2021

Progetto Ematologia Romagna

La leucemia acuta promielocitica

Come è cambiata la terapia

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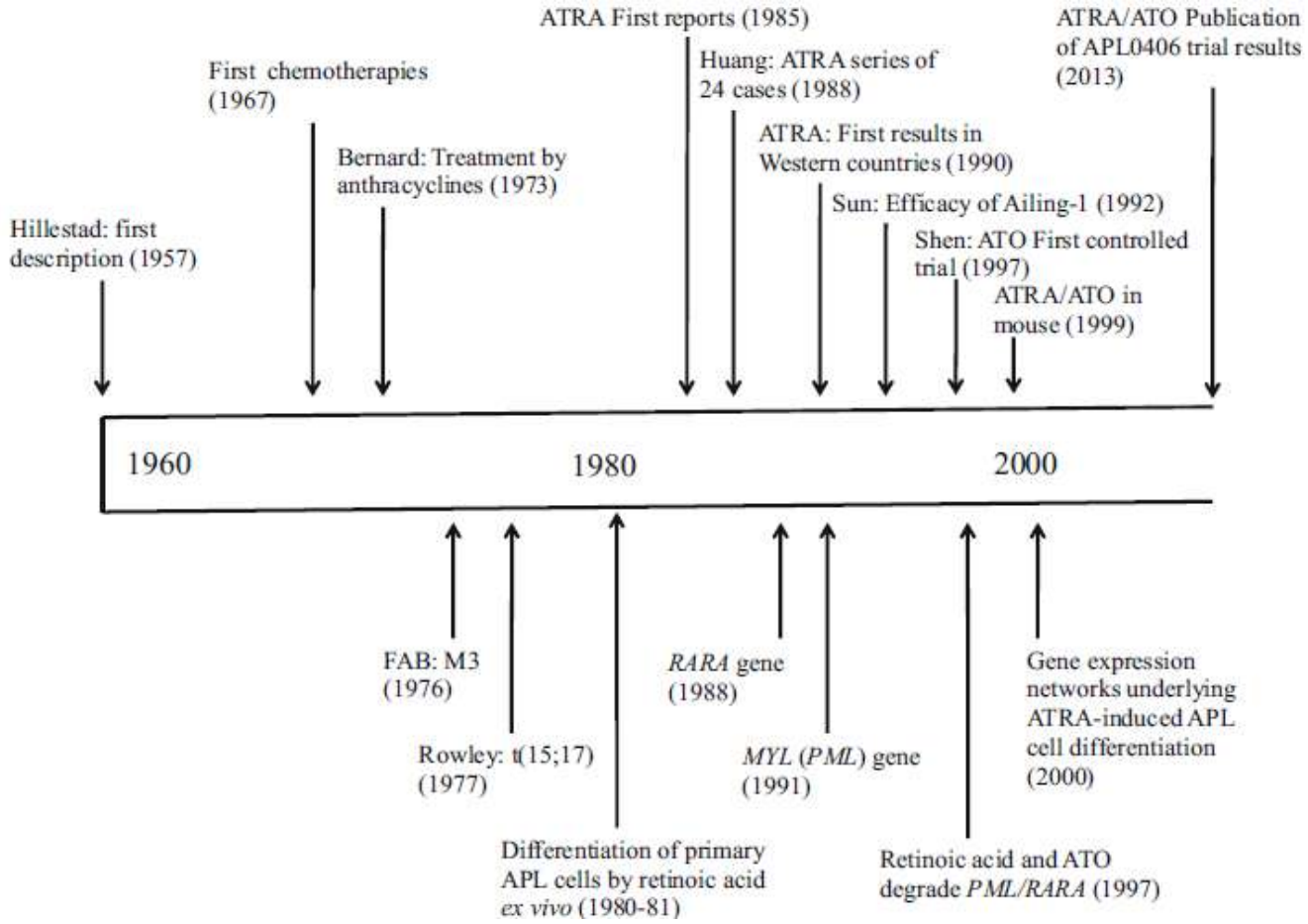
Disclosures

Nothing to disclosure

APL history over 60 years: highlights



Thomas X Oncol Ther (2019):7:33-65

APL first clinical description: 1957

Acute Promyelocytic Leukemia.

By

LEIF K. HILLESTAD.

(Submitted for publication August 13, 1957.)

Summary.

Evidence is presented for the existence of a special type of acute myelogenous leukemia. Three cases are described, characterized by 1) a very rapid fatal course of only a few weeks' duration, 2) a white blood cell picture dominated by promyelocytes, 3) a severe bleeding tendency due to fibrinolysis and thrombocytopenia, 4) a normal ESR, probably caused by the reduced fibrinogen concentration in the plasma.

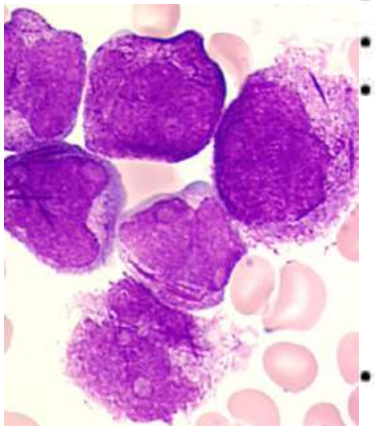
It is suggested that this type is named acute promyelocytic leukemia. It seems to be the most malignant form of acute leukemia.

Mortality > 90%

Hillestad L.K. (1957) Acta Medica Scandinavica, 159, 189–194

APL first morphological classification: FAB

1976



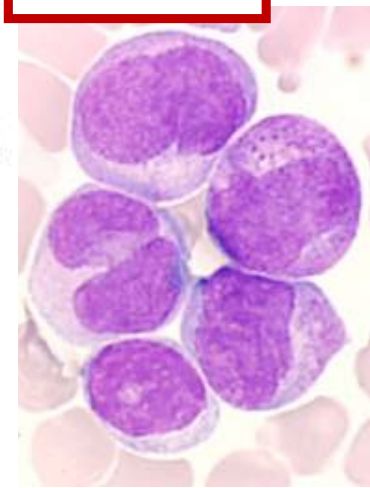
Hypergranular or typical APL (M3)

- 60% to 70% of cases.
- Low white blood cell count.
- Abnormal promyelocytes with numerous red to purple cytoplasmic granules that are typically darker and larger than normal neutrophil granules.
- Identifiable faggot/matchstick cells with numerous Auer rods.

Hypogranular or microgranular APL (M3v)

- Leukocytosis.
- Numerous abnormal promyelocytes readily identified on a peripheral blood smear.
- Irregular nucleus and granulations sparser and finer compared with the hypergranular form.
- Faggot cells with multiple Auer rods less commonly seen.

1980



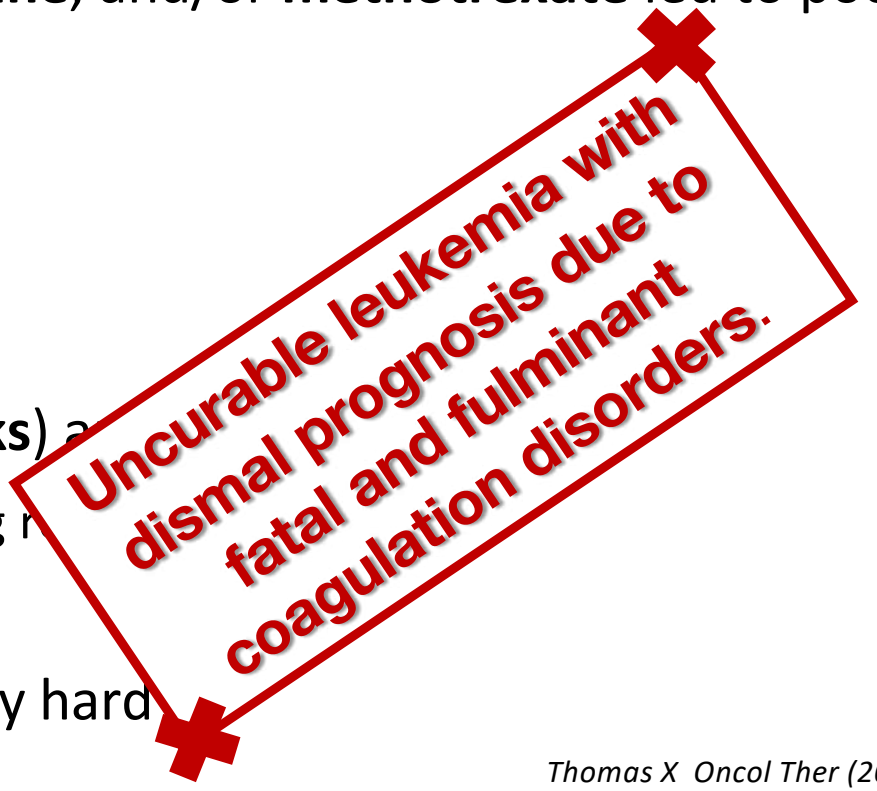
1982

Very rare third variant with high nucleus/cytoplasm ratio and strongly basophilic cytoplasm with sparse or no granules

