AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

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Segreteria Scientifica
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Giornate AIEOP

Leucemia acuta non linfoblastica

BOLOGNA
Zanhotel Europa

14-15 Aprile 2025

Franco Locatelli

Università Cattolica del Sacro Cuore

IRCCS Ospedale Pediatrico Bambino Gesù, Roma

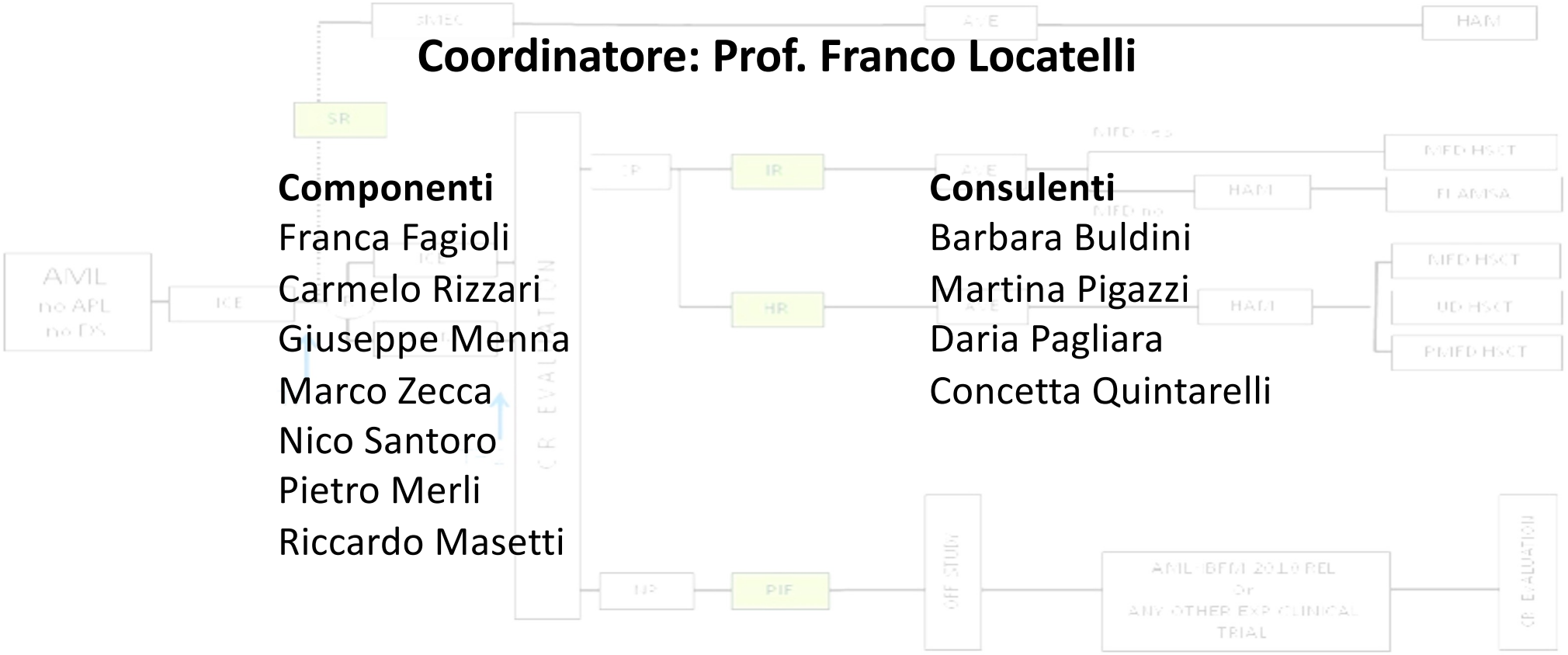
Disclosures of Franco Locatelli

Name of Company	Research Support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Miltenyi					X		
Amgen					X	X	
Novartis					X	X	
BMS					X		
GILEAD					X		
Sanofi						X	
SOBI					X		
Vertex						X	

AIEOP ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

GdL Leucemia acuta non Linfoblastica (LAnL)

Coordinatore: Prof. Franco Locatelli



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MEETING AGENDA APRIL 15TH, 2025

- Update on AIEOP-BFM-AML 2020 protocol
- Scientific papers
- Update on ML-DS 2018 protocol
- Update on ICC APL study 02

AIEOP-BFM-AML 2020: PROTOCOL

INTERNATIONAL MULTICENTER, OPEN-LABEL CLINICAL TRIAL FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA IN CHILDREN AND ADOLESCENTS

Coordinating Investigator	Coordinating Investigator
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AIEOP-BFM-AML 2020: RISK STRATIFICATION

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Risk stratification

RISK GROUP	GENETIC RISK CRITERIA	RESPONSE CRITERIA

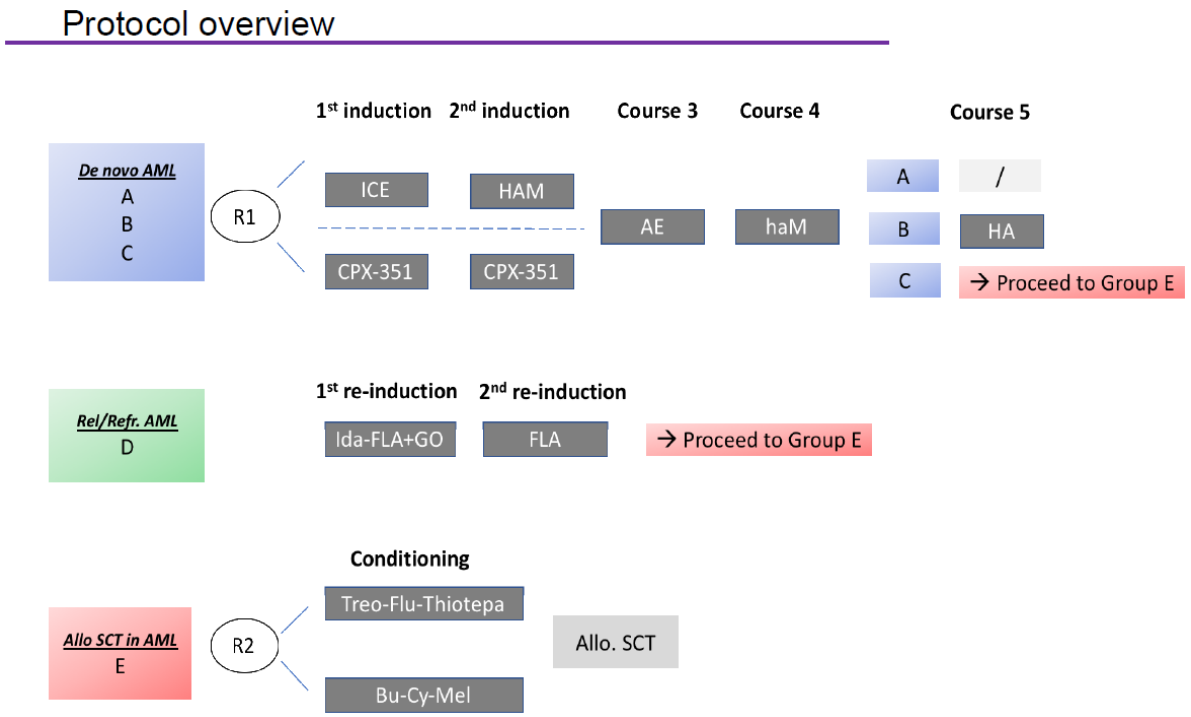
STANDARD RISK (SR)	• CBFβ abnormalities
	  • t(8;21)(q22;q22) with adequate (≥ 2 log) reduction by qPCR at IND 2
	  • inv(16)(p13q22)/t(16;16)(p13;q22)
	• Biallelic CEBPα aberrations
	• t(16;21) *CBFA2T3/RUNX1*
	
