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PARCERIA **soho**
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APOIO
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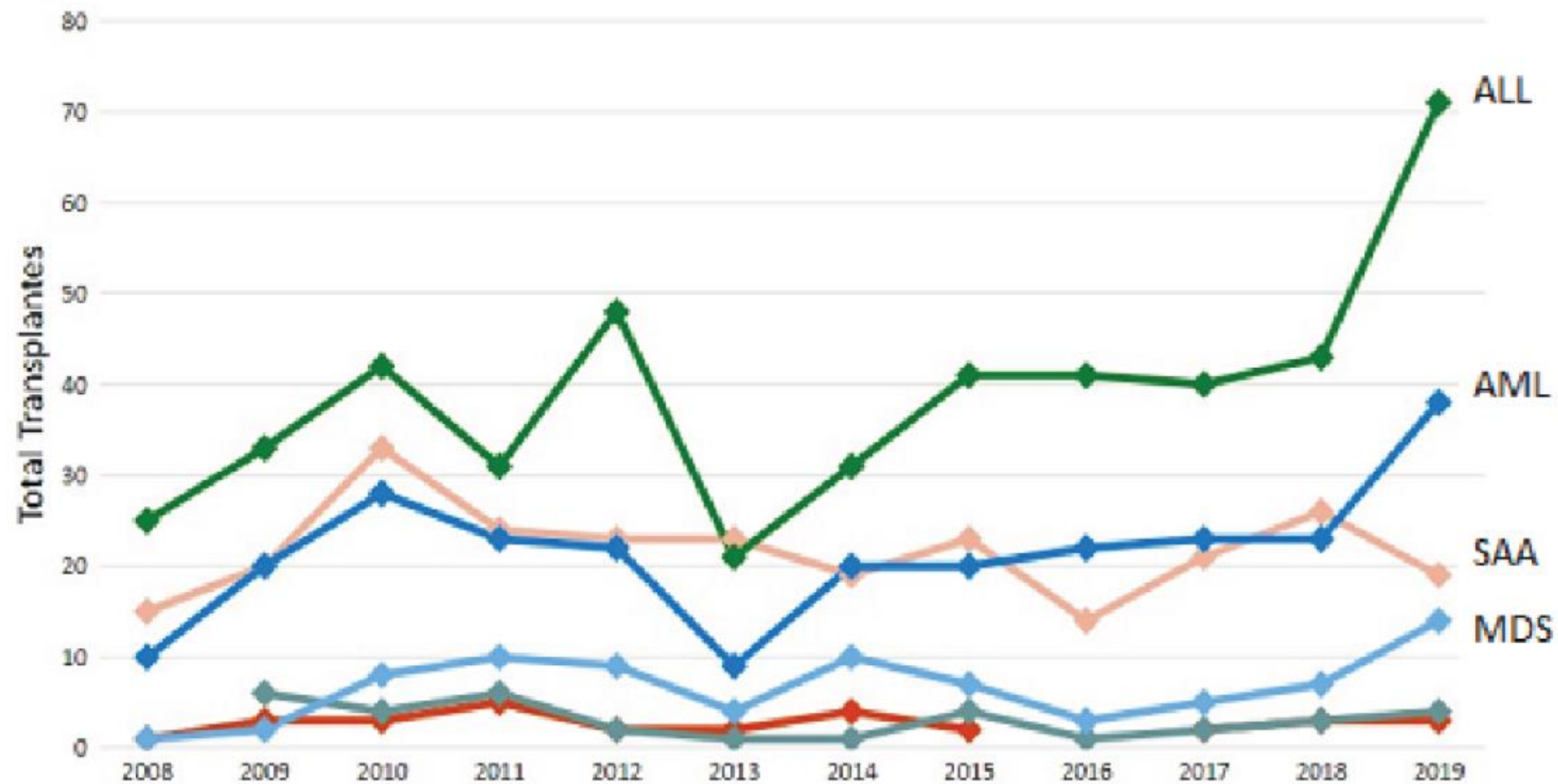
bp Educação
e Pesquisa

Como tenho decidido entre TMO e CAR-T na LLA?

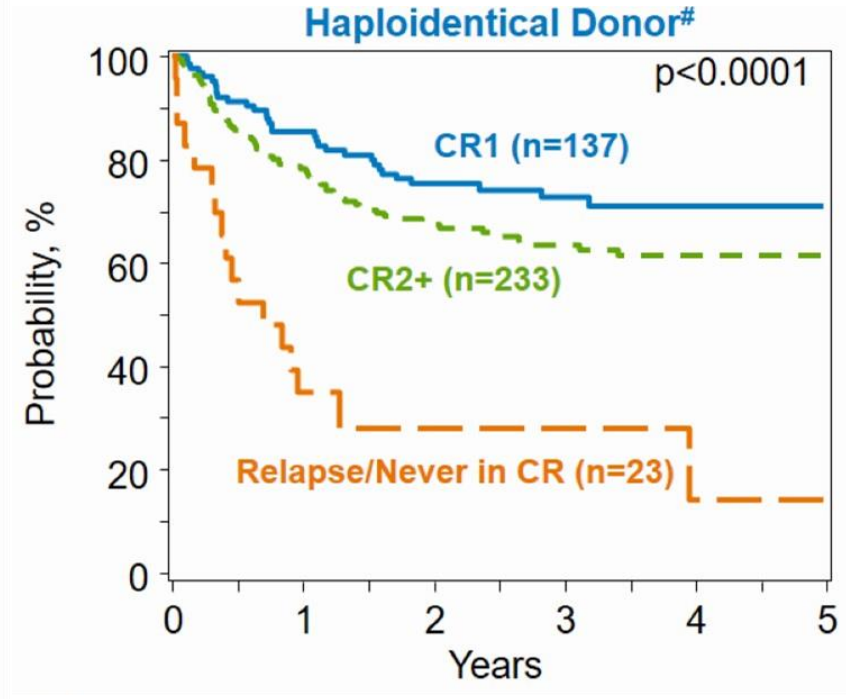
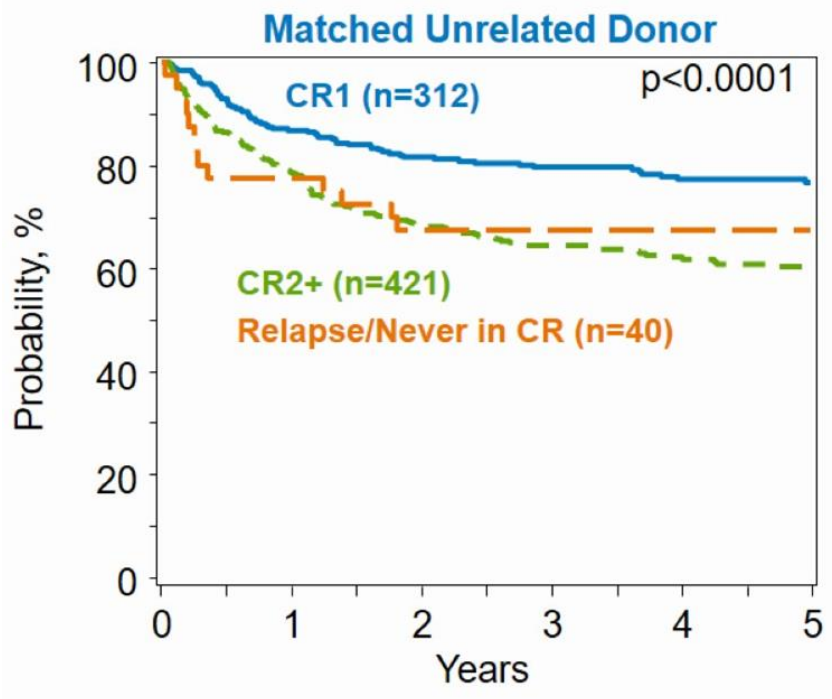
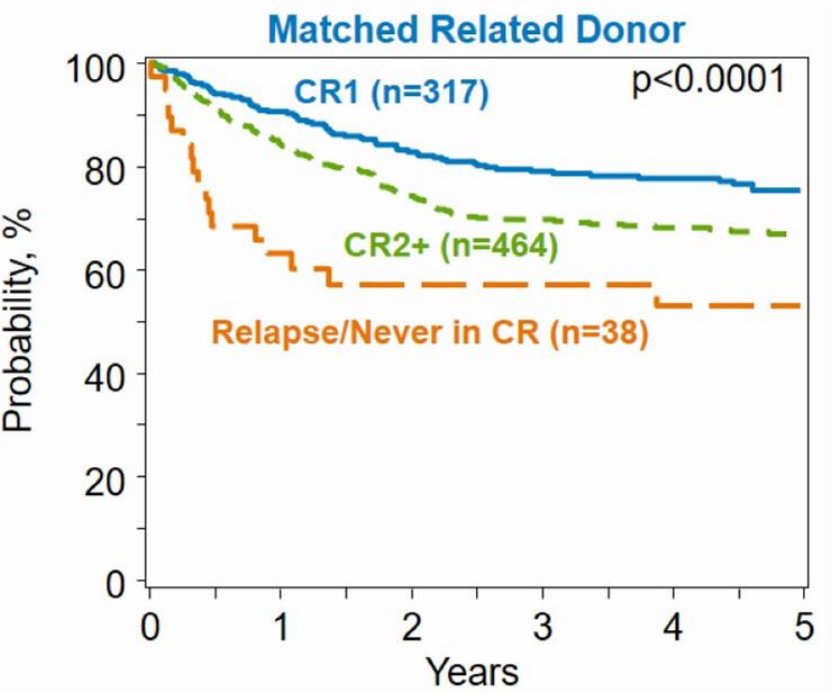
Victor Gottardello Zecchin

Médico Titular - TMO Pediátrico
A Beneficência Portuguesa de São Paulo

Indications for allogeneic transplants (2008-2019; n=1.604)



TCTH em LLA < 18 anos (USA, 2009-2019)



