SINTOMA'25

8 A 10 DE MAIO

HOTEL INTERCONTINENTAL | SÃO PAULO

PARCERIA soho society of hematologic oncology

APOIO INSTITUCIONAL bp Educação e Pesquisa

Diante de sinais de alerta na LLA infantil e AYA quem vou chamar: TMO ou CAR-T?

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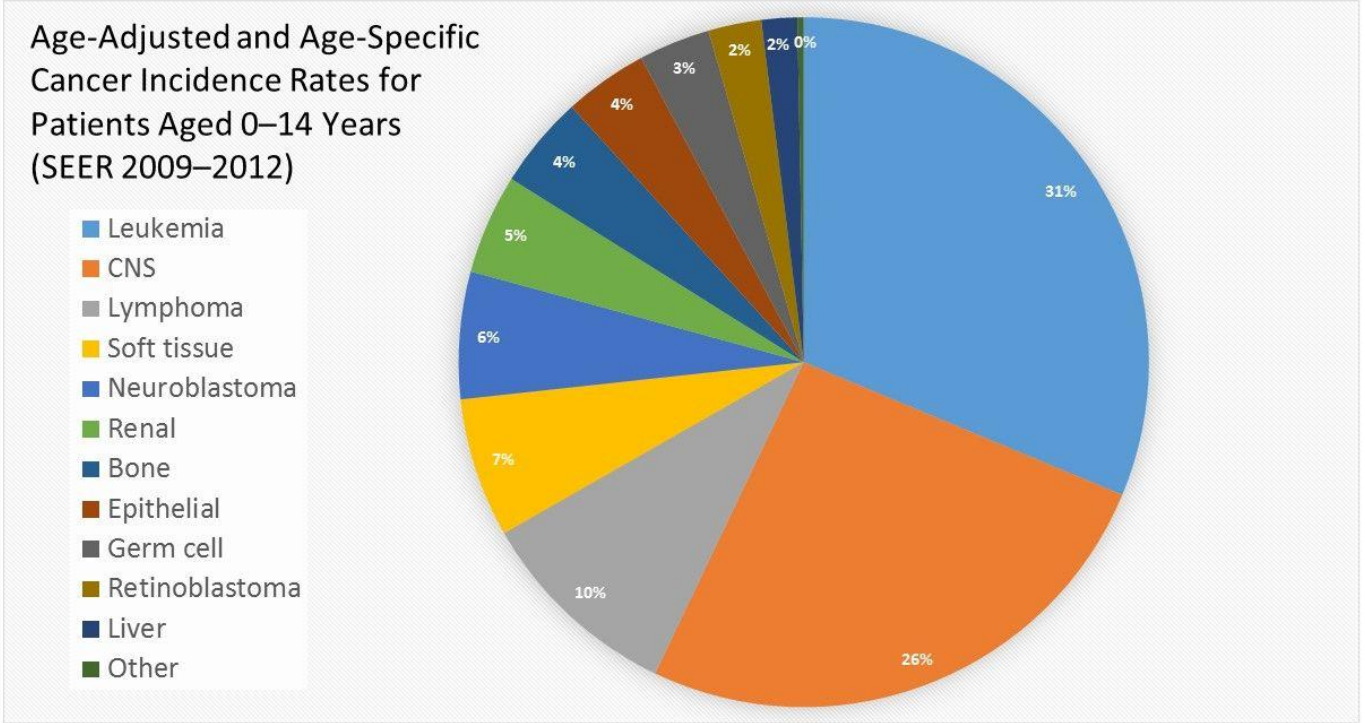
Introdução

- Leucemia Linfoide Aguda (LLA) corresponde a 1/3 das neoplasias pediátricas e 78,6% das leucemias

- Embora as taxas de remissão completa com quimioterapia inicial sejam altas (80-95%), aproximadamente 20% dos pacientes pediátricos com LLA recaem



Pasquini et al. Rev Med (São Paulo), 2022
Laetsch, Yanik, Boyer and Rheingold. Blood Advances, 2022
NCI, 2022

Introdução

- Leucemia Linfoide Aguda (LLA) recidivada: **quarta causa mais frequente de câncer na infância,** com incidência de 9,3 casos/milhão crianças/ano

- Número significativo de recidivas ocorre em pacientes que não são caracterizados inicialmente com aspectos desfavoráveis

- Taxas de segunda remissão são prejudicadas pelos altos índices de morte indutória decorrentes da alta morbidade associada

Sun W et al. Leukemia. 2018

Introdução

- Características iniciais que configuram sinais de alerta em LLA:
  - Idade < 1 ano e > 10 anos
  - Leucometria inicial > 50 mil/mm3
  - Envolvimento do Sistema Nervoso Central (SNC) e outros sítios extramedulares
  - Citogenética de alto risco

Laetsch, Yanik, Boyer and Rheingold. Blood Advances, 2022

Introdução

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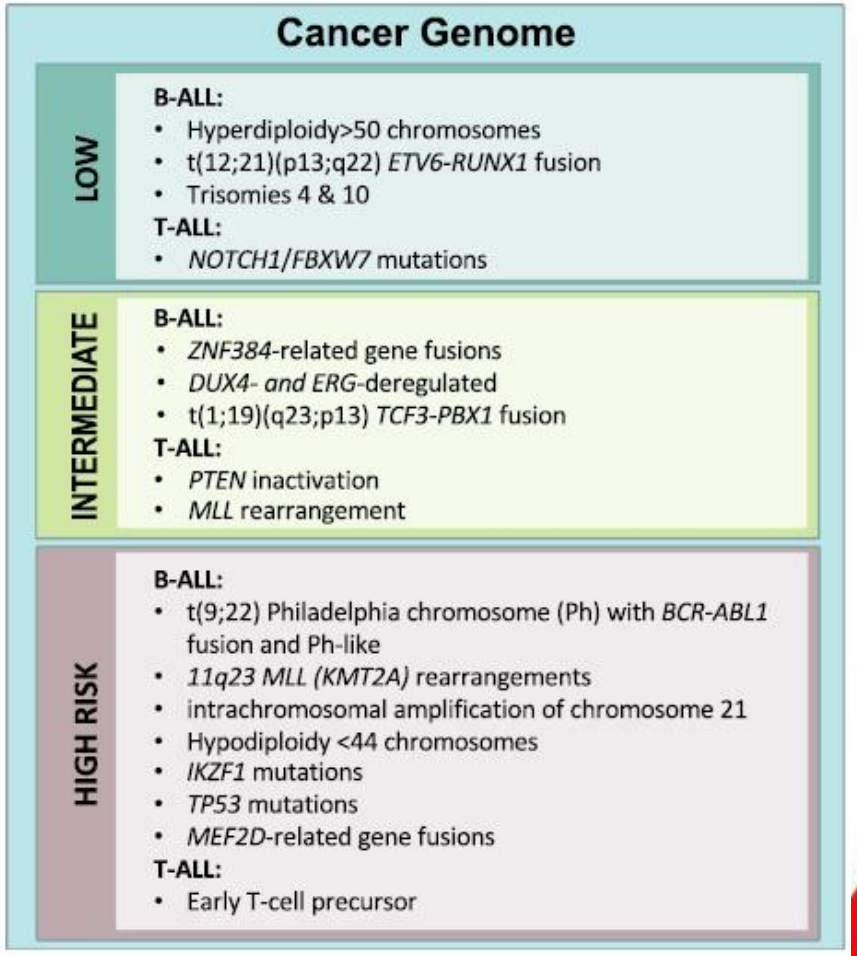


Laetsch, Yanik, Boyer and Rheingold. Blood Advances, 2022
Heikamp EB, Pui CH. J Peds, 2018

Introdução

- Comportamentos da doença que inferem maior risco de falha às terapêuticas convencionais:
  - Doença primária refratária: medula óssea M2 ou M3 após a indução
  - Persistência de Doença Residual Mensurável (DRM): DRM >0,01% ao final da consolidação em pacientes de alto risco
  - Recaída: as precoces (<36 meses do diagnóstico) são consideradas de maior risco

Laetsch, Yanik, Boyer and Rheingold. Blood Advances, 2022

Introdução

- O transplante alogênico de células-tronco hematopoiéticas aumenta de forma significativa a sobrevida de pacientes de alto risco, porém há alguns obstáculos:
  - A doença precisa estar em remissão
  - É necessário um doador de medula compatível, disponível e adequado
  - É necessário que o paciente tenha performance-status adequado para receber um regime de condicionamento mieloablativo, preferencialmente com radioterapia corporal total (TBI)
  - Tratamento prévio com Blinatumomab? Se recebeu, qual foi a resposta?
  - Tempo para ter acesso ao TMO (ou ao CAR T) é crucial!

Laetsch, Yanik, Boyer and Rheingold. Blood Advances, 2022

Indicações de Transplante alogênico de células-tronco hematopoiéticas - TCTH

TABLE 1: HSCT indications for pediatric ALL

HSCT indications for pediatric ALL in first remission:
ALL diagnosed before 6 months of age associated with MLL (KMT2A) rearrangement and with other risk factors, such as hyperleukocytosis (> 300,000/mm3) and non-response to corticosteroids.
Children who fail induction therapy (M2/M3 marrow), except if hyperdiploid ALL and age less than 6 years.
The current evidence does not support the use of HSCT in first remission for children with Ph+ (Bcr/Abl) ALL and hypodiploidy who have a good response to chemotherapy (CT).
HSCT is indicated for B- or T-cell ALL in first remission in patients with an MRD equal to or greater than 10-3, or 0.1%, by the end of the consolidation phase (i.e., after approximately 12 weeks of treatment)
HSCT indications for pediatric ALL in *second remission:*
Early bone marrow (BM) relapse of B-cell ALL (< 36 months after first remission). In late BM or extramedullary relapse of B-cell ALL, CT and HSCT exhibit similar results, so HSCT should be preferred, except in cases with persisting MRD positivity.
Early isolated extramedullary relapse of B-cell ALL (< 18 months of first remission).
Any, early or late, medullary, or extramedullary, relapse of T-cell ALL.

