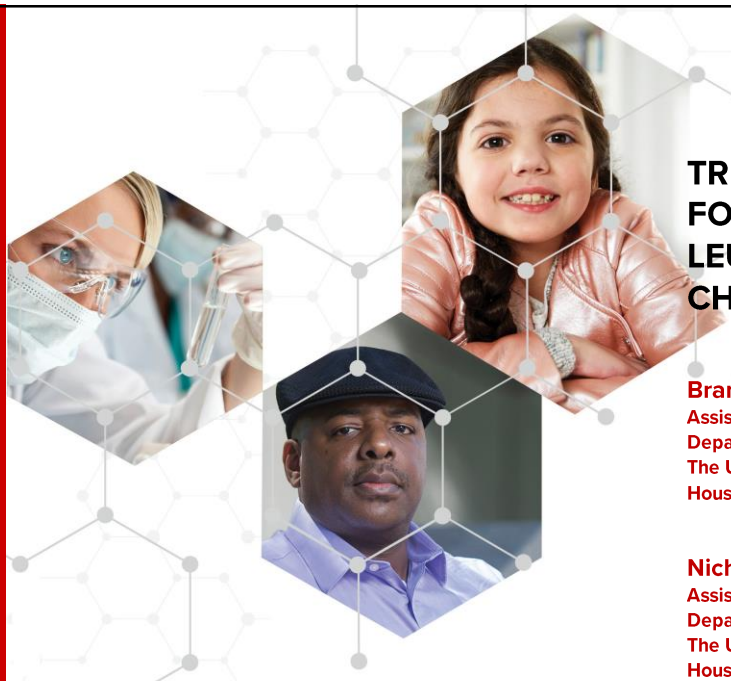

LEUKEMIA & LYMPHOMA SOCIETY®

# TREATMENT ADVANCEMENTS FOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN CHILDREN AND ADULTS

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1

## WELCOMING REMARKS

TREATMENT ADVANCEMENTS FOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN CHILDREN AND ADULTS

**Lizette Figueroa-Rivera, MA**
Sr. Director, Education & Support
The Leukemia & Lymphoma Society

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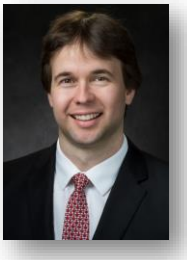
2

# DISCLOSURES

**TREATMENT ADVANCEMENTS FOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN CHILDREN AND ADULTS**



**Branko Cuglievan, MD**

No Financial Disclosures to report.

**Nicholas Short, MD**

Honoraria/Consultation Fee: Adaptive Biotechnologies, Amgen, Astellas Pharma, Inc., BeiGene, GSK, Jazz Pharmaceuticals, Nkarta, Novartis, Pfizer, Inc., and Sanofi.

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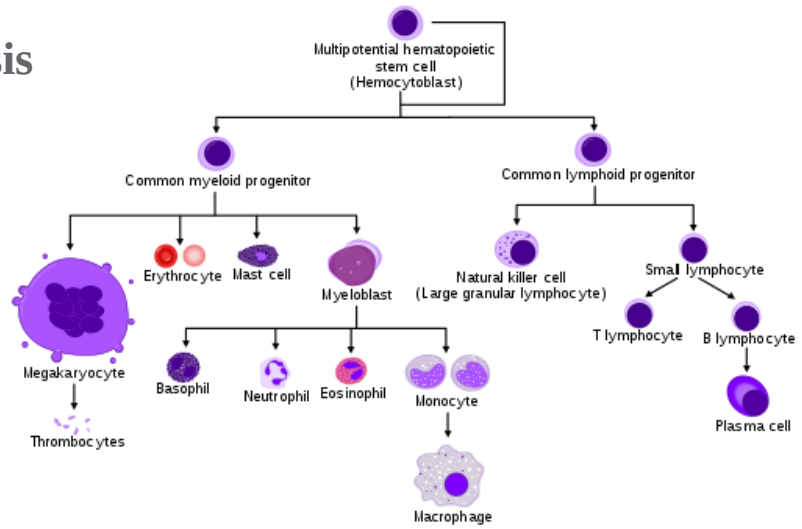
Introduction | Foundation | Therapeutic Advancements | Panel Q&A / Close

# Hematopoiesis

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4

# Mortality Rates

Age 0 -19
Pediatric Cancer Five-year Observed Survival Rates For Two Time Periods

**Table 4. Pediatric Cancer Five-year Observed Survival Rates for Two Time Periods, Ages 0-19**

| | Year of Diagnosis 1975-79 % | 2003-09* % |
|---|---|---|
| All ICCC sites | 63 | 83 |
| Leukemia | 48 | 84 |
| Acute lymphocytic leukemia | 57 | 90 |
| Acute myeloid leukemia | 21 | 64 |
| Lymphomas and reticuloendothelial neoplsams | 72 | 91 |
| Hodgkin lymphoma | 87 | 97 |
| Non-Hodgkin lymphoma | 47 | 85 |
| Brain and CNS | 59 | 75 |
| Ependymoma | 37 | 81 |
| Astrocytoma | 69 | 85 |
| Medulloblastoma | 47 | 70 |
| Neuroblastoma and ganglioneuroblastoma | 54 | 79 |
| Retinoblastoma | 92 | 99 |
| Wilms tumor | 75 | 90 |
| Hepatic tumors | 25 | 74 |
| Bone tumors | 49 | 73 |
| Osteosarcoma | 45 | 71 |
| Ewing sarcoma | 42 | 72 |
| Rhabdomyosarcoma | 49 | 64 |
| Testicular germ cell tumors | 74 | 96 |
| Ovarian germ cell tumors | 75 | 94 |
| Thyroid carcinoma | 99 | 98 |
| Melanoma | 83 | 95 |

ICCC=International classification of childhood cancers.
CNS=Central nervous system.
*Cases were followed through 2010.
Note: Does not include benign and borderline brain tumors.
**Source:** Surveillance, Epidemiology, and End Results (SEER) program, 9 SEER registries, National Cancer Institute.
American Cancer Society, Surveillance Research, 2014

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5



# ALL Epidemiology and Success

Universally fatal disease in the 1960s.

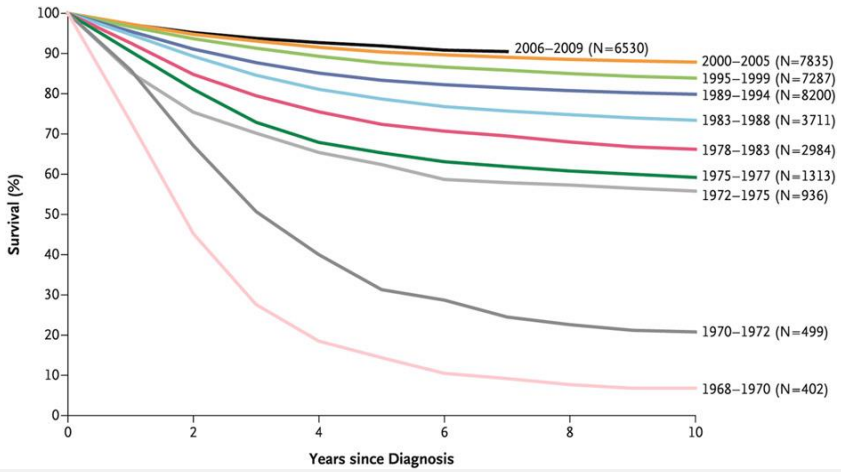
Now with an event-free survival (EFS) of approximately 90%.

Incidence peaks at 2-4 years

Most ALL cases have no identified underlying genetic predisposition

Attributed to the success of:

A) Cooperative group trials
B) IT Chemotherapy
C) Stratification and intensification
**D) Better Drugs**

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Hunger SP, Acute lymphoblastic leukemia in children. N Engl J Med.

