Global Leukemia Academy

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

24 September 2022

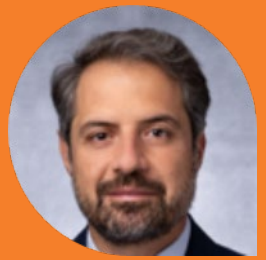
Virtual Breakout: Adult ALL

APTITUDE HEALTH

Global Leukemia Academy

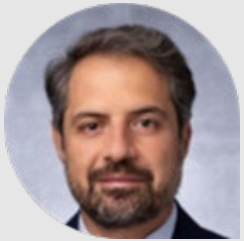
Welcome and Meeting Overview

Elias Jabbour



APTITUDE HEALTH

FACULTY



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

CHAIR

Nicola Gökbuget, MD
University Hospital Frankfurt, Germany

Nicolas Boissel, MD, PhD
Hôpital Saint-Louis, France

Jose María Ribera, MD, PhD
Catalan Institute of Oncology, University Hospital Germans Trias i Pujol, Barcelona, Spain

Virtual Breakout – Adult ALL Sessions (Day 2)

24 September 2022, 11.00 – 13.45 CEST

Chair: Dr Elias Jabbour

Time (CEST)	Title	Speaker
11.00 – 11.10	**Session Open**	Elias Jabbour
11.10 – 11.35	**Optimizing First-Line Therapy in Adult and Older ALL: Integration of Immunotherapy Into Frontline Regimens**	Nicolas Boissel
11.35 – 12.00	**Current Treatment Options for Relapsed ALL in Adult and Older Patients**	Nicola Gökbuget
12.00 – 12.40	**ALL Case-Based Panel Discussion** • Relapsed/Refractory Case 1 • Relapsed/Refractory Case 2	Moderator: Elias Jabbour Loic Vasseur Anjali Cremer All faculty
12.40 – 12.50	***Break***	
12.50 – 13.10	**Beyond the Horizon: New and Future Treatment Approaches for Adult and Older ALL Patients**	Nicola Gökbuget
13.10 – 13.35	**Interactive Discussion: Treatment Landscape Evolution**	Moderator: Elias Jabbour All faculty
13.35 – 13.45	**Session Close**	Elias Jabbour

Virtual Breakout – AML Sessions (Day 2)

24 September 2022, 14.30 – 17.15 CEST

Chairs: Dr Gail J. Roboz/Dr Naval Daver

Time (CEST)	Title	Speaker
14.30 – 14.40	**Session Open**	Gail J. Roboz and Naval Daver
14.40 – 15.00	**Personalized Induction and Maintenance Approaches for AML**	Gail J. Roboz
15.00 – 15.25	**Fit and Unfit AML Patients: How Do We Distinguish? How Do We Treat Differently?**	Agnieszka Wierzbowska
15.25 – 16.05	**AML Case-Based Panel Discussion** • Relapsed/Refractory Case 1 • Relapsed/Refractory Case 2	Moderators: Gail J. Roboz and Naval Daver Agnieszka Pluta Anna Torrent All faculty
16.05 – 16.15	***Break***	
16.15 – 16.40	**Optimizing Management of Relapsed/Refractory AML**	Naval Daver
16.40 – 17.05	**Interactive Discussion: Treatment Landscape Evolution**	Moderators: Gail J. Roboz and Naval Daver All faculty
17.05 – 17.15	**Session Close**	Gail J. Roboz and Naval Daver

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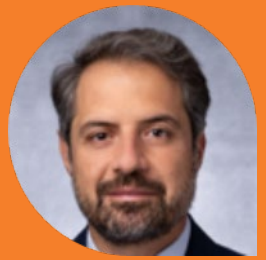
Introduction to the Voting System

Elias Jabbour



APTITUDE HEALTH

Question 1

What age group is considered elderly ALL patients?

1. ≥50 years
2. ≥55 years
3. ≥60 years
4. ≥65 years
5. ≥70 years

Question 2

Which of the following is NOT true for treating ALL?

1. Inotuzumab and blinatumomab + chemotherapy has produced 90% CR rates in salvage therapy and in first line in older patients
2. Blinatumomab and ponatinib can be used as a chemotherapy-free regimen in Ph+ ALL
3. MRD– CR does not correlate strongly with outcome
4. Since 1999, median survival for ALL patients older than 60 has been increasing with each successive decade

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Optimizing First-Line Therapy in Adult and Older ALL: Integration of Immunotherapy Into Frontline Regimens

Nicolas Boissel

APTITUDE HEALTH

Global Leukemia Academy
24 September 2022

Optimizing First-Line Therapy in Adult and Older ALL: Integration of Immunotherapy

Nicolas Boissel

Unité Adolescents et Jeunes Adultes

Hôpital Saint-Louis, AP-HP

Institut de Recherche Saint-Louis, Université de Paris, France

Université Paris Cité

GRAALL
LALA GOELAMS SAKK

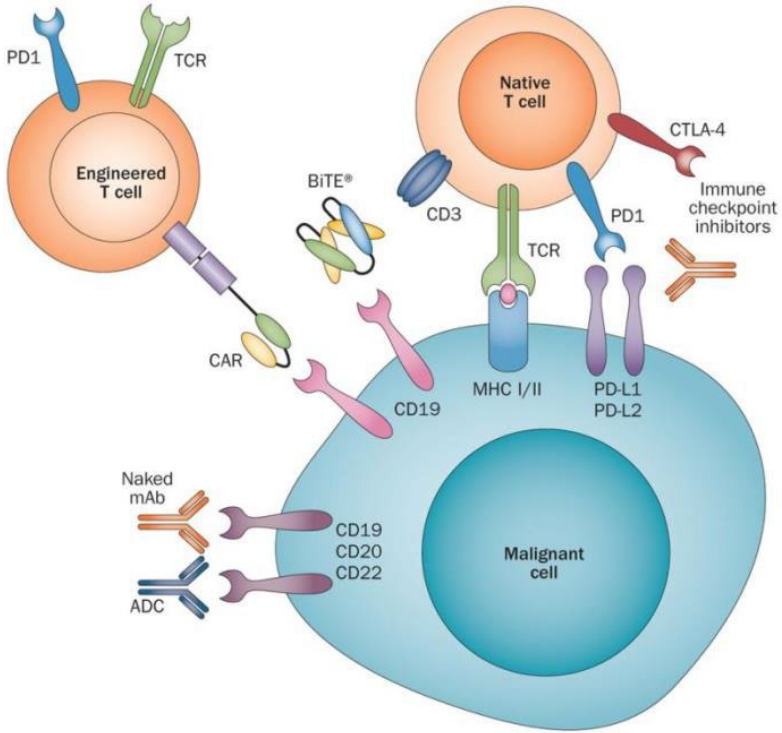
Hôpital Saint-Louis AP-HP

Disclosures

Honoraria (consulting, advisory role)	Amgen Ariad-Incyte Bristol Myers Squibb Celgene Jazz Pharma	Novartis Pfizer Sanofi Servier Shire
Research funding	Amgen Bristol Myers Squibb	Novartis Jazz Pharma

This presentation is not intended for US healthcare professionals. This is a satellite symposium organized by Amgen during the EHA 2022 Hybrid Congress.

Immuno-oncology Therapies in ALL



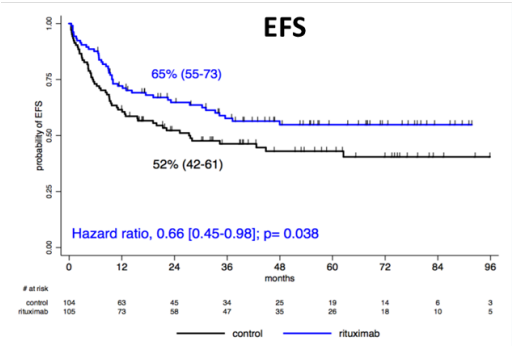
- Antibody-drug conjugate
  - **Inotuzumab ozogamicin** (BESPONSA®)
    - Antibody-drug conjugate
    - R/R CD22+ ALL in adults
- CD19-CD3 immune cell engager
  - **Blinatumomab** (BLINCYTO®)
    - Bispecific T-cell engager
    - R/R CD19+ ALL in adults/children
    - MRD+ B-ALL in adults
    - Consolidation in children with first relapse HR Ph– B-ALL
- CD19 CAR T
  - **Tisagenlecleucel** (KYMRIAH®)
    - CD19/4-1BB/CD3z CAR T cells
    - CD19+ ALL in children, adolescents and young adults, second relapse, first relapse post-HSCT (<26 years)
  - **Brexucabtagene autoleucel** (TECARTUS®)
    - CD19/4-1BB/CD3z CAR T cells
    - R/R CD19+ ALL in adults

Batlevi CL, et al. *Nat Rev Clin Oncol*. 2016;13:25-40.

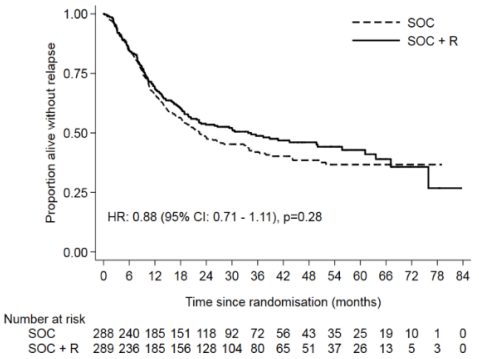
CD20 Monoclonal Antibodies

- **CD20 expressed in 1/3 of B-ALL**
  (upregulated by steroids)
- **What have we learned from phase III studies?**
  - R-GRAALL-2005 and UKALL-14[1,2]
  - Rituximab given throughout the protocol in CD20+ ALL patients reduces the risk of relapse and improves EFS[1]
  - Rituximab given during induction in all patients does not improve EFS[2]
- **Pending questions/issues**
  - Should rituximab be given regardless of CD20 expression?
  - Mechanisms? (direct toxicity, ADCC, CDC, decreases anti-asparaginase immunization . . .)
  - Not approved, but widely used with occasional reimbursement issues
- **New-generation CD20 mAb may provide similar benefit[3]**

Phase III R-GRAALL-2005 study, CD20+ Ph– B-ALL[1]



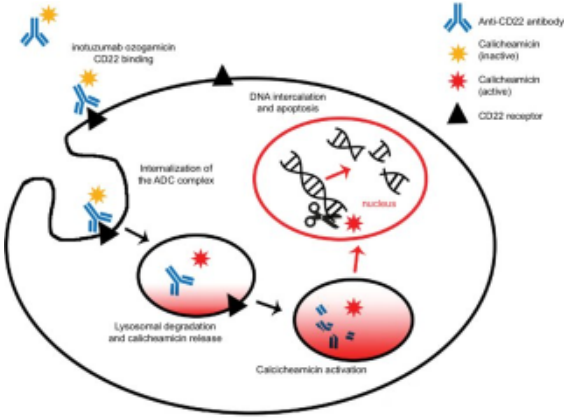
Phase III UKALL-14, Ph– B-ALL[2]



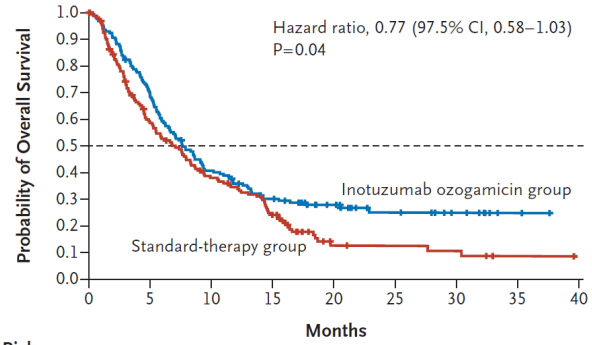
1. Maury S, et al. *N Engl J Med.* 2016;375:1044-1053; 2. Marks DI, et al. *Blood.* 2019;134:739;
3. Chew S, et al. *Best Pract Res Clin Haematol.* 2020;33:101226.

Inotuzumab Ozogamicin

- **Inotuzumab ozogamicin is a CD22 monoclonal antibody conjugated to the cytotoxic antibiotic calicheamicin[1]**
- **Inotuzumab is approved in R/R B-ALL**
- **Pivotal study (INO-VATE) in R/R B-ALL (n = 218)[2]**
  - Overall response rate: 80.7% vs 29.4% for SOC
  - Complete MRD response (<0.01%): 78.4% vs 28.1% for SOC
  - 2-year OS: 23% vs 10% for SOC
- **Safety profile**
  - Cytopenia (febrile neutropenia, thrombocytopenia)
  - Grade 3 hepatic toxicity[3]
  - Veno-occlusive disease, mostly observed after allo-SCT
- **Anecdotal data in MRD+ ALL**



INO-VATE phase III study (R/R B-ALL)



No. at Risk									
Inotuzumab ozogamicin group	164	112	62	41	24	13	8	2	0
Standard-therapy group	162	85	51	30	6	5	4	1	0

1. Uy N, et al. *J Blood Med.* 2018;9:67-74; 2. Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753;
3. Kantarjian H, et al. *Lancet Haematol.* 2017;4:e387-e398.

Inotuzumab Ozogamicin in Frontline B-ALL

		Age, years	Patients, N	Endpoint	NCT
GIMEMA	**ALL2418, MRD study**	18+	76	MRD	NCT03610438
MDACC	**MRD study**	18+	40	RFS	NCT03441061
MDACC	**HCVD (+ Blin)**	14+	80	RFS	NCT02877303
NCI/ALLIANCE	**A041703 (+ Blin)**	18+	64	EFS	NCT03739814
MDACC	**HCVD + INO, ≥60 years**	60+	276	MTD/PFS	NCT01371630
GMALL	**INITIAL-1**	56–74	45	EFS	NCT03460522
ALLIANCE	**A041501***	18–39	310	EFS	NCT03150693
EWALL	**EWALL-INO**	55+	130	OS	NCT03249870
COG	**ALL1732***	1–25, HR	NA	DFS	NCT03959085
ALLTOGETHER	**ALLTOGETHER-1***	1–45, IR-high	NA	DFS	NCT04307576
GRAALL	**2022-B***	18–65, SR and HR	480	DFS	Pending

Comments

- In combination with chemotherapy, ± in place of anthracycline
- In patients with no indication for allo-HSCT
  - Elderly patients
  - Young patients with no VHR features

*Phase III studies.

MiniHCVD + Inotuzumab ± Rituximab

Ph– ALL in older adults

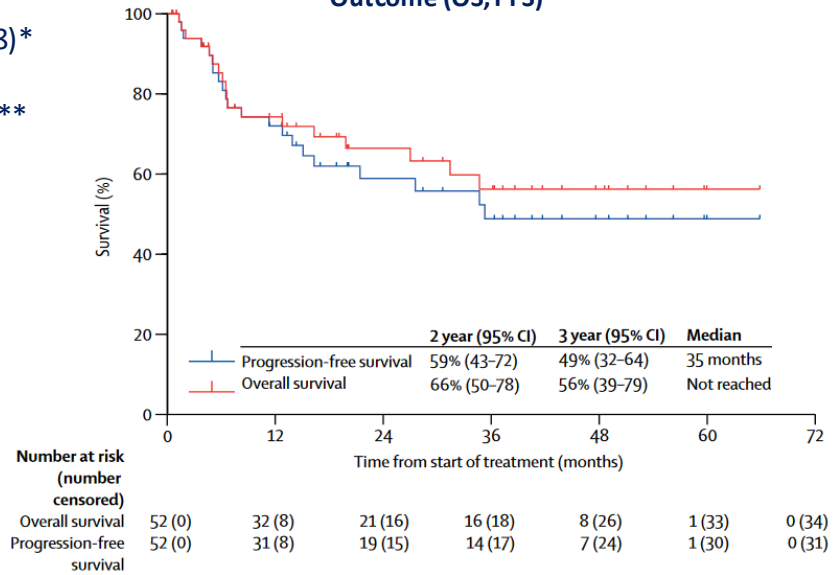
Patient characteristics

	Patients (n=52)
Age (years)	68 (64–72)
Sex	
Male	32 (62%)
Female	20 (38%)
ECOG performance status ≥2	7 (13%)
Median white blood cell count (10^9 cells per l.)	3·0 (1·5–5·6)
White blood cell count ≥50%	4 (8%)
Peripheral blasts (%)	11 (0–45)
Bone marrow blasts ≥50%	43 (83%)
Karyotype	
Diploid	16 (31%)
Low hypodiploidy/triploidy	11 (21%)
t(4;11)	0
High hyperdiploidy	5 (10%)
Tetraploidy	3 (6%)
Complex	1 (2%)
Miscellaneous	6 (12%)
Not done or insufficient metaphases	10 (19%)
Median CD22 expression in the bone marrow (%)	
CD20 expression ≥20% of cells in the bone marrow	31 (60%)
Central nervous system disease at diagnosis	3 (6%)

Early response

- Overall response, 98% (47/48)*
- CR, 85%; CRp, 10%; CRh, 2%
- MRD negativity, 78% (36/46)**

Outcome (OS, PFS)



Number at risk (number censored)							
Overall survival	52 (0)	32 (8)	21 (16)	16 (18)	8 (26)	1 (33)	0 (34)
Progression-free survival	52 (0)	31 (8)	19 (15)	14 (17)	7 (24)	1 (30)	0 (31)

Safety

- 33% grade 3+ liver AEs
- 4 VOD, 1 after allo-SCT

Kantarjian H, et al. *Lancet Oncol*. 2018;19:240-248.

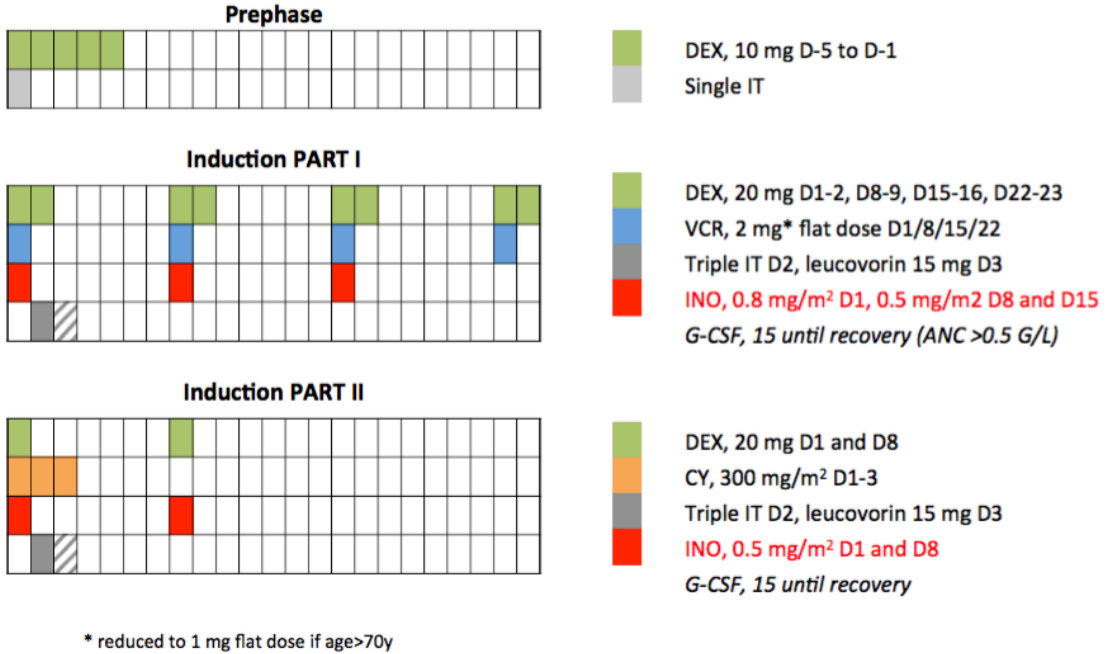
*N = 4 patients enrolled in CR; **Time of CR assessment.

EWALL-INO Phase II Study

Ph– ALL in older adults

European
Working Group for Adult
Acute
Lymphoblastic
Leukemia

- N = 130 patients with Ph– BCP-ALL
- Age 55+ years
- Sequential INO for first 2 courses
  - 0.8/0.5/0.5 mg/m^2 for cycle 1
  - 0.5/0.5 mg/m^2 for cycle 2
- Followed by 6 INO-free consolidation cycles and maintenance



* reduced to 1 mg flat dose if age>70y

Chevallier P, et al. *Blood.* 2021;138:511.

EWALL-INO Phase II Study

European
Working Group for Adult
Acute
Lymphoblastic
Leukemia

Patient characteristics

Patients	
Sex: male/female	39/51
Median age, years (range)	69 (55–84)
Median WBC, Giga/L (range)	4.6 (0.5–601)
Median CD22, % (IQR)	86.5 (60.7–97)
Oncogenetics	
Low hypodiploidy/near triploidy	25 (28%)
Ph-like	10 (11%)
KMT2A-r	9 (10%)
Others	46
Median follow-up, years (range)	1.18 (0.3–3.5)

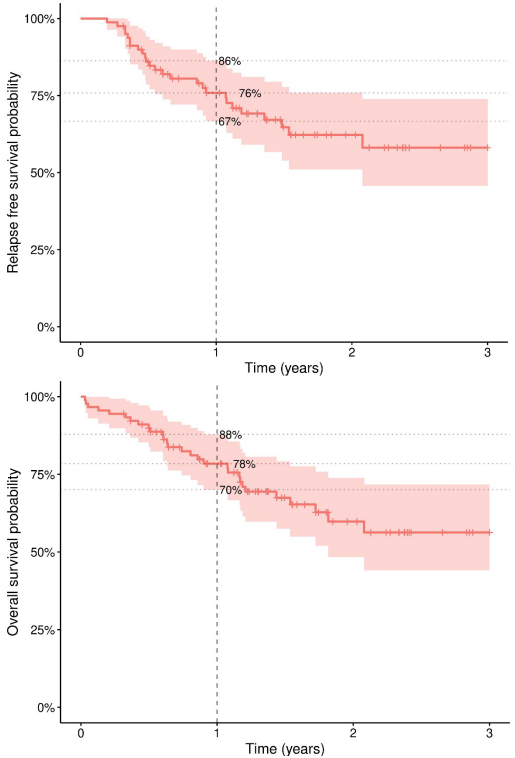
Early response (post-ind 2)

- Overall response, 89% (80/90)
- CR, 80%; CRp, 9%
- MRD negativity, 73% (49/67)

Liver toxicity

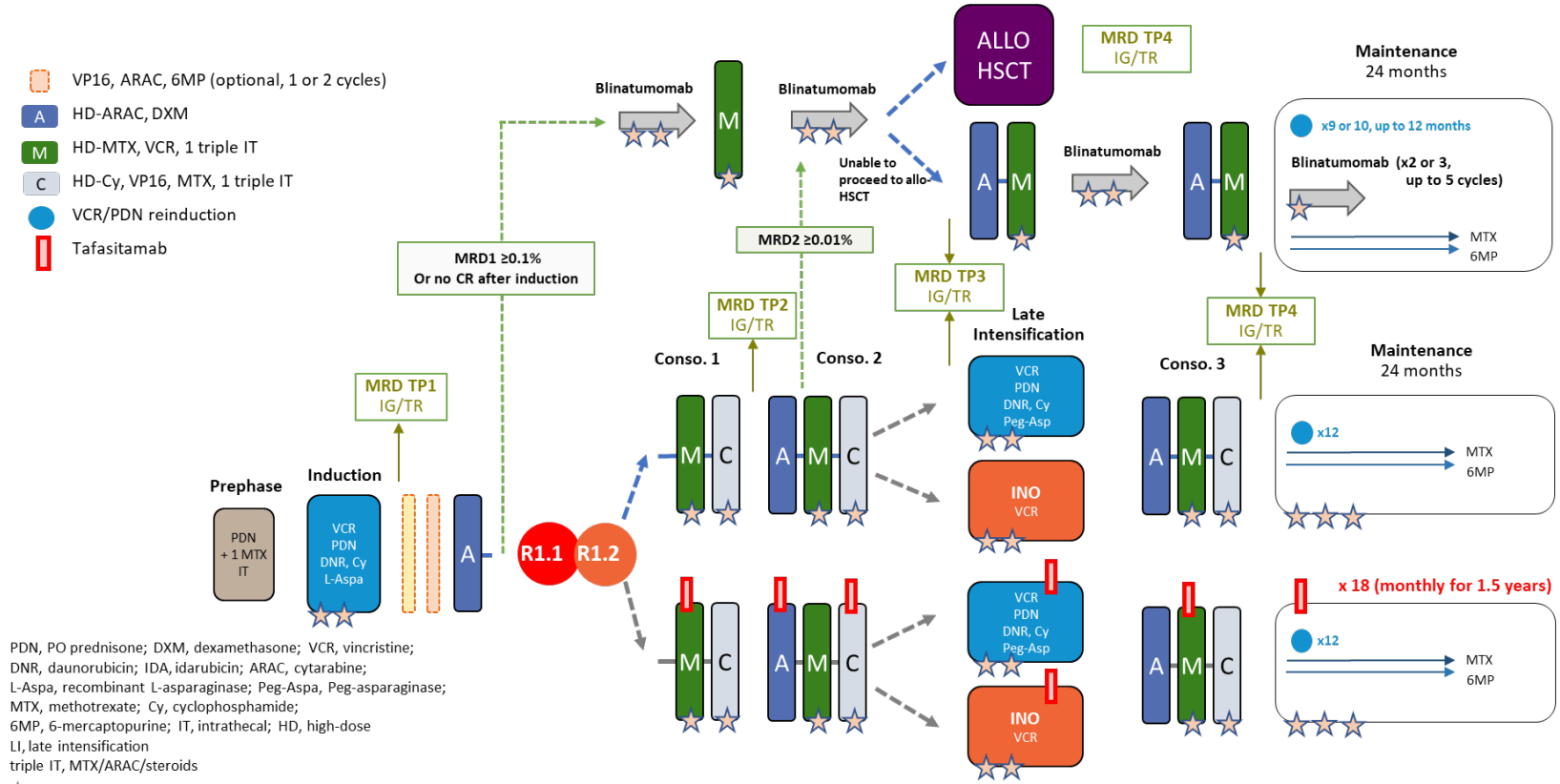
- 8.8% grade 3+ liver AEs
- 3 VOD, 1 after allo-HSCT

Outcome (RFS, OS)



Chevallier P, et al. *Blood.* 2021;138:511.