Thomas X Oncol Ther (2019):7:33-65

APL first therapeutic attempts

- Early studies with **6-mercaptopurine** (6-MP) alone or in combination with **steroids**, **methyl-glyoxalguanylhydrazine**, and/or **methotrexate** led to poor results
- CR rates **5-14**%
- Survival 3–16 weeks (median **3.5 weeks**) a
  - 4 months to more than 6 years among r
- Management of bleeding diathesis very hard



Thomas X Oncol Ther (2019):7:33-65

APL : sensitivity to daunorubicin

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

Daunorubicin induces complete remissions in about 50% of patients with acute promyelocytic leukemia. The median duration of these remission is 26 mo. Failures are mainly due to hemorrhages as a result of disseminated intravascular coagulation during the first 5 days (25%) or due to sepsis during the second and third week (25%). Long-term survivals are more frequent than in the other acute granulocytic leukemias.

- First report about **unique sensitivity** of APL to anthracyclines (DNR).
- Impressive morphologic response as a **single agent** for treating APL far better than in any other subtype of myeloid leukemia.
- Among 33 patients treated **55% CR**

Thomas X Oncol Ther (2019):7:33-65

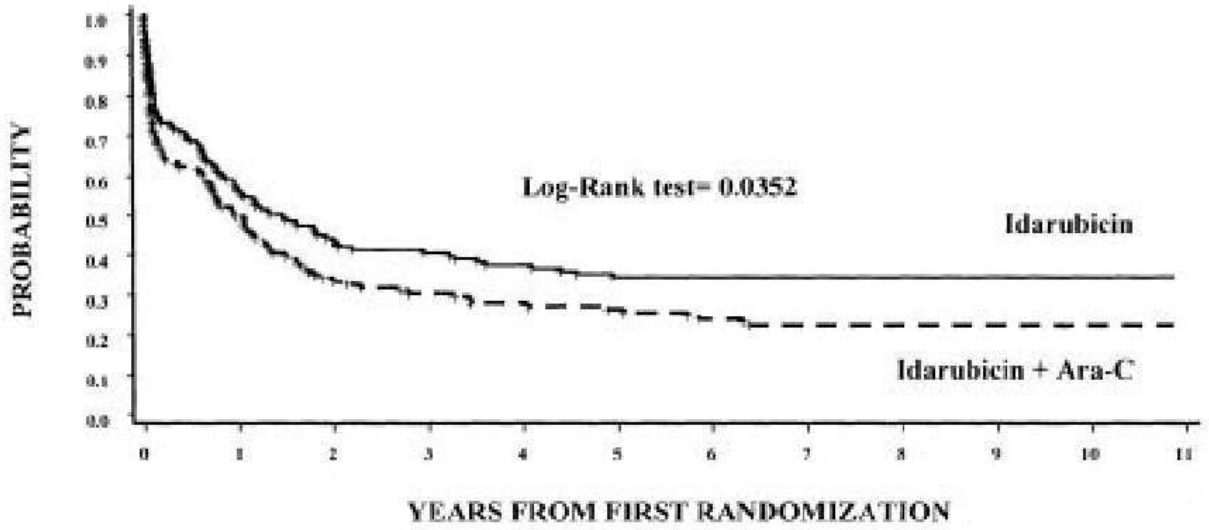
APL therapy: pre-ATRA era 1973-1988

- Beneficial effect of DNR initiated by Bernard et al confirmed by several clinical trial
- **High dose DNR** in induction and consolidation better but **cardiotoxicity**
- 1973: “7+3” efficacy of cytarabine on AML
- **Anthracycline** and **cytosine arabinoside** became the **frontline treatment for APL**
  - **CR** rates until **80%** **NOT different** from anthracycline **alone**
  - **Worsening** of **hemorrhagic diathesis** by chemotherapy during the **first days** of treatment, with high early death rate
  - intensive supportive care based on platelet and fibrinogen support
- **Maintenance** with **6-MP** and **MTX** could result in **longer remissions** than short consolidation

Kennet D H et al . Blood 1995;86(5):1717-1728; Thomas X Oncol Ther (2019):7:33-65

APL therapy: pre-ATRA era 1973-1988

- **GIMEMA LAP0389**: induction randomization IDA alone *vs* IDA/AraC
  - 257 patients enrolled
  - No difference in CR rate (76.3% vs 66.6%) and induction death (15.3% vs 21.4%)
  - 7 years EFS: **35**% vs **23**%

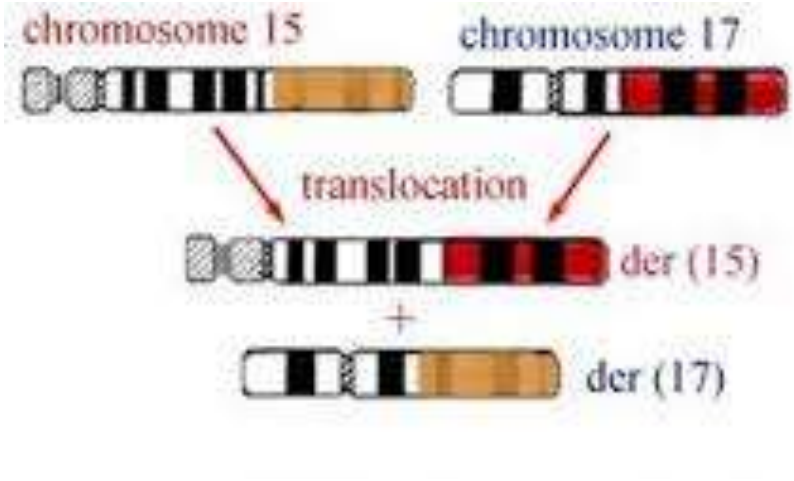


Avvisati et al. Blood 2002 Nov 1;100(9):3141-6

Chromosomal translocation discovery

1977

“ 15;17 TRANSLOCATION, A CONSISTENT CHROMOSOMAL CHANGE IN ACUTE PROMYELOCYTIC LEUKAEMIA”



J.D. Rowley (1977) The Lancet, 309;8010: 549–550

APL therapy: pre-ATRA era 1973-1988

- APL state of art by 1988
  - Clinical features: hemorragic diatesis; hyperfibrinolysis and hypofibrinogenemia;
  - Unique morphology: hypergranular blast and variant
  - Specific cytogenetic: t(15;17)
- Treatment based on anthracyclines, maintenance [illegible] ATX and platelet transfusions:
  - **CR rate** around **75%**
  - **Early mortality** rate **15%**
  - **Resistance** rate **10%**
  - 2-years relapse **5%**
  - **25% of patients long survival** (late relapses rare in [illegible] AML)

Fulminant leukemia potentially curable with chemotherapy

APL therapy: ATRA era 1988-1993

- 1978 Sachs argues with a dogma: **leukemic cells can differentiate** under various agents
  - More than 100 agents were identified (retinoic acid, dimethyl sulphoxide, low dose cytarabine)
- 1981 Breitman shows terminal differentiation in HL-60 cell line and fresh cell of APL patients with retinoic acid:
  - Differentiating effect specific to APL cells
  - Different ability to induce differentiation in retinoid derivatives:
    - Etretinate not effective
    - ATRA (13-*trans* isomer of RA) 10 times more effective than 13-*cis* retinoid
    - Etretinate only RA derivative available in Europe, 13-*cis* RA only RA available in USA, **ATRA** manufactured in **Shaghai**

Degos L et al . BJH, 2003;122:539–553; BreitmanT R et al. Blood 1981;57:1000-1008; Chomienne C et al. Blood 1990;76:1710-1717.