614. ACUTE LYMPHOBLASTIC LEUKEMIA: THERAPY, EXCLUDING TRANSPLANTATION | NOVEMBER 15, 2013

T Cells Engineered With a Chimeric Antigen Receptor (CAR) Targeting CD19 (CTL019) Produce Significant In Vivo Proliferation, Complete Responses and Long-Term Persistence Without Gvhd In Children and Adults With Relapsed, Refractory ALL

Stephan A Grupp, MD, PhD,¹ Noelle V. Frey, MD,² Richard Aplenc, MD, PhD,³ David M Barrett, MD/PhD,^{1,4} Anne Chew, PhD,⁴ Michael Kalos, PhD,⁴ Bruce L. Levine, PhD,⁴ Manuel Litchman, MD,⁵ Shannon L Maude, MD, PhD,¹ Susan R. Rheingold,² Angela Shen, MD,⁵ Christine Strait,¹ David T. Teachey, MD,⁶ Patricia A. Wood, MD, PhD,⁵ David Porter, MD,⁷ Carl H. June, MD

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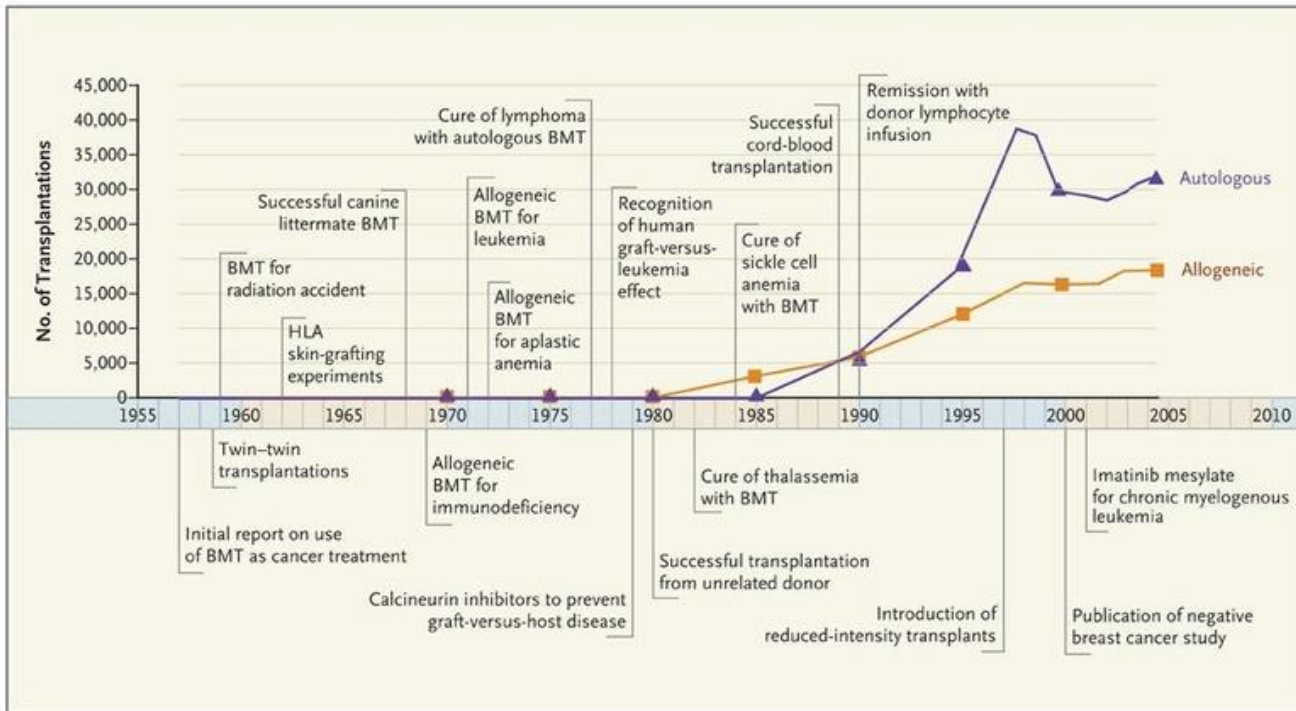
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Blood (2013) 122 (21) : 67.

<http://doi.org/10.1182/blood.V122.21.67.67>



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 ($> 300,000/\text{mm}^3$) 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.

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

- Curto tempo de seguimento:
 - Efeitos colaterais a longo prazo ainda pouco conhecidos - mais comuns:
 - Aplasia de células B
 - Hipogamaglobulinemia

- Doença em remissão ou não (refratária)
- Só LLA B derivada: por enquanto!
- Possibilidade de uso de TBI (idade, RXT prévia, performance)
- Doador disponível para TCTH?
- Transplante prévio ou não
- Doença extramedular (em SNC principalmente)
- Blastos são CD19+? Blinatumomab prévio?
- Paciente aguenta esperar manufatura de CAR T?
- Disponibilidade de acesso ao CAR-T ou não?

Existe uma diferença entre o ideal e o real - não adianta querer algo se é intangível!



ELIANA - 5 Years Follow-up update

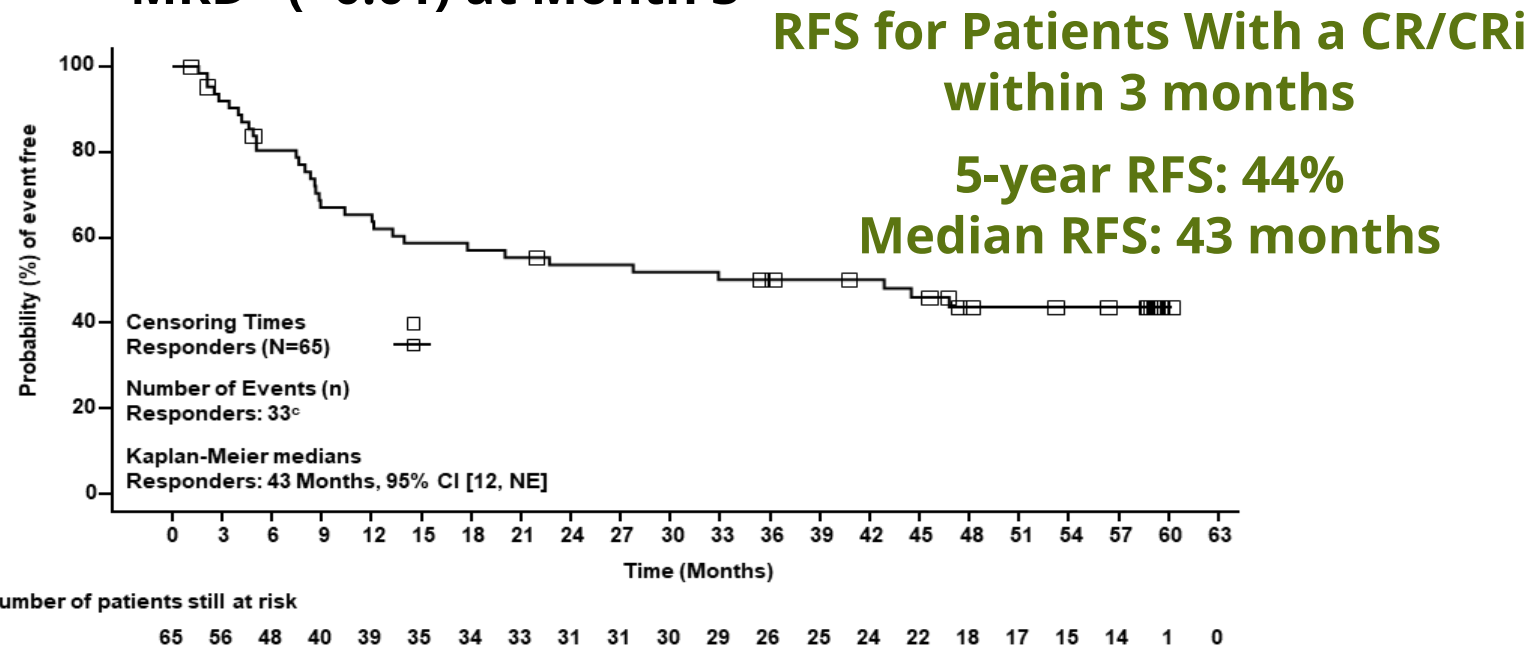
Efficacy (n=79)

ORR:

- **82% (CR: 62%+Cri: 20%)** in patients who achieved BOR within 3 mo by IRC

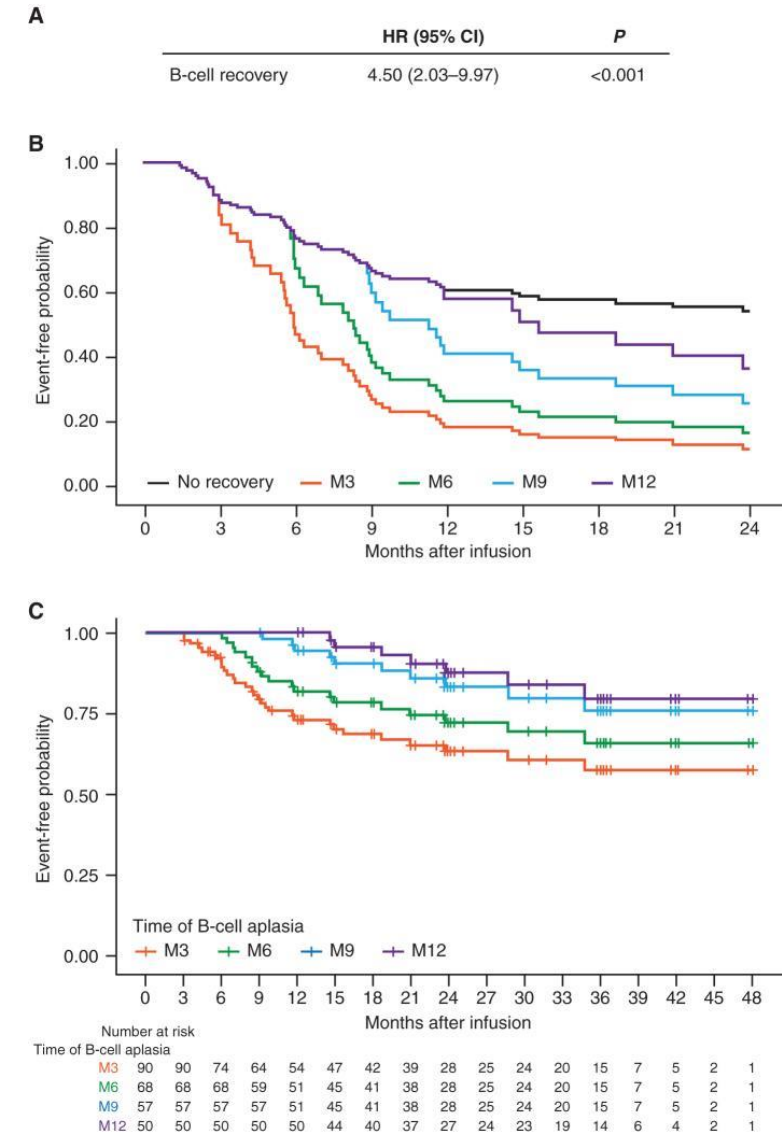
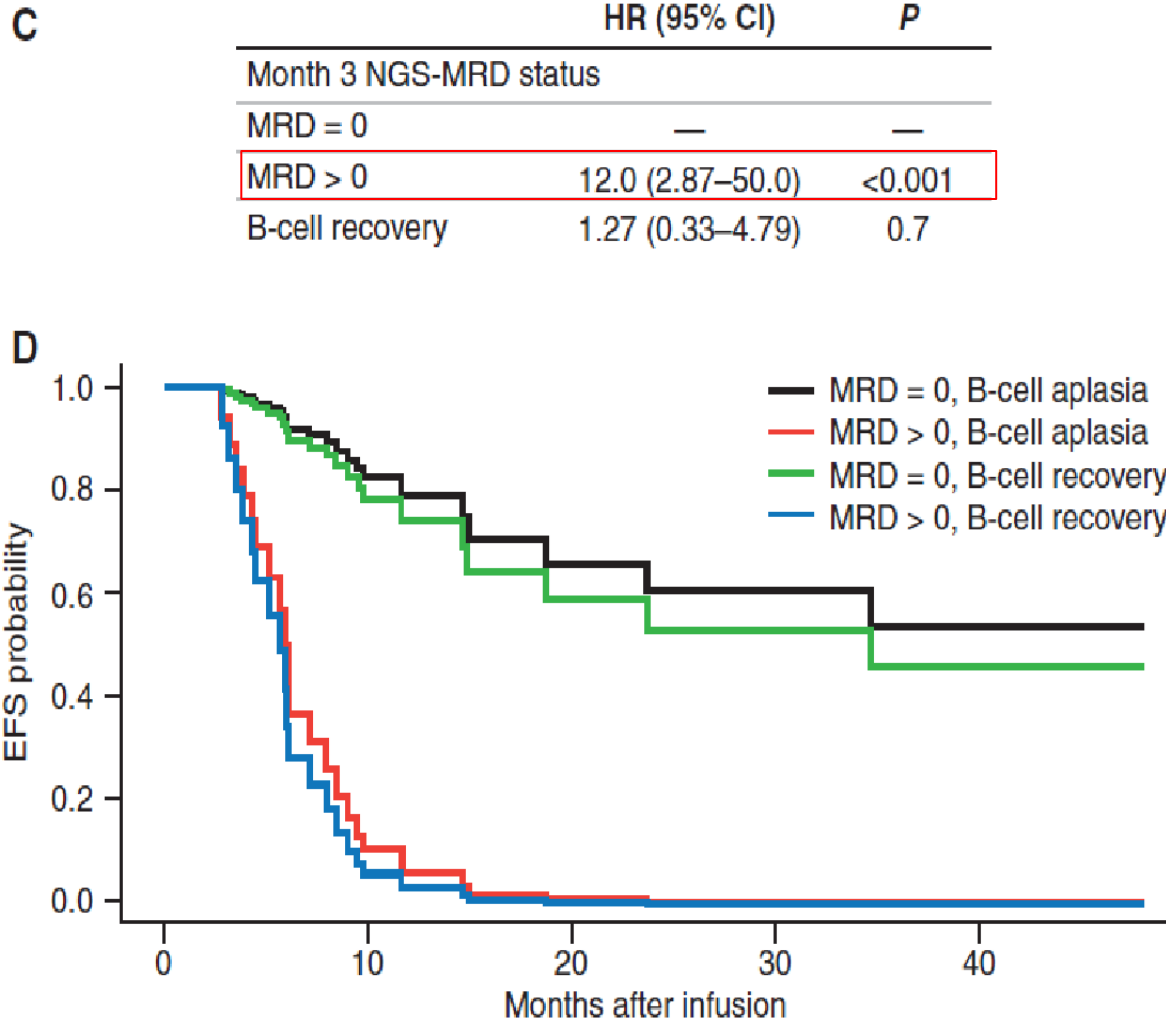
RFS

- **98% of patients who achieved remission were MRD- (<0.01) at Month 3**



- 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

B cell recovery and MRD – prognosis

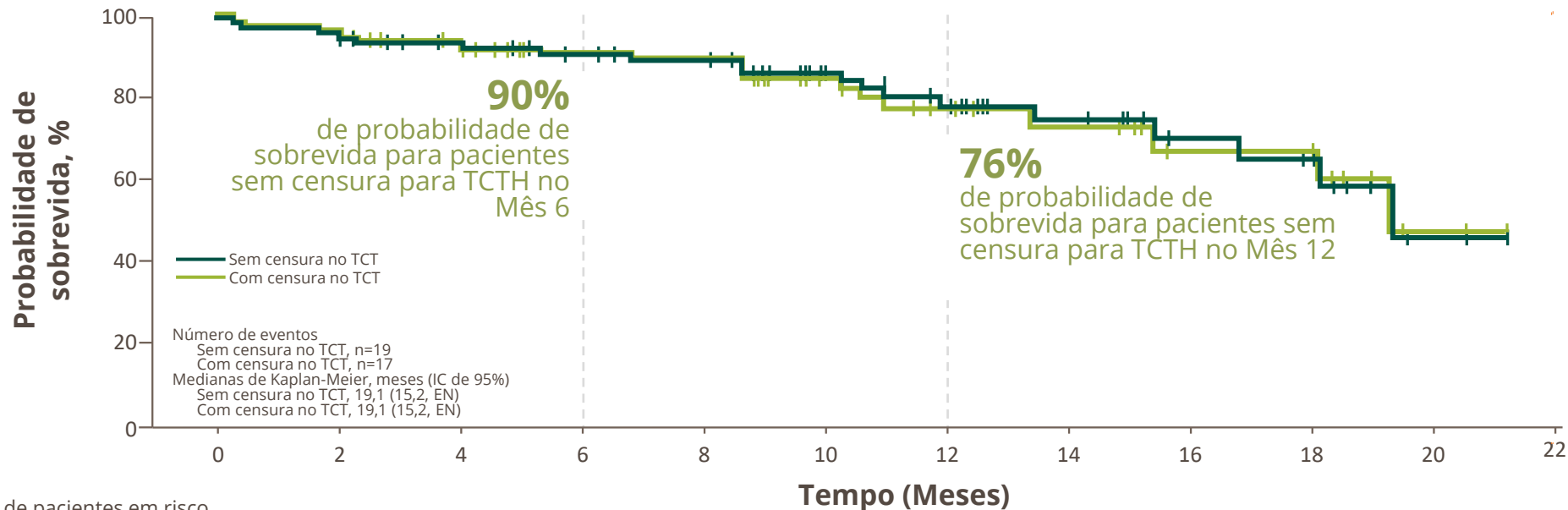


Transplante após CAR T

- 13% dos pacientes foram submetidos ao transplante
- Não houve diferença na sobrevida global

- Apenas 13% dos pacientes receberam transplante durante a remissão após o Kymriah® sem nenhuma melhoria na SG
- Os dados de SG devem ser interpretados com cautela em um estudo de braço único, uma vez que a significância estatística é desconhecida

