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Emerging and Practical Concepts and Controversies in Leukemias

28 October 2021

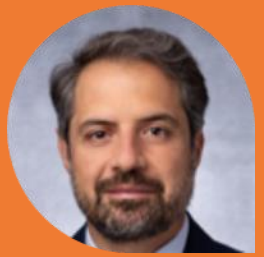
Virtual Breakout – Adult Leukemia Patients

APTITUDE HEALTH

Global Leukemia Academy

Welcome and meeting overview

Elias Jabbour



APTITUDE HEALTH®

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Adult/elderly ALL

AML

CO-CHAIRS

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Richard Schlenk, MD
University Hospital Heidelberg, Germany

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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

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Virtual Breakout – Adult Leukemia Patients (Day 2) 17.00 – 20.00

Chairs – Elias Jabbour, Naval Daver

Time CET	Title	Speaker/Moderator
17.00 – 17.10	**ALL session open**	Elias Jabbour
17.10 – 17.30	**Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens**	Elias Jabbour
17.30 – 17.50	**Current treatment options for relapsed ALL in adult and elderly patients**	Nicola Gökbuget
17.50 – 18.20	**Case-based panel discussion on toxicity management for adult and elderly ALL patients** • Case presentation 1: Fabian Lang • Case presentation 2: Anna Torrent	Moderator: Elias Jabbour *Faculty panel*: E. Jabbour, N. Gökbuget, J.M. Ribera, P. Rousselot
18.20 – 18.30	**Break**	
18.30 – 18.35	**AML session open**	Naval Daver
18.35 – 18.55	**Personalized induction and maintenance approaches for AML**	Richard Schlenk
18.55 – 19.15	**Optimizing management of relapsed/refractory AML**	Charles Craddock
19.15 – 19.45	**Case-based panel discussion or questions to the panel on regional challenges in AML care** • Case presentation 1: Justin Loke • Case presentation 2: Sonia Jaramillo Segura	Moderator: Naval Daver *Faculty panel*: N. Daver, C. Craddock, R. Schlenk
19.45 – 20.00	**Session close**	Elias Jabbour

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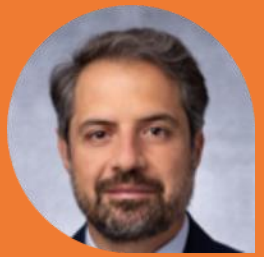
Educational ARS questions

Elias Jabbour



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Question 1

What age group is considered elderly ALL patients?

a) ≥50 years
b) ≥55 years
c) ≥60 years
d) ≥65 years
e) ≥70 years

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Question 2

Which of the following is NOT true for treating ALL?

a) Inotuzumab and blinatumomab plus chemotherapy has produced 90% CR rates in salvage therapy and in first line in older patients

b) Blinatumomab and ponatinib can be used as a chemotherapy-free regimen in Ph+ ALL

c) MRD– CR does not correlate strongly with outcome

d) Since 1999, median survival for ALL patients older than 60 has been increasing with each successive decade

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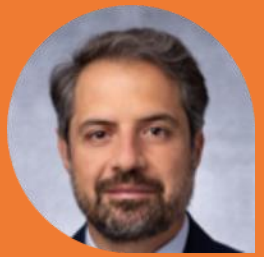
Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens

Elias Jabbour



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Integration of Immunotherapy in the Management of Frontline Acute Lymphocytic Leukemia

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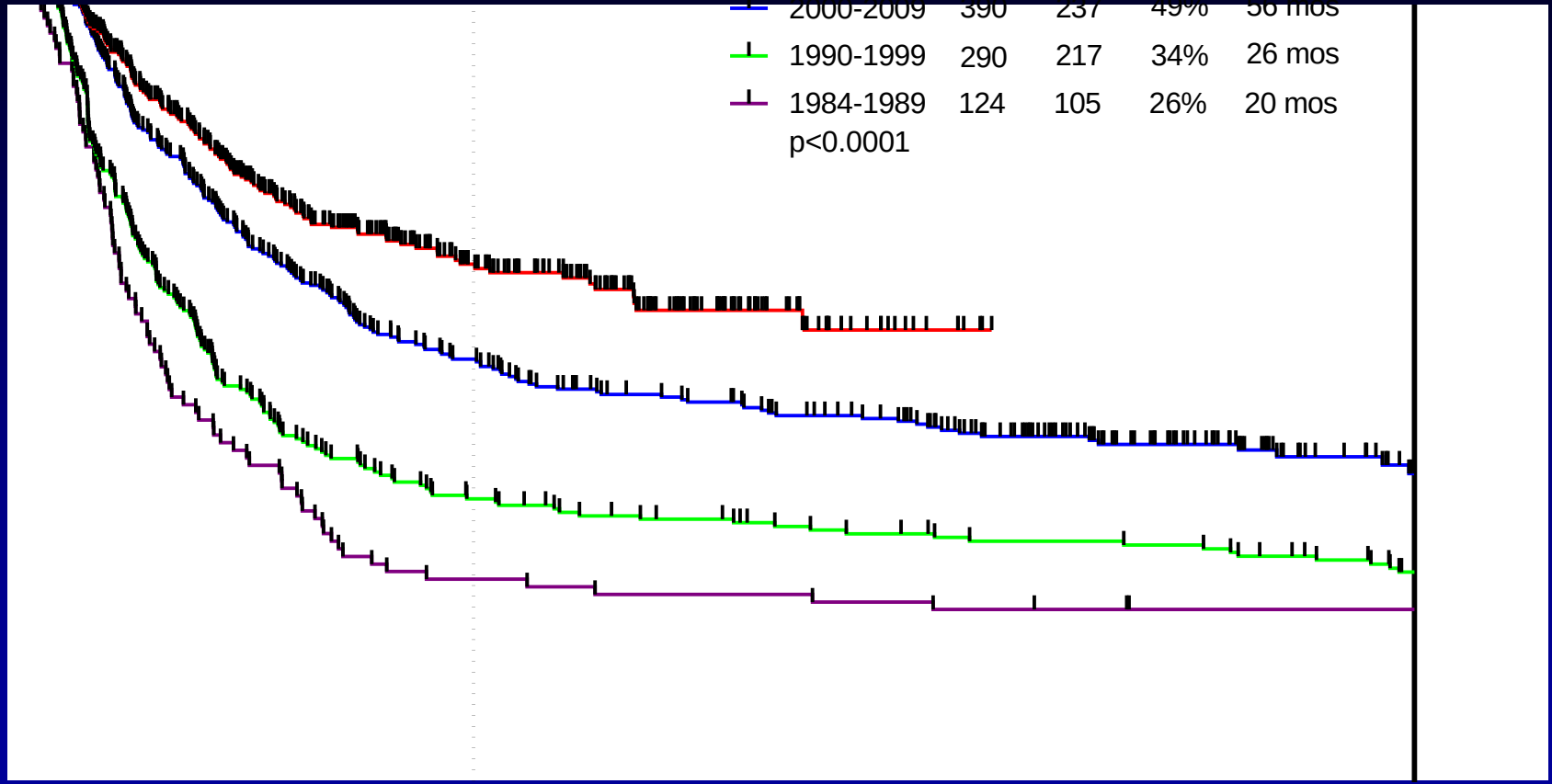
GLA
October 2021

Conflict of Interest Disclosure

- Research grants
  - Pfizer, Takeda, Amgen, AbbVie, Novartis
- Consultancy and advisory roles
  - Pfizer, Takeda, Amgen, AbbVie, BMS

ALL: Survival by Decade (MDACC 1985–2020)



Reasons for Recent Success in Adult ALL

- Addition of TKIs (ponatinib) +/- blinatumomab to chemoRx in Ph-positive ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Addition of CD19 bispecific T-cell engager (BiTE) antibody blinatumomab, and of CD22 monoclonal antibody drug conjugate (ADC) inotuzumab to chemoRx in salvage and frontline ALL Rx
- CAR T therapy
- Importance of MRD in CR (at CR vs 3 mos; NGS)

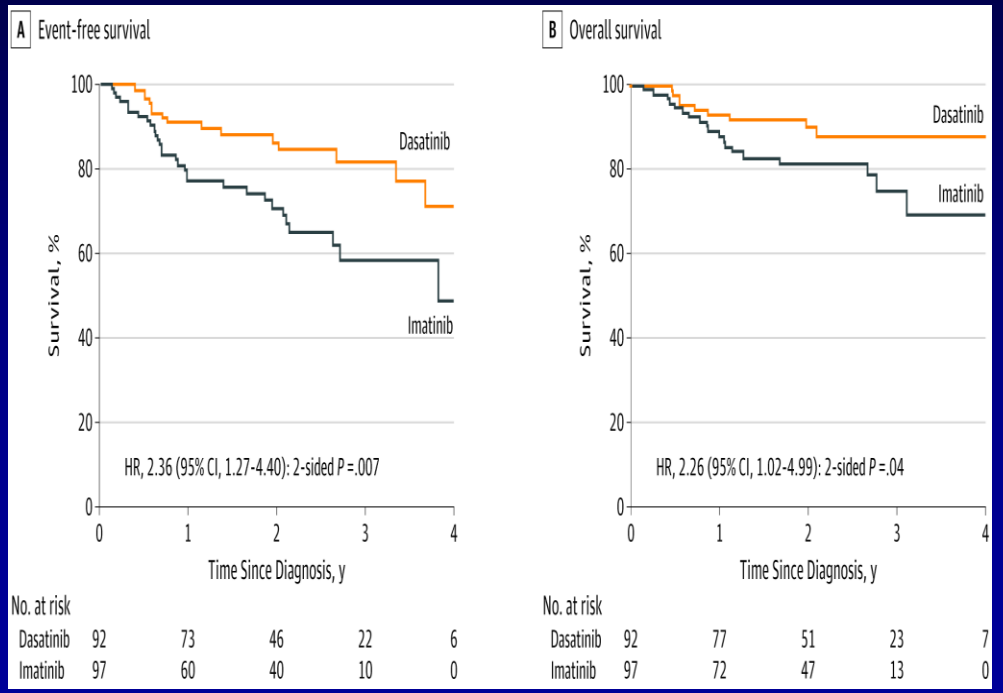
ALL Individualized Therapy in 2021

Entity	Management	% Cure/5-yr survival
Burkitt	HCVAD-R × 8; IT × 16; R/O-EPOCH	80–90
Ph+ ALL	HCVAD + TKI; TKI maintenance; allo SCT in CR1	75+
Ph-like ALL	HCVAD + TKI/MoAbs	60–70
T-ALL (except ETP-ALL)	Lots of HD CTX, HD ara-C, Asp; nelarabine; venetoclax??	60+
CD20+ ALL	ALL chemo Rx+ rituximab/ofatumumab	60–70+
AYA	Augmented BFM; HCVAD-R/O	60–70+
Older ALL >60 yrs	MiniCVD-ino-blina	60?
MRD FCM/molecular (NGS)	Prognosis; need for blina +/- allo SCT in CR1	--

Dasatinib vs Imatinib in Pediatric Ph-Positive ALL

- 189 pts randomized Rx + dasatinib (n = 92) or imatinib (n = 97)
- Median F/U 26 mos; Triple IT 19 or 21

% 4-yr	Dasatinib	Imatinib	*P* Value
EFS	71	49	.005
OS	88	69	.04
Relapse	20	34	.01
CNS	2.7	8.4	.06

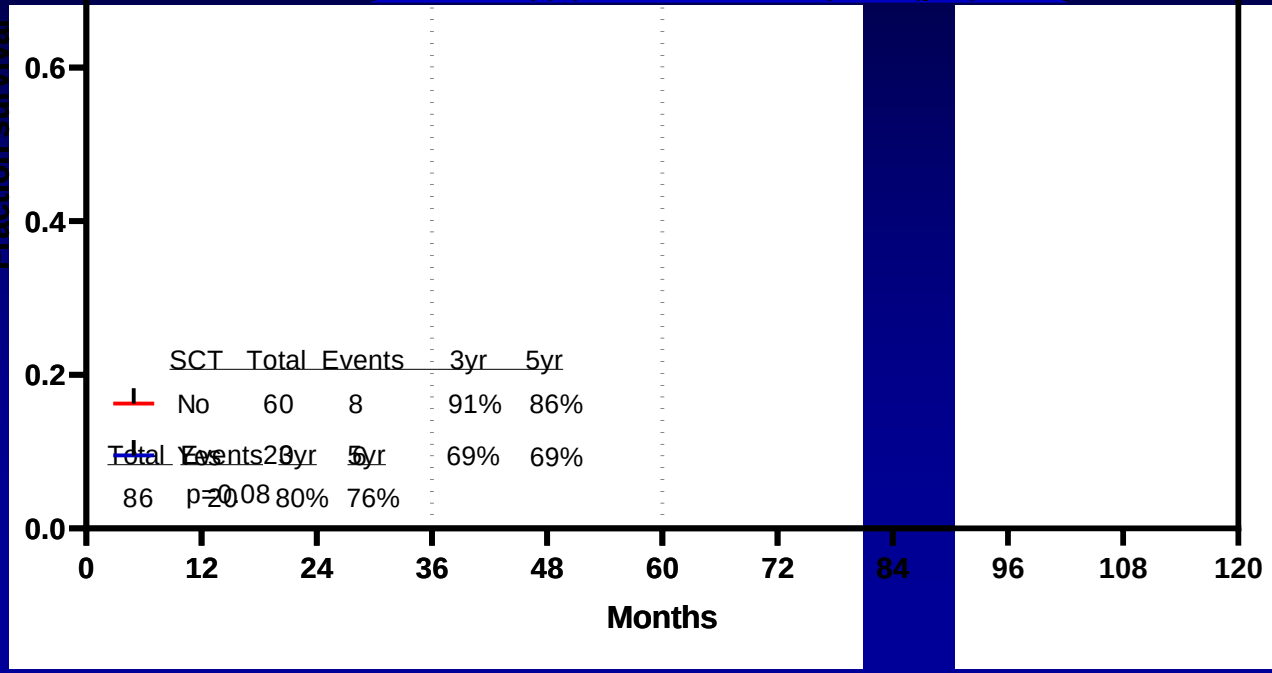


Shen et al. *JAMA Oncol.* 2020;6:358-366.

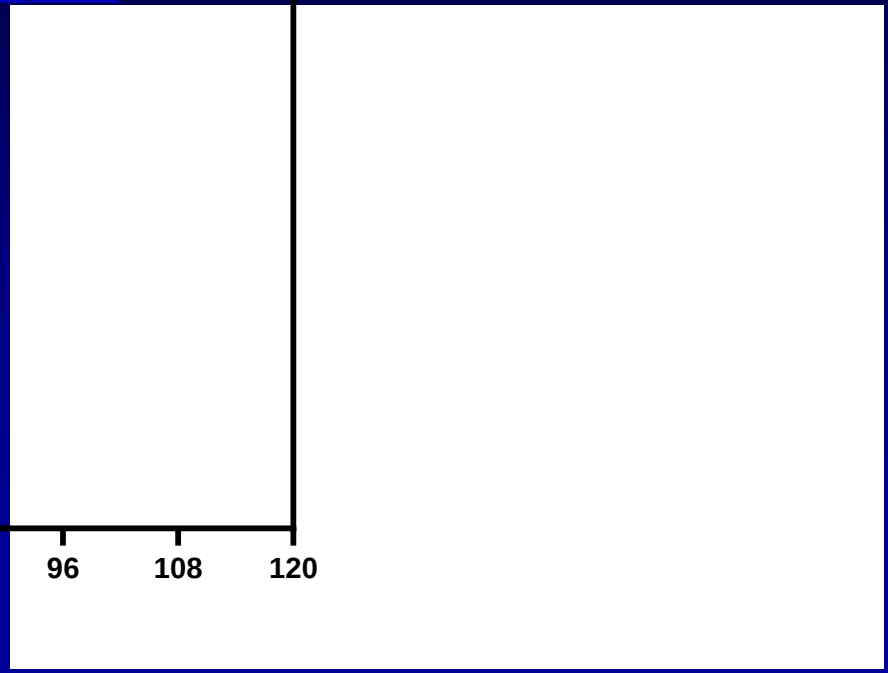
HyperCVAD + Ponatinib in Ph+ ALL

- 86 pts Rx; median age 47 yrs (39–61); median FU 48 mos (10–100)
- CR 68/68 (100%); FCM-MRD negative 85/86 (99%); CMR 84%; 3/5-yr OS 80/76%, EFS 76/71%

Overall Survival

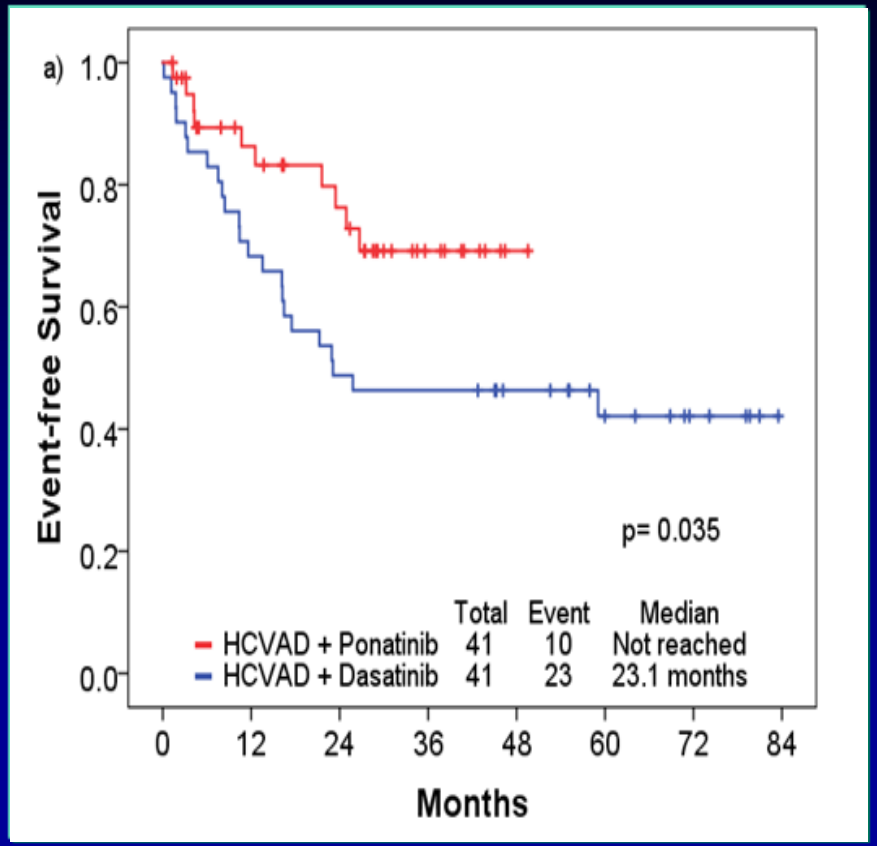


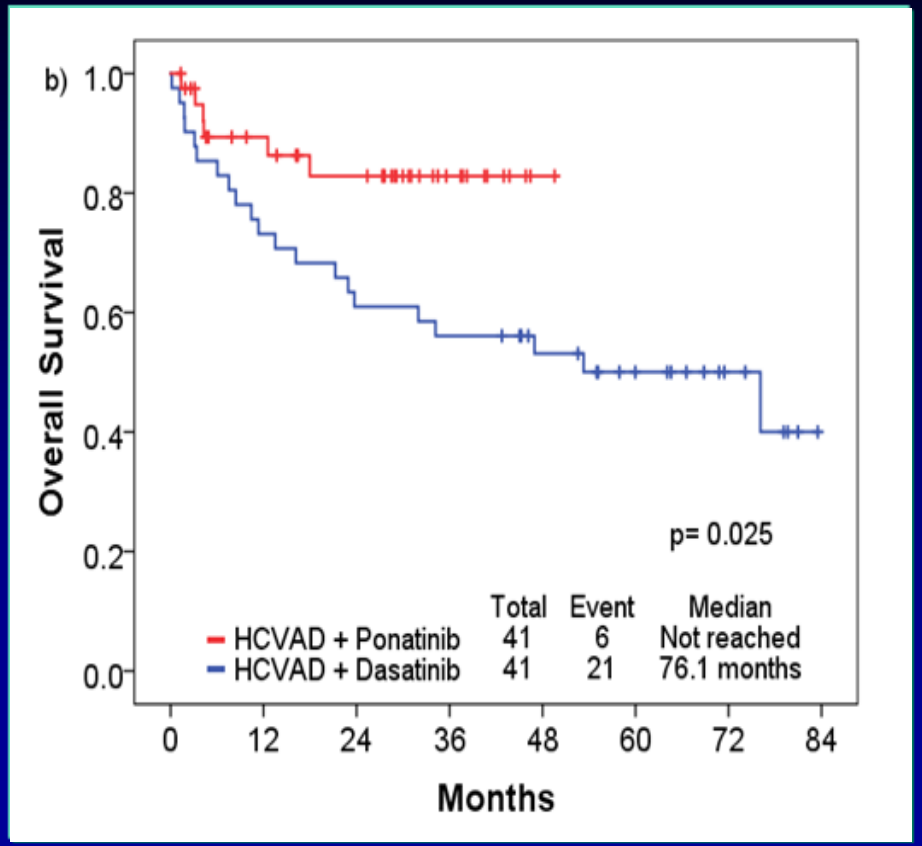
6-Month Landmark



Jabbour E, et al. *Lancet Hematol.* 2018;618:(and update December 2020); Short et al. *Blood.* 2019;134:Abstract 283.

Propensity Score Analysis: HCVAD + Ponatinib vs HCVAD + Dasatinib in Ph+ ALL

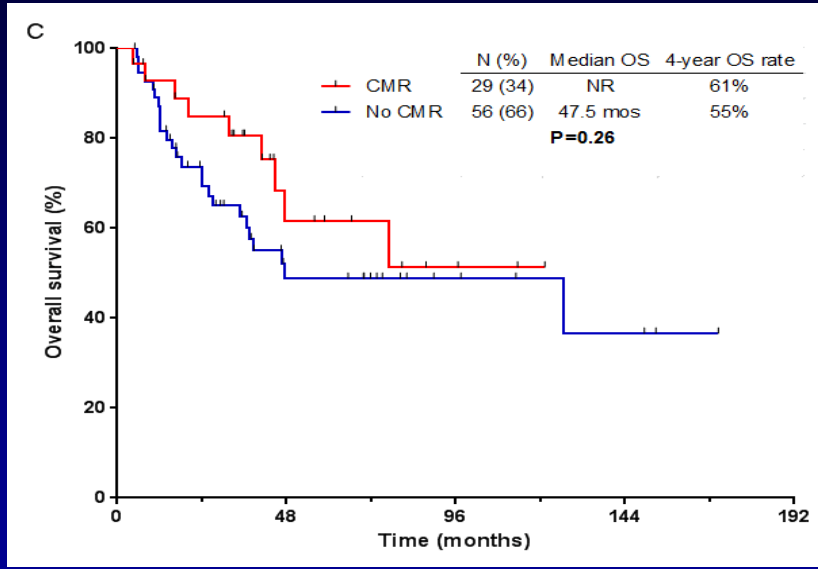




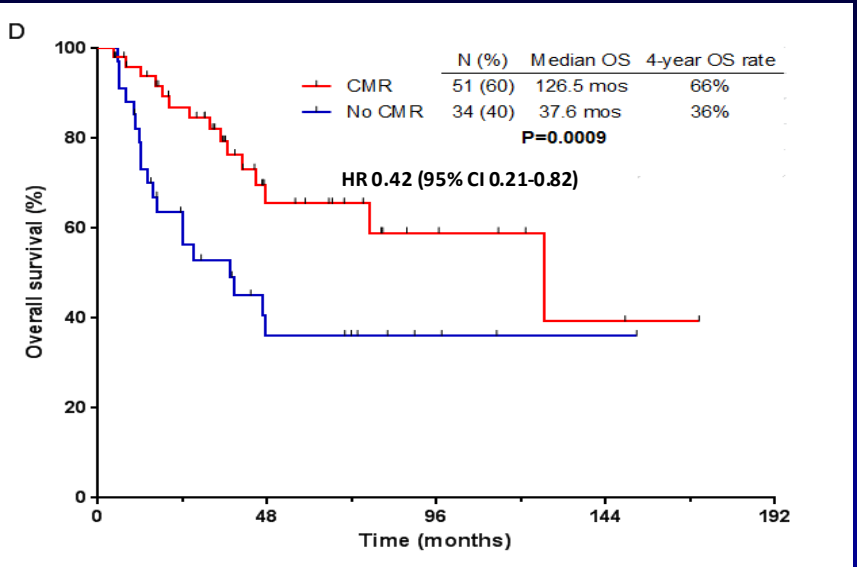
Sasaki et al. *Cancer*. 2016;122(23):3650-3656.

CMR in Ph+ ALL: OS for CMR vs Others

At CR



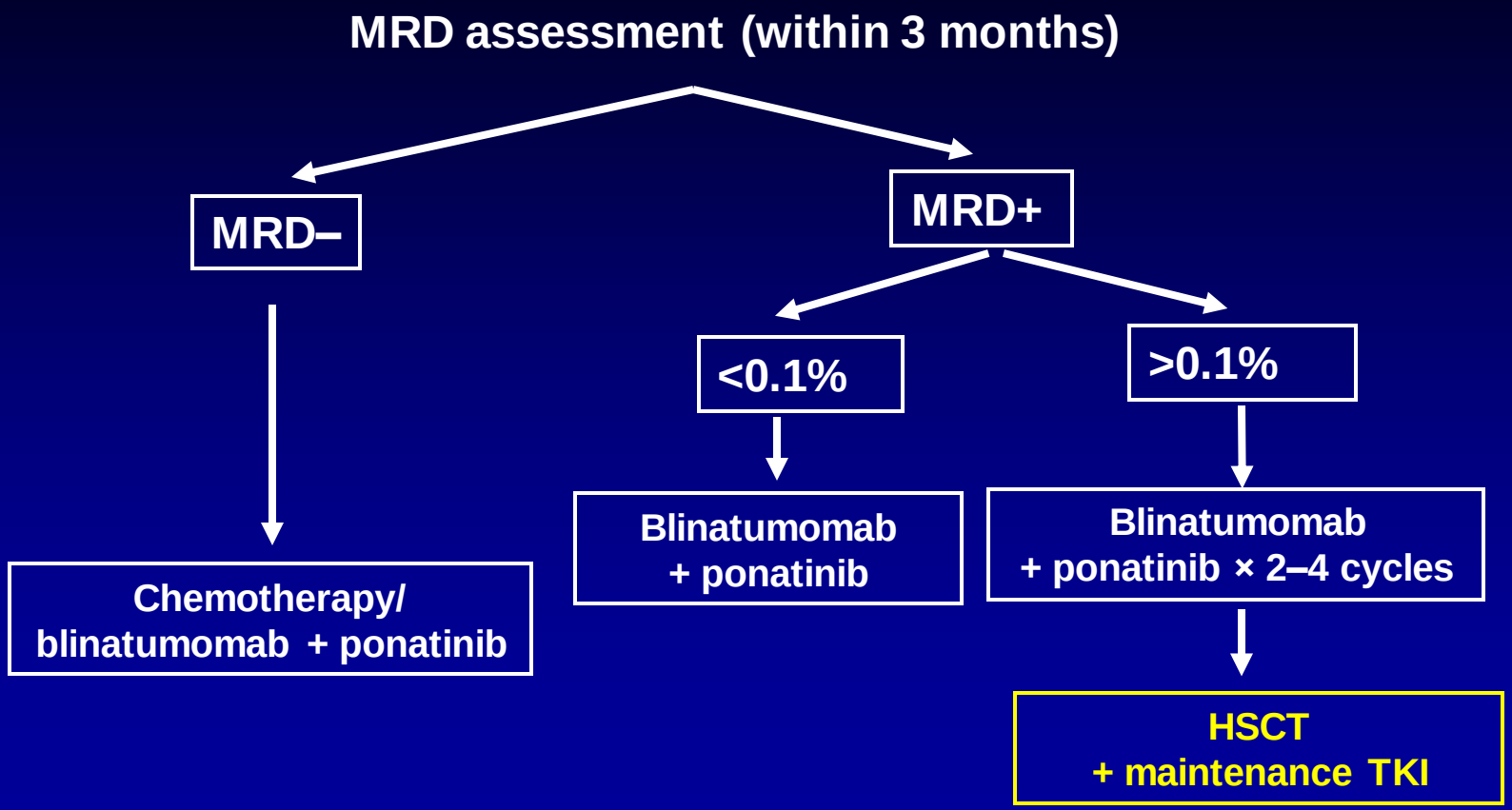
At 3 months



- **MVA for OS**
  CMR at 3 months (HR 0.42 [95% CI: 0.21-0.82]; *P* = .01)

Short et al. *Blood.* 2016;128(4):504-507.

Indications for HSCT: Ph+ ALL

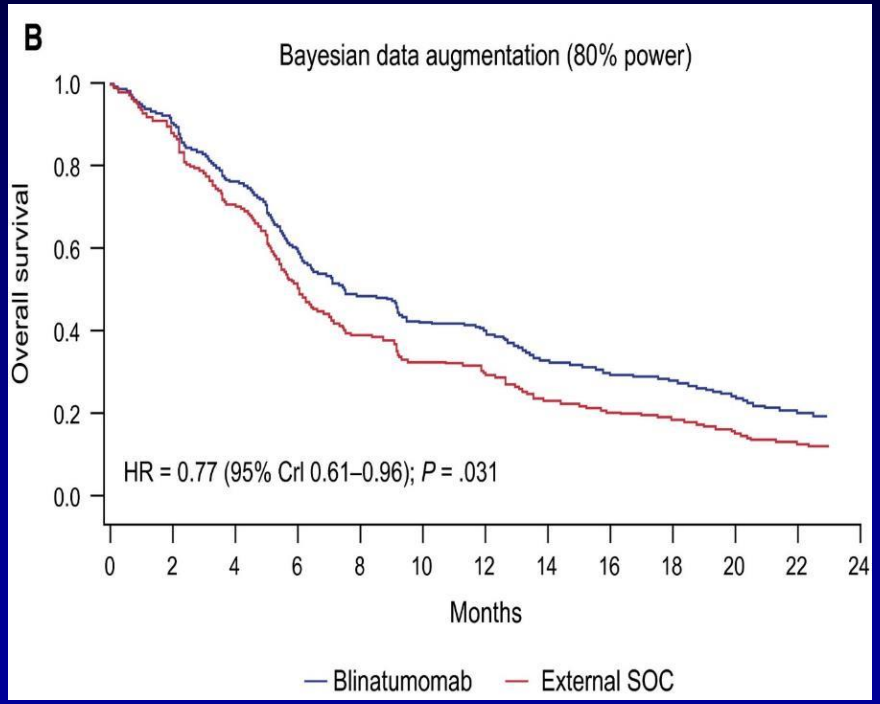


Short et al. *Blood.* 2016;128(4):504-507; Sasaki et al. *Blood.* 2019;134:abstract 1296; Samra et al. *Blood.* 2019;134:abstract 3894.

Blinatumomab and Inotuzumab in R/R Ph+ ALL

Blina vs SOC

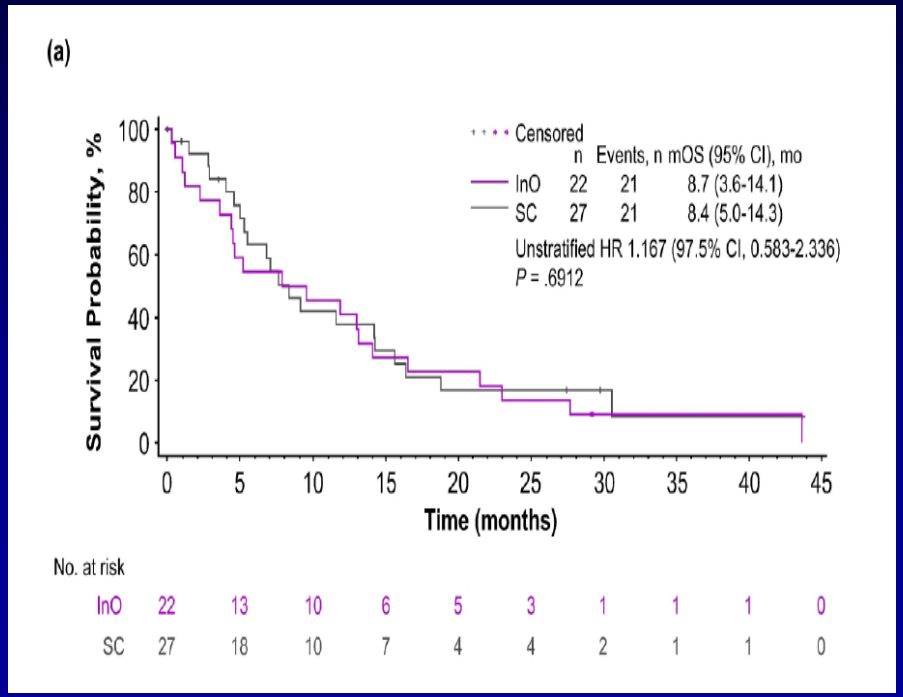
- CR/CRh 36% vs 25%
- 1-yr OS 41% vs 31%



Rambaldi et al. *Cancer*. 2019;126:304-310.

Ino vs SOC

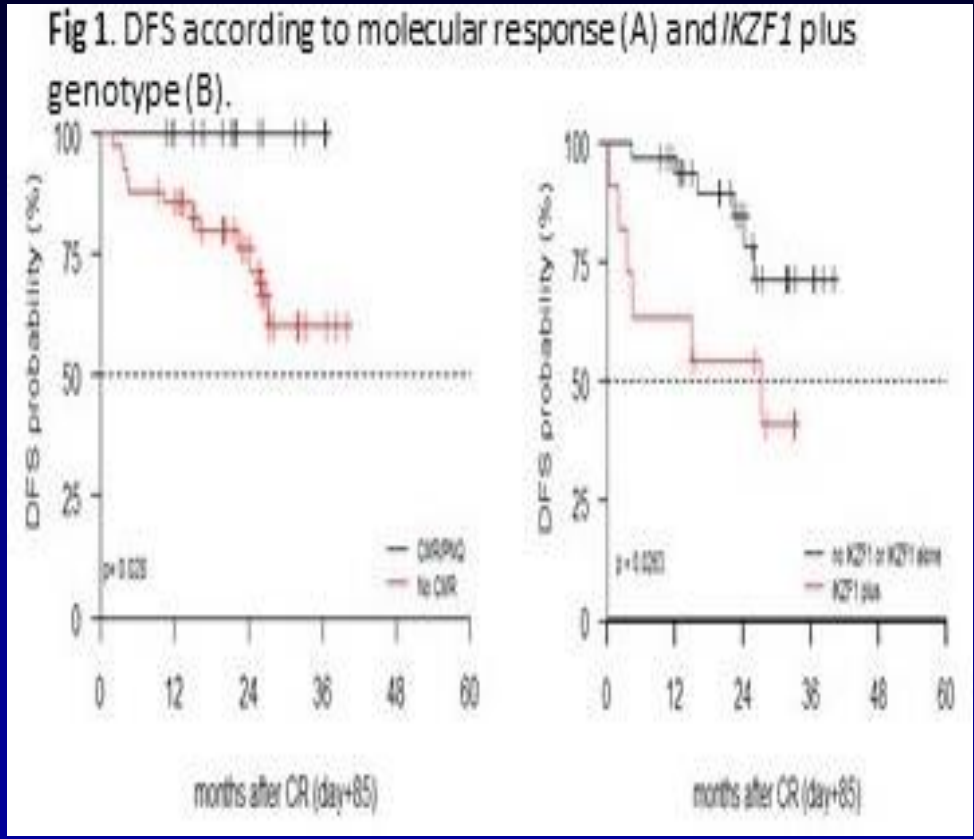
- CR/CRi 73% vs 56%
- 1-yr PFS 20% vs 4.8%



Stock W, et al. *Cancer*. In press 2020

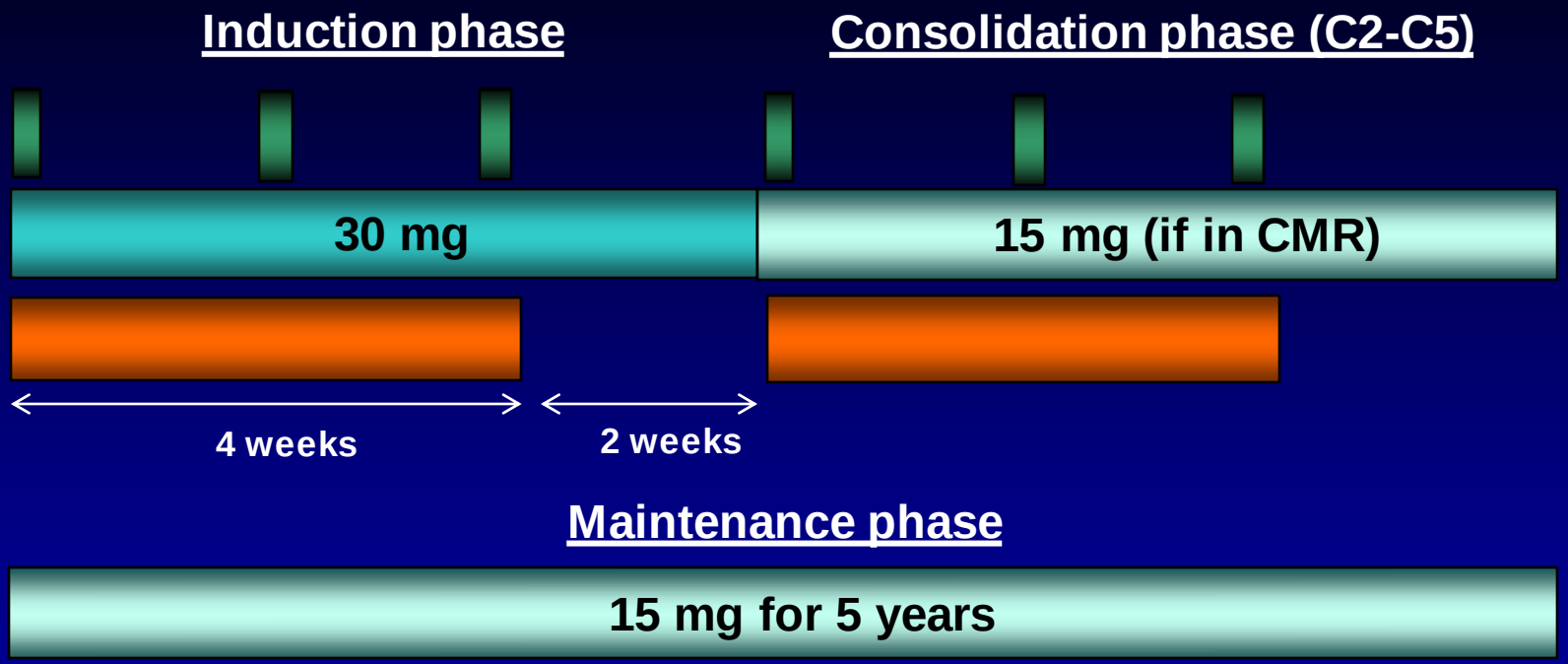
Dasatinib + Blinatumomab (D-ALBA) in Newly- Dx Ph+ ALL – Update

- 64 pts Rx; median age 54 yrs (24-82). Median FU 27 mos
- Molecular response (32/53 = 60%)
  - 22 CMR (41%)
- 29/58 (50%) who started blina has SCT
- 9 relapses: 4 hematologic, 4 CNS, 1 nodal
- 24-mos OS 88%, DFS 80%
- Outcome better if MR: DFS 100% vs 80% (*P* = .028)
- Outcome worse if IKZF1+: 2-yr OS 84% vs 54% (*P* = .026)



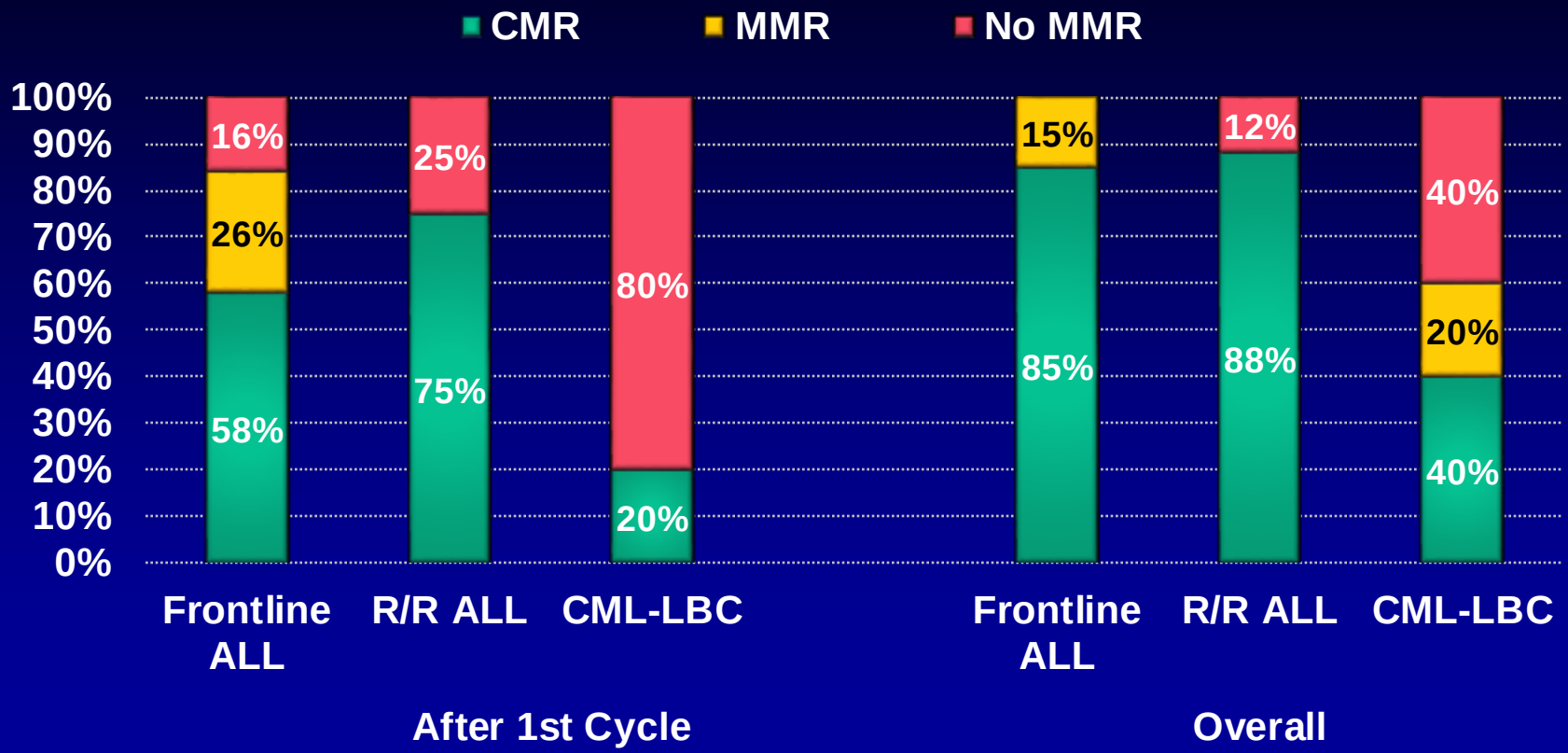
Chiaretti. EHA 2021. Abstract S112.

Ponatinib + Blinatumomab in Ph+ ALL: Regimen



Short NJ, et al. *J Clin Oncol*. 2021;39(suppl 15): abstract 7001.