GRAALL-2022 Ph– BCP-ALL



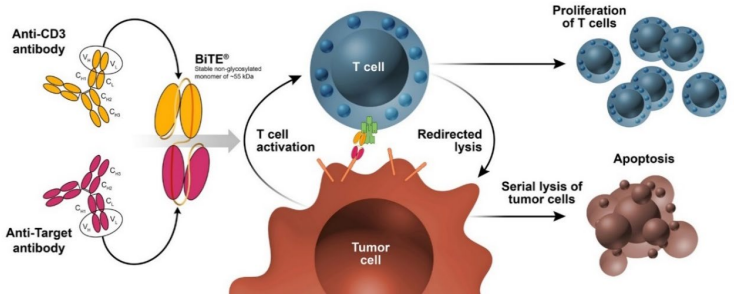
PDN, PO prednisone; DXM, dexamethasone; VCR, vincristine;
DNR, daunorubicin; IDA, idarubicin; ARAC, cytarabine;
L-Aspa, recombinant L-asparaginase; Peg-Aspa, Peg-asparaginase;
MTX, methotrexate; Cy, cyclophosphamide;
6MP, 6-mercaptopurine; IT, intrathecal; HD, high-dose
LI, late intensification
triple IT, MTX/ARAC/steroids

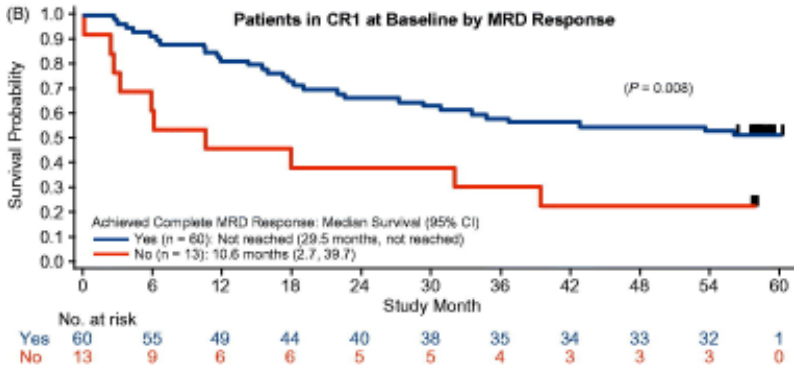
☆ Triple IT (prophylaxis only)

Slide courtesy of N. Boissel.

Blinatumomab in MRD+ Patients

- **Blinatumomab is a bispecific T-cell engager that redirects T-cell cytotoxicity against CD19+ target cells**
- **Blinatumomab was first approved in R/R and MRD+ B-cell ALL[1]**
- **Single-agent blinatumomab in MRD+ B-ALL (BLAST study)[2,3]**
  - Complete MRD response (n = 113): 78% after 1 cycle
  - 5-year OS (n = 110): 50% in complete MRD responders
  - MRD response is predictive of outcome
- **Safety profile (MRD setting, n = 116)[2]**
  - Grade 3+ neurotoxicity: 13%
  - Cytokine release syndrome: 3%
  - Mostly occurring during first cycle





1. Kantarjian H, et al. *N Engl J Med*. 2017;376:836-847; 2. Gökbuget N, et al. *Blood*. 2018;131:1522-1531; 3. Gökbuget N, et al. *Leuk Lymphoma*. 2020;61:2665-2673.

Blinatumomab in Frontline Ph– ALL

	Age, years	Patients, N	Primary endpoint	NCT
NCI ECOG study (randomized study)*	30–70	509	OS	NCT02003222
MDACC study (MRD)	18+	40	RFS	NCT02458014
MDACC Hyper-CVAD study	14+	60	RFS	NCT02877303
GIMEMA study	18–65	149	MRD at week 14	NCT03367299
HOVON study (frontline)	18–70	80	MRD after cycle 1	NCT03541085
PETHEMA (high-risk)	30–55	38	MRD after cycle 2	NCT03523429
GMALL study (MOLACT-1, MRD)	18+	30	MRD after 1 cycle	NCT03109093
GRAALL-QUEST study (high-risk)	18–59	95	MRD after 1 cycle	NCT02617004
EWALL-BOLD study	56–74	50	MRD after cycle 2	NCT03480438
NCI SWOG study	65	44	3-year OS	NCT02143414
AMGEN (Golden Gate study)*	55+ (40+ with comorbidities)	274	EFS^{MRD}	NCT04994717

Comments

- As single drug in CR, with few exceptions (HOVON)
- Frequent MRD studies based on BLAST results
- High-risk groups regardless of MRD response

*Few phase III studies.

Hyper-CVAD + Blinatumomab (+ rituximab/ofatumumab)*

MDACC

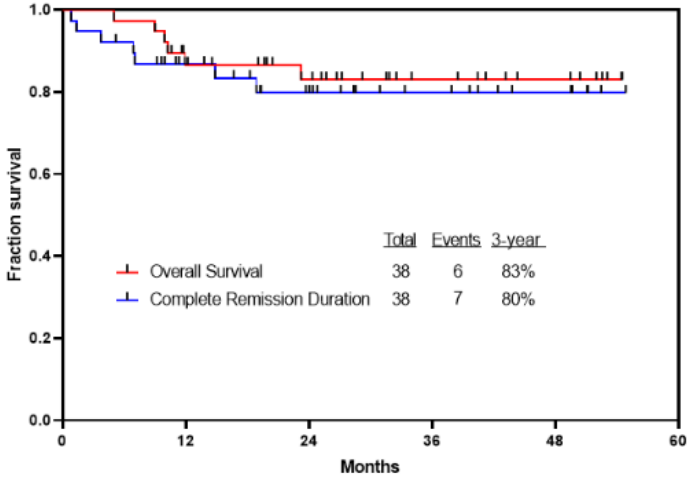
Patient characteristics (N = 34)

Characteristic	N (%) / median [range]
Age (years)	37 [17-59]
ECOG performance status ≥2	8 (21)
WBC (x10^9/L)	3.1 [0.5-360.9]
Karyotype	
Diploid	11 (29)
High hyperdiploidy	3 (8)
Low hypodiploidy / near triploidy	6 (16)
KMT2A rearranged	3 (8)
Complex	3 (8)
Others	12 (32)
CD19 expression	99.8 [41.9-100]
CD20 expression ≥20%	17/33 (52)
CRLF2+	6/32 (19)
***TP53* mutation**	10/37 (27)
Response	
CR after induction	26/32 (81)
CR at any time	32/32 (100)
MRD negativity after induction	22/26 (85)
MRD negativity at any time	37/38 (97)

Safety

Grade 3+ neurotoxicity, 11%

Outcome (OS, CRD)



Median follow-up, 27 months

Short N, et al. *Blood.* 2021;138:1233.

*If CD20+ >1%; 82% of patients.

GIMEMA Phase II Trial (LAL2317)

Blinatumomab in consolidation (2 cycles)

Patient characteristics

Characteristics	N = 146
Male sex, %	54
Age (years), median (range)	41 (18–65)
Age group (years), %	
18–40	47
41–55	35
>55	18
WBC (10^9/L), median (range)	4.43 (4–474)
>30, %	27
<30, %	73
Genetics	
KMT2A-AFF4, n (%)	12 (8.5)
E2A-PBX1, n (%)	5 (3.5)
Ph-like signature, n/N (%)	31/108 (28.7)
IKZF1 del, n/N (%)	40/84 (48)
CDKN2A/B del, n/N (%)	38/84 (45)
ABL class/*CLRF2/JAK2-r*, %	3.8 (each)
Clinical risk class, %	
SR*	62
HR	38

Bassan R, et al. EHA 2021. Abstract S114.

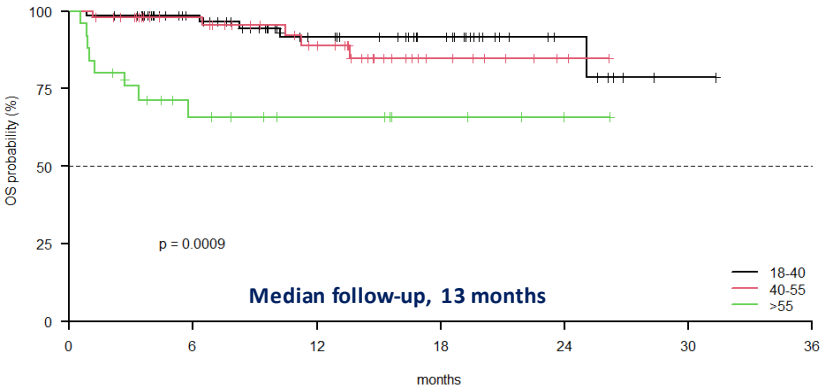
MRD response

- **95%** MRD– after blinatumomab 1
- **81%** MRD+ converted to MRD– after blinatumomab 1

Safety

Grade 3+ neurotoxicity, 15.5%

Outcome



*SR: WBC <30×10^9/L, non-pro-B phenotype, non-HR cytogenetics.

GRAALL-B-2014-QUEST (HR B-ALL)

Blinatumomab in consolidation/maintenance (5 cycles)

Patient characteristics
HR Ph– B-ALL (MRD+, *KMT2A*, *IKZF1*)

	N = 94
Age (years), median (range)	34.6 (18.1–60.0)
Sex, male/female	51/43
WBC (G/L), median (range)	12 (1–449)
Oncogenic subgroup	
KMT2A-r, n (%)	16 (17)
ZNF384-r, n (%)	10 (11)
DUX4/ERG, n (%)	12 (13)
Ph-like, n (%)	17 (18)
Hypo/NearT, n (%)	7 (7)
B-other, n (%)	24 (26)
Unknown, n (%)	8 (9)
***IKZF1* intragenic deletion, n (%)**	37/93 (40)
VHR (eligible for allo-HSCT)	49 (52)

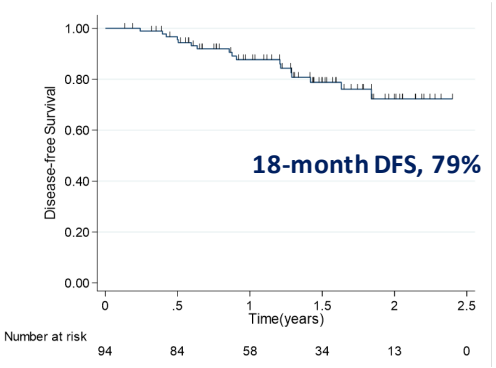
MRD response

- **MRD response after 1 cycle**
  - <0.01% in 89% of patients
  - Undetectable in 74% of patients
- **Factors associated with undetectable MRD**
  - Low MRD prior to blin
  - Not age, WBC, or oncogenic subgroup

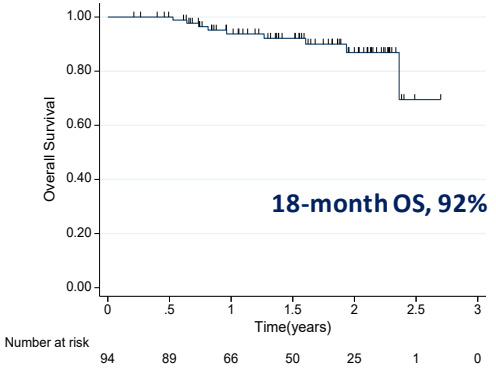
Safety

Grade 3+ neurotoxicity, 7%

Outcome (DFS, OS)



18-month DFS, 79%



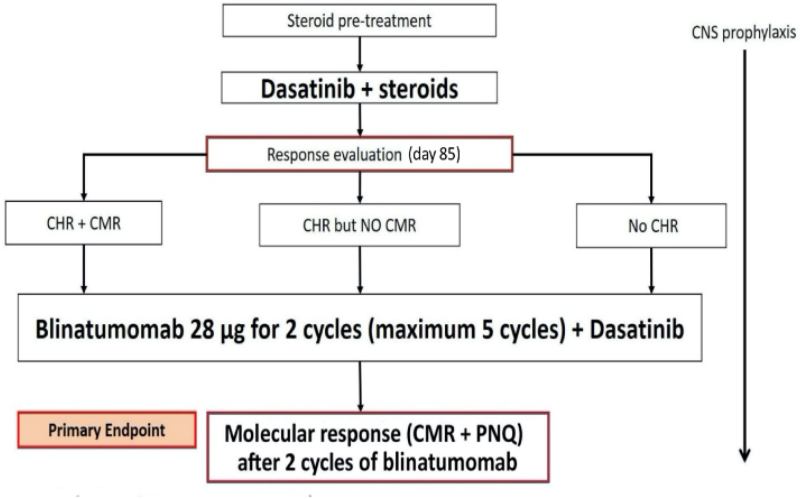
18-month OS, 92%

Median follow-up, 20 months

Boissel N, et al. ASH 2021. Abstract 1232.

GIMEMA D-ALBA Study

Dasatinib-blinatumomab frontline

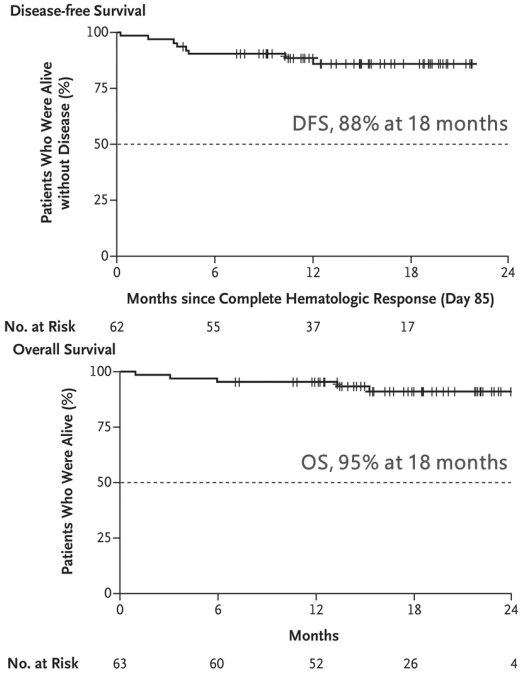


N = 63 patients (median age, 54 years)

- CR rate, 62/63 (98%)
- CMR rate
  - 17/59 (29%) after dasatinib/steroids/ITT
  - 33/55 (60%) after 2 blinatumomab/dasatinib cycles

Foa R, et al. *N Engl J Med*. 2020;383:1613-1623.

Outcome (DFS, OS)



- **Median follow-up, 18 months**
- Choice of post-consolidation Tx made by the investigators (including 24 HSCT)

Blinatumomab + Ponatinib

MDACC

Patient characteristics

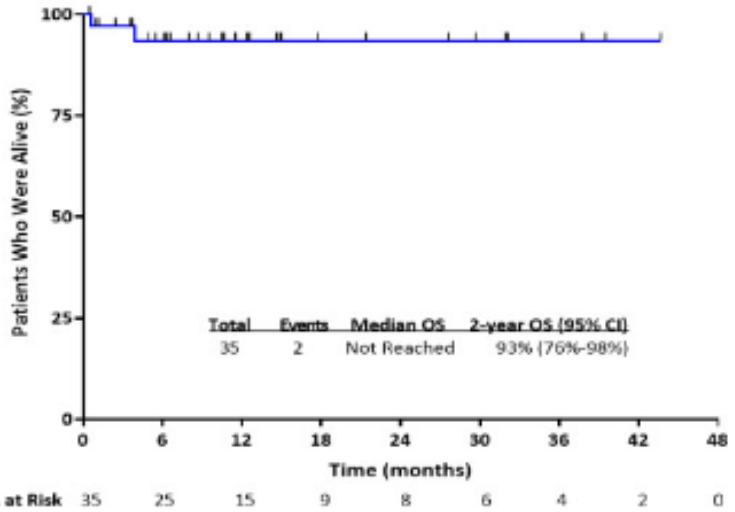
Characteristic N (%) / median [range]	Category	ND Ph+ ALL N = 35	R/R Ph+ ALL N = 14	CML-LBP N=6
Age (years)		57 [22-83]	38 [24-61]	69 [29-82]
CD19 expression		99.8 [74.9-100]	99.9 [98.6-100]	99.7 [98.3-99.9]
BCR-ABL1		26 (74)	13 (93)	0
transcript	p190	9 (26)	1 (7)	6 (100)
	p210			
Line of therapy	Frontline	35 (100)	0	4 (67)
	Primary refractory	0	2 (14)	0
	Salvage 1	0	6 (43)	1 (17)
	Salvage 2+		6 (43)	1 (17)
Response				
CR		21/23 (91)	11/13 (85)	4/6 (67)
CR/CRi		22/23 (96)	12/13 (92)	5/6 (83)
CMR after 1 cycle		21/33 (64)	10/14 (71)	1/6 (17)
CMR overall		28/33 (85)	11/14 (79)	2/6 (33)

Safety

2 pts discontinued ponatinib: 1 stroke, 1 DVT

1 pt discontinued blinatumomab: neurotoxicity

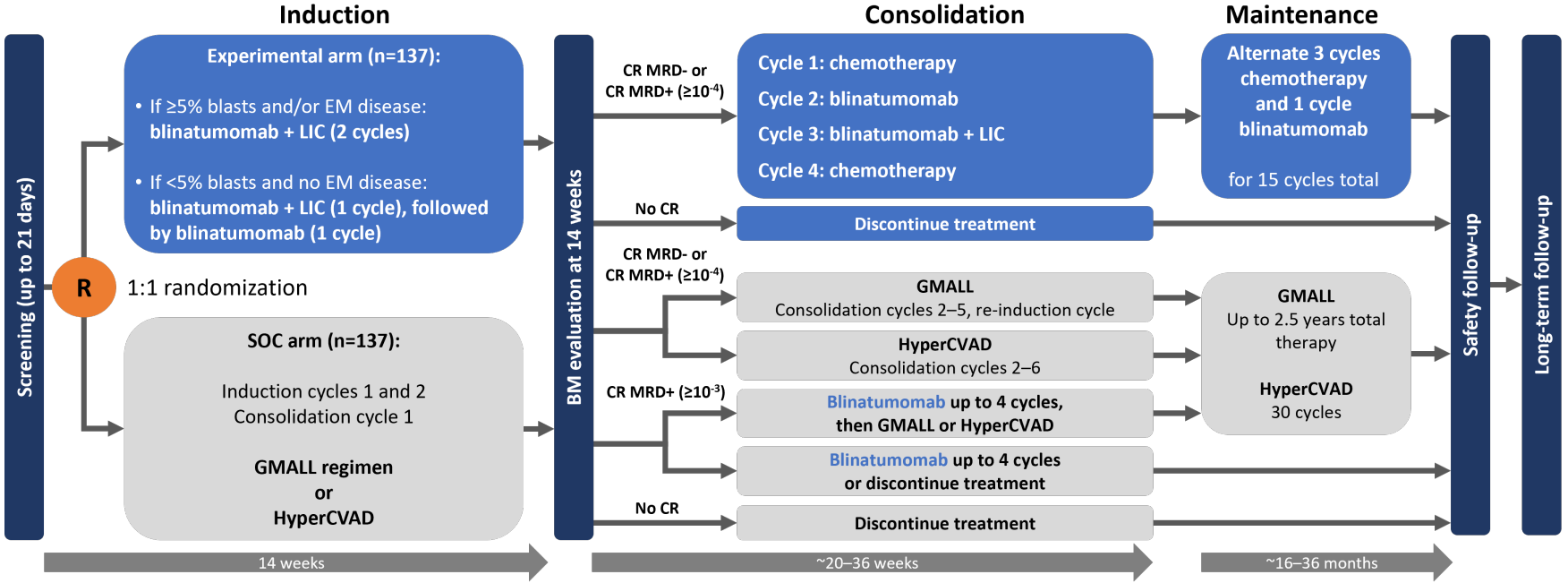
Outcome (ND Ph+ ALL)



Short N, et al. ASCO 2022. Abstract 7009; Short N, et al. EHA 2022. Abstract S114.

Golden Gate Study: Phase III Study Design

Older patients with Ph– ALL



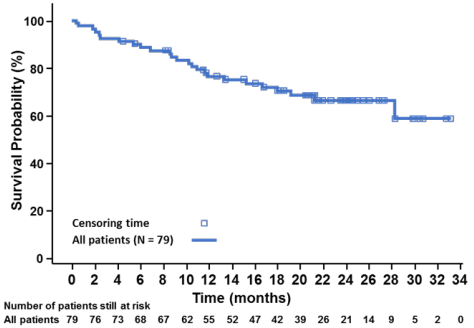
Primary endpoints: treatment-emergent AEs, event-free survival, overall survival
Secondary endpoints: CR rate, MRD response, relapse-free survival

NCT04994717. https://clinicaltrials.gov/ct2/show/NCT04994717.
Study 20190360 protocol.

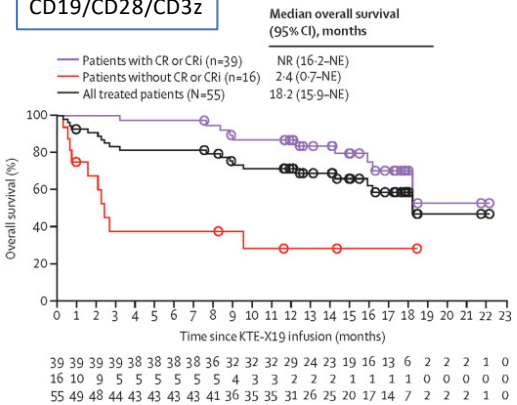
CD19 CAR T Cells in ALL

- Tisa-cel approved in second relapse or first relapse after HSCT in patients aged <26 years with B-ALL[1,2]
- Bruxa-cel approved (by FDA) in R/R B-ALL adult patients[3]
- **Overall results in children/adults with R/R B-ALL**
  - 60%–90% of overall response rate
  - Complete MRD response in >80%
  - 30%–60% relapse rate
- **Challenges**
  1. Safety: CRS/ICANS
  2. Persistence (and CD19+ relapses)
  3. CD19– relapses

ELIANA study[1]
R/R B-ALL
3–21 years
CD19/4-1BB/CD3z



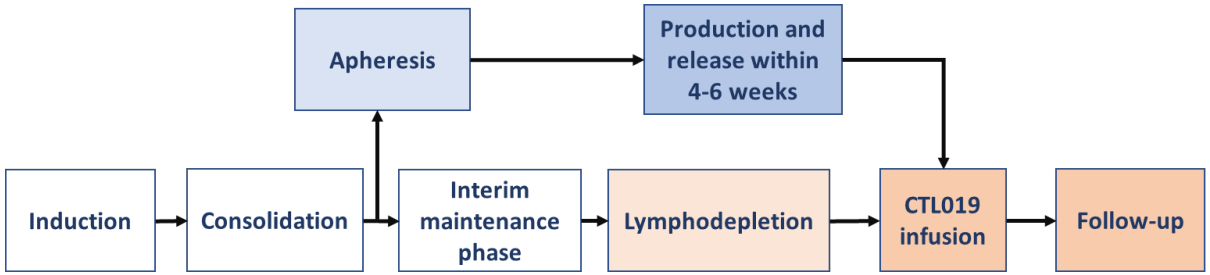
ZUMA-3 study[3]
R/R B-ALL
18 years+
CD19/CD28/CD3z



1. Maude SL, et al. *N Engl J Med.* 2018;378:439-448; 2. Grupp SA, et al. *Blood.* 2018;132:895;
3. Shah BD, et al. *Lancet.* 2021;398:491-502.

CD19 CAR T Toward Frontline Therapy

CASSIOPEIA trial



- **Patients:** children and AYAs (1-25 years)
- CD19+ B-ALL
- *De novo* HR (NCI) B-ALL in CR1 with MRD1 ≥ 0.1% at the end of induction and MRD ≥ 0.05% at the end of consolidation

Primary objective :
DFS at 5 years

Target :
140 infused pts within 4 years

1. Apheresis may be performed at the end of induction or consolidation phases
2. CTL019 may be infused as soon as it is available

NCT03876769. https://clinicaltrials.gov/ct2/show/NCT03876769.

Summary

- The ceiling of chemotherapy intensification has been reached in Ph– adult ALL
- Immunotherapies and small molecules lead to encouraging results in R/R setting
- Several parameters guide the development in frontline
  - Patient age, condition, and comorbidities
  - Disease characteristics and MRD response
  - Eligibility to allo-HSCT
  - Drug safety profile
- Many fields are being explored
  - The best way to combine immunotherapies, small molecules, HSCT
  - The use of sequential immunotherapy targeting the same antigen
  - The place of MRD as surrogate marker

Global Leukemia Academy

Current Treatment Options for Relapsed ALL in Adult and Older Patients

Nicola Gökbuget

APTITUDE HEALTH

Current Treatment Options for Relapsed ALL in Adult and Older Patients

Nicola Gökbuget

Potential Conflicts of Interest

Speaker Honoraria, Travel Support, Advisory Board

- Amgen
- Celgene
- Gilead
- Novartis
- Pfizer
- Jazz Pharmaceuticals
- Incyte
- Autolus

Research Support (institutional)

- Amgen
- Pfizer
- Novartis
- Servier
- Jazz Pharmaceuticals
- Incyte

Topics of the Talk

1. **Definition of Relapse**
2. Results of Standard Chemotherapy
3. Results of Immunotherapy in Relapsed/Refractory ALL
   - Blinatumomab
   - Inotuzumab
   - CAR T
4. How to Optimize the Use of Immunotherapies
5. Consideration for Sequencing of Immunotherapies
6. Relapsed T-ALL
7. General Considerations for Relapsed ALL

Definitions: What Do We Speak About?

