Leucemia acuta linfoblastica

Anticorpi monoclonali bi-specifici: dati recenti ed esperienza Italiana

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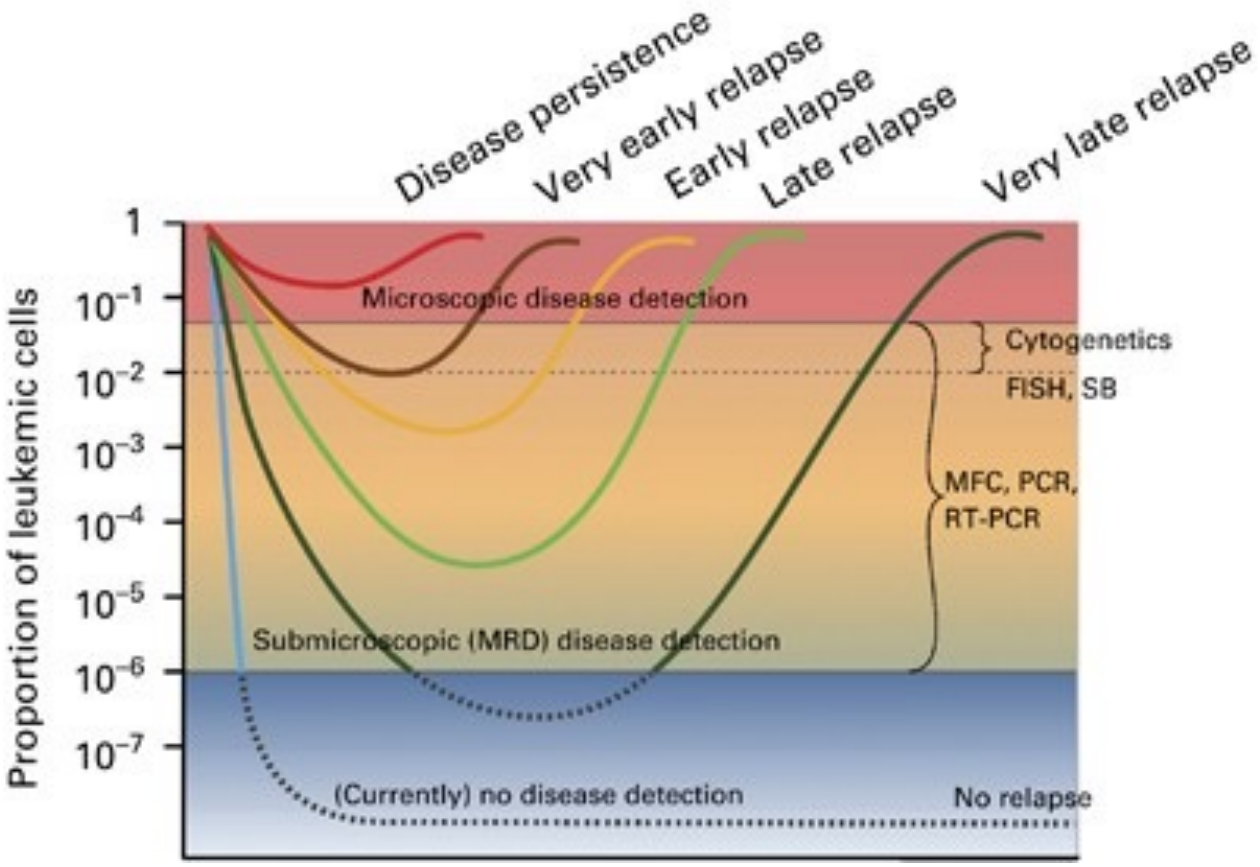
B-lineage Ph- Acute lymphoblastic leukemia

Most frequent neoplasm in childhood → outcome reaching 80-90%

Second peak in adulthood → stepping yet behind, mostly with non-intensive treatment; with MRD-driven and pediatric inspired trials, 3-yrs OS and EFS are 66% and 58% (Bassan R, et al; Blood Advances 2023)

Elderly → still an issue, due to genomic complexity, comorbidities and less compliance

Definition of MRD

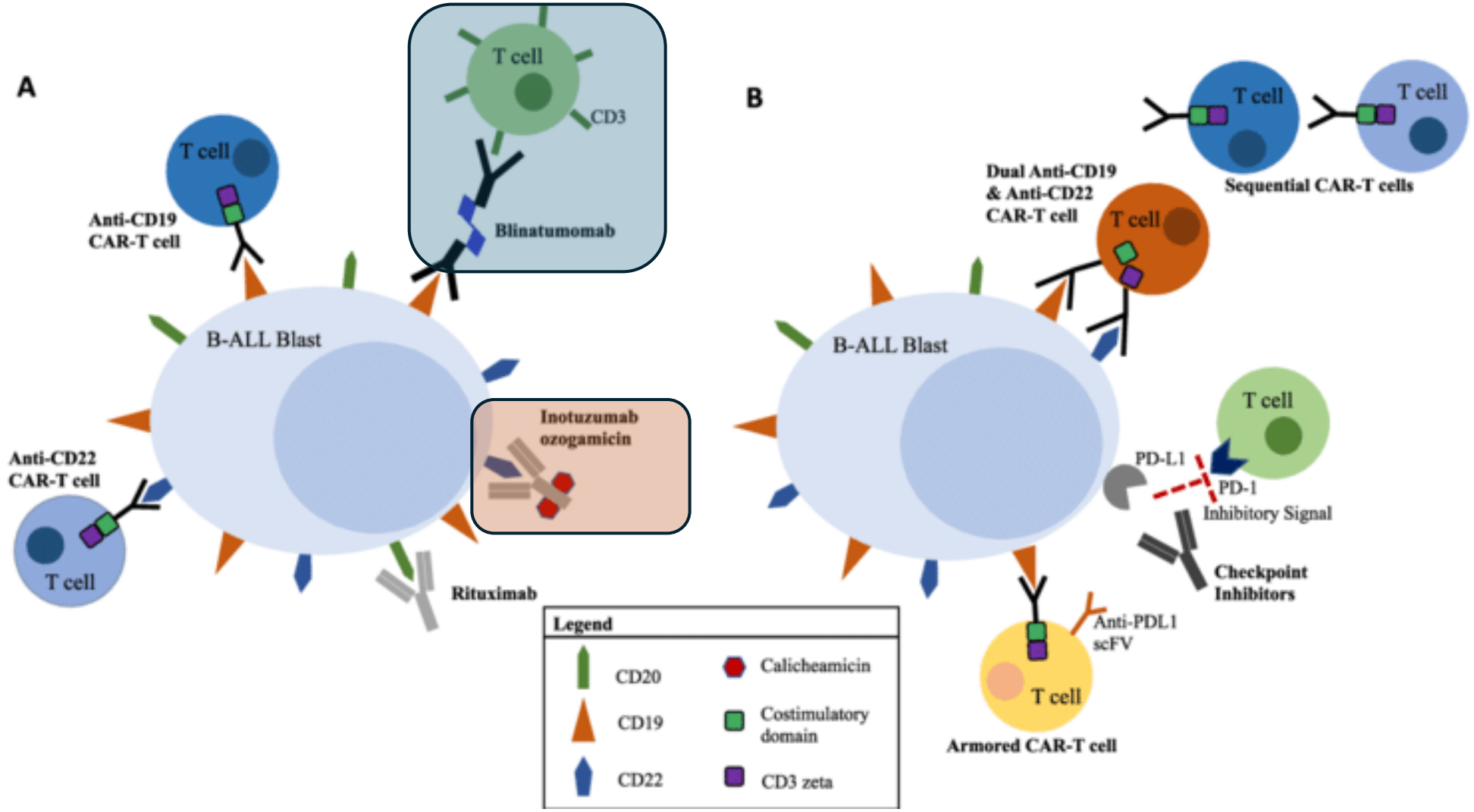


Any technique capable of detecting residual tumor cells beyond the limit of cytomorphology:
cytogenetics, flow cytometry, PCR-based assays

Widely used in ALL, starting form pediatric cases and currently used also in adults

