Update in Acute Lymphoblastic Leukemia

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Disclosure Information

The following relationships exist related to this presentation:

• Dr. Richard Stone has served as a consultant for Abbvie, Amgen, Agios, Arog, Celgene, Cornerstone, Jazz, Karyopharm, Novartis, Orsenix, Pfizer,

Off-Label/Investigational Discussion

In accordance with CME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
ALL: Outline

Ph-Negative: Younger
  Pediatric-like rx
  rituximab
Ph-Negative: Older
Ph-Positive: Younger
  TKI plus chemo
Ph-Positive: Older
  TKI plus steroids

Options for Relapse
Why pediatric-like therapy has surpassed these ‘legacy regimens’

• Newly diagnosed
  – 5-drug induction regimen for CALGB, the so called Larson regimen (C-9111)
    – Hyper-CVAD
    – MRC/ECOG
AYA Studies

• Retrospective data suggest patients have improved outcomes when treated with pediatric regimens
  – Stock et al., Blood 2008

• Prospective trials suggest improved outcomes in young adults using pediatric, pediatric inspired or augmented regimens
  – ALL96: Ribera et al., JCO 2008
  – Toronto Study: Storring et al BJH 2009
  – DFCI Consortium: DeAngelo et al., Leukemia 2015; DeAngelo ASH 2015
  – CALGB 10403: Stock et al., ASH 2014
  – Augmented-BFM: Ryttig et al., Cancer 2014
Event-Free Survival: CALGB (adult group) vs CCG (pediatric group)

Log Rank p < .0001

Ages 16-20

Initial DFCI Adult ALL Consortium Trial (#01-175)

- Regimen based on DFCI Pediatric Consortium Trial (Vrooman et al., JCO 2013)

Induction → CNS Prophylaxis → Consolidation → Maintenance

- IT Chemo + XRT
- Over a period of 30 weeks
- Until 2 years from CR

Adult patients were all treated as High-Risk patients
Native E. coli Asparaginase dose-adjusted per levels

DeAngelo et al., Leukemia 2015
01-175 Adult ALL: Response Data

Total Patients = 92
Response data = 92 patients
CR = 78 (85%)
Induction Deaths = 1 (sepsis)
DFS (4-yr) = 69%
OS (4-yr) = 67%

DeAngelo et al., Leukemia 2015
# 01-175 Toxicity Table

<table>
<thead>
<tr>
<th></th>
<th>Overall n=92</th>
<th>Induction n=92</th>
<th>CNS n=67</th>
<th>Consol n=62</th>
<th>Cont n=48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pancreatitis/ Amylase/Lipase</strong></td>
<td>13 (13%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>8 (13%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td><strong>AST/ALT/Bilirubin</strong></td>
<td>57 (62%)</td>
<td>24 (26%)</td>
<td>5 (7%)</td>
<td>33 (53%)</td>
<td>21 (44%)</td>
</tr>
<tr>
<td><strong>Thrombosis/Emboli sm</strong></td>
<td>16 (17%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>14 (23%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td><strong>CNS event</strong></td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Allergy</strong></td>
<td>5 (5%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>4 (6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

CTC2 used for toxicity criteria

One patient died of grade 5 pancreatitis.

DeAngelo et al., Leukemia 2015
DFCI Adult ALL Trials
01-175 and 06-254 Trials

**Induction** → **CNS Prophylaxis** → **Consolidation** → **Maintenance**

- **Induction**
  - IT Chemo + XRT

- **CNS Prophylaxis**
  - Over a period of 30 weeks

- **Consolidation**
  - Until 2 years from CR

- **Consolidation I**
  - 1A=HDMTX
  - 1B=BFM-like
  - 1C=HiDAC

- **Consolidation II**
  - IT Chemo + XRT
  - 15 doses of PEG over 30 weeks

- **Maintenance**
  - Until 2 years from CR

**Steroid prophase**
**PEG on day +7**
Overall Survival Based on Age

- 18–19 yrs (N=9)
- 20–29 yrs (N=38)
- 30–39 yrs (N=30)
- 40–50 yrs (N=33)
Overall Survival Based on Immunophenotype
Overall Survival
Based on Body-Mass Index (BMI)
Overall Survival

