Advances in Leukemia

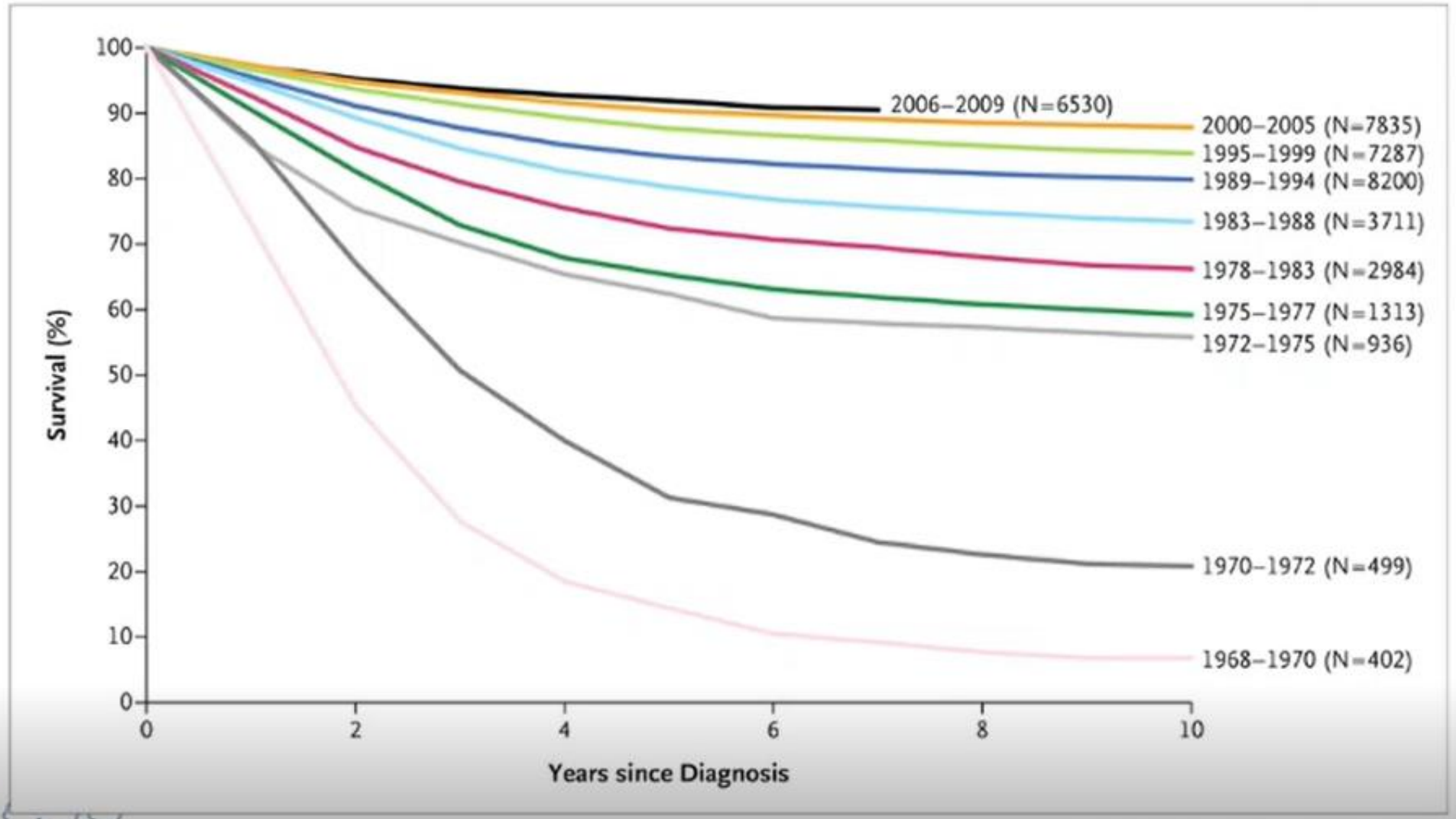
SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

Edited By:

Gr. Bahoush, M.D.

Many patients with ALL can be cured with conventional chemotherapy

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022



Hunger SP, Mullighan CG. N Engl J Med 2015;373:1541-1552

…with agents approved decades ago…and with modern risk stratification implemented more recently…

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

Agent	Year Approved by FDA
6-Mercaptopurine	1953
Methotrexate	1953
Prednisone	1955
Dexamethasone	1958
Cyclophosphamide	1959
Vincristine	1964
Cytarabine	1969
L' Asparaginase	1978
Daunorubicin	1979

Risk "categories" used by COG to inform the intensity of therapy:

1. Age 1-9 or > 10 years
2. Presenting white blood cell count < or > 50,000/dL
3. Leukemia genetics-fav and unfav
4. Early response to therapy in the peripheral blood on day 8 and bone marrow on day 29

(Note: Similar practices used by all other consortia)

5. CNS or testicular Status

Why continue trying to improve outcomes for ALL?

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

- Relapse remains a high burden for this most common of childhood cancers
- Despite better outcomes in general, NCI Standard Risk (SR) patients (age < 10 years, WBC < 50K at diagnosis) contribute to more than half of treatment failures.

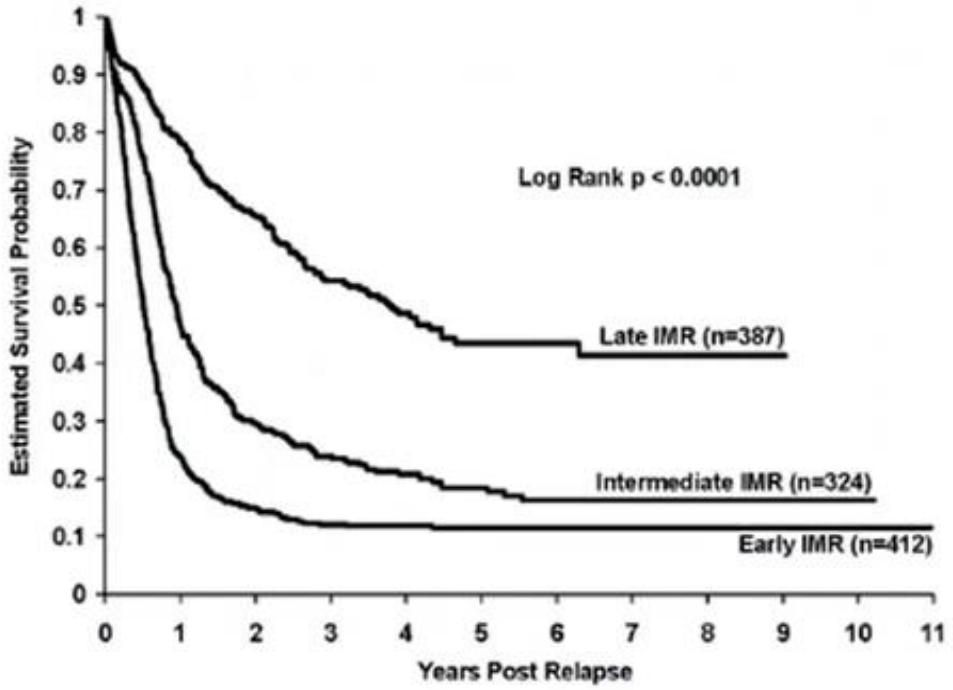
NCI Risk Group (B-ALL, non infant)	No. eligible (%) N=13,771	No. relapse (%) N=1,715
Standard Risk	9797 (71.1%)	961 (56%)
High Risk	3974 (28.9%)	754 (44%)

Patients were enrolled on COG or legacy CCG/POG protocols between 1996-2014.

Rheingold S, Ji L, Bhojwani D et al, in preparation, ASCO 2019, and SIOP 2022

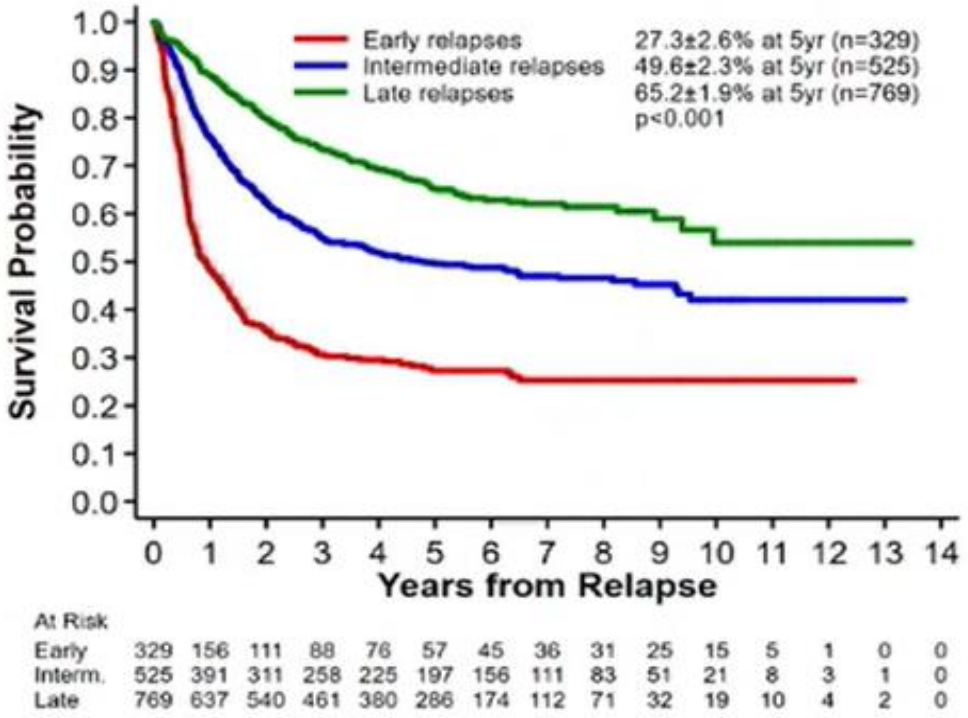
Survival for childhood ALL is worse after relapse

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022



1988-2002

Nguyen et al, Leukemia 2008

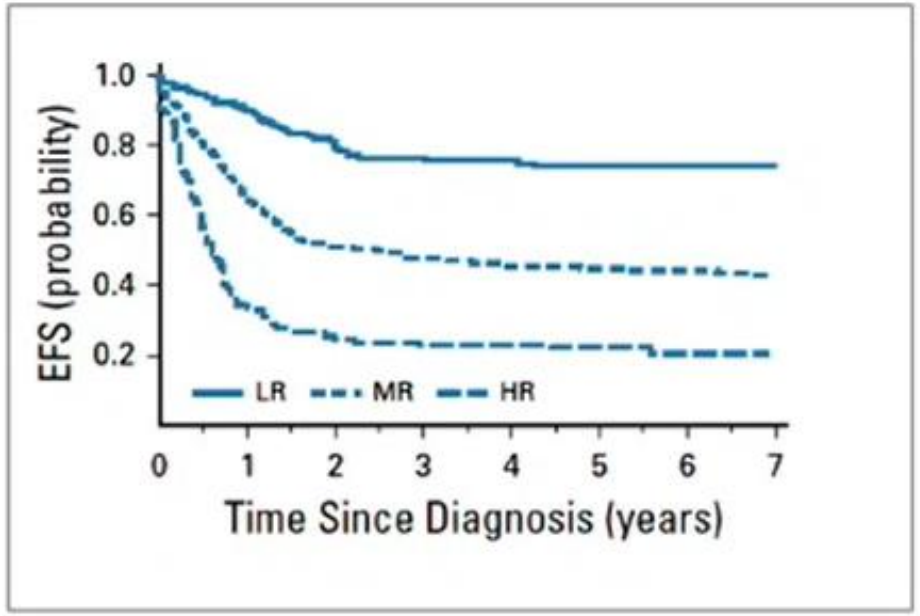


1996-2014

Rheingold, Bhojwani et al, in preparation and ASCO 2019

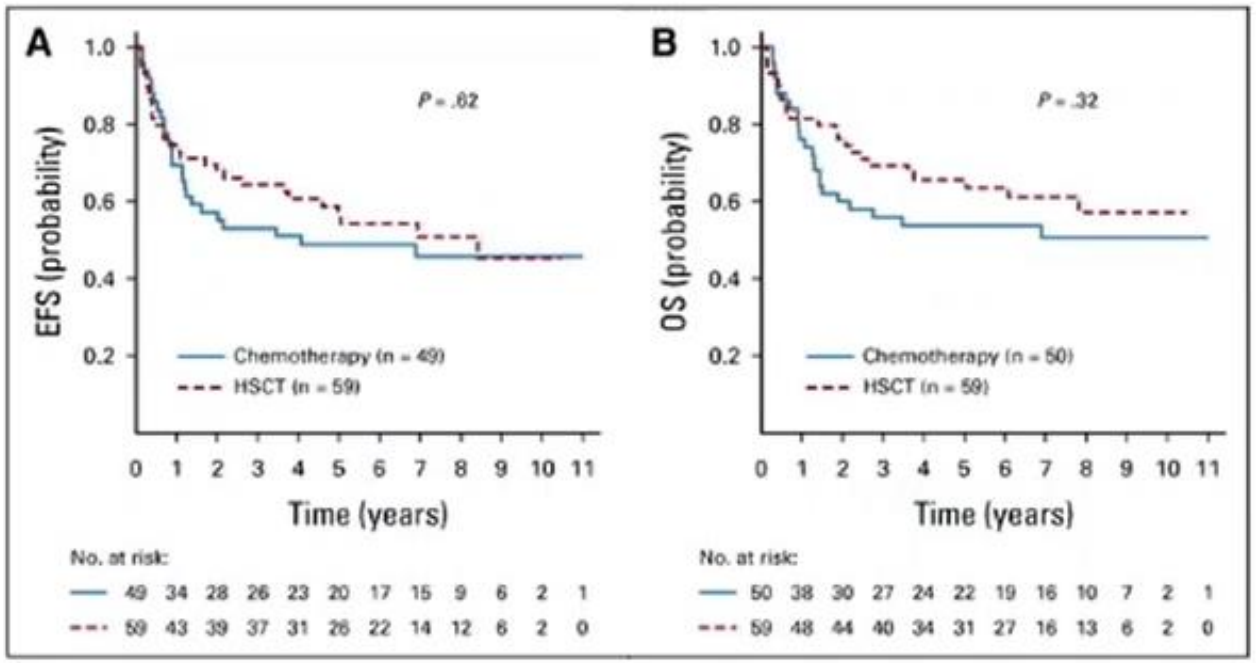
Certain subsets of ALL continue to have poor outcomes…and stem cell transplant may not help….

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022



4 year EFS
LR – 75.5 (Interfant-99 = 74.5)
MR – **45.7** (Interfant-99 = 45.5)
HR – **23.2** (Interfant-99 = 18.6)

Pieters et al. *JCO* 2019



McNeer et al. *JCO* 2019

Intensification of cytotoxic chemotherapy: More is not better!

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

- Second IM + DI (CCG 1961) or DI (CCG 1991)
- Dex vs. Pred (AALL0232, pts ≥10 yrs)
- Intensive consolidation (AALL0331, NCI SR)
- Additional long acting asparaginase (AALL0331, NCI SR)
- Clofarabine/Etoposide/Cyclophosphamide (AALL1131 HR)
- Etoposide/Cyclophosphamide (AALL1131 HR)
- Methotrexate 40 mg/m^2 vs. 20 mg/m^2 (AALL0932 SR)
- Intrathecal triple therapy vs. IT MTX (AALL1131 HR)
- Q 4 pulses of Vincristine/steroids (AALL0932 SR)

All of which begs the question….

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

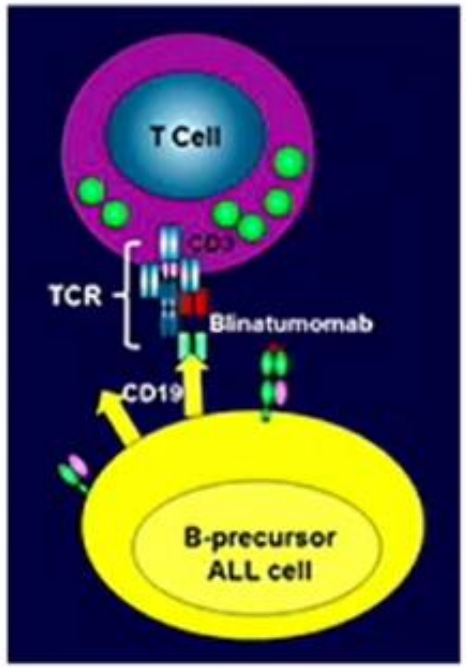
When is it time to stop asking conventional chemotherapy intensification questions in ALL?

And what therapeutics are available?

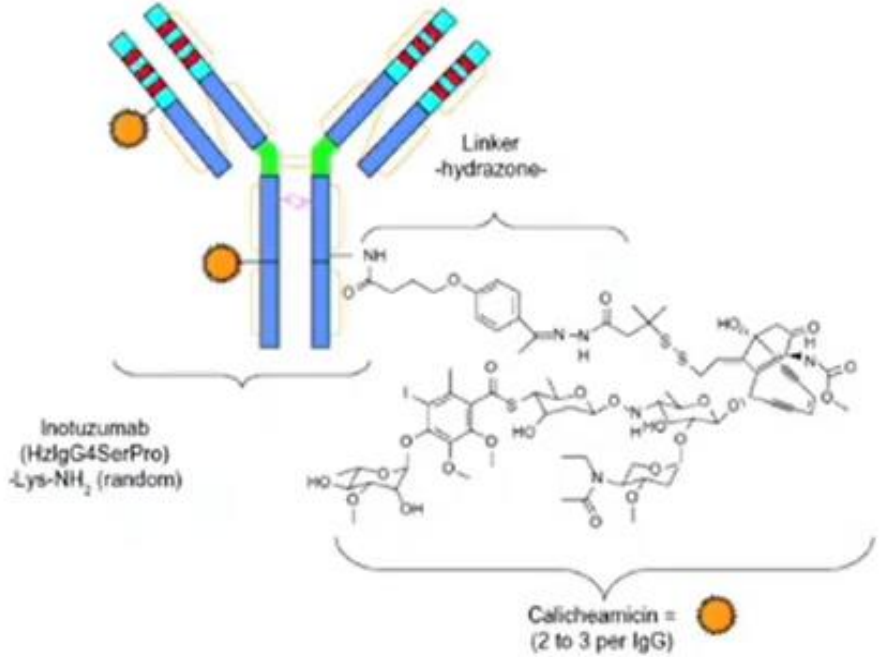
Novel agents for ALL-ready for frontline?

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

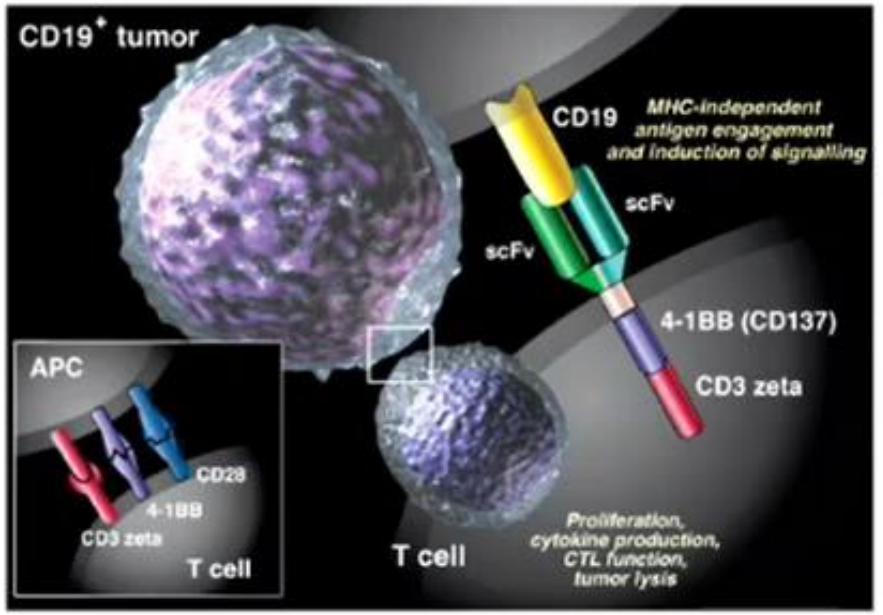
Blinatumomab



Inotuzumab



Chimeric Antigen Receptor therapy



Novel agents and response rates in R/R ALL

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

Immune Therapy	Mechanism of Action	Patient Population Studied	Efficacy
Blinatumomab	Bispecific T cell receptor engager (BiTE) that redirects CD3+ T cells to CD19+ blasts	Adults with R/R Ph- B-ALL Children with Relapsed B-ALL	39% CR **59.3%** 2 yr DFS, AALL1331
Inotuzumab	CD22-directed humanized moAB conjugated to calicheamicin	Adults with CD22+ R/R B-ALL	80.7% CR/CRi
CAR T cells	T cells transduced ex-vivo with chimeric anti-CD19 receptor	Children with CD19+ R/R B-ALL	83% CR/CRi

Kantarjian et al. *N Engl J Med*. 2016;375:740-753, Maury S et al. *N Engl J Med*. 2016;375:1044-1053, Topp M et al. EHA. 2016;149, von Stackelberg A et al. *Blood*. 2016;128:222, Maude et al. *NEJM*, 2014 and 2018, Grupp SA et al. *Blood*. 2016;128:221, Brown, et al. *JAMA* 2021

Introduction of molecularly or immunologically targeted therapy for newly diagnosed B-ALL

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

Risk Group	Projected 5-yr DFS	Protocol	Therapeutic Question
SR-Favorable	>95%	AALL1731	Standard therapy with 2 year duration from IM1
HR-Favorable	>94%	AALL1732	
SR-Avg & High	~89%	AALL1731	Blinatumomab randomization
High Risk	~80%	AALL1732	Inotuzumab randomization
Very High Risk	<50%	AALL1721	CAR T-cell therapy in CR1
Ph+, Ph-like	60-85%	AALL1631 (int) AALL1521	Molecularly targeted therapy

B-ALL

Introduction of molecularly or immunologically targeted therapy for newly diagnosed B-ALL

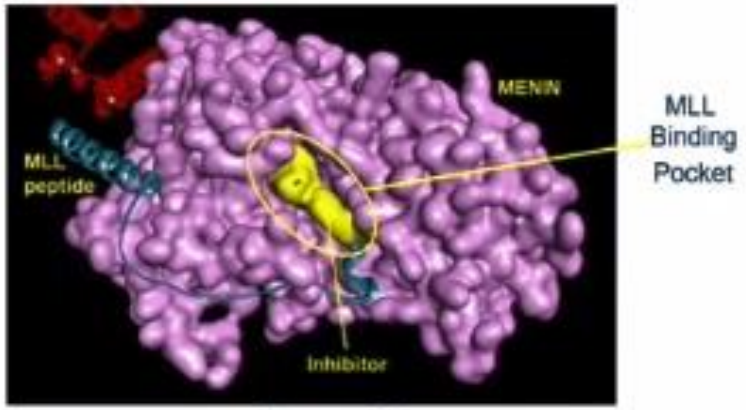
SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

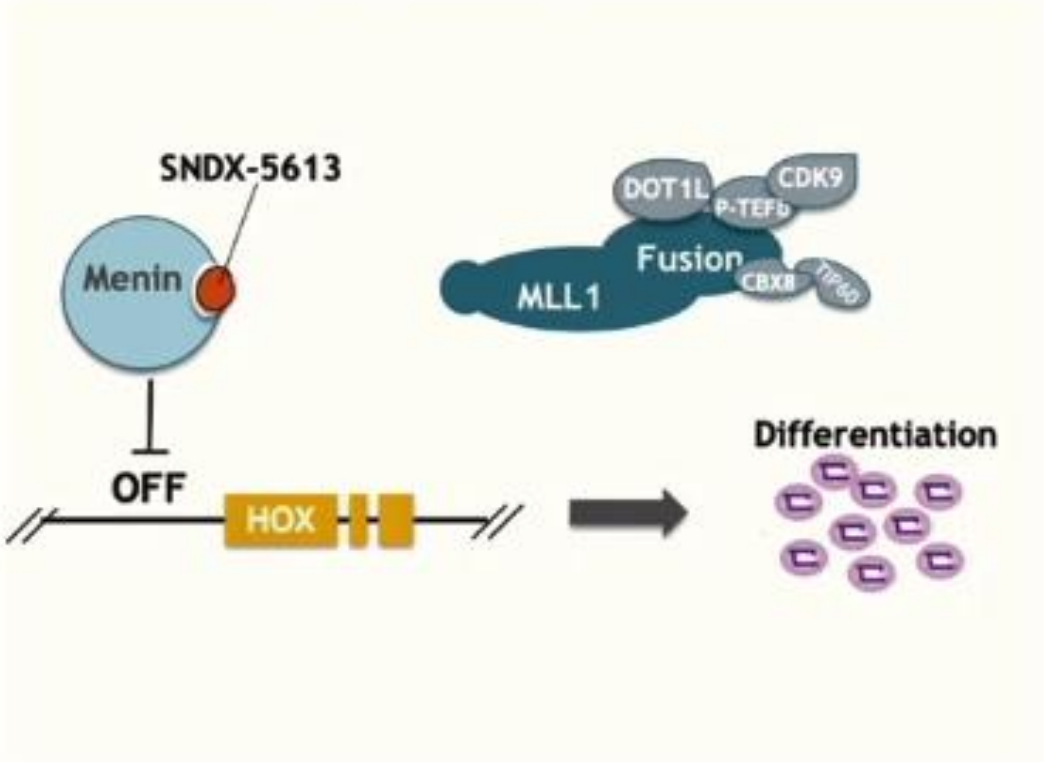
Risk Group	Projected 5-yr DFS	Protocol	Therapeutic Question
SR-Favorable	>95%	AALL1731	Standard therapy with 2 year duration from IM1
HR-Favorable	>94%	AALL1732	
SR-Avg & High	~89%	AALL1731	Blinatumomab randomization
High Risk	~80%	AALL1732	Inotuzumab randomization
Very High Risk	<50%	AALL1721	CAR T-cell therapy in CR1
Ph+, Ph-like	60-85%	AALL1631 (int) AALL1521	Molecularly targeted therapy

