
Under the auspices of SIE - Società Italiana di Ematologia
7th INTERNATIONAL SYMPOSIUM ON
ACUTE PROMYELOCYTIC LEUKEMIA
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Risk-adapted ATRA and chemotherapy in children with newly diagnosed acute promyelocytic leukemia: a 15-year multicentric experience

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ATRA + CHEMOTHERAPY in APL

- ATRA + anthracycline-based chemotherapy: improved results
- Clinical prognostic factors: WBC and PLTs
- Sanz Risk Criteria (*Blood 2000*):
  - Standard Risk: WBC < 10 x 10^9/l + PLTs > 40 x 10^9/l
  - Intermediate Risk: WBC < 10 x 10^9/l + PLTs ≤ 40 x 10^9/l
  - High Risk: WBC ≥ 10 x 10^9/l
- Risk-adapted protocols were conducted by multicenter groups in Europe, Japan, Unites States and Australia

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GIMEMA/AIEOP AIDA 2000 TRIAL

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- First Italian Risk-adapted trial for newly diagnosed APL (adults and children)
- Consolidation therapy according to risk category:
  - SR + IR: ATRA + anthracyclines
  - HR: ATRA + anthracyclines + intercalating agents

- High cumulative anthracycline doses (650 mg/m^2 daunorubicin-equivalent)

- Accrual: June 2000 – December 2008
- 40 Pediatric AIEOP centres

Only difference between children and adults: *ATRA* *dosage (25 mg/m^2/day vs 45 mg/m^2/day)*

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GIMEMA/AIEOP AIDA2000: Protocol design

Induction

ATRA 25 mg/m²/d
X 30 days
IDA 12 mg/m²/d
(d 2,4,6,8)

SR+IR

CONSOLIDATION

ATRA 25 mg/m²/d
X 15 days
IDA 5 mg/m²/d
(d 1,2,3,4)

ATRA 25 mg/m²/d
X 15 days
MTZ 10 mg/m²/d
(d 1,2,3,4,5)

ATRA 25 mg/m²/d
X 15 days
IDA 12 mg/m²/d
(d 1)

HR

CONSOLIDATION

ATRA 25 mg/m²/d
X 15 days
IDA 5 mg/m²/d
(d 1,2,3,4)
ARA-C 1g/m²/d
(d 1,2,3,4)

ATRA 25 mg/m²/d
X 15 days
MTZ 10 mg/m²/d
(d 1,2,3,4,5)
VP-16 100 mg/m²/d
(d 1,2,3,4,5)

ATRA 25 mg/m²/d
X 15 days
IDA 12 mg/m²/d
(d 1)
ARA-C 150 mg/m²/
8h (d 1,2,3,4,5)
6-TG 70 mg/m²/
8h (d 1,2,3,4,5)

PCR evaluation

negative → **CHT + ATRA**

positive → **SALVAGE**

I.T. chemotherapy for HR

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GIMEMA/AIEOP AIDA-2000 Study
Eligibility

- **Age ≥ 1 and < 61 years**
- **Morphologic diagnosis of APL (ATRA started based on the sole morphological diagnosis of APL – FAB criteria)**
- **Confirmed genetical diagnosis based on the presence of the PML/RARα by RT-PCR or t(15;17) traslocation. Presence of additional cytogenetics lesions is not considered an exclusion criterion**
- **Serum creatinine level < 3 times the normal upper limit**
- **Serum alkaline phosphatase and hepatic transaminases levels < 3 times the normal upper limits**
- **WHO performance status ≤ 3**
- **No cardiac controindication for intensive chemotherapy (L-VEF > 50%)**
- **Written informed consent by patients or parents or legal guardian**

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Baseline features of children enrolled in the GIMEMA/AIEOP AIDA 2000 Trial

Characteristics	Pts 127
Gender: M/F	77/50
Age (yrs): median min – max	11.9 1.1-18.0
WBC count (x 10^9/l): median min - max	3.6 0.2-187.0
Platelet count (x 10^9/l): median min - max	27.5 7.0 – 250.0
FAB type: M3/M3v	105 (82.7%) / 22 (17.3%)
PML/RARα isophorm: BCR 1/2/3/NA*	50/6/37/34
Risk group: Standard + Intermediate/High	85 (67%) / 42 (33%)

* NA: not available

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GIMEMA/AIEOP AIDA 2000 TRIAL: INDUCTION RESULTS

	N. pts
Evaluable pts	**126**
Hematological CR	**121 (96 %)**
Induction death:	**5 (4 %)**
Early death (< 14 days)	**4** [d 1,1,2,10]
Aplastic death	**1** [d 20]
Risk category: SR/HR	**0/5**
Causes od death:	
ICH	**4**
Sepsis	**1**

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GIMEMA/AIEOP AIDA 2000 trial:

PML/RARα 3° consolidation course

GIMEMA/AIEOP AIDA 2000	
RT-PCR	**N. Pts 121**
Negative	**118 (97.5%)**
Positive	**3 (2.5%)**

