



# SINTOMA<sup>26</sup>

14 A 16 DE MAIO | HOTEL INTERCONTINENTAL | SÃO PAULO

PARCERIA **soho**  
society of hematologic oncology

APOIO INSTITUCIONAL Faculdade **bp**

GERENCIAMENTO  
E PRODUÇÃO

**RV+**  
EVENTOS

# LEUCEMIA LINFOBLÁSTICA AGUDA

Estratificação de Risco e Terapia Guiada por DRM na LLA :  
Implicações para a Tomada de Decisão clínica

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Coordenadora do Protocolo Brasileiro da LLA na  
Infância e na Adolescência



Os fatores de estratificação de risco são **iguais** nesses dois casos?  
Em que momento a **DRM** será **definidora de conduta**?

- Menino, **16 anos**
  - **História Clínica** : Febre, dor em membros progressiva e incapacitante há 3 meses. Perda de peso, palidez e aumento do volume abdominal
  - **Exame Físico**: MEG, fascie de dor, descorado 3+/4.
  - Micropoliadenomegalias generalizadas
  - Abdomen globoso, com hepatoesplenomegalia volumosa
  - Genitália e períneo: **aumento bilateral de testículos**, que se apresentam extremamente endurecidos à palpação.
  - HEMOGRAMA INICIAL : **Leucócitos : 115.000/mm<sup>3</sup>** Blastos: 90% Hb: 6, 5 g/dl Plaquetas: 25.000/mm<sup>3</sup>
  - IMUNOFENOTIPAGEM : **LLA comum**
  - Cariótipo : **46 XY [ 9 ]**
  - Biologia Molecular : **ETV6- RUNX1 : negativo**  
**TCF3 – PBX1 : negativo**  
**rearranjo KMT2A: negativo**  
**bcr- abl p190 : negativo**
- Líquor: **3 cel/mm<sup>3</sup>** **20 hemácias/mm<sup>3</sup>** Blastos: **8%** PT: **20 mg/dl**

- Menino, **16 anos**
  - História Clínica : Cansaço e falta de ar há dias 15 dias. “ínguas no pescoço há 4 dias”. Febre. Tonturas há 1 dia.
  - Exame Físico: MEG, descorado 1+/4, dispneico 2+/4, FC:120
  - Volumosas adenomegalias cervicais , turgência jugular
  - Abdomen: Hepatoesplenomegalia volumosa
  - Genitália e períneo: sem alterações.
  - RX tórax: **Alargamento mediastinal** importante com DP
  - HEMOGRAMA INICIAL : **Leucócitos : 250.000/mm<sup>3</sup>** Blastos: 90% Hb: 11,2 g/dl Plaquetas: 95.000/<sup>3</sup>
  - IMUNOFENOTIPAGEM : **LLA T**
  - Cariótipo : **46 XY [ 20 ]**
  - Biologia Molecular : **ETV6- RUNX1 : negativo**  
**TCF3 – PBX1 : negativo**  
**rearranjo KMT2A: negativo**  
**bcr- abl p190 : negativo**
- Líquor: **1 cel/mm<sup>3</sup>** **0 hemácias/mm<sup>3</sup>** Blastos: **0%** PT: **20 mg/dl**