Buckley SA, et al. Bone Marrow Transplant. 2013 ;48:630-41

Immunotherapy



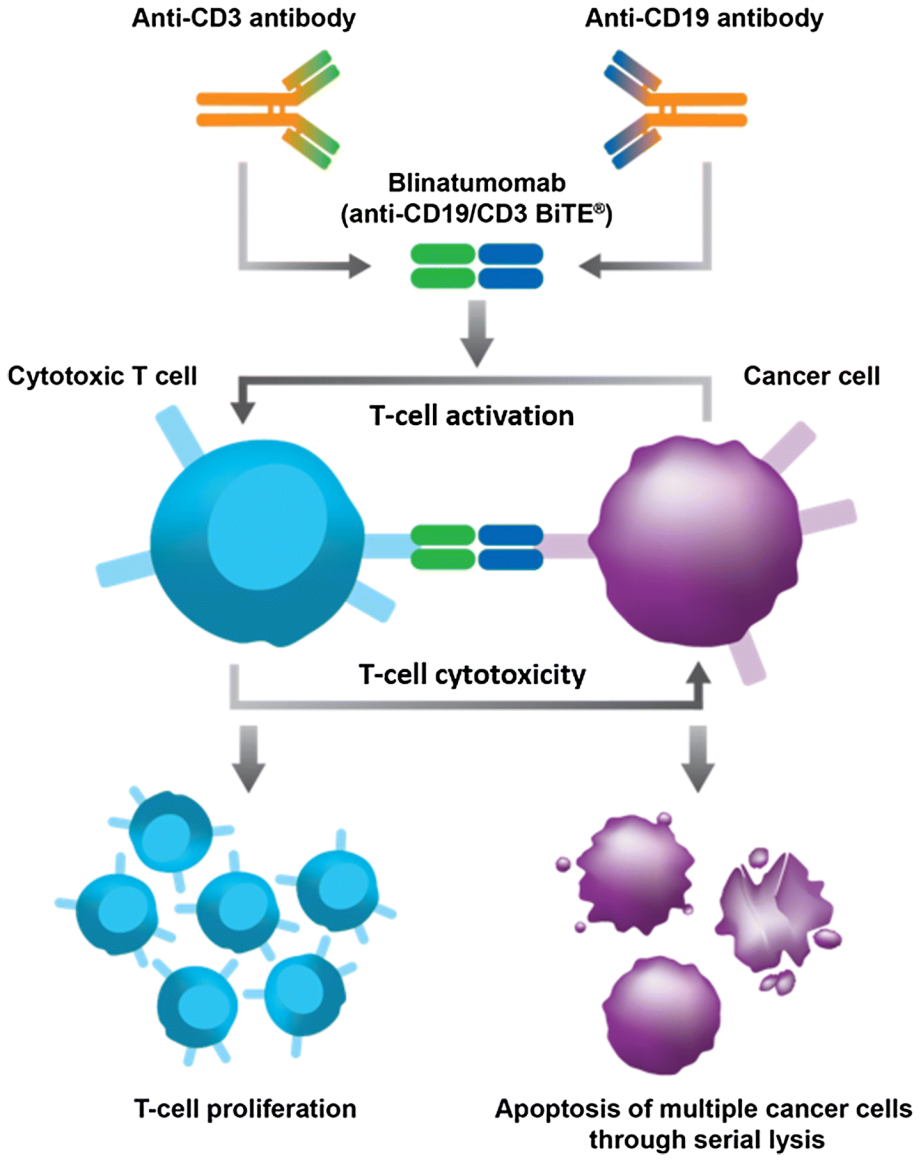
Topics

- Blinatumomab in 1st line setting: B-lineage Ph-ALL

  B-lineage Ph +ALL

Inotuzumab

Blinatumomab

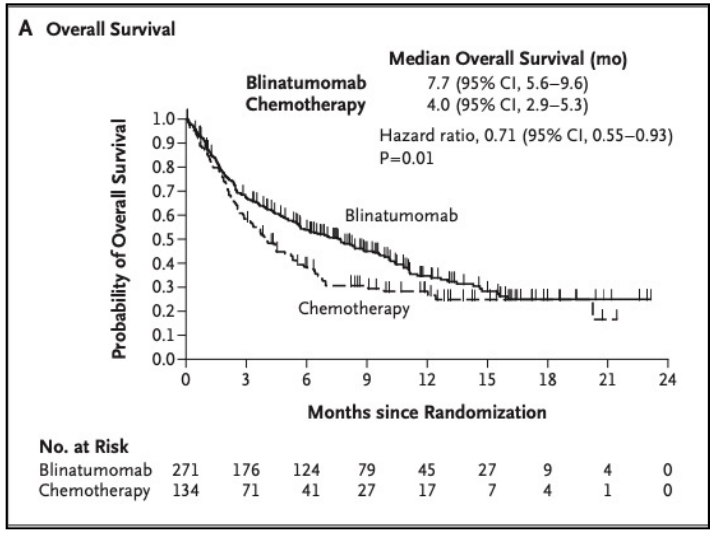


Indicazioni LAL Ph-:

BLINCYTO è indicato in monoterapia per il trattamento di adulti con LLA da precursori delle cellule B negativa per il cromosoma Philadelphia, positiva per il CD19, in prima o seconda remissione completa con malattia minima residua (MRD), superiore o uguale allo 0,1%.

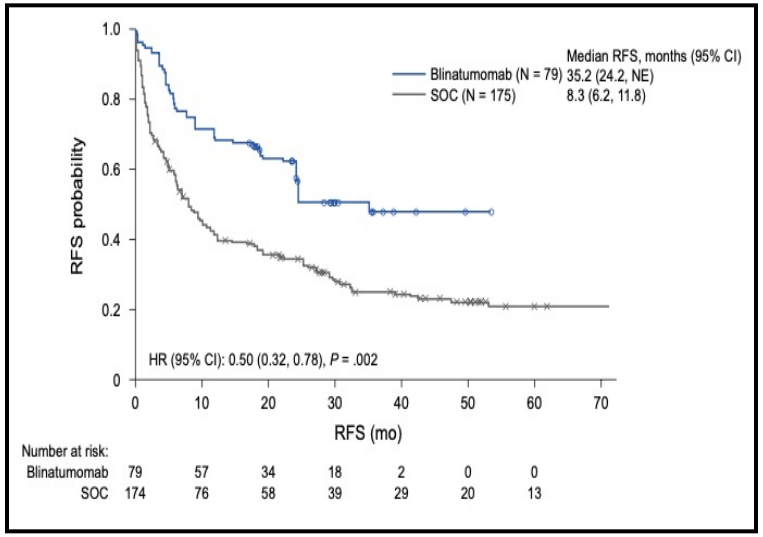
BLINCYTO è indicato in monoterapia per il trattamento di pazienti pediatrici di età pari o superiore a 1 anno con LLA da precursori delle cellule B, recidivante o refrattaria, positiva per CD19, negativa per il cromosoma Philadelphia, in recidiva dopo aver ricevuto almeno due precedenti terapie o in recidiva dopo allotrapianto di cellule staminali ematopoietiche. *AIFA*

TOWER study: B-ALL R/R
Blinatumomab vs standard chemotherapy



Kantarijian H. et al., N Engl J Med 2017; 376-379

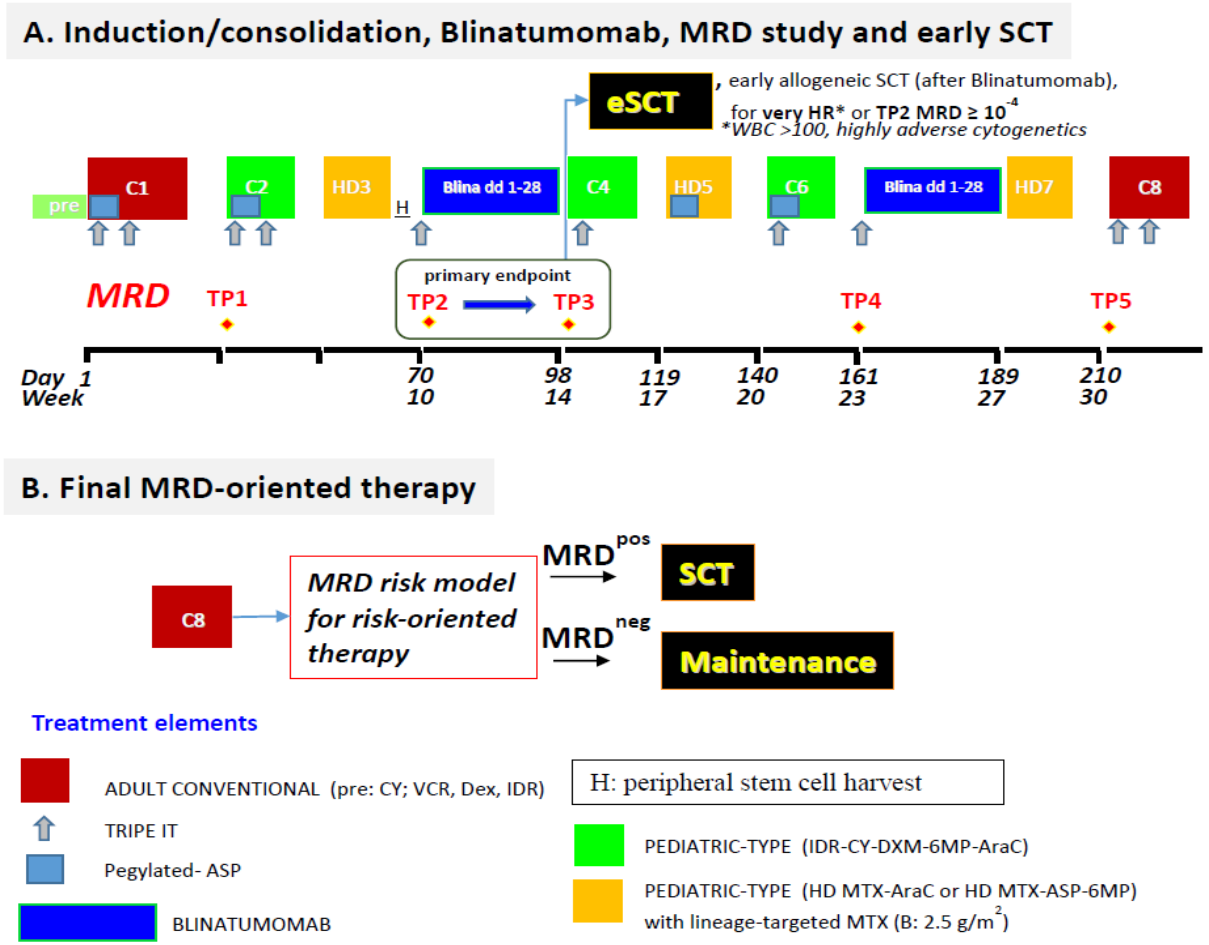
BLAST study: B-ALL with MRD+
Blinatumomab vs standard chemotherapy



Gokbuget N. et al., Eur J Haematol. 2020;104:299–309.

