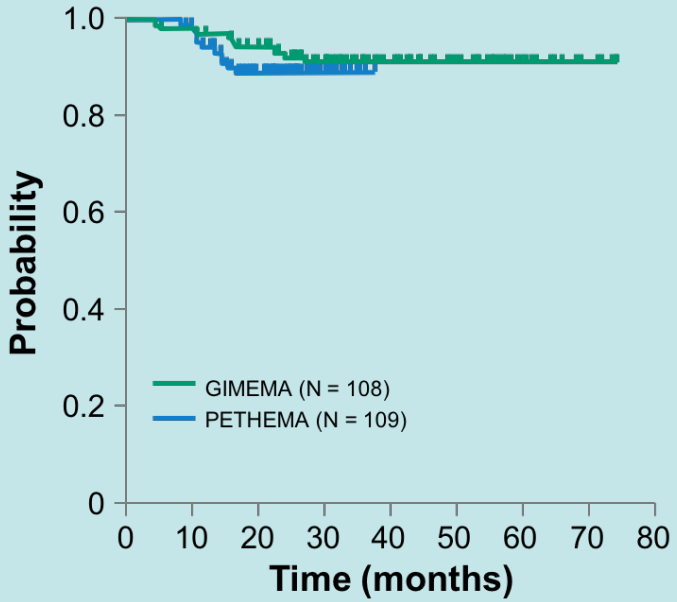
One size fits all

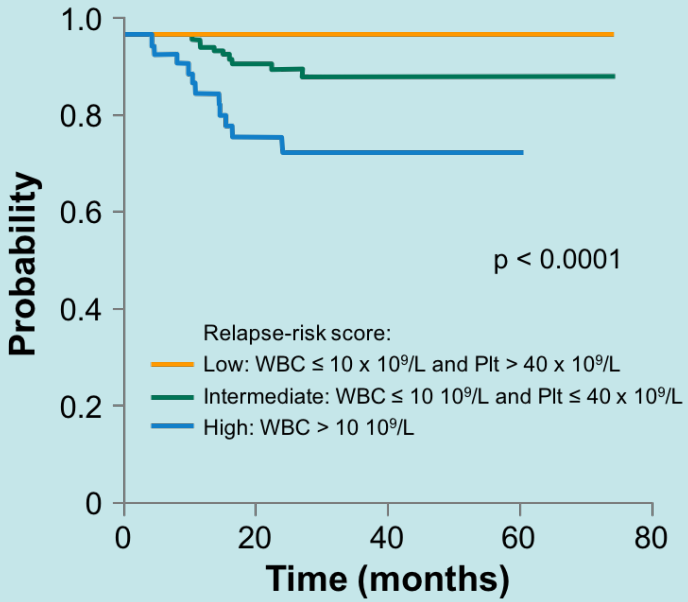
LPA96

Nov. 1996
Oct. 1999

Definition of relapse risk groups

Joint GIMEMA and PETHEMA study



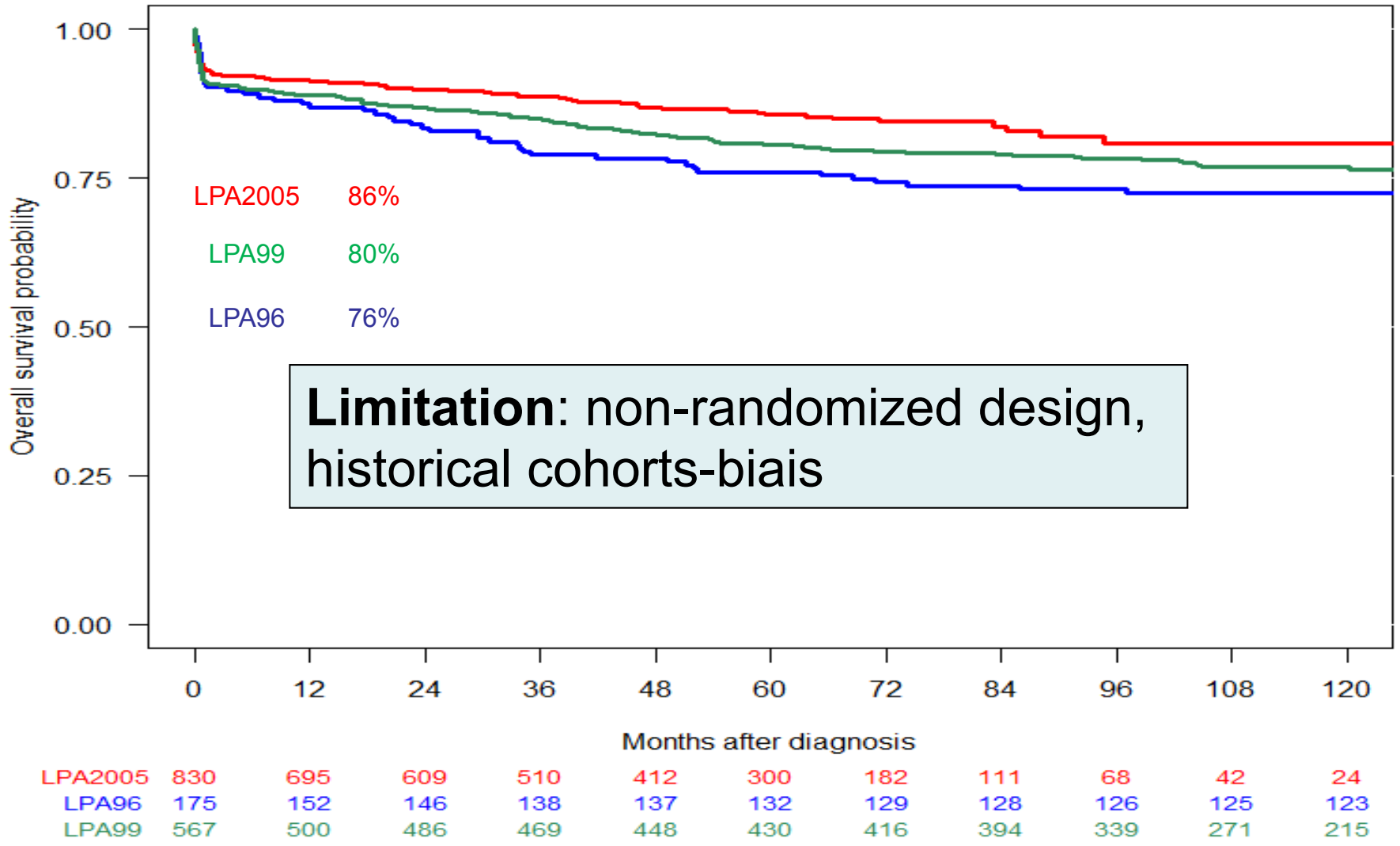


Sanz M, et al. Blood. 2000;96:1247-53.