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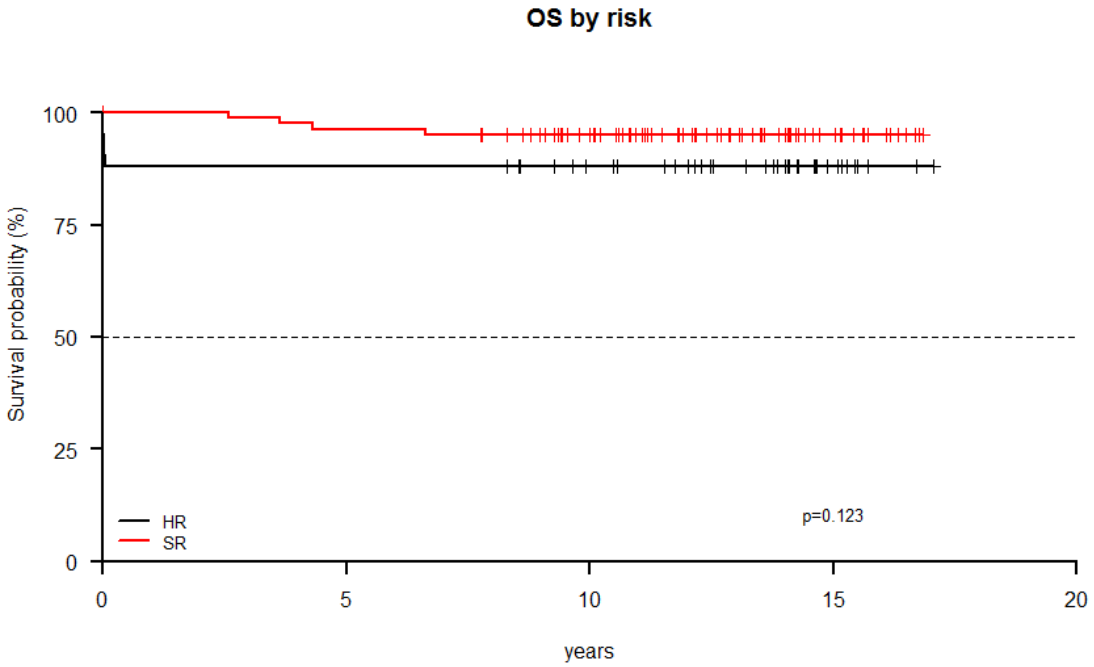
GIMEMA/AIEOP AIDA 2000 trial



risk	years	Survival (%)	Lower 95% Confidence Limit	Upper 95% Confidence Limit
HR	5	88.1	78.8	98.5
SR	5	96.4	92.5	100.0

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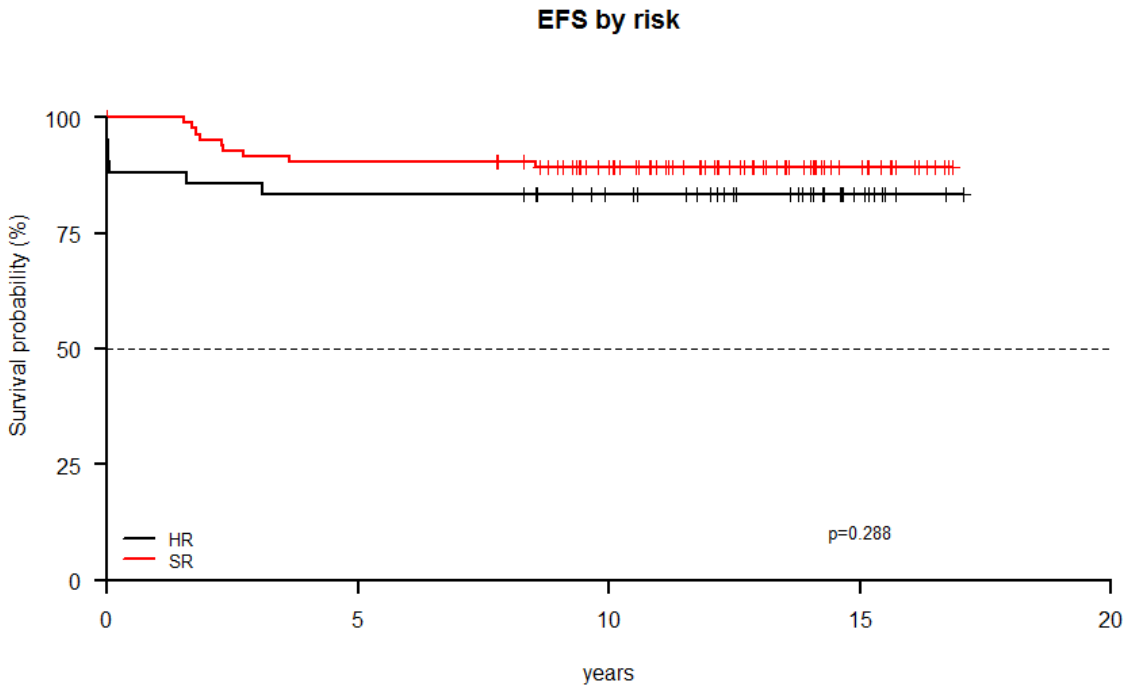
GIMEMA/AIEOP AIDA 2000 trial



risk	years	Survival (%)	Lower 95% Confidence Limit	Upper 95% Confidence Limit
HR	5	83.3	72.8	95.4
SR	5	90.5	84.4	97.0