6


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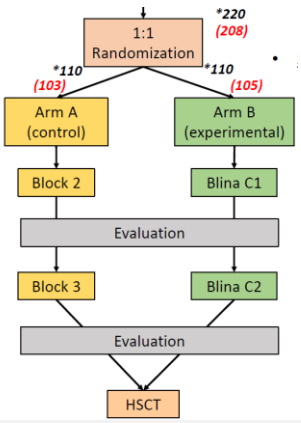
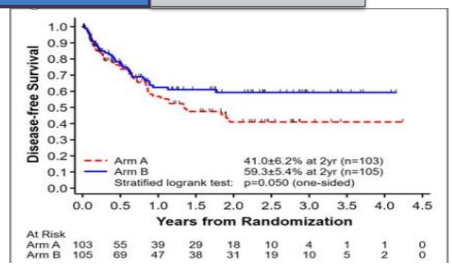
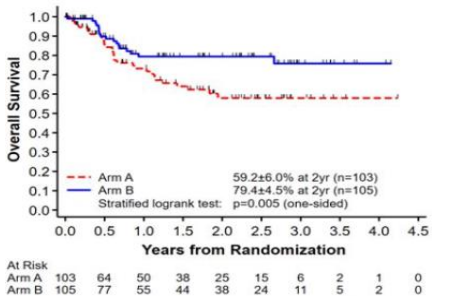
Introduction | Foundation | Therapeutic Advancements | Panel Q&A / Close

## Phase III Study of Blinatumomab in Pediatric Relapsed B-ALL




| Parameter | Blina | Chemo | p |
|---|---|---|---|
| %2-yr DFS | 59 | 41 | .05 |
| %2-yr OS | 79 | 59 | .005 |
| % SCT | 73 | 49 | <.001 |
| % MRD clearance | 79 | 21 | <.001 |

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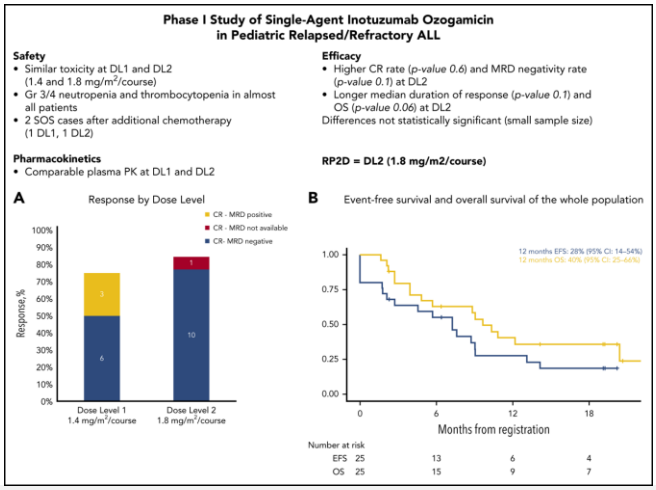
Brown et al. JAMA. 2021

8

# Phase II Study of Inotuzumab in R-R Pediatric ALL

The recommended phase 2 dose established at 1.8 mg/m$^2$ per course.

85% reached CR after 1 course,100% of whom had MRD negativity.



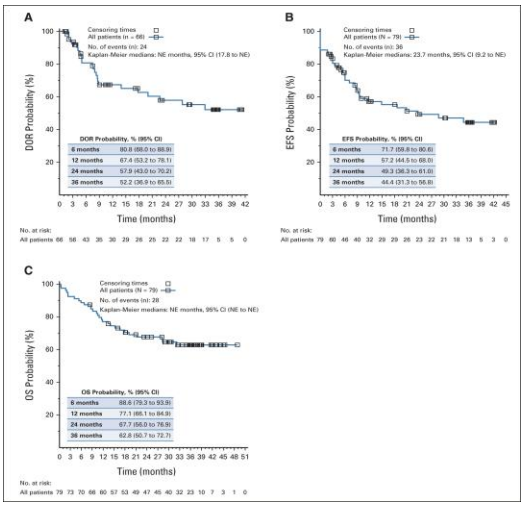

Brivio et al. Blood. 2021

9



# Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

- 255 patients
- Complete remission rate: 85.5%
- 12 month DOR: 60.9%
- EFS: 52.4% OS 77.2%
- CRS 73% and ICANS 40%




Pasquini et al. Blood Advances 2020

Laetsch et al. JCO 2022

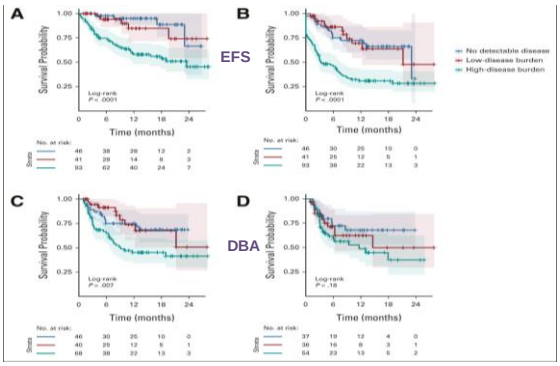
10

## Real Word CAR Consortium and Disease Burden

- 200 pts (185 pts infused); median age 12 yrs (0-26 yrs); CR=85%
- HBD n=94 (47%); LBD n=60 (30%); ND n=46 (23%)
- 12-mos EFS=50%, 12 mos OS=72%
- G3 CRS=21% (35% in HBD); G3 NE=7% (9% in HBD)

OS

DOR

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Schultz. J Clin Oncol. 2022

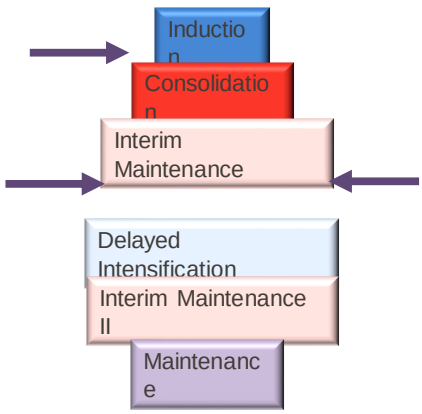
11



## B-ALL Treatment: New Therapies COG

Tisagenlecleucel (CD19 CART-T)
AALL1721

Inotuzumab
AALL1732




Blinatumomab
AALL1731

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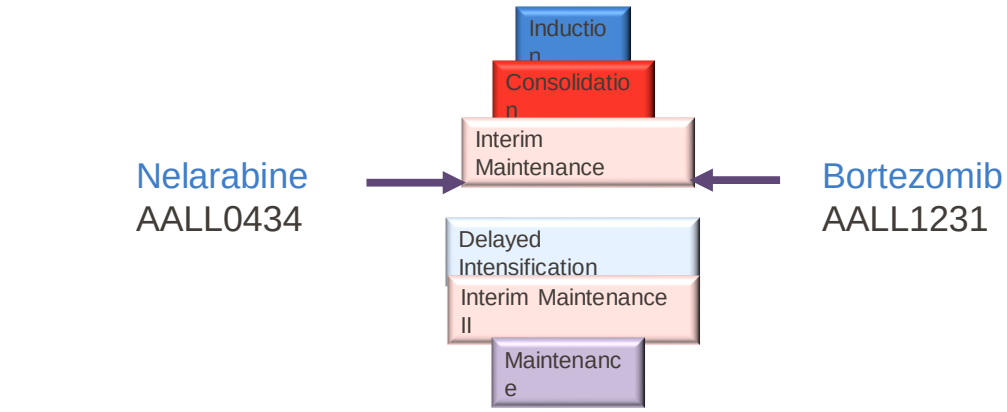
12

