

LAL e LAM : DAY
2026

Stato dell'arte delle Leucemie Acute
ED. SUD

8 aprile 2026 Napoli

EVOLUZIONE DELL'ALGORITMO TERAPEUTICO DEL PAZIENTE CON LAL

**Dalla diagnosi alla malattia refrattaria
nel paziente Ph neg.**

Ferdinando Porretto

UO Ematologia e TMO e Immunoterapia cellulare CAR-T

Dip. oncologico La Maddalena
Palermo

Specific diagnostic workup in adult ALL

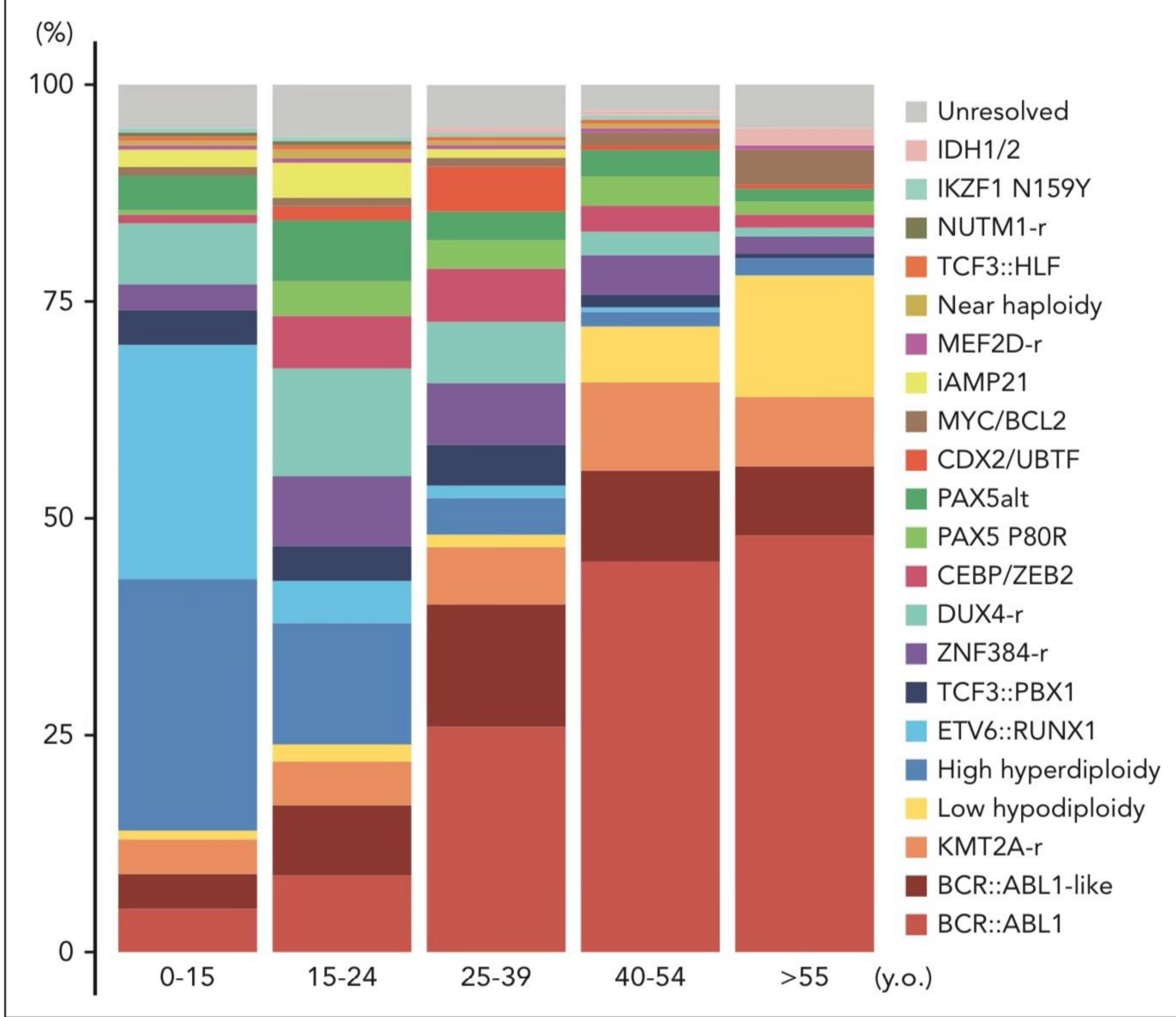
	Recommendation	Outputs
Morphology	Mandatory	Defines infiltration (>25% required for a diagnosis of ALL vs lymphoblastic lymphoma) Allows a differential diagnosis with AML (MPO ⁻ vs + MPO ⁺) Recognizes L3 (Burkitt-type) subsets
Flow cytometry	Mandatory	Allows a differential diagnosis with AML Permits to define the cell of origin Permits to define the stage of differentiation
MPO*	Mandatory	Allows a differential diagnosis with AML.
B-lineage ALL*: CD19, cCD79a, c/sCD22 (minimal requirement), TdT, CD10, CD20, clgM, slg (kappa or lambda)	Mandatory	Pro-B: CD19/CD79a/cCD22 ⁺ /CD10 ⁻ (B-I), NG2 Common: CD10 ⁺ /clgM ⁻ (B-II) Pre-B: clgM ⁺ /slg ⁻ (B-III) Mature: slg ⁺ (B-IV), CD20 ⁺
T-lineage ALL*: c/sCD3, CD7 (minimal requirement), TdT, CD1a, CD2, CD5, CD4, CD8, TCR α/β or γ/δ	Mandatory	Pro-T: cCD3/CD7 ⁺ (T-I) Pre-T: CD2/CD5 ⁺ (T-II) Cortical-T: CD1a ⁺ (T-III) Mature-T: sCD3 ⁺ /CD1a ⁻ (T-IV)
Molecular genetics	Mandatory	t(9;22)/Ph ⁺ / <i>BCR::ABL1</i> t(4;11) ⁺ / <i>KMT2Ar</i> t(1;19) ⁺ / <i>TCF3::PBX1</i> Other high-risk cytogenetics
MRD (molecular or MFC)	Mandatory	Individual MRD assay for further follow-up
Extended genomics (GEP, CNA, WES, WGS, NGS)	In clinical trials and for research purposes	Identification of novel subgroups with prognostic/biologic significance Identification of molecular targets for targeted therapies

Parametri di stratificazione del rischio – linee guida ELN

ALL-ELN RECOMMENDATIONS
Blood 2024

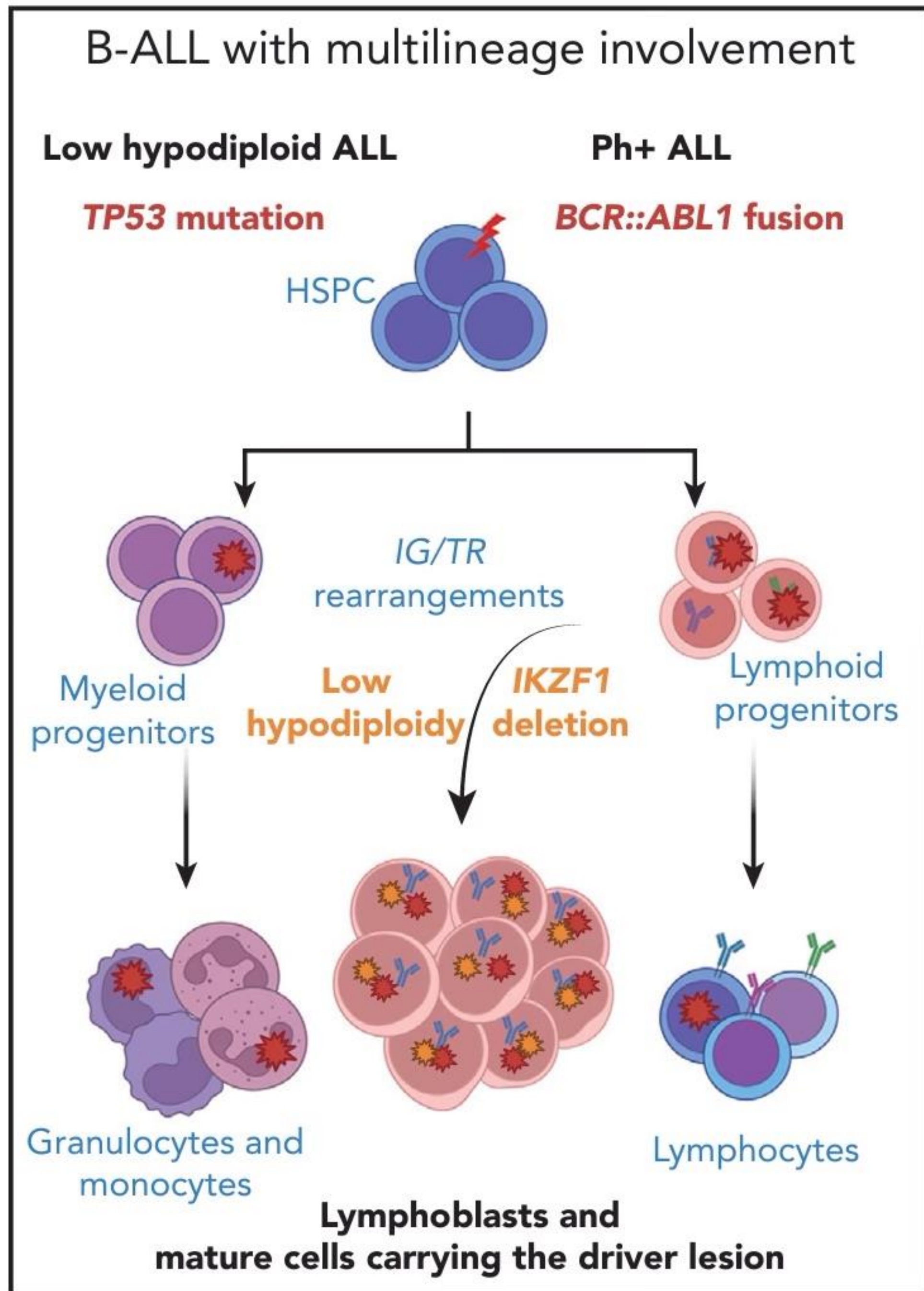
	Risk factors	Annotations
Patient-related Age (y) Performance (ECOG)	 >30-60 y (continuous variable) >55 y (older adults and elderly) >1	 Independent PF, usually not affecting risk model (age-adapted protocols) Retrospective data; relevance in older patients
Disease-related WBC (×10 ⁹ /L) Immunophenotype Cytogenetics and fluorescence in situ hybridization Genetics Miscellaneous	 >30 (B), >100 (T) Pro-B, CD20 ⁺ (B), pro/pre-T, ETP, and mature-T (T) Ph ⁺ , t(4;11), hypodiploidy, and <u>complex*</u> <i>BCR::ABL1⁺, KMT2Ar</i> Ph-like, mutated <u>CLRF2/TP53/JAK-STAT</u> , <u>adverse CNA profile (B)</u> , unmutated <i>NOTCH1/FBWX7</i> , and abnormal <i>RAS/PTEN</i> (T) CNS involvement Poor treatment compliance and undue treatment reductions and delay Pharmacogenomics (affecting antimetabolite disposition) Immune marrow microenvironment Drug response profiling	 Variably considered Variably considered Key prognostic elements; beside Ph ⁺ and <u>KMT2Ar variably considered</u> Key prognostic elements <u>Variably considered</u> Occasionally considered Retrospective data, of greater concern with pediatric-type protocols Data in children, not usually assessed in adults Investigational, for research purposes Investigational, for research purposes
Treatment-response dynamics Corticosteroid sensitivity (prephase) Early/incomplete blast cell clearance (BM morphology) Time to CR (number of courses) MRD (molecular/flow cytometry)	 Poor prednisone response (PB count ≥1 × 10 ⁹ /L at the end of prephase) Day 8-15 or end of induction BM blasts ≥5% >1 cycle (late CR) MRD positivity (from end of induction onwards): ≥0.1%/0.01% after induction ≥0.01%/positive after/during consolidation and pre/post-allogeneic SCT	 Historical relevance, occasionally considered Variably considered Variably considered Key and unifying factor predicting outcome

Distribution of B-ALL genetic subtypes according to age.

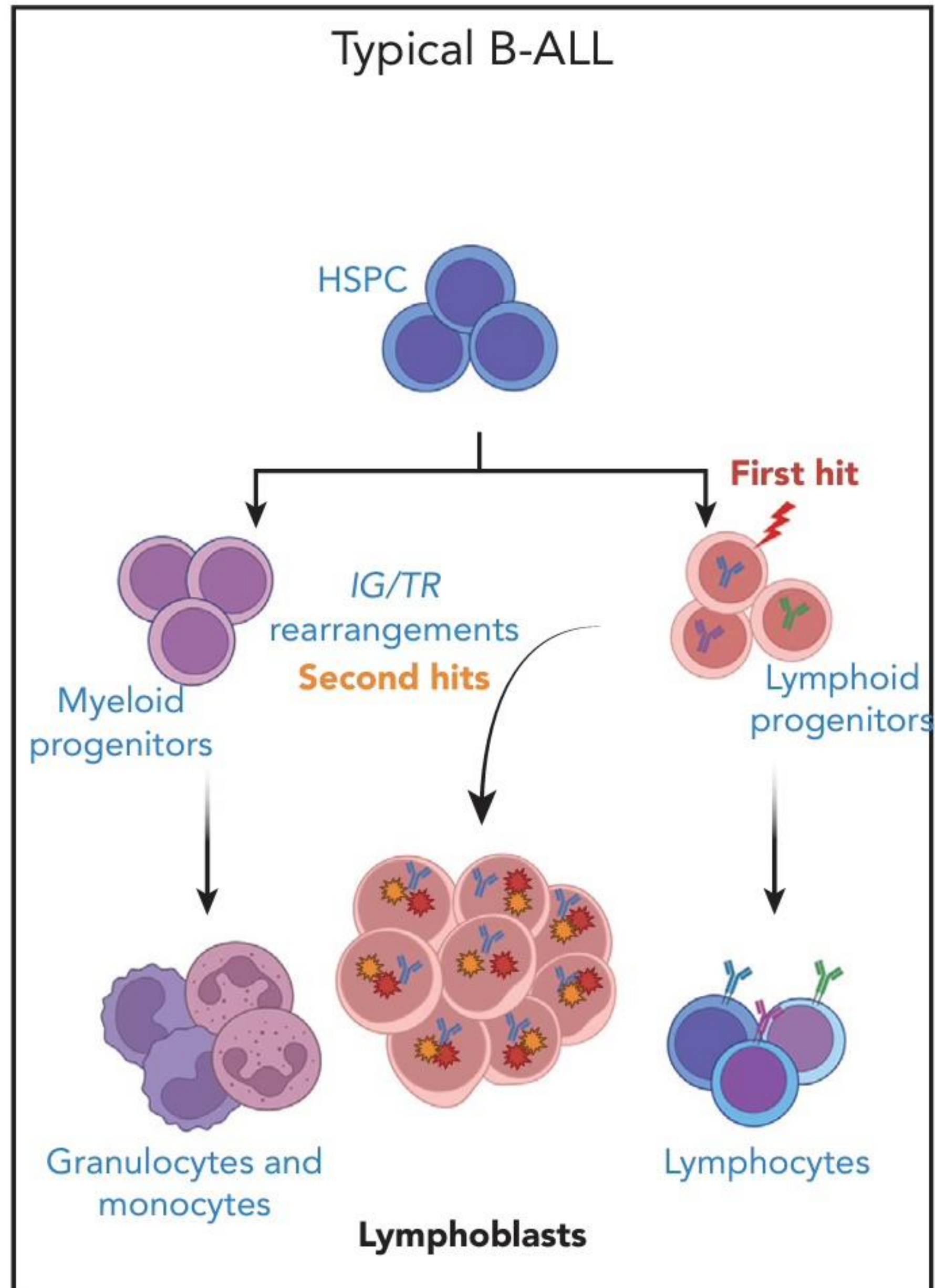


leukemogenesis in adult B-ALL AND MRD

According to this model, MRD monitoring using IG/TR markers reflects more accurately the residual blast burden



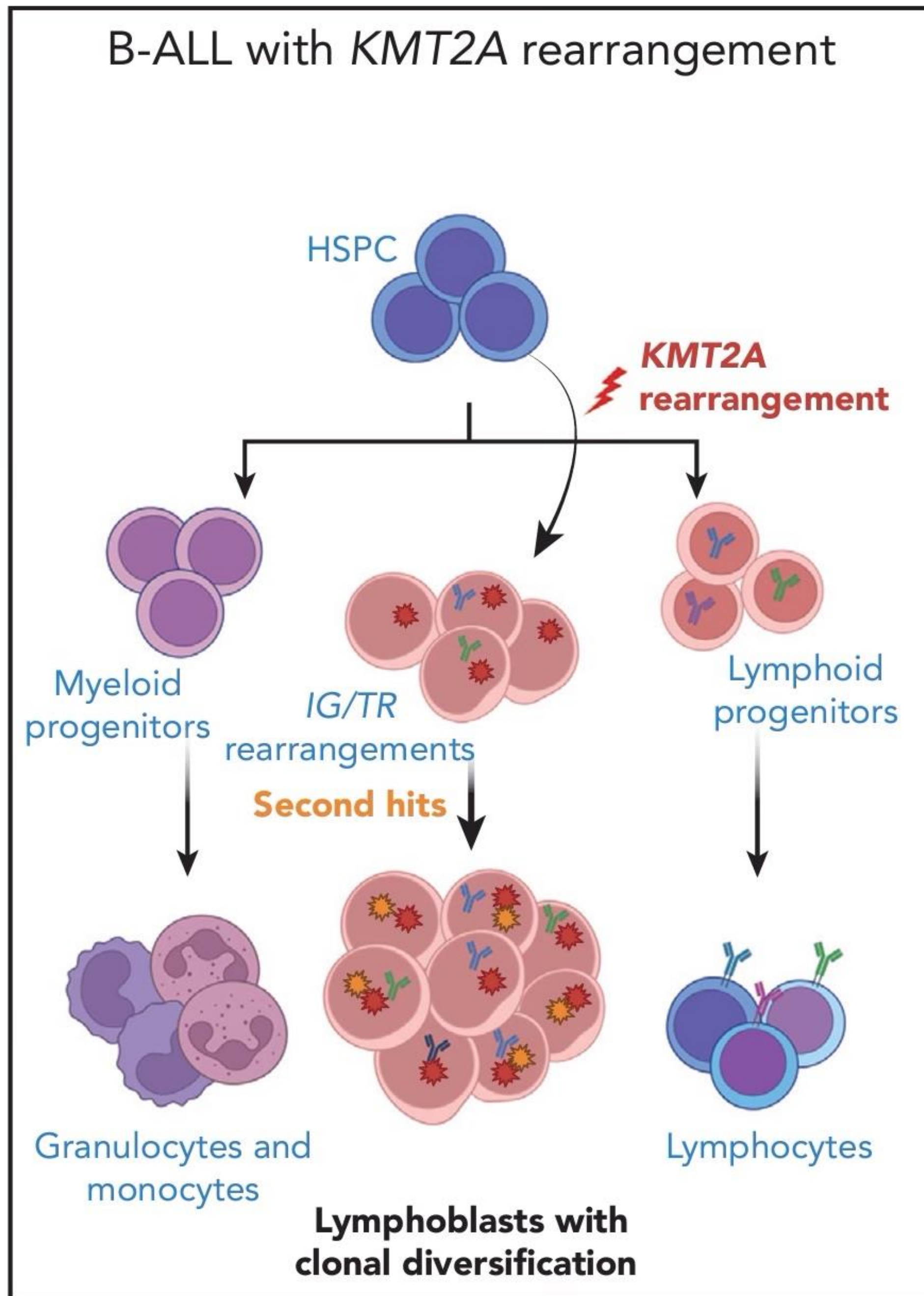
Distinct models of leukemogenesis in adult B-ALL.



**According to this model:
MRD monitoring using IG/TR markers**

C

leukemogenesis in adult B-ALL AND MRD



According to this model, MRD monitoring using *KMT2A*-r marker should be preferred over IG/TR markers, which may be lost through patient follow-up.



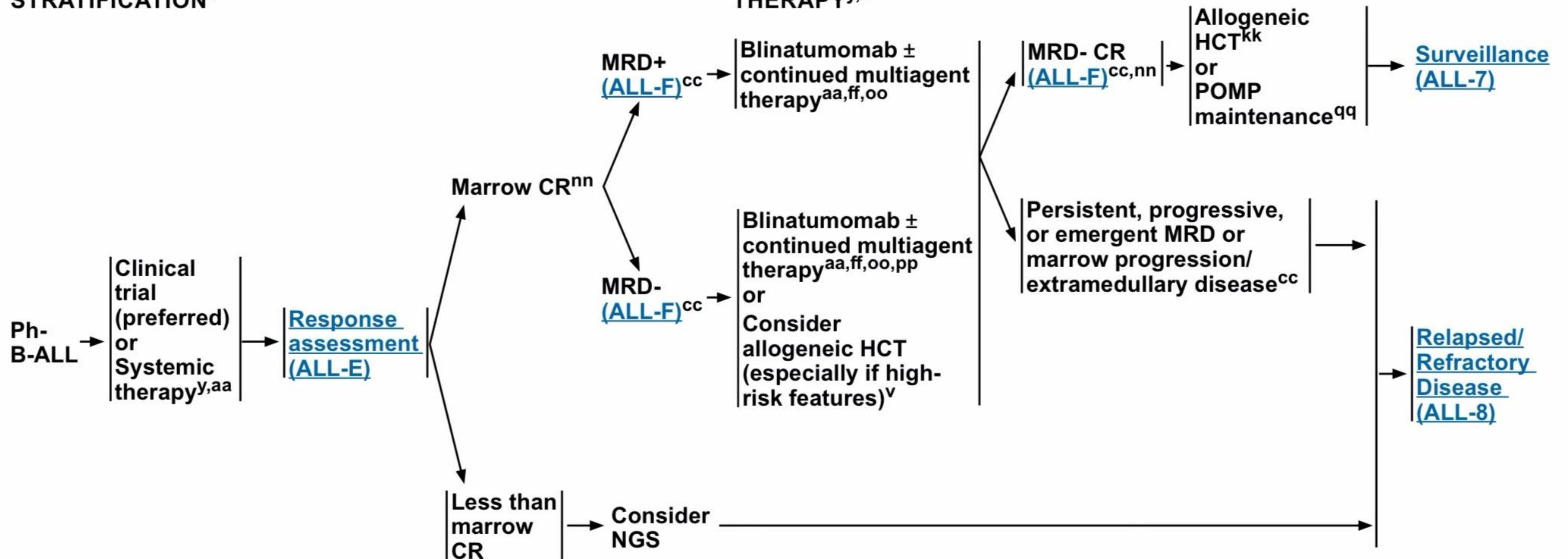
NCCN Guidelines Version 2.2025

Acute Lymphoblastic Leukemia

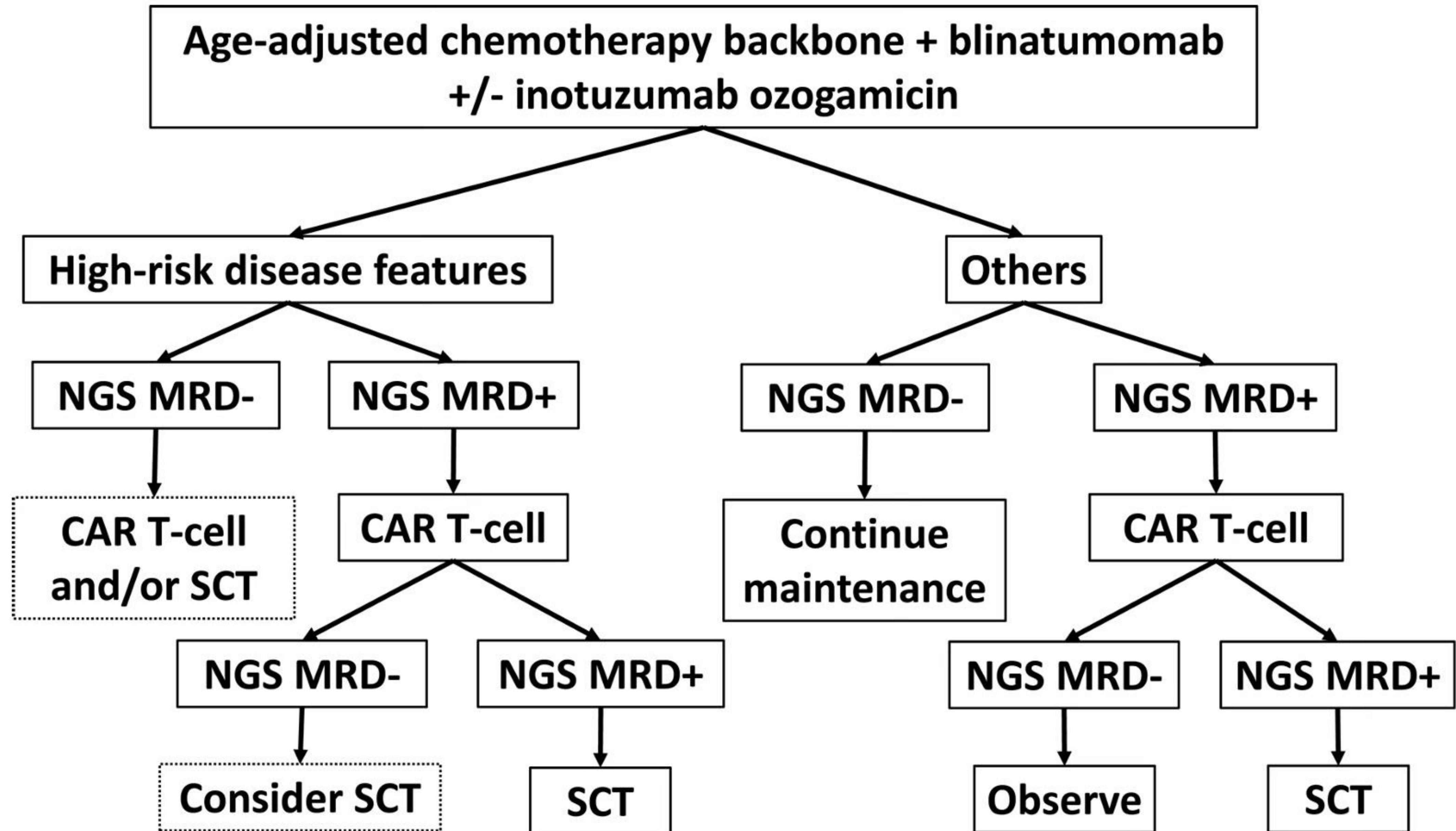
RISK STRATIFICATION^v

TREATMENT INDUCTION^{y,z}

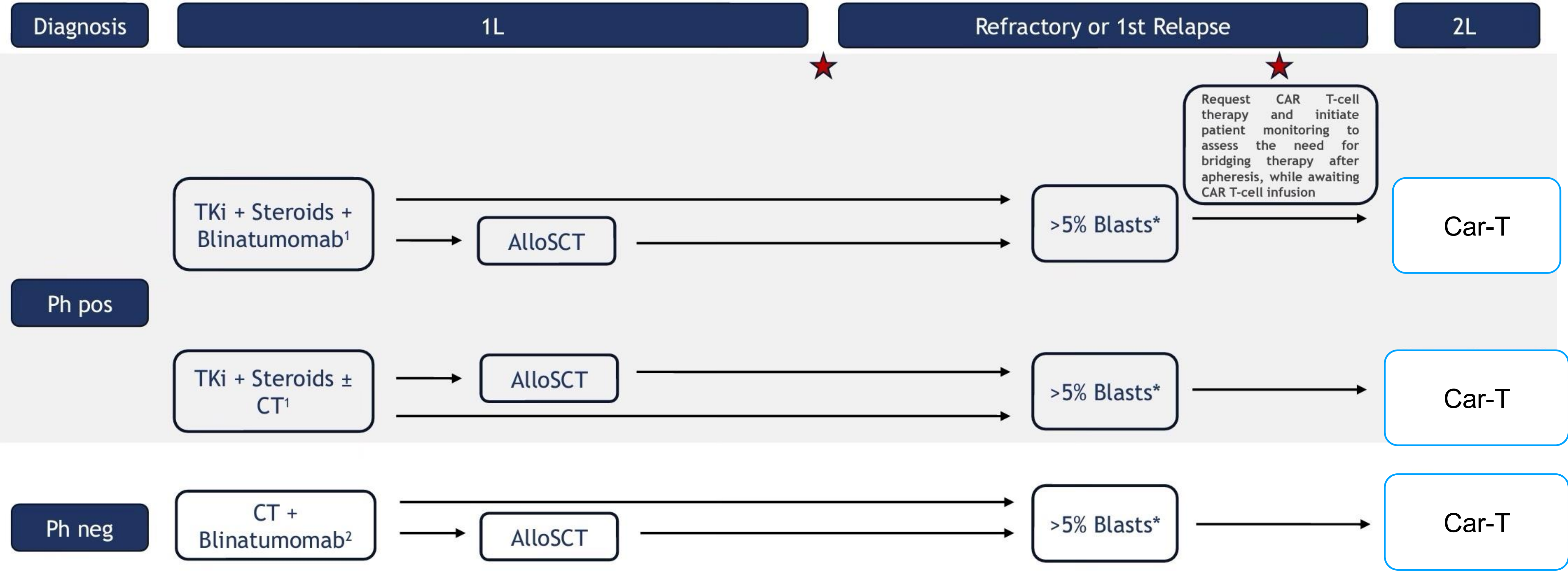
CONSOLIDATION THERAPY^{y,z}



Treatment Algorithm for Frontline Ph-negative B-cell ALL



Patient Journey aALL



Indication for allo-HSCT versus standard consolidation or maintenance therapy based on MRD status and risk stratification

