Translating Guidelines and Clinical Trial Data to Improved ALL Management and Outcomes

Learning Objectives

- Outline the current classification system for ALL and the differences in biology and treatment strategies between pediatric and adult patients with ALL
- Review current evidence for induction, consolidation, maintenance, and transplant strategies in the treatment of ALL in pediatric and adult patients
- Summarize current guideline recommendations for the treatment of both Ph–negative and Ph–positive ALL patients
- Outline strategies for the treatment of patients with refractory or relapse ALL
- Identify emerging treatments and the role of currently available targeted agents in the management of ALL

ALL = acute lymphoblastic leukemia; Ph = Philadelphia chromosome.
Acute Lymphoblastic Leukemia

- 6050 new ALL cases in the United States annually
- ALL accounts for 20% of adults with acute leukemia and ~80% of all childhood leukemia cases
  - 60% of ALL patients are younger than 20 years-of-age
  - ALL accounts for 25% of all childhood cancers
  - ALL is more common in males: 62%
- Greatest incidence in the United States among Hispanics
  - Higher incidence in whites vs blacks
  - Peak incident rate: 2-5 years-of-age; >50 years-of-age


Risk Stratification and Classification of ALL at the Time of Diagnosis

- NCI risk factors for pediatric ALL (BCP>TCP)
  - Age
    - Standard risk: >1 year-of-age; <10 years-of-age
  - WBC
    - ≥50,000 vs <50,000
- Immunophenotype classification (BCP and TCP)
- Genetics of leukemia cells
  - rMLL, hypodiploidy (<45), iAMP21—Unfavorable
  - Double trisomy 4+10, ETV6-RUNX1 fusion gene—Favorable
  - BCR-ABL fusion gene—Requires special treatment

Distribution of the Common Chromosomal Abnormalities According to Age

HeH = high hyperdiploidy.

Genetic Abnormalities Are Not Random

B-Cell Development Stages, Immunophenotype, Major Transcription Factors, and Signaling Molecules

EBF = early B-cell factor; Ig = immunoglobulin; HSC = hematopoietic stem cell; LMPP = lymphoid-primed multipotential progenitor; CD = cluster of differentiation; IL = interleukin.
Age at Diagnosis Correlates with Outcome


Diverse “Associated” Chromosomal Abnormalities

Frequency of Genomic Amplifications and Deletions in Pediatric ALL

<table>
<thead>
<tr>
<th>Group</th>
<th>Subtype</th>
<th>N</th>
<th>Amplifications (mean±SD)*</th>
<th>Deletions (mean±SD)*</th>
<th>All Lesions (mean±SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-ALL</td>
<td>Hyperdiploid with &gt;50 chromosomes</td>
<td>39</td>
<td>9.56±3.59 (5-20)</td>
<td>1.59±2.49 (0-11)</td>
<td>11.13±5.0 (5-27)</td>
</tr>
<tr>
<td>B-ALL</td>
<td>TCF3-PBX1</td>
<td>17</td>
<td>1.59±0.62 (1-3)</td>
<td>2.12±1.17 (1-4)</td>
<td>3.7±1.53 (2-7)</td>
</tr>
<tr>
<td>B-ALL</td>
<td>ETV6-RUNX1</td>
<td>47</td>
<td>0.89±1.51 (0-8)</td>
<td>6.0±4.63 (1-21)</td>
<td>6.8±4.8 (0-21)</td>
</tr>
<tr>
<td>B-ALL</td>
<td>rMLL</td>
<td>11</td>
<td>0.09±0.3 (0-1)</td>
<td>0.91±1.81 (0-6)</td>
<td>1±1.79 (0-6)</td>
</tr>
<tr>
<td>B-ALL</td>
<td>BCR-ABL1</td>
<td>9</td>
<td>4±5.3 (0-12)</td>
<td>4±4.15 (0-12)</td>
<td>6.8±4.52 (0-13)</td>
</tr>
<tr>
<td>B-ALL</td>
<td>Hyperdiploid with 47-50 chromosomes</td>
<td>23</td>
<td>1.70±1.55 (0-7)</td>
<td>3.5±3.12 (0-12)</td>
<td>5.1±3.31 (0-15)</td>
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<tr>
<td>B-ALL</td>
<td>Hypodiploid</td>
<td>10</td>
<td>1.1±1.91 (0-6)</td>
<td>6.0±4.42 (3-18)</td>
<td>7.1±6.12 (3-24)</td>
</tr>
<tr>
<td>B-ALL</td>
<td>Other</td>
<td>36</td>
<td>1.06±3.21 (0-19)</td>
<td>4.6±5.14 (0-20)</td>
<td>5.58±6.57 (0-23)</td>
</tr>
<tr>
<td>B-ALL</td>
<td>Total</td>
<td>192</td>
<td>2.97±4.28 (0-20)</td>
<td>3.83±4.2 (0-21)</td>
<td>6.6±5.56 (0-27)</td>
</tr>
<tr>
<td>T-ALL</td>
<td></td>
<td>50</td>
<td>0.9±1.98 (0-9)</td>
<td>4.9±6.21 (0-30)</td>
<td>5.8±7.12 (0-39)</td>
</tr>
<tr>
<td>All Cases</td>
<td></td>
<td>242</td>
<td>2.5±4.0 (0-20)</td>
<td>4.06±4.69 (0-38)</td>
<td>6.46±5.90 (0-39)</td>
</tr>
</tbody>
</table>

