



# 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

# Imunoterapia de Primeira Linha na LLA: Blinatumomabe, Inotuzumabe e Manejo da Doença Ph+

**Eduardo Cerello Chapchap**

Medico Hematologista – Hospital Israelita Einstein



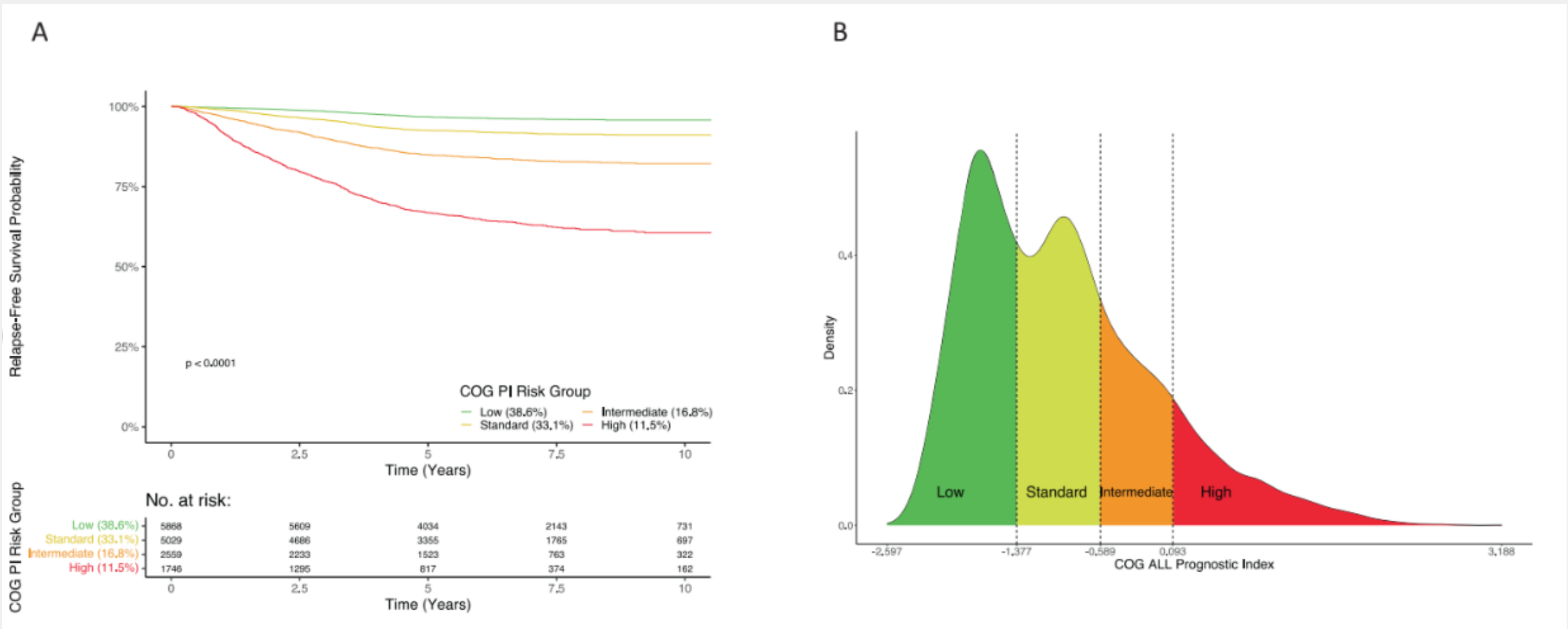
- **DRM positiva**
- **Idade e Leucometria (NCI pediatria) e ?Publico vs Privado?**
- **SNC3**
- **Rearranjo MLL/KMT2A**
- **Rearranjo BCR-ABL1**, reestratificar para risco padrão -> se resposta molecular completa após 3 meses e uso ponatinib
- **Deleção IKZF1 plus**
- **Hipodiploidia**, especialmente se **baixa** (< 40 cromossomos) ou **near-haploide**
- **Mutação TP53**, especialmente se em **homozigose e > 35 anos**
- **Cariotipo complexo (≥ 5 anormalidades)**
- **Número de cópias alteradas (Copy number alterations = CNA)**, geralmente pela técnica de **MLPA ≥ 5**
- **Ph-like**: pacientes com **CRLF2r** ou **mutação/fusão JAK/EPOR** ou **ativação STAT5 + del IKZF1plus** -> **alto risco**
- **Ph-like**: pacientes com fusões envolvendo **ABL/CSF1R/PDGFRB** podem se **beneficiar de TKI** e serem reestratificados quanto a indicação do TMO, conforme resposta terapêutica (DRM)
- **ZNF384-r?** => **taxas DRM negativa < 40%**; **alto risco MEF2D-r ; BCL-2/MYC;**
- **PAX5 plus/alt – pior prognostico, exceto subgrupo mut PAX5 P80R** -> em geral favorável
  
- **EarlyTP (ETP-like)**, **mutações RAS e/ou PTEN** e subgrupos **LYL1/LMO2 e HOXA9** com menores taxas de remissão molecular (33%; 53%) respectivamente. **TLX3-hiper imaturo, TAL1-hiper (DN e sem RLP10), NKX2-5, SPI1**

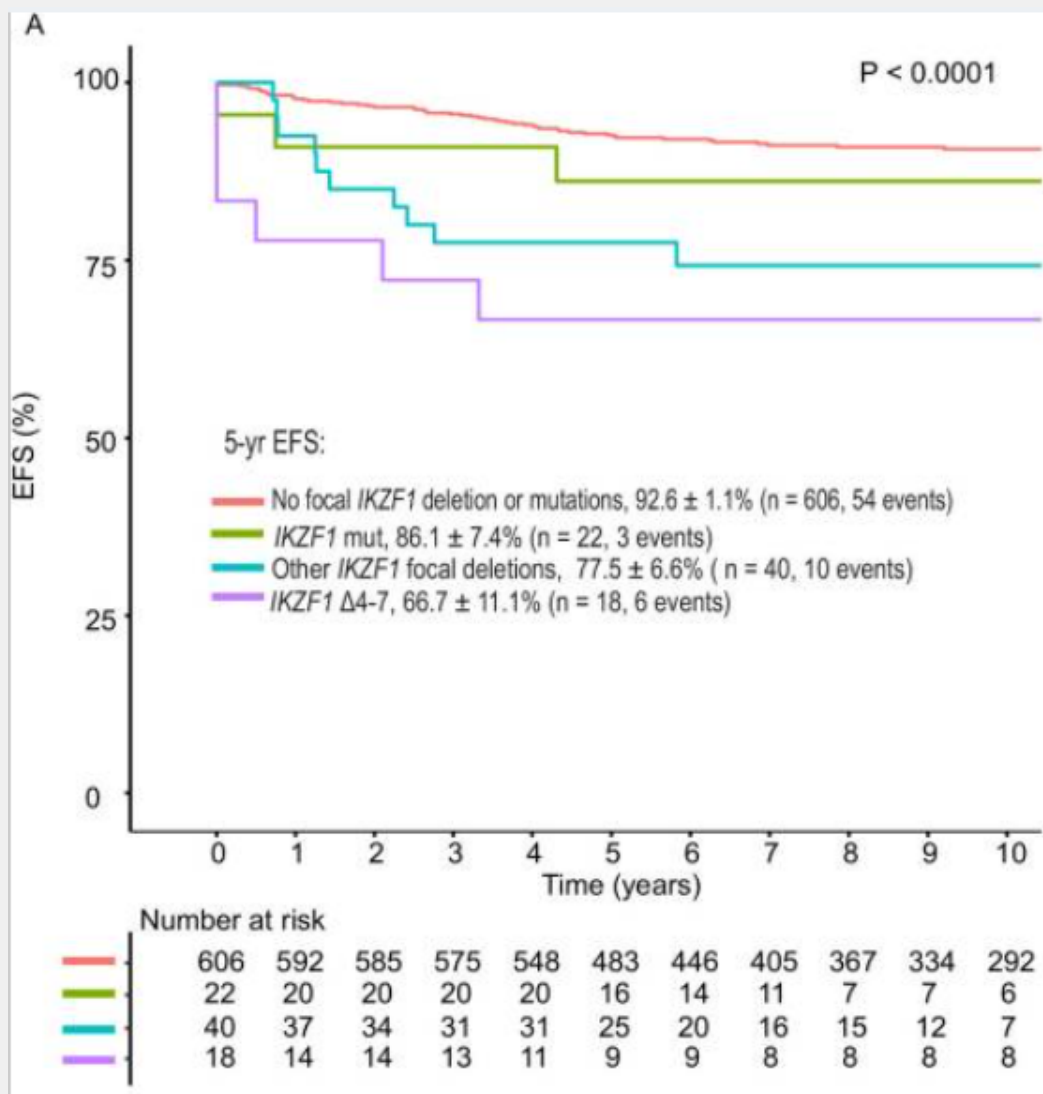
**Table 2.** Summaries of the PI<sub>COG</sub> model derived on the training study population.

Variable	Type	Coefficient	HR (95% CI)	P-value
τ(D29 MRD)	Continuous	-0.102	0.90 (0.89-0.92)	<0.001
τ(D8 MRD)	Continuous	-0.040	0.96 (0.94-0.98)	<0.001
FRG	Binary	-0.741	0.48 (0.41-0.56)	<0.001
URG	Binary	0.644	1.91 (1.59-2.29)	<0.001
WBC <sub>log</sub>	Continuous	0.156	1.17 (1.12-1.22)	<0.001
CNS Status	Categorical			
(Ref = CNS1)	CNS2	0.386	1.47 (1.24-1.74)	<0.001
	CNS3	0.364	1.44 (0.88-2.37)	0.151
Age Dx	Continuous	0.061	1.06 (1.05-1.07)	<0.001

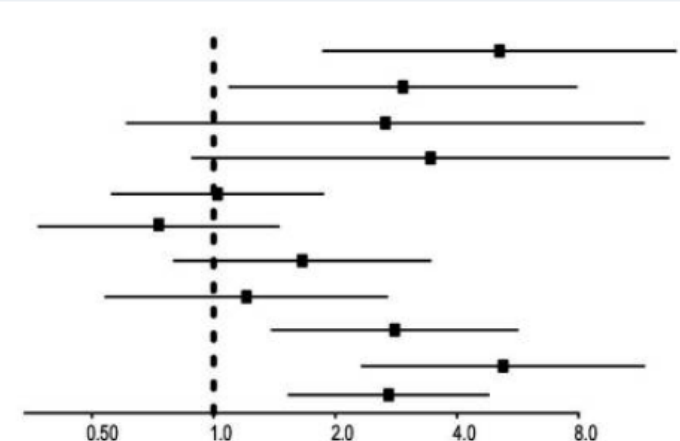
$$\begin{aligned}
 \text{PI}_{\text{COG}} = & [-0.102 * \tau(\text{D29MRD}) - 0.040 * \tau(\text{D8MRD}) - 0.741 * \text{FRG} \\
 & + 0.644 * \text{URG} + 0.156 * \text{WBC}_{\text{log}} + 0.386 * I(\text{CNS2}) \\
 & + 0.364 * I(\text{CNS3}) + 0.061 * \text{Age}]
 \end{aligned}$$

# PI COG ALL PROGNOSTIC INDEX





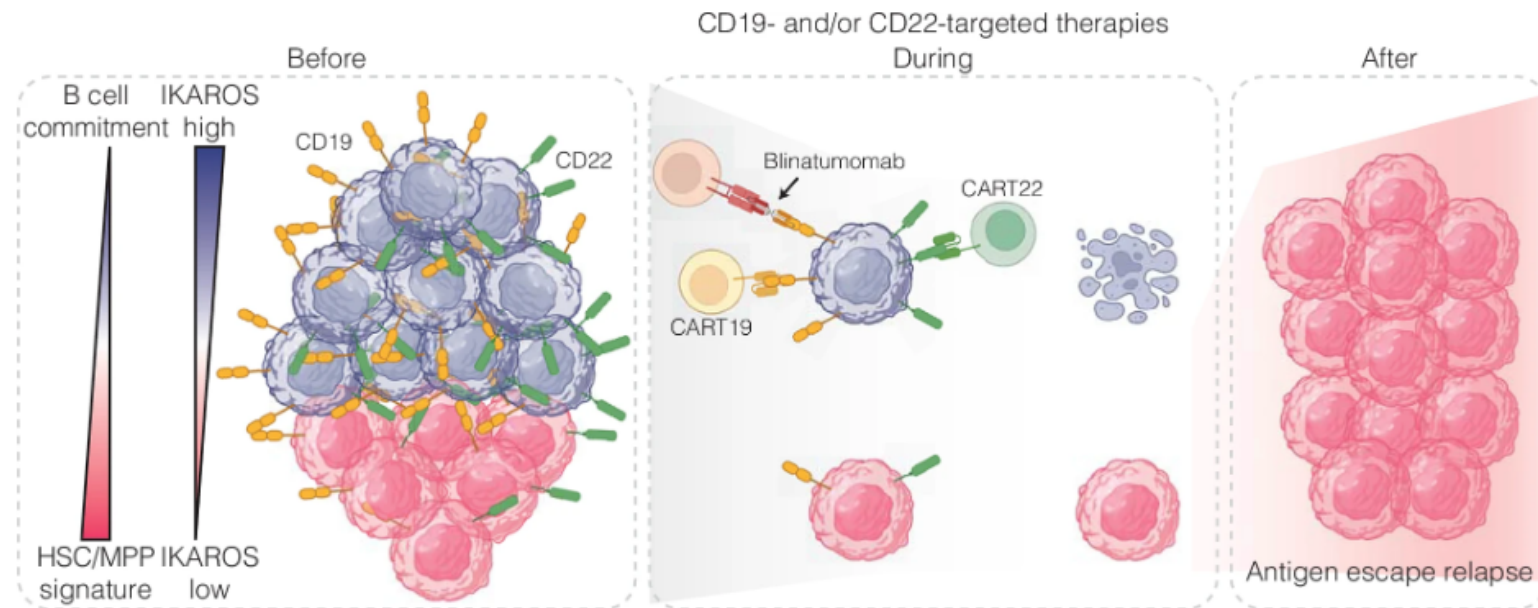
Factor	EFS HR (95% CI)	P value
Genomic <i>IKZF1</i> <sup>plus</sup> (any Δ <i>IKZF1</i> )	5.10 (1.87-13.92)	0.002
<i>IKZF1</i> del (focal and -7/del(7p-))	2.94 (1.09-7.91)	0.03
<i>IKZF1</i> mut	2.66 (0.61-11.59)	0.19
Age <1 year	3.44 (0.87-13.13)	0.07
Age ≥10 years	1.02 (0.56-1.87)	0.94
WBC ≥ 10000 to <50000	0.73 (0.37-1.45)	0.37
WBC 50000 to <100000	1.66 (0.80-3.44)	0.18
WBC ≥ 100000	1.21 (0.54-2.69)	0.65
Intermediate subtype group	2.81 (1.39-5.65)	0.004
Unfavorable subtype group	5.20 (2.33-11.63)	<0.0001
EOI MRD ≥ 0.01%	2.71 (1.53-4.78)	0.0006



## IKAROS levels are associated with antigen escape in CD19- and CD22-targeted therapies for B-cell malignancies

[Pablo Domizi](#) , [Jolanda Sarno](#), [Astraea Jager](#), [Milton Merchant](#), [Kaithlen Zen B. Pacheco](#), [Sean A. Yamada-Hunter](#), [Maria Caterina Rotiroti](#), [Yuxuan Liu](#), [Reema Baskar](#), [Warren D. Reynolds](#), [Brian J. Sworder](#), [Bita Sahaf](#), [Sean C. Bendall](#), [Charles G. Mullighan](#), [Ash A. Alizadeh](#), [Allison B. Leahy](#), [Regina M. Myers](#), [Bonnie Yates](#), [Hao-Wei Wang](#), [Nirali N. Shah](#), [Robbie G. Majzner](#), [Crystal L. Mackall](#), [Stephan A. Grupp](#), [David M. Barrett](#), ... [Kara L. Davis](#)  [+ Show authors](#)

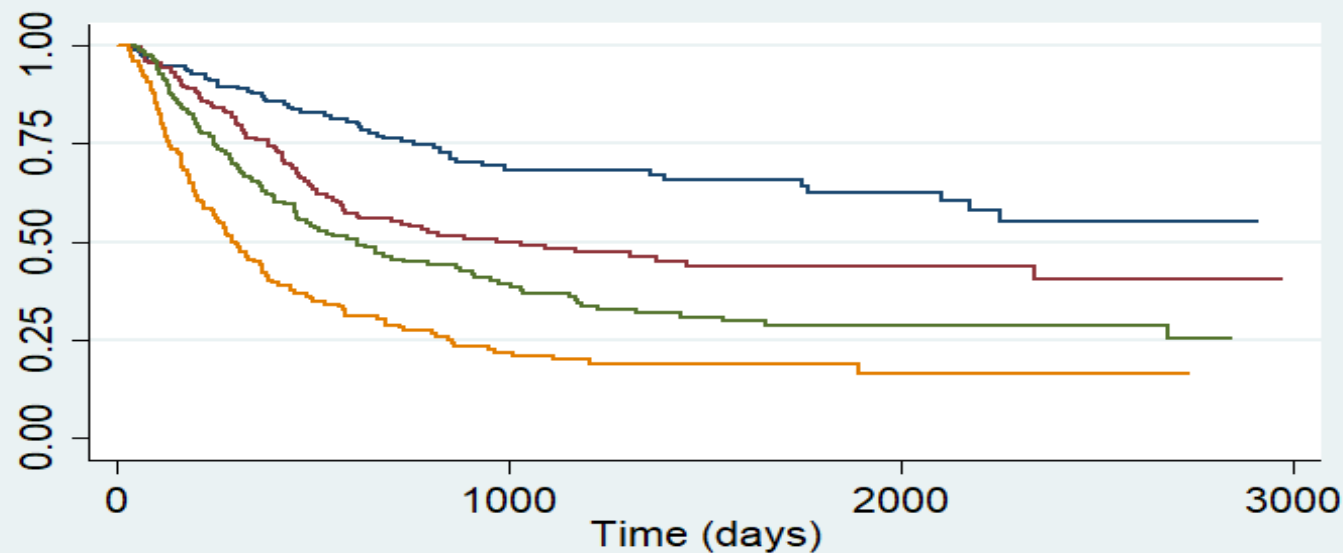
[Nature Communications](#) **16**, Article number: 3800 (2025) | [Cite this article](#)



Before immunotherapy, IKAROS<sup>low</sup> pro-B-like B-ALL cells possess chromatin and gene expression states poised for loss of B-cell identity while maintaining expression of CD19 and CD22. Under immune pressure, IKAROS<sup>high</sup> cells maintain their antigen expression, making them more susceptible to T cell-mediated killing. Conversely, IKAROS<sup>low</sup> cells are more likely to downregulate their antigen expression, giving them a relative advantage to escape immunotherapies, resulting in antigen escape relapse. Created in BioRender<sup>SL</sup>.