	and FLT3-ITD negative
		Genetic standard risk and
		• MRD <0.1% at IND 1
		
		t(8;21) and
		• MRD > 2 log reduction at IND 2 (qPCR)

INTERMEDIATE RISK (IR)	• NON SR and NON HR patients	Genetic standard or intermediate risk and • MRD at IND 1 ≥ 0.1% and < 1% and MRD at IND 2 < 0.1%

HIGH RISK (HR)	• Complex karyotype (≥ 3 aberrations including at least one structural aberration) *excluding those with recurrent translocations*
	• Monosomal Karyotype, i.e. -7, -5/del(5q)
	• 11q23/*KMT2A* rearrangements involving:
	  • t(4;11)(q21;q23) KMT2A/AFF1
	  • t(6;11)(q27;q23) KMT2A/AFDN
	  • t(10;11)(p12;q23) KMT2A/MLLT10
	• t(16;21)(p11;q22) FUS/ERG
	• t(9;22)(q34;q11.2) BCR/ABL1
	• t(6;9)(p22;q34) DEK/NUP214
	• t(7;12)(q36;p13) MNX1/ETV6
	• inv3(q21q26)/t(3;3)(q21;q26) RPN1/MECOM
	• 12p abnormalities
	• *FLT3-ITD* with AR ≥ 0.5 not in combination with other recurrent abnormalities or NPM1 mutations
	• *WT1* mutation and *FLT3-ITD*
	• *inv(16)(p13q24) CBFA2T3/GLIS2*
	• *t(5;11)(q35;p15.5) NUP98/NSD1 and t(11;12)(p15;p13) NUP98/KDM5A*
	• Pure Erythroid leukemia
		• MRD ≥ 1% at IND 1 or ≥ 0.1% at IND 2 or (only if FLOW-result not available/informative) blast count ≥5% at IND 1

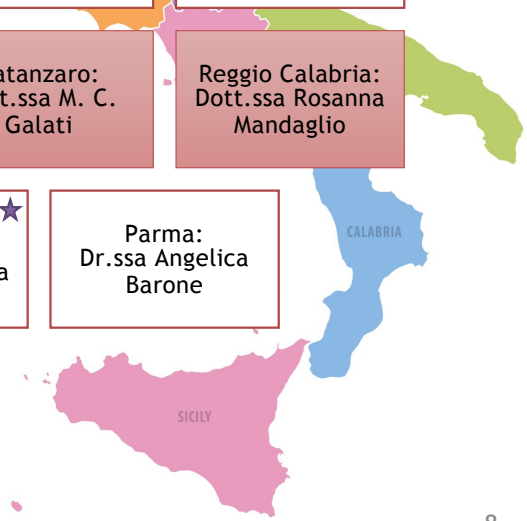
- *If Isolated t(8;16) and/or t(11;16) occur in patients below 1 month of age a watch and wait strategy is recommended*
- *GATA 1 screening will be performed in all patients and if mutations leading to exclusive GATA1s expression are found, these patients will be treated according to the Down Syndrome AML Protocol*

AIEOP-BFM-AML 2020: PROTOCOL OVERVIEW



AIEOP-BFM-AML 2020: Participating Centers (27)

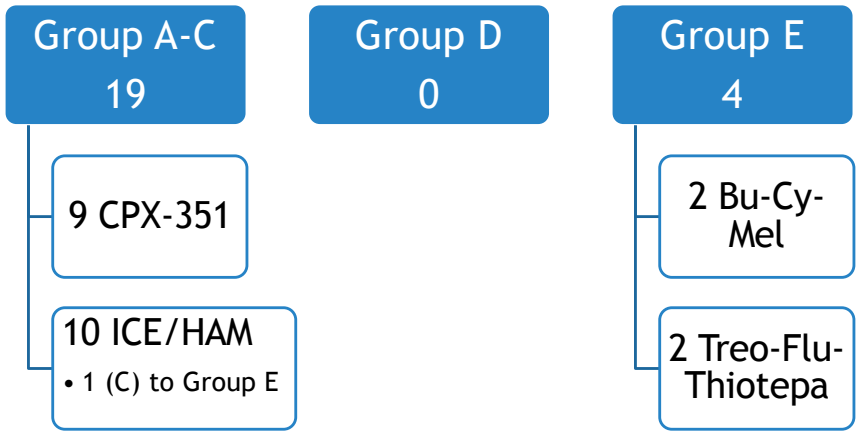
Roma OPBG: Prof. Franco Locatelli	Torino: Prof.ssa Franca Fagioli	Genova: Dott.ssa Concetta Micalizzi	Monza: Prof. Carmelo Rizzari ★	Pavia: Prof. Marco Zecca ★	Bergamo: Dott. Massimo Provenzi	Brescia: Prof. Fulvio Porta ★
Padova: Dott.ssa Manuela Tumino ○	Verona: Dott. Simone Cesaro	Trieste: Dott. Marco Rabusin	Bologna: Prof. Riccardo Masetti ○	Firenze: Dott.ssa Elena Sieni	Pisa: Dott.ssa M. V. Micheletti	Ancona: Dott.ssa Simona Gobbi ★
Pescara: Dott.ssa Nicole Santoro ★	Napoli II Università: Prof.ssa Francesca Rossi	Napoli Santobono Pausilipon: Dott.ssa Rosanna Cuccurullo	Lecce: Dott.ssa Daniela Rizzo	Bari: Dott. Nicola Santoro ★	Catanzaro: Dott.ssa M. C. Galati	Reggio Calabria: Dott.ssa Rosanna Mandaglio
Palermo: Dott. Paolo D'Angelo	Catania: Dott. Luca Lo Nigro	Cagliari: Dott.ssa Rosamaria Mura	Taranto: Dott. Valerio Cecinati	San Giovanni Rotondo: Dott.ssa Raffaela De Santis ★	Parma: Dr.ssa Angelica Barone	



