The Genomic Landscape of Pediatric Acute Lymphoblastic Leukemia and Opportunities for Precision Medicine

Sarah K Tasian, MD
Children's Hospital of Philadelphia
University of Pennsylvania School of Medicine

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Perelman School of Medicine University of Pennsylvania

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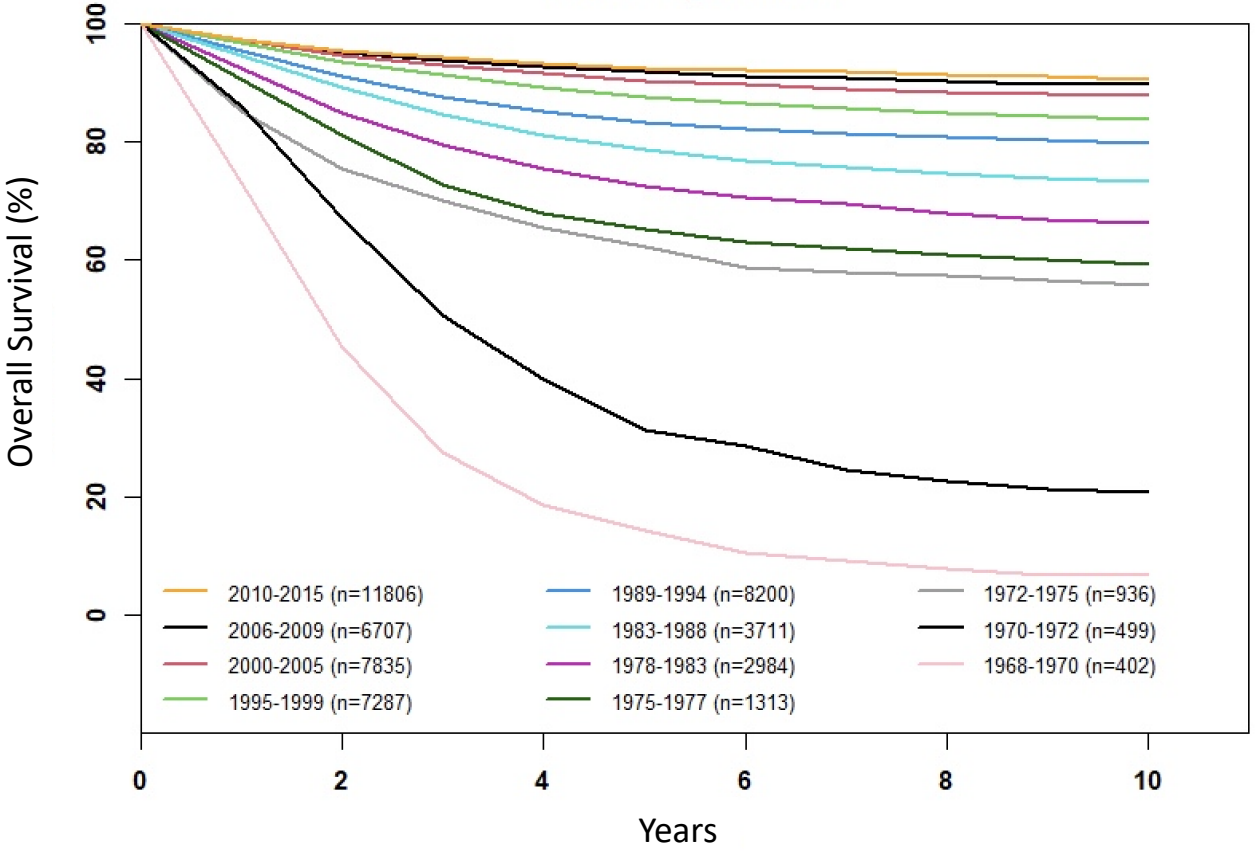
Improved Survival of Patients with ALL Treated on Children's Oncology Group Clinical Trials



] this is still a lot of patients….

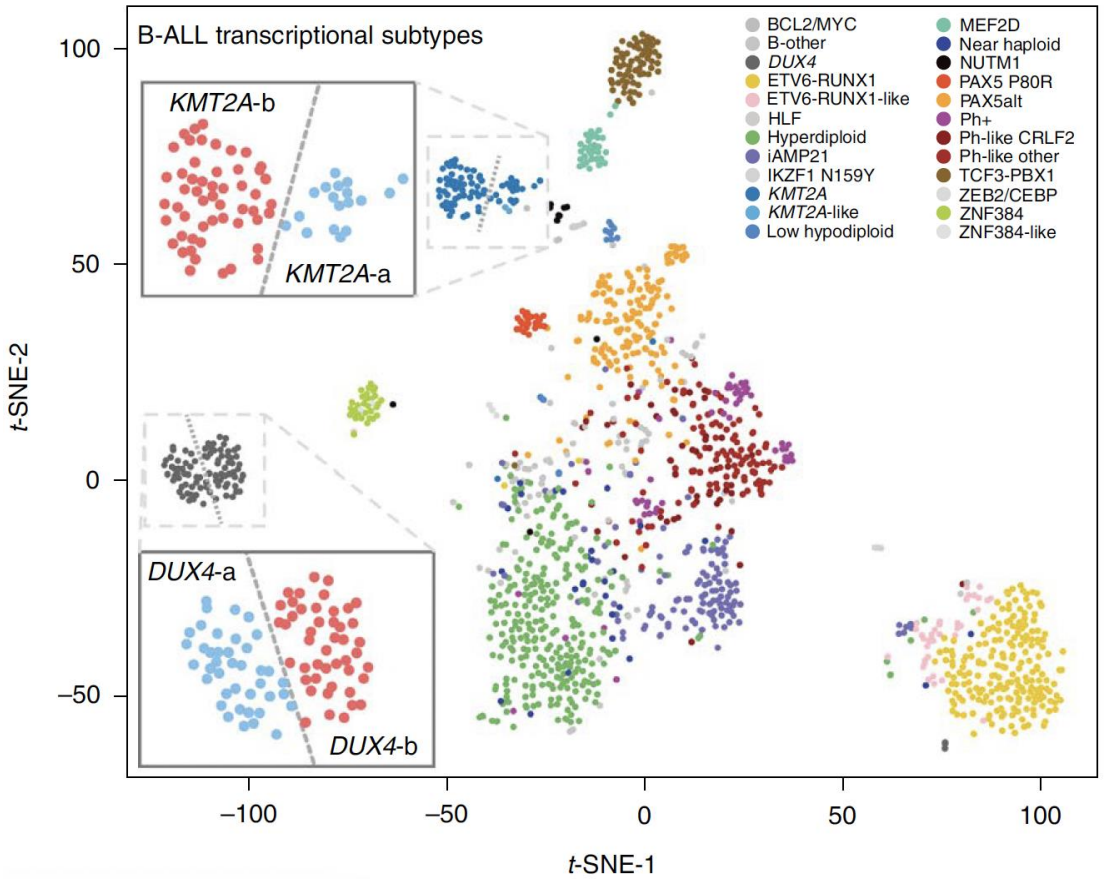
NCI risk status, ALL-associated genetics, and end-induction minimal residual disease response (MRD) contribute to prognosis

