Global Leukemia Academy

GLOBAL LEUKEMIA ACADEMY

Bridging Science and Practice: From Newest Clinical Approaches to Real-World Clinical Cases

September 18–19, 2025 – Europe

Meeting sponsors AMGEN Autolus

APTITUDE HEALTH®

Global Leukemia Academy

Welcome to Day 2

Elias Jabbour

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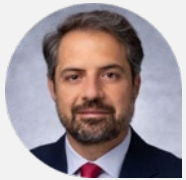
Meet the Faculty

CHAIR



Elias Jabbour, MD
MD Anderson Cancer Center, Houston, TX, USA

FACULTY

Nicola Gökbuget, MD
University Hospital Frankfurt
Frankfurt, Germany

Nicolas Boissel, MD
Saint-Louis Hospital
Paris, France

Josep-Maria Ribera, MD, PhD
Catalan Institute of Oncology
Hospital Germans Trias i Pujol
Badalona, Spain

Objectives of the program (ALL)

- Understand current treatment patterns for ALL including incorporation of new technologies
- Uncover when genomic testing is being done for ALL, and how these tests are interpreted and utilized
- Understand the role of stem cell transplantation in ALL as a consolidation in first remission
- Comprehensively discuss the role of biomarkers in managing and monitoring ALL
- Share insights into antibodies and bispecifics in ALL
- Discuss the evolving role of ADC therapies in ALL
- Review promising novel and emerging therapies in ALL
- Explore and discuss regional challenges in the treatment of ALL across the EU

Day 2: Virtual Plenary Sessions

Friday, September 19, 2025
18.00 – 21.00 UTC +2 (Central European Summer Time)

Time (UTC -5)	Time (UTC +2)	Title	Speaker
11.00 AM – 11.10 AM	18.00 – 18.10	Welcome to Day 2	Elias Jabbour
11.10 AM – 11.40 AM	18.10 – 18.40	Current treatment options for relapsed/refractory (R/R) ALL in fit adults	Nicola Gökbuget
11.40 AM – 12.00 PM	18.40 – 19.00	Current treatment options for R/R ALL in elderly and frail patients	Josep-Maria Ribera
12.00 PM – 12.20 PM	19.00 – 19.20	Current and future role of transplantation in ALL in Europe	Nicola Gökbuget
12.20 PM – 12.30 PM	19.20 – 19.30	Break	
12.30 PM – 1.00 PM	19.30 – 20.00	ALL case-based panel discussion for R/R ALL • Case ALL: AYA – Case 1: Dr Ribera – Case 2: Dr Gökbuget/Dr Lang	All faculty
1.00 PM – 1.20 PM	20.00 – 20.20	Long-term safety considerations for ALL	Nicolas Boissel
1.20 PM – 1.50 PM	20.20 – 20.50	Panel discussion: Open questions in ALL – regional challenges (transplant, CAR T studies, and other) • Who are the ideal patients for CAR T therapy, bispecifics, and transplants in your practice? • What would be needed to make CAR T therapy available to all of your patients? • What would be needed to best position bispecifics in the continuum of care for ALL in adults? • How should transplant be strategically combined with the new therapy modalities?	Moderated by Nicolas Boissel Led by Elias Jabbour and all faculty
1.50 PM – 2.00 PM	20.50 – 21.00	Session close	Elias Jabbour

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Introduction to the voting system

Elias Jabbour

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Question 1

For first salvage of R/R ALL in your setting, which of the following treatments would you consider, if all these therapies were available in your country and have not been used previously in this patient?

A. CD19 CAR T therapy
B. Bispecific antibody (blinatumomab)
C. Antibody-drug conjugate (inotuzumab ozogamicin)
D. Intensive cytotoxic chemotherapy ± targeted TKI
E. Transplant without additional salvage therapy
F. Other

Question 2

What is your opinion of the tolerability of CD19 CAR T cells?

A. All agents are very difficult to tolerate in most patients
B. All agents are hard to tolerate in elderly/frail patients
C. All agents are manageable in most patients
D. Tolerability varies depending on the specific CAR T

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Current treatment options for relapsed/ refractory (R/R) ALL in fit adults

Nicola Gökbuget

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Current Treatment Options in R/R ALL in Fit Adults

Nicola Gökbuget

UNIVERSITÄTS KLINIKUM FRANKFURT
GOETHE-UNIVERSITÄT

GMALL
German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

FRANKFURT CANCER INSTITUTE

uct Universitäres Centrum für Tumorerkrankungen Frankfurt
University Cancer Center

MED2

DKTK German Cancer Consortium

Therapy of Relapsed/Refractory ALL

1. Definitions
2. Results of Standard Therapies
3. Principles of Targeted Therapies
4. B-precursor ALL
5. T-ALL
6. (SCT)
7. Summary

Definitions: What do we mean?

Primary refractory ALL

Early relapse

Refractory relapse (2nd relapse)

BM Relapse

- <5% MRD
- >5% <50%
- >50%

Late relapse

Lymph nodes
CNS (CSF, brain)
Testis
Other extranodal

Combinations with BM

Definitions: What do we mean?

BM Relapse

- <5% MRD
- >5% <50%
- >50%

Isolated extramedullary

Lymph nodes

CNS (CSF, brain)

Testis

Bone

Other extranodal

Increasing?

Combinations

Therapy of Relapsed/Refractory ALL

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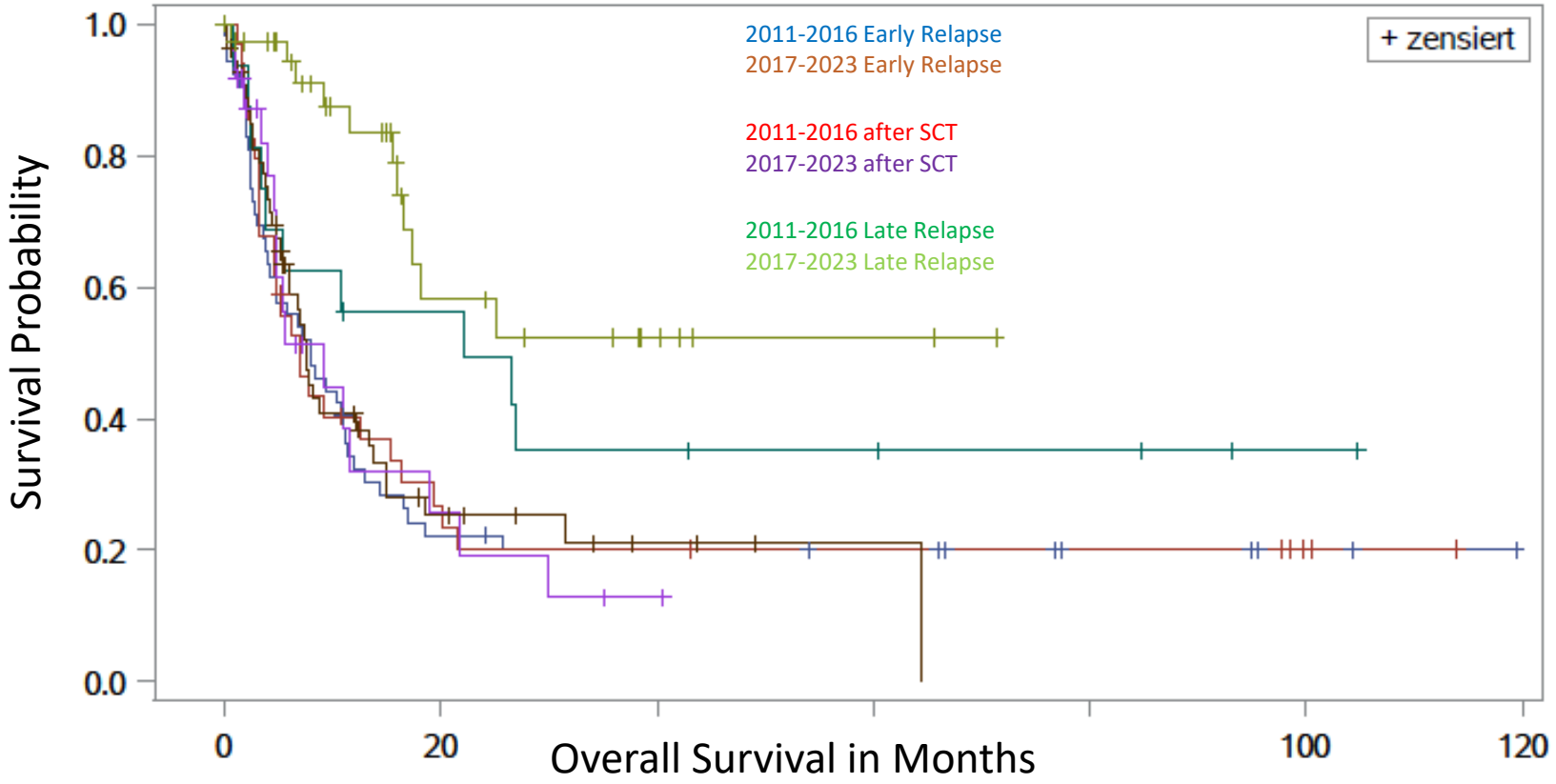
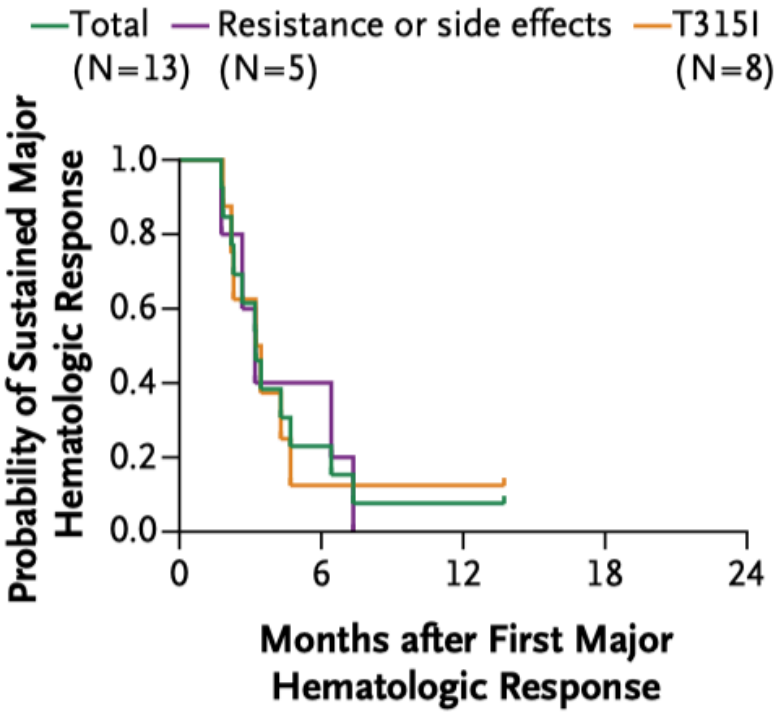
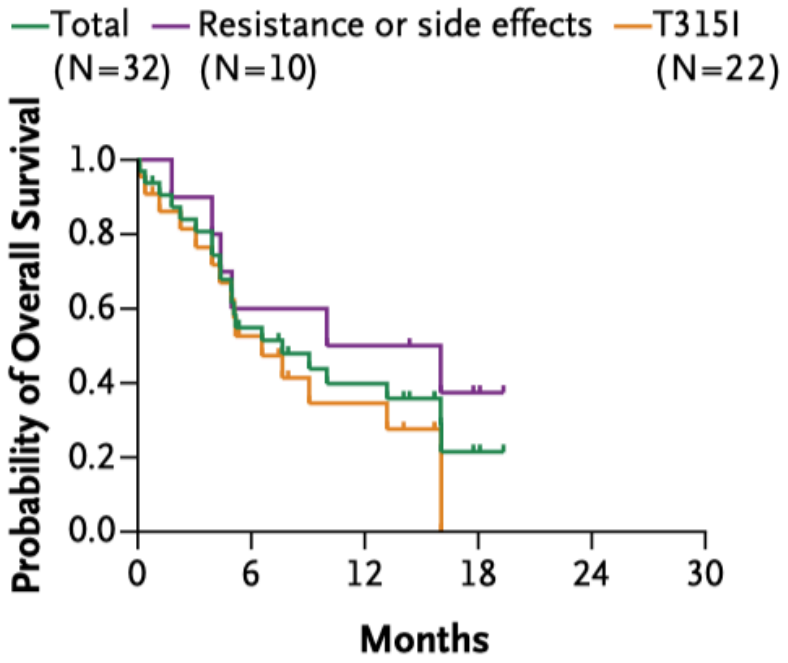
Overall Survival after Relapse in B-Precursor ALL, Ph-neg, 18-55 yrs
GMALL Real-World Data on File



Overall Survival of Ph-Positive ALL after Relapse
Paradigm of Targeted Therapy: Ponatinib

Cortes et al, New Engl J Med 2013





Major Challenges of Relapse Therapy

Overall: Fewer relapses but more difficult to treat

- **B-Lin: after immunotherapy**
- **B-Lin: relapse after/by lineage shift**
- **B-Lin: extramedullary relapses**
- T-Lin: relapse in HR subtypes, eg, early T
- B/T-Lin: relapse after SCT
- B/T-Lin: molecular relapses

Major Challenges of Relapse Therapy

Overall: Fewer relapses but more difficult to treat

- B-Lin: after immunotherapy
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- **B/T-Lin: relapse after SCT**
- **B/T-Lin: molecular relapses**

Therapy of Relapsed/Refractory ALL

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Targeted Therapies – What Does It Need?

Potential Targets

- Surface marker
- Fusion genes
- Activating mutations
- Aberrant signaling pathways
- Epigenetic modifiers

Drug approach (examples)

- Antibodies
- ABL tyrosine kinase inhibitors
- JAK 1/2 inhibitors
- mTOR inhibitors, BCL2 inhibitors
- Histone methyltransferase inhibition

Diagnostic approach

- Method
- Subtype
- Time point

Target Identification – When and Which?

B-Lineage

CD38
CD33
CD52
Flt3
Jak 1/2
ABL1/PDGFRA/PDGFRAB
IDH1/2

T-Lineage

CD38
CD30
CD33
CD52
NUP214::ABL1
Flt3
Jak2
IDH1/2

Time point and method to be defined

Therapy of Relapsed/Refractory ALL

1. Definitions
2. Results of Standard Therapies
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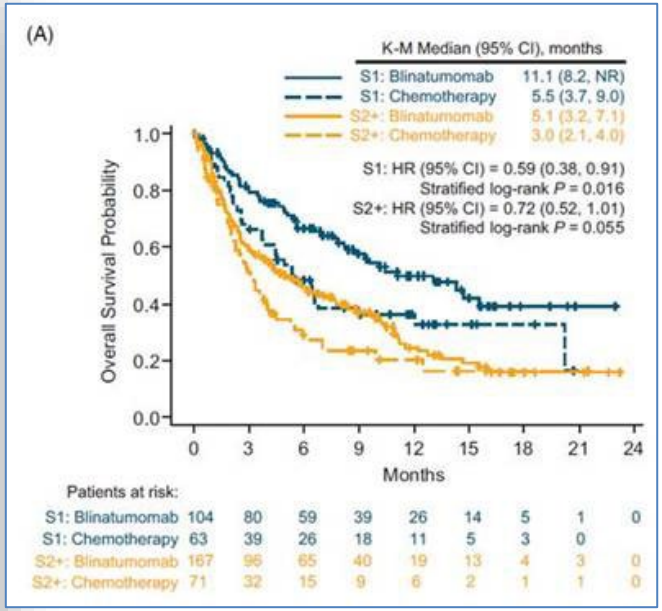
TOWER: Blinatumomab in Relapsed/Refractory ALL

Results of Remission Induction (CR/CRp/CRi) by Subgroups and Outcome by Salvage Line

Kantarjian et al, N Engl J Med 2017

	Blina	Chemo
Age		
<35 yrs	43%	25%
>35 yrs	45%	24%
Salvage line		
First	**53%**	35%
Second	**40%** ↓	16%
Third	**35%**	11%
Previous allo SCT		
Yes	40%	11%
No	46%	32%
BM blasts		
<50%	**65%** ↑	**34%**
>50%	**34%**	**21%**

Dombret et al, Leuk&Lymph, 2019



Salvage 1 vs Salvage 2
CR/CRi/CRh Rate: 51% vs 39%
OS: 5.1 vs 11.1 mo

Inotuzumab in R/R B–Precursor ALL: INO-VATE

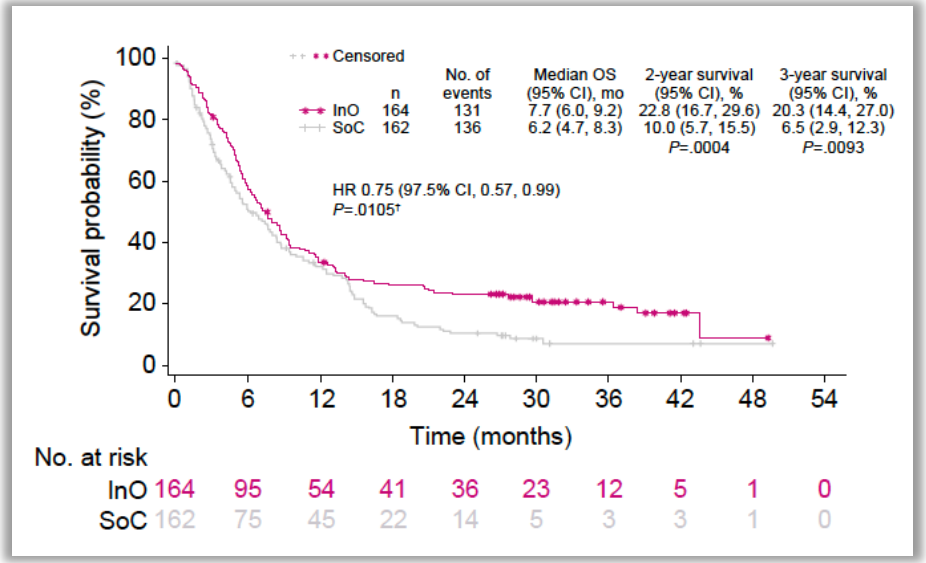
Factors for Achievement of Response

Kantarjian et al, N Engl J Med 2016

	Ino	Chemo
Prior remission duration		
<12 mo	77%	24%
>12 mo	87%	39%
Salvage line		
First	**88%**	**29%**
Second	**67%** ↓	**31%**
Age		
<55 yrs	80%	32%
>55 yrs	81%	25%
Previous allo SCT		
Yes	76%	27%
No	81%	30%
BM blasts		
<50%	**87%**	**41%**
>50%	**78%** ↓	**24%**
PH+	79%	44%

Overall Survival

Kantarjian et al, Cancer 2019



Optimized Use:

- First salvage

Blinatumomab/Inotuzumab in Adult ALL: Optimized Use

- MRD-Setting: Any MRD-positivity after 1st cons
- 1st Salvage!
- Reducing leukemia burden
- Target expression
- Limitation of cycles
- Target loss
- Relapse from extramedullary compartment
- Upregulation of PD-1/PD-L1
- Combination with BH3 mimetics
- Downregulation of T-regs
- Biomarkers
- Early Response
- Consolidation/Maintenance

AVOID FULL RELAPSE

Extramedullary Relapse after Blinatumomab

Aldoss et al, Cancer 2021

Patients:	132
Age	39 (18-88) yrs
History of EMD	34 (26%)
EMD at Blina	11 (8%)
R/R	103
MRD	29
Response	
R/R	58%
MRD	86%
HSCT	48 (56%)

Blina Failure (R/R) after Blina

Refractory	47
Relapse:	42
Total	89
EMD	38 (24 isolated)
CNS	15

Risk Factors for EMD

History of EMD: 53% vs 24% (*P*=.005)

Inotuzumab – Extramedullary Relapse

Kayser et al, Haematologica 2021

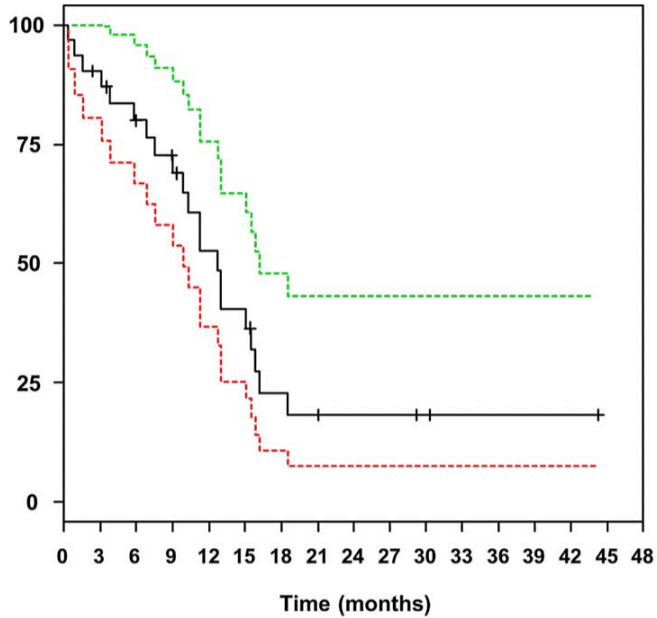
Patient Characteristics

Total	31
Median age	31 (19-81)
BM blasts	10 (0-100)
Lymph node	15
GI	15
Osteolytic	12
Skin	7
Soft tissue	5
Genitals	4
Mediastinal	2
Lung/pleural	2
Epidural	2
Nasopharynx	2
CNS/Epidural	1
Vertebral	1
Pelvic	1
Cardiac	1

Response to Inotuzumab

Cycle 1	24
CR	10 (42%)
PR	9 (37%)
SD	2 (8%)
PD	3 (12%)
Cycle 2	31
CR	17 (55%)
PR	9 (29%)
ED	1 (3%)
SD/RD/PD	4 (13%)
Median OS	12 mo
OS 1y	53%
OS 2y	18%
SCT	N=12

Overall Survival



Blinatumomab vs Chemotherapy Consolidation in Low-Risk 1st Relapse of Pediatric/AYA (1-30) B-cell ALL

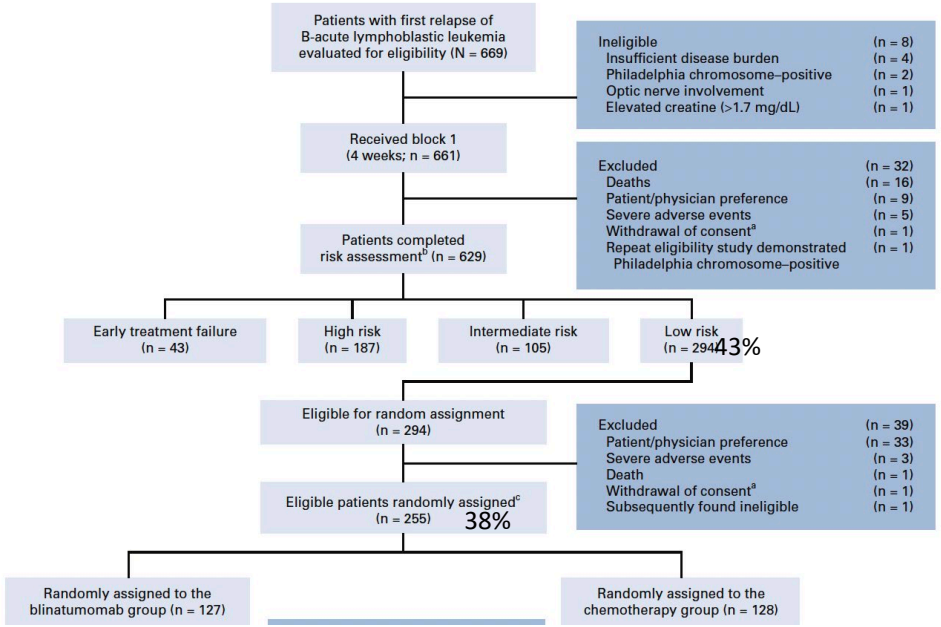
Hogan et al, JCO 2023

Low risk relapse:
BM relapse with/without extramedullary (EM) disease ≥36 months or isolated EM (IEM) relapse ≥18 months from initial diagnosis, who have low (<0.1%) MRD at end of reinduction

Treatment:
Standard reinduction block 1

Arm C: Block 2/block 3/2 continuation chemotherapy cycles/maintenance
Arm D: Block 2/2 cycles of continuation chemotherapy intercalated with 3 blinatumomab blocks/maintenance

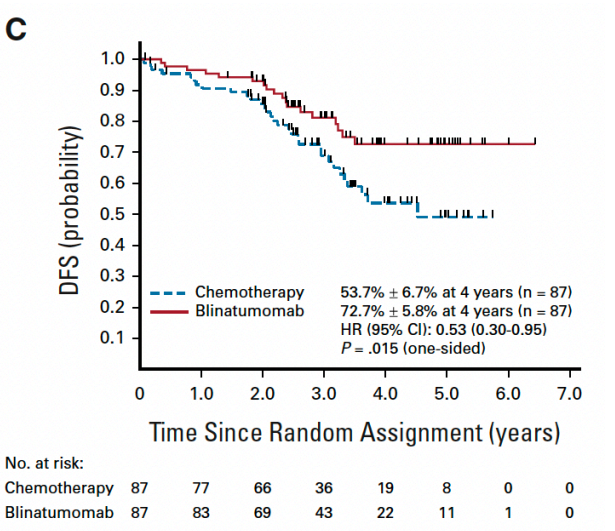
<u>CNS leukemia:</u>
18 Gy cranial radiation during maintenance
+ intensified intrathecal chemotherapy.



Blinatumomab vs Chemotherapy Consolidation in Low-Risk 1st Relapse of Pediatric/AYA (1-30) B-cell ALL

Hogan et al, JCO 2023

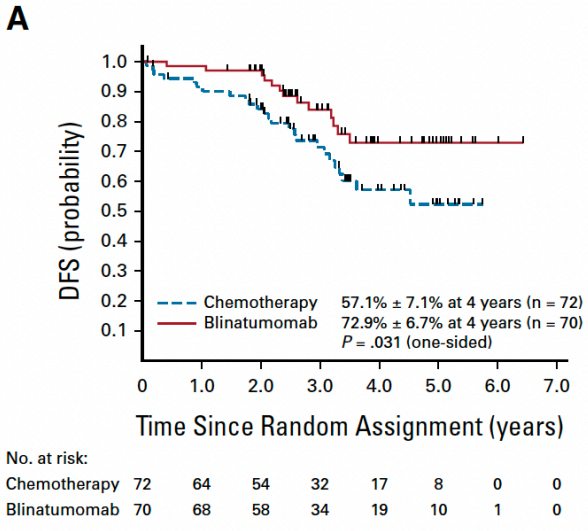
BM+/-EM Relapse



No. at risk:

Chemotherapy	87	77	66	36	19	8	0	0
Blinatumomab	87	83	69	43	22	11	1	0

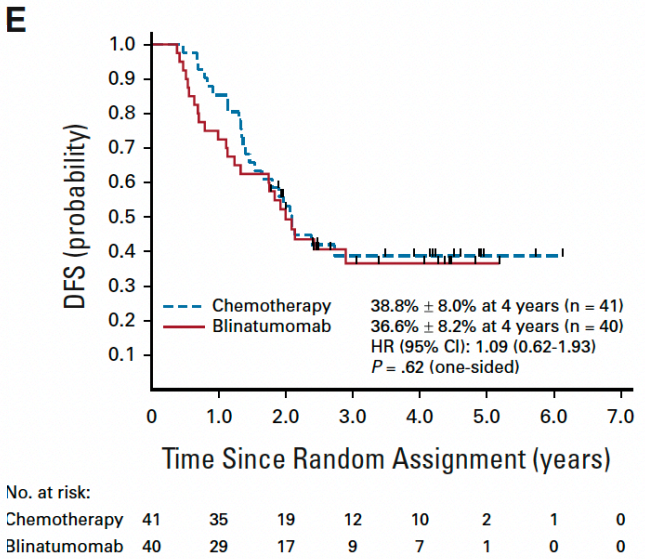
Isolated BM Relapse



No. at risk:

Chemotherapy	72	64	54	32	17	8	0	0
Blinatumomab	70	68	58	34	19	10	1	0

Isolated EM Relapse



No. at risk:

Chemotherapy	41	35	19	12	10	2	1	0
Blinatumomab	40	29	17	9	7	1	0	0

Blinatumomab/Inotuzumab in Adult ALL: Optimized Use

- MRD-Setting: Any MRD-positivity after 1st consolidation
- 1st Salvage!
- Reducing leukemia burden
- Target expression
- Limitation of cycles
- Target loss
- Relapse from extramedullary compartment
  - Avoid long-term single-drug treatment
  - Combine with alternative antibodies/chemotherapy
  - i.th. Prophylaxis
  - MRD measurement in PB and BM
- Upregulation of PD-1/PD-L1
- Combination with BH3 mimetics
- Downregulation of T-regs
- Biomarkers
- Early Response
- Consolidation/Maintenance

Blinatumomab in Adult ALL: Optimized Use

- 1st Salvage!
- Reducing leukemia burden
- Increasing dose
- Target expression
- Target loss
- Relapse from extramedullary compartment
- Upregulation of PD-1/PD-L1
- Combination with BH3 mimetics
- Downregulation of T-regs
- Biomarkers
- Early Response
- **Consolidation/Maintenance**

  In patients without SCT option

  - continued first-line chemotherapy

  - at least maintenance MP/MTX/i.th.

  - booster cycles with Blinatumomab?

CD19 Antibodies

More to come?

- Current bispecific antibody Blinatumomab effective particularly in MRD+ ALL and entered first-line therapy independent of MRD based on randomized trial
- Limited efficacy in higher-tumor burden
- Poor outcome of R/R B-precursor ALL in real-world (GMALL data)
- Issues with 28d continuous infusion
- Relapse after immunotherapy is a relevant issue

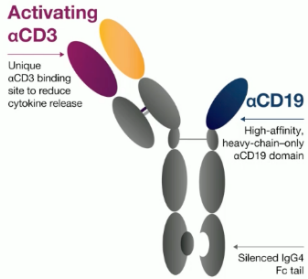
AZD0486 in adolescent and adult patients with R/R B-cell ALL (SYRUS Study)

Aldoss et al, EHA 2025

Introduction

- Surovatamig, previously known as AZD0486, is a novel IgG4 fully human CD19×CD3 bispecific T-cell engager[1] designed for low-affinity CD3 binding to reduce cytokine release from T-cell activation while preserving T-cell cytotoxicity against malignant B cells
- A phase 1, FIH trial in patients with B-NHL (NCT04594642) demonstrated activity and tolerability of surovatamig in R/R FL and DLBCL[2,3]
- Here, we present the preliminary results from a dose-escalation study of surovatamig in patients with R/R B-ALL (SYRUS; NCT06137118)

Surovatamig



B-ALL, B-cell acute lymphoblastic leukemia; B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FC, fragment crystallizable; FIH, first-in-human; FL, follicular lymphoma; IgG, immunoglobulin G; R/R, relapsed/refractory.

1. Malik-Chaudhry HK, et al. *MAbs*. 2021;313:1890411. 2. Hou JZ, et al. *Blood*. 2024;144(Suppl 1):341. 3. Gaballa S, et al. *Blood*. 2024;144(Suppl 1):868.

SYRUS Study (Part A Dose Escalation): Surovatamig in B-ALL

Key Eligibility Criteria

- Age 16y+
- CD19+ (any level of expression)
- R/R after ≥2 prior lines or after 1L if not eligible or has no other available SoC options
- Ph(-); Ph(+) with R/R disease despite treatment with ≥2 different TKIs, or with intolerance or contraindications to TKIs
- Prior exposure to CD19 treatment allowed independent of response

Assessments

- Bone marrow and peripheral blood assessments including PET/CT if needed to confirm EMD involvement
- CRS and ICANS graded using ASTCT criteria[1]
- Disease assessment at end of each cycle following ELN 2022/NCCN criteria using MFC (local lab) and central NGS for MRD assessment

Objectives

- Primary: Safety/tolerability of surovatamig
- Secondary: Efficacy, PK,[a] immunogenicity[a]

1L, first line; ASTCT, American Society for Transplantation and Cellular Therapy; B-ALL, B-cell acute lymphoblastic leukemia; CRS, cytokine release syndrome; ELN, European LeukemiaNet; EMD, extramedullary disease; ICANS, immune effector cell-associated neurotoxicity syndrome; MFC, multiparametric flow cytometry; MRD, minimal residual disease; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PET/CT, positron-emission tomography/computerized tomography; Ph(-)/Ph(+), Philadelphia chromosome negative/positive; PK, pharmacokinetics; R/R, relapsed/refractory; SoC, standard of care; TKI, tyrosine kinase inhibitor; y, years.

[a]Detailed dataon PK and immunogenicity not yet available.

1. Lee DW, et al. Biol Blood Marrow Transplant. 2019;25:625-38.

AZD0486 in adolescent and adult patients with R/R B-cell ALL (SYRUS Study)

Aldoss et al, EHA 2025

Characteristic	Total (N=31) n (%)
Age, median (range), y	56 (17–75)
Female	13 (42)
Ph (+)	6 (19)
Median (range) prior therapies	3 (2–9)
Prior CD19 targeted therapy exposure	19 (61)
Blinatumomab-exposed	16 (52)
CAR-T-exposed	11 (35)
Double-exposed	8 (26)
Allo-SCT	10 (32)
Mean (range) bone marrow blasts	61% (5%–97%)
≥50% bone marrow blasts	21 (68)

Most Common G3+ Treatment-Emergent Adverse Events (>5%)

Adverse Events, N=31, n (%)	G3	G4	G5
Non-Hematologic			
Infection	6 (19)[a]	1 (3)[b]	3 (10)[c]
Febrile neutropenia	6 (19)	-	-
ALT/AST increased	2 (6)	-	-
Hematologic			
Neutropenia	3 (10)	7 (23)	-
Lymphopenia	2 (6)	4 (13)	-
Thrombocytopenia	2 (6)	5 (16)	-
Anemia	2 (6)	-	-

- 2 patients experienced DLTs:
  - Both had prolonged cytopenia in the context of MLFS; 1 also had grade 3 AST increased with concomitant use of posaconazole
  - Both continue to receive the target dose without significant cytopenia
- AEs leading to treatment discontinuation were reported in 4 (13%) patients and were deemed unrelated to surovatamig

Dash (-) indicates no patients with an event.
[a]Sepsis, COVID-19, carbapenemase infection, hepatitis candidiasis, herpes zoster disseminated, oral herpes, pneumocystis jirovecii pneumonia, pneumonia, systemic candida (n=1 each). [b]Sepsis (n=1). [c]Sepsis, septic shock, and COVID-19 (n=1 each). AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; G, grade; MLFS, morphologic leukemia free state.