APL therapy: ATRA era 1988-1993

- 1985 at Rui jin Hospital in Shanghai **first patient** treated with **ATRA**:
  - 5-years old girl refractory to anthracycline-base chemo received ATRA 45 mg/m2/day with CR **3 weeks later**
- 1988 Huang reports successful ATRA treatment in **24 APL patients** (16 newly diagnosed and 8 refractory)
  - 23/24 responsive (CR 96%)

- **Pattern** of **ATRA response**:
  - Terminal differentiation of leukemic cells (Auer rods in mature granulocytes)
  - No coagulopathy exacerbation, no aplasia, no alopecia, few infections
  - High CR rate (> 90%) but relapse within 3-6 months IF ATRA alone

Degos L et al . BJH, 2003;122:539–553; Huang M E et al. Blood 1988;72:567-72

APL therapy: ATRA era 1988-1993

BLOOD

The Journal of
The American Society of Hematology

VOL 76, NO 9 **NOVEMBER 1, 1990**

EDITORIAL

Acute Promyelocytic Leukemia: Another Pseudoleukemia?

IN 1875, William Pepper described the bone marrow of a fatal case of pernicious anemia as pseudoleukemia.[1] In the first part of this century, Minot and Murphy[2] abolished anemia in a series of 45 pernicious anemia patients with daily ingestions of beef liver for months. Ultimately, vitamin B_{12} was demonstrated to be the missing maturation and differentiation inducer,[3] and continuous treatment with that agent uniformly cures the manifestations of the disease, but not the disease itself.

Another pseudoleukemia could be on the way out.

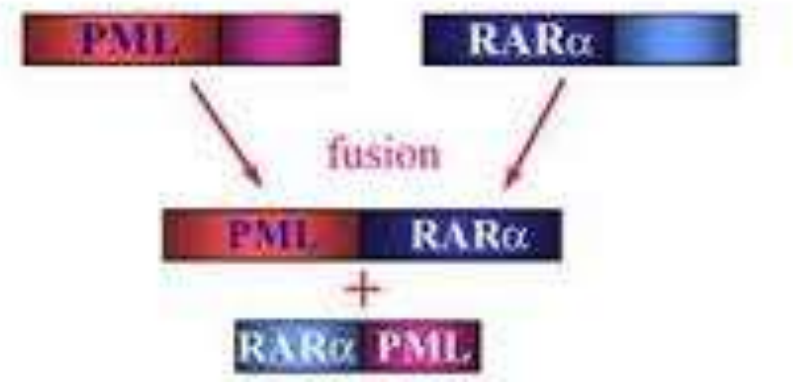
PETER H. WIERNIK
Albert Einstein Cancer Center
Bronx, NY

1990: Molecular gene fusion discovery

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*

J Exp Med. Dec 1, 1990; 172(6): 1571–1575.



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

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

Nature. 347, 558-561 (11 October 1990)

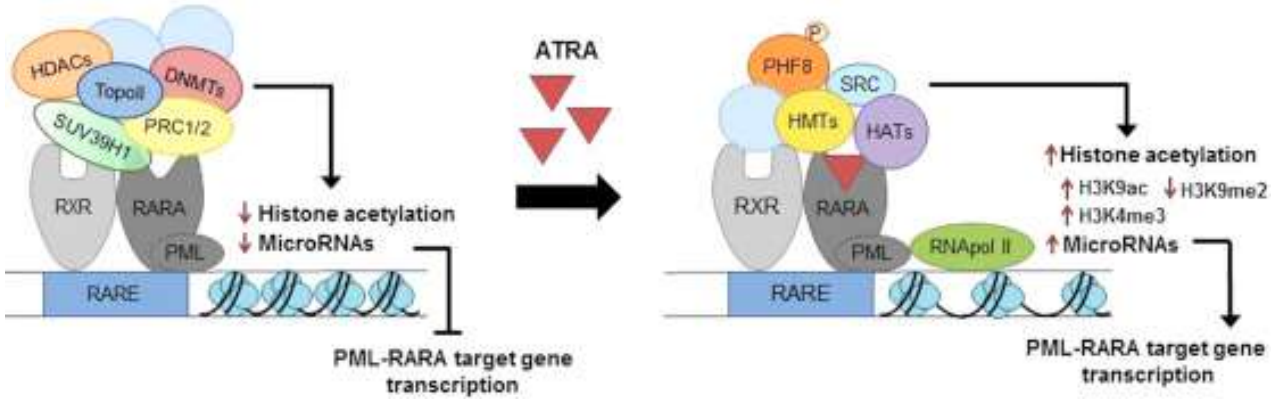
Molecular analysis of acute promyelocytic leukemia breakpoint cluster region on chromosome 17.

J Borrow, AD Goddard, D Sheer, E Solomon

Science. 28 Sep 1990: 249 (4976):1577-15801111111

APL therapy: ATRA mechanism of action

- *PML/RARA* is crucial for the pathogenesis of APL
- PML/RARA homodimes **repress** transcriptional expression of **target genes** essential for granulocytic differentiation **binding to RAREs** in the regulatory region of these genes and recruiting corepressor (CoR) as HDAC and **recruiting** methylating enzymes
- **Genetic defect ⇨ epigenetic alteration**

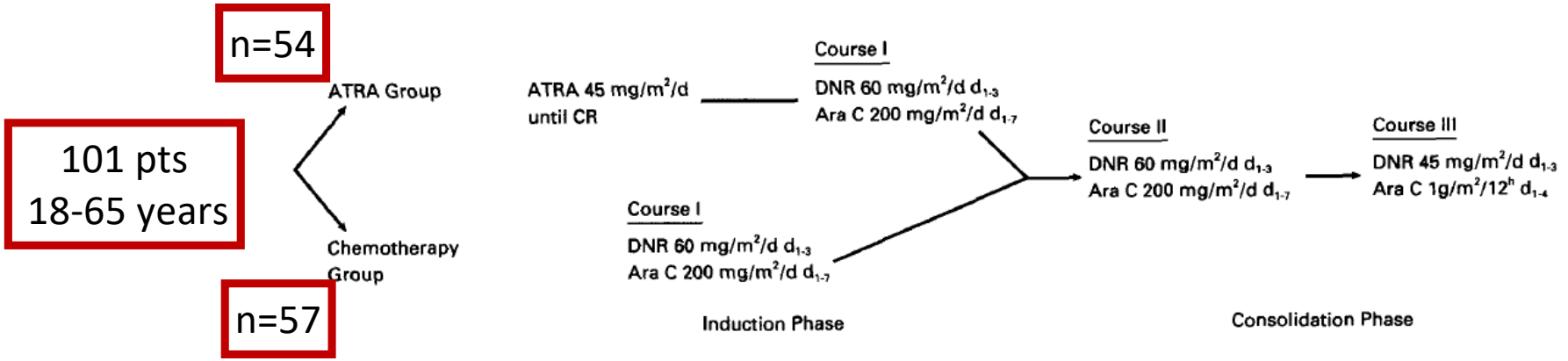


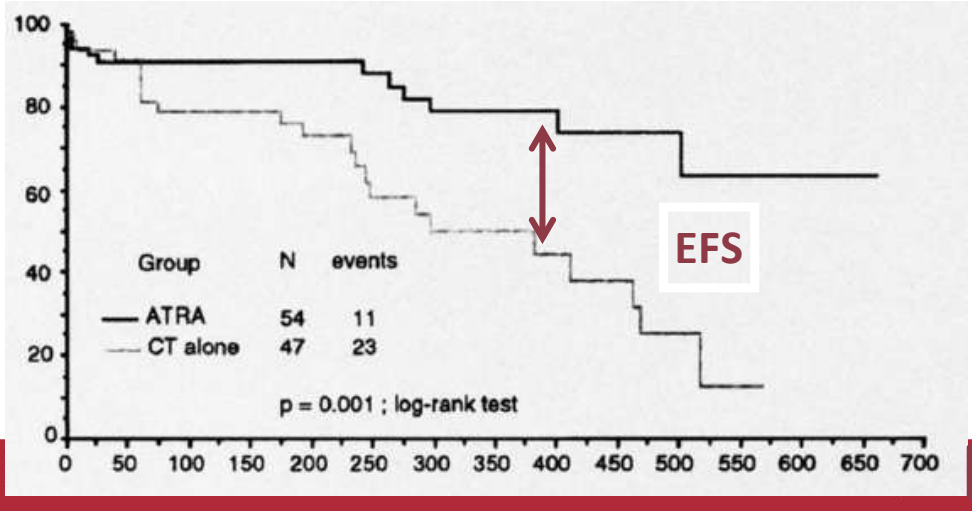
ATRA 10^{-6}-10^{-7} M **changes** PML-RARA configuration, **dissociates** CoR **recruit** CoA complex