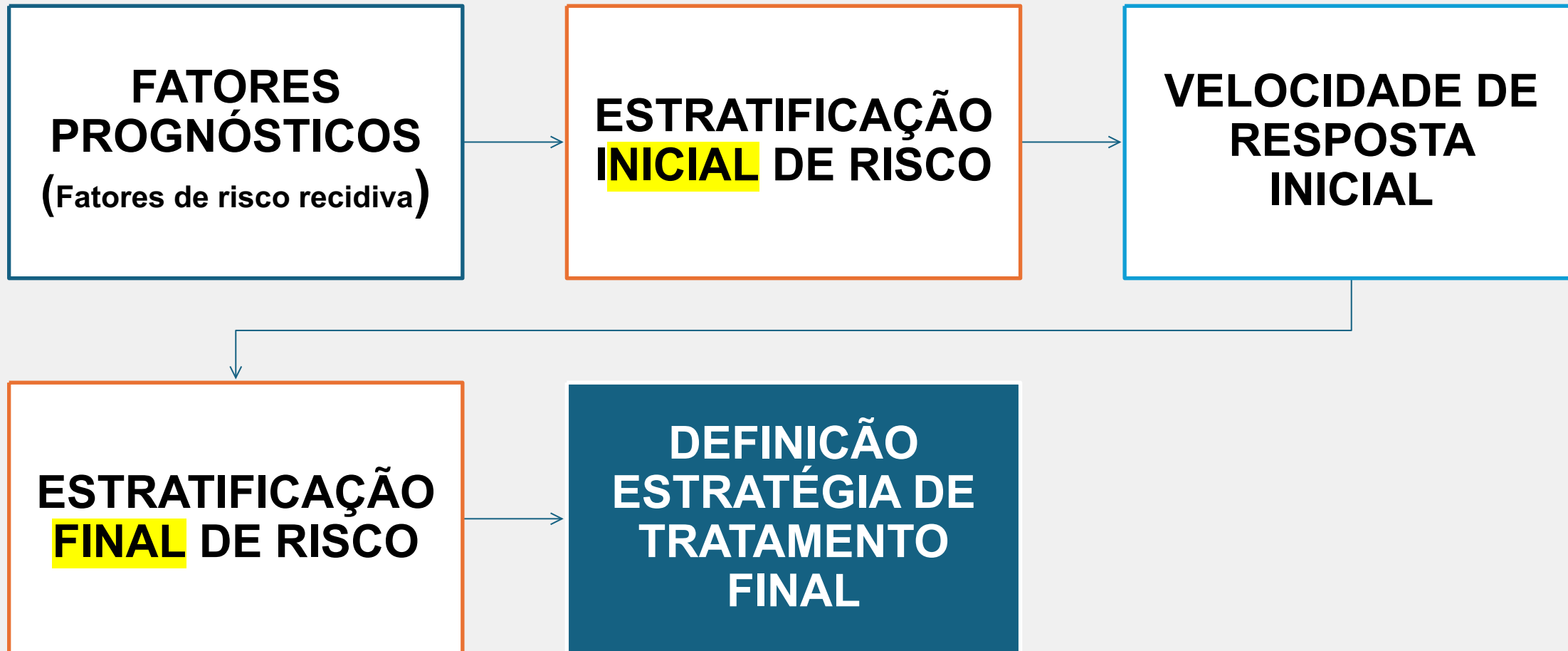
Fatores de  
Risco

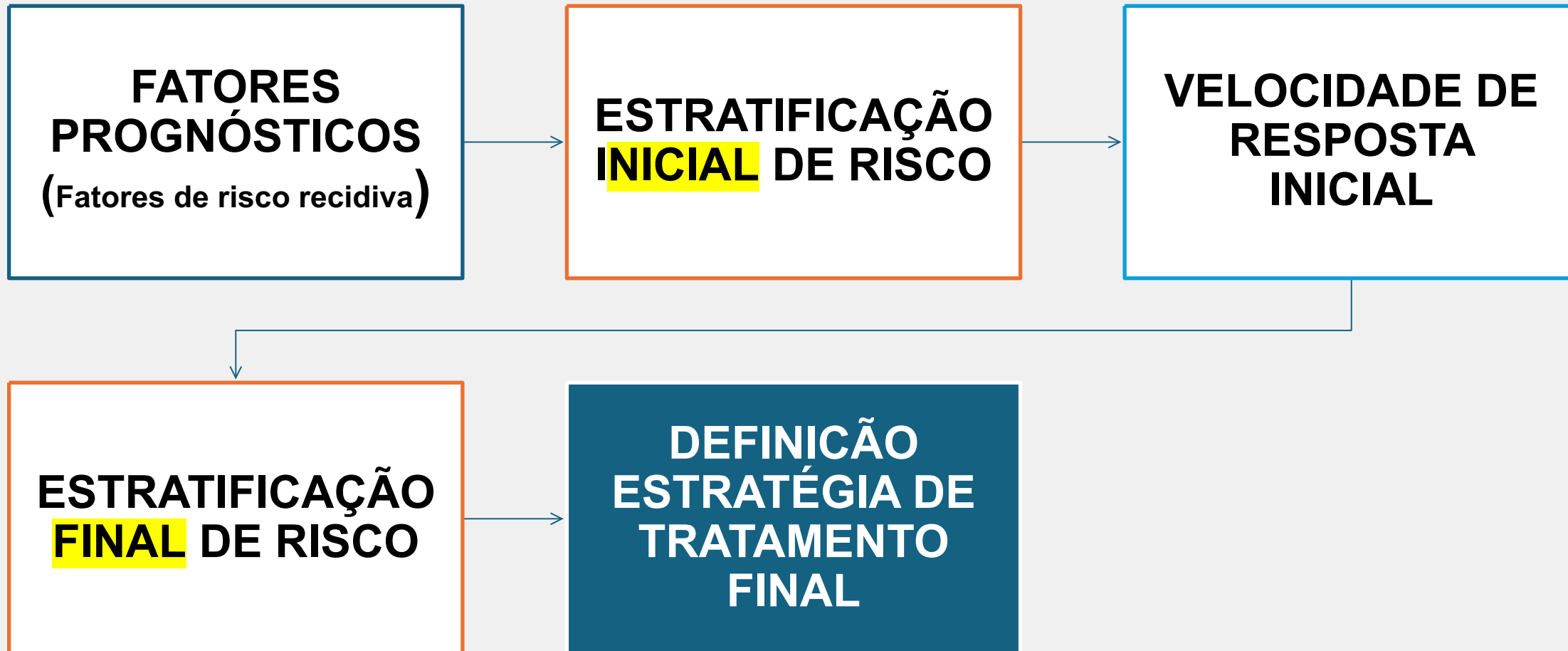
FATORES PROGNÓSTICOS



Estratificação  
de Risco

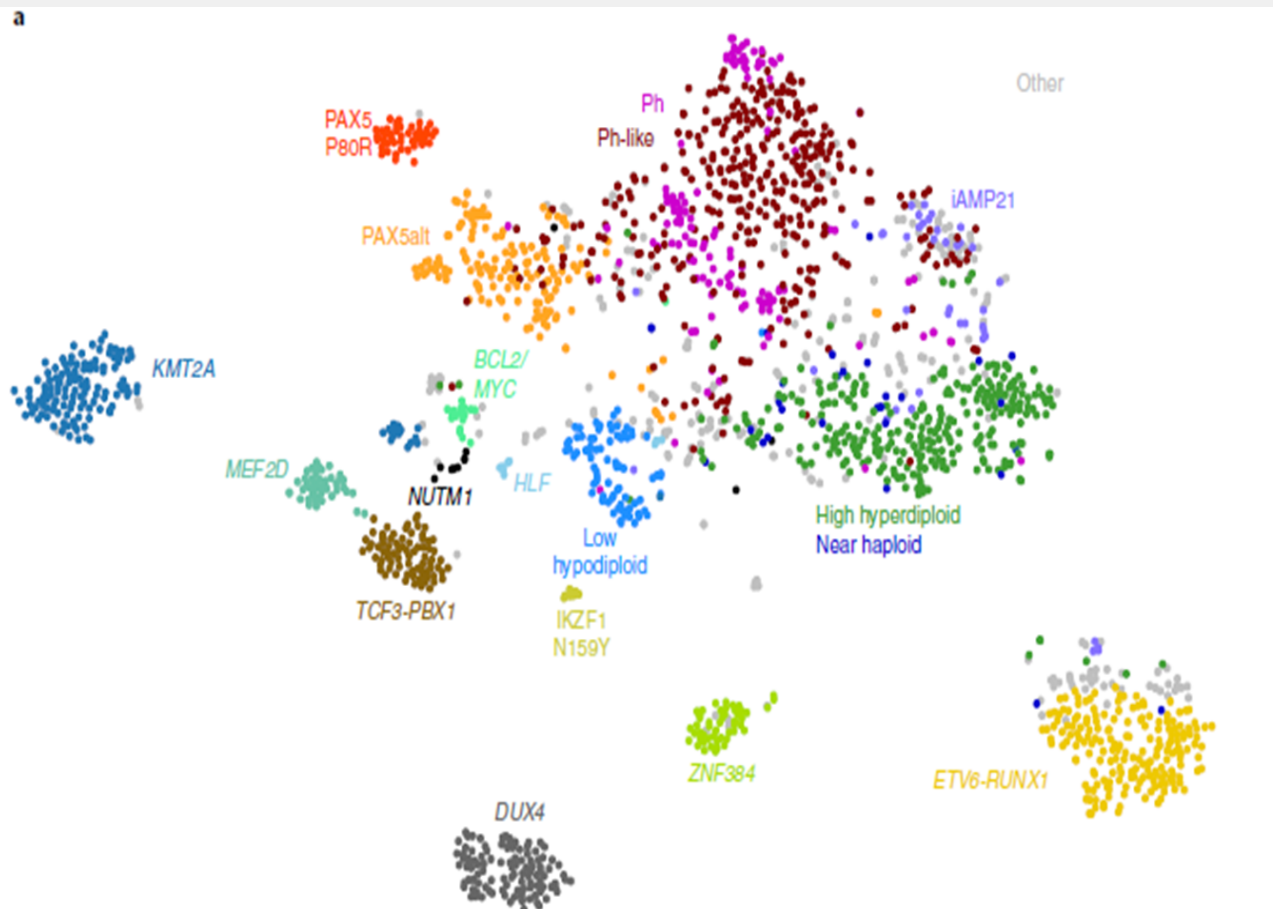
PROTOCOLO TERAPEUTICO



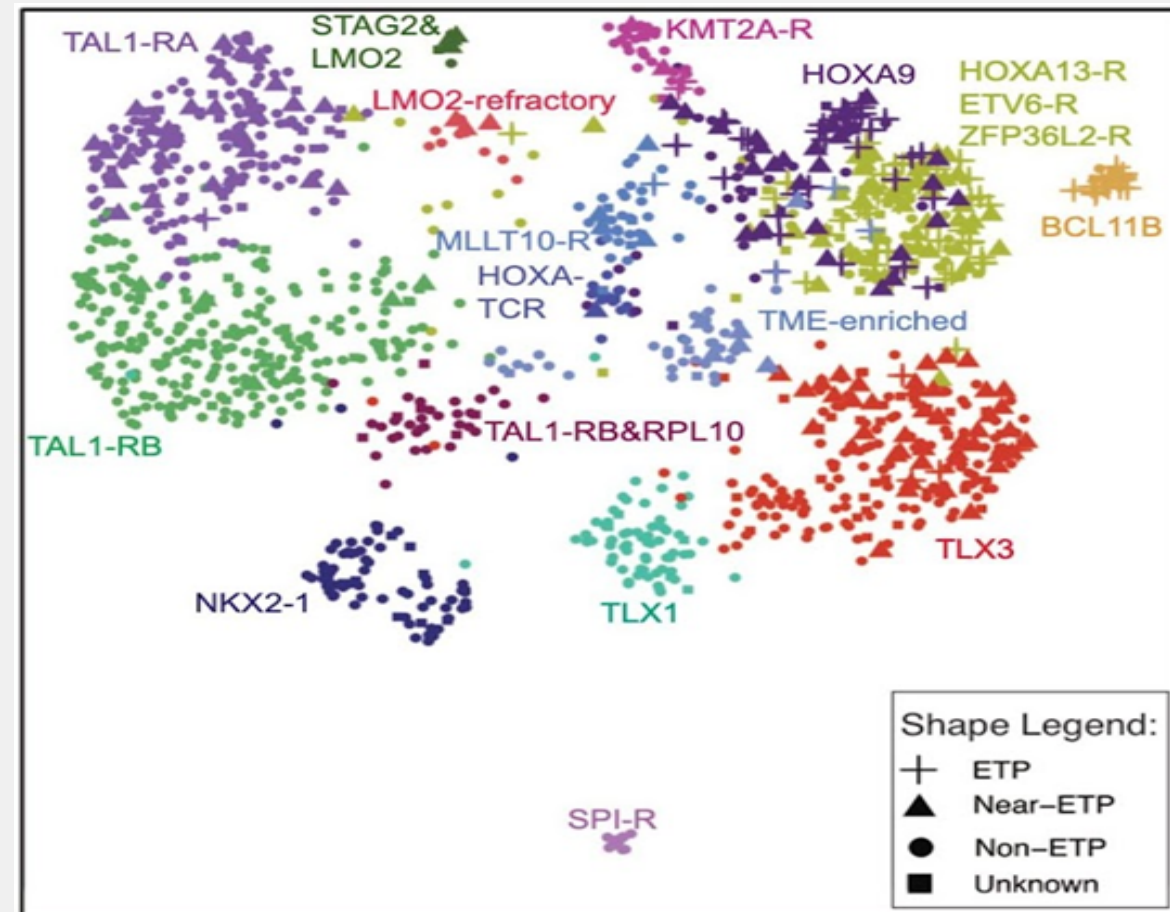


# LLA É UMA DOENÇA BIOLÓGICAMENTE HETEROGÊNEA!

## LLA Precursor B : 23 subtipos



## LLA T : 15 subtipos



## ESTRATIFICAÇÃO RISCO

### LLA B derivada

- **Idade e Leucometria Iniciais** (Critérios NCI )
- **Subtipos Genet Mol** têm impacto
- SNC 1,2,3, PLT
- Infiltração Tx : **alguns protocolos**
- Velocidade resposta p/ DRM:  
**Mudanças de risco mais precoces**



### LLA T/ ETP

- **NEM** idade e **NEM** leucometria inicial como critérios AR ou TMO
- Achados Genet Mol **ainda** não estratificam
- SNC 1,2,3, PLT
- Alargamento Mediastinal: **sem impacto**
- Infiltração Tx sem impacto
- Velocidade resposta p/DRM:  
**Mudanças de risco mais tardia** ( pós consolidação)

**Table 4. Uniform Age and WBC Count Criteria for B-Precursor ALL Standard- and High-Risk Cohorts Adopted at the CTEP/NCI Workshop**

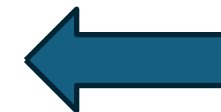
Risk	Definition	4-Year EFS (%) <sup>a</sup>	% of B-Precursor Patients <sup>a</sup>
Standard	WBC count < 50,000/ $\mu$ L and age 1.00-9.99 years	80.3	68
High	WBC count $\geq$ 50,000/ $\mu$ L or age $\geq$ 10.00 years	63.9	32

# Identification of prognostic factors in childhood **T-cell acute lymphoblastic** leukemia: Results from DFCI ALL Consortium Protocols 05-001 and 11-001

	N (%)	5-yr DFS% <sup>2</sup> [95% CI]	p-value	5-yr EFS% [95% CI]	p-value	5-yr OS% [95% CI]	p-value
No. Pts.	123			81 [73-87]		90 [83-94]	
<b>Age</b>							
<10 yrs.	67 (54)			83 [72-90]	0.49	91 [80-96]	0.75
≥10 yrs.	56 (46)			78 [64-87]		89 [78-95]	
<b>WBC</b>							
< 50K	53 (43)			79 [64-88]	0.60	92 [81-97]	0.48
≥ 50K	70 (57)			83 [72-90]		88 [78-94]	
<b>Sex</b>							
Male	91 (74)			81 [72-88]	0.97	90 [81-95]	0.99
Female	32 (26)			80 [60-90]		91 [74-97]	
<b>CNS Status</b>							
CNS 1	71 (58)			87 [76-93]	0.052	94 [85-98]	0.17
CNS 2	42 (34)			76 [60-86]		86 [71-95]	
CNS 3	10 (8)			60 [25-83]		80 [41-93]	
<b>Mediastinal Mass</b>							
Yes	55 (45)			85 [73-92]	0.27	89 [77-95]	0.77
No	68 (55)			77 [65-86]		91 [81-96]	
<b>ETP Phenotype</b>							
Yes	100 (81)			54 [29-74]	0.0006	85 [61-95]	0.31
No	21 (17)			87 [79-92]		92 [84-96]	
Unknown	2 (2)			---		---	
<b>End-induction MRD</b>							
<10 <sup>-3</sup>	69 (75)	94 [85-98]	0.079	---		94 [85-98]	0.24
≥10 <sup>-3</sup>	23 (25)	79 [51-92]		---		86 [65-96]	
<10 <sup>-4</sup>	45 (49)	98 [85-99]	0.031	---		98 [85-99]	0.055
>10 <sup>-4</sup>	47 (51)	84 [69-92]		---		87 [73-94]	