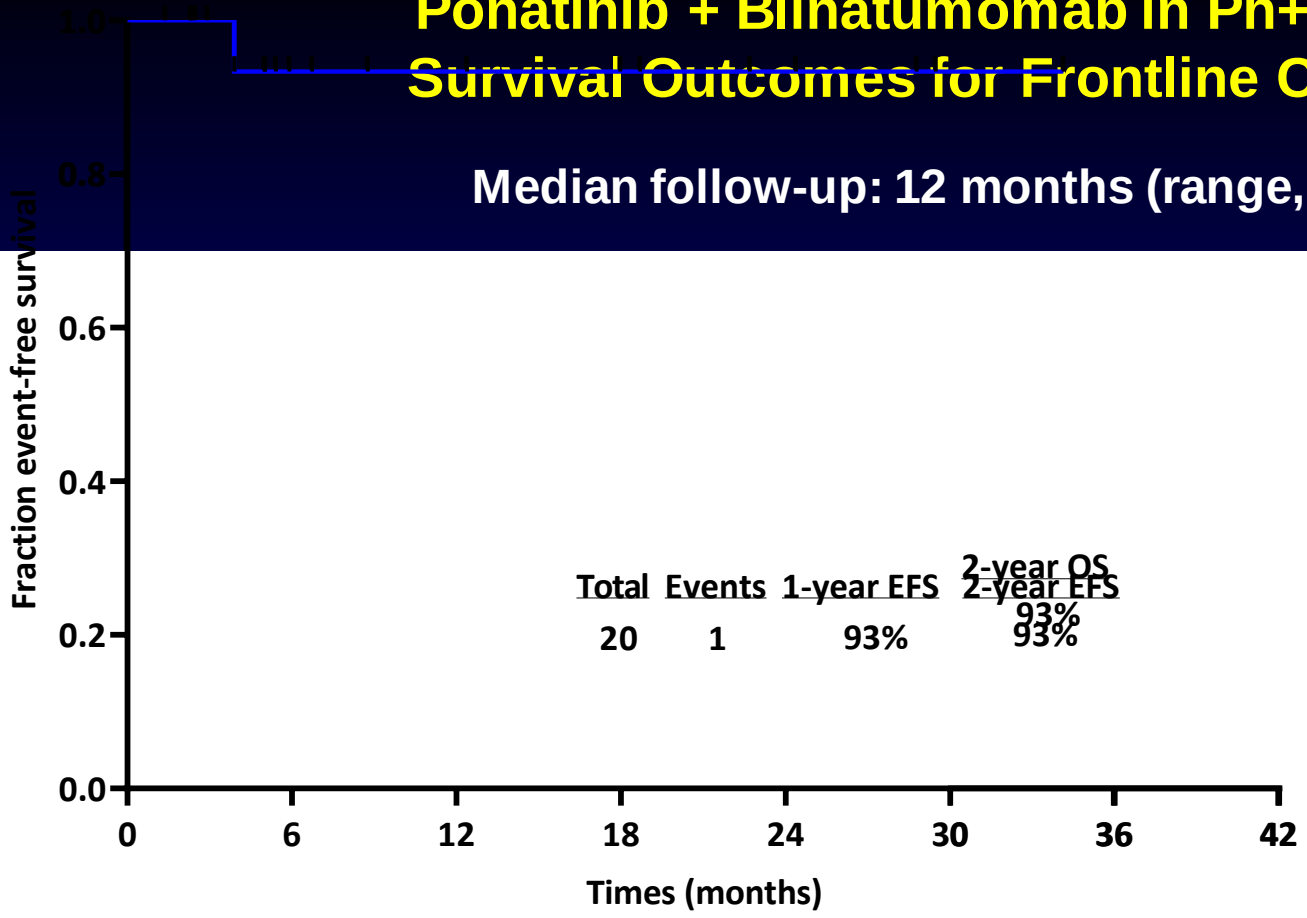
Ponatinib + Blinatumomab in Ph+ ALL: MRD Response Rates



Short NJ, et al. *J Clin Oncol*. 2021;39(suppl 15): abstract 7001.

Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes for Frontline Cohort

Median follow-up: 12 months (range, 1–37)

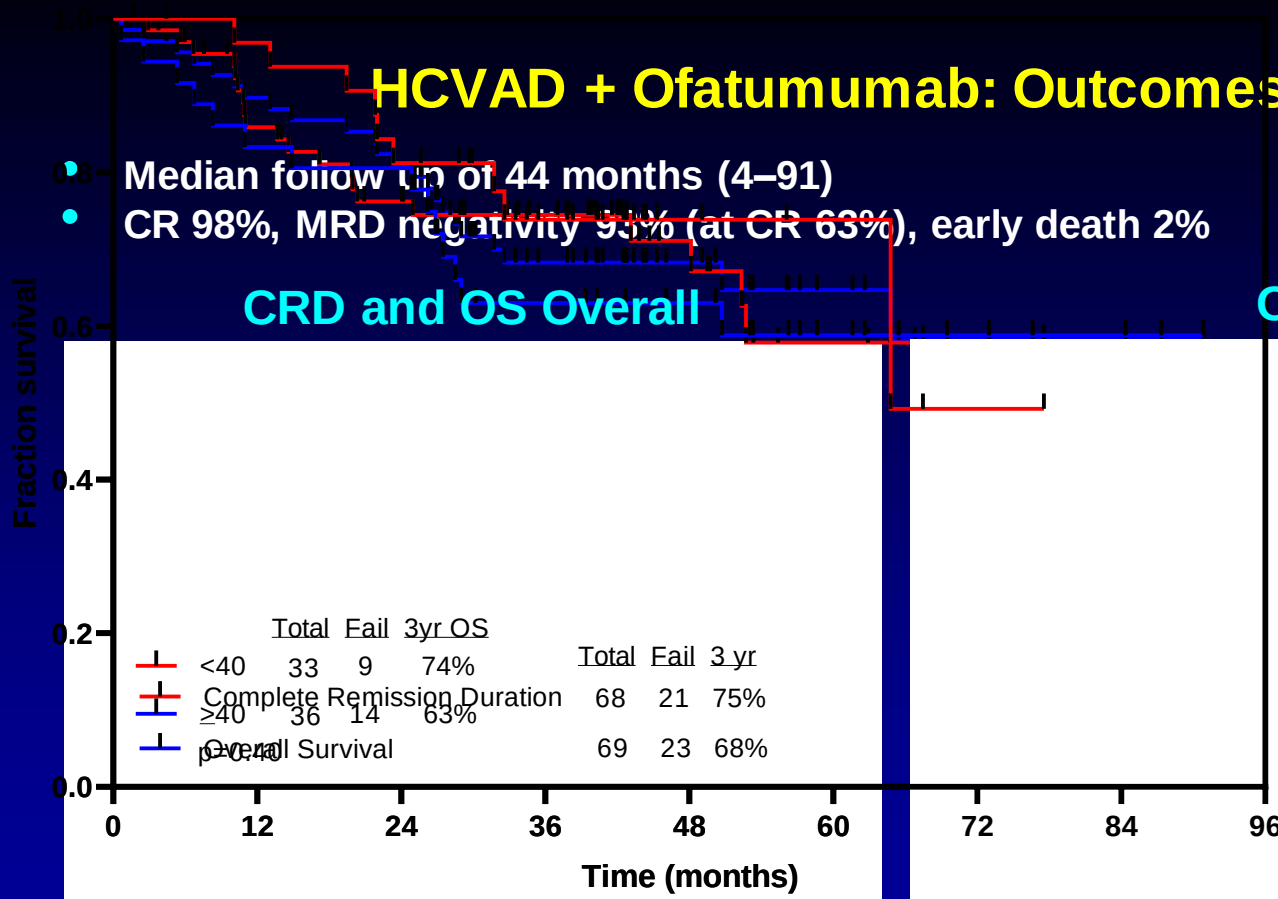


Short NJ, et al. *J Clin Oncol*. 2021;39(suppl 15): abstract 7001.

HCVAD + Ofatumumab: Outcomes (N = 69)

- Median follow up of 44 months (4–91)
- CR 98%, MRD negativity 95% (at CR 63%), early death 2%

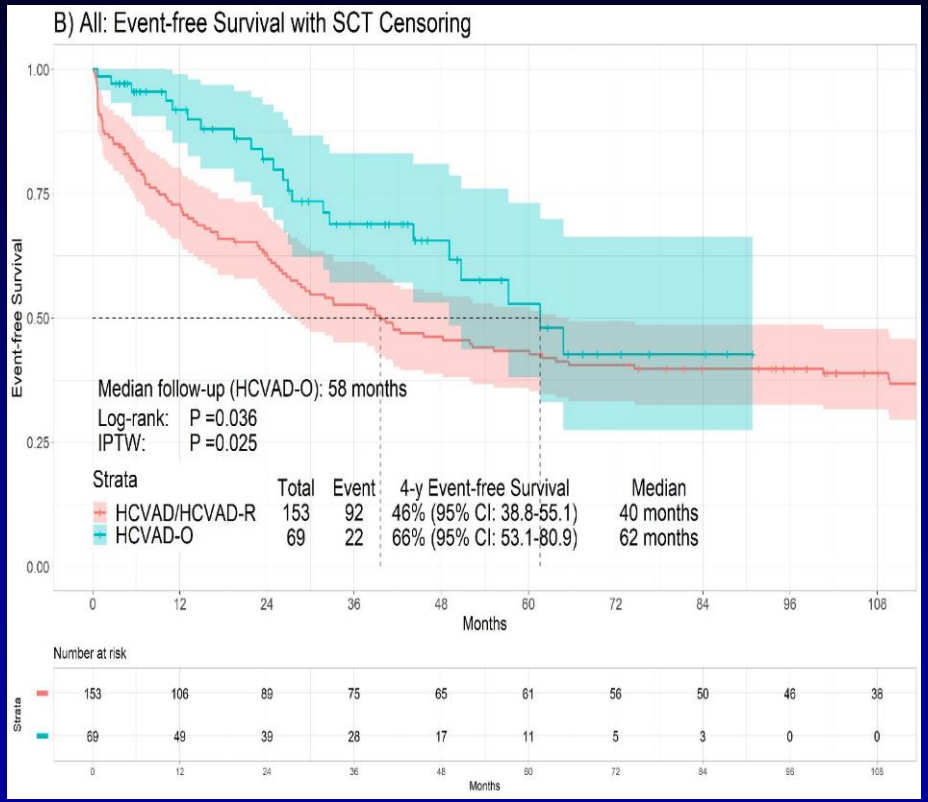
CRD and OS Overall

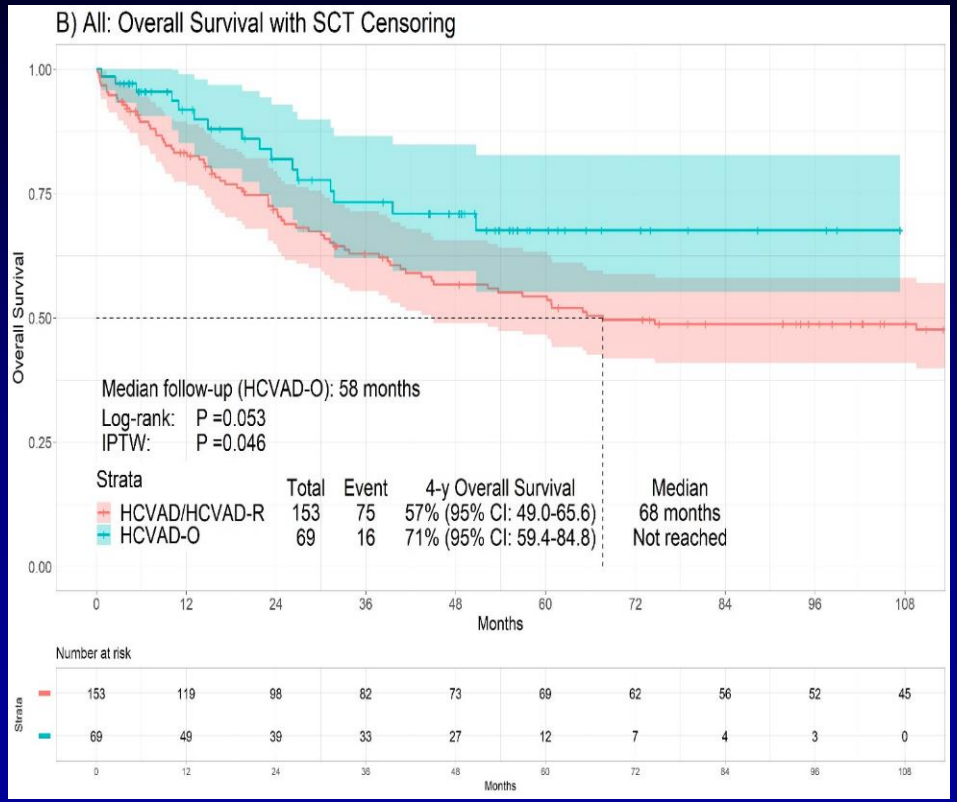


OS by Age

Jabbour E, et al. *Lancet Haematol.* 2020;7:e523-e533.

HCVAD-Rituximab vs HCVAD-Ofatumumab: Propensity Score Matching



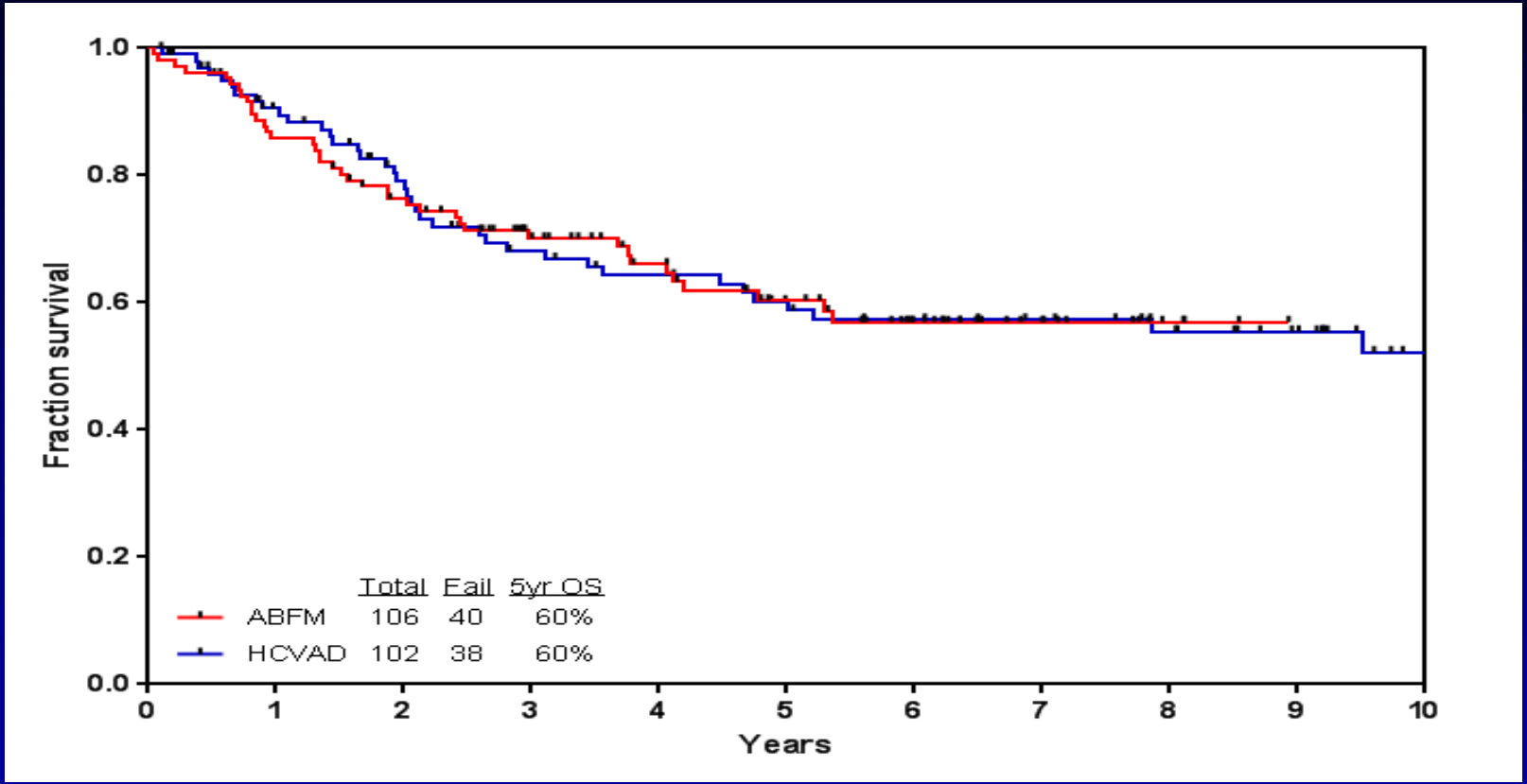


Morita et al. *Blood*. 2020;136:abstract 2387.

CD20-CD3 BiTEs in DLBCL (ASH 2020)

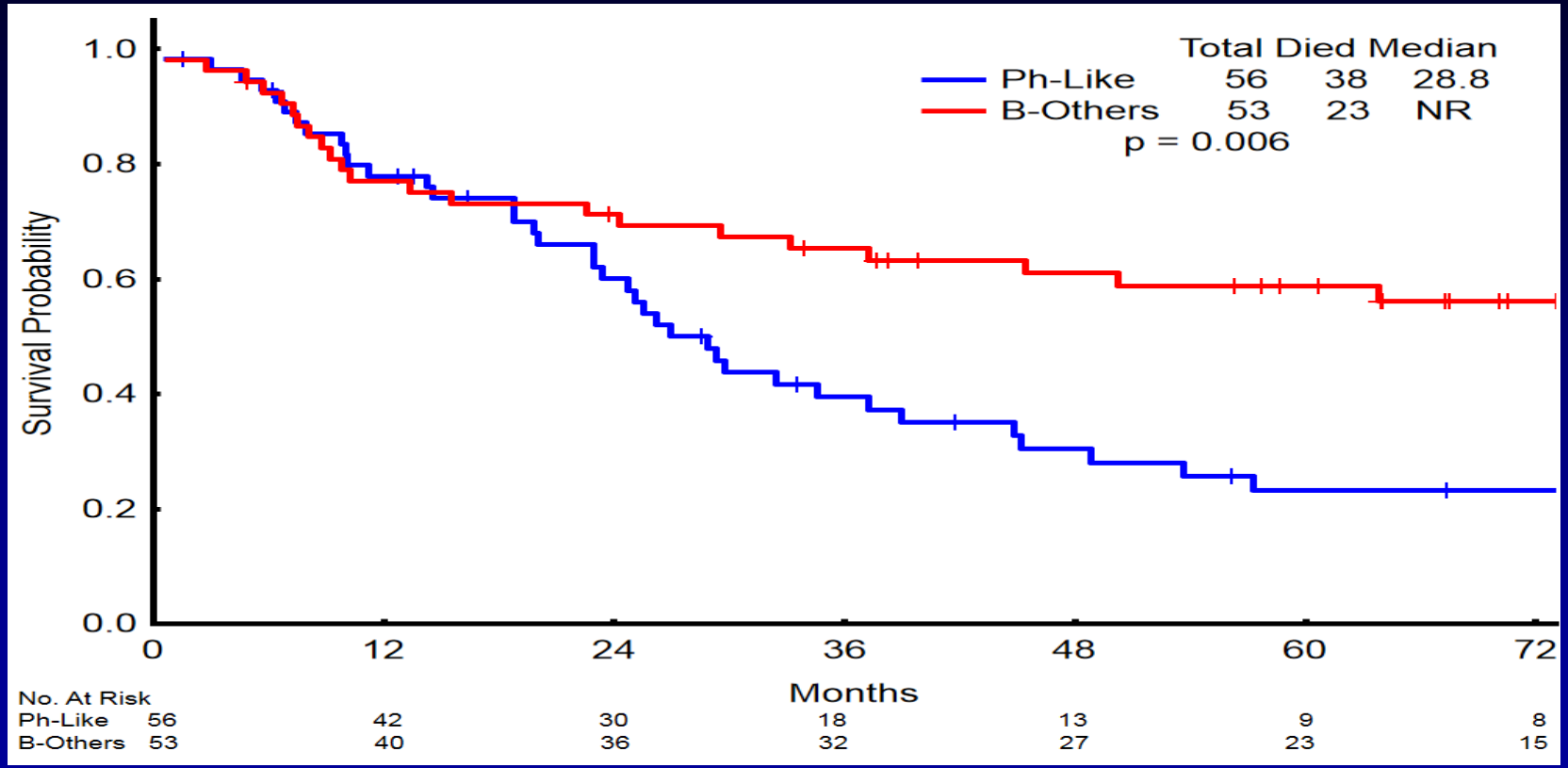
	Mosunetuzumab (Genentech) Olszewski (N = 29)	Odronextamab (REGN1979) Bannerji (N = 78)	Glofitamab (Roche/Genentech) Hutchings (N = 28)	Epcoritamab (Genmab/AbbVie) Hutchings (N = 46)
Patient population	Frontline DLBCL (older adults)	R/R DLBCL	R/R DLBCL	R/R DLBCL
Administration	IV	IV	IV (+obinutuzumab)	SQ
Median age	82 (67-100)	67 (27-89)	68 (44-85)	68 (21-82)
Median prior therapies	None	3	3	3
ORR (CR)	63% (45%) n = 22	40% (31%) n = 35	61% (54%) n = 28	68% (46%) n = 22
CRS	G1-2: 21% G3-4: 0%	G1-2: 54% G3-4: 7%	G1-2: 62% G3-4: 2%	G1-2: 59% G3-4: 0%

Hyper-CVAD vs ABFM: Overall Survival



Rytting et al. *Cancer*. 2014;120:3660-3668; Rytting et al. *Am J Hematol*. 2016;91:819.

Ph-like ALL – Worse Survival



Jain et al. *Blood*. 2017;129:572-581.

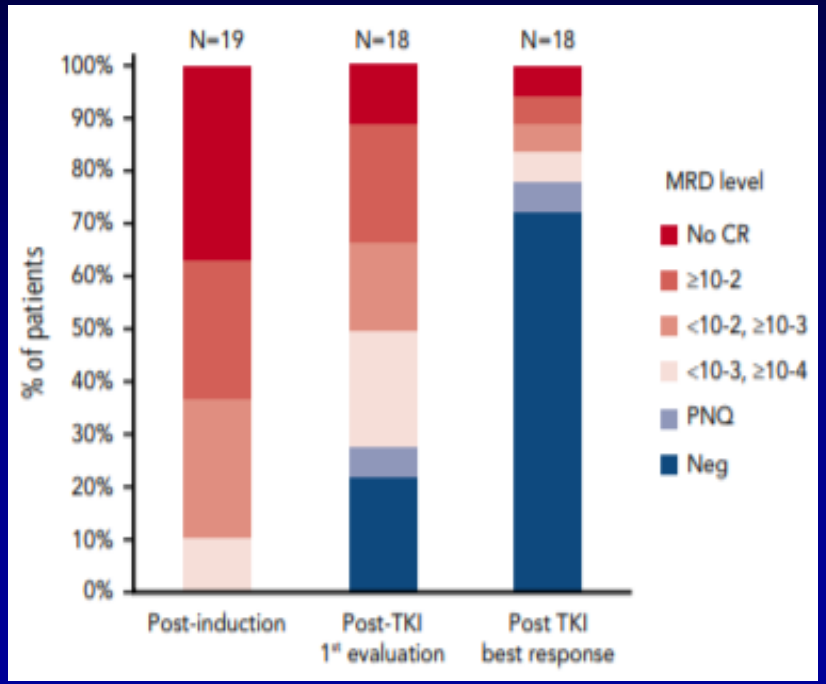
Ph-Like ALL: Higher MRD+ Rate

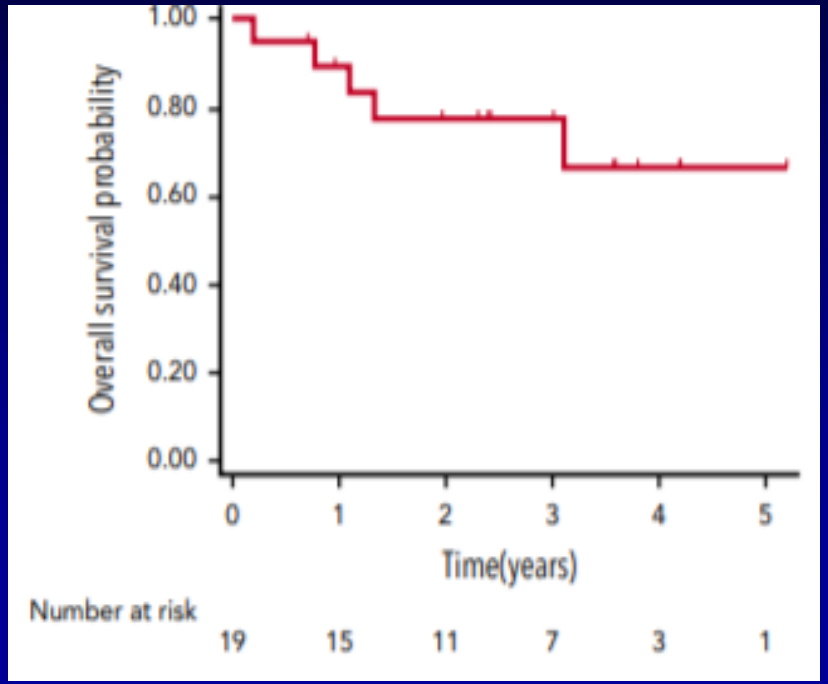
	B-ALL Categories (N = 155)			
	Ph-like	Ph+	B – other	*P* value
N	56	46	53	
CR/CRp	50 (89)	43 (93)	50 (94)	.57
MRD at CR				
Positive	**23 (70)**	**15 (44)**	**4 (13)**	**<.001**
Negative	10 (30)	19 (56)	27(87)	

Jain et al. *Blood*. 2017;129:572-581.

BCR-ABL TKIs + Chemo Rx in Ph-like ALL

- 24 pts with Ph-like ALL: NUP214-ABL1 – 6, ETV6-ABL1 – 3, others – 9. 19 frontline, 5 relapse. All Rx with chemo Rx + TKI

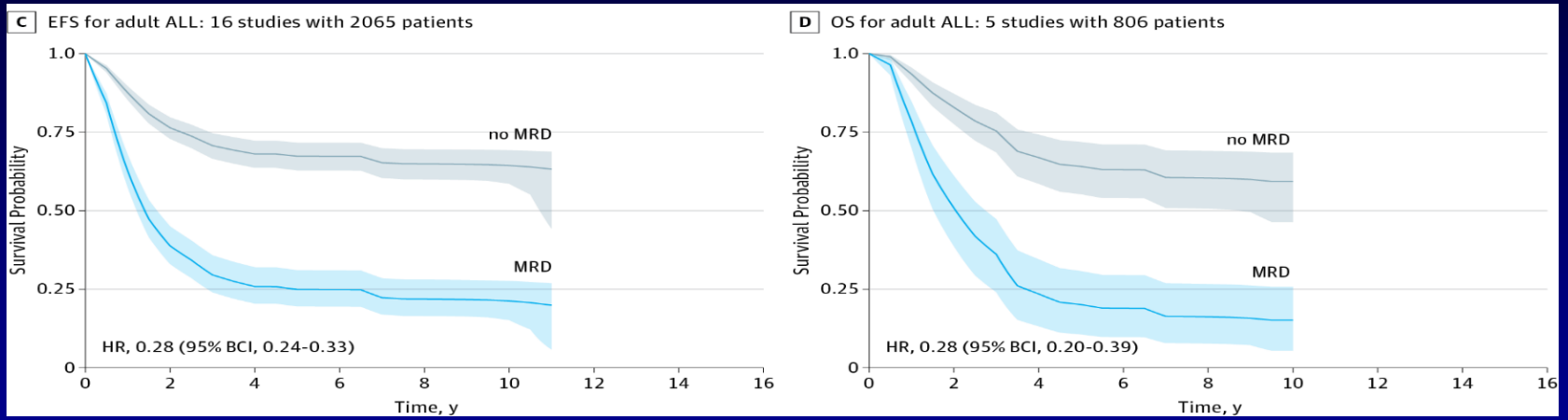




Tanasi I, et al. *Blood*. 2019;134:1351-1355.

NGS MRD in ALL: Background

- MRD is highly prognostic for relapse and survival in Ph-negative ALL

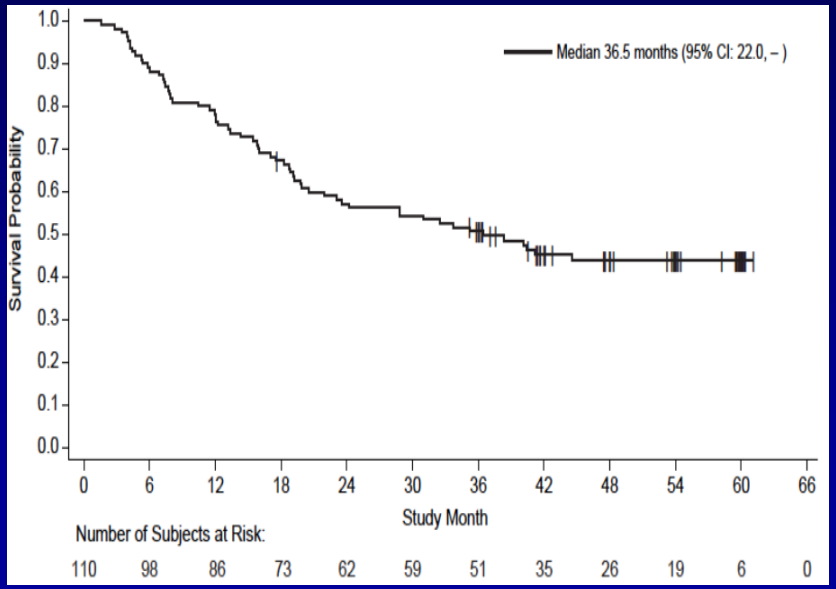


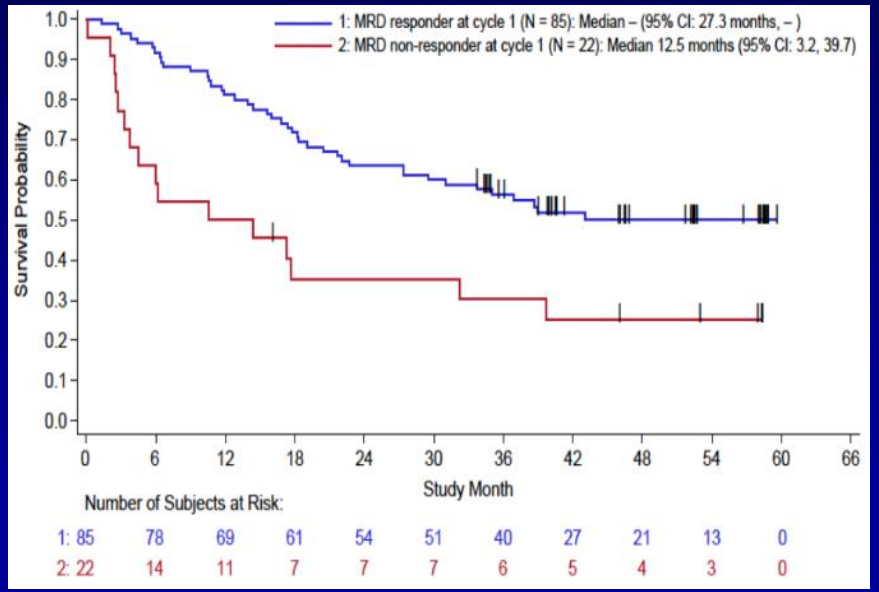
- However, many pts with apparent "MRD negativity" by standard assays still relapse
- Sensitivity of standard MRD assays: 1×10^{-4} (0.01%)

Berry DA, et al. *JAM A Oncol.* 2017;3(7):e170580.

Blinatumomab for MRD+ ALL in CR1/CR2

- 113 pts Rx. Post-blina MRD– 88/113 = 78%
- 110 evaluated (blasts <5%, MRD+); 74 received alloSCT. Median F/U 53 mo
- Median OS 36.5 mo; **4-yr OS 45%; 4-yr OS if MRD– 52%**
- Continuous CR 30/74 post-alloSCT (40%); 12/36 without SCT (33%)

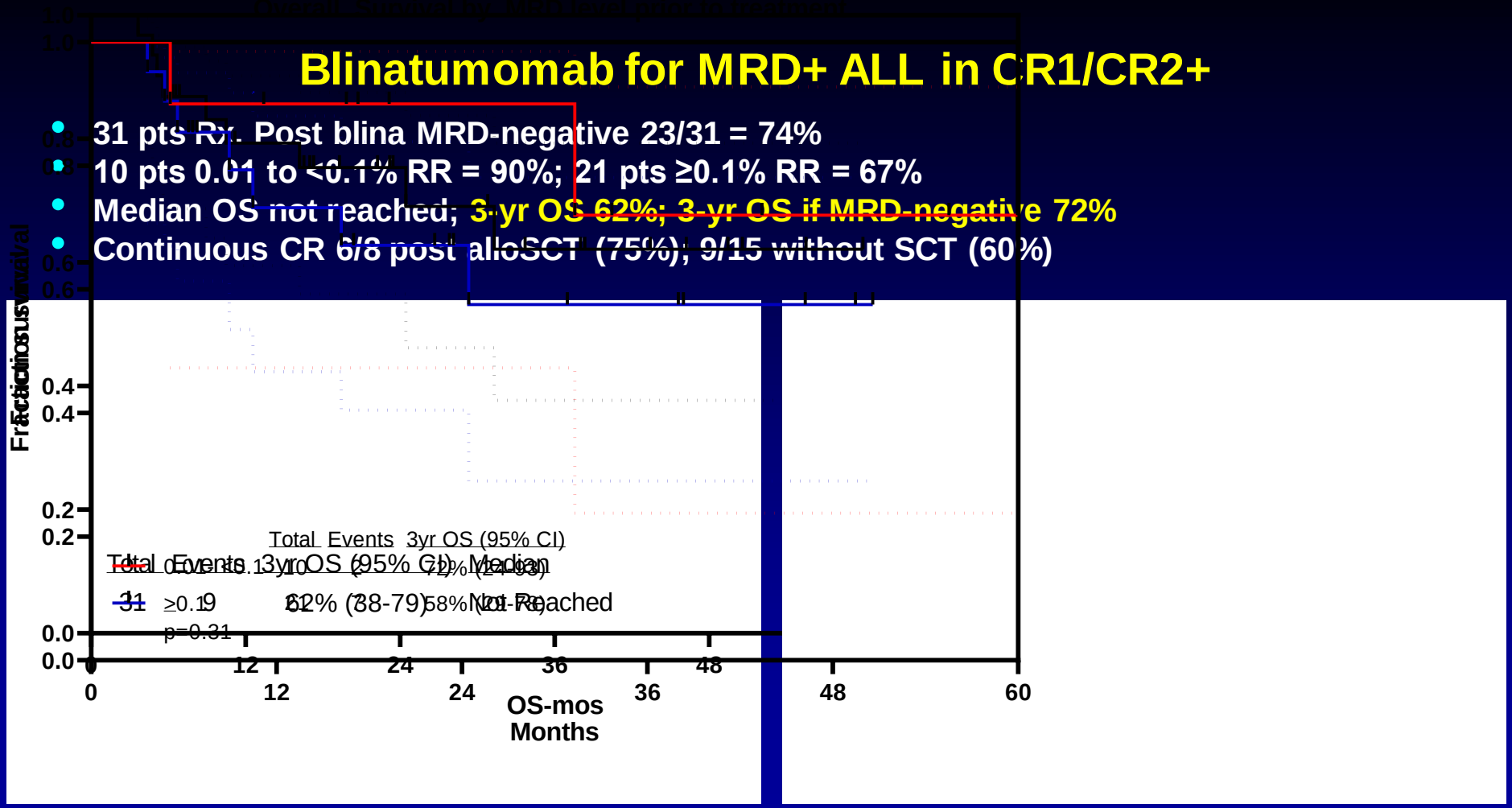




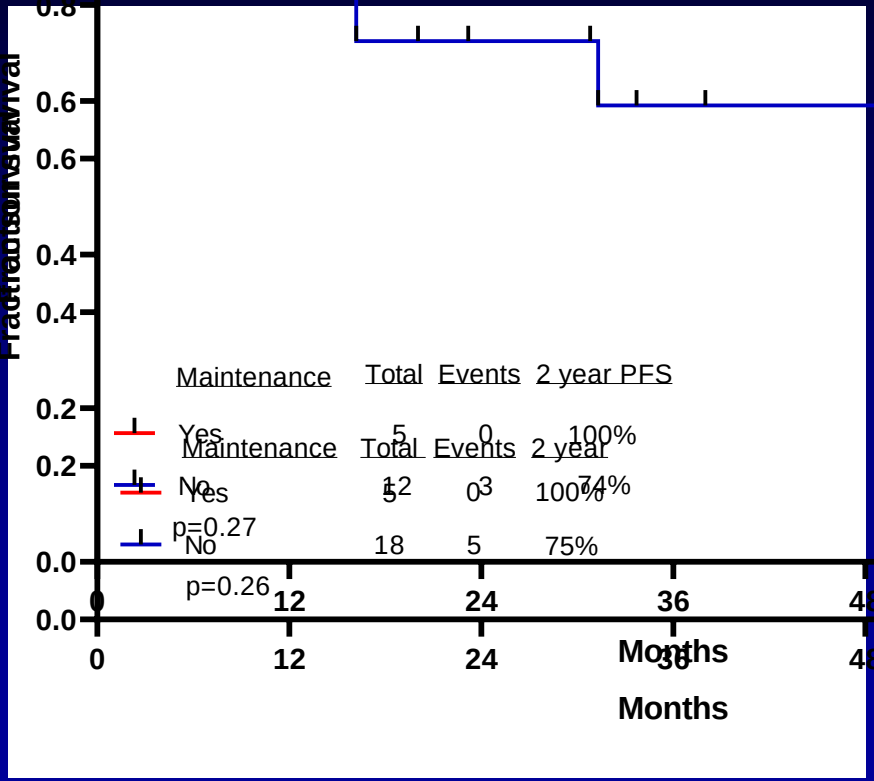
Goekbuget N, et al. *Blood*. 2018;132:abstract 554.

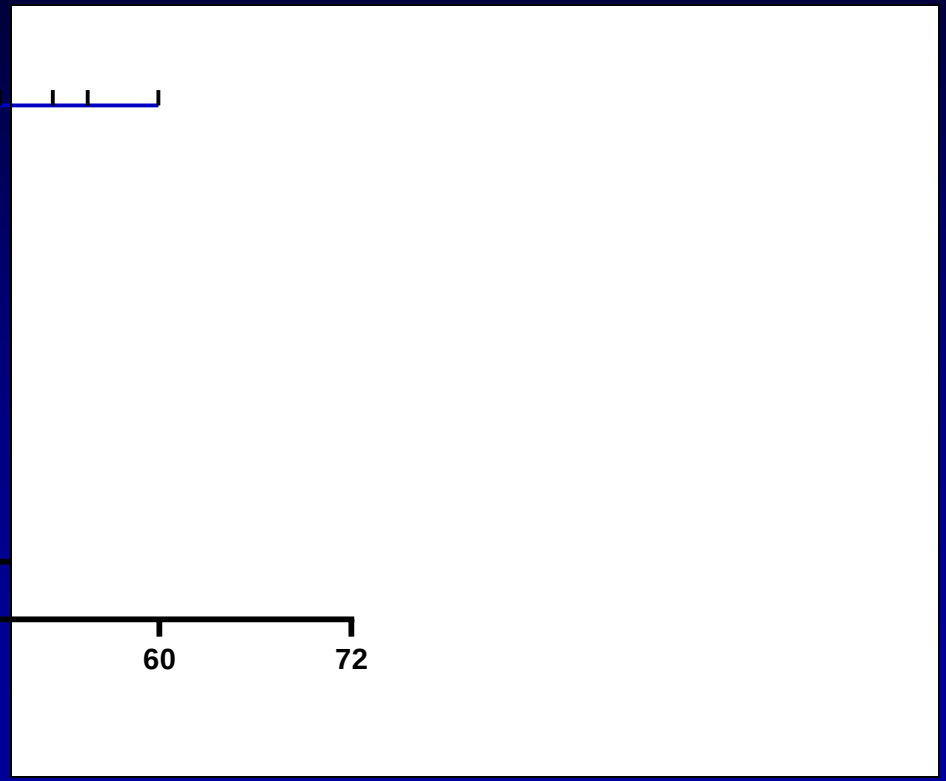
Blinatumomab for MRD+ ALL in CR1/CR2+

- 31 pts Rx. Post blina MRD-negative 23/31 = 74%
- 10 pts 0.01 to <0.1% RR = 90%; 21 pts ≥0.1% RR = 67%
- Median OS not reached; 3-yr OS 62%; 3-yr OS if MRD-negative 72%
- Continuous CR 6/8 post alloSCT (75%); 9/15 without SCT (60%)



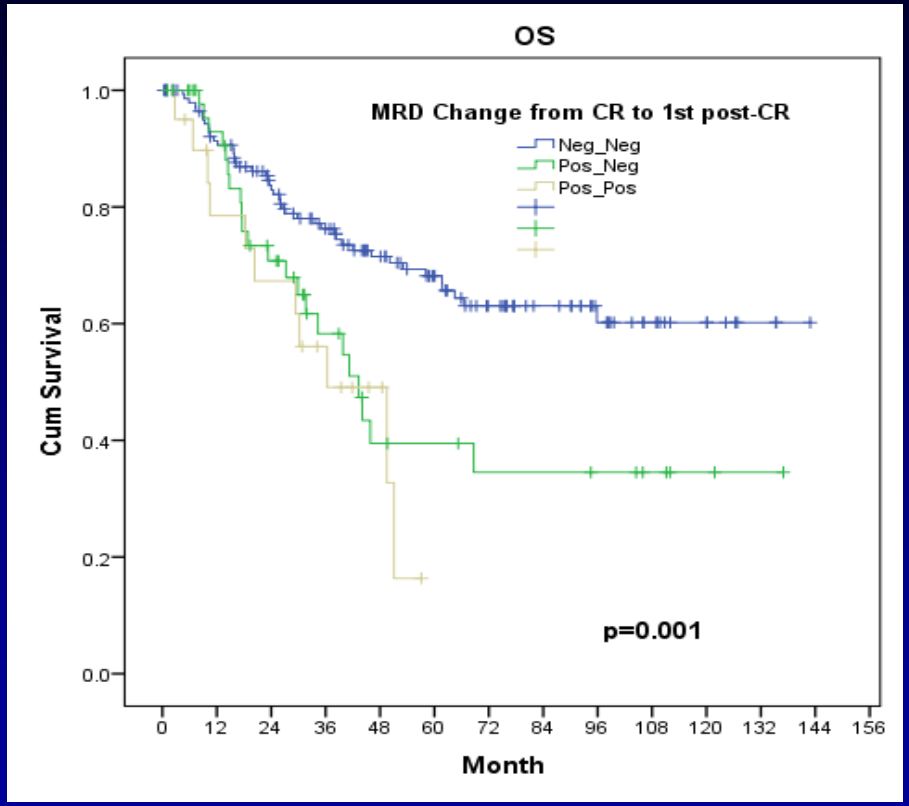
Blinatumomab for MRD+ ALL in CR1/CR2+: Impact of Maintenance





Dynamics of MRD: Outcome

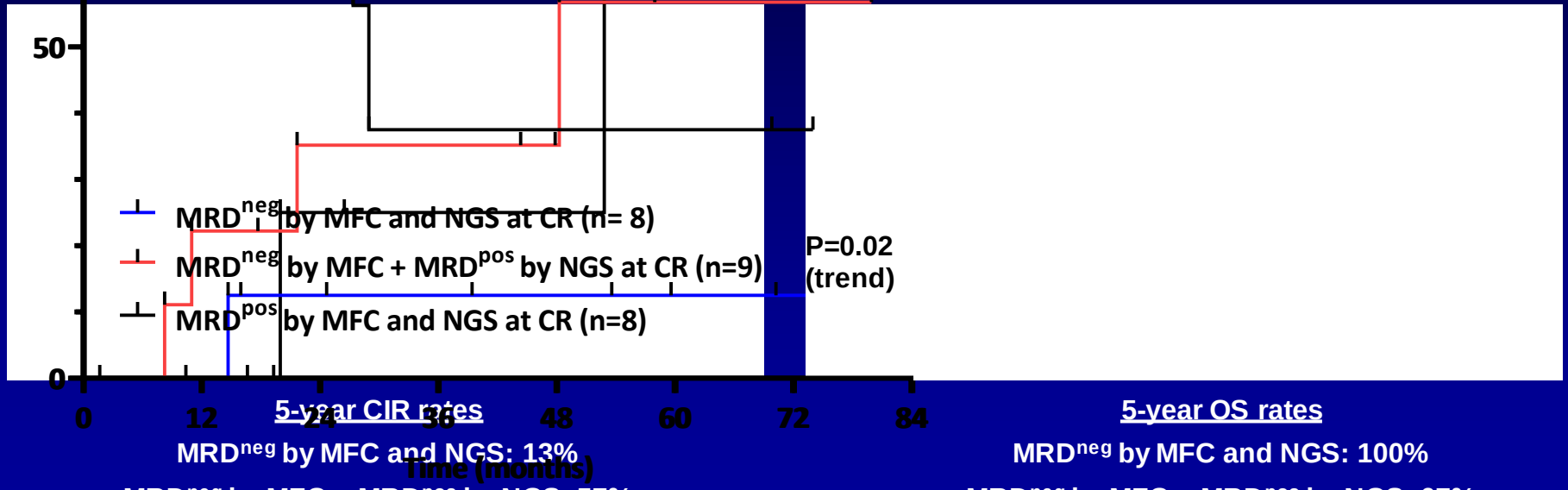
MRD Status		Patients (%) n = 214	5-yr EFS, %	5-yr OS, %
@CR	@ First post-CR			
Negative	**Negative**	**147 (69)**	**56**	**68**
≤0.1%	Negative	14 (7)	31	46
>0.1%	Negative	33 (15)	32	38
Positive	Positive	20 (9)	NA	NA



Yilmaz et al. *Blood*. 2019;134:abstract 1297.