Primary refractory ALL

Early relapse

Refractory relapse (second relapse)

BM Relapse

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

Late relapse

Lymph nodes
CNS (CSF, brain)
Testis
Other extranodal

Combinations with BM

Topics of the Talk

1. Definition of Relapse
2. **Results of Standard Chemotherapy**
3. Results of Immunotherapy in Relapsed/Refractory ALL
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   - Inotuzumab
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Results of Standard Chemotherapy in R/R ALL

Kantarjian *Cancer* 2019, *New Engl J Med* 2017

SOC Arms in	INO-VATE	TOWER
N	162	134
Age	47 (18–79)	41 (18–78)
BM Blast <50%	30%	22%
Salvage 1	63%	48%
CR	31%	25%
MRD-neg	28%*	48%**

*Below the threshold for MRD (Flow)

**Negative MRD (Ig/TCR)

Topics of the Talk

1. Definition of Relapse
2. Results of Standard Chemotherapy
3. **Results of Immunotherapy in Relapsed/Refractory ALL**
   - Blinatumomab
   - Inotuzumab
   - CAR T
4. How to Optimize the Use of Immunotherapies
5. Consideration for Sequencing of Immunotherapies
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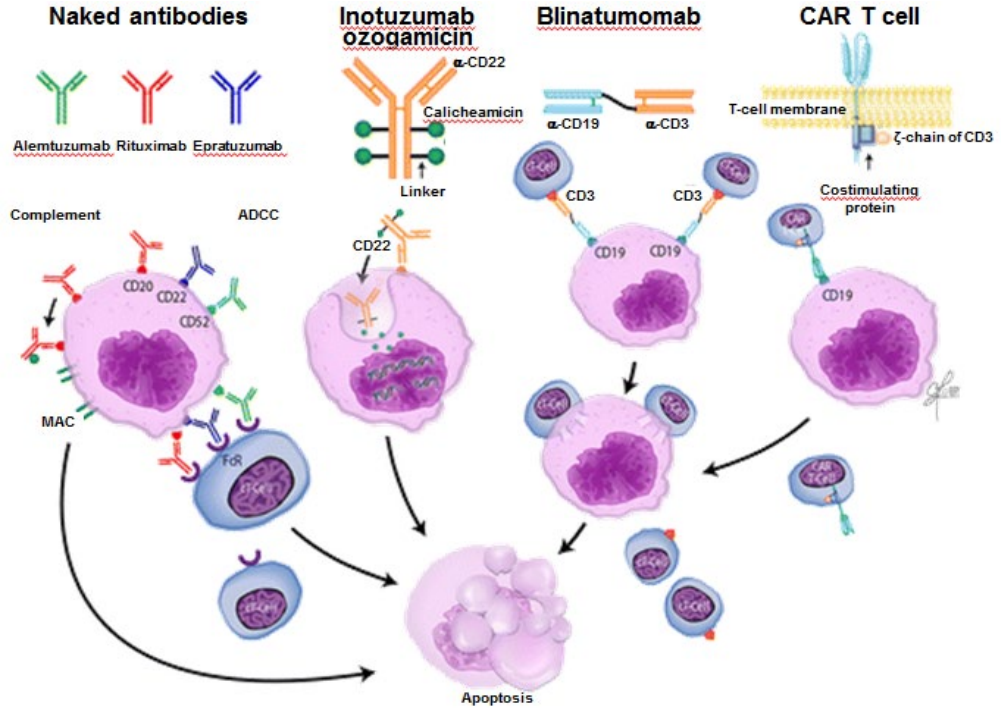
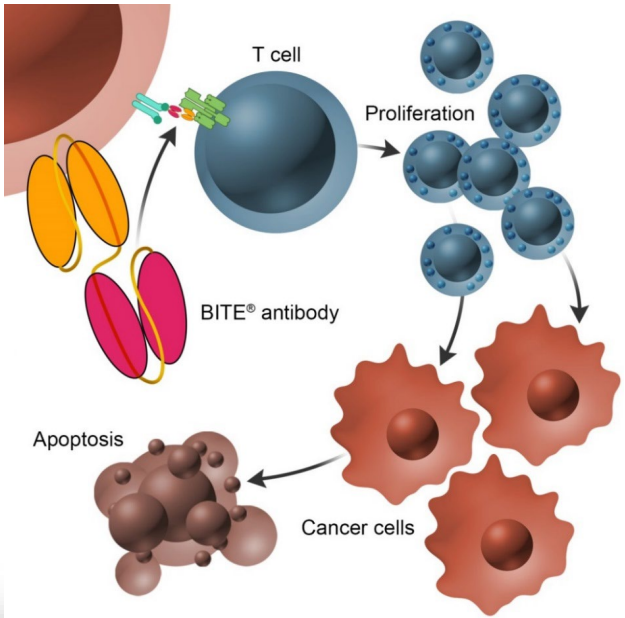
Immunotherapy Approaches to the Treatment of Hematologic Malignancies



Major advantage: Targeted therapy with different mechanism of action!

Blinatumomab: Bispecific Antibody CD19-CD3

- Engagement by BiTE® antibody constructs leads to activation and polyclonal expansion of T cells (CD4/CD8) [1]
- Activation of T cells requires presence of target cells[2]
- Transient increase of cytokines (IL10,IL6, IFNg)



Activity depends on:

1. **Target CD19**
2. **Functional T-cells**
3. **Access to blast cells**

1. Klinger M, et al. *Blood*. 2012;119:6226-6233;
2. Baeuerle PA, et al. *Cancer Res.* 2009;69:4941-4944.

Blinatumomab in R/R B-Precursor ALL: TOWER

Kantarjian, et al. *N Engl J Med.* 2017

Patient Characteristics

	Blina	SOC
N	271	134
Age (median, years)	41	41
Salvage 1	42%	48%
Salvage 2	**34%**	**32%**
Later salvage	**25%**	**20%**
First remission >12 mo	**0**	**0**
Prior SCT	**35%**	**34%**
Ph-positive	0	0
Blasts in BM >50%	74%	78%
PB blasts/µl	4400	5000

Overall Results

	Blina	Chemo
Evaluable	271	134
CR/CRp/CRi	**44%**	**25%**
CR	34%	16%
CRi	1.5%	4.5%
CRp	9%	4.5%
Mol CR (PCR)	**76%**	**48%**

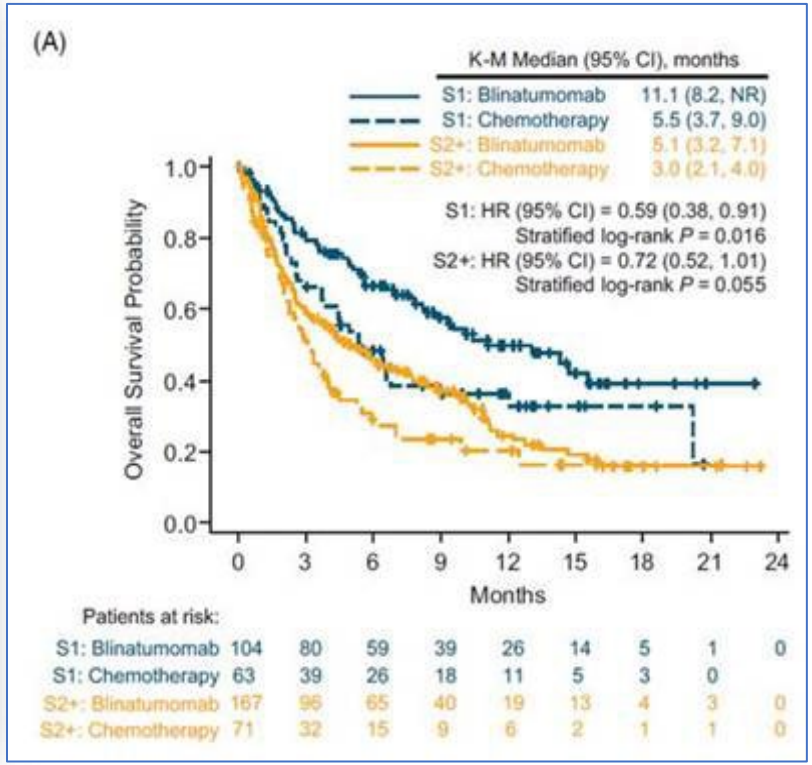
Blinatumomab in R/R B-Precursor ALL: TOWER

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%**

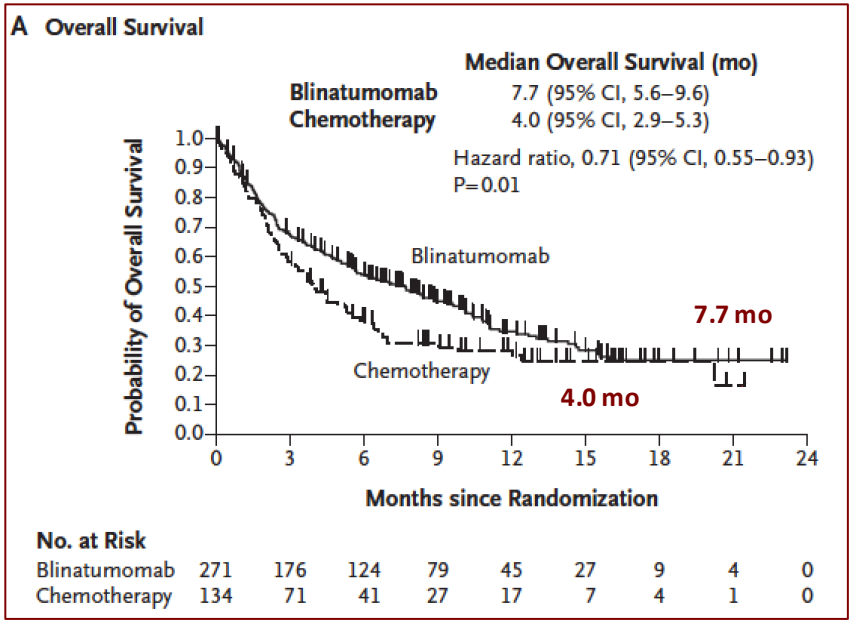
Dombret, et al. *Leuk&Lymph.* 2019.



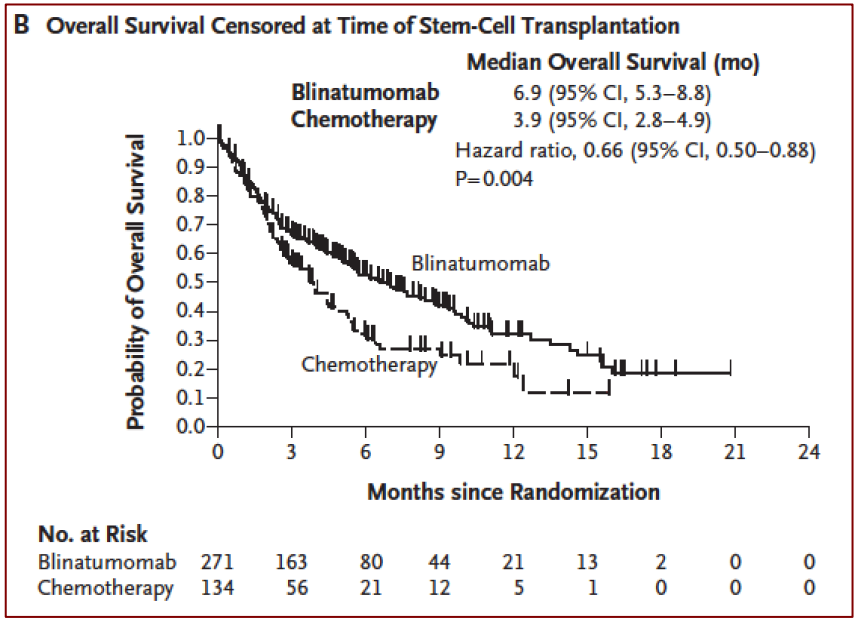
Blinatumomab in R/R B-Precursor ALL: TOWER

Kantarjian, et al. *N Engl J Med.* 2017

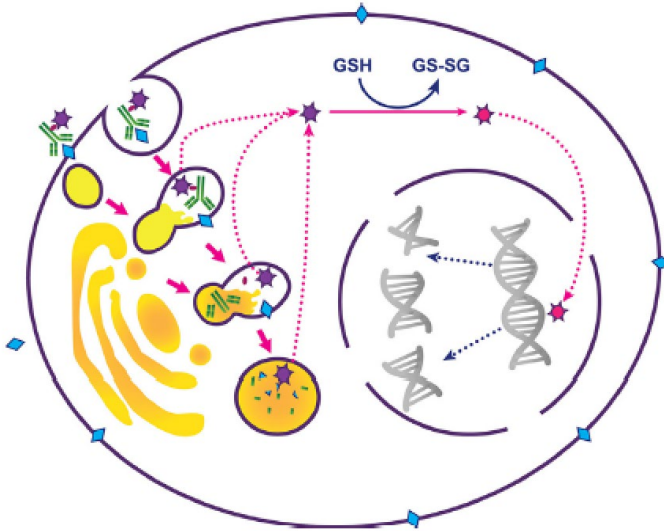
Overall Survival

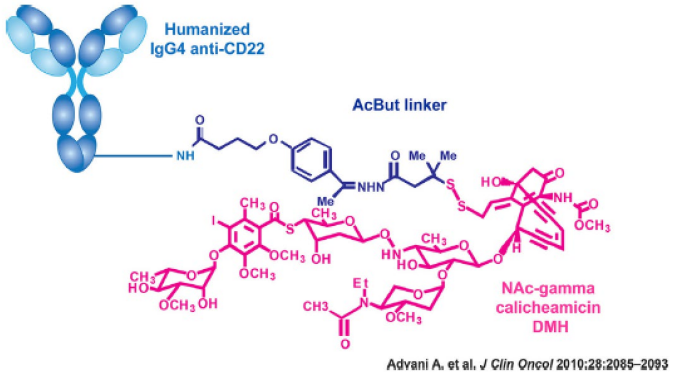


Survival Censored at SCT



Inotuzumab: Conjugated Antibody CD22





Mechanism of Action

- Binding to surface CD22 receptors of target cells
- Internalization as a CD22-ADC complex
- ADC traffics from early to late lysosomes
- Linker cleavage and release of inactive calicheamicin
- Activated by intracellular thiol groups
- Intercalation in DNA
- Double-strand DNA break formation
- Apoptosis induction
- **Calicheamicin activity independent of cell cycle progression**

Shor, et al. *Mol Immunol.* 2014.

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

Kantarjian, et al. *New Engl J Med.* 2016; Kantarjian, et al. *Cancer.* 2019

Patient Characteristics

	Ino	SOC
N	109	109
Age (median, years)	47	47
Salvage 1	**67%**	**63%**
Salvage 2	32%	36%
Later salvage	0	0
First remission >12 mo	**43%**	**35%**
Prior SCT	**16%**	**20%**
Ph-positive	**13%**	**17%**
Blasts in BM >50%	71%	72%
PB blasts/µl	**175**	**39**

Overall Results

	Ino	SOC
CR/CRi	**81%**	**29%**
CR	36%	17%
CRi	45%	12%
MRD CR	**78%**	**28%**

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

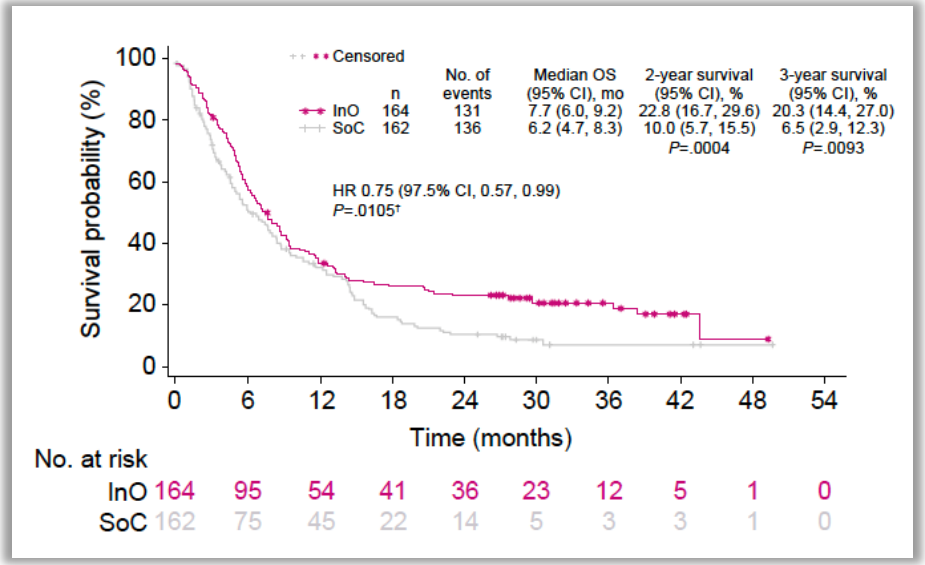
Factors for Achievement of Response

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-positive	79%	44%

Overall Survival

Kantarjian, et al. *Cancer.* 2019.



Optimized Use

- Not more than 2 cycles before SCT (VOD risk)
- No double-alkylators for conditioning

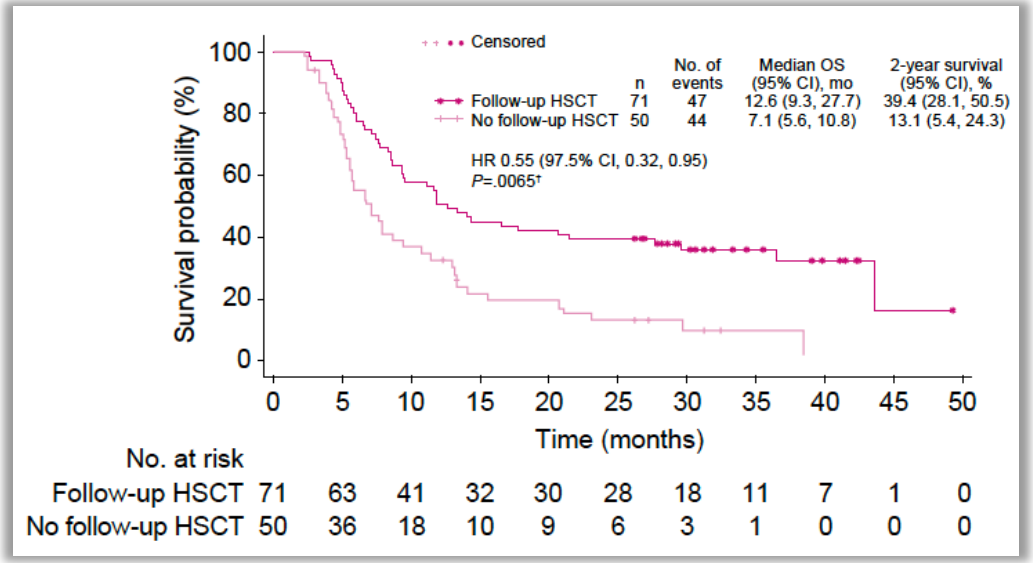
N. Gökbuget 9/2022

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

HSCT Realization After Study Treatment

	Ino	SOC
N	164	162
HSCT any time	48%	22%
HSCT before further chemo	43%	11%
HSCT direct after CR/CRi		
• Proportion of IIT pts	40%	10%
• **Proportion of CR pts**	**54%**	**34%**

Overall Survival by HSCT



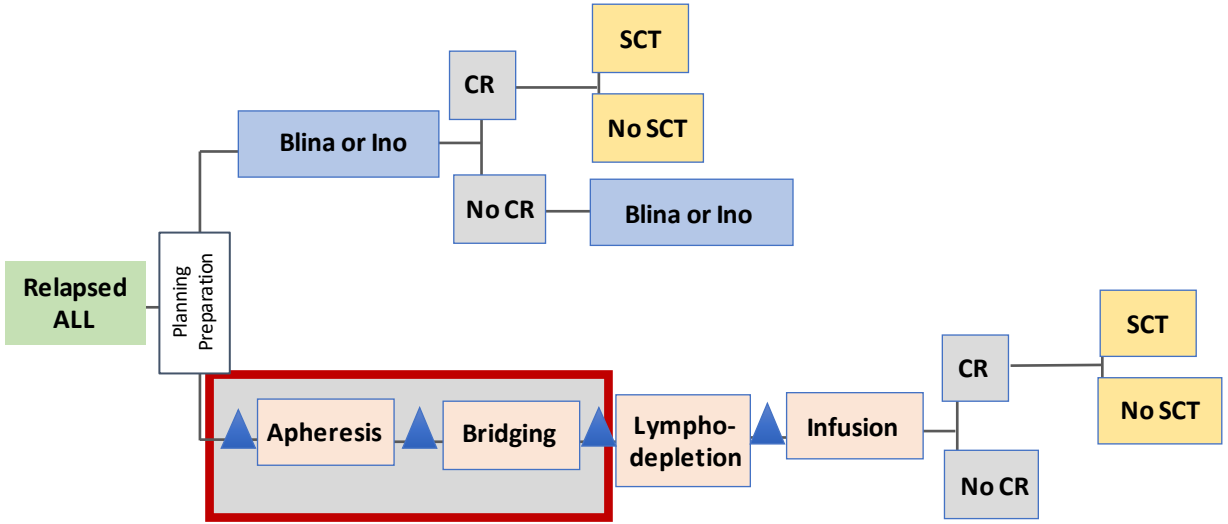
Kantarjian HM, et al. *Cancer*. 2019;25(14):2474–2487.

CD19/CD22 Antibodies in Adult ALL

- Different patient population
- High MRD response rates, but also high relapse rates
- **Better outcomes if used in first salvage**
- **Survival in SCT pts only; potentially high TRM!**
- **Activity in Ph-positive ALL**
- **Toxicity profile favorable compared to SOC (eg, infections)**
  - **Blina: neurologic events**
  - **Ino: VOD**
- **Negative prognostic impact**
  Blin: blast in BM >50%; Ino: WBC >10.000/µL

- **No/limited data on late relapses**
- **No/limited data on extramedullary relapses**
- **Number of cycles needed not clear**

Comparison of Inotuzumab/Blinatumomab vs CAR T-Cell Strategies



Heterogeneity of CAR T Trials

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

CD19 CAR T Cells in Relapsed/Refractory Adult ALL

Park JH, et al. *N Engl J Med.* 2018

Inclusion criteria

- R/R ALL or ALL in CR
- No specification for type of relapse

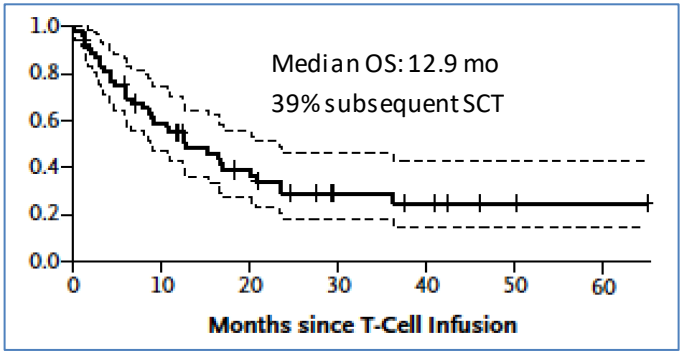
Patient characteristics

>5% BM blasts:	51%
<5% BM blasts + extram:	9%
0.01–5% MRD:	28%
<0.01% no detect MRD	11%

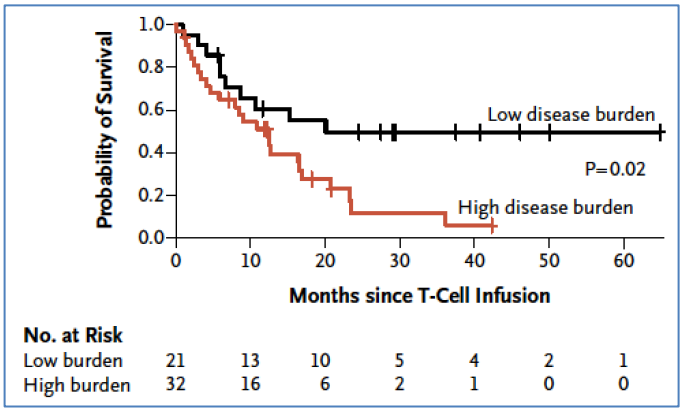
Response rates

Recruited: 83
Treated: 53 64%)
CRi: 44/53 (83%)
Intent-to-treat:44/83 (53%)

Overall Survival

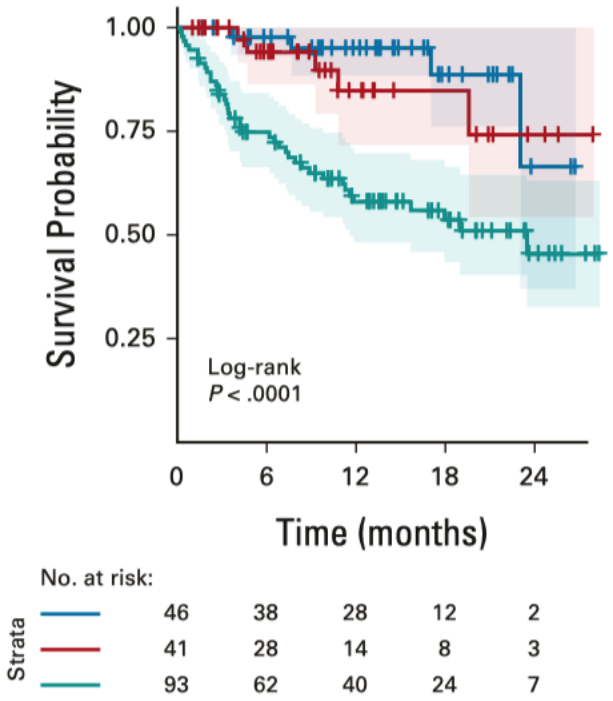


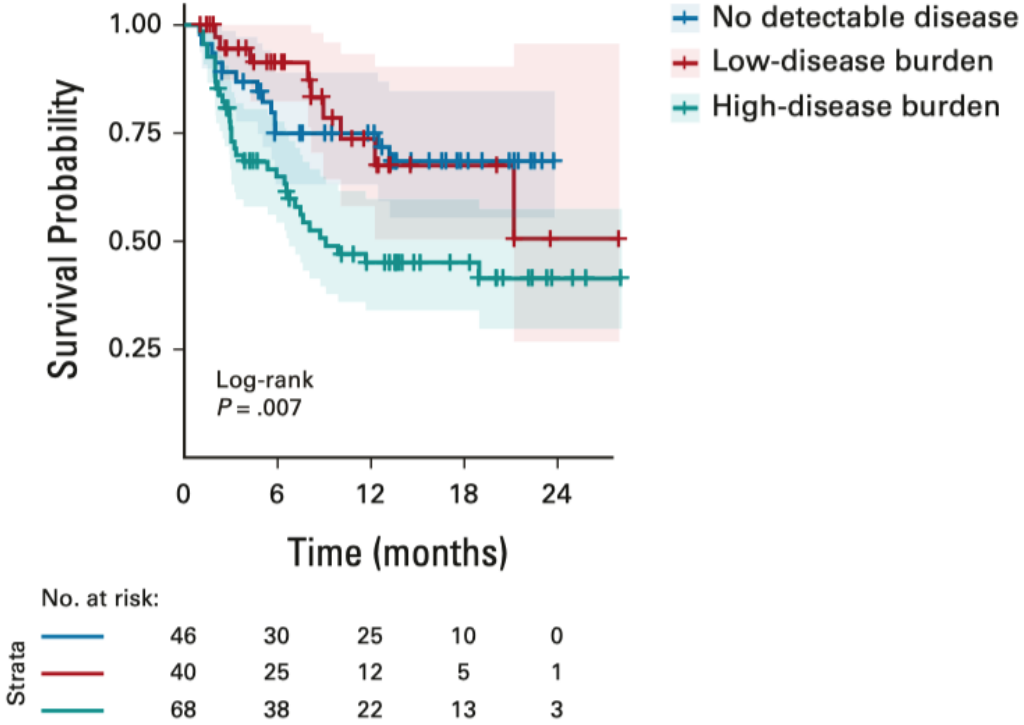
Overall Survival According to Disease Burden



Disease Burden Impacts Outcomes in Pediatric and Young Adult B-Cell Acute Lymphoblastic Leukemia After Commercial Tisagenlecleucel: Results From the Pediatric Real World CAR Consortium (PRWCC)

Schultz, et al. *JCO*. 2021





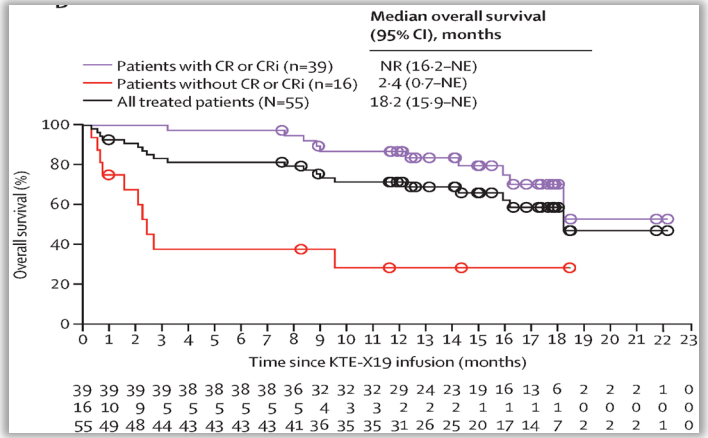
CAR T Cells in Relapsed/Refractory ADULT ALL

Shah, et al. *Lancet.* 2021

Patient Characteristics (Treated; N = 55)

Age	**40 (28–52)y**
ECOG 1	71%
PH-positive	27%
≥3 therapies	47%
Blina	45%
Ino	22%
Allo SCT	42%
Prim refr	33%
BM blast before conditioning	
≤5%	9%
>5–25%	13%
>25%	62%
Median	59% (25–87%)

	Treated	Enrolled
Total N	55	71
CR/CRi	73%	**55%**
Aplastic	5%	6%
No response	16%	15%
Unknown	5%	24%
Median DOR	13 mo	13 mo
Median RFS	12 mo	7 mo
Median OS	18 mo	19 mo



Do We Need a Transplant After CAR-T-Cell Therapy?

