III REUNIÃO EDUCACIONAL DA SBTMO 2017 – REGIÃO SUL
07 JULHO DE 2017
HOSPITAL DE CLÍNICAS DA UFPR

# Qual é a melhor estratégia de tratamento da LLA recidivada em crianças e adolescentes?


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# LLA Recidiva

- 15-20% das LLA recaem
  - Incidência de 0.7/100.000
  - 4ª Neoplasia da Infância
- 4-5ª Causa de Morte por Neoplasia na Infância

# Definição de Risco da LLA Recaída

- Na recaída a maioria dos fatores prognósticos relevantes no diagnóstico perdem o significado
- Permanecendo como mais importantes:
  - Tempo de Remissão
  - Sítio
  - Imunofenótipo

Recaída Precoce
LLA – T
Recaída Medular

Recaída Tardia
Recaída ExtraMedular Isolada

# 2ª RC – TCTH Alogênico Aparentado ou Não Aparentado:

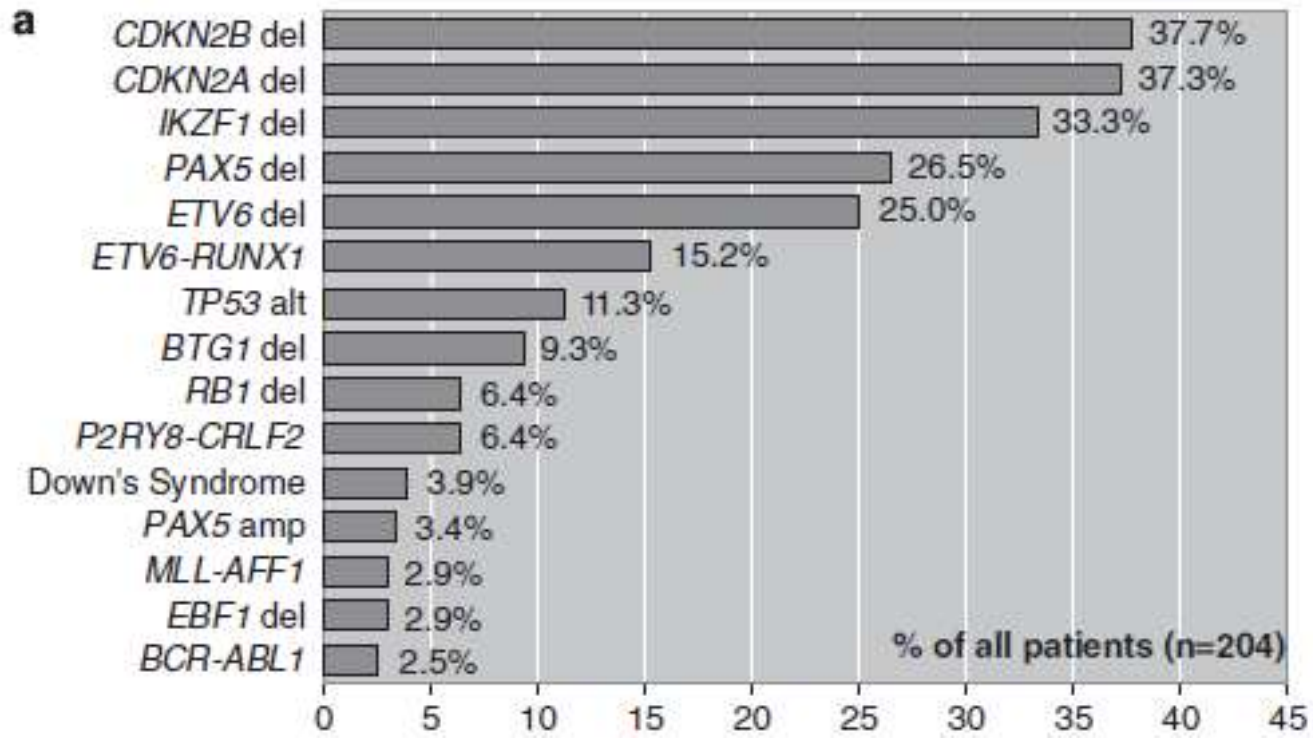
- Recaída medular precoce de linhagem B (< 36 meses da primeira remissão).
- Recaída extramedular isolada precoce de linhagem B (< 18 meses da primeira remissão).
- Qualquer recaída, precoce ou tardia, medular ou extramedular, de linhagem T.

# 3ª RC – TCTH Alogênico Aparentado ou Não Aparentado:

- A partir da terceira remissão, apesar do prognóstico ruim, a SLD em cinco anos com TCTH não aparentado é de 26-33%, contra cerca de 15% apenas com quimioterapia.

# Prognostic value of genetic alterations in children with first bone marrow relapse of childhood B-cell precursor ALL

*Krentz et al*. Leukemia (2013) 27, 295




Frequency of genetic alterations in 204 children with first BM relapse of BCP-ALL. (a) Percentage of genetic alterations in the studied cohort

# Prognostic value of genetic alterations in children with first bone marrow relapse of childhood B-cell precursor ALL

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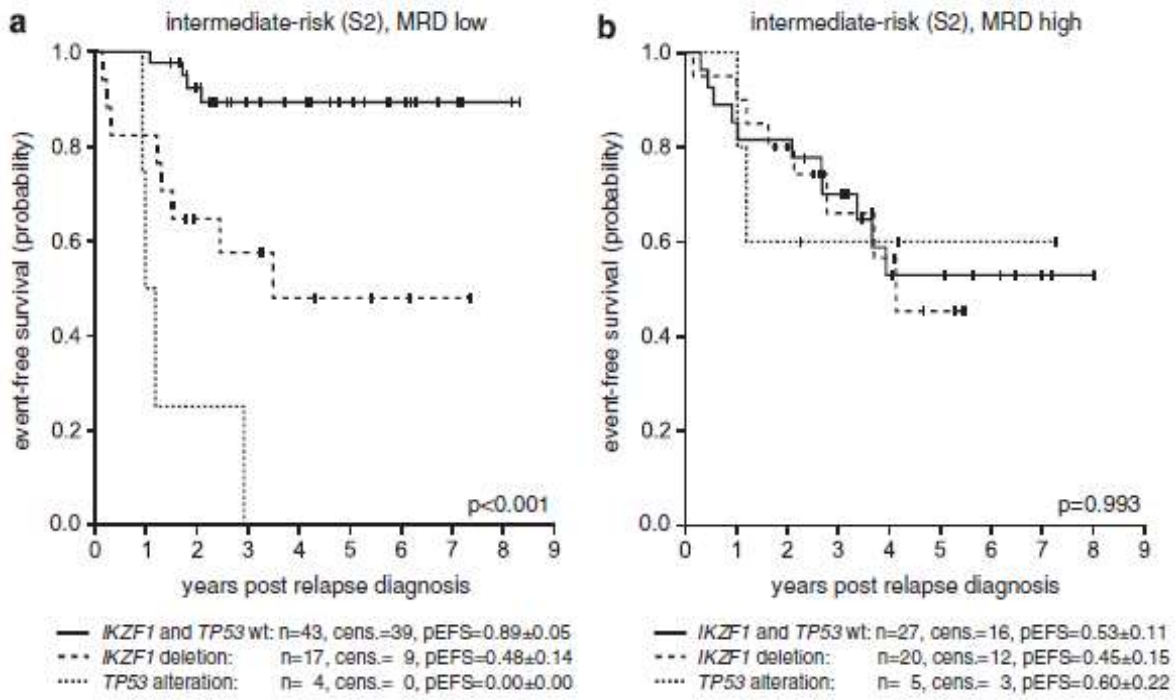



*IKZF1* deletion and *TP53* alteration as prognostic factors to subclassify BCP-ALL relapse patients. (a) Presence of an *IKZF1* deletion or *TP53* alteration results in a significantly decreased pEFS in intermediate-risk (S2) relapse patients with low MRD level (<103) at the end of induction therapy. (b) In contrast, in S2 patients with high MRD level (≥103), *IKZF1* deletion and *TP53* alteration had no significant prognostic value.