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

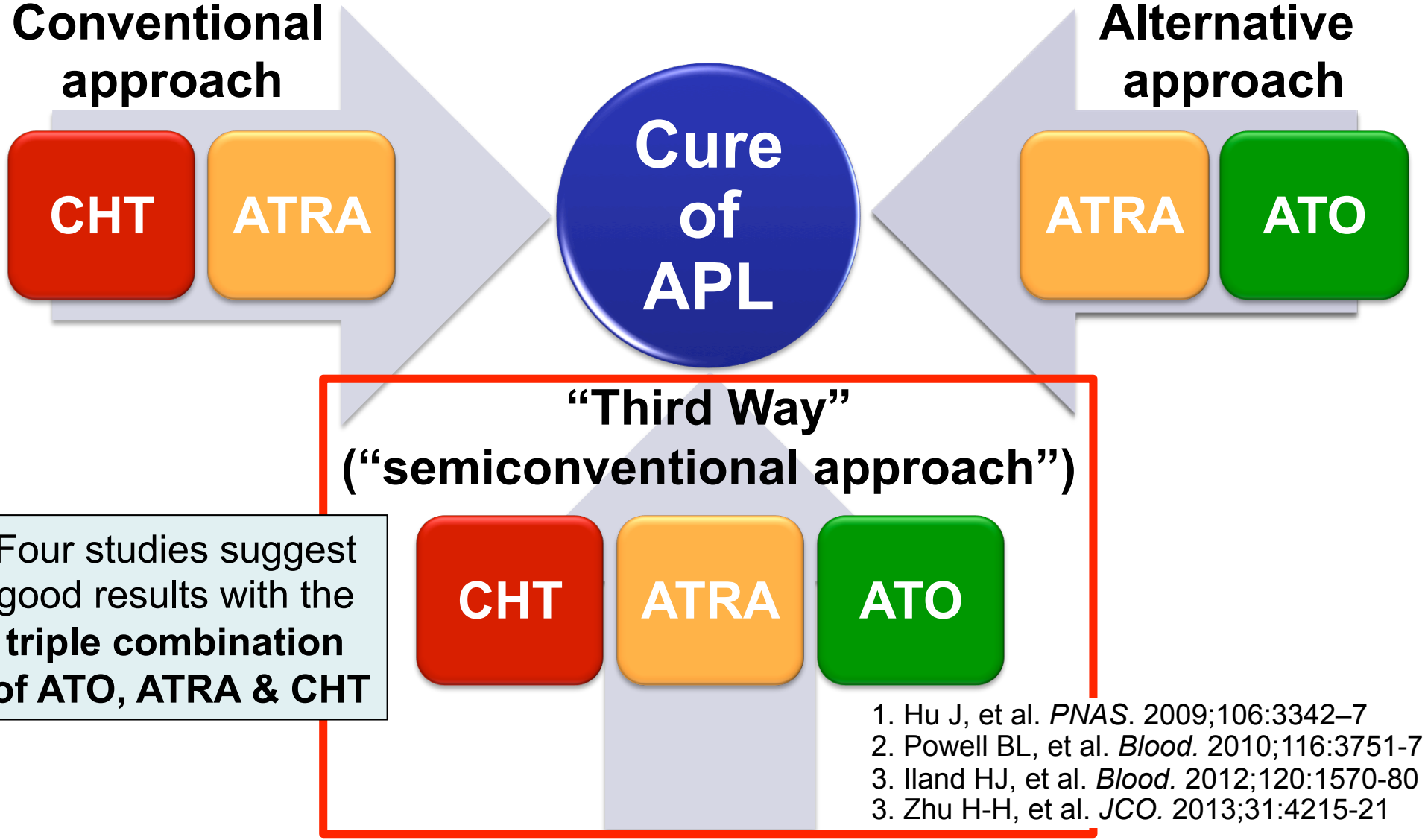
Improved outcomes by risk-adapted trial

5y OS PETHEMA/HOVON/PALG/GATLA



Limitation: non-randomized design, historical cohorts-biais

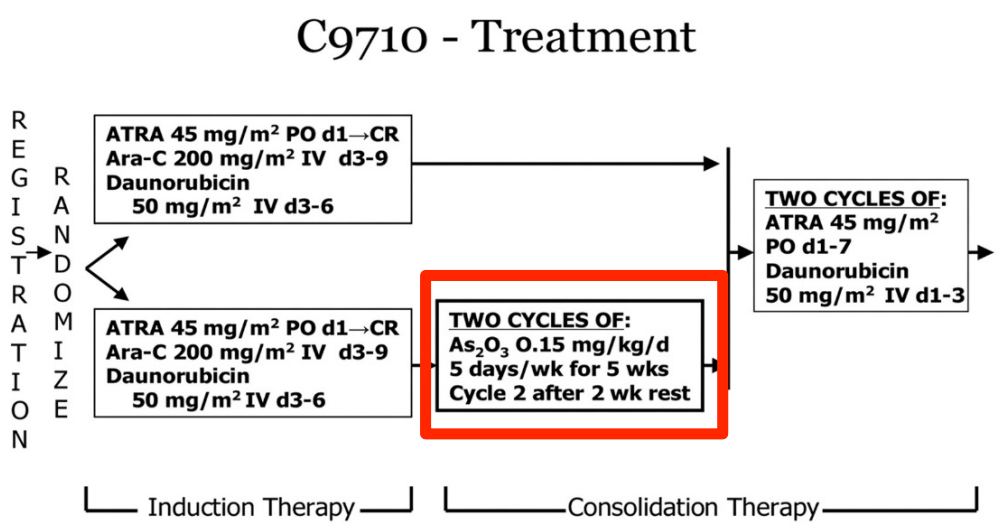
Current Treatment Options in APL

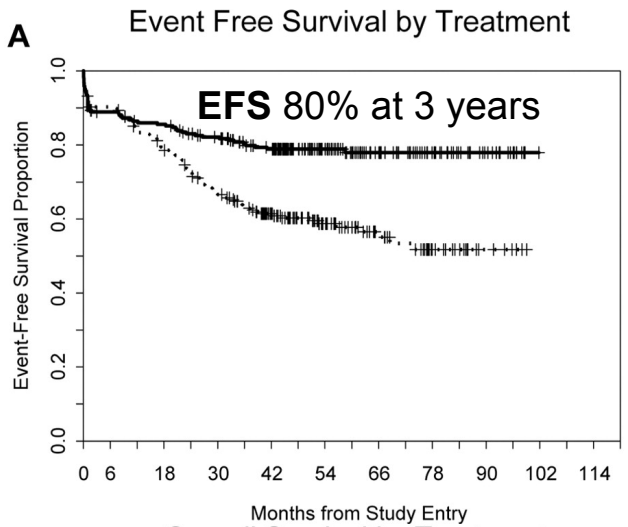


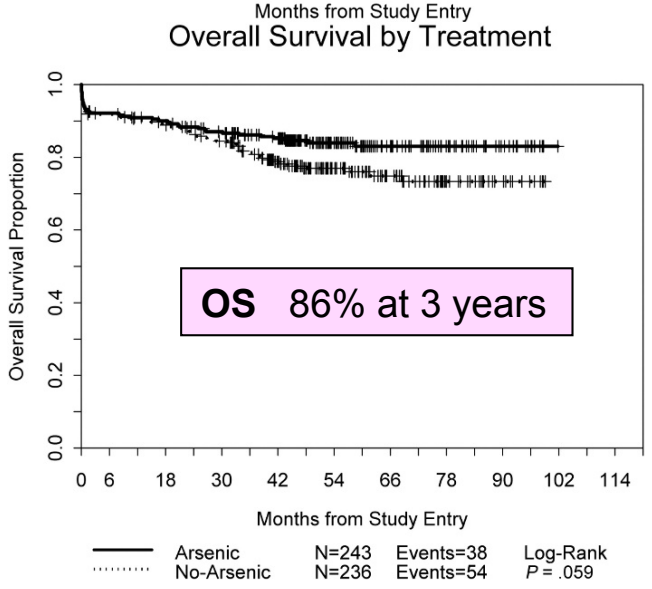
Four studies suggest good results with the **triple combination of ATO, ATRA & CHT**

1. Hu J, et al. *PNAS*. 2009;106:3342–7
2. Powell BL, et al. *Blood.* 2010;116:3751-7
3. Iland HJ, et al. *Blood.* 2012;120:1570-80
3. Zhu H-H, et al. *JCO.* 2013;31:4215-21

ATO + ATRA + CHT
US Intergroup experience







Limitation: The outcomes in the control arm are not comparable with those reported by most groups that used ATRA plus chemotherapy–based schemes.