Van Gils N et al . Exp Hematol 2017;52:12–23

APL therapy: ATRA-CHEMO combinations

- First randomized trial APL91 in newly diagnosed APL



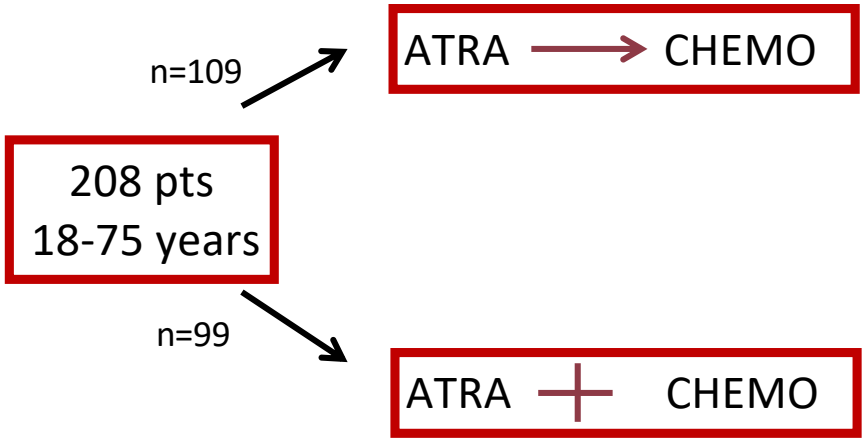


Prematurely stopped because EFS significantly better in ATRA group
EFS 12 months **79**% vs **50**%
4 years EFS **63**% vs **17**%

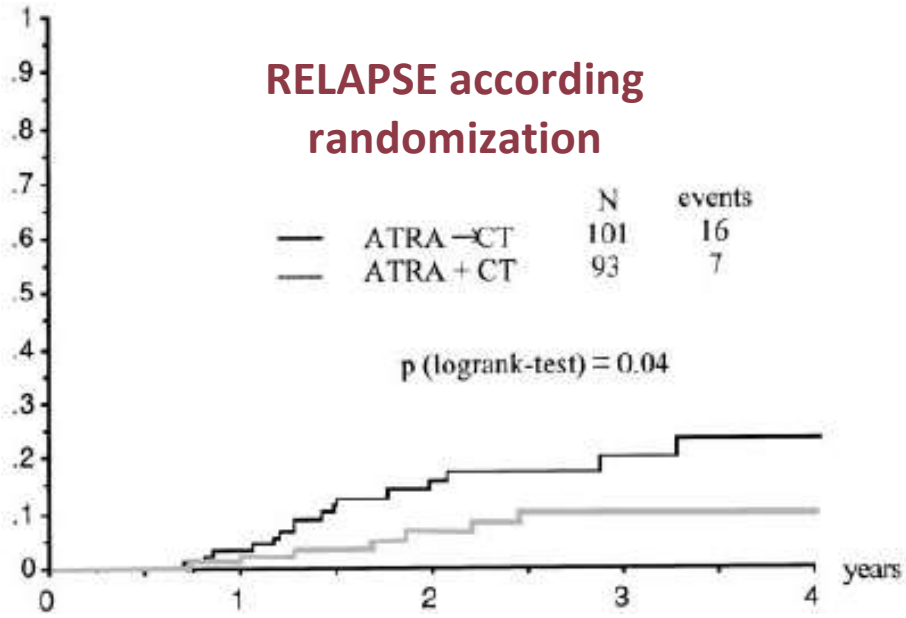
Fenaux P. et al al. Blood 1993;82:3241-9

APL therapy: ATRA-CHEMO combinations

- Randomized trial APL93 in newly diagnosed APL



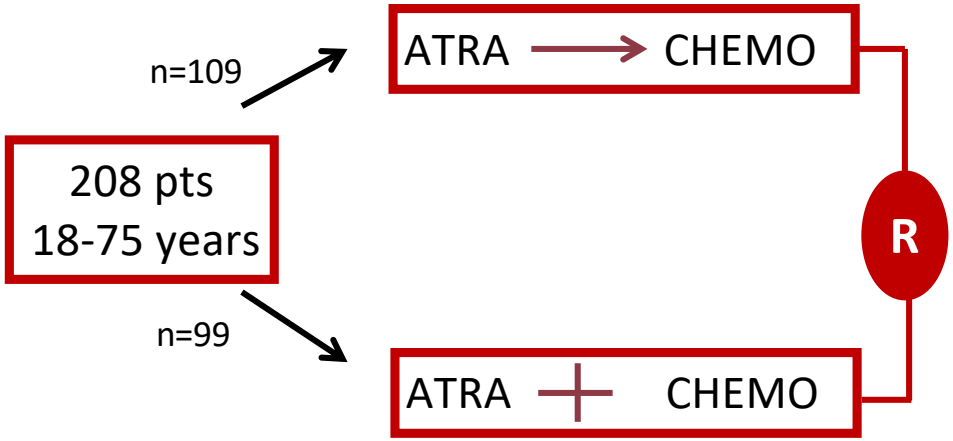
Significantly lower 2 years relapse rate (**6**% vs **16**%) in concurrent *vs* sequential regime



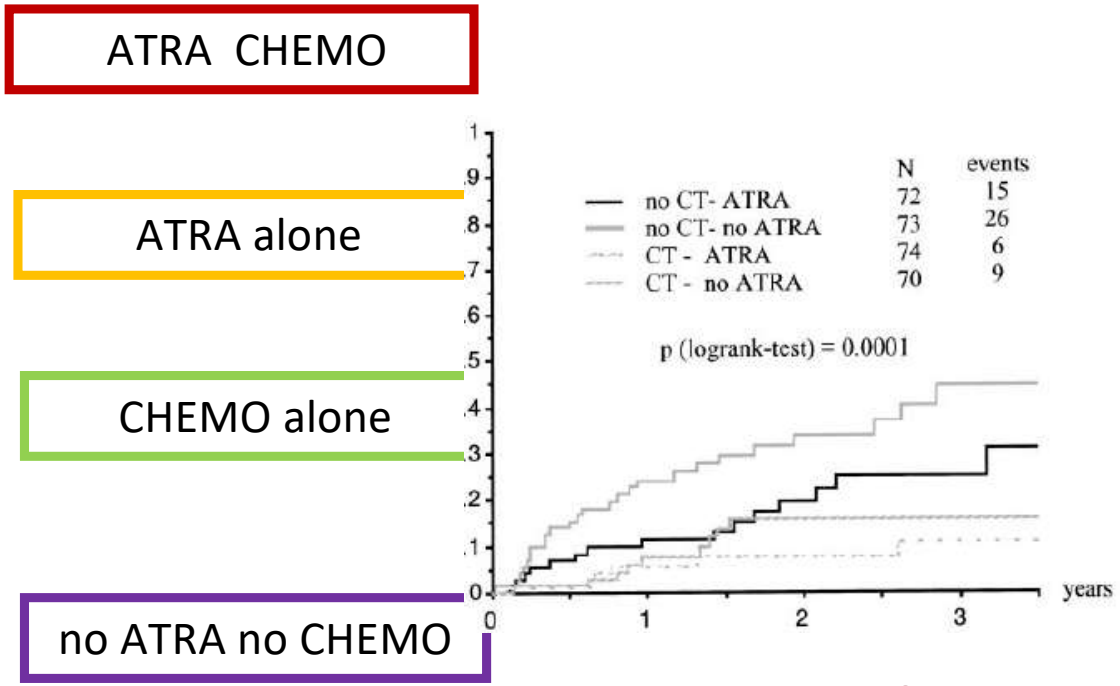
Fenaux P. et al al. Blood 1999;94:1192-200

APL therapy: ATRA-CHEMO combinations

- Role of maintenance



Maintenance for **2 years** with **intermittent ATRA** therapy (2 weeks every 3 months) combined with **low dose chemo** (6MP plus MTX) reduce the risk of relapse



