ALGORITMO TERAPEUTICO NELLA LEUCEMIA LINFOBLASTICA ACUTA

Dott.ssa Saveria Capria
AOU Policlinico Umberto I
Roma

Acute lymphoblastic leukemia ……the past

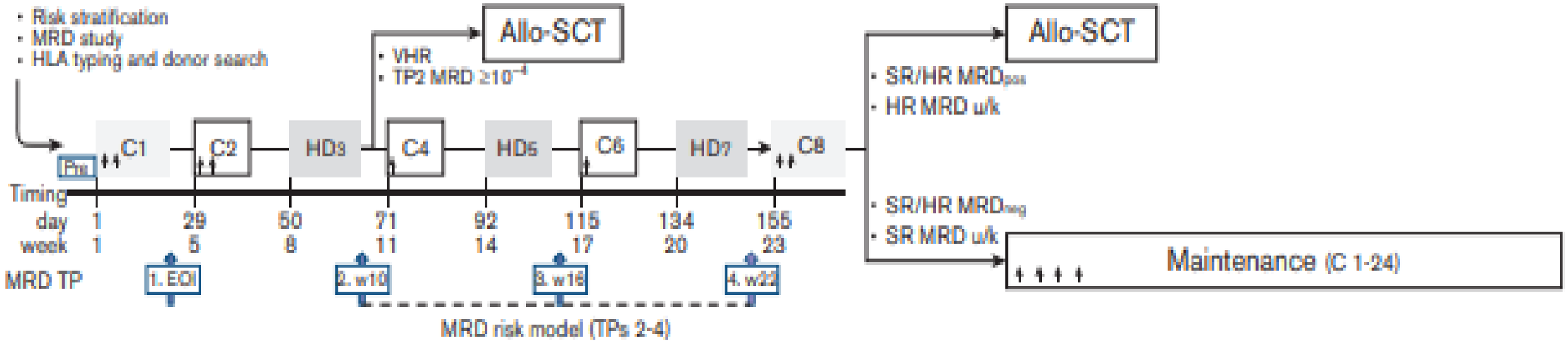
Study	Year	N	Median Age, yr (range)	SCT	CR Rate	Early Death	Survival
CALGB 9111, USA[6]	1998	198	35 (16-83)	Ph+	85%	8%	40% (3 yr)
LALA 87, France[1]	2000	572	33 (15-60)	PO	76%	9%	27% (10 yr)
NILG 08/96, Italy[8]	2001	121	35 (15-74)	PR	84%	8%	48% (5 yr)
GMALL 05/93, Germany[9],†	2001	1,163	35 (15-65)	PR	83%	NR	35% (5 yr)
JALSG-ALL93, Japan[2]	2002	263	31 (15-59)	PO	78%	6%	30% (6 yr)
UCLA, USA[10]	2002	84	27 (16-59)	PR	93%	1%	47% (5 yr)
Sweden[11]	2002	153	42 (16-82)	PR	75%	NR	28% (5 yr)
GIMEMA 0288, Italy[13]	2002	767	28 (12-60)	NR	82%	11%	27% (9 yr)
MD Anderson, USA[7]	2004	288	40 (15-92)	Ph+	92%	5%	38% (5 yr)
EORTC ALL-3, Europe[3]	2004	340	33 (14-79)	PO	74%	NR	36%* (6 yr)
LALA 94, France[12]	2004	922	33 (15-55)	PR	84%	5%	36% (5 yr)
GOELAL02, France[14]	2004	198	33 (15-59)	HR	86%	2%	41% (6 yr)
MRC XII/ ECOG E 2993, UK-USA[4]	2005	1,521	15-59	PO	91%	NR	38% (5 yr)
GIMEMA 0496, Italy[15],†	2005	450	16-60	NR	80%	NR	33% (5 yr)
Pethema ALL-93, Spain[16]	2005	222	27 (15-50)	HR	82%	6%	34% (5 yr)
JCOG-9004[5]	2007	143	41 (>64)	PO	83%	10%	32% (5y)
GMALL 07/03[17],†	2007	713	34 (15-55)	PR	89%	5%	54% (5y)
Weighted mean		7,405			84%	7%	35%

Hoelzer et al. Seminars in hematology 2009

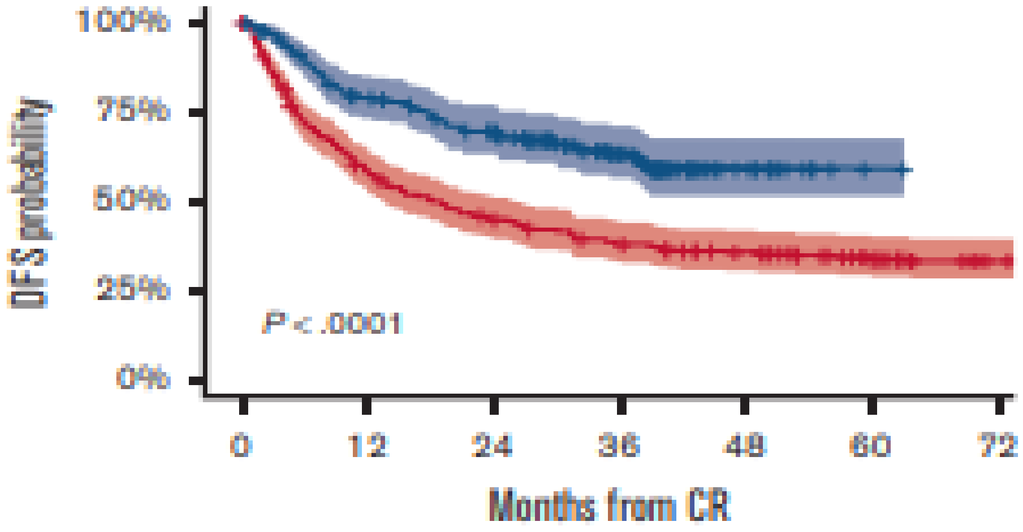
CR rate around 80% but long-term survival unsatisfactory

B and T ALL CHT backbone

GIMEMA LAL 1913



- Case-specific risk classification with early MRD evaluation (all patients)
- Allogeneic SCT for all VHR cases
- Risk-oriented allogeneic SCT for MRD-positive SR/HR patients, the risk being primarily defined by MRD analysis



Optimal selection of frontline therapy pivotal for preventing disease relapse and limiting long-term toxicities

Basic principles

- Age, ALL subtype
- Ph chromosome status and other genetic subgroups
- CNS involvement
- WBC count
- PDN response

New concepts

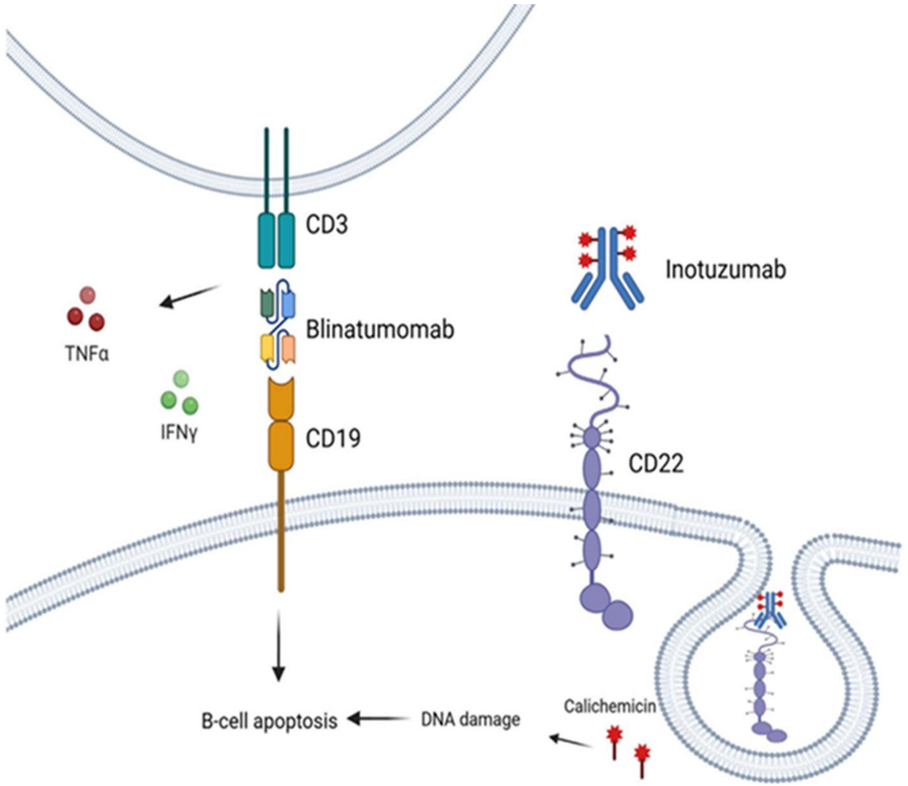
- Time to treatment response (disease burden)
- MRD evaluation
- Risk-stratified HSCT
- Availability of target drugs
- Immunotherapy

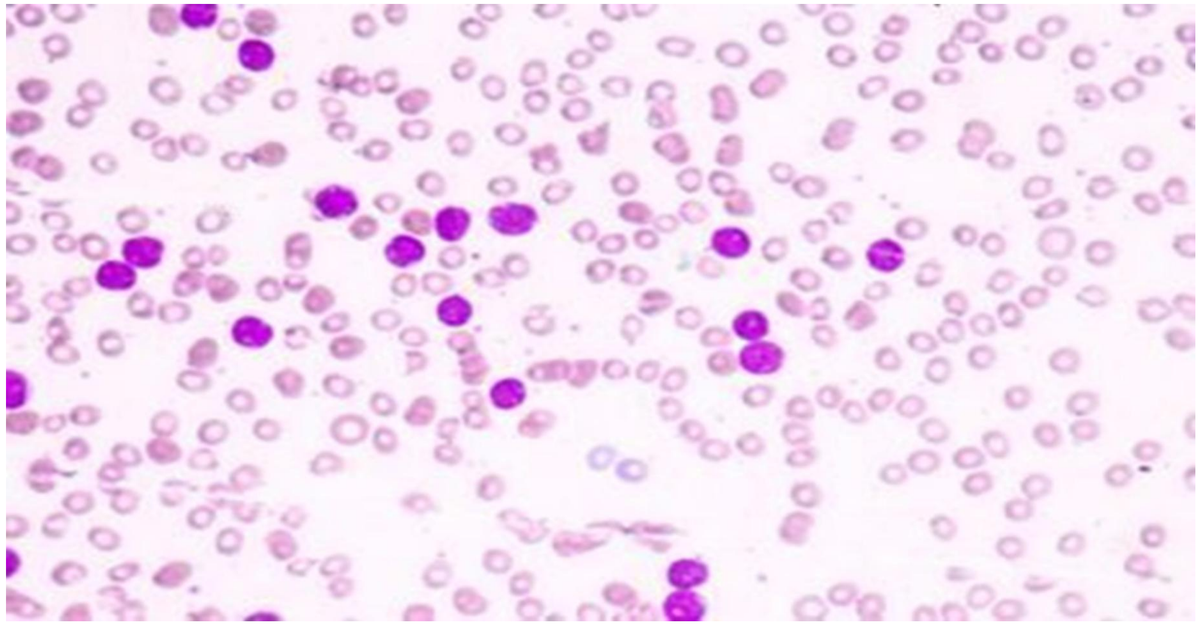
B-ALL: Novel targeted immunotherapy

Blinatumomab, Inotuzumab, CAR-T cells

- Promising results in the R/R setting and currently anticipated in the early phases of the disease
- High response rates and measurable residual disease negativity
- Greater likelyhood of proceeding to HSCT
- Well tolerated, not limited to younger and fit patients

How to choose?