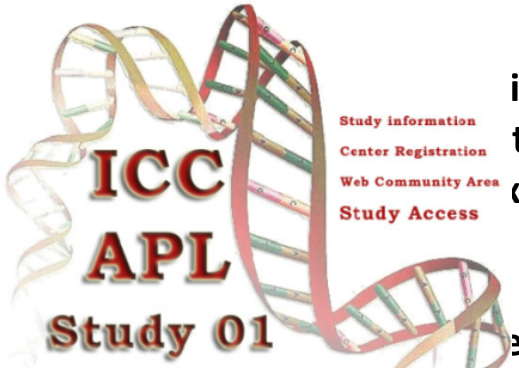
INTERNATIONAL CONSORTIUM FOR CHILDHOOD APL, ICC APL

Background

First multinational, multicenter childhood APL Study 01

EudraCT 2008-002311-40

- The GIMEMA/AIEOP AIDA 2000 trial combining ATRA and anthracyclines at high cumulative doses confirmed the good outcome in children with APL
  EFS 88.1%; OS 93.7%
- Risk-adapted consolida… ive consolidation therapy (no intercalati… ts resulted safe and equally effective, s… icity in this subset of children
- However, high cumula… es significant risk of acute and long-term se… d neoplasms) that could have a relevant impact on long-term outcomes of children with APL



CINECA

Sponsor: AIEOP

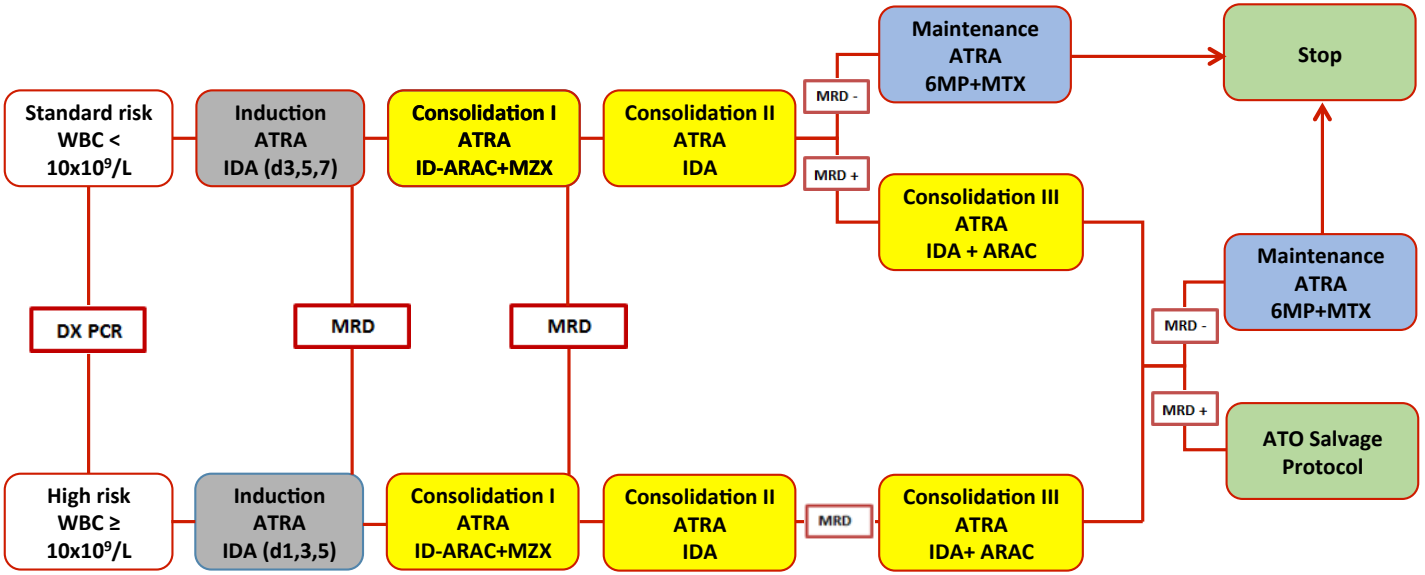
OBJECTIVES

- To deliver risk-stratified treatment according to modified Sanz criteria (SR: WBC count < 10 x10^9/l and HR: WBC ≥ 10 x 10^9/l)

- To reduce cumulative anthracycline dosage
  SR: 355 mg/m^2
  HR: 405 mg/m^2

- To monitor minimal residual disease by RQ-PCR for *PML-RARα* and adjust treatment accordingly

INTERNATIONAL CONSORTIUM FOR CHILDHOOD ACUTE PROMYELOCYTIC LEUKEMIA (ICC APL STUDY 01)