MRD in ALL: NGS vs FCM

- 67 pts Rx (66% HCVAD; 34% mini-HCVD)
- 32/84 (38%) discordant (ie, MRDneg by MFC but MRDpos by NGS)
  - 48% at CR and 30% at mid-consolidation
- MRDneg by NGS highly predictive at CR with HCVAD



5-year CIR rates

MRD^{neg} by MFC and NGS: 13%

MRD^{neg} by MFC + MRD^{pos} by NGS: 57%

MRD^{pos} by MFC and NGS: 63%

5-year OS rates

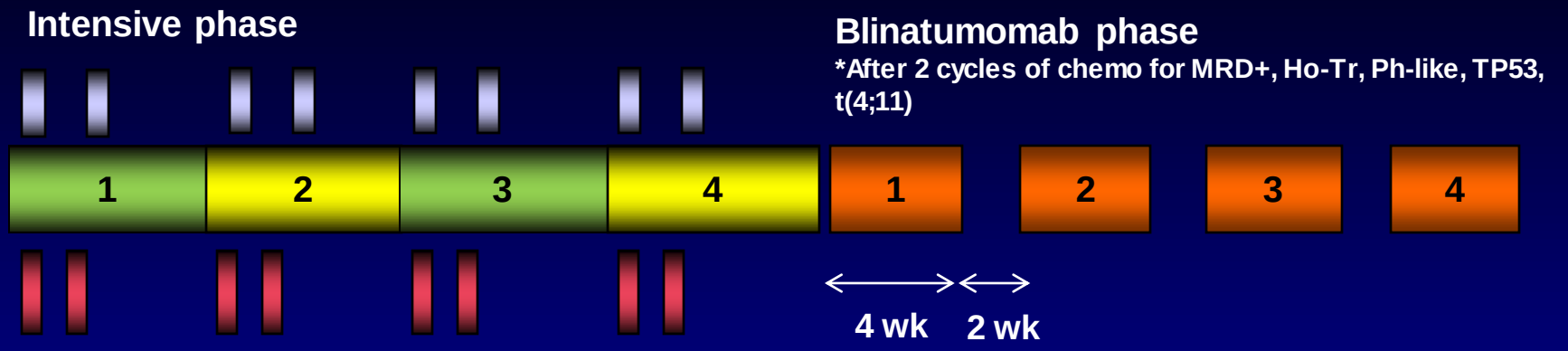
MRD^{neg} by MFC and NGS: 100%

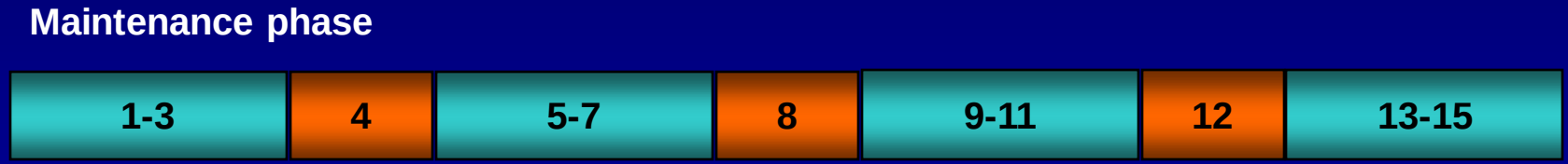
MRD^{neg} by MFC + MRD^{pos} by NGS: 67%

MRD^{pos} by MFC and NGS: 38%

Short et al. *Blood.* 2020;136:abstract 583.

Hyper-CVAD + Blinatumomab in B-ALL: Regimen





Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

MTX + Ara-C

IT MTX/Ara-C × 8

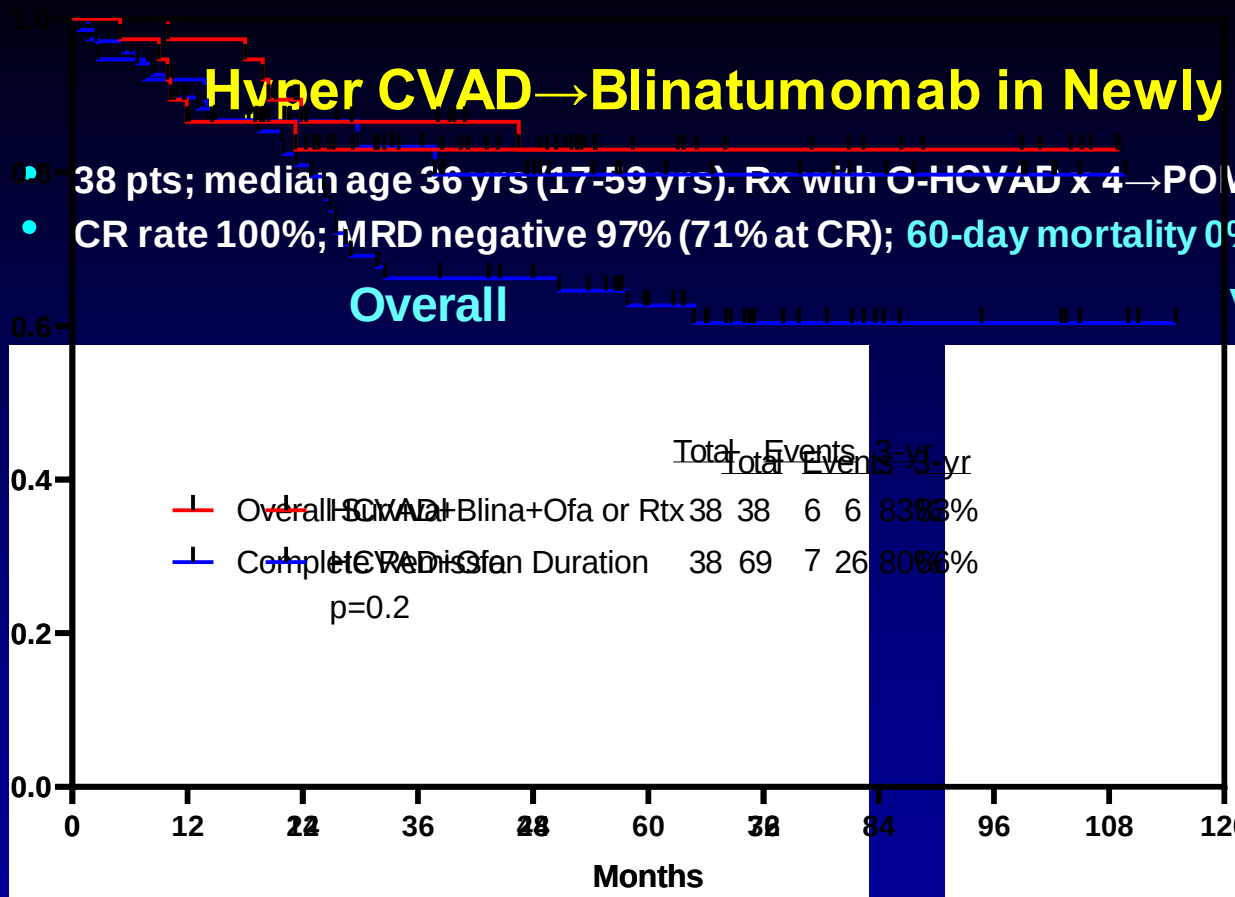
POMP

Short et al. *Blood.* 2020;136:abstract 464.

Hyper CVAD→Blinatumomab in Newly Dx Adult ALL

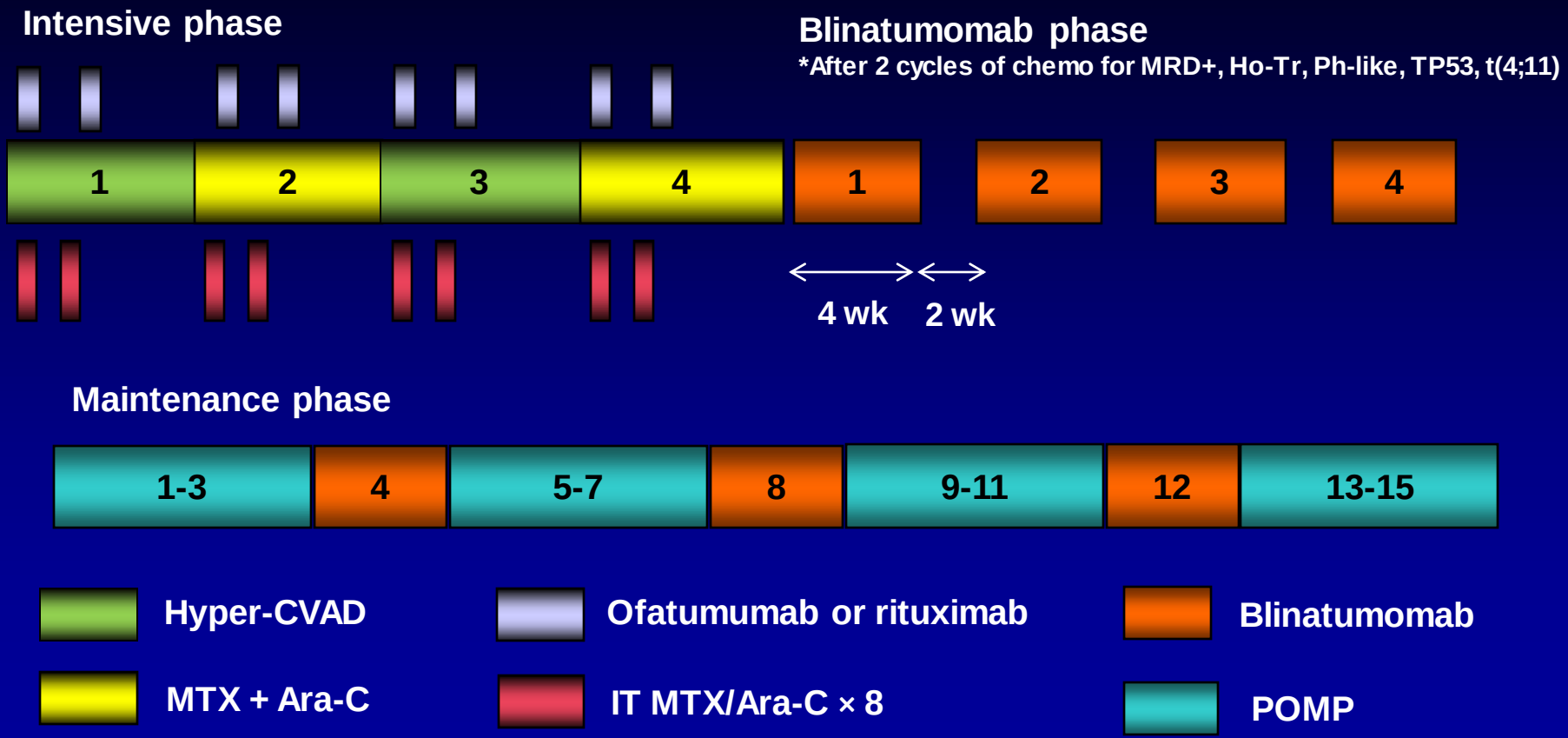
- 38 pts; median age 36 yrs (17-59 yrs). Rx with O-HCVAD x 4→POMP 1 yr with blina Q3 mos
- CR rate 100%; MRD negative 97% (71% at CR); 60-day mortality 0%; 12 (32%) allo-SCT; F/U 24 mos

Overall



Vs Historical

Hyper-CVAD + Blinatumomab in B-ALL: Regimen



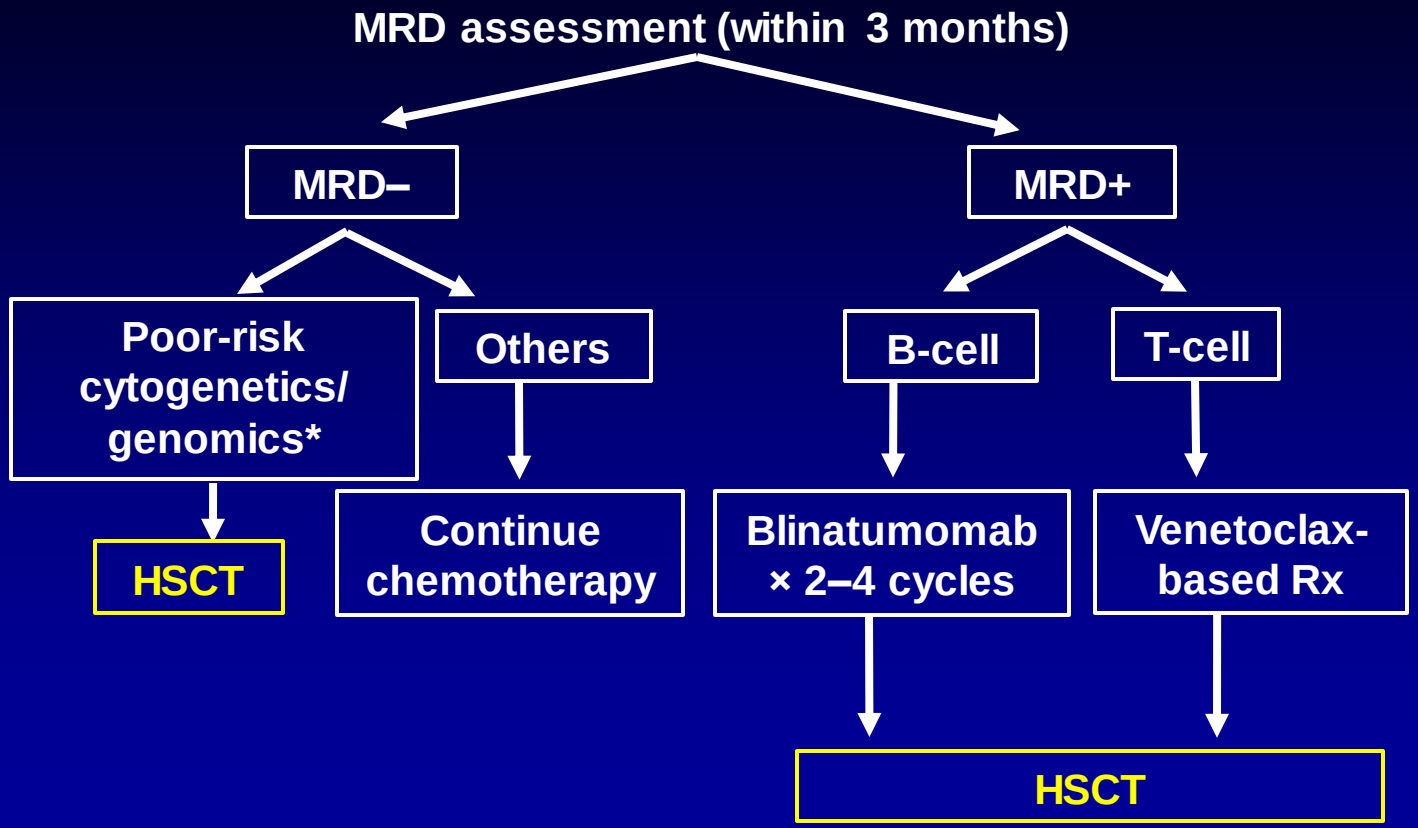
Short et al. *Blood.* 2020;136:abstract 464.

Sequential Chemo Rx and Blinatumomab in Newly Dx ALL

- 149 pts; median age 41 yrs (18–65; 18% >55)
- Chemo Rx GIMEMA LAL1913-blina × 2 post C3 and C6
- CR 90%
- MRD clearance: 73% post early consolidation; 96% post blina × 1. Conversion to MRD-negative post blina 20/23 = 87%
- 12-mos OS 84%, DFS 72%, 12 mos relapse 11%

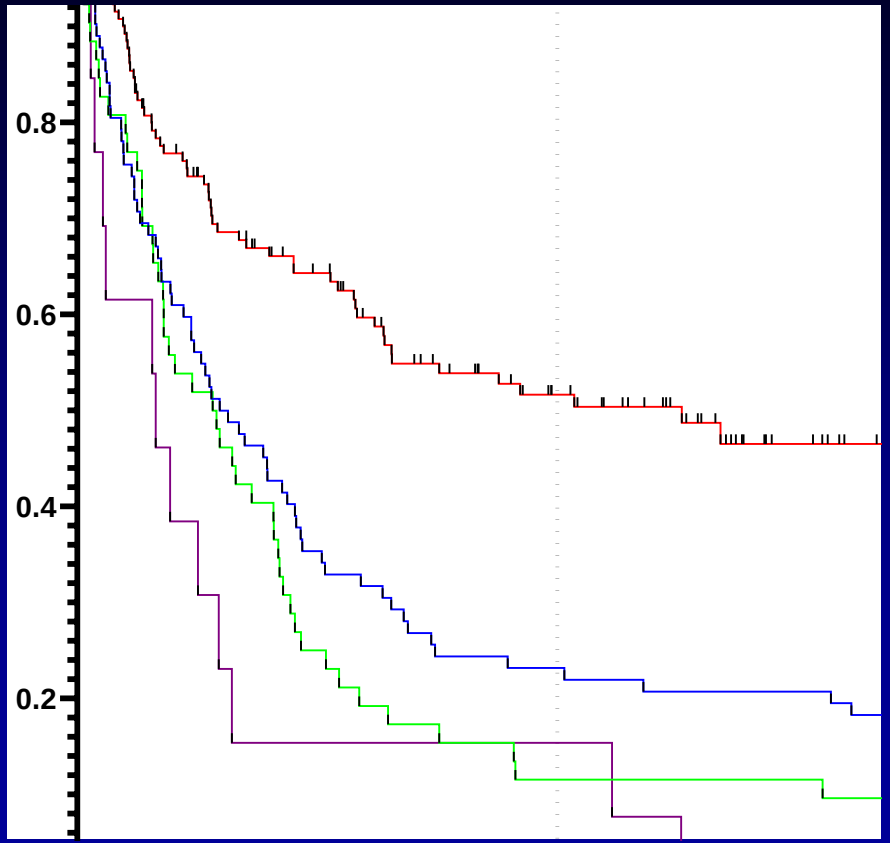
Bassan et al. EHA 2021. Abstract S114.

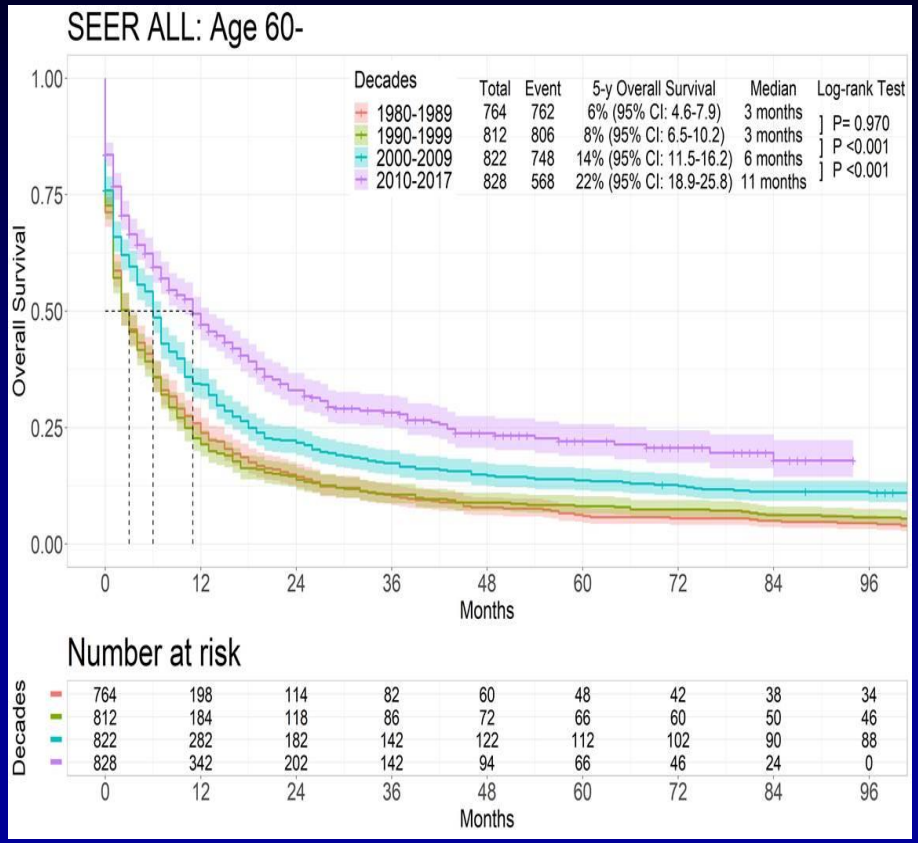
Indications for HSCT: Ph– B-ALL and T-ALL



*Ph-like, 11q23 rearrangement, ETP-ALL, low hypodiploidy, complex cytogenetics

MDACC ALL: Survival by Decades for ≥60 Years





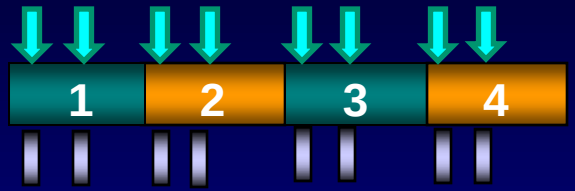
Mini-HCVD + INO ± Blina in ALL: Design

- Dose reduced HyperCVD for 4–8 courses
  - Cyclophosphamide (150 mg/m^2 × 6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m^2) 75% dose reduction
  - Cytarabine (0.5 g/m^2 × 4) 83% dose reduction
- Inotuzumab on D3 (first 4 courses)
  - Modified to 0.9 mg/m^2 C1 (0.6 and 0.3 on D1&8) and 0.6 mg/m^2 C2-4 (0.3 and 0.3 on D1&8)
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- Blinatumomab 4 courses and 3 courses during maintenance
- POMP maintenance for 3 years, reduced to 1 year

Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055.

Mini-HCVD + INO ± Blina in Older ALL: Modified Design

Intensive phase



Mini-HCVD

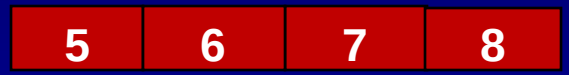
Mini-MTX-cytarabine

IT MTX, Ara-C

Blinatumomab

POMP

Consolidation phase



INO*	Total dose (mg/m^2)	Dose per day (mg/m^2)
C1	0.9	0.6 D2, 0.3 D8
C2-4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m^2

Maintenance phase

18 months

*Ursodiol 300 mg tid for VOD prophylaxis

Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055; Kantarjian H, et al. *Lancet Oncol*. 2018;19:240.

Mini-HCVD + Ino ± Blina in Older ALL (N = 70)

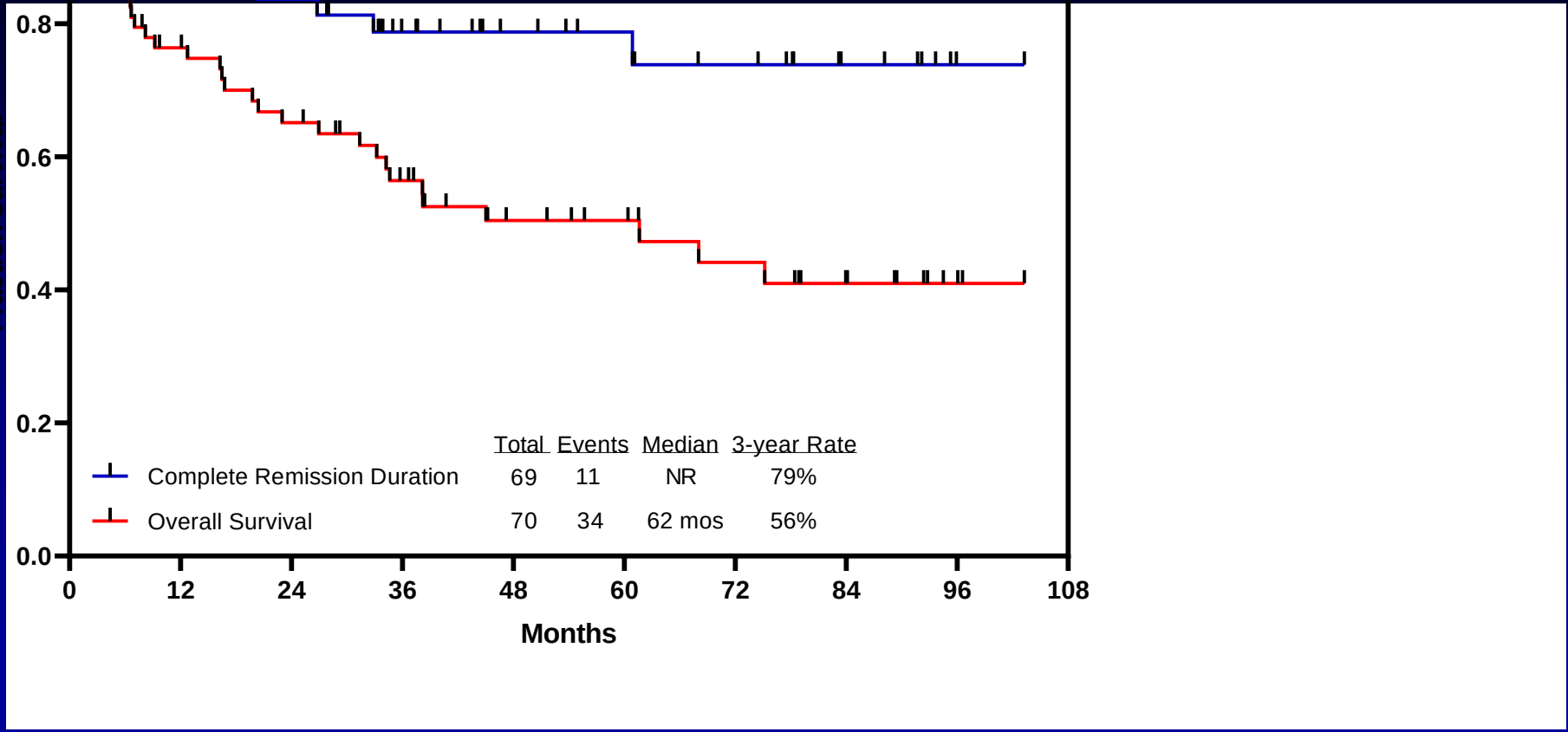
Characteristic	Category	N (%)/Median [range]
Age (years)	**≥70**	**68 [60–81]** **29 (41)**
Performance status	≥2	10 (14)
WBC ($\times 10^9$/L)		3.1 [0.6–111.0]
Karyotype	Diploid HeH **Ho-Tr** **Tetraploidy** **Complex** **t(4;11)** Misc IM/ND	23 (33) 5 (7) **12 (17)** **3 (4)** **3 (4)** **1 (1)** 10 (14) 13 (19)
CNS disease at diagnosis		4 (6)
CD19 expression, %		99.6 [30–100]
CD22 expression, %		96.7 [27–100]
CD20 expression	≥20%	38/64 (59)
***CRLF2*+ by flow**		**7/38 (18)**
***TP53* mutation**		**21/51 (41)**

Response (N = 64)	N (%)
ORR	**63 (98)**
CR	56 (88)
CRp	6 (9)
CRi	1 (2)
No response	1 (2)
Early death	**0**

Flow MRD response	N (%)
D21	53/66 (80)
Overall	**65/68 (96)**

Short et al. *Blood.* 2020;136:abstract 1014.

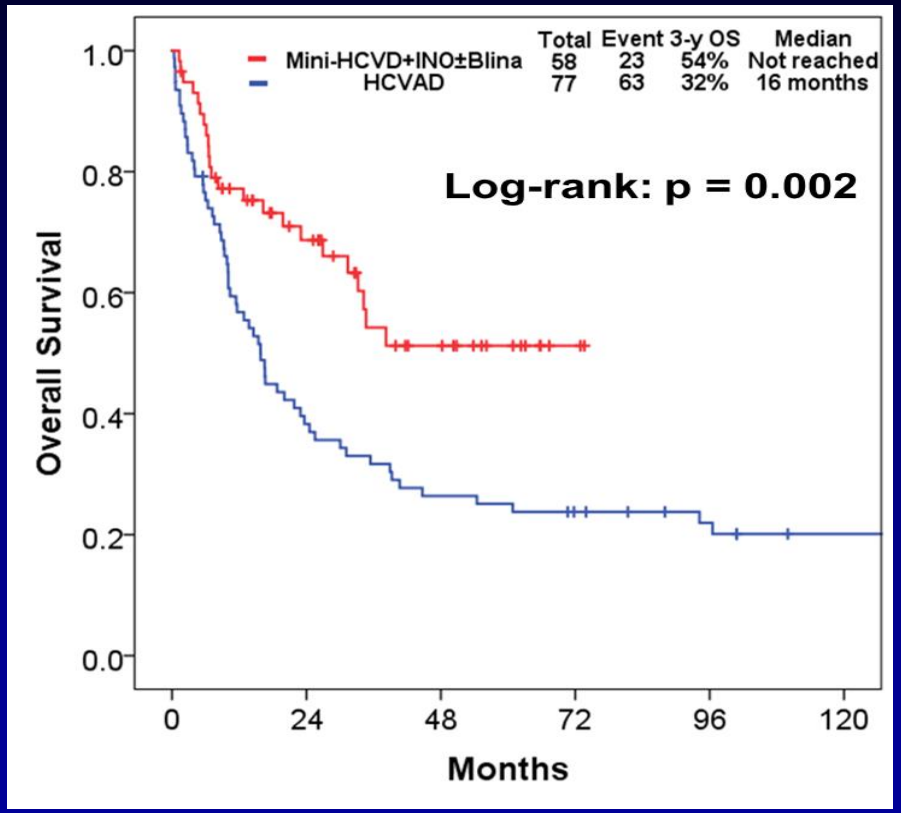
Mini-HCVD + INO ± Blina in Older ALL: CRD and OS (Entire Cohort)



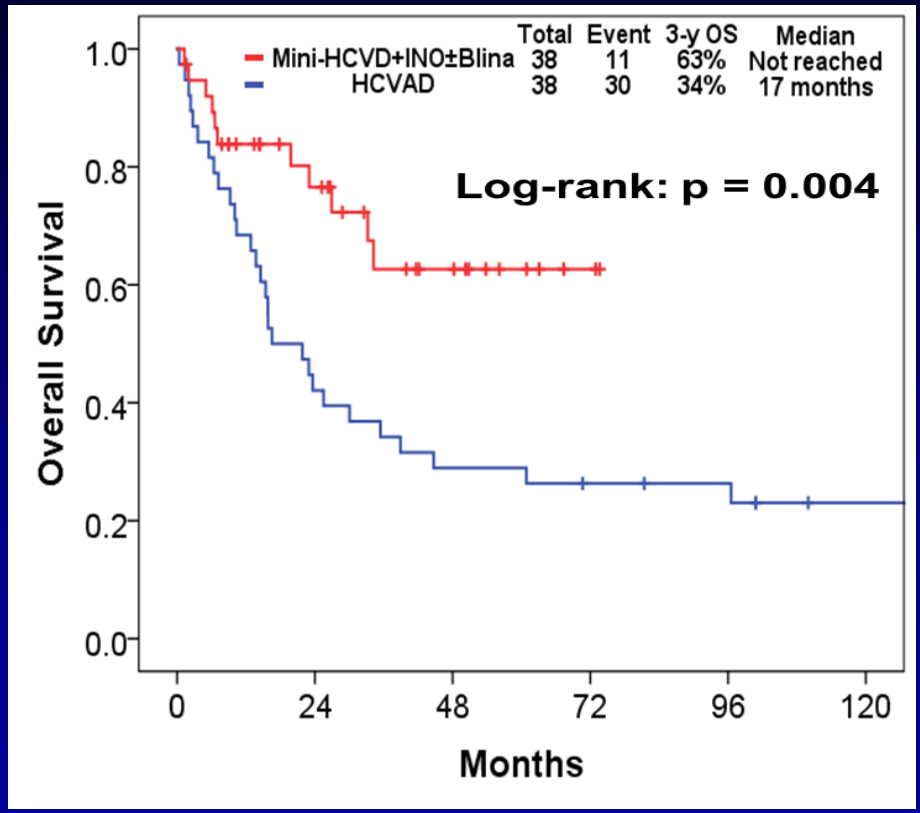
Short et al. *Blood.* 2020;136:abstract 1014.

Mini-HCVD + INO ± Blina vs. HCVAD in Elderly ALL: Overall Survival

Pre-matched



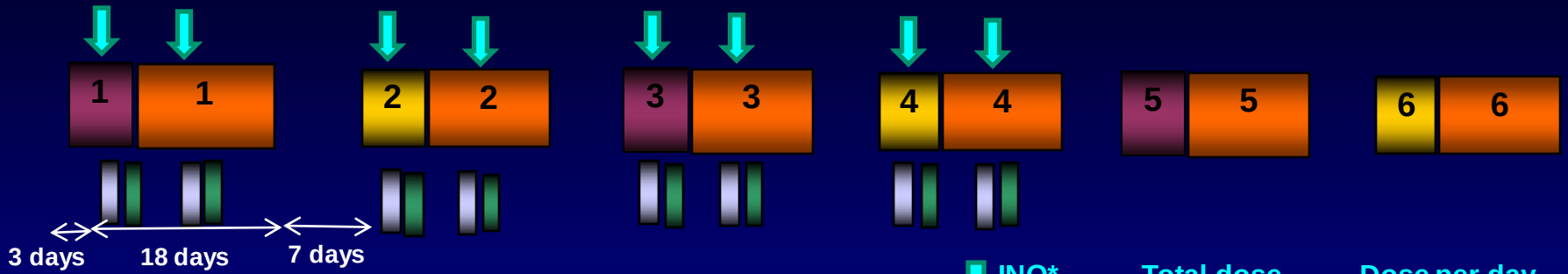
Matched



Sasaki. *Blood.* 2018;132:abstract 34.

Dose-dense Mini-HCVD + INO ± Blina in ALL: Modified Design

Intensive 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 300mg tid for VOD prophylaxis

Maintenance phase

Mini-Hyper-CVD

Mini-MTX-Ara-C

Rituximab

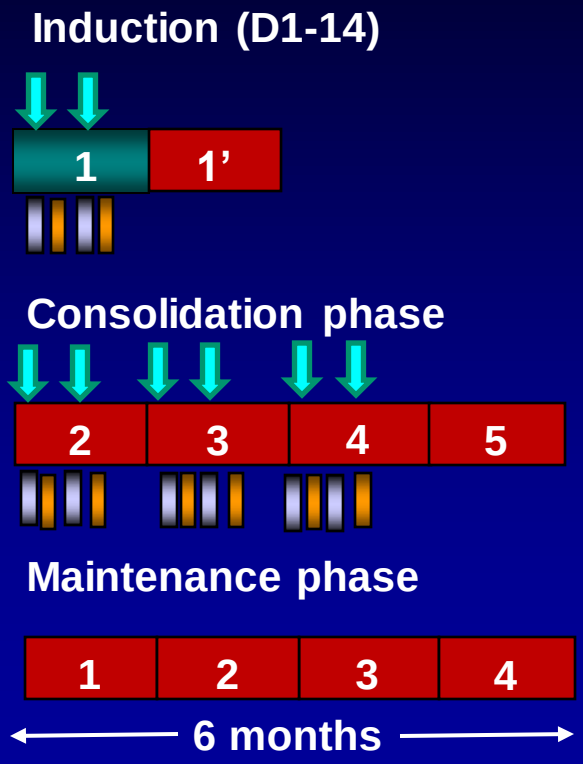
IT MTX, Ara-C

POMP

Blinatumomab

VCR/Steroid

INO + Blina in Older ALL: Amended Design (Pts ≥70 years)



Dexa 20 mg D1-4 and VCR 1 mg D4

Blinatumomab

IT MTX, Ara-C

Rituximab if CD20+

1' Blinatumomab for 2 weeks

INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D1, 0.3 D8
C2-C4	0.6	0.3 D1 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Inotuzumab Followed by Chemo Rx in ALL 55+ Years

- Course 1 – Ino 0.8 mg/m^2 D1, 0.5 g/m^2 D8 and 15 (1.8 mg/m^2) in Course 1
  - CTX-VCR-steroids pre phase – TIT × 1/course
- Courses 2 and 3 – Ino 0.5 mg/m^2 Days 1, 8, 15 (1.5 mg/m^2)
  - 5 consolidations: 3 MTX/Asp, 2 ID-ara-C→1 reinduction IDA-ara-C-CTX-Dex
  - 6MP-MTX maintenance × 1.5 yr
- 36 Rx, results in 31; Median age 65 years (56–80)
- CR/CRi 31/31 (100%); MRD negative 21/27 (78%)
- 1-yr OS 87%; 1-yr EFS 87%
- No VOD

Stelljes et al. *Blood.* 2020;136:abstract 267.

ALL Summary

- Significant progress and improved outcomes across all ALL categories: Ph+, Burkitt, younger and older pre–B-ALL, T-ALL, ALL salvage. Rapidly evolving therapies
- Antibody-based Rxs and CAR Ts both outstanding; not mutually exclusive/competitive (vs); rather complementary (together)
- Future of ALL Rx: 1) less chemotherapy(?) and shorter durations; 2) combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22; 3) CAR Ts in sequence in CR1 for MRD and replacing allo-SCT
- Importance of MRD testing and changing Rx accordingly

The Future of ALL Therapy…

It is plausible that incorporating active monoclonal antibodies/CAR T-cells Rx into frontline adult ALL therapy, in a concomitant or sequential fashion, may induce higher rates of MRD negativity and increase the cure rates to levels achieved in pediatric ALL, and may reduce the need for allo-SCT and intensive and prolonged chemotherapy schedules

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

Thank You

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Global Leukemia Academy

Q&A session

APTITUDE HEALTH®

Global Leukemia Academy

Current treatment options for relapsed ALL in adult and elderly patients

Nicola Gökbuget

APTITUDE HEALTH

Current Treatment Options for Relapsed ALL in Adult (and Older) Patients

Nicola Gökbuget

Goethe University Hospital, Department of Medicine II, Frankfurt

GMALL Study Group Chair

Potential Conflict of Interest

Speaker Honoraria, Travel Support, Advisory Board
- Amgen
- Celgene
- Gilead
- Novartis
- Pfizer
- Jazz Pharmaceuticals
- Incyte

Research support
- Amgen
- Pfizer
- Novartis
- Shire/Servier
- Jazz Pharmaceuticals
- Incyte

Definitions: What Do We Speak About?

Primary refractory ALL

Early relapse

During intensive chemotherapy
Shortly after SCT

Refractory relapse (2nd relapse)

- Chemotherapy resistance
- Genetically unstable clones

Late relapse

After intensive chemotherapy
Late after SCT

Outgrowth of silent clones due to lack of immune surveillance and/or acquired additional mutations

Definitions: What Do We Speak About?

BM Relapse

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

Isolated extramedullary

Lymph nodes

CNS (CSF, brain)

Testis

Bone

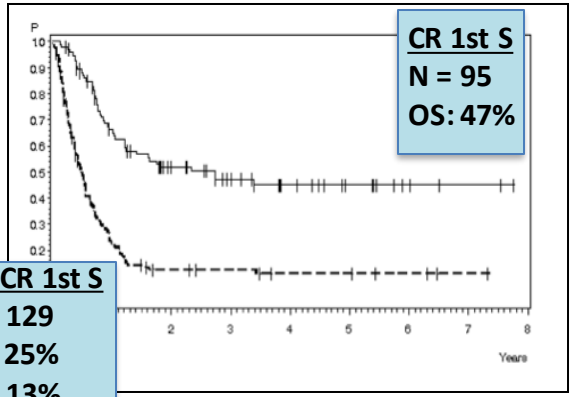
Other extranodal

Combinations

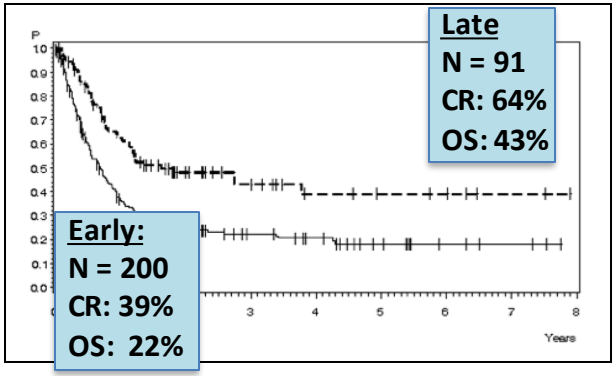
Definitions: What Do We Speak About?
Differences in Outcome of Relapsed/Refractory ALL

GMALL Studies 06/99 – 07/03

First vs Later Salvage

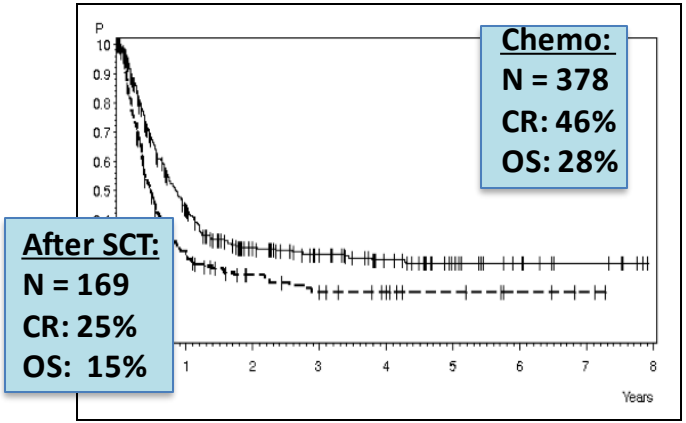


Early vs Late Relapse (18 mo)



Prognostically unfavorable
- Early relapse
- Refractory relapse
- Relapse after SCT

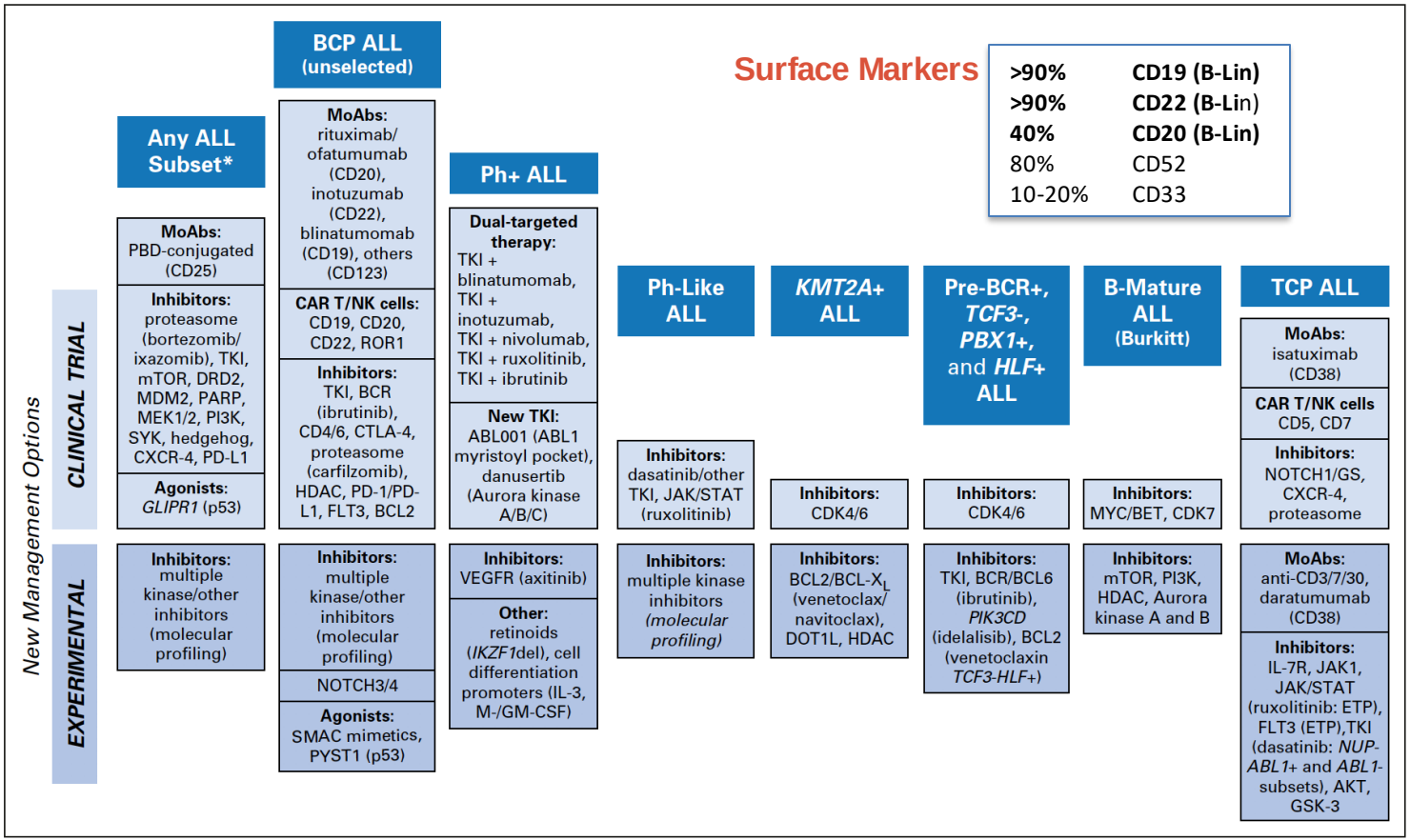
After Chemo vs After SCT



Gökbuget N, *Blood* 2012

Potential Targeted Therapies in ALL

Bassan et al, *JCO* 2018



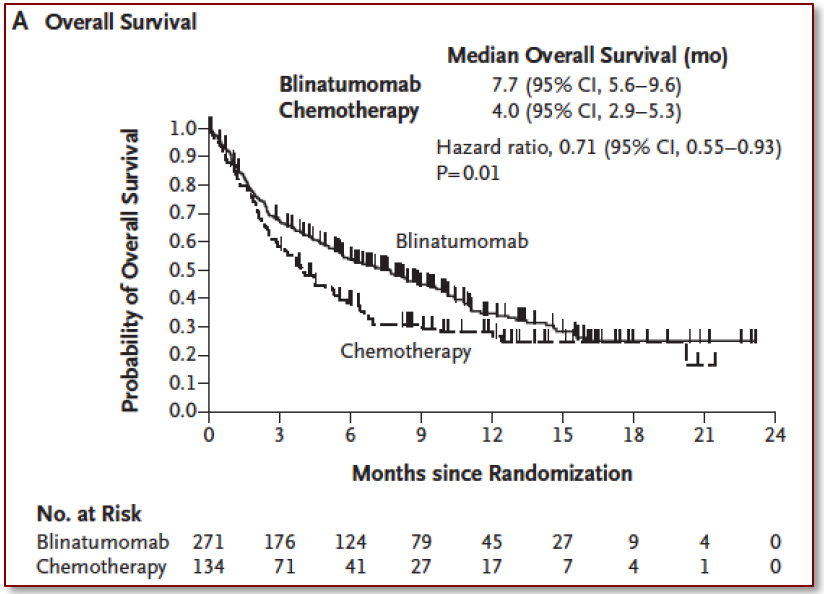
Blinatumomab in Relapsed/Refractory ALL

Kantarjian et al, *New Engl J Med* 2017

Response

	Blina	SOC
CR/CRh/CRp	**44%**	**25%**
CR	34%	16%
CRh	9%	4.5%
CRp	1%	4.5%
Mol CR	**76%**	**48%**
Later SCT	**24%**	**24%**
OS (mo)	**7.7**	**4.0**

Outcome



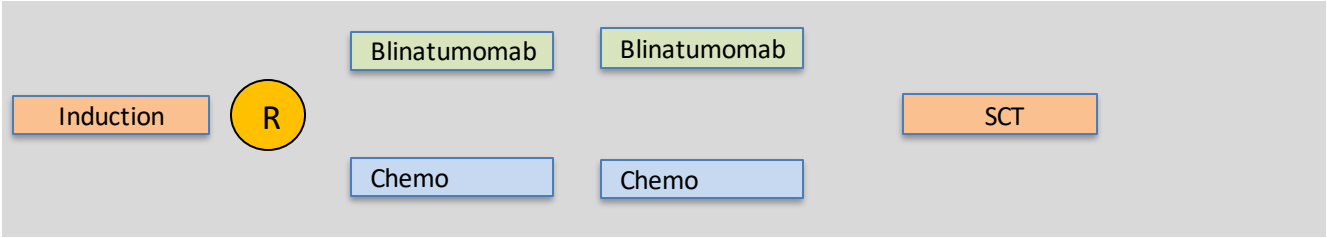
OPTIMISATION

- **Earlier Salvage**
- **Lower leukemia burden**

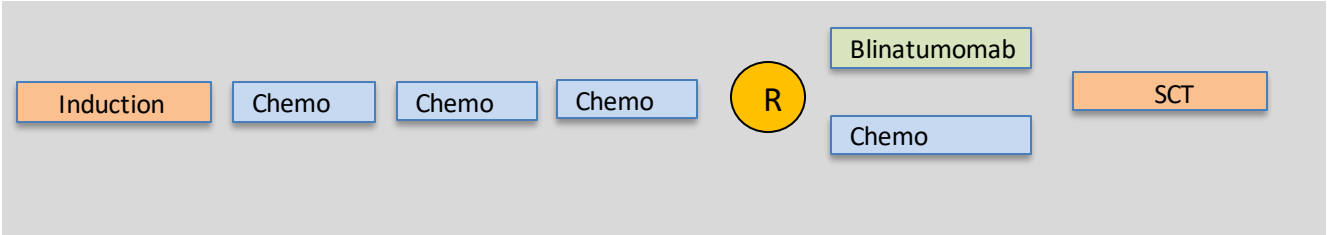
Can Blinatumomab Replace Intensive Chemotherapy Consolidation?