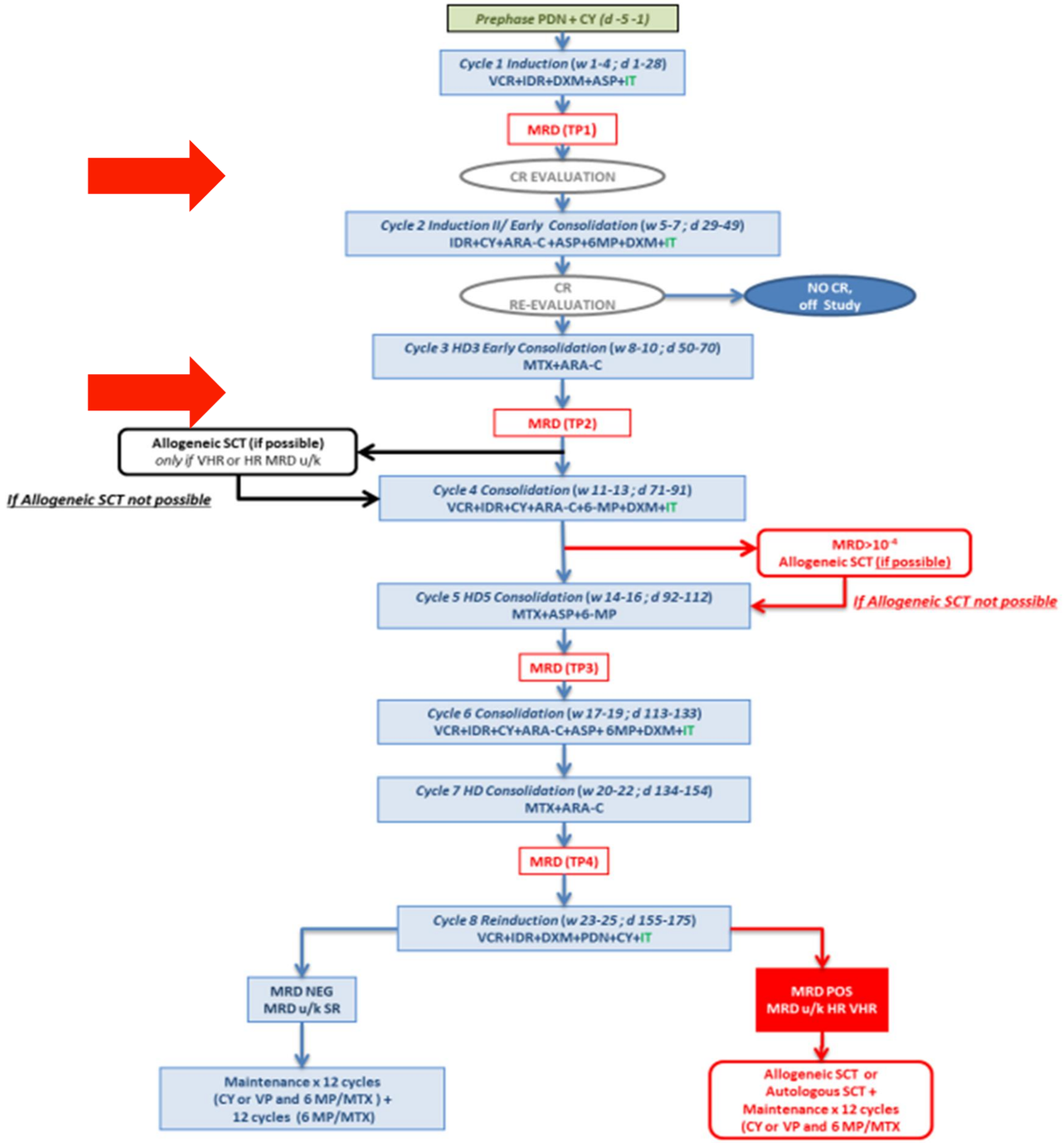




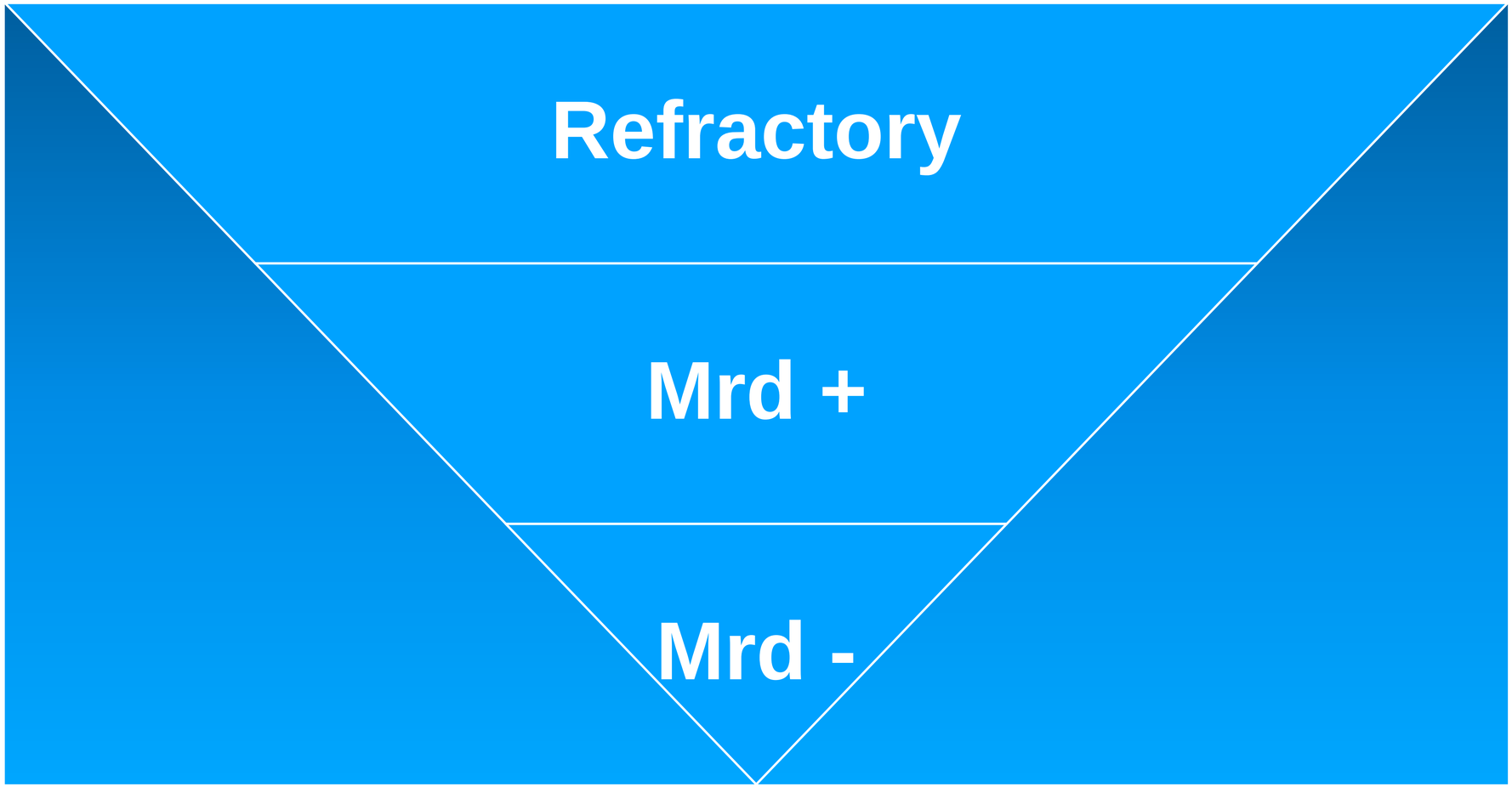
- Optimal drug
- Optimal sequence
- Optimal timepoint

GIMEMA LAL 1913

- Induction (vincristine, anthracyclines, corticosteroids, asparaginase and cyclophosphamide)
- Consolidation (vincristine, anthracyclines, corticosteroids, asparaginase, cyclophosphamide, antimetabolites)
- CNS prophylaxis (IT and systemic HD-MTX)
- Reinduction?
- Maintenance (daily antimetabolites and weekly MTX, vincristine pulses)



Timepoint 1/2



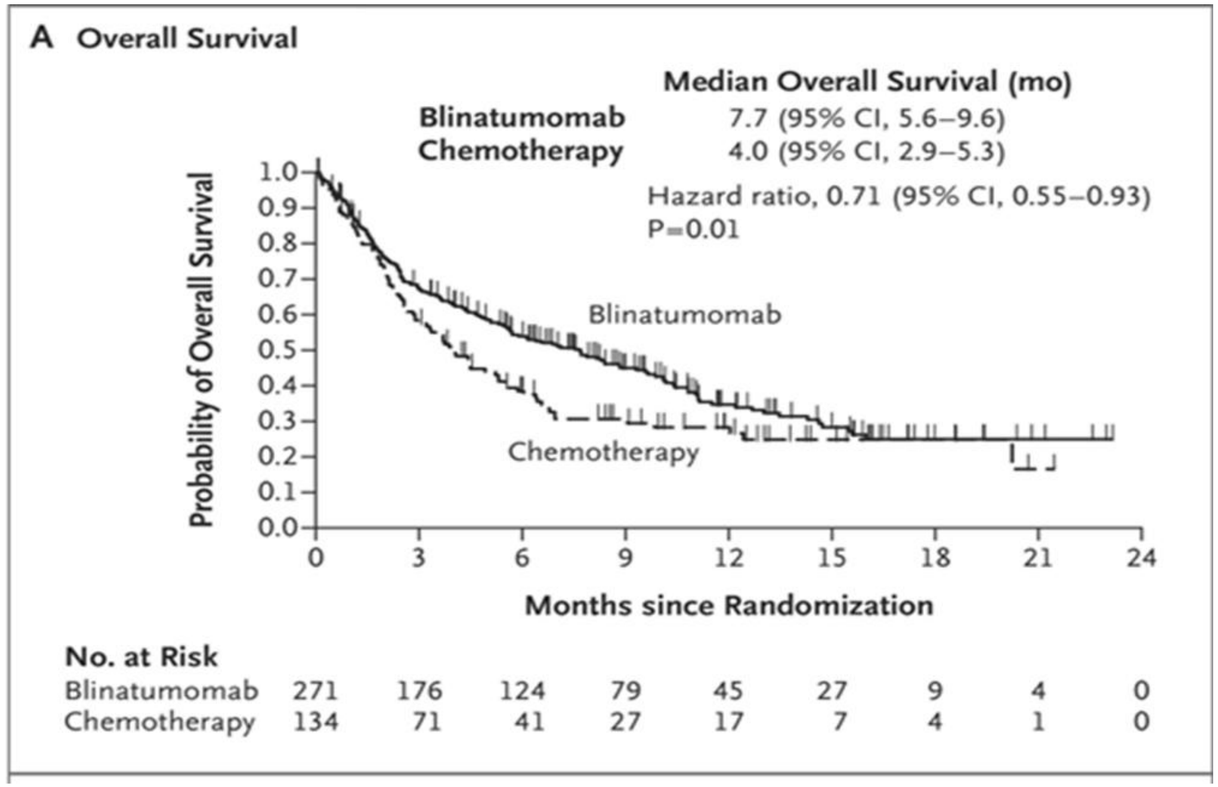
Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study

Topp et al Lancet Oncol 2015

	Patients	Proportion (95% CI)
CR or CRh during the first two cycles	81/189	43% (36–50)
Best response during the first two cycles*		
CR	63/189	33% (27–41)
CRh	18/189	10% (6–15)
No response to therapy†	90/189	48%
Not evaluable‡	18/189	10%
Allogeneic HSCT after CR or CRh	32/81	40%
Allogeneic HSCT after CR	28/63	44%
Allogeneic HSCT after CRh	4/18	22%
100-day mortality from day of HSCT	..	11% (0–23)
MRD response during first two cycles in patients with CR or CRh§	60/73	82% (72–90)

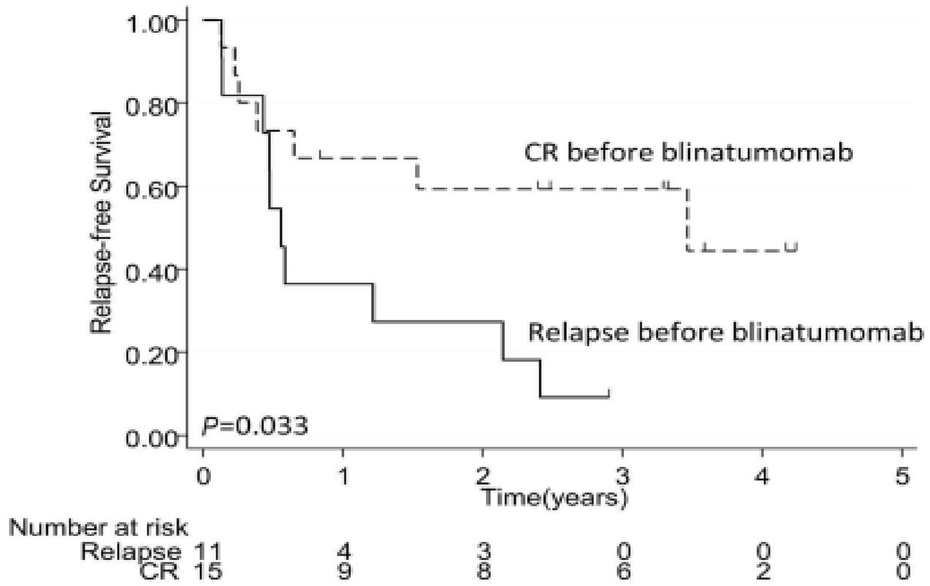
Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia

H Kantarjan NEJM 2017



Blinatumomab main challenges

High tumor burden before blinatumomab has a negative impact on the outcome of adult patients with B-cell precursor acute lymphoblastic leukemia. A real-world study by the GRAALL