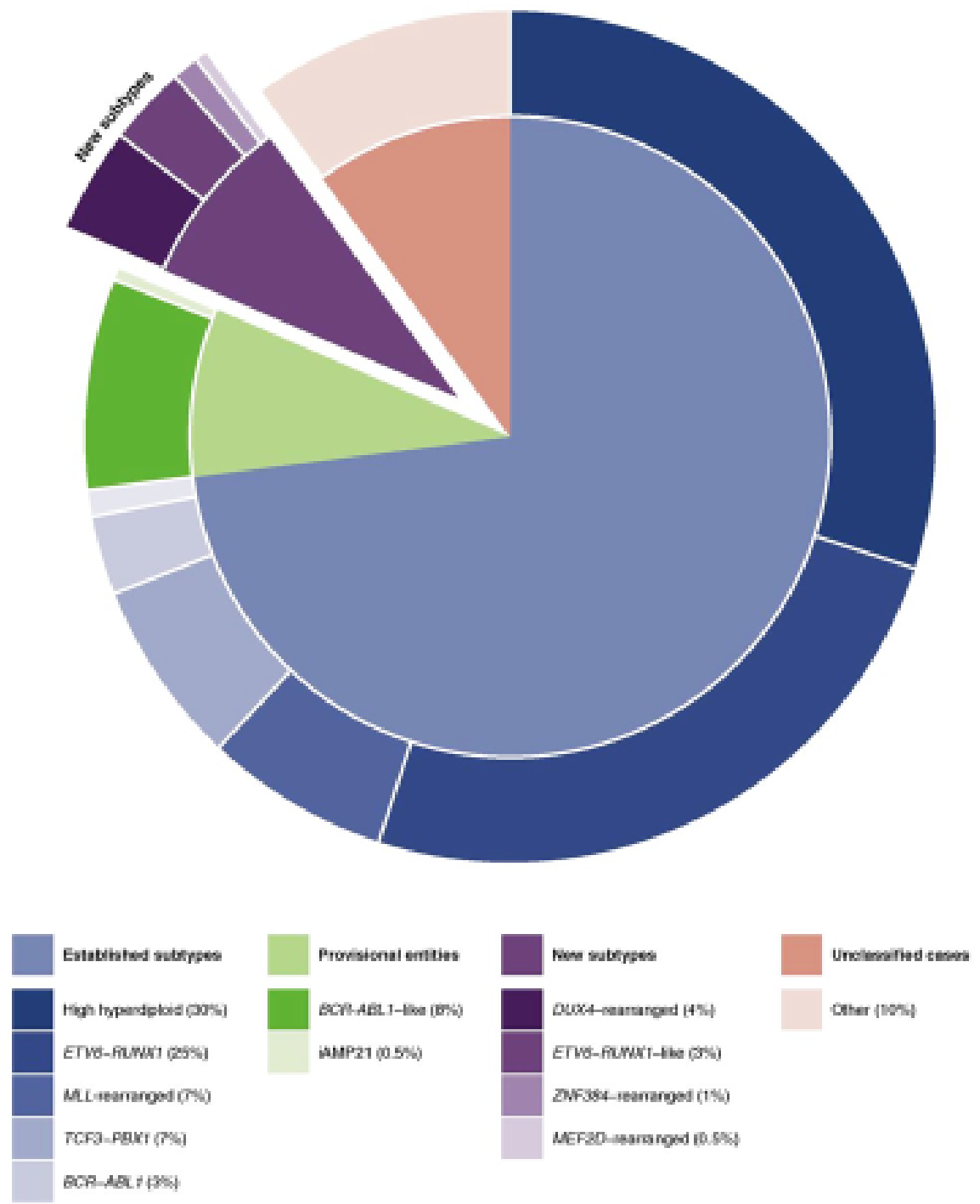
# Resultados Tratamento de acordo SNC1 ou PLT

Study	CNS1	TLP	P value
<b>BFM 95 (1995-1999)<sup>10</sup></b>			
No. patients	1605	135	
% CNS relapse at 5 yr	3.5	8	< 0.05
% 5-yr EFS (SE)	80 (1)	73 (4)	0.003
<b>DCLSG ALL 7 &amp; 8 (1988-1997)<sup>14</sup></b>			
No. patients	304	62	
% CNS relapse at 10 yr	4.9	8	0.24
% 10-yr EFS (SE)	72.6 (2.5)	58 (7.6)	< 0.01
<b>SJCRH XI &amp; XII (1984-1991)<sup>17</sup></b>			
No. patients	336	60	
% CNS relapse at 5 yr	4.3 (1.1)	7.3 (3.5)	0.13
% 5-yr EFS (SE)	77 (2)	60 (6)	0.026
<b>SJCRH XIII B (1994-1998)<sup>15</sup></b>			
No. patients	145	17	
% CNS relapse at 5 yr	0.7 (0.7)	0	0.73
% 5-yr EFS (SE)	80.6 (3.3)	82.4 (8.9)	0.67



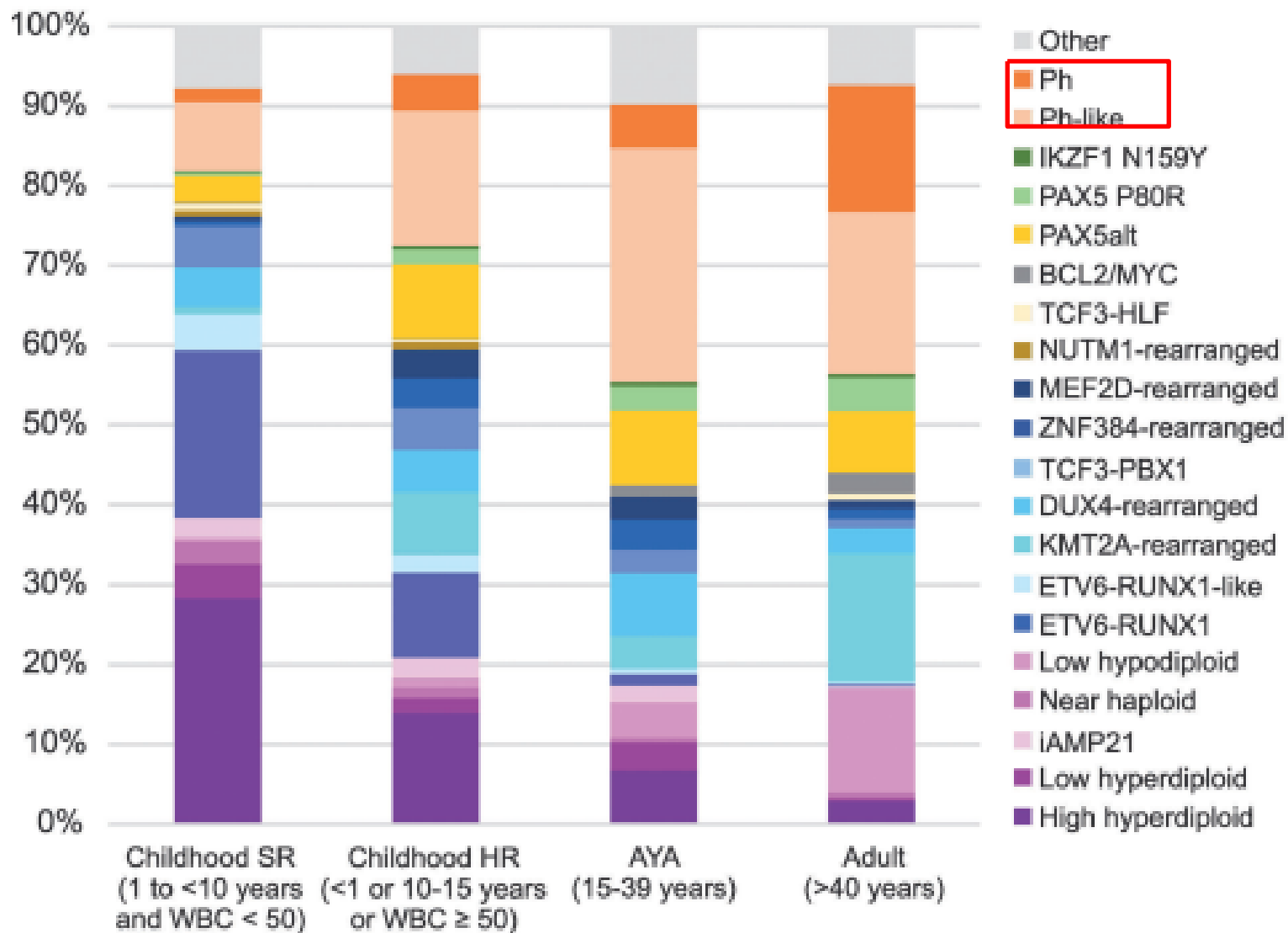
# New Oncogenic Subtypes In Pediatric B-cell Precursor Acute Lymphoblastic Leukemia

“ B others” ALL



Liljebjörn H. and Fioretos T  
Blood 2017 130:1395-1401

# Distribution of B-cell acute lymphoblastic leukemia (B-ALL) subtypes within each age group



## SUBTIPOS GENÉTICOS MOLECULARES X PROGNÓSTICO LLA B derivada

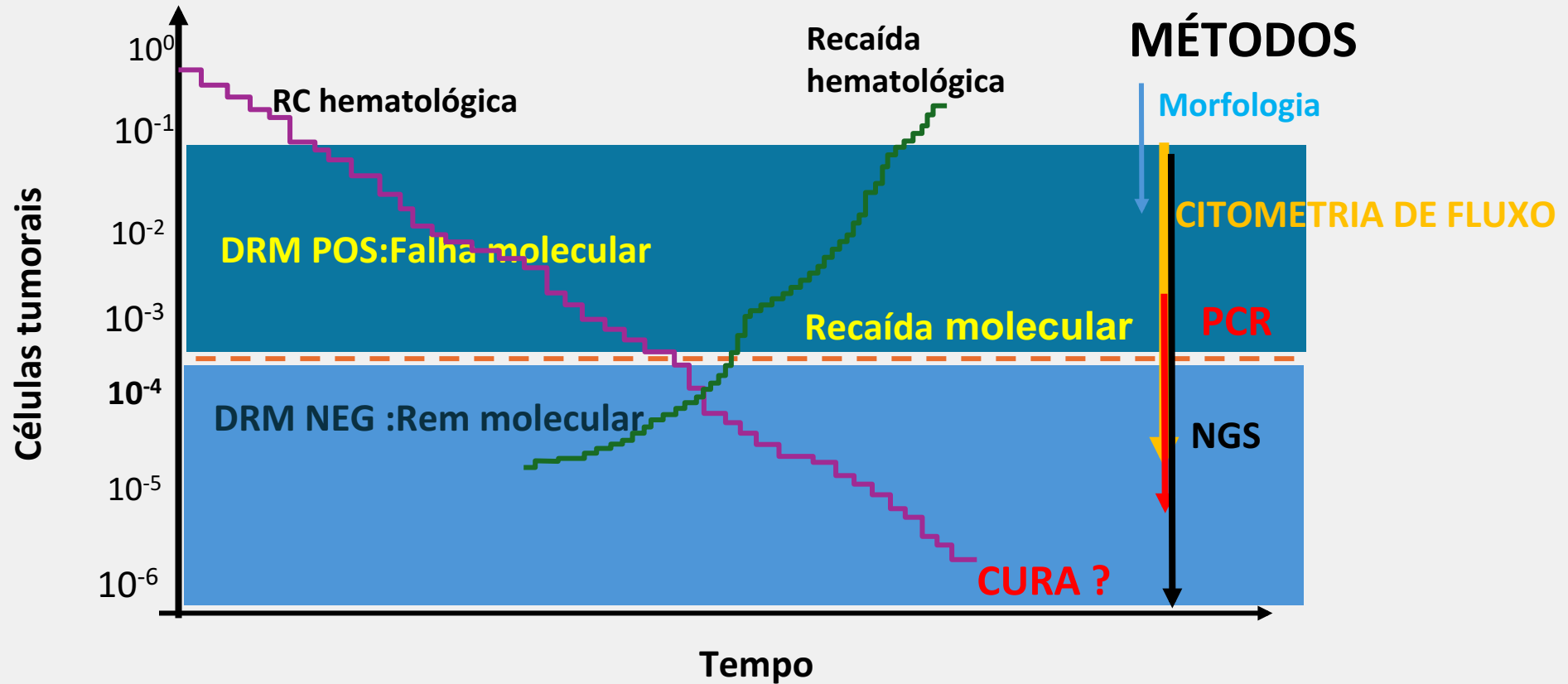
Category	Characteristics	Therapeutic Approach
<b>B-lymphoblastic leukemia</b>		
<b>Low-risk genetics</b>		
<i>ETV6/RUNX1</i>	Excellent prognosis	Reduction of intensity, MRD based
Hyperdiploidy	Excellent prognosis	Reduction of intensity, MRD based
<i>DUX4</i> -rearranged	Most have focal <i>ERG</i> deletions and favorable outcome despite <i>IKZF1</i> alterations	Standard dose intensity, MRD based
<b>Intermediate-risk genetics</b>		
<i>TCF3/PBX1</i>	Higher incidence in African Americans, cytoplasmic $\mu$ -chain	Standard dose intensity, MRD based, intensive intrathecal therapy
<i>PAX5alt</i>	<i>PAX5</i> fusions, mutation, or amplifications	Standard dose intensity, MRD based
<i>PAX5</i> p.Pro80Arg	Frequent signaling pathway alterations	Standard dose intensity, MRD based, JAK inhibitors
<i>ZNF384</i> -rearranged	Peak age and prognosis vary by fusion partner, expression of myeloid markers	Standard dose intensity, MRD based