*Range is shown in parentheses.
B-ALL = acute B-lymphoblastic leukemia; T-ALL = acute T-lymphoblastic leukemia.
The Importance of Early Response to Treatment

Early Response Predicts Outcome

MRD on Day 29 of Induction by Flow Cytometry

- **MRD Negative (≤0.01%)** (n=1588)
  - EFS Probability: 88±1%

- **0.01% < MRD ≤ 0.1%** (n=175)
  - EFS Probability: 59±5%

- **0.1% < MRD ≤ 1.0%** (n=141)
  - EFS Probability: 49±6%

- **MRD > 1.0%** (n=67)
  - EFS Probability: 30±8%

MRD = minimum residual disease; EFS = event-free survival.
MRD on Day 29 of Induction Predicts Both Early and Late Failure

POG9904+9905+9906

Early Relapse

Late Relapse

Relapse-Free Survival Probability

POG = Pediatric Oncology Group.

EFS of NCI SR Patients With Favorable Genetic Features

TEL-AML1 Fusion

Double Trisomies

EFS Probability

MDR Negative (≤0.01%) (n=383)
MDR Positive (>0.01%) (n=383)

POG = Pediatric Oncology Group.
CCR for Patients in the SR and HR Groups According to Molecular Response Status

Week 16 in Adult ALL Patients

Overall Excluding SCT in First CR

Probability of CCR

Molecular CR: 69% (n=384)
Molecular Failure: 26% (n=120)

Molecular CR: 70% (n=333)
Molecular Failure: 12% (n=63)

CCR = complete continuous remission; HR = high-risk; SCT = stem cell transplantation; CR = complete response.
Therapy is the Most Important Prognostic Factor!

DXM = dexamethasone; Aug = augmentation; BFM-D.I. = Berlin-Frankfurt-Munster-delayed intensification; CNS = central nervous system.

Bleyer A. Evolution of ALL therapy in infants, teenagers, and young adults. Presented at: Enzon Oncology Team Meeting; May 31, 2006; Atlanta, Georgia.

ALL Treatment

- Induction
- Post-induction intensification
- Delayed intensification
- Maintenance phases
- CNS prophylaxis

CNS Prophylaxis

Induction → Intensification → Maintenance

Over a period of months

Delayed intensification

2-3 years
**Induction Therapy**

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatric</strong></td>
<td></td>
</tr>
<tr>
<td>New York</td>
<td>Vincristine, prednisone, daunomycin, asparaginase, CPM</td>
</tr>
<tr>
<td>COG/SR</td>
<td>Vincristine, DXM, prednisone, asparaginase</td>
</tr>
<tr>
<td>COG/HR+T-cell</td>
<td>Vincristine, DXM or prednisone, prednisone, asparaginase, daunomycin</td>
</tr>
<tr>
<td><strong>Adult</strong></td>
<td></td>
</tr>
<tr>
<td>Linker</td>
<td>Vincristine, DXM or prednisone, asparaginase, daunomycin</td>
</tr>
<tr>
<td>UKALL XII</td>
<td>Vincristine, DXM or prednisone, asparaginase, daunomycin</td>
</tr>
<tr>
<td>HyperCVAD</td>
<td>Vincristine, DXM, doxorubicin, hyperfractionated CPM</td>
</tr>
</tbody>
</table>


**Presymptomatic CNS Therapy (CNS Prophylaxis)**

- Effective systemic chemotherapy
  - HD MTX, DXM, asparaginase, thioguanine
- Early intensification and optimization of intrathecal therapy
  - Triple IT therapy vs IT MTX
- Cranial irradiation
  - A central role in the 1960’s but employed less because of serious long-term sequelae

Post-Induction Intensification (Consolidation)

CCG-105: Average (Standard) Risk

Induction VPL

Standard Consolidation
6-MP, IT MTX
XRT

Interim Maintenance
Daily 6-MP, Weekly MTX

Delayed Intensification
Maintenance no IT MTX

Intensive Induction VPLD

Standard Consolidation b
6-MP, IT MTX
XRT
CPM, AraC

Interim Maintenance
Daily 6-MP, Weekly MTX

Delayed Intensification
Maintenance IT MTX

Maintenance no IT MTX

Standard Consolidation
6-MP, IT MTX
no XRT

Interim Maintenance
Daily 6-MP, Weekly MTX

Delayed Intensification
Maintenance no IT MTX

Standard Consolidation Ib
6-MP, IT MTX
XRT
CPM, AraC

Interim Maintenance
Daily 6-MP, Weekly MTX

Delayed Intensification
Maintenance IT MTX

Maintenance no IT MTX

C CG = Children's Cancer Group; VPL = vincristine + prednisone + L-asparaginase; VPLD = vincristine + prednisone + L-asparaginase + daunomycin; AraC = cytosine arabinoside; 6-MP = 6-mercaptopurine; XRT = external-beam radiation.


