MINIMAL RESIDUAL DISEASE IN PEDIATRIC ACUTE LEUKEMIA

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Aim of therapy in acute leukemia

- **To induce remission** (clinical and hematological)
- **To maintain remission** by systemic chemotherapy and prophylactic CNS therapy
- **To treat the complications** of therapy and of the disease.

What is remission

Classification	% Blasts in Bone Marrow
M_1 Bone Marrow	≤5%
M_2 Bone Marrow	≤25%
M_3 Bone Marrow	>25%

- True remission requires :
  - M1 marrow status- Based on 200 cell count- with normal marrow cellularity and presence of all cell lines
  - CNS1 CSF status: <5 WBCs/mm3, no blasts on cytocentrifuge slide , TDT neg.
  - Normal CBC: with minimal levels of 500/mm_3 granulocytes, 75,000/ mm_3 platelets and 12 g/dl hemoglobin with no blast cells seen on the blood smear
  - No clinical evidence of leukemic cell infiltration or envolvement (e.g., LAP, HSM, testicular enlargement, neurological sign ,etc.)
  - No symptoms attributable to the disease (e.g., fever and bone pain)

Manual of Pediatric Hematology&Oncology.Lanzkowsky.2011

What is relapse

- Relapse is defined by the appearance of any of the following:
  - More than 50% blasts in a single bone marrow aspirate
  - Progressive repopulation of blasts in excess of 5%, culminating in more than 25% in two or more bone marrow samples separated by 1 week or more
  - More than 25% blasts in the bone marrow and 2% or more circulating lymphoblasts
  - Leukemic cell infiltration in extramedullary organs, for example, CNS or gonads(biopsy proven) (for the diagnosis of isolated extramedullary relapse, the bone marrow
  - should contain less than 5% blasts)
  - Blasts in the CSF with a cell count greater than 5 WBC/mm3.

Manual of Pediatric Hematology&Oncology.Lanzkowsky.2011

Vigorous lympho-hematopoietic regeneration mimicking relapse may occur in patients who are not compliant with post-remission therapy. In these cases, MRD studies can quickly clarify the nature of the morphologically suspect cells.

Dario Campana.*Semin Hematol. 2009 January ; 46(1): 100–106.*

What is MRD?

- Evidence of persistent viable leukemic cells in bone marrow, peripheral blood, and CSF, In case of clinical and hematological Remission:
  - at the end of induction, late in therapy and even in off-therapy patients who do not subsequently clinically relapse.
  - not only for newly diagnosed ALL cases but also for relapsed patients treated with salvage chemotherapy or BMT

principles and practice of pediaric oncology . Pizzo.2011

Main Questions about MRD

- When?
- Why ?
- Which level of sensitivity ?
- What kind of method ?

leukemia-associated property

1) immunophenotypes :sufficiently distinct to allow the detection of 1 leukemic cells among 10,000 normal cells (0.01%)
2) Clonal rearrangement of immunoglobulin (IG) and T-cell receptor (TCR) genes which can be detected by PCR in most cases, with a sensitivity of 0.01% to 0.001%.
3) chromosomal abnormalities and their corresponding gene fusions (such as *BCR-ABL, MLLAF4, E2A-PBX1, and TEL-AML1)*
   - *Less than one-third of patients with ALL*
   - can be studied with Q-PCR in molecular pathology laboratories, allowing the detection of MRD with a sensitivity ranging from 0.1% to 0.001%.

Applications of MRD

- Optimize frontline therapy
  - Identify patients who require more intensive therapy OR may be cured with less intensive therapy
- Early detection of relapse (**postremission** sequential MRD monitoring)
  - intensify therapy and prepare for HSCT
- In the setting of transplant
  - Optimize timing of transplant
  - Modulate immuosuppression, DLI, other interventions
- In the setting of novel therapies
  - Use as surrogate to evaluate response
- Identify molecular determinants of treatment response
- The identification of new markers of leukemia

MRD in the Treatment of *De Novo* ALL

Applications of MRD:
Optimize frontline therapy

International Berlin-Frankfurt-Munster (I-BFM) Study :

- patients with MRD levels of 0.1% or higher on both day 33 and day 78 of treatment had a relapse rate of 75% prompting treatment intensification for this group of patients.

Flohr T,Leukemia 2008;22:771–782

The largest randomized controlled trial using MRD, Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP)-BFM 2000 [4], measured MRD by real-time quantitative-PCR (RT-PCR) at two TPs (day 33 and 78) in 3,184 children with B precursor ALL (pB-ALL). Patients were classified as minimal residual disease standard risk (MRD-SR) (MRD negative at day 33; $\leq 10^{-4}$), minimal residual disease high risk (MRD-HR) (day 78 MRD $\geq 10^{-3}$), and intermediate risk (minimal residual disease intermediate risk [MRD-IR], all others). Negative MRD at the EOI was the strongest outcome predictor, with a 5-year EFS of 92%, 77%, and 50% in MRD-SR (n = 1,348), MRD-IR (n = 1,647), and MRD-HR (n = 189) groups, respectively.

Reduced the importance of conventional prognostic factors such as age, white blood cell (WBC) count at diagnosis, genetic abnormalities, and prednisone response

Vora A, et al. Lancet Oncol 2013;14:199–209.
Conter V, et al.Blood 2010;115:3206– 3214.

Applications of MRD:
Optimize frontline therapy

St Jude Children's Research Hospital, currently use MRD on day 15 and day 42 for treatment assignment:

- On day 15 patients with:
  - the most intensification is reserved for patients with 5% of more leukemic cells.
  - MRD of higher than 1% receive intensified remission induction therapy
  - undetectable MRD (<0.01%) on day 15 receive a slightly less intensive reinduction therapy and lower cumulative doses of anthracyclin.
- on day 42 patients with:
  - standard-risk ALL who have MRD of 0.01% or higher are reclassified as high-risk.
  - Any patient with MRD of 1% or higher at this time point is a candidate for HSCT in first remission.

Dario Campana.*Semin Hematol. 2009 January ; 46(1): 100–106.*

In the COG P9900 series [21], EOI (day 29) BM and PB (induction day 8) MRD was measured by FCM in 2,143 children with pB-ALL. EOI MRD was highly predictive of survival. Patients with negative MRD (≤0.01%) (n = 1,588) had a 5-year EFS of 88% compared to 30% for patients with high MRD (>1%) (n = 67). However, EOI BM MRD was less helpful in identifying a low risk (LR) population compared to the day 8 PB MRD (n = 1,920); 30% of patients were day 8 PB MRD negative with a 5-year EFS of 90%. There was stepwise reduction in EFS at each 10-fold increase in MRD. Interestingly, a high day 8 PB MRD was a poor prognostic factor even if the day 29 MRD was negative. Patients with negative EOI MRD but high day 8 PB MRD (>1%) (n = 269) had poorer EFS compared to those with low day 8 PB MRD (n = 1,174) (79% vs. 90%; $P <$ 0.0001).