★ Critical step for the early identification of disease refractoriness or relapse and for assessing eligibility for CAR T-cell therapy

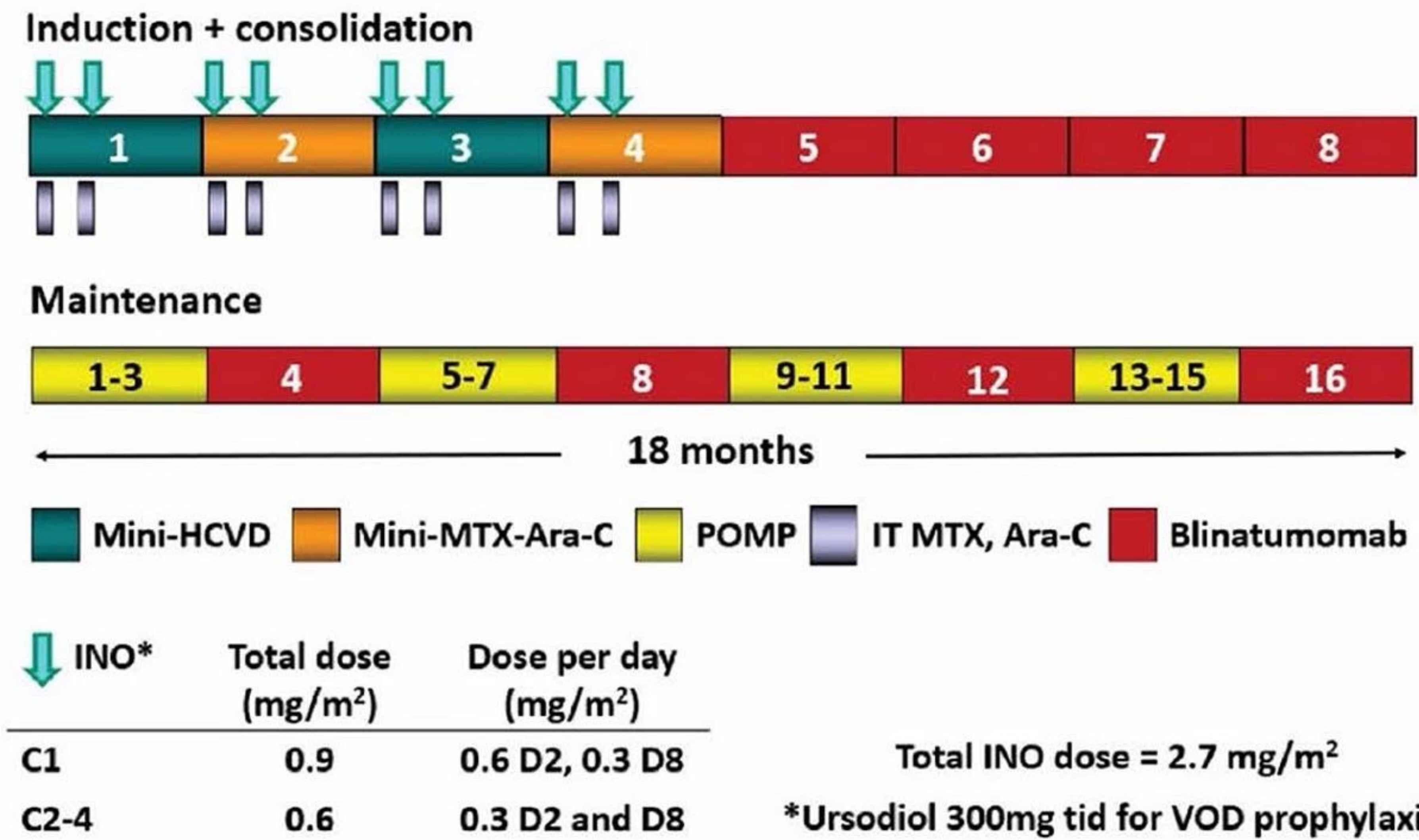
*AIFA Registry block for % medullary blasts ≤ 5% at inclusion
Brexu-cel is not recommended for patients who have CD19-negative disease or an unconfirmed CD19 status

** Subjects with Ph+ disease must be intolerant to TKI therapy, or R/R despite treatment with at least 2 different TKIs

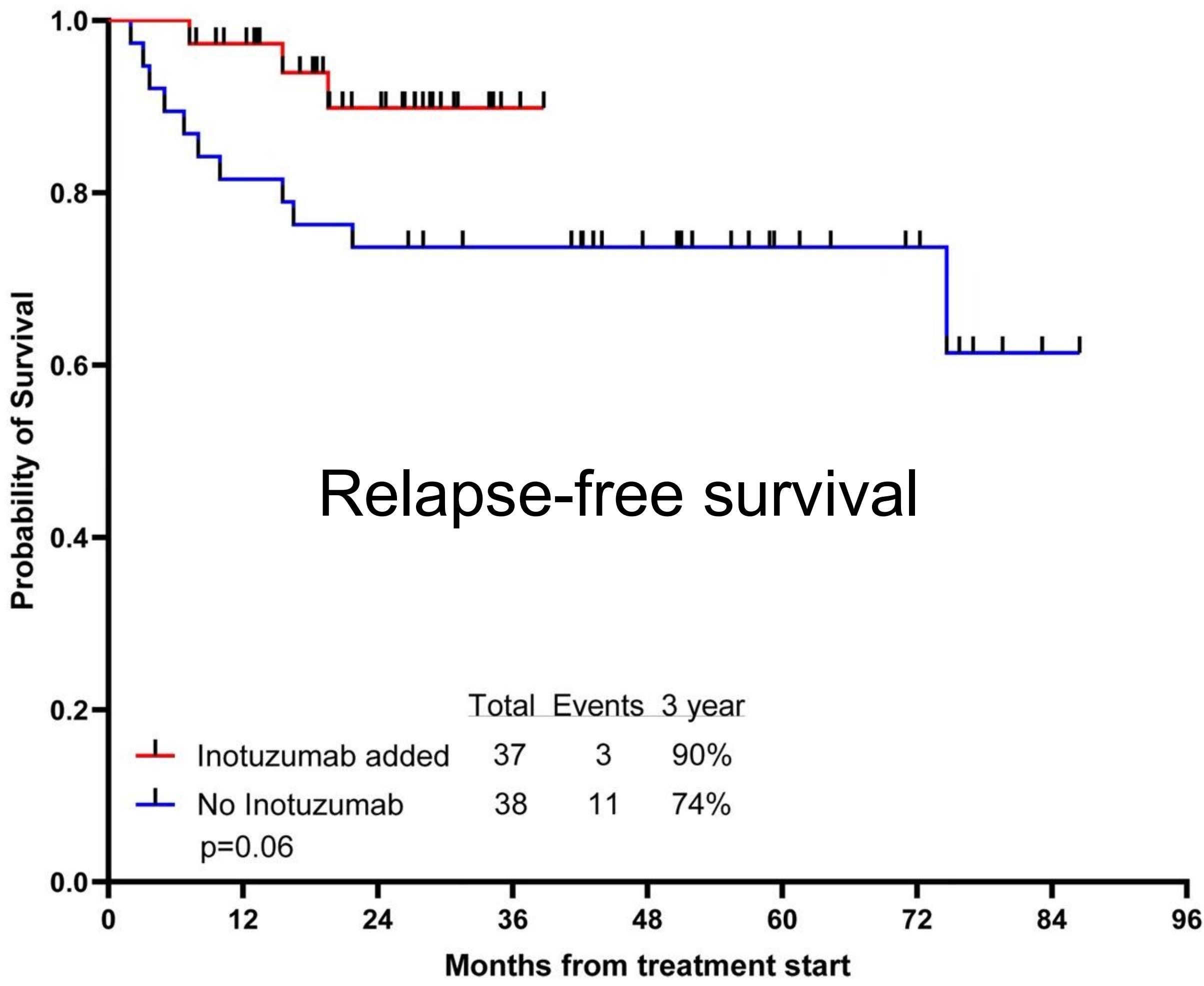
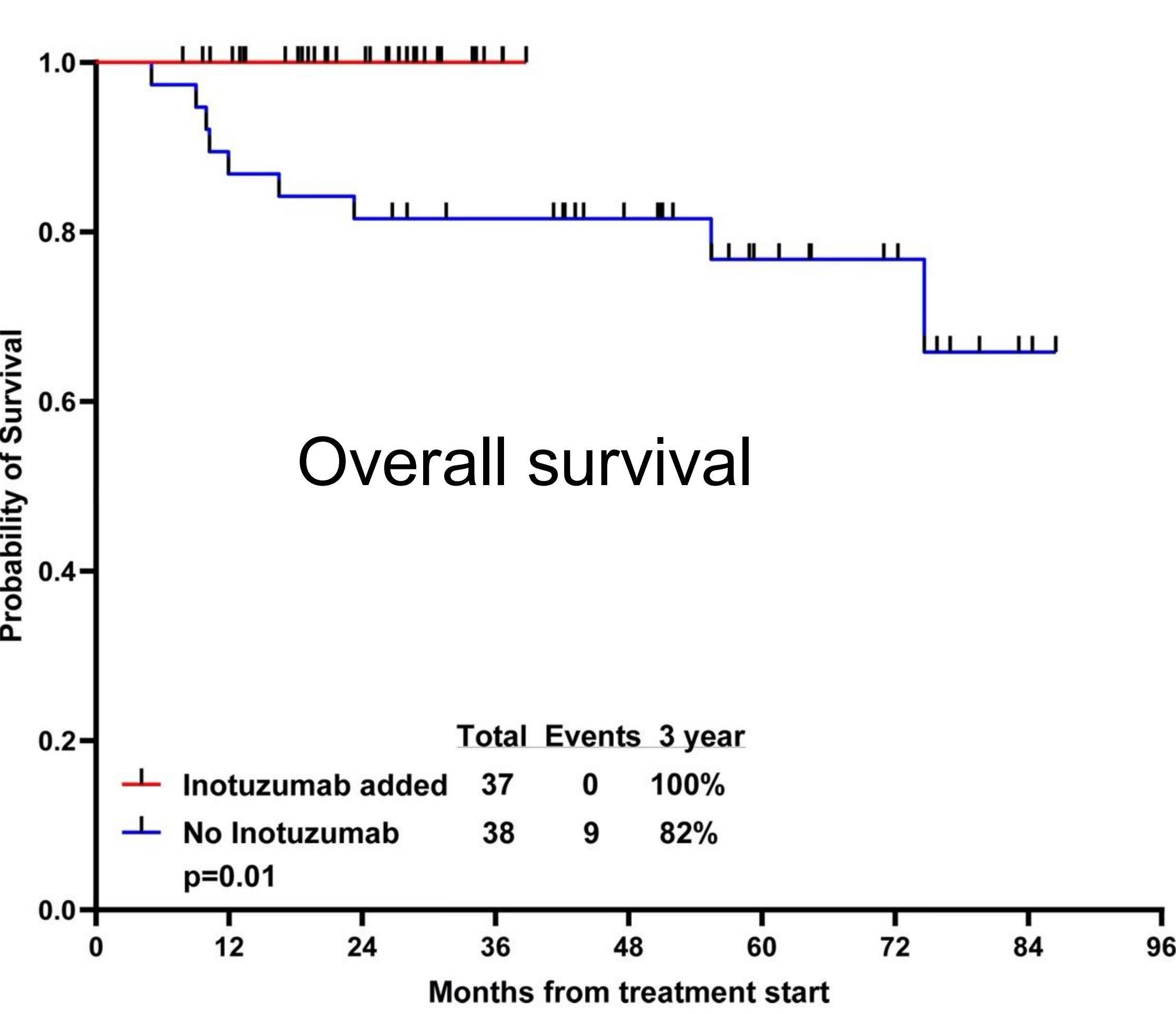
1. Chiaretti S. and Foà R. How I treat adult Ph-positive ALL. Blood 2025 Jan 2; 145 (1):11-19
2. Bassan R. et al. Blood 22 May 2025 Vol 145, N 21

For external use and

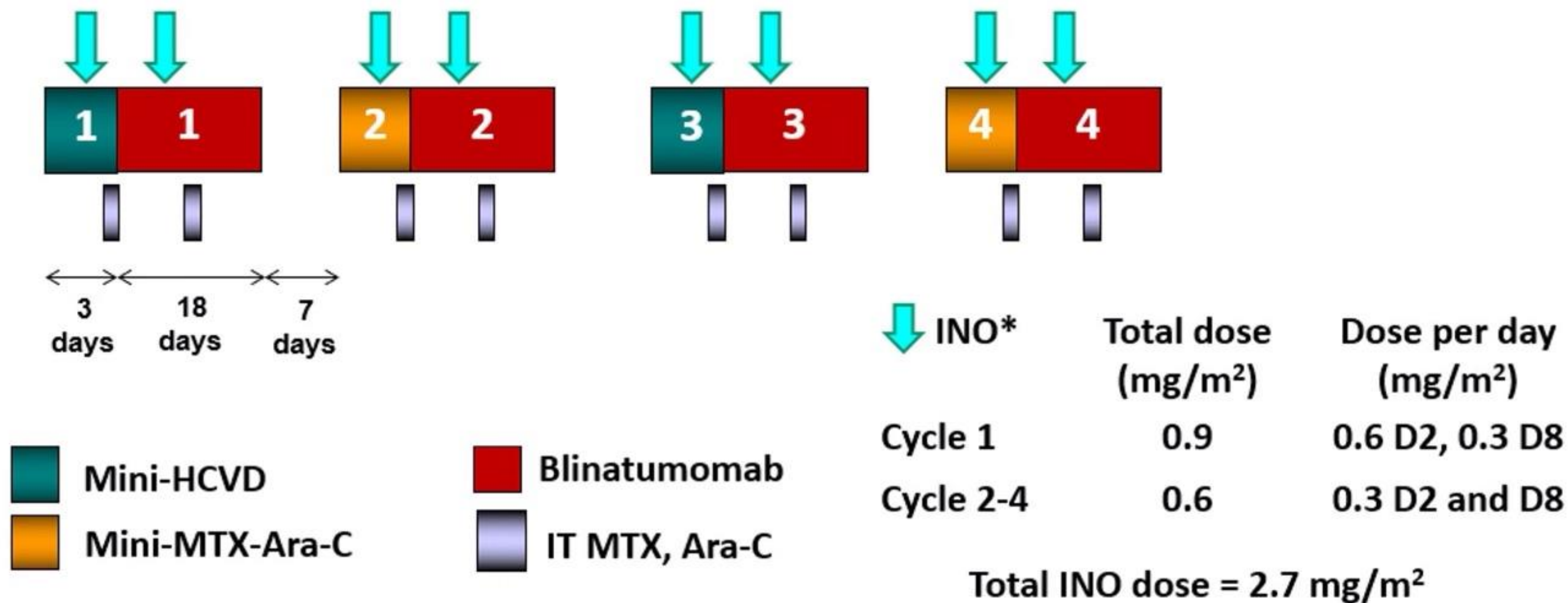
Hyper-CVD plus inotuzumab ozogamicin with sequential blinatumomab



Hyper-CVAD and Sequential Blinatumomab Without and With Inotuzumab

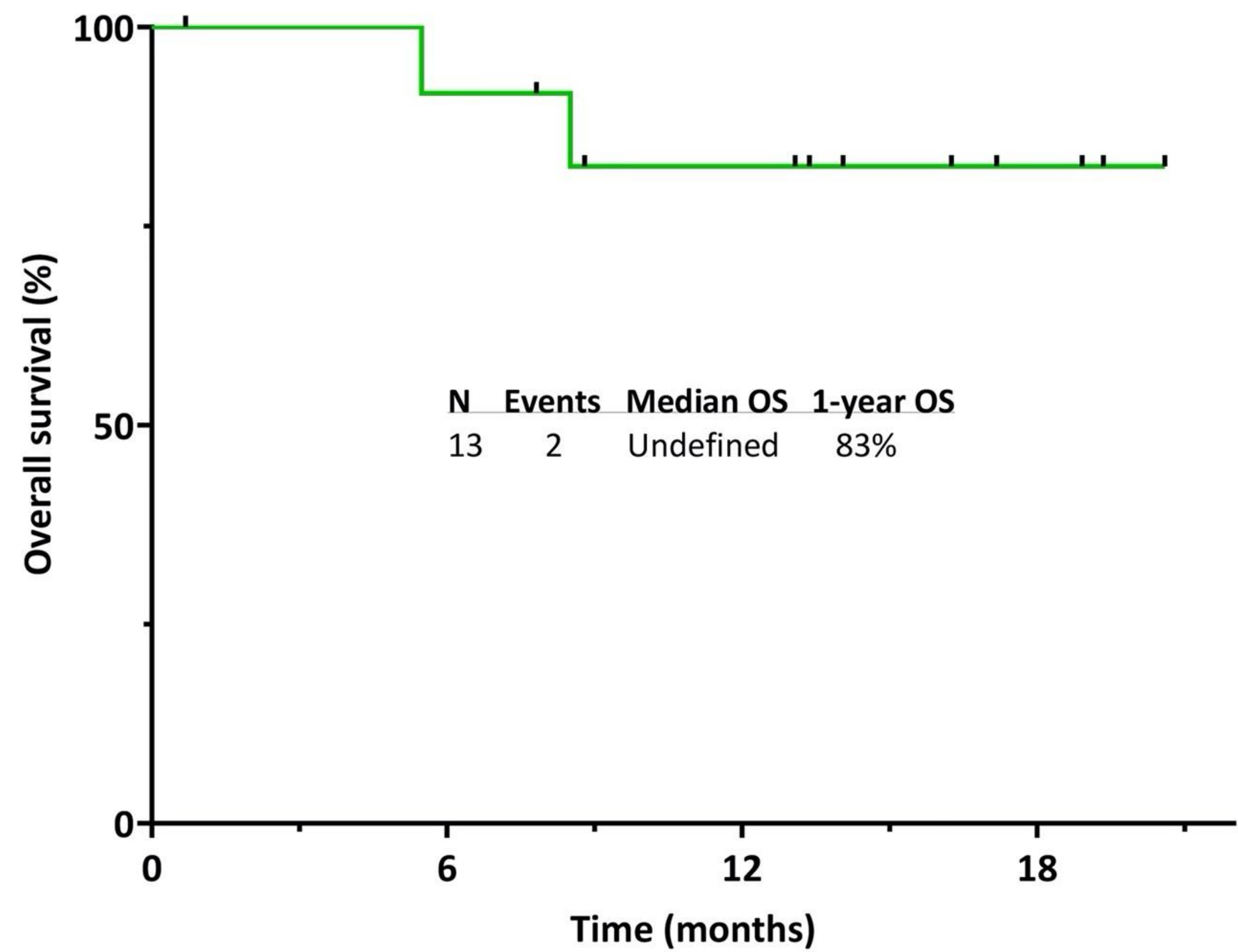


dose-dense mini-hyper-CVD, inotuzumab ozogamicin and blinatumomab regimen



*Ursodiol 300mg tid for SOS/VOD prophylaxis

dose-dense mini-hyper-CVD, inotuzumab ozogamicin and blinatumomab regimen

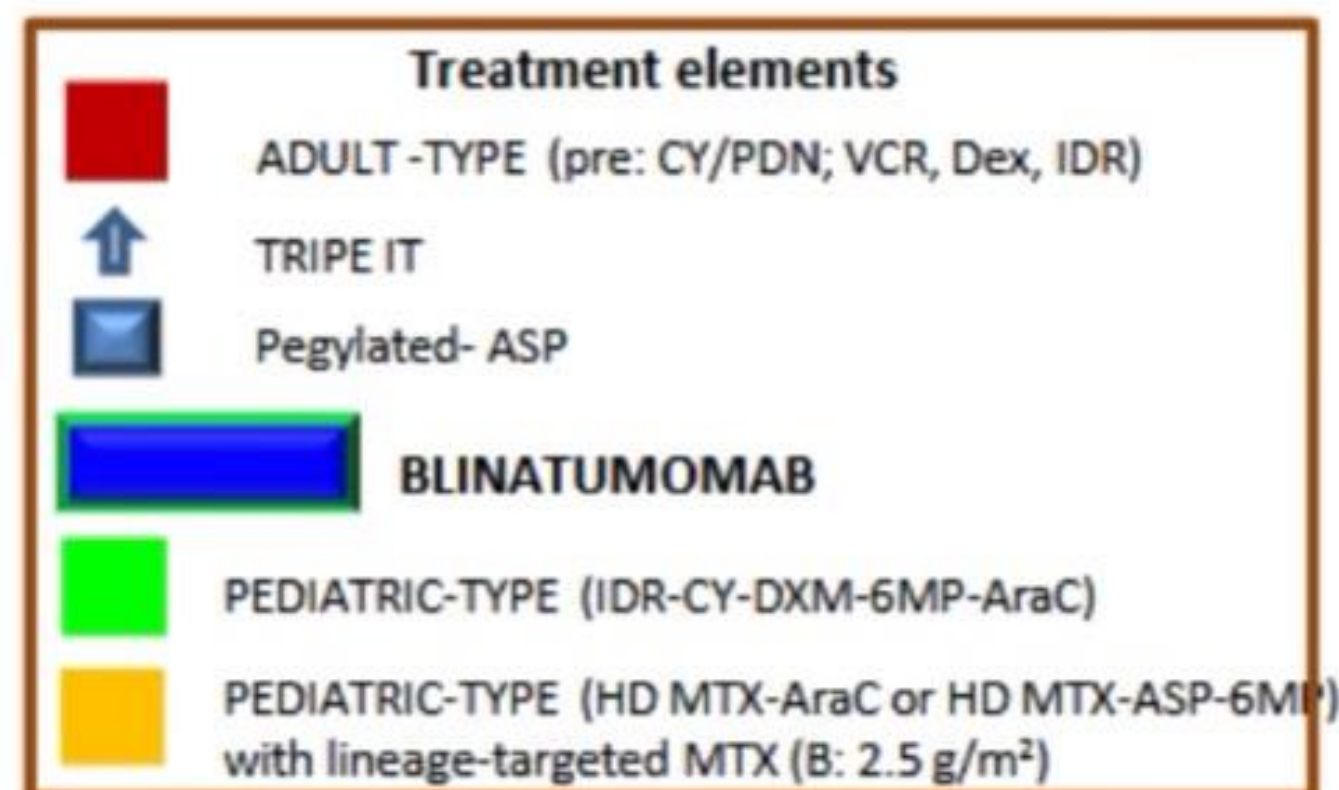
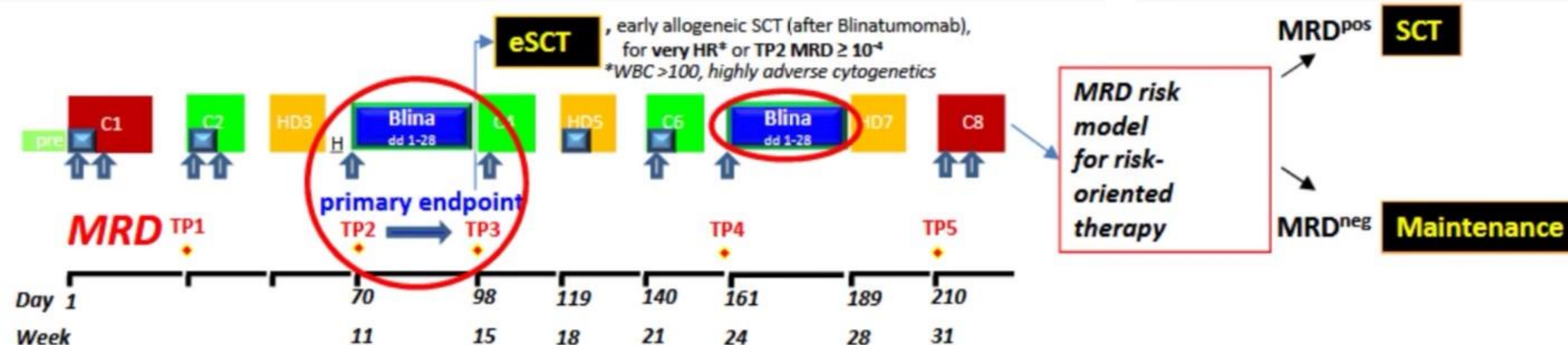


Response N (%)	Frontline (N=9)	MRD-positive consolidation (N=4)	Relapsed/refractory (N=8)
CR/CRi rate [#]	9 (100)	-----	5 (63)
MRD negativity by flow [*]			
After cycle 1	9 (100)	3/3 (100)	5/5 (100)
At any time	9 (100)	3/3 (100)	5/5 (100)
MRD negativity by NGS			
After cycle 1	4/6 (67)	2 (50)	-----
At any time	7/7 (100)	3 (75)	
CAR T-cell consolidation	0	1 (25)	0
AlloSCT consolidation	0	2 (50)	5 (63)

GIMEMA LAL2317 phase 2 study

A. Induction/consolidation, Blinatumomab, MRD study and early SCT

B. Final MRD-oriented therapy



- The number of patients required to evaluate an increase of MRD negativity from 60% (P0) to 75% (P1) is 85.
- Considering approx. 85% CR rate, 75% evaluable for MRD, expected loss of 10%, the total number of patients to enrol is 149.