Pediatric Relapse

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



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

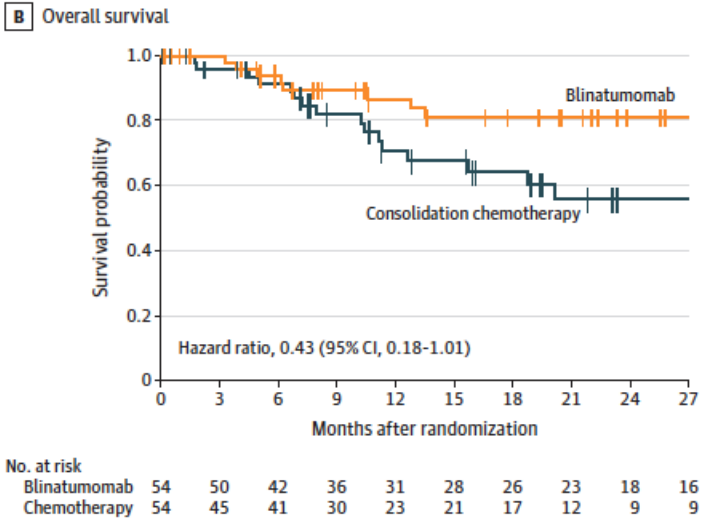


Blinatumomab vs Chemotherapy Consolidation: DFS/OS

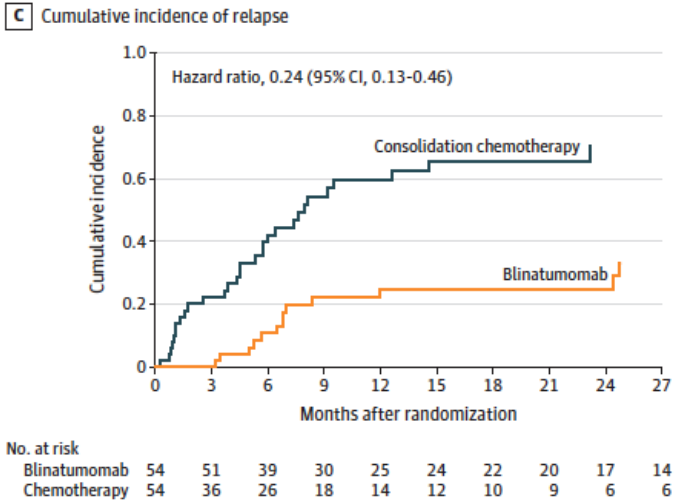
Locatelli et al, *JAMA* 2021

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

Overall Survival



Relapse Incidence



Blinatumomab in MRD-Positive ALL

Gökbuget et al, *Blood* 2018

Selected inclusion criteria

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

Treatment

15 µg/m² as 4-wk civ (= 1 cycle)

i.th. prophylaxis

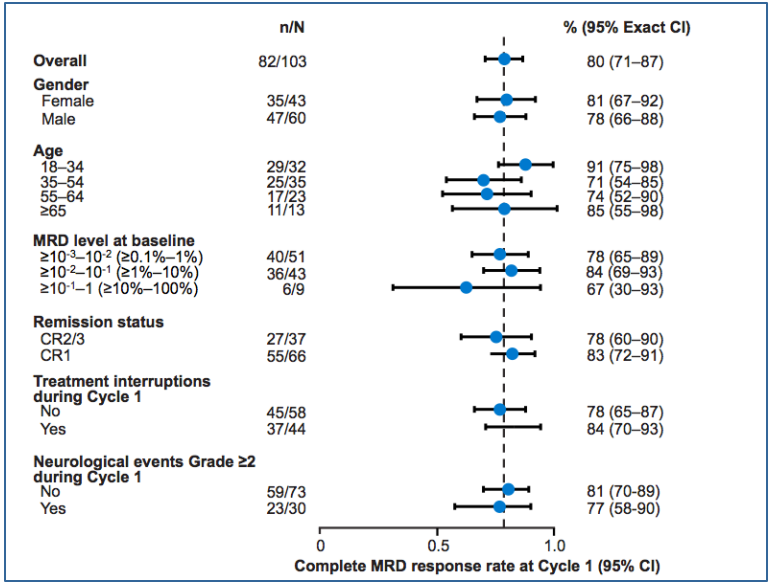
Primary endpoint

MolCR: Complete MRD response after 1 cycle

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

Results

Evaluable	110
Median age	45 (18-76) yr
In 2nd/later CR:	35%
MolCR:	**78%**
Median OS:	36 mo
- Mol CR y/n:	**40 vs 12 mo**
Median RFS:	19 mo
- Mol CR y/n:	35 vs 7 mo
- 1st/later CR:	**25 vs 11 mo**

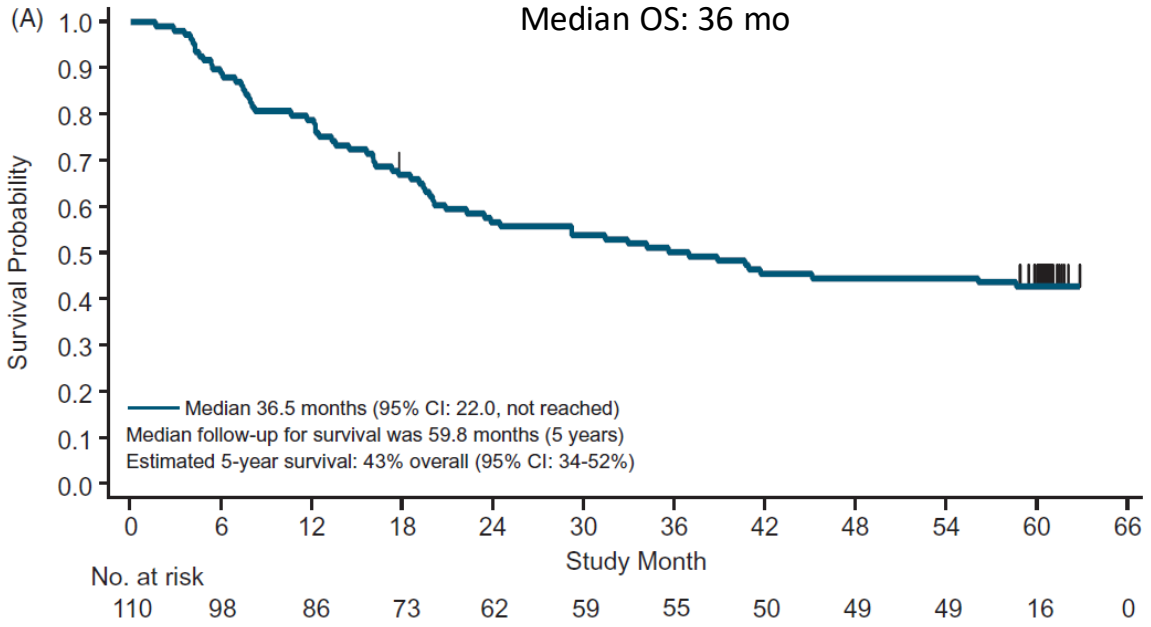


CR - complete remission, Komplettremission; MRD - minimal residual disease, minimale Resterkrankung; SCT - Stem cell transplantation, Stammzelltransplantation

Blinatumomab in MRD-Positive ALL

Gökbuget et al, *Leuk Lymphoma* 2020

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



Blinatumomab in MRD-Positive ALL

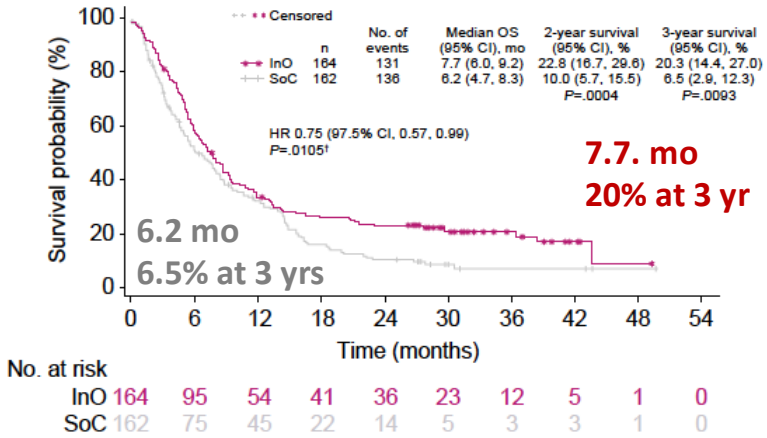
- High response rates in first and later lines
- No dose step
- Good tolerability
- Significant survival benefit for responders
- Overall results superior in MRD setting compared to cytologic relapse

INO-VATE: Inotuzumab in Relapsed/Refractory ALL

Kantarjian et al, *N Engl J Med* 2016

	Ino	Chemo
Evaluable	109	109
CR /CRi	**81%**	**29%**
CR	**36%**	**17%**
CRi	45%	12%
MRD neg (Flow)	**78%**	**28%**

Overall Survival – LTFU



Optimization

- **Up to 2 cycles**
- **Selection conditioning**
- **1st salvage**

CD19/CD22 Antibodies in Adult ALL

- Different patient population
- High MRD response rates, but also high relapse rates
- **Better outcomes if used in 1st salvage**
- **Best outcomes for Blina in MRD+ ALL (lower tumor load)**
- **Survival in SCT pts only; potentially high TRM!**
- **Activity in Ph+ ALL**
- **Toxicity profile favorable compared to SOC (eg, infections)**
  - **Blina: neurologic events**
  - **Ino: VOD (>65 yr, ↑Bili before SCT, 2 alkylators; prior SCT); 2 (max 3) cycles before subsequent SCT**
- **Negative prognostic impact:**
  Blin – blast in BM >50%; Ino – WBC >10.000/µL

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

CD19/CD22 Antibodies in Adult ALL: Overcome Resistance?

- Target loss
- Relapse from extramedullary compartment
- Upregulation of PD-1/PD-L1
- Upregulation of T-regs

CD19/CD22 Antibodies in Adult ALL: Overcome Resistance?

- **Target expression:**
  - **CD22 at different cutoffs (70%, 90%) ?**
  - **No standardized detection method**
- **Target loss**
- **Relapse from extramedullary compartment**
- **Upregulation of PD-1/PD-L1**
- **Upregulation of T-regs**

CD19/CD22 Antibodies in Adult ALL: Overcome Resistance?

- Target expression
- Target loss
- Relapse from extramedullary compartment
- Upregulation of PD-1/PD-L1
- Upregulation of T-regs

Relapse/Resistance to CD19-Targeted Immunotherapy in ALL

Role of CD19 antigen escape

Patients Evaluated for Immunophenotype	Patients, %
Treatment failure (N = 100)	
CD19 positive	85
CD19 negative	**15**
Relapse after CR with blinatumomab (n = 43)	
CD19 positive	77
CD19 negative	23
Refractory disease (n = 57)	
CD19 positive	91
CD19 negative	9

Aldoss I, et al. *Am J Hematol* 2017;92:858–65;
Jabbour E, et al. *Am J Hematol* 2018;93:371–4.

CD19/CD22 Antibodies in Adult ALL: Overcome Resistance?

- **Target expression**
- **Target loss**
- **Relapse from extramedullary compartment**
  - Avoid long-term single-drug treatment
  - Combine with alternative antibodies/chemotherapy
- **Upregulation of PD-1/PD-L1**
- **Upregulation of T-regs**

CD19/CD22 Antibodies in Adult ALL: Overcome Resistance?

- **Target expression**
- **Target loss**
- **Relapse from extramedullary compartment**
- **Upregulation of PD-1/PD-L1**

  Combination trials with PD-L1/PD-1 inhibitor ongoing

  NHL: NCT03340766

  Pediatric ALL: NCT02879695, NCT04546399

  Adult ALL: NCT04524455
- **Upregulation of T-regs**

CD19/CD22 Antibodies in Adult ALL: Overcome Resistance?

- **Target expression**
- **Target loss**
- **Relapse from extramedullary compartment**
- **Upregulation of PD-1/PD-L1**
- **Upregulation of T-regs**
  (Duell J, et al. *Leukemia* 2017;31:2181–90)
  - **Cyclophosphamide pre-phase?**

Duell J, et al. *Leukemia* 2017;31:2181–90.

CD19/CD22 Antibodies in Adult ALL: New Fields

- Efficacy in high-risk subgroups
- Extramedullary relapse
- Sequential treatment

Blinatumomab/Inotuzumab/CAR T in Ph-Like ALL

Aldoss et al, EHA 2021

	Blinatumomab (r/r)	Blinatumomab (MRD+)	Inotuzumab	CAR T-Zellen	Venetoclax/ Navitoclax
Patient Characteristics					
N	43	6	18	13	4
Median age	36 (18-71)	35 (23-49)	32 (22-71)	25 (19-52)	36 (24-48)
CRLF2r	67%	57%	78%	77%	100%
Prior SCT	21%	0%	28%	54%	50%
Prior therapy					
INO	2%		0%	38%	100%
BLINA	0%	-	72%	85%	100%
CAR	0%		6%	0%	25%
Venetoclax/Navitoclax	0%		0%	15%	0%

Results					
CR/CRi	28 (65%)	6 (100%)	16 (89%)	11 (85%)	3 (75%)
MRD- in CR	13 (93%)	6 (100%)	7 (70%)	9 (100%)	2 (67%)
SCT in CR	16 (57%)	5 (83%)	9 (56%)	6 (55%)	1 (33%)
1-year RFS	**67%**		**41%**	**75%**	

Genomic Determinants of Response to Blinatumomab in R/R ALL

Zhao et al, *Blood* 2021

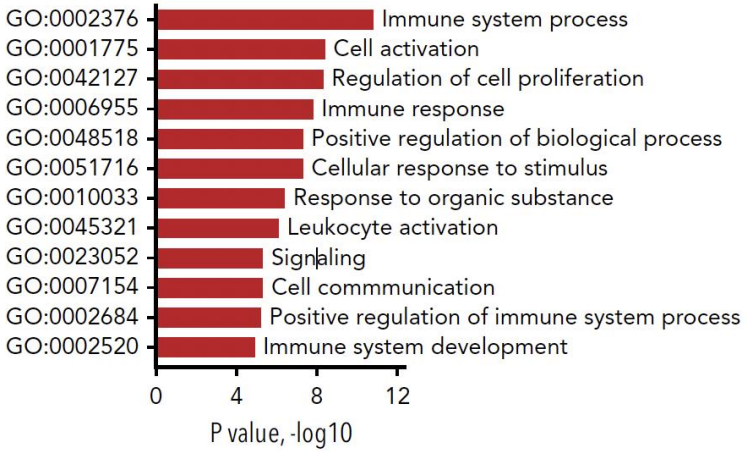
Patients: 44
Age: 34 (18–75)
R/R B-ALL
Up to 5 cycles of Blina
66% Hispanic
55% Ph-like (91% Hispanic)

CR (N = 42): 55%
23 responders
19 nonresponders

CR Rates by Biologic Subgroups

Subtype	Patients	Responders
Ph-like, *CRLF2* rearranged	16 (38.1)	12 (75)
Ph-like, non-CRLF2	7 (16.7)	4 (57.1)
Low hypodiploid	4 (9.5)	2 (50)
KMT2A-like*	3 (7.1)	3 (100)
B-ALL unclassified	3 (7.1)	1 (33.3)
Low hyperdiploid	2 (4.8)	1 (50)
PAX5alt	2 (4.8)	0 (0)
BCR-ABL1	2 (4.8)	0 (0)
DUX4	1 (2.4)	0 (0)
High hyperdiploid	1 (2.4)	0 (0)
TCF3-PBX1	1 (2.4)	0 (0)

Enrichment of Gene Ontology Pathways in Responders



Inotuzumab in Extramedullary Relapse

Kayser et al, EHA 2021

Patient Characteristics	
ECOG ≤2	17 (100 %)
Localization	
• Lymph nodes with other*	9
• Bone	4
• Kidney	1
• Peripheral nerves	1
• Pancreas and bones	1
• Ovary	1
Median follow-up	12.1 months
ASCT	7
a) ≤2 Zyklen InO	4
b) ≤2 Zyklen InO	3

*including gastric and skin; bone and skin; lung, bone and skin; hepatic and bone; hepatic, n=1 in each of these combinations)

Results	
After cycle 1	
CR	7 (41%)
PR	7 (41%)
SD	1 (6%)
Died	1 (6%)
After cycle 2	
CR	9 (56%)
PR	6 (38%)
SD	1 (6%)
Median OS	11.9 Monate
1-year OS	50%
2-year OS	23%
Relapse rate after 12 mo (N = 9)	38%
Subsequent SCT (3 CR)	7

Chemo-Immunotherapy in R/R B-Precursor ALL

Jabbour et al, *Cancer* 2021

Mini–hyper-CVD + Ino ± Blina

Original:
8 cycles Ino-chemo
POMP maintenance

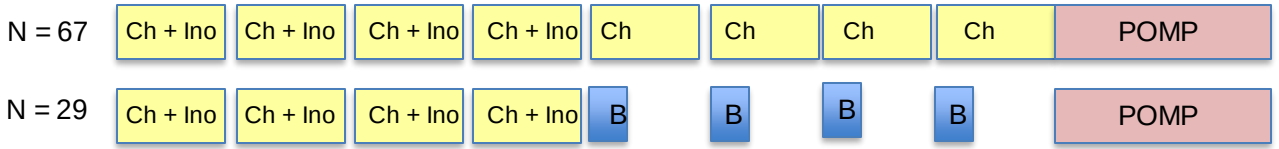
Amendment after 68 pts

Inotuzumab
Cycle 1: 0.6 mg/m^2 day 2 and 0.3 mg/m^2 day 8
Cycle 2-3: 0.3 mg/m^2 day 2 and 0.3 mg/m^2 day 8
4 instead of 8 cycles Ino-Chemo
4 cycles Blina added
Maintenance with POMP shortened

VOD 10% overall; 13% vs 3% with lower dose Ino + sequential Blina

Patient Characteristics

Total:	96
Age:	37 (17-96)
Prior SCT:	20%
Salvage 1	68%
<12 moRD	26%
>12 moRD	33%
-Prim. refr.	8%
Salvage 2:	18%
Salvage ≥3:	15%



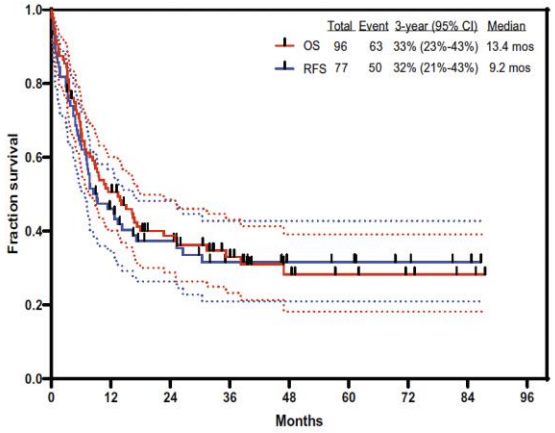
Chemo-Immunotherapy in R/R B-Precursor ALL

Jabbour et al, *Cancer* 2021

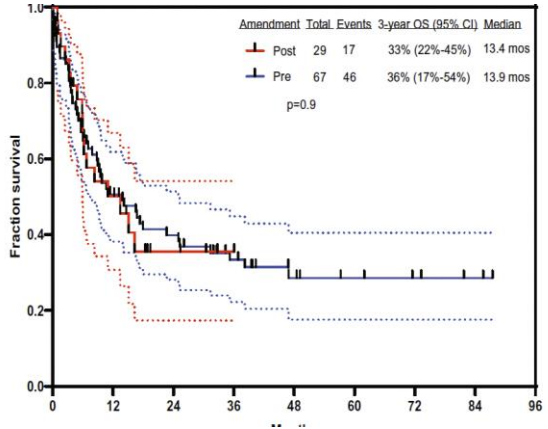
Best Overall Response (ORR)

ORR:	80%
CR	57%
CRp	20%
CRi	3%
ED	7%
Failure	13%
MRD neg:	57%
ORR	
Salvage 1	91%
Salvage 2	59%
Salvage ≥3	57%

Overall Outcome



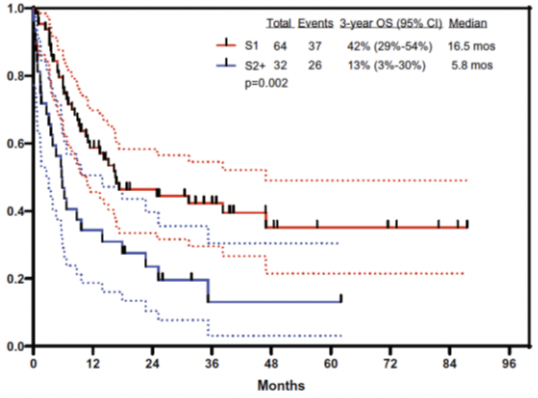
Effect of Amendment



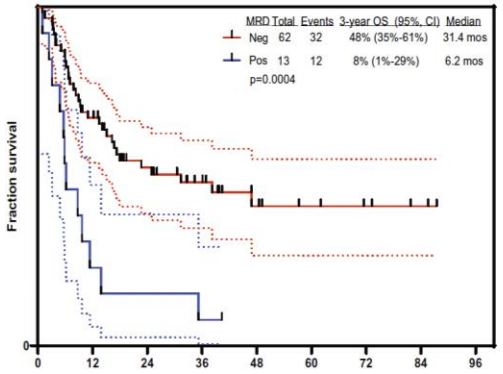
Chemo-Immunotherapy in R/R B-Precursor ALL

Jabbour et al, *Cancer* 2021

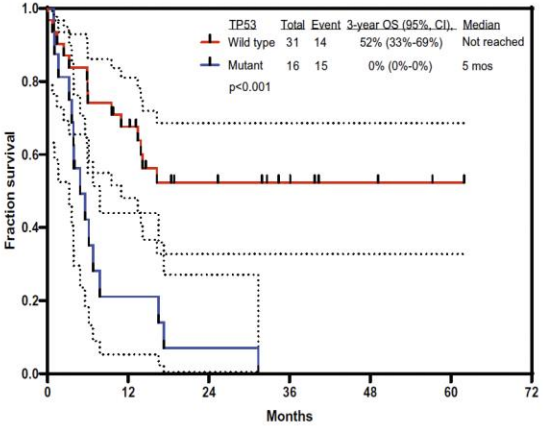
Survival by Salvage Line



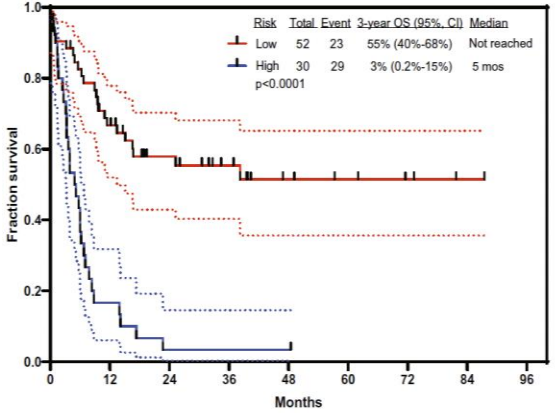
Survival by MRD Response



Survival by *TP53*



Survival by Risk Factors

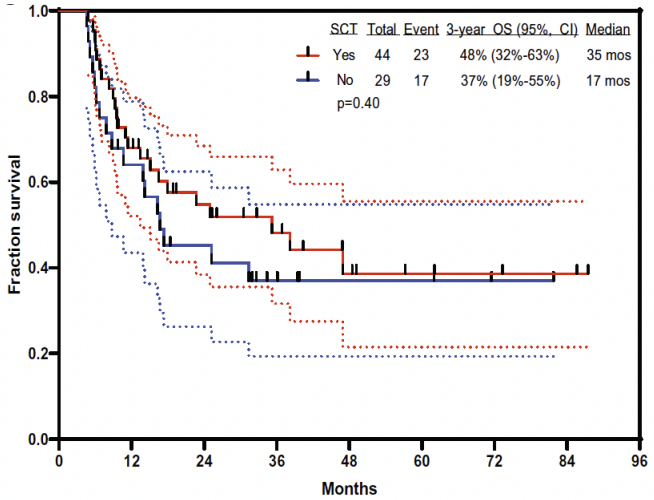


Adverse features:
CD22 expression <70%, or
KMT2A rearrangements, or
Low hypodiploidy/near triploidy

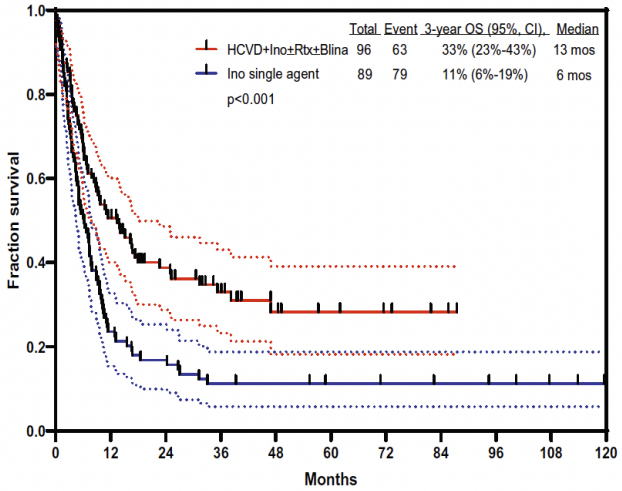
Chemo-Immunotherapy in R/R B-Precursor ALL

Jabbour et al, *Cancer* 2021

Survival by SCT

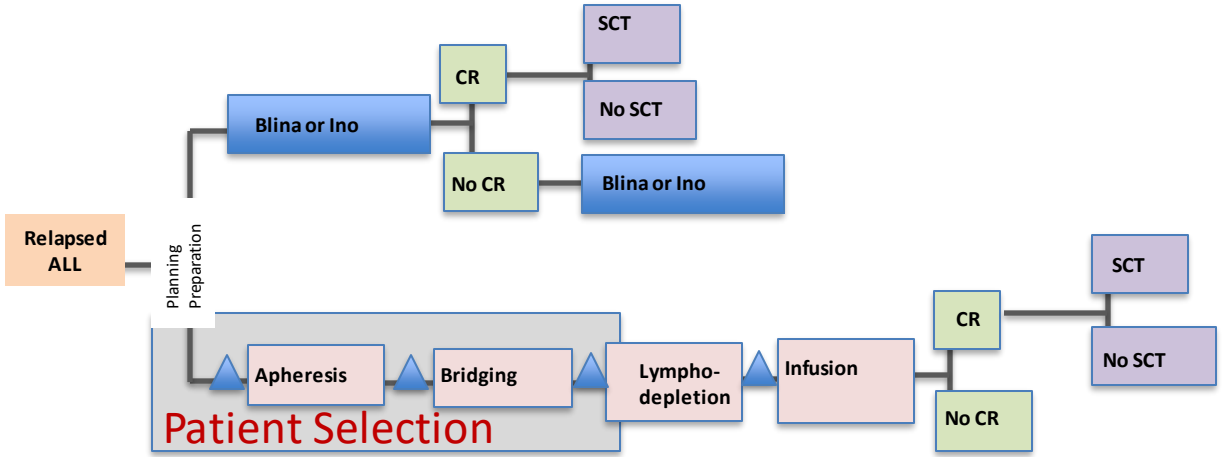


Survival by Combination



Combination/sequential therapy is the goal in R/R ALL

Comparison of Inotuzumab/Blinatumomab vs CAR T-Cell Strategies



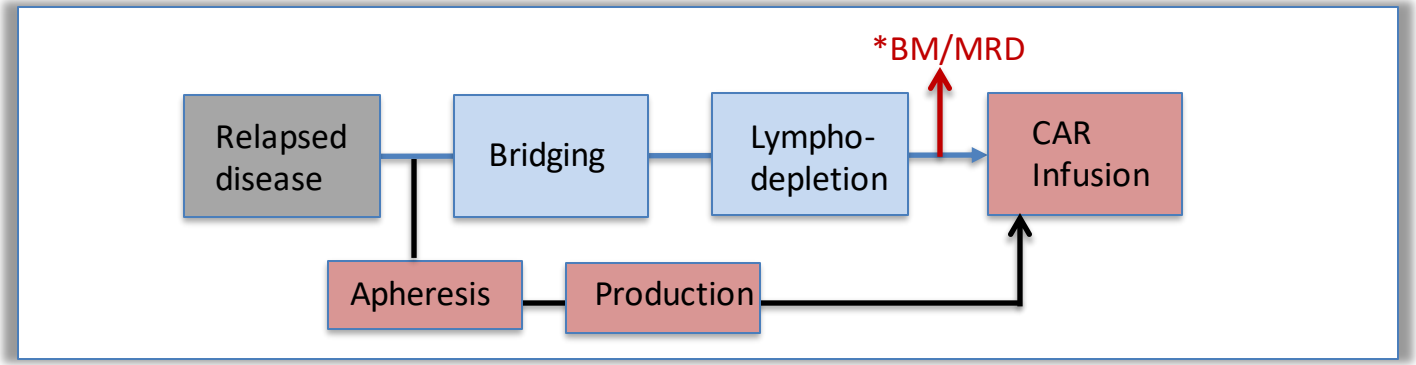
Heterogeneity of CAR T trials

- CAR structure
- Vector
- Autologous/allogeneic
- T-cell selection/subset
- Bridging (chemo, Blina, Ino)
- Lymphodepletion
- Infusion schedule

- Production time
- Selected sites
- Leukaemia burden at infusion

CD19 CAR T Cells in Relapsed/Refractory ALL

Park et al, *N Engl J Med* 2018



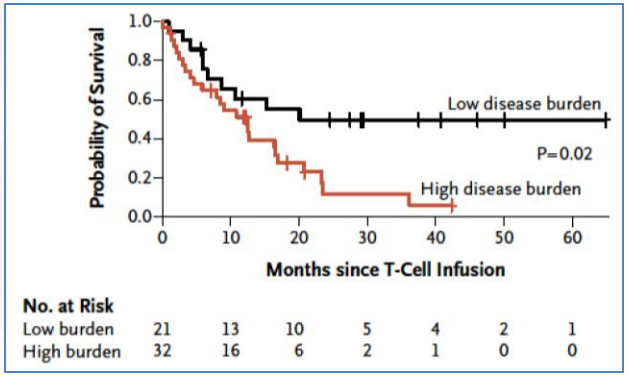
Inclusion Criteria

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

Patient Characteristics

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

Overall Survival According to Disease Burden



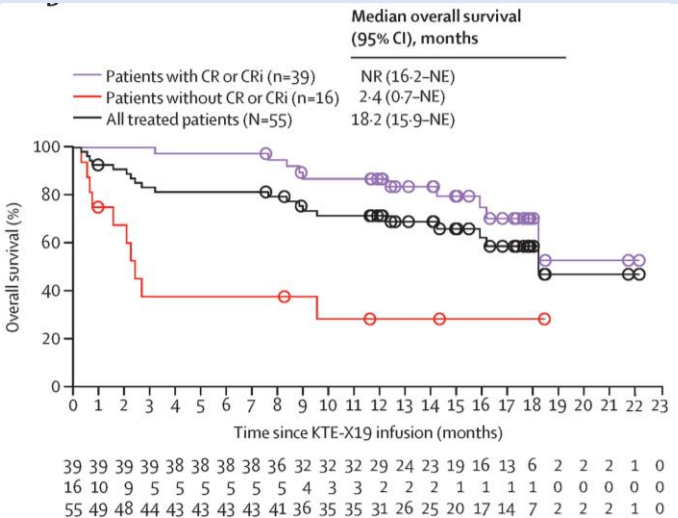
CAR T Cells in Relapsed/Refractory ADULT ALL

Shah et al, *Lancet* 2021; 398: 491–502

Patient Characteristics (Treated; N = 55)

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

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



Question

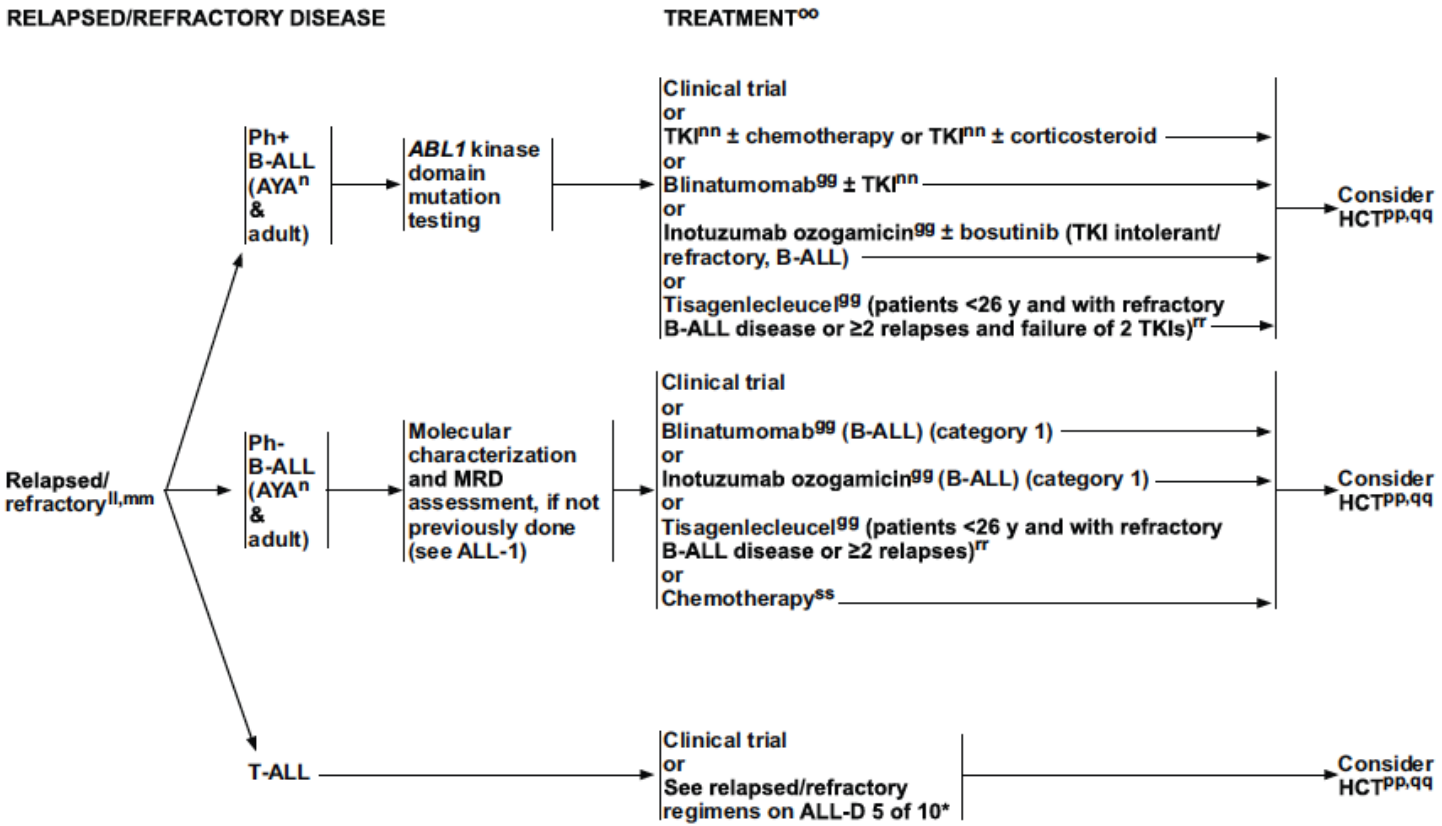
Which would you use for 1st salvage in early relapse of CD19/CD22-positive R/R B-precursor ALL?

a) Chemotherapy first
b) Inotuzumab first
c) Blinatumomab first
d) CAR T cells first
e) Inotuzumab in higher leukemia burden/blinatumomab in lower leukemia burden

Integrated Recommendation for Relapsed/Refractory ALL

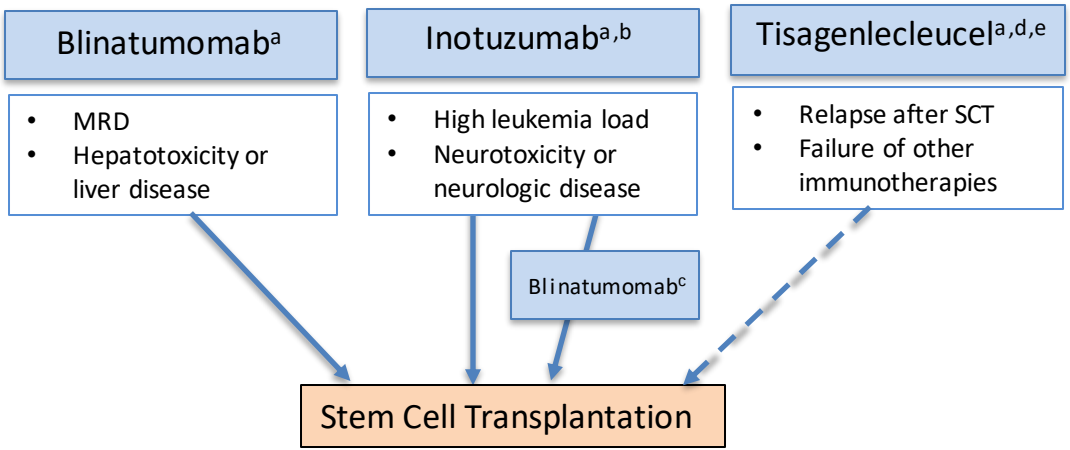
NCCN Guideline for R/R ALL

J Natl Compr Canc Netw 2021;19(9):1079-1109



Decision-Making Blinatumomab-Inotuzumab in 1st Salvage B-Prec

Dhakala et al, *Leuk Lymphoma* 2019



T-ALL: 1st Salvage Nelarabine + X (Cyclo)

R/R ALL: 2nd Line of Salvage

- CAR T trials
- CTL019
- Other clinical trials
- Augmented induction + bortezomib
- Clofarabine-based regimens
- FLAG-Ida
- Experimental “targeted therapy”

R/R ALL: 2nd Line of Salvage

Available options

- **CAR T trials**
- **CTL019**
- **Other clinical trials**
- **Augmented induction + bortezomib**
- **Clofarabine-based regimens**
- **FLAG-Ida**
- **Experimental “targeted therapy”**

Bortezomib Trials in R/R ALL

Rationale for Bortezomib:

Proteasome inhibitor → increased apoptosis
Synergistic with dexamethasone, additive with VCR, ASP, Doxo, AraC
Efficacy in in vitro trials

Authors	Year	n	Regimen	Age (median)	Subtype (n)	Overall Response (CR/CRi)	Early Death	Overall Survival
Messinger	2012	22	**Bortezomib + VXLD** (VCR, DEXA, PEG-ASP, DOXO)	1-22 (12)	**BCP (20)** **T-ALL (2)**	**73%** (64%/9%) **80%** (70%/10%) 0%	14%	**2y 41%**
Bertaina	2017	37	**Bortezomib + VXLD** (VCR, DEXA, PEG-ASP, DOXO)	2-21 (10,6)	**BCP (30)** **T-ALL (7)**	**73%** (62%/11%) **73%** **71%**	8%	**2y 31%** BCP 24% T-ALL 54%
Zhao	2015	9	Bortezomib + Hyper-CVAD oder Hyper-MA ± Imatinib	21-40	**BCP (6)** **T-ALL (3)** **Ph+ (2)**	89% 5/6 3/3 2/2	k.A.	2y 56%
Iguchi	2017	6 (3-A, 3-B)	Bortezomib + Standard Induction A) VCR, DOXO, DEXA, L-ASP B) VCR, Mitox, DEXA, L-ASP	10-16 (13,5)	**BCP**	**4/5**	17%	2y 17%
Yeo	2016	11	BDMV (Bortezomib + DEXA, Mitox, Vinorelbine)	0-23 (17,3)		64% (54,5%/9,1%)	9%	1y 41%

R/R ALL: 2nd Line of Salvage

- CAR T trials
- Other clinical trials
  - Blinatumomab + venetoclax
  - Blinatumomab + PD-L1
  - Notch inhibitor
- CTL019
- Augmented induction + bortezomib
- Clofarabine-based regimens
- FLAG-Ida
- Experimental "targeted therapy"
  - Venetoclax + X
  - CD38 antibodies + X
  - T-ALL: Dasatinib + X
  - T-ALL: HDAC inhibitors + X

Venetoclax and Navitoclax in R/R ALL and LBL

Jabbour et al, EHA 2020

Background and Design

- Ven addition to low-dose Nav may limit Nav DLT
- Phase I examining safety and efficacy of Ven+Nav in R/R ALL and LL
- N = 47
- 25 B-ALL, 18 T-ALL, 3 LL (med 29 yr)

Results

- DLIT in 7 pts – 1 fatal intestinal ischemia
- Nav RP2D 50 mg + 400 mg Ven (≥45 kg) 25 mg Nav <45 kg
- **CR/CRi/CRp in 25 (54%)**
- **MRD undetectable in 15 (33%)**
- OS 9.7 months B-ALL, **6.6 months T-ALL**
- HSCT in 11 (24%)

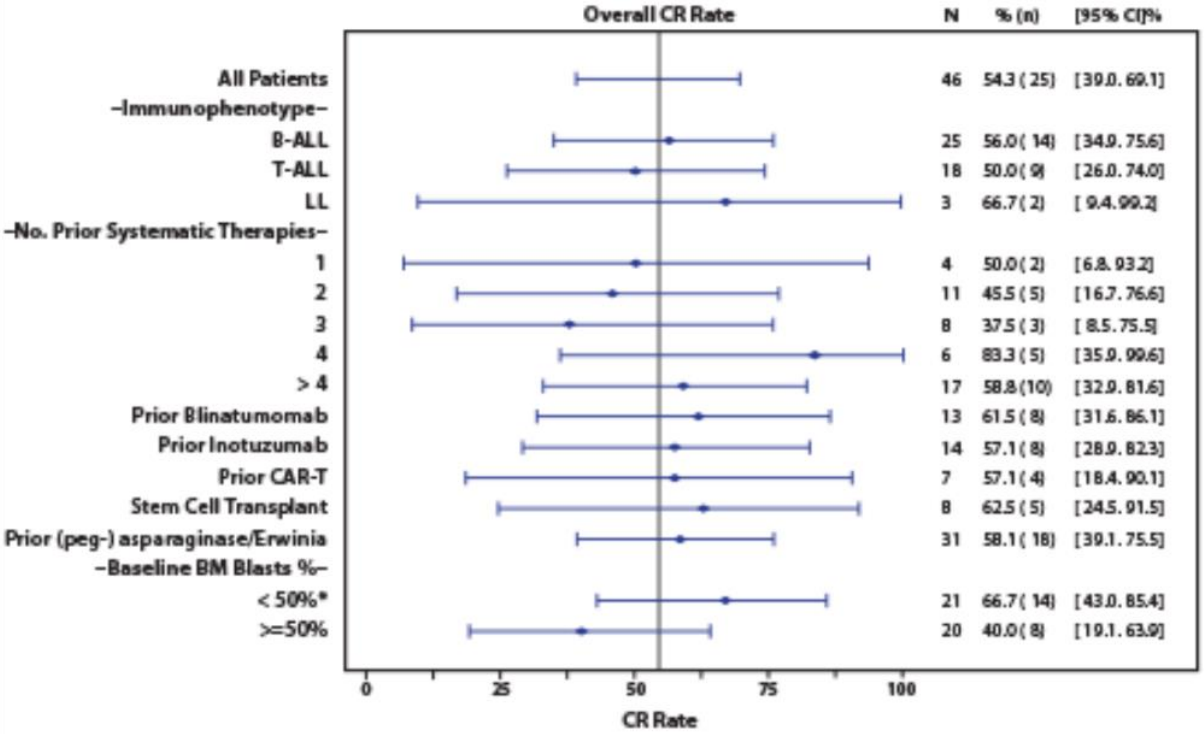
Adverse Events

Grade 3/4
Febrile neutropenia (39%)
Neutropenia (26%)
Hypokalemia (24%)
Vomiting (n = 3)
Increased ALT (n = 2)
Sepsis (n = 2)

Pts could receive chemotherapy (PEG-asparaginase, vincristine, and dexamethasone)

Venetoclax and Navitoclax in R/R ALL and LBL

Jabbour et al, EHA 2020



ALL = acute lymphoblastic leukemia; BM = bone marrow; CAR-T = chimeric antigen receptor T; CR = complete response; CR rate = CR + CRi + CRp; LL = lymphoblastic lymphoma
*5 ALL pts had BM blasts <5% at baseline and are included in the total study population. Of these 5 pts, 4 maintained CR after treatment and achieved sMRD.