MRD assessment by flow in COG P9900:Day 8 PB and Day 29 BM: N= 2143 pre-B ALL

Borowitz et al, Blood 2008;111:5477-85

MRD levels in the day 29 BM were the strongest prognostic factor in this series

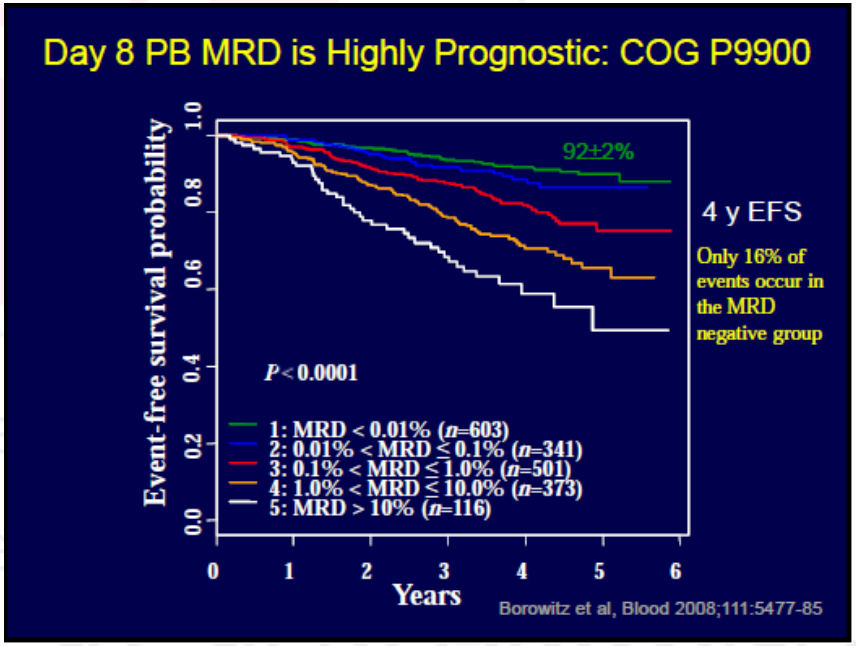
Presence of MRD > 0.01% in <u>either</u> predicted a poorer outcome

Table 2

Cox multivariate analysis

Variable	Hazard ratio	*P*
Day-29 MRD > .01%	4.31	< .001
NCI risk group	2.25	< .001
Trisomies 4 and 10	.570	< .001
Day-8 MRD (PB) > .01%	1.51	.018
TEL-AML1	.778	.151
Day-8 M1 marrow	1.034	.789

All variables shown entered in model.



Conclusions of COG Study

Browitz et al., Blood 111 (12):5477, 2008

- **End of induction MRD is the single most powerful prognostic marker in multivariate analysis.**
- **More intensive intervention may be desirable for all patients with MRD greater than 0.01% at end of induction.**
- **Measurement of MRD in the PB at day 8 provides additional useful information, especially to identify patients at low risk of relapse when combined with other favorable factors.**
- **The 12% of patients with all favorable risk factors, including NCI risk group, genetics, and absence of days 8 and 29 MRD, had a 97% 5-year EFS with non intensive therapy.**

T- cell ALL

Schrappe et al. evaluated the impact of MRD measured by PCR at days 33 and 78 in patients with T-ALL (n = 464) treated on the AIEOP-BFM 2000 protocol.[16] This study showed that EOI MRD level $\leq$ 0.01% was prognostically most favorable and that patients who became MRD negative by the EOC (day 78) also had a favorable outcome. In contrast, patients who continued to show a high MRD level ($\geq$0.1%) at the EOC phase had a high relapse risk.

MRD is also prognostic in early T-cell precursor (ETP) ALL, a more aggressive subset of T-ALL. Therapy intensification, mainly based on high MRD status, has resulted in comparable outcome for ETP and non-ETP patients.[39,40]

Schrappe M, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: Results of the AIEOP-BFM-ALL 2000 study. Blood 2011;118:2077–2084

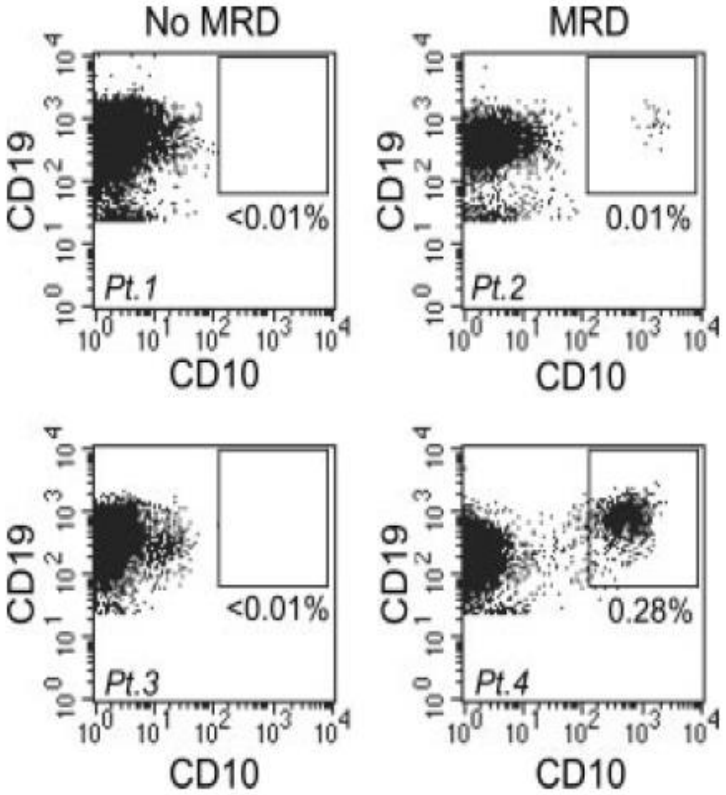
Infantile ALL

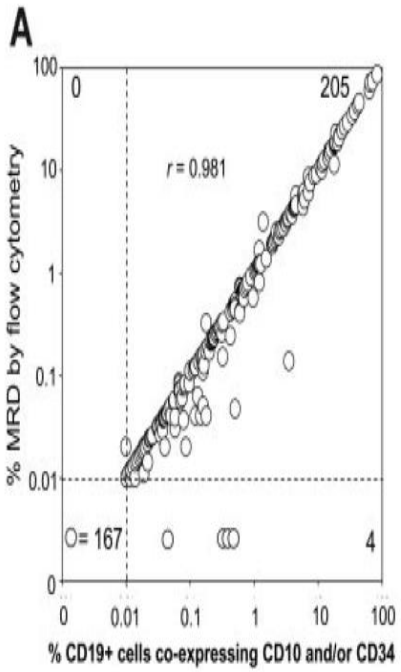
MRD evaluation by PCR at EOI and EOC in 99 infants with ALL treated on the Interfant-99 protocol [41] showed that all patients with high MRD at EOC (≥0.01%; 26% of cohort) relapsed, compared with only 13% of those with low MRD (<0.01% at both TPs; 44% of cohort). For the remaining patients (MRD-IR; 30% patients), the relapse rate was 31%.[41]

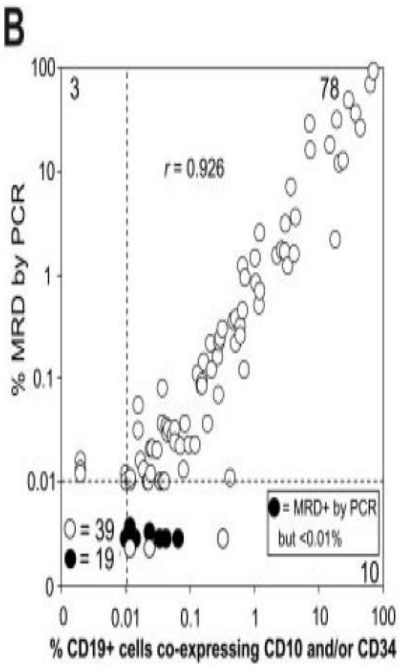
MRD “Light” Concept

Coustan-Smith E, Ribeiro RC, Stow P, Zhou Y, Pui CH, Rivera GK, et al. A simplified flow cytometric assay identifies children with acute lymphoblastic leukemia who have a superior clinical outcome. Blood 2006;108:97–102.