# Escore prognóstico LLA adultos – casos brasileiros e coorte pethema, incorporando idade e impacto aloTMO

Event-free survival



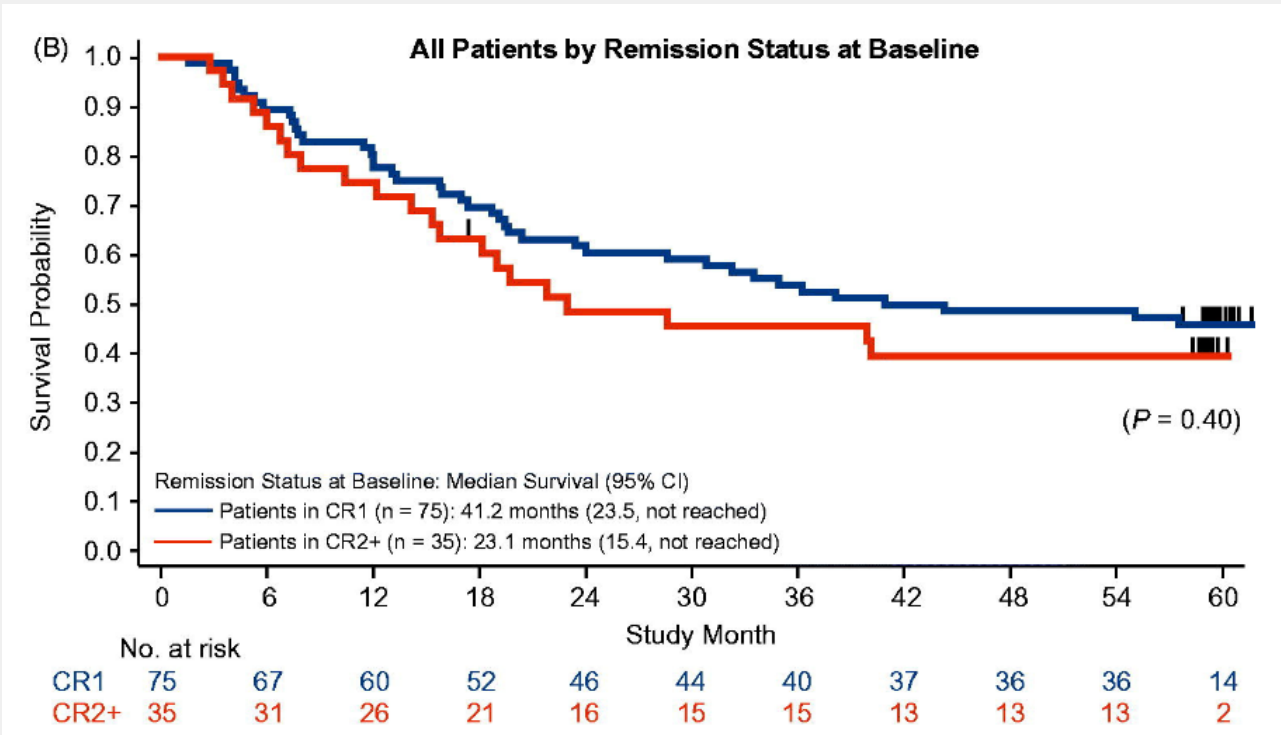
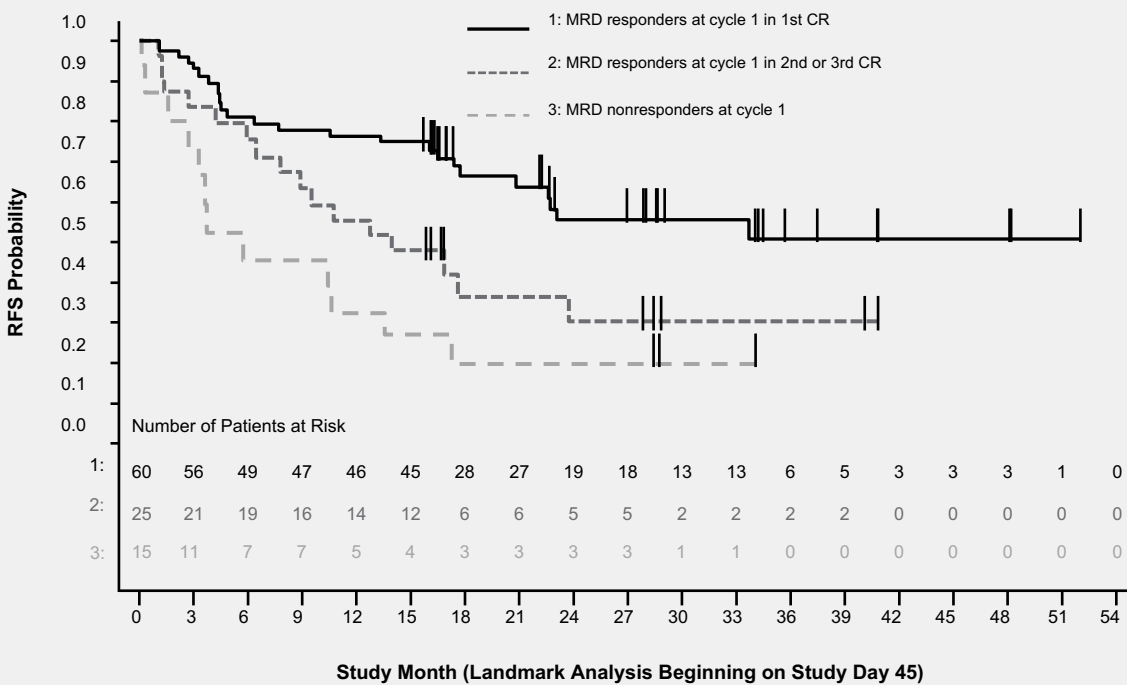
Number at risk				
	0	1000	2000	3000
risk_category = 1	166	71	31	7
risk_category = 2	173	61	19	2
risk_category = 3	170	49	17	7
risk_category = 4	168	26	5	0



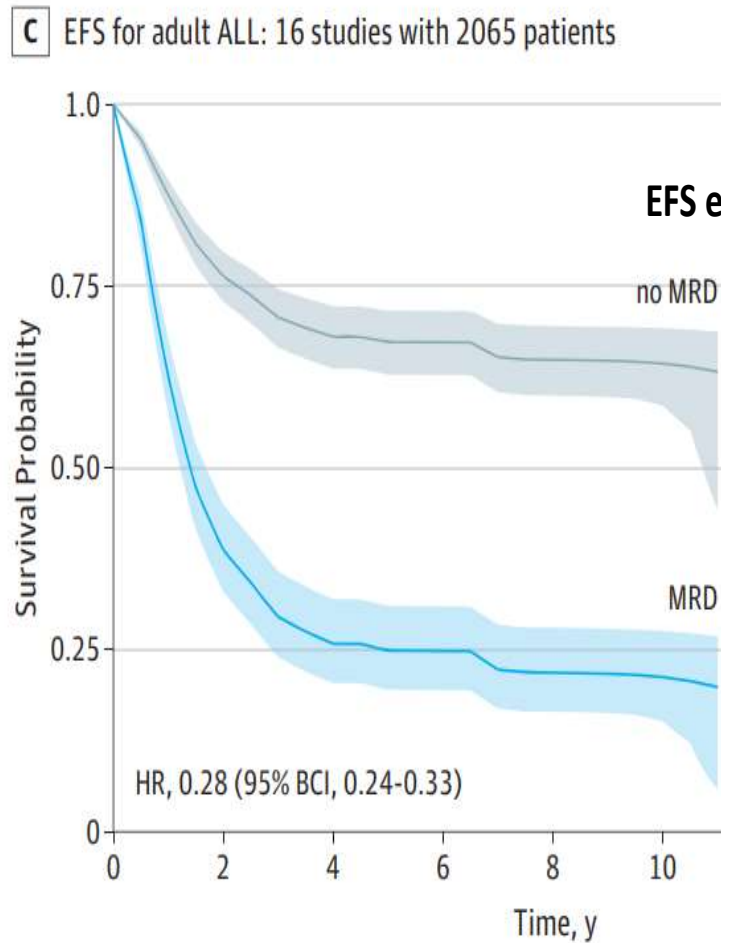
$$mPlall = \mathbb{T}(\text{MRD}) \times -0.218 + \text{CYTO-GR} \times -0.440 + \text{CYTO-SR} \times 0 + \text{CYTO-HR} \times 1.066 + \mathbb{T}(\text{WBC}) \times 0.138 + (\text{allo-HSCT}) \times -0.660 + \mathbb{T}[1.0143^{(\text{Age}-15)}].$$

**BLAST  
(MT103-203)  
Study**

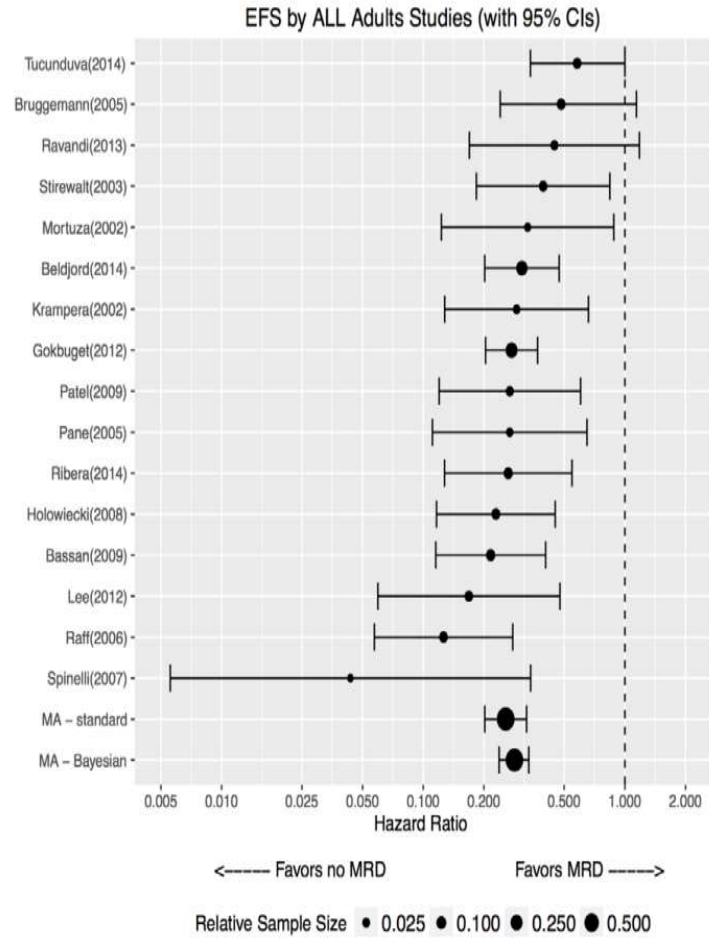
- **Complete MRD response\* (Primary endpoint, FAS): 78% (88/113)**



# MRD-positive adult ALL patients have EFS inferior to 25% at long-term.



**Figure 2.** Hazard ratios of EFS and their 95% confidence intervals for the individual studies used in our pediatric ALL meta-analysis



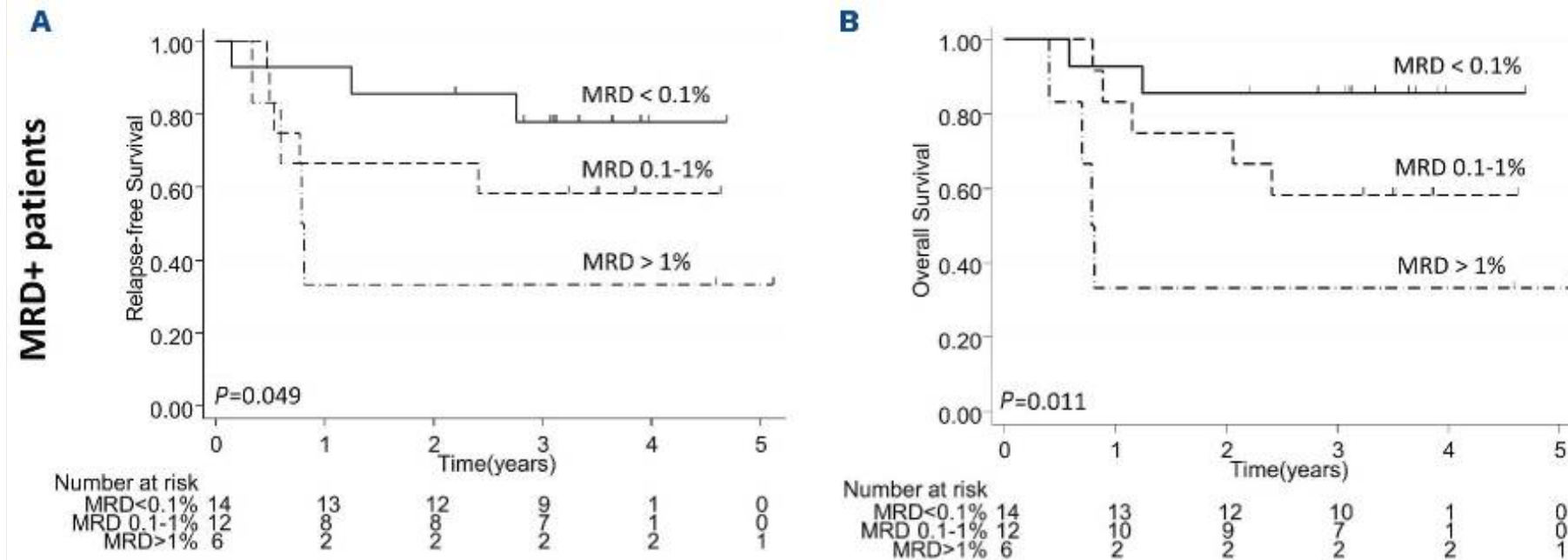
# Experiência GRAALL

OS at 3 years according to **PRE-BLINATUMOMAB MRD LEVELS**

**OS 33%, MRD >1%,**

**OS 58% MRD 0.1- 1%**

**OS 86% MRD <0.1%**



# Experiência GRAALL

	MRD+ cohort						Relapse cohort					
	RFS			OS			RFS			OS		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age*	0.99	(0.96-1.04)	0.99	1.00	(0.96-1.05)	0.97	0.98	(0.95-1.01)	0.17	0.98	(0.95-1.01)	0.24
White blood cell count*	1.00	(0.99-1.00)	0.40	1.00	(0.99-1.00)	0.28	NA	NA	NA	NA	NA	NA
High-risk cytogenetics**	3.09	(0.56-17.0)	0.19	6.83	(0.86-53.99)	0.07	1.08	(0.48-2.39)	0.86	1.70	(0.69-4.19)	0.25
Number of prior relapses*	NA	NA	NA	NA	NA	NA	1.85	(1.10-3.12)	0.02	5.23	(2.56-10.72)	<0.001
Prior allo-HSCT	NA	NA	NA	NA	NA	NA	0.84	(0.37-1.95)	0.69	0.55	(0.19-1.63)	0.28
MRD at blinatumomab***	3.00	(1.15-7.84)	0.03	5.41	(1.67-17.44)	0.005	NA	NA	NA	NA	NA	NA
CR at blin vs. overt relapse	NA	NA	NA	NA	NA	NA	0.13	(0.04-0.37)	<0.001	0.07	(0.02-0.25)	<0.001

Cabannes-Hamy A, Brissot E, Leguay T, Huguet F, Chevallier P, Hunault M, Escoffre-Barbe M, Cluzeau T, Balsat M, Nguyen S, Pasquier F, Alexis M, Lheritier V, Pastoret C, Delabesse E, Clappier E, Dombret H, Boissel N. High tumor burden before blinatumomab has a negative impact on the outcome of adult patients with B-cell precursor acute lymphoblastic leukemia. A real-world study by the GRAALL. *Haematologica*. 2022 Sep 1;107(9):2072-2080. doi: 10.3324/haematol.2021.280078. PMID: 35263986; PMCID: PMC9425331.

# Frontline Consolidation with Blinatumomab for High-Risk Philadelphia-Negative Acute Lymphoblastic Adult Patients. Early Results from the Graall-2014-QUEST Phase 2

N = 95 pts SNCneg

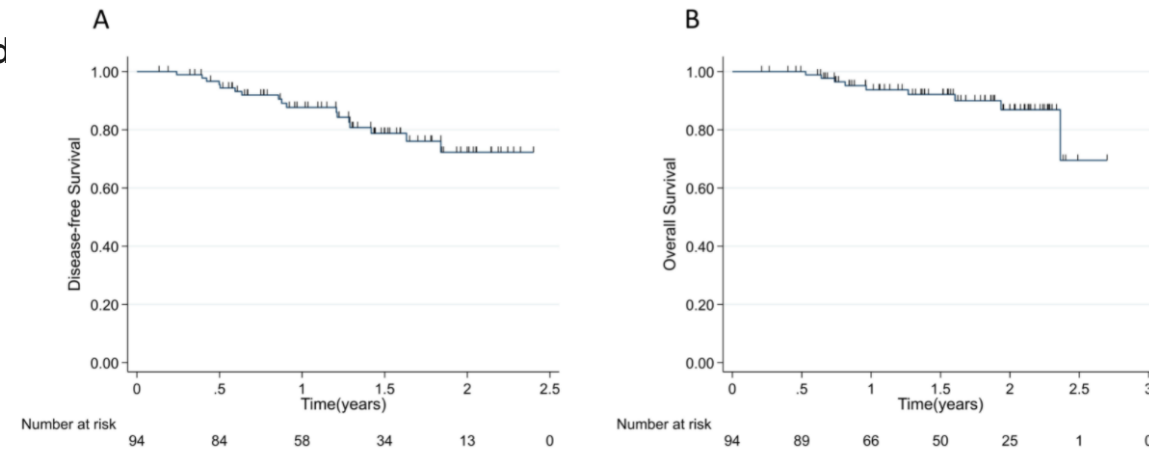
Mediana idade 35 (18-60)

Tratamento GRAALL-2014 (indução + consolidação 1 seguido de Blinatumomab)

Taxas de Resposta

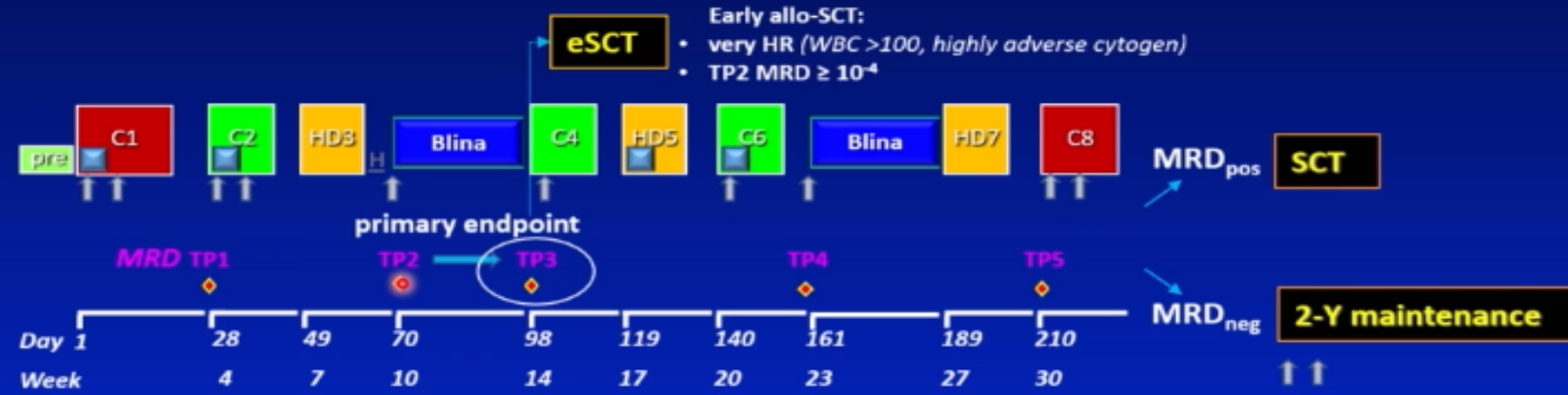
- DRM pos inducao < 0.01% em 51%.
- DRM pos consolidação < 0.01% em 56%
- **Blina 1 a 5 ciclos – Taxa DRM neg foi d**
- 42% seguiram para aloTMO
- Mediana FU – 20 meses

**Figure 1.** Disease-Free Survival (A) and Overall Survival (B) of high-risk Ph-negative ALL patients consolidated with blinatumomab.

