MEDICINA DI PRECISIONE NELLE

LEUCEMIE ACUTE LINFOBLASTICHE (LAL):

dove siamo e dove stiamo andando?

Venezia | 20 novembre 2025 *Ospedale SS. Giovanni & Paolo, Sala S. Domenico*

Strategie di prima linea nelle LAL B Ph–:
il ruolo dell'immunoterapia

Renato Bassan

Disclosures of Renato Bassan, 2024-2025

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
IQVIA (2024)*							

*Amgen-sponsored **Consensus on epidemiology and Italian clinical practice in early-stage ALL** (part 1)

Objective: 100% cure rate up-front

- How much to do ? What the challenge(s) ?
  (current cure rate around 50%*)
- Worst subsets ahead
- Target-focused approaches vs cancer complexity
  (Bredberg A, Front Oncol 2025)

* **Pre-immunotherapy trials**, age range 18-65 years

Many years ago

TREATMENT OF ACUTE LEUKEMIA IN ADULTS

BAYARD D. CLARKSON, MD, MONROE D. DOWLING, MD, TIMOTHY S. GEE, MD, ISABEL B. CUNNINGHAM, AND JOSEPH H. BURCHENAL, MD

Cancer 1975

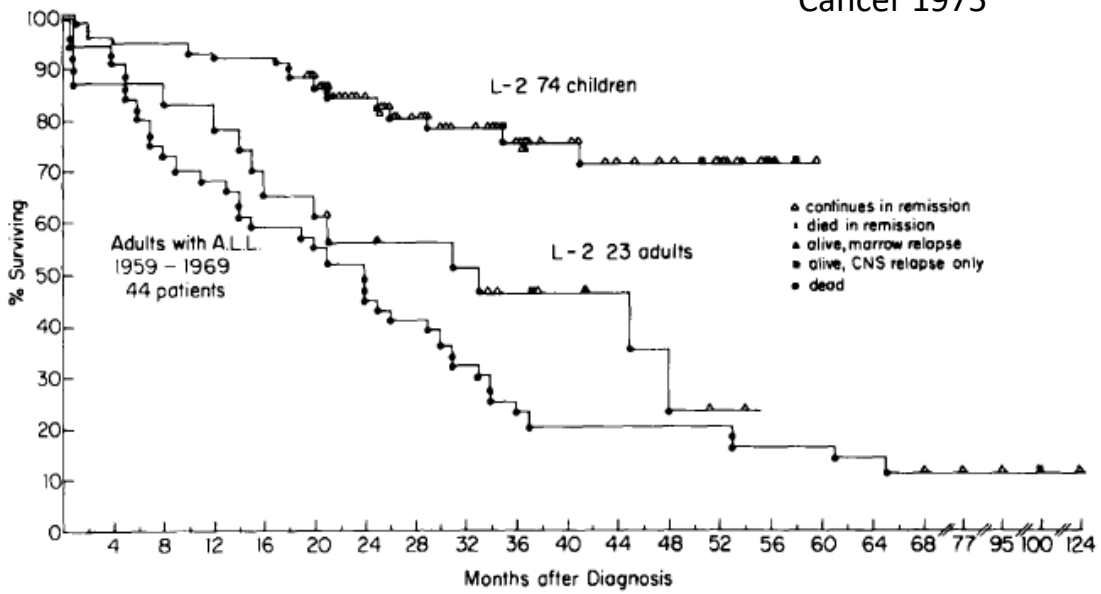


FIG. 11. Survival of children and adults with ALL treated with the L-2 protocol (life-table analysis).

A Four-Year Experience with Anthracycline, Cytosine Arabinoside, Vincristine and Prednisone Combination Chemotherapy in 325 Adults with Acute Leukemia

M. J. KEATING, MB, BS, T. L. SMITH, BS, K. B. MCCREDIE, MB, BS, G. P. BODEY, MD, E. M. HERSH, MD, J. U. GUTTERMAN, MD, E. GEHAN, PHD, AND E. J FREIREICH, MD

Cancer 1981

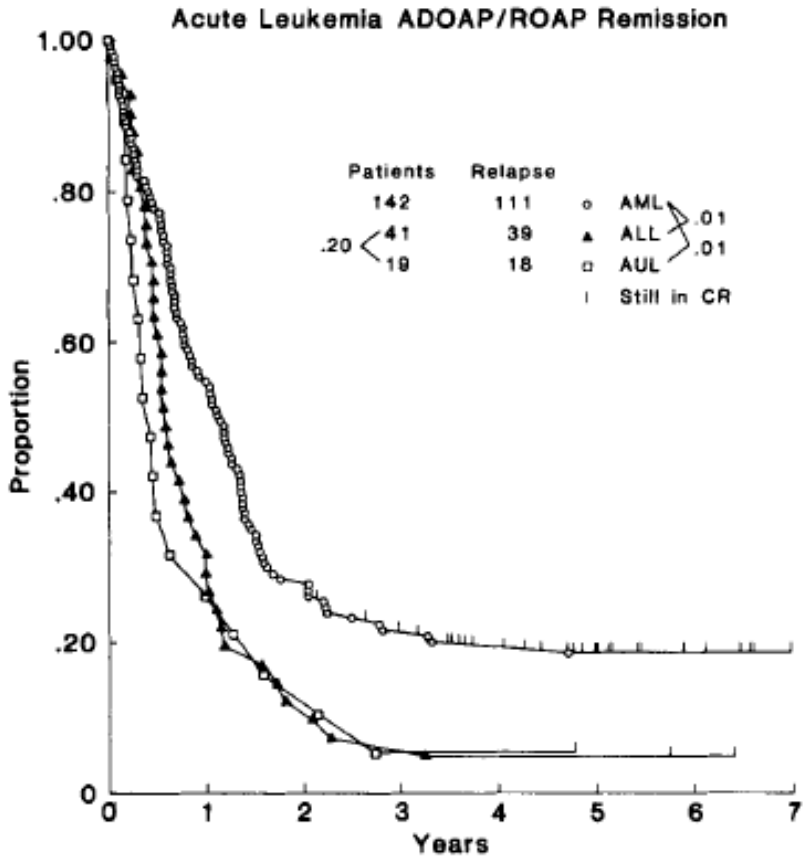
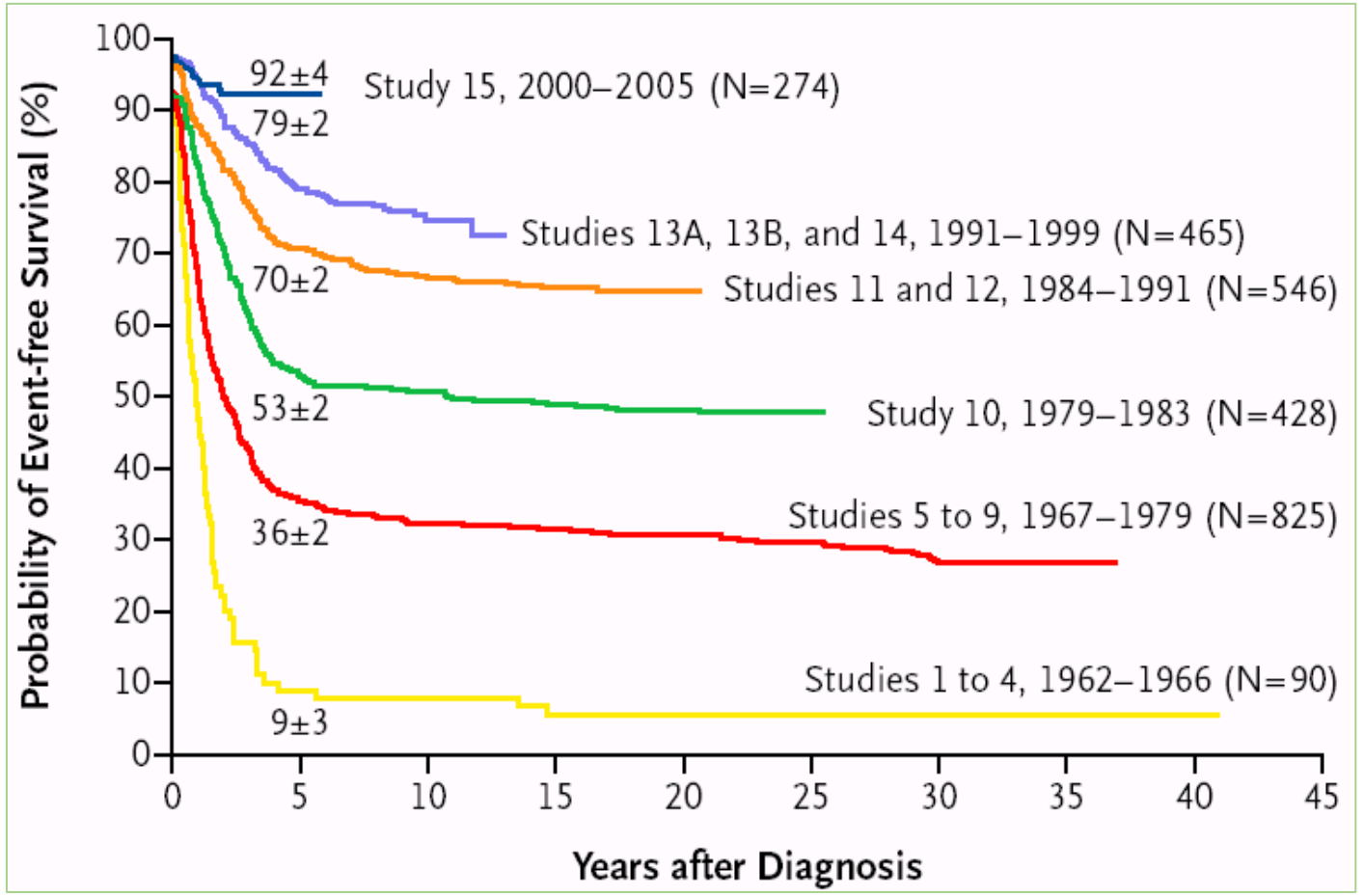


FIG. 1. Duration of hematologic remission according to morphologic diagnosis.

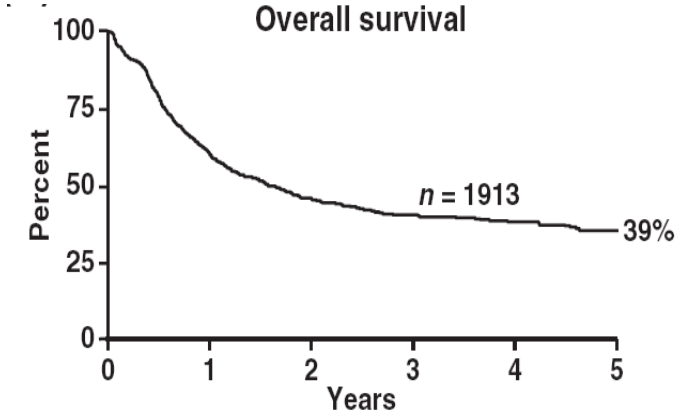
Better in children with chemo intensification

