Development of Precision Medicine Therapies for Pediatric Acute Lymphoblastic Leukemia

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Disclosures

• Stock ownership
  – Amgen, Merck, Pfizer

• Honoraria/Consulting fees
  – Jazz pharmaceuticals, Spectrum Pharmaceuticals, Erytech, Novartis, Amgen
Children’s Oncology Group ALL Trials

• Only NCI sponsored pediatric cooperative group

• ~200 members institutions in US, CA, AUS, and NZ
  • 90-95% of enrolled patients reside in US

• About 2000 newly diagnosed ALL patients enroll in COG ALL trials each year

• In 2009, 68% (1951/2869) of ALL cases predicted to occur among US persons 0-19.99 yrs old enrolled in a COG ALL trial*
  • 69% (1758/2540) of those 0-14.99 yrs old
  • 51% (168/329) of those 15-19.99 yrs old

*Hunger et al, JCO 2012
Improved Survival in Childhood ALL CCG/COG Trials 1968-2009 (n=39,697)

Hunger SP, Mullighan CG. N Engl J Med 2015;373:1541-1552
# Chemotherapy Agents Used in Childhood ALL: FDA Approval

<table>
<thead>
<tr>
<th>Agent</th>
<th>Year Approved by FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine</td>
<td>1953</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1953</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1955</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1958</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1959</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1964</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>1969</td>
</tr>
<tr>
<td>L’ Asparaginase</td>
<td>1978</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>1979</td>
</tr>
</tbody>
</table>

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**Survival (%)**

**Years since Diagnosis**

- 2006–2009 (N=6530)
- 2000–2005 (N=7835)
- 1995–1999 (N=7287)
- 1993–1994 (N=8200)
- 1978–1983 (N=2984)
- 1975–1977 (N=1313)
- 1972–1975 (N=936)
- 1970–1972 (N=499)
- 1968–1970 (N=402)

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**CHILDREN'S ONCOLOGY GROUP**

The world's childhood cancer experts
Intensification/Optimization of Cytotoxic Chemotherapy in ALL: Recent Negative Trials

- Second IM + DI (1961) or DI (1991)
- Dex vs. Pred (AALL0232, pts ≥10 yrs)
- Intensive consolidation (AALL0331, Average risk)
- Additional pegasparagase (AALL0331, Low risk)
- Clofarabine/Etoposide/Cyclosphosphamide (AALL1131)
- Etoposide/Cyclosphosphamide (AALL1131)
- Methotrexate 40 mg/m² vs. 20 mg/m² (AALL0932)
- Intrathecal triple therapy vs. IT MTX (AALL1131)
Survival for Childhood ALL is Much Worse After Relapse

Hunger and Mullighan, NEJM 2015; Nguyen et al, Leukemia 2008
The goal in precision cancer medicine is to improve cure rates and decrease toxicities by identifying the specific genes, proteins and pathways responsible for malignant transformation or progression of individual cancers, and utilize therapies that target these features that distinguish cancer cells from normal cells.
CML: Treatment Status 2018

- TKI therapy has revolutionized treatment of CML
- Stem cell transplant is rarely performed for patients with chronic phase CML and generally reserved for those with advanced stage disease and/or a poor response to TKI
- 2nd generation TKIs approved and are more effective at achieving early endpoints than imatinib
  - Dasatinib (Kantarjian et al, NEJM 2010)
  - Nilotinib (Saglio et al, NEJM, 2010)
- Additional TKIs in various stages of development
  - Ponatinib approved by FDA (2012) and EMA (2013)
  - Bosutinib (2nd generation Abl/SRC TKI)
- Beginning to identify patients that can stop TKI therapy and remain in long term remission (cure)
Sequential Acquisition of Genetic Alterations Contributes to ALL Pathogenesis and Relapse

Hunger SP, Mullighan CG. N Engl J Med 2015;373:1541-1552
Outcomes in Ph\(^+\) ALL: Ponte di Legno Group Analyses

