La leucemia acuta promielocitica oggi e domani

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Lettura in Memoria del Professor Francesco Lo Coco

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N/A = Not Applicable (no conflicts listed)

In memoriam
Prof. Francesco Lo Coco

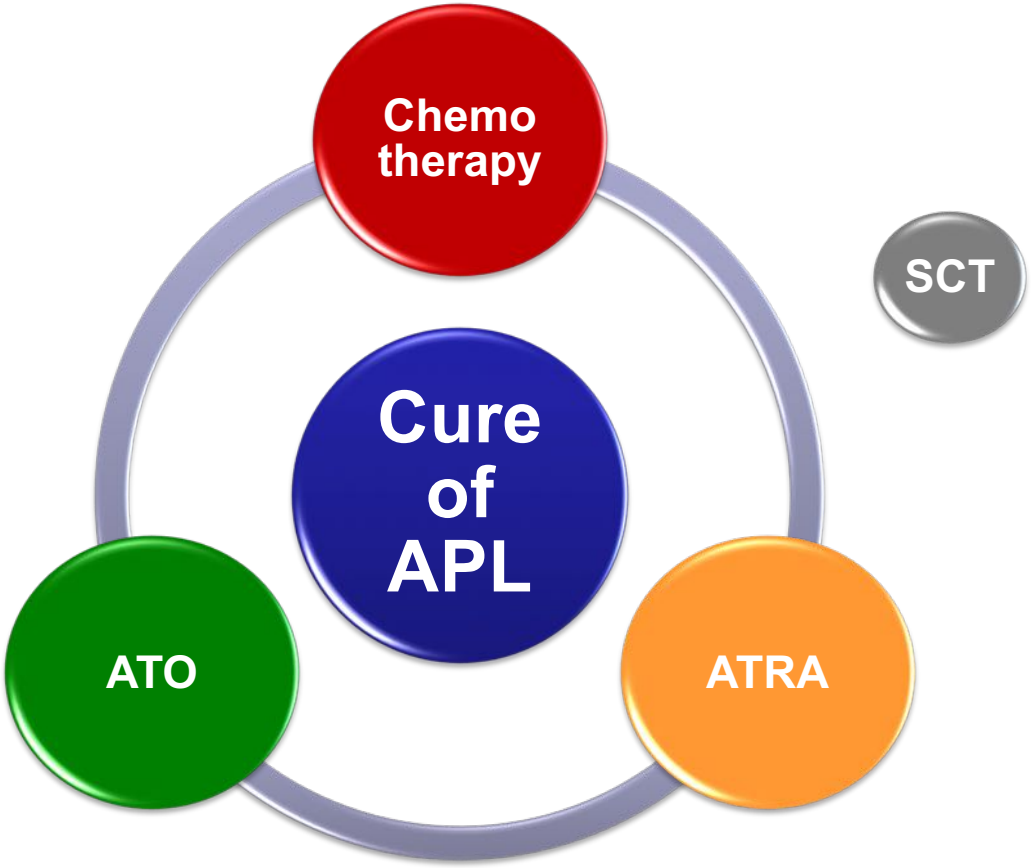
(1955 – 2019)

You will always be in our thoughts and hearts…

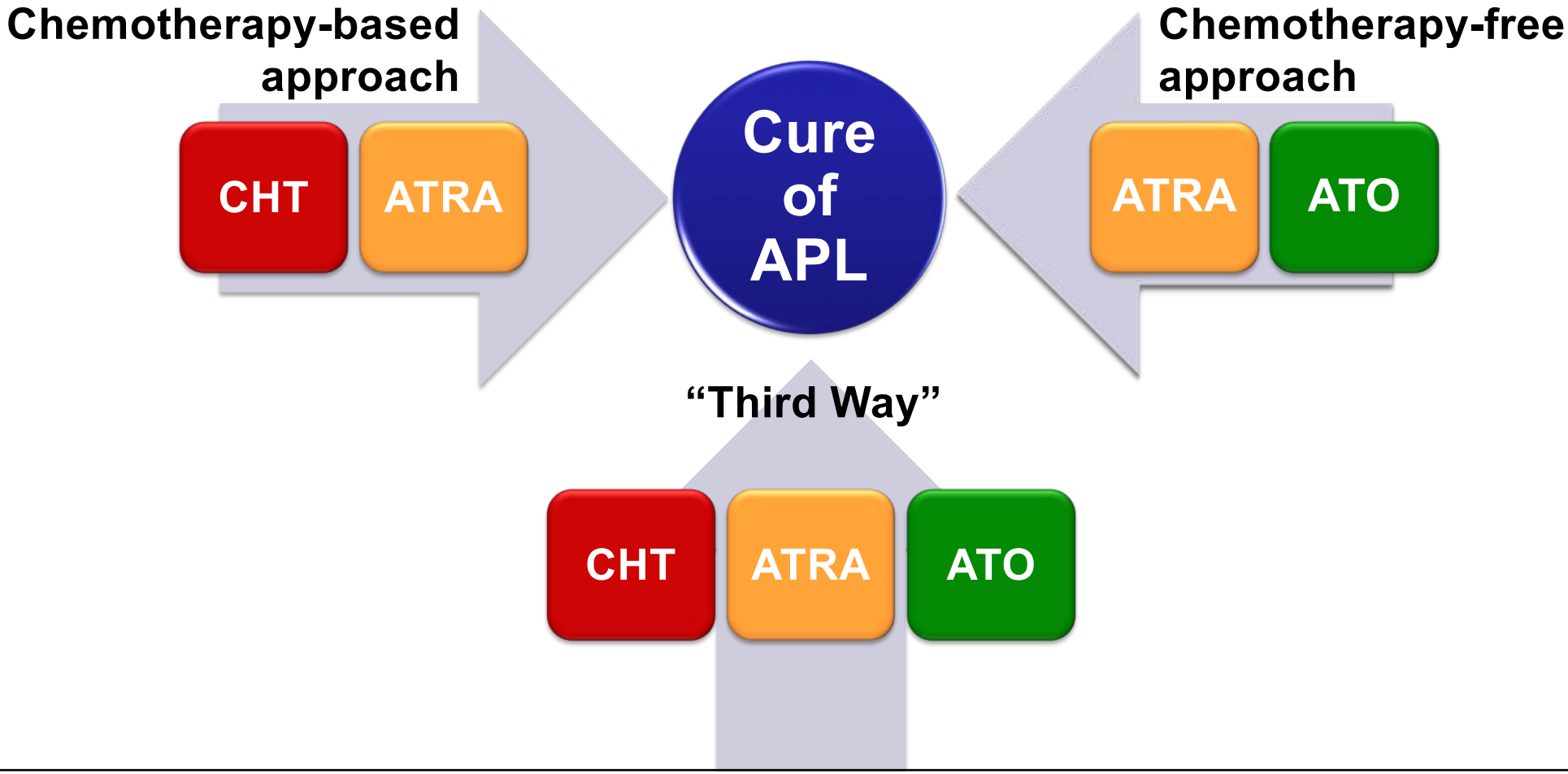
Treatment of APL
Outline

- **Front-line treatment for APL**
  - Current treatment options
  - Lessons learned and controversial issues related to the main strategies
  - Conclusions and future directions
- **Salvage therapy for relapsed APL**
  - rAPL after front-line chemo-based treatment
  - rAPL after front-line ATO-based treatment

