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Emerging and Practical Concepts and Controversies in Leukemias

24 April 2021

Virtual Breakout: Adult Leukemia Patients

APTITUDE HEALTH

Global Leukemia Academy

Welcome and Meeting Overview

Elias Jabbour

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Meet the Faculty

Elias Jabbour, MD
Professor of Medicine
Department of Leukemia
University of Texas
MD Anderson Cancer Center
Houston, TX, USA

Andre Schuh, MD
Associate Professor, University of Toronto
Staff Physician at Princess Margaret
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José Maria Ribera, MD
Chief of the Stem Cell Transplantation at University
Hospital 'Germans Trias I Pujol'
Head of the Clinical Hematology Department for
the Catalan Institute of Oncology
Badalona, Barcelona, Spain

Naval Daver, MD
Associate Professor
Department of Leukemia
University of Texas
MD Anderson Cancer Center
Houston, TX, USA

Eunice Wang, MD
Chief of the Leukemia Service
Roswell Park Comprehensive Cancer Center
Buffalo, NY, USA

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

Virtual Breakout: Adult ALL Patients (Day 2)

Chair: Elias Jabbour

TIME (UTC-3)	TITLE	SPEAKER
10.00 – 10.15	Session open • Educational ARS questions for the audience	Elias Jabbour
10.15 – 10.35	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens • Presentation (15 min) • Q&A (5 min)	Elias Jabbour
10.35 – 10.55	Current treatment options for relapsed ALL in adult and elderly patients (including COVID-19 and vaccination strategy) • Presentation (15 min) • Q&A (5 min)	José Maria Ribera
10.55 – 11.45	Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in adult and elderly patients Panelists: Elias Jabbour, José Maria Ribera, Andre Schuh, local experts Educational ARS questions for the audience	Roberta Demichelis and Wellington Silva
11.45 – 12.00	Break	
12.00 – 12.20	Personalized induction and maintenance approaches for AML • Presentation (15 min) • Q&A (5 min)	Naval Daver
12.20 – 12.40	Optimizing management of relapsed/refractory AML • Presentation (15 min) • Q&A (5 min)	Eunice Wang
12.40 – 13.15	Case-based panel discussion on regional challenges in AML care	Roberta Demichelis and Wellington Silva
13.15 – 13.30	Session close	Elias Jabbour

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Educational ARS Questions

Elias Jabbour

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Q

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

Q

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

Elias Jabbour, MD
Professor of Medicine
Department of Leukemia
The University of Texas MD Anderson Cancer Center, Houston, TX

Conflict of Interest Disclosure

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

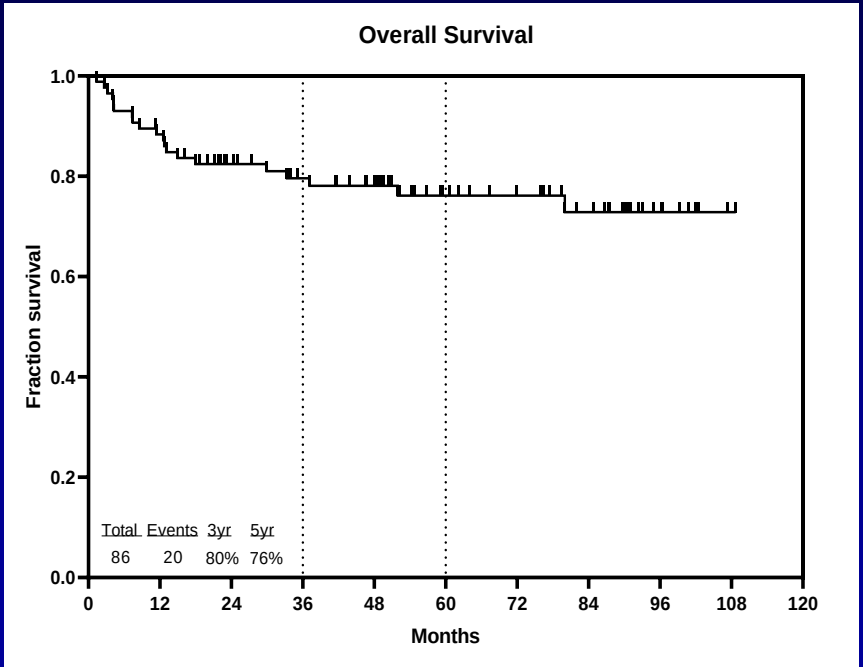
ALL Individualized Therapy in 2021

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	--

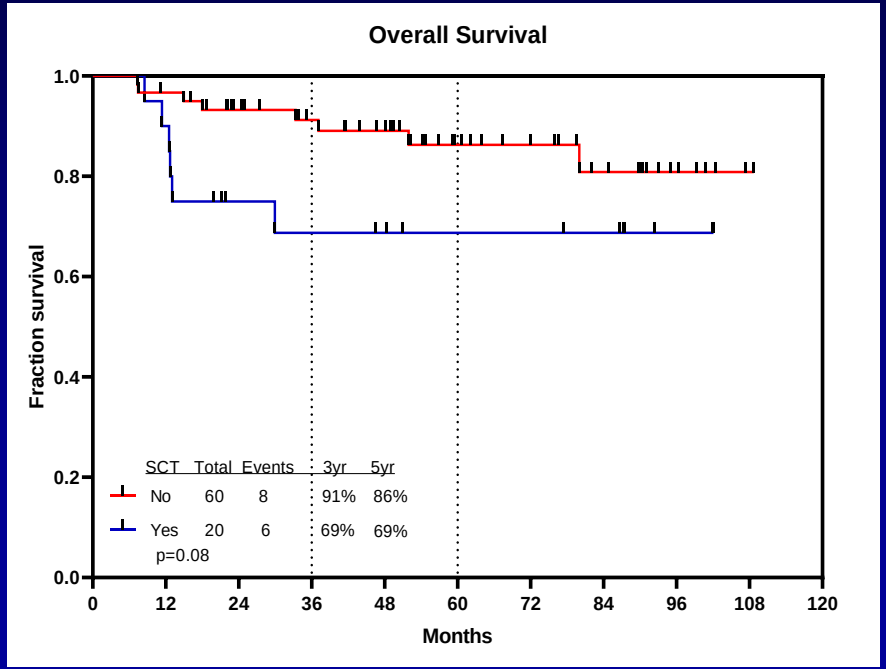
HyperCVAD + Ponatinib in Ph+ ALL

- 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

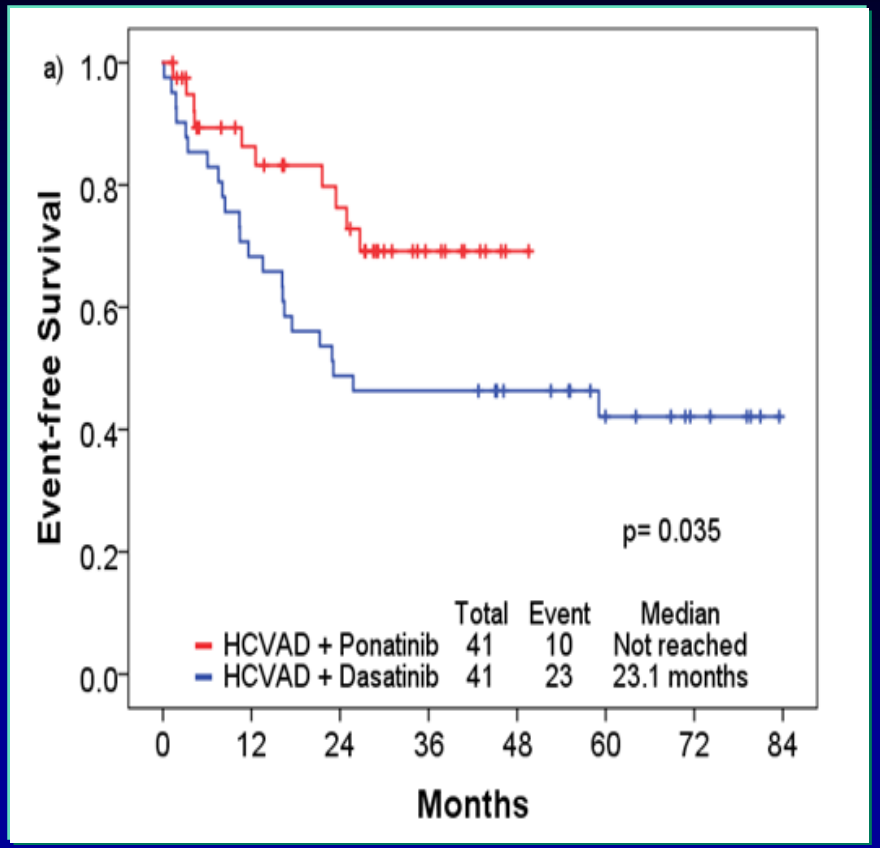


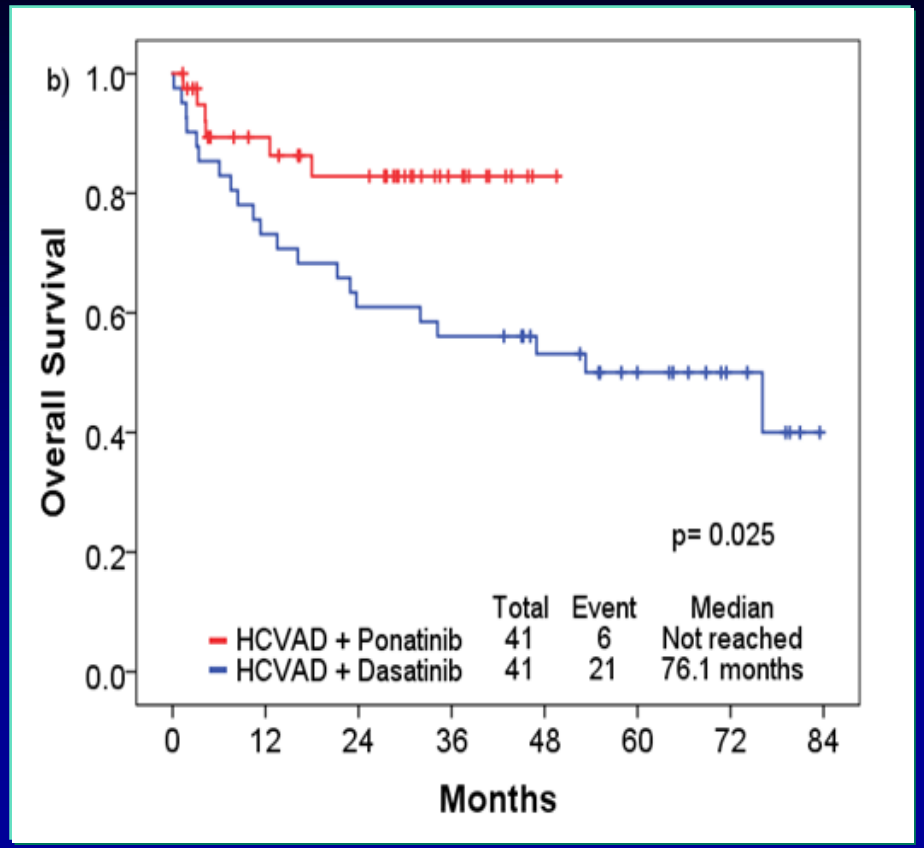
6-Month Landmark



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

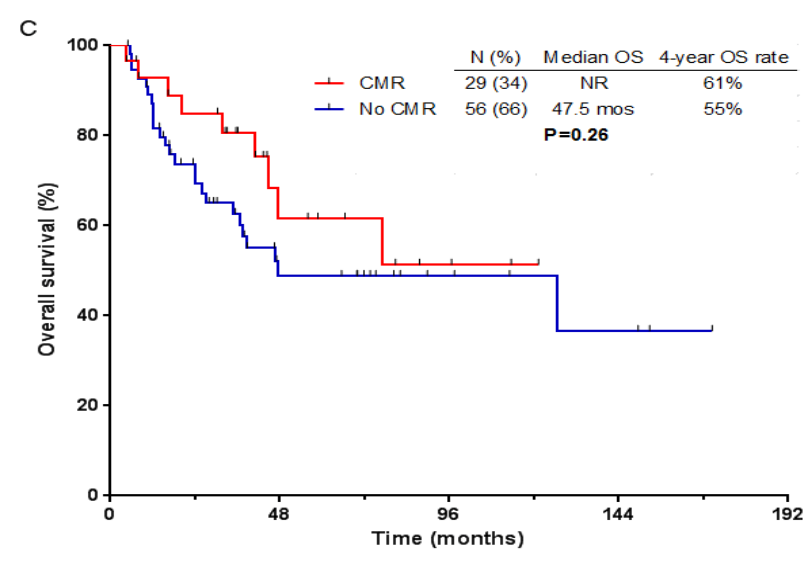




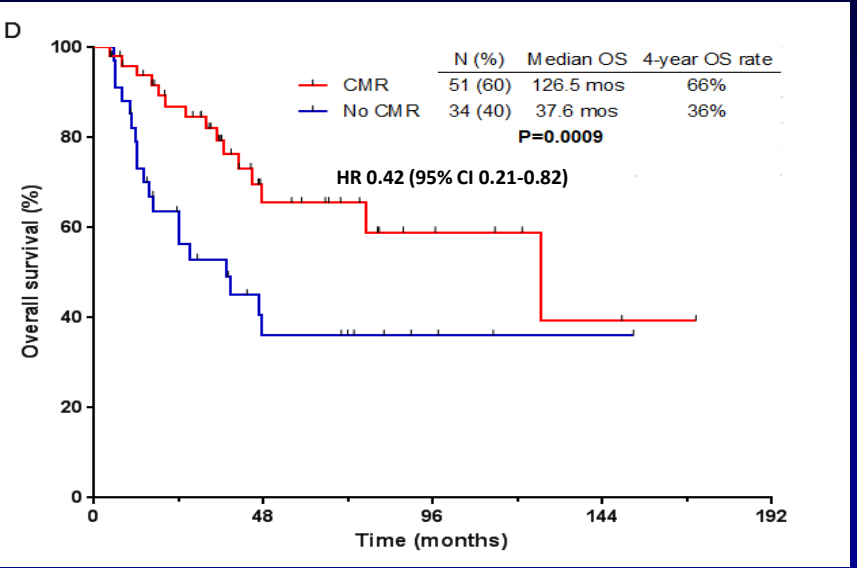
Sasaki et al. *Cancer*. 2016;122(23):3650-3656.

CMR in Ph+ ALL: OS for CMR vs Others

At CR



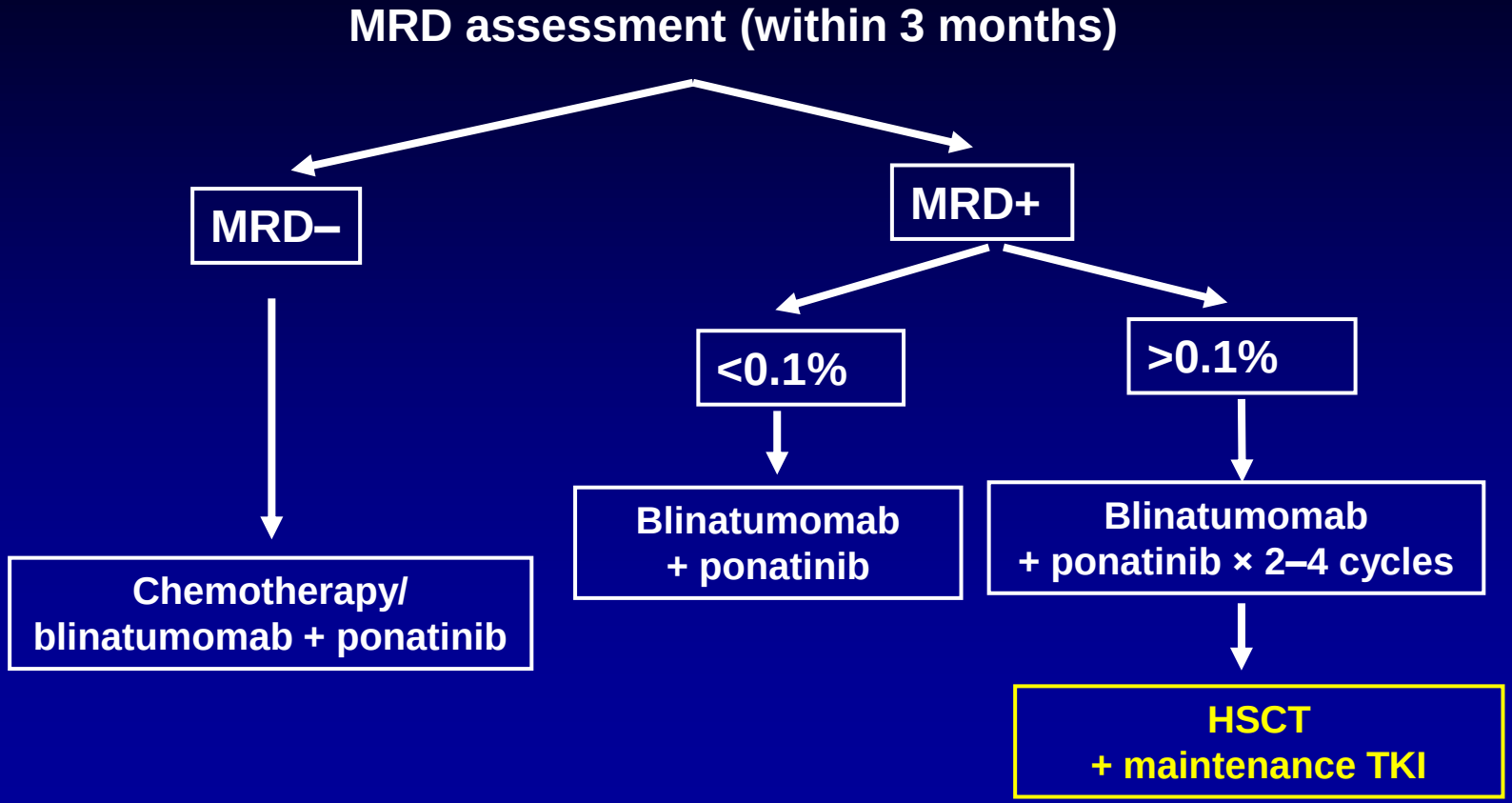
At 3 months



- **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

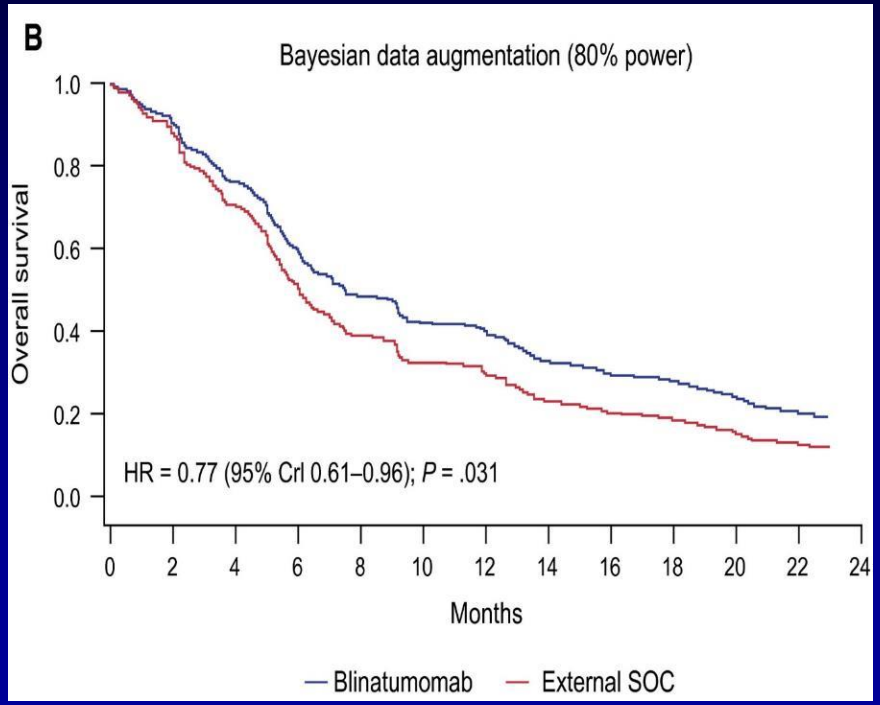


Short et al. *Blood*. 2016;128(4):504-507; Sasaki et al. *Blood*. 2019;134:abstract 1296; Samra et al. *Blood*. 2019;134:abstract 3894.

Blinatumomab and Inotuzumab in R/R Ph+ ALL

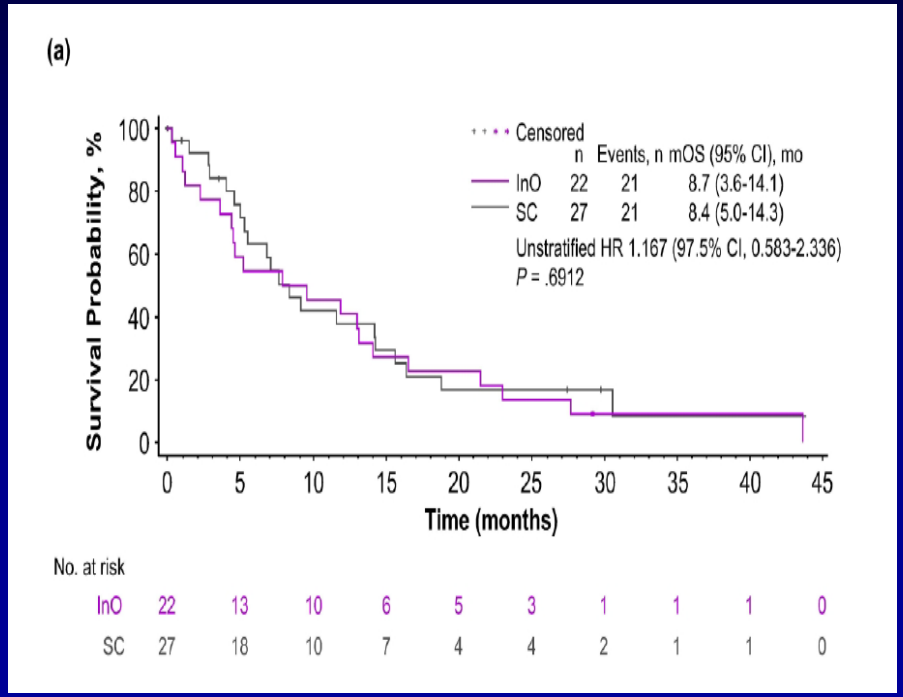
Blina vs SOC

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



Ino vs SOC

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

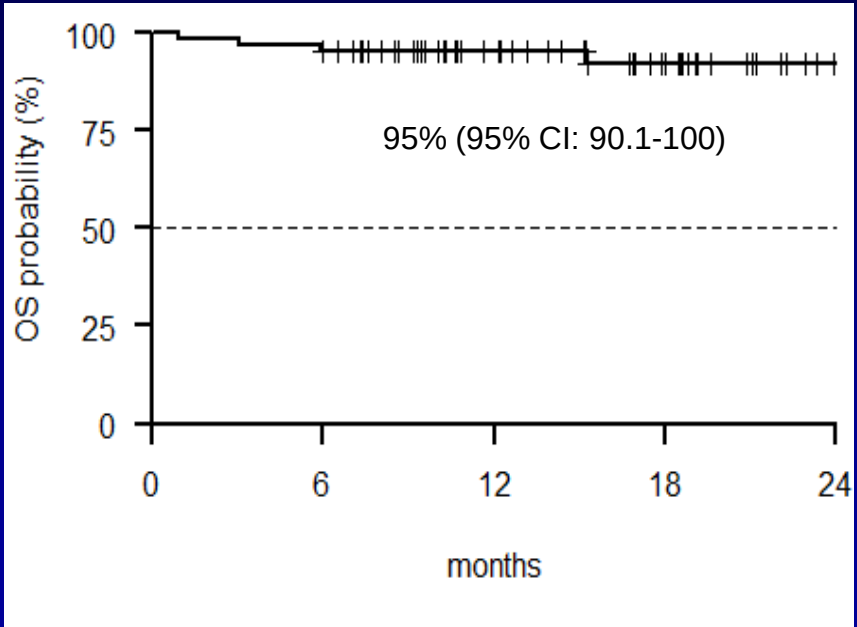


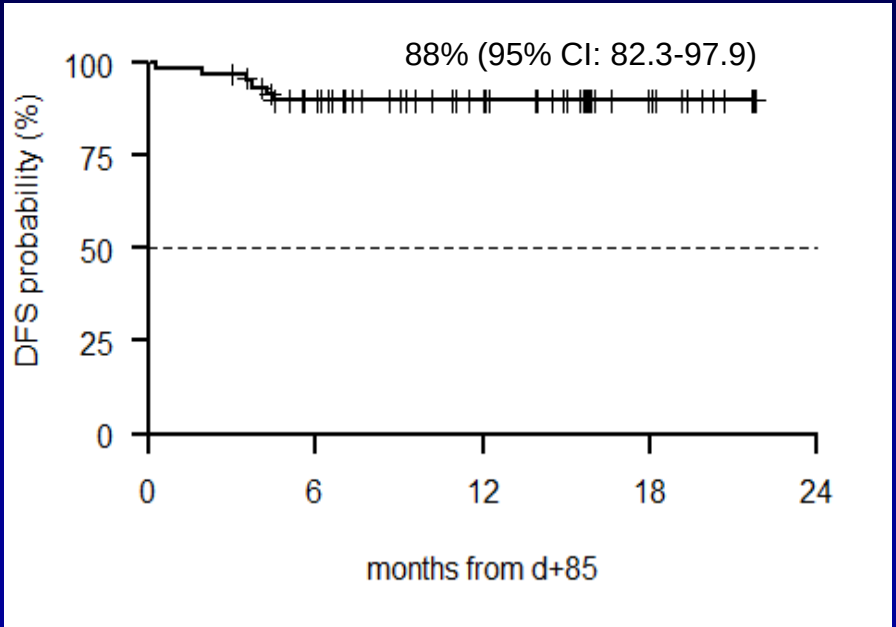
Rambaldi et al. *Cancer.* 2019;126:304-310.

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

Dasatinib-Blinatumomab in Ph+ ALL

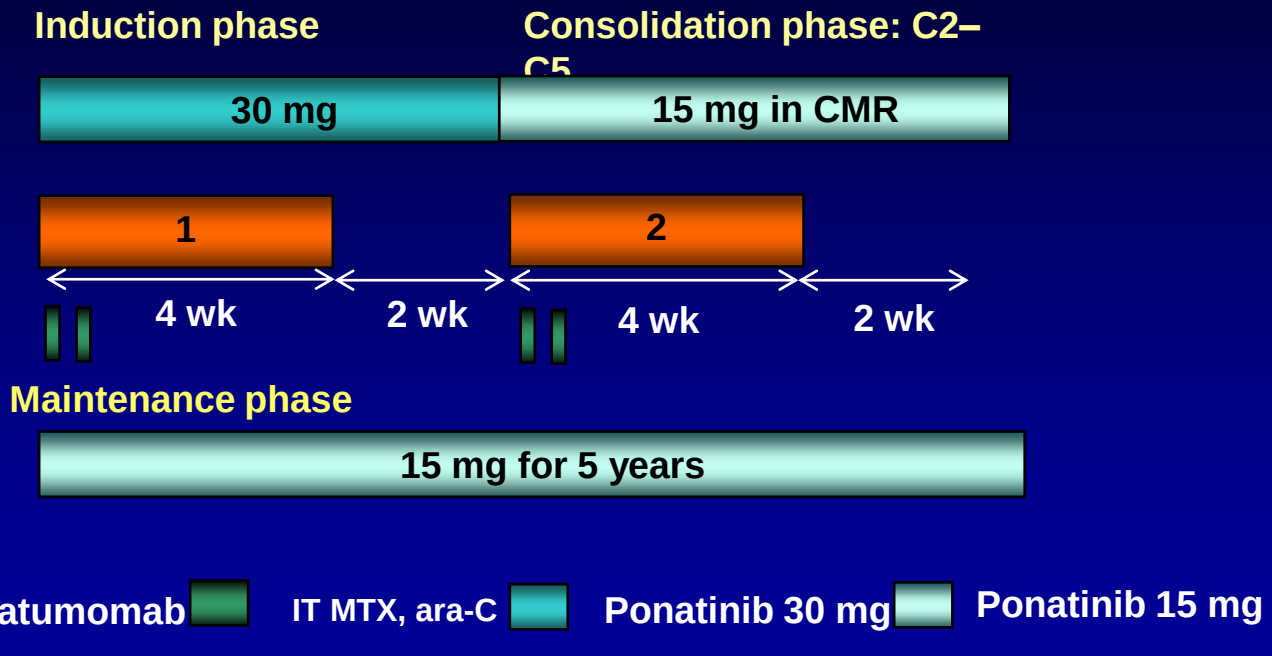
- 63 pts, median age 54 yr (24–82); Dasatinib 140 mg/D × 3 mo; add blinatumomab × 2–5
- 53 post–dasa-blina × 2 – molecular response 32/53 (60%), 22 CMR (41%); MRD ↑ in 15, 6 *T315I*; 12-mo OS 95%; DFS 88%





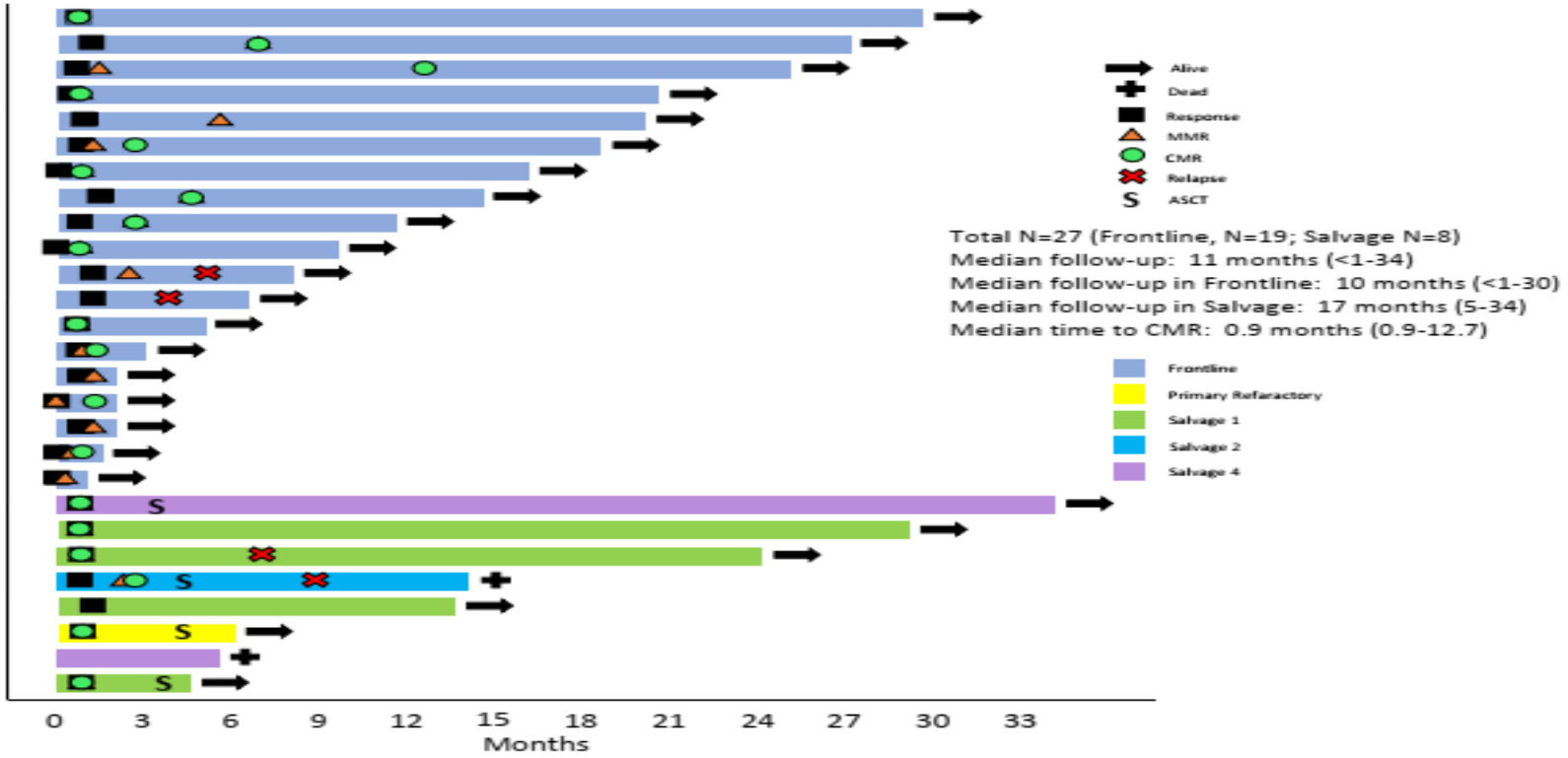
Foa et al. *N Engl J Med.* 2020;383:1613.

Blinatumomab-Ponatinib in Ph+ ALL



Assi et al. *Clin Lymphoma Myeloma Leuk.* 2017;17(12):897-901.

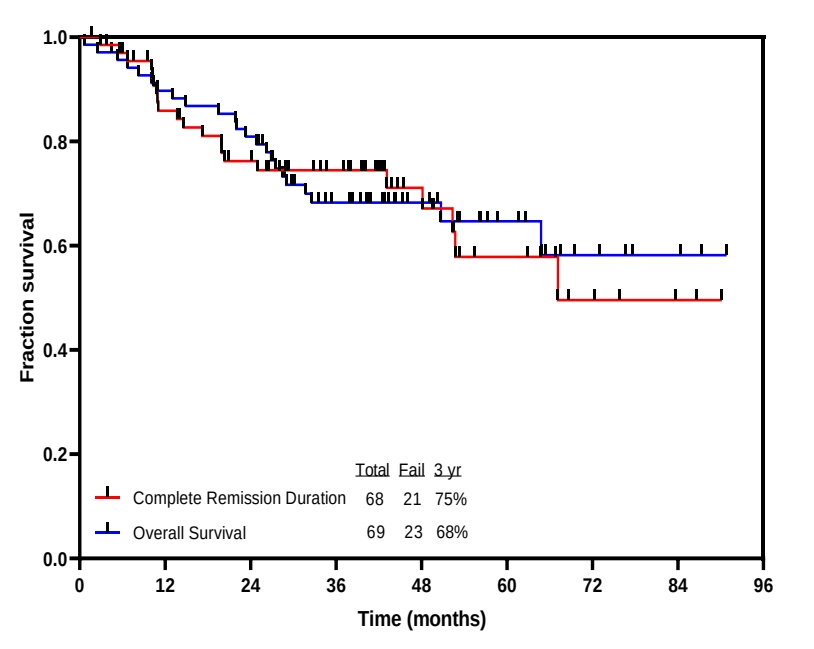
Blinatumomab + Ponatinib Swimmer Plot (N = 27)



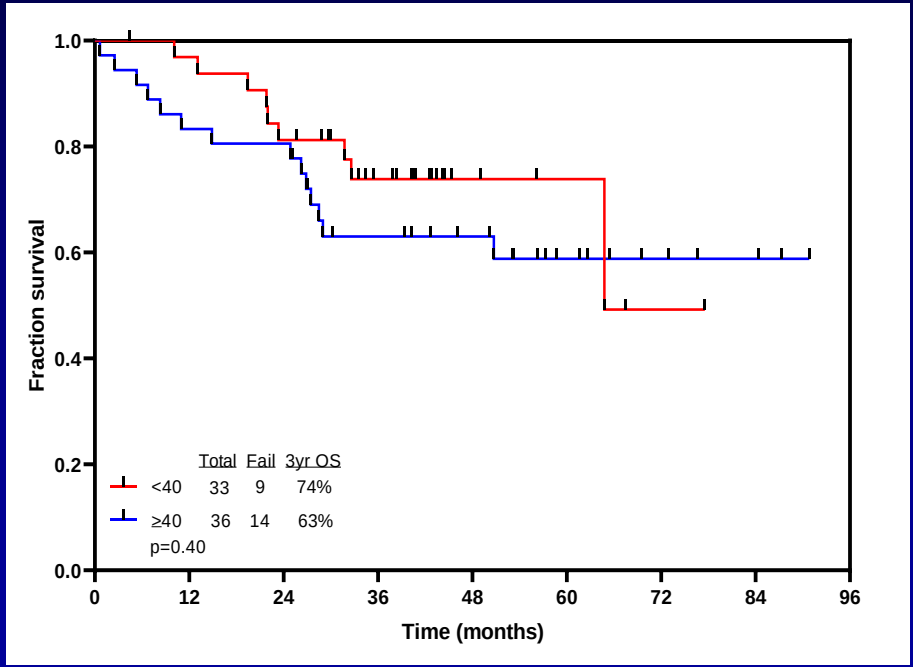
HCVAD + Ofatumumab: Outcomes (N = 69)

- Median follow up of 44 months (4–91)
- CR 98%, MRD negativity 93% (at CR 63%), early death 2%