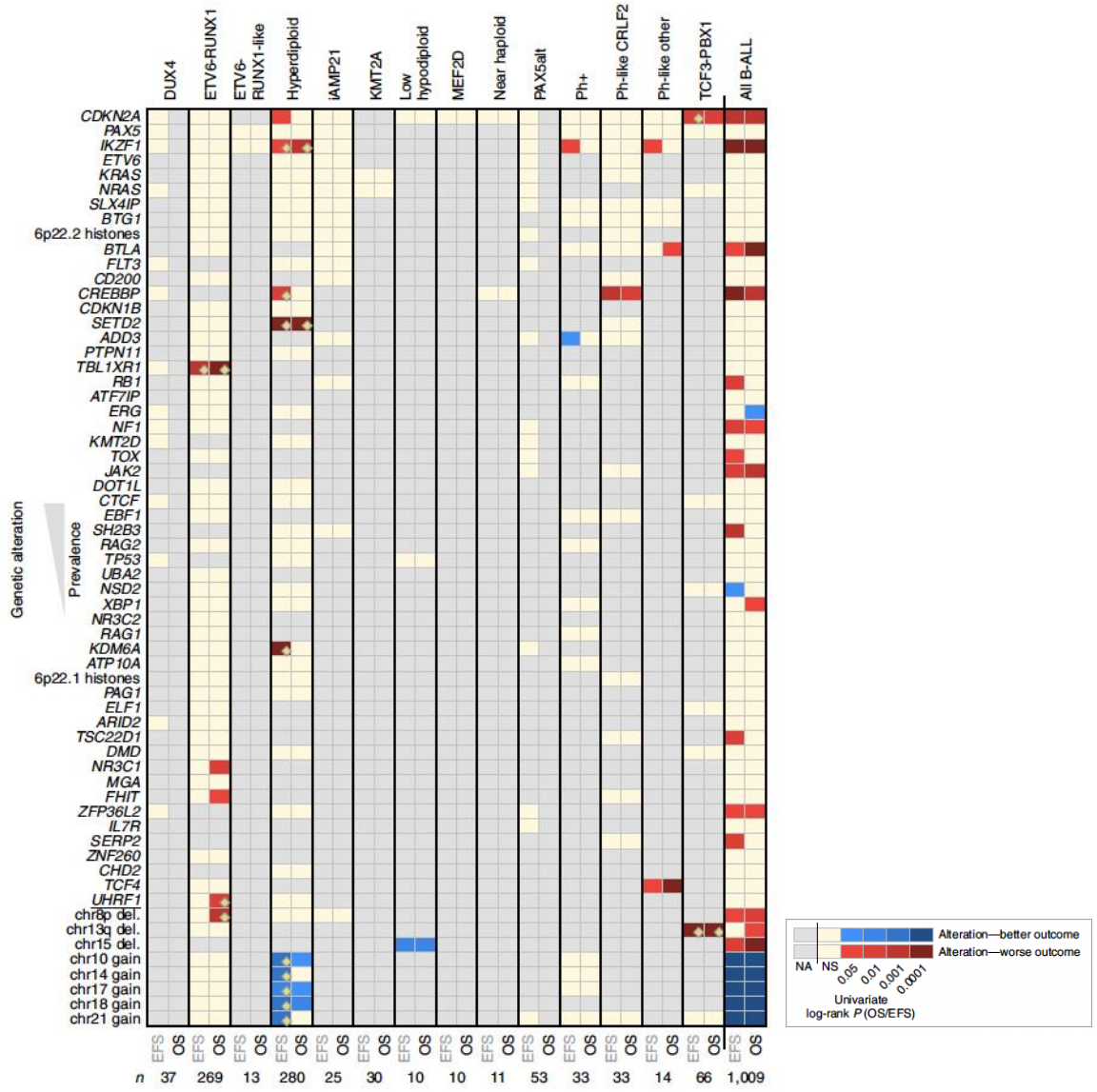
Relapsed ALL remains the leading cause of childhood/AYA cancer mortality

Frontline intervention with targeted inhibitors or immunotherapies for relevant patients may improve outcomes

adapted from Hunger & Mullighan NEJM 2015
Raetz *et al* PBC 2023, submitted

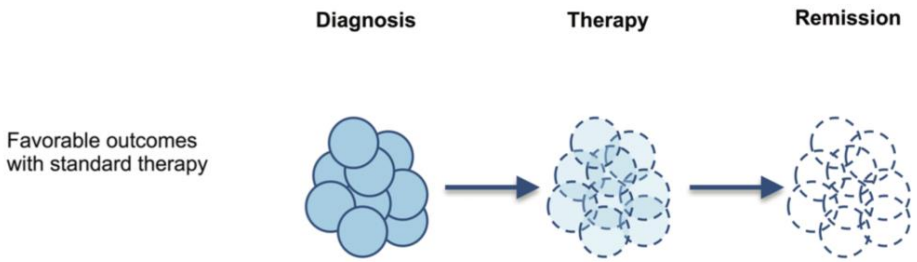
Genetic Heterogeneity of B-ALL Informs Prognosis/Outcomes