Mainstay of Curative Treatment for APL



Current Treatment Approaches in APL

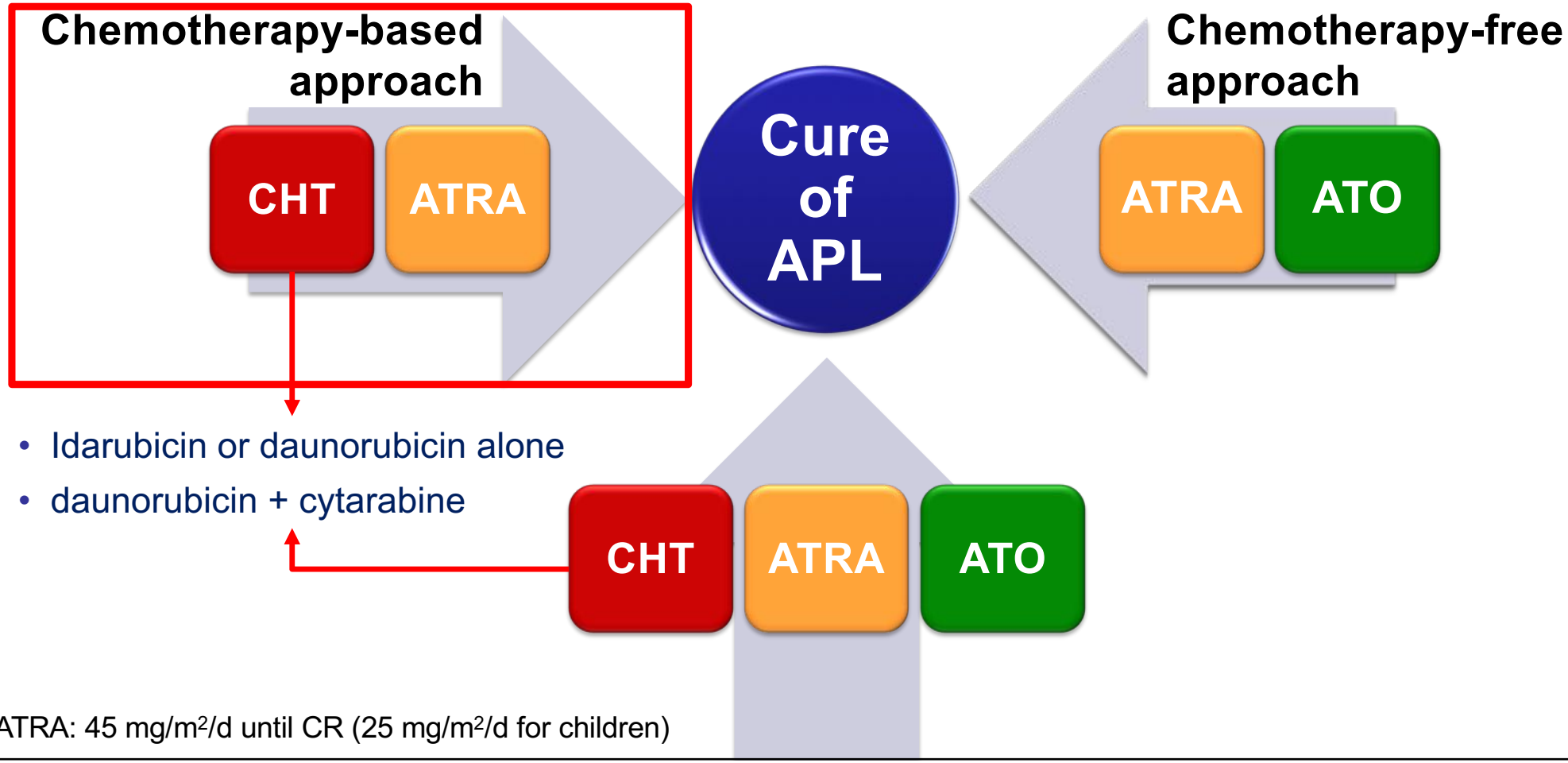


Approach to the patient with suspected APL

- Confirm diagnosis at the genetic level
- Start **ATRA:** 45 mg/m^2/d (25 mg/m^2/d for children)
- **Supportive measures*** to counteract the coagulopathy **with no delay**
  - Transfusions of fibrinogen and/or cryoprecipitate, platelets, and fresh-frozen plasma to maintain the fibrinogen concentration above 100-150 mg/dL, the platelet count above 30 x 10^9/L to 50 x 10^9/L, and the INR below 1.5

* Daily or more than once a day if needed

Current Treatment Approaches in APL



*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 outcomes 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

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

Consolidation Therapy (ATRA + CHT)

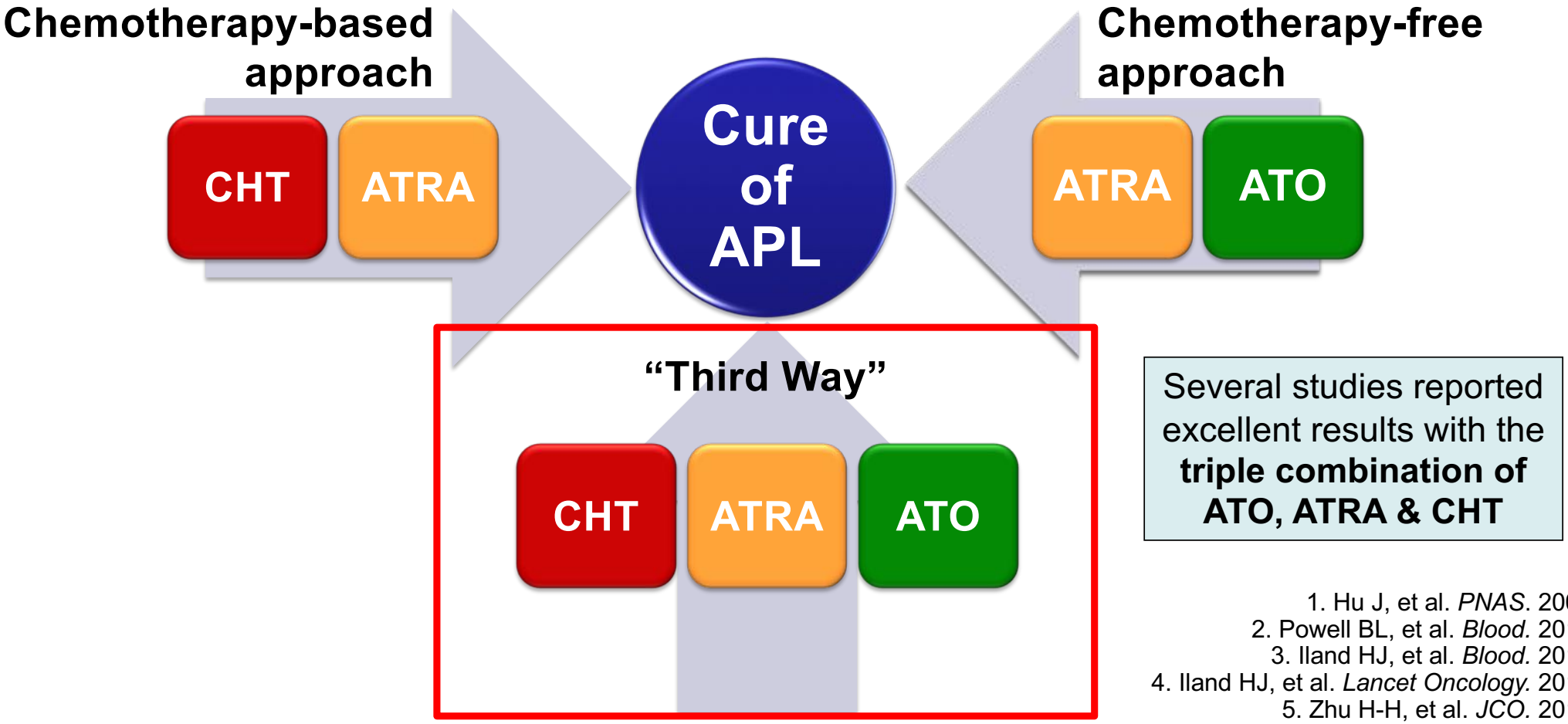
Lessons learned and advances

- **2-3 cycles** of anthracycline ± cytarabine ± ATRA
- In addition to ATRA + CHT, **ATO** can also play a role for consolidation
- Molecular remission after consolidation is achievable in roughly 99%
- CIR at 3 and 5 years 7% to 11%, respectively
- Risk-adapted consolidation is a reasonable strategy (e.g., age, CD56, and relapse risk score).

No role for stem cell transplantation in CR1

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

Current Treatment Approaches in APL



Several studies reported excellent results with the **triple combination of ATO, ATRA & CHT**

1. Hu J, et al. *PNAS*. 2009
2. Powell BL, et al. *Blood*. 2010
3. Iland HJ, et al. *Blood*. 2012
4. Iland HJ, et al. *Lancet Oncology*. 2015
5. Zhu H-H, et al. *JCO*. 2013