Analyses limited to patients treated WITHOUT TKIs

<table>
<thead>
<tr>
<th></th>
<th>1985-1996 (n=326)</th>
<th>1995-2005 (n=610)</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR rate</td>
<td>82%</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>7-yr EFS</td>
<td>25.0 +/- 3.0%</td>
<td>32.0 +/- 2.0%</td>
<td>0.0007</td>
</tr>
<tr>
<td>7-yr OS</td>
<td>36.0 +/- 3.0%</td>
<td>44.9 +/- 2.2%</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Similar presenting features of patients in both cohorts

Outcome improved over time, but still poor without TKI therapy

Arico et al *NEJM* 2000 & *JCO* 2010
COG AALL0031: Imatinib Improves Long-Term Outcome in Ph⁺ ALL

7-yr EFS
AALL0031c5: 72%
POG ALinc 14-16: 27%

Schultz KR, JCO 2009; Leukemia 2014
### Pediatric Trials of TKI Therapy for Ph\(^+\) ALL

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years (# Pts)</th>
<th>Chemo</th>
<th>TKI</th>
<th>cXRT</th>
<th>BMT</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>COG AALL0031(^1)</td>
<td>2002-06 (54)</td>
<td>AALL0031</td>
<td>Imatinib</td>
<td>All</td>
<td>43%</td>
<td>5-yr: 68%</td>
<td>5-yr: 81%</td>
</tr>
<tr>
<td>EsPhALL Randomized(^2)</td>
<td>2004-09 (178)</td>
<td>BFM HR</td>
<td>Imatinib</td>
<td>All</td>
<td>81%</td>
<td>5-yr: 60%</td>
<td>5-yr: 72%</td>
</tr>
<tr>
<td>COG AALL0622(^3)</td>
<td>2008-12 (60)</td>
<td>AALL0031</td>
<td>Dasatinib</td>
<td>CNS3 only</td>
<td>32%</td>
<td>5-yr: 60%</td>
<td>5-yr: 86%</td>
</tr>
<tr>
<td>EsPhALL amended(^4)</td>
<td>2010-14 (155)</td>
<td>BFM HR</td>
<td>Imatinib</td>
<td>All</td>
<td>38%</td>
<td>5-yr: 57%</td>
<td>5-yr: 72%</td>
</tr>
<tr>
<td>CA180-372(^5)</td>
<td>2012-14 (106)</td>
<td>BFM HR</td>
<td>Dasatinib</td>
<td>CNS3 only</td>
<td>14%</td>
<td>3-yr: 65.5%</td>
<td>3-yr: 91.5%</td>
</tr>
</tbody>
</table>

\(^1\)Schultz, JCO 2009 and Leukemia 2015

\(^2\)Biondi, Lancet Oncology 2012

\(^3\)Slayton, JCO in press

\(^4\)Biondi, ASH 2017

\(^5\)Hunger, ASH 2017

- Similar outcomes in all 5 trials
- Decreasing use of cXRT over time
- Decreasing use of BMT in CR1 over time
Ph⁺ ALL: Applicability to Other Very High Risk (VHR) ALL Subsets

- Outcome for VHR ALL subsets can be improved dramatically (without SCT) if:
  - A *driver* molecular lesion exists that is fundamental to the disease process
  - The leukemia is dependent upon continued activity of this molecular lesion (*oncogene addiction*)
  - An effective targeted inhibitor is available that can be combined safely with chemotherapy

- **Further improvements in VHR ALL outcome** require that we identify these lesions and develop effective targeted therapies

7 Year DFS

- Chemo plus Imatinib: 72%
- Historical control: 27%

Schultz et al *JCO* 2009 & *Leukemia* 2014
COG
Stephen Hunger, MD
William Carroll, MD
Mini Devidas, PhD
Mignon Loh, MD
Gregory Reaman, MD