GIMEMA LAL 2317: scheme and patients' features

Enrollment period:: Aug 2018-Jun 2020



Patient characteristics (n=149)

	n (%)
Sex, n (%)	
M/F	81 (54%)/68 (46%)
Median age (range)	41 (18-65)
>55 years	28 (19%)
Median WBC x10⁹/l (range)	4.5 (0.1-474)
Risk, n (%)	
SR	85 (57%)
HR	29 (19%)
VHR	35 (23%)
WBC, n (%)*	
WBC >30x10^-9/L	36 (24%)
WBC <30x10^-9/L	111 (76%)
Immunophenotype, n (%)**	
ALL pro-B/common/pre-B*	23 (16%)/114 (77%)/11 (7.4%)
Molecular findings	
KMT2A/AFF4, n (%)	12 (8.3%)
E2A/PBX1, n (%)	5 (3.4%)
BCR/ABL1-like, n (%)	31 (28%)
Cytogenetics, n (%)***	
Normal	56 (49%)
Adverse (*KMT2A*-rearranged and other)	26 (22%)
Non adverse (*E2A-PBX1*, hyperdiploid and other)	32 (17.5%)
TEL/AML1	1 (0.9%)

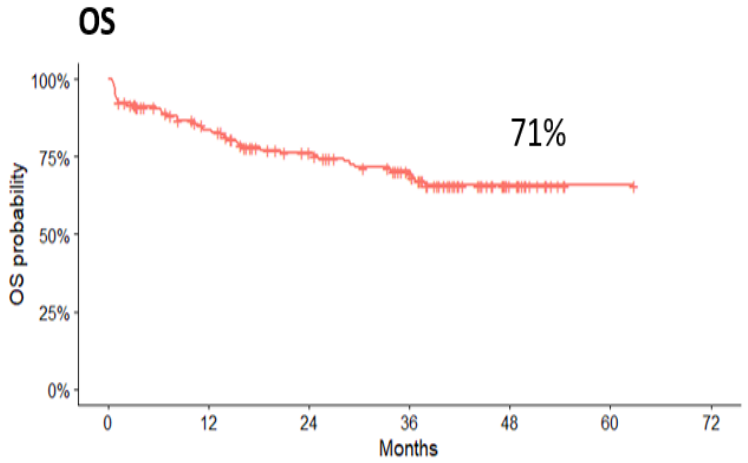
SR: standard risk; HR: high risk; VHR: very high risk; * 2 unknown; **1 unknown; ***34 unknown

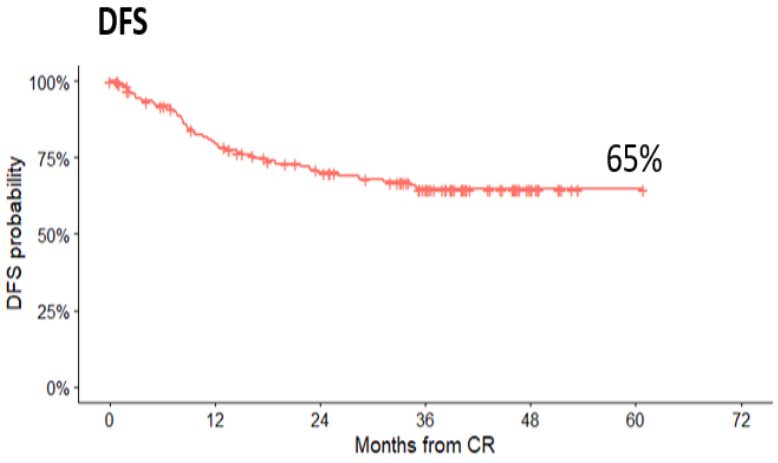
Chiaretti S, et al. ASH 2023 Abs 826; Bassan et al; in submission.

GIMEMA LAL 2317: Results

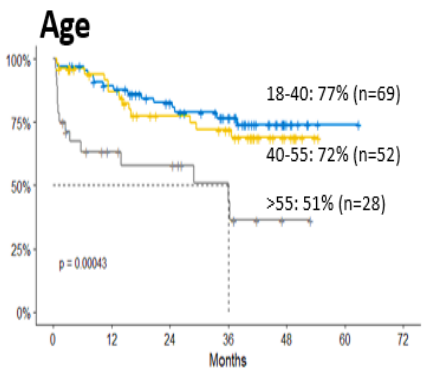
MRD at TP2 (HD3)*	Whole cohort n (%)	Paired samples n (%)	p
MRD-negative	85 (70)	79 (72)	
MRD-positive	37 (30)	30 (28)	
MRD at TP3 (blinatumomab 1)**	**n (%)**	**n (%)**	**<0.001**
MRD-negative	102 (93)	101 (93)	
MRD-positive	8 (7.3)	8 (7.3)	

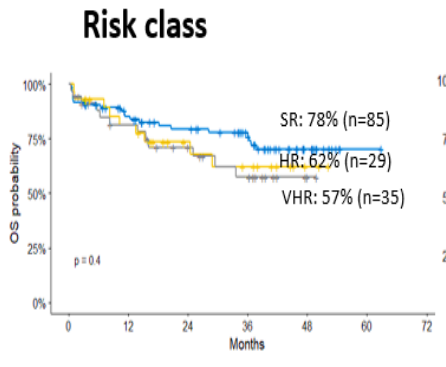
*8 not evaluable; **12 not evaluable

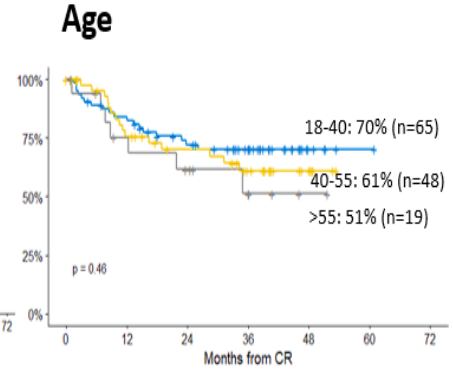


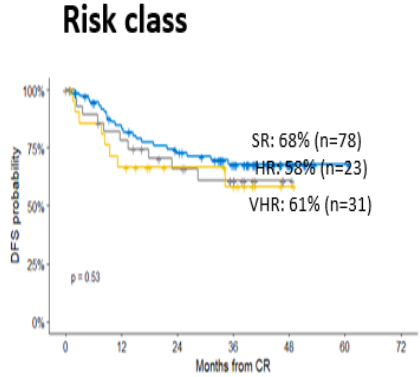


Age class	18-40, n=69 (%)	40-55, n=52 (%)	>55, n=28 (%)	p
MRD at TP3 (blinatumomab #1)				
MRD-negative	49 (89)	40 (95)	13 (100)	0.5
MRD-positive	6 (11)	2 (4.8)	0	
Risk class	**SR, n=85 (%)**	**HR, n=29 (%)**	**VHR, n=35 (%)**	**p**
MRD at TP3 (blinatumomab #1)				
MRD-negative	64 (97)	20 (95)	18 (75)	0.05
MRD-positive	2 (3)	1 (4.8)	5	







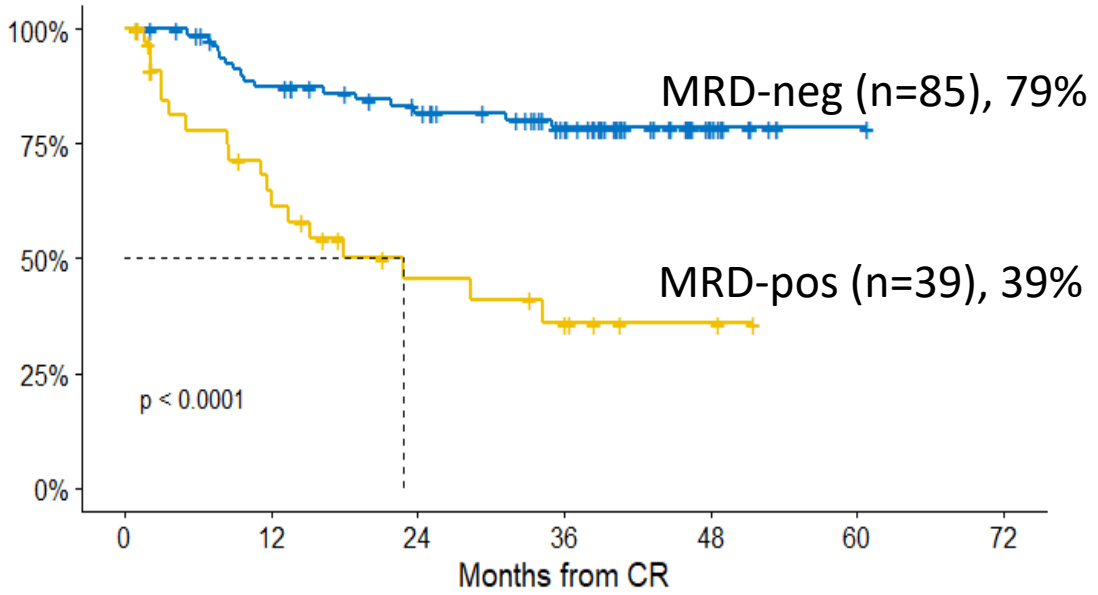


DFS, Disease-free Survival; mFu, Median follow-up; MRD, minimal residual disease, OS, Overall Survival, TP3, time-point 3, y, yeras

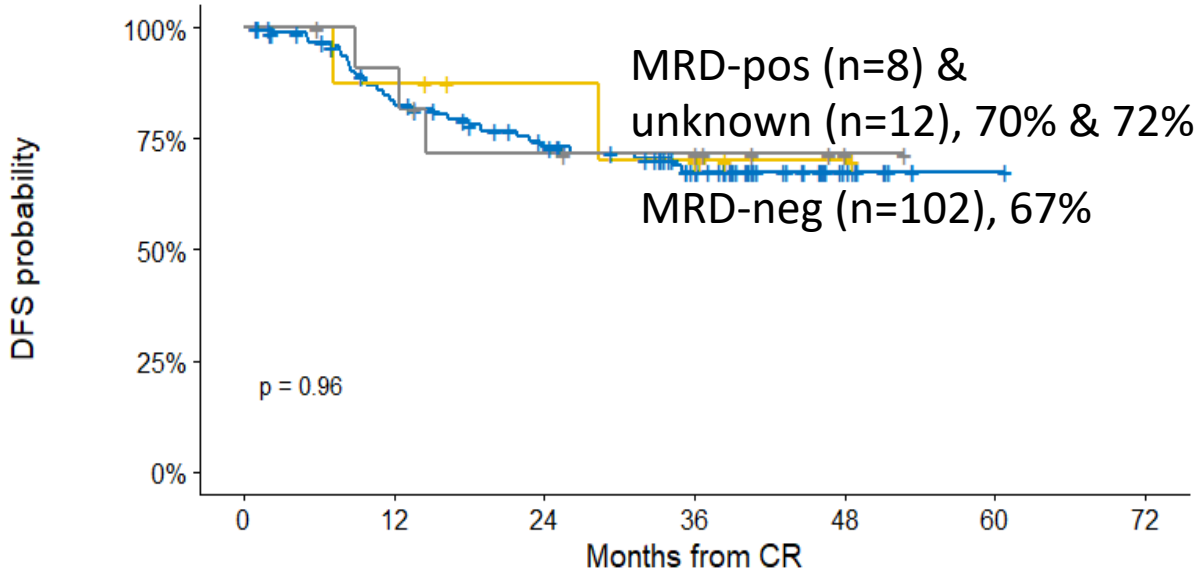
Chiaretti S, et al. ASH 2023 Abs 826; Bassan et al; in submission.

