Global Leukemia Academy

Founding Sponsor
Platinum

AMGEN

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

26 March 2022

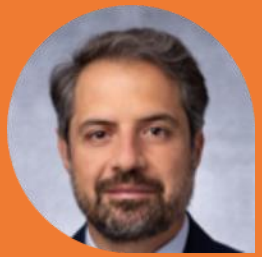
Virtual Breakout: Adult Leukemia Patients

APTITUDE HEALTH

Global Leukemia Academy

ALL session open

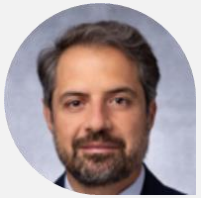
Elias Jabbour



APTITUDE HEALTH

Meet the Faculty

CO-CHAIRS



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

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

FACULTY

Eunice Wang, MD
Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

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

Wellington Silva Fernandes, MD
Instituto do Cancer do Estado de São Paulo (ICESP), Brazil

Roberta Demichelis, MD
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

Paola Omaña, MD
Central Military Hospital Colombia, Bogotá, Colombia

Objectives of the Program

Understand current treatment patterns for frontline and relapsed ALL therapy

Discuss the current approaches in frontline, maintenance, and relapsed AML

Review and discuss clinical insights in ALL and AML, on the basis of patient cases from the LatAm region

Virtual Breakout – Adult Leukemia Patients (Day 2)

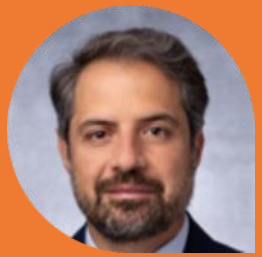
Co-chairs: Elias Jabbour and Naval Daver

TIME (UTC-3)	TITLE	SPEAKER
10.00 – 10.10	ALL session open	Elias Jabbour
10.10 – 10.30	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens	Elias Jabbour
10.30 – 10.50	Current treatment options for relapsed ALL in adult and elderly patients	José Maria Ribera
10.50 – 11.20	ALL case-based panel discussion • Case 1 (10 min) – Paola Omaña (Col) • Case 2 (10 min) – Roberta Demichelis (Mex) • Discussion (10 min) – Panelists: Roberta Demichelis, Wellington Silva Fernandes, Paola Omaña	All
11.20 – 11.30	Break	
11.30 – 11.35	AML session open	Naval Daver
11.35 –11.55	Personalized induction and maintenance approaches for AML	Eunice Wang
11.55 – 12.15	Optimizing management of relapsed/refractory AML	Naval Daver
12.15 – 12.45	AML case-based panel discussion • Case 1 (10 min) – Wellington Silva Fernandes (Bra) • Case 2 (10 min) – Roberta Demichelis (Mex) • Discussion (10 min) – Panelists: Roberta Demichelis, Wellington Silva Fernandes, Paola Omaña	All
12.45 – 13.00	Session close	Naval Daver

Global Leukemia Academy

Introduction to the Voting System

Elias Jabbour



APTITUDE HEALTH

Question 1

What age group is considered elderly ALL patients?

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

Question 2

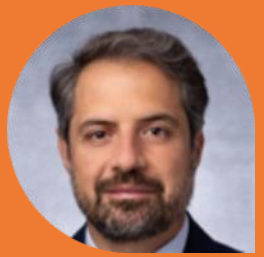
Which of the following is NOT true for treating ALL?

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

Global Leukemia Academy

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

Elias Jabbour



APTITUDE HEALTH

Integration of Immunotherapy in the Management of Frontline Acute Lymphocytic Leukemia

