



The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

STAG2/LMO2 Gamma-Delta ($\gamma\delta$) T-ALL: Identification and Characterization of an Extremely High Risk Group of T-ALL in the Very Young

Shunsuke Kimura, MDPhD¹, Petri Pölönen, PhD¹, Lindsey Montefiori, PhD¹, Kenneth Caldwell, MD², Ilaria Iacobucci, PhD¹, Chelsey Chen¹, Anthony Brown³, Katie Han⁴, Yen-Chun Liu¹, Yunchao Chang, PhD¹, Zhongshan Cheng⁵, Zhou Yinmei⁶, Chun Shik Park, PhD¹, Sharnise Mitchell⁷, Noemi Reyes³, Allen Yeoh, MD⁸, Andishe Attarbaschi⁹, Andrew Moore, MBBS,PhDFRACP¹⁰, Atsushi Manabe, MD PhD¹¹, Barbara Buldini, MDPhD^{12,13}, Kean Hui Chiew¹⁴, Chi Kong Li¹⁵, Ching-Hon Pui, MD⁴, Chunxu Qu¹, Daisuke Tomizawa, MDPhD¹⁶, Elisabeth Pasetta, PhD¹⁷, Franco Locatelli, MD PhD¹⁸, Gabriele Escherich, MD¹⁹, Gao Qingsong¹, Hannah Elisa Muhle¹⁹, Hanne Vibeke Marquart^{20,21}, Hester A. de Groot-Kruseman, PhD²², Jacob M. Rowe, MB,BS²³, Jan Stary, MD DSc²⁴, Jan Trka, MD PhD²⁵, John Kim Choi, MD PhD²⁶, Jules P.P. Meijerink, PhD²², Junko Takita, MD PhD²⁷, Katarzyna Pawinska-Wasikowska, MD PhD²⁸, Kjeld Schmiegelow, MD DMSc²⁹, Mariko Eguchi, MD³⁰, Martin Schrappe, MD³¹, Martin Zimmermann, PhD³², Masatoshi Takagi, MD PhD³³, Melissa Maybury³⁴, Michael Svato, MD³⁵, Michaela Reiterova³⁵, Michal Kicinski³⁶, Motohiro Kato, MD PhD³⁷, Orietta Spinelli³⁸, Pauline Mazilier, MD³⁹, Paul G. Thomas, PhD⁴⁰, Riccardo Masetti, MDPhD⁴¹, Rishi Sury Kotecha, MB ChB, PhD^{42,43}, Rob Pieters, Prof. Dr.²², Sarah Elitzur, MD⁴⁴, Selina M Luger, MDFRCPC⁴⁵, Shuhong Shen, MD PhD⁴⁶, Sima Jeha, MD⁴⁷, Steven M. Kornblau, MD⁴⁸, Szymon Skoczen, Prof.⁴⁹, Takako Miyamura⁵⁰, Tiffaney Vincent⁵¹, Toshihiko Imamura, MD PhD⁵², Valentino Conter, MD⁵³, Yanjing Tang⁵⁴, Zhaohui Gu, PhD⁵⁵, Kathryn G. Roberts, PhD¹, David T. Teachey, MD⁵⁶, Kristine R Crews, PharmD³, Cheng Cheng⁶, Jun J. Yang, PhD³, Hiroto Inaba, MDPhD⁴, Charles G. Mullighan, MBBS, MD¹

¹ Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN

² Gilead Sciences, Saint Petersburg, FL

³ Department of Pharmacy and Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN

⁴ Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN

⁵ Center of Applied Bioinformatics, St. Jude Children's Hospital, Memphis, TN

⁶ Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN

⁷ Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, Memphis, TN

⁸ Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

⁹ Department of Pediatric Hematology and Oncology, St. Anna Children's Hospital, Medical University Vienna, Vienna, Austria

¹⁰ Child Health Research Centre, The University of Queensland, Brisbane, Australia

¹¹ Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, JPN

¹² Pediatric Onco-Hematology, Stem Cell Transplant and Gene Therapy Laboratory, Istituto di Ricerca Pediatrica (IRP)-Città della Speranza, Padova, Italy

¹³ Pediatric Hematology, Oncology and Stem Cell Transplant Division, Maternal and Child Health Department, University of Padova, Padova, Italy

¹⁴ National University of Singapore, Singapore, SGP

¹⁵ Department of Paediatrics, The Chinese University of Hong Kong, Shatin, Hong Kong

¹⁶ Division of Leukemia and Lymphoma, Children's Cancer Center, National Center for Child Health and Development, Tokyo, Japan

¹⁷ Department of Oncology, Montefiore Medical Center, Bronx, NY

¹⁸ Department of Pediatric Hematology-Oncology and Cell and Gene Therapy, IRCCS Ospedale Pediatrico Bambino Gesù, Catholic University of the Sacred Heart, Rome, Italy