IR-AEs, n (%)	During SUD		After TD		
	During SUD1 n=13	During SUD2 n=18	After 2.4 mg n=10	After 7.2 mg n=12	After 15 mg n=6
CRS Any	4 (31)	13 (72)	3 (30)	3 (25)	-
CRS G2	2 (15)	5 (28)	1 (11)	1 (8)	-
CRS G3	-	**1 (6)**	-	-	-

- No G4+ CRS events were reported

AZD0486 in adolescent and adult patients with R/R B-cell ALL (SYRUS Study)

Aldoss et al, EHA 2025

Dose-Dependent Enhanced Efficacy in ITT and CD19-Exposed Populations

Response, n/N (%)	DL1 (SUD: 0.09/0.27/1.0; TD: 2.4 mg) (n=13)	DL2 (SUD: 0.27/1.0/2.4; TD: 7.2 mg) (n=12)	DL3 (SUD: 0.27/1.0/2.4; TD: 15 mg) (n=6)
ORR EoC1 (CR/CRi) (ITT)	**6/13 (46)**	**7/12 (58)**	**5/6 (83)**
CR/CRi MRDneg (local flow [10^{-4}])	5/6 (83)	7/7 (100)	5/5 (100)
Disease relapse	2/6 (33)	0/7	0/5
ORR (CR/CRi) by prior therapy subgroup[a,b]			
Blinatumomab-exposed	4/9 (44)	1/4 (25)	3/3 (100)
CAR-T-exposed	1/3 (33)	2/3 (67)	4/5 (80)
Double-exposed	1/3 (33)	1/2 (50)	3/3 (100)
Triple-exposed (+Inotuzumab)	0/2 (0)	1/2 (50)	3/3 (100)
ORR (CR/CRi) (in patients with EMD)[a]	**2/3 (67)**	**2/2 (100)**	**0/0**

[a]Median follow-up: 97 days (range, 35-401 days); [b]Prior therapy subgroups are not mutually exclusive.
CAR-T, chimeric antigen receptor T-cell therapy; CR, complete response; CRi, complete response with incomplete count recovery; DL, dosing level; EMD, extramedullary disease; ITT, intent-to-treat; MRDneg, minimal residual disease negative; ORR, overall response rate; SUD, step-up dosing; TD, target dose.

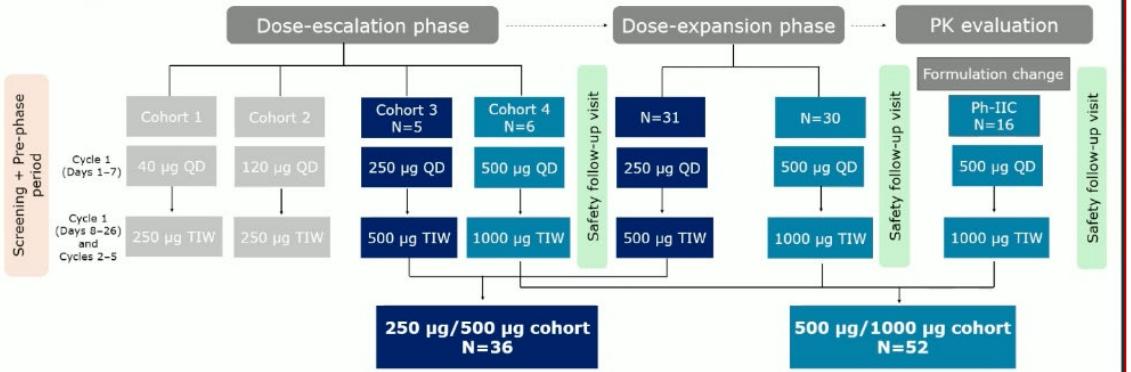
Subcutaneous blinatumomab in R/R B-cell ALL: Phase I/II dose Expansion Study

Jabbour et al, AMJ 2024, EHA 2025, and Lancet Haematol 2025

SC Blinatumomab in R/R B-ALL – Eligibility Criteria

- ✅ Adult patients with R/R B-ALL and:
  - Refractory to primary induction or ≥1 salvage therapy
  - Untreated first or greater relapse
  - Prior anti-CD19 therapy allowed if blasts still express CD19
  - ≥5% bone marrow blasts
  - ECOG score ≤2
- ❌ Patients with
  - Isolated extramedullary or active central nervous system leukemia
    (Patients were included if documented negative CSF following intrathecal chemotherapy)
  - Central nervous system pathology
  - HSCT within 12 weeks, chemotherapy or radiotherapy within 2 weeks, or immunotherapy within 4 weeks

SC Blinatumomab in R/R B-ALL – Study Design and Endpoints



- **Primary endpoint:** CR/CRh within two cycles
- **Select secondary endpoints:** MRD negative CR/CRh, RFS, OS, duration of response, adverse events

Subcutaneous blinatumomab in R/R B-cell ALL: Phase I/II dose Expansion Study

Jabbour et al, AMJ 2024, EHA 2025, and Lancet Haematol 2025

SC Blinatumomab in R/R B-ALL – Baseline Demographics and Clinical Characteristics

Data cut-off: 28 November 2024

Demographics and clinical characteristics	250 µg/500 µg cohort N = 36	500 µg/1000 µg cohort N = 52	Total N = 88
Male	22 (61%)	33 (63%)	55 (63%)
Age, mean [range]	46 [19-78]	50 [19-76]	48 [19–78]
B-ALL Ph+	7 (19%)	8 (15%)	15 (17%)
Prior lines of therapy, median [range]	2 [1-6]	2 [1-7]	2 [1-7]
Patients who received prior anti-cancer therapy			
Blinatumomab	8 (22%)	9 (17%)	17 (19%)
CAR-T cell therapy	7 (19%)	7 (14%)	14 (16%)
HSCT	11 (31%)	14 (27%)	25 (28%)
Inotuzumab ozogamicin	11 (31%)	18 (35%)	29 (33%)
Bone marrow blast %, median [range]	70% [5-99]	59% [5-98]	60% [5-99]
Primary refractory at enrollment	5 (14%)	7 (13%)	12 (14%)
Extramedullary disease	1 (3%)	3 (6%)	4 (5%)

Subcutaneous blinatumomab in R/R B-cell ALL: Phase I/II dose Expansion Study

Jabbour et al, AMJ 2024, EHA 2025, and Lancet Haematol 2025

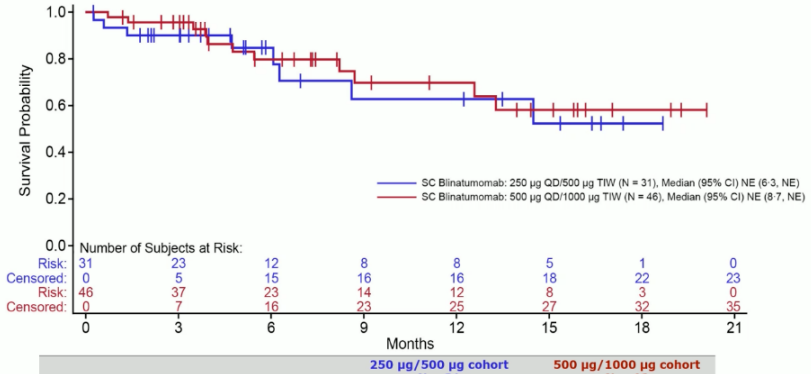
SC Blinatumomab in R/R B-ALL – Complete Remission

	250 µg/500 µg cohort N = 36	500 µg/1000 µg cohort N = 52	Total N = 88
Response within 2 cycles			
CR/CRh	**27 (75%)**	**41 (79%)**	**68 (77%)**
CR/CRh, MRD<10^{-4}	24/27 (89%)	38/41 (93%)	62/68 (91%)
CR/CRh/CRi	32 (89%)	48 (92%)	80 (91%)
CR/CRh/CRi, MRD<10^{-4}	29/32 (91%)	43/48 (90%)	72/80 (90%)

Subcutaneous blinatumomab in R/R B-cell ALL: Phase I/II dose Expansion Study

Jabbour et al, AMJ 2024, EHA 2025, and Lancet Haematol 2025

SC Blinatumomab in R/R B-ALL – Overall Survival (OS)



	250 µg/500 µg cohort N = 31	500 µg/1000 µg cohort N = 46
Duration of follow-up (months), median [IQR]	6 [3–15]	7 [4–16]
12-month OS estimate, % [95% CI]	63 [35–81]	70 [48–84]

SC Blinatumomab in R/R B-ALL – Treatment-related Adverse Events

Treatment-related adverse events (TRAEs)	250 µg/500 µg cohort n = 36	500 µg/1000 µg cohort n = 52
Any TRAE	35 (97%)	52 (100%)
Grade 3	17 (47%)	24 (46%)
Grade 4	11 (31%)	11 (21%)
Serious	20 (56%)	35 (67%)
Fatal	0 (0%)	0 (0%)
Leading to drug interruption	19 (53%)	31 (60%)
Leading to drug discontinuation	6 (17%)	6 (12%)
Key events		
Cytokine release syndrome (CRS)		
Any grade	30 (83%)	49 (94%)
Grade ≥3	6 (17%)	12 (23%)
Grade 4	0 (0%)	1 (2%)
Neurologic events (including ICANS)		
Any grade	20 (56%)	40 (77%)
Grade ≥3	10 (28%)	14 (27%)
Grade 4	1 (3%)	1 (2%)

Most of the CRS and neurologic events resolved with subcutaneous blinatumomab treatment interruption and/or supportive care measures such as corticosteroids, IV fluids, anti-pyretics, and/or tocilizumab, **without blinatumomab discontinuation.**

Experimental Options in B-Precursor ALL by Subgroup

B-precursor ALL

CD20 Bispecifics, CD79a antibody

Philadelphia chromosome-like (Ph-like) ALL

- **Target**: Diverse kinase-activating alterations, eg, JAK-STAT, ABL-class fusions
  - **JAK inhibitors** (eg, **Ruxolitinib**) – for CRLF2 rearrangements or JAK mutations
  - **ABL inhibitors** (eg, **Dasatinib**, **Ponatinib**) – for ABL-class fusions
  - **MEK inhibitors** – if RAS/MAPK pathway is activated
  - **Tropomyosin inhibitor (eg, Larotrectinib) -** NTRK fusions

FLT3-mutant ALL (rare, mostly in KMT2A-rearranged ALL)

- **Target**: FLT3 tyrosine kinase
  - **Midostaurin**, **Gilteritinib** – FLT3 inhibitors

KMT2A-rearranged ALL (MLLr)

- **Target**: Dysregulated epigenetic machinery and menin-MLL interaction
  - **Menin inhibitors** (eg, **SNDX-5613**, **KO-539**) – in clinical trials

MENIN inhibitor-based therapy in acute leukemia: latest updates from the 2024 ASH annual meeting

Sun et al, Exp Hem Onc 2025

Table 1 Updates of MENINi monotherapy for refractory/relapsed AL treatment in the 2024 ASH annual meeting

Inhibitor	Phase	Registration	Disease[1]	Genetic subtypes	Efficacy outcomes						Safety profile	Ref
					Evaluated cases[2]	ORR	cCR	CR/CRh	mTTFR[3] (months)	mDoR (months)		
Revumenib	2	NCT04065399	AML, ALL, MPAL	*KMT2Ar*	97	64% (62/97)	42% (41/97)	23% (22/97)	/	6.4 in CR/CRh	Grade ≥ 3 febrile neutropenia (39%), anemia (20%), thrombocytopenia (16%), DS (15%), neutropenia (15%), leukopenia (15%), QTc prolongation (13%)	[3]
Bleximenib	1	NCT04811560	AML, ALL, other AL	*KMT2Ar*, *NPM1m*	150 mg BID: 20	50% (10/20)	40% (8/20)	30% (6/20)	/	/	All grade DS (13%), neutropenia (12%), thrombocytopenia (11%), QTc prolongation (0.8%)	[4]
					90/100 mg BID: 20	50% (10/20)	40% (8/20)	35% (7/20)	1.0	6.4		
					45 mg BID: 13	39% (5/13)	23% (3/13)	23% (3/13)	/	/		
Enzomenib	1	NCT04988555	AML, ALL	*KMT2Ar*, *NPM1m*, Others	*KMT2Ar*: 22	59% (13/22)	23% (5/22)	/	1.0	/	All grade febrile neutropenia (22.2%), DS (11.1%), QTc prolongation (5.0%)	[5]
					NPM1m: 13	54% (7/13)	23% (3/13)					
					CALM-AF10: 1	100% (1/1)	100% (1/1)					
BN104	1/2	NCT06052813	AML	*KMT2Ar*, *NPM1m*, *NUP98r*	11	89% (8/9)	33% (3/9)	/	0.9	/	All grade febrile neutropenia (20%), DS (10%), QTc prolongation (10%)	[6]

[1]The type of disease for current enrolled patients;

[2]The number of patients whose efficacy was evaluable;

[3]The definition of mTTFR: median time to first response, in which "response" referred to objective response

Menin inhibitors in pediatric acute leukemia

Cuglievan et al, Leukemia 2024

Table 1. Current and future trials of menin inhibitors in pediatric patients.

Current					
Clinical trial/sponsor	**Phase**	**Treatment**	**Biomarkers**	**Age eligibility**	**Location**
AUGMENT-101 (NCT04065399)	1/2	Revumenib monotherapy	*KMT2A-r, NPM1-m, NUP98-r*	All ages; AML and ALL	Multisite- U.S. and Europe
AUGMENT-102 (NCT05326516)	1	Revumenib + FLA	*KMT2A-r, NPM1-m, NUP98-r*	All ages AML and ALL	Multisite- U.S. and Europe
SAVE (NCT05360160)	1/2	Revumenib + Venetoclax+ ASTX727	*KMT2A-r, NPM1-m, NUP98-r* (Frontline and Relapse)	≥12 years AML and MPAL	MD Anderson Cancer Center
TINI 2 (NCT05848687)	1	Ziftomenib + Multiagent	*KMT2A-r*	Infant ALL	Stanford University
AALL2121 / COG (NCT05761171)	2	Revumenib + Multiagent	*KMT2A-r*	30 days to 6 years ALL and MPAL	Multisite US
(NCT04811560)	1	JNJ-75276617 + Multiagent	*KMT2A-r, NPM1-m, NUP98-r, NUP214-r*	>12 years. AML and ALL	Multisite- US and Europe
(NCT06177067)	1	Revumenib + Venetoclax + Azacytidine.	*KMT2A-r, NPM1-m, NUP98-r*	1-30yo. AML and ALL	St Jude Children's Hospital
FUTURE					
	1	Ziftomenib + Venetoclax + Azacytidine	*KMT2A-r, NPM1-m, NUP98-r*	<40 yo; AML and ALL	MD Anderson Cancer Center
APAL2020K ITCC-101/COG/ PEDAL	1	Ziftomenib + FLA	*KMT2A-r, NPM1-m, NUP98-r*	<18 yo; AML and ALL	Multisite- U.S. and Europe
	1	Ziftomenib + Venetoclax + Gemtuzumab	*KMT2A-r, NPM1-m, NUP98-r, UBTF-ITD*	<40 yo; AML and ALL	MD Anderson Cancer Center
	1	Revumenib + AD + Gemtuzumab	*KMT2A-r, NPM1-m, NUP98-r, UBTF-ITD*	<40 yo; AML and ALL	MD Anderson Cancer Center

*Early relapse is defined as relapse within one year of first complete remission.
FLA fludarabine and cytarabine, *IDA* idarubicin, *A* cytarabine, *D* daunorubicin.

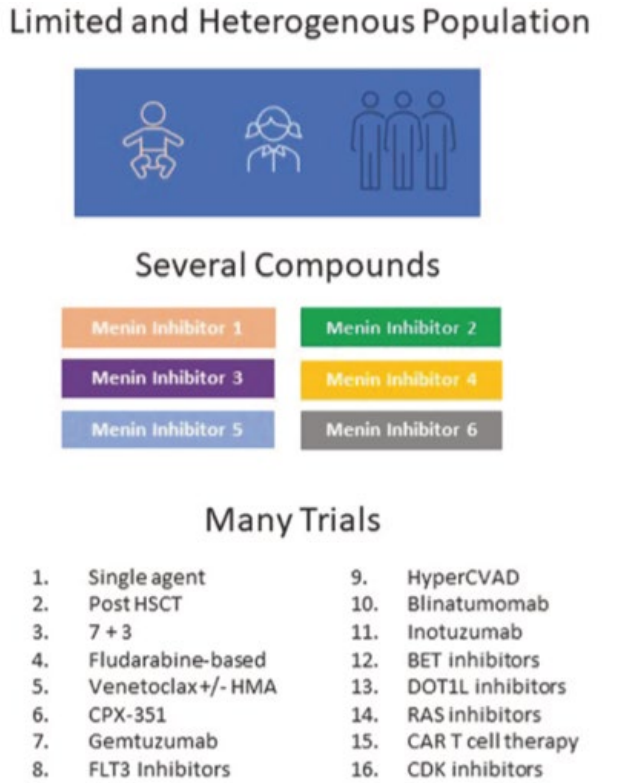


Fig. 4 Future combinations of menin inhibitors in pediatric leukemia. Challenges in a diverse and small population.

Therapy of Relapsed/Refractory ALL

1. Definitions
2. Results of Standard Therapies
3. Principles of Targeted Therapies
4. B-precursor ALL
5. T-ALL
6. (SCT)
7. Summary

Nelarabine in R/R T-ALL

Gökbuget et al, Blood 2011

Table 2. Results of response evaluation in adult patients with clinical relapse (N = 126)

	Result after cycle 1, N (%)	Overall result after 1-3 cycles,* N (%)
CR	40 (32)	45 (36) **36%**
PR	24 (19)	12 (10)
Failure	59 (47)	66 (52)
Death on therapy	1 (1)	1 (1)
Withdrawal	2 (2)	2 (2)

*Result after the last administered cycle.

74% refractory to last approach

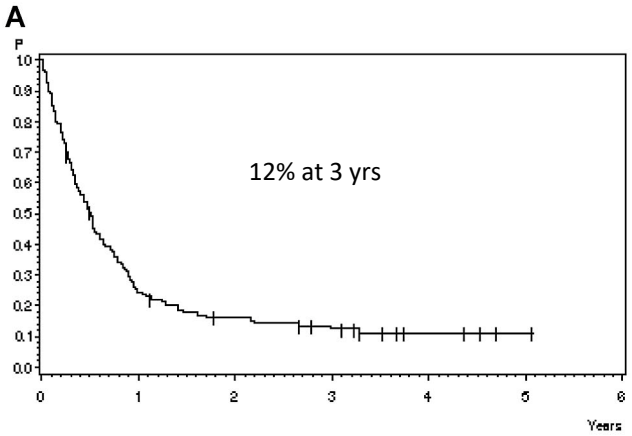
Poor prognostic features

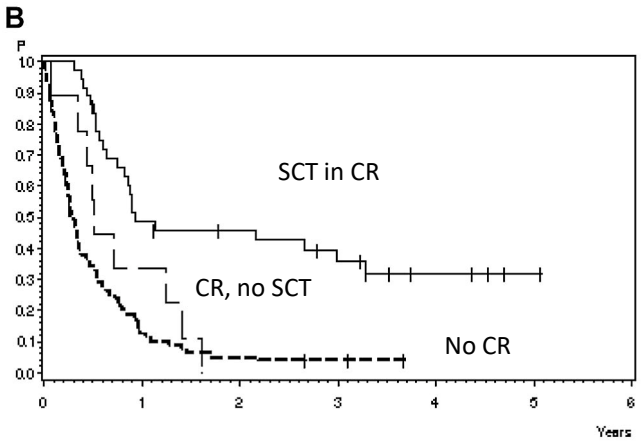
For CR:

Diagnosis:	T-ALL vs LBL (42% vs 0%)
Gender:	Male vs Female (30% vs 52%)
Involvement:	BM vs Extram. (43% vs 21%)

For OS:

Age:	18-45 vs >45 (16% 3y vs 0%)
Phenotype:	Thy vs Other (15% 3y vs 10%)





T-ALL: Relapse BM

Early Relapse

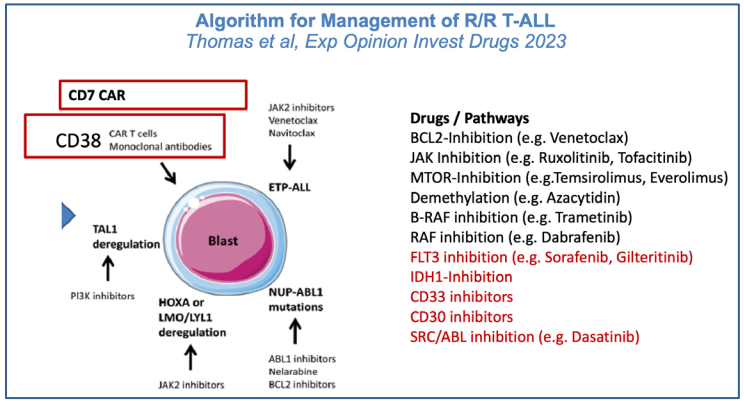
Nelarabine-Cyclo
or **Trial**

- Goal to obtain mol CR
- SCT in mol CR if possible
- If no SCT: Cons./Maint.
- **For "Other": Toolkit of regimens**

Late

Repeated induction + Bortezomib

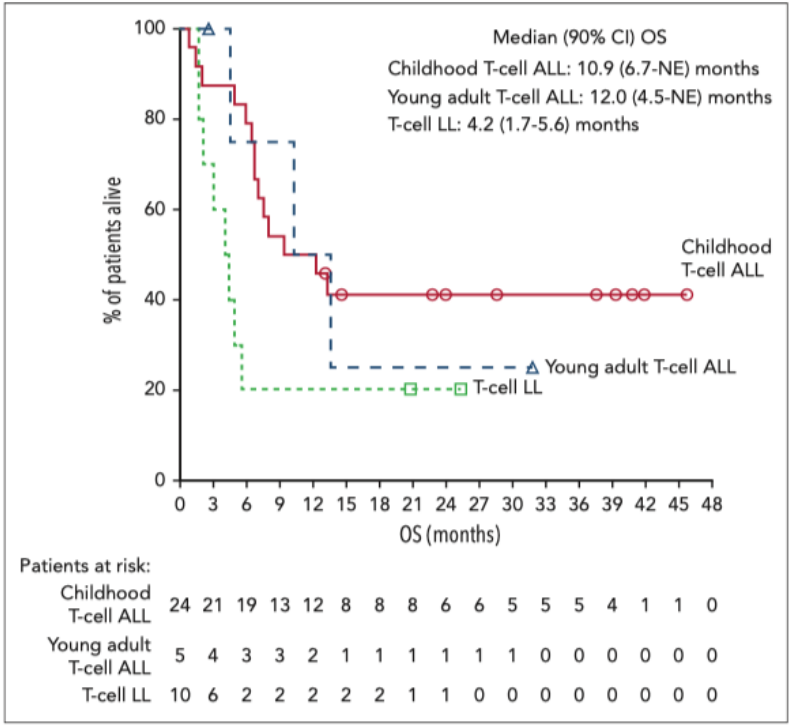
If no CR: Treat as refractory relapse
If no Mol CR: Treat as Mol Fail



Daratumumab in pediatric relapsed/refractory acute lymphoblastic leukemia or lymphoblastic lymphoma: the DELPHINUS study

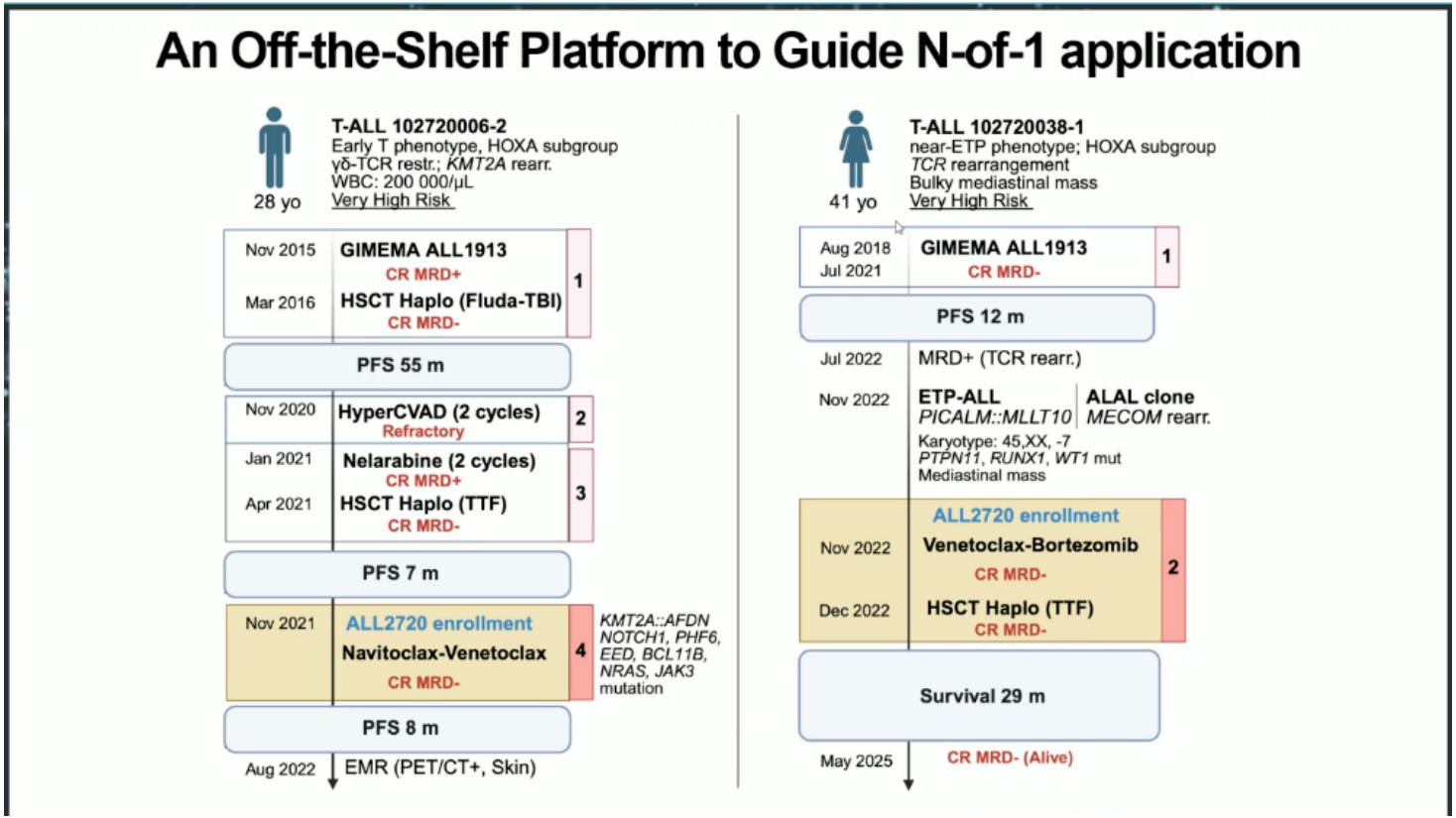
Bhatla et al, Blood 2024

	T-cell ALL	T-LBL
Evaluable	29	10
Age	2-25	5-22
Extramed	17-40%	100%
CR	**52%**	**40%**
CRi/PR*	31%	10%
MRD neg (any)	**41%**	**50%**
SCT rate	**72%**	**30%**



Advancing chemogenomic strategies for functional precision medicine in relapsed/ refractory T-ALL and ETP- ALL: Preliminary results of the GIMEMA ALL2720 trial

Pagliaro et al, EHA 2025



Therapy of Relapsed/Refractory ALL

1. Definitions
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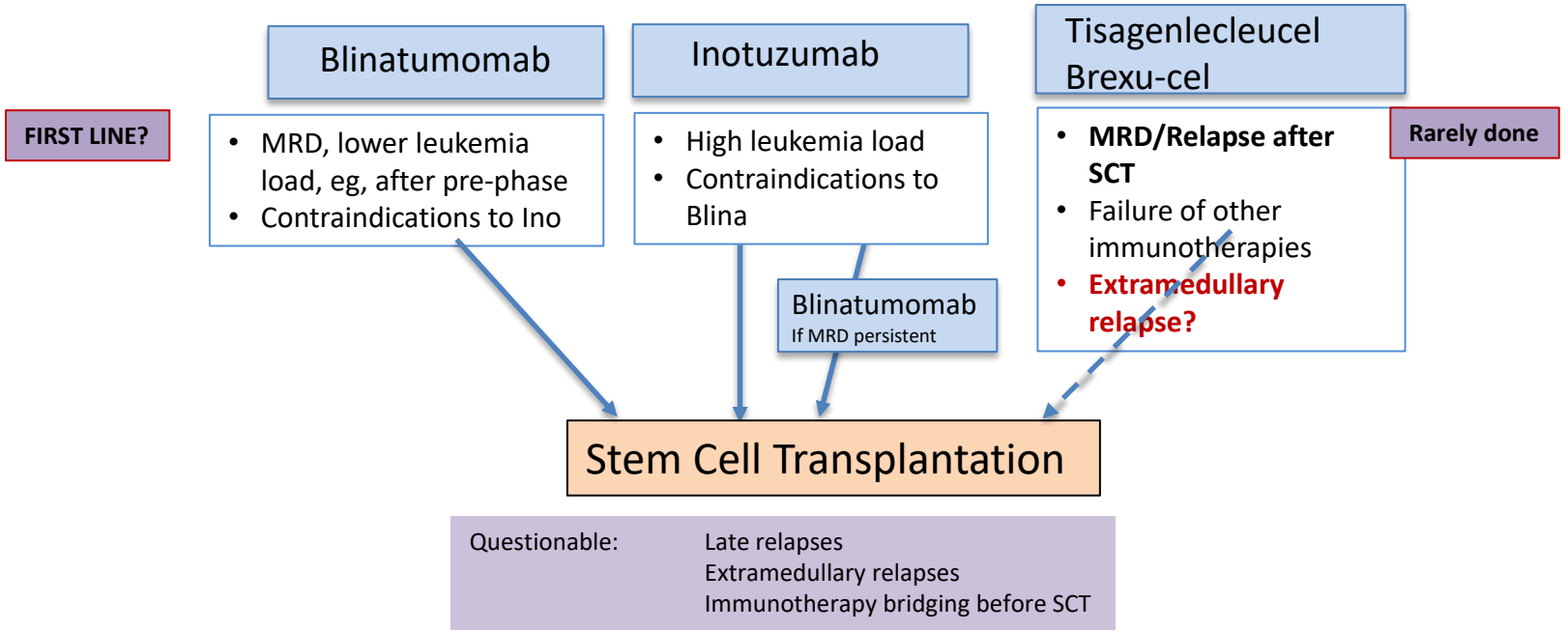
4. B-precursor ALL
5. T-ALL
6. (SCT)
7. Summary

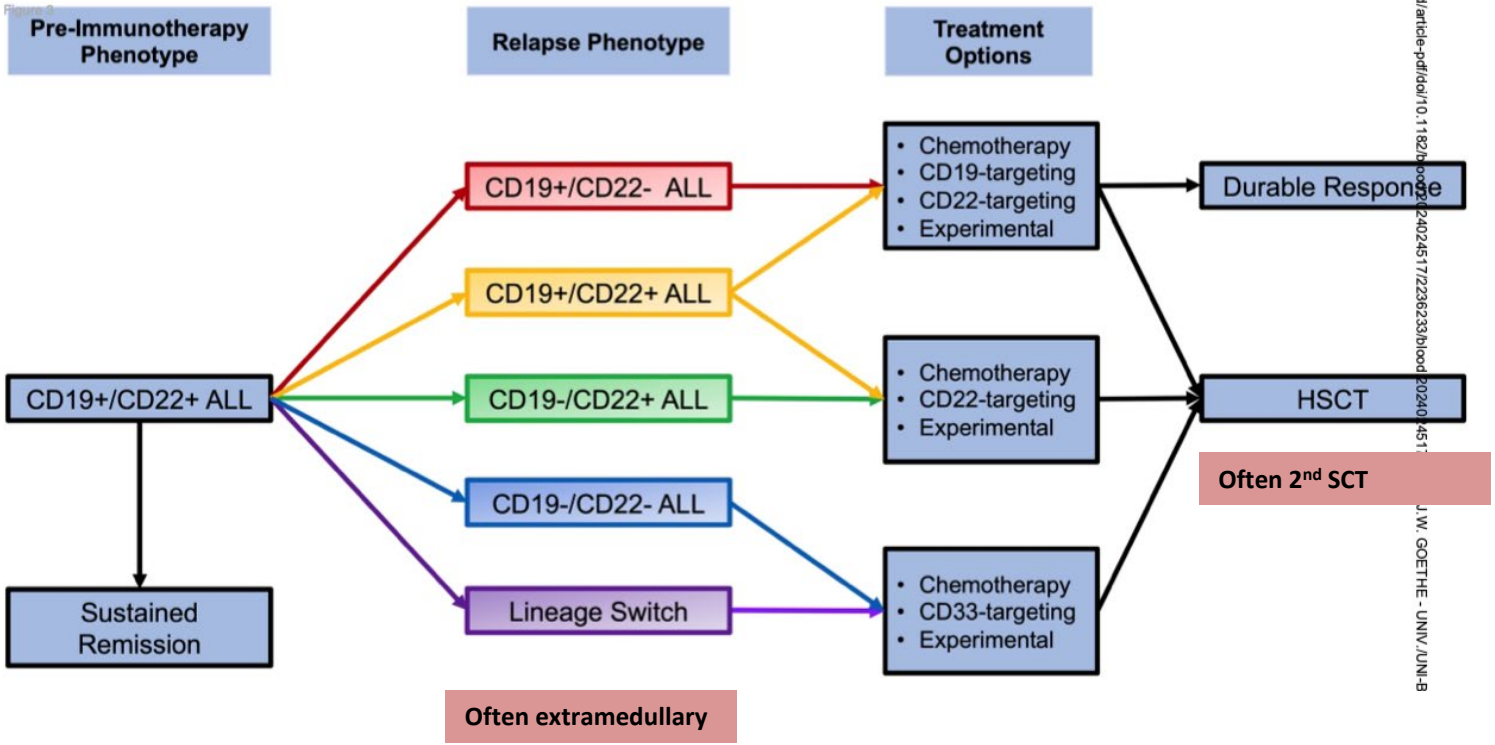
Treatment of R/R B-precursor ALL
Potential Decision Making Blinatumomab-Inotuzumab-CAR T-Cells