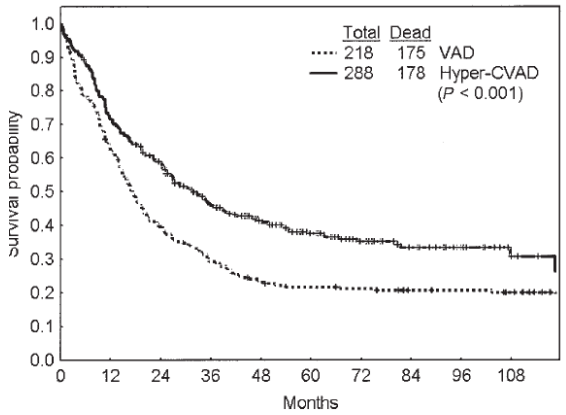
St. Jude's Hospital trials
1962-2005

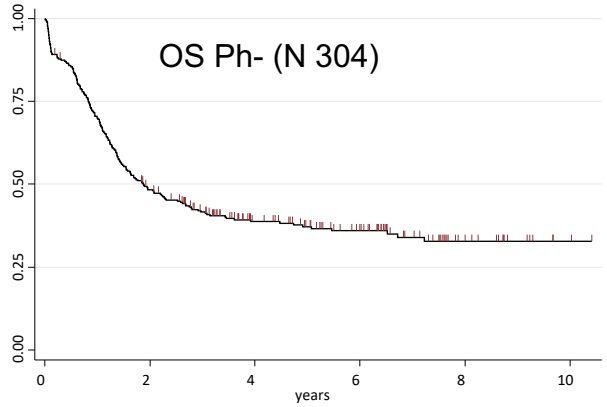


C-H Pui. *Semin Hematol* 50:185–196. 2013

Years of stagnation/frustration







MRC/ECOG International 2991[1]	
N	1913
Age	15-59
5-Y OS	39%
5-Y OS Ph-	**43%**

started 1993

- **allo-SCT oriented**

MDACC Hyper-CVAD[2]	
N	288
Age	15-92
5-Y OS	38%
5-Y OS Ph-	**41%**

started 1992

- **CHT-oriented**

NILG-ALL 09/00[3]	
N	304
Age	16-68
5-Y OS Ph-	**37%**

started 2000

- **MRD-oriented strategy**

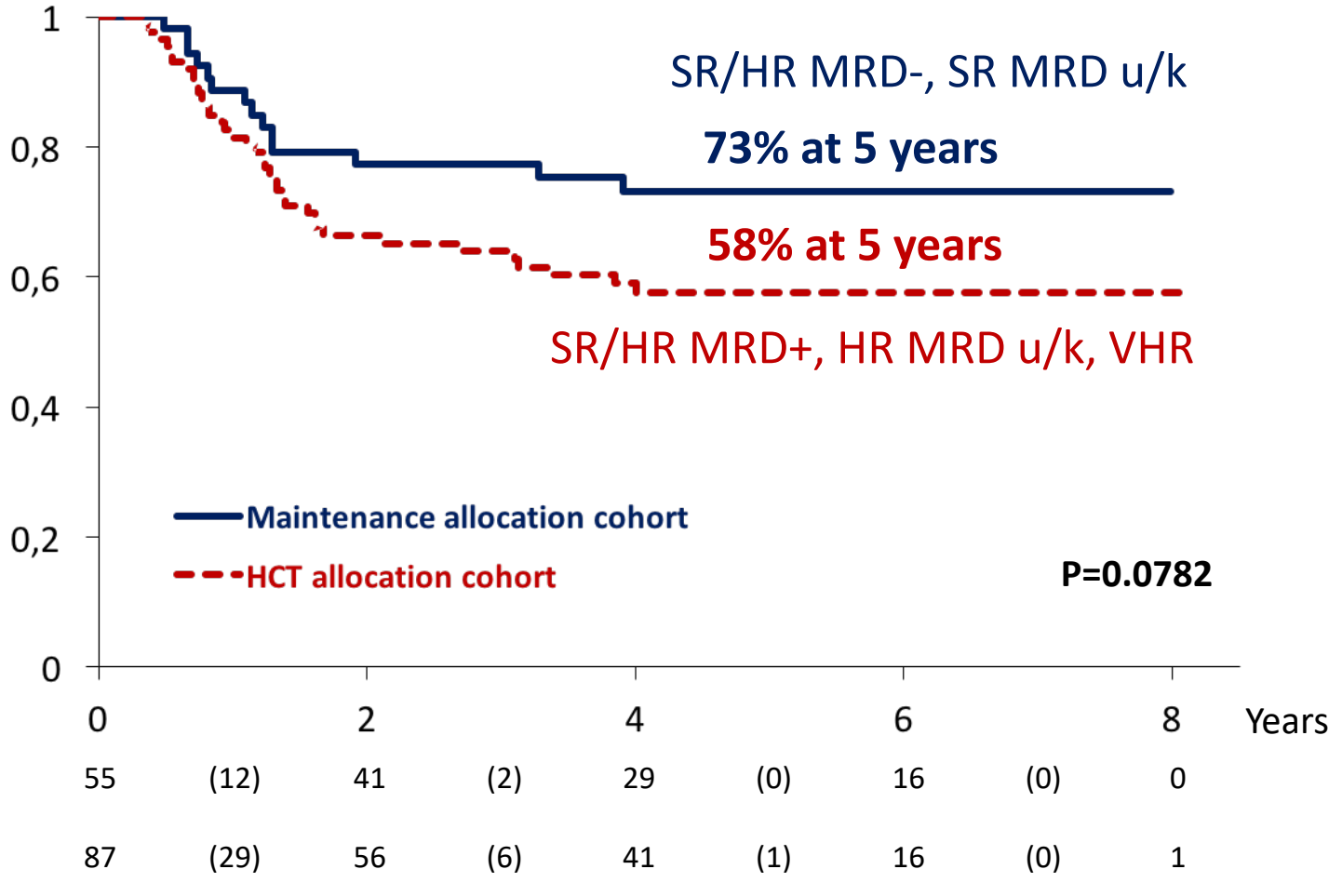
[1]Goldstone AH et al, Blood 2008; [2]Kantarjian H et al, Cancer 2004; [3]Bassan R et al, Blood 2009 (updated EHA 2013 and Blood Cancer J 2014)

Then some good news

- Ph+ ALL on its own (TKI-based therapy, allo-SCT)
- Ph– ALL to modern pediatric-type therapy with risk/MRD-oriented allo-SCT
- **Immunotherapy in B-ALL**

Risk-oriented study NILG 10/07

Survival of CR patients by treatment intention
(age 18-67 Y)

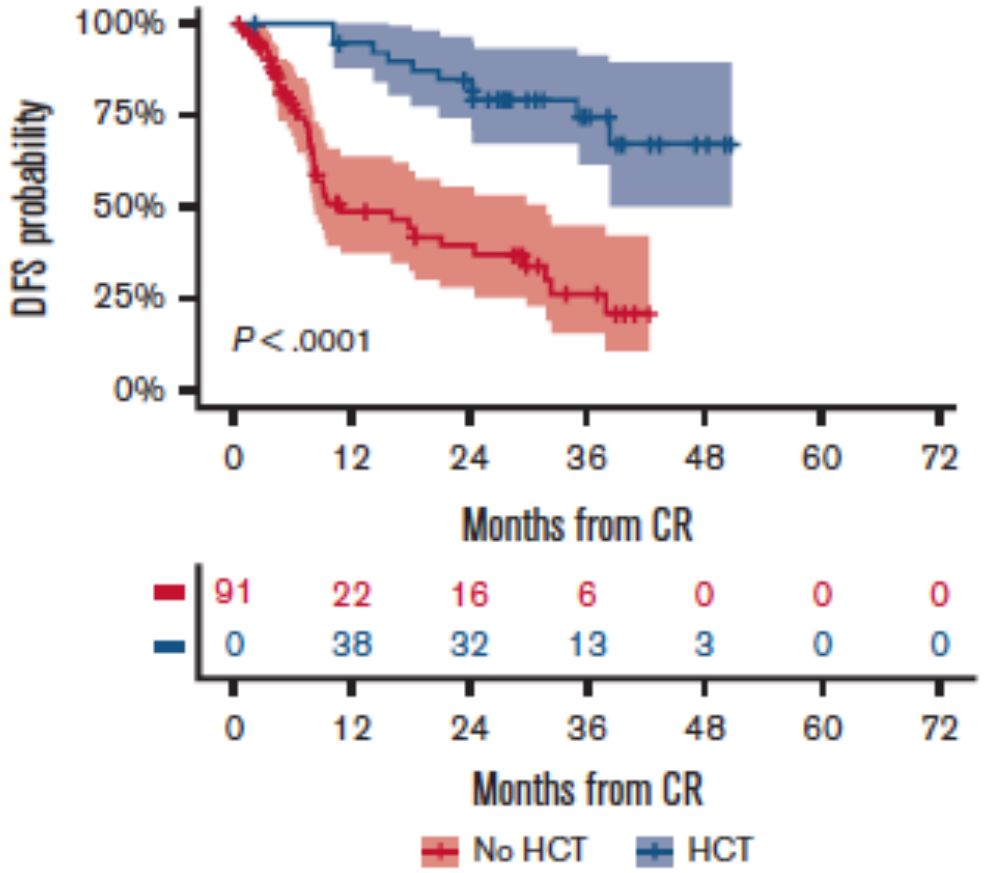


Bassan R et L, Blood Cancer J 2020

Risk-oriented study GIMEMA 1913

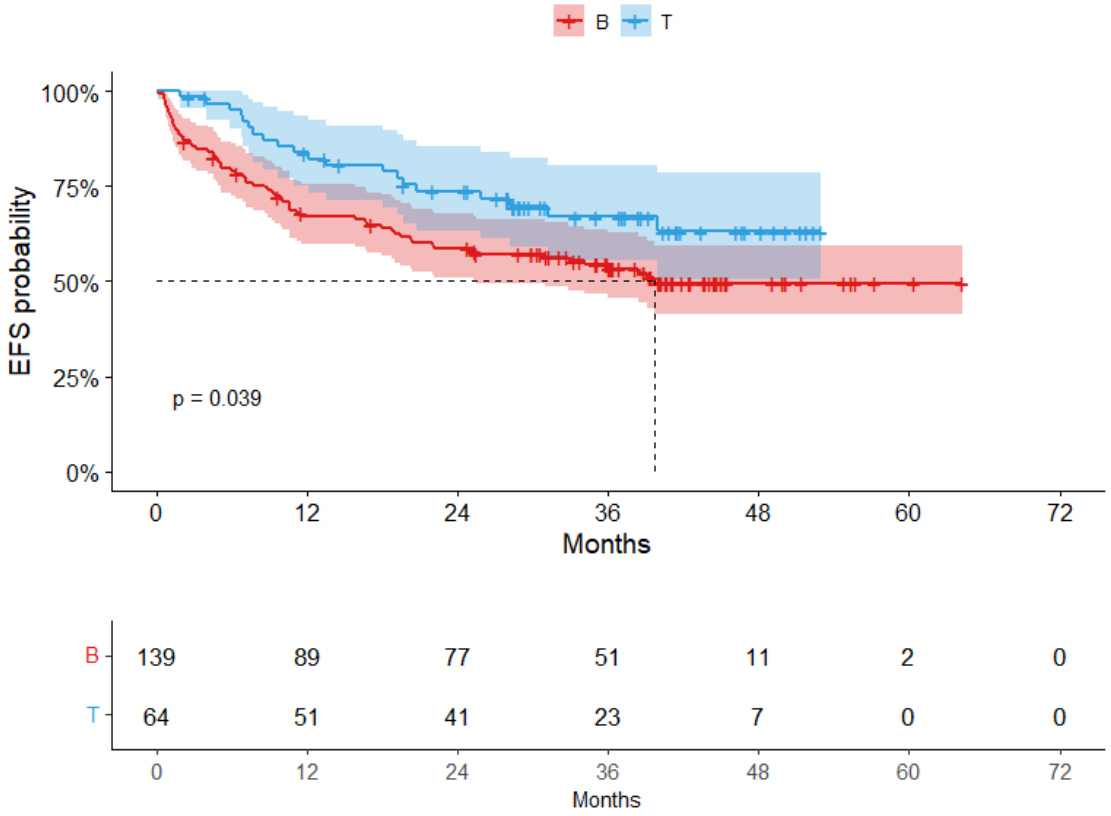
N = 203, age 18-65 years, CR 91%

- **HCT allocation group** (for special attention)