GIMEMA LAL2317 phase 2 study

Context of Research

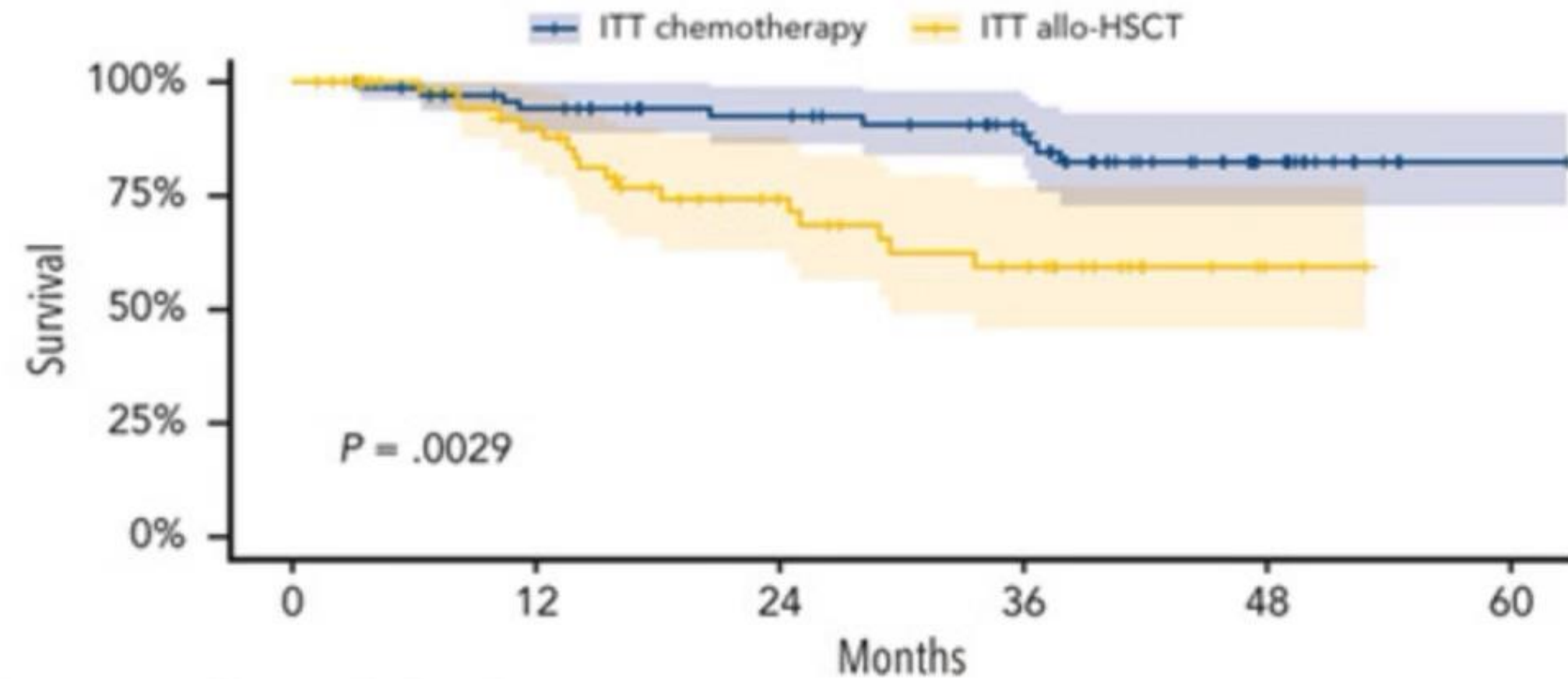
- **Blinatumomab** is a CD19/CD3 bispecific T-cell engager that has shown efficacy in Ph⁻ B-lineage acute lymphoblastic leukemia (**B-ALL**)
- We designed a prospective **phase 2 study** consisting of a **chemotherapy-blinatumomab sequence** for untreated adult patients with Ph⁻ CD19⁺ B-ALL

Patients and Methods

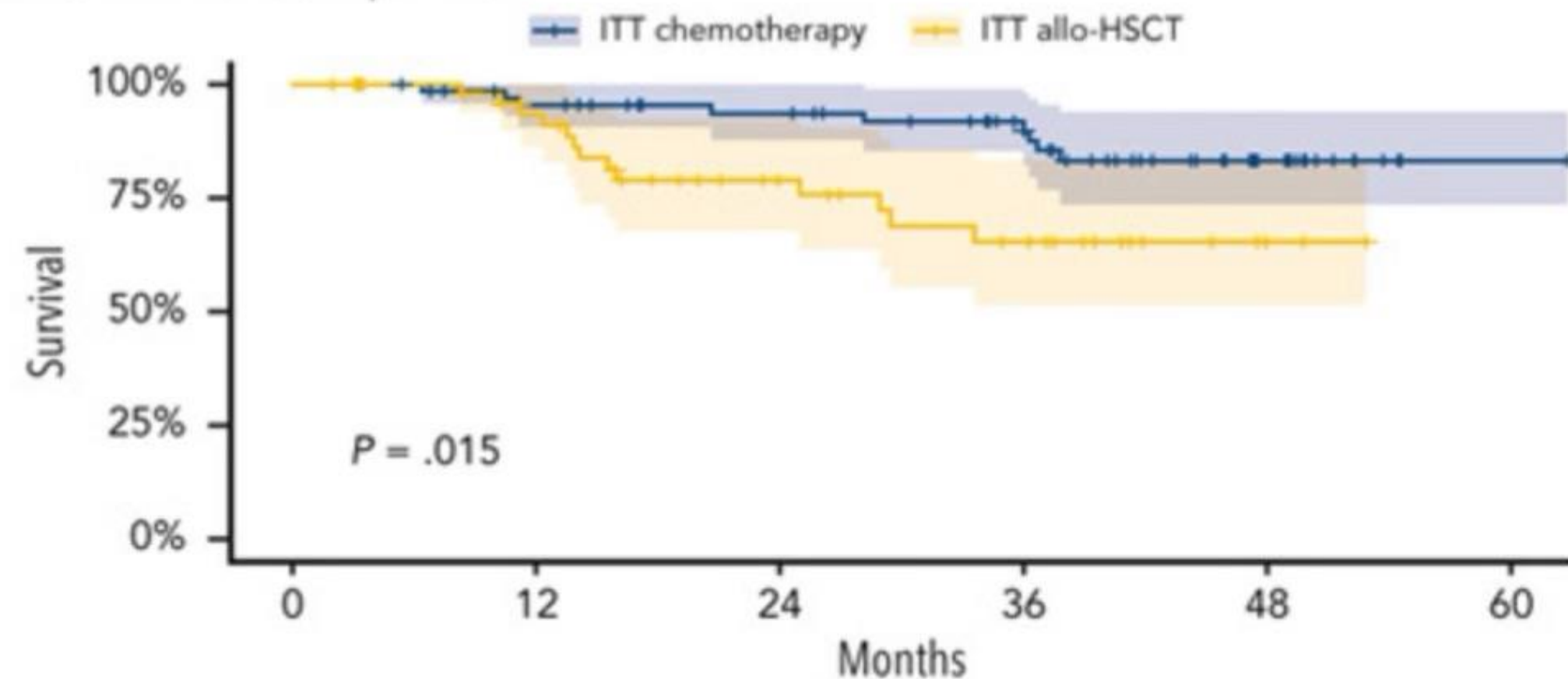
- Details at **ClinicalTrials.gov # NCT03367299**
- 2 cycles of intravenous blinatumomab were administered after chemotherapy cycles 3 and 6
- **The primary endpoint was the number of patients who experienced molecular MRD negativity**
- 149 B-ALL pts were enrolled, 132 entered remission, and 122 received blinatumomab
- **MRD negativity increased from 72% to 93% ($P < .001$) after blinatumomab**

Survival Outcomes

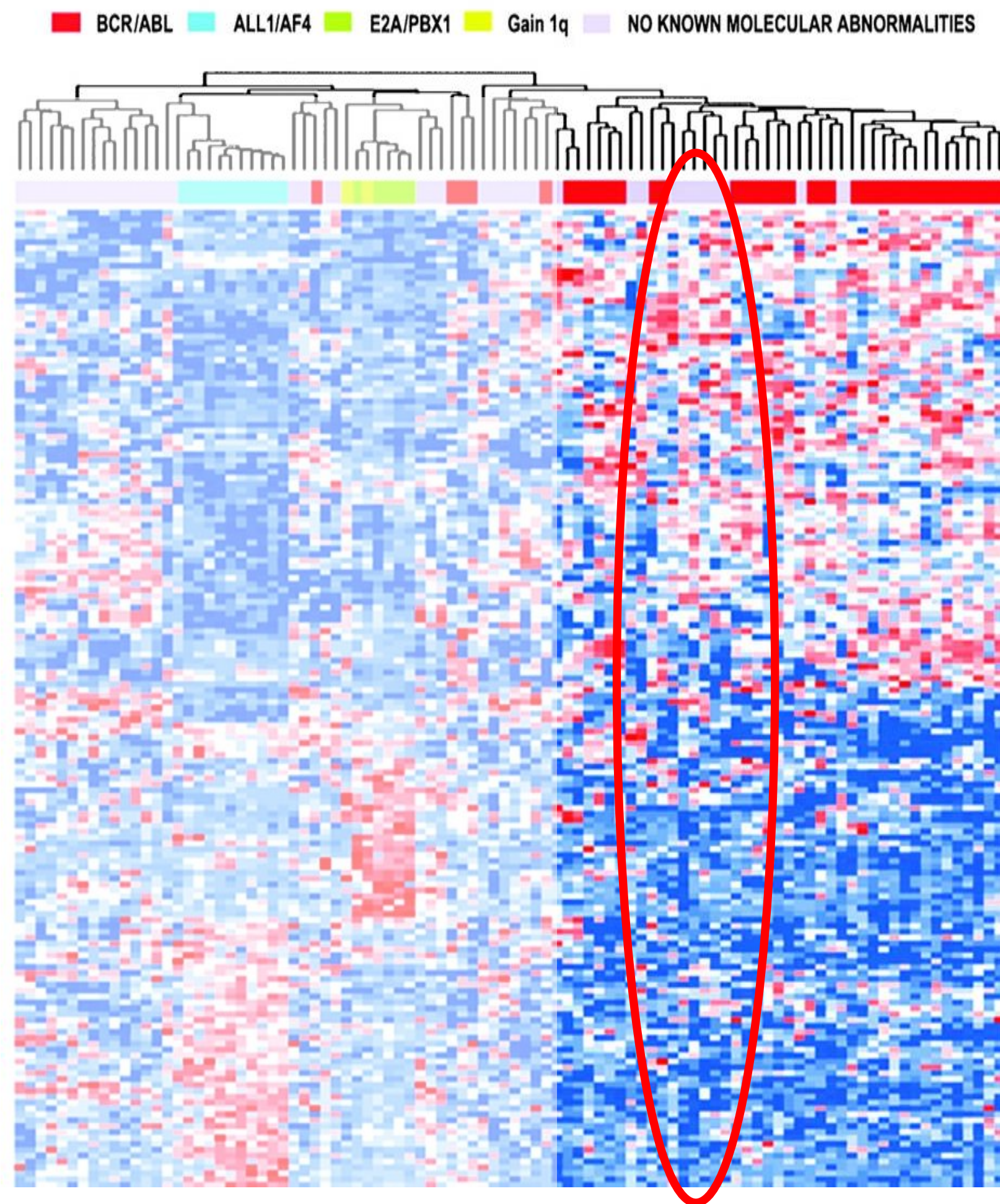
- Patients achieving remission, risk-stratified for allogeneic transplantation or chemotherapy according to the GIMEMA risk model



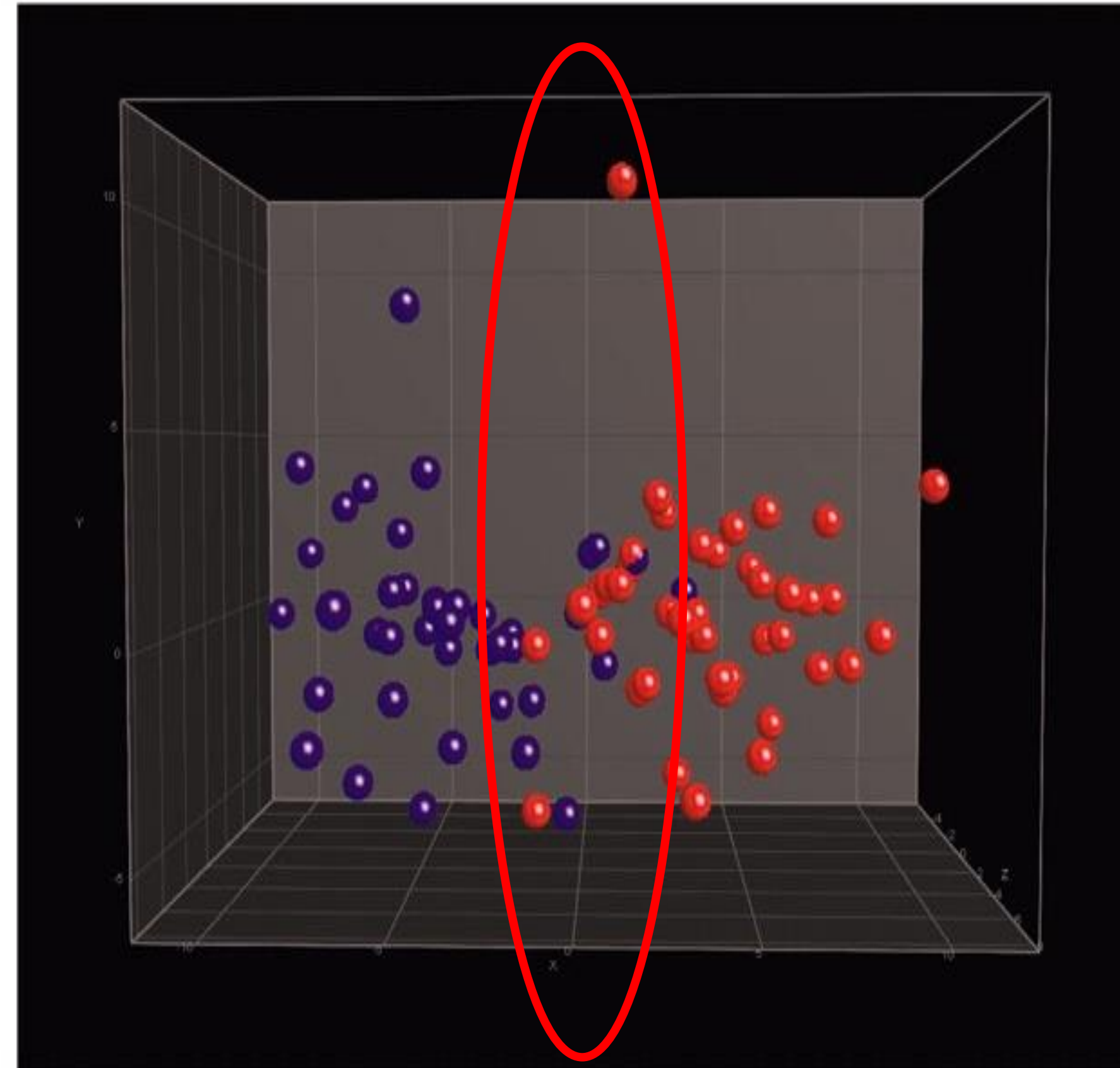
- Blinatumomab recipients



Ph1 Like First report in adult ALLs



Chiaretti et al, CCR 2005



Haferlach et al, Blood 2005

2005: first identification, by GEP, of a subset of adult B-lineage ALL clustering together with *BCR/ABL1*+ ALL cases

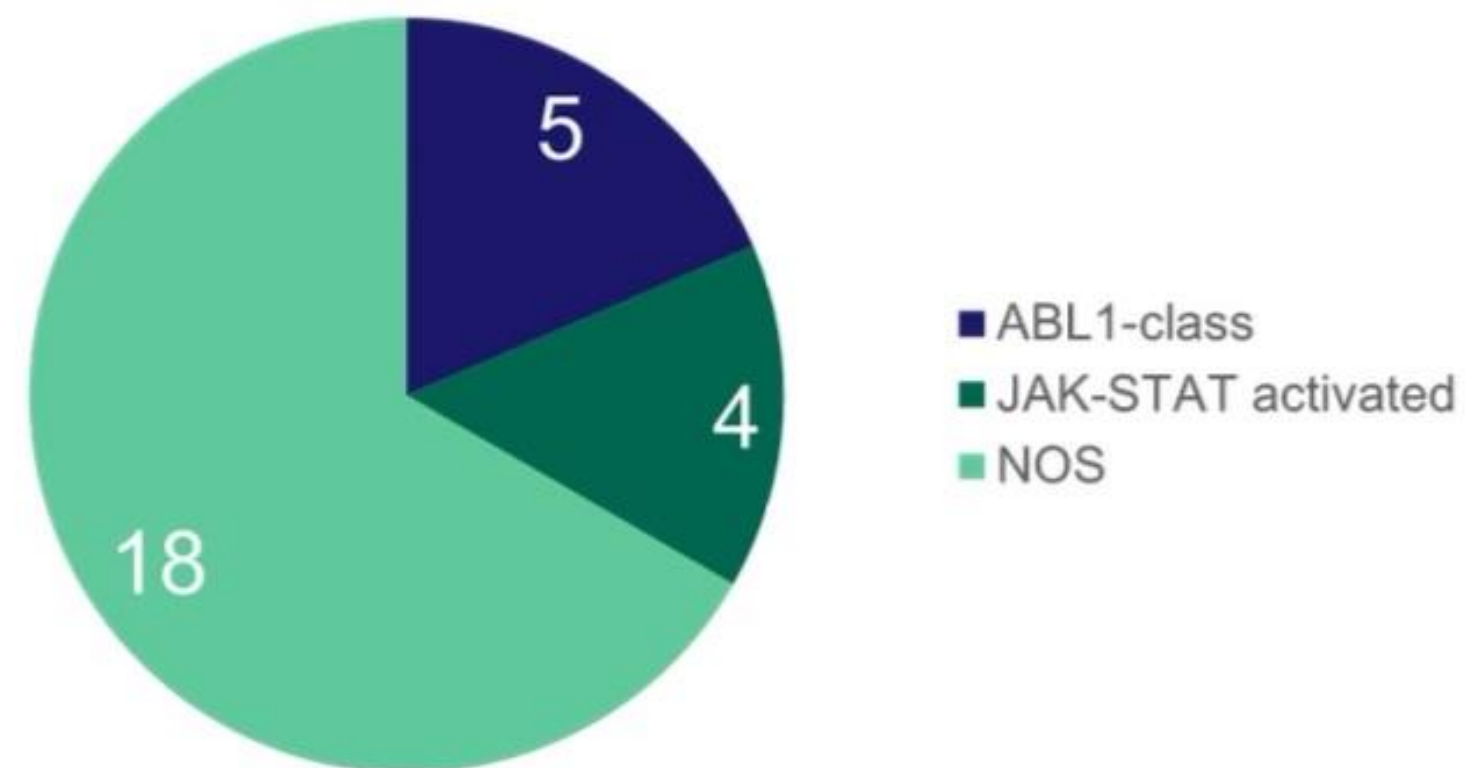
GIMEMA ALL2922 trial: Molecular features

Targeted RNA sequencing performed in 27/32 patients
(2 ongoing)

Rearrangements identified in 9/27 (33%):

- 2 *EBF1::PDGFRB* (1 with additional *ARHGAP27::IKZF1*)
- 1 *MEF2D::CSF1R*
- 1 *JAK2::ATF7IP*
- 2 *ZC3HAV1::ABL2*
- 1 *CLTA::ZCCHC7*
- 2 *PAX5::ZCCHC7*

3 additional *CRLF2*-r patients detected by FISH



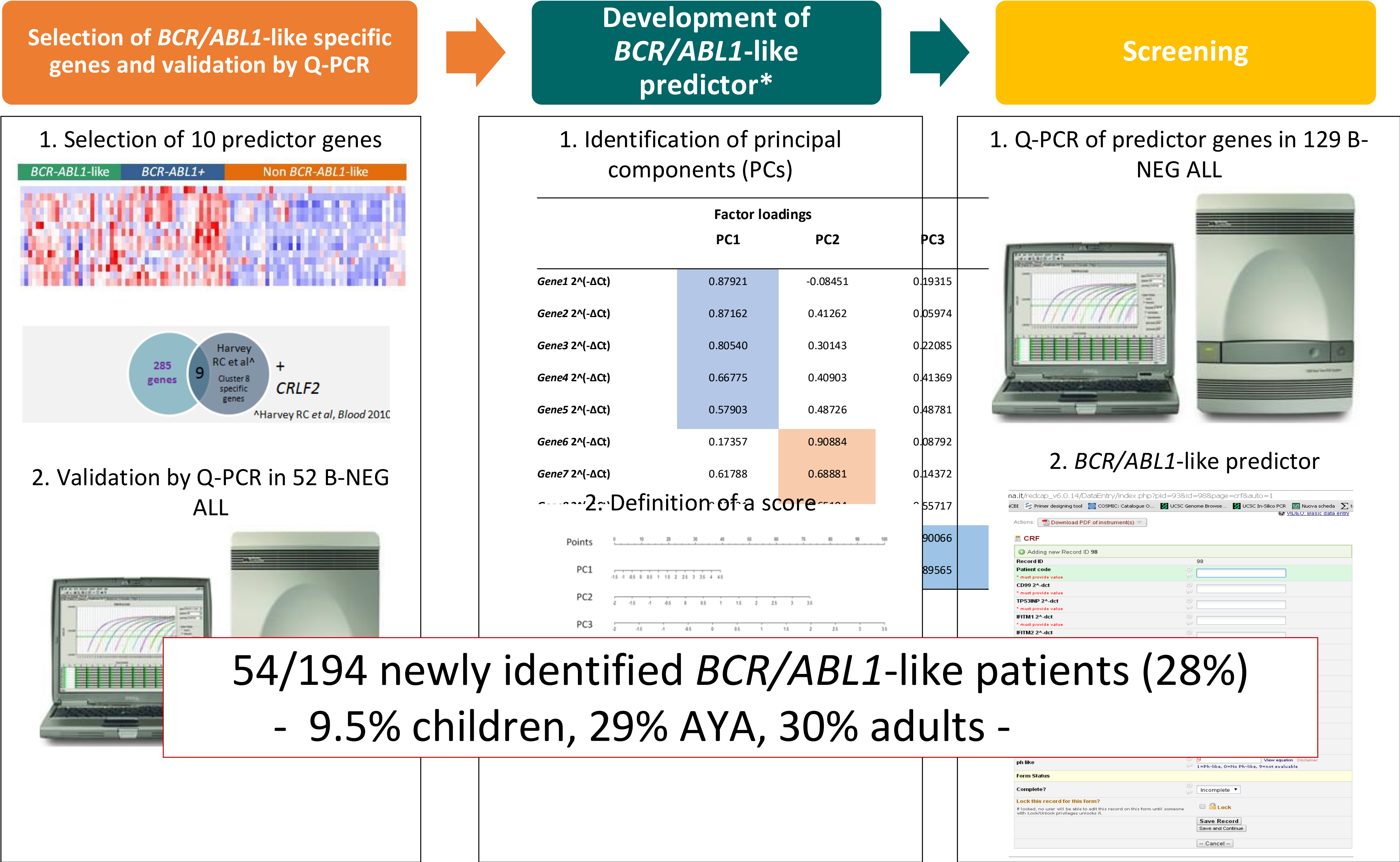
Copy number aberration by MLPA on
26/30:

- 9 *IKZF1*^{plus} (*IKZF1*, *PAX5* and/or *CDKN2A/2B* deletions)
- 4 *IKZF1*^{loss} only

CRLF2 expression:

- 14 HIGH (5 *IKZF1*^{plus}) 44%
- 18 LOW (3 *IKZF1*^{plus}) 56%

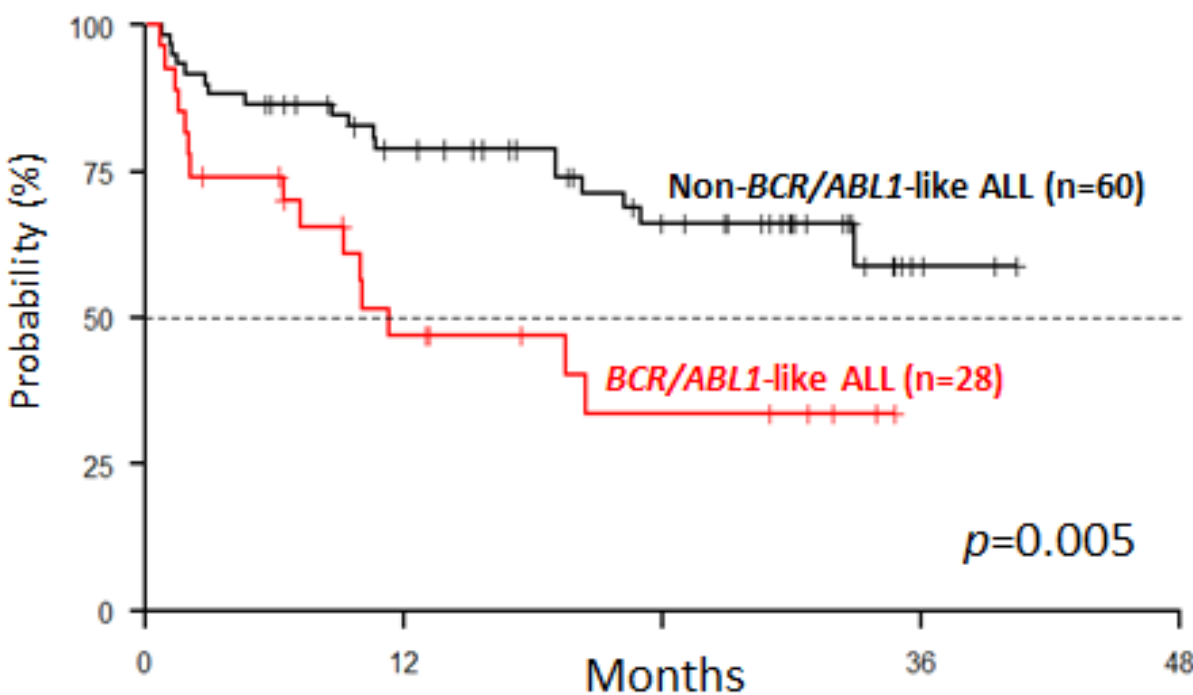
Development of the BCR/ABL1-like predictor and screening



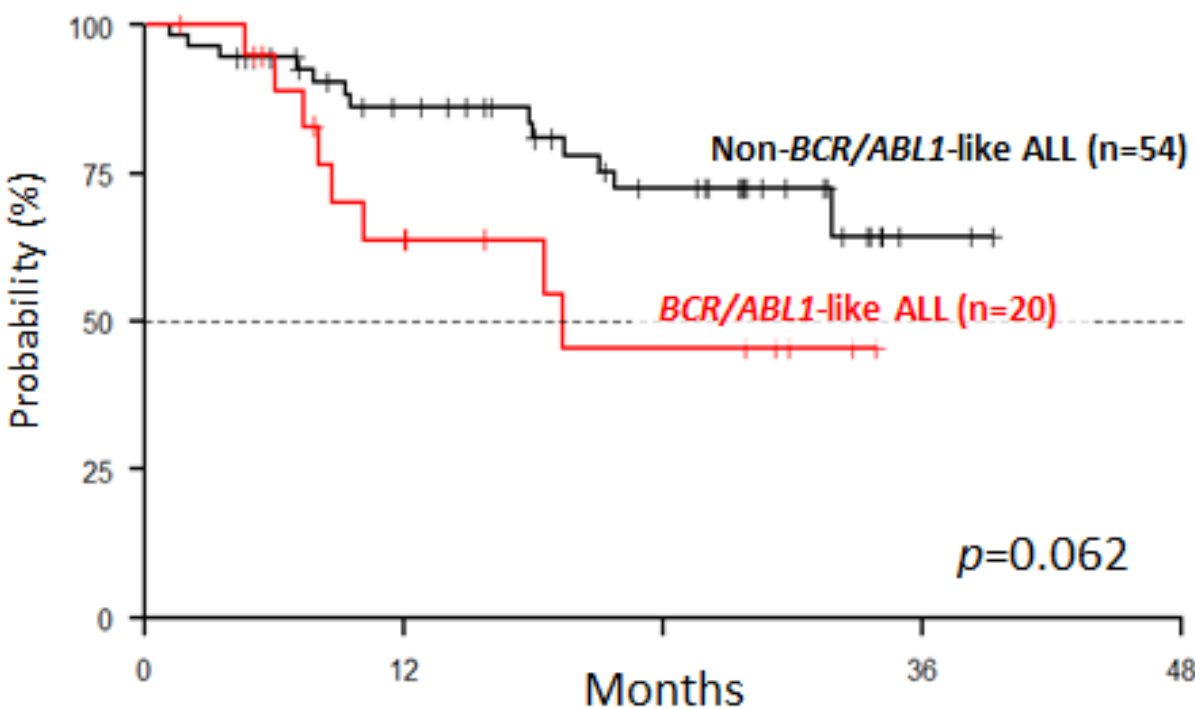
GIMEMA LAL1913: outcome according to Ph-like

28/88 (31.8%) <i>BCR/ABL1</i> -like cases					OR (95%CI)	
		<i>BCR/ABL1</i> -like	Non- <i>BCR/ABL1</i> -like	<i>p</i> -value	<i>BCR/ABL1</i> -like vs non- <i>BCR/ABL1</i> -like	4.5 (1.373-15.508)
No		28	60			
CR (%)	No CR	7 (25.9)	5 (8.5)	0.044		
	CR	20 (74.1)	54 (91.5)			
TP1_MRD (%)	TP1 MRD positive	14 (77.8)	19 (41.3)	0.012		
TP2_MRD (%)	TP2 MRD positive	9 (52.9)	9 (20.5)	0.029		
TP3_MRD (%)	TP3 MRD positive	5 (41.7)	5 (13.5)	0.05		

Event-free survival at 24 months



Disease-free survival at 24 months



	HR (95%CI)	<i>p</i> -value
<i>BCR/ABL1</i> -like vs non- <i>BCR/ABL1</i> -like	2.3 (1.124-4.92)	0.023

BCR/ABL1-like status is ALL is characterized by a lower CR rate, MRD persistence and shorter survival also in a pediatric-oriented and MRD-driven clinical trial.