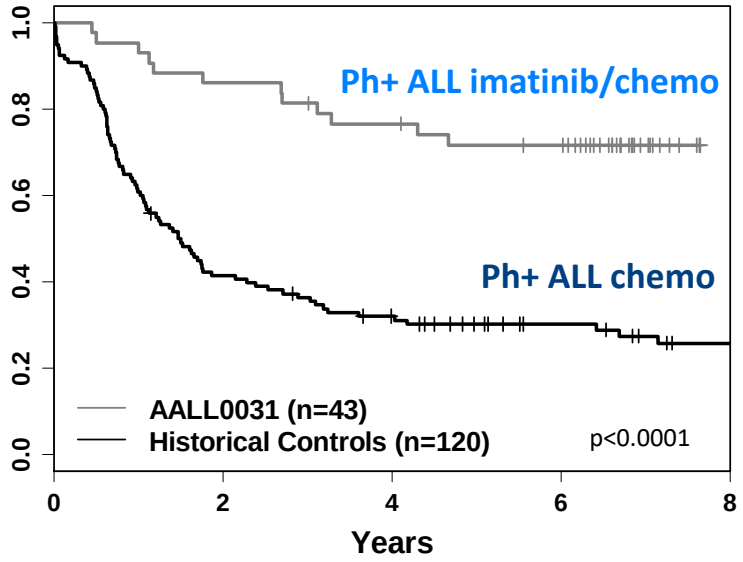
Oncogenic fusions and other driver alterations may be/are likely targetable. Some mutations appear more 'dispensable' and may not be effectively targeted (or may be differentially targeted in B-ALL vs T-ALL).

Risk-Stratified Therapy for Pediatric Patients with B-ALL



adapted from Tasian & Hunger BJH 2017; also Ma *et al* Nat Comm 2015, Waanders *et al* Blood Cancer Disc 2020, Brady *et al* Nat Gen 2022

BCR::ABL1 (Ph+) ALL – A Paradigm for Precision Medicine



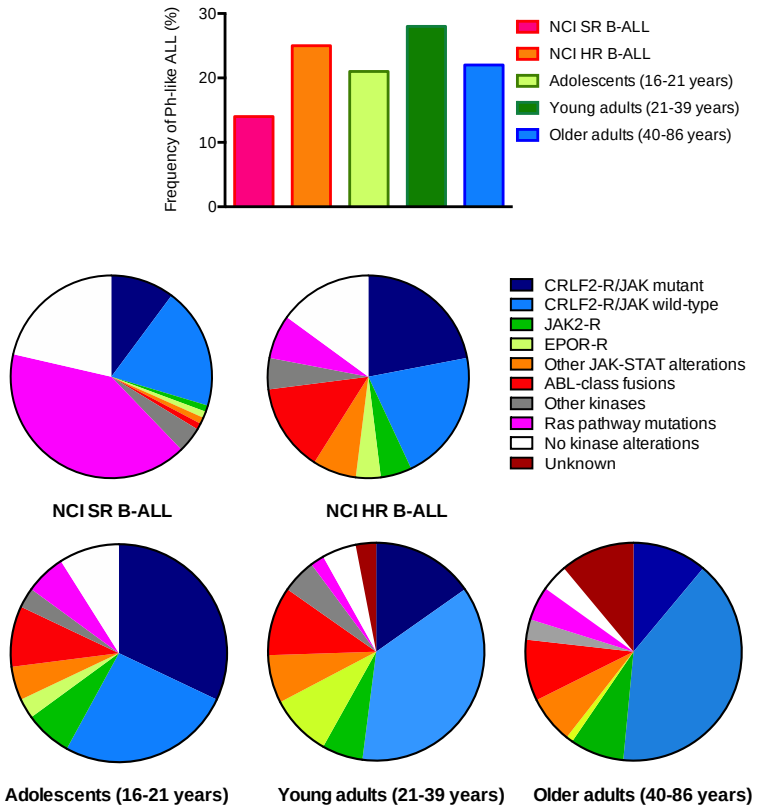
Outcomes for patients with high-risk leukemias can be potentially improved dramatically if:

- 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 outcomes require that we identify such molecular lesions and develop effective targeted therapies

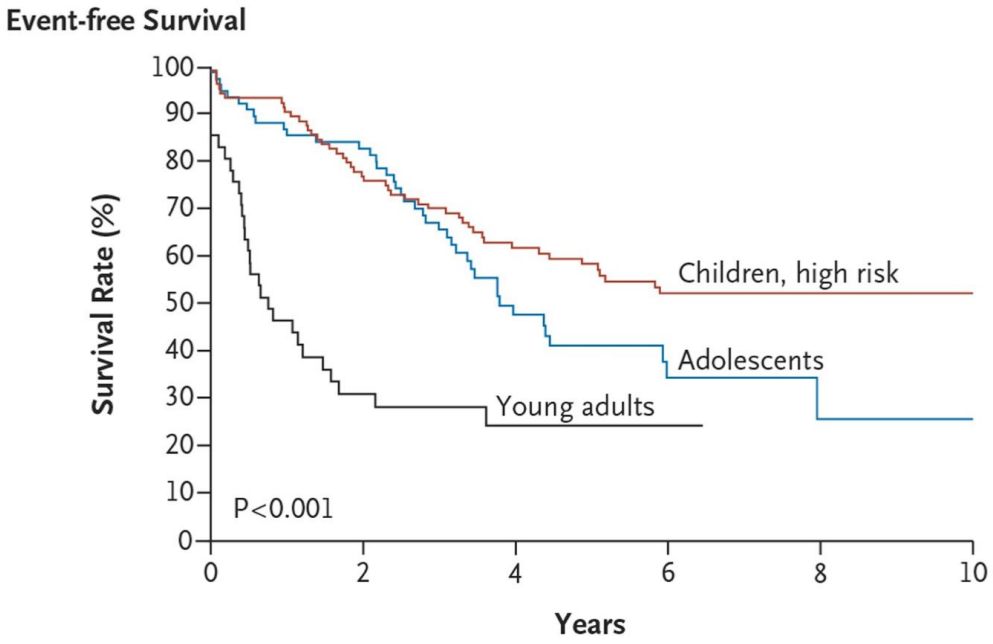
Philadelphia Chromosome-like (Ph-like) ALL: Biology

