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

8th SYMPOSIUM ON

Acute Promyelocytic Leukemia

*Dedicated to **Prof. Francesco Lo Coco***

*Featuring an AML meeting coordinated by **EHA** SWG AML*

10-11 Aprile 2024

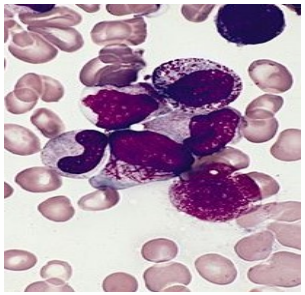
ROMA • Hotel NH Collection Roma Centro

ATRA + CHEMOTHERAPY: RESULTS OF CLINICAL STUDIES IN CHILDHOOD APL

Anna Maria Testi
Department of Translational and Precision Medicine
Sapienza University of Rome

Disclosures of Anna Maria Testi

Nothing to disclosure



PEDIATRIC ACUTE PROMYELOCYTIC LEUKEMIA

- A unique subtype of AML accounting for 5–10% of all pediatric AML cases

- Following the discovery PML-RARA, the use of differentiation therapy with ATRA has significantly improved outcomes and become the standard of care.

- When ATRA was introduced over 3 decades ago, it was first trialed as a single agent and provided CR rates of 75%–85% in adult studies.
- However, relapses remained common and thus combination therapy with both ATRA and conventional chemotherapy became standard
- Anthracyclines appeared to be the most important chemotherapeutic agent to decrease the relapse rate
- Unfortunately the total dose of anthracyclines used in most regimens is very high and associated with the risk of short- and long-term cardiotoxicity

- Childhood APL has been traditionally treated with adult protocols

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ICC APL Study 01
Study information
Center Registration
Web Community Area
Study Access

PEDIATRIC ACUTE PROMYELOCYTIC LEUKEMIA
ATRA + CHEMOTHERAPY

1993	2000	2008
GIMEMA/AIEOP AIDA 0493	GIMEMA/AIEOP AIDA 2000	ICC APL 01

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ATRA dosage: 25 mg/m²/day

ATRA-BASED REGIMEN

RISK-ADAPTED TREATMENT ACCORDING TO SANZ'S SCORE

DE-INTENSIFICATION FOR STANDARD RISK PATIENTS

1993 → **2000** → **2008** → **ATO ERA**

GIMEMA/AIEOP AIDA 0493

Adult and childhood APL:
- Induction: ATRA + idarubicin
- Consolidation: 3 CHT courses
- No ATRA in consolidation
- Maintenance: random 4 arms (CHT, ATRA alone, ATRA+CHT, stop)

Testi AM *et al*, Blood 2005

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- Induction: ATRA + idarubicin
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  SR/IR 3 courses (ATRA+anthracycline)
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Lo Coco F *et al*, Blood 2010; Testi AM *et al*, Blood 2018

ICC APL01

Childhood APL:
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  (PCR- after the 2° course)
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- Maintenance: ATRA+CHT