Adapted from Dhakala et al, Leuk Lymph, 2019



Post-Immunotherapy Relapse B-ALL

Lamble et al, Blood 2024



Multiple Relapsed ALL

- **Best option: Identification of molecular failure or molecular relapse**
- **Molecular characterization and target identification immediately at relapse**
- **Definition of treatment sequence with/without SCT**
- **CNS prophylaxis**
- **Individual concepts in case of extramedullary involvement**
- **Clinical trials/experimental**

What can go wrong in relapse therapy – real world

- Blinatumomab in high tumor burden
- Antibodies only in extramedullary disease
- Many cycles of single drug therapy
- No change of therapy in non-response
- No consolidation/maintenance after achievement of CR
- Postponing SCT to achieve MRD negativity
- Suboptimal conditioning
- No MRD follow-up after SCT

Global Leukemia Academy

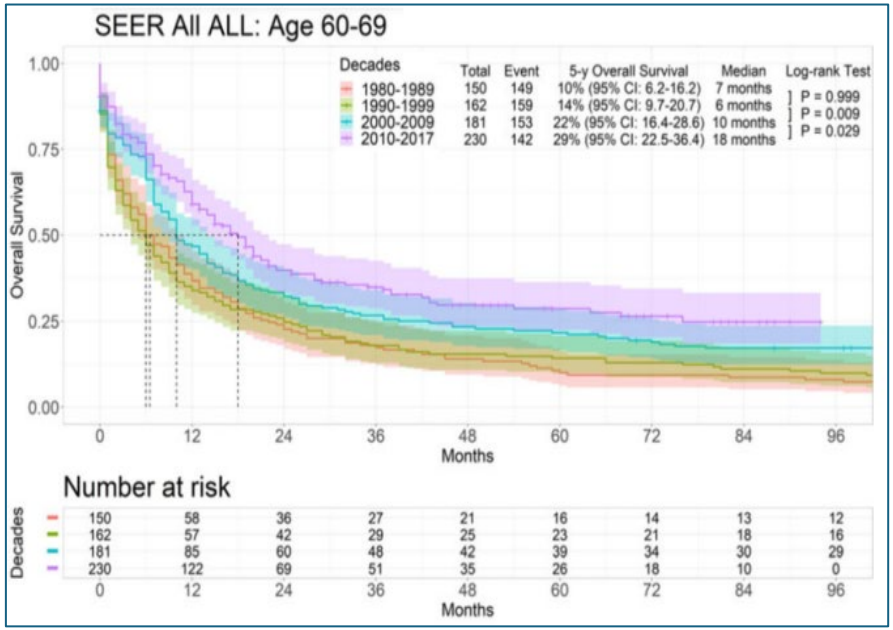
Current treatment options for R/R ALL in elderly and frail patients

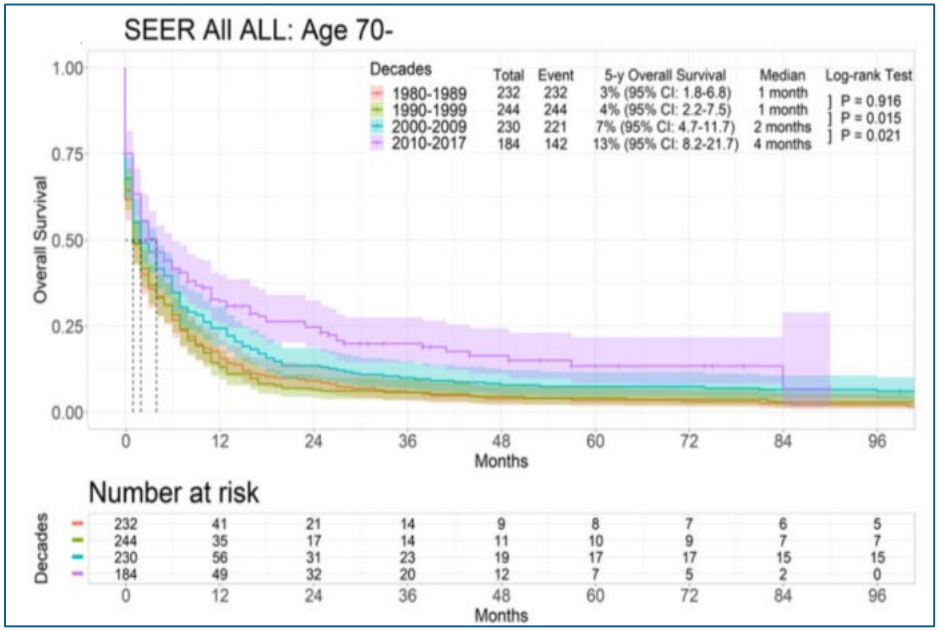
Josep-Maria Ribera

APTITUDE HEALTH®

Historical survival of older/elderly patients with ALL

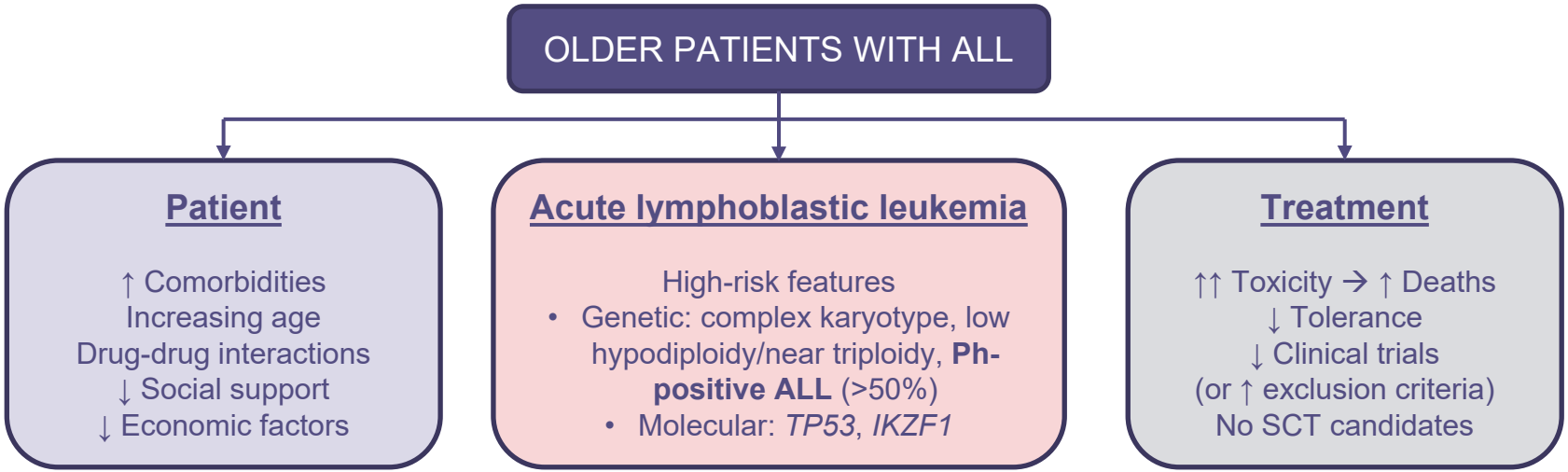
Survival improvement in patients 60–70 years
Poor results for patients older than 70 years





Sasaki K, et al. *J Hematol*. 2021;96:1344.

Acute lymphoblastic leukemia in older/elderly patients



SELF-DESIGN based on: Fedorov VD, et al. *Curr Hematol Malig Rep*. 2016;11:165-174; Aldoss I, et al. *J Oncol Pract.* 2019;15:67-75; Gökbuget N, et al. *Hematology Am Soc Hematol Educ Program*. 2016;2016:573-579; Luskin MR, et al. *Hematology Am Soc Hematol Educ Program*. 2021;2021:7-14; Jammal N, et al. *Clin Adv Hematol Oncol*. 2022;20:161-168; Marks DI, et al. *Am Soc Clin Oncol Educ Book*. 2015;35:e343-e351.

Frailty in older and elderly patients with ALL

Comorbidity scoring

- Incidence of comorbidities is between 60%–84%
- Commonly observed comorbidities include diabetes, vascular disease, heart failure, and chronic lung disease
- Charlson Comorbidity Index (CCI)

Type of comorbidity	Younger patients (<55yrs)	Older patients (>55 yrs)	Frail patients
Arrhythmias	<1%	12%	22%
Cardiac disease	2%	19%	42%
Pulmonary (moderate)	8%	14%	28%
Hepatic (mild)	8%	11%	14%
Prior malignancies	2%	25%	22%
Diabetes	4%	22%	22%
Obesity (BMI >35 kg/m2)	9%	11%	14%
Infections	15%	18%	22%
Low HCT-CI risk score	54%	25%	8%
High HCT-CI risk score	18%	50%	59%

Wermann WK, et al. *Blood*. 2018;132:660.

Geriatric assessment necessary

Comprehensive geriatric assessment

- Necessary for patients >70 years old
- Dynamic!! Can get worse with therapies

- Predict chemotherapy toxicity
- Estimate (noncancer) life expectancy e.g. ePrognosis
- Functional assessment: instrumental activities of daily living (iADL)
- Comorbidity assessment: validated tool e.g. CCI
- Screening for falls: one question or gait/balance tests
- Screening for depression: Geriatric Depression Scale or other validated tool
- Screening for cognitive impairment: Mini-Cog, Mini-Mental etc.
- Screening for malnutrition: weight loss/body mass index, geriatric nutritional index
- Screening for fatigue
- Assessment of social status

Magnuson A, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:e96-e109.

Acute lymphoblastic leukemia in elderly and frail adults

PALLIATIVE APPROACH

LOW DOSES OF CHEMOTHERAPY

LOW DOSES OF CHEMOTHERAPY + IMMUNOTHERAPY

IMMUNOTHERAPY: Chemo free

CELLULAR THERAPY CAR T cells

Improvements evident in first-line therapy

Some improvements in R/R

Approaches to therapy in elderly frail R/R ALL

Immunotherapy (InO, Blin) as single therapy → **Not curative by itself**
SC blin?
AZD0486 (CD3-CD19 BiTE)?

Immunotherapy (InO → Blin) in combination, chemo free → **Data only in first line**

Immunotherapy + low-dose chemotherapy → **Useful for a subset of patients**

CAR T cells → **Potentially curative for a subset of patients. Best if low disease burden**

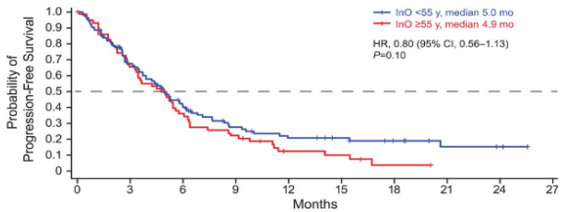
Immunotherapy as single treatment for R/R BCP-ALL in older patients

Inotuzumab: Phase 3, INO-VATE study

164 patients

	Median OS	CR	Median PFS	AlloSCT INO	AlloSCT SOC
<55 (n=104)	8.6 m	75%	5 m	53%	15%
>55 (n=60)	5.6 m	70%	4.9 m	27%	8%

Improved OS if AlloSCT also in >55 (9.4 vs 4.8 m)



AEs in >55 years

Higher incidence of Gr≥3:
Thrombocytopenia 57% vs 32%
Neutropenia 52% vs 44%
Febrile neutropenia 35% vs 22%

Similar rate of G3+

→ VOD 41% vs 17%
VOD mortality: 40% vs 14%
Mortality after HSCT 71% vs 57%

Blinatumomab

Subanalysis of R/R ALL older patients from two phase II trials with blinatumomab

261 patients

	CR	CR/CRh	MRD neg CR	AlloSCT
≥65 (n=36)	39%	56%	60%	15%
<65 (n=225)	35%	46%	70%	59%

SAEs 72% vs 64%

CRS 19% vs 10%

Neurologic AEs 72% vs 48%

Neurol G>3 28% vs 13%

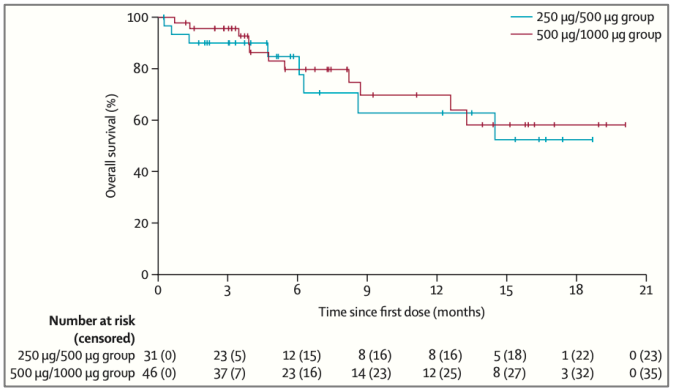
Aphasia/encephalopathy 34% vs 7%

Martinelli G, et al. *Eur J Cancer*. 2021;146:107-114; DeAngelo DJ, et al. *Blood Adv*. 2017;1;1167-1180; Kantarijan HM, et al. *N Engl J Med*. 2016;375:740-753; Jabbour E, et al. *Cancer*. 2018.

Subcutaneous blinatumomab monotherapy in R/R B-ALL

	250 µg/500 µg group (n=36)	500 µg/1000 µg group (n=52)
Sex*		
Male	22 (61%)	33 (63%)
Female	14 (39%)	19 (37%)
Age, years	46 (19–78)	50 (19–76)
Received previous anticancer therapy		
Blinatumomab	8 (22%)	9 (17%)
CAR T-cell therapy	7 (19%)	7 (13%)
HSCT	11 (31%)	14 (27%)
Inotuzumab ozogamicin	11 (31%)	18 (35%)
Criteria for entry to study		
Refractory to frontline therapy	17 (47%)	15 (29%)
Refractory to salvage therapy	4 (11%)	8 (15%)
First relapse with remission duration of <12 months	16 (44%)	24 (46%)
Untreated second or greater relapse	10 (28%)	12 (23%)
Relapse any time after allogeneic HSCT	11 (31%)	15 (29%)
Primary refractory at enrolment‡	5 (14%)	7 (13%)

	250 µg/500 µg group (n=36)	500 µg/1000 µg group (n=52)
Overall survival*	31	46
Alive	22 (71%)	34 (74%)
Overall survival estimates, % (95% CI)		
3-month survival	90% (72–97)	96% (84–99)
6-month survival	85% (63–94)	80% (62–90)
9-month survival	63% (35–81)	70% (48–84)
12-month survival	63% (35–81)	70% (48–84)
18-month survival	52% (23–75)	58% (35–76)
Patients with at least one post-baseline disease assessment	33 (92%)	50 (96%)
Complete remission	25 (69%)	31 (60%)
Complete remission with partial haematological recovery	2 (6%)	10 (19%)
Complete remission with incomplete haematological recovery	5 (14%)	7 (13%)
No response	1 (3%)	1 (2%)
Unevaluable	0	1 (2%)



Jabbour E, et al. *Lancet Haematol.* 2025;12:e529-e541.

AZD0486 (CD3-CD19 BiTE) in R/R ALL

Characteristic	DL1 (n=13)	DL2 (n=11)
Age, median (range), y	56 (25–73)	58 (22–75)
Male	10 (76.9%)	6 (54.5%)
Female	3 (23.1%)	5 (45.5%)
Median (range) prior therapies	3 (2–9)	3 (2–6)
Prior therapy exposure		
Blinatumomab-resistant	9 (69.2%)	3 (27.3%)
CAR-T-resistant	4 (30.8%)	3 (27.3%)
Double-exposed[a]	4 (30.8%)	2 (18.2%)
Mean (range) bone marrow blasts	63.8% (5%–97%)	48.8% (5%–99%)
≥50% bone marrow blasts	9 (69.2%)	5 (45.5%)

CRS	4 (1G2)	2 (1G2)
ICANS	0	1
Cytopenia	1	
Discontinuations	0	0
CR/CRi	6 (46%)	6/9 (67%)
MRD neg	5/6 (83%)	6/6 (100%)
CR in BM bl >50%	8/10	
CR in EMD	3/4	
Relapses	2/12	
Ongoing CR	10 (6-330d)	
HSCT	3	

Aldoss I, et al. EHA 2025. Abstract S117.

Mini-HCVD–InO–Blina in R/R ALL

- 133 pts (median age 37 yr; 17–87) Rx with mini-HCVD–InO (n = 67); same + Blina (n = 44); and DD mini-HCVD–InO–Blina (n = 22). AlloSCT 43%

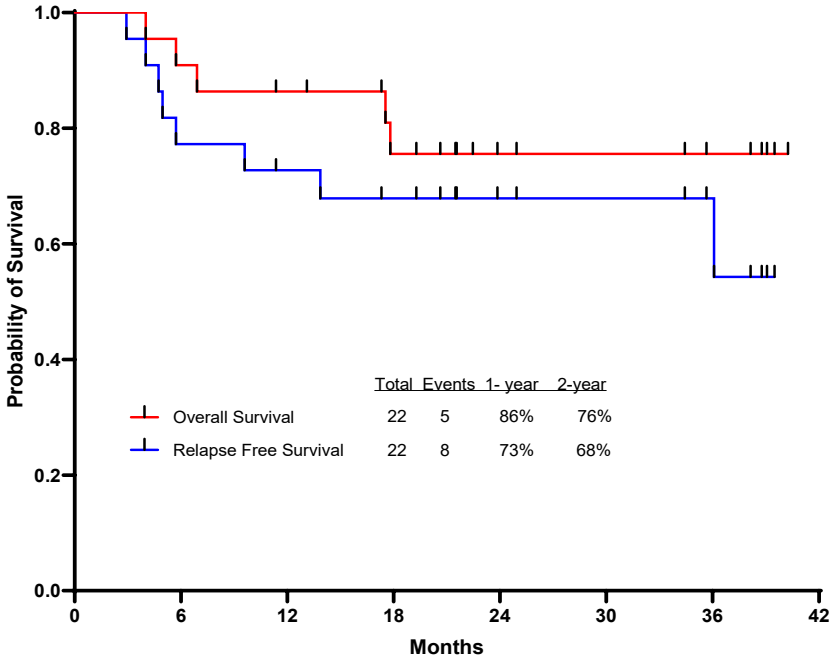
Parameter, %	Total (n = 133)	CT + InO (n = 67)	CT + InO + Blina (n = 44)	DD (n = 22)
ORR	86	76	93	100
CR	65	60	66	81
MRD neg	85	82	85	95
3-yr OS	-	34	50	76
3-yr RFS	-	35	44	68
1-yr OS (S1)	-	51 (63)	66 (66%)	90 (94%)

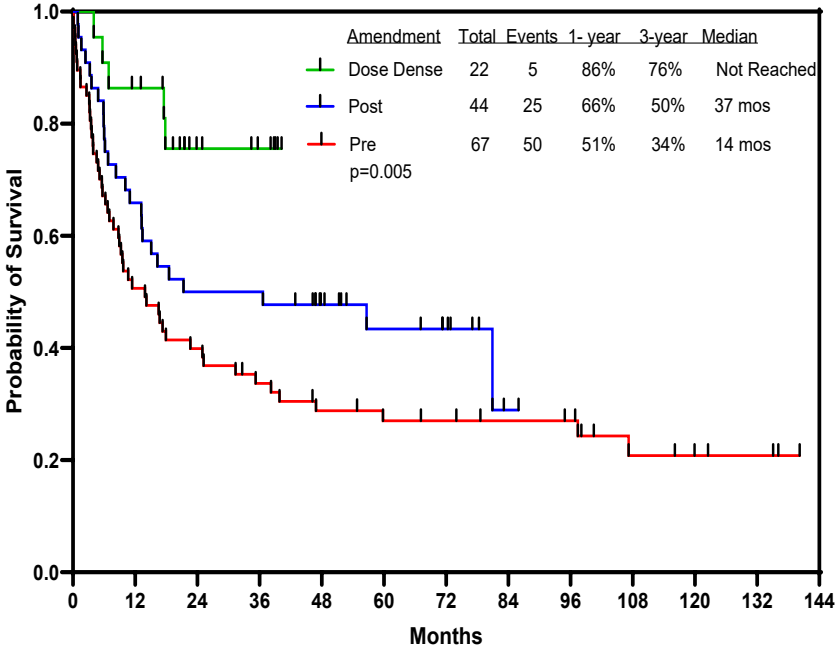
- 3-yr OS 54% in S1, 20% in S2
- 3-yr OS 60% with SCT vs 56% without
- SOS 10 pts: 9 (13%) initial vs (2%) later

Habib D, et al. *Blood*. 2024;144:811.

“Dose-dense” mini-HCVD + InO + Blina in R/R B-ALL

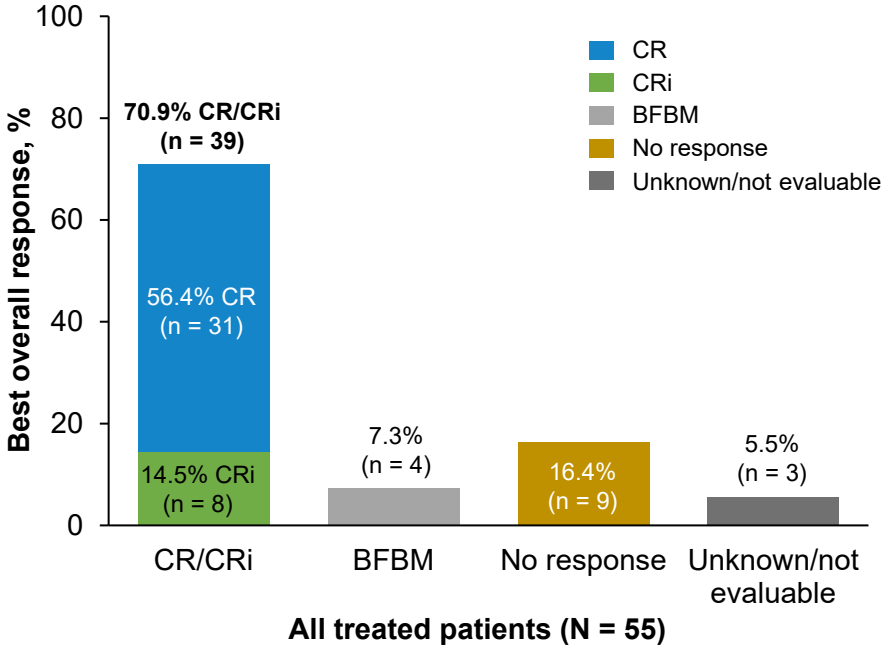
- 22 pts median age 41 yr (19-62) Rx; S1 86%
- ORR 100%, CR 81%; MFC MRD negative 95% (74% after C1); NGS MRD negative 94% (43% after C1)
- Median F/U 29 mo: 2-yr OS 76%; 2-yr RFS 68%





Jabbour E, et al. *Clin Lymphoma Myeloma Leuk*. 2024;24:S153; Jabbour E, et al. SOHO 2024. Abstract ALL-808.

Brexucabtagene in adults with R/R B-ALL (ZUMA-3)

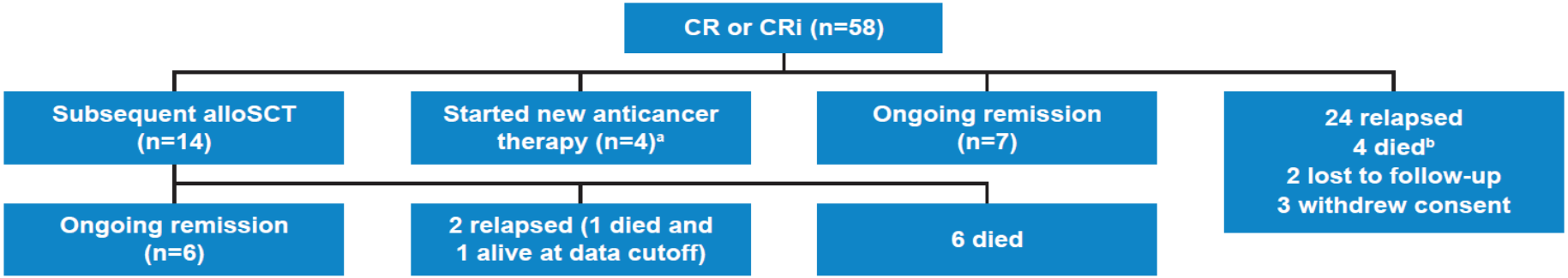


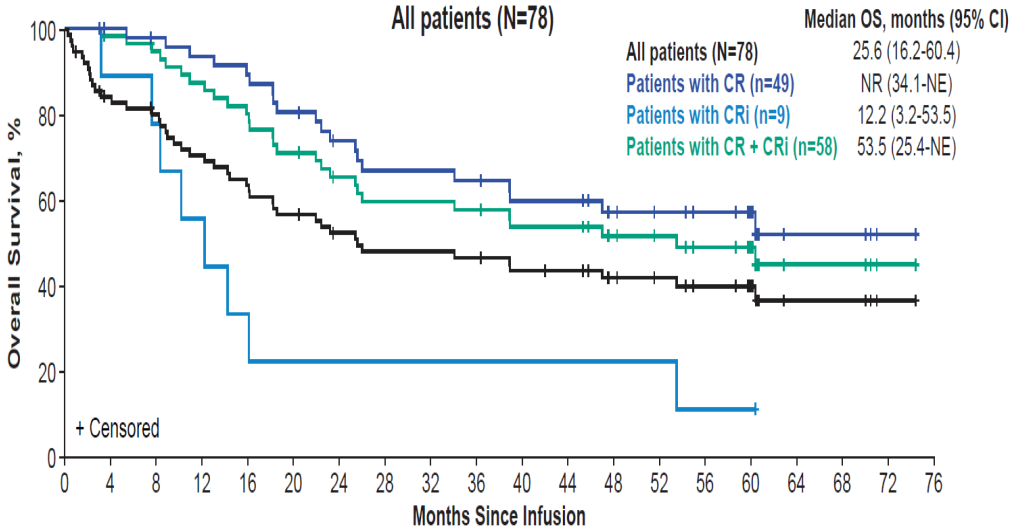
Covariates		Responding Patients/ Evaluable Patients	Percent of Patients With Response (95% CI)
Overall		39/55	71 (57–82)
Sex	Male	25/33	76 (58–89)
	Female	14/22	64 (41–83)
Age (years)	18-39	16/26	62 (41–80)
	40-64	15/21	71 (48–89)
	≥65	8/8	100 (63–100)
Baseline extramedullary disease	Yes	3/6	50 (12–88)
	No	36/49	73 (59–85)
CNS status at screening	CNS-1	34/47	72 (57–84)
	CNS-2	4/5	80 (28–99)
CD19 % lymphoblast baseline category based on central lab	≥95	29/41	71 (54–84)
	<95	9/12	75 (43–95)
% blasts in bone marrow at baseline	0–5	4/5	80 (28–99)
	>5–25	9/10	90 (55–100)
	>25–50	10/11	91 (59–100)
	>50–75	8/10	80 (44–97)
	>75–100	8/19	42 (20–67)
Philadelphia chromosome	Yes	12/15	80 (52–96)
	No	27/40	68 (51–81)

LDC regimen: Flu 25 mg/m^2 × 3d and Cy 900 mg/m^2 × 1d; T-cell dose: 1 × 10^6 CAR T cells/kg

Shah BD, et al. *Lancet*. 2021;398:491-502.

ZUMA-3: 5-year follow-up





- **7 out of 58 (12%) patients are in ongoing remission at 5 yr of follow-up**
- **No additional relapses noted between yr 4 and 5 of extended follow-up**
- **OS remains unchanged at 40%, at 5 yr**
- **No impact of subsequent alloHSCT**

Oluwole O, et al. EHA 2025. Abstract PF374.

Obecabtagene in adults with B-ALL (FELIX)

Overall response rates

Response	Phase 2 (N=111)			All the Patients Who Received Infusion (N=127)
	Cohort A (N=94)	Cohort B (N=10)	Cohort C (N=7)	
CR or CRi				
No. of patients	72	10	6	99
% (95% CI)	77 (67–85)	100 (69–100)	86 (42–100)	78 (70–85)
CR — no. (%)	52 (55)	9 (90)	4 (57)	73 (57)
CRi — no. (%)	20 (21)	1 (10)	2 (29)	26 (20)

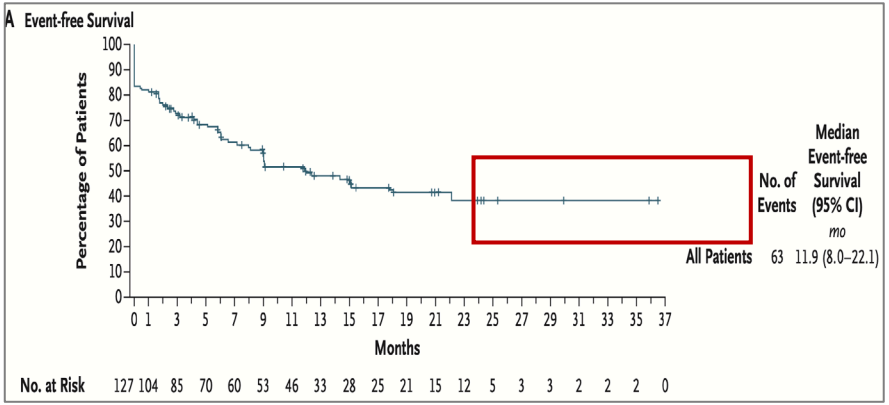
G3 CRS 2.5%; G3 ICANS 7.5%

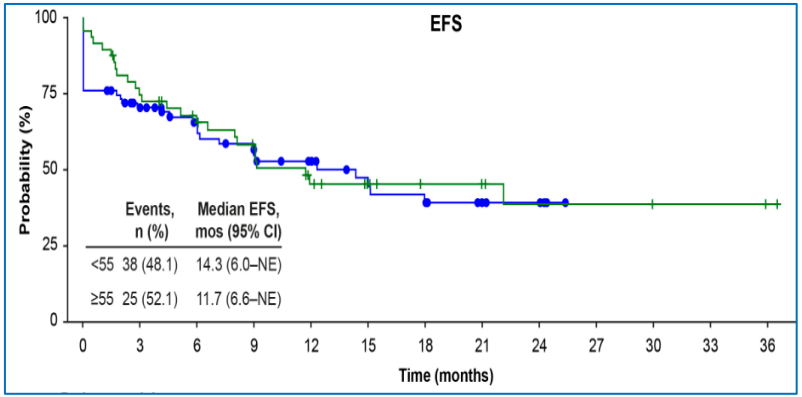
Table 1. Demographic and Disease Characteristics of the Patients before Enrollment.*

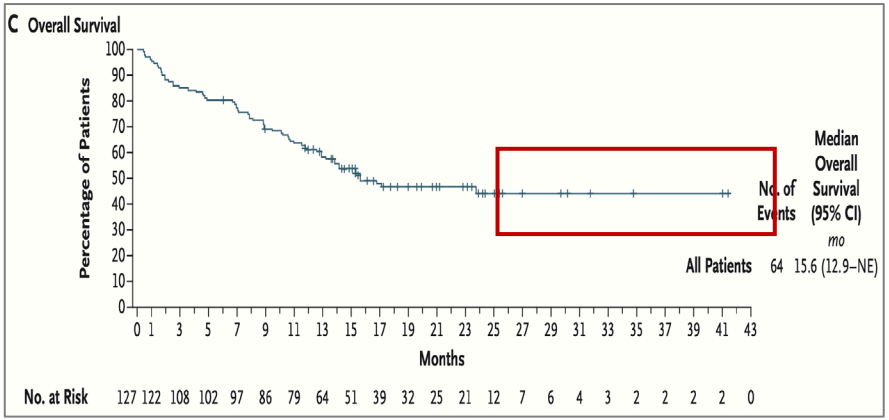
Characteristic	Cohort 2A Patients Who Received Infusion (N=94)†	All the Patients Who Received Infusion (N=127)‡
Demographic characteristics		
Age		
Median (range) — yr	50.0 (20–81)	47.0 (20–81)
≥65 yr — no. (%)	21 (22)	25 (20)
Sex — no. (%)		
Male	47 (50)	66 (52)
Female	47 (50)	61 (48)
Race — no. (%)§		
Asian	10 (11)	16 (13)
Black	2 (2)	2 (2)
White	70 (74)	94 (74)
Unknown	12 (13)	15 (12)
Hispanic or Latino ethnic group — no. (%)§		
Yes	29 (31)	38 (30)
No	58 (62)	80 (63)
Unknown	7 (7)	9 (7)
Previous therapies		
Median no. of previous lines of therapy (range)	2.0 (1–6)	2.0 (1–6)
Refractory to all previous lines of anticancer therapy — no. (%)	12 (13)	13 (10)
Refractory to first-line therapy — no. (%)	24 (26)	32 (25)
Had relapse within 12 mo after receipt of first-line therapy — no. (%)	41 (44)	60 (47)
Refractory to last previous line of therapy — no. (%)	51 (54)	66 (52)
Previous use of blinatumomab — no. (%)	33 (35)	53 (42)
Previous use of inotuzumab ozogamicin — no. (%)	30 (32)	40 (31)
Previous use of blinatumomab and inotuzumab ozogamicin — no. (%)	15 (16)	21 (17)
Previous allogeneic stem-cell transplantation — no. (%)	36 (38)	56 (44)
Disease characteristics		
Median percentage of bone marrow blasts (range) on morphologic analysis¶	58.9 (6–100)	40.0 (0–100)
Extramedullary disease — no. (%)	19 (20)	29 (23)
Philadelphia chromosome–positive disease — no. (%)	25 (27)	36 (28)

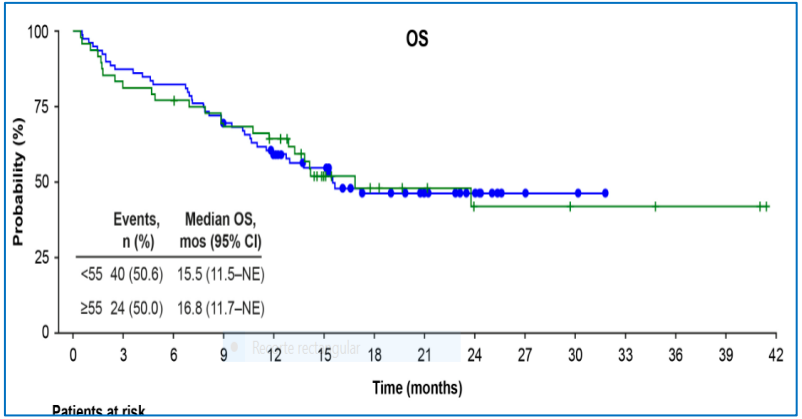
Roddie C, et al. *N Engl J Med*. 2024;391:2219-2230.