Powell B L et al. *Blood* 2010;116:3751-3757

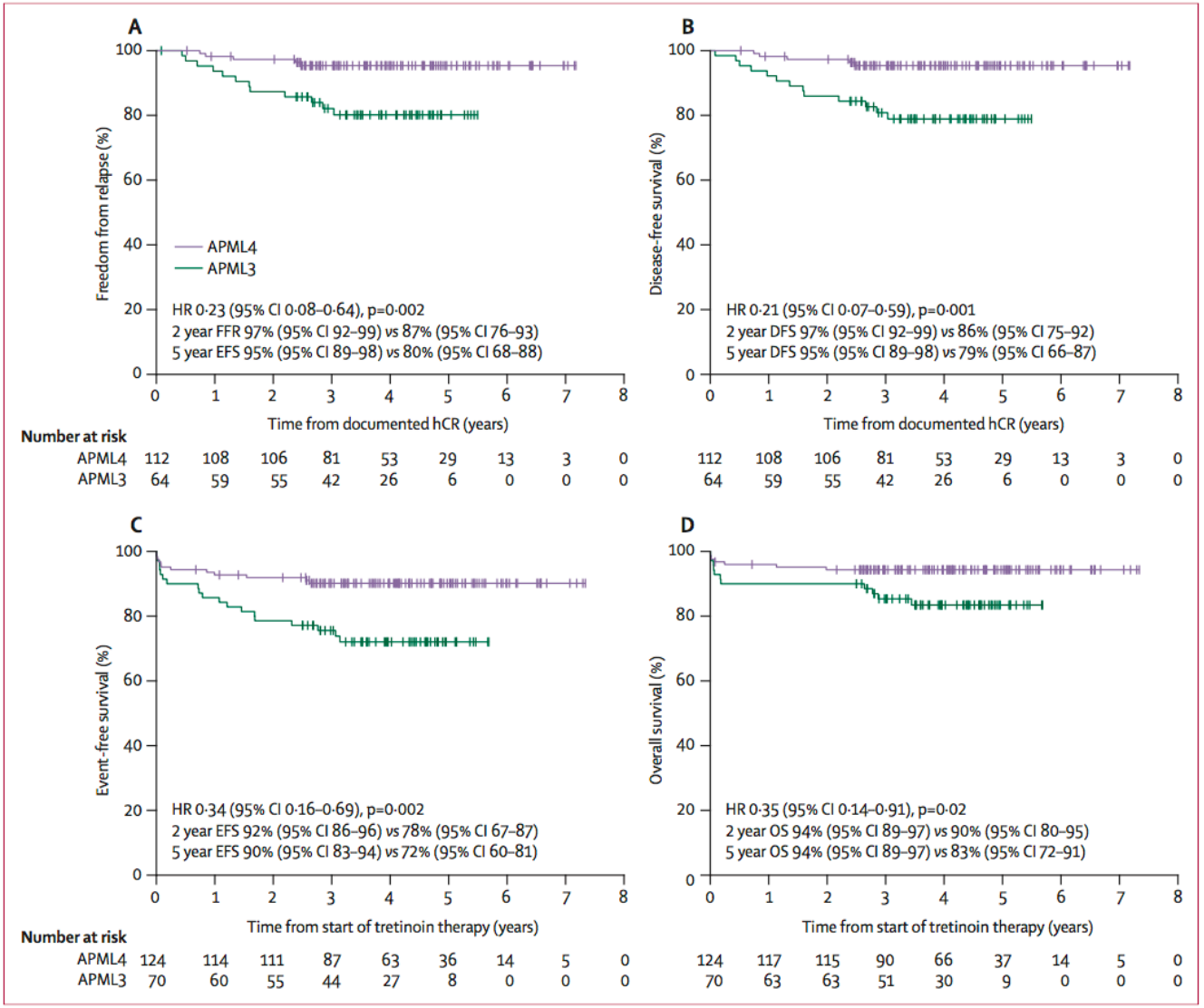
ATRA + ATO + CHT

Australasian Leukemia and Lymphoma Group

Induction
ATRA + ATO + CHT

Consolidation (2)
ATRA + ATO

Maintenance (5)
ATRA + LD-CHT



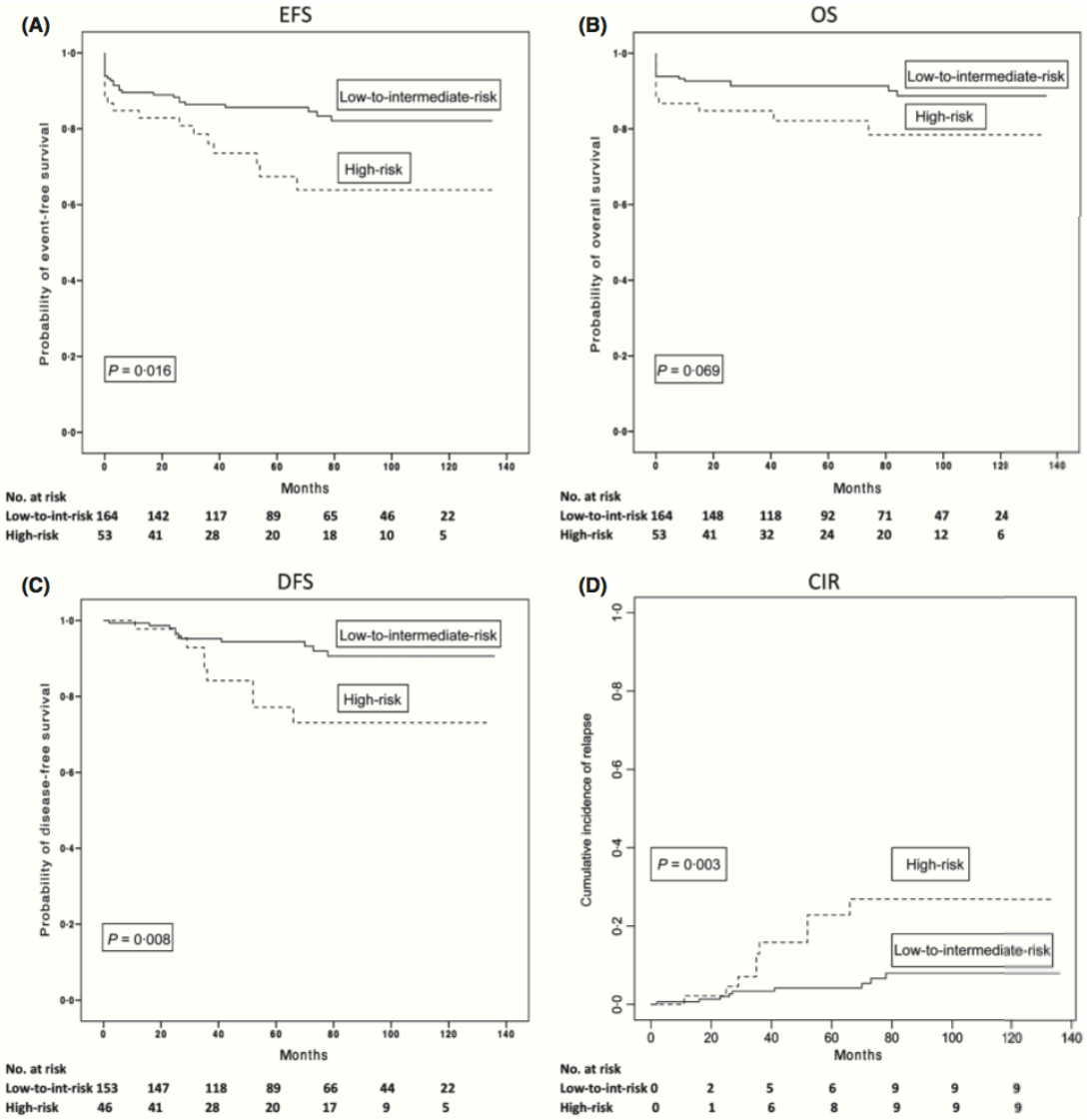
Iland HJ, et al. *Lancet Haematol.* 2015