Cabannes-Hamy Haematologica 2022

Single agent subcutaneous blinatumomab for advanced acute lymphoblastic leukemia

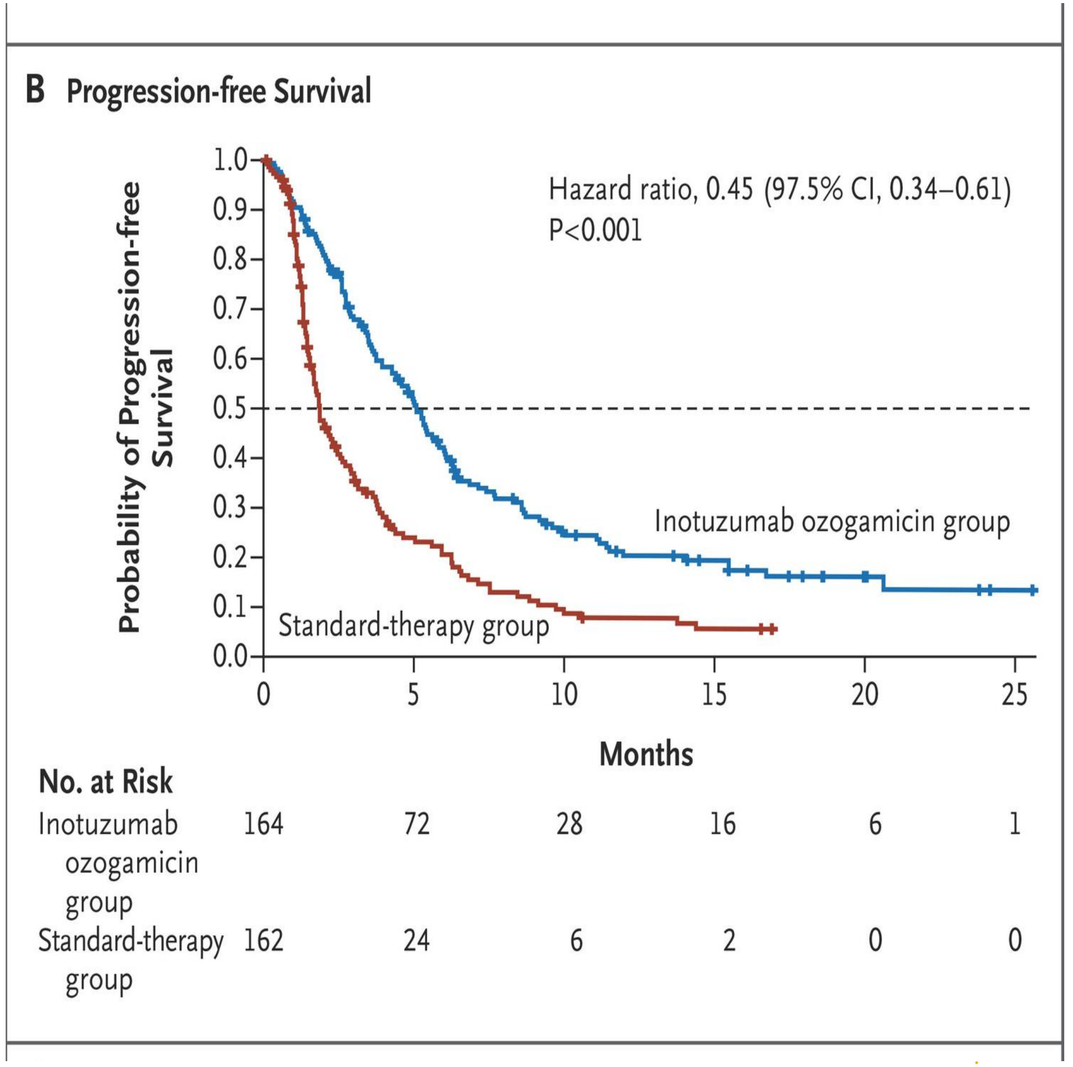
- a global, multicenter phase 1b trial in heavily pretreated adults with R/R B-ALL to determine the safety, efficacy, and pharmacokinetics (PK) of SC blinatumomab
- The subcutaneous (SC) delivery of blinatumomab was developed to evaluate higher doses aiming to further improve efficacy and simplify administration to enhance convenience for patients.
- Treatment with SC blinatumomab resulted in high efficacy, with high MRD-negativity rates and acceptable safety profile in heavily pretreated adults with R/R B-ALL.

Am J Haematol 2024

Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

kantarjan NEJM 2016

- Significant advantage in OS and PFS compared to the chemotherapy arm
- MRD negative through flow cytometry 78% vs 28%
- Efficacy confirmed also in patients with high baseline disease burden with no impact on the safety profile
- Main challenge: short duration of response when employed as single agent.
- VOD still a concern but more manageable with current strategies



CHIMERIC ANTIGEN RECEPTOR T CELLS

- **Tisagenlecleucel (Tisa-cel)**, Kymriah: the first CART medication approved for those patients up to 25 years of age with refractory, post-transplant relapse or second/subsequent relapse. (ELIANA trial 2017)

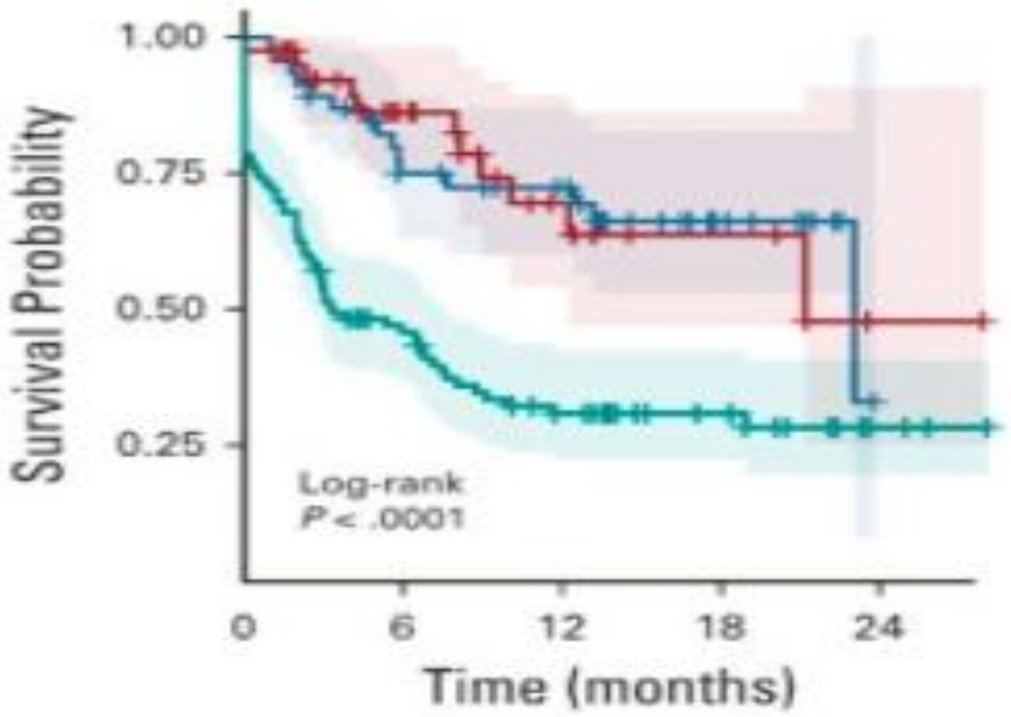
- CR rate and concomitant MRD negativity of 82% in children and young adults

Brexucabtagene autoleucel (Brexu-cel),Tecartus: now approved for the treatment of R/R ALL patients of 26 years of age or more (ZUMA III trial 2021)

- Survival outcomes favorably comparing with those achieved with blinatumomab and inotuzumab

Disease Burden Affects Outcomes in Pediatric and Young Adult B-Cell Lymphoblastic Leukemia After Commercial Tisagenlecleucel: A Pediatric Real-World Chimeric Antigen Receptor Consortium Report

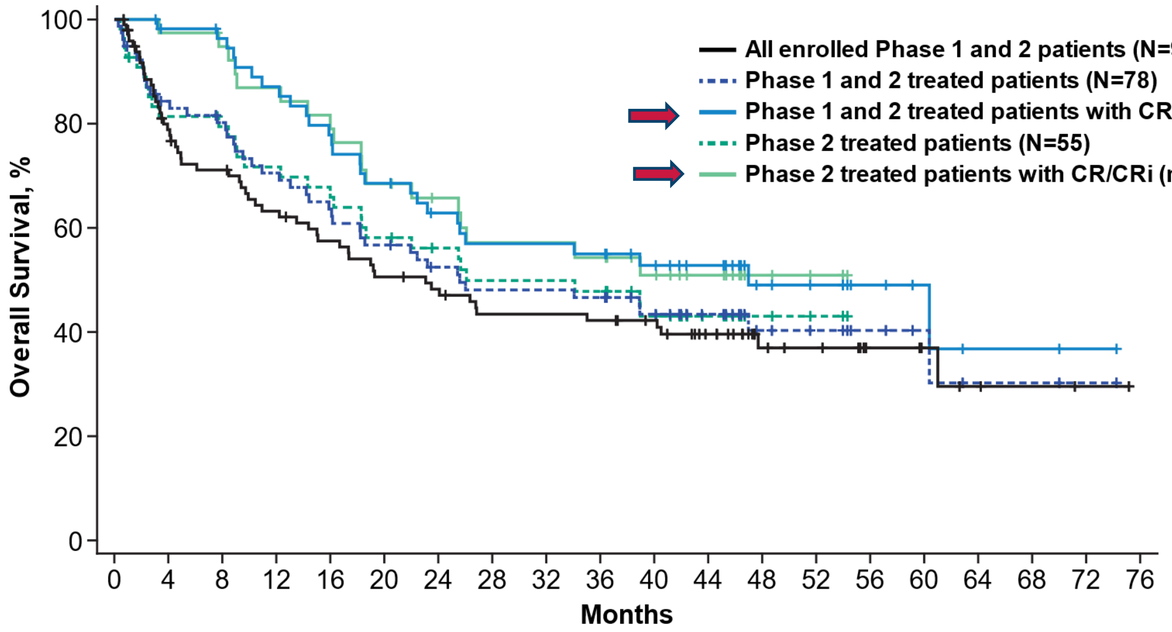
Schultz et al.Jco 2022



Patients entering tisagenlecleucel with high-disease burden are identified as a high-risk patient population who may benefit from further interventional strategies to consolidate chimeric antigen receptor–mediated outcomes

ZUMA-3: OS update

Median follow-up: > 43.5 months



	Median (95% CI), mo
All enrolled Phase 1 and 2 patients (N=99)	23.1 (14.4-40.5)
Phase 1 and 2 treated patients (N=78)	25.6 (16.2-60.4)
Phase 1 and 2 treated patients with CR/CRi (n=57)	47.0 (23.2-NE)
Phase 2 treated patients (N=55)	26.0 (16.2-NE)
Phase 2 treated patients with CR/CRi (n=39)	NR (21.9-NE)

Patients at risk

All enrolled Phase 1 and 2 patients	99	72	64	56	50	44	41	36	36	35	32	25	14	12	7	5	3	2	1	0
Phase 1 and 2 treated patients	78	62	58	51	46	41	36	33	33	32	27	20	12	10	6	4	2	2	1	0
Phase 1 and 2 treated patients with CR/CRi	57	54	52	47	42	37	32	29	29	28	24	20	12	10	6	4	2	2	1	0
Phase 2 treated patients	55	43	41	37	34	30	27	24	24	23	18	11	5	3	0					
Phase 2 treated patients with CR/CRi	39	38	36	33	30	26	23	20	20	19	15	11	5	3	0					