Greenbaum, et al. *Front Oncol.* 2021

Study	# Patients	CAR	ALLO	NO ALLO
Park *et al.*	43	CD19-28z	N=17 Relapse in **35%** TRM **35%**	N= 26 Relapse **65%**
Lee *et al.*	51	CD19-28z	N=21 Relapse **9%**	N=7 Relapse **86%**
Pan *et al.*	45	CD19-41BBz	N=27 Relapse **7%** TRM 7%	N=18 Relapse **50%**
Jacoby *et al.*	20	CD19-28z	N=14 Relapse **14%**	N=7 Relapse **51%**

Most groups recommend SCT after CAR T in adult ALL

Ambiguous situation for relapse after SCT

Potential factors for decision making

- **Leukemia burden before CAR T**
- **CD19 expression before CAR T**
- **MRD after CAR T**
- **Persistence of CAR**
- **Persistence of B-cell aplasia**

CAR T Cells in Adult ALL

- **Promising data in selected, mostly younger patient populations but later treatment lines**
- **Limited data in "real" adults**
- **Limited availability in standard of care**
- **Complex process**
- **Need for subsequent SCT not clear**
- **Limited activity in higher leukemia burden ie, refractoriness to bridging**

- **No comparability with CD19/CD22 antibodies**
- **No/limited data for extramedullary relapses**

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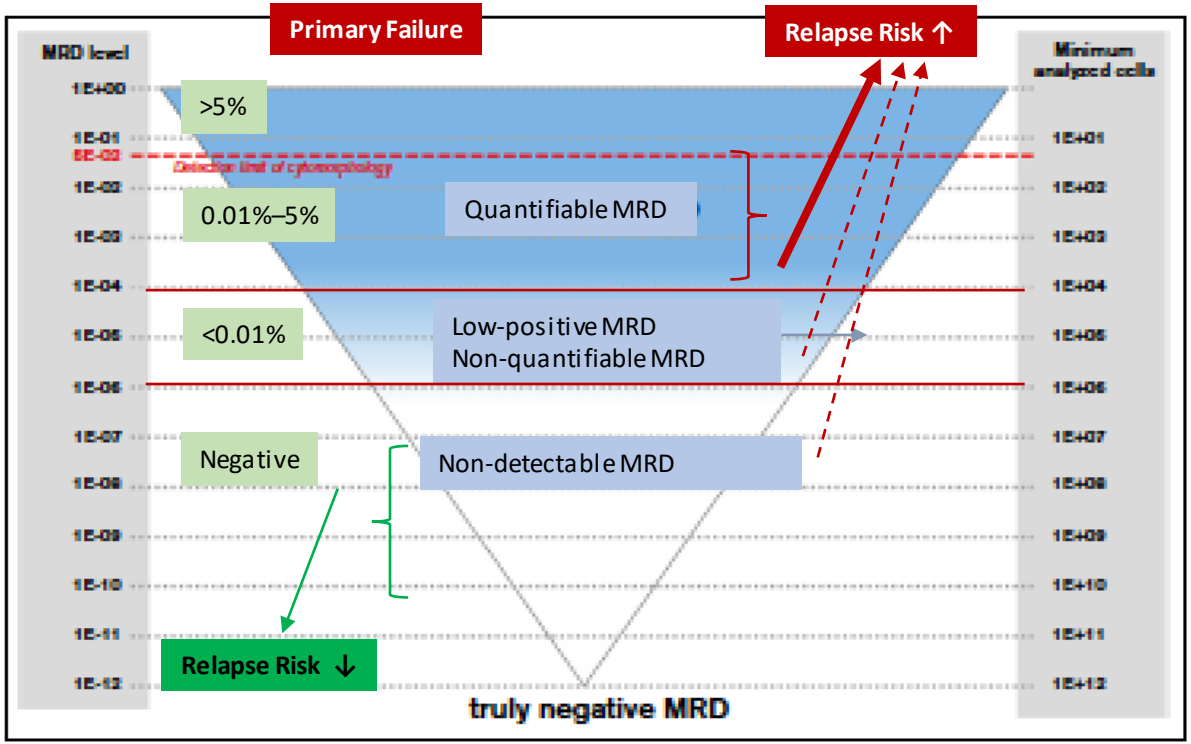
Topics of the Talk

1. Definition of Relapse
2. Results of Standard Chemotherapy
3. Results of Immunotherapy in Relapsed/Refractory ALL
4. **How to Optimize the Use of Immunotherapies**
   - MRD setting
5. Consideration for Sequencing of Immunotherapies
6. Relapsed T-ALL
7. General Considerations for Relapsed ALL

Response and Loss of Response in ALL: A Continuum!



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Blinatumomab in MRD-Positive ALL

Gökbuget, et al. *Blood*. 2018

Selected inclusion criteria

- CD19-positive B-precursor ALL
- Hematologic CR
- MRD ≥10^{-3}
- No prior SCT

Treatment

15 µg/m² as 4-wk civ (=1 cycle)

i.th. prophylaxis

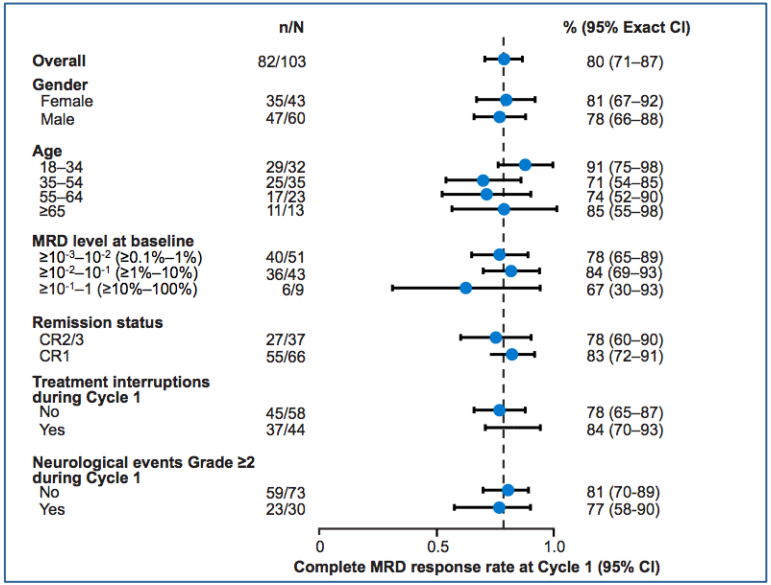
Primary endpoint

MolCR: Complete MRD response after 1 cycle

(MRD-neg with sensitivity of at least 10–4 by PCR in reference lab)

Results

Evaluable	110
Median age	45 (18–76) yrs
Second/later CR	35%
MolCR:	**78%**
Median OS	36 mo
- **Mol CR y/n**	**40 vs 12 mo**
Median RFS	19 mo
- Mol CR y/n	35 vs 7 mo
- **First/later CR**	**25 vs 11 mo**



CR, complete remission; MRD, minimal residual disease; SCT, stem-cell transplantation.

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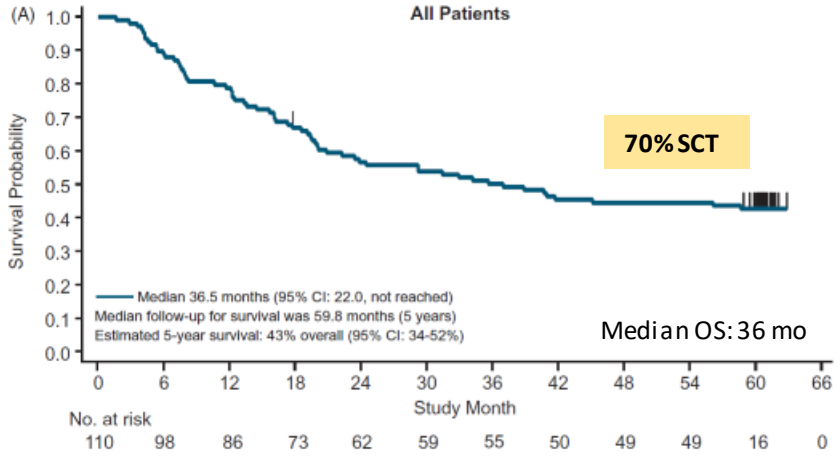
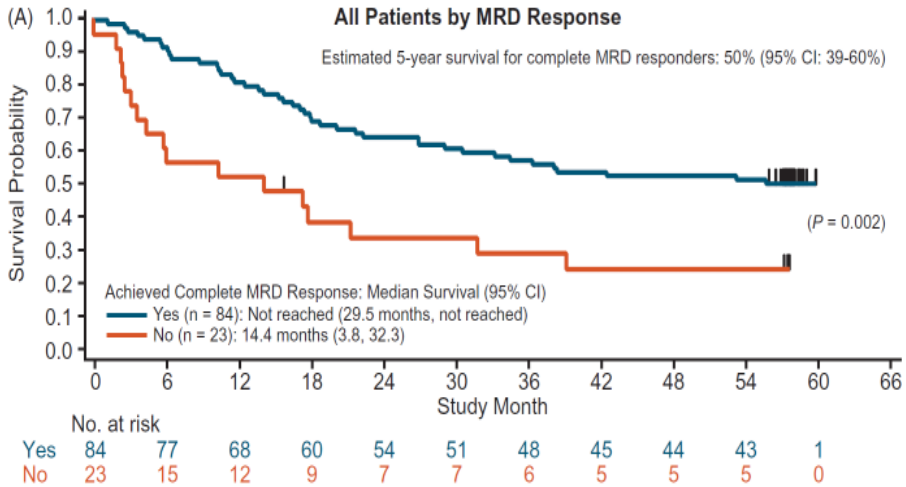
Blinatumomab in MRD-Positive ALL

Gökbuget, et al. *Leuk Lymphoma.* 2020

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



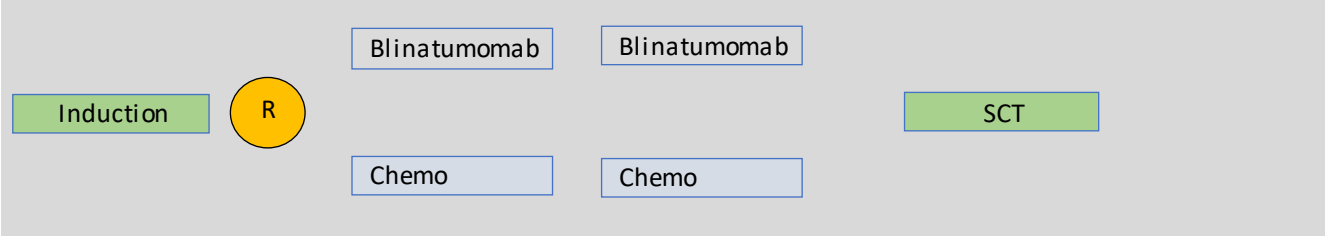
Overall Survival by Complete MRD Response: All patients analyzed



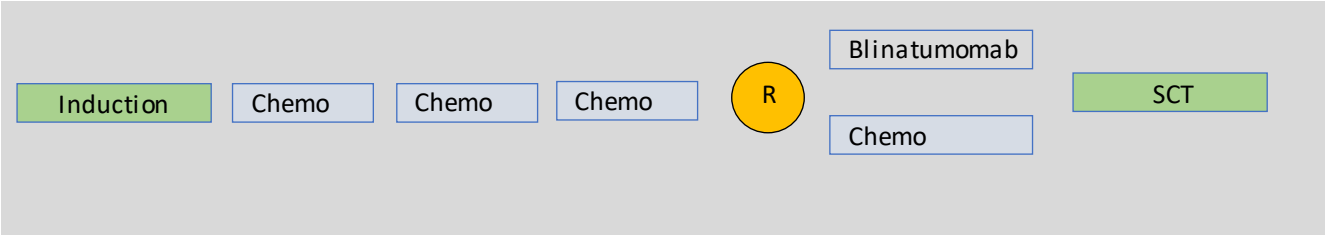
Can Blinatumomab Replace Intensive Chemotherapy Consolidation?

Pediatric Relapse

Brown PA. *JAMA.* 2021: High- and Intermediate-Risk Pediatric R/R ALL



Locatelli, et al. *JAMA.* 2021: High-Risk Pediatric R/R ALL

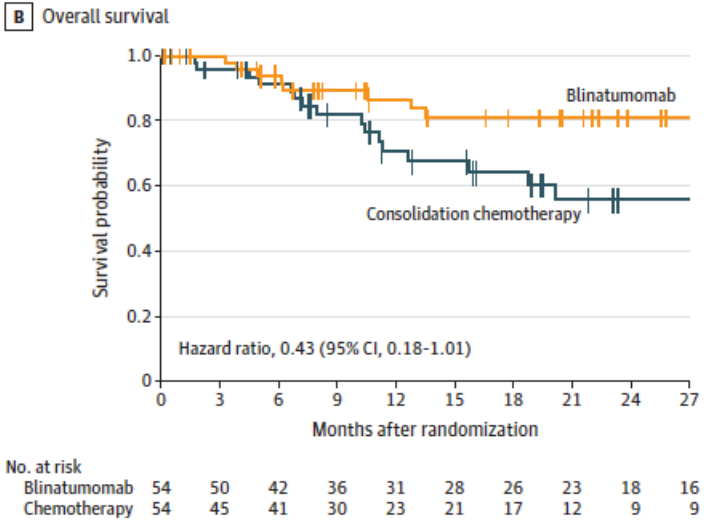


Blinatumomab vs Chemotherapy Consolidation: DFS/OS

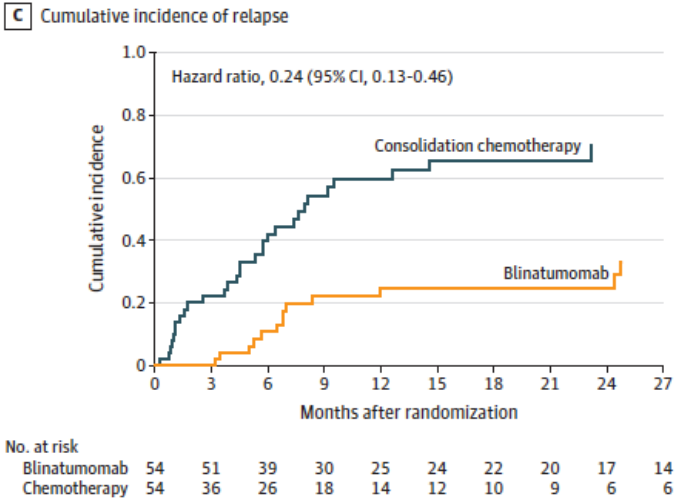
Locatelli, et al. *JAMA*. 2021

- Better DFS and OS
- Lower toxicity
- Improved MRD response in blinatumomab vs chemotherapy arm

Overall Survival

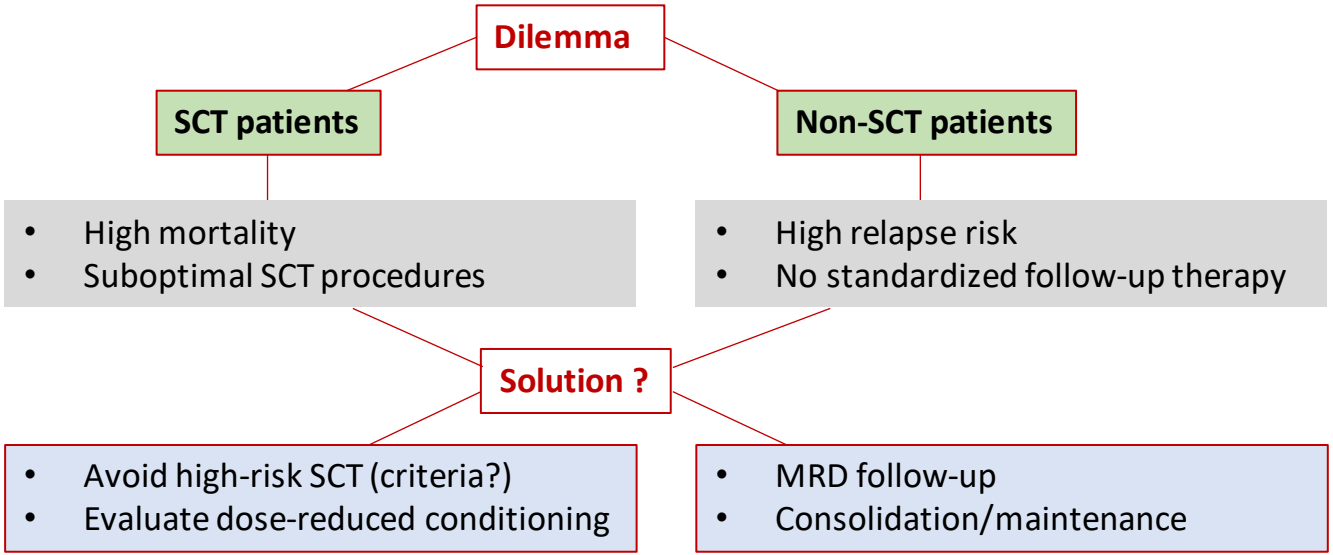


Relapse Incidence



Do We Need SCT After Achievement of MolCR in MRD-Positive ALL?

- **MRD persistence is the most unfavorable prognostic factor in ALL**
- **2–4 cycles of blinatumomab are unlikely to cure this disease subset**



Topics of the Talk

1. Definition of Relapse
2. Results of Standard Chemotherapy
3. Results of Immunotherapy in Relapsed/Refractory ALL
4. How to Optimize the Use of Immunotherapies
    - MRD setting
    - **Further approaches**
5. Consideration for Sequencing of Immunotherapies
6. Relapsed T-ALL
7. General Considerations for Relapsed ALL

Immunotherapy in Adult ALL: Optimized Use

- **Reducing leukemia burden**
- **Optimal target expression**
- **Avoiding target loss**
- **Avoiding relapse from extramedullary compartment**
- **Develop predictive parameters**
  - **Early response**
- **Continuation/maintenance or**
- **Optimized SCT**

Blinatumomab in R/R B-Precursor ALL– Role of Debulking in Italian Registry Trial

Bonifacio, et al. *Front Oncol.* 2022

Patient Characteristics (N = 34)

Age:	45 (20–75) yrs
Ph-positive:	38%
Prior SCT	50%
First line:	20%

Debulking Strategies (invest. choice)

HD steroids:	21%
Low-intensive chemo:	53%
Intensive chemo:	15%
TKI ± steroid ± chemo:	12%

Blast Count Before/After Debulking

	Before	**After**
N	34	22
<20%	21%	82%
20–49%	18%	9%
>50%	59%	9%
Median	69 (6–90%)	8 (0–80%)

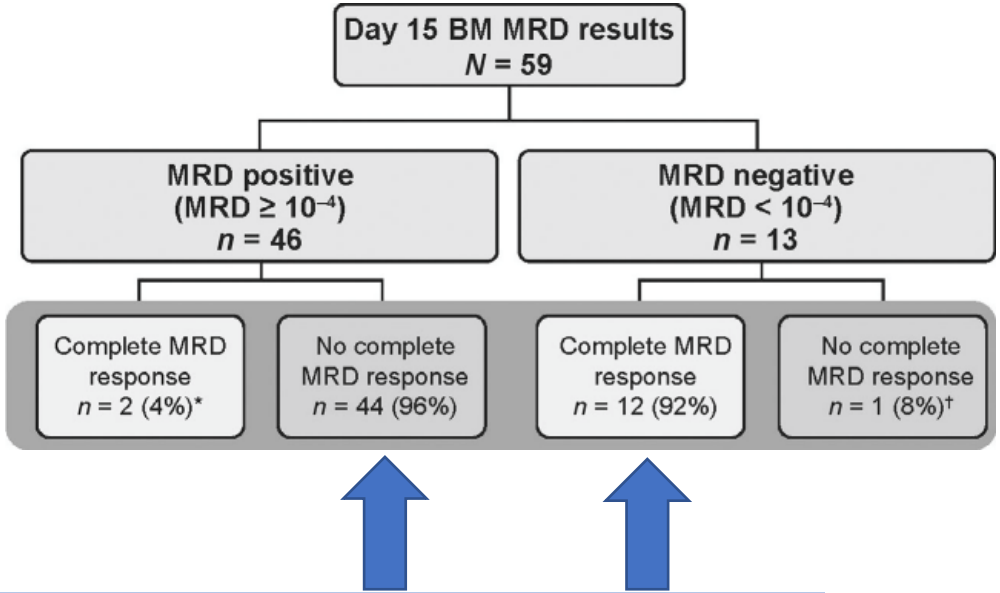
Immunotherapy in Adult ALL: Optimized Use

- Reducing leukemia burden
- Optimal target expression
- Avoiding target loss
- Avoiding relapse from extramedullary compartment
- Develop predictive parameters
  - Early response
- Continuation/maintenance or
- Optimized SCT

Blinatumomab: Day 15 Response in R/R Pediatric ALL

Brown, et al. *BJH.* 2020

Patients	70
Response Assessment	64



- **All patients treated with 2 cycles!**
- MRD result not immediately available; local-flow MRD not sufficient
- Specific high-risk late-stage pediatric patient population
- Number of cycles required for long-term response cannot be defined

Immunotherapy in Adult ALL: Optimized Use

- Reducing leukemia burden
- Optimal target expression
- Avoiding target loss
- Avoiding relapse from extramedullary compartment
- Develop predictive parameters
  - Early response
- Continuation/maintenance or
- Optimized SCT

Topics of the Talk

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Chemoimmunotherapy in R/R B-Precursor ALL

Jabbour, et al. *Cancer.* 2021

Patient 1–67

Mini Hyper-CVD ✕ 8
Inotuzumab
Cycle 1: d 3 1.8–1.3. mg/m^2
Cycle 2–4: d3 1.3–1.0 mg/m^2
Rituximab 2 ✕ /cycle if CD20>20%
Pomp Maintenance 3 years
SCT: Physicians choice

Patient 68-:
Mini Hyper-CVD x 4
Inotuzumab
Cycle 1: d2 0.6 mg/m^2, d8 0.3 mg/m^2
Cycle 2–4: d2 0.3 mg/m^2, d7 0.3 mg/m^2

Blinatumomab 4 cycles

Maintenance shortened (12 courses)
3 ✕ Blina every 3 courses

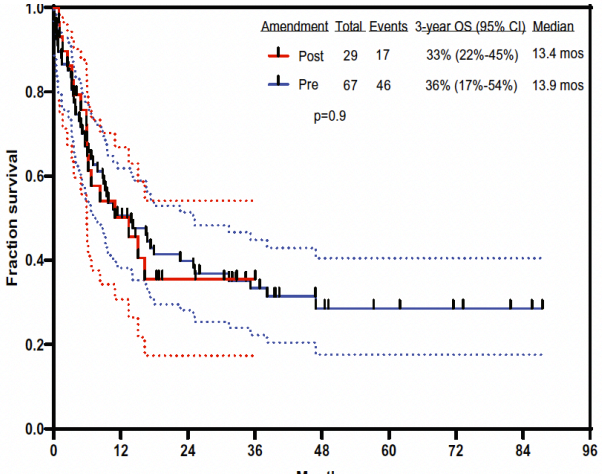
Best Overall Response (ORR)

ORR:	80% (76%/90%)
CR	57%
CRp	20%
CRi	3%
ED	7% (10%/0%)
Failure	13%
MRD-neg:	57% at response
MRD-neg:	83%
ORR	
Salvage 1	91%
Salvage 2	59%
Salvage ≥3	57%