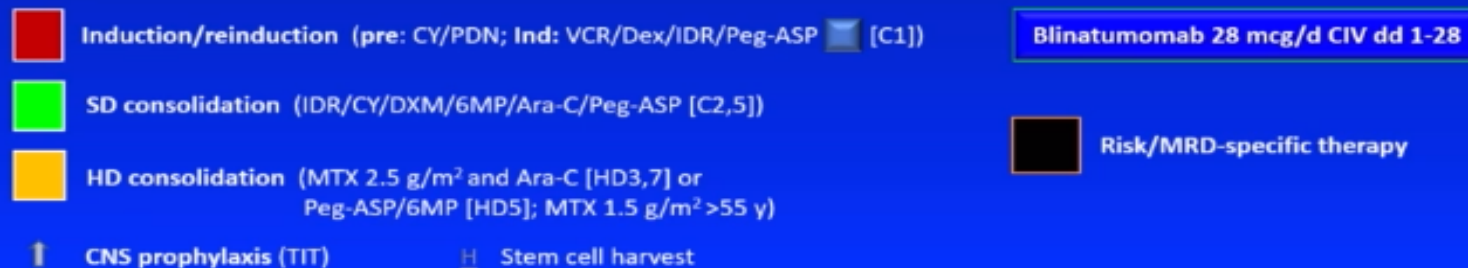


# Blinatumomab na consolidação em 1ª linha GIMEMA

## Study protocol



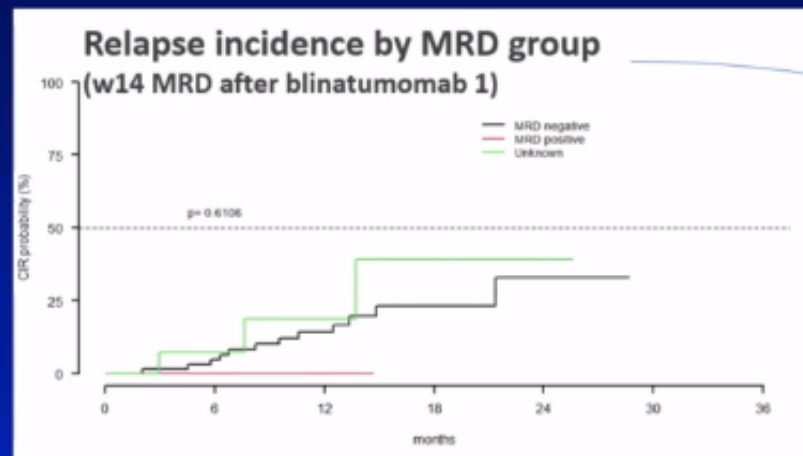
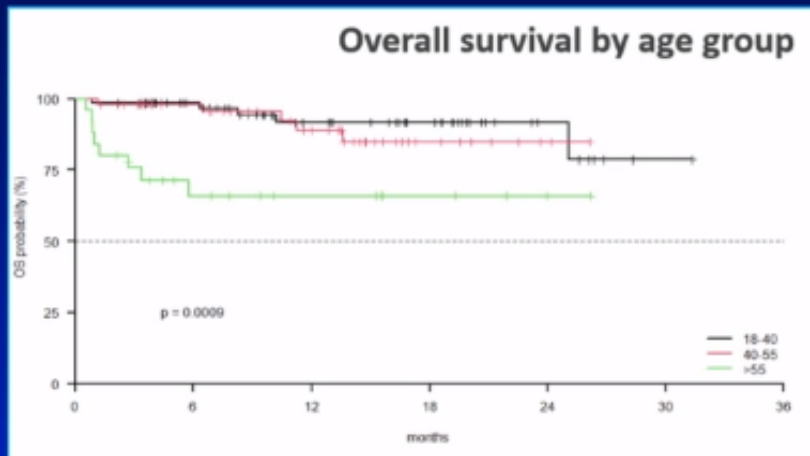
### Treatment elements/strategy



ClinicalTrials.gov ID NCT03367299

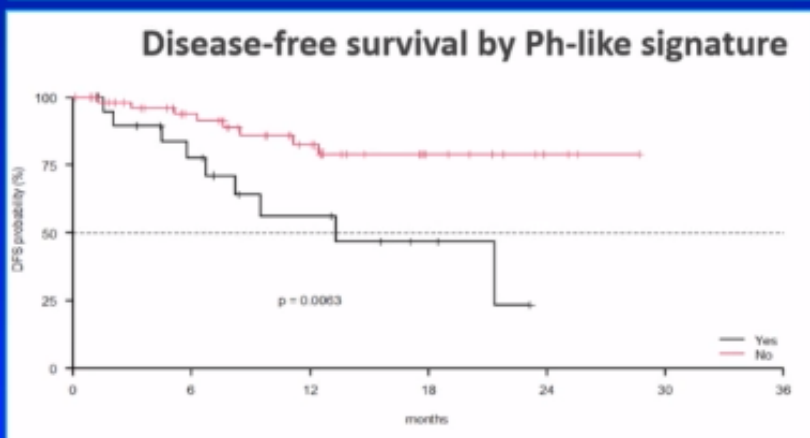
# Ph-like immunotherapy

## Outcomes (median f-up 13 mos. [0.55-31.3 mos.])



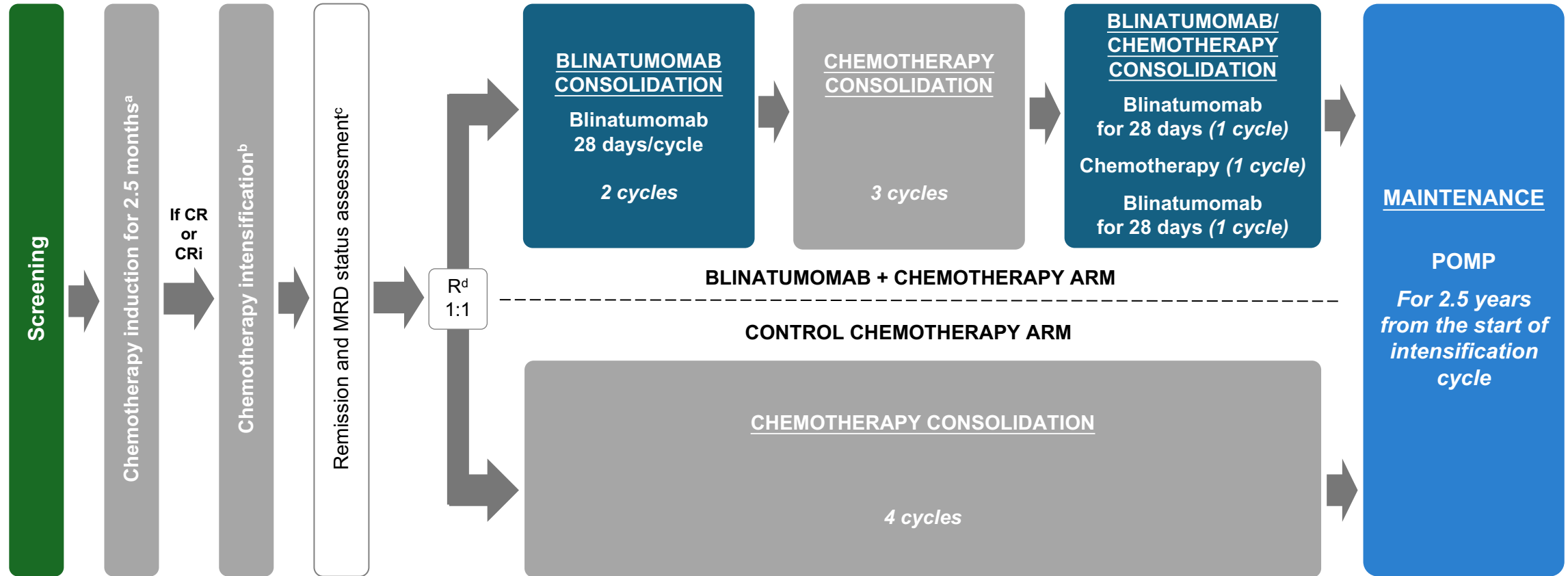
1-year relapse rate

MRD<sub>neg</sub> 14.2 %  
 MRD<sub>pos</sub> 0.0 %  
 MRD<sub>u/k</sub> 18.8 %  
**P=NS**



1-year relapse rate

Ph-like 40.1 %  
 No Ph-like 3.2 %  
**P=0.0005**



Patients proceeded to allogeneic HSCT at the discretion of the treating physician, which was suggested to be done after the first two cycles of blinatumomab in the blinatumomab + chemotherapy arm or at any time following intensification chemotherapy in the control chemotherapy arm. <sup>a</sup>Berlin-Frankfurt-Münster-like regimen adapted from the E2993/UKALLXII clinical study with extended remission induction, addition of PEG-ASP for patients < 55 years of age, and addition of rituximab for CD20+ patients. <sup>b</sup>High-dose MTX with PEG-ASP for CNS prophylaxis. <sup>c</sup>MRD negativity was defined as  $\leq 0.01\%$  by 6-color flow cytometry. <sup>d</sup>Following FDA approval of blinatumomab for MRD+ disease in March 2018, patients who were MRD+ after intensification were assigned to the blinatumomab + chemotherapy arm of the study and no longer randomized.

B-ALL, B-cell acute lymphoblastic leukemia; CD20, cluster of differentiation 20; CNS; central nervous system; CR, complete remission; CRh, complete remission with partial count recovery; CRi, complete remission with incomplete count recovery without CRh; FDA, Food and Drug Administration; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease; MTX, methotrexate; PEG-ASP, pegaspargase; POMP, 6-mercaptopurine, vincristine, methotrexate, and prednisone; R, randomization.

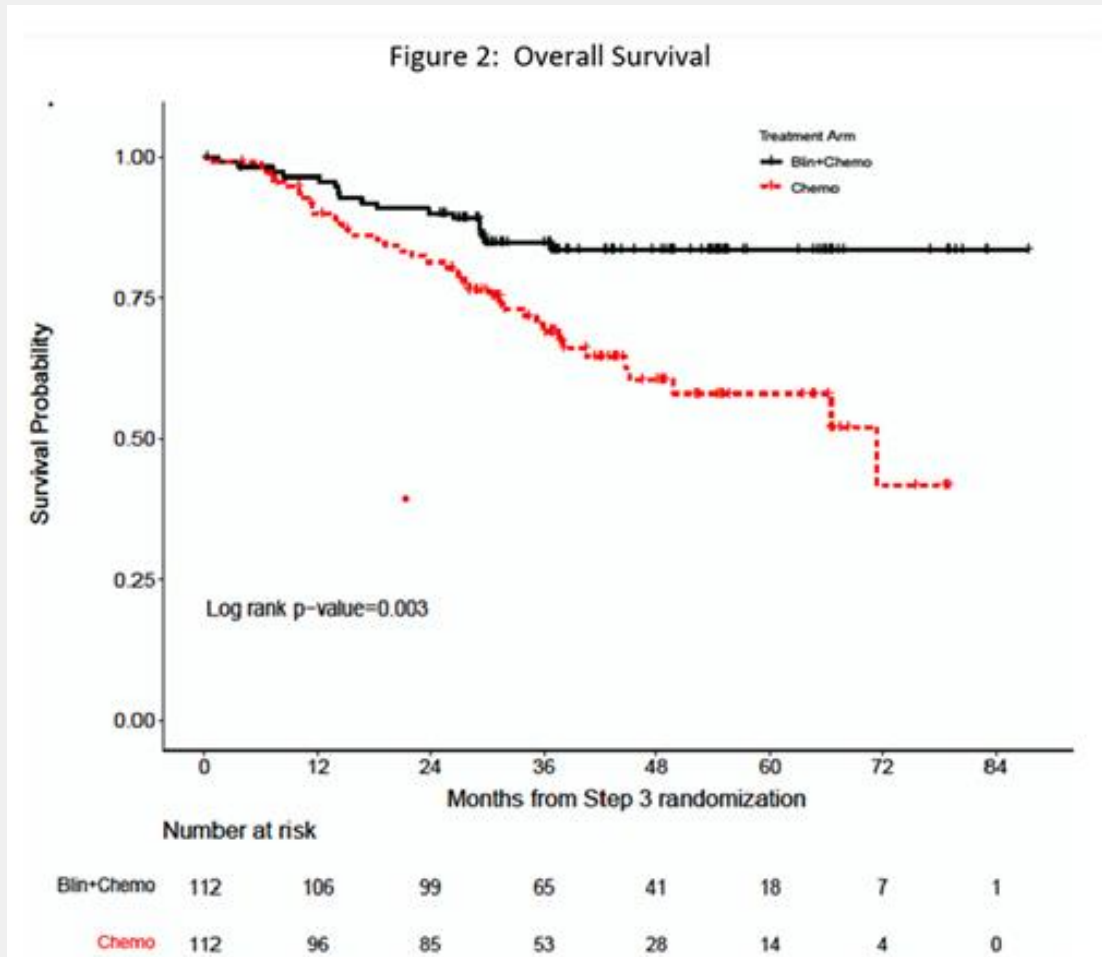
Litzow MR, et al. Presented at: 64th American Society of Hematology (ASH) Annual Meeting; December 10–13, 2022; New Orleans, LA, and virtual. Abstract LBA-1.

## CONSOLIDATION WITH BLINATUMOMAB IMPROVES OVERALL AND RELAPSE-FREE SURVIVAL IN PATIENTS WITH NEWLY DIAGNOSED B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA: IMPACT OF AGE AND MRD LEVEL IN ECOG-ACRIN E1910

Ryan Mattison

Author(s): [Mark Litzow](#), [Zhuoxin Sun](#), [Ryan Mattison](#), [Elisabeth Paietta](#), [Charles Mullighan](#), [Kathryn Roberts](#), [Yanming Zhang](#), [Janis Racevskis](#), [Cheryl Willman](#), [Matthew Wieduwilt](#), [Michaela Liedtke](#), [Julie Bergeron](#), [Hillard Lazarus](#), [Dan Arber](#), [Brent Wood](#), [Jacob Rowe](#), [Keith Pratz](#), [Shira Dinner](#), [Noelle Frey](#), [Steve Gore](#), [Bhavana Bhatnagar](#), [Ehab Atallah](#), [Geoff Uy](#), [Deepa Jeyakumar](#), [Tara Lin](#), [Shejal Patel](#), [Michelle Elliott](#), [Anjali Advani](#), [Daniel DeAngelo](#), [Dimitrios Tzachanis](#), [Pankit Vachhani](#), [Rupali Bhave](#), [Richard Little](#), [Harry Erba](#), [Richard Stone](#), [Selina Luger](#), [Martin Tallman](#)

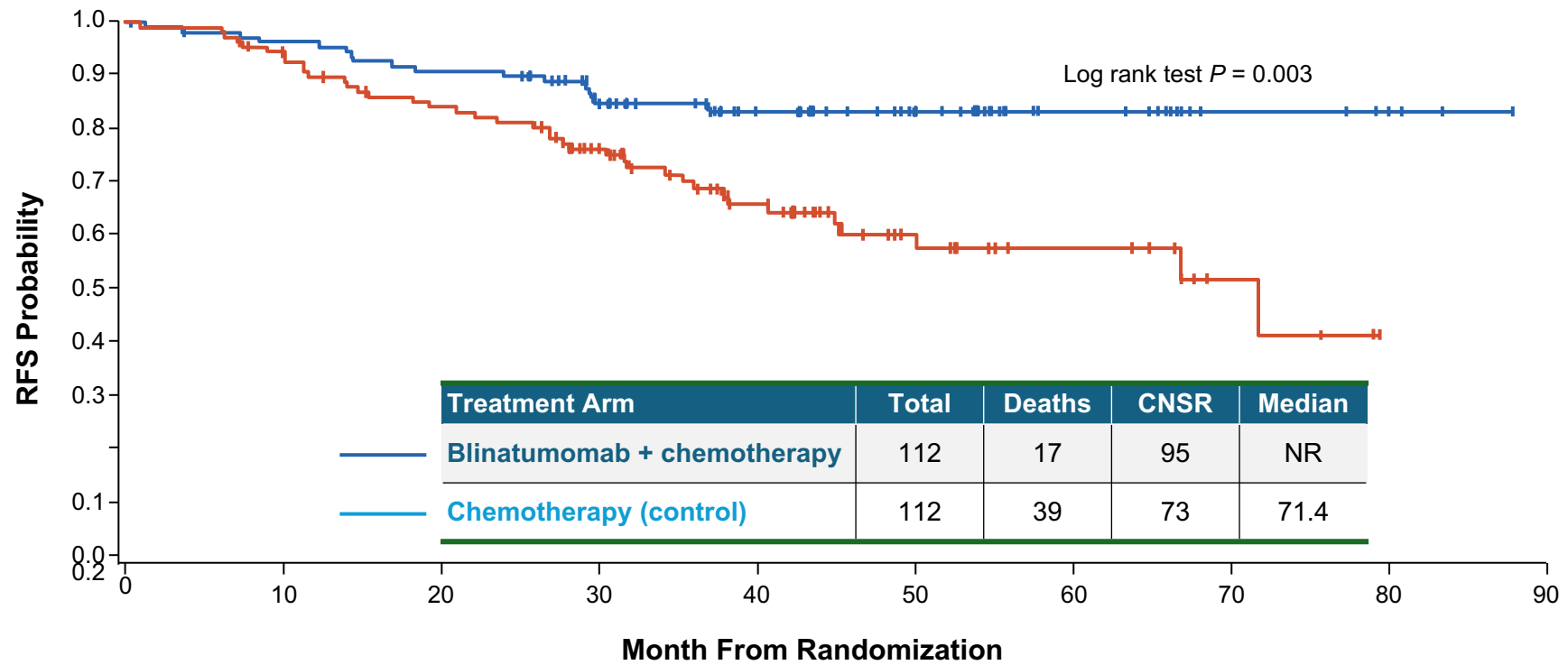
(Abstract release date: 05/11/23) EHA Library. Mattison R. 06/08/2023; 387815; S115



Median age 51  
N= 224

112 em cada braco (QT vs Blina)  
aloTMO 22 em cada braco

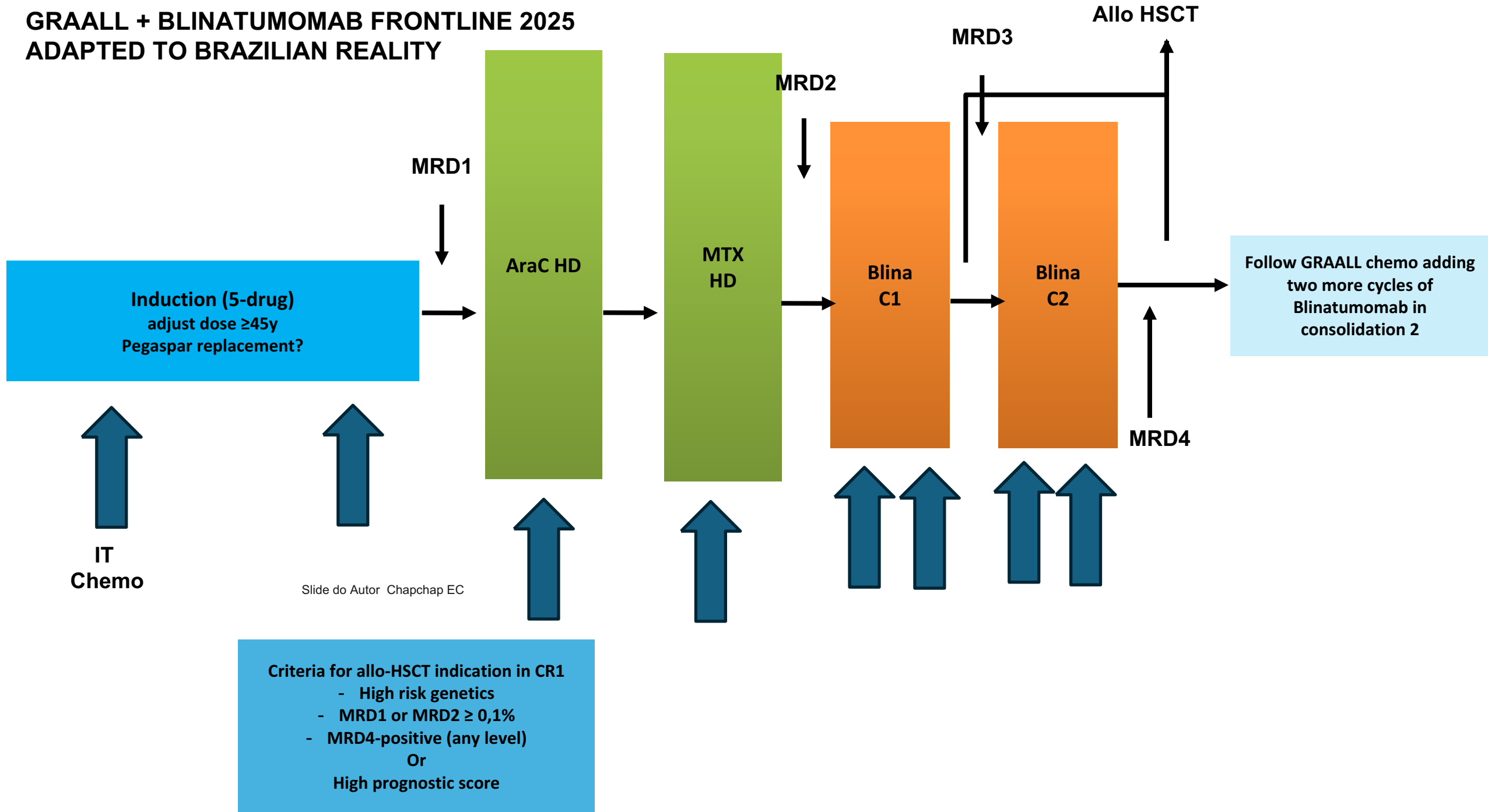
Median OS:  
not reached (Blina) vs. 71m (QT) (HR)  
0.42 p=0.003).