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

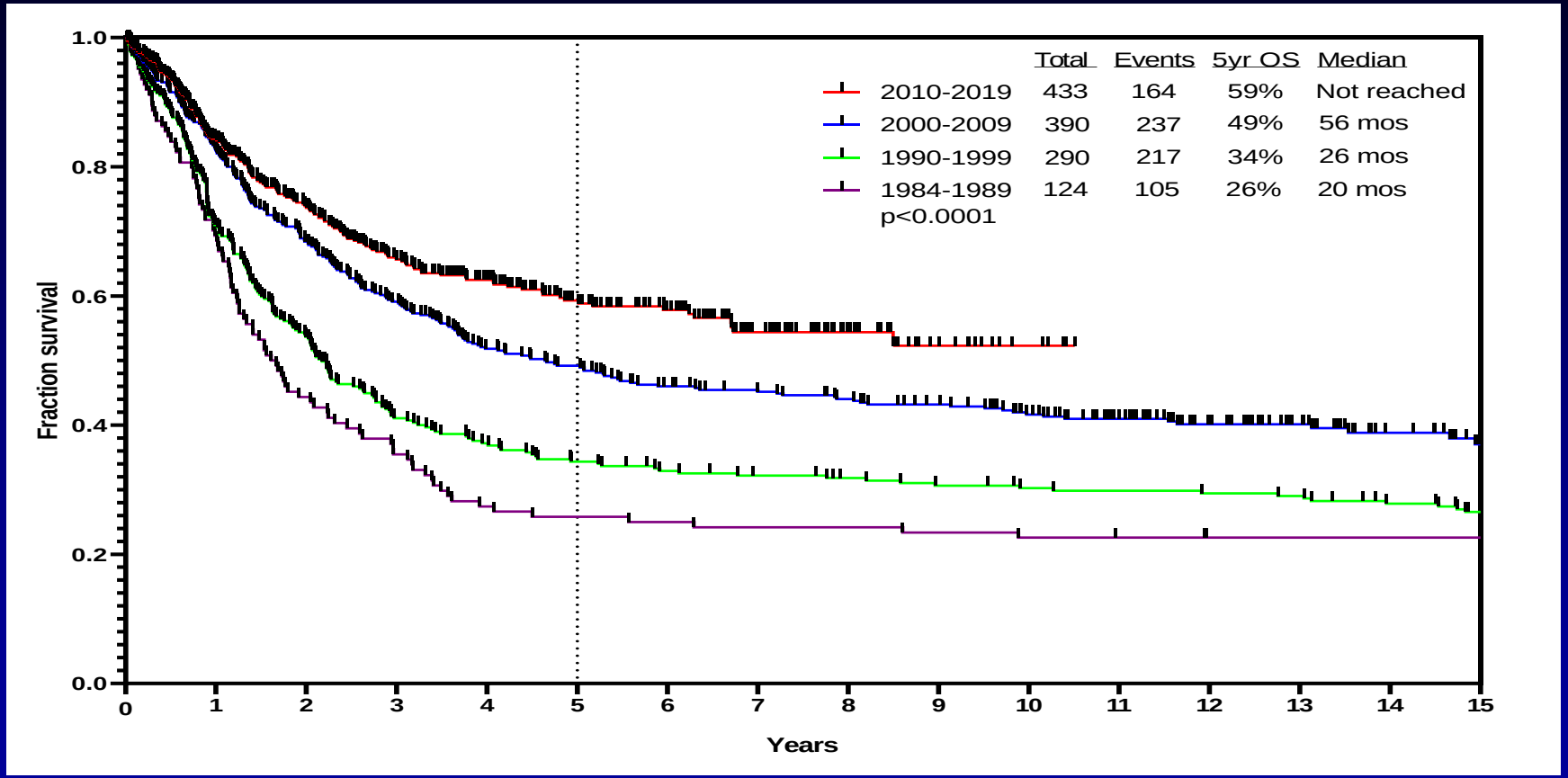
GLA, 2022

Conflict of Interest Disclosure

- **Research Grants**
  - **Pfizer, Takeda, Amgen, AbbVie, Novartis**

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

ALL: Survival by Decade (MDACC 1985–2020)



Reasons for Recent Success in Adult ALL

- Addition of TKIs (ponatinib) +/- blinatumomab to chemoRx in Ph+ ALL
- Addition of rituximab to chemoRx in Burkitt and pre–B-ALL
- Potential benefit of addition of CD19 antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx
- CAR T therapy
- Importance of MRD in CR (at CR vs 3 mos; NGS)