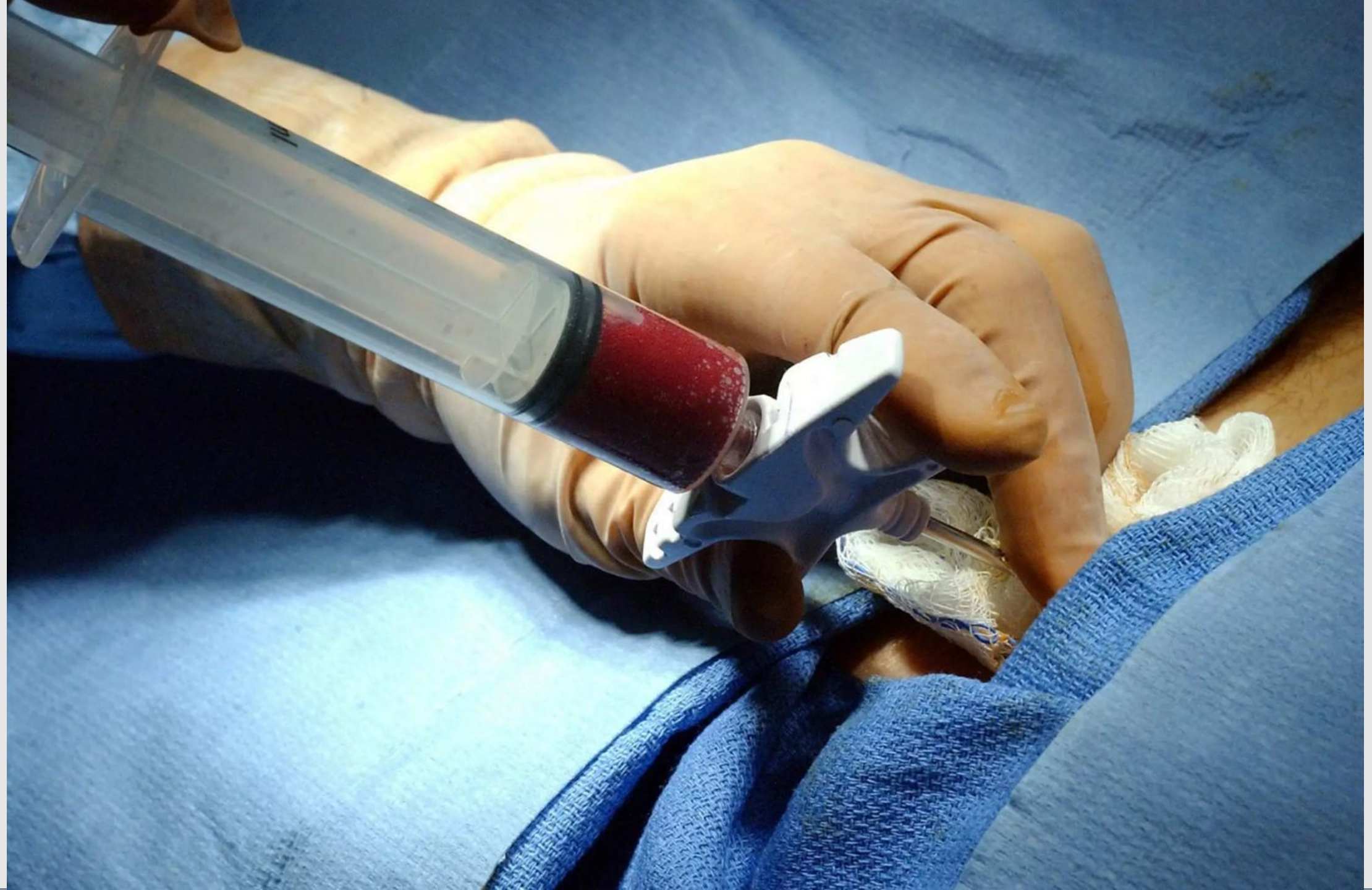
Consenso SBTMO 2021

Indicações atuais de células CAR T

Tratamento de pacientes pediátricos e adultos jovens até e incluindo 25 anos de idade:

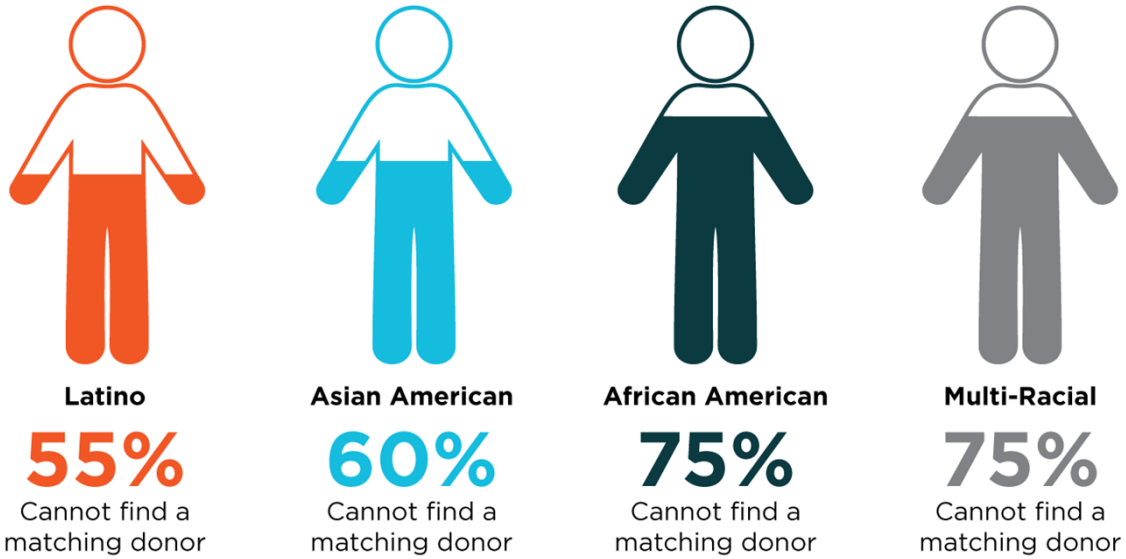
- LLA de precursor B com refratariedade primária
- LLA de precursor B em recidiva refratária
- LLA de precursor B a partir da segunda recidiva
- LLA de precursor B em recidiva após TCTH alogênico
- Pacientes com LLA de precursor B de muito alto risco que têm indicação de TCTH porém não são elegíveis por razões médicas

The EBMT/EHA CAR-T Cell Handbook, 2022



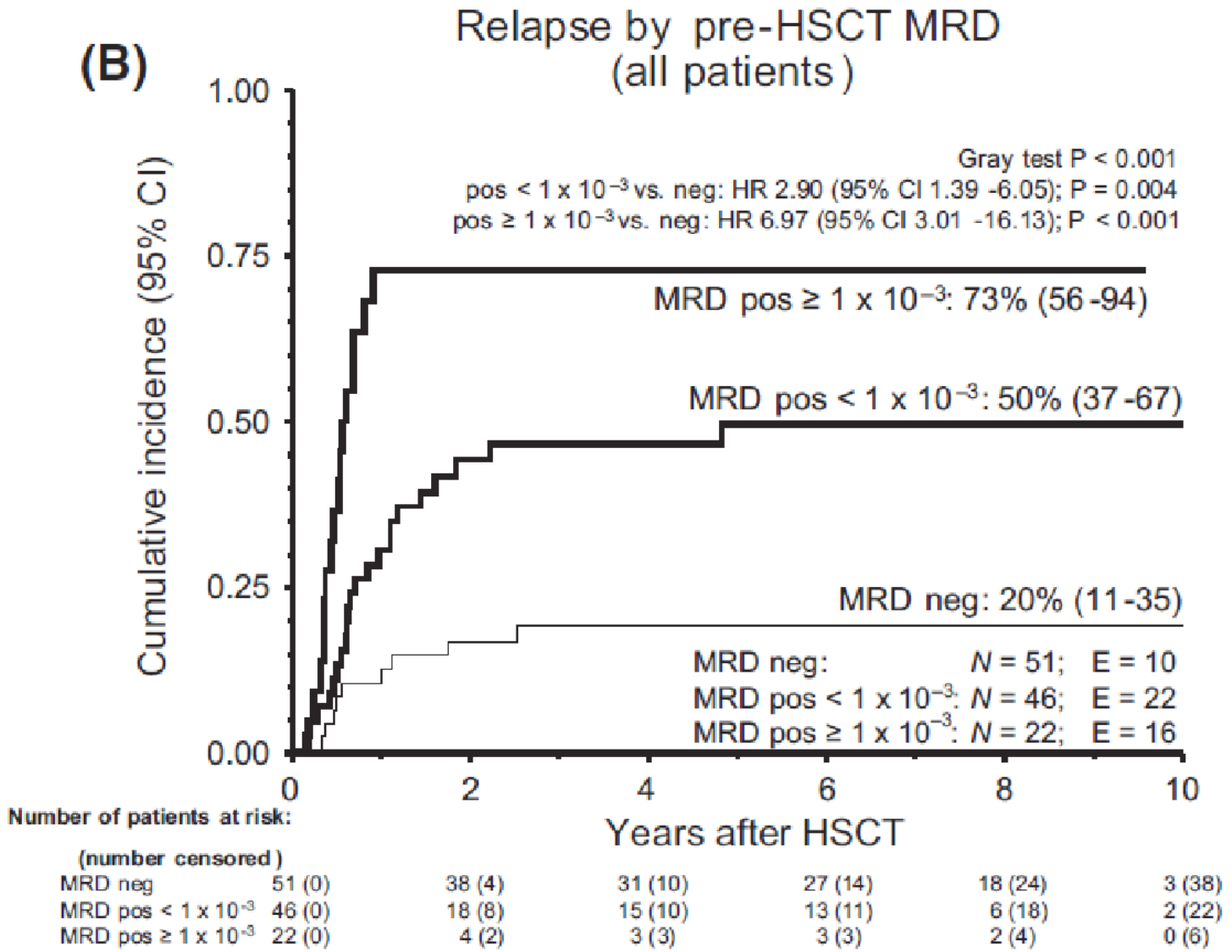
TCTH - busca por doador

- Probabilidade de encontrar doador:
  - Doador familiar HLA compatível em 30 - 40% dos pacientes
  - REDOME: no Brasil chance de 1 em 100 mil
  - Doador haploidêntico: disponível quase universalmente



