Global Leukemia Academy

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

October 16–17, 2024

Meeting sponsors AMGEN rigel

APTITUDE HEALTH®

Global Leukemia Academy

Welcome to Day 2

Naval Daver

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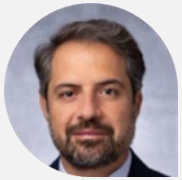
Meet the Faculty

CHAIR



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

CO-CHAIR

Naval Daver, MD
MD Anderson Cancer Center,
Houston, TX, USA

FACULTY

Nicola Gökbuget, MD
University Hospital Frankfurt
Frankfurt, Germany

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

Charles Craddock, CBE, FRCP (UK), FRCPath, DPhil
University of Birmingham
Queen Elizabeth Hospital
Birmingham, UK

Objectives of the Program

- Understand current treatment patterns for acute leukemias including incorporation of new technologies
- Uncover when genomic testing is being done for acute leukemias, and how these tests are interpreted and utilized
- Understand the role of stem cell transplantation in acute leukemias as a consolidation in first remission
- Comprehensively discuss the role of MRD in managing and monitoring acute leukemias
- Gain insights into antibodies and bispecifics in ALL: what are they? When and how should they be used? Where is the science going?
- Discuss the evolving role of ADC therapies in acute leukemias
- Review promising novel and emerging therapies in acute leukemias
- Explore regional challenges in the treatment of acute leukemias across Europe

Agenda: Day 2

Time UTC+2	Title	Speaker
18.30 – 18.40	Welcome to Day 2	Naval Daver
18.40 – 19.00	Current treatment options for relapsed ALL in adult and elderly patients	Elias Jabbour
19.00 – 19.20	Long-term safety considerations for leukemias (focus on ALL)	Nicola Gökbuget
19.20 – 19.40	Current and future role of transplantation in acute leukemias in Europe	Josep-Maria Ribera
19.40 – 19.50	Break	
19.50 – 20.10	Current treatment options for relapsed AML in adult and elderly patients	Charles Craddock
20.10 – 20.40	AML case-based panel discussion • Case 1 AML: Vitor Botafogo (Spain) • Case 2 AML: Samantha Drummond (UK)	Naval Daver Patient case presenters Panelists: All faculty
20.40 – 21.20	Panel discussion: How treatment in first line influences further therapy approaches in ALL and AML • Will CAR T and bispecifics change the treatment landscape? • Role of HSCT – is it still necessary? • What does the future look like? Adoption of therapies and evolving standards of care in Europe	Naval Daver and all faculty
21.20 – 21.30	Session close	Naval Daver

Question 1

What age group is considered elderly for patients with AML?

A. ≥50 years
B. ≥55 years
C. ≥60 years
D. ≥65 years
E. ≥70 years

Question 2

How do you assess MRD for ALL?

A. Multicolor flow
B. Molecular PCR
C. Next-generation sequencing platform
D. We do not check for MRD

Question 3

Which of the following is NOT true for ALL?

A. Inotuzumab and blinatumomab plus chemotherapy is active in both front line and salvage for ALL

B. Kinase inhibitors can be combined with other therapy modalities in Ph+ ALL

C. MRD is highly prognostic for relapse and survival in Ph– ALL

D. There are no effective consolidation treatments for patients who remain MRD+ after induction therapy

Question 4

The prognosis of patients with R/R AML depends on:

A. Age
B. Prior therapy (eg, HSCT)
C. Timing of relapse
D. The mutational and cytogenetic profile of the disease
E. All of the above
F. A and D

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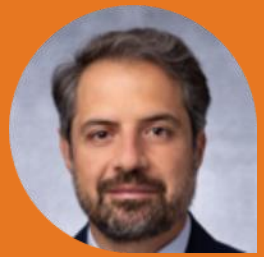
Current treatment options for relapsed ALL in adult and elderly patients

Elias Jabbour



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Adults With R/R Acute Lymphocytic Leukemia in 2024: Immunotherapies and Sequencing of CD19-Targeted Therapies

Elias Jabbour, MD

Department of Leukemia

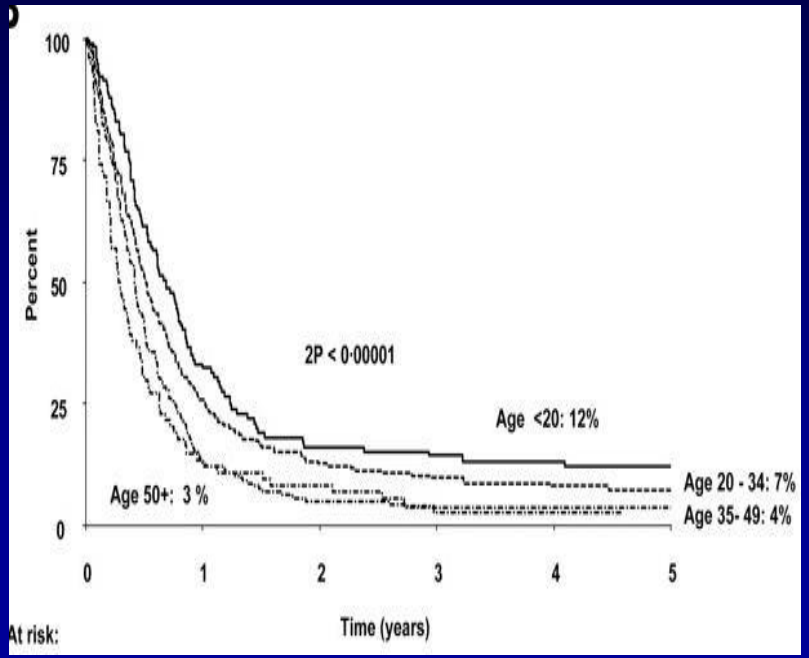
The University of Texas MD Anderson Cancer Center, Houston, USA

Fall 2024

ALL – Historical Survival Rates After First Relapse

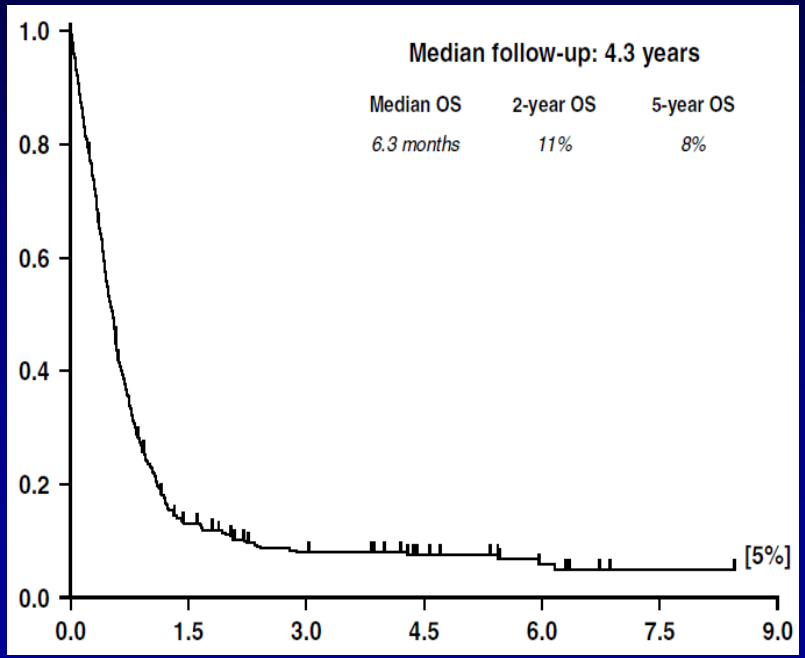
MRC UKALL2/ ECOG2993 Study (n = 609)[1]

Outcome of patients after 1st relapse
5-yr OS: 7%



LALA-94 Study (n = 421)[2]

Outcome of patients after 1st relapse
2-yr OS: 11% and 5-yr OS: 8%



1. Fielding AK, et al. *Blood*. 2007;109:944-950; 2. Tavernier E, et al. *Leukemia*. 2007;21:1907-1914.

Historical Results in R/R ALL

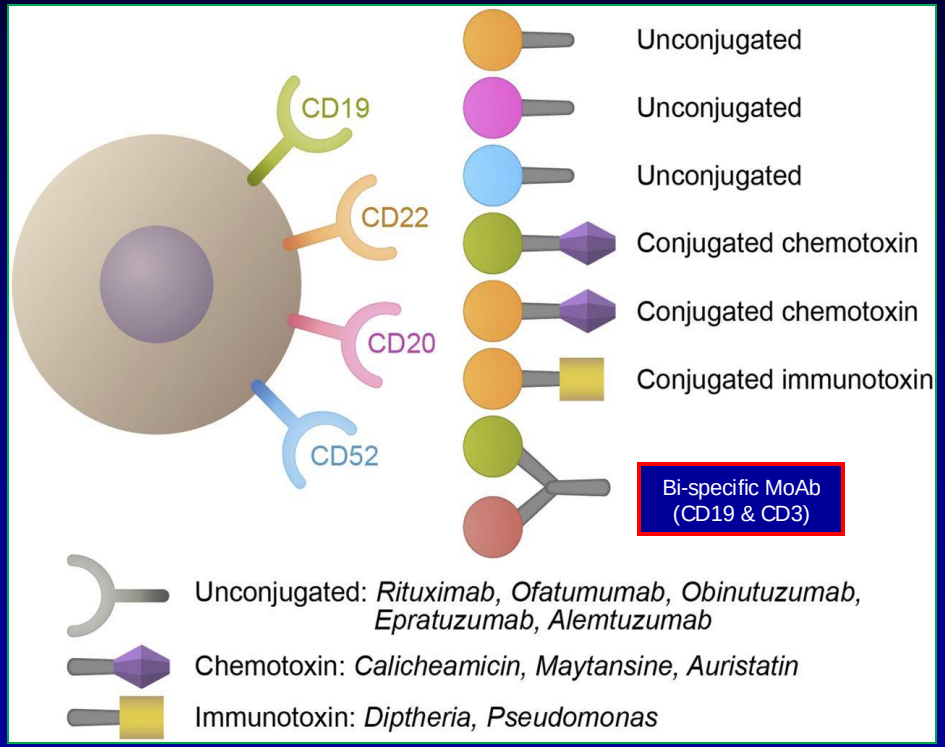
- Poor prognosis in R/R ALL Tx with standard of care (SOC) chemotherapy

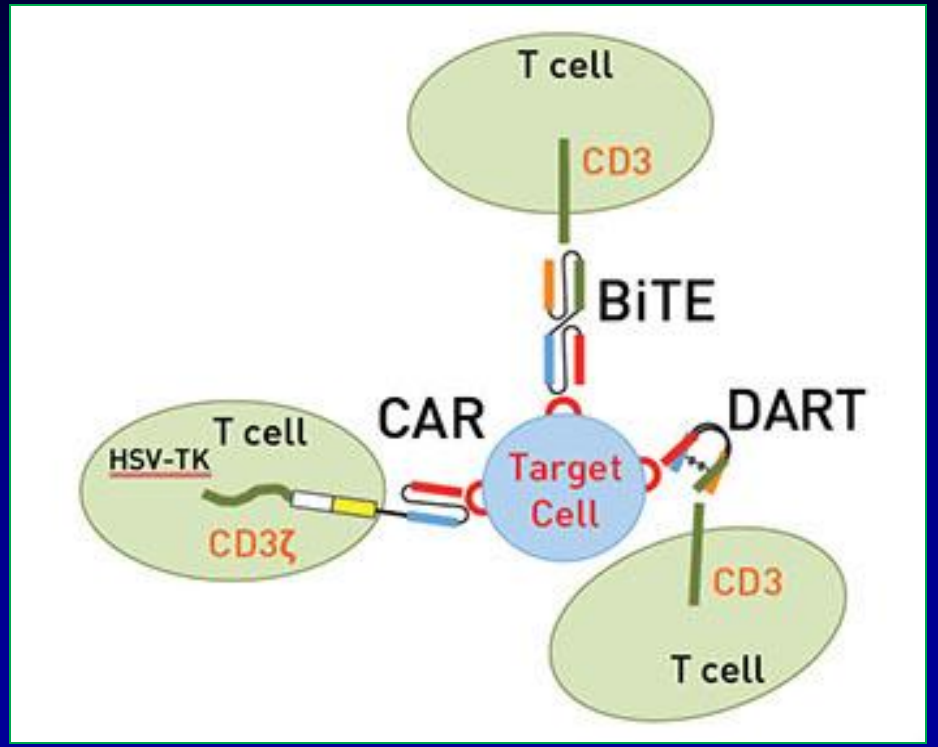
Rate (95% CI)	No Prior Salvage (S1)	One Prior Salvage (S2)	≥2 Prior Salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.7	3.4	2.9

Gökbuget N, et al. *Haematologica.* 2016;101:1524-1533.

Immuno-Oncology in ALL

- **Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR T cells**



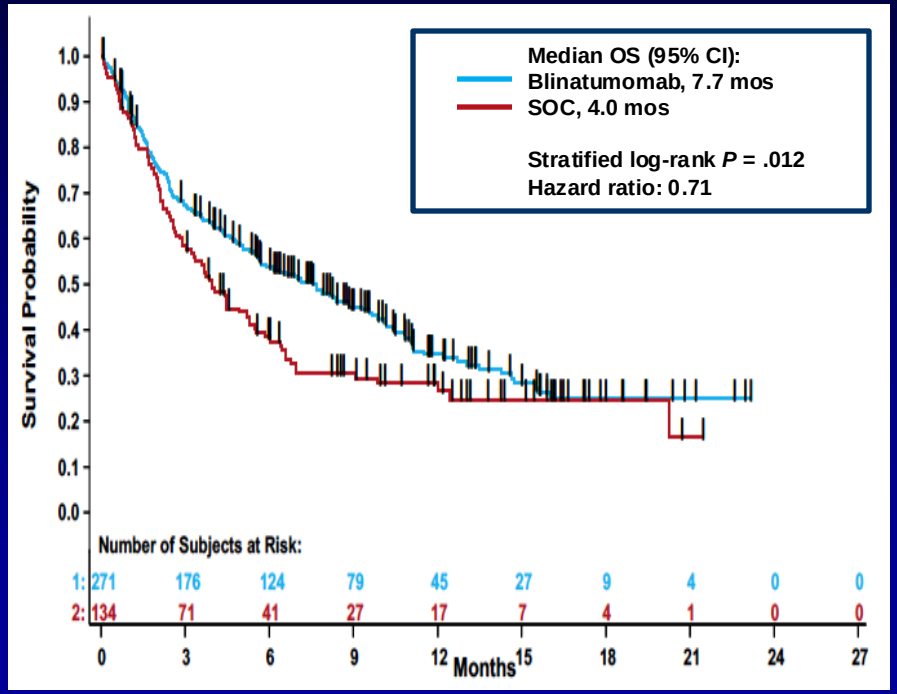


Jabbour E, et al. *Blood.* 2015;125:4010-4016.

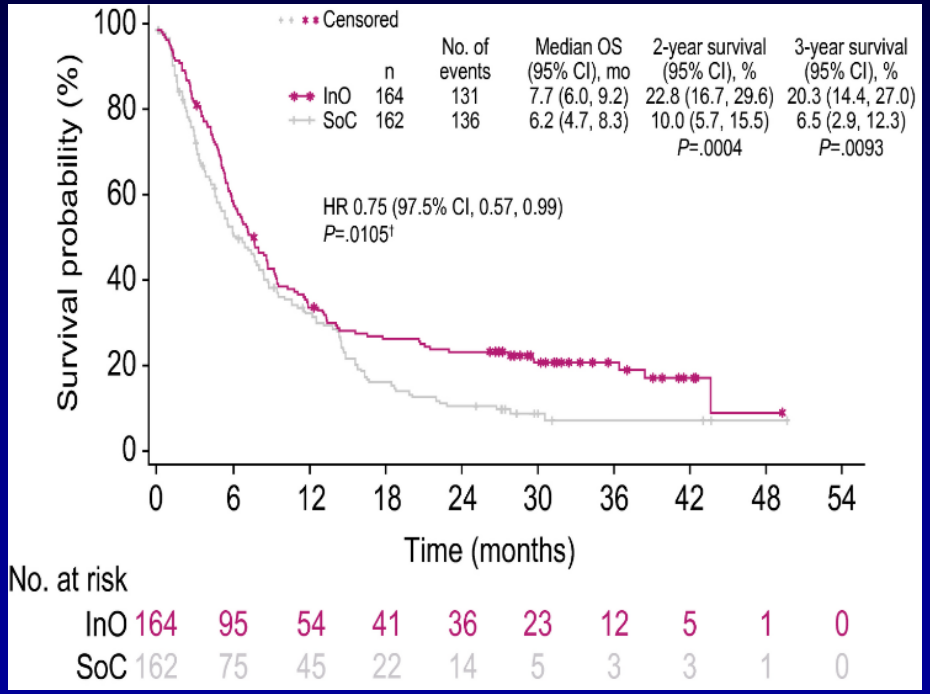
Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

- **Marrow CR**

Blina vs SOC: 44% vs 25%[1]

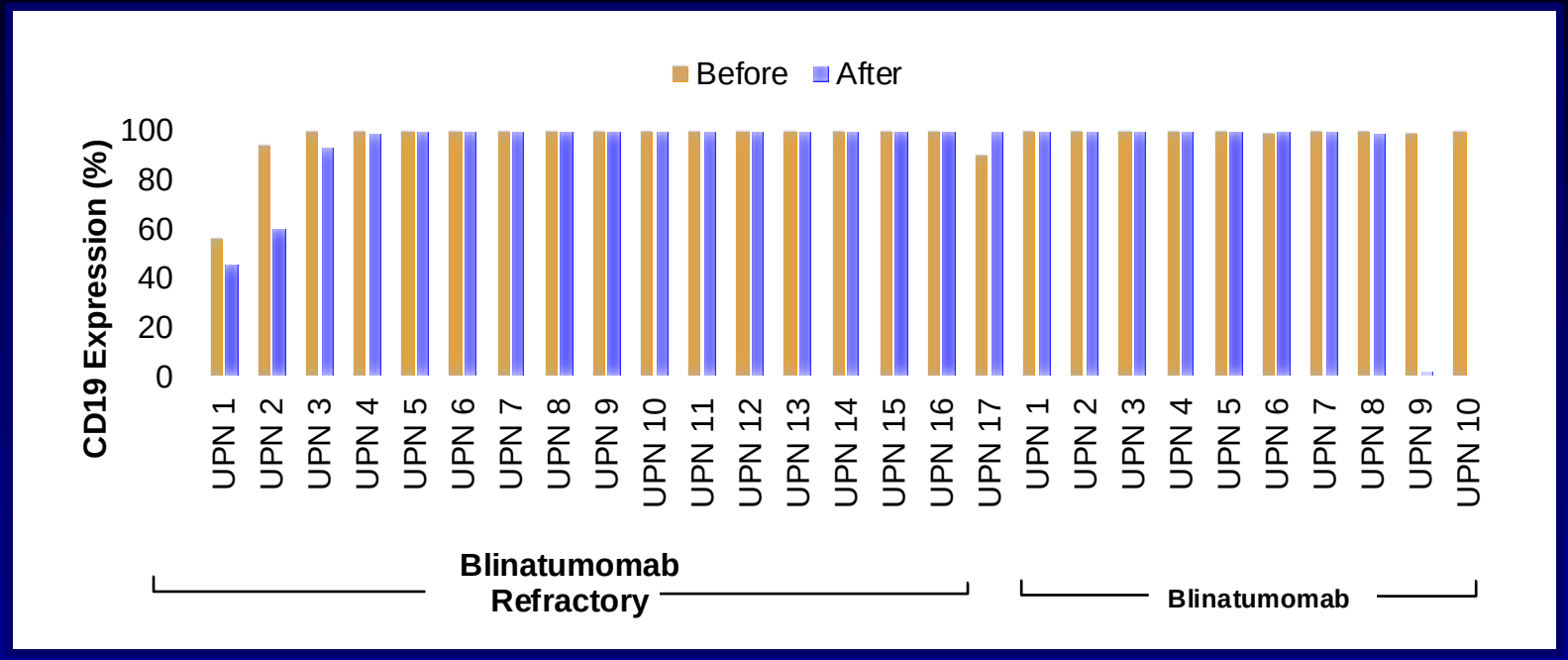


Ino vs SOC: 74% vs 31%[2,3]



1. Kantarjian H, et al. *N Engl J Med*. 2017;376:836-847; 2. Kantarjian H, et al. *N Engl J Med*. 2016;375:740; 3. Kantarjian H, et al. *Cancer*. 2019;125(14):2474-2487.

CD19 (%) Expression Before and After Blinatumomab Therapy

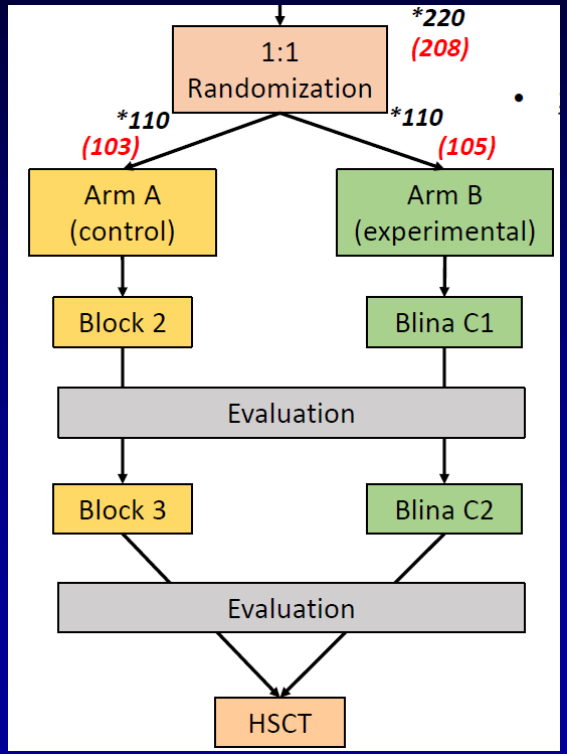


- **61 patients evaluated for immunophenotype; 56 (92%) had CD19-positive disease**
  - 5 (8%) had ALL recurrence with CD19-negative disease
  - 2 patients experienced progression with lower CD19-positive disease

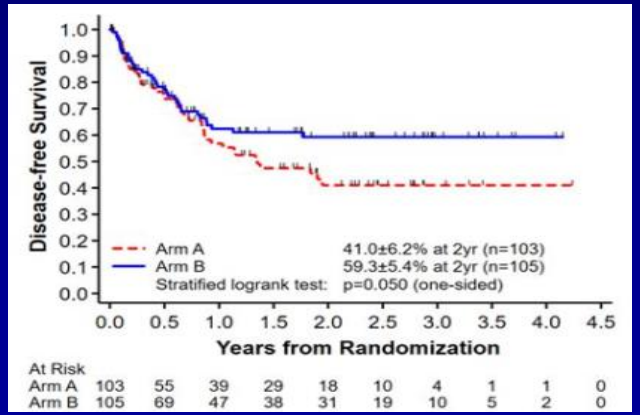
Jabbour E, et al. *Am J Hematol.* 2018;93:371-374.

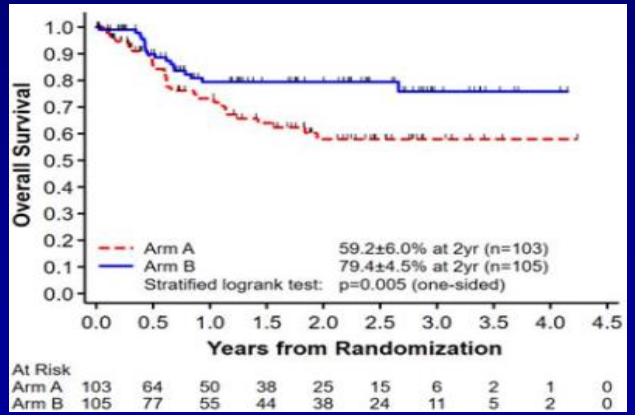
Phase III Study of Blinatumomab vs ChemoRx in Children/AYA in Salvage 1

- 208 pts HR/IR randomized 1:1 to blina (n = 105) vs chemoRx (n = 103) post Block 1 reinduction



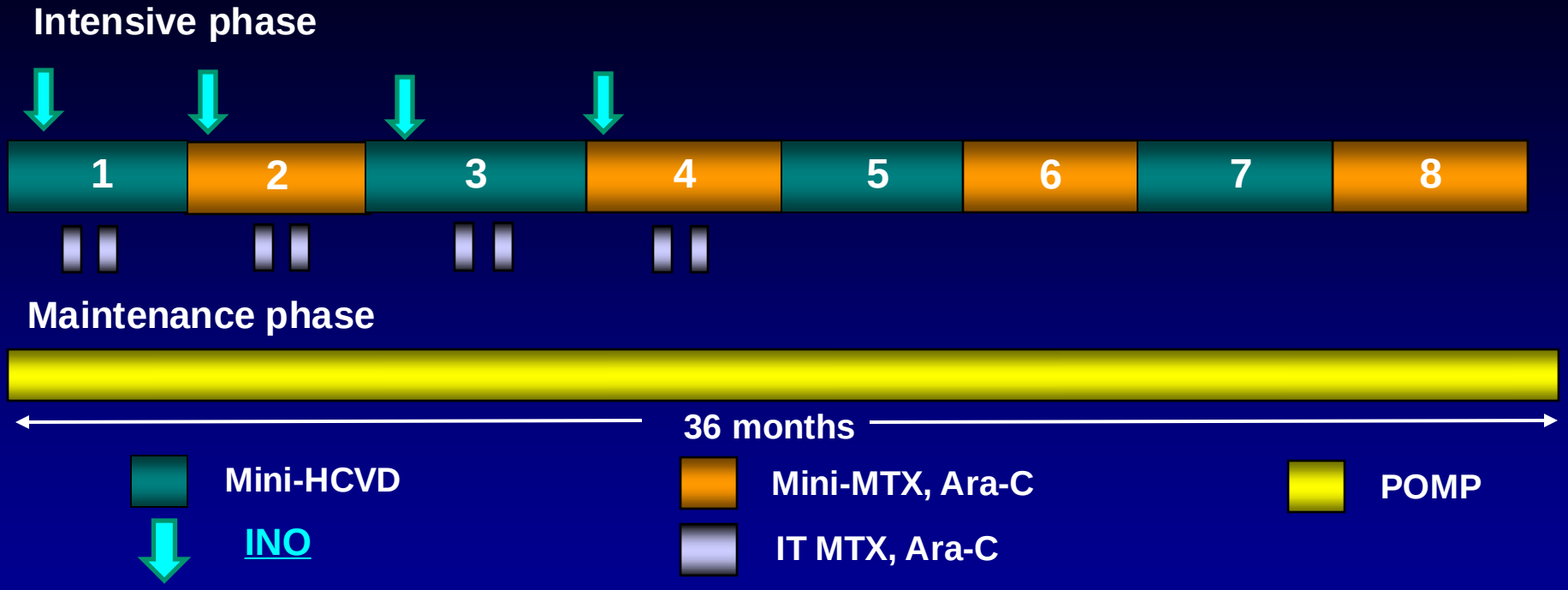
Parameter	Blina	Chemo	*P* Value
2-yr DFS, %	59	41	.05
2-yr OS, %	79	59	.005
SCT, %	70	43	<.001
MRD clearance, %	75	32	<.001





Brown PA, et al. *JAMA*. 2021;325:833-842; Brown PA, et al. ASH 2019. Abstract LBA-1 and oral presentation.

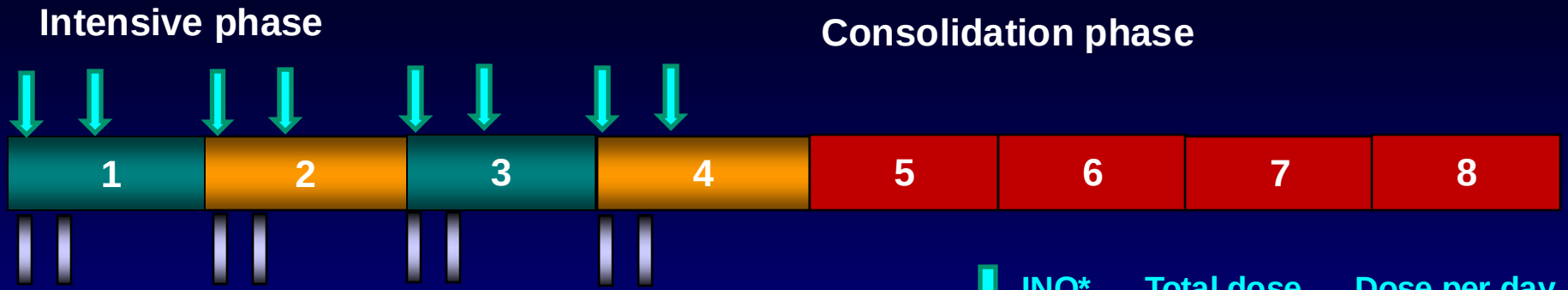
Mini-HCVD + INO ± Blina in R/R B-ALL: Original Design (Pts #1–67)



INO	First 6 pts	7 to 34	35+
C1 (mg/m^2)	1.3	1.8	1.3
C2–4 (mg/m^2)	0.8	1.3	1.0

Short N, et al. EHA 2023; Abstract S119 and oral presentation.

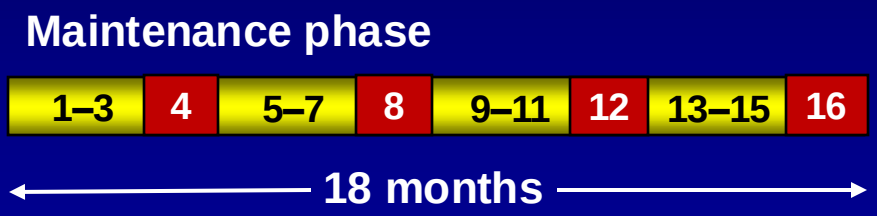
Mini-HCVD + INO ± Blina in R/R B-ALL: Modified Design (Pts #68–110)



INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m²

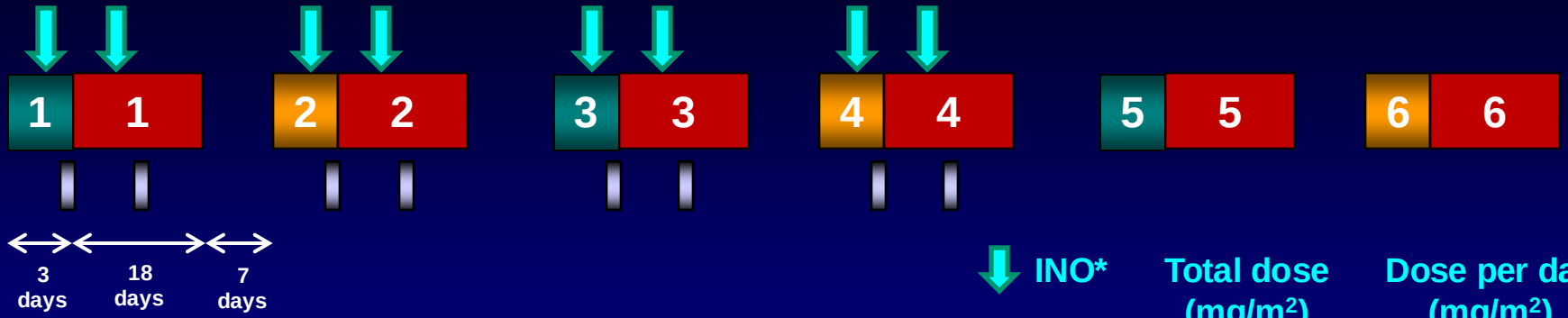
*Ursodiol 300 mg tid for VOD prophylaxis



Mini-HCVD
Mini-MTX, Ara-C
Blinatumomab
IT MTX, Ara-C
POMP

Short N, et al. EHA 2023; Abstract S119 and oral presentation.

Mini-HCVD + INO ± Blina in R/R B-ALL: "Dose-Dense" Design (Pts #111–125+)



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Total INO dose = 2.7 mg/m²

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Maintenance phase

Mini-HCVD

Mini-MTX, Ara-C

Blinatumomab

IT MTX, Ara-C

POMP

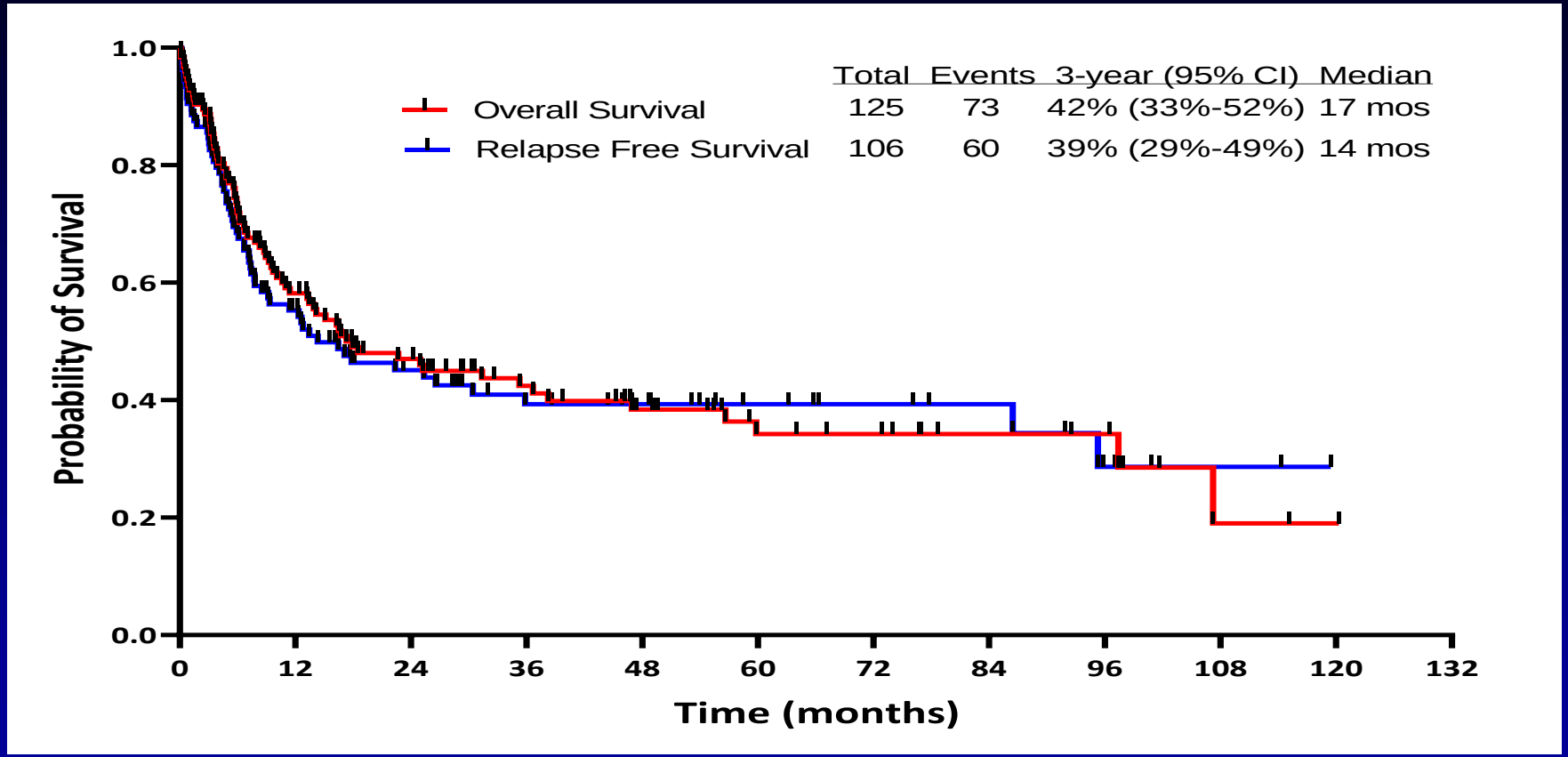
Short N, et al. EHA 2023; Abstract S119 and oral presentation.