- Normal CD19+ cells expressing CD10 and/or CD34 in bone marrow are extremely sensitive to corticosteroids
  - After 2 weeks of remission induction therapy, these Normal CD19+ cells are typically <0.01%
  - CD19+ CD10+ and/or CD34+ cells at day 15-26 indicate MRD
  - their absence indicates good response
- Advantages:
  - Much reduced antibody panel
  - Can be performed with a one-laser cytometer
  - Easy interpretation







Recife Pilot Study #1

Traditional risk features	Day 19 $CD19^+$ $CD10^+$ and/or $CD34^+$	Risk Group
Good	<0.01%	Low
Good	>0.01%	Standard
Poor	Any	High

Poor = T-lineage ALL, or B-lineage ALL with WBC ≥ 50K, age 10-15 yrs, testicular/CNS 3 leukemia, and/or adverse genotypes (*BCR-ABL*, *MLL* rearrangements, hypodiploidy <45 chromosomes)

Current status

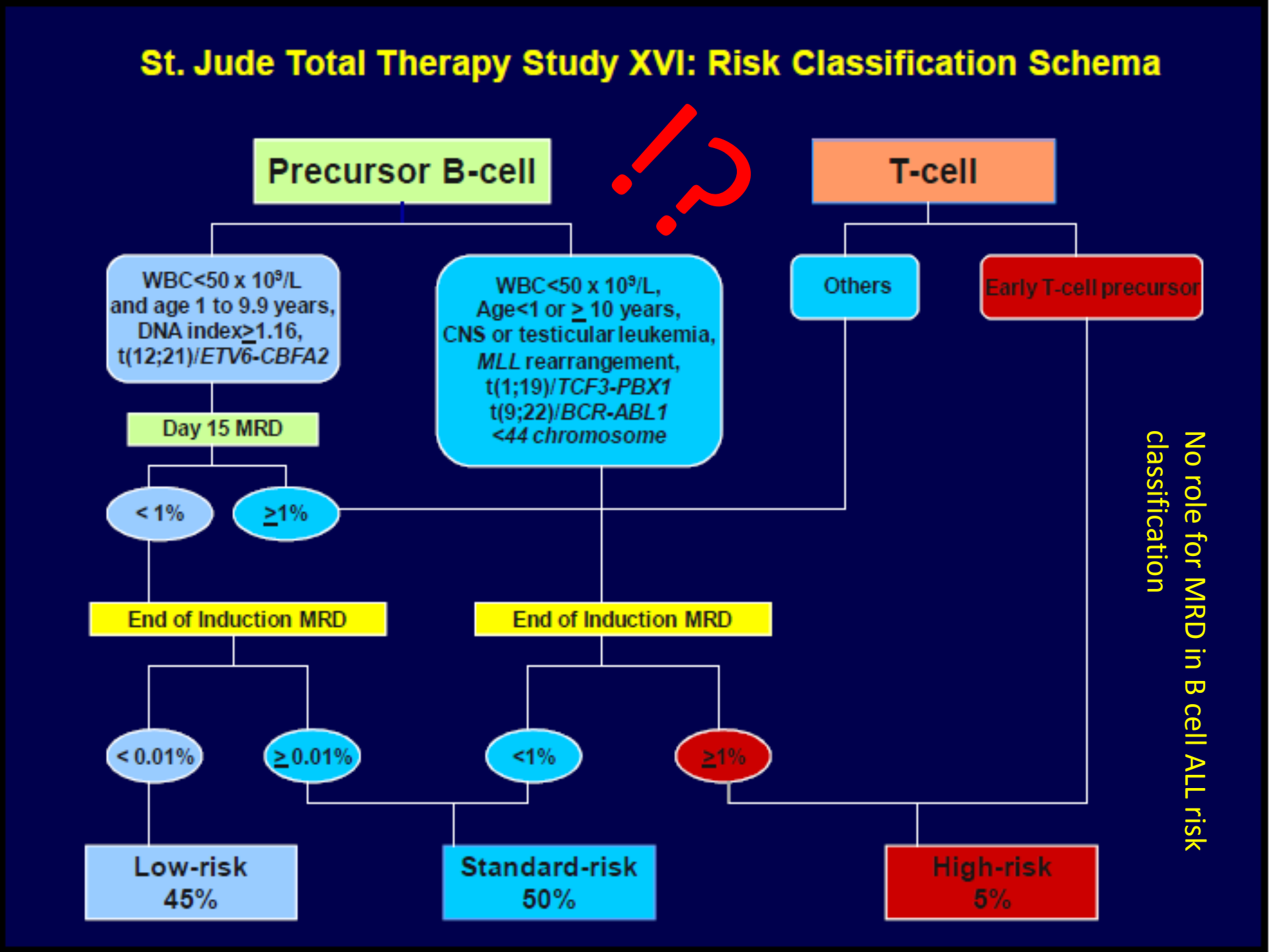
In summary, there is unequivocal evidence (irrespective of study design, chemotherapy protocol, and MRD measurement method) that MRD is a strong and independent prognostic factor. It is important to measure MRD at two TPs in early therapy (EOI and EOC), especially if the EOI MRD is positive. Patients with pB-ALL or T-ALL who have persistent MRD at the EOC are at HR for relapse and may benefit from therapy intensification.