ATRA + ATO + CHT
Shanghai Group

Induction
ATRA + ATO

Consolidation (3)
ATRA + CHT

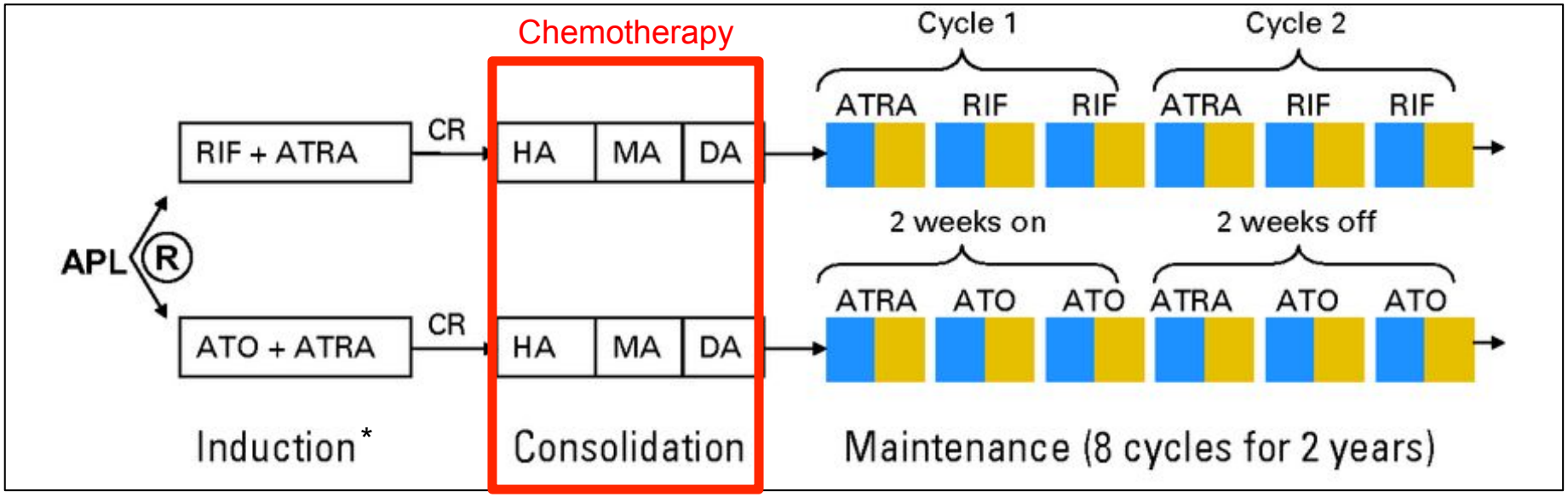
Maintenance (5)
ATRA, ATO & LD-CHT



Zhu H, et al. *Br J Haematol*. 2015

ATO + ATRA + CHT
Chinese APL Cooperative Group

Randomized comparison of oral arsenic derivative *vs*. IV ATO

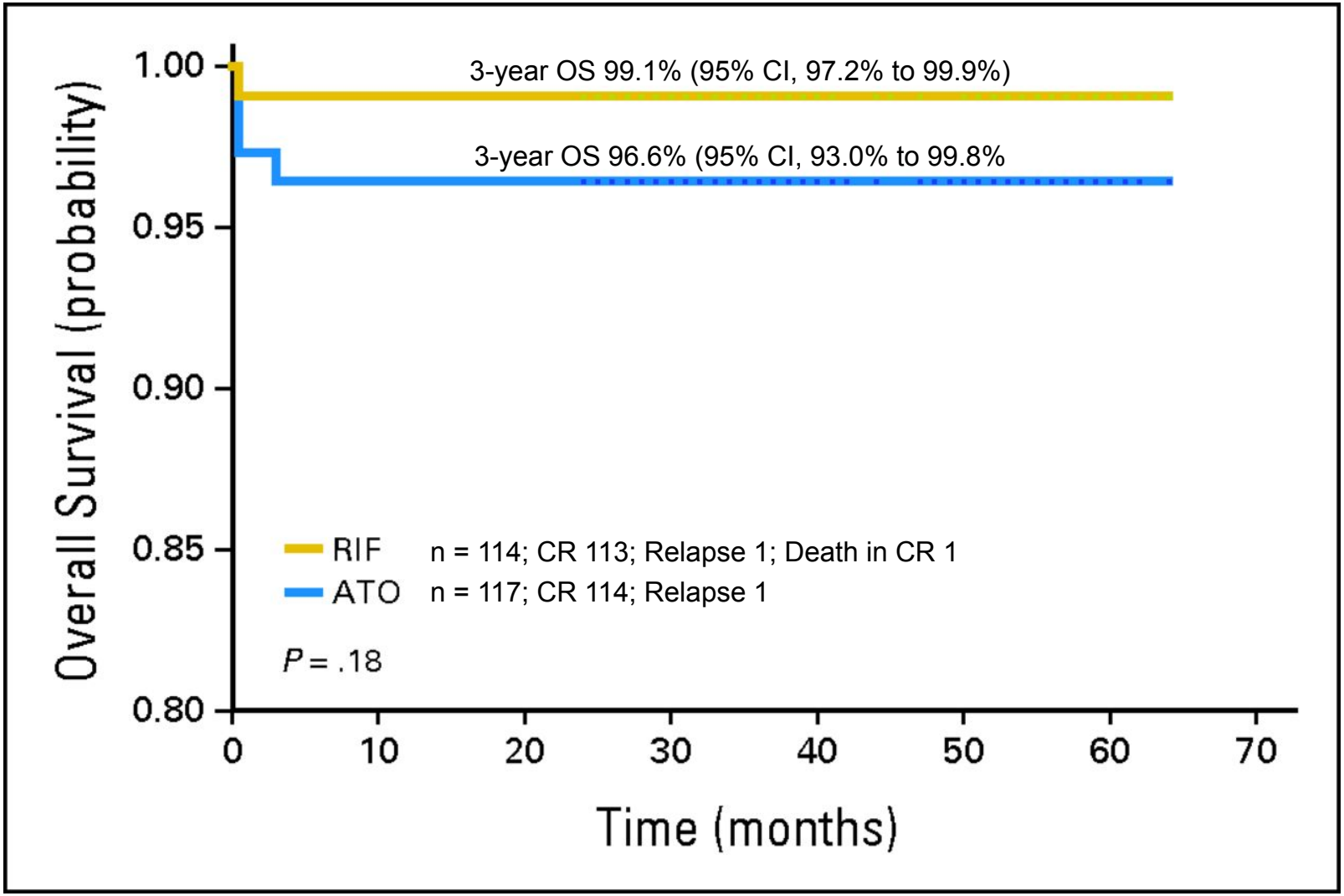


* Mitoxantrone was added at a dose of 1.4 mg/m^2/day on 5 days 4, 5, 6, 7, and 8 (if WBC >10 x 10^9/L start on day 1).

ATRA = all-trans retinoic acid; **ATO** = arsenic trioxide; **RIF** = Realgar-*Indigo naturalis* formula; **HA** = homoharringtonine and cytarabine; **DA** = daunorubicin and cytarabine; **MA** = mitoxantrone and cytarabine

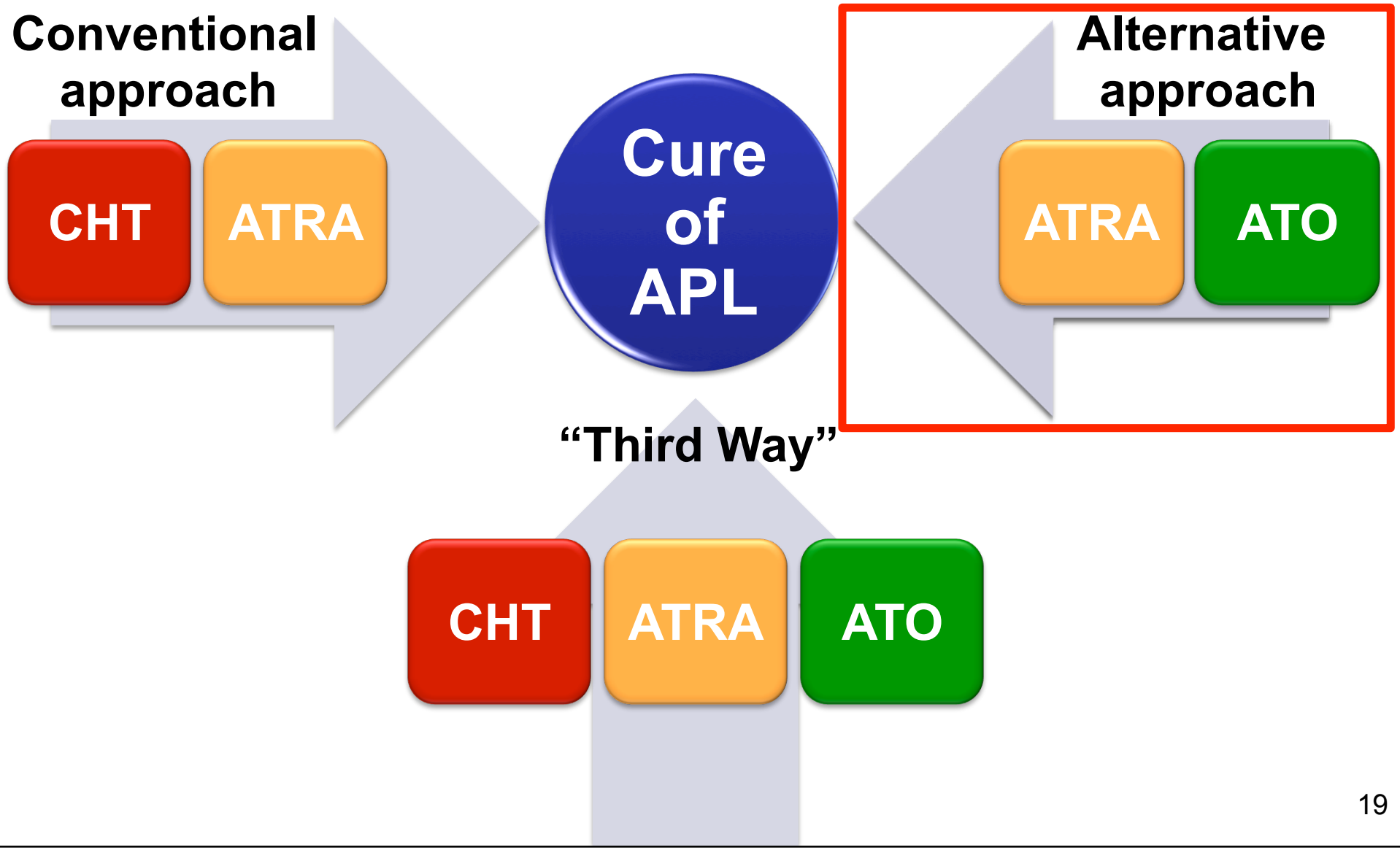
Zhu H et al. JCO 2013;31:4215-4221

ATO + ATRA vs. RIF + ATRA
Chinese APL Cooperative Group



Zhu H et al. JCO 2013;31:4215-4221

Current Treatment Options in APL



ATO-based regimens without or with minimal use of CHT

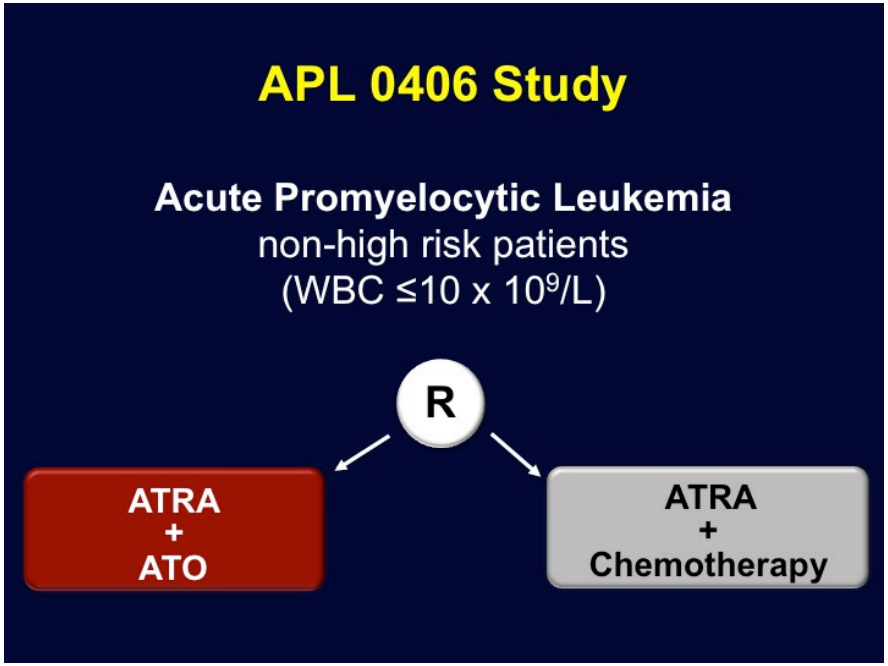
Non-randomized trials

Group (Ref.)	No. patients	CR (%)	OS 5-yrs	EFS 5-yrs	DFS 5-yrs
ATO					
Iran (1)	197	85	67	NA	64
India (2)	72	86	74	69	80
ATO + ATRA					
USA (3)	82	92	76	77	NA

1. Ghavamzadeh A, et al. *J Clin Oncol*. 2011;29:2753-7; **2.** Mathews V, et al. *J Clin Oncol*. 2010;28:3866-71;
3. Ravandi F, et al. *J Clin Oncol*. 2009;27:504-10