The prognostic role of the *BCR/ABL1*-like status is independent from the other clinico-biological and genetic features

Outcome of GIMEMA LAL2317 according to Ph-like status

31 Ph-like cases identified, median follow-up 13 months (0.5-31)

		Post-blinatumomab 1 MRD (w14)		
Characteristic	Overall (N)	MRD _{neg}	MRD _{pos}	p-value
Post-chemo #3 MRD (w10), n (%)	94	89	5	0.001
MRD _{neg}	68	68 (100%)	0 (0%)	
MRD _{pos}	26	21 (81%)	5 (19%)	

95% MRD_{neg} after chemo #3 and blinatumomab 1

81% MRD_{pos} became MRD_{neg} after blinatumomab 1

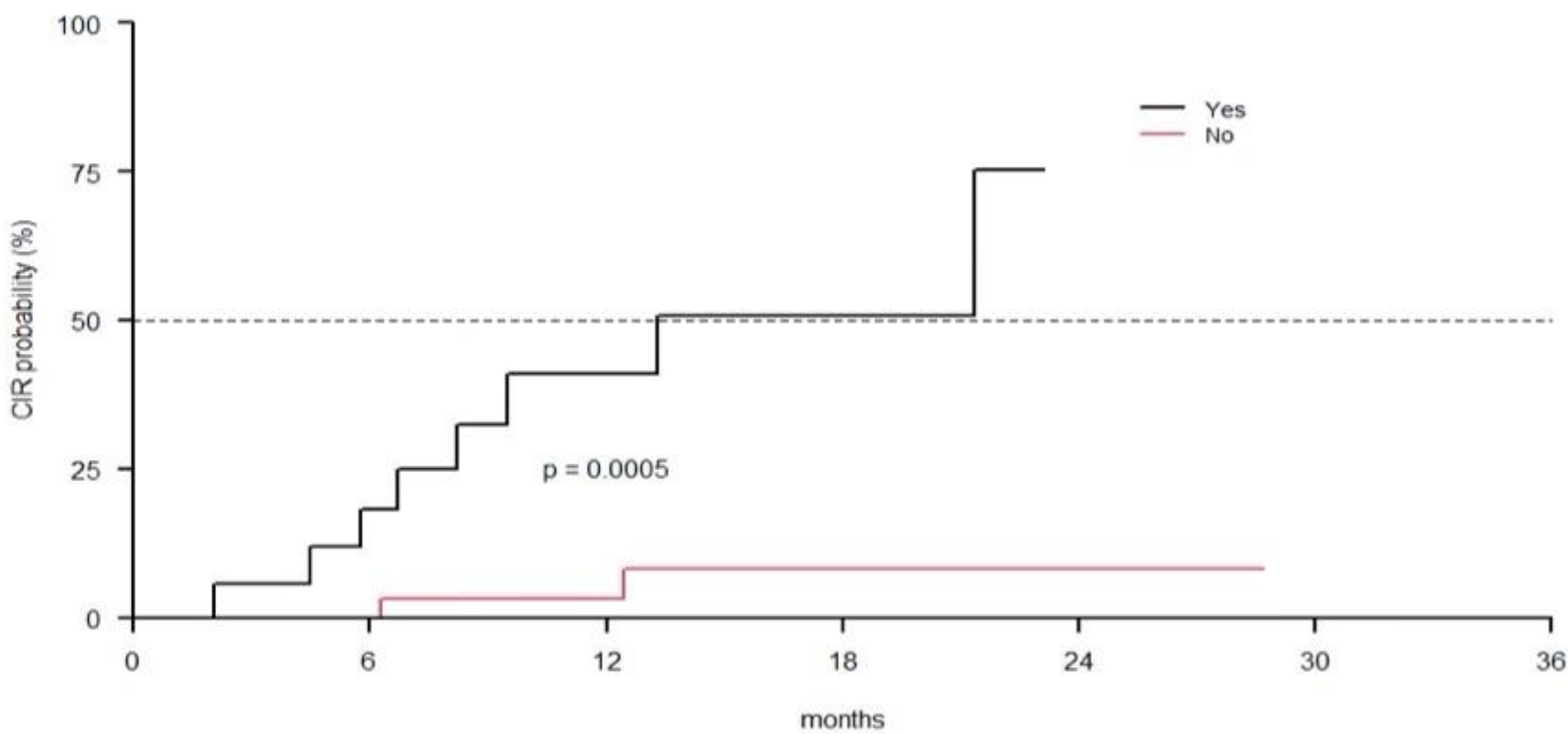
– incl. **10/10 (100%)** Ph-like ALL

4 18-40 Y

3 WBC > 30x10⁹/l

2 *KMT2A*+

2 *IKZF1* del

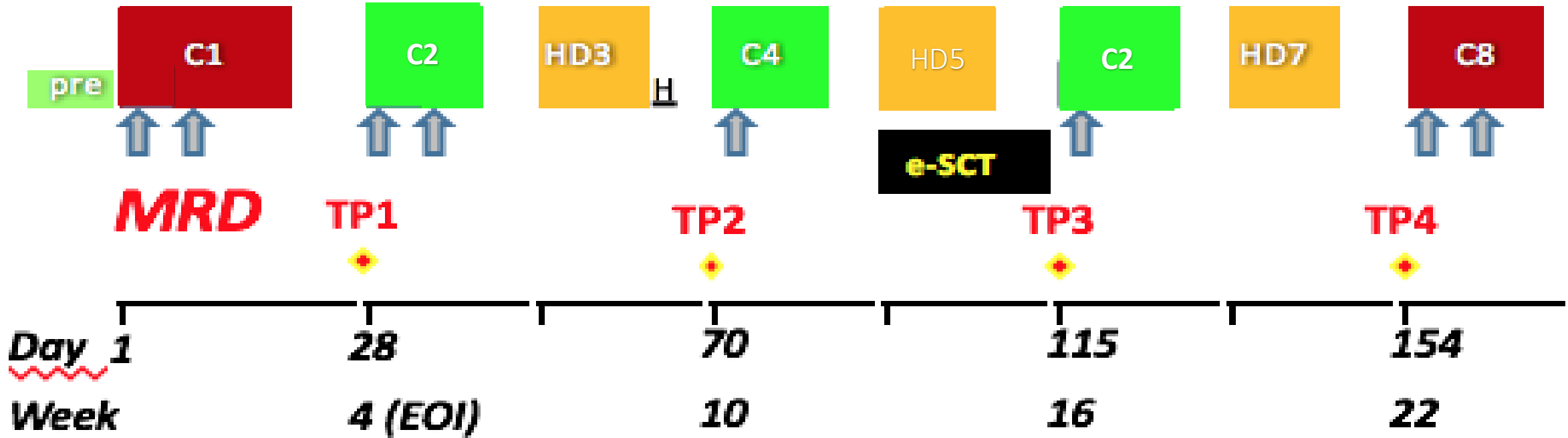
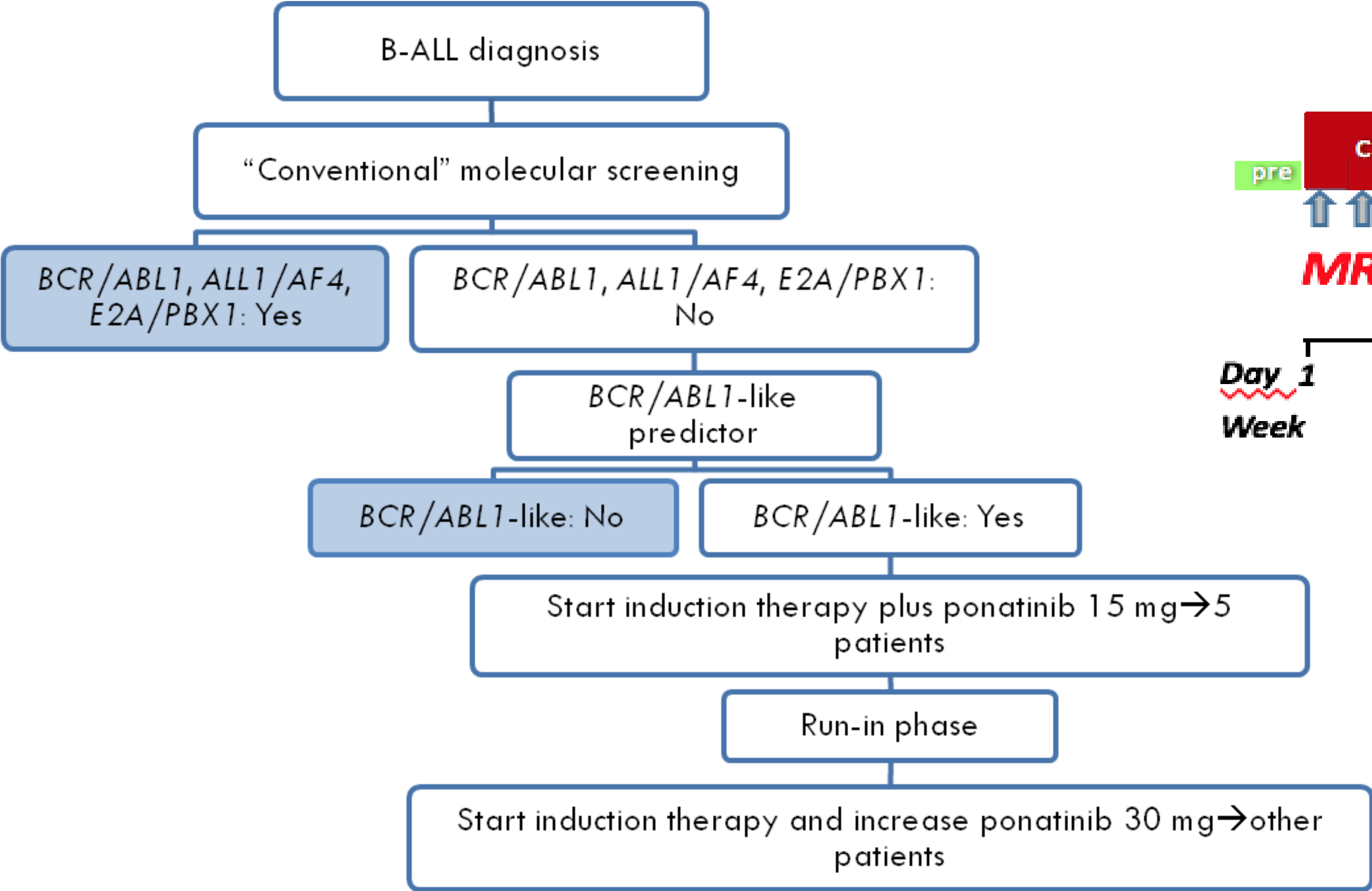


1-year relapse rate

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

Combination of Ponatinib Plus Chemotherapy As Frontline Treatment For Patients With BCR/ABL1-Like Acute Lymphoblastic Leukemia (BCR/ABL1-Like ALL) - BALLik

GIMEMA ALL2922



- Same backbone of GIMEMA LAL1913
- Sample size: 32 patients, enrolling
- Removal of ASP
- Introduction of ponatinib
- Age adjusted treatment

GIMEMA ALL2922 trial.

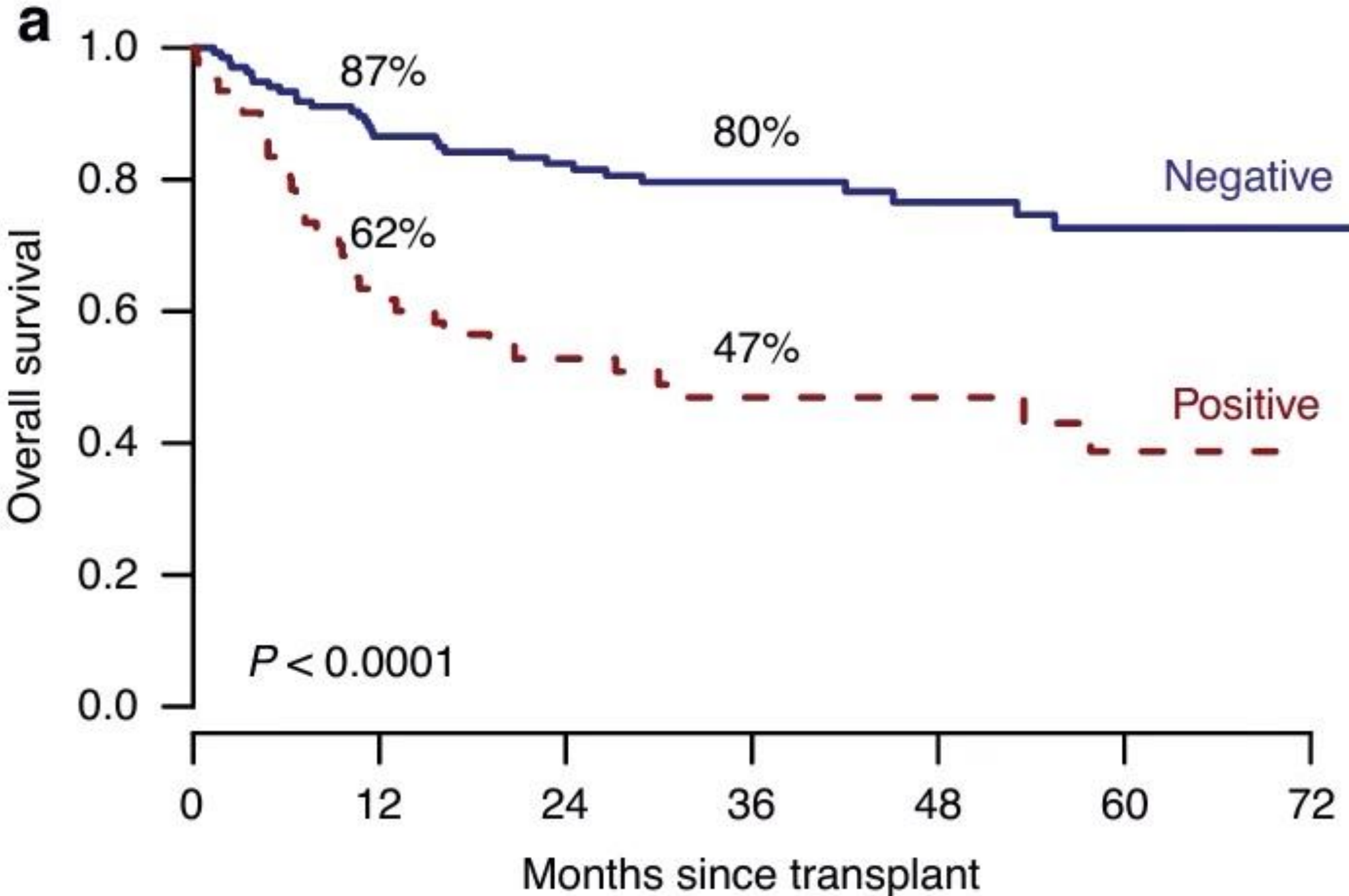
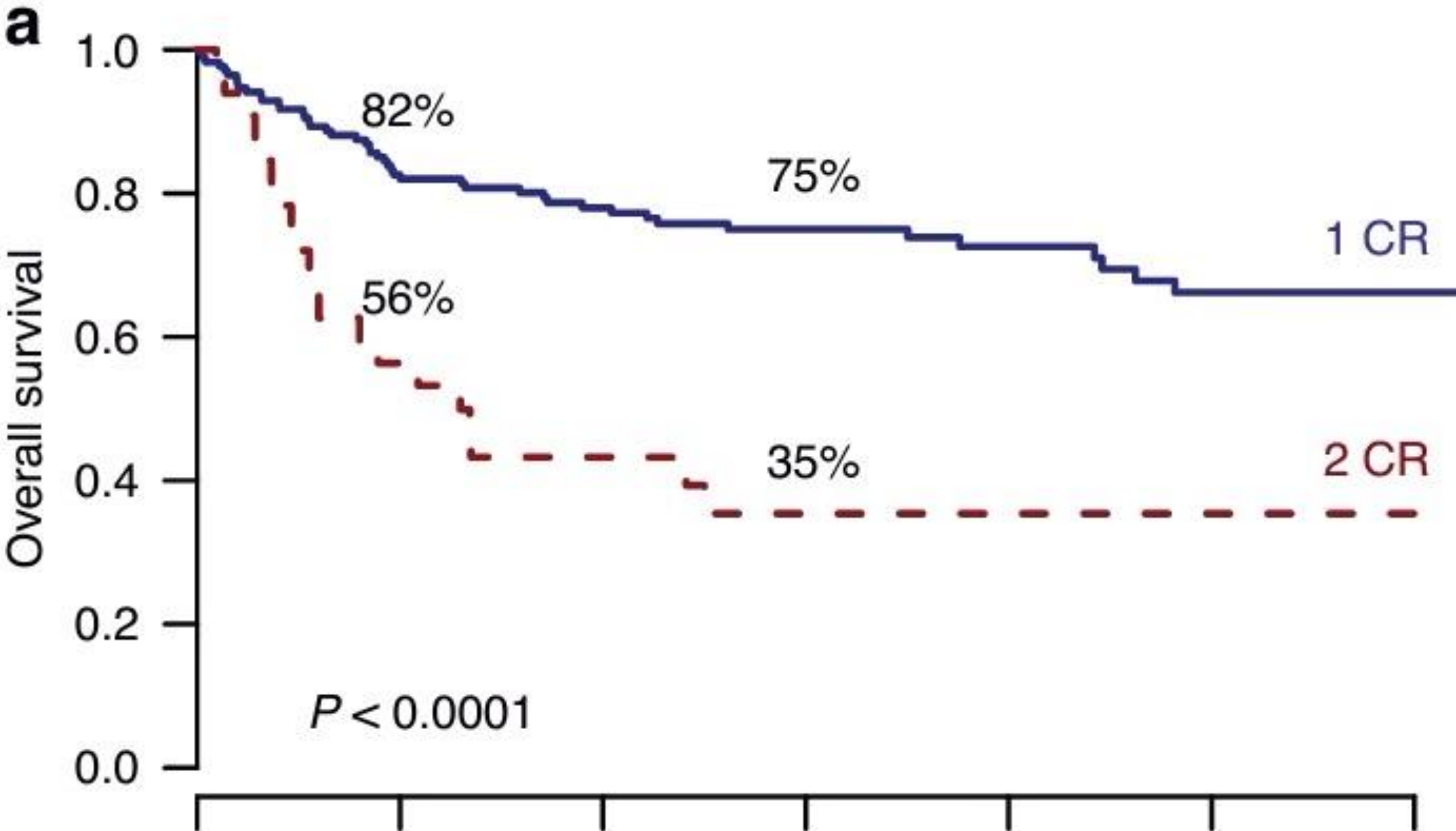
End of induction (C1-C2)	N=32
Complete remission (CR)	24 (83%)
Refractory	5 (15%)
Early Death	0 (0%)
Off study	1 (3.4%)
Ongoing	2

Transplanted in-study	N=11
Age, median (range)	32 (18-64)
TP2 MRD Positive	2 (15%)
Median time to transplant, months (range)	5.3 (3.9-9.7)
TBI, n(%)	9 (75%)

1-year EFS (71%) and DFS (85%)

MRD Response	MRD POS	MRD NEG	N*PTS
TP1	14 (64%)	8 (36%)	22
TP2	12 (60%)	8 (40%)	20

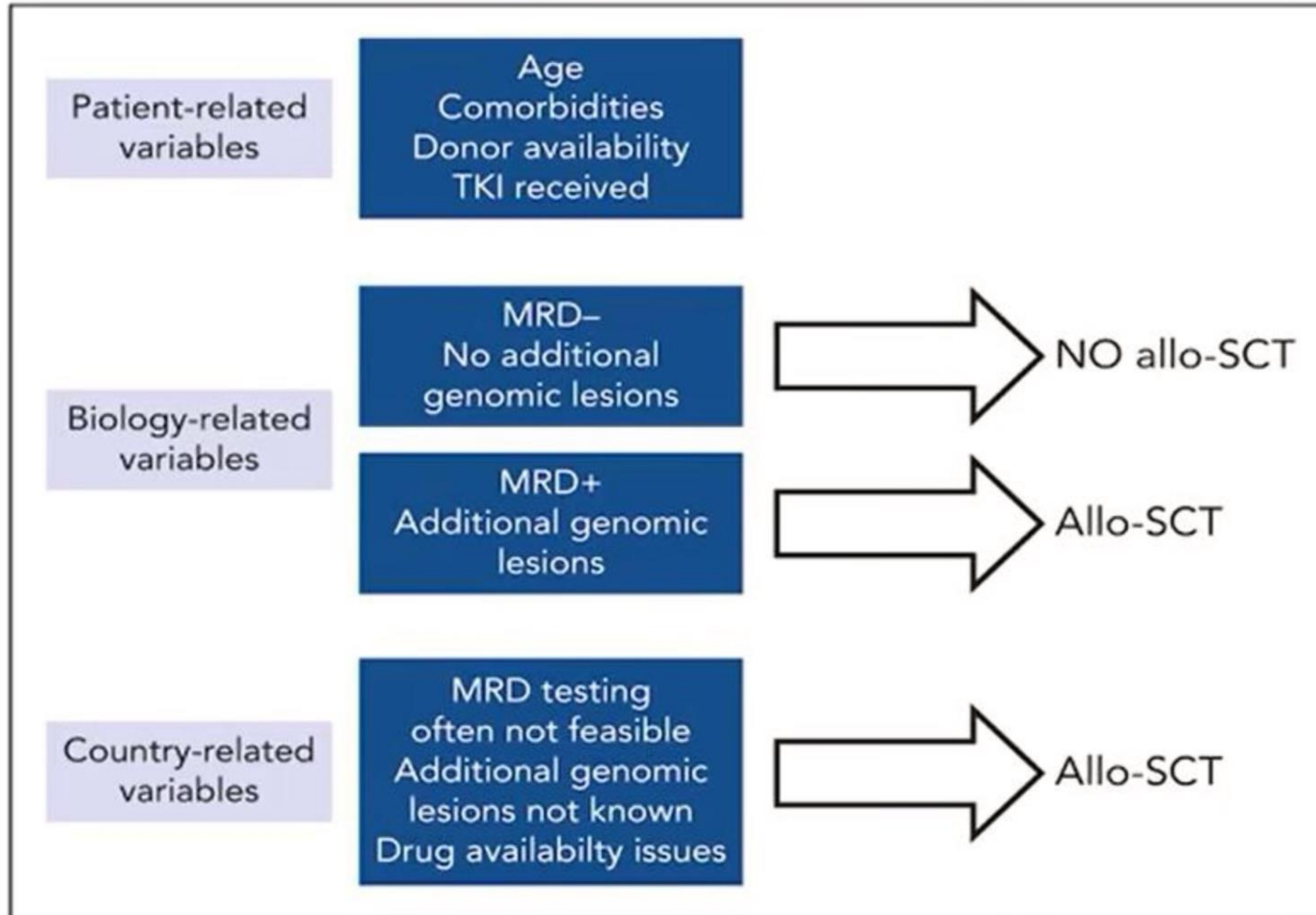
Outcomes of alloHSC in Ph neg ALL treated GIMEMA 1913 protocol. A Campus ALL study



	Overall survival	HR (95% CI)	P value
Age ≥ 55 vs <55		1 (0.45-2.19)	0.99
Lineage T vs B		1.1 (0.62-1.94)	0.74
Clinical risk HR vs SR		0.81 (0.37-1.77)	0.59
Clinical risk VHR vs SR		0.61 (0.32-1.17)	0.14
Remission at transplant CR2 vs CR1		2.22 (1.2-4.13)	0.01
MRD pre-transplant Pos vs Neg		2.8 (1.64-4.79)	0.0002
Conditioning regimen RIC vs MAC		1.37 (0.64-2.95)	0.42
TBI		1.01 (0.57-1.81)	0.96

0.1 1 10

Criteria for selection of allo-HSCT



How I treat older patients with Ph/BCR-ABL–negative acute lymphoblastic leukemia

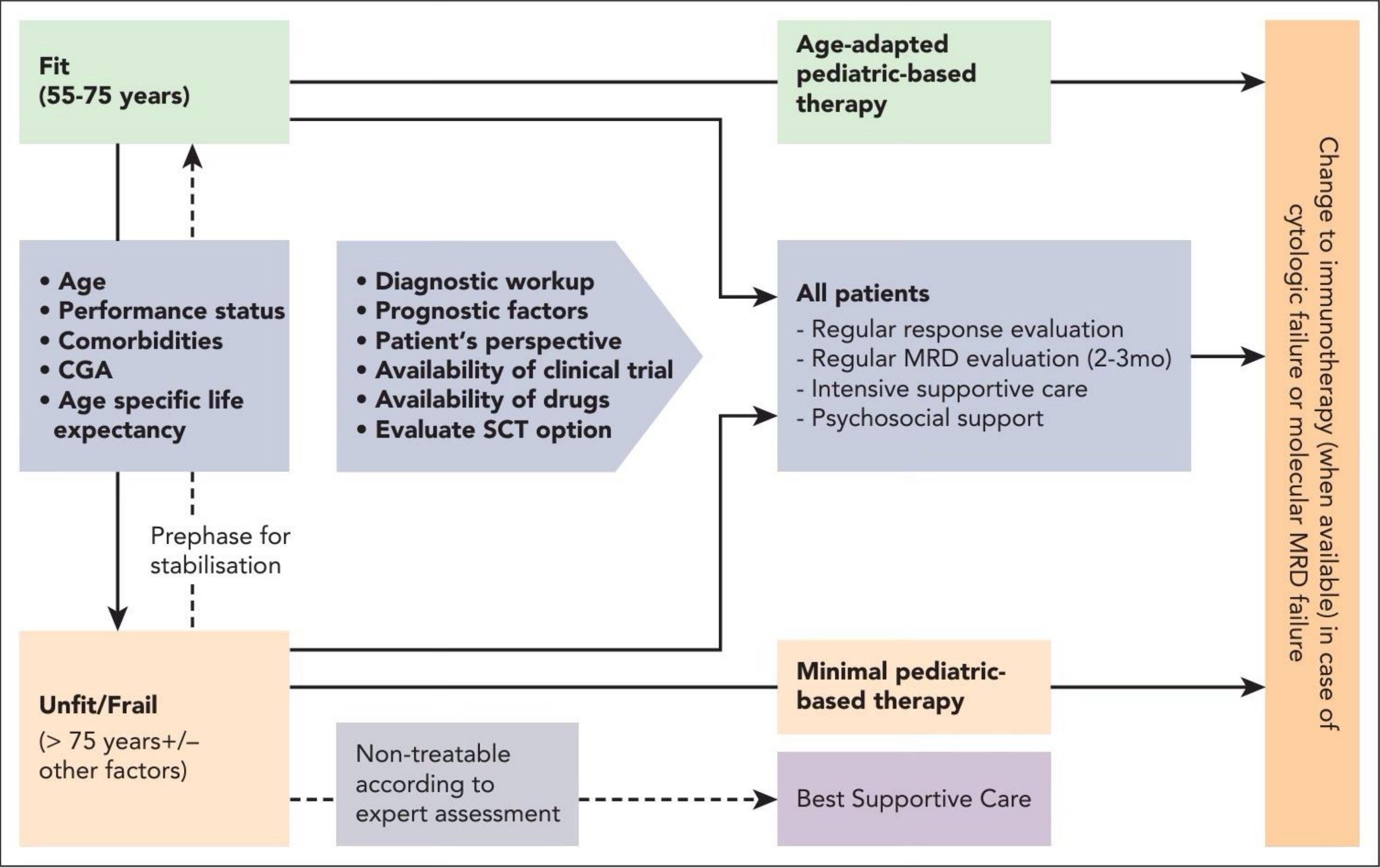


Table 1. Incidence of comorbidities (HCT-CI) in older patients

Type of comorbidity	Younger patients (<55 y), %	Older patients (>55 y), %	Frail patients, %
Arrhythmias	<1	12	22
Cardiac disease	2	19	42
Pulmonary (moderate)	8	14	28
Hepatic (mild)	8	11	14
Prior malignancies	2	25	22
Diabetes	4	22	22
Obesity (BMI >35 kg/m ²)	9	11	14
Infections	15	18	22
Low HCT-CI risk score	54	25	8
High HCT-CI risk score	18	50	59

How I treat older patients with Ph/BCR-ABL–negative acute lymphoblastic leukemia

GÖKBUGET and STEFFEN Blood 2025

Table 2. Results of chemotherapy and antibody therapy in older patients with Ph negative ALL

Author	Year	Feature	Age, y	Patients (N)	CR/CRi	Early death	Failure	Death in CR	CCR*	DFS/EFS*	OS†
Chemotherapy (selected recent trials)											
Hunault-Berger et al ⁴⁴ Ribera et al ⁴⁵ Gökbuget et al ⁴ Jabbour et al ⁴⁶	2011	CI-Dox	68 (55-77)	31	90%	7%	3%	32% (2 y)	32% (2 y)	n.r.	35% (2 y)
	Arm 1	PEG-Dox	66 (60-80)	29	72%	10%	17%	19% (2 y)	52% (2 y)		24% (2 y)
	Arm 2										
	2016	Ped based	66 (56-79)	54	74%	14%	14%	3%	30%	9% (5 y)	12% (5 y)
	2022	Ped based (total)	68 (56-86)	841	73%	14%	13%		37% (3 y)	n.r.	28% (5 y)
	Group 1	Original		593	72%	15%	13%				32%
	Group 2	Int.Cons. + MRD-based Blina		248	75%	9%	16%				50%
	2023	HCVAD ± rituximab	n.r.	60	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	27% (5 y)
Chemoimmunotherapy											
Stelljes et al ⁴⁷	2024	Ino-Chemotherapy C1: 0.8 mg/m ² day 1; 0.5 mg/m ² days 8, 15 C2-3: 0.5 mg/m ² days 1, 8, 15	64 (56-80)	43	100%	0%	0%	17% (3 y)	RR:27%	55% (3 y)	73% (3 y)
Chevallier et al ⁴⁸	2022	Ino-Chemotherapy C1: 0.8 mg/m ² day 1, 0.5 mg/m ² days 8, 15 C2: 0.5 mg/m ² days 1, 8	68 (55-84)	131	90%	3%	7%	18% (2 y)	n.r.	50% (2 y)	54% (2 y)
Gökbuget et al ⁴⁹	2023	Chemotherapy-Blina	66 (56-76)	50	85%	4%	11%	7.5%	83%	60% (3 y)	67% (3 y)
Advani et al ⁵⁰	2022	Blina	75 (66-84)	29	66%	n.r.	n.r.		0%	37% (3 y)	37% (3 y)
Jabbour et al ²³	2023	Ino-Chemotherapy ± Blina	68 (60-87)	80	99%	0%	1%	44%	80% (5y)	44% (5 y)	46% (5 y)
	Pat 1-6	C1: 1.3 mg/m ² day 3 C2-4: 0.8 mg/m ² days 3									
	Pat 7-34	C1: 1.8 mg/m ² day 3 C2-4: 1.3 mg/m ² day 3									
	Pat 35-49	C1: 1.5 mg/m ² day 3 C2-4: 1.0 mg/m ² day 3									
	Pat 50-	C1: 0.6 mg/m ² day 2, 0.3 mg/m ² day 8 C2-4: 0.3 mg/m ² days 2, 8									
Wieduwilt et al ⁵¹	2023	Ino-Blina C1: 0.8 mg/m ² day 1; 0.5 mg/m ² days 8, 15 C2 (CR): 0.5 mg/m ² days 1, 8, 15 C2 (No CR): 0.8 mg/m ² days 1, 8, 15	71 (60-84)	33	97%	n.r.	n.r.	9%		75% (1 y)	84% (1 y)

Predicting relapse in acute lymphoblastic leukemia

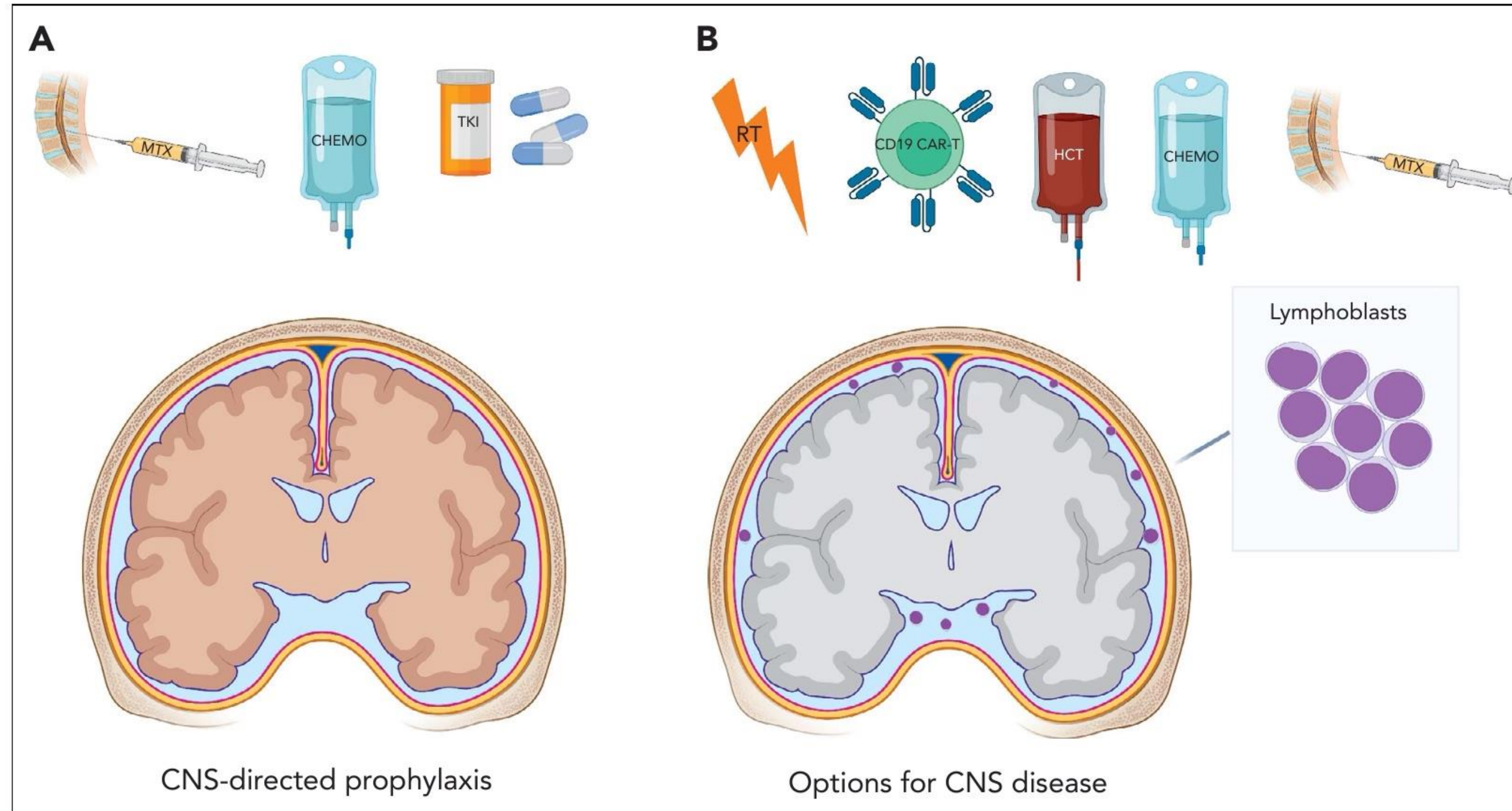
key studies demonstrating impact of mRD on outcomes in ALL.

