Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

23–24 July 2020
Welcome and Meeting Overview

Elias Jabbour and Eduardo Rego
Meet the Faculty

**Elias Jabbour, MD**  
Professor of Medicine  
Department of Leukemia  
University of Texas  
MD Anderson Cancer Center  
Houston, TX, USA

**Patrick Brown, MD**  
Associate Professor of Oncology and Pediatrics, Director Pediatric Leukemia Program  
Johns Hopkins University  
Baltimore, MD, USA

**Aaron Logan, MD, PhD**  
Associate Professor of Clinical Medicine, Director Hematologic Malignancies Tissue Bank  
University of California, San Francisco  
San Francisco, CA, USA

**Eduardo Rego, MD, PhD**  
Professor in the Faculty of Medicine  
Medical School of Ribeirão Preto  
São Paulo, Brazil

**Roberta Demichelis, MD**  
Assistant Professor in the Department of Hematology/Oncology  
INCMNSZ*  
Mexico City, Mexico

*INCMNSZ, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.*
Objectives of the Program

Understand current treatment patterns for ALL including incorporation of new technologies

Uncover when genomic testing is being done for ALL, and how these tests are interpreted and utilized

Understand the role of stem cell transplantation in ALL as a consolidation in first remission

Comprehensively discuss the role of MRD in managing and monitoring ALL

Gain insights into antibodies and bispecifics in ALL: what are they? When and how should they be used? Where is the science going?

Discuss the evolving role of ADC therapies in ALL

Review promising novel and emerging therapies in ALL
## Virtual Plenary Sessions (Day 1)

<table>
<thead>
<tr>
<th>TIME UTC-3</th>
<th>TITLE</th>
<th>SPEAKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.00 – 17.10</td>
<td>Welcome and meeting overview; introduction to the voting system</td>
<td>Elias Jabbour, Eduardo Rego</td>
</tr>
<tr>
<td>17.10 – 17.25</td>
<td>Review of prognostic value of MRD in ALL</td>
<td>Elias Jabbour</td>
</tr>
<tr>
<td>17.25 – 17.40</td>
<td>How and when to check for MRD in ALL</td>
<td>Eduardo Rego</td>
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<tr>
<td>17.40 – 17.55</td>
<td>MRD assessment and management in CR1 vs CR2 and beyond</td>
<td>Aaron Logan</td>
</tr>
<tr>
<td>17.55 – 18.10</td>
<td>Genetic variants in ALL – Ph+ and Ph-like</td>
<td>Elias Jabbour</td>
</tr>
<tr>
<td>18.10 – 18.25</td>
<td>AYA ALL patients – what is the current treatment approach for this diverse patient population?</td>
<td>Patrick Brown</td>
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<tr>
<td>18.25 – 18.45</td>
<td>Break</td>
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<tr>
<td>18.45 – 19.00</td>
<td>Bispecific T-cell engagers as post-reinduction therapy improves survival in pediatric and AYA B-ALL</td>
<td>Patrick Brown</td>
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<tr>
<td></td>
<td>- Experience of HSCT in the region (ARS-guided assessment)</td>
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<td></td>
<td>- Pros and cons of HSCT, COVID-19 impact and measures</td>
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<td></td>
<td>- Discussion and voting</td>
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<td>- CAR T</td>
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<td></td>
<td>- Monoclonal antibodies and bispecifics</td>
<td></td>
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<td></td>
<td>- Discussion and voting</td>
<td></td>
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<td></td>
<td>- Presentation</td>
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<td></td>
<td>- Panel discussion</td>
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<tr>
<td>20.55 – 21.00</td>
<td>Session close</td>
<td>Elias Jabbour, Eduardo Rego</td>
</tr>
</tbody>
</table>
# Virtual Breakout: Pediatric ALL Patients (Day 2)
Chair: Patrick Brown

<table>
<thead>
<tr>
<th>TIME UTC-3</th>
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<th>SPEAKER</th>
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</table>
| 17.00 – 17.15 | Session opening  
• Educational ARS questions for the audience | Patrick Brown                  |
| 17.15 – 17.35 | First-line treatment of pediatric ALL  
• Presentation  
• Q&A | Lia Gore                                      |
| 17.35 – 17.55 | Current treatment options for relapsed ALL in children including HSCT and COVID-19 considerations  
• Presentation  
• Q&A | Franco Locatelli                     |
| 17.55 – 18.15 | Bispecific T-cell engagers for pediatric ALL  
• Presentation  
• Q&A | Patrick Brown                  |
| 18.15 – 18.45 | Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in pediatric patients  
Panelists: María Sara Felice (Arg), Oscar González Ramella (Mex), Adriana Seber (Bra), Carlos Andres Portilla (Col) | Maria Sara Felice  
Carlos Andres Portilla Discussion |
| 18.45 – 19.00 | Session close  
• Educational ARS questions for the audience | Patrick Brown                  |
## Virtual Breakout: Adult ALL Patients (Day 2)

Chair: Elias Jabbour

<table>
<thead>
<tr>
<th>TIME UTC-3</th>
<th>TITLE</th>
<th>SPEAKER</th>
</tr>
</thead>
</table>
| 17.00 – 17.15 | Session opening  
• Educational ARS questions for the audience | Elias Jabbour, Eduardo Rego |
| 17.15 – 17.35 | Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens  
• Presentation  
• Q&A | Elias Jabbour |
| 17.35 – 17.55 | Current treatment options for relapsed ALL in adult and elderly patients  
• Presentation  
• Q&A | Aaron Logan |
| 17.55 – 18.45 | Case-based panel discussion  
Management of long- and short-term toxicities and treatment selection in adult and elderly patients  
Panelists: Elias Jabbour, Eduardo Rego, Aaron Logan, Roberta Demichelis | Roberta Demichelis  
Eduardo Rego  
Discussion |
| 18.45 – 19.00 | Session close  
• Educational ARS questions for the audience | Elias Jabbour |
Introduction to the Voting System

Elias Jabbour
Question 1

Where are you from?

a) Argentina
b) Brazil
c) Colombia
d) Mexico
e) Peru
f) Other
Question 2

How many patients with ALL are you currently following?

a) 0  
b) 1–5  
c) 6–15  
d) 16–20  
e) ≥21
How do you assess for minimal residual disease (MRD)?

a) We do not check for MRD
b) Multicolor flow
c) Molecular PCR
d) Next-generation sequencing platform
Review of Prognostic Value of MRD in ALL

Elias Jabbour
Review of Prognostic Value of MRD in ALL

Elias Jabbour, MD
Professor of Medicine
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX

Summer 2020
Conflict of Interest Disclosure

• Research grants
  — Pfizer, Takeda, Amgen, AbbVie, Novartis

• Consultancy and advisory roles
  — Pfizer, Takeda, Amgen, AbbVie, BMS
Survival of 972 Adults With Ph− ALL

- 972 pts Rx 1980–2016; median F/U 10.4 years

Minimal (measurable) Residual Disease

- Concept first described 40 years ago
- Main methods are flow cytometric detection of leukemic immunophenotype (LIP), detection of ALL fusion transcripts, and detection of antigen receptor rearrangements commonly to $10^{-4}$ (1:10,000 cells)
- Timing of testing varies widely
- Important interaction with leukemic subtype and genomic alterations
- Role of more-sensitive tests, and with newer treatment approaches less clear
When do you assess for MRD?

a) Monthly
b) At CR
c) At 3 months from induction
d) At CR and 3 months from induction, and every 3 months thereafter
e) I never check for MRD
How to Define the Risk?

➔ Can be defined **BEFORE** treatment

➔ And/or redefined **DURING** treatment

• MRD, which can possibly better define transplant candidates

• Steroid pretreatment
## Treatment of ALL Before the MRD Era: High CR Rates but Relapse Is Common

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median Age, Year (range)</th>
<th>Ph+, %</th>
<th>T Cell, %</th>
<th>CR, %</th>
<th>DFS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC/ECOG E2993</td>
<td>1826</td>
<td>31 (15-65)</td>
<td>19</td>
<td>20</td>
<td>91</td>
<td>38 at ≥3 yr</td>
</tr>
<tr>
<td>CALGB 19802</td>
<td>163</td>
<td>41 (16-82)</td>
<td>18</td>
<td>–</td>
<td>78</td>
<td>35 at 3 yr</td>
</tr>
<tr>
<td>GIMEMA ALL 0288</td>
<td>778</td>
<td>27.5 (12.0-60.0)</td>
<td>22</td>
<td>22</td>
<td>82</td>
<td>29 at 9 yr</td>
</tr>
<tr>
<td>GMALL 05/93</td>
<td>1163</td>
<td>35 (15-65)</td>
<td>24</td>
<td>24</td>
<td>83</td>
<td>35-40 at 5 yr</td>
</tr>
<tr>
<td>GOELAMS 02</td>
<td>198</td>
<td>33 (15-59)</td>
<td>22</td>
<td>21</td>
<td>86</td>
<td>41 at 6 yr</td>
</tr>
<tr>
<td>HyperCVAD</td>
<td>288</td>
<td>40 (15-92)</td>
<td>17</td>
<td>13</td>
<td>92</td>
<td>38 at 5 yr</td>
</tr>
<tr>
<td>JALSG-ALL93</td>
<td>263</td>
<td>31 (15-59)</td>
<td>22</td>
<td>21</td>
<td>78</td>
<td>30 at 6 yr</td>
</tr>
<tr>
<td>LALA-94</td>
<td>922</td>
<td>33 (15-55)</td>
<td>23</td>
<td>26</td>
<td>84</td>
<td>36 at 5 yr</td>
</tr>
</tbody>
</table>

MRD in ALL

- Meta-analysis of 39 studies (pediatric and adult), including 13,637 patients with all subtypes
- Prognostic impact of MRD clearance consistent across therapies, MRD method, timing, level of cutoff, and subtypes
Molecular Relapse (MRD– → MRD+) Is Predictive of Cytologic Relapse in Patients in CR1

Probability of continuous CR and survival in n = 24 adult ALL patients in first CR but with molecular relapse

Conversion from MRD– to MRD+ preceded hematologic relapse by a median 2.6 months and predicted poor survival

*Patients with SCT in CR1 excluded.

## MRD Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Flow cytometry for \textit{difference from normal} | $\sim 10^{-4}$ | • Fast  
• Relatively inexpensive  
• Potential to detect phenotypic shifts | • Confounders: increased benign B-cell precursors during marrow recovery; potential phenotypic shifts  
• Requires significant technical expertise  
• Limited standardization (though attempts in progress) |
| RQ-PCR for IGH/TCR gene rearrangements | $\sim 10^{-4}$ to $10^{-5}$ | • Sensitive  
• Well standardized with consensus guidelines | • Time consuming and labor intensive  
• Requires significant technical expertise  
• May not detect small subclones at diagnosis  
• Expensive |
| RQ-PCR for recurrent gene fusions     | $\sim 10^{-4}$ to $10^{-5}$ | • Sensitive  
• Uses standard primers utilized for diagnostic purposes | • Applicable to $<50\%$ of ALL cases  
• Limited standardization |
| Next-generation sequencing            | $\sim 10^{-6}$ | • Very sensitive  
• Fast (uses consensus primers)  
• Potential to track small subclones and clonal evolution | • Requires complex bioinformatics  
• Minimal clinical validation  
• Expensive |

NGS Identified Patients With Improved EFS

EFS was significantly worse in the NGS MRD+/flow cytometry MRD– group than patients who were MRD– by both methods (P = .036).

Six patients were identified as NGS MRD– and MFC MRD+.

NGS, next-generation sequencing; MFC, multiparameter flow cytometry.
Comparison: NGS With RQ-PCR

- Prognostic value of d+33 MRD (pediatric ALL, BFM-based treatment)

**Day 33 RQ-PCR**
- MRD−, n = 37, 5-yr RFS: 84% ± 6%
- MRD+, n = 36, 5-yr RFS: 63% ± 8%

**Day 33 NGS**
- MRD−, n = 41, 5-yr RFS: 90% ± 5%
- MRD+, n = 32, 5-yr RFS: 53% ± 9%

Next-Generation Sequencing vs FMC MRD in ALL

- FDA accepted MRD negativity as Rx endpoint in ALL, regardless of methodology
- Blinatumomab FDA approved (April 2018) for Rx of MRD+ ALL in CR1-CR2 on the basis of *JAMA Oncology* meta-analysis (Don Berry) and German single-arm trial results
- NGS detects MRD at $10^{-6}$; 4- to 8-color FCM detects MRD at $10^{-4}$
- In adult ALL, MRD >0.1% at CR and >0.05%–0.01% 2–3 mo in CR predictive of worse survival on chemoRx
- NGS may predict better – ongoing studies at MDACC of outcome at MRD <$10^{-6}$ vs $10^{-6}$–$10^{-4}$ vs >$10^{-4}$
Postremission Rx of ALL According to FCM MRD

- 307 pts age 15–60 yr with pre-B ALL
- ORR 91%; 83% after induction 1
- If MRD >0.1% at end of induction (week 5), >0.01% at midconsolidation (week 17): chemoRx then alloSCT, otherwise chemoRx alone
- ORR 277/307 = 81%; 94 (31%) assigned to alloSCT and 190 (62%) chemoRx

<table>
<thead>
<tr>
<th>MRD Condition</th>
<th>5-yr CIR, %</th>
<th>5-yr OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>AlloSCT</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>ChemoRx</td>
<td>48</td>
<td>55</td>
</tr>
<tr>
<td>MRD &lt;0.1 at CR and &lt;0.01 at consolidation</td>
<td>42</td>
<td>66</td>
</tr>
<tr>
<td>MRD &lt;0.01 at CR</td>
<td>17</td>
<td>90</td>
</tr>
</tbody>
</table>

Blinatumomab in MRD+ BCP-ALL: MT103-202 Trial

Blinatumomab for MRD+ ALL in CR1/CR2

- 113 pts Rx. Post-blina MRD− 88/113 = 78%
- 110 evaluated (blasts <5%, MRD+); 74 received alloSCT. Median FU 53 mo
- Median OS 36.5 mo; 4-yr OS 45%; 4-yr OS if MRD− 52%
- Continuous CR 30/74 post-alloSCT (40%); 12/36 without SCT (33%)

Outcomes by HSCT Use in CCR: Simon-Makuch Analyses – Landmark of 2 Months

Landmark of 2 months for overall survival and 40 days for other analyses was used to ensure non-zero number of patients in the HSCT group.

CCR, continuous complete remission; HSCT, hematopoietic stem cell transplantation.

Goekbuget N, et al. Slides presented at: 60th ASH Annual Meeting & Exposition of the American Society of Hematology; December 1-4, 2018; San Diego, CA.
## Dynamics of MRD: Outcome

<table>
<thead>
<tr>
<th>MRD Status</th>
<th>Patients (%)</th>
<th>5-yr EFS, %</th>
<th>5-yr OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>@CR</td>
<td>@ First post-CR</td>
<td>n = 214</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>147 (69)</td>
<td>56</td>
</tr>
<tr>
<td>≤0.1%</td>
<td>Negative</td>
<td>14 (7)</td>
<td>31</td>
</tr>
<tr>
<td>&gt;0.1%</td>
<td>Negative</td>
<td>33 (15)</td>
<td>32</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>20 (9)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Ph-Like ALL: Survival and EFS

## Ph-Like ALL: Higher MRD+ Rate

<table>
<thead>
<tr>
<th>B-ALL Categories (N = 155)</th>
<th>Ph-like</th>
<th>Ph+</th>
<th>B – other</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>56</td>
<td>46</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>CR/CRp</td>
<td>50 (89)</td>
<td>43 (93)</td>
<td>50 (94)</td>
<td>.57</td>
</tr>
<tr>
<td>MRD at CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>23 (70)</td>
<td>15 (44)</td>
<td>4 (13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Negative</td>
<td>10 (30)</td>
<td>19 (56)</td>
<td>27 (87)</td>
<td></td>
</tr>
</tbody>
</table>
TKI for Ph+ ALL

Imatinib: 5-yr OS = 43%  
Dasatinib: 5-yr OS = 46%  
Ponatinib: 5-yr OS = 71%

CMR in Ph+ ALL: OS for CMR vs Others

At CR

At 3 months

- MVA for OS
  CMR at 3 months (HR 0.42 [95% CI: 0.21-0.82]; \(P = .01\))

Indications for HSCT: Ph+ ALL

MRD assessment (within 3 months)

**MRD−**
- Chemotherapy/ blinatumomab + ponatinib

**MRD+**
- **<0.1%**
  - Blinatumomab/Ino + ponatinib
- **>0.1%**
  - Blinatumomab/Ino + ponatinib × 2–4 cycles
  - HSCT + maintenance TKI

Indications for HSCT: Ph– B-ALL and T-ALL

MRD assessment (within 3 months)

MRD–
- Poor-risk cytogenetics/genomics*
  - HSCT

MRD+
- Others
  - Continue chemotherapy
- B cell
  - Blinatumomab × 2–4 cycles
  - HSCT
- T cell
  - HSCT

*Ph-like, 11q23 rearrangement, early T-cell precursor, low hypodiploidy, complex cytogenetics.