www.giftolife.org

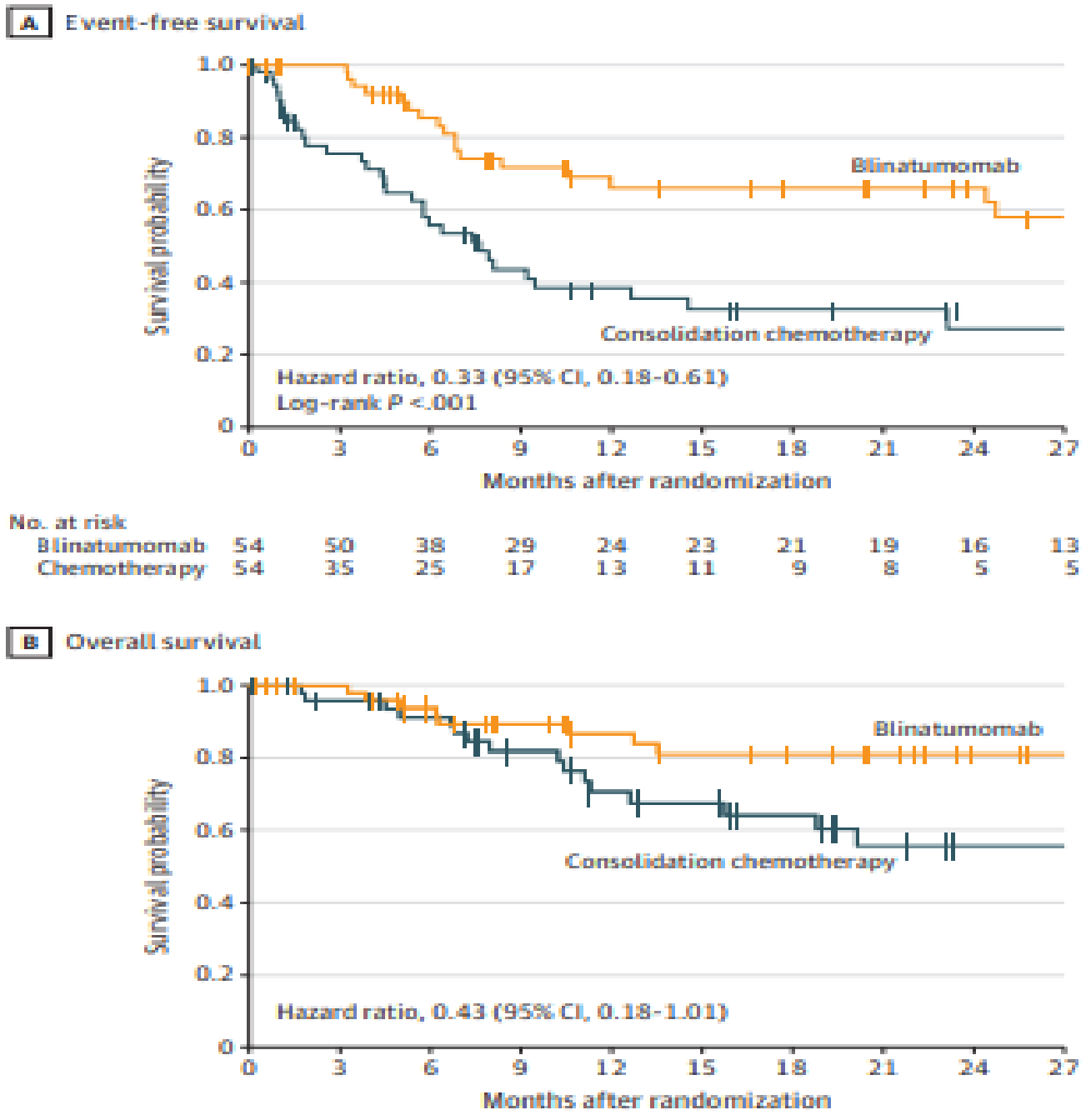
Pre- and post-transplant minimal residual disease predicts relapse occurrence in children with acute lymphoblastic leukaemia



Lovisa et al. BJH, 2018

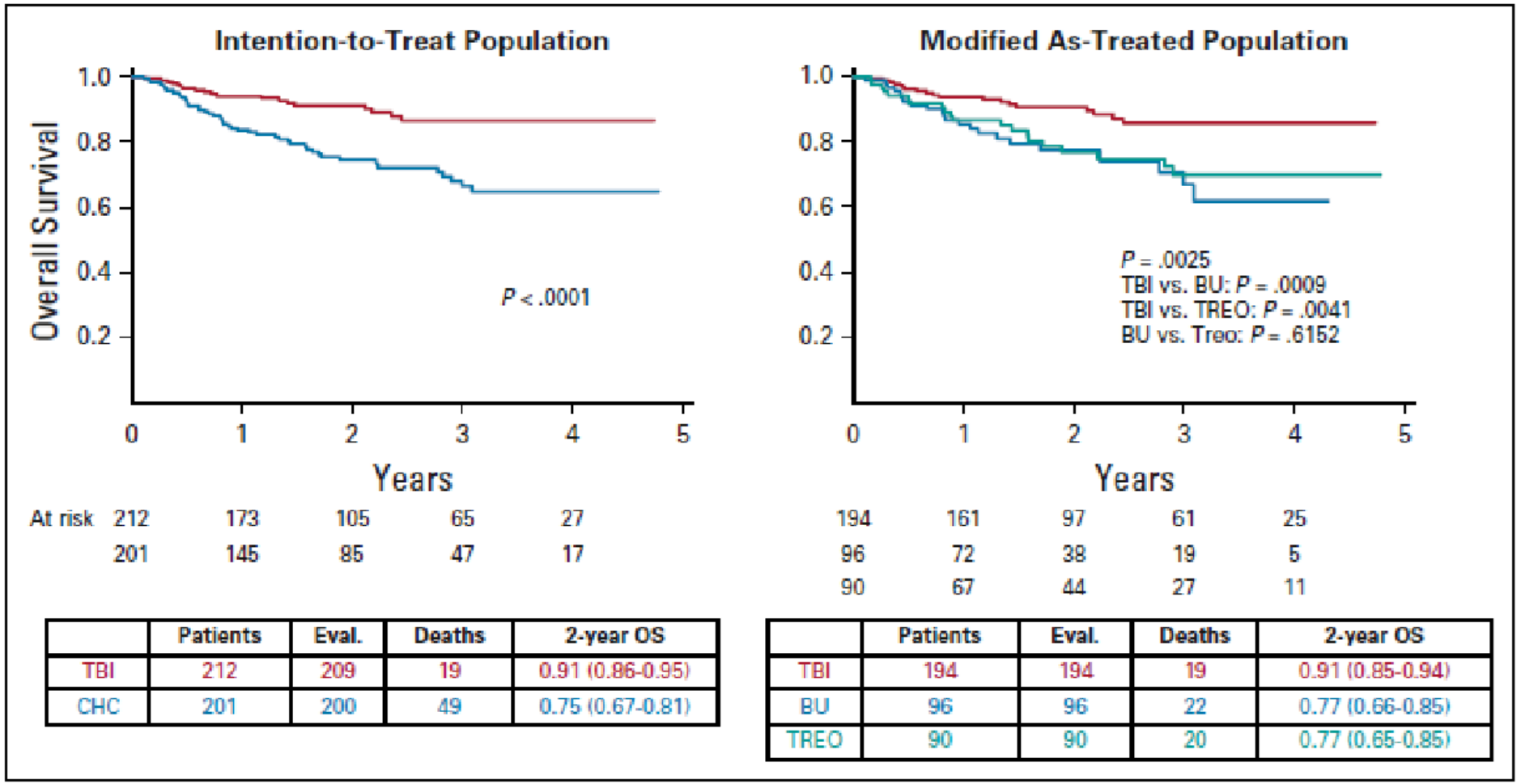
Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse b-cell acute lymphoblastic leukemia: a randomized clinical trial

Morte por qualquer causa:
15% Blina x 30% QT



JAMA 2021; 325 (9): 843-854

TBI *versus* QT para TCTH em LLA



	Patients	Eval.	Deaths	2-year OS
TBI	212	209	19	0.91 (0.86-0.95)
CHC	201	200	49	0.75 (0.67-0.81)

	Patients	Eval.	Deaths	2-year OS
TBI	194	194	19	0.91 (0.85-0.94)
BU	96	96	22	0.77 (0.66-0.85)
TREO	90	90	20	0.77 (0.65-0.85)

FIG 2. Primary end point: Overall survival. BU, busulfan; CHC, chemo-conditioning; CIR, cumulative incidence of relapse; EFS, event-free survival; OS, overall survival; TBI, total body irradiation; TREO, treosulfan; TRM, treatment-related mortality.