Population	Methodology	Timepoint	Key findings	References
Adult, Ph-	Ig/TCR PCR	Post-induction	RFS and OS benefit for SCT in CR1 if post-induction MRD+ ($\geq 10^{-3}$); 3-year RFS benefit for MRD- vs MRD+ ($\geq 10^{-4}$) (85% vs 54%)	[12,13]
Adult, Ph-	Ig/TCR PCR	Post-consolidation	Worse OS if post-consolidation MRD+	[14]
Adult	Ig/TCR PCR	Multiple (<i>D</i> +11, <i>D</i> +24, week 16)	3 risk groups based on MRD (10^{-4}) at multiple time points: Low risk for relapse (MRD- at <i>d</i> +11 and <i>d</i> +24), intermediate risk for relapse (MRD+ at <i>d</i> +11 but MRD- at later time points), high risk for relapse (MRD+ through week 16)	[15]
Pediatric	MFLC, NGS	Post-induction	Post-induction MRD discordance (MFLC-/NGS+) at 10^{-4} have worse outcomes than if MFLC-/NGS-; Excellent outcomes if NGS- at 10^{-6}	[16]
Adult, Ph-	MFLC, NGS	Post-induction	Higher 5-year CIR for NGS+ vs NGS- (45% vs 0%).	[17]
Pediatric	MFLC, NGS	Pre-SCT	2-year CIR 0% vs 53% in NGS- vs NGS+; NGS better at predicting relapse compared to MFLC ($p<.0001$)	[18]
Adult	NGS	Pre-SCT	CIR increased if NGS+ at any level (HR 3.56; 95% CI 1.39-9.15)	[8]
Adult, Ph+	Bcr/Abl1 qPCR	3 months	MRD- had better OS ($p=.005$) and RFS ($p=.002$) compared to MRD+; No benefit for SCT if MRD-	[19,20]

How I prevent and treat central nervous system disease in adults with acute lymphoblastic leukemia

Study	Enrollment period	CNS involvement at diagnosis (%)	CNS-directed therapy	CNS relapse rates (%)
Hyper-CVAD ¹	1992-1998	7	CNS-negative: between 4-16 doses of IT chemotherapy (alternating MTX and ARA-C) over ~6 mo, depending on risk category* CNS-positive: twice weekly IT chemotherapy until CSF cleared (then IT prophylaxis per risk category), followed by remaining prophylaxis schedule plus 24-30 Gy cranial RT, if cranial nerve involvement Systemic therapy: dexamethasone, high-dose MTX, and high-dose ARA-C	4
MRC UKALL XII/ECOG E2993 ²	1993-2003	5	CNS-negative: IT MTX × 5 given through phase 2 (~2 mo) CNS-positive: weekly IT MTX until CSF cleared plus 24 Gy cranial RT and 12 Gy spinal RT Systemic therapy: L-asparaginase, 6-MP, and high-dose MTX	4
GRAALL 2005 ³	2006-2014	5	CNS-negative: IT MTX × 1 in prephase; ITT × 6 through late intensification (~6 mo) ± 18 Gy cranial RT† CNS-positive: ITT × 14 through first consolidation (~2 mo) plus 15 to 24 Gy cranial RT† Systemic therapy: L-asparaginase, high-dose ARA-C, dexamethasone, high-dose MTX, and 6-MP	5
CALGB 10403 ⁴	2007-2012	10.5	CNS-negative: IT ARA-C × 1 and IT MTX × 11 during the first 4 courses (~7 mo) of therapy, then continued during prolonged maintenance‡ CNS-positive: same total doses of IT chemotherapy but weekly during remission induction plus 18 Gy cranial RT Systemic therapy: pegaspargase, 6-MP, dexamethasone, and thioguanine	Not reported

How I prevent and treat CNS in ALL



Evidence of CNS activity of antibody-based therapeutics

Agent	Mechanism of action	Evidence of CNS activity*
Blinatumomab	CD3-CD19 bispecific T-cell engager	Limited: 1 retrospective series ⁸⁴
Inotuzumab ozogamicin	CD22 antibody-drug conjugate	None
Tisagenlecleucel	CD19 CAR T cells	Moderate: pooled post hoc analysis of prospective studies and multiple retrospective series ⁸⁵⁻⁸⁷
Brexucabtagene autoleucel	CD19 CAR T cells	Limited: extrapolated from experience with other CAR T-cell therapies

Refractory or relapsed adult ALL: Unmet need

- Survival rates are low in patients with r/r disease, and certain patients are at an extremely high risk for poor outcomes after disease relapse¹⁻³
- Several factors are associated with poor outcomes in r/r ALL:
 - Early relapse^{1,5,6}
 - Bone marrow relapse^{5,6,7}
 - Age: > 20 or > 30 years^{3,7}
 - Immunophenotype (ie, T-cell lineage)^{1,7}

	5-year Overall Survival, %			
	r/r Disease	Early Relapse ^a	Marrow Relapse	Extramedullary Relapse ^b
Pediatric	~30	21.5	24.1	55.9
Adult	~7-10	5	6	14

1. Ko RH, et al. J Clin Oncol. 2010;28(4):648-654.

2. Oudot C, et al. J Clin Oncol. 2008;26(9):1496-1503.

3. Fielding AK, et al. Blood. 2007;109(3):944-950. (External Use - Display only !Special terms)

4. Nguyen K, et al. Leukemia. 2008;22(12):2142-2150.

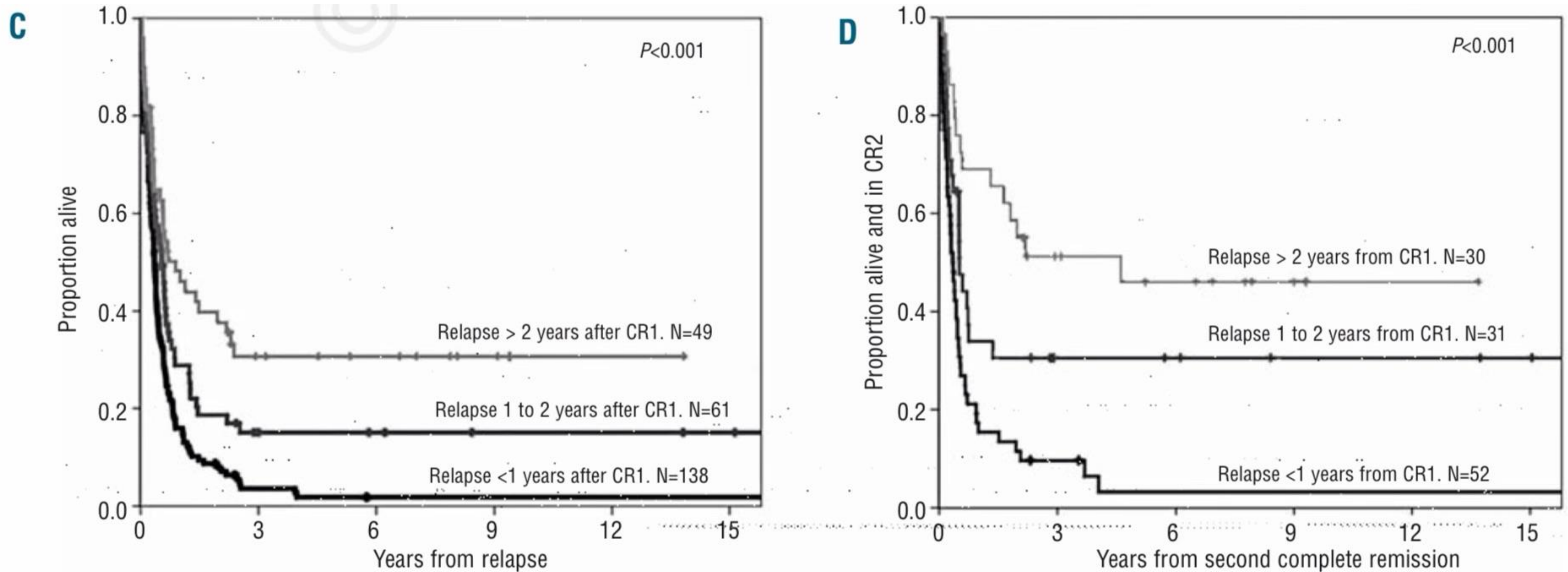
5. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Lymphoblastic Leukemia. V1.2018.

6. Pediatric Acute Lymphoblastic Leukemia, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network , Vol.18(1), p.81

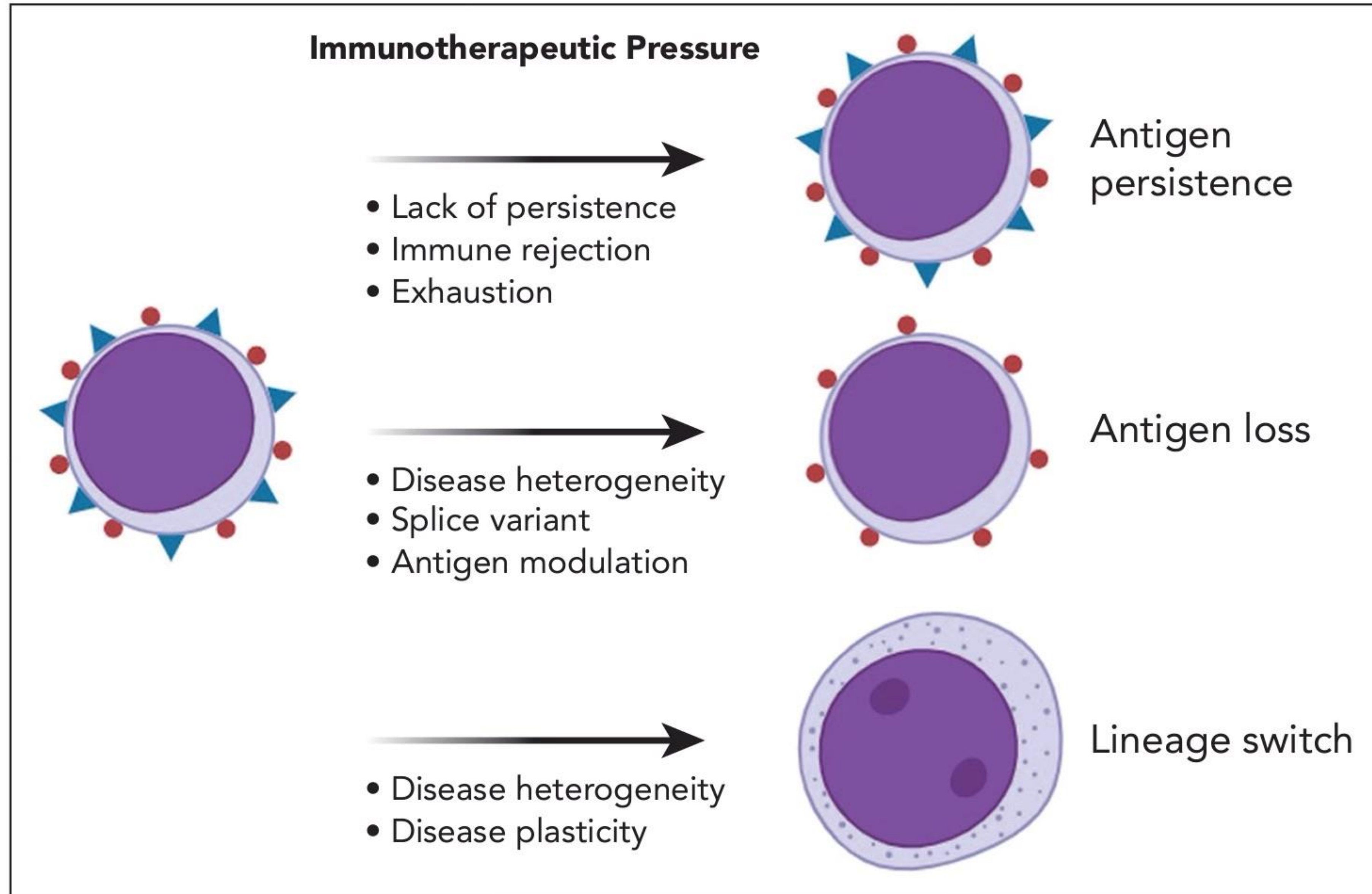
7. Tallen G, et al. J Clin Oncol. 2010;28(14):2339-2347.

Refractory or relapsed adult ALL: Unmet need

Outcome after relapse of adult ALL by the PETHEMA Study Group



Patterns of post immunotherapy relapse based on immunophenotype



CD19-Negative Relapse and Resistance Has Been Observed After Treatment With CD19-Targeted Therapies¹⁻³

Although additional research is needed to better understand the underlying cause of CD19-negative relapse, studies of patients with B-ALL have identified possible mechanisms for the occurrence of low or absent CD19 expression:

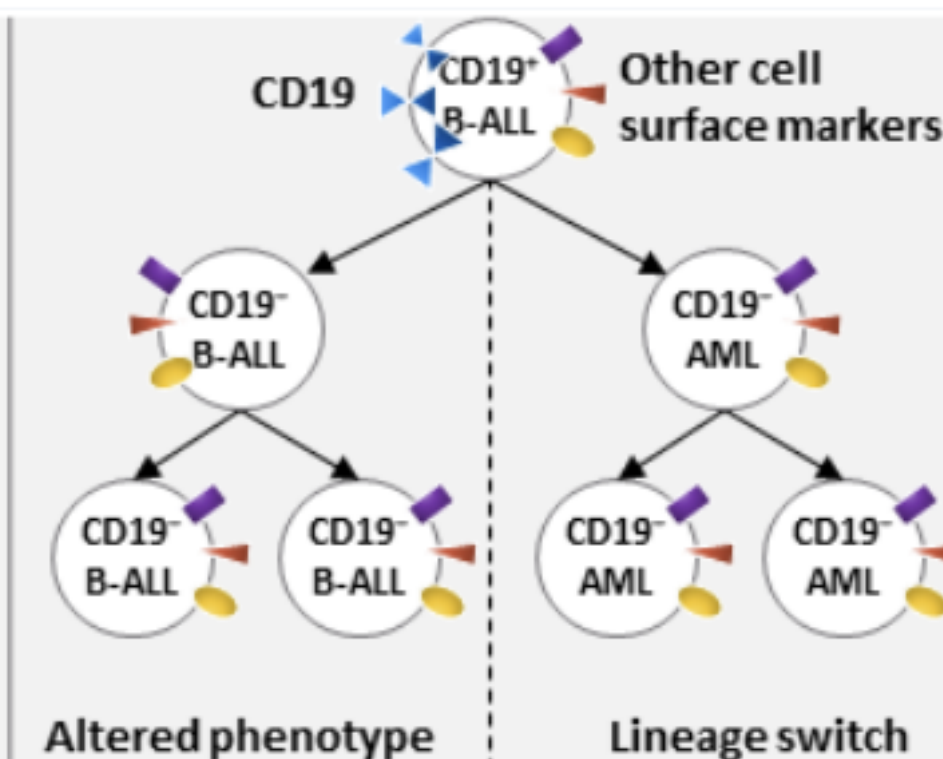
CD19 downregulation¹

CD19-negative relapses may be more common in patients who received prior CD19-targeted therapy, suggesting genetic or epigenetic alterations that result in downregulation of CD19



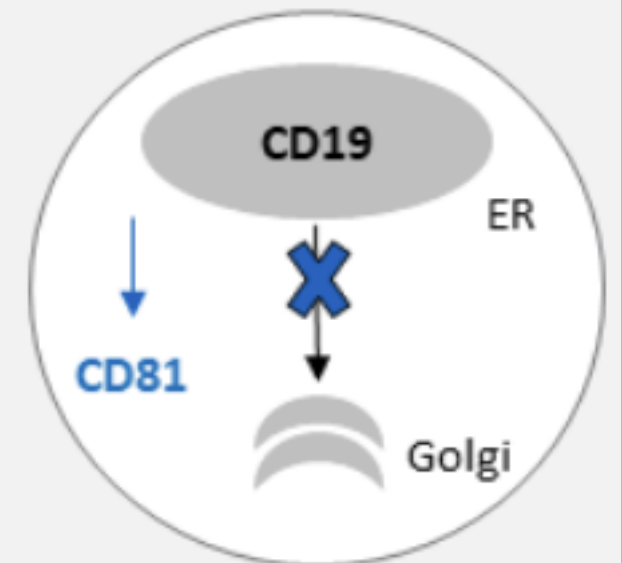
Expansion of CD19-negative clones¹⁻³

- Preserved B-ALL phenotypes, except for CD19 negativity, observed in patients with relapsed B-ALL suggest that an isolated molecular event may result in acquired CD19 loss in a B-ALL blast, which then clonally expands
- Observations in patients treated with CAR T-cell therapies also suggest that leukemic cells may undergo phenotypic lineage switch to CD19-negative AML



Disrupted CD19 transport²

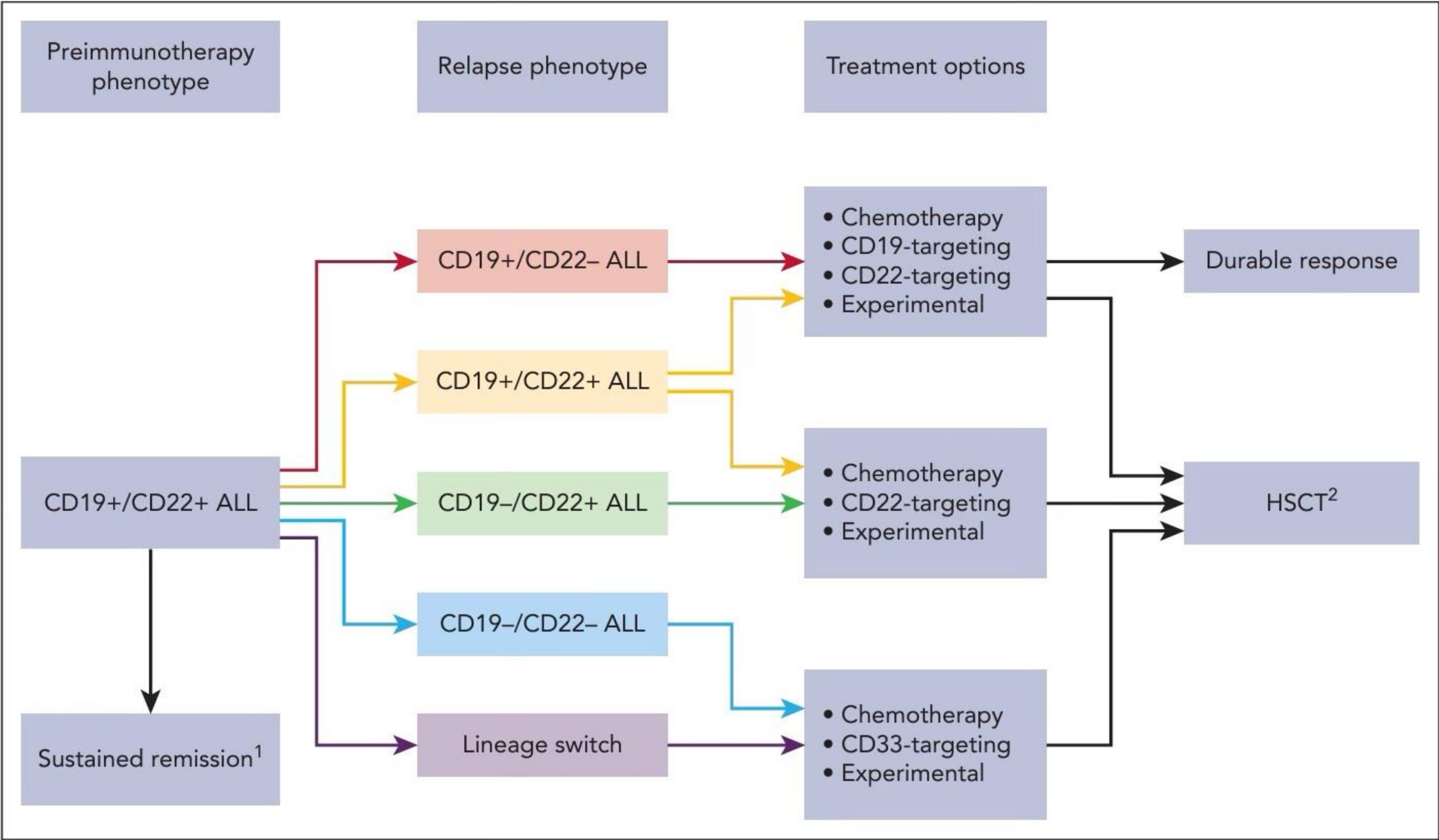
Downregulation of CD81 on leukemic blasts from patients with B-ALL suggests that alterations in CD81 can result in interference of CD19 maturation and trafficking to the cell surface and development of CD19-negative cells



CD19-Negative Relapse Rates Observed With CD19-Targeted Therapies: Blinatumomab Studies

Study ^a	Total N	Population	Method of measuring CD19 expression	Timing of measuring CD19 expression	Rate of CD19-negative disease recurrence among subset of relapsed patients
Aldoss 2017 ¹	65	R/R B-ALL	Flow cytometry	Before and after blinatumomab treatment	35% (6/17 patients who relapsed after response to blinatumomab)
Topp 2014 ²	36	R/R B-ALL	Not reported	Not reported	30% (3/10 patients who relapsed after response to blinatumomab)
Mejstříková 2021 ³	59	R/R B-ALL	Flow cytometry	At diagnosis, and on days 15 and 29 of cycle 1 of blinatumomab	12% (7/59 patients with evaluable data)
Locatelli 2021 ⁴	54 ^b	High-risk first relapse B-ALL	Not reported	Not reported	8% (1/13 patients who relapsed after blinatumomab)
Jabbour 2018 ⁵	84	R/R B-ALL	Flow cytometry	At blinatumomab initiation and treatment failure	13% (4/30 patients who relapsed after response to blinatumomab ^c)
Gore 2018 ⁶	70	R/R B-ALL	Not reported	Not reported	6% (4/67 patients with evaluable data ^d)
Locatelli 2020 ⁷	110	R/R B-ALL	Not reported	Not reported	26% (6/23 patients who relapsed after response to blinatumomab)
Brown 2021 ⁸	214	First relapse B-ALL	Flow cytometry	Following completion of a therapy cycle	44% (4/9 evaluable patients who relapsed after response to blinatumomab)

Postimmunotherapy salvage strategies based on immunophenotype following CD19- and/or CD22-targeting.



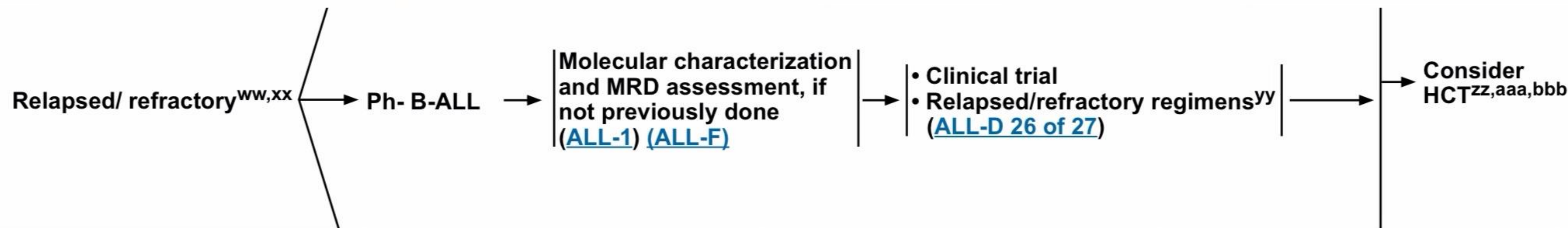


NCCN Guidelines Version 2.2025

Acute Lymphoblastic Leukemia

RELAPSED/REFRACTORY DISEASE

TREATMENT



PRINCIPLES OF SYSTEMIC THERAPY

REGIMENS FOR RELAPSED OR REFRACTORY Ph-NEGATIVE B-ALL^{a,b,c,d}

Preferred Regimens
• Blinatumomab (CD19 antigen directed) (category 1)¹ ± multiagent therapy • Inotuzumab ozogamicin (CD22 antigen directed) (category 1)² • Tisagenlecleucel (CD19 antigen directed) (patients aged <26 years and with refractory disease or ≥2 relapses)³ • Brexucabtagene autoleucel (CD19 antigen directed)⁴ • Obecabtagene autoleucel (CD19 antigen directed)⁵
Other Recommended Regimens ^e
• Inotuzumab ozogamicin + mini-hyperCVD with or without sequential blinatumomab (hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine)^{6,7} • Augmented HyperCVAD: hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, pegaspargase; alternating with high-dose methotrexate, cytarabine⁸ • Clofarabine alone⁹⁻¹² or in combination (eg, clofarabine, cyclophosphamide, etoposide)^{10,13,14} • MOpAD regimen: methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20-positive disease¹⁵ • Fludarabine-based regimens ▶ FLAG-IDA: fludarabine, cytarabine, G-CSF ± idarubicin¹⁶ ▶ FLAM: fludarabine, cytarabine, mitoxantrone¹⁷ • Cytarabine-containing regimens: eg, high-dose cytarabine, idarubicin, IT methotrexate¹⁸ • Alkylator combination regimens: eg, etoposide, ifosfamide, mitoxantrone¹⁹ • Revumenib (<i>KMT2A</i> rearranged)^{f,20}

Conventional chemotherapy trials.