Implications

- More developed data necessary
- Diversity of prior treatments (included Blina, Ino, and CAR T) confound interpretation
- Considerable cytopenias raise toxicity concerns

R/R ALL: 2nd Line of Salvage

- CAR T trials
- Other clinical trials
  - Blinatumomab + venetoclax
  - Blinatumomab + PD-L1
  - Notch inhibitor
- CTL019
- Augmented induction + bortezomib
- Clofarabine-based regimens
- FLAG-Ida
- Experimental "targeted therapy"
  - Venetoclax + X
  - CD38 antibodies + X
  - T-ALL: Dasatinib + X
  - T-ALL: HDAC inhibitors + X

General Treatment Issues in R/R ALL

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

Global Leukemia Academy

Q&A session

APTITUDE HEALTH®

Global Leukemia Academy

Case-based panel discussion – management of long- and short-term toxicities and treatment selection in adult and elderly patients

Presenters: Fabian Lang, Anna Torrent

Faculty panel: Elias Jabbour, Nicola Gökbuget, Josep-Maria Ribera, Philippe Rousselot

APTITUDE HEALTH

Global Leukemia Academy

Management of long- and short-term toxicities and treatment selection in adult and elderly patients – case 1

Fabian Lang

APTITUDE HEALTH

UNIVERSITÄTS KLINIKUM FRANKFURT
GOETHE-UNIVERSITÄT

Case report: Blinatumomab treatment in an elderly patient with Ph+ ALL

Fabian Lang, MD



Goethe University Hospital, Department of Haematology/Oncology, Frankfurt/M, Germany

MED2

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Primary diagnosis

Male, 78 years old

07/2020: Primary diagnosis acute lymphoblastic leukemia

Initial blood count:	leukocytes 34/nL, peripheral blasts 37%
Immunophenotype:	CD19 positive, CD20 negative, CD22 low positive
Cytogenetics:	46 XY
Molecular genetics:	*BCR-ABL1* positive

Comorbidities:	COPD
	arterial hypertension
	A. carotis internal stent insertion
	chronic kidney failure

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Further therapy

07/2020	Induction according to GMALL elderly protocol
09/2020	Worsening of kidney dysfunction, no further intense therapy possible → GMALL frail protocol
12/2020	Switch to dasatinib due to *Bcr-Abl* mutation: Y253H
12/2020	Stop dasatinib due to dyspnea and pleural effusion
01/2021	Restart imatinib

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Bcr-Abl MRD

Date	Material	Target	Target copy number	ABL1 copy number	Ratio	Log change
09.07.2020	KM	m-BCR-ABL1	63932.91	251324.72	2.54E-1	
26.08.2020	KM	m-BCR-ABL1	2114.08	54063.21	3.91E-2	-0.81
15.12.2020	KM	m-BCR-ABL1	38.00	125153.77	3.04E-4	-2.11
26.02.2021	**KM**	**m-BCR-ABL1**	**16458.47**	**92236.16**	**1.78E-1**	**2.77**

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Further therapy

07/2020	Induction therapy according to GMALL elderly protocol
09/2020	Worsening of kidney dysfunction, no further intense therapy possible → GMALL frail protocol
12/2020	Switch to dasatinib due to *Bcr-Abl* mutation: Y253H
12/2020	Stop dasatinib due to dyspnea and pleural effusion
01/2021	Restart imatinib
03/2021	Rising *Bcr-Abl1* ratio: switch to ponatinib
03/2021	Acute cardiac failure (NT-proBNP >70.000 pg/mL) and acute chronic kidney failure due to ponatinib

78-year-old male, acute cardiac failure after ponatinib, rising *Bcr-Abl1* ratio with Y253H mutation

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Which therapeutic option would you choose?

- Restart imatinib 600 mg QD
- Switch to nilotinib 300 mg BID
- Restart ponatinib at lowest dose 15 mg QD
- Start blinatumomab

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Further therapy

04/2021	Start blinatumomab
07/2021	Stop blinatumomab in cycle 3 due to port catheter infection
08/2021	Explantation of port catheter and restart blinatumomab via PICC line catheter
09/2021	After 4 cycles of blinatumomab: hematologic and immunologic CR MRD low positive: *Bcr-Abl1* ratio 3,97E-5

?

78-year-old male, acute cardiac failure after ponatinib, MRD-low positive after 4 cycles of blinatumomab

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Which therapeutic option would you choose for consolidation?

- Imatinib 600 mg QD
- MTX/6MPU
- Ponatinib at lowest dose 15 mg QD
- Evaluation of allogeneic SCT

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Summary

- TKIs show a complex profile of side effects, especially in older patients
- Blinatumomab shows efficacy in elderly Ph+ ALL patients and those with progressive disease under TKI treatment or in case of contraindications for certain TKIs
- The further concept of consolidation in this patient remains unclear, as allogeneic SCT is not an option

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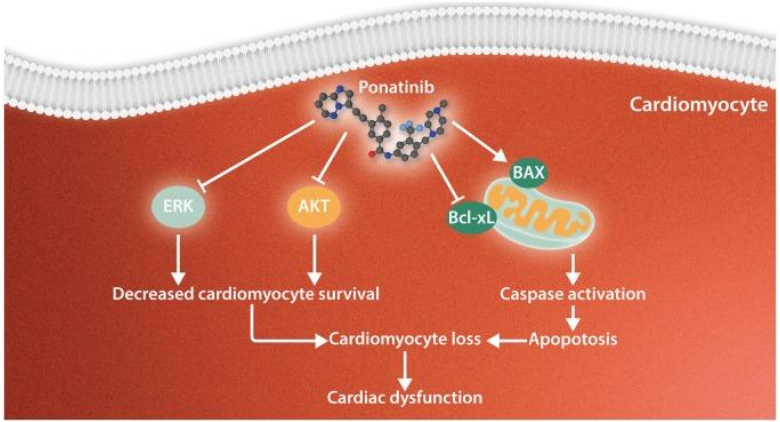
Backup

Cardiotoxicity of ponatinib

CRP i.S. (Part. verst. immun. Trüb ...	6.33	+	M.Val
Natrium i.S. (ISE)	145		M.Val
Kalium i.S. (ISE)	4.81	+	M.Val
Kalium i.S.	*H		
Calcium i.S. (enzymatisch)	2.23		M.Val
Kreatinin i.S. (Jaffe o. Enteiweißung)	3.58	++	M.Val
Krea eGFR nach MDRD (berechnet ...	16.6	--	M.Val
Krea eGFR nach CKD-Epi (berechn ...	15.4	--	M.Val
Harnstoff i.S. (Urease/GLDH Meth)	148	++	M.Val
Harnstoff i.S.	elektronisch nachgefordert		
Harnsäure i.S. (enz. Farbtest)	7.2	+	M.Val
Bilirubin ges. i.S. (enz. Farbtest)	2.5	+	M.Val
Bilirubin dir. i.S. (DPD-Methode)	1.3	++	M.Val
Bilirubin dir. i.S.	*H		
	elektronisch nachgefordert		
GPT i.S. (IFCC)	1844	++	M.Val
GPT i.S.	Ergebnis bestätigt durch Wiederholu		
GGT i.S. (IFCC)	220	++	M.Val
GGT i.S.	elektronisch nachgefordert		
Alk. Phosphatase i.S. (IFCC)	447	++	M.Val
LDH i.S. (IFCC)	3620	++	M.Val
LDH i.S.	*H		
	Ergebnis bestätigt durch Wiederholu		
CK i.S. (IFCC)	851	++	M.Val
CK i.S.	elektronisch nachgefordert		
Troponin T (high sensitiv/STAT) i.S...	256	++	M.Val
Troponin T (high sensitiv/STAT) i.S.	Graubereich = 14-50pg/ml		
	elektronisch nachgefordert		
NT-proBNP (ECLIA)	>70000	++	M.Val
NT-proBNP	elektronisch nachgefordert		
	siehe Bemerkung Biotin		



García-Gutiérrez V, Hernández-Boluda JC. *Front Oncol*. 2019;9:603.

Global Leukemia Academy

Discussion – case 1

Fabian Lang, Anna Torrent

Faculty panel: Elias Jabbour, Nicola Gökbuget, Josep-Maria Ribera, Philippe Rousselot

APTITUDE HEALTH

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Management of long- and short-term toxicities and treatment selection in adult and elderly patients – case 2

Anna Torrent

APTITUDE HEALTH®

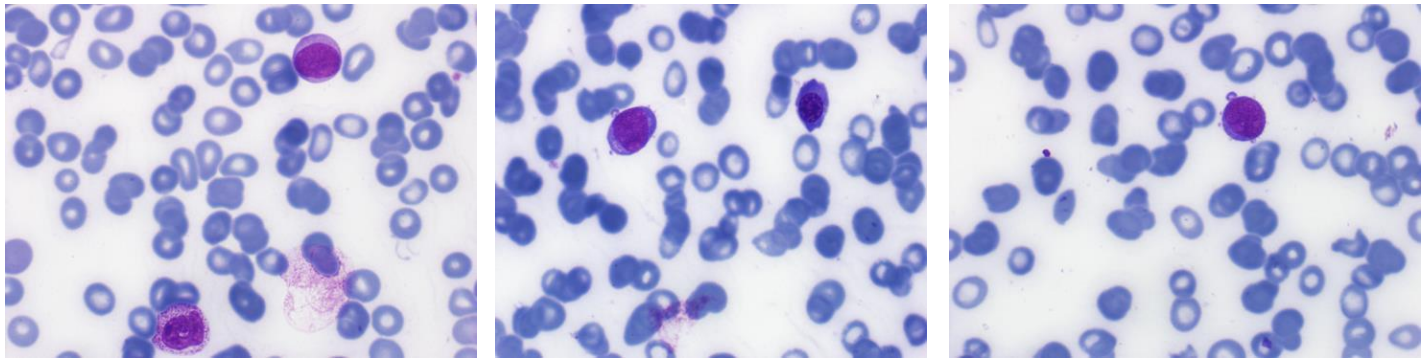
Global Leukemia Academy EU Meeting
October 27–28, 2021

Toxicity in ALL: Clinical case

Anna Torrent, MD
Clinical Hematology Department
ICO-Hospital Germans Trias i Pujol
Institut de Recerca contra la Leucemia Josep Carreras
Badalona

Case presentation

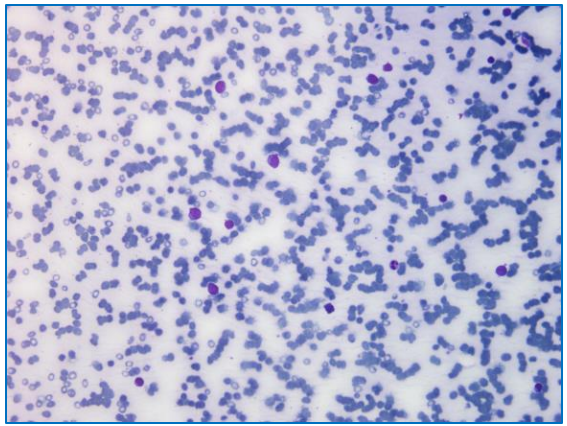
- 40-year-old Black male (Gambia)
- Arterial hypertension (enalapril)
- Fever, malaise, pancytopenia

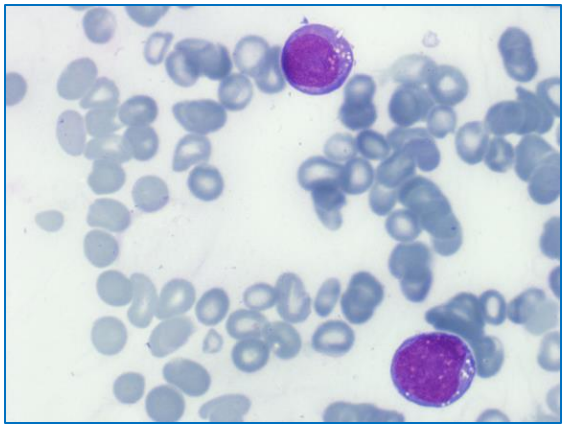


Acute lymphoblastic leukemia

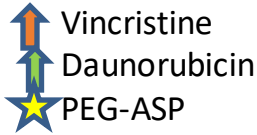
Case presentation

- WBC 5.1 × 10^9/L (19% blast cells), Hb 62 g/L, platelets 31 × 10^9/L
- **Bone marrow**
  - 22% B lymphoblasts (CD19low, CD22low, CD38, CD58, CD81)
  - Low hypodiploid: 36, XY, -2, -3, -4, -6, -7, -10, -12, -13, -14, -15, -16, -17, +21, i(21)(q10), +mar[cp22]/46, XY[20]
  - Mutation/deletion in *IKZF1* and *TP53*

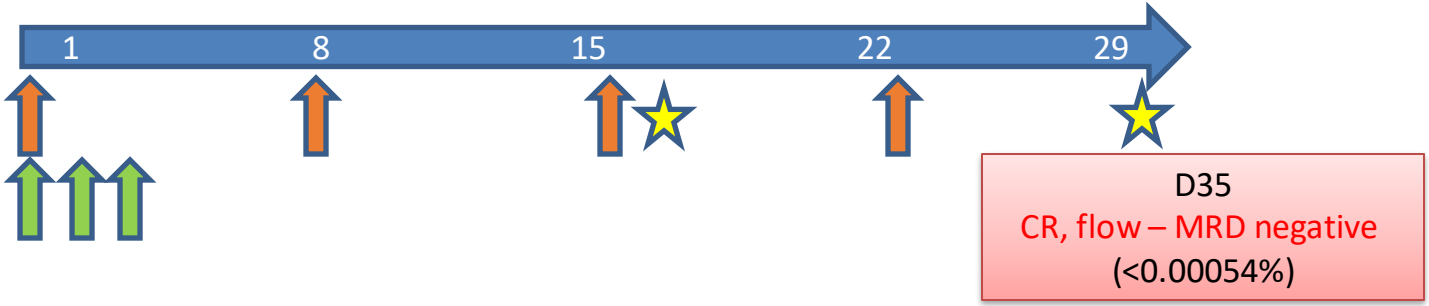




Treatment



PETHEMA ALL19: VCR + DNR + PDN + PEG-ASP + TIT



Hospitalization (D36): Fatigue, abdominal pain, jaundice

Bilirubin 4.48 mg/dL (direct, 2.62 mg/dL), ALP 1130 U/L, GGT 1015 U/L, ALT 217 U/L, AST 172 U/L

Prothrombin activity 65%, platelets 87 × 10^9/L

Albumin 21 g/L

Question 1

Which is the most probable diagnosis?

A. Viral hepatitis reactivation

B. Drug toxicity (PEG-ASP)

C. Opportunistic infection

D. Autoimmune hepatitis

E. Hepatic failure due to septic shock

Asparaginase

- ASP: *Escherichia coli* or *Erwinia chrysanthemi*
- Antineoplastic agent
- Essential drug in ALL
- Depletion of asparagine in serum
- PEG-ASP: *Escherichia coli* + polyethylene glycol

Toxicities

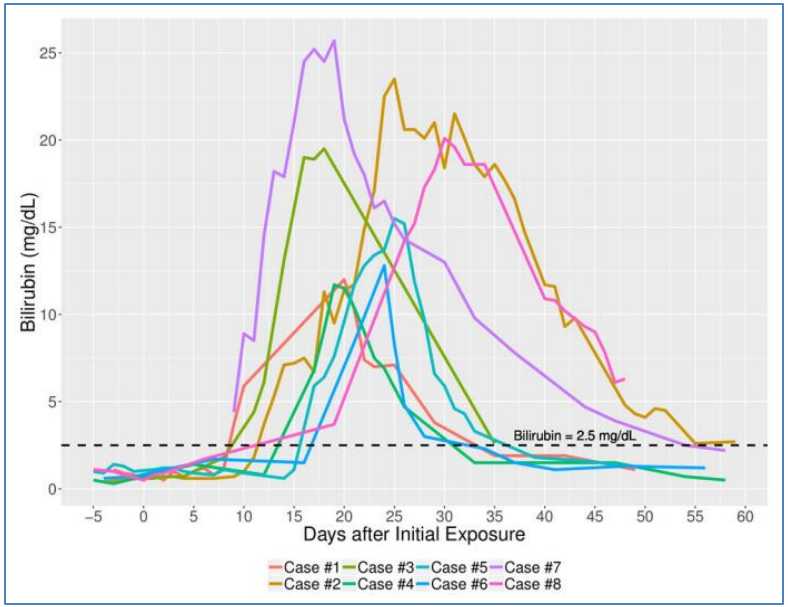
- Hypersensitivity
- Pancreatitis
- Thrombosis
- Hyperglycemia
- Neurologic dysfunction
- Nephropathy
- Hepatotoxicity

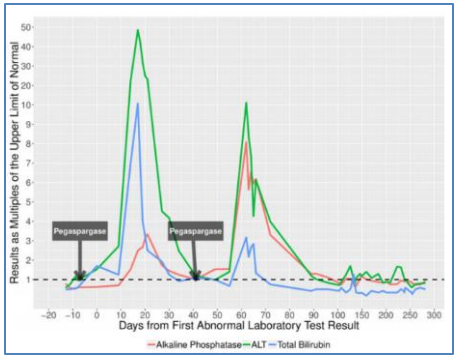
Silva WFD, et al. *Clin Lymphoma Myeloma Leuk.* 2020;20(8):e523-e528; Derman BA, et al. *Leuk Lymphoma*. 2020;61(3):614-622; Ribera JM, et al. *Leuk Lymphoma*. 2018;59(7):1634-1643.

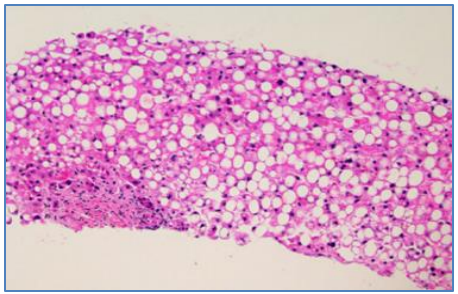
Hepatic toxicity by PEG-asparaginase

DILIN prospective study (NCT00345930)

- Cholestatic liver injury (bilirubin, ALP, GGT)
- Latency of onset: 9 to 21 days after initial dose and 1 to 19 days after second

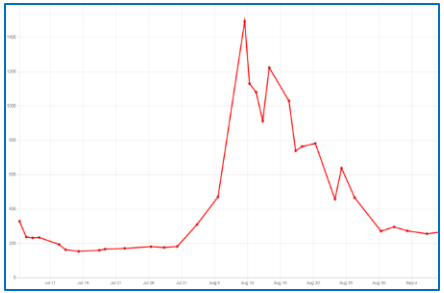




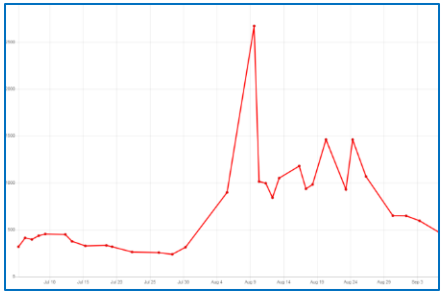


Kamal N, et al. *Hepatol Int.* 2019;13(5):641-648.

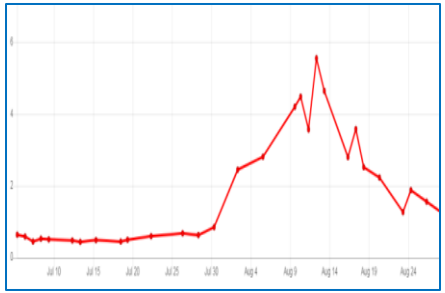
Case continuation



Alkaline phosphatase (ALP)



Gamma glutamyl transpeptidase (GGT)



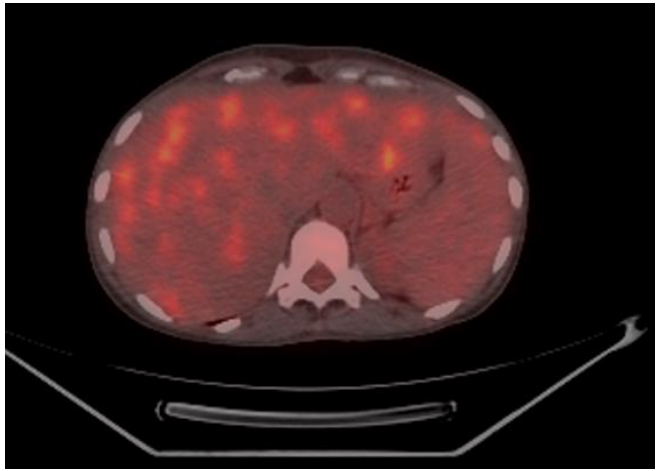
Bilirubin (Bi)

Fever, abdominal pain

- Viral serology: negative (HBV, HCV, CMV, EBV)
- Autoimmunity study: negative
- Cultures (blood, urine): negative

CT scan: multiple liver nodular lesions

PET-CT SCAN: hypermetabolic liver nodules



Question 2

Which is the most probable diagnosis now?

A. Liver metastases of occult cancer

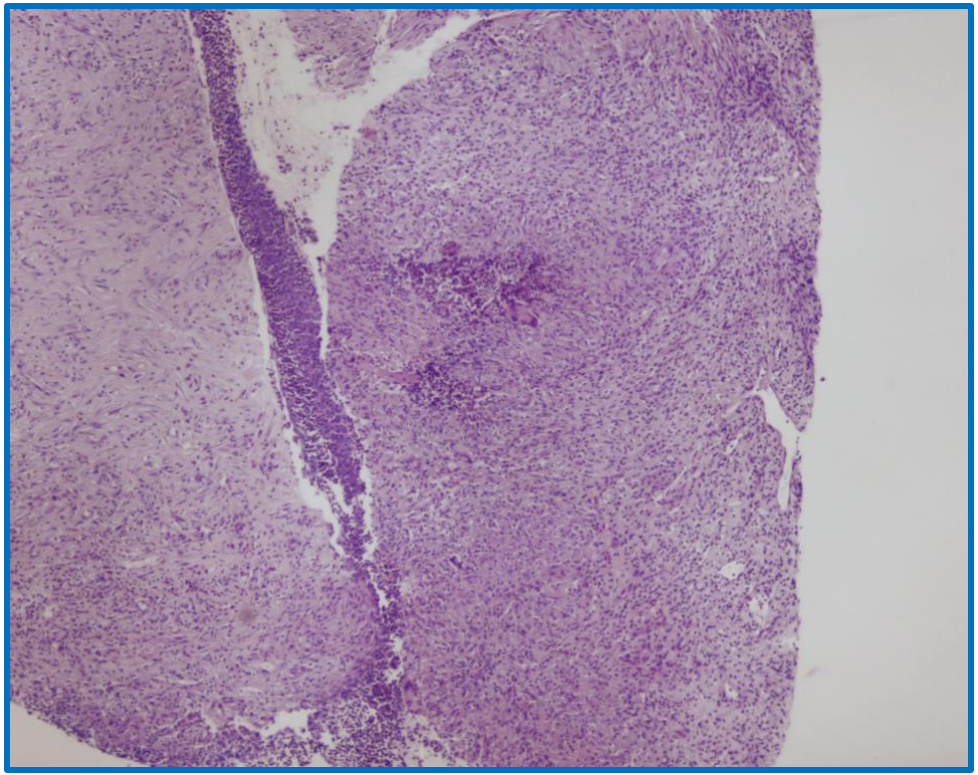
B. Drug toxicity (PEG-ASP)

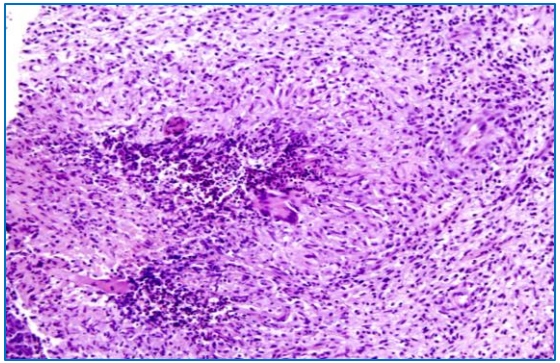
C. Opportunistic infection

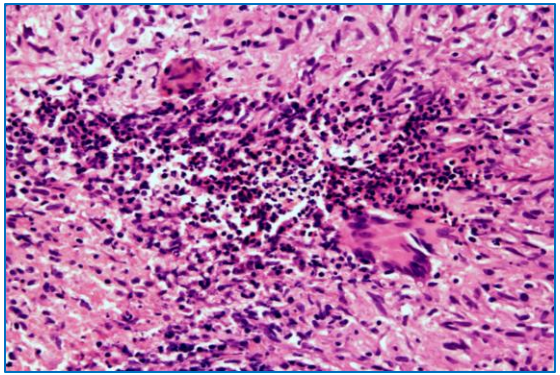
D. Autoimmune hepatitis

E. Extramedullary leukemic metastases

Liver biopsy







Culture: *Mycobacterium tuberculosis*

What is next?

Tuberculosis treatment

Rimstar: 150 mg rifampicin + 75 mg isoniazid + 400 mg pyrazinamide + 275 mg ethambutol

ALL treatment

Relapse: 6% lymphoblasts

FLAG-IDA: fludarabine, idarubicin, cytarabine

What should we do now?

High-risk ALL (hypodiploid, *IKZF1*, *TP53*, poor response).
Need for HSCT (no URD available, no family in Spain, cord blood unit).
Just 2 months of anti-TBC treatment
Rifampicin drug interactions . . .

Conclusions

- Not all suspected drug toxicities are just toxicities
- Infection should always be suspected in ALL patients under myeloablative/immunosuppressive chemotherapy

Thank you so much!

Global Leukemia Academy

Discussion – case 2

Presenters: Fabian Lang, Anna Torrent

Faculty panel: Elias Jabbour, Nicola Gökbuget, Josep-Maria Ribera, Philippe Rousselot

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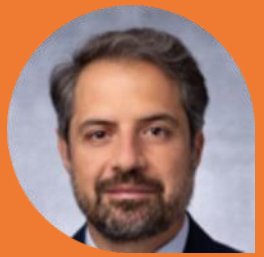
Educational ARS questions

Elias Jabbour



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Repeated Question 1

What age group is considered elderly ALL patients?

a) ≥50 years
b) ≥55 years
c) ≥60 years
d) ≥65 years
e) ≥70 years

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Repeated Question 2

Which of the following is NOT true for treating ALL?

a) Inotuzumab and blinatumomab plus chemotherapy has produced 90% CR rates in salvage therapy and in first line in older patients

b) Blinatumomab and ponatinib can be used as a chemotherapy-free regimen in Ph+ ALL

c) MRD– CR does not correlate strongly with outcome

d) Since 1999, median survival for ALL patients older than 60 has been increasing with each successive decade

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Break

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AML session open

Naval Daver

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AML

CHAIR

Naval Daver, MD
Assistant Professor of Medicine
UT MD Anderson Cancer Center, USA

FACULTY

Prof Charles Craddock, CBE, FRCP (UK), FRCPath, DPhil
Centre for Clinical Haematology at the Queen Elizabeth Hospital, United Kingdom

Richard Schlenk, MD
University Hospital Heidelberg, Germany

Global Leukemia Academy

Virtual Breakout – Adult Leukemia Patients (Day 2) 17.00 – 20.00

Chairs – Elias Jabbour, Naval Daver

Time CET	Title	Speaker/Moderator
17.00 – 17.10	**ALL session open**	Elias Jabbour
17.10 – 17.30	**Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens**	Elias Jabbour
17.30 – 17.50	**Current treatment options for relapsed ALL in adult and elderly patients**	Nicola Gökbuget
17.50 – 18.20	**Case-based panel discussion on toxicity management for adult and elderly ALL patients** • Case presentation 1: Fabian Lang • Case presentation 2: Anna Torrent	Moderator: Elias Jabbour *Faculty panel*: E. Jabbour, N. Gökbuget, J.M. Ribera, P. Rousselot
18.20 – 18.30	**Break**	
18.30 – 18.35	**AML session open**	Naval Daver
18.35 – 18.55	**Personalized induction and maintenance approaches for AML**	Richard Schlenk
18.55 – 19.15	**Optimizing management of relapsed/refractory AML**	Charles Craddock
19.15 – 19.45	**Case-based panel discussion or questions to the panel on regional challenges in AML care** • Case presentation 1: Justin Loke • Case presentation 2: Sonia Jaramillo Segura	Moderator: Naval Daver *Faculty panel*: N. Daver, C. Craddock, R. Schlenk
19.45 – 20.00	**Session close**	Elias Jabbour

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Educational ARS questions

Naval Daver

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Question 1

Which of the following factors are important in assessing AML patients at diagnosis? Select all that apply.

a) Adverse genetic alterations
b) Age
c) Comorbidities
d) Performance status
e) Prior cytotoxic therapy
f) Prior myelodysplasia

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Question 2

Which patients were not included in the VIALE-A study?

a) Patients >75 years of age
b) Patients <75 years of age with ECOG PS 3
c) Patients <75 years of age with significant cardiac co-morbidity
d) Patients <75 years of age with significant pulmonary comorbidities
e) Patients <75 years of age with adverse cytogenetics

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Question 3

Which of the following is not true regarding HMA + venetoclax in AML?

a) The CR/CRi with HMA+VEN in the VIALE-A was >65%

b) HMA+VEN improved median OS compared with HMA alone

c) Lab or clinical TLS is not seen with HMA+VEN in AML

d) The recommended daily dose of venetoclax (without azoles) was 400mg PO Qday in VIALE-A study

e) Neutropenia is commonly seen with HMA+VEN regimen

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Personalized induction and maintenance approaches for AML

Richard Schlenk

APTITUDE HEALTH

Acute Myeloid Leukemia

Personalized Induction and Maintenance Approaches

Richard F. Schlenk, MD

Heidelberg University Hospital
National Center of Tumor Diseases (NCT)
German Cancer Research Center Heidelberg

Webinar 28-10-2021

HEIDELBERG UNIVERSITY HOSPITAL

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION
Research for a Life without Cancer

NCT NATIONAL CENTER FOR TUMOR DISEASES HEIDELBERG

Disclosures of Commercial Support

Richard F. Schlenk

Name of company	Research support	Employee	Consultant	Stockholder	Speaker's bureau	Advisory board	Other
Pfizer	Yes		Yes		Yes	Yes	
Novartis					Yes		DMC
AstraZeneca	Yes						
Roche	Yes						
BerGenBio							DMC
Boehringer Ingelheim	Yes						
PharmaMar	Yes						
Daiichi Sankyo	Yes				Yes	Yes	

Question

In your practice, what are the main parameters you use to assign personalized treatment to newly diagnosed AML patients? Select all that apply.

a) Chronological and biological age

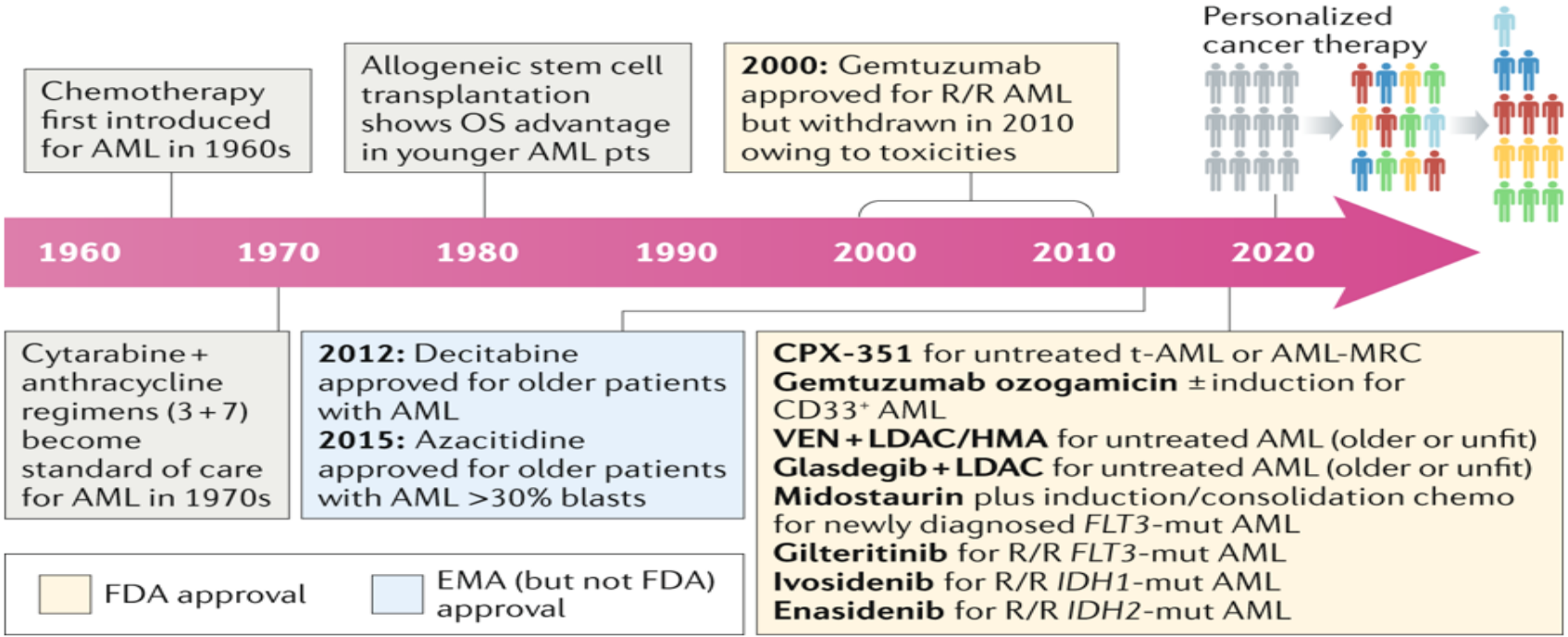
b) Genotype

c) Type of AML (de novo, sAML, tAML)

d) ECOG performance status

e) LDH value, WBC count

AML: Recent Drug Approvals by FDA



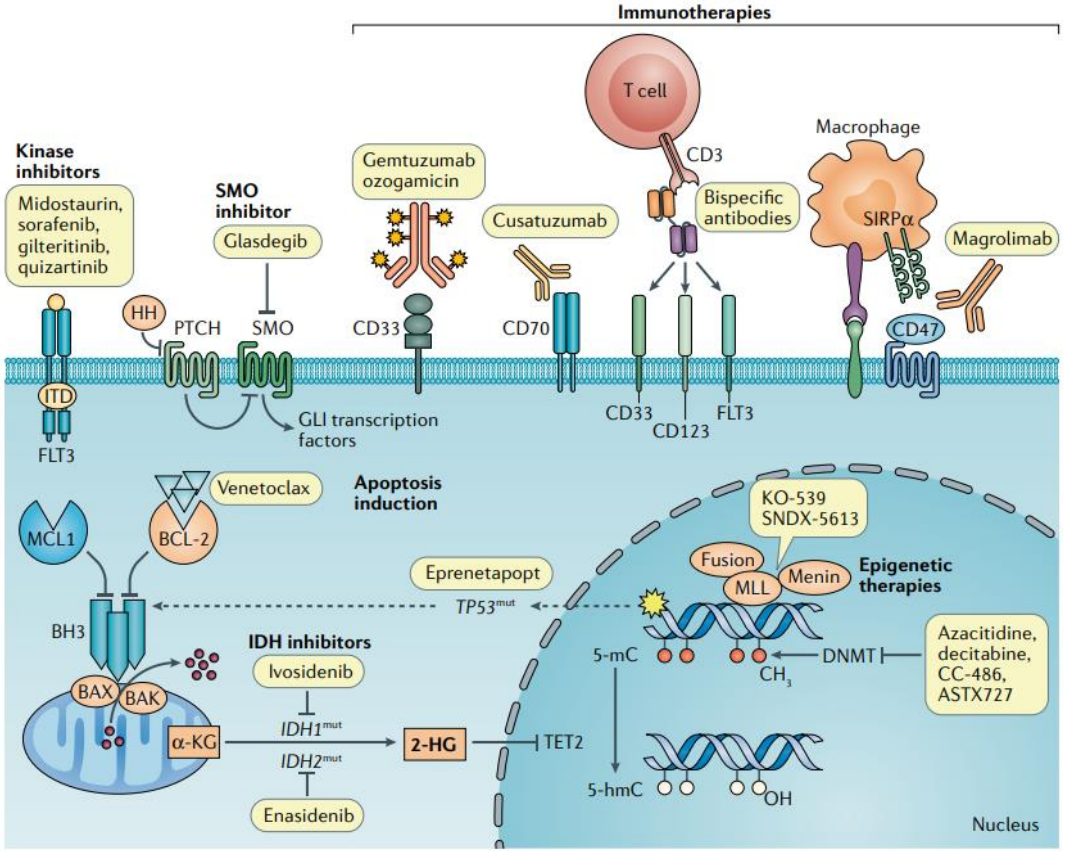
AML, acute myeloid leukaemia; AML-MRC, AML with myelodysplasia-related features; chemo, chemotherapy; EMA, European Medicines Agency; HMA, hypomethylating agent; LDAC, low-dose cytarabine; mut, mutant; OS, overall survival; pts, patients; R/R, relapsed and/or refractory; t-AML, treatment-related AML; VEN, venetoclax.

DiNardo CD, Perl AE. *Nat Rev Clin Oncol.* 2019;16:73-74.

Toward Precision Medicine for AML

First-Line Therapy

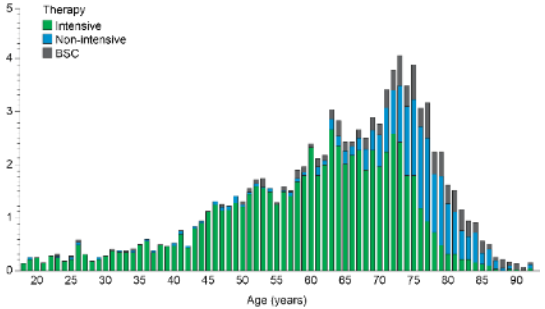
- TKIs targeting mutated *FLT3*
  - Induction/consolidation
  - Maintenance
- CD33 targeting by GO
  - Does genotype matter?
  - Consolidation?
- BCL-2 + epigenetic therapy
  - New standard in older patients
  - Option for younger patients?
- SMO inhibition + LDAC
  - Who benefits – sAML?
- Epigenetic therapy
  - In maintenance



Döhner H, Wei AH, Löwenberg B. *Nat Rev Clin Oncol*. 2021;18(9):577-590.

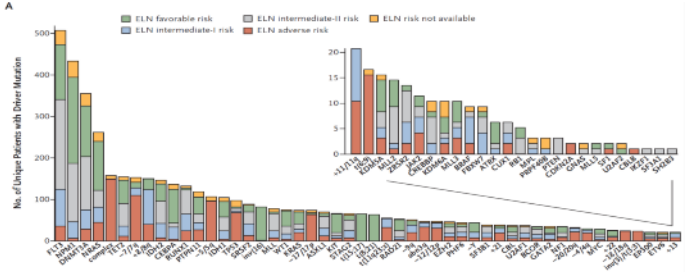
Key Components to Personalize Treatment

Age (chronologic, biologic)



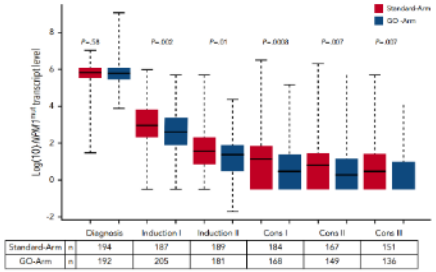
Adapted from Nagel et al. *Ann Hematol.* 2017;96:1993-2003.

Genotype



Papaemmanuil et al. *N Engl J Med.* 2016;374(23):2209-2221.

Measurable residual disease



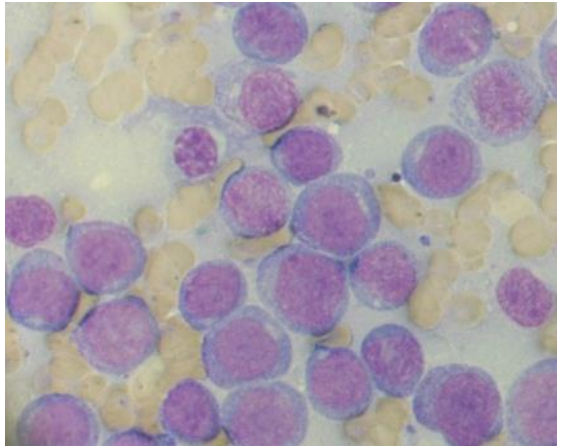
Standard-Arm	n	194	187	189	184	167	151
GO-Arm	n	192	205	181	168	149	136

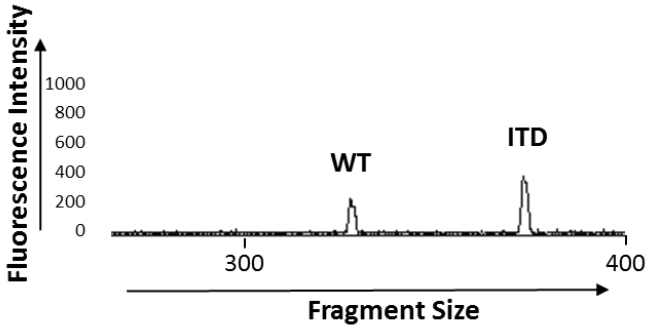
Adapted from Kapp-Schwoerer S, et al. *Blood.* 2020;136(26):3041-3050.

