European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

16 June 2022

European Standard Clinical Practice

ACUTE LYMPHOBLASTIC LEUKEMIA

Presented by

Carmelo Rizzari

Mirella Ampatzidou

Giacomo Gotti

Janine Stutterheim

and *Tomasz Szczepanski*

SIOP Europe
the European Society for Paediatric Oncology

St. Anna Kinderkrebs Forschung

Co-funded by the European Union's Health Programme

COI declarations

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- Carmelo Rizzari:
  - Advisory Board member at Amgen, Jazz, Clinigen, Serb and Servier
  - Sponsored talks for Amgen, Jazz, Clinigen, Serb and Servier
- Tomasz Szczepanski:
  - Advisory Board member at Amgen, Jazz, Novartis, Roche and Servier
  - Sponsored lectures for Amgen, Jazz, Novartis, Roche and Servier
- Mirella Ampatzidou: nothing to declare
- Giacomo Gotti: nothing to declare
- Janine Stutterheim: nothing to declare

Role of the ESCP
European Standard Clinical Practice (ESCP) Guidelines launched by ERN PAED CAN together with SIOPE CRC

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1. Equal standards across Europe
2. To be used when no randomised frontline trial is open in respective countries – whatever the reason

Expectations for ESCP Project

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- **Responsibility and Ownership:**
  remains with the respective European Clinical Trial Group
- **Endorsement:**
  resulting ESCP guidance protocols will be endorsed by SIOPE and ERN PaedCan.
- **Benchmark:**
  ESCPs will be of particular value in providing a benchmark for our Widening Countries.
- **Transparency and dissemination:**
  the ESCP protocols will be made available on relevant websites to provide important information to paediatric haemato-oncologists, patients and families in situations where currently standard best clinical practice is not available.
- **Policy:**
  ECSP protocols may become an important tool when negotiating with healthcare decision makers at the national and international level.

All 16 European SIOPE Clinical Trial Groups committed to participate

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Network Paediatric Cancer (ERN PaedCan)

SIOPE Brain Tumour Group	Brain Tumour	Ewing's Tumour	EUROEWING Consortium
Germ Cell Tumours	Germ Cell Tumours	Hodgkin's Lymphoma	EHL
Histiocyte Society	Langerhans Cell Histiocytosis	Leukemias & Lymphomas	I-BFM
SIOPEL	Liver Tumours	Myelodysplasia	EWOG-MDS
SIOPEN	Neuroblastoma	New Anticancer Agents	ITCC
EICNHL	Non-Hodgkin Lymphoma	Osteosarcoma	EURAMOS
SIOP-RTSG	Renal Tumours	Soft Tissue Sarcomas	CWS
EpSSG	Soft Tissue Sarcomas	Stem Cell Transplantation	EBMT
PanCare	Survivorship & Late Effects	Very Rare Pedatric Tumours	EXPeRT
EURBG	Retinoblastoma		

https://www.siope.eu/european-research-and-standards/clinical-research-council/siopecrc/european-clinical-study-groups/

Achievements - 1

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- SIOPE and ERN PaedCan agreed on a disclaimer
  - General disclaimer on the front page of each ESCP to underline that The ESCP guidance documents are not clinical trial protocols and to clarify the responsibility of the users.
- SIOPE has developed a secured online solution for making the ESCPs available for the community and ten ESCPs are already online (SIOPE Board review completed)

Password protected access

European Reference Network
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Network Paediatric Cancer (ERN PaedCan)

paedcan.ern-net.eu

European Reference Networks | Home | About | Background | Education | E-Health | ESCPs | Community | News | Dissemination | Intranet

The following protocols were delivered in 2021:

- High-Risk Neuroblastoma (available on the SIOPE Portal)
- Pediatric-Onset Langerhans Cell Histiocytosis (available on the SIOPE Portal)
- Non-Hodgkin Lymphoma of Childhood and Adolescence (available on the SIOPE Portal)
- Acute Lymphoblastic Leukemia (ALL) in Children and Adolescents (available on the SIOPE Portal)
- Acute Myeloid Leukemia (AML) in Children and Adolescents
- Adrenocortical tumours in children and adolescents (available on the SIOPE Portal)
- Nasopharyngeal carcinoma in children and adolescents (available on the SIOPE Portal)

Protocols in development – for delivery Q4 2021:

- SIOPE European Osteosarcoma Study Group
- European Soft Tissue Sarcoma Group EpSSG
- SIOPE European Ewing Tumour Consortium
- SIOPEN – Low & Intermediate Risk Neuroblastoma
- SIOPE European Brain Tumour Consortium
- SIOPE- Retinoblastoma Group
- SIOPE- Renal Tumour Study Group
- SIOPEL SIOPE-Epithelial Liver Tumour Study Group
- SIOPE Expert Group (European Cooperative Study Group on Paediatric Rare Tumours)
- Familial Leukaemia

Planned & Scheduled for delivery Q2 2022:

- EHL European Hodgkin's Lymphoma Consortium
- Germ Cell Tumours
- EWOG- MDS (European Working Group of MDS in Childhood)

We would like to thank the Young SIOPE Members, CRC Mentors, the ECTGs Chairs as well as representatives of

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Pages
Welcome to the SIOPE Intranet
SIOP Europe Communication Toolkit
European Standard Clinical Practice (ESCP) protocols

Documents
ESCP: ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
ESCP: ADRENOCORTICAL TUMORS
ESCP: NON-HODGKIN LYMPHOMA OF CHILDHOOD AND ADOLESCENCE
ESCP: HIGH-RISK NEUROBLASTOMA
ESCP: NASOPHARYNGEAL CARCINOMA IN CHILDREN AND ADOLESCENTS
ESCP: PEDIATRIC-ONSET LANGERHANS CELL HISTIOCYTOSIS

Working Group for ALL

Carmelo Rizzari (Italy)
Tomasz Tszczepanski (Poland)
Mirella Ampatzidou (Greece)
Giacomo Gotti (Italy)
Janine Stutterheim (The Netherlands)

Oversight from I-BFM-SG

Martin Schrappe (Germany)
Andrea Biondi (Italy)

Further review:
Valentino Conter – Veronica Leoni (Italy)

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Background

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- ALL is the most common cancer in pediatric population, accounting for 40 cases/million per year in Europe (≈5,000 cases)