Obe-cel: Durable long-term responses in a subset of patients independent of age









Roddie C, et al. *N Engl J Med*. 2024;391:2219-2230.

Shah B, et al. EHA 2024. Abstract S114.

Concluding remarks

- Elderly and frail adults: a difficult-to-treat population, with promising advances in first-line therapy
- R/R: even more difficult to treat. For a subset of patients, the most effective therapies are attenuated chemotherapy combined with immunotherapy and CAR T cells
- Individualization of therapy necessary. Comorbidity and geriatric assessment mandatory

Global Leukemia Academy

Current and future role of transplantation in ALL in Europe

Nicola Gökbuget

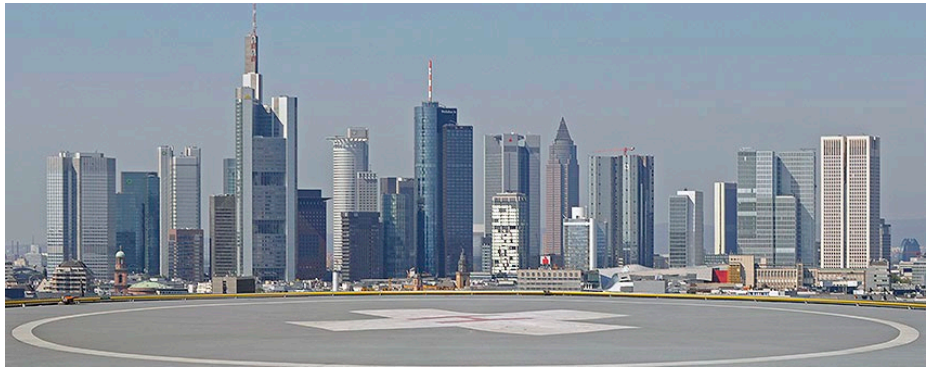
APTITUDE HEALTH®

Current and Future Role of Transplantation in Adult ALL in Europe

Nicola Gökbuget

Goethe University Hospital, Department of Medicine II, Frankfurt

GMALL Study Coordinator



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GOETHE-UNIVERSITÄT

GMALL
German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

uct Universitäres Centrum für Tumorerkrankungen Frankfurt
University Cancer Center

DKTK Deutsches Konsortium für Translationale Krebsforschung

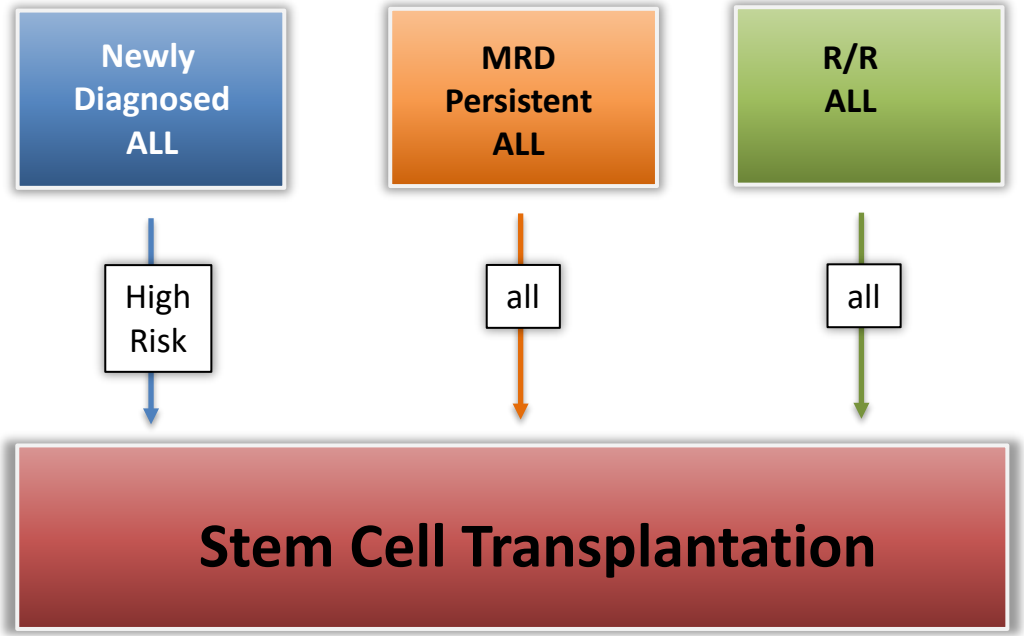
Goals of Allo HSCT in Adult ALL

1. **Maximize antileukemic effect by**
   - TBI
   - High-dose chemotherapy
2. **Utilize graft vs leukemia effect**
3. **Utilize these SCT effects in specific subgroups particularly those with high-risk features**
   - Eg, immature subtypes (pro B/MLL, early T)
   - Ph+ ALL
4. **Achieve definitive cure**

To be balanced with risks ….

- Acute mortality
- Long-term morbidity and mortality

Place of Allo HSCT in Adult ALL: High Risk Features (Classical)



Place of Allo HSCT in Adult ALL

Current Considerations

1. **Conventional prognostic factors vs molecular factors vs MRD**
2. **Prospective trials incorporating SCT in 1st Line**
3. **New compounds for the treatment of ALL**
4. **Mortality of SCT**
5. **Methodological challenges to evaluate the impact of SCT**
6. **SCT as non-standardized/non-standardizable modality**
7. **Guidelines**

ELN ALL Recommendation: Prognostic Factors

Gökbuget et al, Blood 2024

	Risk factors	Annotations
Patient-related		
Age (years)	>30-60 years (continuous variable) >55 years (older adults and elderly)	Independent PF, usually not affecting risk model (age-adapted protocols)
Performance (ECOG)	>1	Retrospective data; relevance in older patients
Disease-related		
WBC (x10^9/L)	>30 (B), >100 (T)	Variably considered
Immunophenotype	Pro-B, CD20+ (B), Pro/Pre-T, ETP, mature-T (T)	Variably considered
Cytogenetics	Ph+, t(4;11), hypodiploidy, complex*	Key prognostic elements; beside Ph+ variably considered
Genetics	**BCR::ABL1+, KMT2Ar**	**Key prognostic elements**
	Ph-like, mutated CLRF2/TP53/JAK-STAT, adverse CNA profile (B), unmutated NOTCH1/FBWX7 and abnormal RAS/PTEN (T)	Variably considered
Miscellaneous	CNS involvement	Occasionally considered
	Poor treatment compliance, undue treatment reductions and delay	Retrospective data, of greater concern with pediatric-type protocols
	Pharmacogenomics (affecting antimetabolite disposition)	Data in children, not usually assessed in adults
	Immune marrow microenvironment	Investigational, for research purposes
	Drug response profiling	Investigational, for research purposes
Treatment response dynamics		
Corticosteroid sensitivity (pre-phase)	Poor prednisone response (peripheral blast ≥1x10^9/L at the end of prephase)	Historical relevance, occasionally considered
Early/incomplete blast cell clearance (BM morphology)	Day 8-15 or end of induction BM blasts ≥5%	Variably considered
Time to CR (no. of courses)	>1 cycle (late CR)	Variably considered
MRD (molecular/flow cytometry)	MRD positivity (from end of induction onwards): ≥0.1%/0.01% after induction ≥0.01%/positive after/during consolidation and pre/post-allogeneic SCT	**Key and unifying factor predicting outcome**

ELN ALL Recommendation: SCT Indications

Gökbuget et al, Blood 2024

		Risk stratification criteria*			
National Study Group	**Patient age (years)**	**Post-induction MRD**	**Cytogenetics/ Genetics§**	**WBC (x10⁹/L)**	**Miscellaneous**
GMALL (Germany)	<55	≥0.01% after consolidation I (week 16 onward)	KMT2A+	>30 (B)	Late CR, Pro-B, early/mature-T
GIMEMA (Italy)	<65	≥0.01% after early consolidation (week 10-16), any positivity (week 22)	Adverse, KMT2A+	>100	Early/mature-T
HOVON (The Netherlands)	<40	≥0.01% after consolidation (wk 14-16)	Adverse KMT2A, hypodiploidy, complex karyotype	>30 (B), >100 (T)	Late CR
PALG (Poland)	<55	≥0.1% after induction ≥0.01% during/after consolidation	KMT2A+	>30 (B), >100 (T)	CNS+
UK NCRI ALL Group (United Kingdom)	<40	≥0.1% after induction and consolidation (mathematical risk model integrating MRD, cytogenetics and WBC)	Adverse	High count	-
FALL (Finland)	<45	≥0.1% after consolidation block B	Abn11q23, hypodiploidy	>100	Late CR, d15 BM blasts >25%
RALL (Russia)	<55	Positive during/after consolidation	t(4;11), t(1;19), KMT2A+	-	Age >30
SVALL (Sweden)	<65	≥0.1% after consolidation	Hypodiploidy, KMT2A+	-	EOI BM blasts >5%
PETHEMA (Spain)	<55 (60 fit)	≥0.1% after induction ≥0.01% during/after consolidation	-	-	-
GRAALL (France/Belgium/ Switzerland)	<60	≥0.1% after induction at week 6 or ≥0.01% after consolidation at week 12	-	-	-
CELL (Czech Republic)	<65	≥0.1% after induction ≥0.01% after consolidation	KMT2Ar	>30 (B)	Early/mature-T

ELN ALL Recommendation: SCT Indications

Gökbuget et al, Blood 2024

PRO:

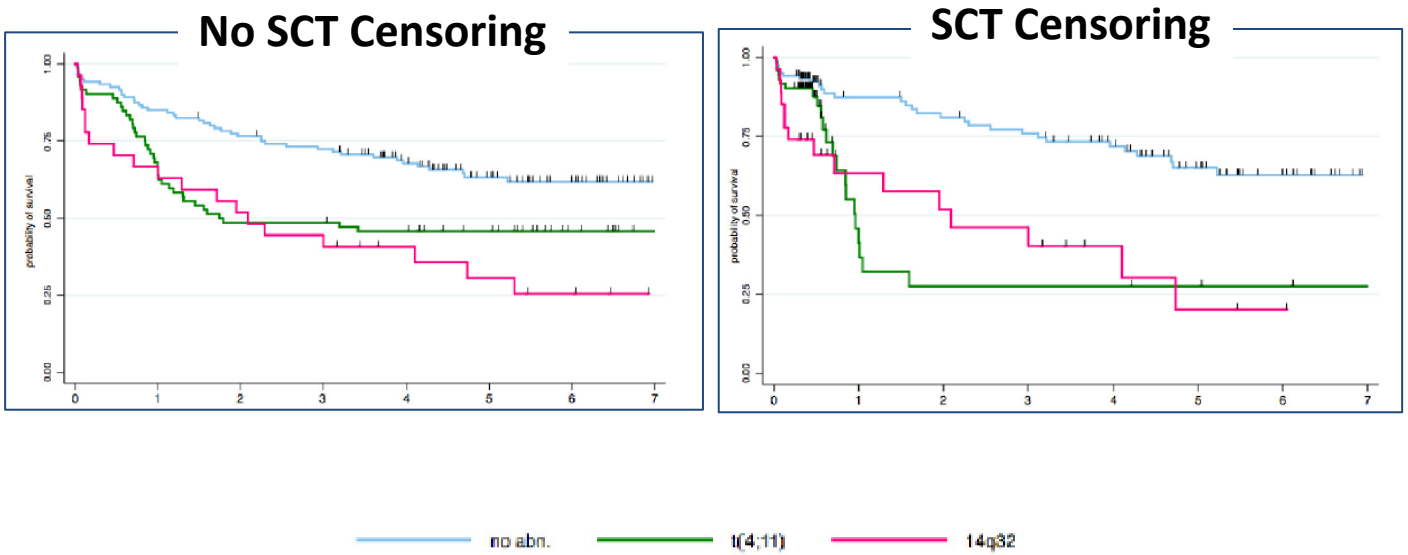
Cytological response:	**late CR**
MRD response:	**>0.1% after induction vs >0.01% after consolidation**
Molecular/Cytogen:	**KMT2a, hypodiploid, t(1;19), complex,**
Clinical:	**WBC >30000/100000,**
Phenotype:	**Early/mature T**

Contra:
Increasing age, comorbidities, complications

Cytogenetic Aberrations in Adult ALL (GRAALL Trials)

Lafage-Pochitaloff et al, Blood 2017

Overall Survival

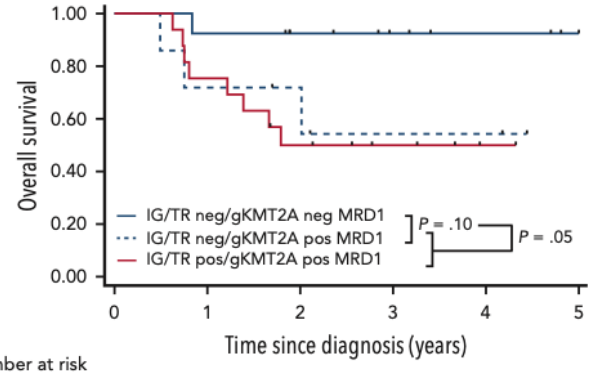


t (4;11) and 14q23 aberrations were the relevant cytogenetic high-risk groups

Disease Biology in KMT2a-Rearranged ALL

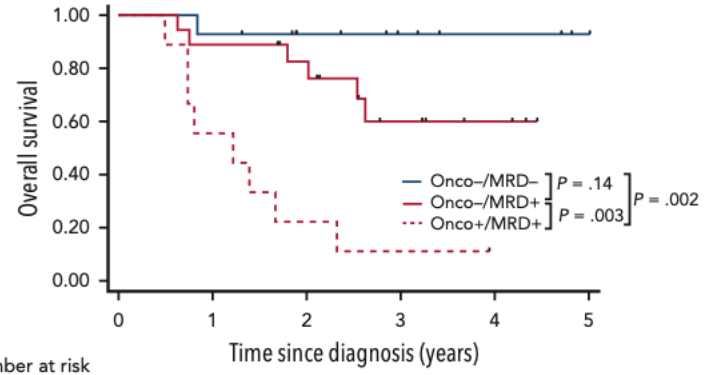
Kim et al, Blood 2023

- KMT2a-MRD vs Ig/TC
- IKZF1
- TP53 alterations



Number at risk						
IG/TR neg/gKMT2A neg MRD1	13	12	9	6	4	2
IG/TR neg/gKMT2A pos MRD1	7	5	4	2	2	0
IG/TR pos/gKMT2A pos MRD1	16	12	7	4	1	0

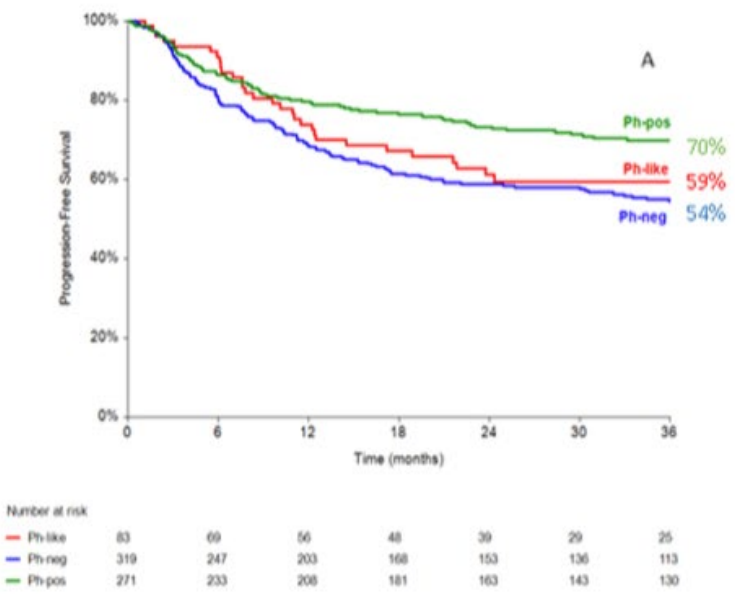
B

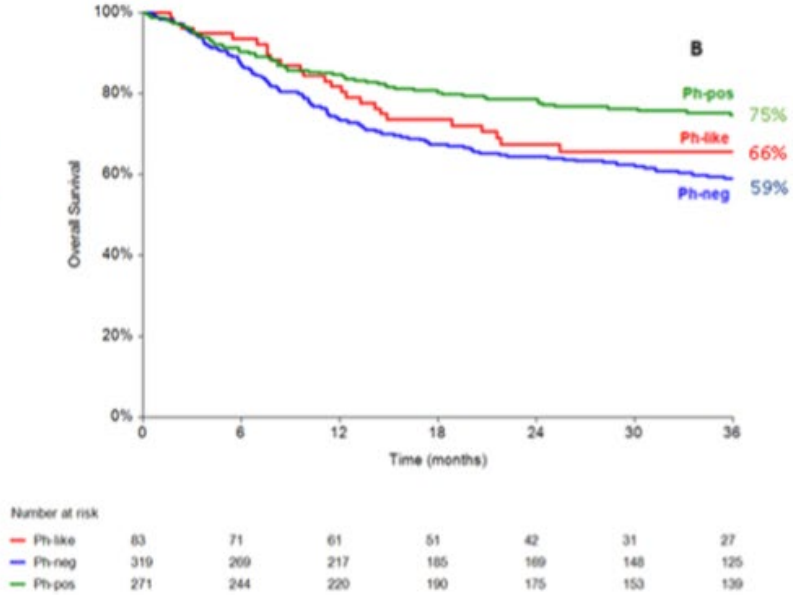


Number at risk						
Onco–/MRD–	14	13	9	6	4	2
Onco–/MRD+	18	16	13	6	3	0
Onco+/MRD+	9	5	2	1	0	0

Outcome of Ph-like ALL vs Other Subtypes After SCT

Rahman et al, Transpl Cellular Therapy 2024

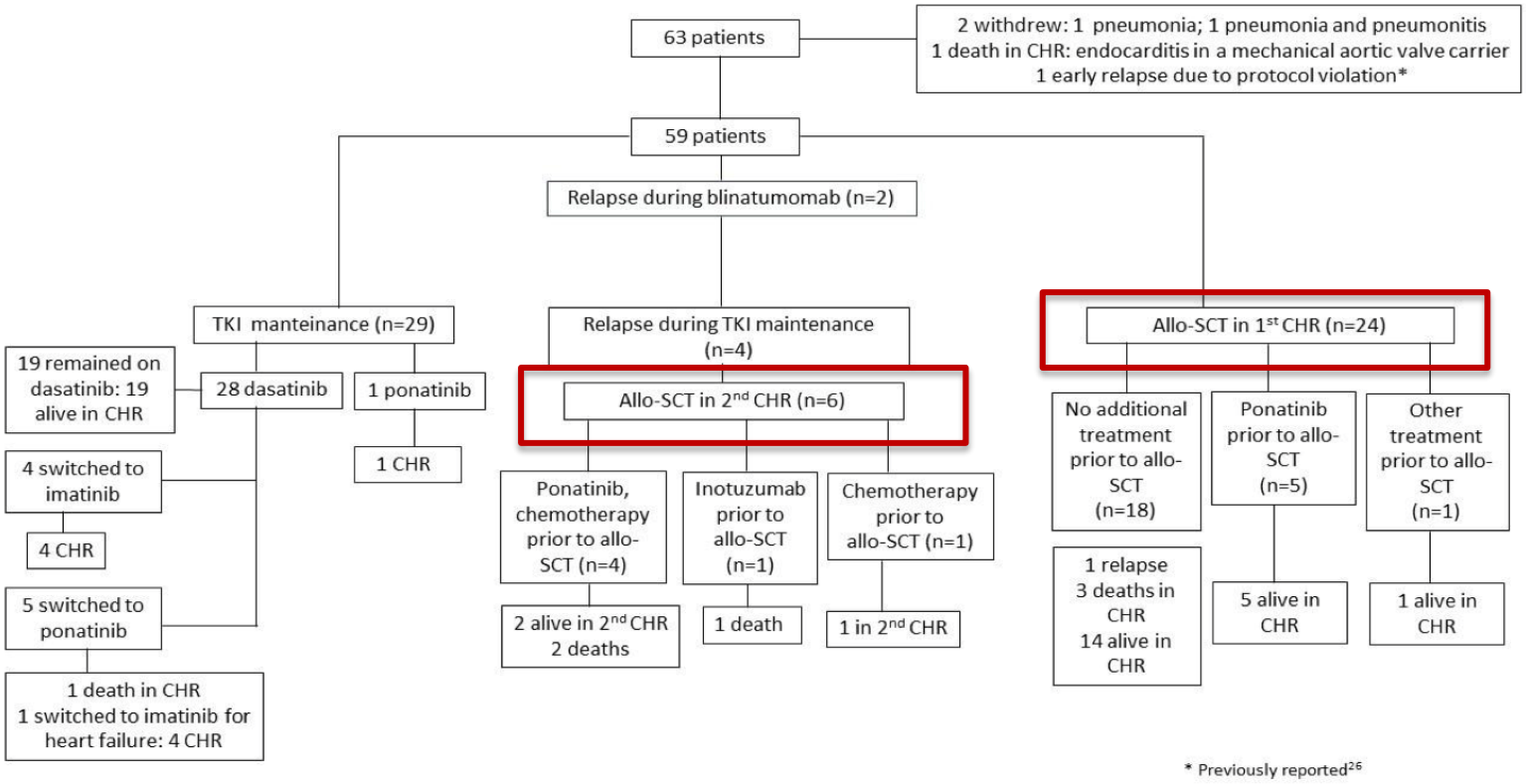




Problem: No up-front standardized and uniform detection of Ph-like ALL

Dasatinib – Blinatumomab in Ph-Positive ALL

Foa et al, JCO 2023

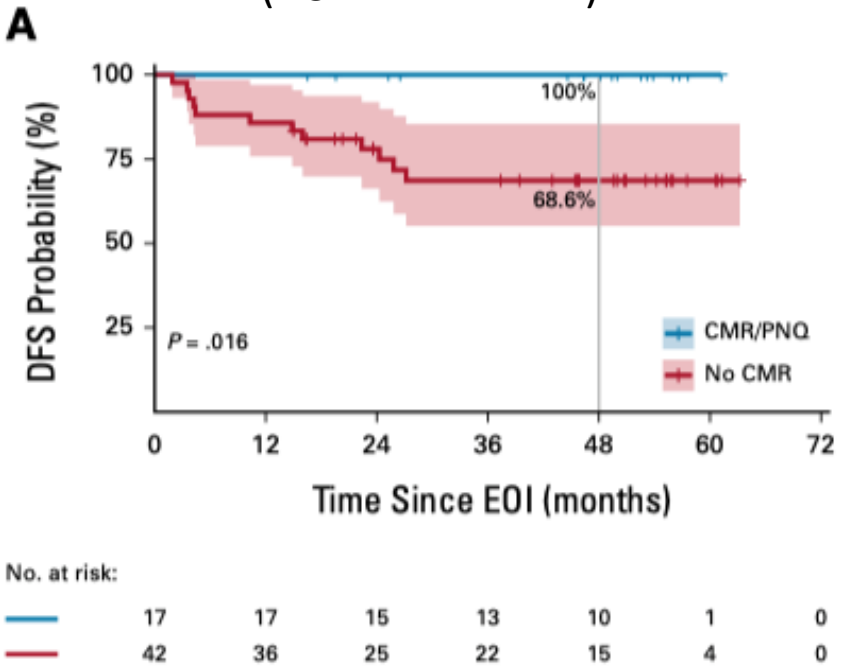


SCT indication: Investigator's Choice

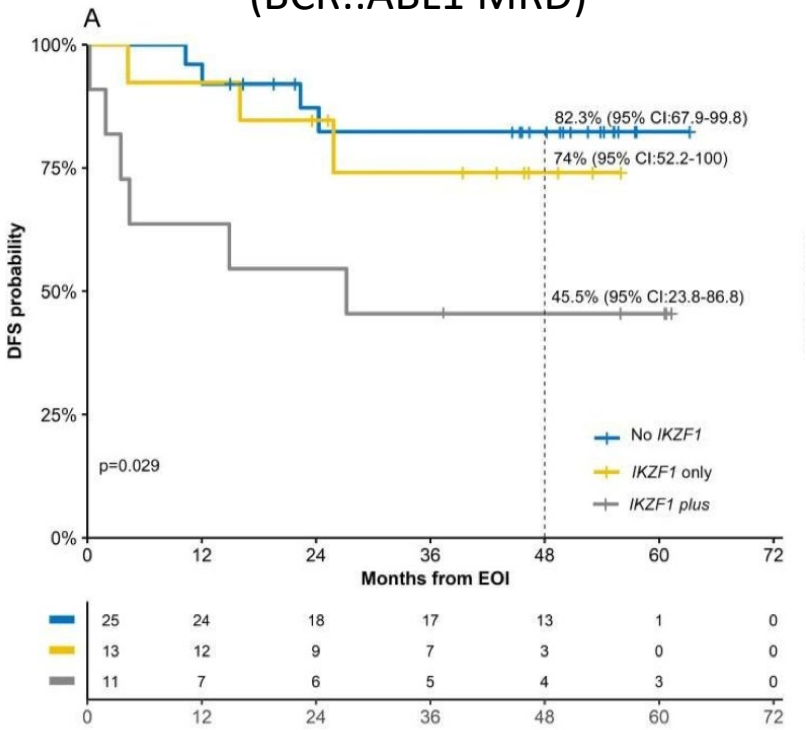
Dasatinib – Blinatumomab in Ph-Positive ALL

Foa et al, JCO 2023

DFS according to MRD Response
(BCR::ABL1 MRD)



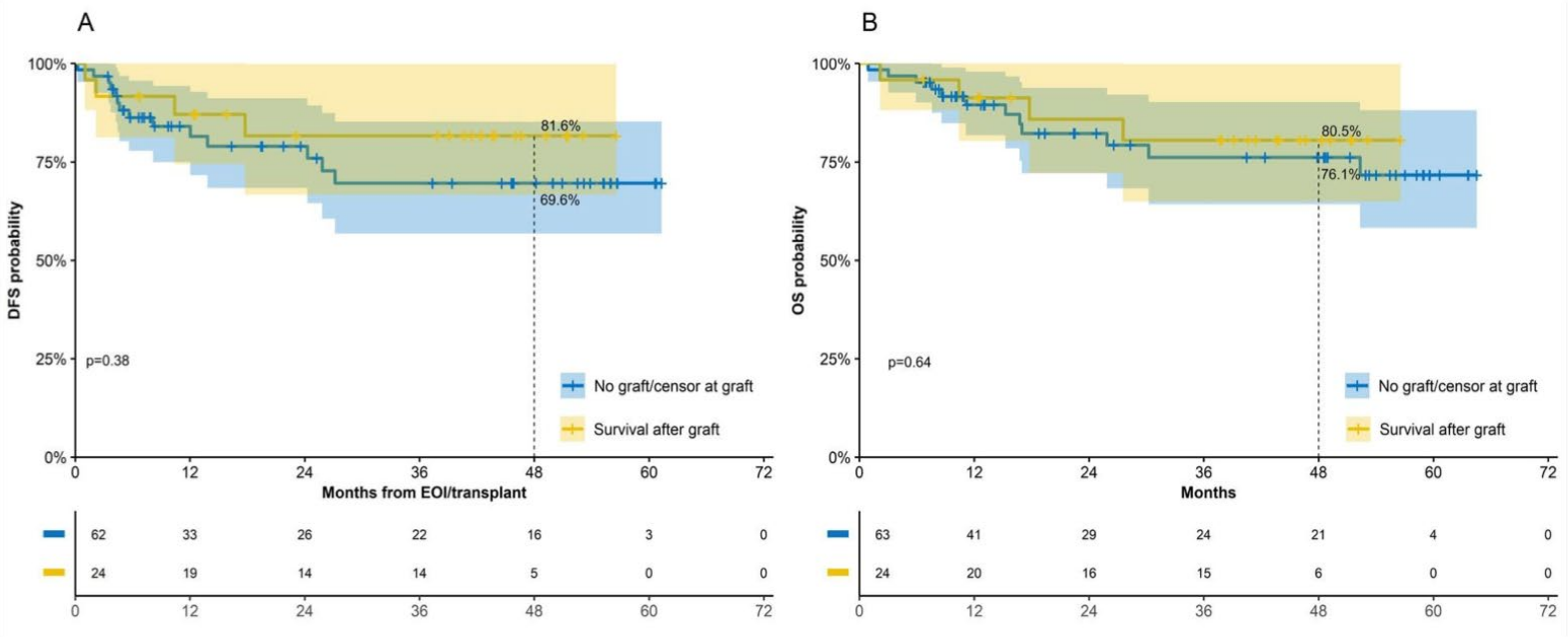
DFS according to IKZF1
(BCR::ABL1 MRD)



Dasatinib – Blinatumomab in Ph-Positive ALL

Foa et al, JCO 2023

Impact of Allo SCT?