NCI
Daniela Gerhard, PhD (OCG)
Malcolm Smith, MD PhD (CTEP)
Jaime Guidry Auvil, PhD

Nationwide Children’s Hospital
Julie Gastier-Foster, PhD
Shalini Reshmi, PhD
Eileen Stonerock, BS

St. Jude Children’s Research Hospital
James Downing, MD
Mary Relling, PhD
Kathryn Roberts, PhD
Charles Mullighan, MD PhD
Jinghui Zhang, PhD

University of New Mexico
Cheryl Willman, MD
Richard Harvey, PhD
I-Ming Chen, PhD
Huining Kang PhD
**ALL TARGET Project: Major Findings**

- Ph-like ALL, IKZF1 deletions and mutations (Mullighan, NEJM 2009)
- JAK mutations in HR-ALL (Mullighan, PNAS 2009)
- CRLF2 genomic alterations in HR and Down syndrome ALL (Mullighan, Nature Genetics 2009; Harvey, Blood 2010; Chen Blood 2012)
- Expression profiles-supervised (Kang, Blood 2010)
- Expression profiles-unsupervised (R8 group) (Harvey, Blood 2010)
- Recurrent mutations in 4 key pathways in HR ALL (Zhang, Blood 2011)
- Kinase activating lesions (Roberts, Cancer Cell 2012) **but no point mutations** (Loh, Blood 2013) in Ph-like ALL
- GATA3 SNPs and risk of Ph-like ALL (Perez Andreu Nature Genetics 2013)
- Comprehensive genomics of Ph-like ALL (Roberts, NEJM 2014)
- Rise and fall of subclones from diagnosis to relapse (Ma, Nature Communications 2015)
- Genomic landscape of T-ALL (Liu, Nature Genetics 2017)
IKAROS (IKZF1) Deletions and Mutations are Associated with Poor Outcome

Deletion of IKZF1 and Prognosis in Acute Lymphoblastic Leukemia

Charles G. Mullighan, M.D., Xiaoping Su, Ph.D., Jinhui Zhang, Ph.D., Ina Radtke, Ph.D., Letha A.A. Phillips, B.S., Christopher B. Miller, B.S., Jing Ma, Ph.D., Wei Liu, Ph.D., Cheng Cheng, Ph.D., Brenda A. Schulman, Ph.D., Richard C. Harvey, Ph.D., I-Ming Chen, D.V.M., Robert J. Clifford, Ph.D., William L. Carroll, M.D., Gregory Reaman, M.D., W. Paul Bowman, M.D., Meenakshi Devidas, Ph.D., Daniela S. Gerhard, Ph.D., Wenjian Yang, Ph.D., Mary V. Relling, Pharm.D., Sheila A. Shurtleff, Ph.D., Dario Campana, M.D., Michael J. Borowitz, M.D., Ph.D., Ching-Hon Pui, M.D., Malcolm Smith, M.D., Ph.D., Stephen P. Hunger, M.D., Cheryl L. Willman, M.D., James R. Downing, M.D., and the Children’s Oncology Group

- 30% of cases had IKZF1 deletions or mutations
- IKZF1 deleted/mutated cases had a 4-year relapse rate of 55% vs. 14% in those with intact IKZF1
- IKZF1 alterations common in cases with Ph-like GEP

The world’s childhood cancer experts

Mullighan et al, NEJM 2009
Philadelphia chromosome-like (Ph-like; BCR-ABL1-like) B-ALL

Leukemias with a gene expression profile similar to that of Ph+ ALL (without BCR-ABL1 fusion) and activated kinase signaling; R8 group on unsupervised clustering (Mullighan NEJM 2009; Den Boer Lancet Onc 2009; Harvey Blood 2010)

Frequency increases with age: 10% in childhood standard-risk ALL, 13% in childhood high-risk ALL, 21% in adolescents, 27% in young adults 20-39 yrs (Roberts, NEJM 2014)