MAT
- ✓ 2% TBI
- ✓ 9% QT

Recidiva 2a
- ✓ 12% TBI
- ✓ 33% QT

SG @ 2 anos:
- ✓ 91% TBI
- ✓ 77% QT

Peters et al. JCO, 2020

Transplante alogênico de células-tronco hematopoiéticas - TCTH

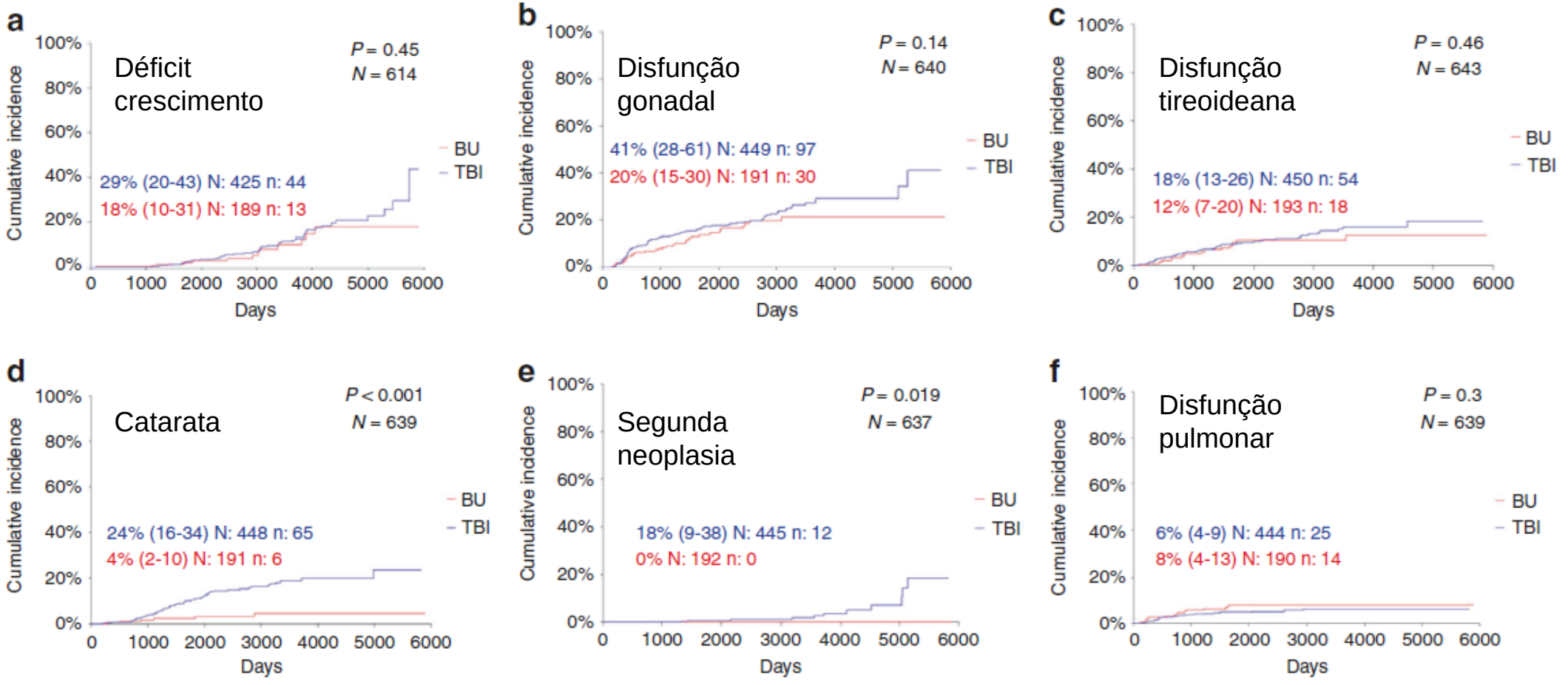
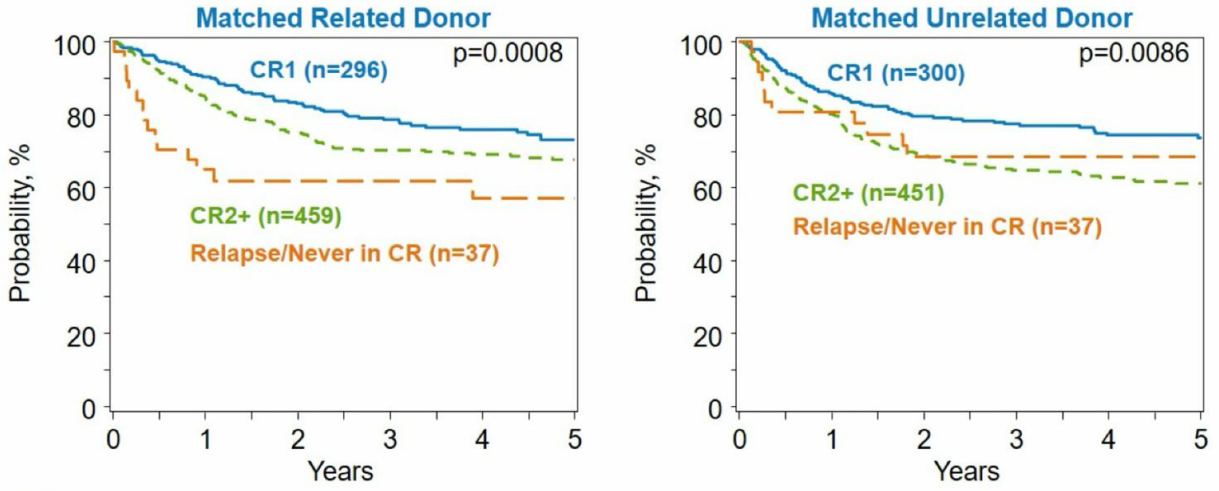


Fig. 1 Cumulative Incidence of long-term effects. Cumulative incidence of (**a**) growth alteration, (**b**) alteration of the gonadal function (**c**) alteration of the thyroid function (**d**) cataract (**e**) secondary malignant neoplasia and (**f**) alteration of the pulmonary function according to the conditioning regimen. TBI total body irradiation BU busulfan iv or oral, 95% CI interval of confidence at 95%, n events.

Saglio et al. BMT, 2019

TCTH em LLA < 18 anos

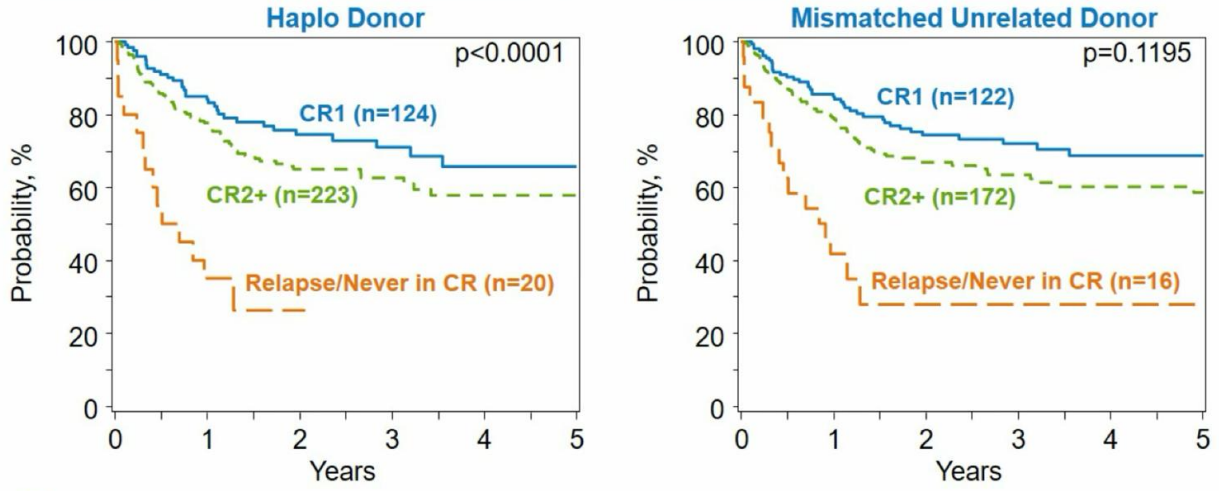
Survival after Allogeneic HCTs for Acute Lymphoblastic Leukemia (ALL), Using Matched Donors, Age <18 Years, in the U.S., 2010-2020



CIBMTR CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

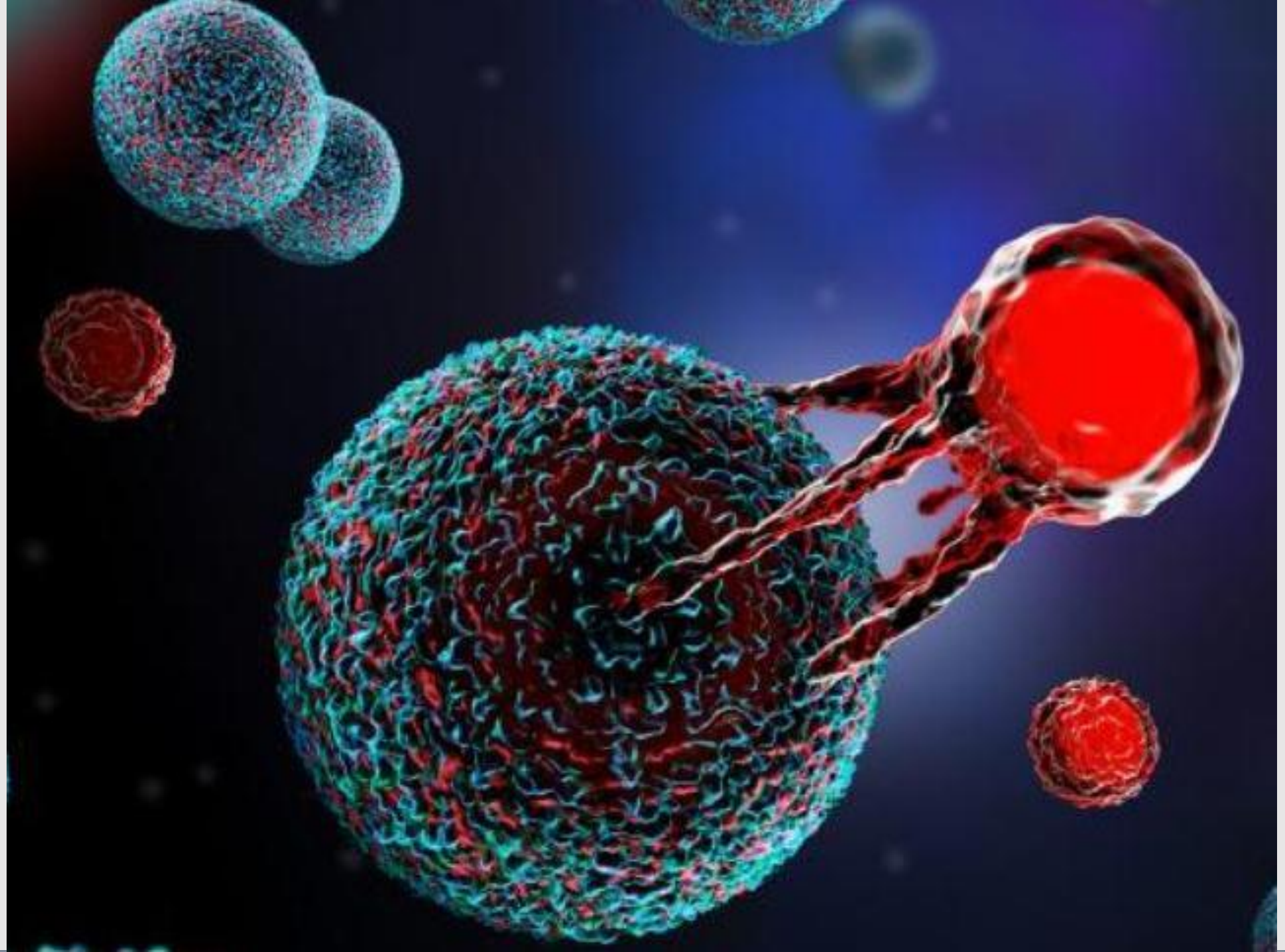
Abbreviation – CR: Complete remission.

