La Leucemia Acuta Promielocitica: Un Paradigma della Terapia Mirata In Oncoematologia

Francesco Lo Coco

Università Tor Vergata, Roma, Gruppo Cooperativo GIMEMA

Aggiornamenti in Ematologia
Treviso 25-26 Novembre 2016

L.S., a professional cyclist, came second one spring Sunday in the race from Paris to Tours, in which he averaged 40 Km/h

The following Monday, he was tired and the fatigue was attributed to his physical effort

On Wednesday he had serious hemorrhages and was taken to hospital

On Thursday, promyelocytic leukemia was diagnosed

He died on Saturday of more hemorrhages

Bernard J, History of APL, Leukemia 1993

Acute Promyelocytic Leukemia:

From Highly **Fatal** to Highly **Curable**

Acta Medica Scandinavica. Vol. CLIX, fasc. III, 1957.

From the Medical Department A, Rikshospitalet, Oslo. Physician in chief: Professor P. A. Owren.

Acute Promyelocytic Leukemia.

By

LEIF K. HILLESTAD.

(Submitted for publication August 13, 1957.)

Summary.

Evidence is here presented for the existence of a special type of acute myelogenous leukemia…

It is suggested that this type is named acute promyelocytic leukemia (APL). It seems to be the most malignant form of acute leukemia

First description of the promyelocyte

Gustavo Pittaluga (1940)

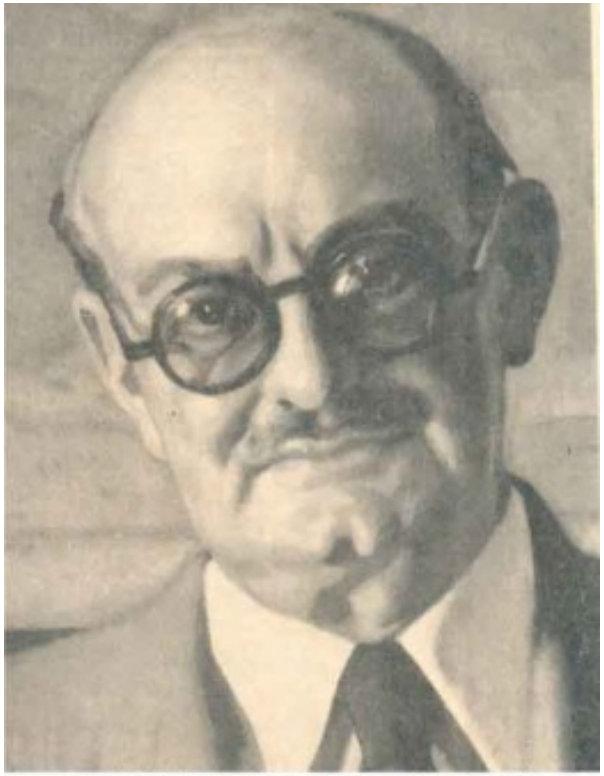
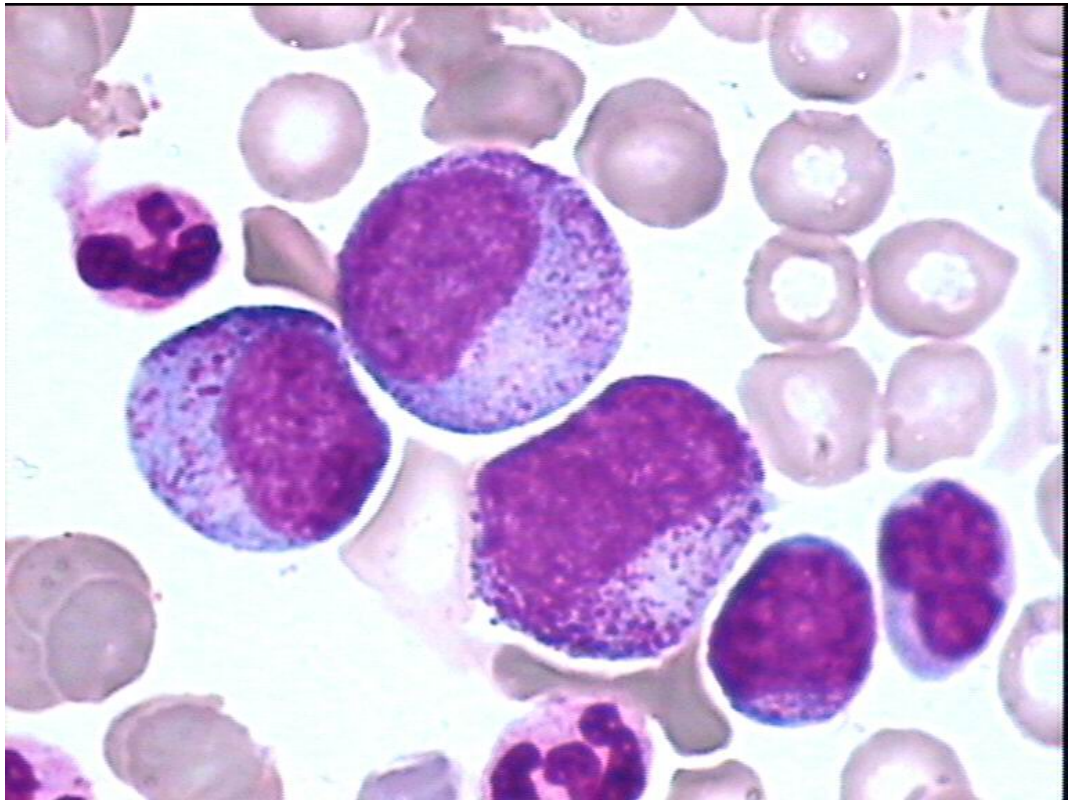


Fig. 12. Dr. Gustavo Pittaluga Fattorini (1876-1956).



Epidemiology

- 10%-15% of acute myeloid leukemias (AMLs)
- 100-120 cases/year in Italy
- Median age 40 (vs 70 in other AMLs)
- Same incidence in M/F
- *De novo* and therapy-related

Main presenting features

- Life-threatening bleeding tendency
- Dysplastic promyelocytes in the marrow
- Usually abrupt onset, with rapidly progressing coagulopathy (medical emergency)

Continuing Early Death in APL

Population-based studies

Study	ED rate (< 30 d)
Swedish Registry[1]	29 %
SEER (USA)[2]	17 %
Stanford University[3]	26 %
Canadian Registry[4]	22 %

[1]Lehman, Leukemia 2011; [2]Park, Blood 2011; [3]McClellan, Haematologica 2011;
[4] Paulson, BJH 2014

Acute Promyelocytic Leukemia:

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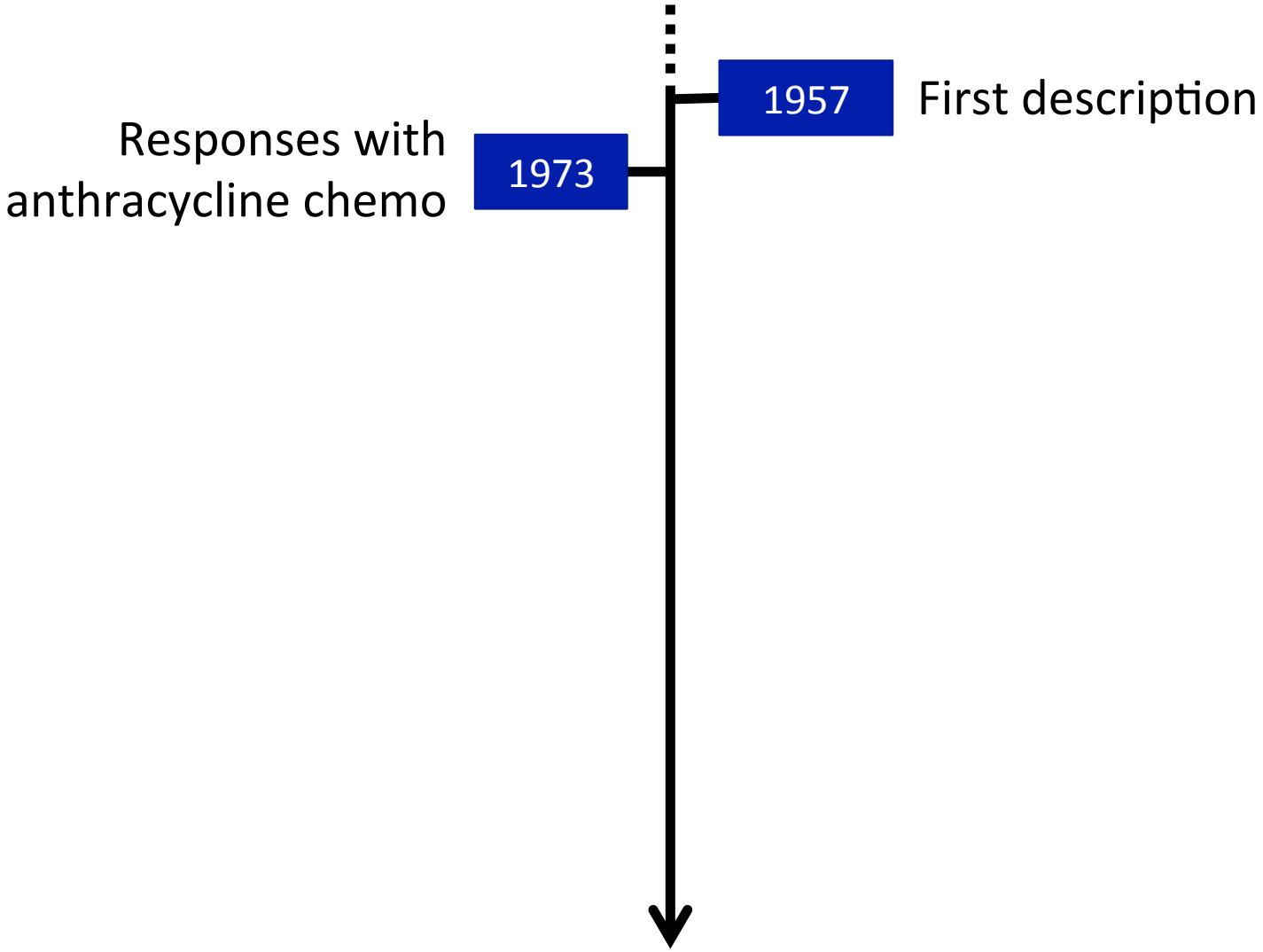