# T-ALL Treatment: New Therapies COG

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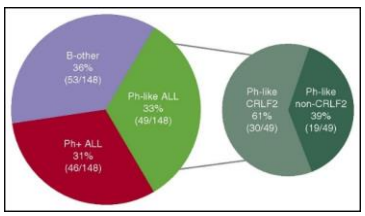
13

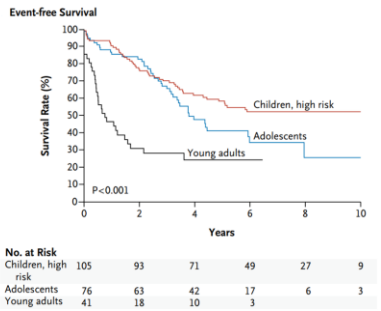


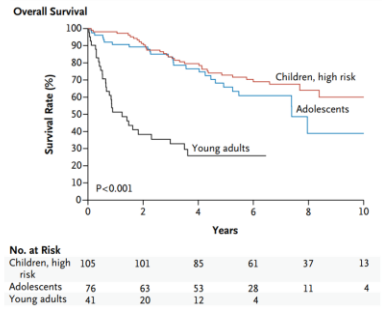
# Philadelphia chromosome-like B-ALL in Pediatrics

Very high-risk subtype of B ALL in children and young adults and accounts for 15% to 25% of B ALL in this age group




Median event-free survival for young adults (24.1%), adolescents (41%), and high-risk children (58%) with Ph-like ALL




Overall survival for young adults (25.8%), adolescents (65.8%), and high-risk children (72.8%) with Ph-like ALL

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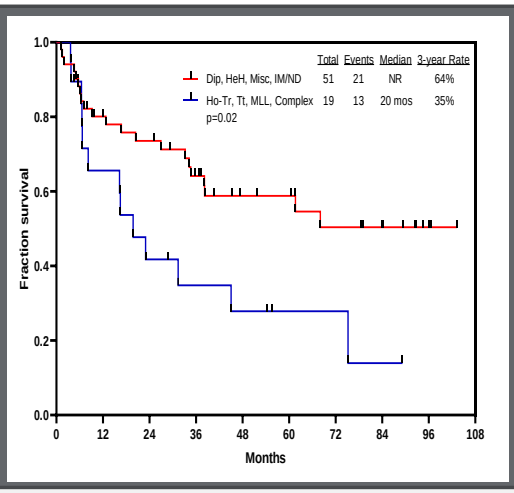
Roberts et al. NEJM 2014

14

# Mini-HCVD + INO + Blinatumomab in adults with ALL




No impact of *TP53* mutation or CRLF2+ by flow on OS

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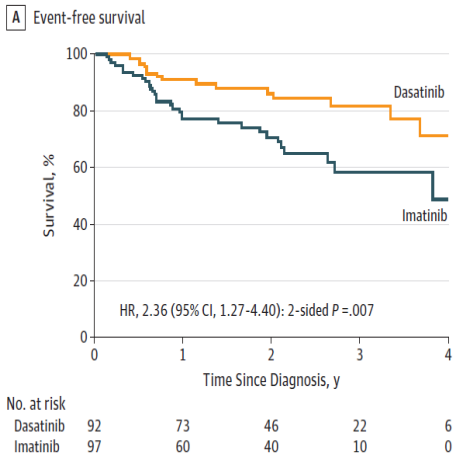
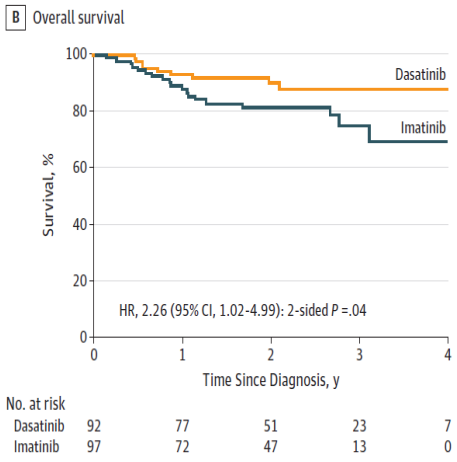
Short. Blood 136: abst 1014; 2020

15



# CCG-ALL-2015: Dasatinib v. Imatinib in Ph+ ALL

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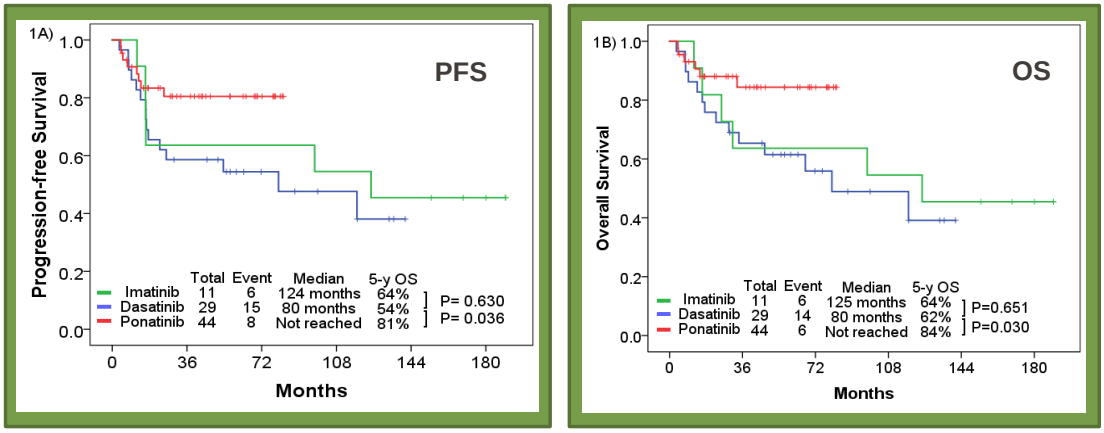
Schultz et al. Leukemia 2014

16

# Outcome of 3-month CMR by TKI




MVA for Outcome
Ponatinib only predictive factor for PFS (HR=0.39; P=0.03) and OS (HR=0.38; P=0.04)

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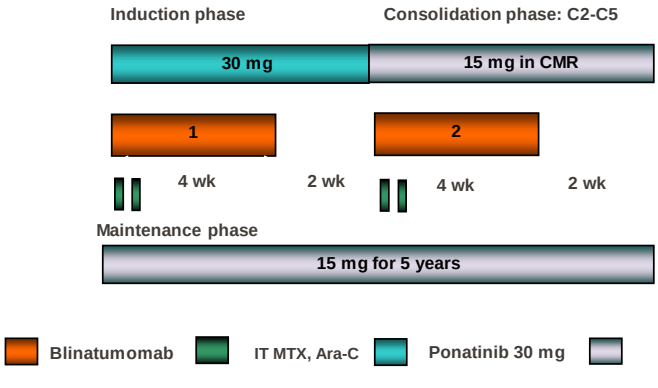
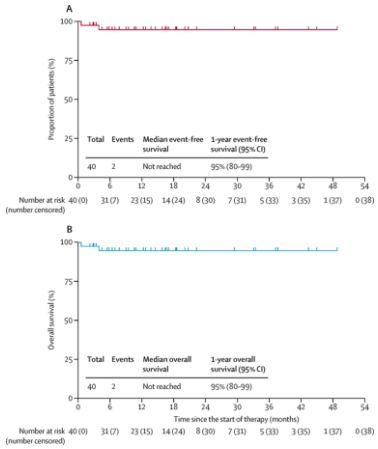
Sasaki. Blood 134 : Abst 1296; 2019