Athale et al. *Pediatr Blood Cancer 2016*

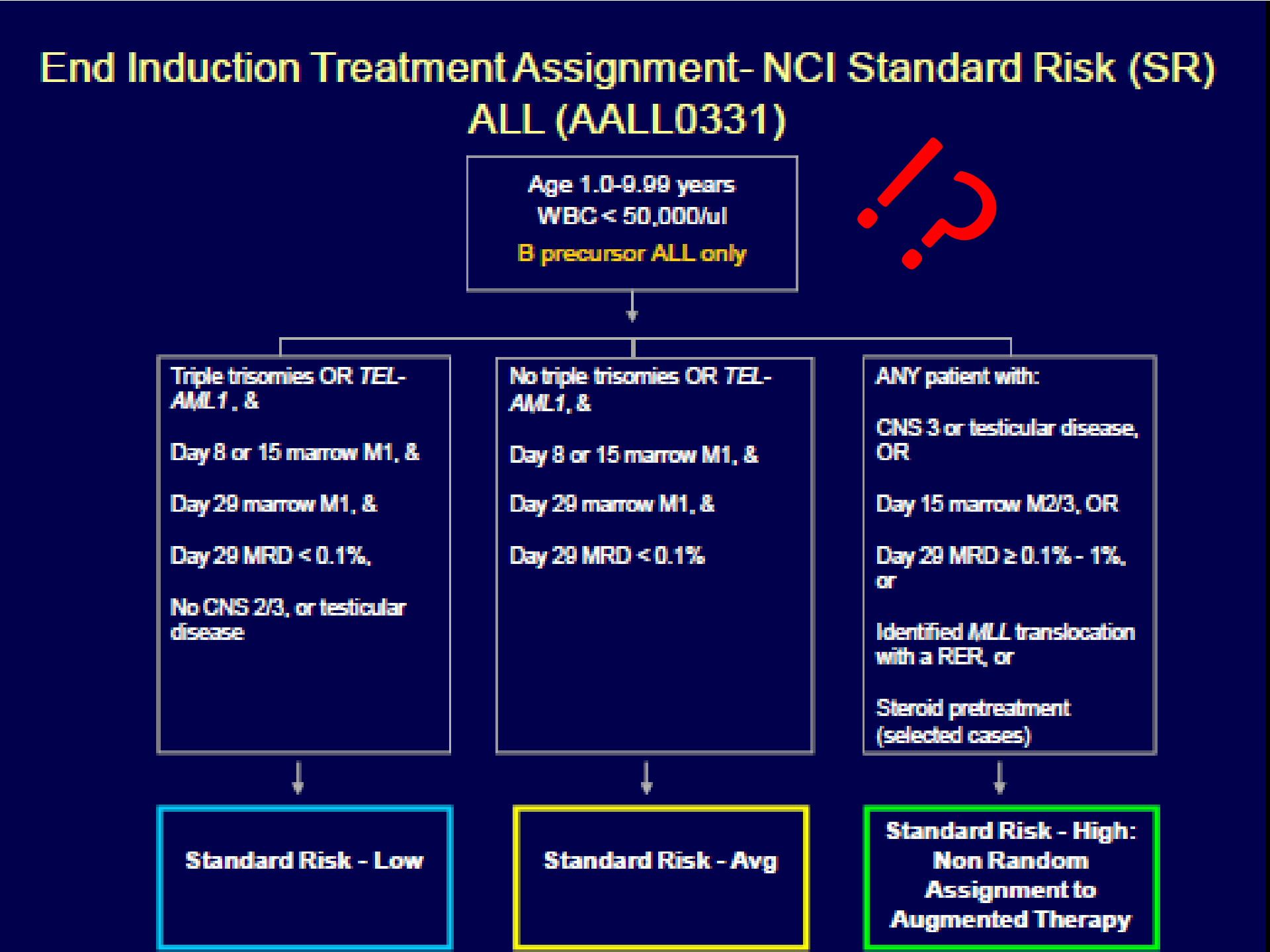
Summary

- MRD is a strong and independent prognostic indicator of relapse risk in children with pB-ALL, T-ALL, and infant ALL irrespective of MRD measurement methods and chemotherapy regimen.
- EOI MRD is a superior prognostic indicator compared to previously used clinical and biological factors.
- MRD measurement at a later TP (e.g., EOC) is important, especially for those with high EOIMRDand those with T-ALL.
- The major cooperative study groups have incorporated MRD into ALL risk stratification and therapy decisions.

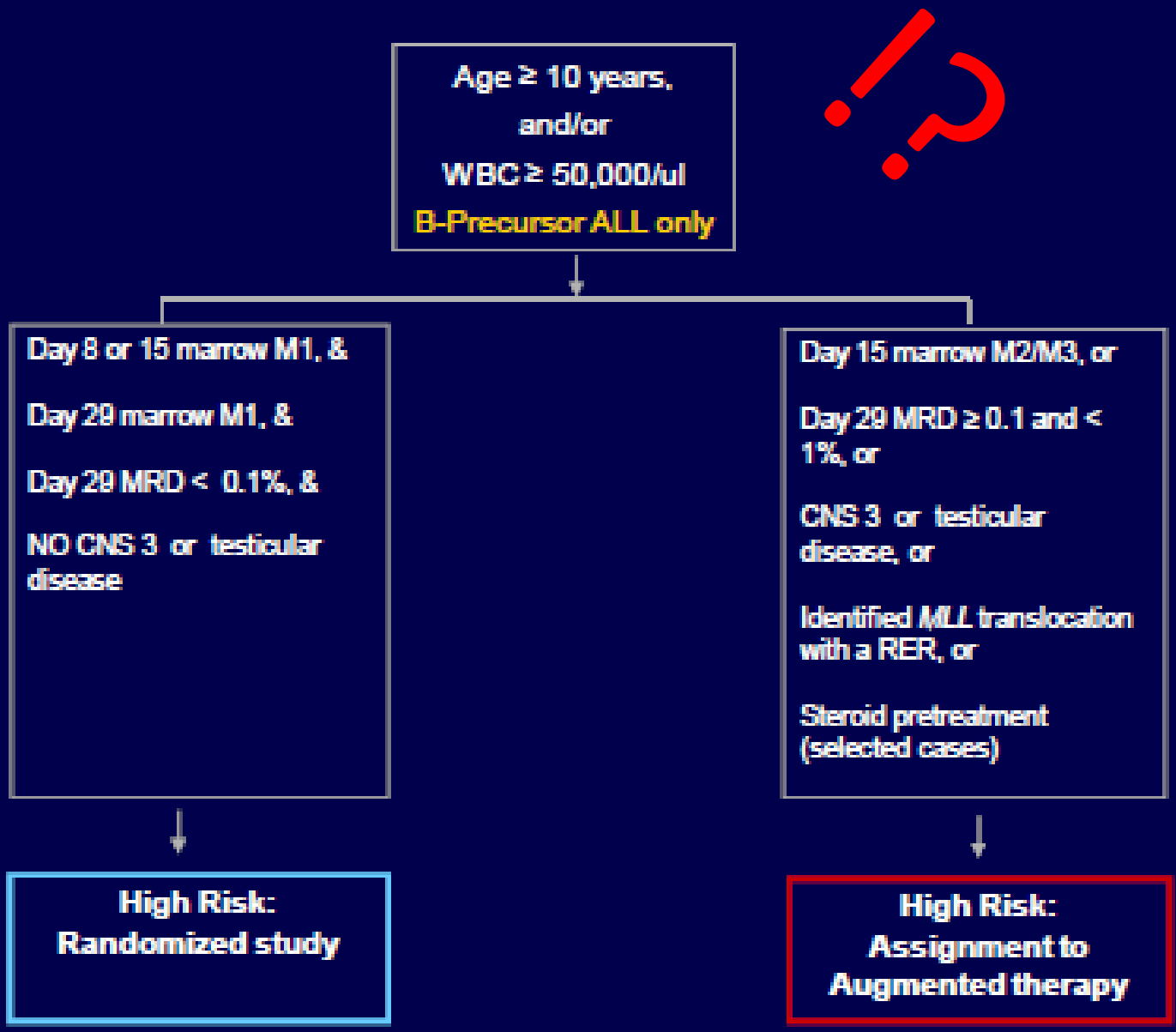
St. Jude Total Therapy Study XVI: Risk Classification Schema



End Induction Treatment Assignment- NCI Standard Risk (SR) ALL (AALL0331)



End Induction Treatment Assignment- NCI High Risk (HR) ALL (AALL0232)



Applications of MRD:

Optimize frontline therapy

Treatment deintensification

- The best way to apply MRD results for treatment deintensification has not yet been defined.
- 183/402 (45.5%) of patients with B-lineage ALL were MRD-negative on day 19, defined as having <0.01% leukemic cells in bone marrow.
  - ✓ early MRD negativity might be a good prognostic feature *only in the context of intensive therapy*
    - ✓ St Jude treatment protocols from 1967 to 1983 (much less intense than today's regimens): 36%- 53% cure
    - ✓ where all treatment stopped 1 year after diagnosis, the mean 5-year event-free survival approached 60%.
  - ✓ Toxicity of intensified treatments leads to less OS

Dario Campana.Semin Hematol. 2009 January ; 46(1): 100–106.

