Acute Lymphoblastic Leukemia

*In Adults*

Overview and Updates

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Fellowship, Hematology/Oncology: University of Pennsylvania, Philadelphia, PA

Clinical Focus: ALL, AML, CML, BPDCN, MDS, and MPNs
Research Focus: ALL, AYAs, novel therapeutics for acute leukemia.
Disclosures

• Pfizer, Advisory Board
• Abbvie, Research Funding
• Novartis, Research Funding
Acute Lymphoblastic Leukemia (ALL)

- **Aggressive hematologic neoplasm of B- or T-lymphoblasts**
  - Acute lymphoblastic leukemia (ALL)
  - Lymphoblastic lymphoma (LBL)

- **Clinical Presentation**
  - Cytopenias (bone marrow failure), adenopathy (enlarged lymph nodes), mediastinal mass (T-cell), hepatosplenomegaly, **central nervous system**.
  - Constitutional symptoms (fatigue, fevers, sweats, weight loss, bone pain).

- **Diagnosis: Morphology (blasts) and immunophenotype (flow cytometry/IHC) to determine lymphoid (B or T) and maturity stage.**
  - B-lymphoblasts: CD10, CD19, CD20 (some), and CD22; Ig negative
  - T-lymphoblasts: cCD3 and other T cell antigens.
ALL – Epidemiology and Demographics

At a Glance

<table>
<thead>
<tr>
<th>Estimated New Cases in 2022</th>
<th>6,660</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of All New Cancer Cases</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Acute lymphocytic leukemia represents 0.3% of all new cancer cases in the U.S.

- Most common leukemia in children.
- Adults: ~50% of diagnoses, but majority of relapses and death.
- Risk factors: Down syndrome, prior chemo/radiation (myeloma).
- In adults, ~1/3 are Philadelphia-chromosome positive

ALL: A Pediatric Oncology Success Story

• **1948:** Sidney Farber described 5 children who responded (temporarily) to the folic acid antagonist *aminopterin.*

• **2022:** 73 years later, most children cured.

ALL in Adults: More Work to be Done

Outcomes worsen with increasing age.
• Particularly impacting older adults.

ALL – Framework for Initial Approach to Adult ALL

Initial therapeutic decisions guided by:

1) Philadelphia-chromosome status

2) Age/fitness for chemotherapy
   • AYA: Pediatric-inspired
   • Adult: Standard intensity
   • Older/With Medical Problems: Less intense
ALL – Approach to Initial Treatment

- **Induction Goal → Achieve Remission**
  - Reduce morphologically apparent leukemia to undetectable levels → complete remission (CR).

- **Consolidation/Maintenance Goal → Prolong Remission/Cure**
  - Reduce minimal residual disease present at CR (*measured or presumed*) to a level low enough to achieve prolonged disease-free survival, sometimes cure.
Philadelphia Chromosome **Negative**

Acute Lymphoblastic Leukemia
## Approach to Ph-Negative ALL Therapy (B and T)

<table>
<thead>
<tr>
<th></th>
<th>Age &lt; ~40 (AYA)</th>
<th>Age 40–70 (Fit) (Adult)</th>
<th>Age &gt;70/Unfit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal</strong></td>
<td>Cure</td>
<td>Cure</td>
<td>Cure? Control!</td>
</tr>
<tr>
<td><strong>Induction</strong></td>
<td>AYA induction</td>
<td>Adult induction</td>
<td>Less intense induction</td>
</tr>
<tr>
<td><strong>Consolidation</strong></td>
<td>Low-risk: Chemotherapy</td>
<td>Low-risk: Chemotherapy</td>
<td>Less intense consolidation/maintenance</td>
</tr>
<tr>
<td></td>
<td>High-risk: Transplant</td>
<td>High-risk: Transplant</td>
<td></td>
</tr>
</tbody>
</table>

**CLINICAL TRIALS**
Philadelphia-chromosome-negative ALL

• Multiple cycles of combination chemotherapy.
  • Complex: numerous drugs in different doses, combinations, and schedules.
  • Prolonged chemotherapy (2-3 years from CR), unless transplant in first CR.
  • Phases: 1) induction, 2) consolidation with CNS phase, 3) maintenance.