17



# Blinatumomab - ponatinib in Ph+ ALL

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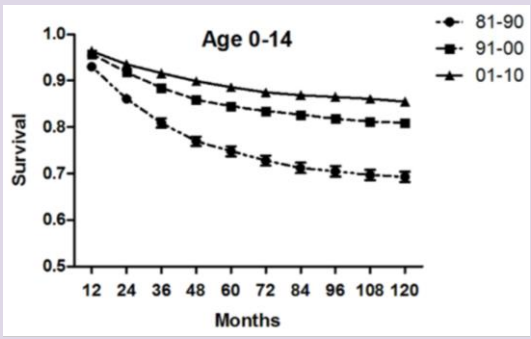
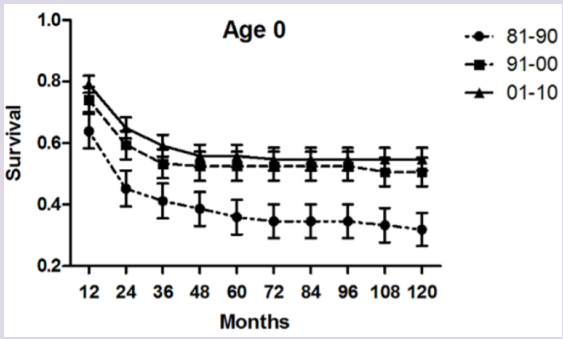
Elias Jabbour, Lancet Hematology 2022

18

# Infant Acute Lymphoblastic Leukemia

- Diagnosed <12 months of age
- Majority have KMT2A or MLL gene rearrangement (KMT2Ar)
- Treatment includes intensive chemotherapy and often HSCT
- 3yr EFS-37% in KMT2Ar

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MA et al. Scientific Reports 2014

19

# KMT2Ar, NPM1m, NUP98r Leukemias

- **SNDX-5613 Menin usage in Adult+Pedi**

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES | NOVEMBER 5, 2021

**Safety and Efficacy of Menin Inhibition in Patients (Pts) with MLL-Rearranged and NPM1 Mutant Acute Leukemia: A Phase (Ph) 1, First-in-Human Study of SNDX-5613 (AUGMENT 101)**

Eytan M. Stein, Ibrahim Aldoss, John F. DiPersio, Richard M. Stone, Martha L. Arellano, Galit Rosen, Michael L. Meyers, Yifan Huang, Steve Smith, Rebecca G. Bagley, Michael Thirman, Manish R. Patel, Ghayas C. Issa

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

The Menin Inhibitor Revumenib (SNDX-5613) Leads to Durable Responses in Patients with *KMT2A*-Rearranged or *NPM1*-Mutant AML: Updated Results of a Phase 1 Study

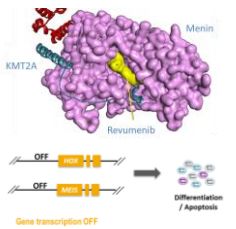
Ghayas C. Issa, MD,[1] Ibrahim Aldoss, MD,[2] John F. DiPersio, MD, PhD,[3] Branko Cuglievan, MD,[4] Richard M. Stone, MD,[5] Martha L. Arellano, MD,[6] Michael Thirman, MD,[7] Manish R. Patel, MD,[8] David Dickens, MD,[9] Shalini Shenoy, MD,[3] Neeraj Shukla, MD,[10] Galit Rosen, MD,[11] Rebecca G. Bagley, MA,[12] Michael L. Meyers, MD, PhD,[12] Kate Madigan, MD,[13] Peter Ordentlich, PhD,[12] Yu Gu, PhD,[12] Steven Smith, PhD,[12] Gerard M. McGeehan, PhD,[12] and Eytan M. Stein, MD[7]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]City of Hope, Duarte, CA; [3]Washington University School of Medicine, St. Louis, MO; [4]Dana-Farber Cancer Institute, Boston, MA; [5]Emory University School of Medicine, Atlanta, GA; [6]University of Chicago, Chicago, IL; [7]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; [8]University of Iowa, Iowa City, IA; [9]Memorial Sloan Kettering Cancer Center, New York, NY; [10]Syndax Pharmaceuticals, Inc., Waltham, MA

| Best Response | Efficacy Population n = 60 (%) |
|---|---|
| **ORR*** | **32/60 (53%)** |
| Best Response | |
| CR | 12 (20%) |
| CRh | 6 (10%) |
| CRp | 5 (8%) |
| MLFS | 9 (15%) |
| CR/CRh MRD$^{neg}$ | 14/18 (78%) |
| CR/CRh/CRp MRD$^{neg}$ | 18/23 (78%) |
| **ORR – *KMT2Ar*** | **27/46 (59%)** |
| CR/CRh | 15/46 (33%) |
| **CCyR – *KMT2Ar*‡** | **16/25 (64%)** |
| **CCyR – *KMT2Ar*‡** | **16/25 (64%)** |
| **ORR – *mNPM1*** | **5/14 (36%)** |
| CR/CRh | 3/14 (21%) |

**30% (18/60) CR/CRh with a median duration of CR/CRh of 9.1 months**

**78% of patients with CR/CRh attained MRD negativity**




1. Issa GC, et al. *Leukemia*. 2021;35:2482–2495.
2. Papaemmanuil, E. *et al. N Engl J Med.* 2016;374: 2209-2221.
*3. Issa GC et al ASH Oral Abstract November 15, 2022*

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20

20

# Treatment Advances for Acute Lymphoblastic Leukemia in Adults

Nicholas Short MD
Assistant Professor, Department of Leukemia
The University of Texas MD Anderson Cancer Center
February 16, 2023

21

## Historical Outcomes in Adult ALL

- Younger adults (e.g. age 18-60 years)
  - Complete remission (CR) rate: >90%
  - Cure rate: ~40%
- Older adults (e.g. age ≥60 years)
  - High early mortality rates (due to chemotherapy-related toxicity)
  - Cure rate: ~20%
  - Many patients did not receive therapy

Kantarjian H et al. *Cancer* 2004;101(12):2788-801
O'Brien S et al. *Cancer* 2008; 113(8):2097-101
Li S et al. *Blood* 2016;128(22):3981

22

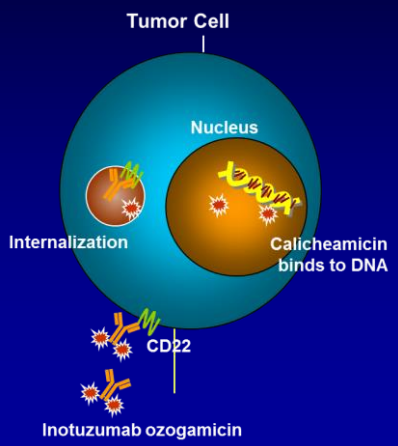
# Reasons for Recent Success in Adult ALL

- Identification of high-risk subtypes where transplant in first remission should be considered (when standard therapies are given)
  - Poor-risk cytogenetics
  - Philadelphia chromosome-like ALL
  - Early T-cell precursor ALL
  - Poor MRD clearance
- Introduction of novel agents
  - Addition of potent TKIs to chemotherapy in Ph+ ALL
  - Addition of anti-CD20 antibody to chemotherapy in Burkitt and pre-B ALL
  - Blinatumomab, inotuzumab ozogamicin and CAR T-cells for R/R disease
  - Use of these novel agents in the frontline setting and in combination

23

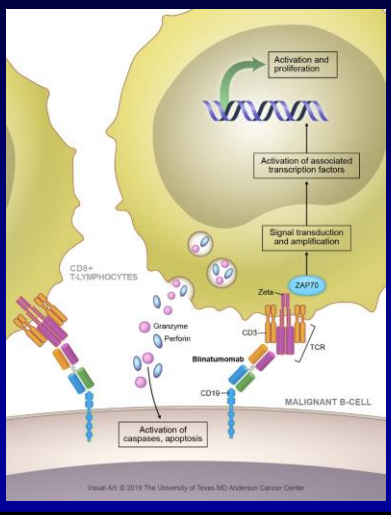
## Inotuzumab Ozogamicin

(CD22 antibody-drug conjugate)