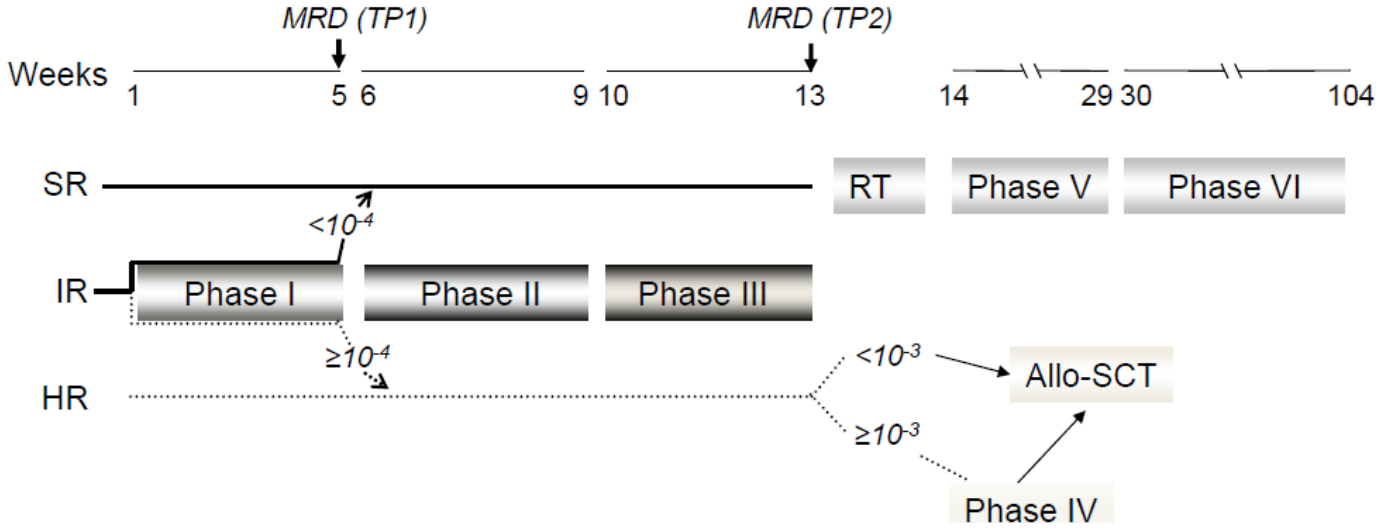
# Integration of genetic and clinical risk factors improves prognostication in relapsed childhood B-cell precursor acute lymphoblastic leukemia

*Irving J et al. Blood 2016 128:91*

A

| Immunophenotype | Site | Time to Relapse: Very Early | Early | Late |
|---|---|---|---|---|
| Non-T | Isolated Extramedullary | H | I | S |
| | Isolated Marrow | H | H | I |
| | Combined | H | I | I |
| T | Isolated Extramedullary | H | I | S |
| | Isolated Marrow | H | H | H |
| | Combined | H | H | H |

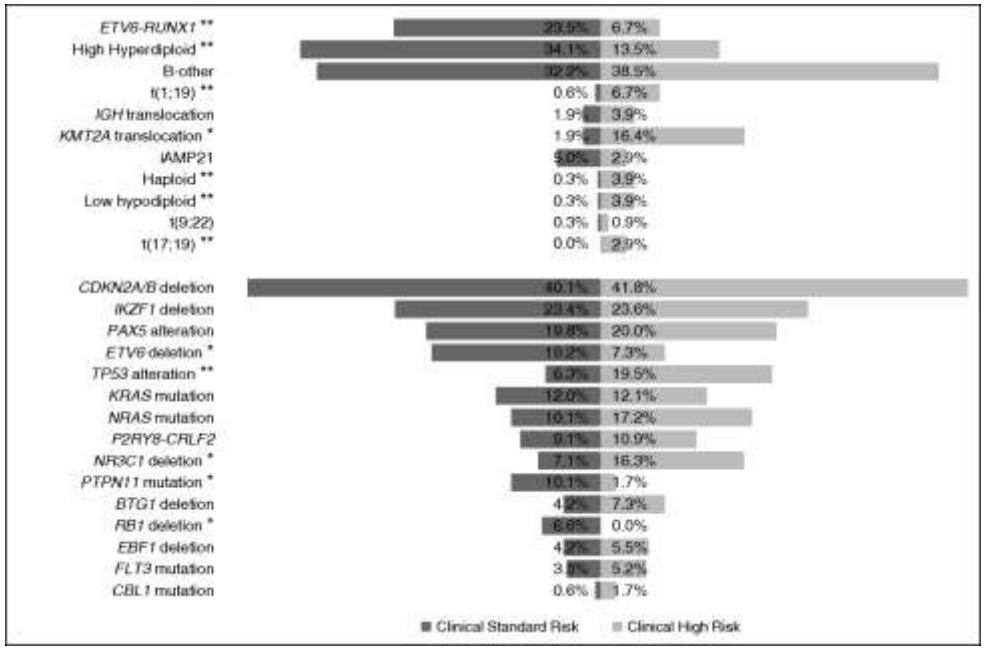
B



# Integration of genetic and clinical risk factors improves prognostication in relapsed childhood B-cell precursor acute lymphoblastic leukemia