Mini-HCVD + INO ± Blina in R/R B-ALL: MRD Negativity Rates

MRD Negativity by Flow Cytometry	N (%)			
	Overall (N = 125)	Before Blinatumomab (n = 67)	After Blinatumomab (n = 43)	Dose Dense (n = 15)
All patients				
End of cycle 1	53/100 (53)	25/49 (51)	18/38 (47)	10/13 (77)
Overall	87/102 (85)	41/50 (82)	34/39 (87)	12/13 (92)
Salvage 1				
End of cycle 1	45/82 (55)	22/34 (65)	17/37 (46)	8/11 (73)
Overall	73/83 (88)	31/35 (89)	32/37 (86)	10/11 (91)
Salvage 2+				
End of cycle 1	6/18 (33)	3/15 (20)	1/1 (100)	2/2 (100)
Overall	14/19 (74)	10/15 (67)	2/2 (100)	2/2 (100)

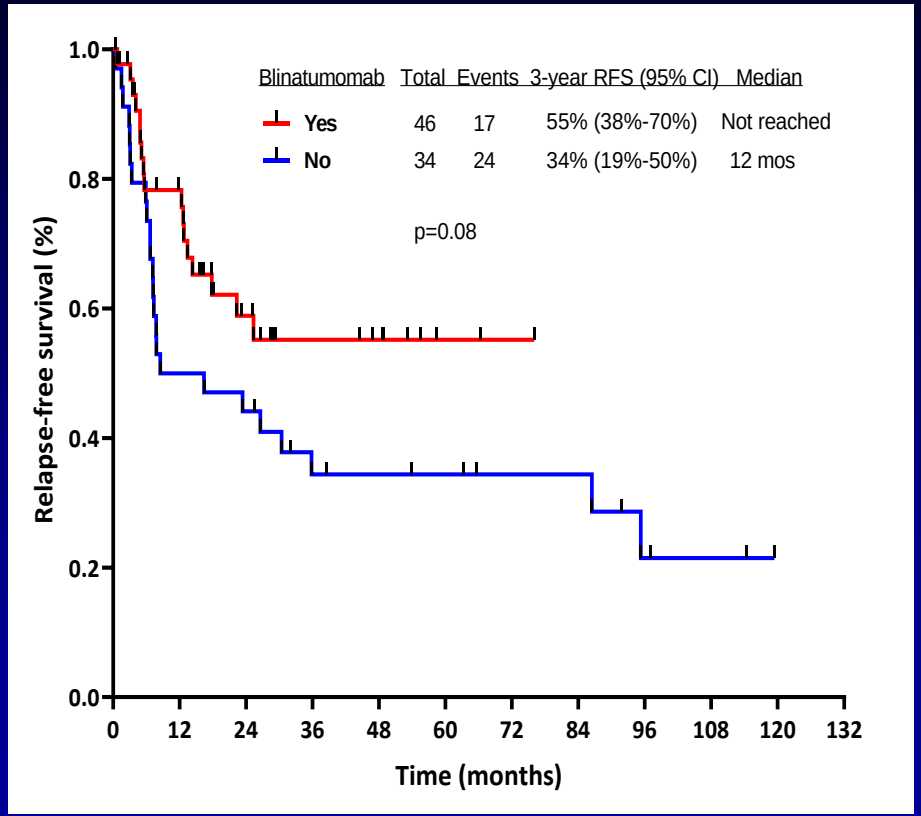
Short N, et al. EHA 2023; Abstract S119 and oral presentation.

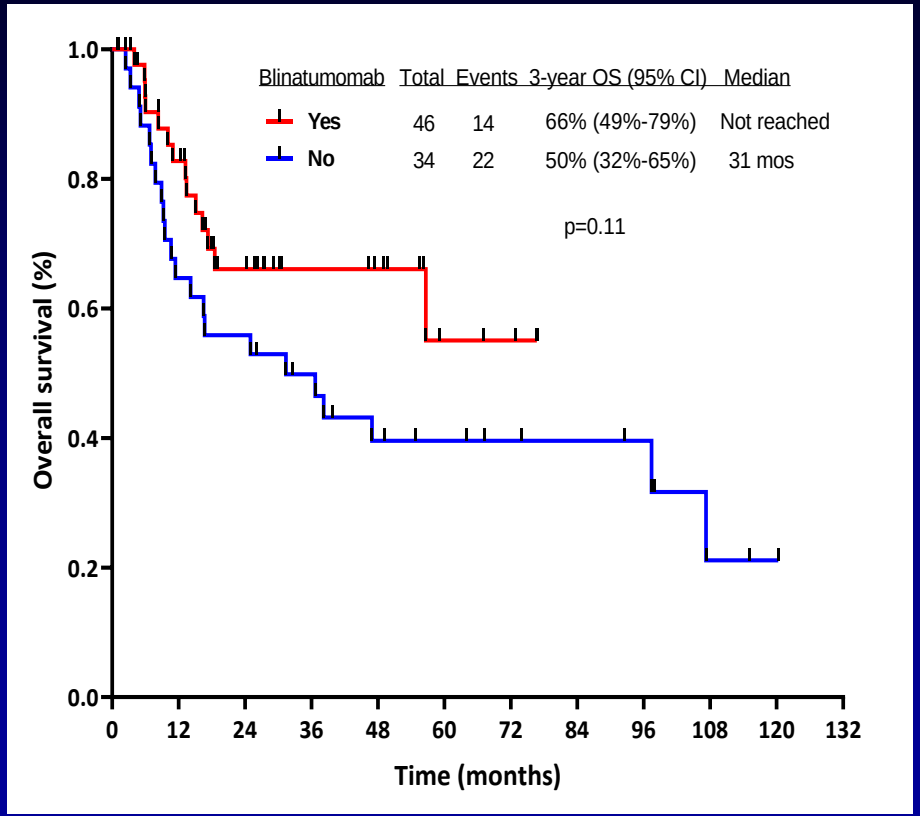
Mini-HCVD + INO ± Blina in R/R B-ALL: RFS and OS (Entire Cohort)



Short N, et al. EHA 2023; Abstract S119 and oral presentation.

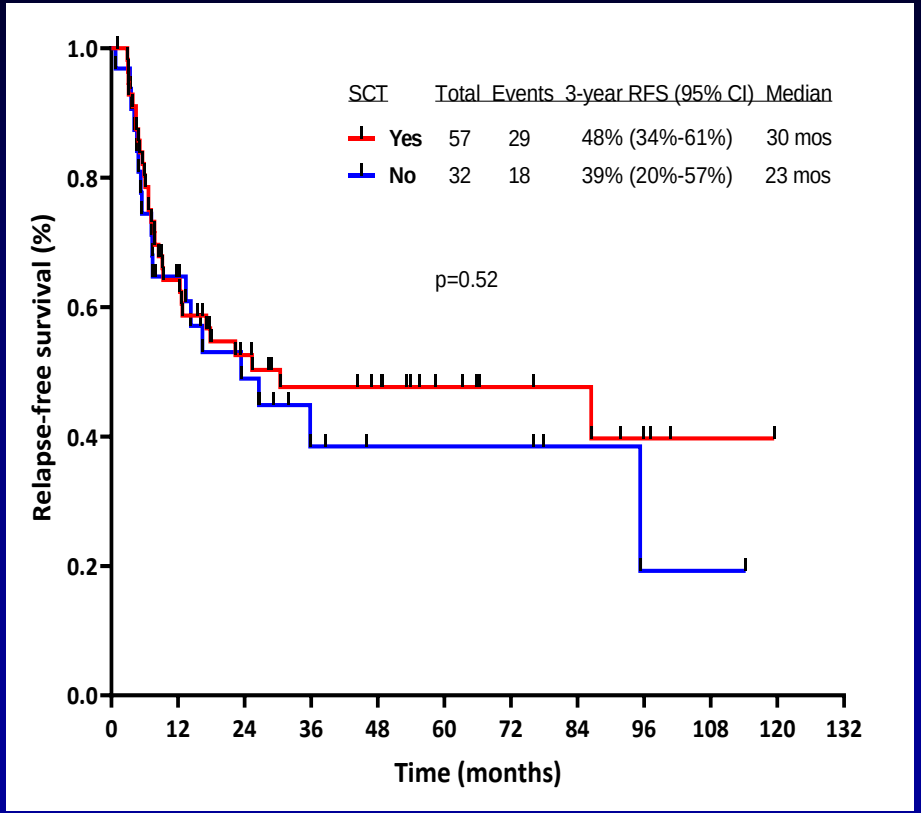
Mini-HCVD + INO ± Blina in R/R B-ALL: OS and RFS by Receipt of Blinatumomab (Salvage 1 Only)

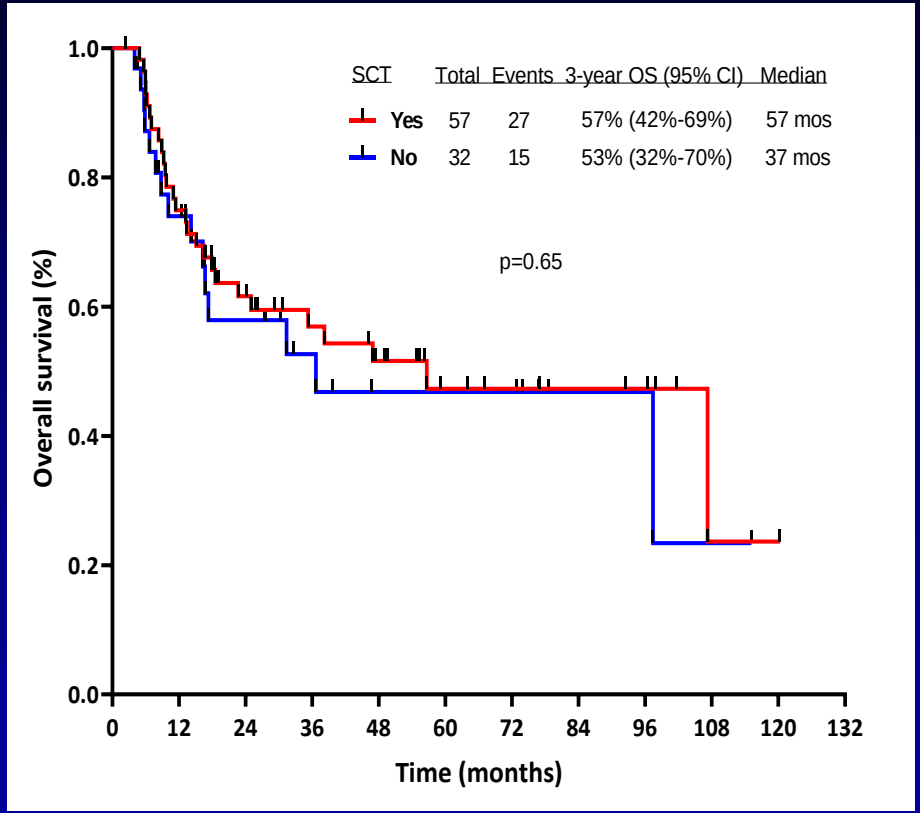




Short N, et al. EHA 2023; Abstract S119 and oral presentation.

Mini-HCVD + INO ± Blina in R/R B-ALL: OS and RFS by HSCT (Landmark Analysis)

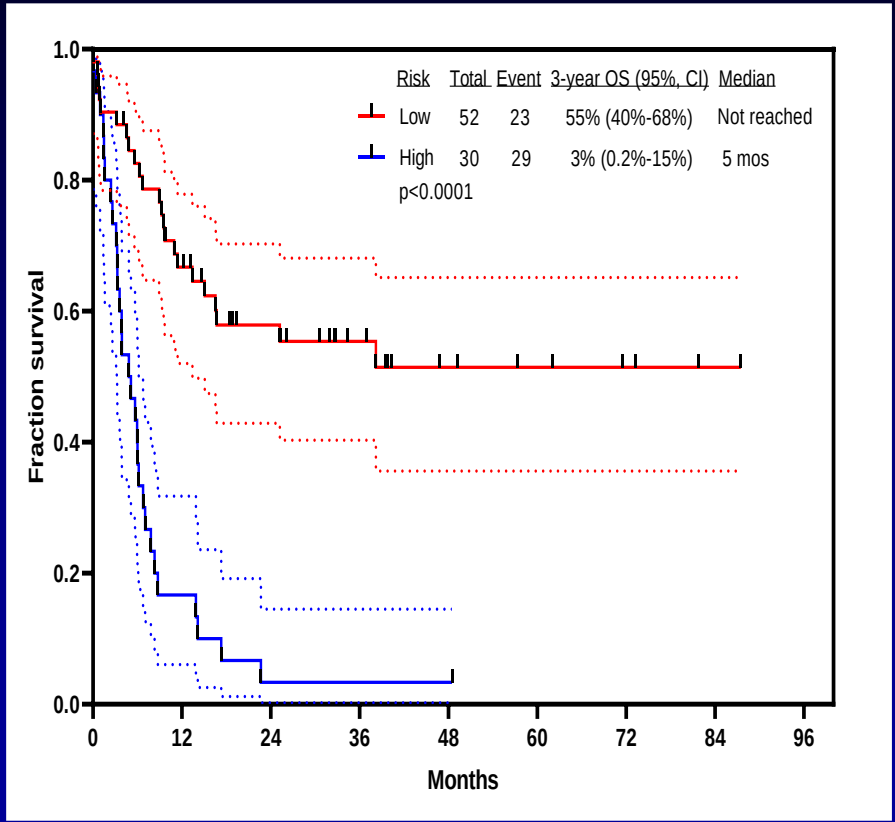




Short N, et al. EHA 2023; Abstract S119 and oral presentation.

Model: mHCVD + INO ± Blina in R/R ALL – a Prognostic Model for Survival

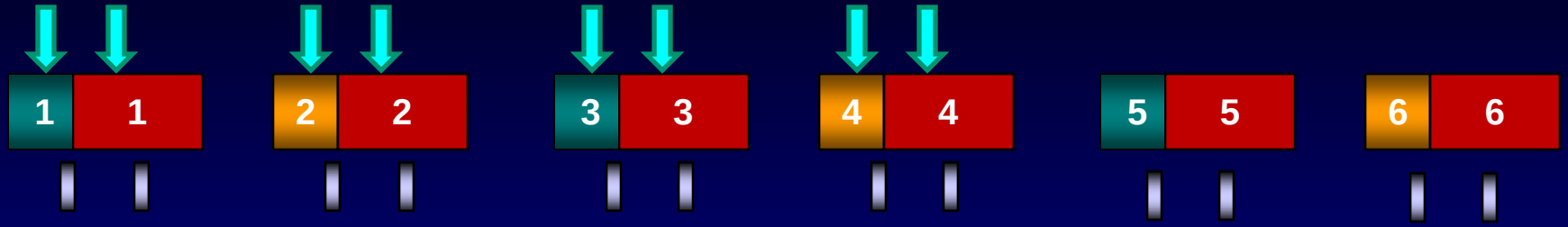
Variable	Risk Classification	
	Low*	High**
% CD22	≥70%	<70%
Cytogenetic	Diploid, complex, others	11q23 rearrangements Ho-Tr



*Low risk required all low-risk criteria.
**High risk required any one of high-risk criteria.

Sasaki Y, et al. *Blood*. 2020;136(suppl 1):abstract 1899.

“Dose-Dense” Mini-HCVD + INO + Blina in R/R B-ALL: Design



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C1	0.9	0.6 D2, 0.3 D8
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*Ursodiol 300 mg tid for VOD prophylaxis

Maintenance phase

Mini-HCVD

Mini-MTX-Ara-C

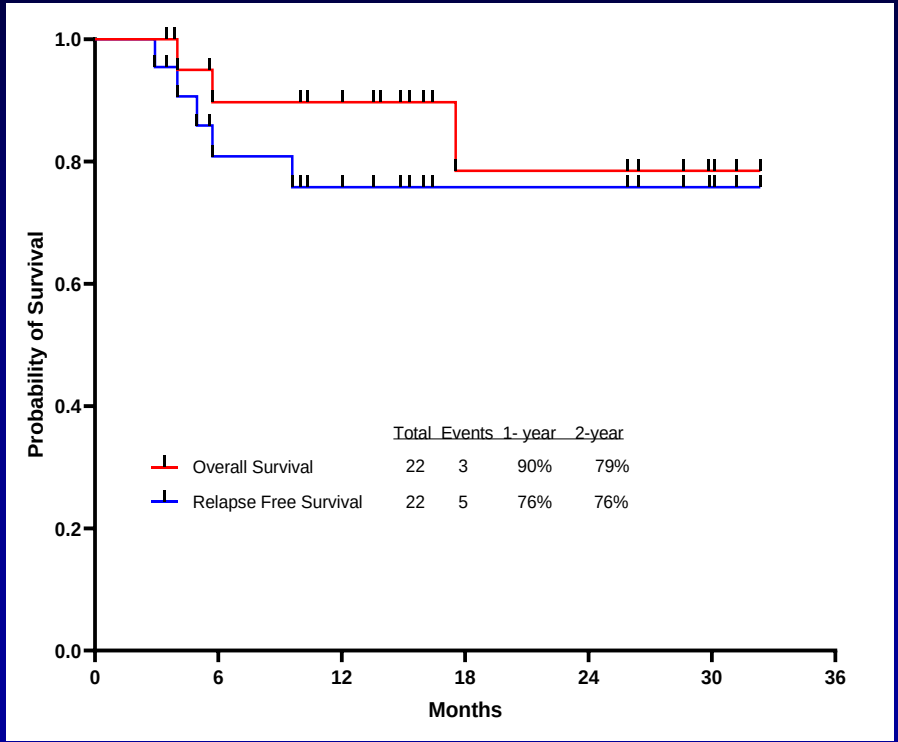
Blinatumomab

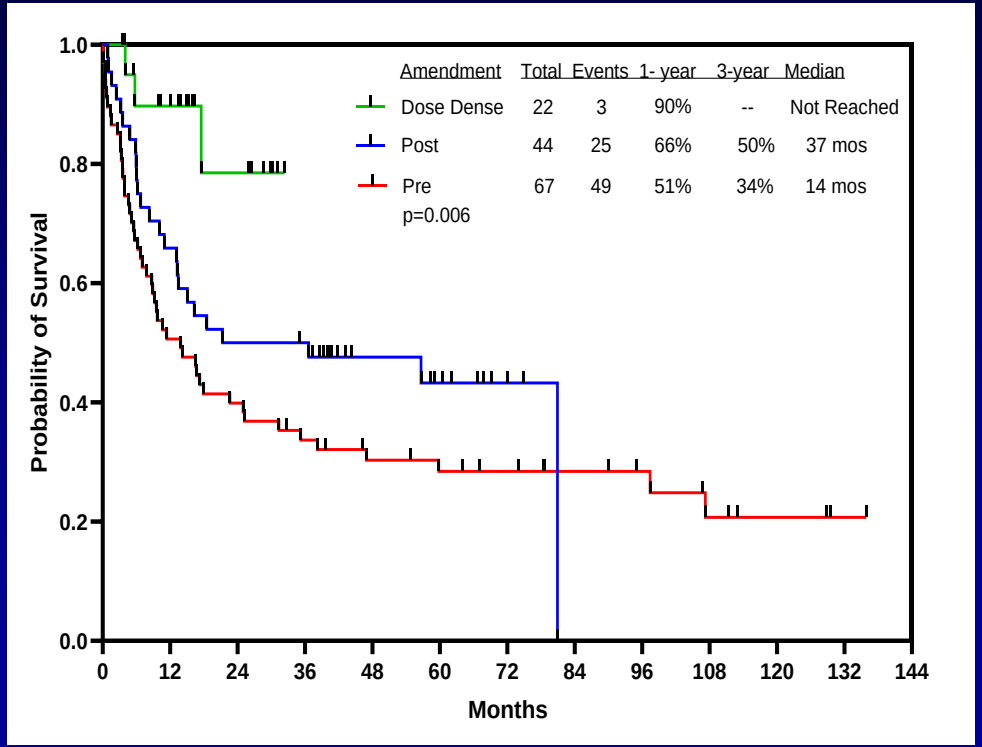
IT MTX, Ara-C

POMP

“Dose-Dense” Mini-HCVD + INO + Blina in R/R B-ALL

- 22 pts median age 41 yrs (19–62) Rx; 86% S1
- ORR 100% -- CR 81%; MFC-MRD negative 95% (74% after C1); NGS-MRD negative 94%
- Median F/U 15 months: 2-year OS 79%; 2-year RFS 76%





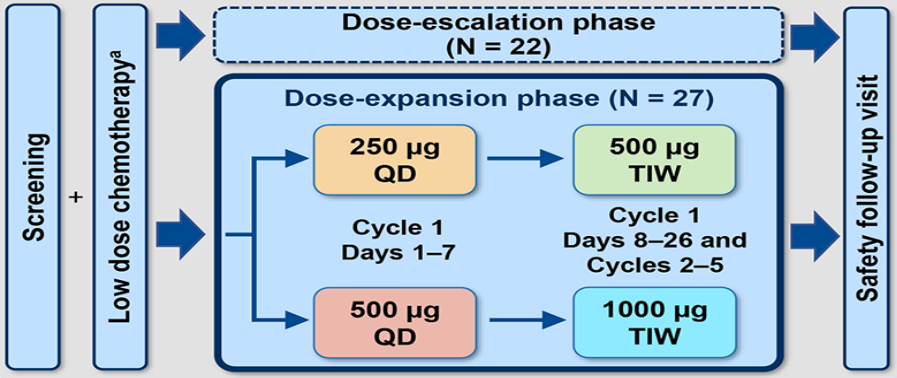
Single Agent Subcutaneous Blinatumomab for Advanced Acute Lymphoblastic Leukemia

Results from the expansion phase of a phase 1b trial

Objective

To assess the efficacy and safety of subcutaneous blinatumomab in heavily pretreated adults with R/R B-ALL at two doses

Study Schema



Results

Efficacy

250 µg QD/500 µg TIW (N = 14)
- CR/CRh: 85.7%
- MRD-neg CR/CRh: 75%

500 µg QD/1000 µg TIW (N = 13)
- CR/CRh: 92.3%
- MRD-neg CR/CRh: 100%

Dosing regimen 500 µg QD/1000 µg TIW demonstrated higher MRD-negative CR/CRh within 2 cycles (100%) compared with dosing regimen 250 µg QD/500 µg TIW (75%)

Safety

250 µg QD/500 µg TIW (N = 14)
- Grade ≥3 CRS[b]: 21.4%
- Grade ≥3 NE[b]: 42.9%

500 µg QD/1000 µg TIW (N = 13)
- Grade ≥3 CRS[b]: 23.1%
- Grade ≥3 NE[b]: 23.1%

- SC injections were well tolerated
- No treatment-related grade 4 CRS or NE

Conclusion

Treatment with single agent SC blinatumomab resulted in a high CR rate, high MRD-negativity rate, and an acceptable safety profile in heavily pretreated adults with R/R B-ALL

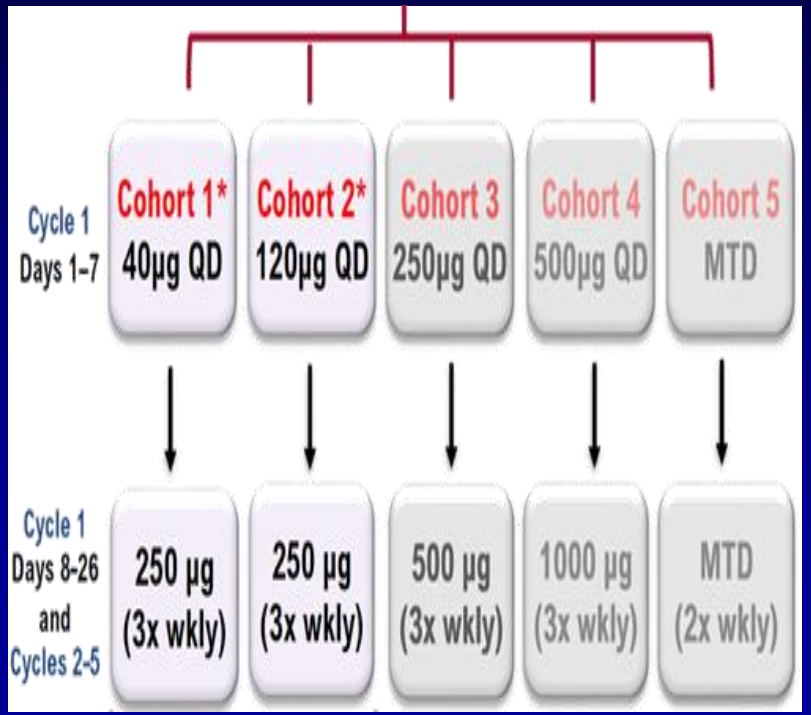
Jabbour E, et al. *Am J Hematol.* 2024;99(4):586-595.

Subcutaneous Blinatumomab in R/R ALL

- 49 R/R pts – dose escalation 22, dose expansion 27
- BLINA 40, 120, 250, 500 mcg SQ daily ×7, then 250 mcg TIW in Cohorts 1 and 2 and 500 mcg in Cohort 3 and 1000 mg in Cohort 4

Cohort	Rx	% marrow CR	% MRD-negative
3 – 250/500	14	86	75
4 – 500/1000	13	92	100

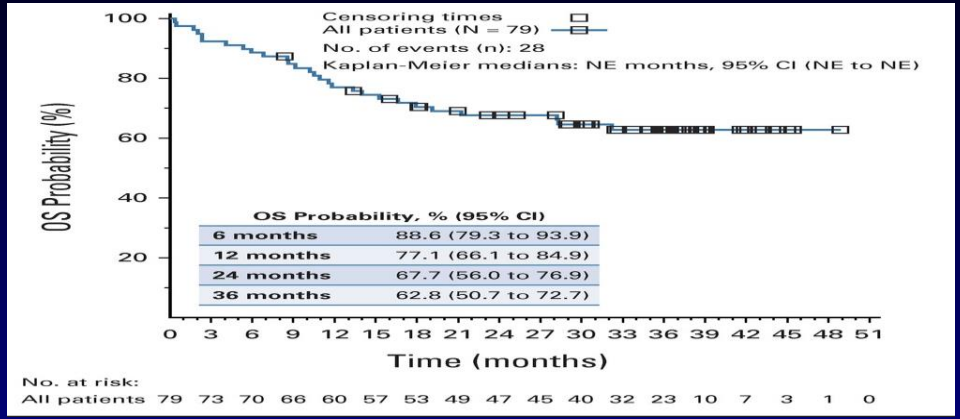
- G3 CRS 22%; G3 CNS 22%

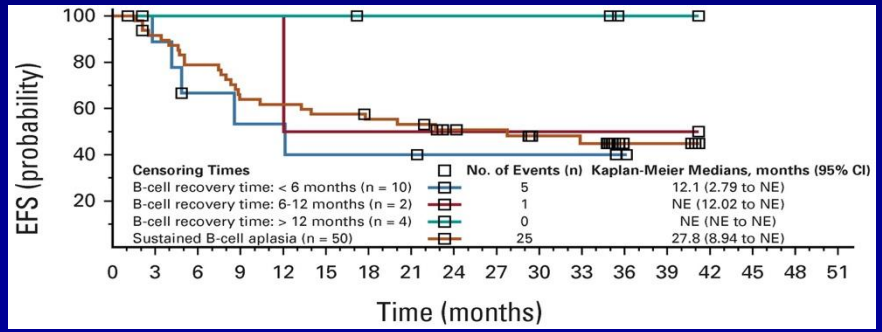


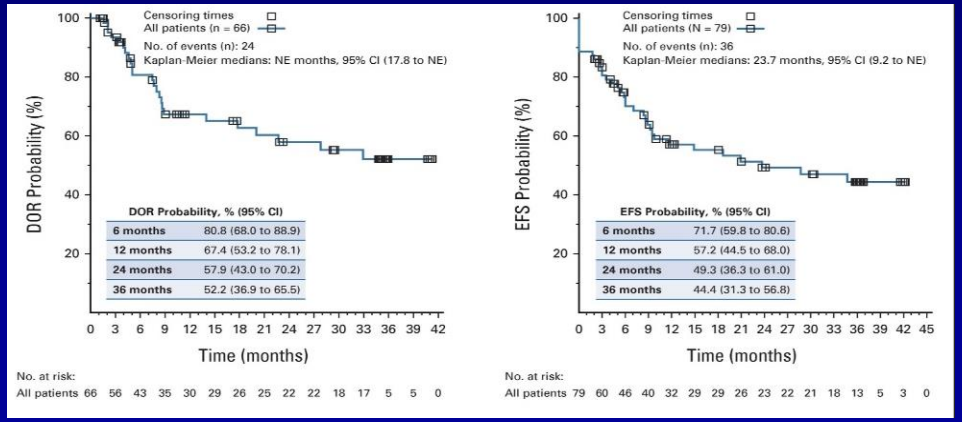
Jabbour E, et al. *Am J Hematol.* 2024;99(4):586-595.

3-Year Update of Tisagenlecleucel in R/R ALL

- 97 pts ≤26 yrs old enrolled
  - 79 (81%) received tisa
- Median age 11 yrs (3–24)
- Median prior Tx 3 (1–8)
- Marrow CR 66 = 82%
  - 66% of denominator
- Median F/U 38.8 mos
- 5-yr RFS 49% in pts in CR/CRi
- 3-yr EFS 44%; 3-yr OS 63%
- Grade 3/4 AE 29%







Laetsch TW, et al. *J Clin Oncol.* 2023;41(9):1664-1669.

Brexucabtagene Autoleucel (CD19 CAR T) in R/R ALL (ZUMA)

- 78 pts Rx with brexu-cel. Median FU 54 mos
- CR/CRi 57/78 = 73%

ALL Subset	No	Median OS (mos)	% 4-yr OS
Total	78	25.6	40
Prior Rx			
1	15	60.4	57
2+	63	25.4	36
Prior blina			
Yes	38	15.9	55
No	40	60.4	24
Later allo SCT			
Yes	14	36.3	-
No	43	60.4	-

Oluwole. *J Clin Oncol.* 2024;24:S6531.

Toxicities of Brexu-Cel in R/R ALL: ROCCA Results

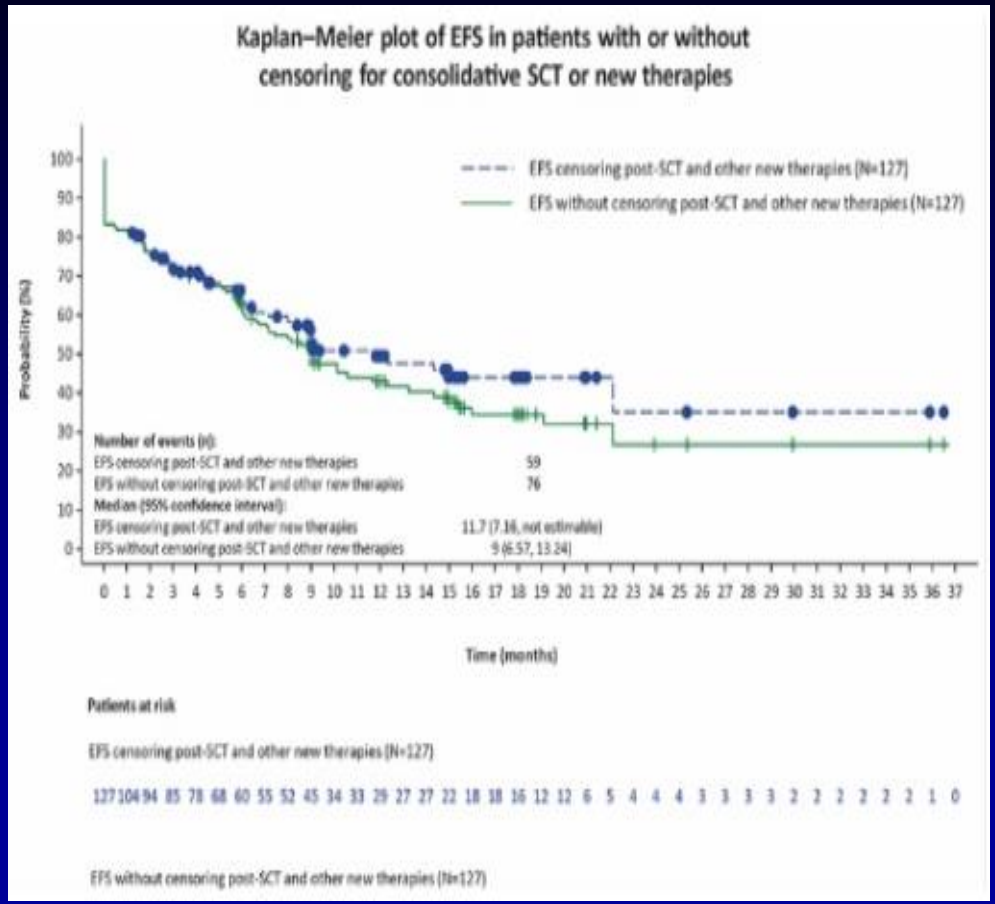
- Retrospective analysis of adults (N = 152) with R/R B-ALL receiving commercial brexu-cel
- Grade 3 CRS higher in ZUMA-3 than seen in the ROCCA dataset, but ICANS rates were comparable
- Grade 3+ CRS showed a numerical increase in patients with active disease at apheresis (>5% marrow blasts and/or EMD); OR: 2.35, 95% CI: 0.69–8.0, *P* = .17
- Grade 3+ ICANS more likely in pts with active disease at apheresis; OR: 2.63, 95% CI: 1.28–5.38, *P* = .008

Factor	ROCCA	ZUMA-3
Patients infused, n	152	55
Any CRS	82%	89%
Grade ≥3 CRS	9%	24%
Time to onset, days	5 (0–14)	–
Any ICANS	56%	60%
Grade ≥3 ICANS	31%	25%
Time to onset, days	7 (0–21)	–
Early death by day 28, n (%)	9 (6)	–

Kopmar NE, et al. ASH 2023. Abstract 522 and oral presentation.

Obecaptagene Autoleucel (OBE-CEL) in Adult R/R ALL (FELIX)

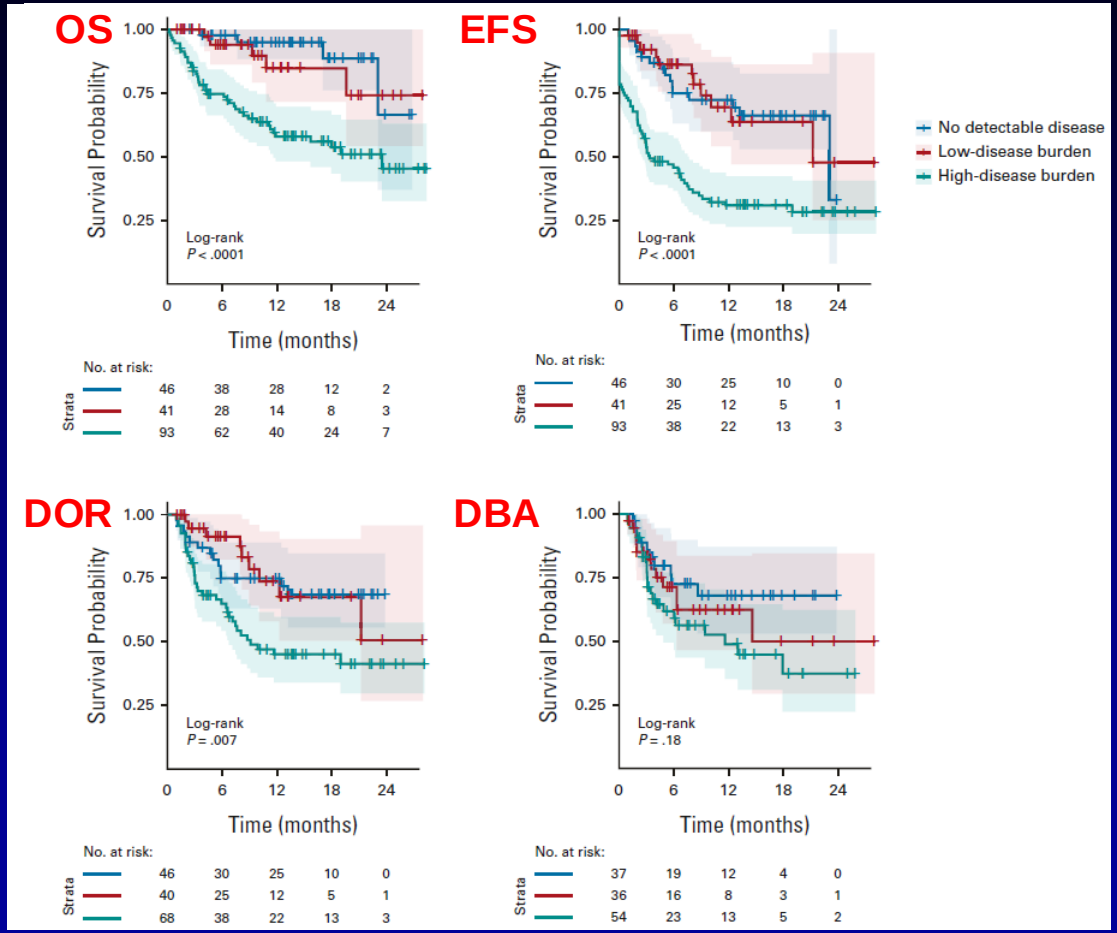
- AUTO 1 fast off-rate CD19 binder CAR T
- 153 enrolled, 127 (83%) infused. Median age 47 yrs
- Prior blina 42%, ino 31%, allo SCT 44%
- cCR-CRi 99/127 = 78% (99/153 = 65%). 19/77 allo SCT
- Loss of CAR T = HR 2.9
- 12-mos EFS 49%, 12-mos OS 61%



Jabbour E, et al. *J Clin Oncol.* 2024;24:S6504; Roddie et al. *HemaSphere*. 2024;8:S114.