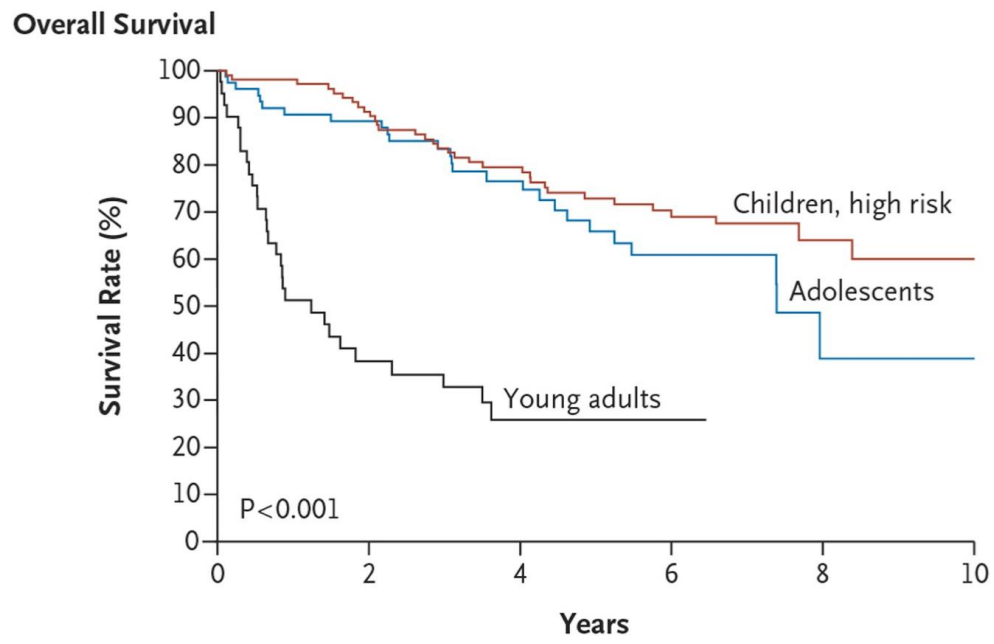
- Ph-like ALL is a common subtype of B-ALL with increasing frequency across the age spectrum
  - Characterized by a kinase-activated gene expression profile similar to that of Ph+ ALL
  - Driven by a variety of genetic alterations involving cytokine receptors and kinases and associated with frequent *IKZF1* and other transcription factor deletions
  - Frequent hyperleukocytosis at diagnosis
  - Associated with high rates of measurable residual disease (MRD) and relapse in patients treated with conventional chemotherapy



Tran & Tasian Clinical Management of Acute Lymphoblastic Leukemia, 2022

Ph-like ALL: Poor Clinical Outcomes Across the Age Spectrum with Conventional Chemotherapy

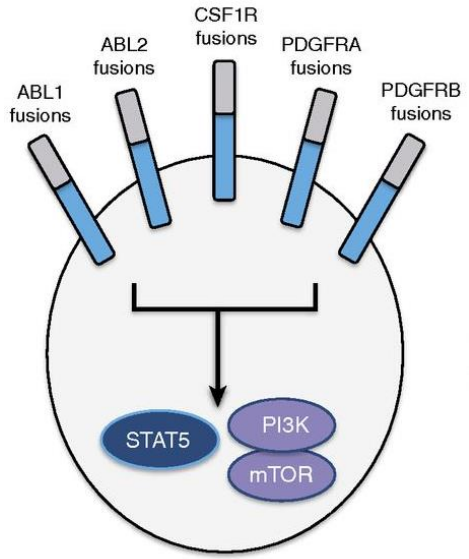




Roberts *et al* NEJM 2014

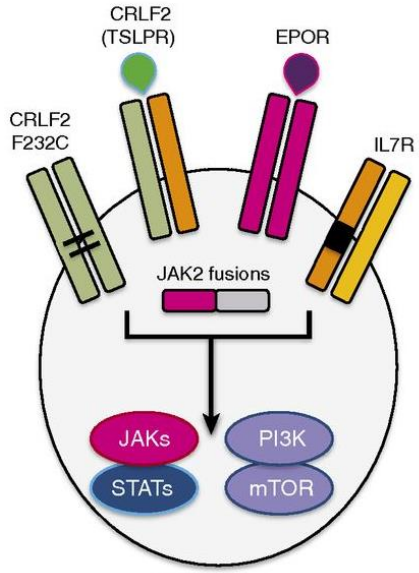
Ph-like ALL: an Opportunity for Targeted Therapeutics

~15% Ph-like ALL

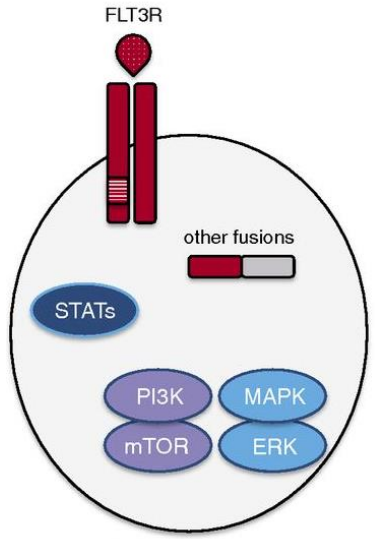


ABL inhibitors
PI3K pathway inhibitors

~70% Ph-like ALL



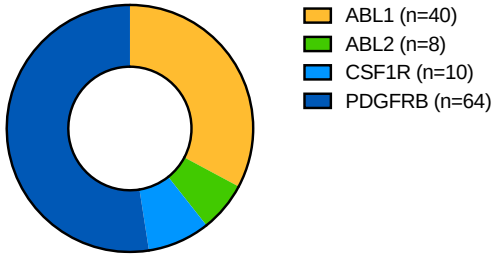
JAK inhibitors
PI3K pathway inhibitors
HDAC inhibitors
anti-TSLPR antibodies & CAR T cells

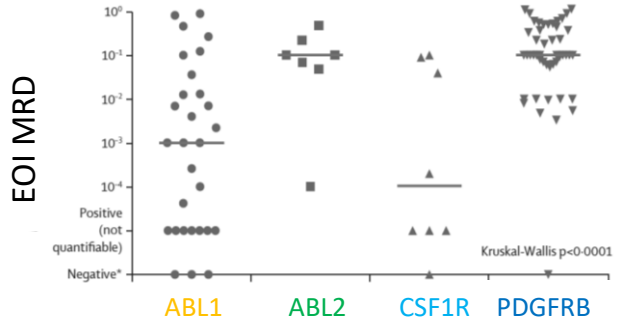


FLT3 inhibitors
TRK inhibitors
FAK inhibitors
PI3K pathway inhibitors
MEK inhibitors