• “Core” drugs: vincristine, steroids, anthracycline
  • YOUNG: “Pediatric-inspired” or “AYA” (adolescent young adult) regimens are more intensive including asparaginase, steroids, vincristine, and escalated CNS prophylaxis, lead to improved outcomes.
  • OLDER: Dose-reduced chemo, *investigational: novel agents*

• CNS prophylaxis is mandatory
  • IT chemotherapy, high dose cytarabine/methotrexate, CNS radiation
Approach to Ph-Neg ALL in Younger Adults

- Patients aged ≤ 40 years (adolescent and young adults, “AYAs”) have improved outcomes when treated on a pediatric-inspired regimen.
- Identified retrospectively → safety and efficacy demonstrated prospectively with favorable outcomes compared to historical controls.

AYAs aged 16–20 years treated on pediatric (CCG) or adult (CALGB) trials 1988–2001

Identical CR rates (90%)

7-year survival:
CCG: 67%
CALGB: 46%

Asparaginase (ASNase): Mechanism of Action

• Asparagine (Asn) is an amino acid that can be synthesized from aspartic acid by most cells using asparagine synthetase (ASNS).

• ALL cells lack ASNS, thus depend on import of Asn from plasma, making them sensitive to depletion of plasma Asn.

• ASNase breaks down Asn to aspartic acid and ammonia.

• ASNase depletes plasma Asn, thereby killing ALL cells but not normal cells that can make their own Asn.

ASNase is a key component of effective contemporary pediatric ALL regimens.

AYA Regimens – Asparaginase a Particular Challenge

- Asparaginase-related
  - Thrombosis/hemorrhage
  - Liver toxicity
  - Pancreatitis
  - Hypertriglyceridemia
  - Hyperglycemia
  - Hypersensitivity

- Steroid + asparaginase related osteonecrosis

Why Bother? More Asparaginase → Better Outcomes

In DFCI 91-01, patients who tolerated <26 wk of planned 30 wk of ASNase therapy had inferior outcome

5-Yr EFS (n = 352)

Asparaginase Tolerance ≤ 25 Wk

Asparaginase Tolerance ≥ 26 Wk

P < .01

DFS of NCI High-Risk Patients on COG AALL0232

P = .0030

DFS Probability

Cumulative Incidence of Relapse by Asparaginase Truncation, Enzyme Activity

Erwinia substitution, received all doses (n = 187)
Missing asparaginase doses (n = 443)
Received all PEG-ASNase doses (n = 1556)

7-Yr CIR, %

Truncated, dAA → %
Nontruncated, dAA

Relapse-specific adjusted HR: 1.69 (P = .03)

DFCI

COG

NOPHO

as required per Section 2.1

Course I is to begin ≤ 5 days of registration (Step 1).

**COURSE I: REMISSION INDUCTION THERAPY**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Days</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX</td>
<td>D1,D2</td>
<td>60 mg/m²</td>
</tr>
<tr>
<td>Ara-C</td>
<td>D1-8</td>
<td>1 g/m²</td>
</tr>
<tr>
<td>VCR</td>
<td>D1</td>
<td>10 mg/m²</td>
</tr>
<tr>
<td>DNR</td>
<td>D1</td>
<td>10 mg/m²</td>
</tr>
</tbody>
</table>

**COURSE II: REMISSION CONSOLIDATION**

Begin Course II within 7 days after peripheral blood counts recover with ANC ≥ 750 μL and platelets ≥ 75,000 μL.

If counts not recovered within 4 weeks, then contact the study chairs. Therapy should be interrupted for patients who are febrile, neutropenic, and proven infected, and resumed at the same point when the signs of infection have abated.

**COURSE III: INTERIM MAINTENANCE (Captopriz Methotrexate)**

Begin Course III within 7 days after peripheral blood counts recover with ANC ≥ 750 μL and platelets ≥ 75,000 μL.