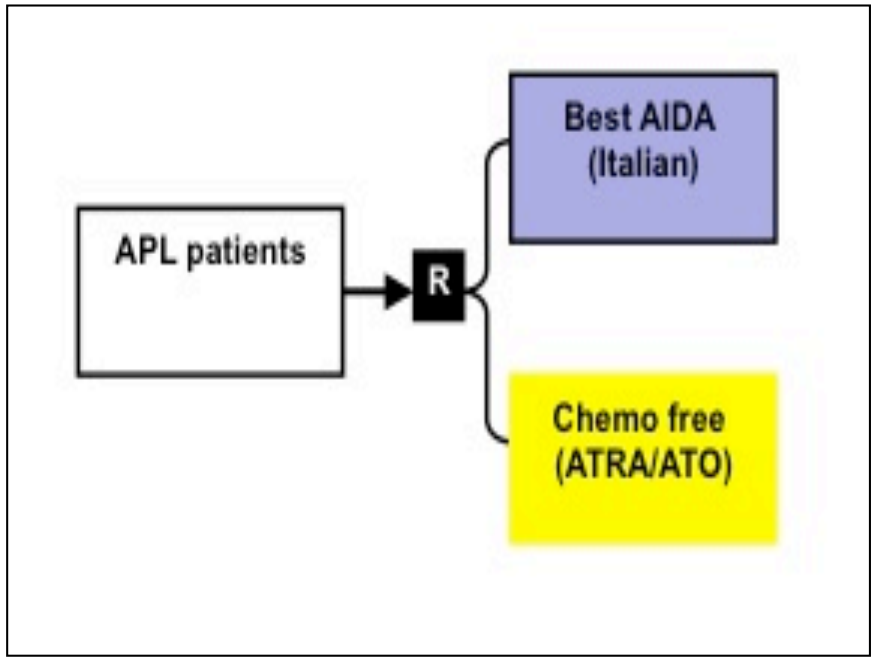
ATO + ATRA without CHT
Randomized trials

GIMEMA-SAL-AMLSG
APL 0406 trial



Lo Coco F, *et al*. NEJM 2013;369:111-21

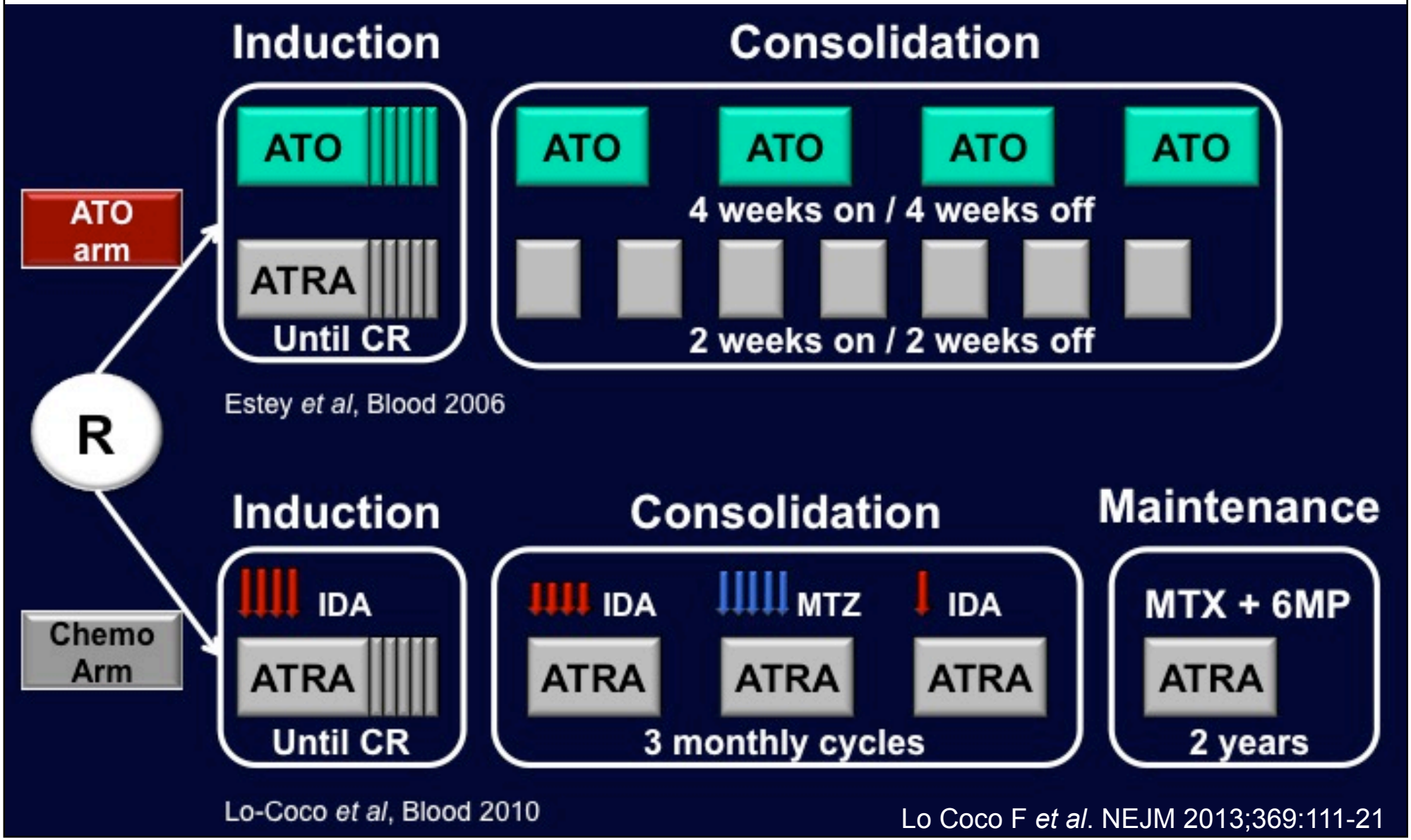
UK NCRI
AML 17 trial



Burnett AK, *et al*. Lancet Oncol 2015;16: 1295–305

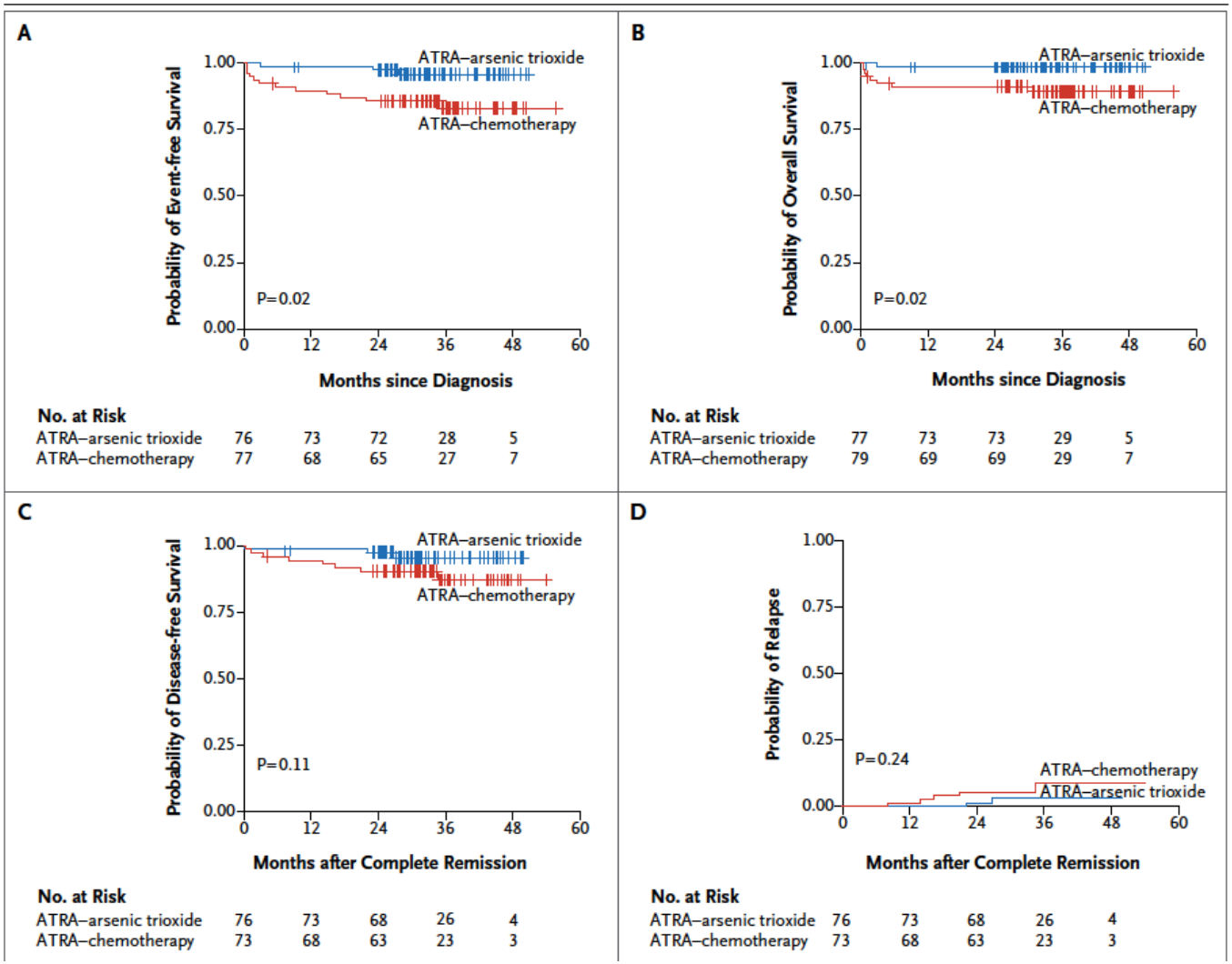
GIMEMA-SAL-AMLSG

APL 0406 study



Lo Coco F *et al*. NEJM 2013;369:111-21

ATO + ATRA *vs.* AIDA
GIMEMA-SAL-AMLSG (APL 0406)