Sobrevida Global em 13,1 Meses no ELIANA (NEJM), N=75

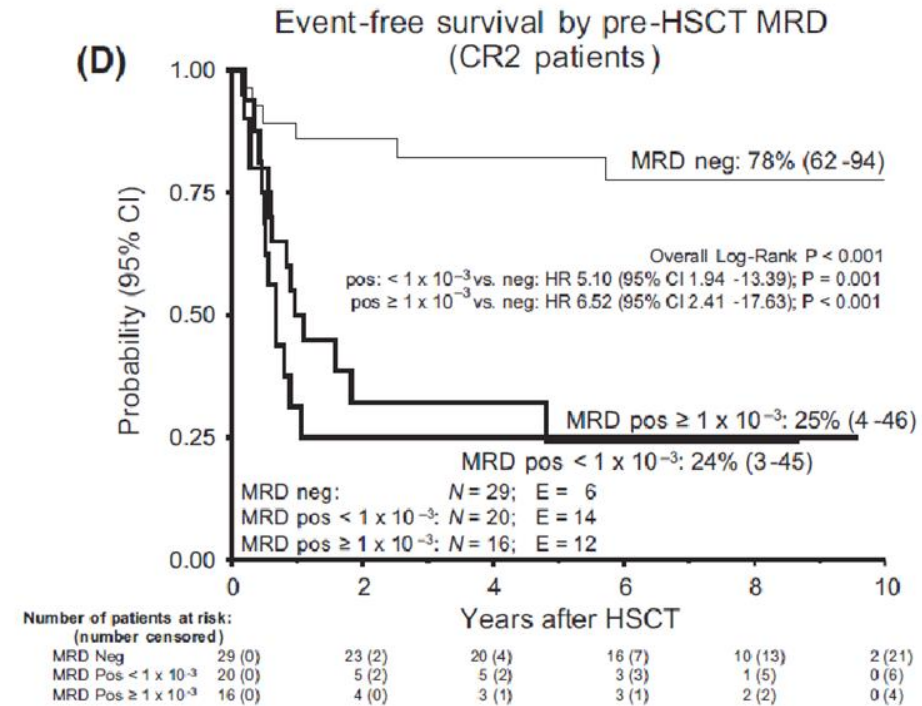
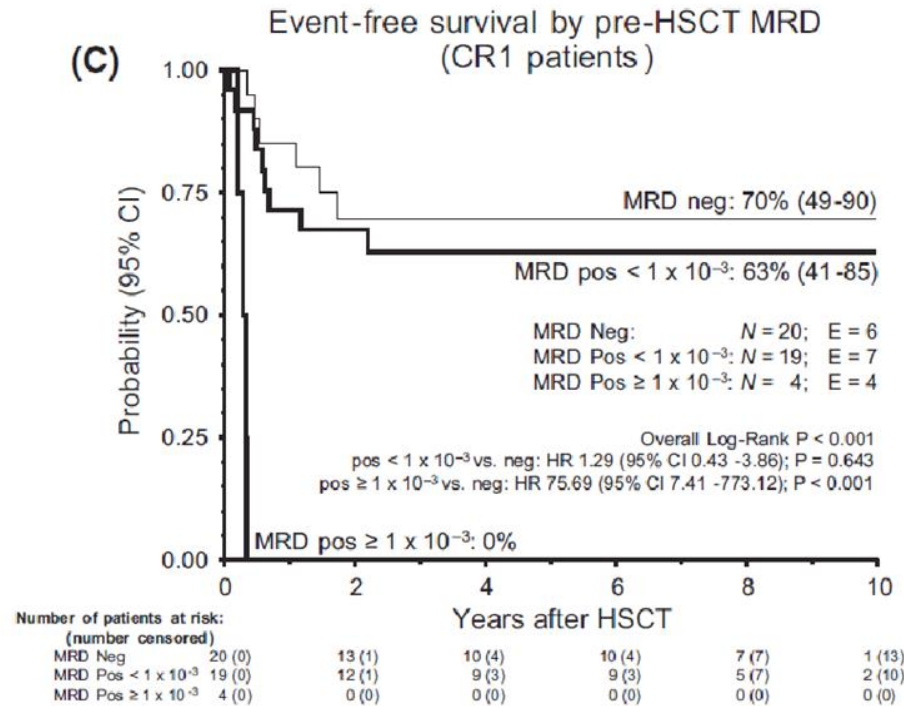


Nº de pacientes em risco

	0	2	4	6	8	10	12	14	16	18	20	22
Sem censura no TCT	75	72	64	58	55	40	30	20	12	8	2	0
Com censura no TCT	75	72	60	48	45	31	21	15	9	7	2	0

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

DRM pré TMO – RQ-PCR



SLE – 1ª remissão:

- DRM negativo 70%
- DRM positivo < 10^{-3} 63%
- DRM positivo $\geq 10^{-3}$ zero

Transplante alogênico de células-tronco hematopoiéticas - TCTH

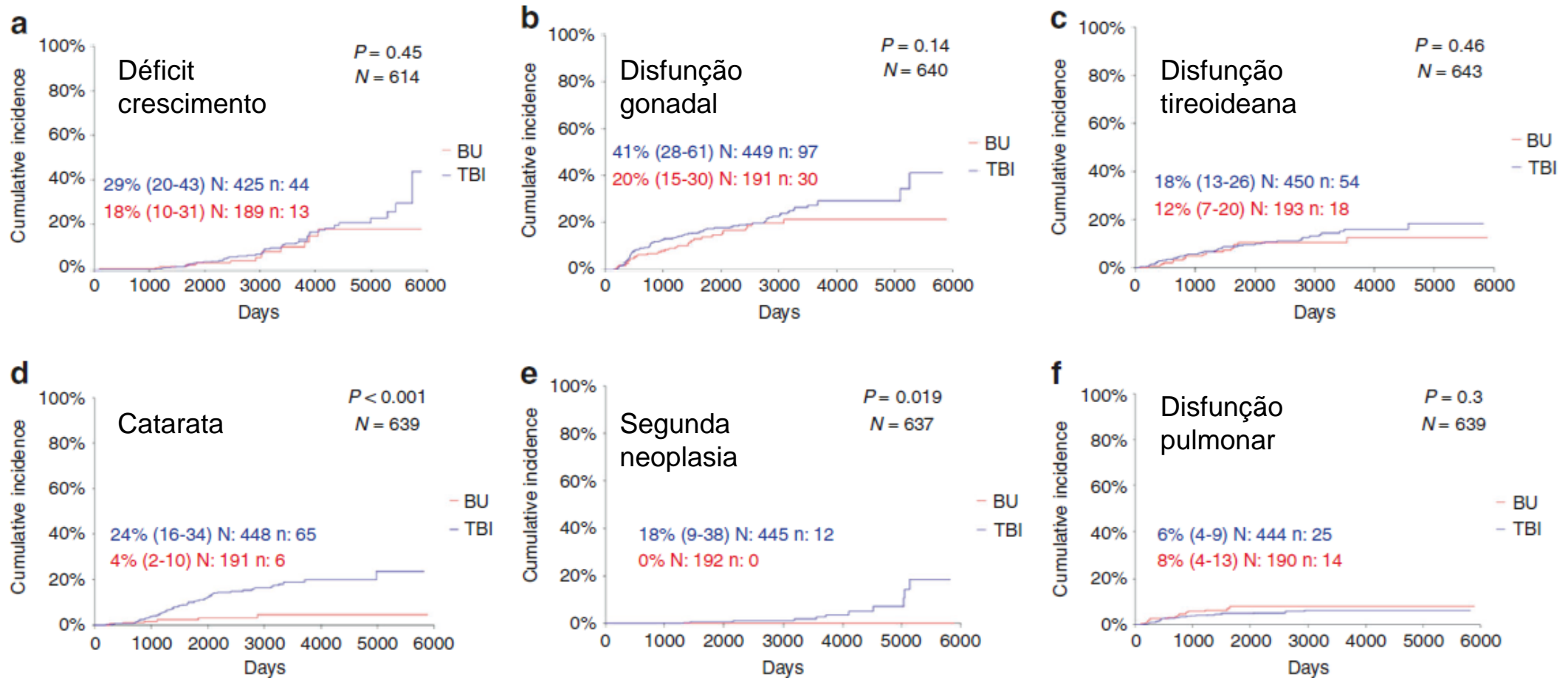
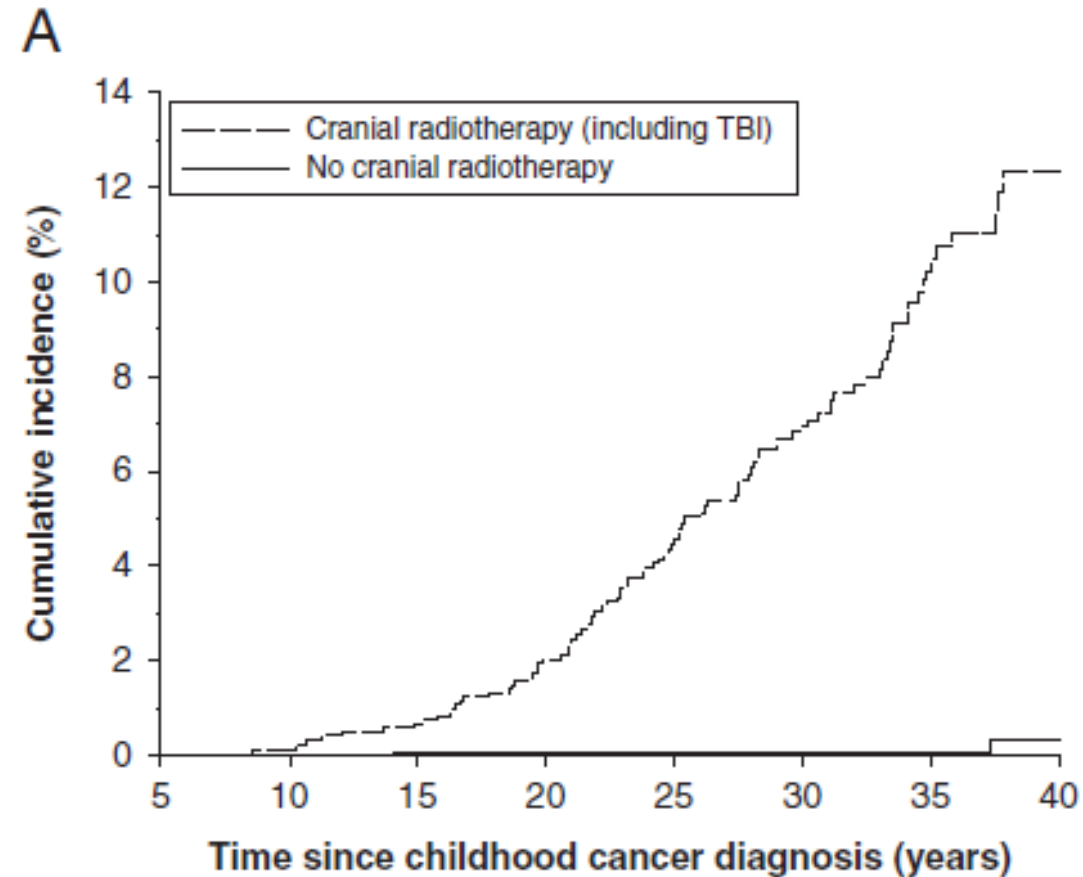


Fig. 1 Cumulative Incidence of long-term effects. Cumulative incidence of (a) growth alteration, (b) alteration of the gonadal function (c) alteration of the thyroid function (d) cataract (e) secondary

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.