Jean Bernard

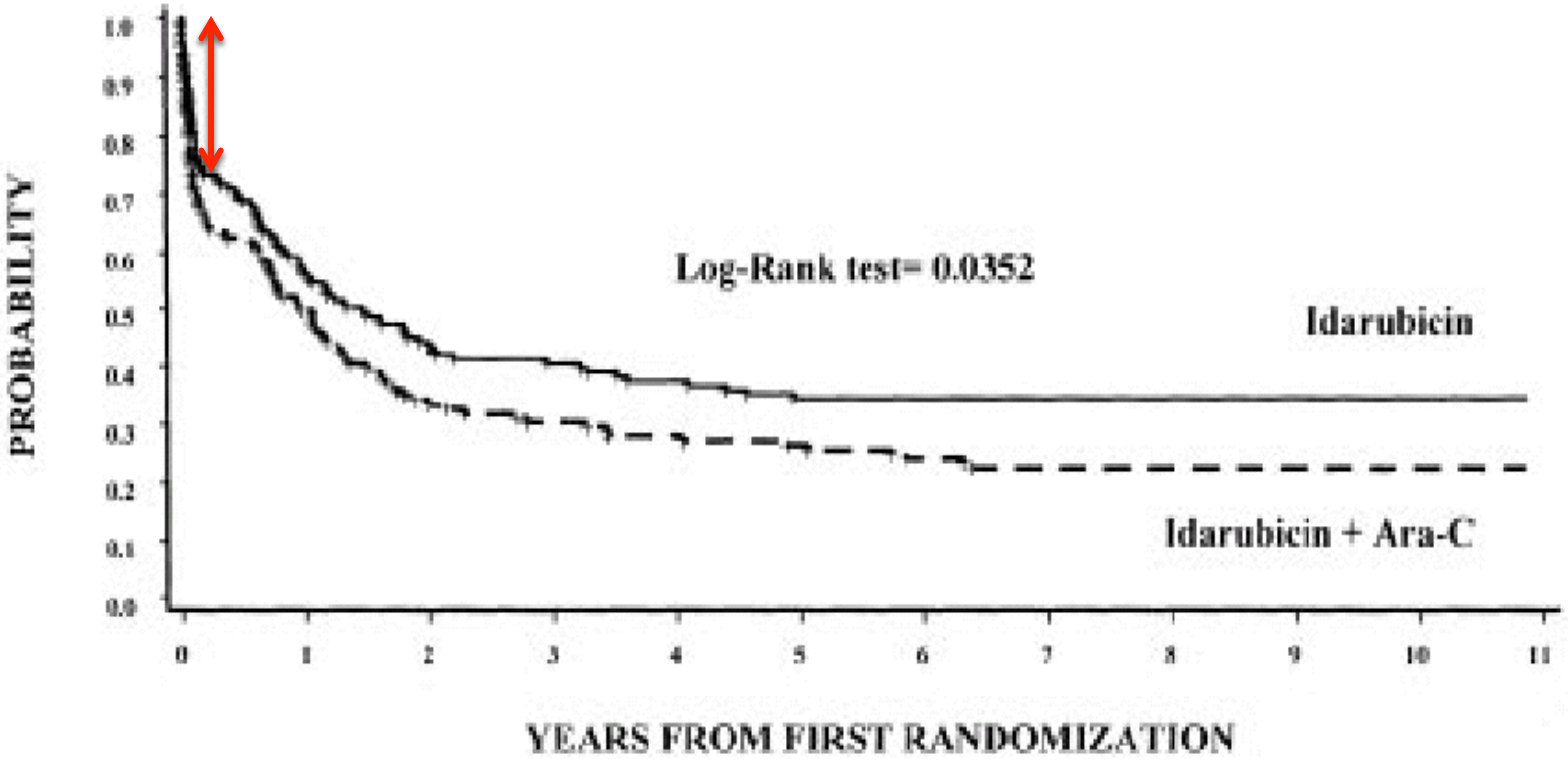
BLOOD *The Journal of Hematology*

VOL. XLI, NO. 4 APRIL 1973

Acute Promyelocytic Leukemia: Results of Treatment by Daunorubicin

By Jean Bernard, Marise Weil, Michel Boiron, Claude Jacquillat, Georges Flandrin, and Marie-François Gemon

Randomized APL0389 Trial (*pre-ATRA era)*



Avvisati *et al*. Blood 2002

GIMEMA trials in newly diagnosed APL

- 77-81: DNR
- 82-88: IDA
- 89-93: IDA vs IDA+AraC
- 93-99: AIDA 0493
- 99-00: MyAIDA
- 00-05: AIDA 2000 (risk-adapted)
- 06-12: AIDA vs ATO+RA

151 Clinical Centers

9 Centralizing Labs

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

Established in 1982

by F. Mandelli

- **Non-profit clinical studies**
- **Homogenize rx in the country**
- **Reference laboratories**
- **Diagnostic standardization**
- **International collaborations**

Acute Promyelocytic Leukemia:

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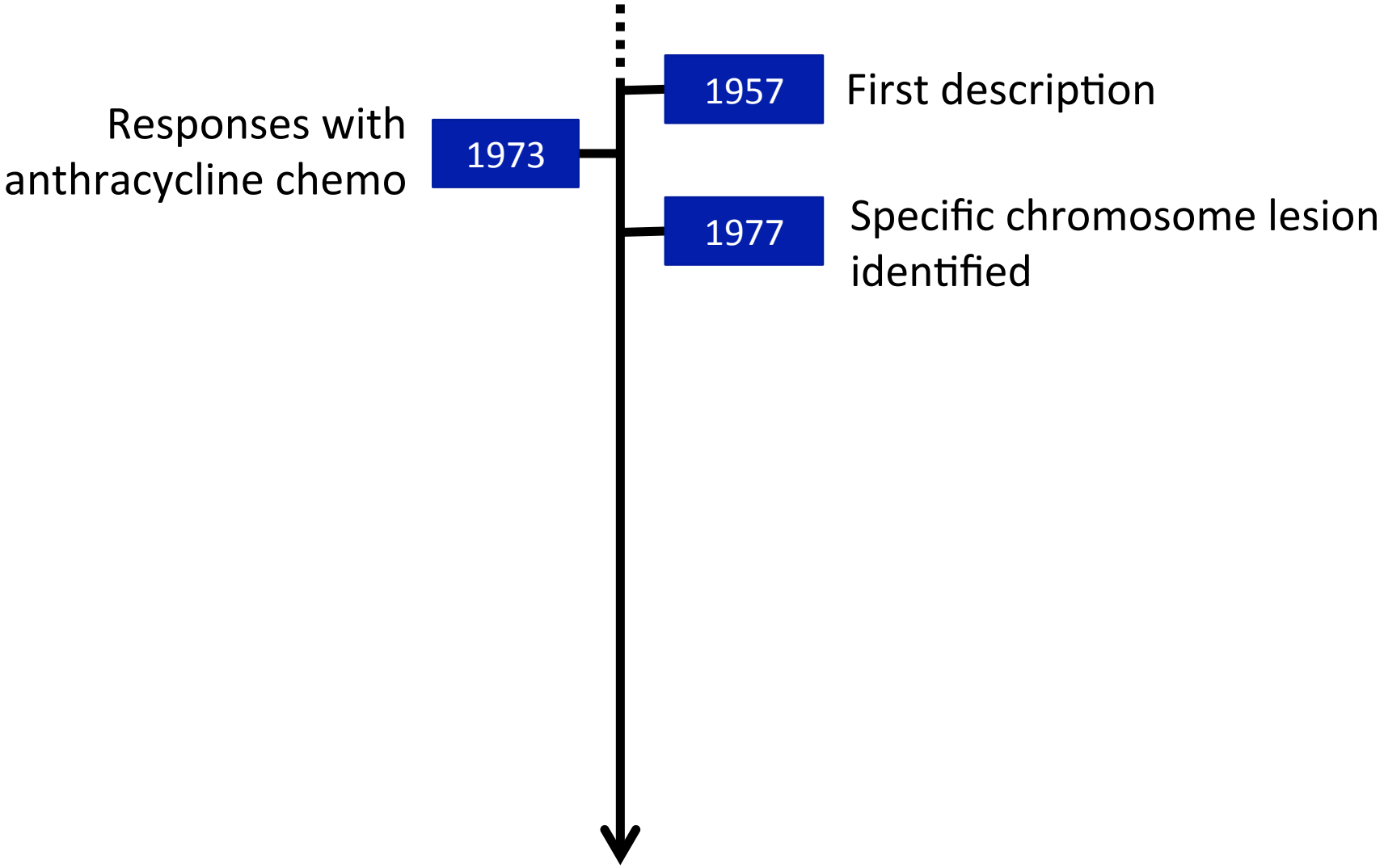
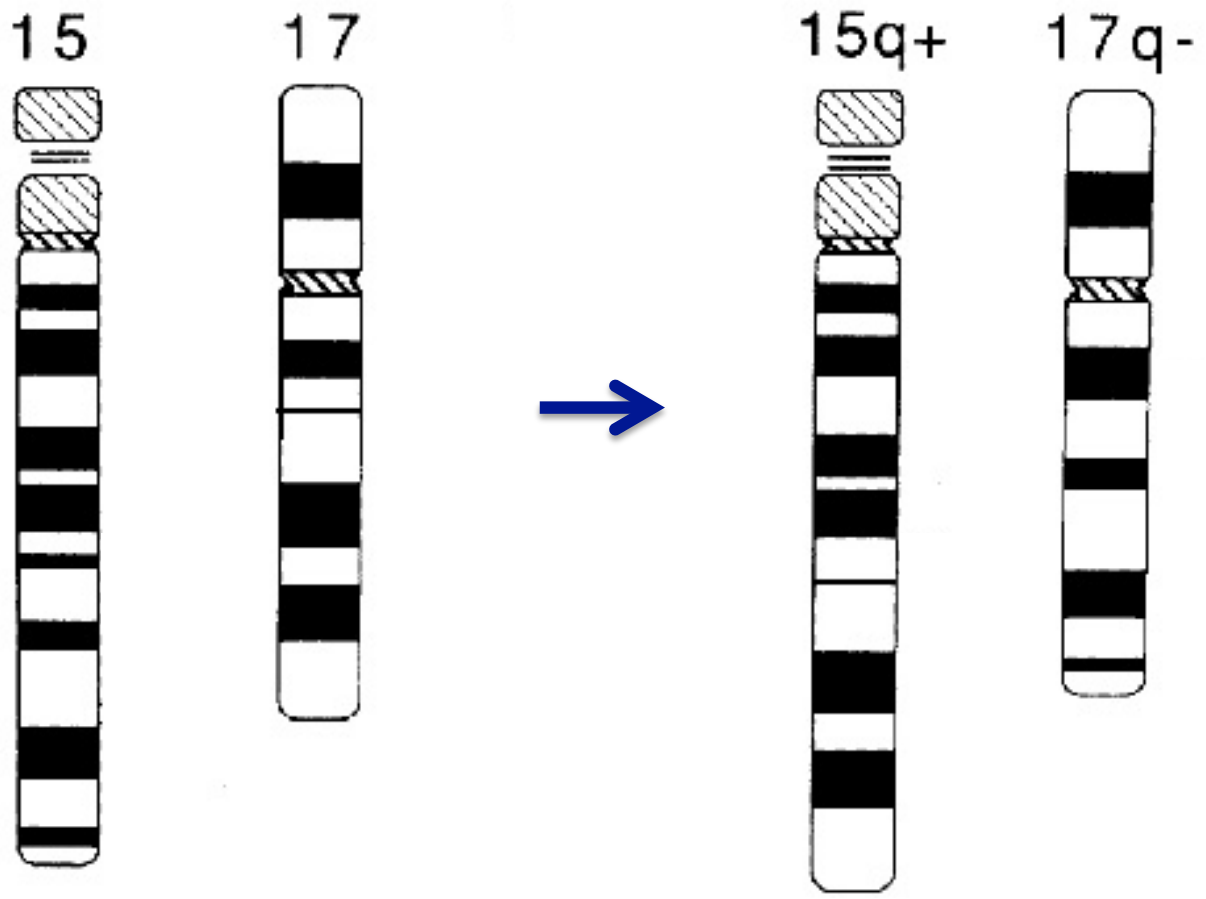


t(15;17) is the Diagnostic Hallmark of AML M3

(J Rowley 1977)