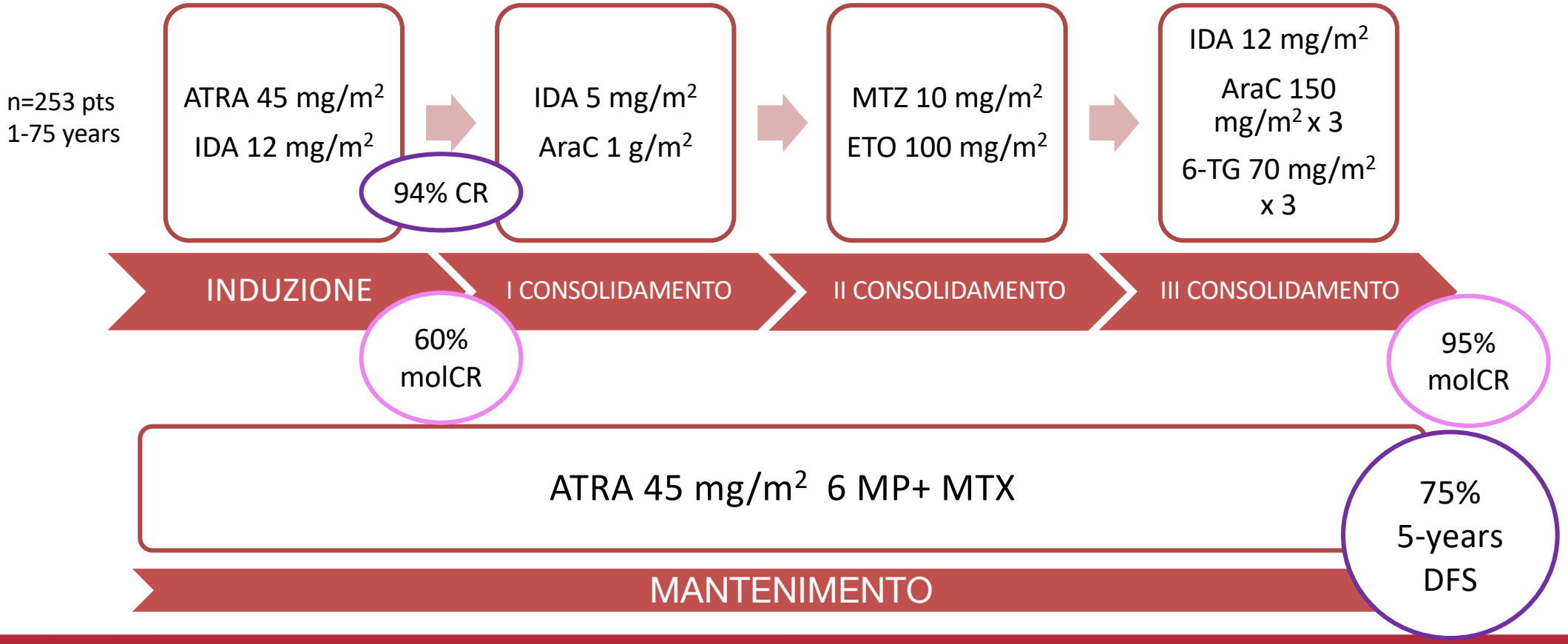
RELAPSE according to maintenance treatment group

Fenaux P. et al al. Blood 1999;94:1192-200

APL therapy: ATRA-CHEMO combinations

- ATRA-IDA (AIDA) induction regimen

GIMEMA APL0493



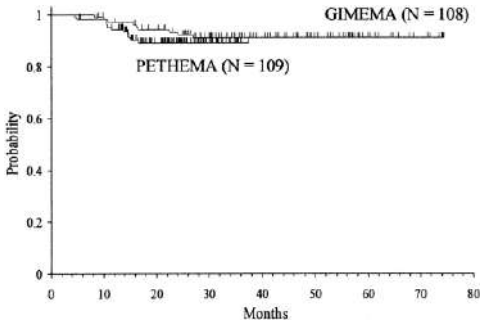
Mandelli F. et al, Blood 1997; 90:1014-1021

APL therapy: ATRA era 1988-1993

- Major concern by 1993
  - ATRA-induce differentiation syndrome ("ATRA syndrome")
    - Fever, hypotension, weight gain, respiratory distress, pulmonary infiltrates, pleural and/or pericardial effusions, renale failure, often associated to WBC increase
    - Until 1/3 patients; high WBC counts risk factor
    - Prophylaxis: **prednisone**; therapy: **dexametasone** 10 mg twice daily until resolution for at least 3 days
  - Secondary resistance:
    - Develops in ALL patients treated with ATRA alone for a long period
    - Reversible: catabolic process that reduce ATRA concentrations
  - Risk factors

APL therapy: risk-adapted treatment

HIGH RISK

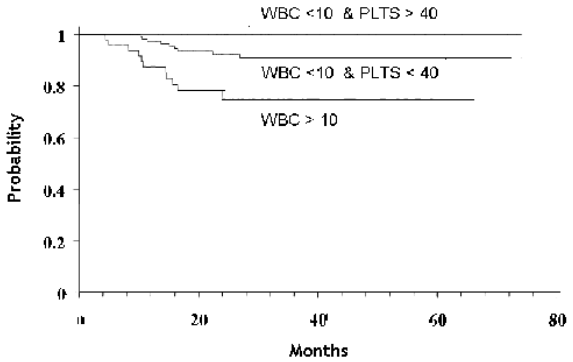


WBC > 10.000/mmc

LOW-INT RISK

WBC < 10.000/mmc

DFS according to risk group in APL pts treated with AIDA-like protocols



LOW RISK

PLTs > 40.000/mmc

INT RISK

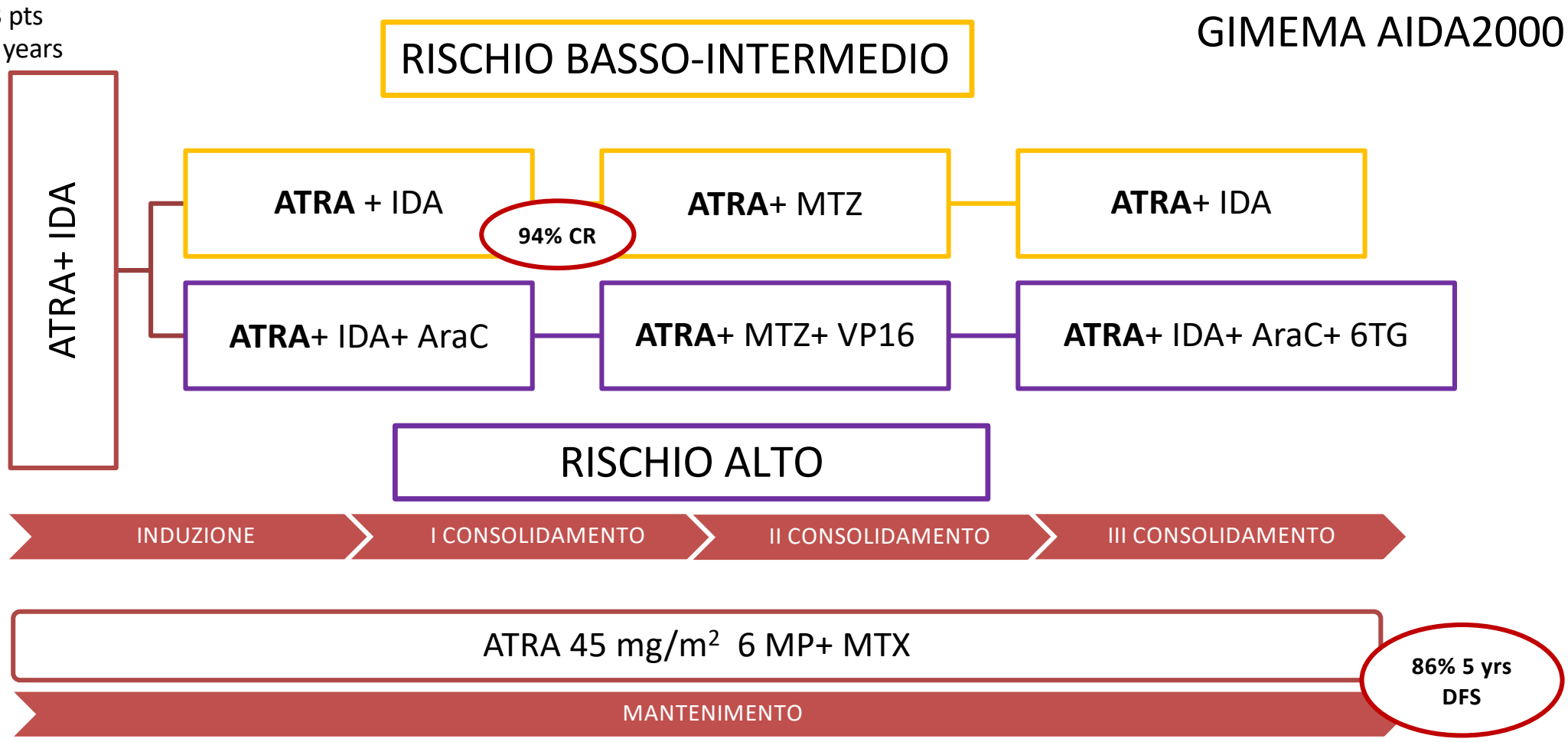
PLTs < 40.000/mmc

Sanz M A. et al al. Blood 2000;15:1247-1253

APL therapy: risk-adapted treatment

n=453 pts
18-61 years

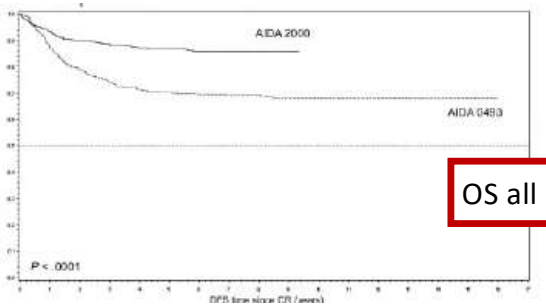
GIMEMA AIDA2000



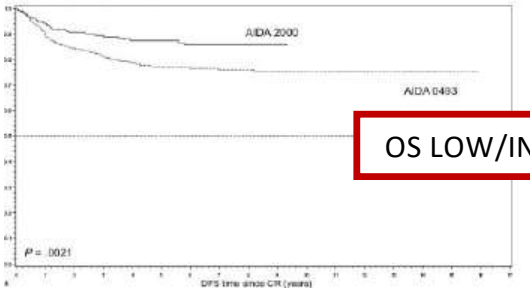
Lo Coco F. et al, Blood 2010; 90:1014-1021