CRD and OS Overall

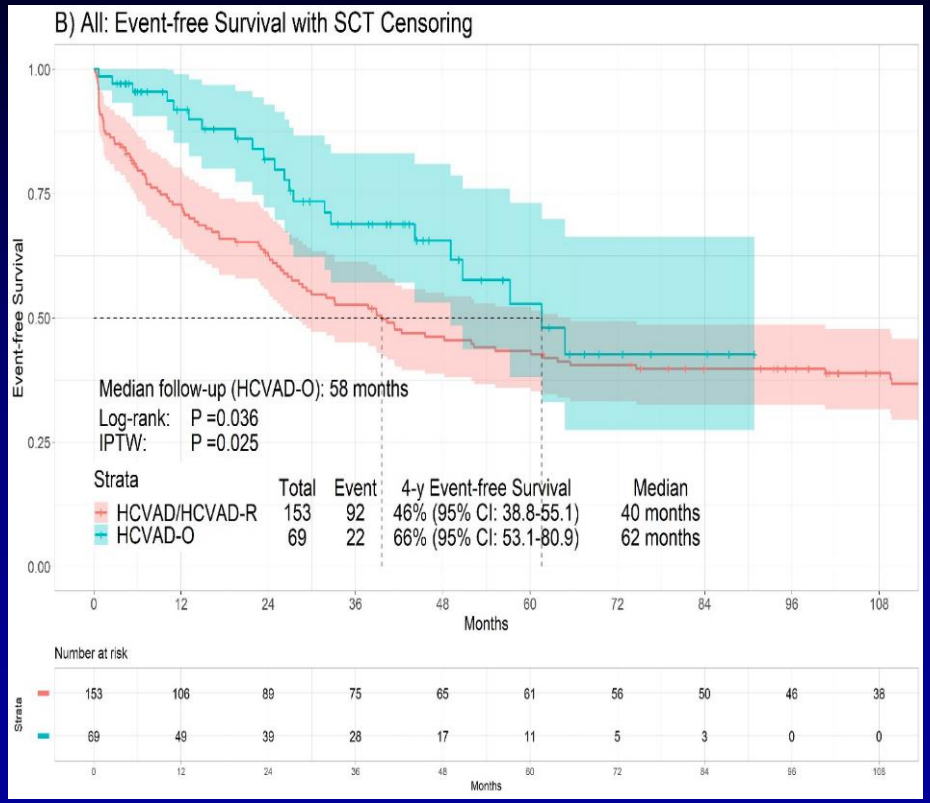


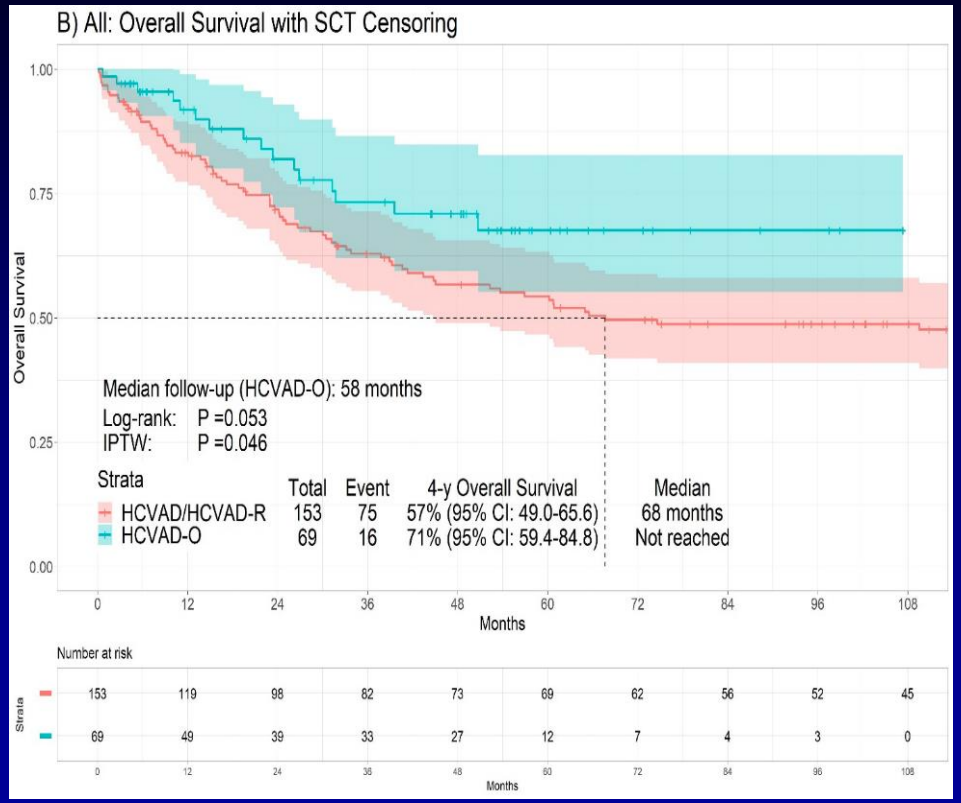
OS by Age



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

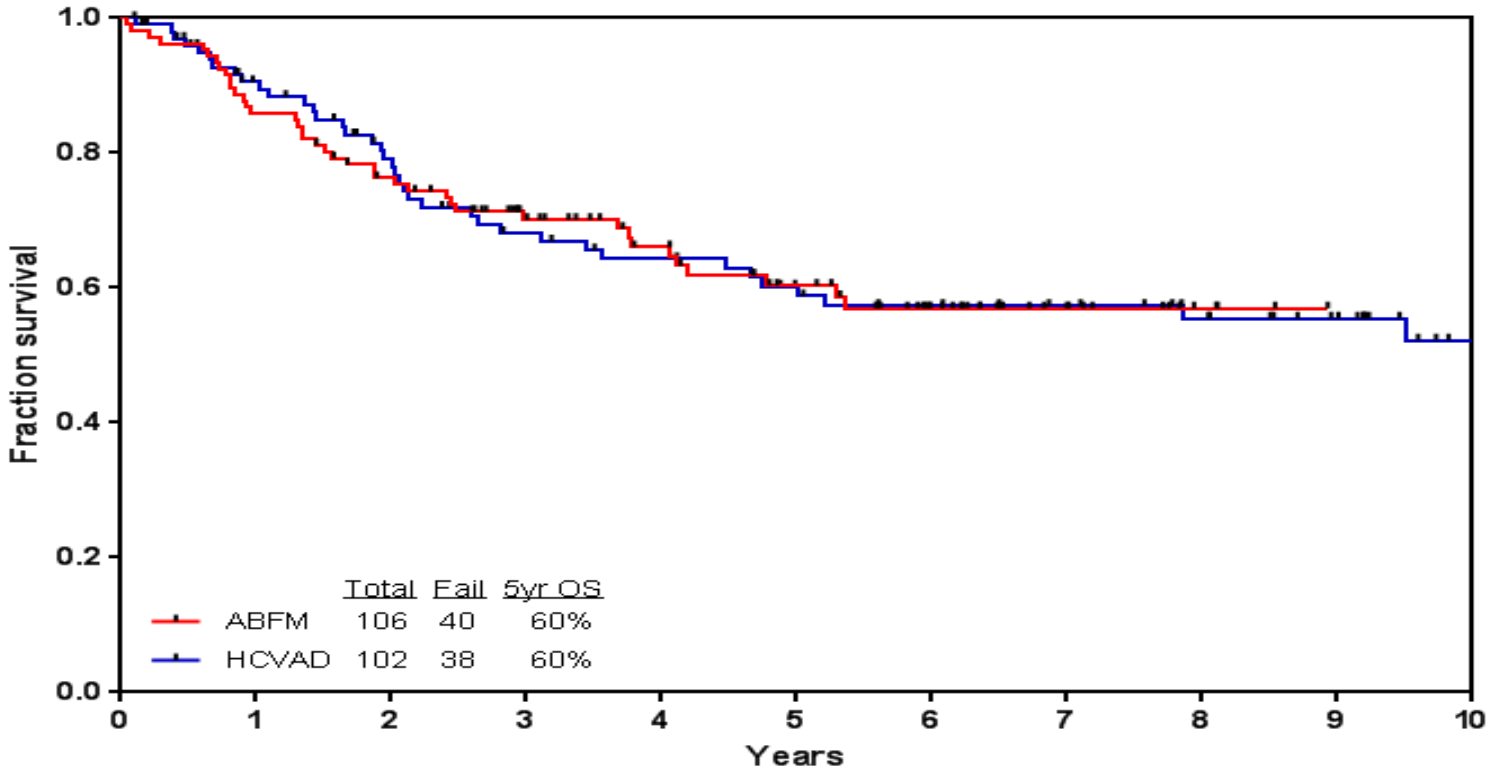
HCVAD-Rituximab vs HCVAD-Ofatumumab: Propensity Score Matching





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

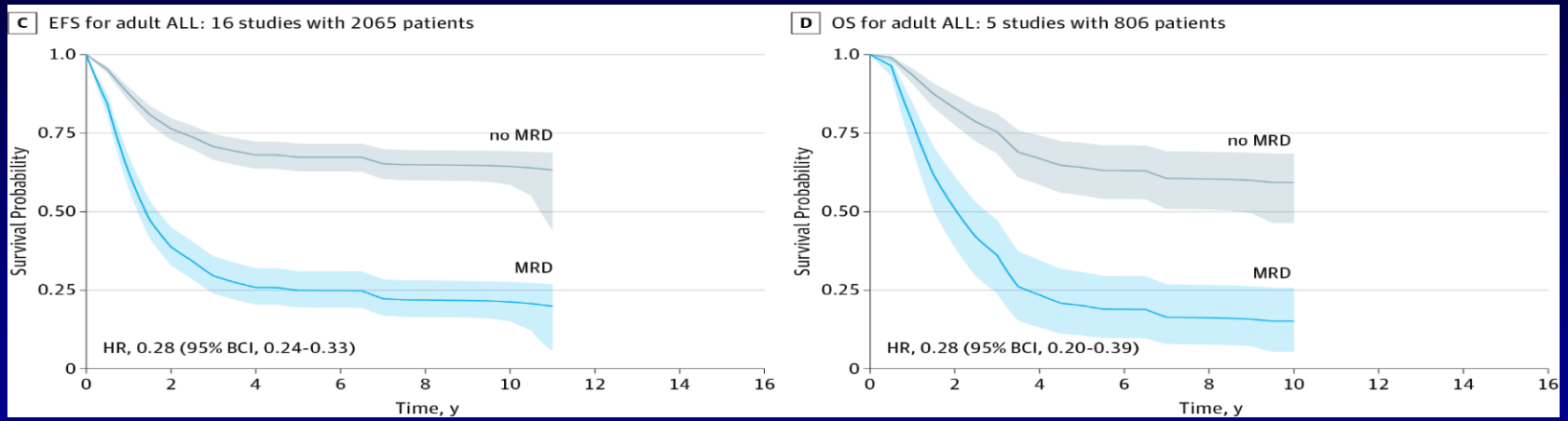
Hyper-CVAD vs ABFM: Overall Survival



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

NGS MRD in ALL: Background

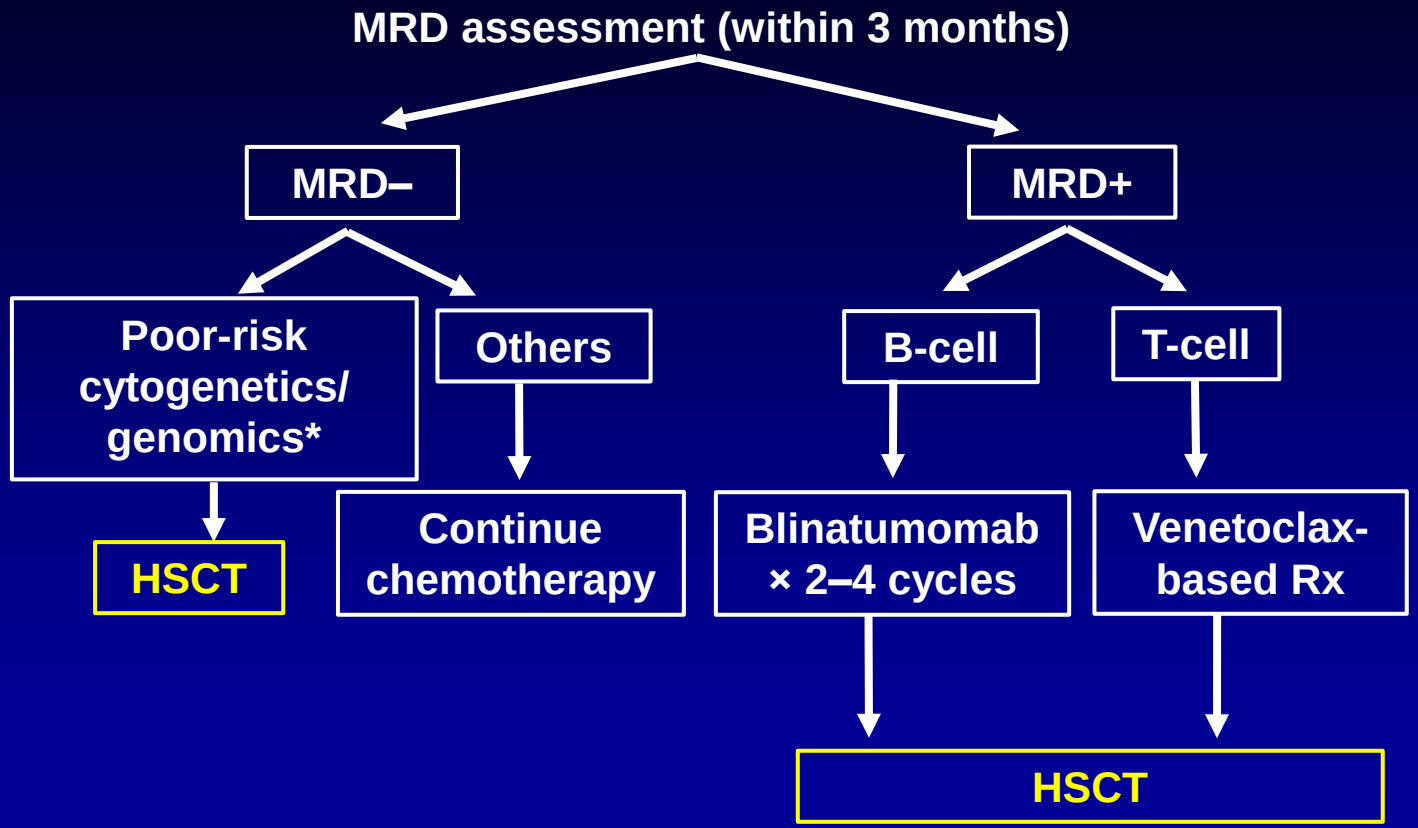
- MRD is highly prognostic for relapse and survival in Ph-negative ALL



- 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. *JAMA Oncol.* 2017;3(7):e170580.

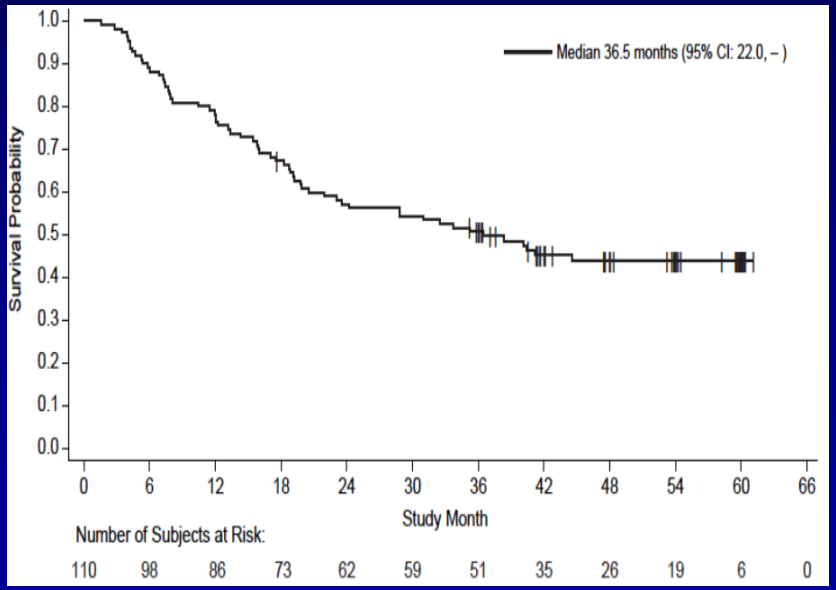
Indications for HSCT: Ph– B-ALL and T-ALL

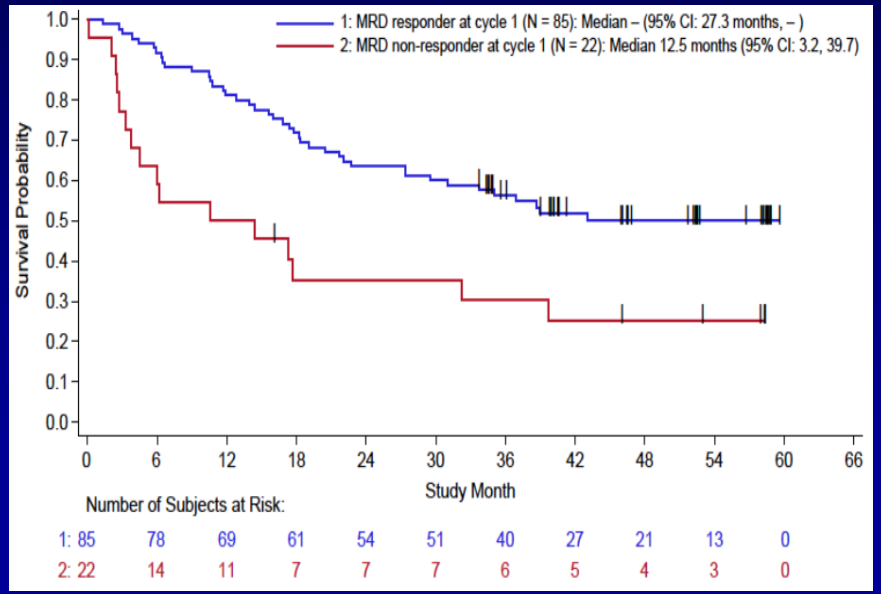


*Ph-like, 11q23 rearrangement, ETP-ALL, low hypodiploidy, complex cytogenetics

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 FU 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%)

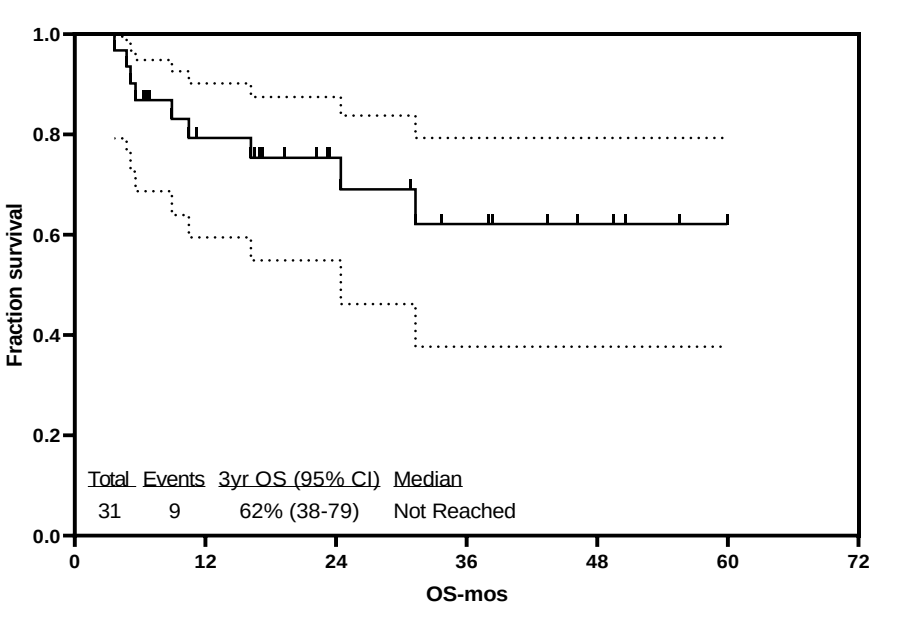


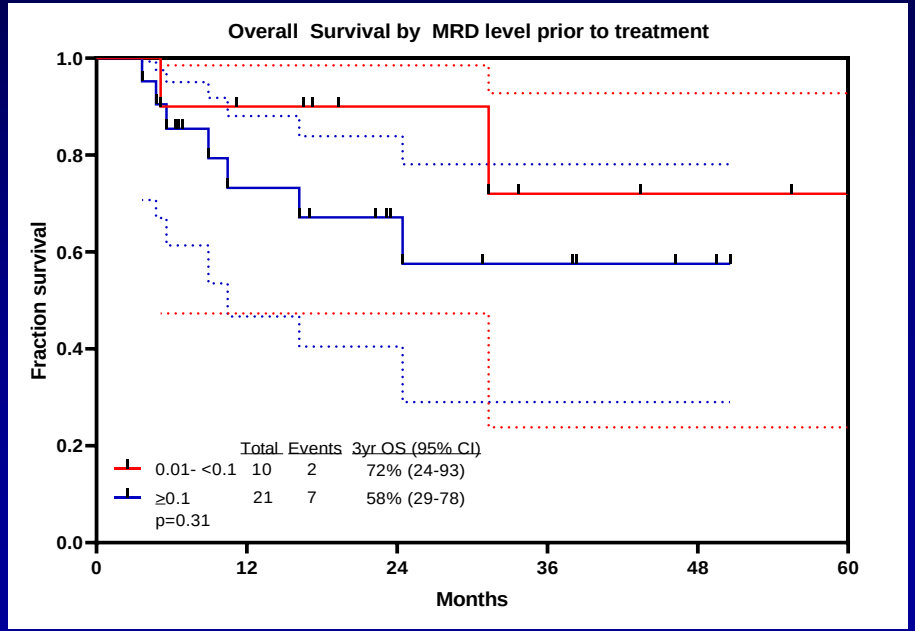


Goekbuget N, et al. *Blood.* 2018;132:abstract 554.

Blinatumomab for MRD+ ALL in CR1/CR2+

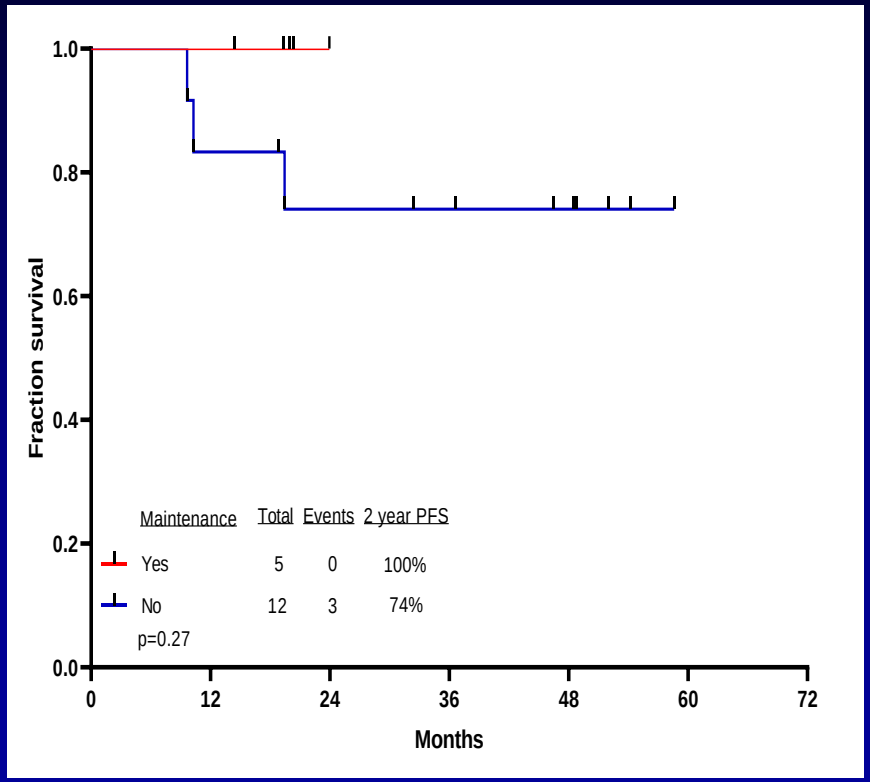
- 31 pts Rx. Post blina MRD-negative 23/31 = 74%
- 10 pts 0.01 to <0.1% RR = 90%; 21 pts ≥0.1% RR=67%
- Median OS not reached; **3-yr OS 62%; 3-yr OS if MRD-negative 72%**
- Continuous CR 6/8 post alloSCT (75%); 9/15 without SCT (60%)





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

PFS



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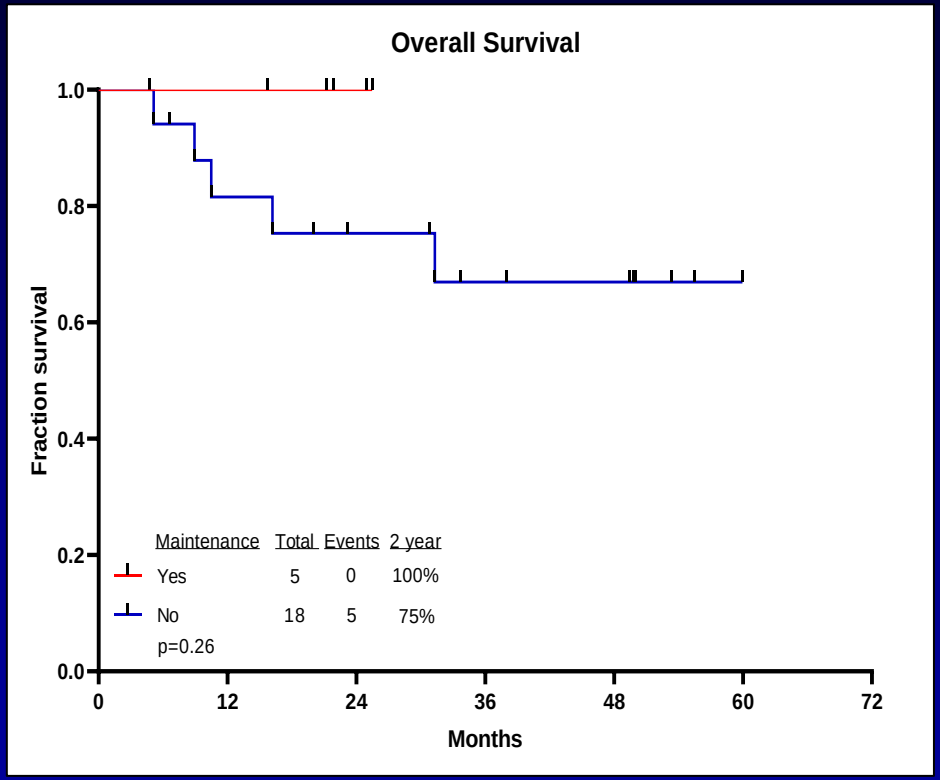


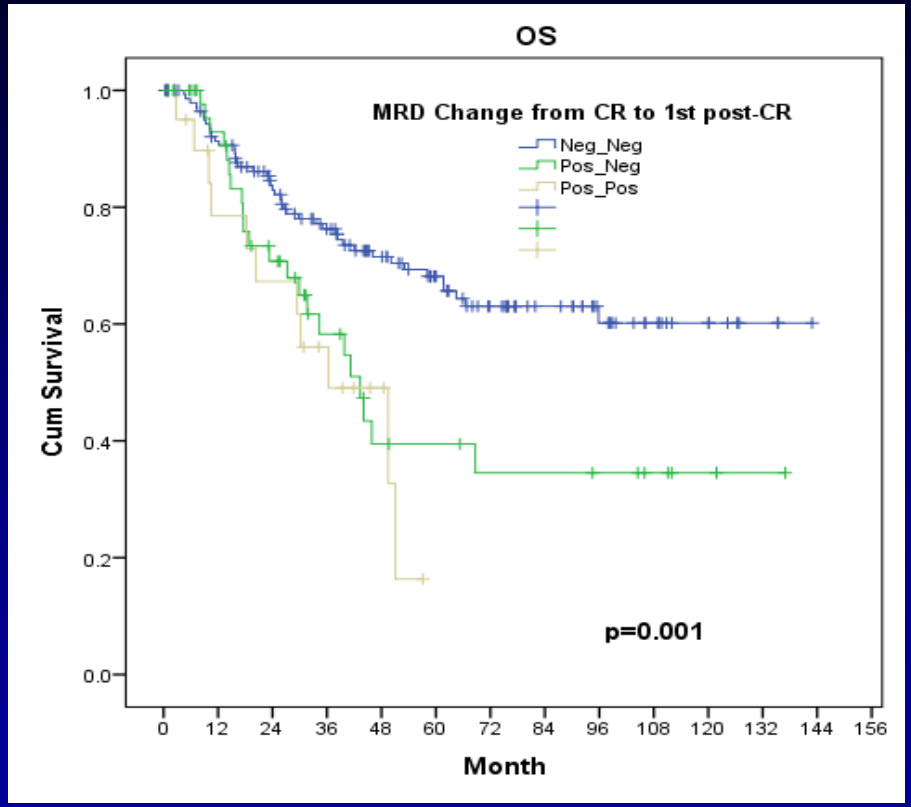
Ph-Like ALL: Higher MRD+ Rate

	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.

Dynamics of MRD: Outcome

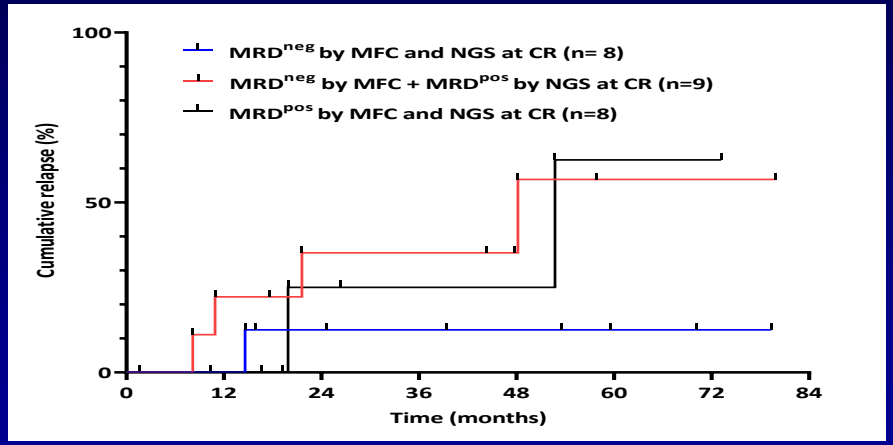
MRD Status		Patients (%) n = 214	5-yr EFS, %	5-yr OS, %
@CR	@ First post-CR			
Negative	**Negative**	**147 (69)**	**56**	**68**
≤0.1%	Negative	14 (7)	31	46
>0.1%	Negative	33 (15)	32	38
Positive	Positive	20 (9)	NA	NA

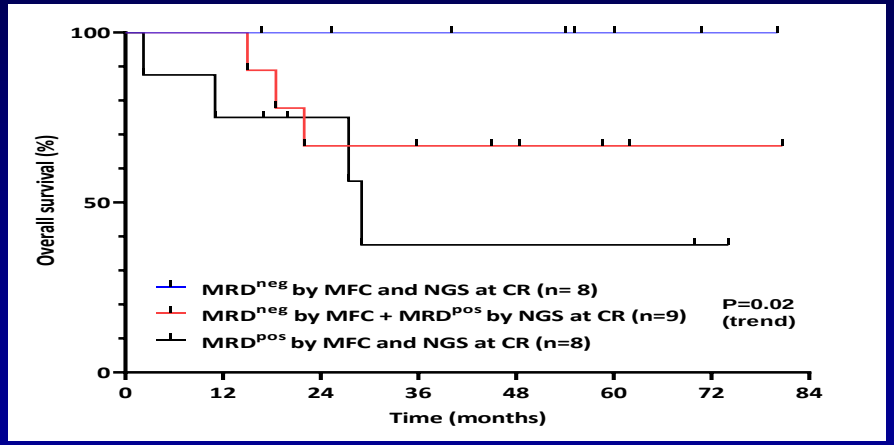


Yilmaz et al. *Blood*. 2019;134:abstract 1297.

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%

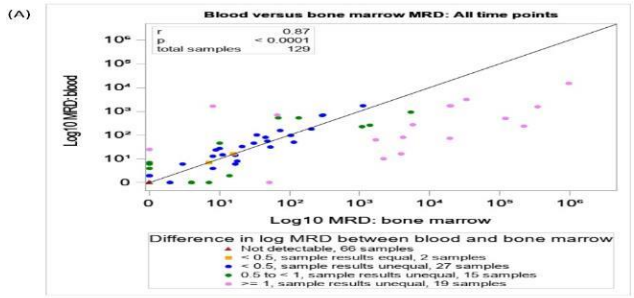
MRD^{pos} by MFC and NGS: 38%

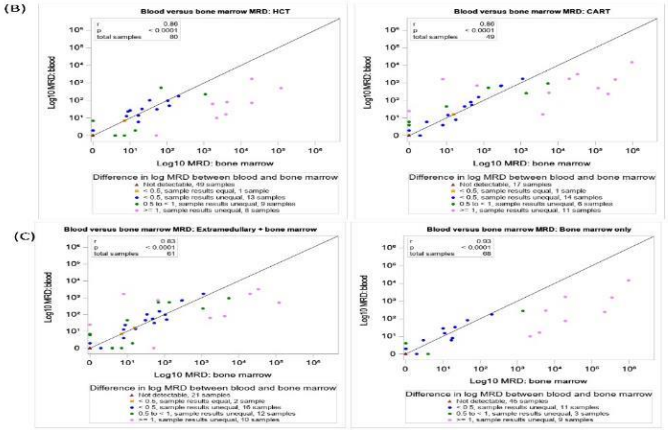
Short et al. *Blood.* 2020;136:abstract 583.

NGS MRD in R/R ALL: PB vs BM

- 62 pts (42 ASCT; 17 CAR T; 3 both); median age 42 yrs (30–53); 87% B-ALL; F/U 341 days
- Evaluation D = +28, D = +90, Q3–6 mos
- 126 paired samples; concordance 88%; r = 0.87– *P* <.0001; 14 discordant samples
- 100% and 85% of relapse post ASCT and CAR T had PB MRD+ within 90 and 60 days days, respectively

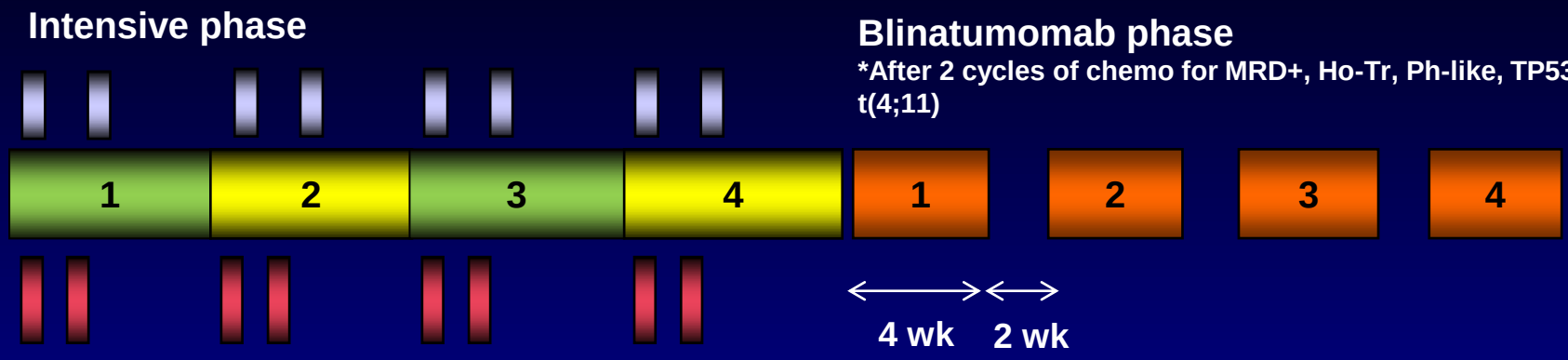
Figure 1. Peripheral Blood Vs. Bone Marrow MRD by NGS, (A) Total Study Cohort (B) HCT and CART (C) Extramedullary +/- Marrow and Marrow Only

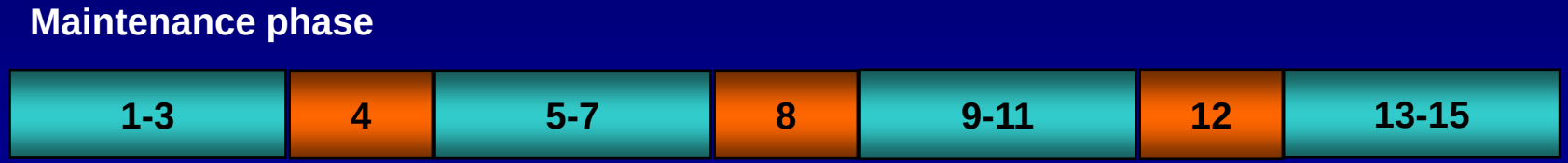




Muffly et al. *Blood*. 2020;136:abstract 975.

Hyper-CVAD + Blinatumomab in B-ALL: Regimen





Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

MTX + Ara-C

IT MTX/Ara-C × 8

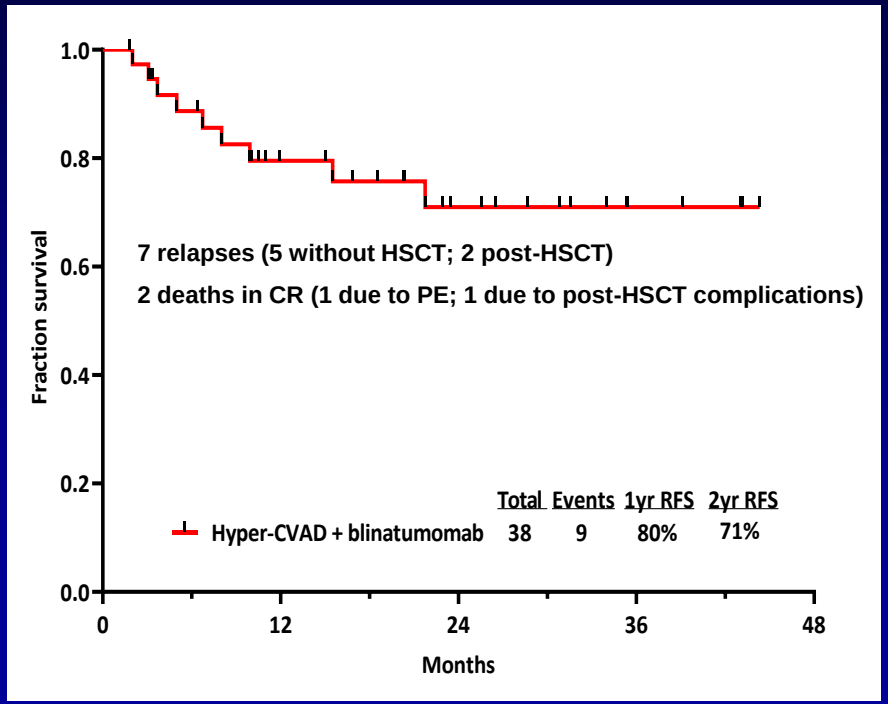
POMP

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

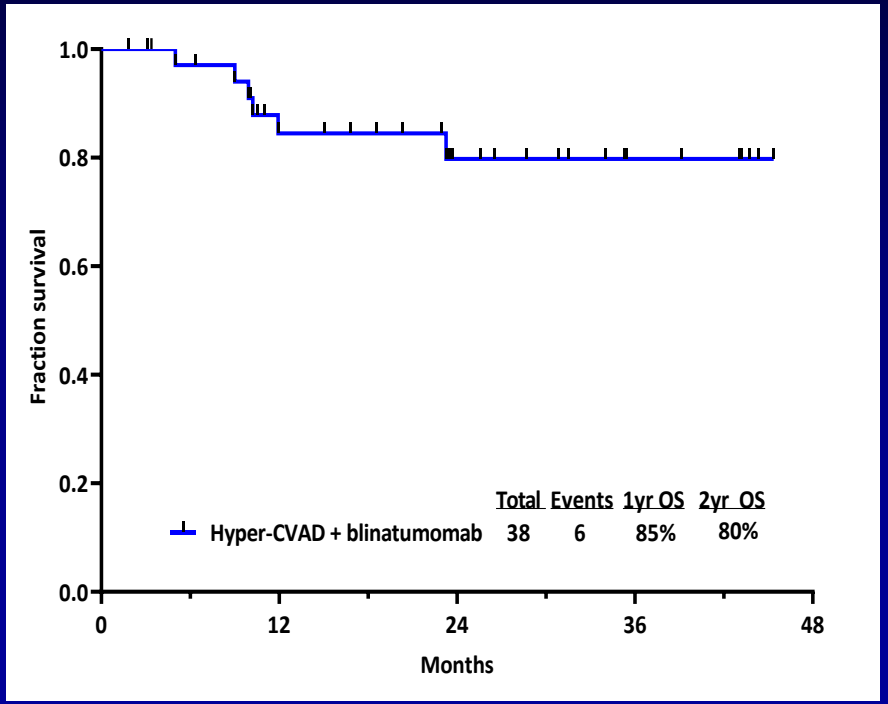
Hyper CVAD→Blinatumomab in Newly Dx Adult ALL

- 38 pts; median age 36 yrs (17–59 yrs). Rx with O-HCVAD × 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

RFS

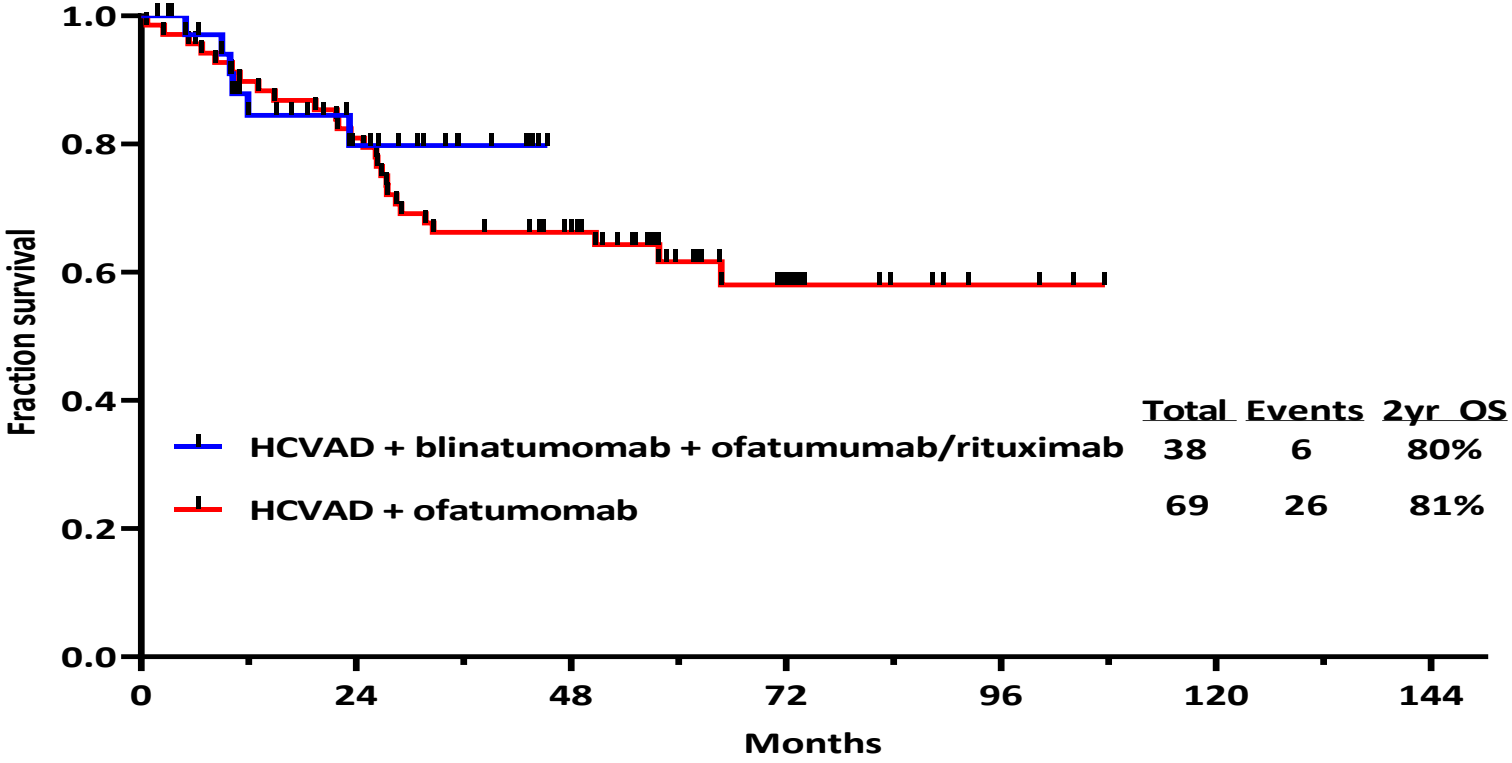


OS



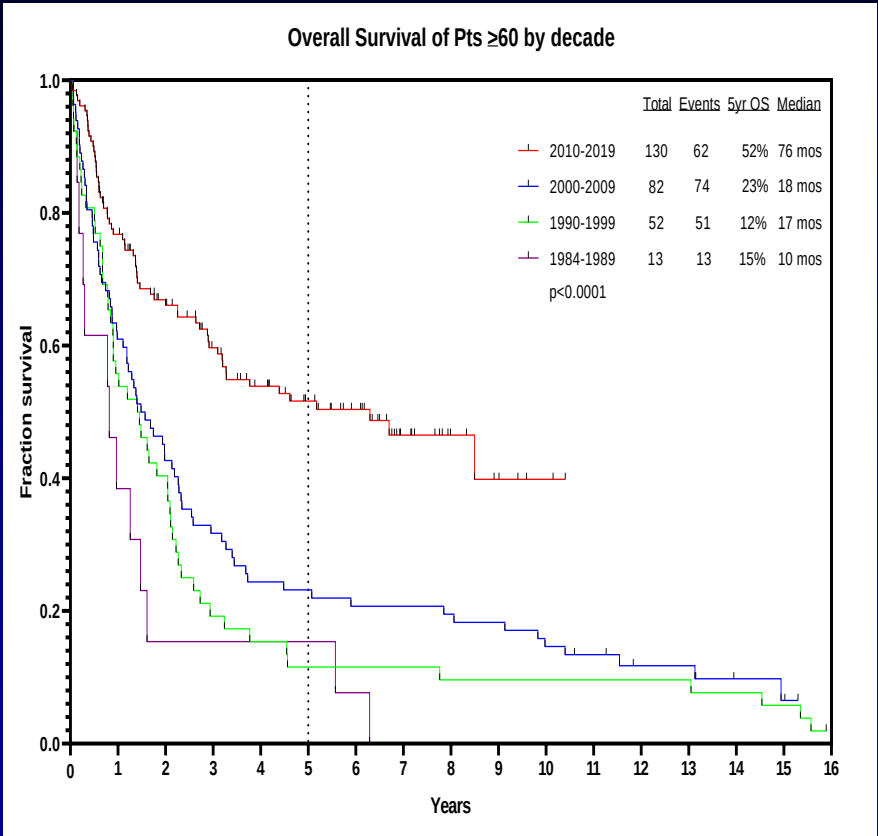
Short et al. *Blood.* 2020;136:abstract 464.