ATRA: 25 mg/m²/day; I.T. chemotherapy for all risks

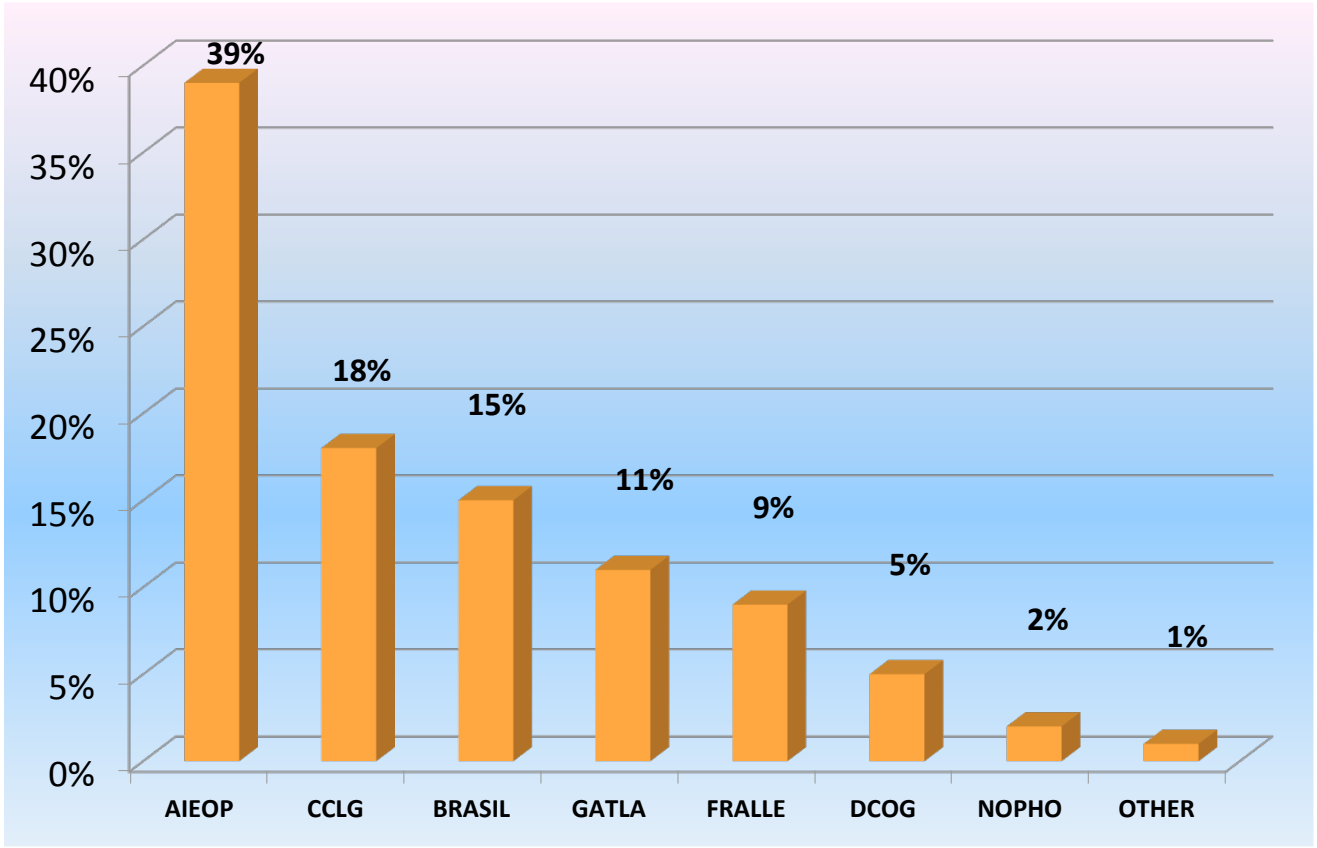
Inclusion Criteria

- Patients with a clinical diagnosis of APL and subsequently confirmed to have *PML-RARα*, *NPM1-RARα* or *NUMA-RARα* fusion transcripts. (APL is a hematological emergency and ATRA should be commenced as soon as the diagnosis is suspected. Treatment should not be deferred until the diagnosis of APL has been confirmed molecularly or cytogenetically)
- Age < 21 years at initial diagnosis (for AIEOP: Age < 18 yrs)
- Considered suitable for anthracycline-based chemotherapy
- Written informed consent available
- Negative pregnancy test for females of childbearing age

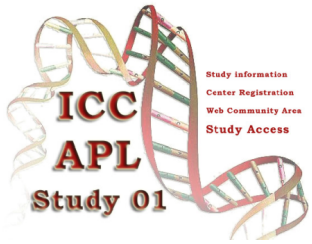
Exclusion Criteria

- Patients with a clinical diagnosis of APL but subsequently found to have *PLZF-RARα* fusion or lacking *PML-RARα*, *NPM-RARα* or *NuMA-RARα* rearrangement should be withdrawn from the study and treated on an alternative protocol
- Refractory/relapsed APL
- Concurrent active malignancy
- Pregnant or lactating patient
- Physician and patient/guardian think that intensive chemotherapy is not an appropriate treatment option
- Patients who have received alternative chemotherapy for 7 days or longer without ATRA for any reason

ICC APL STUDY 01: Distribution of patients by Cooperative Group/country



Baseline features of children enrolled in the ICC APL STUDY 01



Characteristics	PTS: 266
Gender: M/F	141(53.0%) / 125(47.0%)
Age (yrs): median min – max	10.3 1.1-20.7
WBC count (x 10^9/l): median min - max	6.2 0.1-339.0
Platelet count (x 10^9/l): median min - max	23.0 2.0-262.0
FAB type: M3/M3v/NA*	217/44/5
PML/RARα isophorm: BCR 1/2/3/NA*	109/8/106/43
Risk group: SR (%)/ HR (%)	155 (58.3%) / 111 (41.7%)

* NA: not available

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ICC APL Study 01

Baseline features of children enrolled in ICC APL 01 and GIMEMA/AIEOP AIDA 2000 trials