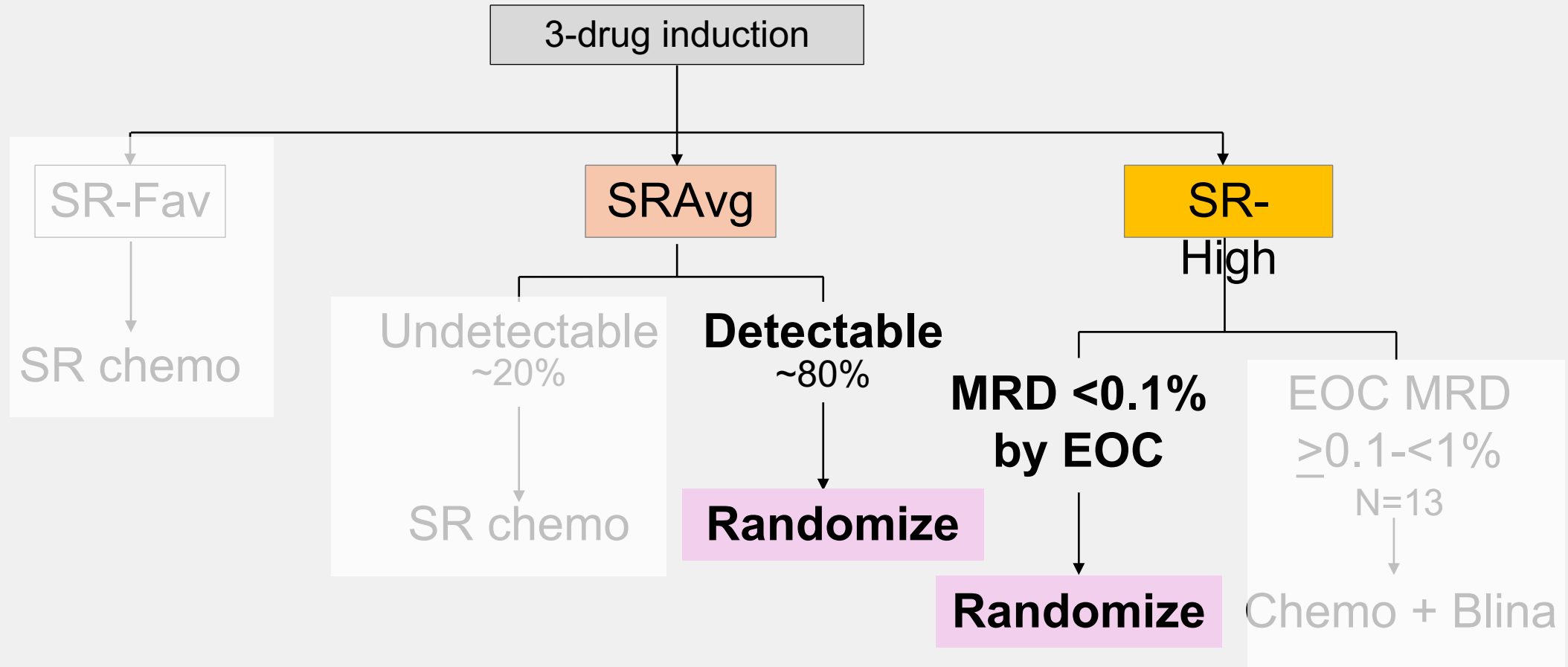
CI, confidence interval; CNSR, censored; HR, hazard ratio; MRD, minimal residual disease; NR, not reached; OS, overall survival.

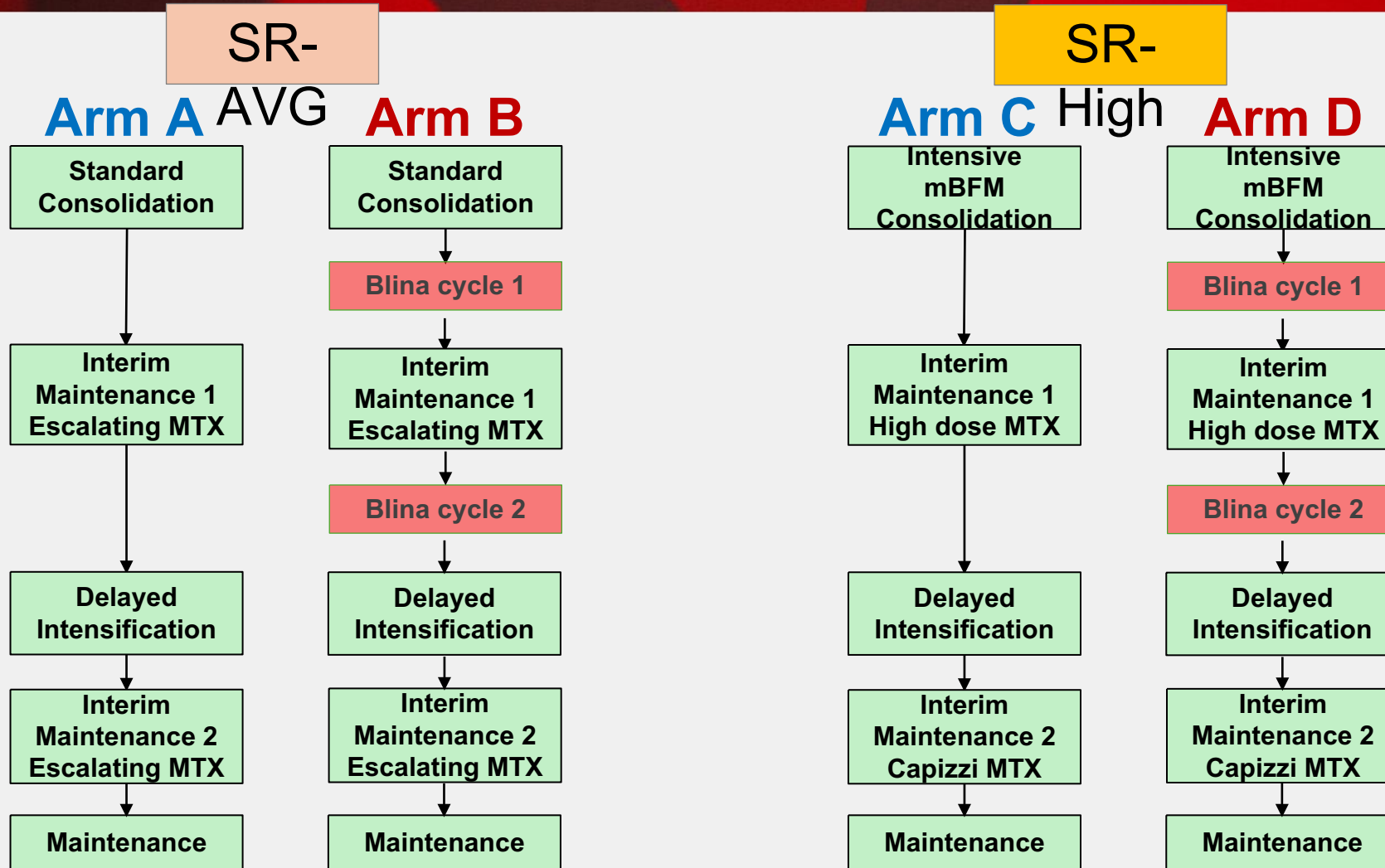
Mattison R, et al. Slides presented at: European Hematology Association (EHA) Meeting 2023; June 8-11, 2023; Frankfurt, Germany, and virtual. Abstract S115.

# GRAALL + BLINATUMOMAB FRONTLINE 2025 ADAPTED TO BRAZILIAN REALITY



# AALL1731 randomized study design

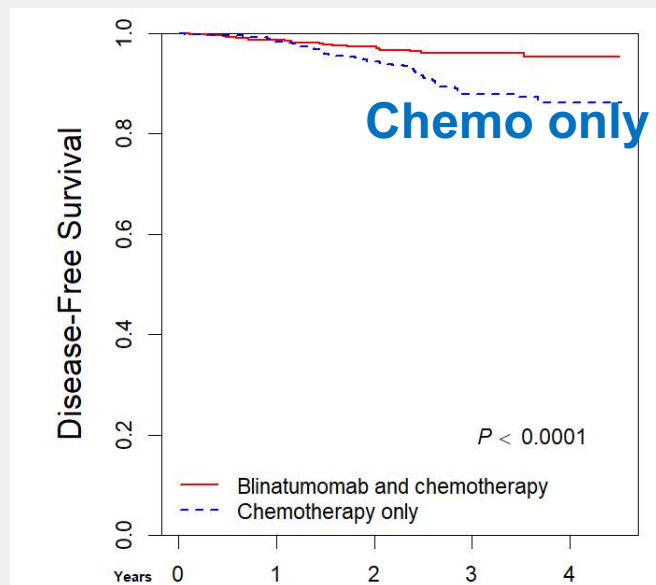




**Blinatumomab cycle**  
 15mcg/m<sup>2</sup>/day x 28 days via continuous IV infusion

## Overall cohort

**Blina + Chemo**

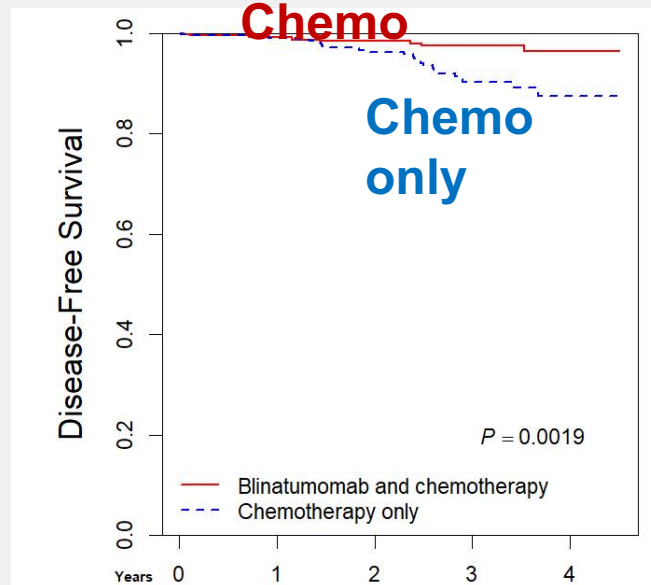


Years

3-yr DFS 87.9 vs 96%  
**Hazard ratio (HR) 0.39**

## SR-Avg

**Blina +  
Chemo**

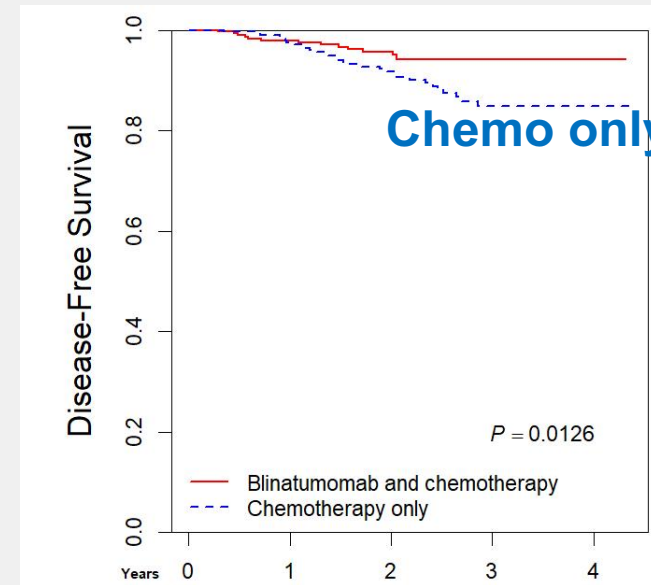


Years

3-yr DFS 90.2 vs 97.5%  
**HR 0.33**

## SR-High

**Blina + Chemo**



Years

3-yr DFS 84.8 vs 94.1%  
**HR 0.45**

- **REPLACEMENT OF HIGH DOSE COMBINATION CHEMOTHERAPY WITH BLINATUMOMAB IN NEWLY DIAGNOSED PEDIATRIC HIGH-RISK B-CELL ALL IMPROVES EFFICACY AND SAFETY IN THE RANDOMIZED PHASE 3 AIEOP-BFM ALL 2017 TRIAL**
- Martin Schrappe

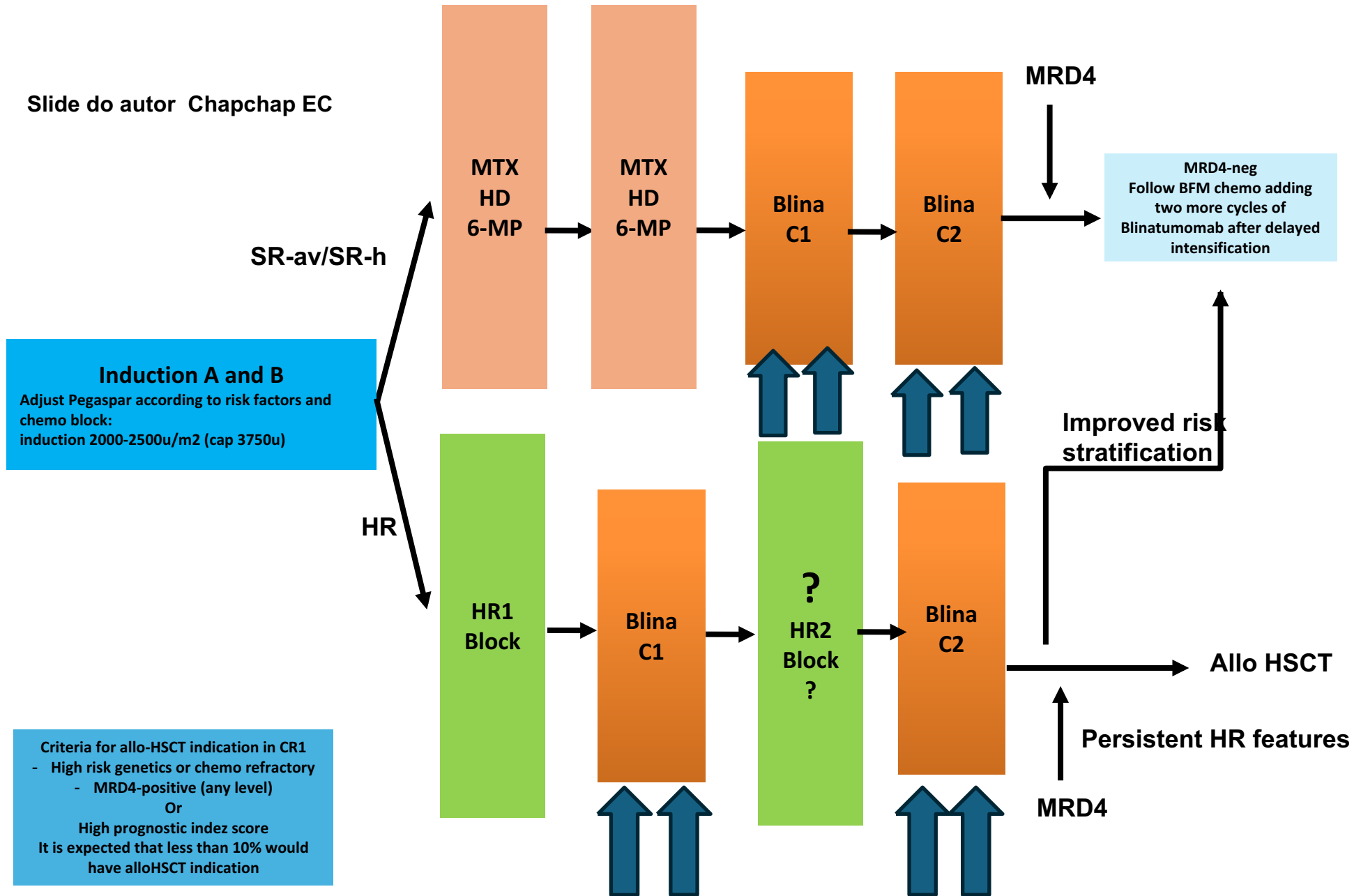
induction, consolidation, and one intensive chemotherapy course (HR-1`) => Blina x2 vs Chemo HR

768 eligible HR patients were randomized to receive either the EA (n=358) or the CA (n=351) arm.

**4y-EFS was 83.0% in the Blina arm**

**4-y EFS was 70.3% in the Chemo (HR blocks) arm**

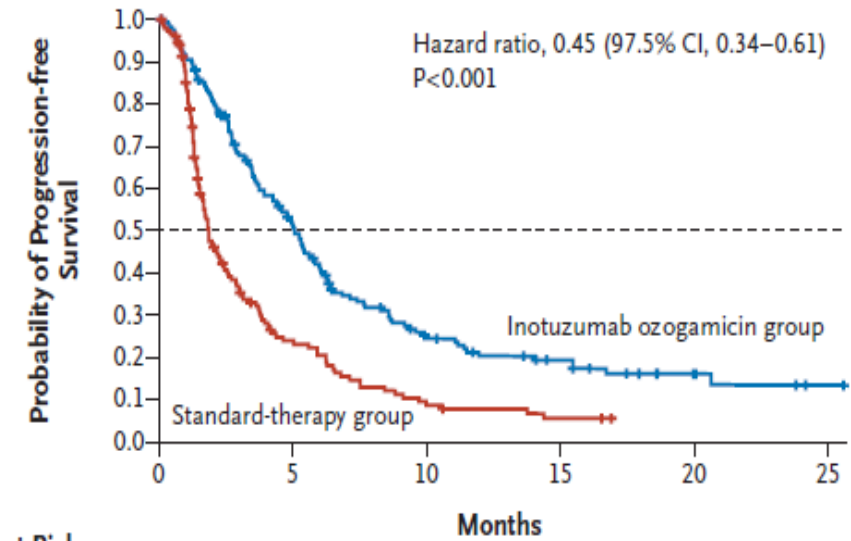
**BFM + BLINATUMOMAB FOR B-ALL Ph-neg 1-17y; note for patients aged 0-1y, follow interfant-06 protocol+Blinatumomab )**



# Inotuzumab ozogamicin CD22+ INOVATE TRIAL INDICACAO LLA-B R/R

Subgroup	No. of Patients		Complete Remission		Between-Group Difference (97.5% CI)	P Value
	Inotuzumab Ozogamicin Group	Standard- Therapy Group	Inotuzumab Ozogamicin Group	Standard- Therapy Group		
			% (95% CI)			
All patients	109	109	80.7 (72.1 to 87.7)	29.4 (21.0 to 38.8)	51.4 (38.4 to 64.3)	<0.001
Peripheral blasts					percentage points	
0	42	48	90.5 (77.4 to 97.3)	41.7 (27.6 to 56.8)	48.8 (29.9 to 67.7)	<0.001
>0 to 1000	32	35	71.9 (53.3 to 86.3)	20.0 (8.4 to 36.9)	51.9 (28.5 to 75.3)	<0.001
>1000	34	25	76.5 (58.8 to 89.3)	20.0 (6.8 to 40.7)	56.5 (32.2 to 80.7)	<0.001
Bone marrow blasts						
<50%	30	29	86.7 (69.3 to 96.2)	41.4 (23.5 to 61.1)	45.3 (20.5 to 70.1)	<0.001
≥50%	77	78	77.9 (67.0 to 86.6)	24.4 (15.3 to 35.4)	53.6 (38.4 to 68.8)	<0.001
CD22 expression						
<90%	24	24	79.2 (57.8 to 92.9)	25.0 (9.8 to 46.7)	54.2 (27.0 to 81.3)	<0.001
≥90%	74	63	82.4 (71.8 to 90.3)	36.5 (24.7 to 49.6)	45.9 (29.1 to 62.8)	<0.001
Karyotype						
Normal	20	20	95.0 (75.1 to 99.9)	30.0 (11.9 to 54.3)	65.0 (39.6 to 90.4)	<0.001
Ph-positive	14	18	78.6 (49.2 to 95.3)	44.4 (21.5 to 69.2)	34.1 (-1.8 to 70.1)	0.08
t(4;11)-positive	3	6	33.3 (0.8 to 90.6)	33.3 (4.3 to 77.7)	0.0 (-74.7 to 74.7)	1.00
Other abnormalities	49	46	85.7 (72.8 to 94.1)	26.1 (14.3 to 41.1)	59.6 (41.3 to 78.0)	<0.001
Previous stem-cell transplantation						
Yes	17	22	76.5 (50.1 to 93.2)	27.3 (10.7 to 50.2)	49.2 (17.8 to 80.6)	0.004
No	92	87	81.5 (72.1 to 88.9)	29.9 (20.5 to 40.6)	51.6 (37.4 to 65.9)	<0.001

**B Progression-free Survival**



# OUTCOMES IN PATIENTS WITH B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA RECEIVING INOTUZUMAB OZOGAMICIN STRATIFIED BY CUMULATIVE DOSE

Wendy Stock, [Elias Jabbour](#), [Anjali Advani](#), [Nicola Gökbüget](#), [Josep Maria Ribera](#), [Wendy Stock](#), [Ryan Cassaday](#), [Daniel J. DeAngelo](#), [Stephanie Dorman](#), [Sherry Williams](#), [Fan Zhang](#), [Erik Vandendries](#), [Hagop Kantarjian](#)

## Outcome by InO Dose in R/R ALL: Demographics

- Baseline characteristics were generally similar between groups.

Total cumulative dose	Patients who Achieved CR/CRi After Cycle 1, n (%)	
	≤3.3 mg/m <sup>2</sup>	>3.3 mg/m <sup>2</sup>
<b>N</b>	62	109
<b>Mean (SD)</b>	2.5 (0.6)	5.7 (1.9)
<b>Number of cycles</b>		
1	15 (24)	0
2	40 (65)	15 (14)
3	7 (11)	37 (34)
≥ 4	0	57 (52)
<b>Salvage status</b>		
Salvage 1	32 (52)	67 (62)
Salvage ≥2	29 (47)	42 (39)
<b>Prior HSCT</b>	13 (21)	25 (23)
<b>Proceeded to HSCT</b>	46 (74)	50 (46)
<b>Proceeded to 2<sup>nd</sup> HSCT</b>	8 (13)	5 (5)
<b>Received ursodiol as SOS prophylaxis</b>	28 (45)	54 (50)

# OUTCOMES IN PATIENTS WITH B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA RECEIVING INOTUZUMAB OZOGAMICIN STRATIFIED BY CUMULATIVE DOSE

Wendy Stock, [Elias Jabbour](#), [Anjali Advani](#), [Nicola Gökbuget](#), [Josep Maria Ribera](#), [Wendy Stock](#), [Ryan Cassaday](#), [Daniel J. DeAngelo](#), [Stephanie Dorman](#), [Sherry Williams](#), [Fan Zhang](#), [Erik Vandendries](#), [Hagop Kantarjian](#)

338 adults with R/R B-ALL in 2 cumulative INO dose groups:

$\leq 3.3$  mg/m<sup>2</sup> (n=161, median dose 2.09) vs  $> 3.3$  mg/m<sup>2</sup> (n=177, median dose 4.98).