Therapy should be interrupted for patients with severe infections and resumed when the signs of infection have abated.

**COURSE IV: DELAYED INTENSIFICATION**

A bone marrow aspirate and biopsy must be obtained prior to initiation of Course IV.

Begin Course IV within 7 days after peripheral blood counts recover with ANC ≥ 750 μL and platelets ≥ 75,000 μL.

If counts not recovered within 4 weeks, then therapy should be interrupted for patients with severe infections.

**Additional Information**

- VCR and IV methotrexate treatment day (See Section 2.4.3)
- If patient has consented to A041A

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**VCR**

- Day 1
- Day 8

**DNR**

- Day 1
- Day 8

**Ara-C**

- Day 1-8
- Day 15-16

**MTX**

- Day 1
- Day 15

**PEG**

- Day 1

**CTX**

- Day 1
- Day 22

**Cyclophosphamide**

- Day 1
- Day 22

**Vincristine 1.5 mg/m²**

**DNR**

- Day 1
- Day 8

**Cyclophosphamide**

- Day 1
- Day 22

**Vincristine 1.5 mg/m²**

**Dex**

- Day 1
- Day 8

**Peg-Asp**

- Day 1
- Day 8

**It-MTX**

- Day 1
- Day 15

**6-MP**

- Day 1
- Day 8

**6-TG**

- Day 1
- Day 8

---

**DNR, MTX, DOX, DEX**

**VCR, Cyclo, Peg-Asp, 6-MP**

**Pred, Dex, It-MTX, 6-TG**

**Ara-C**

**IT-MTX, 6-MP, 6-TG**

**IT-MTX, 6-MP, 6-TG**

**IT-MTX, 6-MP, 6-TG**

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*MTX is given on Day 14 of the first 4 courses of maintenance therapy.

*PO MTX is held on Day 28 of the first 4 courses of maintenance therapy.

*Hold Day 29 chemotherapy until ANC ≥ 750 μL.

*VCR, Vincristine 1.5 mg/m² maximum dose 2 mg IV on Days 1, 8, and 15. Vincristine and prednisone are administered together with vincristine.
Philadelphia Chromosome Negative Acute Lymphoblastic Leukemia

New: Pediatric Regimens for Adolescent and Young Adults (AYAs)
Approach to Ph-Neg ALL in Adults: Chemotherapy

- Regimens based on multiple cycles of intensive multi-agent chemotherapy.
  - Many "standard" regimens.
- Common in the US: ECOG 2993\(^1\), Hyper-CVAD\(^2\), CALGB 9111("Larson").\(^3\)
- Similar Response Rates Across Trials:
  - CR: ~90%; OS/Cure: 40%
- The recent ECOG 1910 trial randomized to blinatumomab consolidation; results awaited.

Older Adults: Poor Outcomes With Conventional Chemotherapy

<table>
<thead>
<tr>
<th>Adult trials, older adult cohorts (dose modifications employed)</th>
<th>Age</th>
<th>CR (%)</th>
<th>Early Death (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9111</td>
<td>≥60</td>
<td>77</td>
<td>17</td>
<td>17 (3 yr)</td>
</tr>
<tr>
<td>ECOG 2993 / UKALL XII</td>
<td>55-65</td>
<td>73</td>
<td>18</td>
<td>21 (5 yr)</td>
</tr>
<tr>
<td>Hyper CVAD</td>
<td>≥60</td>
<td>84</td>
<td>10</td>
<td>20 (5 yr)</td>
</tr>
<tr>
<td>Older adult trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dana-Farber/Harvard</td>
<td>&gt;50</td>
<td>67</td>
<td>13</td>
<td>52 (2 yr)</td>
</tr>
<tr>
<td>GMALL</td>
<td>≥55</td>
<td>76</td>
<td>14</td>
<td>23 (5 yr)</td>
</tr>
<tr>
<td>PETHEMA ALLOLD07</td>
<td>≥55</td>
<td>74</td>
<td>13</td>
<td>12.4 mo med</td>
</tr>
</tbody>
</table>

Numbers reflect treated patients, eligible for and interested in clinical trial.