B-ALL

AALL1731 is also treating all Down Syndrome (DS) patients—HR DS patients have one month of DI substituted by blinatumomab

Menin-KMT2A inhibition in Acute Leukemia



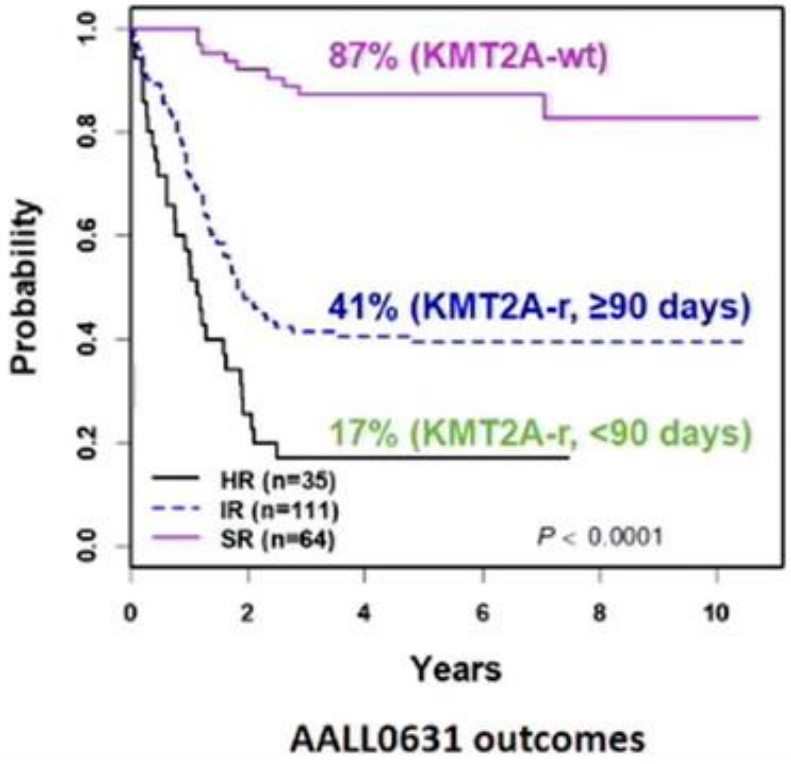


- Menin-KMT2A interaction induces transcriptional deregulation of target genes critical for leukemogenesis
- Menin inhibition occupies the KMT2A binding pocket on Menin leading to:
  - Loss of the leukemic transcription program
  - Disruption of chromatin-associated protein complexes
  - Terminal differentiation and apoptosis

Adopted from: Uckelmann HJ et al, ASH Annual Meeting, 2018
McGeehan J, AACR 2020

What about infants?

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022



AALL0631 outcomes

	INTERFANT-99 (4-year EFS)	INTERFANT-06 (4-year EFS)	COG AALL0631 (3-year EFS)
LR	74.5%	75.7%	87%
MR/IR	45.5%	45.7%	41%
HR	18.6%	23.2%	17%

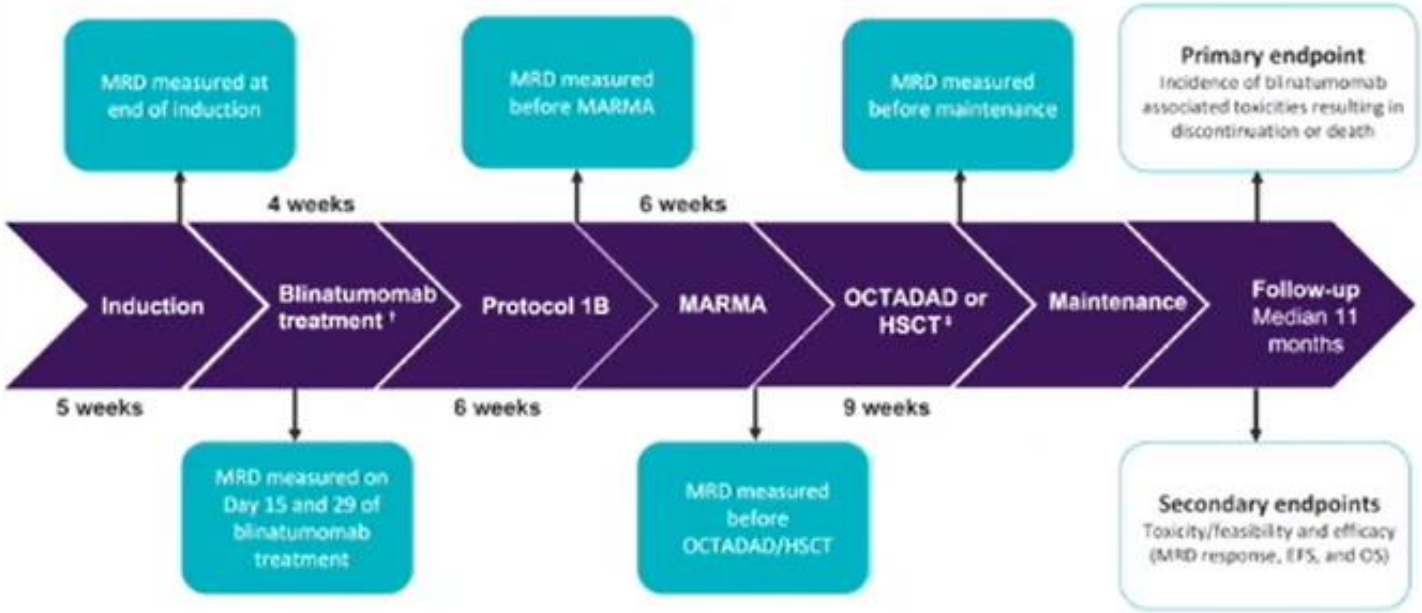
Brown et al, Leukemia, 2021

Pieters et al, JCO 2019 and others

Single course of blina in newly diagnosed infants…

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

Figure 1. Study Design*



EFS, event-free survival; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease; OS, overall survival.

*Adapted from Van Der Sluis, *et al.*[1]

†15 ug/m^2/day, 28-day continuous infusion.

‡Medium risk patients with MRD levels ≥0.05% before OCTADAD and all high-risk patients in complete remission were eligible for HSCT.

Van der Sluis et al, ASH 2021, taken from Reid ALL Hub 2022

...has improved outcomes!

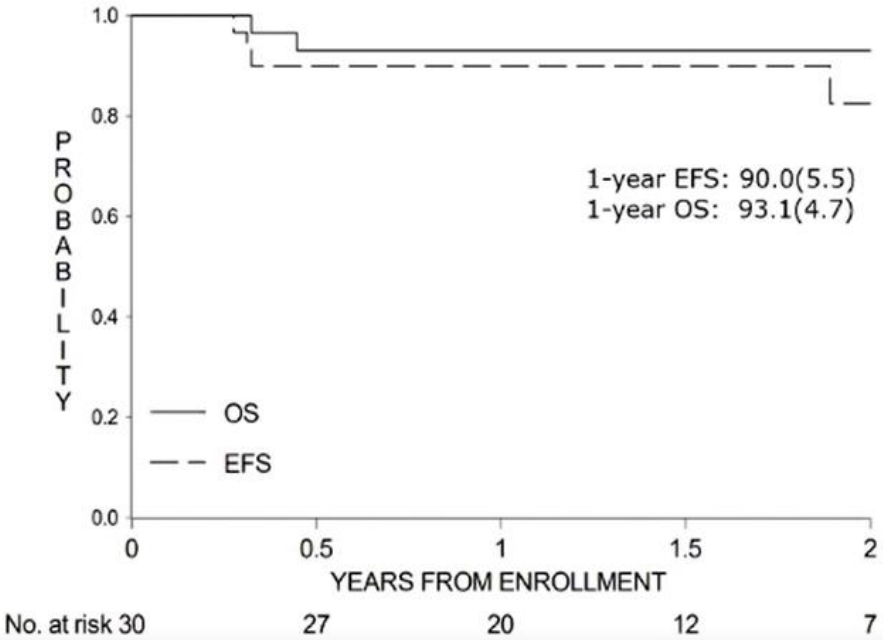
SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN I SEPTEMBER 28 - OCTOBER 1, 2022

Talking: Inge van der Sluis

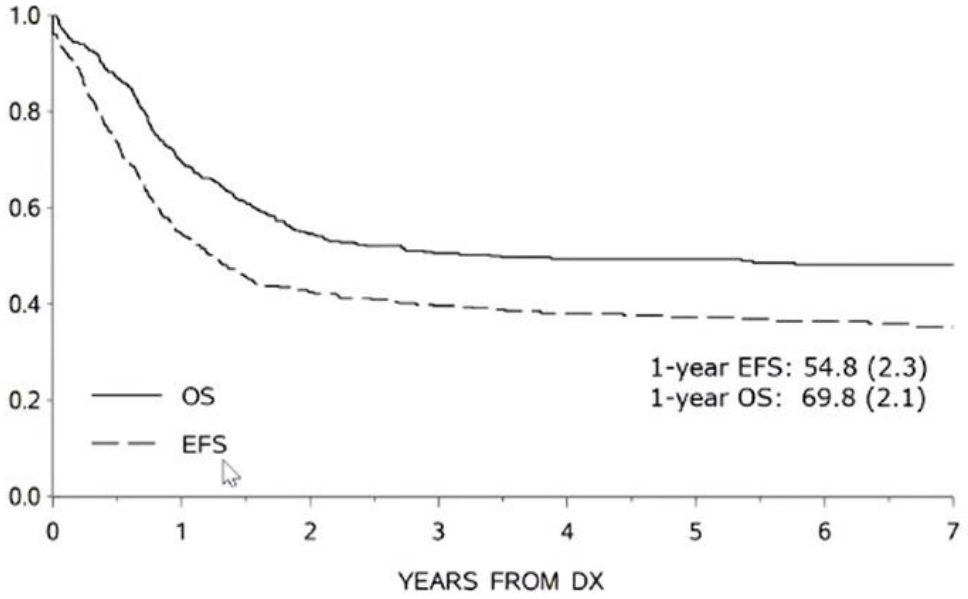
Princess máxima center pediatric oncology

EFS and OS

Blina infant



IF06 (KMT2A-r)



Follow-up (months)
Median: 16.3
Range: 3.3 - 36.7

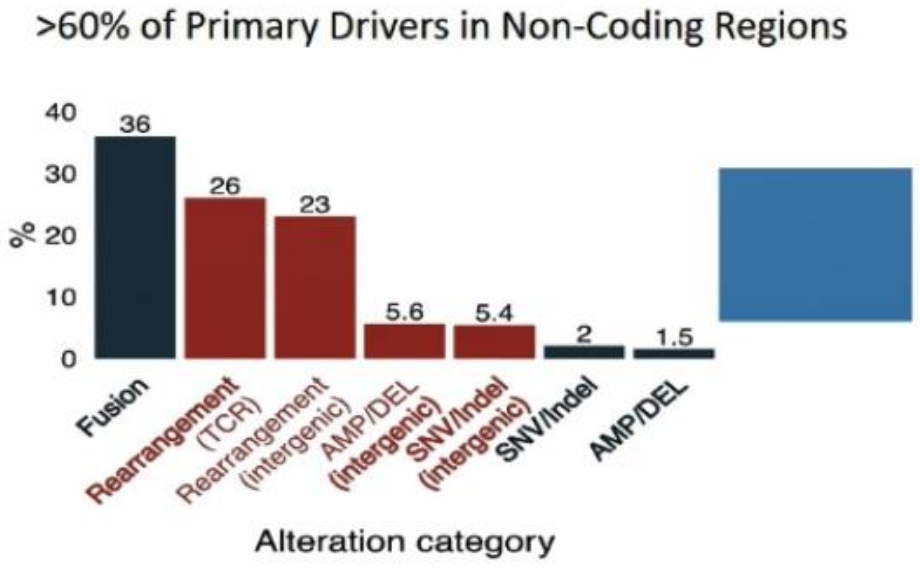
Note: 1/3 of patients (HR) were transplanted

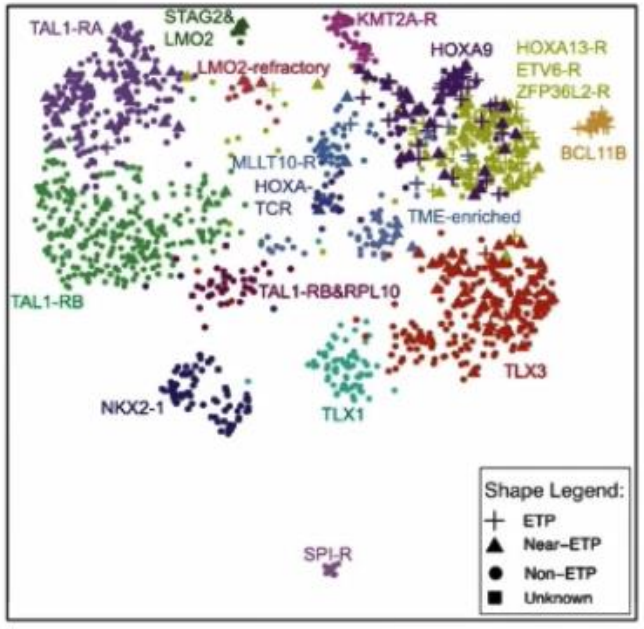
Van der Sluis et al, ASH 2021

What about T-cell?

INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN I SEPTEMBER 28 - OCTOBER 1, 2022

- Dissect out genomics more comprehensively to identify drivers and risk factors for relapse (Teachey, Pölönen, EHA plenary 2022)





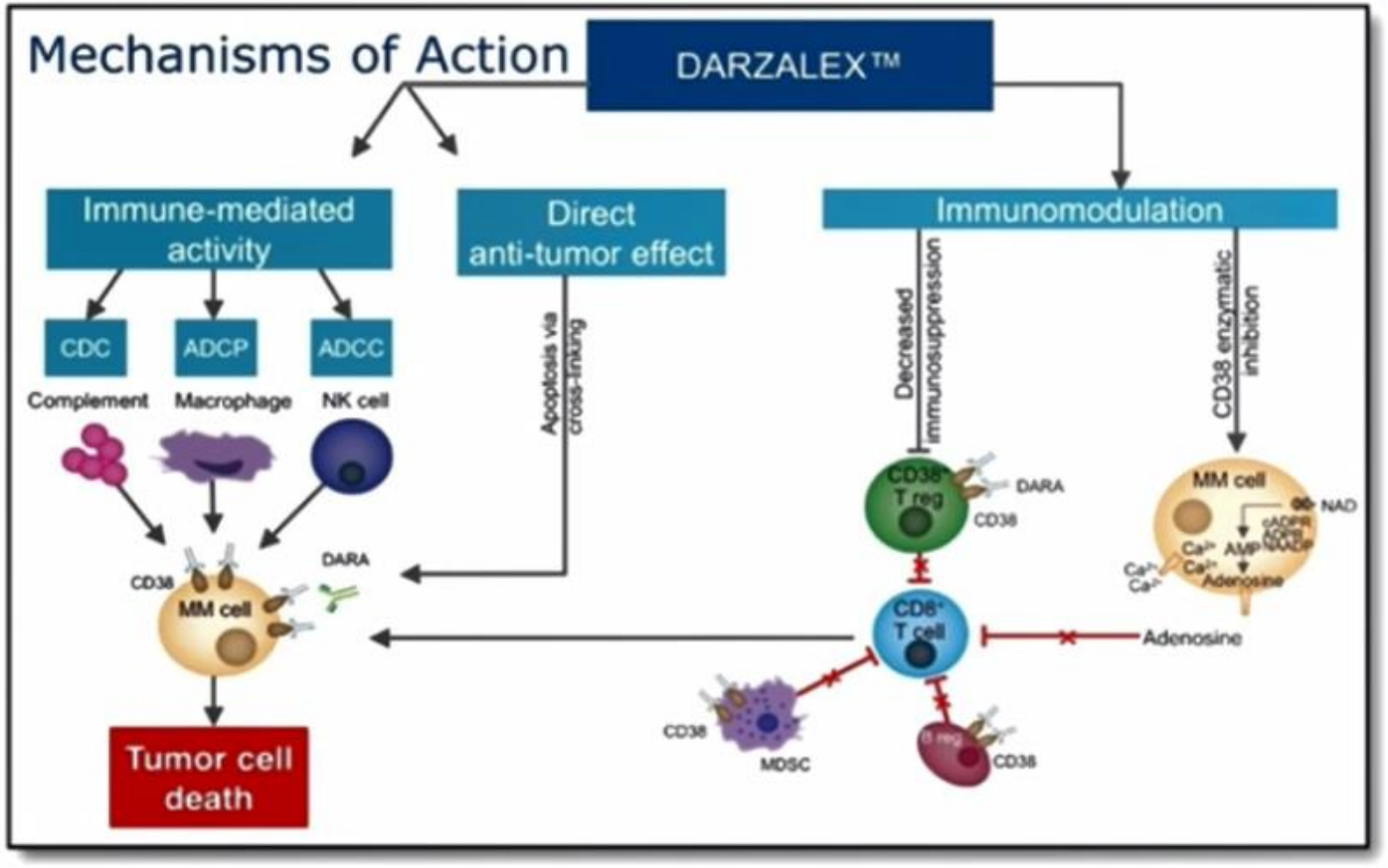
- Randomize to CD38 moAB (daratumumab) (with ALL-Together) (not yet approved by CTEP)
- Utilize bortezomib for T-Lymphoblastic Lymphoma based on AALL1231 results

Teachey et al, *JCO, 2022*

Targeted therapy for T cell ALL?

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN I SEPTEMBER 28 - OCTOBER 1, 2022

- CD38 monoclonal antibody
- FDA approved in MM (effective and safe)
- CD38 is highly expressed in pediatric T-ALL
- Clinical responses observed in 14/15 T-ALL PDX models



Delphinus Phase 2 Trial

ALL			
Cohort	Daratumumab Janssen Delphinus T-cell ALL (1-17 yo) n = 24	Daratumumab Janssen Delphinus T-cell ALL (TOTAL COHORT) n = 29	Bortezomib AALL07P1 T-cell ALL (TOTAL COHORT) n = 22
Response evaluable (n)	22	27	22
12- month Event Free Survival	49.4%	49.5%	45%
12- month Overall Survival	57.9%	59.4%	59%
Received HSCT	62.5%	62.1%	45%

- N.B. In cycle 1 AALL07P1 gave weekly Pegaspargase (4 doses) vs. Delphinus which gave q2 week Pegaspargase (2 total doses)

Hogan, Bhatla, ASCO 2022

SIOP 2022
54TH CONGRESS OF THE INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN
SEPTEMBER 28 - OCTOBER 1
2022

CAR-T Cells for Acute Lymphoblastic Leukemia: ready for prime time ?

André Baruchel

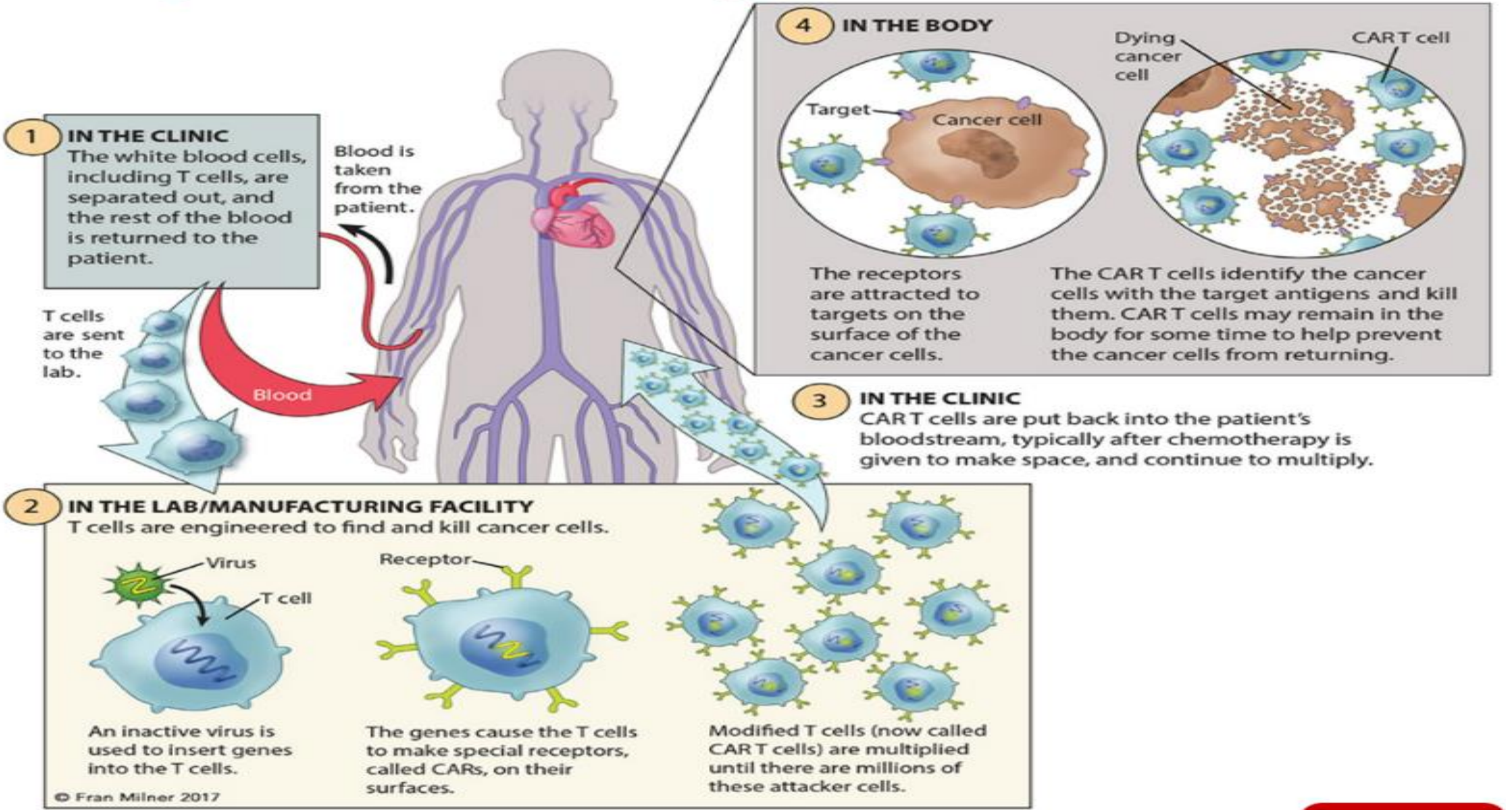
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