Survival after Allogeneic HCTs for Acute Lymphoblastic Leukemia (ALL), Using Mismatched Donors, Age <18 Years, in the U.S., 2010-2020

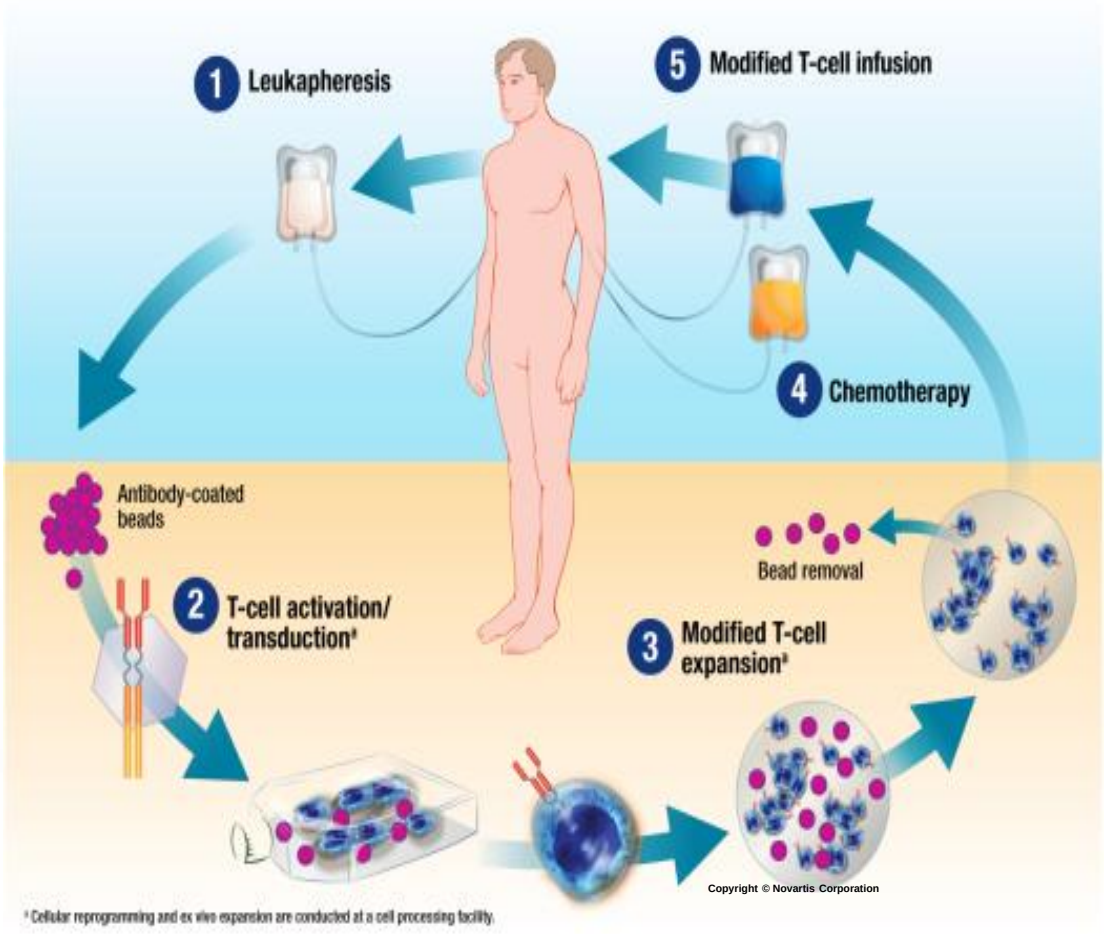


CIBMTR CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Abbreviation – CR: Complete remission; Haplo: ≥2 HLA antigen mismatch; MMUD: Mismatched unrelated donor ≤7/8 HLA allele match, excluding CB.



Cadeia de produção CAR T



Terapia Ponte

Leucaférese: células T são coletadas

Transdução genéticas das células T ex vivo com um vetor lentivirus codificando o receptor anti-CD19

Células CAR-T sofrem expansão ex vivo com beads magnéticos

Quimioterapia linfodepletora administrada antes da infusão das células CAR-T

Infusão das células CAR-T no paciente

ELIANA – 5 Years Follow-up update

Efficacy (n=79)

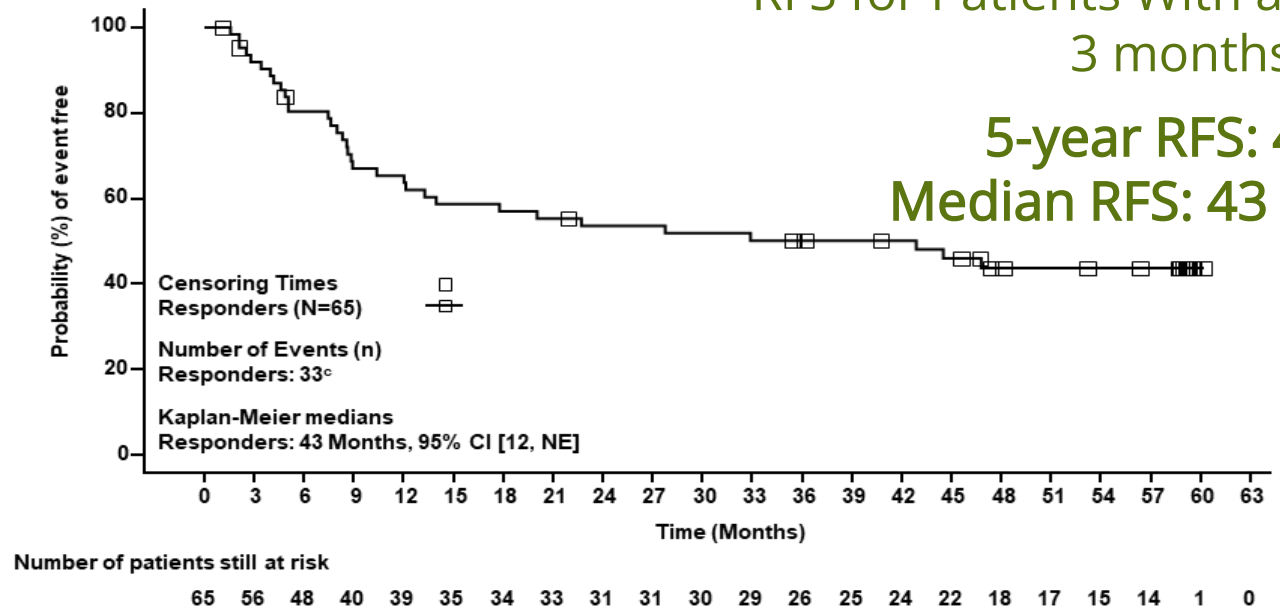
ORR:

- **82% (CR: 62%+Cri: 20%)** in patients who achieved BOR within 3 mo by IRC
- **98% of patients** who achieved remission were MRD– (<0.01) at Month 3

RFS

RFS for Patients With a CR/CRi within 3 months

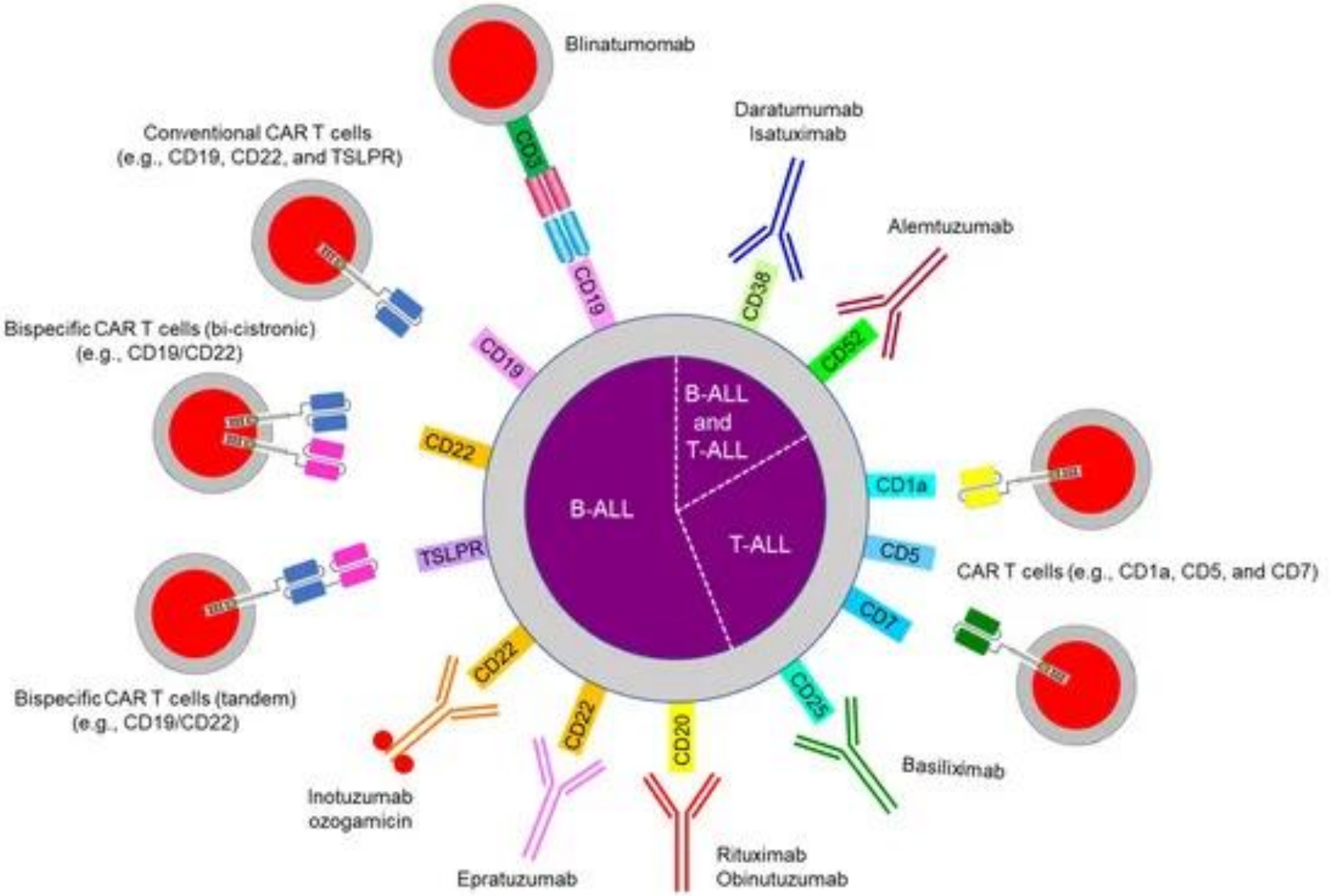
5-year RFS: 44%
Median RFS: 43 months



- Post tisagenlecleucel infusion, 25% of patients underwent alloSCT (in remission/after relapse: 14%/10%)
- Median time to B-cell recovery was 39 months in responders