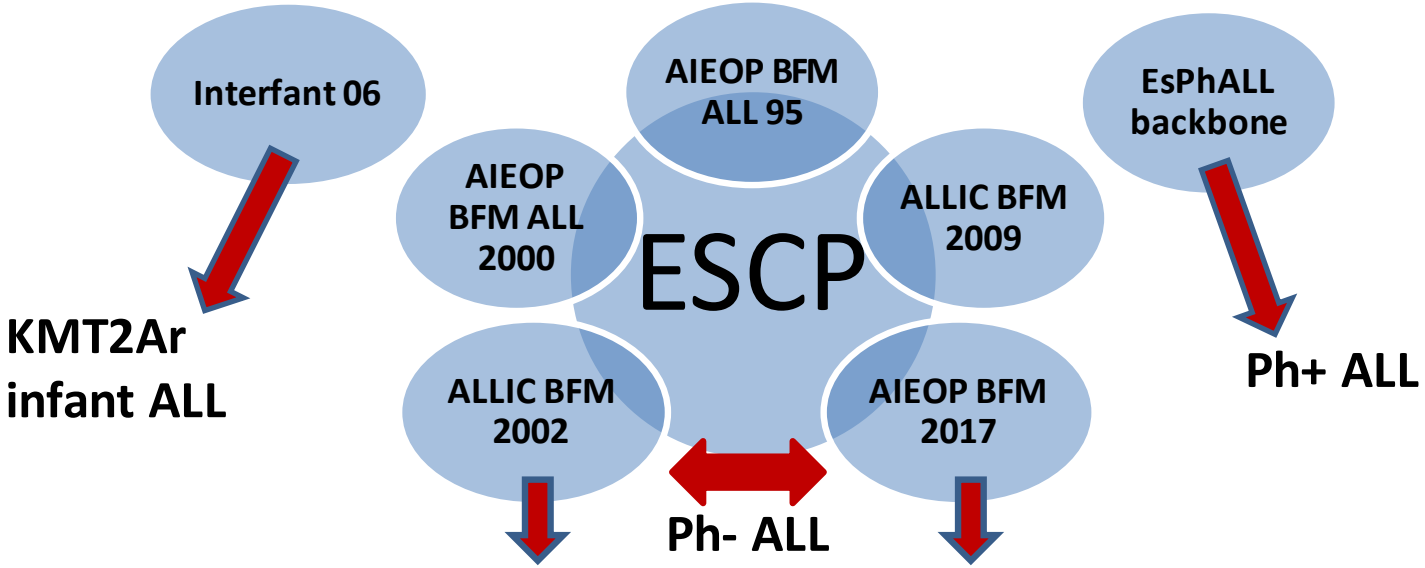
- The survival outcomes have improved dramatically over the past decades.

- Improvements are largely due to advances in the understanding of
  - underlying biology and pathogenesis
  - risk-adapted therapy and response-based stratification (MRD)
- Despite the fact that survival rates approach 90% in developed countries, **children from developing countries show inferior outcomes**.

- **Critical points that affect quality of care in developing countries** are:
  - Limited diagnostic and laboratory skills, lack of centralized laboratories
  - Limited resources impact quality of diagnostic tools (e.g. PCR-MRD)
  - Lack of standardized and updated treatment plan and supportive care

Background

International BFM Study Group (I-BFM-SG) strategy



- Long lasting Familiarity of European countries with a BFM approach
- Proven Feasibility in developing countries
- Wide room to improve adequate diagnostics and treatment
- Implementation of new elements for risk stratification
  - ✓ Genetics
  - ✓ MRD
- Consolidated experience with ESPHALL Interfant strategies

ESCP protocol for Pediatric ALL Aims

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- After preliminary discussions on how to proceed, it was decided to go for the chemotherapy background mainly derived from the experience of the ALLIC-2002 protocol with some modifications possibly derived from more recent or ongoing protocols.

- The current ESCP is focused on standardizing and providing homogenous, accurate, simple and univocal indications for diagnostic assessment, stratification, treatment and supportive care of ALL patients, based on indications mainly derived from a back-bone traditionally adopted in AIEOP/BFM protocols and/or from additional solid experiences/strategies largely used within the consortium.

ESCP protocol for Pediatric ALL

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ESCP protocol for the treatment of pediatric ALL has been subdivided into three main chapters:

1. Philadelphia-chromosome negative ALL (Ph- ALL)
2. Philadelphia-chromosome positive ALL (Ph+ ALL)
3. Infant ALL (KMT2A-rearranged)

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Mirella Ampatzidou - Greece

DIAGNOSTICS AND RISK STRATIFICATION IN ALL

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ESCP structure for Pediatric ALL

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The current **ESCP recommendations** apply to:

- ✓ Newly diagnosed ALL patients
- ✓ Age<18 years
- ✓ Diagnosis of ALL ensured by all the diagnostic criteria defined according to ESCP Guidelines
- ✓ Admission, diagnosis and therapy performed by experienced centers
- ✓ Data registry is encouraged

➢ **Philadelphia negative ALL**

ALLIC BFM 2002 ⟷ ALLIC BFM 2009 ⟷ AIEOP BFM 2017

➢ **Philadelphia positive ALL**

EsPhALL2010

➢ **KMT2Ar infant ALL**

Interfant-06

ALL ESCP

Initial clinical and laboratory Diagnostics for all newly diagnosed ALL pts

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INITIAL DIAGNOSTIC WORKUP	MANDATORY	OPTIONAL
History and physical exam	X	
Complete Blood Count (CBC)/Differential	X	
Chemistry Profile/Liver function tests/Tumor Lysis Syndrome Panel (LDH, uric acid, K, Ca, Phos)	X	
Disseminated Intravascular Coagulation (DIC) Panel (D-dimer, fibrinogen, prothrombin time, partial thromboplastin time)	X	
CT/MRI of head with contrast, in case of neurologic symptoms	X	
Chest X-Ray, to rule out mediastinal mass	X	
Whole Body PET/CT, if lymphoblastic lymphoma suspected		X
Lumbar Puncture (LP), with intrathecal chemotherapy (IT)	X	
Ultrasonography (US) of neck and abdomen	X	
Testicular exam, scrotal ultrasound as indicated	X	
Infection evaluation, screening for opportunistic infections	X	
ECG & Echocardiography (Echo-CG)	X	
Fundoscopy		X
Central venous access of choice	X	
Pharmacogenomic testing for TPMT, NUTD15		X
Cancer predisposition syndromes (i.e. germline TP53 mut in hypodiploidy)		X

ESCP structure for Pediatric ALL

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Diagnostic evaluation method	Initial diagnostics for the biological characterization of ALL
Cytomorphology *[from native material without additives (e.g. EDTA)]*	➢ Bone marrow: Myelogram (MGG) ➢ Peripheral blood: Complete blood count Differential hemogram ➢ CSF: Cell count (counting chamber) MGG stained cytospin preparation
Flow Cytometry	➢ Bone marrow (and/or peripheral blood): Immunophenotyping DNA index (optional) Identification of suitable FCM-MRD targets
Cytogenetics	➢ Bone marrow (and/or peripheral blood): High-resolution G-banding (Numerical & structural aberrations)
Molecular genetics	➢ Bone marrow (and/or peripheral blood): Identification of suitable PCR-MRD targets Comprehensive genetic leukemia characterization (FISH,PCR,MLPA, arrayCGH, NGS)