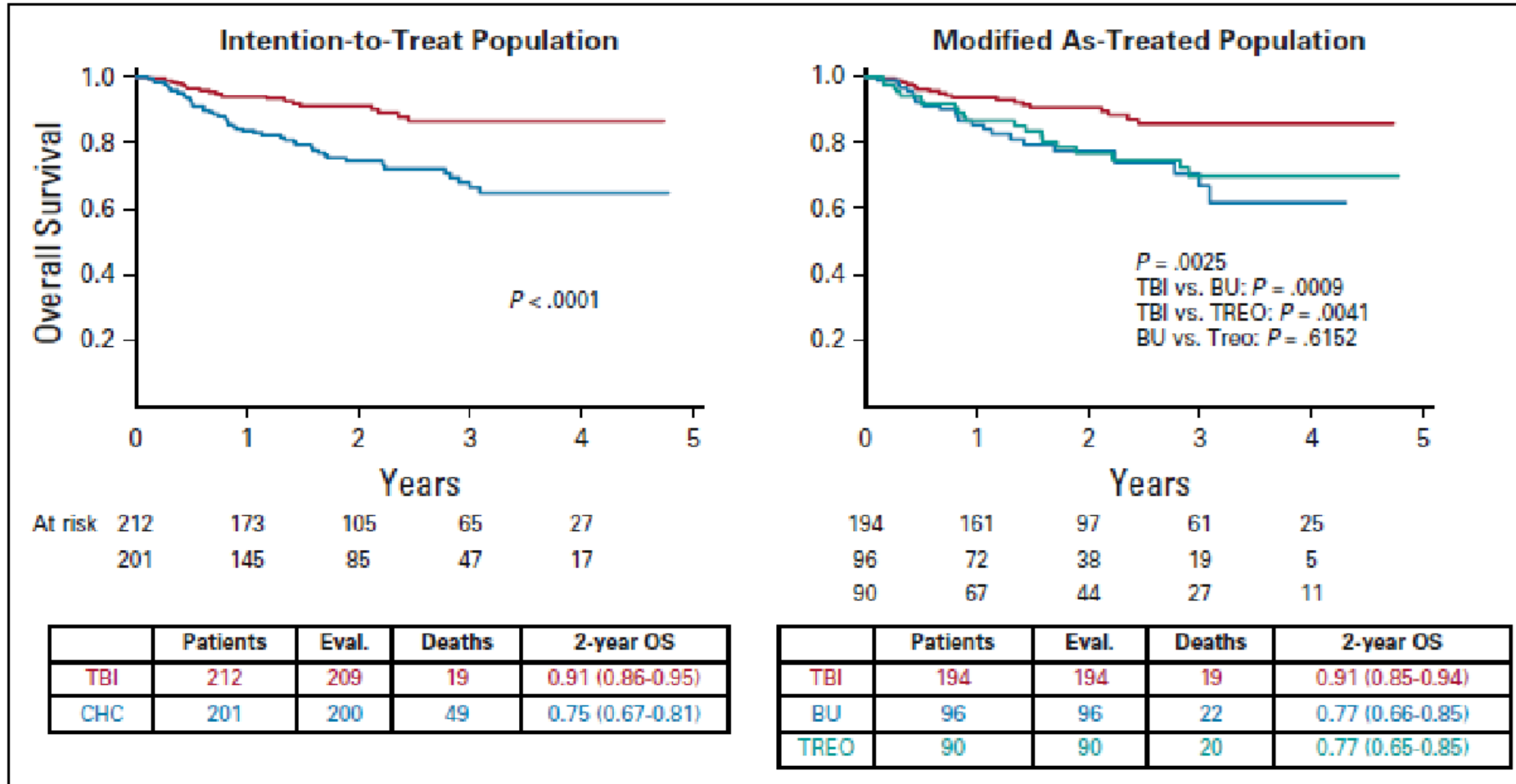
Risk of benign meningioma after childhood cancer in the DCOG-LATER cohort: contributions of radiation dose, exposed cranial volume, and age



No at risk

Cranial radiotherapy (including TBI)	632	856	998	903	702	542	278	79
No cranial radiotherapy	3388	3826	3677	2698	1833	1055	557	241

TBI *versus* QT para TCTH em LLA



MAT

✓ 2% TBI

✓ 9% QT

Recidiva 2a

✓ 12% TBI

✓ 33% QT

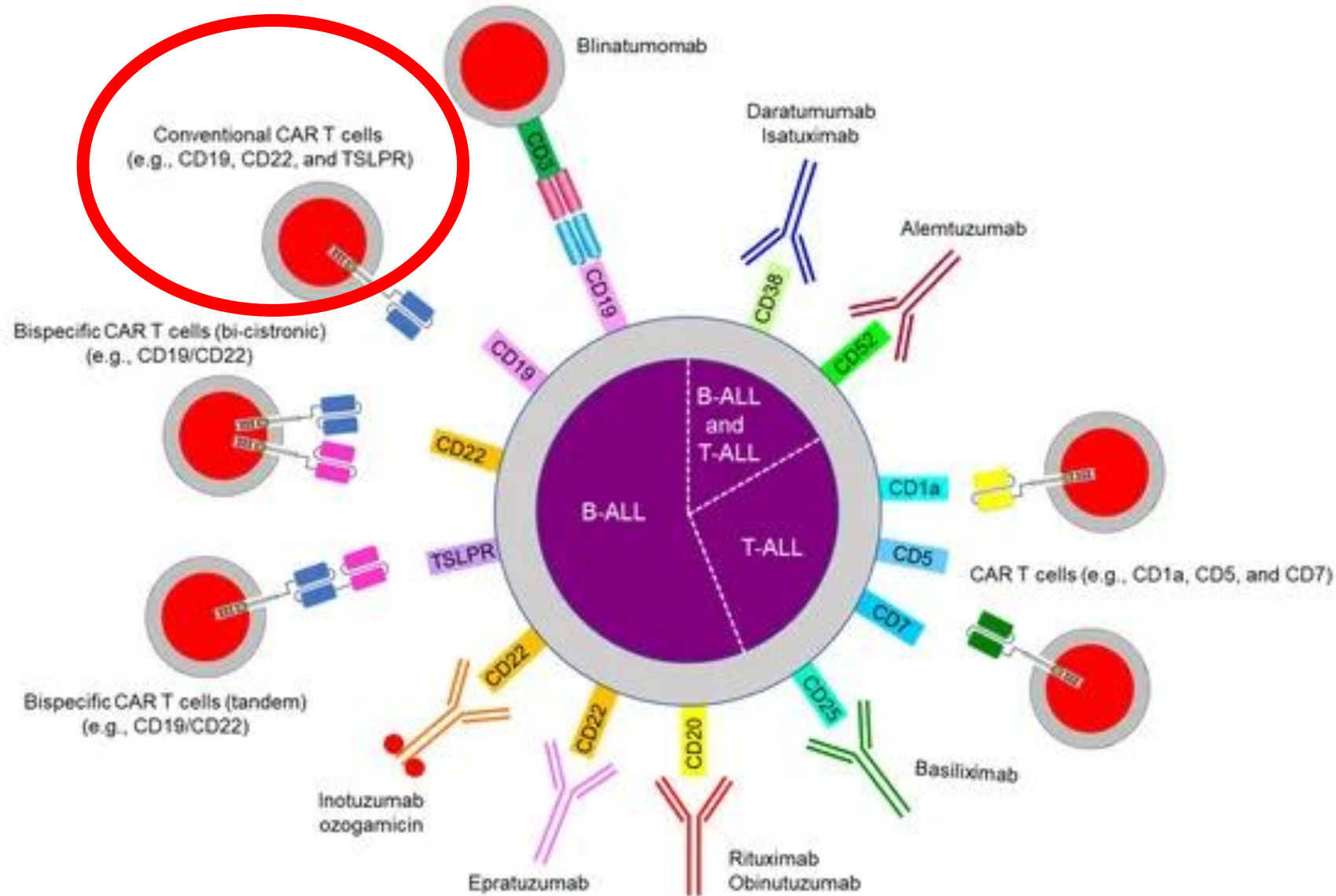
SG @ 2 anos:

✓ 91% TBI

✓ 77% QT

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.