University Hospital Robert Debré & Université Paris Cité

Paris, France

Université Paris Cité

Autologous CAR T-Cell Therapy Process



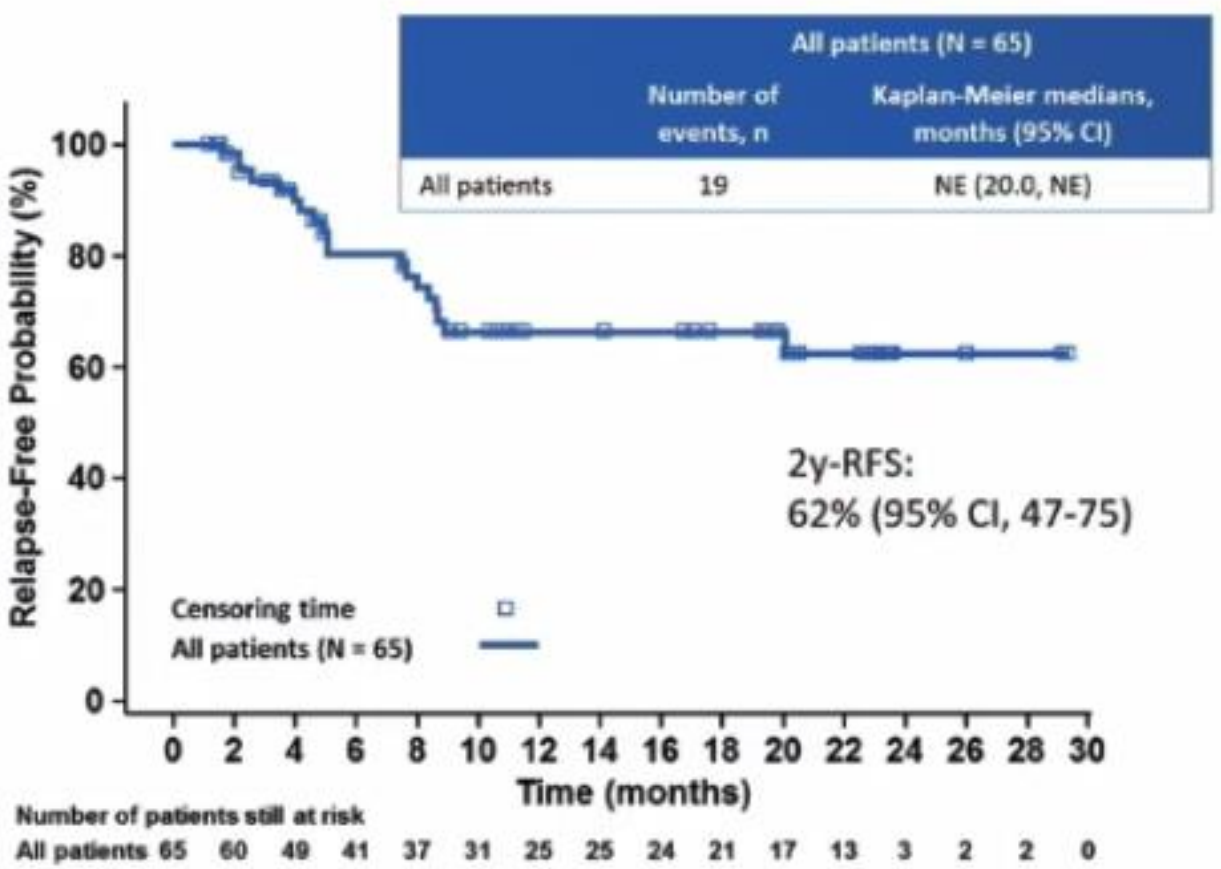
The remaining problems in acute lymphoblastic leukemia

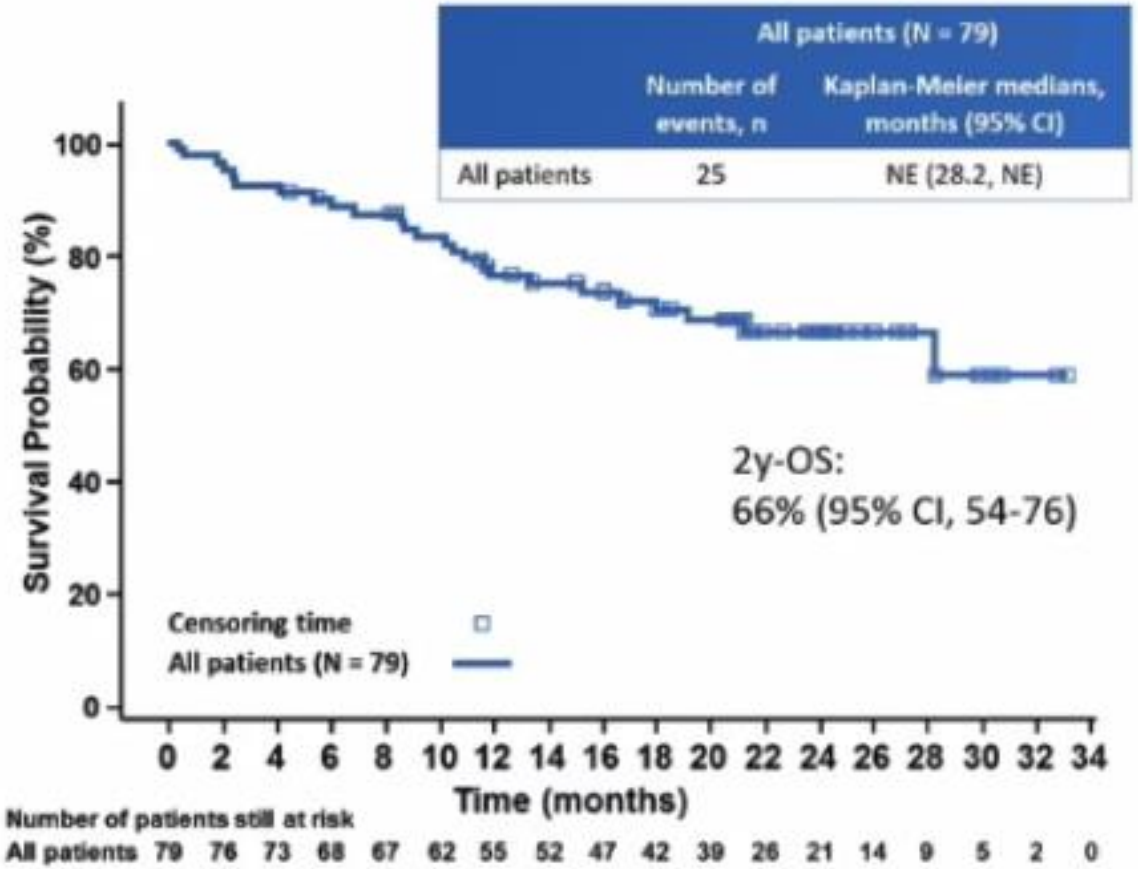
- Efficacy ++ in children (5y-OS >90%)
  - still relapses
    - 15% in children
      - much more in infants (35-40%), adolescents (25%), adults (≥35%+)
    - some relapses rarely curable: t(1;19), t(17;19), hypodiploidy, p53 mut, T-ALL

    overall : unsatisfactory prognosis of relapsed ALL
- Toxicity:
  - non leukemic deaths : induction deaths and deaths in CR
  - prolonged treatment with immune suppression and many treatment-related AEs
    - the more intensive, the longest the therapy, the highest the burden
    - at the top : HSCT (GVHD, TBI-related AEs, etc)

ELIANA trial (Tisagenlecleucel/CTL019): ASH 2018 update

N=79 patients, median follow-up, 24 months



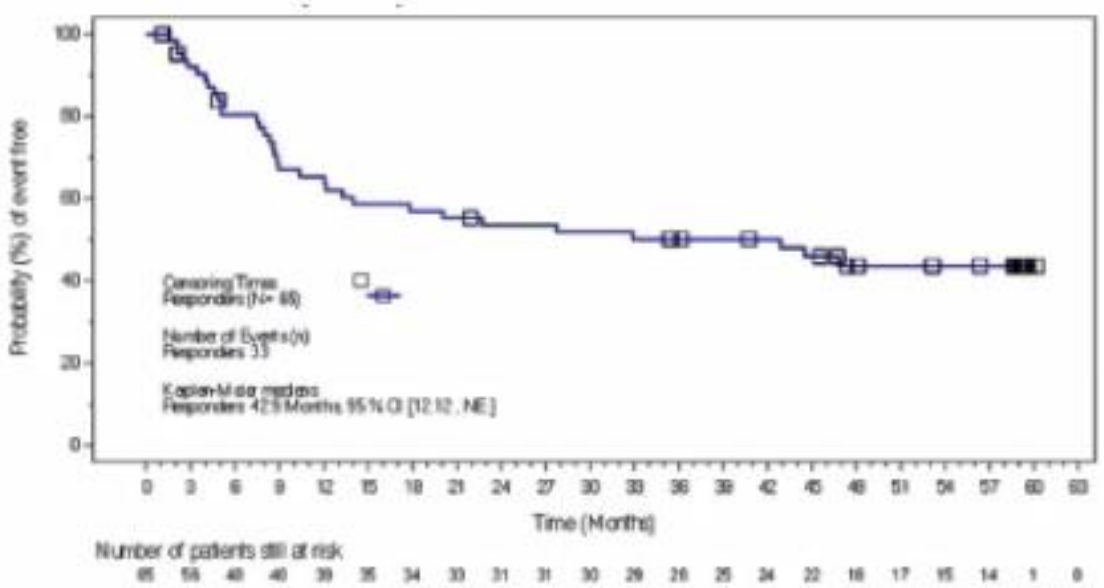


Maude S et al, NEJM 2018
Grupp SA, et al. ASH 2018, abstract 895

ELIANA trial update 2022 (EHA 2022)

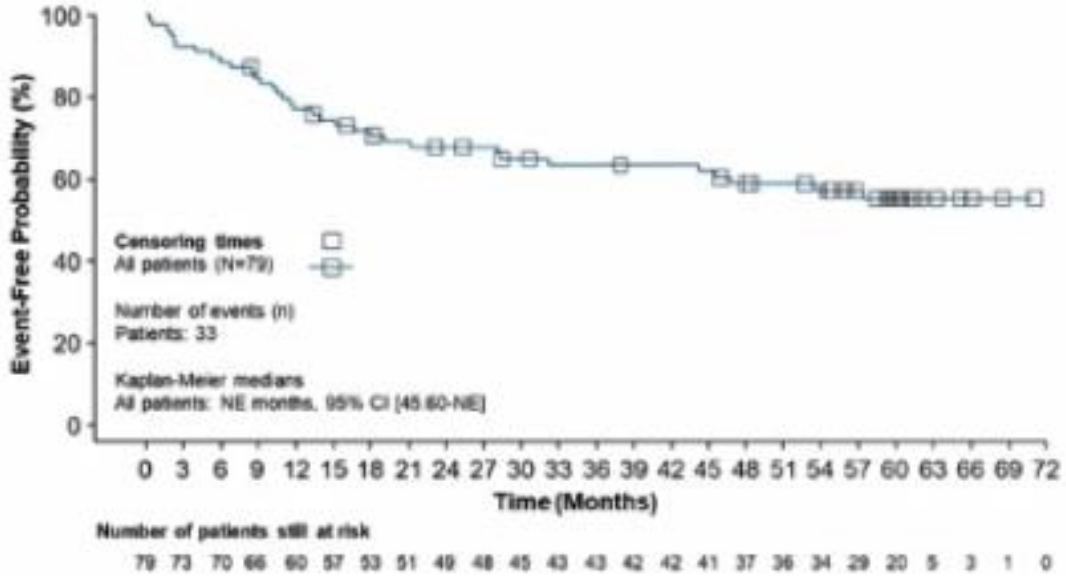
RFS for Patients With a CR/CRi within 3 months

5-year RFS: 43.6% (95% CI, 31%-56%)



Overall Survival

5-year OS: 55% (95% CI, 46%-66%)



Note: OS is without censoring for alloSCT.

17 alloSCT, allogeneic stem cell transplant; NE, not estimable; OS, overall survival.

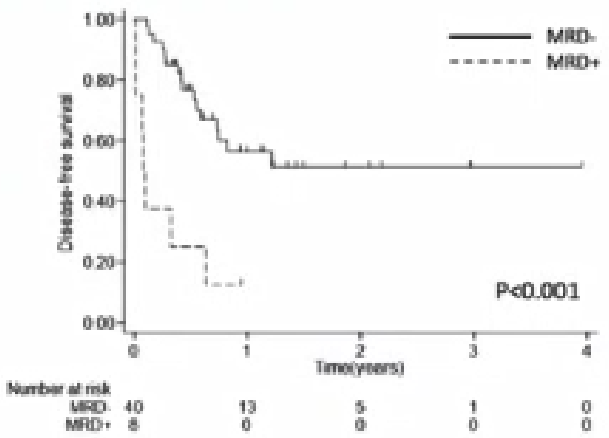
12 **Median time from infusion to data cutoff: 5.5 years**.

Rives S et al, EHA 2022

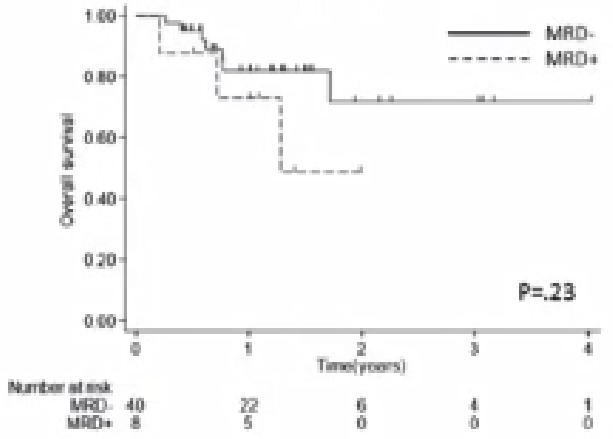
Prognostic impact of early sensitive MRD detection

- **French cohort** (N=51, Tisacel)[1]
  - D28 BM-MRD+ by **qPCR** associated with:
    - shorter DFS
    - CD19 neg. relapse
- **ELIANA + ENSIGN** (N=109, Tisacel)[2]
  - D28 BM-MRD+ by **NGS** associated with;
    - shorter EFS and OS

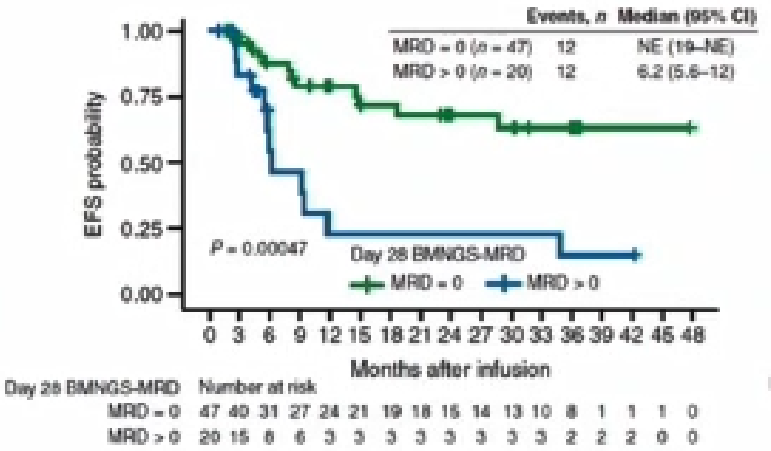
DFS



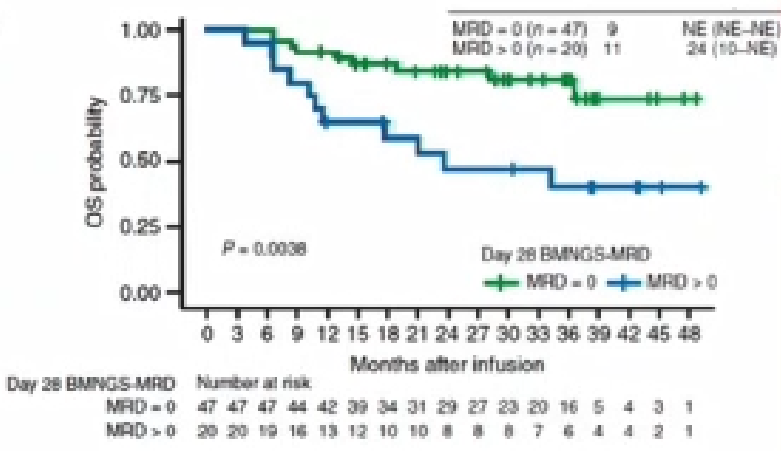
OS (post CR)



EFS



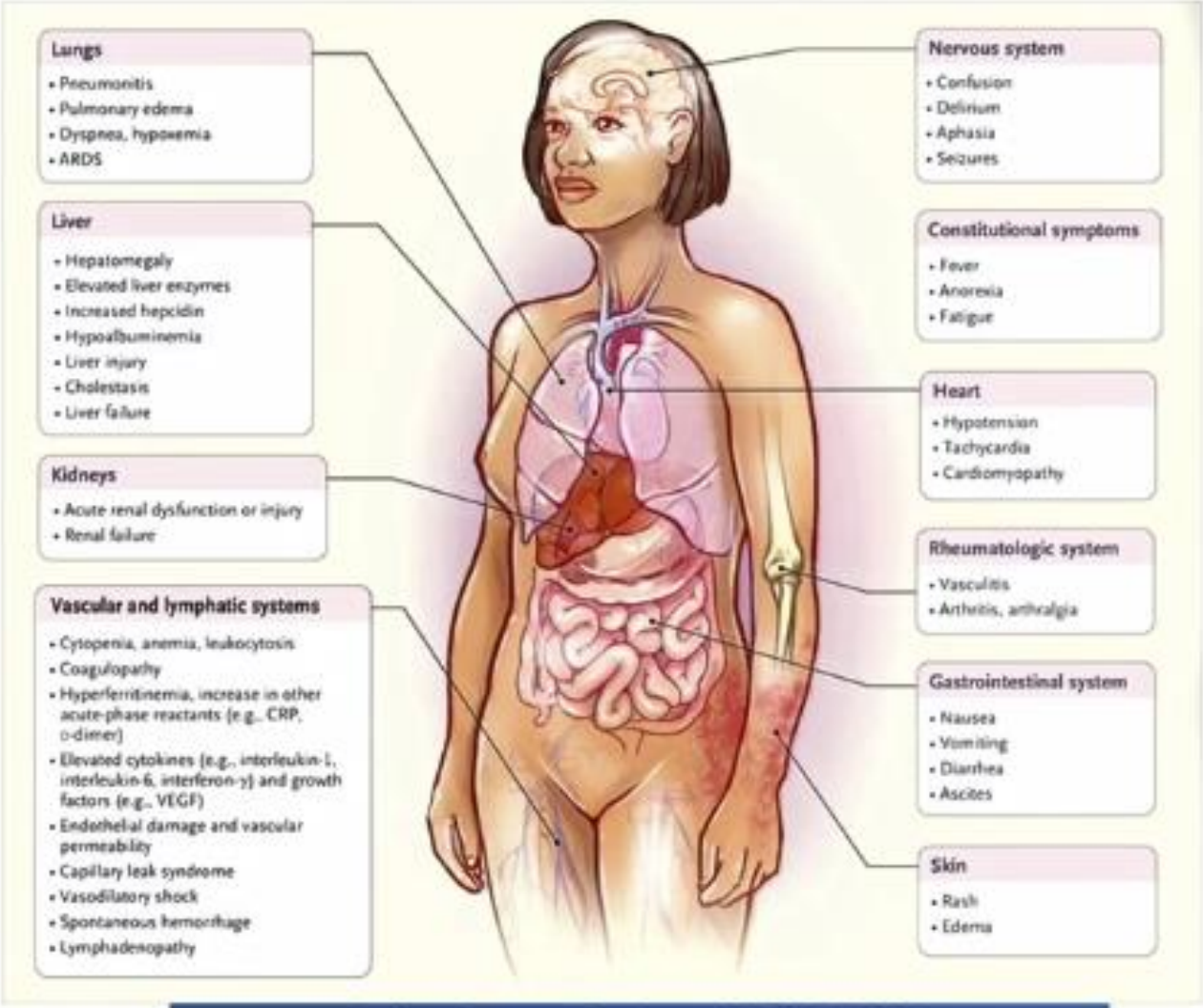
OS



1. *Dourthe ME et al., Leukemia. 2021 Dec;35(12):3383-3393.*
2. *Pulsipher M et al., Blood Cancer Discov. 2022 Jan;3(1):66-81.*

A significant set of AEs

- CRS : « cytokine storm »
- Neurotoxicity
- Macrophage Activation Syndrome
- Prolonged cytopenias
- Infections
- « B-cell aplasia»



Fajgenbaum & June NEJM 2020

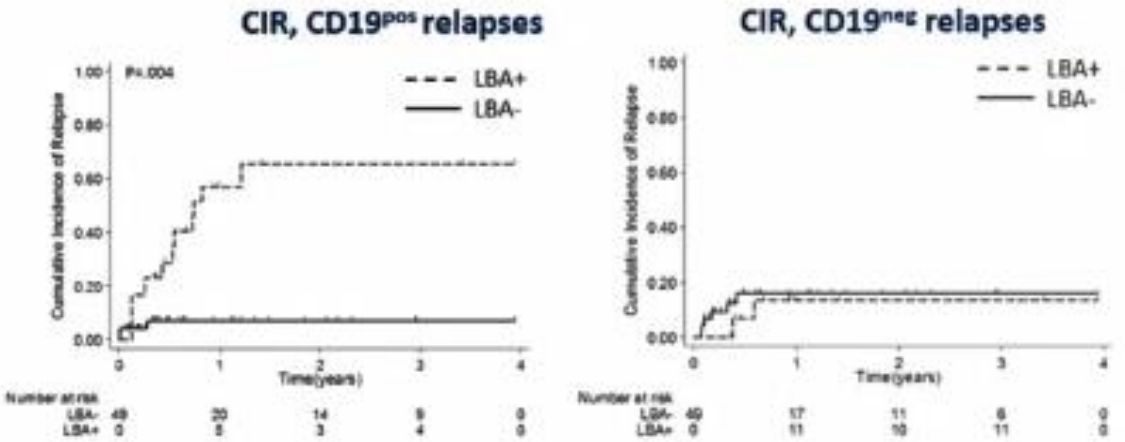
CRS and neurotoxicity in CD19 CAR-T ALL studies

Study	CD19-CAR	N	Population	CR	CRS	Neurotoxicity/CRES
Maude, 2013[1]	4-1BB	30	Ped+Adult	90%	100% 27% severe	43% encephalopathy, seizure, aphasia
Lee, 2015[2]	CD28	21	Ped+YA	68%	76% 28% severe	29% encephalopathy, hallucination
Gardner, 2017[3]	4-1BB	45	Ped+YA	93%	93% 23% severe	49% 21% severe
Maude, 2018[4]	4-1BB	75	Ped+YA	81%	77% ***46% severe***	40% ***13% severe***
Gorashian, 2019	4-1BB	14	Ped +YA	86%	3/14 grade 3	6/14 grade 1-2
Park, 2018[5]	CD28	53	Adult	83%	85% 26% severe	43% **42% severe**
Hay, 2019[6]	4-1BB	53	Adult	85%	75% ***19% severe***	23% severe

Role of CAR T-cell persistence

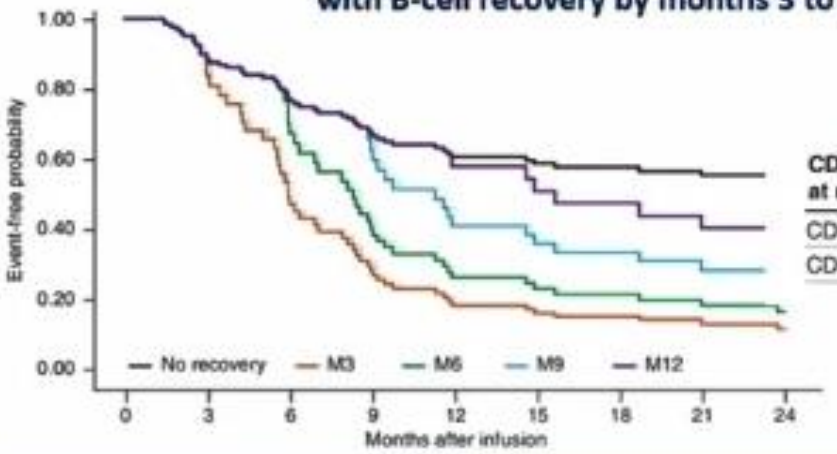
- **B-cell aplasia :**
  - a surrogate of CAR-T persistence/function
  - loss : a time-dependent event
- **Loss of B-cell aplasia** associated with an increased risk of CD19-positive relapse[1,2]
- CD19-negative relapses tend to occur earlier than CD19-positive[1,3]
- **Consequence :**
  - Monthly B-cell count monitoring +++
  - Best cut-off for intervention = 6 months?