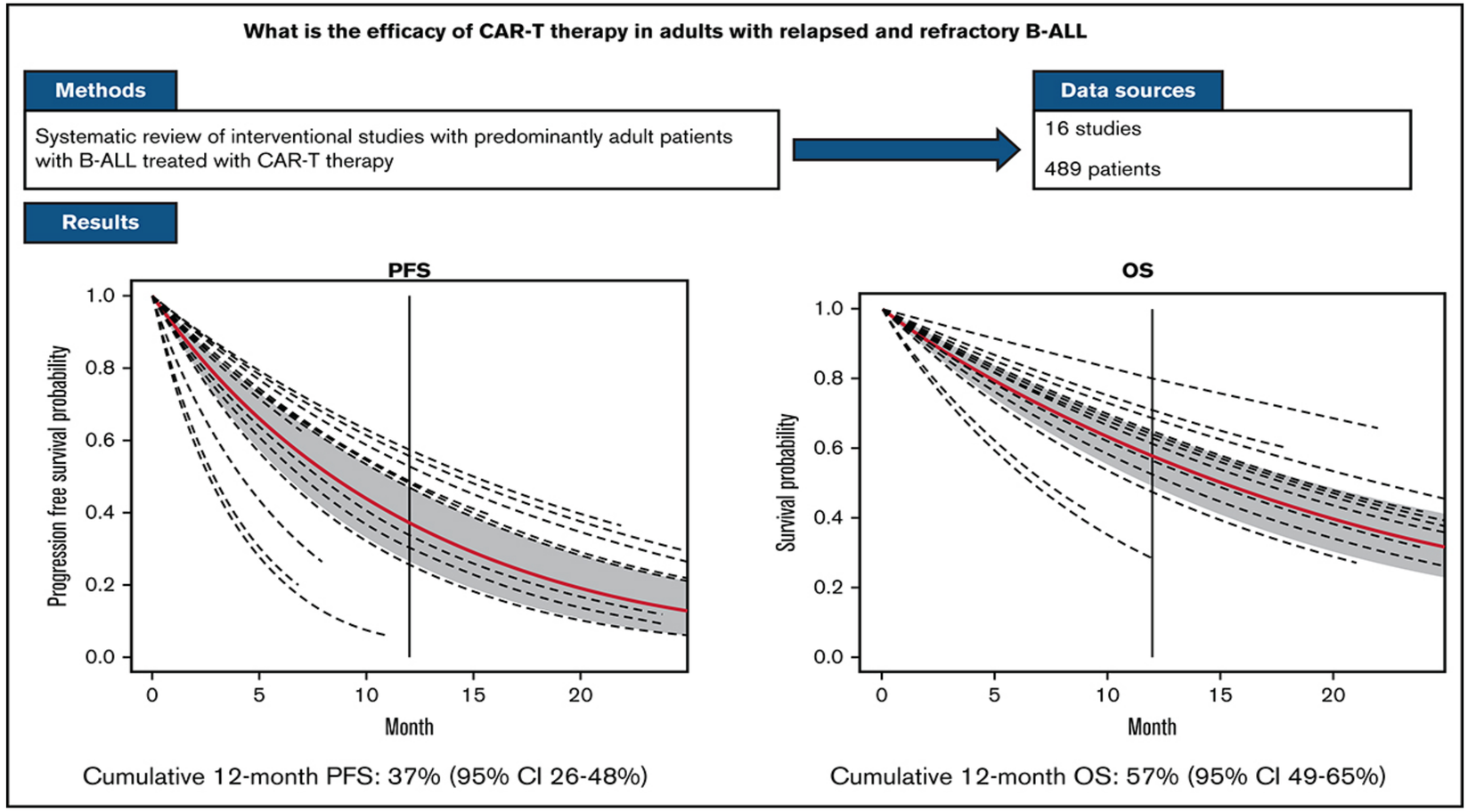
Oluwole OO, et al. ASCO 2024 Abstract #6531

High rate of overall complete remission or complete remission with incomplete haematological recovery

Rapid manufacturing time, a median overall survival of more than 1·5 years, and manageable safety in a heavily pretreated adult patient population with high disease burden

Chimeric antigen receptor T-cell therapy in adults with B-cell acute lymphoblastic leukemia

P. Grover et al. Blood adv 2022



Duration of response remains challenging and the need for a subsequent allogeneic transplant is often considered to be necessary

Consolidative HSCT after INO, Blina, CART?

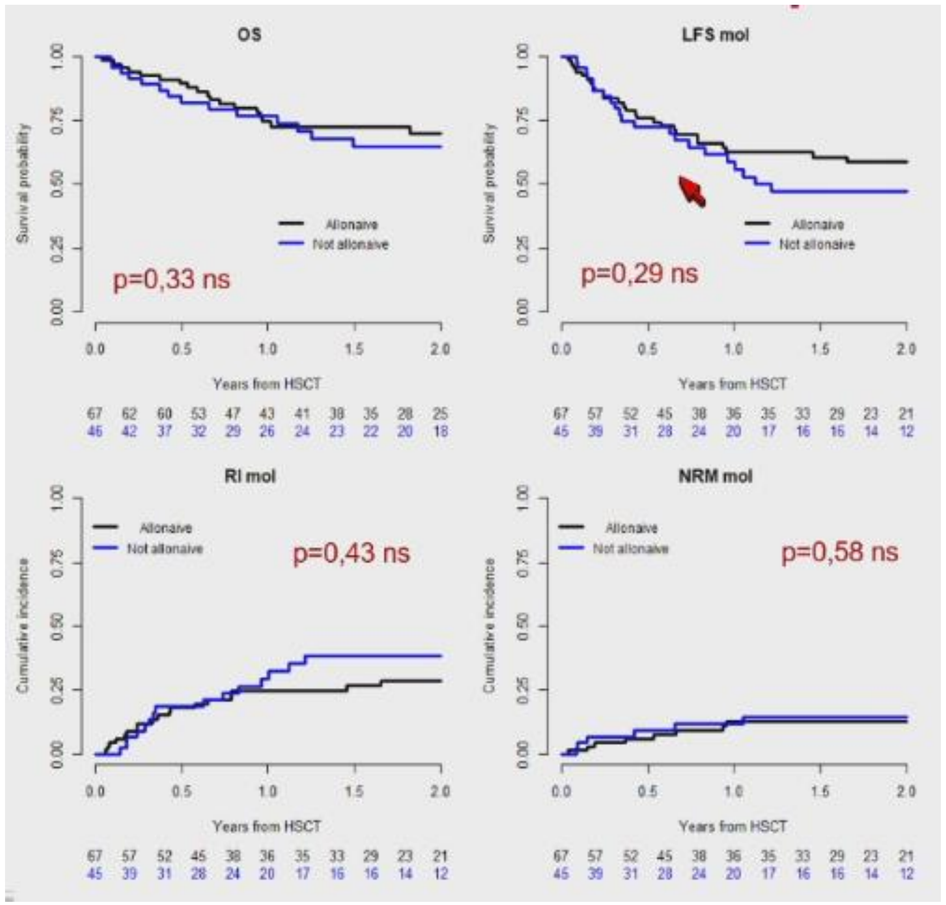
Role not yet been demonstrated but repeatedly suggested

- Published studies not designed to answer this question
- Decision often physician choice
- Conflicting results reported

Subsequent allo-HSCT should be taken into consideration at least for younger and fit patients In order to limit the risk of an early relapse

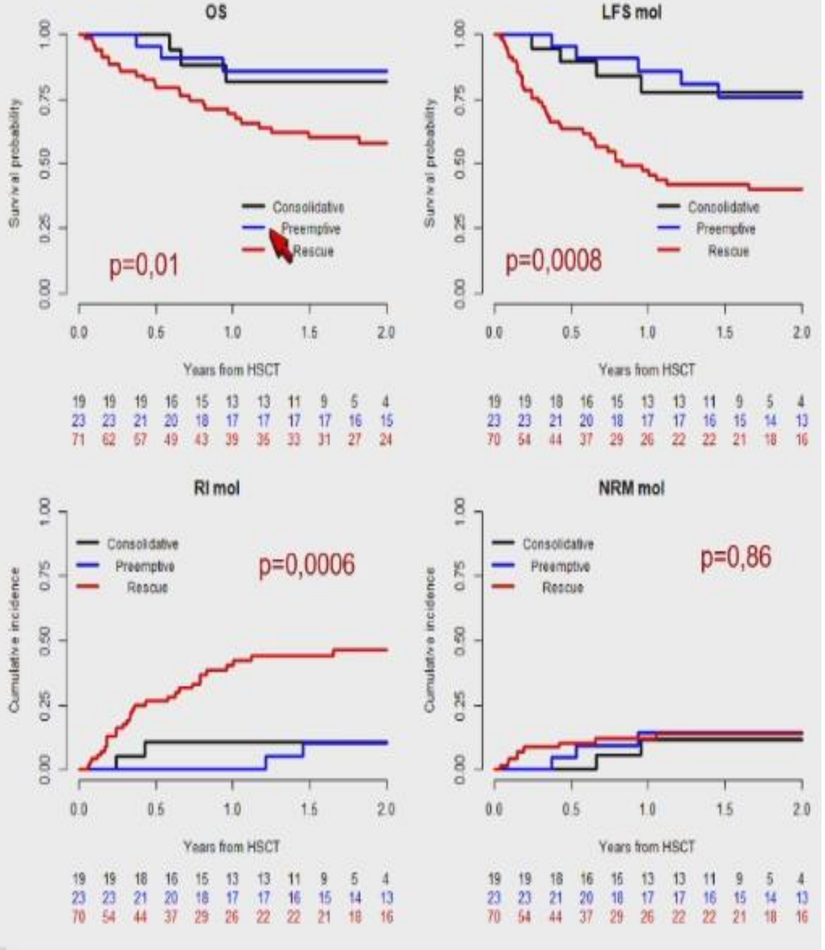
Role of prior and subsequent transplant: GoCART

Prior transplant



		Consolidative (N=19)	Preemptive (N=23)	Rescue (N=71)
Age at this HSCT	median [IQR]	13 [8.3-23.3]	13.6 [8.4-17]	15.9 [8.4-23.2]
Age at this HSCT	Adult	7 (36.8)	5 (21.7)	26 (36.6)
	Child	12 (63.2)	18 (78.3)	45 (63.4)
Allo HSCT before CART	No	17 (89.5)	17 (73.9)	33 (46.5)
	Yes	2 (10.5)	6 (26.1)	38 (53.5)
CART1	Kymriah	15 (78.9)	15 (65.2)	50 (70.4)
	ARI-0001	0 (0)	6 (26.1)	15 (21.1)
	BREYANZI	0 (0)	1 (4.3)	2 (2.8)
	Sheba CART	2 (10.5)	0 (0)	2 (2.8)
	Tecartus	2 (10.5)	1 (4.3)	1 (1.4)
	Tuebingen CART	0 (0)	0 (0)	1 (1.4)
Months first CART to HSCT	median [IQR]	3.5 [2.7-4.2]	4.4 [3.3-5.7]	9.7 [5.8-17.5]
Response after CART1	CR MRD neg	19 (100)	23 (100)	59 (84.3)
	CR MRD pos	0 (0)	0 (0)	8 (11.4)
	No CR	0 (0)	0 (0)	3 (4.3)
	missing	0	0	1
Myeloablative regimen	No	1 (5.3)	4 (18.2)	17 (25)
	Yes	18 (94.7)	18 (81.8)	51 (75)
	missing	0	1	3
TBI in conditioning regimen	No	1 (5.3)	9 (40.9)	32 (46.4)
	Yes	18 (94.7)	13 (59.1)	37 (53.6)
	missing	0	1	2

Consecutive transplant



Ottaviano G, et al. Abs 112. ASH 2024

High disease burden

Inotuzumab should be preferred	Blinatumomab an option in CD22 negative, high risk of hepatotoxicity

CART:

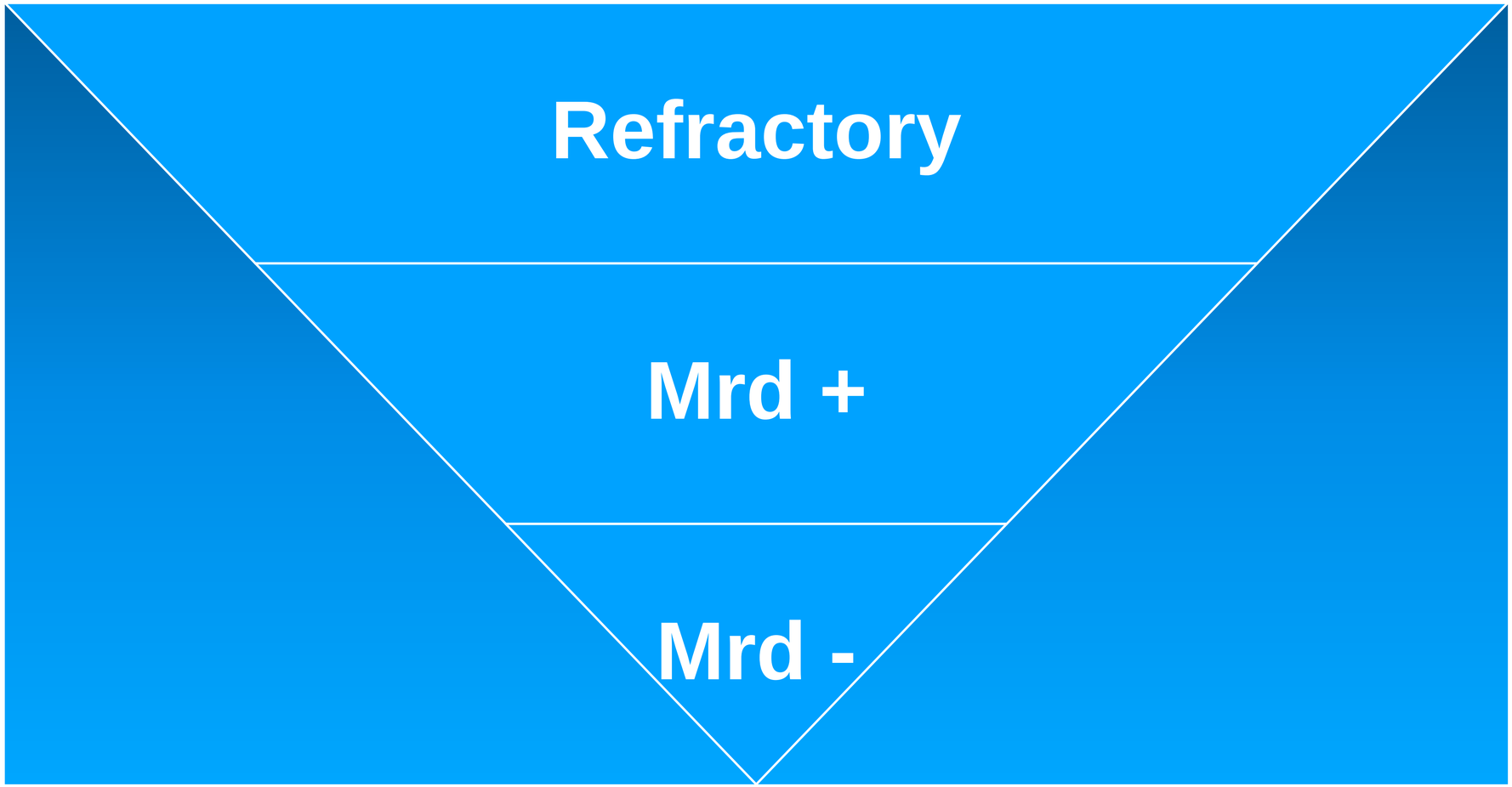
INO bridge to CART	Consolidative HSCT?