ESCP structure for Pediatric ALL
GENETIC ALL CLASSIFICATION

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Favourable Genetic Risk features
- ✓ Hyperdiploidy
- ✓ ETV6/RUNX1
- ✓ ERGdeletion

Unfavourable Genetic Risk features
- ✓ Hypodiploidy
- ✓ KMT2A gene rearrangements
- ✓ TCF3-HLF
- ✓ iAMP21 (combined with impaired MRD clearance)
- ✓ BCR-ABL1 or Ph-positive ALL
- ✓ *IKZF1*plus subgroup
- ✓ BCR-ABL1–like or Ph-like ALL

Genetic abnormalities in T-ALL
- ✓ NOTCH1, FBXW7, TLX1(HOX11), TLX3 (HOX11L2), LYL1, TAL1, KMT2A

GENETIC ABERRATION	FREQUENCY IN CHILDHOOD ALL	FREQUENCY UN ADULT ALL
High hyperdiploidy (51-67 chr.)	25%	7%
t(12;21)(p13;q22)-ETV6/RUNX1	22%	2%
11q23/KMT2A rearrangements	8%	10%
t(1;19)(q23;p13.3)-TCF3/PBX1	5%	3%
t(9;22)(q34;q11.2)-BCR/ABL1	3%	25%
Hypodiplpoidy(<45 chr.)	1%	2%
t(5;14)(q31.1;q32.3)-IL3/IGH	<1%	<1%
2016 PROVISIONAL ENTITIES		
"BCR-ABL1-like" ALL		
Intrachromosomal AML1 amplification (iAMP21)		

The revised World Health Organization (WHO) 2016 ALL genetic classification.

New provisional entities have been included (BCR-ABL1-like ALL and intrachromosomal AML1amplification (iAMP21).

ESCP structure for Pediatric ALL

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Methodology for genetic evaluation and molecular characterization

- Considering the countries recipient of these ESCP, this section aims **to identify and delineate all pertinent lesions that are essential for risk stratification** in the most **comprehensive as well as cost- and time-efficient way**.

- The diagnostic workflow and applied technology should be understood as a **highly recommended suggestion** and can either be **partially replaced or supplemented according to the special local requirements**.

- Depending on the available infrastructure in the various countries and laboratories, the necessary ascertainment procedures may therefore **be adapted and vary accordingly.**

- All the diagnostic procedures required for risk stratification need to undergo **standardization and quality control**, with **centralized laboratories** providing **high level of expertise.**

ESCP structure for Pediatric ALL

Proposed guidelines for basic genomic screening methodology

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Genetic aberrations/ karyotyping abnormality patterns	Methods					
	Array (optional)	FISH	RT-PCR	MLPA	G/R Banding	NGS (optional)
High hyperdiploidy (HeH; 51-65/67 chromosomes)	X				X	X
Low Hypodiploidy (HoL; 30-39 chromosomes)	X				X	X
Near haploidy (NH; 25-29 chromosomes)	X				X	X
iAMP21	X	X				X
KMT2A rearrangements		X			X	X
BCR-ABL1, ETV6/RUNX1, TCF3-HLF, TCF3-PBX1		X	X		X	X
ABL-class fusions and other (i.e. ABL1, ABL2, CSF1R, PDGFRB) (optional)		X				X
Copy Number Alterations BTG1, CDKN2A/2B, EBF1, ETV6, IKZF1, PAR1, PAX5, RB1	X			X		X

Adapted from Moorman AV., SIOPE Meeting, Prague 2019

PROPOSED mandatory and optional genetic diagnostics

of stratification-relevant and other important prognostic aberrations

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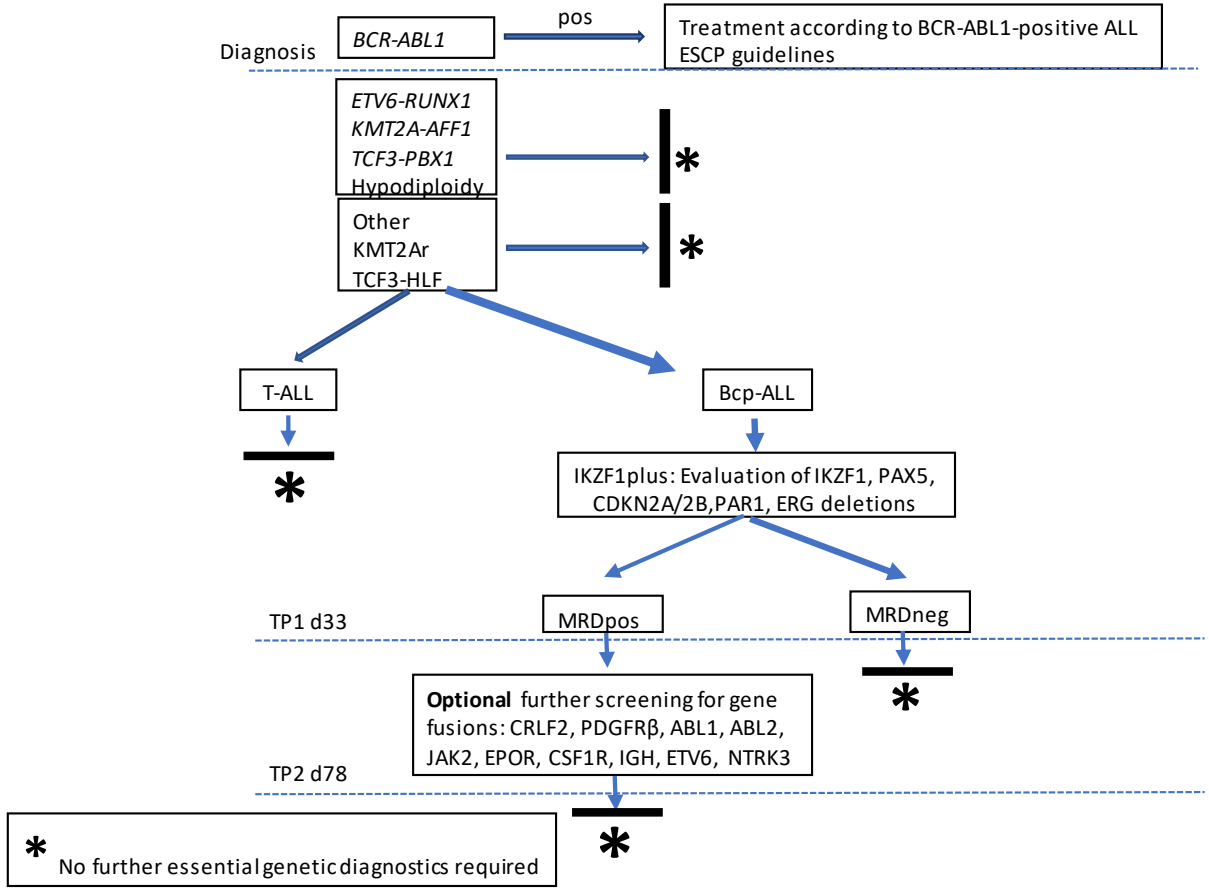
GENETIC ABERRATION	RELEVANT FOR STRATIFICATION	MANDATORY/ OPTIONAL	TARGET PATIENT GROUP
BCR-ABL1	Yes	Mandatory	All patients
KMT2A rearrangement	Yes	Mandatory	All patients
KMT2A/AFF1	Yes	Mandatory	All patients
Identification of other KMT2A partner gene	No	Optional	
ETV6/RUNX1	Yes	Mandatory	All Bcp patients
TCF3/PBX1	No	Mandatory	All Bcp patients
TCF3/HLF	Yes	Mandatory	All Bcp patients
Hypodiploidy	Yes	Mandatory	All Bcp patients
Hyperdiploidy	No	Mandatory	All Bcp patients
IKZF1 deletion	Yes	Mandatory	All Bcp patients, except pts with BCR-ABL1, ETV6/RUNX1, KMT2A rearrangement, TCF3 rearrangement, or hypodiploidy
PAX5 deletion	Yes (only in case of IKZF1plus subgroup)	Mandatory (only in case of IKZF1plus subgroup)	
CDKN2A/2B deletion			
P2RY8/CRLF2 (PAR1 del)			
iAMP21	Yes	Mandatory	All Bcp patients
ERG deletion	Yes (only in case of IKZF1plus subgroup)	Mandatory (only in case of IKZF1plus subgroup)	All patients meeting criteria for IKZF1plus definition
ABL1 rearrangement	No	Optional	All Bcp patients with positive MRD on day 33, except pts with BCR-ABL1, ETV6/RUNX1, KMT2A rearrangement, TCF3 rearrangement, or hypodiploidy
ABL2 rearrangement	No	Optional	
CSF1R rearrangement	No	Optional	
PDGFRB rearrangement	No	Optional	
IGH rearrangement	No	Optional	
CRLF2 rearrangement	No	Optional	
EPOR rearrangement	No	Optional	
ETV6 rearrangement	No	Optional	
NTRK3 rearrangement	No	Optional	
JAK2 mutations	No	Optional	
NOTCH1 mutations	No	Optional	T-ALL pts
TLX1(HOX11),TLX3(HOX11L2), LYL1, TAL1 rearrangements	No	Optional	T-ALL pts