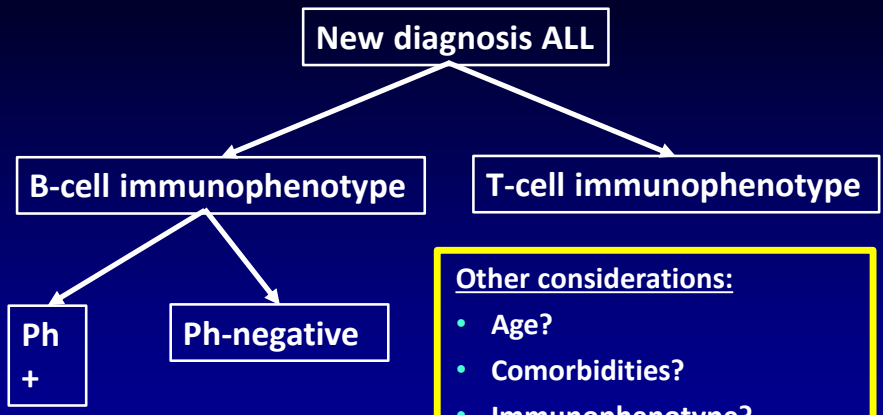

## Blinatumomab

(CD3-CD19 bispecific engager)




24

## Simplified Diagnostic Algorithm for Newly Diagnosed ALL



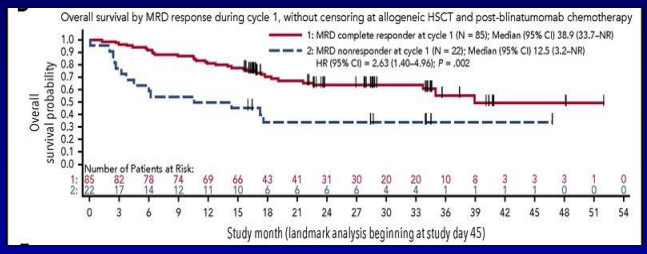

**Other considerations:**

- Age?
- Comorbidities?
- Immunophenotype?
  - B-ALL: CD19, CD20, CD22?
  - T-ALL: Early T-cell precursor?
- Ph-like ALL?

25

## Blinatumomab for MRD in B-Cell ALL

- 116 adults with B-cell ALL in CR with persistent or recurrent MRD (≥0.1%) after at least 3 courses of chemotherapy
- Blinatumomab given up to 4 cycles
- Rate of MRD negativity after 1 cycle = 78%



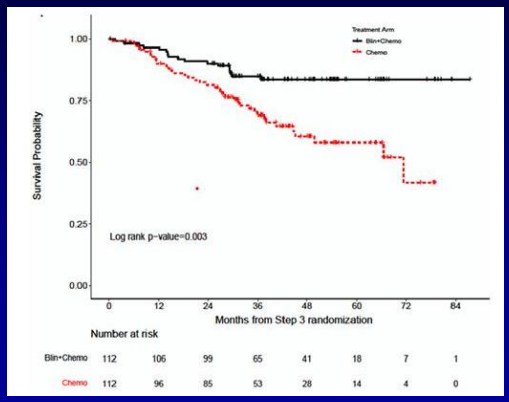

- Unclear benefit of transplant after MRD clearance
- FDA approval in March 2018 for MRD-positive B-ALL (≥0.1%)

Gokbuget N et al. *Blood* 2018;131(14):1522-31

26

# E1910: Randomized Phase 3 Trial: Blina vs SOC as Consolidation in MRD-Negative CR

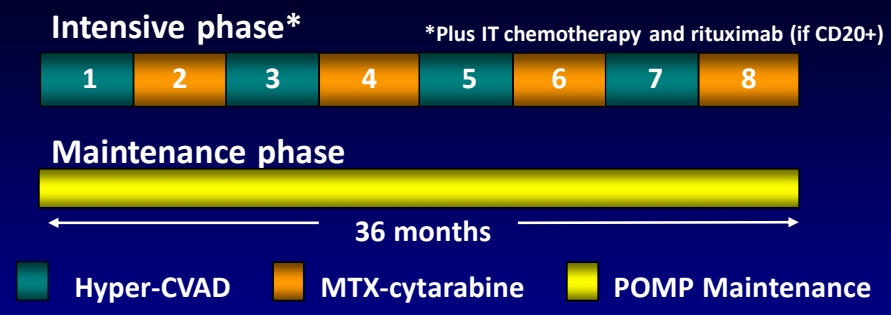
- 224 patients in MRD-negative CR after pediatric-inspired regimen randomized 1:1 to consolidation with chemotherapy vs. chemotherapy + blinatumomab
- 20% in each arm underwent allogeneic SCT
- OS improved with blinatumomab vs. chemotherapy alone (median OS: not reached vs. 71.4 months; P=0.0003)




Litzow MR et al. Blood (2022) 140 (Supplement 2): LBA-1

27

# Basic Hyper-CVAD Schema



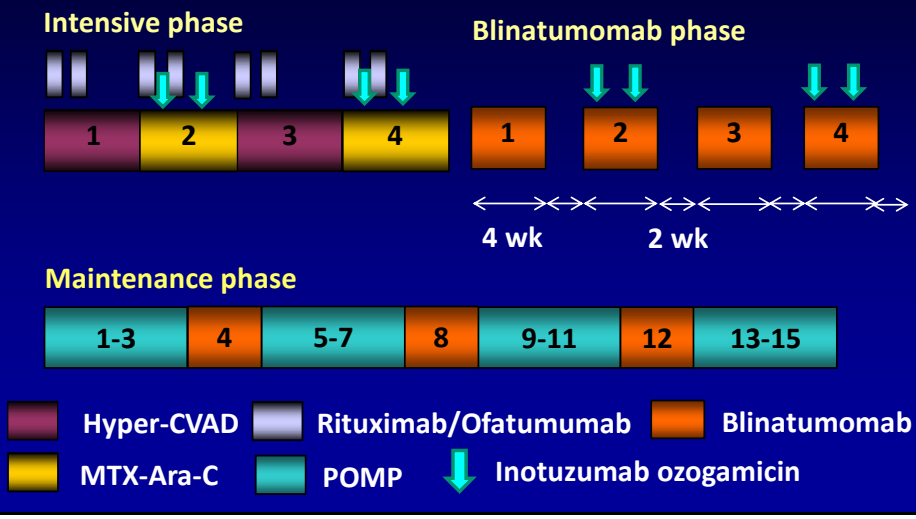

**Hyper-CVAD**
- Cyclophosphamide (hyper-fractionated)
- Vincristine
- Adriamycin (doxorubicin)
- Dexamethasone

**POMP**
- Purinethol (6-MP)
- Oncovin (vincristine)
- Methotrexate
- Prednisone

28

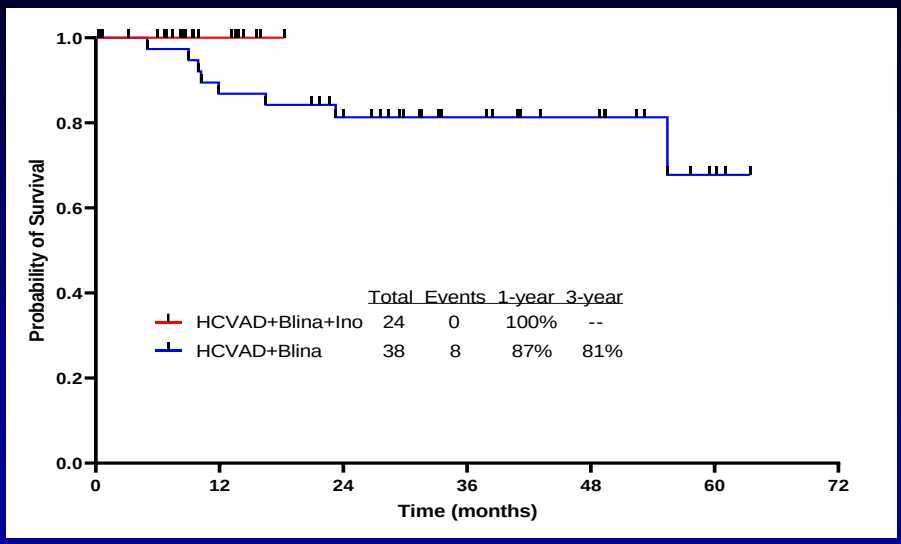
# Optimizing Frontline ALL Therapy:

## Hyper-CVAD + inotuzumab ozogamicin + blinatumomab (<60 years of age)




29

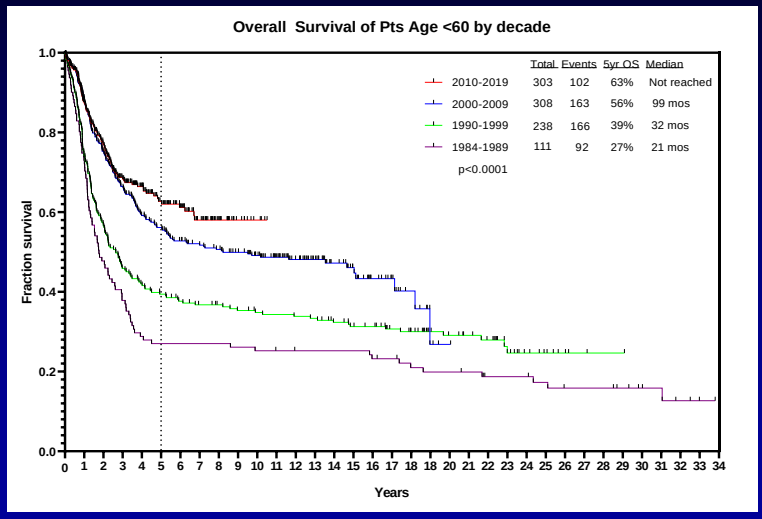
# Hyper-CVAD + Blina + INO in B-ALL: Outcome by Cohort




Short NJ et al. Blood (2022) 140 (Supplement 1): 8966–8968

30

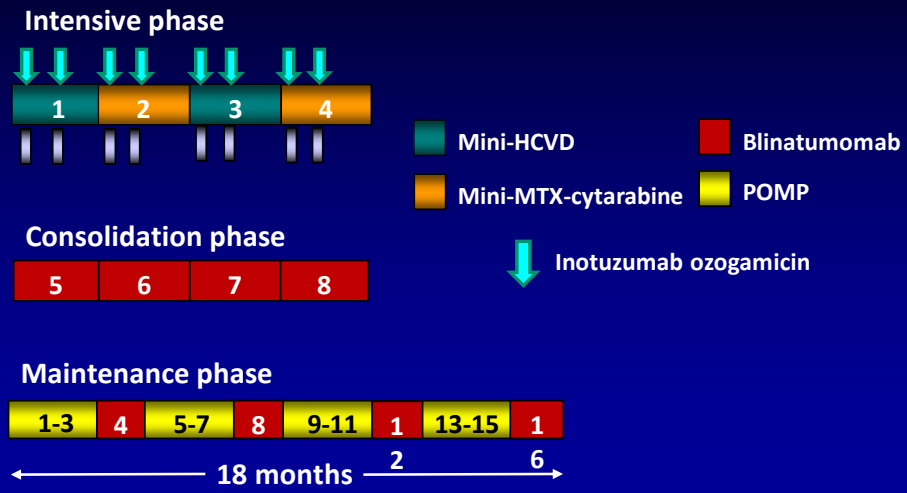
# Survival of ALL at MDACC by Decade (Age 18-60 years)




31

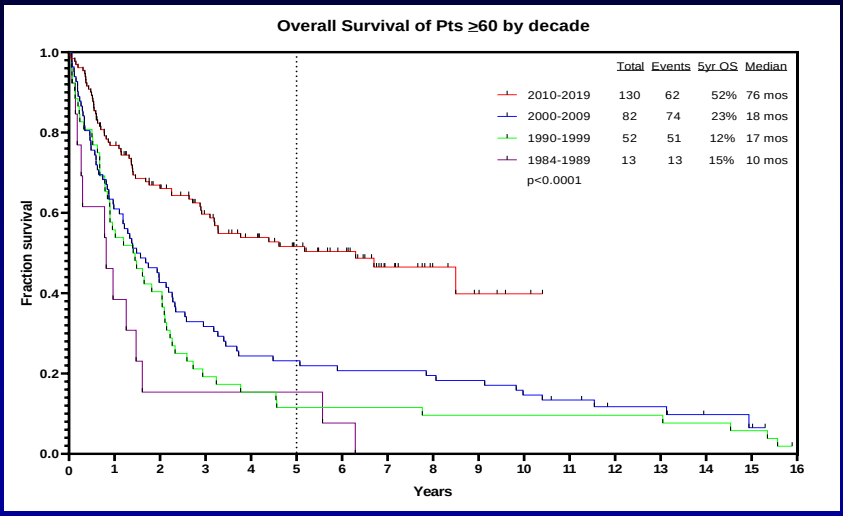
# Optimizing Frontline ALL Therapy:

## Mini-hyper-CVD + inotuzumab ozogamicin + blinatumomab (≥60 years of age)




32

# Survival of ALL at MDACC by Decade (Age ≥60 years)



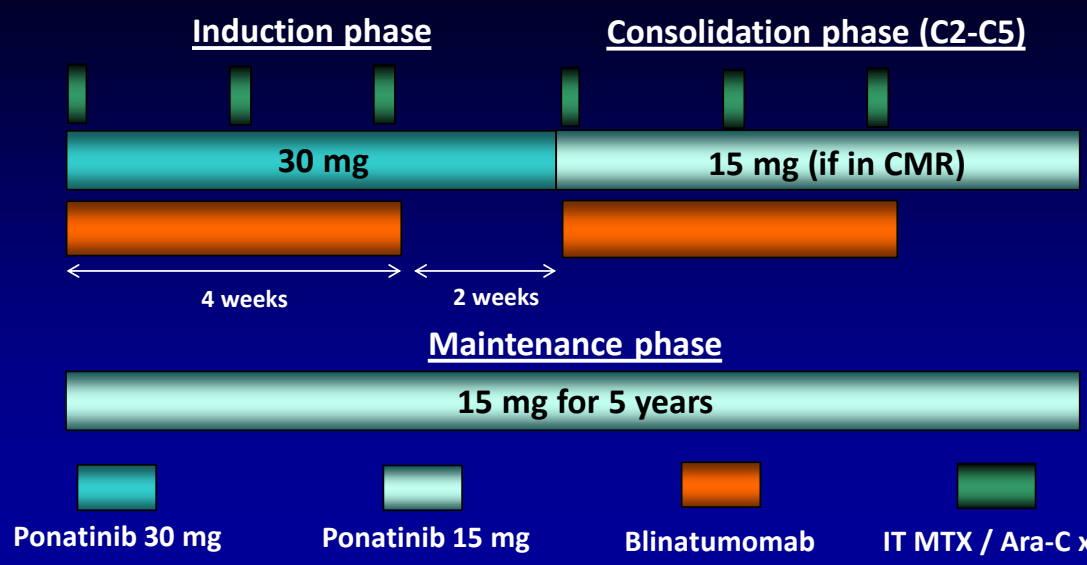

33

# Treatment of Ph+ ALL: General Principles

- BCR::ABL TKI added to chemotherapy improves survival
- TKI options
  - First-generation (imatinib)
  - Second-generation (dasatinib or nilotinib)
  - Third-generation (ponatinib)
- Increased molecular response rates and survival with successive generation of TKIs
- ? Role of intensive chemotherapy vs. low-intensity regimens vs. chemotherapy-free regimens
- ? Role of HSCT in first remission with later-generation TKIs