Real-World CAR Consortium and Disease Burden

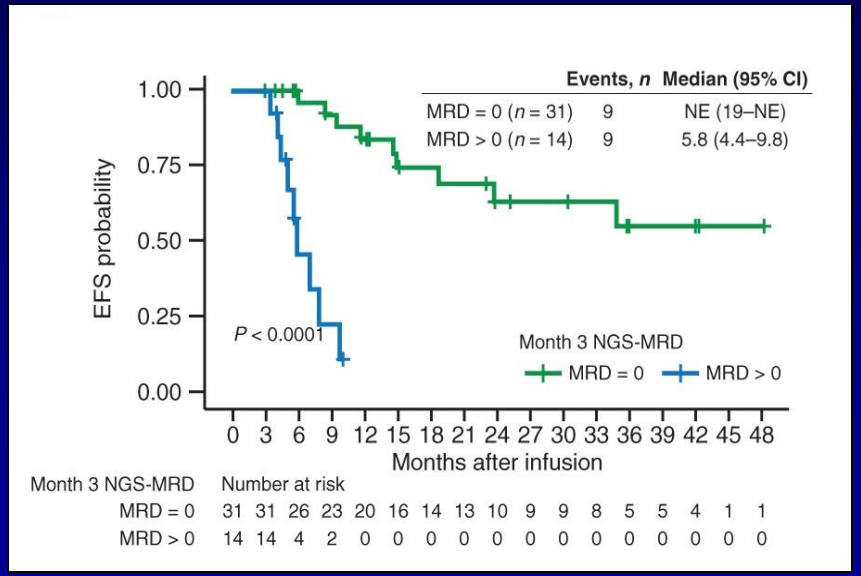
- 200 pts (185 pts infused)
- Median age: 12 yrs (0–26 yrs)
- CR: 85%
- Disease burden
  - HBD: n = 94 (51%)
  - LBD: n = 41 (22%)
  - ND: n = 46 (25%)
- Survival outcomes
  - 12-mo EFS: 50%
  - 12 mo OS: 72%
- Safety
  - G3 CRS: 21% (35% in HBD)
  - G3 NE: 7% (9% in HBD)

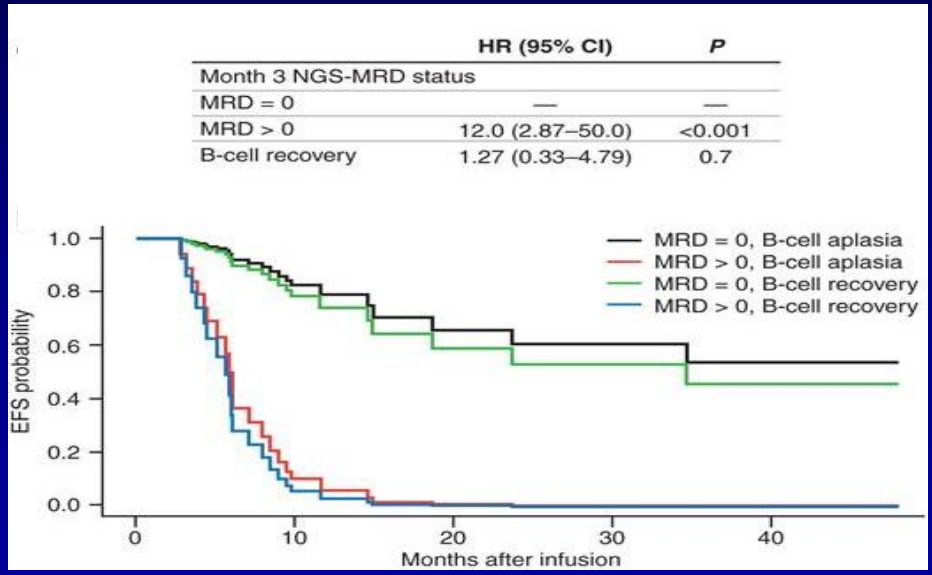


Schultz LM, et al. *J Clin Oncol*. 2022;40(9):945-955.

NGS MRD Negativity After CAR T-Cell Therapy for ALL

- Detectable MRD after tisagenlecleucel by NGS independently predicted for EFS and OS on multivariate analysis
- NGS MRD status at 3 months was superior to B-cell aplasia/recovery at predicting relapse/survival

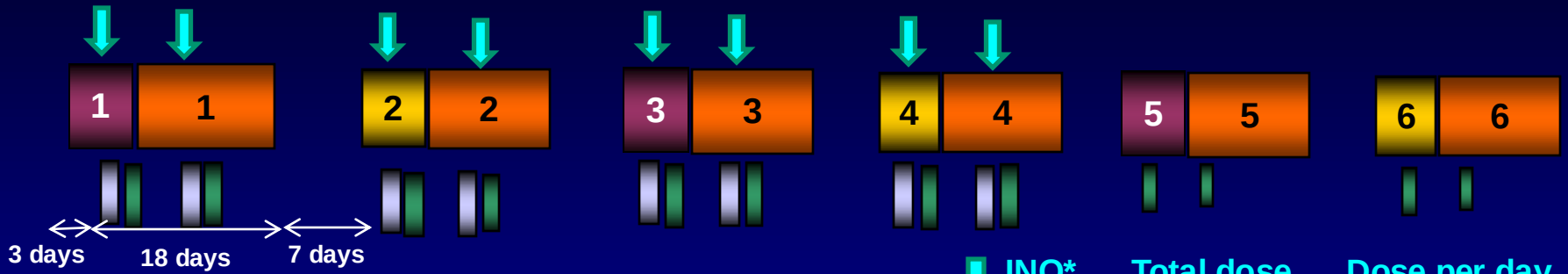




Pulsipher MA, et al. *Blood Cancer Discov.* 2022;3(1):66-81.

Dose-Dense Mini-HCVD + INO + Blina + CAR T Cells in ALL: The CURE

Induction phase: C1–C6



INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Consolidation phase

CAR T Consolidation

Mini-HCVD

Mini-MTX, Ara-C

Rituximab

IT MTX, Ara-C

Blinatumomab

ALL 2024: Conclusions

- Significant improvements across all ALL categories
- Incorporation of Blina-InO in FL therapy highly effective and improves survival
- Early eradication of MRD predicts best overall survival
- Antibody-based Txs and CAR Ts both outstanding; not mutually exclusive/competitive (vs); rather, complementary (together)
- Future of ALL Tx
  1) Less chemotherapy and shorter durations
  2) Combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22
  3) SQ blinatumomab
  4) CAR Ts CD19 and CD19 allo and auto in sequence in CR1 for MRD and replacing ASCT

Thank You

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Global Leukemia Academy

Q&A

APTITUDE HEALTH®

Global Leukemia Academy

Long-term safety considerations for leukemias (focus on ALL)

Nicola Gökbuget

APTITUDE HEALTH

Long-Term Safety After Therapy of Adult ALL

Nicola Gökbuget

Goethe University Hospital, Department of Medicine II, Frankfurt

GMALL Head of Study Group

UNIVERSITÄTS KLINIKUM FRANKFURT GOETHE-UNIVERSITÄT

GMALL German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

DKTK German Cancer Consortium

uct Universitäres Centrum für Tumorerkrankungen Frankfurt University Cancer Center

MED2

FRANKFURT CANCER INSTITUTE

Success and Challenges in the Management of Adult ALL

	CR	ED	OS/LFS
Children	>95%	<3%	ca.90%
AYA 18–40 yr	>90%	<5%	70%–80%
Adults (18–55/65 yr)	85%–90%	7%	40%–70%
Elderly (>55-65 yr)	70%–80%	10%–30%	<10%–50%
Ph-positive ALL	>90%	<5%	>60%–70% (age dependent)
Relapsed ALL	40%–80%	<10%	10%–40%

Improved results of first-line therapy for all age groups

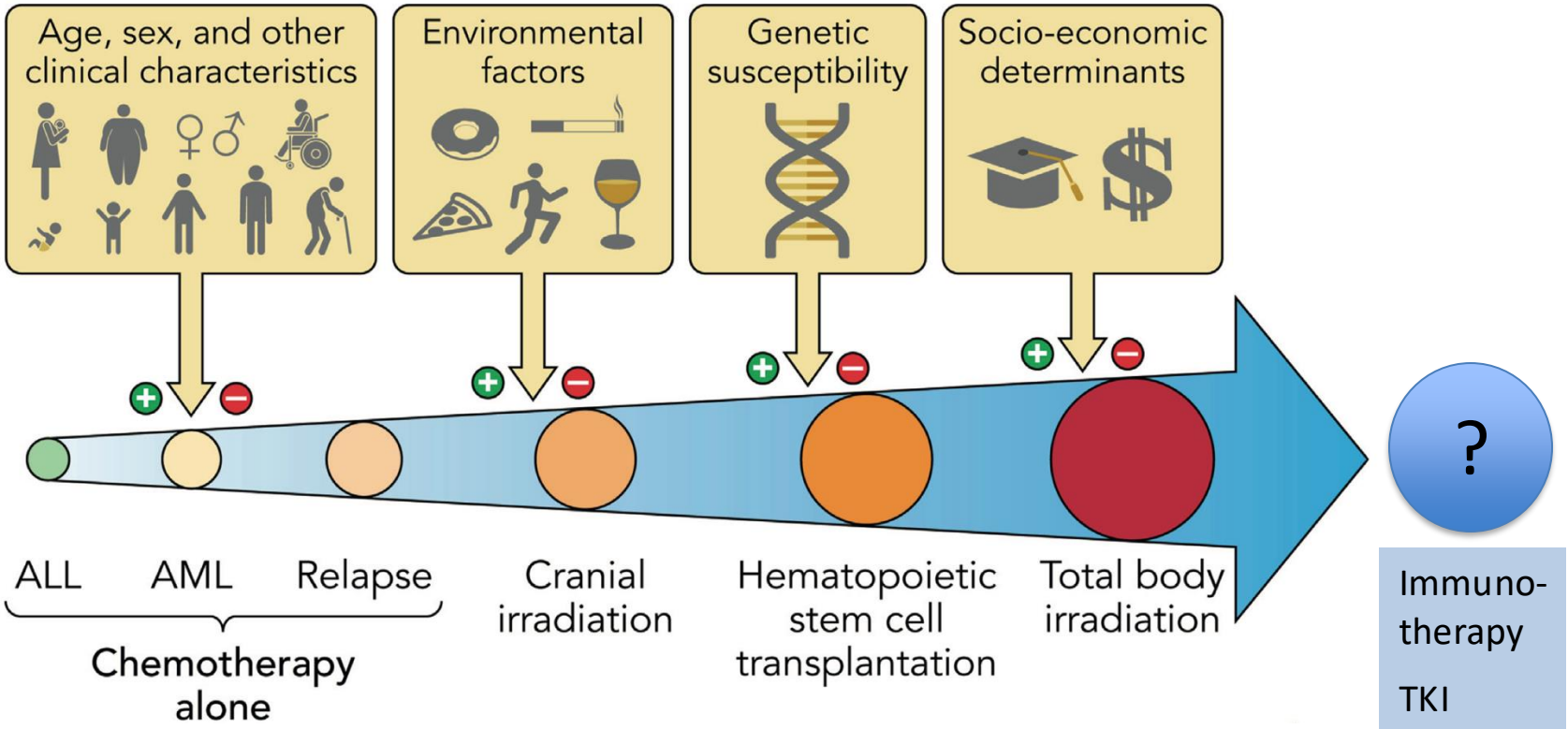
Intensive chemotherapy is essential for cure, but

- Development of resistance
- Non-satisfactory results in R/R disease

Long-term health effects of ALL therapy

Risk of Long-Term Effects of ALL/ALL Therapy

Saultier P, Michel G. *Blood*. 2024;143:1795-1806.



Key Risk Factors for Late Effects

Saultier P, Michel G. *Blood*. 2024;143:1795-1806.

- Relapse chemotherapy increases the risk of long-term complications by up to 2×
- Central nervous system (CNS) irradiation or other CNS-directed therapies are associated with the risk of cognitive impairments and secondary tumors
- Stem cell transplant (SCT) raises the risk for multiple chronic conditions, including cardiovascular and endocrine disorders
- Total body irradiation (TBI) has the most severe long-term toxicity profile with a wide range of complications

25-Year Follow-Up in Pediatric ALL

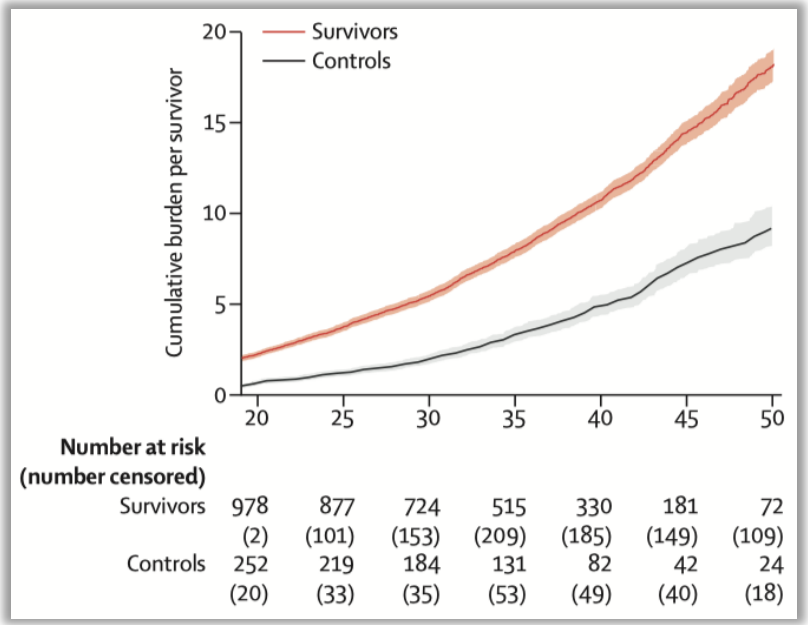
Mody R, et al. *Blood.* 2008;111:5515-5523.

Total	Siblings N = 3083	ALL Survivors N = 2599	*P* Value
Chronic disorders			
Hearing	0.4	1.0	<.001
Vision	0.7	1.2	ns
Endocrine	1.8	4.4	<.001
Pulmonary	1.2	3.0	<.001
Cardia	0.7	3.2	<.001
Gastrointestinal	0.5	0.7	.4
Renal	0.2	0.8	<.001
Musculoskeletal	0.1	0.5	<.001
Neurologic	0.4	2.4	<.001
Adverse health status			
General health	5.1	8.9	<.001
Mental health	9.8	15.0	<.001
Activity limitations	5.8	8.9	<.001
Functional impairment	2.6	8.7	<.001

ns, not significant.

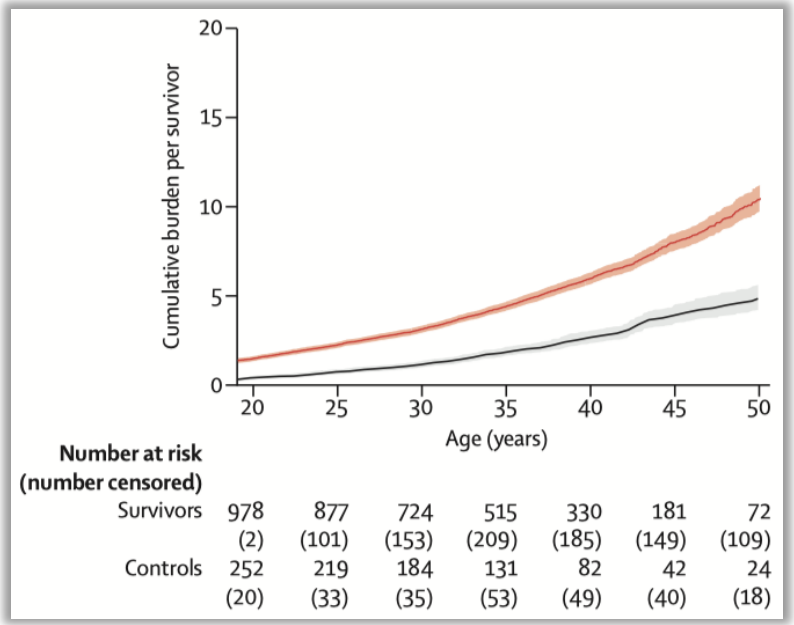
Burden of Health Conditions in Long-Term Follow-Up St Jude Lifetime Cohort Study

Mulrooney DA, et al. *Lancet Haematol.* 2019;6:e306-e316.



Grade 1–4 conditions

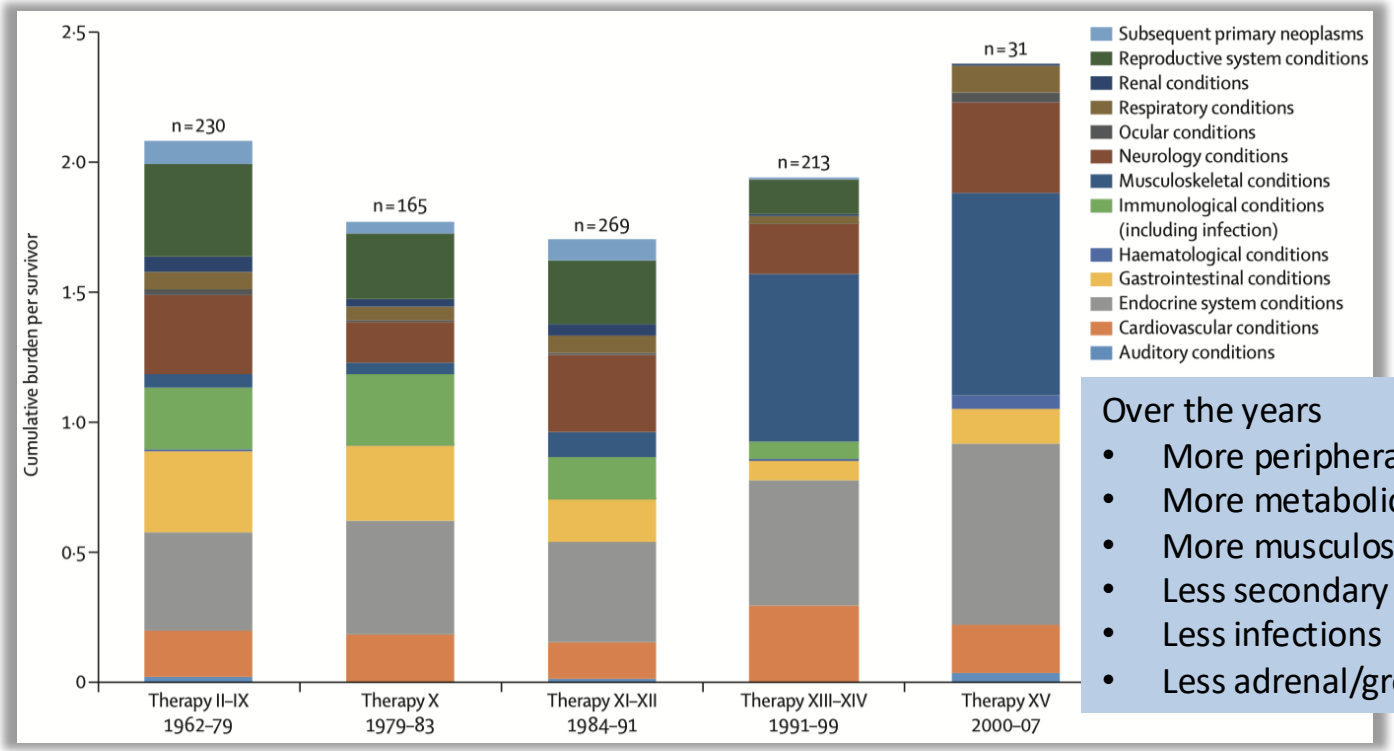
5.4 (95% CI 5.1–5.8) vs **2.0** (1.7–2.2)



Grade 2–4 conditions

Burden of Health Conditions in Long-Term Follow-Up St Jude Lifetime Cohort Study

Mulrooney DA, et al. *Lancet Haematol.* 2019;6:e306-e316.



Over the years

- More peripheral neuropathies
- More metabolic syndromes
- More musculoskeletal issues
- Less secondary malignancies
- Less infections
- Less adrenal/growth hormone insufficiency

Late Effects in Adult and Pediatric ALL Survivors

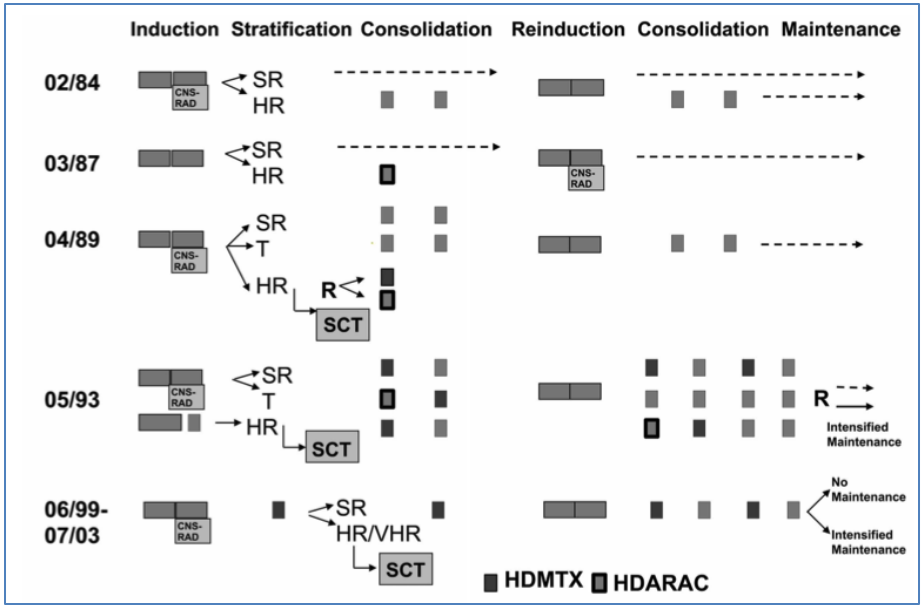
Late Effects	Pediatric Survivors	Adult Survivors
Physical complications		
Cardiovascular complications	Anthracycline-related cardiomyopathy, hypertension	Increased risk of heart disease, stroke, cardiomyopathy
Skeletal problems	Bone density loss, risk of osteoporosis	Osteopenia, osteonecrosis, fractures
Pulmonary complications	Reduced lung capacity, pulmonary fibrosis	COPD, reduced lung function
Secondary cancers		
	Thyroid, breast, skin cancer, meningioma	Higher risk of solid tumors, breast cancer
Endocrine and growth disorders		
Endocrine disorders	Growth hormone deficiency, delayed puberty, thyroid dysfunction	Hypothyroidism, early menopause, infertility
Metabolic syndrome	Obesity, insulin resistance, dyslipidemia, hypertension	Increased risk of diabetes, obesity, high cholesterol
Growth and development	Stunted growth, delayed puberty	N/A
Fertility issues	Delayed puberty, infertility	Early menopause, reduced fertility
Cognitive and mental health issues		
Neurocognitive deficits	Learning disabilities, memory and attention deficits	Cognitive decline, attention deficits
Psychosocial effects	Anxiety, depression, social adjustment difficulties	Depression, anxiety, employment challenges

Most data come from pediatric survivors

Health Condition of Long-Term (>5 yr) Survivors of Adult ALL

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

Patients:	538
Age (at diagnosis):	29 (15–64)
Age (at evaluation):	39 (19–74)
FU time:	7 (3–24) yr



Health Condition of Long-Term (>5 yr) Survivors of Adult ALL

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

Study		**02/84**	**03/87**	**04/89**	**05/93**	**06/99**
Period		**1984–1987**	**1987–1989**	**1989–1993**	**1993–1999**	**1999–2003**
Evaluable		**569**	**353**	**588**	**1212**	**831**
Age	15–25	45%	40%	36%	29%	28%
	26–50	41%	40%	45%	49%	51%
	50–65	14%	20%	20%	22%	21%
CR		**75%**	**75%**	**81%**	**82%**	**81%**
SCT in CR1		**<5%**	**<5%**	**11%**	**16%**	**31%**
Survival		**35%**	**31%**	**37%**	**36%**	**42%**

➔ **Long-term survivors >5 yr after first diagnosis**

Health Condition of Long-Term (>5 yr) Survivors of Adult ALL

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

QUESTIONNAIRES

Organ Systems (8)

- Skin
- Lung
- Nervous system
- Endocrine system
- Kidney/liver
- Cardiovascular system
- Stomach/gut
- Eyes

Specific Syndromes (6)

- Secondary malignancy
- Fatigue
- Chronic GvHD
- Thyroid disease
- Infections
- Osteonecrosis

- Questions regarding diseases that newly occurred after the end of leukemia treatment (date, severity, actual state)
- Documentation according to patient file
- No documentation of patient deaths

Health Condition of Long-Term (>5 yr) Survivors of Adult ALL

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

ORGAN SYSTEMS

	Total
ECOG 0–1	**94%**
Any disease	**66%**
Nervous system	**27%**
Skin and mucosa	**18%**
Cardiovascular	**13%**
Lung	8%
Endocrine system	
Male	**17%**
Female	**24%**
Kidney/liver	10%
Gastrointestinal	6%
Eyes	12%

Health Condition of Long-Term (>5 yr) Survivors of Adult ALL

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

SPECIFIC SYNDROMES

	Total
Infections (12 mo)	**12%**
GvHD/sicca syndrome	**15%**
Fatigue	**13%**
Osteonecrosis	**8%**
Malignancy	4%
Hyperthyroidism	1%
Hypothyroidism	5%

ns, not significant.

Late Effects Example: Metabolic Syndrome

Saultier P, Michel G. *Blood*. 2024;143:1795-1806.

- 25%–35% of survivors show early signs of atherosclerotic lesions
- Risk factors: CNS irradiation, TBI, and chemotherapy
- Case study: A 19-year-old AML survivor developed metabolic syndrome, including obesity (BMI of 33.5), hypertension, and elevated triglycerides (3.4 mmol/L)
- Lifestyle changes (nutrition, physical activity) recommended; no need for medication

Therapeutic exposure	Relative risk[8,a]	Specific characteristics[7,9]	Pathophysiology[10-12]		Early detection[12,13]	Treatment specificities
			Treatment-specific	All survivors		
HSCT with TBI	×6.3 (×9.2 in females)	Increased severity of metabolic syndrome Lower incidence of obesity and lower abdominal circumference, higher triglycerides, and glucose level	Radiation induced alteration of subcutaneous adipose tissue (preadipocyte differentiation) Additional role of pancreatic radiation, testosterone, and growth hormone deficiency	Low-grade chronic inflammation Poor eating habits and reduced activity during prolonged periods Genetic predisposition	Regular monitoring: Blood pressure Abdominal circumference Fasting glucose, triglyceride, HDL- and LDL-cholesterol Potential interest of early biomarkers (adipokines)?	Few specific data Moderate effect of lifestyle modifications in the LEA experience
HSCT without TBI	×2.2	Usually less severe than after HSCT with TBI	Largely unknown Role of testosterone deficiency			
Chemotherapy and CNS irradiation	×2.3	More frequent abdominal obesity Low incidence of hypertension	Important role of obesity Leptin resistance and overproduction (damaged hypothalamic receptors) Growth hormone deficiency			
Chemotherapy without CNS irradiation	×1.7	More frequent hypertension (compared to CNS irradiation)	Largely unknown Uncertain long-term role of steroid and asparaginase			

Mulrooney DA, et al. *Lancet Haematol.* 2019;6:e306-e316.

Late Effects Example: Osteonecrosis

Kuhlen M, et al. *Blood Adv.* 2017;1:981-994

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

Germline polymorphisms

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

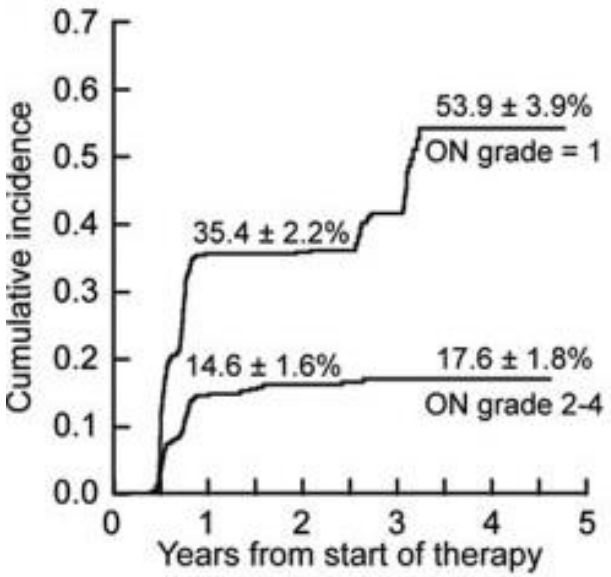
Steroids and Osteonecrosis

Kawedia JD, et al. *Blood*. 2011;117:2340-2556.

Method

- N = 364 pediatric ALL
- Prospective MRI screening (hip and knee)
- Age <18 yr

Any grade (1–4) ON:	**72%**
Symptomatic (grade 2–4) ON:	**18%**



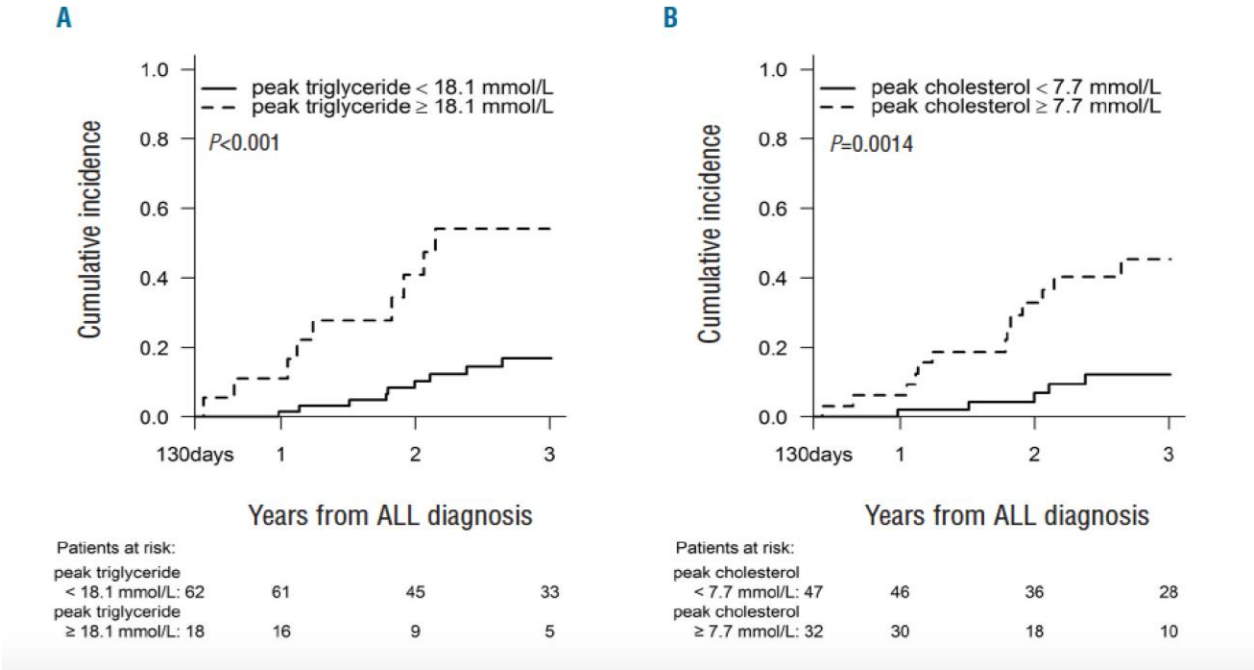
Risk factors

- Age >10 yr
- Risk group
- Lower albumin/higher cholesterol
- Dexamethasone (AUC)
- Polymorphisms of APC-1 (lipid level, osteoblast differentiation)
- **MRI aberrations in week 10 are predictive for grade 2–4 osteonecrosis (26% vs 14%)**
- **Potential predictive molecular aberrations are under investigation**

Correlation Between Hyperlipidemia and Osteonecrosis

Mogensen SS, et al. *Haematologica.* 2017;102:e175-e178.

N = 112
Osteonecrosis: 22.9% (n = 22)
Age: 5.2–37 yr
Grade 2/3: 10/12
Surgery: 10
Multiple joints: 10



Osteonecrosis in Patients With ALL: Treatment Options

Kuhlen M, et al. *Blood Adv.* 2017;1:981-994

1. **Vitamin K and calcium substitution**
2. **Nonweight-bearing therapy**
3. **Pharmacologic options**
   - LMW (intravascular clotting)
   - Prostacyclin analogs (antiedema, anti-inflammatory, antiaggregant, vasodilatory)
   - Lipid metabolism (Statins)
   - Bisphosphonates (reduce osteoclast activity; prevent osteocyte and osteoblast apoptosis)
   - Nuclear factor-kB ligand (RANKL) inhibitors (eg, denosumab)
4. **Nonpharmagologic/nonsurgical**
   - Hyperbaric oxygenation
   - Extracorporeal shock wave therapy
   - Single pulsed electromagnetic fields
5. **Surgical**
   - Core decompression
6. **Cellular therapy**

Kuhlen M, et al. *Hemasphere*. 2021;5:e544.

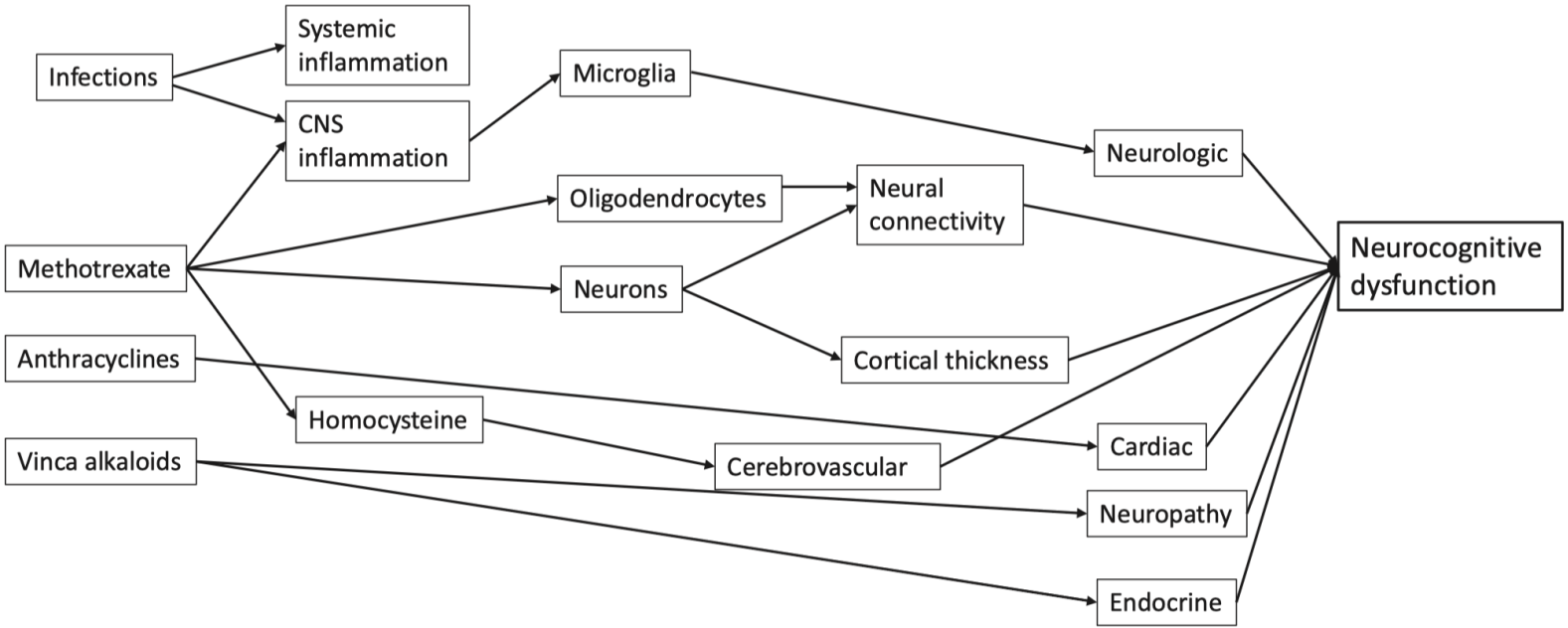
Brief Summary of (Prophylactic) Treatment Options for Osteonecrosis.

Interventions	Suggestions
Pain management	Effective pain management is crucial
Physical therapy	Use of crutches is controversially discussed but is a regular part of care in other osteonecrosis conditions. Osteonecrosis in the upper limbs should be excluded by MRI before use
	Physical therapy is recommended
Pharmacologic interventions	Low-molecular-weight heparin
	Prostacyclin analogs
	Statins
	Bisphosphonates
Surgical interventions	Core decompression
	Reduction of intraosseous pressure
	Promotion of healing processes
	Prn combined with autologous or mesenchymal stem cells
	Arthroplasty
	Surface replacement
	Osteotomy
	Total joint replacement
Others	Antihypertensive treatment
	Treatment of prolonged hypertriglyceridemia/hypercholesterolemia, eg, dietary measure, omega3-fatty acids

- LMW heparin during ASP activity
- Antithrombin III substitution
- Control triglycerides
- Avoid nonprotocol steroids

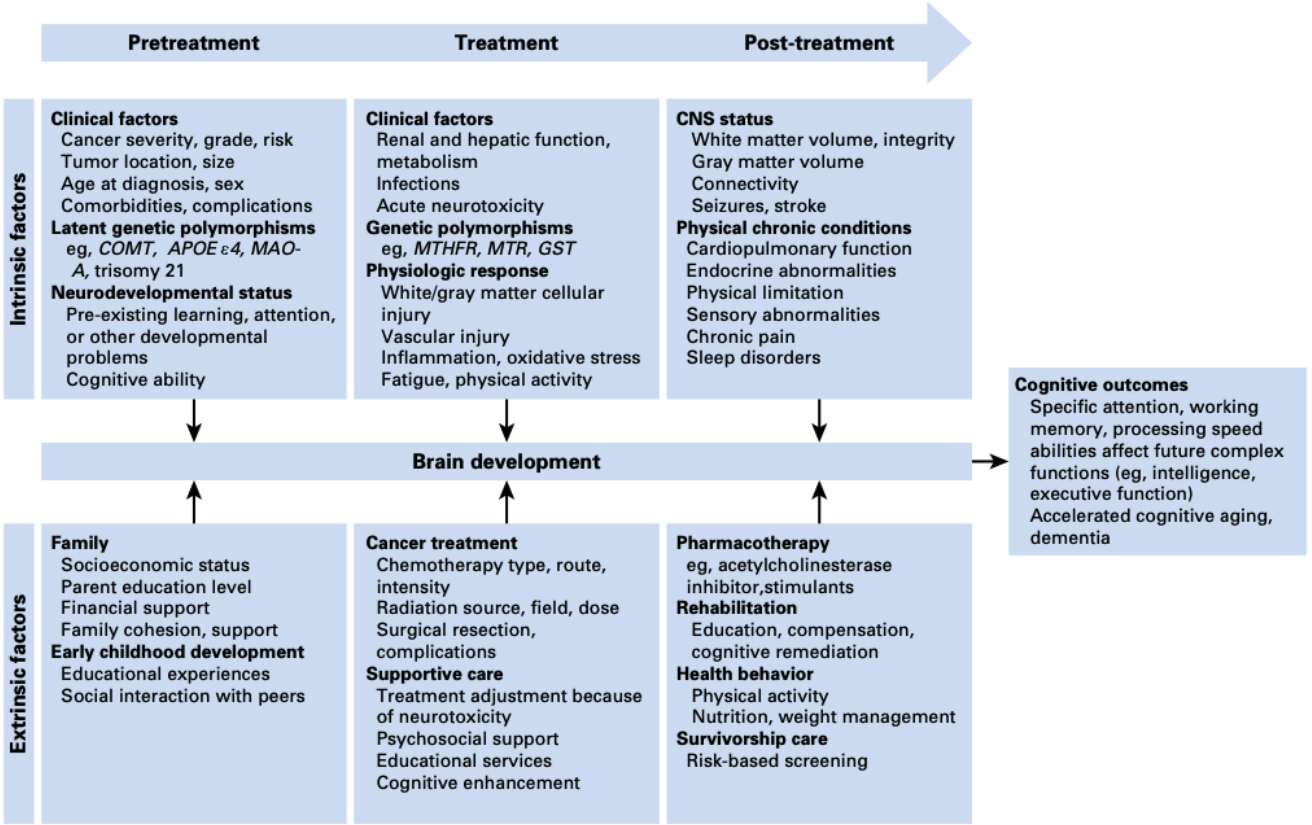
Late Effects Example: Cognitive Disturbances

Krull KR. *Hematology Am Soc Hematol Educ Program.* 2022;2022:259-265.