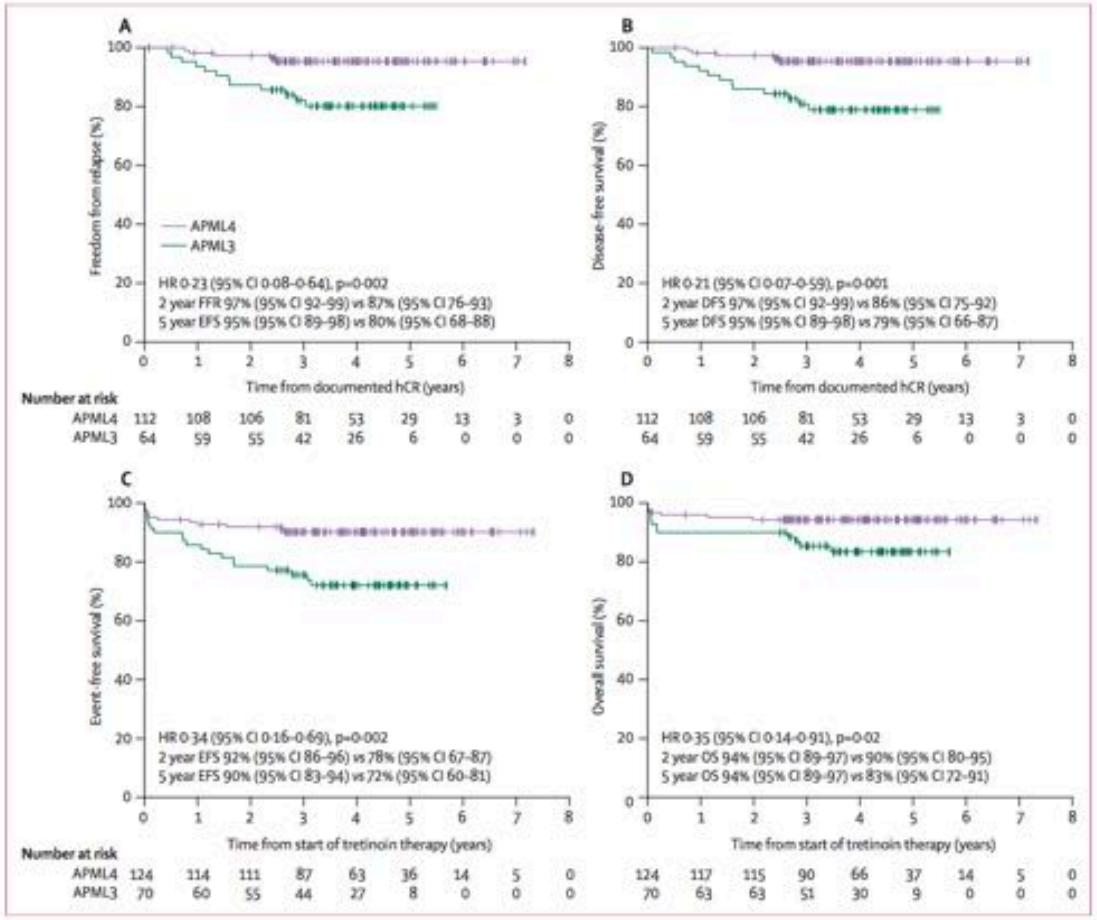
ATRA + ATO + CHT

Australasian Leukemia and Lymphoma Group

Induction
ATRA + ATO + CHT

Consolidation (2)
ATRA + ATO

Maintenance (5)
ATRA + LD-CHT

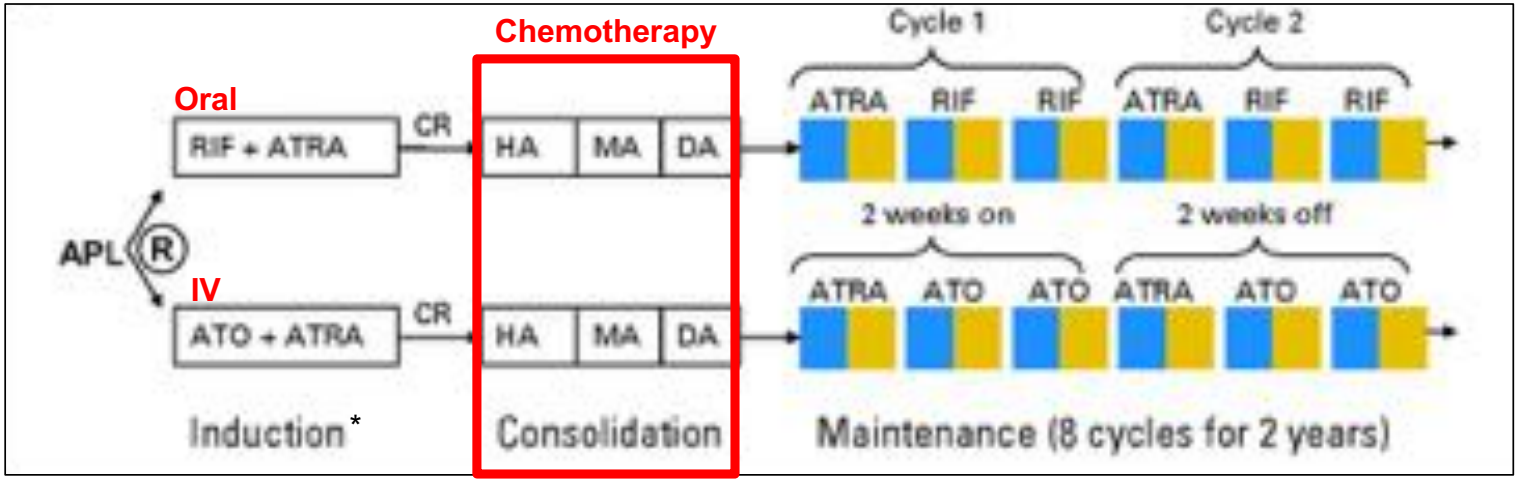


Iland HJ, et al. *Lancet Haematol.* 2015

ATO + ATRA + CHT

Chinese APL Cooperative Group

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



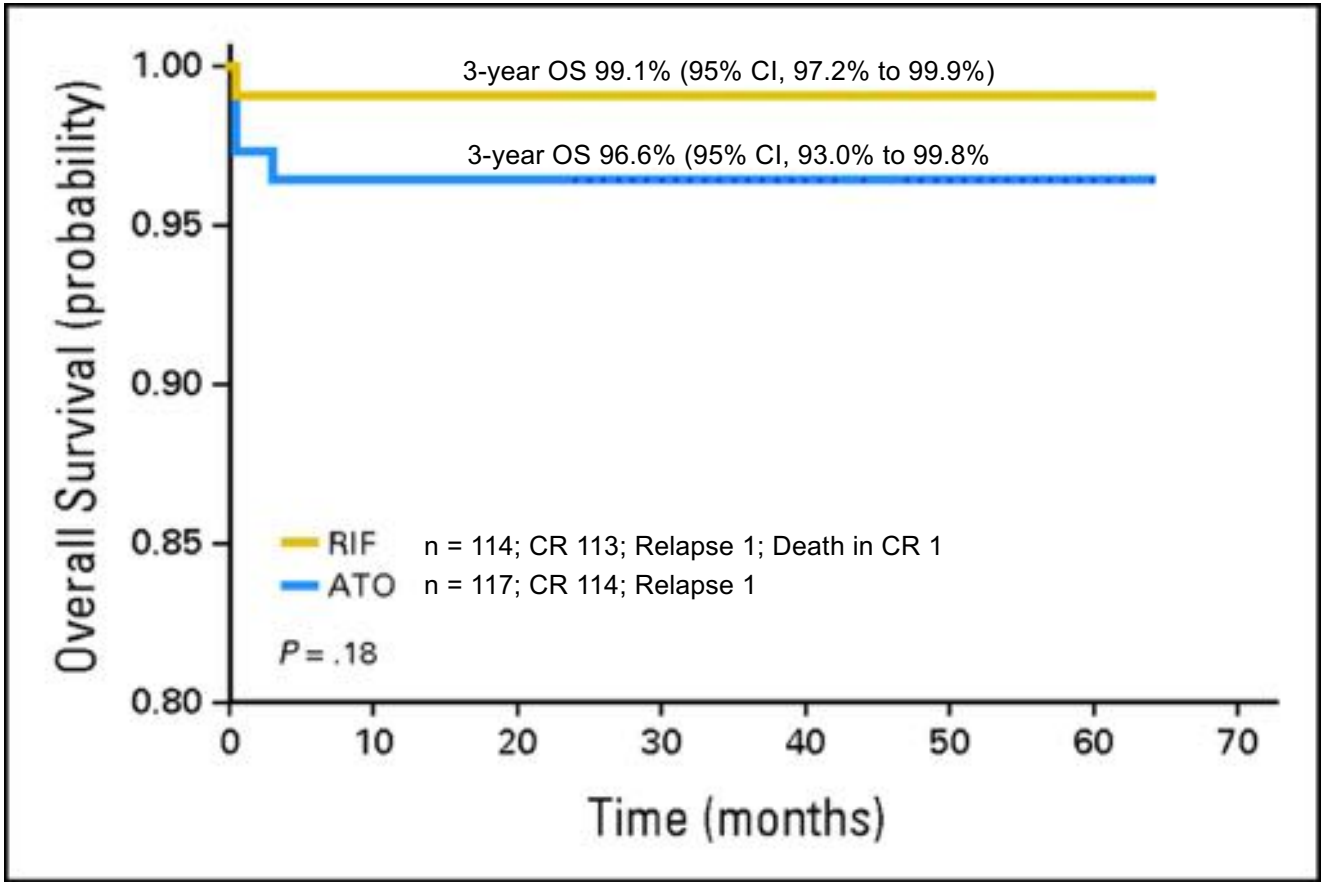
* Mitoxantrone was added at a dose of 1.4 mg/m^2/day on 5 days 4, 5, 6, 7, and 8 (if WBC >10 x 10^9/L start on day 1).