Deletions/mutations in IKZF1 and genes encoding transcription factors that control B-cell differentiation are very common in both Ph+ and Ph-like ALL

Genomics of Ph-like ALL (as defined by COG/SJCRH)

50% have CRLF2 genomic alterations ± JAK mutations

Significant percentage of remaining cases have a variety of gene fusions targeting ABL1, ABL2, CSF1R, PDGFRB, JAK2 and other kinase genes

Ph-like ALL patients have greatly increased risk of treatment failure and death
Targetable Kinase-Activating Lesions in Ph-like Acute Lymphoblastic Leukemia


A Call to Action for Acute Lymphoblastic Leukemia

Timothy A. Graubert, M.D.
15.3% (n=264) Ph-like ALL cases identified; 154 subjected to NGS
Response of *EBF1-PDGFRB* ALL to Imatinib: A Paradigm for Treatment of Ph-like ALL

10 yr boy with refractory B-ALL – 70% blasts at day 29

Cytogenetics: 5q33 deletion at *PDGFRB*

*EBF1-PDGFRB* positive

Started imatinib with immediate clinical improvement

1 week: morphologic remission; 2 weeks: MRD 0.017%

Remains in remission at 2 years

Other similar cases reported (Soulier, *Haematologica* 2013; Schwab, *Blood* 2016)
12 year old with B-ALL and WBC 905k and massive splenomegaly

• t(2;9)(q11.2;q34) and ABL1 split via FISH
  • Later found to have Ph-like GEP and RANBP2-ABL1 fusion

• Poor early response induction; WBC 850,000 at day 5

• Imatinib added; cleared blasts by day 11

• In CR at end induction with normal ABL1 FISH

• In CR at 4 months with chemotherapy + imatinib

Vignette: PAWALS and RANBP2-ABL1

Roberts et al, NEJM 2014
ABL-Class Fusions

The world's childhood cancer experts
Targeting ABL-class Fusions in Experimental Models of Ph-like ALL

ABL-class fusions phenocopy BCR-ABL1 and should be similarly responsive to targeted therapy with chemotherapy plus an ABL class TKI

Roberts Cancer Cell 2012; Roberts NEJM 2014; Roberts Blood Adv 2017
Targeting Alterations that Activate JAK-STAT Signaling in Experimental Models of Ph-like ALL

Development of TKI Therapy for Ph-like ALL Subsets

- Data provide compelling rationale to test TKI therapy in molecularly defined subsets of Ph-like ALL
  - ~20% have ABL-class fusions involving ABL1, ABL2, CSF1, or PDGFRB
    - Test ABL class TKIs (imatinib or dasatinib)
  - ~50% have CRLF2-R; half have JAK mutations
    - Test JAK2 inhibitors such as ruxolitinib
  - ~15% have JAK2 fusions or EPOR-R
    - Test JAK2 inhibitors such as ruxolitinib
  - 10-15% unknown genomic lesions, or lesions that are not easily targeted by available drugs

- How can we identify these patients efficiently in real time?
### Table 1. Kinase fusions identified in Ph-like ALL