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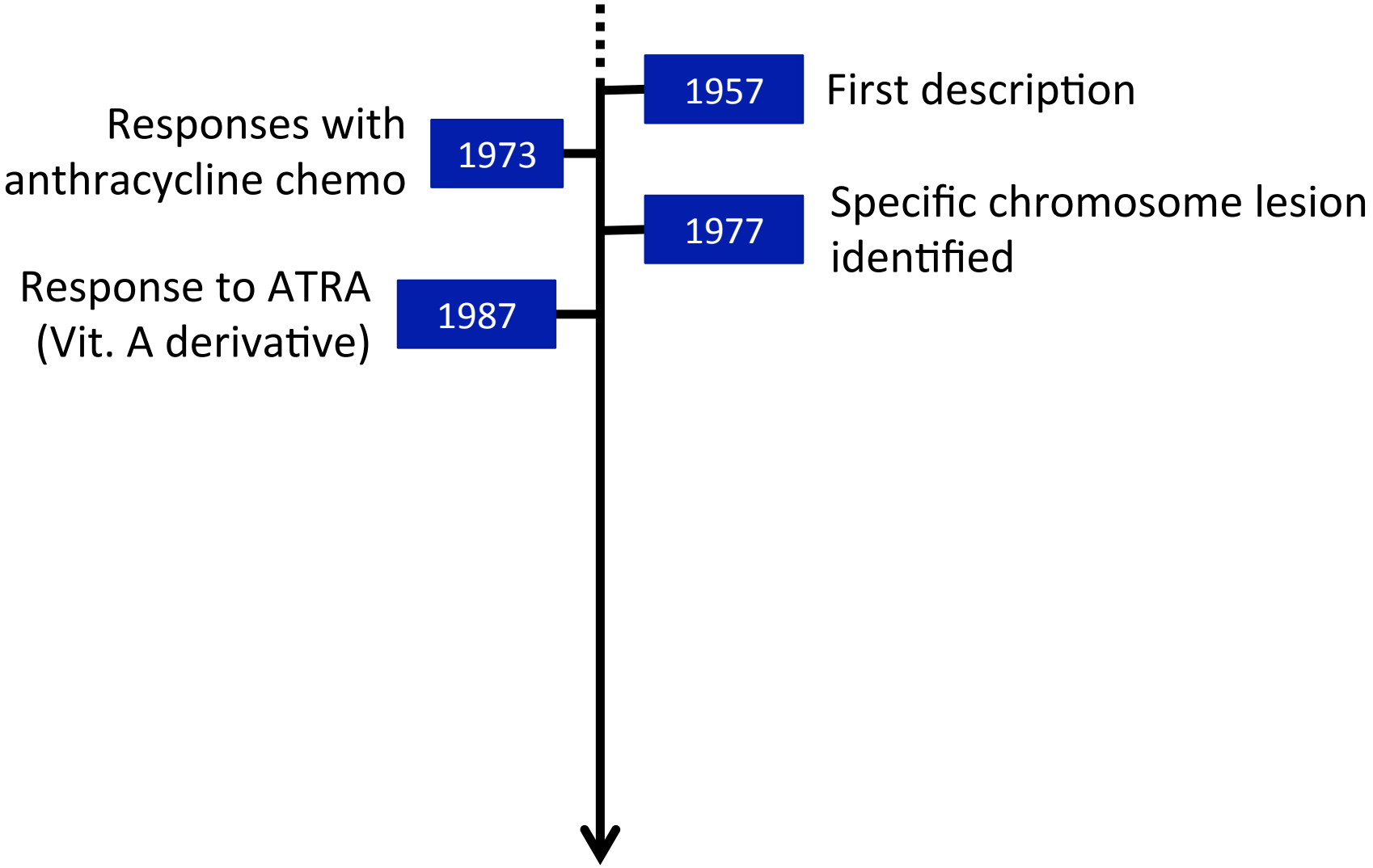


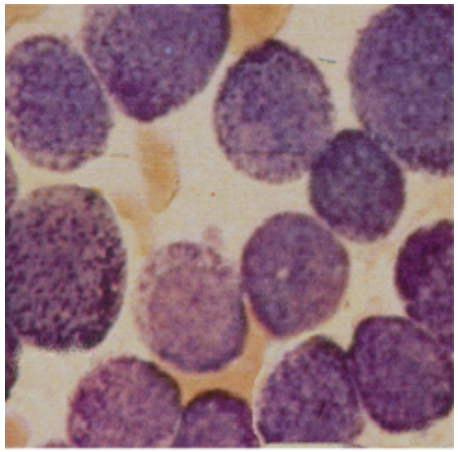
From Confucius to differentiation therapy

"If you use laws to direct the people, and punishments to control them, they will merely try to evade the laws, and will have no sense of shame.

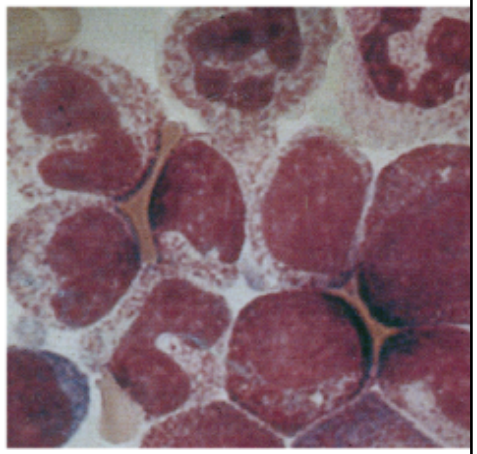
But if by virtue you guide them, and by the rites you control them, there will be a sense of shame and of right."

Confucius 551-479 B.C.

"Malignant cells induced to differentiate with ATRA." **ME Huang, Blood 1988**



Retinoic Acid (ATRA) →



Adapted from Wang ZY & Chen Z, Blood 2008

Acute Promyelocytic Leukemia:

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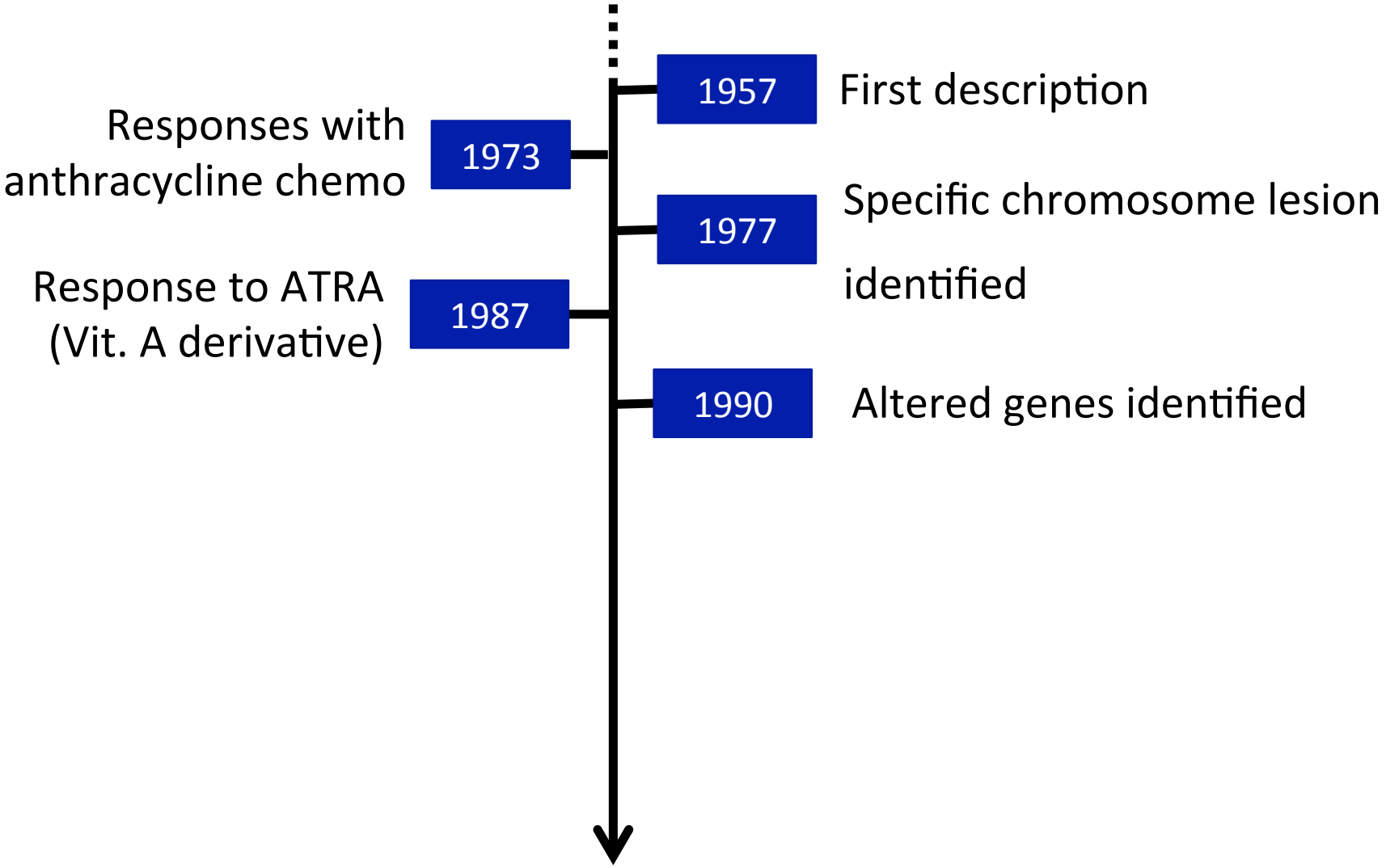

Cloning of the t(15;17)

Rearrangements and Aberrant Expression of the Retinoic Acid Receptor α Gene in Acute Promyelocytic Leukemias

By Letizia Longo,* Pier Paolo Pandolfi,* Andrea Biondi,‡ Alessandro Rambaldi,§ Amedea Mencarelli,* Francesco Lo Coco,‖ Daniela Diverio,‖ Luigi Pegoraro,¶ Giancarlo Avanzi,¶ Antonio Tabilio,* Daniela Zangrilli,** Myriam Alcalay,* Emilio Donti,* Fausto Grignani,* and Pier Giuseppe Pelicci*

*From the *Istituto di Clinica Medica I, University of Perugia, Policlinico Monteluce, 06100 Perugia; the ‡Clinica Pediatrica, University of Milan, Ospedale S. Gerardo, 20052 Monza; the §Divisione di Ematologia, Ospedali Riuniti Bergamo e Istituto Ricerche Farmacologiche "M. Negri", 24100 Bergamo; the ‖Dipartimento di Biopatologia, Divisione di Ematologia, I University of Rome, 00161 Roma; the ¶Istituto di Medicina Interna, University of Turin, Ospedale Maggiore di S. Giovanni, 10126 Torino; and the **Dipartimento di Medicina Interna, Cattedra di Ematologia, II University of Rome, 00100 Roma, Italy*

J. Exp. Med. © The Rockefeller University Press
Volume 172 December 1990 1571–1575

90

The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor α gene to a novel transcribed locus

Hugues de Thé*, Christine Chomienne†, Michel Lanotte‡, Laurent Degos§ & Anne Dejean*

* Unité de Recombinaison et Expression Génétique, INSERM U.163, CNRS URA 271, Institut Pasteur, 28 rue du Docteur Roux, 75724 Paris Cédex 15, France
† Service de médecine nucléaire and INSERM U.204, ‡ INSERM U.301, § Service clinique des maladies du sang and INSERM U.93, Hôpital Saint-Louis, 2 Place du Docteur Alfred Fournier, 75010 Paris, France

Pier Giuseppe Pelicci

Molecular Analysis of Acute Promyelocytic Leukemia Breakpoint Cluster Region on Chromosome 17

JULIAN BORROW, AUDREY D. GODDARD, DENISE SHEER, ELLEN SOLOMON

J. Borrow, A. D. Goddard, E. Solomon, Somatic Cell Genetics Laboratory, Imperial Cancer Research Fund, London WC2A 3PX, United Kingdom.
D. Sheer, Human Cytogenetics Laboratory, Imperial Cancer Research Fund, London WC2A 3PX, United Kingdom.