Extramedullary disease

Still chemotherapy necessary

INO/CART suitable option

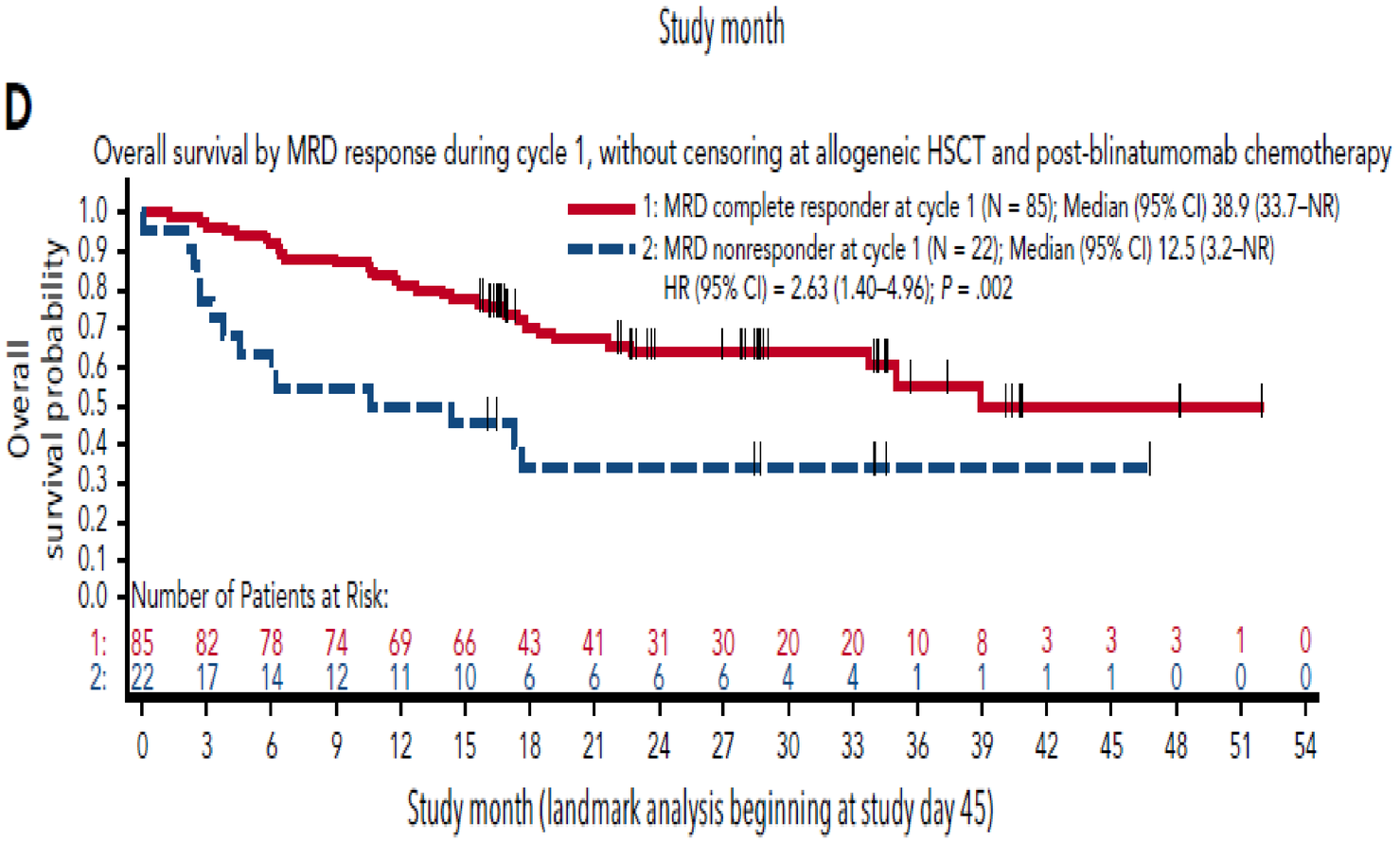
Timepoint 1/2



Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia

Gokbuget Blood 2018

- 78% complete MRD response with blinatumomab.
- Complete MRD response was associated with significantly improved OS
- Although MRD response rates were high in patients treated in second or third CR, RFS, OS, and duration of hematologic remission were inferior compared with patients treated in first CR.
- A number of patients with a complete MRD response remained in long-term remission without subsequent HSCT, which confirms the experience of the pilot study with long-term survivors without subsequent HSCT.



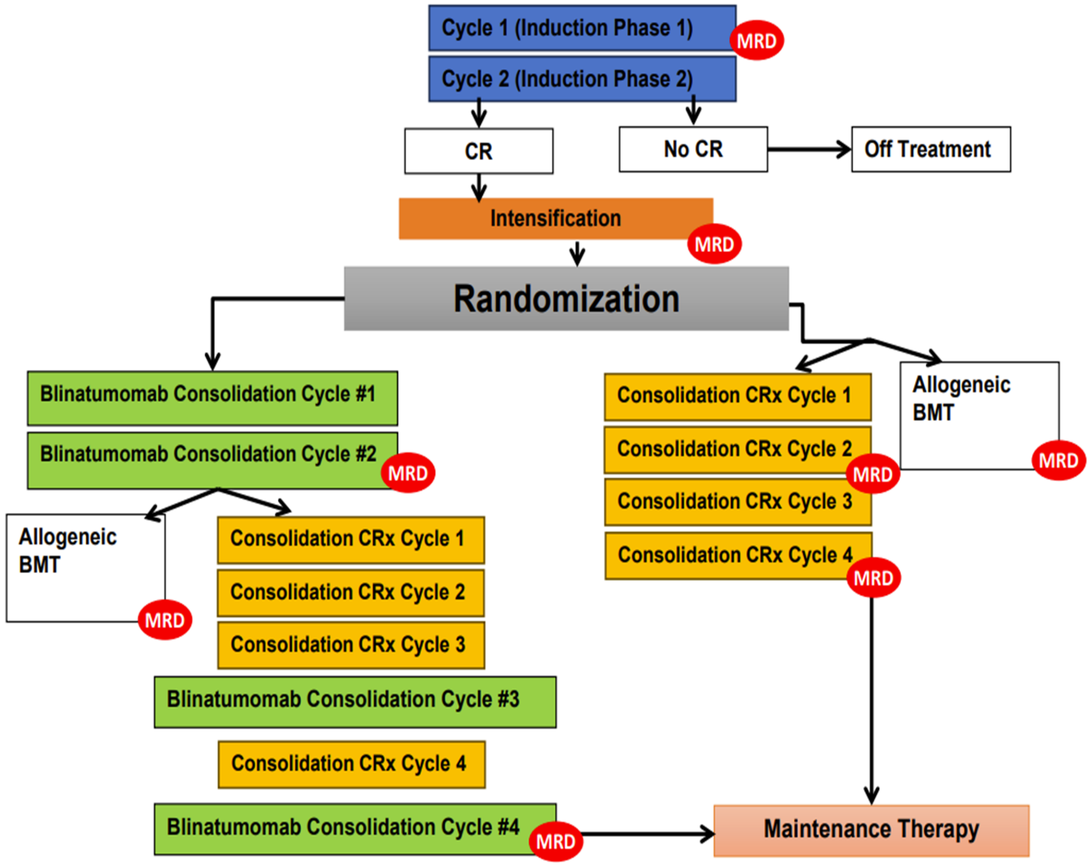
HSCT first-line: when?

Selected young and fit patients with

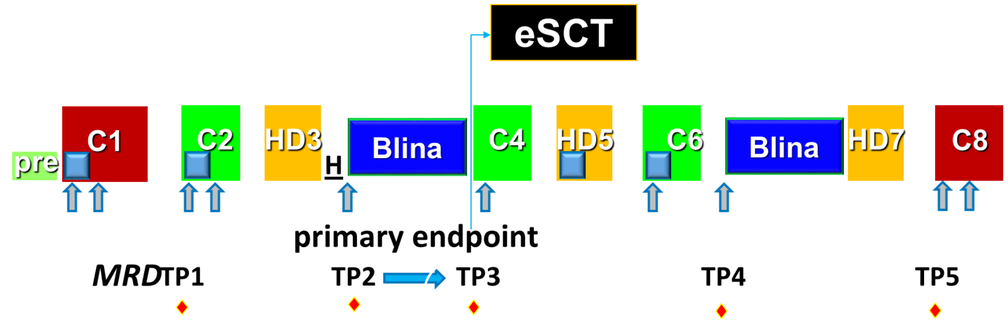
- VHR baseline genetic profile
- Positive MRD after immunotherapy

The 2025 picture of ALL treatment

ECOG-ACRIN E1910



GIMEMA LAL2317



MRD_{pos} **SCT**

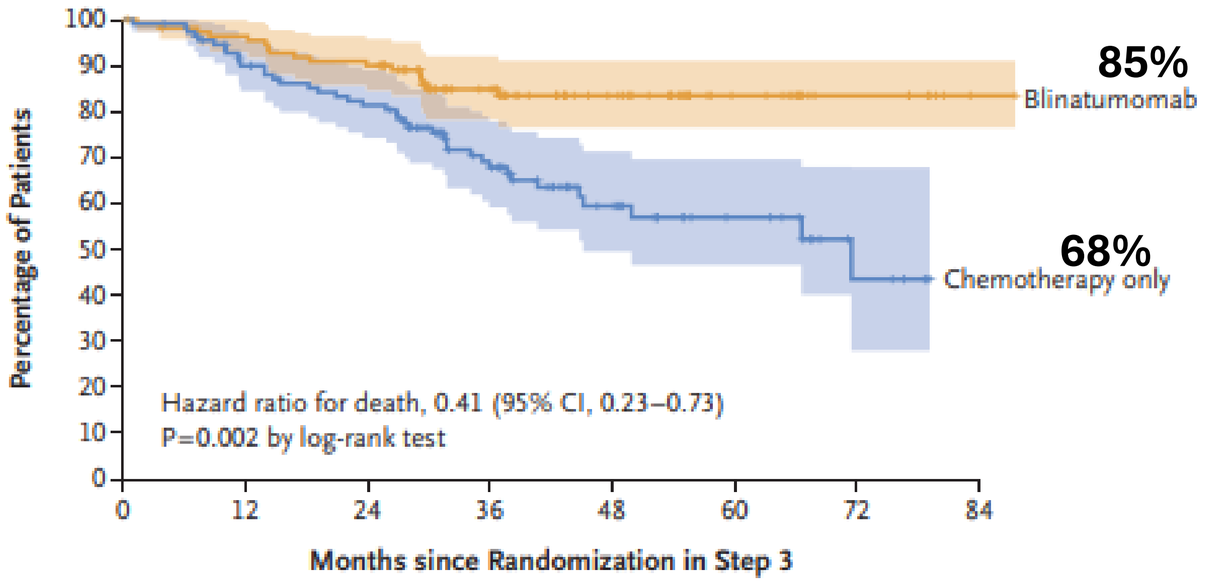
MRD_{neg} **2-Y maintenance**

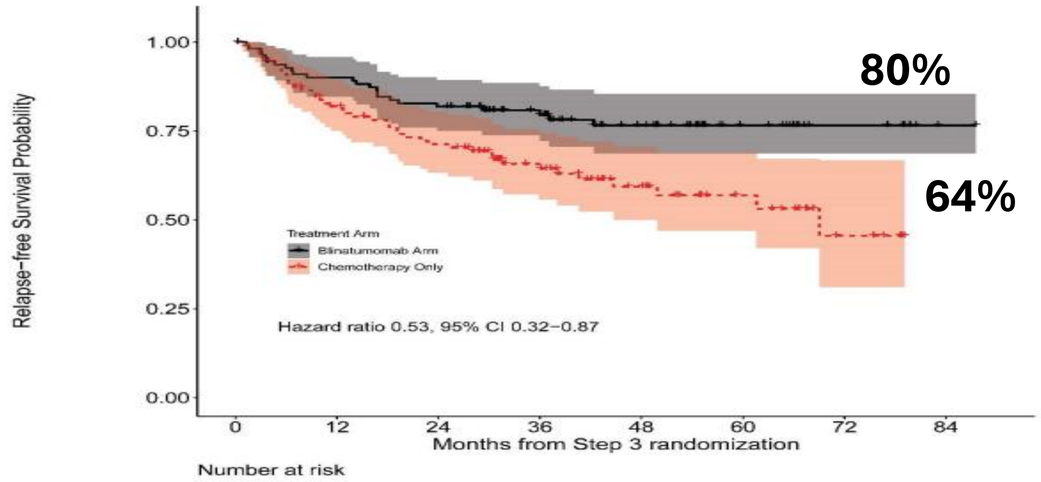
Early allo-SCT:

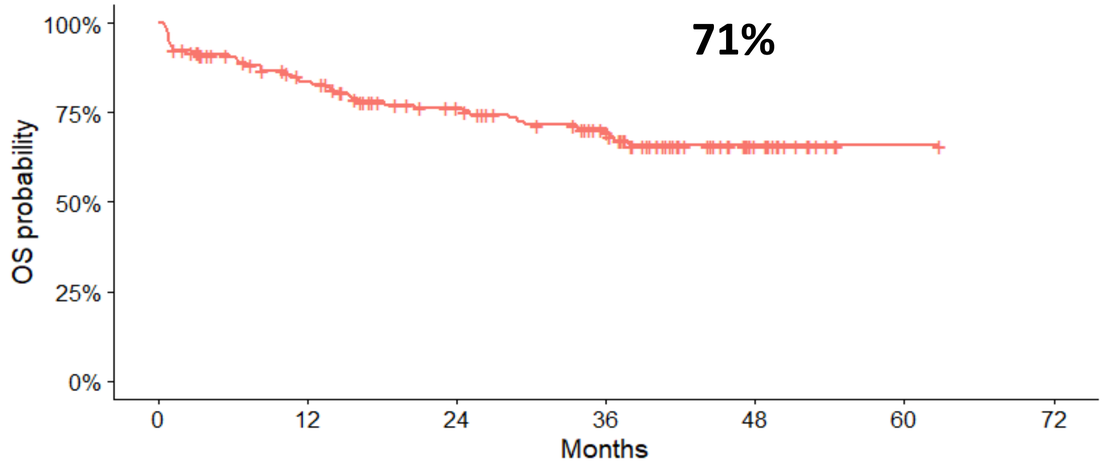
- **Very high risk** ***(WBC >100, highly adverse cytogen)***
- **TP2 MRD ≥10^{-4}**

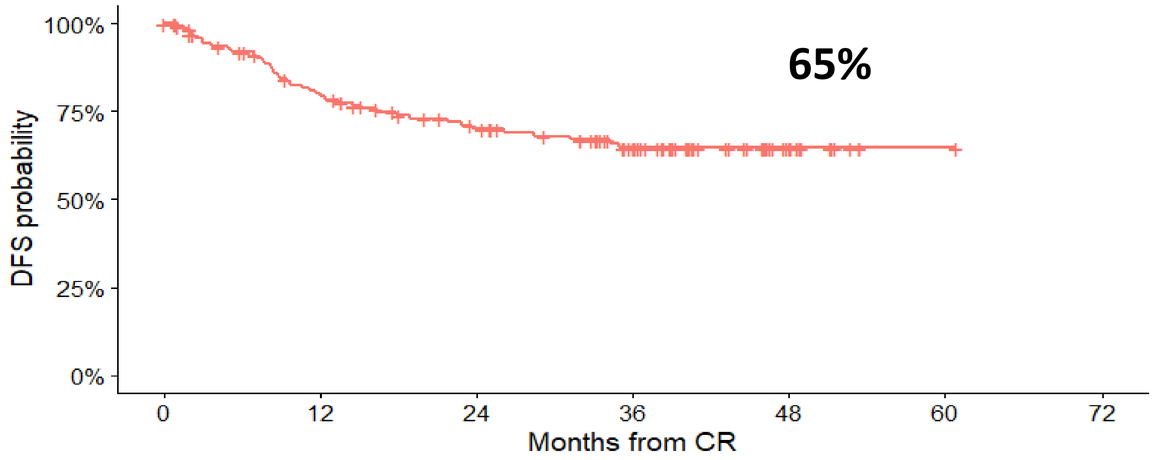
Blinatumomab soon to be approved in the first line setting, regardless of MRD status

The 2025 picture of ALL outcome







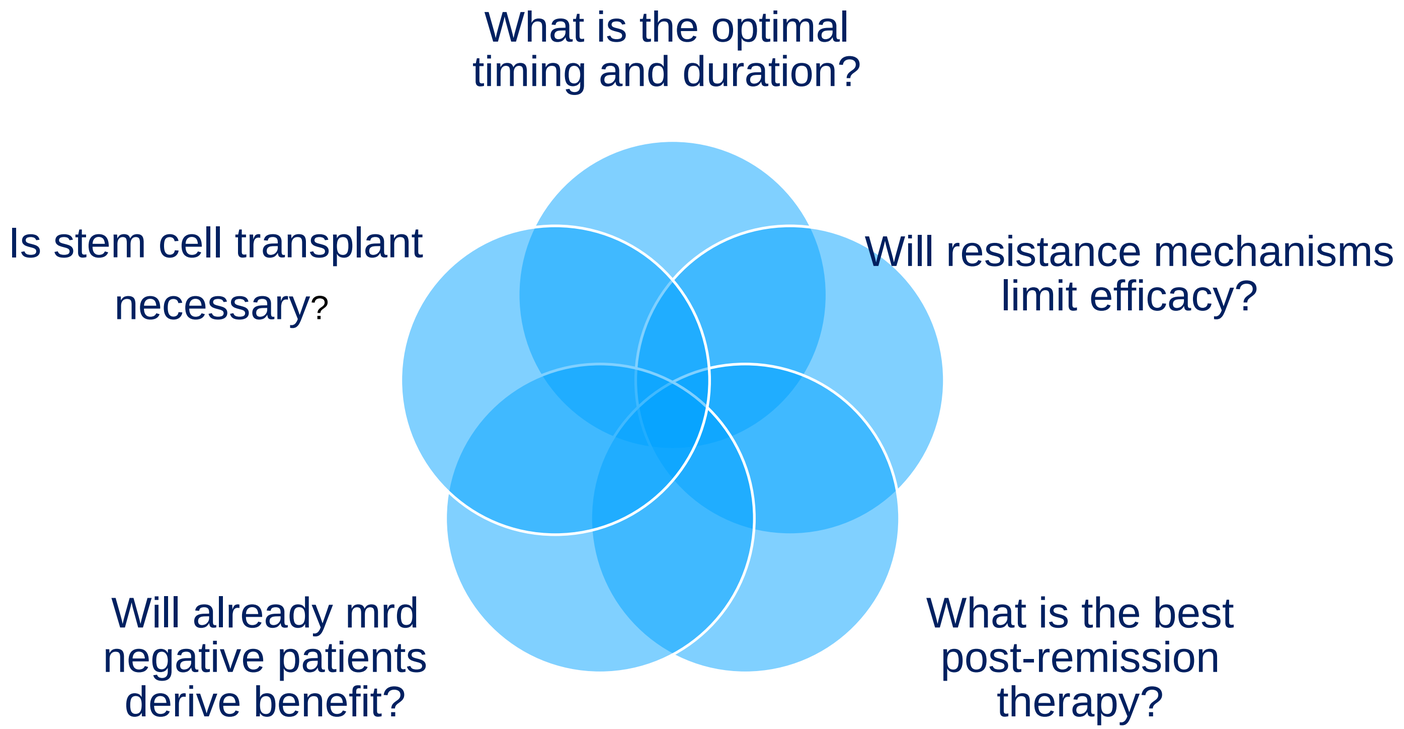


Litzow M. R., et al. N Engl J Med 2024 ;Bassan R, et al. Blood 2025 in press

NCT 04994717 golden gate

- Phase 3 study: Outcomes of blinatumomab alternating with low-intensity chemotherapy in induction consolidation and maintenance compared with adapted GMALL or hyperCVAD regimens in patients aged >55 years with Ph negative BCP-ALL
- Safety run-in: well tolerated with an acceptable safety profile (blood 2022 140 6134)
- Reduction of the overall duration of therapy
- Inducing deeper responses by moving blinatumomab administration to an earlier timepoint

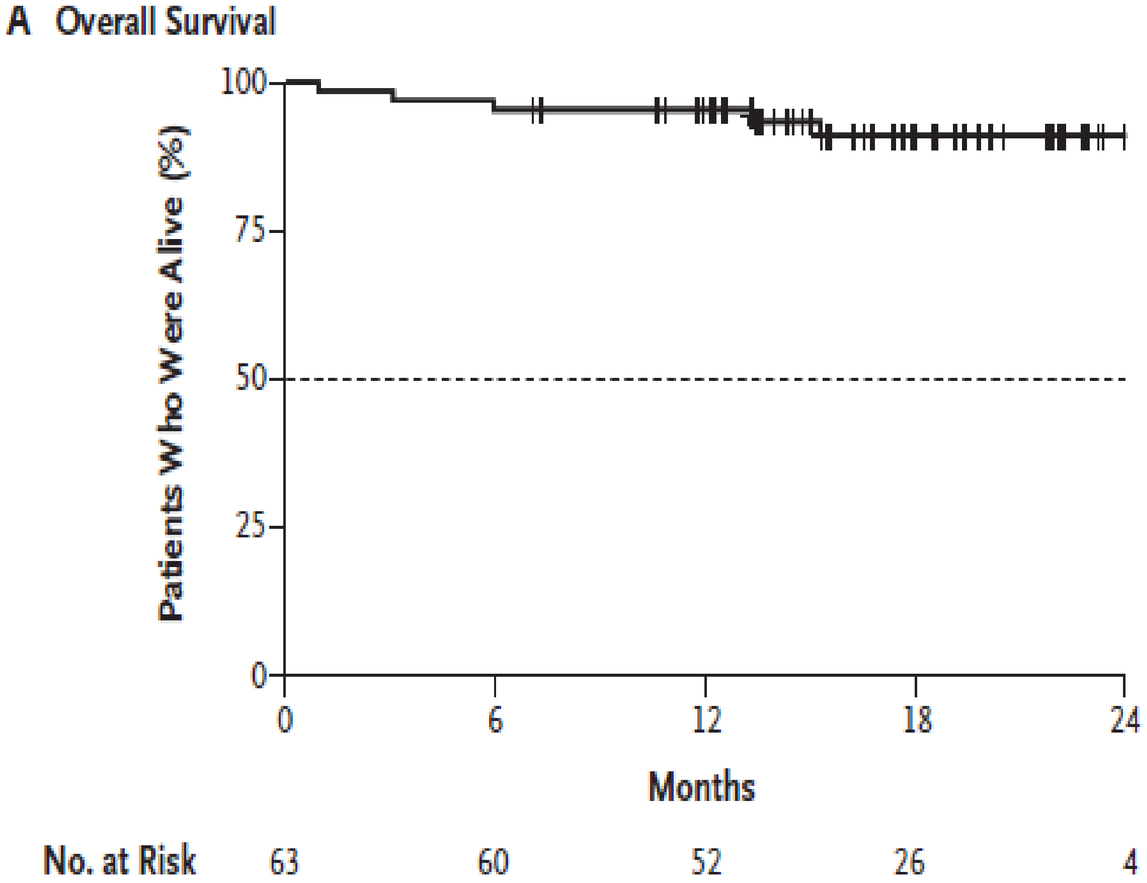
Blinatumomab first-line: Unanswered questions