HR = 3.12 (1.99-4.90); P < 0.0001

AYA: Conclusions

• The administration of a dose-intensified Pediatric regimen in adults is feasible with acceptable toxicity

• This approach *may* translate into better survival for adults with ALL
  – 3-yr OS = 75%; 3-yr DFS = 73% (42.2 month f/u)
  – PEG-asparaginase has increased toxicity in older adult patients as well as patients with high BMI (> 30)

• Many challenges remain
  – Psycho-social issues
  – Practice patterns
  – Biology (Ph-like signature)
  – MRD status

• We need more cooperative groups AYA trials!
CD20 in ALL

• CD20 is expressed in about 40% of patients with B-cell ALL\(^1\)

• CD20 expression is associated with an adverse prognosis in adult ALL

• This suggests that targeting CD20 may affect outcome\(^2\)

Addition of Rituximab Improves Outcome in CD20-Positive Patients

### Chemo Rx ± Rituximab: Results of the Randomized GRAALL-R 2005 in Pre–B-ALL

- 220 patients; median age 40 y (18-59)
- Pediatric inspired GRAALL ± 16-18 rituximab infusions
- Median follow-up 30 months

<table>
<thead>
<tr>
<th>Parameter, %</th>
<th>Chemo Rx + Rituximab N = 105</th>
<th>Chemo Rx N = 104</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>92</td>
<td>91</td>
<td>NS</td>
</tr>
<tr>
<td>MRD neg at CR</td>
<td>65</td>
<td>61</td>
<td>.82</td>
</tr>
<tr>
<td>MRD neg post C3</td>
<td>91</td>
<td>82</td>
<td>.31</td>
</tr>
<tr>
<td>SCT</td>
<td>34</td>
<td>20</td>
<td>.03</td>
</tr>
<tr>
<td>2-y relapse</td>
<td>18</td>
<td>30</td>
<td>.02</td>
</tr>
<tr>
<td>2-y EFS</td>
<td>65</td>
<td>52</td>
<td>.038</td>
</tr>
<tr>
<td>2-y OS</td>
<td>71</td>
<td>64</td>
<td>.095</td>
</tr>
<tr>
<td>2-y OS (allo-SCT censoring)</td>
<td>74</td>
<td>63</td>
<td>.018</td>
</tr>
</tbody>
</table>

Chemo Rx ± Rituximab: Results of the Randomized GRAALL-R 2005 in Pre–B-ALL (Cont’d)¹

Ph-neg, >age 45-50:

- Newly diagnosed
  - 5-drug induction regimen for CALGB, the so-called Larson regimen (C-9111)
  - Hyper-CVAD
  - MRC/ECOG

- No clearcut role for allo SCT
  - Wolach et al (Am Hematol, 2016)
  - Pts over age 40, retrospective;
  - OS and DFS no diff bet chemo (n=40) and SCT (n=40), 46 v 40%; 31 v 40%
Ph-pos, Younger

- TKI plus chemo (e.g., hyperCVAD) is the standard
- But treating with minimal chemo could be OK
- Consolidation with alloSTC still standard, but somewhat controversial
SWOG S0805 – Chemo/dasatinib

Intensive phase

Maintenance phase

Risk-adapted intrathecal CNS prophylaxis

Hyper-CVAD
MTX-cytarabine
Dasatinib 70 mg po daily
Vincristine + prednisone

24 months
SWOG S0805 – Overall Survival

3-year OS: 71%

N = 94, deaths = 26

Ravandi, ASH 2015
Hyper-CVAD + Ponatinib in Ph-Positive ALL. Survival

Median follow up of 39 months (2-59)
Ph-pos, Older

- TKI plus steroid is the standard
- Consolidation with alloSCT still standard, but somewhat controversial
GIMEMA LAL 1509: STUDY DESIGN