*Irving J et al. Blood 2016 128:91*

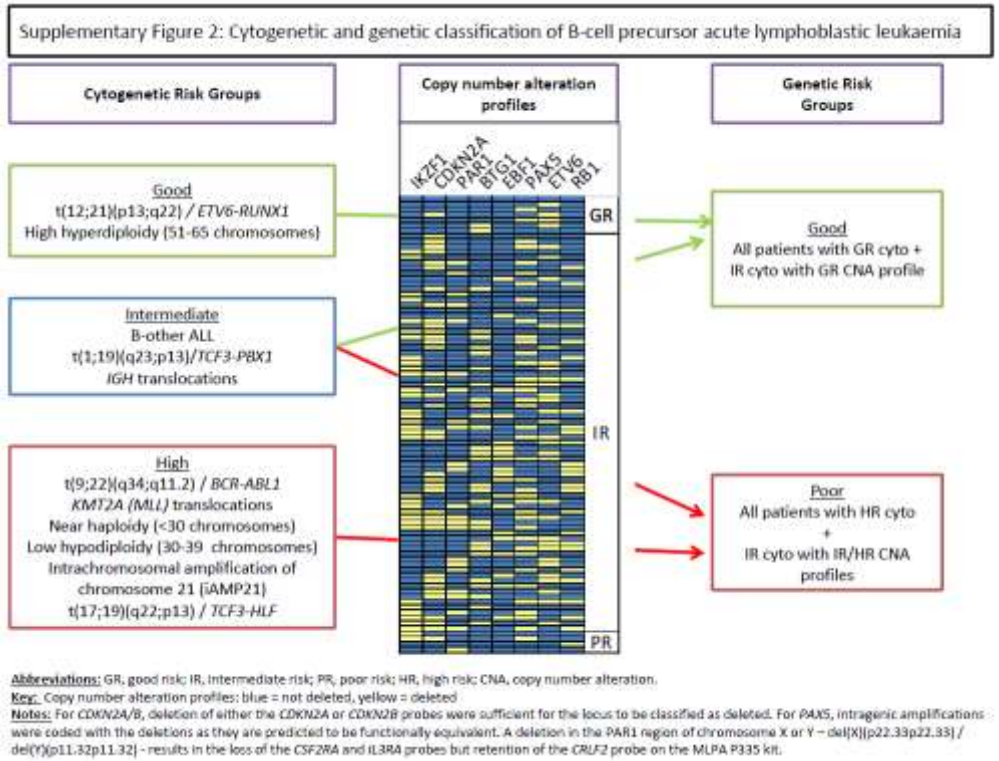
- Standard risk (SR): patients with late (>6 months after stopping frontline therapy) isolated extra-medullary (EM) relapses.
- Intermediate risk (IR): BCP-ALL patients with late relapses involving the bone marrow (BM) or early (<6 months from stopping frontline therapy) isolated EM and combined relapses, as well as T-ALL patients with early isolated EM relapses.
- High risk (HR): (1) patients with a very early relapse (<18 months from initial diagnosis); (2) T-ALL relapses involving the marrow; and (3) BCP-ALL patients with an early isolated BM relapse

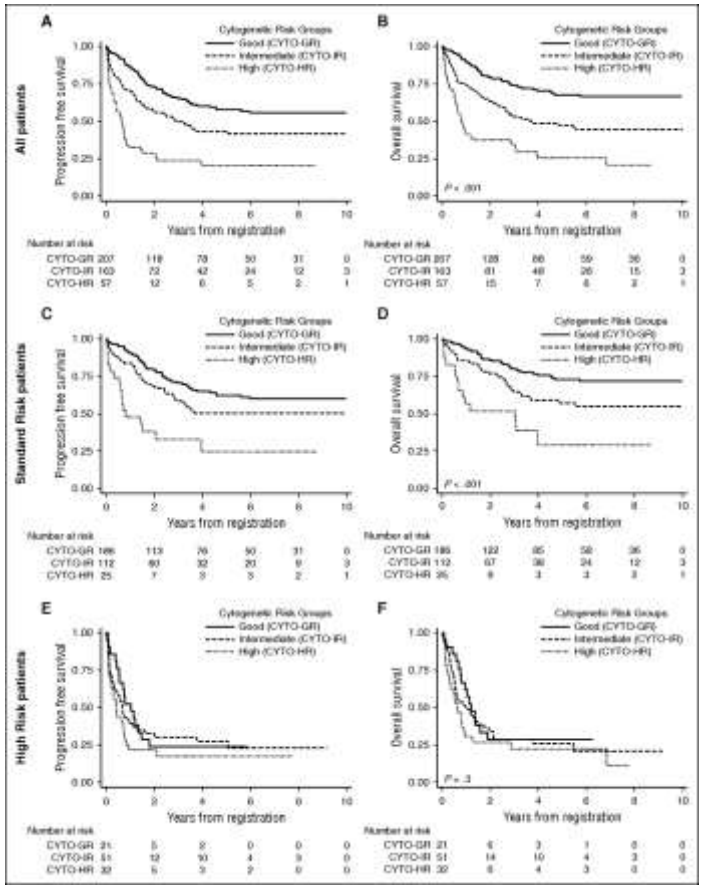



**Cytogenetic, copy number, and mutational profile of relapsed acute lymphoblastic leukemia patients stratified by clinical risk group.** Frequency of individual chromosomal abnormalities, copy number alterations and sequence mutations among clinical standard and high-risk B-cell precursor ALL patients treated in ALLR3. $*P < .05$; $**P < .01$.

# Integration of genetic and clinical risk factors improves prognostication in relapsed childhood B-cell precursor acute lymphoblastic leukemia

*Irving J et al. Blood 2016 128:91*




**Progression-free and overall survival of relapsed B-cell precursor ALL patients stratified by cytogenetic risk and clinical risk group.** Kaplan-Meier survival graphs depicting the PFS and OS of relapsed childhood. Patients with ALL treated on ALLR3 and stratified by cytogenetic risk group.

# Escolha Doador

## Compatibilidade

- Irmão HLA Compatível
- NAP ≥9/10
  - Tipagem molecular de Alta Resolução: HLA-A, -B, -C, -DRB1
  - Diferença de até 1 alelo
- SCUP
- Haploidentico
  - DAS (anti HLA receptor/Doador)