CCG-105—Average (Standard) Risk,
Early vs Delayed Intensification

EFS for Randomized Patients <10 Years-of-Age on Regimens Containing Delayed Intensification

Regimen A – Intensive induction/consolidation + delayed intensification (n=318)
Regimen B – Standard induction/consolidation + delayed intensification (n=312)
Regimen C – Intensive induction/consolidation (n=314)
Regimen D – Standard induction/consolidation (n=313)

### CCG-Modified Standard BFM

<table>
<thead>
<tr>
<th>Induction (5 weeks)</th>
<th>Consolidation (8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPLD</td>
<td>CPM AraC 6-MP</td>
</tr>
<tr>
<td></td>
<td>2 week delay</td>
</tr>
<tr>
<td></td>
<td>CPM AraC 6-MP</td>
</tr>
<tr>
<td></td>
<td>2-week delay</td>
</tr>
</tbody>
</table>

16 weeks of intensive therapy including 6 weeks of delay for count recovery

<table>
<thead>
<tr>
<th>Interim Maintenance Delayed Intensification (8 weeks)</th>
<th>(8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral 6-MP/Oral MTX</td>
<td>Vincristine/DXM/Doxorubicin/L-asparaginase</td>
</tr>
<tr>
<td></td>
<td>CPM AraC 6-MP</td>
</tr>
<tr>
<td></td>
<td>2-week delay</td>
</tr>
</tbody>
</table>


### Augmented BFM

<table>
<thead>
<tr>
<th>Induction (5 weeks)</th>
<th>Consolidation (8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPLD</td>
<td>CPM AraC 6-MP</td>
</tr>
<tr>
<td></td>
<td>Vincristine-L-asparaginase</td>
</tr>
<tr>
<td></td>
<td>CPM AraC 6-MP</td>
</tr>
<tr>
<td></td>
<td>Vincristine-L-asparaginase</td>
</tr>
</tbody>
</table>

No delays—40 weeks of intensive therapy

<table>
<thead>
<tr>
<th>Interim Maintenance #1 Delayed Intensification (8 weeks)</th>
<th>(8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine/Capizzi MTX + L-asparaginase</td>
<td>Vincristine/DXM/Doxorubicin/L-asparaginase</td>
</tr>
<tr>
<td></td>
<td>CPM AraC 6-MP</td>
</tr>
<tr>
<td></td>
<td>Vincristine-L-asparaginase</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interim Maintenance #2 Delayed Intensification (8 weeks)</th>
<th>(8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine/Capizzi MTX + L-asparaginase</td>
<td>Vincristine/DXM/Doxorubicin/L-asparaginase</td>
</tr>
<tr>
<td></td>
<td>CPM AraC 6-MP</td>
</tr>
<tr>
<td></td>
<td>Vincristine-L-asparaginase</td>
</tr>
</tbody>
</table>

Longer and Stronger PII

CCG-1882

PII = post-induction intensification.

Length and Strength of PII

CCG-1961: Higher Risk

EFS During 5 Years of Follow-Up in ALL Patients

EFS According to the Type of Post-Induction Chemotherapy

Log Rank P<.0001
5-Year EFS: Stronger PII 81.2% (AEs 2.4%) vs Standard PII 71.7% (AEs 2.7%)

Number at Risk:

<table>
<thead>
<tr>
<th></th>
<th>Stronger PII</th>
<th>Standard PII</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>650</td>
<td>649</td>
</tr>
<tr>
<td>At Risk</td>
<td>611</td>
<td>598</td>
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<tr>
<td>1 Year</td>
<td>559</td>
<td>536</td>
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<tr>
<td>2 Years</td>
<td>473</td>
<td>448</td>
</tr>
<tr>
<td>3 Years</td>
<td>340</td>
<td>325</td>
</tr>
<tr>
<td>4 Years</td>
<td>220</td>
<td>196</td>
</tr>
<tr>
<td>5 Years</td>
<td>138</td>
<td>111</td>
</tr>
<tr>
<td>6 Years</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>7 Years</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

AEs = adverse effects.

High-Dose MTX with Leucovorin Rescue

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>IV MTX Dose</th>
<th>EFS Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCG-139</td>
<td>IR</td>
<td>0.5 g/m²</td>
<td>No</td>
</tr>
<tr>
<td>CCG-144</td>
<td>SR</td>
<td>33.6 g/m²</td>
<td>No</td>
</tr>
<tr>
<td>CCG-5971</td>
<td>Lymphoblastic lymphoma</td>
<td>5 g/m²</td>
<td>No</td>
</tr>
</tbody>
</table>

IR = intermediate risk.
DXM vs Prednisone; HD vs Escalating IV MTX

AALL0232

Rapid Early Responder
Augmented Consolidation
Vincristine/Capizzi MTX
6-MP/HD MTX
Vincristine/Capizzi MTX
6-MP/HD MTX
Vincristine/Capizzi MTX
6-MP/HD MTX
Vincristine/Capizzi MTX
6-MP/HD MTX

Slow Early Responder
Augmented Consolidation
Delayed Intensification
Vincristine/Capizzi MTX
Vincristine/Capizzi MTX
Vincristine/Capizzi MTX
Vincristine/Capizzi MTX
Vincristine/Capizzi MTX
Vincristine/Capizzi MTX
Vincristine/Capizzi MTX
Vincristine/Capizzi MTX