Steroid pre-treatment

Dasatinib + steroids

Response evaluation (d +85)

CHR+ CMR*

Dasatinib 6-month maintenance

CHR but NO CMR

AlloSCT eligibility

Yes

If >40 days from CHR, Clopha + CTX

Allo SCT

MRD positive

MRD negative

MRD evaluation

MRD increase

Stable MRD

HAM

Positive response

Negative response

Dasatinib maintenance until relapse or progression

Off-treatment

* BCR-ABL1/ABL1=0
OS: 58.3% (CI 95%: 44.4-76.6) at 36 months 
DFS: 49% (CI 95%: 36.8-64.9) at 30 months
The bad guys: Ph-like ALL and MRD positive

- What it is
- What can we do
Philadelphia-like (Ph-like) ALL

Expression profile similar to Ph+ ALL, but do not have BCR-ABL fusion

May have adverse outcomes

Some increase with age into young adults

Mullighan NEJM 2009
IKZF1^del^ Associated With Kinase Fusions

- IKZF1 alterations themselves prognostic but not currently targetable
  
- 80% of Ph+ (BCR-ABL) ALL have IKZF1 alterations (Gleevec)
  
- 78% of Ph-like ALL with kinase rearrangement have IKZF1 alteration
Overall Survival among Patients with Ph–like Acute Lymphoblastic Leukemia

Impact of Molecular MRD on Prognosis in Adult ALL
Northern Italy Leukemia Group (NILG), Standard and High-risk ALL

Disease-Free Survival

- \( MRD_{\text{neg}} (n = 58) \)
- \( MRD_{\text{unknown}} (n = 30) \)
- \( MRD_{\text{pos}} (n = 54) \)

41% of patients had subsequent SCT

- Molecular MRD negativity associated with significant improvement in DFS\(^1\)
- Molecular MRD status is a predictor of hematologic relapse\(^2\)

Conclusions: MRD in Adult ALL

• MRD integrates patient-, treatment-, and leukemia-specific factors and allows refined assessment of treatment efficacy pre–MRD measurement

• Limitations of the method should be considered
  – Sensitivity limit (MRD negativity ≠ eradication of disease)
  – MRD: time-dependent parameter
  – Efficacy of treatment elements after MRD measurement and potential long-term antileukemic (or toxic) drug effects are not assessed

• MRD after induction treatment: most important independent prognostic factor in adult and childhood ALL

• MRD guided treatment is feasible in adult ALL

• Prerequisite: standardized measurement and interpretation
Relapsed ALL

- Standard regimens (HAM, FLAG-ida) not as good as blinatumomab or inotuzumab
- CART cells
Outcome for 609 Adults With Relapsed ALL: MRC UKALL2/ECOG2993 Study

- Outcome of patients after first relapse
- 5-year OS: 7%

Salvage Therapy for ALL: Treatment Options

- Depends on CRD1 duration
- Approved drugs: nelarabine (T-ALL), clofarabine, liposomal VCR

<table>
<thead>
<tr>
<th>Regimen</th>
<th>% CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonals (inotuzumab, blinatumomab)</td>
<td>50%-70%</td>
</tr>
<tr>
<td>CAR T cells</td>
<td>70%-80%</td>
</tr>
<tr>
<td>Hyper-CVAD (± augmented); augmented BFM</td>
<td>30%-70%</td>
</tr>
<tr>
<td>FLAG-IDA, BIDFA ± asp</td>
<td>30%-40%</td>
</tr>
<tr>
<td>MOAD</td>
<td>30%</td>
</tr>
</tbody>
</table>