SO . . . MRD in ALL

- Despite achievement of CR with induction and consolidation, up to 60% of patients with ALL may still be MRD+
- In adult ALL, MRD+ in CR is predictive of worse survival on chemoRx
- FDA accepted MRD negativity as Rx endpoint in ALL, regardless of methodology
- Blinatumomab FDA approved (April 2018) for Rx of MRD+ ALL in CR1–CR2
- No clear benefit for alloSCT after conversion to MRD– with blina, particularly in CR1
- Maintenance blina post-alloSCT?
- Role of Ino? CAR T cells in MRD+ ALL?
How and When to Check for MRD in ALL

Eduardo Rego
How and when to check for MRD in ALL

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UNIVERSITY OF SÃO PAULO
ONCOLOGIA D’OR
BRAZIL
MRD and response duration

- 74%–91% of patients with ALL will achieve CR, but one-third will relapse because of submicroscopic levels of leukemic cells (measurable residual disease [MRD])

Of 272 patients in CR1, baseline MRD was:
- $\geq 10^{-1}$ in 15 (6%)
- $10^{-2}$ to $<10^{-1}$ in 71 (26%)
- $10^{-3}$ to $<10^{-2}$ in 109 (40%)
- $10^{-4}$ to $<10^{-3}$ in 77 (28%)

How?
# Ph-negative ALL

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Ph</th>
<th>MRD method</th>
<th>MRD level</th>
<th>Test location</th>
<th>Phenotype</th>
<th>Disease stage</th>
<th>Pre-MRD tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gökbuget</td>
<td>2015</td>
<td>116 (112)</td>
<td>Neg</td>
<td>PCR</td>
<td>$10^{-4}$</td>
<td>Central</td>
<td>B-cell</td>
<td>CR1</td>
<td>Targeted</td>
</tr>
<tr>
<td>Jabbour</td>
<td>2017</td>
<td>78 (78)</td>
<td>NA</td>
<td>Flow (6color)</td>
<td>$10^{-4}$</td>
<td>Local</td>
<td>B-cell</td>
<td>CR2 or later</td>
<td>Targeted</td>
</tr>
<tr>
<td>Ravandi</td>
<td>2016</td>
<td>340 (260)</td>
<td>Mix</td>
<td>Flow (6color)</td>
<td>$10^{-4}$</td>
<td>Local</td>
<td>B-cell</td>
<td>CR1</td>
<td>Targeted</td>
</tr>
<tr>
<td>Bassan</td>
<td>2014</td>
<td>159 (106)</td>
<td>Neg</td>
<td>PCR</td>
<td>$10^{-4}$</td>
<td>NA</td>
<td>Mix (79% B-cell)</td>
<td>CR1</td>
<td>Chemo</td>
</tr>
<tr>
<td>Beldjord</td>
<td>2014</td>
<td>860 (423)</td>
<td>Neg</td>
<td>PCR</td>
<td>$10^{-4}$</td>
<td>Central</td>
<td>B-cell</td>
<td>CR1</td>
<td>Chemo</td>
</tr>
<tr>
<td>Gökbuget</td>
<td>2012</td>
<td>1648 (580)</td>
<td>Neg</td>
<td>PCR</td>
<td>$10^{-4}$</td>
<td>Central</td>
<td>Mix (66% B-cell)</td>
<td>CR1</td>
<td>Chemo</td>
</tr>
<tr>
<td>Holowiecki</td>
<td>2008</td>
<td>131 (116)</td>
<td>Neg</td>
<td>Flow (3color)</td>
<td>$10^{-3}$</td>
<td>Central</td>
<td>Mix (75% B-cell)</td>
<td>CR1</td>
<td>Chemo</td>
</tr>
<tr>
<td>Patel</td>
<td>2010</td>
<td>161 (161)</td>
<td>Neg</td>
<td>PCR</td>
<td>$10^{-4}$</td>
<td>NA</td>
<td>B-cell</td>
<td>CR1</td>
<td>Chemo</td>
</tr>
<tr>
<td>Bassan</td>
<td>2014</td>
<td>304 (141, [98 included in the analysis])</td>
<td>Neg</td>
<td>PCR</td>
<td>$10^{-4}$</td>
<td>NA</td>
<td>Mix (76% B-cell)</td>
<td>CR1</td>
<td>Chemo</td>
</tr>
<tr>
<td>Gökbuget</td>
<td>2014</td>
<td>189 (73)</td>
<td>Neg</td>
<td>PCR</td>
<td>$10^{-4}$</td>
<td>Central</td>
<td>B-cell</td>
<td>CR2 or later</td>
<td>Targeted</td>
</tr>
<tr>
<td>Giebel</td>
<td>2010</td>
<td>123 (123)</td>
<td>Neg</td>
<td>Mix</td>
<td>$10^{-3}$</td>
<td>Local</td>
<td>B-cell</td>
<td>CR1</td>
<td>Chemo</td>
</tr>
<tr>
<td>Weng</td>
<td>2013</td>
<td>125 (106)</td>
<td>Mix</td>
<td>Flow (6color)</td>
<td>$10^{-4}$</td>
<td>Local</td>
<td>B-cell</td>
<td>CR1</td>
<td>Chemo</td>
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</tbody>
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### MFC – Ph-negative/B and T-ALL

<table>
<thead>
<tr>
<th>Author</th>
<th>MRD+ definition and sensitivity</th>
<th>Ph status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holowiecki et al. 2008</td>
<td>MRD+ defined as expression of ≥2 aberrant phenotypes on &gt;50% leukemic blasts; &gt;0.1% used as cut-off point</td>
<td>Ph−</td>
</tr>
<tr>
<td>Ravandi et al. 2016</td>
<td>MFC (4-color); aberrant expression of ≥2 antigens required for assignment of MRD+; sensitivity 0.01%</td>
<td>Mixed</td>
</tr>
<tr>
<td>Weng et al. 2013</td>
<td>Flow cytometry (8-color) with validation by qRT PCR for BCR-ABL fusion gene MRD−: &lt;10(^{-4})</td>
<td>Mixed</td>
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</tbody>
</table>

Antibody combinations suitable for diagnosis and detection of minimal residual disease in acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Tube</th>
<th>FITC</th>
<th>PE</th>
<th>PerCP-Cy5.5</th>
<th>PE-Cy7</th>
<th>APC</th>
<th>APC-AF750 or BV421</th>
<th>PB, V450, V500</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Kappa</td>
<td>Lambda</td>
<td>CD20</td>
<td>CD19</td>
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<td>CD38</td>
<td>CD5</td>
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<tr>
<td>2</td>
<td>CD20</td>
<td>CD22</td>
<td>CD34</td>
<td>CD19</td>
<td>CD13 + CD33</td>
<td>CD38</td>
<td>CD5</td>
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<td>3</td>
<td>CD20</td>
<td>CD49f</td>
<td>CD34</td>
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<td>CD58</td>
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<td>CD24</td>
<td>CD304</td>
<td>CD34</td>
<td>CD19</td>
<td>CD86</td>
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<td>CD7</td>
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<td>6</td>
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<td>CD1a</td>
<td>CD3</td>
<td>CD2</td>
<td>CD5</td>
<td>CD8</td>
<td>CD4</td>
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<tr>
<td>7</td>
<td>cyMPO</td>
<td>cyCD3</td>
<td>CD34 -</td>
<td>CD7</td>
<td>-</td>
<td>-</td>
<td>HLA-DR</td>
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<tr>
<td>8</td>
<td>cyMPO</td>
<td>cyCD22</td>
<td>cyCD79a</td>
<td>CD19</td>
<td>CD34</td>
<td>-</td>
<td>HLA-DR</td>
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<tr>
<td>9</td>
<td>nTdt</td>
<td>cyCD3</td>
<td>cyCD79a</td>
<td>CD19</td>
<td>CD34</td>
<td>-</td>
<td>HLA-DR</td>
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</table>

Example of MRD+ ALL Ph-negative

# qRT PCR – Ph-negative

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Treatment</th>
<th>HSCT</th>
<th>Method/Definition of MRDneg</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRAALL 2003 and 2005 trials, Dhèdin et al. (2015)</td>
<td>Phase 2 (GRAALL 2003) and Phase 3 (GRAALL 2005)</td>
<td>Chemotherapy</td>
<td>Allogeneic (planned after 3 or 6 blocks of consolidation); some patients received UBCT</td>
<td>qRT PCR for ≥2 Ig/T-cell receptor gene rearrangements; bone marrow samples assessed in a central reference laboratory; sensitivity ≥10&lt;sup&gt;−4&lt;/sup&gt;</td>
</tr>
<tr>
<td>GMALL 06/99 and 07/03 trials, Gökbuget et al. (2012)</td>
<td>Retrospective, German centers</td>
<td>Chemotherapy</td>
<td>Allogeneic (high-risk patients)</td>
<td>qRT PCR for leukemia-specific Ig/T-cell receptor gene rearrangements; assessed in a central laboratory Molecular CR: MRD− with assay sensitivity of ≥10&lt;sup&gt;−4&lt;/sup&gt;</td>
</tr>
<tr>
<td>NILG 09-2000 trial, Mannelli et al. (2012)</td>
<td>Prospective; Italy</td>
<td>Chemotherapy</td>
<td>Allogeneic (high-risk patients)</td>
<td>qRT PCR for BCR-ABL or Ig MRD−: &lt;10&lt;sup&gt;−4&lt;/sup&gt; at Week 16 and negative at Week 22</td>
</tr>
<tr>
<td>UKALL XII trial, Mortuza et al. (2002)</td>
<td>Prospective; UK</td>
<td>Chemotherapy</td>
<td>Allogeneic (for patients with available donor) or autologous PCR</td>
<td>α-32P dCTP PCR and ASO PCR MRD+: 1–5 leukemic cells in 10&lt;sup&gt;2&lt;/sup&gt;–10&lt;sup&gt;3&lt;/sup&gt; normal cells</td>
</tr>
<tr>
<td>UKALL XII/ECOG2993 trial, Patel et al. (2010)</td>
<td>Prospective; multicenter; UK</td>
<td>Chemotherapy</td>
<td>Allogeneic or autologous</td>
<td>qRT PCR for rearrangements in Ig/T-cell receptor genes among others, ASO PCR MRD−: qRT PCR &lt;10&lt;sup&gt;−4&lt;/sup&gt;</td>
</tr>
<tr>
<td>BLAST, Gökbuget et al. (2015)</td>
<td>Phase 2; prospective; Europe</td>
<td>Blinatumomab</td>
<td>HSCT</td>
<td>PCR (per EuroMRD guidelines) MRD response defined as no PCR amplification at a sensitivity of 10&lt;sup&gt;−6&lt;/sup&gt; or &lt;10&lt;sup&gt;−4&lt;/sup&gt; leukemic cells; MRD assessed at central reference laboratory</td>
</tr>
</tbody>
</table>

RT-qPCR detection of Ig/TCR arrangements

1. Bone marrow sample processing at diagnosis
2. Detection and selection of clonal Ig/TCR gene rearrangement at diagnosis
   a) PCR heteroduplex analysis
   b) Sequencing of clonal rearrangements
3. RQ-PCR sensitivity testing
   a) Selection of MRD-PCR targets
   b) Design of allele-specific oligonucleotide primers
4. MRD analysis of follow-up samples
   a) Control gene RQ-PCR analysis
   b) MRD-PCR target RQ-PCR analysis
   c) RQ-PCR MRD data interpretation

Selection of targets, quantitative range, and sensitivity

1. Preferably 2 MRD-PCR targets should be used for each ALL patient
2. MRD-PCR targets should be selected based on: (1) expected stability and (2) expected sensitivity
   a. Monoclonal Ig/TCR gene rearrangements have a much higher stability (80%–90%) than oligoclonal rearrangements (40%–50%)
3. To limit the risk of losing MRD-PCR targets by such processes – select “end-stage” Ig/TCR rearrangements (eg, IGK-Kde or Vγ-Jγ 2.3 rearrangements)
4. Concerns about the variation between replicates evaluated through mean CT values of the replicates
5. The “quantitative range” reflects the part of the standard curve in which the MRD levels can be quantified reproducibly and accurately, whereas the “sensitivity” reflects the lowest MRD level that still can be detected, although not reproducibly and accurately
Overall sensitivities of Ig/TCR gene rearrangements in RQ-PCR assays

<table>
<thead>
<tr>
<th>Rearrangement</th>
<th>Quantitative range of at least $10^{-4}$ (%)$^a$</th>
<th>Sensitivity of at least $10^{-4}$ (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGH  DJ</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>IGK-Kδε</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>IGK Vκ-Jκ</td>
<td>45</td>
<td>80</td>
</tr>
<tr>
<td>Vλ-Jλ</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>TCRD Incomplete</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>TCRD Complete</td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td>Vδ2-Jα</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>TCRB VDJ</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>TCRB DJ</td>
<td>55</td>
<td>90</td>
</tr>
<tr>
<td>TCRG precursor-B-ALL</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>T-ALL</td>
<td>70</td>
<td>80</td>
</tr>
</tbody>
</table>

$^a$Percentage of rearrangements with quantitative range/sensitivity of at least $10^{-4}$
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Ph</th>
<th>MRD method</th>
<th>MRD level</th>
<th>Test location</th>
<th>Phenotype</th>
<th>Disease stage</th>
<th>Pre-MRD tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lussana</td>
<td>2016</td>
<td>106 (73)</td>
<td>Pos</td>
<td>PCR</td>
<td>$10^{-5}$</td>
<td>N/A</td>
<td>B-cell</td>
<td>CR1</td>
<td>Targeted</td>
</tr>
<tr>
<td>Chiaretti</td>
<td>2015</td>
<td>63 (60)</td>
<td>Pos</td>
<td>PCR</td>
<td>N/A</td>
<td>N/A</td>
<td>B-cell</td>
<td>CR1</td>
<td>Targeted</td>
</tr>
<tr>
<td>Nishiwaki</td>
<td>2016</td>
<td>432 (432)</td>
<td>Pos</td>
<td>PCR</td>
<td>$10^{-5}$</td>
<td>Local</td>
<td>B-cell</td>
<td>CR1/Pre-HSCT</td>
<td>Targeted</td>
</tr>
<tr>
<td>Yanada</td>
<td>2008</td>
<td>100 (85)</td>
<td>Pos</td>
<td>PCR</td>
<td>$10^{-5}$</td>
<td>Central</td>
<td>B-cell</td>
<td>CR1</td>
<td>Targeted</td>
</tr>
<tr>
<td>Wetzler</td>
<td>2014</td>
<td>34 (13)</td>
<td>Pos</td>
<td>PCR</td>
<td>N/A</td>
<td>Central</td>
<td>B-cell</td>
<td>CR1</td>
<td>Targeted</td>
</tr>
<tr>
<td>Tucunduva</td>
<td>2014</td>
<td>98 (98)</td>
<td>Pos</td>
<td>Mix</td>
<td>Mix</td>
<td>Local</td>
<td>B-cell</td>
<td>CR1</td>
<td>Targeted</td>
</tr>
<tr>
<td>Yoon</td>
<td>2016</td>
<td>173 (169)</td>
<td>Pos</td>
<td>PCR</td>
<td>$10^{-4}$</td>
<td>Central</td>
<td>B-cell</td>
<td>CR1</td>
<td>Targeted</td>
</tr>
<tr>
<td>Lim</td>
<td>2016</td>
<td>82 (78)</td>
<td>Pos</td>
<td>PCR</td>
<td>$10^{-5}$</td>
<td>Central</td>
<td>B-cell</td>
<td>CR1</td>
<td>Targeted</td>
</tr>
<tr>
<td>Short</td>
<td>2016</td>
<td>202 (122)</td>
<td>Pos</td>
<td>PCR</td>
<td>$10^{-4}$</td>
<td>Local</td>
<td>B-cell</td>
<td>CR1</td>
<td>Targeted</td>
</tr>
</tbody>
</table>