(CR/CRi) rates were 50.9% ( $\leq 3.3$  mg/m<sup>2</sup>) and 90.4% ( $> 3.3$  mg/m<sup>2</sup>)

HSCT 68 (42.2% lower cumulative INO) pts and 75 (42.4% higher cumulative INO)

# OUTCOMES IN PATIENTS WITH B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA RECEIVING INOTUZUMAB OZOGAMICIN STRATIFIED BY CUMULATIVE DOSE

Wendy Stock, [Elias Jabbour](#), [Anjali Advani](#), [Nicola Gökbüget](#), [Josep Maria Ribera](#), [Wendy Stock](#), [Ryan Cassaday](#), [Daniel J. DeAngelo](#), [Stephanie Dorman](#), [Sherry Williams](#), [Fan Zhang](#), [Erik Vandendries](#), [Hagop Kantarjian](#)

## Outcome by InO Dose in R/R ALL: HSCT

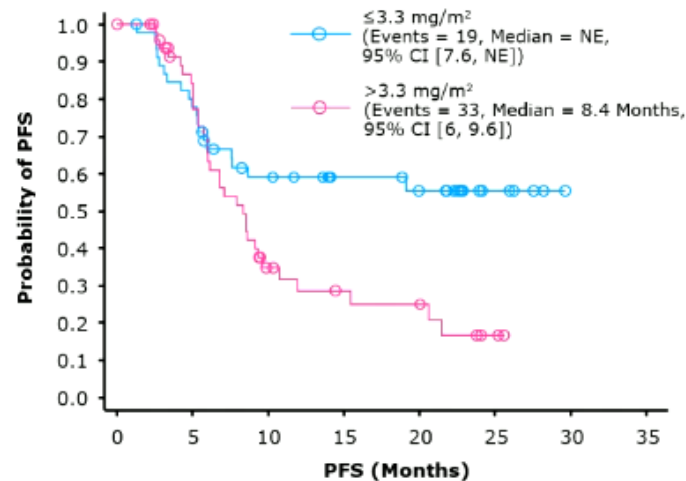
Cycle 1 Responders	≤3.3 mg/m <sup>2</sup> (n = 62)	>3.3 mg/m <sup>2</sup> (n = 109)
Proceeded to HSCT, n (%)	46 (74)	50 (46)
Post-HSCT mortality, n (%)	18 (39)	31 (62)
Post-HSCT NRM, n (%)	13 (28)	22 (44)
Any grade post-HSCT SOS, n (%)	11 (24)	12 (24)
Grade 3–4 post-HSCT SOS, n (%)	7 (15)	9 (18)

# OUTCOMES IN PATIENTS WITH B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA RECEIVING INOTUZUMAB OZOGAMICIN STRATIFIED BY CUMULATIVE DOSE

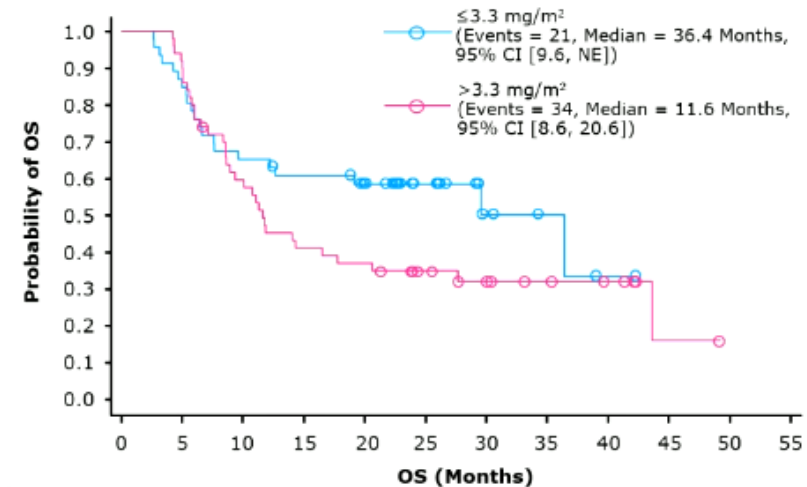
Wendy Stock, [Elias Jabbour](#), [Anjali Advani](#), [Nicola Gökbüget](#), [Josep Maria Ribera](#), [Wendy Stock](#), [Ryan Cassaday](#), [Daniel J. DeAngelo](#), [Stephanie Dorman](#), [Sherry Williams](#), [Fan Zhang](#), [Erik Vandendries](#), [Hagop Kantarjian](#)

## Outcome by InO Dose in R/R ALL: Outcomes in Patients Who Proceeded to HSCT

- Kaplan–Meier plot of PFS (left) and OS (right) by total cumulative dose in responders after cycle 1 in patients who **proceeded** to HSCT.



Number at risk, n	0	5	10	15	20	25	30
$\leq 3.3 \text{ mg/m}^2$	46	35	23	17	14	5	0
$> 3.3 \text{ mg/m}^2$	50	36	12	8	7	2	0
Total	96	71	35	25	21	7	0



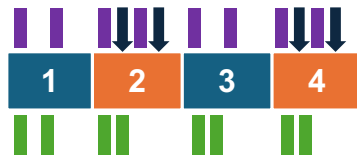
Number at risk, n	0	5	10	15	20	25	30	35	40	45	50	55
$\leq 3.3 \text{ mg/m}^2$	46	30	23	5	1	0						
$> 3.3 \text{ mg/m}^2$	50	29	18	10	5	0						
Total	96	59	41	15	6	0						

# 1ª LINHA INO

## PROTOCOLO HCVAD BLINA + INO

MD ANDERSON

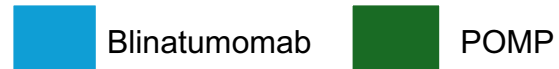
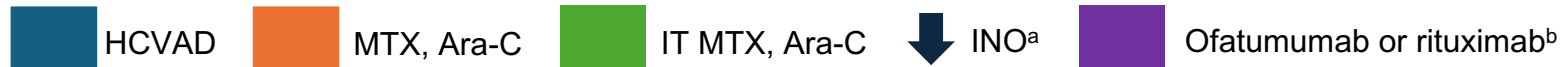
### Intensive Phase



### Consolidation Phase



### Maintenance Phase (blinatumomab + POMP)

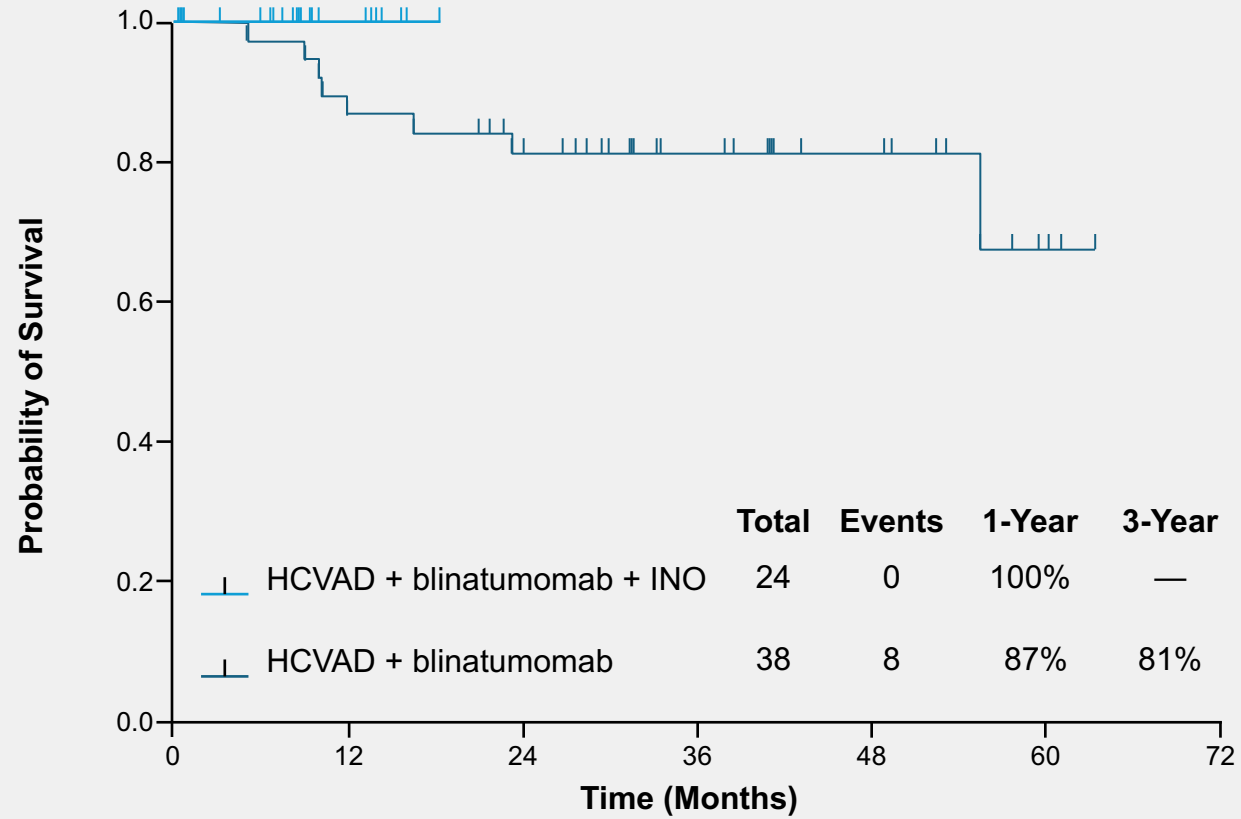


<sup>a</sup>INO was administered beginning with patient number 39, after a protocol amendment; INO dosing was 0.3 mg/m<sup>2</sup>/day on days 1 and 8. <sup>b</sup>Only in patients with CD20-positive disease.

Ara-C, cytosine arabinoside; HCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; INO, inotuzumab ozogamicin; IT, intrathecal; MTX, methotrexate; POMP, 6-mercaptopurine, vincristine, methotrexate, and prednisone.

Short NJ, et al. Poster presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3–7, 2022; Chicago, IL.

# HCVAD + BLINA + INO



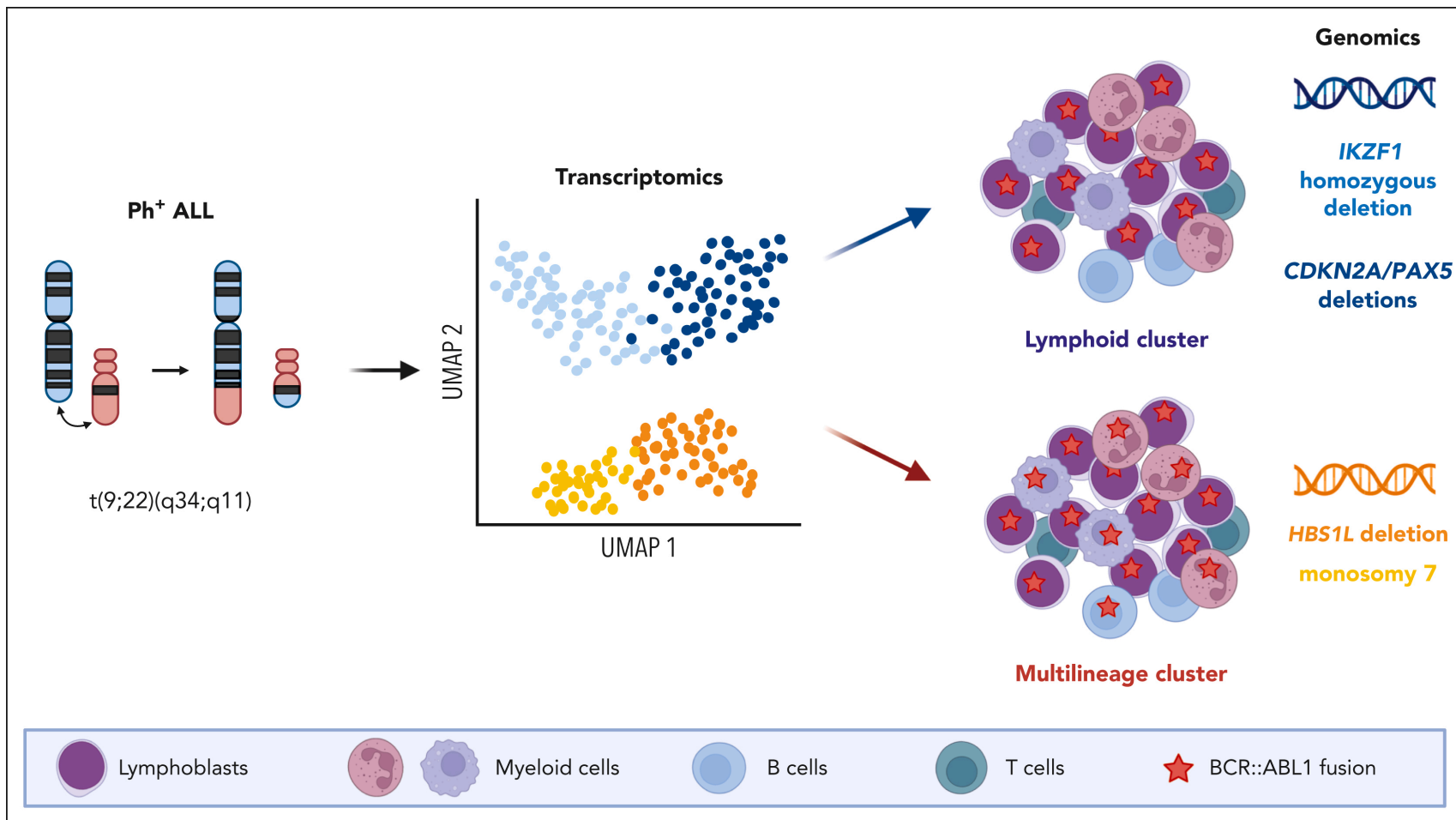
Data cutoff: June 2022; median follow-up: 23 (range, 1–63) months.

HCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; INO, inotuzumab ozogamicin; OS, overall survival.

Short NJ, et al. Presented at: 64th American Society of Hematology (ASH) Annual Meeting; December 10–13, 2022; New Orleans, LA, and virtual. Abstract 4043.

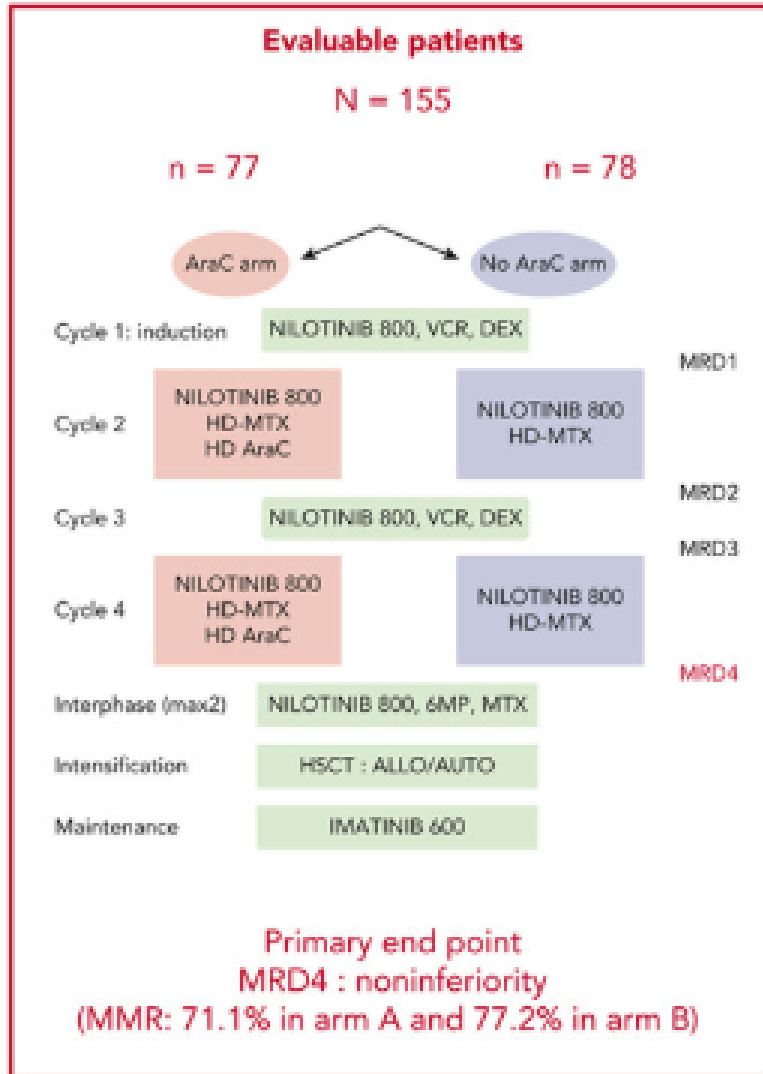
LLA Ph+

# Uncovering new layers of Ph<sup>+</sup> ALL biology

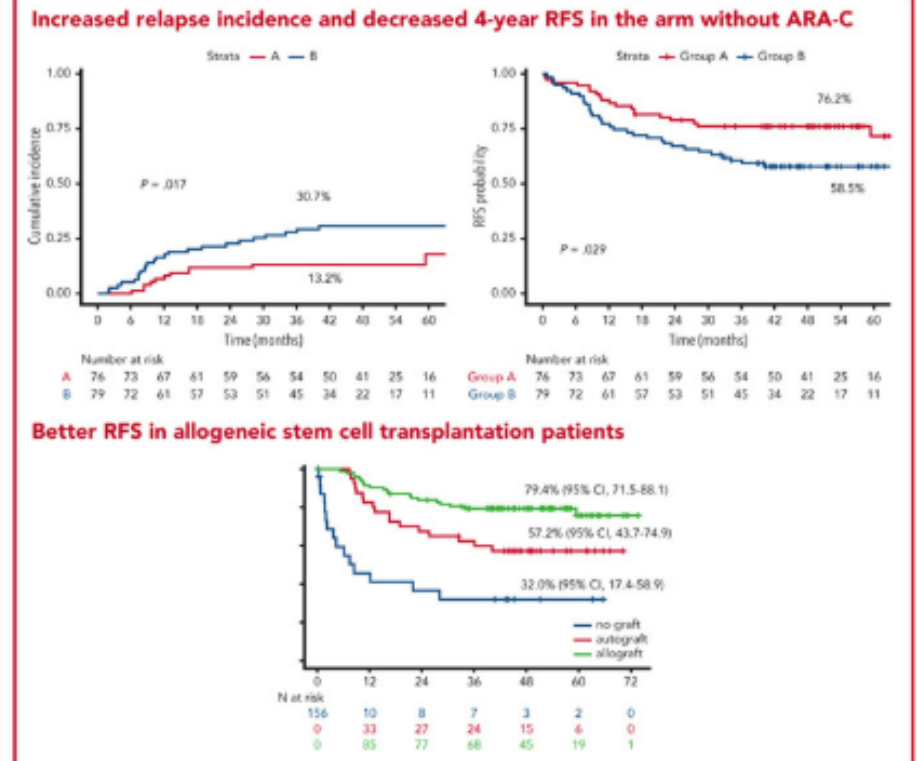
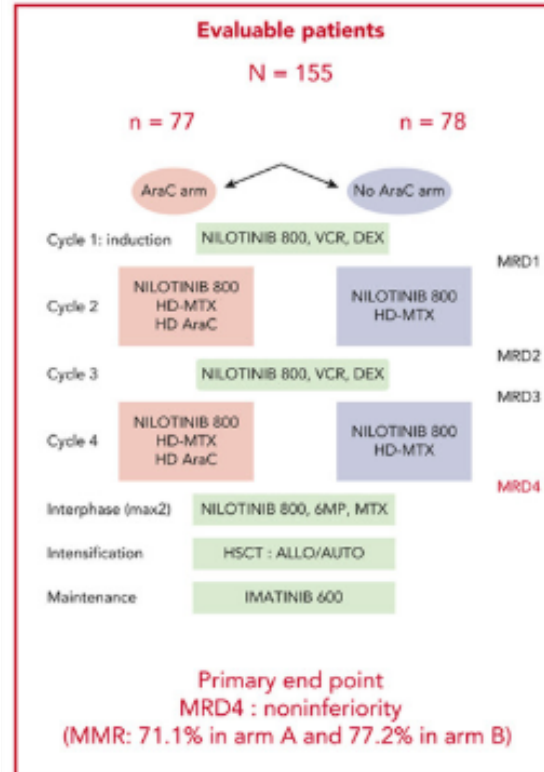


Rathana Kim, Emmanuelle Clappier, Uncovering new layers of Ph<sup>+</sup> ALL biology, Blood, 2024,