## SUBTIPOS GENETICOS MOLECULARES X PROGNOSTICO LLA T/ETP

Non-early T-cell precursor	Deregulation of <i>TAL1</i> , <i>TAL2</i> , <i>LYL1</i> , <i>LMO1</i> , <i>LMO2</i> , <i>TLX1</i> ( <i>HOX11</i> ), <i>TLX3</i> ( <i>HOX11L2</i> ), and <i>HOXA</i> ; <i>NOTCH1</i> activating mutation	Standard dose intensity, MRD based, nelarabine, BCL-2 inhibitors
JAK-STAT activating mutation	Approximately 25% of patients with T-ALL	Standard dose intensity, MRD based, nelarabine, JAK inhibitors, BCL-2 inhibitors
<i>ABL1</i> fusions (e.g., <i>NUP214-ABL1</i> )	Fusion with <i>BCR</i> and <i>NUP214</i> , potentially amenable to tyrosine kinase inhibition	Standard dose intensity, MRD based, <i>ABL1</i> inhibitors, nelarabine, BCL-2 inhibitors
Early T-cell precursor ALL	Mutations in transcriptional regulators, JAK-STAT and Ras signaling, and epigenetic modifiers	Standard dose intensity, MRD based, JAK inhibitors, BCL-2 inhibitors

# DOENÇA RESIDUAL MÍNIMA

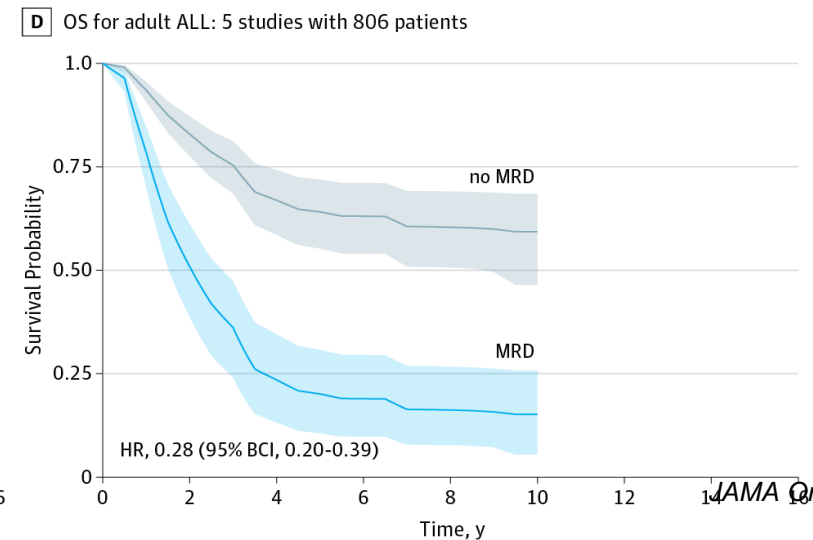
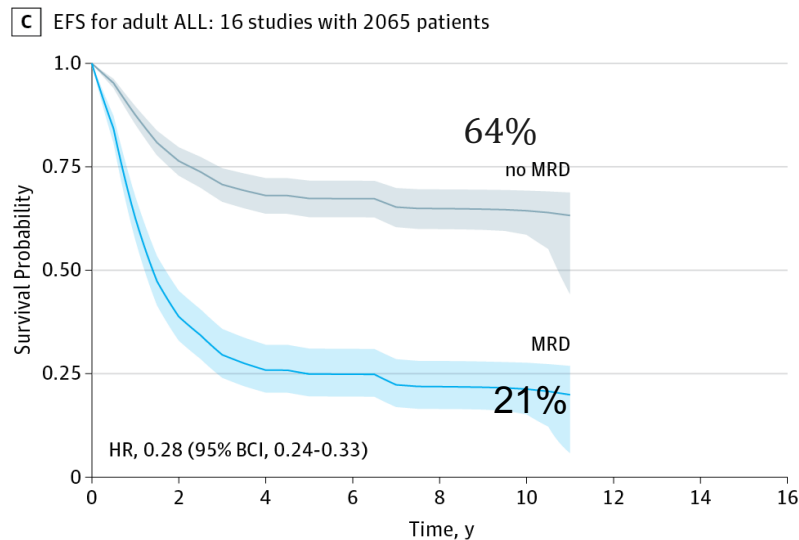
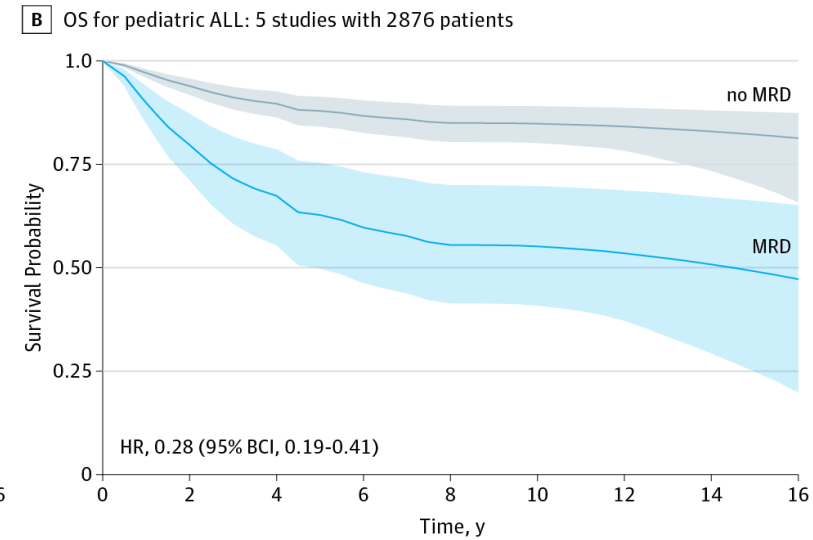
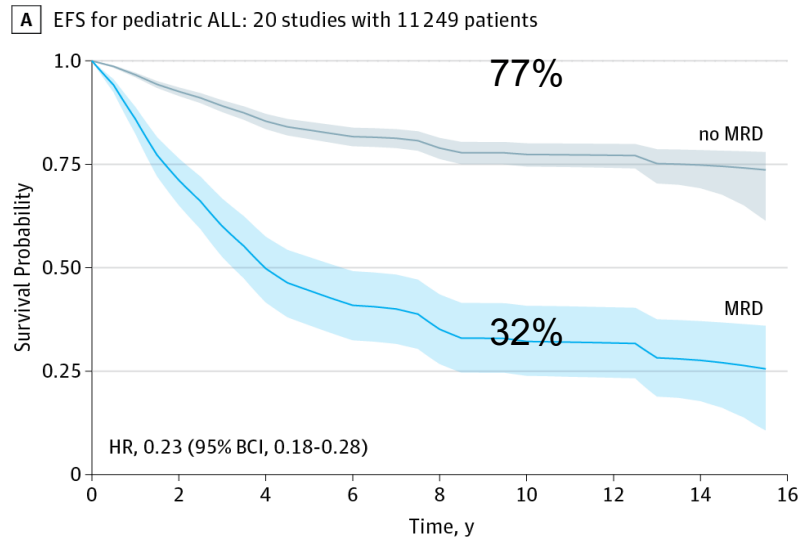
## BIOMARCADOR DA DOENÇA: Mensura a resposta



# Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis

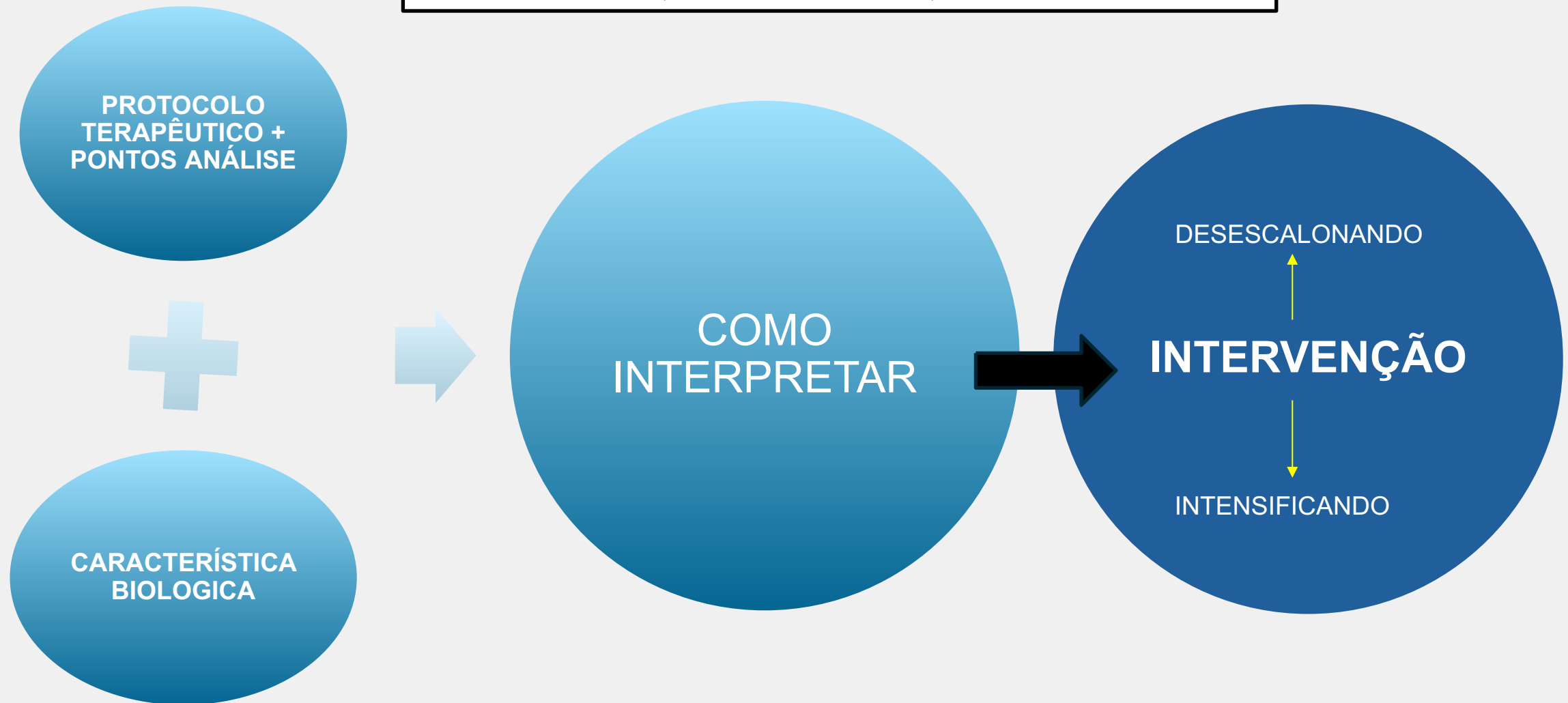
Primeira afirmação:  
DRM NEGATIVA tem impacto nos resultados