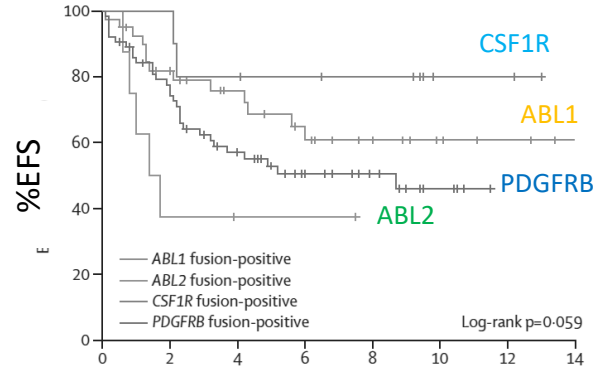
Tasian, Loh, Hunger Blood 2017

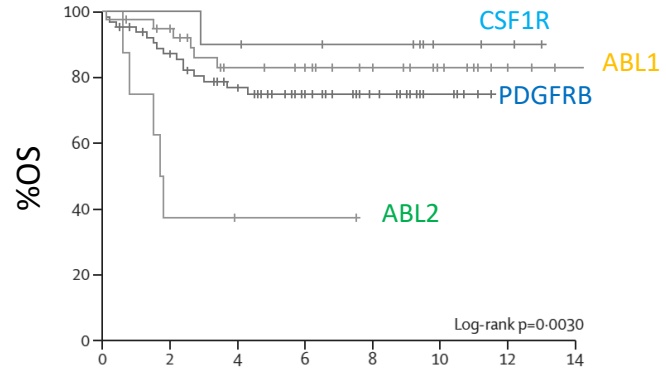
ABL Class Ph-like ALL





- Rearrangements in *ABL1*, *ABL2*, *CSF1R*, and *PDGFRB* (and *PDGFRA*?) comprise this subtype of Ph-like ALL
- *PDGFRB* rearrangements most common and highly associated with diagnostic WBC >100K and induction failure
- Responses to conventional chemotherapy are generally poor and may differ by specific ABL class rearrangement

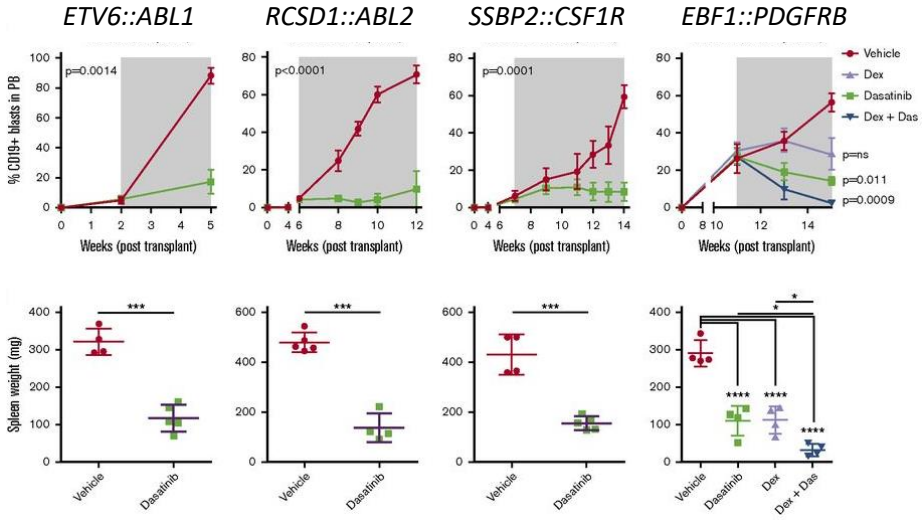




den Boer/Cario/Moorman *et al* Lancet Haematology 2021, Chiaretti *et al* Haematologica 2020

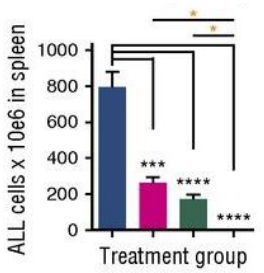
ABL Class Ph-like ALL: +TKI Therapy

- Several studies have reported potent anti-leukemia activity of TKIs in preclinical ABL class Ph-like ALL models & synergy with other drugs

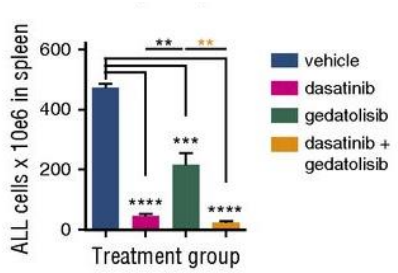


Roberts *et al* Blood Adv 2017

NUP214::ABL1 (NH011)

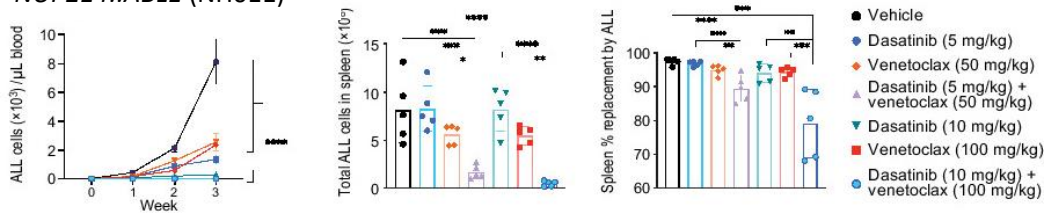


ETV6::ABL1 (PHL3)

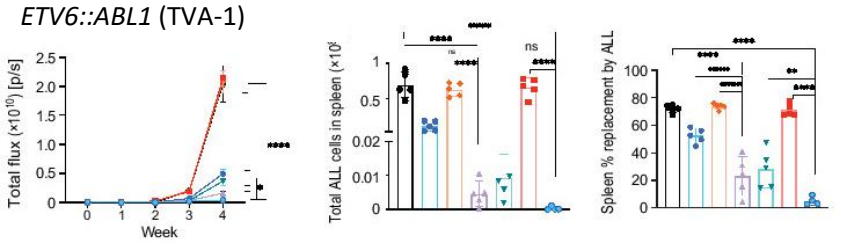


Tasian *et al* Blood 2017a

NUP214::ABL1 (NH011)