Recruiting
★ Next opening
○ Legal exceptions – Negotiation of the site agreement directly with GPOH

AIEOP-BFM-AML 2020: ENROLLMENT STATUS

Enrollment: 22
Randomization: 23 (1 Group C → E)



OPBG - 2 additional pre-identified cases in April:
1 patient for Group E (other front-line protocol)
1 patient Group C to Group E

6/14 centers at least 1 patient

OPBG: 14 (15 randomizations)	•Group A-C: 11 (7 CPX-351 + 5 ICE/HAM) •Group E: 2 Bu-Cy-Mel + 1 Treo-Flu-Thiotepa (previously C)
Bergamo: 1	•Group A-C: 1 ICE/HAM
Palermo: 2	•Group A-C: 2 ICE/HAM
Napoli Santobono: 2	•Group A-C: 1 CPX-351 + 1 ICE/HAM
Torino: 3	•Group A-C: 2 ICE/HAM •Group E: 1 Treo-Flu-Thiotepa
Cagliari: 1	•Group A-C: 1 CPX-351

AIEOP-BFM-AML 2020: TAKE HOME MESSAGES

For the not recruiting centers:	Prioritize with your legal office the finalization of the site agreement in order to activate soon your site
For the recruiting centers:	Accelerate the data entry for the enrolled patients

COG AAML1831

A Phase 3 Randomized Trial for Patients with de novo AML Comparing Standard Therapy Including GO to CPX-351 with GO

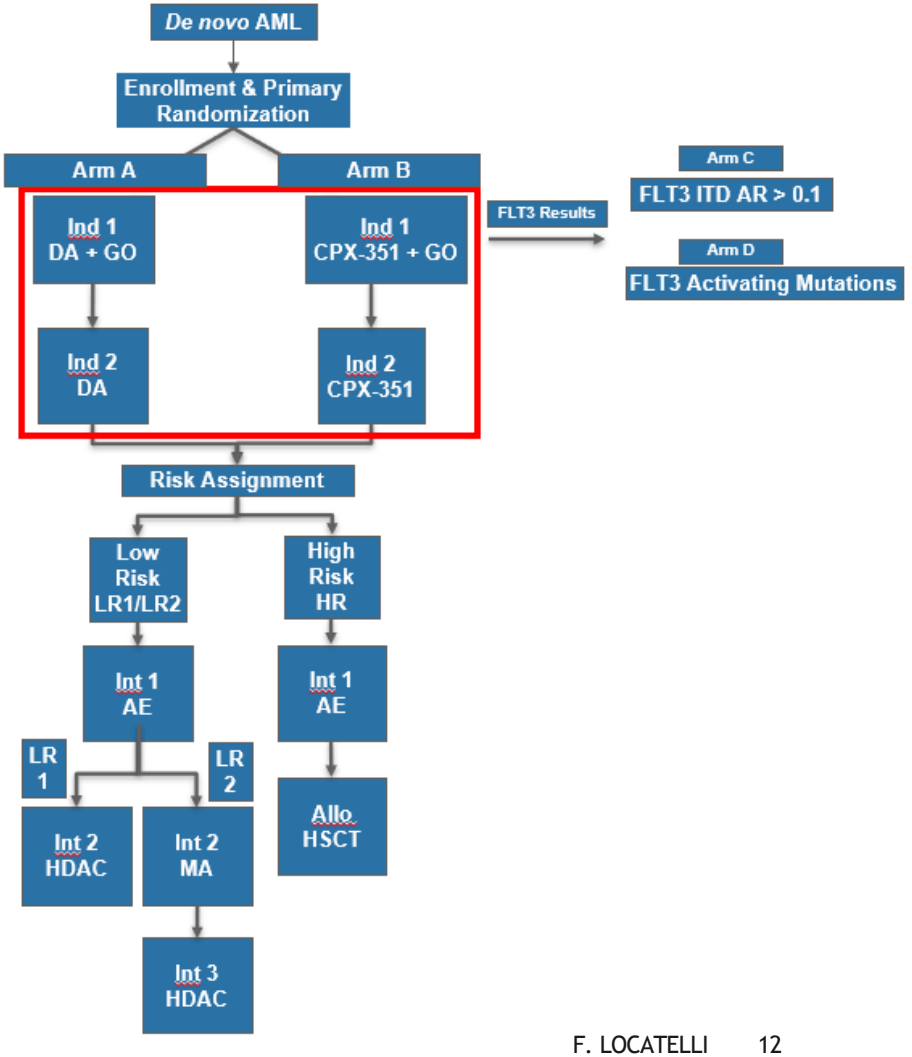
COG AAML1831: SCHEMA

Arm A

- Induction 1 DA(10)+GO
  - Daunorubicin 50mg/m2/dose; d 1, 3, 5
  - Cytarabine 100mg/m2/dose BID; d1-10
  - GO 3mg/m2 x 1 on D6
- Induction 2 DA(8)

Arm B

- Induction 1 CPX-351 + GO
  - CPX-351 d 1, 3, 5
    - Daunorubicin 60mg/m2/dose
    - Cytarabine ~135 mg/m2/dose
    - GO 3mg/m2 x 1 on D6
  - Induction 2 CPX-351 d 1, 3, 5
    - Daunorubcin 50 mg/m2/dose
    - Cytarabine ~115mg/m2/dose



COG AAML1831: INTERIM ANALYSIS

Protocol included interim analyses of efficacy and futility

Study opened 7/20/20 and closed 3/5/24

886 total patients with well-balanced randomization

- Arm A (DA+GO): 358
- Arm B: (CPX351+GO): 363

Patient characteristics (gender, age, race, ethnicity) were not significantly different ($p>0.05$) when comparing proportions for Arm A vs Arm B except for:

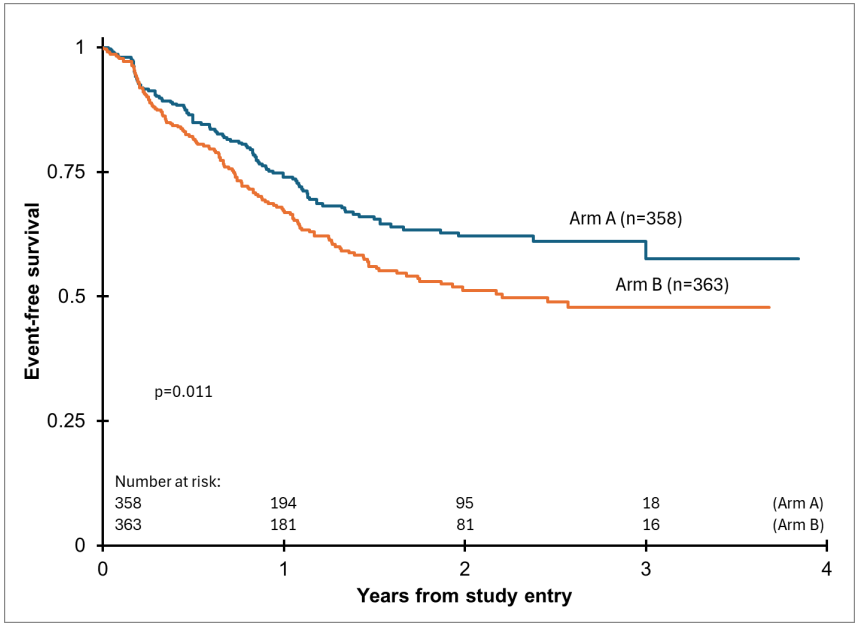
- Median peripheral WBC: Arm A:11.34 vs Arm B:17.01 ($p=0.048$)
- CNS1 status: Arm A: 86% vs Arm B: 79% ($p=0.027$)

ARM A AND ARM B PATIENTS WITHOUT FLT3 MUTATIONS

254 events (59.3% of the expected information) have been observed in patients without FLT3 mutations (110 Arm A, 144 Arm B)

Type of EFS Event	Arm A (N=358) (DA+GO)	Arm B (N=363) (CPX-351)	Chi-square P
Total	110 (30.7%)	144 (39.7%)	0.01
Induction Failure	17 (4.7%)	24 (6.6%)	0.28
Relapse	75 (20.9%)	96 (26.4%)	0.08
Death	18 (5%)	24 (6.6%)	0.36

2-YR EFS FROM STUDY ENTRY: ARM A VS ARM B



Overall: 56.7% (95% CI: 52.3-60.8)

Arm A (DA+GO): 62.2% (95% CI: 56.0-67.8)

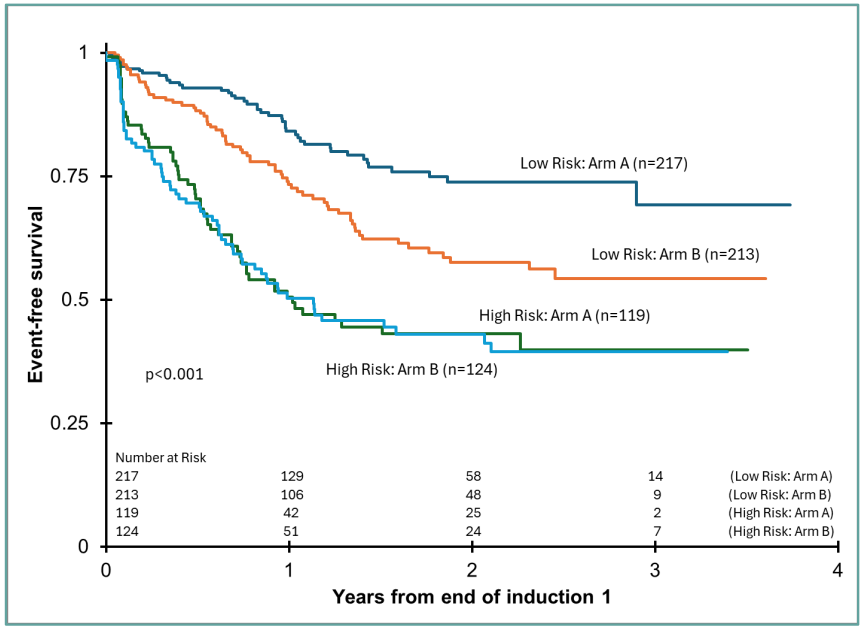
Arm B (CPX+GO): 51.2% (95% CI: 45.0-57.2)

P-value: 0.011

Futility: testing the hypothesis that the EFS relative hazard rate for Arms A and B without FLT3 mutations is 0.762 yields a p-value <0.0001.

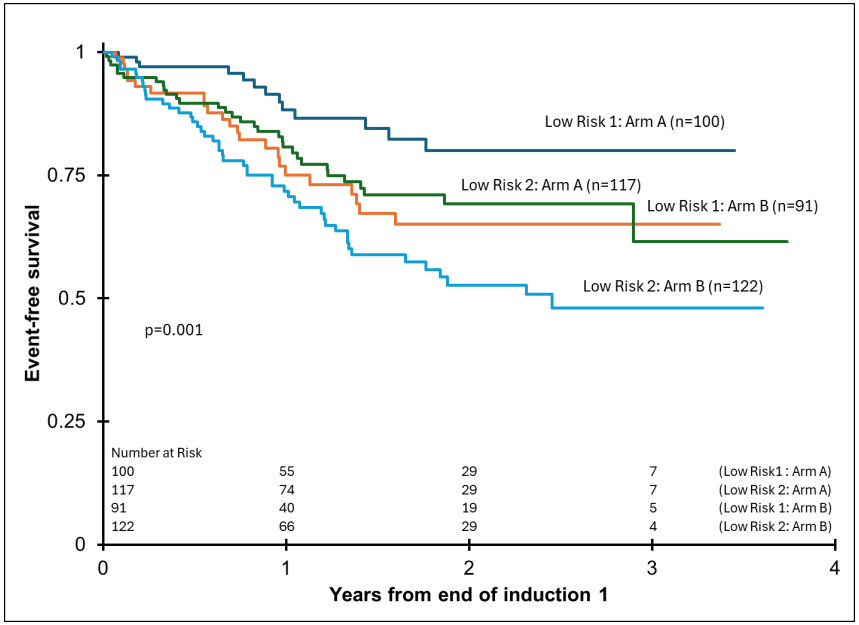
The futility monitoring rule is crossed

2-YR EFS FROM EOI1 BY RISK GROUP



Low Risk (LR)	Arm A (DA+GO):73.8% (95% CI: 66.0-80.2)
	Arm B (CPX+GO): 57.5% (95% CI: 49.0-65.1)
	p-value:<0.001
High Risk (HR)	Arm A (DA+GO): 43.1% (95% CI: 32.9-52.9)
	Arm B (CPX+GO): 43.0% (95% CI: 33.2-52.4)
	p-value:0.871

EFS/OS/CIR FROM EOI1 FOR LOW-RISK PATIENTS



	LR1: Arm A (DA+GO)		LR1: Arm B (CPX+GO)		P-value
	N	% (95% CI)	N	% (95% CI)	
2-year EFS	**100**	**80.1% (67.4-88.2)**	**91**	**65.0% (51.5-75.6)**	**0.019**
2-year OS	100	96.4% (88.8-98.9)	91	91.6% (81.7-96.3)	0.145
2-year CI to relapse	**100**	**17.9% (9.2-28.9)**	**91**	**31.4% (20.0-43.5)**	**0.029**