Neurocognitive Outcomes and Interventions in Long-Term Survivors of Childhood Cancer

Krull KR, et al. *J Clin Oncol.* 2018;36:2181-2189.



Assessment of Cognitive Status: CCSS-NCQ

PROBLEM SOLVING

Q. Below is a list of statements that describe problems people can have. We would like to know if you have had any of these problems over the PAST 6 MONTHS. Please complete all items. Please think about yourself as you read these statements and mark one response on each line.

	Never a problem	Sometimes a problem	Often a problem
1. I get upset easily	☐	☐	☐
2. It takes me longer to complete my work	☐	☐	☐
3. I am disorganized	☐	☐	☐
4. I forget instructions easily	☐	☐	☐
5. I have problems completing my work	☐	☐	☐
6. I have difficulty recalling things I had previously learned (e.g., names, places, events, activities)	☐	☐	☐
7. I get frustrated easily	☐	☐	☐
8. My mood changes frequently	☐	☐	☐
9. I have trouble finding things in my bedroom, closet or desk	☐	☐	☐
10. I forget what I am doing in the middle of things	☐	☐	☐
11. I have problems getting started on my own	☐	☐	☐
12. I am easily overwhelmed	☐	☐	☐
13. I have trouble doing more than one thing at a time	☐	☐	☐
14. My desk/workspace is a mess	☐	☐	☐
15. I have trouble remembering things, even for a few minutes (such as directions, phone numbers, etc.)	☐	☐	☐
16. I have trouble prioritizing my activities	☐	☐	☐
17. I read slowly	☐	☐	☐
18. I am slower than others when completing my work	☐	☐	☐
19. I have trouble solving math problems in my head	☐	☐	☐
20. I don't work well under pressure	☐	☐	☐
21. I have trouble staying on the same topic when talking	☐	☐	☐
22. I have a messy closet	☐	☐	☐
23. People say I am easily distracted	☐	☐	☐
24. I have angry outbursts	☐	☐	☐
25. I have a short attention span	☐	☐	☐
26. I overreact emotionally	☐	☐	☐
27. I have trouble organizing work	☐	☐	☐
28. I overreact to small problems	☐	☐	☐
29. I have problems organizing activities	☐	☐	☐
30. I have emotional outbursts for little reason	☐	☐	☐
31. I leave the bathroom a mess	☐	☐	☐
32. I react more emotionally to situations than my friends	☐	☐	☐
33. I leave my room or home a mess	☐	☐	☐

Never = 1, Sometimes = 2, and Often = 3.

Task Efficiency = 9 items and raw scores will range from 9–27

Items = 2, 6, 14, 16, 17, 21, 22, 23, 25

Emotional Regulation = 3 items and raw scores will range from 3–9

Items = 1, 8, 9

Organization = 3 items and raw scores will range from 3–9

Items = 4, 12, 19

Memory = 4 items and raw scores will range from 4–12

Items = 5, 7, 13, 20

Validated normal values are available

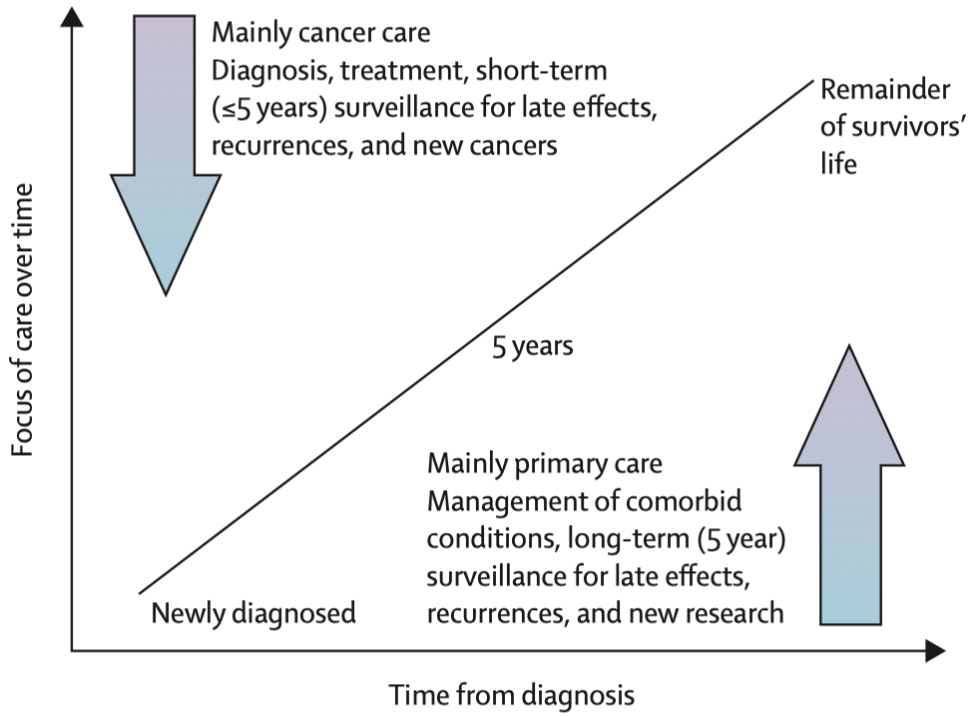
TABLE 4
Mean Childhood Cancer Survivor Study Neurocognitive Questionnaire Scores for Various Survivor Risk Groups

	Group 1 Frontal CRT Mean (SD)	Group 2 Neurologic Mean (SD)	Group 3 Healthy Mean (SD)	Group 4 Sibling Mean (SD)
Task efficiency	16.5 (5.18)	16.2 (5.17)	11.8 (3.26)	11.9 (3.12)
Emotional regulation	5.5 (1.81)	5.7 (1.81)	5.1 (1.67)	5.0 (1.60)
Organization	4.9 (1.77)	5.0 (1.80)	4.4 (1.50)	4.6 (1.61)
Memory	7.6 (2.47)	7.1 (2.36)	5.8 (1.85)	5.8 (1.77)

Surveillance and Aftercare

Needs of Cancer Survivors

Mayer DK, et al. *Lancet Oncol.* 2017;18:e11–e18.



Panel 2: **Conceptual quality-of-life model for cancer survivors**

Physical wellbeing and symptoms
- Functional ability
- Strength or fatigue
- Sleep or rest
- Fertility
- Pain
- Appetite
- Overall physical health

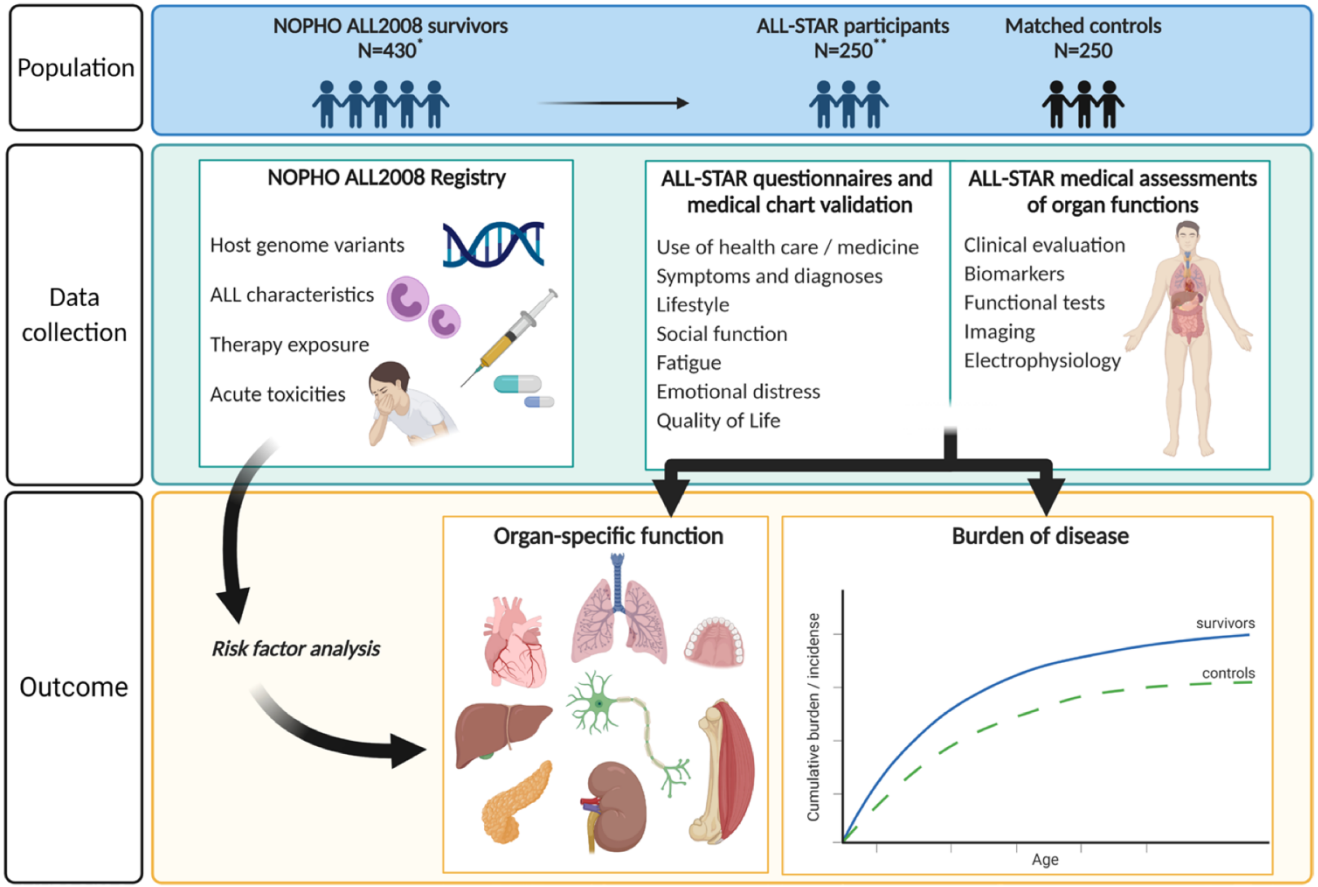
Psychological wellbeing
- Control
- Anxiety or depression
- Enjoyment or leisure
- Pain or distress
- Happiness
- Fear of recurrence
- Cognition or attention
- Overall perception of quality of life
- Distress of diagnosis and treatment

Social wellbeing
- Family distress
- Roles and relationships
- Affection and sexual function
- Appearance
- Employment
- Isolation
- Finances

Spiritual wellbeing
- Meaning of illness
- Religiosity
- Transcendence
- Hope
- Uncertainty
- Hopefulness

ALL-STAR Study Overview

Andrés-Jensen L, et al. *BMJ Open.* 2021;11:e045543.



SURVIVORSHIP ASSESSMENT (Patient Version)
Please answer the following questions:

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Survivorship

NCCN Guidelines Index
Table of Contents
Discussion

ASSESSMENT BY HEALTH CARE PROVIDER (ONCOLOGY OR PRIMARY CARE) AT REGULAR INTERVALS

General Survivorship Principles

- Definition of Survivorship (SURV-1)
- Standards for Survivorship Care (SURV-2)
- General Principles of the Survivorship Guidelines (SURV-3)
- Screening for Subsequent New Primary Cancers (SURV-4)
- Principles of Screening for Treatment-Related Subsequent Primary Cancers (SURV-4A)
- Principles of Cancer Risk Assessment and Counseling (SURV-5)
- Assessment by Health Care Provider at Regular Intervals (SURV-6)
- Survivorship Assessment (SURV-A)
- Survivorship Resources for Health Care Professionals and Survivors (SURV-B)

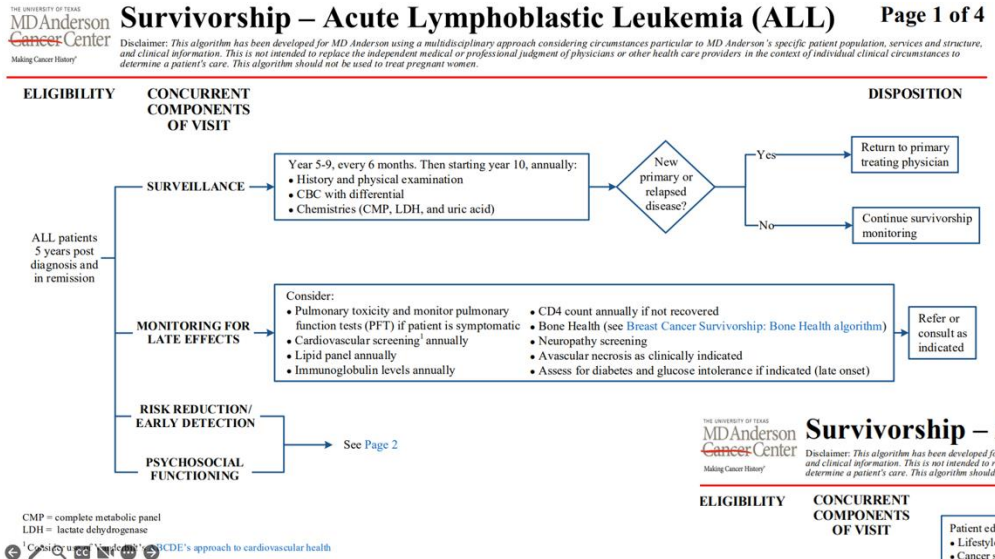
NCCN Guidelines for Patients Survivorship Care for Healthy Living

NCCN Guidelines for Patients Survivorship Care for Cancer-Related Late and Long-Term Effects

Preventive Health

- Healthy Lifestyles (HL-1) Physical Activity (SPA-1)
- Nutrition and Weight Management (SNWM-1)
- Supplement Use (SSUP-1)
- Immunizations and Infections (SIMIN-1)
- Late Effects/Long-Term Psychosocial and Physical Problems
- Cardiovascular Disease Risk Assessment (SCVD-1)
- Anthracycline-Induced Cardiac Toxicity (SCARDIO-1)
- Anxiety, Depression, Trauma, and Distress (SANXDE-1)
- Cognitive Function (SCF-1)
- Fatigue (SFAT-1)
- Lymphedema (SLYMPH-1)
- Pain (SPAIN-1)
- Hormone-Related Symptoms (SHRS-1)
- Sexual Health (SSH-1)
- Fertility (SF-1)
- Sleep Disorders (SSD-1)
- Employment and Return to Work (SWORK-1)

MD Anderson Cancer Center



MD Anderson Cancer Center
Making Cancer History®

Survivorship – Acute Lymphoblastic Leukemia (ALL)

Page 1 of 4

Disclaimer: *This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.*

ELIGIBILITY

ALL patients 5 years post diagnosis and in remission

CONCURRENT COMPONENTS OF VISIT

SURVEILLANCE

Year 5-9, every 6 months. Then starting year 10, annually:
- History and physical examination
- CBC with differential
- Chemistries (CMP, LDH, and uric acid)

New primary or relapsed disease?

- Yes → Return to primary treating physician
- No → Continue survivorship monitoring

MONITORING FOR LATE EFFECTS

Consider:
- Pulmonary toxicity and monitor pulmonary function tests (PFT) if patient is symptomatic
- Cardiovascular screening[1] annually
- Lipid panel annually
- Immunoglobulin levels annually
- CD4 count annually if not recovered
- Bone Health (see Breast Cancer Survivorship: Bone Health algorithm)
- Neuropathy screening
- Avascular necrosis as clinically indicated
- Assess for diabetes and glucose intolerance if indicated (late onset)

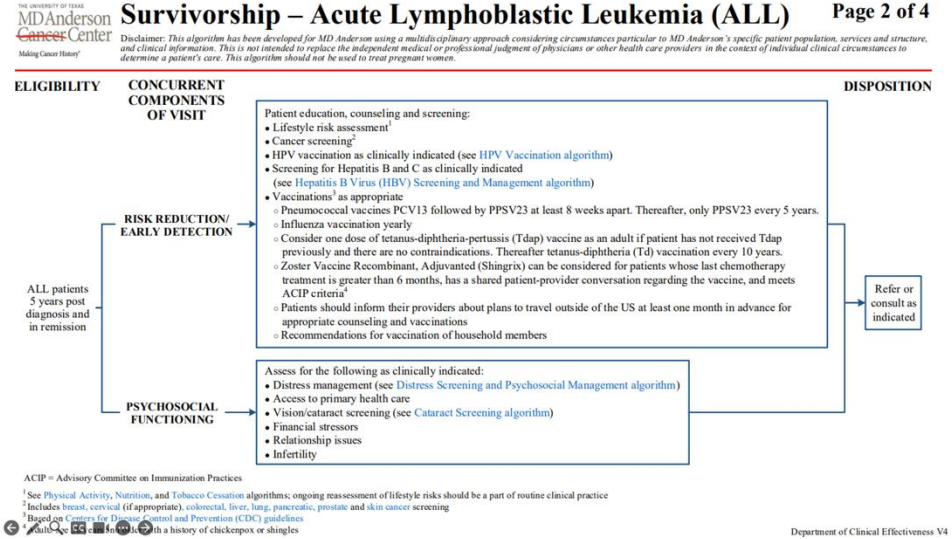
→ Refer or consult as indicated

RISK REDUCTION/ EARLY DETECTION

PSYCHOSOCIAL FUNCTIONING

→ See Page 2

CMP = complete metabolic panel
LDH = lactate dehydrogenase
[1] Consider using the ABCDE's approach to cardiovascular health



MD Anderson Cancer Center
Making Cancer History®

Survivorship – Acute Lymphoblastic Leukemia (ALL)

Page 2 of 4

Disclaimer: *This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.*

ELIGIBILITY

ALL patients 5 years post diagnosis and in remission

CONCURRENT COMPONENTS OF VISIT

RISK REDUCTION/ EARLY DETECTION

Patient education, counseling and screening:
- Lifestyle risk assessment[1]
- Cancer screening[2]
- HPV vaccination as clinically indicated (see HPV Vaccination algorithm)
- Screening for Hepatitis B and C as clinically indicated (see Hepatitis B Virus (HBV) Screening and Management algorithm)
- Vaccinations[3] as appropriate
  - Pneumococcal vaccines PCV13 followed by PPSV23 at least 8 weeks apart. Thereafter, only PPSV23 every 5 years.
  - Influenza vaccination yearly
  - Consider one dose of tetanus-diphtheria-pertussis (Tdap) vaccine as an adult if patient has not received Tdap previously and there are no contraindications. Thereafter tetanus-diphtheria (Td) vaccination every 10 years.
  - Zoster Vaccine Recombinant, Adjuvanted (Shingrix) can be considered for patients whose last chemotherapy treatment is greater than 6 months, has a shared patient-provider conversation regarding the vaccine, and meets ACIP criteria[4]
  - Patients should inform their providers about plans to travel outside of the US at least one month in advance for appropriate counseling and vaccinations
  - Recommendations for vaccination of household members

PSYCHOSOCIAL FUNCTIONING

Assess for the following as clinically indicated:
- Distress management (see Distress Screening and Psychosocial Management algorithm)
- Access to primary health care
- Vision/cataract screening (see Cataract Screening algorithm)
- Financial stressors
- Relationship issues
- Infertility

→ Refer or consult as indicated

DISPOSITION

ACIP = Advisory Committee on Immunization Practices

[1] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[2] Includes breast, cervical (if appropriate), colorectal, liver, lung, pancreatic, prostate and skin cancer screening
[3] Based on Centers for Disease Control and Prevention (CDC) guidelines
[4] Adults age [illegible] with a history of chickenpox or shingles

Department of Clinical Effectiveness V4

Medical Need for Aftercare in ALL

- Long-term surveillance in standard of care and clinical trials; funding?
- Structured assessment
  - Morbidities
  - Social situation
  - Cognition
- Aftercare pass
- Specialized units
- Involvement of hematology practices
- Interdisciplinary expert groups
- Contact points for patients/patient involvement
- New challenges: Long-term effects of third-generation TKI and immunotherapies

Global Leukemia Academy

Q&A

APTITUDE HEALTH®

Global Leukemia Academy

Current and future role of transplantation in acute leukemias in Europe

Josep-Maria Ribera

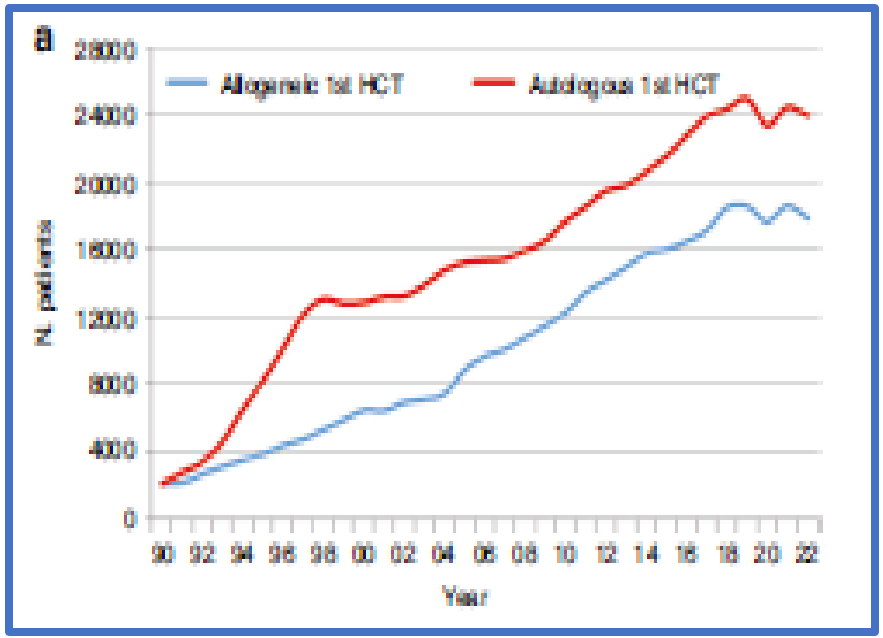
APTITUDE HEALTH®

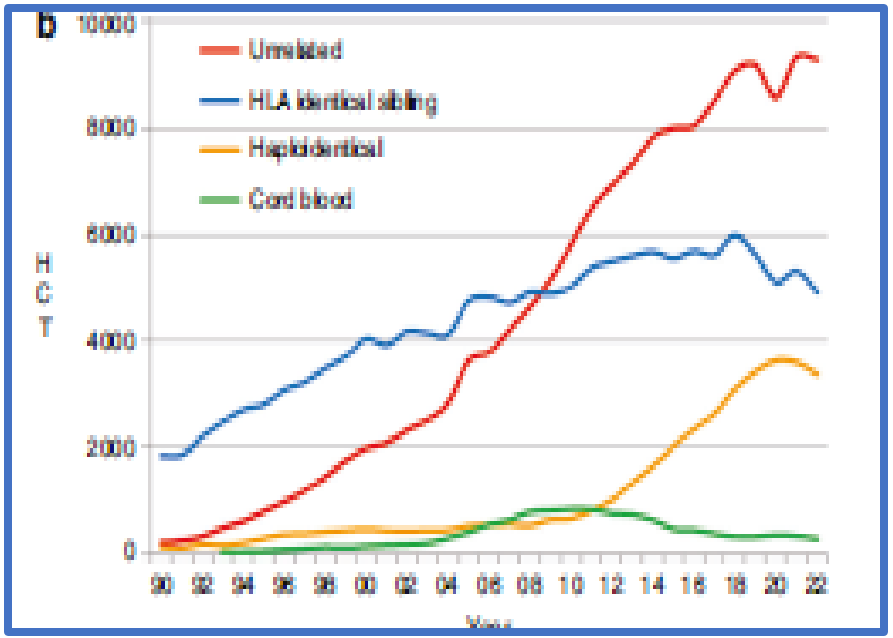
Who should receive alloHSCT in CR1?

Type of ALL	HSCT Indication	Comment
Ph-positive	Lack of CMR at end-consolidation	Especially if 1st or 2nd-generation TKI are used upfront
	IKZF1^{plus} signature	Poor prognosis with any TKI ± immunotherapy
Ph-negative and T-ALL	KMT2A rearrangement	Demonstrated in prospective studies
	Low hypodiploidy	Prospective and retrospective studies
	Complex karyotype	Prospective and retrospective studies
	IKZF1^{plus} signature	Prospective and retrospective studies
	BCR-ABL1 *like*	Targeted therapy could modify this indication
	Early T-cell precursor	HSCT could abrogate the poor prognosis
	End-induction and/or end-consolidation MRD+	Evidence from prospective studies After MRD-neg achievement with Blin?

Ribera JM, et al. *Clin Lymphoma Myeloma Leuk*. 2022;22(suppl 2):S47-S49.

Transplant activity has slowed in Europe in recent years



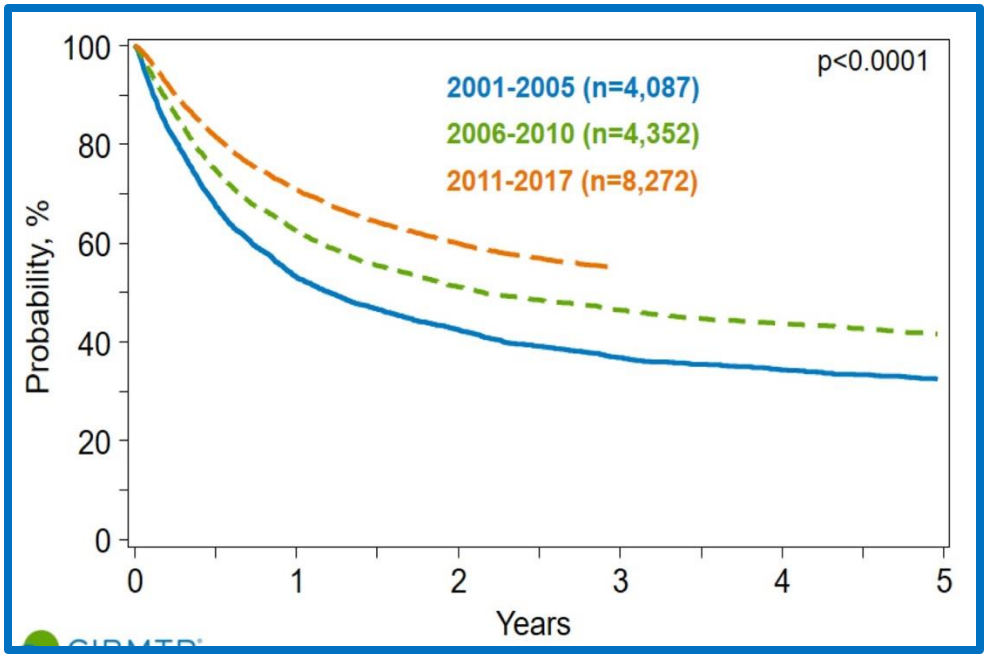


AlloHSCT 2022 vs 2021: ↓ 4%

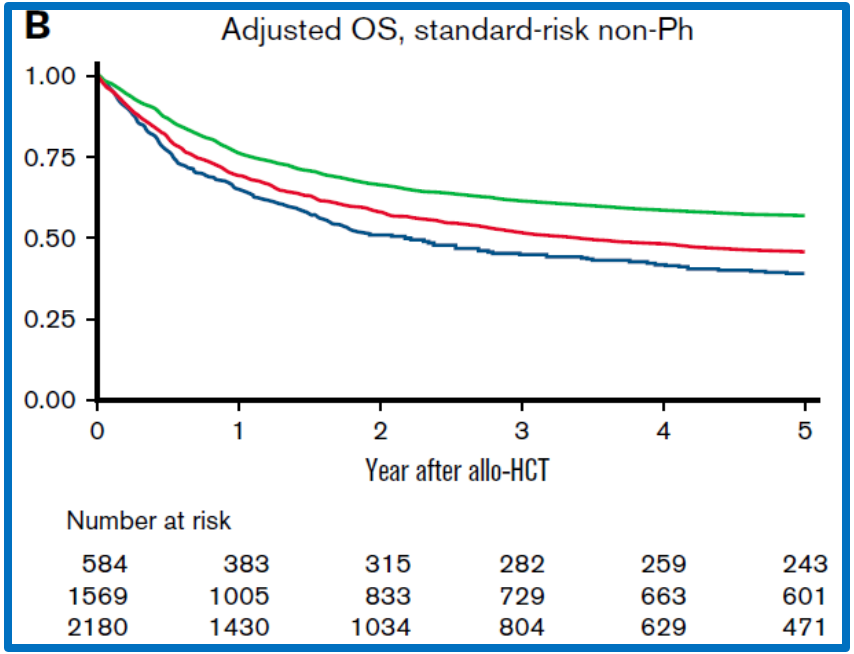
Passweg JR, et al. *Bone Marrow Transplant*. 2024;59:803-812.

Allogeneic HSCT in ALL: improved survival over time

Patients ≥18 y, CIBMTR, 2001–2017



JSTCT, Japan



D'Souza A, et al. *Biol Blood Marrow Transplant*. 2020;26:e177-e182.

Nishiwaki S, et al. *Blood Adv.* 2022;6:4558-4569.

AlloHSCT in Ph+ ALL

An evolving matter with the advent of 3rd-generation TKI and immunotherapy

No benefit of alloHSCT in pts with Ph+ ALL who achieve CMR at 3 months
Retrospective study (n = 230)

Patients: 230, from 5 US transplant centers

Criteria:

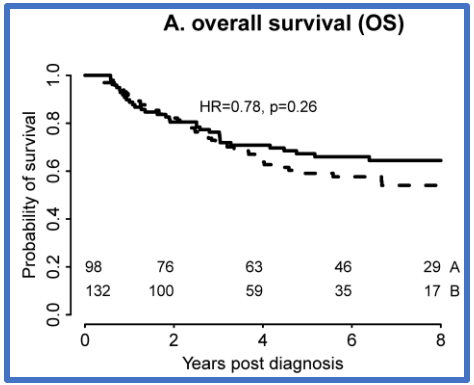
Age ≥18y, Dx: 2001–2018

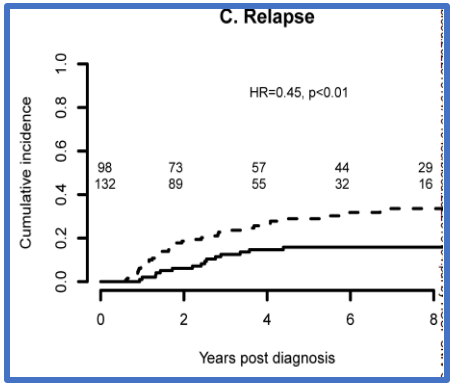
Persistent CMR from d90 (RQ PCR *BCR::ABL* $<10^{-4}$)

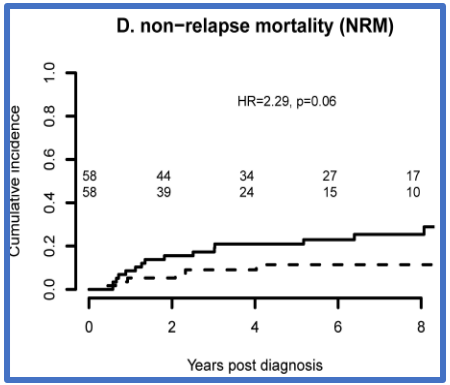
Cohorts

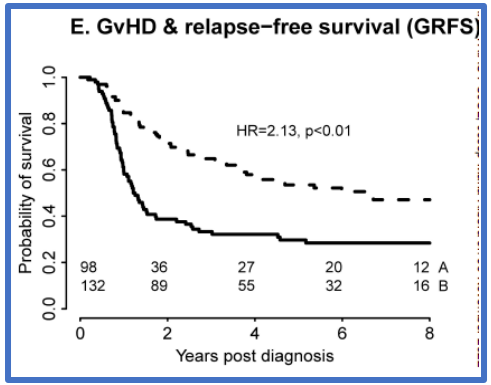
AlloHSCT (n = 98), Non HSCT (n = 132)

- AlloHSCT in CR1 does not improve survival for patients achieving a deep molecular remission
- AlloHSCT in CR1: lower incidence of relapse but increased treatment-related mortality



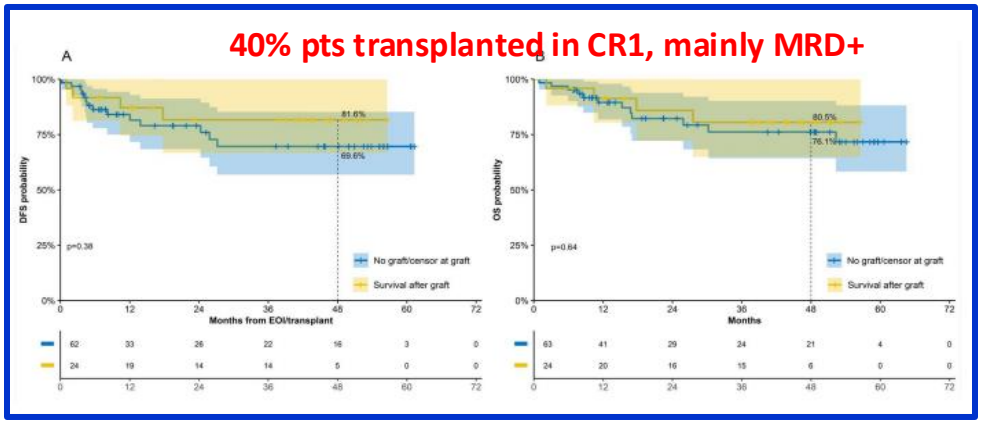






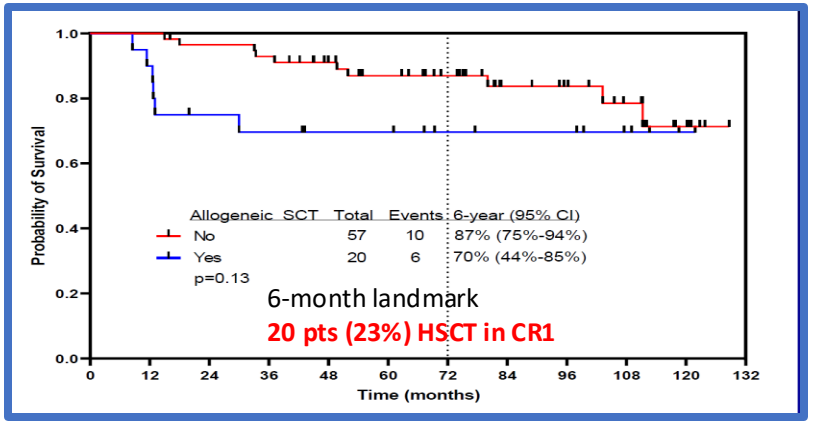
Ghobaldi A, et al. *Blood.* 2022;140(20):2101-2112.