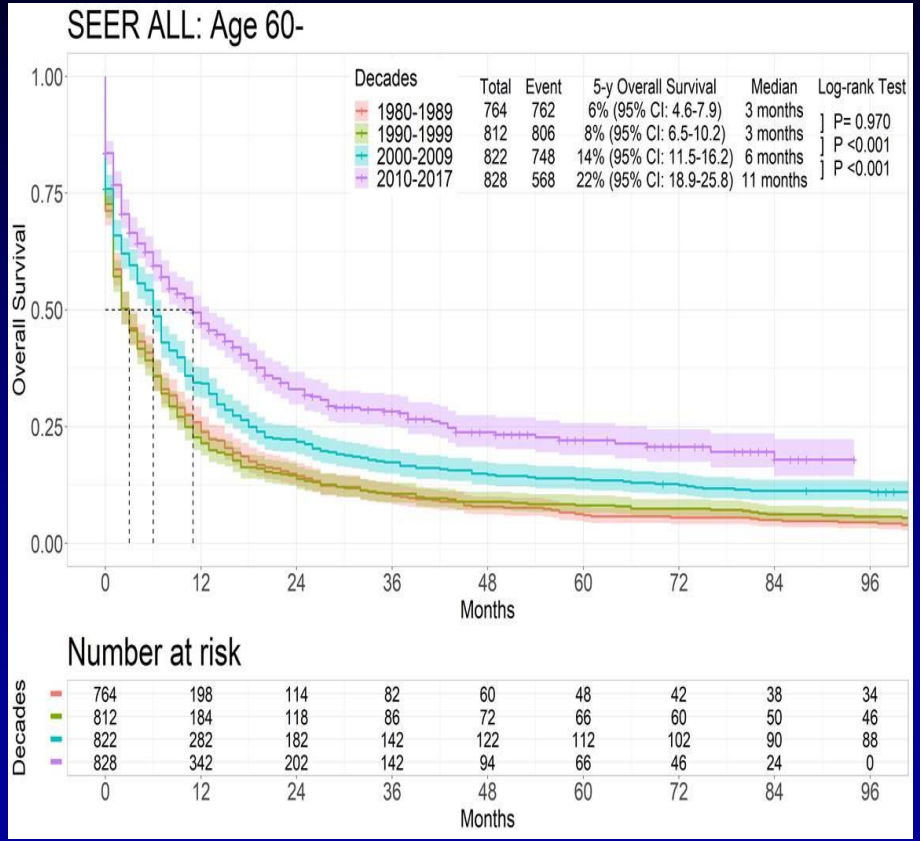
Hyper CVAD→Blinatumomab in Newly Dx Adult ALL



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

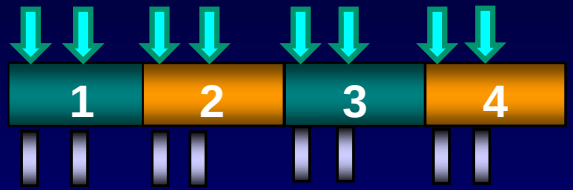
MDACC ALL: Survival by Decades for ≥60 Years





Mini-HCVD + INO ± Blina in Older ALL: Modified Design (Pts 50+)

Intensive phase



Mini-HCVD

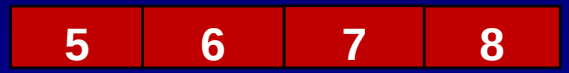
Mini-MTX-cytarabine

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)

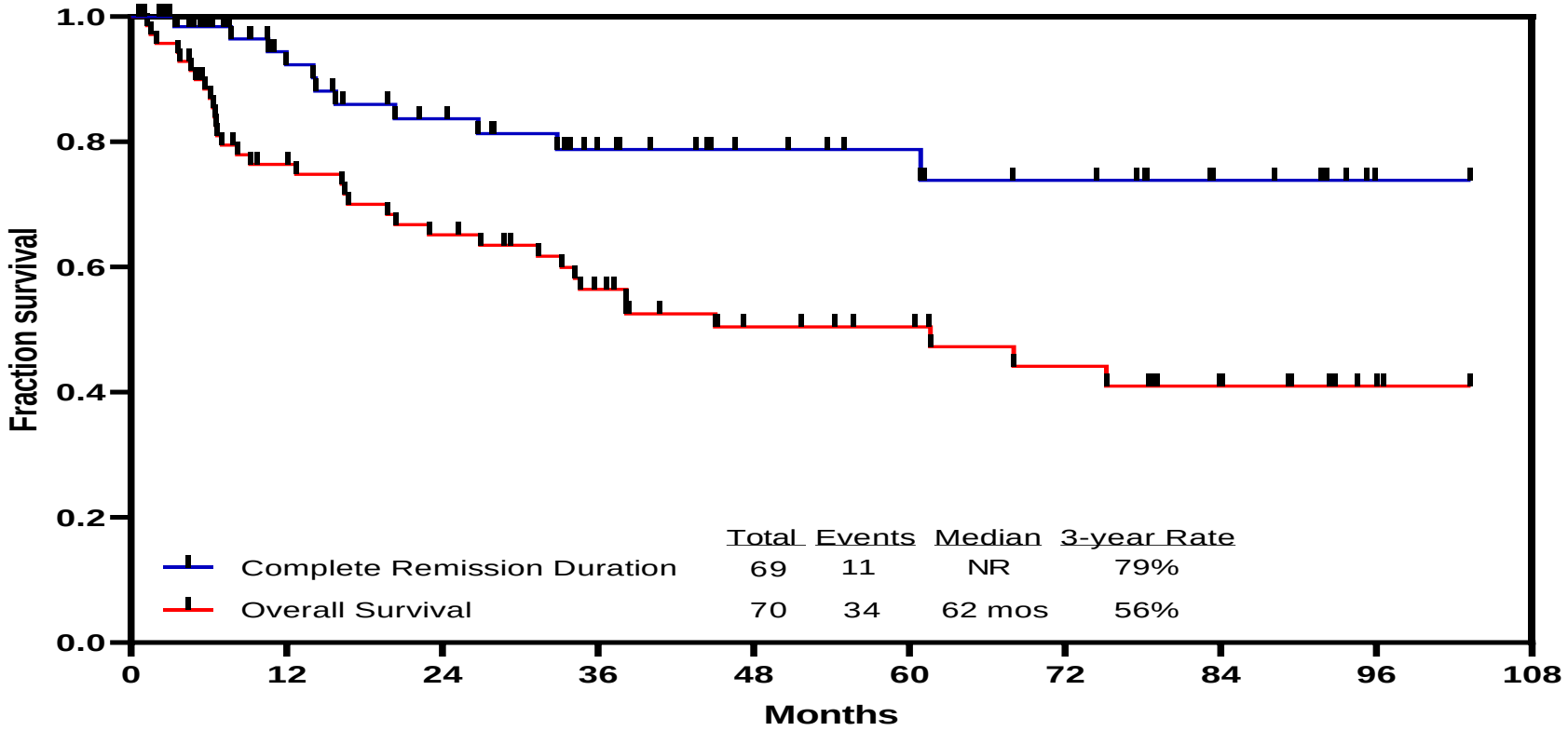
Characteristic	Category	N (%)/Median [range]
Age (years)	**≥70**	**68 [60–81]** **29 (41)**
Performance status	≥2	10 (14)
WBC ($\times 10^9$/L)		3.1 [0.6–111.0]
Karyotype	Diploid HeH **Ho-Tr** **Tetraploidy** **Complex** **t(4;11)** Misc IM/ND	23 (33) 5 (7) **12 (17)** **3 (4)** **3 (4)** **1 (1)** 10 (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)**

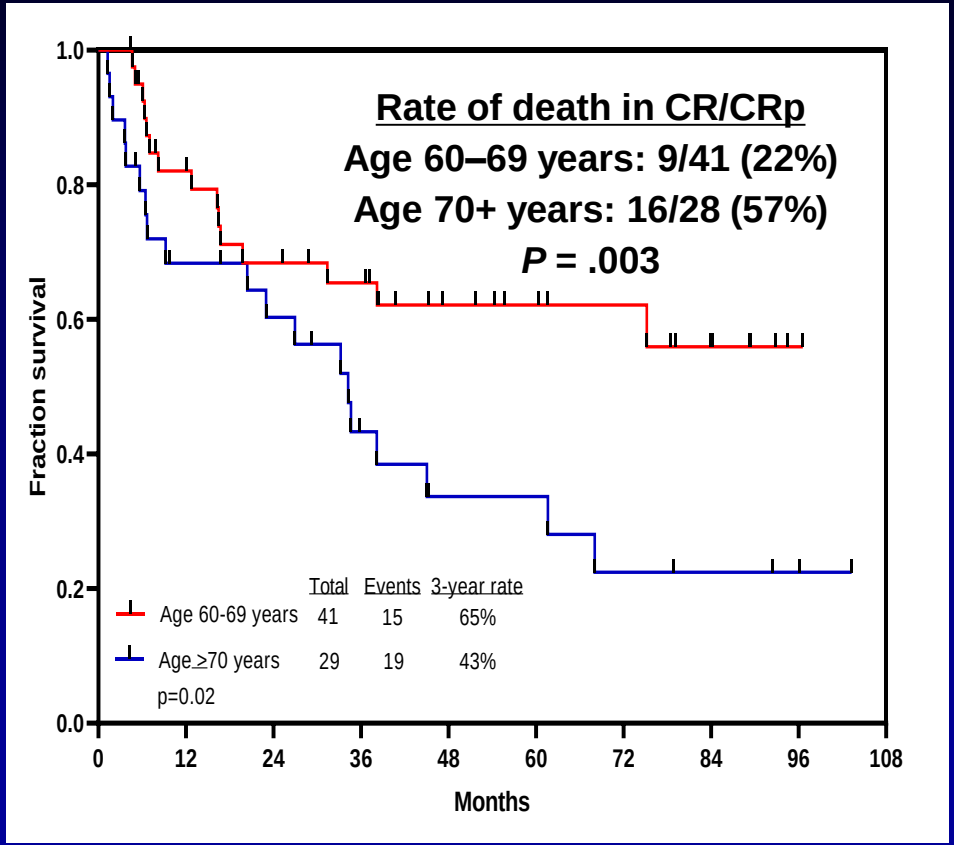
Short et al. *Blood.* 2020;136:abstract 1014.

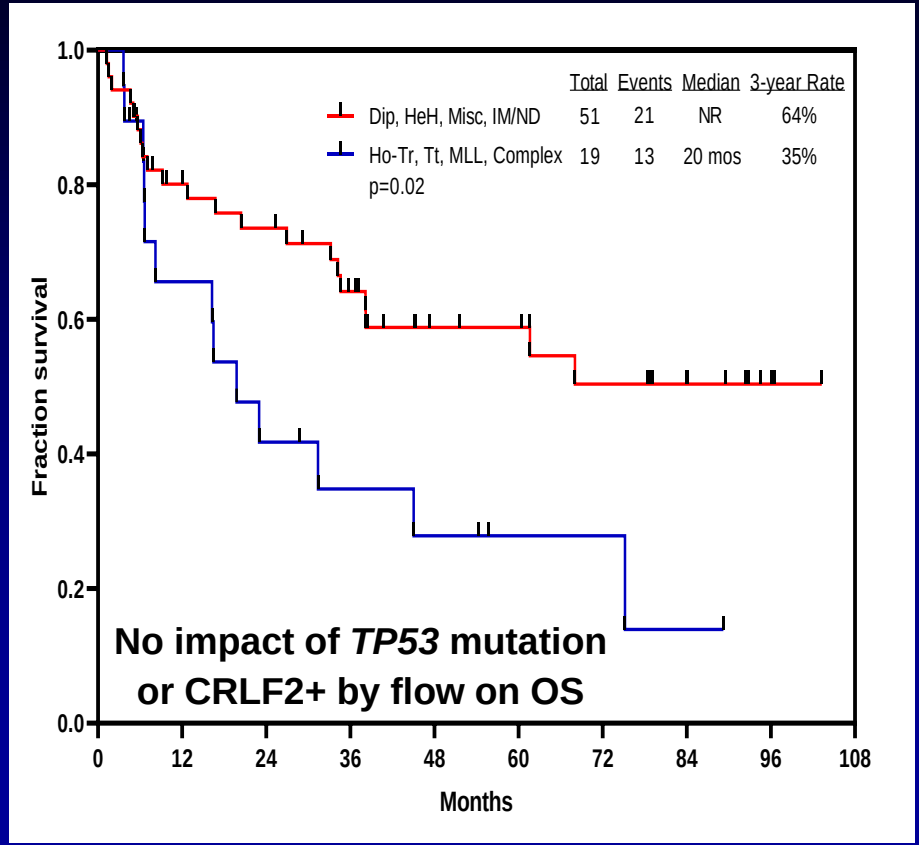
Mini-HCVD + INO ± Blina in Older ALL: CRD and OS (Entire Cohort)



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

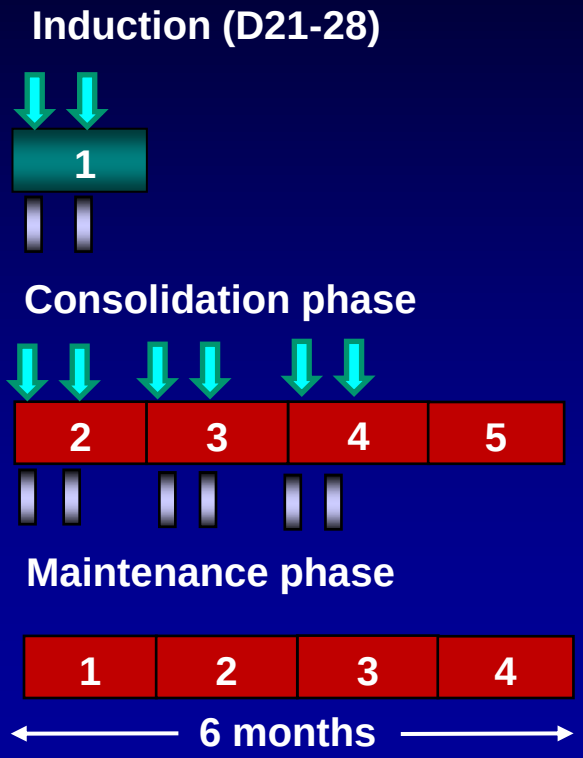
Mini-HCVD + INO ± Blina in Older ALL: Impact of Age and CG (OS)





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

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

INO*	Total dose (mg/m^2)	Dose per day (mg/m^2)
C1	0.9	0.6 D2, 0.3 D8
C2–C4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis

ALL 2021: Conclusions

- Ino and blina + chemoRx in salvage and frontline
  - S1 – mini-CVD-ino-blina CR 90%; 3-y OS 42%
  - Older frontline – CR 90%; 3-yr OS 56%
  - Moving younger adults (HCVAD-blina-ino)
- Great outcome in Ph+ ALL
  - 5-yr OS 76%
  - Chemotherapy-free regimens: Blinatumomab and ponatinib
- Bcl2-Bclxl inhibitors
  - Venetoclax-navitoclax combo in R/R ALL RR 50%
  - Mini CVD + ven in older frontline CR 90+%
- MRD eradication
  - NGS > FCM and PCR; NGS PB = NGS BM
  - MRD-negative CR best predictor for outcome
- CAR T cells; Strategies redefining their role in early savage and frontline
  - Dual CD19-22; Fast-off CD19; allo CAR T cells (CD19, CD22, CD20?)
- Incorporate new strategies
  - Blinatumomab SQ TIW, blinatumomab + checkpoint inhibitors

Thank You

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Global Leukemia Academy

Current treatment options for relapsed ALL in adult and elderly patients (including COVID-19 and vaccination strategy)

José Maria Ribera

APTITUDE HEALTH®

Global Leukemia Academy
Virtual Breakout – Adult Leukemia Patients
April 24, 2021

Current Treatment Options for R/R ALL in Adult and Elderly Patients (including COVID-19 and vaccination)

JM Ribera
Clinical Hematology Department
ICO-Hospital Germans Trias i Pujol
Institut de Recerca contra la Leucèmia Josep Carreras
Universitat Autònoma de Barcelona, Spain

Disclosures

- Pfizer: speaker and advisory boards honoraria, clinical trials
- AMGEN: speaker and advisory boards honoraria, research support, clinical trials
- Shire: speaker and advisory boards honoraria
- Ariad: speaker and advisory boards honoraria, clinical trials
- Takeda: speaker and advisory boards honoraria, clinical trials
- Novartis: speaker and advisory boards honoraria

How Can We Improve the Outcome of Elderly Patients With R/R ALL?

Ph+ ALL

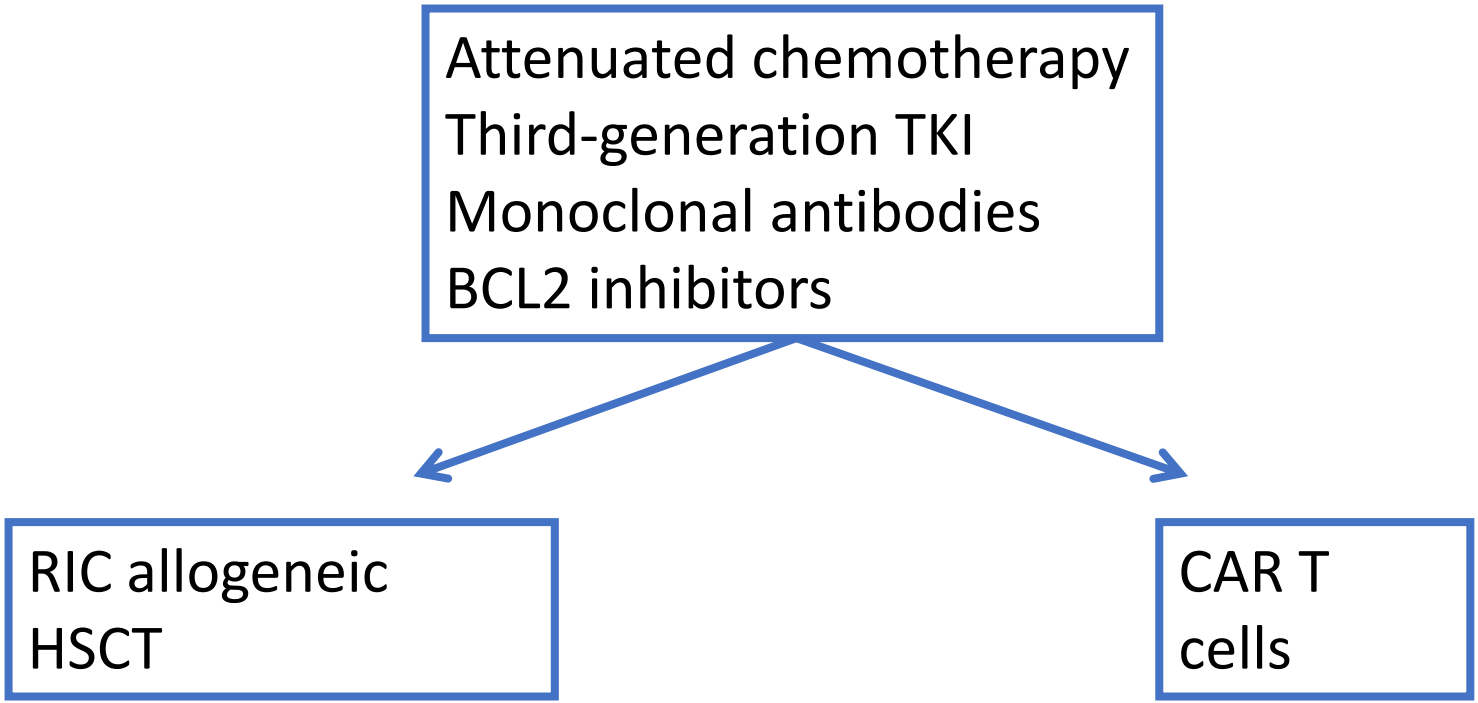
Ph– ALL

Prospective Trials in Older Patients With Newly Diagnosed Ph+ ALL

Author	Year	N	Age (median)	Induction	Post-induction	CR (%)	OS (%)
Vignetti	2007	29	69	IM + PRED	IM + physician's choice	100	74 (1 y)
Foa*	2011	53	54	DASA + PRED	DASA + physician's choice	100	69 (1.5 y)
Pfeifer	2012	121	66	IM ± CHT	IM + CHT	88	22 (5 y)
Ottmann	2014	47	66	NILO + CHT	NILO + CHT	97	-
Ribera	2016	53	66	IM + CHT	IM + CHT	87	41 (5 y)
Rousselot	2016	71	69	DASA + CHT	DAS + CHT	96	36 (5 y)
Ottmann	2017	72	66	NILO + CHT	NILO + CHT	94	40 (5 y)
Jabbour*	2018	68	46 (>60: 20)	**PONA** + CHT	PONA + CHT	100	74 (5 y)
Martinelli	2017	44	68	**PONA**	**PONA**	90	89 (1 y)
Foa*	2020	63	54	DASA	DASA + **BLINA**	98	87 (2 y)
Jabbour*	2020	27		**PONA + BLINA**	**PONA + BLINA**	100	100 (1 y)

*Not specifically designed for elderly patients.

Strategies Potentially Useful in R/R Ph+ ALL in Elderly



Inotuzumab as Single Drug for R/R Ph+ ALL: INO-VATE (n = 22) + Phase I/II Trial (n = 16)

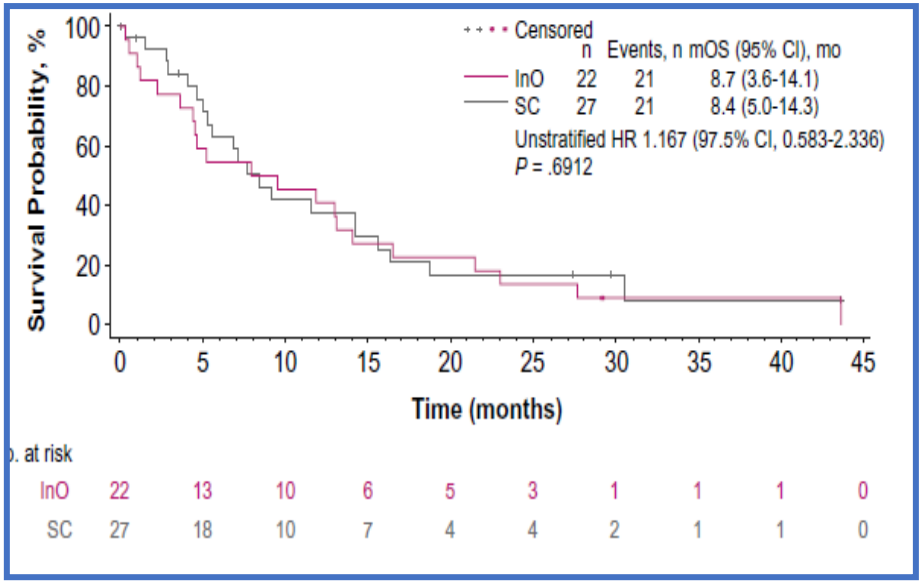
Efficacy Endpoints	Study 1022 InO (n = 22)	Study 1022 SC (n = 27)	Study 1022 *P*	Study 1010 InO (n = 16)
CR/CRi, n (% [95% CI])	16 (72.7 [49.8-89.3])	15 (55.6 [35.3-74.5])	.1075	9 (56.3 [29.9-80.3])
CR, n (% [95% CI])	10 (45.5 [24.4-67.8])	8 (29.6 [13.8-50.2])	.1265	4 (25.0)
CRi, n (% [95% CI])	6 (27.3 [10.7-50.2])	7 (25.9 [11.1-46.3])	.4577	5 (31.3)
MRD negativity, n (% [95% CI])[a]	13 (81.3 [54.4-96.0])	5 (33.3 [11.8-61.6])	.009	9 (100.0 [66.4-100.0])
OS				
Median, mo (95% CI)	8.7 (3.6-14.1)	8.4 (5.0-14.3)		7.4 (4.3-11.3)
HR (95% CI)	1.17 (0.64-2.14)		.6912	—
PFS				
Median, mo (95% CI)	3.9 (2.1-9.2)	3.1 (1.1-6.2)		4.4 (1.8-5.9)
HR (95% CI)	0.65 (0.34-1.25)		.0963	—

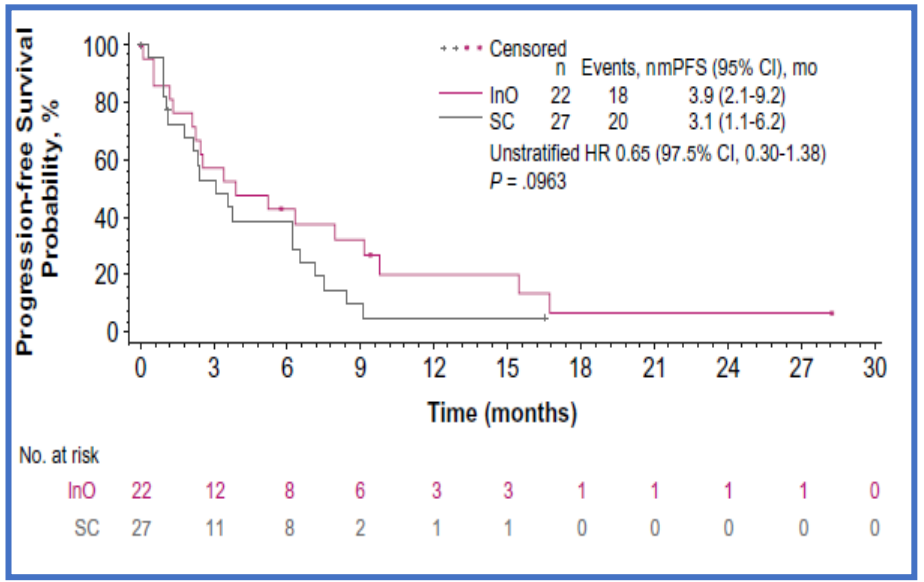
TABLE 2. Efficacy Endpoints Stratified According to Whether Ph+ Patients Received Follow-up HSCT

	Study 1022				Study 1010	
	+ Follow-up HSCT		No Follow-up HSCT		+ Follow-up HSCT	No Follow-up HSCT
	InO (n = 9)	SC (n = 5)	InO (n = 13)	SC (n = 22)	InO (n = 3)	InO (n = 13)
PFS, mo, median (95% CI)	9.2 (1.3-NE)	6.5 (2.2-NE)	2.4 (0.6-6.3)	2.4 (1.0-6.2)	5.4 (4.3-NE)	3.5 (1.7-5.9)
OS, mo, median (95% CI)	16.5 (4.7-43.6)	16.4 (11.6-30.6)	4.4 (1.1-8.0)	6.9 (4.1-9.1)	11.3 (4.3-NE)	7.4 (3.5-11.3)

Stock SW, et al. *Cancer.* 2021;127:905-913.

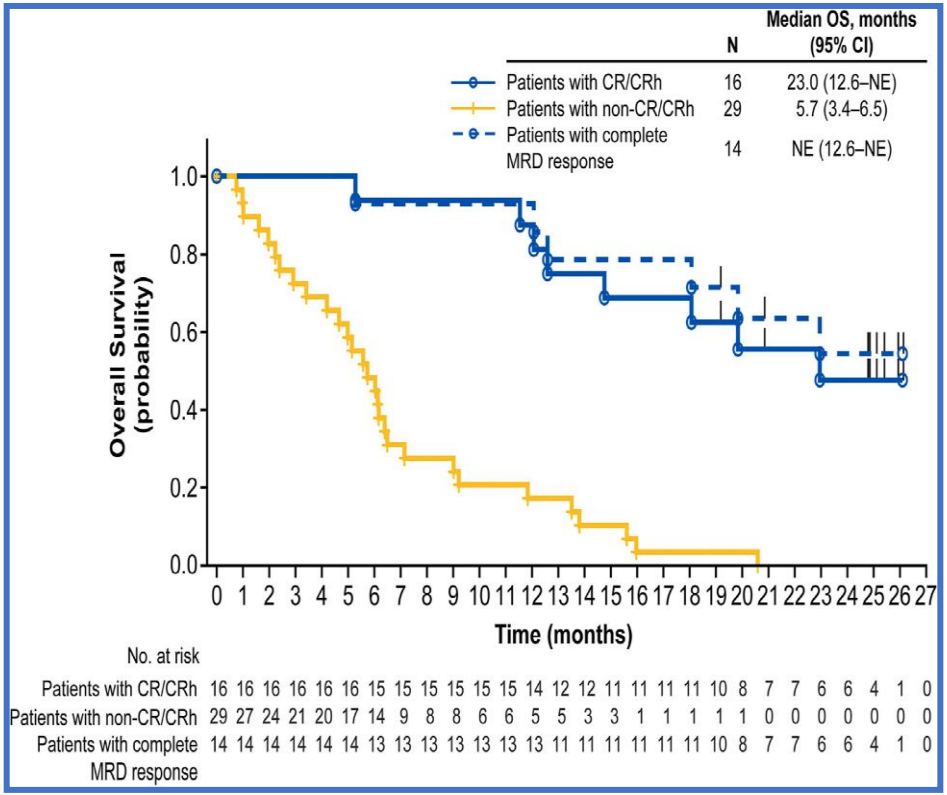
Inotuzumab as Single Drug for R/R Ph+ ALL: Outcomes From INO-VATE Trial





Blinatumomab in R/R Ph+ ALL

Outcome	Responders/ Evaluable	%
CR/CRh	16/45	36
T315I mutation	4/10	40
2 prior therapies	7/21	33
≥3 prior TKI therapies	8/17	47
Prior ponatinib	8/23	35
Prior alloSCT	5/20	25
Best response during the first 2 cycles: CR	14/45	31
CRh	2/45	4
Complete MRD response	14/16	88
Proceed to alloHSCT	4/16	25



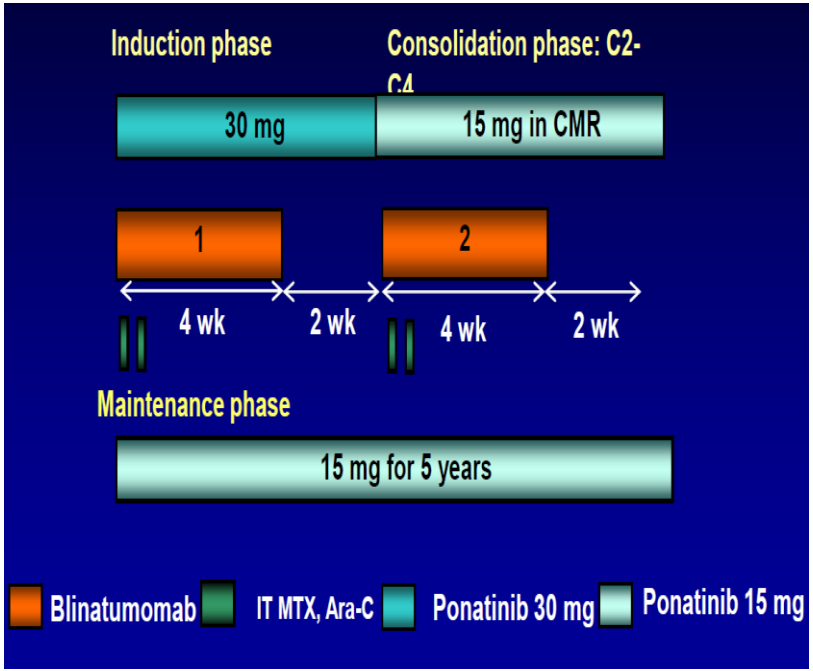
Martinelli G, et al. *Cancer*. 2021;146:107-114.

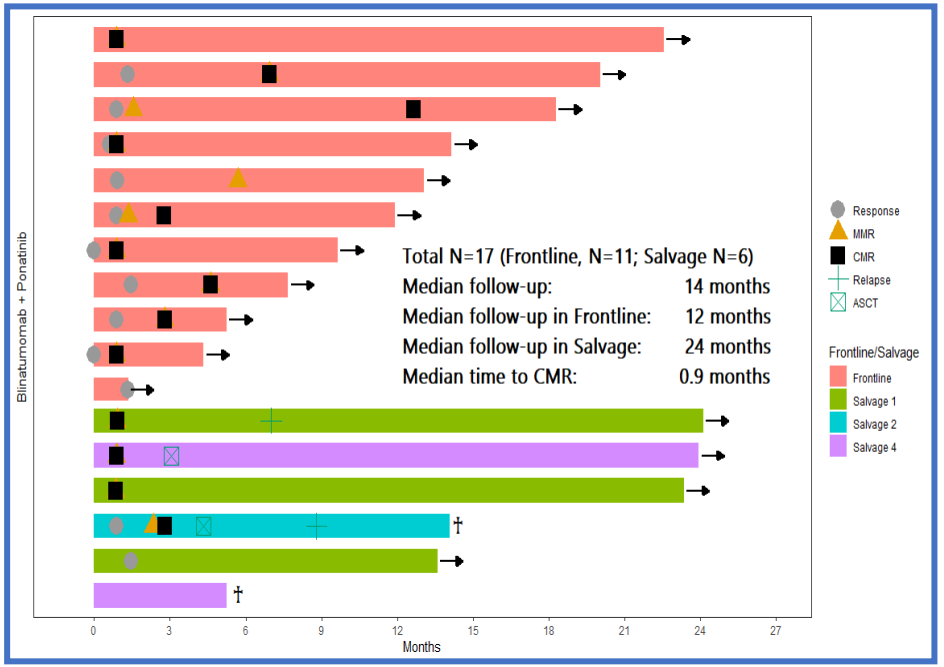
Blinatumomab and Inotuzumab in R/R Ph+ ALL

Parameter	Blinatumomab	Inotuzumab
No. Rx	45	38
No. CR/marrow CR (%)	16 (36)	25 (66)
MRD negative in CR, %	88	63
Median OS (mo)	7.1	8.1
Later alloSCT, %	44	32

Martinelli G, et al. *J Clin Oncol*. 2017;35:1795-1802; Stock W, et al. ASCO 2018. Abstract 7030.

Blinatumomab + Ponatinib Swimmer Plot (N = 17)





Personal communication from Dr Jabbour.