SCIENCE, VOL. 249

The PML/RARα fusion protein

Why so important in diagnosis and treatment

- Unique to APL (disease hallmark)
- Strongly correlated with pathogenesis
- Targeted by specific therapies
- Detection predicts response to ATRA & ATO
- Ideal marker for residual disease monitoring

Molecular evaluation of residual disease as a predictor of relapse in acute promyelocytic leukaemia

FRANCESCO LO COCO DANIELA DIVERIO
PIER PAOLO PANDOLFI ANDREA BIONDI
VINCENZO ROSSI GIUSEPPE AVVISATI
ALESSANDRO RAMBALDI WILLIAM ARCESE
MARIA C. PETTI GIOVANNA MELONI
FRANCO MANDELLI FAUSTO GRIGNANI
GIUSEPPE MASERA TIZIANO BARBUI
PIER GIUSEPPE PELICCI

Fig 1—Three different breakpoints of the PML gene in APL.

The three types of chimeric junctions due to variability of PML breakpoints (bcr1 - bcr2 - bcr3) are illustrated.

Acute Promyelocytic Leukemia:

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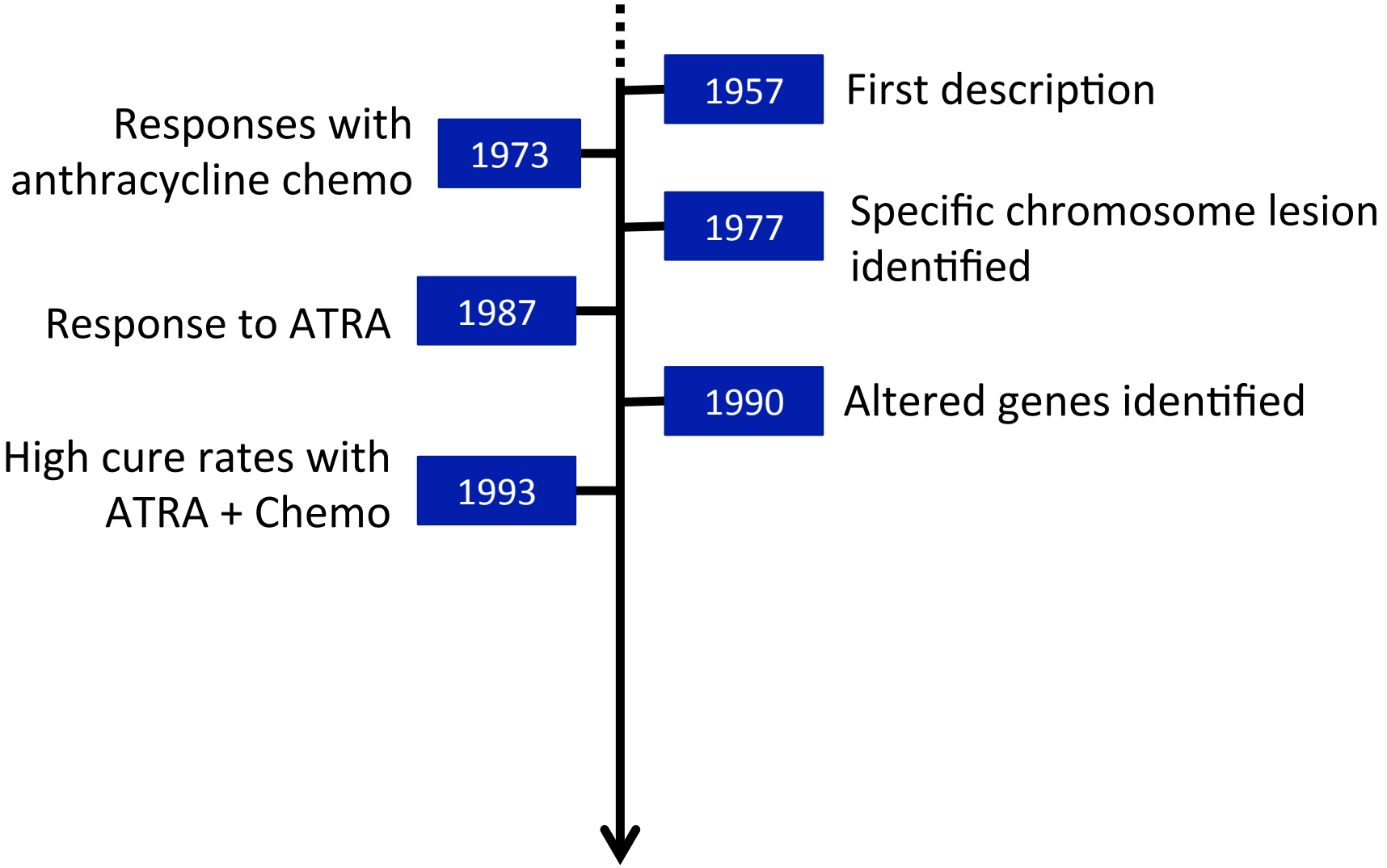


blood

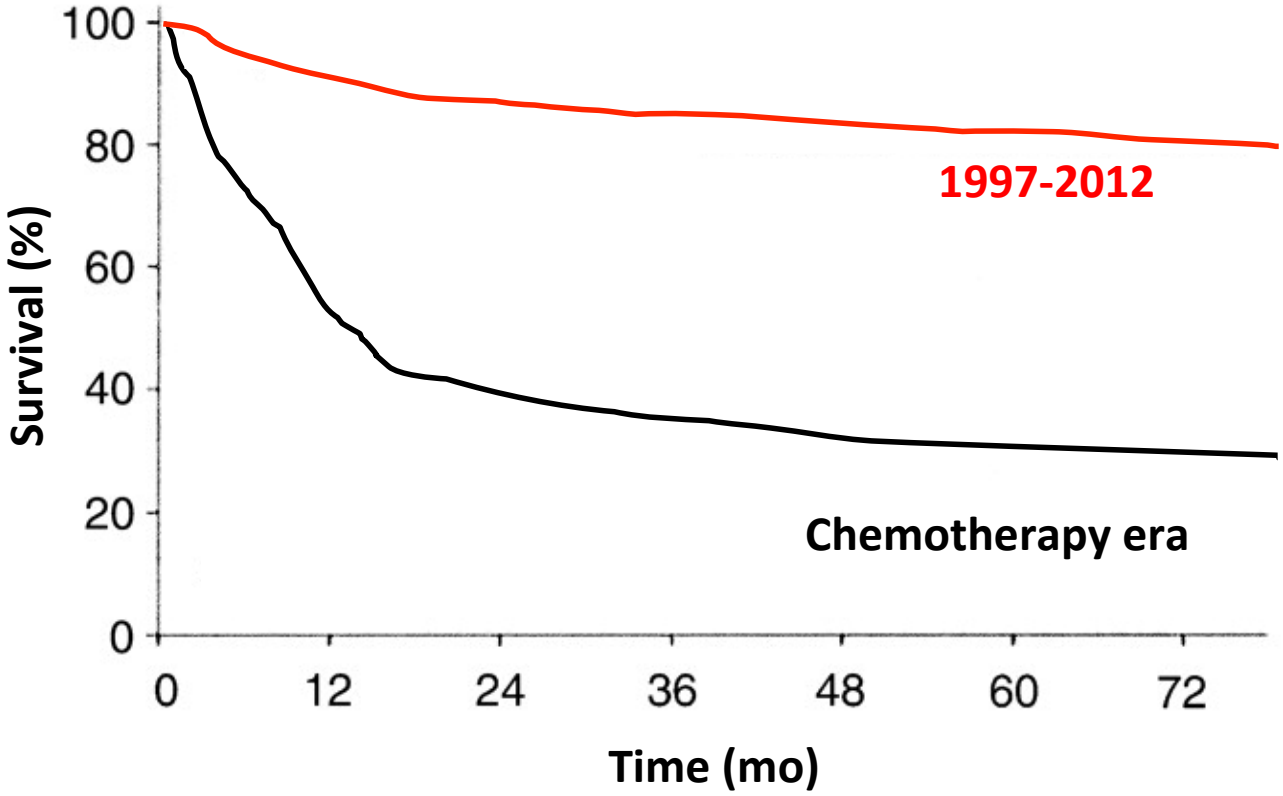
1996 88: 1390-1398

AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study

G Avvisati, F Lo Coco, D Diverio, M Falda, F Ferrara, M Lazzarino, D Russo, MC Petti and F Mandelli

G. Avvisati

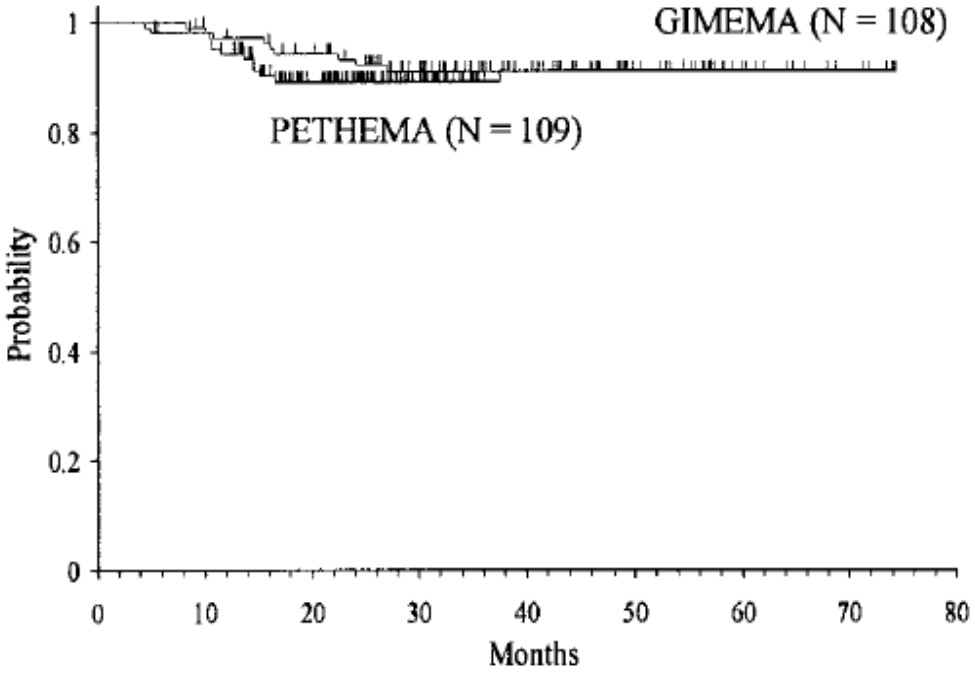
Reported outcomes for APL pre- and after ATRA