D-ALBA Trial



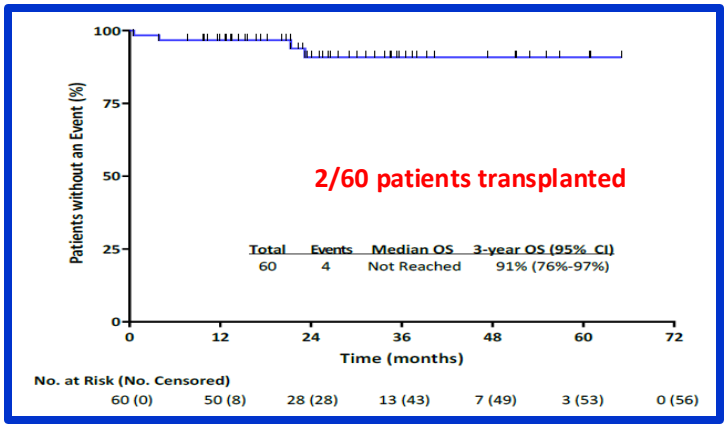
Foa R, et al. *J Clin Oncol.* 2024;42(8):881-885

HCVAD + ponatinib



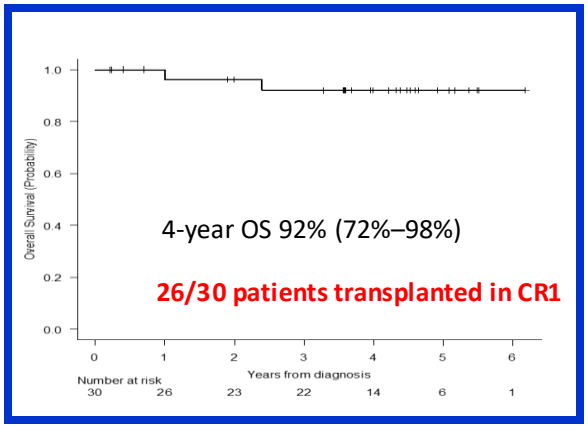
Kantarjian H, et al. *Am J Hematol.* 2023;98:493-501

Ponatinib + Blinatumomab

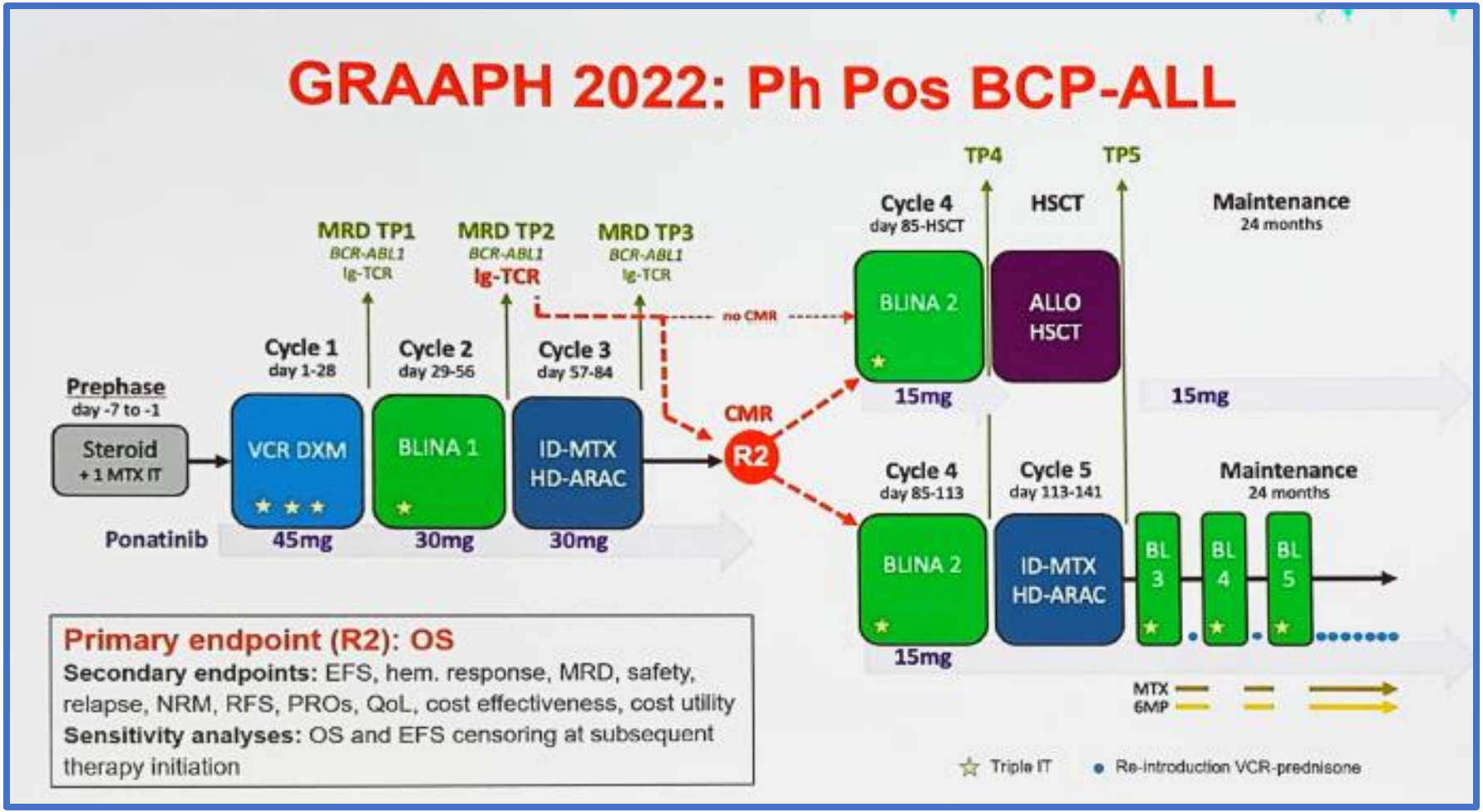


Kantarjian H, et al. *J Clin Oncol.* 2024 (in press)

Ponatinib + CHT + alloHSCT



Ribera JM, et al. *HemaSphere.* 2024



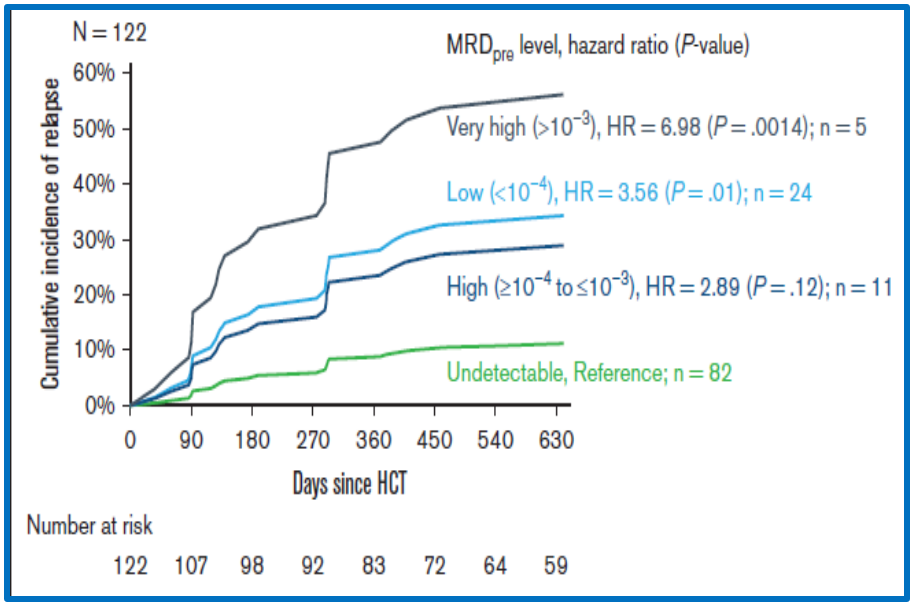
Courtesy of N Boissel.

HSCT in Ph-Negative ALL

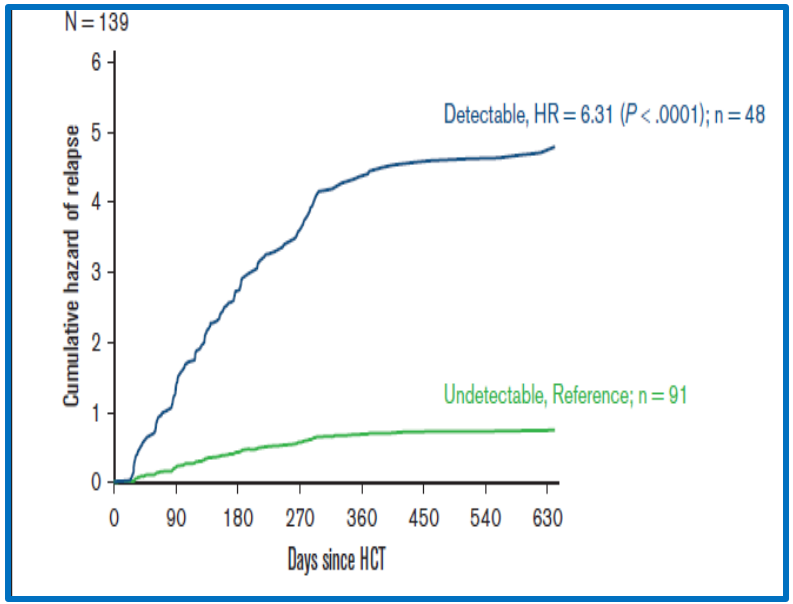
MRD level and genetic background are decisory

Impact of pre- and post-HSCT MRD level on transplant outcome

MRD level pre HSCT



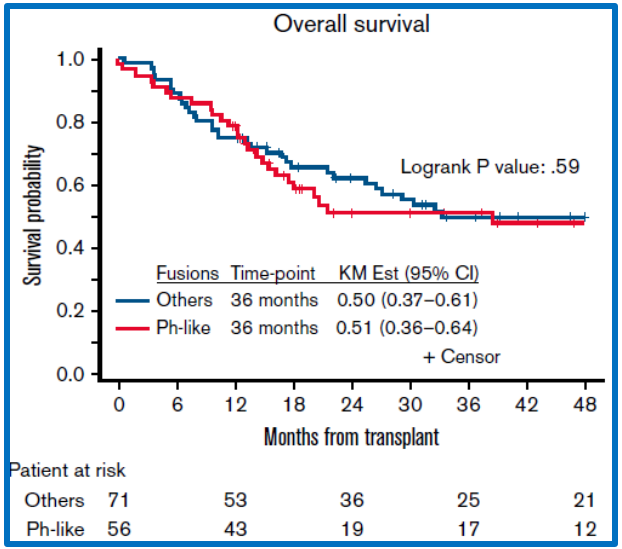
MRD level post HSCT

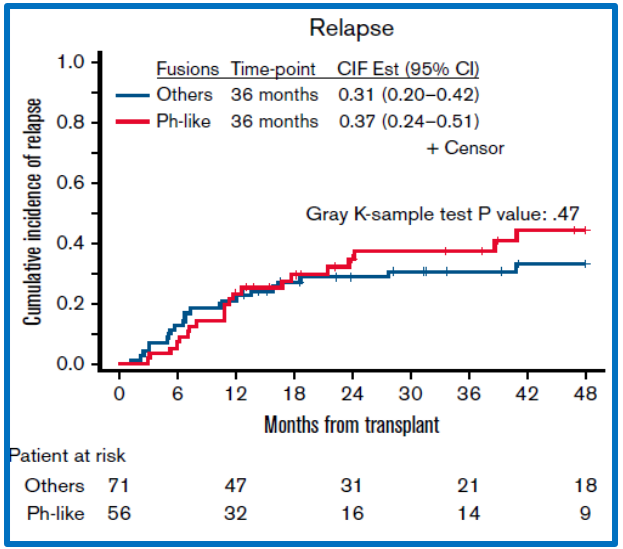


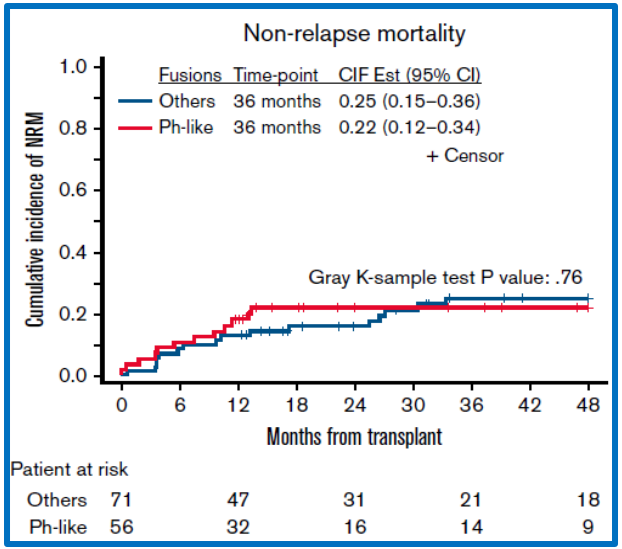
Try to transplant at the lowest MRD level possible!
Immunotherapy useful for this purpose

Liang EC, et al. *Blood Adv.* 2023;7:3395-3402.

Outcomes of alloHSCT in Ph-like ALL: City of Hope experience







Outcome after HSCT similar to that of non-Ph–like patients

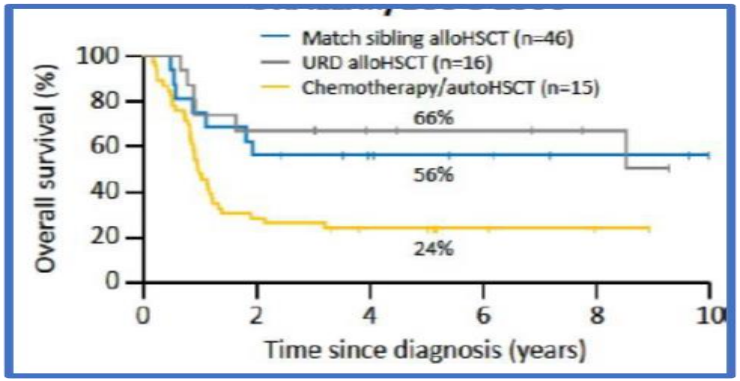
Problem: to attain a negative MRD level!

Aldoss I, et al. *Blood Adv.* 2022;6:4936-4948.

KMT2A ALL: AlloHSCT for all patients?

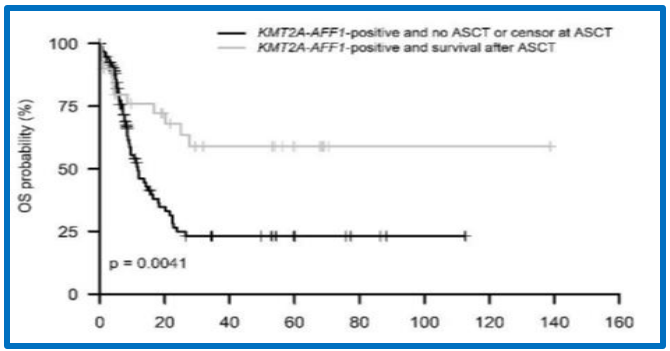
Classical approach

UKALL XII/ECOG2993



Marks DI. *Haematologica.* 2013;98:945-452

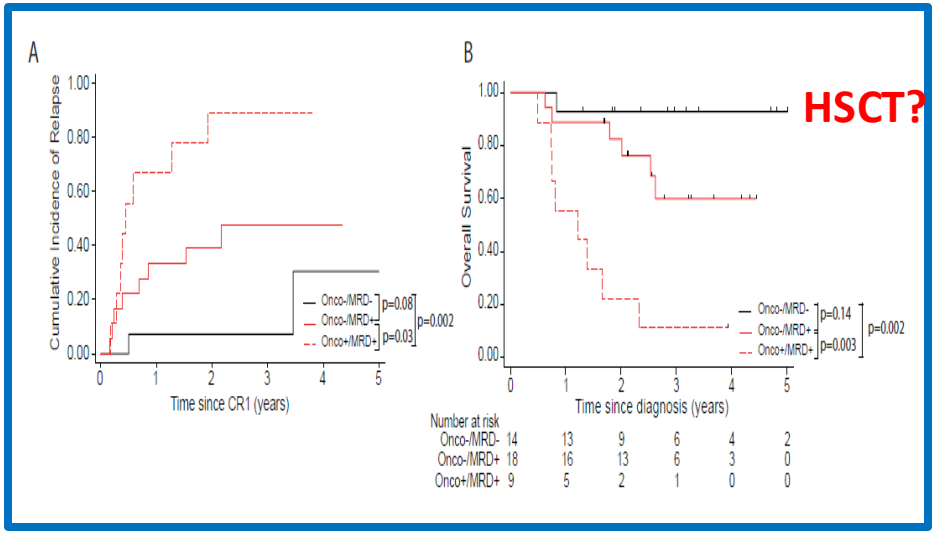
GIMEMA



Picicocci A. *Am J Hematol.* 2021;96:E334-E338.

Modern approach

GRAALL study



Onco+: *TP53* and/or *IKZF1* alterations

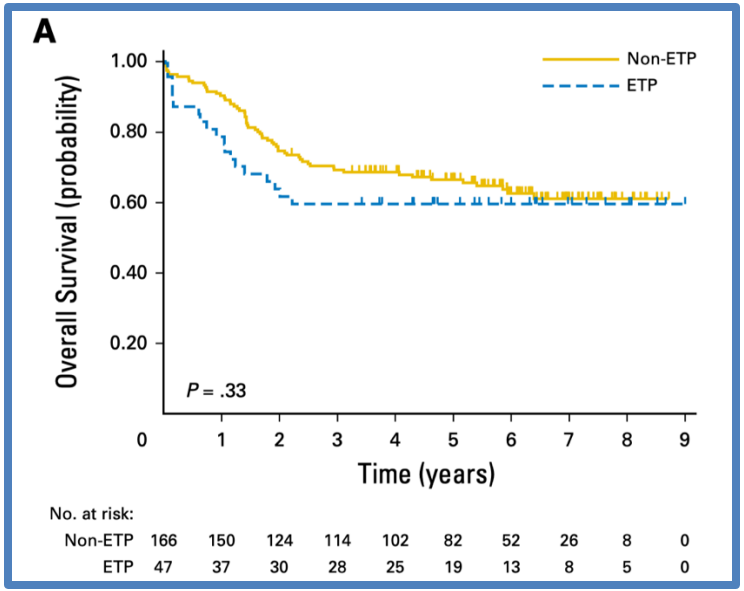
MRD assessed by *KMT2A* genomic fusion

Kim R, et al. *Blood.* 2024 (in press).

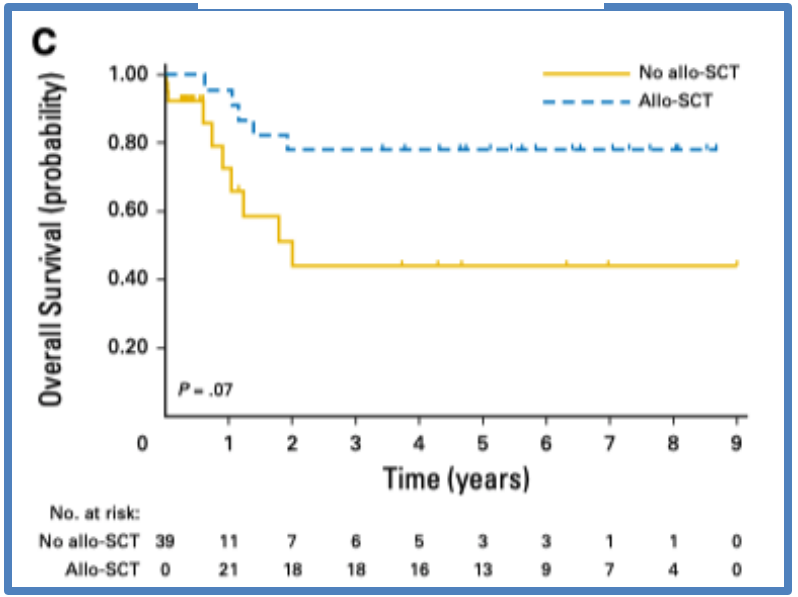
Outcome of T-ALL according to alloSCT in CR1

Overall Survival

Non-ETP vs ETP ALL



SCT in ETP ALL



HSCT could abrogate the poor prognosis of ETP ALL

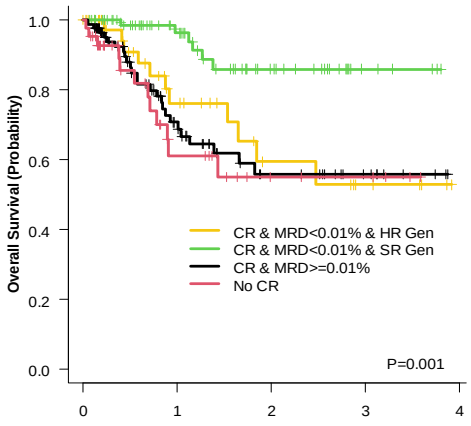
Bond et al. *J Clin Oncol.* 2017.

Combining MRD and genetic background for alloHSCT decision: PETHEMA ALL 2019 trial

MRD high risk
- MRD level >0.01% end induction
- MRD level >0.001% after consolidation

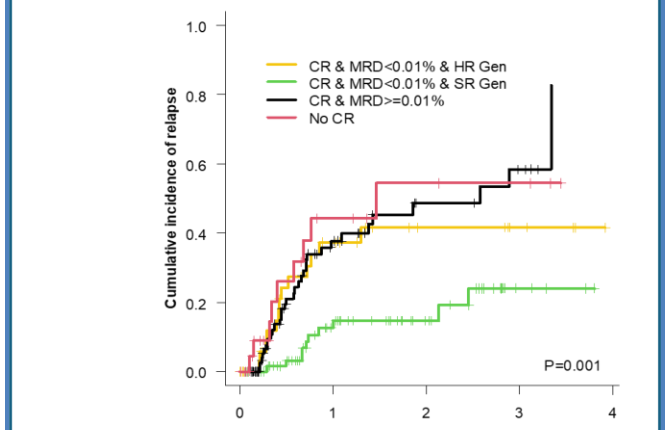
High-risk genetics: Any of the following
- Hypodiploidy <40 chromosomes and age >35 yr
- *KMT2A* (MLL) rearrangements
- *TP53* deletion/mutation in homozygosis
- Deletions of *IKZF1* and *CDKN2A/B* in B-cell precursor ALL
- *NOTCH1/FBXW7* unmutated and/or *RAS/PTEN* mutated in T-ALL

N = 237



Number at risk

CR & MRD<0.01% & HR Gen	48	19	9	5	0
CR & MRD<0.01% & SR Gen	75	44	21	5	0
CR & MRD>=0.01%	88	36	16	8	0
No CR	43	13	5	4	0



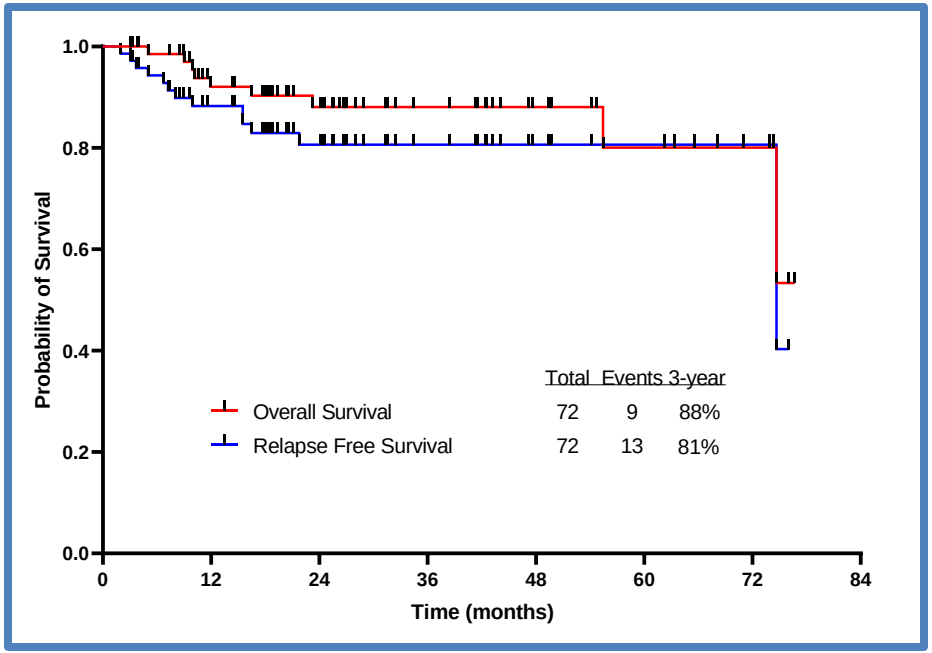
Number at risk

CR & MRD<0.01% & HR Gen	48	15	7	4	0
CR & MRD<0.01% & SR Gen	75	39	21	4	0
CR & MRD>=0.01%	88	26	8	4	0
No CR	28	7	4	3	0

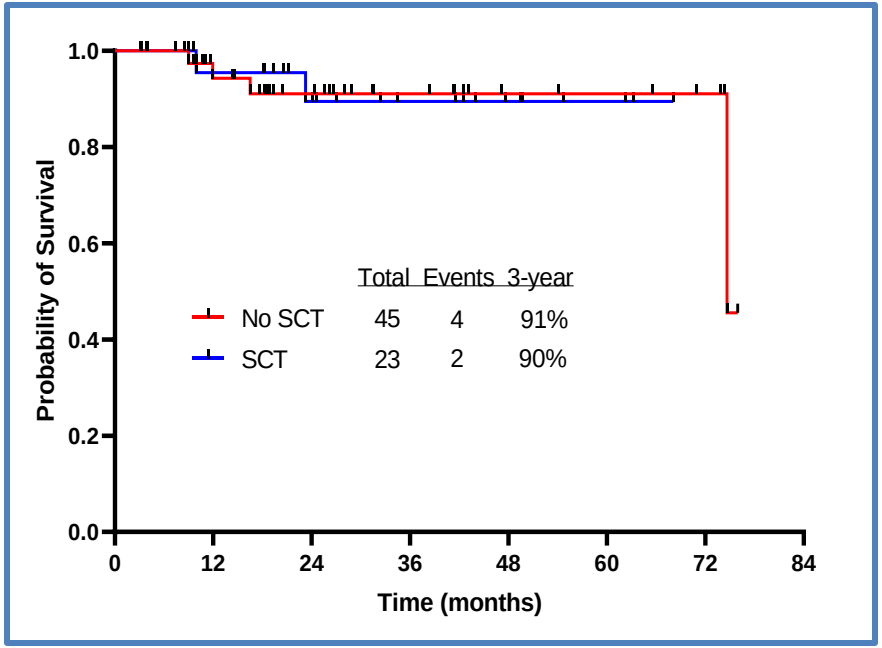
NCT04179929

PETHEMA data on file.

Will immunotherapy in first line reduce the indication of alloHSCT in CR1? Hyper-CVAD + Blinatumomab + InO in B-ALL: Outcome



Effect of alloHSCT



Short N, et al. *HemaSphere*. 2023;7:abstract P358.

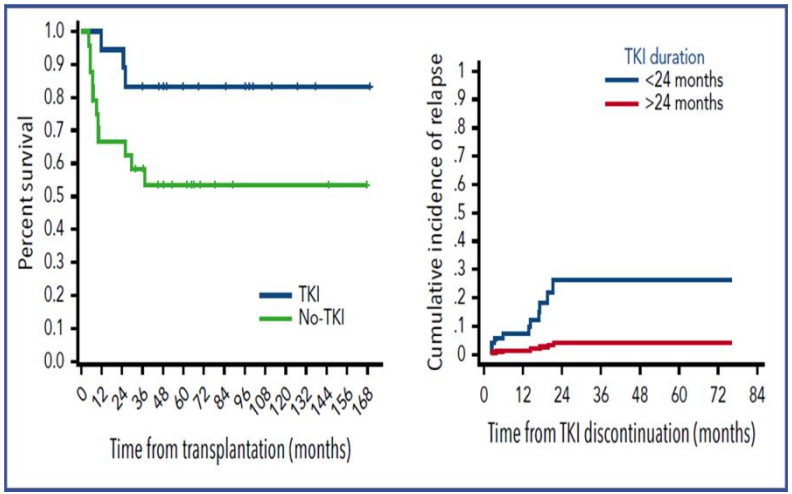
Prevention of relapses after HSCT

Feasible for Ph+ ALL

Feasible and effective in the remaining subtypes?

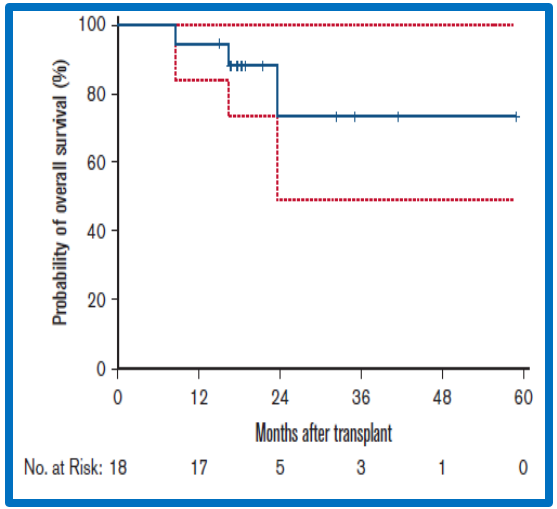
Prevention of relapse after alloHSCT

Ph-positive ALL: TKI

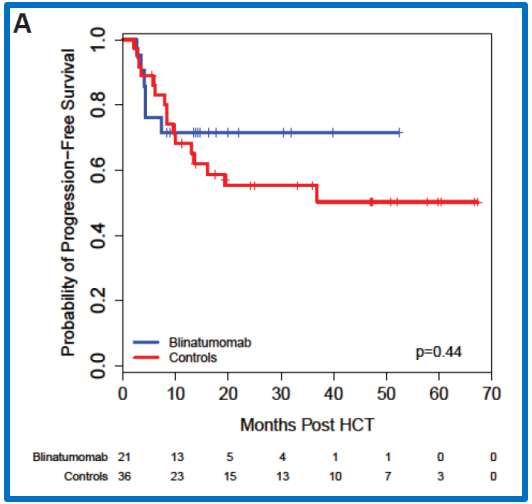


Saini N, et al. Blood . 2020; 136:1786-1789

Ph-negative ALL: InO or Blinatumomab?



Metheny LL, et al. *Blood Adv*. 2024;8:1384-1391



Gaballa MR, et al. *Blood*. 2022;139:1908-1919

Consolidative HSCT after CAR T?

It depends . . .

CAR T construct, CAR T persistence, MRD after CAR T . . .

CAR T studies with HSCT consolidation

Study	Co-stimulatory domain	N	Age in years, median (range)	CR/CRi (%)	Outcomes (EFS/RFS/LFS/OS)	Allo-HCT in CR	Outcomes post-HCT vs no HCT in CR patients
Shah BD et al., 2021 NCT02614066	CD28	55	40 (28–52)	71	6-month RFS of 58% Median OS 25.4 months	10	HCT: 6/10 alive in CR No HCT: 6/29 alive in CR *median DOR unchanged by allo-HCT
Shah NN et al., 2021 NCT01593696	CD28	50	14 (4-30)	62	Median OS of 10.5 months 6-months EFS of 38%	21	HCT: 12/21 alive in CR No HCT: 0/7 alive in CR
Park et al., 2018 NCT01044069	CD28	53	44 (23-74)	83	Median OS 12.9 months Median EFS 6.1 months	17	HCT: 5/17 alive in CR No HCT: 9/26 alive in CR *no diff in EFS/OS in MRD- CR
Maude et al., 2018 NCT02435849	4-1BB	79	11 (3-23)	82	3-year RFS of 44% 3-year OS of 63%	11	HCT: 8/8 alive in CR with data available
Hay et al., 2019 NCT01865617	4-1BB	53	39 (20-76)	85	Median OS 20 months in responders Median EFS 7.6 months in responders	18	HCT: 11/18 alive in CR No HCT: 5/27 alive in CR *allo-HCT associated with improved EFS (HR=0.29) with MRD- CR
Frey et al., 2019 NCT01029366 NCT02030847	4-1BB	35	34 (21 – 70)	69	Median OS 19.1 months Median EFS 5.6 months	9	HCT: Not reported No HCT: Not reported *allo-HCT associated with improved EFS
Roddie et al., 2021 NCT02935257	4-IBB	20	42 (18-62)	85	2-year OS 58% 2-year EFS 48.3%	3	HCT: Not reported No HCT: Not reported
Gu et al., 2020 NCT02975687	4-1BB	20	18 (3-52)	90	Median OS 12.9 mo. Median RFS 6.9 mo.	14	HCT: 7/14 alive in CR No HCT: 0/4 alive in CR
Zhang et al., 2020 NCT03173417	4-1BB/CD28	110	12 (2-61)	93	1-year OS 64% 1-year LFS 58%	75	HCT: 10/75 relapsed No HCT: 13/27 relapsed *allo-HCT associated with improved OS, LFS

Kebraiei P, et al. SOHO 2024.

Concluding remarks

- HSCT stabilized in recent years
- Results improve over time
- Ph+ ALL: modern therapies led to reduced HSCT indications
- Ph-neg ALL: MRD and genetics, best tools for HSCT decision in CR1
- HSCT indication can be modulated by immunotherapy in first line

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Current treatment options for relapsed AML in adult and elderly patients

Charles Craddock

APTITUDE HEALTH

Current Treatment Options for Relapsed AML in Adult and Elderly Patients

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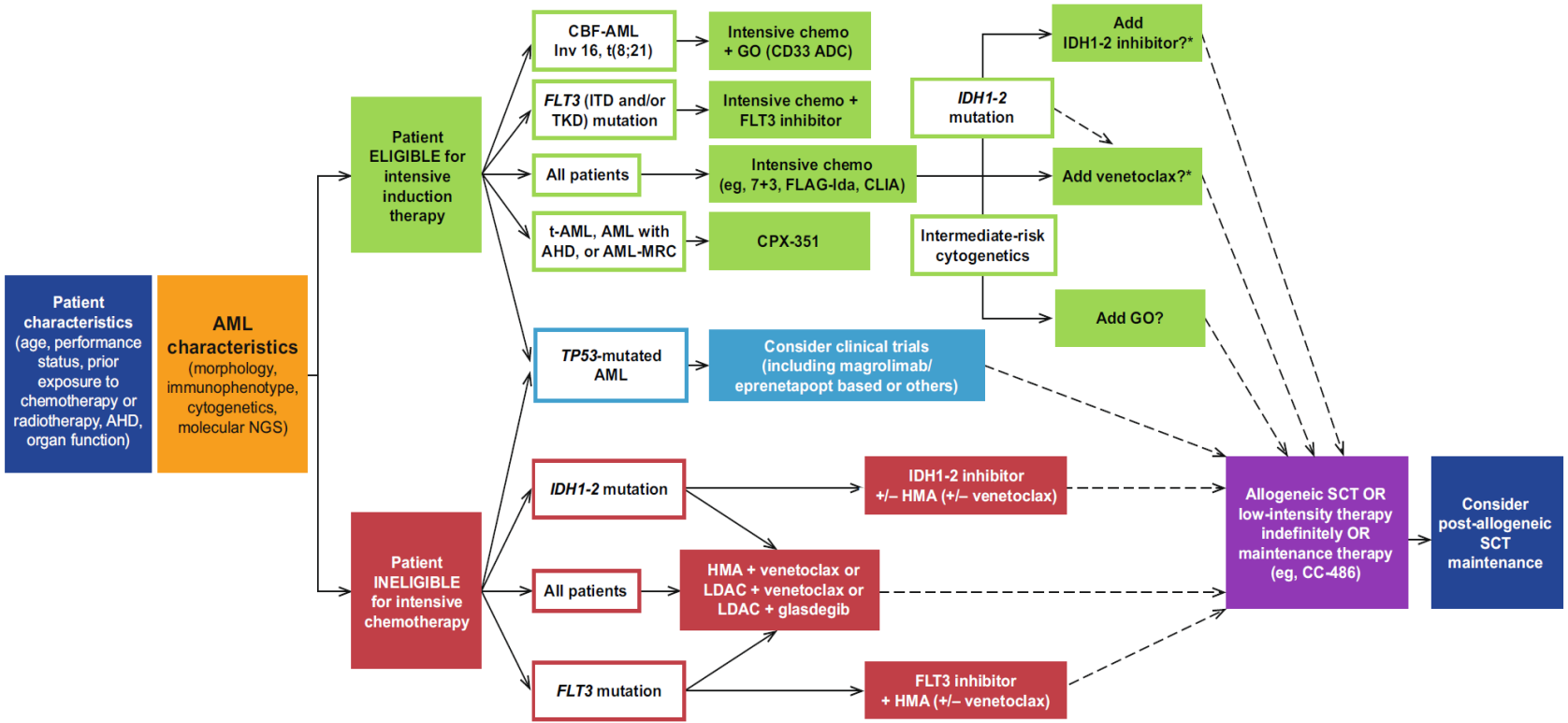
Evolving Diagnostic and Treatment Paradigm for Newly Diagnosed AML



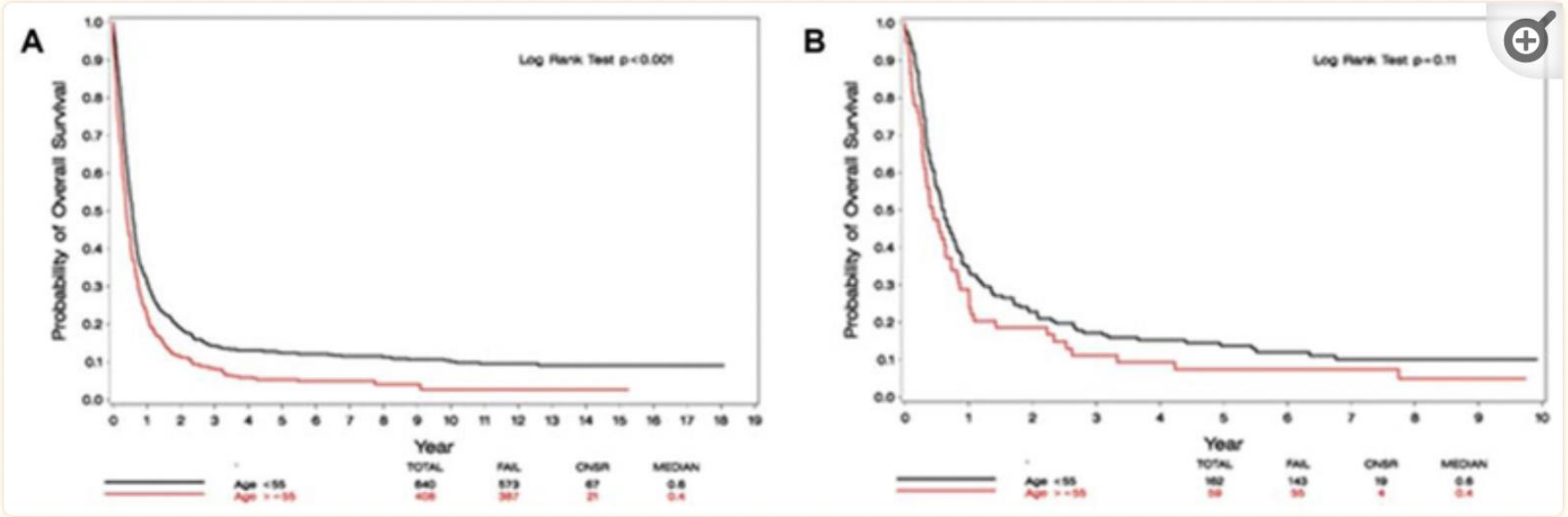
Daver N, et al. *Blood Cancer J*. 2020;10:107.