Testi AM *et al*, Blood 2018

GIMEMA/AIEOP AIDA 0493 trial: baseline features of children

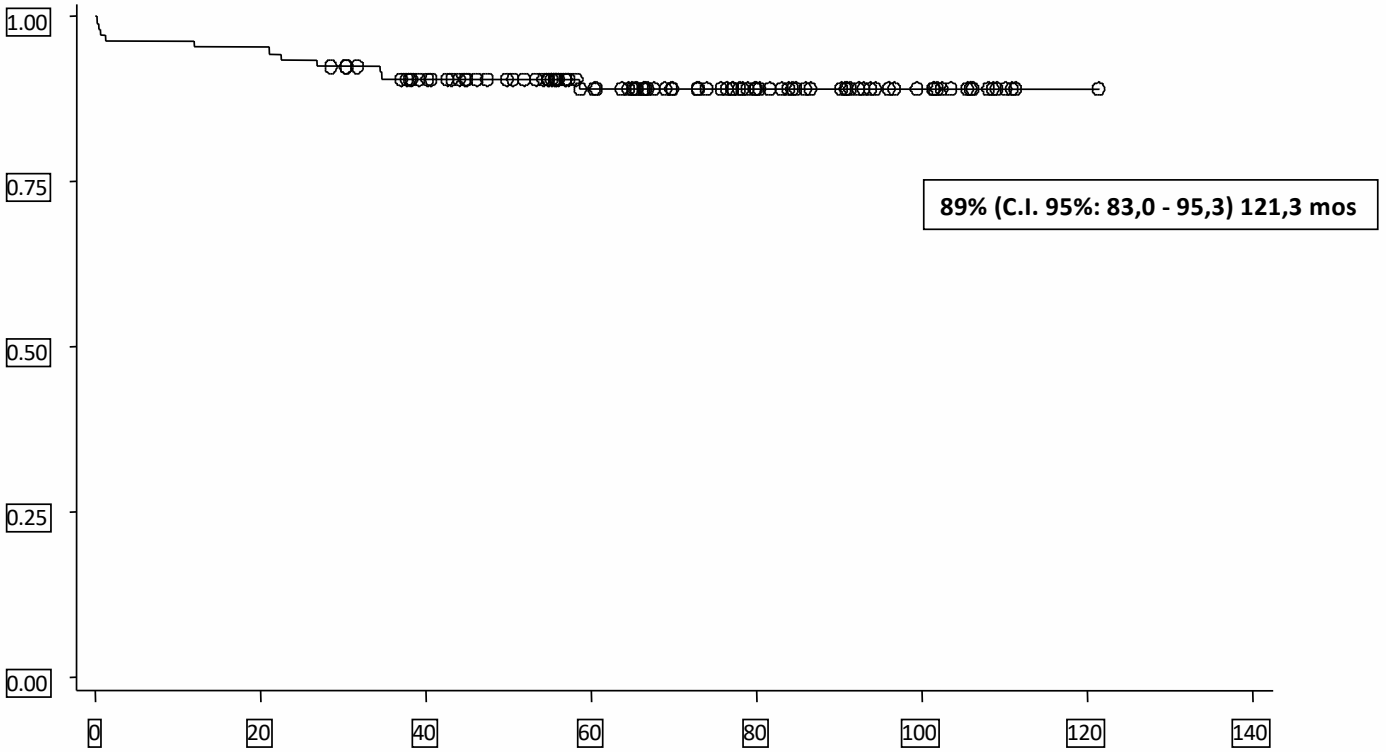
	AIDA 0493 N. pts 110 (January 1993-June 2000)
Follow-up; median (range)	12.1 (0.03-16.3)
Gender: M/F	55/55
Age - years; median (min-max)	11.6 (1.4-17.97)
WBC $x10^9$/L; median (min-max)	3.95 (0.3-180.0)
Plts $x10^9$/L; median (min-max)	20.0 (3.0-48.0)
FAB type: M3/M3v	98/12
PML/RARA isoform Bcr: 1/2/3/nk	57/5/36/12
Risk group: SR/HR (%)	72 (65)/38 (35)

GIMEMA/AIEOP AIDA 0493 trial: induction and consolidation results

Trial	AIDA 0493
Evaluable pts.	107
HCR, n. (%)	103 (96)
Early death, n. (%)	4 (4)
Risk category	4 HR
Cause of death	3 ICH; 1 sepsis
N. resistant pts	0

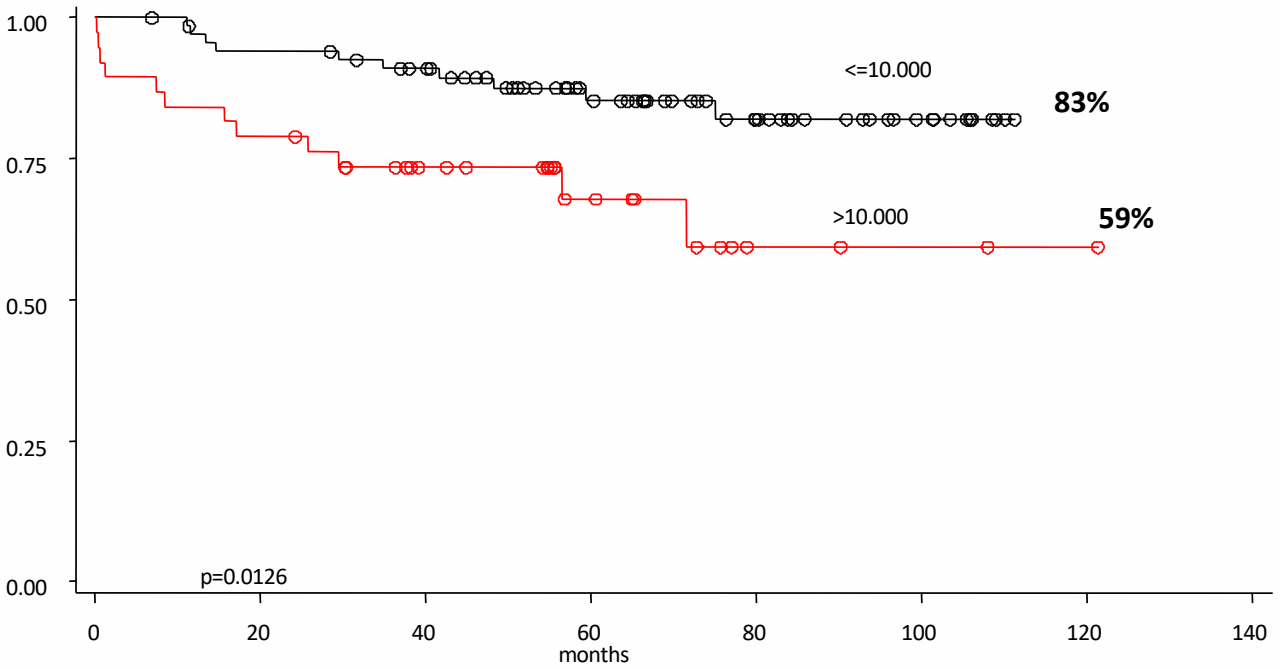
PCR	N. pts 95
Negative (%)	92 (96.8)
Positive (%)	3 (3.16)