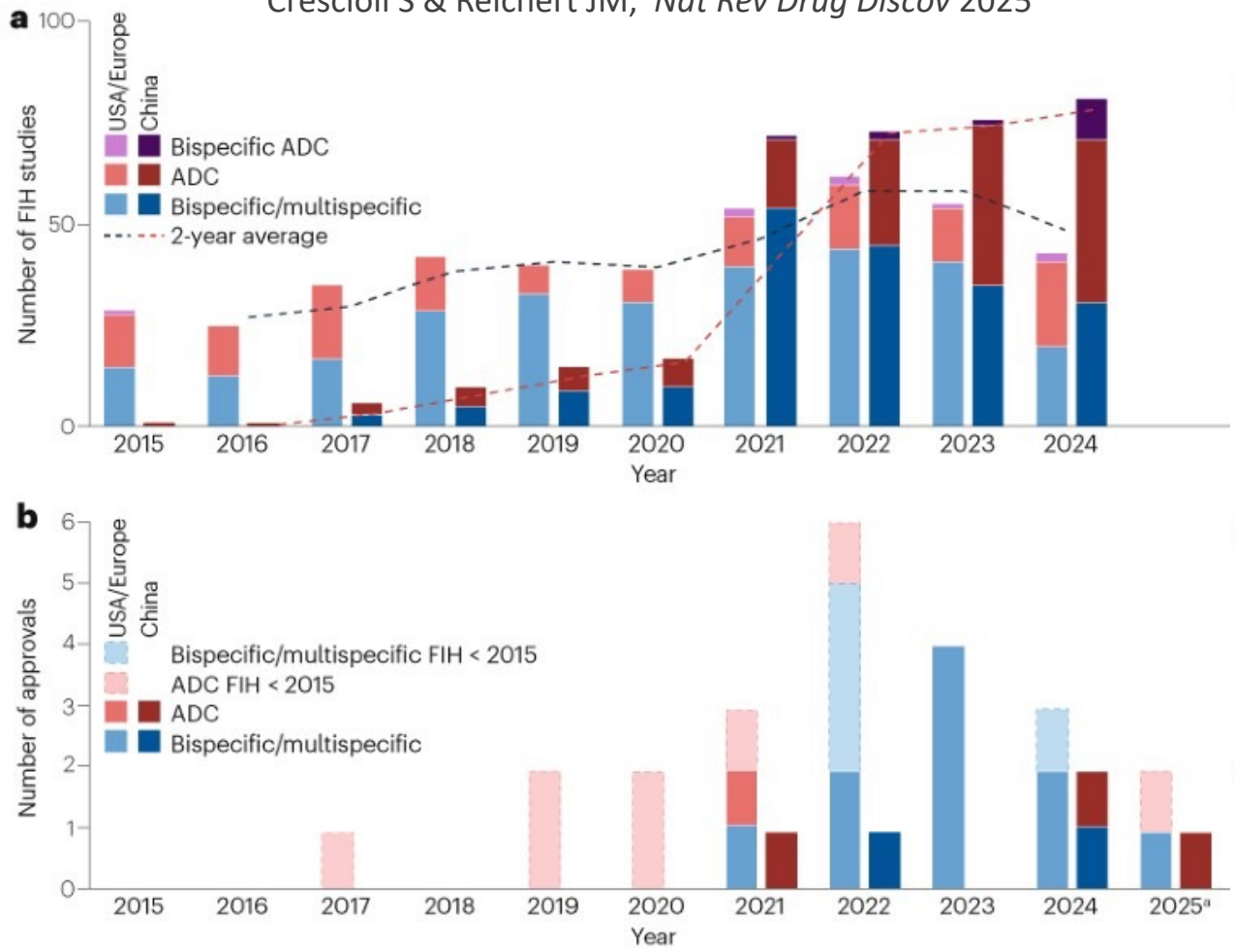
- **EFS by B- or T-ALL subset**

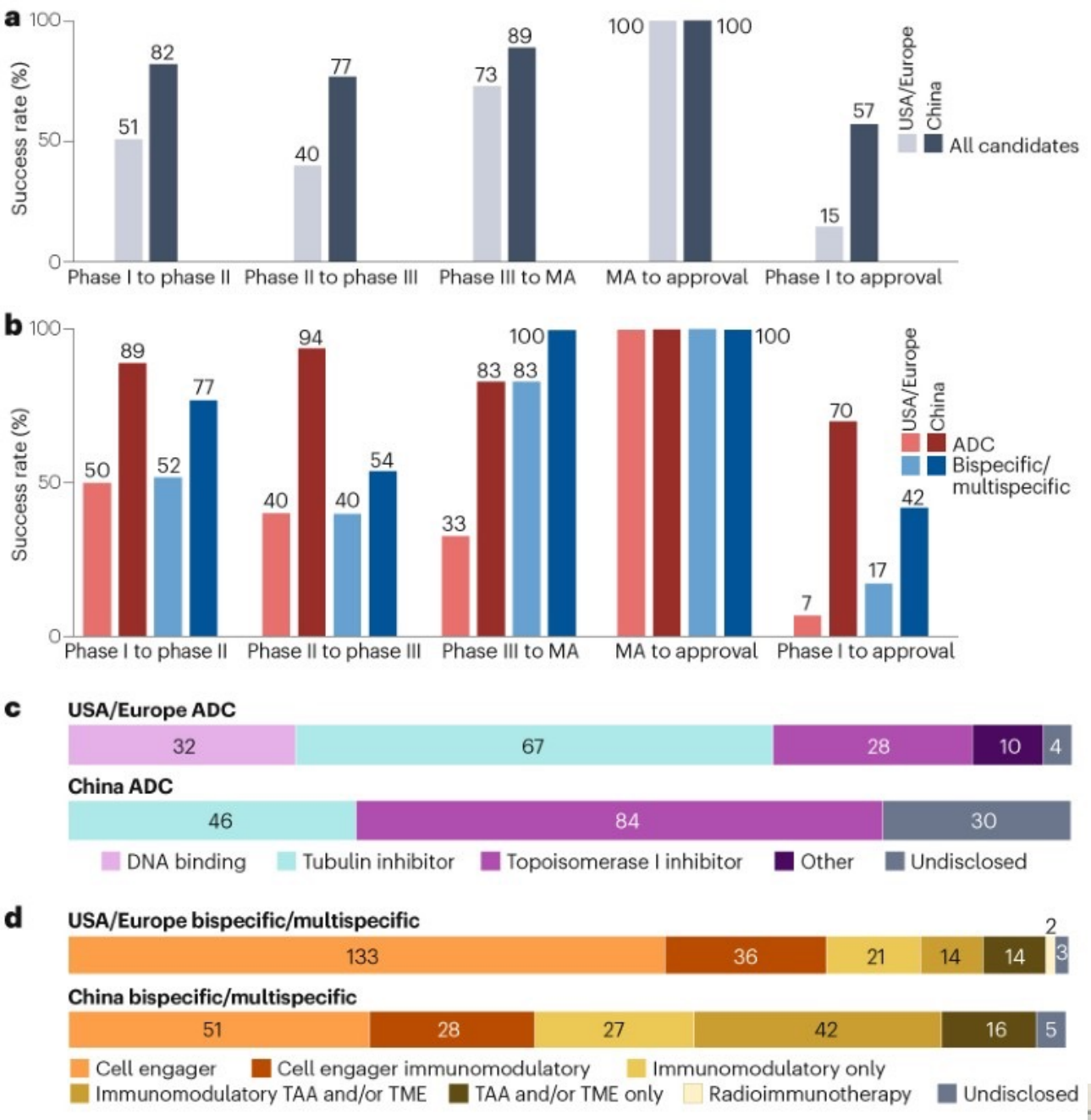
(→**new immunotherapy option for B-ALL**)



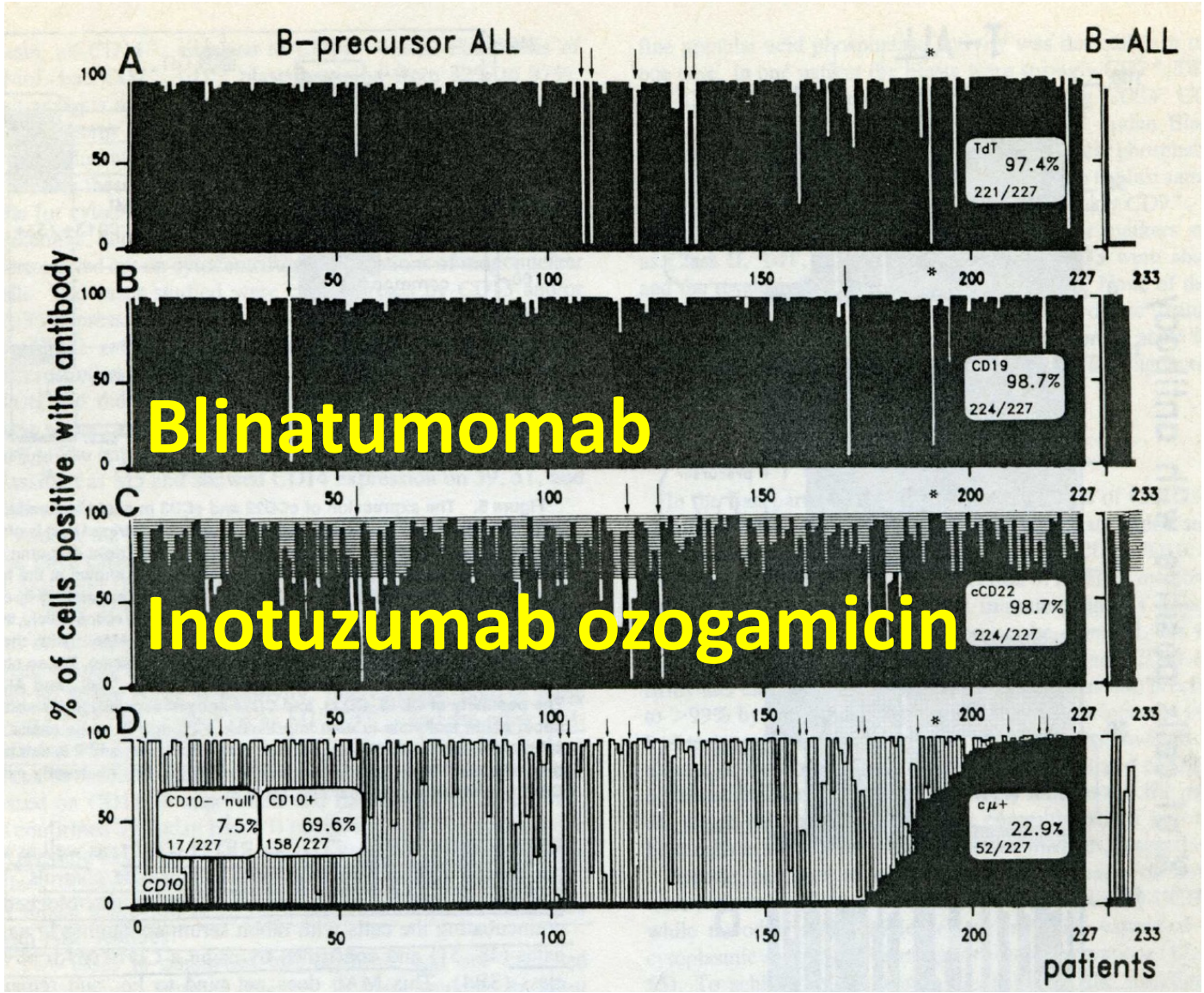
The ongoing bispecifics and ADCs revolution

Crescioli S & Reichert JM, *Nat Rev Drug Discov* 2025





CD19 and CD22 B-cell antibody targets

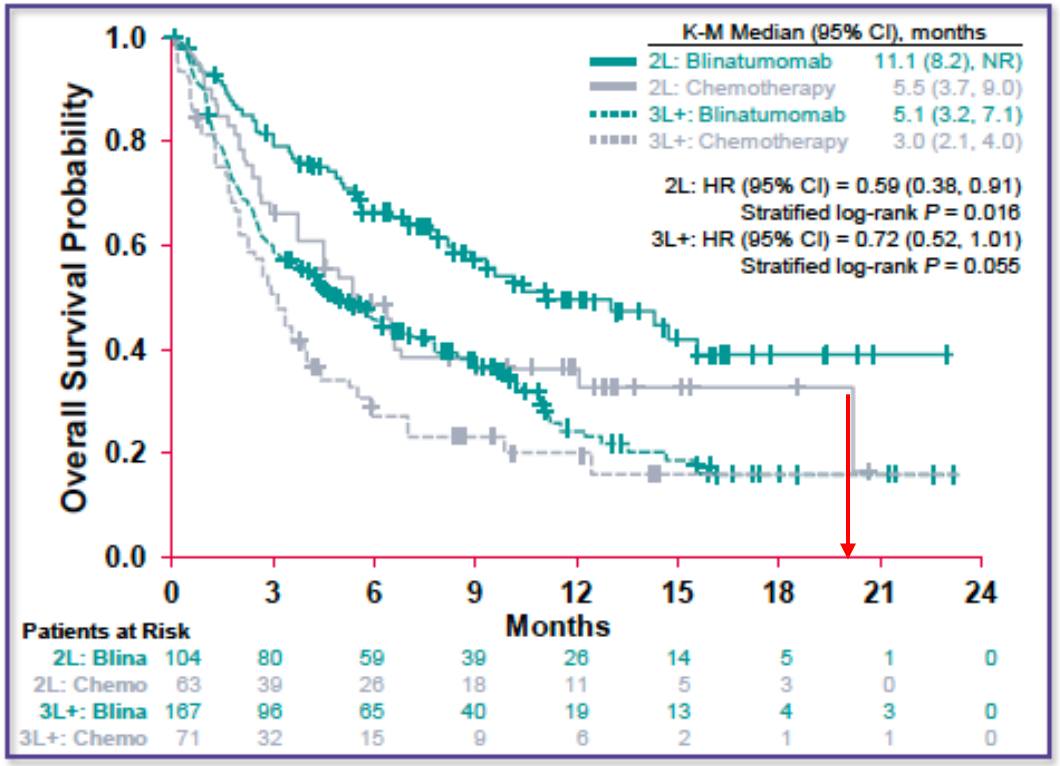


from Janossy G, Coustan-Smith E, Campana D. Leukemia, 1989

Survival after Blinatumomab or Inotuzumab (R/R)