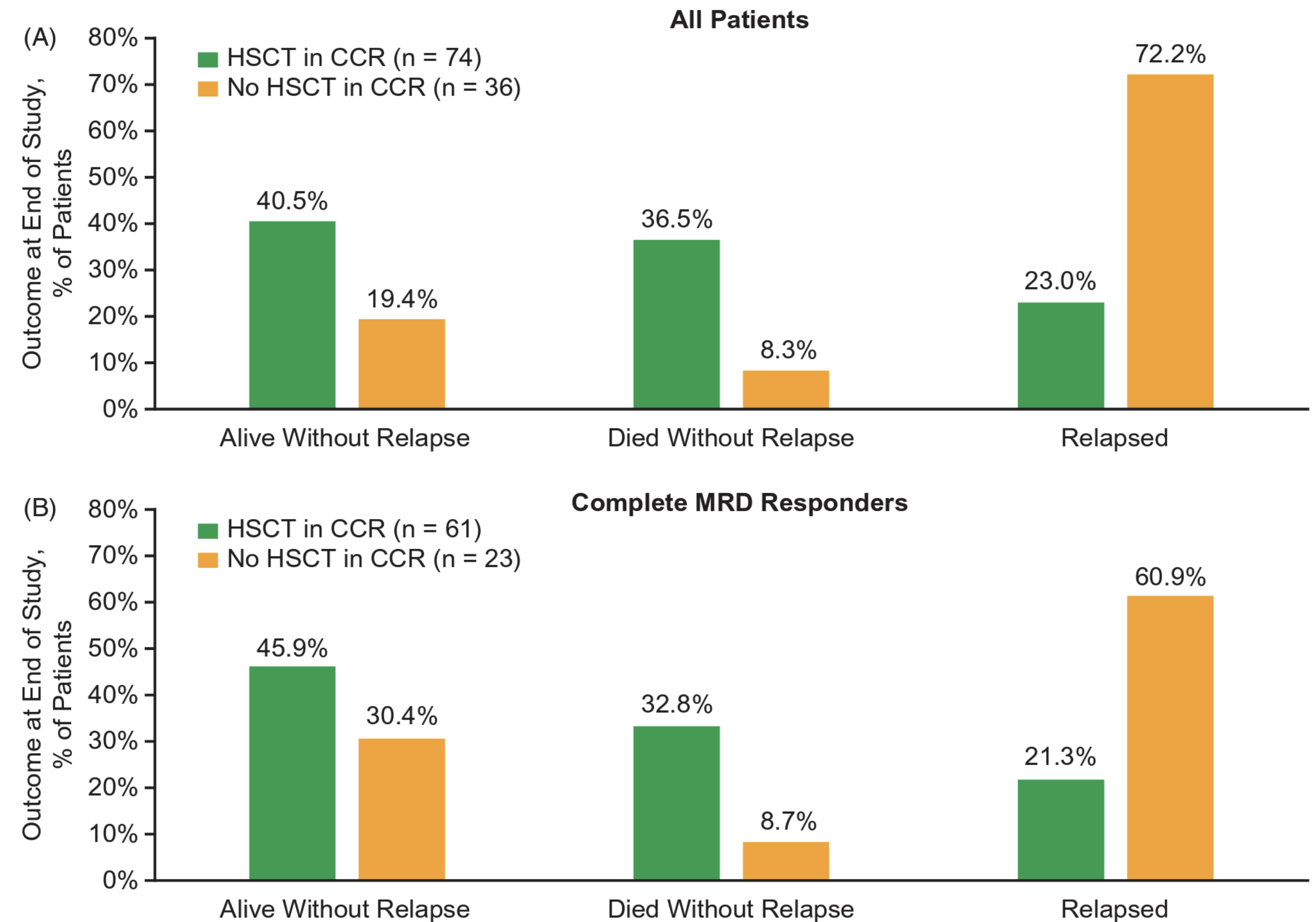
Drug	Study	No. of Patients	ORR (%)	Median OS (Months)
Cytarabine (5 g/m ²) + Mitoxantrone (40 mg/m ²) + Etoposide (500 mg/m ²)	Liedtke <i>et al.</i> [4]	40	30	6.5
Cytarabine (5 g/m ²) + Mitoxantrone (40 mg/m ²) +/- Etoposide (500 mg/m ²)	Ahn <i>et al.</i> [5]	46	48	6.2
Cytarabine (15 g/m ²) + Amsacrine (600 mg/m ²)	Arlin <i>et al.</i> [6]	40	72	n.a.
Clofarabine-based regimens (<i>n</i> = 5 CLO-single agent)	Barba <i>et al.</i> [9]	31	31	5.0
Clofarabine (200 mg/m ²) + Cytarabine (5 g/m ²)	Advani <i>et al.</i> [10]	37 (phase II trial)	17	3.0
Clofarabine (200 mg/m ²) + Cytarabine (5 g/m ²) + Epratuzumab (360 mg/m ² × 4 doses)	Advani <i>et al.</i> [11]	31 (phase II trial)	52	5.0
Clofarabine (120 mg/m ²) + Cyclophosphamide (1.2 g/m ²)	Faderl <i>et al.</i> [13]	50 (phase I trial)	14	3.0
Liposomal Vincristine (2.25 mg/m ² weekly)	O'Brien <i>et al.</i> [14]	65 (phase II trial)	35	4.6

ORR: Overall response rate; OS: Overall survival.

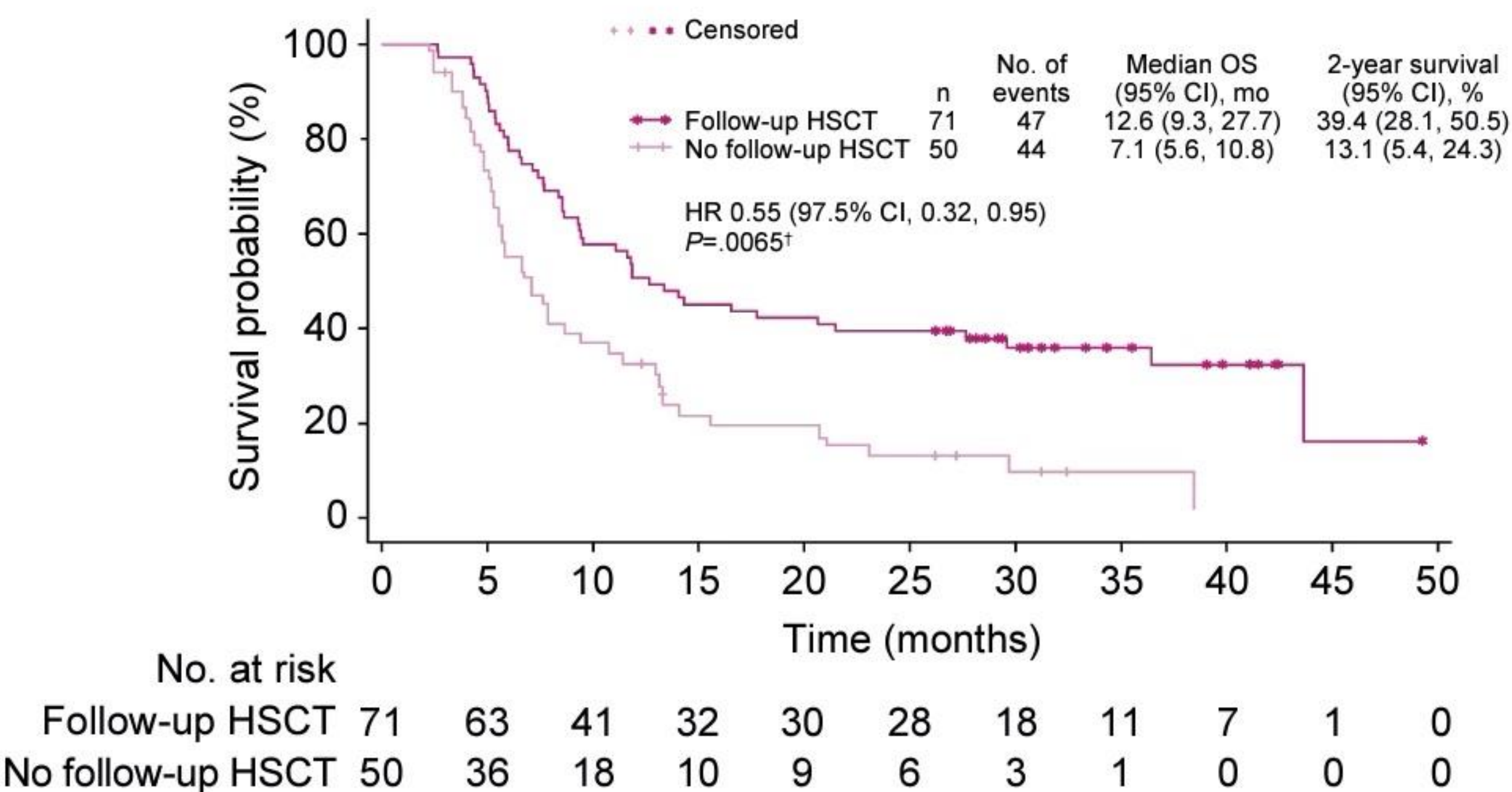
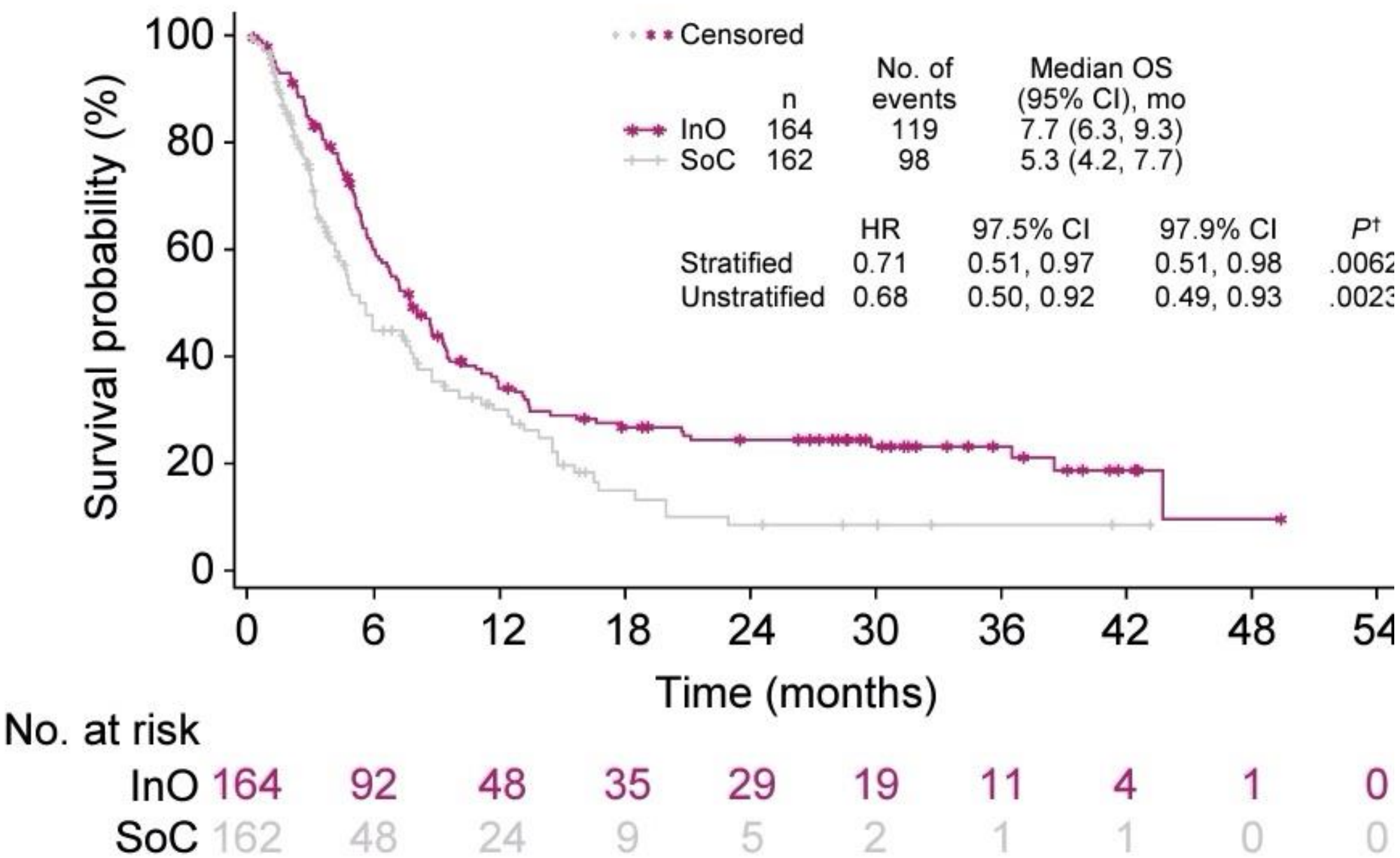
Outcomes with or without HSCT in CCR after blinatumomab.(BLAST STUDY)

Characteristics of Patients Receiving HSCT in CCR

	HSCT in CCR (n = 74)
Age, years Median (range) > 35	42 (18–67) 48 (65%)
Conditioning Myeloablative Reduced intensity Missing	55 (74%) 14 (19%) 5 (7%)
HSCT donor Matched, sibling Matched, unrelated Mismatched Missing	17 (23%) 20 (27%) 25 (34%) 12 (16%)

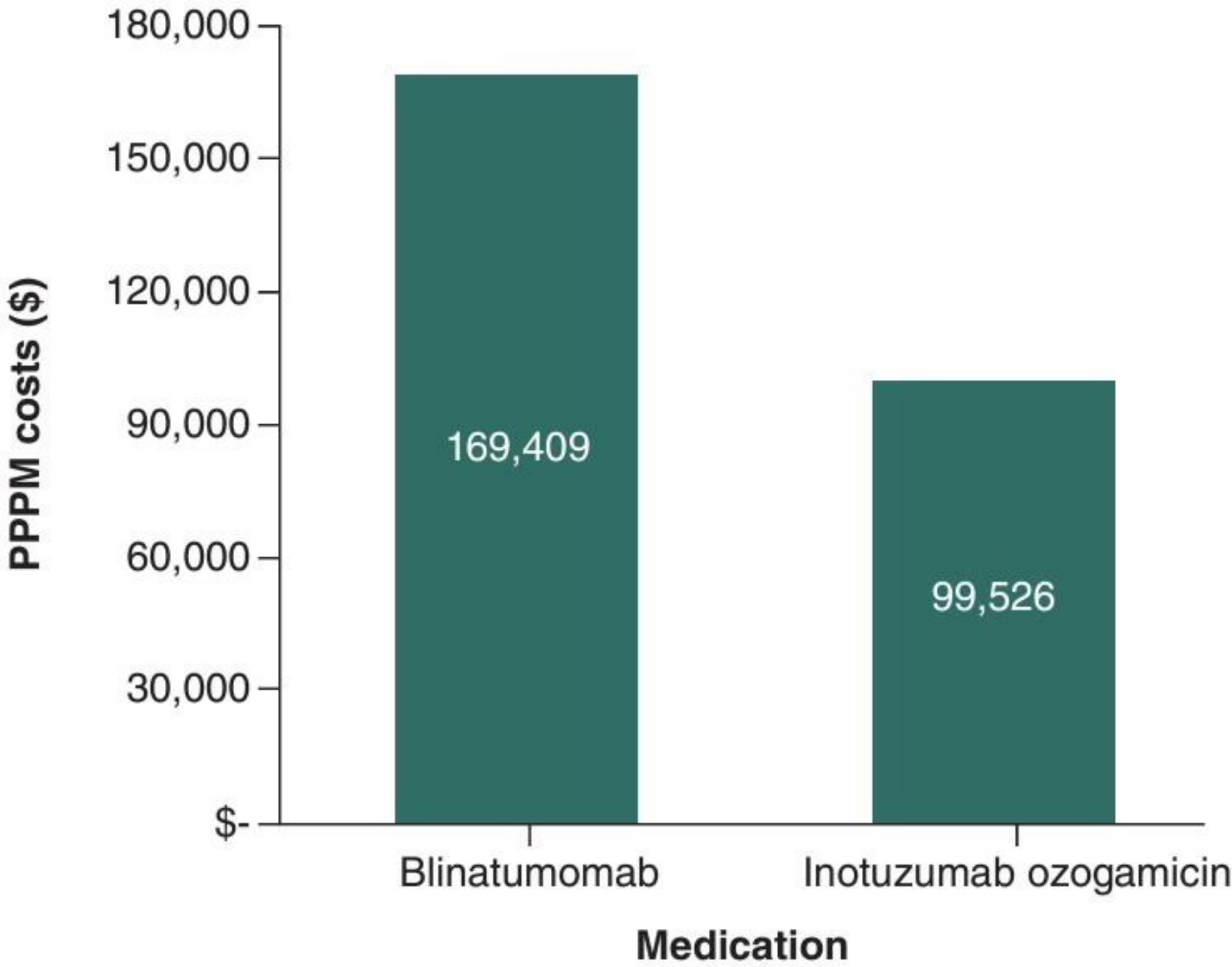


Inotuzumab Ozogamicin Versus Standard of Care in Relapsed or Refractory Acute Lymphoblastic Leukemia: Final Report and Long-Term Survival Follow-Up From the Randomized, Phase 3 INO-VATE Study

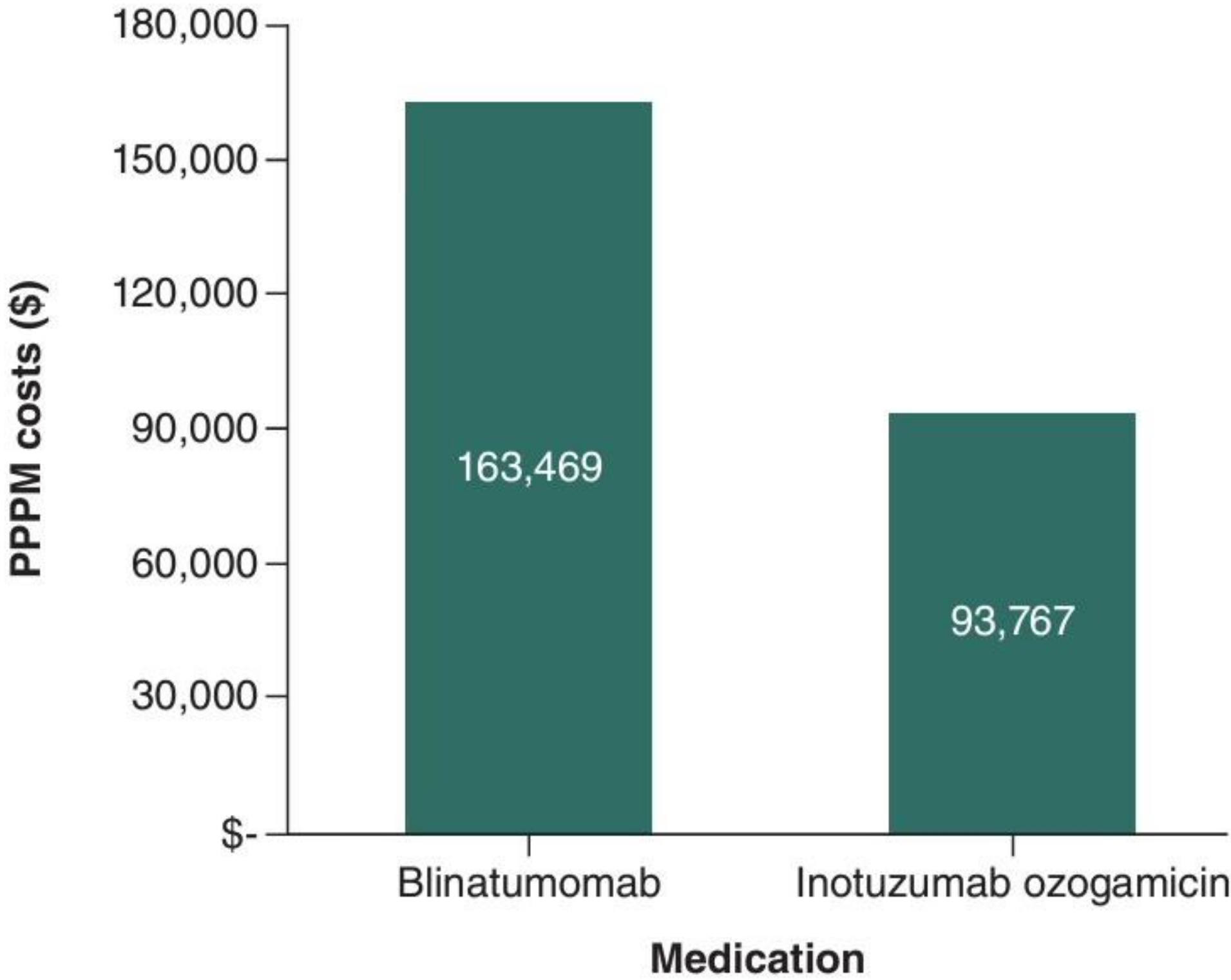


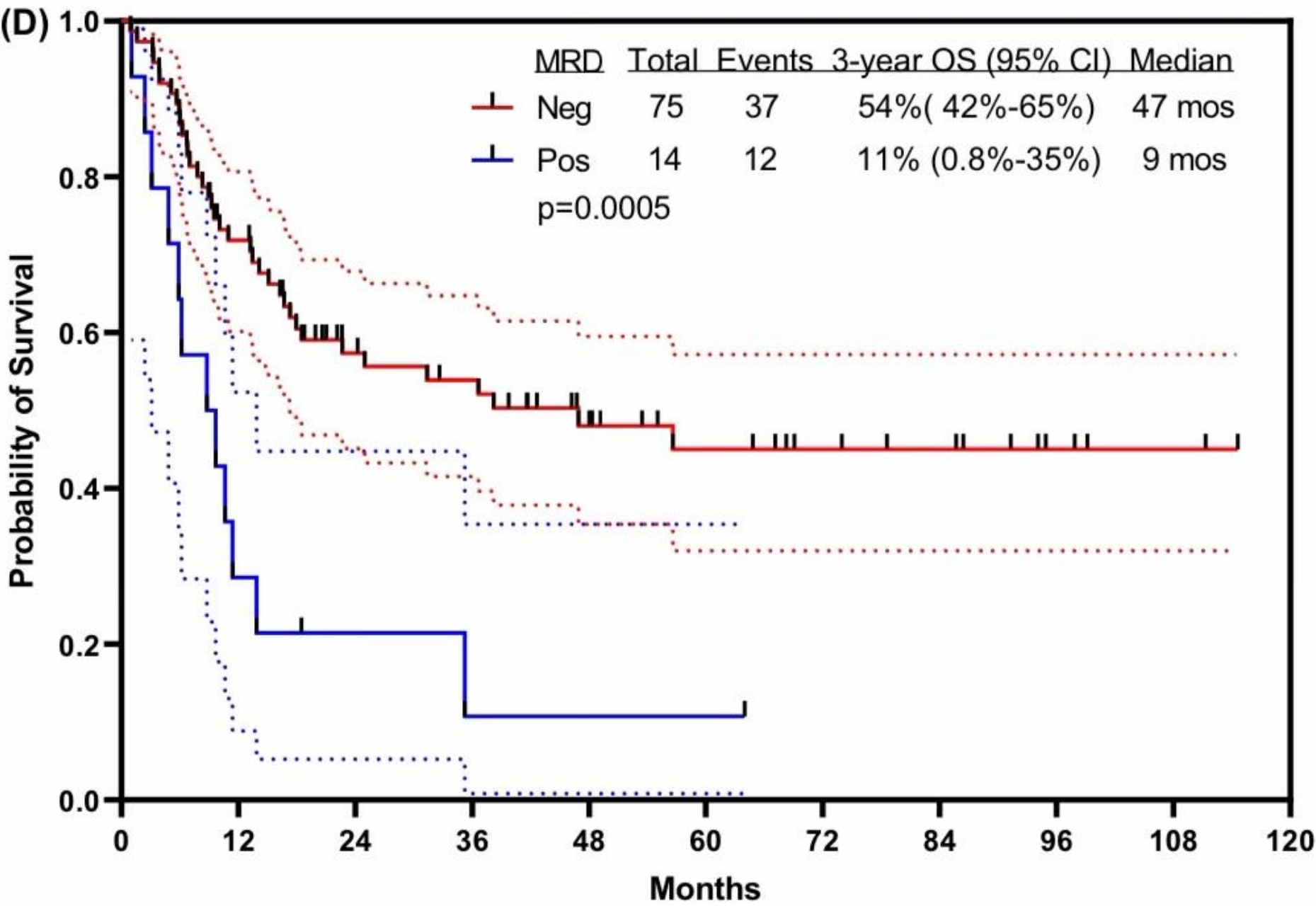
Real-world use of inotuzumab ozogamicin is associated with lower health care costs than blinatumomab in patients with acute lymphoblastic leukemia in the first relapsed/refractory setting