Case

- A 69-year-old man presents with fatigue
- 60% BM blasts
- Diagnosed with AML with the presence of a *FLT3*-ITD and mutated *NPM1*

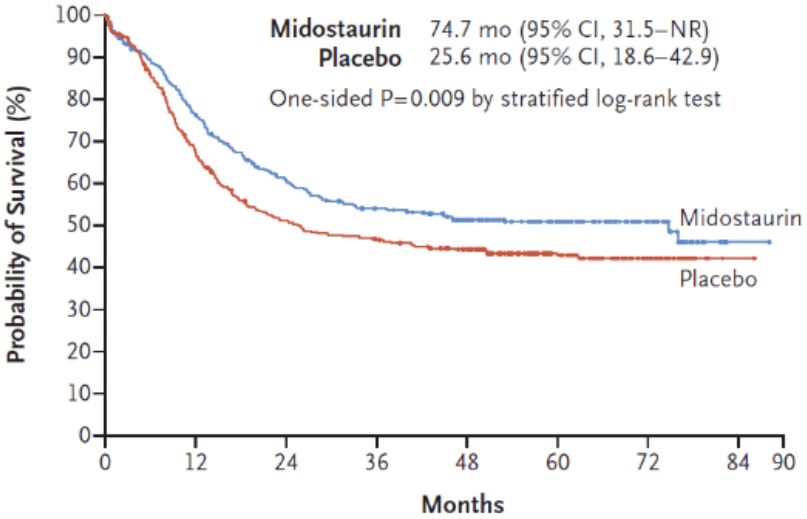
- Comorbidities include
  - T2D treated with oral antidiabetics
  - Renal impairment (CrCl 60 mL/min)
  - No history of cardiac disorders



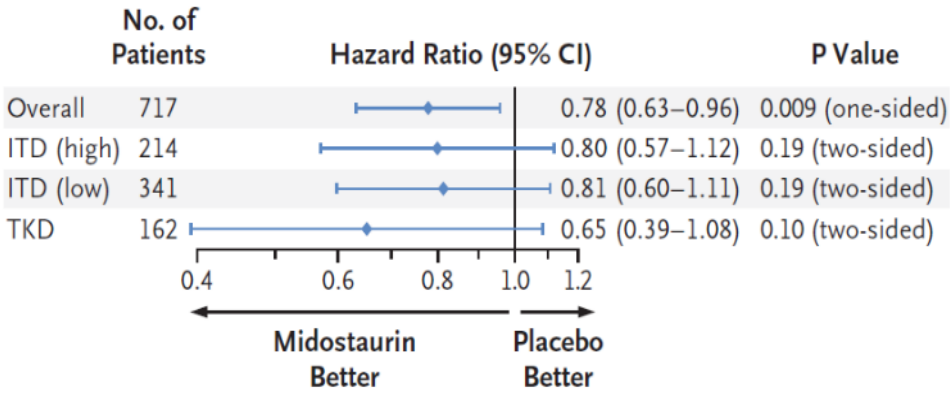


CALGB 10603: Overall Survival (age 18–59)

Median OS



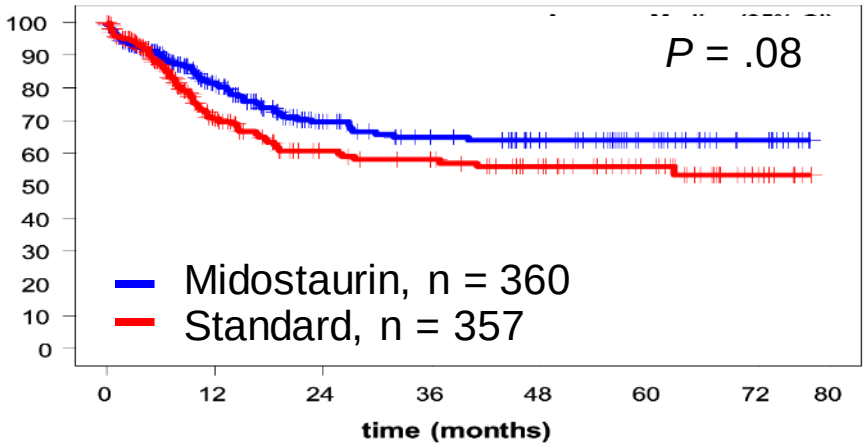
OS Subgroup Analysis



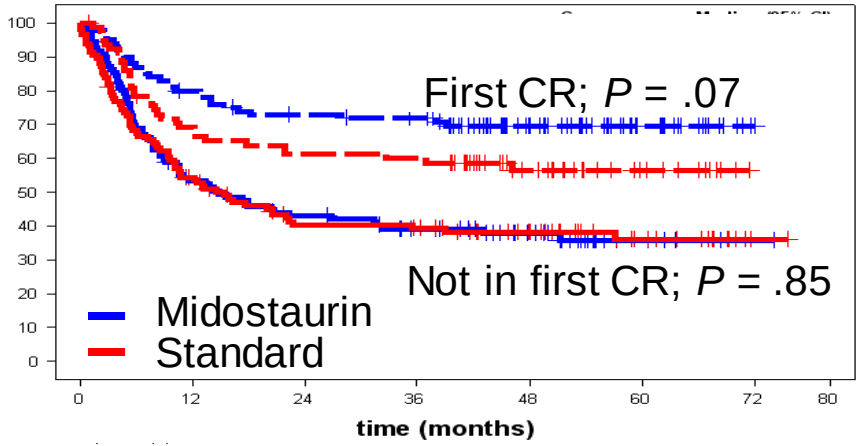
Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

CALGB 10603-RATIFY: Effect of Allogeneic HSCT on Outcome

Allo-HSCT censored



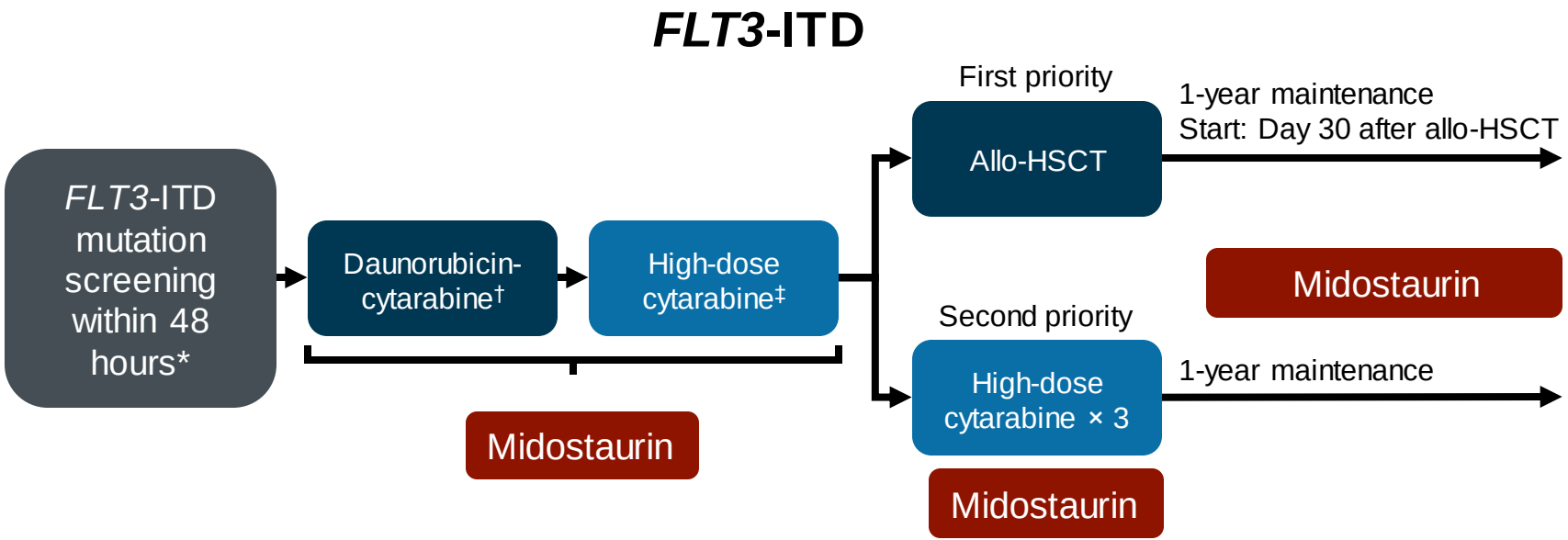
Allo-HSCT (first CR and R/R)



Cumulative Incidence of Relapse	HR (95% CI)	*P* Value
All patients with CR after induction	0.72 (0.55, 0.94)	.02
Allo-HCT censored	0.81 (0.60, 1.10)	.18
Only allo-HCT	0.47 (0.26, 0.87)	.02

Stone RM, et al. *N Engl J Med*. 2017;377:454-464; Stone RM, et al. ASH 2017. Abstract 2580.

Midostaurin in Older Patients: Results of the AMLSG 16-10 Study (age 18–70 years)

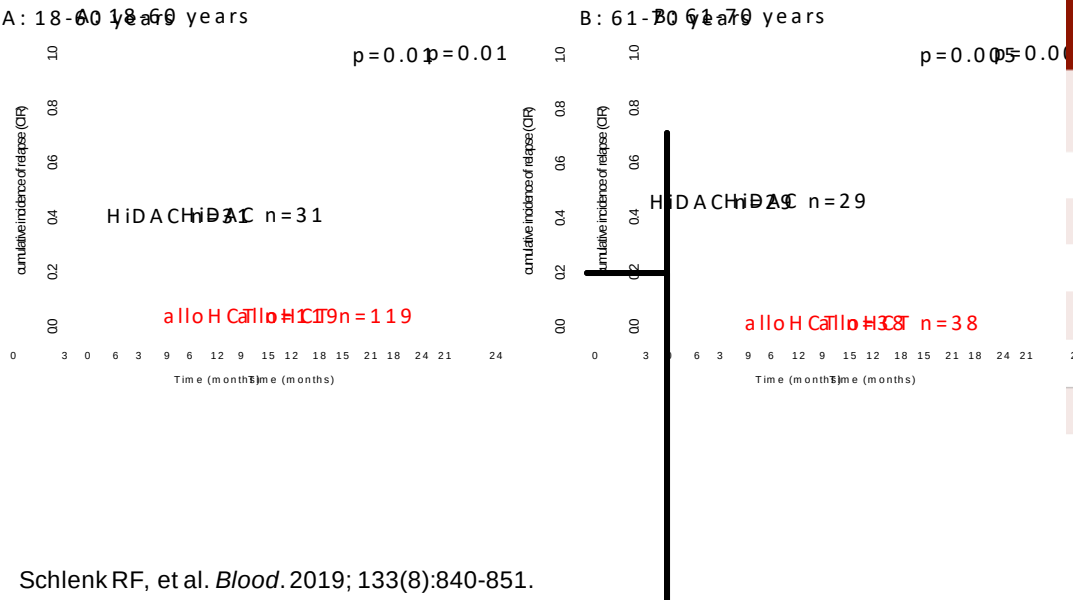


*Patients may receive hydroxyurea during screening phase; †Optional second cycle in patients achieving PR after cycle I; ‡Cytarabine: 18–65 years, 3 g/m^2, q12h, day 1, 3, 5; >65 years, 1 g/m^2, q12h, day 1, 3, 5; optional for patients before allo-HSCT.

Schlenk RF, et al. *Blood*. 2019; 133(8):840-851.

Cumulative Incidence of Relapse and Feasibility of Maintenance Therapy

CIR



Time on maintenance therapy and reasons for early termination

	All n = 97	Allo-HCT n = 75	HDAC n = 22	P
Median time on maint, mo (range)	9 (1, 13)	9 (1, 13)	10.5 (1, 12)	.82
Early termination, %	62	59	73	.32
Death	2	2	0	.99
IC/patients' wish	18	25	0	.06
Mido toxicity	47	55	25	.29
Other	12	5	31	.006
Relapse	22	14	44	.009

Schlenk RF, et al. *Blood*. 2019; 133(8):840-851.

Head-to-Head Comparisons vs Mido

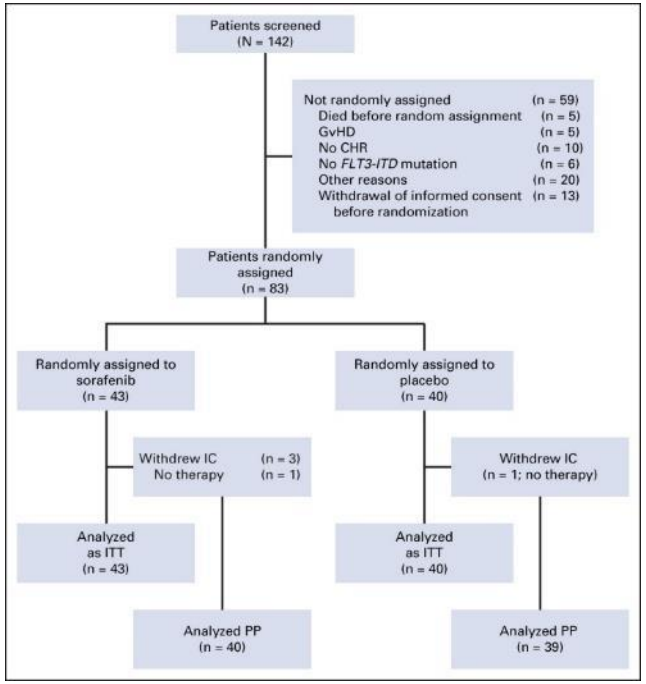
TKI	Gilt. vs Mido	Gilt. vs Mido	Quiz. vs Mido
Short Title	PrE0905	HOVON-156 AML AMLSG 28-18A	Q-SOC
Key in. criteria	AML *FLT3*-TKD and/or –ITD ECOG 0–3 Age ≥18 to ≤65 years	AML/MDS EB-2 *FLT3*-TKD and/or –ITD ECOG 0–2 Age ≥18	AML *FLT3*-ITD ECOG 0–2 Age ≥18
Key ex. criteria	APL, CBF	APL, t(9;22)	APL, t(9;22)
Sample size	n=179	n=768	n=156
ClinicalTrials	NCT03836209	NCT04027309	NCT04676243

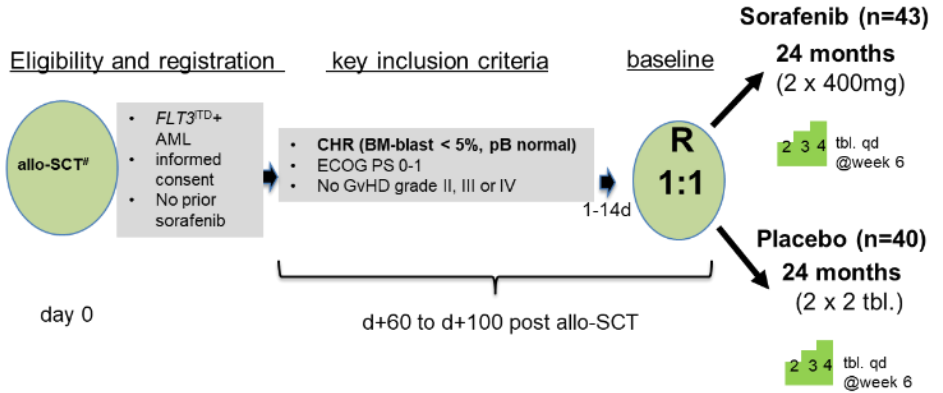
ECOG-ACRIN cancer research group
Reshaping the future of patient care

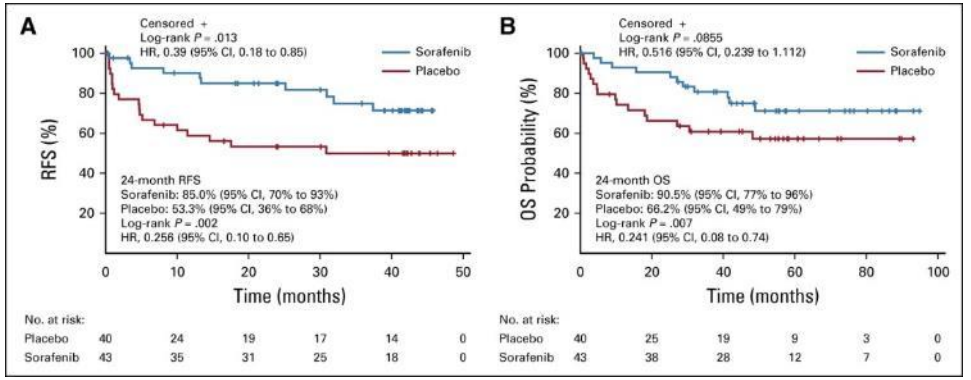
HOVON

SAL PETHEMA

Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With FLT3 Internal Tandem Duplication Mutation (SORMAIN)

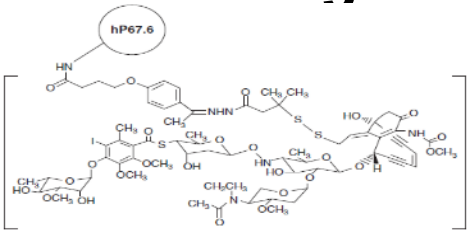


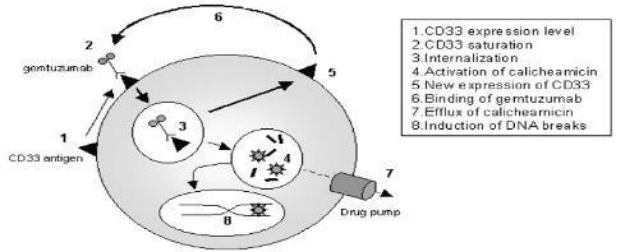


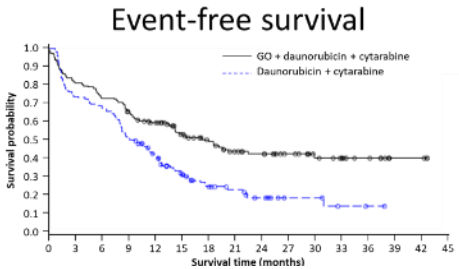


Burchert A, et al. *J Clin Oncol*. 2020;38(26):2993-3002.

Gemtuzumab Ozogamicin: Targeting CD33 in Acute Myeloid Leukemia







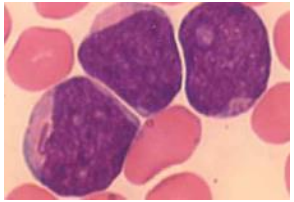
- hP87.6 is a humanized CD33-binding murine antibody (p67.6) of the IgG4 subtype
- Calicheamicins belong to the enediyne family of antitumor antibiotics originally isolated from the soil microorganisms (actinomycete) *Micromonospora echinospora* sp. calichensis. They bind on double-stranded DNA and have high extreme cytotoxic potency
- The antibody is bound to the calicheamicin derivative by a covalent linkage of a bifunctional linker, 4-(4-acetylphenoxy) butanoic acid
- Through this linkage, both the hydrolytic stability at pH 7.4 and sufficient drug release in the lysosomes at pH 4.0 are achieved
- Approved for de novo CD33-positive AML (excl. APL) in combination with daunorubicin and cytarabine

van der Velden VHJ, et al. *Leukemia.* 2004;18:983-988; Review: Thol F, Schlenk RF. *Expert Opin Biol Ther.* 2014;14(8):1-11; Lambert J, et al. *Haematologica.* 2019;104(1):113-119.

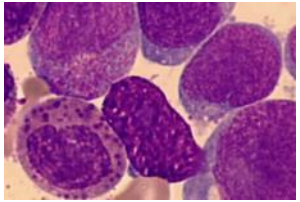
Gemtuzumab Ozogamicin: Does the Genotype Matter?

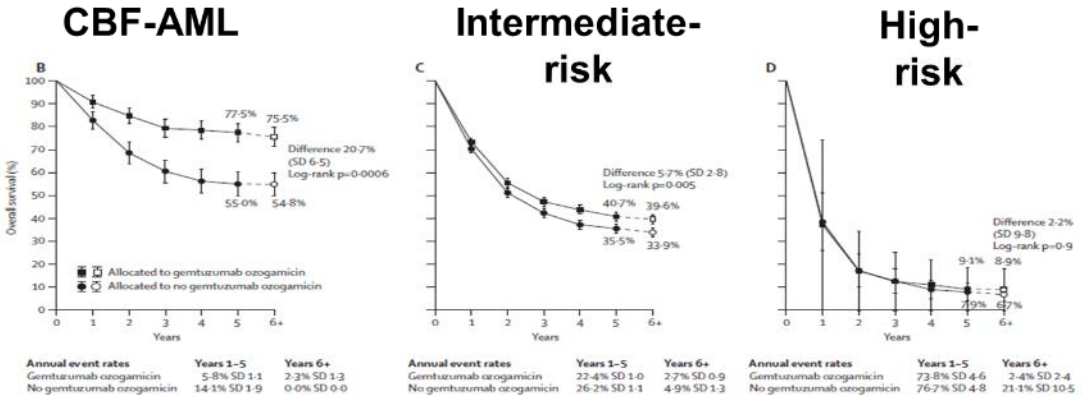
Core-binding factor AML

t(8;21); *RUNX1-RUNX1T1*



Inv(16); *CBFβ-MYH11*

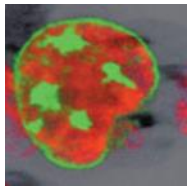




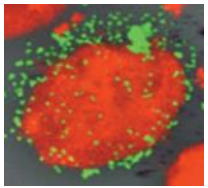
Hills RK, et al. *Lancet Oncol.* 2014;15:986-996

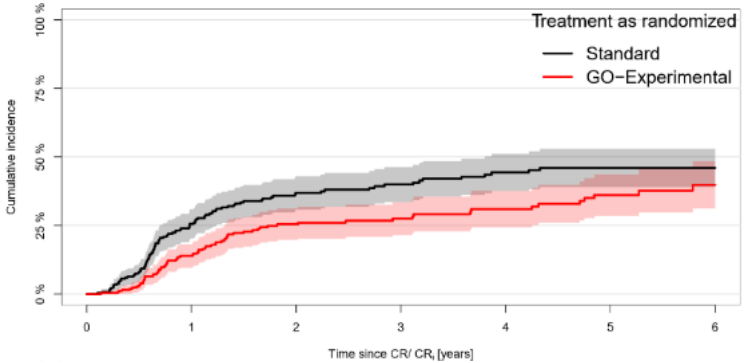
Mutated *NPM1*

Wild type



Mutated

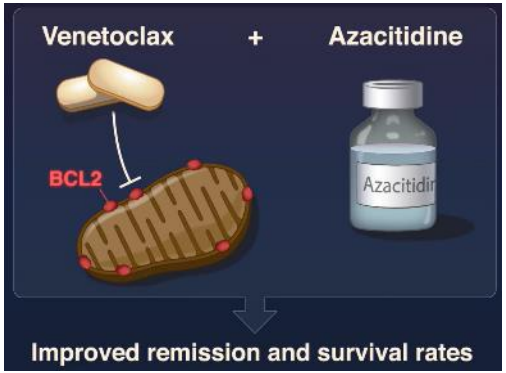


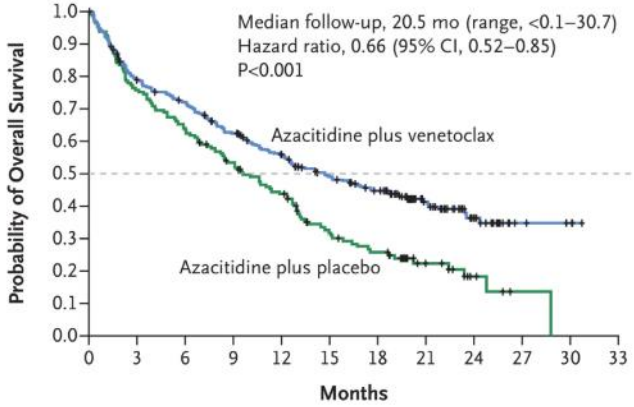


Age-stratified HR, 0.66
P = .005

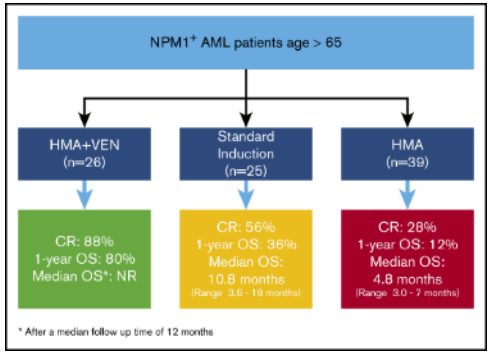
Schlenk RF, et al. *J Clin Oncol*. 2020;38(6):623-632.

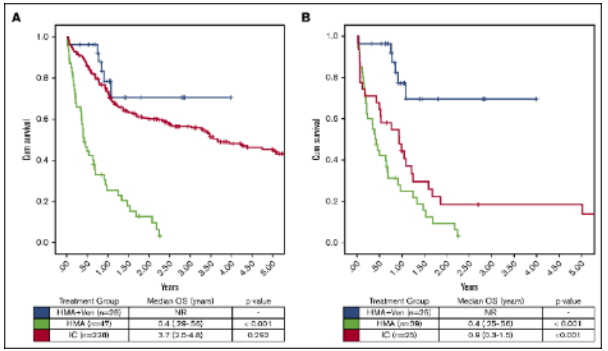
BCL-2 Inhibition in Older Patients





DiNardo CD, et al. *N Engl J Med.* 2020;383:617-629.



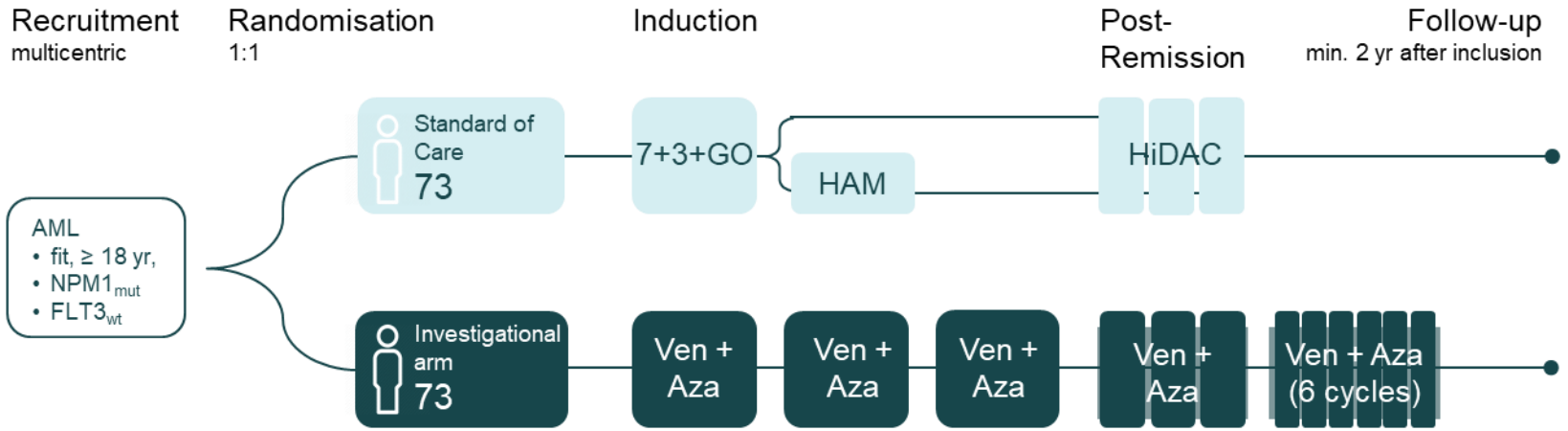


Lachowiez CA, *Blood Adv.* 2020;4(7):1311-1320.

Venetoclax + Azacitidine vs Standard Intensive Chemotherapy for Patients With Newly Diagnosed Acute Myeloid Leukemia (AML) and *NPM1* Mutations Eligible for Intensive Treatment

Randomized, controlled, open-label, phase II trial

EudraCT-Number: *2021-003248-26*

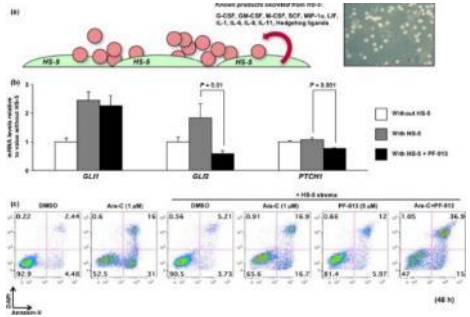


Primary endpoint: mEFS – events primary treatment failure or hematologic relapse or molecular relapse or death

Statistics: noninferiority – margin $\delta = 0.15$; $H_0: \lambda_2 - \lambda_1 \geq \delta$, $H_1: \lambda_2 - \lambda_1 < \delta$

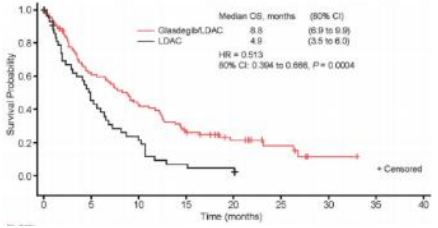
Hedgehog Pathway Inhibitor in AML

- Glasdegib (PF-04449913) sensitizes dormant AML cells to cytarabine



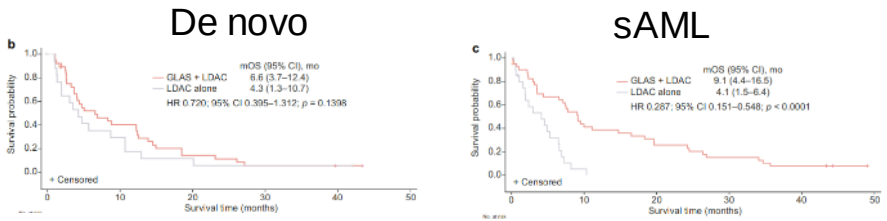
Fukushima N, et al. *Cancer Sci.* 2016;107(10):1422-1429.

- Better survival in unfit older patients with glasdegib + LD Ara-C compared with LD Ara-C



Cortes JE, et al. *Leukemia.* 2019;33(2):379-389.

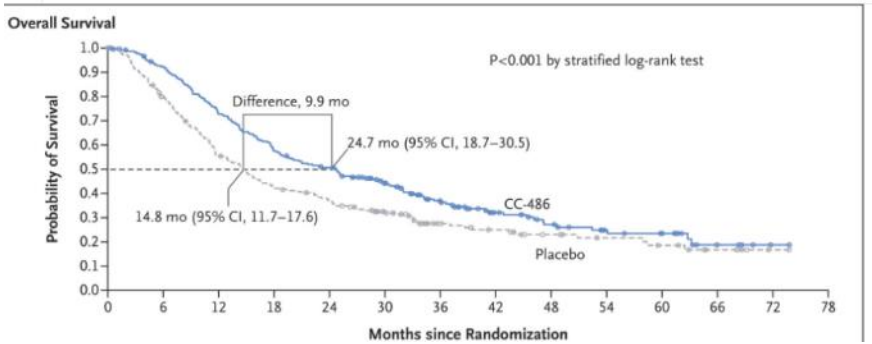
- sAML patients seem to benefit most
  (cave sec. HMA treatment has to be considered)



Heuser M, et al. *Ann Hematol.* 2021;100:1181-1194.

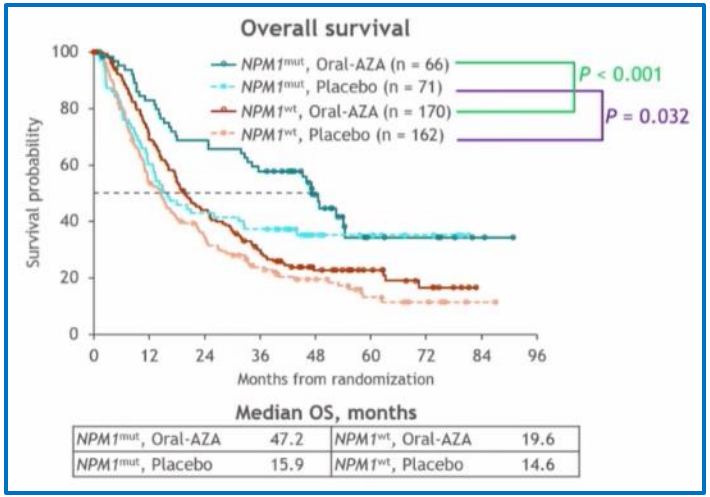
Oral AZA (CC-486) in Maintenance Therapy

- CC-486 as maintenance therapy prolongs RFS and OS



Wei AH, et al. *N Engl J Med.* 2020; 383:2526-2537.

- According to subgroup analysis, mostly patients with *NPM1*-mutated AML benefit from CC-486 maintenance therapy



Döhner H, et al. EHA 2021. Abstract S131.

Summary

First-Line Therapy

TKIs targeting mutated *FLT3*
- Induction/consolidation
- Maintenance

CD33 targeting by GO
- Does genotype matter?
- Consolidation?

BCL-2 + epigenetic therapy
- New standard in older patients
- Option for younger patients?

SMO inhibition + LDAC
- Who benefits – sAML?

Epigenetic therapy
- In maintenance

Agent/Genotype

Midostaurin
- *FLT3*-ITD, *FLT3*-TKD
- Unclear

Gemtuzumab ozogamicin
- t(8;21), inv(16), *NPM1*-mut
- Unclear

Venetoclax + AZA
- Yes
- Ongoing studies

Glasdegib + LDAC
- sAML

CC-486
- Yes, *NPM1*-mut

To Consider

Allo-HCT in CR1

GO1 vs GO147

How long?

In consolidation?
- With HDAC

+ VEN?

Global Leukemia Academy

Q&A session

APTITUDE HEALTH®

Global Leukemia Academy

Optimizing management of relapsed/refractory AML

Charles Craddock

APTITUDE HEALTH®

Optimizing management of relapsed/refractory AML

Charles Craddock FRCP, FRCPath, FMedSCi

Centre for Clinical Haematology,
Queen Elizabeth Hospital Birmingham
University of Birmingham, UK

UNIVERSITY OF BIRMINGHAM

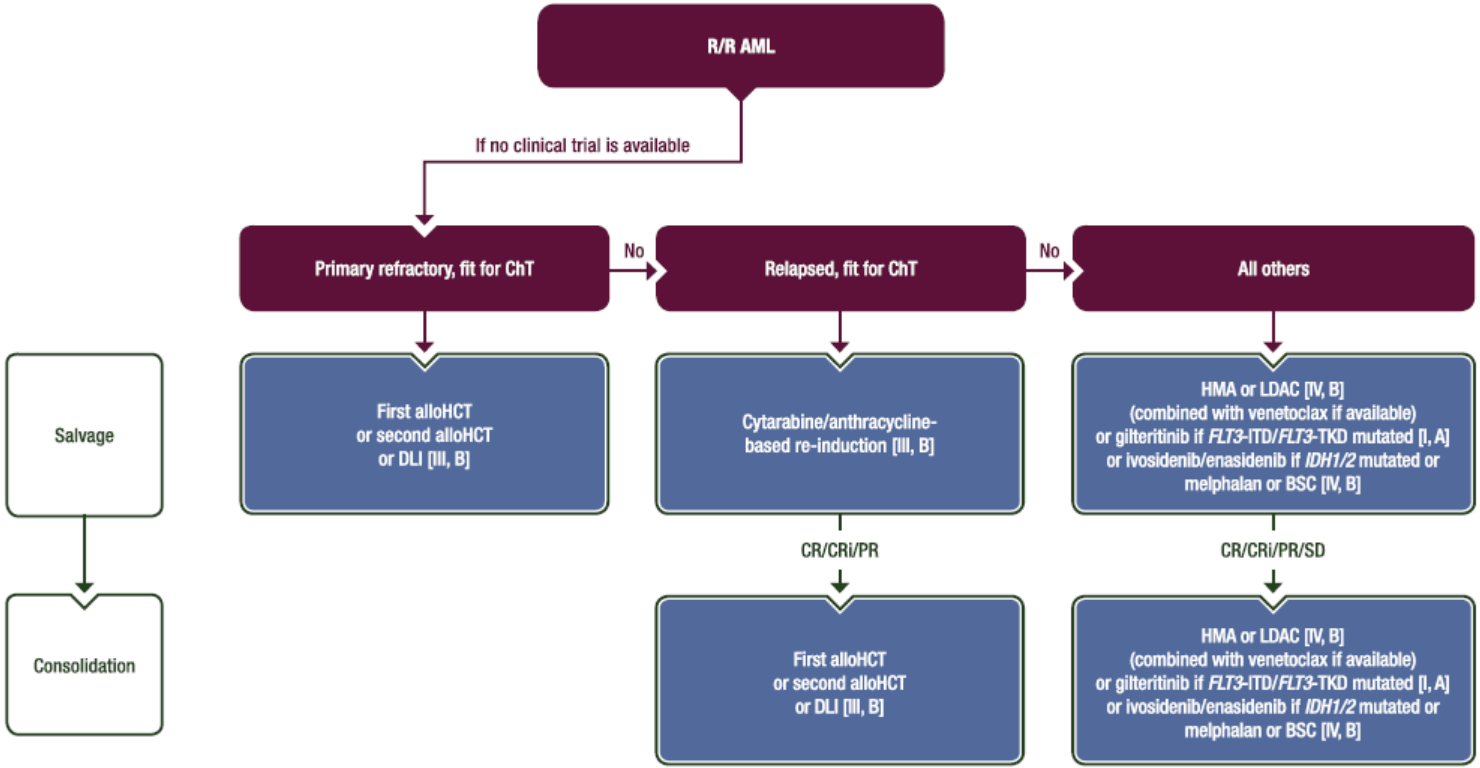
University Hospital Birmingham NHS Foundation Trust

Disclosures

Research Support/P.I.	Celgene
Employee	
Consultant	
Major Stockholder	
Speakers Bureau	
Honoraria	Celgene, Janssen, Pfizer
Scientific Advisory Board	Celgene

Presentation includes discussion of the off-label use of a drug or drugs

ESMO guidelines for R/R AML



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

Primary refractory AML

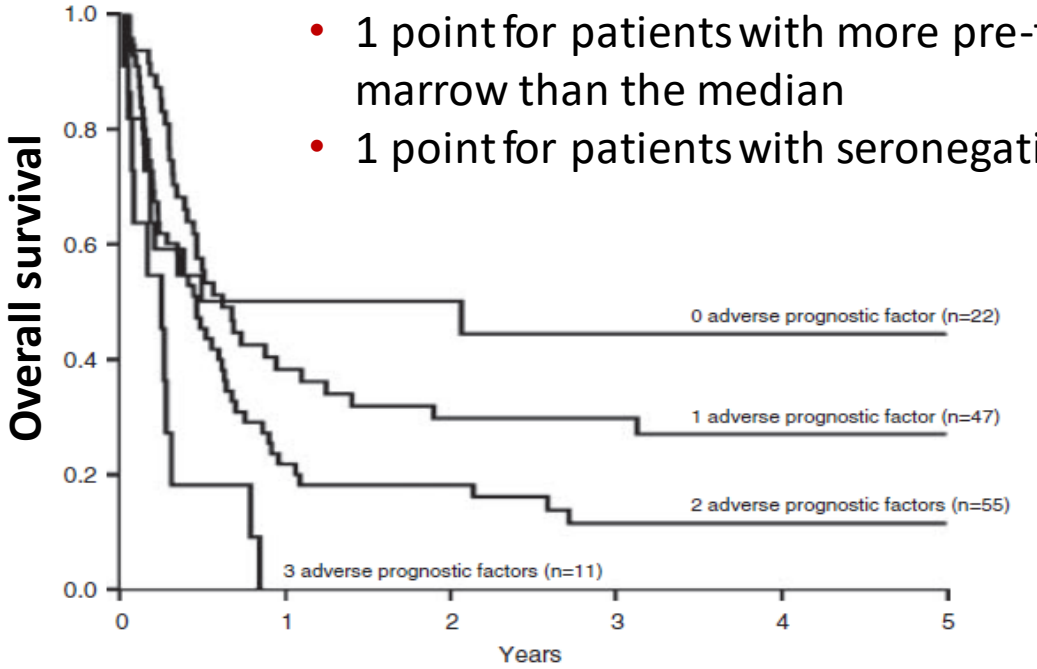
- Up to 30% of adults with newly diagnosed AML fail to achieve a morphological CR after 1–2 courses of induction chemotherapy (IC)
- Currently there is no consensus definition of Primary Refractory AML (PREF AML)
- This lack of a diagnostic consensus has compromised the development of treatment strategies in PREF AML

CR, complete remission.

Allogeneic SCT can deliver long-term survival in selected patients with PREF AML

Overall survival according to scoring system:

- 1 point for patients who had received > 2 induction courses
- 1 point for patients with more pre-transplant blasts in the bone marrow than the median
- 1 point for patients with seronegative CMV serology

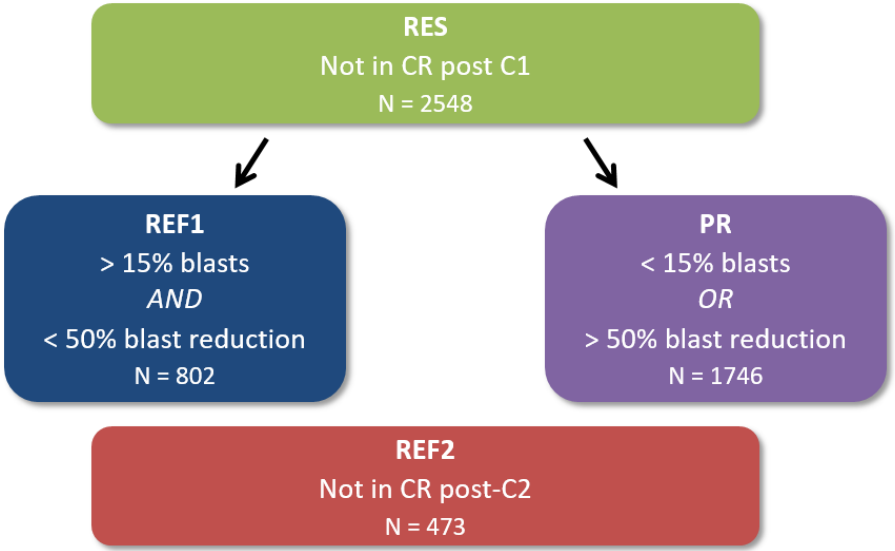


CMV, cytomegalovirus.

Craddock et al Leukemia 2011;25:808-13.

Defining primary refractory AML to identify patients for whom allogeneic SCT represents the only curative therapy

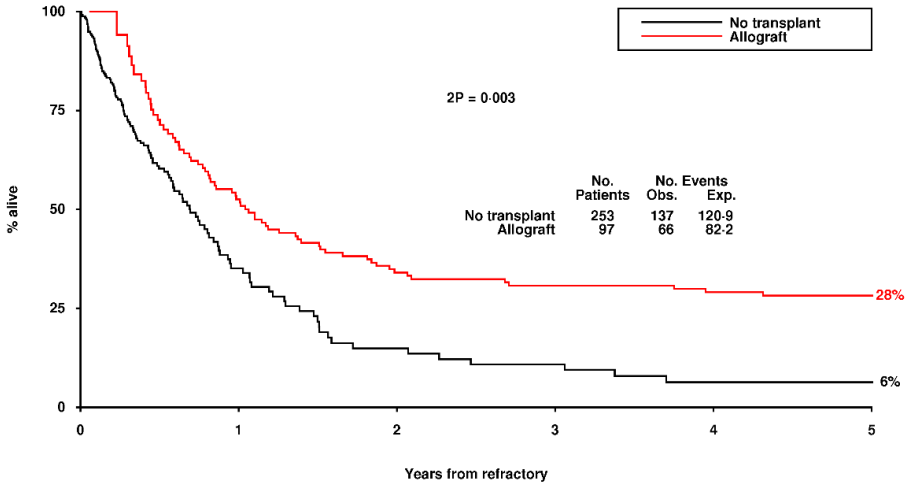
- Retrospective analysis of 8907 patients with non-promyelocytic AML treated with IC on the UK MRC/NCRI AML 10–16 trials
- Disease response assessed by morphological bone marrow evaluation approximately 21 days after completion of IC
- Applied four differing criteria for PREF AML following 1 or 2 cycles of IC and correlated these with patient outcome
- Evaluated the impact of AlloSCT on long-term survival of patients defined by each of the four definitions of PREF AML



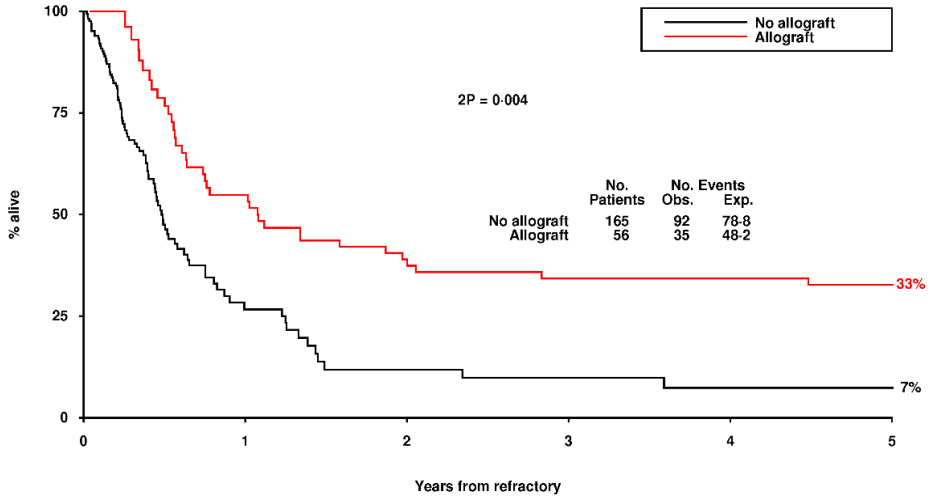
Ferguson et al. Haematologica 2016;101:1351-8.