AALL0232 = high-risk precursor B-ALL protocol.
Maintenance

- Daily mercaptopurine + weekly MTX since the 1960s
  - Full dose is more effective than half dose
  - CPM and cytarabine add toxicity but no benefit
  - Childhood ALL is unique in requiring prolonged therapy
    - 2 years > 18 months; 3 years > 2 years
    - L92-13 study with 1 year of intensive therapy
      - 60% EFS for HR and 60% EFS for SR
  - Vincristine/steroid pulses
  - Parenteral vs oral MTX

**Pediatric BCP Risk Stratification**

**AALL0932/AALL1131**

<table>
<thead>
<tr>
<th>Subset/MRD</th>
<th>Day 8 PB MRD</th>
<th>Day 29 BM MRD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;.01%</td>
<td>&lt;.01%</td>
</tr>
<tr>
<td>Age &lt;1 year</td>
<td>Infant</td>
<td></td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>Ph+</td>
<td></td>
</tr>
<tr>
<td>CNS 3</td>
<td>VHR</td>
<td></td>
</tr>
<tr>
<td>Age &gt;13 years</td>
<td>VHR</td>
<td></td>
</tr>
<tr>
<td>Induction failure</td>
<td>VHR</td>
<td></td>
</tr>
<tr>
<td>Hypodiploid, iAMP21, rMLL</td>
<td>VHR</td>
<td></td>
</tr>
<tr>
<td>NCI SR, TEL-AML1 fusion, Trisomy 4+10</td>
<td>LR, SR</td>
<td>HR</td>
</tr>
<tr>
<td>NCI SR, Other</td>
<td>SR, HR</td>
<td>VHR</td>
</tr>
<tr>
<td>NCI HR, Age &lt;13 years</td>
<td>HR</td>
<td>VHR</td>
</tr>
</tbody>
</table>

AALL0932 = newly diagnosed standard-risk precursor B-ALL protocol; AALL1131 = newly diagnosed high-risk precursor B-ALL protocol; PB = peripheral blood; BM = bone marrow; LR = low-risk.

**COG B-Cell Precursor Subsets**

<table>
<thead>
<tr>
<th>Subset</th>
<th>Subsets</th>
<th>Percent</th>
<th>Expected EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>1</td>
<td>3%</td>
<td>50%</td>
</tr>
<tr>
<td>Ph+</td>
<td>1</td>
<td>3%</td>
<td>75%</td>
</tr>
<tr>
<td>VHR</td>
<td>8</td>
<td>22%</td>
<td>&lt;80%</td>
</tr>
<tr>
<td>HR</td>
<td>3</td>
<td>23%</td>
<td>88-90%</td>
</tr>
<tr>
<td>SR</td>
<td>2</td>
<td>34%</td>
<td>90-95%</td>
</tr>
<tr>
<td>LR</td>
<td>1</td>
<td>15%</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

Risk Stratification: Pediatric, T-Cell

AALL0434

<table>
<thead>
<tr>
<th>Presenting Features</th>
<th>M1 on Day 8 or 15</th>
<th>M1 on Day 29</th>
<th>M2/3 on Day 29 or Day 29 MRD &lt; .1%</th>
<th>Day 29 MRD .1%-1%</th>
<th>Day 29 MRD &gt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 1-9 years</td>
<td>LR</td>
<td>IR</td>
<td>HR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC &lt; 50,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Testes disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;10 years</td>
<td>IR</td>
<td>HR</td>
<td></td>
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<tr>
<td>WBC &gt; 50,000</td>
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</tr>
<tr>
<td>Testes disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS 3</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- No validity of conventional age/WBC
- End consolidation MRD (day 85!)
- Adverse ETP

M1, 2, 3 = bone marrow morphology stages; ETP = early T-phenotype.

Early T-Cell Phenotype: Molecularly Heterogeneous

CD1a(-), CD8(-), CD5(weak) with Stem-Cell or Myeloid Markers

Chromosomal rearrangements
- Interchromosomal (CTX)
- Intrachromosomal (ITX)

Regional changes
- Amplification
- Deletion
- Loss of heterozygosity

Gene-specific changes
- Somatic SNVs
- Non-silent SNVs
- Indels
- Genes in in-frame fusions
- Genes targeted by SVs

Early T-Cell Phenotype: Molecularly Heterogeneous

CD1a(-), CD8(-), CD5(weak) with Stem-Cell or Myeloid Markers

Remission Failure/ Hematologic Relapse

EFS 1.0

Typical-ALL 87 13 74 5
ETP-ALL 22% 57%

AIEOP = Associazione Italiana Ematologia Oncologia Pediatrica.