Ponatinib-Venetoclax for R/R Ph+ ALL

Ponatinib
- 45 mg/d
- 30 mg/d if CR/CRi
- 15 mg/d if CMR

Dex 40 mg 4 days/cycle

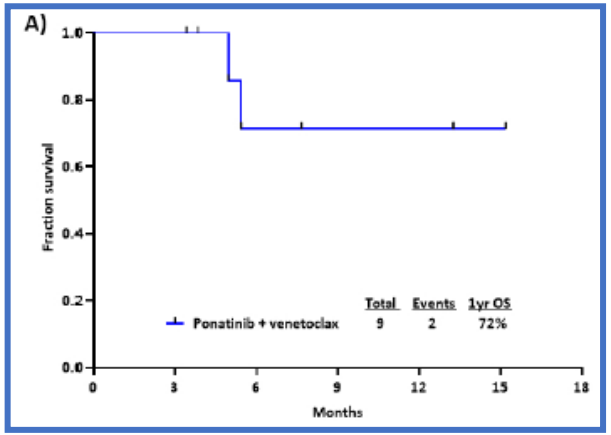
Venetoclax 400-800 mg

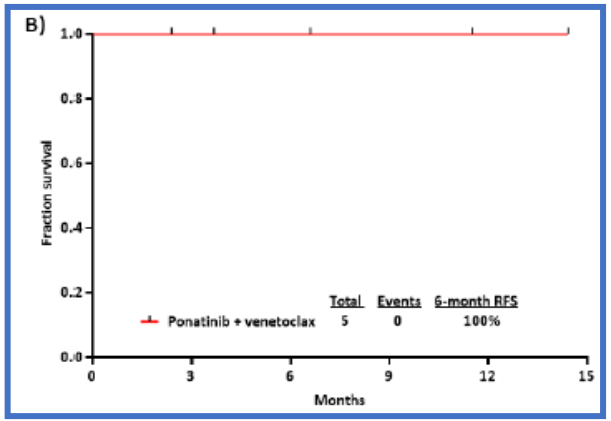
9 pts; *T315I* (4/8); prior therapies 3 (2-4)

CR/CRi: 56%

CMR: 44%

1-yr OS: 72% (2 deaths)





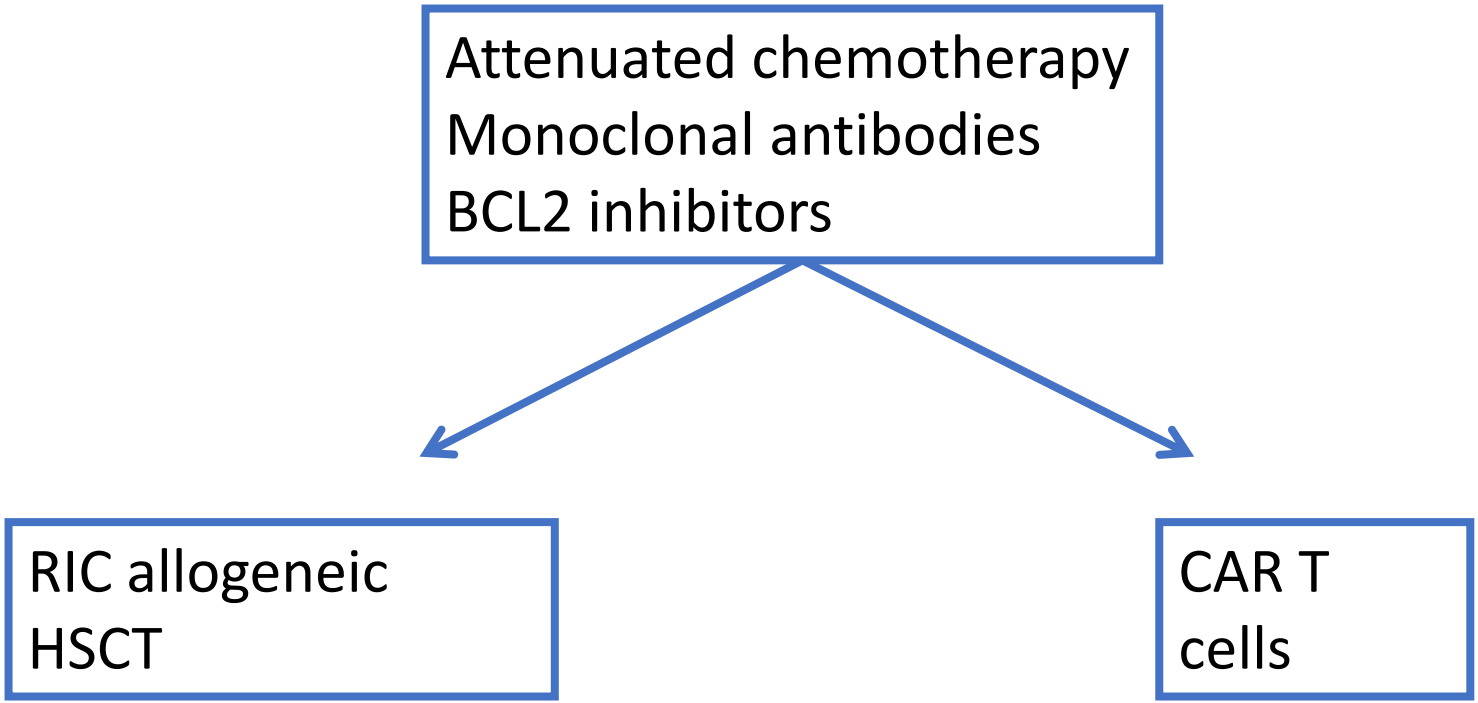
Short NJ, et al. *Am J Hematol*. 2021. doi: 10.1002/ajh.26175.

How Can We Improve the Outcome of Elderly Patients With R/R ALL?

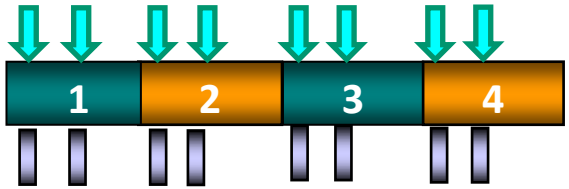
Ph+ ALL

Ph– ALL

Strategies Potentially Useful in R/R Ph– ALL in Elderly



Mini-HCVD + INO ± Blina in Salvage ALL and Frontline Older ALL: Modified Design (Pts #50+)



Mini-HCVD

Mini-MTX–cytarabine

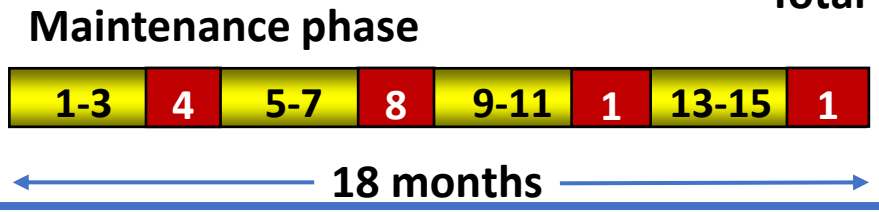
MTX

Blinatumomab

POMP

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



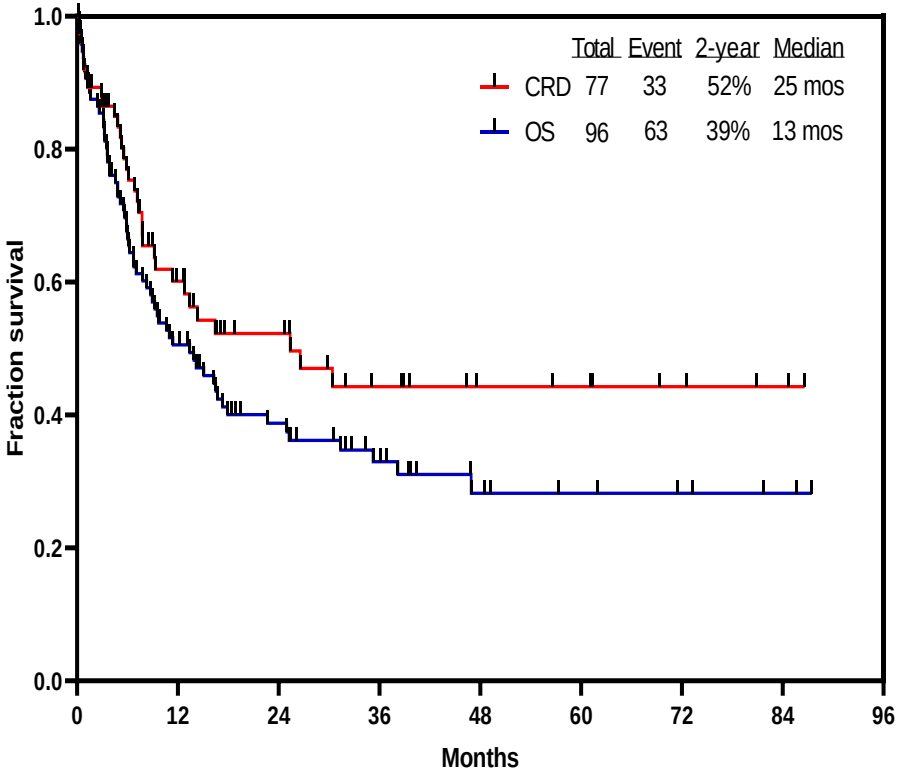
Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055; Short N, et al. ASH 2018. Abstract 36.

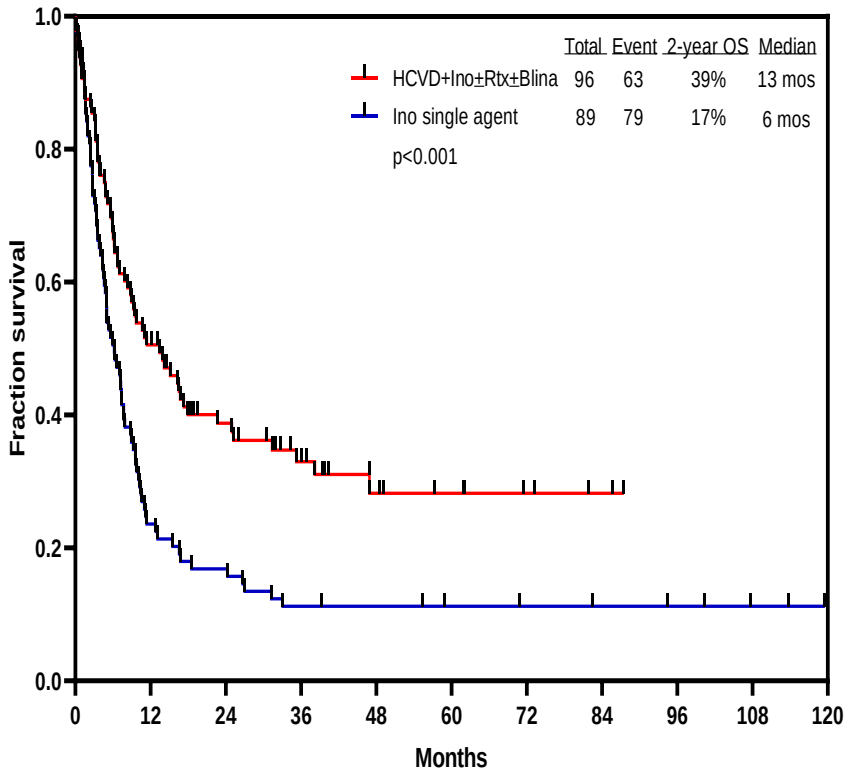
Mini-HCVD + INO ± Blinatumomab in R/R ALL: Response by Salvage (N = 96)

Response	N	Percentage
Salvage 1	58/64	**91**
S1, primary refractory	8	100
S1, CRD1 <12 mo	21	84
S1, CRD1 ≥12 mo	29	94
Salvage 2	11	61
Salvage ≥3	8	57
Overall	77	80
MRD negativity	62/75	83
Salvage 1	50/56	**89**
Salvage ≥2	12/19	63
Early death	7	7

Jabbour E, et al. *JAMA Oncol*. 2018;4:230-234.

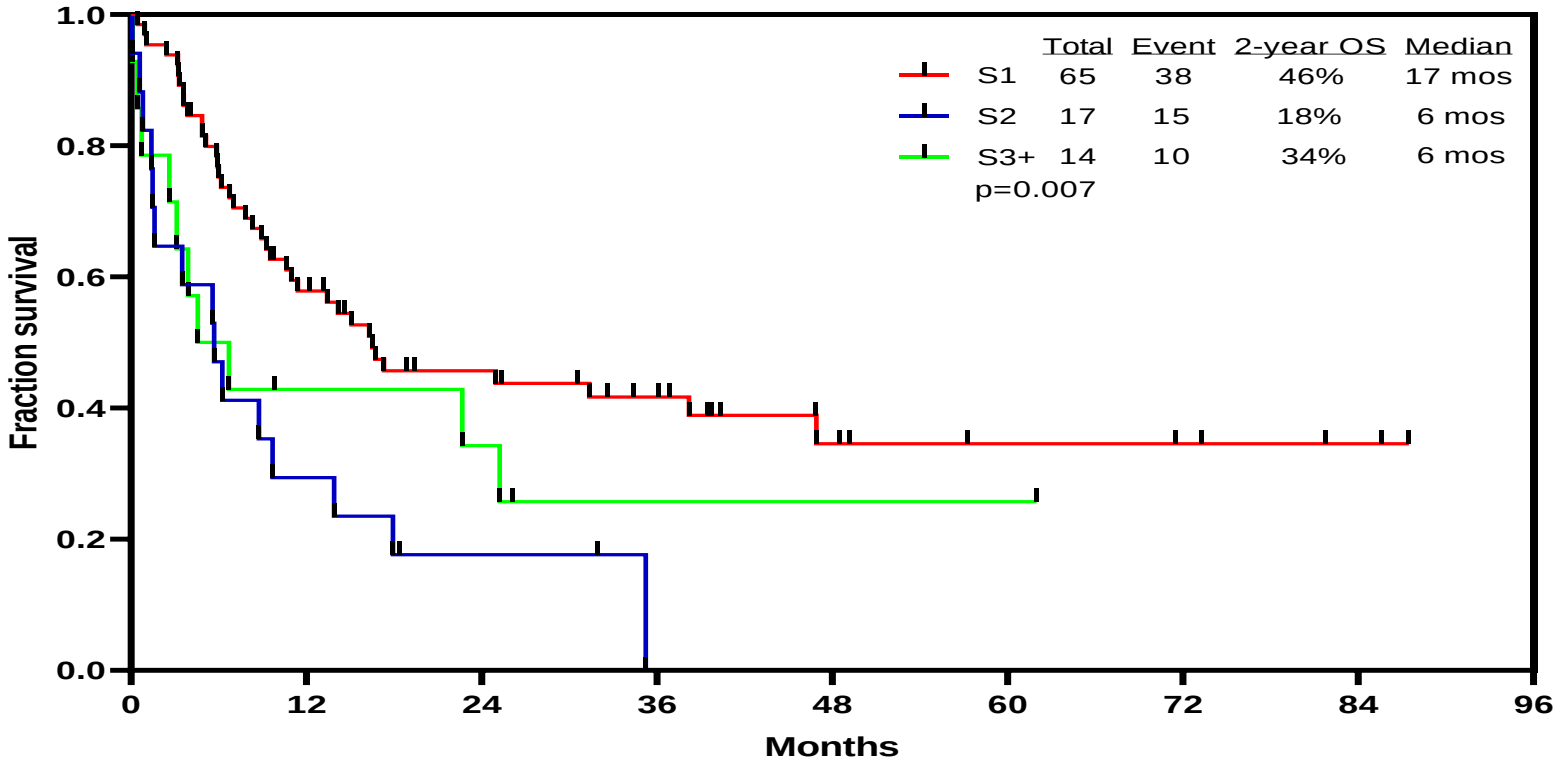
Mini-HCVD + Inotuzumab/Blinatumomab in R/R ALL





Jabbour E, et al. *JAMA Oncol*. 2018;4:230-234.

Mini-HCVD + INO ± Blinatumomab in R/R ALL: OS by Salvage Status



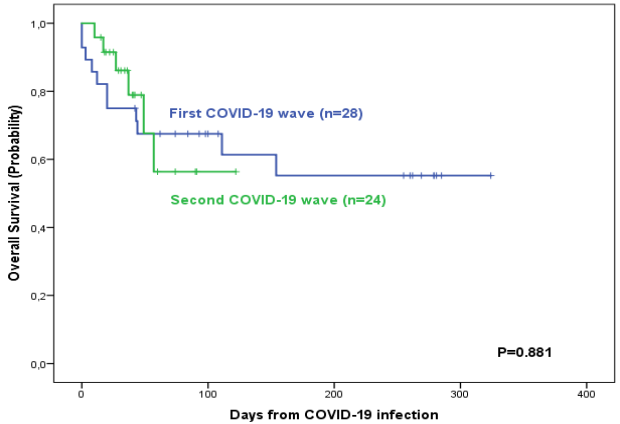
Sasaki K, et al. ASH 2018. Abstract 553; Jabbour E, et al. *JAMA Oncol*. 2018;4:230-234.

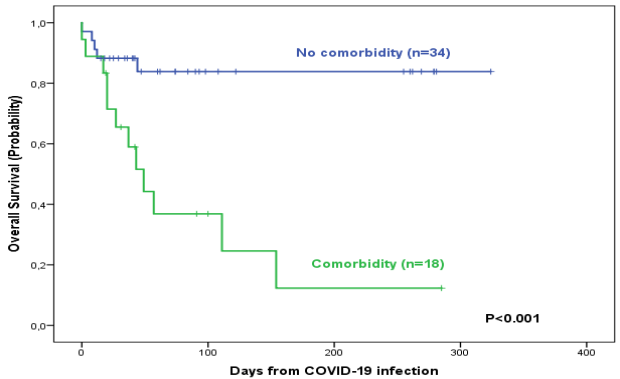
Conclusion

- Treatment of R/R elderly patients with ALL: unmet need
- Better approach for salvage therapy
  - Ph– ALL: attenuated chemotherapy + immunotherapy (INO, Blina)
  - Ph+ ALL
    - Third-generation TKI + immunotherapy
    - Third-generation TKI + BCL2 inhibitors
- Do not forget cell therapy
  - RIC alloHSCT
  - CAR T

Spanish Registry of ALL and COVID-19 Infection: Outcomes in First vs Second Pandemic Wave

	Overall (n = 52)	First COVID-19 Wave (n = 28)	Second COVID-19 Wave (n = 24)	*P* Value
COVID-19 infection resolution	36 (69)	18 (64)	18 (75)	.404
Infection onset-clinical recovery interval, days, median (range)	14 (2-47)	17 (2-47)	12.5 (5-39)	.095
Alive patients at close of follow-up	35 (67)	17 (61)	18 (75)	.274
Causes of death (n = 17)				
COVID-19 infection	10	6	4	
Pseudomonas sepsis and COVID-19 infection	3	2	1	
Leukemia progression and COVID-19 infection	2	2	0	.467
Leukemia progression	1	1	0	
ALL treatment-related mortality	1	0	1	
Infection onset-death interval, days, median (range)	20 (0-154)	20 (0-154)	32 (10-57)	.335





Ribera JM, et al. (submitted).

Spanish Society of Hematology: Recommendations for Vaccination in ALL

1) Patients under conventional chemotherapy

1) Once CR is obtained
2) Between consolidation cycles
3) At any time during maintenance

2) Patients treated with monoclonal antibodies (mAbs)

1) Anti-CD20: Delay vaccination until at least 3 months after the last dose
2) Bispecific monoclonal antibodies: Vaccination indicated due to vulnerability of these patients. Avoid overlapping with continuous infusion of blinatumomab
3) Immunoconjugated mAb: Priority for vaccination due to vulnerability of these patients

3) Patients treated with tyrosine kinase inhibitors: As other ALL patients

4) Patients in complete remission without active treatment

1) Vaccination as soon as possible

Manuscript in preparation.

Q

Question #1

The best approach to date in treatment of R/R Ph– ALL in elderly has been:

A. Inotuzumab as single drug
B. Blinatumomab as single drug
C. Attenuated chemotherapy + inotuzumab
D. Attenuated chemotherapy + ofatumumab
E. Allogeneic HSCT upfront

Question #1

The best approach to date in treatment of R/R Ph– ALL in elderly has been:

A. Inotuzumab as single drug
B. Blinatumomab as single drug
C. Attenuated chemotherapy + inotuzumab
D. Attenuated chemotherapy + ofatumumab
E. Allogeneic HSCT upfront

Q

Question #2

Venetoclax has demonstrated activity in:

A. Ph+ ALL only
B. Ph– ALL only
C. Ph+ and Ph– ALL
D. T-ALL
E. C and D answers are correct

Question #2

Venetoclax has demonstrated activity in:

A. Ph+ ALL only
B. Ph– ALL only
C. Ph+ and Ph– ALL
D. T-ALL
E. C and D answers are correct

Global Leukemia Academy

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

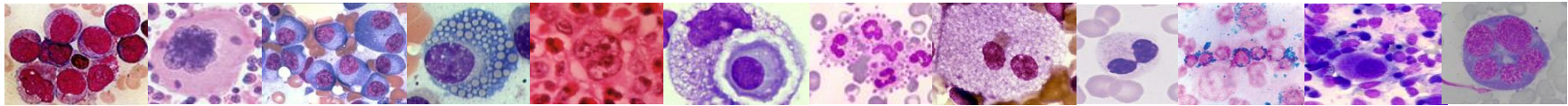
Panelists: Elias Jabbour, Naval Daver, José Maria Ribera, Andre Schuh, Eunice Wang, and local experts

Presenters: Roberta Demichelis, Wellington Silva

APTITUDE HEALTH®

ALL in Hispanic Adults: Clinical Case

Dra Roberta Demichelis
INCMNSZ
Mexico City



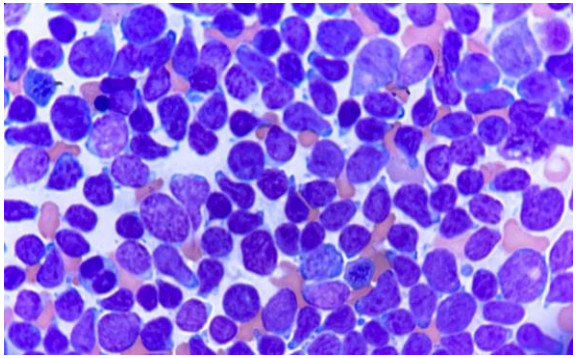
DISCLOSURES

- **Advisory/speaker: AbbVie, Amgen, Celgene, Novartis**
- **Research funding: Novartis**

MEDICAL HISTORY – DIAGNOSIS

25-year old man

Relevant history:
Medical student
BMI: 30.1 kg/m^2



August 2020: fever, headache, weight loss

- ✓ WBC 39.4 × 10^9/L, Hb 5 g/dL, plat 5 × 10^9/L
- ✓ 90% blasts
- ✓ FC: CD34, CD10, CD19, CD20, CD79a, and IgMc
- ✓ B-cell ALL FISH: partial deletion of *CDK2A* gene region and *CRLF2*/*IGH* fusion in 50% of nuclei – "BCR-ABL1–like" B-ALL

MEDICAL HISTORY – DIAGNOSIS

25-year old man

Relevant history:
Medical student
BMI: 30.1 kg/m^2

B-cell ALL, AYA patient
Ph-like
Obesity

August 2020: fever, headache, weight loss

- ✓ WBC 39.4 × 10^9/L, Hb 5 g/dL, plat 5 × 10^9/L
- ✓ 90% blasts
- ✓ FC: CD34, CD10, CD19, CD20, CD79a, and IgMc
- ✓ B-cell ALL FISH: partial deletion of *CDK2A* gene region and *CRLF2*/*IGH* fusion in 50% of nuclei – "BCR-ABL1–like" B-ALL

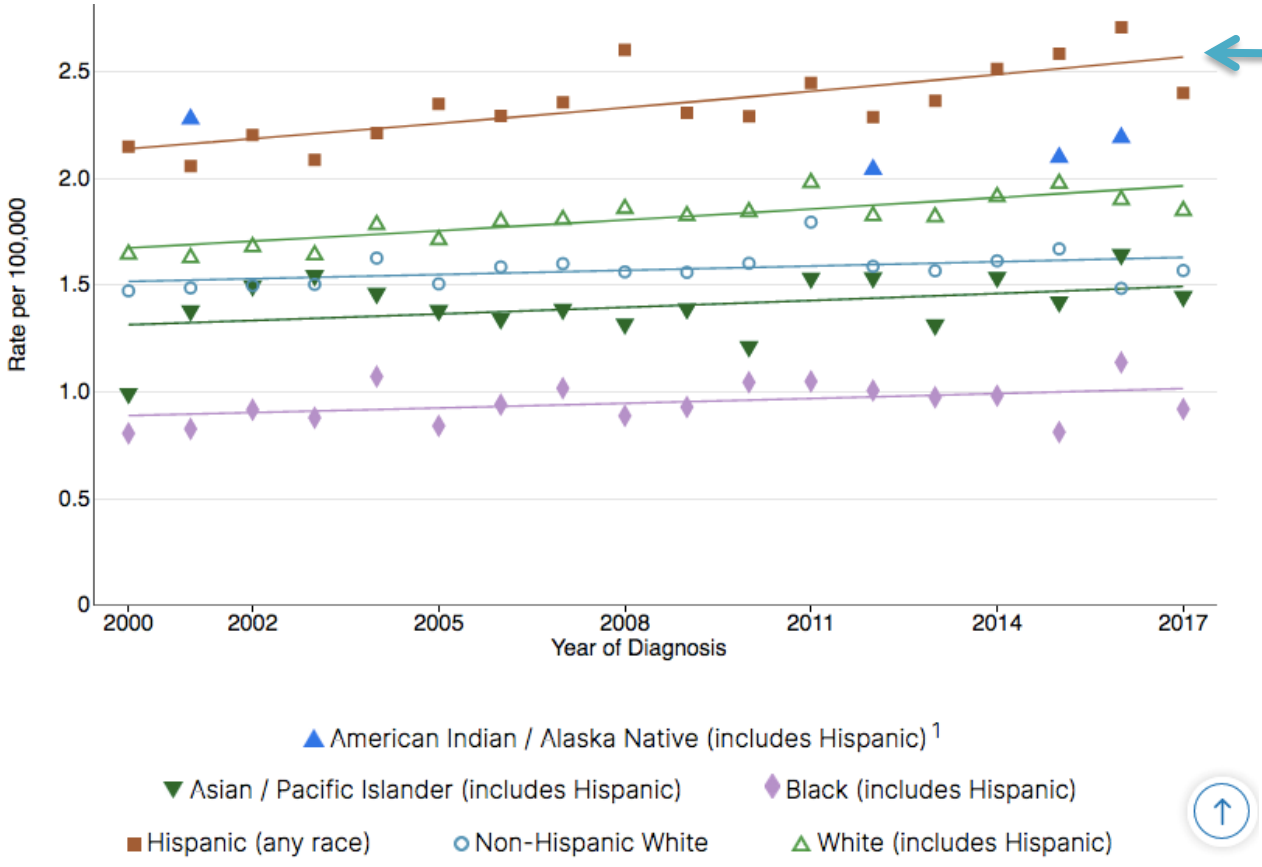
Q

QUESTION 1

In your practice, what would be the frontline treatment for this patient?

A. Rituximab + HyperCVAD
B. Rituximab + pediatric-inspired regimen (BFM-like)
C. HyperCVAD
D. Pediatric-inspired regimen (BFM-like)
E. Other

LATINO: THE HIGHEST INCIDENCE



Hispanic

34.8% of the SEER registry between 2000–2016 are Latinos

- California 53.9%
- Higher incidence increase in the AYA group

AYA, adolescents and young adults 15–39 years.

SEER statistics 2000-2017. Feng, et al. *Am J Epidemiol.* 2020.

HISPANICS UNDERREPRESENTED IN CLINICAL TRIALS

ORIGINAL ARTICLE

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Hagop Kantarjian, M.D., Anthony Stein, M.D., Nicola Gökbuget, M.D., Adele K. Fielding, M.B., B.S., Ph.D., Andre C. Schuh, M.D., Josep-Maria Ribera, M.D., Ph.D., Andrew Wei, M.B., B.S., Ph.D., Hervé Dombret, M.D., Robin Foà, M.D., Renato Bassan, M.D., Önder Arslan, M.D., Miguel A. Sanz, M.D., Ph.D., et al.

8.9%–9.6%

A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403

Wendy Stock, Selina M. Luger, Anjali S. Advani, Jun Yin, Richard C. Harvey, Charles G. Mullighan, Cheryl L. Willman, Noreen Fulton, Kristina M. Laumann, Greg Malnassy, Elisabeth Paietta, Edy Parker, Susan Geyer, Krzysztof Mrózek, Clara D. Bloomfield, Ben Sanford, Guido Marcucci, Michaela Liedtke, David F. Claxton, Matthew C. Foster, Jeffrey A. Bogart, John C. Grecula, Frederick R. Appelbaum, Harry Erba, Mark R. Litzow, Martin S. Tallman, Richard M. Stone, and Richard A. Larson

Blood 2019 133:1548–1559; doi: https://doi.org/10.1182/blood-2018-10-881961

15.3% (N = 45)

ORIGINAL ARTICLE

Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

Hagop M. Kantarjian, M.D., Daniel J. DeAngelo, M.D., Ph.D., Matthias Stelljes, M.D., Giovanni Martinelli, M.D., Michaela Liedtke, M.D., Wendy Stock, M.D., Nicola Gökbuget, M.D., Susan O'Brien, M.D., Kongming Wang, Ph.D., Tao Wang, Ph.D., M. Luisa Paccagnella, Ph.D., Barbara Sleight, M.D., et al.

"Other" 9%–10%

HyperCVAD?

ALL Particularities in Hispanic/Latino?

HIGHER MORTALITY RATE

Table 3. Regression-derived mortality rate ratios for acute lymphoid leukemia for children and adults by race and Hispanic subgroup.

	All combined	Children	Adults
Whites	1 (reference)	1 (reference)	1 (reference)
Blacks	0.83 (0.69–1.00)	1.07 (0.69–1.67)	0.79 (0.64–0.97)
Asian and Pacific Islanders	0.82 (0.68–0.99)	1.13 (0.71–1.80)	0.78 (0.64–0.95)
Hispanics[a]	1.80 (1.58–2.05)	2.27 (1.68–3.06)	1.73 (1.50–1.99)
Continental Hispanics	2.09 (1.82–2.39)	2.56 (1.93–3.40)	2.01 (1.73–2.33)
Mexicans	2.10 (1.81–2.42)	2.55 (1.89–3.43)	2.02 (1.72–2.38)
Central Americans	2.35 (1.88–2.93)	2.66 (1.64–4.31)	2.31 (1.80–2.96)
South Americans	1.67 (1.28–2.18)	2.59 (1.43–4.66)	1.55 (1.15–2.08)
Caribbean Hispanics	1.27 (1.05–1.54)	1.23 (0.74–2.03)	1.28 (1.04–1.58)
Puerto Ricans	1.34 (1.04–1.74)	*	1.39 (1.05–1.84)
Cubans	1.14 (0.84–1.54)	*	1.13 (0.82–1.55)
Dominicans	1.22 (0.83–1.79)	*	1.21 (0.79–1.84)

MORE HIGH-RISK GENETICS

ALL MDACC (N = 155)

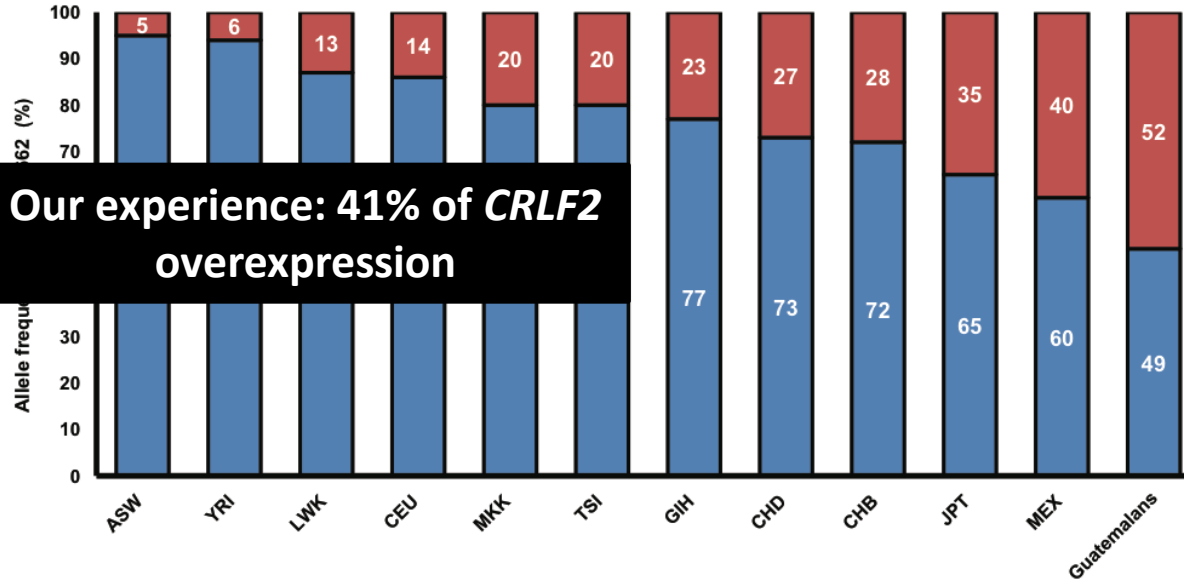
Ph-like: 36%

Hispanics: 68%
White: 23%
***P* <.001**

Pediatric ALL:
***CRLF2* overexpression –**
Hispanics 35.3% vs 7.1%

***GATA3* genetic variants**

- ✓ More frequent in Hispanics
- ✓ Predisposition to ALL
- ✓ Association with Ph-like



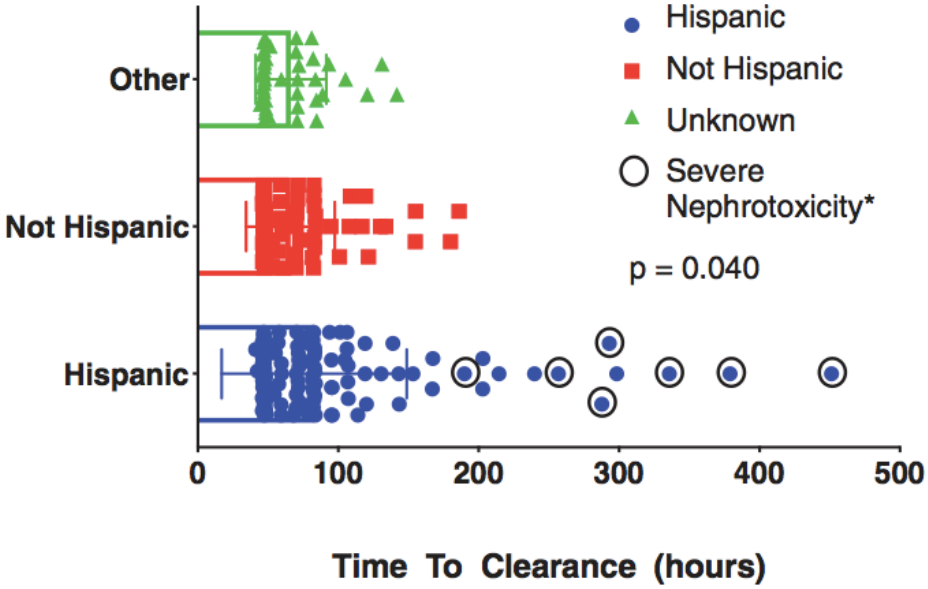
Our experience: 41% of *CRLF2* overexpression

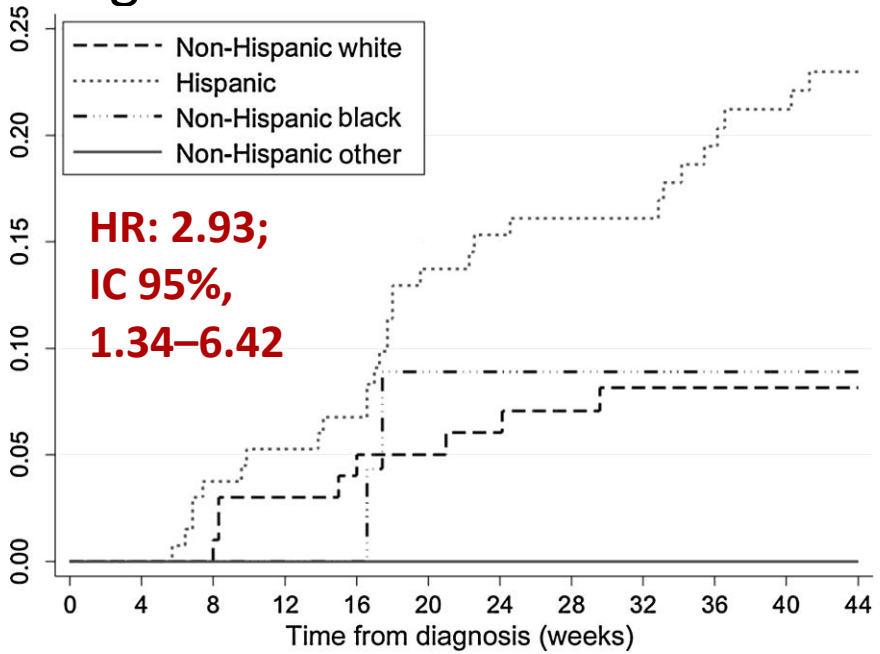
Jain, et al. *Blood.* 2017;129(5):572-581; Harvey, et al. *Blood.* 2010;115:5312; Almanza, et al. EHA 2020. EP429.

MORE TOXICITY?

✓ More **methotrexate-related toxicity**

CHILDREN/ADOLESCENTS: renal/neurologic





Mullikin, et al. *Leuk Lymphoma.* 2020;61(11):2771; Taylor, et al. *Clin Cancer Res*. 2018;24:5012.

MORE TOXICITY?

✓ **Asparaginase-related hepatotoxicity**

Up to 60% and related to hepatic steatosis

ASH global award: Pharmacogenomics and asparaginase-related toxicity in Mexican adults with ALL

Obesity (OR: 3.03)

Hispanic ethnicity (OR: 2.87)

Mexico

- **34% >15 years: obesity**
- **Hepatic steatosis up to 63%**
- **High rate of dyslipidemia predisposition**

Aldoss, et al. *Eur J Haematol.* 2016;96(4):375; Bernal, et al. *Rev Gastroenterol Mex.* 2019;84(1):69; Aguilar, et al. *Metabolism.* 2014;63(7):887.

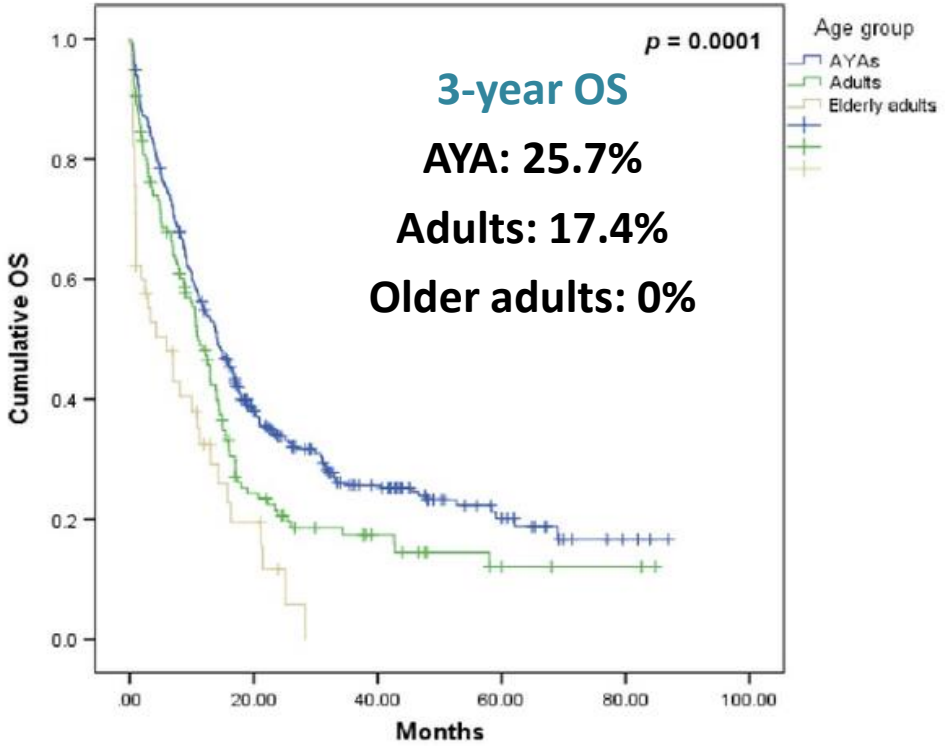
IN MEXICO: HISTORICALLY, ALL IS VERY FREQUENT AND HAS POOR OUTCOMES

51% of acute leukemia in adults

N = 559
47% treated with hyperCVAD

Induction-related mortality: 10.6%
In >39 years: 18%

Mortality during consolidation: 10.6%
AlloHSCT: 5.7%



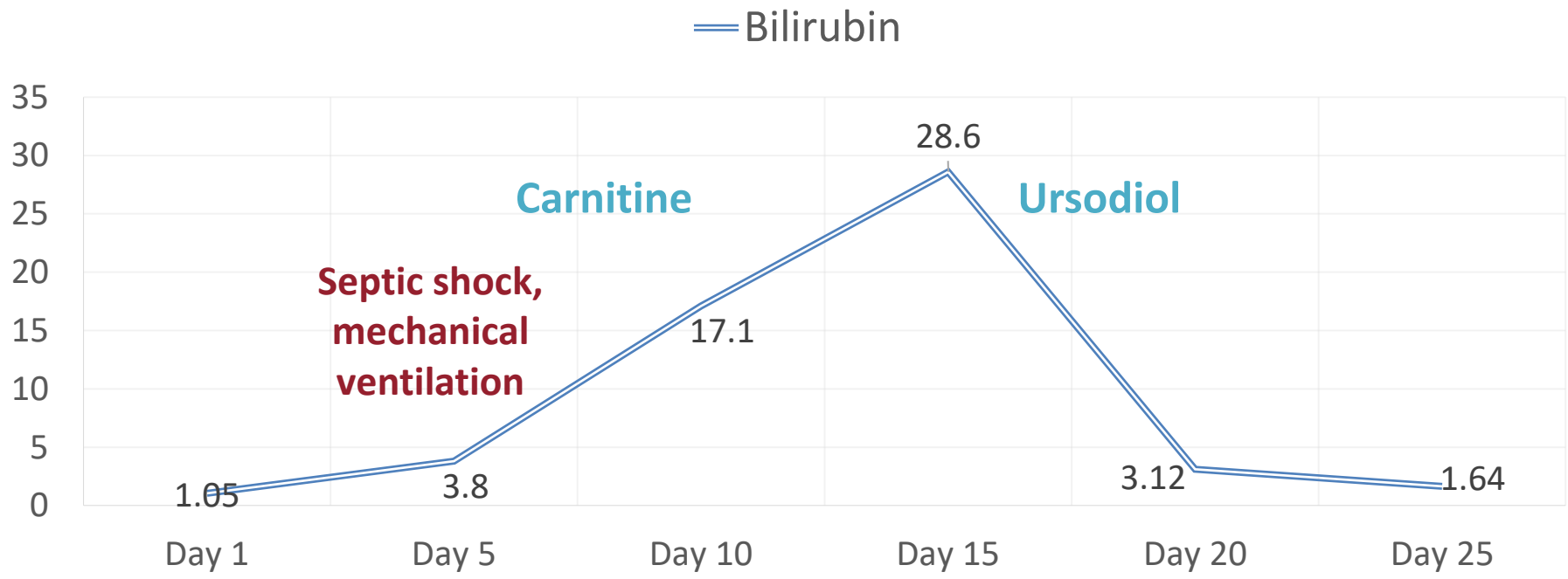
Crespo, et al. *Cancer Med*. 2018;7(6)2423-2433. Gómez-Almaguer, et al. *Clin Lymphoma Myeloma Leuk*. 2017;17(1):46-51.