	LR2: Arm A (DA+GO)		LR2: Arm B (CPX+GO)		P-value
	N	% (95% CI)	N	% (95% CI)	
2-year EFS	**117**	**69.2% (58.5-77.7)**	**122**	**52.7% (41.7-62.6)**	**0.024**
2-year OS	117	83.6% (74.3-89.8)	122	80.7% (70.4-87.8)	0.769
2-year CI to relapse	**117**	**27.9% (19.0-37.6)**	**122**	**45.5% (34.7-55.7)**	**0.015**

COG AAML1831: TOXICITY COMPARISON

	Induction 1		Induction 2	
Arm	A (DA+GO)	B (CPX-351)	A (DA+GO)	B (CPX-351)
N	355	358	311	305
ANC recovery (≥ 500)	74.4%	75.6%	82.6%	75.1%
Median time to ANC recovery (days)	30	33	28	39
Median course length (days)	35	38	35	44
Grade 3+ infection	20.6%	23.7%	7.4%	27.2%
Grade 3 Sepsis	8.5%	5.2%	3.2%	13.8%
Grade 4+ sepsis	0.8%	0.6%	0.3%	1.6%
Death	1.7%	1.4%	0.6%	1.0%

DIAGNOSIS AND MANAGEMENT OF ACUTE MYELOID LEUKEMIA IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

Consensus Recommendations from an International Pediatric Expert Panel on Behalf of the European LeukemiaNet

A MASSIVE COLLABORATIVE EFFORT

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Todd Cooper
Barbara De Moerloose
Michael Dworzak
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Andy Kolb
Dirk Reinhardt
Sarah Tasian
Daisuke Tomizawa
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Maddelena Benetton
Richard Dillon
Hélène Lapillonne
Margarita Maurer-Granofszky
Milica Miladinovic
Karin Nebral
Kees-Jan Pronk
Claire Schwab
Claudia Tregnago
Vincent van der Velden
Nils von Neuhoff
Harm van Tinteren

RATIONALE FOR INTERNATIONAL CONSENSUS PAPER

Adult ELN – impactful, influential, educational.

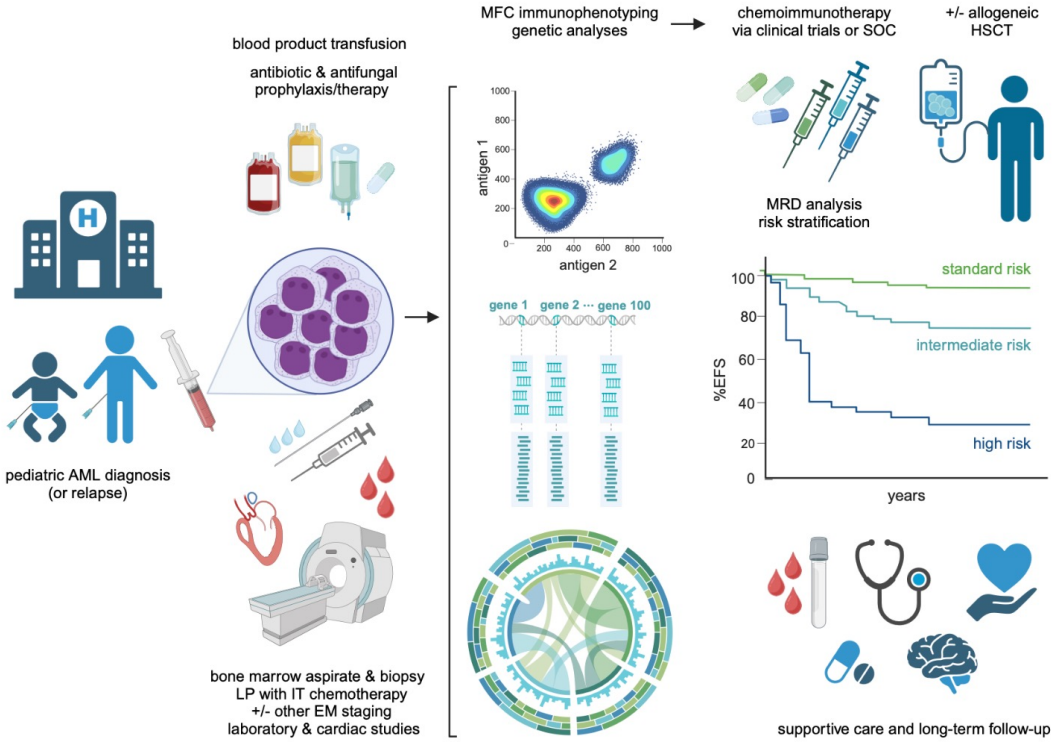
No International Consensus recommendations since 2012, Creutzig et al.

Support of European LeukemiaNet(ELN) enhances impact of manuscript.

Peds AML – unique cytomolecular features; opportunity to share advances in diagnostic/response modalities, therapy, risk, supportive care.

Potential opportunity to solidify international recommendations that could impact standard practice and perceived regulatory hurdles.

INTERNATIONAL CONSENSUS RECOMMENDATIONS



INTERNATIONAL CONSENSUS PAPER: COMPONENTS

Diagnostics
Genetic Characteristics
Peds AML Classification
Risk Stratification
Special Conditions: APL, Germline predisposition, t-AML (MN-pCT), TAM, ML-DS
Response Assessment
Therapy – de novo; CNS-directed, HSCT, Off therapy monitoring, relapse
Clinical Trials – efficacy endpoints, safety endpoints, DLTs, PROs, statistical considerations in early phase trials
Supportive Care – antibiotic prophylaxis, antifungal prophylaxis, cardiac toxicity, hematopoietic growth factors