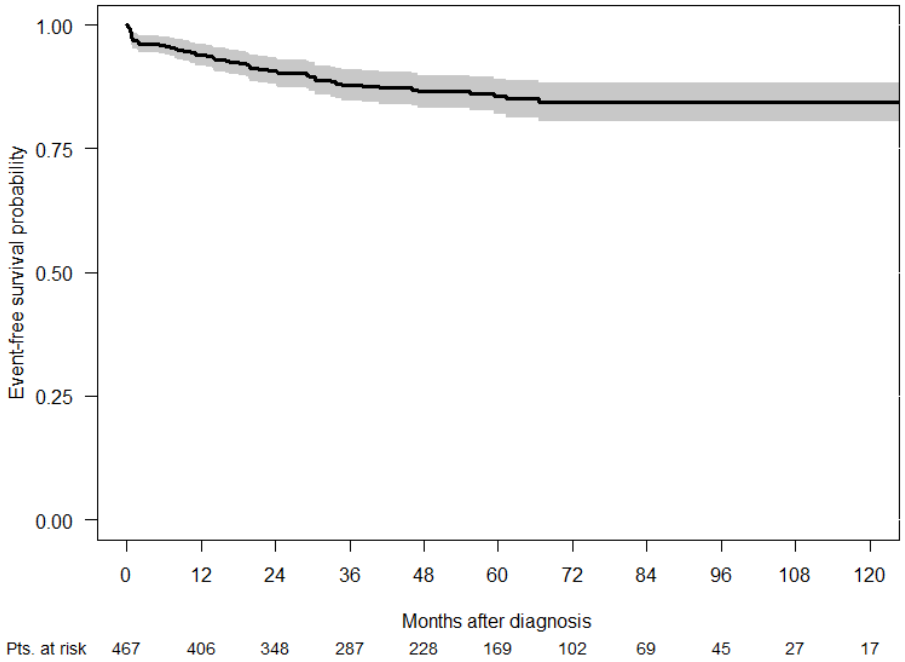


ATRA + ATO is at least not inferior and **may be superior** to **ATRA + CHT** in the treatment of patients with **low-to-intermediate-risk APL**

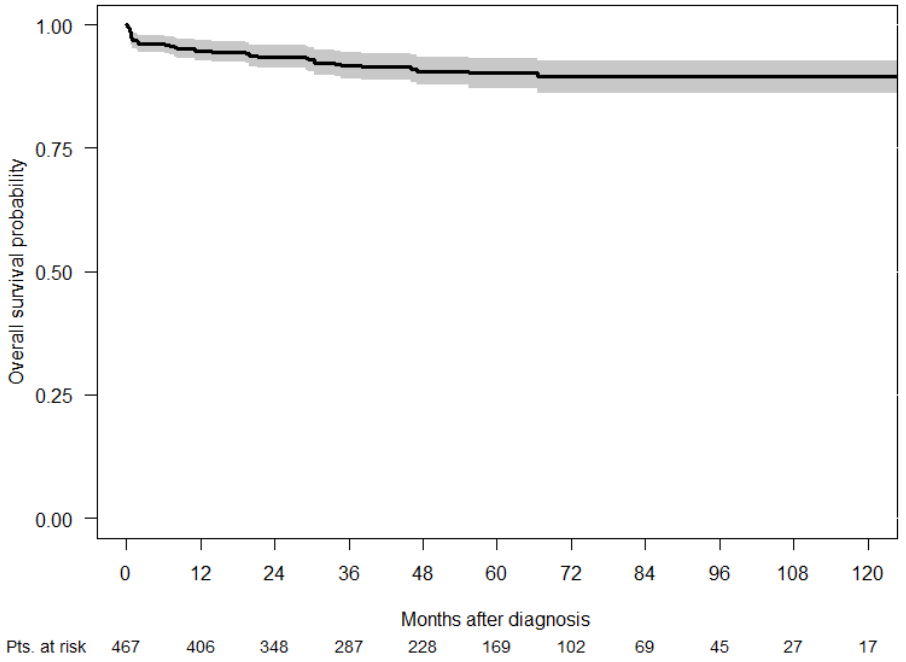
Lo Coco F *et al*. NEJM 2013;369:111-21

PETHEMA LPA2005 results
APL-0406-like cohort

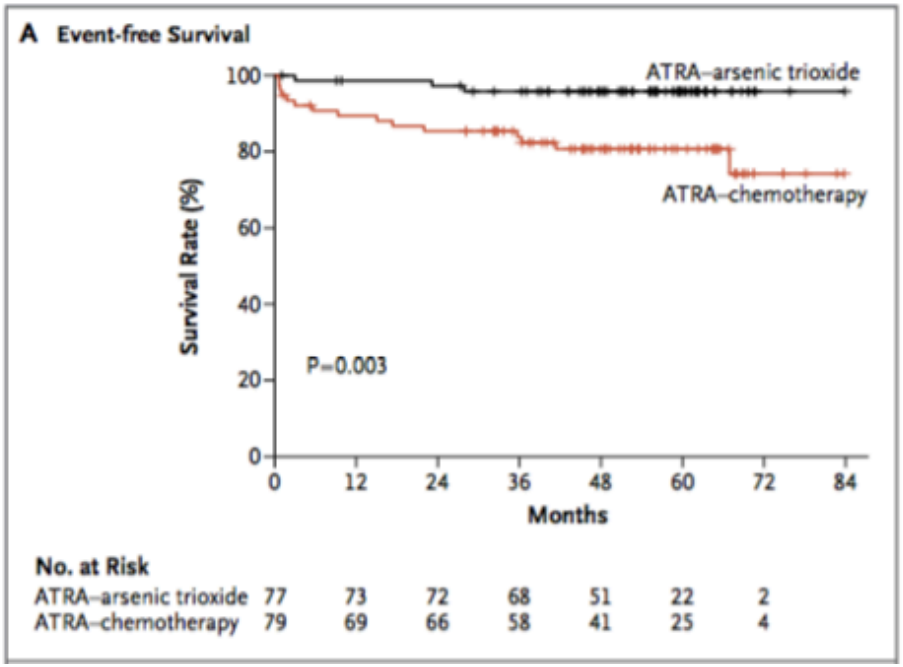
5-year EFS 86%

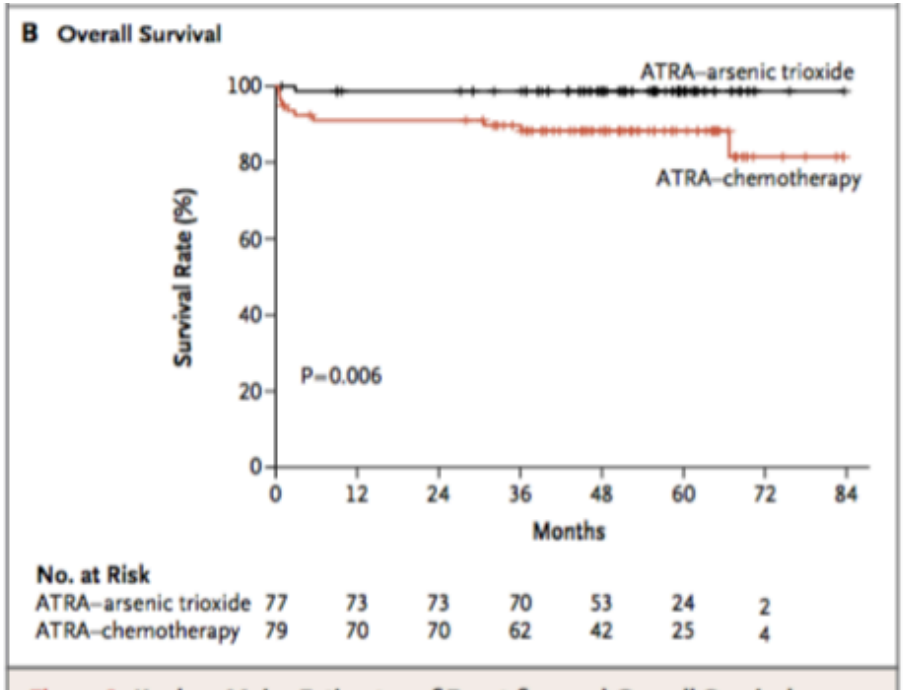


5-year OS 90%



ATO + ATRA *vs.* AIDA
GIMEMA-SAL-AMLSG (APL-0406)