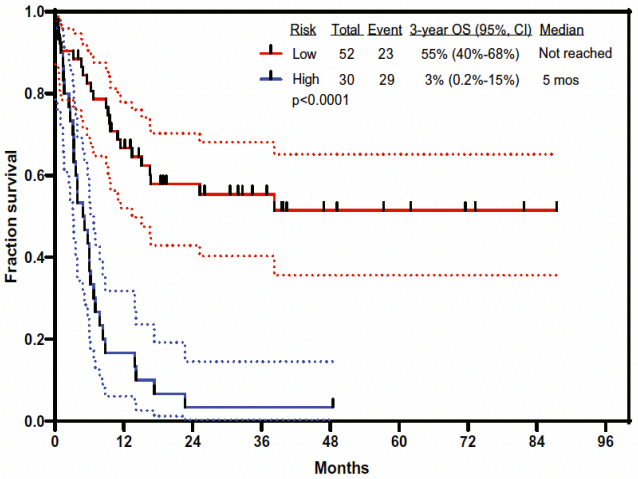
Chemoimmunotherapy in R/R B-Precursor ALL

Jabbour, et al. *Cancer.* 2021

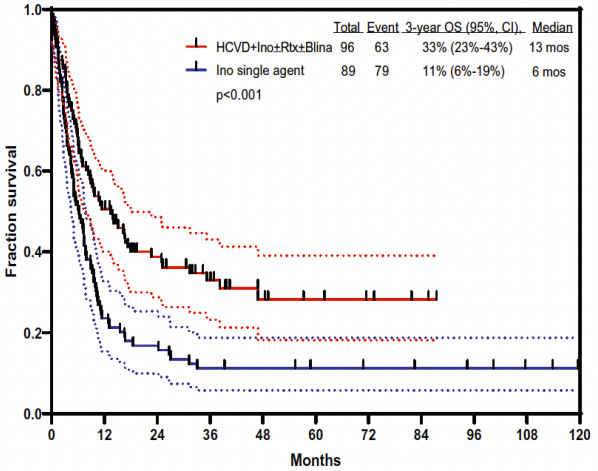
Effect of Amendment



Survival by Risk Factors



Survival by Combination



Adverse features

CD22 expression <70%, or

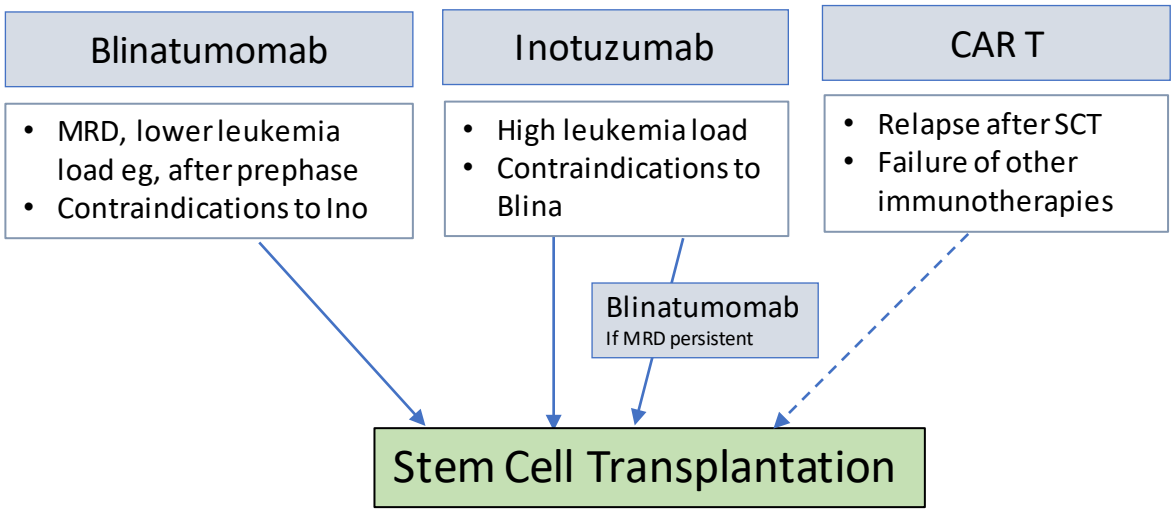
KMT2A rearrangements, or

Low hypodiploidy/near triploidy

N. Gökbuget 9/2022

Treatment of R/R B-Precursor ALL – Potential Decision-Making: Blinatumomab-Inotuzumab-CAR-T-Cells

Adapted from Dhakala, et al. *Leuk Lymph*. 2019



Questionable: Late relapses
Extramedullary relapses

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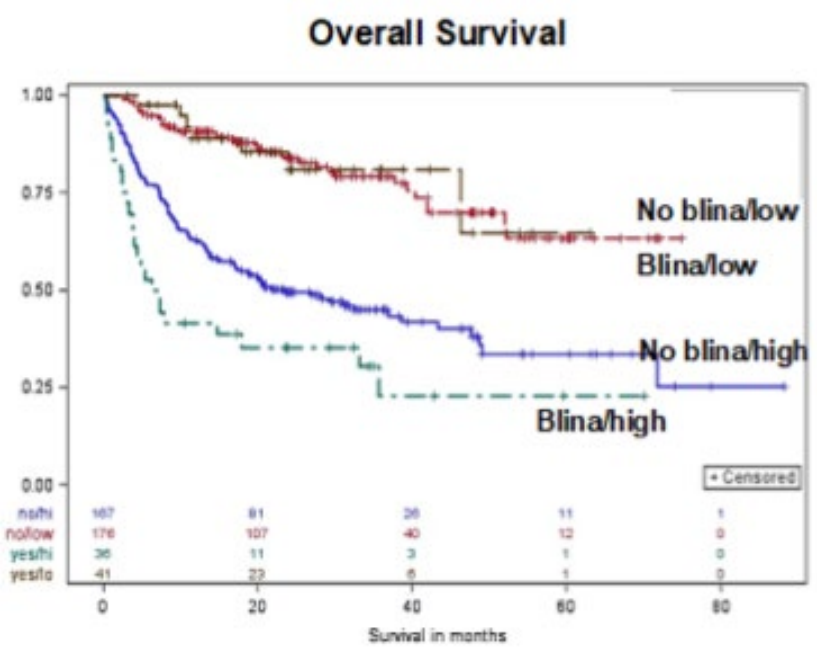
What About Sequencing Blinatumomab and CAR T Cells?

Myers, et al. *JCO.* 2021

Characteristic	All	Blina No CR	Blina CR	Blina Naive	
N	412	31	42	339	
CR	91%	64%	93%	93%	<.0001
MRD-neg CR	88%	61%	93%	90%	<.0001
CIR 24 mo	42%	74%	43%	40%	0.0001*
RFS 24 mo	56%	23%	57%	59%	<0.0001*
OS 24 mo	65%	38%	76%	66%	.0001*

*Naive vs Blina noCR



CAR T Cells in Relapse Algorithm

Buechner, et al. *Front Pediatrics.* 2022

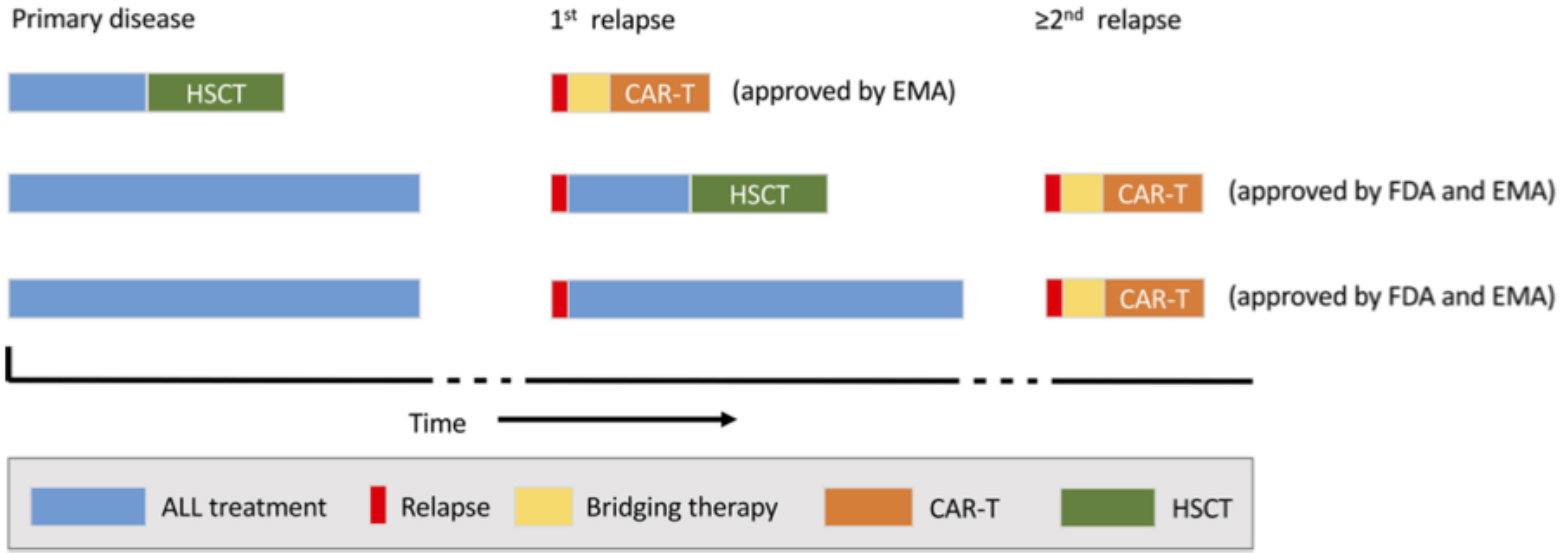


FIGURE 2 | Current indications for commercial chimeric antigen receptor (CAR) T-cell therapy (tisagenlecleucel). The possible timing of CAR-T (orange) within the treatment sequence for acute lymphoblast leukaemia (ALL) and relative to haematopoietic stem cell transplantation (HSCT; blue) is shown. EMA, European Medicines Agency; FDA, US Food and Drug Administration.

R/R ALL: MoAbs and CAR T Cells

First salvage based on evidence and availability, ie, MoAbs

Intercomparability of CAR T cells questionable

CAR T cells in SOC reserved for later lines

- **Cost issues**
- **Delays in availability**

How will things change when MoAbs become part of first line?

More clinical trials for CAR T cells needed

- **Need for subsequent SCT?**
- **Decision criteria for SCT?**
- **Standards for bridging?**
- **Data for earlier lines, eg, MRD setting**

Topics of the Talk

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GMALL Approach to Relapsed T-ALL

Late Relapse:	Repeated induction ± Bortezomib
Early Relapse:	Nelarabine/cyclo
Experimental:	Venetoclax + induction CD38 Antibody + induction Dasatinib Anti-CD3–CAR T cells High doses MTX/asparaginase In vitro drug testing
Extramedullary:	Individual approach

Topics of the Talk

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7. **General Considerations for Relapsed ALL**

General Treatment Issues in R/R ALL

1. Re-establish MRD test (clonal evolution?)
2. Initiate RNA-sequencing
3. Initiate prephase treatment as soon as all diagnostics are done
4. Plan CNS prophylaxis
5. Treatment plan with regular reassessment (at least 4 weekly)
6. Plan SCT
7. Avoid interruptions and delays
8. Avoid long-term single drug treatment
9. Head for cycling consolidation/maintenance

Global Leukemia Academy

Case 1: Adult ALL

Loic Vasseur

APTITUDE HEALTH

Clinical Case Presentation: ALL in Relapse

Loïc Vasseur
Adolescent and Young Adult Hematology Unit
Saint Louis Hospital
Assistance Publique-Hôpitaux de Paris (AP-HP)
Paris, France
23rd September 2022

22y-old patient with R/R BCP-ALL

At diagnosis

20y-old male patient, engineering student, w/o medical history

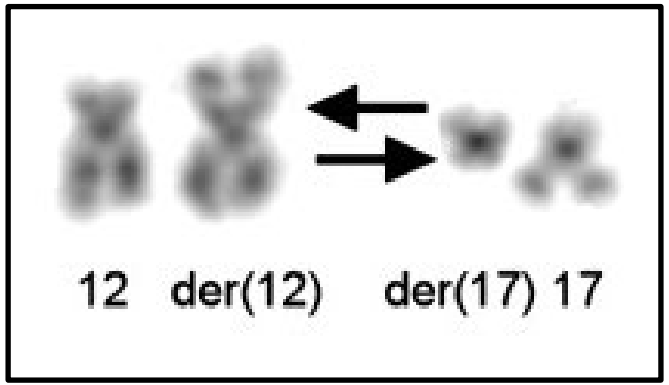
Leukocytes: 1.1 G/L, no CNS infiltration

Pro-B ALL

t(12;17), +X with *ZNF384-TAF15, IKZF1*wt

GRAALL-2014 (pediatric inspired)

MRD1 (week-6): 2×10^{-4}, MRD2 (week 12): <0 (by IG/TR qPCR)



Bone marrow relapse during maintenance phase

CR1 duration: 20 months

No CNS infiltration

CD19+, CD22+, same molecular characteristics

Nyquist KB, Thorsen J, Zeller B, Haaland A, Trøen G, Heim S, et al. Identification of the TAF15–ZNF384 fusion gene in two new cases of acute lymphoblastic leukemia with a t(12;17)(p13;q12). *Cancer Genetics*. 2011;204(3):147-152.

ZNF384-rearranged ALL

ZNF384

Transcription factor

Fusion with: *EWSR1, EP300, TCF3, TAF15, CREBBP, BMP2K . . .*

Overexpression of hematopoietic stem cell genes

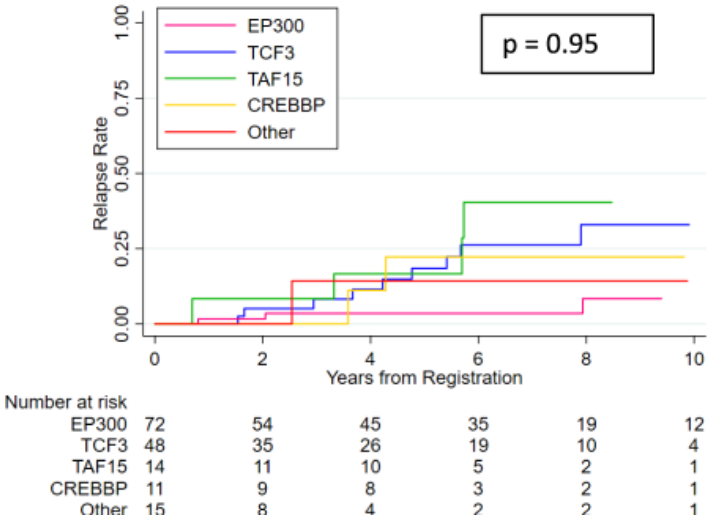
***ZNF384-r* BCP-ALL**

3-5% of BCP-ALL

CD10+ low CD13/CD33+ CD25+

Cases of mixed-phenotype ALL and myeloid switch

Intermediate risk



Hirabayashi S, Butler ER, Ohki K, Kiyokawa N, Bergmann AK, Möricke A, et al. Clinical characteristics and outcomes of B-ALL with ZNF384 rearrangements: a retrospective analysis by the Ponte di Legno Childhood ALL Working Group. *Leukemia.* 2021;35(11):3272-3277.

Alexander TB, Gu Z, Iacobucci I, Dickerson K, Choi JK, Xu B, et al. The genetic basis and cell of origin of mixed phenotype acute leukaemia. *Nature.* 2018;562(7727):373-379.

22y-old patient with R/R BCP-ALL

Chemotherapy base salvage

HD AraC, mitoxantrone, VP-16, asparaginase
Hyperammonemic encephalopathy
Failure (85% blasts) at D35
Decision of proceed to CAR T-cell therapy
Successful apheresis (TNC: 0.7×10^8/kg, CD3+: 5.7×10^8/kg)

WHICH BRIDGING STRATEGY WOULD YOU CHOOSE FOR THIS PATIENT?

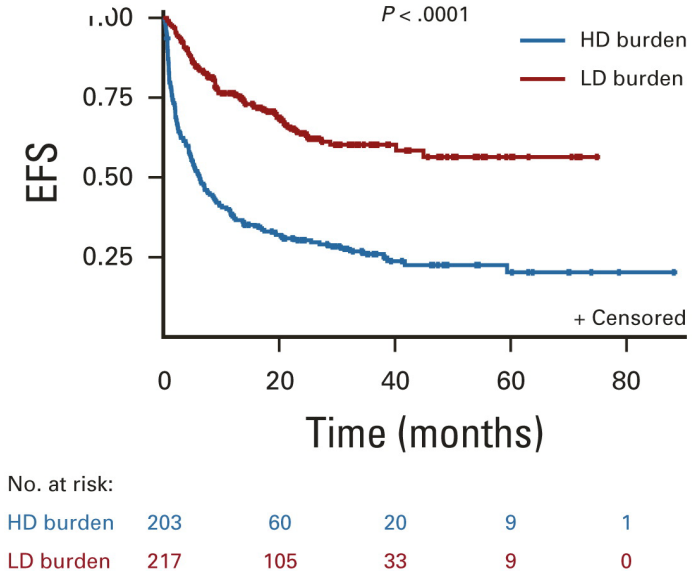
A. Blinatumomab
B. Inotuzumab with chemotherapy
C. Inotuzumab monotherapy
D. Weekly VCR-DEX
E. Chemotherapy with hyperCVAD

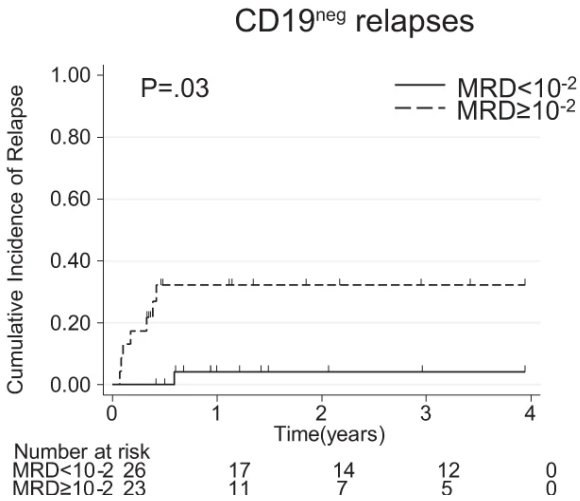
Tumor burden before CAR T cells

Safety

Impact on
- CRS/ICANS
- Cytopenias
- Infectious risk

Outcomes
- Shorter OS/DFS
- CD19- relapse





Myers RM, Taraseviciute A, Steinberg SM, Lamble AJ, Sheppard J, Yates B, et al. Blinatumomab Nonresponse and High-Disease Burden Are Associated With Inferior Outcomes After CD19-CAR for B-ALL. *J Clin Oncol*. 2022;40(9):932-944.

Dourthe ME, Rabian F, Yakouben K, Chevillon F, Cabannes-Hamy A, Méchinaud F, et al. Determinants of CD19-positive vs CD19-negative relapse after tisagenlecleucel for B-cell acute lymphoblastic leukemia. *Leukemia*. 2021;35(12):3383-3393.

Bridging strategy

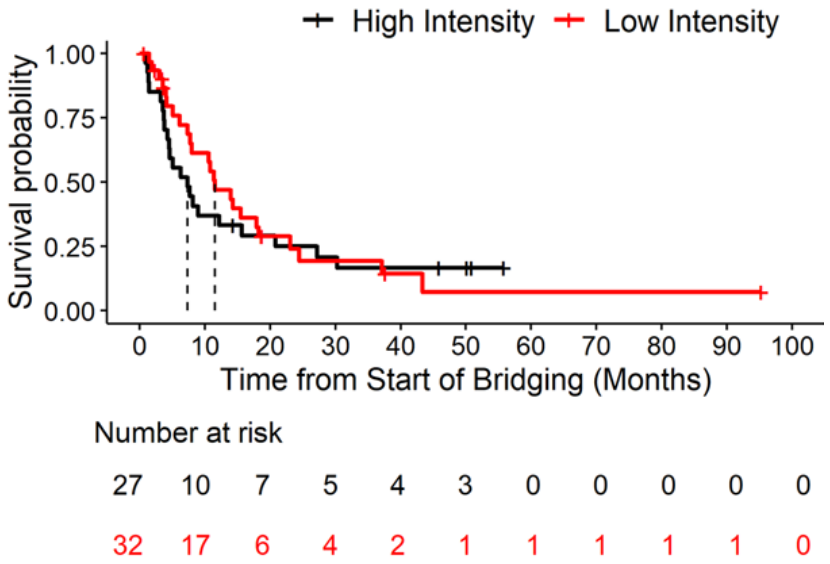
Low vs high intensity

Prevent disease progression

Reduce tumor burden

Limit risk of complications

No demonstration of higher-intensity bridging strategy



Perica K, Flynn J, Curran KJ, Rivere I, Wang X, Senechal B, et al. Impact of bridging chemotherapy on clinical outcome of CD19 CAR T therapy in adult acute lymphoblastic leukemia. *Leukemia*. 2021;35(11):3268-3271.

22y-old patient with R/R BCP-ALL

Decision to proceed to CAR T-cell therapy

Bridging therapy

- Weekly VCR/DEX + ITT (D1, D8): peripheral blasts at D15
- HDAC (D15): colitis, septic shock, transfer to ICU (norepinephrin), persistant peripheral blasts
- Inotuzumab ozogamicin (D28, D35)
- Prelymphodepletion (D45): cytopenia, 6% of BM blasts

22y-old patient with R/R BCP-ALL

CAR T-cell therapy

Lymphodepletion

Cy 500 mg/m² D-4, D-3, FLU 30 mg/m² D-5 to D-2

Tisagenlecleucel

Fever at D1

Hypotension at D3 (volume expansion), treatment with tocilizumab

ICU D3 to D6 : DEX for 2 days at D5 and D6, no vasopressor

T_{max} = D9, C_{max} = 1.200/µL

Neutrophil recovery at D9 with G-CSF

Discharge at D16

22y-old patient with R/R BCP-ALL

D28 evaluation

B-cell aplasia

Complete remission, MRD: 1×10^{-4}

WHICH STRATEGY WOULD YOU CHOOSE FOR THIS PATIENT?

A. HSCT
B. Follow-up
C. Blinatumomab

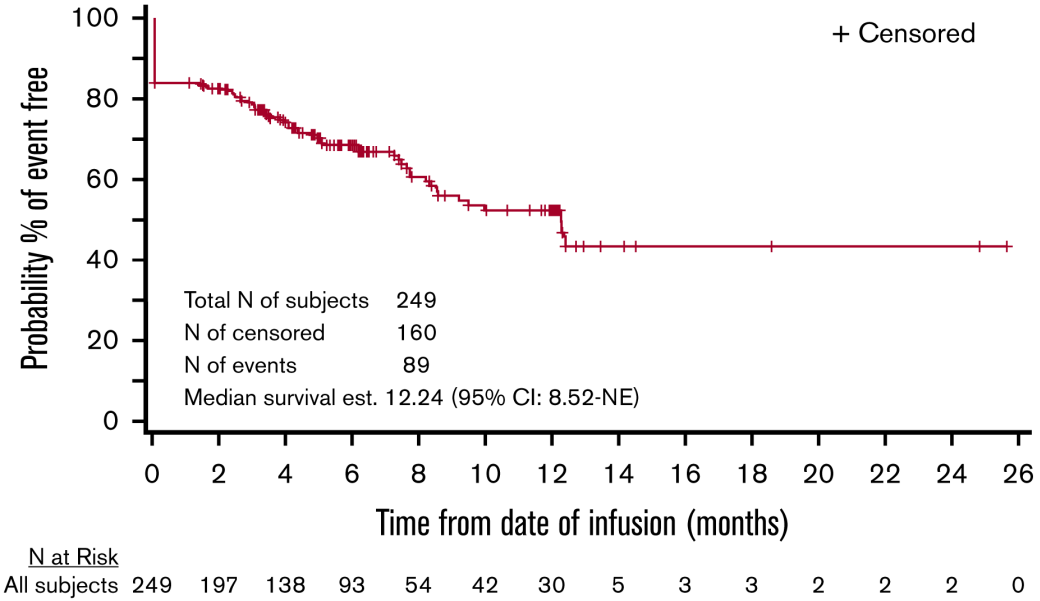
Real-world data of CAR T

CIBMTR

N = 410 patients

CR rate: 86.8%

PFS 6 months: 38.7% (30.5-46.9)



Pasquini MC, Hu ZH, Curran K, Laetsch T, Locke F, Rouce R, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Blood Adv.* 2020;4(21):5414-5424.

MRD after CAR T cells

MRD M1

CIBMTR

85.5% of CR

MRD- in CR patients: 99.1% (115/116)

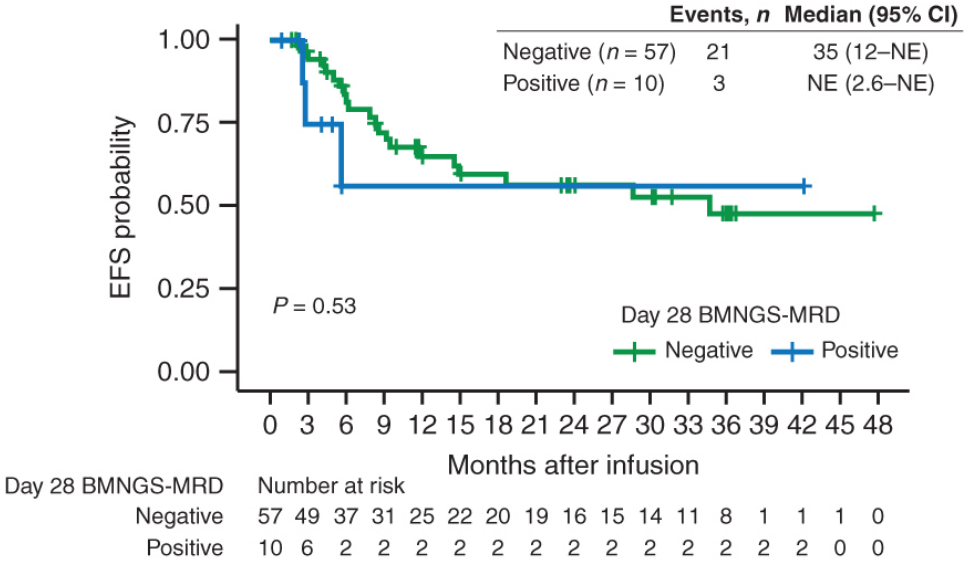
46% of MRD- before infusion

ENSIGN, ELIANA

MRD NGS (sensitivity 10^{-6})

No difference at D28 in CR patients

Long-term responders



Pulsipher MA, Han X, Maude SL, Laetsch TW, Qayed M, Rives S, et al. Next-Generation Sequencing of Minimal Residual Disease for Predicting Relapse after Tisagenlecleucel in Children and Young Adults with Acute Lymphoblastic Leukemia. *Blood Cancer Discov.* 2022;3(1):66-81.