French cohort
(N=51, Tisacel)[5]



ELIANA + ENSIGN
(N=109, Tisacel)

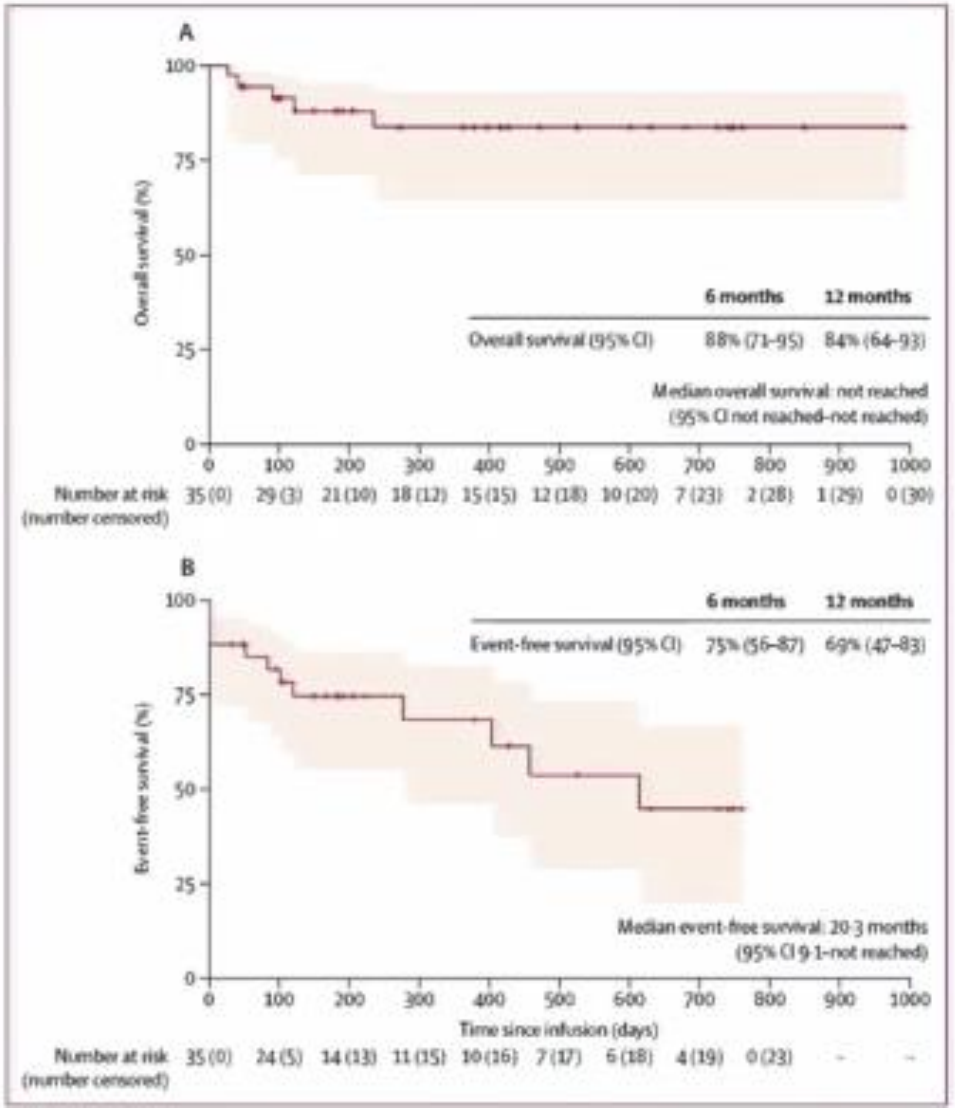
Adjusted EFS curves for patients with B-cell recovery by months 3 to 12



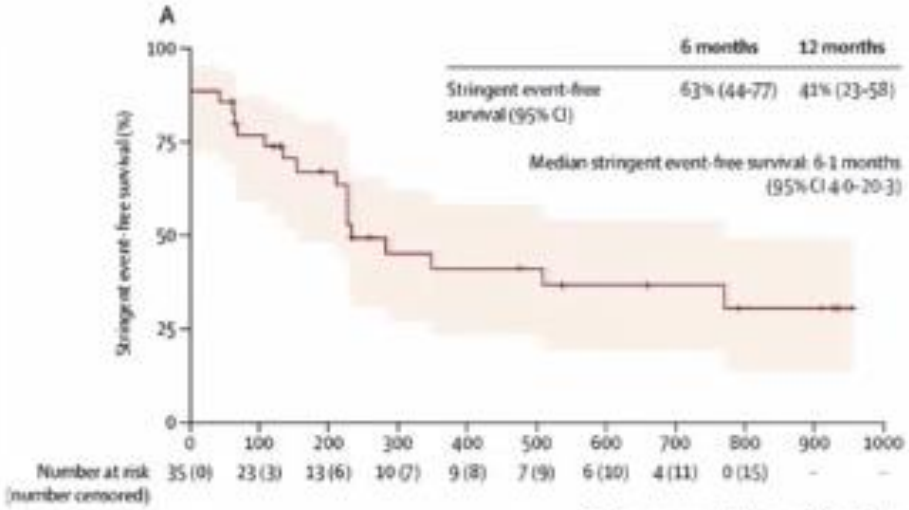
CD19 status at relapse	B-cell status: B-cell recovery	B-cell status: B-cell aplasia
CD19⁻	3 (12%)	22 (88%)
CD19⁺	11 (78%)	3 (22%)

1. Dourthe ME, et al. Leukemia. 2021 Dec;35(12):3383-3393
2. Pulsipher M, et al. Blood Cancer Discov. 2022 Jan;3(1):66-81.
3. Hay KA, et al. Blood. 2019 Apr 11;133(15):1652-1663.

Tisa-cel for children less than 3 years (35 pts; 76% MLL-R): - an IBFM retrospective study -

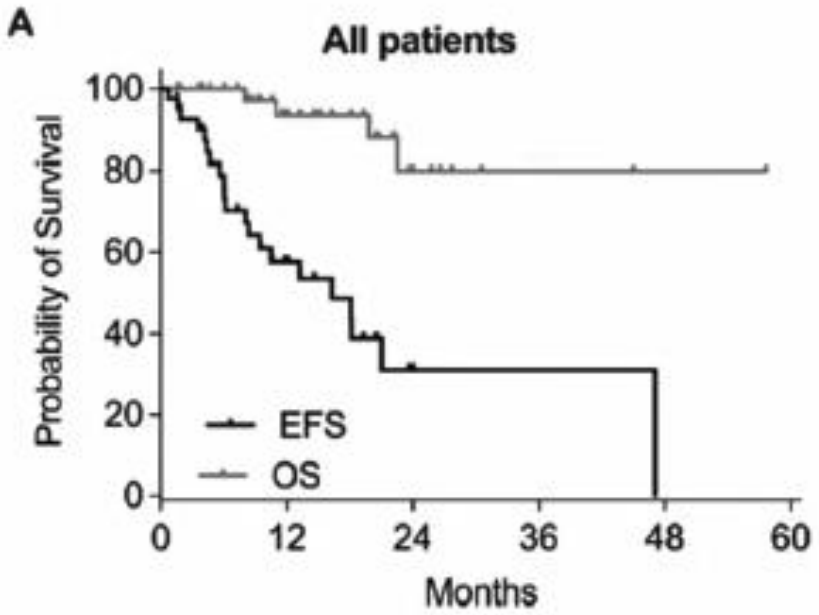


« STRINGENT EFS »



Ghorashian S et al. Lancet Haematol 2022

Tisa-cel for combined (33 pts) vs isolated CNS relapse (8 pts): - an IBFM retrospective study-



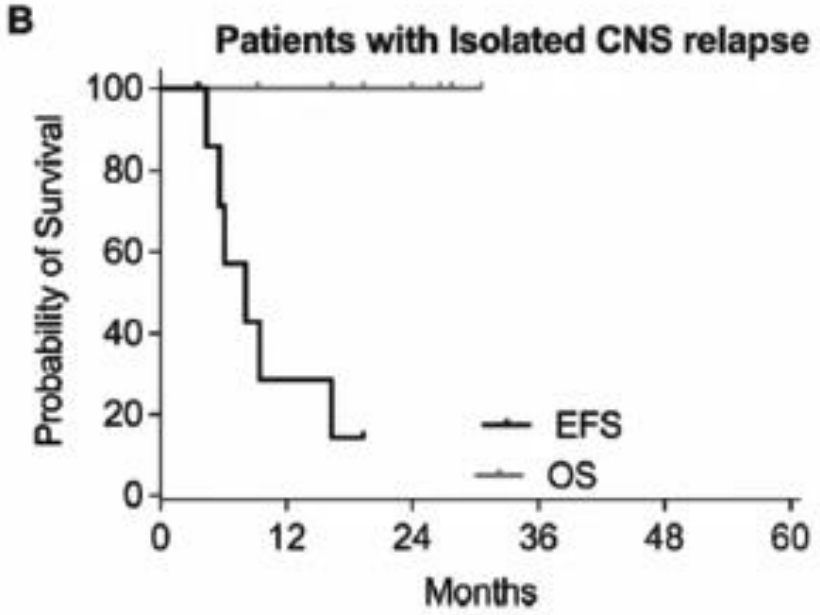


Table 4. Cause-specific hazard regression for CNS relapse of patients treated with 4-1BB-based CAR T-cells.

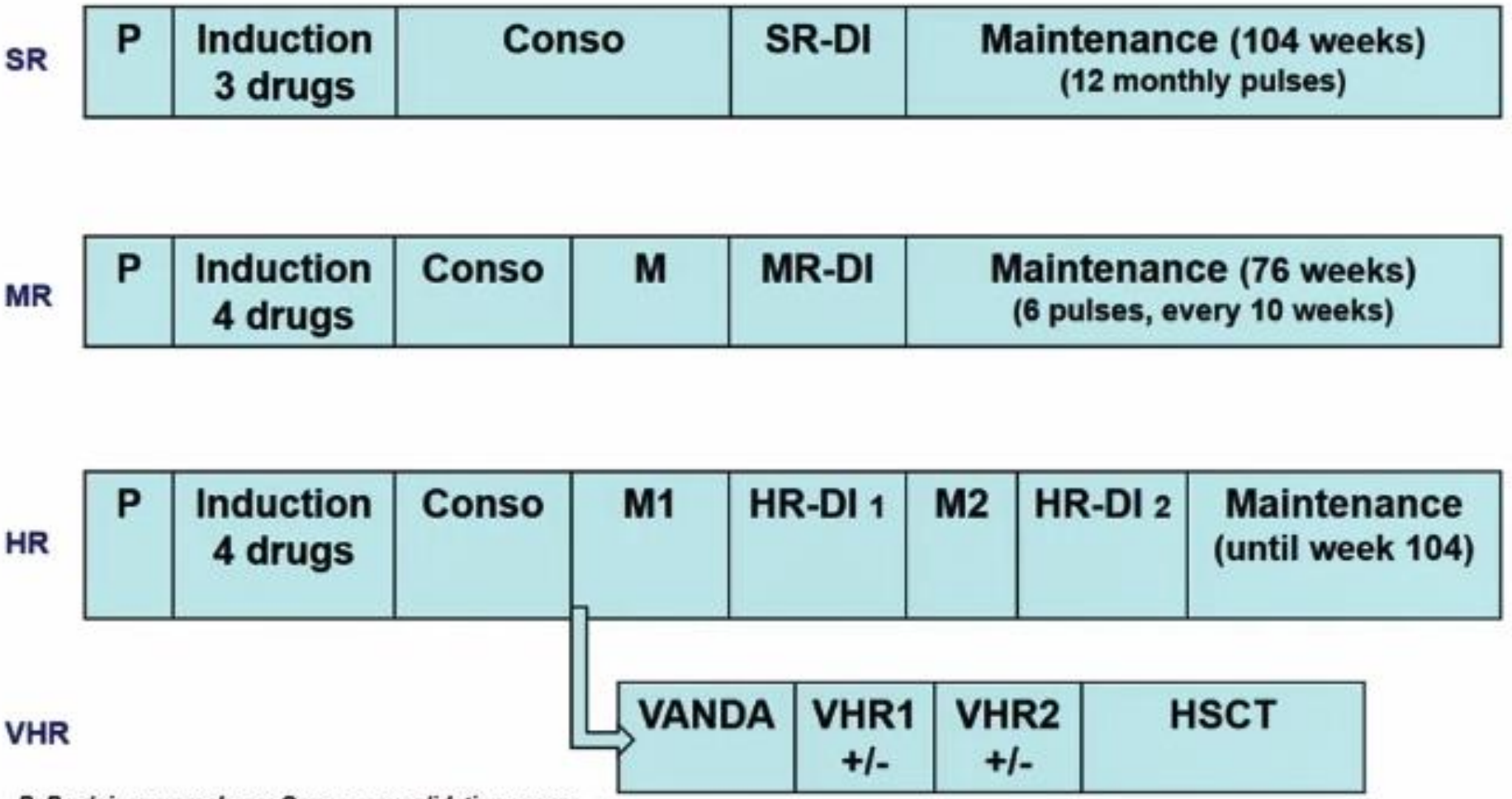
	CNS relapse	
	HR (95% CI)	***P***
Previous HSCT	0.598 (0.1–3.46)	0.56
Previous CNS radiation	0.78 (0.230–2.99)	0.72
CNS-positivity pre LD	4.29 (1.01–18.12)	0.047
Isolated CNS relapse	5.254 (1.2–22.95)	0.02

Jacoby E et al, Leukemia 2022

Current products available in (some) EU centers

	NOVARTIS Tisagenlecleucel	KITE ZUMA 4 Phase 2	CELGENE JCAR-017 Phase 1	
Indication or eligibility criteria	• Primary refractory: not achieving a CR/CRi after 2 or more induction regimens (or not achieving CR/CRi after 1 cycle of schemotherapy for relapsed ALL • 2nd relapse or more • Post HSCT, any	• Primary refractory • *1st early relapse (<18 m)* • 1st refractory relapse • 2nd relapse or more • Post HSCT, any • Disease burden : M2 or MRD+ ($\geq 10^{-4}$)	• Primary refractory: not achieving a CR/CRi after 2 or more induction regimens (or not achieving CR/CRi after 1 cycle of chemotherapy for relapsed ALL • First or greater marrow relapse • Post HSCT, any • Ineligible for allogeneic HSCT • Disease Burden: M2	
Status	commercial use (except CASSIOPEIA clinical trial : 1st line NCI HR ALL patients with MRD+ after consolidation)	clinical trial: opened	clinical trial: opened	
Age	0-25	≤ 21 y and weight ≥ 6 kg	< 18y and weight ≥ 6 kg	
Peexposure to blina	Y	Y	Y	
Preexposure to ino	Y	Y	Y	
Prev. anti-CD19 CAR	Y	N	N	

CAALL-F01: B-lineage ALL groups

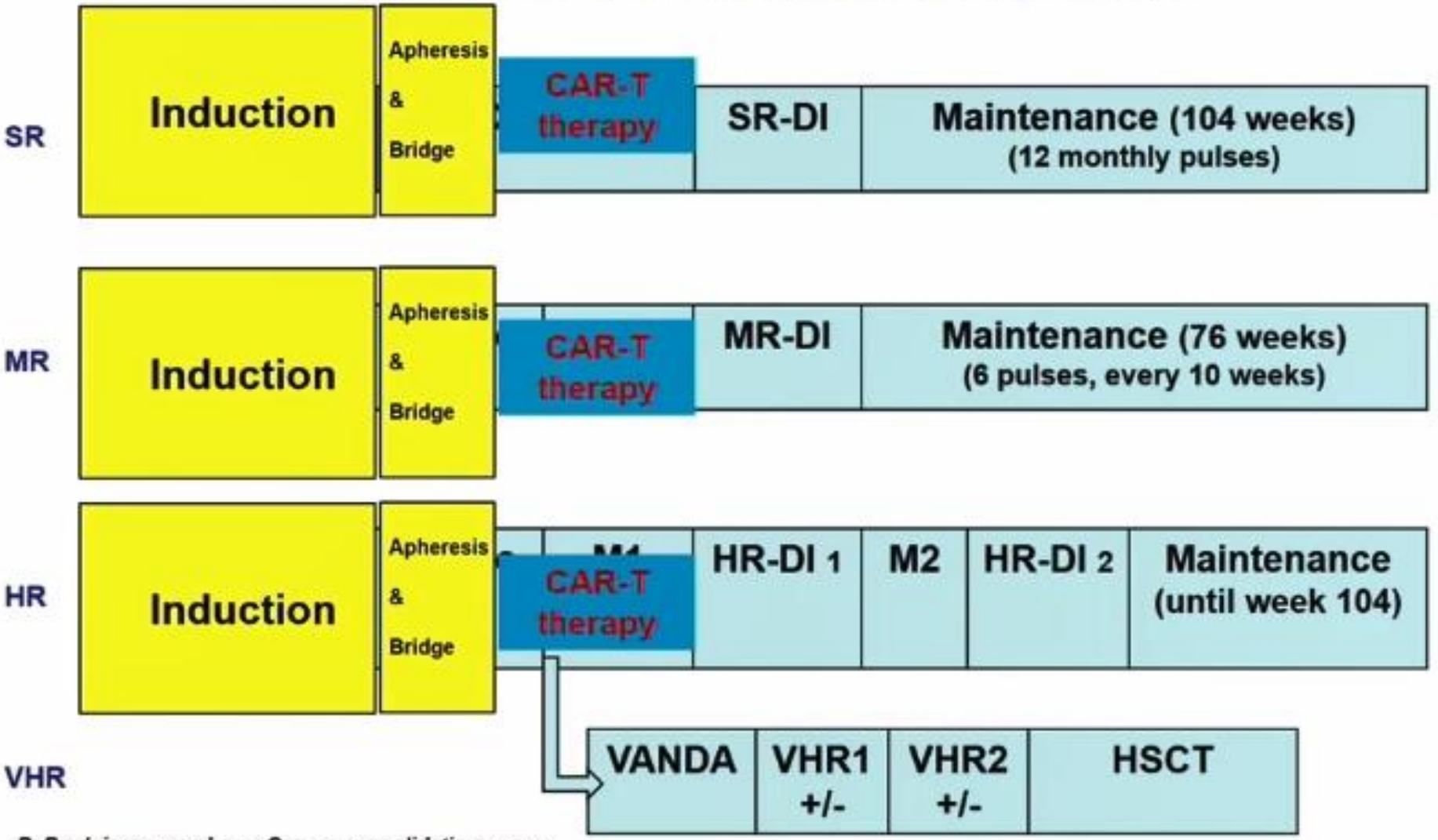


P: Prednisone prephase; Conso: consolidation course

DI: delayed intensification; M: high dose MTX cycles;

HSCT: hematopoietic stem cell transplantation; VANDA/VHR1V/HR2: intensive courses pre HSCT

CAALL-F01: B-lineage ALL groups



P: Prednisone prephase; Conso: consolidation course

DI: delayed intensification; M: high dose MTX cycles;

HSCT: hematopoietic stem cell transplantation; VANDA/VHR1V/HR2: intensive courses pre HSCT

To Transplant or Not to Transplant?

SIOP 2022
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

- No clear consensus on consolidative HSCT after CD19 CAR-T in transplant-naïve patients
- Probable benefit in relapse reduction
- Blanket approach may incur excess toxicity

Table 1. Outcomes of HSCT post CD19 CAR T-cell therapy

Reference	Number of subjects	Age years. Median (range)	CAR costimulatory domain	Median time from CAR to HCT days (range	EFS HCT vs No HCT at 2 yrs	Post-HSCT relapse and TRM in HCT arm
Frey [43]	HCT *N* = 9 No HCT *N* = 15	HCT 39 (24–50) No HCT 36 (26–63)	4–1BB	78 (51–162)	HCT ~85% No HCT ~35%	Not specified
Hay [17▪]	HCT *N* = 18	HCT 35 (22–73)	4–1BB	70 (44–138)	HCT 61%	Relapse 17% TRM 23%
Jiang [44]	HCT *N* = 21 No HCT *N* = 26	Not specified	4–1BB	Not specified	HCT ~70% No HCT ~30%	Not specified
Summers [26]	HCT *N* = 23 No HCT *N* = 27	HCT 15 (1–25) No HCT 12 (1–22)	4–1BB	Approximately 3 months	HCT 75% No HCT 40%	Relapse 5/23 (22%) TRM 1/23 (4.3%)
Zhang [24]	HCT *N* = 75 No HCT *N* = 27	(all) 12 (2–61)	CD28 and 4–1BB	63 (63–120)	HCT 76.9% No HCT 11.6%	Relapse 10/75 (13.3%) TRM 3/75 (4%)
Shah [23▪▪]	HCT *N* = 21 No HCT *N* = 7	(all) 13.5 (4.3–30.4)	CD28	54 (42–97)	HCT 62% No HCT 0%	Relapse 9.5% TRM 6/21 (29%)
Park [12]	HCT *N* = 17 no HCT *N* = 16	(all) 44 (23–74)	CD28	74 (44–312)	HCT ~30% No HCT ~30%	Relapse 6/17 (35%) TRM 6/17 (35%)
Curran [15▪]	HCT *N* = 15 no HCT *N* = 3	(all) 13.5 (1–22.5)	CD28	57 (30–200)	HCT 8/15 No HCT 0/3	Relapse 4/15 (26.7%) TRM 3/15 (20%)

CAR, chimeric antigen receptor; EFS, event-free survival; HCT, hematopoietic cell transplantation; OS, overall survival

Qayed M, Bleakley M, and Shah NN. *Curr Opin Hematol* 2021, 27:000-000

Possible Concepts if CARs make it

(LTFU efficacy & safety)

years to come

Autologous & persistent CARS

1. could first replace allo HSCT for :

- advanced disease
  - relapse ≥ 2, relapse post HSCT, refractory relapse
  - 1st high-risk relapse
- 1st line Very-High Risk ALL (non responding to I+C chemo)

2. could replace prolonged intensive and toxic chemo in 1st line HR ALL :

- e.g. induction-(consolidation)-bridge-CAR

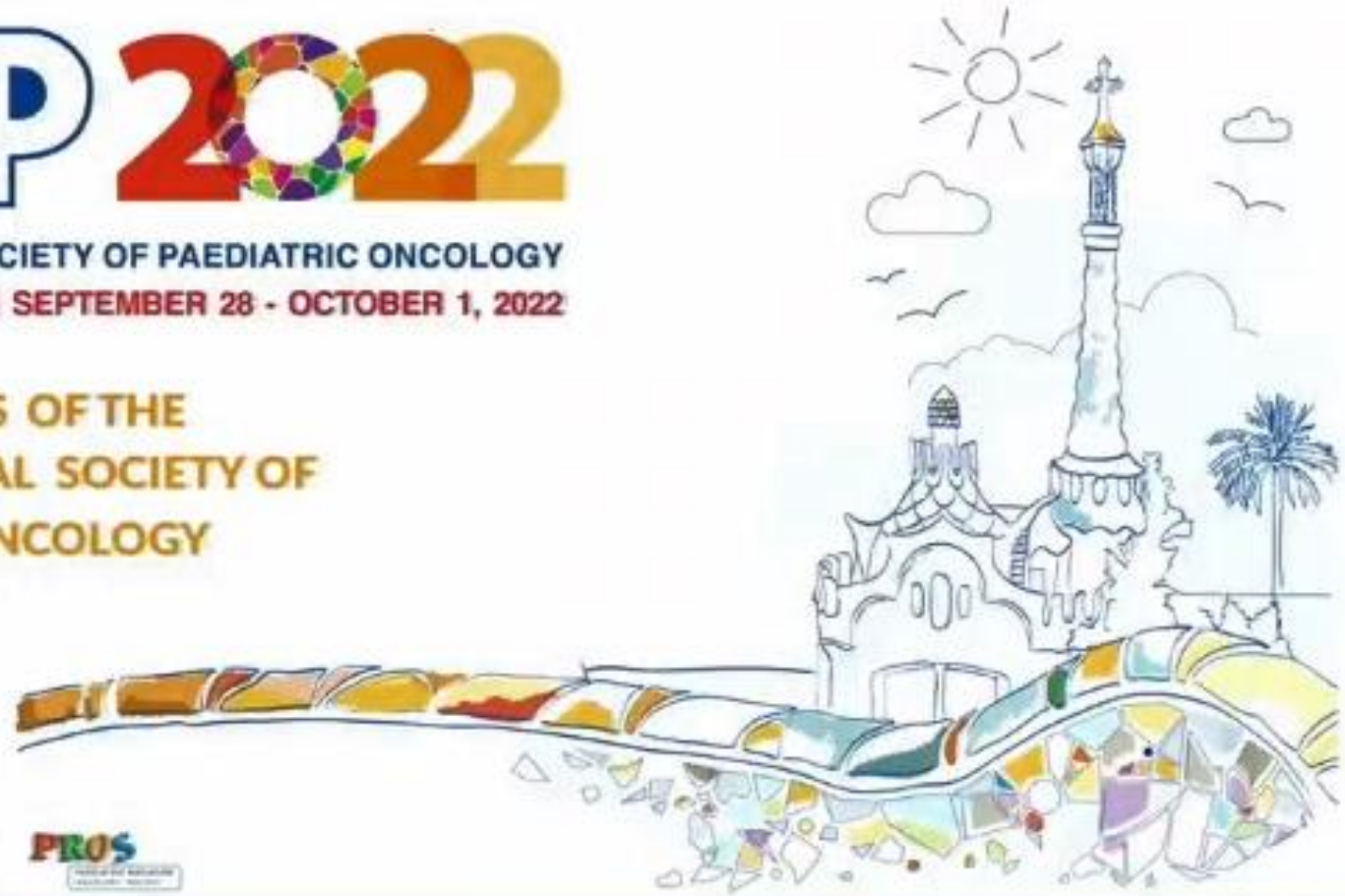
Management of refractory and relapsed childhood AML