## Fonte

- Medula Óssea
  - Mobilização - GSF?
- SCUP

# DRM+ pré TMO

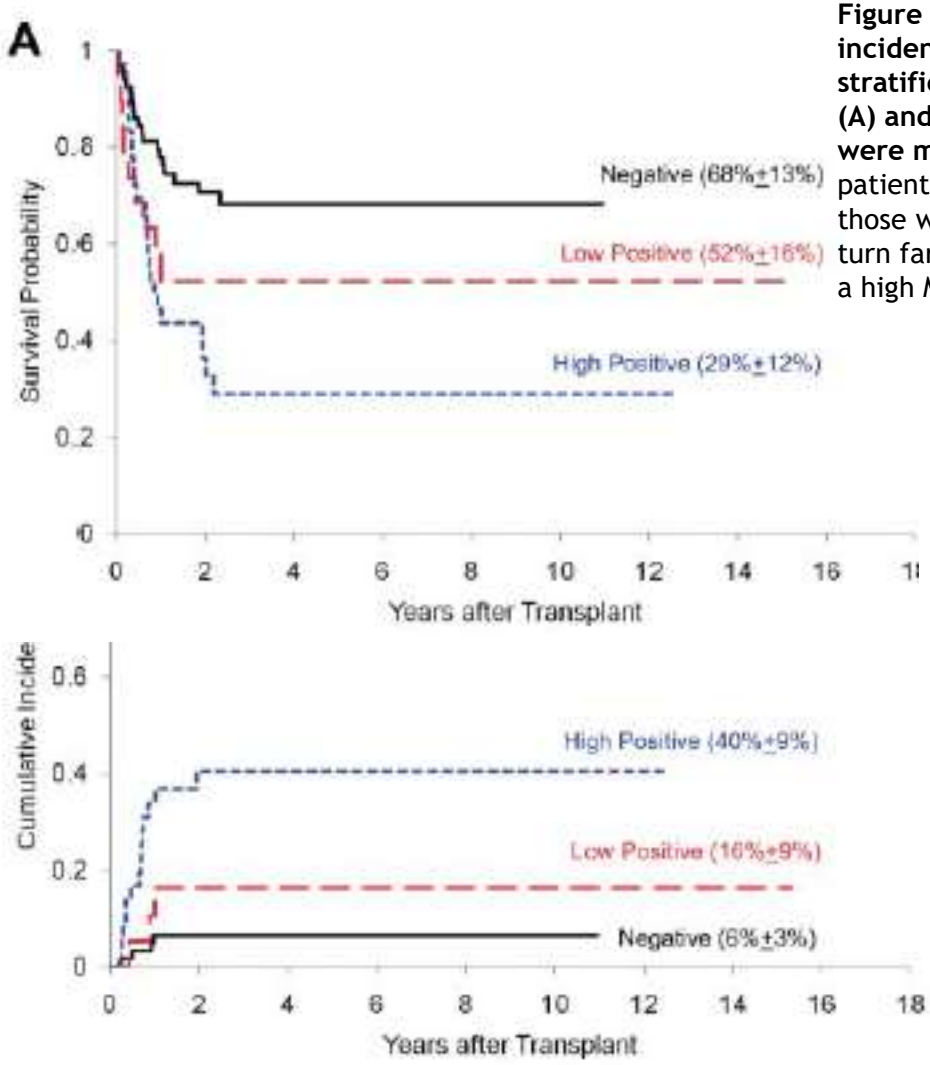



**Figure 1. Survival and cumulative incidence of relapse after HCT stratified by MRD level. The survival (A) and relapse (B) probabilities were more favorable among** patients with negative MRD than those with a low MRD level, who in turn fared better than patients with a high MRD level.

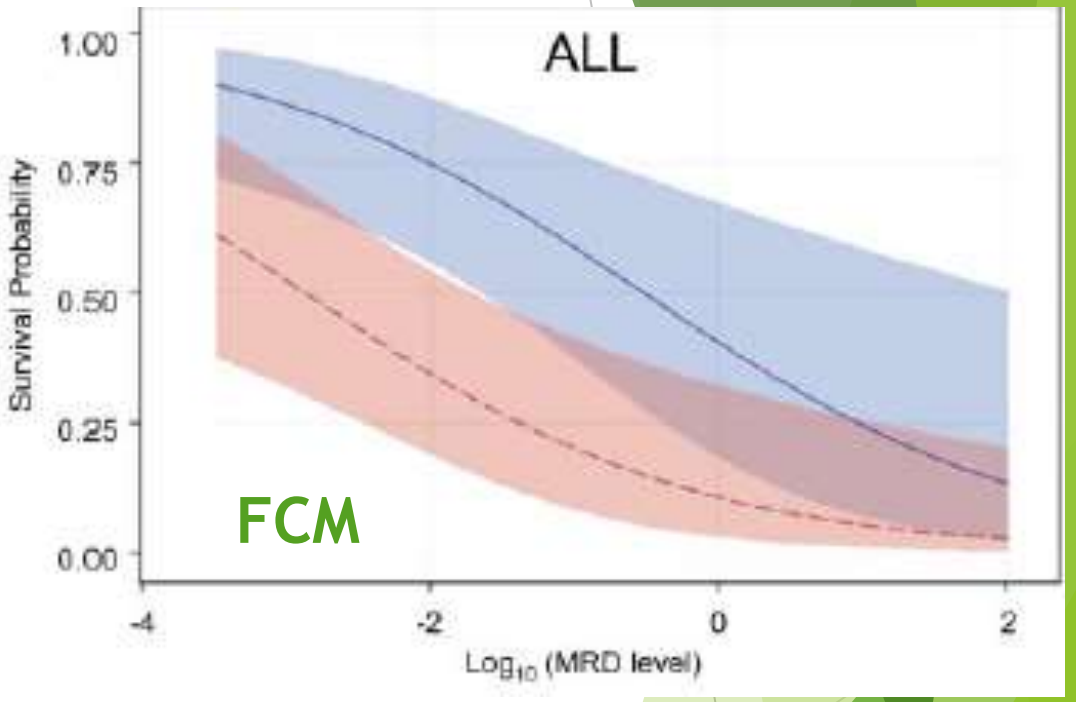



**Figure 3. Survival probability based on the level of MRD stratified by leukemia type and treatment era. Probability of survival during the observation period in patients with ALL** after HCT in the earlier era (red) or the recent cohorts (blue). The confidence bands represent 95% CI limits. ALL patients treated in the recent era fared significantly better than those in the early era (*P=.005 and P =.007, respectively). The impact of MRD level on survival was significant f or ALL (P=.002)*

**Wing Leung et al. Blood. 2012;120(2):468-72**

# Condicionamento

- CY + TBI (Irradiação Corporal total)
  - Ciclofosfamida = 60mg/Kg/dia – EV, durante 2 dias – dose total= 120mg/Kg
    - Mesna = nos mesmos dias da ciclofosfamida - 1,4X a dose total da Ciclofosfamida.
      - 20 mg/kg antes da ciclofosfamida
      - 20 mg/kg 3h, 6h, 9h e 12h após a Ciclofosfamida.
  - TBI = 12 Gy fracionada em 6 sessões (2Gy 12/12h), durante 3 dias. D-3, D-2 e D-1.

- VP + TBI
  - VP16 (60 mg/kg por 4 h) (max 3600mg)
  - TBI: 1200 cGy, 2xd 3 dias)

# TBI

- Radioterapia SNC
- Radioterapia Testículo

## Efficacy of prophylactic additional cranial irradiation and intrathecal chemotherapy for the prevention of CNS relapse after allogeneic hematopoietic SCT for childhood ALL.

Fukano R, Nishimura M, Ito N, Nakashima K, Kodama Y, Okamura J, Inagaki J.
Pediatr Transplant. 2014 Aug;18(5):518-23

We evaluated the efficacy of CRT and IT chemotherapy, in addition to conditioning including TBI, for the prevention of CNS relapse, in allogeneic HSCT for childhood ALL. From January 1999 to December 2009, a total of 48 patients, without previous or presenting CNS involvement, underwent HSCT for ALL. All patients received myeloablative conditioning including TBI of 12 or 13.2 Gy and IT chemotherapy twice between days -10 and -2 prior to HSCT. Twenty-five patients received CRT prior to TBI (CRT+), and 23 patients did not (CRT-). CRT+ and CRT- patients had a seven-yr EFS rate of 40.0 ± 9.8% and 41.7 ± 10.6%, respectively (p = 0.8252). The seven-yr relapse rates for CRT+ and CRT- patients were 45.0 ± 11.2% and 38.4 ± 11.6%, respectively (p = 0.7460). CNS relapses were evident in 1 (4.0%) CRT+ patient and 1 (4.4%) CRT- patient (p = 1.000). There were no significant differences in EFS and the probability of CNS relapse between CRT+ and CRT- patients.

These results demonstrate that CRT and IT chemotherapy, in addition to conditioning chemotherapy, may not be necessary in childhood ALL patients without previous or presenting CNS involvement.

# Condicionamento

- BUCY 16/120 (+VP 40mg/kg*)
  - Busulfan = 1mg/Kg/dose – 6h/6h= 4 doses/dia – VO – durante 4 dias (4mg/Kg/dia)
  - D-7, D-6, D-5 e D-4
  - BU IV = dose equivalência/Kg 1xdia
  - Ciclofosfamida = 60mg/Kg/dia – EV, durante 2 dias – dose total= 120mg/Kg
  - Mesna = nos mesmos dias da ciclofosfamida - 1,4X a dose  total da Ciclofosfamida.