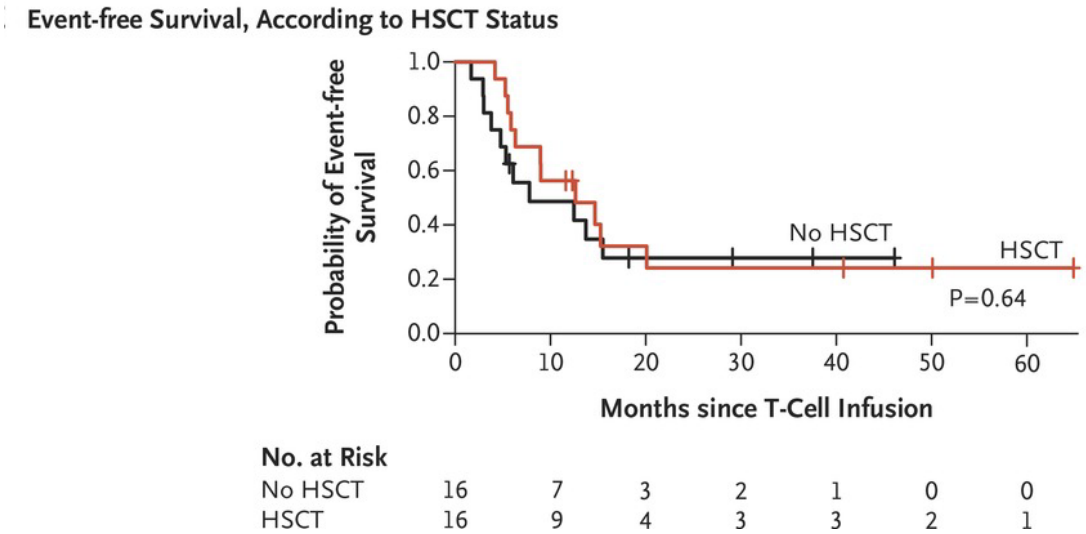
HSCT after CAR T cells

HSCT

CIBMTR: n = 34 (16;5%)

MSKCC: n=17 (38.6%)

No difference in HSCT in CR MRD- patients



Park JH, Rivière I, Gonen M, Wang X, Sénéchal B, Curran KJ, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. *N Engl J Med.* 2018;378(5):449-459.

22y-old patient with R/R BCP-ALL

Follow-up after CAR T cells

MRD1 control at 1.5 months: undetectable

MRD control at 2 months: positive not quantifiable (1 out of 2 targets, sensitivity 10^{-4})

MRD control at 2.5 months: undetectable

At 6 months without further therapy

- Persistence of complete MRD response
- Persistence of B-cell aplasia
- Back to engineering school

Global Leukemia Academy

Case 2: Adult ALL

Anjali Cremer

APTITUDE HEALTH

Clinical Case: Relapsed/Refractory Adult ALL

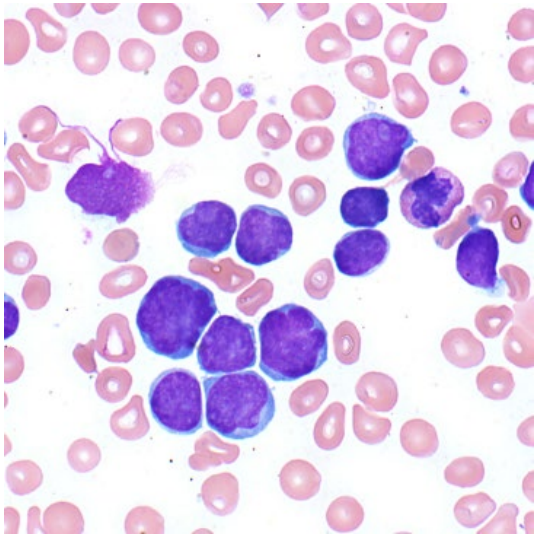
Global Leukemia Academy EU Meeting

Dr med Anjali Cremer
University Hospital Frankfurt
Department of Hematology/Oncology

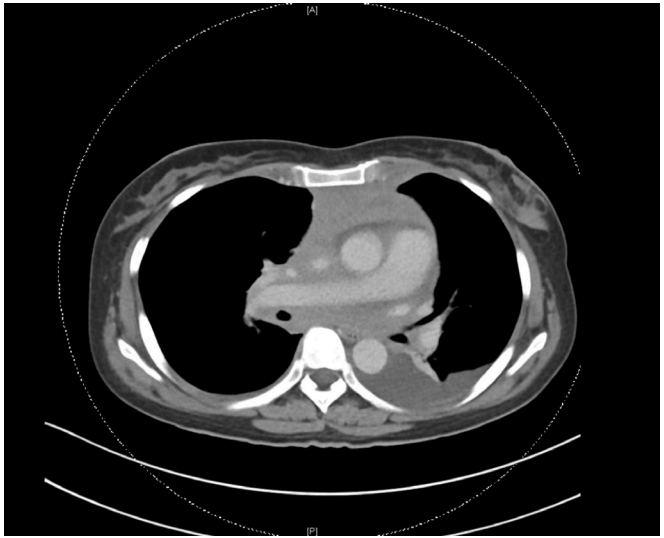
September 23–24, 2022

Clinical Characteristics

- Female, 42 yr
- Presents with fatigue, dyspnea, and cough lasting a few weeks, weight loss during the last month
- Leukocytes 264/nL, thrombocytes 208/nL, Hb 8.3 g/dL, blasts 72%



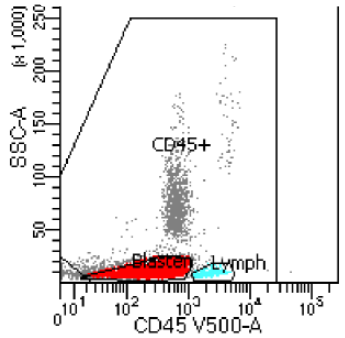
www.cap.org



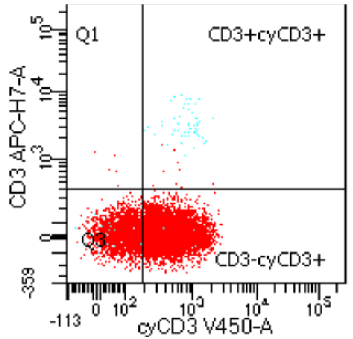
Prof Vogl, Frankfurt

Initial Immunophenotype

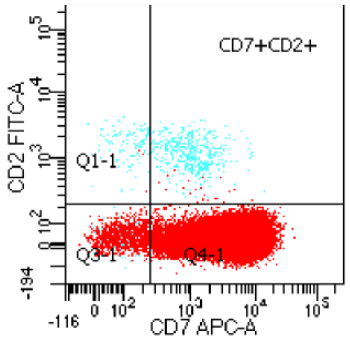
Singlets



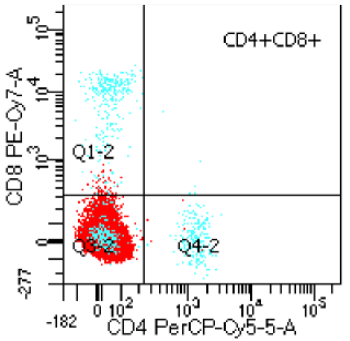
Lymph/Blasts



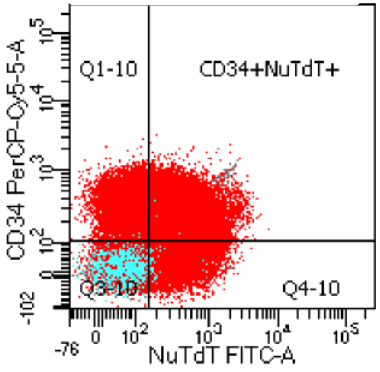
Lymph/Blasts



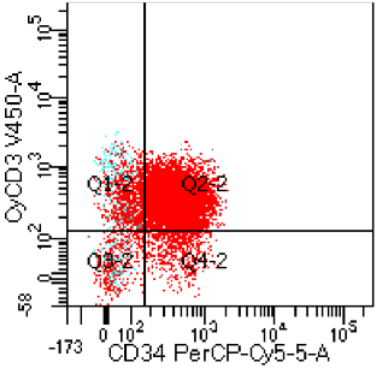
Lymph/Blasts



Lymph/Blasts



Lymph/Blasts



Blasts = red
Lymphocytes = blue

➡ What is the diagnosis? **Pro-T/ETP-ALL**

Dr Anne Wilke

Risk Factors

High leukocyte counts	>30 G/L B-cell precursor ALL
Subtype	Pro-B, early T, mature T
Late CR	>3 weeks (after Induction II)
Cytogenetics/Molecular aberrations	t(9;22) – *BCR-ABL* t(4;11) – *KMT2A-AFF1*
Minimal residual disease (MRD)	MRD level $>10^{-4}$ MRD increase $>10^{-4}$ after previous CR

In which setting would a 50-year-old patient NOT receive allogeneic stem cell transplantation?

1. Early T-ALL, MRD positive (after Consolidation I)
2. Early T-ALL, MRD negative (after Consolidation I)
3. Mature T-ALL, MRD positive (after Consolidation I)
4. Thymic T-ALL, MRD positive (after Consolidation I)
5. Thymic T-ALL, MRD negative (after consolidation I)

Treatment

- 11/2020 Primary diagnosis: Early T-cell precursor ALL
- 11-12/2020: GMALL study protocol: Induction I, Induction II

  > *MRD positive <10^{-4}*
- 2/2021: Consolidation I

  > *hCR, PET: negative, MRD positive 2 × 10^{-4}*
- 3/2021: Consolidation III instead of II – bridge to transplant to avoid PEG-asparaginase toxicity

  > *MRD positive 5 × 10^{-4}*
- 4/2021: Nelarabine (1500 mg/m^2 d1, 3, 5)

  > *MRD before SCT: MRD 2 × 10^{-3}*
- 5/2021: Allogeneic stem cell transplantation MUD, fludarabine 30 mg/m^2 day –6 until –3, TBI 2 × 2 Gy d –3, –2

Treatment After SCT

MRD

- 5/2021 Before SCT: 2×10^{-3}
- 7/2021 After SCT: $<3 \times 10^{-5}$
- 8/2021 $<3 \times 10^{-5}$
- 9/2021 $<3 \times 10^{-5}$
- 10/2021 3×10^{-4}

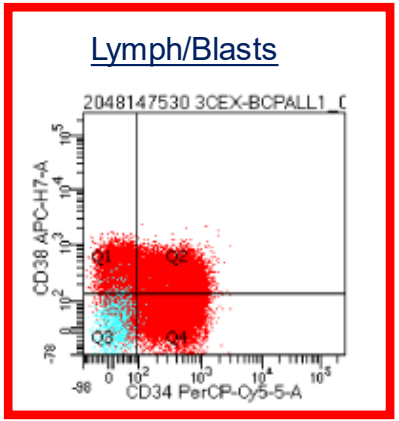
Chimerism

- 7/2021 After SCT: $<3 \times 10^{-5}$
- 8/2021 $<3 \times 10^{-5}$
- 9/2021 100%
- 10/2021 100%

➡ What would you do?

Treatment

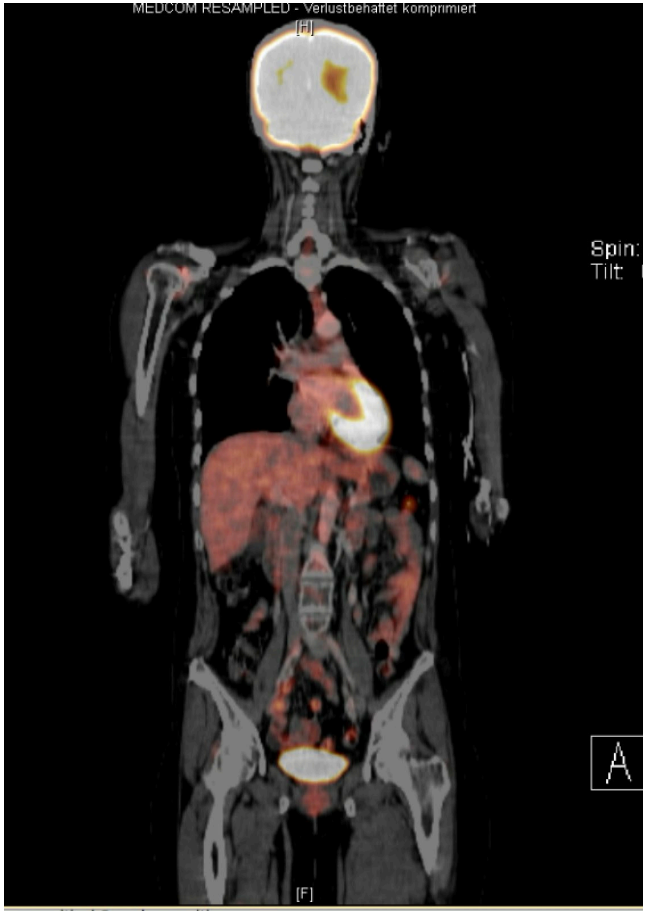
➡ Daratumumab cycle 1–2
Donor lymphocyte infusion (DLI) up to 0.5×10^{7} CD3+ cells



Treatment After SCT

MRD

- 5/2021 Before SCT: 2×10^{-3}
- 7/2021 After SCT: $<3 \times 10^{-5}$
- 8/2021 $<3 \times 10^{-5}$
- 9/2021 $<3 \times 10^{-5}$
- 10/2021 3×10^{-4}



Treatment

➡ Daratumumab cycle 1–2
Donor lymphocyte infusion (DLI) up to 0.5×10^{7} CD3+ cells

Global Leukemia Academy

BREAK

APTITUDE HEALTH

Global Leukemia Academy

Beyond the Horizon: New and Future Treatment Approaches for Adult and Older ALL Patients

Nicola Gökbuget

APTITUDE HEALTH

Beyond the Horizon: New and Future Treatment Approaches for Adult and Older ALL Patients

Nicola Gökbuget

Potential Conflicts of Interest

Speaker Honoraria, Travel Support, Advisory Board

- Amgen
- Celgene
- Gilead
- Novartis
- Pfizer
- Jazz Pharmaceuticals
- Incyte
- Autolus

Research Support (institutional)

- Amgen
- Pfizer
- Novartis
- Servier
- Jazz Pharmaceuticals
- Incyte

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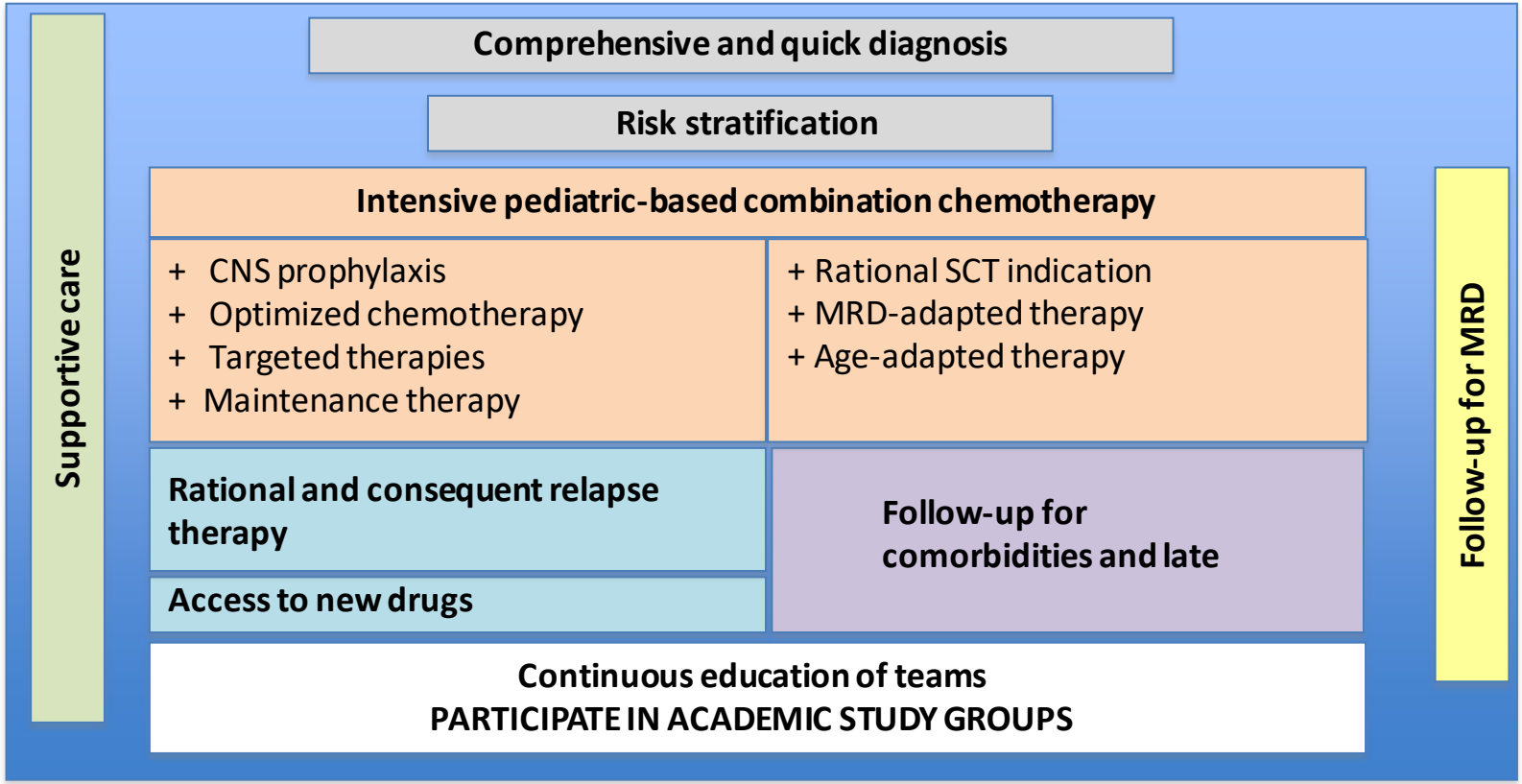
Modern Management of ALL for All Age Groups



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Selection of Topics

1. **Age Groups**
2. Diagnostics
3. Risk Stratification
4. Younger Patients
5. Older Patients
6. Ph-Positive ALL
7. Overarching Questions
8. Personalized Medicine in ALL
9. Late Effects

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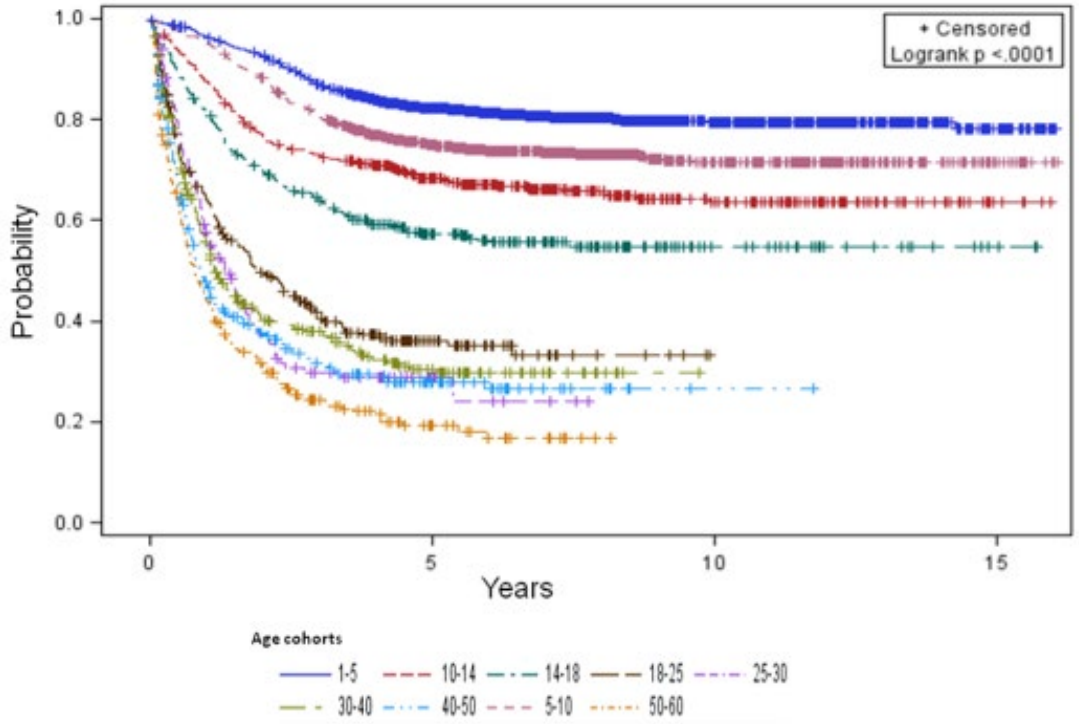
Treatment Results in ALL Depends on Age: Children vs Adults



Essential factors for decreasing survival with increasing age

- Lower-dose intensity and higher risk of complications
- Increasing proportion of patients with high-risk features
  - Pro B-ALL
  - MLL rearranged ALL
  - Hypodiploid ALL
  - Early T-ALL
  - (Ph-positive)
- Unknown factors of disease biology

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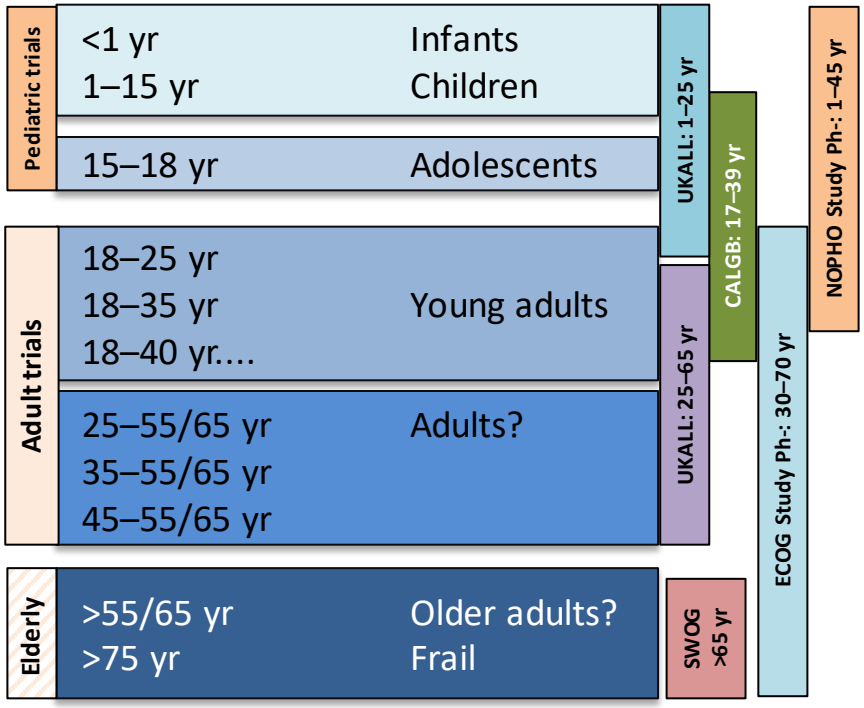
Chiaretti S, et al. *Haematologica.* 2013;98.

What Is the Meaning of “Young” and ‘Old’ in the ALL World?



Will we come to new, reasonable age definitions,

eg, depending on general condition and comorbidities and planned treatments?

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Selection of Topics

1. Age Groups
2. **Diagnostics**
3. **Risk Stratification**
4. Younger Patients
5. Older Patients
6. Ph-Positive ALL
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Diversity of Adult ALL

At First diagnosis

1. **Clinical**
   - Bone marrow involvement
   - Extramedullary involvement
   - Blood counts
   - Age
   - ECOG status
   - Comorbidities
   - BMI

2. **Biological**
   - Subtype
   - Genetic aberrations
     - Translocations
     - Other genetic aberrations like mutations, deletions
     - Aberrant gene expression
     - Gene polymorphisms

During First-Line Treatment

1. Cytologic response
2. Molecular response
3. Clinical toxicities/complications

Risk factors for

- Non-response
- Complications
- Early death
- Death in CR
- Molecular failure
- Relapse
- Late complications

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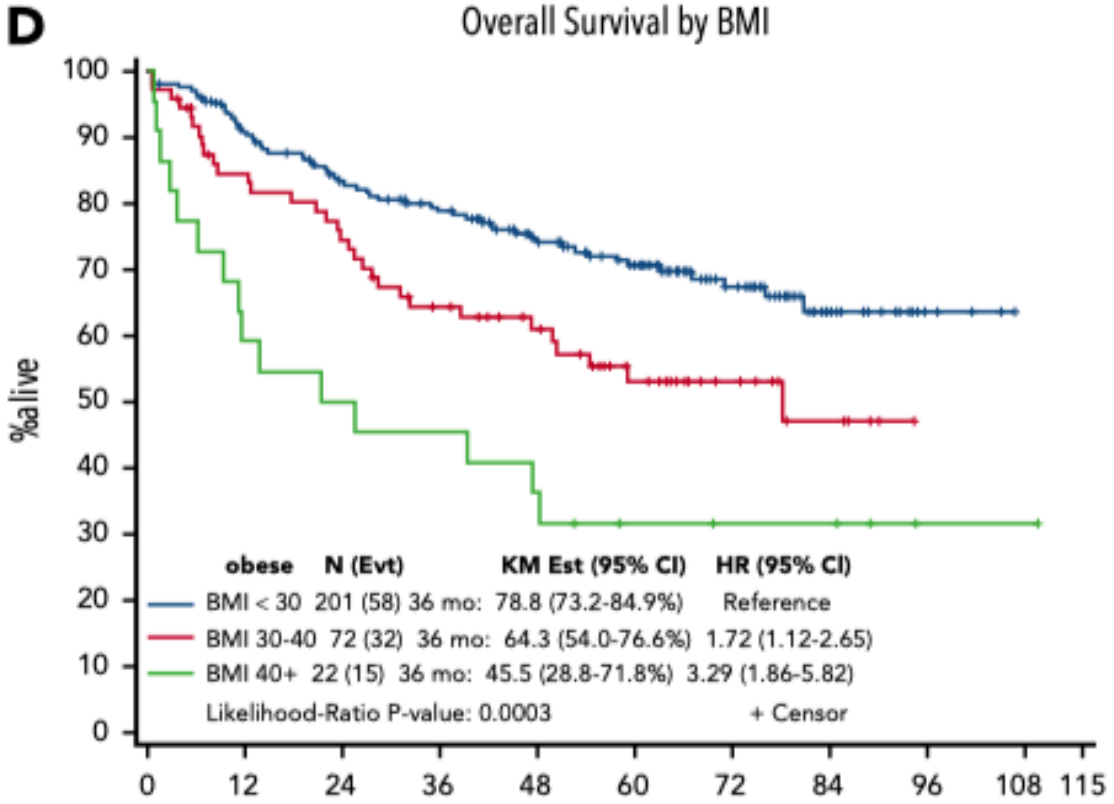
Pediatric Regimen in AYA (17–39 yr)

Stock, et al. *Blood*. 2019.