## Ph-positive – Type of response

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Treatment</th>
<th>HSCT</th>
<th>MRD detection methodology</th>
</tr>
</thead>
</table>
| Kim et al. (2015) | Prospective; single-center; Korea | Chemotherapy + imatinib | Allo | qRT PCR for BCR-ABL transcript; measured at a central reference laboratory MRD stratified by 3 groups after 2 courses of consolidation  
1. EMRs (early and persistent MRD− [BCR-ABL:ABL ratio ≤0.1% or ≥3-log reduction in BCR-ABL transcript level from baseline])  
2. LMRs (conversion from MRD+ to MRD−)  
3. PMRs (MRD+: MRD levels >1% or <3-log reduction in BCR-ABL transcript level from baseline) |
When?
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Ph</th>
<th>MRD method</th>
<th>Disease stage</th>
<th>MRD timing</th>
<th>Pre-MRD tx</th>
<th>Post-MRD Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gökbuget</td>
<td>2015</td>
<td>116 (112)</td>
<td>Neg</td>
<td>PCR</td>
<td>CR1</td>
<td>≤3 months from induction</td>
<td>Targeted</td>
<td>Mix</td>
</tr>
<tr>
<td>Jabbour</td>
<td>2017</td>
<td>78 (78)</td>
<td>NA</td>
<td>Flow (6color)</td>
<td>CR2 or later</td>
<td>≤3 months from induction</td>
<td>Targeted</td>
<td>Mix</td>
</tr>
<tr>
<td>Ravandi</td>
<td>2016</td>
<td>340 (260)</td>
<td>Mix</td>
<td>Flow (6color)</td>
<td>CR1</td>
<td>≤3 months from induction</td>
<td>Targeted</td>
<td>Mix</td>
</tr>
<tr>
<td>Bassan</td>
<td>2014</td>
<td>159 (106)</td>
<td>Neg</td>
<td>PCR</td>
<td>CR1</td>
<td>≥3 months from induction</td>
<td>Chemo</td>
<td>Mix</td>
</tr>
<tr>
<td>Beldjord</td>
<td>2014</td>
<td>860 (423)</td>
<td>Neg</td>
<td>PCR</td>
<td>CR1</td>
<td>≤3 months from induction</td>
<td>Chemo</td>
<td>Mix</td>
</tr>
<tr>
<td>Gökbuget</td>
<td>2012</td>
<td>1648 (580)</td>
<td>Neg</td>
<td>PCR</td>
<td>CR1</td>
<td>≤3 months from induction</td>
<td>Chemo</td>
<td>Mix</td>
</tr>
<tr>
<td>Bassan</td>
<td>2014</td>
<td>304 (141, [98 included in the analysis])</td>
<td>Neg</td>
<td>PCR</td>
<td>CR1</td>
<td>&gt;3 months from induction</td>
<td>Chemo</td>
<td>Mix</td>
</tr>
<tr>
<td>Gökbuget</td>
<td>2014</td>
<td>189 (73)</td>
<td>Neg</td>
<td>PCR</td>
<td>CR2 or later</td>
<td>≤3 months from induction</td>
<td>Targeted</td>
<td>Mix</td>
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<td>Weng</td>
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<td>Mix</td>
<td>Flow (6color)</td>
<td>CR1</td>
<td>≤3 months from induction</td>
<td>Chemo</td>
<td>Mix</td>
</tr>
<tr>
<td>Lussana</td>
<td>2016</td>
<td>106 (73)</td>
<td>Pos</td>
<td>PCR</td>
<td>CR1</td>
<td>Pre-HSCT</td>
<td>Targeted</td>
<td>HSCT</td>
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<tr>
<td>Tucunduva</td>
<td>2014</td>
<td>98 (98)</td>
<td>Pos</td>
<td>Mix</td>
<td>CR1</td>
<td>Pre-HSCT</td>
<td>Targeted</td>
<td>HSCT</td>
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<tr>
<td>Yoon</td>
<td>2016</td>
<td>173 (169)</td>
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<td>PCR</td>
<td>CR1</td>
<td>Pre-HSCT</td>
<td>Targeted</td>
<td>HSCT</td>
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<tr>
<td>Lim</td>
<td>2016</td>
<td>82 (78)</td>
<td>Pos</td>
<td>PCR</td>
<td>CR1</td>
<td>≤3 months from induction</td>
<td>Targeted</td>
<td>Mix</td>
</tr>
<tr>
<td>Short</td>
<td>2016</td>
<td>202 (122)</td>
<td>Pos</td>
<td>PCR</td>
<td>CR1</td>
<td>≤3 months from induction</td>
<td>Targeted</td>
<td>Target</td>
</tr>
</tbody>
</table>
Regarding MRD analysis in acute lymphoblastic leukemia, which statement is true?

a. The prognostic relevance of residual measurable disease detection (MRD+) is higher in Ph-positive ALL than in Ph-negative ALL

b. Threshold levels for MRD detection at the level of 10^{-4} distinguish between patients that are more likely to relapse, but have no impact in the overall survival

c. The detection of MRD in Ph-negative B-cell ALL is feasible both by PCR and flow cytometry methodologies

d. Regarding MRD detection by PCR methods, the terms “quantitative range” and “sensitivity” are synonyms
Meta-analysis relapse-free survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Favor MRD pos</th>
<th>Favor MRD neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD level: $10^{-1}$</td>
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<tr>
<td>$10^{-2}$</td>
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<td>Ph status: mixed</td>
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<tr>
<td>Ph negative</td>
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<td>Ph positive</td>
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<td>Phenotype: B-cell mixed</td>
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<td>mixed</td>
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<td>Post MRD tx: mixed</td>
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<td>Pre MRD tx: HSCT only</td>
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<td>targeted therapy</td>
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<td>standard risk</td>
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<td>MRD testing location:</td>
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<td></td>
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<tr>
<td>central</td>
<td></td>
<td></td>
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<tr>
<td>local</td>
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<td></td>
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<tr>
<td>Timing of MRD:</td>
<td></td>
<td></td>
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<tr>
<td>$\leq 3$ months from induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&gt;3$ months from induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRD methodology: flow</td>
<td></td>
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<tr>
<td>PCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The earlier, the better?

- Stock et al (2014) – Pts with Ph-negative B-ALL or T-ALL
  - MRD levels as early as 28 days following the initiation of induction therapy predicted outcomes

- Bruggemann et al (2006) – Patients with Ph-negative B-ALL or T-ALL
  - An early MRD response (day 11) was associated with the best prognosis

- Dhèdin et al (2015) – Patients with Ph-negative ALL
  - Lack of MRD response 6 weeks after induction initiation could identify patients who would benefit most from HSCT

MRD detection could be used to spare pts from more-toxic treatments?

- PETHEMA ALL-AR03 – MRD to guide treatment decisions at the end of consolidation
  - HSCT could be avoided in patients who reached MRD-neg without adversely affecting their prognosis

- GRAALL-2003 or -2005 – MRD analysis
  - HSCT prolonged RFS compared with chemotherapy among those who did not achieve an early MRD response, but was no better than chemotherapy in patients who did achieve an early MRD response
Conclusions

✓ Achieving MRD negativity was consistently associated with better survival outcomes

✓ The prognostic ability of MRD negativity is the same in Ph-positive and Ph-negative cohorts

✓ Although the exact value for cut-off values between MRD+ and MRD− is controversial, the threshold of $10^{-4}$ was recommended by ESMO

✓ Timing of MRD assessment showed that there was no difference in RFS improvement for patients who achieved MRD negativity at early timepoints compared with those who achieved it at later timepoints. But controlled prospective trials suggest that MRD negativity could be used to spare patients from more-toxic regimens

MRD Assessment and Management in CR1 vs CR2 and Beyond

Aaron Logan
Measurable Residual Disease (MRD) Assessment and Management in CR1 vs CR2 and beyond

Aaron Logan, MD, PhD
UCSF Division of Malignant Hematology and Blood and Marrow Transplantation

aaron.logan@ucsf.edu

@hemedoc
### MRD Case Study

#### Identification

<table>
<thead>
<tr>
<th>Age</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Ph-negative B-cell ALL</td>
</tr>
</tbody>
</table>

#### Presentation at Time of Diagnosis

| CBC                     | WBC count: 46,000/mcL  
|                        | Hb: 6.5 g/dL          |
|                        | Platelet count: 28,000/mcL |
| Blast count            | 60% peripheral & marrow blasts |
| Immunophenotype        | CD10+, CD19+, CD20+, CD34+ |
| Karyotype/Mutations    | t(4;11)(q21;q23) (MLL/KMT2A+) |

#### Treatment History

Achieved remission with hyper-CVAD, but relapsed during cycle 2B.

The patient then received blinatumomab and achieves a second remission and has a 10/10 HLA matched sibling donor identified for transplant.

---

For this patient, is MRD testing useful?
Is MRD testing useful for this patient in CR2 before he proceeds to allogeneic transplantation?

a. No, MRD is not prognostic at this time point.

b. Yes, MRD is prognostic after first salvage therapy.

c. Yes, MRD is prognostic prior to allogeneic hematopoietic cell transplantation.

d. B and C
MRD Strongly Predicts Outcome in Pediatric and Adult ALL

A. EFS for Pediatric ALL:
20 Studies With 11249 Patients

B. OS for Pediatric ALL:
5 Studies With 2876 Patients

C. EFS for Adult ALL:
16 Studies With 2065 Patients

D. OS for Adult ALL:
5 Studies With 806 Patients

HR: 0.23 (95% CI: 0.18-0.28)

HR: 0.28 (95% CI: 0.19-0.41)

HR: 0.28 (95% CI: 0.24-0.33)

HR: 0.28 (95% CI: 0.20-0.39)

MRD at Any Point in Therapy Predicts Outcome

A

Induction Consolidation Reinduction Consolidation

Sampling time points GMALL 06/99

Day Wk
0 11 24 44 11 16 22 30 41 52

B

Sampling timepoints GMALL 065/93 MRD pilot trial

Day Wk
0 29 13 21 33 46 52

C

Probability of DFS According to MRD

Day +24

\[ P = .003 \]

Wk +22

\[ P < .001 \]

Wk +52

\[ P < .001 \]

MRD Quantified Using Quantitative PCR

<table>
<thead>
<tr>
<th>MRD</th>
<th>n</th>
<th>3-Yr DFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative/&lt;10^{-4}</td>
<td>75</td>
<td>68.6 (55.0-82.2)</td>
</tr>
<tr>
<td>&gt;10^{-4}</td>
<td>82</td>
<td>37.8 (24.5-51.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRD</th>
<th>n</th>
<th>3-Yr DFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative/&lt;10^{-4}</td>
<td>10</td>
<td>65.4 (54.1-76.7)</td>
</tr>
<tr>
<td>&gt;10^{-4}</td>
<td>1</td>
<td>11.8 (0-31.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRD</th>
<th>n</th>
<th>3-Yr DFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative/&lt;10^{-4}</td>
<td>11</td>
<td>67.9 (56.9-80.6)</td>
</tr>
<tr>
<td>&gt;10^{-4}</td>
<td>3</td>
<td>14.6 (0.0-40.0)</td>
</tr>
</tbody>
</table>

MRD Predicts RFS at Achievement of CR2 (1/3)

Table 2. Response and minimal residual disease status after first relapse therapy.

<table>
<thead>
<tr>
<th>Relapse therapy</th>
<th>Type of complete response, n (%)</th>
<th>MRD status, n (%)³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR (n%)</td>
<td>CRp (n%)</td>
</tr>
<tr>
<td>Hyper-CVAD (n = 32)</td>
<td>25 (78)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>BFM-based (n = 19)</td>
<td>14 (74)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>HDAC± Mitoxantrone (n = 15)</td>
<td>10 (67)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Inotuzumab² (n = 11)</td>
<td>8 (73)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Nelarabine³ (n = 7)</td>
<td>7 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Blinatumomab³ (n = 5)</td>
<td>3 (60)</td>
<td>0</td>
</tr>
<tr>
<td>Other chemotherapy (n = 17)</td>
<td>11 (65)</td>
<td>4 (23)</td>
</tr>
</tbody>
</table>

Table 3. Correlation of MRD with response to first relapse therapy.

<table>
<thead>
<tr>
<th>MRD status</th>
<th>All patients, n (%)</th>
<th>CR, n (%)</th>
<th>CRp, n (%)</th>
<th>CRI, n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>61</td>
<td>47</td>
<td>11</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>16 (26)</td>
<td>11 (23)</td>
<td>2 (18)</td>
<td>3 (100)</td>
<td>.01</td>
</tr>
<tr>
<td>Negative</td>
<td>45 (74)</td>
<td>36 (77)</td>
<td>9 (82)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

CR: complete response; CRI: complete response with incomplete count recovery; CRp: complete response with incomplete platelet recovery; MRD: minimal residual disease.

### Table 5. Multivariable Cox regression analysis of prognostic factors for overall and relapse-free survival after first relapse.

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Overall survival, months</th>
<th>Relapse-free survival, months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>1.01 (1–1.03)</td>
<td>.28</td>
</tr>
<tr>
<td>WBC count at diagnosis (×10^9/L) (continuous)</td>
<td>1.01 (1–1.02)</td>
<td>.02</td>
</tr>
<tr>
<td>Time to relapse (&lt;18 versus ≥18 months)</td>
<td>1.19 (0.62–2.34)</td>
<td>.6</td>
</tr>
<tr>
<td>Response to first relapse therapy CRh versus CR</td>
<td>1.77 (0.91–3.3)</td>
<td>.09</td>
</tr>
<tr>
<td>MRD status at relapse response (positive versus negative)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCT after relapse (yes versus no)</td>
<td>0.32 (0.17–0.6)</td>
<td>.0005</td>
</tr>
</tbody>
</table>
MRD Predicts RFS at Achievement of CR2 (3/3)

Blinatumomab – Results Best in 1st Salvage

Table 3. Best hematologic response and minimal residual disease response within 12 weeks of treatment initiation.

<table>
<thead>
<tr>
<th>Response category</th>
<th>First salvage</th>
<th>Second or later salvage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blinatumomab</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>(N = 104)</td>
<td>(N = 63)</td>
</tr>
<tr>
<td>No. % 95% CI</td>
<td>No. % 95% CI</td>
<td>p*</td>
</tr>
<tr>
<td>Best hematologic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>46 44.2 34.5, 54.3</td>
<td>18 28.6 17.9, 41.3</td>
</tr>
<tr>
<td>CRh</td>
<td>6 5.8 2.1, 12.1</td>
<td>2 3.2 0.4, 11.0</td>
</tr>
<tr>
<td>CRI</td>
<td>1 1.0 0.0, 5.2</td>
<td>3 4.8 1.0, 13.3</td>
</tr>
<tr>
<td>CR/CRI/CRIi</td>
<td>53 51.0 41.0, 60.9</td>
<td>23 36.5 24.7, 49.6</td>
</tr>
<tr>
<td>MRD responses among patients with CR/CRI/CRIi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any MRD response</td>
<td>33 62.3 47.9, 75.2</td>
<td>13 56.5 34.5, 76.8</td>
</tr>
<tr>
<td>Complete MRD response</td>
<td>26 49.1 35.1, 63.2</td>
<td>9 39.1 19.7, 61.5</td>
</tr>
</tbody>
</table>

*P<0.05 for the difference between the rates of complete remission or CR/CRI/CRIi (yes/no). For MRD response, a mixed-effects model was used. The within-patient correlation coefficient is 0.70, and the between-patient correlation coefficient is 0.58. The multivariable model used for the CR/CRI/CRIi (yes/no) response included treatment, age, and transplant status as covariates.

Blinatumomab – MRD Response Predicts Outcome in 1st Salvage

Relapse-free survival in patients who achieve CR/CRh

<table>
<thead>
<tr>
<th>RFS</th>
<th>n</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD–</td>
<td>75</td>
<td>9.0</td>
<td>(6.2–14.6)</td>
</tr>
<tr>
<td>MRD+</td>
<td>15</td>
<td>2.3</td>
<td>(1.2–7.5)</td>
</tr>
</tbody>
</table>

Median (95% CI), months
- MRD–, S1: NR (14.3, NR)
- MRD+, S1: NR (8.30, NR)
- MRD–, S2+: 12.7 (11.05, NR)
- MRD+, S2+: 10.8 (5.08, NR)

Patients at risk:
- MRD–, S1: 33 29 21 15 7 2 0 0
- MRD+, S1: 11 10 6 3 2 0 0 0
- MRD–, S2+: 41 31 19 11 7 2 1 0
- MRD+, S2+: 12 6 5 3 3 2 2 0

Inotuzumab – MRD Response Predicts Outcome in 1<sup>st</sup>/2<sup>nd</sup> Salvage

Mini-HyperCVD + Inotuzumab – R/R ALL (1/2)

**Intensive phase**
- 1: Mini-hCVD
- 2: Mini-MTX-cytarabine
- 3: Blinatumomab
- 4: IT MTX/AraC

**Consolidation phase**
- 5: POMP
- 6: IT MTX/AraC
- 7: Mini-MTX-cytarabine
- 8: Blinatumomab

**Maintenance phase**
- 1-3: C
- 4: 1
- 5-7: C2-4
- 8: 0.3 D1 and D8
- 9-11: 0.6 D1, 0.3 D8
- 12: Total Ino dose = 2.7 mg/m²

Mini-HyperCVD + Inotuzumab – R/R ALL (2/2)

Mini-HyperCVD + Inotuzumab – Predictive Value of MRD Negativity Decreases After 1\textsuperscript{st} Salvage

---


**Blinatumomab BLAST Trial – Preemption of B-ALL Relapse Using MRD-Directed Treatment**

1: Patients in 1st CR (n = 75); median: 36.5 (95% CI: 20.6-NR)

2: Patients in 2nd or 3rd CR (n = 41); median: 19.1 (95% CI: 11.9-NR)
### Complete MRD Response at Cycle 1

<table>
<thead>
<tr>
<th></th>
<th>n/N</th>
<th>% (95% Exact CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>82/103</td>
<td>80 (71-87)</td>
</tr>
<tr>
<td>MRD Level at Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10^{-3} to &lt;10^{-2}</td>
<td>40/51</td>
<td>78 (65-89)</td>
</tr>
<tr>
<td>≥10^{-2} to &lt;10^{-1}</td>
<td>36/43</td>
<td>84 (69-93)</td>
</tr>
<tr>
<td>≥10^{-1} to &lt;1</td>
<td>6/9</td>
<td>67 (30-93)</td>
</tr>
<tr>
<td>Relapse History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR2/3</td>
<td>27/37</td>
<td>73 (56-86)</td>
</tr>
<tr>
<td>CR1</td>
<td>55/66</td>
<td>83 (72-91)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35/43</td>
<td>81 (67-92)</td>
</tr>
<tr>
<td>Male</td>
<td>47/60</td>
<td>78 (66-88)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>11/13</td>
<td>85 (55-98)</td>
</tr>
<tr>
<td>55-64</td>
<td>17/23</td>
<td>74 (52-90)</td>
</tr>
<tr>
<td>35-54</td>
<td>25/35</td>
<td>71 (54-85)</td>
</tr>
<tr>
<td>18-34</td>
<td>29/32</td>
<td>91 (75-98)</td>
</tr>
</tbody>
</table>