End Consolidation MRD in T-ALL

Relapses by Risk Group

MRD Negative at TP2
Relapses by MRD at TP1

Relapses by MRD at TP2

TP1 = time point 1; TP2 = time point 2; CI = confidence interval; MR = medium-risk.
## “Targeted Therapy”

**Ph+ ALL in Children; Pre-Imatinib**

<table>
<thead>
<tr>
<th>Study Groups (Years of Study)</th>
<th>N</th>
<th>Percentage</th>
<th>CR</th>
<th>EFS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dana-Farber (1981-89)</td>
<td>15</td>
<td>3.5</td>
<td>80</td>
<td>0</td>
<td>Fletcher et al (1991)</td>
</tr>
<tr>
<td>POG (1981-89)</td>
<td>58</td>
<td>2.3</td>
<td>78</td>
<td>7</td>
<td>Crist et al (1990)</td>
</tr>
<tr>
<td>BFM/AEIOP (1986-95)</td>
<td>61</td>
<td>1.3</td>
<td>75</td>
<td>38</td>
<td>Schrappe et al (1998)</td>
</tr>
<tr>
<td>UKALL (1990-97)</td>
<td>25</td>
<td>2</td>
<td>NA</td>
<td>27</td>
<td>Hann et al (2001)</td>
</tr>
<tr>
<td>Dana-Farber (1991-95)</td>
<td>6</td>
<td>1.6</td>
<td>100</td>
<td>50</td>
<td>Silverman et al (2001)</td>
</tr>
</tbody>
</table>

AEIOP = Associazione Italiana Ematologia Oncologia Pediatrica; NOPHO = Nordic Society for Pediatric Hematology and Oncology.


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## Imatinib + Chemotherapy Improves Outcome for Childhood Ph+ ALL (AALL0031)

### EFS by Cohort 1-2 vs 3-5

- **P = 0.0178**

<table>
<thead>
<tr>
<th>Years</th>
<th>EFS Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>0.95</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>3</td>
<td>0.85</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

### AALL0031 Cohort 5 vs Historical Control

- **P = 0.0062**

<table>
<thead>
<tr>
<th>Years</th>
<th>EFS Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>0.95</td>
</tr>
<tr>
<td>4</td>
<td>0.9</td>
</tr>
<tr>
<td>6</td>
<td>0.85</td>
</tr>
<tr>
<td>8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

AALL0031 = Evaluation of imatinib mesylate into an intensive chemotherapy regimen for children with Ph+ ALL.

Targeted Therapy

- Every agent has molecular targets
  - MTX and DHFR
- Targeted therapy requires a patient population for whom the molecular target is critical
  - ATRA → acute promyelocytic leukemia
  - TKIs → chronic myelogenous leukemia
  - Abnormal gene product (BCR-ABL; RARα)
  - Over-expression?
- Target should clonal—not sub-clonal
  - “Early” vs “late” disease
    - Chronic myelogenous leukemia vs Ph+ ALL

DHFR = dihydrofolate reductase; ATRA = all-trans-retinoic acid; TKIs = tyrosine-kinase inhibitors; RARα = retinoic acid receptor-alpha.

CRLF2 and JAK2 in B-Cell Progenitor ALL: A Novel Association in Oncogenesis

Ruxolitinib?

Potential therapeutic intervention

- Anti-CRLF2 antibody approaches
- JAK2 mutation (30%-70%)
- CRLF2 overexpression (5%-15% B-ALL, 65% DS-ALL)
- Mutation of other kinases? (15%-40%)
- Unknown Kinases
- Aberrant signaling contributing to B-ALL development

Overexpression of CRLF2

Heterodimer (with unknown partner)

- Normal CRLF2 function
- CRLF2 heterodimer (with unknown partner)
- CRLF2 monomer

Unknown Kinases

Aberrant growth control signaling in B-ALL

WT = wild-type; MT = mutated; TSLP = thymic stromal lymphopoietin; IL7Rα = interleukin 7 receptor alpha.

Adolescents and Young Adults

<table>
<thead>
<tr>
<th>Trials</th>
<th>Age (years)</th>
<th>Induction Rate</th>
<th>EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adult</td>
<td>Pediatric</td>
</tr>
<tr>
<td>FRALLE-93/LALA-94</td>
<td>15-20</td>
<td>83%</td>
<td>94%</td>
</tr>
<tr>
<td>DCOG/HOVON</td>
<td>15-18</td>
<td>91%</td>
<td>98%</td>
</tr>
<tr>
<td>NOPHO92/Swedish Group</td>
<td>15-18/15-20</td>
<td>90%</td>
<td>99%</td>
</tr>
<tr>
<td>ALL97/UKALL XII</td>
<td>15-17</td>
<td>94%</td>
<td>98%</td>
</tr>
<tr>
<td>CCG/CALGB</td>
<td>16-20</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>NOPHO/Finnish Group</td>
<td>10-16/16-25</td>
<td>97%</td>
<td>96%</td>
</tr>
</tbody>
</table>

FRALLE = French Acute Lymphoblastic Leukemia Group; LALA-94 = Leucemias Aigues Lymphoblastiques de l’Adulte-94; DCOG = Dutch Childhood Oncology Group; HOVON = Dutch Haematology-Oncology Association Studies; CALGB = Cancer and Leukemia Group B.