**If T-ALL:** Nelarabine

**If Ph-positive ALL:** Add TKI
## Monoclonal Antibodies and Their Targets in ALL

<table>
<thead>
<tr>
<th>Antigen Target</th>
<th>Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19</td>
<td>Blinatumomab</td>
</tr>
<tr>
<td></td>
<td>SGN19a</td>
</tr>
<tr>
<td></td>
<td>SAR3419</td>
</tr>
<tr>
<td></td>
<td>Combotox</td>
</tr>
<tr>
<td>CD20</td>
<td>Rituximab</td>
</tr>
<tr>
<td></td>
<td>Ofatumumab</td>
</tr>
<tr>
<td>CD22</td>
<td>Epratuxumab</td>
</tr>
<tr>
<td></td>
<td>Inotuzumab</td>
</tr>
<tr>
<td></td>
<td>Combotox</td>
</tr>
<tr>
<td></td>
<td>BL22, HA22</td>
</tr>
<tr>
<td>CD52</td>
<td>Alemtuzumab</td>
</tr>
</tbody>
</table>
Mode of Action of BiTE Antibody
Blinatumomab

- A BiTE antibody designed to direct cytotoxic T-cells to CD19-expressing cancer cells
- Approved for use in relapsed/refractory Ph− B-ALL

Blinatumomab in Relapsed/Refractory ALL: Response

- 189 patients Rx with blinatumomab 28 mcg/d CIV x 4 weeks, every six weeks

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>63 (33)</td>
</tr>
<tr>
<td>CRh</td>
<td>18 (10)</td>
</tr>
<tr>
<td>CR + CRh</td>
<td>81 (43)</td>
</tr>
<tr>
<td>No marrow blasts</td>
<td>17 (9)</td>
</tr>
<tr>
<td>MRD response during first two cycles in patients with CR or CRh</td>
<td>60/73 (82%)</td>
</tr>
</tbody>
</table>

- Median OS: 5.9 mo; median RFS: 6.1 mo

Phase 3 TOWER Study: Randomization and Dosing

Patients with relapsed/refractory ALL  
N = 405

Induction (2 cycles)
If ≤5% blasts

Consolidation (3 cycles)
If ≤5% blasts

Maintenance (up to 12 mo)

Follow-up

Randomization 2:1 (blinatumomab:SOC)  
Stratified by age, prior salvage, and prior allo-HSCT

Blinatumomab
Continuous infusion  
4 wk on, 2 wk off; 9 mcg/d for 7 d, then 28 mcg/d wk 2-4

SOC chemotherapy
Investigator’s choice:  
FLAG ± anthracycline, HiDAC-based, high-dose MTX-based, or clofarabine-based

Continuous infusion  
4 wk on, 8 wk off; 28 mcg/d

Overall Survival (ITT)

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

- Stratified log-rank $P = 0.012$
- Hazard ratio = 0.71 (0.55, 0.93)

- At 76% of events, the stratified log-rank test surpassed the O’Brien-Fleming boundary ($P < .0194$) to stop the study for benefit.

Topp MS et al. EHA 2016. Abstract S149.
Inotuzumab Ozogamicin (InO)

- Average loading of calicheamicin derivative on mAb is 5-6 moles of calicheamicin/mole of mAb (range, 3-9) for InO
  - ~100% of mAbs conjugated
# Inotuzumab: Clinical Data in Relapsed/Refractory ALL\textsuperscript{1-4}