GIMEMA LAL2317: DFS according to MRD

MRD at TP2 (HD3)



MRD at TP3 (blinatumomab 1)

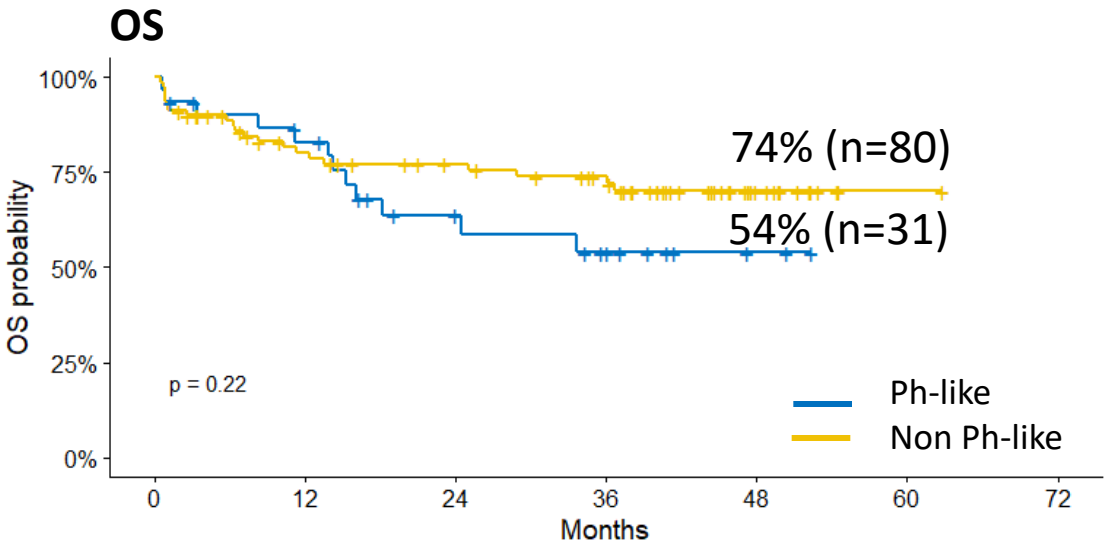


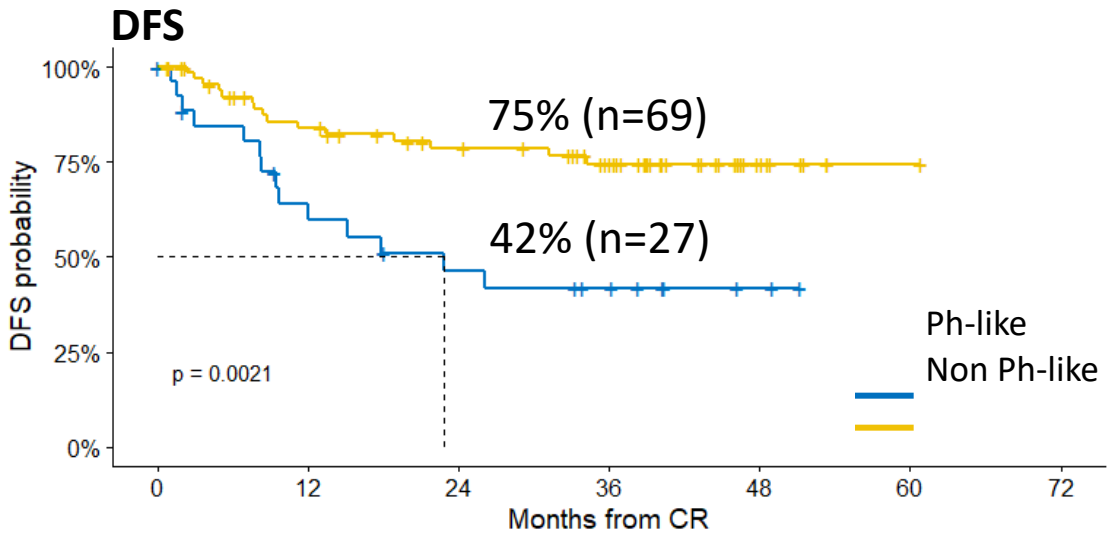
MRD after HD MTX and prior to blinatumomab highly predcitive of DFS

Chiaretti S, et al. ASH 2023 Abs 826; Bassan et al; in submission.

GIMEMA LAL2317: Focus on Ph-like

MRD at TP2 (HD3)	Overall (n=81, %)	Ph-like (n=22, %)	Non Ph-like (n=59, %)
MRD-negative	59 (73)	15 (68)	44 (75)
MRD-positive	22 (27)	7 (32)	15 (25)
MRD at TP3 (blinatumomab #1)	**n (%)**		
MRD-negative	78 (96)	22 (100)	56 (95)
MRD-positive	3 (3.7)	0	3 (5.1)





The NEW ENGLAND JOURNAL of MEDICINE

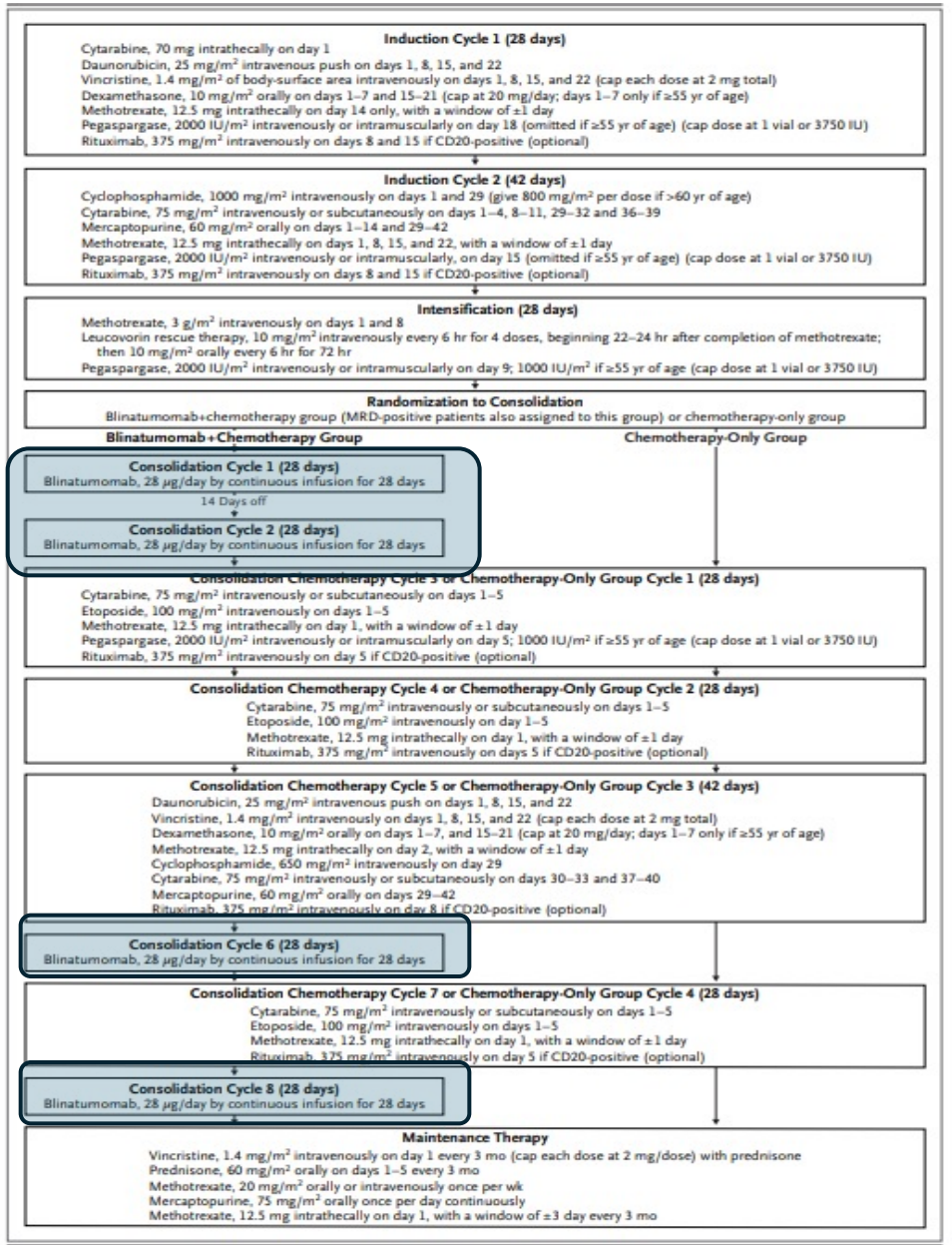
ORIGINAL ARTICLE

Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults

M.R. Litzow, Z. Sun, R.J. Mattison, E.M. Paietta, K.G. Roberts, Y. Zhang, J. Racevskis, H.M. Lazarus, J.M. Rowe, D.A. Arber, M.J. Wieduwilt, M. Liedtke, J. Bergeron, B.L. Wood, Y. Zhao, G. Wu, T.-C. Chang, W. Zhang, K.W. Pratz, S.N. Dinner, N. Frey, S.D. Gore, B. Bhatnagar, E.L. Atallah, G.L. Uy, D. Jeyakumar, T.L. Lin, C.L. Willman, D.J. DeAngelo, S.B. Patel, M.A. Elliott, A.S. Advani, D. Tzachanis, P. Vachhani, R.R. Bhave, E. Sharon, R.F. Little, H.P. Erba, R.M. Stone, S.M. Luger, C.G. Mullighan, and M.S. Tallman