Acute Leukemia

Predominance of blast cells in bone marrow

Assignment of B, T, or Myeloid- Ontogony

B cell

Tdt+, PAS+/-, FAB L1,L2

Pro-B/early preB

CD34+/CD19+
t(4;11)+, t(9;22), hyper-
Diploid and others
(Table 19.1)

Common ALL(cALL)

CD 34+/-,CD19+/CD10+
FAB L1 (occasionally L2)
Hyperdiploid, t(12;21), t(9;22),6q-

Pre-B ALL

CD 34-/CD19+/CD20+/CD22+
FAB L1/L2
Cytogenetics frequently similar to
cALL but often t(1;19) or t(9;22)

B-ALL

CD10+/-CD19+,Tdt-
FAB L3
Burkitt translocations: t(8;14) and
alternatives t(2:8), t(8;20) between
Ig receptors and cmyc (Table 19.1)

T cell

PAS (block positivity)

Pro-T

CD3+/CD7+
Multiple TF /TCR
translocations
(Table 19.1)

Pre- T

CD2+/CD5+//CD8+
Multiple TF/TCR
(Table 19.1)

Common T

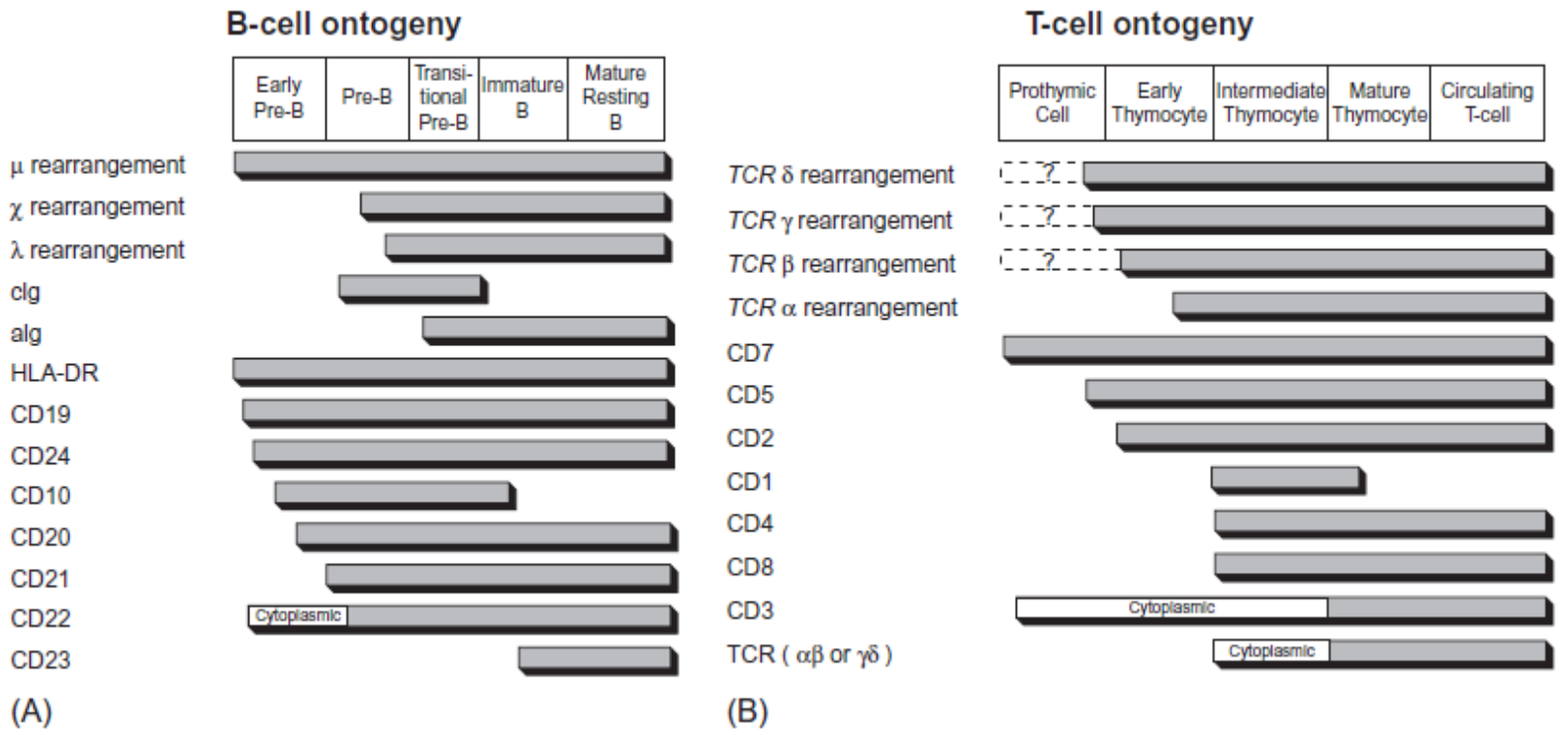
CD2+/CD5+/8+
Multiple TF/TCR

Late T-ALL

TCR α/β +, γ/δ+

Myeloid

granules,
Auer rods,
Sudan Black+
Esterase +/-
(See Chapter 20)


B-cell ontogeny
Early Pre-B
Pre-B
Transi-tional Pre-B
Immature B
Mature Resting B
μ rearrangement
χ rearrangement
λ rearrangement
clg
alg
HLA-DR
CD19
CD24
CD10
CD20
CD21
CD22
CD23
Cytoplasmic
(A)
T-cell ontogeny
Prothymic Cell
Early Thymocyte
Intermediate Thymocyte
Mature Thymocyte
Circulating T-cell
TCR δ rearrangement
TCR γ rearrangement
TCR β rearrangement
TCR α rearrangement
CD7
CD5
CD2
CD1
CD4
CD8
CD3
TCR (αβ or γδ)
?
Cytoplasmic
Cytoplasmic
(B)

MRD in the Treatment of Relapsed ALL

- Patients withHRrelapsed ALL typically are treated with allogeneic HSCT
- In contrast, SR relapsed ALL patients are treated with chemotherapy (with or without cranial irradiation).
- The decision regarding the HSCT use has been most challenging in the largest group of IR patients.:
  - Availability of a matched sibling donor
  - MRD at EORI