APL therapy: risk-adapted treatment

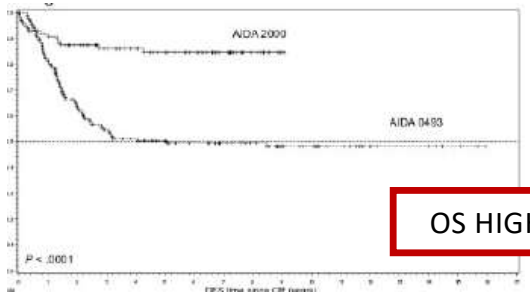
- AIDA 0493 versus AIDA 2000 risk adapted
  - 6 –year OS **78.1**% *vs* **87.4**%
  - 6-years CIR **27.7** *vs* **10.7**%
  - Significant **lower CIR** rates in AIDA2000 **for high risk group** (**49.7**% *vs* **9.3**%)
- Anthracycline-based consolidation equally effective as cytarabine-containing for low/int risk
- ATRA in consolidation improves outcome in newly diagnosed APL
- Cytarabine has a role in high risk consolidation in association to anthracycline and ATRA



OS all risk



OS LOW/INT risk



OS HIGH risk

Lo Coco F. et al, Blood 2010; 90:1014-1021

APL therapy: ATRA era 1988-1993

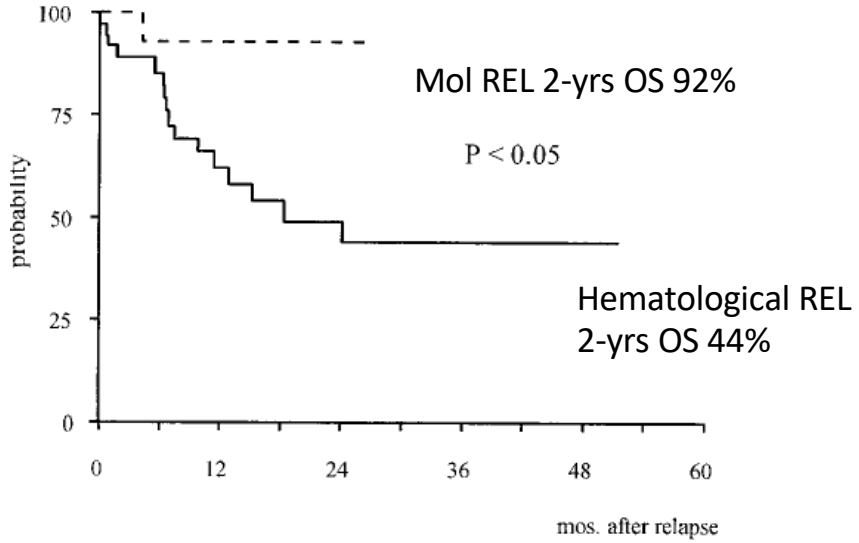
- APL state of art by 1993
  - Clinical features: hemorragic diatesis; hyperfibrinolysis and hypofibrinogenemia;
  - Unique morphology: hypergranular blast and variant
  - Specific cytogenetic: t(15;17)
  - Molecular hallmark: *PML/RARA*
- Treatment based on ATRA-anthracycline co… …on, ATRA-risk adapted chemo consolidation, ATRA-lov… …2 years maintenance:
  - **High CR rate with lower early mortality**
  - **Absence of primary resistance**
  - **75% of patients long survival**

APL therapy: post-ATRA era 1993-2002

- About 20% patient relapse after risk-adapted ATRA-CHEMO regimens
  - 90% 2nd CR with ATRA-CHEMO reinduction +/- autoHSCT or alloHSCT if MRD positive

- **Treatment** of **molecular relapse** is associated to **longer OS**
  - ↑ treatment tolerance ↓ days of hospitalization ↓ early deaths ↓ differentiation syndrome

- **New drugs: arsenic tryoxide**



Lo Coco F. et al. Blood 1999;94:2225-9

APL therapy: ATO era

- **Fowler's solution** (1% potassium arseniate) one of the first agent used to treat leukemias:
  - 1931 Forkner and Scott to treat CML
  - Early 1970 in China: Ailing-1 (1% arsenic trioxide and traces of mercury chloride)
    - Sun: CR achieved in 21/32 (**66**%) APL patients with OS 30% at 10 years
    - First trial APL: 60 pts (30 de novo and 30 relapse): 73% and 53% CR
- **Like ATRA improves bleeding diathesis**
  - Eliminates not only primary fibrinolysis BUT also DIC
- **Like ATRA induces differentiation syndrome**
  - Differentiation at low concentrations; apoptosis at higher concentrations

Sun H.D. et al. Chin J Integrat Chin West Med 1002;12:170-1; Chen Z. C. et al. Seminars in Hematol 1996;38:26-36; Zhu J. et al. Leukemia 1999;13:1062-1070

APL therapy: ATO in relapse setting

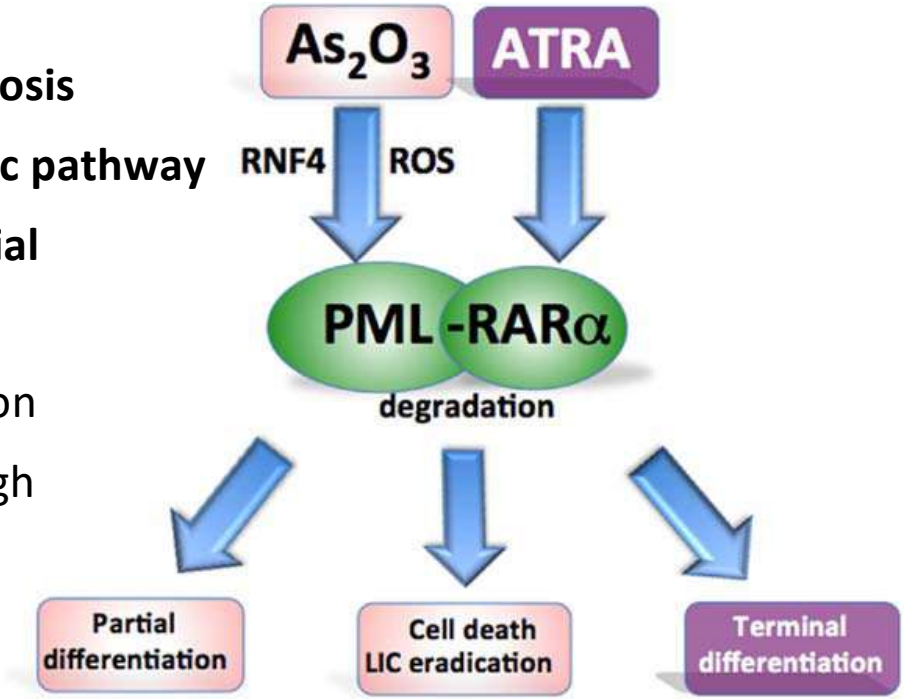
Reference	n° pts	CR/ days to CR	RD/ED	Post induction	OS
Shen et al.	15	93%	7%	ATO (1c)	> 80% (1.5y)
		38 (28–54)[a]	0		
Soignet et al.	52	87%	12%	ATO (5c)	66% (1.5y)
		(24–85)	1%	Auto (3), Allo (14)	
Niu et al.	47	85%	6%	ATO ± CT or CT	50% (2y)
		31	9%		
Shen et al.	20	80%	10%	DNR	62% (2y)
		ND	10%		
Kwong et al.	8	100%	0	Ida	ND
		45	0		
Leoni et al.	7	86%	0	HD-AraC, MTZ	> 80% (2y)
		(20–40)	14%	Auto (2), Allo (2)	
Ohnishi et al.	14	79%	14%	ATO (1c), CT ± ATRA	ND
		43 (27–60)	7%	Allo (2)	
Lazo et al.	12	100%	0	ATO (4c) ± CT	ND
		52 (27–75)	0	Allo (1)	
Raffoux et al.	20	80%	10%	ATO (1–2c) ± ATRA	59% (2y)
		42 (14–86)	10%	Auto (1), Allo (7)	
Carmosino et al.	11	73%	0	ATO (1c) ± ATRA ± Ida	ND
		38 (28–50)	27%	Auto (2), Allo (2)	
Shigeno et al.	34	91%	6%	ATO (1c) ± CT + ATRA	56% (2y)
		46 (26–60)	3%	Auto (1), Allo (9)	
Thomas et al	25	84%	8%	ATO (1c) ± CT, MT	77% (2y)
		49	8%	Auto (9), Allo (3)	
Aribi et al.	8	100%	0	ATO (5c) + ATRA + GO, MT	75% (3y)
		39 (21–56)	0	Allo (1)	
Alimoghaddam et al.	31	77%	10%	ATO (1–4c)	81% (2y)
		30	13%		