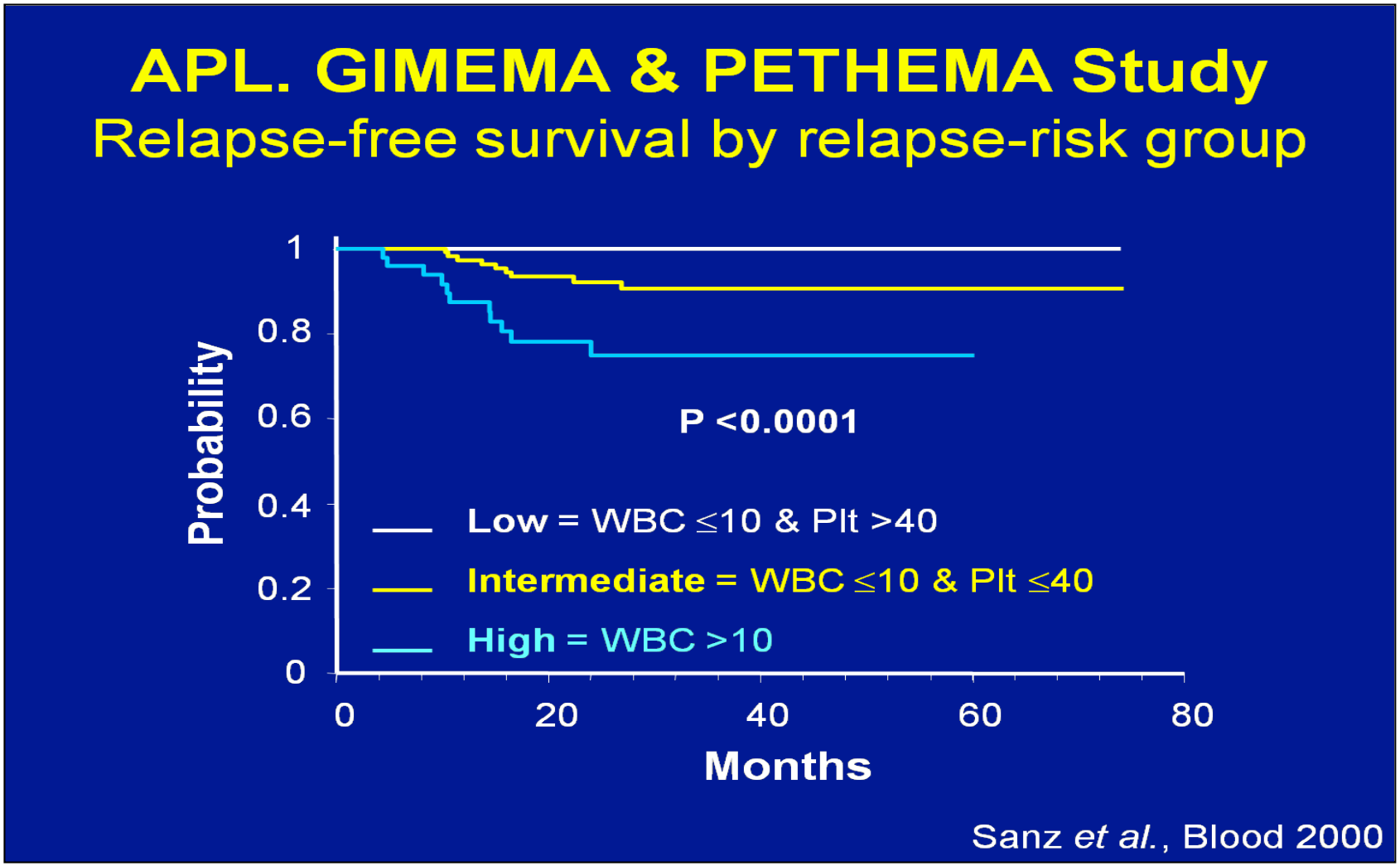
Fenaux et al, 1993; Mandelli et al, 1997; Sanz et al, 1999; Burnett et al, 1998;Tallman et al 2002, Asou et al, 2007; Lengfelder et al 2009, Iland et al, 2012

AIDA protocol is exported (and refined)

Miguel A Sanz



Definition of Relapse Risk Groups



Problems with ATRA and Chemotherapy

- Induction death
- Death in remission
- Toxicity of consolidation therapy
- Therapy-related MDS/AML (t-MN)

Acute Promyelocytic Leukemia:

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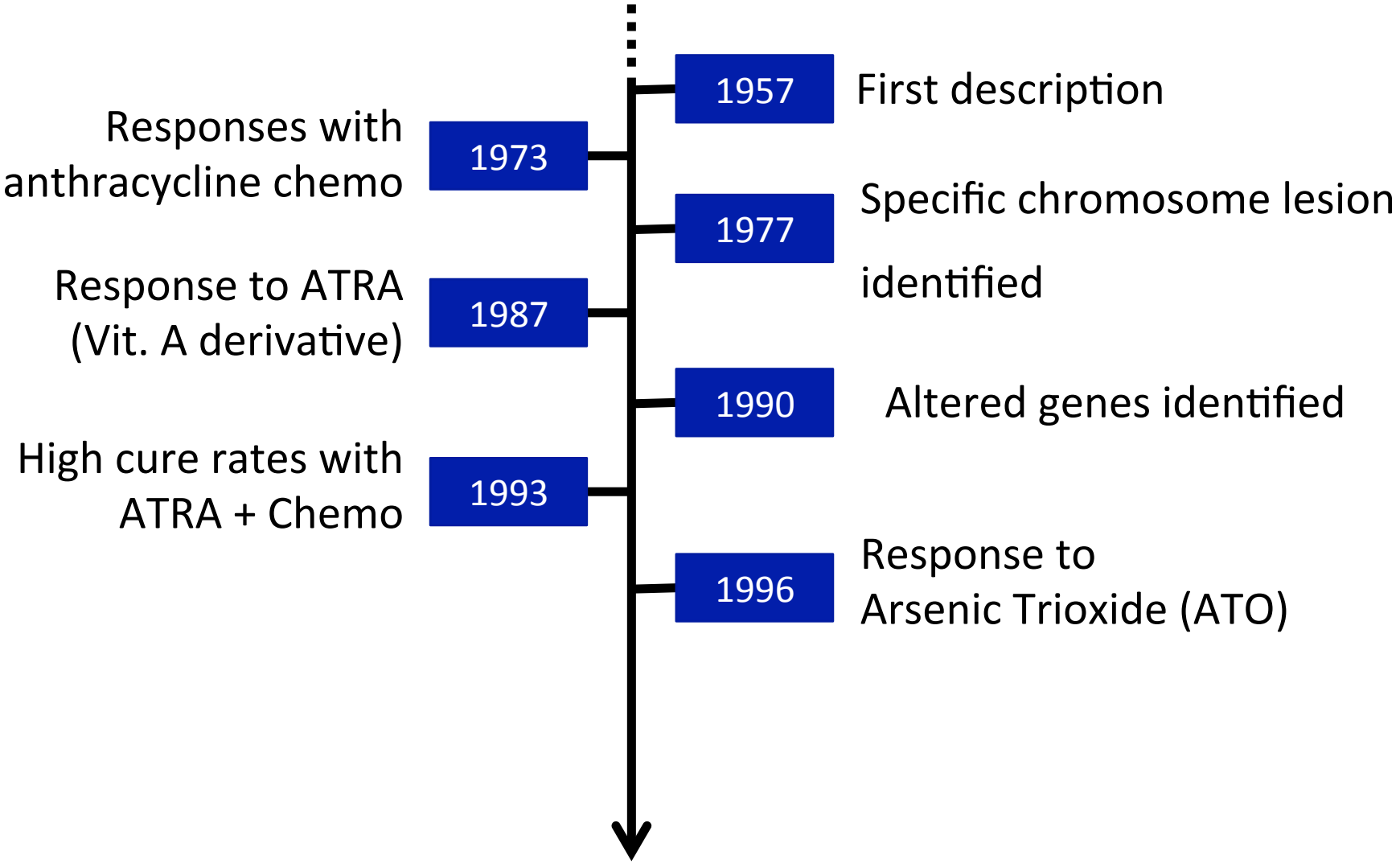

blood

2006 107: 2627-2632
Prepublished online December 13, 2005;
doi:10.1182/blood-2005-08-3532

Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: durable remissions with minimal toxicity

Vikram Mathews, Biju George, Kavitha M. Lakshmi, Auro Viswabandya, Ashish Bajel, Poonkuzhali Balasubramanian, Ramachandran Velayudhan Shaji, Vivi M. Srivastava, Alok Srivastava and Mammen Chandy

Acute Promyelocytic Leukemia:

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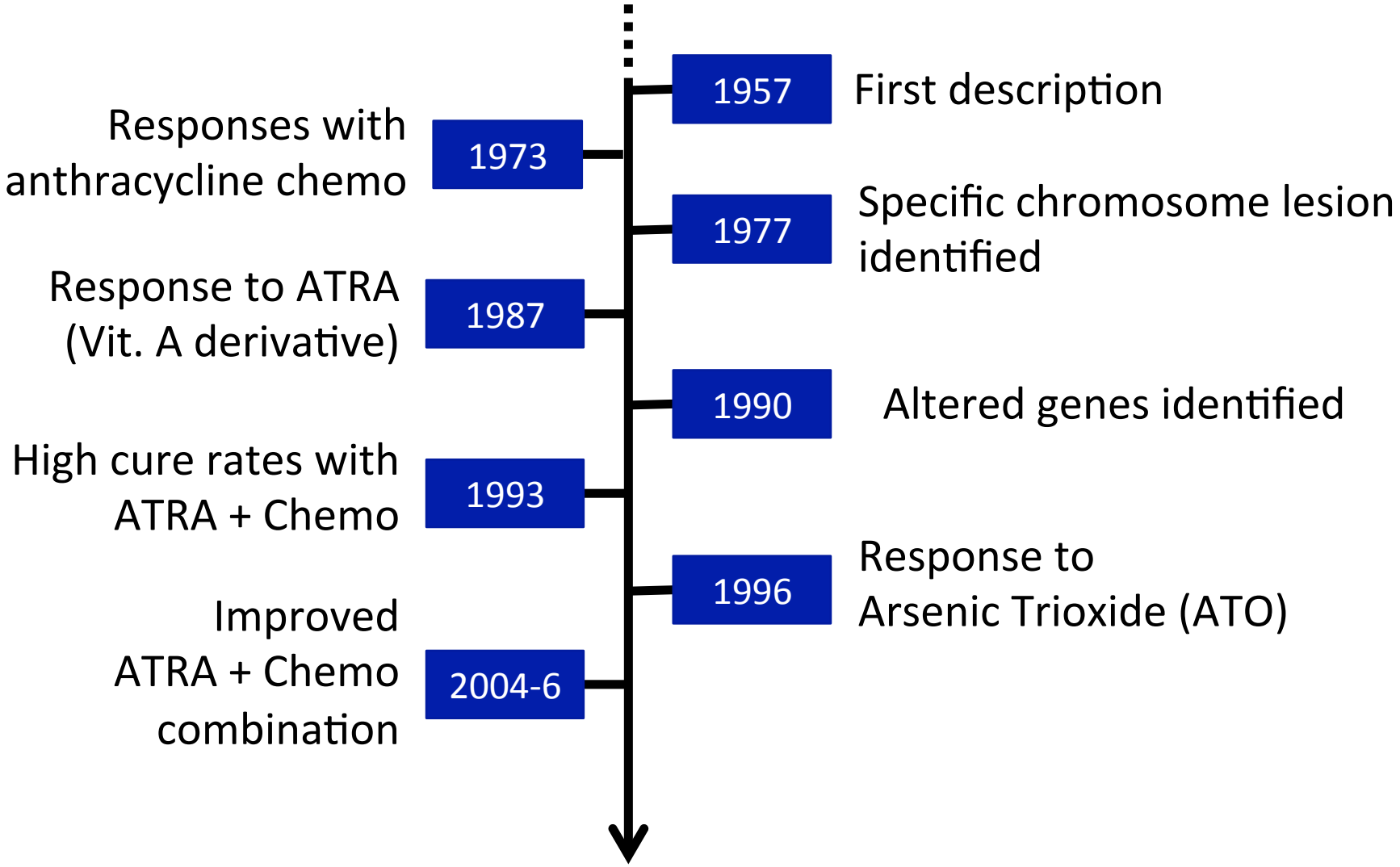
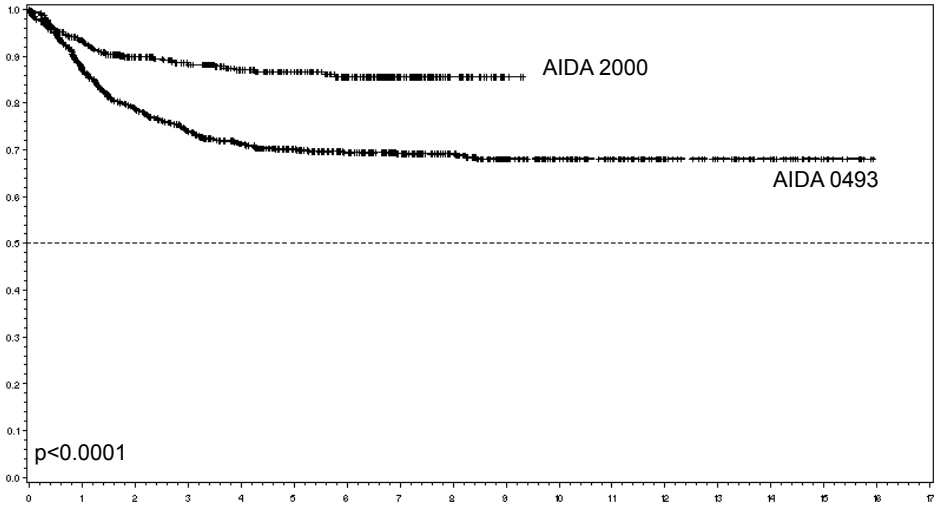
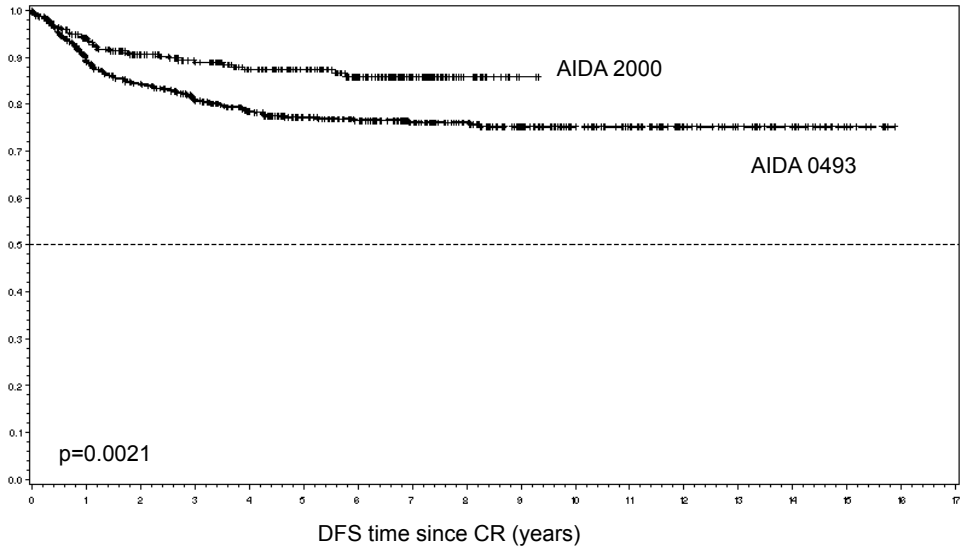