Lo Coco F *et al*. NEJM 2016;374:1197-8

Less myelotoxicity using ATO+ATRA

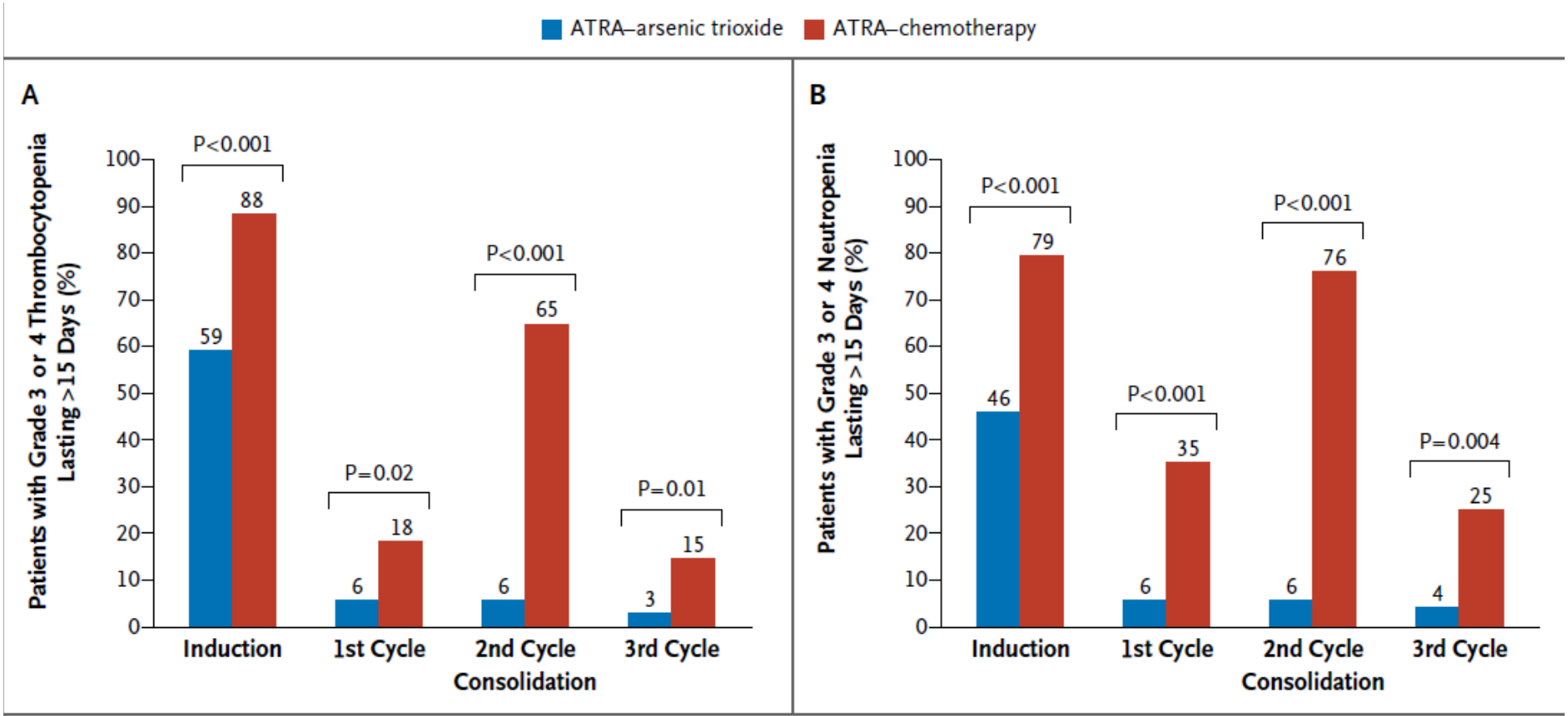
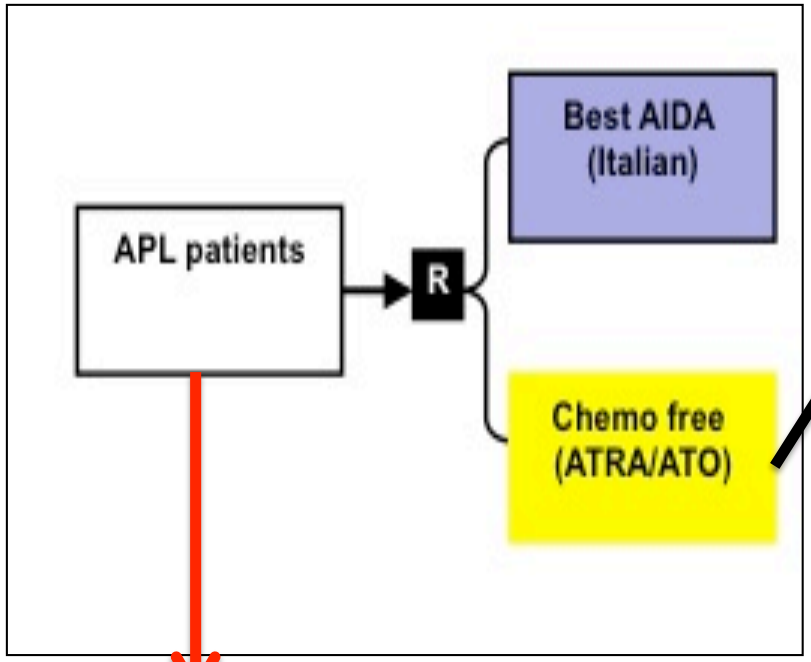


Figure 4. Hematologic Toxic Effects.

Lo Coco F *et al*. NEJM 2016;374:1197-8

ATO + ATRA *vs.* AIDA
UK NCRI - AML 17 trial



High-risk patients

GO 6 mg/m^2 as a single infusion within the first 4 days (on day 1 if possible and on day 4 if necessary).

Induction

- **ATO** 0.3 mg/kg days 1-5 in week 1 **followed by** ATO 0.25 mg/kg twice a week for 7 weeks
- **ATRA** 45 mg/m^2/d 9 weeks

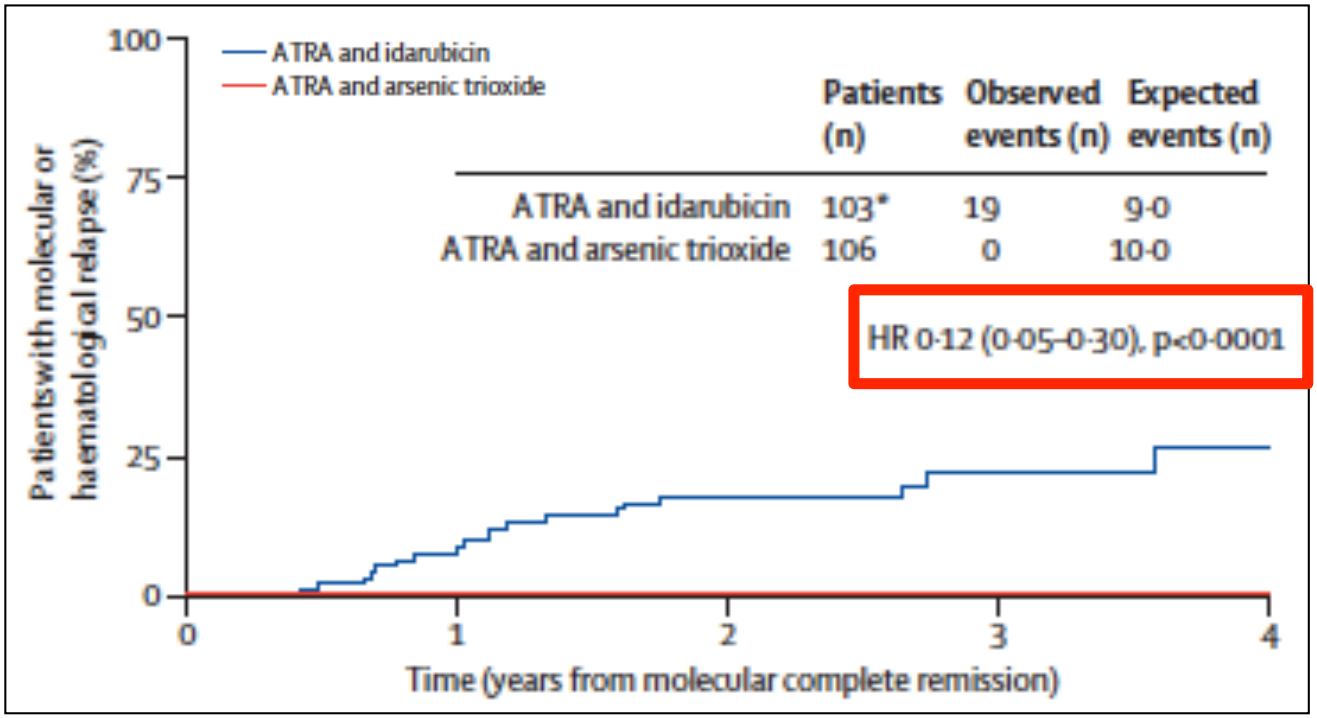
Consolidation (5 courses)

- **ATO** 0.3 mg/kg days 1-5 in week 1 **followed by** ATO 0.25 mg/kg twice a week for 3 weeks
- **ATRA** 45 mg/m^2/d 2 weeks on 2 weeks off