<table>
<thead>
<tr>
<th>Kinase gene</th>
<th>TKI</th>
<th>Fusion partners identified to date, n</th>
<th>5’ Fusion partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL1</td>
<td>Imatinib/dasatinib</td>
<td>13</td>
<td>CENPC, ETV6, FOXP1, LSM14A, NUP153, NUP214, RANBP2, RCSD1, SFPQ, SNX1, SNX2, SPTNA1, ZMIZ1</td>
</tr>
<tr>
<td>ABL2</td>
<td>Imatinib/dasatinib</td>
<td>3</td>
<td>PAG1, RCSD1, ZC3HAV1</td>
</tr>
<tr>
<td>CSF1R</td>
<td>Imatinib/dasatinib</td>
<td>3</td>
<td>MEF2D, SSBP2, TBL1XR1</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>Imatinib/dasatinib</td>
<td>1</td>
<td>FIP1L1</td>
</tr>
<tr>
<td>PDGFRB</td>
<td>Imatinib/dasatinib</td>
<td>8</td>
<td>ATF7IP, EBF1, ETV6, SNX29, SSBP2, TNIP1, ZEB2, ZMYND8</td>
</tr>
<tr>
<td>LYN</td>
<td>Imatinib/dasatinib</td>
<td>2</td>
<td>GATAD2A, NCOR1</td>
</tr>
<tr>
<td>CRLF2</td>
<td>JAK2 inhibitor</td>
<td>3</td>
<td>CSF2RA, IGH, P2RY8</td>
</tr>
<tr>
<td>JAK2</td>
<td>JAK2 inhibitor</td>
<td>21</td>
<td>ATF7IP, BCR, EBF1, ETV6, GOLGA5, HMBOX1, OFD1, PAX5, PCM1, PPFIBP1, RFX3, SMU1, SNX29, SSBP2, STRN3, TERF2, TPR, USP25, ZBTB46, ZNF274, ZNF340</td>
</tr>
<tr>
<td>EPOR</td>
<td>JAK2 inhibitor</td>
<td>4</td>
<td>IGH, IGK, LAIR1, THADA</td>
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<tr>
<td>TSLP</td>
<td>JAK2 inhibitor</td>
<td>1</td>
<td>IQGAP2</td>
</tr>
<tr>
<td>TYK2</td>
<td>TYK2 inhibitor</td>
<td>3</td>
<td>MYB, SMARCA4, ZNF340</td>
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<tr>
<td>IL2RB</td>
<td>JAK1/JAK3 inhibitor</td>
<td>1</td>
<td>MYH9</td>
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<td>NTRK3</td>
<td>TRK inhibitor</td>
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<td>ETV6</td>
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<td>PTK2B</td>
<td>FAK inhibitor</td>
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<td>KDM6A, STAG2, TMEM2</td>
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<td>Ponatinib</td>
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<td>FLT3</td>
<td>FLT3 inhibitor</td>
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<td>ZMYM2</td>
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<td>DKGK</td>
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<td>1</td>
<td>ZFAND3</td>
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<tr>
<td>BLNK</td>
<td></td>
<td>1</td>
<td>DNTT</td>
</tr>
<tr>
<td>CBL</td>
<td></td>
<td>1</td>
<td>KANK1</td>
</tr>
</tbody>
</table>
Ph-like ALL is Defined by Unsupervised Clustering of Affymetrix Gene Expression Profiles* Using ROSE or PAM Clustering Methods

*Assess ~55,000 genes

Kang and Harvey UNM, S. Chen, SJCRH
Blood or bone marrow is collected
Total RNA is isolated from nucleated cells
cDNA is generated from 1 µg total RNA

Steps Prior to Device

Device Steps ~2.5 hours

cDNA and master mix are loaded on card
Cards are centrifuged, sealed and run on instrument
Raw data are reviewed and bad wells are omitted

Positive samples are sent for downstream analysis to test for CRLF2 lesions if high CRLF2. Remaining cases are tested for targetable kinase fusions (with confirmation by Sanger sequencing)

Modeling algorithm is run with exported ΔCts

Low density array (LDA) card developed to identify Ph-like ALL by measuring expression of 8 of 15 genes
Ph-like ALL Defined by LDA Card: Genomic Features and Outcome

- Cases defined as Ph-like by LDA with downstream identification of genomic lesions
- Cases with targetable ABL-class fusions (\(ABL1\), \(ABL2\), \(CSF1R\) and \(PDGFRB\)) have extremely poor outcomes
- Other potentially-targetable fusions (\(JAK2\) and \(EPOR\)) have similarly poor outcomes
- Cases with \(JAK\) mutations have similarly dismal responses
LYMPHOID NEOPLASIA

Targetable kinase gene fusions in high-risk B-ALL: a study from the Children’s Oncology Group