**Resistant Disease**
- Lower CR rate/refractory
- Relapse

**Toxicity**
- High early death (10-20%)
- Death in CR

Many not even treated: US Medicare analysis (2019) – only 51.1% ≥ 66 years treated within 90 days. Most (78.3%) untreated were 75+ years.

Extremely Poor Outcomes in Older Adults with ALL. Little Improvement for 3 decades.

**SEER Analysis**

- **n=1675; 1980-2011**

<table>
<thead>
<tr>
<th>Population</th>
<th>3-year OS (%)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>13%</td>
<td>4</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>24%</td>
<td>9</td>
</tr>
<tr>
<td>≥ 75</td>
<td>10%</td>
<td>&lt;3</td>
</tr>
<tr>
<td><strong>Era</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-1990</td>
<td>10%</td>
<td>3</td>
</tr>
<tr>
<td>2000-2011</td>
<td>16%</td>
<td>6</td>
</tr>
</tbody>
</table>

ALL in Older Adults: Improving Outcomes
Conventional Chemotherapy → Novel Agents

**Disease (Chemotherapy Resistance)**
- ↓CR rate  ↑Relapse
Need: More effective therapies

**Patient (Chemotherapy Tolerability)**
- ↑Early mortality, ↑Death in CR
Need: Less toxic therapies.

**Social, Logistical (Access)**
- ↑No or minimal treatment
Need: Therapies that are **not too complicated**.
Philadelphia-chromosome-negative (Ph-) ALL
Incorporating Novel Agents

- Until recently, only option available for Ph- ALL was conventional chemotherapy.
- Blinatumomab (2014) and inotuzumab ozogamicin (2017) approved for relapsed and refractory B-ALL.
- Other novel agents being investigated for ALL, including venetoclax.

<table>
<thead>
<tr>
<th>Goals</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better efficacy</td>
<td>Add novel agents</td>
</tr>
<tr>
<td>Less toxicity</td>
<td>Reduce/omit conventional chemotherapy</td>
</tr>
</tbody>
</table>
Inotuzumab + mini-hyper-CVD

Phase 2, single center, untreated patients ≥ 60 years

Outcomes updated ASH 2021 (n=79, 38% ≥ 70 years)
• Early mortality: 0%
• MRD-negative CR: 94%; 3-yr OS: 55%
• Death in CR: 34% (29/79); most ≥ 70 yrs (sepsis, VOD, MDS/AML).

Modifications:
• Inotuzumab dose reduced/fractionated
• Chemotherapy cycles decreased, omitted ≥ 70 years
• Blinatumomab added

Philadelphia-chromosome-negative (Ph-) ALL
Incorporating Novel Agents

Philadelphia-chromosome-negative (Ph-) ALL Incorporating Novel Agents **SUMMARY**

- High CR rates (80-90%).
- Most MRD negative (80-90%).
- Low induction mortality - <5%.
- Late toxicity still a problem.
- **Long-term outcomes awaited!**
- NCTN plans randomized comparison to establish new standard.

ALL in Older Adults: Starting to Improve?

• Little progress over time: US SEER (n=1675), >60 yrs, 3-yr OS 10% → 16% (1980-2011)
• Now, glimmers of hope?
• More patients being treated →

• Updated SEER analysis shows improvement in the 2010s
  • Age 60-69 (n=723): 1990s Median OS 6 mos → 2010s 18 mos (5-yr OS: 14→29%)
  • Age 70+ (n=890): 1990s Median OS 1 mo → 2010s 4 mos (5-yr OS: 4→13%)

Philadelphia Chromosome Negative Acute Lymphoblastic Leukemia

New: Novel Agent Being Studied In Initial Therapy To Improve Outcomes, Especially Important for Older Adults
Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

$\text{Ph}^+ = t(9;22) = BCR-ABL$ fusion. ABL kinase is a major driver of disease.
Philadelphia Chromosome Positive (Ph+) ALL

- Present in ~1/3% of ALL cases.
- Prevalence increases with age (>50% over age 50 years).
- Historically adverse prognosis.