TOWER

Dombret H et al., *Leuk Lymphoma*. 2019 Sep;60(9):2214-2222

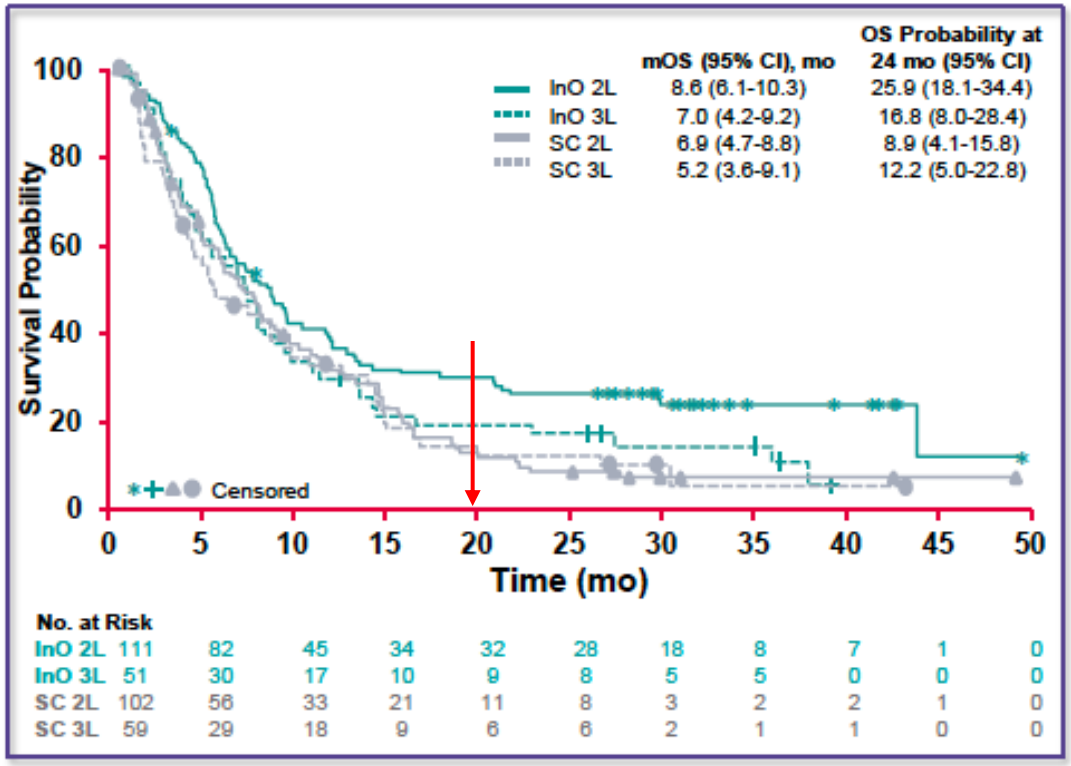


In adults with Ph- R/R B-ALL treated with blinatumomab or chemo in 2L or 3L+, median OS:[1]

- 2L: blinatumomab (n=104), **11.1 mo** (95% CI 8.2–NE); chemo (n=63): 5.5 mo (95% CI, 3.7–9.0)
- 3L+: blinatumomab (n=167), **5.1 mo** (95% CI 3.2–7.1); chemo (n=71), 3.0 mo (95% CI 2.1–4.0)

INO-VATE

Jabbour E et al, *Leuk Lymphoma.* 2020; **61**: 2012-2015



In a study of adults with R/R ALL treated with inotuzumab (n=164) or chemo (n=162), a subgroup analysis by treatment line showed **2-year OS rates**:[2]

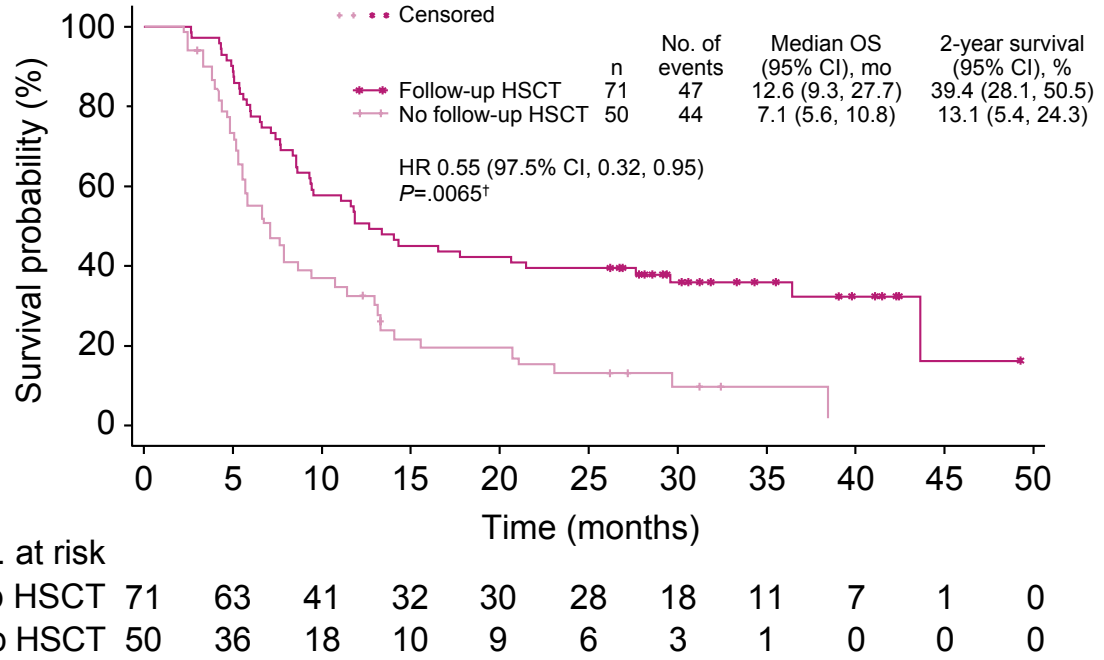
- 2L: inotuzumab, **25.9%** (95% CI 18.1–34.4); chemo, 8.9% (95% CI 4.1–15.8)
- 3L: inotuzumab, **16.8%** (95% CI 8.0–28.4); chemo, 12.2% (95% CI, 5.0–22.8)

Survival of **Blinatumomab**-treated patients according to follow-up **SCT (NEUF)**

	MRD+		R/R B-cell ALL
	All MRD+ ($n=56$)	Ph− ($n=50$)[a]	Ph−[b] ($n=29$)
Mortality following HSCT, % (95% CI)[d]			
3 months	5.5 (1.9–16.3)	4.1 (1.1–15.2)	10.7 (3.4–34.0)
6 months	5.5 (1.9–16.3)	4.1 (1.1–15.2)	14.8 (5.8–37.4)
12 months	10.1 (4.3–23.8)	9.0 (3.3–24.4)	19.3 (9.3–40.4)
Events, *n* (%)			
Nonrelapse deaths	6 (11)	5 (10)	5 (17.2)
Relapse	11 (20)	11 (22)	8 (27.6)
Death due to undocumented relapse	3 (5)	3 (6)	2 (6.9)
Death due to unknown causes	1 (2)	1 (2)	0 (0.0)
Patients alive without relapse	34 (61)	29 (58)	14 (48.3)

Boissel N et al. *Blood Cancer J* 2023;13:2

Survival of **InO**-treated patients according to follow-up **SCT (INO-VATE)**



Kantarjian HM et al. *Cancer* 2019;125:2474-2487

Frontline blinatumomab and/or inotuzumab

Viewpoint

Frontline treatment of adults with newly diagnosed B-cell acute lymphoblastic leukaemia

Ibrahim Aldoss, Gail J Roboz, Renato Bassan, Nicolas Boissel, Daniel J DeAngelo, Shaun Fleming, Nicola Gökbuget, Aaron C Logan, Selina M Luger, Tobias Menne, Jae Park, Andre C Schuh, Bijal Shah, Elias Jabbour

In the past decade, there has been considerable progress in the treatment of adults with newly diagnosed B-cell acute lymphoblastic leukaemia. This evolution is the product of a more profound understanding of acute lymphoblastic leukaemia biology, innovations in measurable residual disease quantification that led to precise disease-risk stratification, adoption of contemporary paediatric-inspired regimens, inclusion of tyrosine kinase inhibitors in the treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia, and the introduction of immunotherapy in the frontline setting. Nevertheless, outcomes of acute lymphoblastic leukaemia in adults are inferior compared with those of children, with excessive rates of treatment failure, and therapy-related morbidity and mortality. Simultaneously, transplant consolidation has continued to be used frequently for high-risk adults with acute lymphoblastic leukaemia in first complete remission. Considering the rapid pace of evolution in acute lymphoblastic leukaemia management, novel trial designs are warranted to accelerate advancements and streamline approaches. Here, we summarise progress in the treatment of adults with newly diagnosed acute lymphoblastic leukaemia, which adds to previously published guidelines by focusing specifically on first-line decisions for B-cell acute lymphoblastic leukaemia and how to best personalise treatment. This Viewpoint also includes experiences with regimens and testing approaches currently available not only in Europe, but also on multiple continents with different practices and resources.

Lancet Haematol 2024; 11: e959–70

Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, CA, USA (I Aldoss MD); Clinical and Translational Leukemia Program, Weill Medical College of Cornell University, New York, NY, USA (Prof G J Roboz MD); Department of Hematology, Ospedale dell'Angelo and Ospedale SS Giovanni e Paolo, Mestre Venezia, Italy (R Bassan MD); Department of Hematology, Hôpital Saint-Louis, AP-HP, Institut de Recherche Saint-Louis,

2024

Incorporation of Immunotherapy Into Adult B-Cell Acute Lymphoblastic Leukemia Therapy

Fadi G. Haddad, MD[1]; Hagop Kantarjian, MD[1]; Nicholas J. Short, MD[1]; Nitin Jain, MD[1]; Jayastu Senapati, MD[1]; Farhad Ravandi, MD[1]; and Elias Jabbour, MD[1]

Abstract

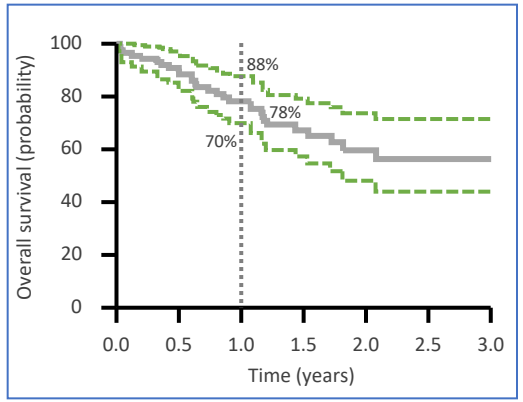
Blinatumomab and inotuzumab ozogamicin have demonstrated efficacy in treating relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL) and improving outcomes compared with conventional chemotherapy. Encouraging results have been observed in both younger and older patients with Philadelphia chromosome (Ph)–positive and Ph-negative B-ALL treated with these immunotherapy agents across several clinical trials. Treatment with inotuzumab ozogamicin and/or blinatumomab leads to high rates of deep measurable residual disease negativity and may enhance survival compared with chemotherapy-only approaches, reducing the need for intensive chemotherapy, and potentially the need for allogeneic stem cell transplantation. Herein, we review the incorporation of blinatumomab and/or inotuzumab ozogamicin into frontline B-ALL regimens, including the potential use of chemotherapy-free approaches in select patient subgroups. We also explore the potential role of CAR T-cell therapies in the frontline setting for high-risk patients, as well as novel strategies to further improve outcomes in patients with B-ALL.