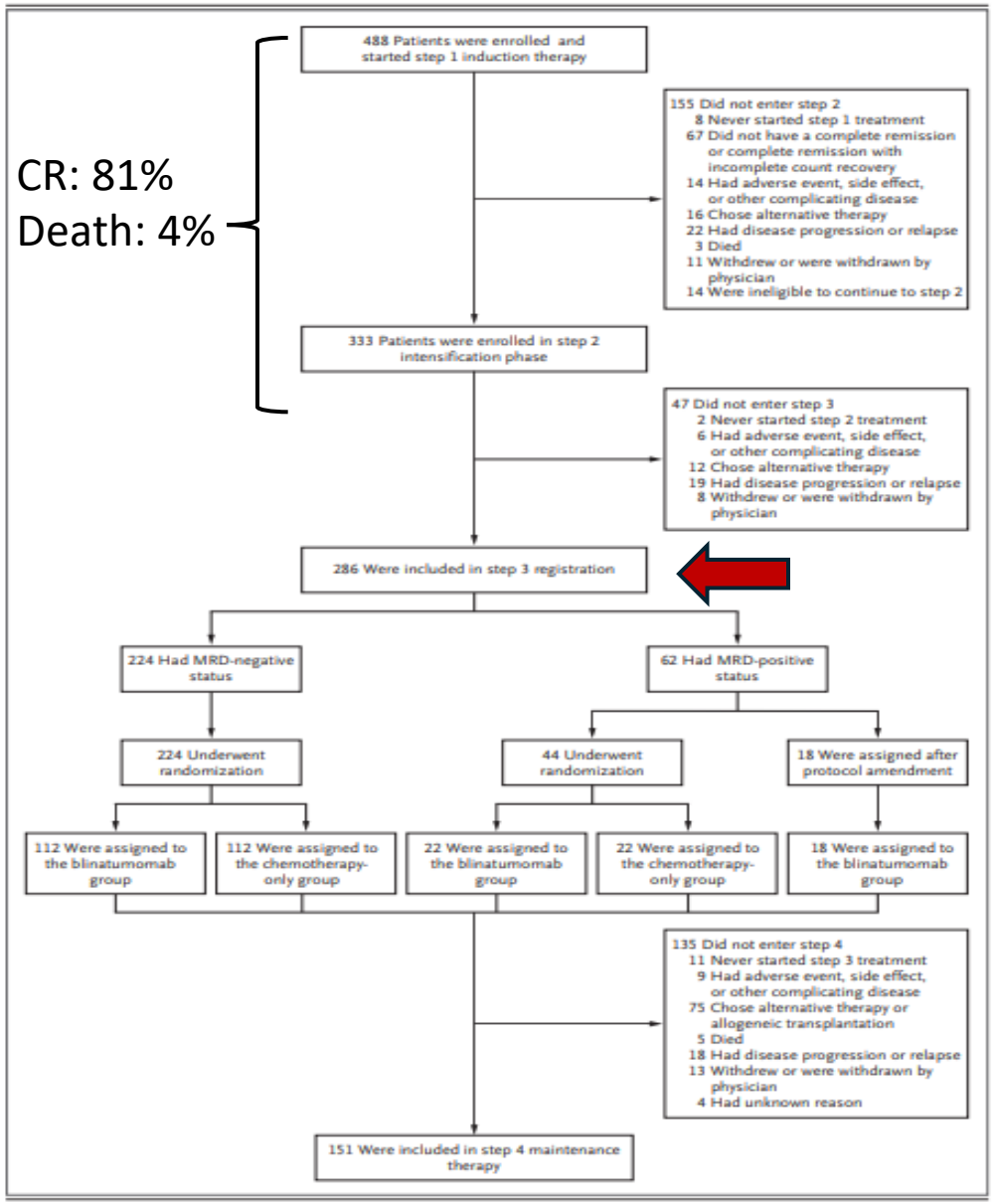
Primary end point: overall survival from the time of randomization, assessed among patients with MRD-negative status.

MRD negativity evaluated by means of flow cytometry.
Cytogenetic and molecular risk definition:
-favorable: *DUX4-r*, high-hyperdiploid, *TCF3::PBX1*, or PAX5 P80R,
-intermediate: PAX5-altered, *PAX5::ETV6*, *MEF2D-r*, *ZNF384-r*
-unfavorable: *KMT2A-r,* low-hypodiploid or near-haploid , BCR::ABL1-like, *BCL2-* or *MYC-r*, *ETV6::RUNX1-like* with *IGH::CRLF2* fusion, and high-hyperdiploid with *BCR::ABL1-like*, *CRLF2-r*



Litzow MR, et al. NEJM 2024

E1910: Patients disposition

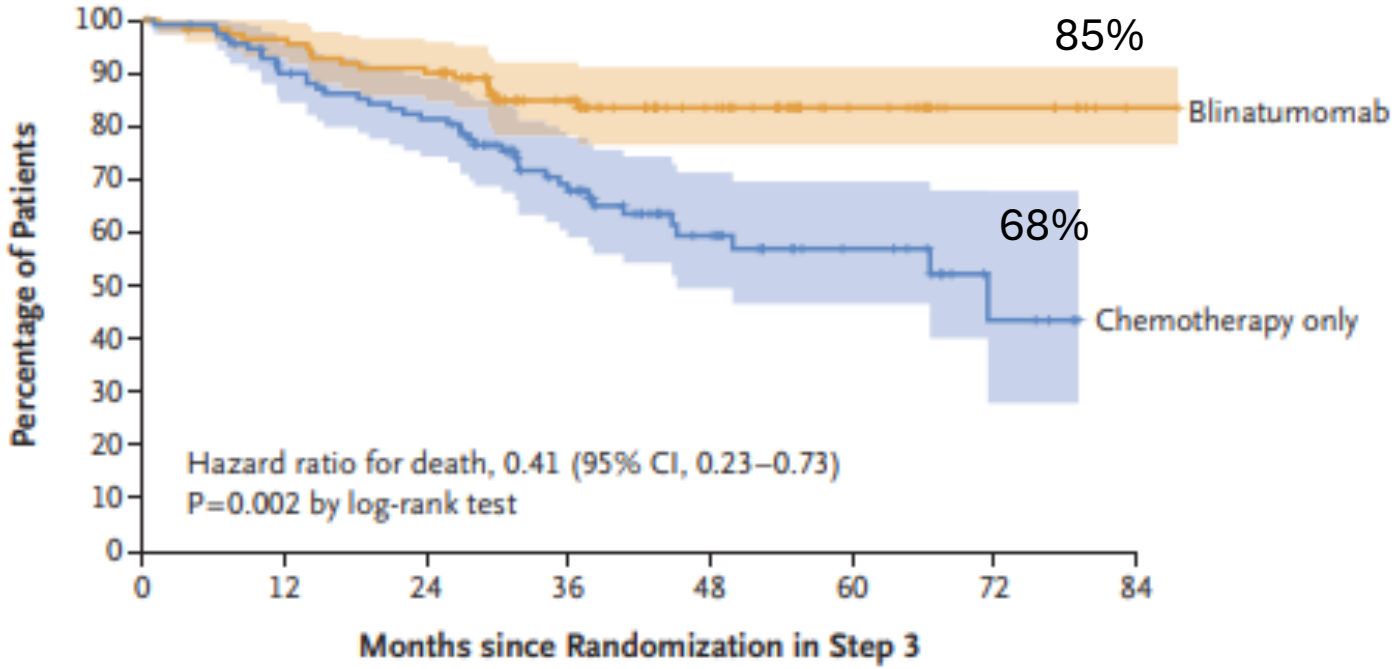


488 patients enrolled; median age: 51 years (range 30-70); 42% >55 yrs.
Median follow-up: 43 months
Pro-B : 15% overall
Unfavorable risk: 57% overall (42% at randomization, n=224)

48 patients did not complete the 4 blinatumomab cycles:

- 26 received an allogeneic transplant
- 4 for toxicity
- 18 patients due to disease progression, patient withdrawal, or other unrelated complications.

E1910: 3-years OS



No. at Risk								
Blinatumomab	112	106	99	65	41	19	8	1
Chemotherapy only	112	96	85	53	28	15	5	0

Transplant performed equally in both arms.
Treatment-related non-hematologic toxicity:
gr. 3 43% vs 36%
gr. 4 in 14% vs 15%
gr. 5 in 2% and 1% in blina vs chemo arm

Figure S4. Overall survival for MRD-negative patients <55 years by treatment arm

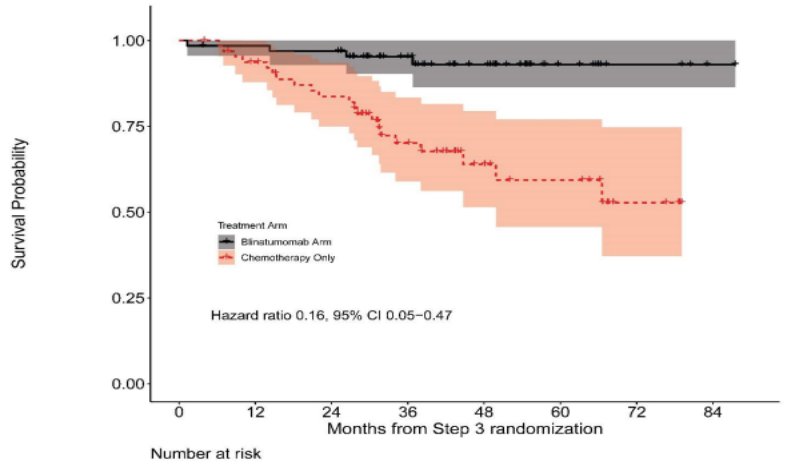
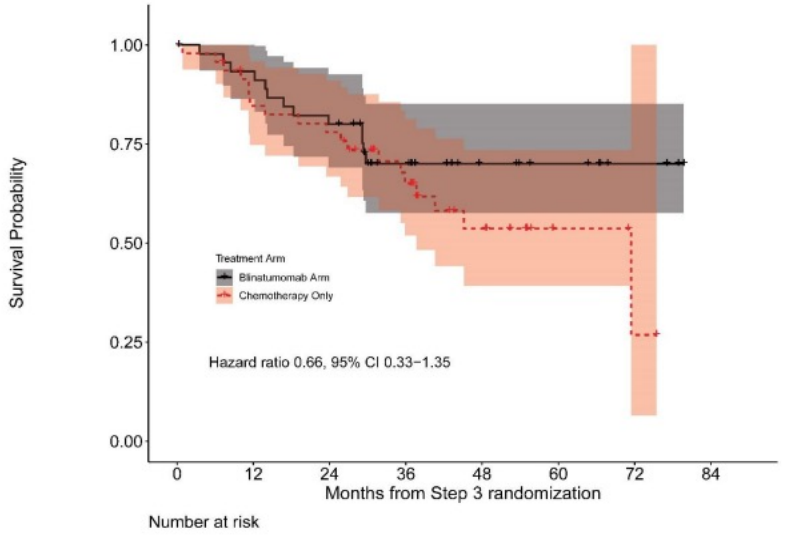