¹⁹ Clinic of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

²⁰ Department of Clinical Immunology, Rigshospitalet, Copenhagen, Denmark

- ²¹ Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
- ²² Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands
- ²³ Department of Hematology, Shaare Zedek Medical Center, Jerusalem, Israel
- ²⁴ Department of Pediatric Hematology and Oncology, Second Faculty of Medicine, Charles University/University Hospital Motol, Prague, Czech Republic
- ²⁵ CLIP - Childhood Leukaemia Investigation Prague, Department of Paediatric Haematology and Oncology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic
- ²⁶ University of Alabama at Birmingham, BIRMINGHAM
- ²⁷ Department of Pediatrics, Graduate School of Medicine Kyoto University, Kyoto, JPN
- ²⁸ Department of Pediatric Oncology and Hematology, Jagiellonian University Medical College, Wielicka, Poland
- ²⁹ Department of Pediatrics and Adolescent Medicine, Rigshospitalet University Hospital, Copenhagen, Denmark
- ³⁰ Department of Pediatrics, Ehime University, Toon, Ehime, JPN
- ³¹ Department of Pediatrics, University Hospital Schleswig-Holstein, Kiel, Germany
- ³² Department of Pediatric Hematology and Oncology, Medical School Hannover, Hannover, Germany
- ³³ Department of Pediatrics and Developmental Biology, Tokyo Medical and Dental University, Tokyo, Japan
- ³⁴ Child Health Research Centre, The University of Queensland, Brisbane, Australia
- ³⁵ CLIP - Childhood Leukaemia Investigation Prague, Department of Paediatric Haematology and Oncology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, CZE
- ³⁶ EORTC Headquarters, Brussels, BEL
- ³⁷ Department of Pediatrics, Tokyo University, Tokyo, JPN
- ³⁸ Hematology and Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy
- ³⁹ Pediatric hemato-oncology and transplantation, HUB - HUDERF, Brussels, Belgium
- ⁴⁰ Department of Immunology, St. Jude Children's Research Hospital, Memphis, TN
- ⁴¹ Pediatric Hematology and Oncology, IRCCS Azienda Ospedaliero Universitaria di Bologna, University of Bologna, Bologna, Italy
- ⁴² Leukaemia Translational Research Laboratory, Telethon Kids Cancer Centre, Telethon Kids Institute, University of Western Australia, Perth, Australia
- ⁴³ Department of Clinical Haematology, Oncology, Blood and Marrow Transplantation, Perth Children's Hospital, Perth, Australia
- ⁴⁴ Department of Pediatric Hematology and Oncology, Schneider Children's Medical Center and Tel Aviv University, Petah Tikva, Israel
- ⁴⁵ Perelman School of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA
- ⁴⁶ Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
- ⁴⁷ Department of Global Pediatric Medicine, St. Jude Children's Research Hospital, Memphis, TN
- ⁴⁸ Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
- ⁴⁹ Department of Pediatric Oncology and Hematology, Jagiellonian University Medical College, Krakow, POL
- ⁵⁰ Department of Pediatrics, Osaka University, Osaka, JPN
- ⁵¹ The Children's Hospital of Philadelphia, Philadelphia, PA
- ⁵² Department of Pediatrics, Kyoto Prefectural University of Medicine, Kyoto, JPN
- ⁵³ Tettamanti Center, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
- ⁵⁴ Shanghai Children's Medical Center, Shanghai, China
- ⁵⁵ COH, Duarte, CA
- ⁵⁶ Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, PA

Background

The prognosis of pediatric T-cell acute lymphoblastic leukemia (T-ALL) has improved with minimal residual disease (MRD)-stratified therapy, however, gamma delta T cell receptor positive ($\gamma\delta$) T-ALL remains a high-risk (HR) group. Limited studies have explored the clinical and genomic characteristics of $\gamma\delta$ T-ALL, prompting us to conduct a comprehensive analysis of this entity and to identify determinants of outcome.

Methods

Through a consortium of 13 groups, we assembled a cohort of 200 patients up to 25 years of age with $\gamma\delta$ T-ALL enrolled in clinical trials between 2000 and 2018. Clinical data of patients with non- $\gamma\delta$ T-ALL enrolled on the same clinical trials were collected ($n = 1,067$). Complete remission (CR) was defined when bone marrow (BM) showed M1 cytology and/or MRD $<1\%$ without evidence of extramedullary disease at end of induction/consolidation (EOI/EOC) and failure to achieve CR was considered treatment failure. A total of 76 $\gamma\delta$ T-ALL samples were analyzed by whole genome (WGS) and/or transcriptome (RNAseq) sequencing.