# Profilaxia DECH

- CSA (+MTX ± ATG)
  - Ciclosporina* 1,5 a 2mg/Kg infusão venosa contínua:  Início D-2
    - MUD MMD: Metotrexate: 15mg/m2 - D + 1;  10 mg/m2 - D + 3, D + 6 e (D + 11) – (Acido folinico na mesma dose do metotrexate, com exceção do d+11,em que a dose é de 50 mg)
    - MUD MMD: ATG 7,5 a 10 mg/kg
  - Metronidazol: 500 mg 8 /8 horas 10mg/kg/dose 8/8 horas pediatria

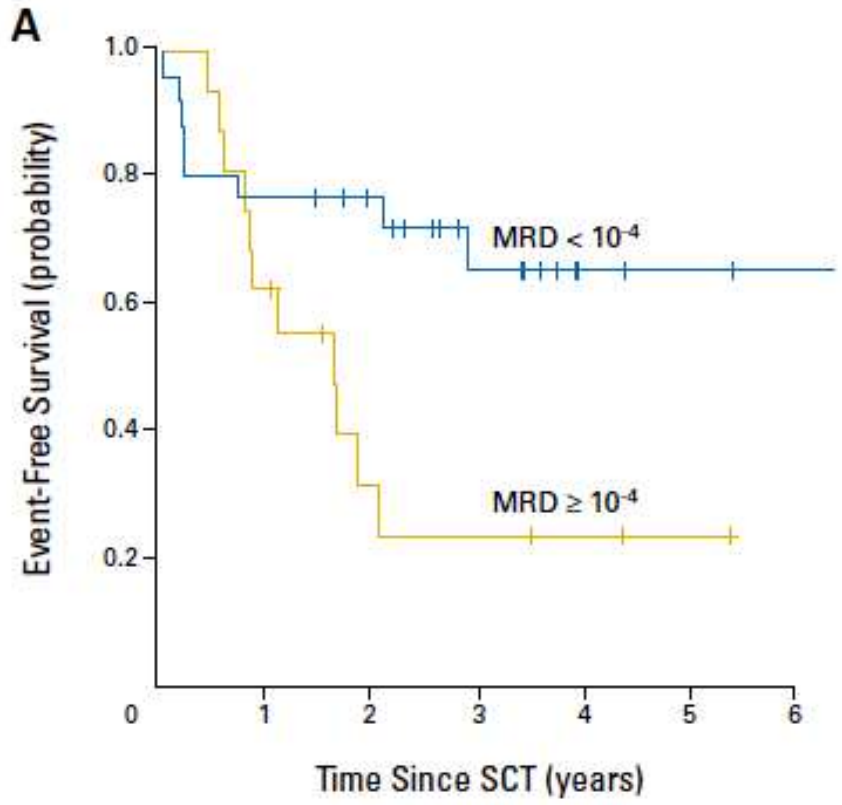
*CSA 200 a 400 ng/mL*

*(após 100-300 por 3 a 6 meses)*

# Onde e Como Podemos Intervir?

# Prognostic Value of Minimal Residual Disease Quantification Before Allogeneic Stem-Cell Transplantation in Relapsed Childhood Acute Lymphoblastic Leukemia: The ALL-REZ BFM Study Group

*Bader et al. J Clin Oncol 2008 27:377*




**Event - free survival probability (pEFS) in intermediate - risk patients with ALL relapse (S2 group in CR2, n=35) by MRD status of *v <10-4 leukemic cells before allogeneic* SCT.** MRD ≥$10^{-4}$ leukemic cells: n=14; censored, n=4; deaths, n=1; relapses, n=9; pEFS (4 years) = 0.20±0.12. MRD<$10^{-4}$ leukemic cells: n=21; censored, n=15; deaths, n=5; relapses, n=1; pEFS (5 years) = 0.68±0.12. EFS, log-rank, *P .020*.

# Persistent MRD before and after allogeneic BMT predicts relapse in children with acute lymphoblastic leukaemia. *Sutton R et al. BJH, 2015, 168, 395*

- MRD levels were measured by real-time quantitative polymerase chain reaction (qPCR) to detect T-cell receptor and immunoglobulin gene rearrangements with patient specific primers and generic probes
- While the most discriminating MRD threshold before HSCT for predicting outcome was MRD positive/negative; within the MRD-positive group, higher levels of MRD (>1 x $10^{-2}$) were associated with lower survival (OS = 50%, Fig 3A,B).
- Analysis of post-HSCT MRD samples (collected within 1–3 months) showed that MRD positivity after transplant was prognostic of both LFS and OS (Fig 3C,D)
- MRD persistence post-HSCT was associated with an increased risk of any event [HR 55 95% confidence interval (CI) 15–195, 95% CI] compared to MRD negativity.

# Persistent MRD before and after allogeneic BMT predicts relapse in children with acute lymphoblastic leukaemia.

*Sutton R et al. BJH, 2015, 168, 395*

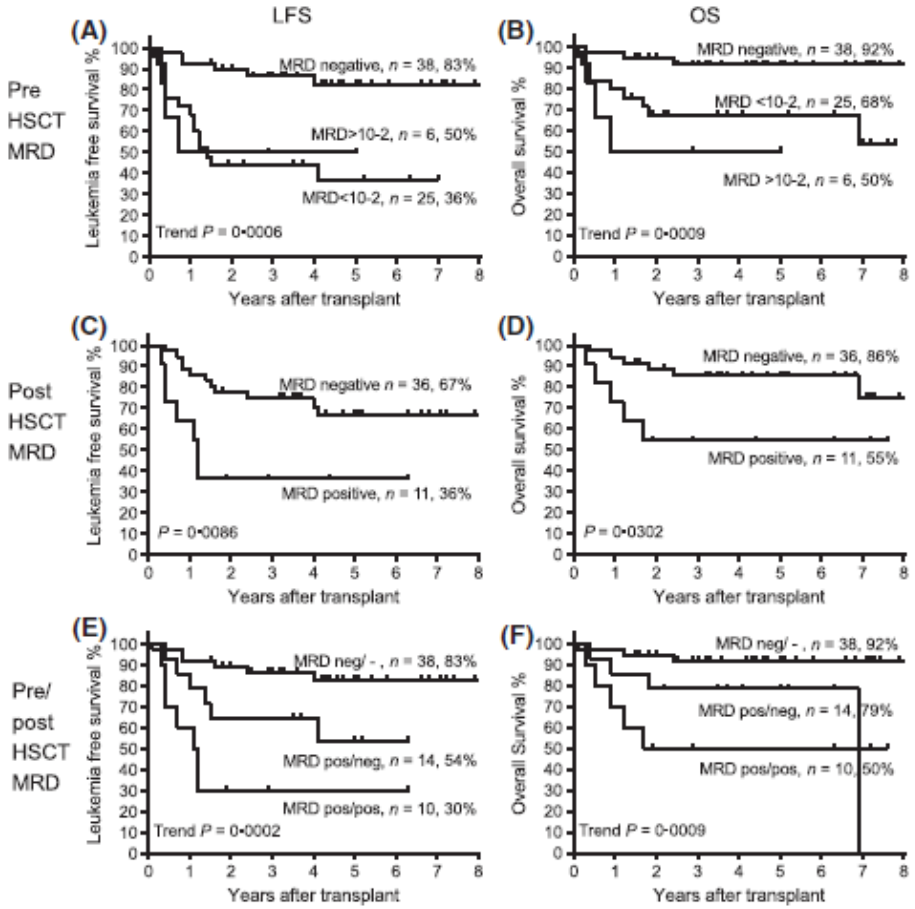



Fig 3. Prognostic value of MRD in bone marrow in ALL HSCT patients. Kaplan Meier plots showing leukaemia-free survival (LFS) and overall survival (OS) in haematopoietic stem cell transplant (HSCT) patients dependent on minimal residual disease (MRD) levels in bone marrow, (A, B) immediately before conditioning for HSCT; (C, D) after bone marrow recovery and (E, F) taking both time points into consideration. The MRD neg/- group in E and F includes 15 patients not tested post-HSCT.