Characteristic	ICC APL 01 Pts 266	AIDA 2000 Pts 127	P value
Median follow-up (years)	4.3 (0.1 – 11.5)	12.9 (7.8 – 17.0)	<.0001
Gender: M/F	125/141	77/50	0.01
Age (yrs): median min - max	10.3 1.1 - 20.7	11.9 1.1 - 18.0	0.23
WBC count (x 10^9/l) median min – max	 6.2 0.1 – 339.0	 3.6 0.2 – 187.0	0.13
Platelet count (x 10^9/l) median min - max	 23 2.0 - 262.0	 27.5 7.0 - 250.0	0.79
FAB type: M3/M3v/NA*	217/44/5	105/22	0.89
PML/RARα isophorm: BCR 1/2/3/NA*	109/8/106/43	50/6/37/34	0.27
SR / HR	155 (58%) / 111 (42%)	85 (67%) / 42 (33%)	0.12

* NA: not available

ICC APL 01 and GIMEMA/AIEOP AIDA 2000 TRIALS: INDUCTION RESULTS

Trial	ICC APL 01	GIMEMA/AIEOP AIDA-2000
Evaluable pts	258	126
Hematological CR	250 (97%)	121 (96%)
Induction death ED/AD Risk category: SR/HR	8 (3%) 8/0 1/7	5 (4%) 4/1 0/5
Causes of Death: ICH Sepsis	 8 -	 4 1

P-value: 0.76

ICC APL 01 Trial: PML/RARα after 2° and 3° consolidation course

PML/RARα	SR	HR	Total
	N. Pts 125	N. Pts 93	N. Pts 218
2°cons			
Negative	117 (93.6%)	64/68 (94.2%)	181 (93.7%)
Positive	8 (6.4%)	4/68 (5.8%)	12 (6.2%)
Not done	-	25	25
3° cons			
Negative	122 (97.6%)	91 (97.8%)	213 (97.7%)
Positive	3 (2.4%)	2 (2.2%)	5 (2.3%)

ICC APL 01 and GIMEMA/AIEOP AIDA 2000 trials: PML/RARα end consolidation course

PML/RARα	ICC APL 01	AIDA-2000
	N. Pts 218	N. Pts 121
Negative	213 (97.7%)	118 (97.5%)
Positive	5 (2.3%)	3 (2.5%)

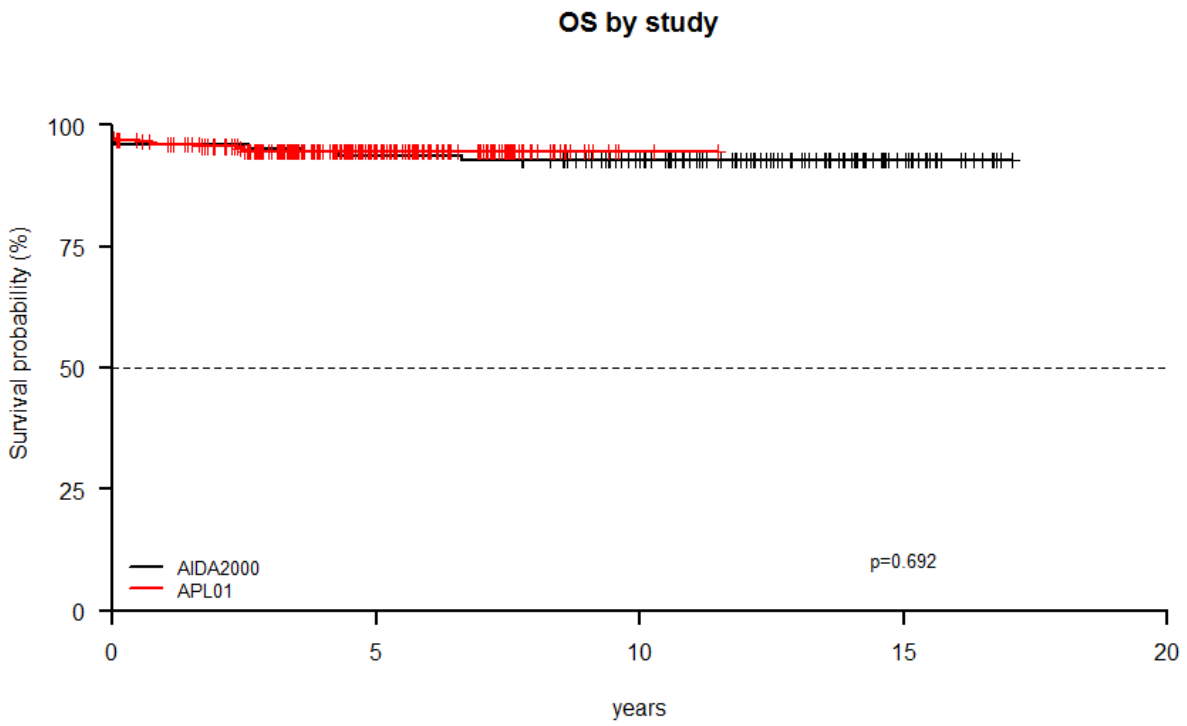
p-value: 1.0

ICC APL STUDY 01 and AIDA 2000: Post-consolidation events

	ICC APL 01 N. pts	AIDA 2000 N. pts
Evaluable patients	213	118
Death in mCR	1	0
Relapses	27	11
Type of relapse (median time to relapse - months) :		
Hematological	5 SR; 5 HR 10 (15.0)	4 SR; 2 HR 6 (25.5)
Molecular	8 SR; 8 HR 16 (24.8)	4 SR; 1 HR 5 (21)
Extramedullary	1 (43)	-
Alive with salvage therapy	25/27*	8/11
2° Neoplasm	2 (thyroid cancer; t-AML)	4 (t-AML 2; thyroid cancer 1; Ewing sarcoma 1)
Median Follow-up (years)	4.3 (range: 0.1-11.5)	12.9 (7.8 – 17)