39 estudos; N 13 637 pts



# DOENÇA RESIDUAL MÍNIMA

REFINAR , ESTRATIFICAR , DIRECIONAR



# CONTEXTO CLÍNICO GERAL DA DRM

Definição Critérios  
Prognósticos do Protocolo  
**Paciente + Características  
da Doença**

**Estratificação INICIAL de  
Risco**



**PROTOCOLO  
TERAPÊUTICO**



**Pontos de Avaliação :**

D8 ;D15 Indução  
Término da indução  
Pós consolidação)

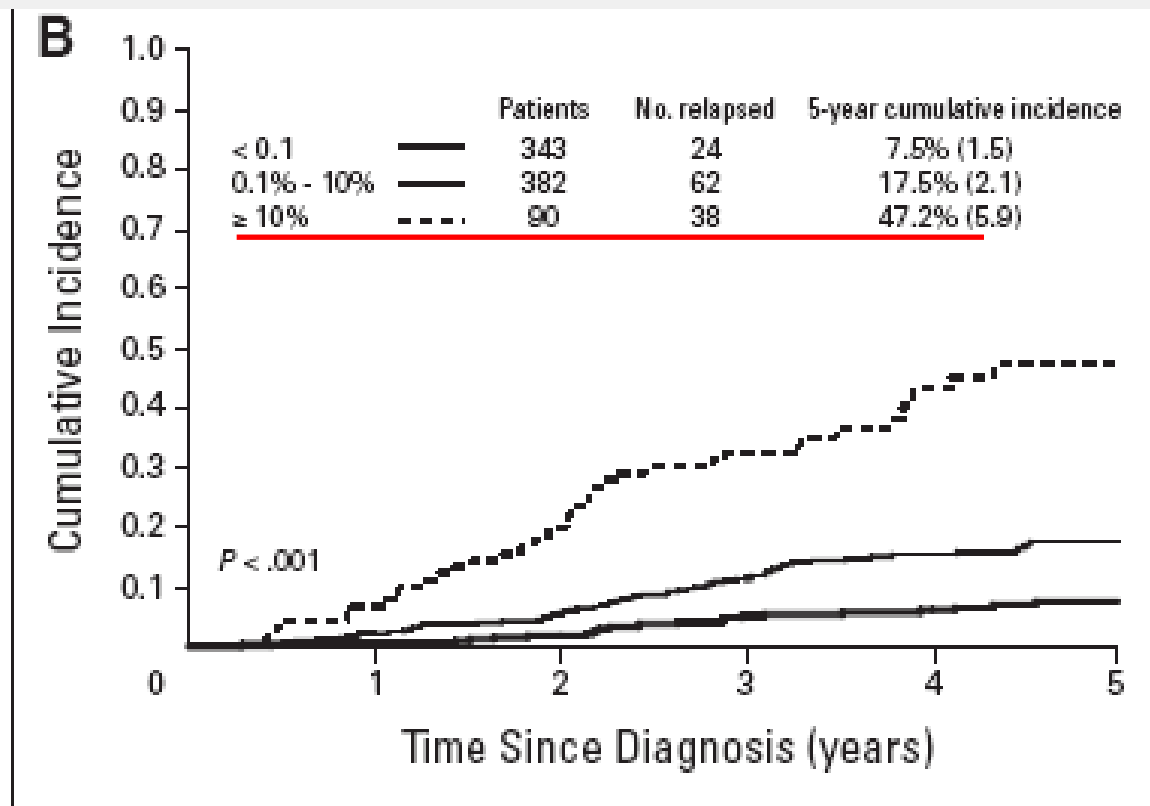
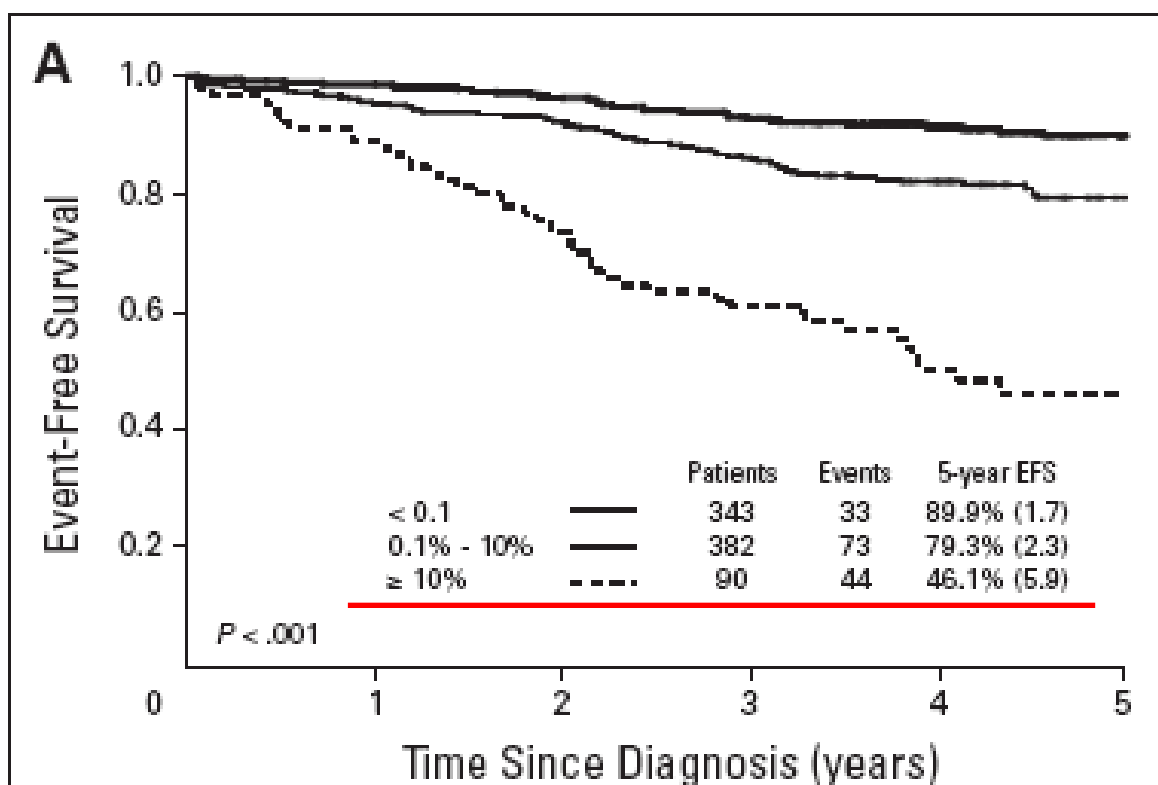
**Níveis** : < 0,01%,  
≤ 0,1%, ≥1%



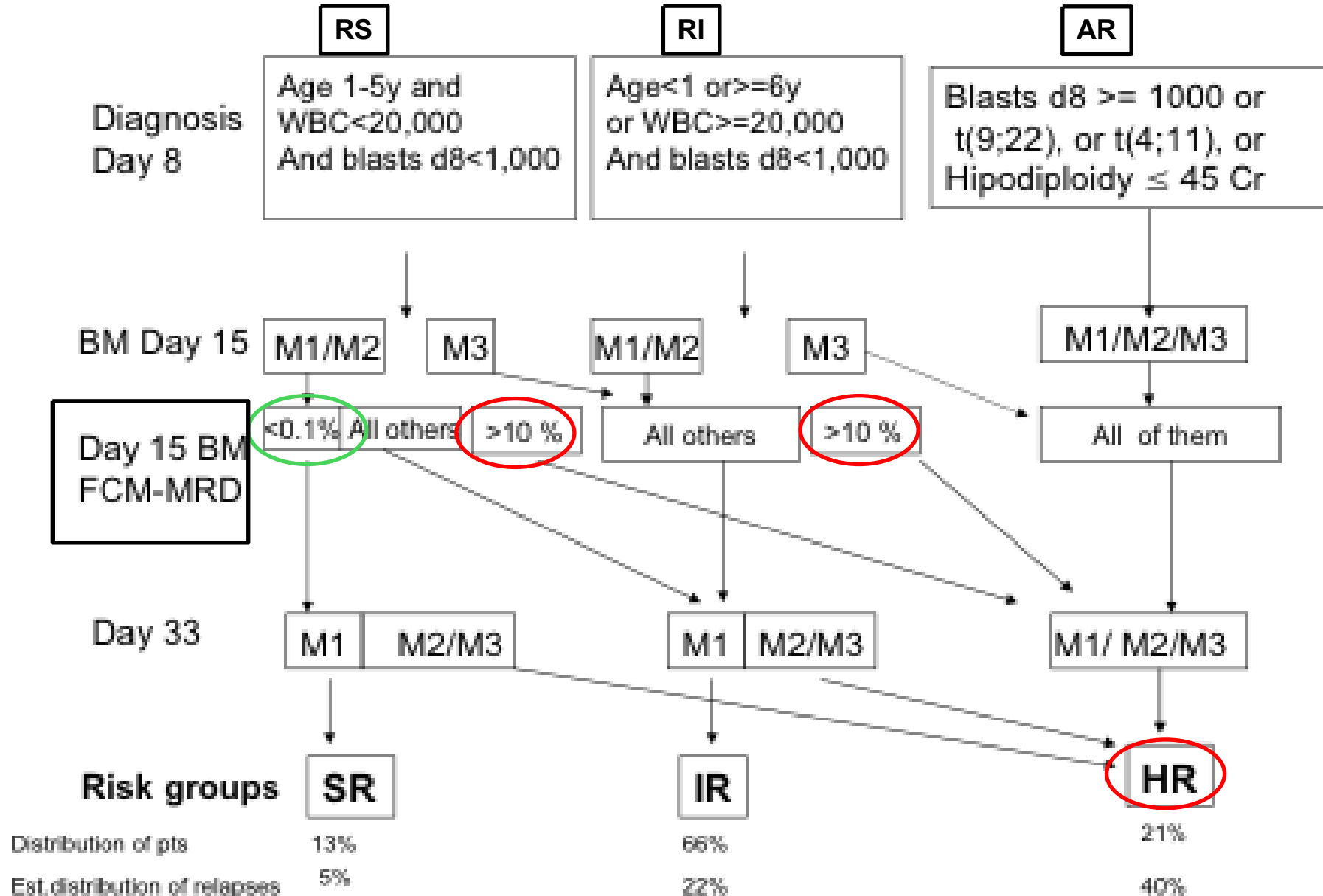
**Estratificação FINAL de  
Risco**

## Risk of Relapse of Childhood Acute Lymphoblastic Leukemia Is Predicted By Flow Cytometric Measurement of Residual Disease on Day 15 Bone Marrow