GIMEMA/AIEOP AIDA 0493 Trial
OVERALL SURVIVAL



Testi et al, Blood 2005

GIMEMA-AIEOP AIDA 0493
EVENT-FREE SURVIVAL according to diagnostic WBC



GIMEMA-AIEOP AIDA 0493 PROTOCOL

Messages from the trial

- **Induction combination of ATRA + idarubicin: highly effective with no patient showing evidence of resistance to treatment**
- **In pediatric age, ATRA is equally effective and less toxic at a daily dose of 25 mg/m^2**
- **Presenting WBC count significantly affected patients' outcome**
- **The combination of intermittent maintenance ATRA and chemotherapy improved the DFS in all patients and appeared to be particularly useful for HR patients**
- **PML/RARA positivity at the end of induction is not predictive of relapse**
- **Patients in mCR who converted to positive PCR, confirmed in 2 consecutive bone marrow samples, were considered eligible for salvage treatment**

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ICC APL01

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  HR/SR PCR+: 3 courses ATRA+CHT
- Maintenance: ATRA+CHT

Testi AM *et al*, Blood 2018

GIMEMA/AIEOP AIDA 0493 and 2000 trials: baseline features of children

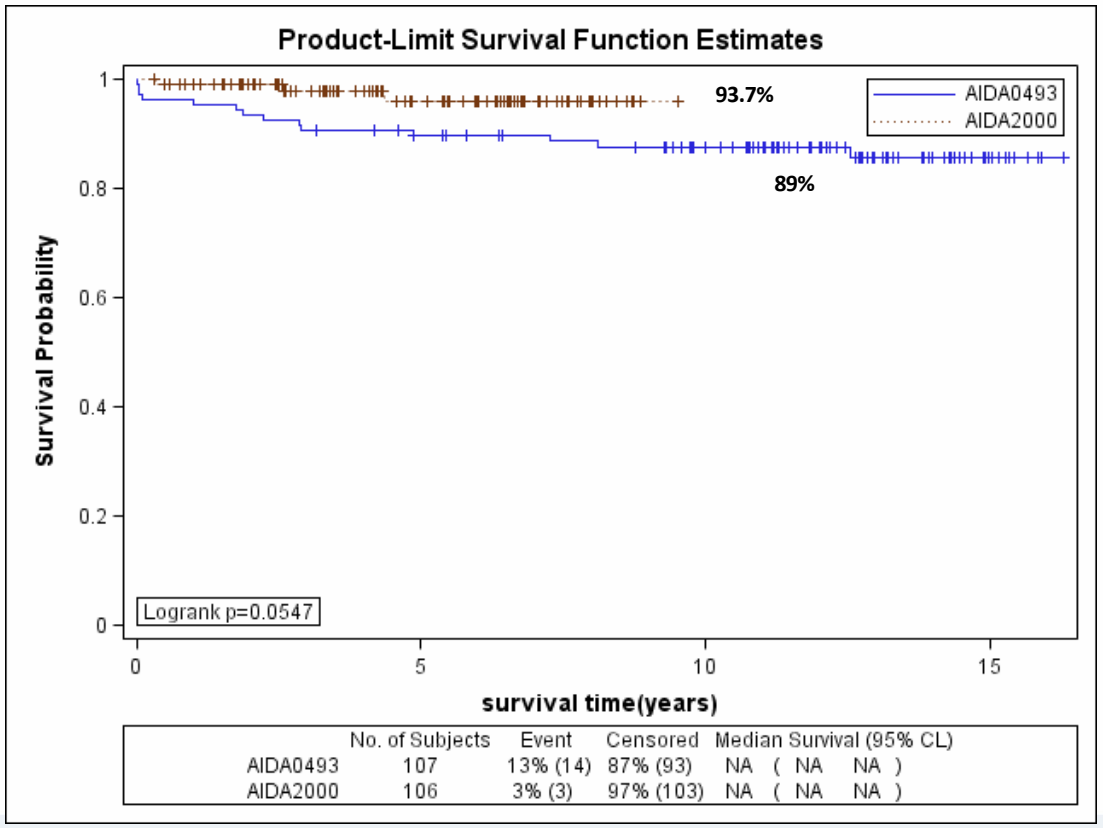
	AIDA 0493 N. pts 110	AIDA 2000 N. Pts 127 (July 2000- Dec. 2007)	p value
Follow-up; median (range)	12.1 (0.03-16.3)	12.9 (7.8-17.0)	
Gender: M/F	55/55	77/50	ns
Age - years; median (min-max)	11.6 (1.4-17.97)	11.9 (1.1-17.98)	ns
WBC x10^9/L; median (min-max)	3.95 (0.3-180.0)	3.60 (0.20-187.0)	ns
Plts x10^9/L; median (min-max)	20.0 (3.0-48.0)	27.5 (7.0-205.0)	ns
FAB type: M3/M3v	98/12	105/22	ns
PML/RARA isoform Bcr: 1/2/3/nk	57/5/36/12	50/6/37/34	ns
Risk group: SR/HR (%)	72 (65)/38 (35)	85 (67)/42 (33)	ns