# LLA Ph-positiva



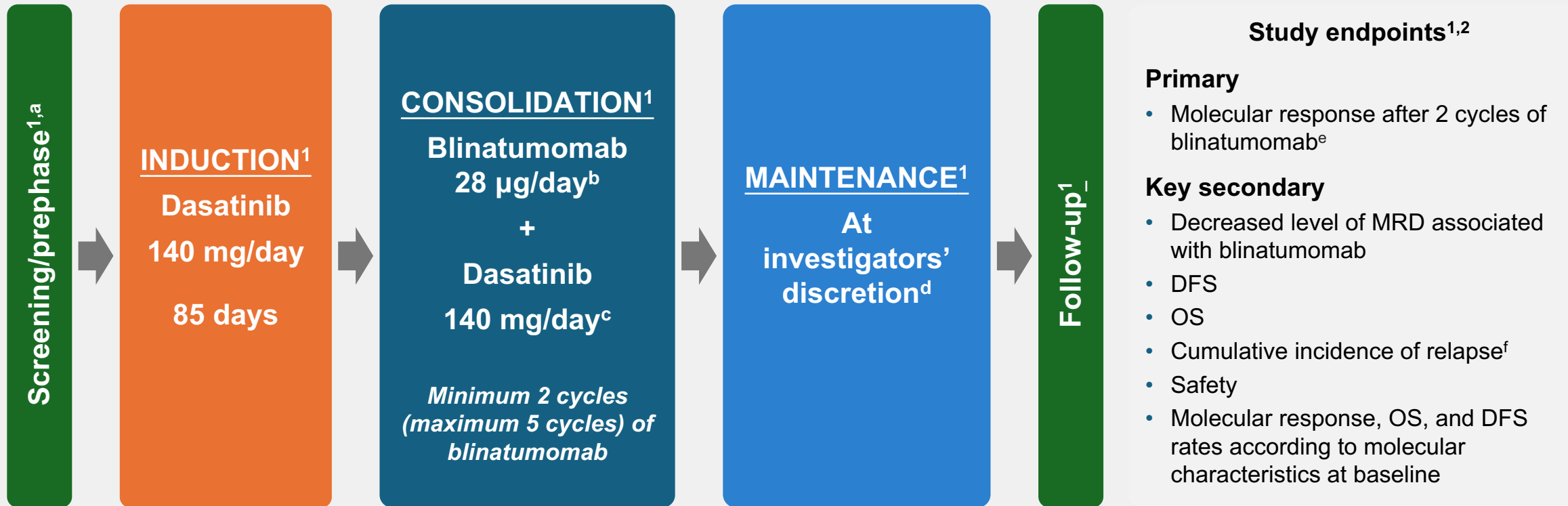
# Nilotinib with or without Cytarabine for Philadelphia Positive Acute Lymphoblastic Leukemia

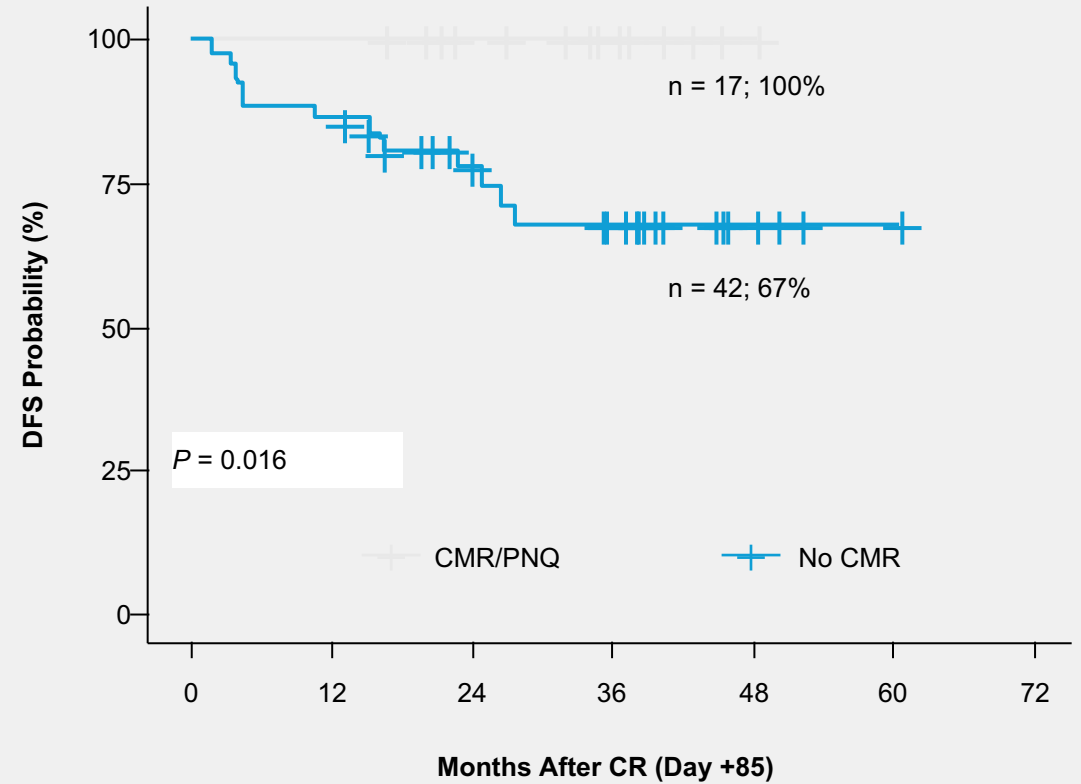
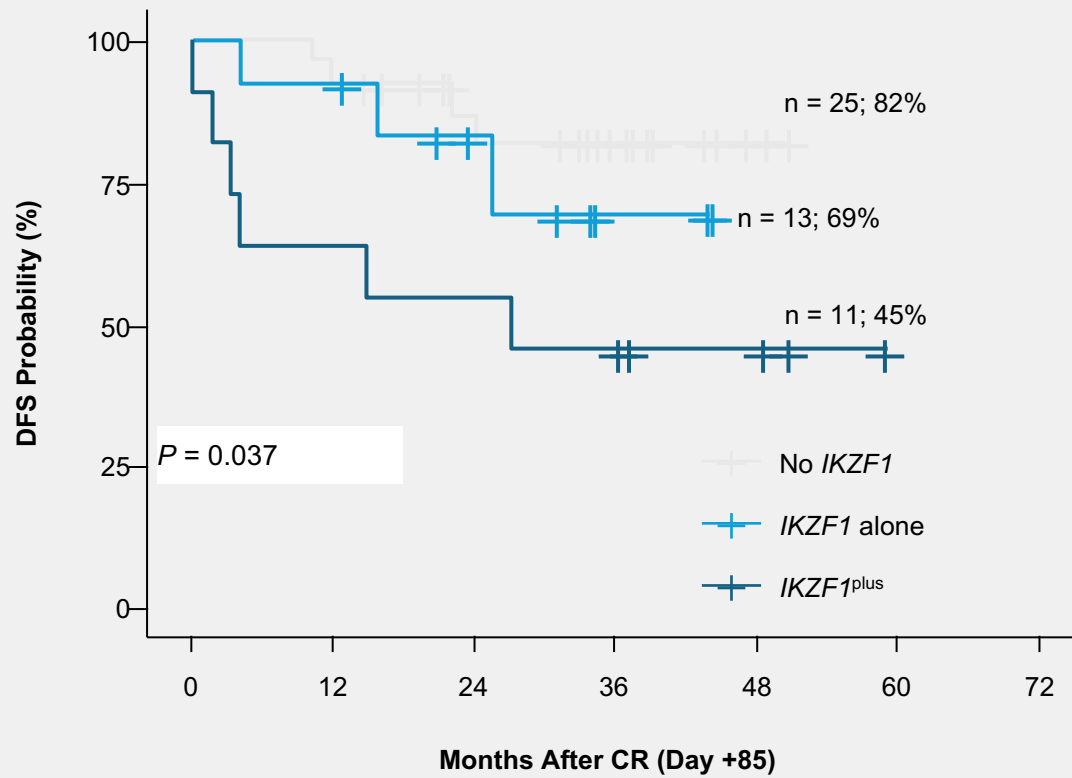


**Conclusions:** 1) Despite a noninferior rate of major molecular response, more relapses were observed when ARA-C was omitted without impact on survival; 2) 4-year OS was 79.0% in standard arm A vs 73.4% in arm B without ARA-C.

Chalandon et al. DOI: 10.1182/*blood*.2023023502

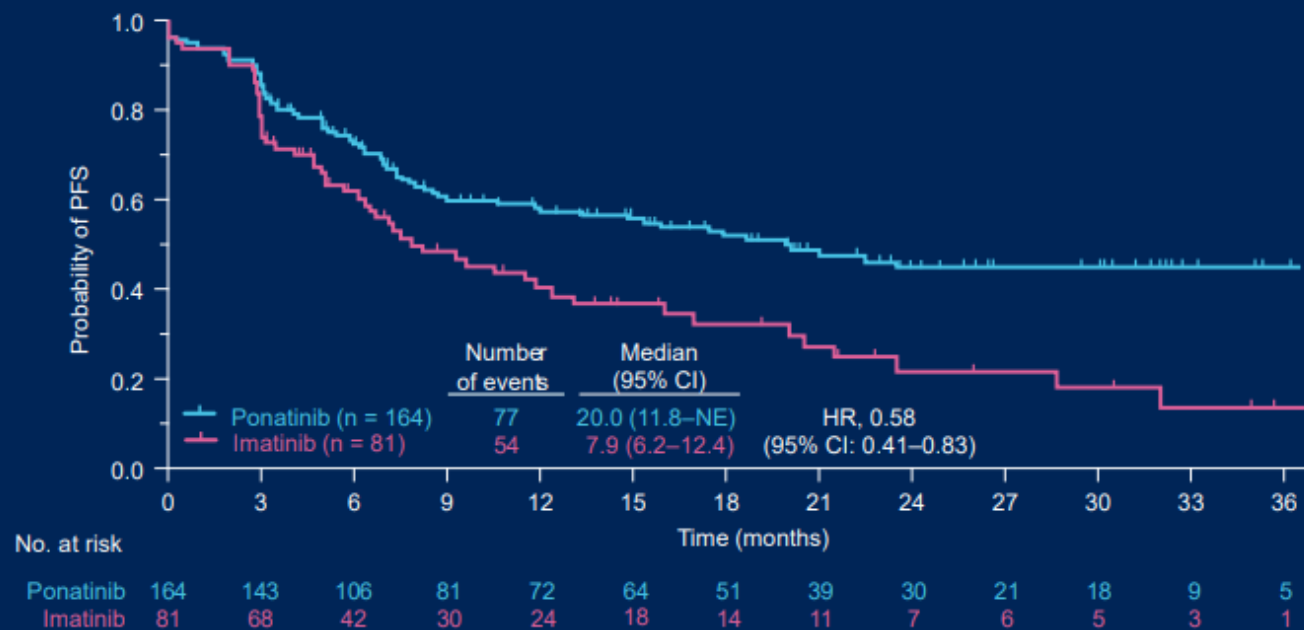






# PhALLCON: Progression-free survival

- PFS event definition: death due to any cause, failure to achieve CR by the end of induction, relapse from CR, failure to achieve MRD-negativity by the end of treatment, or loss of MRD-negativity<sup>a</sup>



<sup>a</sup> Post-hoc analysis

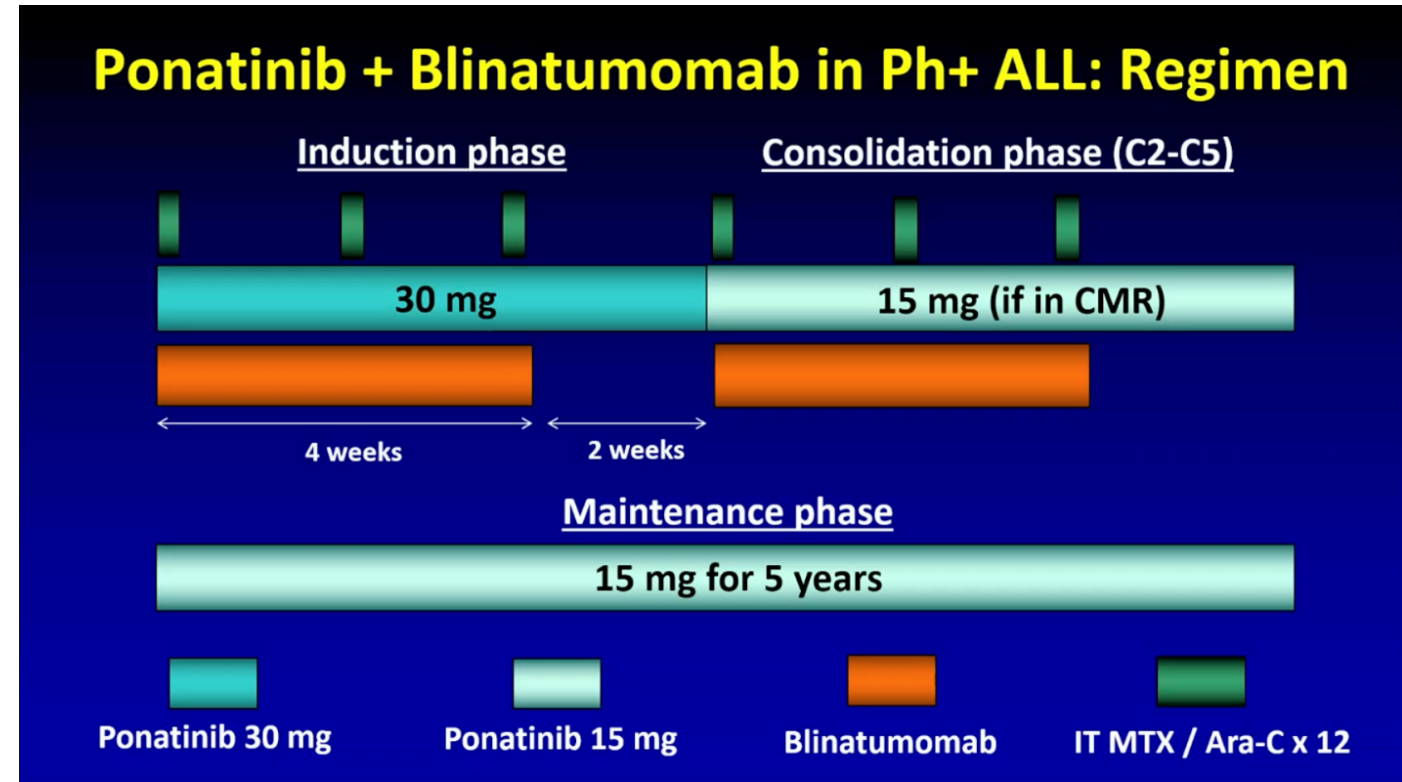
# Frontline Blinatumomab + Ponatinib Ph+ LLA-B

A CHEMOTHERAPY-FREE  
COMBINATION OF PONATINIB  
AND BLINATUMOMAB FOR  
PATIENTS WITH NEWLY  
DIAGNOSED PHILADELPHIA  
CHROMOSOME-POSITIVE  
ACUTE LYMPHOBLASTIC  
LEUKEMIA: SUBGROUP  
ANALYSIS FROM A PHASE II  
STUDY

Dr. Nicholas Short

Author(s): [Nicholas Short](#), [Elias Jabbour](#), [Nitin Jain](#),  
[Xuelin Huang](#), [Walid Macaron](#), [Lewis Nasr](#),  
[Guillermo Montalban-Bravo](#), [Tapan Kadia](#),  
[Naval Daver](#), [Kelly Chien](#), [Yesid Alvarado](#),  
[Ghayas Issa](#), [Fadi Haddad](#), [Cedric Nasnas](#),  
[Marianne Zoghbi](#), [Rebecca Garris](#),  
[Marina Konopleva](#), [Farhad Ravandi](#),  
[Hagop Kantarjian](#)

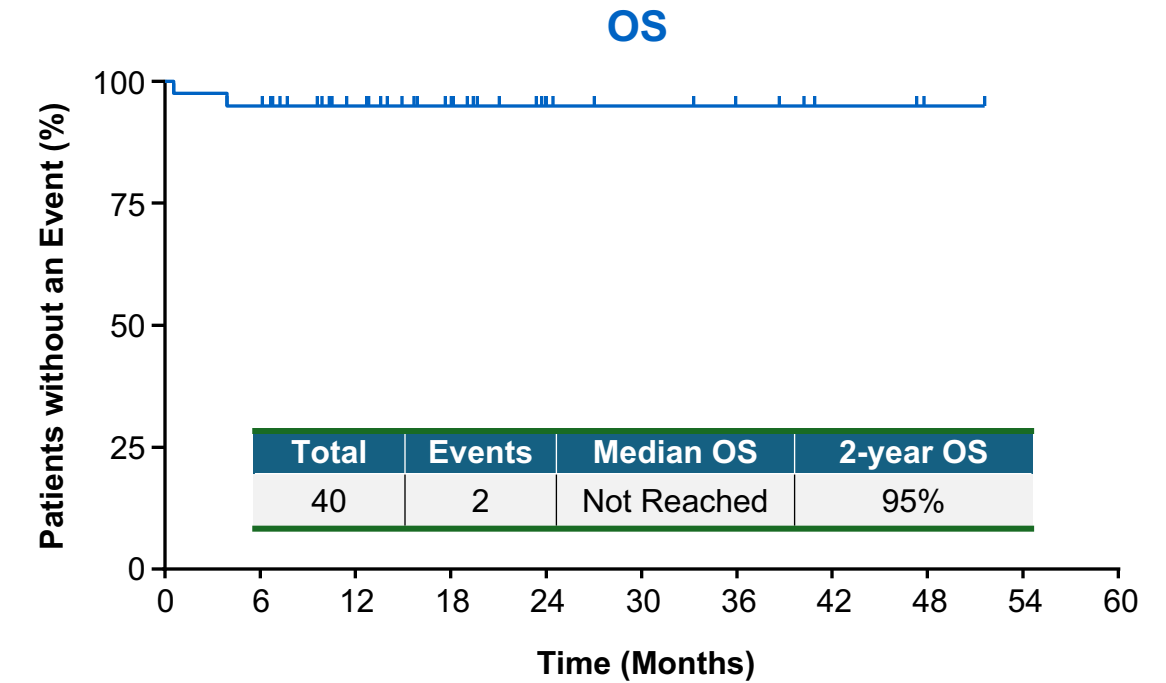
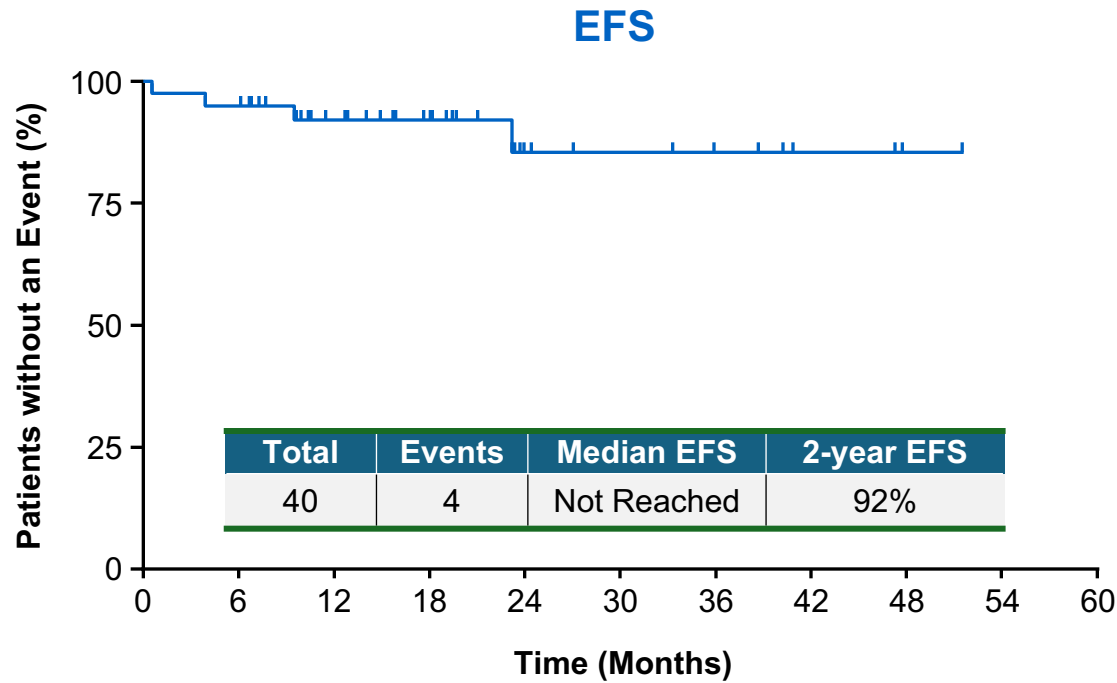
(Abstract release date: 05/11/23) EHA Library. Short N.  
06/08/2023; 387818; S118