Transplant outcomes in PREF AML

REF1B cohort: <50yrs



REF2 cohort: <50 yrs



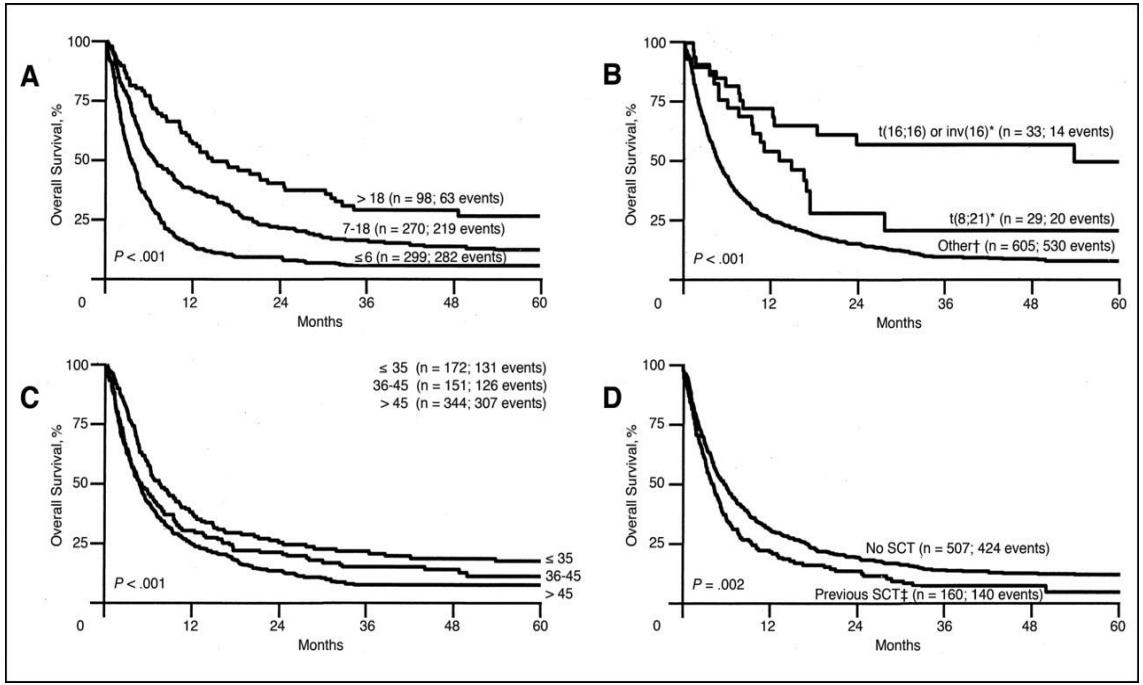
Ferguson et al. Haematologica 2016;101:1351-8.

Relapsed AML

- Allo- SCT remains the only curative strategy in relapsed AML
- Requires acquisition of 2nd CR
- CR rates after salvage therapy are highly variable
- Intensive chemotherapy associated with substantial mortality and morbidity in relapsed disease
- Novel salvage strategies in relapsed AML are required
- Optimising outcomes in patients who relapse after allo-SCT remains a major unmet need

CR, complete remission.

Cumulative rates of overall survival among patients with AML in first relapse according to (A) relapse-free interval from first complete remission, (B) cytogenetics, (C) age and (D) prior stem-cell transplantation (SCT)

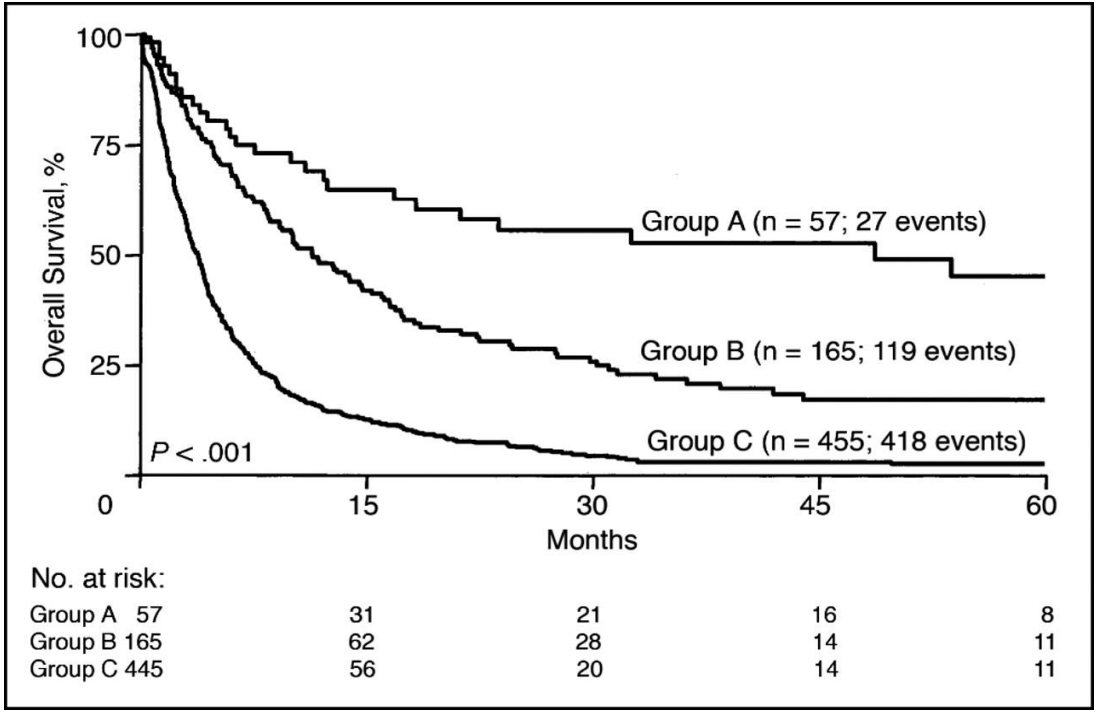


Breems et al JCO 2005

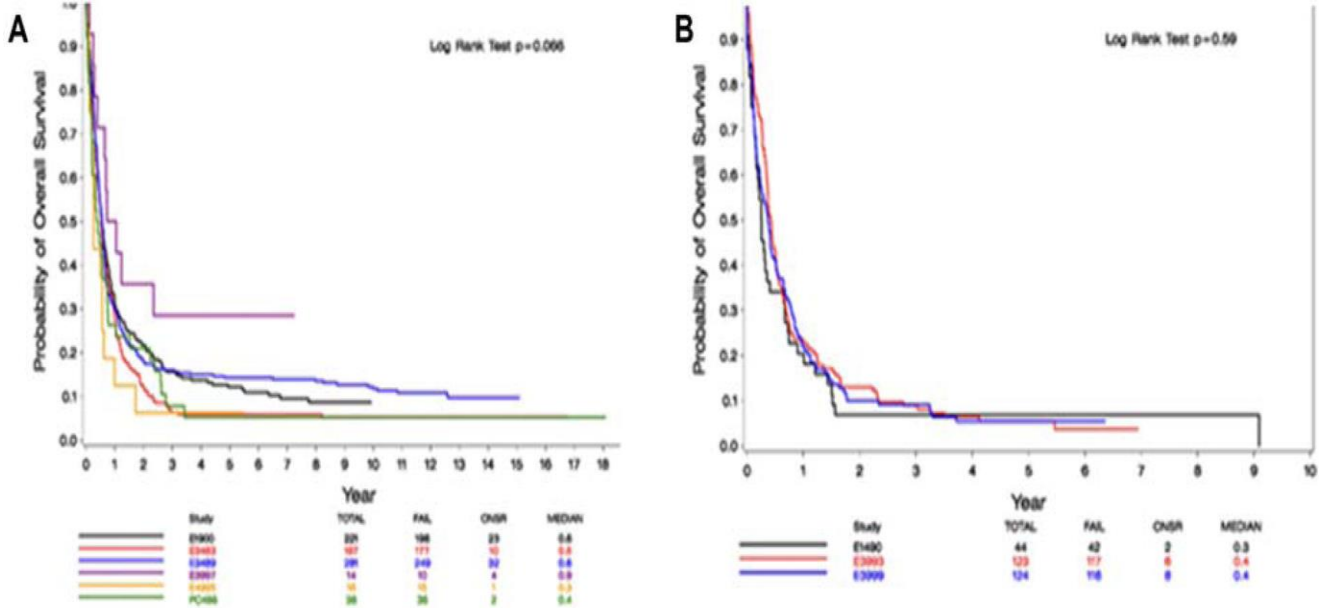
Cumulative rates of overall survival among acute myeloid leukemia patients in first relapse according to prognostic group.

Prognostic model:

- Age
- Cytogenetics
- CR1 duration
- Previous SCT

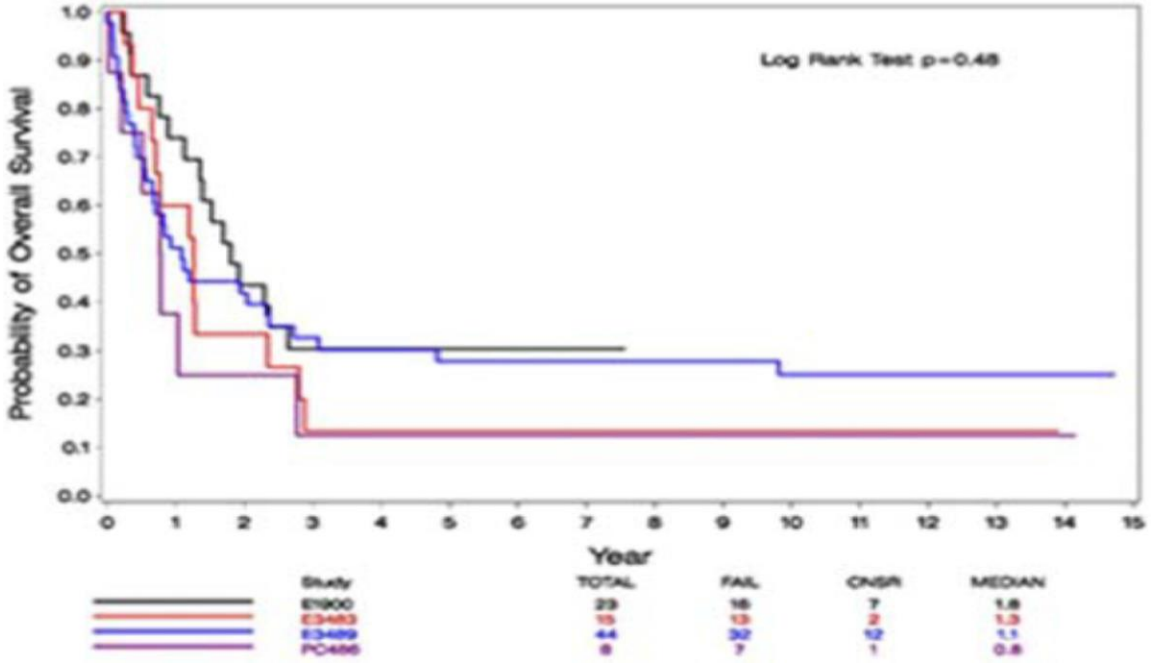


Outcome in relapsed AML: ECOG-ACRIN experience



Ganzel et al 2018

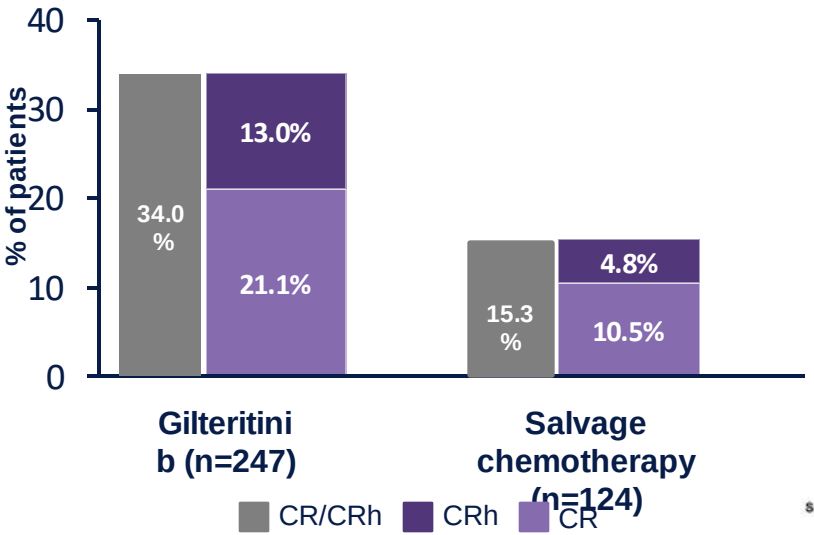
Outcome in relapsed AML according to patient age (<40) and CR1 duration (>12 months))



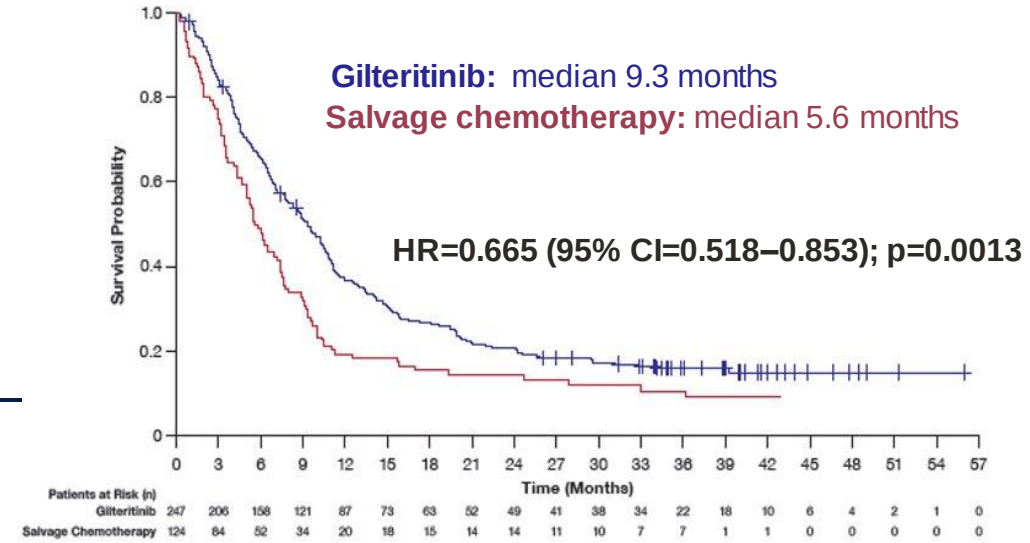
Ganzel et al 2018

ADMIRAL: Randomized, phase 3 trial of gilteritinib salvage in patients with R/R *FLT3*^{mut} AML

CR/CRh (co-primary endpoint): 34.0% (gilteritinib) vs 15.3% (chemo)[1]



OS (ITT population; N=371)[2]



CRh, CR with partial hematologic recovery.

1. Perl AE, *et al. N Engl J Med* 2019; **381:**1728–1740 ; 2. Perl AE, *et al.* EHA 2021; Abstract EP441 (Poster).

Gilteritinib single-agent Safety in the relapsed/refractory setting
ADMIRAL: Randomized, phase 3 trial in patients with R/R *FLT3*^{mut} AML

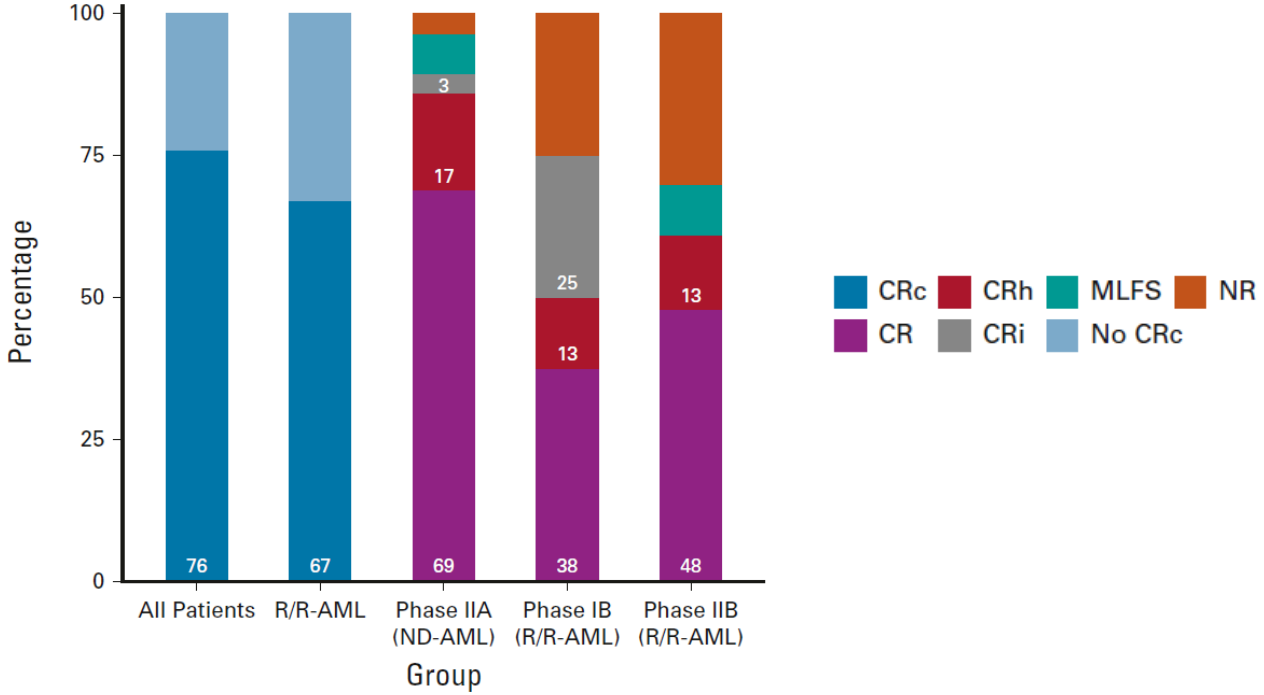
Grade ≥3 AEs in ≥10% of patients in either arm, n (%)	Gilteritinib n=246	Salvage chemotherapy, n=109
Febrile neutropenia	113 (45.9)	40 (36.7)
Anemia	100 (40.7)	33 (30.3)
Platelet count decreased	54 (22.0)	27 (24.8)
Thrombocytopenia	56 (22.8)	18 (16.5)
ALT increased	34 (13.8)	5 (4.6)
AST increased	36 (14.6)	2 (1.8)
Hypokalemia	32 (13.0)	12 (11.0)

Other safety events, n (%)	Gilteritinib	Salvage chemotherapy
Discontinuation due to AE	27 (11.0)	*Not reported*
30-day mortality (ITT population)	(2.0)	(10.2)
60-day mortality (ITT population)	(7.7)	(19.0)

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

Venetoclax + FLAG-IDA: Response outcomes

Phase 1b/2 study of venetoclax + FLAG-IDA in ND and R/R AML



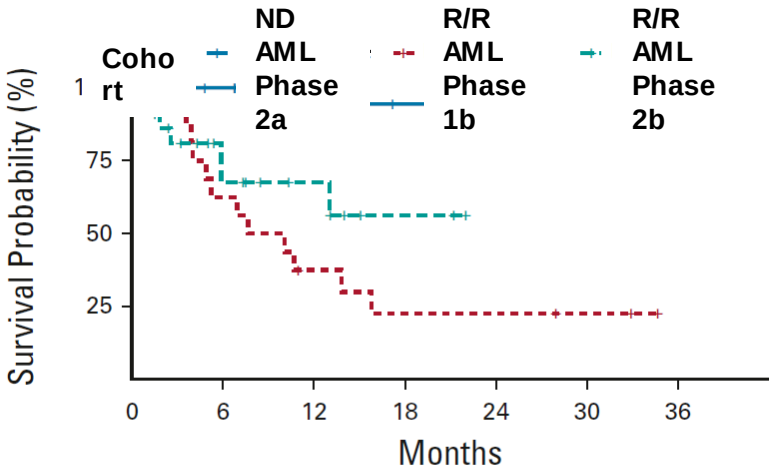
CR, complete response; CRc, composite CR; CRh, CR with partial hematologic recovery; CRi, CR with incomplete count recovery; HSCT, hematopoietic stemcell transplantation; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; ND-AML, newly diagnosed acute myeloid leukemia; NR, not reached; PD, progressive disease; R/R-AML, relapsed or refractory acute myeloid leukemia.

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

Venetoclax + FLAG-IDA: OS

Phase 1b/2 study of venetoclax + FLAG-IDA in ND and R/R AML

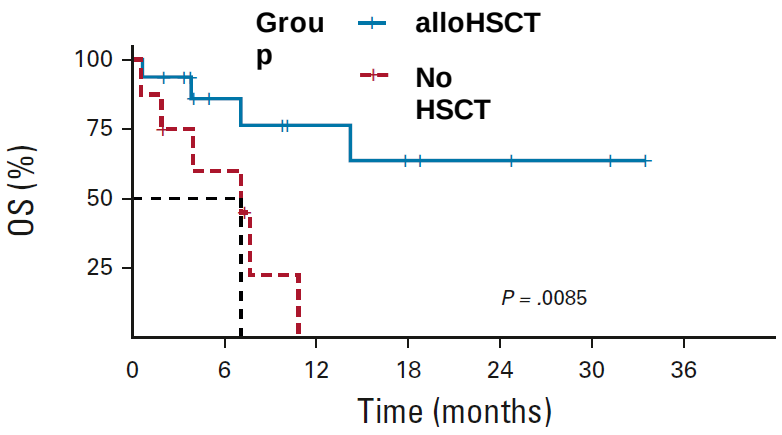
OS by cohort



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 attaining CRc.



No. at risk:

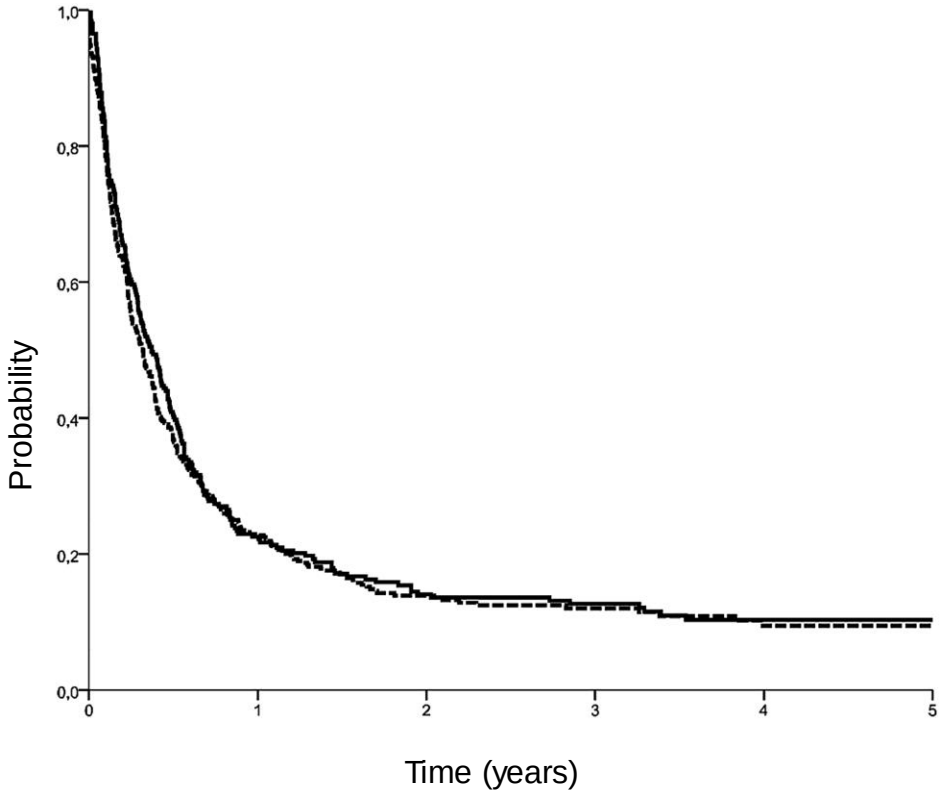
alloHSCT	16	9	6	4	3	2	0
No HSCT	8	4	0	0	0	0	0

DiNardo CD, et al. J Clin Oncol 2021.

Management of relapse post-transplant

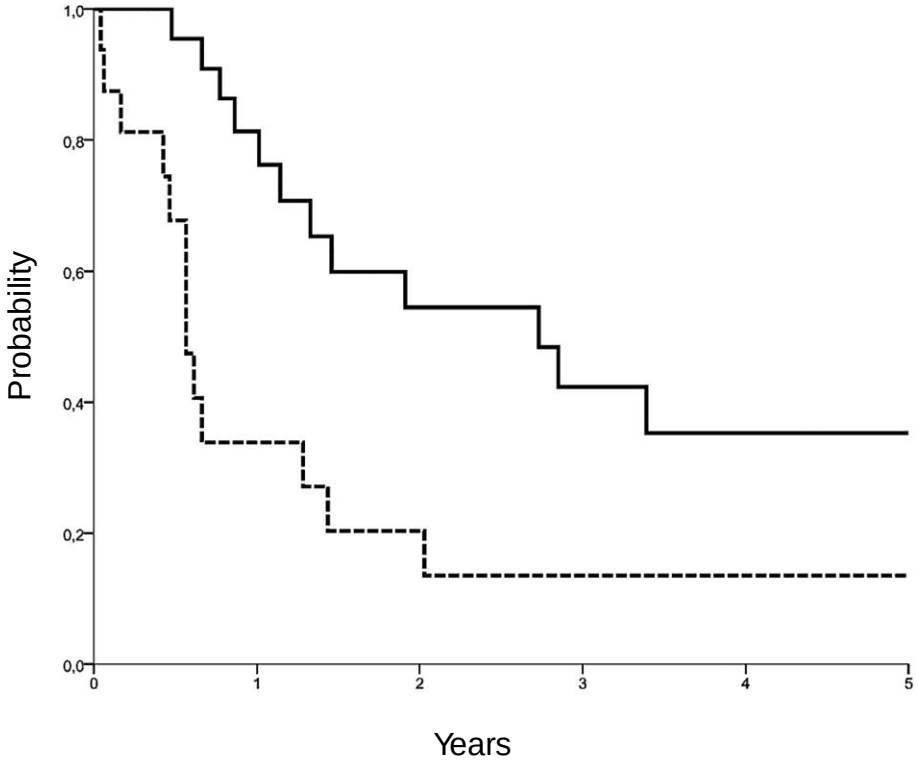
- In patients relapsing post allograft acquisition of CR is a pre-requisite of long term survival
- Approximately 20-30% of patients treated with salvage chemotherapy achieve a second CR but toxicity is significant
- Alternative salvage strategies include:
  - Immunosuppression taper
  - Salvage azacitidine
  - Lenalidomide/azacitidine combination therapy

Long-term survival in patients who relapse after allogeneic SCT for AML



Schmid *et al*. Blood 2012;

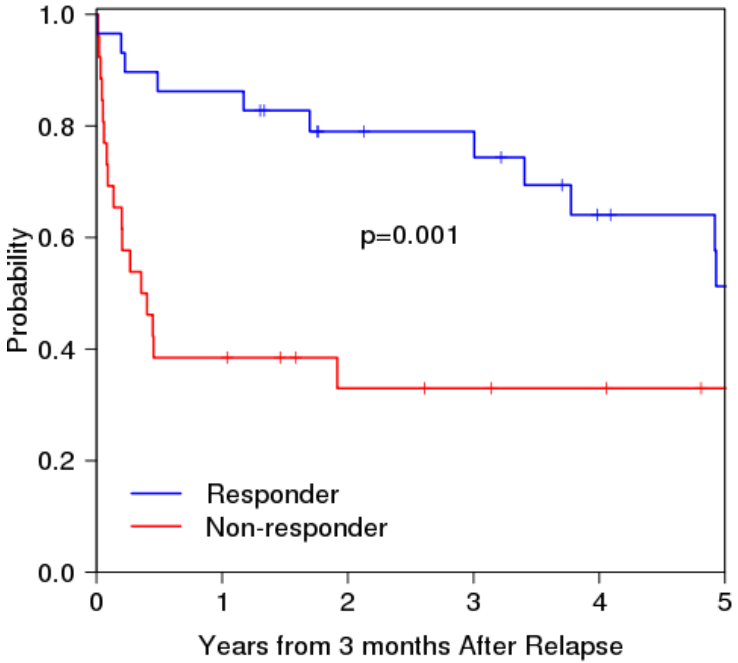
Acquisition of CR after salvage therapy is a pre-requisite of long term survival in patients relapsing post allograft



Schmid *et al*. Blood 2012

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 IS taper alone
- 1/22 MA (2.5%) and 33/101 RIC (32.7%) responded to IS taper alone (p=0.0073)



Kekere, *et al.* ASH 2014, Haematologica 2015

Salvage azacitidine in patients who relapse after allogeneic SCT for AML/MDS

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

  Interval time transplant to relapse >12 months (p=0.04)

  Good risk cytogenetics (p=0.02)
- Multivariable analysis of predictors of OS at 2 years:

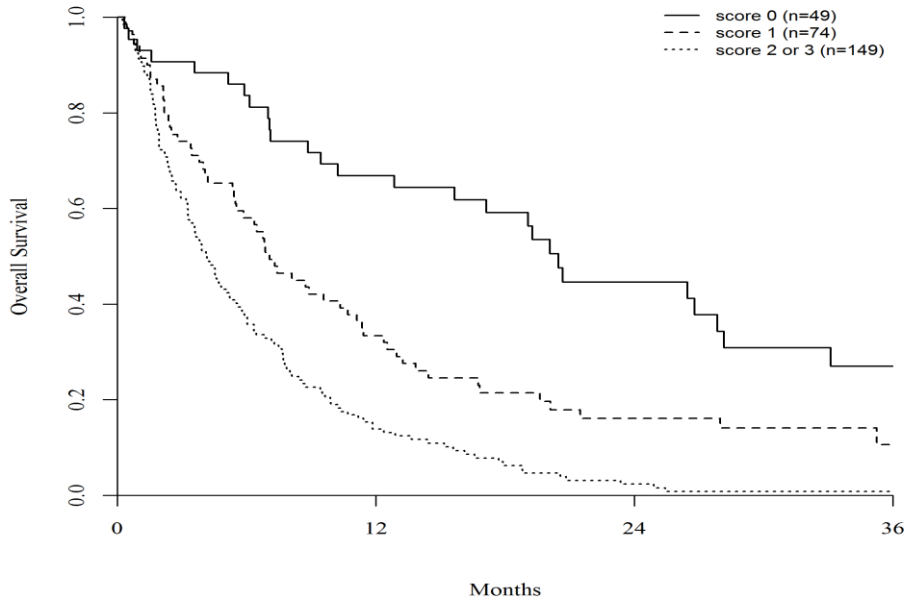
  Blasts in BM at relapse <median (p=0.02)

  Interval time transplant to relapse
  - 6–12 *vs* <6 months (p=0.0006)

Prognostic score for patients receiving salvage azacitidine

Prognostic Score		
		Score
Interval Tx relapse	<6 mo (ref)	0
	6–12 mo *vs* <6 mo	1
	>12 mo *vs* <6 mo	2
Cytogenetics	Good (reference)	0
	Intermediate *vs* good	1
	Poor *vs* good	2
Blast in BM at relapse >median		1

Overall survival after salvage azacitidine in patients relapsing after an allograft for AML/MDS



Craddock et al. Haematologica 2016 .

Combined lenalidomide and azacitidine as an alternative salvage strategy in patients relapsing post allograft

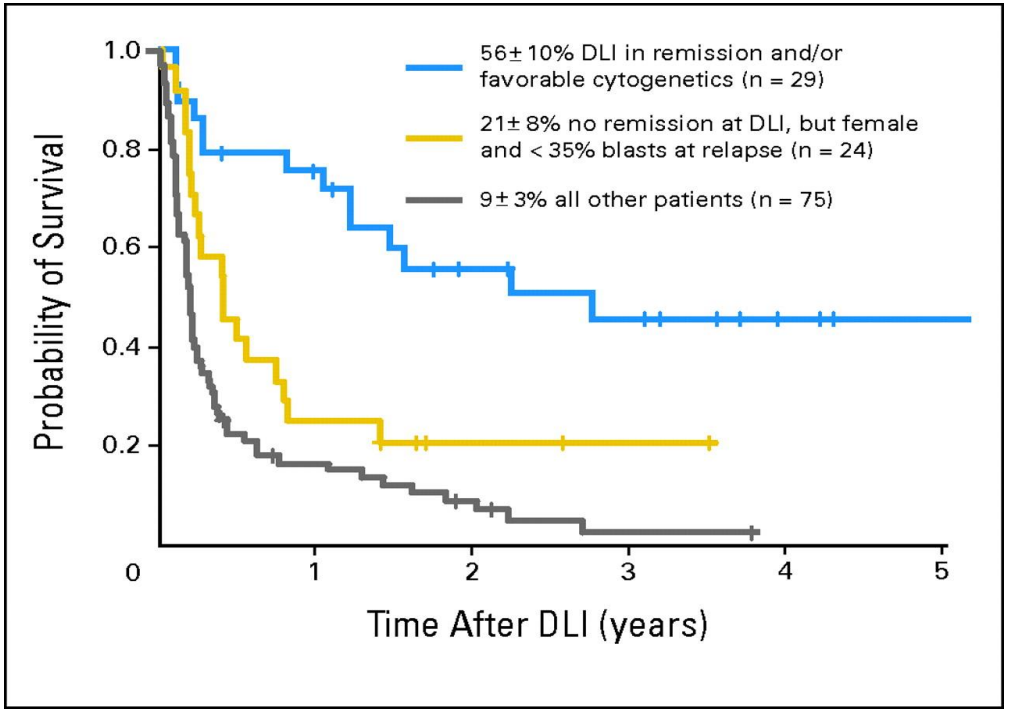
- Lenalidomide (LEN) demonstrates anti-tumor activity in high-risk AML
- LEN exhibits multiple immunomodulatory activities including T and NK cell activation
- Sockel, *et al* (2012) LENAMAINT study

  - 10 mg/day LEN x 21 days per month commencing 2 months post allograft

  -Trial discontinued because of severe acute GVHD within 2 weeks of commencing LEN in 6/10 patients

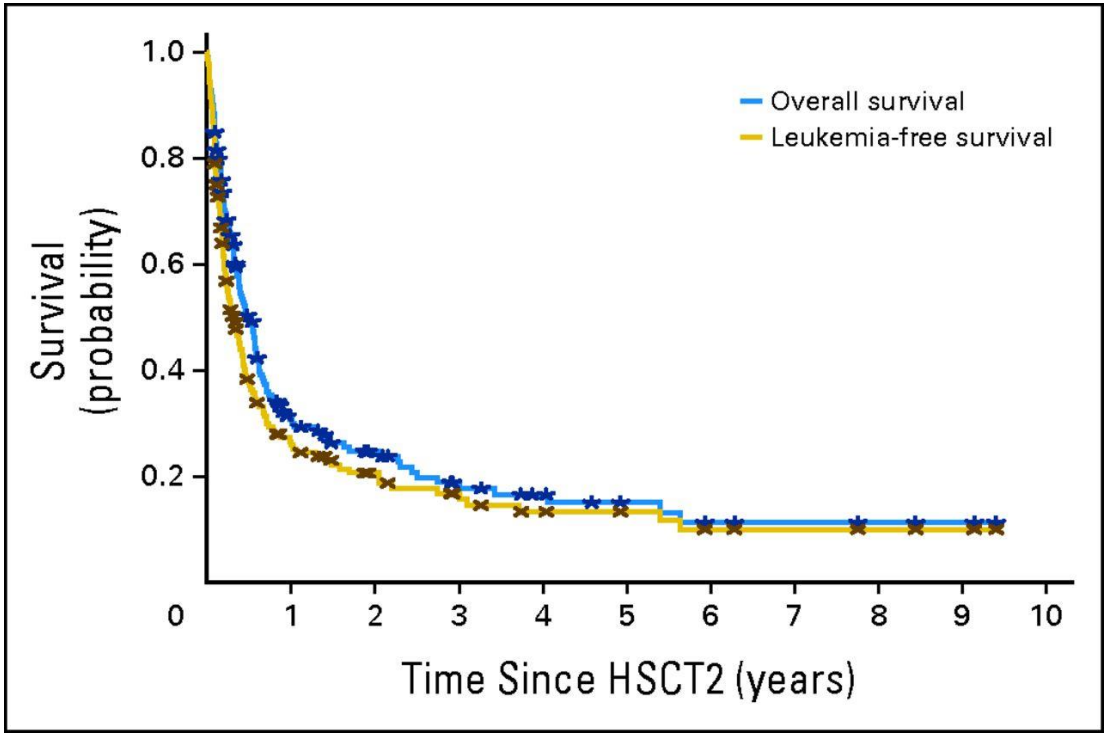
- UK NCRN VIOLA study: combined LEN/AZA in patients with AML who relapse post allograft
  - Well tolerated combination- MTD 25 mg LEN
  - 7/15 patients achieved major clinical response

Outcome after DLI is determined by cytogenetics, disease status at time of DLI and duration of CR post-transplant



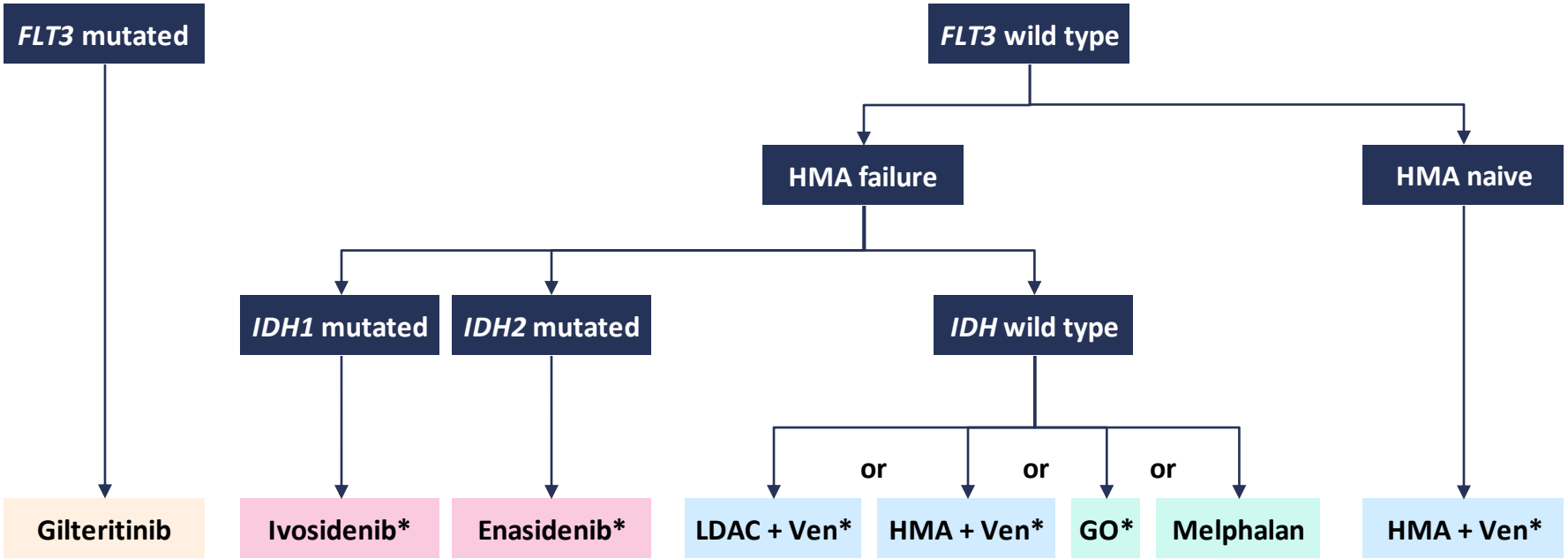
Schmid C et al. JCO 2007

Outcome after 2nd allograft is determined by duration of CR post-transplant and disease status at transplant but not by changing donor



Christopeit *et al*. J Clin Oncol 2013.

Onkopedia 2021 updates to guidelines for patients with R/R AML ineligible for allogeneic stem cell transplant

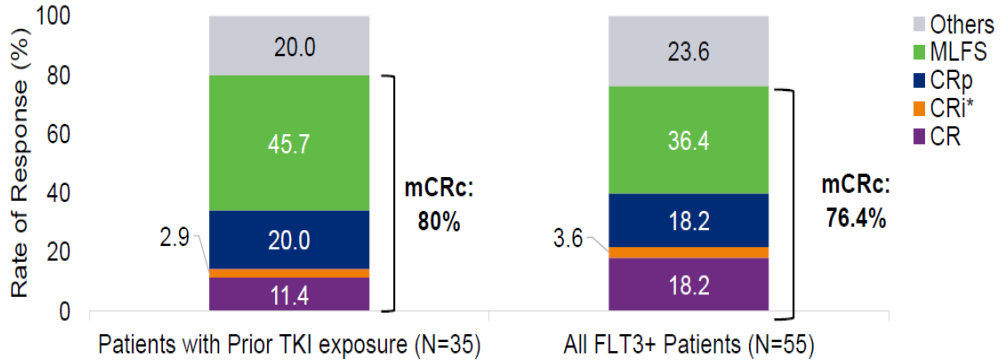


* Ivosidenib, enasidenib, GO, and venetoclax in combination with HMA/LDAC are not approved by the EMA for use in patients with R/R AML.
GO, gemtuzumab ozogamicin; HMA, hypomethylating agent; LDAC, low-dose cytarabine; Ven, venetoclax.
Adapted from: Röllig C, *et al.* Onkopedia Guideline AML January 2021 update;
Available at: https://www.onkopedia.com/de/onkopedia/guidelines/akute-myeloische-leukaemie-aml/@@guideline/html/index.html (accessed September 2021).

Venetoclax + gilteritinib: Outcomes

Phase 1b study of venetoclax + gilteritinib in R/R *FLT3*^{mut} AML[1]

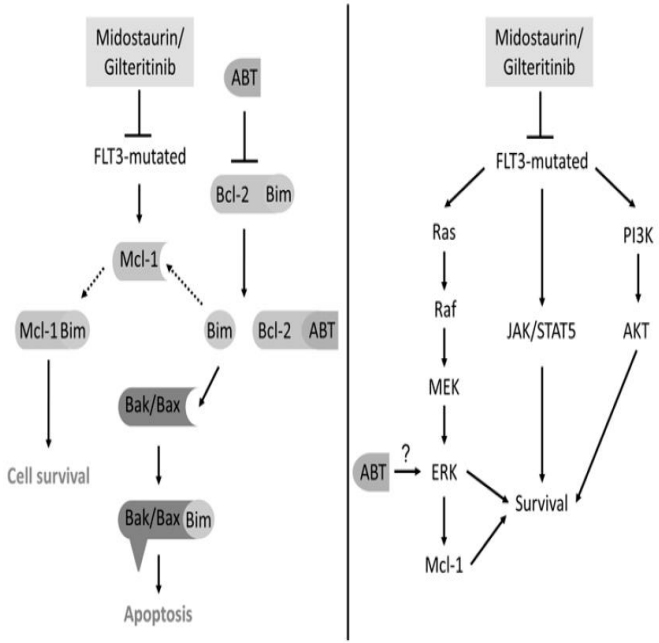
Summary of best responses[1]



	FLT3+ Patients with Prior TKI (N=35)	All FLT3+ Patients (N=55[a])
mCRc, n (%)	28 (80.0)	42 (76.4)
CR+CRp+CRi*	12 (34.3)	22 (40.0)
MLFS	16 (45.7)	20 (36.4)
Time to mCRc (months), median (range)	0.9 (0.7, 4.2)	0.9 (0.7, 4.6)

The mCRc rate was **76.4**% compared to the CRc rate of 54% (using the same response parameters) in the single agent Gilt ADMIRAL phase 3 study[2]

Inhibition of FLT3 synergizes with venetoclax via 2 proposed mechanisms in *FLT3*-mutated AML



Note: Venetoclax + gilteritinib is a combination therapy under investigation and is not EMA-approved for the treatment of patients with AML.