# Persistent MRD before and after allogeneic BMT predicts relapse in children with acute lymphoblastic leukaemia. *Sutton R et al. BJH, 2015, 168, 395*

- The patients who had persistent MRD but did not relapse were examined for potential ameliorating factors.
- aGVHD occurred in all 4 such patients whose MRD persisted after HSCT:
  - 2 became MRD-negative while receiving treatment for aGVHD;
  - 1 had withdrawal of immunosuppression, developed GVHD treated with Sirolimus, and became MRD-negative and
  - 1 had rapid withdrawal of immunosuppression despite recent GVHD followed by serial DLI with development of GVHD and subsequent MRD clearance.
- 2/8 non-relapsing patients, in whom MRD persisted until HSCT but not afterwards, had rapid withdrawal of immunosuppression, which may have contributed to MRD clearance

# Minimal residual disease before and after transplantation for childhood acute lymphoblastic leukaemia: is there any room for intervention? *Balduzzi et at. BJH 2014, 164, 396*

- MDR por PCR-RT: ≥ 1 x $10^{-4}$
- Intervenção Pré-TCTH
  - FLA±"D"
- Condicionamento: TBI+VP16 (ou CY) / BuMelCy / TTCy / TreoFlu
  - Profilaxia: CSA (150 ng/ml) D+90 + MTX ± ATG
- Intervenção Pós – TCTH
  - Suspender IS
  - DLI

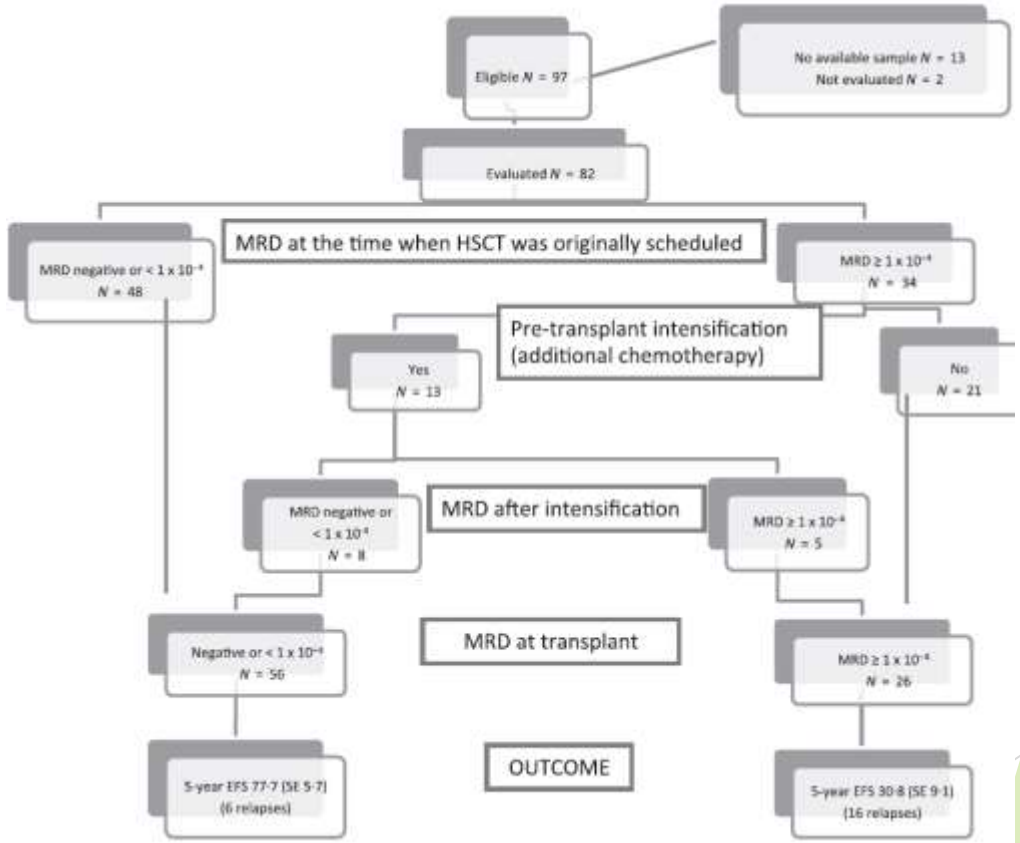



Fig 1. Flow diagram reporting outcome data according to pre-transplant intervention, by means of chemotherapy intensification, and MRD at transplant.

# Minimal residual disease before and after transplantation for childhood acute lymphoblastic leukaemia: is there any room for intervention? *Balduzzi et at. BJH 2014, 164, 396*

**Table II.** MRD at transplantation. Multivariate analyses of any event (relapse, death in remission) and relapse only. All 82 patients with ALL in CR who entered the study are included in the models.

| | Multivariate analysis | | |
|---|---|---|---|
| | Hazard ratio | 95% CI | *P*-value |
| Any event | | | |
| MRD at transplant | | | |
| Negative or $<10^{-4}$ | 1 | | |
| $\geq 10^{-4}$ | 5·5 | 2·58–11·52 | <0·001 |
| Disease phase at transplant | | | |
| CR1 | 1 | | |
| CR2 or CR3 | 2·3 | 0·97–5·35 | 0·06 |
| Acute GVHD | | | |
| 0–I | 1 | | |
| II–IV | 0·8 | 0·39–1·70 | 0·59 |
| Relapse | | | |
| MRD at transplant | | | |
| Negative or $<10^{-4}$ | 1 | | |
| $\geq 10^{-4}$ | 9·2 | 3·54–23·88 | <0·001 |
| Disease phase at transplant | | | |
| CR1 | 1 | | |
| CR2 or CR3 | 2·5 | 0·91–6·80 | 0·07 |
| Acute GVHD | | | |
| 0–I | 1 | | |
| II–IV | 0·5 | 0·19–1·24 | 0·13 |

MRD, minimal residual disease; CR, complete remission; ALL, acute lymhoblastic leukaemia; GVHD, graft-versus-host disease; 95% CI, 95% confidence interval.