CLINICAL CASE (continued)

Induction with modified CALGB 10403

Drug	Dose	D1	D8	D15	D22	D29
Vincristine	1.5mg/m2/m2 IV	*	*	*	*	
Daunorrubicin	25mg/m2 IV	*	*	*	*	
E. Coli Asparaginase	6,000 UI/m2 IM	D3 D5 D7 D9 D11 D13				
Dexametasone	5mg/m2 cada 12h	D1-D7		D15-D21		
Rituximab	375mg/m2		*			
IT QT AraC/MTX/ Dexa		*				*

CLINICAL CASE (continued)



CLINICAL CASE (continued)

Induction with modified CALGB 10403

Drug	Dose	D1	D8	D15	D22	D29
Vincristine	1.5mg/m2/m2 IV	*	* X	* X	* X	
Daunorrubicin	25mg/m2 IV	*	*	*	*	
E. Coli Asparaginase	6,000 UI/m2 IM	D3 D5 D7 D9 D11 D13 X X X				
Dexametasone	5mg/m2 cada 12h	D1-D7		D15-D21		
Rituximab	375mg/m2		*			
IT QT AraC/MTX/ Dexa		*				

Day 29: fully recovered; CR with negative MRD

Q

QUESTION 2

What would be the ideal subsequent management?

1. **Continue with full-dose CALGB 10403**
2. **Continue CALGB 10403 with a dose reduction of asparaginase**
3. **Change to another regimen (eg, hyperCVAD)**

CLINICAL CASE (continued)

- ✓ The patient continued with full-dose CALGB 10403
- ✓ No new episodes of hepatotoxicity, only grade 3 hypertriglyceridemia
- ✓ No hospitalizations/infectious complications
- ✓ He is at the end of the late intensification
- ✓ Last MRD still negative

1 HLA-identical brother

Q

QUESTION 3

The patient has high-risk genetics (Ph-like) with persistent negative MRD. What do you think about transplant?

1. **The patient should be consolidated with an alloHSCT because of the high-risk genetics**
2. **The patient should not be consolidated with alloHSCT if MRD is persistently negative**
3. **I don´t know**

OPEN QUESTIONS

1. **How to prevent and manage hepatotoxicity with asparaginase-based regimens? Obesity?**

2. **Best treatment strategy for high-risk genetic groups:**

Targeted-therapies for Ph-like?

First-line immunotherapy?

MRD-based consolidation strategy?

AlloHSCT for all?

THANK YOU

ALL in Latin America

Clinical Case

Wellington Silva, MD
Institute of Cancer, University of Sao Paulo, Brazil

DISCLOSURES

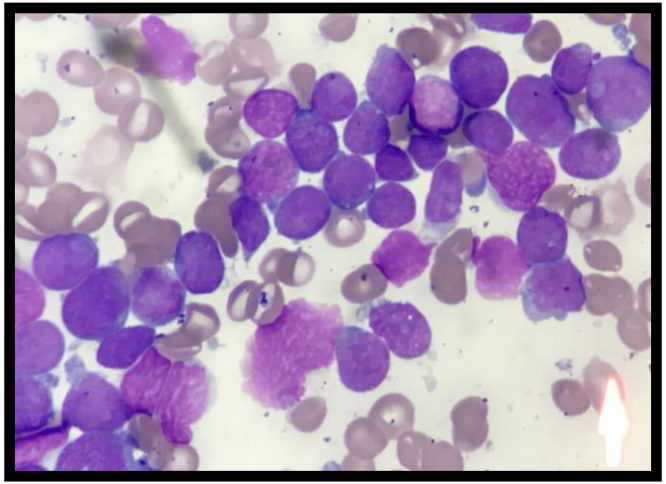
Advisory: Pfizer; Amgen; Daychio; Takeda.

Speaker: Pfizer; Amgen; Servier; Pintpharma.

Medical History

- 25-year old female, domestic worker
- No prior comorbidities

- **Easy bruising**
- **Cervical adenopathy**
- **Headache and blurred vision**



Peripheral blood: Hb 8.1 g/dl, WBC 10.9x10^9/L (48% blasts), Plat 40x10^9/L
Immunophenotyping: CD34+, CD19+, CD38+, CD22+,CD79a+, CD10+, CD20+, cyIgM+, CD13+,CD33+ → **B-cell lymphoblastic leukemia**

Medical History

- **FISH for t(9;22): positive**
- BM karyotype:
  52,XX,+X,+16,t(9;22)(q34;q11.2),+der(22),t(9;22)(q34;q11.2),
  +14,+17,+21[15]/46,XX[5]
- **BCR-ABL1 p190**

CSF assessment during pre-phase: 7 cells/mm^3, positive blasts in cytospin, 27.5% blasts confirmed by flow --> **CNS 3 disease**
RM brain → diffuse meningeal thickening in skull base (**infiltration**) / associated **cerebral venous thrombosis**

Q

Ph-positive B-cell lymphoblastic leukemia in AYA patient with CNS infiltration

Question

In your practice, what would be the frontline treatment for this patient?

A. R-HyperCVAD plus ITK
B. HyperCVAD plus ITK
C. Pediatric protocol plus ITK
D. Low-intensity induction (CS+ITK±vincristine) followed by chemo (“GRAAPH-2005”)
E. Other

Clinical Case

Induction with dexamethasone pulses + weekly vincristine + dasatinib 140 mg/d (‘GRAAPH-2005’ regimen) plus intrathecal chemo

BCR-ABL qPCR: 1.34%

Consolidation courses with alternating HCVAD courses plus dasatinib

Cranial irradiation 18Gy after C4

BCR-ABL qPCR: 0 (after C3 onwards)

Q

Question 2

In your practice, how would you manage CNS infiltration?

A. Intrathecal therapy only
B. Intrathecal plus radiotherapy
C. Intrathecal, radiotherapy and modification of chemotherapy regimen
D. Other

Clinical Case

- In the neutropenia post-C6, she developed a **severe septic shock** due to *E. coli* bloodstream infection
  - ARDS → Mechanic ventilation for 10 days
  - Ischemic limb necrosis
  - Severe kidney injury --> renal replacement therapy
  - UCI for 30 days

Without chemo and TKI for 40 days

BCR-ABL qPCR: 0.25

ABL mutation screening: negative

Q

Question 3

In your practice, which consolidation therapy do you choose in eligible patients?

A. Allogeneic HSCT regardless of molecular response status
B. Allogeneic HSCT only if no molCR
C. Autologous HSCT in pts with molCR
D. Continuous TKI in pts with molCR
E. Other

Clinical Case

Maintenance phase

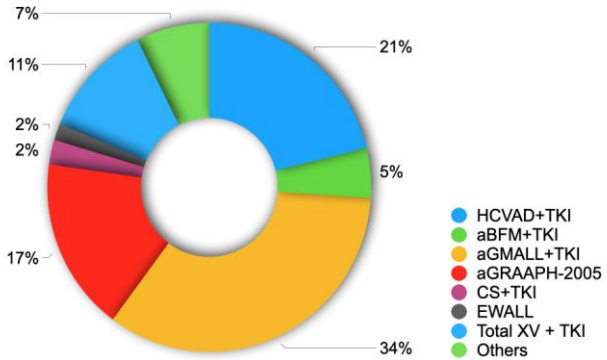
Prednisone + vincristine + dasatinib + intrathecal therapy

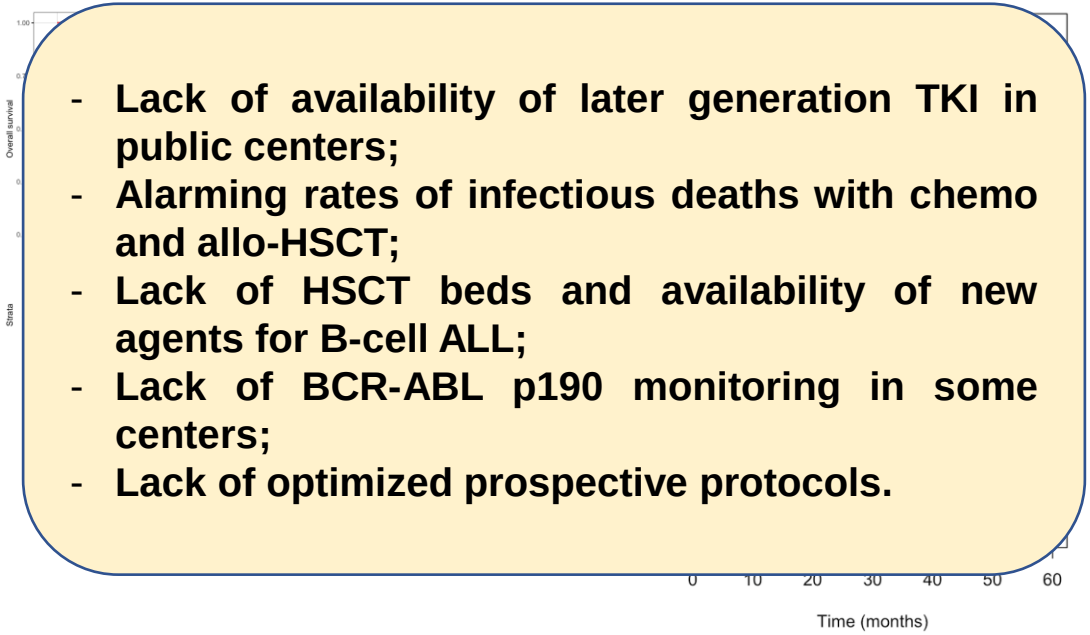
Patient promptly recovered the molecular complete response

Patient remains in molecular CR for 3 years – continuous dasatinib

Brazilian scenario of Ph+ ALL

Retrospective 10y cohort study (n=123) from 5 centers
- Median age 42 y (15-81)
- 29% Allo-SCT (pts<60y)



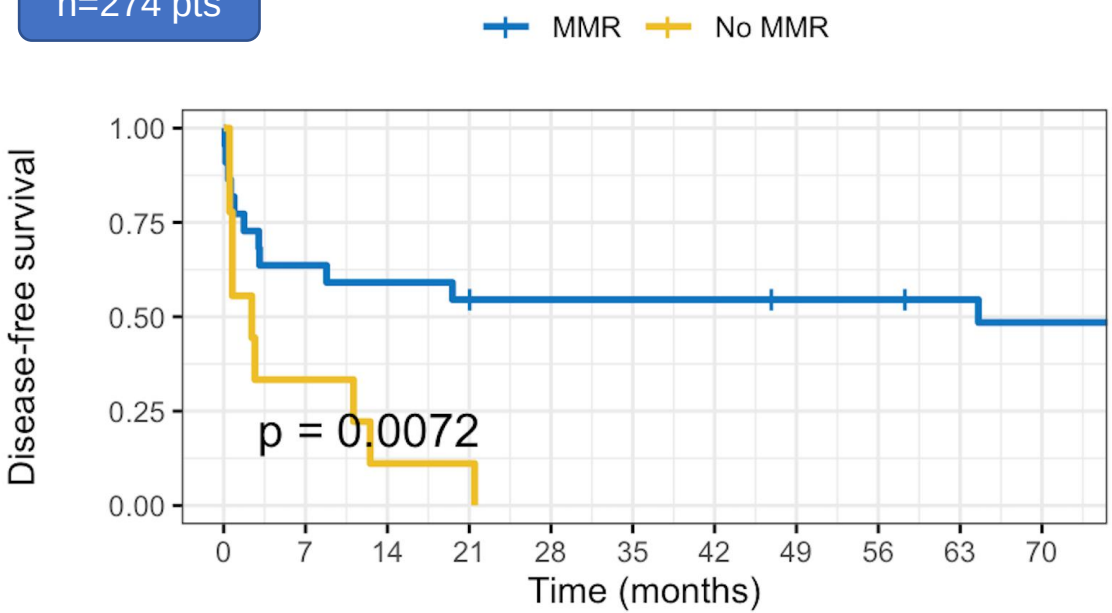


- **Lack of availability of later generation TKI in public centers;**
- **Alarming rates of infectious deaths with chemo and allo-HSCT;**
- **Lack of HSCT beds and availability of new agents for B-cell ALL;**
- **Lack of BCR-ABL p190 monitoring in some centers;**
- **Lack of optimized prospective protocols.**

Silva WF et al. Submitted for publication.

Brazilian scenario of HSCT in Ph+ ALL

n=274 pts



- 5y CIR: 29.7% (95% CI 23.6-36)
- 5y NRM: 33.9% (95% CI (27.6-40.5)

Ph-positivity – NRM: 27.5 vs 42.4% (HR = 3.14 [95% CI 1.07-9.2])

Silva WF et al. Unpublished data.

Open Questions

- **Do all patients draw benefit from third-generation TKIs (ponatinib)?**
- **How and when do you search for ABL mutation?**
- **How many courses and in which intensity of chemotherapy is needed to sustain complete remission?**
- **Is there still a role for cranial irradiation?**
- **How to apply new agents in frontline in Ph+ pts?**
- **How to better select pts for allo-HSCT in CR1?**

Thank you!

wellington.fernandes@hc.fm.usp.br

Global Leukemia Academy

Educational ARS Questions

Elias Jabbour

APTITUDE HEALTH®

Q

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

Q

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-negative 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

Global Leukemia Academy

Break

APTITUDE HEALTH®

Global Leukemia Academy

Personalized induction and maintenance approaches for AML

Naval Daver

APTITUDE HEALTH®

Personalized induction and maintenance approaches for AML

APRIL 2021

Naval Daver, MD
Director, Leukemia Research Alliance Program,
Associate Professor
Department of Leukemia
MD Anderson Cancer Center

Clinical Applications of Molecular Studies in AML

- ***FLT3* mutations – add *FLT3* inhibitor (midostaurin, sorafenib, quizartinib, gilteritinib), consider allo-SCT**
- ***IDH1-2* mutations – add *IDH* inhibitor: enasidenib (AG-221/IDH2 inhibitor), ivosidenib (AG-120/IDH1 inhibitor)**
- ***NPM1* mutation in diploid CG – Ara-C sensitivity, VEN sensitivity**
- ***TP53* mutation – consider decitabine 10 days ± others (GO, venetoclax); new agents (APR, CD47) refer to allo-SCT**
- ***RAS* mutations – no targetable therapies in AML, common resistance to VEN, FLT3i, IDHi; consider clinical trials**

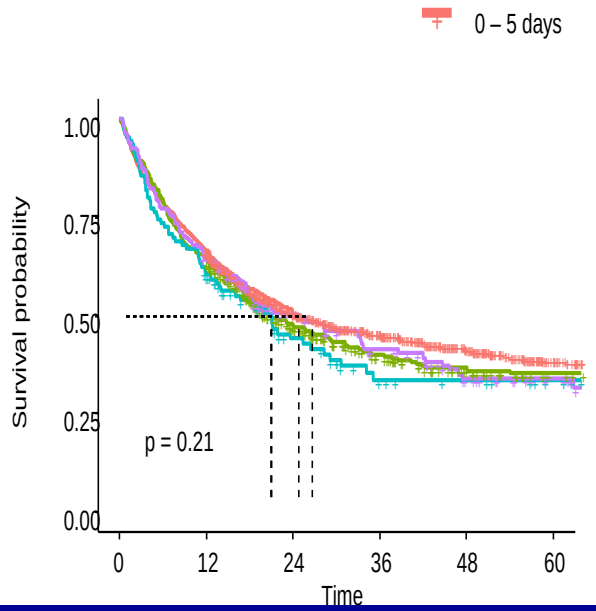
National Comprehensive Cancer Network. NCCN Guidelines. Acute Myeloid Leukemia v2.2018.

Time from diagnosis to treatment does not affect outcome in intensively treated patients with newly diagnosed acute myeloid leukemia

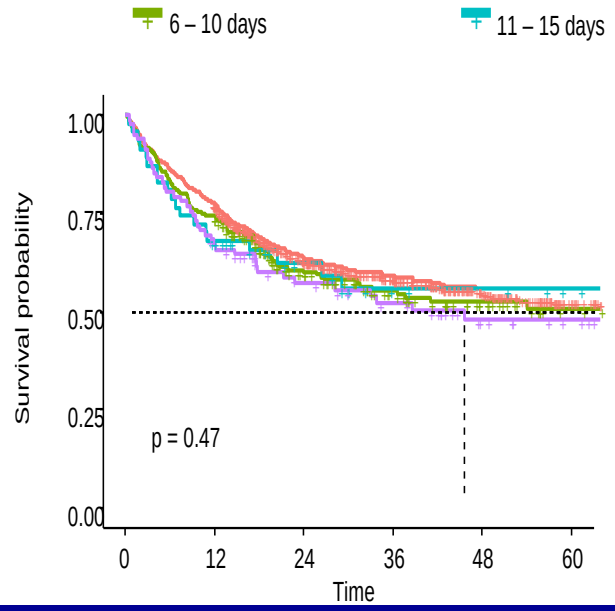
Röllig C, Kramer M, Schliemann C, Mikesch JH, Steffen B, Krämer A, Sauer T, Hänel M, Herbst R, Schäfer-Eckart K, Noppeney R, Jost E, Brümmendorf TH, Krause S, Kunzmann V, Einsele H, Scholl S, Hochhaus A, Fransecky L, Kaufmann M, Neubauer A, Niemann D, Schaich M, Frickhofen N, Kiani A, Heits F, Krümpelmann U, Kaiser U, Kullmer J, Wass M, Klein S, Stölzel F, von Bonin M, Middeke JM, Thiede C, Schetelig J, Ehninger GE, Baldus CD, Müller-Tidow C, Platzbecker U, Serve H, Bornhäuser M

TDT Groups: Overall Survival

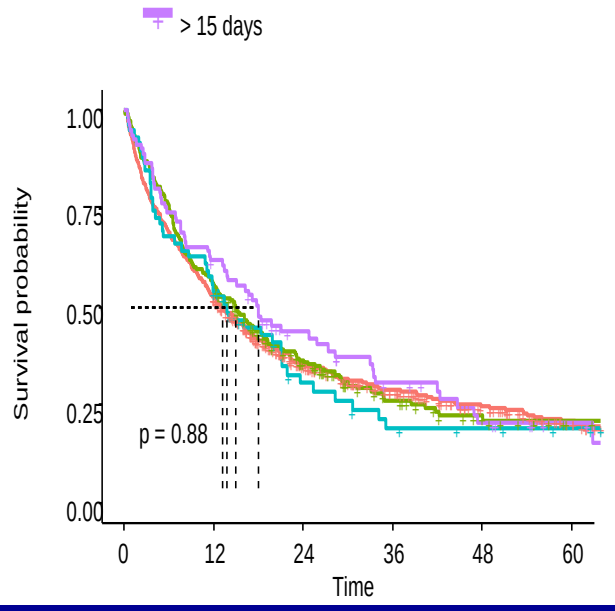
All ages



≤60 years



>60 years



No impact of TDT on CR, early death, and OS in multivariable models.
In practice, would avoid delays >5–7 days if possible.

1. APL: ATRA + As_2O_3 Without Chemotherapy in APL: MD Anderson Experience

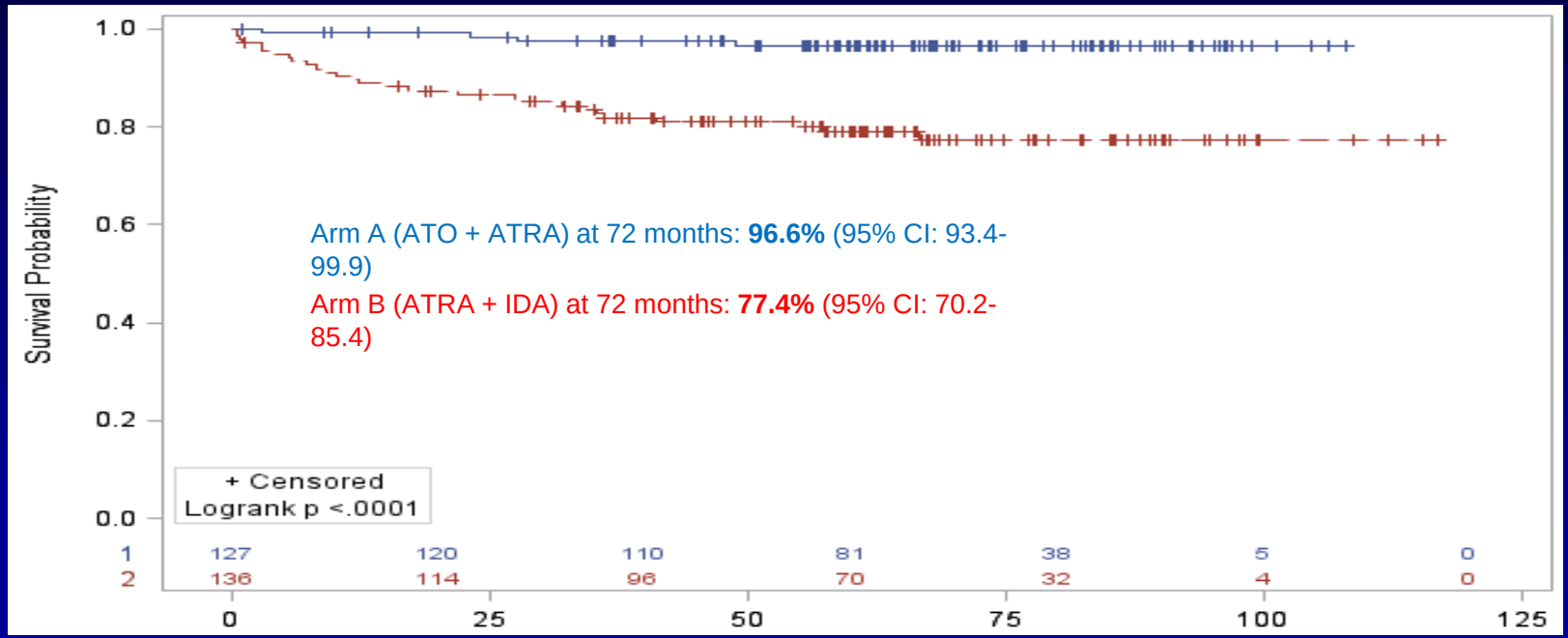
- **Induction**
  - ATRA 45 mg/m^2/D until CR
  - As_2O_3 0.15 mg/kg/D until CR
  - Gemtuzumab (GO) 9 mg/m^2 × 1 if WBC >10 × 10^9/L
- **Maintenance**
  - ATRA 45 mg/m^2/D × 2 wk Q mo × 6
  - As_2O_3 0.15/kg/D × 4 wk Q2 mo × 3
  - GO in PCR+

Ravandi F, et al. *J Clin Oncol*. 2009;27:504-510.

APL0406: Updated Event-Free Survival

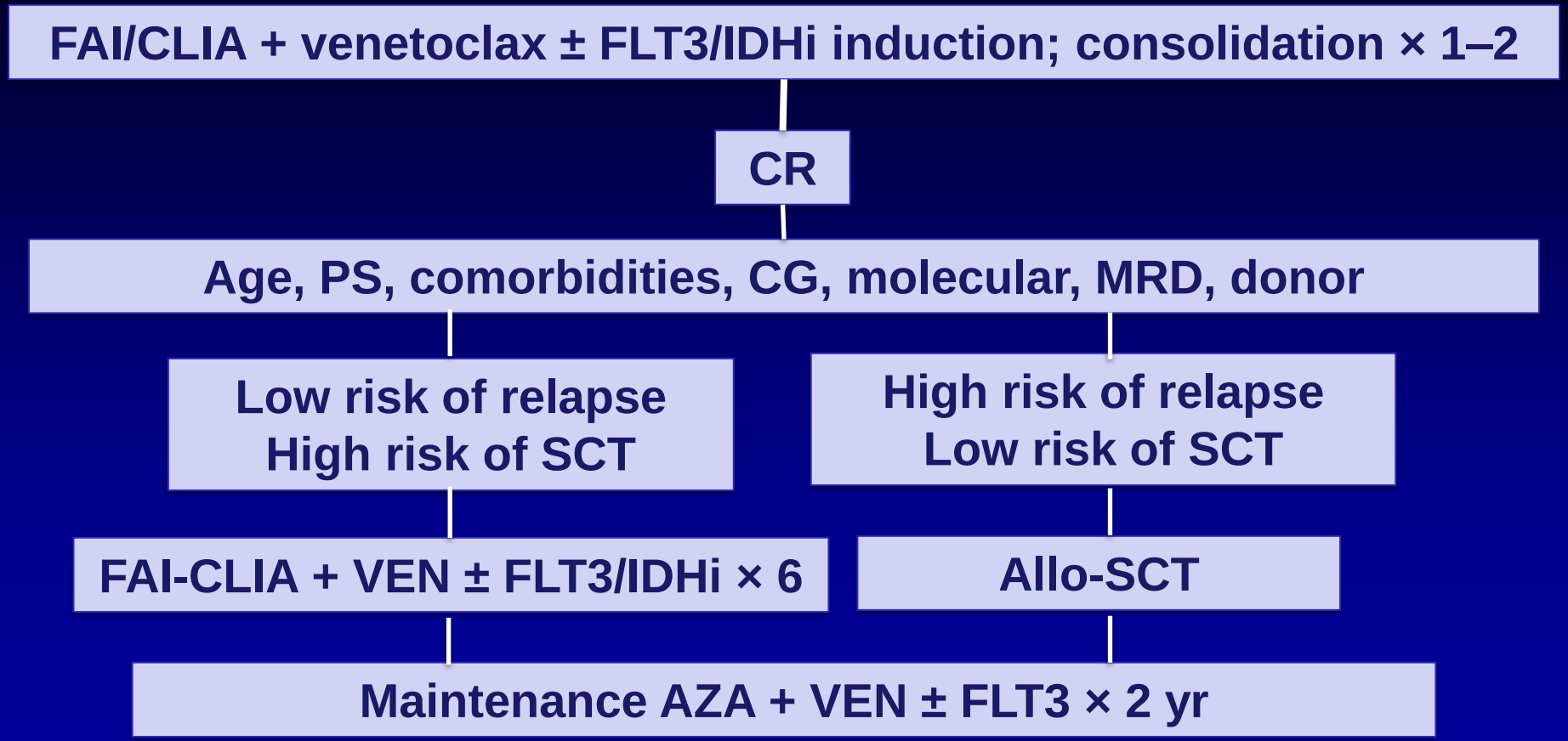
276 pts; follow-up 67 months

Event-free survival

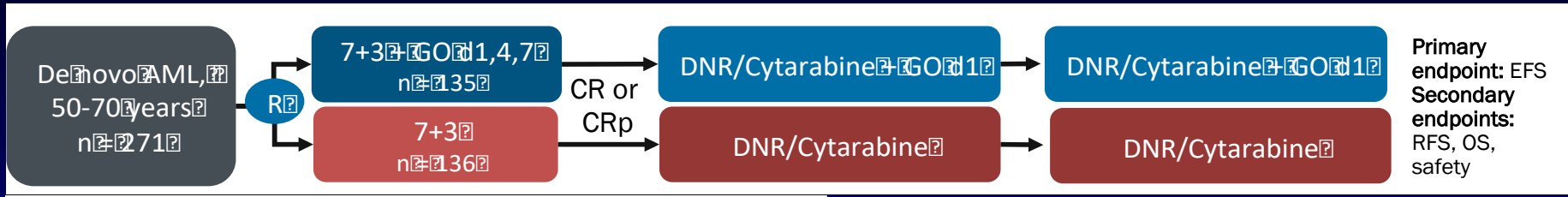


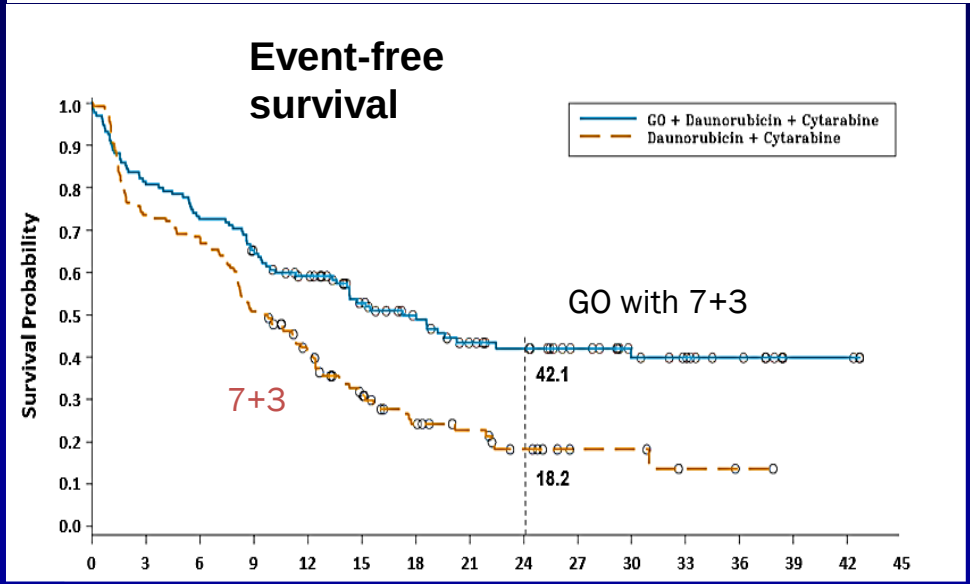
Intl Symposium on APL, Rome, Sept 2017 (unpublished)

Since 2009: Therapy of Younger AML at MD Anderson in 2020+



2. CD33-Targeted Therapy – Gemtuzumab Ozogamicin
ALFA-0701: Phase III Trial of GO Plus 7+3 vs 7+3



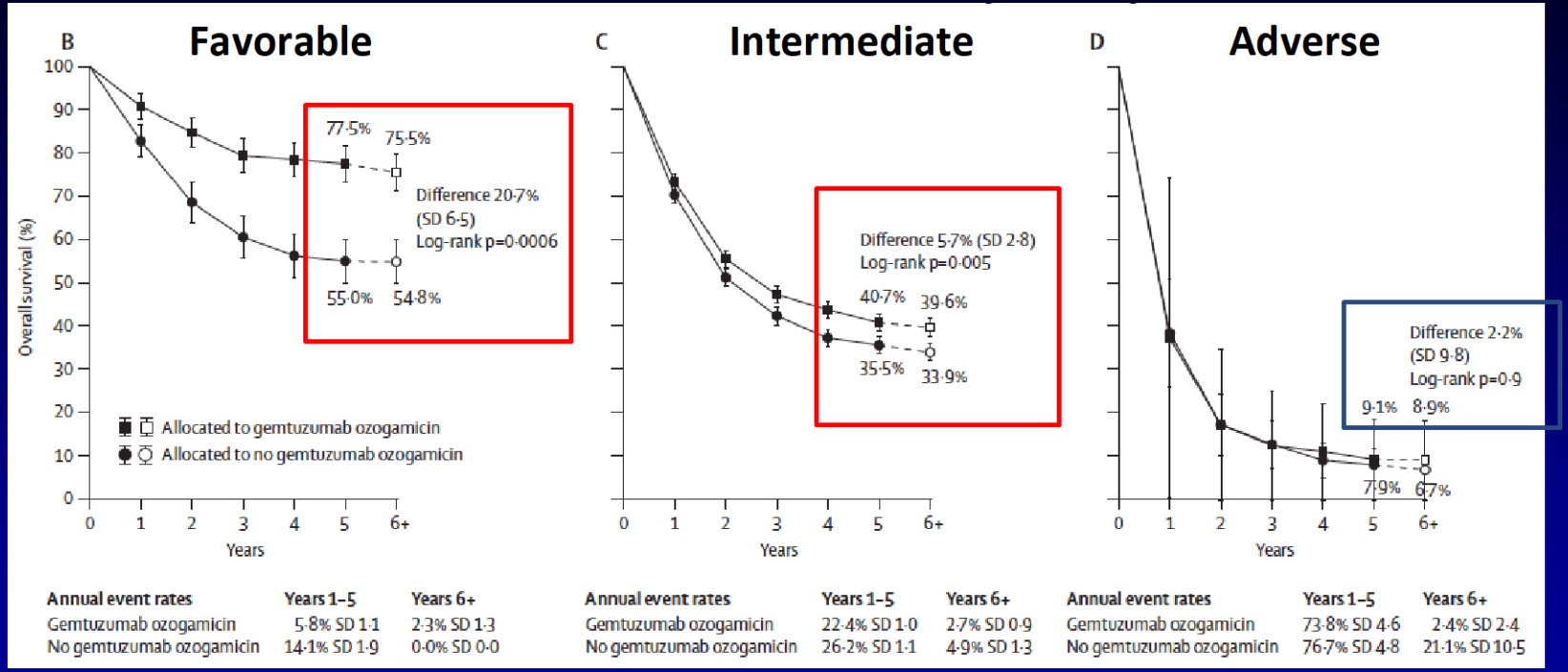


- GO better for favorable/intermediate risk

- Increased grade 3 hemorrhage
- Prolonged thrombocytopenia
- No increase in early mortality (3.8% vs 2.2%) with GO
- VOD 4.6% (GO/7+3) vs 1.5% (7+3)

Lambert J, et al. *Haematologica.* 2019;104(1):113-119.

Meta-analysis of Gemtuzumab Ozogamicin Plus 7+3



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Meta-analysis of overall survival of 3325 AML patients stratified by cytogenetic risk

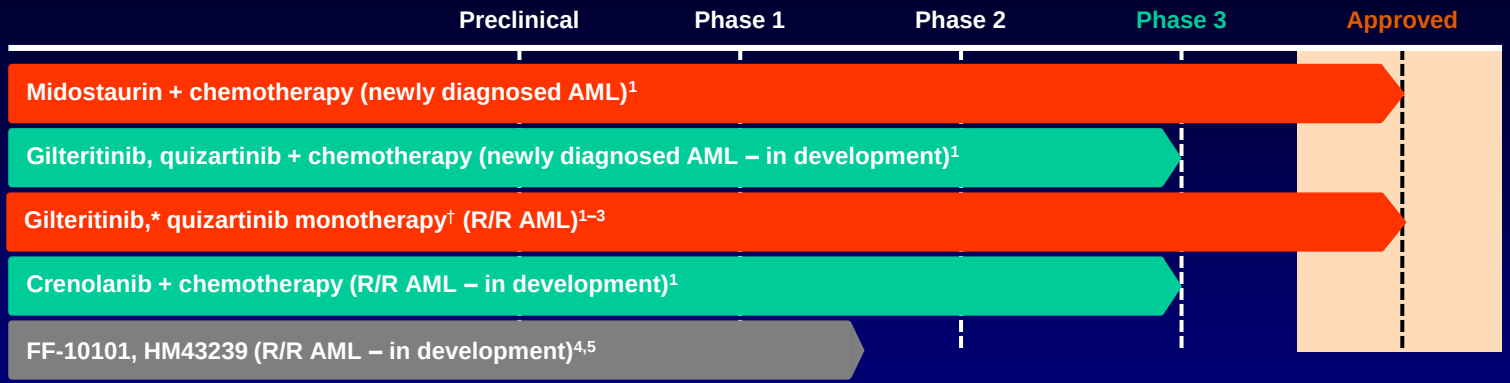
Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

MDACC: FLAG-GO in CBF AML

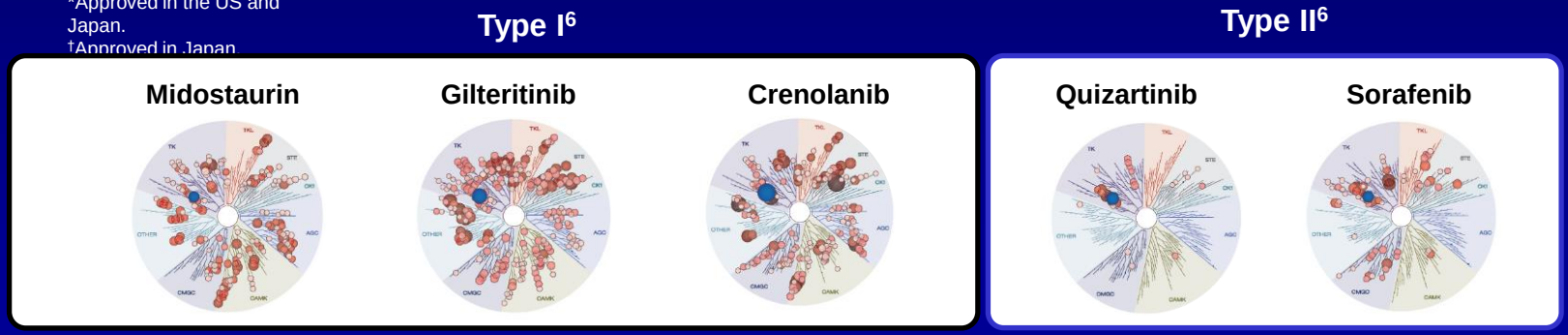
- Induction: fludarabine (FL) 30 mg/m^2 days 1–5; cytarabine (A) 2 g/m^2 IV days 1–5; gemtuzumab ozogamicin (GO) 3 mg/m^2 day 1; G-CSF (G) 5 μg/kg day –1 until neutrophil recovery (can use peg-filgrastim 6 mg × 1 day 4)
- Consolidation: FL and A for 4 (amended to 3) days, GO (in cycle 2/3 and 5/6) and G as in induction for 6 cycles
- Peg–G-CSF instead of G-CSF allowed beyond day 5 (induction) or day 4 (consolidation)

Replaced GO with low-dose idarubicin 6 mg/m^2 days 3 and 4 after patient 50

3. Current and Future Induction Approaches for *FLT3*-Positive AML

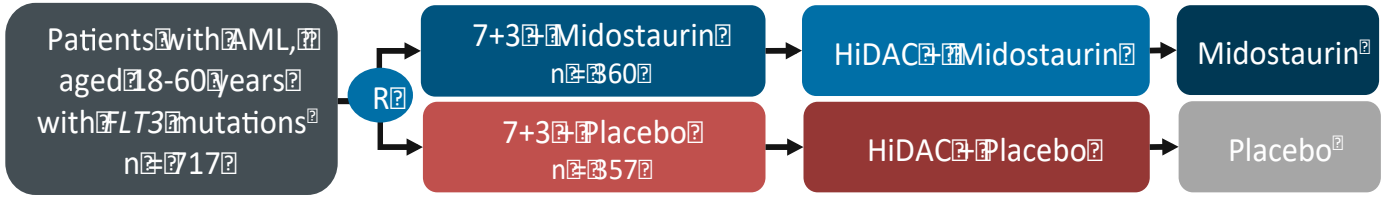


*Approved in the US and Japan.
†Approved in Japan

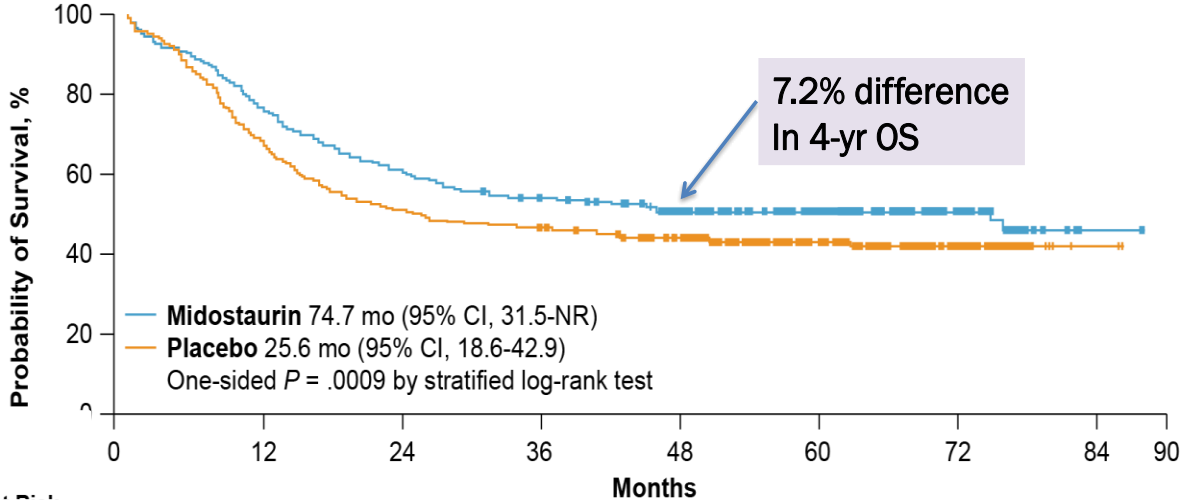


1. Short NJ, et al. *Ther Adv Hematol.* 2019;10:2040620719827310; 2. Daiichi Sankyo. Press release. Available at: https://www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/007030.html; 3. Astellas. Press release. Available at: https://www.astellas.com/en/news/14271; 4. ClinicalTrials.gov. NCT03194685. Available from: https://clinicaltrials.gov/ct2/show/NCT03194685; 5. ClinicalTrials.gov. NCT03850574. Available from: https://clinicaltrials.gov/ct2/show/NCT03850574; 6. Aikawa T, et al. Presented at the 2019 Annual Meeting of the AACR; March 29–April 03, 2019; Atlanta, GA. Abstract 131.8