Rives et al. EHA, 2022

Imunofenótipo da LLA

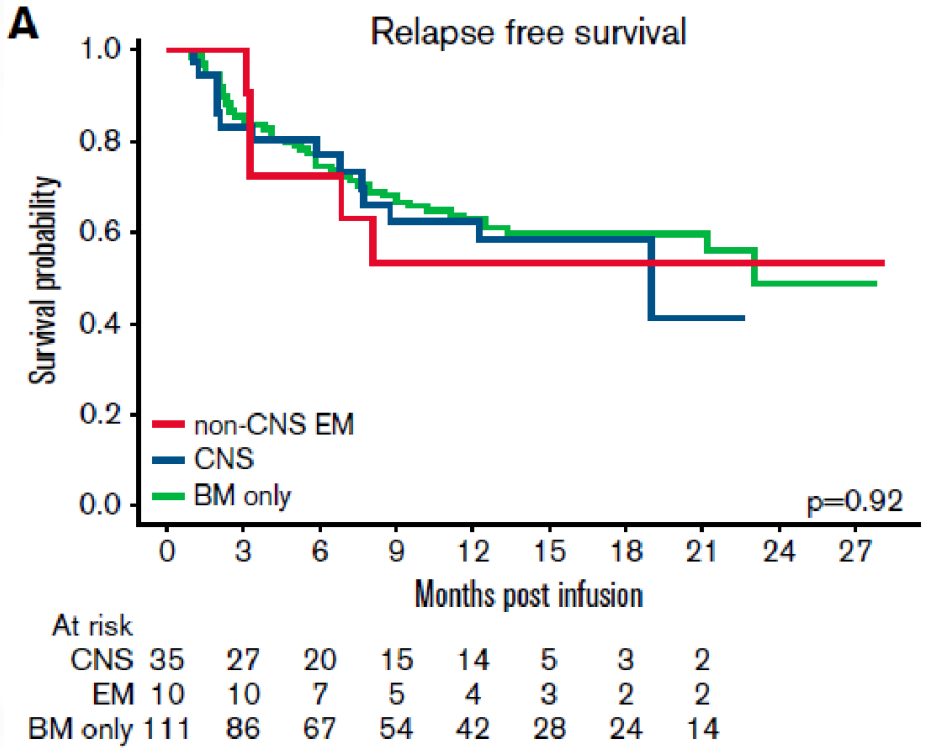


LLA B derivada: 85% dos casos em pediatria

LLA T derivada: 10-15% dos casos em pediatria

Tasian et al. Cancer, 2015
Inaba and Pui. J. Clin. Med. 2021

CAR T e doença extramedular



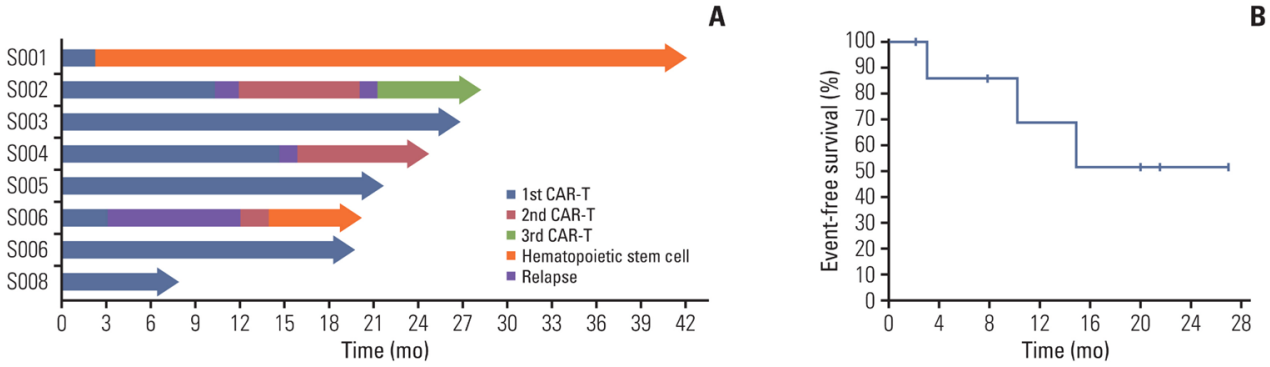
n = 184
55 extramedular relapses (CNS =40)

Fabrizio et al. Blood Advances, 2022

EMD[b], *n* (%)	
No	24 (88.9)
Yes	3 (11.1)

Doença extramedular: remissão completa em apenas 11%

Pu et al. Scand J Immunol. 2024



8 pacientes com doença extramedular: todos remitiram, 3 recidivaram. 8/8 vivos

Wang X e cols. Cancer Res Treat. 2022

CAR T e leucemia em SNC

ELIANA[11] Tisagenlecleucel NCT02435849	CASSIOPEIA[32] Tisagenlecleucel NCT03876769	CHOP Humanized CAR-T[33] huCART19 NCT03792633	National Cancer Institute[10] Anti-CD19 CAR NCT01593696	PLAT-02[7] Seattle Children's Hospital CD19+ CAR-T NCT02028455	CHP959[20] Murine CAR-T19 NCT01626495
Age ≥ 3 years at screening and ≤ 21 years at diagnosis	**Age** 1 to 25 years at screening	**Age** 1 to 29 years at screening	**Age** 1 to 30 years	**Age** 12 to 27 years and ≥ 10 kg in weight	**Age** 1 to 24 years
Prior Therapies r/r B-ALL: ≥ 2 BM relapse Any BM relapse ≥ 6 months after alloSCT if there is no active GVHD Primary refractory Ph+ with 2 failed lines of TKI Contraindicated for TKI Ineligible for or refuses alloSCT	**Prior Therapies** De novo NCI HR B-ALL who received first-line treatment and are MRD ≥ 0.01% at EOC Prior induction and consolidation chemotherapy allowed: first-line subjects: ≤ 3 blocks of standard chemotherapy for first-line B-ALL (defined as 4-drug induction, augmented BFM consolidation, and interim maintenance with high-dose MTX)	**Prior Therapies** **COHORT A** r/r B-ALL: Newly diagnosed NCI HR B-ALL with induction failure First BM relapse at < 36 months ≥ 2 relapse Any relapse ≥ 4 months after alloSCT Refractory disease† Ineligible for alloSCT **Prior Therapies** **COHORT B** r/r B-ALL: Previously treated with B-cell–directed engineered cell therapy: • Partial response or no response to prior cell therapy • CD19+ relapse after prior cell therapy • Demonstrated early (≤ 6 months from infusion) B-cell recovery suggesting loss of engineered cells	**Prior Therapies** r/r B-ALL with ≥ 1 standard chemotherapy and 1 salvage regimen Either ineligible, refused, or has disease activity that prohibits alloSCT Patients with a history of alloSCT are eligible if ≥ 100 days post-transplant, if there is no active GVHD, and if no longer taking immunosuppressive agents for ≥ 30 days prior to enrollment	**Prior Therapies** Confirmed recurrence defined as ≥ 0.01% disease in the marrow or isolated extramedullary disease following alloSCT OR **No prior history of alloSCT:** 2nd or greater relapse, with or without extramedullary disease If first relapse, ≥ 0.01% persistent MRD after reinduction Primary refractory alloSCT is indicated but ineligible for alloSCT	**Prior Therapies** **Ineligible for alloSCT:** Age Comorbid disease Contraindications to TBI-based conditioning Lack of donor Prior SCT Declines alloSCT Any relapse after prior SCT
Disease Burden BM with ≥ 5% lymphoblasts by morphologic assessment at screening	**Exclusion Criteria** Patients with Ph+ ALL and prior TKI therapy are excluded	**CNS Disease** Patients with prior or current history of CNS3 disease will be eligible if CNS disease is responsive to therapy	**CNS Disease** Absence of neurologic symptoms suggestive of CNS leukemia		**CNS Disease** With CNS disease if responsive to therapy