After a retrospective study indicated a significant impact of MRD on EFS [25], the BFM study group prospectively evaluated the prognostic impact of BM MRD (measured by PCR) at the end of reinduction (EORI) therapy (week 5) for patients with IR relapsed ALL.[19,25,32] The first part of this study, during which participants were blinded to MRD results for the determination of HSCT indication [32], revealed a major prognostic difference between the MRD-negative ($<10^{-3}$) and MRD-positive group ($\geq 10^{-3}$) with regard to 10-year EFS (76% vs. 18%) and cumulative incidence of relapse (CIR, 21% vs. 61%).[32] Based on these results, all patients with IR relapse and a high EORI MRD level ($\geq 10^{-3}$, n = 99) were assigned to HSCT from either a matched sibling or matched unrelated donor in the subsequent study (ALL-REZ BFM 2002). In contrast, those with low MRD levels continued treatment with chemotherapy and cranial irra-

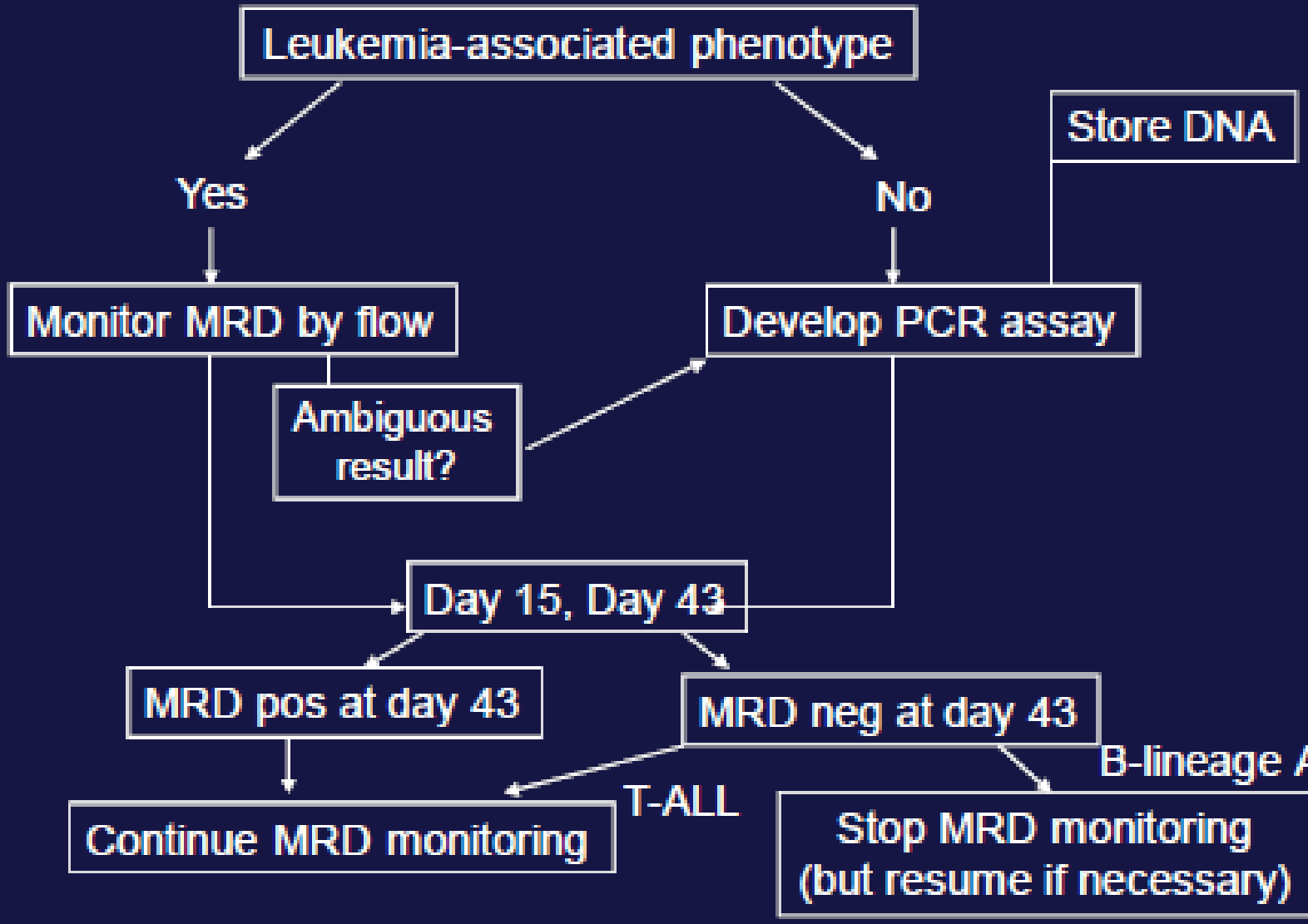
High MRD IR relapse ALL: Alogenic HSCT (sibling or unrelated)
Low MRD IR relapse ALL: Chemotherapy

In summary, (i) the use of MRD-based HSCT indication in patients with IR relapsed ALL improved EFS for patients with high MRD to the same level observed in patients with low MRD (without HSCT) and (ii) HSCT did not improve the survival of patients with IR relapse and low MRD even when a sibling donor was available, allowing de-escalation of therapy (no HSCT).

Applications of MRD
Postremission sequential MRD monitoring)

- To identify relapse before its detection by morphology or cytogenetics: re-intensify treatment,enough time to find donor for HSCT,etc.
  - Vigorous lympho-hematopoietic regeneration mimicking relapse: to confirm or rule out it
  - those patients who are in remission but who remain MRD-positive at the end of remission induction therapy:
    - Conversion of MRD-positive to MRD-negativity is associated with a favorable outcome
  - Conversion to MRD-positive or persistence or increase in levels of MRD carries a high hazard of relapse

MRD Plans for TXVI – Risk Assignment



MRD Prior to HSCT

Several studies demonstrated that high BM MRD levels (10^{-2}–10^{-3}) prior to HSCT were associated with a high probability of post-HSCT leukemic relapse (80%), whereas low (10^{-5}) and undetectable MRD was associated with a relapse probability of only 25–30% after HSCT.[51–57] A landmark study prospectively examined the prognostic significance of MRD

2005.[33] MRD was measured at a median of 13 days prior to HSCT by PCR, and clinicians were blinded to the results. Patients with MRD level $<10^{-4}$ prior to HSCT (n = 46) had an

MRD-negative vs. MRD-positive group). MRD prior to HSCT was the only independent prognostic factor in a multivariate analysis predicting AEs after HSCT (risk ratio 2.45).

Applications of MRD

Optimize timing of transplant & Modulate immuosuppression

- **before HSCT** : patients with MRD positivity who are candidates for transplant are associated with an increase risk of relapse may receive additional courses of chemotherapy in efforts to reduce the levels of MRD, possibly below detection threshold,
- **After transplant** : detection of MRD can serve as an indicator for decreasing immunosuppressive therapy and/or administering donor lymphocyte infusions.