Results

The frequency of $\gamma\delta$ T-ALL was 8.0% of T-ALL cases. Patients with $\gamma\delta$ T-ALL exhibited a higher rate of poor prednisone response ($P < 0.01$), MRD $> 1\%$ at day 15 ($P < 0.01$), at EOI ($P < 0.01$) and EOC ($P < 0.01$), compared to non- $\gamma\delta$ T-ALL cases. Furthermore, patients with $\gamma\delta$ T-ALL showed significantly worse 5-year event free survival (EFS, 65% v. 78%, $P < 0.01$) and overall survival (OS,

77% vs 83%, $P=0.048$). Almost all relapses of $\gamma\delta$ T-ALL were isolated BM, while the central nervous system was the main site of relapse in non- $\gamma\delta$ T-ALL, suggesting slow treatment response and chemo-resistance to the current treatment in $\gamma\delta$ T-ALL. However, $\gamma\delta$ T-ALL showed a higher rate of toxic death during treatment (7.6% vs 4.0%, $P<0.01$), suggesting the need for different therapeutic strategies and risk-classification, rather than treatment intensification.

Strikingly, patients less than 3 years of age with $\gamma\delta$ T-ALL exhibited significantly poor EFS (33% v. 70% [3-10 years] and 73% [>10], $P<0.01$) and OS (49% v. 78% [3-10] and 82% [>10], $P<0.01$) (**Fig. A**), a difference not observed in non- $\gamma\delta$ T-ALL. MRD $>1\%$ at EOI showed poor EFS (51% v. 96% [MRD $<0.01\%$] and 91% [1% $>$ MRD $>0.01\%$], $P<0.01$) and OS (66%).

Integrated analysis of WGS and RNAseq identified enrichment of several genomic subtypes in $\gamma\delta$ T-ALL, including STAG2/LMO2, hyperdiploidy with recurrent gains of chromosomes 8, 10, 11, 13q and 19, a recently identified "LMO2 $\gamma\delta$ -like" subtype with distinct gene expression and LMO2/MYC/MYCN alterations, TLX3-rearranged (-R), and PICALM::MLLT10. No TAL1 nor TLX1-R were detected. STAG2/LMO2 was associated with age at diagnosis before 3 years, and extremely poor outcome, with 4 out of 5 cases dying within three years of diagnosis (**Fig. B**).

Of 24 STAG2/LMO2 T-ALL (additional 5 non- $\gamma\delta$, 13 TCR unknown cases), 22 of which were diagnosed by age three. All STAG2/LMO2 cases had alterations resulting in LMO2 activation and STAG2 inactivation, most commonly a single rearrangement between these two genes, and upregulation of HBE1, the LIN28-let7 pathway and stem cell proliferation pathways, suggesting a fetal hematopoietic origin.

STAG2 has a critical role in the maintenance of enhancer-promoter looping mediated by the cohesin complex. To examine the consequences of STAG2 alterations, we performed integrated genomic/epigenomic analysis of the STAG2/LMO2 (MOLT-14 and PER-117) and STAG2 knockout (KO)/addback T-ALL lines. Chromatin loop sizes defined by H3K27ac HiChIP was highest in STAG2/LMO2 lines compared to other T-ALL. Following restoration of STAG2 expression in MOLT-14, CD34 and ID1/2 were down-regulated and H3K27ac was enriched in pathways related to T-cell differentiation. STAG2 KO in the non- STAG2/LMO2, LMO2-activated line PF382 identified genes also upregulated in STAG2/LMO2 primary samples, including CDK4 and STAG1. STAG2 KO lines exhibited partial compensation of STAG2 binding sites by STAG1 and upregulation of $\gamma\delta$ -related genes, RORC and ID1/3. High throughput screening of 2,050 small molecules identified efficacy of HDAC, CDK and PARP inhibitors in STAG2/LMO2 lines.

Conclusion

Very young onset $\gamma\delta$ T-ALL, but not non- $\gamma\delta$ T-ALL, is enriched for the STAG2/LMO2 subtype and is a very high risk form of T-ALL. STAG2 loss perturbs chromatin organization and hematopoietic differentiation. Moreover, we demonstrate efficacy of novel therapeutic approaches that are needed to cure this form of leukemia.