Burnett AK, *et al*. Lancet Oncol 2015;16: 1295–305

ATO + ATRA vs. AIDA
UK NCRI - AML 17 trial

Cumulative incidence of molecular or hematological relapse



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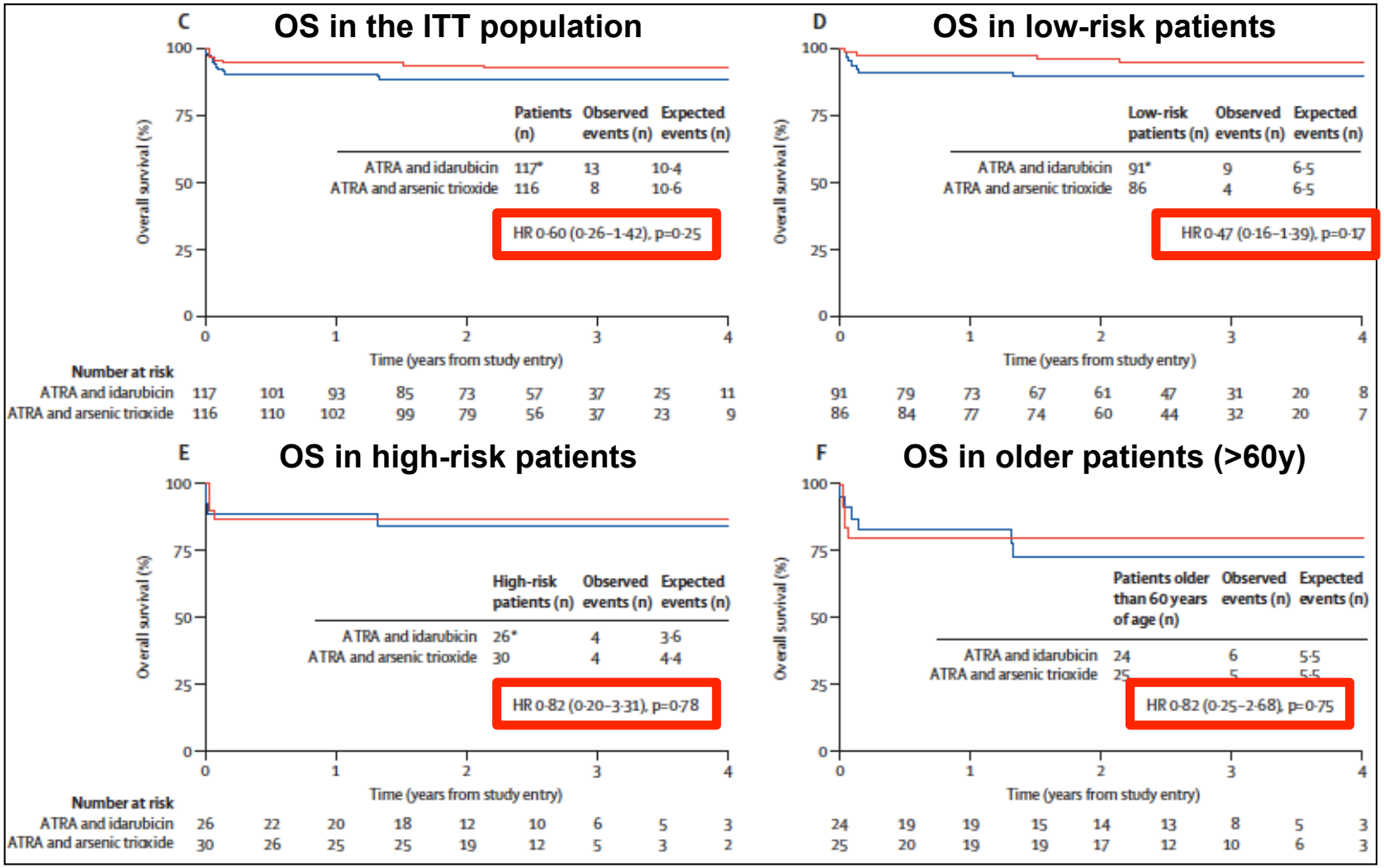
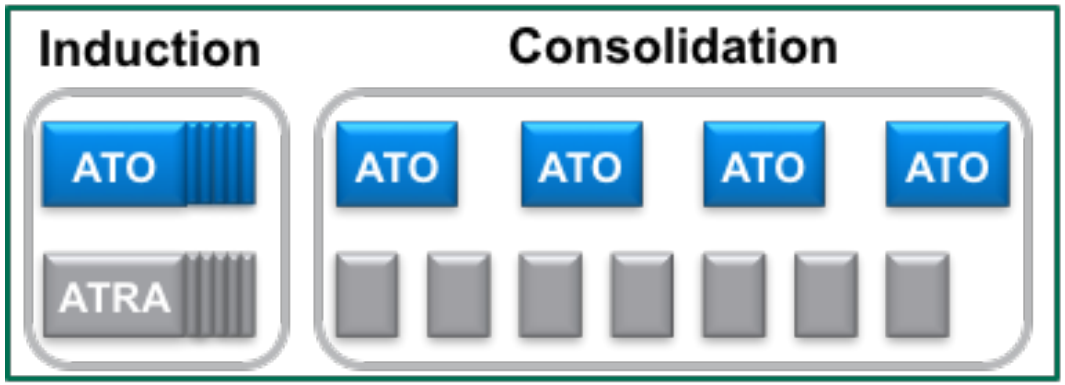
ATO + ATRA vs. AIDA
UK NCRI - AML 17 trial



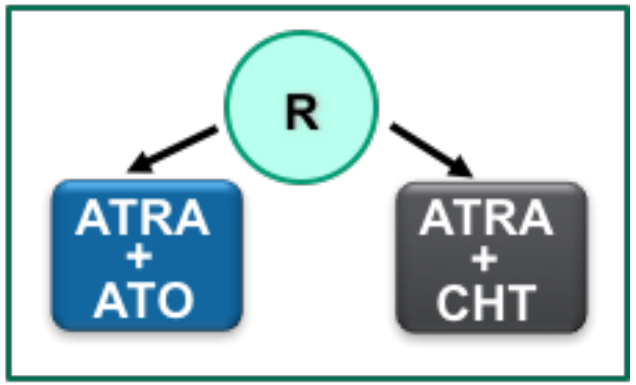
Burnett AK, *et al*. Lancet Oncol 2015;16: 1295–305

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)

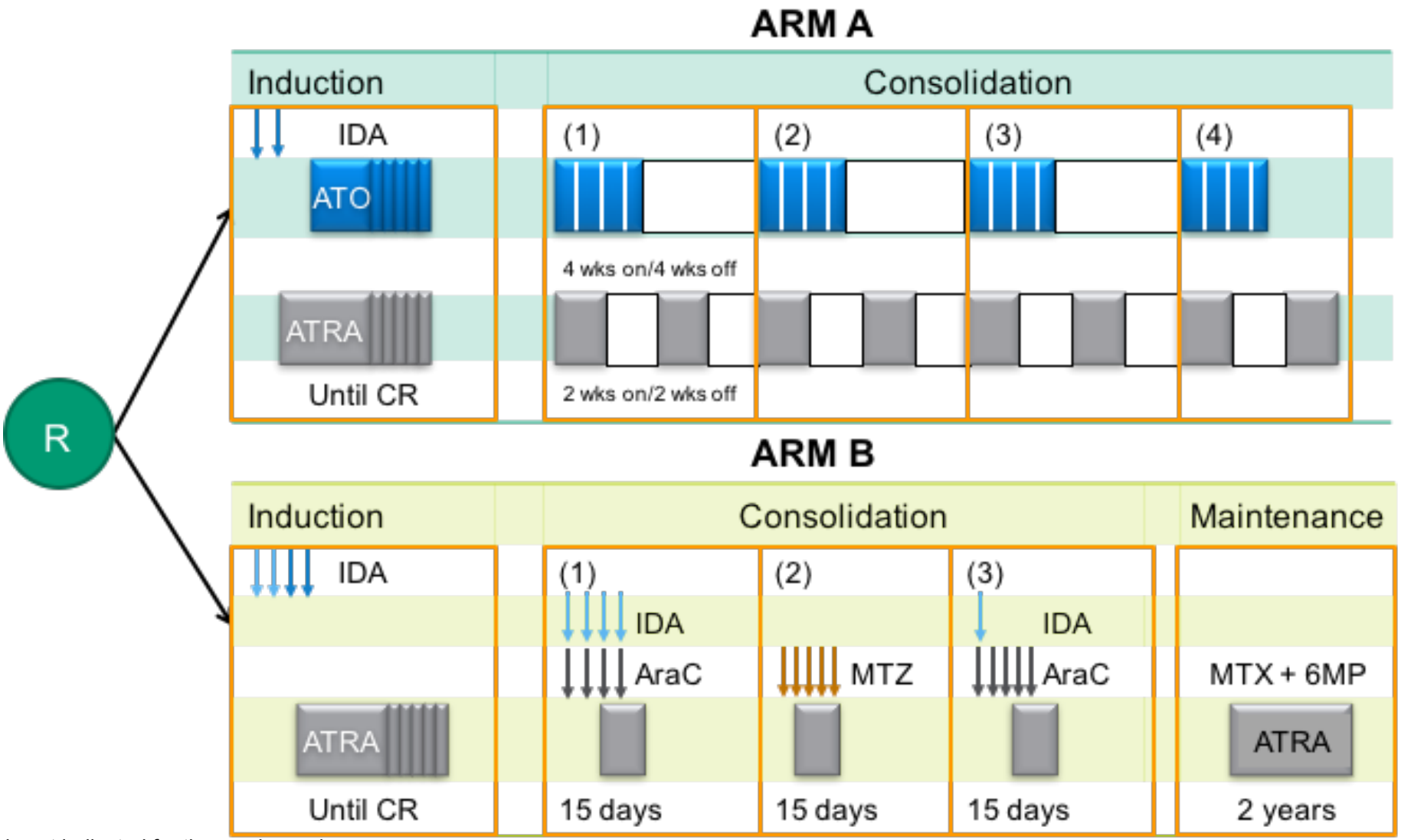


APOLLO trial

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

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.

Mainstay of Curative Treatment for APL
Front-line differentiating agents

- ATO (Trisenox, Teva)
  - Indicated in combination with ATRA (low/intermediate risk patients)

- ATRA (Vesanoid, Ceplapharm):
  - Indicated in combination with chemotherapy (all patients)
  - Indicated in combination with ATO (low/intermediate risk patients)

Front-line Therapy in APL
Current status and future directions

- High cure rates can be achieved with optimized combinations of:
  - ATRA + ATO
  - ATRA + CHT
  - ATRA + CHT + ATO (“Third way”)
- **Oral arsenic** formulation seems a promising alternative to IV arsenic.
- Will we use chemotherapy in the future? And what about Mylotarg?