TKIs (Imatinib) Improve Outcome in Chemotherapy Treated Patients

• Imatinib improves outcome when combined with chemotherapy.
• Higher CR rates, higher OS, more patients → BMT.
• Better outcomes if introduced earlier in treatment.

Ph+ (20%): 25%
Ph− (80%): 41%

Key Points

• Imatinib improves outcomes for adults with Ph+ ALL at least in part by facilitating allogeneic stem cell transplant.

Tyrosine Kinase Inhibitors $\rightarrow$ CR with Minimal Tox

- **GRAAPH-2005** $\rightarrow$ IM + VCR/Dex: ↑CR rate and ↓mortality compared to IM + hyperCVAD.

- **GIMEMA** $\rightarrow$ Successful “chemotherapy-free” induction (imatinib LAL 0201-B; dasatinib LAL 1205, ponatinib LAL 1811).
  - High CR rates (>90%).
  - 2G/3G TKIs - Deeper and more durable.
  - Minimal toxicity.

TKIs allow reduction or omission of conventional chemotherapy during induction in Ph+ ALL.

Ph+ ALL: Which TKI is Best?

- In combination with chemotherapy, retrospective comparison (hyper-CVAD context) suggest better outcomes with 2G and 3G TKIs (deeper remissions, improved survival).

- Ponatinib is potent and active again T315I, a common mechanism of resistance to earlier generation TKIs, but associated with cardiovascular toxicity.

Ph+ ALL: Best Post-Remission Approach Not Defined, Approach Individualized

- **TKI** is not curative.
- Options (and/or):
  - Allogeneic hematopoietic stem cell transplant (HSCT)
  - Chemotherapy: Age-adjusted
  - ?Novel agents: Blinatumomab
- One size fits all vs age/co-morbidity tailored and risk adapted approach.
  - Here is where roads diverge!

Benefit of HSCT for Ph+ ALL in CR1

GRAAPH-2005
imatinib + chemotherapy

RFS
Transplant
No Transplant

OS
Transplant
No Transplant

US Intergroup
dasatinib + hyperCVAD

D  Landmark overall survival, 175 days after CR/CRi

Transplant
No Transplant

Log-rank p-value = 0.037

C  Landmark relapse–free survival, 175 days after CR/CRi

Transplant
No Transplant

Log-rank p-value = 0.038

Ph+ ALL: Do All Patients Need HSCT for Cure?

- Some patients may not benefit. But which ones?

- **Good outcomes without HSCT.**
  - Some patients treated with TKI + chemo rapidly achieve deep responses → favorable long-term outcomes without HSCT.

- **Risk of HSCT.**
  - Increased patient age, comorbidities increase toxicity.
  - Transplant advances may reduce toxicity.

---

HSCT May Be Unnecessary after Optimal Response to Intensive Chemo (hyper-CVAD)

Figure 1

A. overall survival (OS)

- A. ALLO–HCT
- B. non–HCT

<table>
<thead>
<tr>
<th>Probability of survival</th>
<th>Years post diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>0.4</td>
<td>4</td>
</tr>
<tr>
<td>0.6</td>
<td>6</td>
</tr>
<tr>
<td>1.0</td>
<td>8</td>
</tr>
</tbody>
</table>

98 76 63 46 29 A
132 100 59 35 17 B

HR=0.78, p=0.26

B. relapse–free survival (RFS)

<table>
<thead>
<tr>
<th>Probability of survival</th>
<th>Years post diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>0.4</td>
<td>2</td>
</tr>
<tr>
<td>0.6</td>
<td>4</td>
</tr>
<tr>
<td>0.8</td>
<td>6</td>
</tr>
<tr>
<td>1.0</td>
<td>8</td>
</tr>
</tbody>
</table>