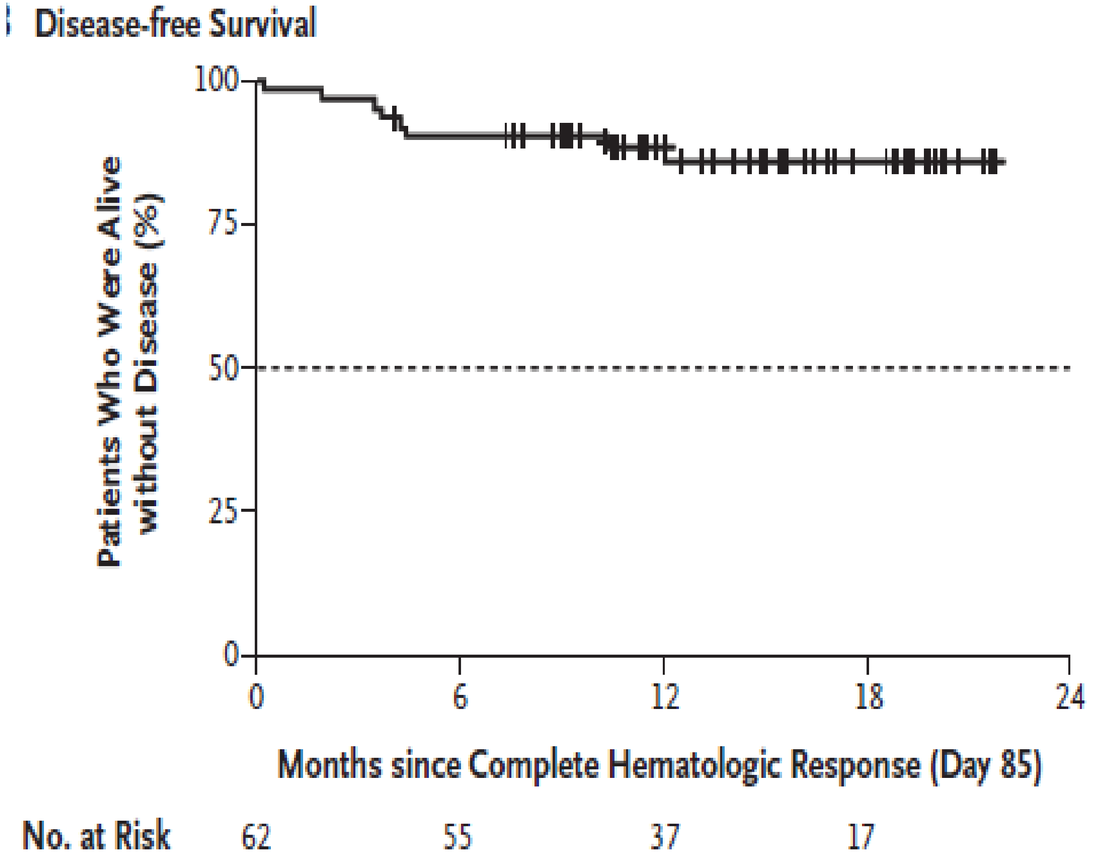


Improved MRD detection methods may further refine our ability to evaluate the impact of specific treatment modalities and guide therapeutic targeting

Dasatinib–Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults (D-albA)

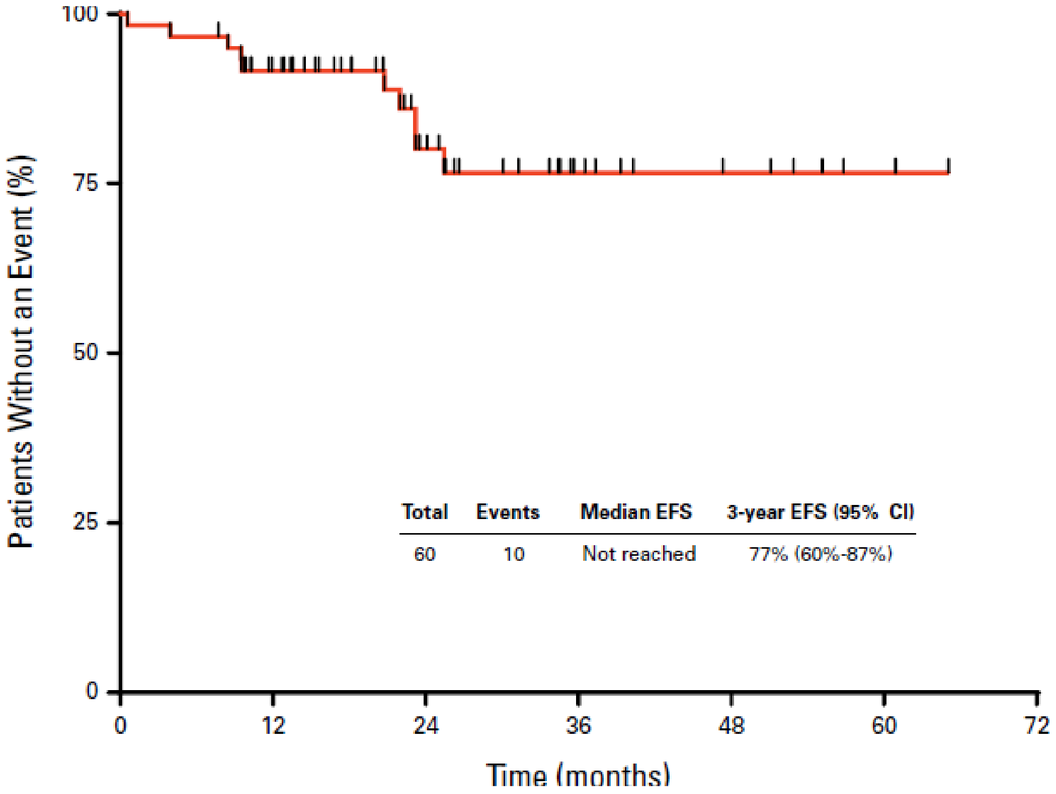
Foa R. et al NEJM 2020

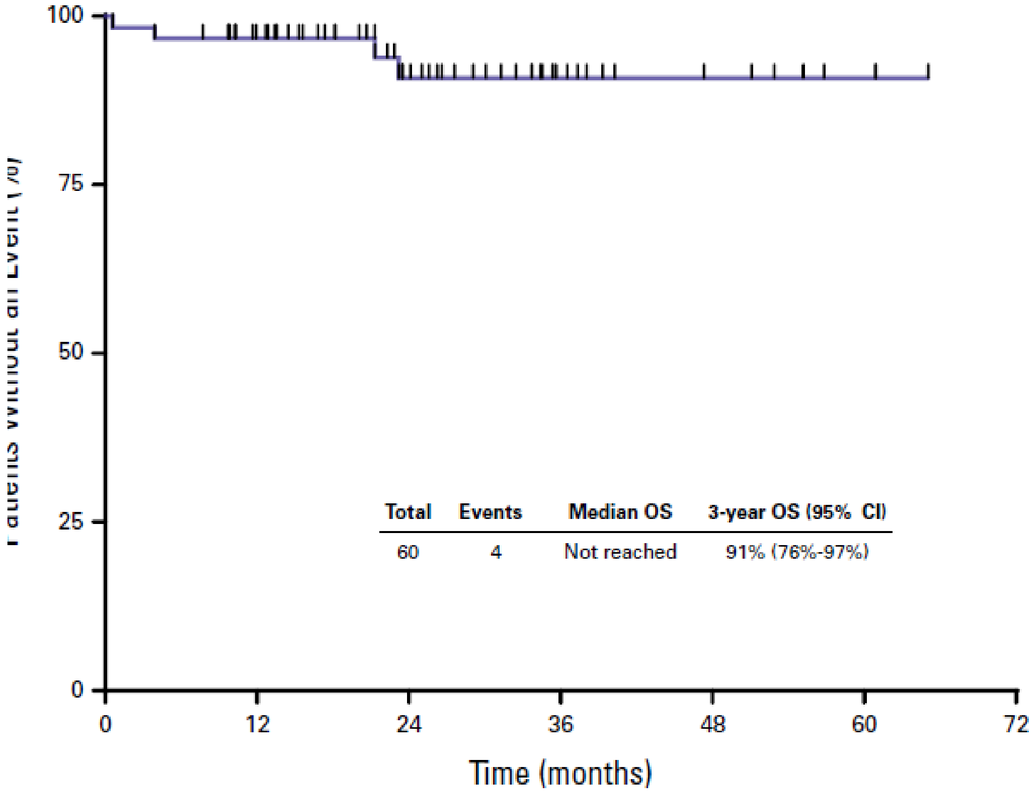




Results of the Simultaneous Combination of Ponatinib and Blinatumomab in Philadelphia Chromosome-Positive ALL

H Kantarjan, JCO 2024

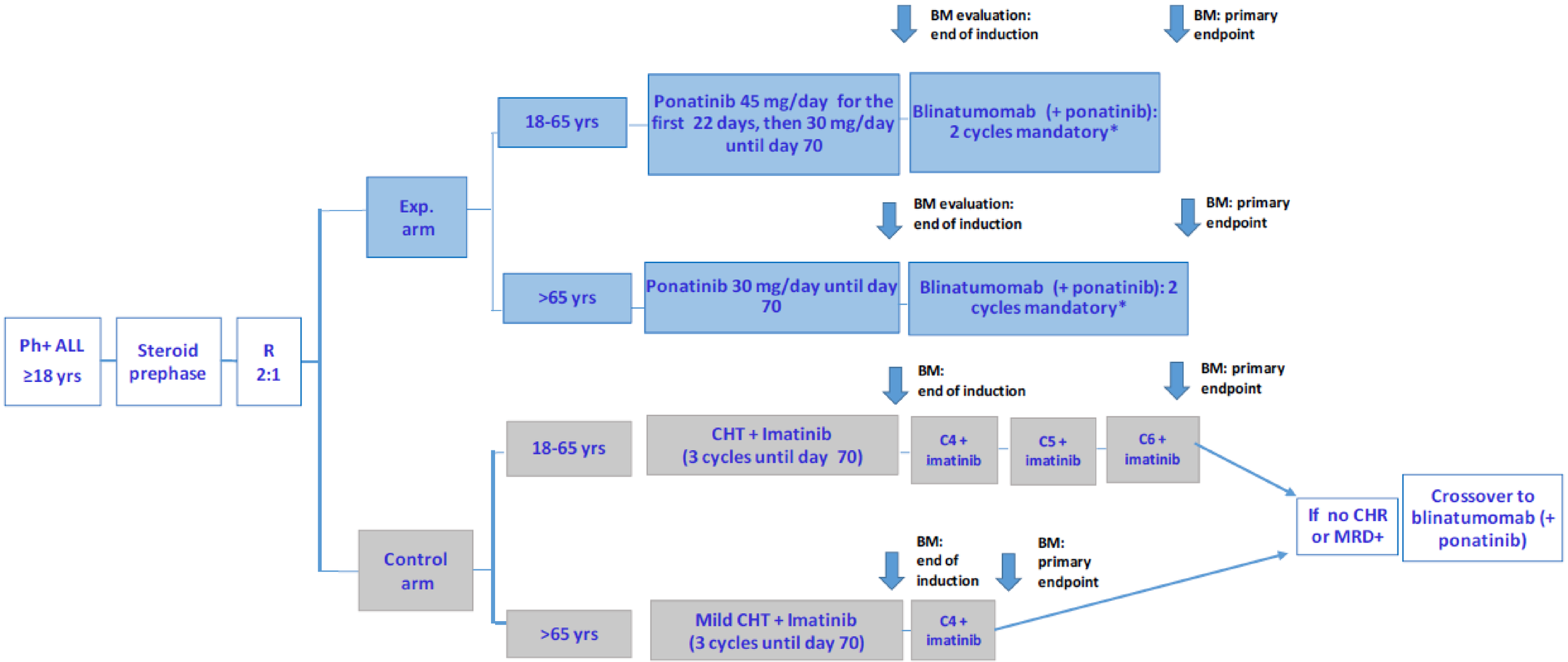




Newly Diagnosed Adult Philadelphia ChromosomePositive Acute Lymphoblastic Leukemia (Ph+ ALL). Sequential Treatment with Ponatinib and the Bispecific Monoclonal Antibody Blinatumomab vs Chemotherapy and Imatinib