Potential New Risk Factors in Ph+ ALL

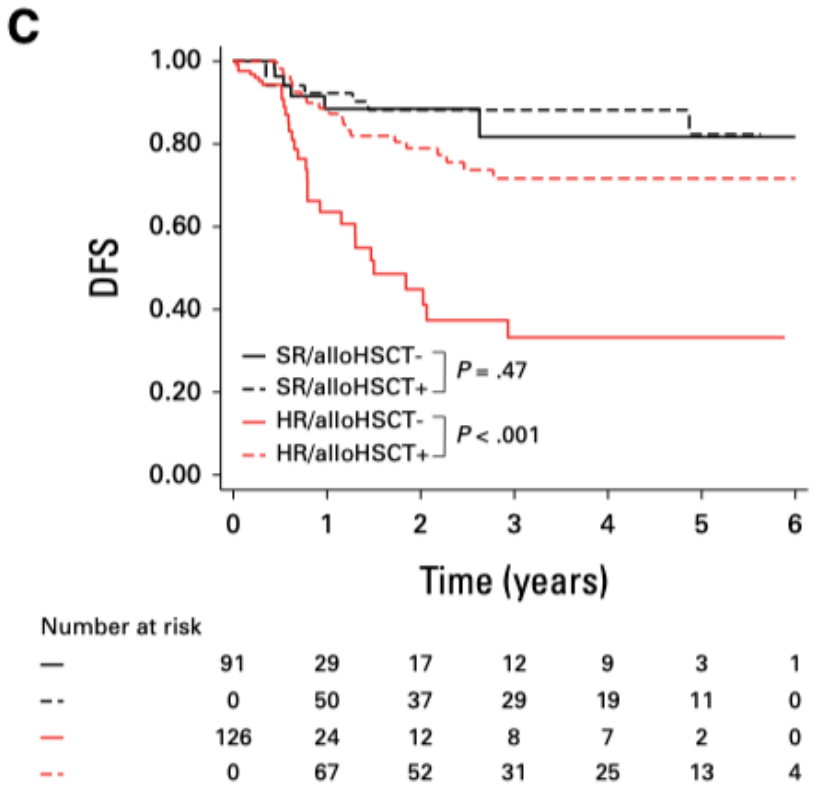
Kim et al, JCO 2024

- WBC >30.000
- Ig/TC MRD >0.01%

= 58% of pts

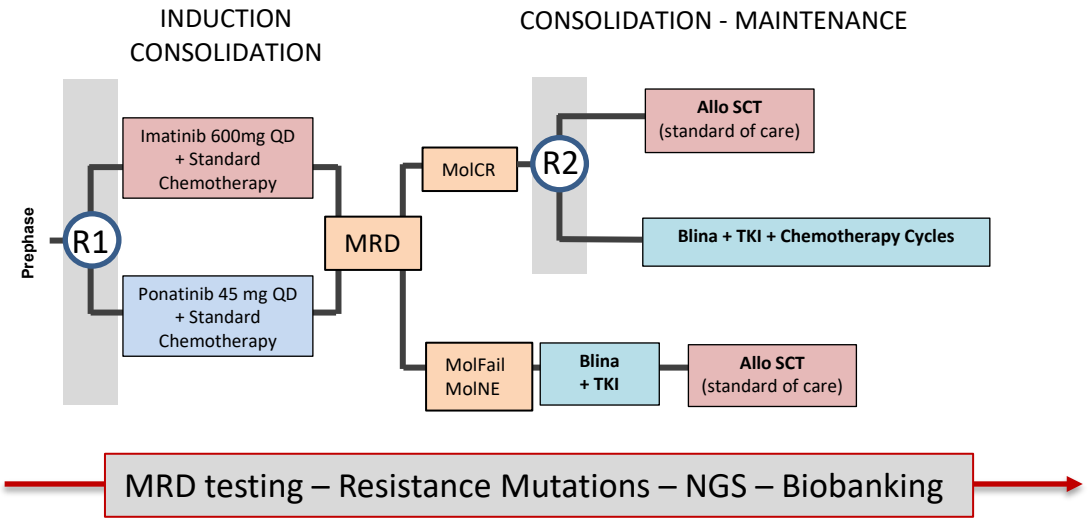
Further:

Lymphoid vs Multilineage?
BCR::ABL MRD?
IKZF1/IKZF1plus



GMALL Evolve Trial in Ph+ ALL

Lang et al, Oncology Research and Treatment, 2024



1. Challenging standard of care tyrosine kinase inhibitor (MRD endpoint)
2. Challenging standard of care stem cell transplantation (OS endpoint)
3. Establish MRD-based risk assessment
4. Implement immunotherapy (Blinatumomab) in 1st line

Potential Adverse Cytogenetic/Molecular Prognostic Factors in ALL at Diagnosis

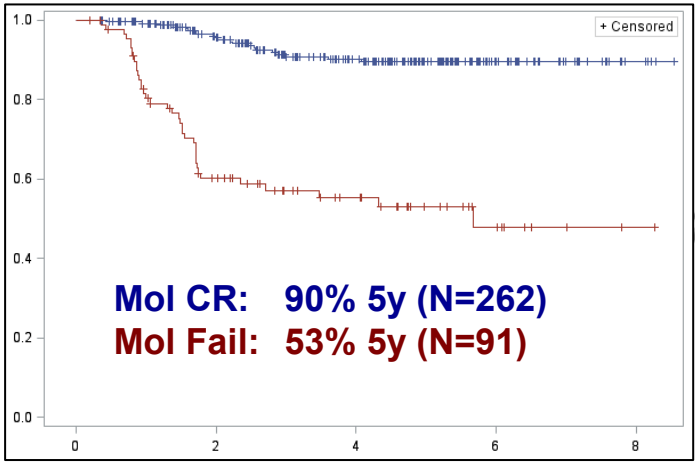
1. Unclear whether applicable for modern regimens
2. High heterogeneity and small patient groups: Prognostic impact on weak basis
3. Unclear whether additional information in pts with MRD
4. Unclear whether SCT benefit

Prognostic Impact of MRD After Induction/Consolidation in Pediatric and Adult ALL

Overall Survival "Adult"

GMALL 07/2003

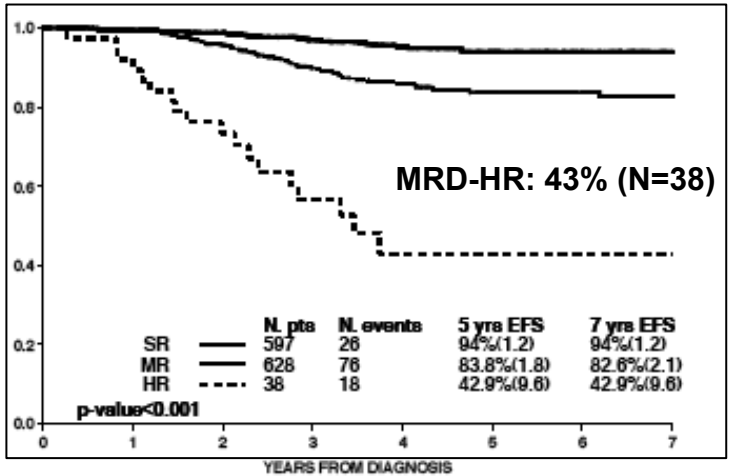
Gökbuget et al, Blood 2012



Event-Free Survival "Pediatric"

AIEOP-BFM ALL 2000

Conter et al, Blood 2010



Incidence of MRD-HR: 26%

Incidence of MRD-HR: 3%

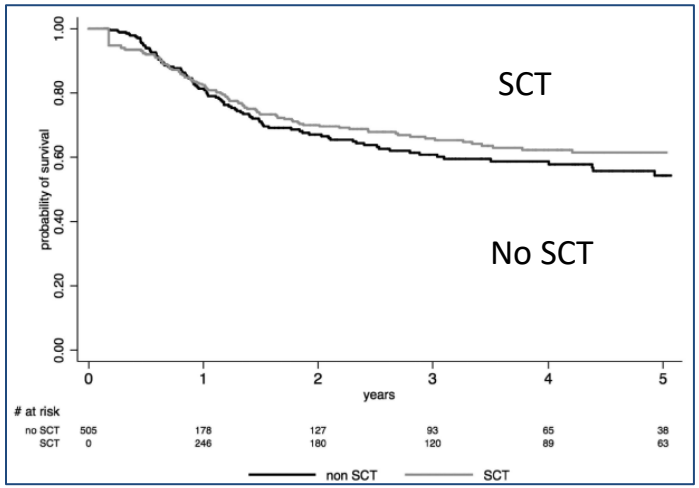
Therapeutic action based on MRD is one central challenge in management of ALL in all age groups

Impact of SCT in Ph-negative HR ALL in 1st CR

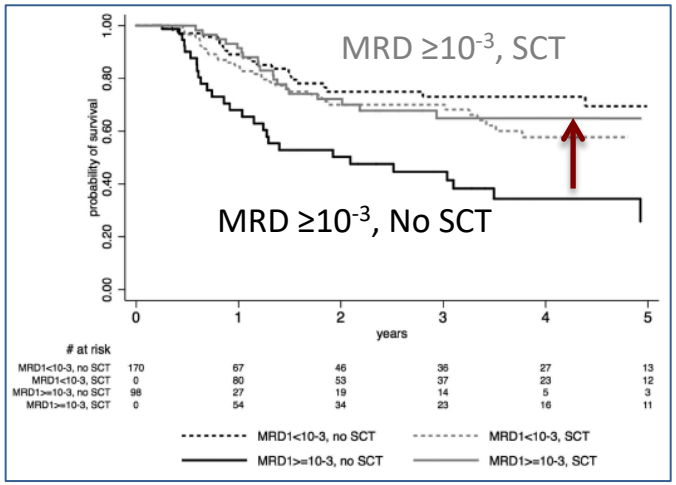
Dhedin et al, Blood 2014

GRAALL studies 2003/2005
15-55 yr; Ph-negative
Conventional and MRD-based risk stratification
N=522 HR ➔ SCT in 282 (54%)

Overall Survival*



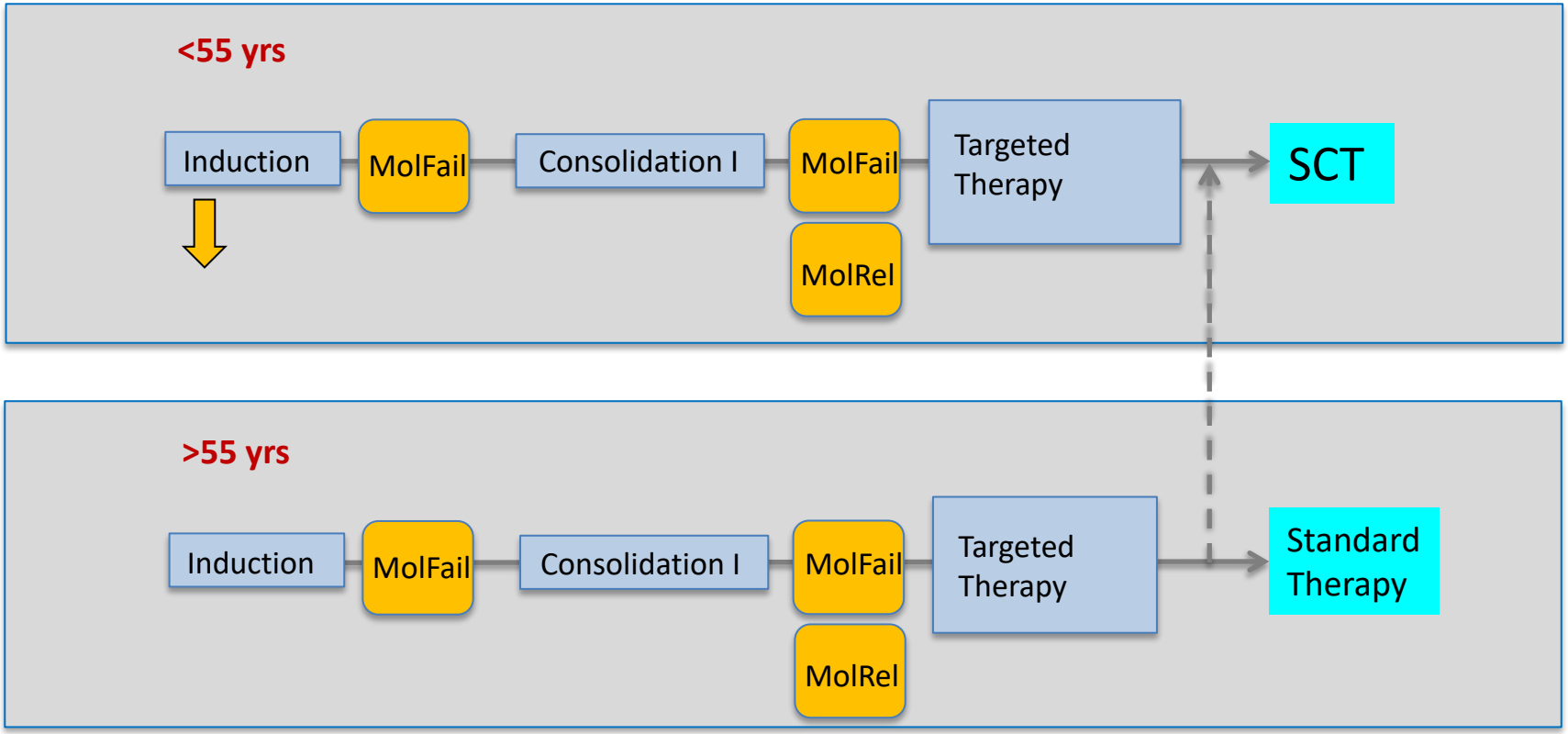
Overall Survival in MRD +/- Pts*



*Simon Makuch Plots with SCT as time-dependent covariate.

GMALL
German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

MRD-Based Management



Place of Allo HSCT in Adult ALL

Current Considerations

1. **Conventional prognostic factors vs molecular factors vs MRD**
   - **Most study groups rely on MRD only**
     Goekbuget et al, Blood 2024
   - Immediate SCT is probably not the optimal approach for high MRD
   - A number of biologic risk factors still relevant for SCT indication: Ph+, KMT2a, early/mature T
2. Prospective trials incorporating SCT in 1st Line
3. New compounds for the treatment of ALL
4. Mortality of SCT
5. Methodological challenges to evaluate the impact of SCT
6. SCT as non-standardized/non-standardizable modality
7. Guidelines

Place of Allo HSCT in Adult ALL

Current Considerations

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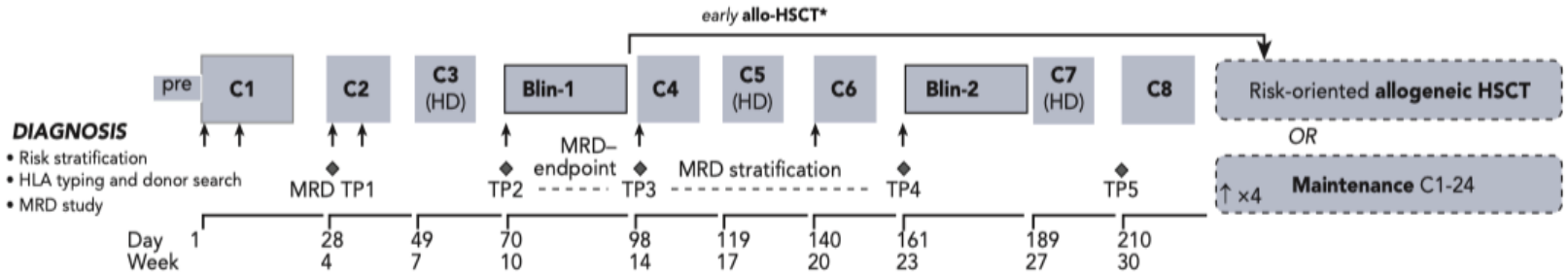
Prospective Risk-Adapted SCT Including Blina 1st Line

Bassan et al, Blood 2025



Clinical risk class[1]	MRD status[2]	Final stratification and risk-oriented therapy
Standard risk (SR) *all the following:* • WBC count ≤ 30x10⁹/l, • non-pro-B phenotype, • non-adverse genetics/cytogenetics, • CR at cycle 1	MRD– *or* MRD u/k	Low risk to consolidation/maintenance
	MRD+	High risk to allogeneic HSCT
High risk (HR) *non-VHR and any of the following:* • WBC count >30 to 100x10⁹/l, • pro-B phenotype, • CR at cycle 2 (late CR)	MRD–	Low risk to consolidation/maintenance
	MRD+ *or* MRD u/k	High risk to allogeneic HSCT
Very high risk (VHR) *any of the following:* • WBC count >100x10⁹/l, • adverse genetics/cytogenetics[1]	Any[3]	

Abbreviations: WBC, white blood cells; CR, complete remission; MRD, minimal residual disease; HSCT, hematopoietic stem cell transplantation

[1] Adverse genetics/cytogenetics (per protocol specifications): t(4;11)/*KMT2A*-rearrangemrent or 11q23 abnormalities, +8, -7, del6q, t(8;14), hypodiploidy (30-39 chromosomes), near-triploidy (60-78 chromosomes), complex karyotype with ≥5 unrelated clonal abnormalities

[2] MRD risk model according to MRD timepoint (TP) 2, 3 and 4 (i.e. weeks, 10, 14 and 20):
- MRD negative (–): MRD negative/<10^{-4} at TP2-3 and MRD negative at TP4,
- MRD positive (+): MRD ≥ 10^{-4} at TP2-3 and MRD positive (any level) at TP4,
- MRD unknown (u/k) when lacking MRD study

[3] MRD status assessed for prognostic analysis, not entered in risk-oriented treatment algorithm (all VHR patients defined high risk eligible to allogeneic HSCT

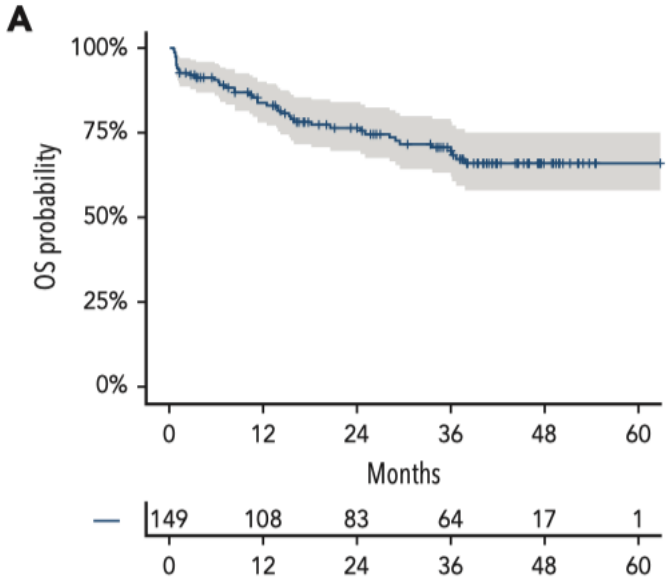
After TP2MRD and Blin-1 (early):
VHR, HR MRD unknown, SR/HR with TP2MRD ≥ 10^{-4} (any of these)

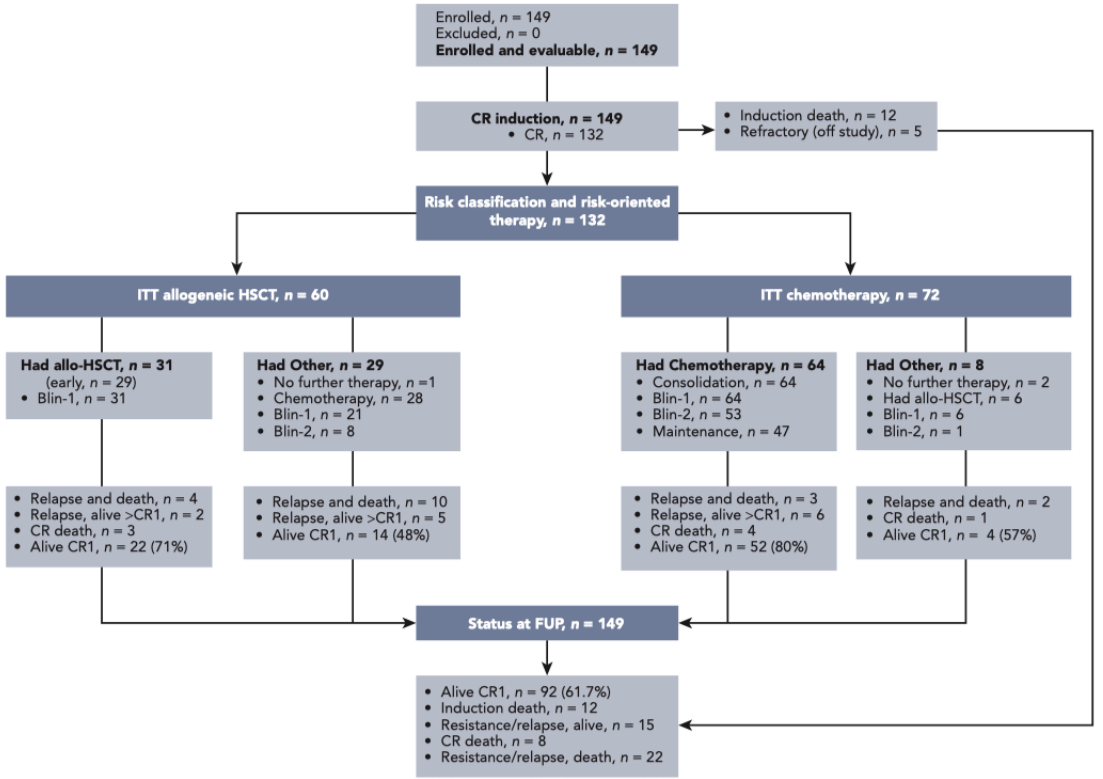
After TP4MRD and Blin-2:
SR/HR TP2 MRD– but TP3 or TP4 MRD+

SCT:
SR: MRD+
HR: MRD+/Unk
VHR

Prospective Risk-Adapted SCT Including Blina 1st Line

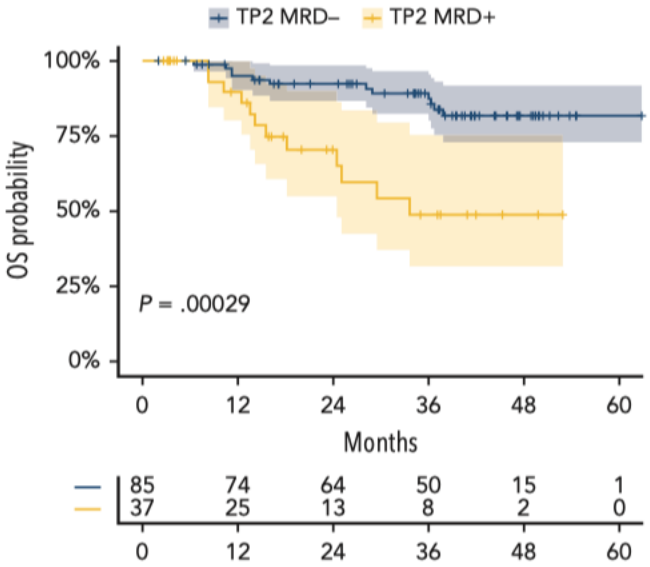
Bassan et al, Blood 2025

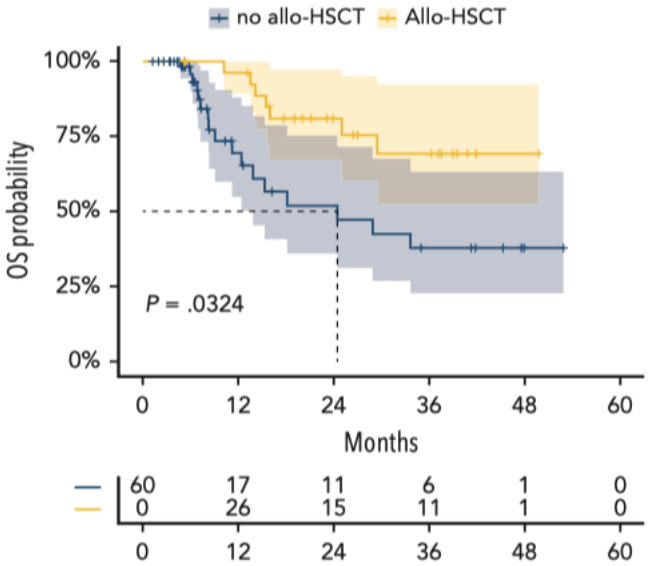




Prospective Risk-Adapted SCT Including Blina 1st Line

Bassan et al, Blood 2025

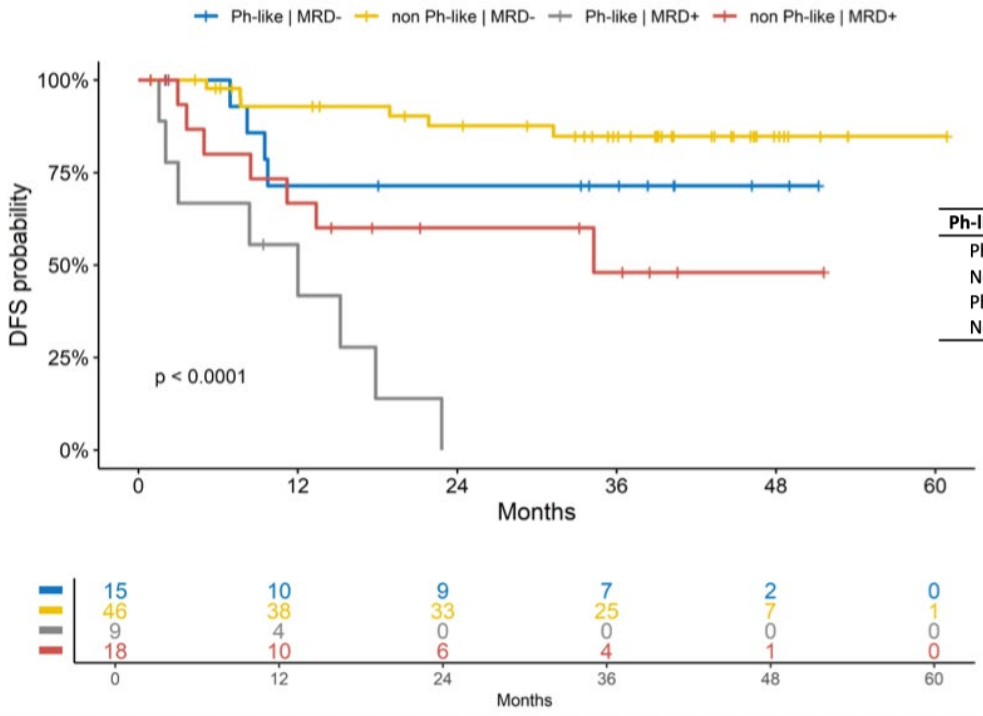




Prospective Risk-Adapted SCT Including Blina 1st Line

Bassan et al, Blood 2025

Ph-Like ALL

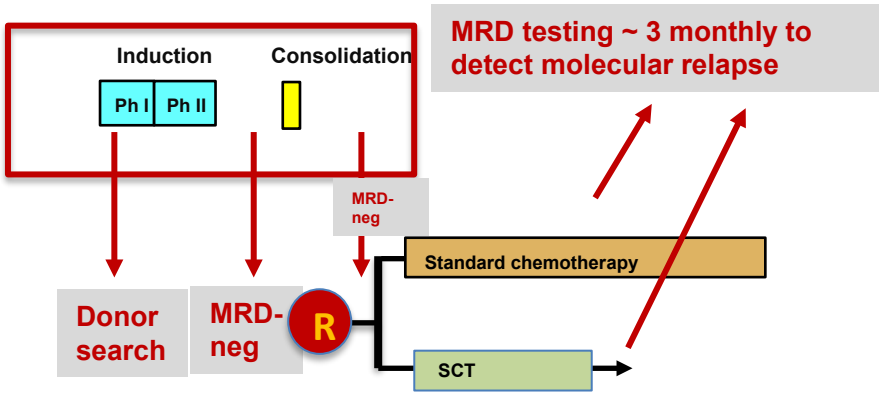


Ph-like ALL and TP2 MRD	12 Months	24 Months	36 Months
Ph-like, MRD–	71% (51%, 99%)	71% (51%, 99%)	71% (51%, 99%)
No Ph-like, MRD–	93% (85%, 100%)	88% (78%, 98%)	85% (74%, 97%)
Ph-like, MRD+	56% (31%, 100%)	N/A	N/A
No Ph-like, MRD+	67% (47%, 95%)	60% (40%, 91%)	48% (26%, 88%)

N/A, not achieved

Randomization II: Disease-Free Survival ITT Population in HR ALL With MolCR - GMALL Trial 08/2013

Gökbuget et al, ASH 2024



Patients:

285 Pat. HR ALL
102 (37%) molCR after induction II
96 (91%) randomized

Age: 31 (18-55) yrs

B-Precursor ALL:
63% (36% c/preB; 26% pro B)

T-Lineage ALL:
38% (19% early; 14% mature; 5% thymic)

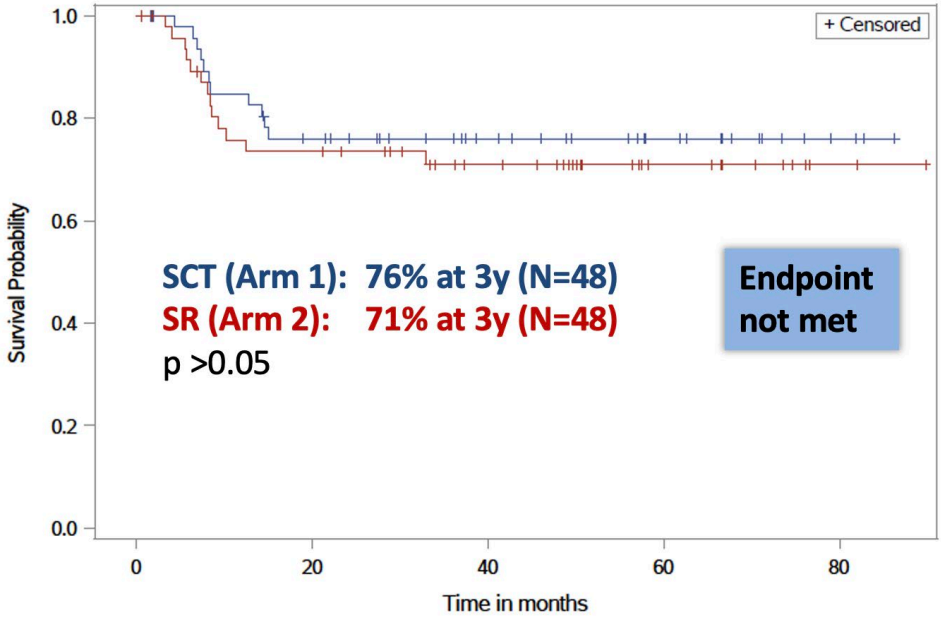
Allocated treatment realized:

SCT-Arm: 79%
SR-Arm: 88%

Randomization II: Disease-Free Survival ITT Population in HR ALL With MolCR - GMALL Trial 08/2013

Gökbuget et al, ASH 2024

Disease-Free Survival



Notes:
T-Lin: Standard treatment superior
B-Lin: SCT superior

11/12 pts with molecular or cytological relapse died despite suitable salvage approaches

Place of Allo HSCT in Adult ALL

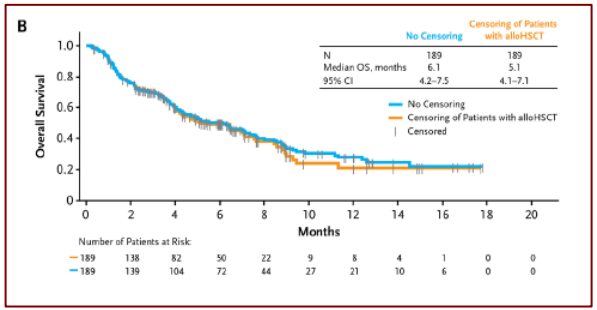
Current Considerations

1. Conventional prognostic factors vs molecular factors vs MRD
2. Prospective trials incorporating SCT in 1st Line
3. **New compounds for the treatment of ALL**
4. Mortality of SCT
5. Methodological challenges to evaluate the impact of SCT
6. SCT as non-standardized/non-standardizable modality
7. Guidelines

Impact of SCT Post-Blinatumomab/Inotuzumab

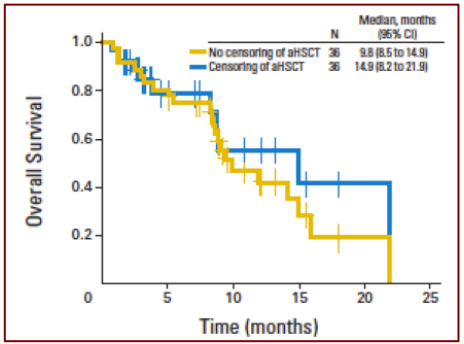
Blinatumomab (211 Trial)

Topp & Gökbuget et al, Lancet Oncol 2015



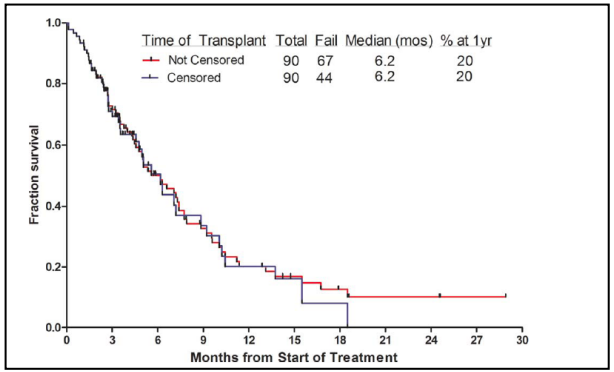
Blinatumomab (206 Trial)

Topp & Gökbuget et al, JCO 2014



Inotuzumab

Kantarjian et al. Lancet Oncology 2012

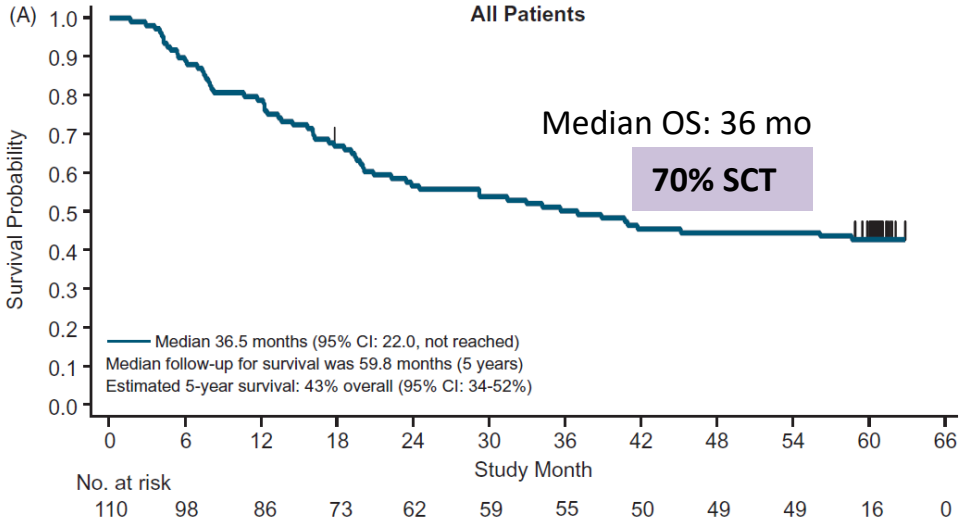


No clear impact of SCT ?
Relevant mortality (>30%) of SCT
No long-term survivors without SCT

Blinatumomab in MRD-Positive ALL

Gökbuget et al. Leuk Lymphoma 2020

Overall survival: Ph-negative patients with BCP-ALL and MRD



Outcome of SCT vs No SCT

	SCT in CCR	No HSCT
All patients		
Total	**74**	**36**
Alive w/o relapse	**40%**	**19%**
Died w/o relapse	**36%**	**8%**
Relapse	**23%**	**72%**
Median OS	**NR**	**56 mo**

SCT after relapse: 12 (46%)