total all-cause healthcare costs

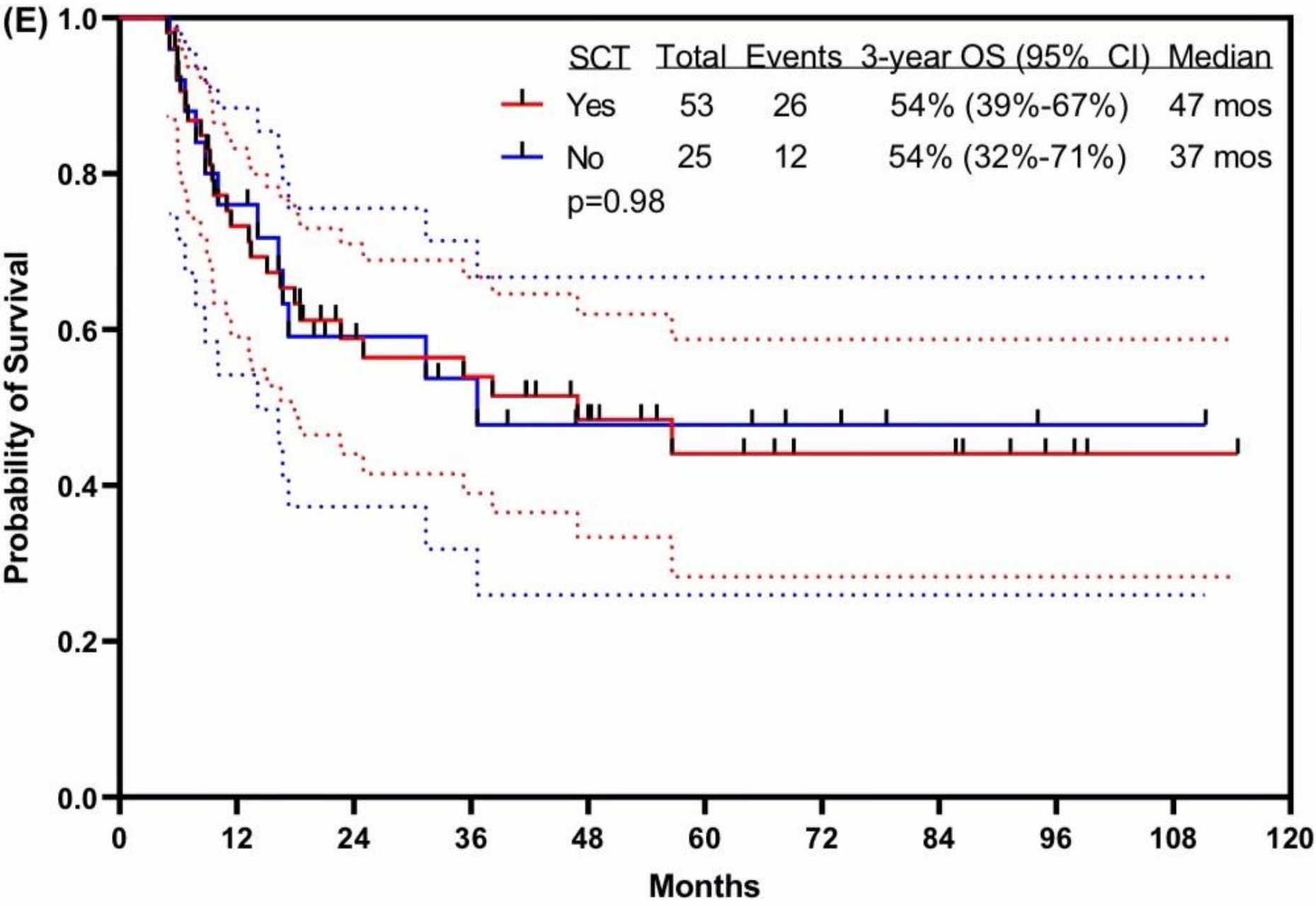


total acute lymphoblastic leukemia-related healthcare costs



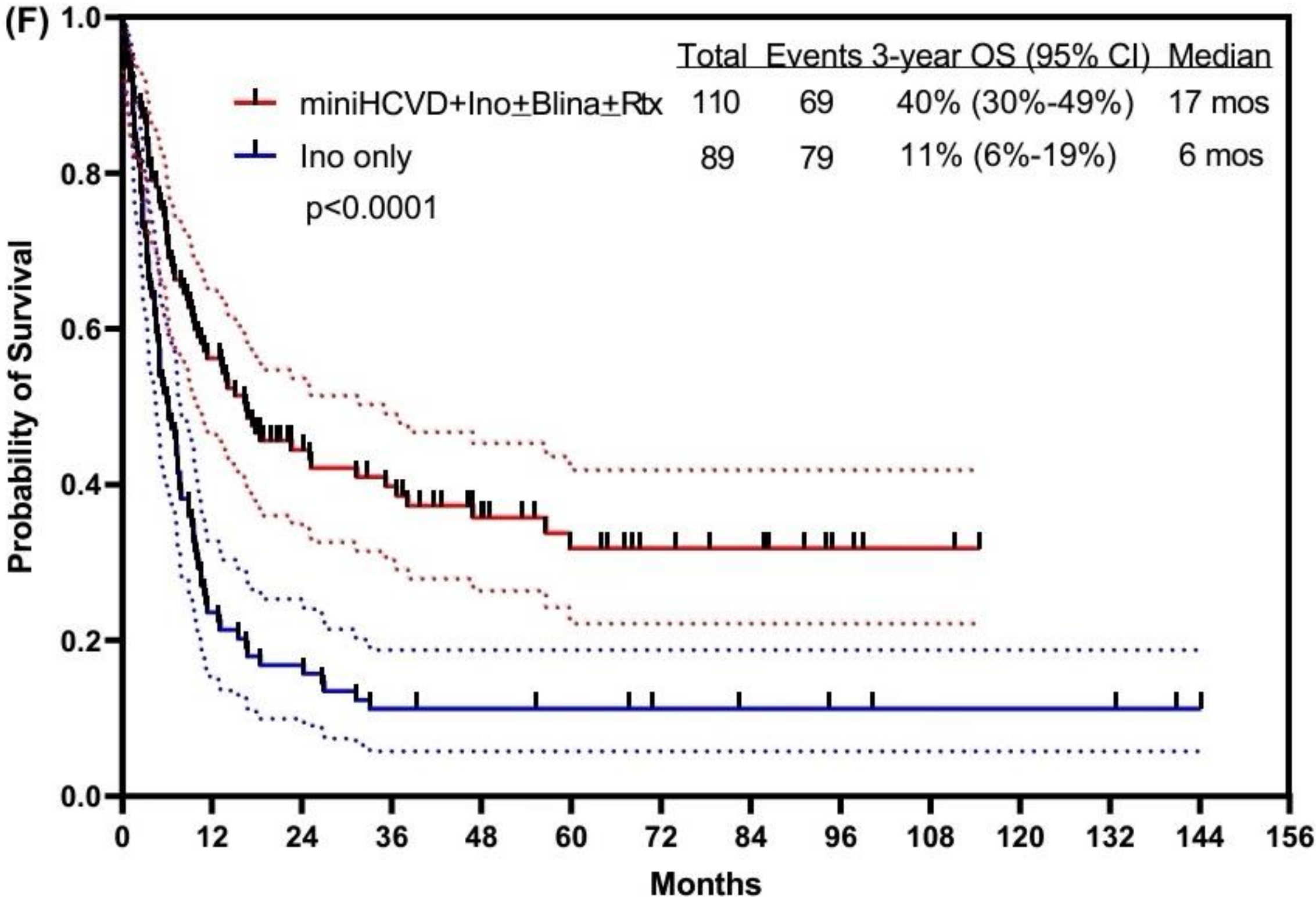
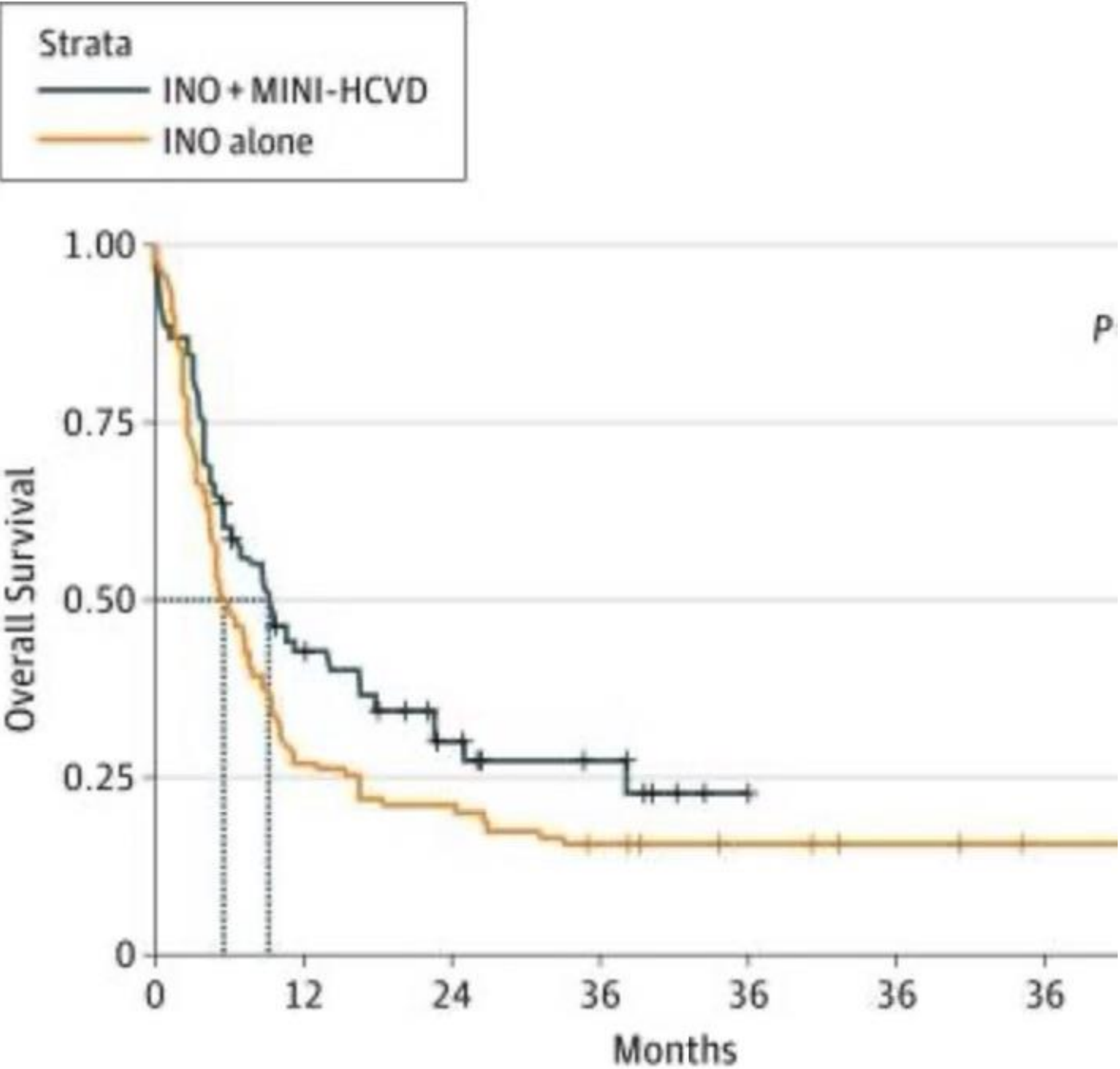


Results of salvage therapy with mini-hyper-CVD and inotuzumab ozogamicin with or without blinatumomab in pre-B acute lymphoblastic leukemia



Results of salvage therapy with mini-hyper-CVD and inotuzumab ozogamicin with or without blinatumomab in pre-B acute lymphoblastic leukemia

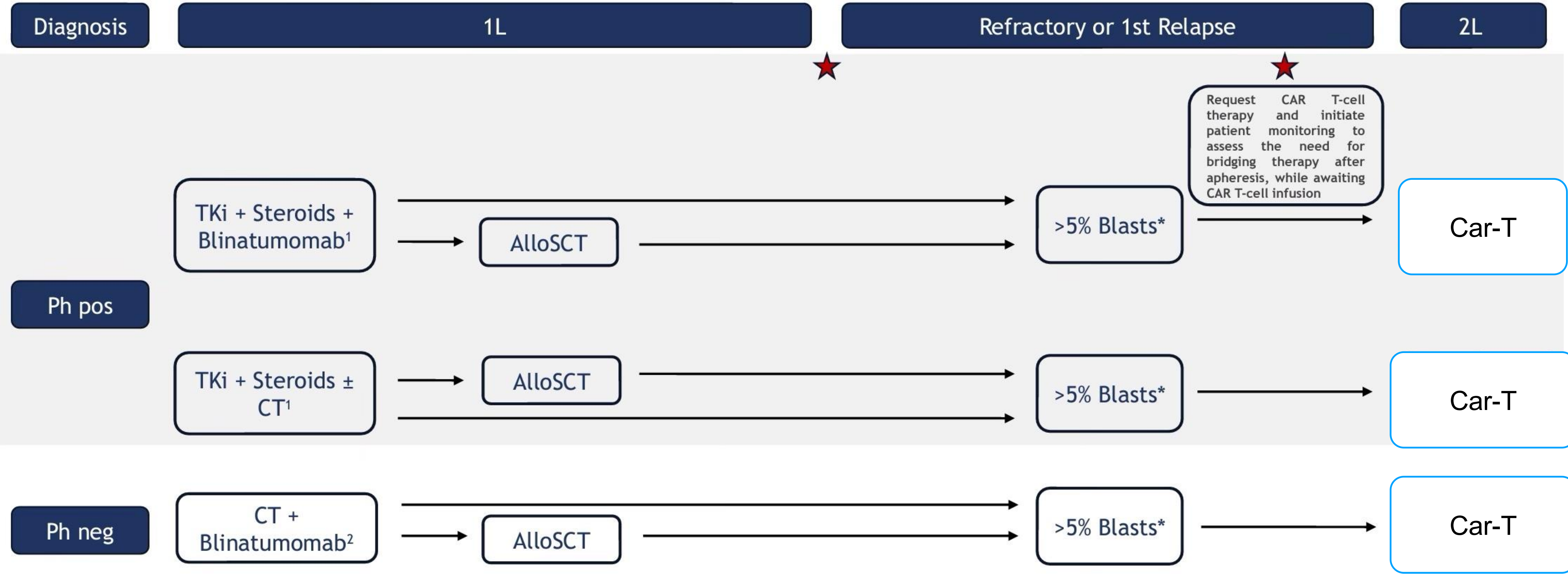
D OS by therapy



Kantarjian et al. Journal of Hematology & Oncology 2023

Elias Jabbour et al JAMA Oncol 2018

Patient Journey aALL



Indication for allo-HSCT versus standard consolidation or maintenance therapy based on MRD status and risk stratification

★ Critical step for the early identification of disease refractoriness or relapse and for assessing eligibility for CAR T-cell therapy

*AIFA Registry block for % medullary blasts ≤ 5% at inclusion
Brexu-cel is not recommended for patients who have CD19-negative disease or an unconfirmed CD19 status

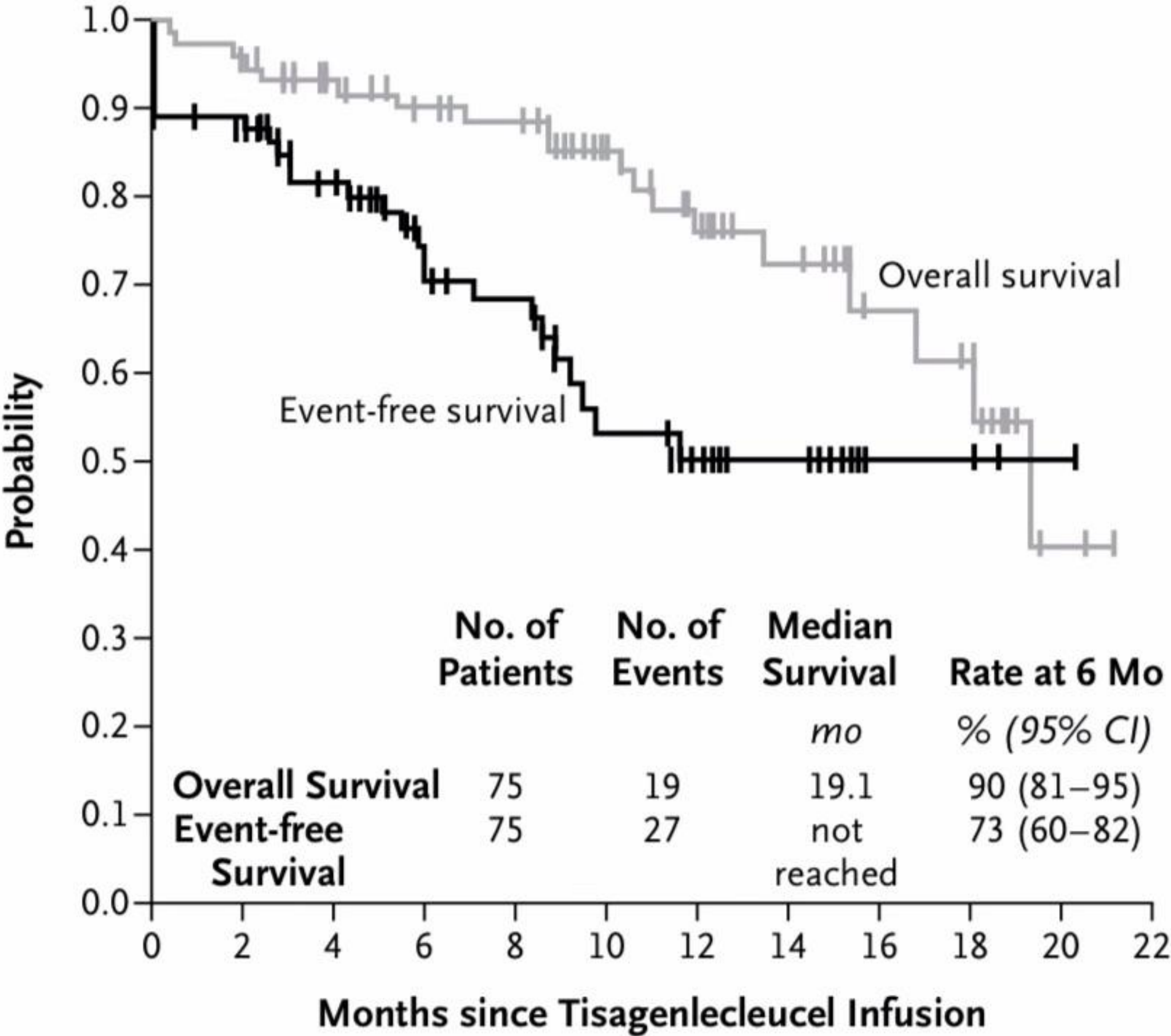
** Subjects with Ph+ disease must be intolerant to TKI therapy, or R/R despite treatment with at least 2 different TKIs

1. Chiaretti S. and Foà R. How I treat adult Ph-positive ALL. Blood 2025 Jan 2; 145 (1):11-19
2. Bassan R. et al. Blood 22 May 2025 Vol 145, N 21

For external use and

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

B Event-free and Overall Survival



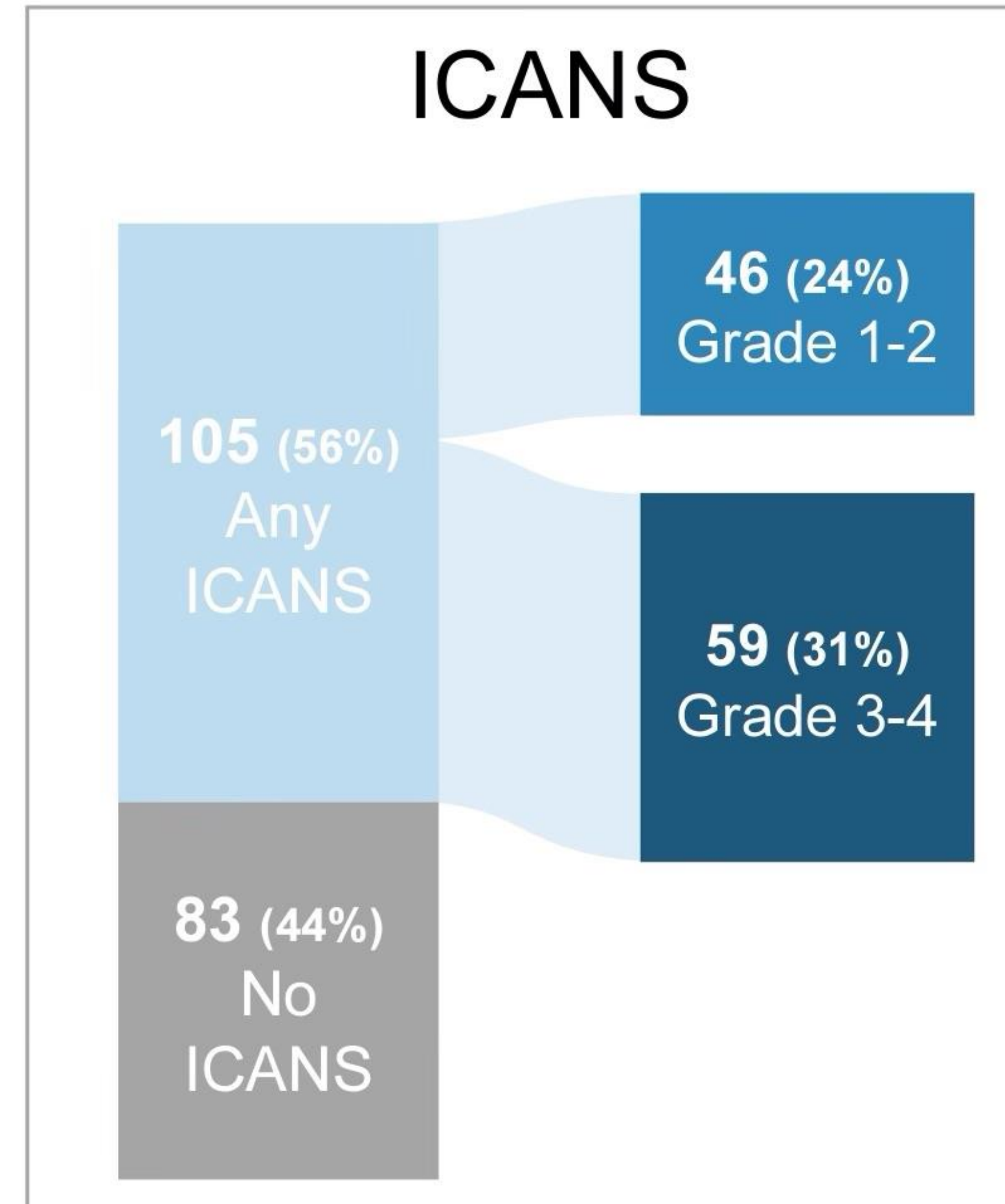
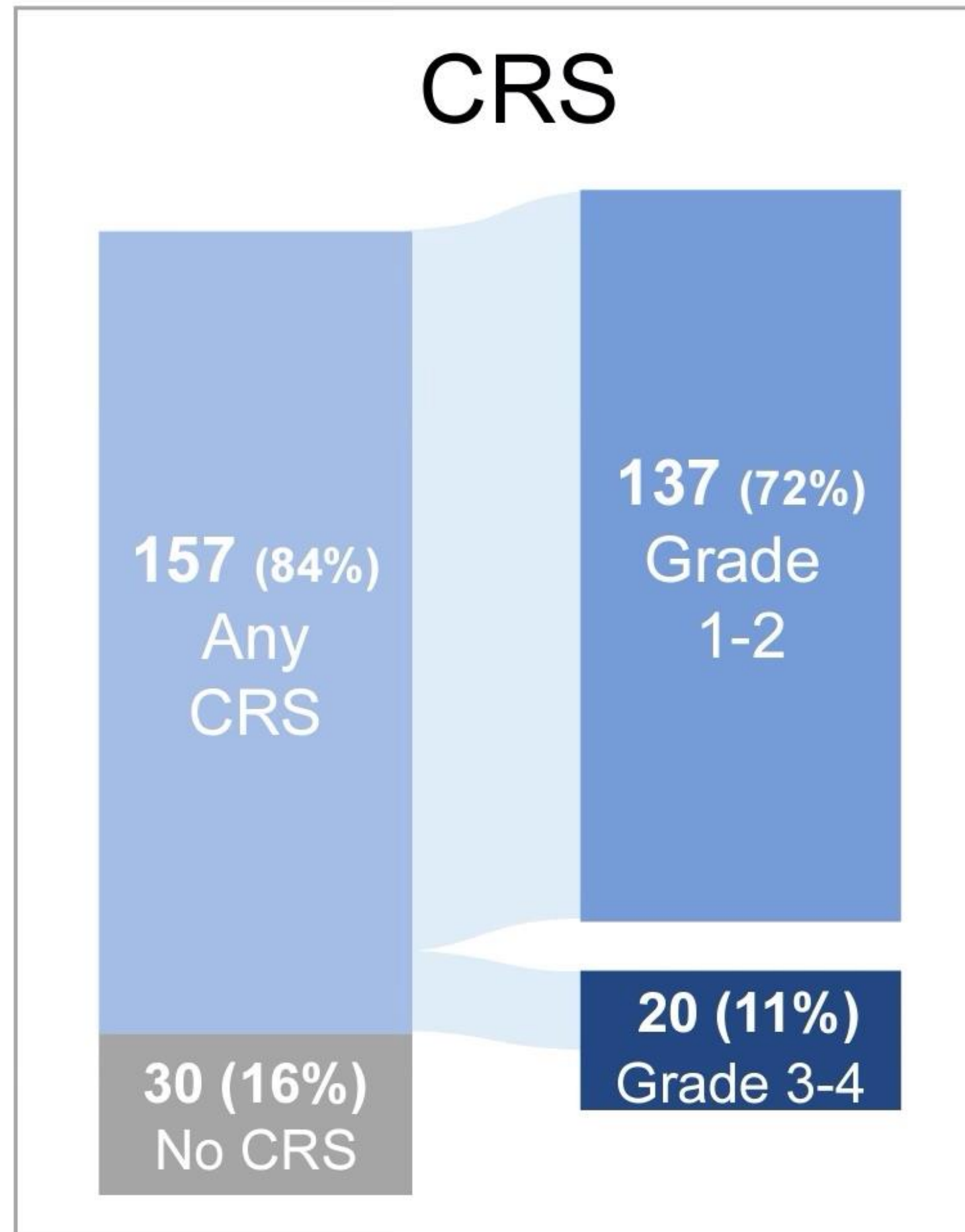
ELIANA trial:
(18 patients with Ph+ ALL,

100% CR
2-year RFS of 88%

2-year OS: Ph+ disease
compared to Ph- ALL (88% vs.
73%)

Brexucabtagene Autoleucel in Adults with R/R B-ALL: US Real-World Outcomes

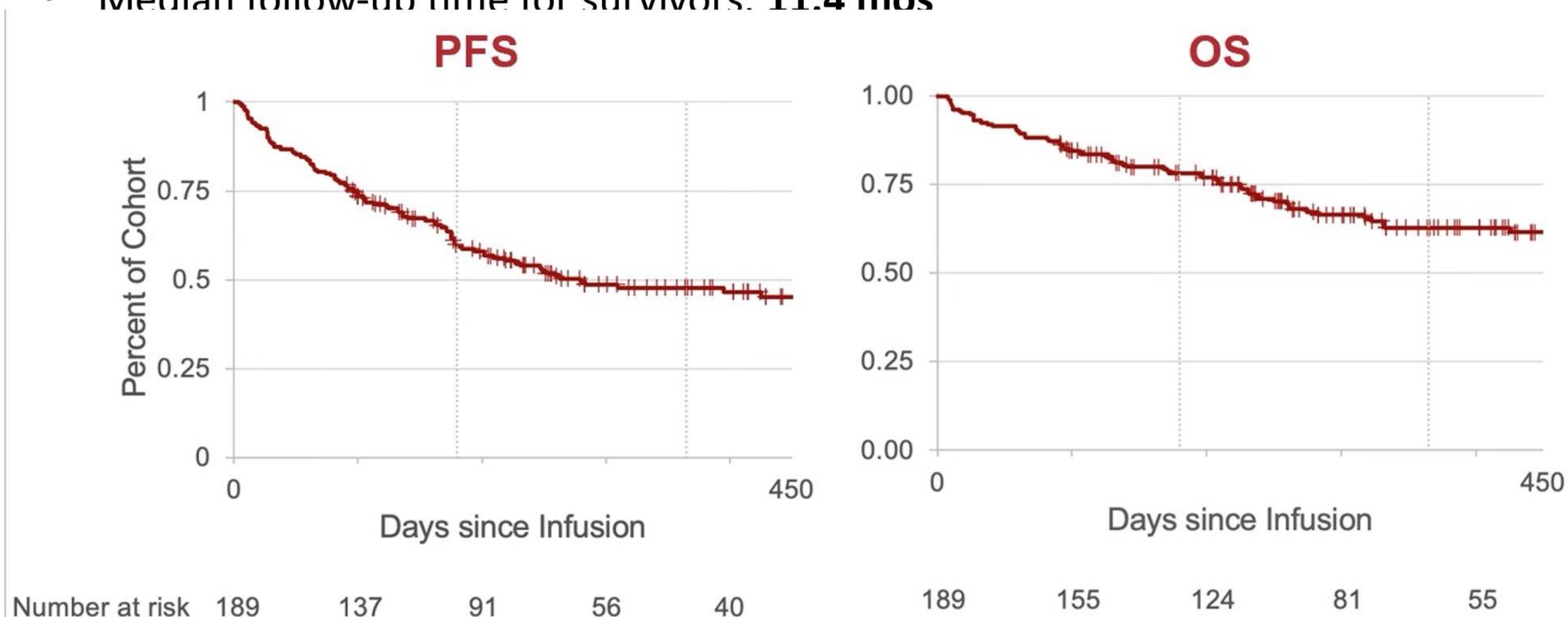
Toxicities



Brexucabtagene Autoleucel in Adults with R/R B-ALL: US Real-World Outcomes

Survival Outcomes

- Median follow-up time for survivors: **11.4 mos**

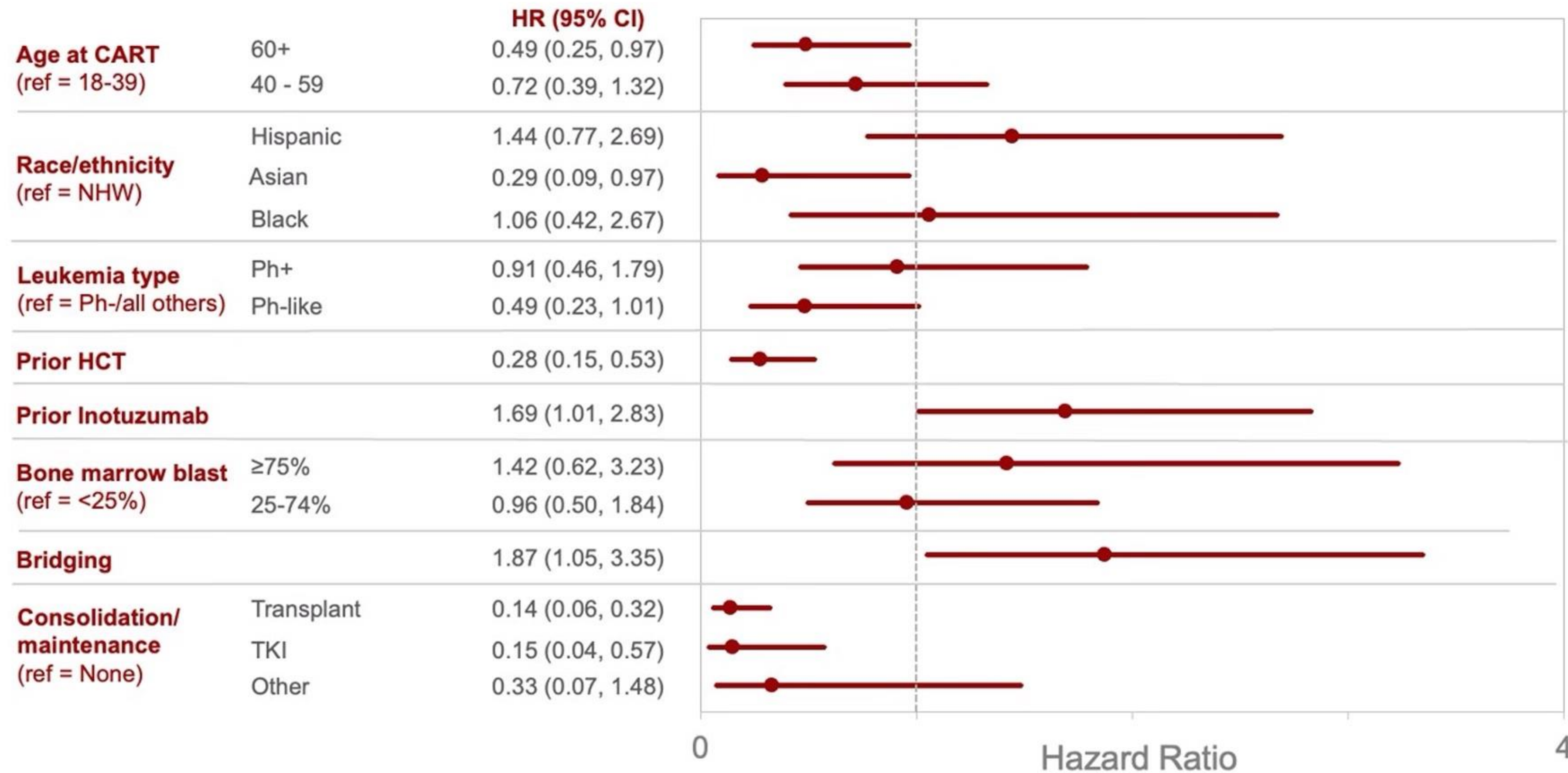


PFS: 6 month = 59%; 12 month = 48%

OS: 6 month = 78%; 12 month = 63%

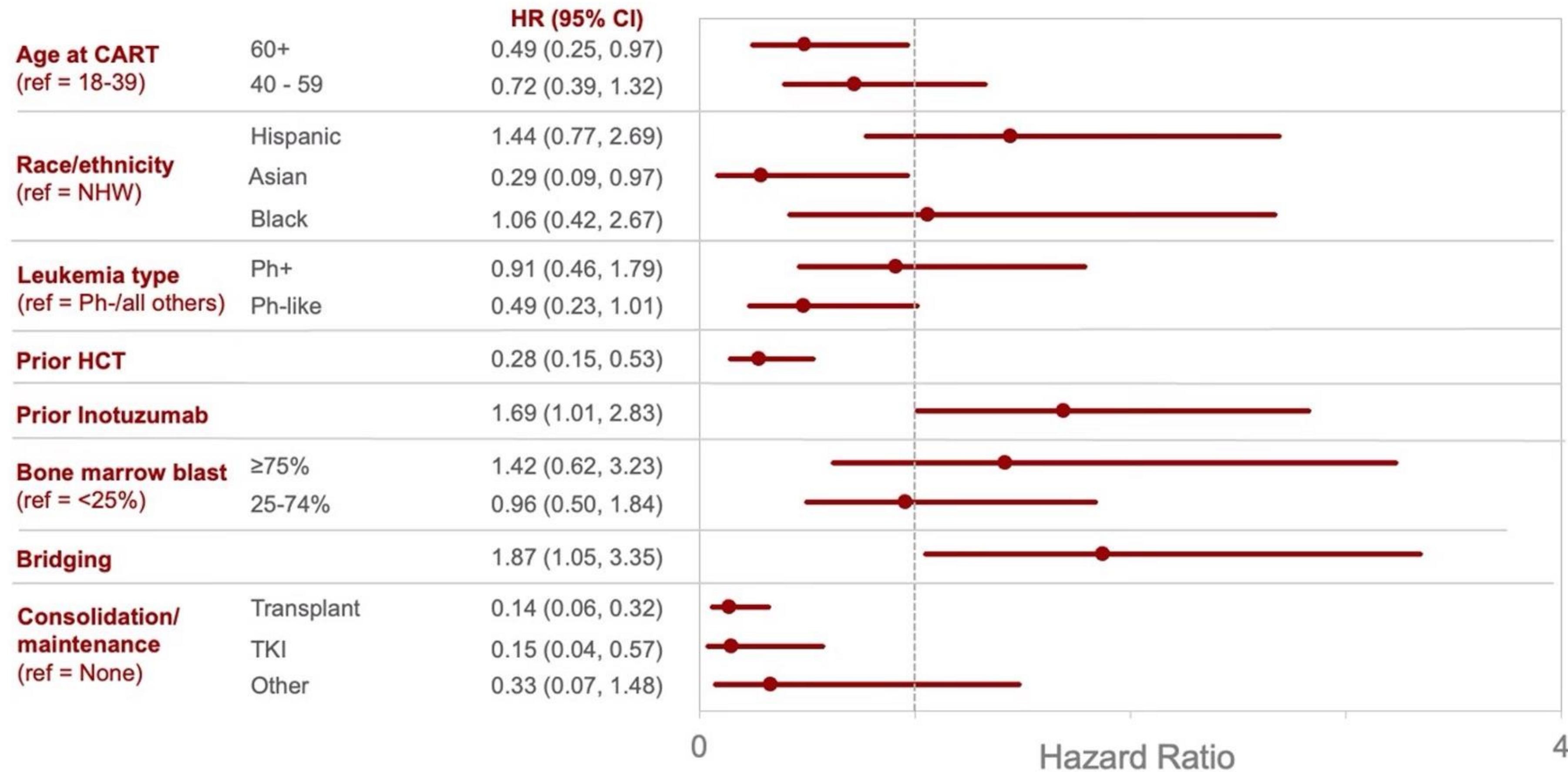
Brexucabtagene Autoleucel in Adults with R/R B-ALL: US Real-World Outcomes