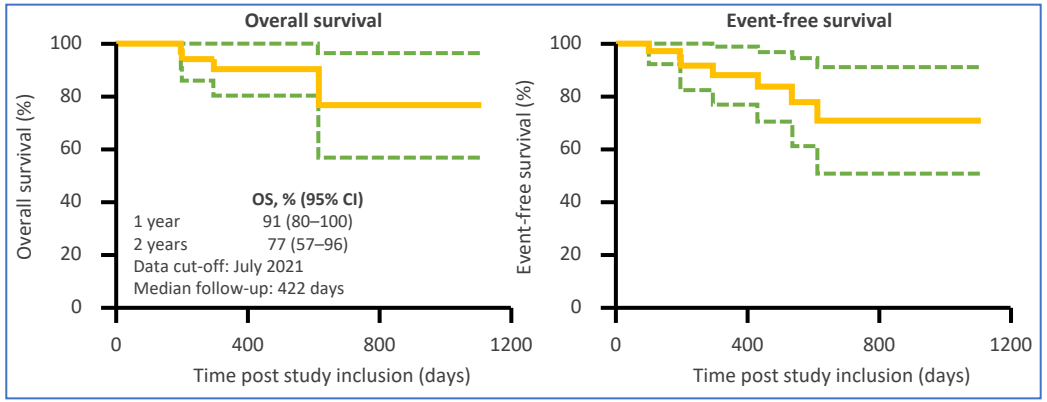
J Natl Compr Canc Netw, doi:10.6004/jnccn.2025.7050
Published online July 14, 2025

2025

Improved outcomes in elderly ALL

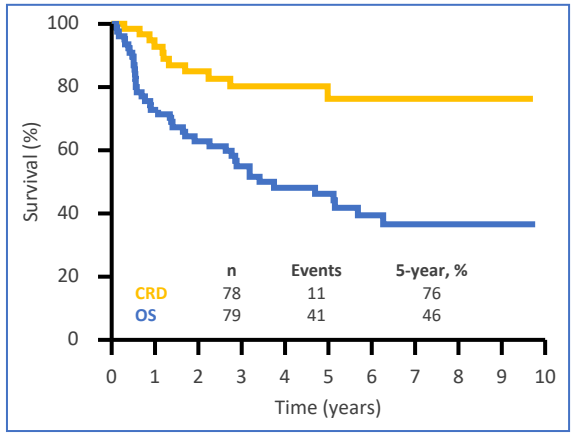
Fractionated **InO** With Low-Intensity Chemotherapy in **Older Patients** With ND CD22+ Ph- B ALL: First Results from EWALL-INO Multicenter Phase 2 Study[1]
N=90, CR 85.5%
MRD_{neg} NR



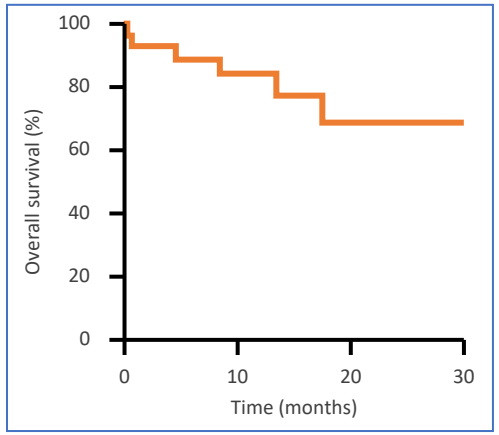


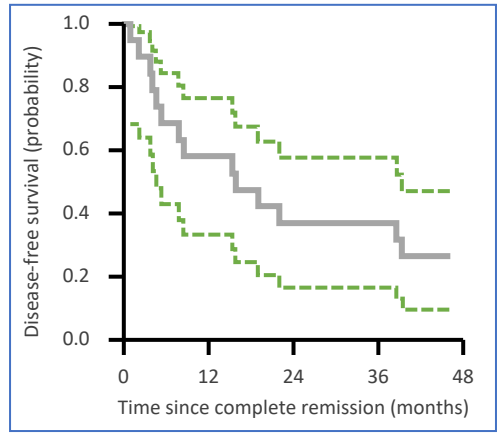
Phase 2 German Multicenter Study Using **InO** for Induction Therapy, Followed by a Conventional Chemotherapy in **Patients ≥56 Years** With ND B-ALL (INITIAL-1 Trial)[2]
N=42, CR 100%
MRD_{neg} 74%

Phase 2 Study of Mini-Hyper-CVD Plus **InO** ± **Blina** in **Patients ≥60 Years** with ND Ph- B-ALL[3]
N=75, CR 99%
MRD_{neg} 96%



Reduced Chemotherapy and **Blina** for **Older Patients** with B-ALL: GMALL Bold Trial[4]
N=34, CR 76%
MRD_{neg} 69%



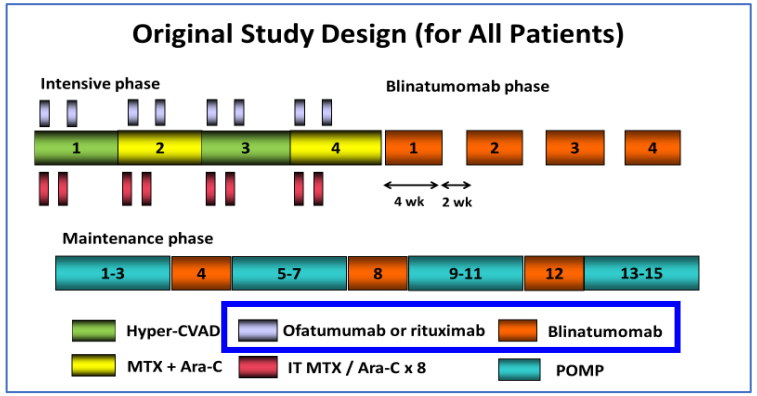


SWOG Study of **Blina** Induction Monotherapy and POMP Maintenance In **Elderly** (66–84 years, median 75 years) Ph- ALL[5]
N=29, CR 66%
MRD_{neg} 92%

- 1. Chevallier P, et al. Blood 2021;138(Supplement 1):511; 2. Stelljes M, et al. Blood 2021;138(Supplement 1):2300; 3. Short NJ, et al. Blood 2021;138(Supplement 1):3400; 4. Gökbuget N, et al. Blood 2021;138(Supplement 1):3399–401; 5. Advani AS, et al. J Clin Oncol 2022;40:1574–82.

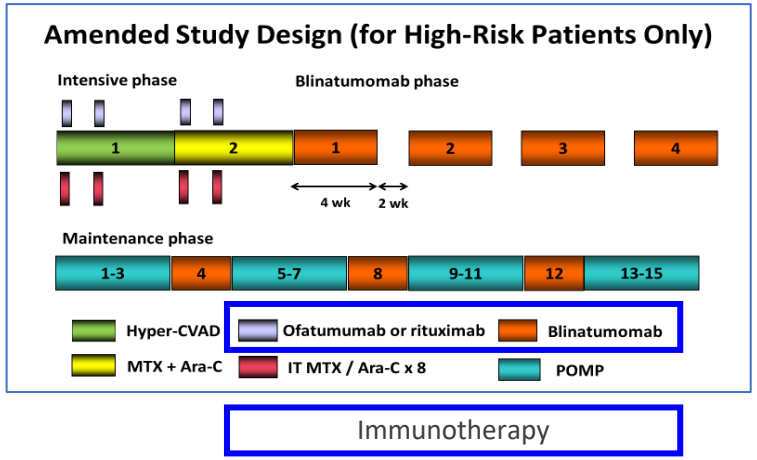
MDACC phase 2 study in adults

50% less intensive chemo*

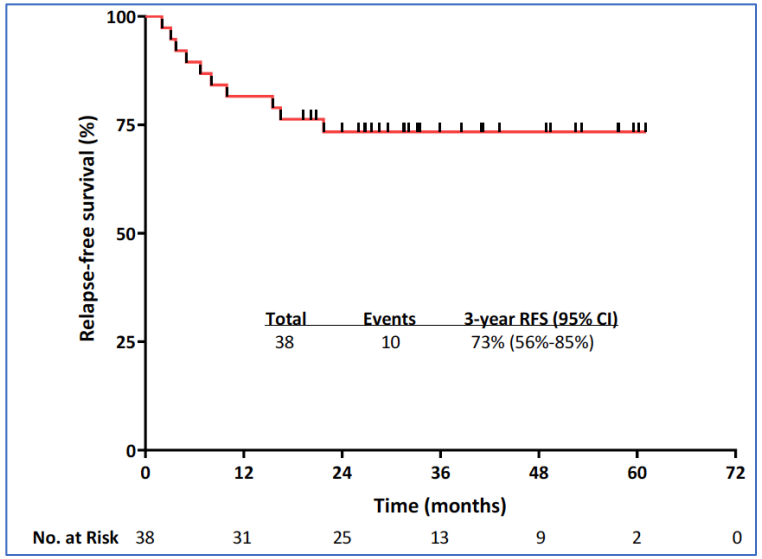


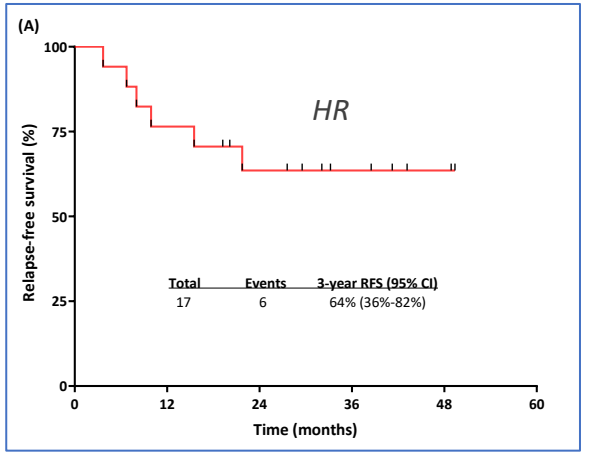
*vs standard hyper-CVAD regimen

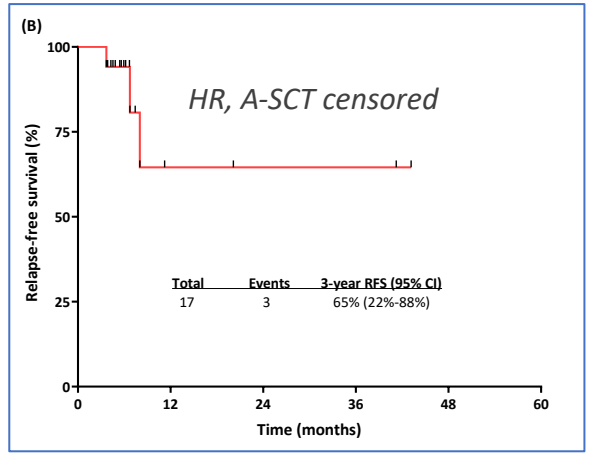
75% less intensive chemo*



- **MD Anderson Cancer Center**
  - **N=38**: CR 100%, MRD_{neg} 76–97%
  - **3-yr RFS 73%**, 3-year RFS HR 64%







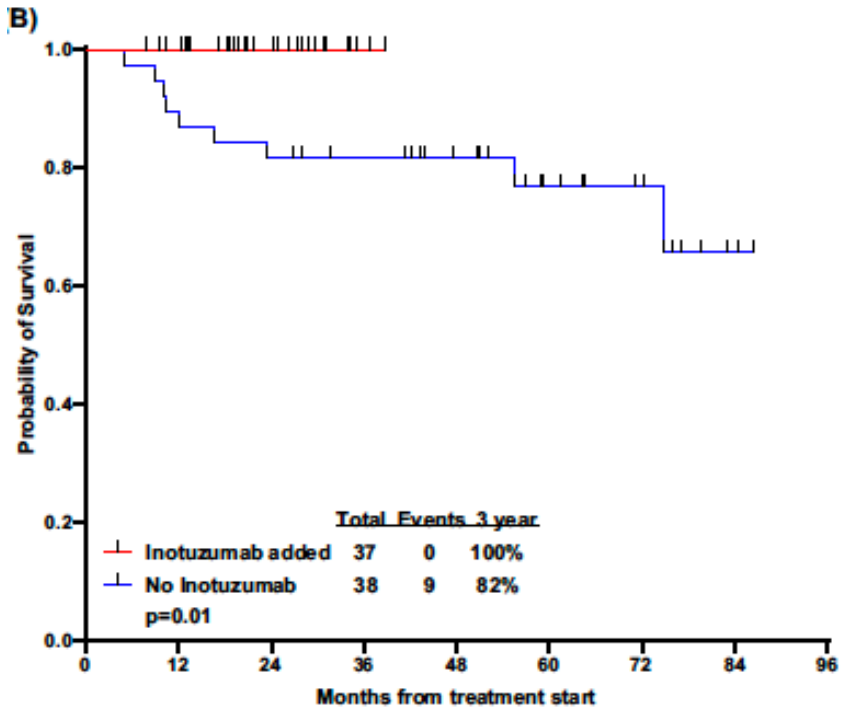
- Jabbour ES, et al. Lancet Haematol 2022 (Online ahead of print).
- A-SCT, allogeneic stem cell transplantation.