Proposed genetic algorithm, basic genetic diagnostic requirements and workflow

Algorithm of basic genetic diagnostics



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ESCP structure for Pediatric ALL

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Diagnostics during the course of therapy-Response evaluation

Minimal Residual Disease (MRD)

MRD by PCR of clone-specific TCR and Ig gene rearrangements (TP1 d33, TP2 d78/92)

- It is essential that the required guidelines for **EuroMRD membership** are followed and that the MRD analyses is performed according to the **EuroMRD consortium** guidelines and approved by the **EuroMRD consortium.**
  (van der Velden, et al 2007)

- **FCM-MRD on day 15**

- **FCM-MRD on TP1 and TP2 if no PCR-MRD is available**
- It is essential that the FCM-MRD analyses is performed according to the published guidelines of the **AIEOP-BFM Flow Network and the fully standardized EuroFlow ALL MRD strategy.**
  (Dworzak M, Cytometry B Clin Cytom 2008, Bruggemann M et al, Leukemia 2010, Theunissen P et al, Blood 2017, Dworzak M et al, Cytometry B Clin Cytom 2018)

The risk-group stratification scheme in the ALL-IC BFM 2002 trial

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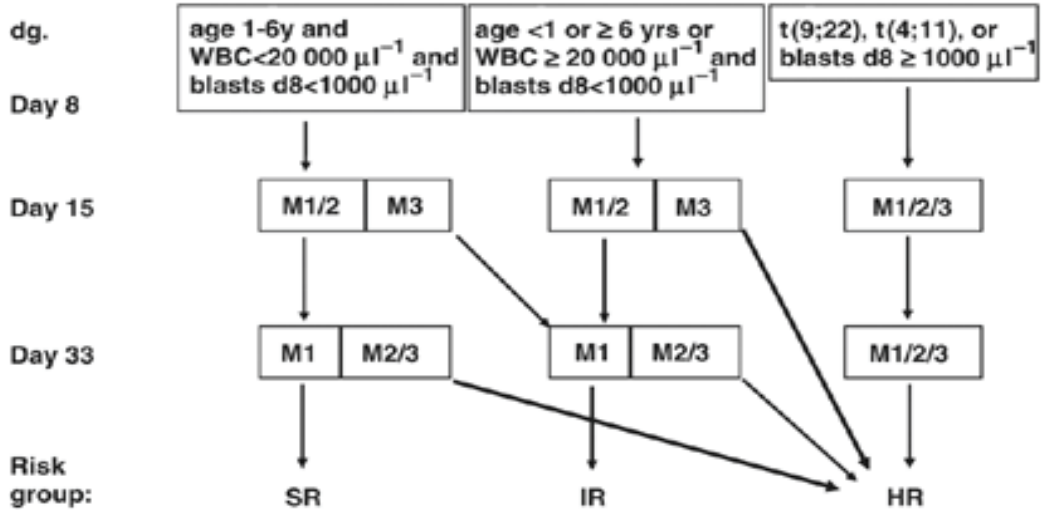

M1/2/3, BM status according to morphology, M1 (<5% blasts), M2 (5–24% blasts) and M3 (⩾25% blasts). BM, bone marrow

- **Cornerstone pillar for basic risk group assignment**
- **Prognostic stratification in a non-MRD based approach**
- **Setting up the scene** for **basic** diagnostics and treatment

ESCP structure for Pediatric ALL

Risk Group Assignment

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Risk group assignment by MRD values in ALL patients

	MRD TP2 (MRDd78)	
	$<5x10^{-4}$	$\geq 5x10^{-4}$
FCM-MRDd15 <0,1%	SR	HR
FCM-MRDd15 0,1-10%	IR	HR
FCM-MRDd15 >10%	HR	HR
Any HR criteria at TP1 (day 33)	HR	HR
No HR criteria at TP1 (day 33) and MRD at TP1 (MRDd33)		
$<5x10^{-4}$ and SR criteria fulfilled	SR	HR
$<5x10^{-4}$ and SR criteria not fulfilled	IR	HR
$\geq 5x10^{-4}$	HR	HR