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International Consensus Classification of Myeloid Neoplasms and Acute Leukemia: Integrating Morphological, Clinical, and Genomic Data

Arber, et al. *Blood.* 2022.

Table 28. Classification of acute lymphoblastic leukemia (synonym: lymphoblastic leukemia/lymphoma)

B-acute lymphoblastic leukemia (B-ALL)
- B-ALL with recurrent genetic abnormalities
  - B-ALLwith t(9;22)(q34.1;q11.2)/*BCR::ABL1* !
    - with lymphoid only involvement
    - with multilineage involvement
  - B-ALLwith t(v;11q23.3)/*KMT2A* rearranged
  - B-ALL with t(12;21)(p13.2;q22.1)/*ETV6::RUNX1*
  - B-ALL, hyperdiploid
  - B-ALL, low hypodiploid
  - B-ALL, near haploid
  - B-ALL with t(5;14)(q31.1;q32.3)/*IL3::IGH*
  - B-ALL with t(1;19)(q23.3;p13.3)/*TCF3::PBX1*
  - B-ALL, *BCR*::*ABL1*–like , ABL-1 class rearranged
  - B-ALL, *BCR*::*ABL1*–like , JAK-STAT activated
  - B-ALL, *BCR*::*ABL1*–like , NOS
  - B-ALL with iAMP21
  - B-ALL with *MYC* rearrangement
  - B-ALL with *DUX4* rearrangement
  - B-ALL with *MEF2D* rearrangement
  - B-ALL with *ZNF384(362)* rearrangement
  - B-ALL with *NUTM1* rearrangement
  - B-ALL with *HLF* rearrangement
  - B-ALL with *UBTF::ATXN7L3/PAN3,CDX2* ("CDX2/UBTF")
  - B-ALL with mutated *IKZF1* N159Y
  - B-ALLwith mutated *PAX5* P80R
    - Provisional entity: B-ALL, *ETV6::RUNX1*-like
    - Provisional entity: B-ALL, with *PAX5* alteration
    - Provisional entity: B-ALL, with mutated *ZEB2* (p.H1038R)/IGH::*CEBPE*
    - Provisional entity: B-ALL, *ZNF384* rearranged-like
    - Provisional entity: B-ALL, *KMT2A* rearranged-like
- B-ALL, NOS

New Subtypes !

DUX4	Excellent
ZNS384	Variable
NUTM1	Good
IKZF1	Intermediate
PAX5P80R	Intermediate
MYC	Poor
MEFD2	Poor
CDX2/UBTF	Poor
HLF	Very poor

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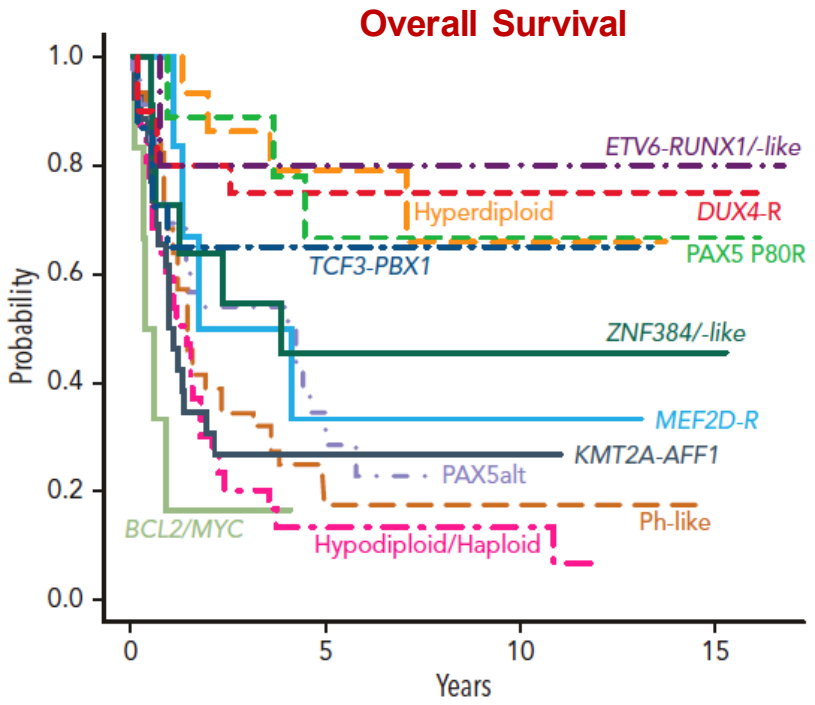
Molecular Classification in Adult Ph-Negative B-Precursor ALL

Paietta, et al. *Blood*. 2021.

UKALLXII/ECOG-ACRIN E2993; 1993–2006
N = 1229
Tested: 264

Molecular subgroup	Number of patients	%
DUX4-R	22	7.8
ETV6-RUNX1/-like*	5	1.8
TCF3-PBX1	15	5.3
KMT2A-AFF1	27	9.6
KMT2A-non-AFF1	10	3.5
PAX5alt	27	9.6
PAX5 P80R	10	3.5
Ph-like *CRLF2*-R	30	10.6
Ph-like non-*CRLF2*-R	18	6.4
ZNF384-R/-like*	11	3.9
MEF2D-R	6	2.1
BCL2/MYC	12	4.3
ZEB2/CEBPE	4	1.4
iAMP21	3	1.1
TCF3-HLF	1	0.4
HH	16	5.7
LH/NH	34	12.1

9.6%
3.5%
9.6%
10.6%
6.4%
4.3%
12.1%



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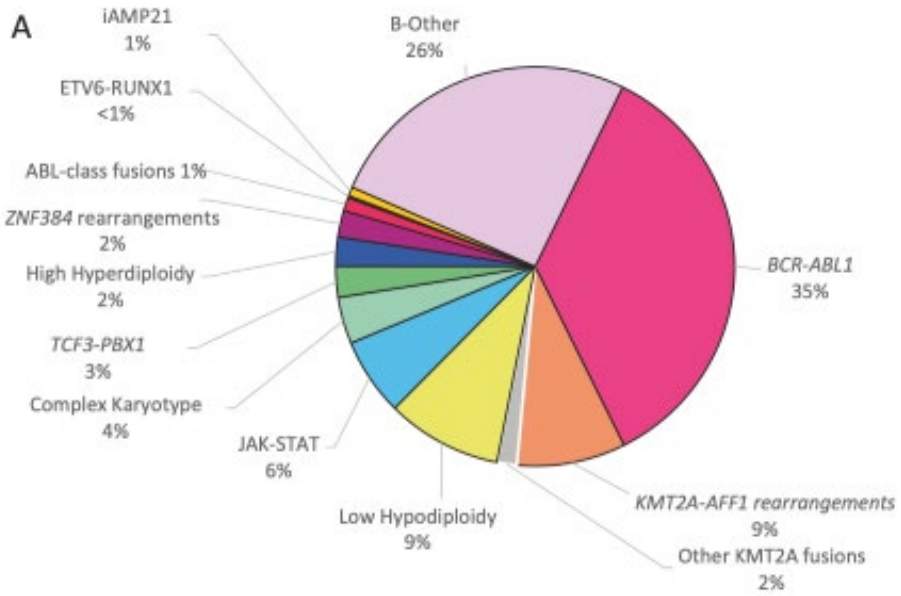
Prognostic Impact of Molecular Aberrations in B-Precursor ALL

Moorman, et al. *Leukemia*. 2022.

De novo ALL 25–65 yr (UKALL14): N = 652

Frequency of Aberrations



Suggested Risk Groups

Genetic Risk Group	Definition	Freq
Standard risk (SR)	BCP-ALL with *ZNF384*-r, HeH and other abnormalities	34%
High risk (HR)	*KMT2A*-r	10%
Very High Risk (VHR)	Low hypodiploid, complex karyotype, JAK-STAT abnormalities	19%
Tyrosine kinase activating (TKA) fusions	*BCR-ABL1*, ABL-class fusions	36%

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Risk factors for

- Non-response
- Complications
- Early death
- Death in CR
- Molecular failure
- Relapse
- Late complications

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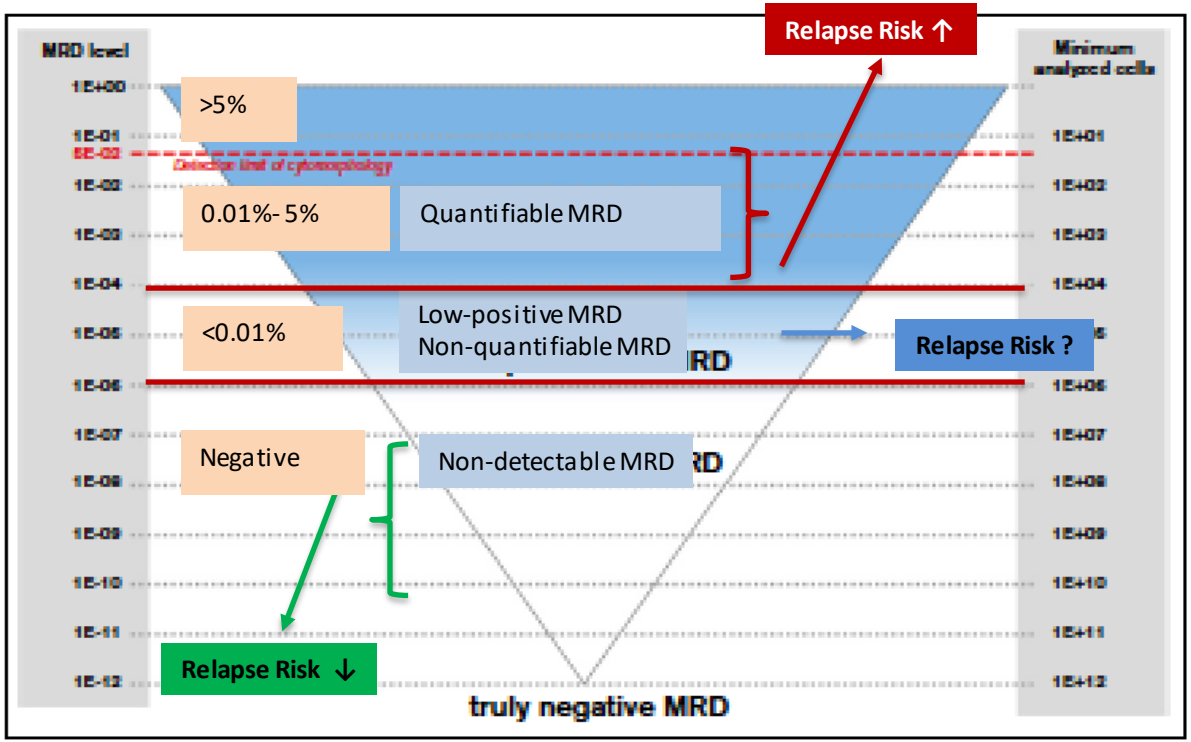
What Does MRD Mean?



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Minimal Residual Disease

Relevance of MRD Level in Correlation with Sensitivity

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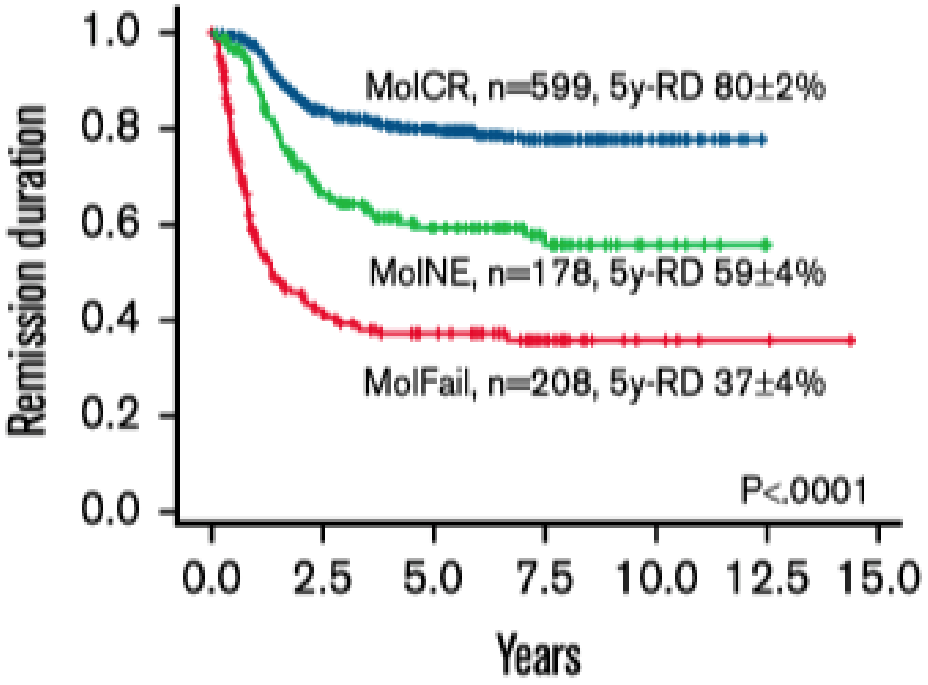
Clarification of Intermediate MRD by NGS (week 16)

Kotrova, et al. *Blood Advances.* 2022.

Total N:	1019
MolCR:	**603 (59%)**
MolFail	**238 (23%)**
MolNE	**178 (17%)**
MRD insuff Sens	50 (28%)
MRD $<10^{-4}$, quant	4 (2%)
MRD $<10^{-4}$ not q	57 (32%)
MRD not quant	67 (38%)



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Diagnostics and Risk Stratification

- All pts sequencing (genome, RNA, SNP)?
- Risk stratification integrating molecular and MRD markers?
- New goals of risk stratification?
- MRD sensitivity? How deep will we go? Consequences? Bone marrow vs PB vs other sites?

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Outcomes of Younger Adults With Pediatric-Based Therapies

For Several Decades, Many Adult ALL Study Groups Have Used Pediatric-Based Regimens[1]

Author	N	Age	CR	OS
Ribera, 2008	81	29 (15–30)	98%	69% (6y)
Huguet, 2009	225	31 (15–60)	93%	60% (3y)
Gökbuget, 2010	1226	35 (15–55)	91%	60%/67%[a] (3y)
Haiat, 2011	40	33 (18–55)	90%	75% (3y)
Rijneveld, 2011	54	26 (17–40)	91%	72% (2y)
Rytting, 2014	85	21 (13–39)	94%	74% (3y)
De Angelo, 2015	92	28 (18–50)	85%	67% (4y)
Stock, 2019	295	24 (17–39)	89%	73% (3y)

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[a] Asparaginase doses at start of induction.

1. Boissel N et al. *J Adolesc Young Adult Oncol*. 2015;4:118-128.

Further Treatment Optimization in Younger Patients With ALL

- Asparaginase-intensification
- Rituximab in CD20-positive ALL
- Maintenance therapy
- Optimized management of T-ALL/LBL
- Targeted therapy in molecular failure
- Stem Cell transplantation

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Further Treatment Optimization in Younger Patients With ALL

- Asparaginase-intensification
- Rituximab in CD20-positive ALL
- Maintenance therapy
- Optimized management of T-ALL/LBL
- Targeted therapy in molecular failure
- Stem Cell transplantation

- **Immunotherapy in First Line for B-Prec**
  - to replace chemotherapy cycles
  - to replace SCT
- **Optimized management of T-ALL/LBL**
  - Nelarabin?
  - Asparaginase?
  - New compounds
    - Bortezomib
    - CD38 antibodies
    - Venetoclax

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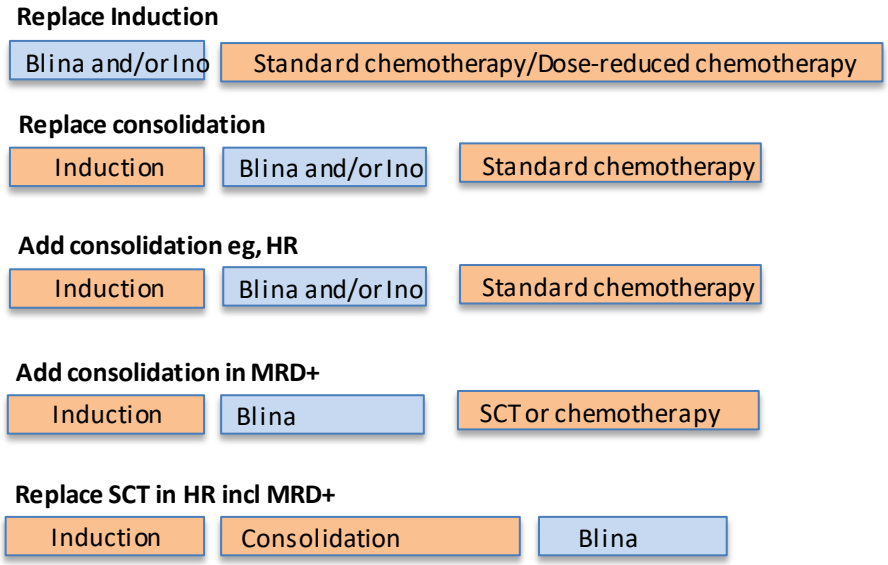
Selection and Sequencing of Immunotherapies

First-Line: Principles Including Pediatric Relapse



How to achieve marketing authorization?
How to achieve reimbursement?

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De Novo: Younger Patients
18–55 yr, Ph-Negative

- Replacement of intensive, toxic chemotherapies by immunotherapy
- Optimization of pediatric-based therapy
- Focus on ALL-type compounds
- Reduction of SCT
- New targeted approaches for high-risk patients (to be defined)
- Improve patient involvement

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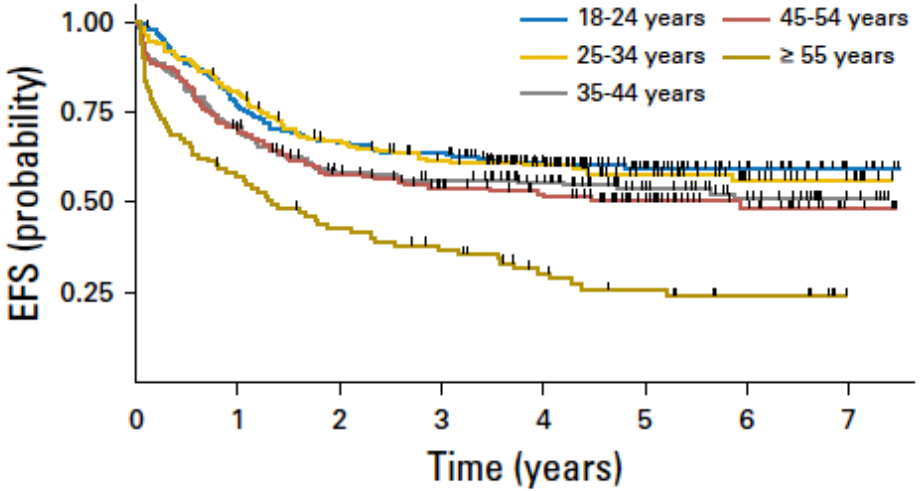
Upper Age Limit for a Pediatric-Inspired Therapy?

Huguet, et al. *J Clin Oncol.* 2018.



No. at risk:								
18-24 years	200	153	130	124	92	65	38	20
25-34 years	172	138	112	98	78	56	35	24
35-44 years	171	122	93	87	72	49	36	21
45-54 years	151	104	81	68	57	38	23	8
≥ 55 years	93	52	38	31	21	16	11	5

18–54 yr

56–59 yr

N	93
CR	79%
Early death	18%
Death in CR	27%

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Hyper-CVAD in Older Patients (>60 yr)

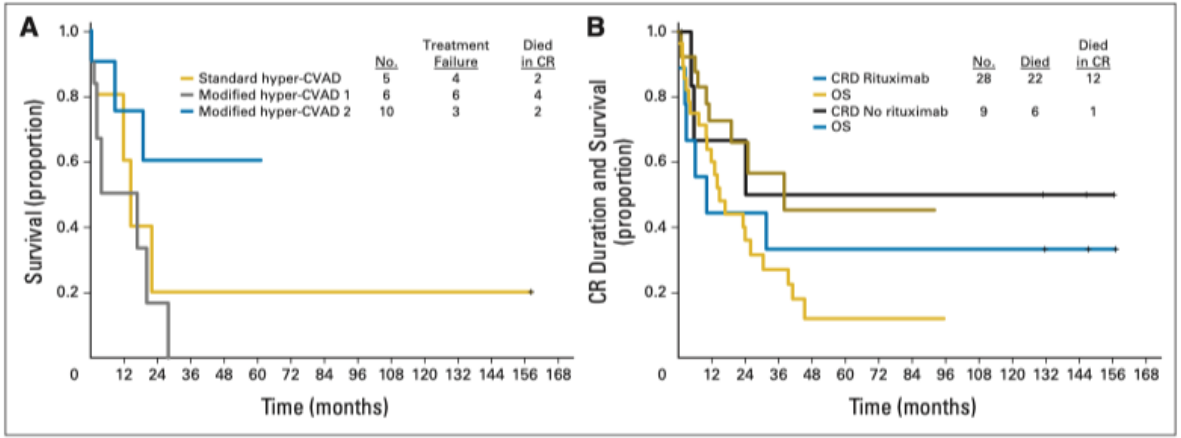
Thomas, et al. *JCO.* 2010.

Total 58
CR 88%

RD 3 yr 53%
OS 3 yr 29%

Death in CR:
N = 18 (31%)

Standard hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) regimen
Standard, modified hyper-CVAD 1 with rituximab inclusive of anthracycline intensification,
Modified hyper-CVAD 2 with rituximab eliminating anthracycline intensification are depicted.



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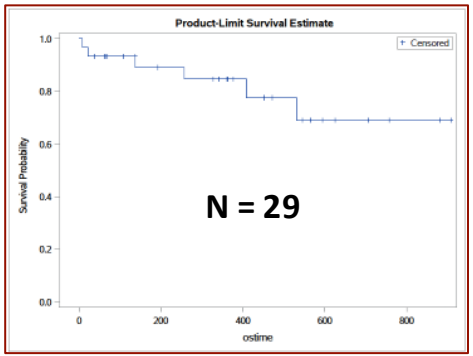
New Immunotherapy Approaches in Older Patients

Bold

Gökbuget, et al. ASH 2021.

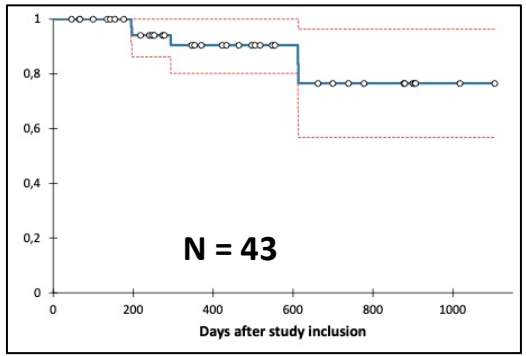
Overall Survival



Initial-1

Stelljes, et al. ASH 2021.

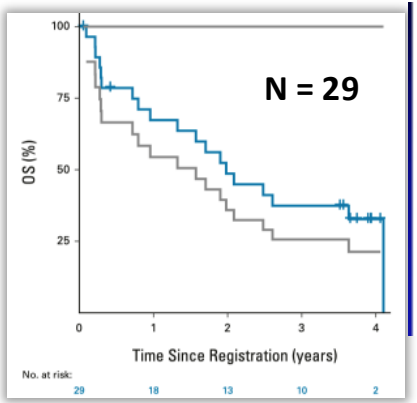
Overall Survival



SWOG

Advani, et al. JCO. 2022.

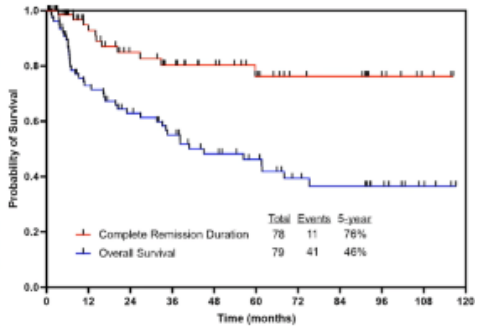
Overall Survival



Mini-CVD + Ino ± Blina

Short, et al. ASH 2021.

Overall Survival



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Blinatumomab Alternating With Low-Intensity Chemotherapy vs Chemotherapy Standard of Care in Ph/BCR-ABL–Negative Older ALL Patients

Major inclusion criteria

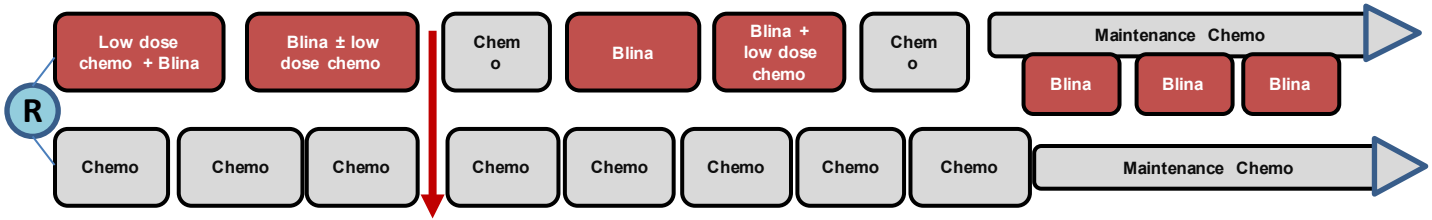
- ≥55 years of age

Primary Endpoints

- Event Free Survival (EFS)
- Overall Survival (OS): time from randomization(enrollment) until death due to any cause

Patient Number: 274

Design: global, randomized pivotal phase III trial after safety run-in



GMALL Elderly or reduced Hyper-CVAD

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De Novo: Older Patients
>55–? Yr, Ph-Negative

- New age limits
- Full integration of MRD-based therapy
- Dose-reduced chemo + immunotherapy in first line
- Selective role of SCT
- Optimization of care standards
- Frail: chemo-free regimens

Gökbuget 9/2021

Selection of Topics

1. Age Groups
2. Diagnostics
3. Risk Stratification
4. Younger Patients
5. Older Patients
6. **Ph-Positive ALL**
7. Overarching Questions
8. Personalized Medicine in ALL
9. Late Effects

Gökbuget 9/2021

Management of Ph/BCR-ABL–Positive ALL: First Line

Foa and Chiaretti. *N Engl J Med.* 2022.