AIDA 2000 Vs AIDA 0493 (historical)

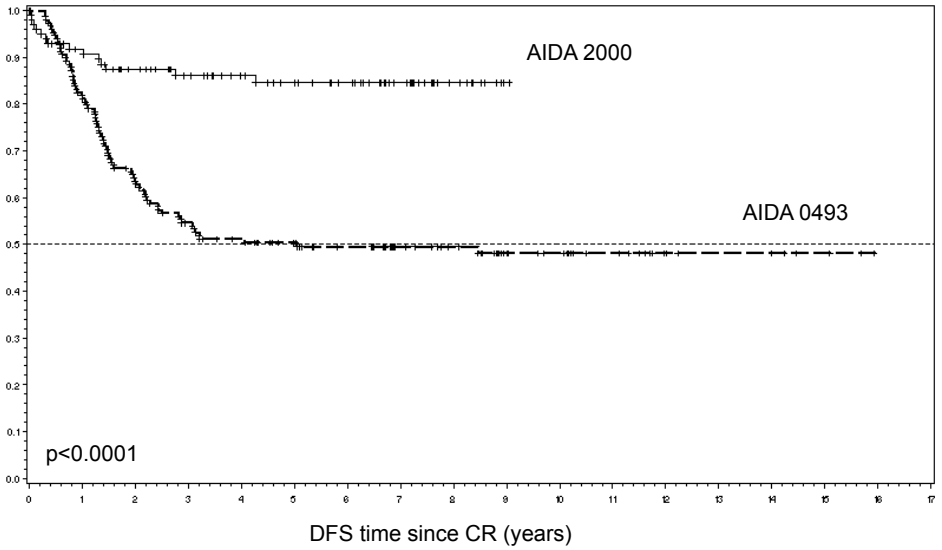
A: all patients



B: Low/Intermediate

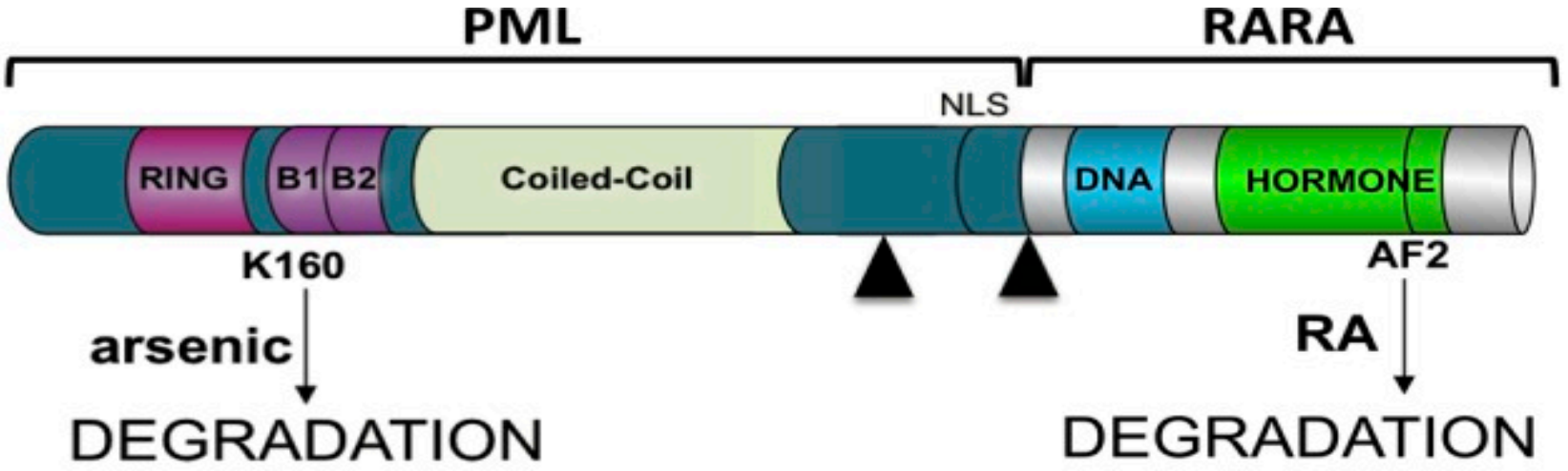


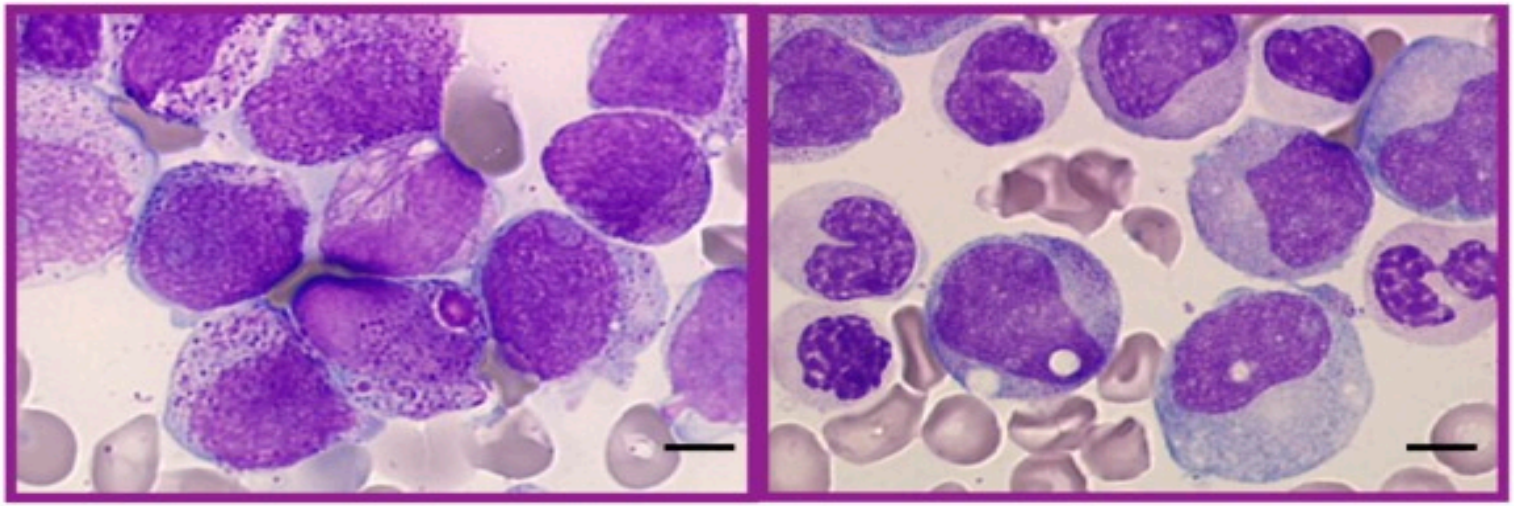
C: High



Lo-Coco *et al*, Blood 2010

PML/RARα: functional domains





Untreated Differentiation by RA

de Thé *et al.* J Cell Biol 2012

blood

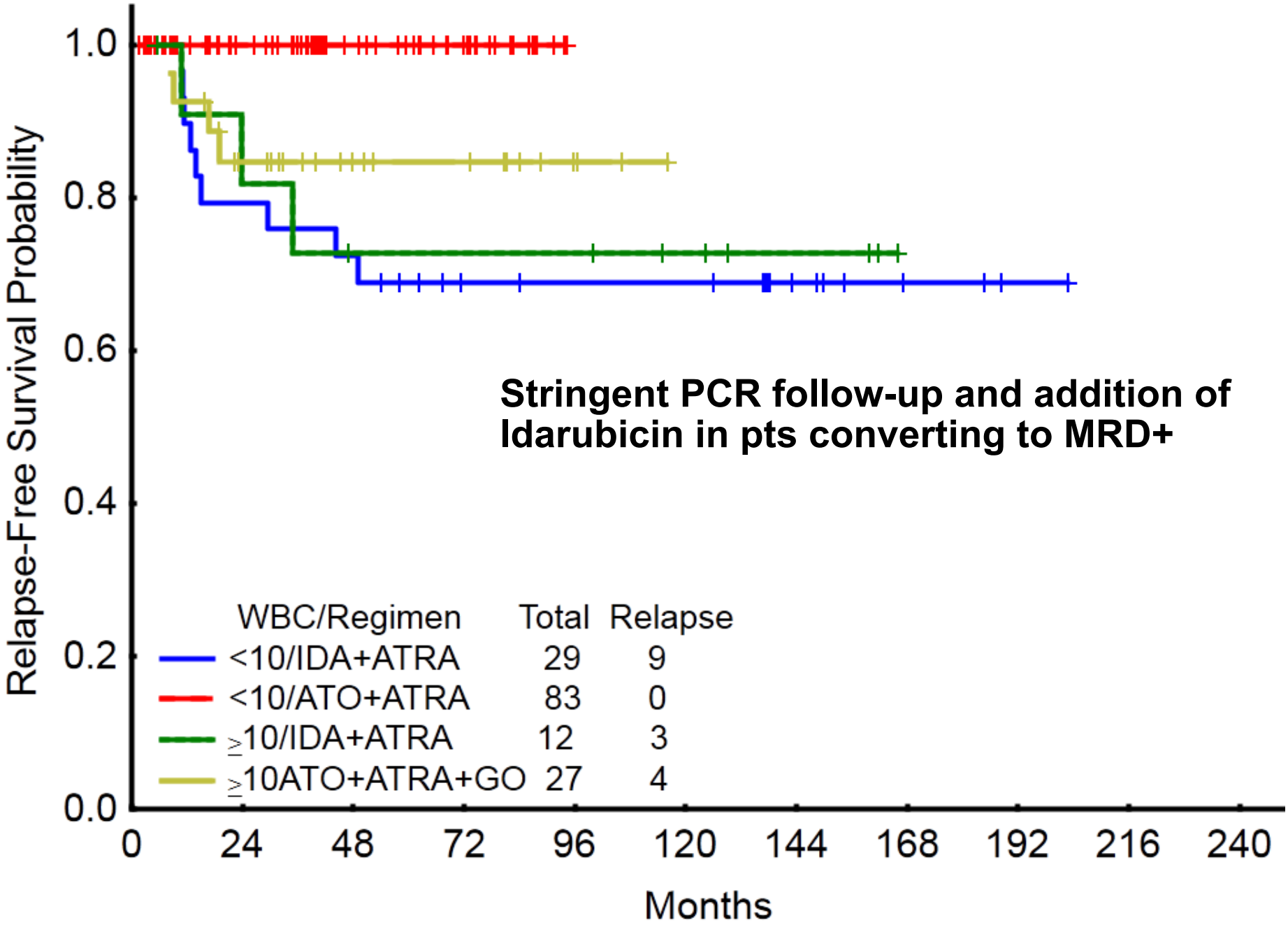
2006 107: 3469-3473
Prepublished online December 22, 2005;
doi:10.1182/blood-2005-10-4006