GIMEMA/AIEOP AIDA 0493 and AIDA 2000 trials: induction and consolidation results

Trial	AIDA 0493	AIDA 2000
Evaluable pts.	107	125
HCR, n. (%)	103 (96)	121 (97)
Early death, n. (%)	4 (4)	4 (3)
Risk category	4 HR	4 HR
Cause of death	3 ICH; 1 sepsis	3 ICH; 1 sepsis
N. resistant pts	0	0

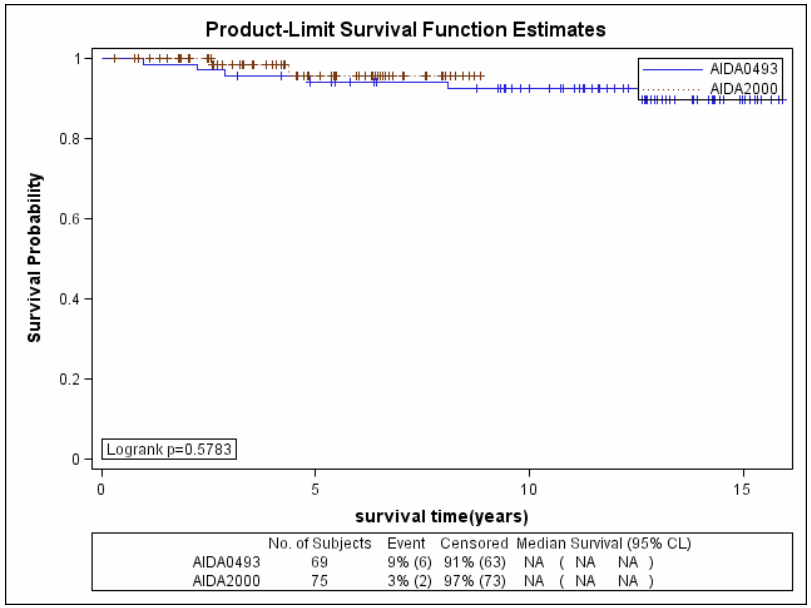
PCR	N. pts 95	N. pts 121
Negative (%)	92 (96.8)	118 (97.5)
Positive (%)	3 (3.16)	3 (2.48)

OVERALL SURVIVAL
GIMEMA-AIEOP AIDA 0493 and 2000 PROTOCOLS (all risks)