Disease Relapse Is the Major Barrier to Long-Term Survival in Adult AML

- Disease relapse remains the major cause of failure in adults with AML treated with curative intent using either IC or allo-SCT
- Outcome after relapse is poor, and strategies with the potential to reduce disease recurrence are urgently required
- Key to the effective implementation of strategies to reduce the risk of relapse is characterization of relapse biology

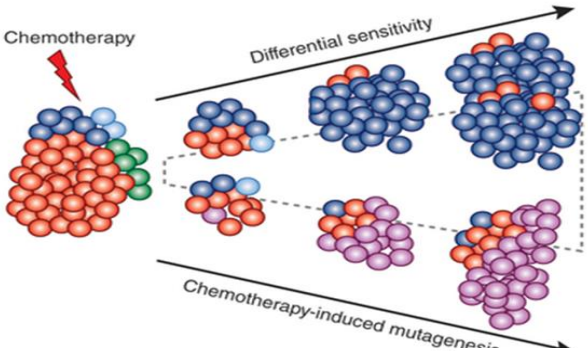
Loke J, et al. *Br J Haematol.* 2020;188:129-146.

Outcome in Relapsed AML: Age, Cytogenetics, Duration of CR1, and Allograft Exposure Predict Survival



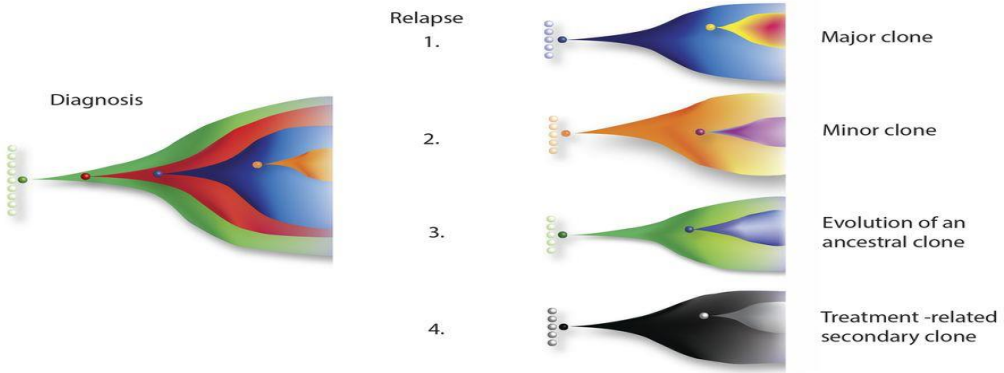
Ganzel C, et al. *Am J Hematol.* 2018;93:1074-1081.

Clonal Evolution and Importance of Repeat Genomic Testing at Time of AML Recurrence



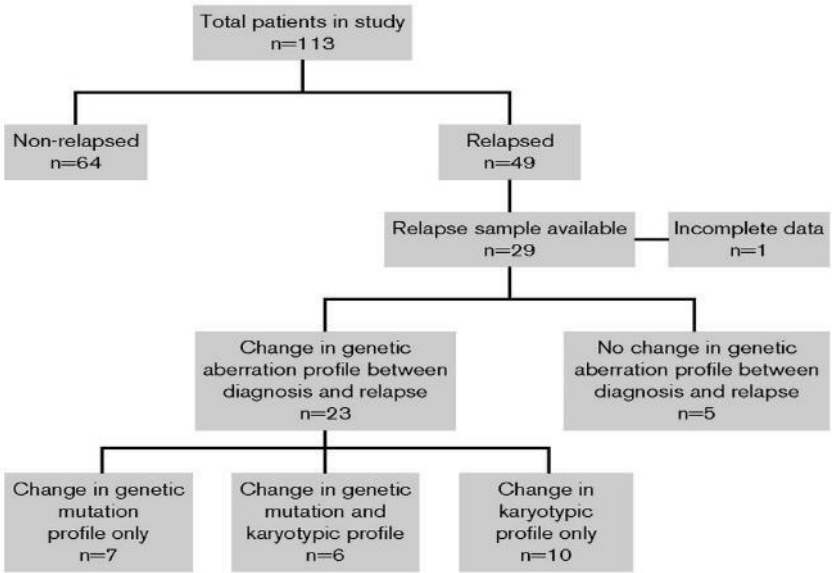
Leukemia is not a static condition

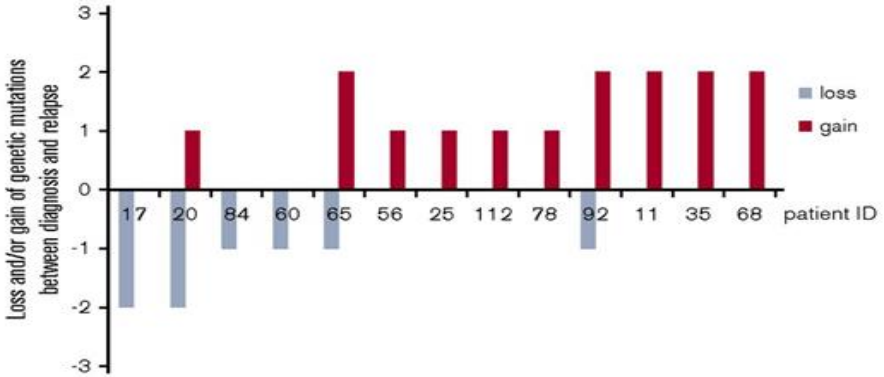
Repeat genomic analysis at relapse is necessary



Kleppe M, Levine RL. *Nat Med.* 2014;20:342-344; Grimwade D, et al. *Blood*. 2016;127:29-41.

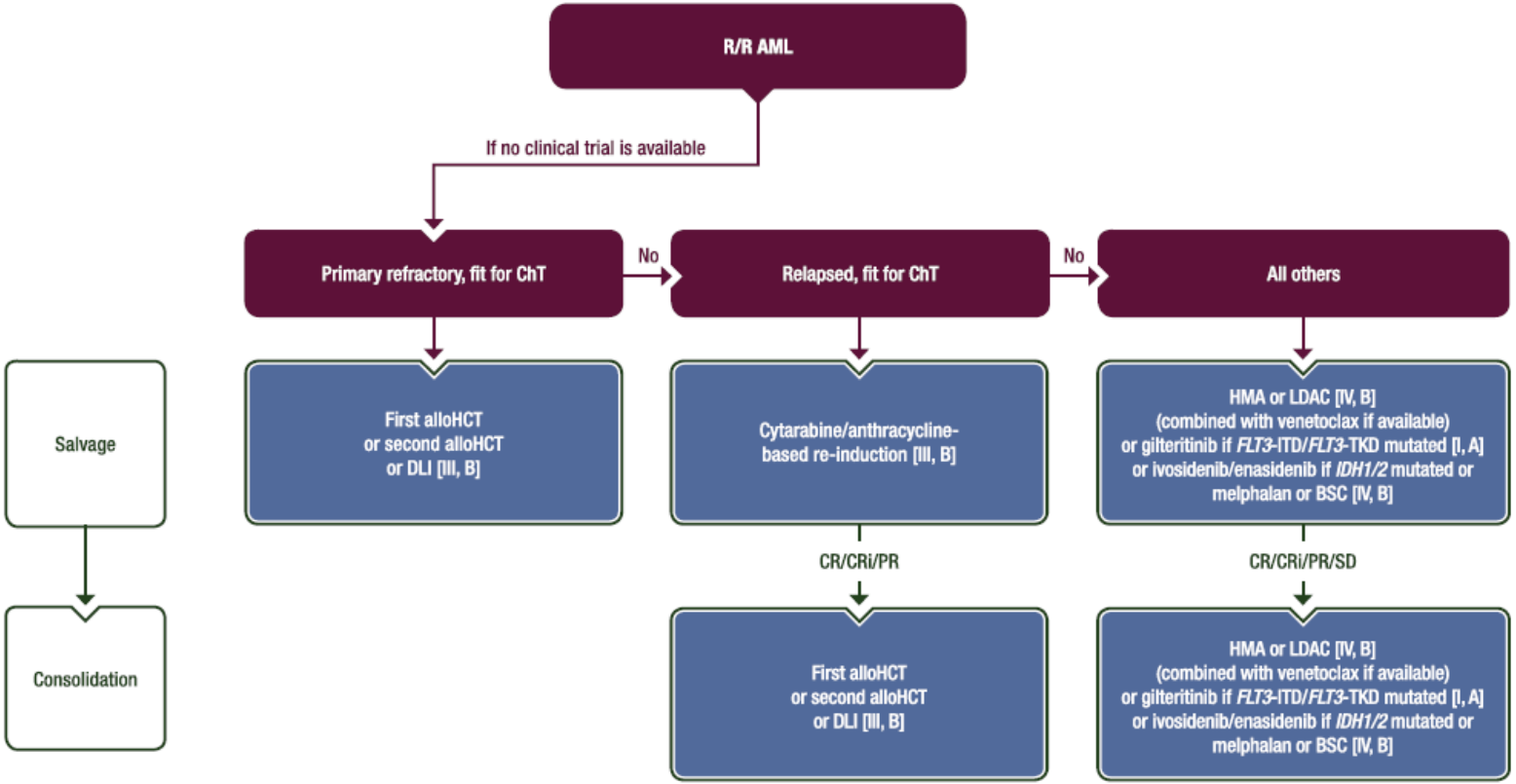
Mutational Instability at Disease Relapse Informs the Choice of Relapse Therapies





Quek L, et al. *Blood Adv.* 2016;1:193-204.

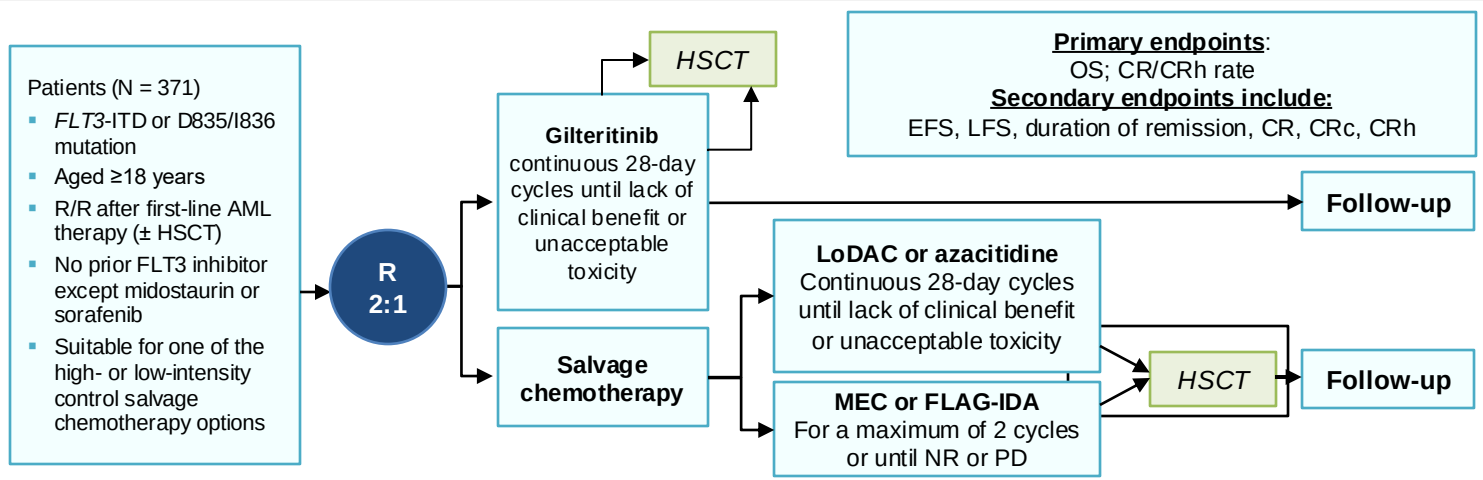
ESMO Guidelines for R/R AML



Heuser M, et al. *Ann Oncol.* 2020;31:697-712.

Gilteritinib: Phase III ADMIRAL Trial

MONOTHERAPY VS SALVAGE CHEMOTHERAPY (ADMIRAL; NCT02421939)



- ADMIRAL addresses gilteritinib efficacy in the R/R disease setting compared with salvage chemotherapy; the study includes patients who are and are not fit for high-intensity chemotherapy
- On the basis of data from the ADMIRAL study, gilteritinib is approved in over 40 other countries for treatment of adults with *FLT3*-mutated R/R AML

Perl AE, et al. *N Engl J Med.* 2019;381:1728-1740.

ADMIRAL: Baseline Demographics

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	All Patients (N=371)	Gilteritinib (N=247)	Salvage Chemotherapy (N=124)
Age — yr			
Median	62.0	62.0	61.5
Range	19.0–85.0	20.0–84.0	19.0–85.0
Female sex — no. (%)	201 (54.2)	131 (53.0)	70 (56.5)
Cytogenetic risk status — no. (%)			
Favorable	5 (1.3)	4 (1.6)	1 (0.8)
Intermediate	271 (73.0)	182 (73.7)	89 (71.8)
Unfavorable	37 (10.0)	26 (10.5)	11 (8.9)
Unknown	58 (15.6)	35 (14.2)	23 (18.5)
Previous therapy for AML — no. (%)			
Anthracycline	311 (83.8)	205 (83.0)	106 (85.5)
FLT3 inhibitor	46 (12.4)	32 (13.0)	14 (11.3)
HSCT	74 (19.9)	48 (19.4)	26 (21.0)
Response to first-line therapy before enrollment — no. (%)†			
Relapse	225 (60.6)	149 (60.3)	76 (61.3)
Primary refractory disease without HSCT	146 (39.4)	98 (39.7)	48 (38.7)
Preselected salvage chemotherapy per IRT — no. (%)			
High-intensity chemotherapy	224 (60.4)	149 (60.3)	75 (60.5)
Low-intensity chemotherapy	147 (39.6)	98 (39.7)	49 (39.5)
FLT3 mutation subtype — no. (%)‡			
ITD only	328 (88.4)	215 (87.0)	113 (91.1)
TKD only	31 (8.4)	21 (8.5)	10 (8.1)
ITD and TKD	7 (1.9)	7 (2.8)	0

* The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding. AML denotes acute myeloid leukemia, HSCT hematopoietic stem-cell transplantation, ITD internal tandem duplication, and TKD tyrosine kinase domain.
† Response was based on findings from interactive response technology (IRT).
‡ Central laboratory confirmed the *FLT3* mutation status. Five patients (1.3%) had unconfirmed *FLT3* mutations; four patients (1.6%) were assigned to the gilteritinib group and one (0.8%) to the chemotherapy group.

Perl AE, et al. *N Engl J Med.* 2019;381:1728-1740.

ADMIRAL: Adverse Event Profile

Table 3. Incidence of Adverse Events during Treatment That Occurred in at Least 20% of the Patients in Either Treatment Group (Safety Analysis Population).*

Event	Gilteritinib (N=246)			Salvage Chemotherapy (N=109)		
	Adverse Event of Any Grade	Grade ≥3 Adverse Event	Serious Adverse Event	Adverse Event of Any Grade	Grade ≥3 Adverse Event	Serious Adverse Event
	number of patients (percent)					
Febrile neutropenia	115 (46.7)	113 (45.9)	76 (30.9)	40 (36.7)	40 (36.7)	9 (8.3)
Anemia	116 (47.2)	100 (40.7)	8 (3.3)	38 (34.9)	33 (30.3)	0
Pyrexia	105 (42.7)	8 (3.3)	32 (13.0)	32 (29.4)	4 (3.7)	1 (0.9)
Alanine aminotransferase increased	103 (41.9)	34 (13.8)	13 (5.3)	10 (9.2)	5 (4.6)	0
Diarrhea	81 (32.9)	9 (3.7)	10 (4.1)	32 (29.4)	3 (2.8)	0
Aspartate aminotransferase increased	99 (40.2)	36 (14.6)	10 (4.1)	13 (11.9)	2 (1.8)	0
Hypokalemia	71 (28.9)	32 (13.0)	0	34 (31.2)	12 (11.0)	1 (0.9)
Constipation	76 (30.9)	2 (0.8)	0	16 (14.7)	0	0
Fatigue	70 (28.5)	6 (2.4)	4 (1.6)	14 (12.8)	2 (1.8)	1 (0.9)
Platelet count decreased	56 (22.8)	54 (22.0)	5 (2.0)	28 (25.7)	27 (24.8)	0
Cough	72 (29.3)	1 (0.4)	2 (0.8)	11 (10.1)	0	0
Thrombocytopenia	63 (25.6)	56 (22.8)	4 (1.6)	18 (16.5)	18 (16.5)	1 (0.9)
Headache	64 (26.0)	3 (1.2)	5 (2.0)	16 (14.7)	0	0
Peripheral edema	59 (24.0)	1 (0.4)	0	13 (11.9)	0	0
Vomiting	53 (21.5)	1 (0.4)	1 (0.4)	15 (13.8)	0	0
Dyspnea	58 (23.6)	10 (4.1)	10 (4.1)	7 (6.4)	3 (2.8)	2 (1.8)
Blood alkaline phosphatase increased	56 (22.8)	7 (2.8)	1 (0.4)	2 (1.8)	0	0

* The events shown are limited to adverse events that had a difference in incidence of more than 2 percentage points between the treatment groups. The safety population comprised all the patients who had received at least one dose of trial treatment.

- Incidence of exposure-adjusted AE of grade ≥3 was 19.4 events/PY in the gilteritinib group vs 42.44 in the chemotherapy group
- Mortality at 30/60 days of ITT in the gilteritinib group was 2.0%/7.7% and 10.2%/19.0% in the chemotherapy group
- Drug-related fatal AEs occurred in 7 patients in the gilteritinib group vs 4 in the chemotherapy group

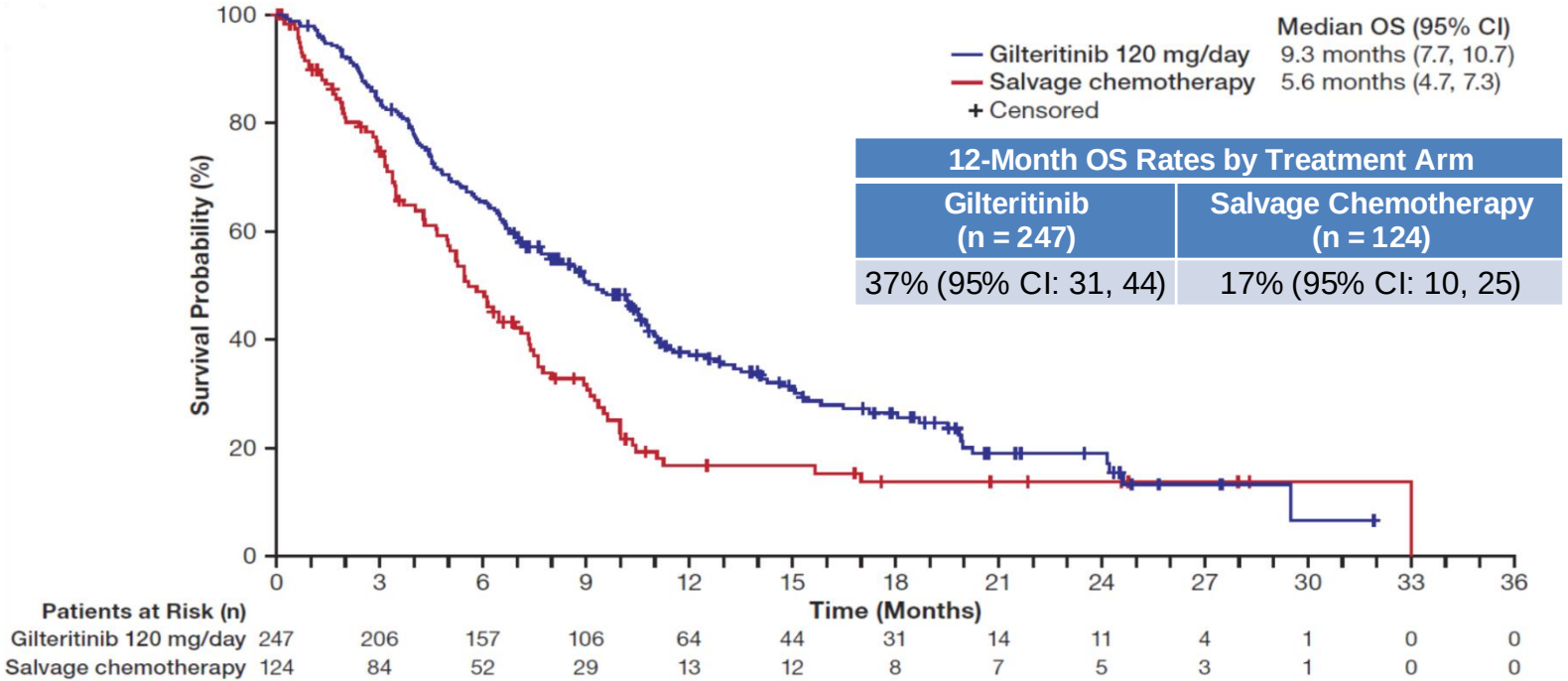
Perl AE, et al. *N Engl J Med.* 2019;381:1728-1740.

ADMIRAL: Response Outcomes (ITT population: N = 371)

Response Parameter	Gilteritinib (n = 247)	Salvage Chemotherapy (n = 124)
CR, n (%)	**52 (21)**	**13 (11)**
CRh, n (%)	32 (13)	6 (5)
CRi, n (%)	63 (26)	14 (11)
CRp, n (%)	19 (8)	0 (0)
CRc, n (%)	**134 (54)**	**27 (22)**
CR/CRh, n (%)	**84 (34)**	**19 (15)**
PR, n (%)	33 (13)	5 (4)
ORR, n (%)	167 (68)	32 (26)
NR, n (%)	66 (27)	43 (35)
Mean time to achieve CRc (SD), months	2.3 (1.9)	1.3 (0.5)
Median DOR (95% CI), months	11.0 (4.6, NE)	1.8 (NE, NE)
Allogeneic HSCT, n (%)	**63 (26)**	**19 (15)**

Perl AE, et al. *N Engl J Med.* 2019;381:1728-1740.

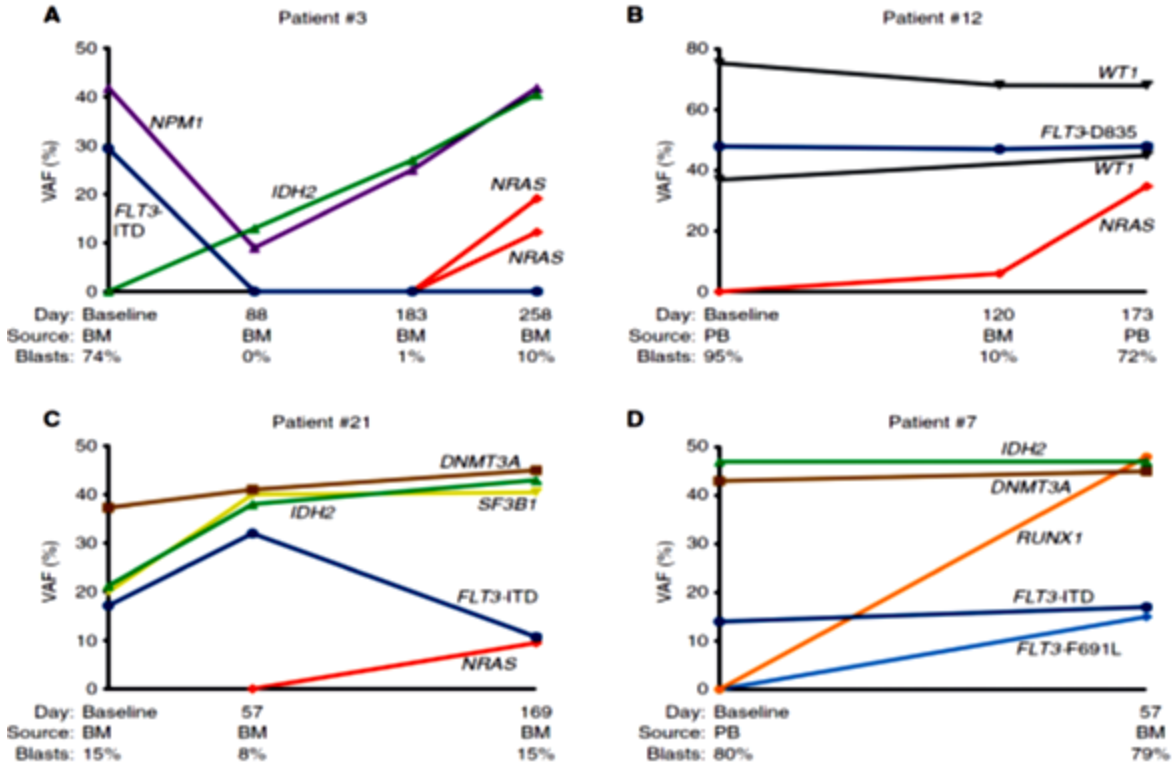
ADMIRAL: Overall Survival (ITT population: N = 371)



12-Month OS Rates by Treatment Arm	
Gilteritinib (n = 247)	Salvage Chemotherapy (n = 124)
37% (95% CI: 31, 44)	17% (95% CI: 10, 25)

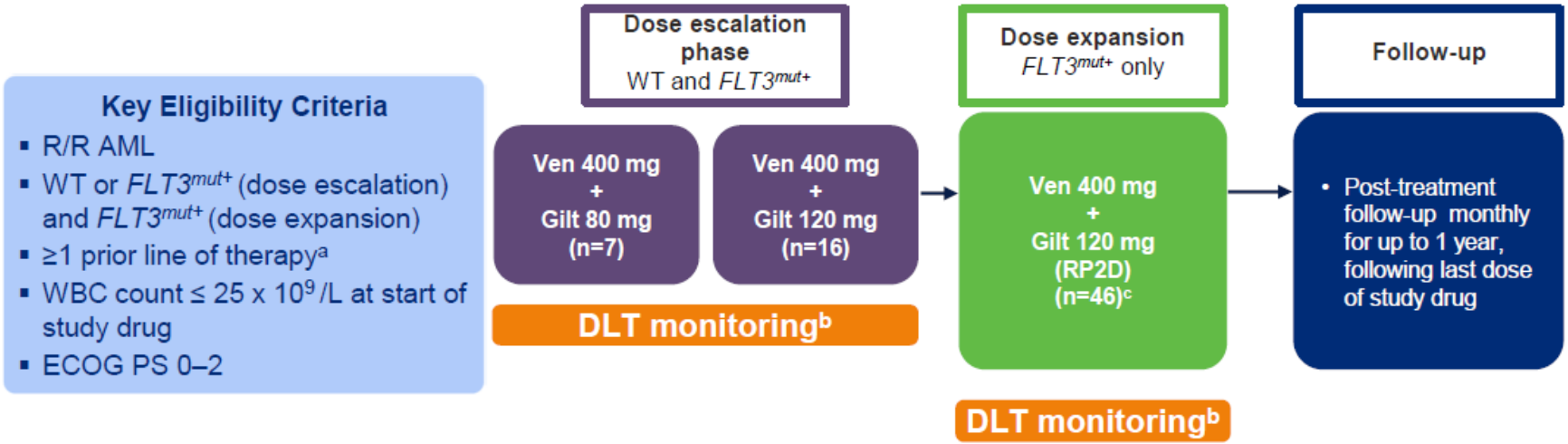
Perl AE, et al. *N Engl J Med.* 2019;381:1728-1740.

Multiple Mechanisms of Gilteritinib Resistance

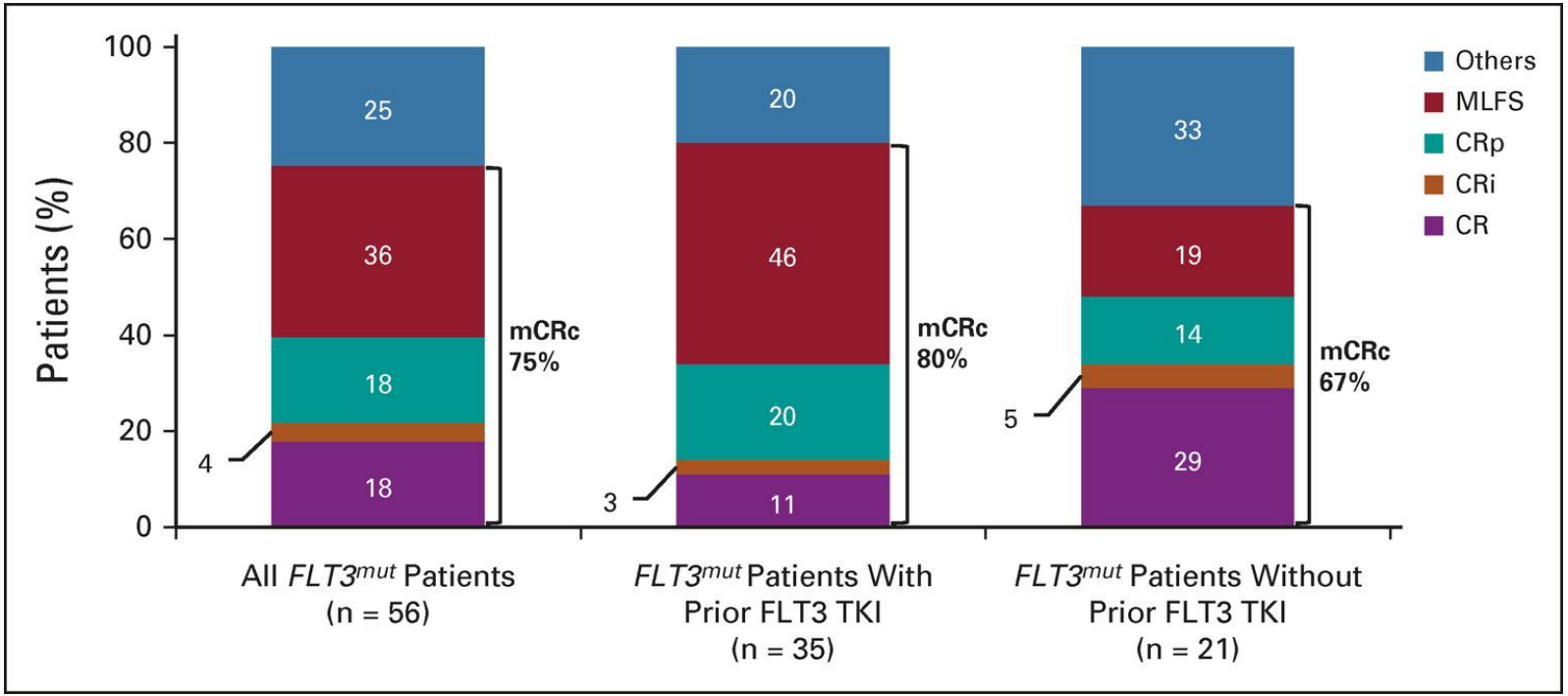


McMahon CM, et al. *Cancer Discov.* 2019;9:1050-1063.

Gilteritinib + Venetoclax: Phase Ib Study for *FLT3*-Mutated R/R AML

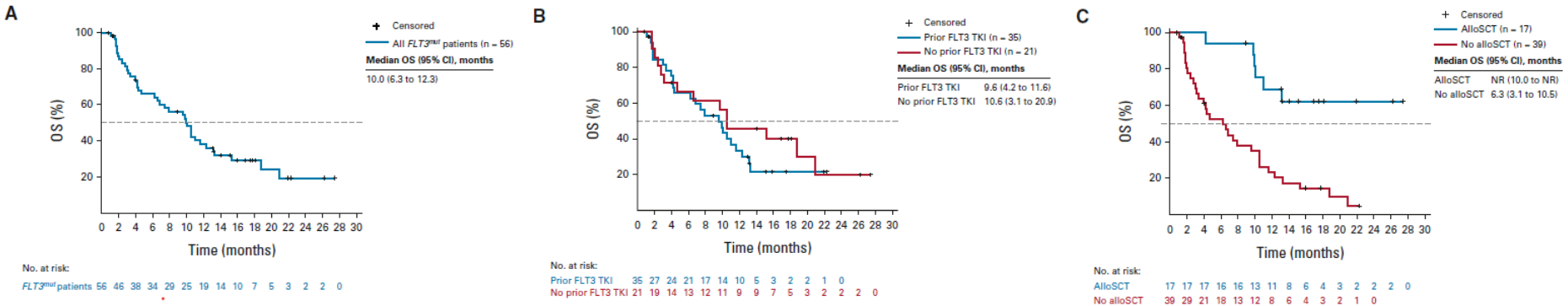


Gilteritinib + Venetoclax Is an Effective Salvage Therapy in Relapsed *FLT3*-Mutated AML



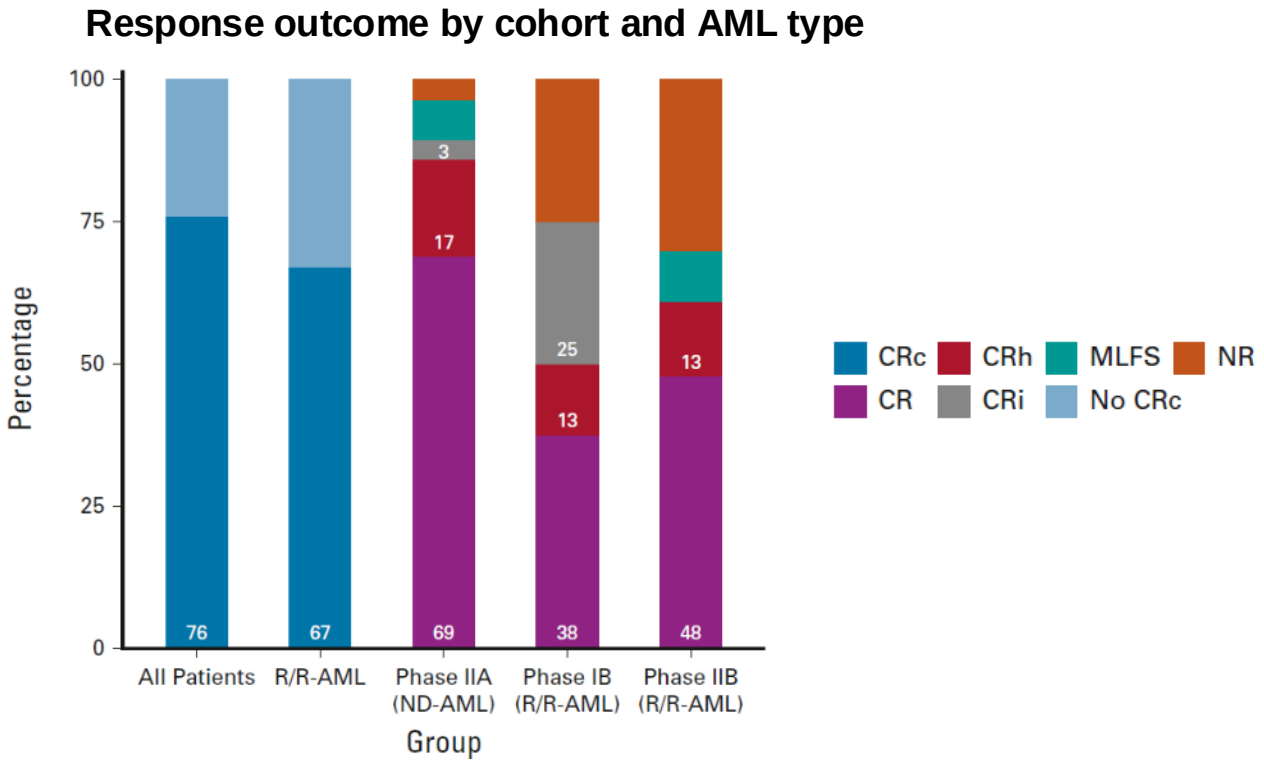
Daver N, et al. *J Clin Oncol.* 2022;40:4048-4059.

Overall Survival in Relapsed *FLT3*-Mutated AML: Impact of 1) Prior FLT3 Inhibitor Exposure, and 2) Stem Cell Transplantation



Daver N, et al. *J Clin Oncol.* 2022;40:4048-4059.