Hyper-CVAD and Sequential Blinatumomab Without and With Inotuzumab in Young Adults With Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia

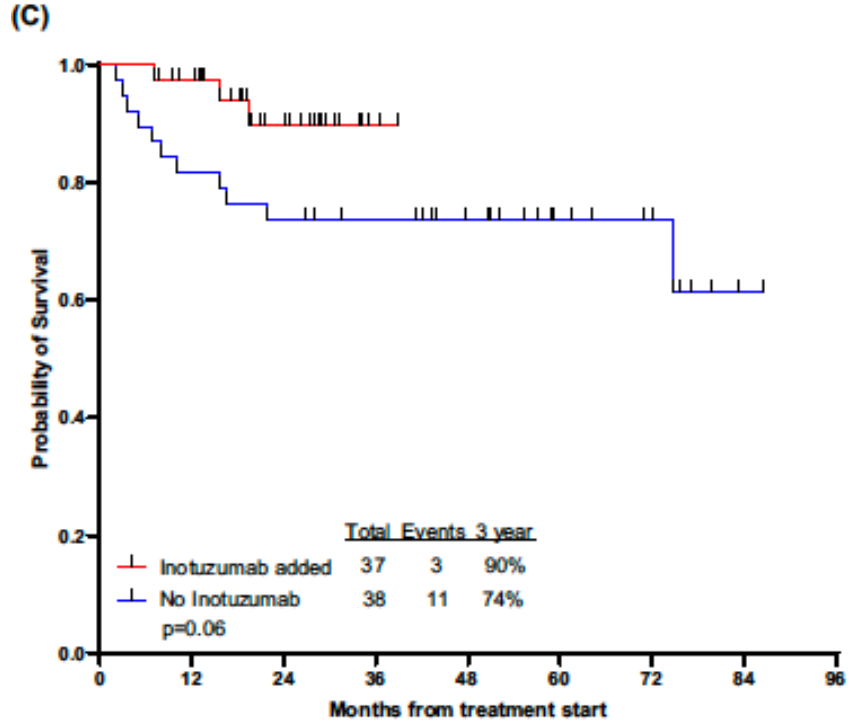
Hagop Kantarjian | Nicholas J. Short | Nitin Jain | Fadi G. Haddad | Tapan Kadia | Musa Yilmaz | Alessandra Ferrajoli | Koji Sasaki | Yesid Alvarado | Naveen Pemmaraju | Jayastu Senapati | Rebecca Garris | Farhad Ravandi | Elias Jabbour

American Journal of Hematology, 2025; 100:402–407
https://doi.org/10.1002/ajh.27576

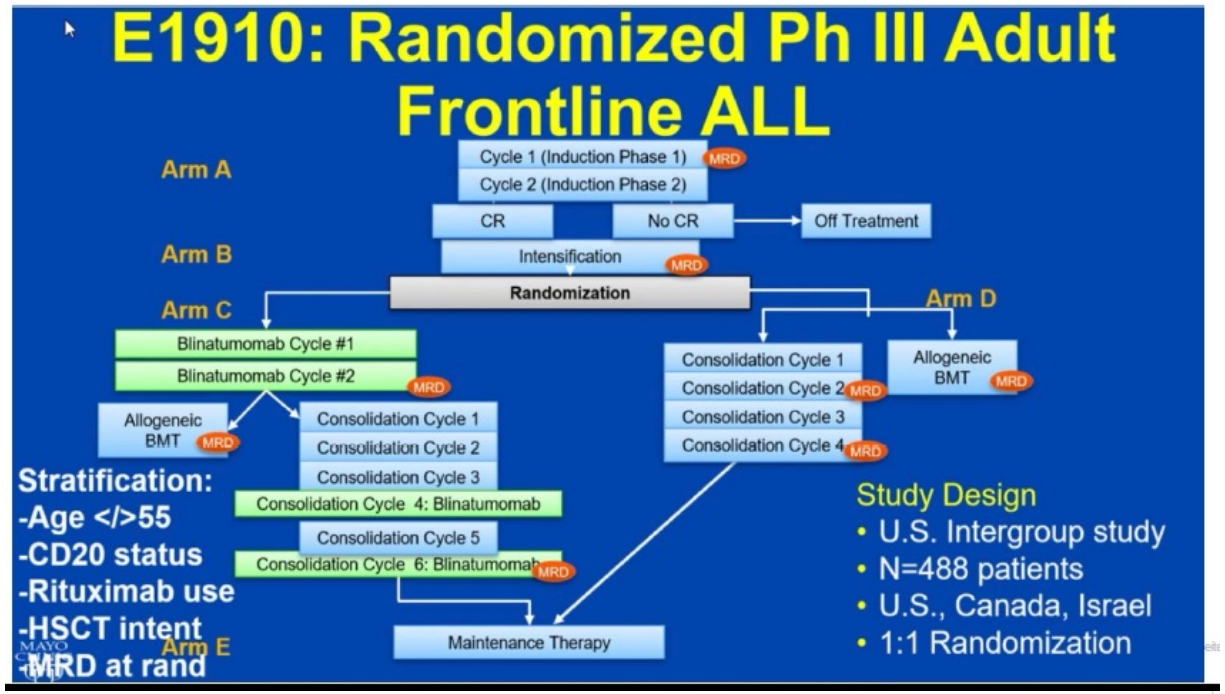
Overall survival

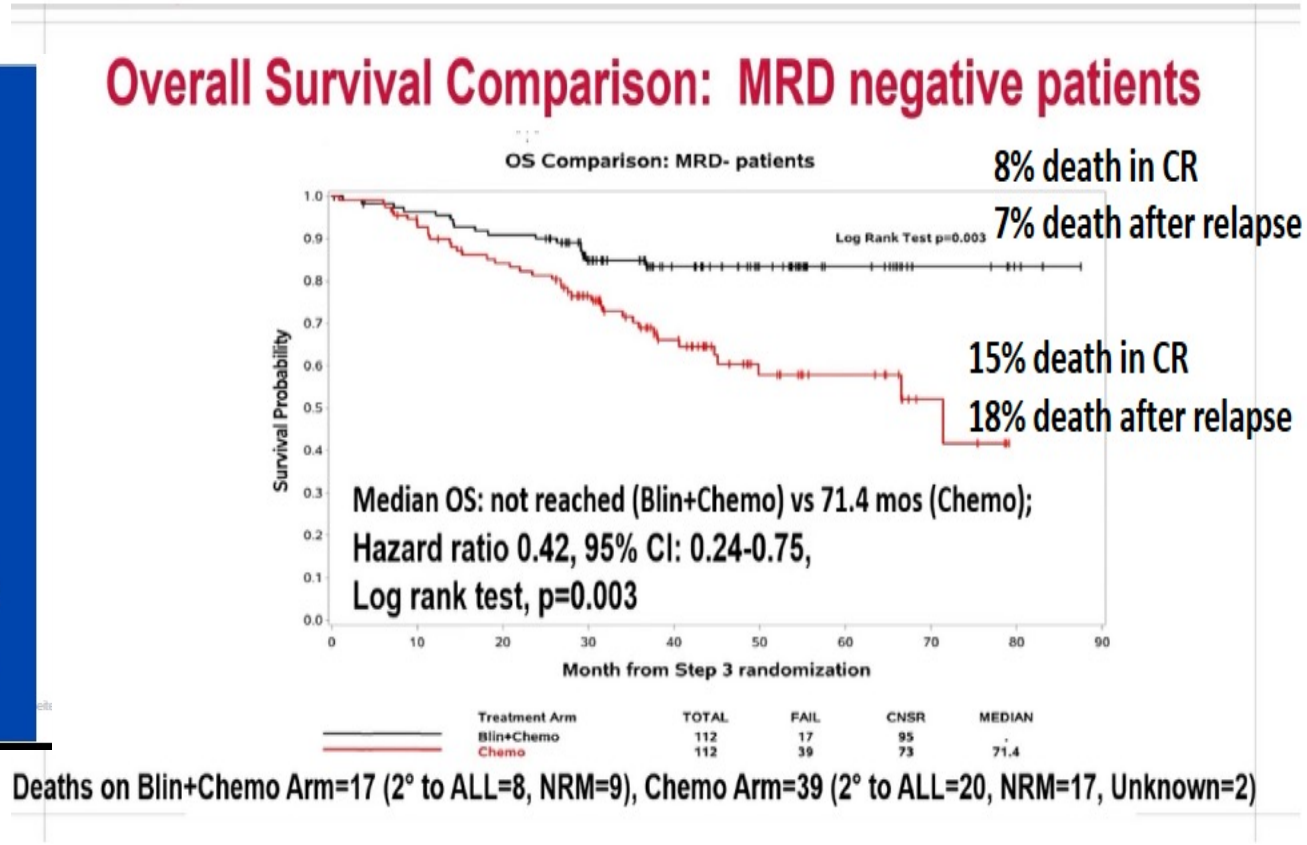


Relapse-free survival



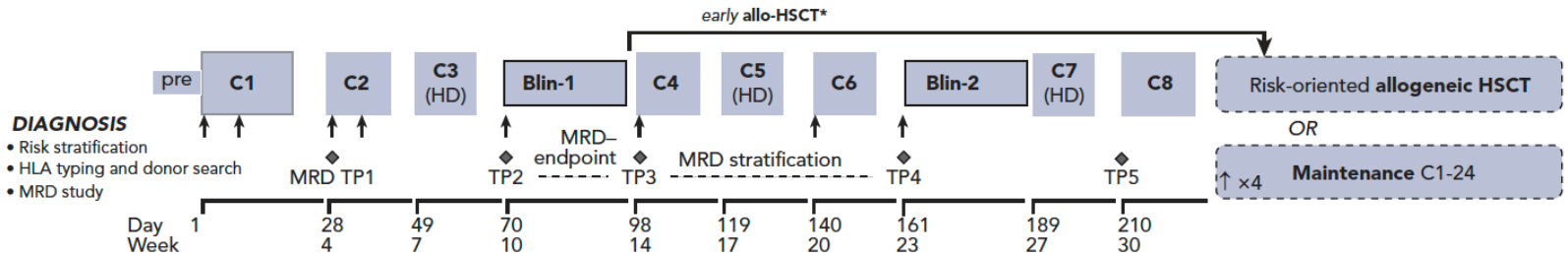
ECOG-ACRIN phase 3 study in adults 30-70 years





STUDY PATIENTS: **MRDneg prior to Blinatumomab**

Litzow M et al, NEJM 2024



blood® Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Up-front blinatumomab improves MRD clearance and outcome in adult Ph⁻ B-lineage ALL: the GIMEMA LAL2317 phase 2 study

Renato Bassan,[1] Sabina Chiaretti,[2] Irene Della Starza,[2,3] Alessandra Santoro,[4] Orietta Spinelli,[5] Manuela Tosi,[5] Loredana Elia,[2] Deborah Cardinali,[2] Maria Stefania De Propris,[2] Matteo Piccini,[6] Federico Lussana,[5,7] Mario Annunziata,[8] Patrizia Chiusolo,[9,10] Patrizia Zappasodi,[11] Erika Borlenghi,[12] Matteo Leoncin,[1] Catello Califano,[13] Monica Bocchia,[14] Francesco Di Raimondo,[15] Francesco Grimaldi,[16] Mario Tiribelli,[17] Anna Candoni,[17,18] Albana Lico,[19] Emesta Audisio,[20] Monia Lunghi,[21] Anna Maria Mianulli,[22] Mariangela Di Trani,[2] Valentina Arena,[23] Monica Messina,[23] Alfonso Piciocchi,[23] Paola Fazi,[23] Alessandro Rambaldi,[5,7] and Robin Foà[2]