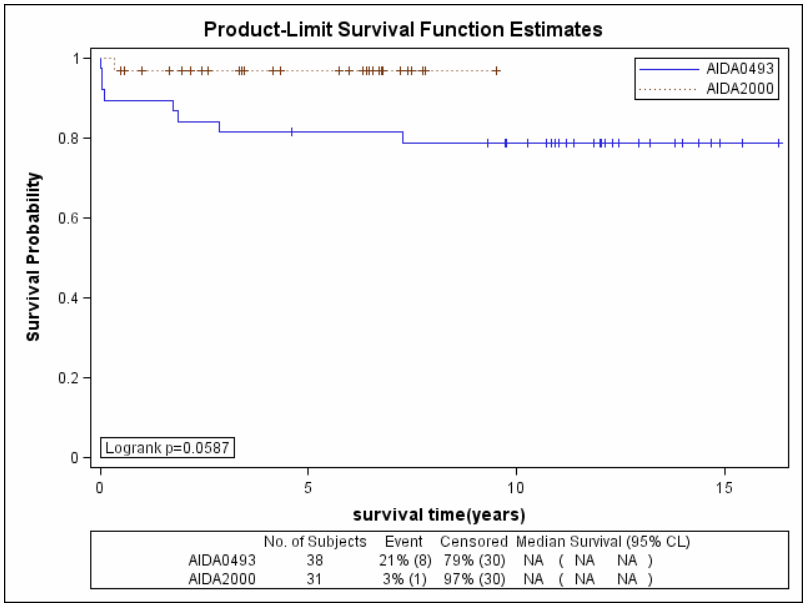


OVERALL SURVIVAL
GIMEMA-AIEOP AIDA 0493 and 2000 PROTOCOLS

Low-Risk



High-Risk



GIMEMA-AIEOP AIDA 2000 PROTOCOL: Risk-adapted Trial

Messages from the trial

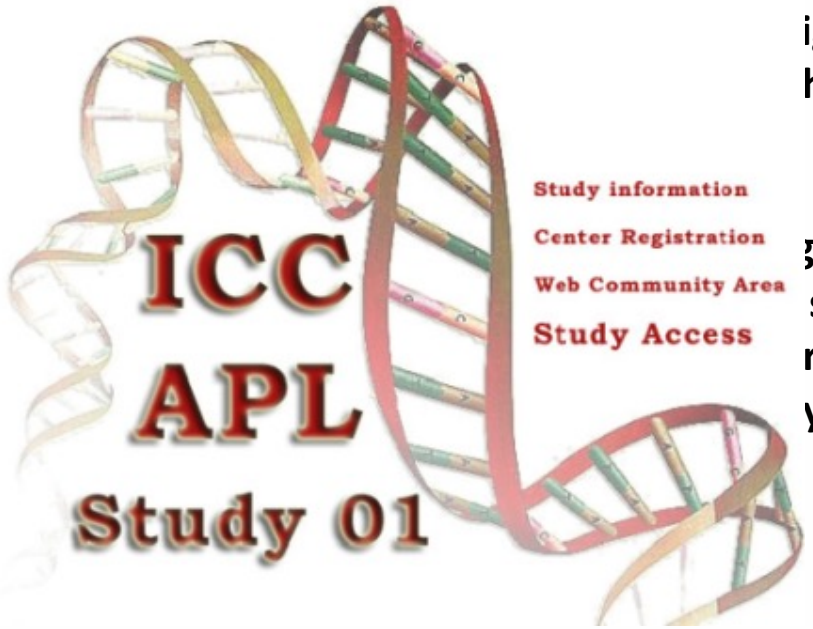
- **Induction ATRA + idarubicin: confirmed the very high efficacy with a virtual absence of resistant disease in pediatric patients**
- **ATRA extended consolidation improved results in all risk categories**
- **Less intensive consolidation for SR patients did not affected the outcome**
- **ATRA + intensive consolidation in HR patients improved the results in this category**
- **MRD assessment at the end of consolidation is confirmed to be the major treatment objective in APL**
- **Cumulative anthracycline dosage: very high for all categories (650 mg/m^2 of anthracycline daunorubicin equivalence)**

INTERNATIONAL CONSORTIUM FOR CHILDHOOD APL, ICC APL

First multinational, multicenter childhood APL Study 01
EudraCT 2008-002311-40

- **The combined … igh cumulative doses (650 mg … hildren with APL**
- **However, high … gnificant risk of both acute an… second neoplasms), a significant o… rm favorable outcome, espe… y**

An international …



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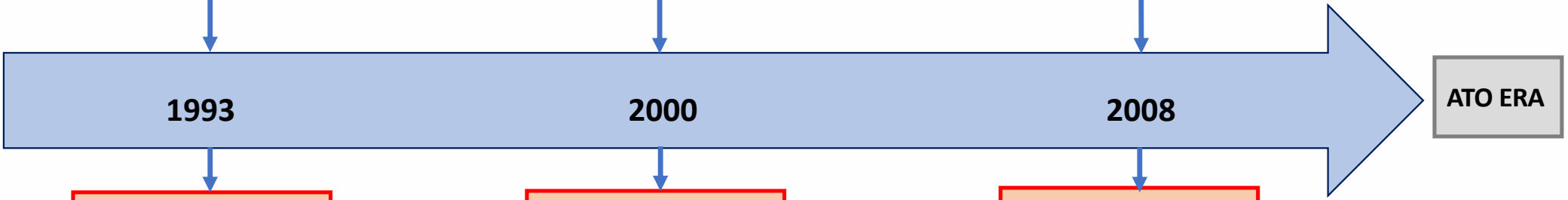

GIMEMA/AIEOP AIDA 0493

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- No ATRA in consolidation
- Maintenance: random 4 arms (CHT, ATRA alone, ATRA+CHT, stop)

Testi AM *et al*, Blood 2005

GIMEMA/AIEOP AIDA 2000

Adult and childhood APL:
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Lo Coco F *et al*, Blood 2010; Testi AM *et al*, Blood 2018

ICC APL01

Childhood APL:
- Induction: ATRA + idarubicin
- Consolidation:
  SR 2 courses ATRA+ CHT
  (PCR- after the 2° course)
  HR/SR PCR+: 3 courses ATRA+CHT
- Maintenance: PCR- ATRA+CHT; PCR+ salvage therapy

Testi AM *et al*, Blood 2018

GIMEMA/AIEOP AIDA and ICC APL 01 trials: baseline features of children enrolled in the 3 protocols