Multivariable Model of PFS



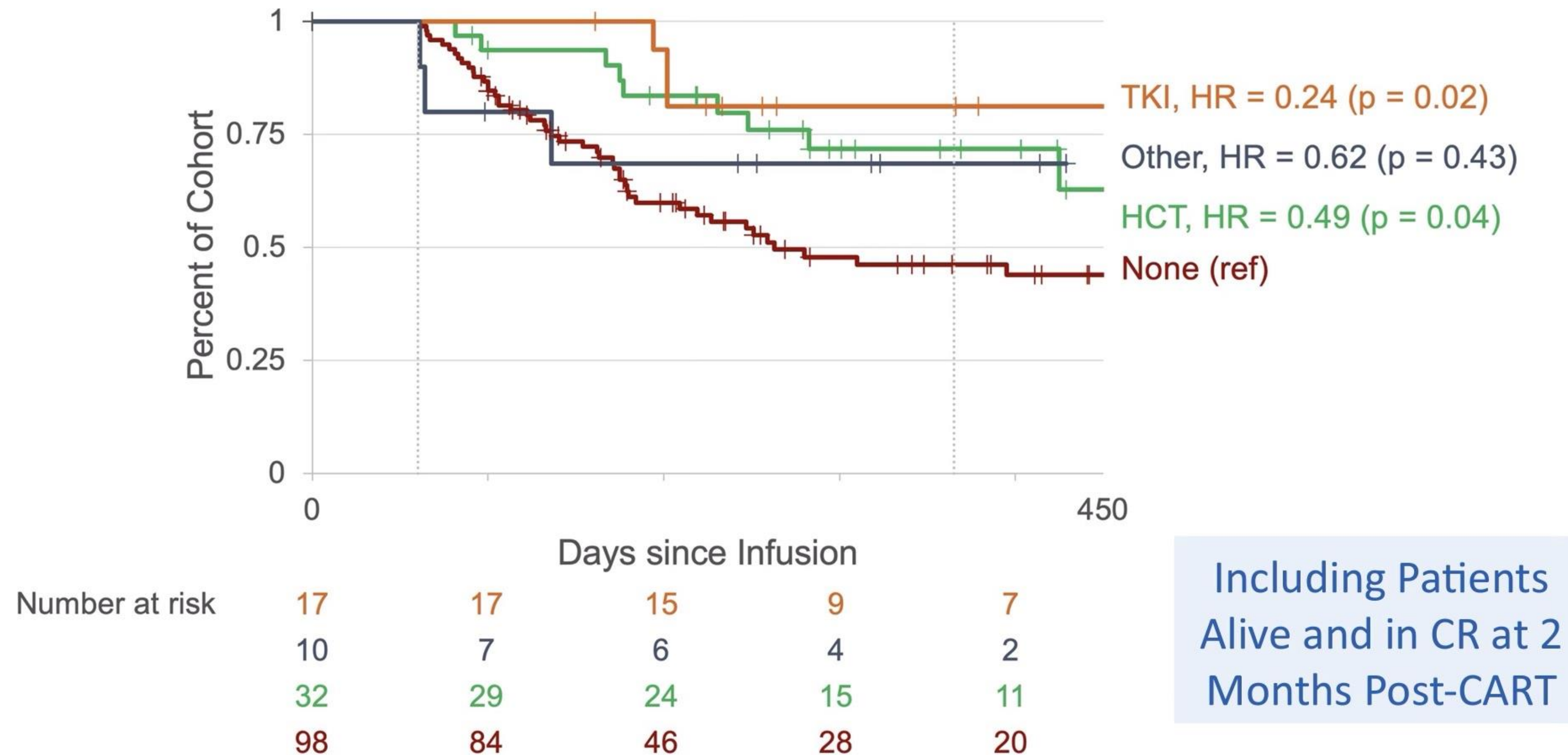
Brexucabtagene Autoleucel in Adults with R/R B-ALL: US Real-World Outcomes

Multivariable Model of PFS



Brexucabtagene Autoleucel in Adults with R/R B-ALL: US Real-World Outcomes

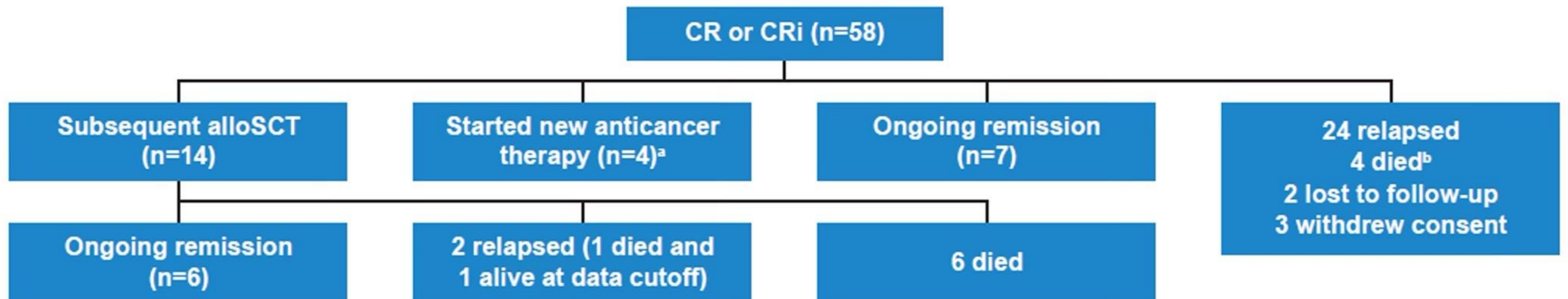
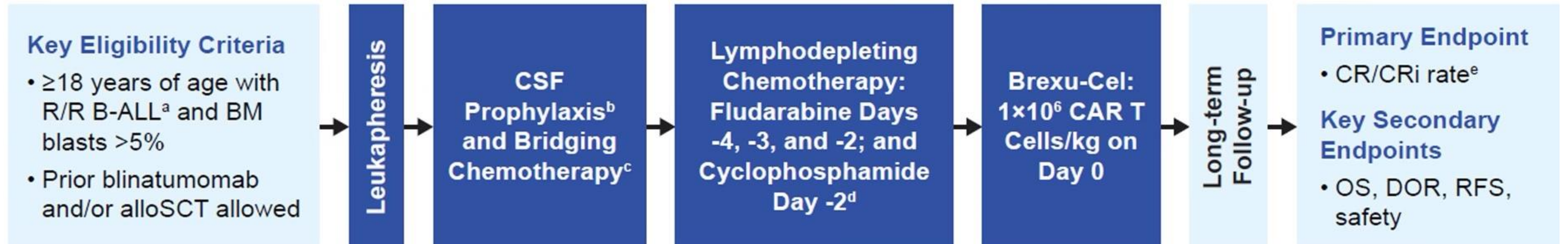
Landmark PFS (N=157)



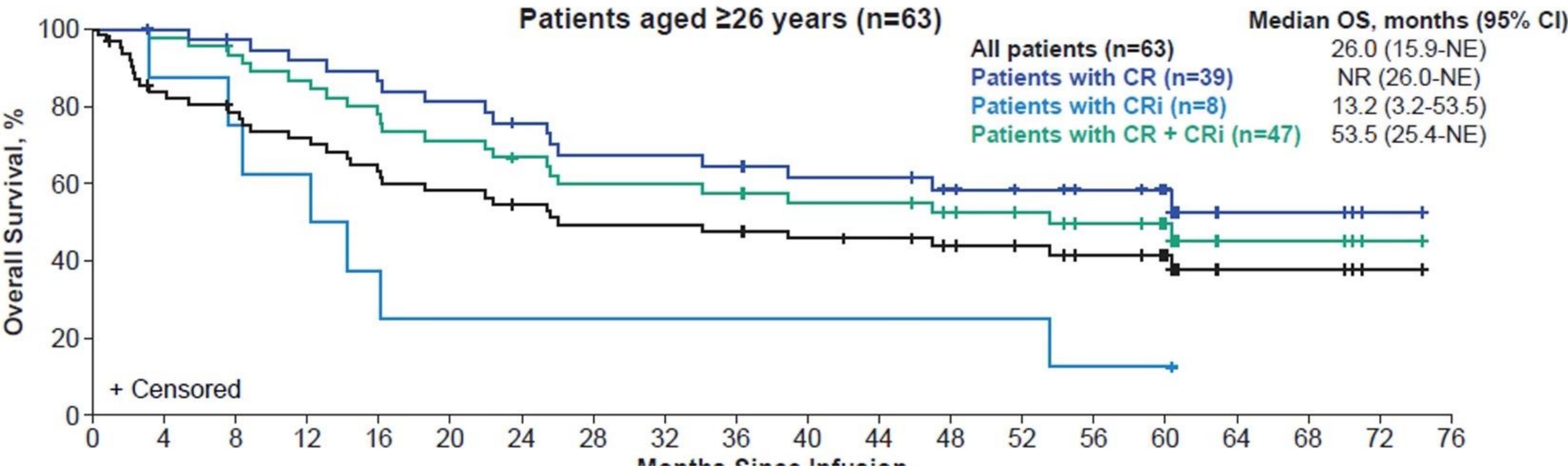
Brexucabtagene Autoleucel in Adults with R/R B-ALL: US Real-World Outcomes

- CRS is common but severe CRS is relatively rare;
gr. 3-4
- ICANS occurred in 31%
- Rates of CR are high (90%),
 - 79% MRD-negative
 - 1-year PFS (48%) and OS (63%)
- Age 60+, prior HCT → superior PFS;
- prior Ino, bridging → inferior PFS-
- In patients achieving CR following brexu-cel, use of TKI (Ph+) or HCT as maintenance/consolidation appears to improve PFS

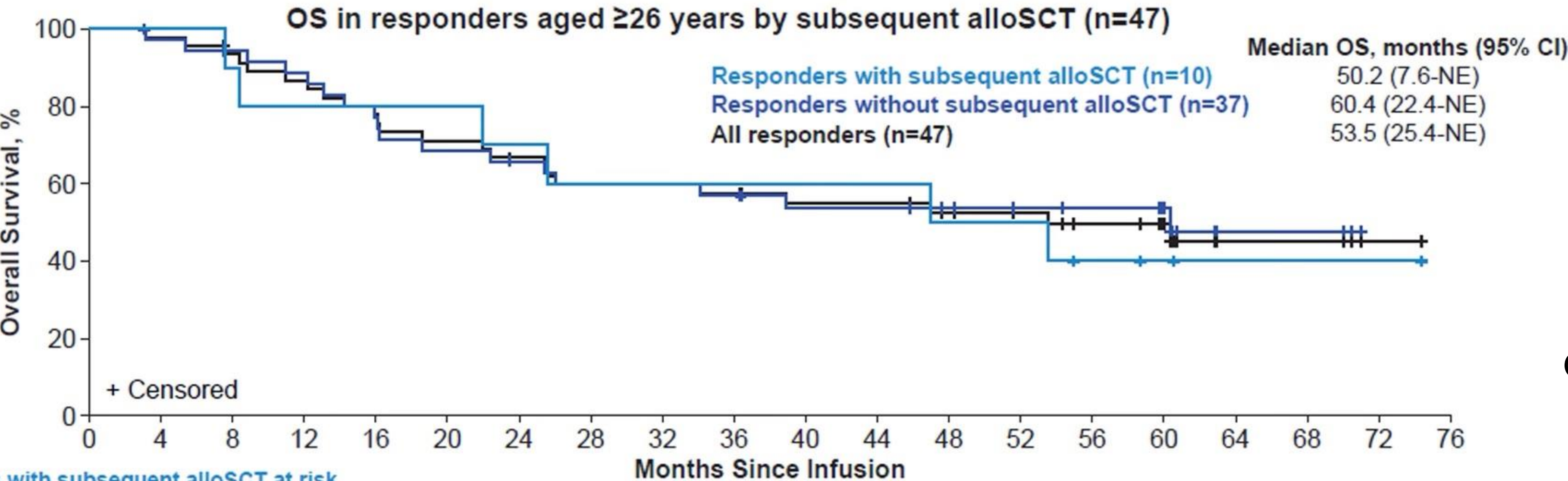
Five Year Survival Outcomes of Patients With Relapsed or Refractory B Cell Acute Lymphoblastic Leukemia Treated With Brexucabtagene Autoleucel in ZUMA 3



Overall Survival Update in ZUMA 3

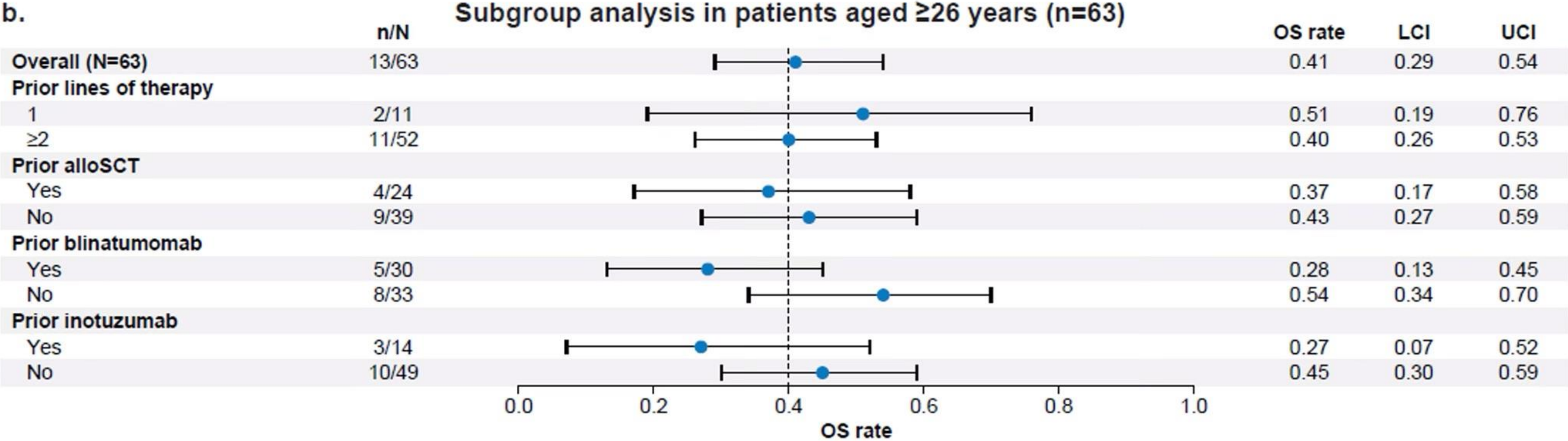


b.



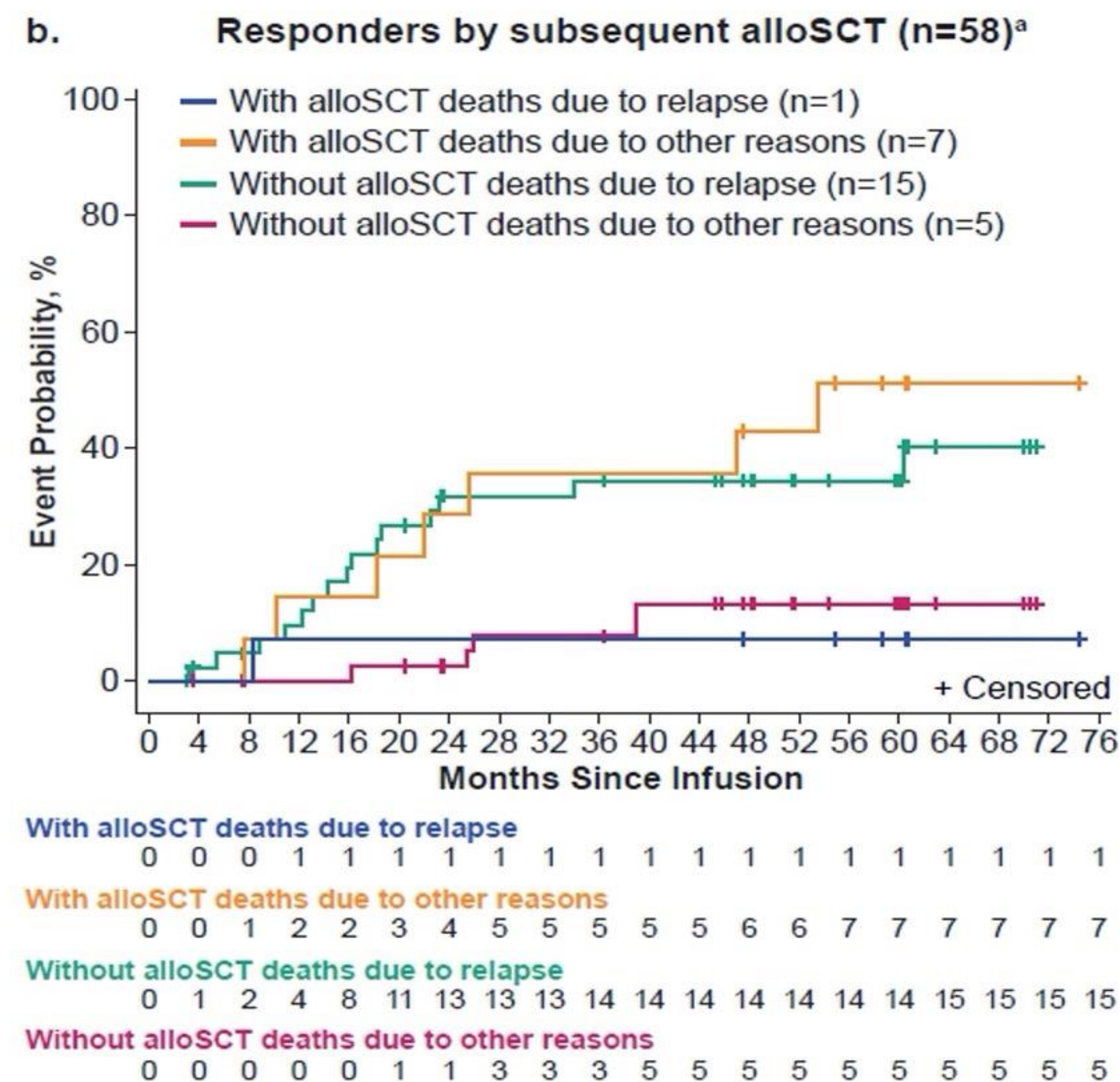
Responders with subsequent alloSCT at risk

Overall Survival Rates at 5 Years in ZUMA 3 by Key Subgroups



- Among patients aged ≥ 26 years, the 5-year OS rates were (Figure 5b):
 - 51% for patients with 1 prior therapy (n=11) and 40% for patients with ≥ 2 prior therapies (n=52)
 - 37% for patients with prior alloSCT (n=24) and 43% for patients without prior alloSCT (n=39)
 - 28% for patients with prior blinatumomab (n=30) and 54% for patients without (n=33) prior blinatumomab
 - 27% for patients with prior inotuzumab (n=14) and 45% without prior inotuzumab (n=49)

Zuma 3 : Cause Specific Mortality in All Patients and by Subsequent AlloSCT in Responders



- Of the 14 responders who received subsequent alloSCT, 8 had died by OS data cutoff, 1 (7%) due to relapse and 7 (50%) due to non-relapse-related reasons (**Figure 6b**)
 - The estimated 60-month cumulative incidence of relapse-related mortality and non-relapse-related mortality in responders with subsequent alloSCT were 7% (0.4–28.6) and 51% (21.4–74.8), respectively
 - Whereas the estimated 60-month cumulative incidence of relapse-related mortality and non-relapse-related mortality in responders without subsequent alloSCT were 34% (20.2–49.1) and 13% (4.7–26.2), respectively
 - Since the 4-year analysis, 1 new adverse event and death were reported, both in the same patient who had previously received post-brexu-cel alloSCT, cervical cancer and death due to pulmonary failure (both deemed unrelated to brexu-cel)
- No secondary T-cell malignancies were reported in ZUMA-3 at any time

Tisagenlecleucel vs Blinatumomab or Inotuzumab for Patients With Relapsed/Refractory B-cell Precursor Acute Lymphoblastic Leukemia (OBERON)

ClinicalTrials.gov Identifier: NCT03628053

 The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details.

[Recruitment Status](#) ⓘ : Withdrawn (Novartis is no longer pursuing this study because of planned investigation of novel CAR-T therapies in this patient population.)

[First Posted](#) ⓘ : August 14, 2018

[Last Update Posted](#) ⓘ : July 9, 2020

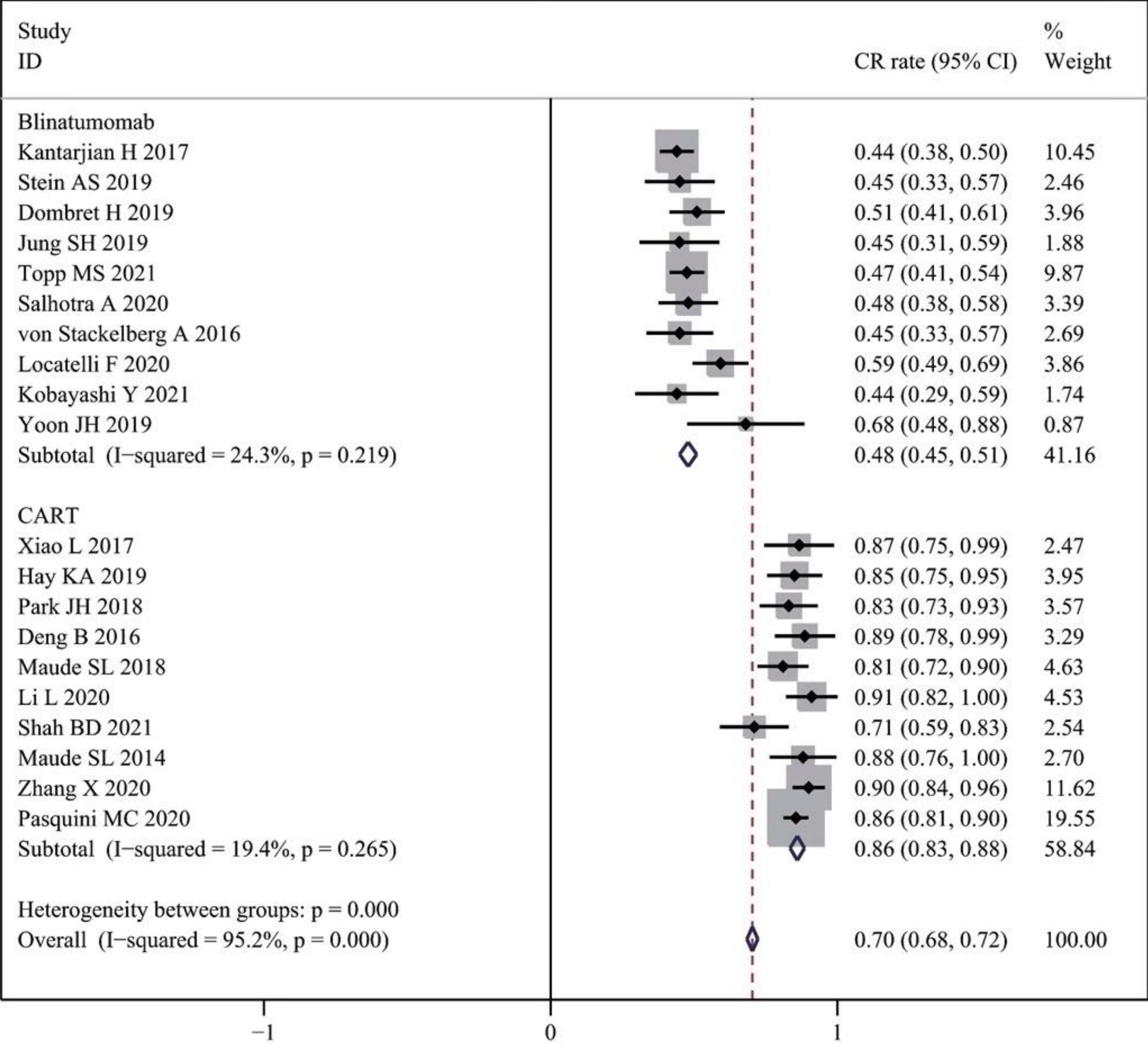
Sponsor:

Novartis Pharmaceuticals

Information provided by (Responsible Party):

Novartis (Novartis Pharmaceuticals)

Forest plot for the CR rate.



Blina Vs CAR T-cell therapy in R/R: a systematic review and meta-analysis

CAR T-cell therapy was more effective for achieving CR and bridging to allo-SCT than blinatumomab (2-year OS 75% vs. 57%).

blinatumomab bridging agent pre- SCT, for patients who achieve an MRD-negative state pre-SCT, post-SCT outcomes are expected to be the same as CAR-T

For adverse effects (AEs), blinatumomab was associated with a lower rate of grade ≥3 hematological toxicity, CRS, and neurological events.

Conclusions

- Risk assessment and MRD “target” at diagnosis
- Therapy: age and MRD oriented
- AlloHSCT:
 - In I CR In High Risk
 - MRD + ???
- Next frontiers:
 - Car-T in I line
 - Novel Agents/combinations

Recent Advances in Managing Acute Lymphoblastic Leukemia

Daniel J. DeAngelo, MD, PhD¹; Elias Jabbour, MD²; and Anjali Advani, MD³

**TREATING RELAPSED-REFRACTORY ALL
TOO MANY OPTIONS, WHICH ONE TO PICK?**

- Tkis
- Anti-CD19 Bispecific T-Cell Engager: Blinatumomab
- Anti-CD22 Antibody-Drug Conjugate: Inotuzumab Ozogamicin
- CAR T-Cell Therapies
- BH3 Mimetics
- Allo HSCT

These treatment modalities are not competitive but rather complementary, and they could be administered sequentially to produce the deepest remissions possible.