Henrik Hasle
Department of Pediatrics
Aarhus University Hospital, Denmark

SIOP 2022

INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
BARCELONA, SPAIN | SEPTEMBER 28 - OCTOBER 1, 2022

54TH CONGRESS OF THE INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY



In conjunction with:

Childhood Cancer International

PROS

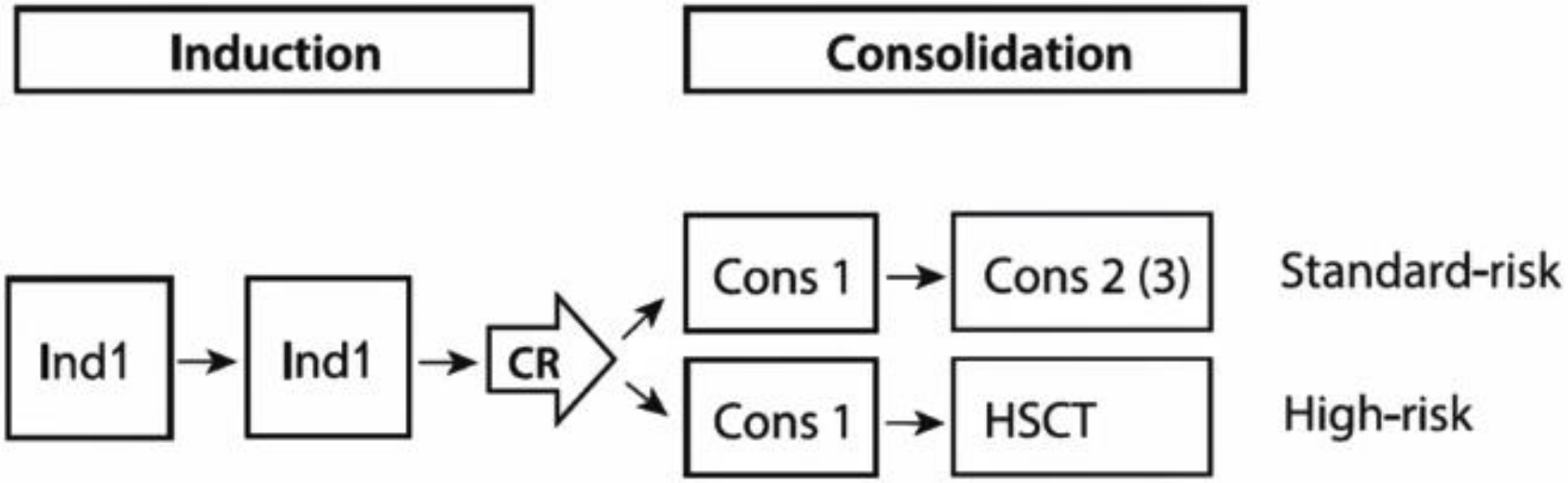
Management of refractory and relapsed childhood AML

Definitions

- Refractory AML
  - No complete remission (blasts >5%) after 2 induction courses
- Relapse
- A single PB/BM sample showing ≥ 5% leukemic blasts by morphology, flow cytometry, or karyotype/FISH
- A single bone marrow sample with at least two tests showing ≥ 1% leukemic blasts examples of tests include:
  - Flow cytometry showing leukemia by multidimensional flow cytometry (MDF).
  - Karyotypic abnormality.
  - FISH abnormality identical to diagnosis (above level of sensitivity of specific FISH probe).
  - PCR or NGS-based demonstration of leukemogenic lesion (e.g., fusion, mutation) matching diagnosis
- Two consecutive PB/BM sample with at least two tests showing a one log increase of leukemic cells with the second tests quantified as ≥ $5x10^{-4}$
- Extramedullary relapse
  - CNS leukemia or biopsy proven extramedullary disease after documented CR

Therapy and risk stratification for children with de novo AML

Hasle. Br J Haematol 2014; 116: 23



Duration of standard therapy approximately 6 months

The ratio of high-risk (i.e. HSCT in CR1) varies between protocols from 10 to 40%

Risk stratification in current European protocols

NOPHO-DBH AML 2012

HR
≥ 15% LC after C1
≥ 0.1% LC after C2
FLT3-ITD wo NPM1 mut

All other patients are Standard risk

BFM-AML2012

HR
Poor response after C2
t(4;11)
t(5;11)/NUP98/NSD1
t(6;11)
t(10;11)
t(6;9)
t(7;12)
der(12p)
-7 (isolated)
t(9;22)
FLT3-ITD-WT1 mut
Complex karyotype

MyeChild

HR
≥ 0.1% LC after C2
t(4;11)(q21;q23)/KMT2A-AFF1
t(5;11)(q35;p15.5)/NUP98-NSD1
t(6;11)(q27;q23)/KMT2A-KMT2AT4
t(10;11)(p11-14;q23)/KMT2A-KMT2AT10
t(6;9)(p23;q34)/DEK-NUP214
abnormal 12p

monosomy 7
t(9;22)(q34;q11)/BCR-ABL1
FLT3-ITD wo favorable genetic features
inv(3)(q21;q26)/t(3;3)(q21;q26)/abn(3q)
inv(16)(p13.3;q24.3)/CBFA2T3-GLIS2
monosomy 5/del(5q)

AIEOP

HR
> 1% LC after C1
> 0.1% LC after C2
t(4;11)
t(5;11)
t(6;11)
t(10;11)
t(6;9)
t(7;12)
der(12p)
-7 (isolated)
t(9;22)
FLT3-ITD-WT1 mut
Complex karyotype

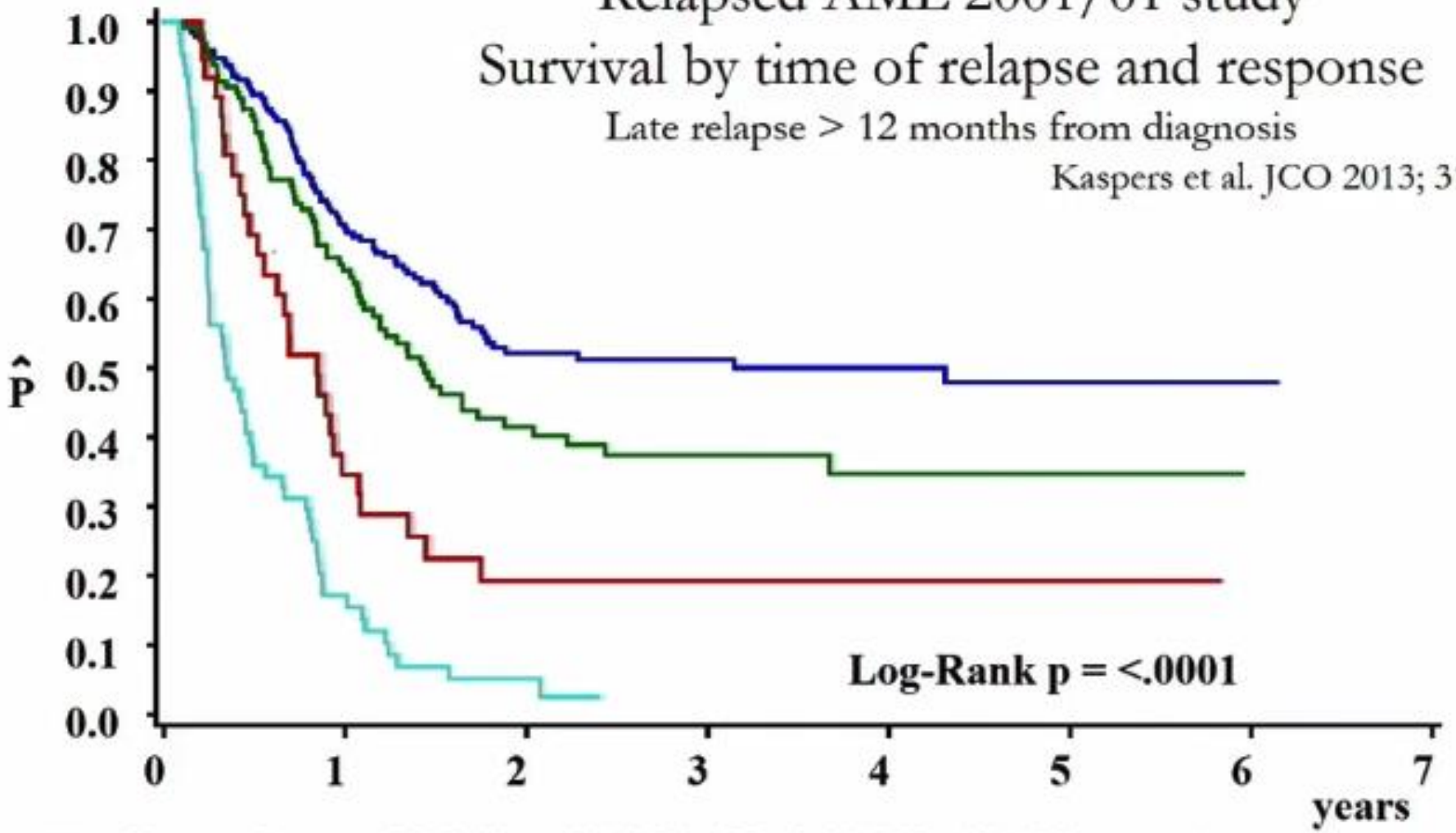
All groups now use SCT as consolidation therapy for HR patients

Relapsed AML 2001/01 study

Survival by time of relapse and response

Late relapse > 12 months from diagnosis

Kaspers et al. JCO 2013; 31: 599



Late relapse BM 28<=20 0.50, SE=0.04 (N=195, 85 events)

Late relapse BM 28> 20 0.19, SE=0.07 (N= 39, 28 events)

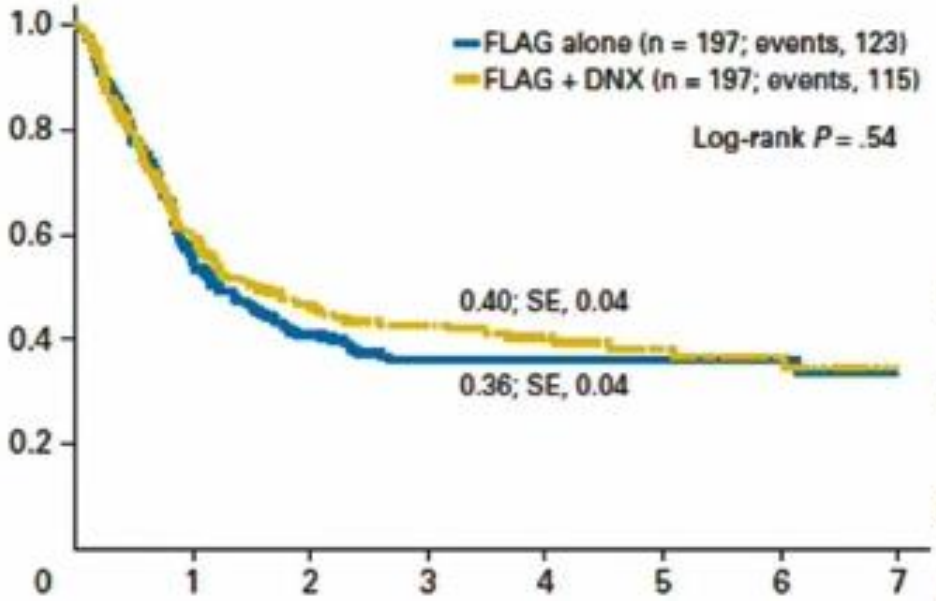
Early relapse BM 28<=20 0.35, SE=0.05 (N=130, 69 events)

Early relapse BM 28> 20 0.03, SE=0.02 (N= 64, 61 events)

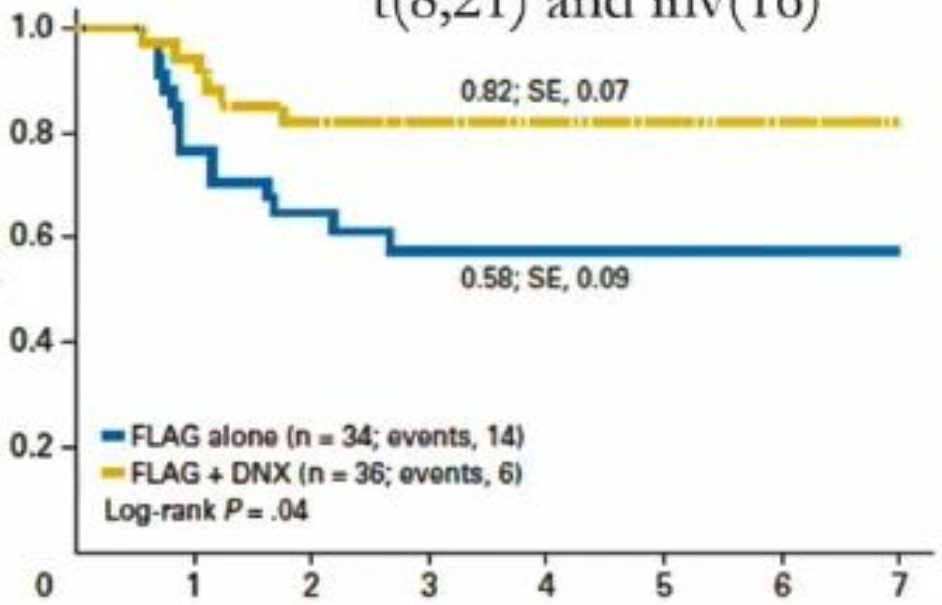
Relapsed AML 2001/01 study - Overall Survival by induction course FLAG +/- DNX

Kaspers et al. JCO 2013; 31: 599

All patients



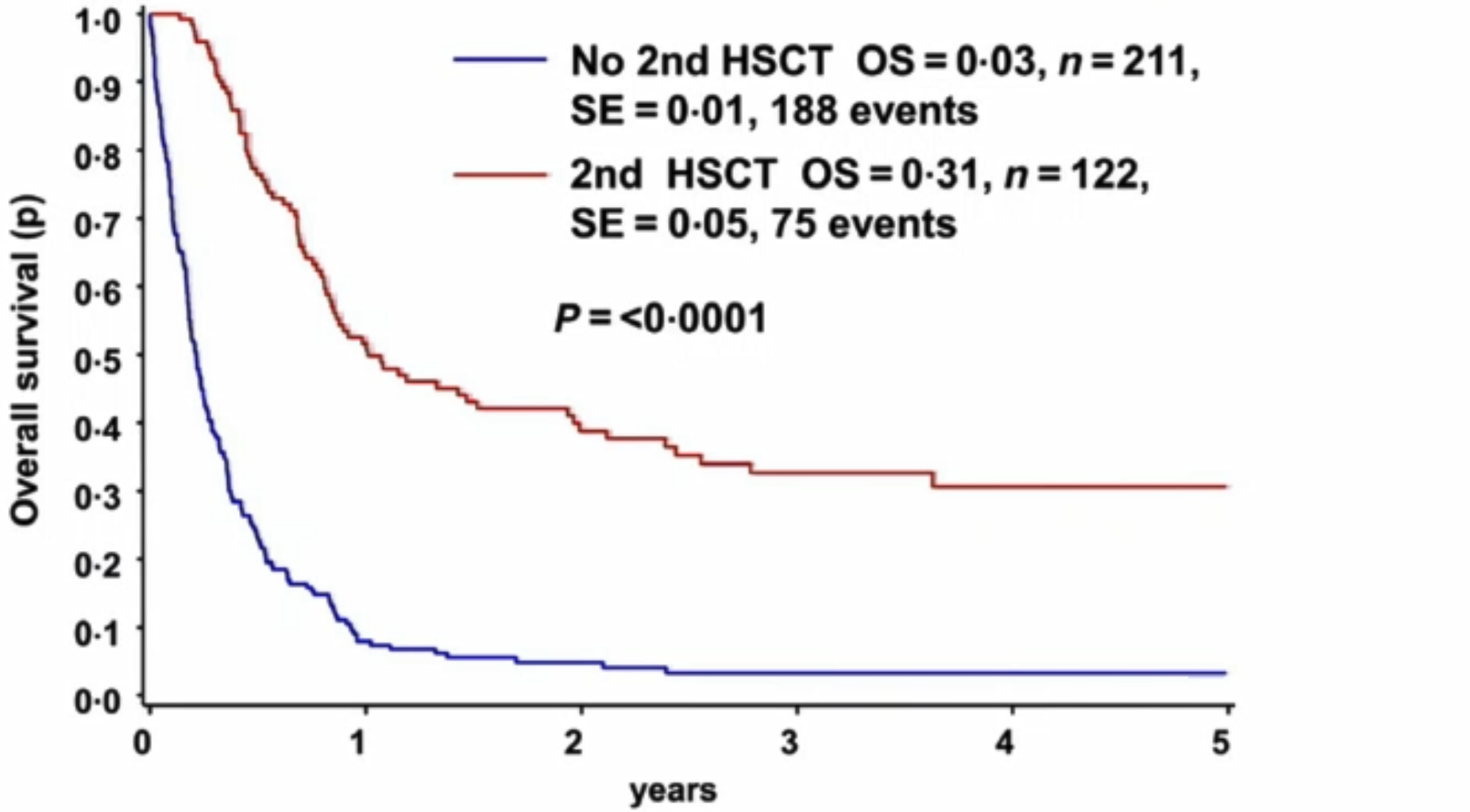
CBF AML t(8;21) and inv(16)



Outcome of children relapsing after HSCT for AML

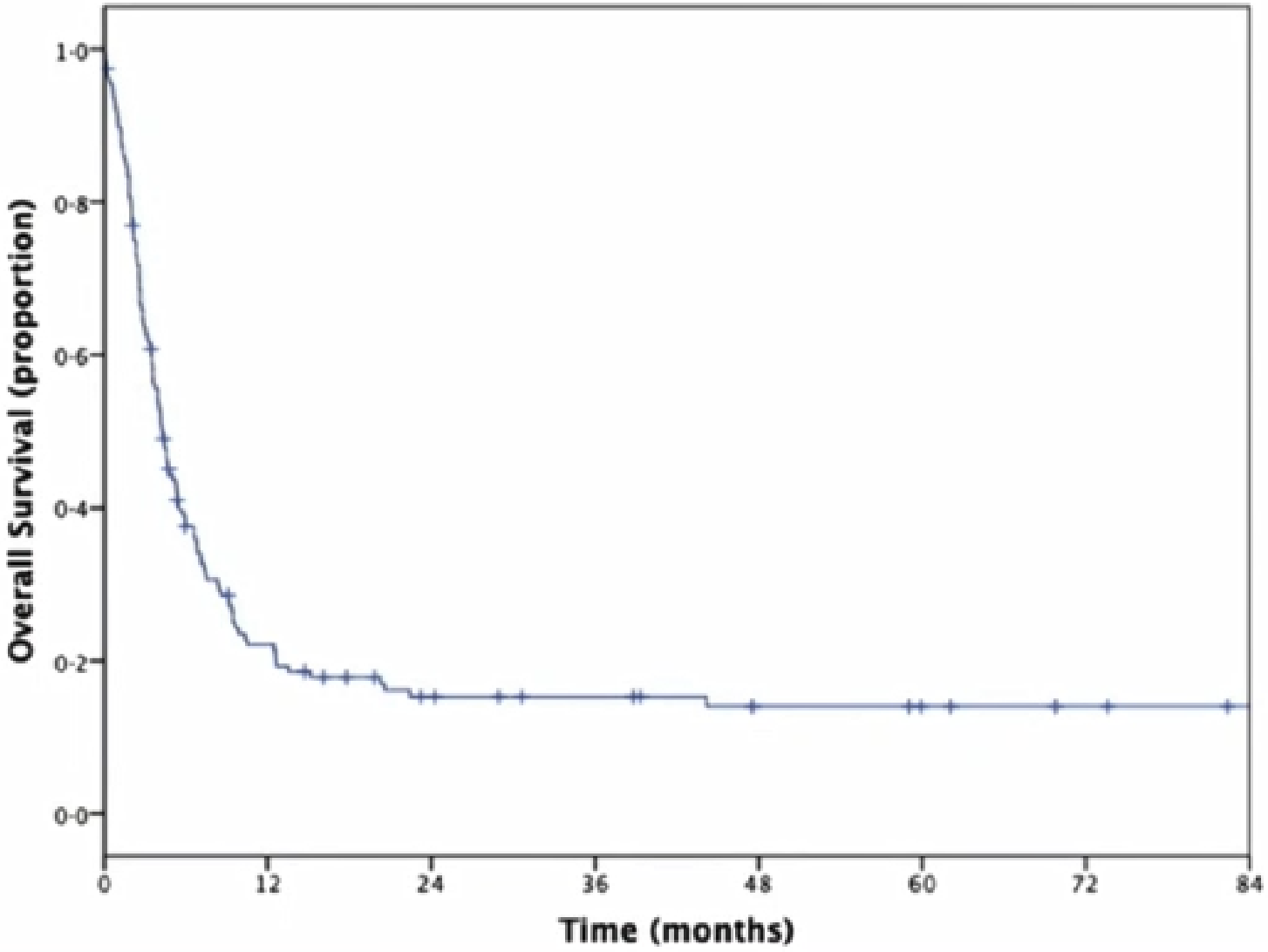
a retrospective I-BFM analysis of 333 children

Uden et al. BJH 2020

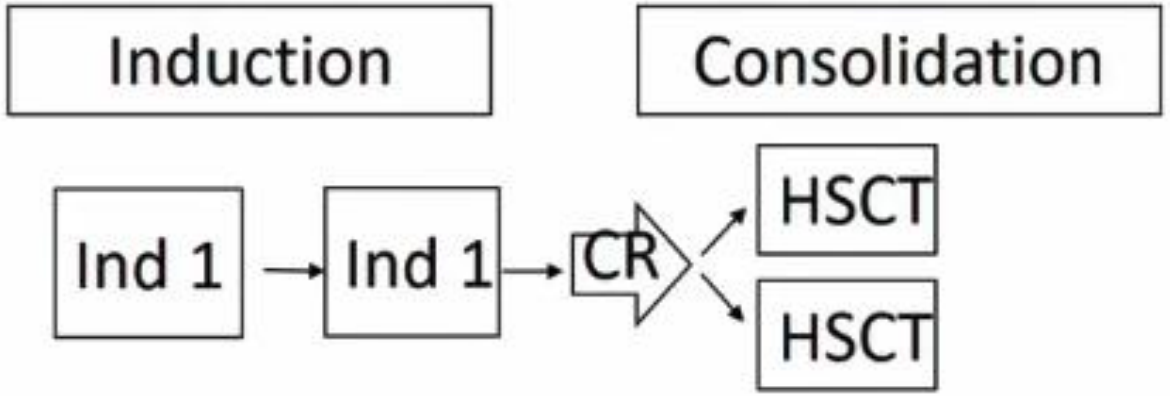


Survival of 157 patients with a refractory first relapse or second relapse from the NOPHO-DB-SHIP consortium

White T et al, BJH 2022



Current therapy for children with relapsed AML



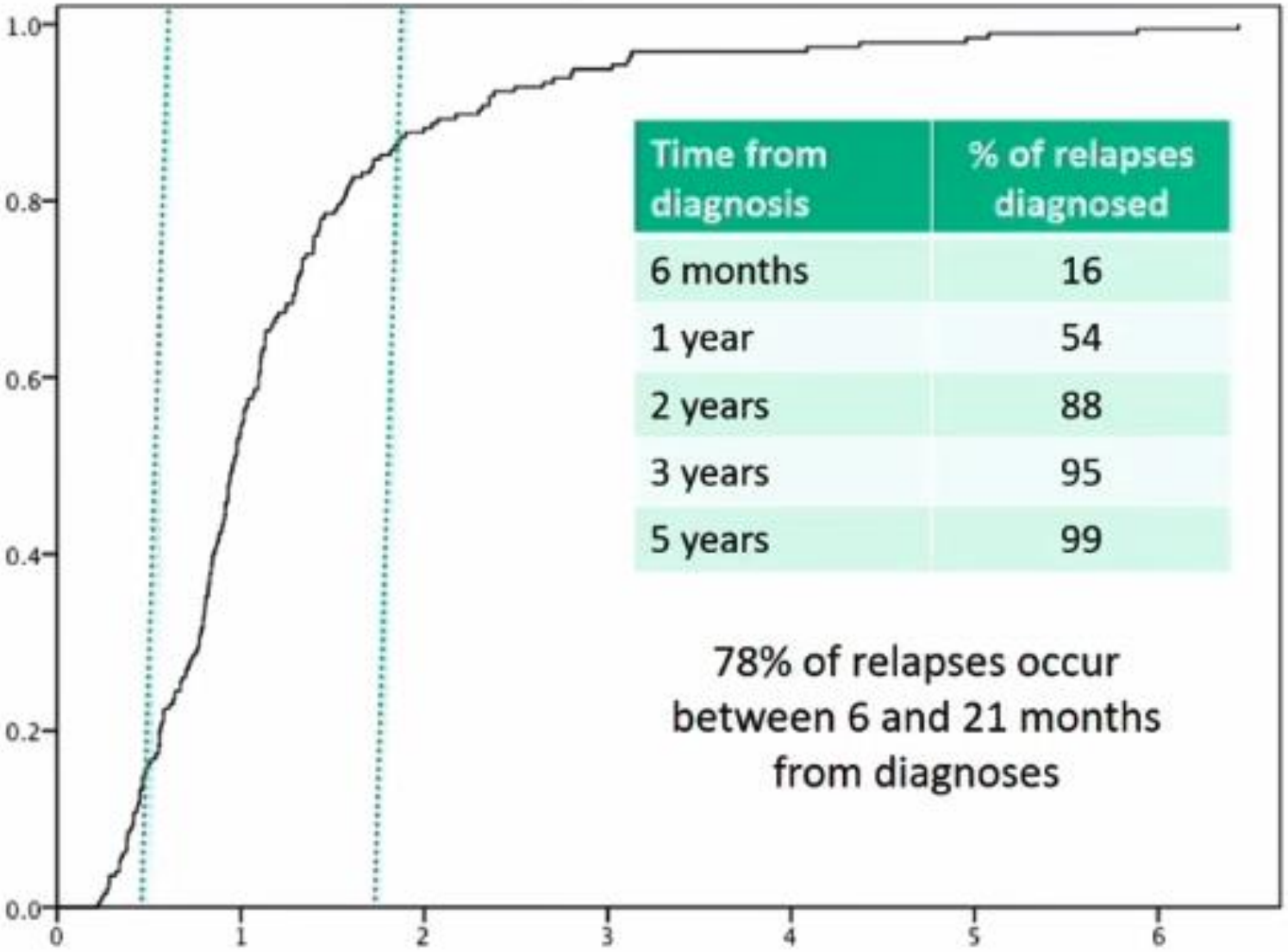
Outcome has improved but less than 50% of the patients are cured
Therapy based upon intensity chemotherapy followed by HSCT
Major acute and long-term toxicity
Limited targeted therapy

How to improve therapy for children with relapsed AML?