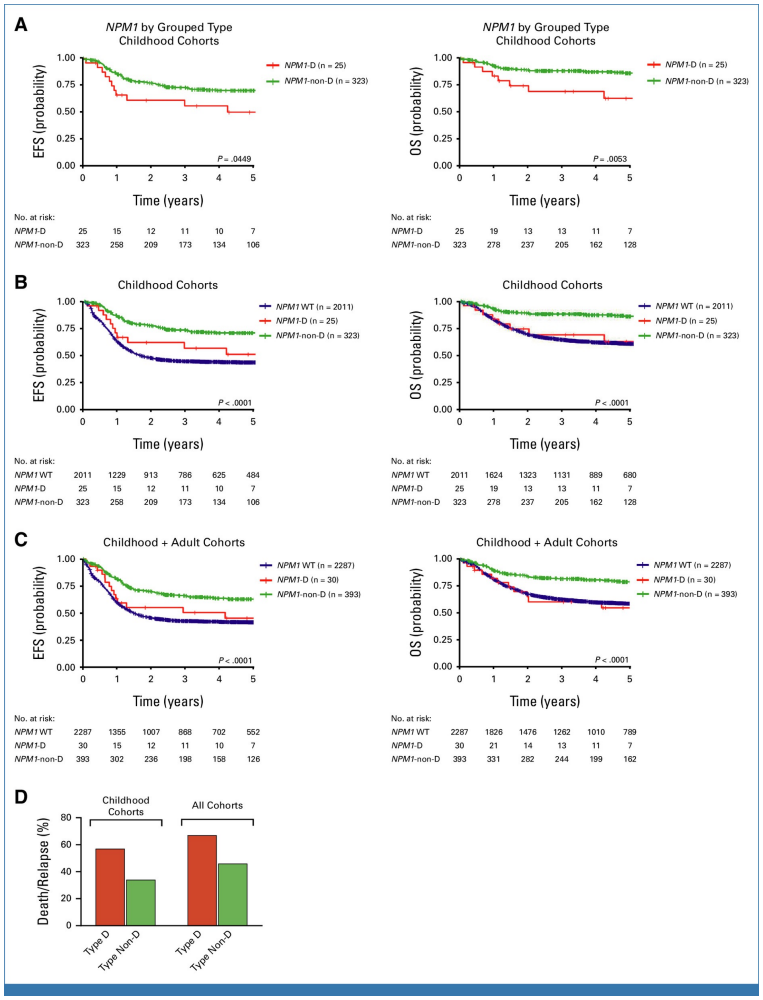


FIG 2. Influence of type D NPM1 on survival in AML pediatric and adult cohorts. (A and B) Kaplan-Meier curves for EFS and OS of type D versus type non-D NPM1 AML pediatric patients (P = .0449 and P = .0053 in EFS and OS, respectively, A), and including AML pediatric patients with wild-type NPM1 (P < .0001 in EFS and OS, B). (C) Kaplan-Meier curves for EFS and OS among type D, type non-D NPM1 AML and NPM1-WT, merging pediatric (n = 2359) and adult (n = 351) patients (P < .0001 in EFS and OS). (D) Incidence of death among patients with relapsed AML in the childhood cohorts (type D: four dead of seven relapsed patients, 57%; type non-D: 23 dead of 68 relapsed patients, 34%), and in all cohorts including adults (type D: six dead of nine relapsed patients, 67%; type non-D: 48 dead of 104 relapsed patients, 46%). EFS, event-free survival; OS, overall survival; WT, wild type.

Published in: Claudia Tregnago; Maddalena Benetton; Rhonda E. Ries; Jack H. Peplinski; Todd A. Alonzo; Derek Stirewalt; Megan Othus; Nicolas Duployez; Edwin Sonneveld; Jonas Abrahamsson; Linda Fogelstrand; Nils von Neuhoff; Henrik Hasle; Dirk Reinhardt; Soheil Meshinchi; Franco Locatelli; Martina Pigazzi JCO 2024 12-2

ML-DS 2018

Phase III clinical trial for CPX-351 in myeloid leukemia in children with Down syndrome

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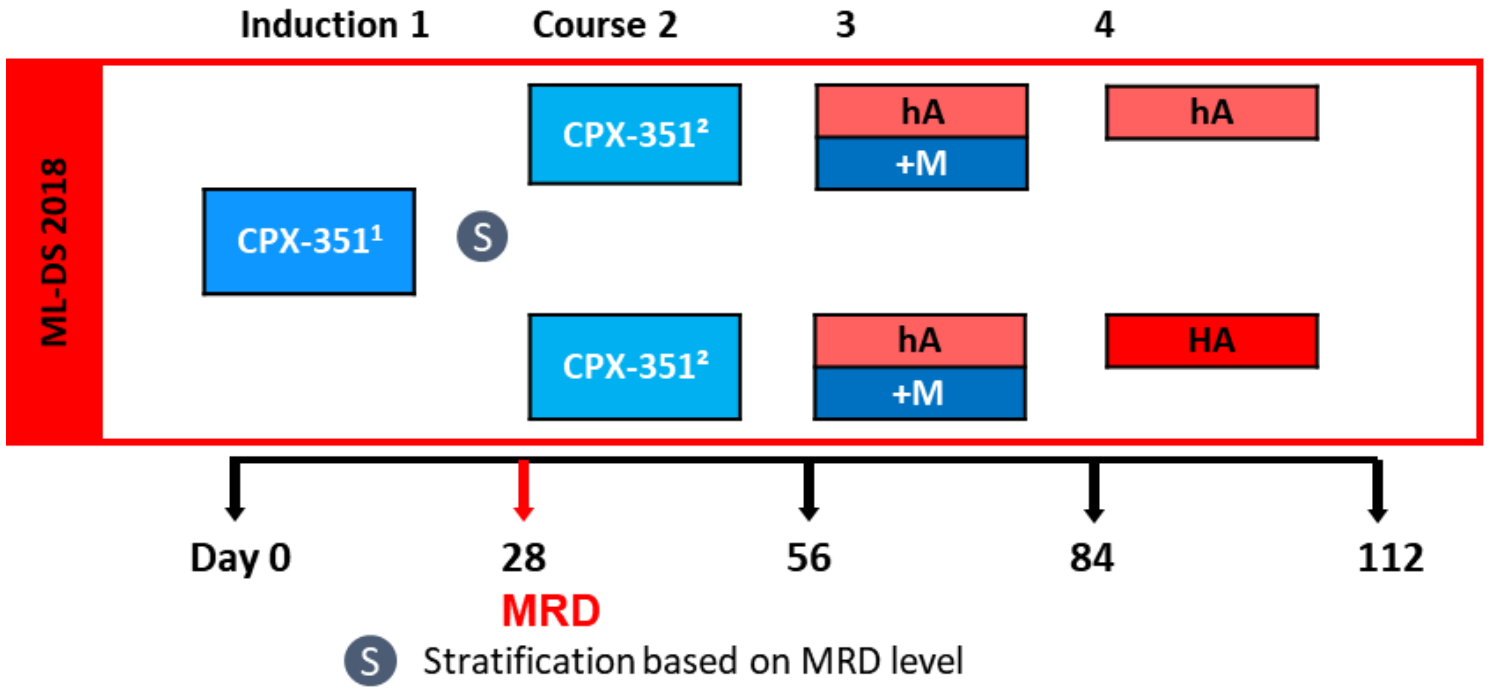
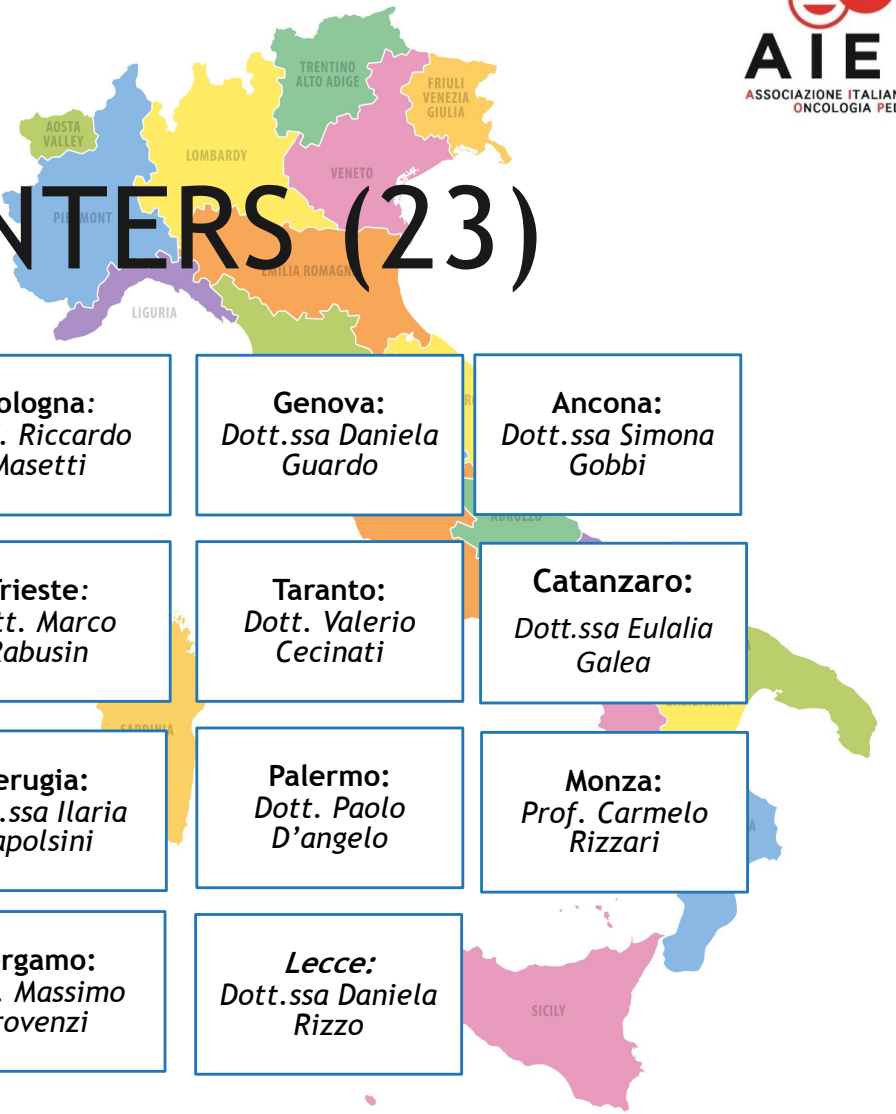
ML-DS 2018: CLINICAL TRIAL OUTLINE