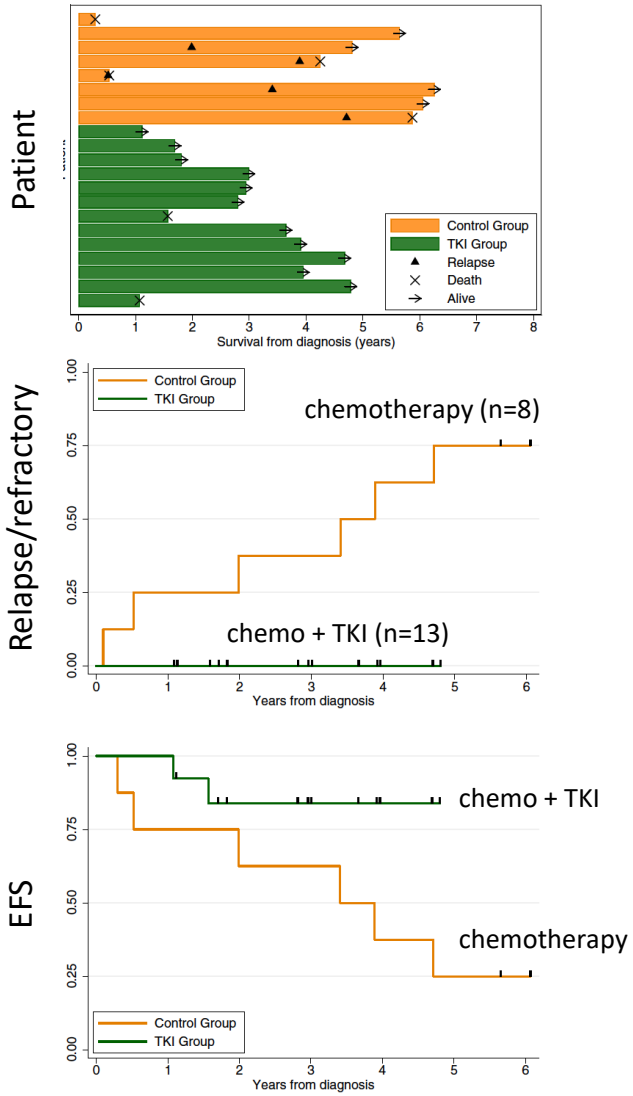
ETV6::ABL1 (TVA-1)



Ding *et al* CCR 2021

ABL Class Ph-like ALL: +TKI Therapy

- Strong precedent of success with TKI-based therapies for analogous patients with Ph+ ALL
- It is presumed that TKI addition to chemotherapy will improve MRD-negative remission & EFS/OS for patients with ABL class Ph-like ALL
- Clinical case reports/series have demonstrated benefit of TKI (*eg*, imatinib, dasatinib, ponatinib) addition to chemotherapy for patients with ABL class Ph-like ALL

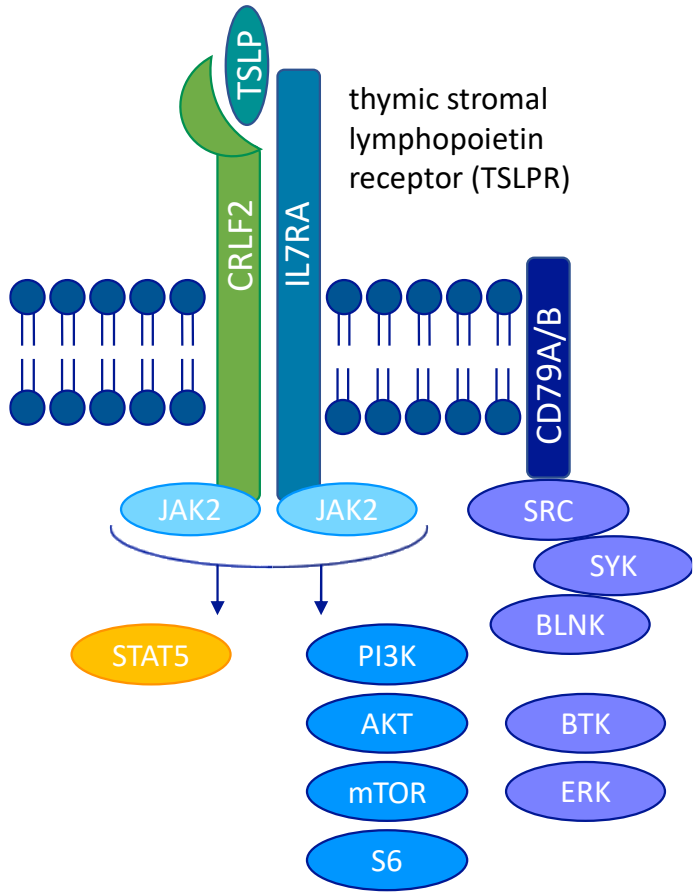


Gotesman *et al* Oncotarget 2018, Tasian *et al* Blood 2017a, Schwab *et al* Blood 2016, Roberts *et al* Cancer Cell 2012

den Boer/Cario/Moorman *et al* Lancet Haematology 2021, Chiaretti *et al* Haematologica 2020

CRLF2-Rearranged Ph-like ALL

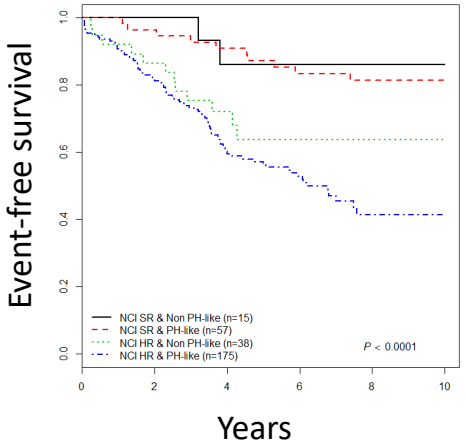
- *CRLF2* rearrangements comprise ~50% of Ph-like ALL cases and are enriched in patients of Hispanic/Latinx or Native American ancestry
  - *P2RY8::CRLF2* fusions from PAR1 deletion on chromosome X or Y
  - *IGH::CRLF2* rearrangement from t(X;14) or t(Y;14) → increased incidence with age
  - Frequent co-occurrence of *JAK2* mutations (especially R683G), *JAK1* point mutations, or *IL7R* indels
  - Associated with constitutive JAK/STAT and other kinase network signaling