ESCP structure for Pediatric ALL

Risk Group Assignment

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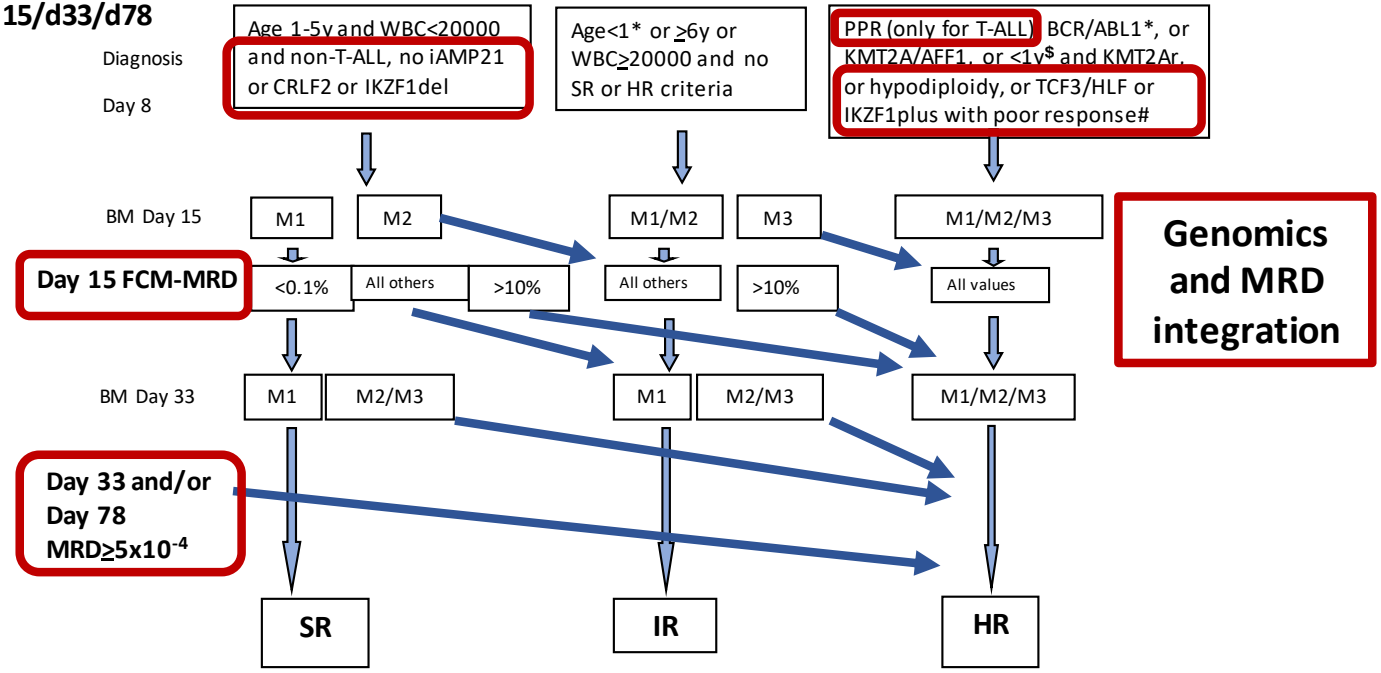
Proposed Risk Group stratification based on WBC, age, genetics and treatment response on d15/d33/d78



Estimated distribution of pts 15% 60% 25%

* BCR/ABL1+ pts should be stratified and treated according to ESCP Guidelines for Ph+ ALL
$Infants <1 year should be stratified and treated according to ESCP Guidelines for Infant ALL
\# IKZF1plus with FC-MRDd15≥0.1% or MRDd33/d78≥5x10^{-4}

Intermission

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Do you have any questions so far?

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Giacomo Gotti - Italy

DIFFERENTIATON PH-/PH+ ALL

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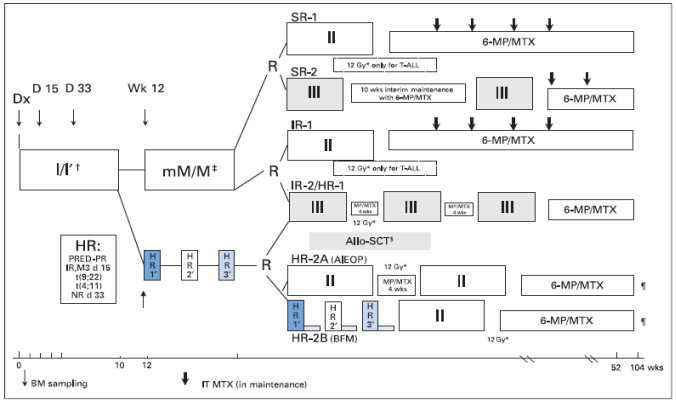
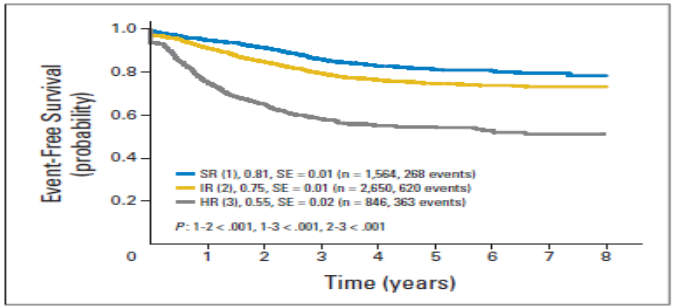
ALLIC BFM ALL 2002

- To determine the impact of an alternative Delayed Intensification (DI) among the three risk groups
- 5,060 children were treated (2002-2007) in 15 countries on three continents
- No benefit from alternative DI
- Overall outcomes were 74% of EFS and 85% of OS
- Results varied among countries, but a general improvement in survival was observed
- Treatment toxicity represented an important cause of death (5% died in 1st CR – 13% among HR group)