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

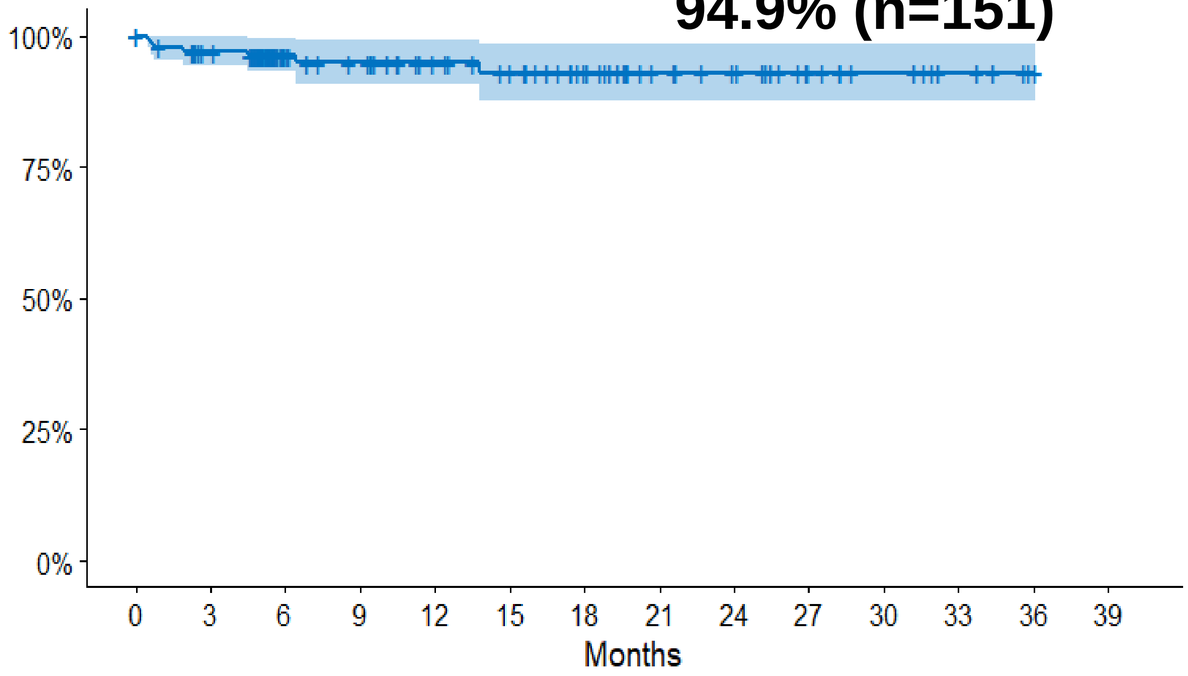
GIMEMA ALL2820



Estimated 12-months OS and DFS

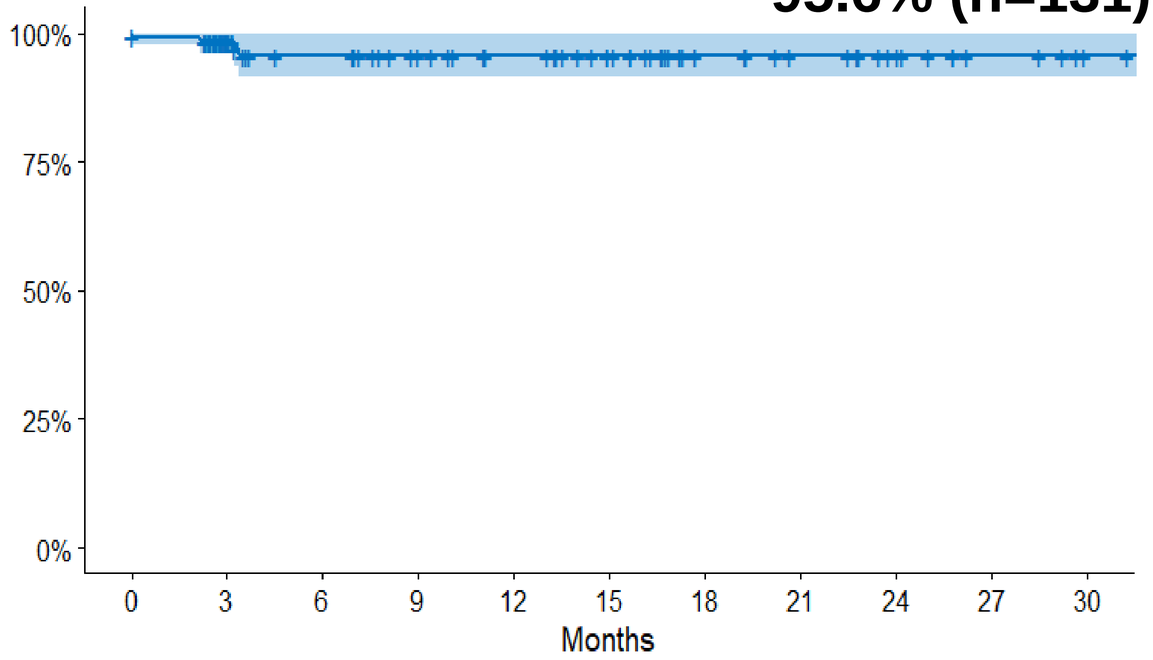
OS

94.9% (n=151)



DFS

95.6% (n=131)



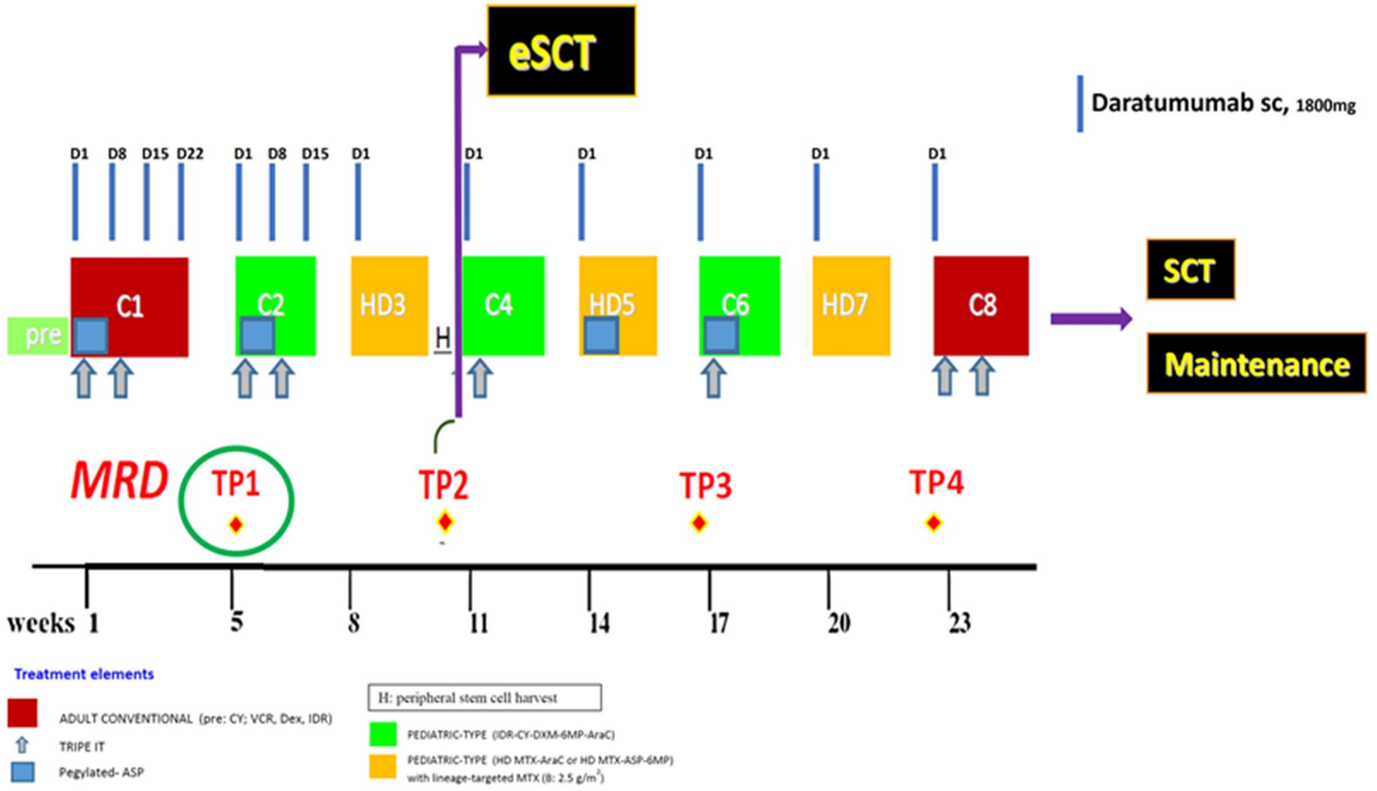
Median follow-up: 8.5 months (0.1 - 36.1)

Daratumumab in Adults with Very High-Risk T-Lineage Acute Lymphoblastic Leukemia (ALL) Treated According to the ALL National Treatment Program (DARATALL-VHR)

GIMEMA ALL3024

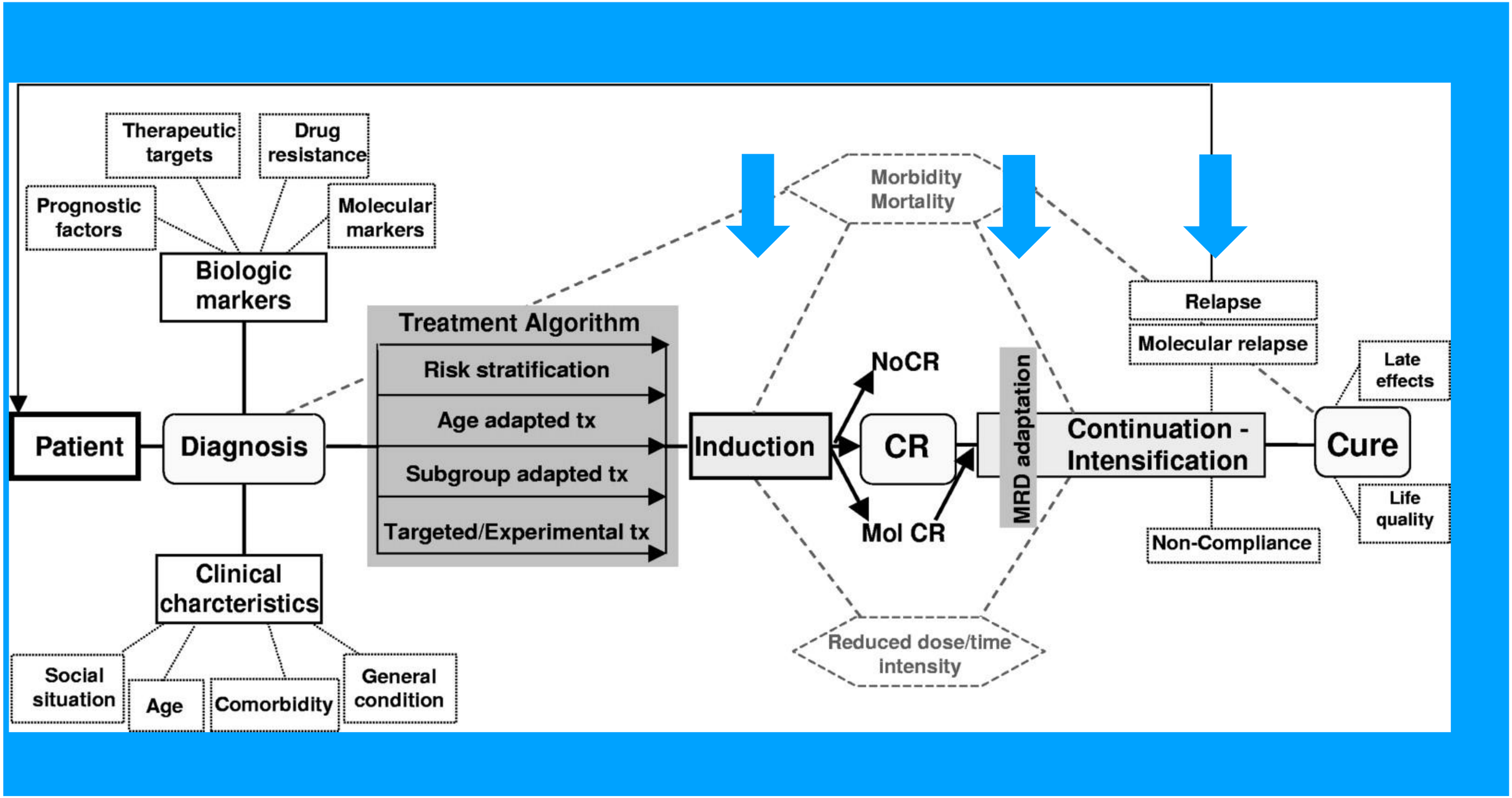
EU CT number 2024-511627-34-00
CT.gov identifier NCT06253637

Sample size: 31 patients



Inclusion criteria

1. Age 18-65 years.
2. A diagnosis of T-ALL according to the 2022 International Consensus Classification (ICC) is required, either *de novo* or secondary to chemo-radiotherapy for another cancer. Pre-treatment with low-dose corticosteroids +/- cyclophosphamide in patients presenting with hyperleukocytosis is allowed.
3. Availability of fresh bone marrow (BM) (or peripheral blood (PB) in patients with hyperleukocytosis) samples to perform diagnostic procedures.).
4. Bone marrow blast percentage at diagnosis ≥20%.
5. CD38 positivity on ALL blasts (any level of positivity).
6. ETP and near ETP at diagnosis according to internationally accepted criteria (appendix G) at diagnosis or other VHR T-ALL subtypes (WBC count >100 x10^9/L; complex karyotype with ≥5 unrelated anomalies; other CD1a-negative immunophenotypes). T-Myeloid MPAL according to the 2022 ICC of Acute Leukemias of Ambiguous Lineage (appendix H) can also be eligible and considered as VHR.


Therapeutic targets
Drug resistance
Prognostic factors
Molecular markers
Biologic markers
Patient
Diagnosis
Clinical charcteristics
Social situation
Age
Comorbidity
General condition
Treatment Algorithm
Risk stratification
Age adapted tx
Subgroup adapted tx
Targeted/Experimental tx
Induction
NoCR
CR
Mol CR
MRD adaptation
Continuation - Intensification
Cure
Late effects
Life quality
Non-Compliance
Relapse
Molecular relapse
Morbidity Mortality
Reduced dose/time intensity

Grazie