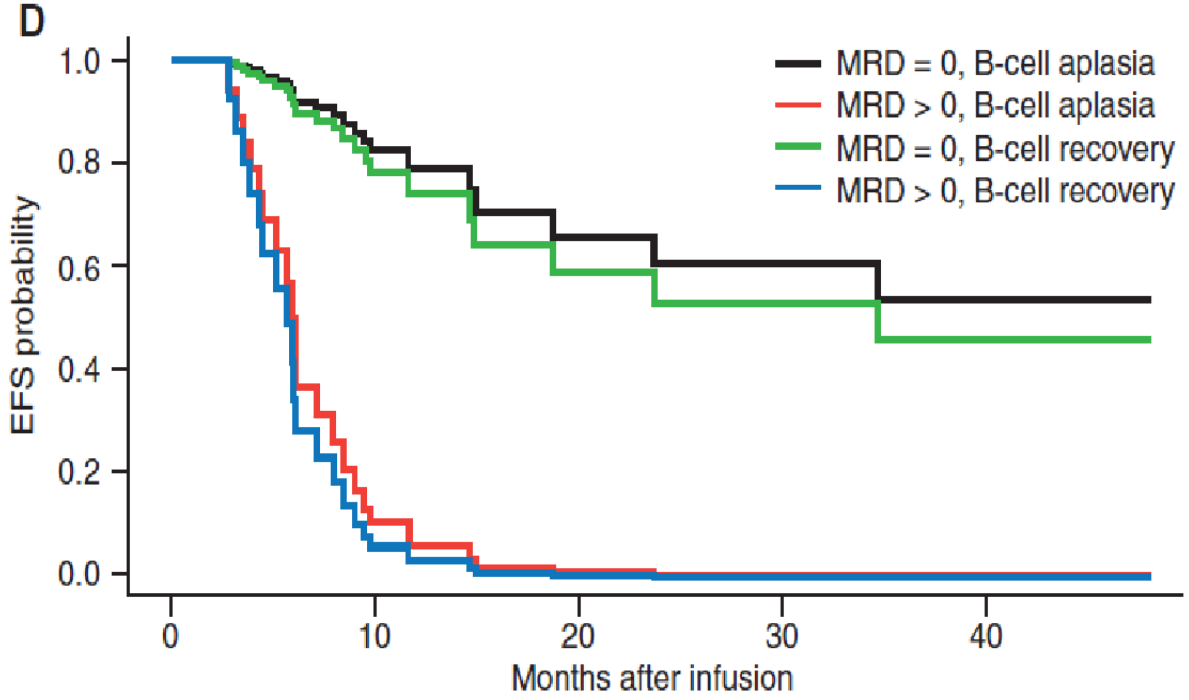
Laetsch et al. Blood Reviews. 2021

B cell recovery and MRD – prognosis

C

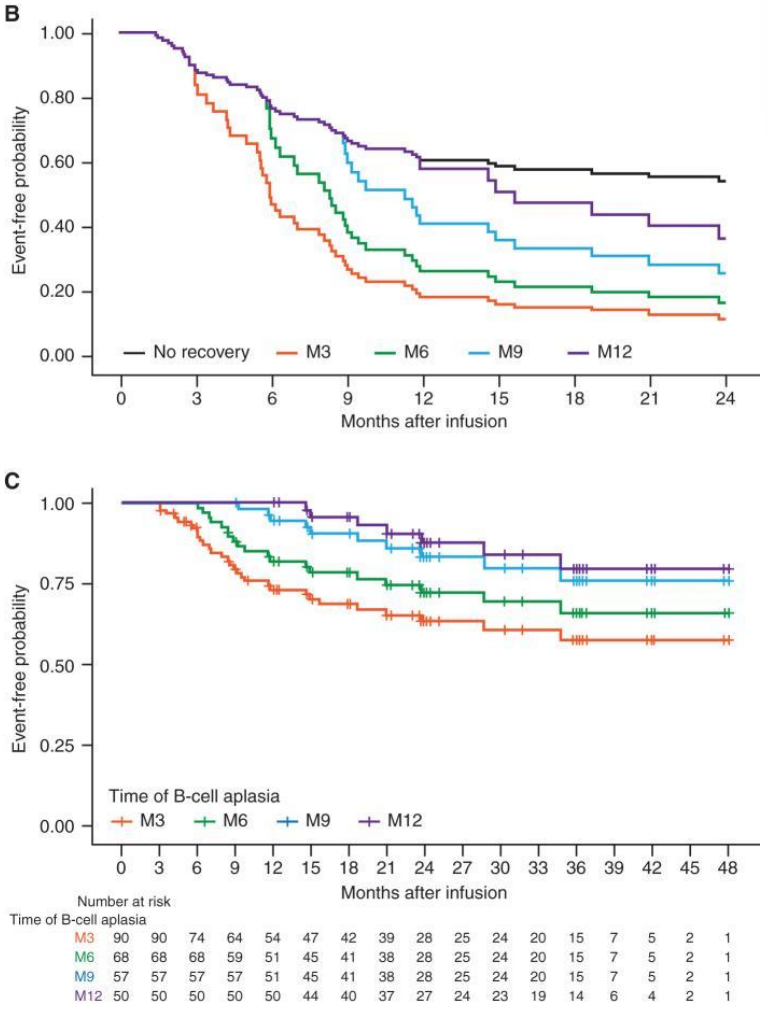
	HR (95% CI)	P
Month 3 NGS-MRD status		
MRD = 0	—	—
MRD > 0	12.0 (2.87–50.0)	<0.001
B-cell recovery	1.27 (0.33–4.79)	0.7

D



A

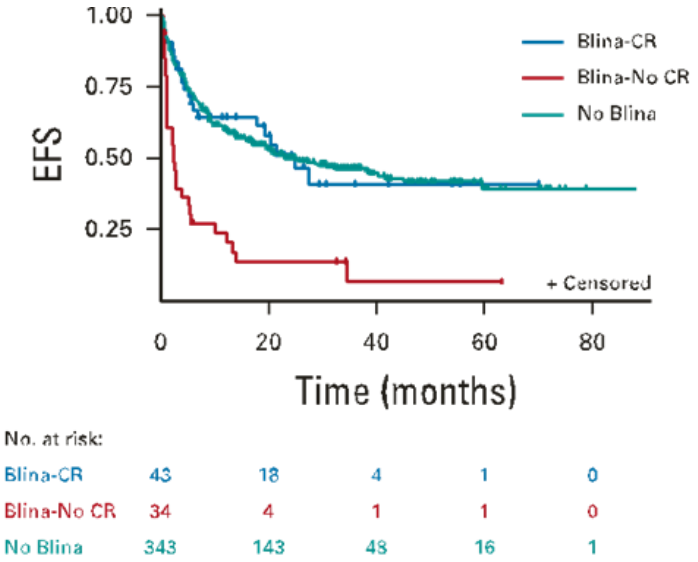
	HR (95% CI)	P
B-cell recovery	4.50 (2.03–9.97)	<0.001

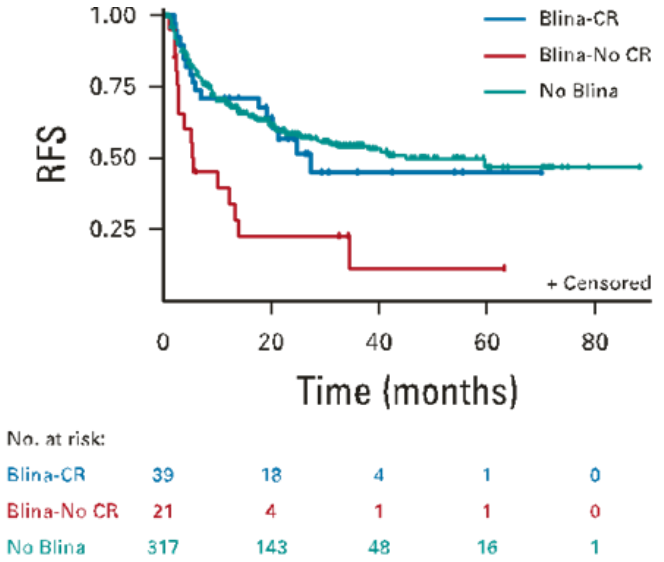


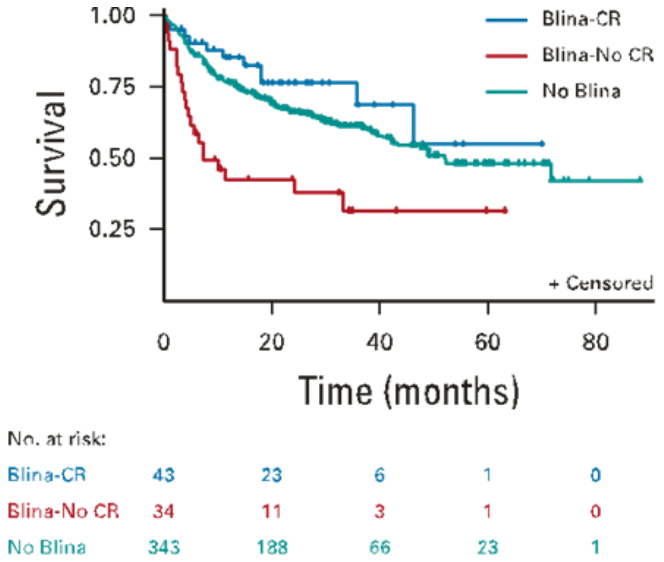
Pulsipher et al. Blood Cancer Discovery, 2022

Blinatumomab Nonresponse and High-Disease Burden Are Associated With Inferior Outcomes After CD19-CAR for B-ALL

n = 420
Mediana idade 12,7 anos







	Resposta completa a Blina	Sem Blina prévio	Refratário a Blina	P
DRM negativo	93%	90%	61%	<0.0001
Mediana livre de recidiva	27 m	45 m	5,6 m	0.7
SLE (12 meses)	65%	60%	24%	<0.0001
SG (12 meses)	86%	77%	43%	0.0001

Myers et al. JCO. 2021

frontiers in Pediatrics

REVIEW
published: 25 January 2022
doi: 10.3389/fped.2021.784024

Chimeric Antigen Receptor T-Cell Therapy in Paediatric B-Cell Precursor Acute Lymphoblastic Leukaemia: Curative Treatment Option or Bridge to Transplant?

Jochen Buechner[1], Ignazio Caruana[2], Annette Künkele[3], Susana Rives[4], Kim Vettenranta[5], Peter Bader[6], Christina Peters[7,8], André Baruchel[9] and Friso G. Calkoen[10]*

FIGURE 5 | Proposed approach to HSCT consolidation after CAR-T for paediatric patients and AYA with BCP-ALL based on treatment- and disease-related risk factors for relapse. *MRD positivity defined at >0.01%. AUC, area under the curve; AYA, adolescent and young adult; BCA, B-cell aplasia; CAR-T, chimeric antigen receptor T-cell therapy; FCM, flow cytometry; HSCT, haematopoietic stem cell transplantation; KMT2A, lysine methyltransferase 2A; MRD, minimal residual disease; NGS, next-generation sequencing; OOS, out of specification; PCR, polymerase chain reaction.

Buechner et al. Frontiers in Pediatrics, 2022

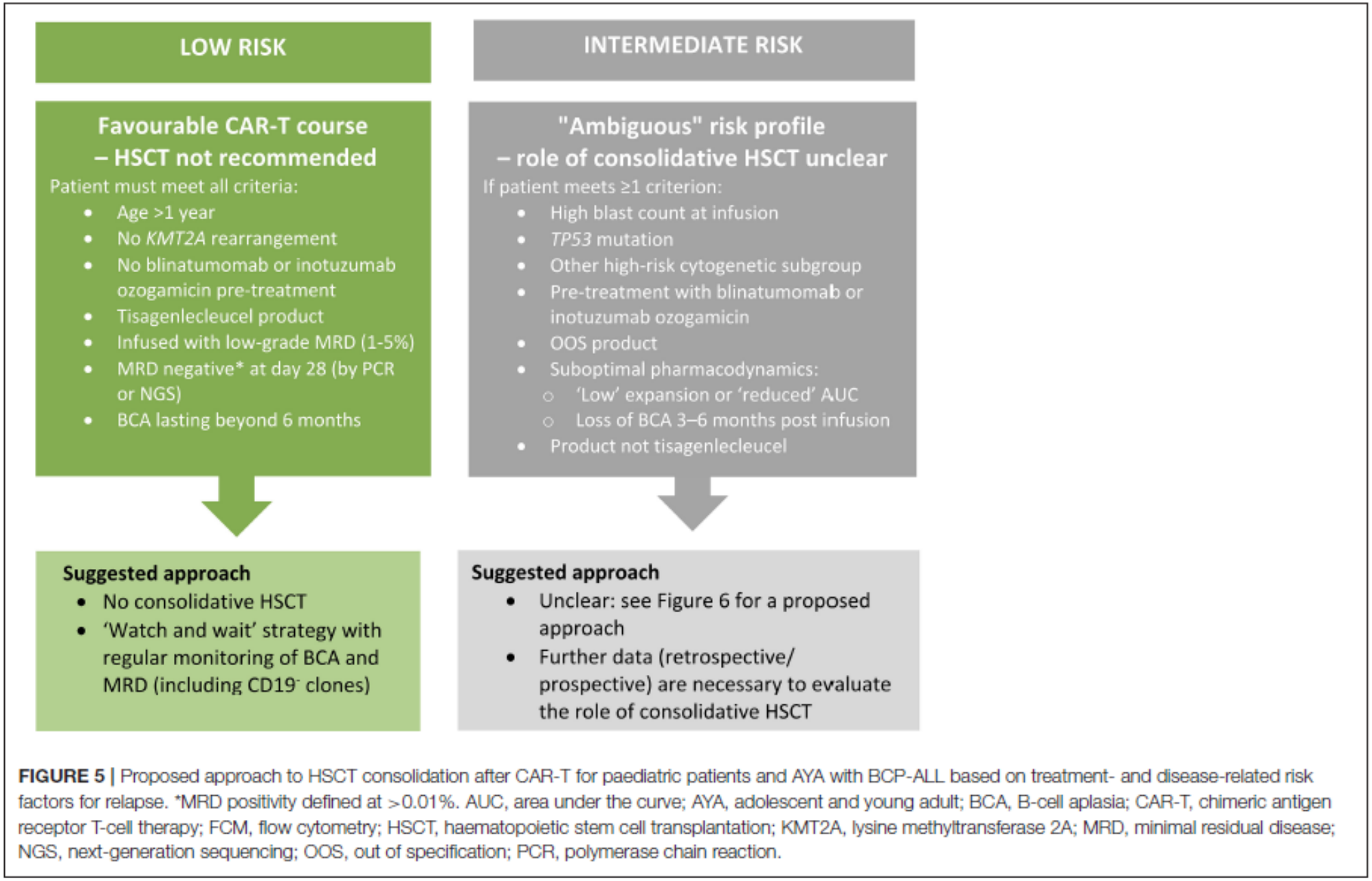


FIGURE 5 | Proposed approach to HSCT consolidation after CAR-T for paediatric patients and AYA with BCP-ALL based on treatment- and disease-related risk factors for relapse. *MRD positivity defined at >0.01%. AUC, area under the curve; AYA, adolescent and young adult; BCA, B-cell aplasia; CAR-T, chimeric antigen receptor T-cell therapy; FCM, flow cytometry; HSCT, haematopoietic stem cell transplantation; KMT2A, lysine methyltransferase 2A; MRD, minimal residual disease; NGS, next-generation sequencing; OOS, out of specification; PCR, polymerase chain reaction.