Optimal supportive care
Preemptive therapy
New trials including targeting drugs

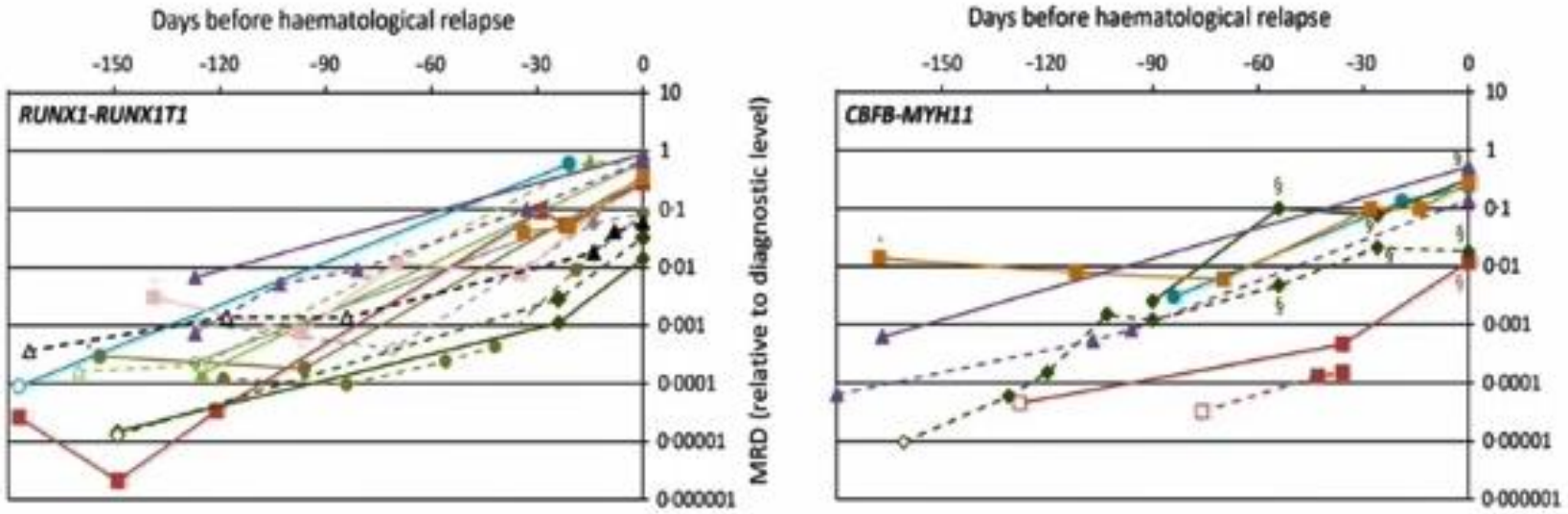
Time to relapse (n=196)

Data from NOPHO-AML 1993 and 2004 trials (unpublished)



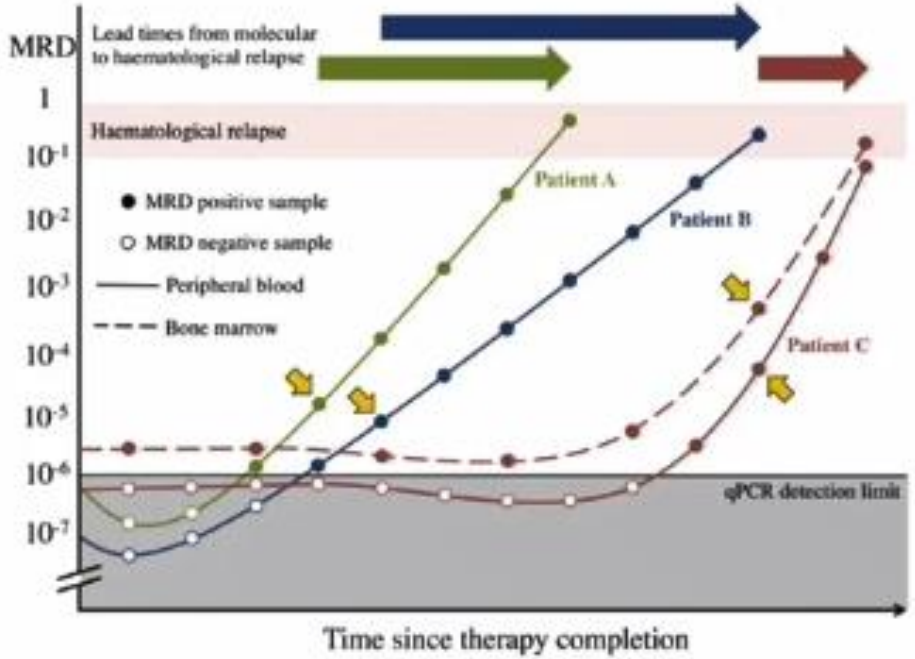
Time from diagnosis	% of relapses diagnosed
6 months	16
1 year	54
2 years	88
3 years	95
5 years	99

78% of relapses occur between 6 and 21 months from diagnoses



MRD monitoring by qPCR in PB after end of therapy

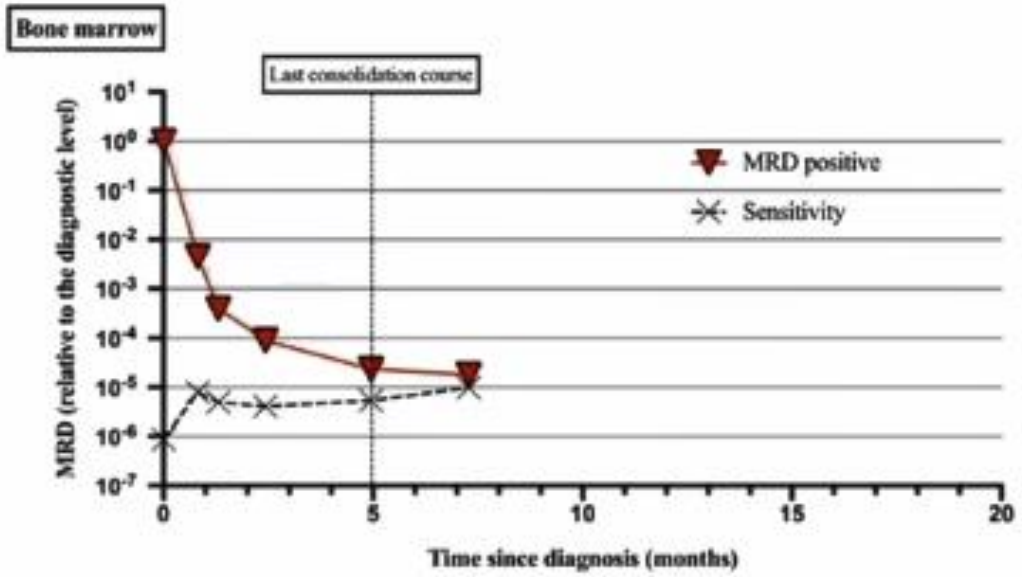
Juul-Dam et al. Br J Haematol 2020; 190: 198

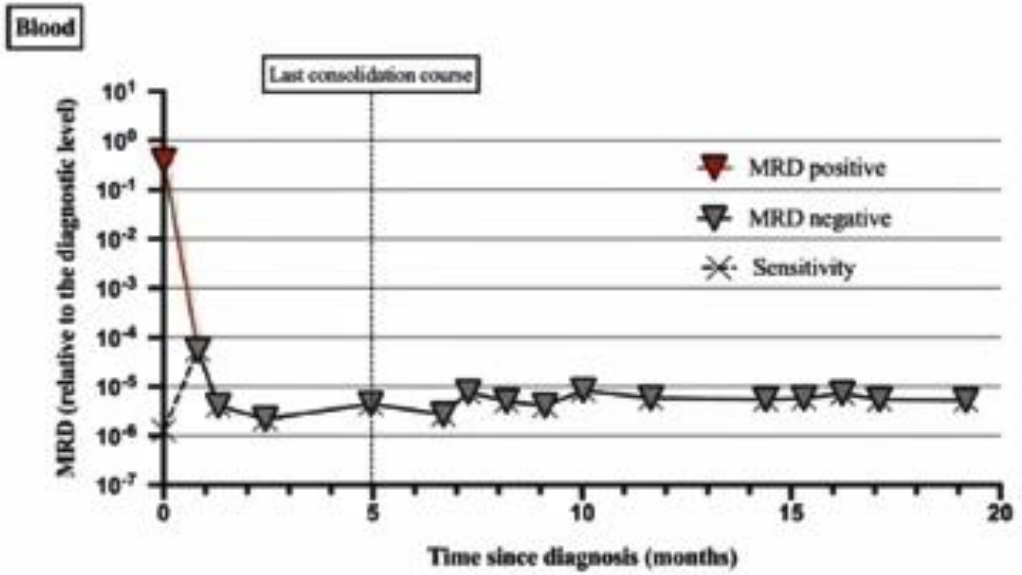


Leukemic growth depended on AML subtypes:
inv(16) *CBFB::MYH11* AML regrowth of 0.3 log/month
t(8;21) *RUNX1::RUNX1T1* AML regrowth of 0.6 log/month

Skou et al. Br J Haematol 2021 PMID: 33851435

MRD monitoring by qPCR in PB after end of AML therapy



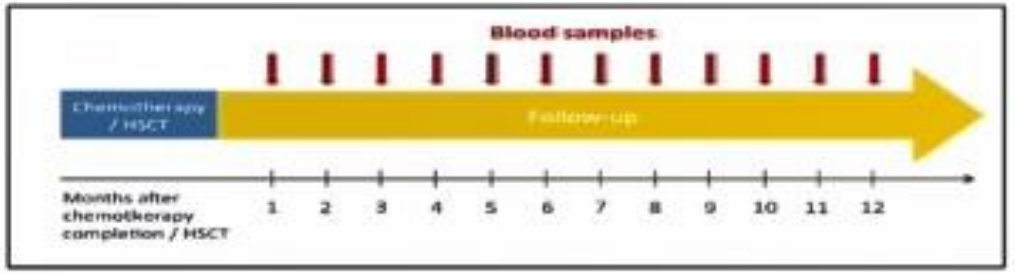


- Shifting from MRD negative to positive (>5 x 10^{-4}) in PB predicts subsequent relapse
- BM may remain MRD pos with PCR without relapse

Recommendation

PB at monthly intervals until 12–18 months from therapy
Increase by 1 log or to >5 x 10^{-4} defines molecular relapse
Confirmed in a paired PB and BM sample

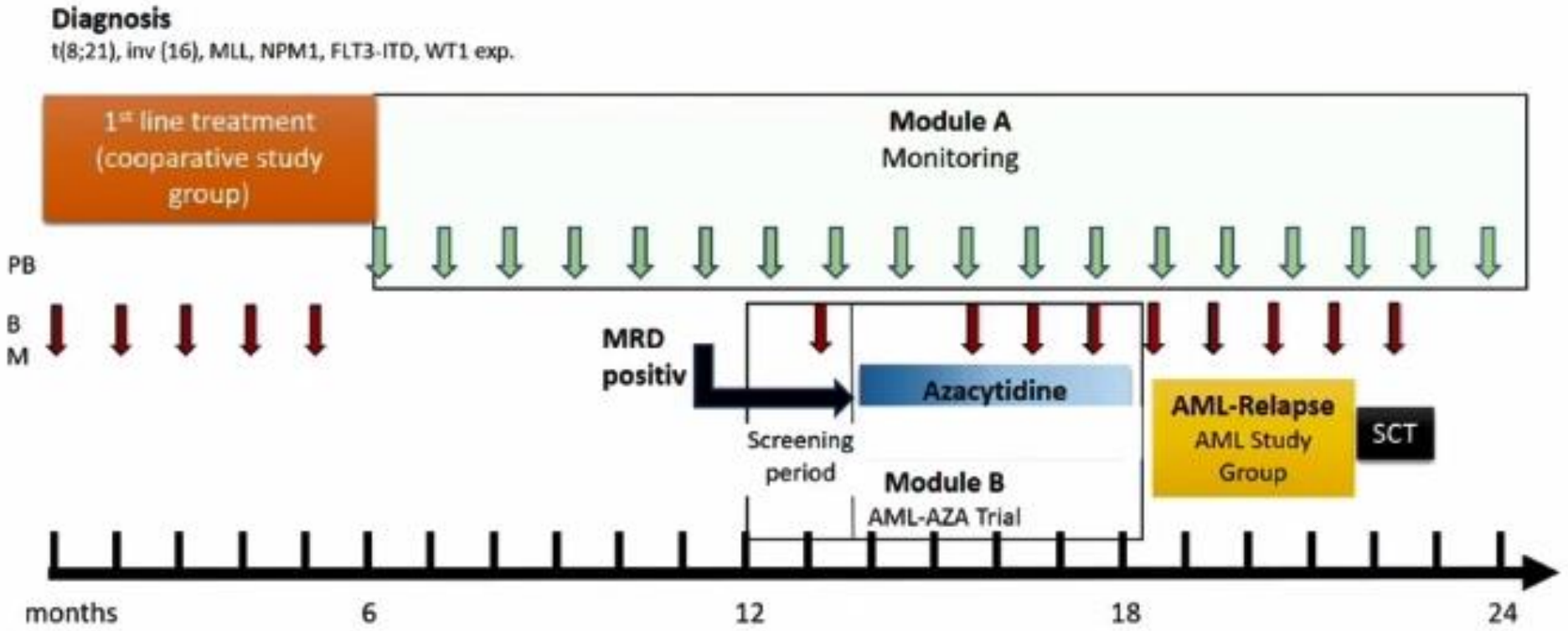
Skou et al. Br J Haematol 2021 PMID: 33851435



Preemptive therapy of molecular relapse

AMoRe2017

A) Detection and confirmation of molecular relapses in pediatric acute myeloid leukemia (AML)
B) Treatment of molecular relapse in (AML) with azacitidine

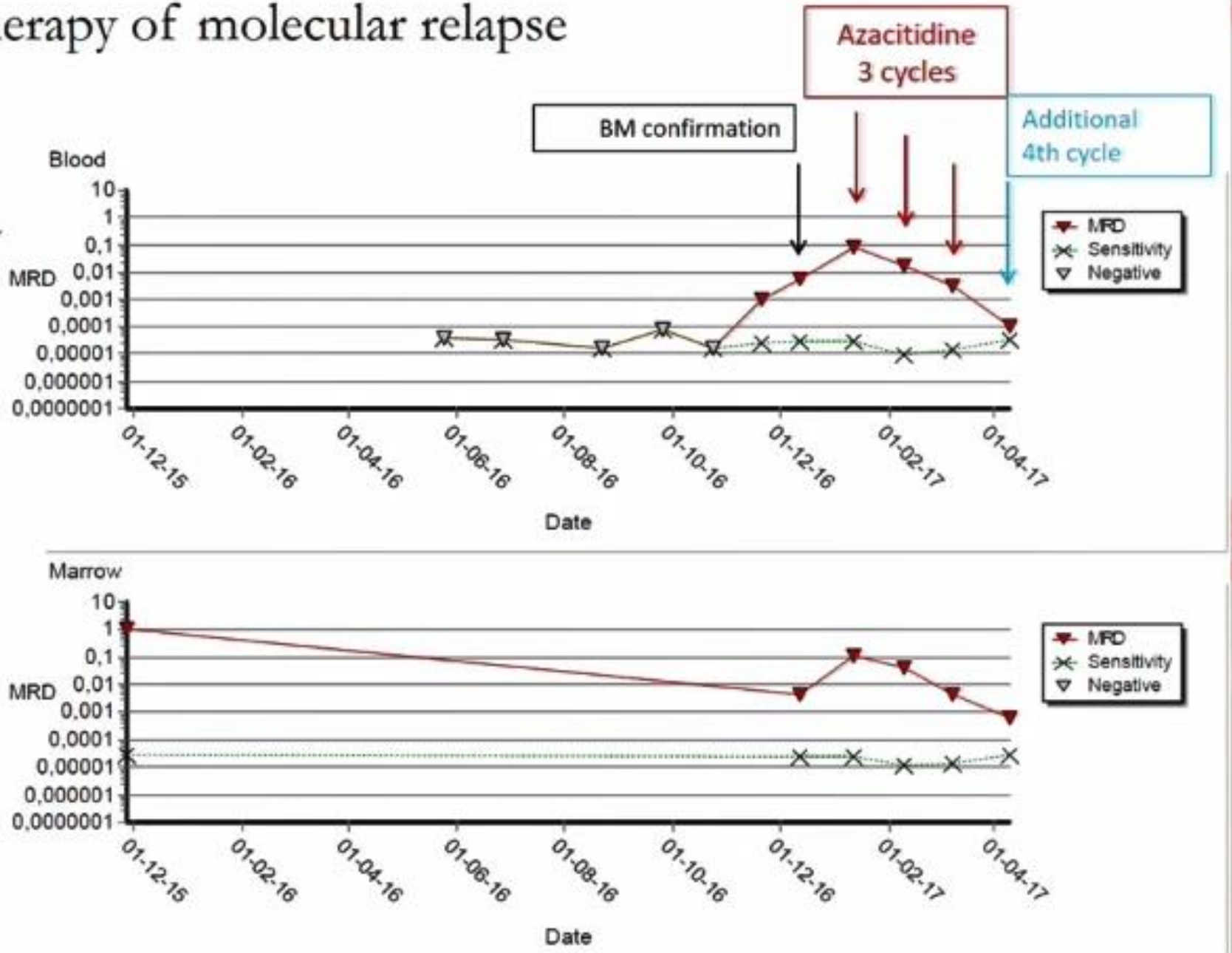


Example of preemptive therapy of molecular relapse

Aim:

Disease control with little toxicity

HSCT with low MRD



Current and future targets by therapeutic subclass

Zarnegar-Lumley et al,
Leukemia 2022; 36: 1951

Extramedullary relapse

- Should be considered and treated as systemic relapse
- Local therapy (except for i.t. chemotherapy) is not indicated

Myeloid Leukemia in Down syndrome

International European multicenter study of ML-DS 2006

AIE

	day
cytarabine 100 mg/m²/d	1,2
cytarabine 100 mg/m²/12h	3-8
idarubicin 8 mg/m²/d	3,5,7
etoposide 150 mg/m²/d	6,7,8
cytarabine i.th.	1