Imunofenótipo da LLA



LLA B derivada:
85% dos casos em pediatria

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

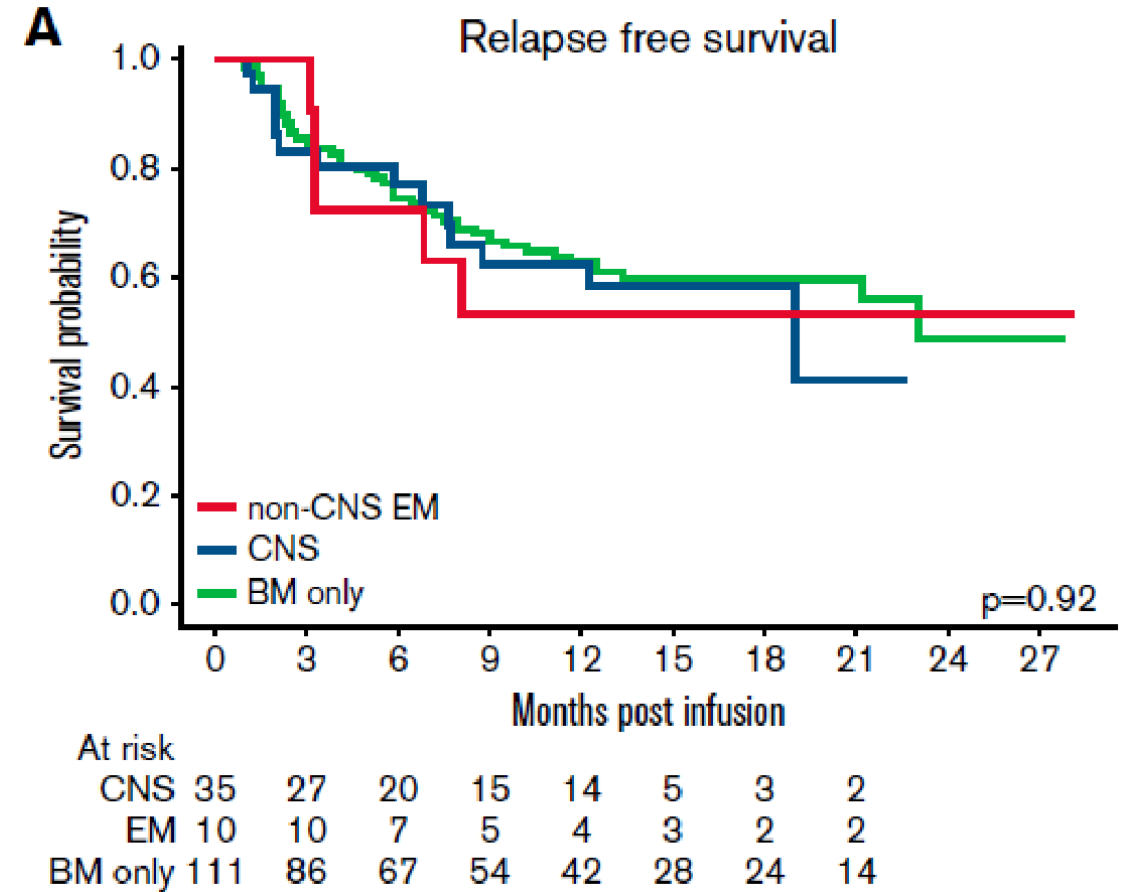
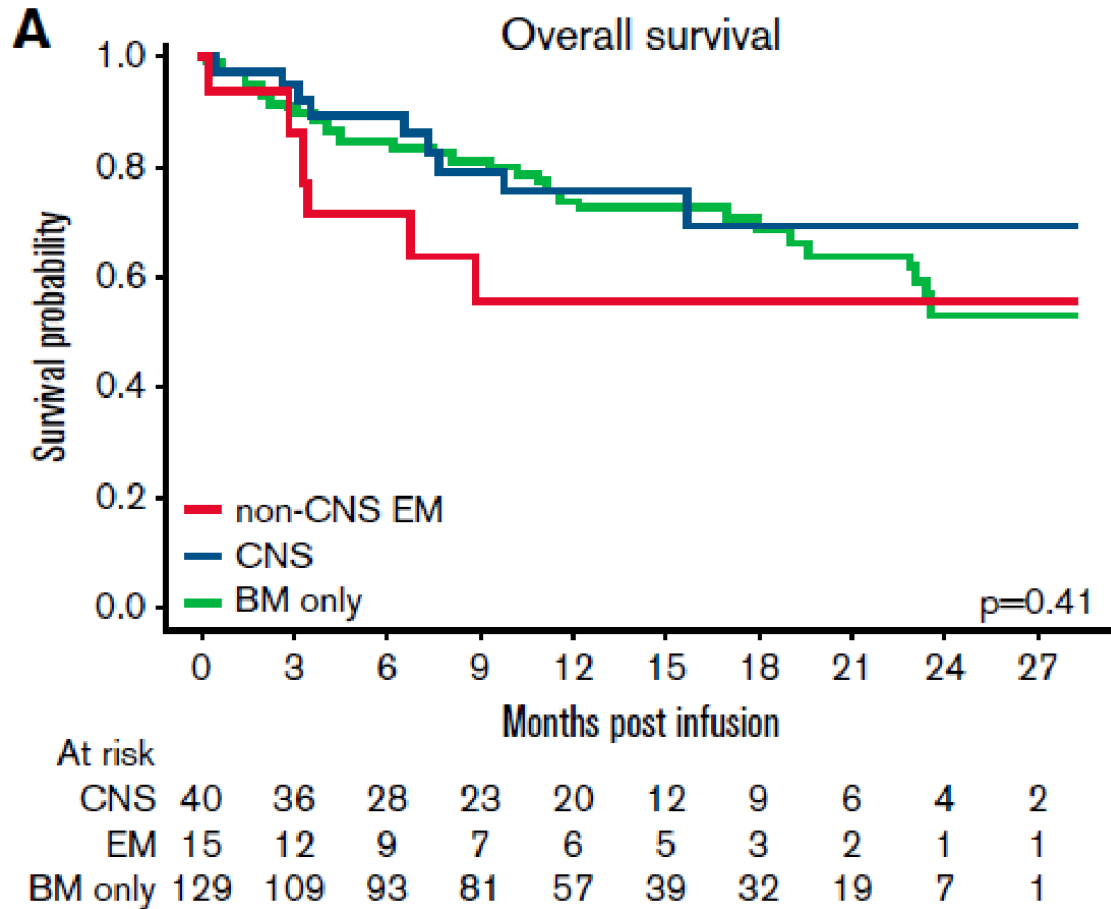
- Ainda não foi identificado um antígeno alvo específico contra blastos T
- Devido à necessidade de identificar um antígeno presente nos blastos e também nos linfócitos T normais, as células CAR T poderiam induzir ao fratricídio (células CAR T matando outras células CAR T)
- Linfopenia T prolongada é uma condição incompatível com a vida, necessitando resgate com transplante alogênico
- Risco de contaminação do produto de leucoaférese com células tumorais
- Futuro: uso de células NK para gerar células CAR T? CAR T alogênico?

CAR T e leucemia em SNC

ELIANA¹¹ Tisagenlecleucel NCT02435849	CASSIOPEIA³² Tisagenlecleucel NCT03876769	CHOP Humanized CAR-T³³ huCART19 NCT03792633		National Cancer Institute¹⁰ Anti-CD19 CAR NCT01593696	PLAT-02⁷ Seattle Children's Hospital CD19+ CAR-T NCT02028455	CHP959²⁰ 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)	<table border="1"> <thead> <tr> <th data-bbox="682 525 1026 575">Prior Therapies</th> <th data-bbox="1026 525 1403 575">Prior Therapies</th> </tr> <tr> <th data-bbox="682 575 1026 625">COHORT A</th> <th data-bbox="1026 575 1403 625">COHORT B</th> </tr> </thead> <tbody> <tr> <td data-bbox="682 625 1026 1068"> 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 disease¹ Ineligible for alloSCT </td> <td data-bbox="1026 625 1403 1068"> r/r B-ALL: Previously treated with B-cell-directed engineered cell therapy: <ul style="list-style-type: none"> • 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 </td> </tr> </tbody> </table>		Prior Therapies	Prior Therapies	COHORT A	COHORT B	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 ¹ Ineligible for alloSCT	r/r B-ALL: Previously treated with B-cell-directed engineered cell therapy: <ul style="list-style-type: none"> • 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: <table border="1"> <tr> <td data-bbox="2168 589 2527 861"> Age Comorbid disease Contraindications to TBI-based conditioning Lack of donor Prior SCT Declines alloSCT </td> </tr> </table> Any relapse after prior SCT	Age Comorbid disease Contraindications to TBI-based conditioning Lack of donor Prior SCT Declines alloSCT
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Age Comorbid disease Contraindications to TBI-based conditioning Lack of donor Prior SCT Declines alloSCT													
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							

- 53 pacientes 4-24 anos (mediana 11 anos)
- 50 remissões completas = 94% / 45 pacientes com DRM < 0,01%
- Mediana de acompanhamento: 10 meses (1-39)
 - > 29 se mantinham em remissão
 - > sobrevida livre de eventos = 70% em 6 meses, 45% em 12 meses
 - > sobrevida global = 78% em 12 meses
- **46/47 pacientes tinham CAR-T detectável no liquor**

CAR T e doença extramedular

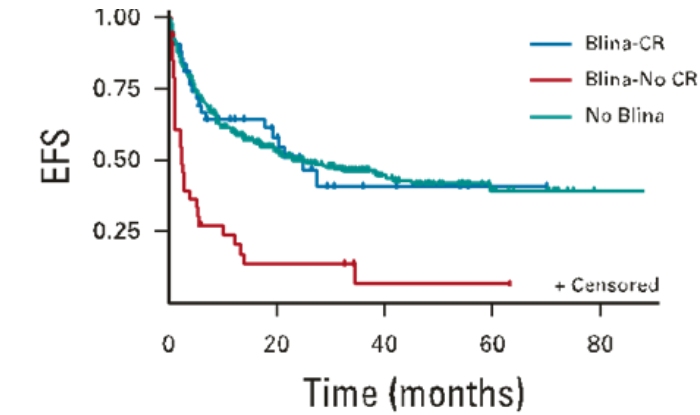


n = 184

55 extramedular relapses (CNS =40)

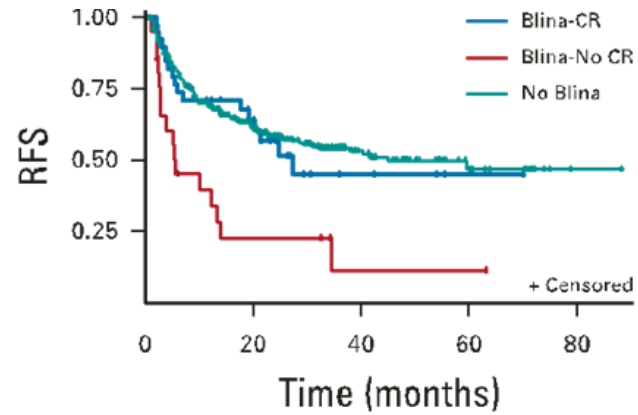
Blinatumomab Nonresponse and High-Disease Burden Are Associated With Inferior Outcomes After CD19-CAR for B-ALL

n = 420
 Mediana idade 12,7 anos



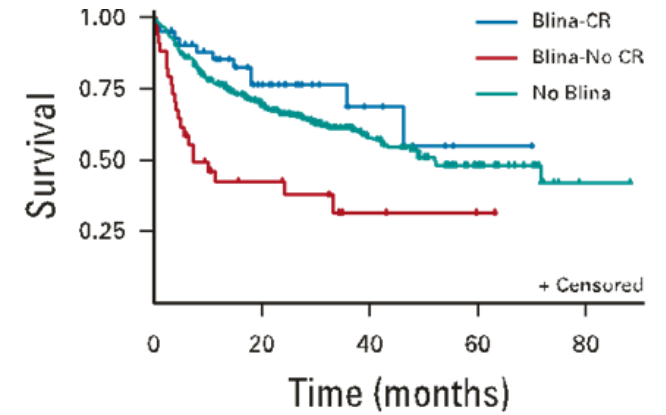
No. at risk:

Blina-CR	43	18	4	1	0
Blina-No CR	34	4	1	1	0
No Blina	343	143	48	16	1



No. at risk:

Blina-CR	39	18	4	1	0
Blina-No CR	21	4	1	1	0
No Blina	317	143	48	16	1

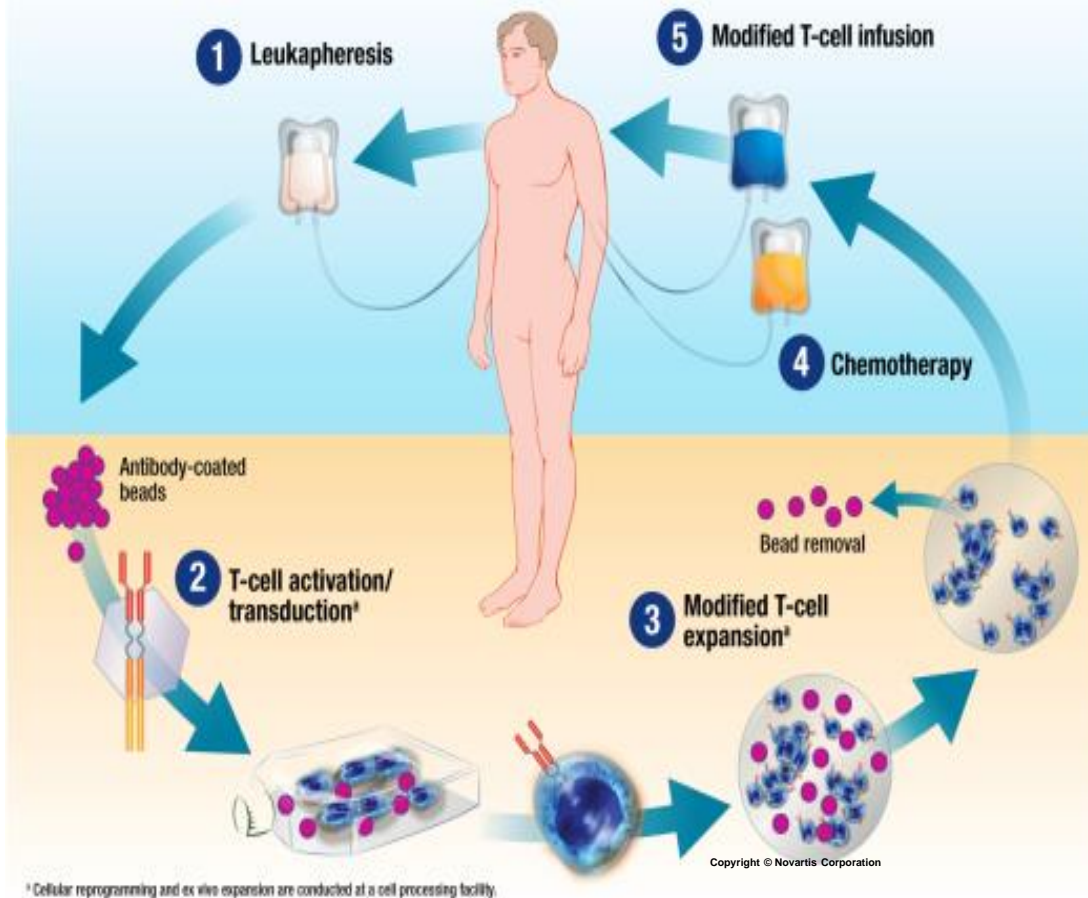


No. at risk:

Blina-CR	43	23	6	1	0
Blina-No CR	34	11	3	1	0
No Blina	343	188	66	23	1

	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

Cadeia de produção CAR T



Terapia Ponte

- 1. Leucaférese:** células T são coletadas
- 2. Transdução genéticas das células T ex vivo** com um vetor lentivirus codificando o receptor anti-CD19
- 3. Células CAR-T sofrem expansão ex vivo** com beads magnéticos
- 4. Quimioterapia linfodepletora** administrada antes da infusão das células CAR-T
- 5. Infusão das células CAR-T** no paciente

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 Caruana², Annette Künkele³, Susana Rives⁴, Kim Vettenranta⁵, Peter Bader⁶, Christina Peters^{7,8}, André Baruchel⁹ and Friso G. Calkoen¹⁰*

LOW RISK

Favourable CAR-T course – HSCT not recommended

Patient must meet all criteria:

- Age >1 year
- No *KMT2A* rearrangement
- No blinatumomab or inotuzumab ozogamicin pre-treatment
- Tisagenlecleucel product
- Infused with low-grade MRD (1-5%)
- MRD negative* at day 28 (by PCR or NGS)
- BCA lasting beyond 6 months



Suggested approach

- No consolidative HSCT
- 'Watch and wait' strategy with regular monitoring of BCA and MRD (including CD19⁺ clones)

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.

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Favourable CAR-T course – HSCT not recommended

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Suggested approach

- No consolidative HSCT
- 'Watch and wait' strategy with regular monitoring of BCA and MRD (including CD19⁺ clones)

INTERMEDIATE RISK

"Ambiguous" risk profile – role of consolidative HSCT unclear

If patient meets ≥1 criterion:

- High blast count at infusion
- *TP53* mutation
- Other high-risk cytogenetic subgroup
- Pre-treatment with blinatumomab or inotuzumab ozogamicin
- OOS product
- Suboptimal pharmacodynamics:
 - 'Low' expansion or 'reduced' AUC
 - Loss of BCA 3–6 months post infusion
- Product not tisagenlecleucel



Suggested approach

- Unclear: see Figure 6 for a proposed approach
- Further data (retrospective/prospective) are necessary to evaluate the role of consolidative HSCT

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.

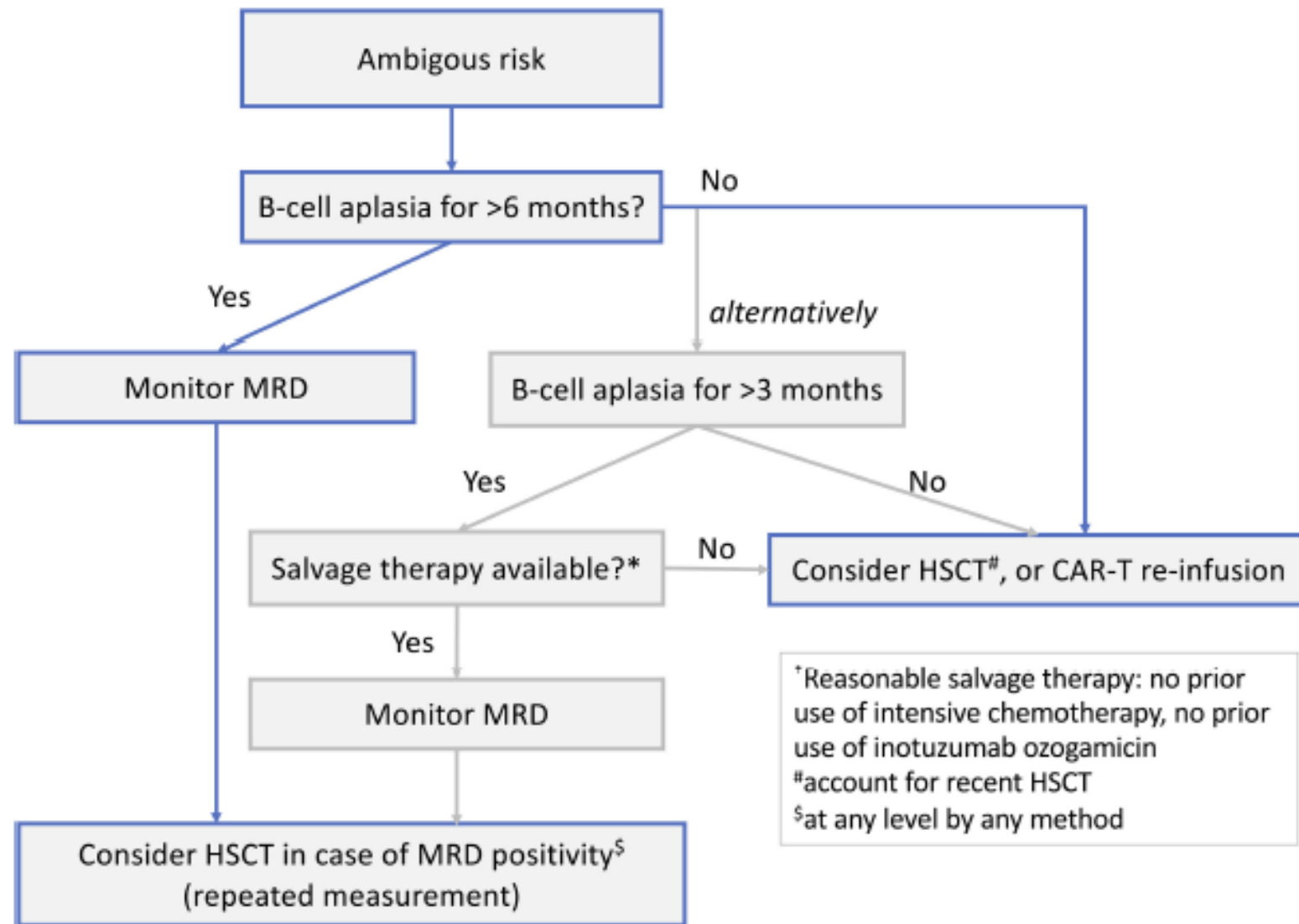


FIGURE 6 | Follow-up guidance after CAR-T for paediatric patients and AYA with BCP-ALL and an "ambiguous risk profile" (see **Figure 5** for criteria for an ambiguous risk profile).