Stary J, JCO 2014

Proposal for an ESCP structure for Ph- Pediatric ALL outline

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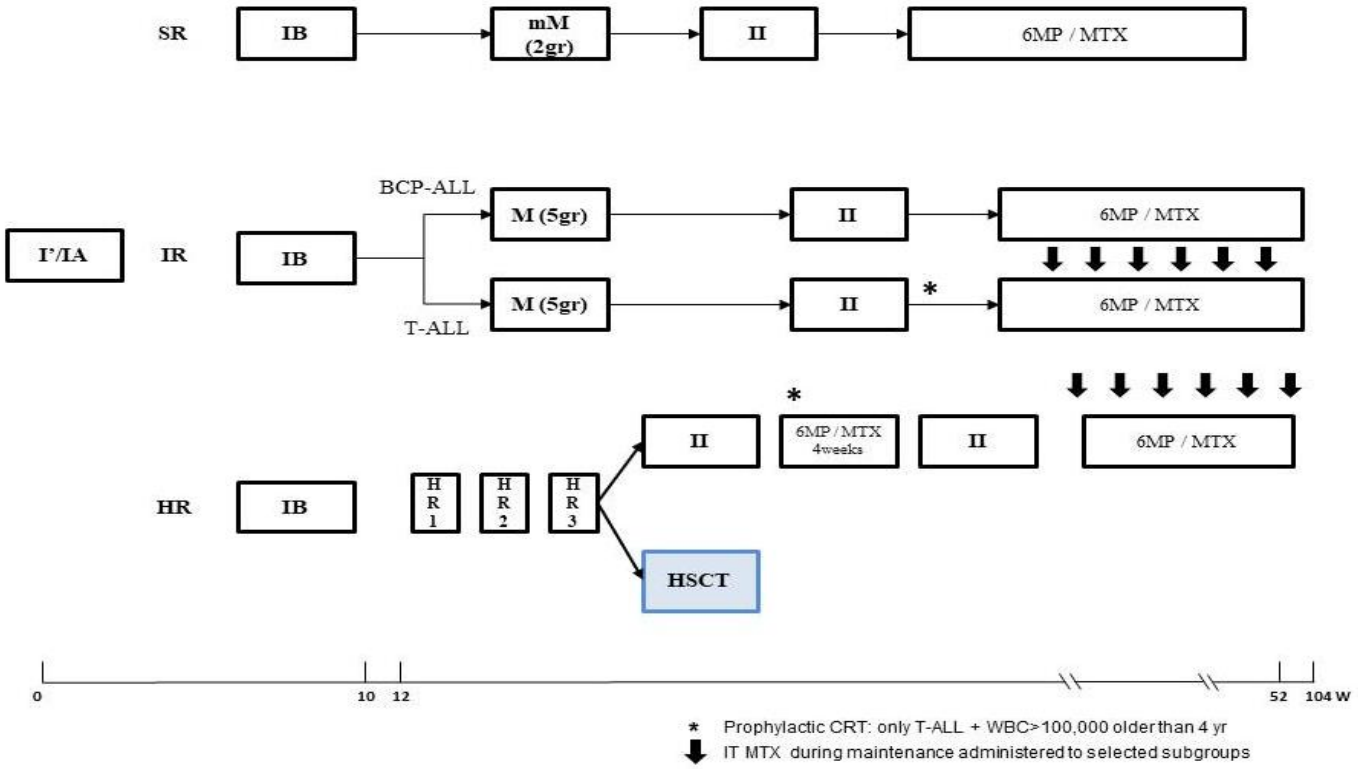

Proposal for an ESCP structure for Pediatric ALL
Cranial irradiation

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- No longer administered in patients younger than 4 yo
- Dose of 12 Gy, limited to specific group of patients ≥ 4 years
- Intensified intrathecal therapy during maintenance

Age	Risk group	CNS neg (CNS 1 or CNS 2)			CNS pos (CNS 3)
		pB-ALL	T-ALL		
			init. WBC <100 000/µl	init. WBC ≥100 000/µ	
< 4 years	non-HR	0 Gy	0 Gy + i.th. MTX in MT*	0 Gy + i.th. MTX in MT*	0 Gy + i.th. MTX in MT*
	HR	0 Gy + i.th. MTX in MT*	0 Gy + i.th. MTX in MT*	0 Gy + i.th. MTX in MT*	0 Gy + i.th. MTX in MT*
≥ 4 years	non-HR	0 Gy	0 Gy + i.th. MTX in MT*	12 Gy	12 Gy
	HR	0 Gy + i.th. MTX in MT*	0 Gy + i.th. MTX in MT*	12 Gy	12 Gy

ESCP structure for Pediatric ALL Indications for HSCT

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- Indications are based on current AIEOP-BFM ALL 2017 protocol

	PCR-MRD				
	TP1 neg	TP1 pos and TP2 $<5x10^{-4}$	MRD-HR TP1 pos and TP2 $\geq5x10^{-4}$ $<5x10^{-3}$	MRD-HR TP1 pos and TP2 $\geq5x10^{-3}$	No MRD
No CR d33	No	MD	MMD	MMD	MMD
Hypodiploidy < 44 chr or DNA index < 0.8	No	MD	MD	MMD	MD
KMT2A/AFF1 t(4;11)	No	MD	MD	MMD	MD
TCF3-HLF	MMD	MMD	MMD	MMD	MMD
IKZF1plus MRD≥10% on day 15	No	MD	MD	MMD	MD
IKZF1plus MRD<10% on day 15	No	No	MD	MMD	MD
T-ALL + PPR	No	No	MD	MMD	MD
T-ALL + FCM-MRD d15 ≥10%	No	No	MD	MMD	MD
None of the above	No	No	MD	MMD	No

MD: HLA-matched sibling or non-sibling donor

MDD: HLA-matched or HLA-mismatched donor

EsPhALL and COG experience

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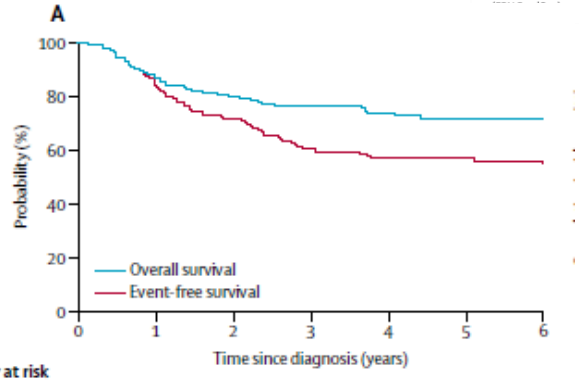
Network Paediatric Cancer

EsPhALL 2010

- Impact of continuous administration of Imatinib (300 mg/m2/day) from day 15 of induction with EsPhALL backbone and restricted criteria for HSCT (MRD-based). Cranial radiotherapy to all non-transplanted patients
- High rate of CR at end of induction (97% vs 78% in EsPhALL 2004), similar survival to previous EsPhALL 2004, less patients transplanted in 1° CR (38% vs 81%)
- MRD at end of consolidation as a strong indicator of prognosis
- High rate of death in CCR



Number at risk (number censored)							
Event-free	155 (0)	130 (0)	111 (0)	79 (16)	62 (29)	42 (49)	19 (71)
Overall	155 (0)	135 (0)	124 (0)	98 (21)	77 (39)	49 (65)	23 (91)

COG AALL0031

- Intensive chemotherapy + imatinib (340 mg/m^2), after induction. Donor available → HSCT in CR1, otherwise cranial radiation.
- No significant difference between chemotherapy and HSCT.

COG AALL0622 (2008-2012)

- Dasatinib instead of imatinib because of a better CNS penetration and less resistance, 5-year EFS was 58% and 5-year OS 86%.