Midostaurin Plus 7+3 vs 7+3 in De Novo *FLT3*-Mutant AML

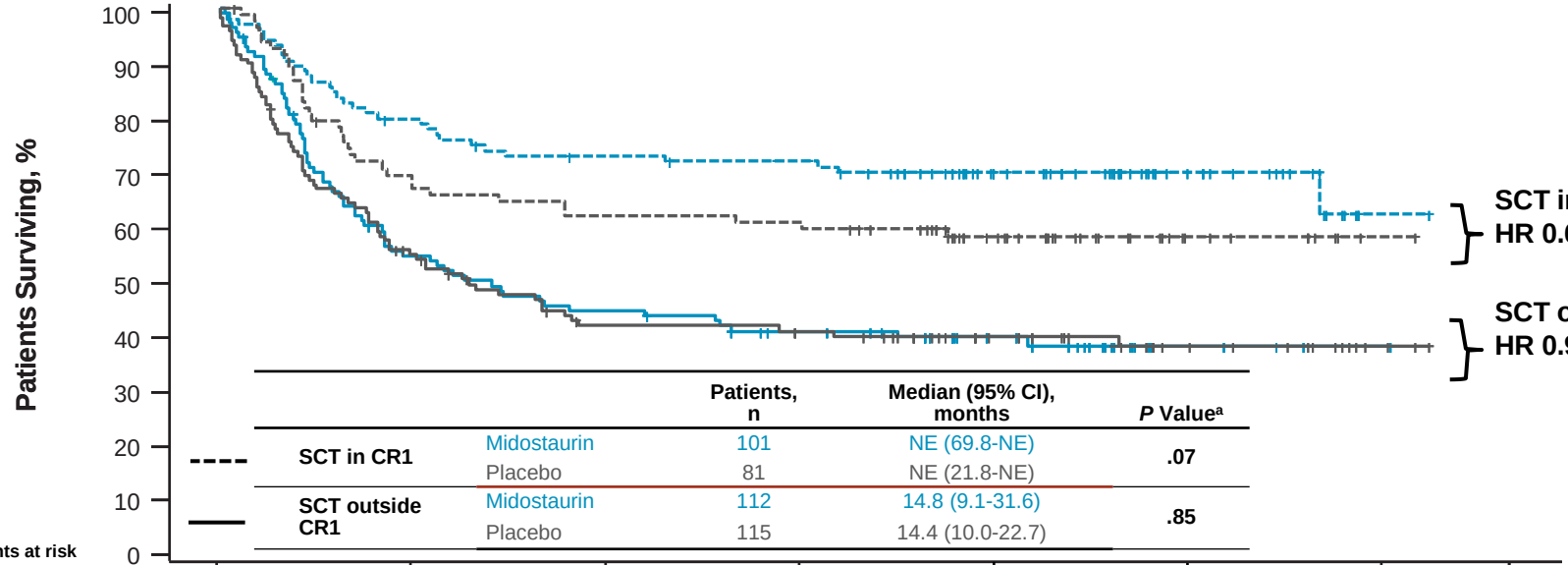


Primary endpoint: OS
Secondary endpoints: EFS, OS, CR, DFS



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

OS, Posttransplant With 3+7 Plus Mido vs 3+7 Plus Placebo



		Patients, n	Median (95% CI), months	*P* Value[a]
SCT in CR1	Midostaurin	101	NE (69.8-NE)	.07
	Placebo	81	NE (21.8-NE)	
SCT outside CR1	Midostaurin	112	14.8 (9.1-31.6)	.85
	Placebo	115	14.4 (10.0-22.7)	

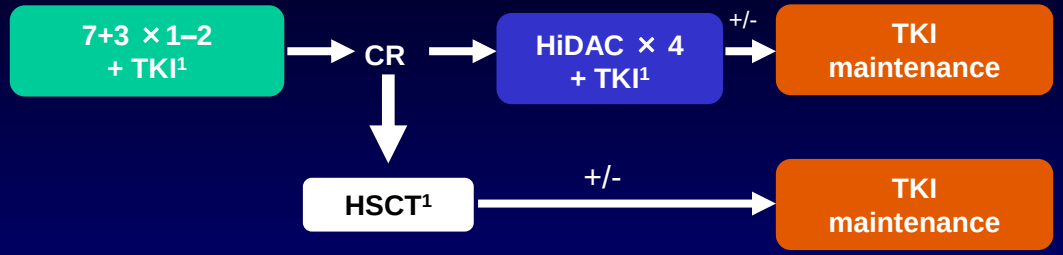
Patients at risk

SCT in CR1					
Midostaurin	101	71	63	21	0
Placebo	81	50	45	12	0
SCT outside CR1					
Midostaurin	112	49	36	5	0
Placebo	115	47	37	13	0

*Stratified on *FLT3* subtype; two-sided, long-rank *P* value.

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

Combining FLT3 Inhibitors With Standard Therapies
Frontline Intensive Chemotherapy Plus FLT3 Inhibitor

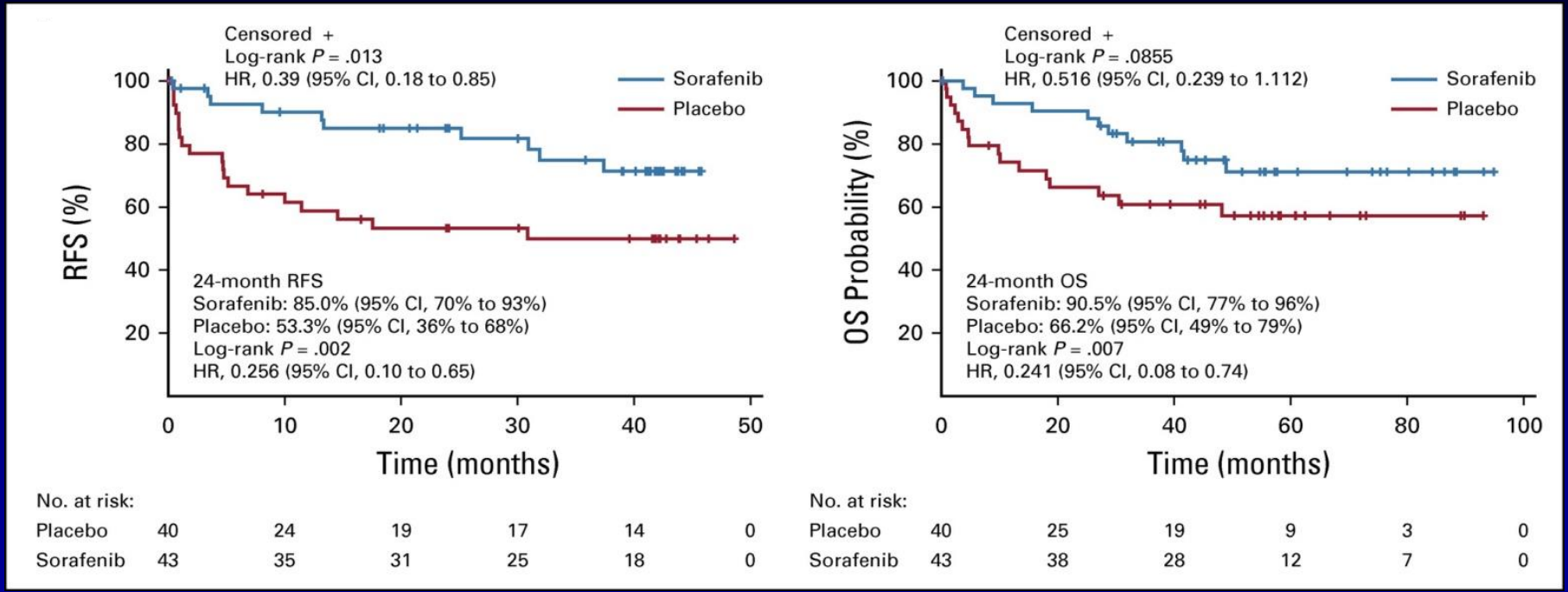


RATIFY[2]	Midostaurin (n = 360)	Placebo (n = 357)	*P* Value*
CR by day 60, n (%)	212 (59)	191 (53)	.15
CR in induction/ consolidation, n (%)	**239 (66)**	211 (59)	.045
Days to CR, median (range)	37 (20–99)	36 (20–112)	

Second-Generation FLT3 Inhibitor	CRc Rate, n (%)
Gilteritinib plus 7+3[3]	31/33 (94)
Crenolanib plus 7+3[4]	24/25 (96)
Quizartinib plus 7+3[5]	16/19 (84)†

*_P_ value is 2-sided and was calculated with the use of Fisher's exact test; †Includes CRc/MLFS.
CR, complete remission; HiDAC, high-dose cytarabine; HSCT, hematopoietic stem cell transplantation; TKI, tyrosine kinase inhibitor.
1. American Cancer Society. Treatment of AML. Available at: https://www.cancer.org/cancer/acute-myeloid-leukemia/treating/typical-treatment-of-aml.html. Accessed October 2019; 2. Stone RM, et al. *Blood.* 2015;126:abstract 6; 3. Pratz K, et al. ASH 2017. Abstract 722; 4. Wang ES, et al. ASH 2016. Abstract 1071; 5. Altman JK, et al. *Am J Hematol.* 2018;93:213-221.

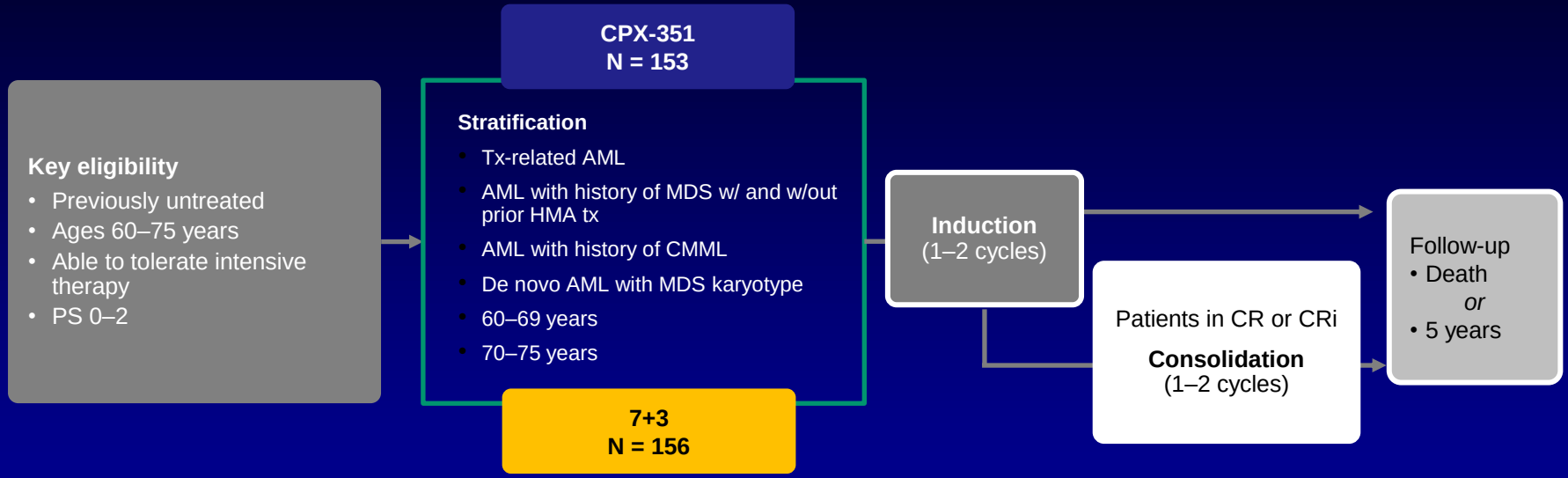
RFS and OS in FLT3+ AML in CR After HCT Treated With Sorafenib vs Placebo (SORMAIN)



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

4. AML With Myelodysplasia-Related Changes (AML-MRC)

Phase III Study of CPX-351 vs 7+3 in Older Patients With Newly Diagnosed High-Risk AML

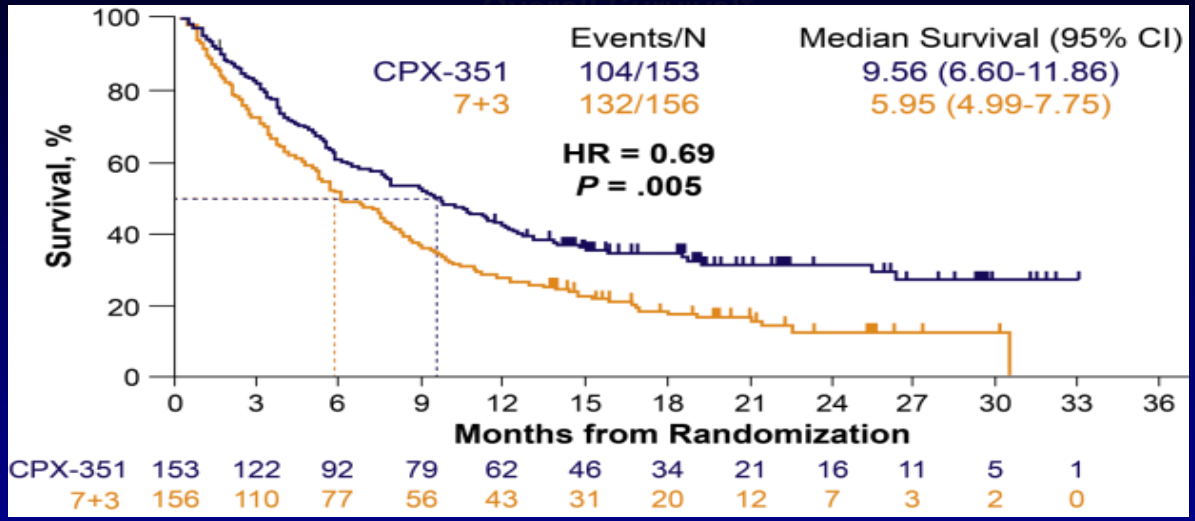


Primary endpoint: overall survival

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete remission; Cri, complete remission with incomplete platelet recovery; HMA, hypomethylating agents; MDS, myelodysplastic syndromes; PS, patient performance status; Tx, therapy.

Lancet J, et al. ASCO 2016. Abstract 7000.

CPX-351 vs 7+3 in Newly Diagnosed Secondary AML: Clinical Outcomes

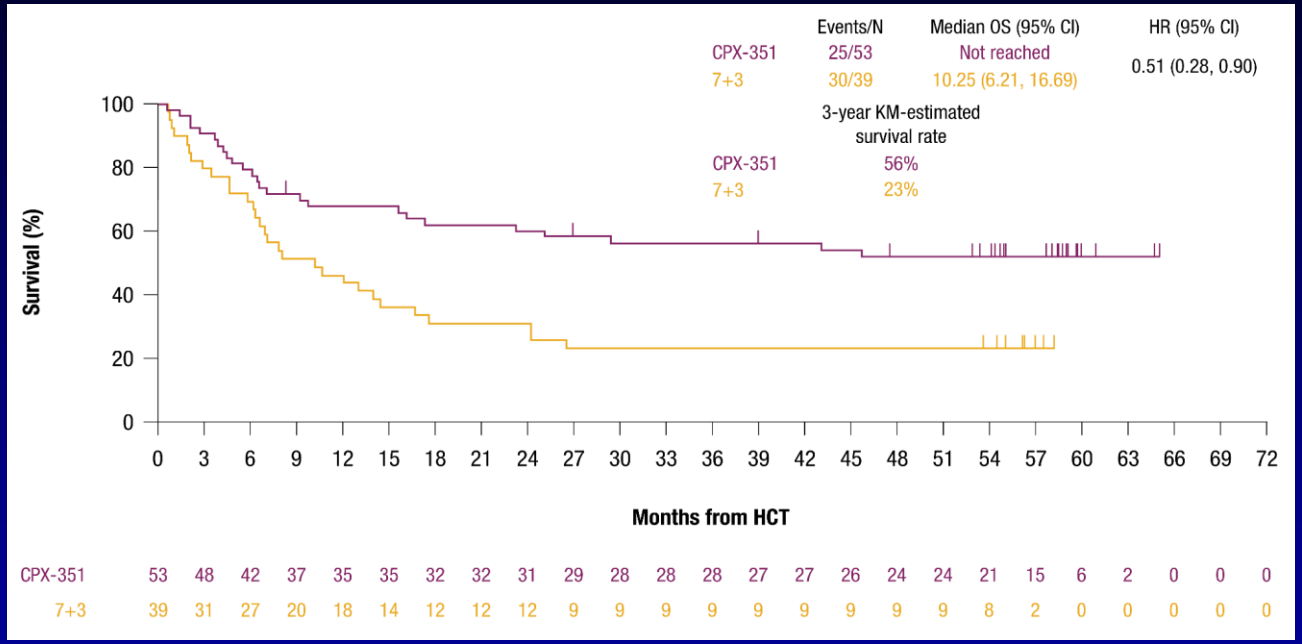


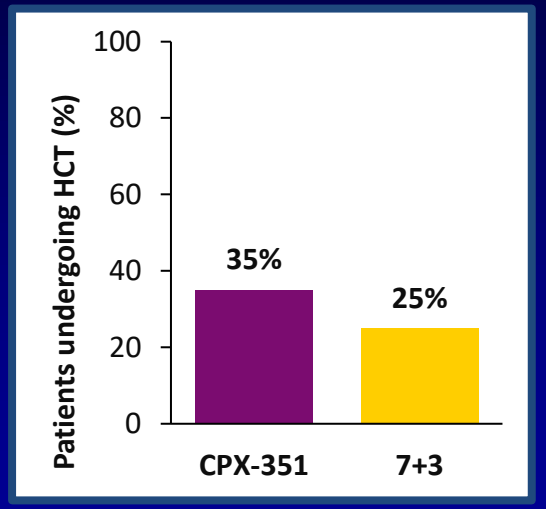
	CPX-351 (n = 153)	7+3 (n = 156)	Odds Ratio	*P* Value
CR + CRi	**47.7%**	**33.3%**	**1.77 (1.11, 2.81)**	**.016**
HCT rate	34.0%	25.0%	1.54 (0.92, 2.56)	.098
Deaths ≤60 days*	**13.8%**	**21.8%**		

*Kaplan-Meier estimate.

Medeiros BC, et al. ASH 2016; Abstract 902.

Overall Survival Landmarked From the HCT Date (long-term follow-up of CPX351 vs 3+7 phase III)





Kaplan-Meier–estimated survival rate landmarked from the date of HCT was >50% at 3 and 5 years for patients treated with CPX-351

Lancet J, et al. ASH 2020. Abstract 635.

5. Novel Intensive Therapy Approaches: Nonmolecular or Cytogenetic Targeted Groups – FLAG-IDA-VEN: Study Cohorts and Treatment Schedule

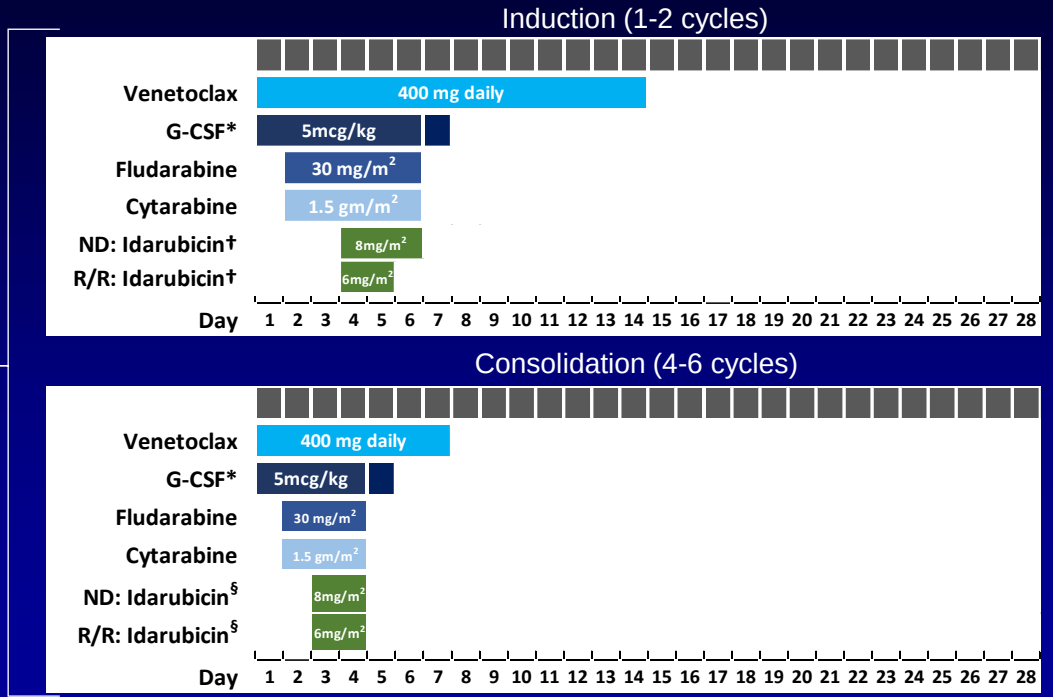
Phase 1b	Phase 2A	Phase 2B
R/R AML	ND AML	R/R AML
N = 16	N = 29	N = 23

Induction	Consolidation
Venetoclax 400 mg D1-14	Venetoclax 400 D1-7
G-CSF D1-6	G-CSF D1-4
Pegfilgrastim or biosimilar D7	Pegfilgrastim or biosimilar D5
Fludarabine 30 mg/m^2 D2-6	Fludarabine 30 mg/m^2 D2-4
Cytarabine 1.5 gm/m^2 D2-6	Cytarabine 1.5 gm/m^2 D2-4
ND: Idarubicin 8 mg/m^2 D4-6	ND: Idarubicin 8 mg/m^2 D3-4
R/R: Idarubicin 6 mg/m^2 D4-5	R/R: Idarubicin 6 mg/m^2 D3-4

Phase 1b		Phase 2
Cytarabine 2 gm/m^2	RP2D*	**Cytarabine 1.5 gm/m^2**
Venetoclax D1-21		**Venetoclax D1-14**

*5/6 initially enrolled phase Ib patients developed bacteremia/sepsis with phase Ib dosing

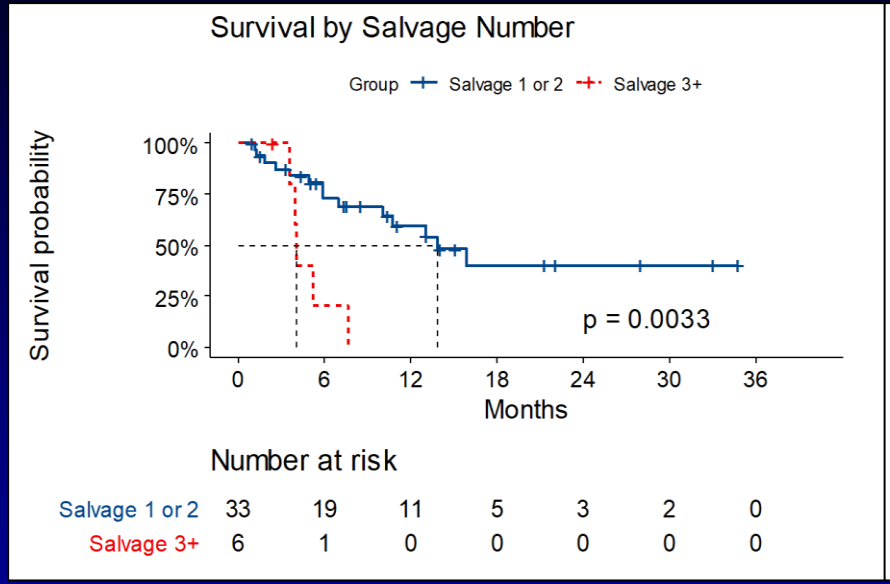
Phase 2 Induction/Consolidation Schedule

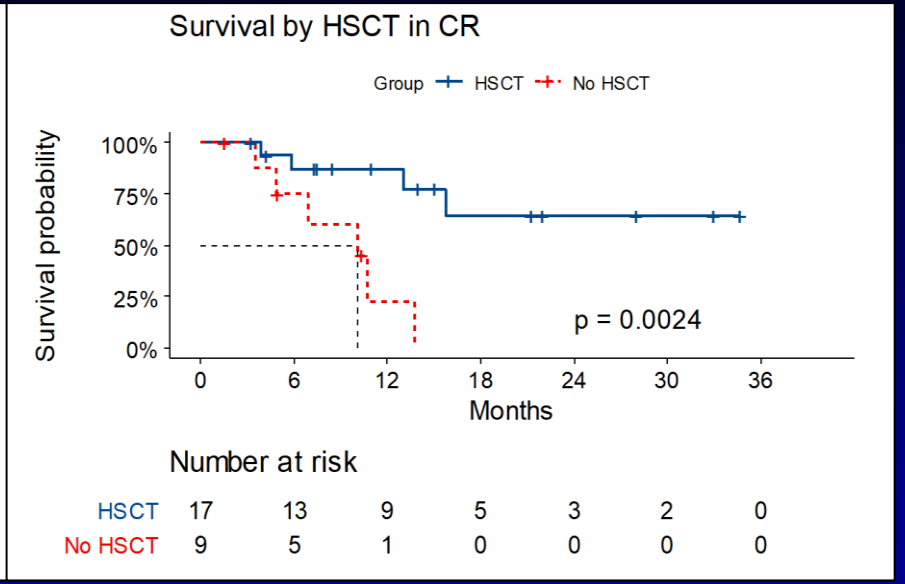


*G-CSF: 5 mcg/kg the day prior to and days of IV chemotherapy followed by 1 dose of pegfilgrastim or biosimilar each 28 D cycle.
†Induction: ND AML = Idarubicin 8 mg/m^2 days 4–6; R/R AML = Idarubicin 6 mg/m^2 days 4 and 5.
§Consolidation: Idarubicin permitted on days 3 and 4 in 2 postremission cycles (ie, C2 or C3 and C5 or C6) at physician discretion.

Lachowiez C, et al. ASH 2020. Abstract 332.

FLAG-IDA-VEN: R/R AML Outcomes

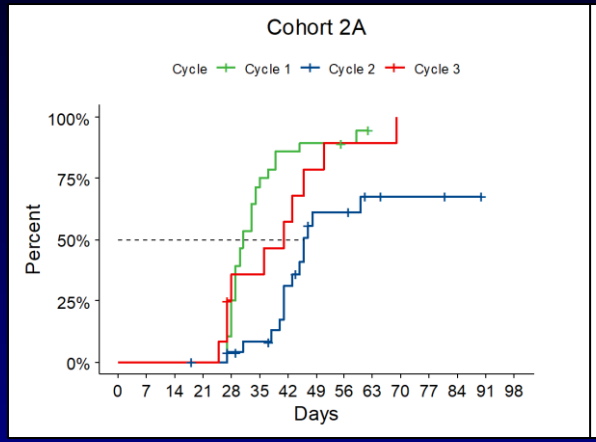


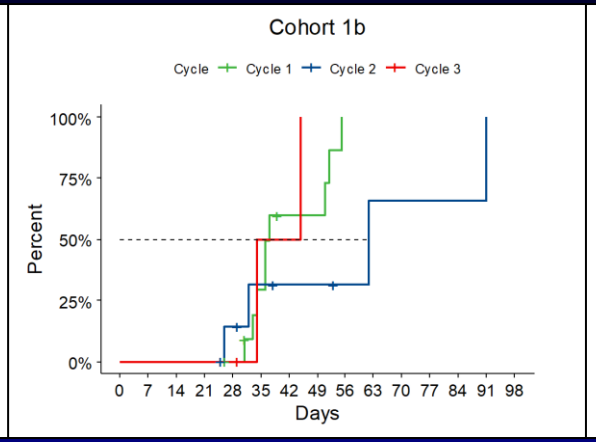


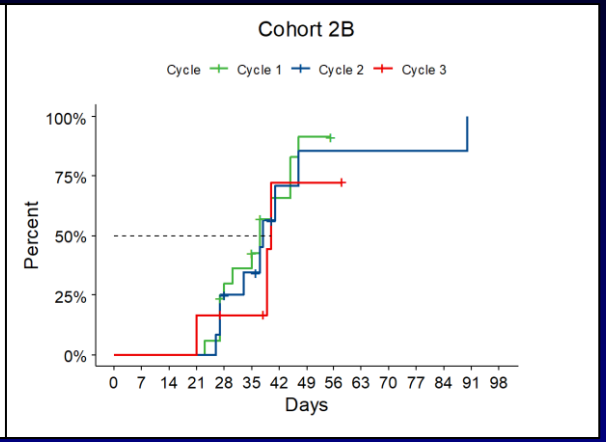
Variable	Salvage #1	Salvage #2	Salvage #3	CRc	HSCT
Event-Free Survival	11 (5-NE)	10 (7-NE)	-	11 (9-NE)	NR (16-NE)
Overall Survival	16 (7-NE)	14 (11-NE)	4 (3.8-NE)	16 (11-NE)	NR (16-NE)

Lachowiez C, et al. ASH 2020. Abstract 332.

FLAG-IDA-VEN: Median Time to Count Recovery*





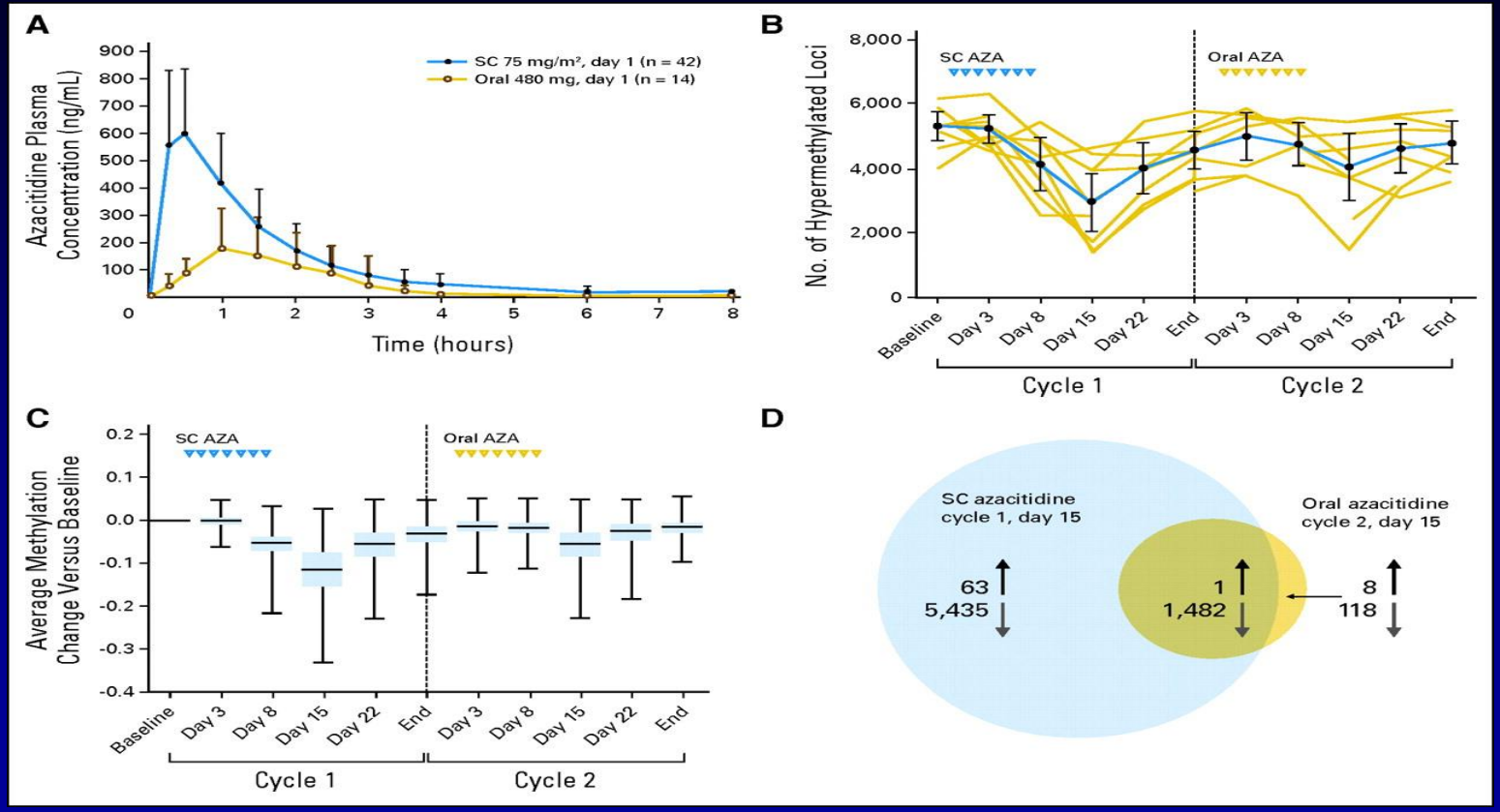


	Phase 2A ND AML (N = 29)	Phase Ib (Dose Finding) R/R AML (N = 16)	Phase 2B (Expansion) R/R AML (N = 23)
Cycle #1	31 days	37 days	37 days
Cycle #2	46 days	62 days	38 days
Cycle #3	41 days	40 days	40 days

*Count recovery: ANC ≥500 and platelet count ≥ 50,000 /µL

Lachowiez C, et al. ASH 2020. Abstract 332.

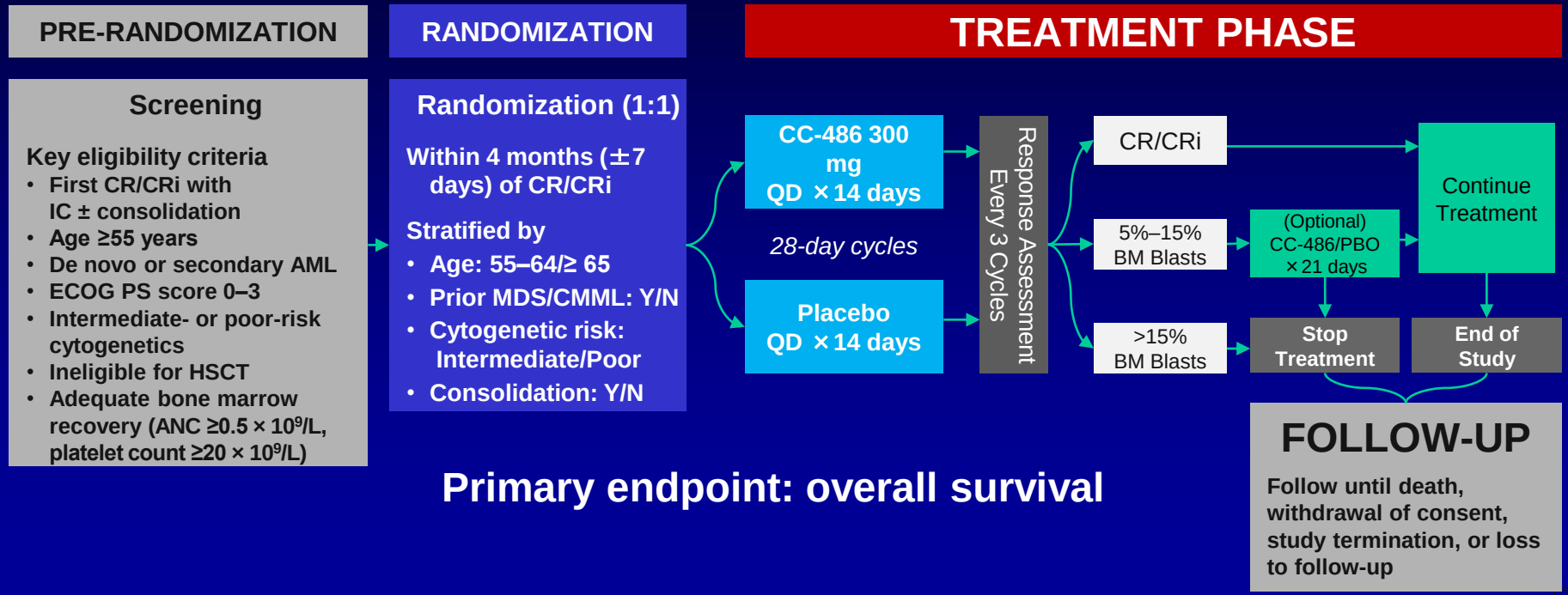
Maintenance: CC486 in MDS and AML



Garcia-Manero G, et al. *J Clin Oncol.* 2011;29(18):2521.

QUAZAR AML-001: Study Design

- International, multicenter, placebo-controlled, double-blind, randomized, phase III study that enrolled patients from 148 sites in 23 countries (NCT01757535)

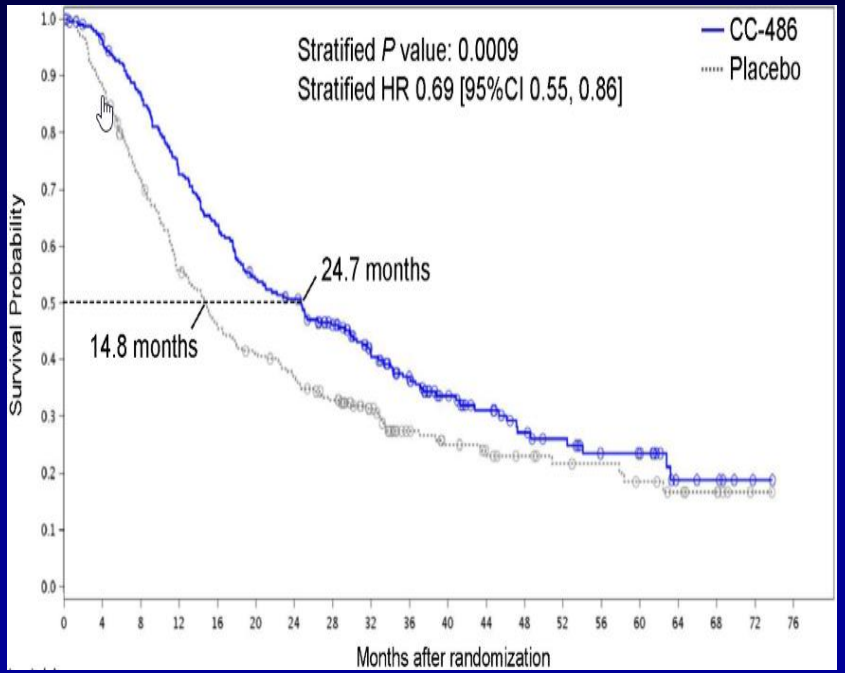


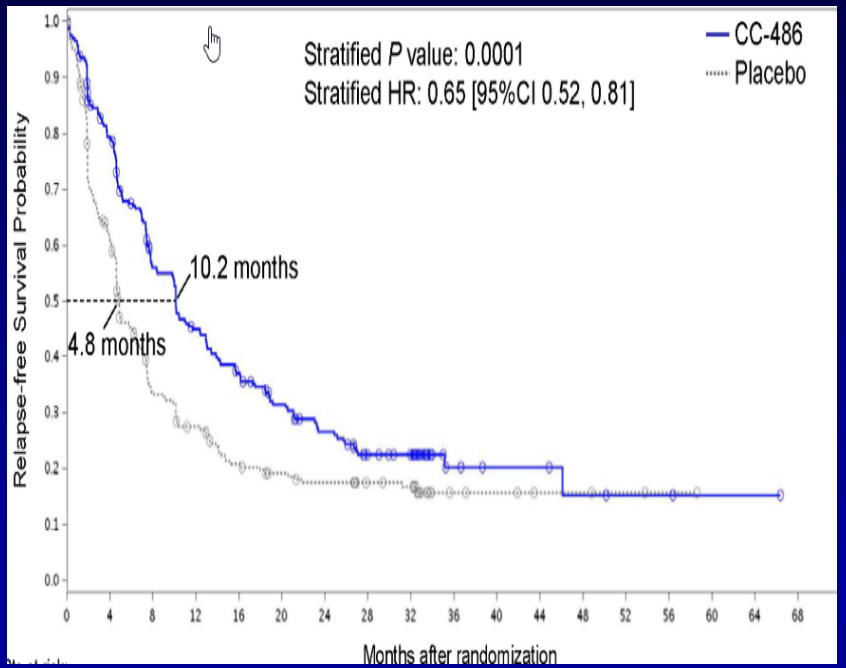
Primary endpoint: overall survival

Wei AH, et al. *Blood.* 2019;134: LBA 3.