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

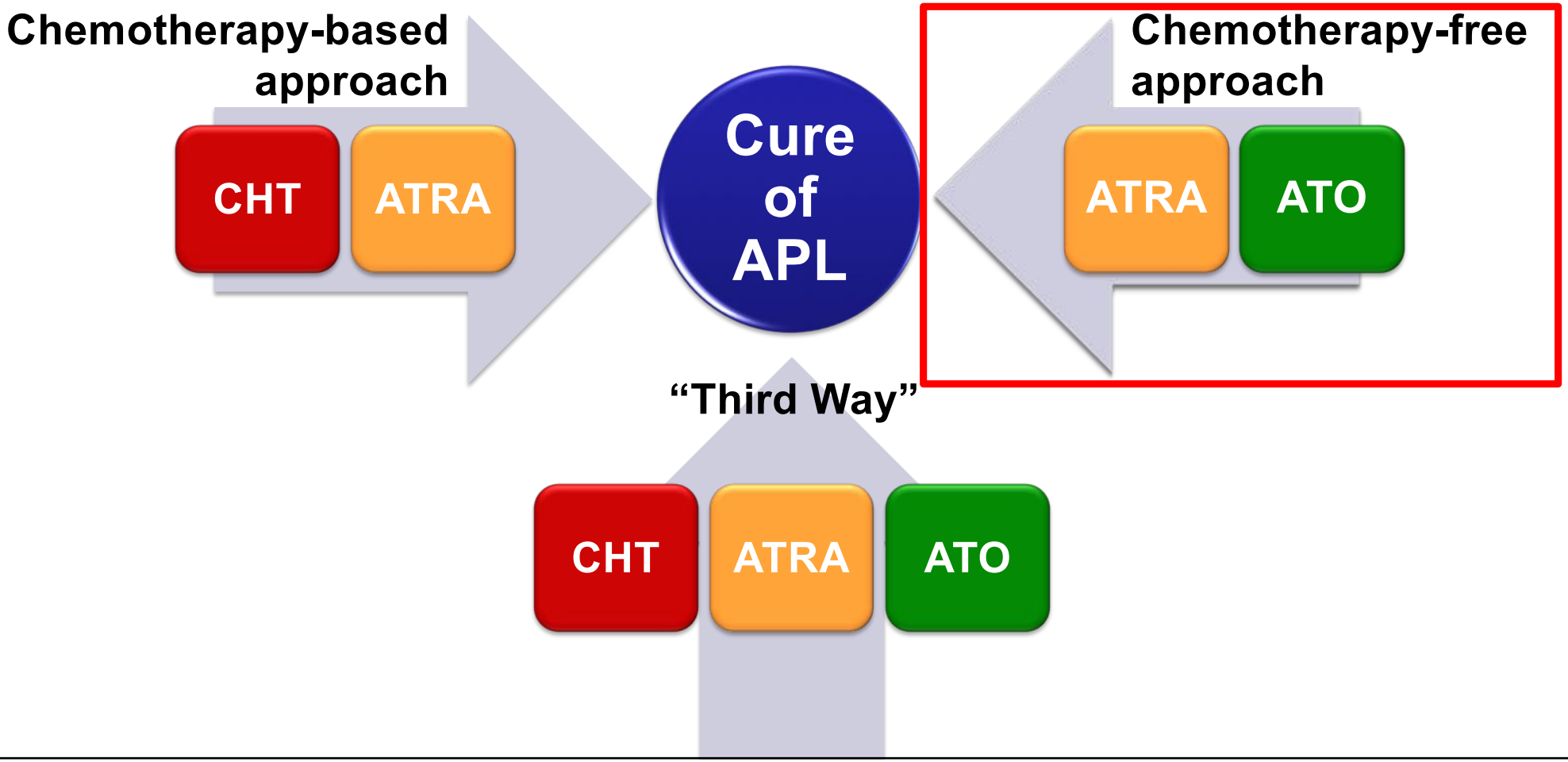
ATO + ATRA vs. RIF + ATRA

Chinese APL Cooperative Group



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

Current Treatment Approaches in APL



ATO-based regimen 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

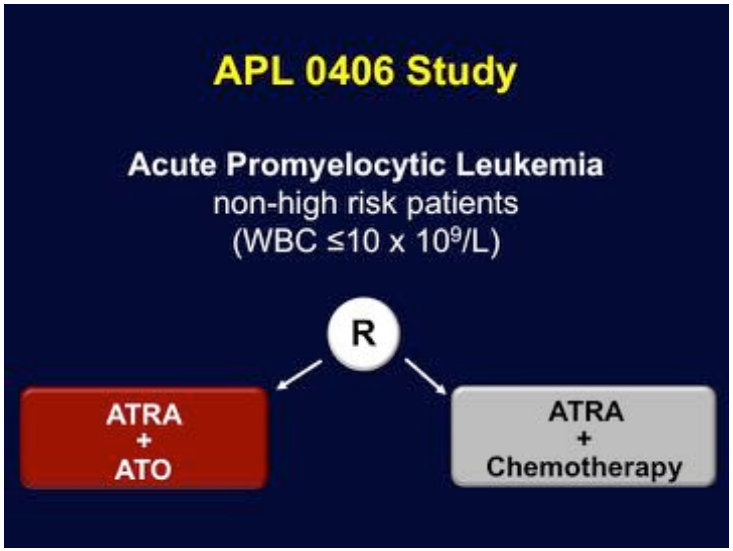
1. Ghavamzadeh A, et al. *J Clin Oncol*. 2011;29:2753-7; **2.** Mathews V, et al. *J Clin Oncol*. 2010;28:3866-71;
3. Ravandi F, et al. *J Clin Oncol*. 2009;27:504-10