Shalini C. Reshmi,1,2,* Richard C. Harvey,3,* Kathryn G. Roberts,4,∗ Eileen Stonerock,1 Amy Smith,5 Heather Jenkins,1 I-Ming Chen,3 Marc Valentine,6 Yu Liu,7 Yongjin Li,7 Ying Shao,4 John Easton,7 Debbie Payne-Turner,4 Zhaohui Gu,4 Thai Hoa Tran,8 Jonathan V. Nguyen,8 Meenakshi Devidas,9 Yunfeng Dai,9 Nyla A. Heerema,2 Andrew J. Carroll III,10 Elizabeth A. Raetz,11 Michael J. Borowitz,12 Brent L. Wood,13 Anne L. Angiolillo,14 Michael J. Burke,15 Wanda L. Salzer,16 Patrick A. Zweidler-McKay,17 Karen R. Rabin,18 William L. Carroll,19 Jinghui Zhang,7 Mignon L. Loh,8,† Charles G. Mullighan,4,† Cheryl L. Willman,3,† Julie M. Gastier-Foster,1,2,20,† and Stephen P. Hunger21,†

Key Points

• Ph-like ALL is characterized by a diverse array of genetic alterations activating cytokine receptor and tyrosine kinase signaling.

• Pediatric patients with Ph-like ALL can be identified in real time for effective treatment stratification.
Algorithm to Identify Ph-like ALL Cases and Characterize Genomic Lesions

BCR-ABL1 or ETV6-RUNX1

Positive → LDA Model
Negative → STOP

CRLF2 expression

High → STOP
Low → mPCR

P2RY8-CRLF2

Negative → STOP
Positive → Targeted JAK sequencing

CRLF2 FISH

Negative → Targeted JAK sequencing + Other CRLF2 or new fusion
Positive → IGH-CRLF2

Targeted JAK sequencing

RNA Seq

Positive → Sanger confirmation
Negative → mPCR

RNAseq for discovery, results not available in real time for Rx
Retrospective analysis of 1389 patients from COG AALL1131

Patients had NCI HR ALL or NCI SR ALL and were MRD+ ≥0.01% at end induction

Reshmi et al, Blood 2017
CRLF2-Rearrangements in 80% of Ph-like CRLF2-High Cases

45% of CRLF2-R Have Concomitant JAK1/JAK2 Mutations

50% of CRLF2-R have IGH-CRLF2 and 50% have P2RY8-CRLF2

Reshmi et al, Blood 2017
Targetable Lesions are Present in 66.6% of Ph-like HR ALL Cases

• Target with dasatinib/imatinib
  • ABL-class fusions in 14.1% of Ph-like ALL
  • 4% of NCI HR ALL
    • Similar to 5% incidence of Ph+ among NCI HR ALL patients

• Target with ruxolitinib
  • CRLF2-R in 43.7% of Ph-like ALL
  • JAK1/JAK2 mutations in 45%
  • JAK2 fusions or EPOR-R in 8.8% of Ph-like ALL

Reshmi et al, Blood 2017
Genomic and outcome analyses of Philadelphia chromosome-like ALL in NCI standard-risk patients: a report from the Children’s Oncology Group

Kathryn G. Roberts¹*, Shalini C. Reshmi²,³*, Richard C. Harvey⁴*, I-Ming Chen⁴, Kinnari Patel², Eileen Stonerock², Heather Jenkins², Yunfeng Dai⁵, Marc Valentine⁶, Zhaohui Gu¹, Yaqi Zhao¹, Yu Liu⁷, Yongjin Li⁷, Jinghui Zhang⁷, Debbie Payne-Turner¹, Meenakshi Devidas⁵, Nyla A. Heerema³, Andrew J. Carroll⁸, Elizabeth A. Raetz⁹, Michael J. Borowitz¹⁰, Brent L. Wood¹¹, Anne Angiolillo¹², Michael J. Burke¹³, Wanda L. Salzer¹⁴, Patrick A. Zweidler-McKay¹⁵, Karen R. Rabin¹⁶, Leonard Mattano¹⁷, Kelly W. Maloney¹⁸, William L. Carroll¹⁹, Mignon L. Loh²⁰**, Charles G. Mullighan¹**, Cheryl L. Willman⁴**, Julie M. Gastier-Foster²,³**, Stephen P. Hunger²¹**
Retrospective analysis of 1023 unselected SR-ALL patients from COG AALL0331
Genomic Landscape of Ph-Like Standard Risk ALL