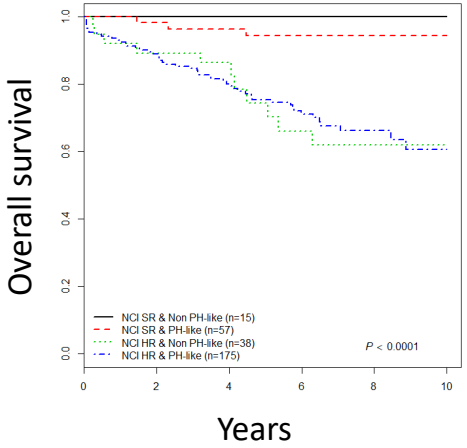


Harvey & Tasian Blood Advances 2020, Tasian *et al* Blood 2017c, Tasian *et al* Blood 2012, Russell *et al* Blood 2010, Collins-Underwood *et al* 2010, Mullighan *et al* PNAS 2009, den Boer *et al* Lancet Oncology 2009

CRLF2-Rearranged Ph-like ALL: Outcomes Vary by Risk Status

- Pediatric and AYA patients with *CRLF2*-rearranged NCI high-risk Ph-like ALL have inferior clinical outcomes compared to those with *CRLF2* wild-type ALL
- Prognostic impact of *CRLF2* rearrangements appears relatively minimal in children with standard-risk ALL (and may or may not be Ph-like)
- Somewhat differential outcomes have been reported in European versus North American studies – perhaps related to different ancestries?
- Data in children with DS-ALL parallel those of Ph-like ALL



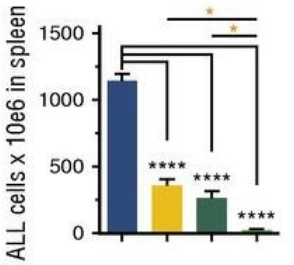


Rabin *et al* SIOP 2022 #234, Tasian *et al* ASH 2020 #1095, Roberts *et al* Blood 2018, Roberts *et al* JCO 2017, Vesely *et al* Leukemia 2017, Loh *et al* Blood 2013, Ensor *et al* Blood 2011, Harvey *et al* Blood 2010

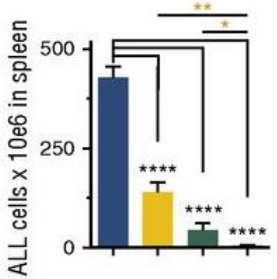
CRLF2/JAK Pathway Ph-like ALL: +TKI Therapy

- Studies have reported potent anti-leukemia activity of the JAK inhibitor ruxolitinib in preclinical Ph-like ALL models with *CRLF2*, *JAK2*, *EPOR* rearrangements, *SH2B3* deletions, or *IL7R* indels

IGH::CRLF2, *JAK2* R683G (ALL121)

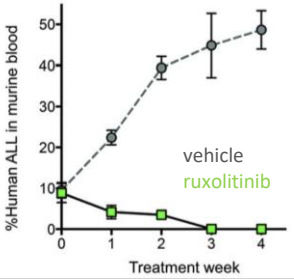


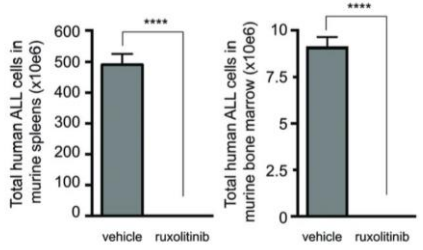
P2RY8::CRLF2, *JAK2* R683G (ALL4364)



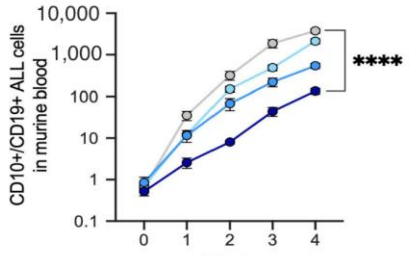
vehicle
gedatolisib
ruxolitinib
gedatolisib + ruxolitinib

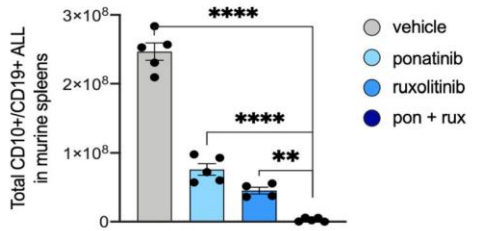
GOLGA5::JAK2 (PAXDBJ)



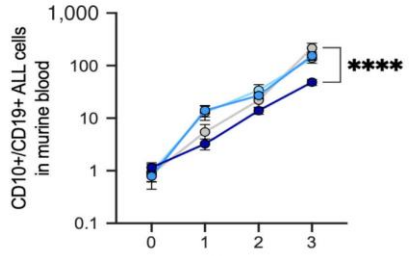


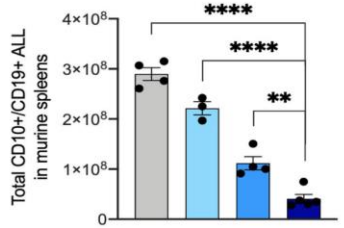
IGH::EPOR (PAVRCK)





IGH::EPOR (PAVDRS)



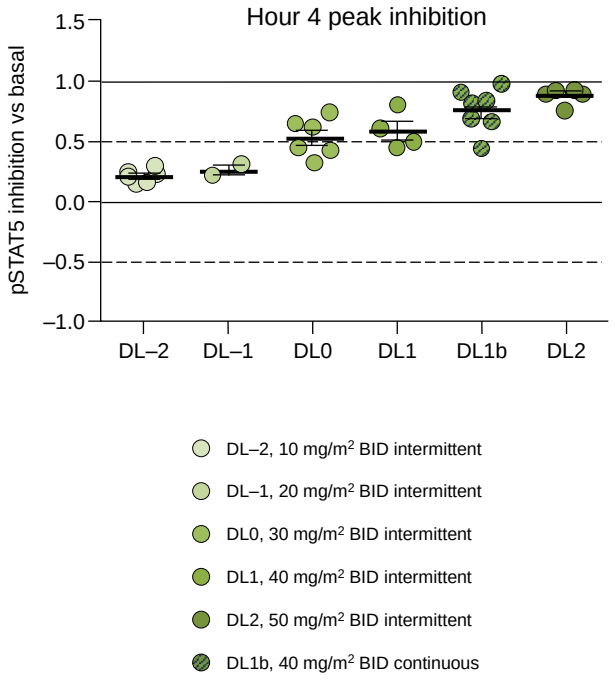


Niswander *et al* Haematologica 2022, Ding *et al* Clinical Cancer Research 2021, Roberts *et al* Blood Adv 2017, Tasian *et al* Blood 2017a, Iacobucci *et al* Cancer Cell 2016