COG experience demonstrated that the continuous and early start of administration impact significantly the long-term outcome

Proposal for an ESCP structure for Ph+ Pediatric ALL

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

- **Eligibility**: evidence of t(9;22)(q34;q11) determined by cytogenetics or FISH and/or presence of BCR-ABL fusion transcript by RT-PCR
- Patients are stratified in **two risk groups according to MRD** at end of consolidation IB
- MRD is assessed by PCR-based detection of **immunoglobulin T-cell receptor** (IgH-TCR)

Standard risk (SR)	High risk (HR)
MRD < $5x10^{-4}$ or negative at end of induction IB	MRD ≥ $5x10^{-4}$ at end of induction IB

Proposal for an ESCP structure for Ph+ Pediatric ALL

European Reference Network
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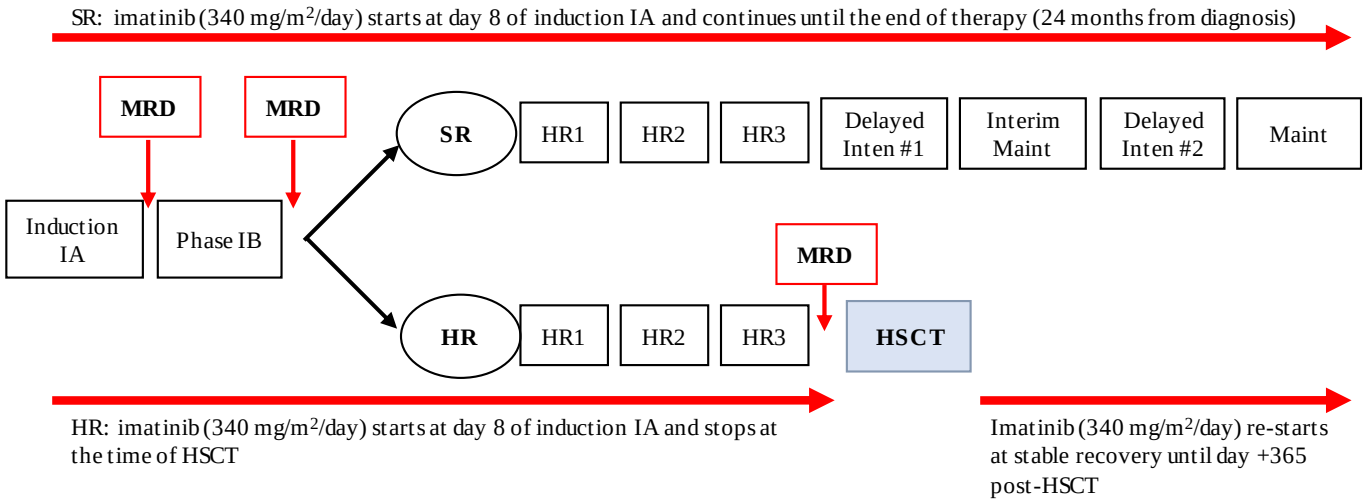
- Treatment based on the **current Standard arm of the COG/EsPhALL trial** (EsPhALL backbone)
- **Imatinib** (340 mg/m^2/day) is the TKI of choice, starting from day 8 of induction, continuous administration
- All HR patients are addressed to **HSCT** (imatinib after transplant is indicated)
- Cranial radiotherapy only to CNS-3 patients who do not proceed to transplant



Intermission

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Do you have any questions so far?

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Janine Stutterheim – The Netherlands

INFANT ALL

Co-funded by the European Union's Health Programme

SIOP Europe
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St. Anna Kinderkrebs Forschung

KMT2Ar infant ALL

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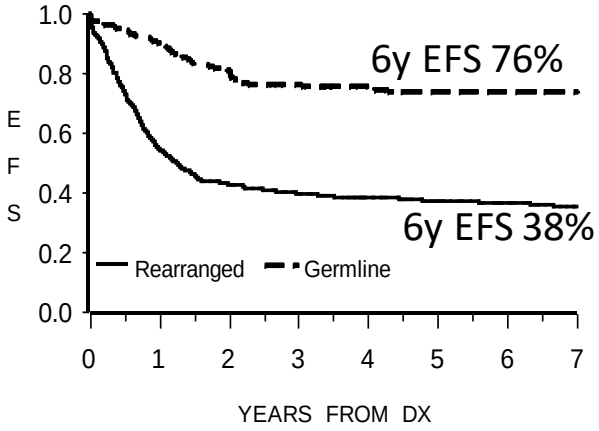
Network Paediatric Cancer (ERN PaedCan)

- Infant ALL (< 1 year)
- KMT2A rearrangement associated with poor prognosis
- In vitro/ in vivo sensitivity to cytarabine
- Interfant trials:
  - ALL backbone + low and high dose araC



Pieters et al JCO 2019

Interfant 06

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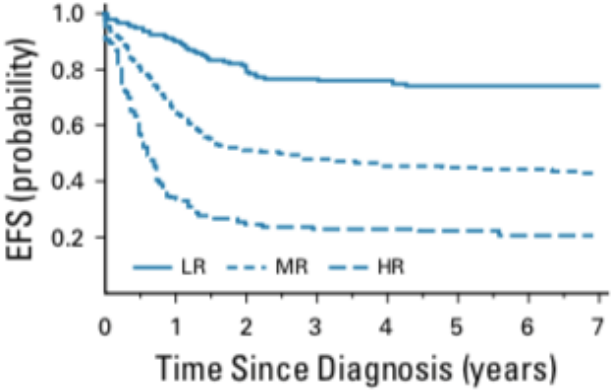
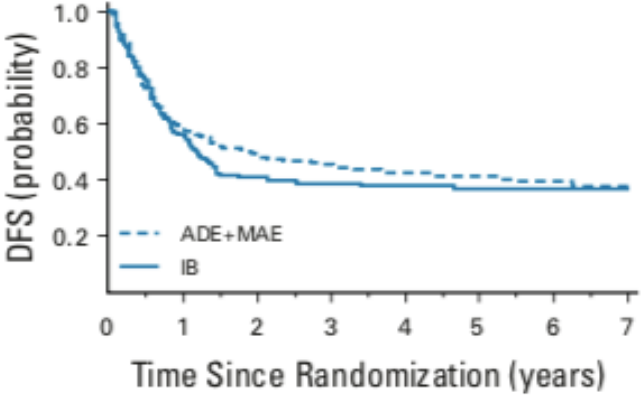
- Risk stratification according to age, WBC at diagnosis and prednisolone response
  - LR KMT2A germline
  - MR KMT2Ar, other
  - HR KMT2Ar age < 6mo, and WBC>300 and/or PPR

- Goal: To assess the role of an early intensification of two "AML" induction blocks versus protocol IB directly after induction, in a randomized way in MR and HR patients





Pieters et al JCO 2019

Patient group

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The current ESCP recommendations apply to:

- Patients with newly diagnosed B-precursor acute lymphoblastic leukemia (ALL) or mixed-phenotype acute leukemia according to WHO 2016 criteria.
- < 365 days of age at time of diagnosis of ALL
- 11q23/ *KMT2A* rearrangement
- Admission, diagnosis and therapy performed by experienced centers