**Table IV.** MRD after transplantation. Multivariate analyses on any failure according to the timing of post-transplant MRD positivity.

| | Multivariate analysis | | |
|---|---|---|---|
| | Hazard ratio | 95% CI | *P*-value |
| Early post-transplant MRD* | | | |
| MRD 1–3 months after transplant | | | |
| Negative | 1 | | |
| Positive† | 2·5 | 1·05–5·75 | 0·04 |
| Disease phase at transplant | | | |
| CR1 | 1 | | |
| CR2 or CR3 | 2·3 | 0·93–5·73 | 0·07 |
| MRD at transplant | | | |
| Negative or $<10^{-4}$ | 1 | | |
| $\geq 10^{-4}$ | 5 | 2·13–11·73 | <0·001 |
| Acute GVHD | | | |
| 0–I | 1 | | |
| II–IV | 0·7 | 0·32–1·69 | 0·46 |
| Late post-transplant MRD‡ | | | |
| MRD 6–12 months after transplant | | | |
| Negative | 1 | | |
| Positive† | 7·8 | 2·20–27·78 | 0·002 |
| Disease phase at transplant | | | |
| CR1 | 1 | | |
| CR2 or CR3 | 1·9 | 0·51–7·28 | 0·34 |
| MRD at transplant | | | |
| Negative or $<10^{-4}$ | 1 | | |
| $\geq 10^{-4}$ | 3·5 | 1·04–11·50 | 0·04 |
| Acute GVHD | | | |
| 0–I | 1 | | |
| II–IV | 3·2 | 0·98–10·48 | 0·06 |

MRD, minimal residual disease; CR, complete remission; ALL, acute lymhoblastic leukaemia; GVHD, graft-versus-host disease; 95% CI, 95% confidence interval.
*This model, analysing the impact of early post-transplant MRD positivity, included the 71 patients who were alive in remission at the first time-point and had their MRD assessed at either one or both time-points 1 and 2, i.e., at 1 and 3 months after transplantation.
†Any positive level was taken into account for MRD analyses after transplantation.
‡This model, analysing the impact of late post-transplant MRD positivity, included the 60 patients who were alive in remission at the third time-point and had their MRD assessed at any of the timepoints 3, 4, 5, i.e., at 6, 9 or 12 months after transplantation.

# Minimal residual disease before and after transplantation for childhood acute lymphoblastic leukaemia: is there any room for intervention? *Balduzzi et at. BJH 2014, 164, 396*

- (i) MRD status before transplantation has the strongest impact on outcome and remains relevant also after adjusting for post-transplant MRD pattern,
- (ii) MRD positivity after transplantation does not necessarily imply relapse, mostly if detected at a low level early after transplantation,
- (iii) additional intensified chemotherapy given to MRD-positive patients pre-transplant may be effective in improving ultimate outcome,
- (iv) early tapering of immunosuppression (but not DLI) in patients who have MRD detected before or after transplantation may reduce the risk of relapse.

# Redução DRM pré TCTH

- Altas Doses
  - “FlAgs”
  - Mitoxantrona
  - Clofarabina
- Bortezomibe (TACL)
- Nelarabina
- Tkis

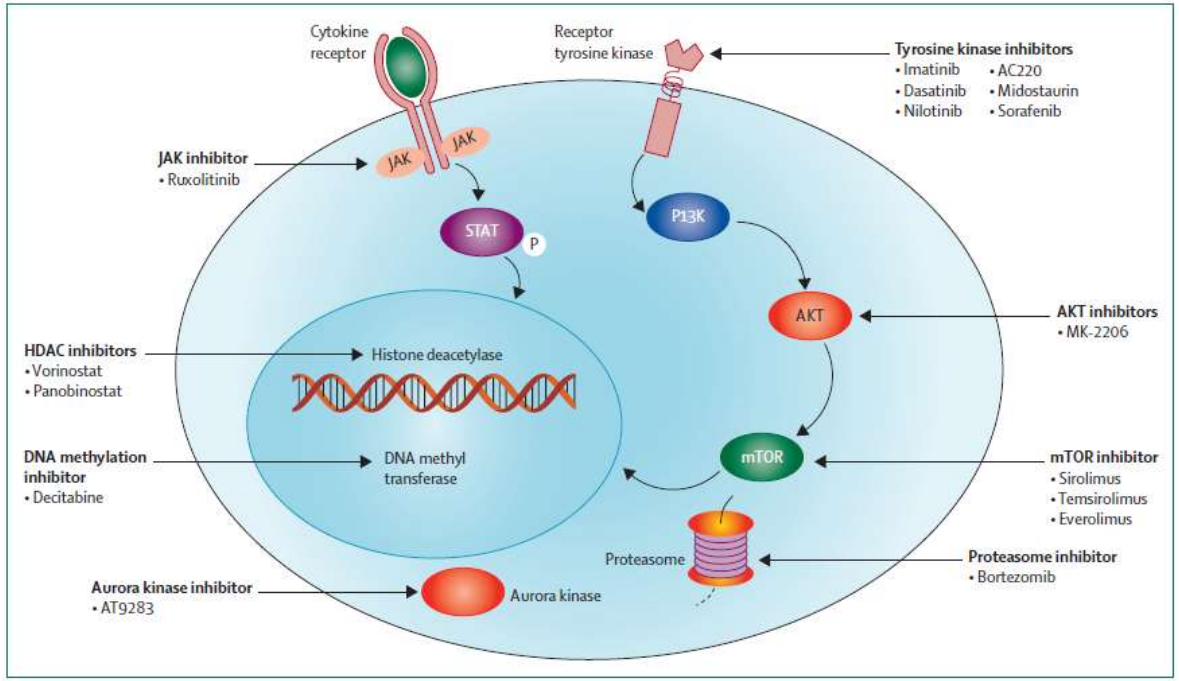



***Figure 2:*** **Molecular targets under evaluation in clinical trials for childhood acute lymphoblastic leukaemia (ALL)** Preclinical studies have identifi ed multiple pathways and molecular targets for therapeutic intervention. These include small molecule tyrosine kinase inhibitors (targeting BCR-ABL1, FLT3, JAK), inhibitors of the PI3K/AKT/mTOR pathway, and inhibitors of vital cellular machinery (proteasome, aurora kinase). Epigenetic therapies target enzymes responsible for chromatin modifi cation. mTOR=mammalian target of rapamycin. JAK=janus kinase. HDAC=histone deacetylase. *Bhojwani & Pui. Lancet Oncol, 2013*