1. Altman JK, *et al.* EHA 2021; Abstract S135 (Oral presentation);
2. Perl AE, *et al. N Engl J Med* 2019; **381**:1728–1740 (incl. suppl.); 3. Ma J, *et al. Clin Cancer Res* 2019; **25**:6815–6826.

Clinical Trials in Stem Cell Transplantation: a Major Unmet Need in 2021

- Stem cell transplantation is an increasingly important curative treatment modality for children and adults.
- Despite the almost universal availability of stem cell donors many patients die of transplant toxicity or recurrent disease.
- >50% of patients die post transplant as a result of regimen related toxicity or relapse.
- <5% of patients enter prospective transplant trials.
- Basic scientific advances have underpinned the development of new therapies but their adoption into routine transplant practice is very slow

IMPACT Overview and Structure

- ✓ £3.4 million funding secured from Anthony Nolan, NHSBT and Leuka for four year pilot of IMPACT (Platform for Accelerated Trials) with aim of delivering 9-12 stem cell transplant RCTs
- ✓ Central Hub at the University of Birmingham CRCTU: responsible for trial design, setup, management and publication
- ✓ 11 funded transplant centres able to recruit to IMPACT studies
- ✓ 11 affiliated transplant centres able to recruit to IMPACT studies

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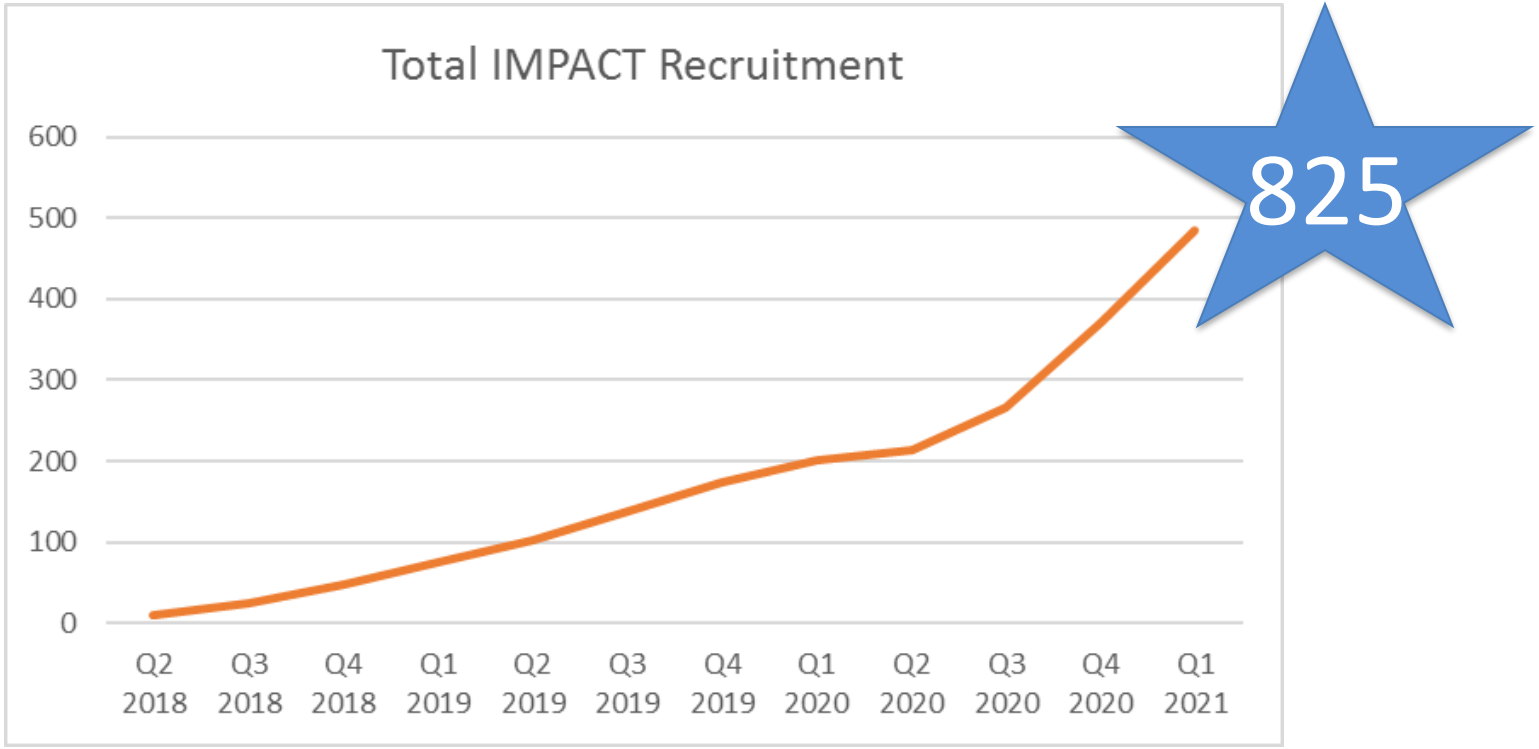
IMPACT Recruitment



Conclusions

- Management of refractory/relapse disease remains a major challenge and novel treatment strategies are required
- Targeted therapies (gilteritinib and venetoclax) represent potential game-changes-eitehr as monotherapy or in combination with intensive chemotherapy
- Hypomethylating agents represent an important treatment option in selected patients who relapse post-allograft eitehr alone or in combination with lenalidomide or venetoclax
- Prospective trials with the ability to examine novel salvage and transplant strategies are urgently required

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Q&A session

APTITUDE HEALTH®

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Case based panel discussion – regional challenges in AML care

Presenters: Justin Loke, Sonia Jaramillo Segura

Faculty panel: Naval Daver, Charles Craddock, Richard Schlenk

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Regional challenges in AML care – case 1

Justin Loke

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Case Presentation

Dr Justin Loke
CRUK-AACR Transatlantic Fellow
Birmingham, UK and Boston, USA

APTITUDE HEALTH

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67-Year-Old Female Patient

- AML, diagnosed – significantly dysplastic features on morphology
- No significant past medical history
- Lives independently with partner, ECOG PS 1

- CPX-351 × 2 cycles – uneventful, morphological CR

- Normal karyotype, *DNMT3A, TET2, RAD21, NPMI, FLT3-ITD* (low AR), *CEBPA* mutations

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Options for Consolidation?

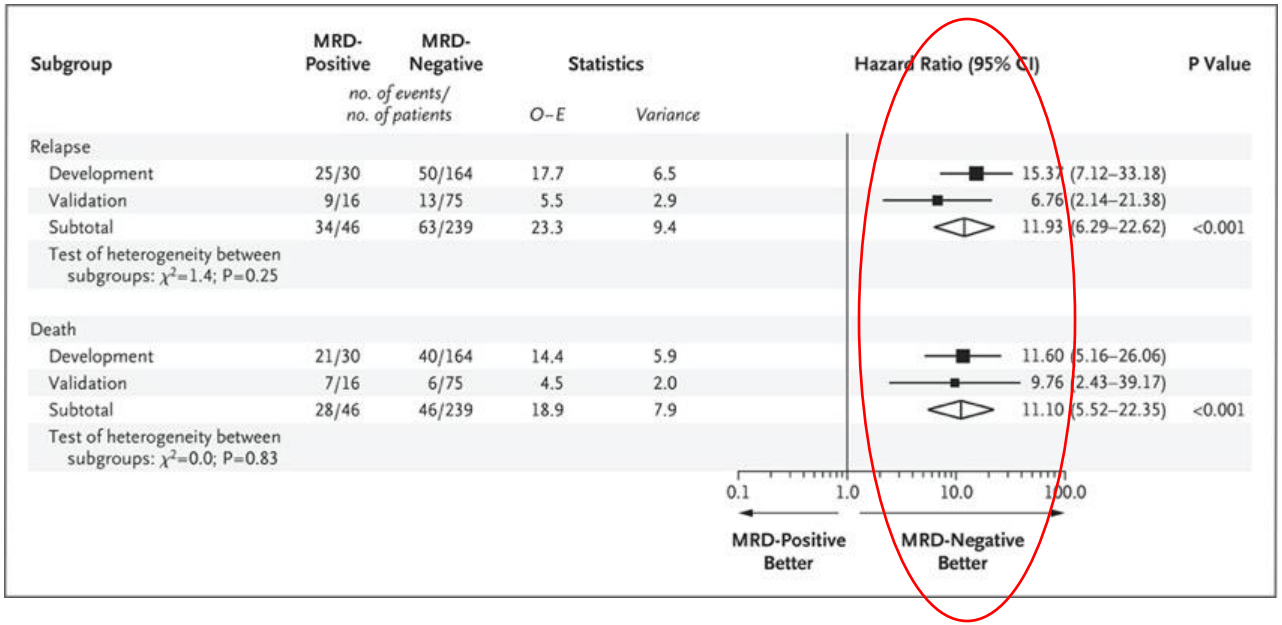
a) Further cycle of CPX-351 alone

b) Switch to midostaurin combination consolidation and maintenance

c) RIC allograft only if *NPM1* MRD results are high

d) RIC allograft regardless of *NPM1* MRD results

Presence of MRD Predicts for Relapse After Second Course of Chemotherapy for AML With *NPM1* Mutation



Irrespective of co-occurring mutation or FLT3 ITD ratio?

Study of younger patients, numbers small in subgroups

Ivey A, et al. *N Engl J Med.* 2016.

The NEW ENGLAND JOURNAL of MEDICINE

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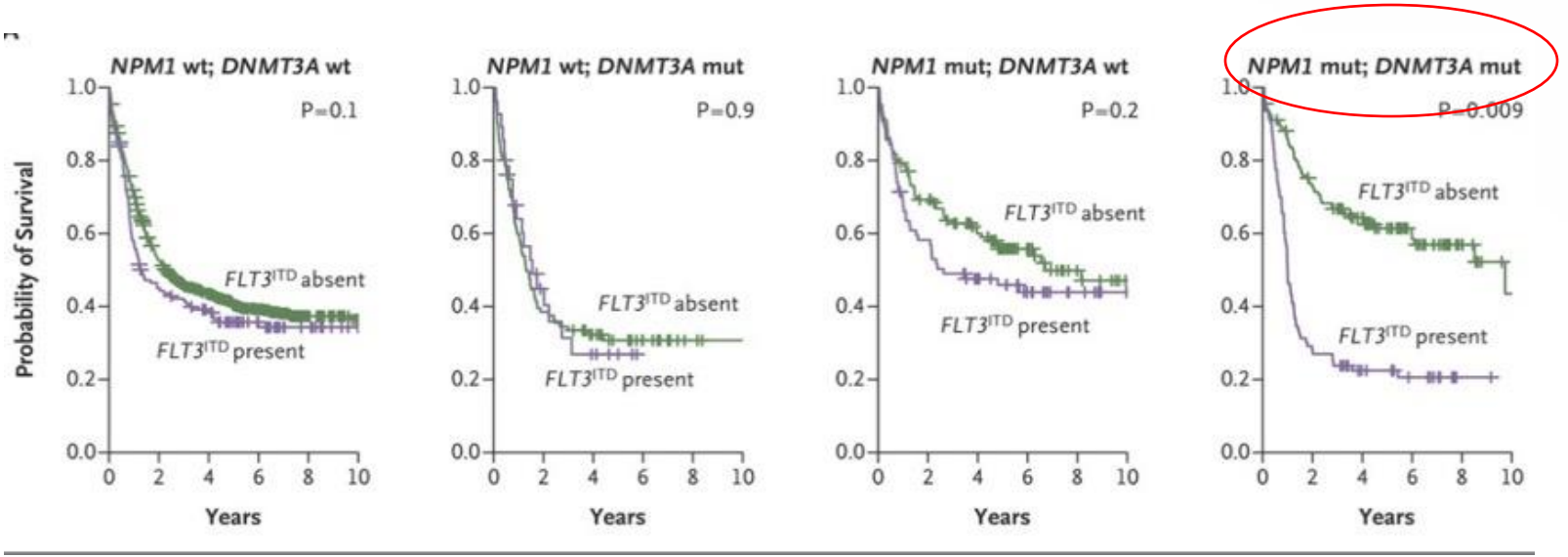
Influence of Gene-Gene Interactions on Overall Survival

NPM1, DNMT3A, FLT3^{ITD}

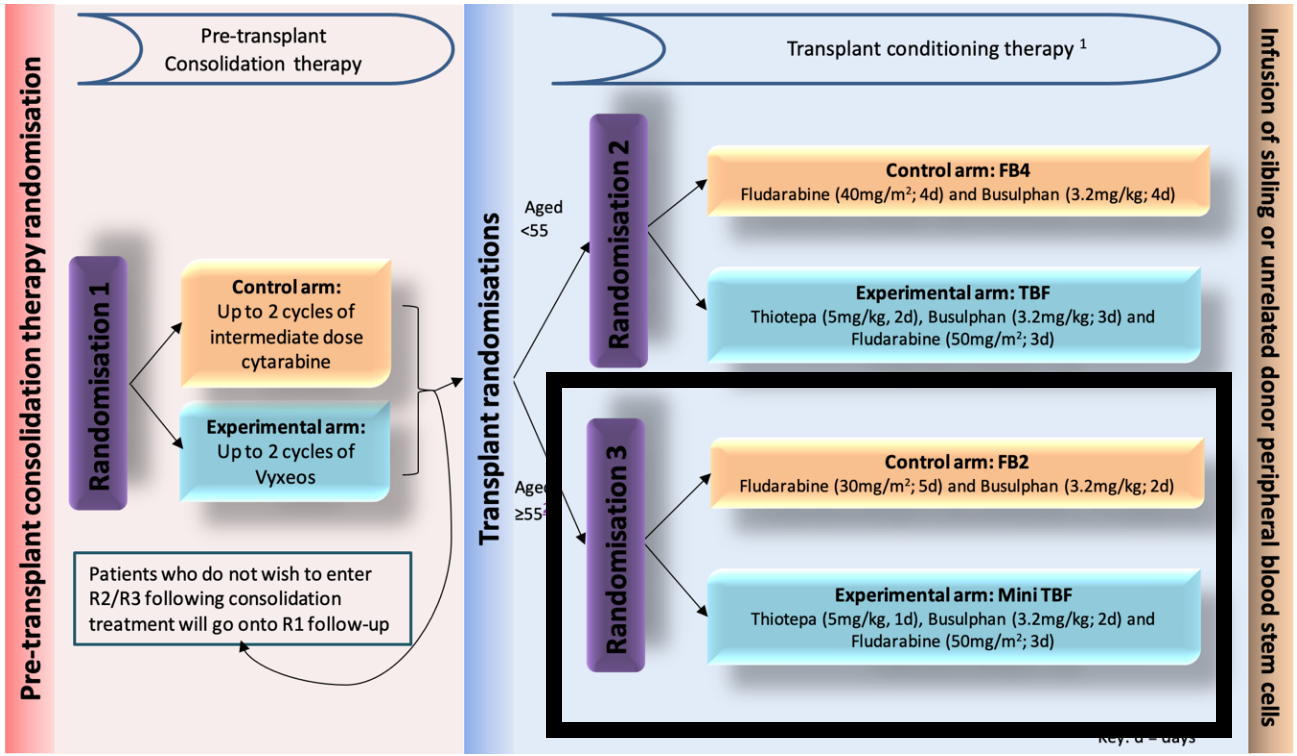


Papaemmanuil E, et al. *N Engl J Med.* 2016;374:2209-2221.

The NEW ENGLAND JOURNAL of MEDICINE

NPM1 MRD post course 2 positive in peripheral blood

TRANSPLANT DETAILS: UK IMPACT COSI trial, reduced-intensity mini TBF-conditioned allograft from sibling donor



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Case

- Relapsed AML with *NPM1* mutation post-allograft, (+4 months)
  - 12% blasts, 87% donor chimerism, 60 bp *FLT3*-ITD (8%), TET2 (6%), RAD21 (4%), *NPM1* positive

- Options?

a) Intermediate dose/intensive chemotherapy (eg, Ara-C)

b) Venetoclax + Aza or LDAC

c) Straight to donor lymphocyte infusion

d) Gilteritinib

Global Leukemia Academy

Case

- Relapsed AML with *NPM1* mutation post-allograft, (+4 months)
  - 12% blasts, 87% donor chimerism, 60 bp *FLT3*-ITD (8%), TET2 (6%), RAD21 (4%), *NPM1* positive

- Gilteritinib 120 mg od
  - Complications: cytopenias especially thrombocytopenia, normal QTc
  - Post cycle 1: Hypoplastic complete remission (5% cellularity)

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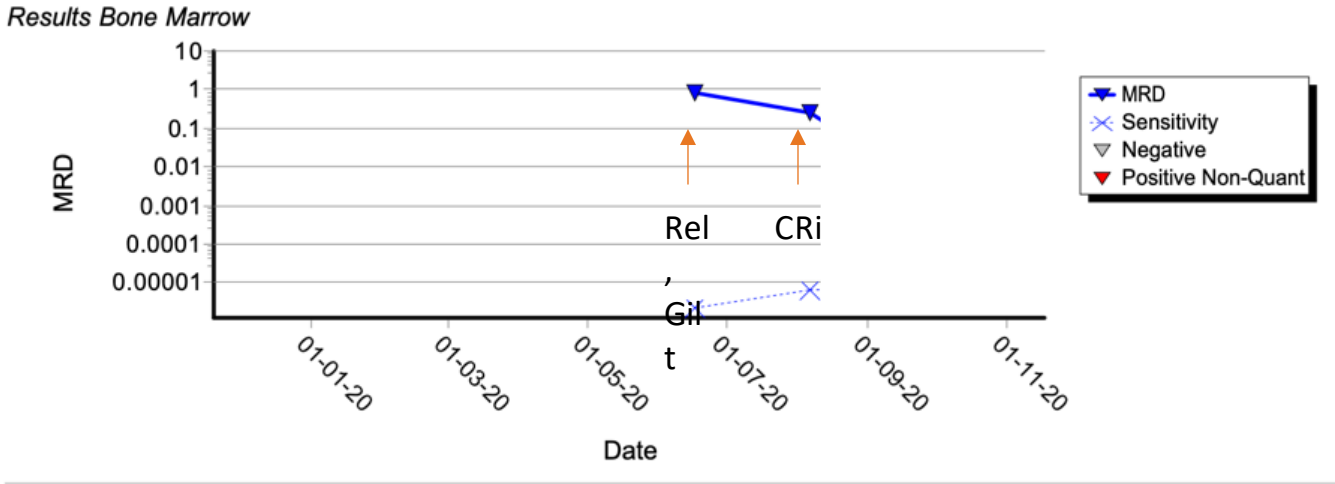
Interpreting Response to Gilteritinib

Table 2. Antileukemic Responses (Intention-to-Treat Population).*

Variable	Gilteritinib (N=247)	Salvage Chemotherapy (N=124)	Hazard Ratio or Risk Difference (95% CI)†
Median overall survival (95% CI) — mo	9.3 (7.7–10.7)	5.6 (4.7–7.3)	0.64 (0.49–0.83)
Median event-free survival (95% CI) — mo	2.8 (1.4–3.7)	0.7 (0.2–NE)	0.79 (0.58–1.09)
Response — no. (%)			
Complete remission	52 (21.1)	13 (10.5)	10.6 (2.8–18.4)
Complete remission or complete remission with partial hematologic recovery	84 (34.0)	19 (15.3)	18.6 (9.8–27.4)
Complete remission with partial hematologic recovery	32 (13.0)	6 (4.8)	ND
Complete remission with incomplete hematologic recovery	63 (25.5)	14 (11.3)	ND
Complete remission with incomplete platelet recovery	19 (7.7)	0	ND
Partial remission	33 (13.4)	5 (4.0)	ND
No response	66 (26.7)	43 (34.7)	ND
Composite complete remission‡	134 (54.3)	27 (21.8)	32.5 (22.3–42.6)
Overall response	167 (67.6)	32 (25.8)	
Median duration of remission (95% CI) — mo§	11.0 (4.6–NE)	NE (NE–NE)	NE
Time to composite complete remission — mo	2.3±1.9	1.3±0.5	NA
Median leukemia-free survival (95% CI) — mo	4.4 (3.6–5.2)	6.7 (2.1–8.5)	NE

Perl A, et al. *N Engl J Med.* 2019.


Results Bone Marrow
MRD
10
1
0.1
0.01
0.001
0.0001
0.00001
Rel, Gil
CRi
01-01-20
01-03-20
01-05-20
01-07-20
01-09-20
01-11-20
Date
MRD
Sensitivity
Negative
Positive Non-Quant

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Case

- Relapsed AML with *NPM1* mutation (4%) post-allograft, (+4 months)
- Gilteritinib 120 mg od
  - Complications: cytopenias especially thrombocytopenia, normal QTc
  - Post cycle 1: Hypoplastic complete remission (5% cellularity)

- Options?

a) Donor lymphocyte infusion/CD34 top up

b) Continue current dose of gilteritinib

c) Increase dose of gilteritinib

d) Switch to alternative FLT3i

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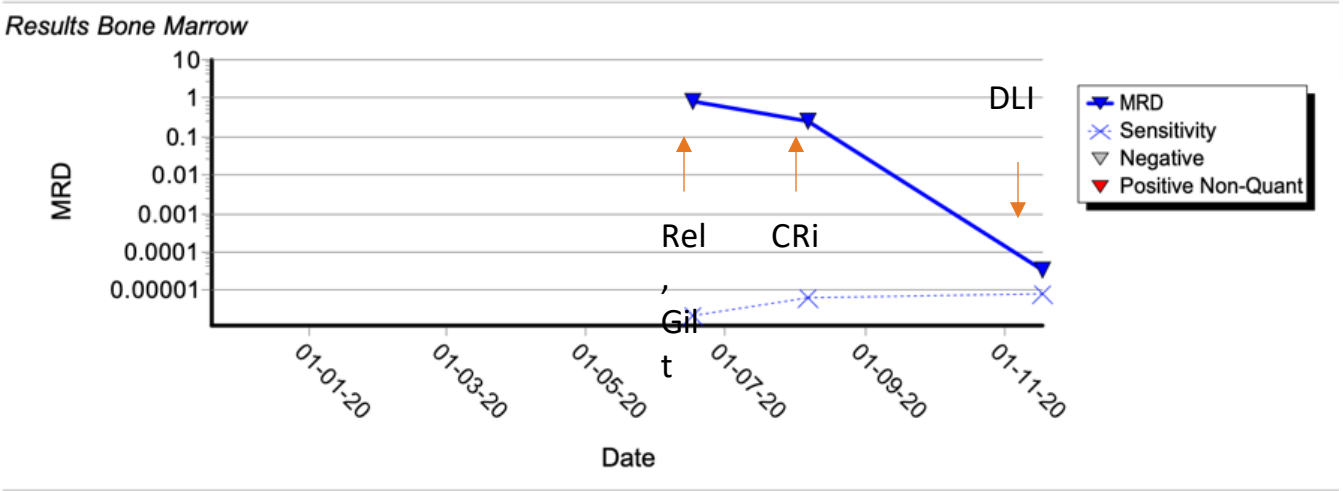
Case

- Relapsed AML with *NPM1* mutation (4%) post-allograft, (+4 months)
  - 12% blasts, 87% donor chimerism, 60 bp *FLT3*-ITD (8%), TET2 (6%), RAD21 (4%)
- Gilteritinib 120 mg od
  - Complications: cytopenias especially thrombocytopenia, normal QTc
  - Post cycle 1: Hypoplastic complete remission (5% cellularity)
- CD34-positive selected top-up and DLI
- T-cell chimerism 100% donor, 1% blasts


Results Bone Marrow
MRD
10
1
0.1
0.01
0.001
0.0001
0.00001
01-01-20
01-03-20
01-05-20
01-07-20
01-09-20
01-11-20
Date
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MRD
Sensitivity
Negative
Positive Non-Quant

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Summary

- Combined diagnostics and molecular monitoring allow accurate prognostication of patients with AML
- Decision to proceed to allograft reliant on accurate prediction of relapse risk and TRM
- Novel targeted therapies may provide treatment options that may be better for QoL
- Importance of consolidating responses and dealing with new treatment toxicities

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Discussion – case 1

Faculty panel: Naval Daver, Charles Craddock, Richard Schlenk

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Regional challenges in AML care – case 2

Sonia Jaramillo Segura

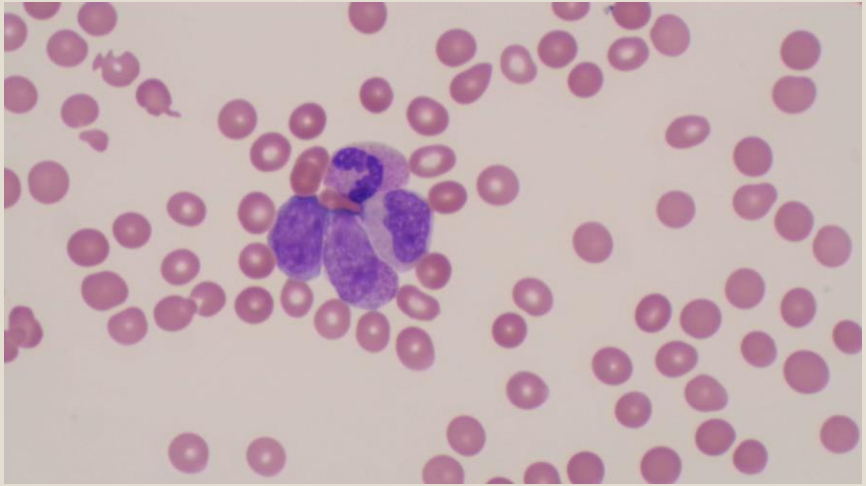
APTITUDE HEALTH

HEIDELBERG
FACULTY OF
MEDICINE

AML Clinical Case

SONIA JARAMILLO SEGURA – UNIVERSITY HOSPITAL HEIDELBERG

Medical History



First consultation: 12/2017

Age: 52

No prior comorbidities

Symptoms: dyspnea, fatigue, lethargy, and gingival bleeding

Laboratory Findings and Classification

Blood count: leukocytes 10.52/nL, platelets 836/nL, Hb 7.4 g/dL, blasts (PB) 29%

Bone marrow cytology: FAB M2, 32% blasts

Immunophenotyping: HLA-DR 68.31%, **CD33 56.56%**, CD11c 54.4%, CD13 54.9%, CD15 26.06%, CD41 13.26%, MPO 15.43%, CD117 40.56%

Cytogenetics: 46XX

Molecular genetics: ***NPM1*** **mutated,** *CEBPA*+1bp TAD-insertion, *IDH* (0.4%)

WHO classification: AML with recurrent genetic abnormalities

ELN classification: favorable risk

Question #1

In your practice, what would be the induction regimen for this patient?

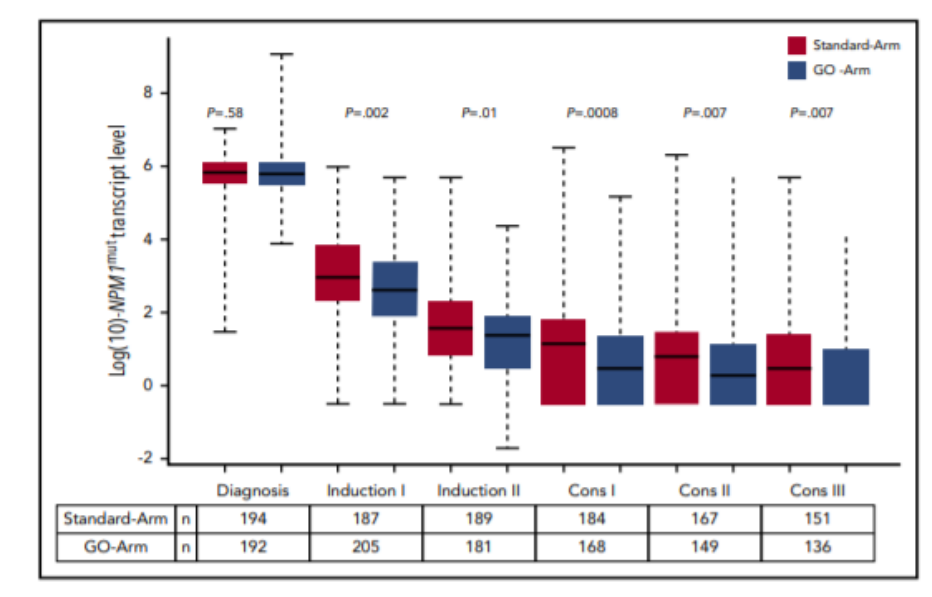
A. 7+3

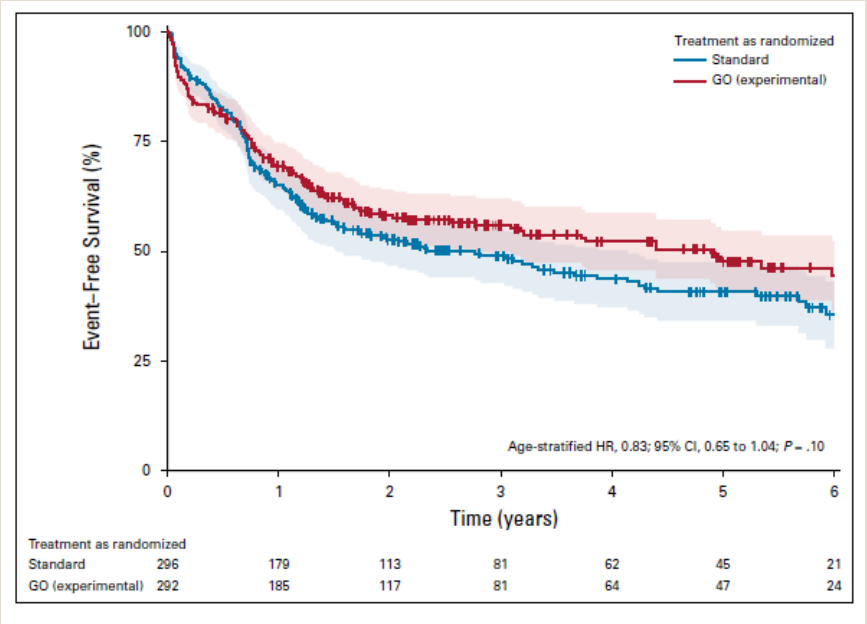
B. 7+3 + GO

C. Clinical study

D. Other

Impact of Gemtuzumab Ozogamicin on *NPM1* MRD





Kapp-Schwoerer S, et al. *Blood*. 2020;136(26):3041-3050.

Schlenk RF, et al. JCO. 2020; 38:6, 623-632 .

Therapy and Course of Disease

12/2017 – 01/2018:	***DaunoDouble*** study induction I and II (7+3) (NCT02140242)
01/2018:	Hematologic complete remission (CR) Haploidentical sister identified Unrelated donor search started
03–04/2018:	Consolidation I and II with 2 × 3 g cytarabine, d 1–3
08/2018:	Molecular remission
02/2020:	Molecular relapse: *NPM1* with $602/10^4$ *ABL* copies in bone marrow (BM) and $9/10^4$ *ABL* copies in peripheral blood (PB)

Question #2

In your practice, what do you do if you detect an *NPM1* increase after consolidation therapy?

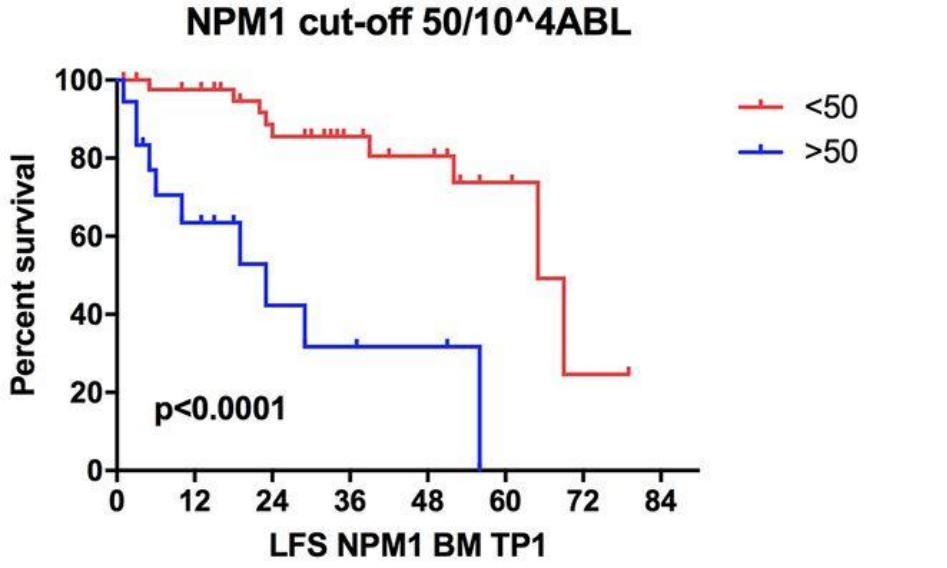
A. Control until *NPM1* >50/10^4 *ABL* and then initiate treatment

B. Control until *NPM1* >200/10^4 *ABL* and then initiate treatment

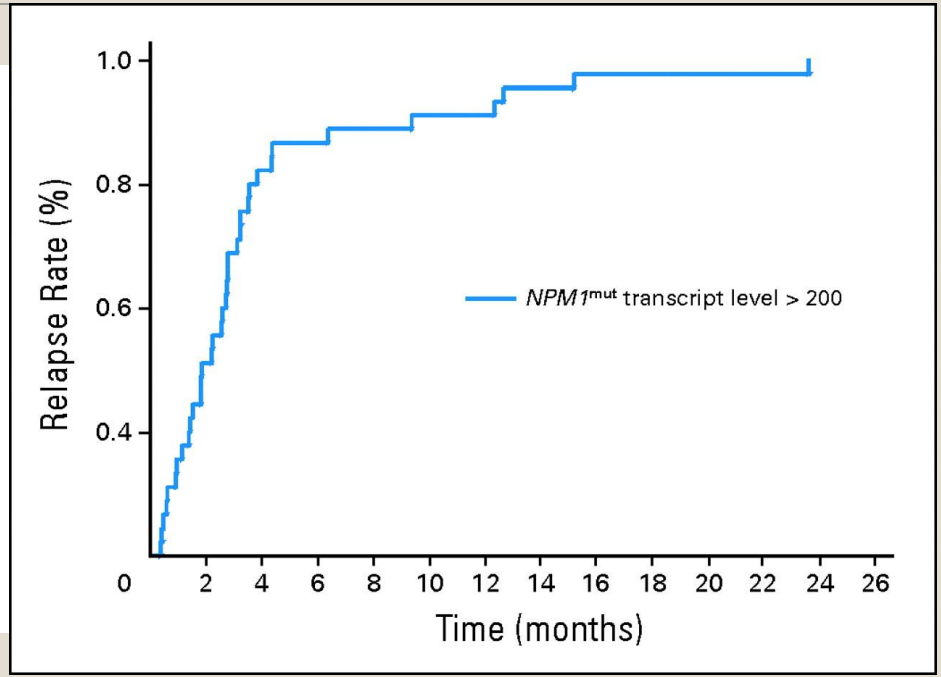
C. Initiate treatment as soon as *NPM1* turns positive

D. Initiate treatment after observing a hematologic relapse

NPM1 and Leukemia-Free Survival



Schieppati F, et al. Blood. 2017;130(suppl 1): 3931.



Krönke J, J Clin Oncol. 2011 Jul 1;29(19):2709-16.

Therapy and Course of Disease

02/2020: Inclusion in the **FLYSYN** study (NCT02789254)
FLYSYN 0.5 mg/m² day 1, FLYSYN 14.5 mg/m² day 2, FLYSYN 15 mg/m² day 15, FLYSYN 15 mg/m² day 29
FLYSYN: chimeric and Fc-optimized IgG1 antibody targeting the FLT3 receptor; mode of action – apoptosis, CDC, ADCC

05/2020: Complete remission, *NPM1* 77/10^4 *ABL* copies in BM, *NPM1* 4/10^4 *ABL* copies in PB

11/2020: *NPM1* 323/10^4 *ABL* copies in BM

11/2020: Inclusion in the **PemAZA** study (azacitidine-pembrolizumab) (NCT03769532)
Pembrolizumab every 3 weeks, azacitidine d 1–7 every 4 weeks

12/2020: Rapidly increasing levels of *NPM1*: *NPM1* 4273/10^4 *ABL* copies in BM
Discontinuation of therapy in the **PemAZA** study

Question #3

In your practice, what therapy would you give next?

A. Azacitidine-venetoclax

B. HAM

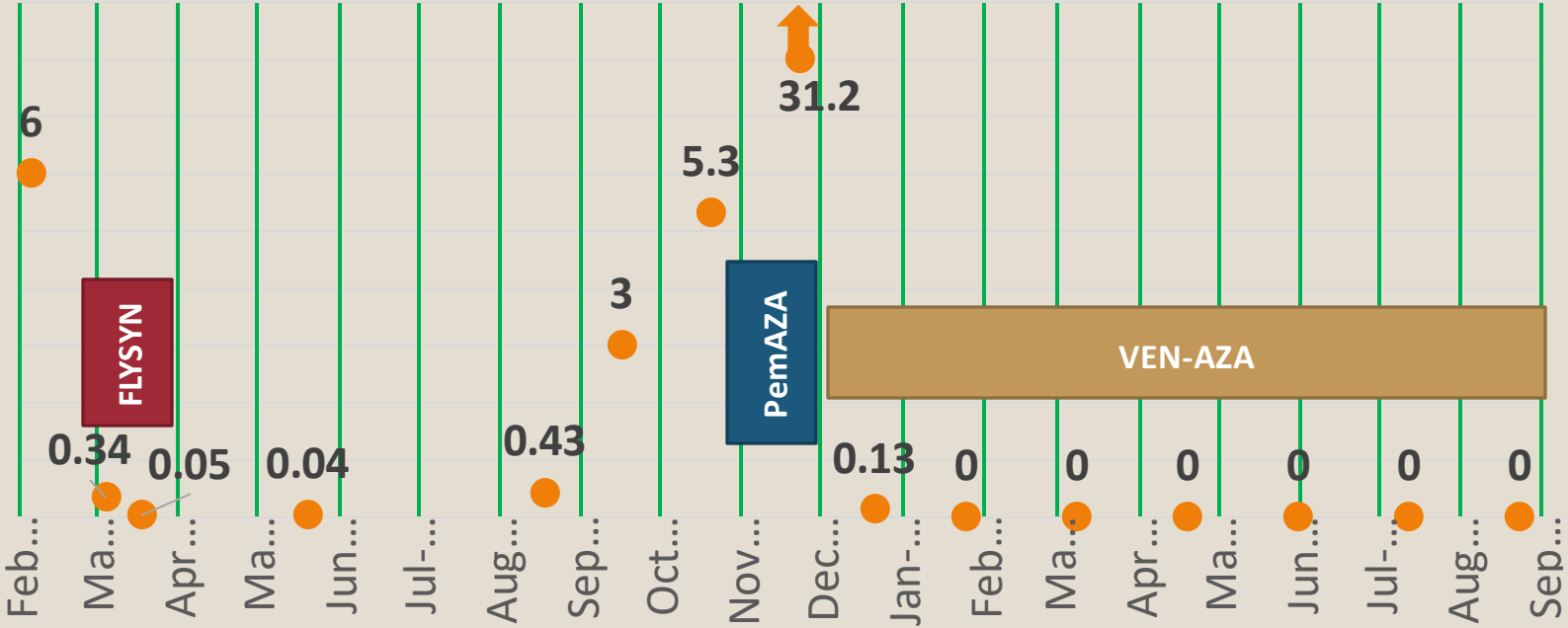
C. FLAG-IDA ± gemtuzumab ozogamicin

D. Upfront allogeneic stem cell transplantation (allo-HCT)

Therapy and Course of Disease

12/2020:	Azacitidine 75 mg/m² for 7 days and venetoclax 400 mg for 28 days
01/2021:	Hematologic CR, *NPM1* 0/10^4 *ABL* copies in BM
05/2021 – present:	Azacitidine 75 mg/m² for 5 days and venetoclax 400 mg for 14 days No serious adverse events
10/2021:	Hematologic CR, *NPM1* 0/10^4 *ABL* copies in BM

NPM1/ABL [%] After Molecular Relapse



Question # 4

When do you transplant a patient with *NPM1* molecular relapse?

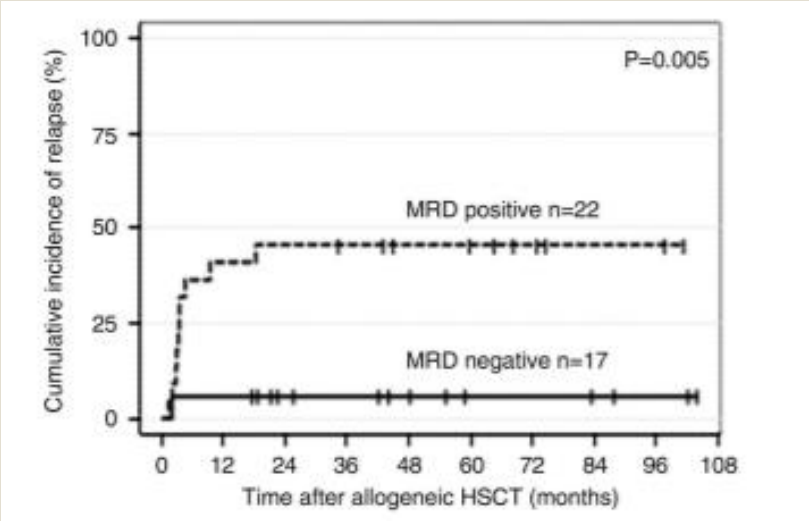
A. After achieving MRD negativity

B. Directly after salvage therapy

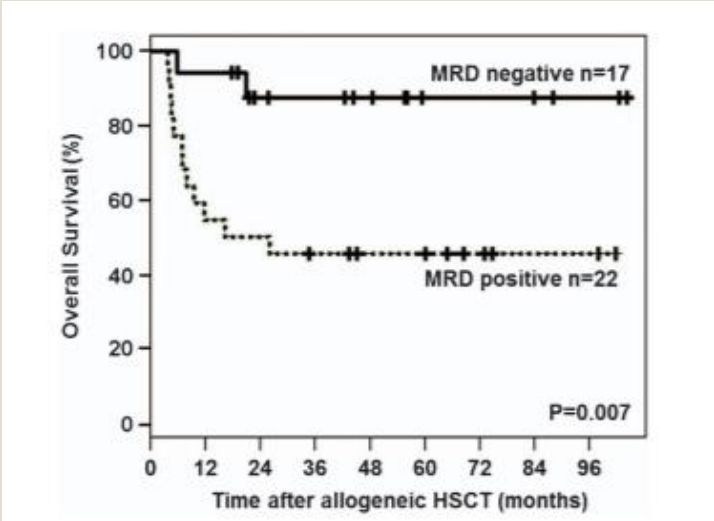
C. I don’t transplant patients with molecular relapse

D. After achieving a significant reduction of *NPM1* MRD

Impact of *NPM1* MRD on OS and RFS and Incidence of Relapse After Allo-HCT



Relapse-free survival (RFS)



Overall survival (OS)

Kayser S, et al. *Blood Cancer J.* 2016;6:e449.

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Discussion – case 2

Faculty panel: Naval Daver, Charles Craddock, Richard Schlenk

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Educational ARS questions

Naval Daver

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Repeated Question 1

Which of the following factors are important in assessing AML patients at diagnosis? Select all that apply.

a) Adverse genetic alterations
b) Age
c) Comorbidities
d) Performance status
e) Prior cytotoxic therapy
f) Prior myelodysplasia

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Repeated Question 2

Which patients were not included in the VIALE-A study?

a) Patients >75 years of age
b) Patients <75 years of age with ECOG PS 3
c) Patients <75 years of age with significant cardiac co-morbidity
d) Patients <75 years of age with significant pulmonary comorbidities
e) Patients <75 years of age with adverse cytogenetics

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Repeated Question 3

Which of the following is not true regarding HMA + venetoclax in AML?

a) The CR/CRi with HMA+VEN in the VIALE-A was >65%

b) HMA+VEN improved median OS compared with HMA alone

c) Lab or clinical TLS is not seen with HMA+VEN in AML

d) The recommended daily dose of venetoclax (without azoles) was 400mg PO Qday in VIALE-A study

e) Neutropenia is commonly seen with HMA+VEN regimen

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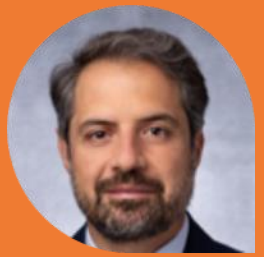
Closing remarks

Elias Jabbour



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