34

# Ponatinib + Blinatumomab in Ph+ ALL: Regimen

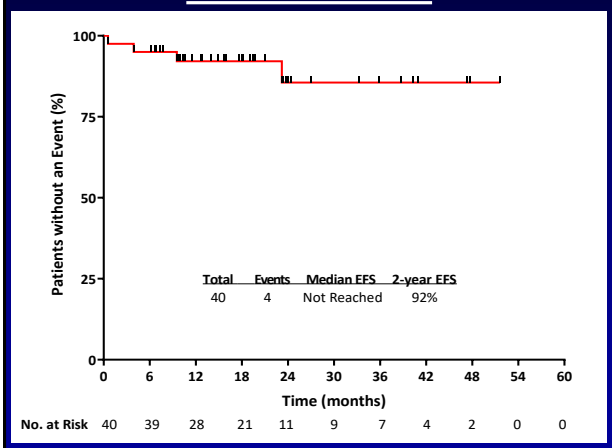


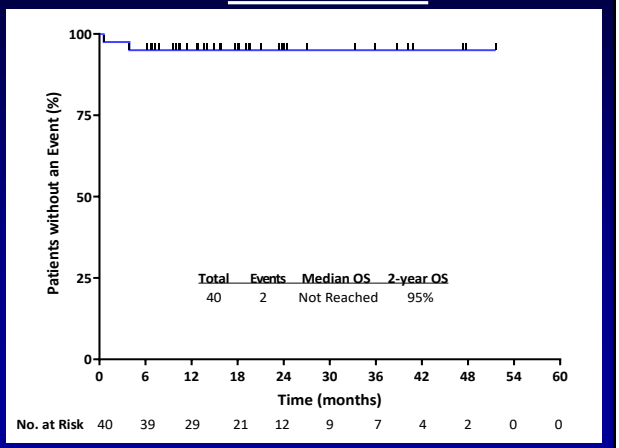

Short NJ et al. Blood (2022) 140 (Supplement 1): 513–515

35

# Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes

Median follow-up: 18 months (range, 6-52+)

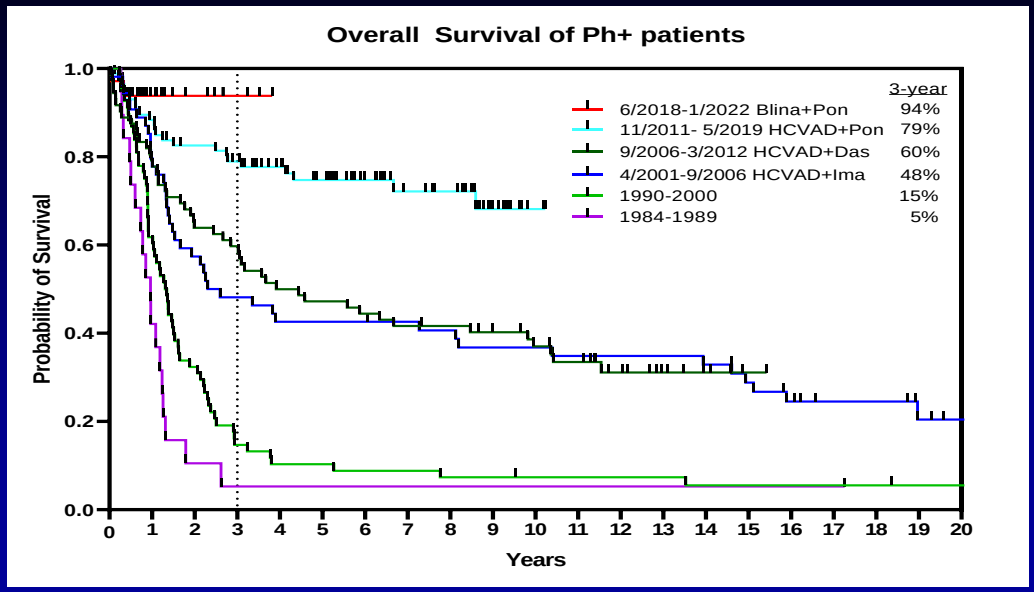



Short NJ et al. Blood (2022) 140 (Supplement 1): 513–515

36

# Survival of Ph+ ALL by Decade at MDACC (1985-2022)




37

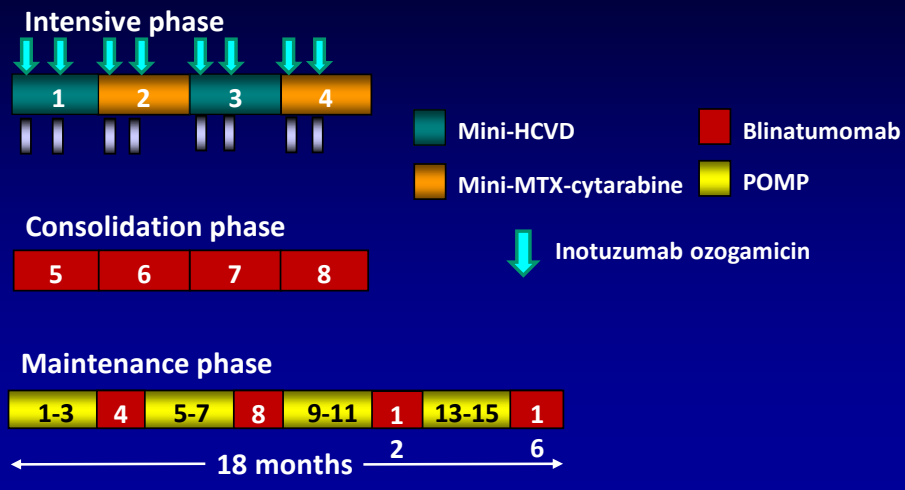
# Novel Agents Recently Approved for Relapsed/Refractory B-Cell ALL (in U.S.)

| Agent | Mechanism of Action | Year of Approval |
|---|---|---|
| Blinatumomab | CD3-CD19 bispecific antibody | 2014 (R/R B-cell ALL)<br>2018 (MRD+ B-cell ALL) |
| Inotuzumab ozogamicin (INO) | Anti-CD22 antibody-drug conjugate | 2017 |
| Tisagenlecleucel | CD19-directed autologous CAR T-cell | 2017 |
| Brexucabtagene autoleucel | CD19-directed autologous CAR T-cell | 2021 |

38

# Optimizing Therapy for Relapsed/Refractory ALL

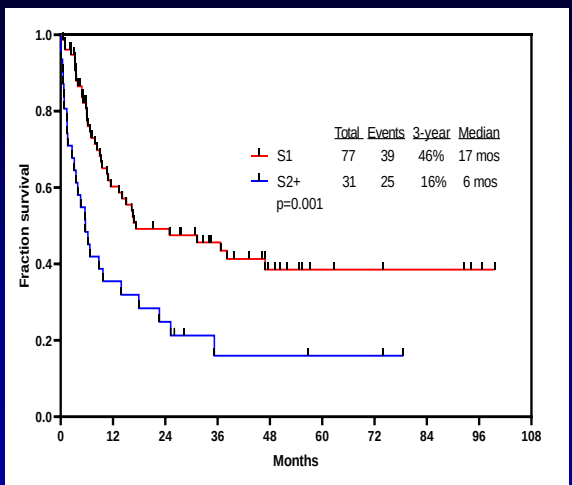
## Mini-hyper-CVD + inotuzumab ozogamicin + blinatumomab