ATO + ATRA without CHT

Randomized trials

GIMEMA-SAL-AMLSG

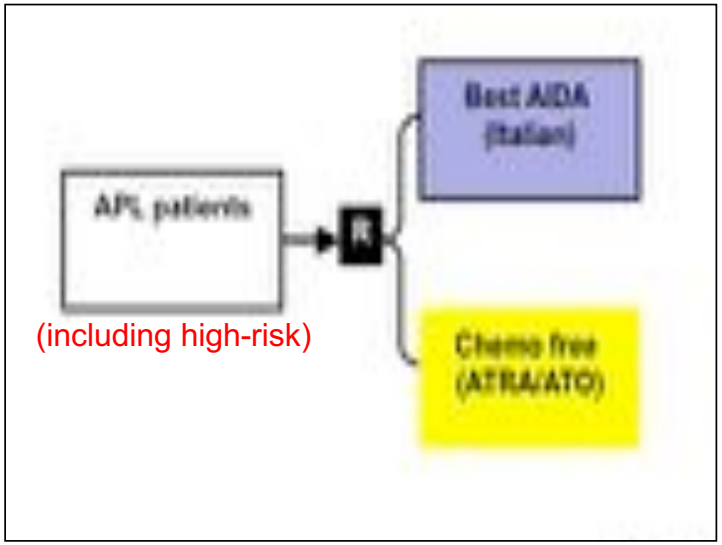
APL 0406 trial



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

UK NCRI

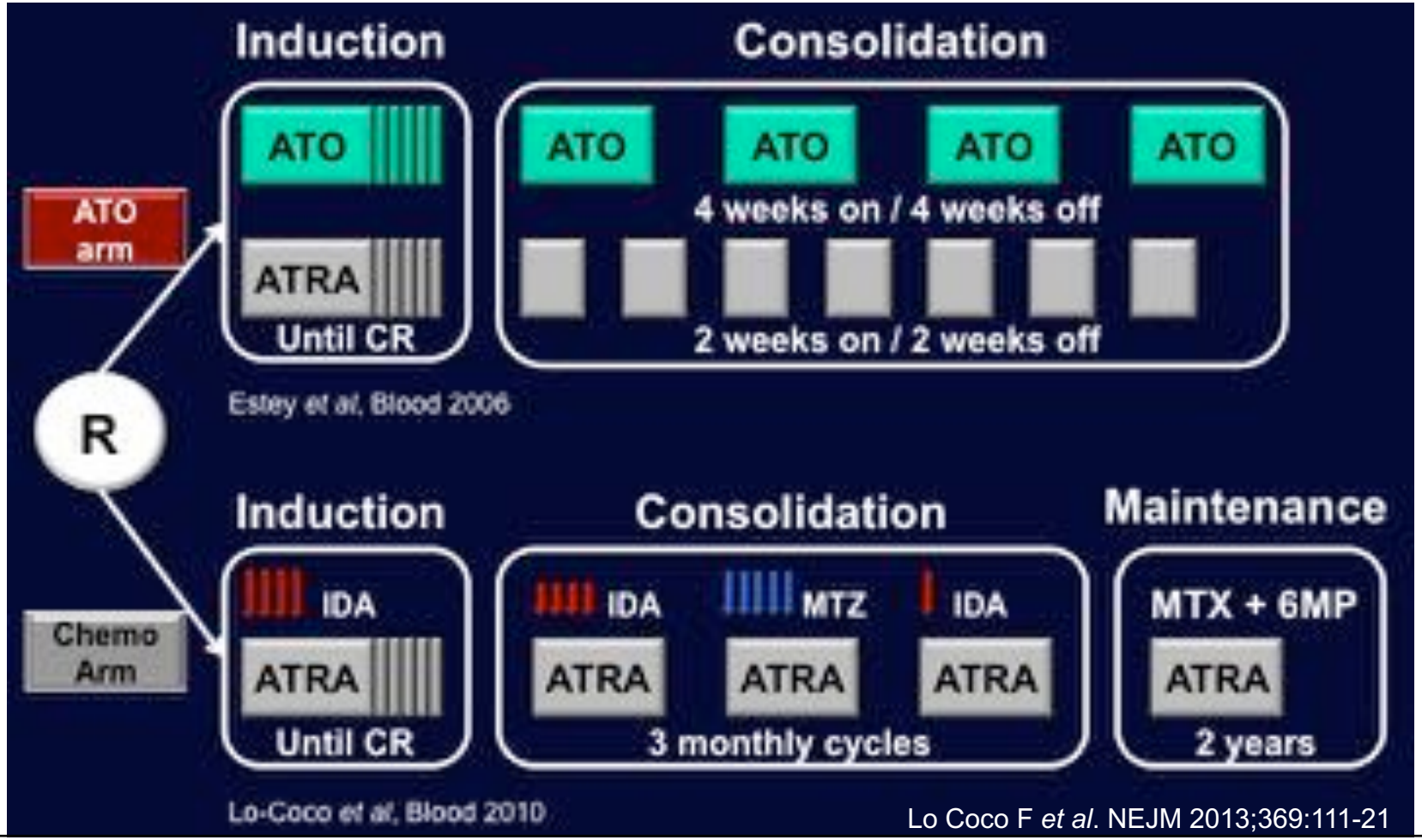
AML 17 trial



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

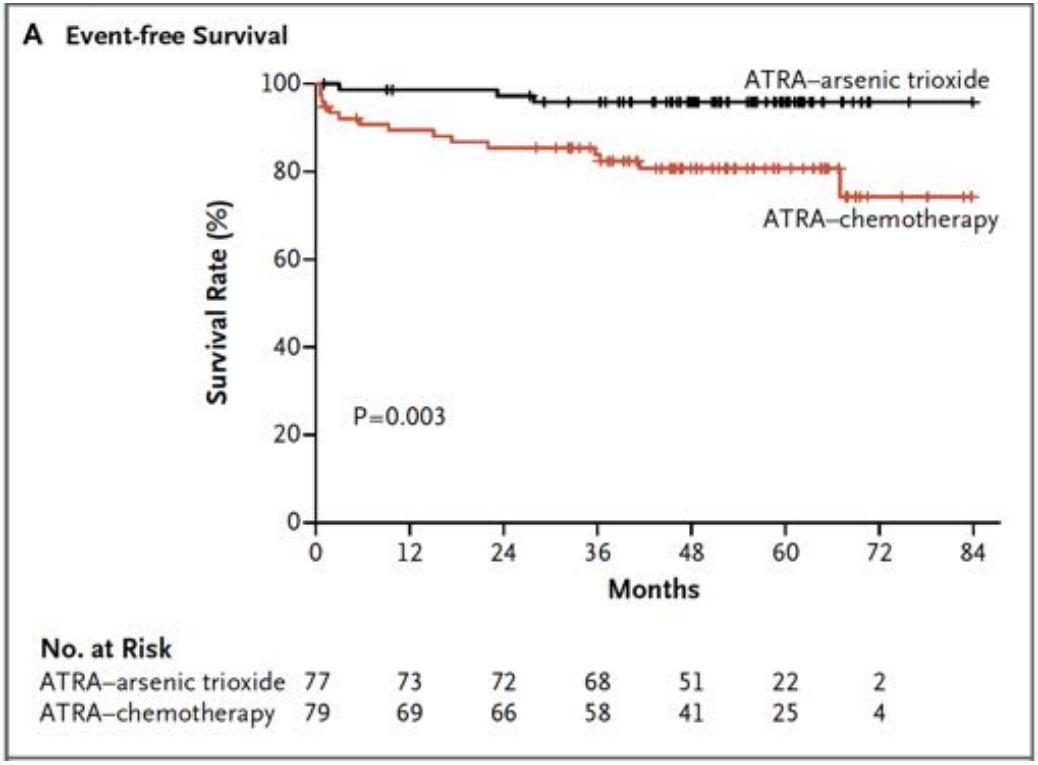
GIMEMA-SAL-AMLSG

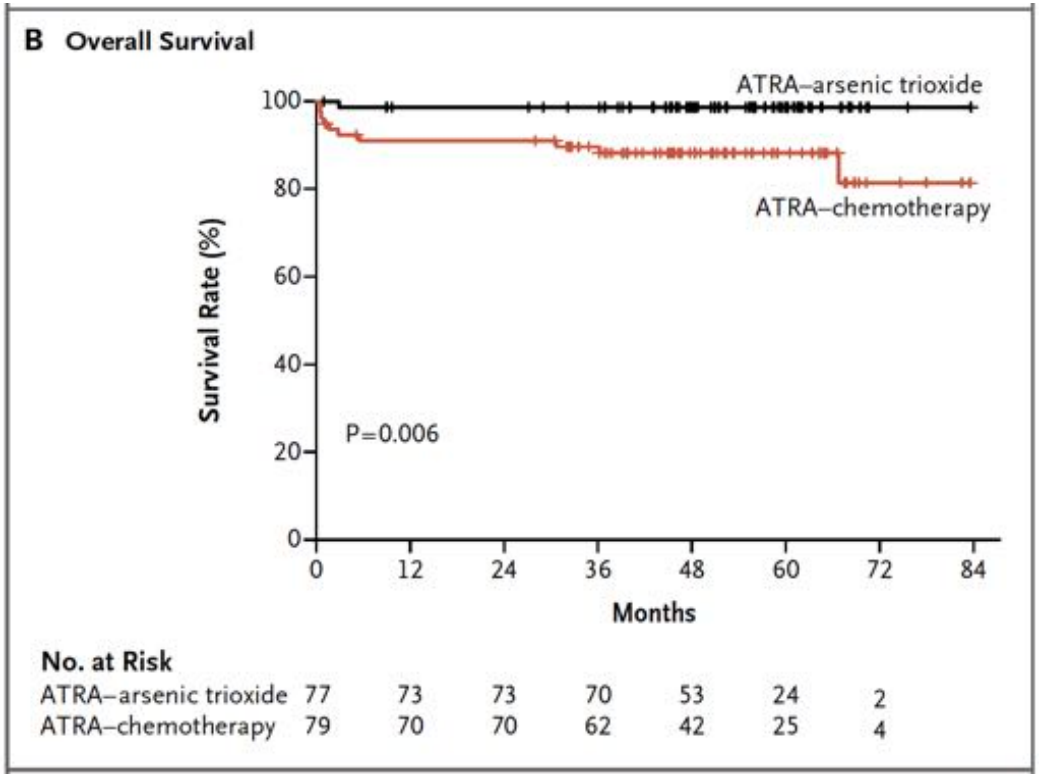
APL 0406 study



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

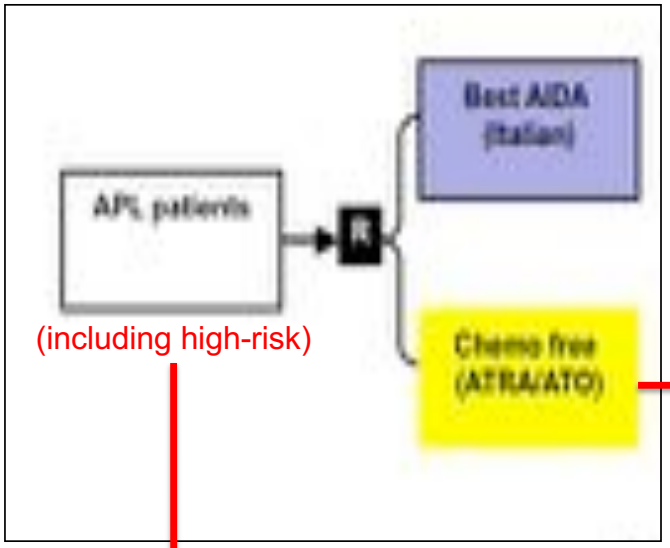
ATO + ATRA *vs.* AIDA
GIMEMA-SAL-AMLSG (APL 0406)





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

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



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

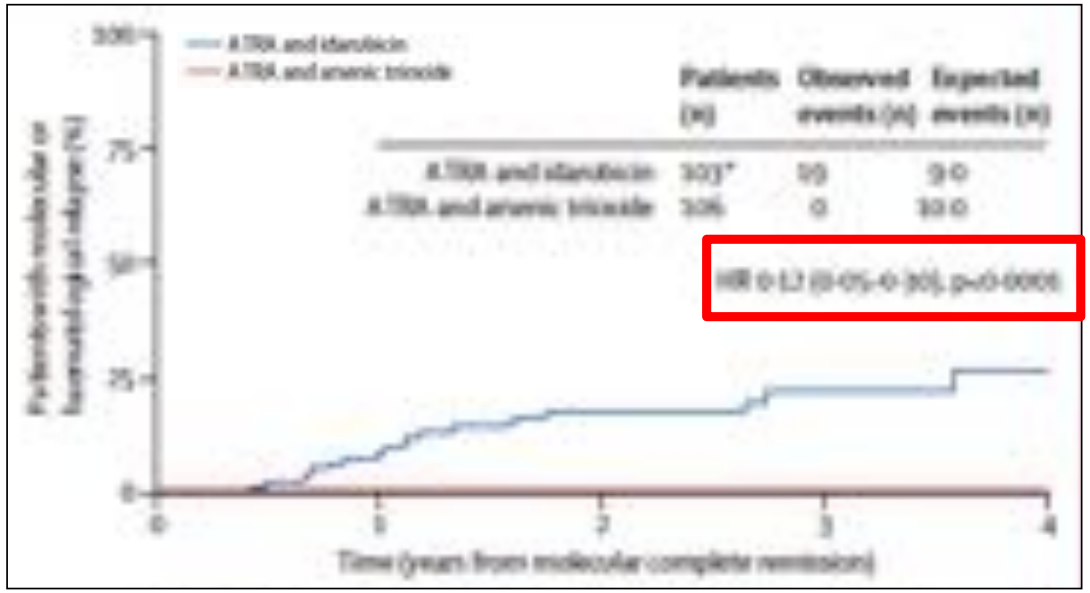
High-risk patients

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).

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

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

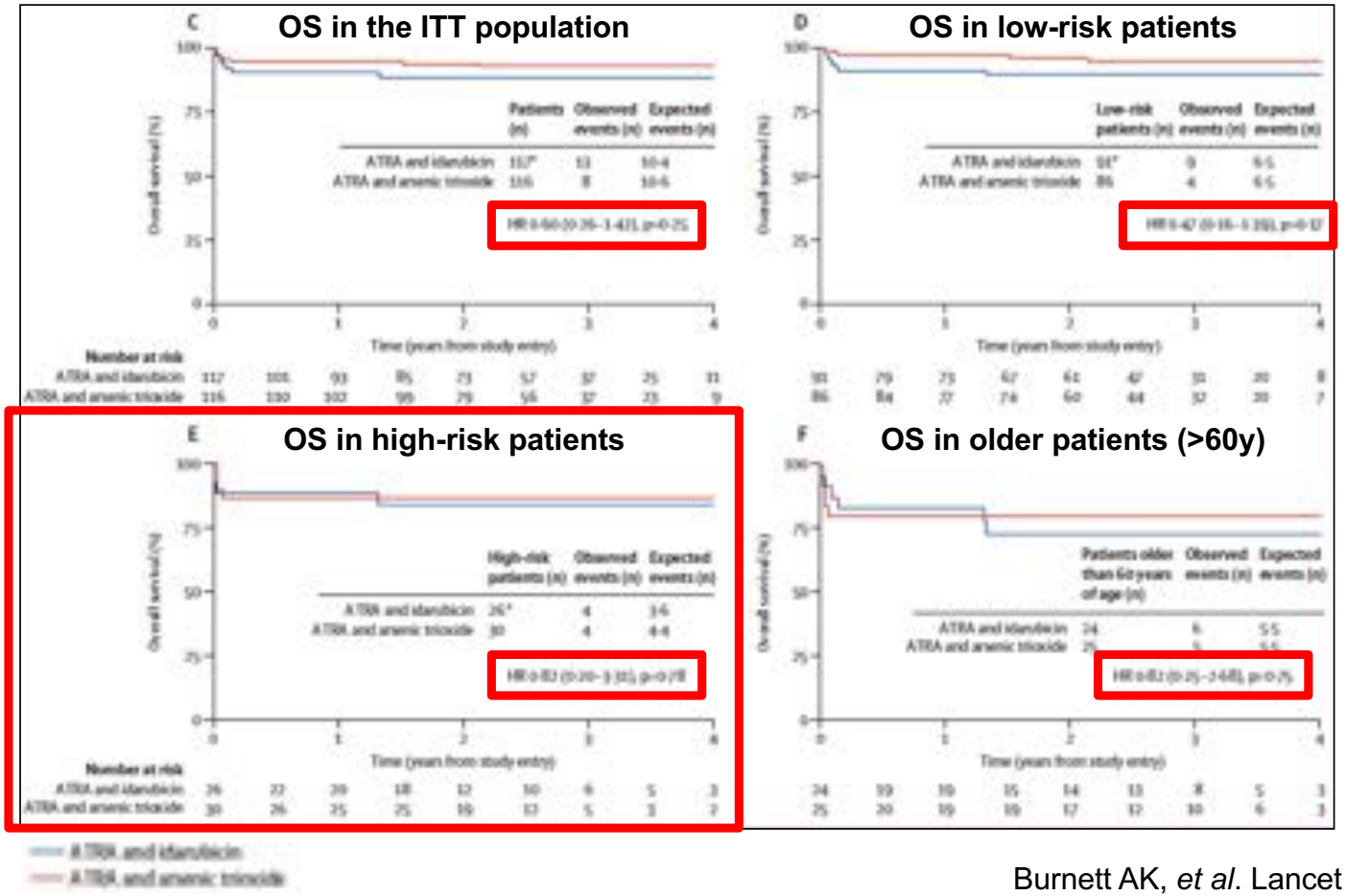
Cumulative incidence of molecular or hematological relapse