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution/Center</th>
<th>N</th>
<th>Dosing</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2\textsuperscript{1}</td>
<td>MDACC</td>
<td>49</td>
<td>Every 4 weeks 1.8 mg/m\textsuperscript{2}</td>
<td>57%</td>
</tr>
<tr>
<td>Phase 2\textsuperscript{2}</td>
<td>MDACC</td>
<td>41</td>
<td>Weekly 1.8 mg/m\textsuperscript{2} (0.8−0.5−0.5)</td>
<td>59%</td>
</tr>
<tr>
<td>Phase 1/2\textsuperscript{3,4}</td>
<td>Multicenter</td>
<td>37 (1/2)\textsuperscript{3} + 35 (2)\textsuperscript{4} S2+\textsuperscript{4}</td>
<td>Weekly 1.2-1.8 mg/m\textsuperscript{2} (total)</td>
<td>68%\textsuperscript{3} 69%\textsuperscript{4}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response</th>
<th>1.2 mg/m² (n = 2)</th>
<th>1.6 mg/m² (n = 9)</th>
<th>1.8 mg/m² (n = 8)</th>
<th>1.8 mg/m² Exp (n = 6)</th>
<th>1.8 mg/m² S2+ (n = 24)²</th>
<th>Total (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD-negative, a n (%)</td>
<td>2 (100)</td>
<td>8 (89)</td>
<td>8 (100)</td>
<td>6 (100)</td>
<td>18 (75%)</td>
<td>42 (86)</td>
</tr>
<tr>
<td>Median (range) time to MRD negativity, d</td>
<td>99 (98-99)</td>
<td>32 (22-64)</td>
<td>30 (22-141)</td>
<td>38 (21-134)</td>
<td>26 (21-80)</td>
<td>34 (21-141)</td>
</tr>
<tr>
<td>Response</td>
<td>1.2 mg/m² (n = 2)</td>
<td>1.6 mg/m² (n = 9)</td>
<td>1.8 mg/m² (n = 8)</td>
<td>1.8 mg/m² Exp (n = 6)</td>
<td>1.8 mg/m² S2+ (n = 24)²</td>
<td>Total (n = 49)</td>
</tr>
</tbody>
</table>

Ara-C = cytarabine; FLAG = fludarabine/ara-C/granulocyte colony-stimulating factor; HIDAC = high-dose ara-C; Ph = Philadelphia chromosome

An ongoing phase 3 study: 326 patients randomized at 117 sites in 19 countries (INO-VATE ALL; NCT01564784)

Study Design

**Inotuzumab ozogamicin (InO)**
- Starting dose 1.8 mg/m²/cycle
- 0.8 mg/m² on day 1;
- 0.5 mg/m² on days 8 and 15 of a 21–28 day cycle (≤6 cycles)

**Standard of Care (SOC)**
- FLAG or
- Ara-C plus mitoxantrone or
- HIDAC
- ≤4 cycles

**1:1 Randomization** (N=326)

Stratifications:
- Duration of 1st remission ≥12 vs <12 mo
- Salvage 2 vs 1
- Aged ≥55 y vs <55 y

- InO dose was reduced to 1.5 mg/m²/cycle once the patient achieved CR/CRi

DeAngelo et al., EHA 2015, LBA abstract
### INO-VATE: Treatment Response

<table>
<thead>
<tr>
<th></th>
<th>InO</th>
<th>SOC</th>
<th>1-Sided P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(^a)</td>
<td>109</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>CR/CRi,% (95% CI)</td>
<td><strong>80.7</strong> (72-88)</td>
<td><strong>33.3</strong> (24-44)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CR</td>
<td>35.8 (27-46)</td>
<td>19.8 (12-29)</td>
<td>.0056</td>
</tr>
<tr>
<td>CRi</td>
<td>45.0 (35-55)</td>
<td>13.5 (7-22)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

**MRD negativity among responders, n (%) [95% CI]**

<table>
<thead>
<tr>
<th></th>
<th>InO</th>
<th>SOC</th>
<th>1-Sided P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRi</td>
<td>69/88 (78.4) [68-87]</td>
<td>9/32 (28.1) [14-47]</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CR</td>
<td>35/39 (89.7) [76-97]</td>
<td>6/19 (31.6) [13-57]</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CRi</td>
<td>34/49 (69.4) [55-82]</td>
<td>3/13 (23.1) [5-54]</td>
<td>.0034</td>
</tr>
</tbody>
</table>

- In both arms, most patients achieved CR/CRi in cycle 1 (InO, 73%; SOC, 91%).