Table 1. Trials of Tyrosine Kinase Inhibitors (TKIs) for Frontline Treatment of Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia.*

Study Group and Regimen	No. of Patients	Age	CHR	Molecular Response†	Disease-free Survival	Overall Survival	Allo-SCT Allocation
		median (range)			*percent*		
First-generation TKI							
GMALL[17]	92		96				
Imatinib + CHT, alternating regimen	47	46 yr (21–65)		26 after cycle 2 of induction	52 at 2 yr (EPR)	36 at 2 yr	77
Imatinib + CHT, concurrent regimen	45	41 yr (19–63)		27 after cycle 2 of induction	61 at 2 yr (EPR)	43 at 2 yr	77
GMALL[18]: imatinib vs. CHT (induction)	55						
Imatinib	28	66 yr (54–79)	96	5.6×10^{-5} at wk 4†	29.5 at 18 mo	57 at 18 mo	NA
CHT	27	68 yr (58–78)	50	3.2×10^{-4} at wk 4†	35 at 18 mo	41 at 18 mo	
GRAALL[19]: imatinib + CHT	30	65.8 yr (58–78)	72	NA	58 at 1 yr (RFS)	66 at 1 yr	NA
GRAALL[20]: imatinib + CHT	45	45 yr (16–59)	96	29 after induction	51 at 18 mo	65 at 18 mo	48
GRAALL[21] (updated): imatinib + CHT	45	45 yr (16–59)	96	29 after induction	44 at 4 yr	52 at 4 yr	53
GRAALL[22]: group 1, imatinib + low-dose CHT; group 2, imatinib + CHT	268	47 yr (18–59)	Group 1: 98 Group 2: 91	Group 1: 28.6 Group 2: 22.6 After cycle 2 of induction	54 at 5 yr	45 at 5 yr	63
JALSG[23]: imatinib + CHT	80	45 yr (15–64)	96	NA	60 at 1 yr (EFS)	76 at 1 yr	61
JALSG[24] (updated): imatinib + CHT	99	45 yr (15–64)	97	NA	50 at 5 yr	43 at 5 yr	61
PETHEMA[25]: imatinib + CHT	30	44 yr (8–62)	90	21 after induction	30 at 4 yr	30 at 4 yr	53
PETHEMA[26]: imatinib + low-dose CHT	29	38 yr (NA)	100	39 after induction	63 at 2 yr (EFS)	NA	90
NILG[27]: imatinib + CHT	59	45 yr (20.4–66)	92	25 at wk 10	39 at 5 yr	38 at 5 yr	57
Canada[28]: imatinib + CHT	32	46 yr (18–60)	94	10 after induction	50 at 3 yr (EFS)	53 at 3 yr	50
UKALL[29]: imatinib + CHT	175	42 yr (16–64)	92	NA	50 at 4 yr (RFS)	38 at 4 yr	46
GIMEMA[30]: imatinib only	29	69 yr (61–83)	100	4 after induction	48 at 1 yr	74 at 1 yr	NA
GIMEMA[31]: imatinib followed by CHT	49	45.9 yr (16.9–59.7)	100	NA	50 at 3 yr	69 at 3 yr	
MDACC[32] (updated): imatinib + CHT	45	51 yr (17–84)	93	20 after induction	43 at 5 yr	43 at 5 yr	18

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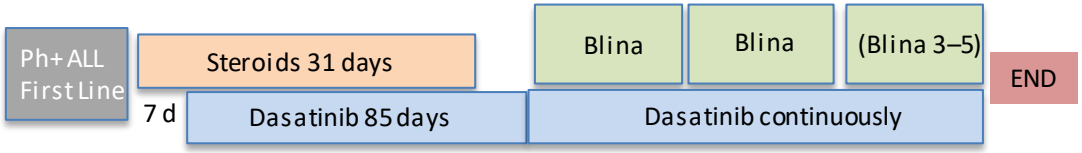
Blinatumomab in First-Line Ph-Positive ALL: D-ALBA Trial

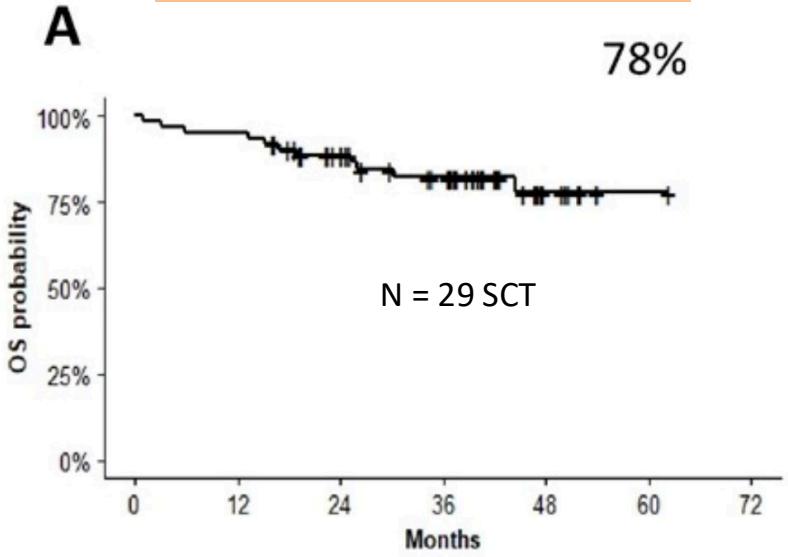
Foa, et al. *N Engl J Med.* 2020.



Update EHA 2022: Chiaretti, et al.

Evaluable: 63
Median Age: 54 (28–81) d
CR d 85 62 (98%)

	Dasa mono	Blina 1	Blina 2	Blina 3–5
Mol CR	10%	**35%**	42%	50-55%
Mol Response	29%	**64%**	60%	70-81%



Predictive: IKZF1-Plus, MRD Response

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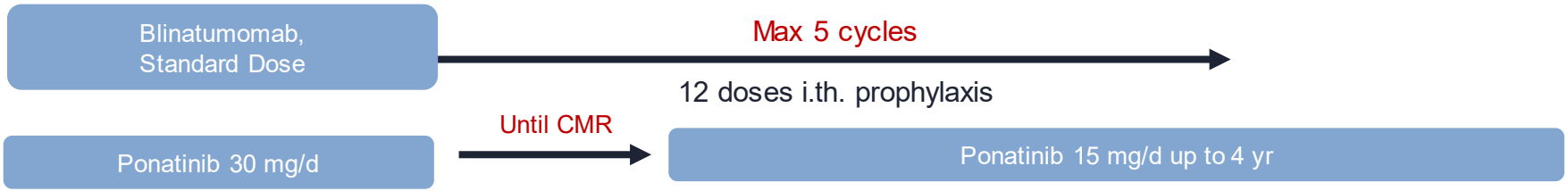
Ponatinib and Blinatumomab in First-Line Ph+ ALL

Short, et al. EHA 2022.

- Age ≥18 yr, **de novo Ph+ ALL or R/R Ph+ ALL or CML-LBP**



Patient Characteristics

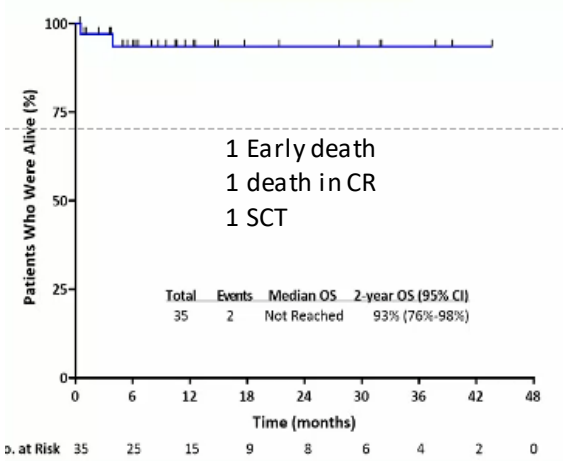
N	35
Age	51 (22–83)

*12/35 in CR at inclusion!

Response and Outcome De Novo

	De novo
CR/CRi (Total)	96 %
CMR (cycle 1/Total)	64% / 85 % 11/15 (73%) NGS -
EFS (2 yr)	93 %
OS (2 yr)	93 %

Overall Survival De Novo



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De Novo, Ph-Positive

- Risk stratification
- Reduction of SCT
- Post-transplant strategies for HR
- Integration of immunotherapy
- Definition of optimal TKI (tolerance and efficacy)

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Selection of Topics

1. Age Groups
2. Diagnostics
3. Risk Stratification
4. Younger Patients
5. Older Patients
6. Ph-Positive ALL
7. **Overarching Questions:**
   - Can Immunotherapy Replace Chemo?
   - Role of SCT
8. Personalized Medicine in ALL
9. Late Effects

Gökbuget 9/2021

Blinatumomab/Inotuzumab in First Line for Adult ALL

- Promising results from phase II trials, but without long-term follow-up
  - High CR rates
  - Trend to lower relapse rates
  - Still considerable morbidity/mortality in older pts
- Few randomized trials
- Costs/reimbursement?
- Available for all: MRD based Blinatumomab
- Role of CAR T: ± SCT, earlier lines, clinical trails
- Open questions
  - Can treatment intensity be reduced by immunotherapy
  - Combination of new compounds
  - Clinical trial designs
  - Reimbursement and marketing authorization

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Place of Allo HSCT in Adult ALL – Current Considerations

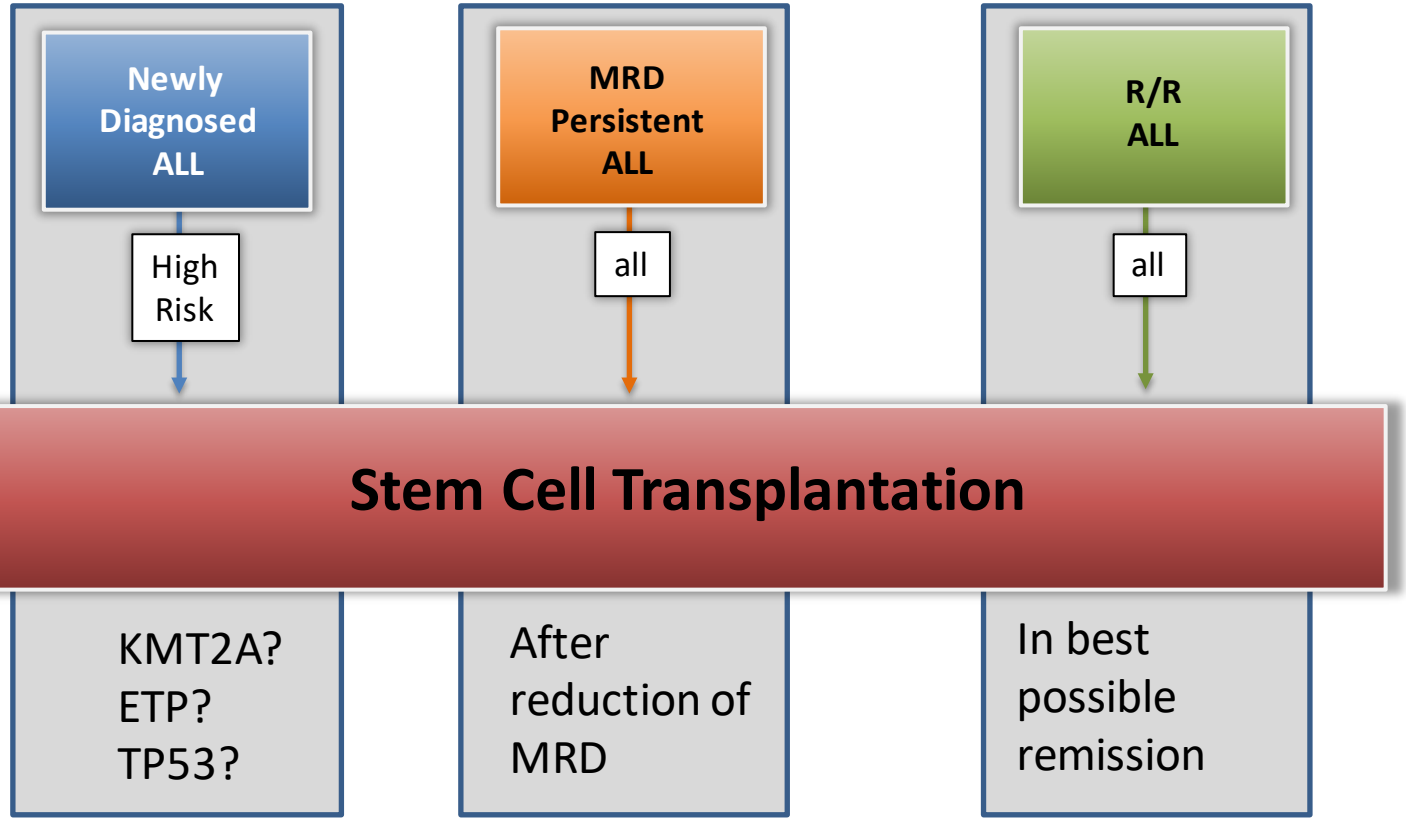
High risk definition
- Risk of relapse
- Risk of mortality

Timepoint of risk
- At diagnosis
- Later

Age

Type of chemo
Type of SCT

New compounds
- Antibodies
- BiTEs
- CARs



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Selection of Topics

1. Age Groups
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9. Late Effects

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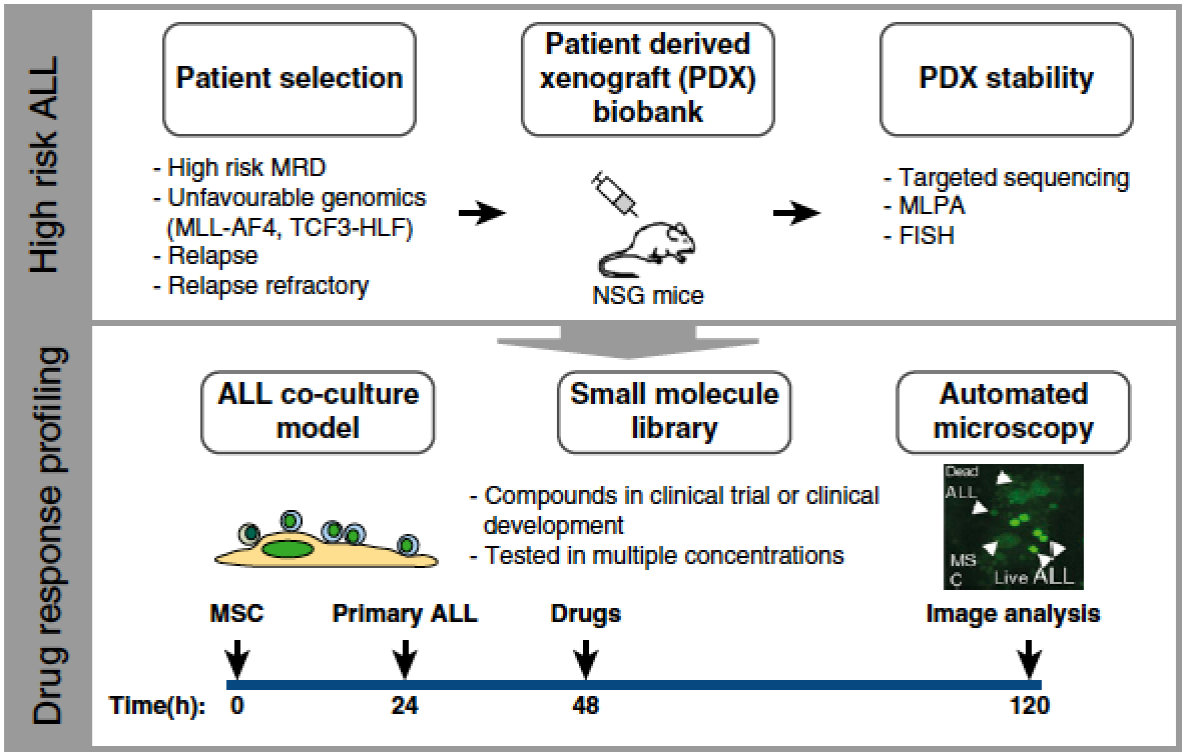
Ex Vivo Drug Response Profiling in Drug-Resistant ALL

Frismantas, et al. *Blood.* 2017.



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Ex Vivo Drug Response Profiling in Drug-Resistant ALL

Frismantas, et al. *Blood.* 2017.

- 60 drugs on 68 ALL, samples mostly from resistant disease
- Cocultures of bone marrow stromal cells
- Patient-derived xenografts retained the original pattern of mutations found

Exceptional Responses

- **BCL2-inhibitor** venetoclax was highly active in some ALLs predicting in vivo activity as a single agent and in combination with Dexa/VCR

- **Dasatinib** activity in 2 independent T-ALL cohorts
- A patient with refractory T-ALL was treated with dasatinib on the basis of drug profiling information and achieved a 5-month remission.

LEAP Consortium Trial in Pediatric HR or R/R Leukemias or MDS

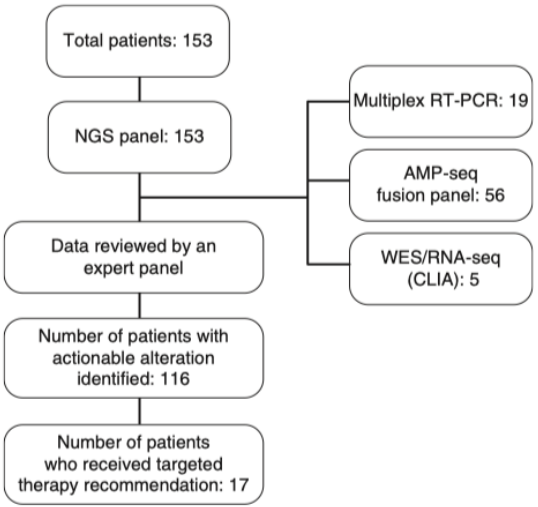
Pikman, et al. *Cancer Discovery.* 2021.

- 15 major institutions
- DNA-based NGS and RNA-based fusion testing
- Multidisciplinary tumor board
- Ex-vivo drug testing

ALL: 49 (56 relapse/4 newly diagnosed)
T-ALL 10/49

Druggable Leason → Board Recommendation

N = 153
Average turnaround
DNA: 5.2 days
RNA: 16.6 days
Board review: 15 days from results



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LEAP Consortium Trial in Pediatric HR or R/R Leukemias or MDS

Pikman, et al. *Cancer Discovery.* 2021.

Patient number	Disease	Target	Proposed drug or target/pathway inhibitor	Drug used	Tier	Toxicity attributed to targeted therapy	How targeted therapy was accessed?	Detected with NGS only
18	B-ALL, refractory	*EPOR-IGH*	Ruxolitinib	Ruxolitinib	3	None	Clinical trial (NCT02723994)	X
16	B-ALL, relapsed	*NRAS*	MEK inhibitor mTOR inhibitor	Everolimus	3 5	None	Off label	X
37	B-ALL, relapsed	*NUP214-ABL1*	Imatinib/dasatinib	Dasatinib	3	None	Off label	X
38	B-ALL, relapsed	*RCSD1-ABL2*	Imatinib/dasatinib	Imatinib	3	[a]	Off label	X
43	B-ALL, relapsed	*NRAS, KRAS*	MEK inhibitor	Trametinib	3	None	Off label	X
55	B-ALL, relapsed	*ABL1* p.T315I	Ponatinib	Ponatinib	1	None	FDA-authorized indication	X
153	B-ALL, relapsed	*TCF3-HLF*	Venetoclax	Venetoclax	3	[a]	Off label	

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Relapsed/Refractory ALL

- Sequential/combined therapies
- Role of CAR T cells
- Management of pts without SCT option
- Integration of further compounds
  - T-ALL
  - Targeted drugs
- New study designs and international trials

Gökbuget 9/2021

Selection of Topics

1. Age Groups
2. Diagnostics
3. Risk Stratification
4. Younger Patients
5. Older Patients
6. Ph-Positive ALL
7. Overarching Questions
8. Personalized Medicine in ALL
9. **Late Effects**

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GMALL Trial on Medical Conditions in Long Term Survivors (>5 yr) of ALL

GMALL Trials 02/84–07/03

Comorbidities (N = 538)

No comorbidity	**66%**
Skin	18%
Lung	8%
Cardiac	13%
Gastrointestinal	6%
Neurologic	**27%**
Kidney/Liver	10%
Eyes	12%
Endocrine (f/m)	24%/17%
Infections	12%
Fatigue	**13%**
GvHD	15%
Osteonecrosis	**8%**
Malignancy	**4%**
Hypothyreosis	5%
Hyperthyreosis	1%

ECOG (N = 522)

0	**70%**
1	**24%**
2	**4%**
3	**2%**
4	**<1%**

Gökbuget 9/2021

Gökbuget, et al. In revision.

Osteonecrosis in ALL: Pathogenesis and Risk Factors

Kuhlen, et al. *Blood Advances.* 2017.

Pathogenetic Mechanisms

Imbalance between the actual and the required bone perfusion,

- Intravascular clotting/embolism (intraluminal obliteration)
- Increased marrow pressure (extraluminal obliteration)
- Direct blood vessel injury
- Direct toxic effects on osteoblasts and osteocytes

Clinical Factors

- Female age (in children)
- Adolescent age

ALL Therapy

- Steroid (continuous exposure, dexa > pred)
- Asparaginase?
- Methotrexate

Hypertriglyceridemia
Hypertonia

Germline Polymorphisms

- Pharmacodynamics of chemotherapy
- Bone metabolism
- Adipogenesis
- Glutamate signaling pathway
- Mesenchymal stem cell differentiation

Incidence of Osteonecrosis in a Pediatric Regimen Used for Adults

Mogensen, et al. *Haematologica*. 2017.

Total:	1,489 ALL pts (1–45 yr)
Osteonecrosis:	N = 67 (4.5%)
Cum. Incidence* 5y:	6.3% (4.9–8.0%)

**Kaplan-Meier*

Risk factors:	
Adolescents vs children:	**20%** (15–27%) vs 2.2% (1.4-3.3%); p <.0001
Adults vs children:	**15%** (7.5–29%) vs 2.2% (1.4-3.3%); p <.0001
Adolescents vs adults:	Similar
Female vs male:	7.5 (5.5–10.0)% vs 5.2 (3.6–7.7)% ; p = 0.02

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Future Management of ALL

High volume of "privileged" centers

- All new drugs available
- All diagnostic tests available
- Clinical trials quickly established
- Motivated patients

Creative new regimens

Standard "first world" centers

- Drugs only in trials or if reimbursement is guaranteed
- Diagnostic tests
- Multicenter trials with long setup, high logistic challenges and long duration

Creation of accepted evidence

Standard "second- or third-world" centers

Can achieve a lot with "some" standards

Gökbuget 9/2021

Global Leukemia Academy

Interactive Discussion: Treatment Landscape Evolution

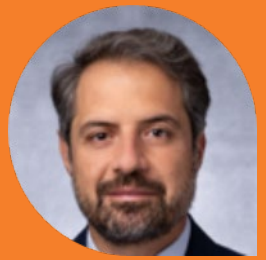
All faculty

APTITUDE HEALTH

Global Leukemia Academy

Session Close

Elias Jabbour



APTITUDE HEALTH

Question 1

What age group is considered elderly ALL patients?

1. ≥50 years
2. ≥55 years
3. ≥60 years
4. ≥65 years
5. ≥70 years

Question 2

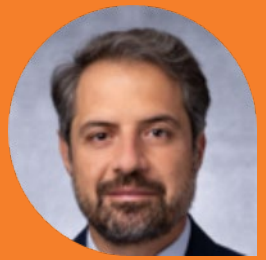
Which of the following is NOT true for treating ALL?

1. Inotuzumab and blinatumomab + chemotherapy has produced 90% CR rates in salvage therapy and in first line in older patients
2. Blinatumomab and ponatinib can be used as a chemotherapy-free regimen in Ph+ ALL
3. MRD– CR does not correlate strongly with outcome
4. Since 1999, median survival for ALL patients older than 60 has been increasing with each successive decade

Global Leukemia Academy

Closing Remarks

Elias Jabbour



APTITUDE HEALTH

Virtual Breakout – AML Sessions (Day 2)

24 September 2022, 14.30 – 17.15 CEST

Chairs: Dr Gail J. Roboz/Dr Naval Daver

Time (CEST)	Title	Speaker
14.30 – 14.40	**Session Open**	Gail J. Roboz and Naval Daver
14.40 – 15.00	**Personalized Induction and Maintenance Approaches for AML**	Gail J. Roboz
15.00 – 15.25	**Fit and Unfit AML Patients: How Do We Distinguish? How Do We Treat Differently?**	Agnieszka Wierzbowska
15.25 – 16.05	**AML Case-Based Panel Discussion** • Relapsed/Refractory Case 1 • Relapsed/Refractory Case 2	Moderators: Gail J. Roboz and Naval Daver Agnieszka Pluta Anna Torrent All faculty
16.05 – 16.15	***Break***	
16.15 – 16.40	**Optimizing Management of Relapsed/Refractory AML**	Naval Daver
16.40 – 17.05	**Interactive Discussion: Treatment Landscape Evolution**	Moderators: Gail J. Roboz and Naval Daver All faculty
17.05 – 17.15	**Session Close**	Gail J. Roboz and Naval Daver

Thank you!

- Thank you to our sponsors, expert presenters, and to you for your participation
- Please complete the **evaluation link** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the globalleukemiaacademy.com website within a few weeks
- If you have a question for any of our experts that was not answered today, you can submit it through the GLA website in our Ask the Experts section

THANK YOU!

Global Leukemia Academy

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

APTITUDE HEALTH