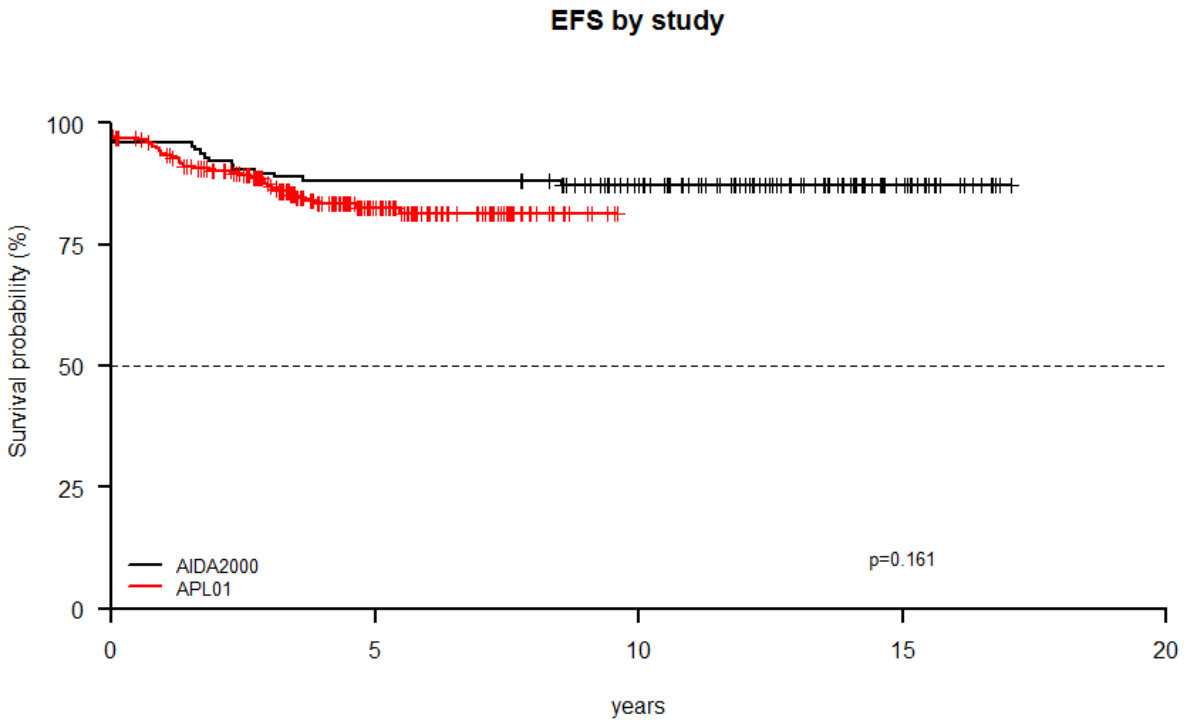
*ATO salvage therapy; Allo-HSCT in 5: 4 alive, 1 transplant-related death

ICC APL 01 and GIMEMA/AIEOP AIDA 2000



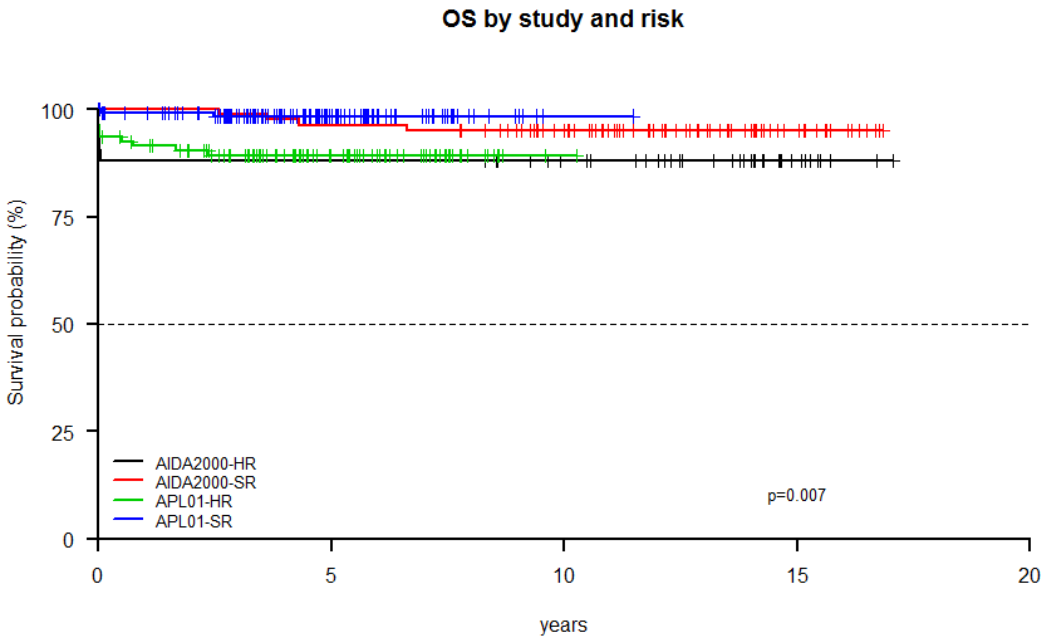
study	years	Survival (%)	Lower 95% Confidence Limit	Upper 95% Confidence Limit
AIDA2000	5	93.7	89.5	98.0
APL01	5	94.6	91.7	97.5