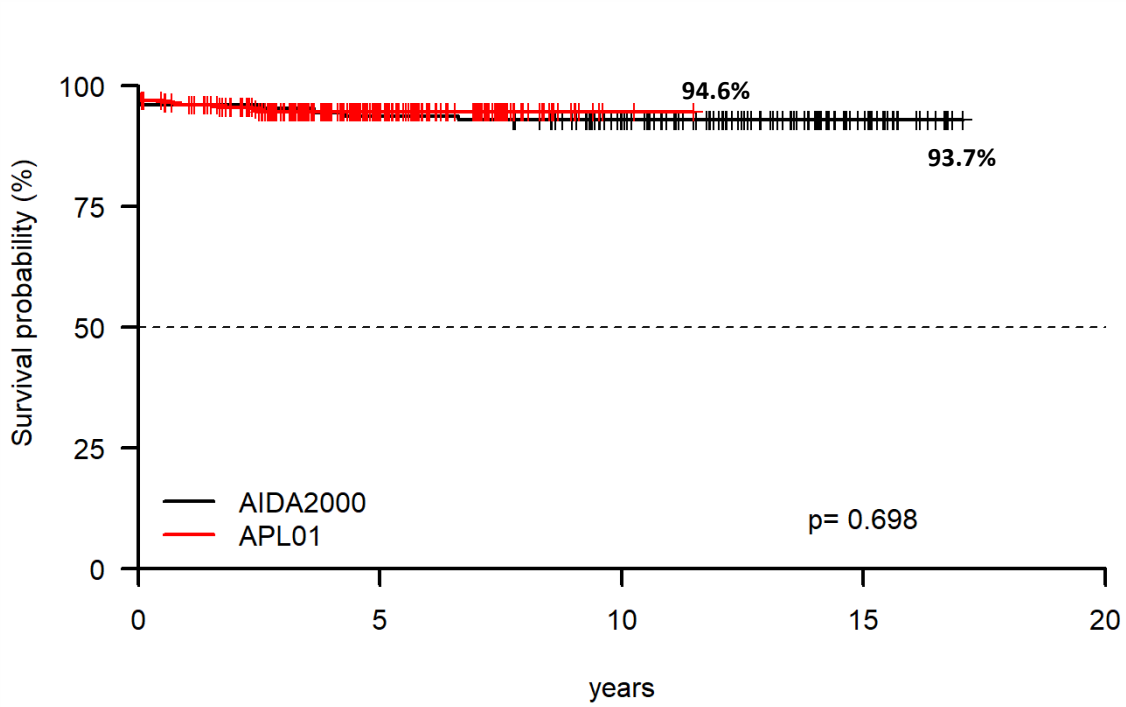
	AIDA 0493 N. pts 110	AIDA 2000 N. Pts 127	ICC APL 01 N. Pts 258	p value
Follow-up; median (range)	12.1 (0.03-16.3)	12.9 (7.8-17.0)	4.4 (0.1 – 9.5)	
Gender: M/F	55/55	77/50	121/137	ns
Age - years; median (min-max)	11.6 (1.4-17.97)	11.9 (1.1-17.98)	10.3 (1.1-20.7)	ns
WBC $x10^9$/L; median (min-max)	3.95 (0.3-180.0)	3.60 (0.20-187.0)	6.3 (0.08-339.0)	ns
Plts $x10^9$/L; median (min-max)	20.0 (3.0-48.0)	27.5 (7.0-205.0)	23.0 (2.0-262.0)	ns
FAB type: M3/M3v/na	98/12	105/22	210/44/4	ns
PML/RARA isoform Bcr: 1/2/3/nk	57/5/36/12	50/6/37/34	110/7/102/39	ns
Risk group: SR/HR (%)	72 (65)/38 (35)	85 (67)/42 (33)	149 (58)/109 (42)	ns

GIMEMA/AIEOP AIDA and ICC APL 01 trials: induction and consolidation results of the 3 consecutive protocols

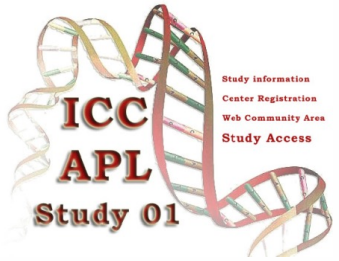
Trial	AIDA 0493	AIDA 2000	ICC APL 01
Evaluable pts.	107	125	258
HCR, n. (%)	103 (96)	121 (97)	250 (97)
Early death, n. (%)	4 (4)	4 (3)	8 (3)
Risk category	4 HR	4 HR	1 SR/ 7 HR
Cause of death	3 ICH; 1 sepsis	3 ICH; 1 sepsis	8 ICH
N. resistant pts	0	0	0

PCR	N. pts 95	N. pts 121	N. pts 218
Negative (%)	92 (96.8)	118 (97.5)	213 (97.7)
Positive (%)	3 (3.16)	3 (2.48)	5 (2.3)

OVERALL SURVIVAL
ICC APL 01 and GIMEMA/AIEOP AIDA 2000 PROTOCOLS



ICC APL 01 PROTOCOL



Messages from the trial

- **Reduced cumulative anthracycline dose (SR 355 mg/m^2; HR 405 mg/m^2) is associated with responses not inferior to those observed with significantly higher doses**
- **The most common adverse event was febrile neutropenia due to myelosuppression (42% in induction; 60% in consolidation)**
- **Whether or not maintenance treatment with oral chemotherapy and intermittent ATRA is required was debated**