Risk stratification

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High risk (HR)	*KMT2A* rearranged AND
	• age at diagnosis < 6 months AND • WBC>300 x 10^9/L and/or prednisone poor response
Medium risk (MR)	All other cases so including those with:
	• *KMT2A* rearranged AND age ≥ 6 months OR • *KMT2A* rearranged AND age < 6 months AND WBC< 300 x 10^9/L AND prednisone good response

ESCP structure for KMT2A-r BCP infant ALL

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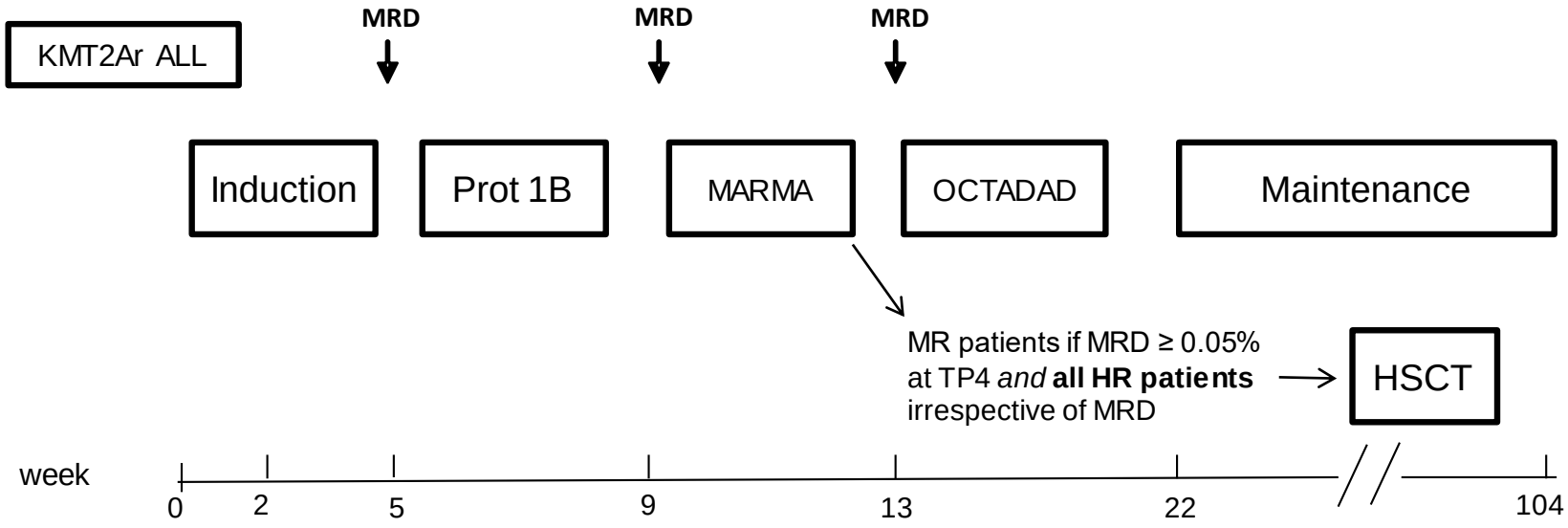
- Treatment based on Interfant06 backbone (Pieters R, 2019)
- All MR patients with high MRD after MARMA are addressed to **HSCT** (as amended Interfant 2009)



Treatment KMT2A-r BCP infant ALL

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Dose modification guidelines

Age	Dose modification
<6 months	2/3 of the calculated dose based on BSA
6 through 12 months	3/4 of the calculated dose based on BSA
>12 months	full dose

Note. New Interfant-21 protocol will open Q4 2022
Guidelines in Interfant-21 will be implemented in ESCP guidelines

Supportive care and Follow up

European Reference Network
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Network Paediatric Cancer (ERN PaedCan)

- Appendices for treatment modification, supportive care and follow up recommendations based upon AIEOP BFM 2017
  - Tumor lysis syndrome
  - Infection prevention and treated
  - Asparaginase related toxicity

Intermission

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Network Paediatric Cancer (ERN PaedCan)

Do you have any questions so far?

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Janine Stutterheim – The Netherlands

DATA COLLECTION - ESCP REGISTRY

SIOP Europe
the European Society for Paediatric Oncology

St. Anna Kinderkrebs Forschung

Co-funded by the European Union's Health Programme

ESCP Registry

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

This registry was developed to capture data regarding the use and impact of European Standard Clinical Practice (ESCP) Guidance Documents across Europe, especially in Widening Countries*. It captures data on the availability of treatment protocols and drugs recommended in the ESCP guidance documents.

Data entered in this registry is pseudonymized via the most up to date version of the EUPID system and not publicly searchable. Adherence to the most up-to date security standards is a core tenant of this project.

No patient-identifying data is stored in this registry.

The data will be stored in secured data hosting centres, located within Europe.

*Widening countries as defined in HORIZON2020: Bulgaria, Croatia, Cyprus, Czechia, Estonia, Greece, Hungary, Latvia, Lithuania, Malta, Poland, Portugal, Romania, Slovakia and Slovenia

ESCP Registry

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

- Ready for release (pending final validation checks)
- Specific modules available at release:
  - Acute Lymphoblastic Leukemia
  - CNS Germ Cell Tumour
  - High Risk Neuroblastoma
  - Langerhans Cell Histiocytosis
  - Medulloblastoma
  - Non-Hodgkin Lymphoma
  - Retinoblastoma

ALL specific variables

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WBC (µl)	
CNS	CNS1 | CNS2 | CNS3
Genetic category	Hyperdiploidy | Hypodiploidy | ETV6/RUNX1 | BCR/ABL1 | KMT2Ar | TCF3/HLF | TCF3/PBX1 | IKZF1plus | iAMP21 | No findings | Other
Immunophenotype	B | T | Biphenotypic
Therapy Risk Group	Standard Risk | Intermediate Risk | High Risk
Prednisone response	Good Prednisone response | Poor Prednisone response | Not assessed
BM d15	M1 | M2 | M3
FC-MRD d15 (%)	
BM d33	M1 | M2 | M3
MRD Method for days 33 and 78	Flow Cytometry | PCR
MRD d33 (%)	
MRD d78 (%)	
Cranial Randiotherapy (CRT)	No | Prophylactic | Therapeutic CRT
allo-SCT	No | Yes
CR status	CR | No CR

Q&A - Discussion

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

Pediatric Acute Lymphoblastic Leukemia

Carmelo Rizzari

Questions?

Tomasz Szczepanski

Questions?

Mirella Ampatzidou

Questions?

Giacomo Gotti

Questions?

Janine Stutterheim

Questions?

ESCP protocol for Pediatric ALL

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

THANKS

EU Health Program

ERN Paed CAN Coordination Unit

(Prof Ruth Ladenstein, Zoltan Dobai, Martin Schalling, St Anna - Wien)

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