Clinically informative MRD levels

- **The 0.01% threshold is commonly used to define MRD positivity, simply because this represents the typical limit of detection for routine flow cytometric and molecular assays.**
- **prognostic indicator for relapse rate:**
- Children's Oncology Group (COG) : **0.01% or higher** on day 29 predicted a poorer outcome *Blood. 2008i*
- Cave et al. : cut-off **level of 0.1%** at the end of remission induction and thereafter *Childhood Leukemia Cooperative Group. N Engl J Med 1998;339:591–598.*
- I-BFM Study Group : **0.1% or higher** on days 33 and 78 *Blood 2002;99:1952–1958*
- those of the Austrian BFM group: also the **cut-off level of 0.1%** on day 33
- the Dana-Farber Cancer Institute ALL Consortium: an MRD **threshold of 0.1%** best predicted relapse hazard *Blood 2007;110:1607–1611*

Clinical significance of low levels of MRD at the end of remission induction therapy in childhood ALL

(Blood. 2010;115(23):4657-4663)

- **Patients with low level of MRD (0.001%-< 0.01%) had a 12.7% (5.1%; SE) cumulative risk of relapse at 5 years, compared with 5.0% (1.5%) for those with lower or undetectable MRD (*P* < .047).**
- **Low levels of MRD (0.001%-< 0.01%) at the end of remission induction therapy have prognostic significance in childhood ALL, suggesting that patients with this finding should be monitored closely for adverse events**

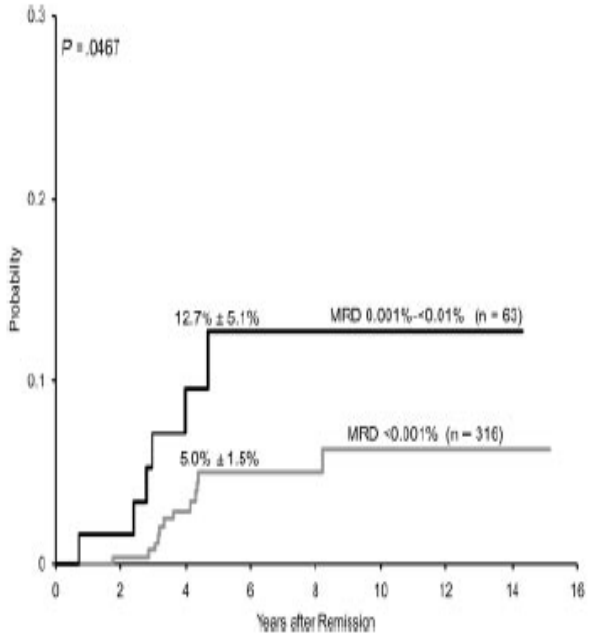


Figure 2. Cumulative incidence of relapse (mean ± SE) among 379 children with B-lineage ALL whose MRD levels were less than 0.01% on day 46 (end of remission induction therapy). Patients with MRD 0.001% to less than 0.01% had a significantly higher incidence of relapse than those with lower levels or undetectable MRD by PCR.

What is the best method to study MRD?

- Both flow cytometry and PCR amplification of antigen receptor genes;
  - yield similar results when MRD is at levels of 0.01% or above,
  - produce MRD estimates within 24 hours of sample collection.
  - In some experience, the overall cost of the two methods is similar but others have estimated PCR to be more expensive.
- Flow cytometry
  - is more likely to be readily available and,
  - studies at early time points during therapy, like day 15, has an advantage over PCR, as the development of a patient-tailored PCR assay typically requires more than two weeks.
- PCR
  - might be preferable for studies post-HSCT or at the end of therapy because of its high sensitivity.
- Eventually, the most important factor:
  - expert laboratory
  - available to a cancer center
  - cooperative.

Can MRD be determined in peripheral blood?

- In patients with B-lineage ALL, MRD is usually present at higher levels in bone marrow than in peripheral blood.

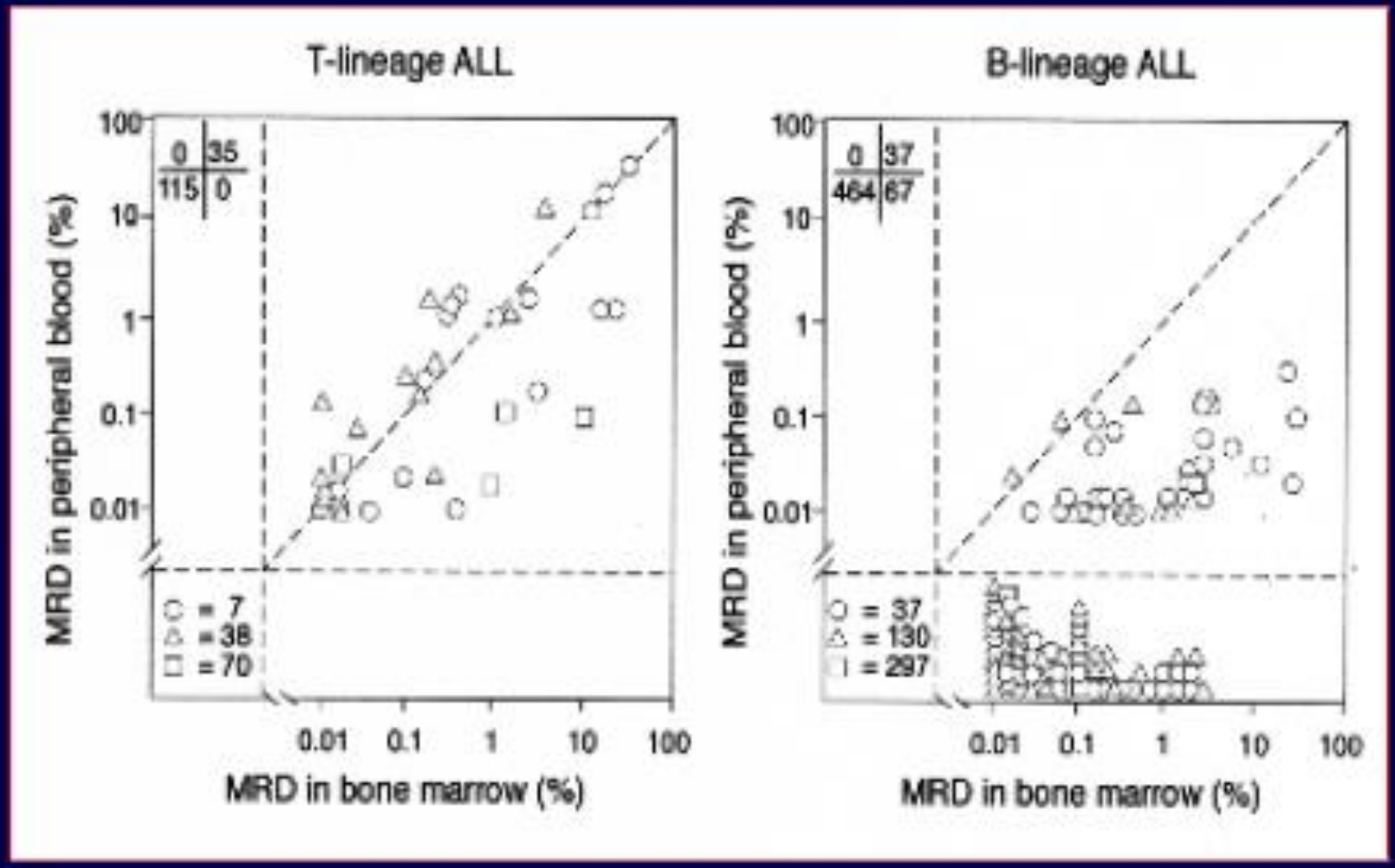
- In T-ALL, MRD levels in peripheral blood are similar to those in bone marrow: sequential MRD testing can be performed in blood

Brisco.et.al,. Br J Haematol 1997;99:314–319

Coustan-Smith E, et.al,Blood 2002;100:2399–2402

van der Velden Vet.al, Leukemia 2002;16:1432– 1436.