Phase III Study of Oral Azacitidine vs Placebo as Maintenance in AML (QUAZAR-AML-001)

- 472 pts 55+ yr (median age 68 yr) with AML in CR-Cri <4 mo randomized to CC-486 300 mg/ daily × 14 Q mo (n = 238) or PBO (n = 234)

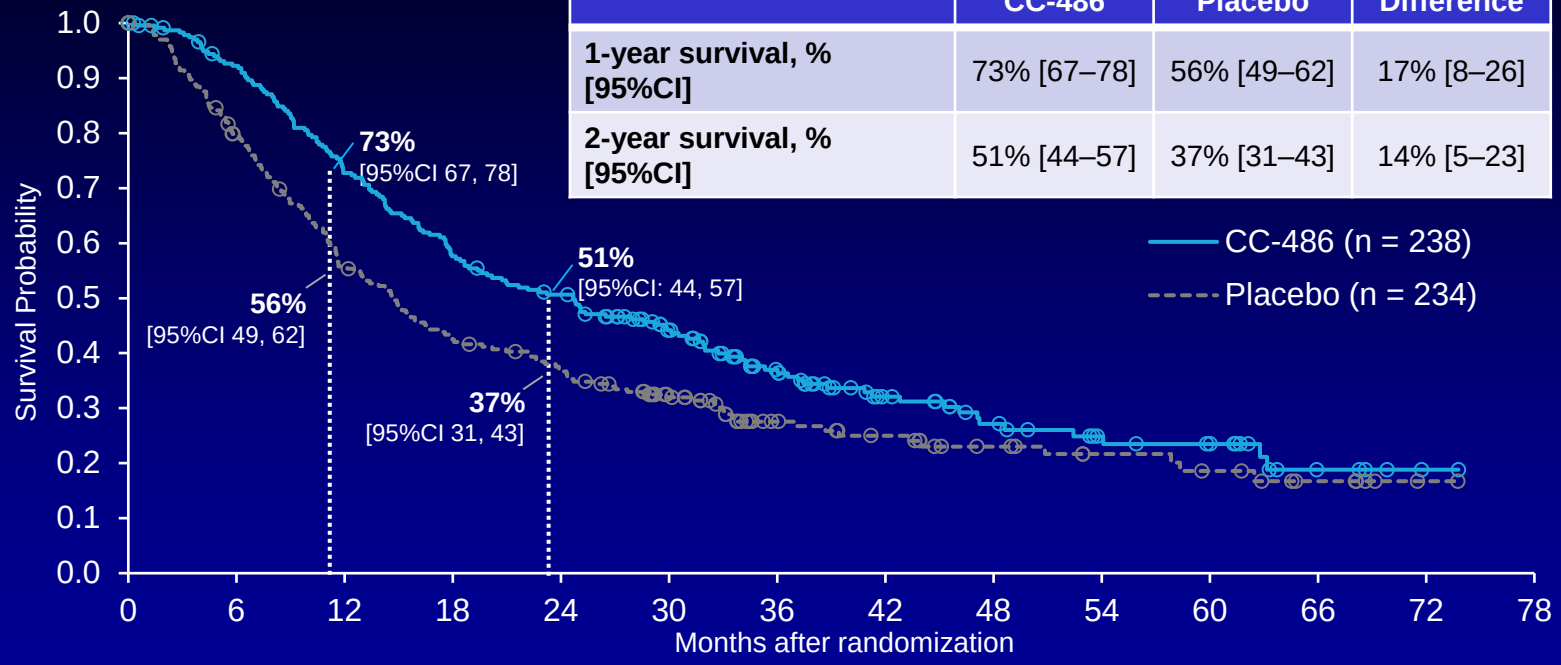




Wei AH, et al. *Blood.* 2019;134: LBA 3.

One-Year and 2-Year Survival

	CC-486	Placebo	Difference
1-year survival, % [95%CI]	73% [67–78]	56% [49–62]	17% [8–26]
2-year survival, % [95%CI]	51% [44–57]	37% [31–43]	14% [5–23]



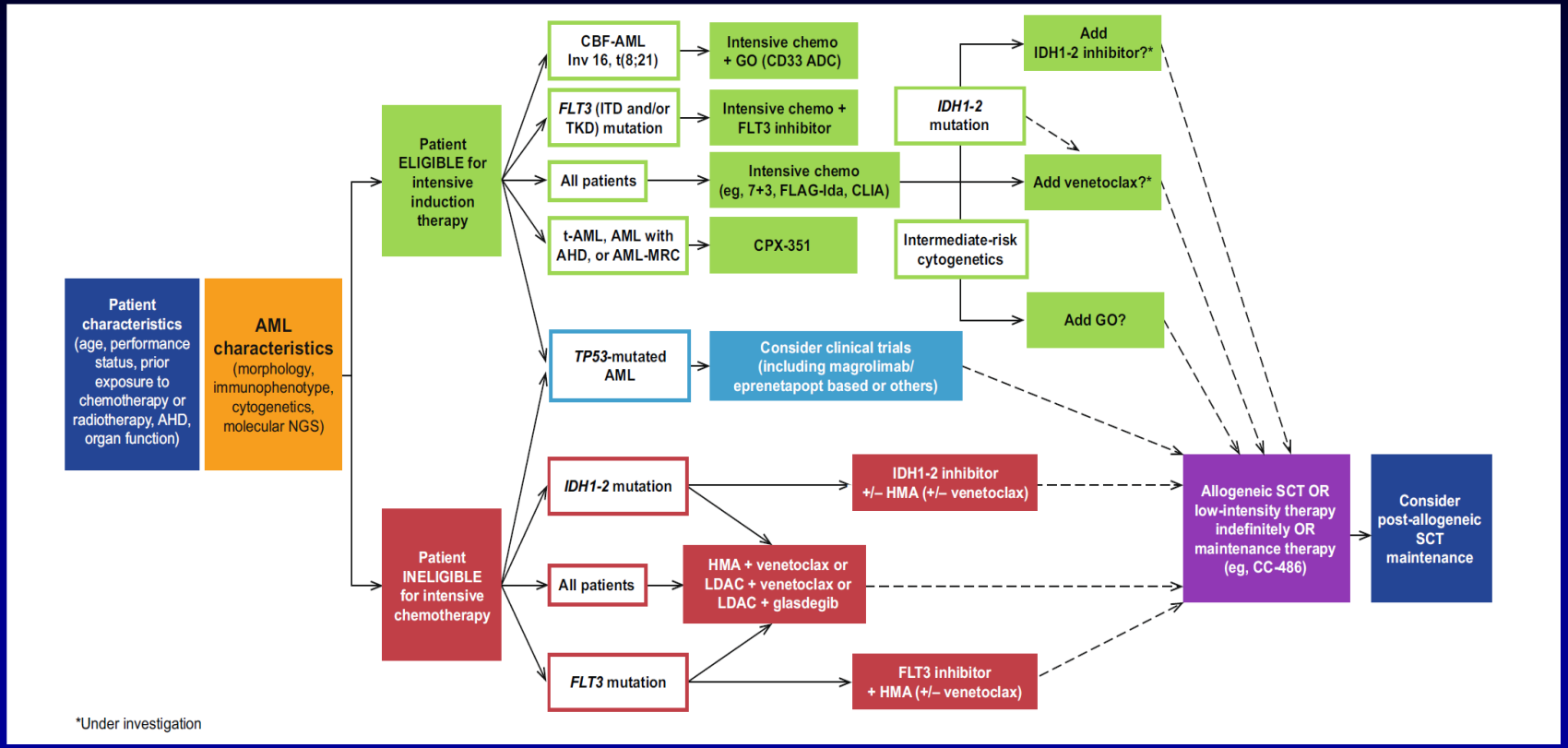
Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Data cutoff: July 15, 2019.

OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 vs placebo by stratified log-rank test. Hazard ratios (HRs) and 95% CIs were generated using a stratified Cox proportional hazards model.

Evolving Diagnostic and Treatment Paradigm for Newly Dx AML



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

Questions: ndaver@mdanderson.org

Global Leukemia Academy

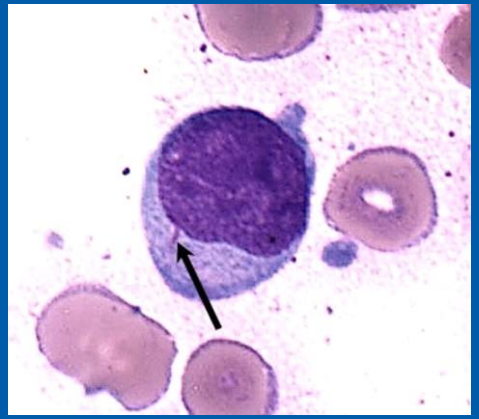
Optimizing management of relapsed/refractory AML

Eunice Wang

APTITUDE HEALTH®

Optimizing management of relapsed/refractory AML

Global Leukemia Academy



ROSWELL PARK COMPREHENSIVE CANCER CENTER

Eunice S. Wang, MD
Chief, Leukemia Service
Professor of Oncology

Disclosures: Eunice Wang, MD

- Advisory board: AbbVie, Astellas, BMS/Celgene, Genentech, GlaxoSmithKline, Jazz, Kite Pharmaceuticals, Kura Oncology, Novartis, Pfizer, Stemline, Takeda
- Consulting: Mana Therapeutics
- Speaker role: Stemline, Kura, Pfizer, DAVA Oncology
- Data monitoring committees: AbbVie, Rafael Pharmaceuticals

Cytotoxic Chemotherapy for R/R AML[1-5]

Chemotherapy

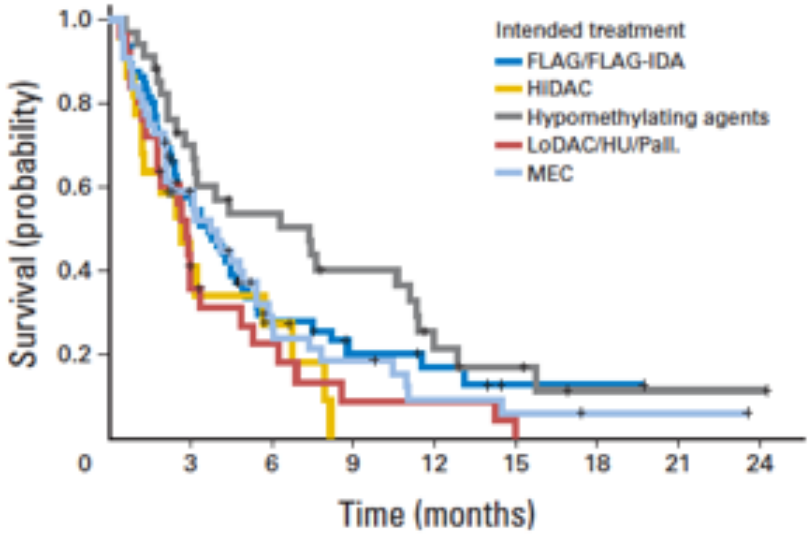
Less aggressive

- Low dose AraC
- HMA (aza, dec)
- Venetoclax + LDAC or HMA

Aggressive

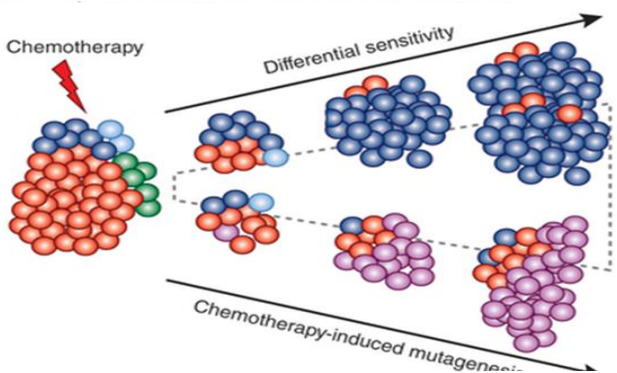
- CLAG + Ida/Mito
- HIDAC + Ida/Daun/Mito
- FLAG + Ida
- Etop/AraC/Mito
- Clof+AraC+Ida

Overall survival



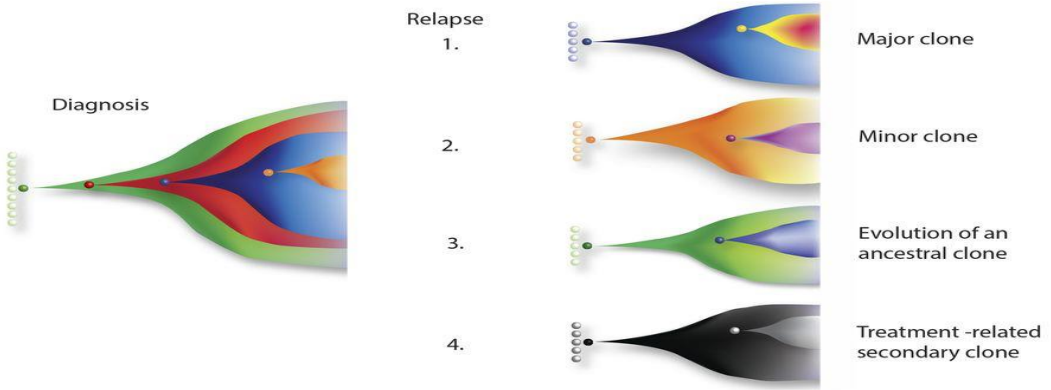
1. Roboz GJ, et al. *J Clin Oncol.* 2014;32(18)1919-1926; 2. Stein EM, et al. *Blood.* 2017;130(6):722-731; 3. DiNardo CD. *N Engl J Med.* 2019;379(12):1186; 3. Taskin AL, et al. *Leukemia*. 2007;21(1):66-71; 5. Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

Clonal Evolution and Therapy Resistance at Relapse



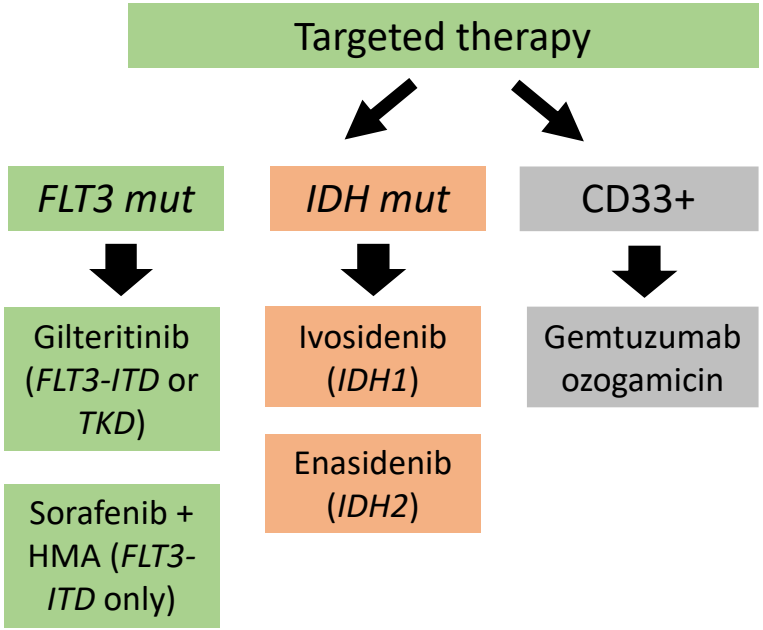
Leukemia is not a static condition!

Repeat genomic analysis at relapse is necessary



Kleppe M, Levine RL. Nat *Med*. 2014;20(4):342;Grimwade D, et al. *Blood*. 2016;127(1):29-41.

Targeted Therapy for R/R AML



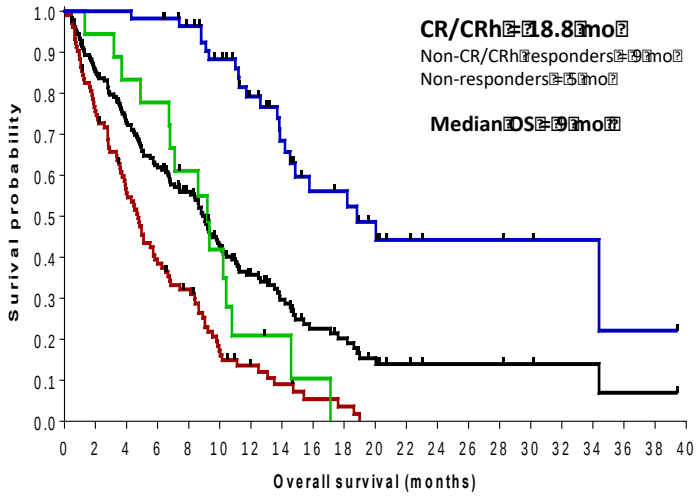
Outcomes of clinical trials

Drug Name	AML Subset	ORR	Median OS
Enasidenib[2]	*IDH2* mutant	40.3%	9.3 mos
Ivosidenib[3]	*IDH1* mutant	41.6%	8.8 mos
GO[4]	CD33+ AML	26%	11.6 mos
Gilteritinib[5]	*FLT3* mutant	34%	9.3 mos

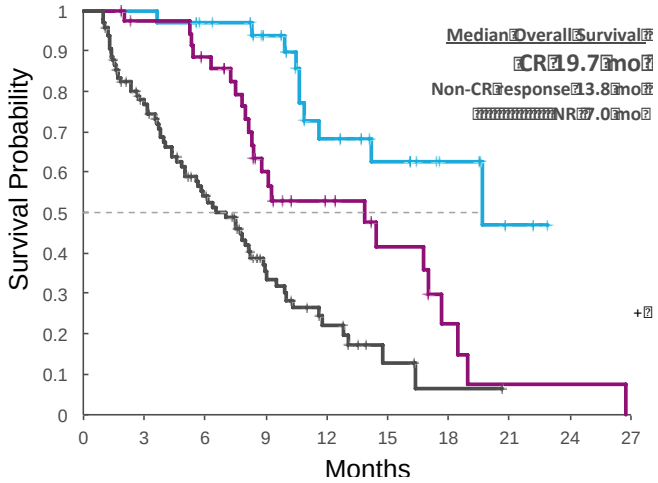
Stein EM, et al. *Blood*. 2017;130(6):722-731; DiNardo CD. *N Engl J Med*. 2019;379(12):1186; Taskin AL, et al. *Leukemia*. 2007;21(1):66-71; Perl AE, et al. *N Engl J Med*. 2019;381(18):1728-1740.

IDH1/2 Inhibitors for *IDH*-Mutant R/R AML

Ivosidenib (*IDH1*): R/R AML



Enasidenib (*IDH2*): R/R AML

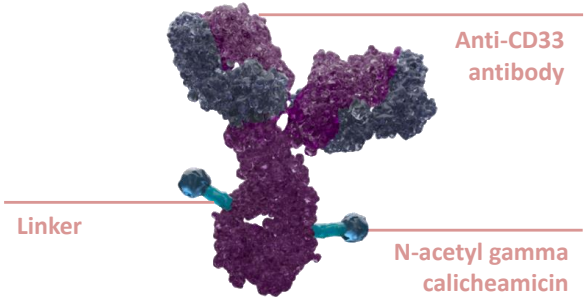


<u>Mechanisms of resistance</u>: Mutant isoform switch (m*IDH1* <-> m*IDH2*), *IDH2* mutations (trans or cis), presence or development of co-mutations (ie, *RAS, FLT3*)

DiNardo CD, et al. *N Engl J Med.* 2018;378(25):2386; Stein EM, et al. *Blood*. 2017;130(6):722-731.

Gemtuzumab Ozogamicin for CD33+ RR-AML

GEMTUZUMAB OZOGAMICIN



Eligibility criteria:

- ≥18 years old
- Confirmed CD33+ AML
- First untreated relapse
- Duration of CR1: ≥3 but ≤18 months
- ECOG PS: 0–2
- Serum creatinine:

<180 µmol/L

- ALT and AST levels: <2 x ULN
- Patients with secondary leukemia, AML3, AML after MDS/MPD, or prior HSCT were excluded

Induction

Monotherapy with GO

2-hr IV infusion of 3 mg/m^2 on Days 1, 4, and 7

Consolidation

GO with high-dose cytarabine for patients in CR/CRp

<55 years:

3 mg/m^2 IV Q12h for 3 days

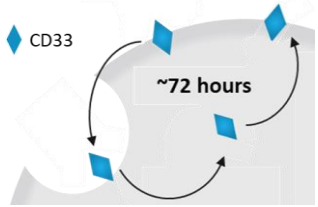
>55 years and/or creatinine clearance <50 mL/min:

1 mg/m^2 IV Q12h for 3 days

HSCT allowed for eligible patients

90 days recommended between GO and HSCT

Re-expression of CD33 sites occurred every ~72 hours[4]



Frequent gemtuzumab ozogamicin dosing may facilitate prolonged saturating serum levels and more efficient drug targeting

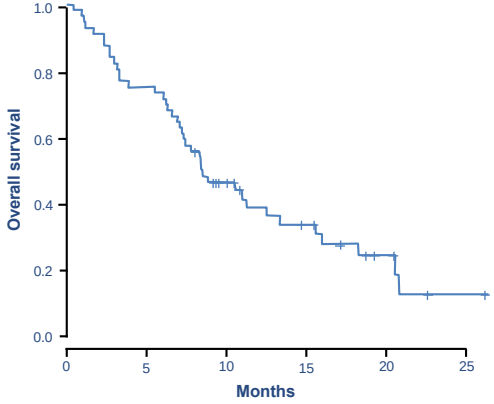
Median OS =8.4 months

Median OS similar in pts <60 yo(8.3 mos) and >60 yo (8.9 mos)

Pts in CR/Crp had ANC >500/µL in median 23 days and plts >50K in median 20 days

No VOD prior to or after HSCT

OS among all patients from first dose of GO

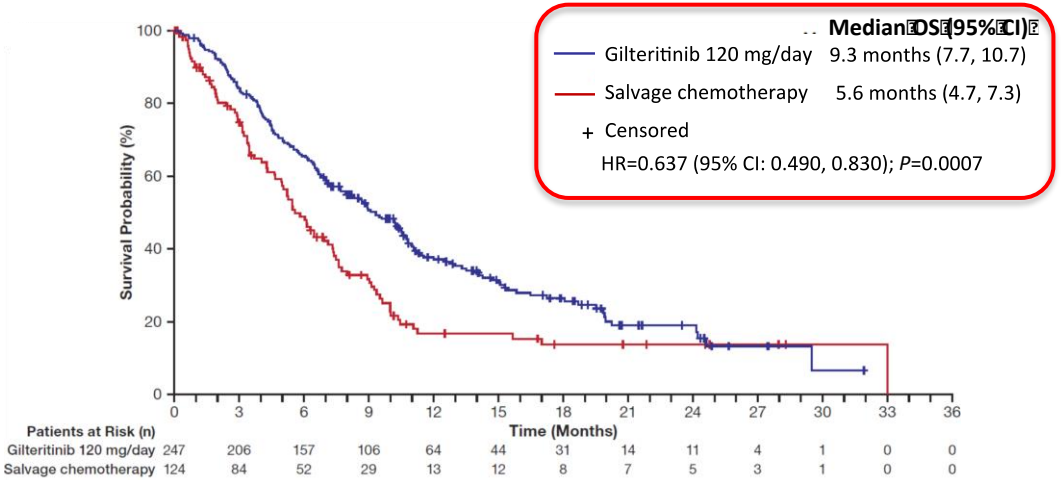


Caron PC, et al. Blood 1994;83:1760; Taksin A-L et al. Leukemia 2007;21:66

FLT3 Inhibitors for *FLT3*-Mutant R/R AML

	Other Kinases	IC_{50} (Plasma)
Lestaurtinib	JAK2, TrkA	700 nM
Midostaurin	cKIT, PKC, PDGFR, VEGFR	1000 nM
Sorafenib	cKIT, PDGFR, RAF, VEGFR	265 nM
Quizartinib	cKIT, PDGFR, RET	18 nM
Crenolanib	PDGFR	48 nM
Gilteritinib	AXL	43 nM

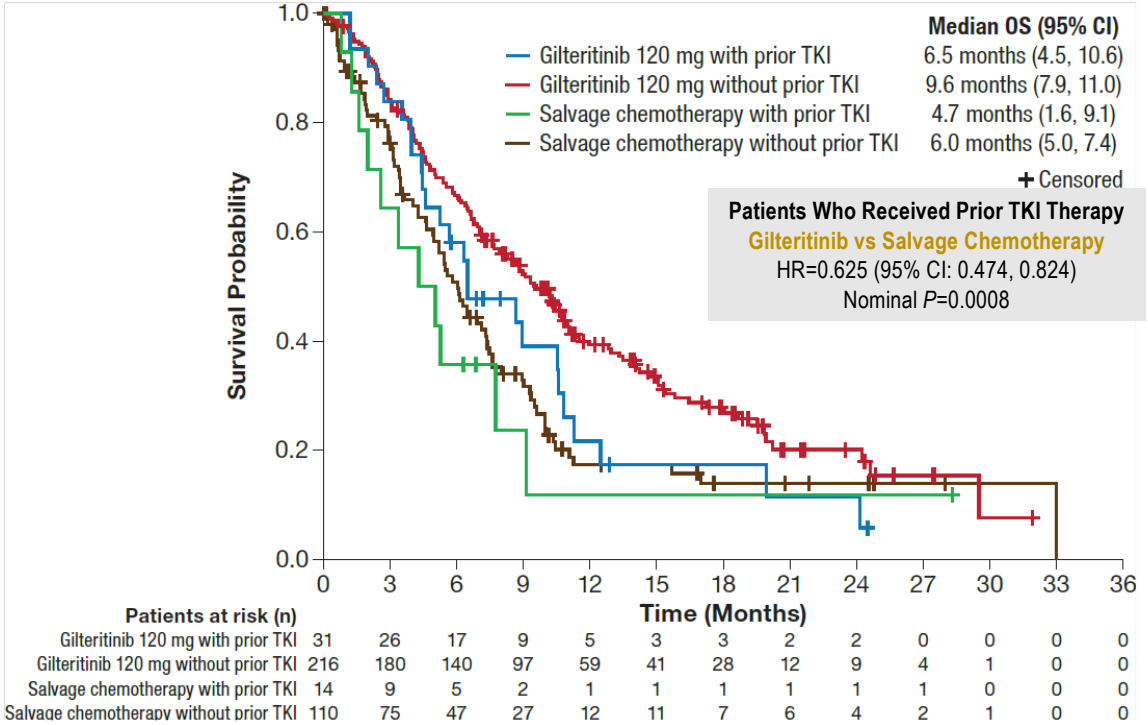
Gilteritinib vs salvage chemo in *FLT^{mut}* R/R AML



Pratz KW, et al. *Blood.* 2010;115(7):1425-1432;
Zarrinkar PP, et al. *Blood.* 2009;114(14):2984-2992;
Galanis A, et al. *Blood.* 2014;123(1):94-100;
Levis MJ, et al. *J Clin Oncol.* 2015;33(15_suppl): abstract 7003.

Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

FLT3-Mutant AML: Gilteritinib vs Chemotherapy

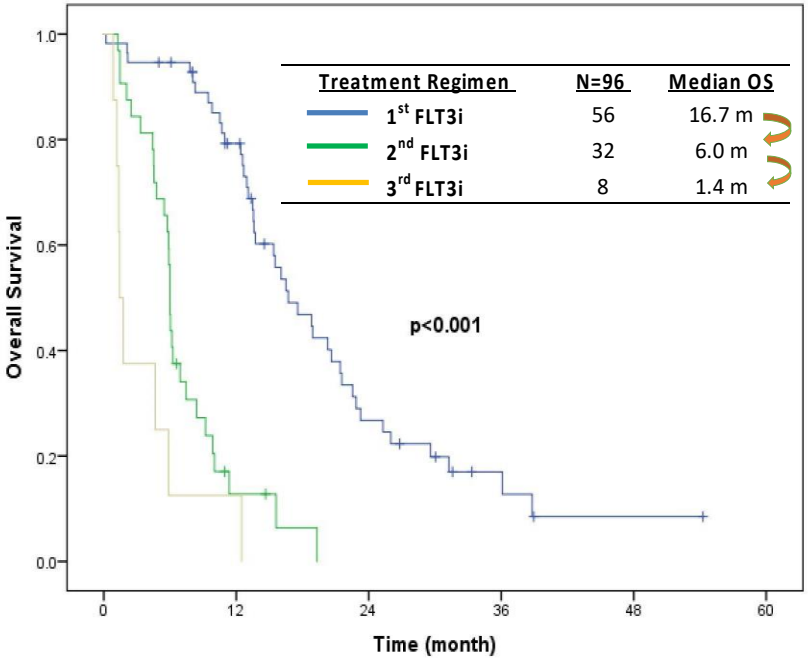


Median OS, mos (95% CI)	Gilteritinib	
	Prior TKI	No Prior TKI
***FLT3* Mutation Type**		
FLT3-ITD	6.5 (4.4, 10.8)	10.2 (7.7, 11.1)
FLT3-TKD	4.6 (1.2, 24.1)	8.0 (3.0, 24.6)
FLT3-ITD and -TKD	13.2 (4.0, NE)	10.2 (8.9, 20.2)
Relapsed or Refractory Status		
Relapsed	6.5 (4.0, 11.3)	8.9 (6.7, 10.8)
Refractory	10.5 (2.4, 24.1)	10.3 (7.9, 13.5)

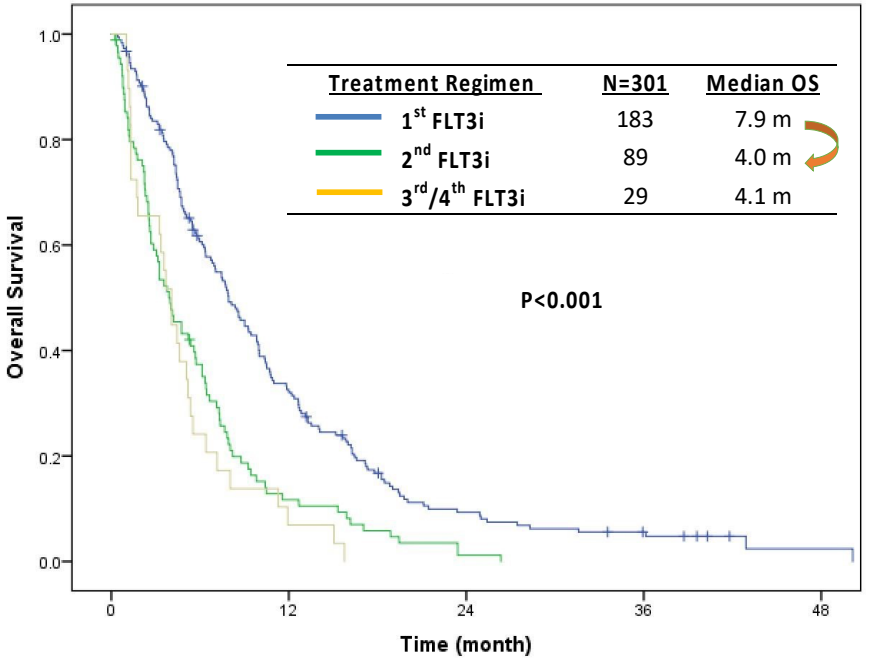
Perl AE, et al. ASH 2020. Abstract 262.

Sequential FLT3 Inhibitor Therapy for R/R AML

Frontline Cohort (n=96)



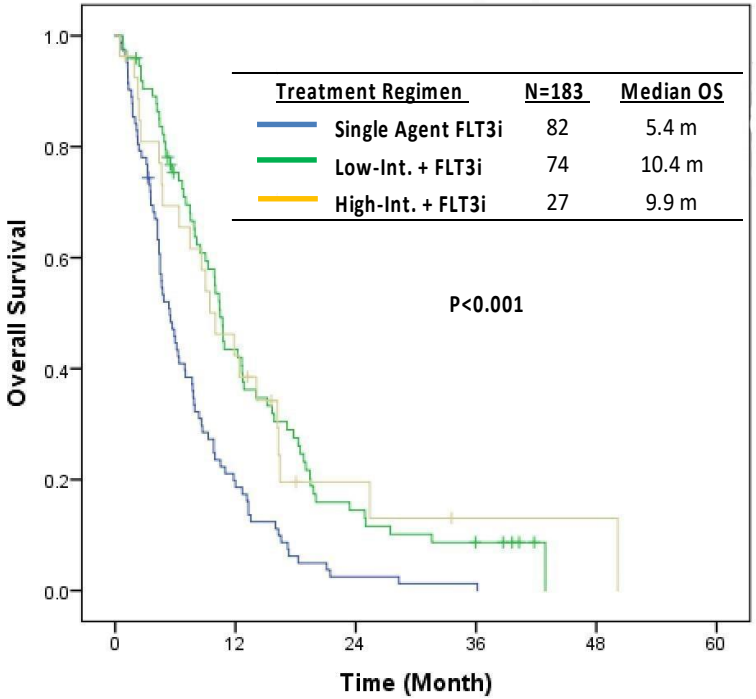
Salvage Cohort (n=301)



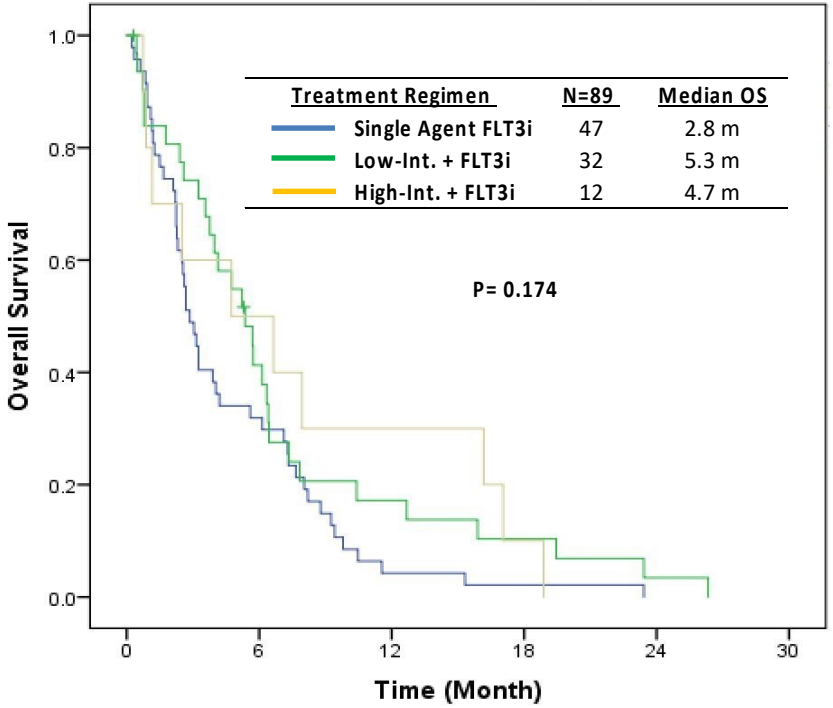
Yilmaz M, et al. ASH 2020. Abstract 29.

Combination vs Single-Agent FLT3 Inhibitor Salvage

1st FLT3i exposure (n=183)



2nd FLT3i exposure



Yilmaz M, et al. ASH 2020. Abstract 29.

FLT3-Mutant R/R AML: Venetoclax + Gilteritinib

Key Eligibility Criteria
- R/R AML
- WT or *FLT3*$^{mut+}$ (dose escalation) and *FLT3*$^{mut+}$ (dose expansion)
- ≥1 prior line of therapy[a]
- WBC count ≤ 25 x 10^9 /L at start of study drug
- ECOG PS 0–2

Dose escalation phase
WT and *FLT3*$^{mut+}$

Ven 400 mg + Gilt 80 mg (n=7)

Ven 400 mg + Gilt 120 mg (n=16)

DLT monitoring[b]

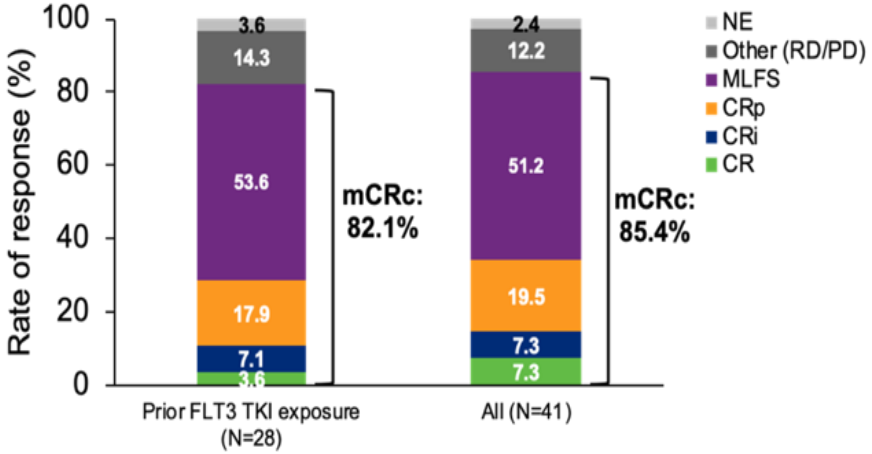
Dose expansion
FLT3^{mut+} only

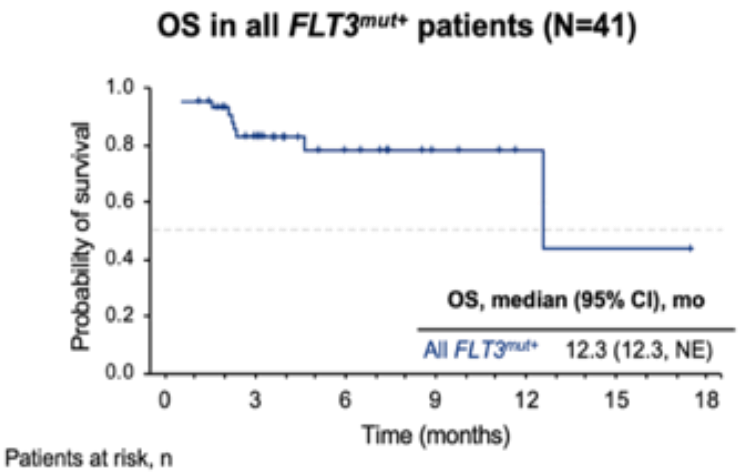
Ven 400 mg + Gilt 120 mg (RP2D) (n=46)[c]

DLT monitoring[b]

Follow-up

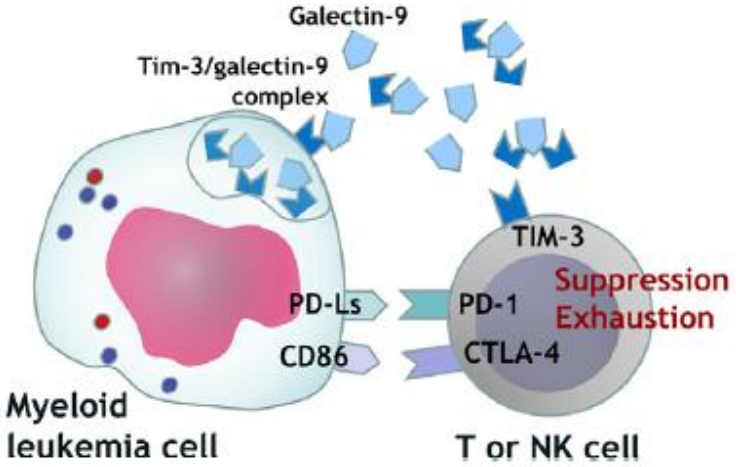
- Post-treatment follow-up monthly for up to 1 year, following last dose of study drug

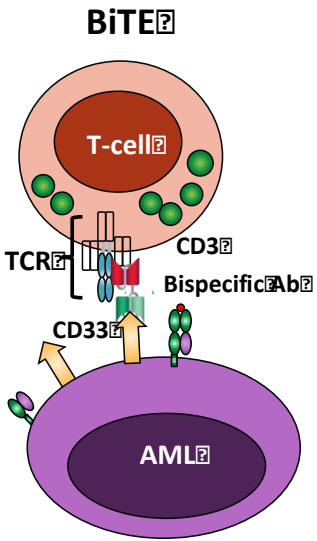


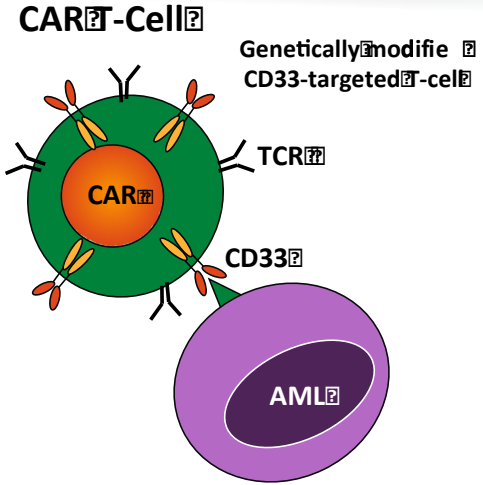


Daver N, et al. ASH 2020. Abstract 335.