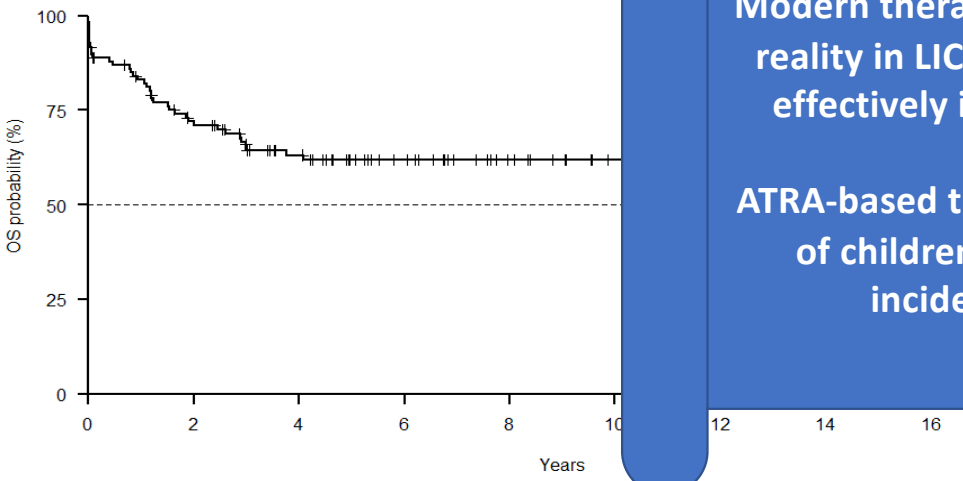
Pediatric APL: Results in Low-income Countries
ATRA + Chemotherapy

SIOP2023
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
OTTAWA, CANADA | OCTOBER 11-14, 2023

AHOPCA
Asociación Hemato-Oncológica Pediátrica CentroAmericana

Pediatric APL in Iraq: Overall Survival

Testi AM, et al. Leuk Lymphoma, 2022

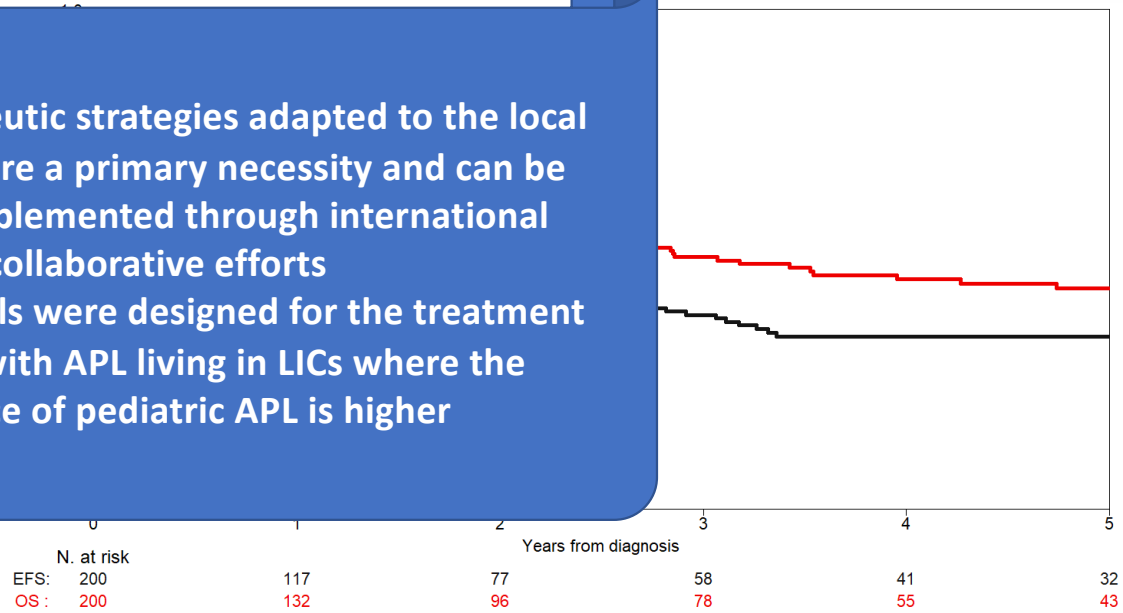


Incidence of pediatric APL: 27.5% of all childhood AML

Modern therapeutic strategies adapted to the local reality in LICs are a primary necessity and can be effectively implemented through international collaborative efforts

ATRA-based trials were designed for the treatment of children with APL living in LICs where the incidence of pediatric APL is higher

Pediatric APL in Central A ca

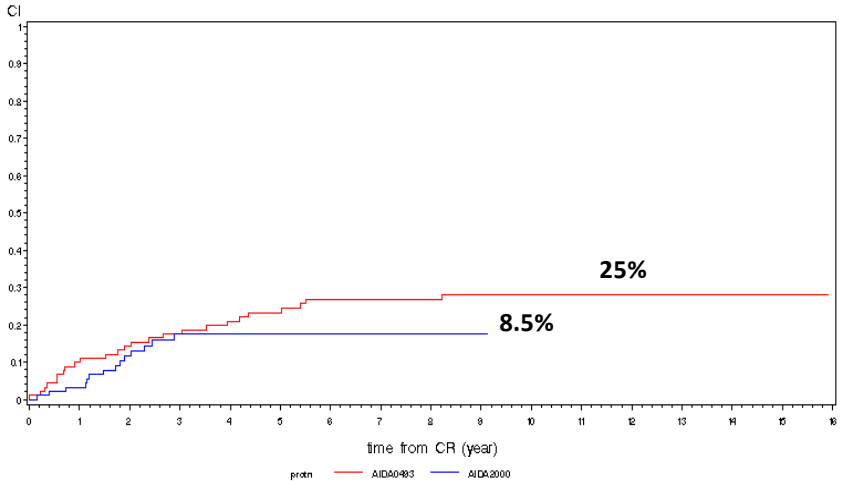


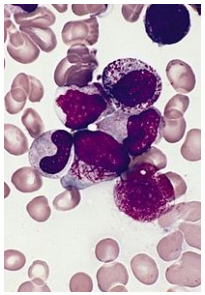
Incidence of pediatric APL: 17% of all childhood AML