Use of all-*trans* retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia

Elihu Estey, Guillermo Garcia-Manero, Alessandra Ferrajoli, Stefan Faderl, Srdan Verstovsek, Dan Jones and Hagop Kantarjian

Elihu Estey

Experience with Arsenic in APL (Estey et al.)



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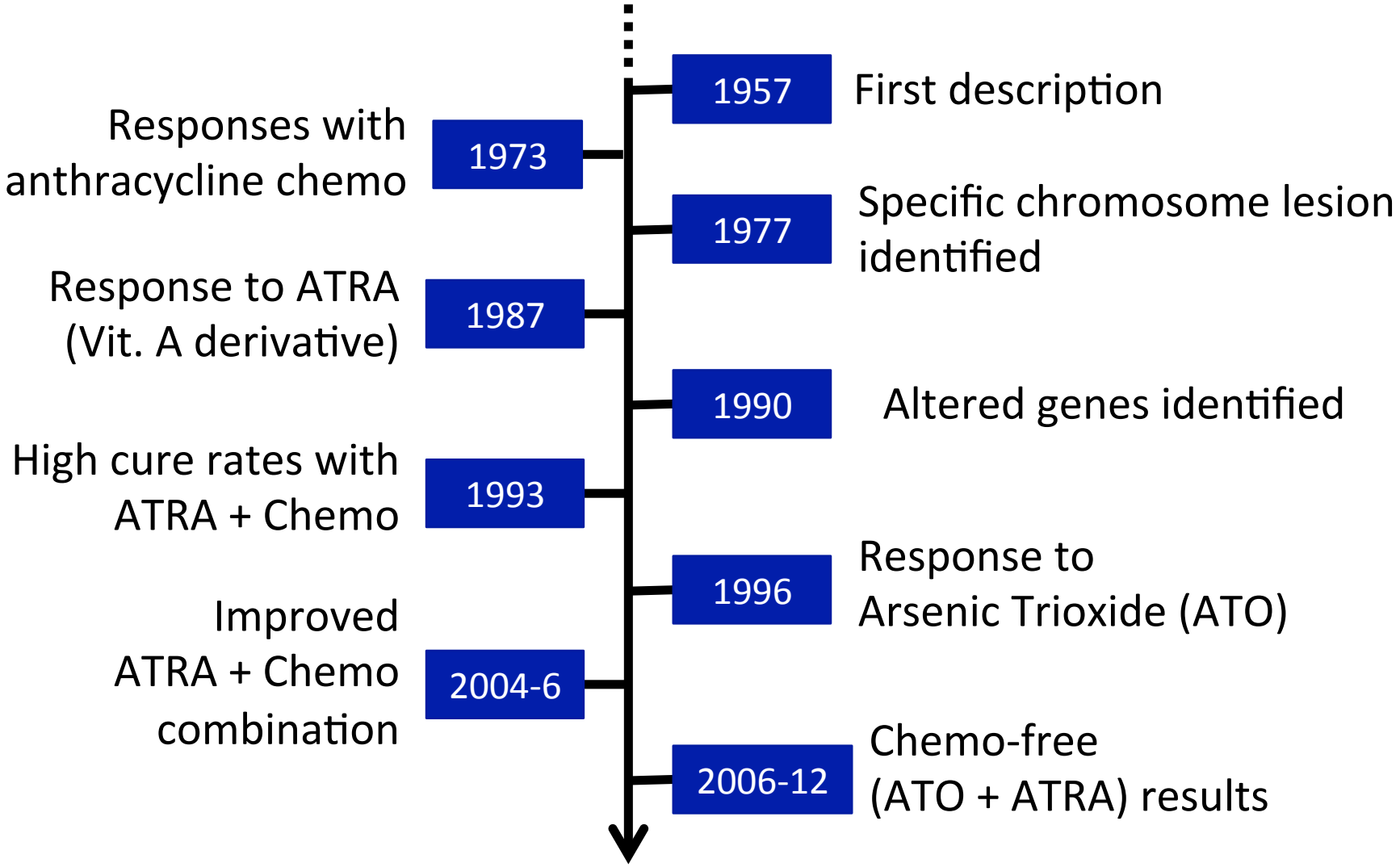


Terapia della Leucemia Acuta Promielocitica

Stato dell'arte nel 2006

Acido Retinoico + Arsenico

?

Acido Retinoico + Chemioterapia

- Terapia "mirata"
- Alta efficacia
- Ridotta tossicità
- % guarigioni ?

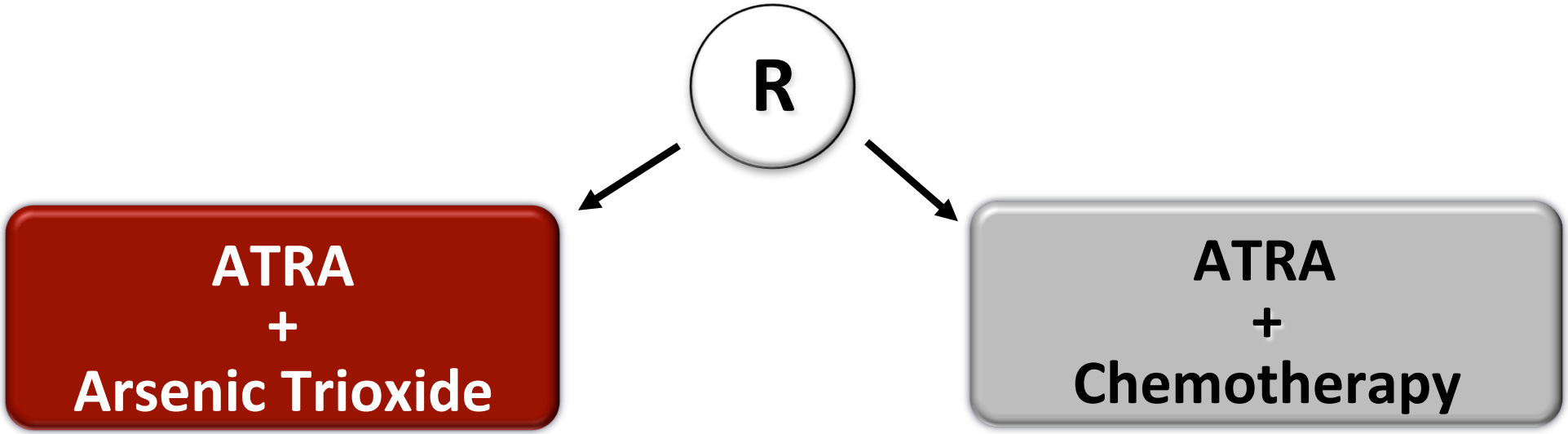
- Terapia non specifica
- Tossicità importante
- 80% guarigioni