AI

	day
cytarabine 500 mg/m²/d	1- 4
idarubicin 7 mg/m²/d	3,5
cytarabine i.th.	1

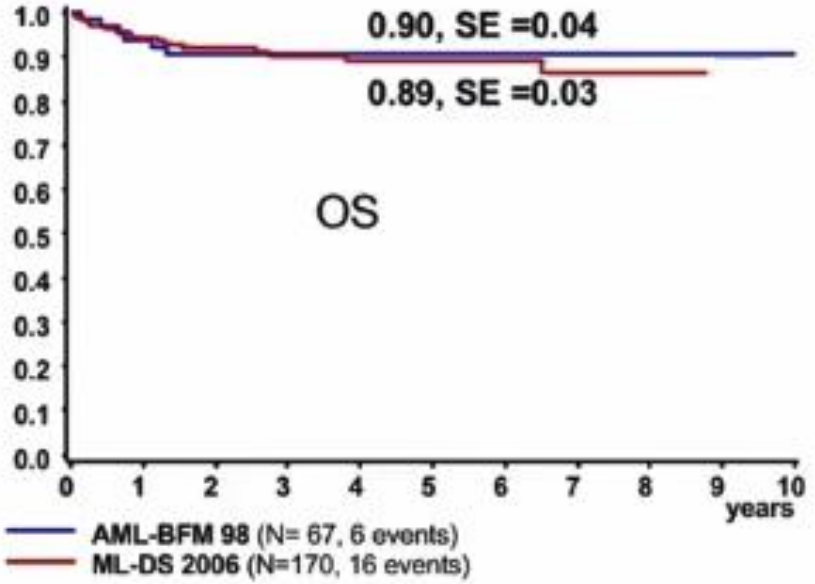
haM

	day
HD-cytarabine 1 g/m²/12h	1-3
mitoxantrone 7 mg/m²/d	3, 4
cytarabine i.th.	1

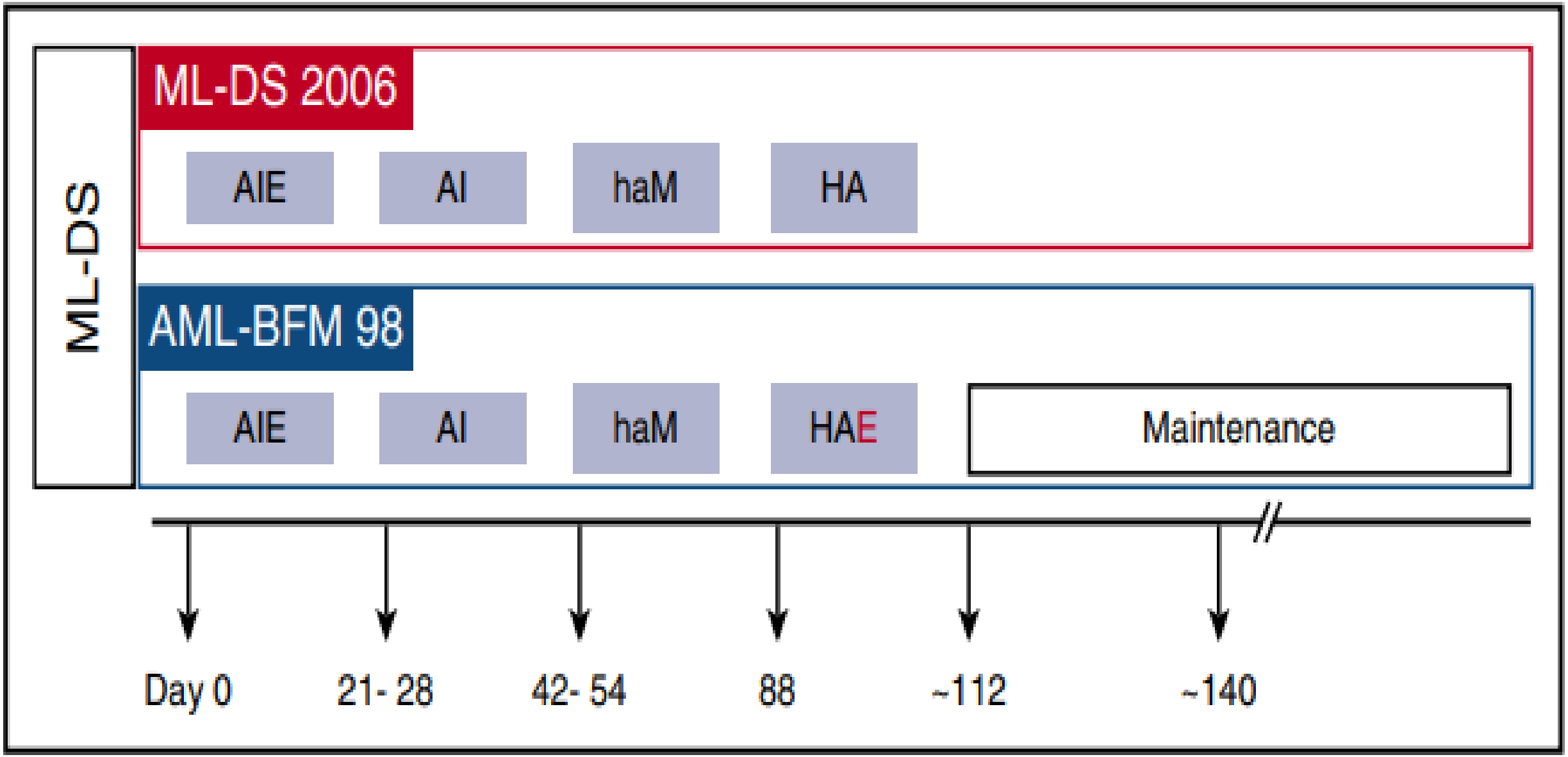
HA

	day
HD-cytarabine 3 g/m²/12h	1-3
cytarabine i.th	1

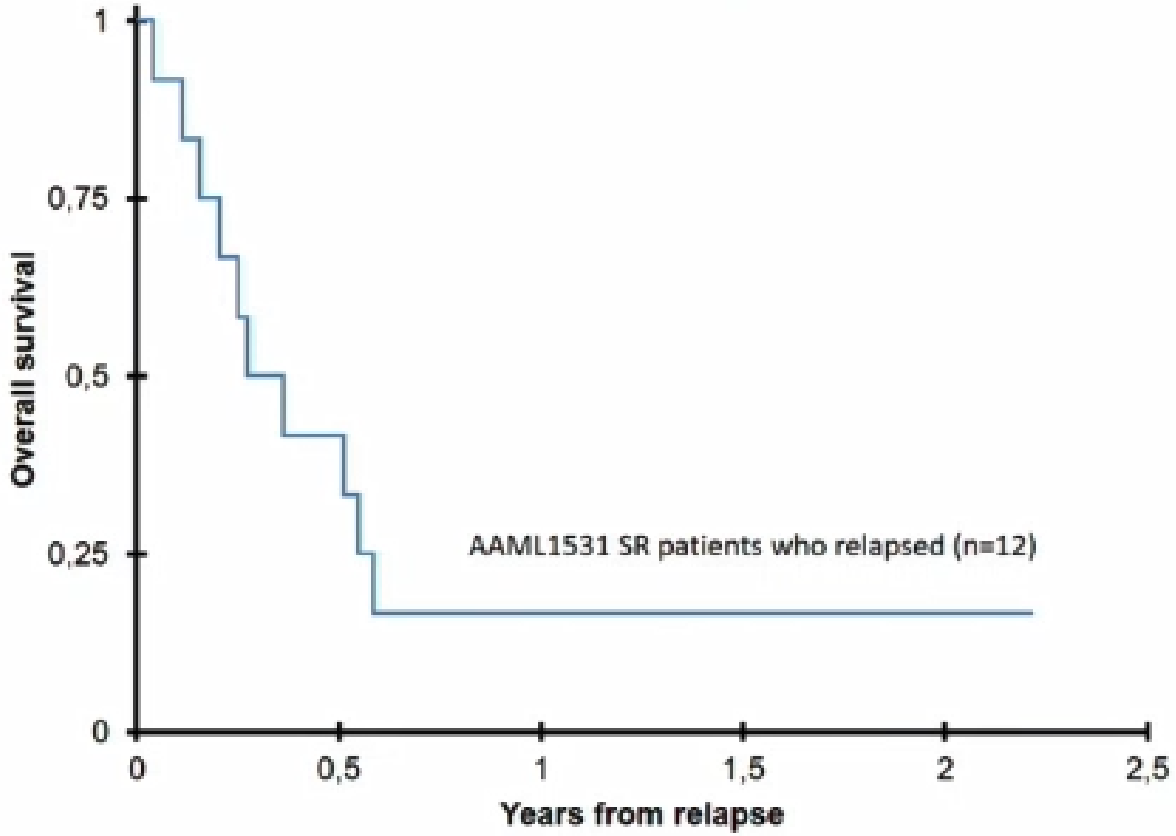
OS about 90% reported from Europe, Japan, NA



Uffmann et al. Blood 2017; 129: 3314


ML-DS
ML-DS 2006
AIE
AI
haM
HA
AML-BFM 98
AIE
AI
haM
HAE
Maintenance
Day 0
21- 28
42- 54
88
~112
~140

Overall Survival of Standard Risk ML-DS Patients after Relapse (AAML1531)



	Number at risk at year					
Group	0	0.5	1	1.5	2	2.5
AAML1531 SR relapse patients	12	5	1	1	1	0

Hitzler et al. Blood 2021

Management of relapsed AML
Summary

- Avoid relapse
  - Improve therapy and risk classification
    - MRD monitoring
    - Targeted therapy
    - Risk group adapted therapy
      - Identifying the right target and treatment
      - International subgroup therapy
    - Improvements in supportive care
    - Better SCT indications and regimens

St. Jude Children's Research Hospital

The outcomes of patients with *ETV6-RUNX1* and hyperdiploid B-acute lymphoblastic leukemia treated in the St. Jude Total XV and XVI studies

Katelyn Purvis, MD[1]; Yinmei Zhou, MS[2]; Seth E. Karol, MD[1]; Jeffrey E. Rubnitz, MD, PhD[1]; Raul C. Ribeiro, MD[1]; Shawn Lee, MD[3]; Jun J. Yang, PhD[3]; Cheng Cheng, PhD[2]; Charles G. Mullighan, MBBS, MSc, MD[4]; Sima Jeha, MD[1,5]; Ching-Hon Pui, MD[1,5]; Hiroto Inaba, MD, PhD[1]

Departments of [1]Oncology, [2]Biostatistics, [3]Pharmacy and Pharmaceutical Sciences, [4]Pathology, and [5]Global Pediatric Medicine

Background: Risk Classification

NCI Risk Classification (Standard Risk)

- WBC <50 x 10^9/L and Age 1-9.9 years

St Jude Risk Classification (Low Risk)

- WBC <50 x 10^9 and Age 1-9.9 years
- Hyperdiploid with DNA Index ≥ 1.16
- *ETV6-RUNX1*

- No testicular involvement
- No CNS 3
- No *TCF3-PBX1*, *BCR-ABL1*, hypodiploid
- MRD Day 15 <1% and end of induction <0.01%

St. Jude Children's Research Hospital

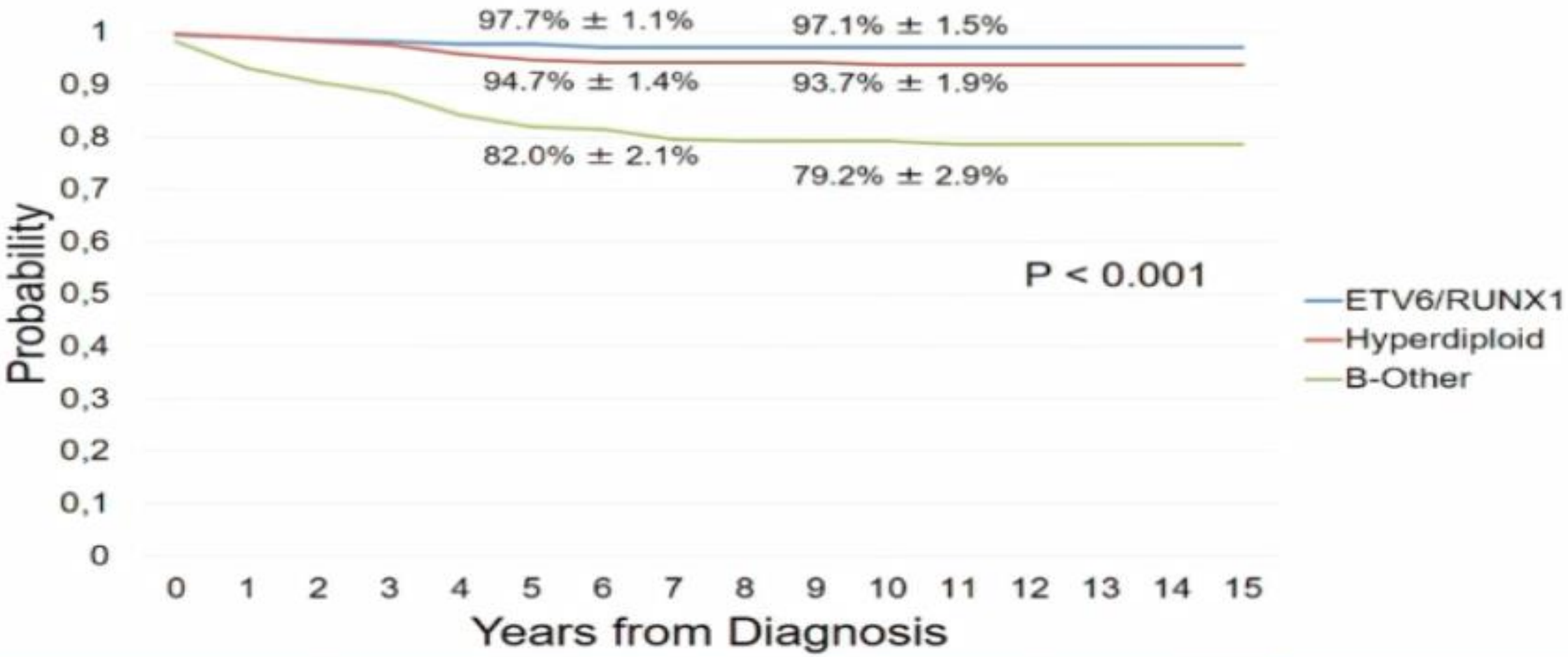
Patient Demographics

Clinical Features	*ETV6/RUNX1* (A) (N= 222)	Hyperdiploid (B) (N= 296)	Other B-ALL (C) (N=388)	A + B vs. C	A vs. B
Age Groups					
1-10 years	211 (95%)	256 (86.5%)	224 (57.7%)	<0.001	0.001
≥10 years	11 (5%)	40 (13.5%)	164 (42.3%)		
Initial WBC					
<50 x 10^9/L	192 (86.5%)	276 (93.2%)	284 (73.2%)	<0.001	0.010
≥50 x 10^9/L	30 (13.5%)	20 (6.8%)	104 (26.8%)		
Race					
White	169 (76.1%)	260 (87.8%)	300 (77.3%)	0.075	<0.001
Black	39 (17.6%)	21 (7.1%)	65 (16.8%)		
Other	14 (6.3%)	15 (5.1%)	23 (5.9%)		
CNS Status					
CNS1	175 (78.9%)	192 (64.9%)	245 (63.1%)	0.038	<0.001
CNS2	34 (15.3%)	90 (30.4%)	111 (28.6%)		
CNS3	1 (0.5%)	5 (1.7%)	13 (3.4%)		
TLP with blasts	12 (5.4%)	9 (3.0%)	19 (4.9%)		

Patient Demographics

Clinical Features	*ETV6/RUNX1* (A) (N= 222)	Hyperdiploid (B) (N= 296)	Other B-ALL (C) (N=388)	A + B vs. C	A vs. B
MRD day 15					
<1%	210 (94.6%)	231 (78.0%)	251 (64.7%)	<0.001	<0.001
≥1%	10 (4.5%)	60 (20.3%)	130 (33.5%)		
Not available	2 (0.9%)	5 (1.7%)	7 (1.8%)		
MRD End of Induction					
<0.01%	201 (90.5%)	267 (90.2%)	297 (76.5%)	<0.001	0.445
≥0.01% to <1%	20 (9.0%)	24 (8.1%)	65 (16.8%)		
≥1%	0 (0.0%)	2 (0.7%)	21 (5.4%)		
Not available	1 (0.5%)	3 (1.0%)	5 (1.3%)		
NCI Risk Group					
Standard risk	182 (82.0%)	237 (80.1%)	163 (42.0%)	<0.001	0.583
High risk	40 (18.0%)	59 (19.9%)	225 (58.0%)		
St. Jude Risk Group					
Low risk	195 (87.8%)	220 (74.3%)	85 (21.9%)	<0.001	<0.001
Standard/high risk	27 (12.2%)	76 (25.7%)	303 (78.1%)		

EFS by B-ALL Subtype



Outcomes for *ETV6/RUNX1* by NCI and St. Jude Risk

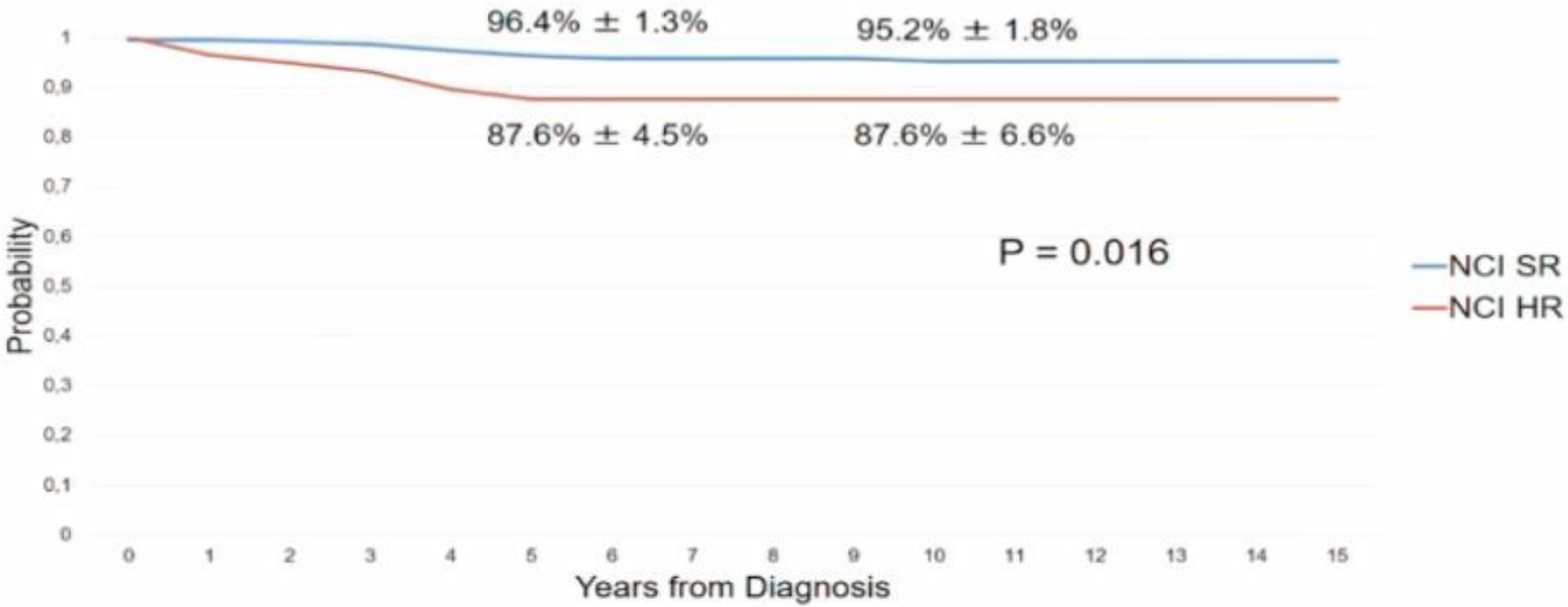
	NCI Risk		*P*	St. Jude Risk		*P*
	SR (N=182)	HR (N=40)		LR (N=195)	SR (N=27)	
5-year EFS	97.8 %±1.2%	97.5%±2.6%	0.917	97.4% ± 1.2%	100.0%	0.360
5-year OS	99.5%± 0.6%	97.5%±2.6%	0.511	99.0% ± 0.8%	100.0%	0.521
5-year CIN	1.1%± 0.8%	2.5%± 2.5%	0.733	1.6% ± 0.9%	0.0%	0.455

Outcomes for Hyperdiploid by NCI and St. Jude Risk

	NCI Risk		P	St. Jude Risk		P
	NCI SR (N=237)	NCI HR (N=59)		SJ LR (N=220)	SJ SHR (N=76)	
5-year EFS	96.4% ± 1.3%	87.6% ± 4.5%	0.016	96.1% ± 1.4%	90.6% ± 3.6%	0.133
5-year OS	99.2% ± 0.6%	94.9% ± 3.0%	0.023	99.1% ± 0.7%	96.1% ± 2.4%	0.079
5-year CIN	3.1% ± 1.2%	7.2% ± 3.5%	0.282	3.0% ± 1.2%	6.7% ± 2.9%	0.288

NCI HR had worse EFS/OS than NCI SR patients

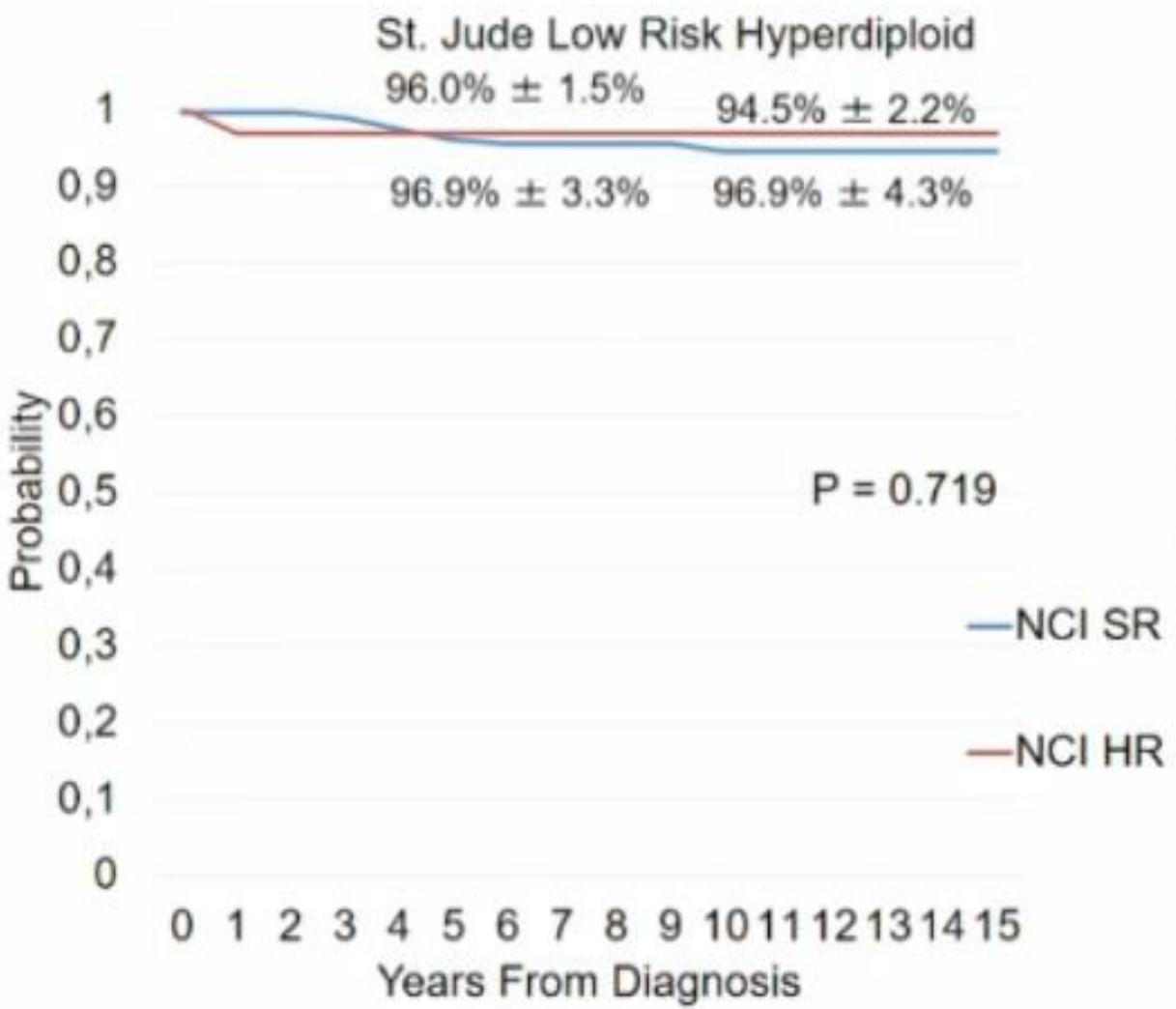
EFS in Hyperdiploid Patients by NCI risk

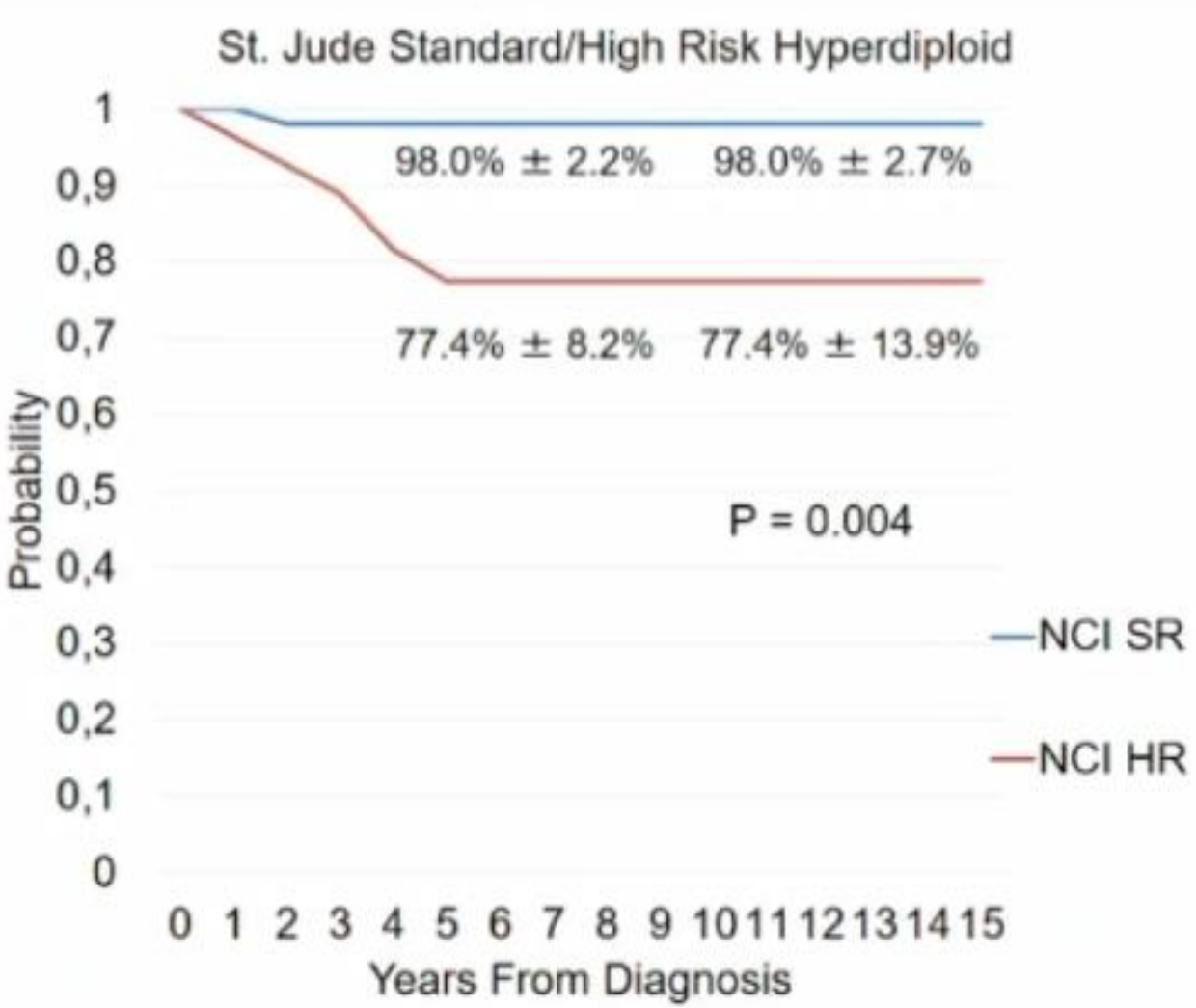


Outcomes for Hyperdiploid by St. Jude and NCI Risk

	St. Jude LR		P	St. Jude SHR		P
	NCI SR (N=188)	NCI HR (N=32)		NCI SR (N=49)	NCI HR (N=27)	
5-year EFS	96.0% ± 1.5%	96.9% ± 3.3%	0.719	98.0% ± 2.2%	77.4% ± 8.2%	0.004
5-year OS	99.5% ± 0.6%	96.9% ± 3.2%	0.156	98.0% ± 2.2%	92.6% ± 5.1%	0.244
5-year CIN	3.4% ± 1.4%	0.0%	0.249	2.0% ± 2.0%	15.2% ± 7.2%	0.034