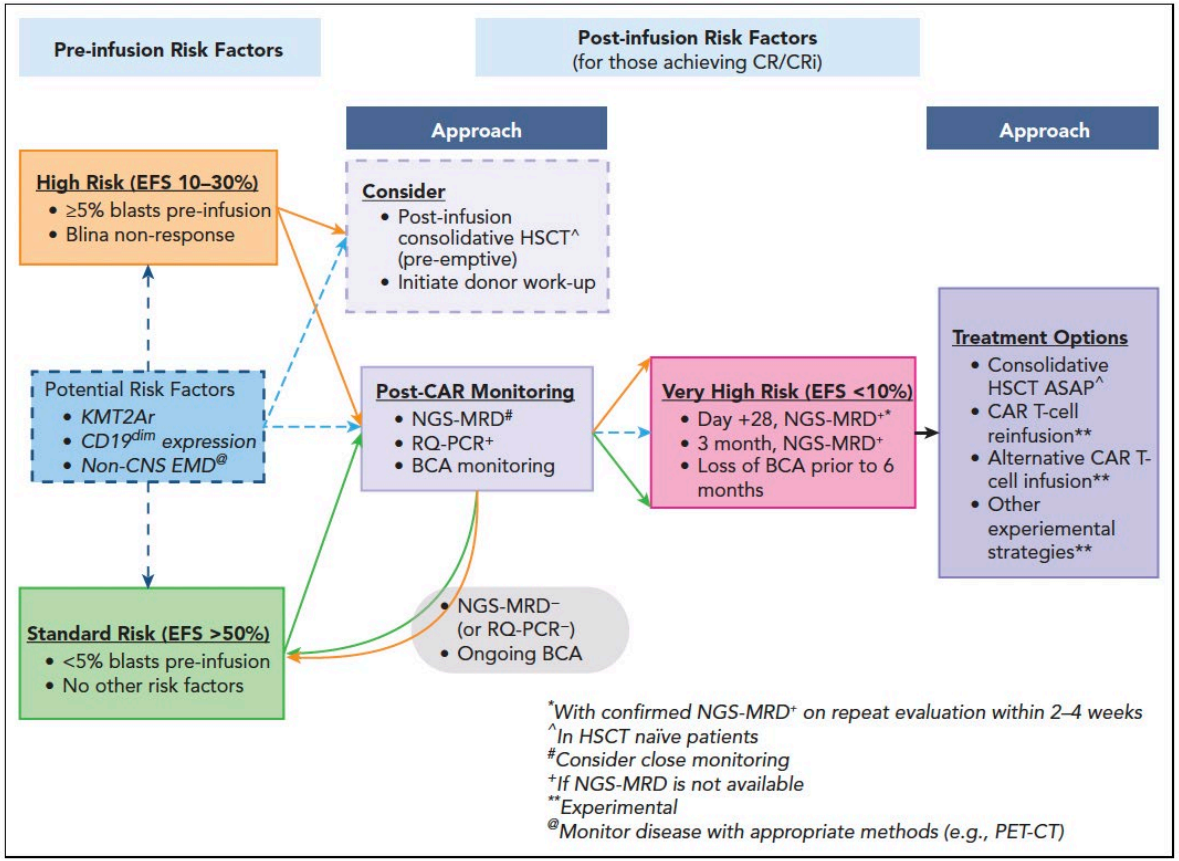
Outcome of CAR T in R/R ALL: Obe-Cel

Roddie et al, New Engl J Med 2024

SCT Censoring

Decision-Making on CAR T Sequence

Gardner et al, Blood 2023



Place of Allo HSCT in Adult ALL

Current Considerations

1. Conventional prognostic factors vs molecular factors vs MRD
2. Prospective trials incorporating SCT in 1st Line
3. **New compounds for the treatment of ALL**
   - **SCT is still standard in R/R ALL including MRD+ after new compounds**
   - **In non-transplant pts follow-up procedures important**
   - **Role of CAR T as stand-alone replacing SCT remain to be defined**
4. Mortality of SCT
5. Methodological challenges to evaluate the impact of SCT
6. SCT as non-standardized/non-standardizable modality
7. Guidelines

Place of Allo HSCT in Adult ALL

Current Considerations

1. Conventional prognostic factors vs molecular factors vs MRD
2. Prospective trials incorporating SCT in 1st Line
3. New compounds for the treatment of ALL
4. **Mortality/Morbidity of SCT**

   Decreasing mortality by

   - **better donor selection**
   - **improved GvHD prophylaxis**
   - **treatment in better condition including MRD status**

   Standards should be established

   No high-risk procedures in MRD negative patients including older pts
5. Methodological challenges to evaluate the impact of SCT
6. SCT as non-standardized/non-standardizable modality
7. Guidelines

Place of Allo HSCT in Adult ALL

Current Considerations

1. Conventional prognostic factors vs molecular factors vs MRD
2. Prospective trials incorporating SCT in 1st Line
3. New compounds for the treatment of ALL
4. Mortality of SCT
5. **Methodological challenges to evaluate the impact of SCT**
6. SCT as non-standardized/non-standardizable modality
7. Guidelines

Challenges with Regard to Statistical Comparison of SCT vs Chemotherapy

1. **Only possible in prospective trials**
2. **How to account for potential bias**
   - CR patients only
   - Donor availability
   - Insurance status
   - Age, general condition, comorbidities
   - Early relapse
   - Transplant realization rate
3. **How to account for time to SCT (“immortal person-time”)**
   - Censoring vs non-censoring of SCT
   - Landmark analysis
   - Mantel-Byar analysis
   - Simon-Makuch Plot

Place of Allo HSCT in Adult ALL

Current Considerations

1. Conventional prognostic factors vs molecular factors vs MRD
2. Prospective trials incorporating SCT in 1st Line
3. New compounds for the treatment of ALL
4. Mortality of SCT
5. Methodological challenges to evaluate the impact of SCT
6. **SCT and CAR T as non-standardized/non-standardizable modality**
7. Guidelines

SCT vs CAR T Heterogeneity

SCT

- Patient selection (age, subtype, molecular...)
- Stage of disease
- Leukemia burden
- Timing
- Donor type (sibling, MUD, haplo)
- HLA compatibility
- T-cell depletion
- Conditioning
- GvHD prophylaxis
- Immunosuppression
- DLI

CAR T

- Patient selection
- Bridging (chemo, blina, INO)
- Leukemia burden at infusion
- CAR structure
- Vector
- Autologous/allogeneic
- T-cell selection/subset
- Lymphodepletion
- Infusion schedule/dose
- Production time
- Selected sites
- Persistence of CAR T-cells
- Subsequent SCT

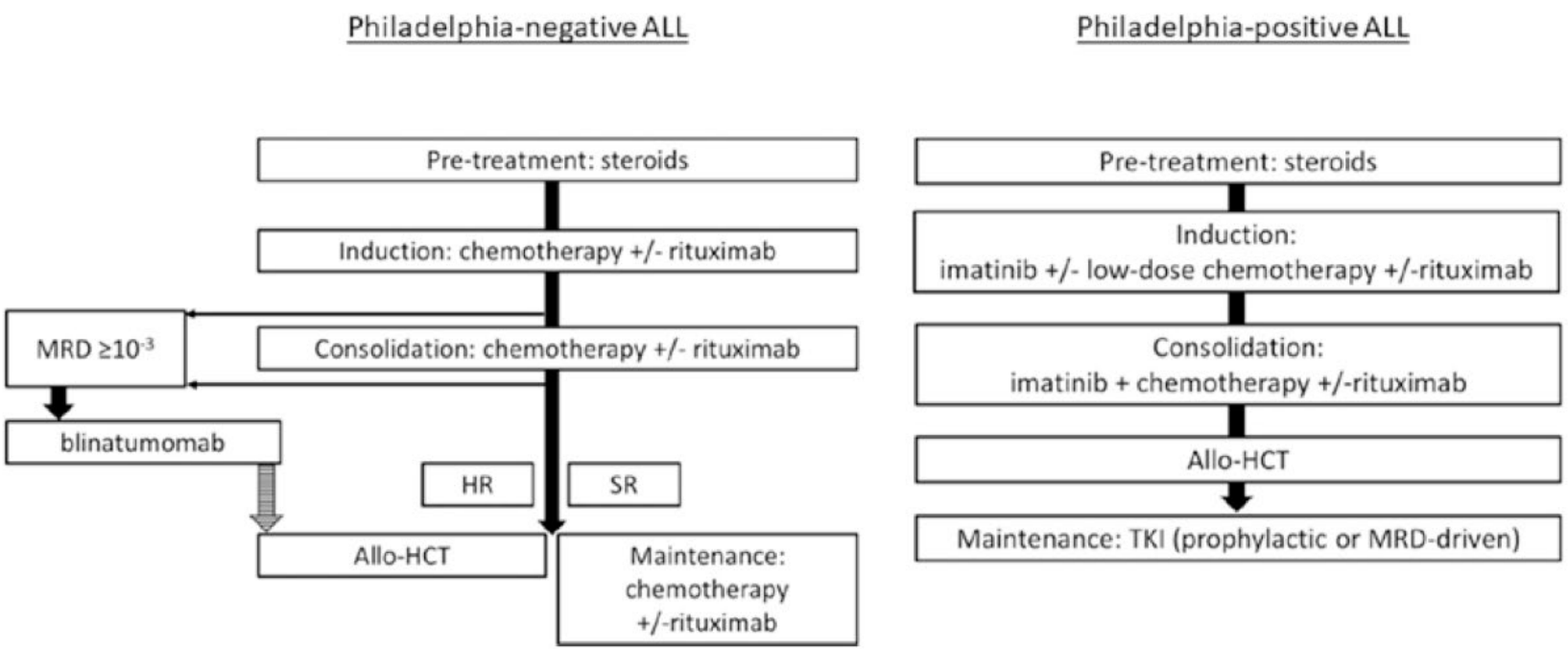
Place of Allo HSCT in Adult ALL

Current Considerations

1. Conventional prognostic factors vs molecular factors vs MRD
2. Prospective trials incorporating SCT in 1st Line
3. New compounds for the treatment of ALL
4. Mortality of SCT
5. Methodological challenges to evaluate the impact of SCT
6. SCT as non-standardized/non-standardizable modality
7. **Guidelines**

EBMT Handbook 2024

Stelljes & Marks & Giebel



SCT Indications: ASH Education 2024

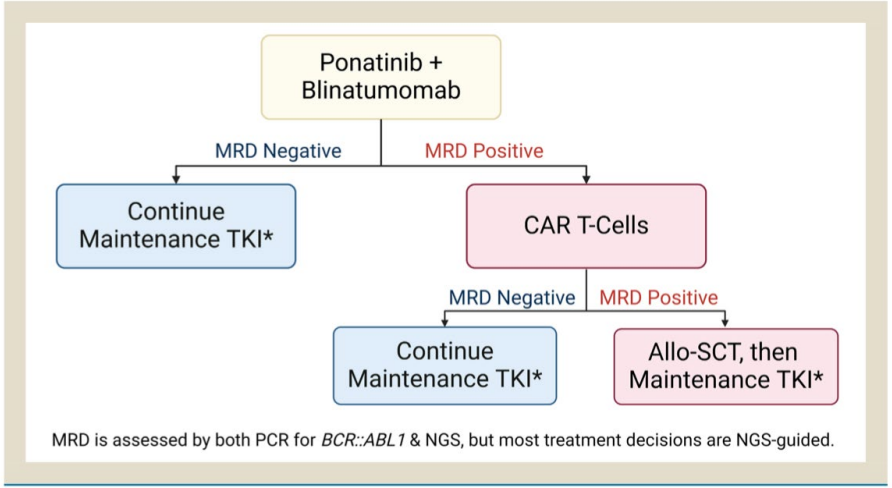
Marcoux & Kebriaei et al

Indication for transplant*	
**Early referral of high-risk patients for prompt donor search and personalized/collaborative decision-making is critical*	
Immunophenotype	Early T-cell precursor
Karyotype	Complex karyotype; low hypodiploid (32–39 chromosomes); near haploid (24–31 chromosomes)
Unfavorable molecular genetic profile	*IKZF1; BCR::ABL1-like* (Ph-like); *KMT2A* rearranged; *MEF2D* rearranged; *MYC* rearranged; *TP53*; *iAMP21*
Slow response to therapy	Time to morphologic CR >4 weeks
	Persistent MRD post-induction using flow or NGS
No added benefit to transplant consolidation	
BCR::ABL1 rearranged (Ph+) • With incorporation of TKI therapy, studies suggest no benefit to HCT in patients who develop prompt, deep response AND have no evidence for unfavorable molecular features.	
Absence of high-risk molecular genetic features AND prompt, deep response to induction therapy.	
Role of transplant consolidation not clear	
Consolidation post-CAR-T therapy • Patients with very high risk features and patients with evidence for MRD following CAR-T likely benefit from HCT consolidation; toxicity from extensive prior therapy may result in adverse survival in other patients.	

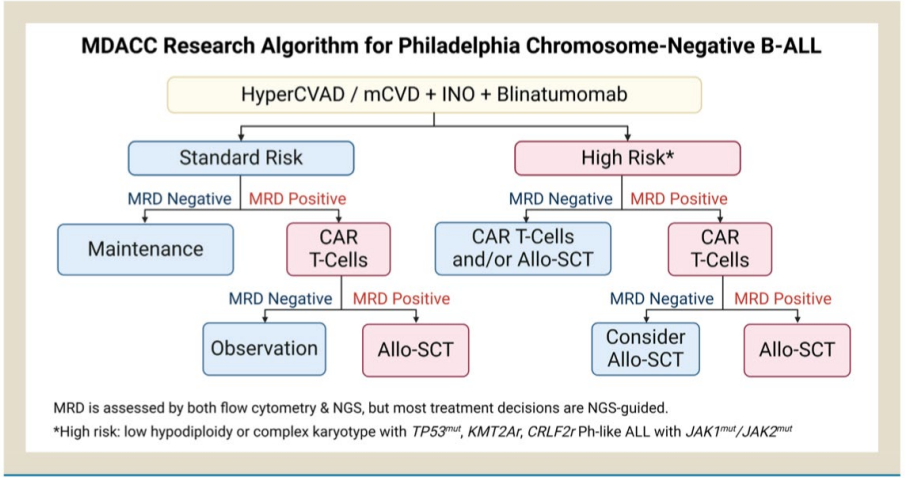
MD Anderson Research Algorithm

Jen et al, Clinical Lymphoma, Myeloma and Leukemia, 2024

Ph-Positive



Ph-Negative



Place of Allo HSCT in Adult ALL

Current Considerations

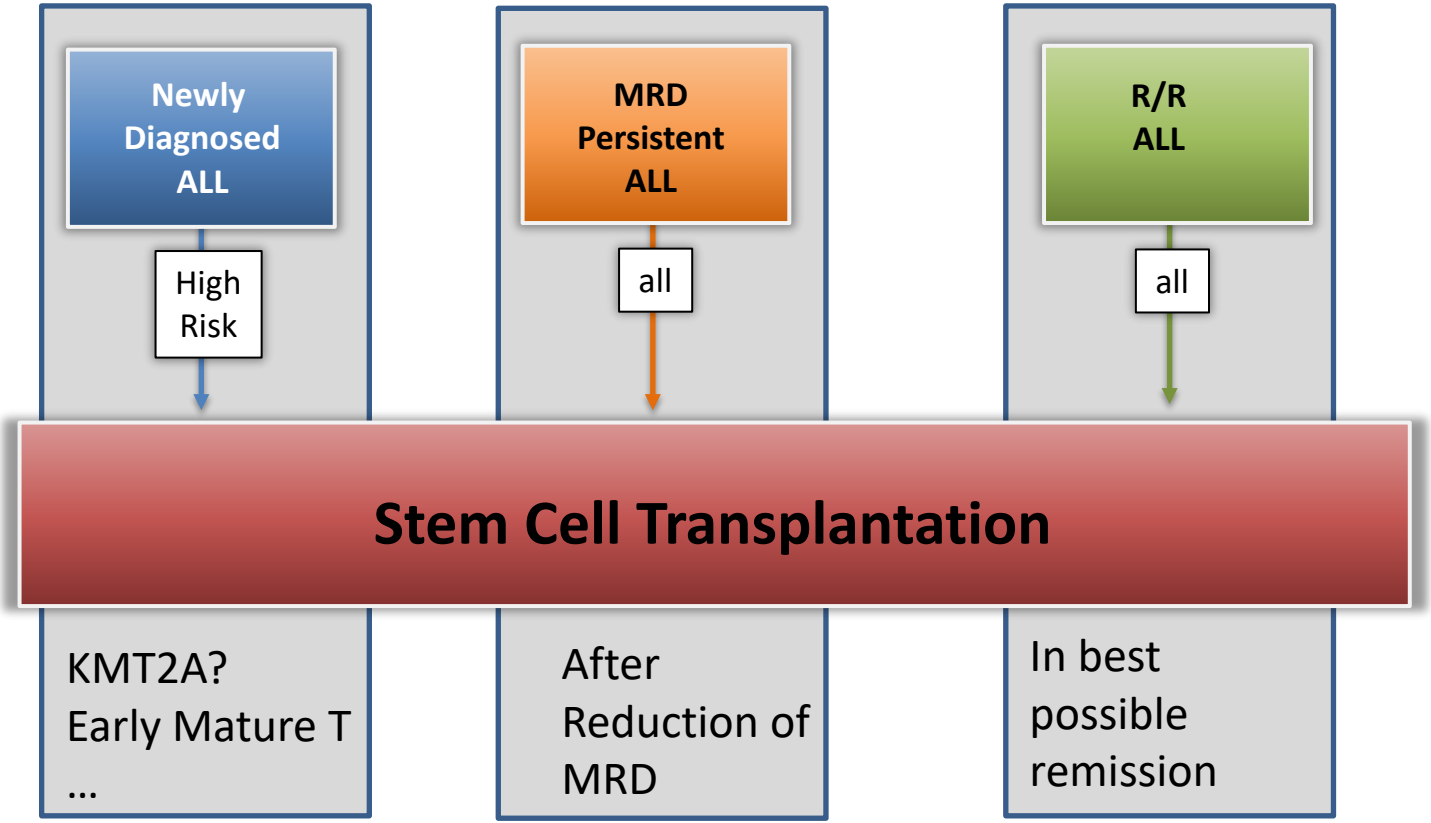
High risk definition
- Risk of relapse
- Risk of mortality

Time point of risk
- At diagnosis
- Later

Age

Type of chemo
Type of SCT

New compounds
- Antibodies
- BiTEs
- CARs



Stem Cell Transplantation in Adult ALL

Future Indications

1. SCT is still recommended in HR ALL by most guidelines
2. Outcome of SCT in later lines very poor: Postponing SCT is no good idea!
3. Is a solely MRD-based SCT indication the right way?
4. Can we improve SCT outcome and reduce TRM?
5. Will the rate of SCT indications be reduced with more molecular remissions in first line and fewer relapses?
6. Which role for alternative donors/dose-reduced conditioning?
7. Are CAR T cells an alternative to SCT, and how to demonstrate in clinical trials?
8. Chance to evaluate transplant-free regimens in older pts

Global Leukemia Academy

BREAK

APTITUDE HEALTH®

Global Leukemia Academy

R/R ALL case-based panel discussion: Case 1

Josep-Maria Ribera

APTITUDE HEALTH

24 y, male, born in El Salvador

June 2019

- Urticaria → WBC 42 × 10^9/L (64% eosinophils, no atypical cells), Hb 136 g/L platelet count: 187x10e9/L
- Screening for secondary hypereosinophilic syndrome: negative → Steroids
- *Endolimax nana* and *Dientamoeba fragilis* → Metronidazol

September 2019

- Palpitations, fever, chest pain, hypotension, cardiac failure
- Cardiac MRI: endomyocardial disease (Loeffler syndrome)
- Hb 84 g/L, WBC 96 × 10^9/L (82% eosinophils, no atypical cells), platelets 95 × 10^9/L
- BM aspirate: 18% lymphoblasts, CD19, CD79a dim, CD22 dim
- Cytogenetics: 47, XY, +X, t(15;14)(q31;q32)[2]/46, XY [20]
- NGS: normal

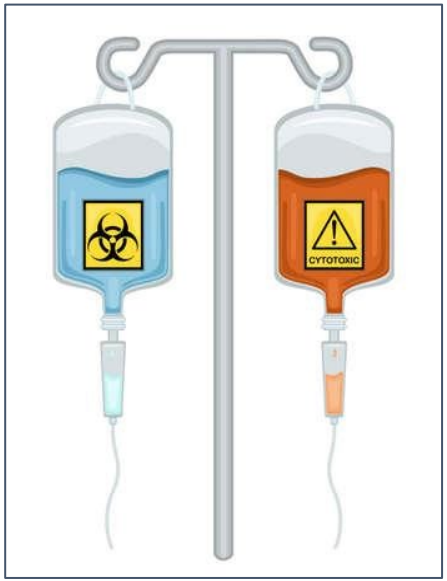
Diagnosis: B-ALL with t(5;14)(q31.1;q32.1); IGH::IL3

Question 1

In B-ALL with t(5;14)(q31.1;q32.1); IGH::IL3, the eosinophils

A. Are morphologically atypical
B. Do not belong to the leukemic clone
C. Show the t(5;14) rearrangement
D. Are hyperdiploid

Treatment



*Induction **PETHEMA LAL HR11***

CR, **MRD+ (2.25%)**, normal genetics

Vincristine, daunorubicin, prednisone, L-asparaginase, and ITT

*2nd induction: **FLAG-IDA***

CR, **MRD- .0004%**

Idarubicin, fludarabine, AraC, G-CSF, ITT

1st consolidation

CR, **MRD+ .01%**

Methotrexate, vincristine, dexamethasone, L-asparaginase, ITT

*

Bridge to HSCT

CR, MRD <.0001%

Inotuzumab × 2 cycles

Allogeneic HSCT

PB: HLA-matched (10/10), unrelated donor

- **Conditioning:** cyclophosphamide and TBI 13 Gy
- **GVHD prophylaxis:** cyclosporine, methotrexate, and ATG
- **CNS prophylaxis:** intrathecal MTX (-7 y -3)

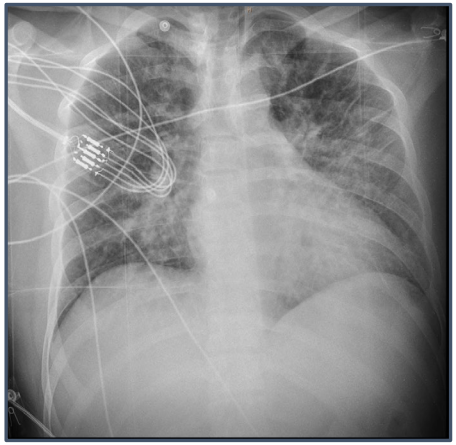
Complications

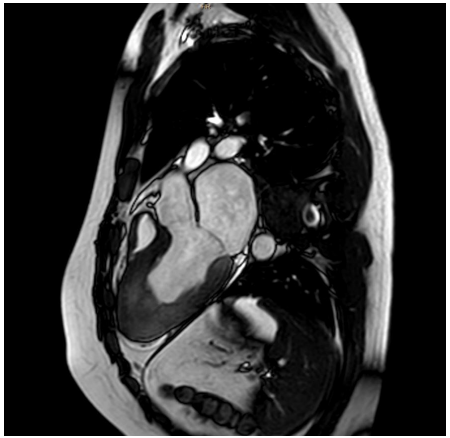
- **+2: gastrointestinal mucositis** G2
- **+3: bacteremia** *S. aureus and S. mitis multisensitive*

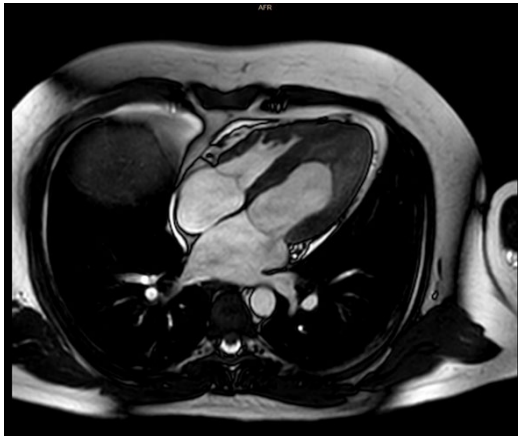
During the following 2 years: CR, undetectable MRD, normal CG, and complete donor chimerism

Chest pain, cardiac failure, acute pulmonary edema, ICU supportive care

- Hb 13.1 g/dL, **WBC 88 × 10^9/L** (66% eosinophils), platelets 83 × 10^9/L
- CD19/CD10/CD22 positive
- 47 XY, +X (t5;14)(q31;q32)[2]/46, XY [20]
- Normal NGS study





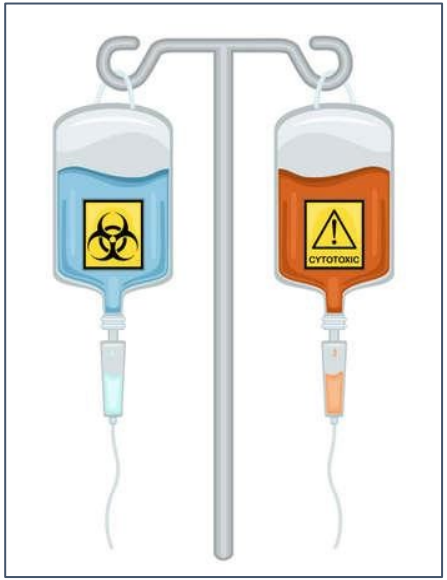


Question 2

What will be the most appropriate rescue therapy? (Blinatumomab not allowed in Spain at the time of relapse)

A. Rescue chemotherapy followed by CAR T
B. CAR T direct
C. Inotuzumab followed by CAR T
D. Rescue chemotherapy followed by second alloHSCT

Salvage therapy



Induction PETHEMA LAL 2019

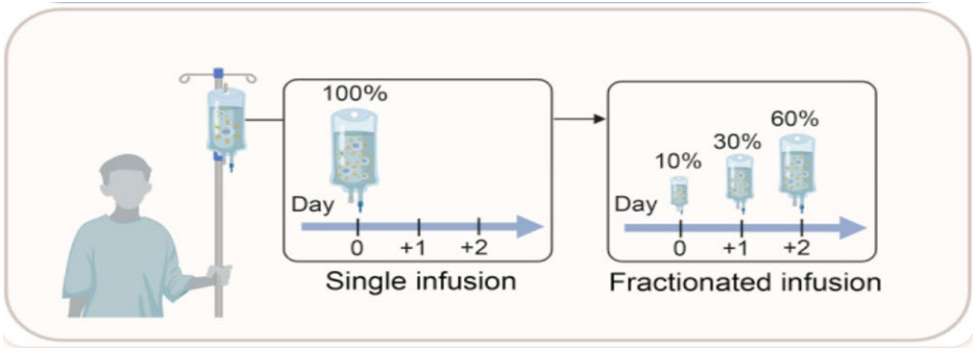
50% blast, MRD 50%

Vincristine, ~~daunorubicin,~~ prednisone, Peg-asparaginase, ITT

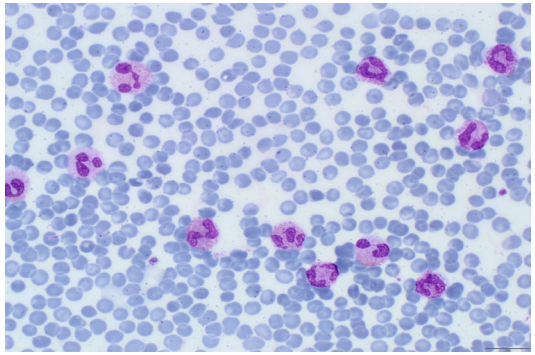
CAR T

Grade 1 CRS: tocilizumab × 2

ARI-0001 (CART19-BE02)
NCT04778579



Follow-up



April/2024 (15 months post-CAR T)

- Increase in eosinophil counts in PB
- BM aspirate: no B-ALL blasts, negative MRD, and complete donor chimerism

June/2024

- **Exophthalmos** and eosinophilia (2.0×10^9/L)
- Cranial CT scan: soft tissue mass at **right maxillary** sinus and ethmoid cells
- Mass biopsy: B-ALL
- **CSF analysis**: positive for B-ALL cells
- BM aspirate: no B-ALL blasts, negative MRD, and complete donor chimerism

Question 3

What to do now?

A. Local therapy and CAR T reinfusion
B. Local therapy, systemic therapy, and CAR T reinfusion
C. Local therapy, systemic therapy, and second alloHSCT
D. Local palliative therapy only

Treatment for relapse

- Cyclophosphamide and prednisone (5 days)
- RT for cranial mass: 24 Gy (12 fractions)
- Inotuzumab (1 cycle) and 5 doses of triple ITT (weekly) – bridge to HSCT
- Before HSCT: RT (3 days) for residual mass at right maxillary sinus

Treatment for relapse

HSCT (July 2024)

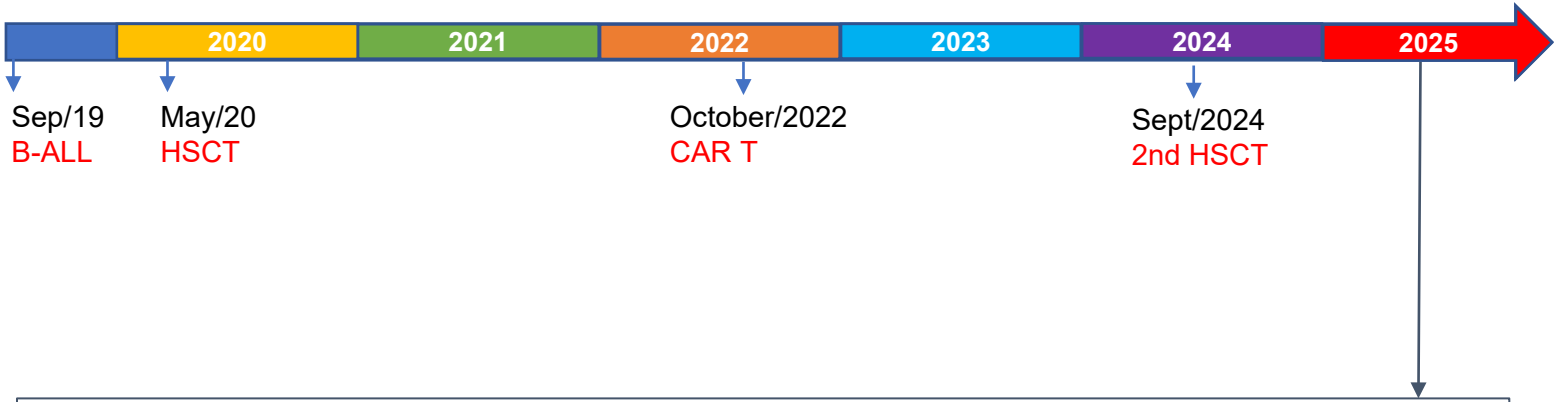
- Haploidentical donor: brother
- Conditioning: thiotepa, busulfan, and fludarabine
- GVHD profilaxis: PTCy, tacrolimus, and mycophenolate

Main complications

- Cardiac failure due to fluid overload (furosemide in continuous infusion)
- Sinusoidal obstruction syndrome (defibrotide for 21 days)

Now (September 2025), the patient is in complete remission with negative MRD and complete donor chimerism

As current complication, he has mild hepatic dysfunction, probably related to grade 1 hepatic GVHD



- Is the patient cured?
- Do we have any options for relapse prophylaxis in his case?
- What should we do if the patient has a new relapse?
- How can we monitor the residual disease in this patient?

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R/R ALL case-based panel discussion: Case 2

Fabian Lang

APTITUDE HEALTH®

Male patient, 33 years old

- 11/2023 Primary diagnosis: pre–T-ALL
  - Initial blood count: leukocytes 56.000/µL; Hb 13,9 g/dL; thrombocytes 168.000/µL
  - Bone marrow: 13% lymphatic blast infiltration
  - Immunology: CD7, CD3, CD2, TdT positive
  - Cytogenetics: 46 XY
  - Molecular genetics: no findings
  - No extramedullary disease

- Comorbidities
  - None

Treatment course: Male patient, 33 years old

Induction I + II
GMALL
VCR/Dex
Dauno-6MP
PEG-Asp
MTX i.th.

11-12/2023

During treatment: severe Loeffler endocarditis with cardiac output failure

Treatment course: Male patient, 33 years old

Induction I + II
GMALL
VCR/Dex
Dauno-6MP
PEG-Asp
MTX i.th.

11-12/2023

Consolidation III
GMALL
HD-AraC
Cyclo

MTX i.th.

02/2024

During treatment: severe Loeffler endocarditis with cardiac output failure
Mitral valve replaced

MRD positive:
- 10^{-4}

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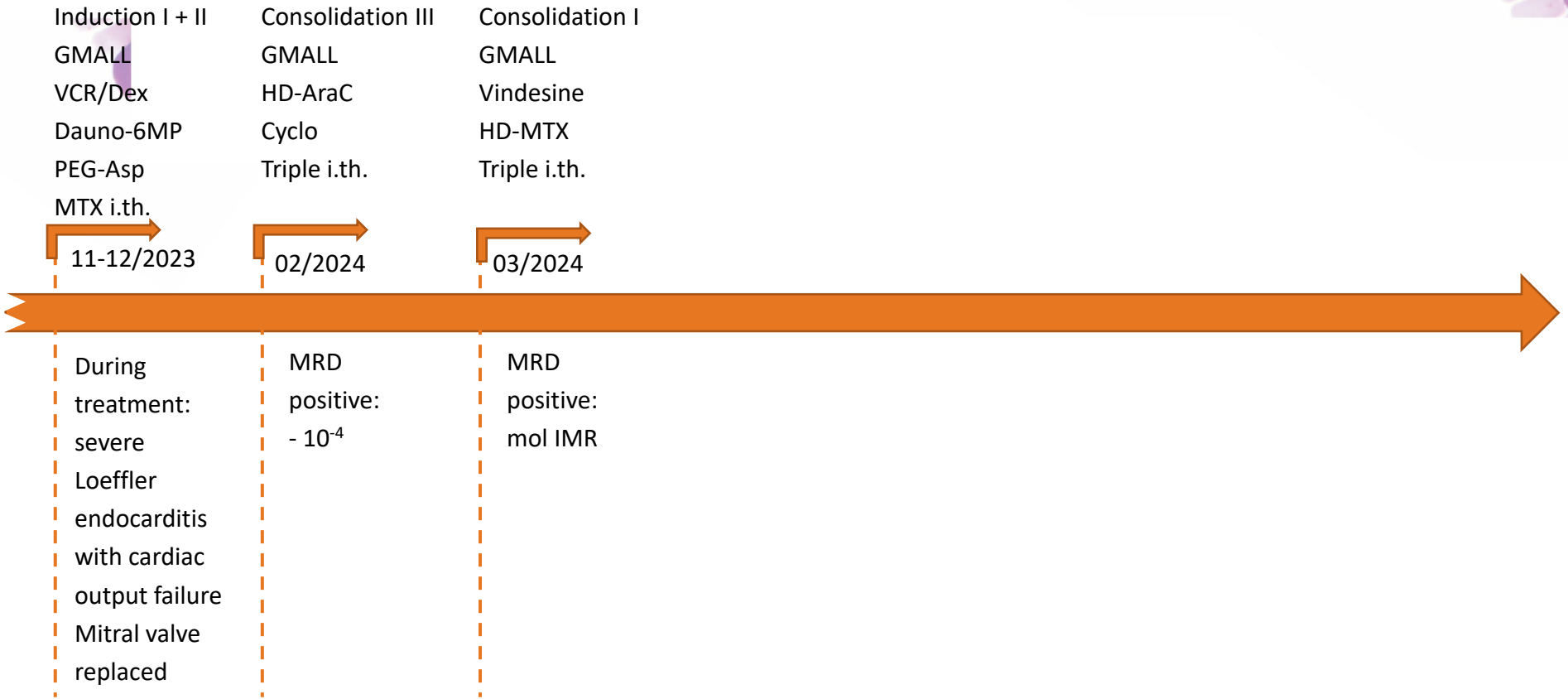
Treatment course: Male patient, 33 years old



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Male patient, 33 years old, low level MRD positive after 3× CTX

Which therapeutic option would you choose?