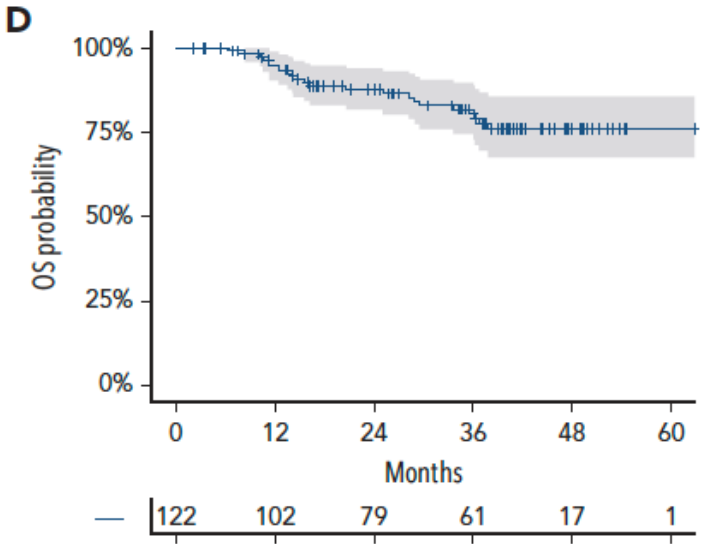
Treatment phase	Drugs	Dosing and route	Days
Prephase	PDN	20 mg/m²/bd IV	–5 to –1
	CY	300 (200 >55 y) mg/m²/d IV over 30′	–3 to –1
Cycle 1	IDR	12 (9 >55 y) mg/m²/d IV over 30′	1,2
	VCR	1.4 mg/m²/d (max. 2) IV push	1,8,15,22
	Dex	5 mg/m²/bd IV over 5′ q12h	1-5,15-19
	PEG-Asp	1500 (1000 >55 y) IU/m²/d IV over 120′	10
	IT (†)		1,15
Cycles 2,4,6	VCR	1.4 mg/m² (max. 2) IV push	1,8 (no course 2)
	IDR	12 (9 >55 y) mg/m²/d IV over 30′	1
	CY	1000 mg/m²/d IV over 60′	1
	Dex	5 mg/m²/bd PO	1-5
	Ara-C	75 mg/m²/d SC	2-5
	PEG-Asp	2000 (1000 >55 y) IU/m²/d IV over 120′	8 (no course 4)
	6-Mp	60 mg/m²/d PO	1-10
	IT (†)		1,15 (course 2)
HD cycles 3,7	MTX	2500 (1500 >55 y) mg/m²/d IV over 24 h; FAR	1
		2000 mg/m²/bd over 120′	3,4
	Blinatumomab	28 μg/d cIV	1-28
	Dex	20 mg/d IV	1
	Levetiracetam	500 mg/bd PO	1-28
	IT (†)		–1

Treatment phase	Drugs	Dosing and route	Days
HD cycle 5	MTX	2500 (1500) mg/m²/d IV over 24h; FAR	1
	PEG-Asp	2000 (1000 >55 y) IU/m²/d IV over 120′	3
	6-MP	25 mg/m²/d PO	8-18
Cycle 8	VCR	1.4 mg/m²/d (max. 2) IV push	1,8
	IDR	10 (7.5 >55 y) mg/m²/d IV over 30′	1,8
	Dex	5 mg/m²/bd PO	1-5
	CY	300 (200 >55 y) mg/m²/d IV over 30′	1-3
	PDN	20 mg/m²/bd PO	8-12
	IT (†)		1,15
Maintenance cycles 1,3,5,7,9,11	CY	100 mg/m²/d PO	1-4
	6-MP	75 mg/m²/d PO	8-28
	MTX	15 mg/m²/d PO/IM	8,15,22
	IT (†)		1 (courses 3,5)
2,4,6,8,10,12	VCR	1 mg/m²/d (max. 2) IV push	1
	PDN	20 mg/m²/bd PO	1-5
	6-MP	75 mg/m²/d PO	8-28
	MTX	15 mg/m²/d PO/IM	8,15,22
	IT (†)		1 (courses 2,4)
13-24	6-MP	75 mg/m²/d PO	8-28
	MTX	15 mg/m²/d PO/IM	1,8,15,22

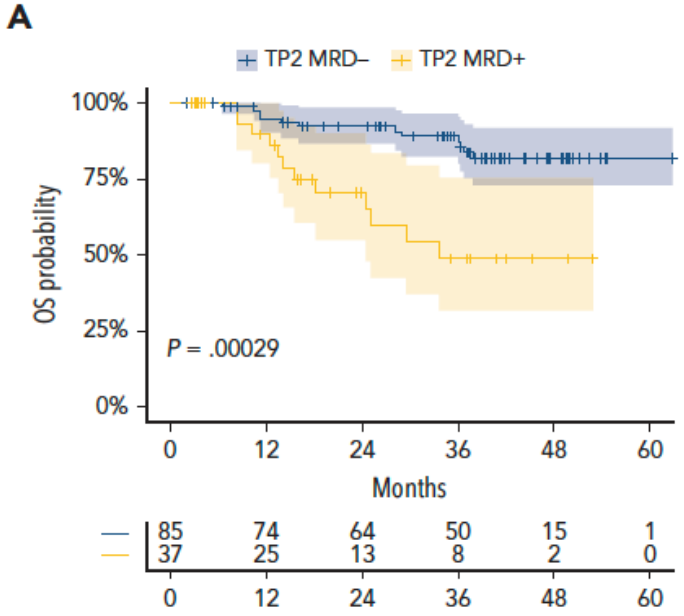
After TP2MRD and Blin-1 (early):
VHR, HR MRD unknown, SR/HR with TP2MRD ≥ 10^{-4} (any of these)

After TP4MRD and Blin-2:
SR/HR TP2 MRD– but TP3 or TP4 MRD+

Blood 2025;145:2447



3-year OS of patients receiving blinatumomab = **82%**



3-year OS of patients who were TP2 MRDneg = **89%**

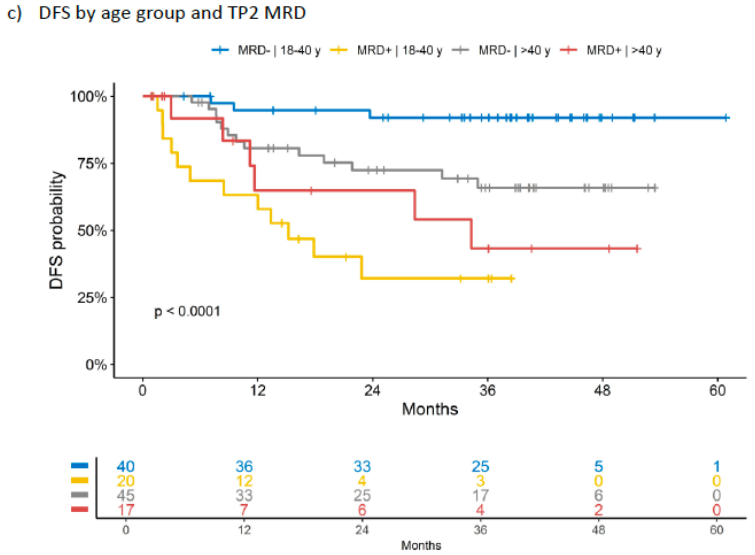
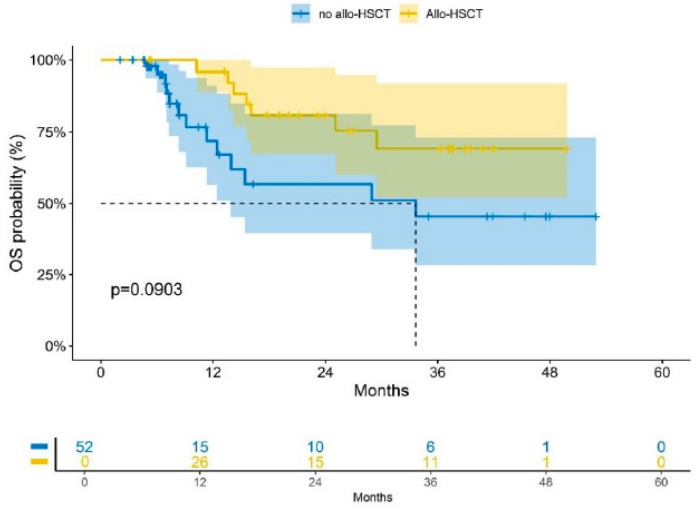


Figure S7. OS according to Simon-Makuch statistics of 52 blinatumomab-treated and HSCT-eligible patients.



Patient group	12 Months	24 Months	36 Months
No HSCT or censoring at allograft	72% (57%,91%)	57% (40%, 81%)	45% (28%, 73%)
HSCT	96%(89%,100%)	81% (67%, 97%)	69% (52%, 92%)

Ex vivo cell growth predicts outcome

BLOOD

The Journal of The American Society of Hematology

VOL. 48, NO. 6 DECEMBER 1976

A Simplified In Vitro Classification for Prognosis in Adult Acute Leukemia: The Application of In Vitro Results in Remission-predictive Models

By Gary Spitzer, Karel A. Dicke, Edmund A. Gehan, Terry Smith, Kenneth B. McCredie, Barthel Barlogie, and Emil J Freireich

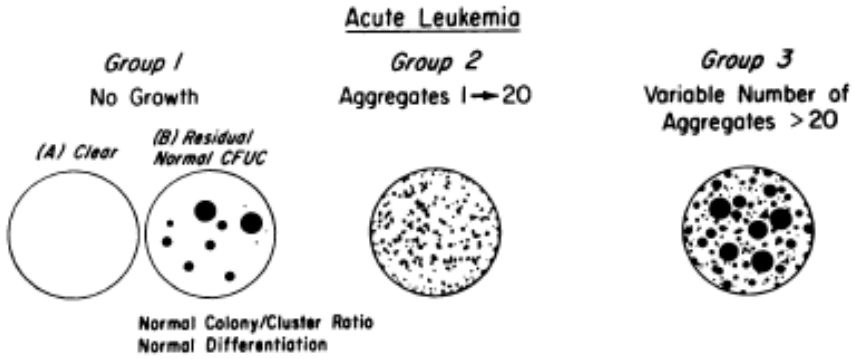


Fig. 1. Schematic representation of the growth pattern of normal bone marrow and the three subdivisions of acute leukemic growth.

CR	4/7	1/1	**0/2**

nature medicine

Article

https://doi.org/10.1038/s41591-022-02112-7

Pharmacotypes across the genomic landscape of pediatric acute lymphoblastic leukemia and impact on treatment response

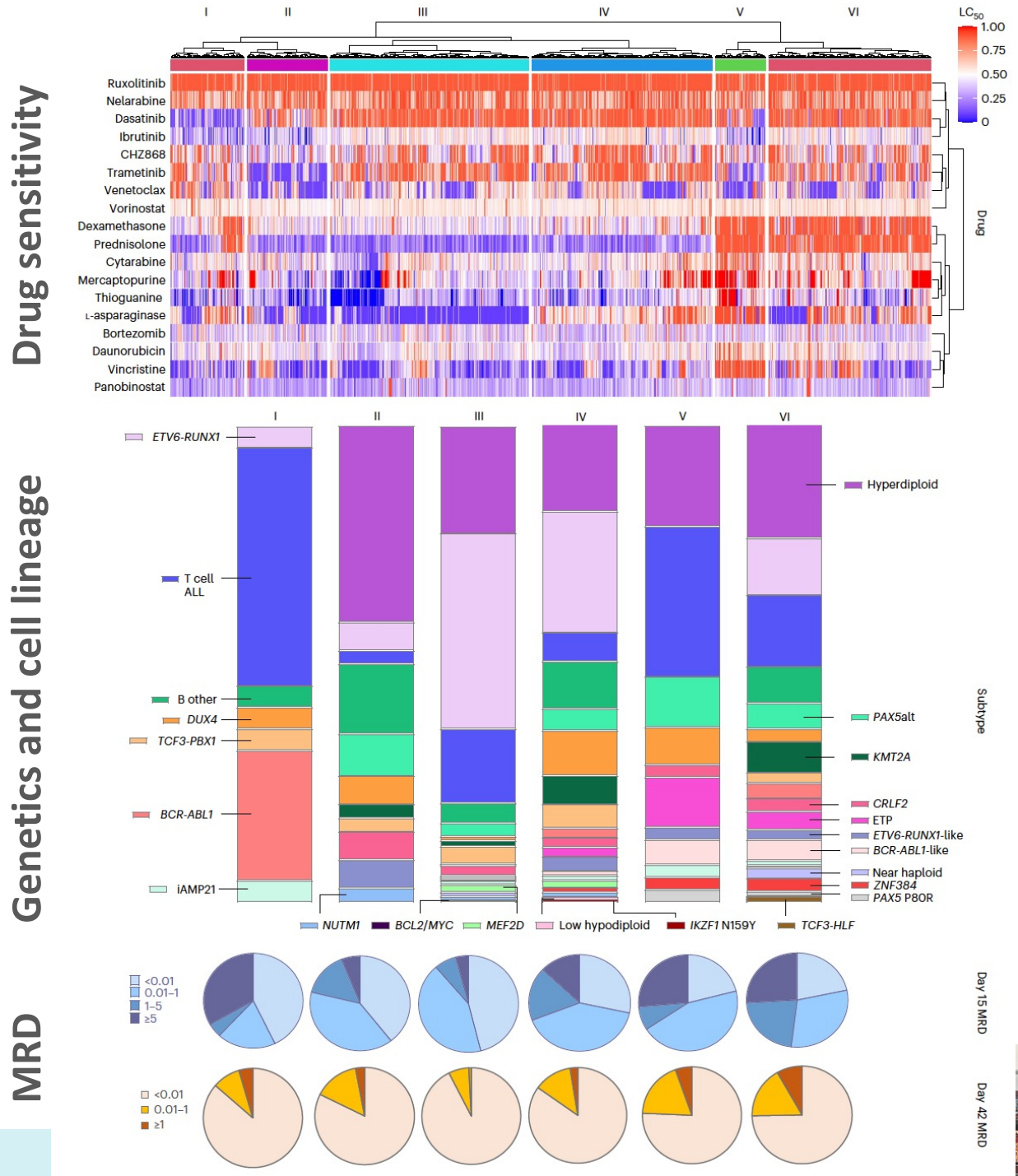
Received: 4 April 2022

Accepted: 28 October 2022

Published online: 05 January 2023

Check for updates

Shawn H. R. Lee[1,2,3,8], Wenjian Yang[1,8], Yoshihiro Gocho[1], August John[1], Lauren Rowland[1], Brandon Smart[1], Hannah Williams[1], Dylan Maxwell[1], Jeremy Hunt[1], Wentao Yang[1], Kristine R. Crews[1], Kathryn G. Roberts[4], Sima Jeha[5], Cheng Cheng[6], Seth E. Karol[5], Mary V. Relling[1], Gary L. Rosner[7], Hiroto Inaba[5], Charles G. Mullighan[4], Ching-Hon Pui[5], William E. Evans[1,9] & Jun J. Yang[1,5,9]