EFS in Hyperdiploid Patients by SJ and NCI Risk





St. Jude Children's Research Hospital

Conclusions

- Compared with *ETV6/RUNX1*, patients with hyperdiploid have
  - Older age, low initial WBC, less African American
  - Poor initial response and more St. Jude SHR (no difference in NCI risk)

- Contemporary MRD-directed therapy provided excellent outcomes in NCI HR and SJ LR patents with a low-intensity regimen
  - 37 of 40 (93%) *ETV6-RUNX1* patients
  - 32 of 59 (54%) hyperdiploid patients

- Hyperdiploid patients with both NCI HR and SJ S/HR features require new therapeutic approach to improve the outcomes

iAMP21 Predicts Poor Outcomes in B-Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group AALL1131

Faculty Disclosure

Nothing to Disclose

Background – Intrachromosomal Amplification of Chromosome 21 (iAMP21)

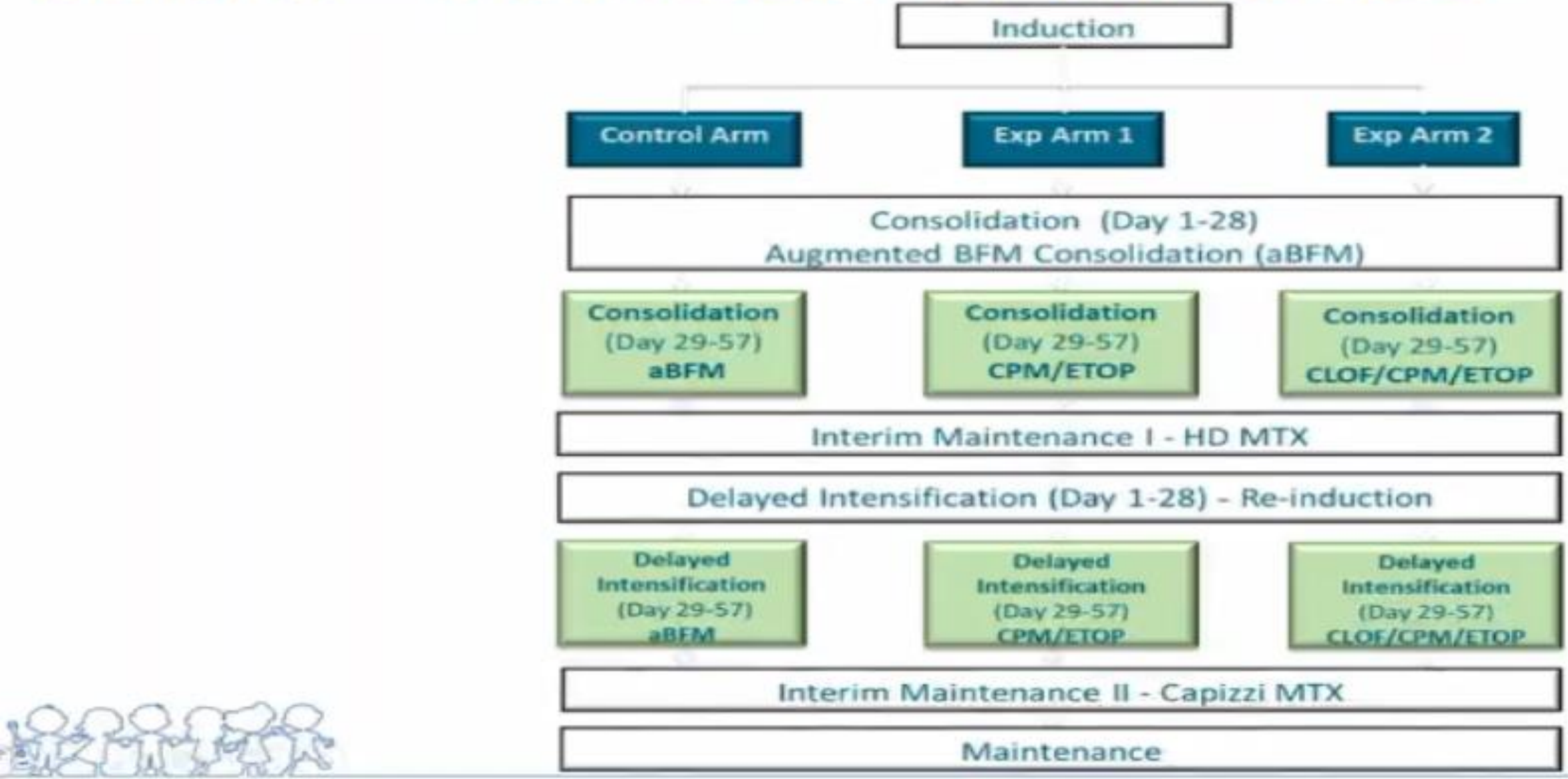
- iAMP21 is defined as multiple copies of RUNX1 on chromosome 21
- 2% of children and young adults with B-ALL have iAMP21
- iAMP21 is associated with a high risk of relapse, and this risk is higher for patients treated with lower intensity regimens
- NCI Standard Risk (SR) and High Risk (HR) patients with B-ALL and iAMP21 treated on COG AALL0331 and COG AALL0232, respectively, had a 4 year event free survival (EFS) of 72.7% $\pm$ 5.8% (Heerema, 2013)
- iAMP21, identified by central fluorescent in situ hybridization (FISH) review, was defined on this study as at least 4 copies of RUNX1 on a single chromosome
- SR and HR patients with iAMP21 were assigned to the Very High Risk (VHR) Arms of COG AALL1131

Eligibility – Post-Induction COG AALL1131 VHR B-ALL

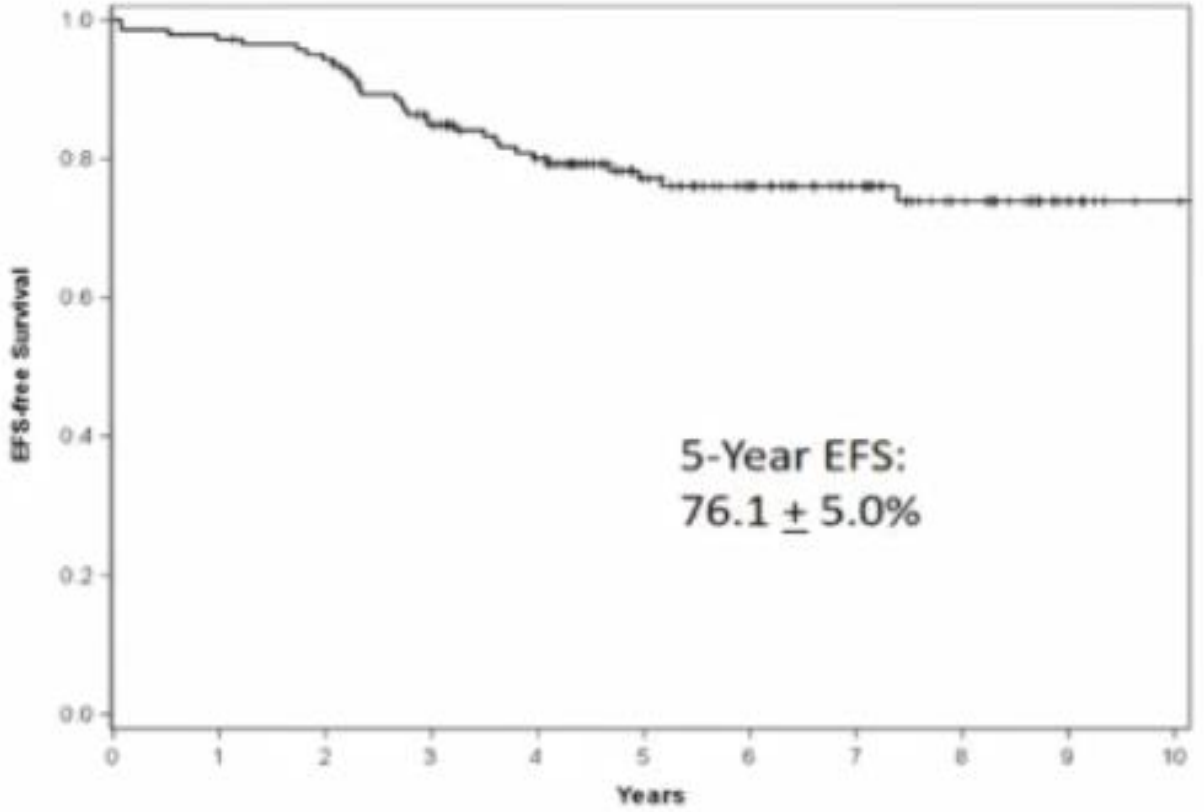
- 1 - 30 years of age with newly diagnosed B-ALL who at the completion Induction therapy are identified as VHR
- Induction was completed on COG AALL0932 for SR patients and COG AALL1131 for HR patients
- VHR criteria include any of the following:
  - ≥13 years of age
  - *KMT2A* rearrangements
  - **iAMP21**
  - Hypodiploidy (< 44 chromosomes/DNA index < 0.81)
  - Central nervous system disease (CNS3)
  - End of Induction (EOI) MRD positive ≥ 0.01% (and no *ETV6-RUNX1* or double trisomies 4+10 for NCI SR patients)
  - Induction Failure - >25% blasts

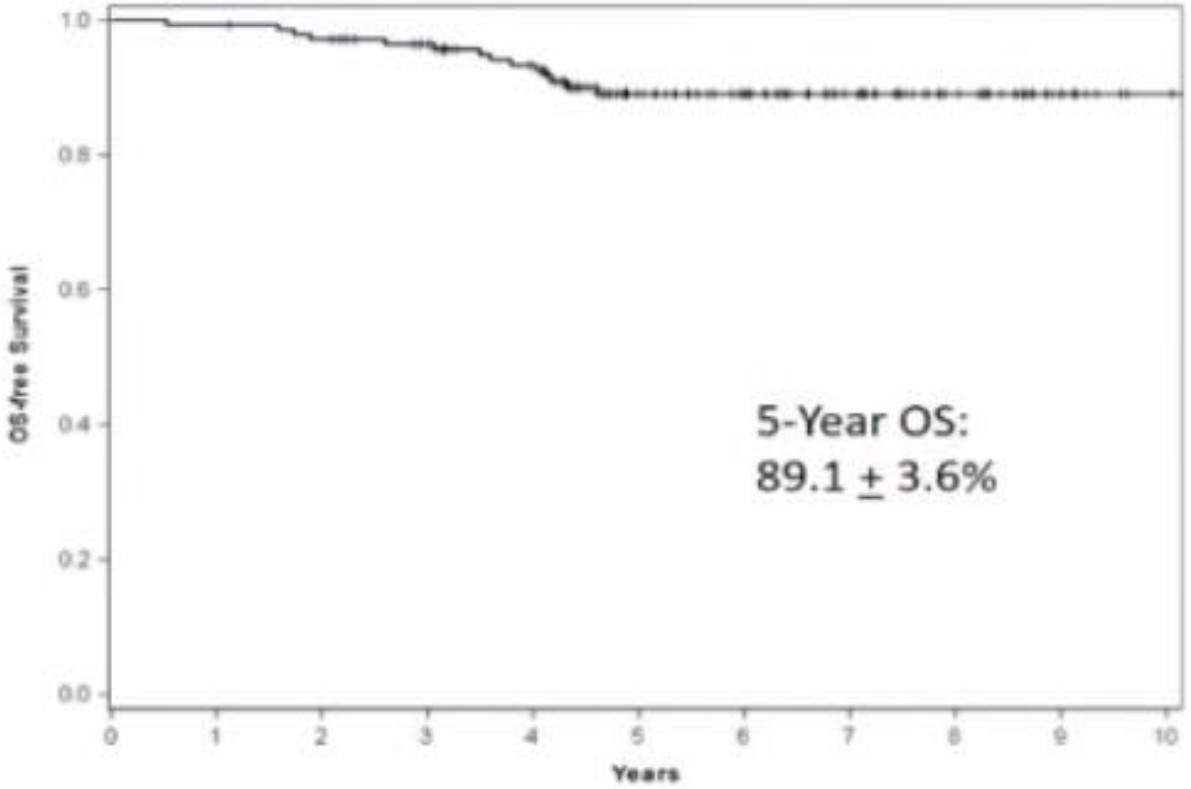
Salzer, Wanda

Schema – COG AALL1131 VHR B-ALL



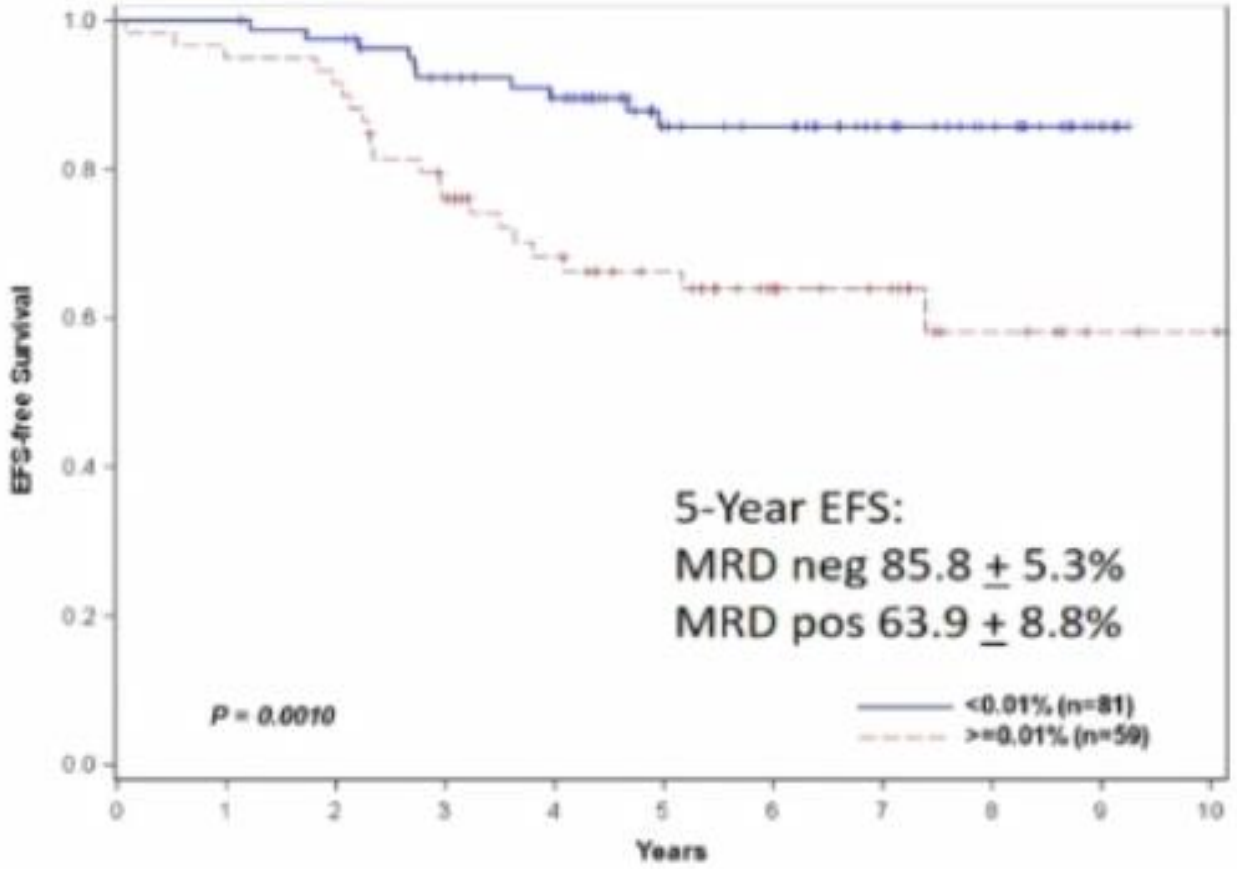
Survival – NCI SR



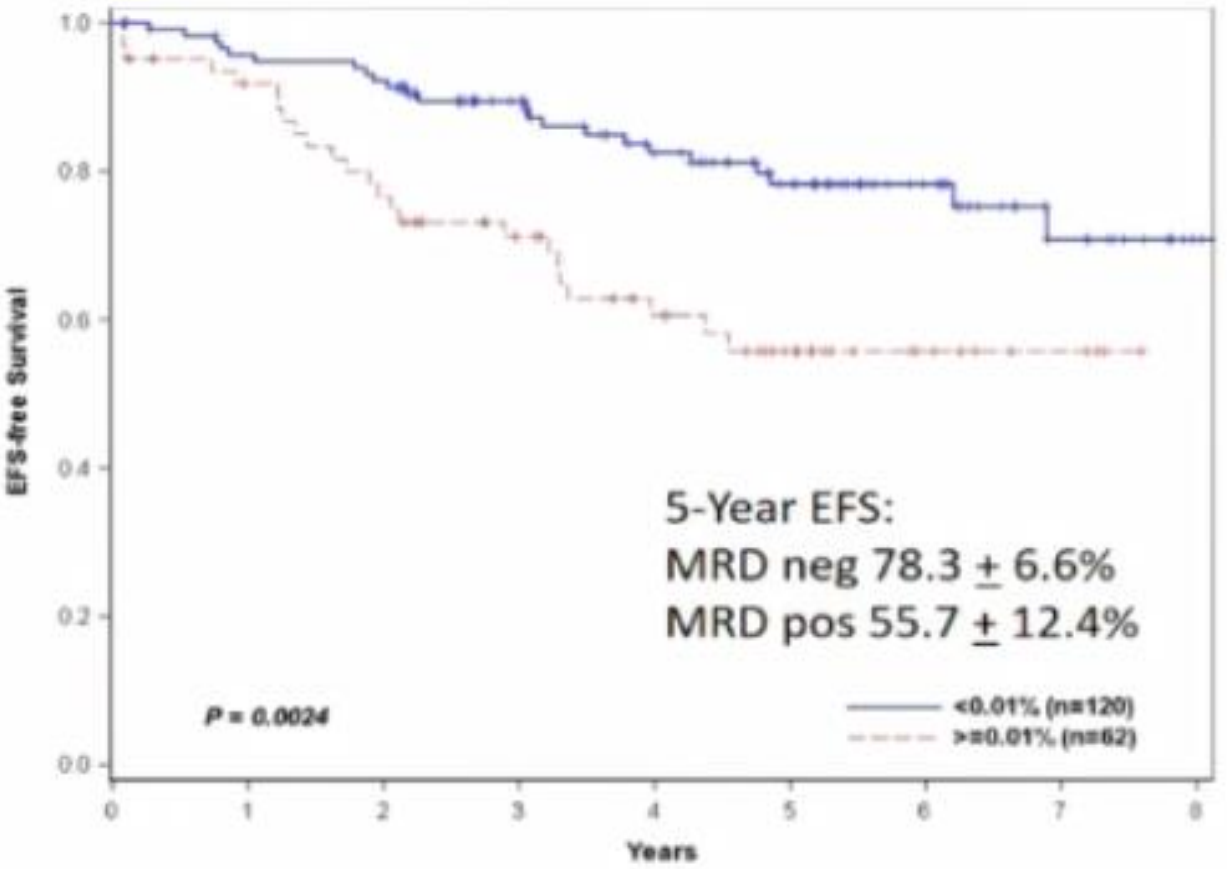


Survival – NCI SR and HR Based on EOI MRD

NCI SR

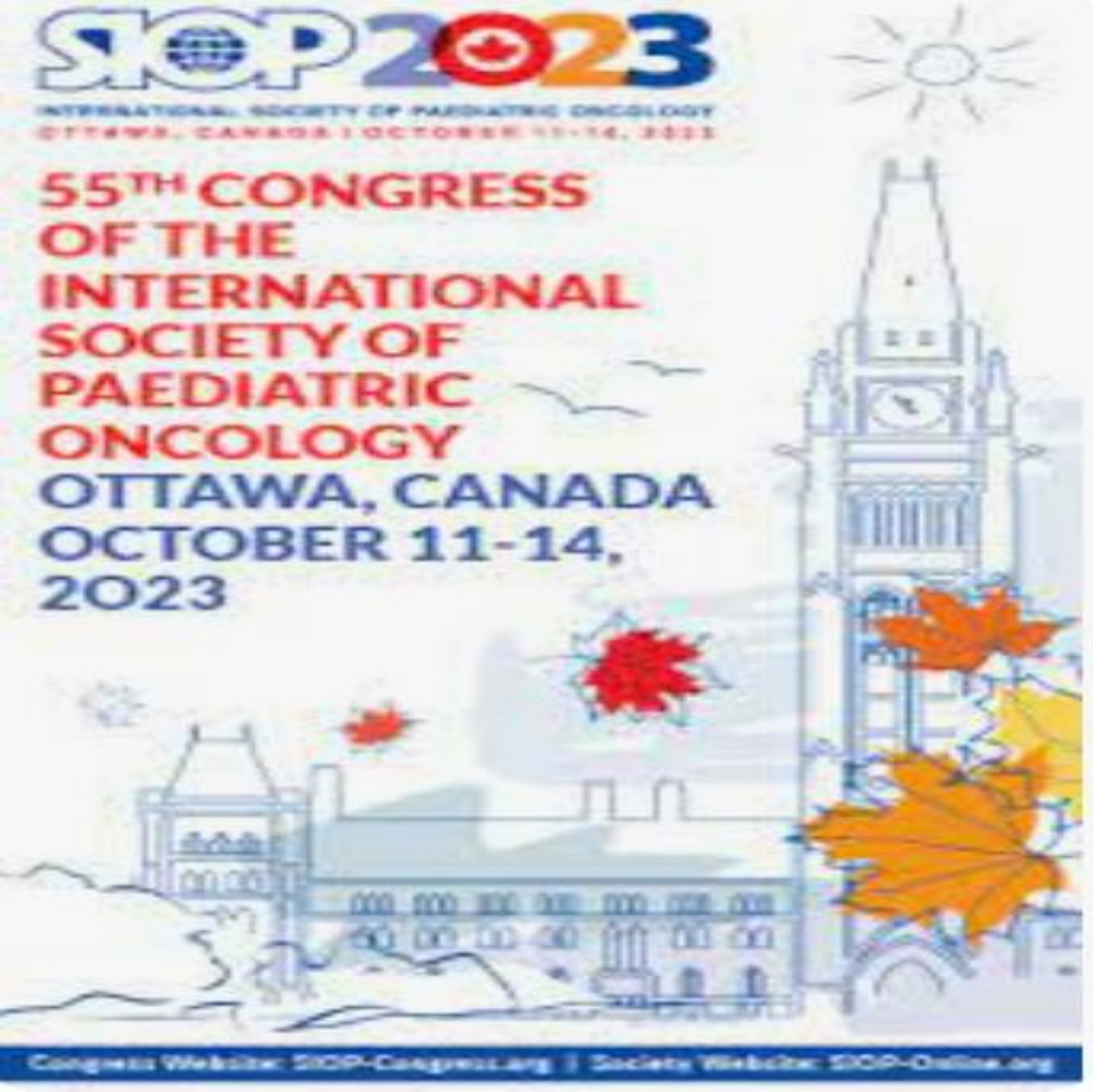


NCI HR



COG AALL1131 – iAMP21 B-ALL Conclusion

- Outcomes remain inferior for patients with NCI SR and HR B-ALL and iAMP21
- Patients with iAMP21 who are EOI MRD-positive have significantly inferior EFS, warranting new treatment approaches for these patients
- Since most patients were not randomized post-induction due to closure of the VHR arms of COG AALL1131, it is not possible to compare outcomes based on treatment regimen



THANK YOU FOR YOUR ATTENTION