N = 82, age <1-20
MRD by ASO-PCR
Median f/u 4.9 yrs

HCT in CR1 if
- Day +78: $>5 \times 10^{-4}$ MRD
- Induction failure
- Ph+, MLL+
- T-lin w/ WBC >100K

HCT for all CR2+

N = 43, age 18-63
MAC alloHCT in CR1

MRD quant:
TCR/Ig ASO-PCR
or
BCR/ABL Q-PCR
or
MLL/AF4 Q-PCR

MRD Status Pre-Transplant Predicts RFS and OS (2/2)
MRD in CR2 Pre-Transplant Predicts Outcome

- N = 91 in CR2 (77) or CR3 (14)
- Pediatric ALL-REZ BFM study
MRD Assessment in CR2 and Beyond Summary

- MRD in CR2 remains a useful predictor of relapse-free survival in studies with chemotherapy and novel agents.
- MRD in CR2 also a predictor of overall survival with use of novel agents (inotuzumab, blinatumomab).
- MRD may have limited predictive value for RFS/OS in CR3+.
- MRD pre-transplant is highly predictive of outcome in CR1 and CR2+.
- Patients treated with blinatumomab for MRD positivity in CR2/3 have similar likelihood for conversion to MRD negativity (78%) as patients treated for MRD positivity in CR1 (83%), but shorter median OS (19.1 vs 36.5 mos).
Thank you!
Genetic Variants in ALL – Ph+ and Ph-Like

Elias Jabbour
Ph-Like ALL

## 2016 WHO Classification

### B-lymphoblastic leukemia/lymphoma

- B-lymphoblastic leukemia/lymphoma, NOS
- B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
- B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); BCR-ABL1
- B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); KMT2A rearranged
- B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1
- B-lymphoblastic leukemia/lymphoma with hyperdiploidy
- B-lymphoblastic leukemia/lymphoma with hypodiploidy
- B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) IL3-IGH
- B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); TCF3-PBX1

- **Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like**

- **Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21**

### T-lymphoblastic leukemia/lymphoma

- **Provisional entity: Early T-cell precursor lymphoblastic leukemia**
Ph-Like ALL Occurs in 25%–30% of Young Adults With B-cell ALL
Recurring Kinase Alterations in Ph-Like ALL

Ph-Like ALL: Survival and EFS

Ph-Like FISH Testing Algorithm

BCR-ABL1 Positive?

Yes: STOP

No: Positive for CRLF2 by Flow Cytometry?

Yes: FISH for CRLF2
MDL for JAK2 mutation study

No: Sending out for Kinase Fusion testing
Run targeted FISH based on chromosomal abnormalities

STOP

STOP
BCR-ABL TKIs + Chemo Rx in Ph-Like ALL

- 24 pts with Ph-like ALL: NUP214-ABL1 – 6, ETV6-ABL1 – 3, others –9; 19 frontline, 5 relapse. All Rx with chemo Rx + TKI
## Ph-Like ALL: Higher MRD+ Rate

<table>
<thead>
<tr>
<th>B-ALL Categories (N = 155)</th>
<th>Ph-like</th>
<th>Ph+</th>
<th>B – other</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>56</td>
<td>46</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td><strong>CR/CRp</strong></td>
<td>50 (89)</td>
<td>43 (93)</td>
<td>50 (94)</td>
<td>.57</td>
</tr>
<tr>
<td><strong>MRD at CR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>23 (70)</td>
<td>15 (44)</td>
<td>4 (13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Negative</td>
<td>10 (30)</td>
<td>19 (56)</td>
<td>27(87)</td>
<td></td>
</tr>
</tbody>
</table>

HCVAD + Ofatumumab: Outcome (N = 69)

- Median follow up of 44 months (4–91)
- CR 98%, MRD negativity 93% (at CR 63%), early death 2%

### CRD and OS overall

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Fraction survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>0.8</td>
</tr>
<tr>
<td>24</td>
<td>0.6</td>
</tr>
<tr>
<td>36</td>
<td>0.4</td>
</tr>
<tr>
<td>48</td>
<td>0.2</td>
</tr>
<tr>
<td>60</td>
<td>0.0</td>
</tr>
<tr>
<td>72</td>
<td>0.0</td>
</tr>
<tr>
<td>84</td>
<td>0.0</td>
</tr>
<tr>
<td>96</td>
<td>0.0</td>
</tr>
</tbody>
</table>

- Complete Remission Duration
  - Total: 68, Fail: 21, 3 yr: 75%
- Overall Survival
  - Total: 69, Fail: 23, 3 yr: 68%

### OS by age

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Fraction survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>0.8</td>
</tr>
<tr>
<td>24</td>
<td>0.6</td>
</tr>
<tr>
<td>36</td>
<td>0.4</td>
</tr>
<tr>
<td>48</td>
<td>0.2</td>
</tr>
<tr>
<td>60</td>
<td>0.0</td>
</tr>
<tr>
<td>72</td>
<td>0.0</td>
</tr>
<tr>
<td>84</td>
<td>0.0</td>
</tr>
<tr>
<td>96</td>
<td>0.0</td>
</tr>
</tbody>
</table>

- <40
  - Total: 33, Fail: 9, 3 yr OS: 74%
  - #p=0.40
- ≥40
  - Total: 36, Fail: 14, 3 yr OS: 63%
HCVAD + Ofatumumab: Outcome by Ph-Like (RNA-seq)
Hyper-CVAD + Ofatumumab: Molecular Alterations and Outcome

### Event free survival

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>p. value</th>
<th>Multivariate analysis</th>
<th>p. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AYA</td>
<td>0.7578</td>
<td>0.4389</td>
<td></td>
</tr>
<tr>
<td>WBC high</td>
<td>1.254</td>
<td>0.5638</td>
<td></td>
</tr>
<tr>
<td>Ho-Tr</td>
<td>0.9261</td>
<td>0.8754</td>
<td></td>
</tr>
<tr>
<td>Ph-like</td>
<td>1.727</td>
<td>0.2410</td>
<td></td>
</tr>
<tr>
<td>TP53mut</td>
<td>1.316</td>
<td>0.5245</td>
<td></td>
</tr>
<tr>
<td>JAK2mut</td>
<td>4.707</td>
<td>0.008104</td>
<td></td>
</tr>
<tr>
<td>CDKN2A/2Bdel</td>
<td>1.549</td>
<td>0.2862</td>
<td>4.118(1.125-15.07)</td>
</tr>
<tr>
<td>IKZF rdel</td>
<td>1.282</td>
<td>0.5511</td>
<td></td>
</tr>
<tr>
<td>PAX5del</td>
<td>1.122</td>
<td>0.8062</td>
<td></td>
</tr>
<tr>
<td>VPREB rdel</td>
<td>1.738</td>
<td>0.1802</td>
<td></td>
</tr>
<tr>
<td>RB rdel</td>
<td>2.262</td>
<td>0.08883</td>
<td></td>
</tr>
<tr>
<td>CD200/BTL rdel</td>
<td>1.274</td>
<td>0.6338</td>
<td>1.269(0.5136-3.134)</td>
</tr>
<tr>
<td>ETV6 rdel</td>
<td>2.922</td>
<td>0.05383</td>
<td></td>
</tr>
<tr>
<td>EBF rdel</td>
<td>1.518</td>
<td>0.4498</td>
<td></td>
</tr>
<tr>
<td>BTG rdel</td>
<td>2.763</td>
<td>0.1142</td>
<td></td>
</tr>
<tr>
<td>14q del</td>
<td>2.079</td>
<td>0.1102</td>
<td></td>
</tr>
<tr>
<td>MRD neg (1 mo)</td>
<td>0.7484</td>
<td>0.4176</td>
<td>0.6752(0.296-1.54)</td>
</tr>
</tbody>
</table>

### Overall survival

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>p. value</th>
<th>Multivariate analysis</th>
<th>p. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AYA</td>
<td>0.6243</td>
<td>0.2744</td>
<td></td>
</tr>
<tr>
<td>WBC high</td>
<td>1.185</td>
<td>0.7212</td>
<td></td>
</tr>
<tr>
<td>Ho-Tr</td>
<td>1.114</td>
<td>0.8462</td>
<td></td>
</tr>
<tr>
<td>Ph-like</td>
<td>2.065</td>
<td>0.1880</td>
<td></td>
</tr>
<tr>
<td>TP53mut</td>
<td>2.489</td>
<td>0.04951</td>
<td></td>
</tr>
<tr>
<td>JAK2mut</td>
<td>8.062</td>
<td>0.001461</td>
<td>5.136(1.251-21.09)</td>
</tr>
<tr>
<td>CDKN2A/2Bdel</td>
<td>3.936</td>
<td>0.01598</td>
<td>2.628(1.069-7.482)</td>
</tr>
<tr>
<td>IKZF rdel</td>
<td>2.664</td>
<td>0.03932</td>
<td>2.986(0.980-9.05)</td>
</tr>
<tr>
<td>PAX5del</td>
<td>2.067</td>
<td>0.1480</td>
<td></td>
</tr>
<tr>
<td>VPREB rdel</td>
<td>3.659</td>
<td>0.008578</td>
<td></td>
</tr>
<tr>
<td>RB rdel</td>
<td>3.855</td>
<td>0.00316</td>
<td></td>
</tr>
<tr>
<td>CD200/BTL rdel</td>
<td>1.532</td>
<td>0.4548</td>
<td></td>
</tr>
<tr>
<td>ETV6 rdel</td>
<td>4.347</td>
<td>0.01063</td>
<td></td>
</tr>
<tr>
<td>EBF rdel</td>
<td>4.766</td>
<td>0.02014</td>
<td></td>
</tr>
<tr>
<td>BTG rdel</td>
<td>3.729</td>
<td>0.00812</td>
<td></td>
</tr>
<tr>
<td>14q del</td>
<td>0.4432</td>
<td>0.05702</td>
<td>0.3955(0.1391-1.124)</td>
</tr>
<tr>
<td>MRD neg (1 mo)</td>
<td>0.7484</td>
<td>0.4176</td>
<td></td>
</tr>
</tbody>
</table>
### Dynamics of MRD: Outcome

<table>
<thead>
<tr>
<th>MRD Status</th>
<th>Patients (%) (n = 214)</th>
<th>5-yr EFS, %</th>
<th>5-yr OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>@CR</td>
<td>@ First post-CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>147 (69)</td>
<td>56</td>
</tr>
<tr>
<td>≤0.1%</td>
<td>Negative</td>
<td>14 (7)</td>
<td>31</td>
</tr>
<tr>
<td>&gt;0.1%</td>
<td>Negative</td>
<td>33 (15)</td>
<td>32</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>20 (9)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Hyper-CVAD + Blinatumomab in B-ALL (Ph− B-ALL <60 years): Treatment Schedule

**Intensive phase**

1. Hyper-CVAD
2. MTX–ara-C
3. Ofatumumab or rituximab
4. Blinatumomab

**Blinatumomab phase**

*After 2 cycles of chemo for Ho-Tr, Ph-like, t(4;11)*

1. Blinatumomab
2. Blinatumomab
3. Blinatumomab
4. Blinatumomab

**Maintenance phase**

1–3, 4, 5–7, 8, 9–11, 12, 13–15

- **Hyper-CVAD**
- Ofatumumab or rituximab
- **MTX–ara-C**
- **8 × IT MTX, ara-C**
- **POMP**

Hyper-CVAD + Blinatumomab in FL B-ALL (N = 34)

- CR 100%, MRD negativity 97% (at CR 87%), early death 0%

CRD and OS Overall

OS: HCVAD-Blina vs O-HCVAD

TKI for Ph+ ALL

Imatinib: 5-yr OS = 43%

Dasatinib: 5-yr OS = 46%

Ponatinib: 5-yr OS = 71%

Low-Intensity Chemo Rx + Dasatinib in Ph+ ALL ≥55 Years

- 71 pts (2007–2010); median age 69 yr (58–83)
- Dasatinib 100–140 mg/D, VCR 1 mg Q wk, dex 20–40 mg/D × 2, Qwk
- Consolidations: dasatinib 100 mg/D; MTX-asp C1, 3, 5; ara-C C2, 4, 6. Maintenance: dasatinib + POMP
- CR 96%; MMR 65%; CMR 24%
- 5-yr survival 36%; EFS 25%
- \textit{T315I} at dx 23% by NGS
- 36 relapses; \textit{T315I} in 75%

Hyper-CVAD + Ponatinib: Design

Intensive phase

- 45
- 30/15

1  2  3  4  5  6  7  8

Maintenance phase

- 30/15
- 30/15

24 months

12 intrathecal CNS prophylaxis

- Hyper-CVAD
- MTX-cytarabine
- Ponatinib 45 mg →30 mg →15 mg
- Vincristine + prednisone

- After the emergence of vascular toxicity, protocol was amended: beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

Hyper-CVAD + Ponatinib in Ph+ ALL: Response Rates

Median follow-up: 44 months (4–94 months)

<table>
<thead>
<tr>
<th>Response</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>68/68 (100)</td>
</tr>
<tr>
<td>CCyR</td>
<td>58/58 (100)</td>
</tr>
<tr>
<td>MMR</td>
<td>80/85 (94)</td>
</tr>
<tr>
<td>CMR</td>
<td>73/85 (86)</td>
</tr>
<tr>
<td>3-month CMR</td>
<td>63/85 (74)</td>
</tr>
<tr>
<td>Flow negativity</td>
<td>83/85 (95)</td>
</tr>
<tr>
<td>Early death</td>
<td>0</td>
</tr>
</tbody>
</table>

Hyper-CVAD + Ponatinib in Ph+ ALL: Outcome

EFS and OS

Impact of allo-SCT: 6-mo landmark

IT × 8 vs IT × 12 in Ph+ ALL: 6-Month Landmark – CNS Relapse-Free Survival

Median follow-up: 73 months
Log-rank: P = 0.023

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>Event</th>
<th>6-y CNS Relapse-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>IT 8 times</td>
<td>74</td>
<td>9</td>
<td>87%</td>
</tr>
<tr>
<td>IT &gt;8 times</td>
<td>44</td>
<td>0</td>
<td>100%</td>
</tr>
</tbody>
</table>

Propensity Score Analysis: HCVAD + Ponatinib vs HCVAD + Dasatinib in Ph+ ALL

Event-Free Survival/Overall Survival (entire cohort, N = 107)

**Event-free survival**

- AYA, age <40
- Sex, female
- WBC, high
- CDKN2A2B del
- IKZF1 del
- IKZF1 (exon4-7) del
- PAX5 del
- VPREB1 del
- Anti-CD20 mAb therapy
- TKI type, ponatinib

**Overall survival**

- AYA, age <40
- Sex, female
- WBC, high
- CDKN2A2B del
- IKZF1 del
- IKZF1 (exon4-7) del
- PAX5 del
- VPREB1 del
- Anti-CD20 mAb therapy
- TKI type, ponatinib

**Univariate analysis**

- Hazard ratio (95% CI)  |  P value
- 0.9522 (0.4723-1.92)  |  .8911
- 0.7494 (0.4194-1.339) |  .3299
- 1.246 (0.7027-2.211) |  .4513
- 1.181 (0.5842-2.389) |  .6427
- 1.694 (0.8978-3.197) |  .1037
- 2.049 (1.107-3.792)  |  .02239
- 1.45 (0.7328-2.869)  |  .2859
- 2.145 (1.166-3.945)  |  .01408
- 1.345 (0.7382-2.45) |  .333
- 0.3309 (0.1703-0.6427)|  .001095

**Multivariate analysis**

- Hazard ratio (95% CI)  |  P value
- 0.7017 (0.3761-1.309) |  .2657
- 0.8493 (0.3956-1.823) |  .6753

**Univariate analysis**

- Hazard ratio (95% CI)  |  P value
- 0.7735 (0.3562-1.679) |  .5161
- 0.6641 (0.3539-1.246) |  .2025
- 1.089 (0.5942-2.028) |  .7655
- 1.236 (0.5864-2.606) |  .5775
- 1.948 (0.9659-3.927) |  .06245
- 2.517 (1.281-4.945)  |  .007392
- 1.664 (0.8268-3.35)  |  .1536
- 1.954 (1.019-3.749)  |  .04389
- 1.625 (0.8674-3.045) |  .1296
- 0.2918 (0.1385-0.6149)|  .0012

**Multivariate analysis**

- Hazard ratio (95% CI)  |  P value
- 0.6136 (0.3106-1.212) |  .1596
- 0.5868 (0.2487-1.384) |  .2234

**Univariate analysis**

- Hazard ratio (95% CI)  |  P value
- 1.875 (0.923-3.81)  |  .08213
- 1.597 (0.8075-3.157) |  .1785
- 1.597 (0.8075-3.157) |  .1785
- 0.3491 (0.1482-0.8223)|  .01606
CMR in Ph+ ALL: OS for CMR vs Others