MRD in Peripheral Blood vs. Bone Marrow



Coustan-Smith et al, Blood 2002;100:2399-2409

MRD & childhood AML

- Currently, the Children's Oncology Group (COG) is using 15 % to define to define primary induction failure cutoff in their clinical trials
- *Molecular MRD:*
  - leukemia-specific fusion genes are found in only about 30% of patients
    - t(15;17) fusion product PML-RAR (The only AML subtype for which PCR inconclusively utilized for MRD detection is APL)
    - abnormal t(8;21) and inv(16) real-time quantitative PCR (RQ-PCR)
    - Nonspecific genes like Wilms' tumor 1 *(WT1)*
- *Immunophenotypic MRD.*
  - at least 80% of patients have an aberrant phenotype: as current international clinical trial needs
  - can detect one cell with a leukemic immunophenotype in 1,000 to 10,000 normal cells.

The absence of broadly applicable molecular markers in blasts of pediatric AML has favored the use of MRD measurement by FCM. Emerging evidence suggests that MRD is strongly prognostic in AML when measured early in therapy. In

- In 1999, Campana and Coustan Smith estimated that the top four combinations for acute leukemia MRD detection in flow were
- (i) CD19/CD34/CD10;
- (ii) CD13/CD33/CD34,
- iii)CD13/CD33/CD117
- iv) CD13/CD34/CD117

Table 2. Combinations identifying LAIP with CD34 lack of expression.[122]

$CD11b^{+}/CD117^{+}/CD34^{-}$	n=9
$CD34^{-}/CD135^{+}/CD117^{+}$	n=5
$CD34^{-}/CD15^{++}/CD33^{+}$	n=1
$CD38^{+}/CD34^{-}/CD90^{+}$	n=1
$CD65^{+}/CD87^{++}/CD34^{-}$	n=1
$CD7^{+}/CD33^{+}/CD34^{-}$	n=1
$DR^{-}/CD33^{+}/CD34^{-}$	n=7
$CD34^{-}/CD56^{+}/CD33^{+}$	n=3
$CD34^{-}/7.1^{+}/CD33^{+}$	n=1

M.C. Béné and J.S. Kaeda haematologica 2009; 94(8)

- Recent multivariate analysis by COG showed:
  - up to one third of patients thought to have residual leukemic blasts by morphologic assessment, are MRD Neg by FCM
  - end of first induction MRD was the only factor that remained prognostic when compared with cytogenetic and molecular risk groups
  - MRD is a potent tool to stratify treatment for pediatric AML.

Loken MR, et al.. Blood 2012;120:1581–1588.

- TheMRD–AML–BFM study group
  - while the presence of MRD correlated with poorer outcomes, it did not contribute to overall risk stratification.[62]

Langebrake C, et al.. J Clin Oncol 2006;24:3686–3692.

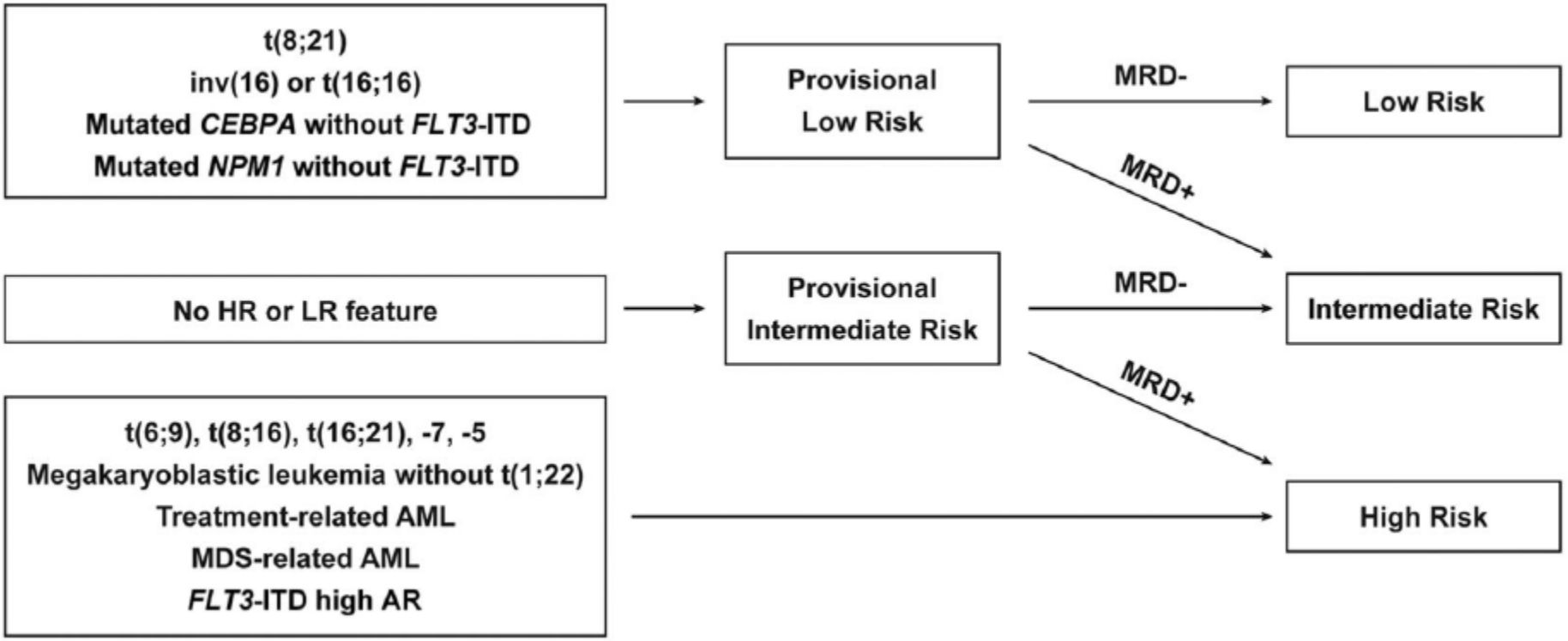


TABLE III. POGO MRD Working Group's Recommended Indications for MRD Measurement for Pediatric Leukemias

Type of pediatric leukemia	Recommended indication for MRD measurement
Pediatric ALL	-To optimize the accuracy and timeliness of reporting, *a diagnostic (baseline MRD panel) specimen* should be conducted for all patients. -All patients, regardless of immunophenotype, should receive assessment of MRD at *day 8* after start of induction therapy in peripheral blood and *end of induction* in bone marrow. -Patients with positive MRD at the end of induction should have MRD repeated at the *end of the consolidation phase.* -For *patients with intermediate risk relapse of ALL*, MRD should be tested *after re-induction* to facilitate risk stratification for HSCT. -For *relapsed patients proceeding to HSCT*, MRD should be repeated *prior to transplant*.
Pediatric AML	-To optimize the accuracy and timeliness of reporting, a *diagnostic (baseline MRD panel) specimen* should be conducted for all patients. -MRD should be assessed at the *end of first course of induction therapy* on all newly diagnosed patients to aid in risk stratification.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease.

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