**Treatment Allocation—Adult**

- The Best Management of Any Patient Is a Clinical Trial
  - **Ph- ALL**
    - Age 15-39 or >65 years and no substantial comorbidities
      - Chemotherapy as in pediatrics
        - Allogeneic BMT if MRD+ or HR
    - Aged >65 years or comorbidities
      - Multiagent chemotherapy
        - Dose reductions
        - Corticosteroids
  - **Ph+ ALL**
    - Aged 15-64 years, no comorbidities
      - Chemotherapy + TKI
        - Allogeneic BMT (donor)
    - Aged >65 years or comorbidities
      - Corticosteroids + TKI

BMT = bone marrow transplantation.
ALL Relapse and Its Affect on Patient Survival

Relapsed ALL is the 7th Most Common Childhood Malignancy

AML = acute myeloid leukemia.
**Algorithm for Treatment of BM Relapse ALL in Children**

- **BM Relapse**
  - Combined with Extramedullary Localization:
    - Treat as Isolated BM Relapse
      - If CNS Relapse, Cranial Radiotherapy
      - If Testicular Relapse, Local Radiotherapy or Orchidectomy
    - Reinduction and Consolidation Chemotherapy
  - Isolated:
    - SR (BCP-ALL Relapsing >6 Months from Treatment Discontinuation)
    - HR (BCP-ALL Relapsing <6 Months from Treatment Discontinuation, T-ALL, Ph+ ALL, ≤43 Chromosomes)
    - If CNS Relapse, Cranial Radiotherapy
    - If Testicular Relapse, Local Radiotherapy or Orchidectomy
    - Reinduction and Consolidation Chemotherapy
    - Reinduction and Consolidation Chemotherapy

  - MRD <10⁻⁴ on Week 12-15
  - MRD >10⁻⁴ on Week 12-15

  - Chemotherapy
  - Allogeneic-HSCT
  - Allogeneic-HSCT

**IEM = isolated extra-medullary relapse; HSCT = hematopoietic stem cell transplantation.**


**Despite Successful Remission, Induction, and BMT, Most ALL Patients Who Relapse Die**

**CCG-1900 series trials—Survival after 1st Relapse**

<table>
<thead>
<tr>
<th>Site of Relapse (n)</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated BM(1123)</td>
<td>24%</td>
</tr>
<tr>
<td>Combined BM (264)</td>
<td>39%</td>
</tr>
<tr>
<td>Isolated CNS (409)</td>
<td>59%</td>
</tr>
<tr>
<td>Isolated testes (104)</td>
<td>58%</td>
</tr>
<tr>
<td>Average</td>
<td>35%</td>
</tr>
</tbody>
</table>

### BM Relapse

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=3712, (n)</td>
<td>N=9585, (n)</td>
</tr>
<tr>
<td>Very Early CR1 &lt;18 months</td>
<td>Isolated 6% (233)</td>
<td>11% (412)</td>
</tr>
<tr>
<td></td>
<td>Combined 6% (34)</td>
<td>12% (86)</td>
</tr>
<tr>
<td>Intermediate CR1 18-36 months</td>
<td>Isolated 11% (193)</td>
<td>18% (324)</td>
</tr>
<tr>
<td></td>
<td>Combined 11% (26)</td>
<td>40% (54)</td>
</tr>
<tr>
<td>Late CR1 &gt;36 months</td>
<td>Isolated 43% (215)</td>
<td>43% (387)</td>
</tr>
<tr>
<td></td>
<td>Combined 49% (60)</td>
<td>60% (124)</td>
</tr>
</tbody>
</table>


### AALL01P2—First BM Relapse Outcomes in MRD Positive vs Negative

#### Early Relapse Patients in CR at End of Block 1

<table>
<thead>
<tr>
<th>EFS Probability</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80</td>
<td>0.12</td>
</tr>
<tr>
<td>0.70</td>
<td>0.17</td>
</tr>
<tr>
<td>0.60</td>
<td>0.22</td>
</tr>
<tr>
<td>0.50</td>
<td>0.27</td>
</tr>
<tr>
<td>0.40</td>
<td>0.32</td>
</tr>
<tr>
<td>0.30</td>
<td>0.37</td>
</tr>
<tr>
<td>0.20</td>
<td>0.42</td>
</tr>
<tr>
<td>0.10</td>
<td>0.47</td>
</tr>
</tbody>
</table>

MRD $\leq 0.01\%$ (n=9) vs MRD $>0.01\%$ (n=27) $P=.0120$

#### Late Relapse Patients in CR at End of Block 1

<table>
<thead>
<tr>
<th>EFS Probability</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80</td>
<td>0.12</td>
</tr>
<tr>
<td>0.70</td>
<td>0.22</td>
</tr>
<tr>
<td>0.60</td>
<td>0.32</td>
</tr>
<tr>
<td>0.50</td>
<td>0.42</td>
</tr>
<tr>
<td>0.40</td>
<td>0.52</td>
</tr>
<tr>
<td>0.30</td>
<td>0.62</td>
</tr>
<tr>
<td>0.20</td>
<td>0.72</td>
</tr>
<tr>
<td>0.10</td>
<td>0.82</td>
</tr>
</tbody>
</table>

MRD $\leq 0.01\%$ (n=21) vs MRD $>0.01\%$ (n=22) $P=.0904$

AALL01P2 = intensive induction therapy for children with ALL who experience a BM relapse.