- Clinical trial with ATO in 304 relapsed APL patients:
  - 301 hematological REL and 3 mol REL
  - ≥ 2^ relapse
  - CR rate **86**% (range 73-100%)
  - **7% died** during induction
  - Median time to remission **30-59** days

Thomas X Oncol Ther (2019):7:33-65; Lengfelder E. et al. 2012;26(433-442)

APL therapy: ATO mechanism of action

- ATO **high** concentrations (0.5-2.0 µmol/L) induces **apoptosis** activating the mitochondria-mediated **intrinsic apoptotic pathway**
- ATO **low** concentrations (0.1-0.5 µmol/L) promotes **partial differentiation**
  - ATO **does not activate** RARA-dependent transcription
  - ATO binds to **PML** promoting its **degradation** through 11S proteasome and ROS restoring **nuclear bodies**
- ATO single agent is **definitively curative** in up to 70% APL while ATRA single agent is not eradicating
- ATO crosses the blood-brain barrier (up to 12% SNC relapse in APL patients)



Thomas X Oncol Ther (2019):7:33-65; Lengfelder E. et al. 2012;26(433-442)

APL therapy: ATO in frontline setting

- ATO for remission induction

Reference	No. of patients	ATO dose	CR (%)	mCR (%)	OS
Ravandi et al.	82	0.15 mg/kg + ATRA ± GO ± Ida	91	73	85% (3y)
Hu et al.	85	0.16 mg/kg + ATRA	94	100	92% (5y)
Mathews et al.	72	10 mg	86	76	74% (5y)
Ghavamzadeh et al.	197	0.15 mg/kg	86	92	64% (5y)

Thomas X Oncol Ther (2019):7:33-65

APL therapy: CHEMO-FREE ATO-ATRA

The NEW ENGLAND JOURNAL of MEDICINE

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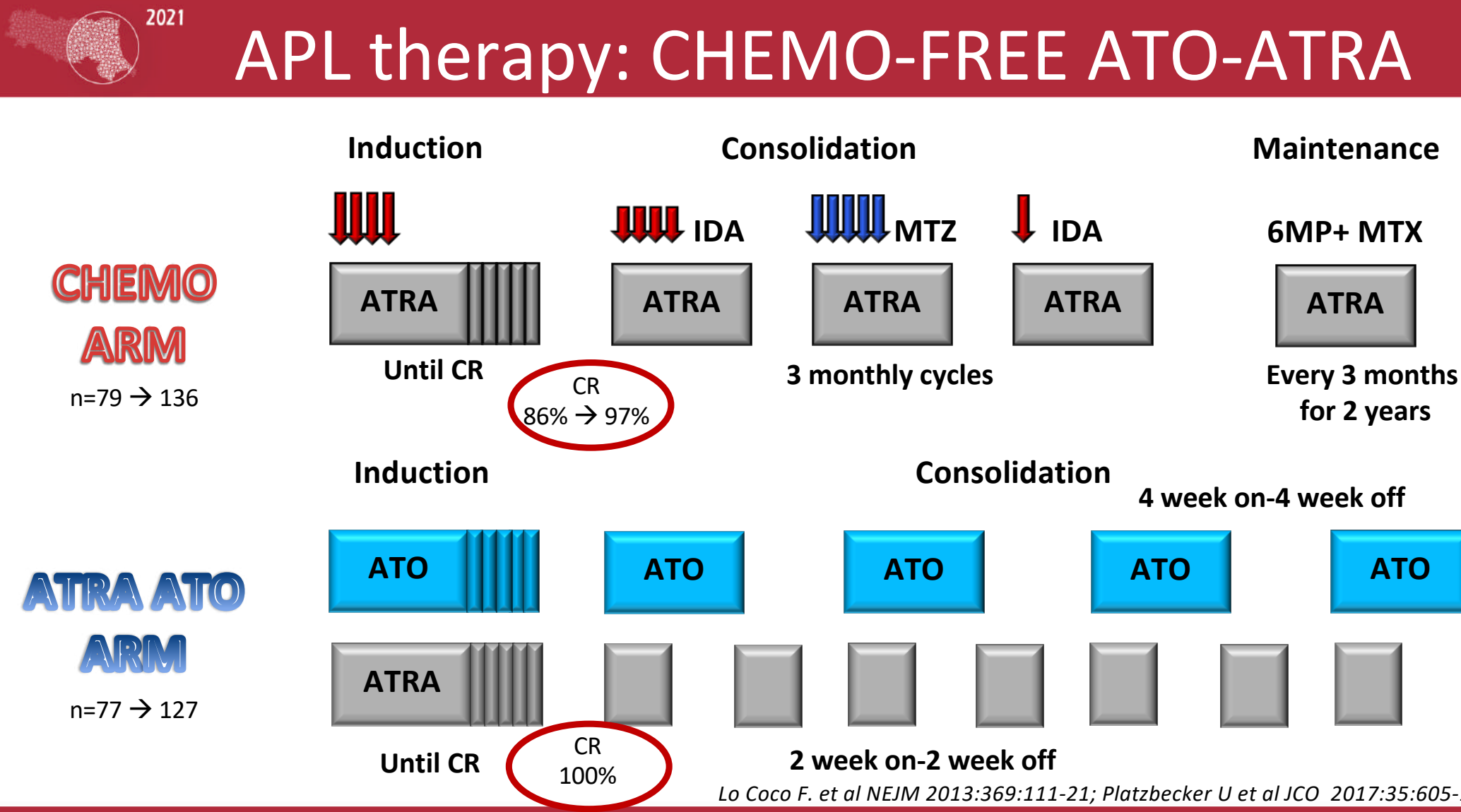
Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia

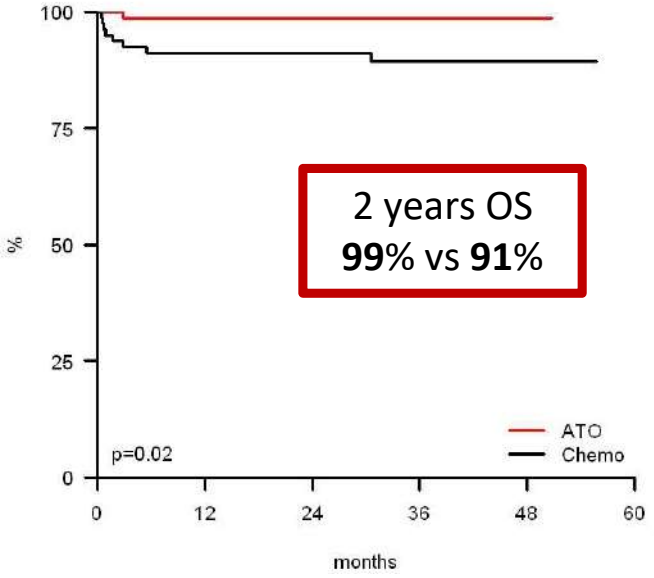
F. Lo-Coco, G. Avvisati, M. Vignetti, C. Thiede, S.M. Orlando, S. Iacobelli, F. Ferrara, P. Fazi, L. Cicconi, E. Di Bona, G. Specchia, S. Sica, M. Divona, A. Levis, W. Fiedler, E. Cerqui, M. Breccia, G. Fioritoni, H.R. Salih, M. Cazzola, L. Melillo, A.M. Carella, C.H. Brandts, E. Morra, M. von Lilienfeld-Toal, B. Hertenstein, M. Wattad, M. Lübbert, M. Hänel, N. Schmitz, H. Link, M.G. Kropp, A. Rambaldi, G. La Nasa, M. Luppi, F. Ciceri, O. Finizio, A. Venditti, F. Fabbiano, K. Döhner, M. Sauer, A. Ganser, S. Amadori, F. Mandelli, H. Döhner, G. Ehninger, R.F. Schlenk, and U. Platzbecker for Gruppo Italiano Malattie Ematologiche dell'Adulto, the German–Austrian Acute Myeloid Leukemia Study Group, and Study Alliance Leukemia