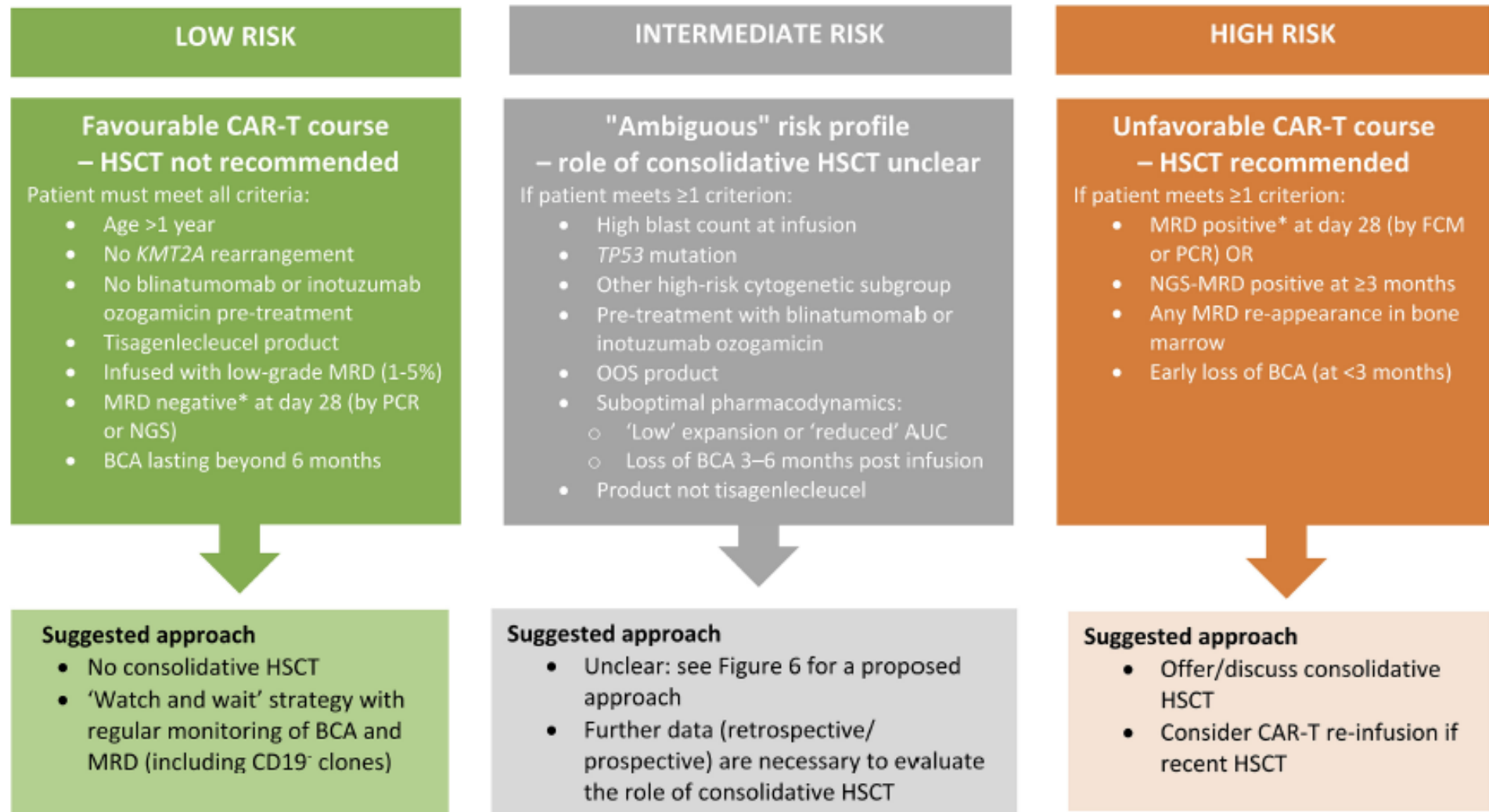
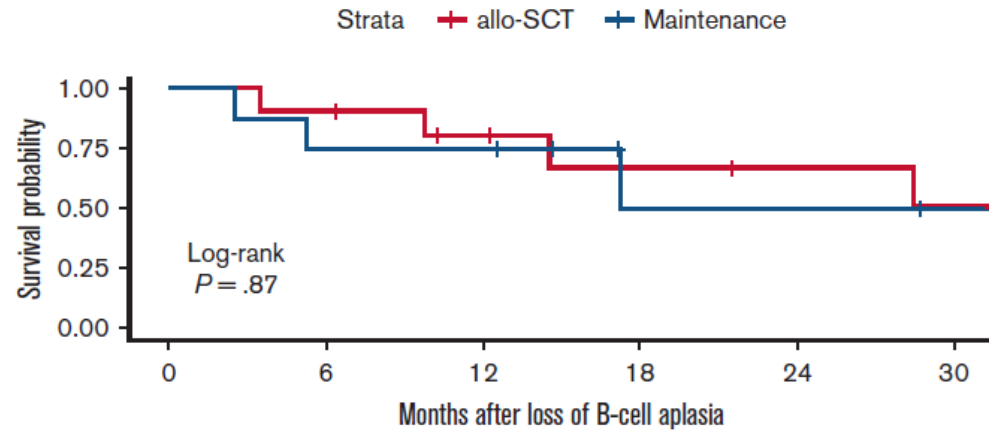


FIGURE 5 | Proposed approach to HSCT consolidation after CAR-T for paediatric patients and AYA with BCP-ALL based on treatment- and disease-related risk factors for relapse. *MRD positivity defined at >0.01%. AUC, area under the curve; AYA, adolescent and young adult; BCA, B-cell aplasia; CAR-T, chimeric 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.

Maintenance therapy for early loss of B-cell aplasia after anti-CD19 CAR T-cell therapy

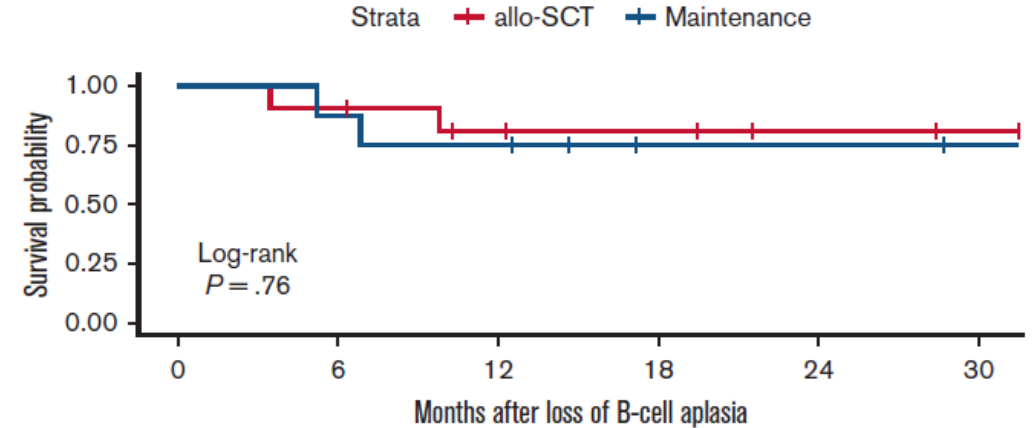
Gabelli et al. Blood Adv, Apr. 2024

A



	0	6	12	18	24	30
Number at risk						
allo-SCT	11	10	7	5	4	3
Maintenance	8	6	6	2	2	1
Cumulative number of events						
allo-SCT	0	1	2	3	3	4
Maintenance	0	2	2	3	3	3

B



	0	6	12	18	24	30
Number at risk						
allo-SCT	11	10	7	6	4	3
Maintenance	8	7	6	3	3	2
Cumulative number of events						
allo-SCT	0	1	2	2	2	2
Maintenance	0	1	2	2	2	2

- n = 19 / 11 TCTH e 8 manutenção após perda da aplasia B após Tisagenlecleucel ou experimental 41BBz anti-CD19 and anti-CD19/anti-CD22 CAR T (NCT02443831)
- 4,9-12,2 anos
- Manutenção: Mercaptopurina 75 mg/m² + MTX semanal 20 mg/m² + MADIT trimestral por 2 anos (\pm pulsos mensais de VCR 1,5 mg/m² e Dexa 6 mg/m²/dia x 5 dias dependendo da toxicidade prévia)

- A dúvida sobre se CAR T é uma terapia definitiva ou uma ponte para remissões mais profundas para chegar ao TCTH ainda não pode ser respondida para todos os pacientes, com base nos conhecimentos atuais
- As indicações de CAR T cells ainda estão em evolução e devem ser aprimoradas
- No cenário atual, podemos considerar CAR T e TCTH como terapias complementares

- Principais fatores a ser levados em consideração atualmente na escolha pelo TCTH ou CAR T:
 - TCTH prévio e tempo entre o TCTH e a recidiva
 - Possibilidade de uso de TBI e seus efeitos a longo prazo
 - Imunofenótipo da doença em tratamento - presença ou não de CD19
 - Obtenção de remissão profunda com DRM negativa pré TMO ou não
 - Resposta à terapia reindutória - doença refratária
 - Recidiva extramedular/SNC
 - Efeitos colaterais a longo prazo de ambas as terapias



Obrigado!

victor.zecchin@bp.org.br