Pre-BMT MRD Predicts Post-BMT Relapse

EFS Probability and Cumulative Incidence of Subsequent Relapse in Intermediate-Risk Patients with ALL


MRC R3: Mitoxantrone vs Idarubicin

MRC R3: Mitoxantrone vs Idarubicin

<table>
<thead>
<tr>
<th>Number at Risk:</th>
<th>Mitoxantrone</th>
<th>Idarubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone</td>
<td>103</td>
<td>109</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>109</td>
<td>109</td>
</tr>
</tbody>
</table>

No difference in reinduction rates or MRD


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Clofarabine in Pediatric Patients with Refractory or Relapsed ALL

- An open label, multicenter study
- Pediatric patients with refractory or relapsed ALL received clofarabine 52 mg/m² IV daily for 5 days, every 2-6 weeks for up to 12 cycles

CRp = CR with incomplete platelet recovery; PR = partial response.
**Clofarabine, Etoposide, and CPM in Pediatric Patients with Refractory or Relapsed ALL**

Multicenter study

Pediatric patients with refractory or relapsed ALL received clofarabine 40 mg/m², etoposide 100 mg/m², and CPM 440 mg/m² given daily for 5 days in induction and 4 consecutive days in consolidation.


**Indications for Allogeneic BMT**

**Pediatrics**
- 1st remission
  - Hypodiploidy?
  - Ph+?
  - Induction failure?
  - rMLL infants, <6 months-of-age and slow response?
  - MRD >0.1 after 3 months?
- Early marrow relapse
- Late marrow relapse
  - MRD positive at end induction/consolidation (~1 month/~3 months)

**Adults**
- 1st remission—medically fit
  - Aged <39 years
    - High WBC
    - Unfavorable cytogenetics
    - MRD positive
  - Aged 40-65 years—medically fit
- 2nd remission—medically fit

Candidate Agents

**Chemotherapy**
- Antipurines
  - Clofarabine, nelarabine
- Liposomal vincristine
- FLT3 inhibitors
  - Lestaurtinib*, quizartinib (AC220)*
- Proteosome inhibitors
  - Bortezomib, carfilzomib
- mTOR inhibitors
  - Temsirolimus, evrolemus
- Aurora kinase inhibitors*
- BCL-2 inhibitors – obatoclax*
- Notch inhibitors
- Survivin inhibitors – EZN3042*
- Epigenetic strategies
  - Vorinostat/decitabine
- Toll-like receptor 9 agonists
- CXCR4 inhibitor – plerixafor

**Immune directed therapies**
- Monoclonals
  - Rituximab, Epratuzumab*
- Immunotoxins
- Moxetumomab*, SGN3419*, Inotuzumab ozogamicin*, SAR19a*, Combotox*
- Immune constructs
  - Blinatumomab*

*Investigational drug not currently FDA approved.

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Blinatumomab

![Blinatumomab diagram](image)

α-CD3 Monoclonal Antibody
BITE® Single-Chain Antibody
α-CD3/α-CD19
α-CD19 Monoclonal Antibody

T-cell
Cytotoxic Granule
CD3
CD19
CD19+ B-cell

Toll-Like Receptors

- TLR are pattern recognition receptors
  - Part of our innate immunity
- Perhaps T-cells are capable of recognizing other leukemia-specific antigens
  - Support for a role of host immune responses in the maintenance of post-chemotherapy remission
  - Relapse ALL possesses changes consistent with evasion of immune effector mechanisms
- **CpG-oligodeoxynucleotide**: TLR agonist for MRD-positive leukemia

*CpG = cytosine-phosphate-guanine.*

Another Approach: Chimeric Antigen Receptor

- Autologous chimeric antigen receptor
  - Extracellular domain derived from an antibody combined with the intracellular signaling domain of CD3
  - Allows tumor cells to be recognized in non-MHC manner
- 10 patients with CLL/ALL using CD19 as target
  - 4 CR
  - 2 PR in CLL

*MHC = major histocompatibility complex; CLL = chronic lymphocytic leukemia.*
The Right Stuff

The Right Drug
The Right Target
The Right Disease
The Right Context
The Right Schedule
The Right Dose
The Right Population


Conclusions

- Substantial numbers of young people and adults are cured with current risk-adapted strategies
  - Various post-induction intensification schemes yield similar outcomes with similar prognostic factors
  - Allogeneic BMT remains important for adults
  - AVN in adolescents and TRM in adults
- Relapse remains the major barrier to cure
  - BMT is not the complete answer to the challenge of relapse
- Targeted therapy requires identification of 'molecularly' homogenous subpopulations

AVN = avascular necrosis; TRM = treatment-related mortality.
Post-Activity Evaluation

To receive documentation of credit, please print and complete the evaluation and mail or fax it to NACCME.

Location of Meeting __________________________ Date of Meeting ______________

NACCME would appreciate your feedback on the quality and impact of this activity. Please answer the following questions, some of which are rated on a 5-point Likert scale (1 = strongly disagree/poor/very little; 5 = strongly agree/excellent/great deal).