A CHEMOTHERAPY-FREE COMBINATION OF PONATINIB AND  
BLINATUMOMAB FOR PATIENTS WITH NEWLY DIAGNOSED  
Short N. Jun 8, 2023; 387818; S118



# Frontline Blinatumomab + Ponatinib Ph+ LLA-B



**No. at Risk** 40 39 28 21 11 9 7 4 2 0 0  
 Median FU 16 months n=54

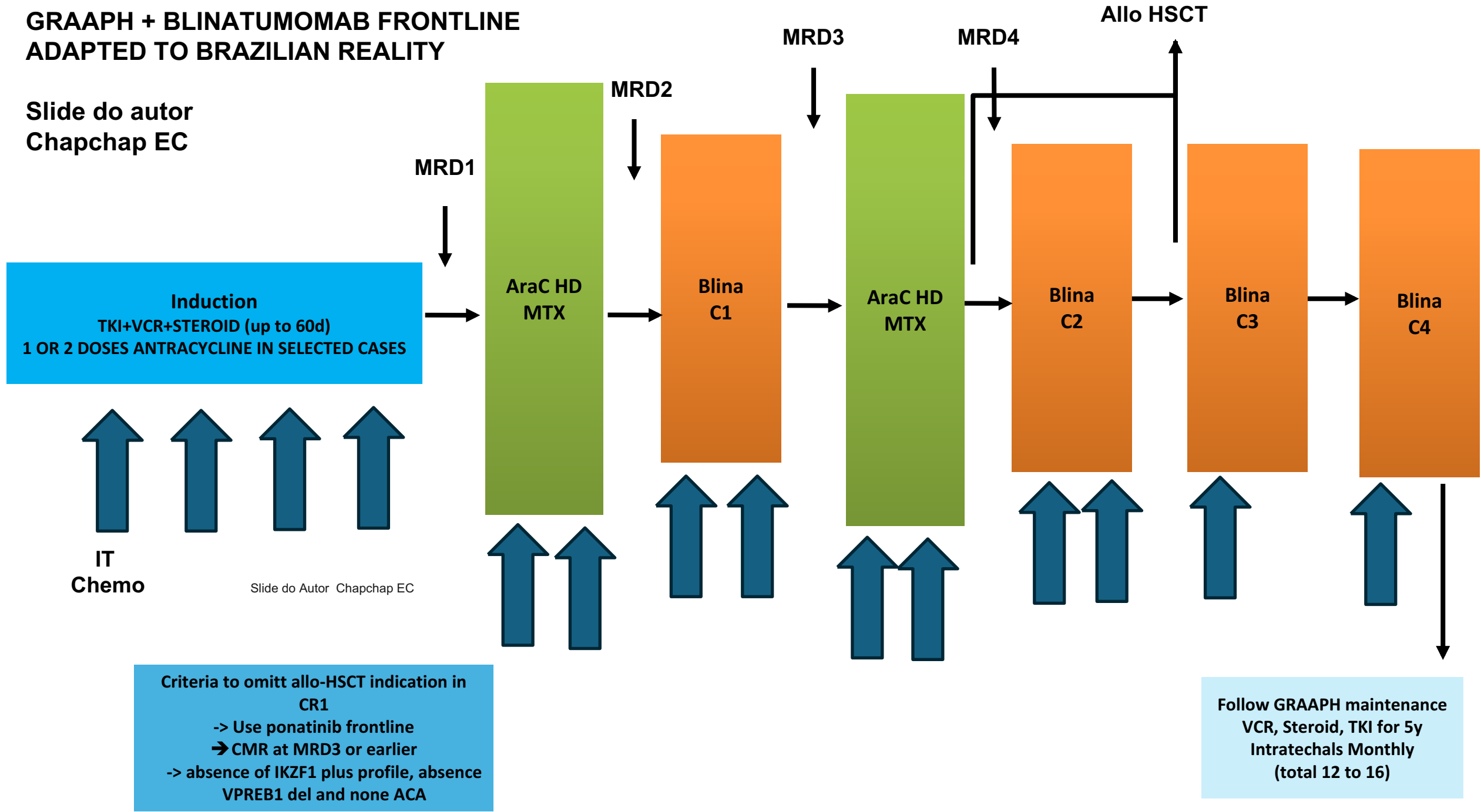
**No. at Risk** 40 39 29 21 12 9 7 4 2 0 0

CR/CRi=97%  
 CMR NGS or qBCRABL = 90% (71% post C1)

Death other = 2 cases / Relapse = 3 cases (2 extra and 1 bone marrow) / AlloHSCT = 1 case (persistent MRD+)  
 2-year EFS is 80%  
 2-year OS is 90%  
 CRS 14% / Neurologic 18%  
 Discontinuation ponatinib = 2 cases

# GRAAPH + BLINATUMOMAB FRONTLINE ADAPTED TO BRAZILIAN REALITY

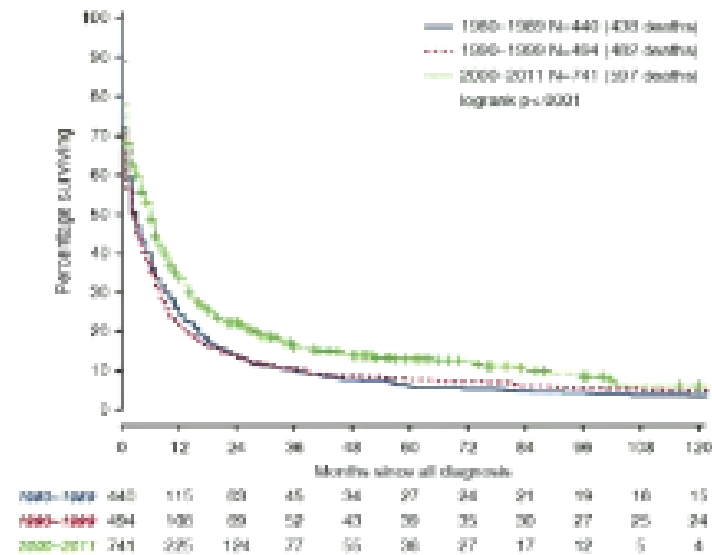
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Chapchap EC



LLA idoso

# LLA-B idosos – desfechos com quimioterapia

## SEER Registry, ALL (age 60y+)<sup>5</sup> Outcome by treatment era (1980-89, 1990-99, 2000-11)



4. GRAALL, unpublished data on file.

5. Geyer MB, et al. Blood. 2017 Mar 30;129(13):1878-1881.

# 728 Older Age and TP53 Mutations Are Predictors for the Development of Therapy-Related Myeloid Neoplasms in Adults Undergoing Frontline Therapy for Acute Lymphoblastic Leukemia

Monday, December 9, 2024: 10:45 AM (Oral)

Roberta Santos Azevedo<sup>1\*</sup>, Hagop M. Kantarjian, MD<sup>1</sup>, Koichi Takahashi, MD, PhD<sup>1</sup>, Cedric Christophe Nasnas, MD<sup>1\*</sup>, Sanam Loghavi, MD<sup>2</sup>, Nitin Jain, MD<sup>1</sup>, Fadi G. Haddad, MD<sup>1</sup>, Jayastu Senapati, MD, DM, MBBS<sup>1</sup>, Ghayas C. Issa, MD<sup>1</sup>, Hussein A. Abbas, MD, PhD<sup>1</sup>, Tapan M. Kadia, MD<sup>1</sup>, Kelly S. Chien, MD<sup>1</sup>, Guillermo Montalban-Bravo, MD<sup>1</sup>, Rebecca Garriss<sup>1\*</sup>, Farhad Ravandi, MBBS<sup>1</sup>, Elias Jabbour, MD<sup>3</sup> and Nicholas J. Short, MD<sup>1</sup>

**Patients with ALL** (from 1992 to 2022, treated hypercvad 91% or mini-hypercvd 9% at MD Anderson) (**n=875**)  
**Aged 18 to 87y**, Median FU 46 months  
**TP53 mutation – 19% (53/283)**

→ **4% developed t-MNs, median time 38months (2.9-178), MDS=68% and AML=29%**

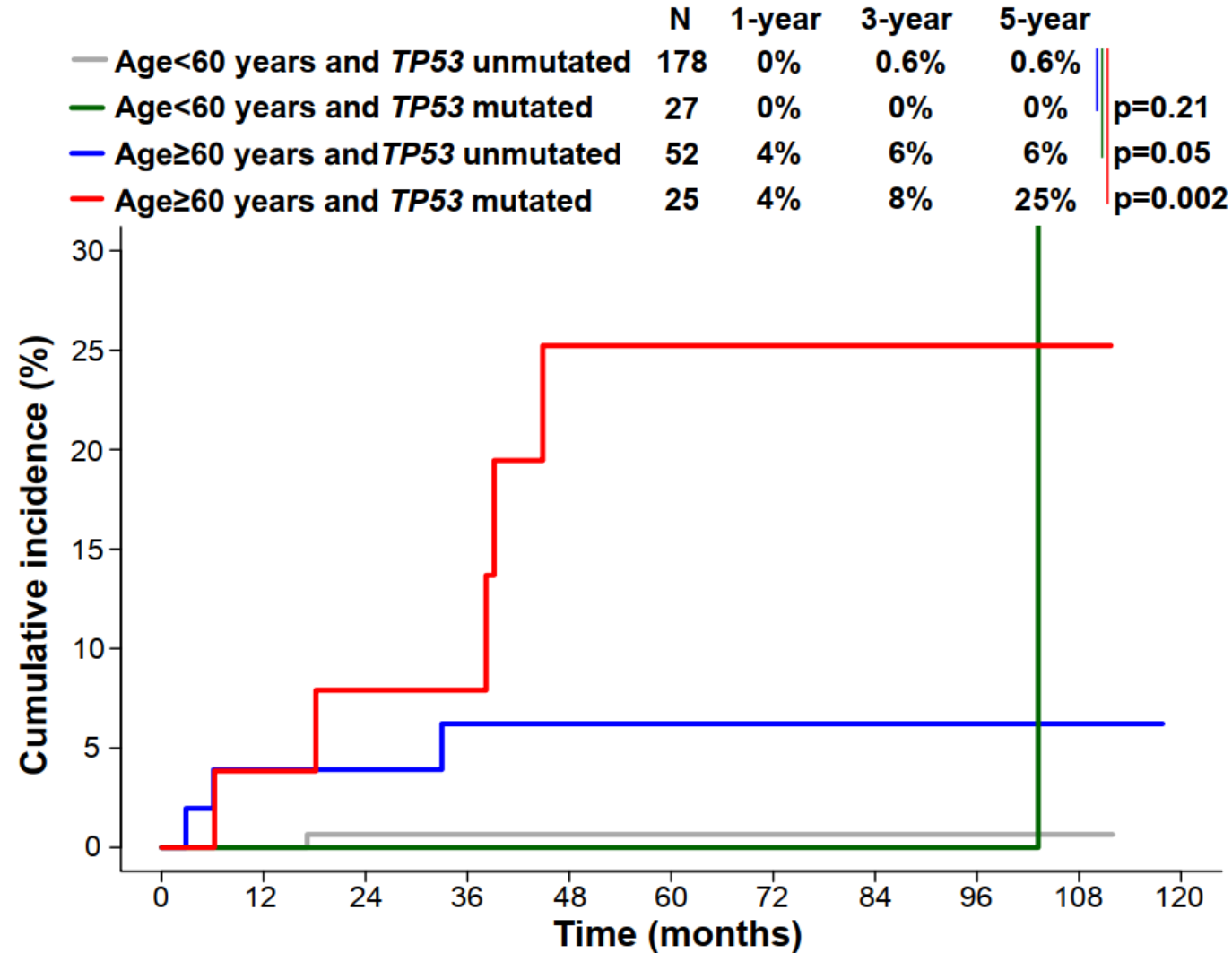
→ Frequency of t-MNs was higher - **Age  $\geq 60y$  7% vs 3% and TP53mut 9% vs 1%**

→ Comparing ALL and t-MN diagnoses samples, **86% shared at least one mutation**

→ **Poor prognosis median OS t-MN was 8.9 months; 2-year OS rate was 20%.**



# t-MN after ALL Therapy: CI of t-MN stratified by age and *TP53* status



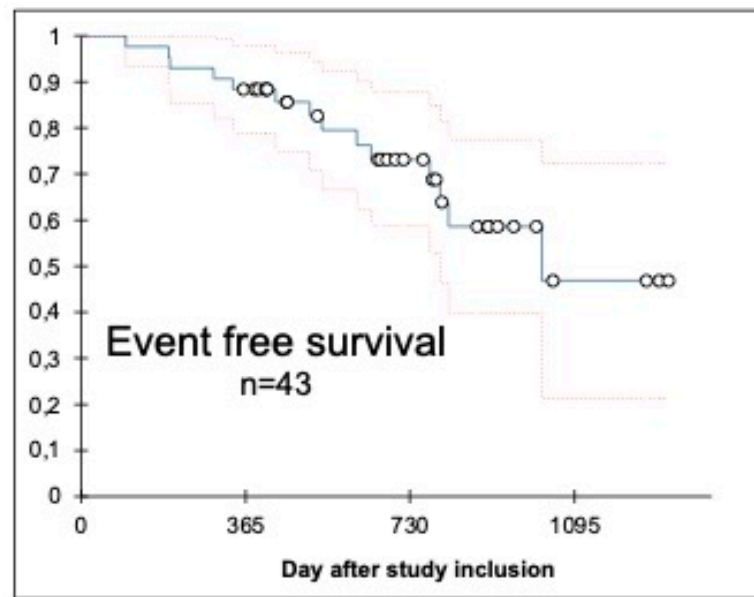
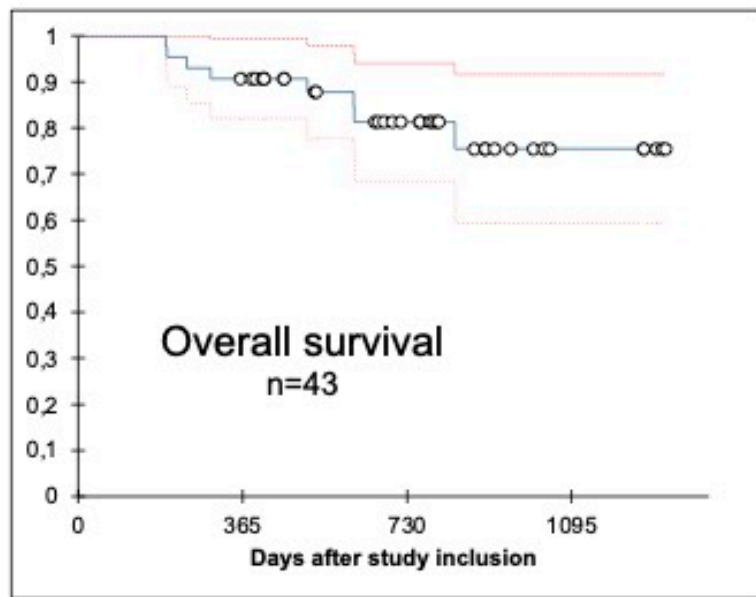
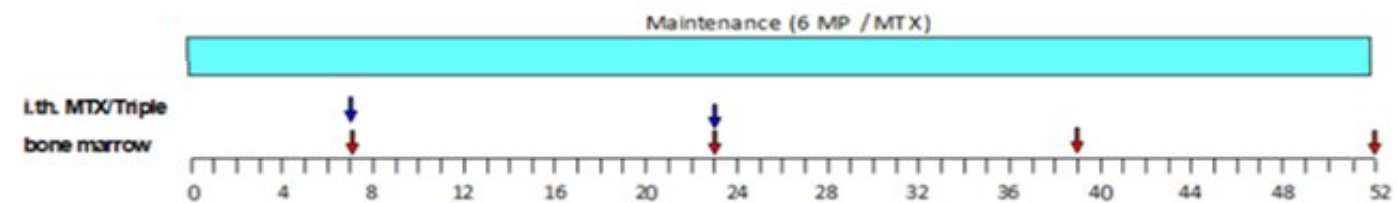
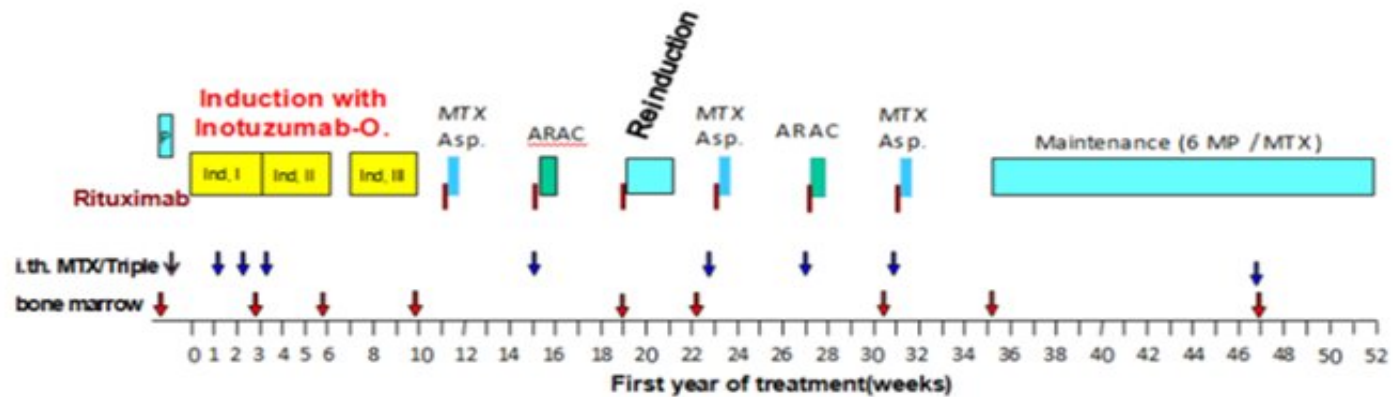


Acute Lymphoblastic Leukemia

## ALL-040 The Impact of Age-Related Clonal Hematopoiesis on Outcomes of Adults With Acute Lymphoblastic Leukemia

Caner Saygin MD 1, Ibrahim Aldoss MD 2, Todd Knepper MS 3,  
Alexandra Rojek MD 1, Peng Wang MD 1, Angela Lager PhD 1, Jeremy Segal MD 1,  
Sandeep Gurbuxani MBBS 1, Girish Venkataraman MBBS 1, Jason Cheng MD 1,  
Bijal Shah MD 3, Wendy Stock MD 1

Apos os 40 anos, foi identificada hematopoiese clonal subjacente em torno de 41% dos pacientes com LLA (destes 17% TP53mut) e sobrevida mediana significativamente inferior - 32 meses vs 84 meses





## 511 Fractionated Inotuzumab Ozogamicin Combined with Low-Intensity Chemotherapy Provides Very Good Outcome in Older Patients with Newly Diagnosed CD22+ Philadelphia Chromosome-Negative B-Cell Precursor Acute Lymphoblastic Leukemia: First Results from the EWALL-INO Study

Program: Oral and Poster Abstracts

Type: Oral

Session: 614. Acute Lymphoblastic Leukemias: Therapies, Excluding Transplantation and Cellular Immunotherapies II

Hematology Disease Topics & Pathways:

Clinical Trials, Biological, Clinical Research, Therapies, Monoclonal Antibody Therapy

Sunday, December 12, 2021: 4:30 PM

Patrice Chevallier, MD<sup>1</sup>, Thibault Leguay<sup>2\*</sup>, Michael Doubek, MD, PhD<sup>3</sup>, Françoise Huguet, MD<sup>4\*</sup>, Cyril Salek<sup>5\*</sup>, Aurélie Cabannes, MD<sup>6\*</sup>, Ulla Wartiovaara-Kautto, MD<sup>7</sup>, Colombe Saillard, MD<sup>8\*</sup>, Emmanuel Raffoux, MD<sup>9\*</sup>, Thomas Cluzeau,