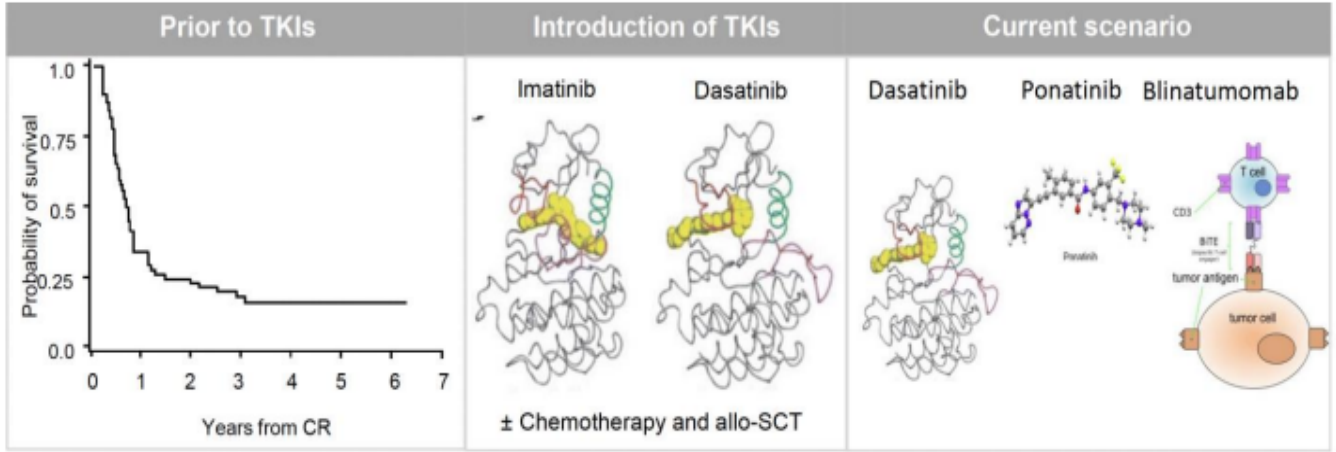
Figure S5. Overall survival for MRD-negative patients ≥55 years by treatment arm



Ph+ ALL: changes over the years

How I Treat Adult Ph-Positive Acute Lymphoblastic Leukemia (ALL)

Ph+ ALL management over the years

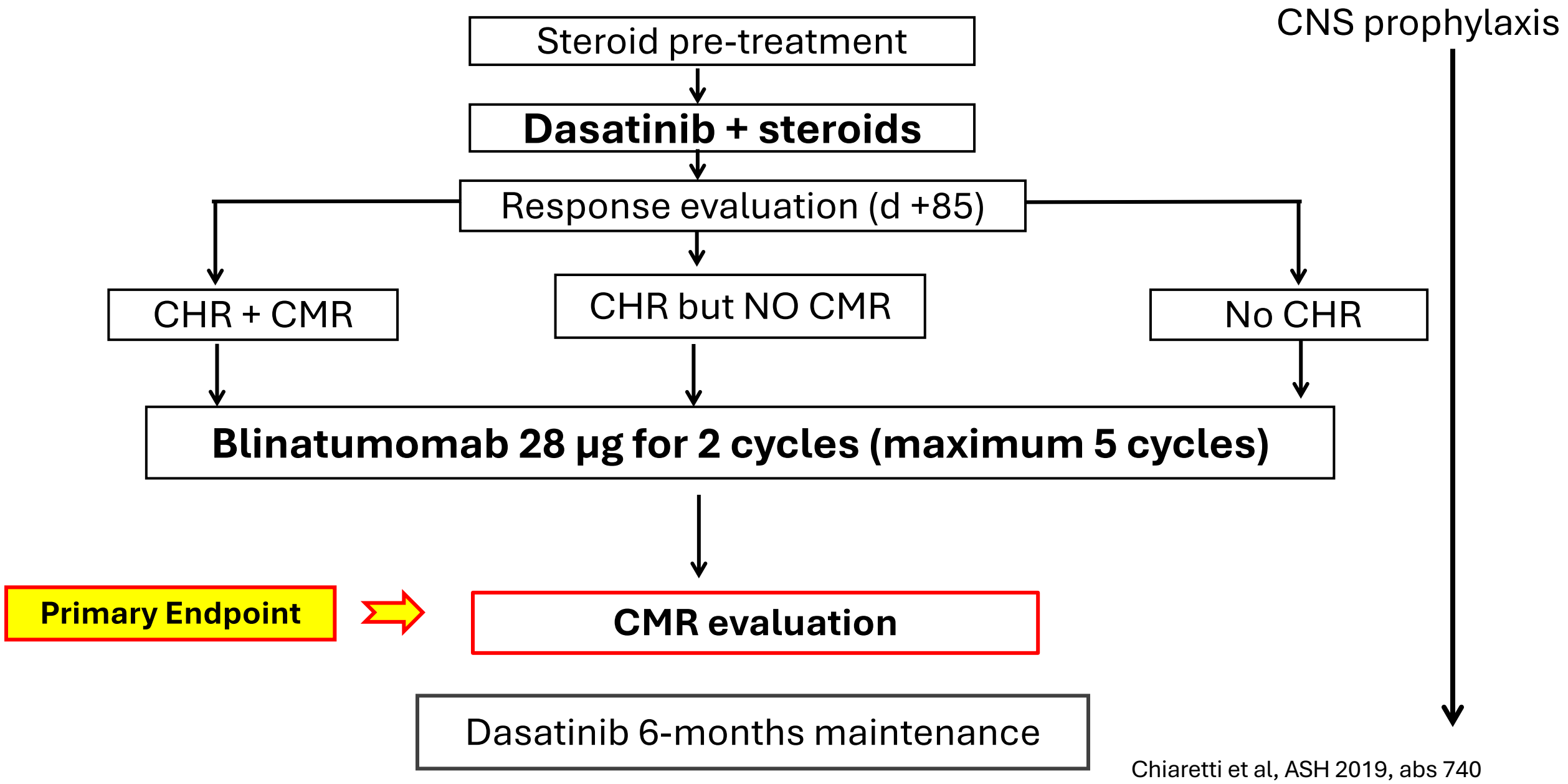


Conclusions: **The outcome and management of Ph+ ALL patients have greatly improved since the incorporation of 1st, 2nd, and 3rd generation TKIs into the therapeutic backbone, and continue to change with the recent introduction of immunotherapy. Meanwhile, new challenges are emerging.**

*Chiaretti & Foà, DOI: 10.xxxx/**blood**.2024xxxxxx*

blood Visual Abstract

D-ALBA: treatment scheme



Chiaretti et al, ASH 2019, abs 740

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2020 VOL. 383 NO. 17

Dasatinib–Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults

Robin Foà, M.D., Renato Bassan, M.D., Antonella Vitale, M.D., Loredana Elia, M.D., Alfonso Piciocchi, M.S., Maria-Cristina Puzzolo, Ph.D., Martina Canichella, M.D., Piera Viero, M.D., Felicetto Ferrara, M.D., Monia Lunghi, M.D., Francesco Fabbiano, M.D., Massimiliano Bonifacio, M.D., Nicola Fracchiolla, M.D., Paolo Di Bartolomeo, M.D., Alessandra Mancino, M.S., Maria-Stefania De Propris, Ph.D., Marco Vignetti, M.D., Anna Guarini, Ph.D., Alessandro Rambaldi, M.D., and Sabina Chiaretti, M.D., Ph.D., for the GIMEMA Investigators*

- At the primary endpoint (after 2 cycles of Blinatumomab), molecular responses were recorded in 60% of cases
- OS was 95%
- DFS was 88%
- *IKZF1*^{plus} cases emerged as the subset with the worse DFS

Median follow-up: 18 months

Foà et al, NEJM 2020; 383(17):1613-1623

D-ALBA: updated molecular responses

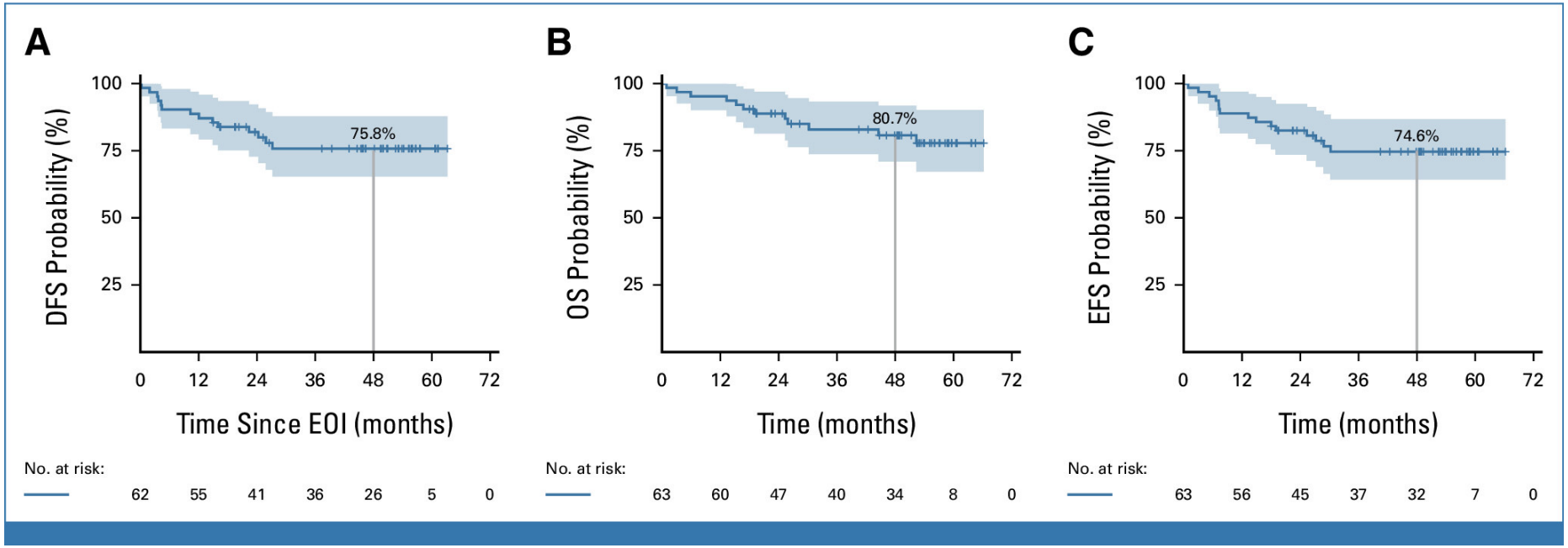
	No molecular response (%)	CMR	PNQ	Overall molecular response (%)
Day 85	42/59 (71)	6/59	11/59	17/59 (**29**)
After cycle II	22/55 (40)	23/55	10/55	33/55 **(60)**
After cycle III	12/40 (30)	20/40	8/40	28/40 **(70)**
After cycle IV	7/36 (19)	17/36	12/36	29/36 **(81)**
After cycle V	8/29 (19)	16/29	5/29	21/29 **(72)**