1. To what extent were you able to achieve each of the following learning objectives?

   Outline the current classification system for ALL and the differences in biology and treatment strategies between pediatric and adult patients with ALL 1 2 3 4 5

   Review current evidence for induction, consolidation, maintenance, and transplant strategies in the treatment of ALL in pediatric and adult patients 1 2 3 4 5

   Summarize current guideline recommendations for the treatment of both Ph–negative and Ph–positive ALL patients 1 2 3 4 5

   Outline strategies for the treatment of patients with refractory or relapse ALL 1 2 3 4 5

   Identify emerging treatments and the role of currently available targeted agents in the management of ALL 1 2 3 4 5

2. Please rate the faculty in terms of their knowledge and expertise.

   1 2 3 4 5

3. Please rate the faculty in terms of their teaching ability.

   1 2 3 4 5

4. Please rate the following components relating to this activity:

   Content 1 2 3 4 5

   Relevance to your practice 1 2 3 4 5

   Educational format 1 2 3 4 5

   Audience-participation portions (eg, Q&A, pre/post-testing) 1 2 3 4 5

   Handouts and/or other materials supporting the activity 1 2 3 4 5

   Overall 1 2 3 4 5

5. How much did you learn as a result of this CE program? 1 2 3 4 5
6. Of the patients you see on a weekly basis, how many will benefit from the information you learned today?
   □ 10 or fewer    □ 20    □ 30    □ 40    □ 50 or more

7. Did this activity meet your educational needs?
   □ Yes    □ No

8. Did this activity increase your knowledge?
   □ Yes    □ No

9. Did this activity increase your competence?
   □ Yes    □ No

10. Did this activity increase your confidence?
    □ Yes    □ No

11. The therapeutic recommendations presented in this activity did not encourage inappropriate or excessive use of products/devices.
    □ Agree    □ Disagree

12. The information presented in this activity did not serve to advance a proprietary interest of any commercial entity.
    □ Agree    □ Disagree

13. How many patients with ALL do you impact on a weekly basis?
    □ 5 or fewer    □ 10    □ 15    □ 20    □ 25 or more

14. According to Nguyen et al, what is the average 5-year survival rate for children with ALL after a first relapse?
    a. Less than 25%
    b. 25% to 50%
    c. 51% to 75%
    d. More than 75%

15. How confident are you in your ability to optimize outcomes in children with ALL?
    a. Very confident
    b. Confident
    c. Somewhat confident
    d. Not confident

16. How do you rate your ability to appropriately treat patients with relapsed or refractory ALL?
    a. Excellent
    b. Good
    c. Fair
    d. Poor
17. How often do you intend to use novel chemotherapy for reinduction in children with more than 1 relapse of ALL?
   a. Always
   b. Often
   c. Rarely
   d. Never

18. Why do you plan to increase use of novel chemotherapy for reinduction in children with more than 1 relapse of ALL?
   □ Because novel chemotherapy has demonstrated the potential to increase survival rates
   □ Because of challenges associated with treatment alternatives
   □ I do not intend to increase because I already adhere to this recommendation
   □ I do not intend to increase because I disagree with this approach
   □ I do not intend to increase because of barriers outside of my control

19. Do you intend to make any changes to your practice?
   □ Yes, please specify:_______________________________________________________
      ______________________________________________________________________
      ______________________________________________________________________
   □ No

20. What barriers outside of your control prevent you from changing your practice and/or optimizing patient outcomes? (check all that apply)
   □ Lack of available guidelines for ALL treatment
   □ Formulary placement
   □ Affordability concerns on the part of the patient or caregiver
   □ Patient adherence
   □ Lack of patient or caregiver education regarding disease/treatment
   □ Adverse effects of ALL therapies
   □ Lack of influence over treatment selection
   □ Other:_________________________________________________________________

21. How might future activities help you address those barriers?
    ______________________________________________________________________
    ______________________________________________________________________
    ______________________________________________________________________
22. Would you be interested in additional educational activities within this therapeutic area?
   □ Yes – what topics would you like to learn more about?___________________________
   □ No

23. In which of the following other therapeutic or practice areas do you have educational needs?
   (check all that apply)
   □ Anemia
   □ Anesthesia
   □ Bacterial Infections
   □ Breast Cancer
   □ Colorectal Cancer
   □ Deep Vein Thrombosis
   □ Fungal Infections
   □ Hematologic Malignancies
   □ Hemostasis
   □ Law
   □ Lung Cancer
   □ Medication Errors/Safety
   □ Oncology Supportive Care
   □ Pain
   □ Prostate Cancer
   □ Psychiatry
   □ Transition of Care
   □ Transplant Medicine
   □ Other:_____________________

24. In which of the following formats do you prefer to receive education? (check all that apply)
   □ Live symposium
   □ Small-group meeting
   □ Phone teleconference
   □ Live web meeting
   □ On-demand web
   □ Handheld/mobile device
   □ Enduring print
   □ Other:_________________________________________________________________

25. How much time did you spend participating in this activity?
   _______________________________________________________________________

REQUEST FOR CREDIT
Please complete all sections to be eligible for credit and return to course registrar at the meeting site.

E-mail [REQUIRED] ___________________________ Degree ____________________________
Name ___________________________ Title/Specialty ____________________________

REQUIRED FOR PHARMACISTS: Date of Birth (MM/DD) ________________ NABP ID ________________
Address ___________________________ Affiliation ____________________________
City ___________________________ State _____________ Zip ___________ Phone__________________

NACCME: 300 Rike Drive, Suite A, Millstone Township, NJ 08535; Phone: 609-371-1137; Fax: 609-371-2733