- **At CR**
- **At 3 months**

- MVA for OS
  - CMR at 3 months (HR 0.42 [95% CI: 0.21-0.82]; P = .01)

Ponatinib only predictive factor for PFS (HR 0.39; \( P = .03 \)) and OS (HR 0.38; \( P = .04 \))

# Two Evolving Strategies to Treat Ph+ ALL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hyper-CVAD + Ponatinib</th>
<th>TKIs With Minimal ChemoRx</th>
</tr>
</thead>
<tbody>
<tr>
<td>% CR</td>
<td>90-100</td>
<td>90-100</td>
</tr>
<tr>
<td>% CMR</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Allo-SCT required</td>
<td>Only if no CMR</td>
<td>In all</td>
</tr>
<tr>
<td>Outcome p190 vs p210</td>
<td>Same</td>
<td>P190 better</td>
</tr>
<tr>
<td>% 3-yr survival/DFS</td>
<td>70-80</td>
<td>40-50</td>
</tr>
</tbody>
</table>

Indications for HSCT: Ph+ ALL

MRD assessment (within 3 months)

MRD–
- Chemotherapy + TKI
  or
- Blinatumomab + TKI

MRD+
- ≤3 logs
  - Blinatumomab + TKI
- >3 logs
  - Blinatumomab + TKI × 2–4 cycles
  - HSCT + maintenance TKI

### Blinatumomab and Inotuzumab in R-R Ph+ ALL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Blinatumomab</th>
<th>Inotuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Rx</td>
<td>45</td>
<td>38</td>
</tr>
<tr>
<td>No. CR/marrow CR (%)</td>
<td>16 (36)</td>
<td>25 (66)</td>
</tr>
<tr>
<td>MRD negative in CR, %</td>
<td>88</td>
<td>63</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>7.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Later allo-SCT, %</td>
<td>44</td>
<td>32</td>
</tr>
</tbody>
</table>
Dasatinib-Blinatumomab in Ph+ ALL

- 63 pts, median age 54 yr (24–82)
- Dasatinib 140 mg/D \times 3 \text{ mo}; add blinatumomab \times 2–5
- 53 post–dasa-blina \times 2 – molecular response 32/53 (60\%), 22 CMR (41\%); MRD ↑ in 15, 6 T315I; 12-mo OS 96\%; DFS 92\%

OS

DFS

Blinatumomab-Ponatinib in Ph+ ALL

- **Induction phase**: 30 mg
- **Consolidation phase: C2–C4**: 15 mg in CMR

- **Maintenance phase**: 15 mg for 5 years

- **1 week**: IT MTX, ara-C
- **2 weeks**: Ponatinib 30 mg
- **4 weeks**: Ponatinib 15 mg

Blinatumomab + Ponatinib Swimmer Plot (N = 15)

- Median follow-up: 14 months
- Median follow-up in Frontline: 9 months
- Median follow-up in Salvage: 16 months
- Median time to CMR: 0.9 months
Questions in Ph+ ALL

- Do we need allo-SCT? – not always, never?
  - Identify patients who can be cured without allo-SCT, eg, 3-mos CMR, others

- Ponatinib best TKI? – 3 mos-CMR 86%; 5-year OS rate 74%
  - Phase III low-dose CT + imatinib vs low-dose CT + ponatinib

- How much chemoRx – low-Intensity vs intensive chemo Rx?
  - Mini-HCVD-ponatinib-blinatumomab

- Can we cure Ph+ ALL without chemoRx or allo-SCT? – ponatinib + blinatumomab

- Duration of TKI maintenance
  - At least 5 years
AYA ALL Patients – What Is the Current Treatment Approach for This Diverse Patient Population?

Patrick Brown
Considerations in Adolescents and Young Adults (AYA) With Acute Lymphoblastic Leukemia (ALL)

Patrick Brown, MD

Director, Pediatric Leukemia Program
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Chair, NCCN ALL Guideline Committee
Learning Objectives

• Describe the AYA oncology patient, and recognize the challenges that have led to inferior outcomes in this group

• Understand that optimal AYA ALL outcomes require treatment with “pediatric-inspired” treatment regimens

• Know the difference in prevalence of sentinel genetic abnormalities in childhood vs AYA ALL

• Understand the importance of minimal residual disease (MRD) in risk stratification in AYA ALL

• Know that AYA patients are at higher risk of specific adverse events (AEs), and know the strategies to mitigate this risk
The AYA Oncology Patient – Key Phenotypic Features

• Do not “fit in” in either the peds or adult worlds, where environment and treatment intensities are tailored to median ages (10 y/o or 50 y/o)
• Un/underinsured, unlikely “primary care” relationship
• In transition to independence from parents
• In the midst of intense educational program
• Lack of firmly established career path
• Early stages of starting a family (engaged, newlywed, children planned or already arrived)
The AYA Oncology Patient – Medical Consequences of Phenotype

- Delayed diagnosis
- Low rates of clinical trial enrollment
- Lack of uniformity in treatment
- Poor adherence
- Enhanced concerns about fertility and other late effects
- Unique psychosocial hardships

Poor outcomes
AYA Deficit in Progress in Cancer Survival

Average annual percentage change in survival over 20 previous years

Case Presentation

• 23 y/o female presents to outside ER with 2 week history of progressive diffuse bone pain and fatigue; in last week, developed intermittent low-grade fevers and nosebleeds

• PE: Pallor, diffuse lymphadenopathy and hepatosplenomegaly, scattered petechiae

• CBC
  – WBC 69,000 per uL, 94% blasts; ANC 950 per uL; Hgb: 6.6 gm/dl; PLT: 33,000 per uL

Peripheral Blood Smear

Suspected diagnosis: ALL
Case Presentation (continued)

- LDH 488
- Uric Acid 5.9
- K 4.1, Phos 3.6, Ca 9.3
- DIC panel normal

- CSF: WBC 1, RBC 0, no blasts on cytospin

- Normal echo, EKG

Diagnosis: B-Lymphoblastic Leukemia
Question 1:
Which of the following factors is MOST important in deciding which initial ALL treatment regimen should be used for this patient?

a. The level of expression of CD19 on the surface of the ALL blasts
b. The presence or absence of hepatosplenomegaly and lymphadenopathy
c. The age of the patient
d. Whether the patient is being treated by an adult oncologist or a pediatric oncologist
e. Whether the patient is being treated in an academic center or in a community hospital
AYA ALL: Superior Outcomes With Pediatric Protocols

Comparison of survival of patients ages 16–21 treated in CALGB (adult) or CCG (pediatric)

- Multiple subsequent prospective studies of “pediatric-inspired” regimens in “young adults” (variably defined) have demonstrated feasibility and better outcomes compared with historical controls

Primacy of \textit{Ph Status} and \textit{Age} in NCCN Adult ALL Treatment Recommendations

\textit{Guidelines separated as follows}

- Ph+ ALL (AYA)
- Ph+ ALL (Older Adults)
- Ph– ALL (AYA)
- Ph– ALL (Older Adults)

\begin{itemize}
  \item “AYA” (NCI, NCCN): \textit{age at diagnosis of 15 to 39 years}
  \item Wide recognition that age imperfectly defines of the “AYA oncology phenotype”
\end{itemize}
### PRINCIPLES OF SYSTEMIC THERAPY
#### INDUCTION REGIMENS FOR Ph-NEGATIVE ALL

**AYA Patients:**

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CALGB 10403 regimen: daunorubicin, vincristine, prednisone, and pegasparagase (ongoing study in patients aged &lt;40 years)</td>
</tr>
<tr>
<td>• COG AALL0232 regimen: daunorubicin, vincristine, prednisone, and pegasparagase (patients aged ≤21 years)</td>
</tr>
<tr>
<td>• COG AALL0434 regimen with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, and pegasparagase, nelarabine added to consolidation regimen</td>
</tr>
<tr>
<td>• DFCI ALL regimen based on DFCI Protocol 00-01: doxorubicin, vincristine, prednisone, high-dose methotrexate, and pegasparagase (ongoing study in patients aged &lt;50 years)</td>
</tr>
</tbody>
</table>

**Other Recommended Regimens**

- GRAALL-2005 regimen: daunorubicin, vincristine, prednisone, pegasparagase, and cyclophosphamide (patients aged <60 years), with rituximab for CD20-positive disease
- PHEMA ALL-96 regimen: daunorubicin, vincristine, prednisone, pegasparagase, and cyclophosphamide (patients aged <30 years)
- Hyper-CVAD ± rituximab: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; with or without rituximab for CD20-positive disease
- USC ALL regimen based on CCG-1882 regimen: daunorubicin, vincristine, prednisone, and methotrexate with augmented pegasparagase (patients aged 18–57 years)
- Linker 4-drug regimen: daunorubicin, vincristine, prednisone, and pegasparagase

---

### PRINCIPLES OF SYSTEMIC THERAPY
#### INDUCTION REGIMENS FOR Ph-POSITIVE ALL

**Protocols for AYA Patients:**

<table>
<thead>
<tr>
<th>Other Recommended Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• EsPhALL regimen: TKI + backbone of the Berlin-Frankfurt-Münster regimen (cyclophosphamide, vincristine, daunorubicin, dexamethasone, cytarabine, methotrexate, pegasparagase, and prednisone)</td>
</tr>
<tr>
<td>• TKI + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate, and cytarabine</td>
</tr>
<tr>
<td>• TKI + multiagent chemotherapy (daunorubicin, vincristine, prednisone, and cyclophosphamide)</td>
</tr>
<tr>
<td>• TKI + corticosteroid</td>
</tr>
<tr>
<td>• TKI + vincristine + dexamethasone</td>
</tr>
<tr>
<td>• CALGB 10701 regimen: TKI + multiagent chemotherapy (dexamethasone, vincristine, daunorubicin, methotrexate, etoposide, and cytarabine)</td>
</tr>
</tbody>
</table>

---
Case Presentation (continued)

• Initial treatment: standard induction for pediatric “high-risk” ALL
  – 4 weeks of vincristine, prednisone, PEG-asparaginase, daunorubicin, intrathecal methotrexate

• 7 days into treatment, genetic results are finalized
Question 2: Of the following leukemia-specific genetic abnormalities, which is MOST likely to be present in this patient?

a. 46,XX; FISH+ for ETV6-RUNX1 fusion
b. 46,XX,t(9;22)(q34;q11.2); FISH+ for BCR-ABL1 fusion; PCR+ for p190 BCR-ABL1
c. 52,XX,+4,+9,+10,+17,+18,+21 (high hyperdiploidy)
d. 46,XX,t(4;11)(q21;q23); FISH+ for KMT2A (MLL) rearrangement
e. 36,XX,-3,-7,-8,-9,-12,-14,-15,-18,-20,-21 (low hypodiploidy)
Frequency of Genetic Abnormalities by Age

Children
- Hyperdiploidy (>50) - 25%
- Hypodiploidy (<44) - 15%
- t(9;22)(q34;q11) BCR-ABL1 - 22%
- t(12;21)(p13;q22) ETV6-RUNX1 - 8%
- t(v;11q23) KMT2A-r - 26%
- BCR-ABL1-like - 3%
- Other - 1%

Adults
- Hyperdiploidy (>50) - 25%
- Hypodiploidy (<44) - 10%
- t(9;22)(q34;q11) BCR-ABL1 - 29%
- t(12;21)(p13;q22) ETV6-RUNX1 - 7%
- t(v;11q23) KMT2A-r - 2%
- BCR-ABL1-like - 25%
- Other - 2%
Case Presentation (continued)

- Patient confirmed to have diagnosis of B-ALL with BCR-ABL1 fusion
- Imatinib 400 mg daily added to induction chemotherapy beginning day 8 of induction
- End induction marrow
  - Complete morphologic remission
  - Flow cytometry for residual B-lymphoblasts and RT-PCR for BCR-ABL negative → no minimal residual disease (MRD negative)
- The patient’s brother is determined to be HLA-identical
Minimal Residual Disease (MRD) in ALL

• State of the art for risk stratification based on early response to therapy

• MRD is defined as the presence of cells following chemotherapy below the level of morphologic detection, generally down to 1/10,000 cells ($10^{-4}$)

• Flow cytometry and molecular (NGS, PCR) methods can be used to detect MRD

• In North America, flow is generally preferred over others, although NGS (ClonoSEQ) is gaining
• End induction MRD is a powerful and independent prognostic factor in ALL

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>P Value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 29 marrow MRD</td>
<td>4.31</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>NCI risk group</td>
<td>2.25</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Trisomy 4&amp;10</td>
<td>.570</td>
<td>.0005</td>
<td></td>
</tr>
<tr>
<td>Tel-AML1</td>
<td>.778</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Day 8 marrow morphology</td>
<td>1.034</td>
<td>.79</td>
<td></td>
</tr>
</tbody>
</table>

Case Presentation (continued)

- Patient proceeded to consolidation chemotherapy, consisting of cyclophosphamide, cytarabine, PEG-asparaginase and mercaptopurine (6MP)
- 3 weeks into consolidation, patient developed severe abdominal pain radiating to the back, anorexia, and nausea
- Workup revealed elevated serum amylase and lipase and enlarged pancreas on abdominal ultrasound (acute pancreatitis) and steroids
Question 3:
Which of the following medications is MOST likely to be responsible for the acute pancreatitis in this patient?

a. Cyclophosphamide
b. Cytarabine
c. 6MP
d. Vincristine
e. PEG-asparaginase
AYA ALL: Risk of Adverse Events

- **L-asparaginase preparations (PEG, Erwinia)**
  - Higher risk of toxicity in AYA compared with children (but less compared with older adults)
  - AEs: Pancreatitits, thrombosis (line-associated, sagittal sinus), hepatotoxicity, allergy

- **Corticosteroids**
  - High risk of osteonecrosis (hips, knees) in AYA patients relative to children and older adults

- **Mitigation**
  - Enhanced lab monitoring and high index of clinical suspicion
  - Anticoagulant prophylaxis for PEG-asparaginase (clinical trials ongoing)
Learning Objectives (How did we do?)

- Describe the AYA oncology patient, and recognize the challenges that have led to inferior outcomes in this group.
- Understand that optimal AYA ALL outcomes require treatment with “pediatric-inspired” treatment regimens.
- Know the difference in prevalence of sentinel genetic abnormalities in childhood vs AYA ALL.
- Understand the importance of minimal residual disease (MRD) in risk stratification in AYA ALL.
- Know that AYA patients are at higher risk of specific adverse events (AEs), and know the strategies to mitigate this risk.
Bispecific T-Cell Engagers as Post-reinduction Therapy Improves Survival in Pediatric and AYA B-ALL

Patrick Brown
A Randomized Phase 3 Trial of Blinatumomab Vs. Chemotherapy As Post-Reinduction Therapy in High and Intermediate Risk (HR/IR) First Relapse of B-ALL in Children and AYAs Demonstrates Superior Efficacy and Tolerability of Blinatumomab

A Report from Children’s Oncology Group Study AALL1331

Patrick A. Brown, Lingyun Ji, Xinxin Xu, Meenakshi Devidas, Laura Hogan, Michael J. Borowitz, Elizabeth A. Raetz, Gerhard Zugmaier, Elad Sharon, Lia Gore, James A. Whitlock, Michael A. Pulsipher, Stephen P. Hunger, Mignon L. Loh

Background

- Poor survival for first-relapse B-ALL in children, adolescents, and young adults (AYA), especially early relapses
- Standard treatment approach
  - Reinduction chemotherapy -> 2nd remission
  - Consolidation
    - Early relapse: Intensive chemo -> HSCT
      - Goal: MRD negativity prior to HSCT
    - Late relapse
      - “MRD high”: same as early
      - “MRD low”: intensive chemo -> maintenance therapy

Blinatumomab (CD19 BiTE)

- In multiply relapsed/refractory setting (pediatrics)
  - CR 35%–40%
  - MRD-negative CR 20%–25%

- In MRD+ setting (adults)
  - 80% MRD clearance
  - 60% subsequent DFS (bridge to HSCT)

Objective of COG AALL1331:
To determine if substituting blinatumomab for intensive consolidation chemotherapy improves survival in first relapse of childhood/AYA B-ALL

Adapted from Brown P. Blood. 2018; 131: 1497–1498

von Stackelberg et al. JCO. 2016; 34:4381-4389

Gokbuget et al. Blood. 2018; 131: 1522-1531
First Relapse B-ALL

- All first relapse (any CR1 duration, any site)
- Ages 1-30
- Major exclusions: Down syndrome, Ph+, prior HSCT, prior blinatumomab

Block 1

Risk Assignment

UKALLR3, Mitoxantrone Arm*
- DEX 20 mg/m²/day D1-5, 15-19
- VCR 1.5 mg/m² D1, 8, 15, 22
- PEG 2500 IU/m² D3, 17
- Mitoxantrone 10 mg/m² D1, 2
- IT MTX D1, then IT MTX or ITT

Treatment Failure

- M3 (≥25% blasts) and/or
- Failure to clear EM

Refractory

High Risk
- iBM or combined BM + EM
  - CR1 <36 mo or
  - iEM
  - CR1 <18 mo

Late relapse

Intermediate Risk
- iBM or combined M + EM
  - CR1 ≥36 mo and
  - EB1 MRD ≥0.1% EOI