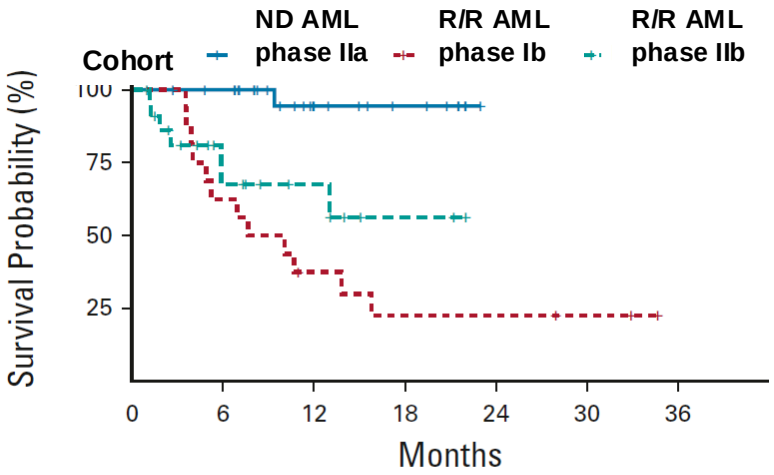
Venetoclax + FLAG-IDA: Response Outcomes
Phase Ib/II study of venetoclax + FLAG-IDA in ND and R/R AML



DiNardo CD, et al. *J Clin Oncol*. 2021;39:2768-2778.

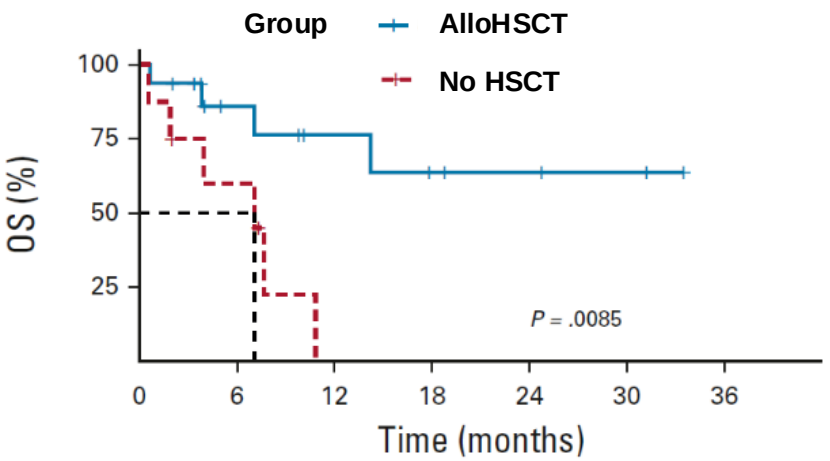
Venetoclax + FLAG-IDA: OS
Phase Ib/II study of venetoclax + FLAG-IDA in ND and R/R AML

OS by cohort



No. at risk:							
PIIA: ND-AML	29	26	12	7	0	0	0
PIB: R/R-AML	16	10	5	3	3	2	0
PIIB: R/R-AML	23	10	6	2	0	0	0

3-month landmark analysis of HSCT in patients with CRc



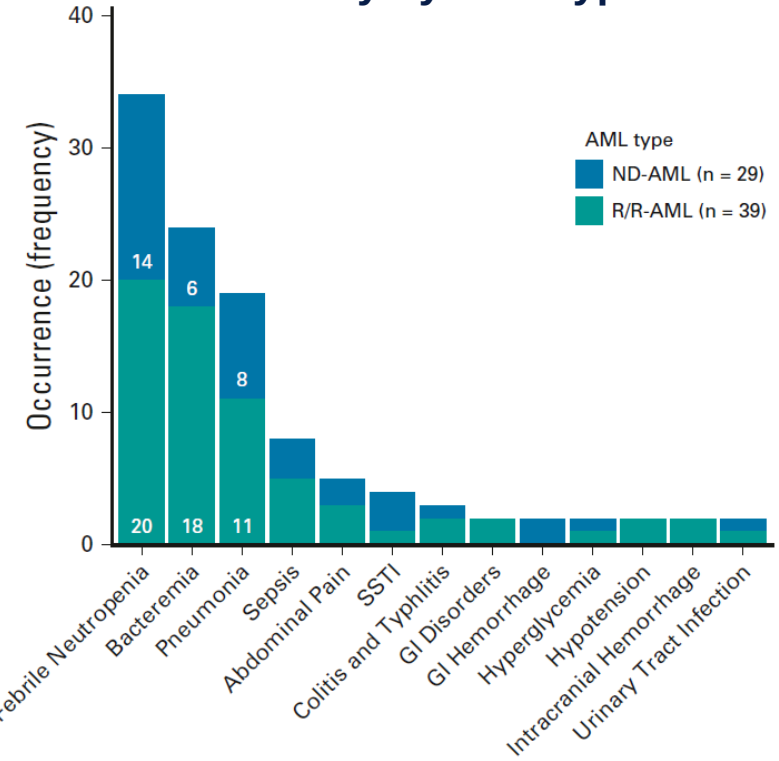
No. at risk:							
alloHSCT	16	9	6	4	3	2	0
No HSCT	8	4	0	0	0	0	0

DiNardo CD, et al. *J Clin Oncol.* 2021;39:2768-2778.

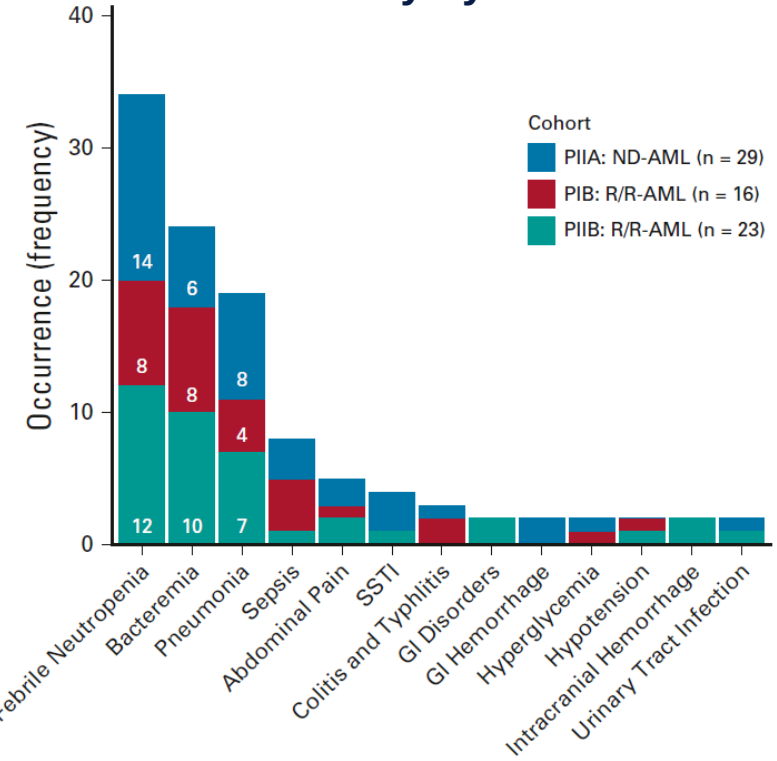
Venetoclax + FLAG-IDA: Safety

Phase Ib/II study of venetoclax + FLAG-IDA in ND and R/R AML

Safety by AML type

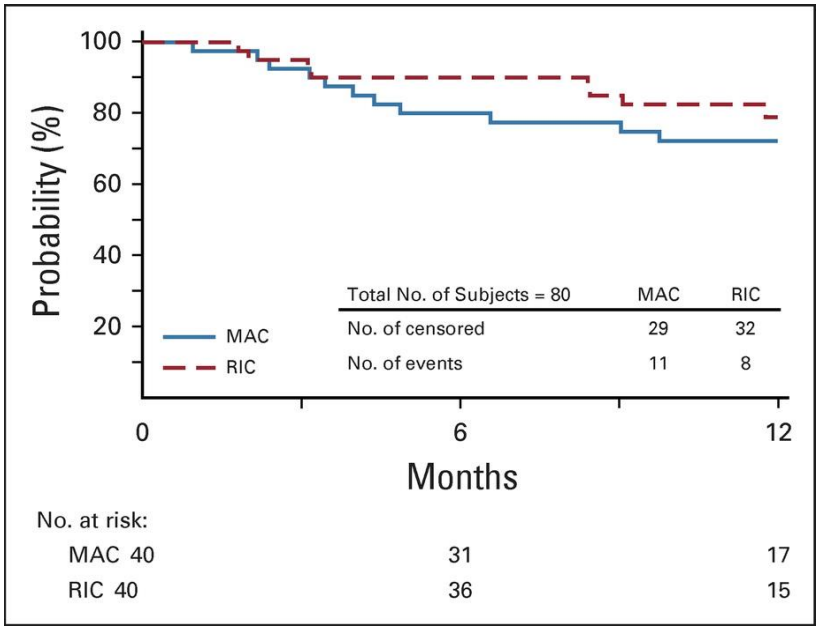


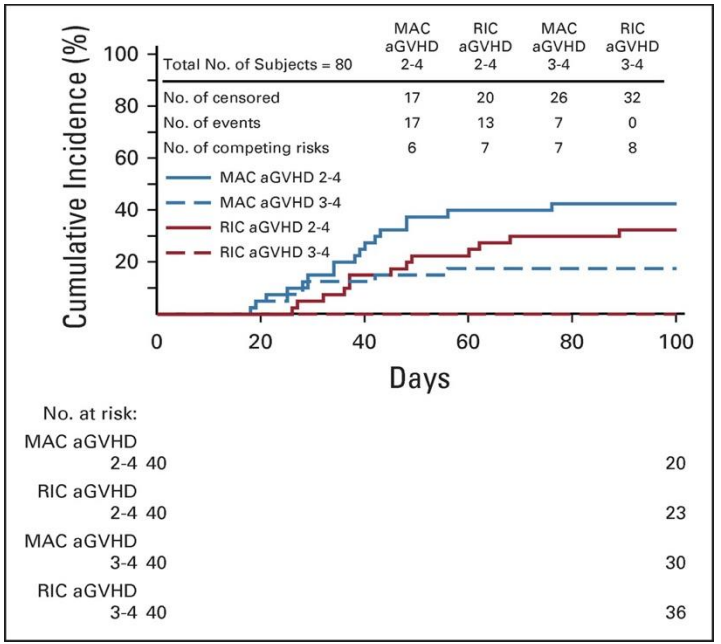
Safety by cohort



DiNardo CD, et al. *J Clin Oncol*. 2021;39:2768-2778.

Post-Transplant Cyclophosphamide Improves Outcomes in Adults Transplanted Using Mismatched Unrelated Donors

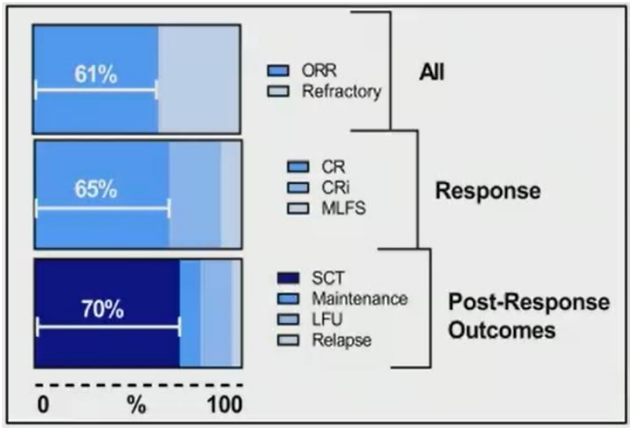




Shaw BE, et al. *J Clin Oncol.* 2021;39:1971-1982.

Updated Results From a Phase IIb Study of Venetoclax and FLAG-IDA in R/R AML: Response Rates

Response	N = 33, n (%)
ORR	20 (61)
Composite response	18 (55)
CR	13 (40)
CRi	5 (15)
MRD negative	13 (40)
MLFS	2 (6)
Follow-up	
ASCT	14 (42)
Maintenance	2 (6)
LFU after response	3 (9)
Relapse on-trial	1 (3)
Refractory	13 (40)



13/18 CRc patients (72%) were MRD negative

ELN Risk	N	CRc
Favorable	7/33 (21%)	6/7 (85%)
Intermediate	4/33 (12%)	3/4 (75%)
Adverse	22/33 (67%)	9/22 (41%)

Mutation	N	CRc
NPM1	5/33 (15%)	4/5 (80%)
RUNX1	7/33 (21%)	4/7 (57%)
ASXL1	6/33 (18%)	2/6 (33%)
TP53	7/33 (21%)	1/7 (14%)

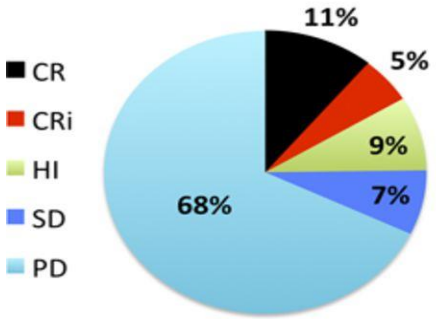
AML, acute myeloid leukemia; ASCT, allogeneic SCT; CR, complete remission; CRc, composite remission rate; CRi, CR with incomplete count recovery; ELN, European LeukemiaNet; LFU, lost to follow-up; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; ORR, objective response rate; R/R, relapsed/refractory; SCT, stem cell transplant.

Desikan SP, et al. ASH 2022. Abstract 221 (oral presentation).

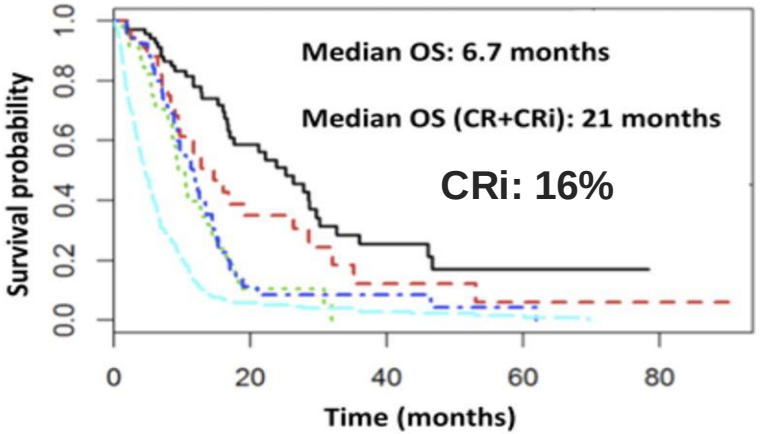
Hypomethylating Agents in R/R AML

655 RR-AML patients treated with HMAs

Response



Overall survival (OS)



10-day schedule of decitabine

< 5% PB blasts

Response

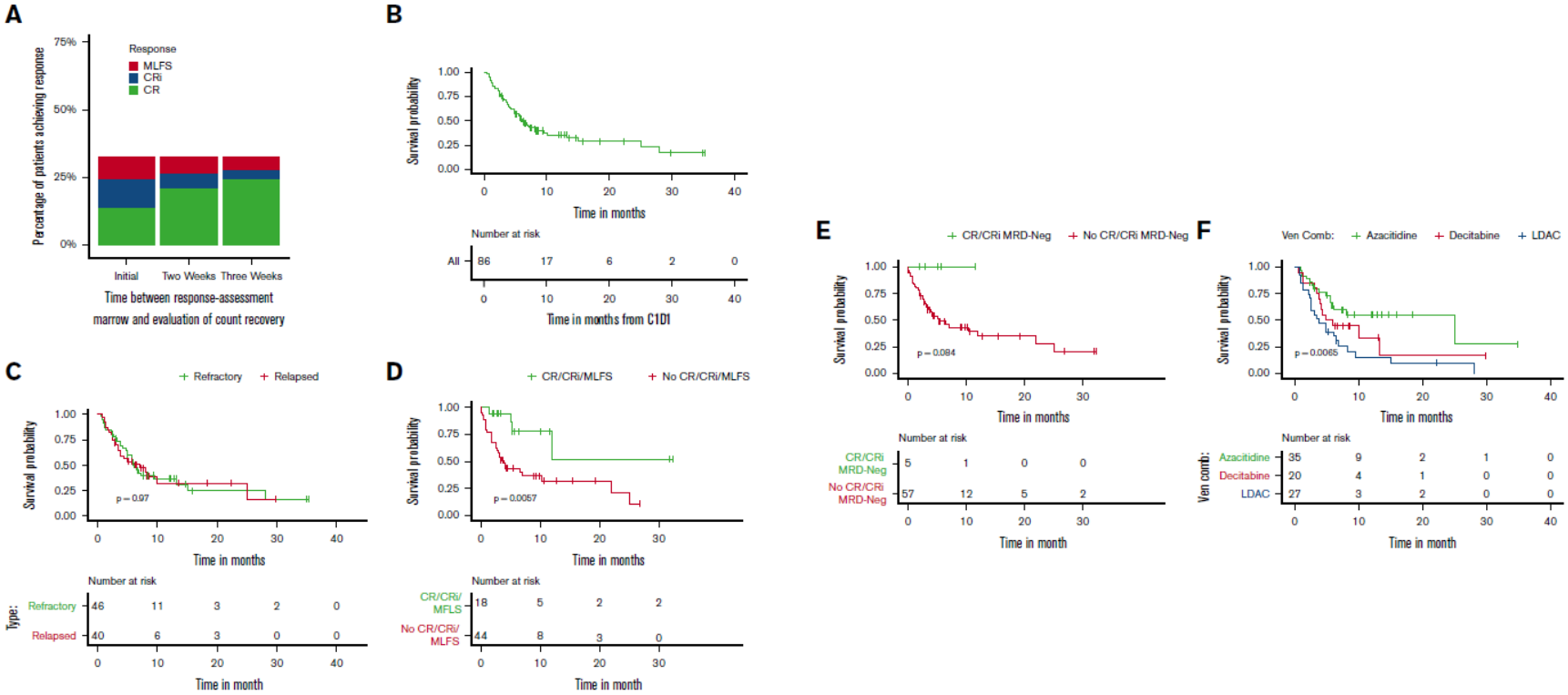
> 20% BM blasts

> 5% PB blasts

Overall survival

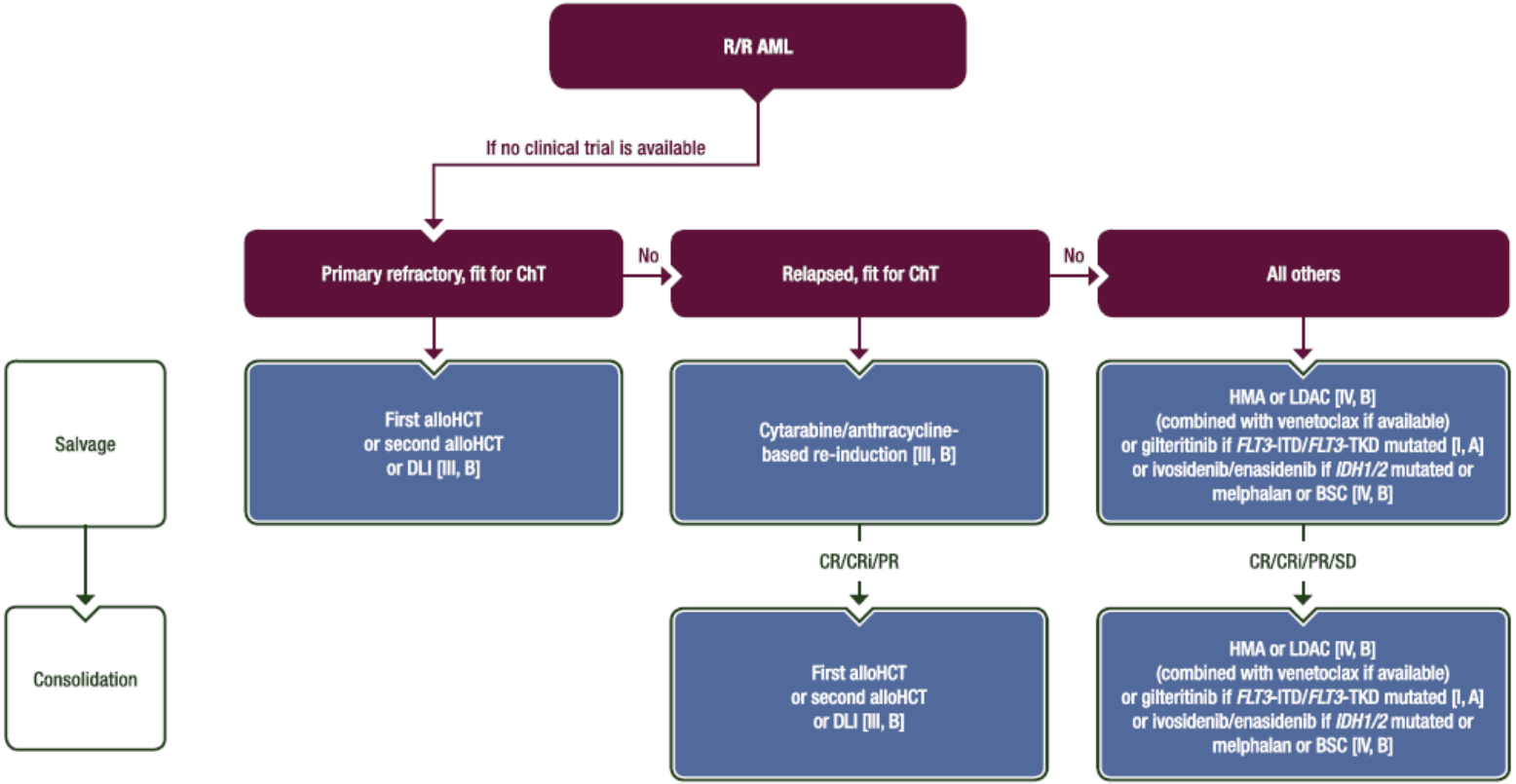
Stahl M, et al. *Blood Adv.* 2018;2:1765-1772.

Venetoclax Combination Therapy for R/R AML: Response



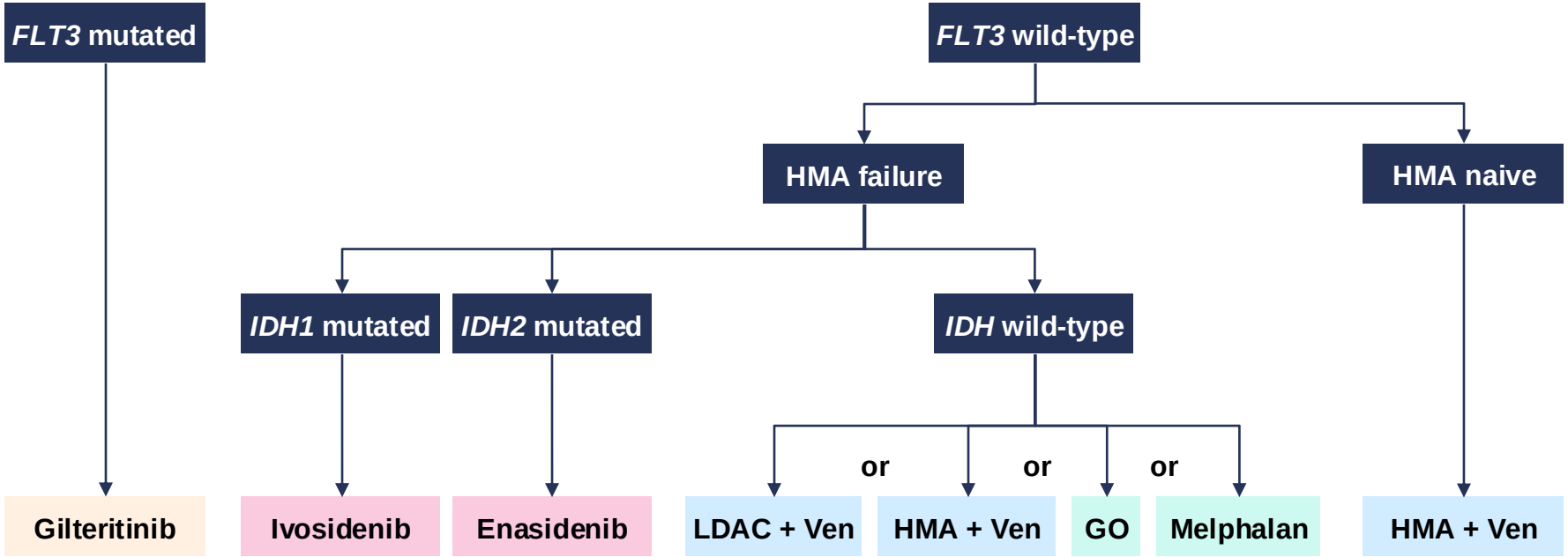
Stahl M, et al. *Blood Adv*. 2021;5:1552-1564.

ESMO Guidelines for R/R AML



Heuser M, et al. *Ann Oncol.* 2020;31:697-712.

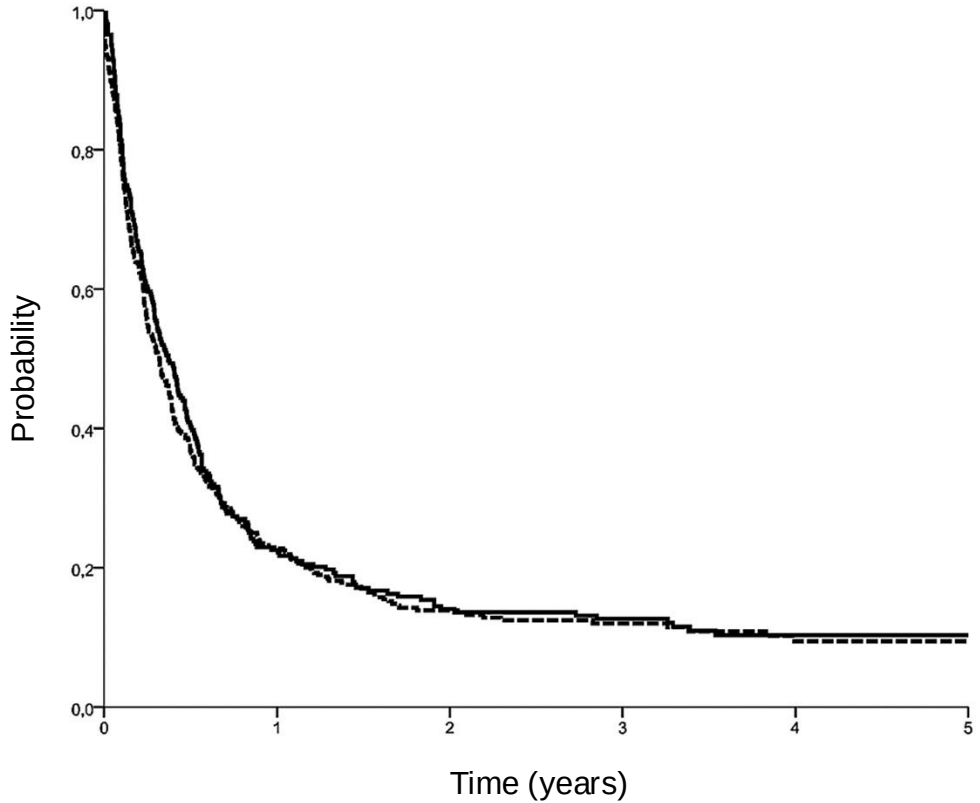
Onkopedia Updates to Guidelines for Patients With R/R AML Ineligible for Allogeneic Stem Cell Transplant



Management of Disease Relapse Post-Transplant

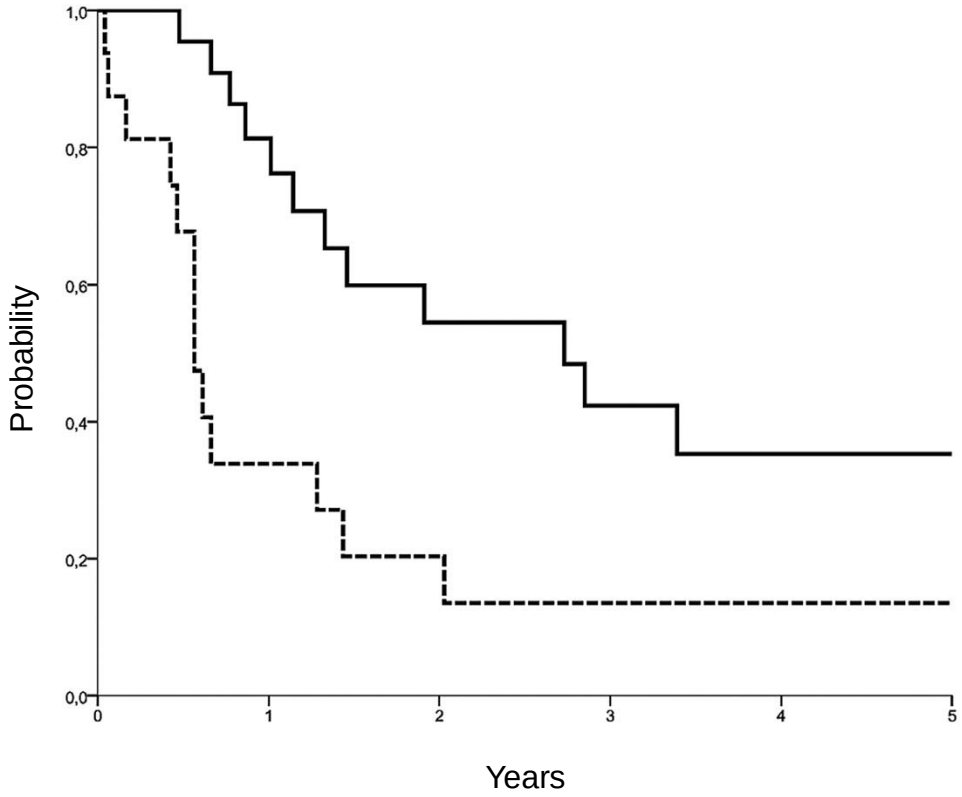
- In patients with relapse post-allograft, acquisition of CR is a prerequisite of long-term survival
- Approximately 20%–30% of patients treated with salvage chemotherapy have a second CR, but toxicity is significant
- Alternative salvage strategies include
  - Immunosuppression taper
  - Salvage azacitidine
  - Lenalidomide-azacitidine combination therapy

Long-Term Survival in Patients With Relapse After Allogeneic SCT for AML



Schmid C, et al. *Blood*. 2012;119:1599-1606.

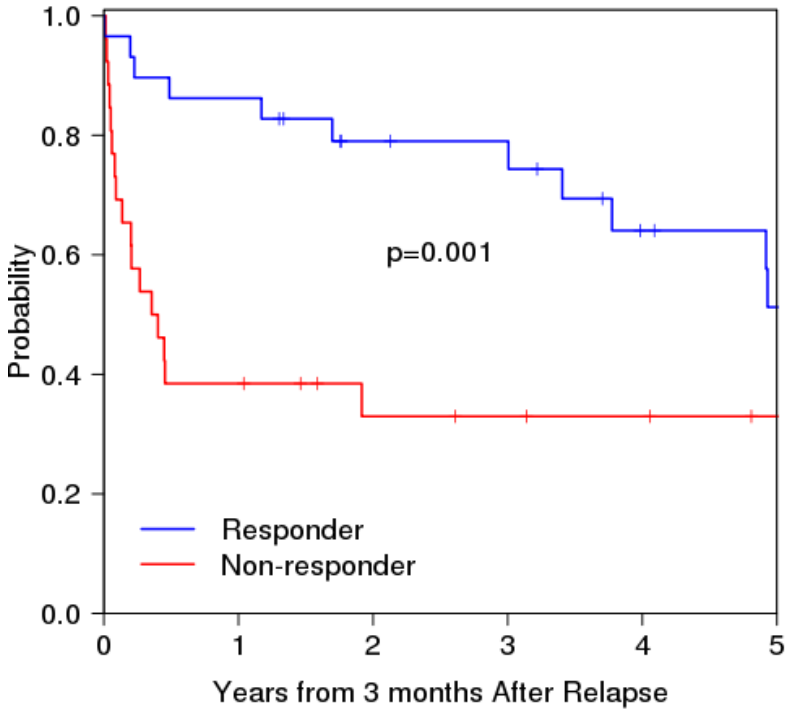
Acquisition of CR After Salvage Therapy Is a Prerequisite of Long-Term Survival in Patients With Relapse Post-Allograft



Schmid C, et al. *Blood*. 2012;119:1599-1606.

Immunosuppression Taper as Sole Therapy for Relapse Post-Allograft

- 535 patients who relapsed after HCT at DFCI between 2004 and 2012 were identified
- 123 received immunosuppression taper as primary treatment of disease relapse
- 34 out of 123 responded to immunosuppression taper alone
- 1/22 MA (2.5%) and 33/101 RIC (32.7%) responded to immunosuppression taper alone (*P* = .0073)



Kekre N, et al. *Blood*. 2014;124:2504.

Salvage Azacitidine in Patients With Relapse After Allogeneic SCT for AML/MDS

- 272 patients on EBMT AMLWP database with relapsed AML/MDS who received salvage AZA
- Outpatient therapy
- Response rate 15% CR, (CR + PR) 24%
- Multivariable analysis of predictors of CR

  Interval time transplant to relapse >12 months (*P* = .04)

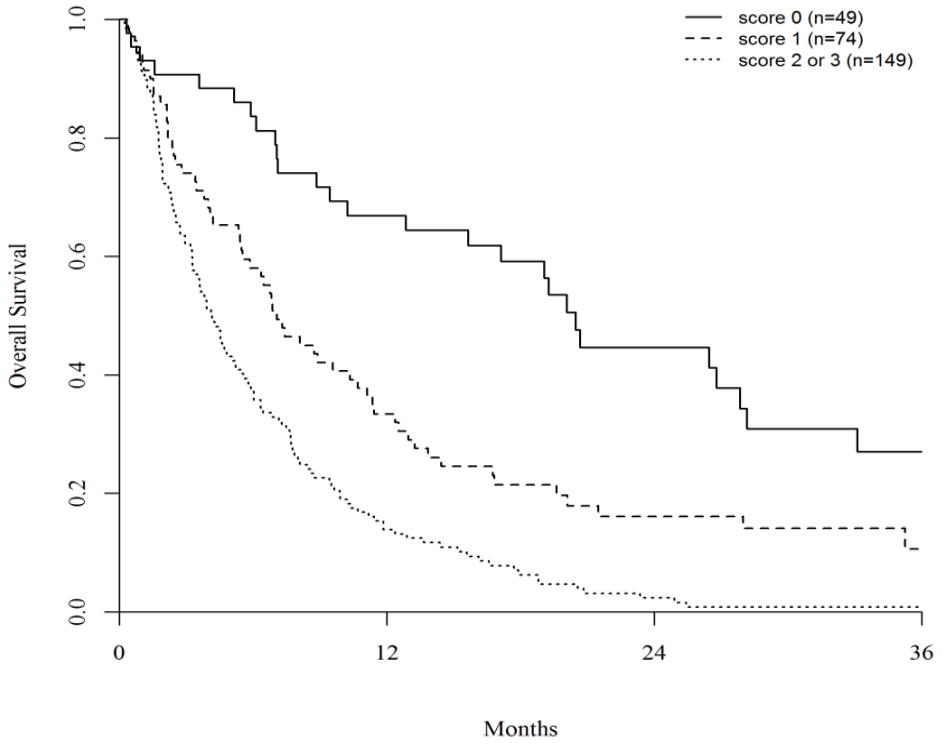
  Good-risk cytogenetics (*P* = .02)
- Multivariable analysis of predictors of OS at 2 years

  Blasts in BM at relapse <median (*P* = .02)

  Interval time transplant to relapse

  – 6–12 vs <6 months (*P* = .0006)

Overall Survival After Salvage Azacitidine in Patients With Relapse After an Allograft for AML/MDS

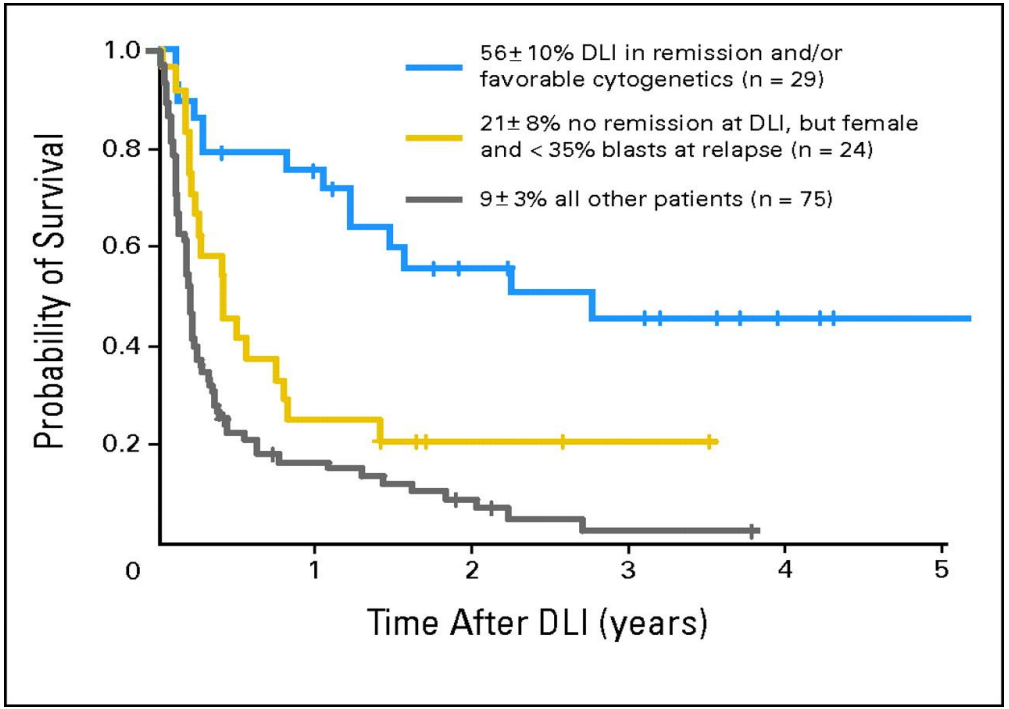


Craddock C, et al. *Blood*. 2014;124:2506.