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

ATO + ATRA vs. AIDA

UK NCRI - AML 17 trial



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

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

Oral arsenic plus ATRA versus intravenous arsenic plus ATRA **for non-high-risk acute promyelocytic leukemia**: a non-inferiority, randomized phase 3 trial

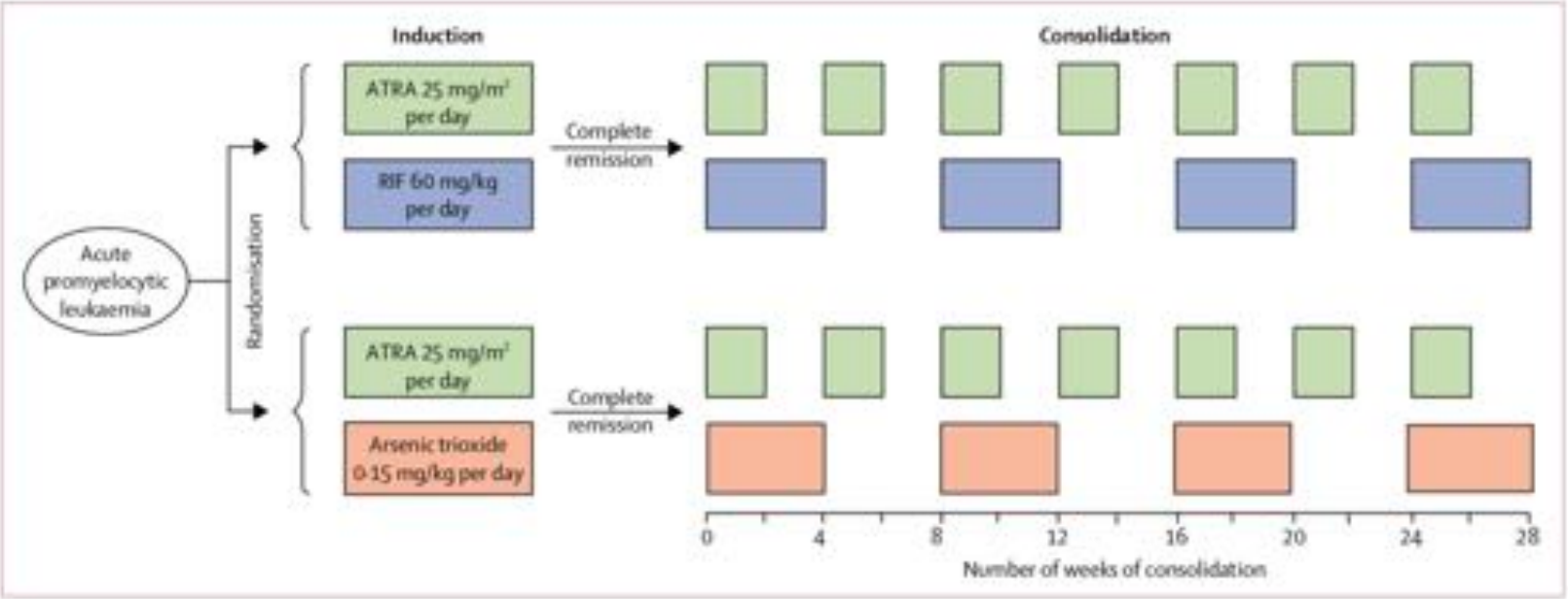
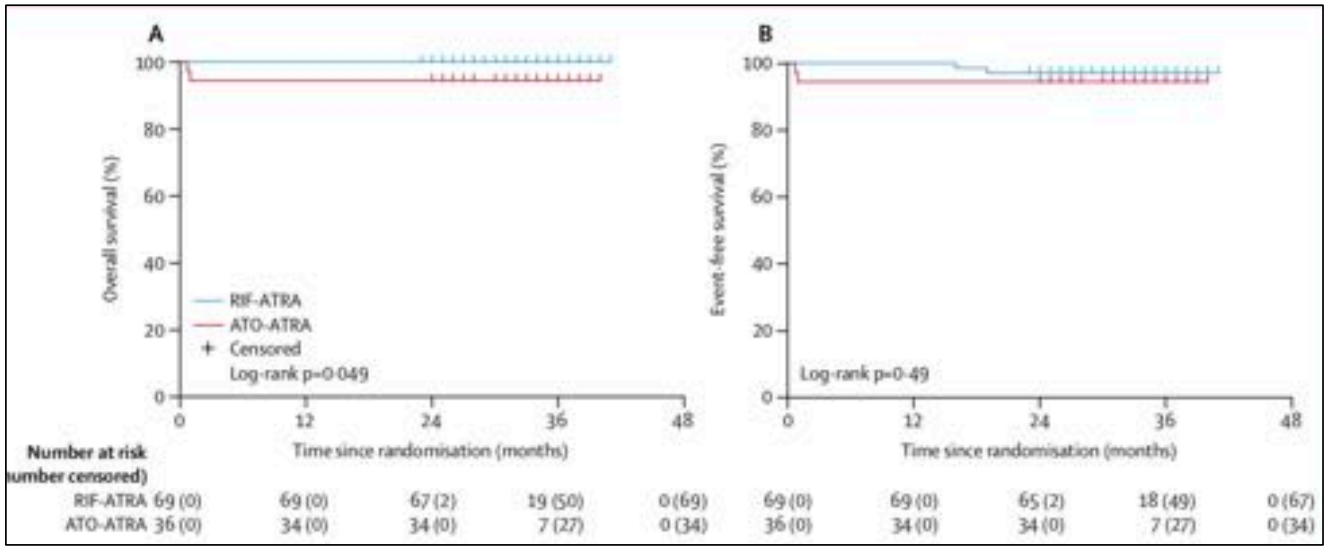


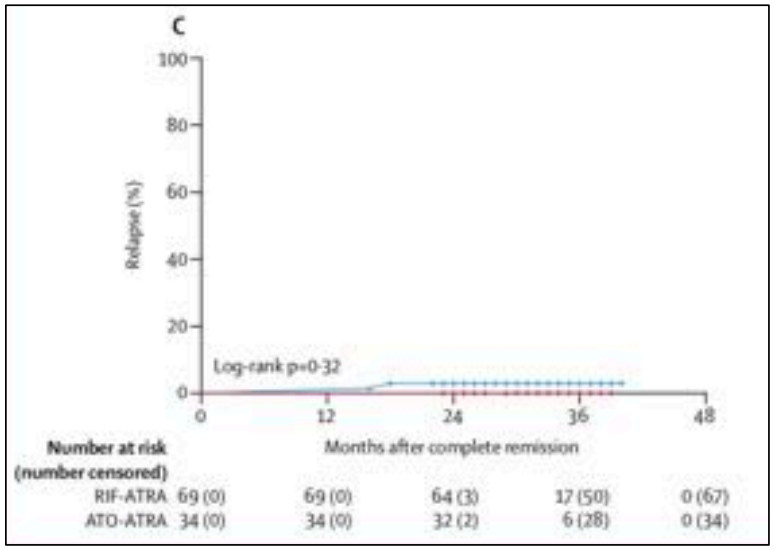
Figure 1: Study design
ATRA=all-trans retinoic acid. RIF=realgar-Indigo naturalis formula.