❑ Differentiation Syndrome

❑ Relapse: Salvage Treatment

Cumulative incidence of relapse: GIMEMA/AIEOP AIDA 0493 – 2000 and ICC APL 01





DIFFERENTIATION SYNDROME

- Following the initiation of ATRA treatment: risk of differentiation syndrome (DS)
- ATRA induces the differentiation of APL blasts to mature myeloid cells, and when this occurs in excess, DS can result, leading to life-threatening complications
- Symptoms: weight gain, fever, respiratory distress, hypotension and even renal failure
- Patients with HR disease are at greater risk of DS, though it may occur in SR patients

- The early recognition and treatment of DS is necessary to minimize fatalities, and patients should be closely monitored for DS after the initiation of therapy
- Treatment strategies include steroids (dexamethasone) and hydroxyurea as soon as DS is suspected, though leukapheresis should be avoided as it does not affect outcomes and subjects patients to unnecessary bleeding risk
- As DS is a significant contributor to early death in APL, prophylactic low-dose steroids have been employed to prevent DS with successful reductions in DS-related deaths

UNSOLVED PROBLEM: EARLY DEATH

- Early death rate:< 5% in ATRA + chemotherapy clinical trials
- Mortality rate before diagnosis is still unknown
- Possible discordance between clinical trials results and data from real world

Need for continuous educational effort:
primary care
emergency centers

- Improve early diagnosis
- Early referral to specialized centers

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Testi AM *et al*, Blood 2005

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Lo Coco F *et al*, Blood 2010; Testi AM *et al*, Blood 2018

DE-INTENSIFICATION FOR STANDARD RISK PATIENTS — 2008 — **ICC APL01**

Childhood APL:
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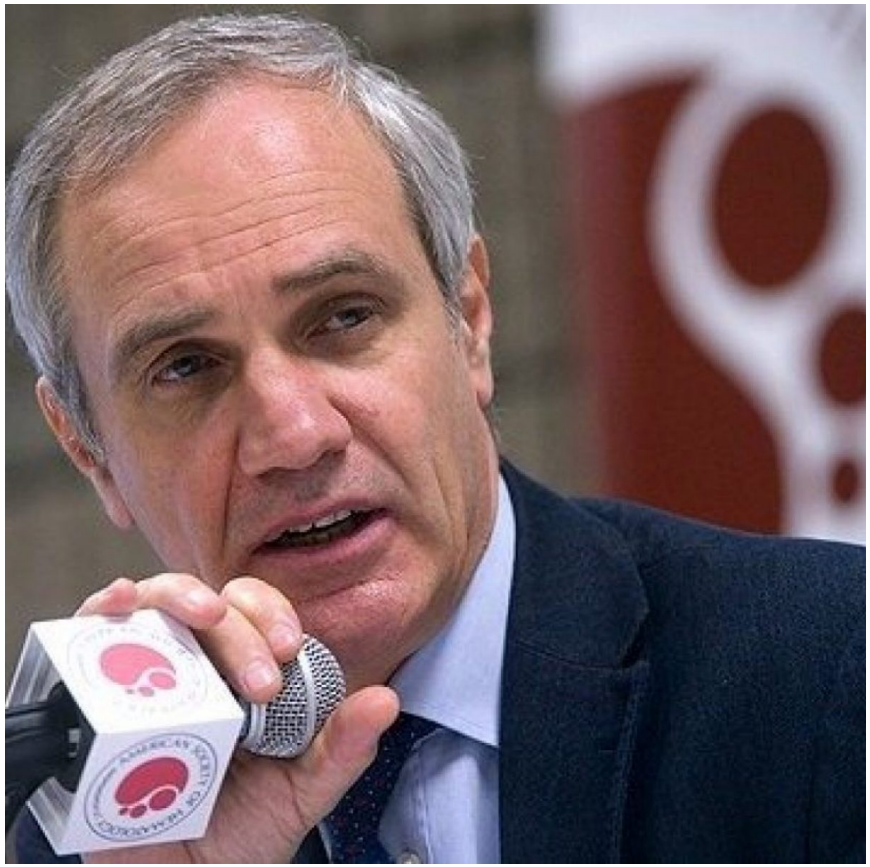
- Maintenance: ATRA+CHT

Testi AM *et al*, Blood 2018

ATO ERA
Additional step in the success story of APL

Prof. Locatelli



THANK YOU FRANCESCO

Scientific Community and all Patients