Early relapse

Low Risk
- iBM or combined BM + EM
  - CR1 ≥36 mo
- iEM
  - CR1 ≥18 mo

Late relapse

HR/IR


**Stratifications**
- Risk group (HR vs IR)
- For HR
  - Site (BM vs iEM)
  - For BM: CR1 duration (<18 vs 18-36 mo)

**UKALLR3, Block 2***
- VCR, DEX week 1
- ID MTX, PEG week 2
- CPM/ETOP week 3
- IT MTX or ITT

**UKALLR3, Block 3***
- VCR, DEX week 1
- HD ARAC, *Erwinia* weeks 1-2
- ID MTX, *Erwinia* week 4
- IT MTX or ITT


**Endpoints**
- Primary: DFS
- Other: OS, MRD response, ability to proceed to HSCT

**Sample size n=220 (110 per arm)**
- Power 85% to detect HR 0.58 with 1-sided $\alpha=0.025$
- Increase 2-yr DFS from 45% to 63%

**First patient randomized Jan 2015**
**Randomization halted Sep 2019 (95% projected accrual)**

**Blina C1 and Blina C2**
- Blinatumomab $15 \mu g/m^2/\text{day} \times 28$ days, then 7 days off
- Dex $5 \mu g/m^2/\text{dose} \times 1$ premed (C1 only)

Early Closure Recommended by DSMC

• Scheduled review by DSMC Sep 2019 using data cutoff 6/30/2019 (~60% of projected events)

• Despite the monitoring threshold for DFS not being crossed, the DSMC recommended
  • Permanent closure of accrual to HR/IR randomization
  • Immediate crossover to experimental Arm B for patients still receiving therapy

• DSMC recommendation based on
  • The difference in **DFS and OS** between arms
  • The profound difference in **toxicity** between arms
  • The highly significant difference in **MRD** clearance rates between arms

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Arm A (n = 103)</th>
<th>Arm B (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at enrollment, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>9 (1-27)</td>
<td>9 (1-25)</td>
</tr>
<tr>
<td>1-9</td>
<td>55 (53%)</td>
<td>55 (52%)</td>
</tr>
<tr>
<td>10-17</td>
<td>30 (29%)</td>
<td>35 (33%)</td>
</tr>
<tr>
<td>18-30</td>
<td>18 (18%)</td>
<td>15 (14%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>49 (48%)</td>
<td>48 (46%)</td>
</tr>
<tr>
<td>Male</td>
<td>54 (52%)</td>
<td>57 (54%)</td>
</tr>
<tr>
<td><strong>NCI risk group at diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>60 (58%)</td>
<td>59 (56%)</td>
</tr>
<tr>
<td>Standard risk</td>
<td>43 (42%)</td>
<td>46 (44%)</td>
</tr>
<tr>
<td><strong>Cytogenetic groups at diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable (Tri 4/10, ETV6-RUNX1)</td>
<td>16 (18%)</td>
<td>21 (23%)</td>
</tr>
<tr>
<td>KMT2A rearranged</td>
<td>9 (10%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Hypodiploidy</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>65 (71%)</td>
<td>63 (69%)</td>
</tr>
<tr>
<td>None</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>
## Randomization Stratification Factors

<table>
<thead>
<tr>
<th>Stratification Factors</th>
<th>Arm A (n=103)</th>
<th>Arm B (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Group Assignment After Block 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk (late relapse, MRD high)</td>
<td>34 (33%)</td>
<td>36 (34%)</td>
</tr>
<tr>
<td>High risk (early relapse)</td>
<td>69 (67%)</td>
<td>69 (66%)</td>
</tr>
<tr>
<td><strong>High-Risk Subsets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Marrow, CR1 &lt;18 months (very early)</td>
<td>18 (26%)</td>
<td>18 (26%)</td>
</tr>
<tr>
<td>• Marrow, CR1 18-36 months (early)</td>
<td>41 (59%)</td>
<td>41 (59%)</td>
</tr>
<tr>
<td>• IEM, CR1 &lt;18 months</td>
<td>10 (14%)</td>
<td>10 (14%)</td>
</tr>
</tbody>
</table>
Survival: Arm A (chemotherapy) vs Arm B (blinatumomab)

Median follow-up 1.4 years

Adverse Events

• N = 4 postinduction Grade 5 AEs on Arm A (all infections)
• N = 0 on Arm B
• Ages of Arm A deaths: 2, 17, 23, and 26 years old (AYA-skewed)
• NOTE: AE rates significantly higher in AYA (Hogan, et al. ASH Abstract 2018)

# Blinatumomab-Related AEs on Arm B

<table>
<thead>
<tr>
<th>Blinatumomab-Related AEs</th>
<th>Blina C1 (n = 99)</th>
<th></th>
<th>Blina C2 (n = 83)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade (%)</td>
<td>Grade 3-4 (%)</td>
<td>Any Grade (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>22%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>18%</td>
<td>3%</td>
<td>11%</td>
<td>2%</td>
</tr>
<tr>
<td>Seizure</td>
<td>4%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Other (encephalopathic)</td>
<td>14%</td>
<td>2%</td>
<td>11%</td>
<td>2%</td>
</tr>
</tbody>
</table>

MRD Clearance (for iBM and BM+EM)

Arm A (n=96)

- End B1: 22% MRD positive, 76% MRD negative
- End B2: 19% MRD positive, 52% MRD negative
- End B3: 14% MRD positive, 53% MRD negative

p = 0.65

Arm B (n=95)

- End B1: 18% MRD positive, 81% MRD negative
- End BlinC1: 8% MRD positive, 76% MRD negative
- End BlinC2: 15% MRD negative

p < 0.0001

No data (off protocol)
MRD positive
MRD negative
Dropout/HSCT Rates: Arm A vs Arm B

A significant contributor to the improved outcomes for Arm B (blina) vs Arm A (chemo) in HR/IR relapses may be the ability of blinatumomab to successfully bridge to HSCT.

Conclusions

- For children and AYA patients with HR/IR first relapse of B-ALL, blinatumomab is superior to standard chemotherapy as post-reinduction consolidation prior to HSCT, resulting in
  - Fewer and less severe toxicities
  - Higher rates of MRD response
  - Greater likelihood of proceeding to HSCT
  - Improved disease-free and overall survival
- Blinatumomab constitutes a new standard of care in this setting
- Future: Optimizing immunotherapy in relapsed ALL
  - Combination of blinatumomab and checkpoint inhibitors
  - Immunotherapy to replace or augment reinduction chemotherapy
  - CAR T cells to replace or augment HSCT

Multiple Choice Question 1

Which of the following is NOT true of blinatumomab relative to chemotherapy as post-reinduction therapy for HR/IR first relapse of pediatric ALL?

a) Lower rate of clearance of residual disease
b) Lower rate of serious adverse events
c) Lower rate of relapse
d) Higher rate of proceeding to HSCT
AALL1331 Study Committee

- **Chair**: Pat Brown
- **Vice Chair**: Jim Whitlock
- **Stats**: Lingyun Ji, Mini Devidas
- **Heme/Onc**
  - Lia Gore
  - Laura Hogan
  - Terzah Horton
  - Stevie “Nix” Hunger
  - Kala Kamdar
  - Mignon Loh
  - Jen McNeer
  - Maureen O'Brien
  - Mike Pulsipher
  - Sue Rheingold
  - Teena Bhatla
  - Sarah Tasian
  - Richard Tower

- **Lab/Path**
  - Mike Borowitz
  - Andrew Carroll
  - Fady Mikhail
  - Julie Gastier-Foster

- **Rad Onc**: Stephanie Terezakis

- **Pharmacy**
  - Brooke Bernhardt
  - Olga Militano

- **CRA**: Christopher Henchen

- **Nursing**
  - Deb Schissel
  - Susan Zupanec

- **Research Coordinator**: Susan Conway, Don Sortillon, Naira Setrakian

- **Protocol Coordinator**: Rachel Vasquez

Funding

• NCTN Operations Center Grant U10CA180886
• NCTN Statistics & Data Center Grant U10CA180899
• St. Baldrick’s Foundation
• Blinatumomab provided by Amgen via Collaborative Research and Development Agreement (CRADA) with NCI/CTEP

Questions?
Panel Discussion on the Role of HSCT
Experience of HSCT in the Region

Eduardo Rego
HSCT IN BRAZIL

Eduardo M. Rego
University of São Paulo
Oncologia D’Or
Number of Transplants per Year (2009–2019)

- Bone
- Cornea
- HSCT
- Skin

Number of Transplants
Overall Survival

Curva de Sobrevida: Registro iniciado em 01/01/2010
(Medula Óssea)

- AUTOLOGOUS
- RELATED
- UNRELATED

Transplantes Autólogo: 8.514
Transplantes Alogénico
Aparentado: 3.908
Não aparentado: 1.404

Sobrevivência paciente
1º ano 2º ano 3º ano 4º ano 5º ano 6º ano 7º ano 8º ano

- Autólogo 86% 81% 77% 73% 70% 68%
- Aparentado 62% 55% 53% 50% 48% 47%
- Não Aparentado 57% 51% 49% 46% 44% 44%
**Country-Level Macroeconomic Indicators Predict Early Post-Allogeneic Hematopoietic Cell Transplantation Survival in Acute Lymphoblastic Leukemia: a CIBMTR Analysis**

### Effect of Human Expenditure per Capita and Human Development Index on the Number of HSCT

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 4 (&gt;55904)</td>
<td>8714</td>
</tr>
<tr>
<td>Quartile 3 (52508-55903)</td>
<td>864</td>
</tr>
<tr>
<td>Quartile 2 (5797-52507)</td>
<td>1413</td>
</tr>
<tr>
<td>Quartile ≤797</td>
<td>249</td>
</tr>
</tbody>
</table>

### Effect of Human Expenditure per Capita and Human Development Index on 100-day Overall Survival Following Allogeneic HCT for ALL*

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 4 (&gt;5094)</td>
<td>8714</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 3 (52508-55903)</td>
<td>864</td>
<td>1.25</td>
<td>0.97-1.62</td>
<td>0.0872</td>
</tr>
<tr>
<td>Quartile 2 (5797-52507)</td>
<td>1413</td>
<td>1.45</td>
<td>0.82-2.55</td>
<td>0.2032</td>
</tr>
<tr>
<td>Quartile ≤797</td>
<td>249</td>
<td>1.56</td>
<td>1.11-2.18</td>
<td>0.0098</td>
</tr>
</tbody>
</table>

### Human Development Index

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 4 (&gt;0.913)</td>
<td>8937</td>
</tr>
<tr>
<td>Quartile 3 (0.8806-0.912)</td>
<td>1092</td>
</tr>
<tr>
<td>Quartile 2 (0.780-0.8805)</td>
<td>528</td>
</tr>
<tr>
<td>Quartile 1 (&lt;0.780)</td>
<td>698</td>
</tr>
</tbody>
</table>

Brazil’s HDI = 0.76
Brazil HEPC = US $1318.00

In all multivariable models, other statistically significant associations were seen for the following variables: age, ALL subtype, time from diagnosis to HCT, KPS, conditioning regimen intensity, and year of treatment.

Regarding causes of death in the first 100 days after 100 days of HSCT, which statement is true?

a. The leading cause of death among patients who submit to HSCT for ALL in high-income countries (HIC) is GVHD
b. The leading cause of death among patients who submit to HSCT for ALL in intermediate-income countries is organ toxicity
c. There is no difference in the incidence of death due to graft-failure between HIC and low-income countries (LIC)
d. Unknown causes of death are approx 2-fold higher in LIC/MIC compared with HIC
Causes of Death by Country-Level GNI Grouping

QUESTION 1: DO PATIENTS HAVE ACCESS TO STEM CELL TRANSPLANT IN YOUR REGION?

a. Yes
b. No
c. It depends on their financial situation
QUESTION 2: WHAT PROPORTION OF YOUR PATIENTS WITH NEWLY DIAGNOSED ALL ARE TRANSPLANT ELIGIBLE?

a. 0%–20%
b. 21%–40%
c. 41%–60%
d. 61%–80%
e. 81%–100%
QUESTION 3: WHAT PROPORTION OF YOUR TRANSPLANT-ELIGIBLE PATIENTS WILL RECEIVE TRANSPLANT?

a. 0%–20%
b. 21%–40%
c. 41%–60%
d. 61%–80%
e. 81%–100%
Pros and Cons of HSCT, COVID-19 Impact and Measures

Aaron Logan
Pros and Cons of Hematopoietic Cell Transplantation in ALL

Aaron Logan, MD, PhD
UCSF Division of Malignant Hematology and Blood and Marrow Transplantation

aaron.logan@ucsf.edu

@hemedoc
Relapsed/Refractory ALL is associated with poor prognosis

Transplant improves survival in relapsed ALL

UKALL12/ECOG 2993

GMALL 06/99 and 07/03

Transplant

No transplant


Survival after HLA-Matched Sibling Donor HCT for ALL, Age ≥18 Years, 2007-2017

- Early (n=3,264)
- Intermediate (n=877)
- Advanced (n=386)

p<0.001
Survival after Unrelated Donor HCT for ALL, ≥18 Years, 2007-2017

- Early (n=4,025)
- Intermediate (n=1,570)
- Advanced (n=567)

p<0.001
Trends in Survival after Allogeneic HCT for ALL, ≥18, 2001-2017

- 2001-2005 (n=4,087)
- 2006-2010 (n=4,352)
- 2011-2017 (n=8,272)

p<0.0001

Years

Probability, %

0 20 40 60 80 100

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
Selected Disease Trends for Allogeneic HCT in the US

Number of Transplants

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Allogeneic HCT Recipients in the US, by Donor Type

- URD-BM/PB, HLA-matched
- HLA-identical sibling
- Other relative, ≥2 HLA antigen mismatch
- URD-BMPB, HLA mismatch unknown
- URD-CB
- HLA-matched other relative
- Other relative, 1 HLA antigen mismatch
- URD-BMPB, HLA match unknown

Number of Transplants

- MUD
- Matched related
- HaploHCT
Haploidentical HCT Recipients in the US, by Disease

- AML
- ALL
- Lymphoma
- MDS / MPN
- Non-malignant disease*

*Not including aplastic anemia.

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In ALL CR1, HaploHCT associated with outcomes similar to MUD: EBMT

HaploHCT for ALL associated with favorable outcomes in Argentina
Indications for alloHCT in ALL

- Ph+ (?) — probably can avoid in most using ponatinib
- Ph-like lesions
- MLL/KMT2A rearrangements
- MRD >10^-4 after 1–3 cycles of chemotherapy
- All in CR2+
HyperCVAD + ponatinib for Ph+ ALL: Long-term results

<20% went to alloHCT

Indications for alloHCT in ALL

- Ph+ (probable can avoid in most using ponatinib)
- Ph-like lesions
- *MLL/KMT2A* rearrangements
- MRD >10⁻⁴ after 1–3 cycles of chemotherapy
- All in CR2+
MRD status pre-HCT predicts outcome of transplant

N = 82, age <1–20
MRD by ASO-PCR
Median f/u 4.9 yr

HCT in CR1 if
• Day +78: >5 × 10^{-4} MRD
• Induction failure
• Ph+, MLL+
• T-lin w/WBC >100K

HCT for all CR2+

Pre-HCT MRD

MRD status pre/post-HCT predicts RFS and OS

N = 43, age 18–63
MAC alloHCT in CR1

MRD quant: TCR/Ig ASO-PCR or BCR/ABL or MLL/AF4 Q-PCR

Screening and enrollment

- MRD $\geq 10^{-3}$ (0.1%) with minimum sensitivity $10^{-4}$ after $\geq 3$ blocks of intensive chemotherapy

Blinatumomab 15 $\mu$g/m$^2$/day cIV infusion for 4 wk
Inpatient treatment days 1–3
MRD assessment on day 29
Treatment-free period for 2 wk

2-yr efficacy/
5-yr survival follow-up

Up to 4 cycles

HSCT for suitable patients after at least 1 treatment cycle, per investigator recommendation

- N = 116
- Median age 45 (18–76)
- CR1 65%

Blinatumomab BLAST trial: Preemption of B-ALL relapse using MRD-directed treatment

Screening and enrollment

- MRD $\geq 10^{-3}$ (0.1%) with minimum sensitivity $10^{-4}$ after $\geq 3$ blocks of intensive chemotherapy

Blinatumomab 15 $\mu$g/m$^2$/day cIV infusion for 4 wk
- Inpatient treatment days 1–3
- MRD assessment on day 29
- Treatment-free period for 2 wk

Up to 4 cycles

- 2-yr efficacy/
- 5-yr survival follow-up

- HSCT for suitable patients after at least 1 treatment cycle, per investigator recommendation

- N = 116
- Median age 45 (18–76)
- CR1 65%

** 75% underwent alloHCT **

Blinatumomab BLAST trial: Preemption of B-ALL relapse using MRD-directed treatment – results


1. Patients in 1st CR (n = 75); median: 36.5 (95% CI: 20.6-NR)
2. Patients in 2nd or 3rd CR (n = 41); median: 19.1 (95% CI: 11.9-NR)