98 73 57 44 29 A
132 89 85 32 16 B

HR=0.75, p=0.15

C. Relapse

<table>
<thead>
<tr>
<th>Cumulative incidence</th>
<th>Years post diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
<td>0</td>
</tr>
<tr>
<td>0.04</td>
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<tr>
<td>0.06</td>
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<tr>
<td>0.08</td>
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<tr>
<td>0.10</td>
<td>8</td>
</tr>
</tbody>
</table>

98 73 57 44 29 A
132 89 85 32 16 B

HR=0.46, p=0.01

D. non–relapse mortality (NRM)

<table>
<thead>
<tr>
<th>Probability of survival</th>
<th>Years post diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
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</tr>
<tr>
<td>0.04</td>
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<tr>
<td>0.10</td>
<td>8</td>
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</tbody>
</table>

98 73 57 44 29 A
132 89 85 32 16 B

HR=1.31, p=0.29

E. GvHD & relapse–free survival (GRFS)

<table>
<thead>
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<th>Probability of survival</th>
<th>Years post diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
<td>0</td>
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<tr>
<td>0.04</td>
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<td>4</td>
</tr>
<tr>
<td>0.08</td>
<td>6</td>
</tr>
<tr>
<td>0.10</td>
<td>8</td>
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</tbody>
</table>

98 36 27 20 12 A
132 89 55 32 16 B

HR=2.13, p=0.01

GRAAPH-2014: TKIs are Great, but Not Enough

- **New Ph+ ALL, ages 18-60**
- **Design:** Random evaluation of no HiDAC consolidation.
- **Primary endpoint:** MMoIR BCR-ABL1 ≤0.1% after 4th treatment cycle (MRD4).
- **TKI:** Imatinib → nilotinib.
- **Chemo:** 4 cycles prior to BMT.
- **BMT:** Allo HSCT in CR1 if matched donor (MSD or MUD).
- **Maintenance:** 2-yr IM post BMT.

ASH 2021 Abstract 614: Rousselot et al.
• Randomization stopped early due to excess relapse in Arm B (no HiDAC).
• Transplanted patients in Arm B (no HiDAC) had dramatically better outcomes.
• Outcomes of patients in Arm A (HiDAC) were similar regardless of alloSCT status.

GRAAPH-2014 study – Omission of HiDAC consolidation in younger patients (18-60 years) → frequent relapses in the absence of HSCT (Take Home: Need intensification with chemotherapy or HSCT, can’t omit both!)
GIMEMA D-ALBA Study

- N=63, median age 54 (range 24-82) yrs
- Follow-up still short.
- Approximately half → HSCT.

**Note:**  
Follow-up still short.
Approximately half → HSCT.

- Day 85 – 29% Molecular Response
- Blina C2 (n=55) – 60% Molecular Response
- Blina C4 – 81% Molecular Response

- 36-month DFS and OS rates 71% and 80%, respectively (median follow-up 28.8 months).
- Worse outcomes in *IKZF1* deletion.
Ponatinib + Blinatumomab in Ph+ ALL: Regimen

**Induction phase (C1)**
- Ponatinib 30 mg
- 4 weeks

**Consolidation phase (C2-C5)**
- Ponatinib 15 mg (if in CMR)
- 2 weeks
- IT MTX / Ara-C x 12

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

A phase II trial of a chemotherapy-free combination of ponatinib and blinatumomab in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL)

Nicholas Short, Hagop Kantarjian, Marina Konopleva, Guillermo Montalban-Bravo, Farhad Ravandi, Nitin Jain, Tapan Kadia, Yesid Alvarado, Kelly Chien, Naval Daver, Waldid Macaron, Koji Sasaki, Jennifer Thakerahan, Ricardo Delumbe, Eiroyhene Mayor, William Du, Christopher Leteille, Monica Kwo, Rebecca Garris, Elias Jabbour

Department of Leukemia
The University of Texas MD Anderson Cancer Center, Houston, TX
Ponatinib + Blinatumomab in Ph+ ALL: MRD Response Rates

End of Cycle 1

- FL Ph+ ALL: 64% CMR, 12% MMR, 3% No MMR, 3% No CR
- R/R Ph+ ALL: 71% CMR, 14% MMR, 7% No MMR, 7% No CR
- CML-LBC: 67% CMR, 17% MMR, 3% No MMR, 3% No CR