ML-DS 2018: PARTICIPATING CENTERS (23)



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Cagliari: *Dott.ssa Rosamaria Mura*	**San Giovanni Rotondo:** *Dott.ssa Raffaela De Santis*	**Catania:** *Dott. Luca Lo Nigro*	**Bergamo:** *Prof. Massimo Provenzi*	***Lecce:*** *Dott.ssa Daniela Rizzo*	

ML-DS 2018: NEXT STEPS

Site Agreement between AIEOP and each italian participating center

- Under revision
- Feasibility package will be soon circulated

OPBG as Coordinator center will activate all other participating centers

SIV planning ongoing

ICC APL STUDY 02

Treatment study for children and adolescents with Acute Promyelocytic Leukemia

Protocol Version 4.0, sep 25, 2024

COORDINATING CENTER

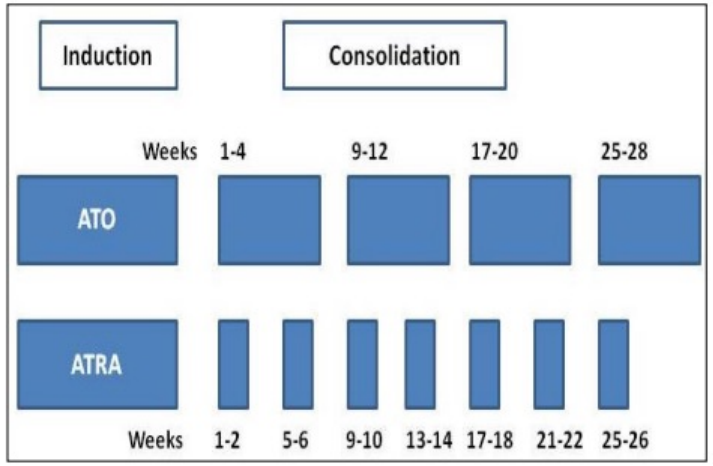
Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
Prof. Franco Locatelli
Department of Onco-Hematology, Cell and Gene Therapy

INTERNATIONAL SPONSOR

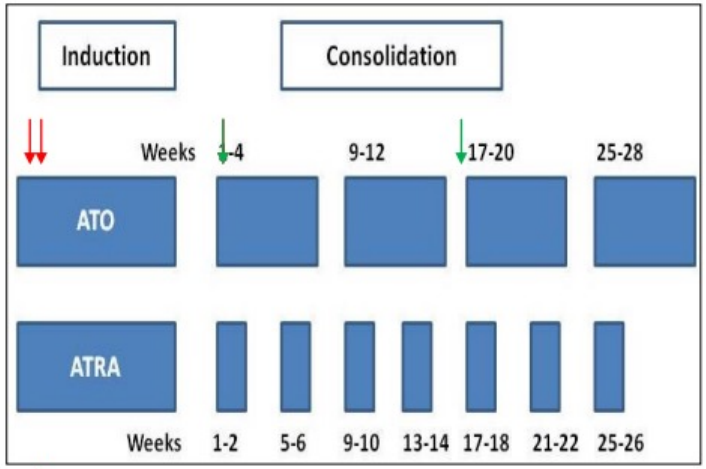
AIEOP
Associazione Italiana di Ematologia e Oncologia Pediatrica