Giuseppe Basso, Marinella Veltroni, Maria Grazia Valsecchi, Michael N. Dworzak, Richard Ratei, Daniela Silvestri, Alessandra Benetello, Barbara Buldini, Oscar Maglia, Giuseppe Maserà, Valentino Conter, Maurizio Arico, Andrea Biondi, and Giuseppe Gaipa

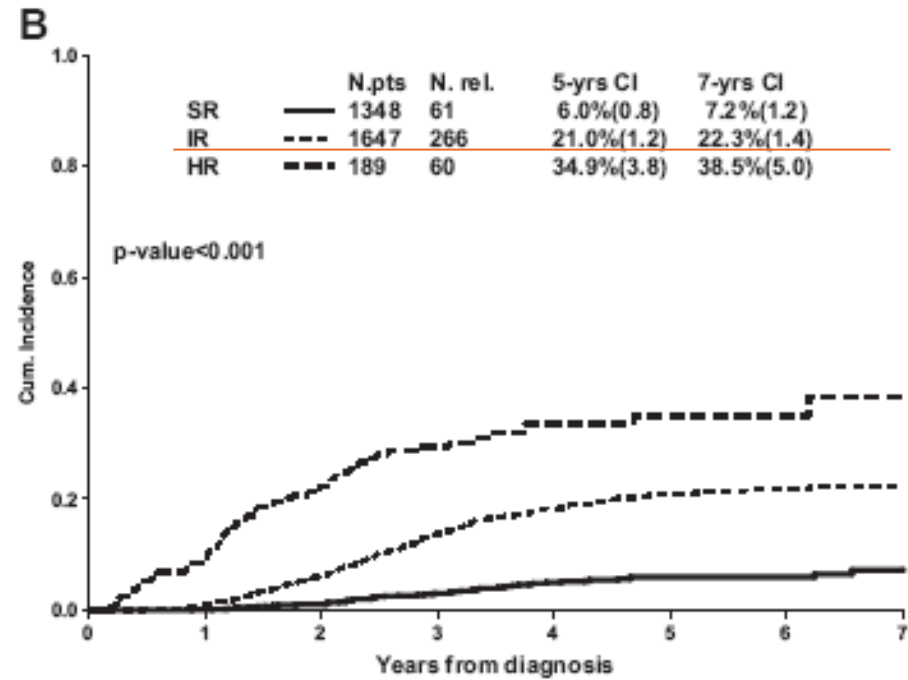
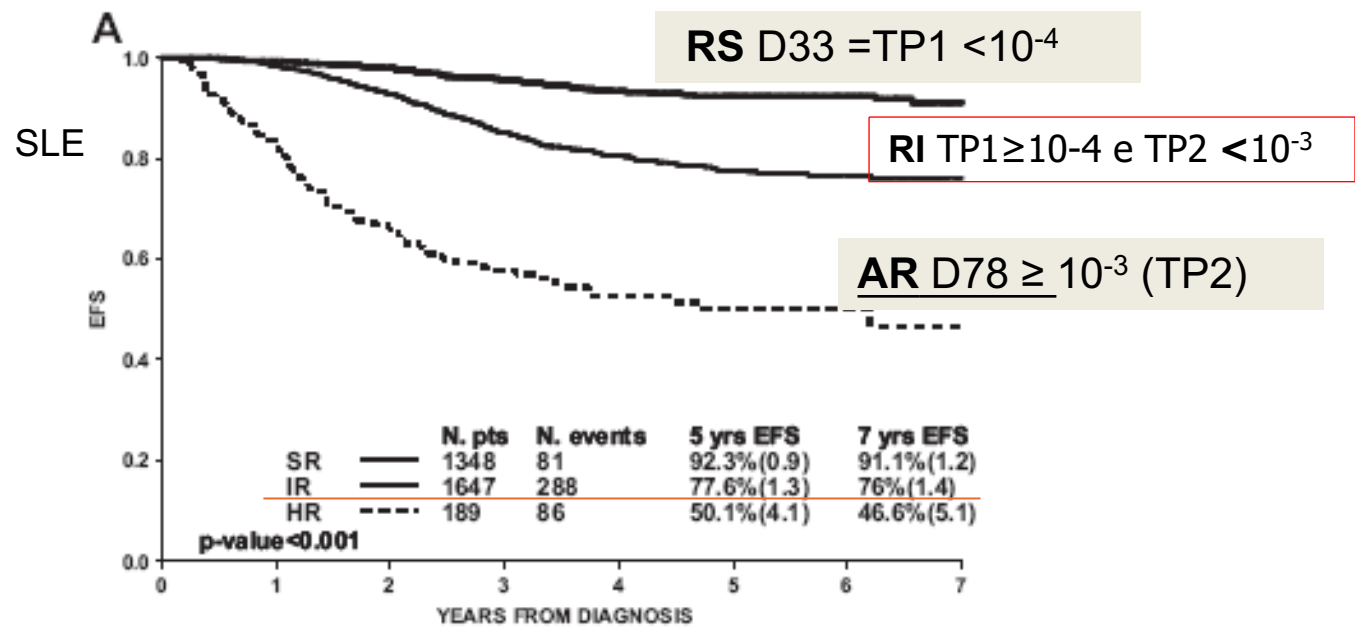


# ALL IC-BFM 2009 CLASSIFICATION



Molecular response to treatment redefines all prognostic factors in children and adolescents with **B-cell precursor acute lymphoblastic leukemia**: results in 3184 patients of the AIEOP-BFM ALL 2000 study

Estratificação de DRM  
 Baixo Risco = DRM NEG no D33  
 ( 42%)  
 Alto risco = DRM  $\geq 10^{-3}$  no D78  
 ( 6%)



Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study

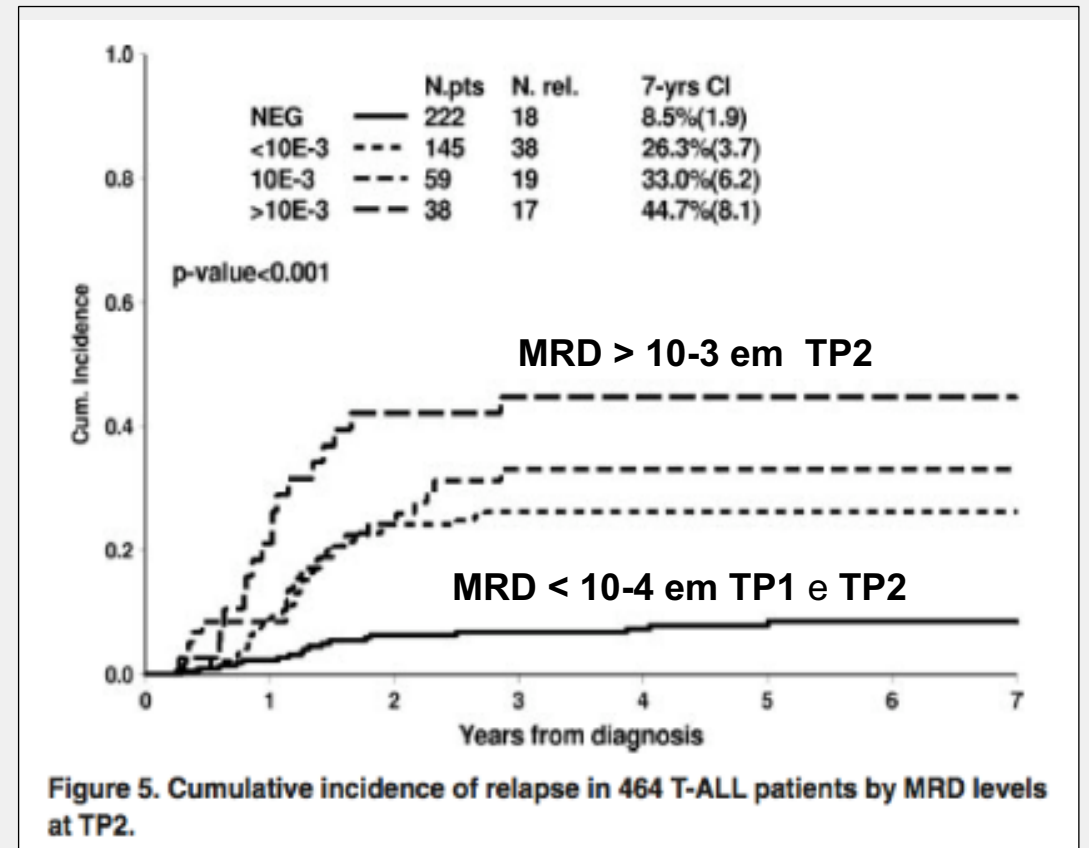
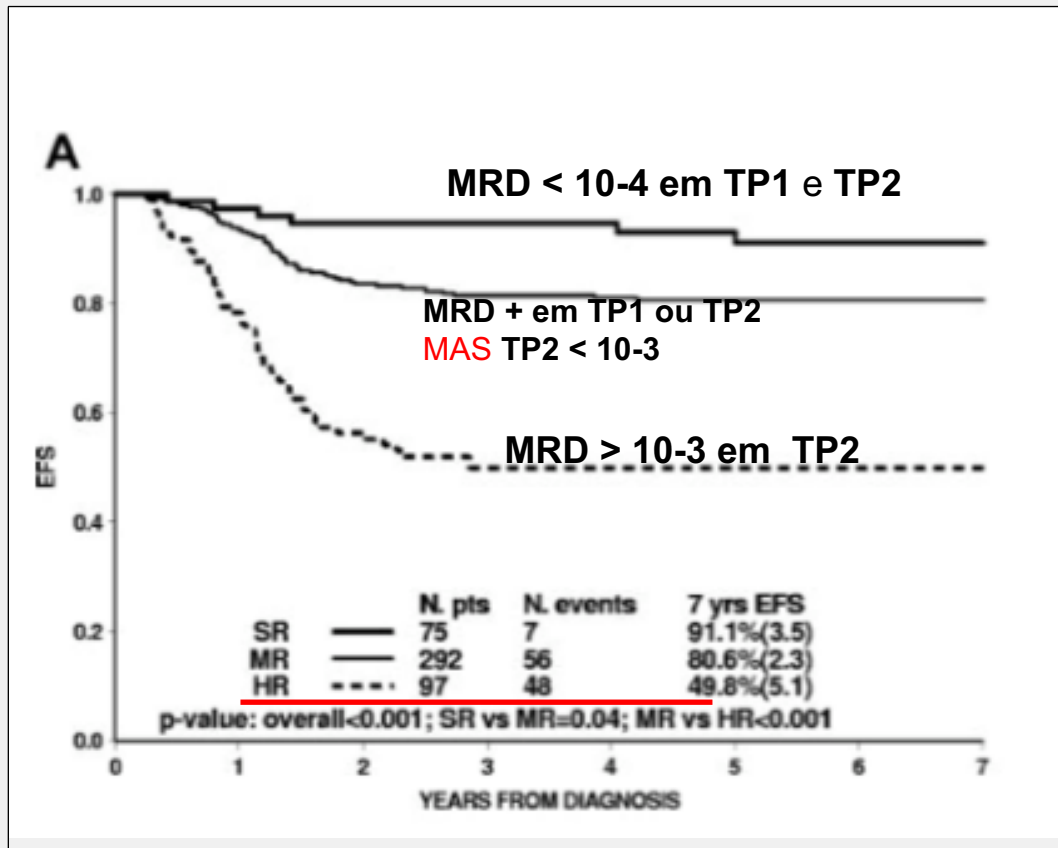
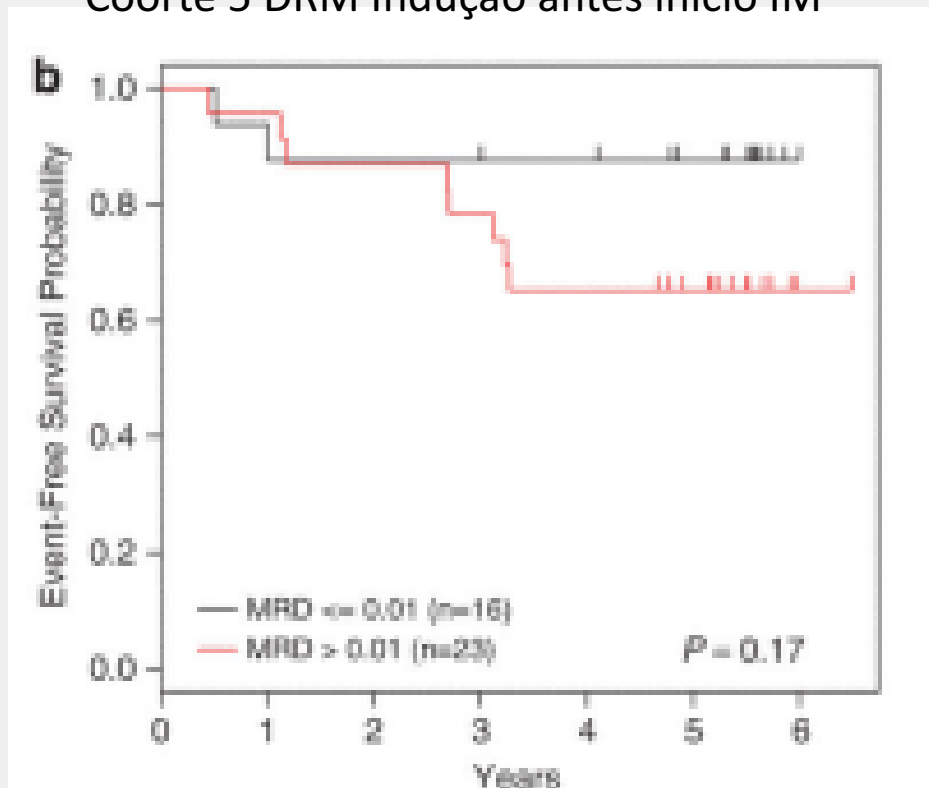