Overall

- FL Ph+ ALL: 85% CMR, 7% MMR, 3% No MMR, 17% No CR
- R/R Ph+ ALL: 79% CMR, 7% MMR, 17% No MMR, 17% No CR
- CML-LBC: 33% CMR, 33% MMR, 17% No MMR, 17% No CR
Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes for Frontline Cohort

Median follow-up: 11 months (range, 1-41)

**Event-Free Survival**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Patients without an Event (%)</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
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<tr>
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<tr>
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<td>2</td>
</tr>
<tr>
<td>48</td>
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<td>0</td>
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</tbody>
</table>

- Total Events: 2
- Median EFS: Not Reached
- 2-year EFS (95% CI): 93% (76%-98%)

**Overall Survival**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Patients Who Were Alive (%)</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>35</td>
</tr>
<tr>
<td>6</td>
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<td>12</td>
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<td>4</td>
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<tr>
<td>42</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>48</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Total Events: 2
- Median OS: Not Reached
- 2-year OS (95% CI): 93% (76%-98%)

- Transplanted patient had persistently detectable BCR-ABL1 transcript levels of 0.01%-0.05%
- No patient has relapsed with median CR duration of 10 months (range, 1 to 43 months)

**Notes:**
- Death in CR, n=1
  - Due to post-procedural bleeding and hypovolemic shock
- Early Death, n=1
  - Due to intracranial hemorrhage
- Ongoing response with HSCT in CR1, n=1*
- Ongoing response without HSCT, n=32
• Currently accruing.

**Induction:** TKI plus steroids.
• *Choice:* DAS or PON

**Consolidation:** Randomized to TKI+hyper-CVD or TKI+blinatumomab.

**Transplant:** Allowed, not proscribed.

• Will we get answers about best consolidation approach?
• Enrolling to randomized trials is important.
Ph+: ALL Conclusions and Questions

• **Known:** TKIs improve outcomes and are an essential component of therapy for Ph+ B-ALL.

• **Question:** What is the best TKI?
  - In US, most use 2G dasatinib, but there is interest in 3G TKI ponatinib.
  - Concerns about toxicity of 3G TKI.
    - Mitigated by optimized dosing (de-escalate after response)?
    - Can patients be appropriately selected based on disease risk and comorbidities?
  - **Investigational:** combination of catalytic domain and allosteric inhibitor?
    - Dasatinib plus ABL001 – DFCI protocol 18-170
Ph+: What We Know and (Mostly) What Don’t Know

INDUCTION: Is intensive chemotherapy needed? In general no, associated with higher toxicity/early mortality.
- Do some patients benefit from early chemotherapeutic intensification?
- Should less toxic, novel agents (i.e. blina) be introduced early (before CR)?

CONSOLIDATION (FIT): TKI is not enough. Best addition? HSCT or intensive chemo, blina
- HSCT remains an accepted standard, but patients who respond optimally to intensive chemotherapy may not need.
- Long-term outcomes in patients treated with 2G/3G TKI plus novel agents (blina) unknown. Appear very effective, but curative?
- For transplant INeligible, how to best consolidate?
Philadelphia Chromosome Negative
Acute Lymphoblastic Leukemia

New:
Many options – Potent TKIs, novel agents (blinatumomab), chemotherapy, BMT. Adverse prognosis being reversed?
Relapsed ALL
Relapsed ALL: Historically, Dismal Prognosis


609 adults with relapsed ALL treated on ECOG 2993

“Favorable” findings
• Younger (<20 years)
• Long first remission

HSCT needed

OS at 5 years after relapse was 7% (95% CI: 4%–9%)
ALL – Antibodies for B-ALL in Relapse

- **Blinatumomab (TOWER)** - Bispecific monoclonal antibody targeting CD19 and CD3. Enables CD3+ T-cells to recognize and destroy CD19+ cells (malignant and normal).
  - **Toxicity:** CRS, neurotoxicity
  - **Strengths:** Lower disease burden, MRD +
  - **Logistics:** Continuous infusion.