MEDICINA DI PRECISIONE NELLE
LEUCEMIE ACUTE LINFOBLASTICHE (LAL):
dove siamo e dove stiamo andando?

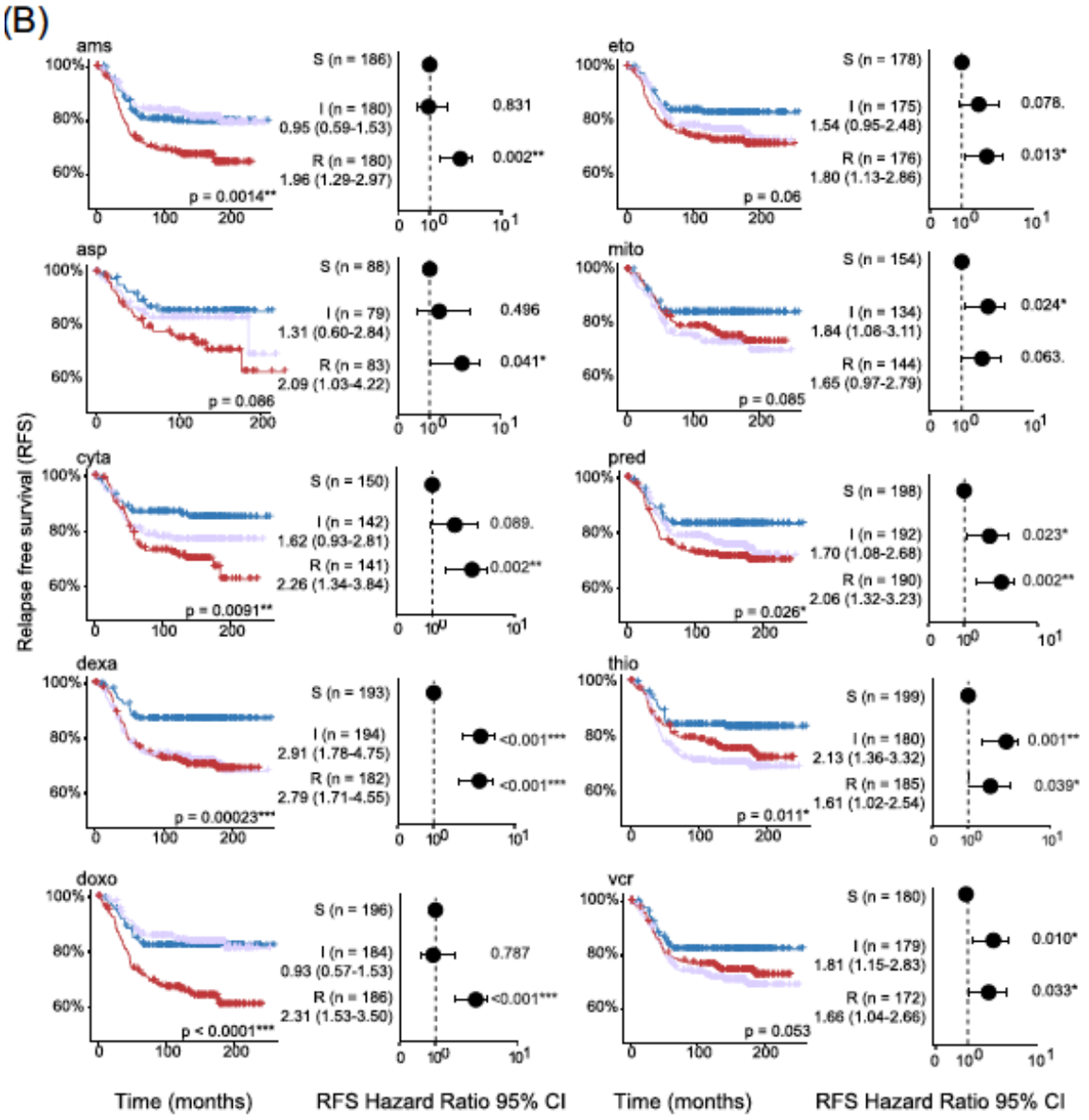
Received: 22 December 2024 | Accepted: 28 May 2025
DOI: 10.1002/hem3.70176

HemaSphere eha

ARTICLE

Ex vivo drug responses and molecular profiles of 597 pediatric acute lymphoblastic leukemia patients

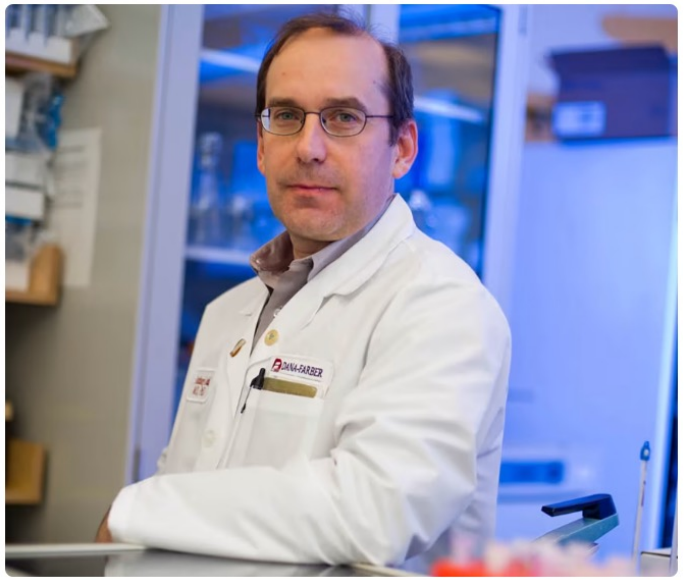
Anna Pia Enblad[1,2,3] | Olga Krali[1,2] | Henrik Gezelius[1,2] | Anders Lundmark[1,2] | Kristin Blom[1] | Claes Andersson[1] | Josefine Palle[3] | Britt-Marie Frost[3] | Samppa Ryhänen[4,5] | Trond Flægstad[5,6] | Ólafur G. Jónsson[5,7] | Kjeld Schmiegelow[5,8] | Mats Heyman[5,9] | Arja Harila[3,5] | Peter Nygren[10] | Rolf Larsson[1] | Gudmar Lönnerholm[3] | Jessica Nordlund[1,2]



MEDICINA DI PRECISIONE NELLE
LEUCEMIE ACUTE LINFOBLASTICHE (LAL):
dove siamo e dove stiamo andando?
Venezia | 20 novembre 2025
Ospedale SS. Giovanni & Paolo

SEPTEMBER 29, 2025

Dr. Anthony Letai appointed as Director of National Cancer Institute



Sf(PM)

Society for Precision Medicine

Precision medicine in AML: Function plus -omics is better than either alone

Anthony Letai[1,2,3,*]
[1]Dana-Farber Cancer Institute, Boston, MA 02215, USA
[2]Harvard Medical School, Boston, MA 02115, USA
[3]Broad Institute, Cambridge, MA 02142, USA
*Correspondence: anthony_letai@dfci.harvard.edu
https://doi.org/10.1016/j.ccell.2022.07.009

Perspective

Functional precision oncology: Testing tumors with drugs to identify vulnerabilities and novel combinations

Anthony Letai,[1,2] Patrick Bhola,[2,3] and Alana L. Welm[4,*]
[1]Dana-Farber Cancer Institute, Boston, MA 02215, USA
[2]Harvard Medical School, Boston, MA 02215, USA
[3]Brigham and Women's Hospital, Boston, MA 02115, USA
[4]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112, USA
*Correspondence: alana.welm@hci.utah.edu
https://doi.org/10.1016/j.ccell.2021.12.004

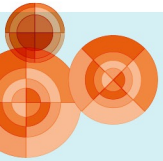
Seyfried et al. *Cell Death and Disease* (2019)10:571
https://doi.org/10.1038/s41419-019-1801-0

Cell Death & Disease

ARTICLE Open Access

Prediction of venetoclax activity in precursor B-ALL by functional assessment of apoptosis signaling

Felix Seyfried[1], Salih Demir[1,2], Rebecca Louise Hörl[1], Felix Uli Stimweiß[1,2], Jeremy Ryan[3], Annika Scheffold[4], Mariana Villalobos-Ortiz[3], Elena Boldrin[1,2], Julia Zinngrebe[1], Stefanie Enzenmüller[1], Silvia Jenni[5], Yi-Chien Tsai[5], Beat Bornhauser[5], Axel Fürstberger[6], Johann Michael Kraus[6], Hans Armin Kestler[6], Jean-Pierre Bourquin[5], Stephan Stilgenbauer[4], Anthony Letai[3], Klaus-Michael Debatin[1] and Lüder Hinrich Meyer[1]



MEDICINA DI PRECISIONE NELLE
LEUCEMIE ACUTE LINFOBLASTICHE (LAL):
dove siamo e dove stiamo andando?

Ospedale SS. Giovanni & Paolo

AI-optimized drug discovery

DrugReflector*

An artificial intelligence (AI) model trained on complex data from human cells. The AI method incorporates gene-expression data to speed up drug discovery

Up to 17 times more effective at finding relevant compounds than randomly selecting compounds from a chemical library

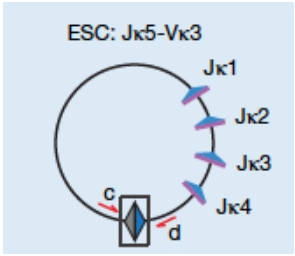
*deep-learning model on publicly available data about how each of nearly 9,600 chemical compounds perturbs gene activity in more than 50 kinds of cells.

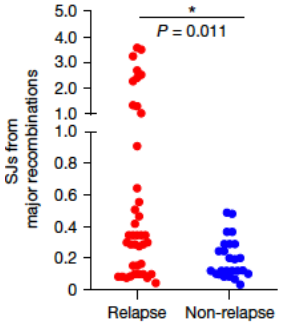
Active learning framework leveraging transcriptomics identifies modulators of disease phenotypes
BENJAMIN DEMEO ET AL. ***SCIENCE*** 23 Oct 2025 First Release DOI: 10.1126/science.adi8577

In the end

- **First line B-ALL immunotherapy works**: Rituximab, Inotuzumab, Blinatumomab (various combinations)
- **Blinatumomab**: Most effective in early MRD responders in age range 18-70 years (ECOG-ACRIN 1910 and GIMEMA 2317)
  - Mind resistance mechanisms: from dysfunctional T cells to CD19 target disruption and, possibly, circular extrachromosomal DNA (ESC)

In B-ALL, ESC replicates, persists and triggers ESC-mediated mutations associated with leukemia relapse(Gao Z et al, Nature 2025)





- **Warning**: Individual drug resistance/sensitivity profiles largely overlooked by adult ALL experts. Time and room for improved precision medicine plus ‘rapid’ detection of new effective agents