Zhu H et al. Lancet Oncology 2018;19:871-879

ATO + ATRA vs. RIF + ATRA

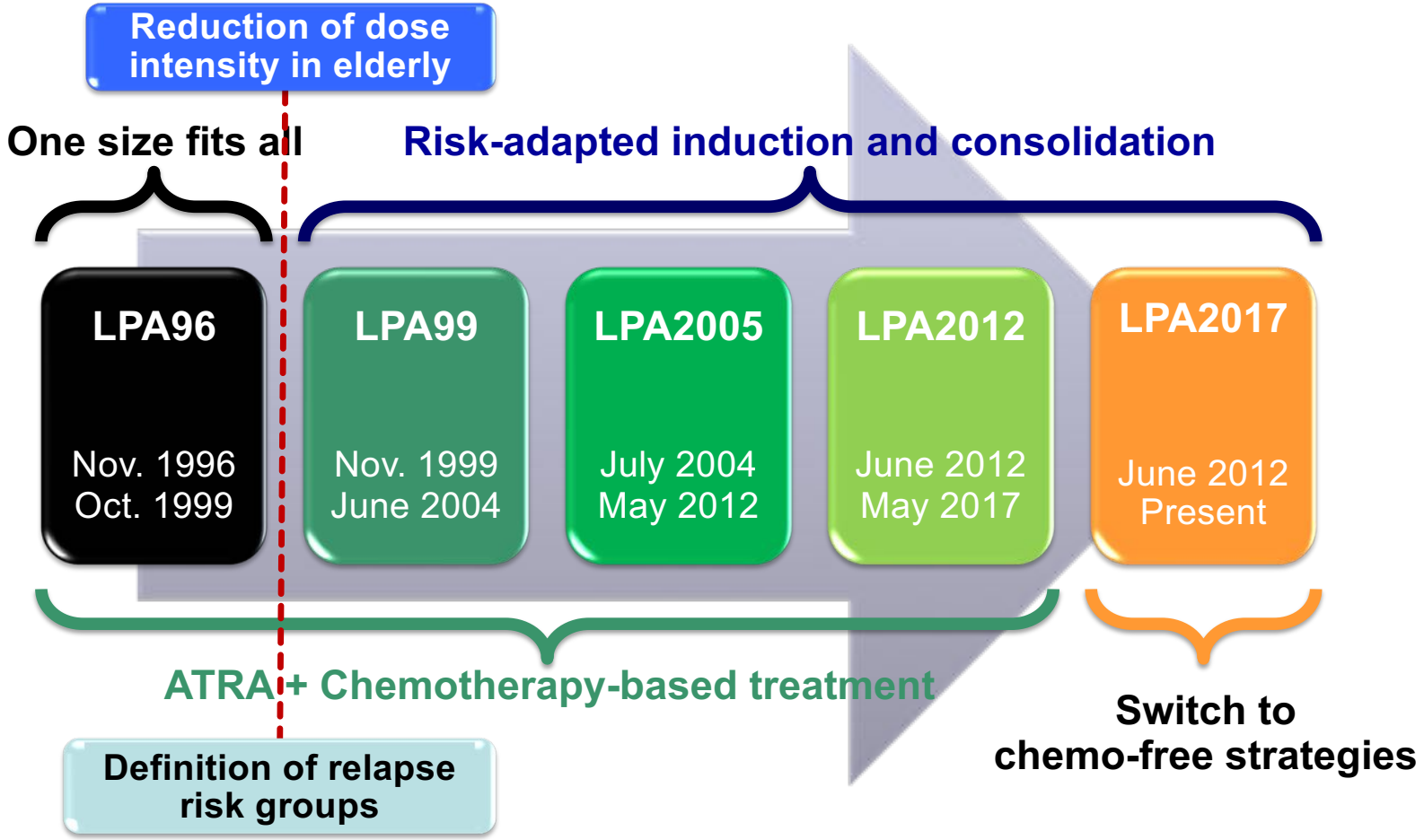
Chinese APL Cooperative Group





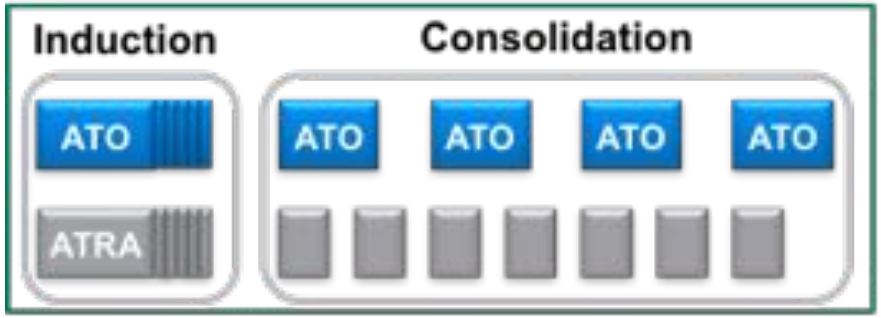
Zhu H et al. Lancet Oncology 2018;19:871-879

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

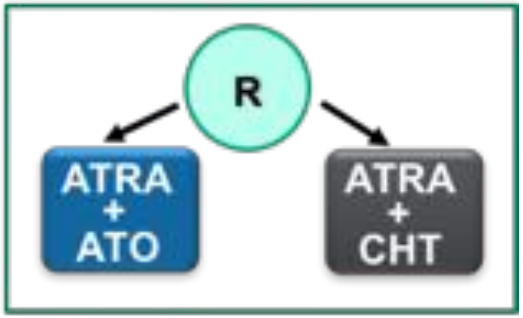


Risk-adapted strategy in APL without or with minimal use of chemotherapy (PETHEMA)

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



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

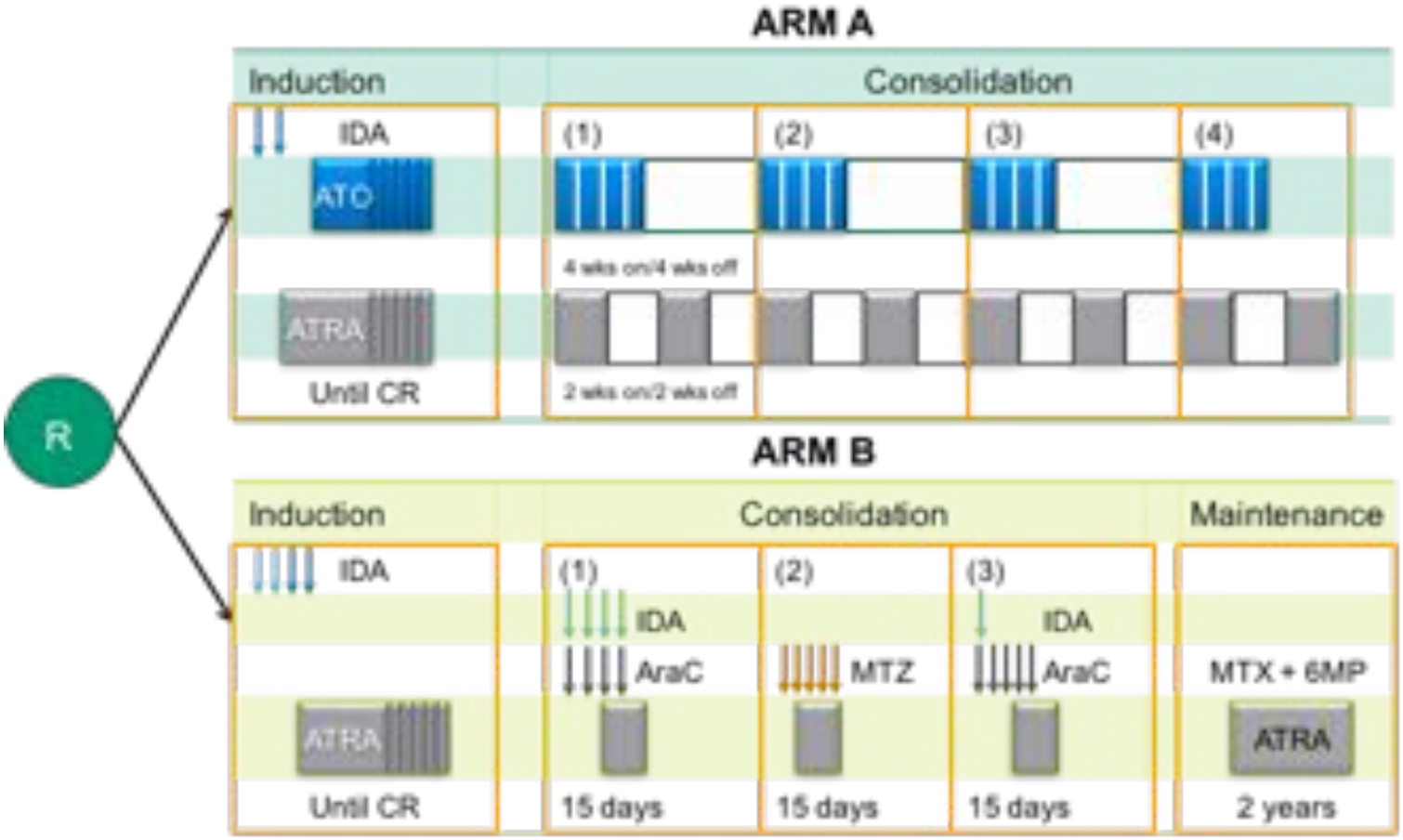


APOLLO trial
(NCT02688140)

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

1. Lo-Coco F, et al. N Engl J Med. 2013;369:111-21

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



Front-line Therapy in APL
Current status and remaining issues

Exploring the far side of the Moon

Updated recommendations for the management of APL

Review article

Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet

Miguel A. Sanz,[1] David Grimwade,[2] Martin S. Tallman,[3] Bob Lowenberg,[4] Pierre Fenaux,[5] Elihu H. Estey,[6] Tomoki Naoe,[7] Eva Lengfelder,[8] Thomas Büchner,[9] Hartmut Döhner,[10] Alan K. Burnett,[11] and Francesco Lo-Coco[12]