39

# Mini-Hyper-CVD + INO ± Blina in R/R ALL: Outcomes

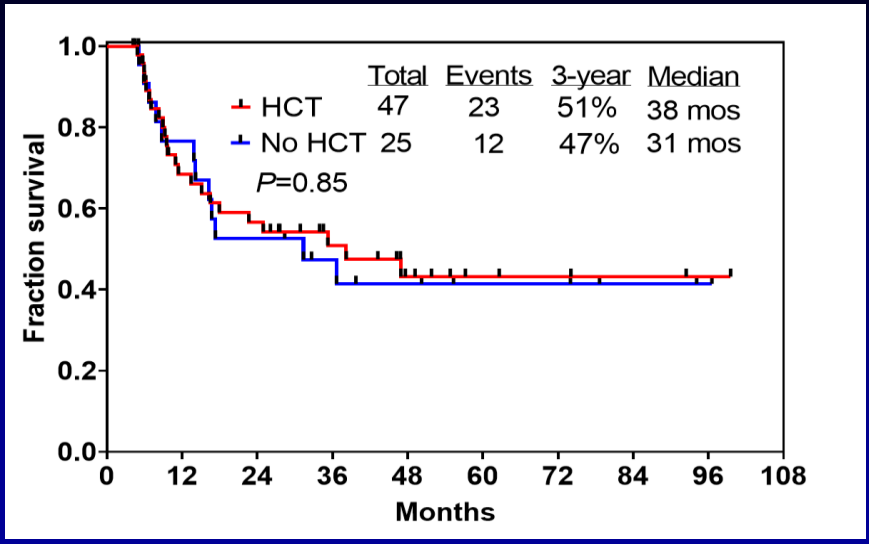
| Response | N (%) |
|---|---|
| Salvage 1 | 71/77 (93) |
| Salvage 2 | 10 (59) |
| ≥ Salvage 3 | 8 (57) |
| MRD negativity | 71/87 (82) |
| Salvage 1 | 59/69 (86) |
| ≥ Salvage 2 | 12/18 (67) |
| Early death | 7 (6) |




Jabbour E et al. *Cancer* 2021;127(12):2025-38

40

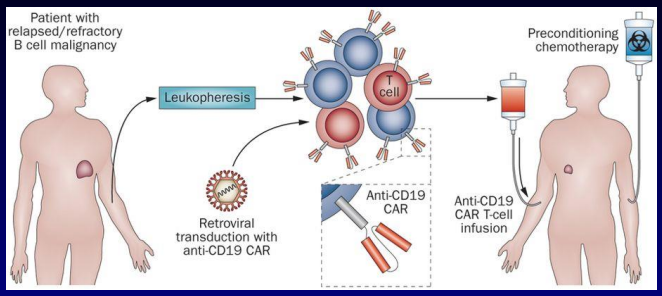
# Mini-HCVD + INO ± Blina in R/R ALL: Survival by Transplant

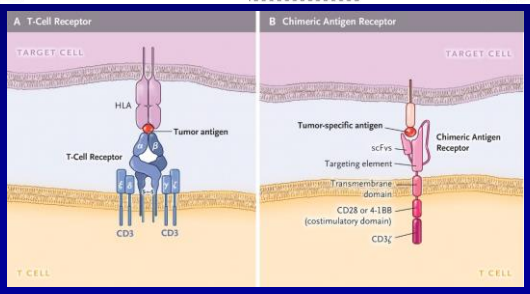



Jabbour E et al. *Cancer* 2021;127(12):2025-38

41

# CAR T-cell Therapy




Klebanoff CA et al. *Nat Rev Clin Oncol* 2014;11(12):685-6 June CH, *N Engl J Med* 2018;379:64-73

42

# Conclusions

- There has been great progress in the treatment of adults with ALL, particularly in older adults, B-cell ALL, and Ph+ ALL
- Optimal frontline therapy is rapidly evolving but moving towards:
  - Incorporation of most active agents early in disease course
  - Less chemotherapy (no chemotherapy in some cases)
  - Less need for stem cell transplantation
  - Shorter duration of therapy
  - Higher response rates, higher MRD negativity rates, and higher cure rates
- Enrollment in a clinical trial remains the best option for most patients

43

## ASK A QUESTION

TREATMENT ADVANCEMENTS FOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN CHILDREN AND ADULTS

### Ask a question by phone:

Press star (*) then the number 1 on your keypad.

### Ask a question by web:

Click “Ask a question”
Type your question
Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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44

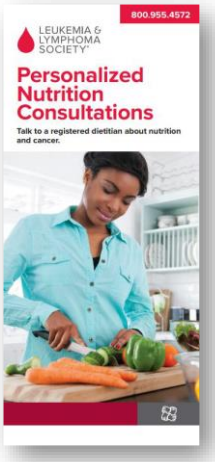
# LLS EDUCATION & SUPPORT RESOURCES

**HOW TO CONTACT US:**

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

**Call: (800) 955-4572**
Monday to Friday, 9 a.m. to 9 p.m. ET
**Chat live online: www.LLS.org/InformationSpecialists**
Monday to Friday, 10 a.m. to 7 p.m. ET
**Email: www.LLS.org/ContactUs**
All email messages are answered within one business day.

**CLINICAL TRIAL SUPPORT CENTER**
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
**www.LLS.org/Navigation**




**NUTRITION CONSULTATIONS**
**Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.**
**www.LLS.org/Consult.**

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45

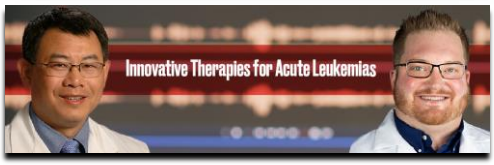
# LLS EDUCATION & SUPPORT RESOURCES


**Online Chats**

Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**

**Education Videos**

View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**




**Patient Podcast**

***The Bloodline with LLS*** is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**

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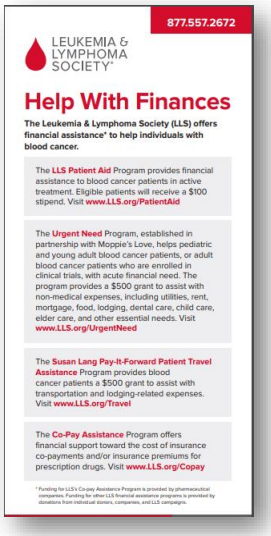
46

# LLS EDUCATION & SUPPORT RESOURCES


877.557.2672

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**Help With Finances**

**The Leukemia & Lymphoma Society (LLS) offers financial assistance* to help individuals with blood cancer.**

The **LLS Patient Aid** Program provides financial assistance to blood cancer patients in active treatment. Eligible patients will receive a $100 stipend. Visit **www.LLS.org/PatientAid**

The **Urgent Need** Program, established in partnership with Moppie's Love, helps pediatric and young adult blood cancer patients, or adult blood cancer patients who are enrolled in clinical trials, with acute financial need. The program provides a $500 grant to assist with non-medical expenses, including utilities, rent, mortgage, food, lodging, dental care, child care, elder care, and other essential needs. Visit **www.LLS.org/UrgentNeed**

The **Susan Lang Pay-It-Forward Patient Travel Assistance** Program provides blood cancer patients a $500 grant to assist with transportation and lodging-related expenses. Visit **www.LLS.org/Travel**

The **Co-Pay Assistance** Program offers financial support toward the cost of insurance co-payments and/or insurance premiums for prescription drugs. Visit **www.LLS.org/Copay**

* Funding for LLS's Co-pay Assistance Program is provided by pharmaceutical companies. Funding for other LLS financial assistance programs is provided by donations from individual donors, companies, and LLS campaigns.

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: www.LLS.org/Finances


To order free materials: **www.LLS.org/Booklets**

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47


48