	Overall molecular responses (%)*
3rd month follow-up	**77**
6th month follow-up	**77**
9th month follow-up	**95**
12th month follow-up	**89**

* Carried out in a subset of the whole population

Chiaretti et al, EHA 2022 P353

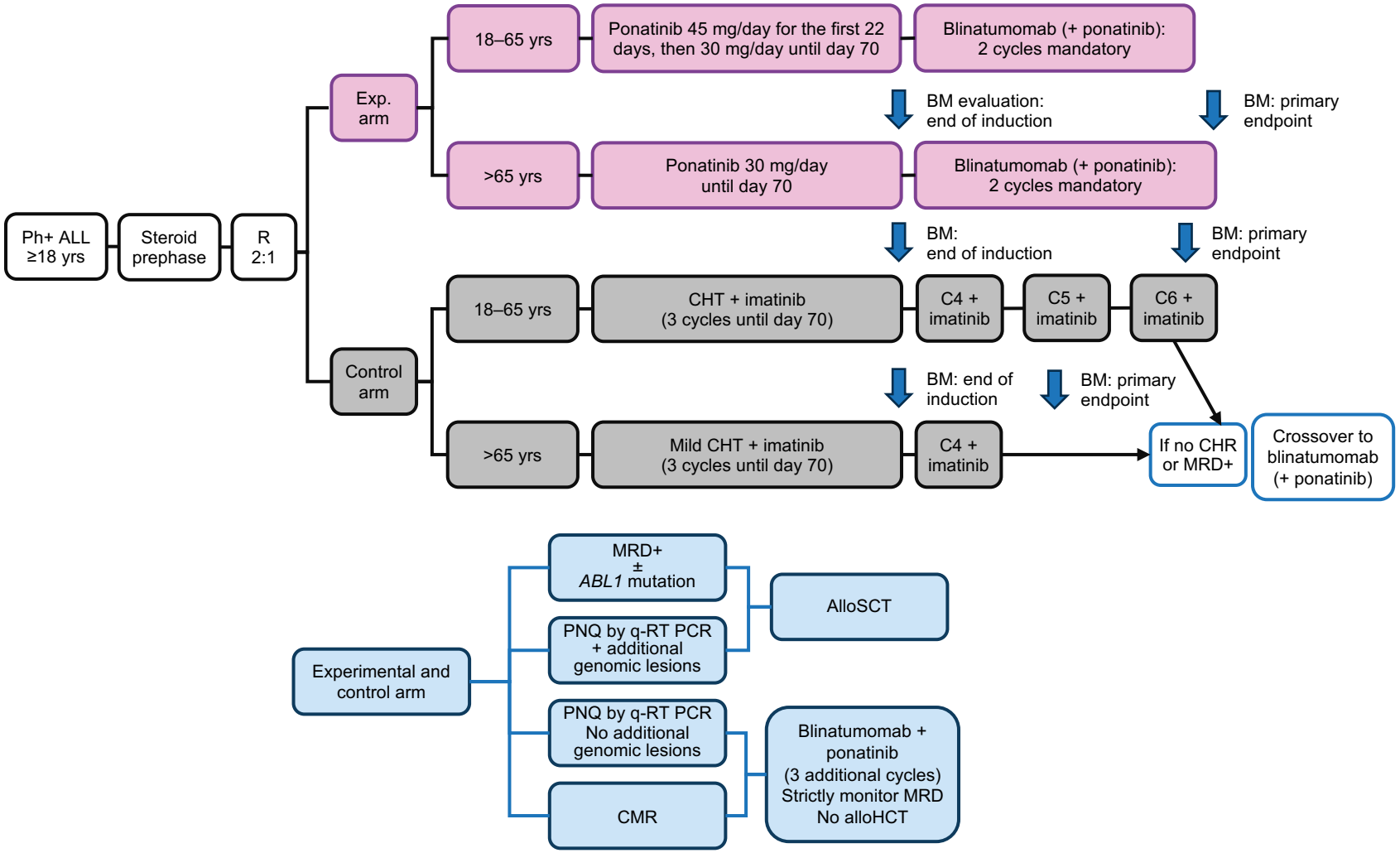
D-ALBA: Long-Term results

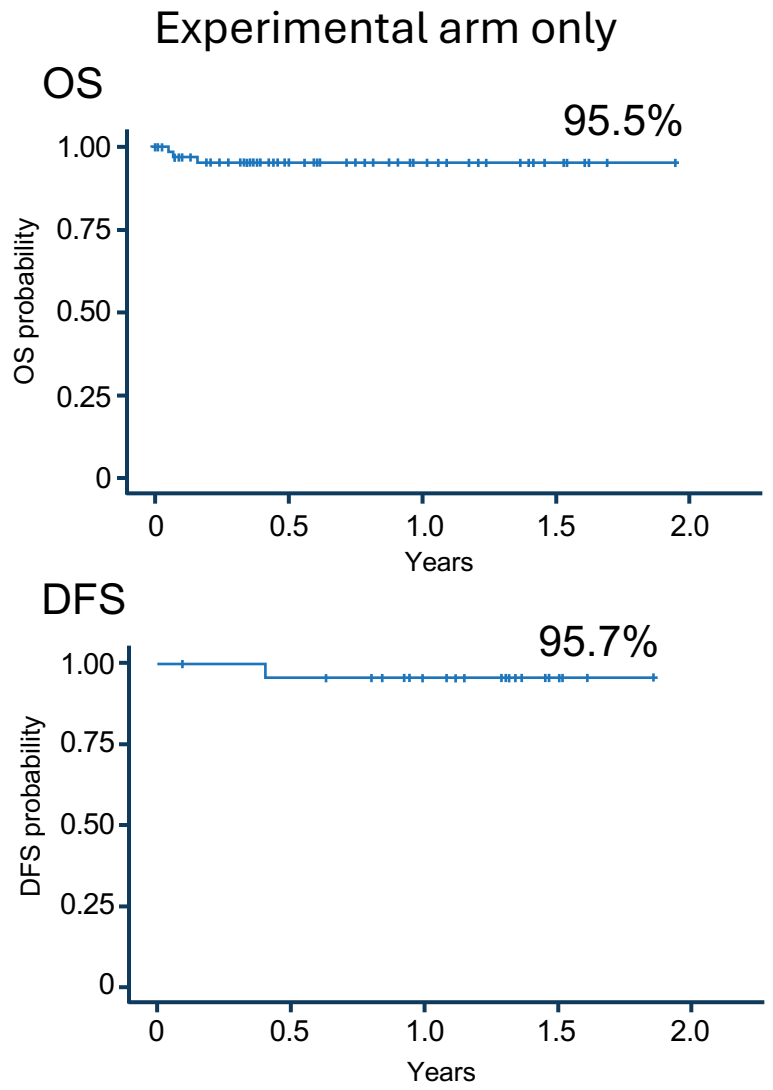


At a median follow-up of 53 months, DFS, OS and EFS are **75.8% , 80.7%** and **74.6%** respectively.

Foà R, et al. JCO 2024

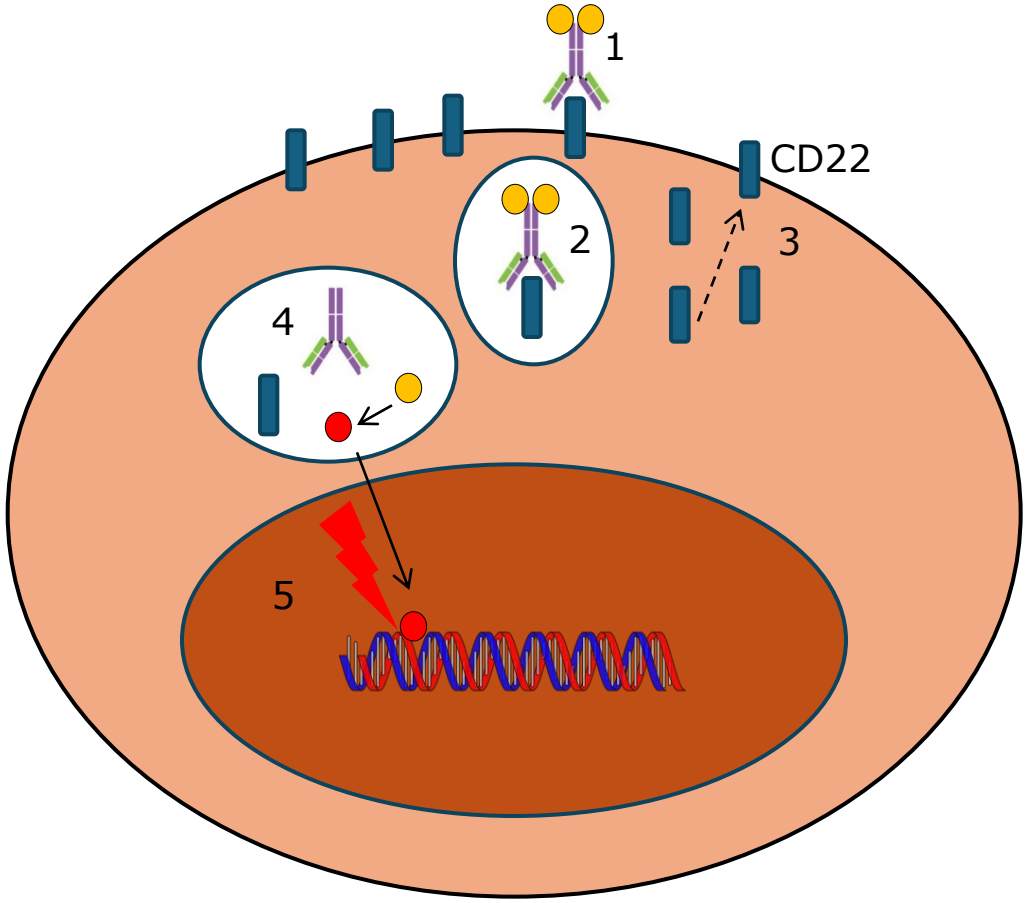
GIMEMA ALL2820: Ponatinib-blinatumomab frontline