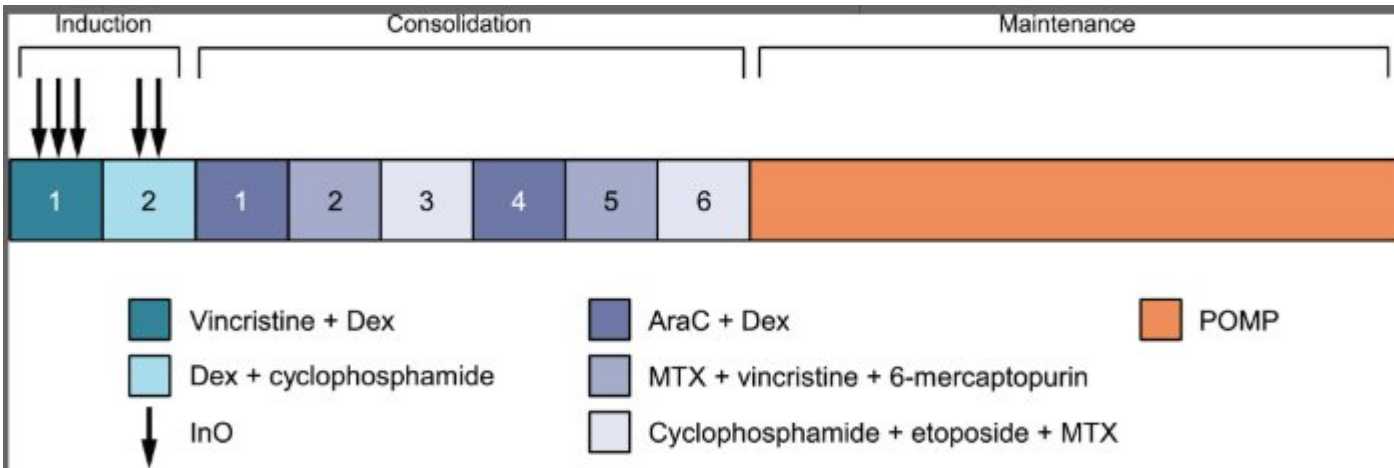
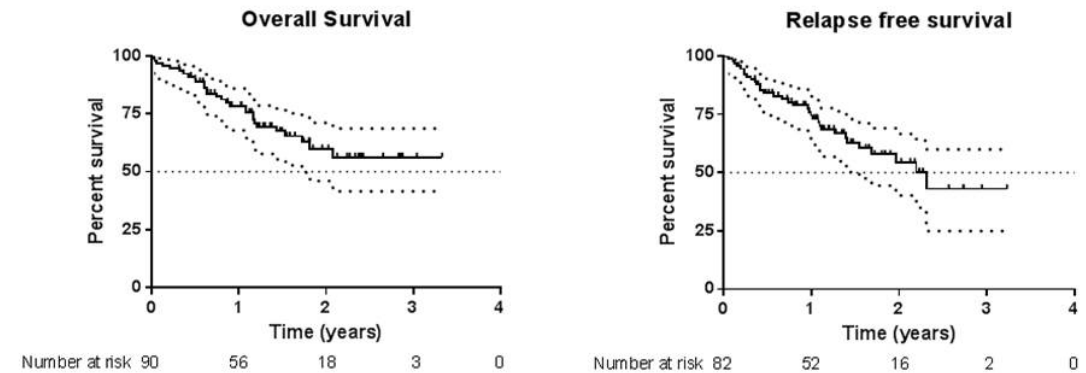


Figure 1



N=90

Mediana FU = 1.2 anos

28% hipodiploidia

11% Ph-like

10% KMT2A r

81% completaram 5 doses de inotuzumab

6.6% seguiram com alo-TMO

CR=88% (DRMneg em 73%)

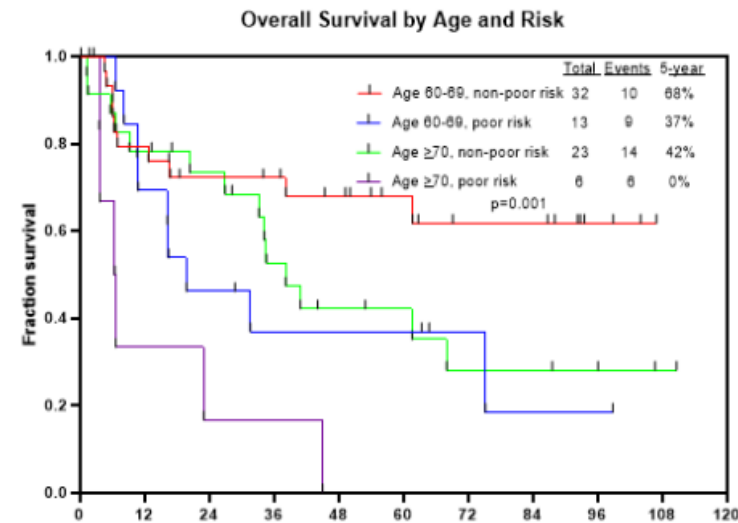
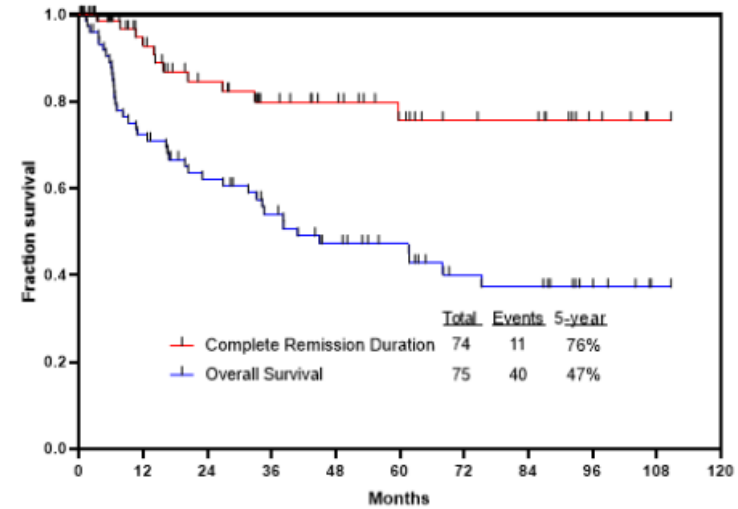
VOD = 3.3% e Tox Hepatica = 8.8%

# Minihypercvd + inotuzumab 1a linha em IDOSOS com LLA (ASH, 2021)

**Table 1.** Patient characteristics

Characteristic	Category	N (%) / median [range]
Age (years)		68 [60-87]
Performance status	≥2	10 (13)
WBC (x10 <sup>9</sup> /L)		3.1 [0.6-111.0]
Karyotype	Diploid	25 (33)
	HeH	5 (7)
	Ho-Tr	12 (16)
	Tetraploidy	3 (4)
	Complex	3 (4)
	t(4;11)	1 (1)
	Misc	13 (17)
	IM/ND	13 (17)
CD19 expression	Median [range]	99.6 [26-100]
CD22 expression	Median [range]	96.7 [27-100]
CD20 expression	≥ 20%	42/69 (61)
Ph-like ALL		8/43 (19)
TP53 mutation		22/56 (49)

**Figure 1.** (A) Continuous remission duration (CRD) and overall survival (OS) for the whole cohort; (B) overall survival stratified by age and cytogenetic risk



## GMALL – BOLD TRIAL

Incorporação Blinatumomab após indução atenuada

Seguido de 3 ciclos de Blina na consolidação, alternando com QT dose intermediária

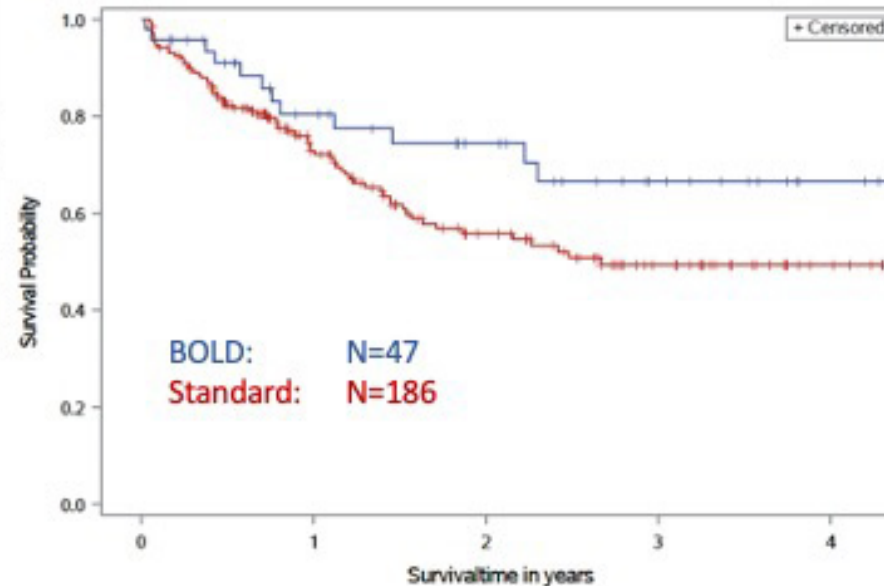
**Table 1: Results of Remission Induction**

	Induction I	Blina I
<b>N Hematologic Response*</b>	50	47
<b>Hematologic CR</b>	38 (76%)	40 (85%)
<b>Early death</b>	2 ( 4%)	2 ( 4%)
<b>Failure/PR/Relapse</b>	10 (20%)	5 (11%)
<b>N Molecular Response**</b>	34	37
<b>Molecular CR</b>	6 (18%)	28 (82%)
<b>Molecular IMR</b>	5 (15%)	2 (6%)
<b>Molecular Failure</b>	23 (68%)	4 (12%)

\* Evaluable pts with remission control after the respective cycles

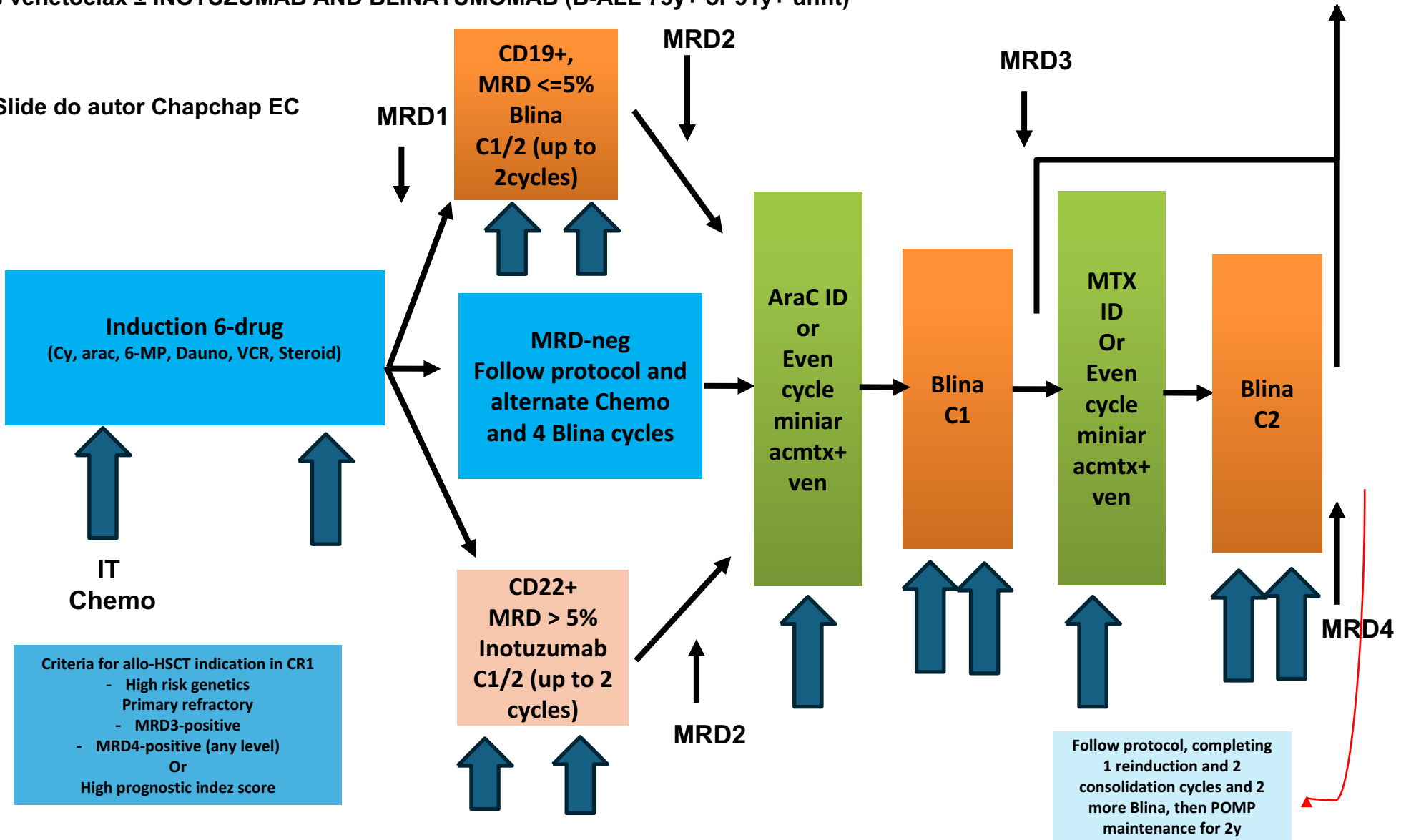
\*\* Pts with evaluable MRD test after the respective cycle; calculated in relation to CR pts; **Molecular CR (MoICR)**: MRD negative with sensitivity of 0.01%; **Molecular Failure (MoIFail)**: MRD positive above 0.01%; **Intermediate Risk (IMR)**: MRD below 0.01% or not quantifiable; **Molecular not evaluable**: Negative with sensitivity above 0.01%, lack of marker or material

**Figure 1: Overall Survival BOLD vs GMALL Standard of Care**



**EWALL adapted ± INOTUZUMAB AND BLINATUMOMAB (B-ALL Ph-neg 51-74y; dose adjust at 65y+)**  
**Minihypercvd plus venetoclax ± INOTUZUMAB AND BLINATUMOMAB (B-ALL 75y+ or 51y+ unfit)**

Slide do autor Chapchap EC

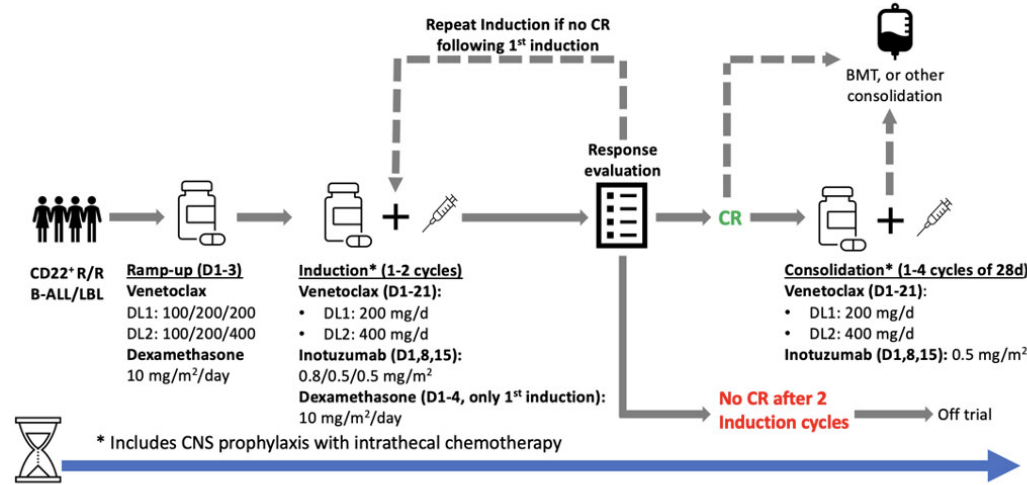


Nicola Goekbuget, Stefan Schwartz, Christoph Faul, Max S. Topp, Marion Subklewe, Andrea Renzelmann, Andrea Stoltefuss, Bernd Hertenstein, Anne Wilke, Simon Raffel, Nadja Jäkel, Vladan Vucinic, Dirk Markus Niemann, Lena Reiser, Hubert Serve, Monika Brüggemann, Andreas Viardot; Dose Reduced Chemotherapy in Sequence with Blinatumomab for Newly Diagnosed Older Patients with Ph/BCR::ABL Negative B-Precursor Adult Lymphoblastic Leukemia (ALL): Preliminary Results of the GMALL Bold Trial. *Blood* 2023; 142 (Supplement 1): 964. doi: <https://doi.org/10.1182/blood-2023-180472>

Stelljes M, Raffel S, Alakel N, Wäsch R, Kondakci M, Scholl S, Rank A, Hänel M, Spriewald B, Hanoun M, Martin S, Schwab K, Serve H, Reiser L, Knaden J, Pfeifer H, Marx J, Sauer T, Berdel WE, Lenz G, Brüggemann M, Gökbüget N, Wethmar K. Inotuzumab Ozogamicin as Induction Therapy for Patients Older Than 55 Years With Philadelphia Chromosome-Negative B-Precursor ALL. *J Clin Oncol*. 2024 Jan 20;42(3):273-282. doi: 10.1200/JCO.2023.00546. Epub 2023 Oct 26. PMID: 37883727.

Luskin MR, Shimony S, Keating J, Winer ES, Garcia JS, Stone RM, Jabbour E, Flamand Y, Stevenson K, Ryan J, Zeng Z, Letai A, Konopleva M, Jain N, DeAngelo DJ. Venetoclax plus low-intensity chemotherapy for adults with

# A Phase I Study of Venetoclax in Combination with Inotuzumab Ozogamicin for Relapsed or Refractory ALL in Adults



**Panel A: Trial Schema**

Pt #	DL	Age	Sex	Race/Ethnicity	Disease	Prior Rx #	Prior BMT	Genetics	CNS	Best Response	CR to Best Response	Best MRD (MPFC), Cycle	Best MRD (Cleared), Cycle	Cycles	Consolidation	Relapse status, duration of CR	Alive	OS, days	DLT
1	1	35	F	Other, H	EM, MRD- BM	1	No	NK	Neg	CR	2	N/A	N/A	3	XRT	No, 530	Yes	530	No
2	1	25	F	Other, H	BM	2	No	NK; 2 copy del <i>CDKN2A, CDKN2B</i>	Neg	CR	1	Neg, <0.01% (1)	36 (2)	2	BMT	No, 473	Yes	473	No
3	1	45	F	Black, NH	BM	1	No	NK; <i>TCF3::PBX1</i> ; 2 copy del <i>CDKN2A/B</i>	Pos	CR	1	Neg, <0.01% (1)	0 (1)	2	BMT	Yes, 177	No	262	No
4	2	74	F	White, NH	BM	2	Yes	Tetraploid w <i>t(9;22)</i> ; <i>ABL1</i> T315I	Neg	CR	1	Neg, <0.01% (1)	51 (2)	5	Bli <sup>10a</sup>	No, 195	Yes	195	No
5	2	59	M	White, NH	EM, MRD+ BM	1	Yes	Hypodiploid, <i>TP53</i>	Neg	CR	2	Neg, <0.01% (1)	0 (1)	4	DLI	No, 170	Yes	170	No
6	2	31	M	White, NH	BM	2	No	<i>t(4;11)</i> ; <i>KRAS</i> (p.G12V)	Neg	CR	1	Neg, <0.01% (1)	N/A	2	N/A	Yes, 48	No	155	No
7	2	27	M	White, NH	BM	1	No	NK, <i>IKFZ1</i> del, 1 copy del <i>CDKN2A/B</i>	Neg	CR	1	Pos, 0.012% (2)	63 (1)	2	Bli <sup>10a</sup>	No, 80	Yes	80	No
8	2	48	F	White, NH	BM	1	No	NK	Neg	CR	1	Neg, <0.01% (1)	9 (1)	2*	N/A	No, 44	Yes	44	No
9	2	62	M	White, NH	BM	2	Yes	<i>BCR-ABL1</i> + (FISH)	Neg	CR	1	Neg, <0.01% (1)	5 (1)	2*	N/A	No, 42	Yes	42	No

Data lock – 07/20/23

\*Treatment ongoing

**Legend:** ALL/LBL (acute lymphoblastic leukemia/lymphoblastic lymphoma); BM, bone marrow; BMT, bone marrow transplant; CNS, central nervous system; CR, complete remission; DL, dose level; DLI, donor lymphocyte infusion; DLT, dose-limiting toxicity; EM, extramedullary; F, female; H, Hispanic; M, male; MPFC, multi-parameter flow cytometry; MRD, measurable residual disease; NH, non-Hispanic; NK, normal karyotype; OS, overall survival; Pt, patient; R/R, relapsed or refractory; XRT, radiation

**Panel B: Patient Disposition and Outcome**

- **Blinatumomab incorporado “TODOS” LLA-B 1ª linha**, em geral após 3 blocos QT (podendo antecipar a depender do perfil paciente, resposta e toxicidade esperada)
- **Alvo 4 ciclos**
  
- DRM-pos => DRM-pre, Genetica, N ciclos para DRM-neg
- DRM-neg => Idade, Genetica, escore prognostico (multivariado)
  
- Quem transplantar em CR1 em uso Blina ? Duvida persiste.....analisar outros fatores (doador, tipo Tmo, experiencia centro) -> aprender a identificar/monitorar subpopulações leucêmicas CD19-neg
  
- **Inotuzumab ozogamicin**
- Refratrios e maior carga tumoral/EMD e 1ª linha (**offlabel**) idosos CD22+
- DRM-pos e/ou escape pos Blina
- Combinado a miniCVD+Blina (1ª linha MD anderson)
- Papel manutenção pos TMO, ponte pre-CART? , Manutencao pos CART
  
- **Ph+**
- Incorporacao Blina (**off-label, se DRMneg**) e Pona em 1ª linha (onlabel FDA) e otimizacao abordagem CNS => TMO se tornara terapia de exceção => altas taxas de sobrevida livre a longo prazo
  
- **Novos agentes imunoterapicos surgindo => SUROVATAMIG, BLINA SC, DARA, (preclinica anti-CRLF2 e Luskervimab)**

**Obrigado(a)!**

**Eduardo Cerello Chapchap**

Cargo/ Função

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