Patients at Risk, n
1: 75 74 67 62 60 56 43 34 32 27 23 17 9 5 5 3 3 1 0
2: 41 39 36 29 27 25 20 14 13 11 9 8 7 5 2 1 1 0

OS Probability

Mos

+ Censored

1: Patients in 1st CR (n = 75); median: 36.5 (95% CI: 20.6-NR)
2: Patients in 2nd or 3rd CR (n = 41); median: 19.1 (95% CI: 11.9-NR)
Blinatumomab BLAST trial: Long-term outcomes

Management of adult ALL patients in first complete remission

**Good risk**
- No high-risk lesions
- MRD– <10^{-4}

**High risk**
- Ph+ (avoid HCT with ponatinib?)
- Ph-like
- MLL rearranged
- MRD+ >10^{-4}

**Continue chemotherapy consolidation and maintenance**

**Converts to MRD+**
- MRD–
  - AlloHCT
- MRD+
  - Blinatumomab -> AlloHCT

**HCT eligible**
- Continue consol/maint

**HCT ineligible**
- MRD–
  - Continue consol/maint
- MRD+
  - Blinatumomab -> maintenance
Pros and cons of HCT in ALL: Summary

• The substantial toxicities of transplant require judicious use of this treatment modality; however, there is not yet a therapy to replace transplant for high-risk patients

• All patients with relapsed ALL should be considered for alloHCT

• For patients in CR1, alloHCT may be considered for those with MRD >10^{-4} after 1–3 cycles of therapy or high-risk genetic lesions (eg, Ph-like, MLL)

• Patients with Ph+ ALL may be able to avoid alloHCT with ponatinib

• The presence of MRD prior to alloHCT is associated with high relapse risk. Blinatumomab as bridge to HCT should be considered
Considerations for ALL patients in COVID-19 era

Considerations for ALL patients in COVID-19 era

- COVID-19 testing recommended prior to starting chemotherapy cycles. Patients presenting with newly diagnosed ALL and COVID positivity with mild-moderate symptoms should receive standard therapy with curative intent. In those with respiratory failure, consider dexamethasone-vincristine to temporize.
- In general, it is prudent to NOT delay alloHCT, given the logistics involved and curative nature of the therapy for those with high-risk disease.
- Treatment for ALL must be timely and uninterrupted, since relapsed disease is difficult to recapture. Consider blinatumomab as bridge to transplant if delay needed.
- The ramifications of SARS-CoV-2 infection during the course of immunotherapies such as blinatumomab and CAR T cells remain to be determined.
- ALL patients may not develop protective immunity to SARS-CoV-2 from natural infection or vaccination (when available).
Considerations for ALL patients in COVID-19 era

www.hematology.org/covid-19

- COVID-19 and Aggressive Non-Hodgkin Lymphoma (Version 3.0; last updated June 15, 2020)
- COVID-19 and Acute Lymphoblastic Leukemia - Adult (Version 1.1; last reviewed June 4, 2020)
- COVID-19 and Acute Lymphoblastic Leukemia - Pediatric (Version 2.0; last updated June 15, 2020)
- COVID-19 and Acute Myeloid Leukemia (Version 1.2; last reviewed June 4, 2020)
- COVID-19 and Chronic Lymphocytic Leukemia (Version 2.0; last updated June 9, 2020)
- COVID-19 and Chronic Myeloid Leukemia (Version 1.2; last updated July 20, 2020)
- COVID-19 and Hodgkin Lymphoma (Version 3.0; last updated June 15, 2020)
- COVID-19 and Indolent Lymphomas (Version 3.0; last updated June 15, 2020)
- COVID-19 and Myelodysplastic Syndromes (Version 3.1; last updated June 8, 2020)
- COVID-19 and Myeloproliferative Neoplasms (Version 3.0; last updated July 20, 2020)
- COVID-19 and Multiple Myeloma (Version 1.2; last updated July 21, 2020)
- COVID-19 and HCT (Version 1.0; last updated July 20, 2020)
Thank you!
Panel Discussion on the Role of HSCT: Discussion and Voting
Question 1

In your practice, what is the most important factor for deciding ineligibility for HSCT?

a) Age ≥65 years
b) Frailty
c) Comorbidities
Question 2

Do you think that MRD can guide your decision on HSCT?

a) Yes, as patients who achieve MRD negativity are on the way to cure and do not require HSCT

b) No, as HSCT is the SOC today and should be part of the treatment algorithm of patients independently of MRD

c) I do not know
Question 3

What are the factors influencing the increased probability of relapse post-HSCT?

a) Disease status
b) Chemosensitivity at the time of transplantation
c) Development of graft-vs-host disease
d) All of the above
e) None of the above
Debate on CD19-Targeted Approaches
Question 1

What is your preferred ALL treatment choice in salvage if all these therapies were made available in your country?

a) CAR T therapies

b) Monoclonal antibodies or bispecifics
Question 2

Do you think that children and young adults with active nonbulky CNS disease can safely be treated with CD19 CAR T cells?

a) Yes
b) No
c) I do not know
Question 3

What advantages do you see in bispecifics vs CAR T cells?

a) Readily available off the shelf
b) Dosing can be easily interrupted in case of toxicity
c) Can be combined with chemotherapy
d) I do not know
Debate on CD19-Targeted Approaches: CAR T

Patrick Brown
Debate on CD19-targeted approaches:

CAR T cells

Patrick Brown, MD
Director, Pediatric Leukemia Program
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Chair, NCCN ALL Guidelines Committee
### Setting up the debate: Some factors to be considered

<table>
<thead>
<tr>
<th>Factor</th>
<th>CAR T</th>
<th>BiTE</th>
<th>ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial response rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durability of response</td>
<td></td>
<td></td>
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</tr>
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<td>Need for HSCT as consolidation</td>
<td></td>
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<tr>
<td>Adverse event profile</td>
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</tr>
<tr>
<td>Ease of administration</td>
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<tr>
<td>Timing of administration</td>
<td></td>
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<td></td>
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<tr>
<td>Resource intensity</td>
<td></td>
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<tr>
<td>Others?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Response rates and survival in relapsed/refractory B-ALL

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type</th>
<th>Target</th>
<th>Responses (CR/MRD–)</th>
<th>Toxicities</th>
<th>FDA indication</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinatumomab</td>
<td>BiTE</td>
<td>CD19</td>
<td>44%/33%</td>
<td>CRS, neurotoxicity</td>
<td>Adult and pediatric R/R B-ALL, MRD+</td>
<td>$180K</td>
</tr>
<tr>
<td>Inotuzumab</td>
<td>Immuno-conjugate</td>
<td>CD22</td>
<td>81%/63%</td>
<td>Hepatotoxicity</td>
<td>Adult R/R B-ALL</td>
<td>$168K</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>CAR T cell</td>
<td>CD19</td>
<td>81%/81%</td>
<td>CRS, neurotoxicity</td>
<td>Refractory or 2nd/greater relapse; age up to 26 years</td>
<td>$475K</td>
</tr>
</tbody>
</table>
Durable survival improvement, but long-term EFS is in the 50% range; failures include
- Failed manufacture
- No response
- Loss of B-cell aplasia +/- CD19+ relapse
- CD19 escape
Survival in R/R ALL

Blina: improved survival initially, but not durable

Survival in R/R ALL

Ino: improved survival initially, but not durable

Early clearance of the leukemic clone by HTS associated with better outcome


Median OS: 26.9 vs 6.8 months
HSCT after CAR T?

AlloHSCT in MRD– patients after CAR T


<table>
<thead>
<tr>
<th>Agent</th>
<th>Type</th>
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<td>CRS, neurotoxicity</td>
<td>Refractory or 2nd/greater relapse; age up to 26 years</td>
<td>$475K</td>
</tr>
</tbody>
</table>

Adverse events in relapsed/refractory B-ALL
AEs after CAR T cells or blinatumomab

- CRS 40%–80% (20%–40% Gr3+), Neuro 10%–30% (5%–10% Gr3+)

Incidence of CRS strikingly lower in MRD+ setting; neurotox is similar

Adapted from/courtesy of Novartis.
CAR T-cell process:
A multistep treatment process involving many stakeholders

Adapted from/courtesy of Novartis.
CAR T-cell treatment schema

- **Screening**
- **Leukapheresis**
- **Conditioning Chemotherapy**
- **CAR T-Cell Infusion**
- **First Tumor Assessment**

- **Day 0**
- **Day −5**
- **Day 7**
- **Day 30**

**Manufacturing** 6–10 Days (3 weeks door-to-door)
**Close Monitoring** 7–21 Days
**Follow-up Period** (post-treatment assessment and long-term follow-up)

Adapted from/courtesy of Kite.
CAR T cells: Putting the plan into practice

- Insurance approval
- Schedule pheresis
  - Surgery – Shiley catheter
  - Pheresis team
  - Cell therapy laboratory
- Local housing
- Appropriate central venous access
- Bridging chemotherapy
- CAR T-cell infusion
- Follow-up
Setting up the debate: Some factors to be considered . . .

<table>
<thead>
<tr>
<th>Factor</th>
<th>CAR T</th>
<th>BiTE</th>
<th>ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial response rate</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durability of response</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for HSCT as consolidation</td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event profile</td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ease of administration</td>
<td>✗</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing of administration</td>
<td>✗</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resource intensity</td>
<td>✗</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Overcoming failures

• Failure to manufacture (CAR): infants, heavily pretreated
  – Optimizations (earlier pheresis, improved ex vivo techniques)
  – Universal CAR T cells (using TALEN/CRISPR gene editing)
    • *Would also address ease/access

• Failure to engraft or lack of persistence (CAR)
  – Optimizations
    • Co-stimulatory domains (4-1BB vs CD28, for example)
    • T-APCs
      • Fully humanized CAR T cells
  – Checkpoint inhibitors (anti–PD-1, PD-L1)

• Antigen escape: multi-antigen targeting
Can use of immunotherapy in ALL be expanded?

• For B-ALL, earlier in disease course?
  – First relapse?
  – First remission with persistent MRD?
  – Upfront?

• T-ALL/Lly?
Where are CAR T cells in NCCN adult ALL guidelines?

NCCN Guidelines Version 1.2020
Acute Lymphoblastic Leukemia

RELAPSED/REFRACTORY DISEASE

**Ph+ ALL (AYA & Adult)**
- ABL1 kinase domain mutation testing
- Molecular characterization and MRD assessment, if not previously done (see ALL-1)

**Ph- ALL (AYA & Adult)**

TREATMENT

**Clinical trial**
- TKI ± chemotherapy or TKI ± corticosteroid
- Blinatumomab (TKI intolerant/refractory, B-ALL)
- Inotuzumab ozogamicin (TKI intolerant/refractory, B-ALL)

**Consider HCT**

**Tisagenlecleucel** (patients <26 y and with refractory B-ALL disease or ≥2 relapses and failure of 2 TKIs)

**Clinical trial**
- Blinatumomab (B-ALL) (category 1)
- Inotuzumab ozogamicin (B-ALL) (category 1)

**Consider HCT**
Where are CAR T cells in NCCN pediatric ALL guidelines?
Where are CAR T cells in NCCN pediatric ALL guidelines?
Where are CAR T cells in NCCN pediatric ALL guidelines?
Where are CAR T cells in NCCN pediatric ALL guidelines?
Debate on CD19-Targeted Approaches: Monoclonal Antibodies and Bispecifics

Elias Jabbour
### Historical Results in R-R ALL

- Poor prognosis in R-R ALL Rx with standard of care (SOC) chemotherapy

<table>
<thead>
<tr>
<th>Rate (95% CI)</th>
<th>No Prior Salvage (S1)</th>
<th>1 Prior Salvage (S2)</th>
<th>≥2 Prior Salvages (S3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of CR, %</td>
<td>40</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>5.8</td>
<td>3.4</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Blinatumomab vs Chemotherapy in R-R ALL

Median OS (95% CI):
- Blinatumomab, 7.7 months (5.6–9.6)
- SOC, 4.0 months (2.9–5.3)

Stratified log-rank $P = .012$
Hazard ratio: 0.71 (0.55–0.93)

Phase III TOWER Study: Survival by Salvage

K-M Median (95% CI), months
- S1: Blinatumomab 11.1 (8.2, NR)
- S1: SOC chemotherapy 5.5 (3.7, 9.0)
- S2+: Blinatumomab 5.1 (3.2, 7.1)
- S2+: SOC chemotherapy 3.0 (2.1, 4.0)

S1: Stratified log-rank P = 0.016
S2+: Stratified log-rank P = 0.055

Survival Probability

Patients at risk:
- S1: Blinatumomab 104
  - S1 SOC 63
  - S2+: Blinatumomab 167
  - S2+: SOC 71

Months

+ Censored NR = not reached

61 patients evaluated for immunophenotype; 56 (92%) had CD19+ disease
- 5 (8%) had ALL recurrence with CD19– disease
- 2 patients progressed with lower CD19+ disease
OS After Censoring

AlloSCT Post-inotuzumab in R-R ALL

- 236 pts Rx with inotuzumab; 103 (43%) alloSCT
- Ino as S1 in 62%; prior SCT 15%
- Median OS post-SCT 9.2 mo; 2-yr OS 46%
- 73 pts had alloSCT in CR post-Ino: 2-yr OS 51%
- VOD 19/101 = 20%
- Lower risk of mortality post-HSCT associated with MRD negativity and no prior HSCT

Phase II Study of Inotuzumab in R-R Children-AYA ALL (COG ALL0232)

- 48 pts; median age 9 yr (1–21). S2+ 67%. Prior blina 29%; prior alloSCT 23%; prior CAR T 23%
- Inotuzumab weekly × 3: 0.8–0.5 mg/m² D1, 0.5 mg/m² D8 and D15. Total 1.8–1.5 mg/m²/course, up to 6 courses
- CR/CRi 30/48 (62%), MRD– 19/29 (65%)
- 12-mo EFS 36%; 12-mo OS 40%
- 19 pts (39%) received alloSCT
- 5 VOD (10.4%): all post-SCT: 5/19 (26%)

Mini-HCVD–Ino–Blina in ALL: Design

- Dose-reduced hyperCVD for 4–8 courses
  - Cyclophosphamide (150 mg/m² × 6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m²) 75% dose reduction
  - Cytarabine (0.5 g/m² × 4) 83% dose reduction
- Inotuzumab on D3 (first 4 courses)
  - Modified to 0.9 mg/m² C1 (0.6 and 0.3 on D1 and 8) and 0.6 mg/m² C2–4 (0.3 and 0.3 on D1 and 8)
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- Blinatumomab 4 courses and 3 courses during maintenance
- POMP maintenance for 3 years, reduced to 1 year

Mini-HCVD + Ino ± Blinatumomab in R-R ALL: Modified Design

Intensive phase

Consolidation phase

Maintenance phase

Ino

Total Dose (mg/m²)

Dose per Day (mg/m²)

C1
0.9
0.6 D1, 0.3 D8

C2–4
0.6
0.3 D1 and D8

Total Ino dose = 2.7 mg/m²

Min-HCVD + Ino ± Blinatumomab in R-R ALL: Response by Salvage (N = 96)

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvage 1</td>
<td>58/64</td>
<td>91</td>
</tr>
<tr>
<td>S1, primary refractory</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>S1, CRD1 &lt;12 mo</td>
<td>21</td>
<td>84</td>
</tr>
<tr>
<td>S1, CRD1 ≥12 mo</td>
<td>29</td>
<td>94</td>
</tr>
<tr>
<td>Salvage 2</td>
<td>11</td>
<td>61</td>
</tr>
<tr>
<td>Salvage ≥3</td>
<td>8</td>
<td>57</td>
</tr>
<tr>
<td>Overall</td>
<td>77</td>
<td>80</td>
</tr>
<tr>
<td>MRD−</td>
<td>62/75</td>
<td>83</td>
</tr>
<tr>
<td>Salvage 1</td>
<td>50/56</td>
<td>89</td>
</tr>
<tr>
<td>Salvage ≥2</td>
<td>12/19</td>
<td>63</td>
</tr>
<tr>
<td>Early death</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Mini-HCVD + Ino ± Blinatumomab in R/R ALL: CR Duration and OS (median F/U 48 months)

Mini-HCVD + Ino ± Blinatumomab in R/R ALL: Historical Comparison

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Event</th>
<th>2-year OS</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCVD+Ino±Rtx±Blina</td>
<td>96</td>
<td>63</td>
<td>39%</td>
<td>13 mos</td>
</tr>
<tr>
<td>Ino single agent</td>
<td>89</td>
<td>79</td>
<td>17%</td>
<td>6 mos</td>
</tr>
</tbody>
</table>

Mini-HCVD + Ino ± Blinatumomab in R/R ALL: OS by Salvage Status

<table>
<thead>
<tr>
<th>Total</th>
<th>Event</th>
<th>2-year OS</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>65</td>
<td>38</td>
<td>46%</td>
</tr>
<tr>
<td>S2</td>
<td>17</td>
<td>15</td>
<td>18%</td>
</tr>
<tr>
<td>S3+</td>
<td>14</td>
<td>10</td>
<td>34%</td>
</tr>
</tbody>
</table>

p=0.007

Mini-HCVD + Ino ± Blina in ALL: VOD

- N = 96 pts
  - 67 pts Rx monthly InO; of them, 22 (33%) received subsequent alloSCT
  - 29 pts Rx weekly low-dose InO followed by Blina; of them, 15 (52%) received subsequent alloSCT

- VOD = 9 (9%); all had at least 1 alloSCT, 3 had 2 alloSCT
  - 9/67 (single; 13%) vs 0/29 (weekly LD; 0%)
Where Does CAR T-Cell Therapy Stand?