Disclosures Attarbaschi: JazzPharma: Honoraria. **Meijerink:** Acerta Pharma: Current Employment, Other: full time senior director biotech. **Schmiegelow:** Medscape: Other: Speaker's fee; Amgen: Other: Speaker's fee; Servier: Honoraria, Other: Educational grants; Jazz Pharmaceuticals: Honoraria; Illumina: Honoraria. **Kicinski:** Pierre Fabre: Research Funding; BMS: Research Funding; MSD: Research Funding; JnJ: Research Funding; Immunocore: Research Funding. **Thomas:** Shennon Bio, Immunoscape, Cytoagents: Consultancy, Membership on an entity's Board of Directors or advisory committees; JNJ, Pfizer: Consultancy, Speakers Bureau; Elevate Bio: Research Funding. **Pieters:** Servier: Consultancy; Clinigen: Consultancy. **Elitzur:** Jazz Pharmaceuticals: Honoraria; Medison Pharma: Honoraria. **Luger:** Amgen: Honoraria, Membership on an entity's Board of Directors or advisory committees; AbbVie: Membership on an entity's Board of Directors or advisory committees; Marker Therapeutics: Membership on an entity's Board of Directors or advisory committees; Novartis: Consultancy; Bristol-Myers Squibb: Honoraria; Onconova: Research Funding; Astellas: Honoraria. **Jeha:** Amgen: Other: As part of the mission of St. Jude Global Hiroto Inaba, Victor Santana, Sima Jeha and Caitlyn Duffy participate in the Blincyto Humanitarian Access Program and provide in kind support for this program. **Teachey:** BEAM: Research Funding; Neoimmune Tech: Research Funding; Sobi: Membership on an entity's Board of Directors or advisory committees, Research Funding; Jazz: Membership on an entity's Board of Directors or advisory committees, Research Funding. **Yang:** Takeda Pharmaceutical Company: Research Funding. **Inaba:** Servier: Consultancy; Amgen: Other: As part of the mission of St. Jude Global Hiroto Inaba, Victor Santana, Sima Jeha and Caitlyn Duffy participate in the Blincyto Humanitarian Access Program and provide in kind support for this program.. **Mullighan:** Illumina: Honoraria; Amgen: Honoraria; Pfizer: Research Funding; Abbvie: Research Funding.

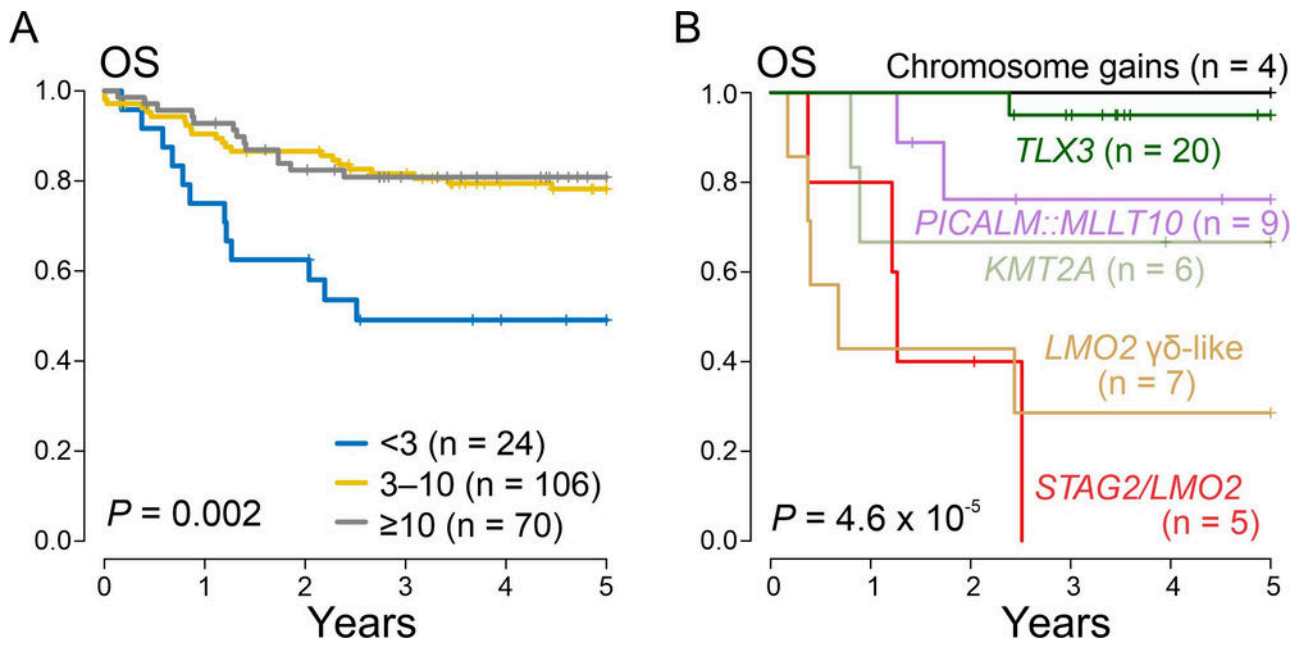


Figure 1

<https://doi.org/10.1182/blood-2023-178688>