Immunotherapeutic Approaches for R/R AML







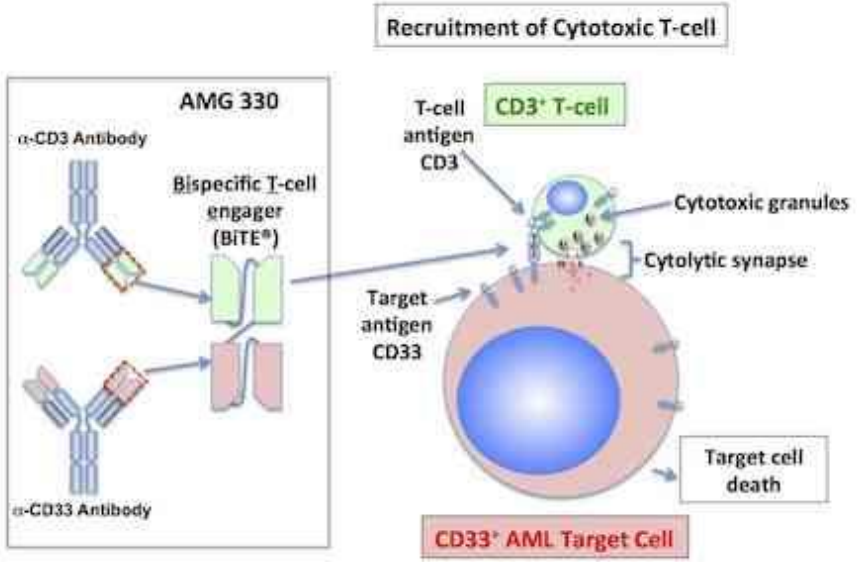
Targeting immune checkpoints

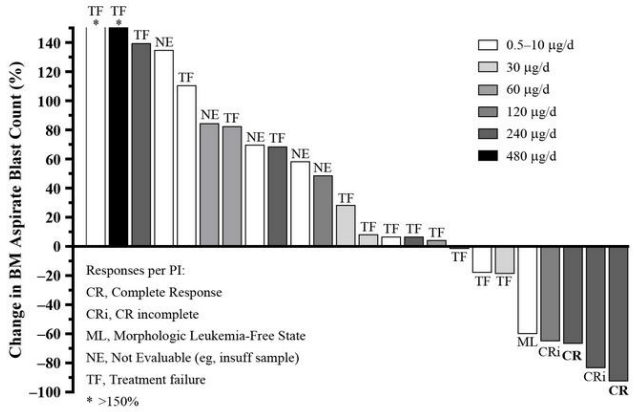
- Ipilimumab (anti–CTLA-4 ab)
- Magrolimab (anti-CD47 ab)
- MBG453 (anti-TIM3 ab)

AML cell antigens

- **CD33**
- **CD123**
- Folate Rc β
- **CLL1**
- **Wildtype FLT3**
- Lewis Y

AMG 330: CD33/CD3 Bispecific Antibody



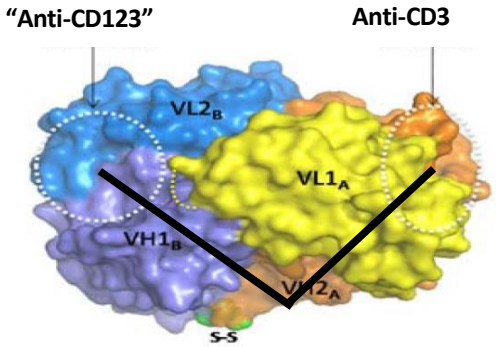


35 pts on 12 dose cohorts (40% prior alloSCT)
DLTs grade 2 CRS, grade 4 VF
Target dose = 240 µg/day
Responses: 2 CR, 2 CRi at 120–240-µg/day dosing
CRs seen after 1 cycle of therapy

Laszlo GS, et al. *Blood*. 2014;123(4):554-561; Harrington KH, et al. *PLOS One*. 2015;10(8):e0135945; Ravandi F, et al. ASH 2018. Abstract 25.

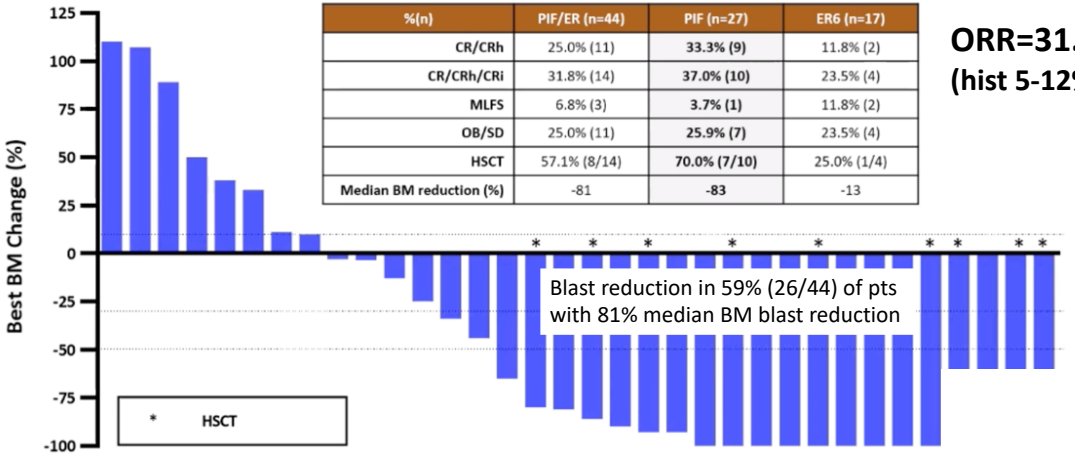
Flotetuzumab: Primary Induction Failure/Early Relapse

- Flotetuzumab (MGD006/S80880) redirects T-cell killing of CD123+ Cells



Root, et al. Antibodies 2016, 5, 6
Chichili, et al. Sci Transl Med. 2015 May 27;7(289)

Responses to therapy in PIF/ER AML pts



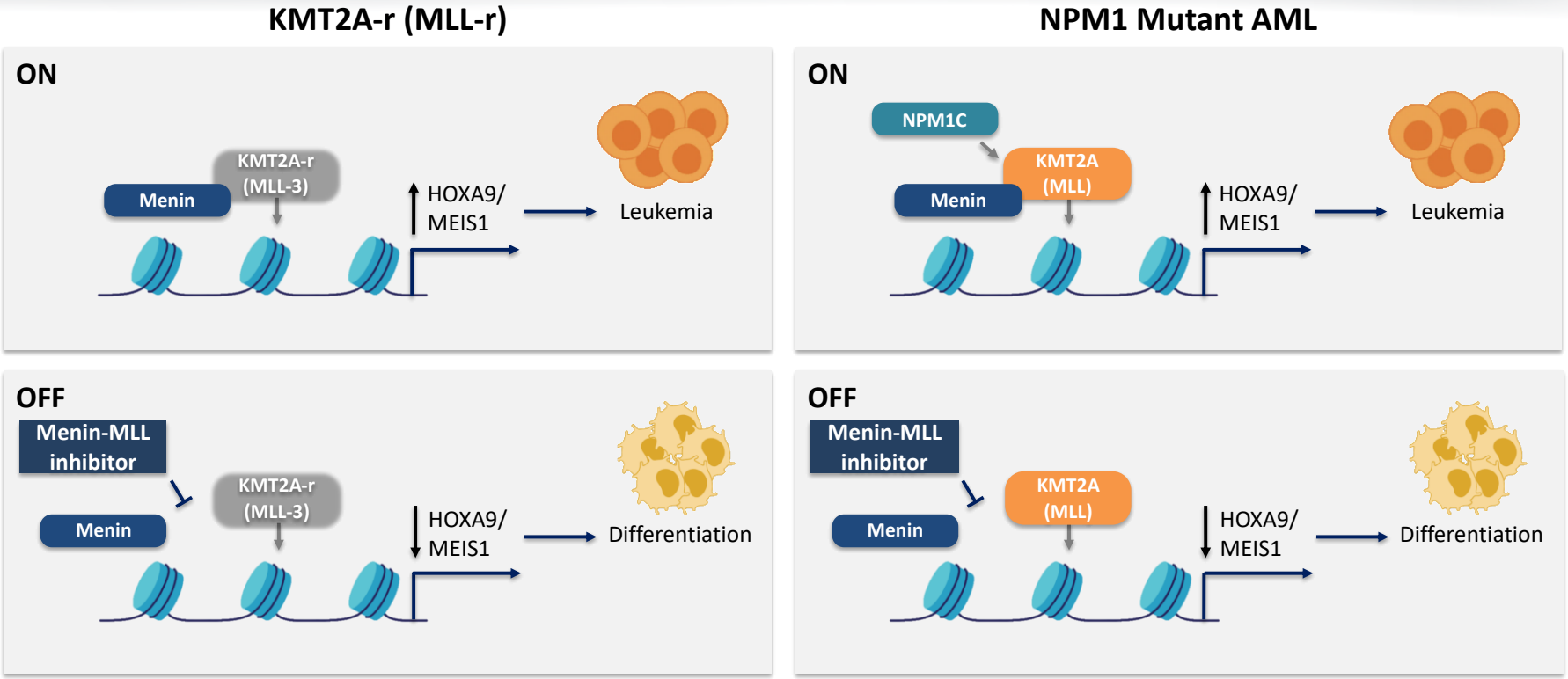
%(n)	PIF/ER (n=44)	PIF (n=27)	ER6 (n=17)
CR/CRh	25.0% (11)	**33.3% (9)**	11.8% (2)
CR/CRh/CRi	31.8% (14)	**37.0% (10)**	23.5% (4)
MLFS	6.8% (3)	**3.7% (1)**	11.8% (2)
OB/SD	25.0% (11)	**25.9% (7)**	23.5% (4)
HSCT	57.1% (8/14)	**70.0% (7/10)**	25.0% (1/4)
Median BM reduction (%)	-81	**-83**	-13

ORR=31.8%
(hist 5-12%)

Need for <u>hospitalization (min 8 d) in all patients</u>
100% infusion reaction/cytokine release
Outpatient dosing after day 8 feasible

Aldoss I, et al. ASH 2020. Abstract 331.

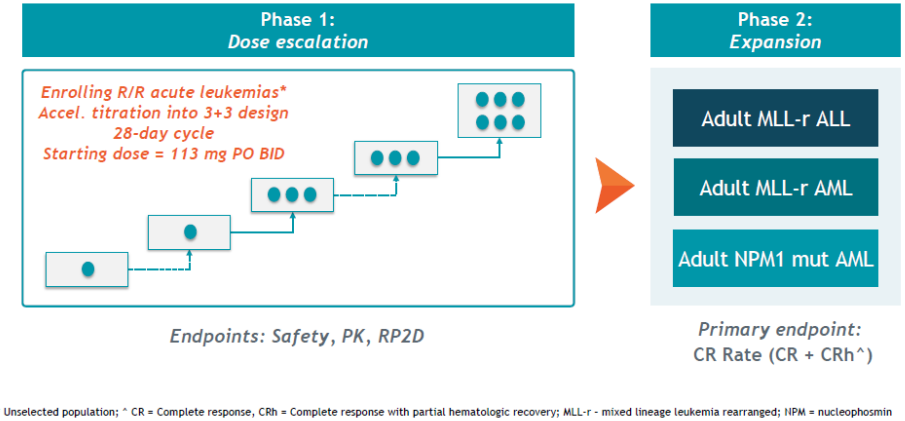
KMT2A-r and *NPM1*-Mutant AML: Menin Inhibition



Wang ES, et al. ASH 2020. Abstract 1015.

Phase I Clinical Trials for *KMT2A*-r/*NPM1*-Mutant AML

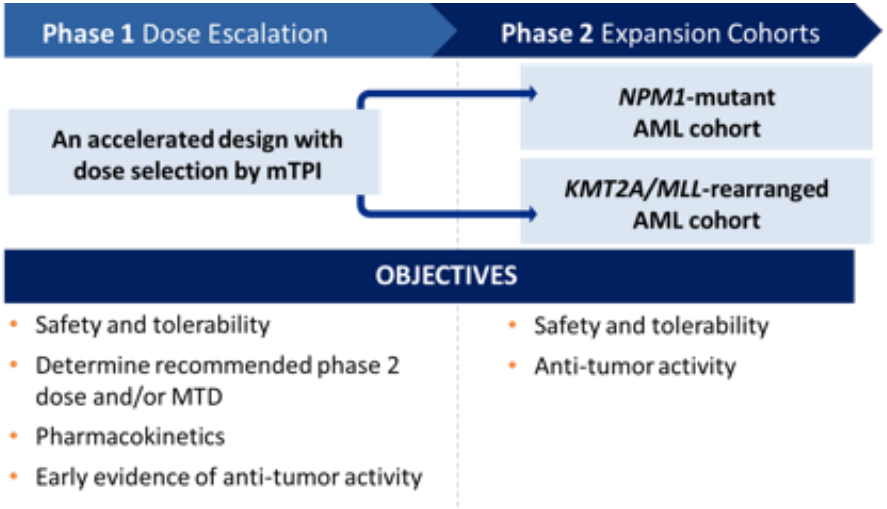
AUGMENT-101 schema: ALL and AML pts



* Unselected population; ^ CR = Complete response, CRh = Complete response with partial hematologic recovery; MLL-r - mixed lineage leukemia rearranged; NPM = nucleophosmin

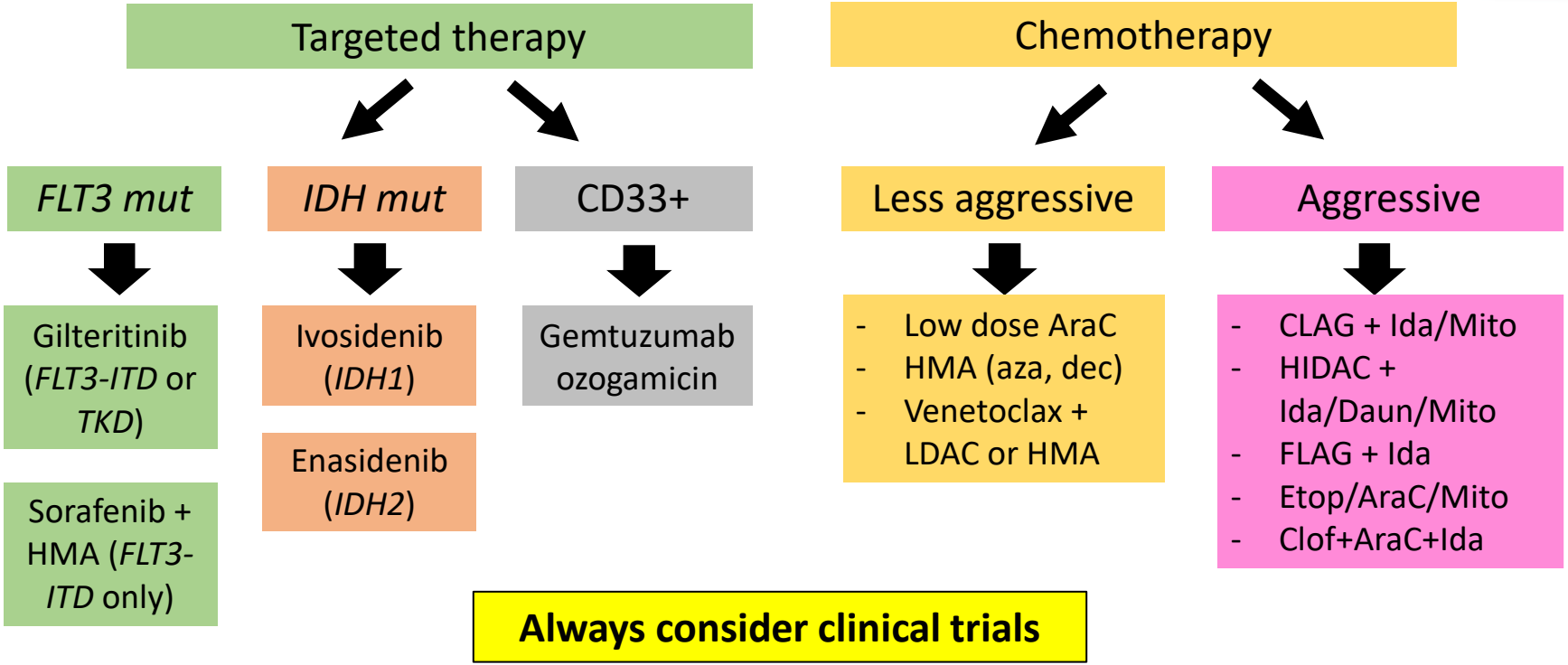
PK: QTC prolongation, interactions with azoles (CYP inhibitors)

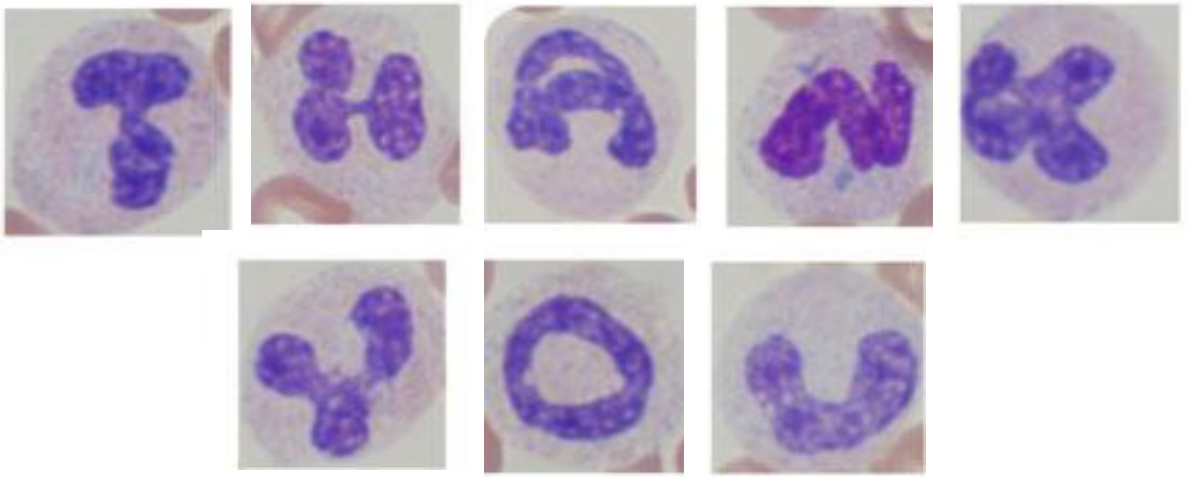
KOMET-001: Phase I/IIA trial



McGeehan J. AACR 2020 meeting; Wang ES, et al. ASH 2020 meeting.

Summary: Optimizing Therapy of R/R AML





Email: Eunice.wang@roswellpark.org

Global Leukemia Academy

Case based panel discussion: regional challenges in AML care

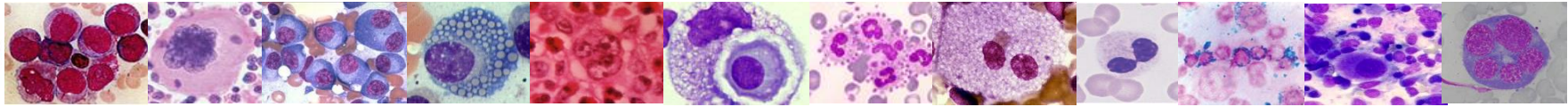
Panelists: Elias Jabbour, Naval Daver, José Maria Ribera, Andre Schuh, Eunice Wang, and local experts

Presenters: Roberta Demichelis, Wellington Silva

APTITUDE HEALTH®

AML Case

Dra Roberta Demichelis
INCMNSZ
Mexico City



DISCLOSURES

- **Advisory/Speaker: AbbVie, Amgen, Celgene, Novartis**

- **Research funding: Novartis**

MEDICAL HISTORY: DIAGNOSIS

38-year-old woman

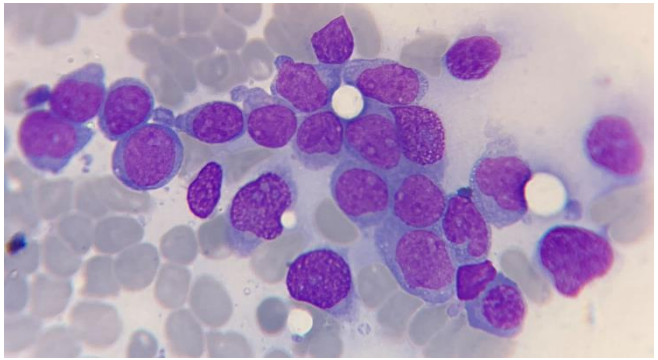
Relevant history:

Systemic lupus erythematosus (arthritis and mucocutaneous involvement)

Treatment: hydroxychloroquine

May 2019: during follow-up

- ✓ WBC 19.4 × 10^3/µL, Hb 7 g/dL, plat 78 × 10^3/µL
- ✓ 50% blasts
- ✓ FC: CD34, CD13, CD33, CD117
- ✓ Molecular: *CBF/MYH11A*+, *FLT3* negative
- ✓ Cytogenetics: 46,XX;inv(16)(p13;q22) (20)



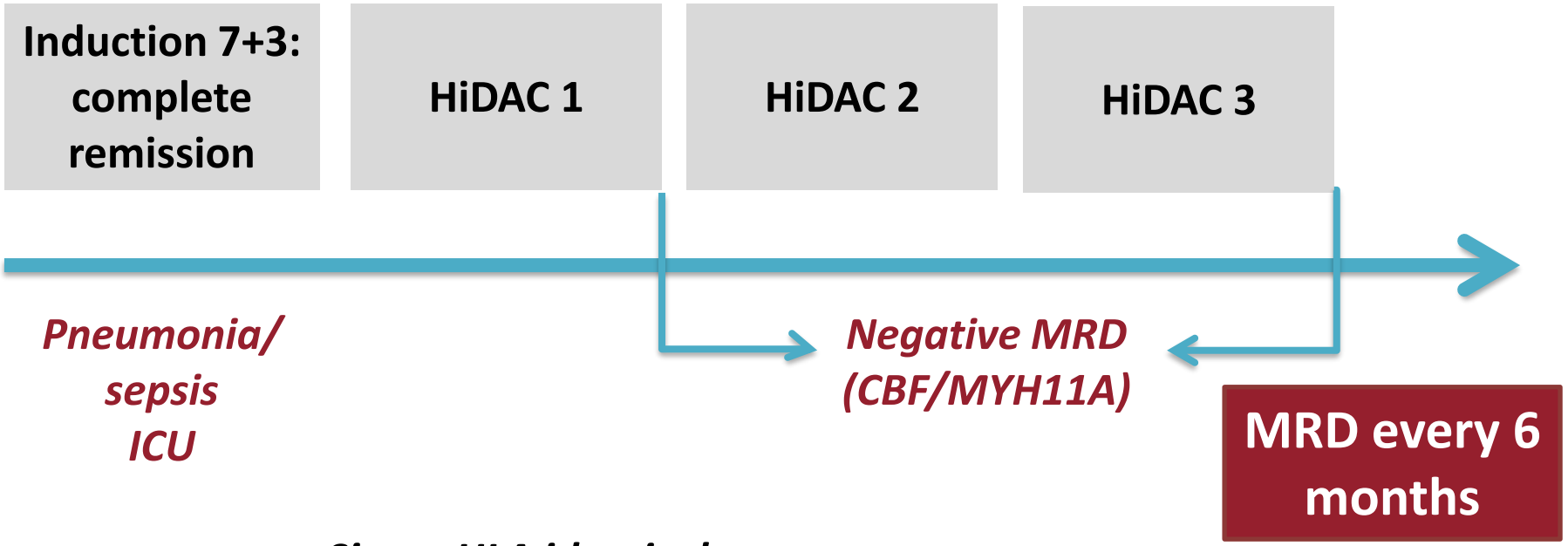
Q

QUESTION 1

In your practice, what would be the frontline treatment for this patient?

A. **Gemtuzumab ozogamicin + FLAG-Ida**
B. **Gemtuzumab ozogamicin + 7+3**
C. **FLAG-Ida**
D. **7+3**
E. **Other**

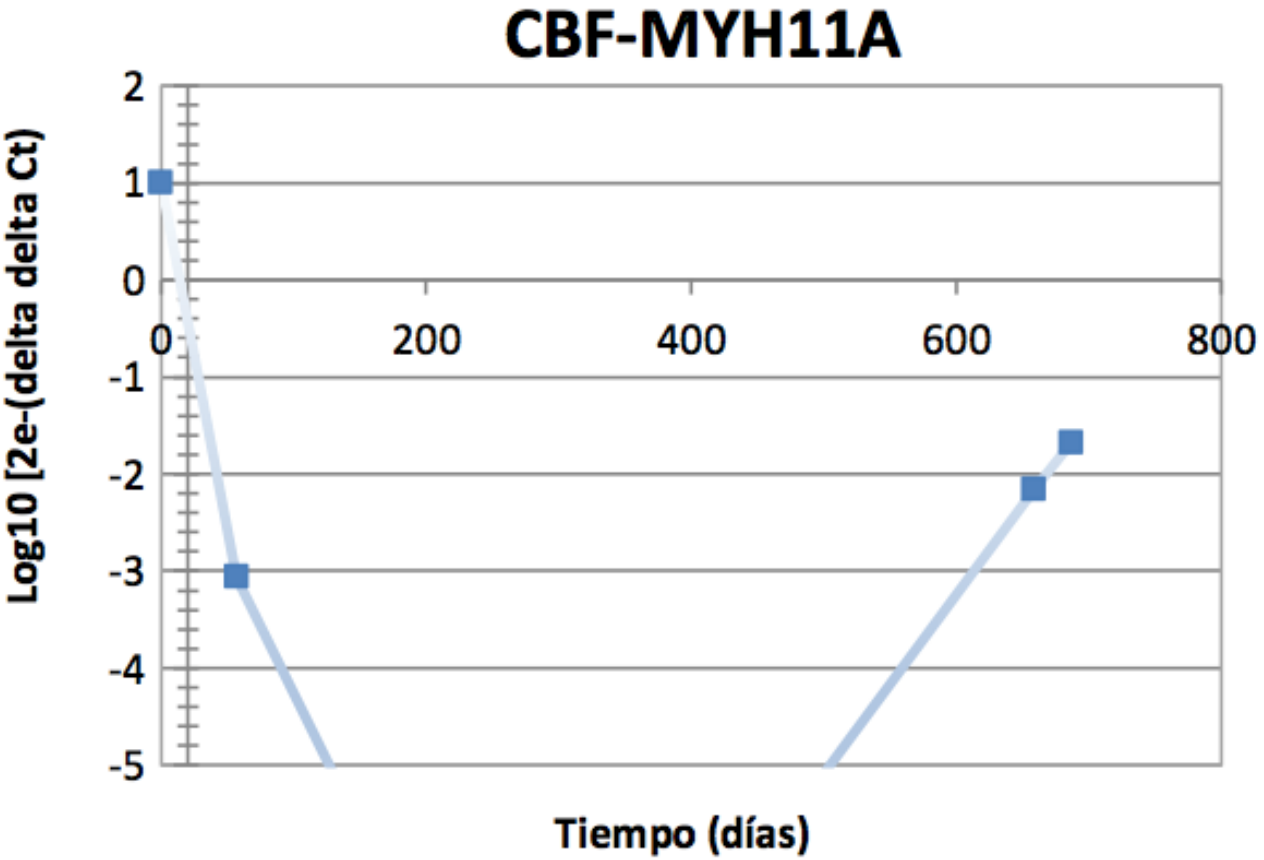
CASE: FOLLOW-UP



Sister: HLA identical

HiDAC: cytarabine 3 g/m^2 every 12 hours, 6 doses

CASE: FOLLOW-UP



March 2021:

Positive MRD Confirmed at 4 weeks in a new sample

No blasts
MRD by flow cytometry: 0.4%

Cytogenetics and molecular: pending

CONSIDERATIONS

1. **What is the significance of MRD+?**

2. **Is MRD itself an indication for treatment?**
   What treatment?

3. **Is this an indication for alloHSCT?**

Chemotherapy and then alloHSCT, or go straight to alloHSCT?

Q

QUESTION 2

What would you do?

A. **Go straight to alloHSCT**
B. **FLAG-Ida (+/– GO)**
C. **Azacitidine**
D. **Azacitidine + venetoclax**

CONSIDERATIONS

1. **What is the significance of MRD+?**

74.4% morphologic relapse in <100 days

2. **Is MRD itself an indication for treatment?**
   What treatment?
   No GO available in Mexico

HMA eradicates MRD in 11/17 of CBF AML

3. **Is this an indication for alloHSCT?**
   Chemotherapy and then alloHSCT, or go straight to alloHSCT?

AlloHSCT in CR2 (EBMT)
If MRD+ before transplant
- **LFS: 49 vs 61.6% (*P* = .046)**
- **IR: 29.3 vs 16.2% (*P* = .003)**

Puckrin R, et al. *Haematologica*. 2021;106(1):56-63; Ragon BK, et al. *Am J Hematol.* 2017;92(9):845-850; Halaburda K, et al. *Haematologica*. 2020;105(6):1723-1730.

CASE: FOLLOW-UP

PLAN:

Aza + Ven → MRD after 2 cycles → AlloHSCT

Open question:

What would be the best strategy in this case?

THANK YOU

AML in Latin America

Clinical Case

Wellington Silva, MD
Institute of Cancer, University of Sao Paulo, Brazil

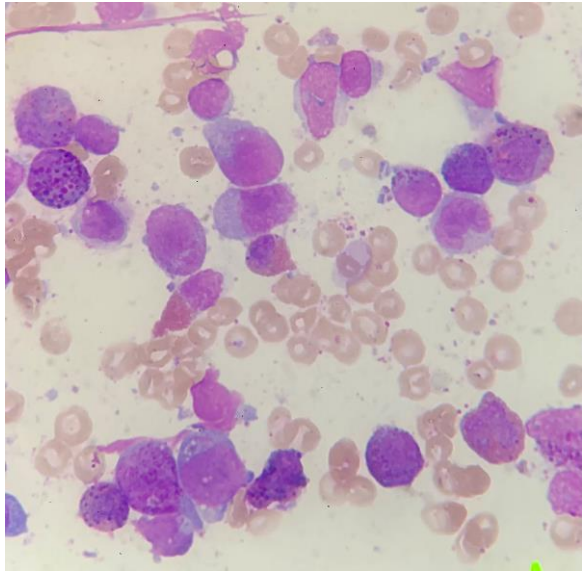
DISCLOSURES

Advisory: Pfizer, Amgen, Daiichi Sankyo, Takeda

Speaker: Pfizer, Amgen, Servier, Pint-Pharma

Medical History

- 22-year-old male, student
- No prior comorbidities



- **Sore throat for 15 days**
- **Fever and easy bruising**

Peripheral blood: Hb 9.3 g/dL, WBC 153.48 × 10^9/L (84% blasts), Plat 17 × 10^9/L
Immunophenotyping → **AML with monocytic component**

Medical History

- **Molecular evaluation: *CBFB-MYH11* fusion (inv16)**
- BM karyotype: 46,XY,inv(16)(p13.1q22)[20]
- ***FLT3*-ITD – allelic ratio 0.11**

- Remaining fusions, *NPM1* and *CEBPA,* resulted negative

Q

AML with inv(16) and *FLT3*-ITD – low AR

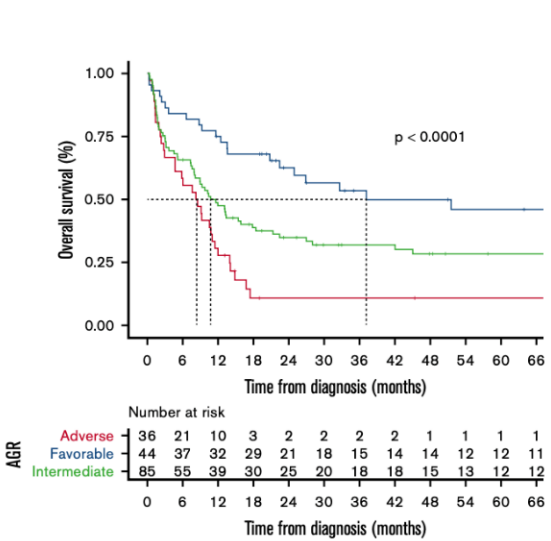
Question

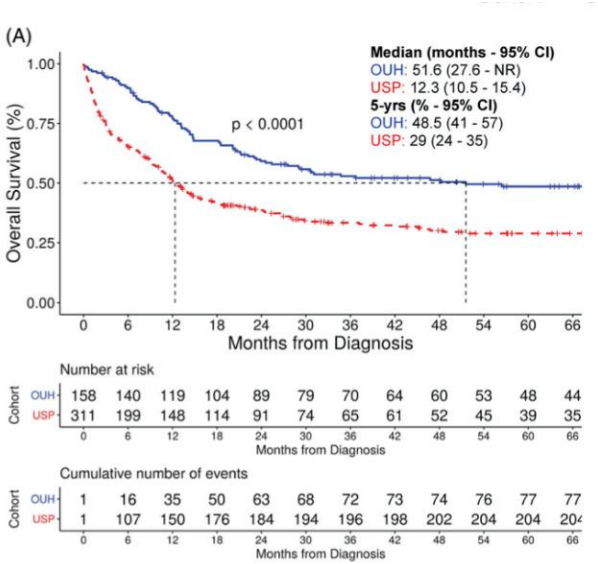
In your practice, what would be the remission induction regimen for this case?

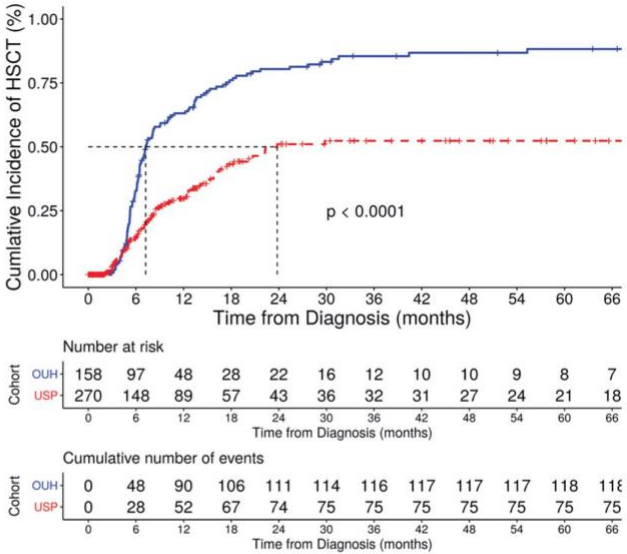
A. “7+3” (anthracycline + low-dose cytarabine)
B. FLAG-IDA
C. “7+3” plus midostaurin
D. “7+3” plus gilteritinib
E. Other

AML in Brazil

- Lower survival rates than developed countries: more toxic deaths and less HSCT







Silveira D, et al. *Blood Adv*. 2020;4(10):2339-2350; Silveira D, et al. *Leuk Lymphoma.* 2021;62(1):147-157.

Clinical Case

Not eligible for clinical trial with FLT3 inhibitor due to indirect bilirubin elevation >>
Induction with “7+3” (daunorubicin 60 mg/m^2 + cytarabine 200 mg/m^2)

Complete response after 1 course with neg MRD by flow

Lumbar puncture – no CSF infiltration

No matched related or unrelated donor, only haploidentical

Four consolidation courses with intermediate-dose AC (1.5 g/m^2)

MRD neg by flow

Q

Question 2

In your practice, what would be the post-remission therapy?

A. **Intermediate- or high-dose cytarabine**
B. **Autologous transplant**
C. **Chemo plus FLT3 inhibitor**
D. **Allogeneic stem cell transplant followed by FLT3 inhibitor**
E. **Other**

Clinical Case

Relapse 3 months after the end of IDAC

Hb 12.5, L 32.9 × 10^9/L (blasts 79%), Plat 18 × 10^9/L
KT: inv(16)
FLT3-ITD – allelic ratio: 0.74
New-onset Bell's palsy → CSF infiltration (6480 cells/mm^3 with myeloblasts)

Salvage with MEC (mitoxantrone, etoposide, and high-dose cytarabine) plus sorafenib off-label (for 14 days) + intrathecal chemotherapy

- Sorafenib was stopped at 8th day due to liver toxicity
- Prolonged myelosuppression (60 days)
- 3 episodes of febrile neutropenia

Second complete remission

Q

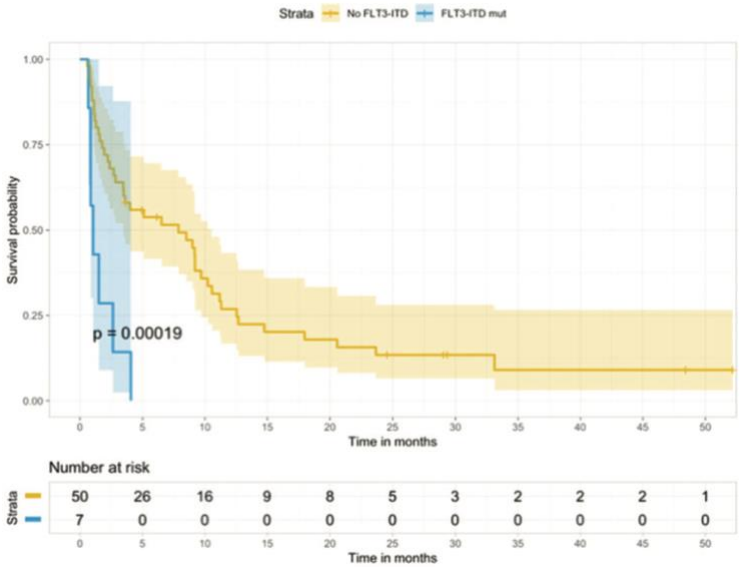
Question 3

In your practice, how would you treat this relapse?

A. First-generation FLT3 inhibitor plus chemo
B. Second-generation FLT3 inhibitor plus chemo
C. High-dose chemo (MEC, FLAG-IDA)
D. Hypomethylating agent plus venetoclax
E. Gemtuzumab ozogamicin plus chemo
F. Other

R/R AML in Brazil

- Dismal long-term survival rates – median OS 4 months
- No difference regarding salvage regimens
- Strong negative impact of *FLT3*-ITD mutation on response and survival



Silva WF, et al. *Clinics* (Sao Paulo). 2020;75:e1566.

Clinical Case

Enrolled in a compassionate use program – quizartinib

He stayed in CR for 6 months under quizartinib monotherapy

AlloSCT with haploidentical donor (father)

- **Prep regimen: busulfan plus fludarabine**
- **Several toxicities: severe VOD, dyalitic AKI, fungal pneumonia, CMV reactivation, allergic reaction to sulfa**

→ Delayed quizartinib resumption (4 months)

A new relapse after 1 month of quizartinib → palliative therapy > death

Thank you!

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Global Leukemia Academy

Closing Remarks

Elias Jabbour

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Thank You!

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