Emergent Salvage Strategies in Patients With Relapse Post-Allograft

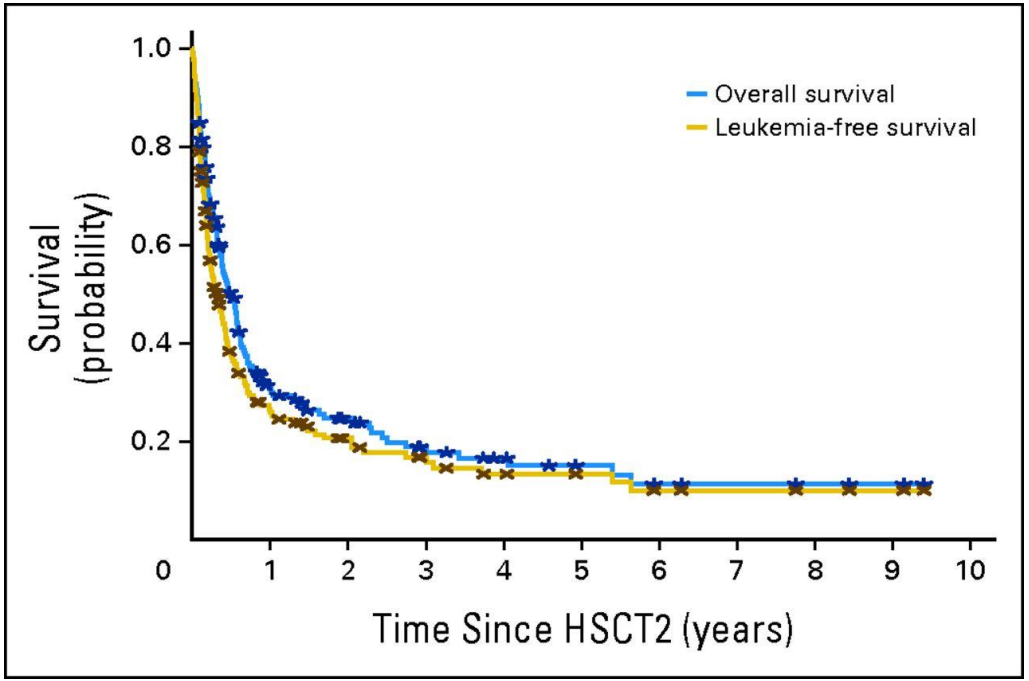
- Gilteritinib-VEN in *FLT3*-mutated AML
- FLAG-IDA + VEN
- VEN-AZA
- CAR T cells

Outcome After DLI Is Determined by Cytogenetics, Disease Status at Time of DLI, and Duration of CR Post-Transplant



Schmid C, et al. *J Clin Oncol*. 2007;25:4938-4945.

Outcome After Second Allograft Is Determined by Duration of CR Post-Transplant and Disease Status at Transplant but Not by Changing Donor



Christopeit M, et al. *J Clin Oncol.* 2013;31:3259-3271.

Conclusions

- Biological characterization of the cellular origin of disease relapse post-transplant is required
- A personalized approach to defining both relapse risk and kinetics is required
- Improved strategies to induce a second CR in patients with relapse post-allograft are required
- Second transplant and DLI represent potentially curative options in the minority of patients who have a CR

Global Leukemia Academy

Q&A

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AML case-based panel discussion

Case 1 AML: Vitor Botafogo (Spain)

Case 2 AML: Samantha Drummond (UK)

Moderator: Naval Daver

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Case 1

Vitor Botafogo (Spain)

APTITUDE HEALTH®

Case presentation

- 47-year-old woman, no allergies, past medical history of **breast cancer** in 2022 treated with surgery + RT + trastuzumab and chemotherapy (doxorubicin and cyclophosphamide)

- **April 2024:** pancytopenia and atypical monocytes in peripheral blood smear
- **Bone marrow aspirate: 36% monocytic cells with aberrant morphology**
- **Immunophenotype:** 70% of aberrant monocytic cells, **compatible with monocytic leukemia**

- **Karyotype: complex with t(9;11)**
  - **45,XX,der(6;18)(q10;q10),?t(9;11)(p21;q23),t(11;17)(q13;q23),-19,+mar[20]**
- **NGS:** pathogenic mutation in *WT1* (VAF 2.6%), probably pathogenic mutation in *PPM1D* (VAF 36%) and ***KMT2A*::*MLLT3*** rearrangement
- **Final diagnosis**: AML with *KMT2A* rearrangement; therapy related (WHO/ICC 2022)

Which treatment would you choose for this patient?

A. CPX-351

B. 3+7 schedule (anthracycline + Ara-C)

C. Clinical trial

D. Azacitidine + venetoclax

Which treatment would you choose for this patient?

A. CPX-351

B. 3+7 schedule (anthracycline + Ara-C)

C. Clinical trial

D. Azacitidine + venetoclax

Fit patient with high-risk AML

ELN 2022 guidelines: High-risk AML

Fit for intensive chemotherapy	Induction	Consolidation*	Maintenance
AML with *FLT3* mutation	Daunorubicin 60 mg/m^2 IV d1-3; or idarubicin 12 mg/m^2 IV d1-3; and cytarabine 100-200 mg/m^2/d CIV d1-7; plus midostaurin 50 mg q12h PO d8-21 Re-induction: either 2nd cycle "7 + 3" or regimen containing higher dose of cytarabine, each plus midostaurin, preferable the latter in patients with no response to 1st cycle	3-4 cycles of IDAC 1000-1500 mg/m^2 IV (500-1000 mg/m^2 if ≥60 y old) over 3h q12h d1-3; plus midostaurin 50 mg q12h PO d8-21 (in all cycles)†	Midostaurin 50 mg q12h PO d1-28, q4 wk, over 12 cycles‡
Non-*FLT3* mutant§	Daunorubicin 60 mg/m^2 IV d1-3, idarubicin 12 mg/m^2 IV d1-3, or mitoxantrone 12 mg/m^2 IV d1-3; and cytarabine 100-200 mg/m^2/d CIV d1-7 Re-induction: either 2nd cycle "7 + 3" or regimen containing higher dose of cytarabine, preferable the latter in patients with no response	3-4 cycles of IDAC 1000-1500 mg/m^2 IV (500-1000 mg/m^2 if ≥60 y old) over 3h q12h d1-3	Oral azacitidine 300 mg PO daily d1-14, q4 wk, until disease progression‖

Global Leukemia Academy

Döhner H, et al. *Blood*. 2022;140:1345-1377.

Back to our case: Initial treatment response

- Our patient received first induction with **daunorubicin** (d1–3) and **cytarabine** (d1–7). Demonstrated CR (2% BM blasts)
- Second induction with **high-dose cytarabine**. Daunorubicin was removed due to cardiotoxicity in the first cycle

After second induction, the patient's disease relapsed, with the presence of 43% aberrant monocytic cells in bone marrow with a similar immunophenotype from diagnosis.

Which salvage therapy would you propose?

A. FLAG-IDA + venetoclax

B. Menin inhibitor

C. Decitabine monotherapy

D. Azacitidine and venetoclax

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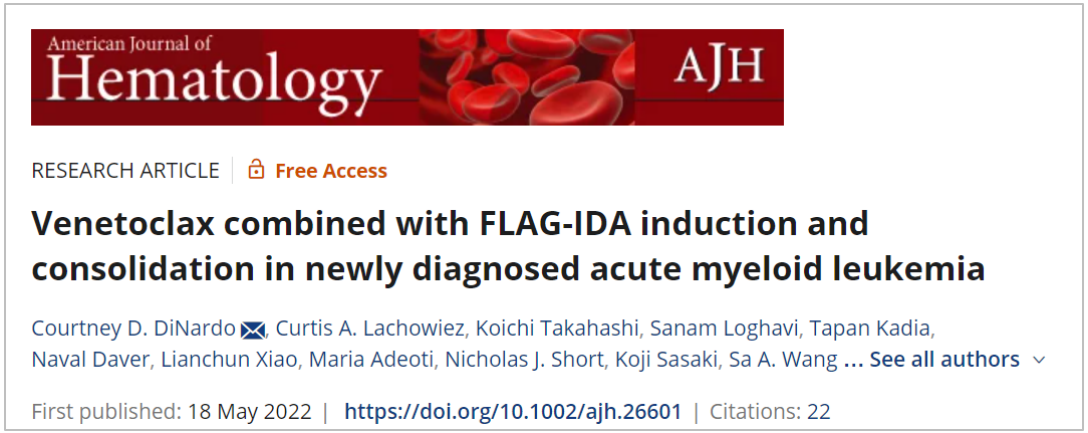


American Journal of Hematology AJH

RESEARCH ARTICLE | Free Access

Venetoclax combined with FLAG-IDA induction and consolidation in newly diagnosed acute myeloid leukemia

Courtney D. DiNardo, Curtis A. Lachowiez, Koichi Takahashi, Sanam Loghavi, Tapan Kadia, Naval Daver, Lianchun Xiao, Maria Adeoti, Nicholas J. Short, Koji Sasaki, Sa A. Wang ... See all authors

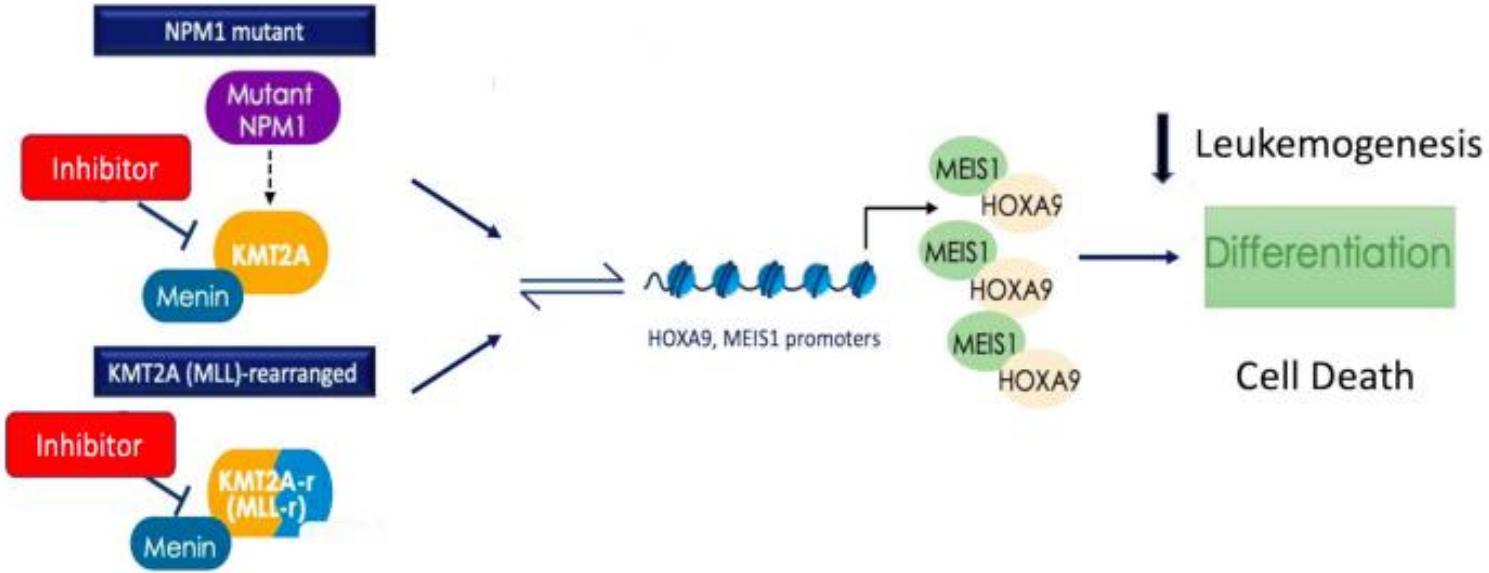
First published: 18 May 2022 | https://doi.org/10.1002/ajh.26601 | Citations: 22

Global Leukemia Academy

DiNardo CD, et al. *Am J Hematol*. 2022;97:1035-1043.

Menin inhibitors mechanism of action

Interaction between menin and KMT2A proteins favors blast cell proliferation in acute leukemias with NPM1 mutation and KMT2A rearrangement



Swaminathan M, et al. *Cancer J*. 2022;28:62-66.

Main trials with menin inhibitors for AML

Revumenib

Enzomenib

Ziftomenib

Bleximenib

Trial code	Drug	Phase	Study population	Status
NCT04065399	SNDX-5613 **(revumenib)**	I/II	R/R AL with *KMT2Ar* or *NPM1* mutation	Recruiting
NCT06226571	**Revumenib** + intensive chemo	I	De novo AML with *KMT2Ar*, *NPM1* mutation, and NUP98r	Recruiting
NCT04988555	DSP-5336 (**enzomenib**)	I/II	R/R AL with or without *KMT2Ar* or *NPM1* mutation	Recruiting
NCT05735184	**Ziftomenib** + Aza-Ven, Ven, or intensive chemo	I	De novo or R/R AML with *KMT2Ar* or *NPM1* mutation	Recruiting
NCT04811560	JNJ-75276617 (**bleximenib**)	I	R/R AL with *KMT2Ar* or *NPM1* mutation	Recruiting
NCT05453903	**Bleximenib** + Aza, Ven, or Aza + Ven	I	**De novo or R/R AML with *KMT2Ar* or *NPM1* mutation**	Recruiting

Source: ClinicalTrials.gov

Menin inhibitors for AML

57 A First-in-Human Phase 1 Study of the Menin-KMT2A (MLL1) Inhibitor JNJ-75276617 in Adult Patients with Relapsed/Refractory Acute Leukemia Harboring *KMT2A* or *NPM1* Alterations

Program: Oral and Poster Abstracts
Type: Oral

Bleximenib

Session: 616. Acute Myeloid Leukemias: Investigational Therapies, Excluding Transplantation and Cellular Immunotherapies: Upcoming Therapies in Newly Diagnosed and Relapsed/Refractory AML
Hematology Disease Topics & Pathways:
Research, clinical trials, Lymphoid Leukemias, ALL, Acute Myeloid Malignancies, AML, adult, Clinical Research, drug development, Diseases, Therapies, Lymphoid Malignancies, Adverse Events, Myeloid Malignancies, Study Population, Human

Saturday, December 9, 2023: 10:00 AM

CR and CRh: n = 7/33 (21%) Jabbour E, et al. ASH 2023.

THE LANCET
Oncology

ARTICLES · Volume 25, Issue 10, P1310-1324, October 2024 Download Full Issue

Ziftomenib in relapsed or refractory acute myeloid leukaemia (KOMET-001): a multicentre, open-label, multi-cohort, phase 1 trial

Prof Eunice S Wang, MD [a,*] · Ghayas C Issa, MD [b,*] · Prof Harry P Erba, MD [c] · Prof Jessica K Altman, MD [d] · Pau Montesinos, MD [e] · Stephane DeBotton, MD [f] · et al. Show more

CR and CRh: 9/36 (25%) *NPM1* + *KMT2Ar*

Wang E, et al. *Lancet Oncol.* 2024;25(10):1310-1324.

Phase I/II study: revumenib – AUGMENT-101

TABLE 3. Response

Parameter	Efficacy Population (n = 57)
Overall response rate, No. (%)[a]	36 (63.2)
95% CI	49.3 to 75.6
Time to first response, months, median (range)	0.95 (0.9-2.0)
Duration of response, months, median (range)	4.3 (1.9-NR)
CR + CRh rate, No. (%)	13 (22.8)
95% CI	12.7 to 35.8
P value, one-sided	0.0036
Time to first CR + CRh, months, median (range)	1.87 (0.9-4.6)
Duration of CR + CRh, months, median (95% CI)	6.4 (3.4 to NR)
CRc, No. (%)[b]	25 (43.9)
95% CI	30.7 to 57.6
Best response, No. (%)	
CR	10 (17.5)
CRh	3 (5.3)
CRi	1 (1.8)
CRp	11 (19.3)
Morphological leukemia-free state	10 (17.5)
Partial remission	1 (1.8)
Progressive disease	4 (7.0)
No response	14 (24.6)
Other[c]	3 (5.3)
MRD negative rate within evaluable patients[d]	
Within CR + CRh, No. (%)	7/10 (70.0)
Within CRc, No. (%)	15/22 (68.2)
Time to negative MRD status for patients with CR + CRh, months, median (range)	1.08 (1.0-3.9)

Issa GC, et al. *J Clin Oncol*. 2024. Online ahead of print.

Back to our case: Salvage therapy

- The patient was enrolled in a **phase Ib study** with bleximenib + Aza-Ven or Aza-Ven. She was included in cohort A1 (**bleximenib + venetoclax**)
- After the first treatment cycle, she demonstrated **morphologic CR,** but **6% of pathologic cells** were detected by **flow** in bone marrow
- The patient is currently receiving the **second cycle** of bleximenib + Ven
- She has a **9/10 HLA-compatible** non-related donor for **HSCT**

Be careful! Differentiation syndrome

Take-home messages

- **AML with *KMT2A* rearrangement** is included in the **adverse-risk category** according to ELN 2022
- **Fit patients** should receive treatment with **intensive chemotherapy** (7+3) or be included in **clinical trials**
- **Menin inhibitors** may be a therapeutic option for AML and ALL with *KMT2A* rearrangement. However, **clinical trials are in early phases** and more data are needed
- **HSCT** is still necessary in most cases

THANK YOU

Salut/ ICO Institut Català d'Oncologia

Josep Carreras LEUKAEMIA Research Institute

Germans Trias i Pujol Hospital

Global Leukemia Academy

Case 1 – Discussion

Vitor Botafogo (Spain)

APTITUDE HEALTH®

Global Leukemia Academy

Case 2

Samantha Drummond (UK)

APTITUDE HEALTH®

Case Presentation

Samantha Drummond

West of Scotland Haematology Trainee

Initial presentation

January 2020

16-year-old male

- Three-week history of feeling generally unwell
- No significant PMH
- No significant FH
- Pale mucous membranes noted when attended dentist

- Full blood count
  - Hemoglobin 87g/L, white cell count 76.9 $\times 10^9$/L, platelets 41 $\times 10^9$/L
- Bone marrow
  - Trilineage dysplasia
  - Blasts ~60%
- Cytogenetics
  - 46XY, t(6;9)(p22;34), del(18)(q23)
- Molecular
  - *FLT3*-ITD detected

WHO classification

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with PML::RARA fusion
Acute myeloid leukaemia with RUNX1::RUNX1T1 fusion
Acute myeloid leukaemia with CBFB::MYH11 fusion
Acute myeloid leukaemia with DEK::NUP214 fusion
Acute myeloid leukaemia with RBM15::MRTFA fusion
Acute myeloid leukaemia with BCR::ABL1 fusion
Acute myeloid leukaemia with KMT2A rearrangement
Acute myeloid leukaemia with MECOM rearrangement
Acute myeloid leukaemia with NUP98 rearrangement
Acute myeloid leukaemia with NMP1 mutation
Acute myeloid leukaemia with CEBPA mutation
Acute myeloid leukaemia, myelodysplasia related
Acute myeloid leukaemia with other defined genetic alterations

Khoury JD, et al. *Leukemia*. 2022;36:1703-1719.

ELN risk classification

Risk Category	Genetic Abnormality
Favourable	t(8;21)/RUNX1::RUNX1T1 Inv16/CBFB::MYH11 Mutated NPM1 **without** FLT3-ITD CEBPA mutation (bZIP in-frame)
Intermediate	Mutated NPM1 **with** FLT3-ITD Wild type NPM1 **with** FLT3-ITD t(9;11)/MLLT3::KMT2A Cytogenetic/Molecular abnormalities not classified as favourable or adverse
Adverse	T(6;9)/DEK::NUP214 T(v;11)/KMT2A-rearranged T(9;22)/BCR::ABL1 T(8;16)/KAT6A::CREBBP Inv(3)/GATA2, MECOM(EVI1) T(3;v)/MECOM(EVI1)-rearranged -5 or del(5q), -7, -17/abn(17p) Complex karyotype Monosomal karyotype Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2 Mutated TP53

Döhner H, et al. *Blood.* 2022;140:1345-1377.

AML t(6;9)

- Previously known as DEK-CAN
- Now DEK:NUP214
- Occurs in <2% of patients
- Associated with
  - Multilineage dysplasia and basophilia
  - High prevalence of *FLT3*-ITD
  - Poor prognosis
- Allogeneic SCT is considered the standard of care

Díaz-Beyá M, et al. *Br J Haematol*. 2020;189:920-925; Kayser S, et al. *Haematologica*. 2020;105:161-169; Oyarzo MP, et al. *Am J Clin Pathol*. 2004;122:348-358; Tarlock K, et al. *Br J Haematol*. 2014;166:254-259.

Management

- Commenced on hydroxycarbamide while results pending
- Presented at regional multidisciplinary team meeting

- What would be your treatment approach for this patient?
- Consensus was for FLAG-IDA with plan for allogeneic transplant in first CR

Progress

January 2020

- FLAG-IDA commenced
- Counts not recovered by D+32
- Blood film – circulating blasts
- Bone marrow confirmed refractory disease

Question 1

Refractory disease post-first cycle FLAG-IDA.

How should we proceed?

A. Second cycle of FLAG-IDA
B. CPX-351
C. DA
D. Alternative regimen

Progress

January 2020

- FLAG-IDA commenced
- Counts not recovered by D+32
- Film reviewed – circulating blasts
- Bone marrow confirmed refractory disease

March 2020

- CPX-351 commenced
- Persistent blasts on film
- Bone marrow again confirmed refractory disease

What treatment now?

blood®

616.ACUTE MYELOID LEUKEMIA: NOVEL THERAPY, EXCLUDING TRANSPLANTATION | NOVEMBER 13, 2019

Venetoclax in Combination with Gilteritinib in Patients with Relapsed/Refractory Acute Myeloid Leukemia: A Phase 1b Study

Alexander E. Perl, MD,[1] Naval G. Daver, MD,[2] Keith W. Pratz, MD,[3] Joseph Maly, MD,[4] Wan-Jen Hong, MD,[5] Erkut Bahceci,[6] Bo Tong, PhD,[*,7] Tian Tian, PhD,[*,8] Kimberley Dilley, MD MPH[*,9]

Commenced venetoclax-gilteritinib April 2020
Complete morphologic response

Transplant

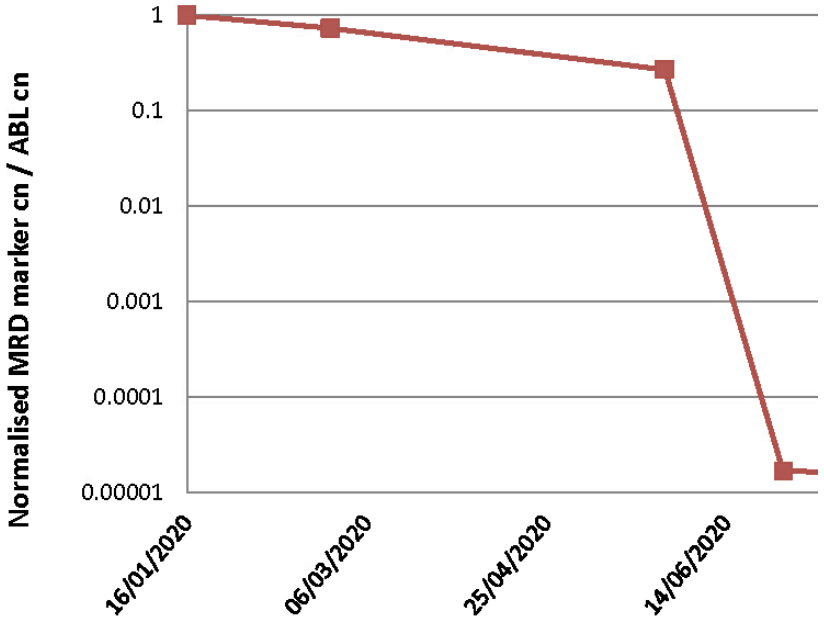
- Haploidentical transplant
- TB3F PTCy
- D0 04/06/2020

- Issues during transplant
  - Mucositis
  - Infection
  - Nutrition

- Discharged D+28

Posttransplant

- D+28 marrow showed an ongoing CR

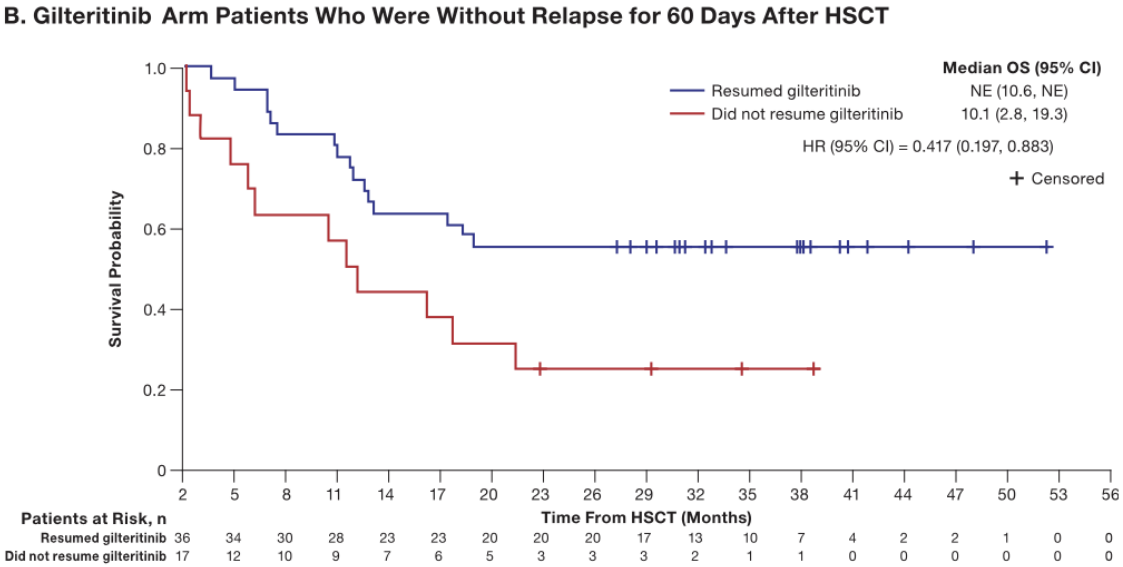


Question 2

Should this patient receive maintenance therapy?

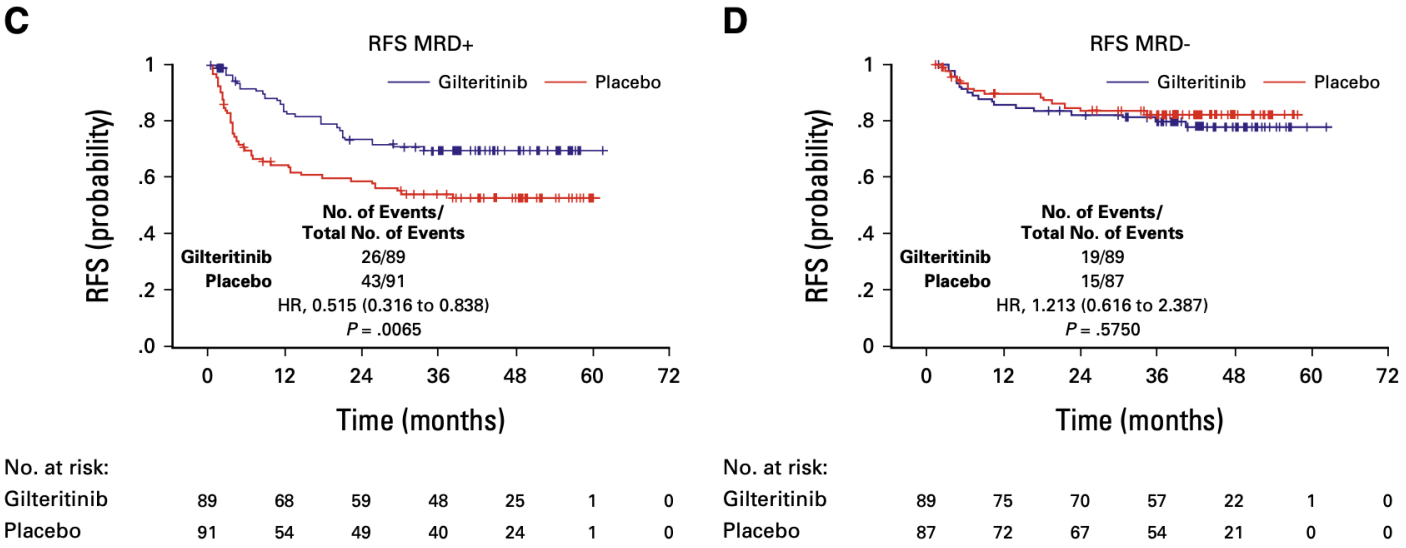
A. No maintenance therapy
B. Maintenance sorafenib
C. Maintenance gilteritinib

Maintenance gilteritinib?



Perl AE, et al. *Transplant Cell Ther*. 2023;29:265.e1-265.e10.

Maintenance gilteritinib?



Levis MJ, et al. *J Clin Oncol*. 2024;42:1766-1775.

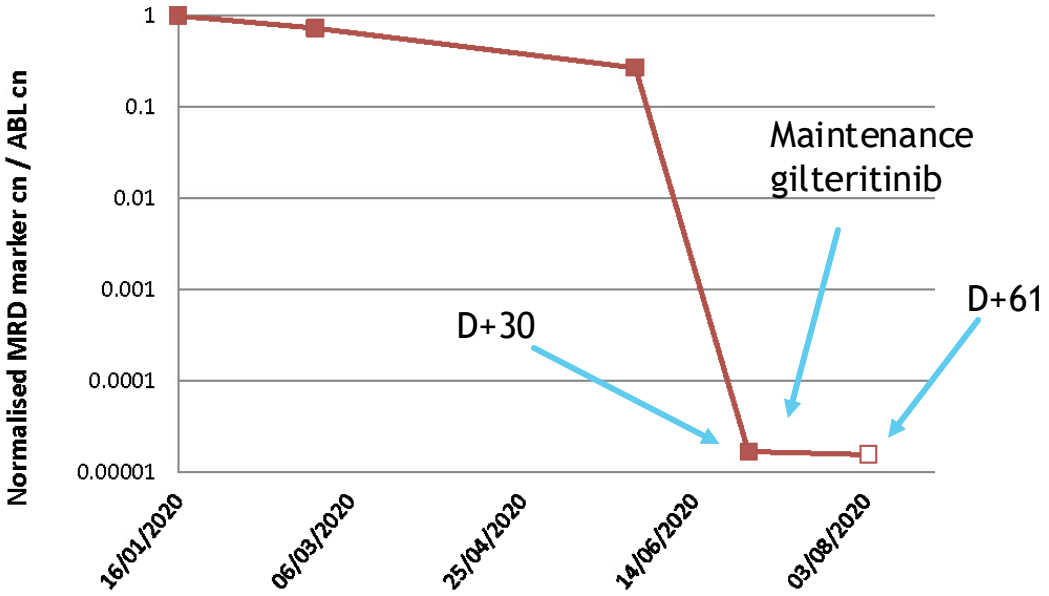
Posttransplant course

- Maintenance gilteritinib
  - Started July 2020
  - Suspended due to cytopenias in October 2020
  - Restarted at reduced dose
  - Completed 2 years of posttransplant gilteritinib August 2022

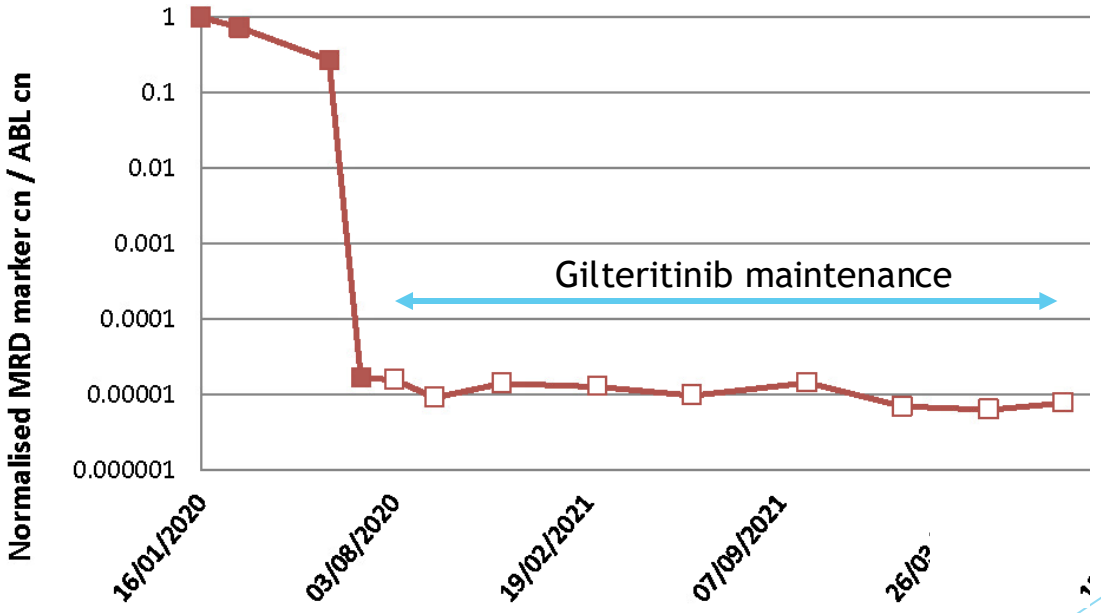
Posttransplant course

- Two admissions
  - D+63
    - Admission with fever and GI symptoms
    - Completed a course of antibiotics for VRE
  - D+78
    - Fever: empiric antibiotic therapy
    - Hypoxia: improved once dapsone discontinued; ? dapsone induced methemoglobinemia
- Grade 2 skin GVHD
  - Managed with steroids

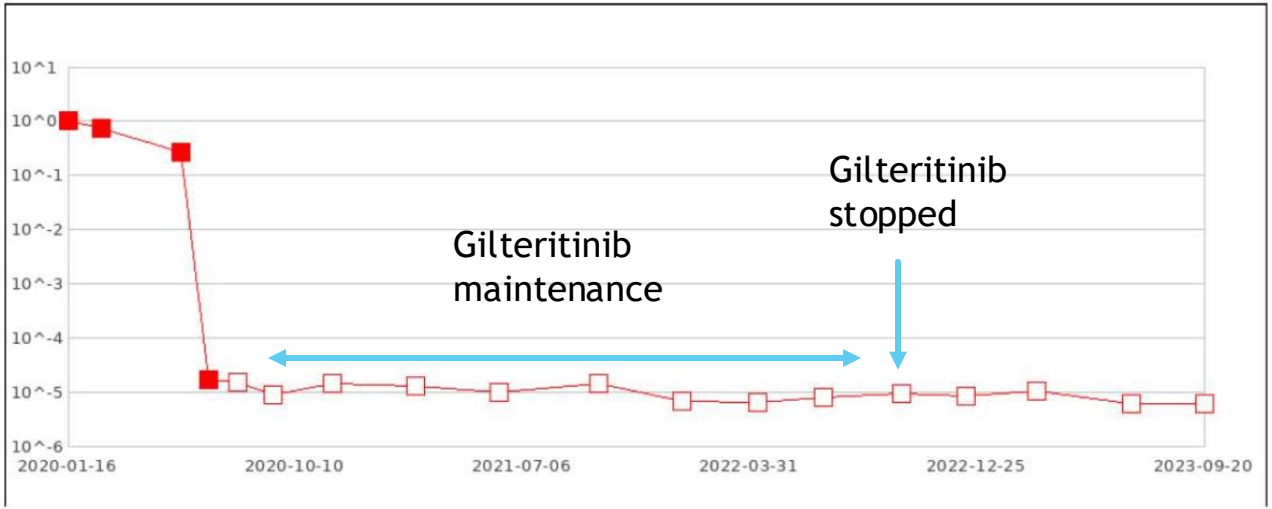
MRD monitoring



MRD monitoring



MRD monitoring



Most recent follow-up

June 2024

- Remains in remission
- Completed surveillance marrows
- Annual late-effects review
- At university

Questions?

References

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Case 2 – Discussion

Samantha Drummond (UK)

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Panel discussion: How treatment in first line influences further therapy approaches in ALL and AML

Naval Daver and all faculty

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Panel Discussion

> Will CAR Ts and bispecifics change the treatment landscape?

> What is the evolving role of HSCT – is it still necessary?

> What does the future in Europe look like in terms of

- Adoption of new therapies?
- Evolving standards of care?

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Panel Discussion

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ARS questions

Naval Daver

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Question 3 [REPEATED]

Which of the following is NOT true for ALL?

A. Inotuzumab and blinatumomab plus chemotherapy is active in both front line and salvage for ALL

B. Kinase inhibitors can be combined with other therapy modalities in Ph+ ALL

C. MRD is highly prognostic for relapse and survival in Ph– ALL

D. There are no effective consolidation treatments for patients who remain MRD+ after induction therapy

Question 4 [REPEATED]

The prognosis of patients with R/R AML depends on:

A. Age
B. Prior therapy (eg, HSCT)
C. Timing of relapse
D. The mutational and cytogenetic profile of the disease
E. All of the above
F. A and D

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