[1]University Hospital La Fe, Valencia, Spain; [2]King's College London, London, United Kingdom; [3]Northwestern University, Chicago, IL; [4]Erasmus University Medical Center, Rotterdam, The Netherlands; [5]Hopital Avicenne, Paris, France; [6]Seattle Cancer Care Alliance, WA; [7]Nagoya University, Nagoya, Japan; [8]Universitaetsklinikum Mannheim, Heidelberg, Germany; [9]University of Munster, Munster, Germany; [10]University of Ulm, Ulm, Germany; [11]Cardiff University, Cardiff, United Kingdom; and [12]Tor Vergata University, Rome, Italy

The introduction of all-trans retinoic acid (ATRA) and, more recently, arsenic trioxide (ATO) into the therapy of acute promyelocytic leukemia (APL) has revolutionized the management and outcome of this disease. Several treatment strategies using these agents, usually in combination with chemotherapy, but also without or with minimal use of cytotoxic agents, have provided excellent therapeutic results. Cure of APL patients, however, is also dependent on peculiar aspects related to the management and supportive measures that are crucial to counteract life-threatening complications associated with the disease biology and molecularly targeted treatment. The European LeukemiaNet recently appointed an international panel of experts to develop evidence- and expert opinion–based guidelines on the diagnosis and management of APL. Together with providing current indications on genetic diagnosis, modern risk-adapted front-line therapy and salvage treatment, the review contains specific recommendations for the identification and management of most important complications such as the bleeding disorder, APL differentiation syndrome, QT prolongation and other ATRA- and ATO-related toxicities, as well as for molecular assessment of response to treatment. Finally, the approach to special situations is also discussed, including management of APL in children, elderly patients, and pregnant women. (Blood. 2009;113:1875-1891)

1. Introduction

Although the real incidence of acute promyelocytic leukemia (APL) is unknown, it is a relatively rare hematologic malignancy. The number of newly diagnosed cases per year in the United States is estimated to be 600 to 800.[1,2] One of the most striking features of APL is its age-associated incidence rate. The disease is very uncommon in children less than 10 years of age. Its incidence increases steadily during the teen years, reaches a plateau during early adulthood, and remains constant until it decreases after age 60 years.[3] This is in marked contrast to other subtypes of acute myeloid leukemia (AML), where there is a steady rise to age 55 years, after which there is an exponential increase. There is also a suggestion in the literature that APL arising as a complication of previous exposure to chemotherapy (particularly drugs targeting topoisomerase II) or radiotherapy is becoming more prevalent, particularly in patients with a history of breast cancer.[4-6] With respect to the incidence of APL among ethnic groups, contradictory data regarding a presumed higher incidence of APL in persons from Mexico, Central and South America, Italy, and Spain have been reported in the literature.[2,7] Therefore, this epidemiologic issue is still a matter of controversy and deserves additional investigation.

The introduction of all-*trans* retinoic acid (ATRA, tretinoin) into the therapy of APL completely revolutionized the management and outcome of this disease. This agent represents one of the most spectacular advances in the treatment of human cancer, providing the first paradigm of molecularly targeted treatment. After the advent of ATRA, the introduction of arsenic trioxide (ATO), probably the most biologically active single drug in APL, has provided a valuable addition to the armamentarium and may have contributed to further improvements in the clinical outcome of this disease. Several treatment strategies using these agents, usually in combination with chemotherapy, have provided excellent therapeutic results with survival rates exceeding 70% in multicenter clinical trials. Cure of patients with APL depends not only on the effective use of combination therapy involving differentiating and classical cytotoxic agents, but also, critically, upon supportive care measures that take into particular account the biology of the disease and the complications associated with molecularly targeted therapies. Moreover, it is important to consider diagnostic suspicion of APL as a medical emergency (uncommon in AML) that requires several specific and simultaneous actions, including immediate commencement of ATRA therapy, prompt genetic diagnosis, and measures to counteract the coagulopathy.

Although there are some recent exhaustive reviews addressing the management of APL[8-10] and national guidelines from the United States and United Kingdom[11,12] on the management of AML that include some specific items on APL, no comprehensive yet succinct guidelines focused on APL have been produced. Therefore, the European LeukemiaNet appointed an international panel of experts to develop evidence- and expert opinion–based guidelines on the management of APL. The publication of guidelines for the management of challenging malignant diseases provides an excellent tool to spread knowledge of the optimum

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blood Special Report

Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet

Miguel A. Sanz,[1,2] Pierre Fenaux,[3,4] Martin S. Tallman,[5] Elihu H. Estey,[6] Bob Löwenberg,[8] Tomoki Naoe,[9] Eva Lengfelder,[10] Hartmut Döhner,[11] Alan K. Burnett,[12] Sai-Juan Chen,[13] Vikram Mathews,[14] Harry Iland,[15] Eduardo Rego,[16,17] Hagop Kantarjian,[18] Lionel Adès,[3,4] Giuseppe Avvisati,[19] Pau Montesinos,[1,2] Uwe Platzbecker,[20] Farhad Ravandi,[18] Nigel H. Russell,[21] and Francesco Lo-Coco[22]

[1]Departamento de Hematología, Hospital Universitari i Politècnic La Fe, Valencia, Spain; [2]Department of Medicine, University of Valencia, Valencia, Spain; [3]Centro de Investigación Biomédica en Red de Cáncer, Instituto Carlos III, Madrid, Spain; [4]Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris, Paris, France; [5]Department of Hematology, Université Paris Diderot, Paris, France; [6]Memorial Sloan Kettering Cancer Center, New York, NY; [7]Seattle Cancer Care Alliance, Seattle, WA; [8]Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands; [9]National Hospital Organization Nagoya Medical Center, Nagoya, Japan; [10]Department of Haematology, University Hospital Mannheim, University of Heidelberg, Mannheim, Germany; [11]Department of Internal Medicine III, Ulm University Hospital, Ulm, Germany; [12]Department of Haematology, Glasgow University, Glasgow, United Kingdom; [13]State Key Laboratory of Medical Genomics, Shanghai Institute of Hematology, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [14]Department of Hematology, Christian Medical College, Vellore, India; [15]Royal Prince Alfred Hospital, Camperdown, NSW, Australia; [16]Hematology Division and [17]Clinical Oncology Division, Department of Internal Medicine, University of São Paulo, Ribeirao Preto, Brazil; [18]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [19]Hematology, Campus Bio-Medico University, Rome, Italy; [20]Medical Clinic and Polyclinic I, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany; [21]Centre for Clinical Haematology, Department of Haematology, Nottingham University Hospital, Nottingham, United Kingdom; and [22]Department of Biomedicine and Prevention, Tor Vergata University of Rome, Rome, Italy

Since the comprehensive recommendations for the management of acute promyelocytic leukemia (APL) reported in 2009, several studies have provided important insights, particularly regarding the role of arsenic trioxide (ATO) in frontline therapy. Ten years later, a European LeukemiaNet expert panel has reviewed the recent advances in the management of APL in both frontline and relapse settings in order to develop updated evidence- and expert opinion–based recommendations on the management of this disease. Together with providing current indications on genetic diagnosis, modern risk-adapted frontline therapy, and salvage treatment, the review contains specific recommendations for the identification and management of the most important complications such as the bleeding disorder APL differentiation syndrome, QT prolongation, and other all-trans retinoic acid– and ATO-related toxicities, as well as recommendations for molecular assessment of the response to treatment. Finally, the approach to special situations is also discussed, including management of APL in children, elderly patients, and pregnant women. The most important challenges remaining in APL include early death, which still occurs before and during induction therapy, and optimizing treatment in patients with high-risk disease. (Blood. 2019;133(15):1630-1643)

Introduction

After the initial therapeutic success reported in 1973 using an anthracycline (daunorubicin),[1] the management and outcome of acute promyelocytic leukemia (APL) has been revolutionized by the introduction of all-trans retinoic acid (ATRA; tretinoin) and arsenic trioxide (ATO) in 1988[2] and 1996,[3] respectively. Multicenter studies over the past 3 decades have demonstrated the efficacy of ATRA plus chemotherapy and, subsequently, of ATRA plus ATO, with or without chemotherapy. However, the optimal management of APL also requires early diagnosis, institution of aggressive supportive measures, appropriate management of treatment-related complications, and monitoring of measurable residual disease (MRD).

In 2009, a detailed list of recommendations for the management of APL was reported by an expert panel on behalf of the European LeukemiaNet (ELN).[4] Since then, several studies have provided important insights about frontline therapy. In particular, 2 large randomized trials exploring the role of ATO have established a new standard of care in this setting.[5,6] Based on the results of these studies, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recently approved ATO for the treatment of newly diagnosed patients with low-to-intermediate risk APL (defined as white blood cell [WBC] count ≤10 × 10⁹/L). This review will address this and other recent advances in the management of APL in both frontline and relapse settings.

Methods

The panel included 21 members with recognized clinical and research expertise in APL. We identified relevant articles appearing between the publication of the 2009 version of the ELN recommendations[4] and June 2018 by systematically searching and

Treatment of APL
Current status and future directions

- High cure rates can be achieved with optimized combinations of:
  - ATRA + CHT
  - ATRA + ATO
  - ATRA + CHT + ATO
- **Oral arsenic** formulations seem a promising alternative to IV arsenic.
- Research should now be focused on some remaining issues for a small proportion of APL patients (mainly among high-risk APL):
  - Death before induction (patients who arrive at very poor clinical condition)
  - Induction death: mainly hemorrhagic deaths, but not only
  - Death in CR
  - Relapse

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- Francesco Lo-Coco (GIMEMA, Italy) – **R.I.P.**