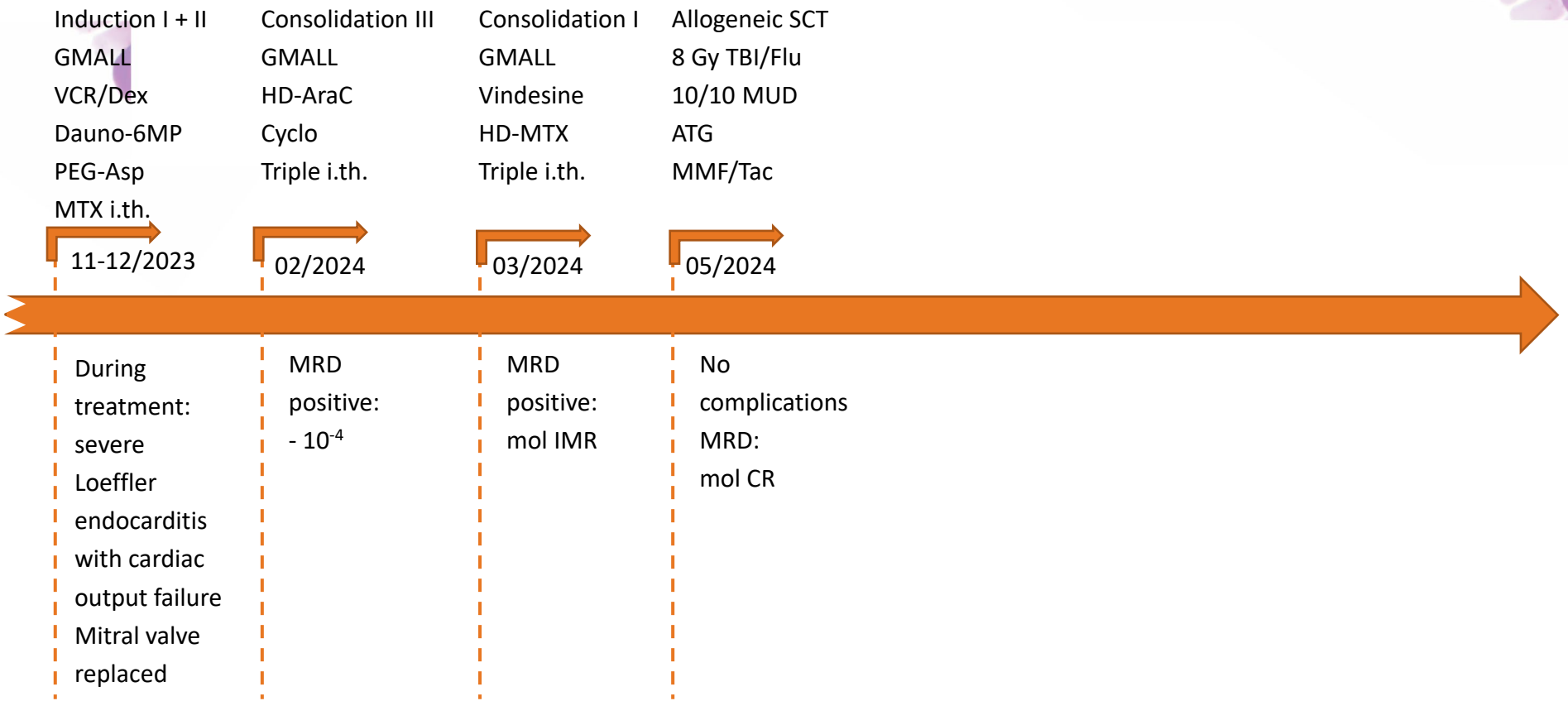
- Allogeneic SCT (12 Gy TBI/Cy)
- Allogeneic SCT (8 Gy TBI/Flu)
- Cont. CTX
- Daratumumab + CTX

Male patient, 33 years old, low level MRD positive after 3× CTX

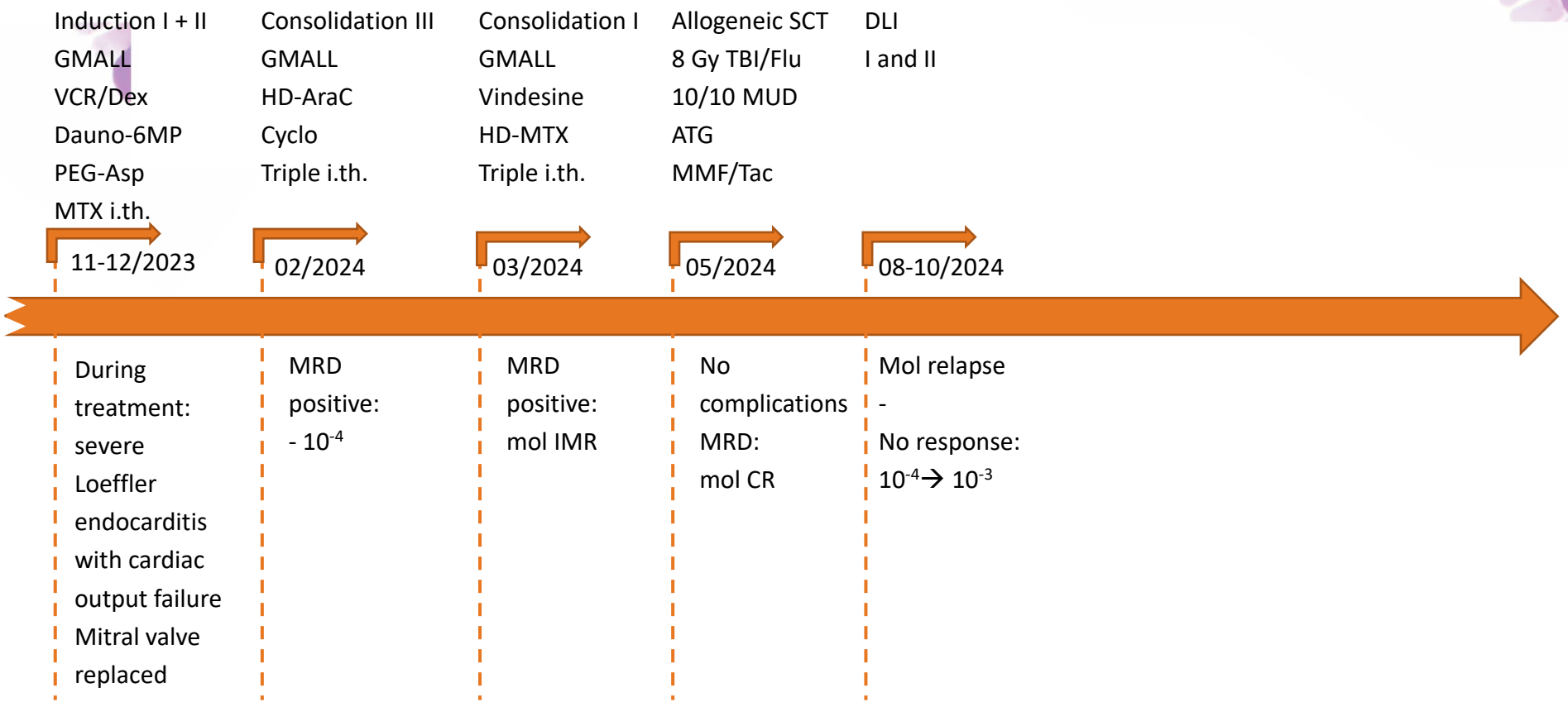
Which therapeutic option would you choose?

- Allogeneic SCT (12 Gy TBI/Cy)
- Allogeneic SCT (8 Gy TBI/Flu)
- Cont. CTX
- Daratumumab + CTX

Treatment course: Male patient, 33 years old



Treatment course: Male patient, 33 years old



Male patient, 33 years old, increasing mol relapse after alloSCT

Which therapeutic option would you choose?

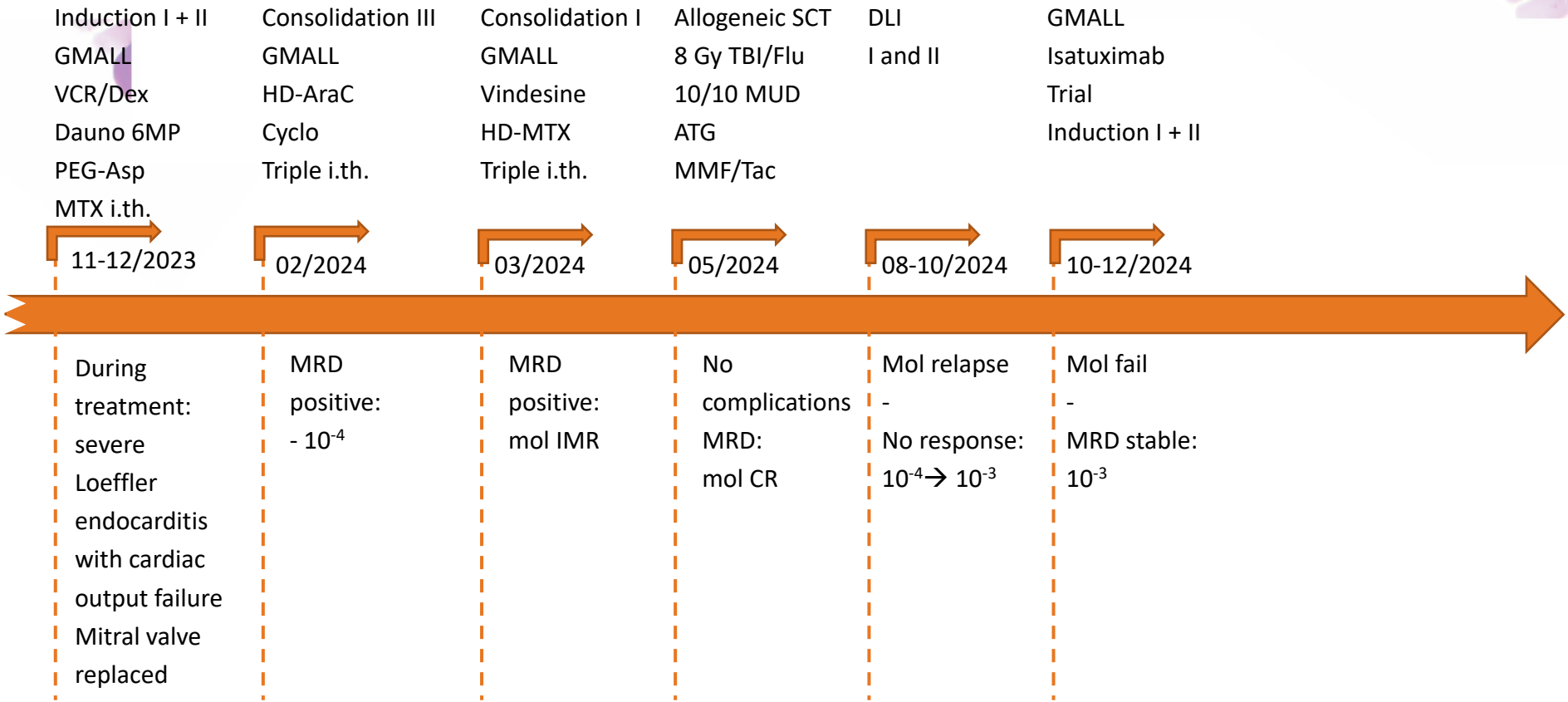
- Second allogeneic SCT (Flu/Mel)
- CAR T cells
- Isatuximab + CTX
- Decitabine-venetoclax

Male patient, 33 years old, increasing mol relapse after alloSCT

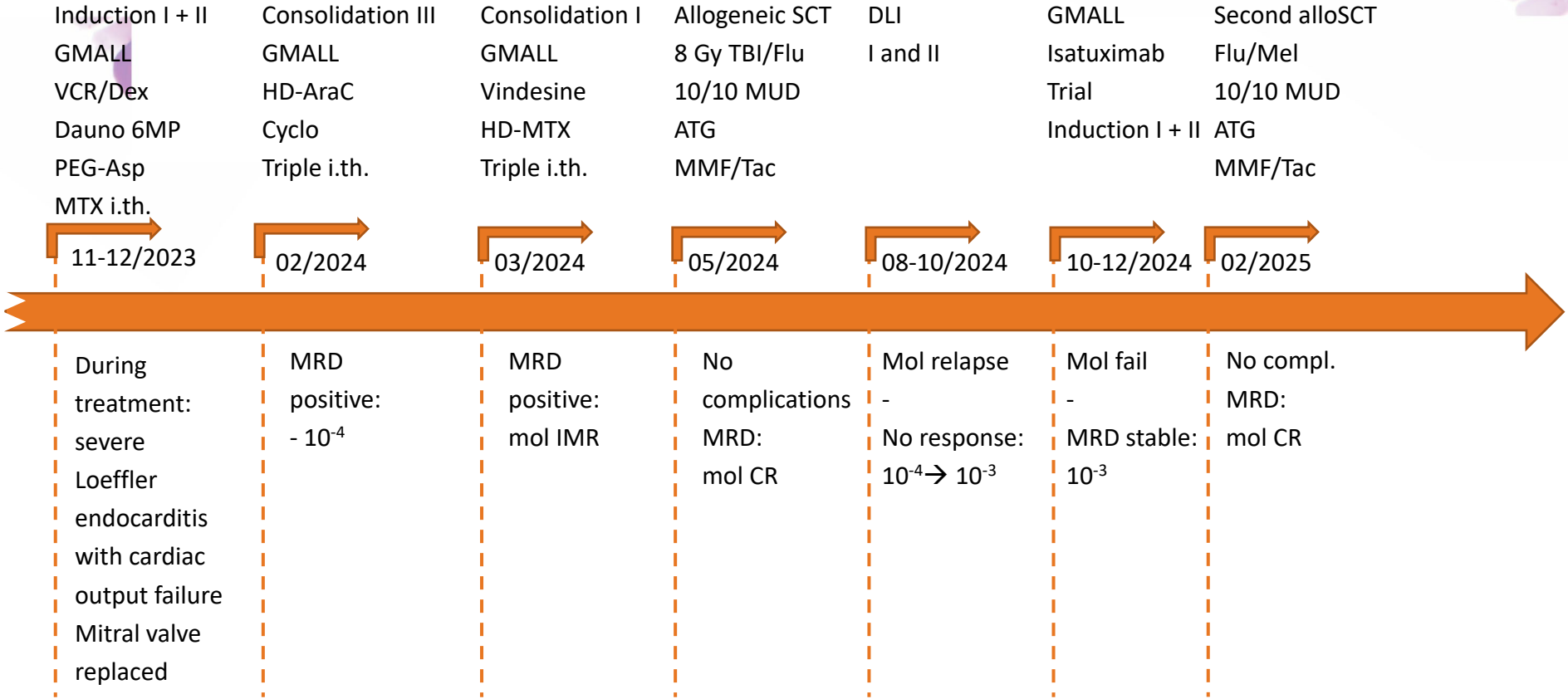
Which therapeutic option would you choose?

- Second allogeneic SCT (Flu/Mel)
- CAR T cells
- **Isatuximab + CTX**
- Decitabine-venetoclax

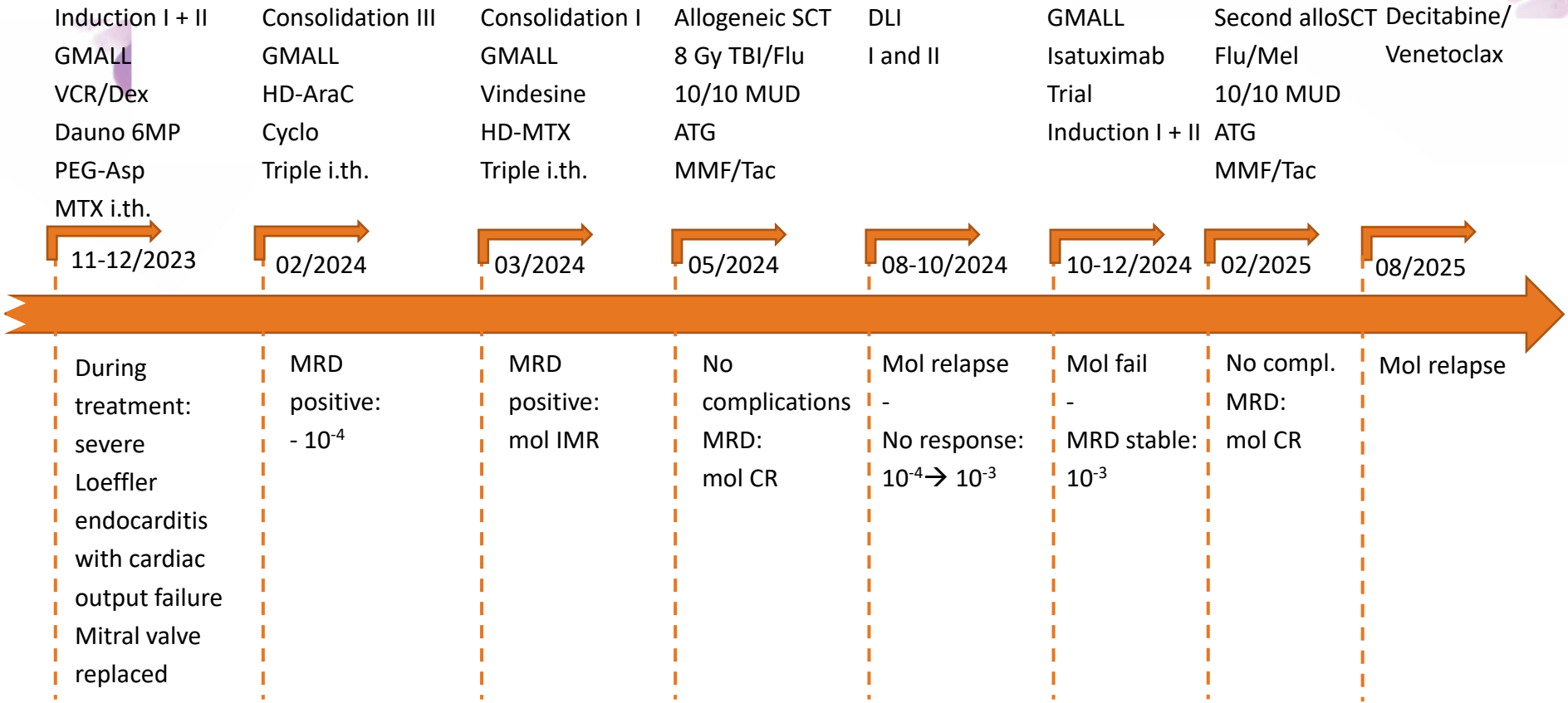
Treatment course: Male patient, 33 years old



Treatment course: Male patient, 33 years old



Treatment course: Male patient, 33 years old



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Main messages/questions from this case

> Strict MRD assessment needed in T-ALL treatment

> Second allogeneic SCT feasible in young patients

> Pre T-ALL with mol relapse after alloSCT difficult to treat

> When are CAR T cells for T-ALL available?

> Urgent medical need for therapy improvement

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Long-term safety considerations for ALL

Nicolas Boissel

Global Leukemia Academy

September 19, 2025

Long-Term Safety Considerations for ALL

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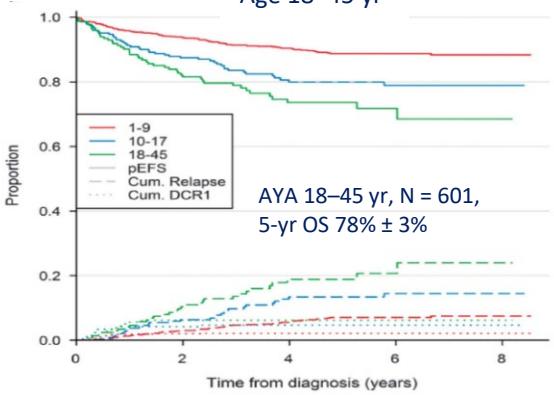
Research funding	Amgen Incyte	Jazz Pharma Novartis

Intensified strategies in AYA

Pediatric and pediatric-inspired protocols

NOPHO-2008[1]
(children and AYA)

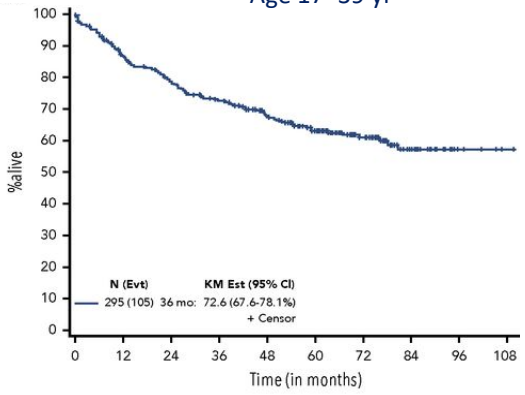
Age 18–45 yr



HSCT: 20% (18–45 yr)

CALGB 10403[2]
(AYA)

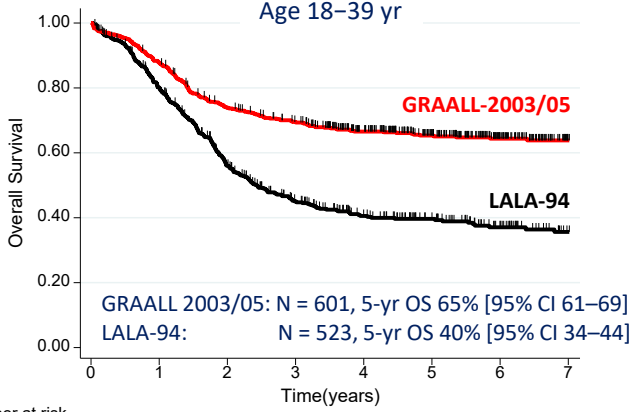
Age 17–39 yr



HSCT: 8%

GRAALL-2003/05[3,4]
(AYA)

Age 18–39 yr



HSCT (GRAALL): 31%

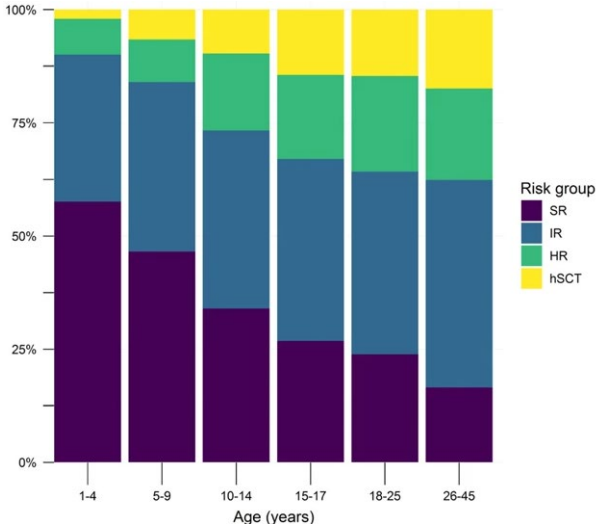
- More intensive trials improve the outcome of AYA
- Early MRD response is the most robust prognostic factor
- Disparities in HSCT eligibility criteria persist

1. Toft N, et al. *Leukemia*. 2018;32:606-615; 2. Stock W, et al. *Blood*. 2019;133:1548-1559;
3. Updated from Huguet F, et al. *J Clin Oncol*. 2009;27:911-918; 4. Updated from Huguet F, et al. *J Clin Oncol*. 2018;20;36:2514-2523.

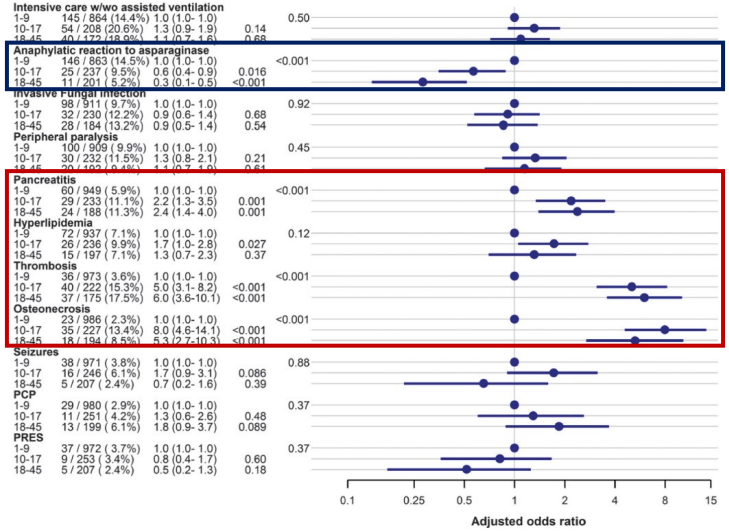
Toxicity across age groups

Children and AYA (1–45 yr), NOPHO-2008 (n = 1509)

Risk stratification according to age



Toxicities according to age



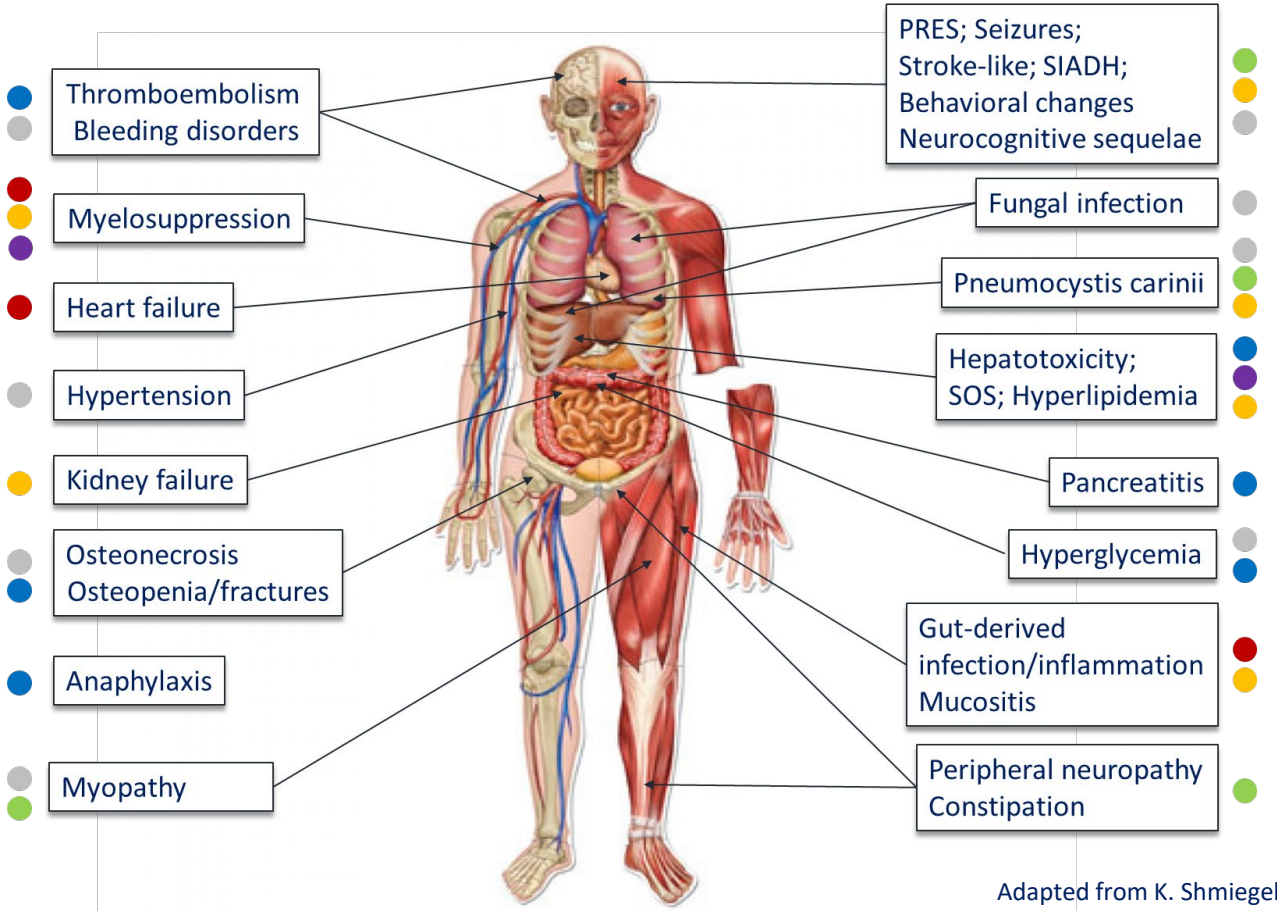
- Age is associated with higher-risk profile (baseline disease characteristics, MRD)
- Higher incidence of some toxicities (pancreatitis, thrombosis, ONA) usually in age 10+ yr

Toft N, et al. *Leukemia*. 2018;32:606-615.

Major toxicity in ALL

AlloHSCT excepted

- Steroids
- Alkaloids
- Asparaginase
- Anthracycline
- Methotrexate
- Purine analogs



Adapted from K. Shmiegelow.

Major toxicity in ALL

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- Steroids
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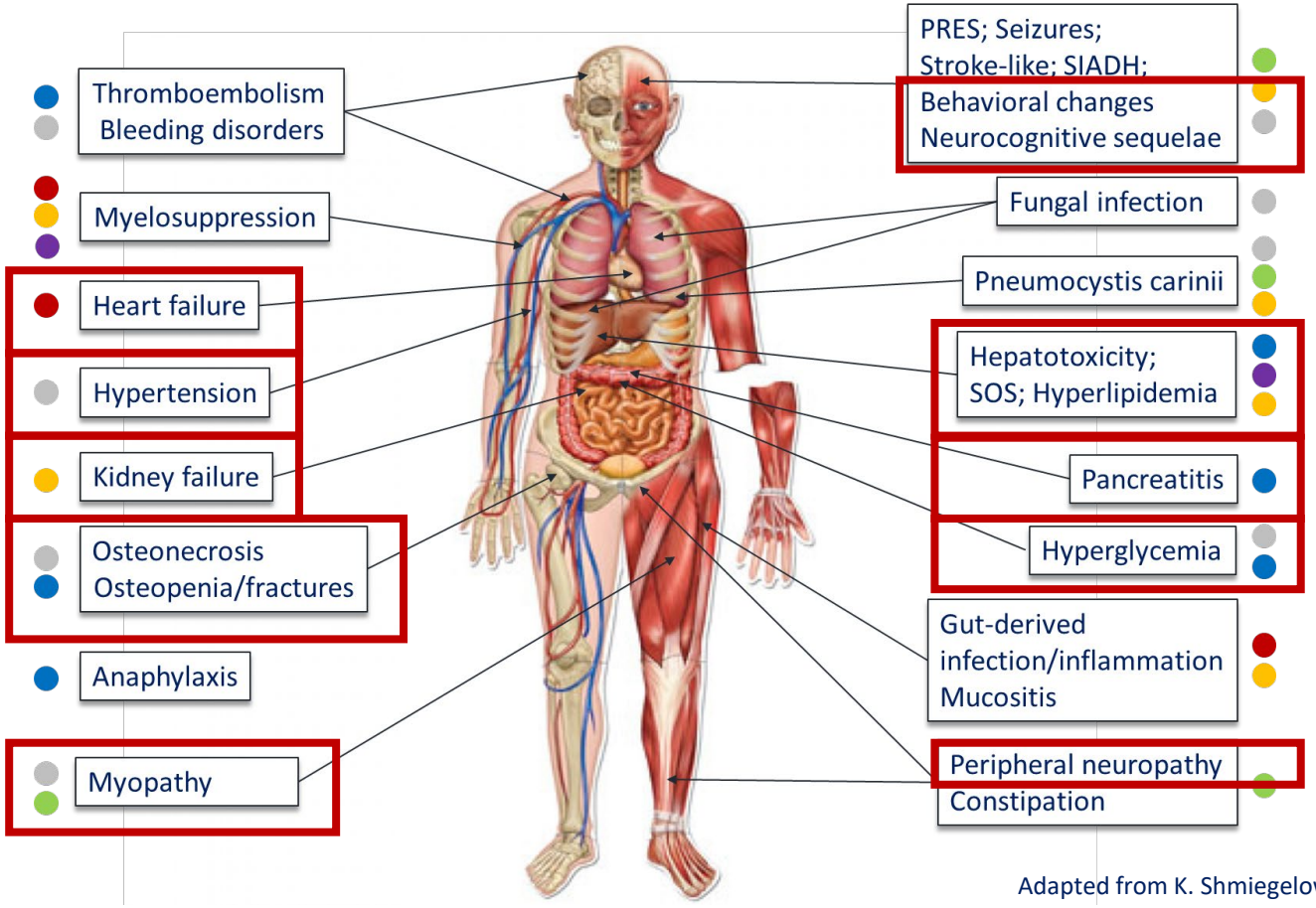
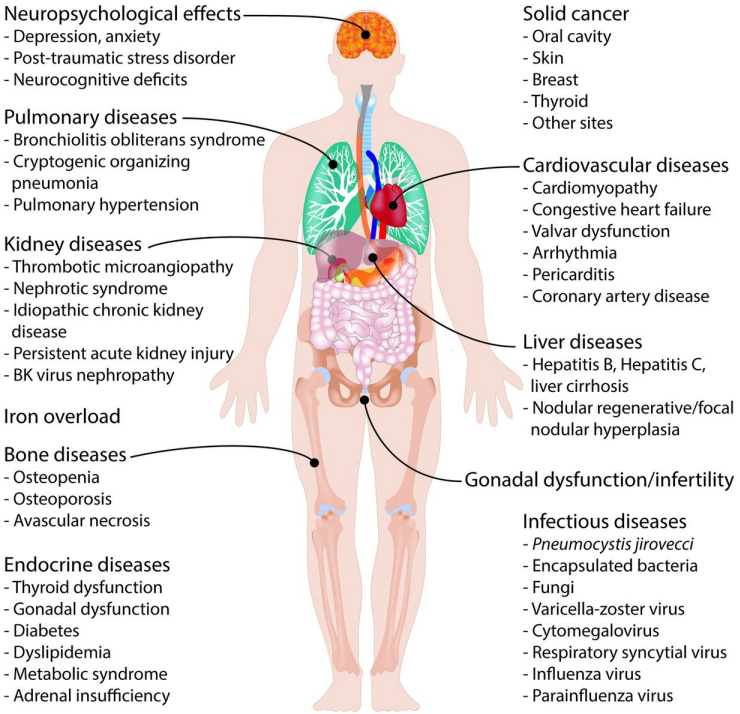


Adapted from K. Shmiegelow.