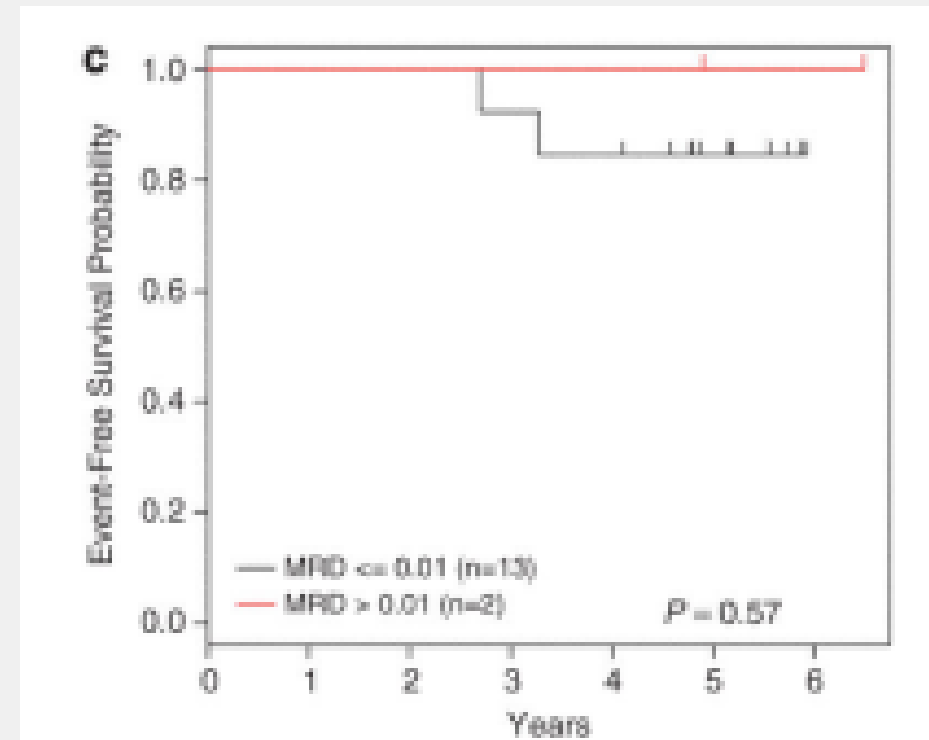
Figure 5. Cumulative incidence of relapse in 464 T-ALL patients by MRD levels at TP2.

# Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group Study AALL0031

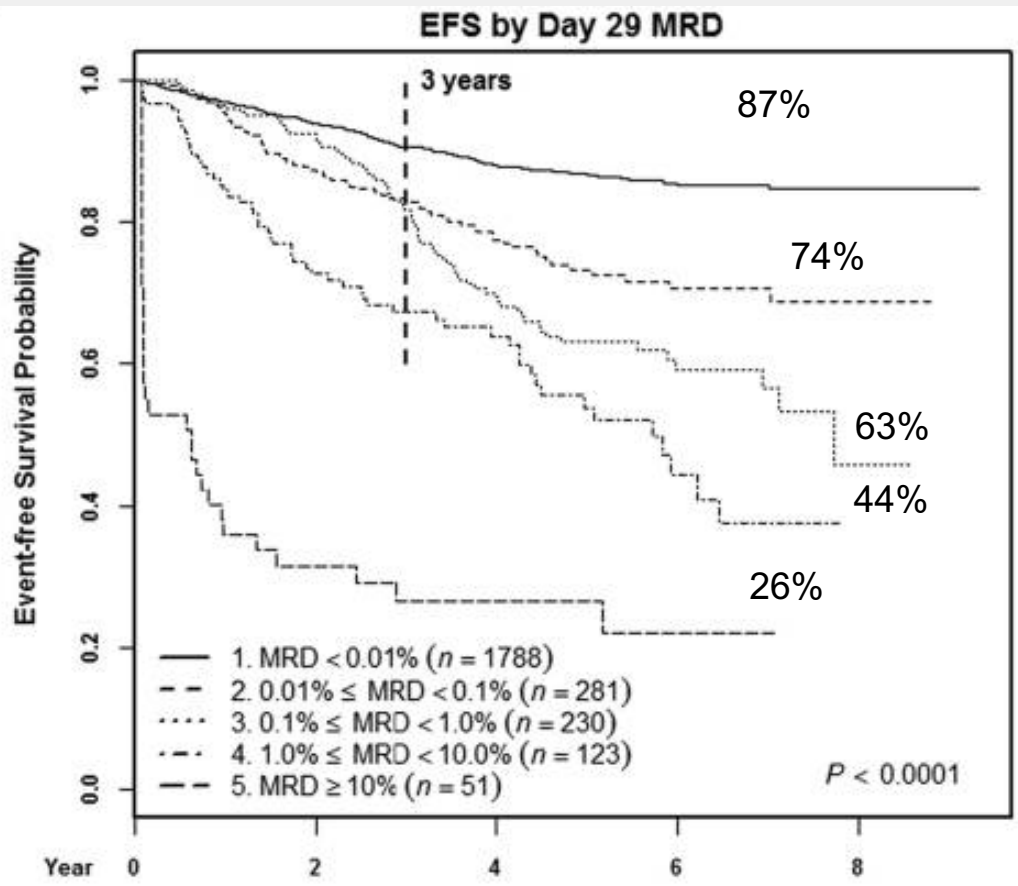
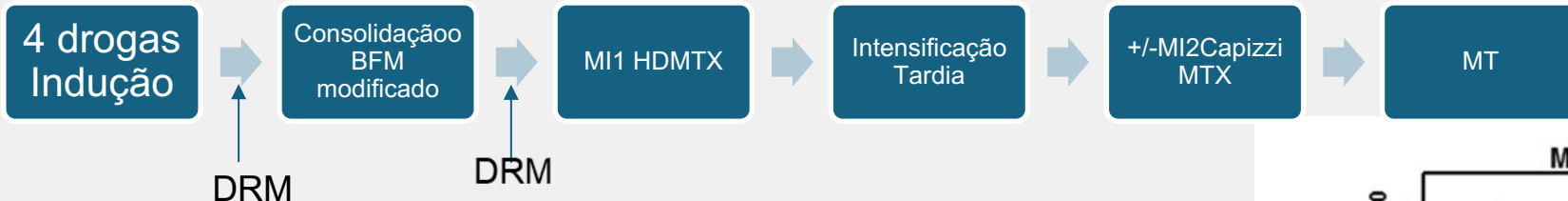
Coorte 5 DRM Indução antes início IM