Buechner et al. Frontiers in Pediatrics, 2022

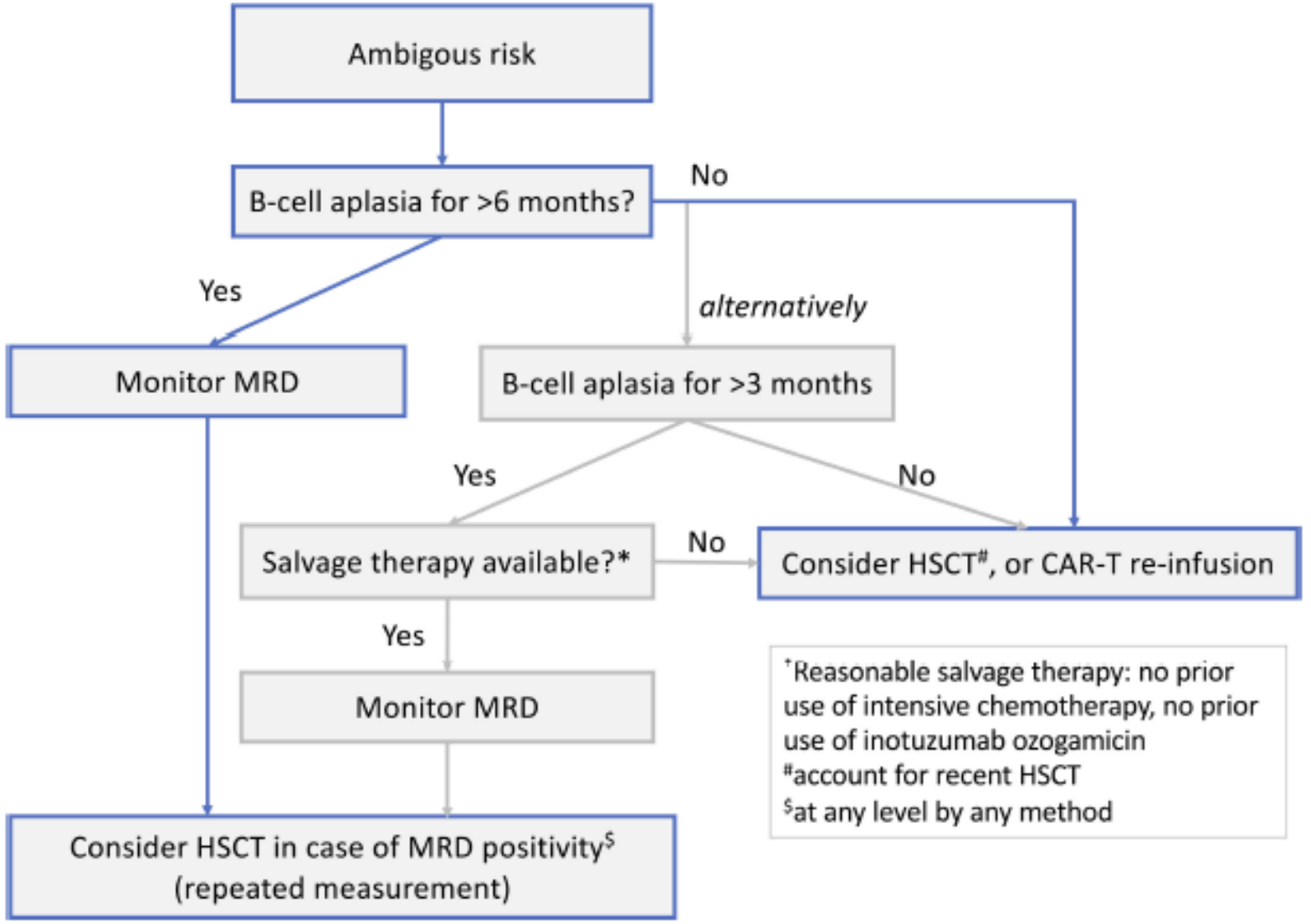
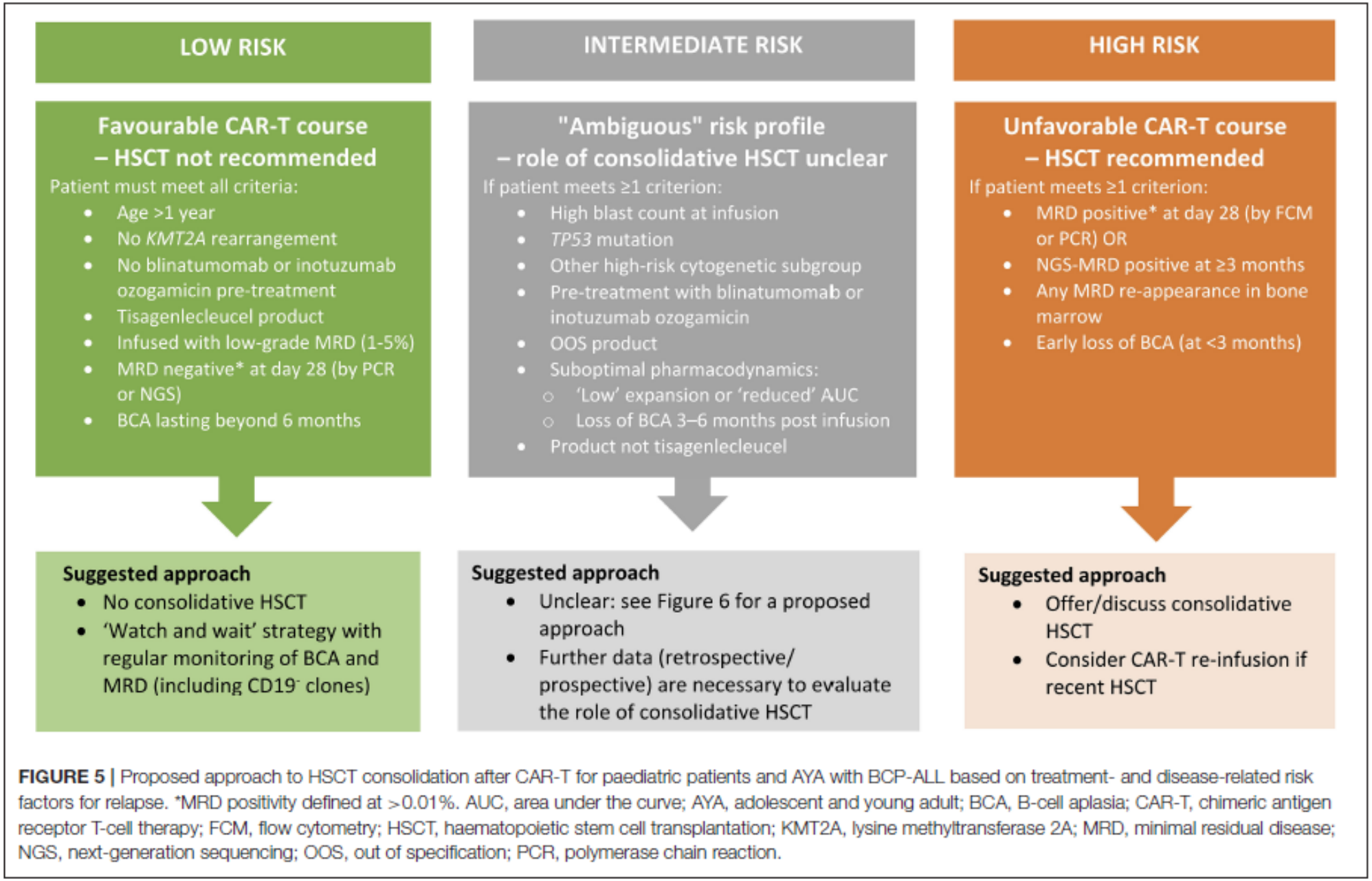


FIGURE 6 | Follow-up guidance after CAR-T for paediatric patients and AYA with BCP-ALL and an "ambiguous risk profile" (see **Figure 5** for criteria for an ambiguous risk profile).

Buechner et al. Frontiers in Pediatrics, 2022



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Buechner et al. Frontiers in Pediatrics, 2022

Conclusões

- A decisão entre a terapia com células CAR T e o TCTH no tratamento da LLA de alto risco ou recidivada/refratária é complexa e deve ser individualizada
- A estratificação de risco precisa e o monitoramento da DRM são cruciais para guiar as decisões terapêuticas e melhorar os resultados para esses pacientes
- A terapia com células CAR T é altamente eficaz para alcançar remissão em pacientes refratários, podendo ser uma ponte para o transplante ou uma terapia definitiva
- O TCTH alogênico continua sendo uma modalidade importante para a consolidação e para o aproveitamento do efeito do enxerto contra a leucemia
- A sequência ideal e a combinação dessas terapias ainda estão sendo definidas

Conclusões

LLA B alto risco em remissão
- Sem TCTH prévio
- Performance-status adequado

→ **TCTH**

LLA B alto risco refratária

→ **Blinatumomab*** → (remissão) → **TCTH**

→ **CAR T** → **TCTH**

→ **CAR T** → **Watch and wait**

LLA B alto risco + recidiva após TCTH → **CAR T**

*Atenção à carga tumoral!

Obrigado!

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