- **Inotuzumab ozogamicin (INO-VATE)** - Humanized IgG4 anti-CD22 antibody covalently linked to a cytotoxic agent (calicheamicin) → double-strand DNA breaks and apoptosis.
  - **Toxicity:** Cytopenias, liver toxicity (VOD)
  - **Strengths:** Effective at high and low disease burden, extramedullary disease
  - **Logistics:** Weekly Infusion


CR: 34 vs 16% (P<0.001)
CR plus CRi: 44 vs 25% (P<0.001)

Median OS
7.7 vs 4.0 mos
HR for death 0.71 (P=0.01)
(24% in each group → transplant)

51.34% difference  
*P* < .001
# Key Anti-CD19 CAR T-Cell Therapy Trials: B-ALL

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Study Population</th>
<th>CAR T-cell Agent</th>
<th>CR, %</th>
<th>Median OS, mos</th>
<th>Median EFS, mos</th>
<th>Median DoR, mos</th>
<th>Median follow-up, mos</th>
<th>FDA approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Pediatric/young adults with R/R B-ALL</td>
<td>Tisagenleucel</td>
<td>MRD negative: 81</td>
<td>19.1</td>
<td>NR</td>
<td>NR</td>
<td>13.1</td>
<td>FDA approved</td>
</tr>
<tr>
<td>I</td>
<td>Adults with relapsed B-ALL</td>
<td>JCAR015</td>
<td>Overall: 83</td>
<td>12.9</td>
<td>6.1</td>
<td>--</td>
<td>29</td>
<td>Halted</td>
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<tr>
<td>I/II</td>
<td>Adults with R/R B-ALL</td>
<td>KTE-X19</td>
<td>Overall: 68</td>
<td>--</td>
<td>--</td>
<td>RP2D: 12.9</td>
<td>16</td>
<td>FDA approved</td>
</tr>
</tbody>
</table>

Current Treatment Algorithm for R/R B-ALL

**SCT naive**
- MRD and CR19+ = Blina
- Low disease burden and CD19+ = Blina
- Bulk disease or extramedullary disease and CD22+ = INO
- CD19- and CD22- = chemo

**Remission = SCT**

**Relapse post SCT**
- CD19+ = CAR T-cell
- CD19-/CD22+ = INO
- CD19- and CD22- = chemo

- If CAR T-cell would watch
- If INO or chemo = Consider 2\textsuperscript{nd} SCT
Relapsed T-ALL: Nelarabine

- Nelarabine is the prodrug of AraG; the active metabolite AraGTP accumulates in T lymphoblasts to a greater extent than in B cells or mature T cells due to decreased AraGTP degradation
- Associated with peripheral and CNS toxicities, myelosuppression dose dependent
- In adult R/R setting, 31% CR rate, 1-year OS 28% (DeAngelo Blood 2007); similar in children (Berg J Clin Oncol 2005)
- Approved for relapsed/refractory T-cell ALL

Relapsed T-ALL: Nelarabine Combinations

Shimony, Luskin, DeAngelo DFCI experience, unpublished data
Relapsed ALL

New: Effective salvage, particularly for B-ALL
ALL Conclusions

• ALL is a rare disease - approximately 50% of cases in adults.

• Outcomes in adults lag excellent pediatric outcomes, but improving.

• Treatment is dictated by age and Philadelphia chromosome status.

• Innovation is focused on improved risk stratification (MRD techniques) and incorporation of novel agents – TKIs, antibody therapies, cellular therapy, and optimization of transplant – in first line and relapsed disease.
Much Left To Be Done.

• T-cell ALL remains an area of unmet need.

• Further studies to define best way to incorporate novel agents, CAR-T, BMT into the treatment of adults with ALL, tailored to age, disease subtype (B vs T, genetic subtype), and response.

• Careful reporting of long-term as well as short term outcomes.

• Attention to representative enrollment to clinical trials based on age, race, ethnicity, socio-economic resources, geography – this is key.
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