Much Lower Frequency of Kinase-Activating Lesions, Particularly Gene Fusions

48.8% of Ph-like $CRLF2_{high}$ have $CRLF2-R$

12% of $CRLF2-R$ have $IGH-CRLF2$

and 88% have $P2RY8-CRLF2$

Only 5/1023 cases had a kinase fusion
<table>
<thead>
<tr>
<th></th>
<th>NCI HR (n=884)</th>
<th>MRD+ NCI SR (n=505)</th>
<th>NCI SR (n=1023)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-like ALL</td>
<td>198 (22.4%)</td>
<td>86 (17.0%)</td>
<td>139 (13.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>CRLF2-R</strong></td>
<td>96 (10.9%)</td>
<td>29 (5.7%)</td>
<td>41 (4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>IGH-CRLF2</strong></td>
<td>56 (6.3%)</td>
<td>5 (1.0%)</td>
<td>5 (0.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>P2RY8-CRLF2</strong></td>
<td>40 (4.5%)</td>
<td>24 (4.8%)</td>
<td>36 (3.5%)</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>CRLF2-R + JAK/STAT mutation</strong></td>
<td>46 (5.25)</td>
<td>17 (3.4%)</td>
<td>14 (1.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>CRLF2-R no JAK/STAT mutation</strong></td>
<td>50 (5.7%)</td>
<td>12 (2.4%)</td>
<td>27 (2.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Non CRLF2-R</td>
<td>102 (11.5%)</td>
<td>57 (11.3%)</td>
<td>98 (9.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>ABL-class fusion</td>
<td>35 (4.0%)</td>
<td>5 (1.0%)</td>
<td>2 (0.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>JAK2-R</strong></td>
<td>9 (1.0%)</td>
<td>5 (1.0%)</td>
<td>2 (0.2%)</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>EPOR-R</strong></td>
<td>11 (1.2%)</td>
<td>0</td>
<td>0</td>
<td>0.0001</td>
</tr>
<tr>
<td>No kinase identified</td>
<td>18 (2.0%)</td>
<td>24 (4.8%)</td>
<td>56 (5.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Reshmi Blood 2017 & Roberts et al, Submitted
Outcome of Ph-Like Standard Risk ALL: COG AALL0331

7-year EFS: $82.4 \pm 3.6\%$ vs. $90.7 \pm 1.0\%$

7-year OS: $93.2 \pm 2.4\%$ vs. $95.8 \pm 0.7\%$
The prevalence of Ph-like ALL is lower in children with NCI standard-risk ALL compared to high-risk ALL.

Ph-like ALL in standard-risk patients harbor few targetable kinase fusions and have improved outcome compared to high-risk Ph-like ALL.

Real Time Identification of Ph-Like ALL for Precision Medicine Trials

HR B-ALL
AALL1131

Ph+ → imatinib/dasatinib + chemo

LDA

Ph-like

CRLF2+ → CRLF2-R + JAK1/JAK2 mutation analysis
FISH & PCR

CRLF2-

multiplex RT-PCR kinase fusion

ABL class kinase fusion
JAK2 fusion
IL7R alteration

EPOR rearrangement
Other fusions?

Risk-adapted chemotherapy

Not Ph-like

Post-induction

AALL1131
dasatinib

AALL1521
ruxolitinib

Post-induction

Induction

Tasian, Loh and Hunger; Blood 2017
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