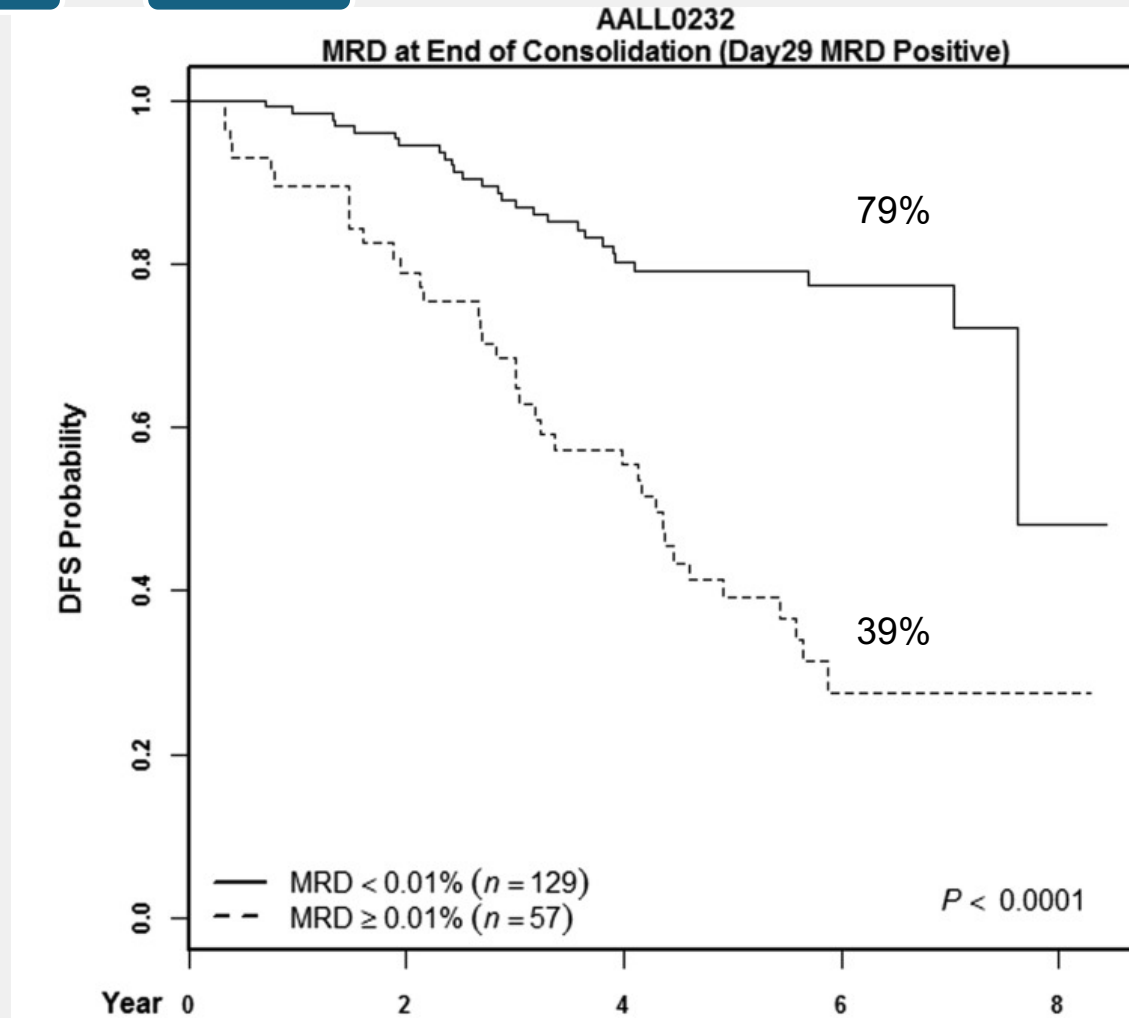
Coorte 5 DRM pós consolidação 2



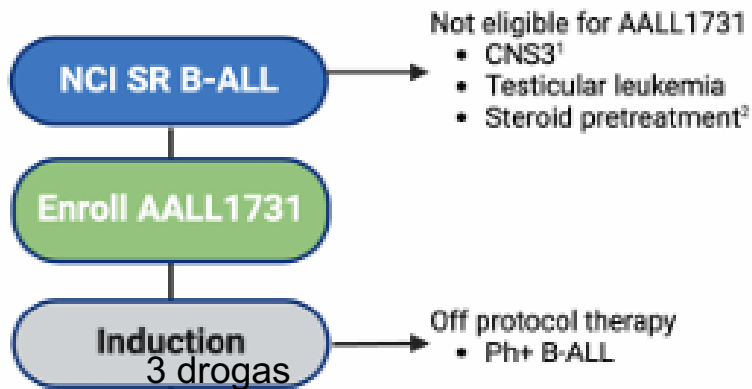
# EFS of subjects with HR ALL treated on COG AALL0232 as a function of MRD levels at end of induction



PÓS INTENSIFICAÇÃO



# Blinatumomab in Standard-Risk B-Cell Acute Lymphoblastic Leukemia in Children



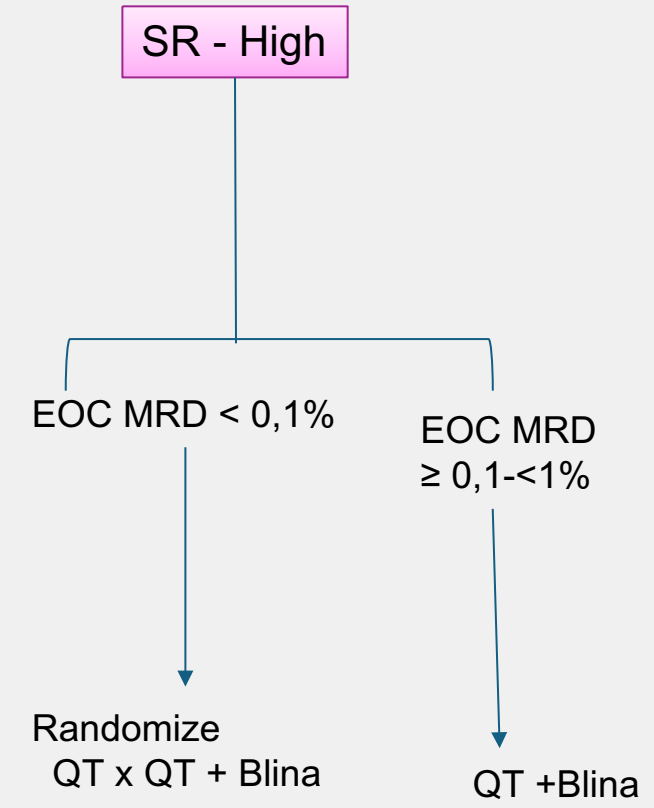
- SR-Fav**
- Must have all:
- Favorable genetics<sup>3</sup>
  - CNS1/2
  - Induction Day 8 PB MRD <1%
  - EOI BM MRD <0.01%

**SR-Avg**

Not SR-Fav  
Not SR-High

- SR-High**
- One or more of:
- Unfavorable genetics<sup>4</sup>
  - EOI MRD ≥ 0.1% and DT
  - EOI BM MRD ≥0.01% and not DT
  - Neutral genetics<sup>5</sup> and CNS2

\* iAMP21, KMT2A rg, < 44cr, t ( 17;19)



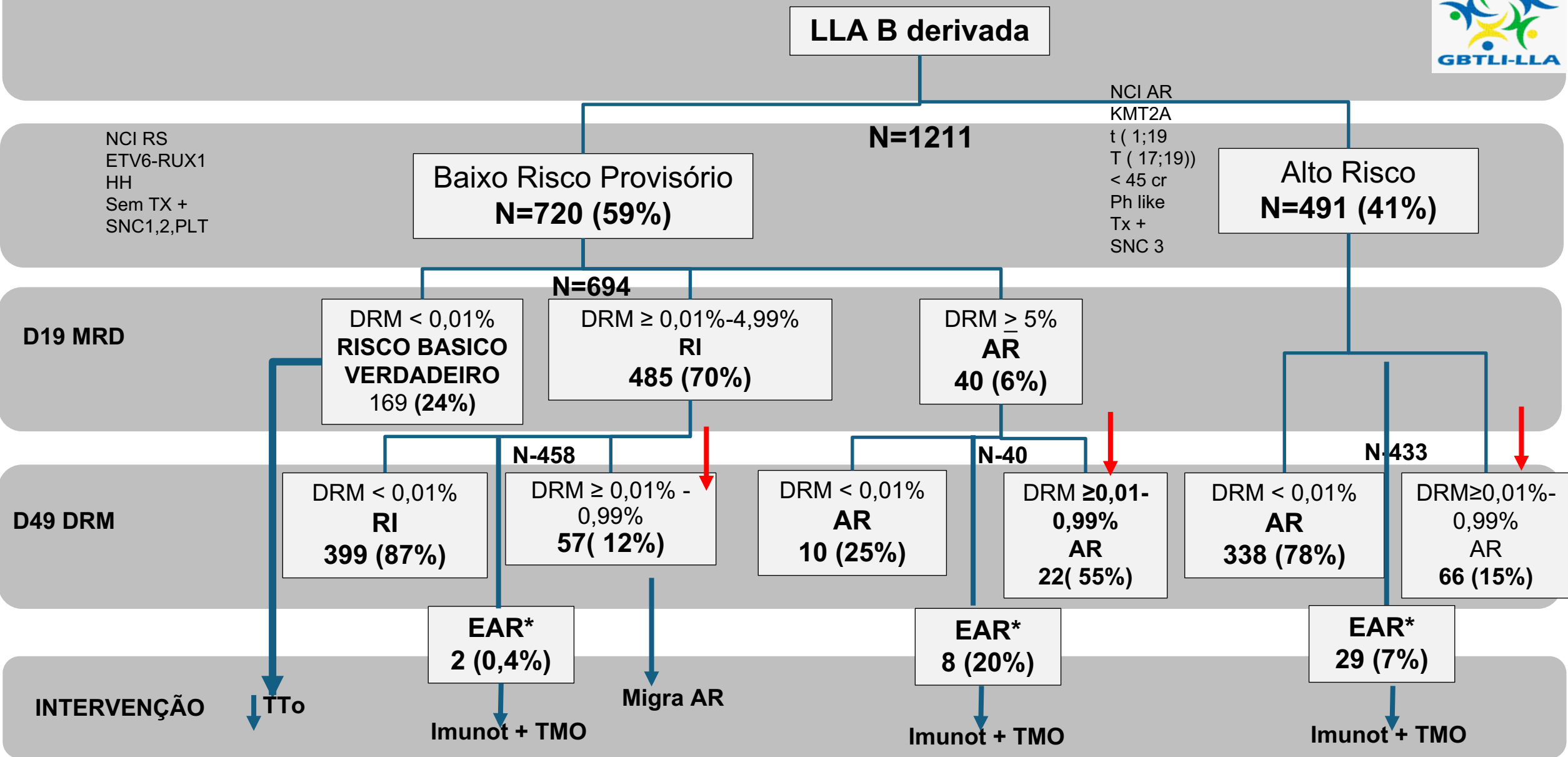
## Blina melhora os resultados entre os grupos de DRM

4 anos SLD

Ponto Analise	DRM	QT	QT + Blina
Término da Indução	< 0,01%	89,7 ± 1,7% N=455	95,9 ±1,1% N = 451
	≥ 0,01%	82,3 ± 2,7 N 270	92,8 ± 1,9% N=268
Término da Consolidação	< 0,01%*	84,7 ± 3,2% N= 176	91,8 ±2,5% N 180
	≥ 0,01% *	30,8 ± 16,8% N=16	81,8 ± 11,6% N= 13

Grupo SR –High com DRM ≥ 0,01% no Final Indução

# Dados preliminares Maio 2026 Protocolo GBTLI LLA 2021



NCI RS  
ETV6-RUX1  
HH  
Sem TX +  
SNC1,2,PLT

NCI AR  
KMT2A  
t ( 1;19)  
T ( 17;19)  
< 45 cr  
Ph like  
Tx +  
SNC 3

D19 MRD

D49 DRM

INTERVENÇÃO

↓ Pontos de Novas intervenções no próximo estudo

\* D49 c/ FI ou DRM≥1% ou DRM + pós Cons

## Next Question #2

Do we need to rethink how we risk stratify patients?

## OCORRERÃO MUDANÇAS NO FUTURO ?

Somatic genetics	SR-Average		SR-High	
	Chemotherapy only	Blinatumomab and Chemotherapy	Chemotherapy only	Blinatumomab and Chemotherapy
DT	N=104 89.2% ± 4.8%	N=109 97.3% ± 2.3%	N=39 86.5% ± 9.6%	N=32 95.5% ± 6.8%
<i>ETV6::RUNX1</i>	N=10 80.0% ± 17.9%	N=18 100.0% ± 0.0%	N=57 95.2% ± 5.4%	N=41 100% ± 0.0%
<i>KMT2A-r</i>	-	-	N=10 74.1% ± 18.9%	N=15 84.9% ± 14.8%
iAmp21	-	-	N=34 77.6% ± 15.0%	N=33 96.7% ± 5.1%
Hypodiploid	-	-	N=17 68.2% ± 22.2%	N=16 84.9% ± 14.8%

**Obrigada!**

**Maria Lucia M Lee**