APL therapy: CHEMO-FREE ATO-ATRA

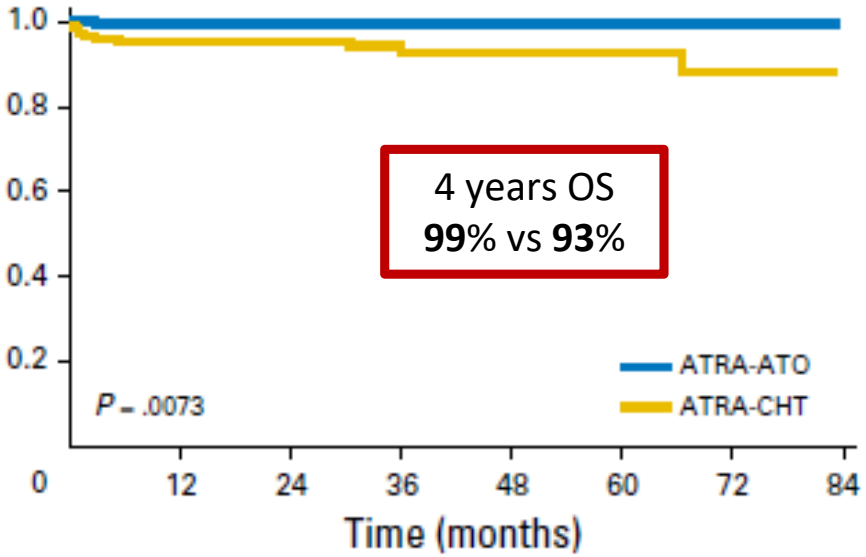


Lo Coco F. et al NEJM 2013:369:111-21; Platzbecker U et al JCO 2017:35:605-12

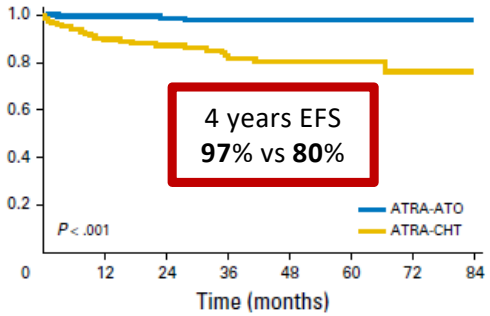
APL therapy: CHEMO-FREE ATO-ATRA



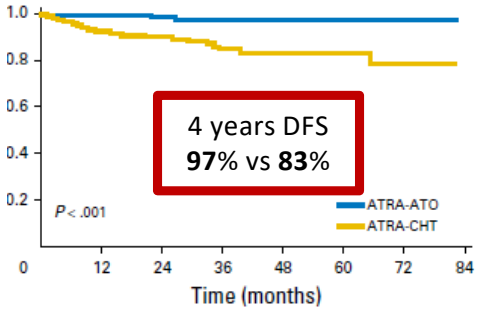
2 years OS
99% vs **91**%



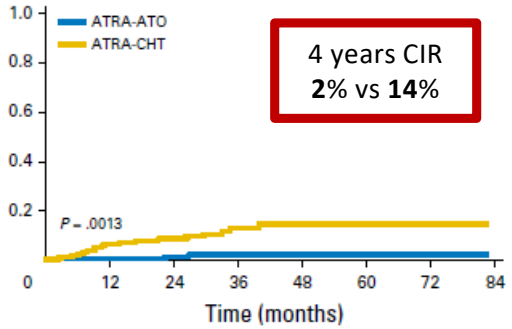
4 years OS
99% vs **93**%



4 years EFS
97% vs **80**%



4 years DFS
97% vs **83**%

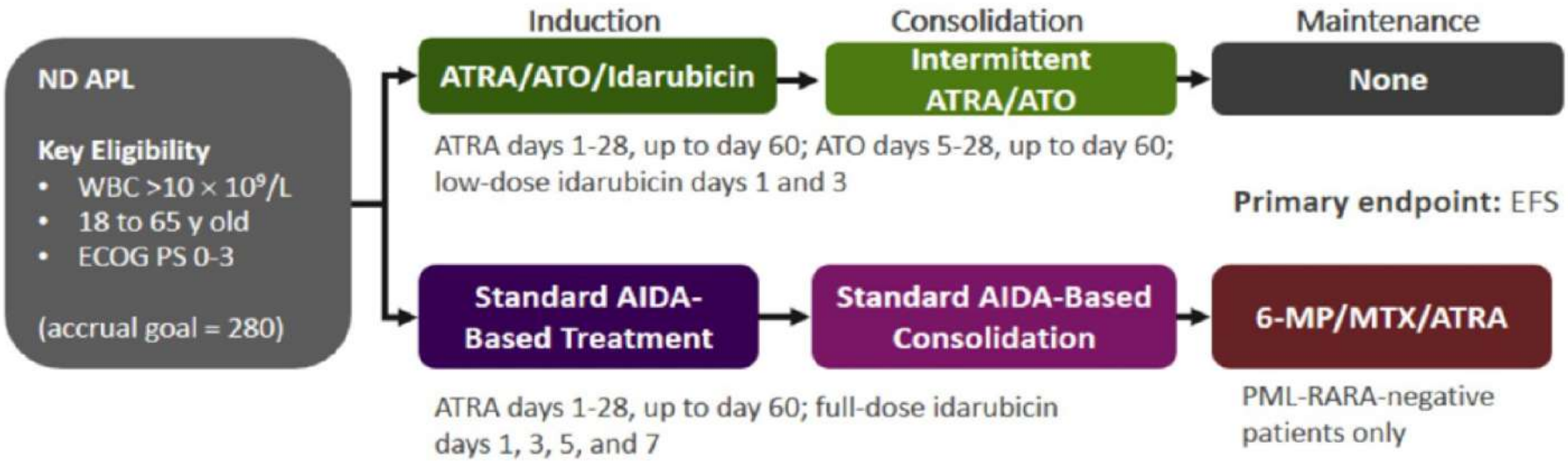


4 years CIR
2% vs **14**%

Lo Coco F. et al NEJM 2013:369:111-21; Platzbecker U et al JCO 2017:35:605-12

APL therapy: ATO-ATRA in HR APL

Randomized Phase III clinical trial **ATRA/ATO/Idarubicin** *vs* **AIDA in newly diagnosed High-Risk APL**



ClinicalTrials.gov. NCT0268840

APL therapy: ATRA-ATO era 2003-ongoing

APL state of art by 2021

- Clinical features: hemorragic diatesis; hyperfibrinolysis and hypofibrinogenemia;
- Unique morphology: hypergranular blast and variant
- Specific cytogenetic: t(15;17)
- Molecular hallmark: *PML/RARA*

- Treatment based on ATRA-anthracycline combination induction, ATRA-ri… …, ATRA-low dose chemo for 2 years maintenance:
  - **High CR rate with lower early mortality**
  - **Absence of primary resistance**
  - **75% of patients long survival**
- **Chemo-free regimen ATRA-ATO based** for **low/int …**
  - **99% of patients long survival**
- **Triple combinations (ATRA-ATO-IDA e/o GO) for high ri…**

Fulminant leukemia from highly fatal to highly curable with Chemo-free regimens

APL therapy: conclusions

- APL best example of how **targeted therapy** can lead to **cure**
- Major obstacle to cure: **early deaths**
- **Long –term toxicity** of chemo-free treatment
- **Q**uality **o**f **L**ife
- **Oral formulation ATO** with outpatient care
- Best therapy for **high risk** patients
- **New drugs** for **relapsed** disease

A colui che ha

Ricercato con ardore,

Insegnato con passione,

Curato con amore...

2021

Thanks for the attention

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