# Redução DRM pré TCTH

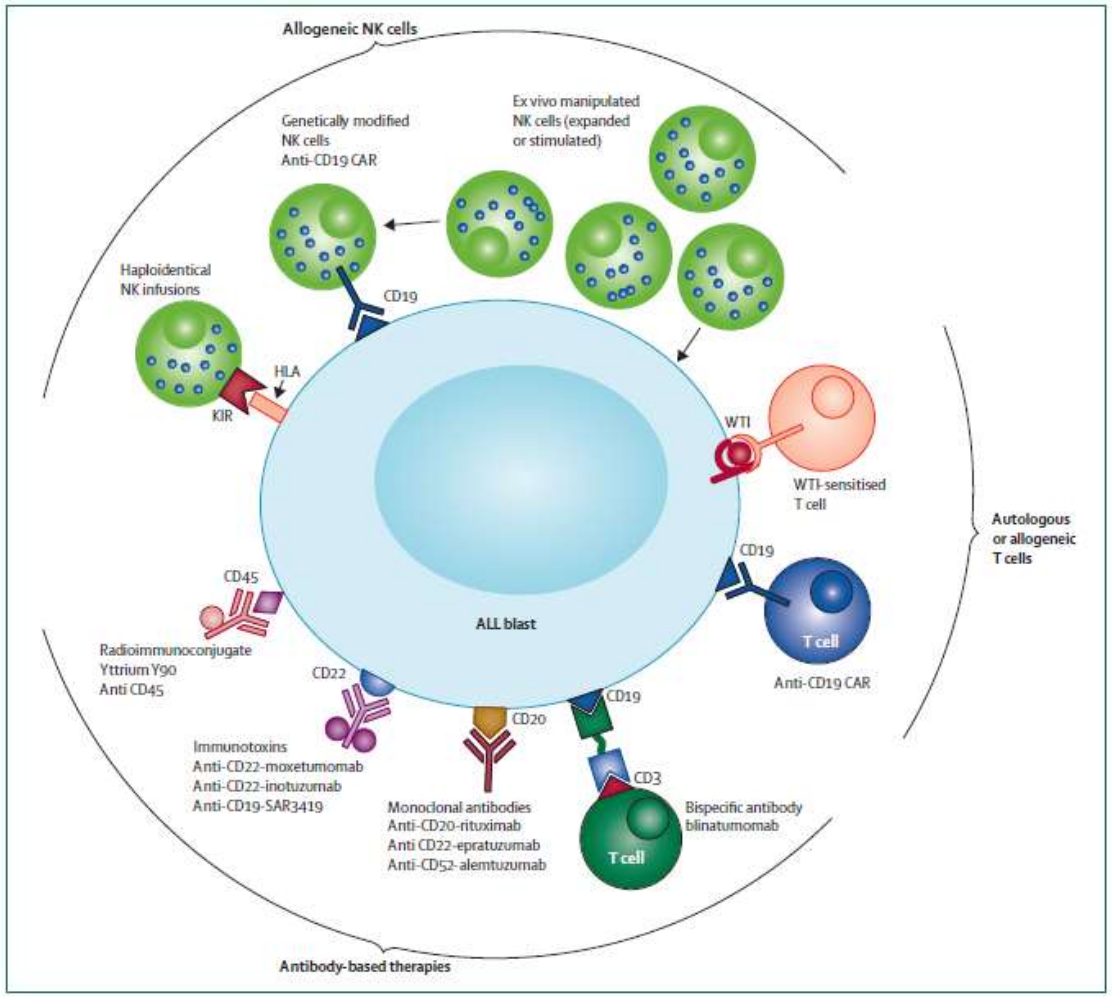



***Figure 3:*** **New immunological approaches under investigation for childhood relapsed acute lymphoblastic leukaemia (ALL).** The lymphoblast can be targeted by various immunological mechanisms, which include monoclonal antibodies, immunotoxins, and immunoconjugates. Adoptive transfer of engineered T cells or natural killer cells with chimeric antibody receptors against CD19 or WT1-sensitised T cells are also under investigation in childhood relapsed ALL. NK=natural killer. KIR=killer immunoglobulin receptor. HLA=human leucocyte antigen.. *Bhojwani & Pui. Lancet Oncol, 2013*

# Monitoramento Pós TCTH

**Table 2**
Multivariate Cox Proportional Hazard Regression Analysis Estimating the Effect of Chimerism and MRD Status on Relapse, NRM, and OS

| | Relapse | | NRM | | OS | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| $CD4^+$ blood | | | | | | |
| CC | 1 | | 1 | | 1 | |
| ll-MC | 1.71 (0.46-6.36) | .42 | 3.68 (0.82-16.40) | .088 | 2.49 (0.88-7.01) | .085 |
| de-MC | 0.84 (0.25-2.81) | .78 | 0.24 (0.03-1.88) | .17 | 0.51 (0.19-1.37) | .18 |
| in-MC | 5.32 (2.10-13.45) | <.001 | 4.61 (0.91-14.88) | .063 | 4.17 (2.05-8.51) | <.001 |
| $CD8^+$ blood | | | | | | |
| CC | 1 | | 1 | | 1 | |
| ll-MC | 0.91 (0.25-3.33) | .89 | 4.24 (1.35-13.37) | .014 | 2.14 (0.99-4.63) | .053 |
| de-MC | 0.46 (0.14-1.53) | .21 | 0.19 (0.02-1.49) | .113 | 0.444 (0.16-1.21) | .11 |
| in-MC | 4.15 (1.64-10.51) | .003 | 3.38 (0.84-13.67) | .087 | 4.19 (1.99-8.86) | <.001 |
| $CD19^+$ blood | | | | | | |
| CC | 1 | | 1 | | 1 | |
| ll-MC | 0.61 (0.17-2.25) | .46 | 0.85 (0.18-4.03) | .84 | 0.96 (0.35-2.62) | .93 |
| de-MC | 0.52 (0.17-1.61) | .25 | 0.18 (0.02-1.43) | .11 | 0.53 (0.20-1.44) | .21 |
| in-MC | 4.10 (1.55-10.80) | .004 | 5.13 (0.96-27.37) | .056 | 3.65 (1.71-7.81) | .001 |
| $CD34^+$ bone marrow | | | | | | |
| CC | 1 | | 1 | | 1 | |
| ll-MC | 1.14 (0.26-4.98) | .86 | 2.72 (0.23-31.62) | .42 | 3.07 (0.58-16.31) | .19 |
| de-MC | 0.46 (0.11-1.98) | .29 | 3.90 (0.46-33.43) | .21 | 3.22 (0.68-15.24) | .14 |
| in-MC | 3.58 (1.26-10.191) | .017 | 7.03 (0.86-57.63) | .069 | 8.99 (2.11-38.31) | .003 |
| MRD bone marrow | | | | | | |
| Negative | 1 | | 1 | | 1 | |
| Relapse | 24.64 (1.58-384.19) | .022 | 0.04 (0-13074423) | .75 | 9.67 (1.93-48.50) | .006 |

HR indicates hazard ratio.
Prognostic variables examined were transplant year, sex, age, Karnofsky Performance Status, HCT-CI, disease status, lineage, cytogenetic risk group, donor type, stem cell source, ATG infusion, and the time-dependent covariates application of DLI, occurrence of aGVHD, late aGVHD, and cGVHD, chimerism status, and MRD status. Only results for chimerism and MRD status are shown here. Other variables with significant prognostic impact in the multivariate setting were disease status and occurrence of cGVHD for relapse and OS and HCT-CI for NRM. HR and *P* values refer to the comparison of the respective category with the first one.

*Terwey at al. BBMT 2014*

# Principais Estratégias para Intervenção na LLA Recaída

## Pré TCTH

- Identificação de Fatores de Risco
- Doença Residual Mínima
  - Estratégia de Redução
    - QXT
    - Novas Drogas

## Pós TCTH

- Monitoramento
  - MDR
  - Quimerismo
- Intervenção
  - Redução IS
  - DLI / Terapia Celular
  - TKI, outras drogas alvo


**Quinta-feira 17 de agosto / Thursday, August 17th**
Sala / Room: Ballroom 3
Sessão Conjunta SBTMO - SOBOPE / Joint Session SBTMO – SOBOPE

**14:00 - 14:25** - Sessão plenária pediátrica: lições aprendidas no tratamento da LLA recidivada / Pediatric plenary session: Lessons learned in the treatment of relapsed ALL

Palestrante: **Michael Pulsipher**