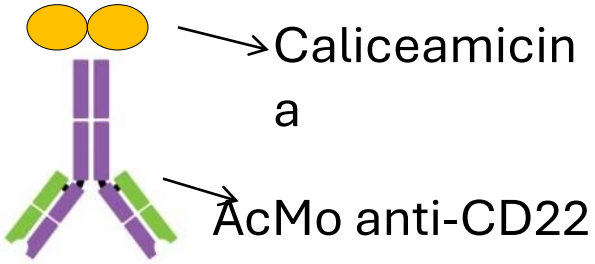




Chiaretti S, et al. ASH 2023; Abstract 4249.

Inotuzumab Ozogamicin





Tower study (Kantarjian et al, NEJM 2016)
CR : 80.7%

Allo-SCT: 41%

Caveat :VOD

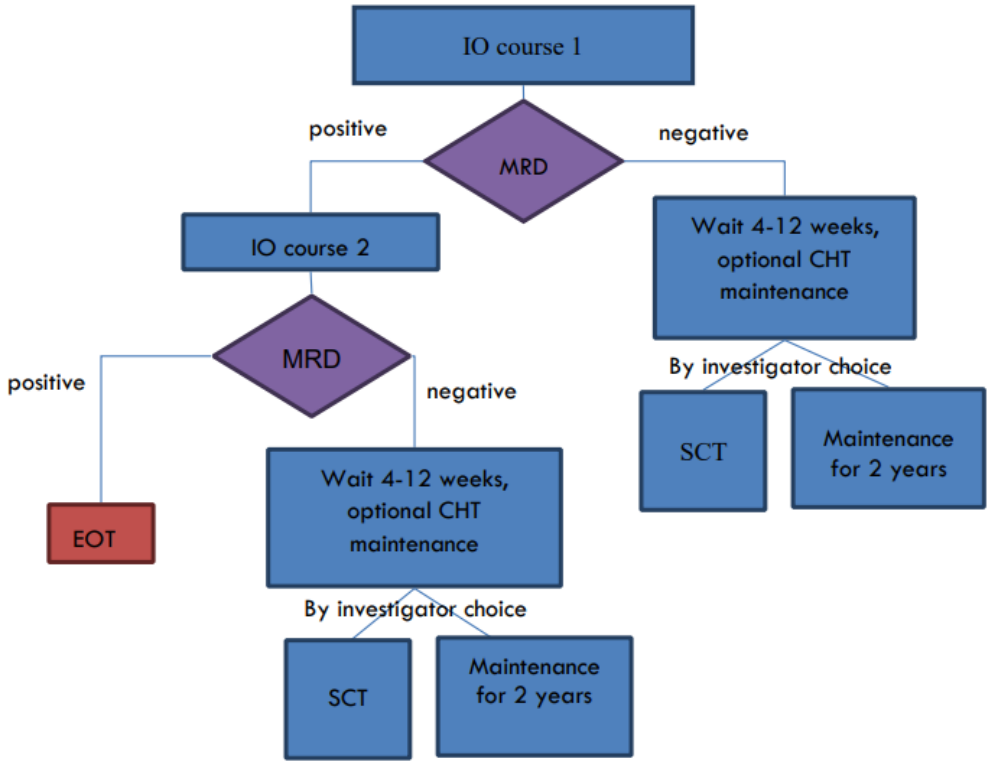
Inotuzumab in the MRD setting

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

A Phase IIA Study of Feasibility and Effectiveness of Inotuzumab Ozogamicin (IO) in Adult Patients with B-Cell Acute Lymphoblastic Leukemia with positive Minimal Residual Disease before any Hematopoietic Stem Cell Transplantation

GIMEMA Study ALL2418

EudraCT number 2018-003006-32
NCT number 03610438

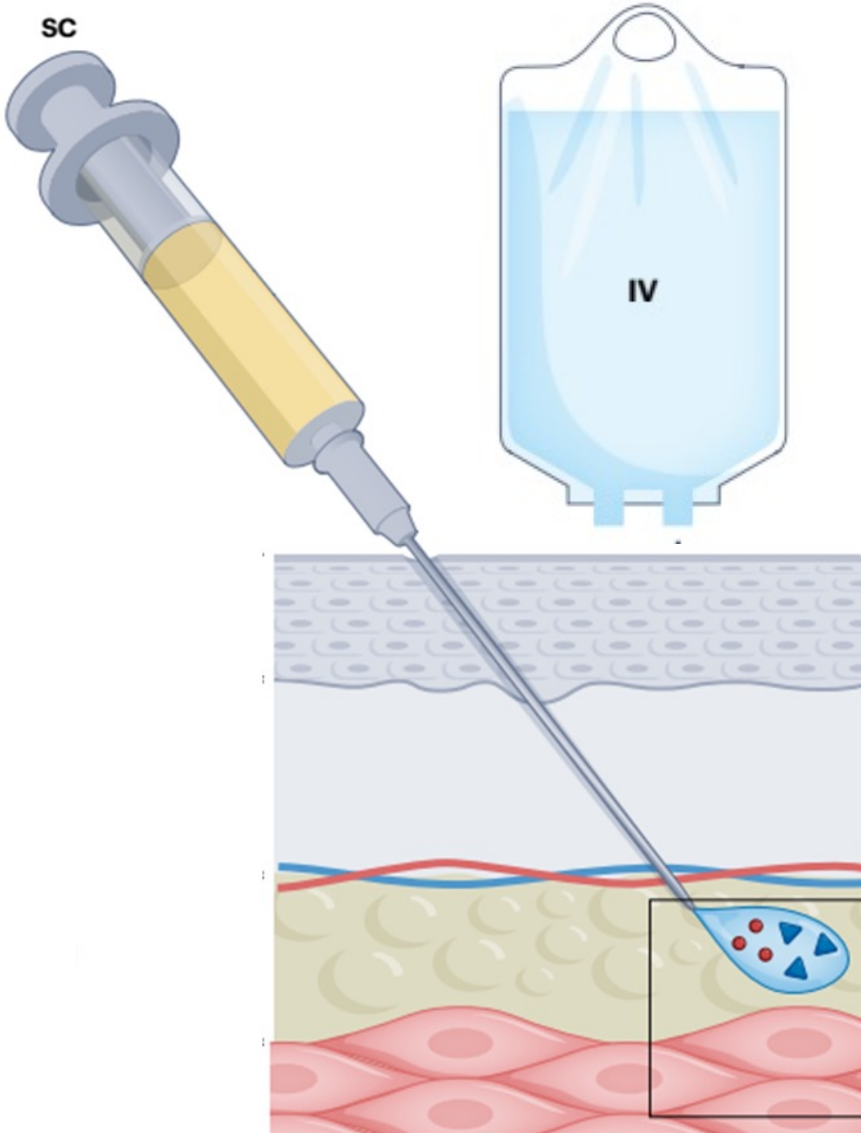


For both Ph+ and Ph- ALL, enrolling

Conclusions

- In the front-line setting, significant advantage in adding immunotherapy regardless of age, phenotype and genetic/molecular features ALSO IN MRD NEGATIVE PATIENTS
- Next steps: Moving immunotherapy in early phases appears the optimal strategy (new drugs formulation)
- Significant chemotherapy burden reduction: possibly the next frontier

Subcutaneous (SC) blinatumomab



Blinatumomab as a continuous IV infusion is a standard treatment regimen utilized in patients with R/R B-ALL

Higher doses to improve efficacy and simplify administration

Can simplify administration, improve convenience, reduce treatment burden, and decrease cost for patients

Eliminate the need for a central line or continuous venous access and an infusion device (pump)

Abrogate the risk of device-related complications such as overdose caused by incorrect pump settings and dose interruptions from intravenous line occlusion

Deliver the target dose earlier (cycle 1, day 1) and over all a higher dose of blinatumomab to patients

Improve overall health health-related quality of life of the patients

Martinez Sanchez, P et al. Presented at: 64th Annual Meeting of the American Society of Hematology: December 10-13, 2022; New Orleans, LA. Poster 2727. B-ALL, B-cell precursor acute lymphoblastic leukemia; BiTE, bispecific T-cell engager; CD, cluster of differentiation; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; R/R, relapsed/refractory; SC, subcutaneous.1. Jabbour E, et al. Am J Hematol. 2024;99:586–595

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Maria Stefania De Propris
Maurizio Martelli
Antonella Vitale
Mariangela Di Trani
Anna Guarini
Alessandro Rambaldi
Renato Bassan
Robin Foà

GIMEMA Centers

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Alfonso Piciocchi
Monica Messina
Valentina Arena
Stefano Soddu
Paola Fazi
Marco Vignetti

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X AIRC = RICERCA