ICC APL 01 and GIMEMA/AIEOP AIDA 2000



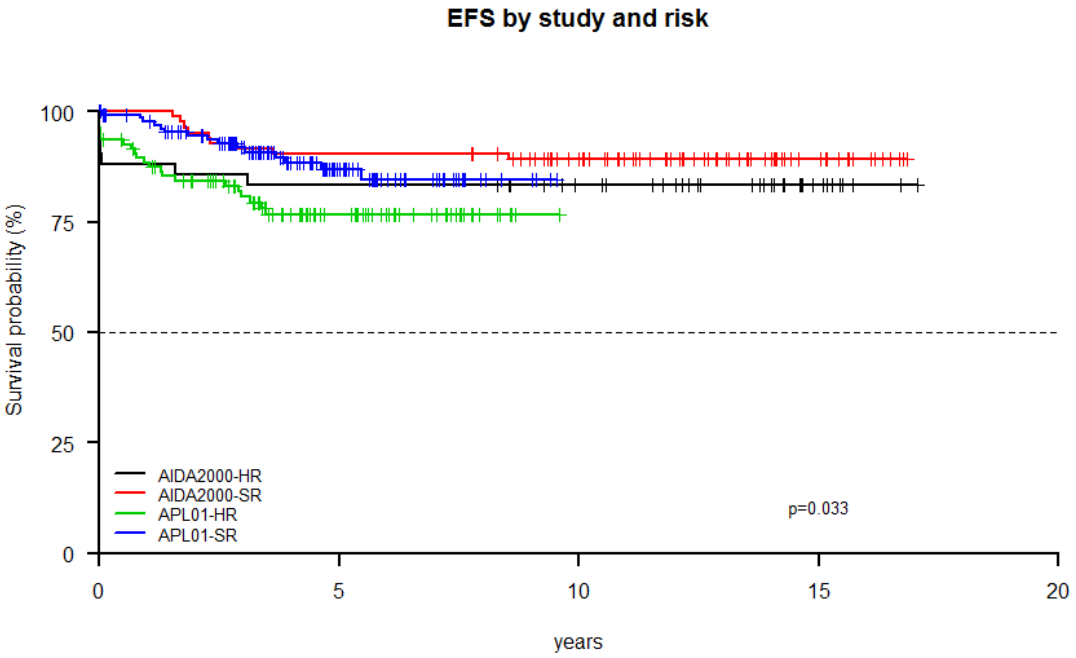
study	years	Survival (%)	Lower 95% Confidence Limit	Upper 95% Confidence Limit
AIDA2000	5	88.1	82.6	93.9
APL01	5	82.4	77.2	88.0

ICC APL 01 and GIMEMA/AIEOP AIDA 2000



study	risk	years	Survival (%)	Lower 95% Confidence Limit	Upper 95% Confidence Limit
AIDA2000	HR	5	88.1	78.8	98.5
AIDA2000	SR	5	96.4	92.5	100.0
APL01	HR	5	89.4	83.6	95.5
APL01	SR	5	98.5	96.4	100.0

ICC APL 01 and GIMEMA/AIEOP AIDA 2000



study	risk	years	Survival (%)	Lower 95% Confidence Limit	Upper 95% Confidence Limit
AIDA2000	HR	5	83.3	72.8	95.4
AIDA2000	SR	5	90.5	84.4	97.0
APL01	HR	5	76.6	68.3	85.8
APL01	SR	5	86.8	80.4	93.8

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COMMENTS

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

- **Largest pediatric multicenter APL cohort treated with specific risk-adapted protocols based on extended ATRA**

- **Risk-adapted consolidation strategy, resulted in excellent outcome of SR children with newly diagnosed APL**
  - **no intercalating agents, AIDA 2000 → OS 96.4%; EFS 90%**
  - **reduced cumulative anthracycline dose, ICC APL 01 → OS 98.5%; EFS 87%**

- **The role of other risk-factors is ongoing:**
  - **biological parameters (FLT3-ITD; CD56; CD2/CD34; additional gene mutation)**
  - **according to the different therapeutic strategies including ATO**


thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
merci
obrigado
bedankt
dziękuję
спасибо
go raibh maith agat
mochchakkeram
sukriya
kop khun krap
terima kasih
grazie
arigatô
dakujem
takk
tapadh leat
dank je
hvala
mauruuru
sagolun
taiku
мерси
감사합니다
ありがとう
ευχαριστώ
рахмат
Баярлалаа
faafetai lava
kiitos
dhanyavad
dankie
blagodaram
vinaka
mersi
barka
welalin
tack
spas
misaotra
matondo
paldies
grazzi
mahalo
хвала
asante
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obrigada
tenki
murakoze
chokrane
mamnun
djiere dieuf
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дякую
sulpáy
chnorakaloutioun
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gràcies
akun
dankon
enkosi
nanni
nandri
bayarlalaa
gràcie
köszönöm
sobodi
dekuji
mèsi
didi madloba
najis tuke
kam sah hamnida
rahmat
tanemirt
rahmet
diolch
dhanyavadagalu
shukriya
mercé
trugarez
xiexie