CRLF2/JAK Pathway Ph-like ALL: +TKI Therapy

- Case reports have documented use of ruxolitinib with chemotherapy in children with refractory CRLF2/JAK pathway-mutant Ph-like ALL

- Clinical trials are investigating the potential benefit of ruxolitinib addition to chemotherapy for patients with newly-diagnosed high-risk Ph-like ALL
  - COG AALL1521: safety and RP2D of ruxolitinib identified; ongoing efficacy and correlative analyses (NCT02723994)
  - University of Chicago phase 1 trial (NCT03571321)
  - It is not yet known if JAKi addition to chemotherapy for patients with CRLF2/JAK+ Ph-like ALL will reduce relapse risk



Ding *et al* Haematologica 2018, Mayfield *et al* PBC 2017

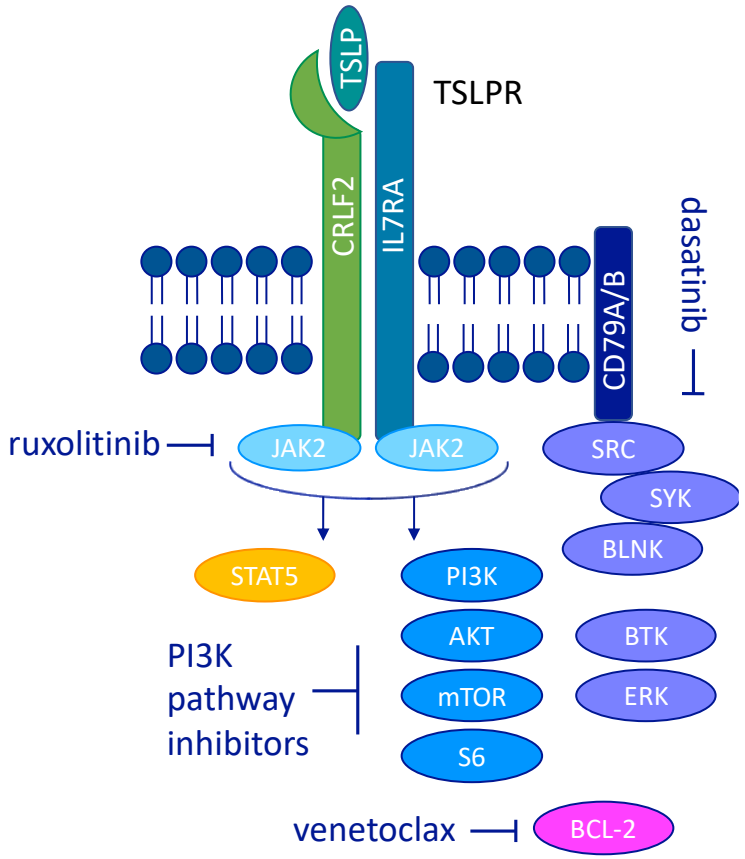
Tasian *et al* ASH 2022 #2725, Tasian *et al* ASH 2018 #555

CRLF2/JAK Pathway Ph-like ALL: Potential for Multi-TKI Therapy?

- Preclinical studies suggest that JAKi is likely insufficient for *CRLF2*-R Ph-like ALL due to additional essential signaling pathways, but that *JAK2*-R and *EPOR*-R ALL may be differentially addicted and quite sensitive to JAKi

- Preclinical studies show that combinatorial approaches may be quite effective (chemotherapy + JAKi, JAKi + PI3Ki + SRCi, JAKi + BCL-2i)

- Preclinical studies have also credentialed TSLPR-targeted CAR T cells in *CRLF2*-rearranged Ph-like ALL and DS-ALL → coming soon to phase 1 clinical trial investigation



Bagashev *et al* Hemasphere 2022, Niswander *et al* Haematologica 2022, Ding *et al* CCR 2021, Böhm *et al* Leukemia 2021, Chang *et al* Blood 2021, Hurtz *et al* JCI 2020, Tasian *et al* Blood 2017a, Qin *et al* Blood 2015

Summary: Integrating Genomics and Therapeutics in Ph-like ALL

- Ph+ ALL precedent exists for TKI addition to frontline chemotherapy for patients with ABL class Ph-like ALL with emerging favorable case series-level data
  - Current & planned clinical trials will elucidate the potential benefit of imatinib/ other TKI addition to chemotherapy specifically in ABL class Ph-like ALL
  - The EsPhALL2017/COG AALL1631 trial will also help to identify an optimal chemotherapy backbone with TKI for patients with Ph+ or ABL class Ph-like ALL

- The optimal therapeutic approach for patients with CRLF2/JAK pathway-mutant Ph-like ALL has not been identified
  - Current clinical trials will help to elucidate the potential benefit (or not) of ruxolitinib addition to frontline chemotherapy

The Future of Ph-like ALL: TKI + Immunotherapy?

- Clinical trials of CD19- and CD22-targeting antibody-based and cellular immunotherapies have been enriched in patients with Ph-like ALL
- Recent clinical studies in adults with Ph+ or ABL class Ph-like ALL have demonstrated safety and activity of blinatumomab + imatinib, dasatinib, nilotinib, or ponatinib
  - Preclinical studies have suggested potential TKI antagonism with blinatumomab and CD19 CAR T cell immunotherapy, however
- The randomized EsPhALL2020/COG AALL2131 phase 3 trial will investigate the efficacy of imatinib + chemotherapy versus chemotherapy/blinatumomab in children and AYAs with ABL class Ph-like or Ph+ ALL (opening 2023)

Short *et al* ASCO 2022 #7009, Advani *et al* ASH 2021 #3397, Foà *et al* NEJM 2020, King *et al* Leukemia Research 2019
Leonard *et al* Blood 2021, Weber *et al* Blood Advances 2019, Mestermann *et al* Science Translational Medicine 2019

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Children's Oncology Group ALL Committee collaborators

Mignon Loh, MD
Stephen Hunger, MD
Richard Harvey, PhD
I-Ming Chen, DVM MS
Shalini Reshmi, PhD
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Rohde family
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Questions/¿Preguntas?

tasians@chop.edu

La Malédiction