ELIANA Trial Update

- 113 screened, 97 enrolled, 79 infused
- 3-mo CR 65/79 = 82%, or 65/97 = 67%
- 24-mo OS 66%; RFS 62%. Grade 3–4 CRS 49%. ICU 48%
CD19-CD28z CAR (MSKCC): Outcome by Tumor Burden

- **High tumor burden**
  - Bone marrow blasts $\geq 5\%$ (n = 27)
  - Bone marrow blasts <5% + extramedullary disease (n = 5)
- **Low tumor burden (MRD+ disease; n = 21)**

---

**Event-free Survival, According to Disease Burden**

<table>
<thead>
<tr>
<th>Months since T-Cell Infusion</th>
<th>Low disease burden</th>
<th>High disease burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>10</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>20</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>30</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>40</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>50</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
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*P* = 0.01

**Overall Survival, According to Disease Burden**

<table>
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<tr>
<td>50</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*P* = 0.02

---

**Median EFS**
- Low tumor burden (MRD+): 10.6 mo
- High tumor burden: 5.3 mo

**Median OS**
- Low tumor burden (MRD+): 20.1 mo
- High tumor burden: 12.4 mo

---

## Adult R-R ALL: CAR T vs MoAb

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HCVD-Ino-Blina</th>
<th>MSKCC (R-R)</th>
<th>MSKCC (MRD)</th>
<th>Blina (MRD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>ITT</td>
<td>Evaluable</td>
<td></td>
<td>ITT</td>
</tr>
<tr>
<td>ORR, %</td>
<td>78</td>
<td>75</td>
<td>95</td>
<td>NA</td>
</tr>
<tr>
<td>MRD–, %</td>
<td>83</td>
<td>67</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>14</td>
<td><strong>12.4</strong></td>
<td><strong>20.1</strong></td>
<td><strong>36</strong></td>
</tr>
<tr>
<td>Salvage 1, mo</td>
<td><strong>25</strong></td>
<td>Not reported</td>
<td>Not reported</td>
<td>40</td>
</tr>
<tr>
<td>Toxicities</td>
<td>VOD (10%)</td>
<td>G3–4 CRS (26%); NE (42%)</td>
<td>G3–4 CRS (2%); NE (13%)</td>
<td></td>
</tr>
</tbody>
</table>

*Personal communication from Dr Jabbour.*
Venetoclax + Navitoclax in R/R ALL

- Navitoclax inhibits BCL2, BCL-XL, and BCL-W
- Venetoclax-navitoclax synergistic antitumor activity
- Rx with Ven/Nav + chemoRx (PEG-ASP, VCR, Dex)
- 47 pts (25 B-ALL + 19 T-ALL + 3 LL), median age 29
- Median 4 prior therapies; 28% post-ASCT, 13% post-CAR T
- ORR 28/47 (60%); MRD negativity 15/26 (58%)
- 4/32 (13%) CR/CRi/CRp at D8 after Ven/Nav
- Median OS 7.8 mo; 9.7 mo (B-ALL) and 6.6 mo (T-ALL)
- Preliminary BH3 profiling analysis revealed a trend in BCL2 dependence at baseline in T-ALL cells vs both BCL2 and BCL-XL dependence in B-ALL cells

Salvage Therapies in ALL: Conclusions

• Very effective salvage therapy in R/R ALL
  — High MRD-negativity rate
  — Best outcome in salvage 1
• Combination with low-dose chemotherapy
  — Safe and effective
  — Median survival 14 months
  — Salvage 1: 24 months (2-year OS rate >50%)
• AEs better controlled
  — CRS: debulk with sequential chemotherapy
  — VOD lower doses explored
• CAR T-cell Rx offered post-blinatumomab and -inotuzumab failure
  — Salvage 2 and high-risk salvage 1 (eg, MLL)
  — Consolidation in high-risk patients (replacing alloSCT)
• Better “blinatumomab” and “inotuzumab” needed
  — Better “Blina”: long half-life; SQ; no neurotoxicities
  — Better “InO”: no VOD
Debate on CD19-Targeted Approaches: Discussion and Voting
Question 1

What is your preferred ALL treatment choice in salvage, after the debate?

a) CAR T therapies
b) Monoclonal antibodies or bispecifics
Question 2

Do you think that children and young adults with active nonbulky CNS disease can safely be treated with CD19 CAR T cells?

a) Yes
b) No
c) I do not know
Question 3

What advantages do you see in bispecifics vs CAR T cells?

a) Readily available off the shelf
b) Dosing can be easily interrupted in case of toxicity
c) Can be combined with chemotherapy
d) I do not know

EM: postdiscussion questions for this session: should be comparative
Emerging Data and the Management of ALL Patients During COVID-19

Elias Jabbour
Question 1

Has the COVID-19 pandemic impacted the number of new cancer patients you are seeing in your clinic?

a) No, I am seeing about the same number of new cancer patients per month

b) Yes, I am seeing fewer new cancer patients per month

c) Yes, I am seeing more new cancer patients per month
Question 2

Do you feel that associations like NCCN, ASCO, or ASH have provided sufficient guidance on caring for cancer patients during the COVID-19 pandemic?

a) Yes

b) No
Treating Leukemia in the Time of COVID-19

- Clinical infection <1%–2% worldwide
  - Mortality rate of 1%–5% in COVID-infected patients in the general population
  - Potentially ≥30% in patients with cancer

- Careful consideration to the risk of COVID-19 in leukemia vs
  - Reducing access of patients to specialized cancer centers
  - Modifying therapies to those with unproven curative benefit
Patients with leukemia have uniquely higher risk of COVID-19 infection for multiple reasons associated with:

- Underlying disease
- Treatment
- Patient-specific factors

### Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Cause</th>
<th>Leukemia Diagnosis</th>
<th>Treatment</th>
<th>Patient Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Depressed immune function</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Organ dysfunction (cardiac, renal, liver, pulmonary)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
# Treating Leukemia in the Time of COVID-19

<table>
<thead>
<tr>
<th>Leukemia Type</th>
<th>Possible Risk Factors</th>
</tr>
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</table>
| **ALL**       | - Myelosuppression due to underlying disease and treatment  
                - Hypogammaglobulinemia  
                - Impaired B-cell function due to CD20-targeted monoclonal antibodies  
                - Prolonged steroid exposure  
                - Pulmonary and renal impairment due to methotrexate therapy  
                - Cardiac dysfunction due to anthracycline exposure  
                - Increased risk of COVID-19–associated thrombosis with asparaginase |
| **AML**       | - Myelosuppression due to underlying disease and treatment  
                - Cardiac dysfunction due to anthracycline exposure  
                - Pulmonary injury due to midostaurin |
| **CML**       | - Cardiac injury due to dasatinib, nilotinib, ponatinib  
                - Pulmonary injury due to dasatinib  
                - Increased risk of COVID-19–associated thrombosis with ponatinib and nilotinib |
| **CLL**       | - Hypogammaglobulinemia  
                - Impaired B-cell function due to CD20-targeted monoclonal antibodies  
                - Impaired innate immune response as well as B-cell and T-cell function with Bruton’s tyrosine kinase (BTK) inhibitors |
Weigh the treatment of a lethal, acute illness requiring aggressive therapy against the systemic limitations of inpatient stays, frequent clinic visits, and increasingly restricted blood product supply.

Development of several targeted therapies to treat acute leukemia may allow a reduction of dose-intensity while preserving the efficacy and the potential for cure.

Patients who are candidates for intensive Rx to be tested upfront.
Patients with leukemia have uniquely higher risk of COVID-19 infection for multiple reasons associated with
✓ Underlying disease
✓ Treatment
✓ Patient-specific factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Cause</th>
<th>Leukemia Diagnosis</th>
<th>Treatment</th>
<th>Patient Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Depressed immune function</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Organ dysfunction (cardiac, renal, liver, pulmonary)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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## Treating ALL in the Time of COVID-19

<table>
<thead>
<tr>
<th>Type</th>
<th>Induction/Consolidation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>Ph−</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;60 y.o.</td>
<td>• HCVAD × 4 cycles followed by Blina × 4 cycles</td>
</tr>
<tr>
<td></td>
<td>≥60 y.o.</td>
<td>• Mini-HCVD + Ino × 4 cycles followed by Blina × 4 cycles</td>
</tr>
<tr>
<td></td>
<td>≥70 y.o.</td>
<td>• Mini-HCVD + Ino × 2 cycles followed by Blina × 8 cycles</td>
</tr>
<tr>
<td></td>
<td>MRD+</td>
<td>• Move to Blina early after 2 cycles of HCVAD or mini-HCVD + Ino or clinical trial for MRD positivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Allogeneic SCT can be considered if benefit outweighs risks</td>
</tr>
<tr>
<td></td>
<td>Ph+</td>
<td>• Blina + TKI or Ino + TKI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blinatumomab + ponatinib preferred</td>
</tr>
</tbody>
</table>

- Important to still give maintenance
- May omit vincristine to reduce clinic visits and reduce steroids
- May transition to maintenance early if MRD negativity achieved and administering HCVAD or mini-HCVD is logistically difficult
- Incorporate Blina or low-dose Ino in late intensification

- Asparaginase possibly increases the thrombotic risk: complication of COVID-19
- If necessary, peg-asparaginase recommended

HyperCVAD + Blinatumomab in B-ALL (Ph− B-ALL <60 years): Treatment Schedule

**Intensive phase**

1. HyperCVAD
2. MTX–ara-C
3. Ofatumumab or rituximab
4. Blinatumomab

**Blinatumomab phase**

*After 2 cycles of chemo for Ho-Tr, Ph-like, t(4;11)*

1. Blinatumomab
2. Blinatumomab
3. Blinatumomab
4. Blinatumomab

**Maintenance phase**

1–3
4
5–7
8
9–11
12
13–15

- HyperCVAD
- Ofatumumab or rituximab
- MTX–ara-C
- 8 × IT MTX, ara-C
- POMP

HyperCVAD + Blinatumomab in FL B-ALL (N = 34)

- CR 100%, MRD negativity 97% (at CR 87%), early death 0%

CRD and OS Overall

OS – HCVAD-Blina vs O-HCVAD
Mini-HCVD + Ino ± Blina in Older ALL: Modified Design (pts 50+)

**Intensive phase**
- 1
- 2
- 3
- 4

**Consolidation phase**
- 5
- 6
- 7
- 8

**Maintenance phase**
- 1–3
- 4
- 5–7
- 8
- 9–11
- 12
- 13–15
- 16

**Total Ino dose = 2.7 mg/m²**

*Ursodiol 300 mg tid for VOD prophylaxis.

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## Mini-HCVD + Ino ± Blina in Older ALL (N = 64)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>N (%)/Median [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>≥70</td>
<td>68 [60-81] 27 (42)</td>
</tr>
<tr>
<td>Performance status</td>
<td>≥2</td>
<td>9 (14)</td>
</tr>
<tr>
<td>WBC (× 10⁹/L)</td>
<td></td>
<td>3.0 [0.6-111.0]</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Diploid</td>
<td>21 (33)</td>
</tr>
<tr>
<td></td>
<td>HeH</td>
<td>5 (8)</td>
</tr>
<tr>
<td></td>
<td>Ho-Tr</td>
<td>12 (19)</td>
</tr>
<tr>
<td></td>
<td>Tetraploidy</td>
<td>3 (5)</td>
</tr>
<tr>
<td></td>
<td>Complex</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>t(4;11)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Misc</td>
<td>9 (14)</td>
</tr>
<tr>
<td></td>
<td>IM/ND</td>
<td>12 (19)</td>
</tr>
<tr>
<td>CNS disease at diagnosis</td>
<td></td>
<td>4 (6)</td>
</tr>
<tr>
<td>CD19 expression, %</td>
<td></td>
<td>99.6 [30-100]</td>
</tr>
<tr>
<td>CD22 expression, %</td>
<td></td>
<td>96.6 [27-100]</td>
</tr>
<tr>
<td>CD20 expression ≥20%</td>
<td></td>
<td>32/58 (57)</td>
</tr>
<tr>
<td><strong>CRLF2</strong> by flow</td>
<td></td>
<td>6/31 (19)</td>
</tr>
<tr>
<td><strong>TP53</strong> mutation</td>
<td></td>
<td>17/45 (38)</td>
</tr>
<tr>
<td>Response (N = 59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td></td>
<td>58 (98)</td>
</tr>
<tr>
<td>CR</td>
<td></td>
<td>51 (86)</td>
</tr>
<tr>
<td>CRp</td>
<td></td>
<td>6 (10)</td>
</tr>
<tr>
<td>CRi</td>
<td></td>
<td>1 (2)</td>
</tr>
<tr>
<td>No response</td>
<td></td>
<td>1 (2)</td>
</tr>
<tr>
<td>Early death</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Flow MRD response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D21</td>
<td></td>
<td>50/62 (81)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>60/63 (95)</td>
</tr>
</tbody>
</table>

Mini-HCVD + Ino ± Blina in Older ALL: Outcome

CRD and OS overall

OS by age

Rate of death in CR/CRp for pts age 60–69 yr vs ≥70 yr:
8/37 (22%) vs 13/27 (48%), \( P = .03 \)
7/7 sepsis and 3/4 MDS-AML

Mini-HCVD + Ino ± Blina vs HCVAD in Elderly ALL: Overall Survival

**Prematched**

![Prematched Kaplan-Meier curve showing overall survival](image1)

Log-rank: $p = 0.002$

**Matched**

![Matched Kaplan-Meier curve showing overall survival](image2)

Log-rank: $p = 0.004$

Mini-HCVD + Ino ± Blina in Older ALL: Amended Design (pts ≥70 years)

**Intensive phase**

1. Mini-HCVD
2. Mini-MTX–cytarabine

**Consolidation phase**

5. IT MTX, ara-C
6. POMP
7. Blinatumomab
8. Total Ino dose = 1.5 mg/m²

**Maintenance phase**

1 2 3 4

6 months

**Ino**

<table>
<thead>
<tr>
<th>Total Dose (mg/m²)</th>
<th>Dose per Day (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 0.9</td>
<td>0.6 D2, 0.3 D8</td>
</tr>
<tr>
<td>C2 0.6</td>
<td>0.3 D2 and D8</td>
</tr>
</tbody>
</table>

**Total Ino dose = 1.5 mg/m²**

*Ursodiol 300 mg tid for VOD prophylaxis.*
Treating ALL in the Time of COVID-19: Advantage of These Regimens

- Blina significantly less myelosuppressive. Although currently administered after 4 courses of HCVAD or mini-HCVD, pts switch to Blina earlier, after 2 courses, to avoid additional myelosuppression
- No or low tumor burden after intensive Rx, no CRS: need for hospitalization significantly reduced. Blina dose-escalation on day 5 instead of day 8
- 7-day bags: outpatient setting with reduced clinic visits
- Blina earlier deepens MRD response and safely shortens maintenance from 30 months to 18 months
Dasatinib-Blinatumomab in Ph+ ALL

- 63 pts, median age 54 yr (24–82)
- Dasatinib 140 mg/D × 3 mo; add blinatumomab × 2–5
- 53 post–dasa-blina × 2 – molecular response 32/53 (60%), 22 CMR (41%); MRD ↑ in 15, 6 T315I; 12-mo OS 96%; DFS 92%

Blinatumomab + Ponatinib Swimmer Plot (N = 17)

Total N=17 (Frontline, N=11; Salvage N=6)
Median follow-up: 14 months
Median follow-up in Frontline: 12 months
Median follow-up in Salvage: 24 months
Median time to CMR: 0.9 months

Personal communication from Dr Jabbour.
HyperCVD + Ponatinib + Blinatumomab in Ph+ ALL

Intensive phase

30
30/15
1 2 3 4 1 2 3 4
4 wk 2 wk

Maintenance phase

30/15
16 months 5 years
4 8 12

Risk-adapted intrathecal CNS prophylaxis (N = 12)

- Mini-hyperCVD
- Ponatinib 30 mg →15 mg
- Mini-MTX–cytarabine
- Vincristine + prednisone
- Blinatumomab

https://clinicaltrials.gov/ct2/show/NCT03147612
Treating Leukemia in the Time of COVID-19

- Risk of COVID-19 complications weighed very carefully vs restricting access of patients to highly specialized centers and of advocating for regimens without known equivalent curative potential
- Efforts should be prioritized to reduce patient and staff exposure while maintaining optimal care
- Utilizing less-intensive Rx, reducing patient visits, and establishing collaborative care at local centers or through telemedicine
- Rx decisions individualized on the basis of patient-related factors, risk of added toxicity, and feasibility of treatment administration
- Standard hygiene and social distancing measures to be pursued
Emerging Data and the Management of ALL Patients During COVID-19

Panel Discussion
Session Close

Elias Jabbour and Eduardo Rego
Closing Remarks

Elias Jabbour and Eduardo Rego
THANK YOU FOR YOUR PARTICIPATION!