hello! come with

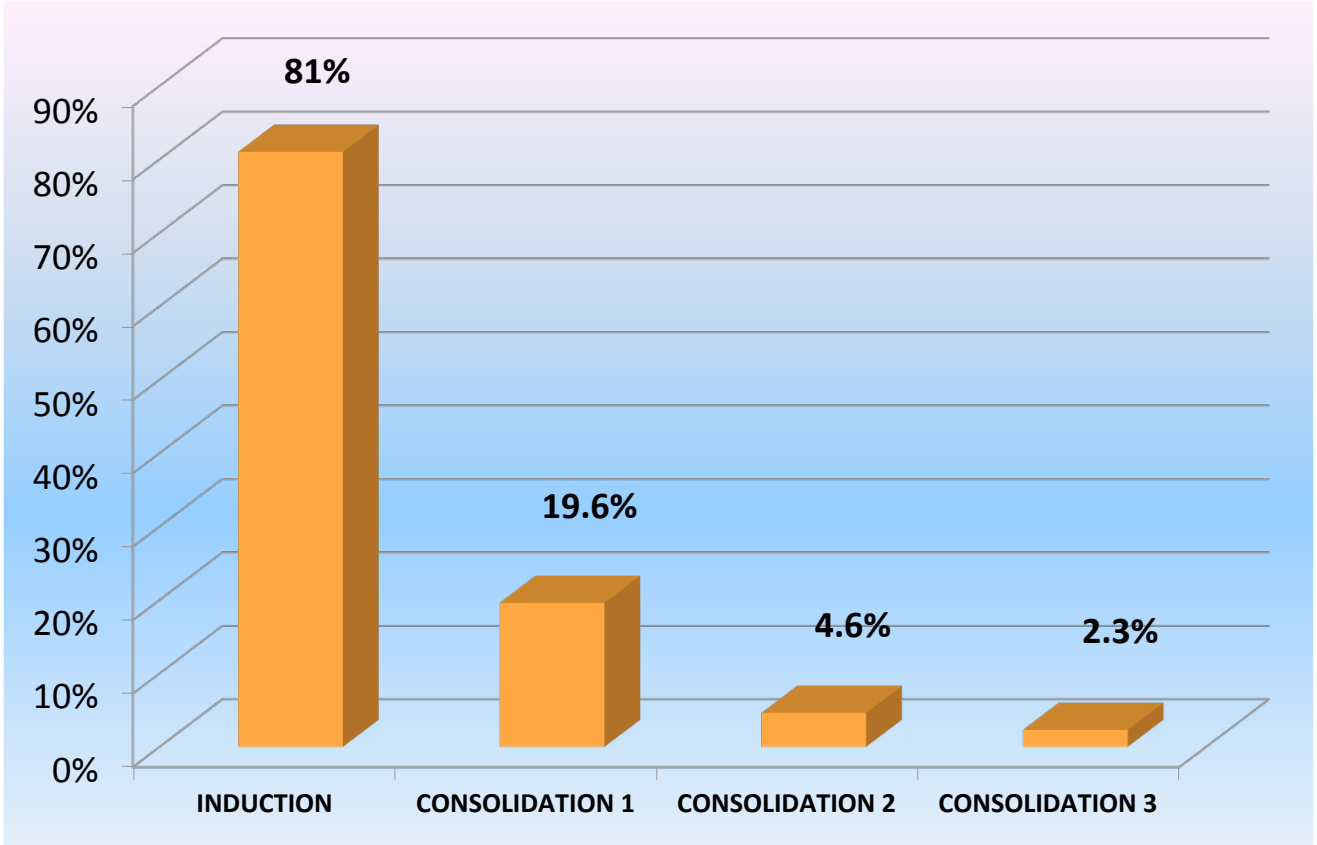
ICC APL STUDY 01: Induction Toxicity

	ICC APL 01
Symptoms of DS	11%
Pseudotumor Cerebri	6%
Hemorrhage (WHO ≥3)	4%^
Thrombosis (WHO ≥3)	1%
FUO	42%
Infections	37%*
Liver toxicity (WHO=3)	1%

*30% blood coltures positive; 5% sepsis; 2% local
^ 3% fatal

ICC APL STUDY 01: MRD monitoring

% of PCR positive patients at different time-points



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GIMEMA/AIEOP AIDA 2000: Post-consolidation events

	No. of Patients
Evaluable patients	118
Death in mCR	0
Relapses	11
Type of relapse (median time to relapse) :	
Hematological	4 SR; 2 HR — 6 (25.5 months)
Molecular	4 SR; 1 HR — 5 (21.0 months)
Alive with salvage therapy	8/11
2° Neoplasm	4 (t-AML 2; thyroid cancer 1; Ewing sarcoma 1)
Median Follow-up (years)	12.9 (range: 7.8 -17.0)

ICC APL STUDY 01: Post-consolidation events

		No. of Patients
Evaluable patients		213
Death in mCR		1
Relapses		27
Type of relapse (median time to relapse) :		
Hematological	5 SR; 5 HR	10 (15.0 months)
Molecular	8 SR; 8 HR	16 (24.8 months)
Extramedullary		1 (43 months)
Alive with salvage therapy		25/27*
2° Neoplasm		2 (thyroid cancer; t-AML)
Median Follow-up (years)		4.3 (range: 0.1-11.5)

*HSCT: 5; 4 alive, 1 transplant-related death