Late effects of alloHSCT



- **500K long-term alloHSCT survivors worldwide**
- **66% have ≥1 chronic condition**
  (18% severe/life threatening)
- **Life expectancy 30% lower** vs general population

- **Late effects:** multiorgan damage, secondary cancers, chronic GvHD, infections
- **Main late mortality causes:** relapse, secondary cancer, pulmonary, infection, CVD

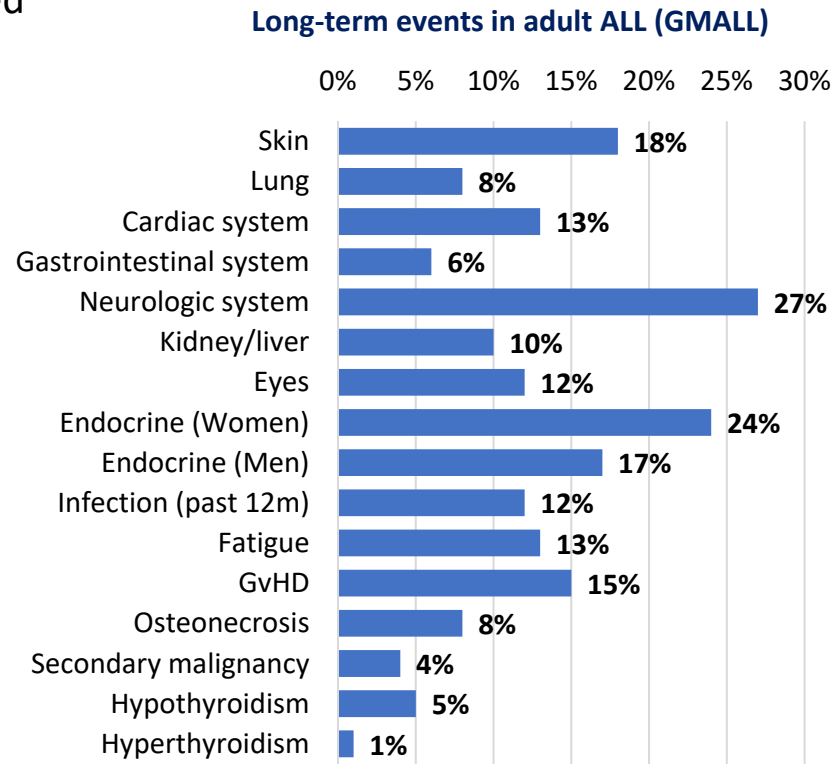
- Need structured long-term follow-up and preventive care

Inamoto Y, Lee SJ. *Haematologica*. 2017;102:614-625.

Survivorship

GMALL experience (N = 538)

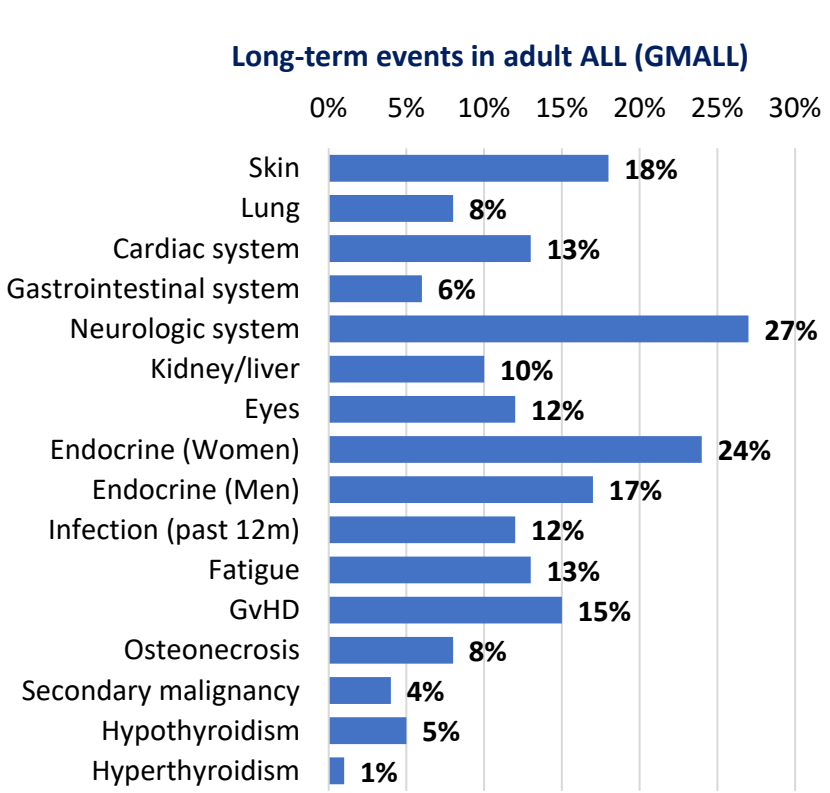
- Retrospective, cross-sectional, questionnaire based
- **Patients aged 15–65 yr** at ALL diagnosis
- 6 consecutive **GMALL trials (1984–2003)**
  - Pediatric-based chemotherapy (BFM backbone)
  - Prophylactic CNS irradiation, intrathecal therapies
  - Consolidation including HD-MTX/AraC
  - Maintenance therapy
- **Inclusion criteria**
  - Alive at least 3 yr at time of data collection
  - ALL treatment completed
  - Data collected from physicians
- **Median age at diagnosis 29 yr (range 15–64)**
- **Median follow-up 7 yr (3–24)**
- **SCT 31%**

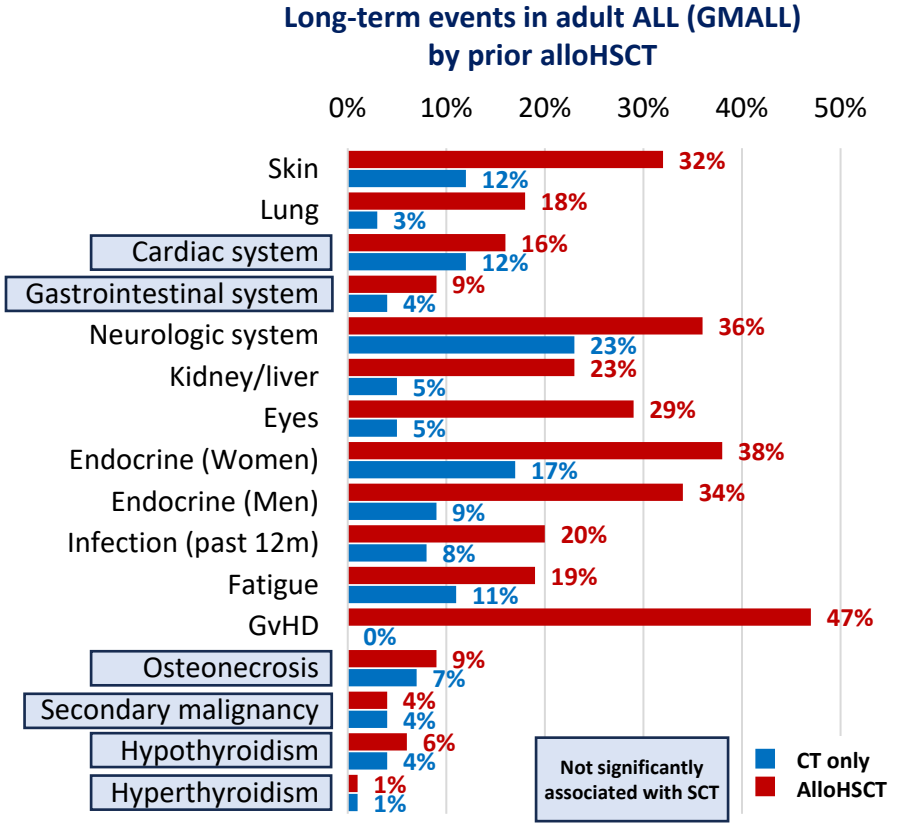


Gökbuget N, et al. *Haematologica*. 2023;108:1758-1767.

Survivorship

GMALL experience (N = 538)

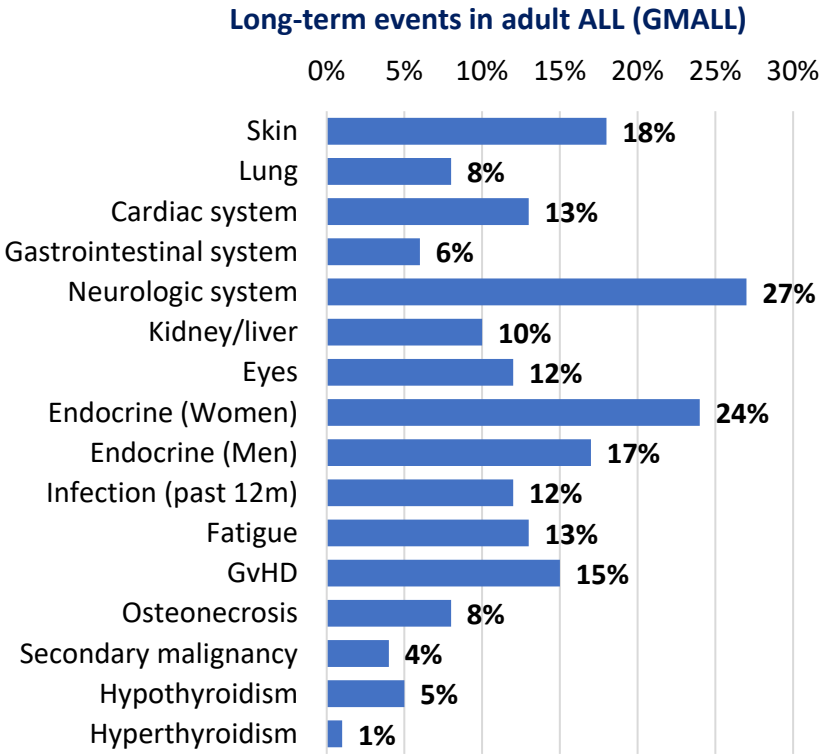


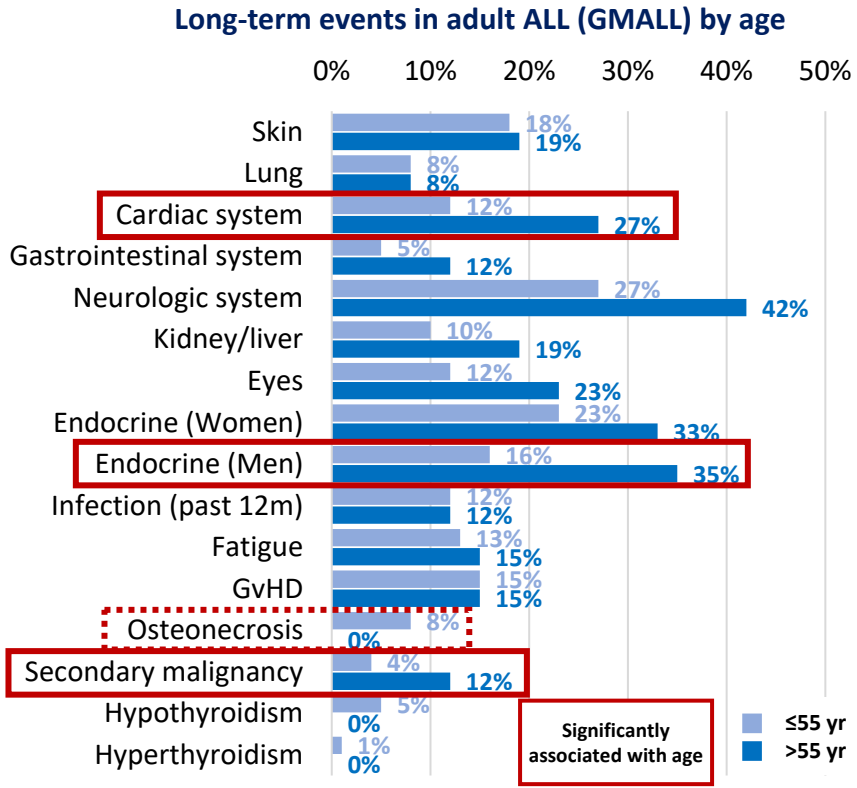


Gökbuget N, et al. *Haematologica*. 2023;108:1758-1767.

Survivorship

GMALL experience (N = 538)



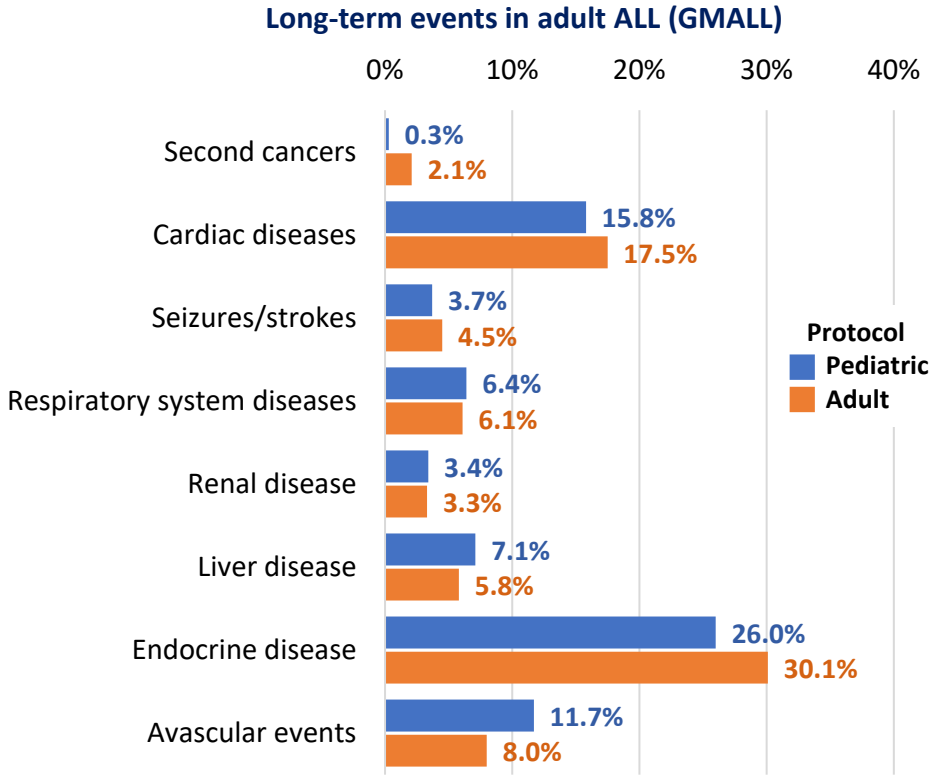


Gökbuget N, et al. *Haematologica*. 2023;108:1758-1767.

Late effects in survivors of AYA ALL

Population-based California Cancer Registry

- **Population-based study** (California, 1995–2012)
  - 1,069 AYA ALL survivors (age 15–39 at diag)
  - Survived ≥3 yr; median follow-up 8.2 yr
  - Data sources: California Cancer Registry, linked hospitalization data (OSHPD)
- **Risk factors**
  - AlloHSCT
  - Public/no insurance (vs private/military); also if CT only
  - No impact of protocol (pediatric vs adult)
  - Low socioeconomic status if alloHSCT

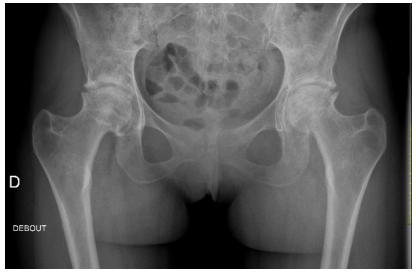


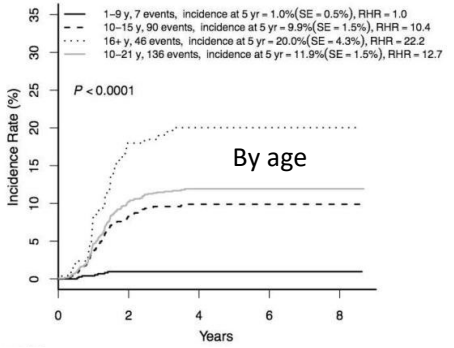
Muffly L, et al. *JNCI Cancer Spectr*. 2020;4:pkaa025.

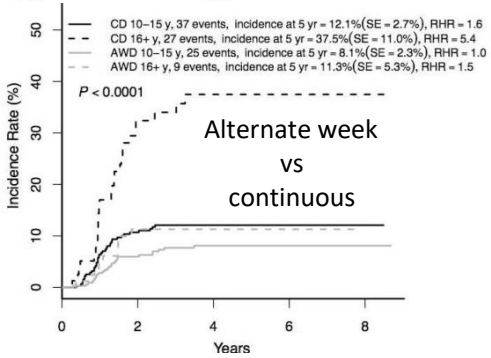
Avascular necrosis

A specific long-term event in AYA

- **Cause**
  - Cumulative dose of corticosteroids
  - Asparaginase, high-dose MTX
- **Risk**
  - Higher risk in children >10 yr and AYA
  - 4% in adults, up to 25% in patients 15 yr (pediatric trials)
  - Within 3 yr after diagnosis
- **Other factors** associated with risk of AVN are
  - Hypertriglyceridemia
  - Higher BMI
  - Continuous steroid administration
  - HSCT, GvHD
- **Special consideration**
  - Alternate week for dosing of dexamethasone







Relling MV, et al. *J Clin Oncol*. 2004;22:3930-3936; Mattano LA, et al. *Lancet Oncol*. 2012;13:906-915; Mogensen SS, et al. *Haematologica*. 2017;102:e175-e178; Patel B, et al. *Leukemia.* 2008;22:308-312.

Cardiovascular late effects

- **Causes:** anthracyclines, chest/mediastinal RT
- **Risks**
  - Cardiomyopathy, LV dysfunction, CHF . . .
  - 10% LVEF decrease within 1 yr of treatment completion
- **Monitoring**
  - Echo ± strain, ECG (baseline)
  - After cumulative dose of 200–250 mg/m^2 and after additional 100 mg/m^2
  - At 6–12 mo after treatment completion
  - Long-term according to dose and radiation
- **Counseling**
  - Manage BP, BMI, lipids, glucose
  - Encourage exercise
- **Special considerations**
  - TKI with cardiovascular toxicity
  - Pregnancy needs extra monitoring

Recommended frequency of echocardiogram (COG LTFU Guidelines)

Anthracycline Dose*	Radiation Dose**	Recommended Frequency
None ot <100mg/m^2	None to <15Gy	No screening
None to <100mg/m^2 ≥100 to <250mg/m^2	15Gy to <30Gy None to <15Gy	Every 5 years
≥100 to <250mg/m^2 None to Any ≥ 250mg/m^2	≥15Gy ≥30Gy None to Any	Every 2 years
*Based on doxorubicin isotonic equivalent dose. **Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI).		

Children's Oncology Group. Long-Term Follow-Up Guidelines. Version 6.0. 2023. Available from: https://www.survivorshipguidelines.org/pdf/2023/COG_LTFU_Guidelines_Only_v6.pdf. Accessed September 17, 2025; Curigliano G, et al. *Ann Oncol*. 2020;31:171-190; Stone JR, et al. *JCO Oncol Pract*. 2021;17:228-236.

Secondary neoplasms

- **Causes**
  - Alkylating agents, topoisomerase inh, radiation
- Heterogeneous diagnoses
- **Risk**
  - 2%–5%
  - Median time to second neoplasm 11 yr (range 2–23)
- Similar incidence in transplanted vs nontransplanted patients
- **Special considerations**
  - Predisposing mutations (*TP53*, *RUNX1*, *ETV6* . . .), and syndromes (DS, FA, NF . . .)
  - Clonal hematopoiesis

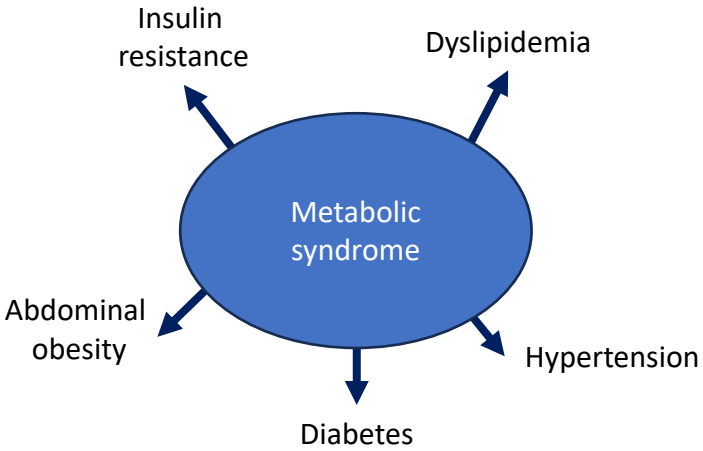
GMALL (N = 538)
N = 21 (4%)
Melanoma (n = 4)
Basal cell carcinoma (n = 4)
Hem malignancies (n = 4)
Breast cancer (n = 2)
Prostate cancer (n = 2)
Glioblastoma (n = 1)
Small intestine cancer (n = 1)
Stomach cancer (n = 1)
Cervix cancer (n = 1)
Sarcoma (n = 1)

California Registry
N = 19 (1.8%)
Lip
Salivary gland
Soft tissue
Melanoma
Other non-epithelial skin
Breast
Vulva
Testis
Thyroid
Hodgkin lymphoma
Miscellaneous

Gökbuget N, et al. *Haematologica*. 2023;108:1758-1767; Muffly L, et al. *JNCI Cancer Spectr*. 2020;4:pkaa025.

Dysmetabolic syndrome

- **Definition**
  - Obesity, insulin resistance, type 2 diabetes
  - Hypertension, dyslipidemia → cardiovascular disease
- 10% of children survivors
- **Drivers**
  - Prolonged corticosteroid exposure
  - AlloHSCT
  - Cranial radiotherapy
- **Evidence**
  - Mostly in childhood ALL survivors
- **Surveillance and care**
  - Regular BMI, waist circumference, BP, fasting glucose, lipids
  - Lifestyle counseling: diet, exercise, smoking cessation
  - Early cardiology/endocrinology referral if abnormalities



Nottage KA, et al. *Br J Haematol*. 2014;165:364-374; Oudin C, et al. *Haematologica*. 2018;103:645-654.

Premature ovarian failure (POF)

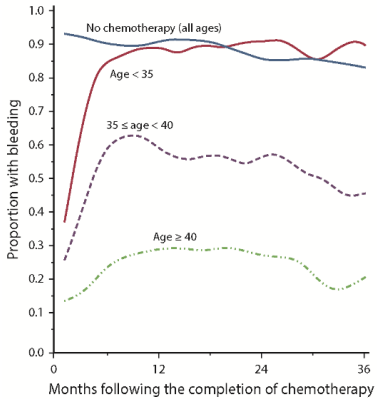
Overview in ALL

- **The risk of POF** in ALL is low and depends on
  - Patient age
  - Treatment strategy (HSCT)
  - Type of drugs and cumulative doses
- **The likelihood of POF/early menopause** for a given age after intensive pediatric-inspired protocols w/o HSCT is unknown
- **Fertility preservation at diagnosis** is usually impaired by
  - Treatment emergency
  - Blood clotting disorders (thrombocytopenia, DIC . . .)
  - Infectious risk (neutropenia)
- **Ovarian tissue may be contaminated by leukemic cells,** source of disease reimplantation

Risk of POF in acute leukemia

High risk	Low risk	Very low risk
Total body irradiation (ICT) **Alkylating agents** (cyclophosphamide, busulfan, melphalan . . .)	Other drugs (anthracycline, cytarabine, antimetabolites . . .)	Vincristine Methotrexate Steroids

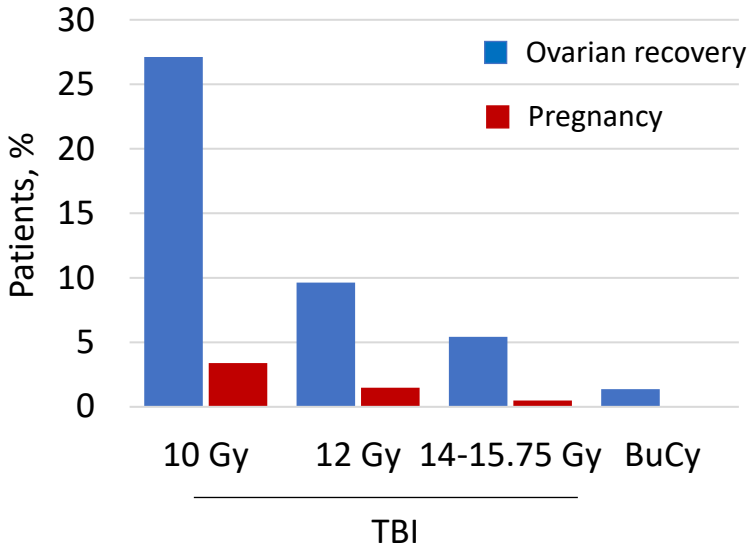
Likelihood to resume menses after chemotherapy (breast cancer)



Petrek JA, et al. *J Clin Oncol.* 2006;24:1045-1051.

Ovarian function after HSCT for ALL

- **Infertility is common after alloHSCT**
- **POF is reported in**
  - >80% of females after myeloablative regimen
  - Almost all patients after Bu-Cy
- Incidence of pregnancy <3%
- **Increased risk for maternal and fetal complications after TBI-based regimen**



Sanders JE, et al. *Blood.* 1996;87:3045-3052; Salooja N, et al. *Lancet.* 2001;358:271-276.

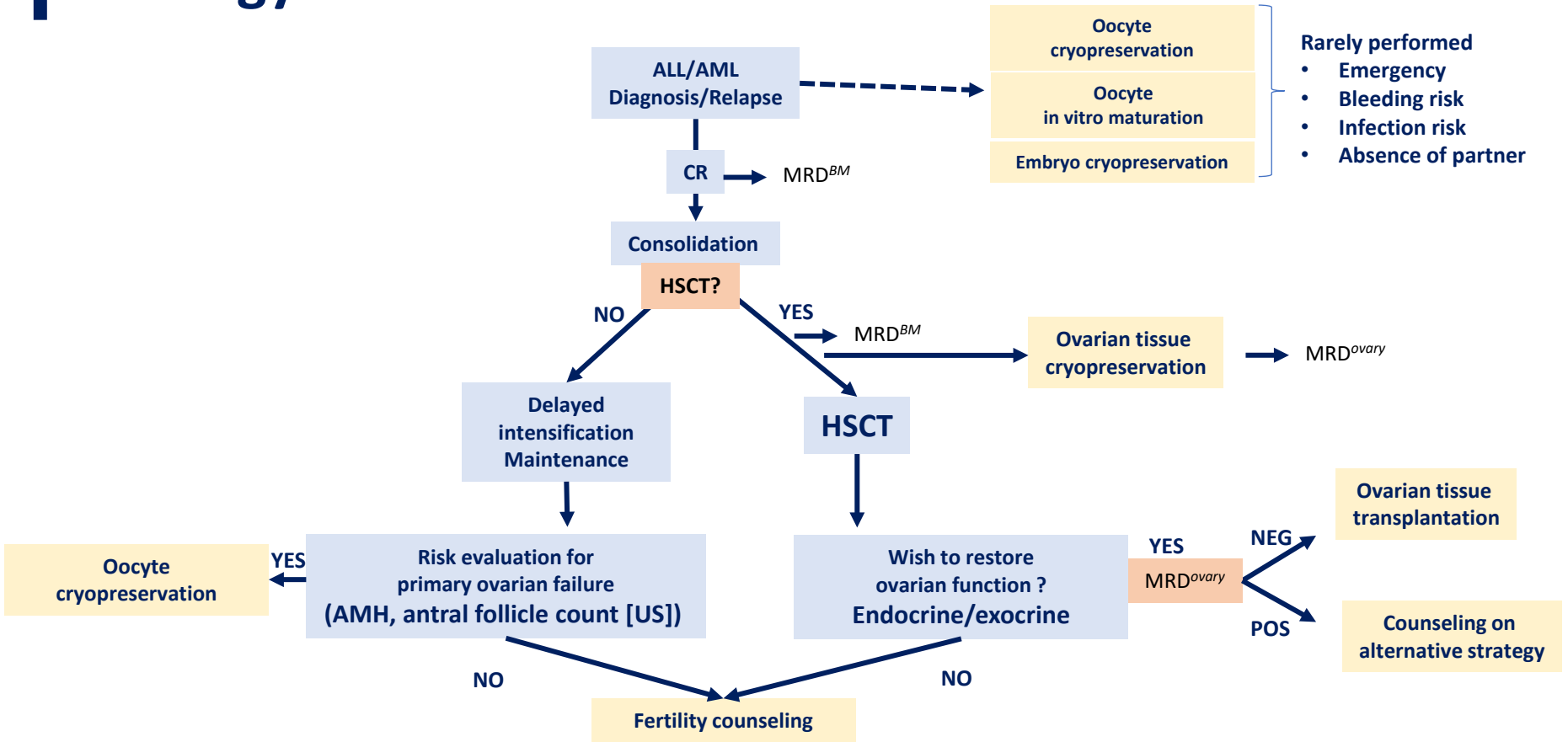
Ovarian tissue cryopreservation and transplantation

French experience in acute leukemia

- N = 13 patients, median age 20 yr at OTC, 33 yr at OTT
- Undetectable MRD in 9/13 (*NPM1*, IG/TR, *KMT2A*::*AFDN*, *RUNX1*)
- **Endocrine recovery**
  - 77% regained ovarian function within 4.4 mo of OTT
- **Fertility outcomes**
  - 4 pregnancy attempts → 1 live birth, 3 miscarriages
  - Lower success vs other series
- **Safety**
  - MRD-negative ovarian tissue
  - 1 medullary relapse (B-ALL, MRD <0)

Chevillon F, et al. *Haematologica*. 2025. Online ahead of print.

Strategy for acute leukemia



Hudson MM, Bhatia S. *J Clin Oncol*. 2024;42:617-620;
Armenian SH, et al. *J Clin Oncol*. 2024;42:735-742.

Long-term safety for ALL

Conclusion

- Long-term toxicity is still largely driven by **alloHSCT**
- Adult data are scarce – most evidence extrapolated from pediatrics
- **Multidisciplinary surveillance** is essential (cardiology, endocrinology, fertility, rheumatology, etc)
- **Lifelong survivorship care plans** should include nontransplanted patients, **adapted to individual risk**
- Frontline immunotherapy may allow de-escalation of chemotherapy and HSCT, improving overall safety

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Panel discussion: Open questions in ALL – regional challenges (transplant, CAR T studies, and other)

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Panel discussion: Open questions in ALL – regional challenges (transplant, CAR T studies, and other)

- Who are the ideal patients for CAR T therapy, bispecifics, and transplants in your practice?
- What would be needed to make CAR T therapy available to all of your patients?
- What would be needed to best position bispecifics in the continuum of care for ALL in adults?
- How should transplant be strategically combined with the new therapy modalities?

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ARS questions

Elias Jabbour

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Question 1 [REPEATED]

For first salvage of R/R ALL in your setting, which of the following treatments would you consider, if all these therapies were available in your country and have not been used previously in this patient?

A. CD19 CAR T therapy
B. Bispecific antibody (blinatumomab)
C. Antibody-drug conjugate (inotuzumab ozogamicin)
D. Intensive cytotoxic chemotherapy ± targeted TKI
E. Transplant without additional salvage therapy
F. Other

Question 2 [REPEATED]

What is your opinion of the tolerability of CD19 CAR T cells?

A. All agents are very difficult to tolerate in most patients
B. All agents are hard to tolerate in elderly/frail patients
C. All agents are manageable in most patients
D. Tolerability varies depending on the specific CAR T

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Session close

Elias Jabbour

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