\(^a\) Analysis of CR/CRi based on a modified ITT population excluding 13 untreated patients from the SOC arm (ie, n = 96 for the SOC arm rather than n = 109).

INO-VATE: InO vs SOC in R/R ALL: Progression-Free Survival

INO-VATE: InO vs SOC in R/R ALL: Overall Survival

- Data appeared to depart from proportional hazards assumption
- 2-y survival probability higher with InO (23% [95% CI, 16-30%] vs 10% [5-16%])

## INO-VATE and TOWER\(^1,2\) Overall Survival

<table>
<thead>
<tr>
<th>Overall Survival, mos [95% CI]</th>
<th>Blina/Ino [mos]</th>
<th>SOC [mos]</th>
<th>1-sided P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOWER (Blinatumomab)(^1)</td>
<td>7.7 [5.6–9.6]</td>
<td>4.0 [2.9–5.3]</td>
<td>0.012 HR 0.71</td>
</tr>
<tr>
<td>INO-VATE (Inotuzumab)(^2)</td>
<td>7.7 [6.0–9.2]</td>
<td>6.7 [4.9–8.3]</td>
<td>0.020 HR 0.72</td>
</tr>
</tbody>
</table>

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VOD/SOS Among Inotuzumab-Treated Patients

- VOD incidence: InO, 13% (n = 22) vs SOC, 1% (n = 1)
- 5 (3%) patients had VOD during study Rx (2 with pre-study SCT)
- 77/164 (47%) on InO had post-study SCT vs 33/162 (20%) in the SOC arm
- 17/77 (22%) on InO had VOD post-SCT (5/17 also had pre-study SCT)
- Median (range) time to VOD after SCT: 15 (3-57) days

MVA Analysis of Factors Associated With Post-SCT VOD

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylator conditioning (dual vs single)</td>
<td>7.6 (1.7-33.8)</td>
<td>.008</td>
</tr>
<tr>
<td>Age (≥55 vs &lt;55 y)</td>
<td>4.8 (1.0-22.0)</td>
<td>.043</td>
</tr>
</tbody>
</table>
# Anti-CD19 CARs in ALL

<table>
<thead>
<tr>
<th>2015 Abstract# Author</th>
<th>Co-stim Domain</th>
<th>Age</th>
<th>Clinical Outcomes</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>682 – Park MSKCC Phase 2</td>
<td>CD28</td>
<td>Adults n=46</td>
<td>82% CR 6mo OS &gt;65%</td>
<td>Severe CRS 24%, Neuro 28%</td>
</tr>
<tr>
<td>681-Grupp UPENN Phase 2</td>
<td>41BB</td>
<td>Age &lt;24 N=59</td>
<td>93% CR 1yr OS 78%</td>
<td>88% CRS, 1 Grade 4, 27% tx’d</td>
</tr>
<tr>
<td>684 – Lee NIH Phase 2</td>
<td>CD28</td>
<td>Kids and young adults N=39</td>
<td>59% CR LFS 17.7 mos if MRD neg CR</td>
<td>6% Gr ¾ CRS after CTX stratification</td>
</tr>
</tbody>
</table>
The Chemical Structures of Nelarabine and ara-G (on conversion via adenosine deaminase): approved in adv T-ALL

Kisor et al. JCO 2000
ECOG-E1910: Blinatumomab in BCR-ABL–Negative B-Lineage ALL¹

- Phase 3 study enrolling 360 patients with newly diagnosed BCR-c-ABL oncogene 1, non-receptor tyrosine kinase (ABL)-negative B lineage ALL

**Induction CT**
- 2 cycles, followed by 4-week rest period

**Intensification chemotherapy**
- 1 cycle

**Maintenance therapy**
- Blinatumomab
- No blinatumomab
- Allo-HCT or consolidation

Primary endpoint: OS
PI: Mark R. Litzow, MD

Proposed US Intergroup AYA Trial Schema

- **Primary endpoint**: 3-year EFS
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Patients and their families!!!!