ICC APL STUDY 02: CLINICAL TRIAL OUTLINE

Standard-Risk Protocol



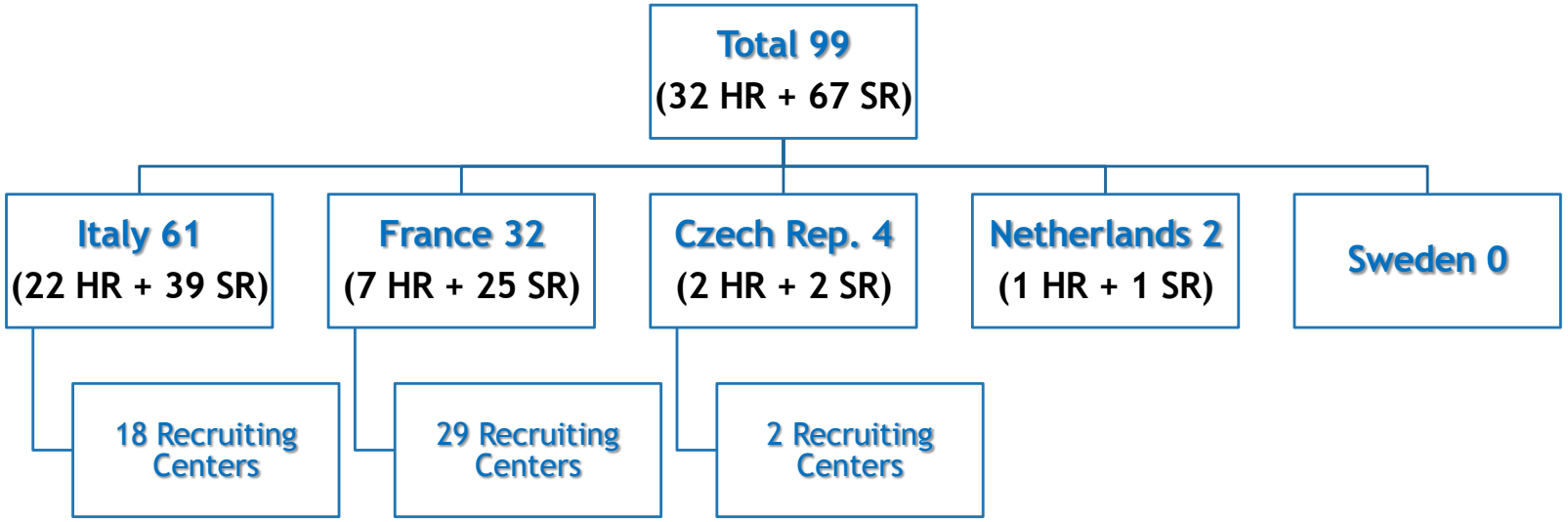
High-Risk Protocol



GO will be administered on days 2 and 4, at 3 mg per m^2 per dose

LP: drug dosage according to patient's age

ICC APL STUDY 02:
ENROLLMENT STATUS



ICC APL STUDY 02:

ITALY - 18 RECRUITING CENTERS

Monza - Ospedale San Gerardo
SR: 9, HR: 4

Torino – AOU Città della Salute
SR: 5, HR: 2

Genova – Istituto Gaslini
SR: 2

Firenze – A.O.U. Meyer
SR: 1, HR: 1

Pisa: A.O.U. Pisana

Roma - OPBG
SR: 9, HR: 7

Napoli - Ospedale Pausilipon
SR: 4, HR: 3

Cagliari – A.O. Brotzu
HR: 1

Napoli – 2° Università di Napoli
HR: 1

Palermo - ARNAS Civico

Bergamo - Ospedale San Gerardo

Verona - Ospedale Donna Bambino

Padova - Azienda Ospedale-Università
SR: 2

Pavia - Policlinico San Matteo
SR: 2, HR: 1

Bologna - Policlinico Sant'Orsola
HR: 1

Bari - AOU Policlinico Ospedale Giovanni XXIII
SR: 1

San Giovanni Rotondo - Ospedale "Casa Sollievo della Sofferenza"
SR: 2

Catania - *AOU Policlinico Vittorio Emanuele*
SR: 2, HR: 1

Overall patients enrolled: 61

SR: 39 - HR: 22

ICC APL STUDY 02: ENROLLMENT STATUS

	High Risk = 32		Standard Risk = 67	
99 patients enrolled	25 patients phase of treatment end in molecular remission	+ 1 molecular refractoriness	54 patients phase of treatment end in molecular remission	+ 1 molecular relapse
	1 patients phase of 4° consolidation		2 patient phase of 4° consolidation	
	1 patient phase of 2° consolidation		3 patients phase of 3° consolidation	
	1 patient phase of 1° consolidation		1 patients phase of 2° consolidation	
			3 patients phase of 1° consolidation	
	1 patient induction - ongoing	1 fatal event during induction	3 patient induction - ongoing	

Male/Female = 56/43
Median age = 11 years (range 1-17)

ICC APL STUDY 02:
CASES DISCUSSION

Patient IT0101APL02IT004 – Refractory disease / Molecular relapse 1 M after the EoT

- Re-Induction: 2 doses of GO administered on 23/08/2024 and 10/09/2024 (post-infusion course complicated by G3 liver toxicity)
- First molecular remission on 01/10/2024
- Autologous HSCT on 13/11/2024 with Bus-Cyclo conditioning. Regular hematologic recovery. No significant toxicity
- Bone marrow aspiration on day +55 (08/01/2025) - molecular remission
- Follow-up on day +119 (11/03/2025) confirmed molecular remission

Patient IT0101APL02IT003 – Molecular relapse 11 M after the EoT

- Treated according to ICCAPL01 protocol (ATO – ATRA - ATO).
- Follow-up on 18/02/2025: molecular remission re-achieved.
- The patient has started the second cycle of ATO, which is currently ongoing. No significant toxicity observed.

Patient IT0101APL02IT006 – Serious Breach

- Serious breach: Infusion of expired experimental drug. No significant toxicity observed.
- Therapy continued as per protocol. Currently in the Induction phase.
- Full Reporting to the Competent Authority – No queries released

ICC APL STUDY 02: PHARMACOVIGILANCE DATA

Overall well-tolerated treatment

- No Suspected Unexpected Serious Adverse Reaction (SUSAR)
- No permanent treatment withdrawal per intolerance

Common and known toxicities

- Pseudotumor Cerebri: 9 EVENTS (2 SAEs)
- Differentiation Syndrome: 11 EVENTS (7 SAEs)
- Headache: 4 EVENTS (2 SAEs)
- Electrocardiogram - QTc interval evaluation (3 SAEs)
- Other intercurrent illness: 16 EVENTS

Suspected GO-related toxicity:

- 1 SAE for myocarditis - outcome: resolved without sequelae

Death, other:

- 1 HR subject experienced fatal intracranial haemorrhage due to the disease under study – no relationship causality with IMP

CAR T CELLS IN CHILDHOOD AML

1. CD7 targeting CAR T cells with the intracellular retention domain (15% of childhood AML; 2 patients already treated);
2. CAR T cells targeting FOLR-1

3. CLEC2-A directed CAR T cells (KMT2A-r AML and monosomy 7)
4. Mesothelin-directed ARTEMIS CAR T cells (Mesothelin transcript can be detected in ~30-40% of all AML)