APL 0406 Italian-German

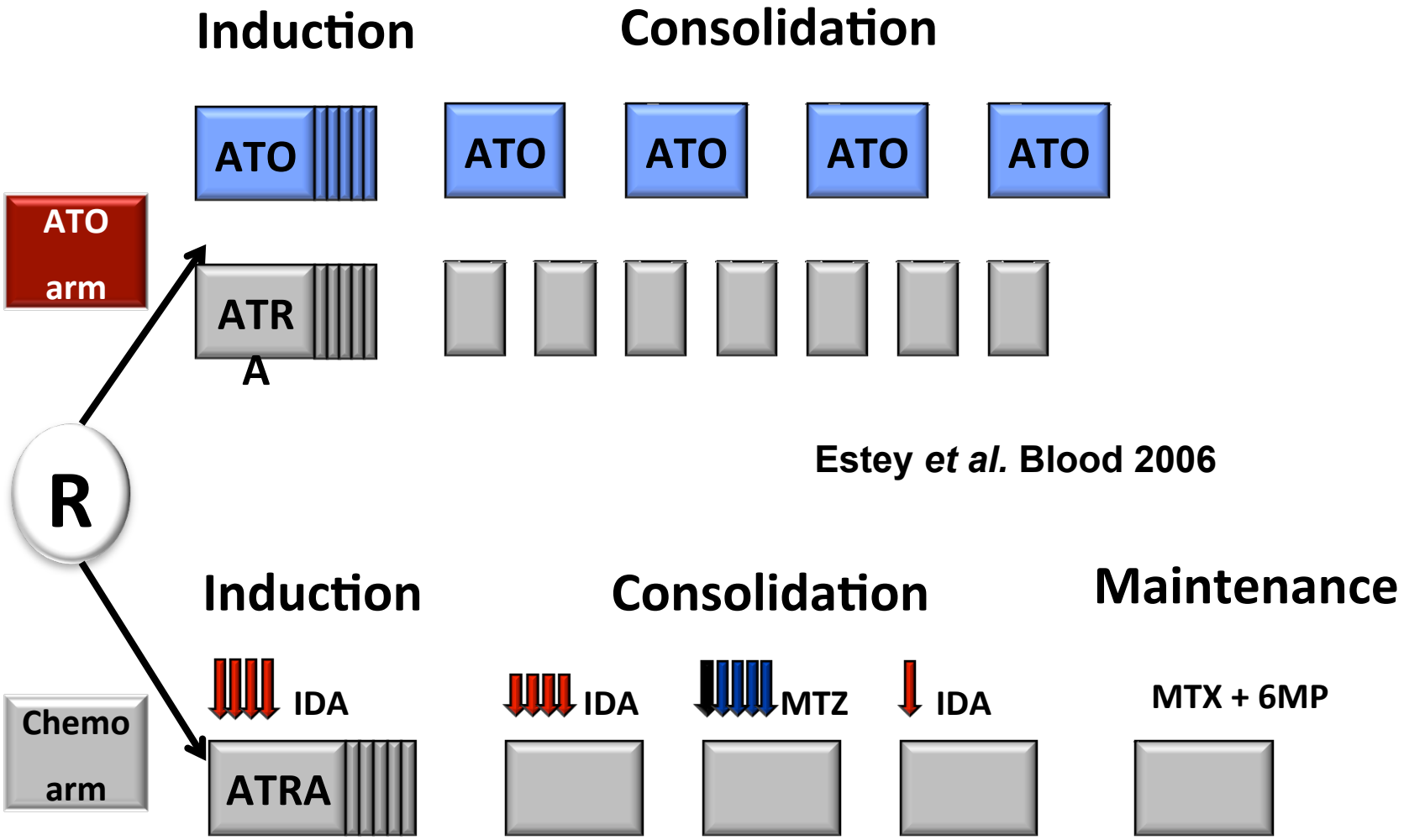
Phase III Study

Acute Promyelocytic Leukemia

Low-intermediate risk

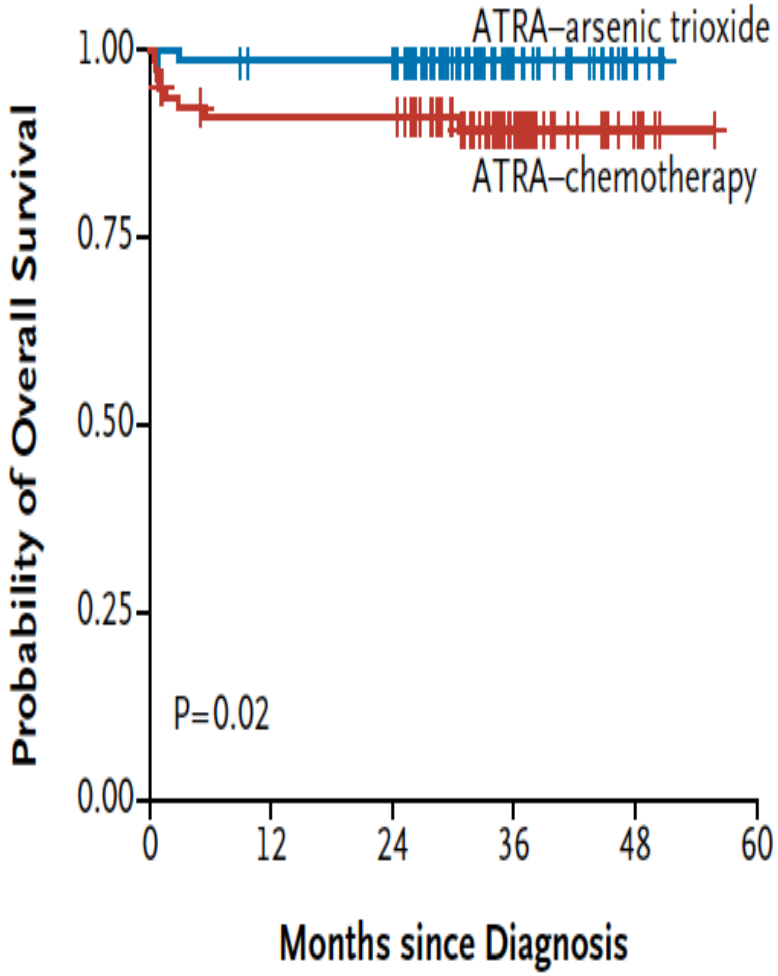


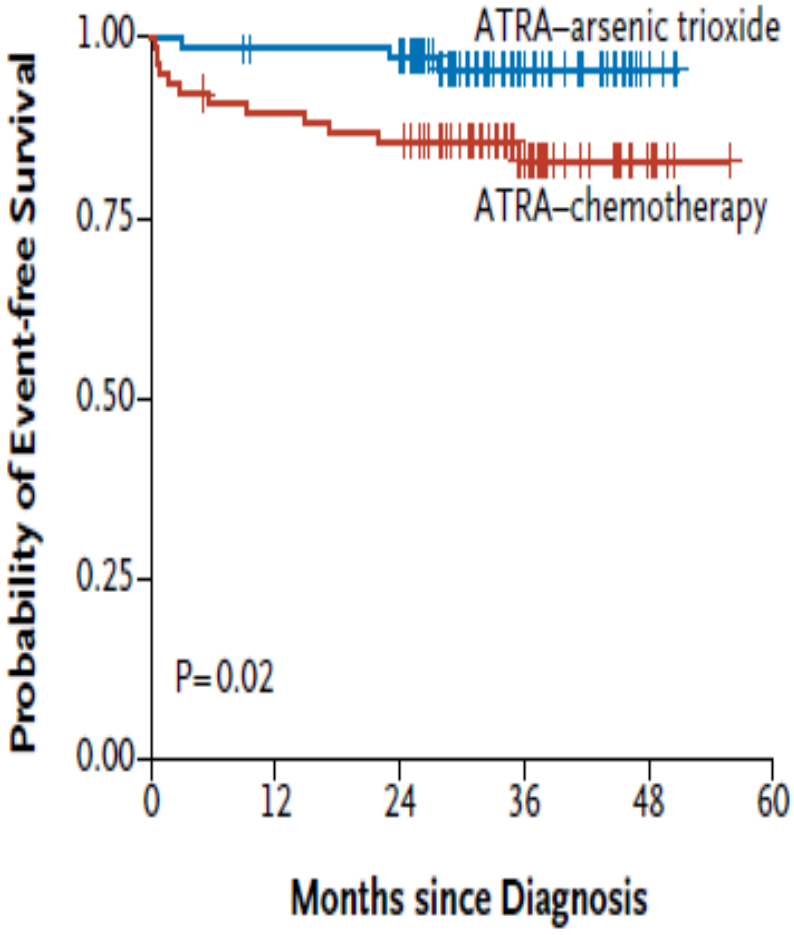
APL-0406 Study in non-high risk
(GIMEMA-AMLSG-SAL)



APL0406 trial original series

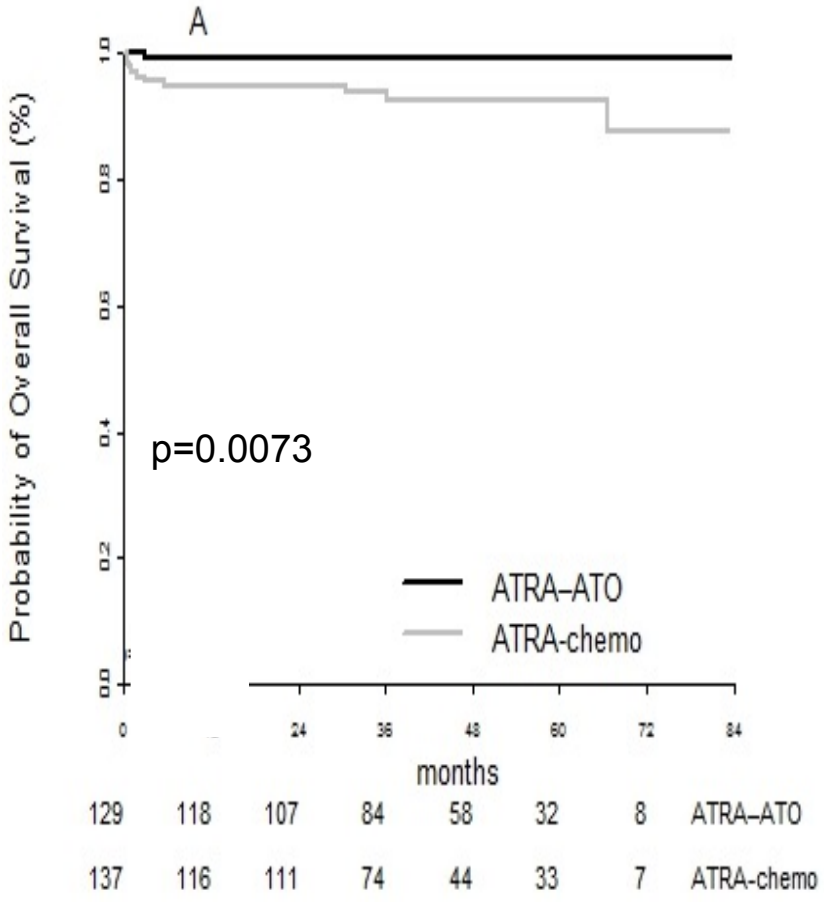
Median follow-up 34 m.

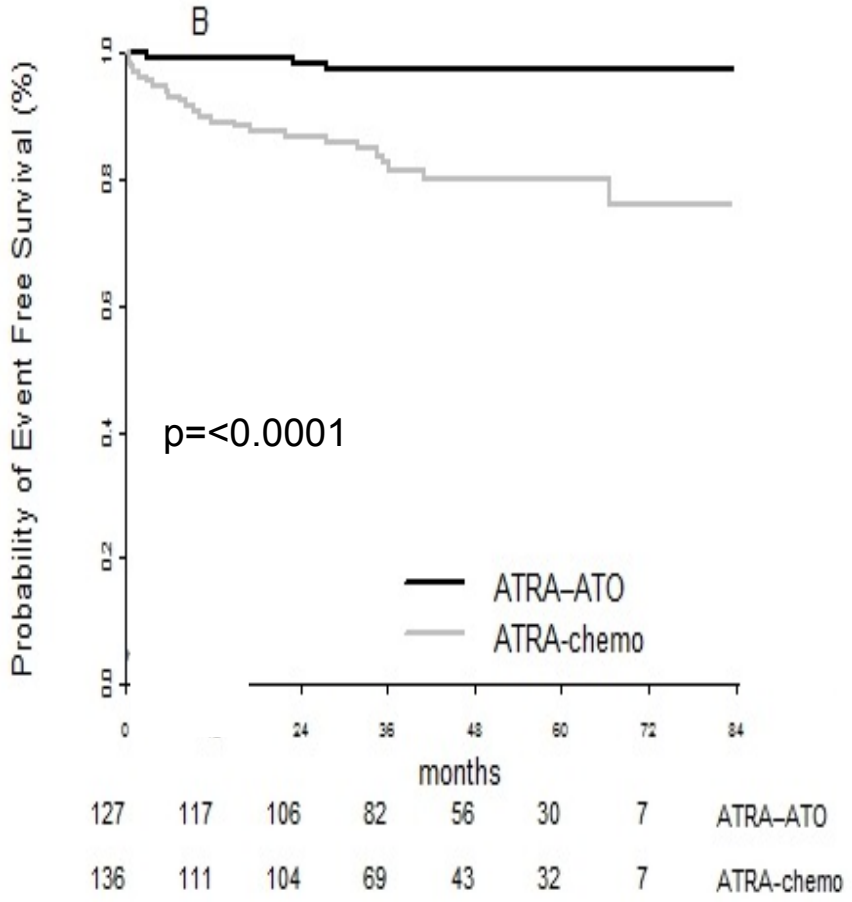




Lo-Coco et al. NEJM 2013

APL 0406: Updated Follow-up (41.9 mos)





Platzbecker et al., J Clin Oncol 2016

November 2016

EU Commission grants extension of indication to first line use of Trisenox® in combination with retinoic acid

November 2016

EU Commission grants extension of indication to first line use of Trisenox® in combination with retinoic acid

*Decision solely based on **published academic data** endorsing the benefit of Trisenox® as first chemotherapy-free treatment for APL and marks important advancement for patients in Europe*

Lessons learned from APL

1) Cancer is **not** an **irreversible condition** (malignant cells can transformed rather than killed)

2) **Targeted therapy** may eradicate leukemia stem cells

3) Acute leukemia is **curable without chemotherapy**

A few key features of the APL saga must be stressed:

- Hallmark findings made by chance more than design
- Progress relied primarily on the academic world
- Basic science accompanied clinical explorations providing a spectacular illustration of the power of translational research
- International cooperation was the key to success

H de Thé, Blood 2013

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G. Avvisati

F. Mandelli

L.Franceschini

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D. Grimwade

A.K. Burnett

(NCRI, UK)

M.A. Sanz

(Valencia, Spain)

H. Döhner

A. Ganser

K. Döhner

R. Schlenk


7th INTERNATIONAL SYMPOSIUM ON
ACUTE PROMYELOCYTIC LEUKEMIA
Save the date !
Rome, September 24- 27, 2017
Chairmen: F. Lo-Coco, M.A. Sanz