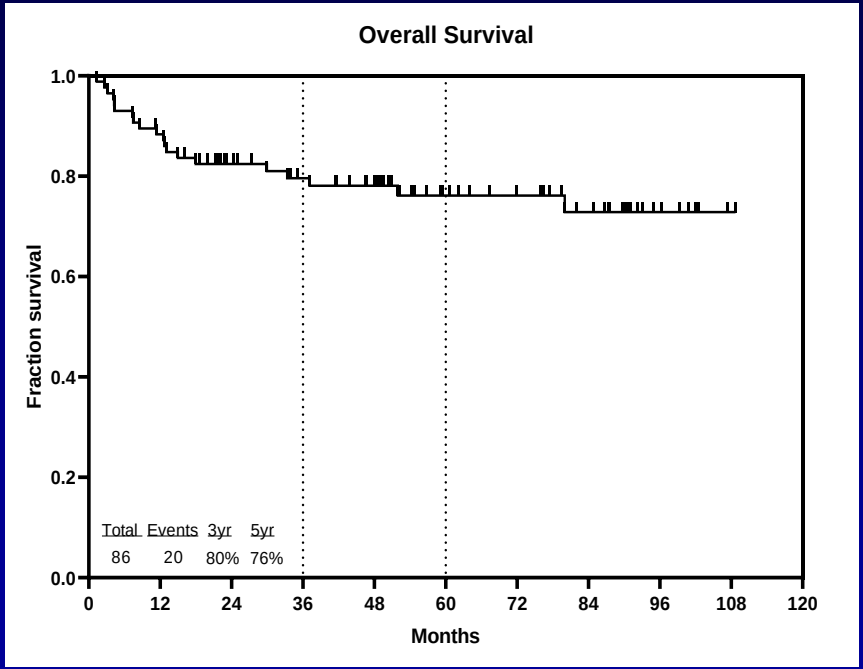
ALL Individualized Therapy in 2022

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	--

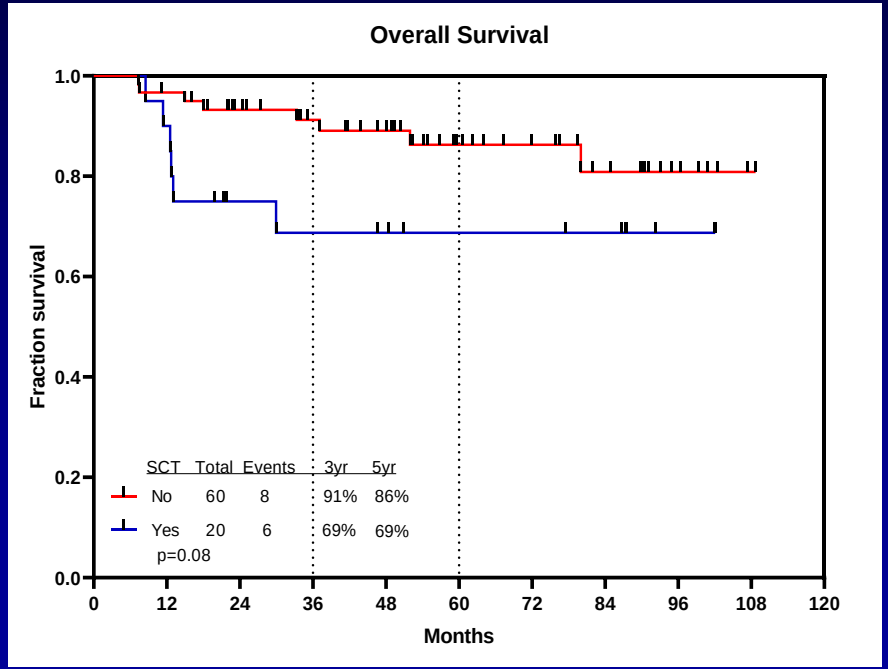
HyperCVAD + Ponatinib in Ph+ ALL

- 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

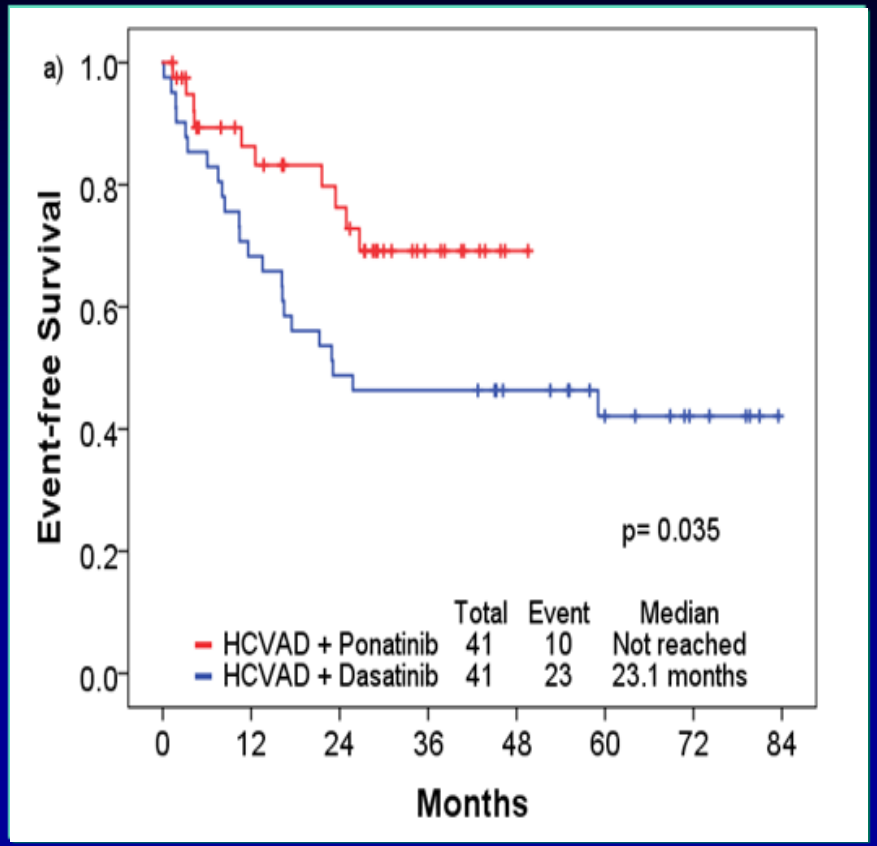


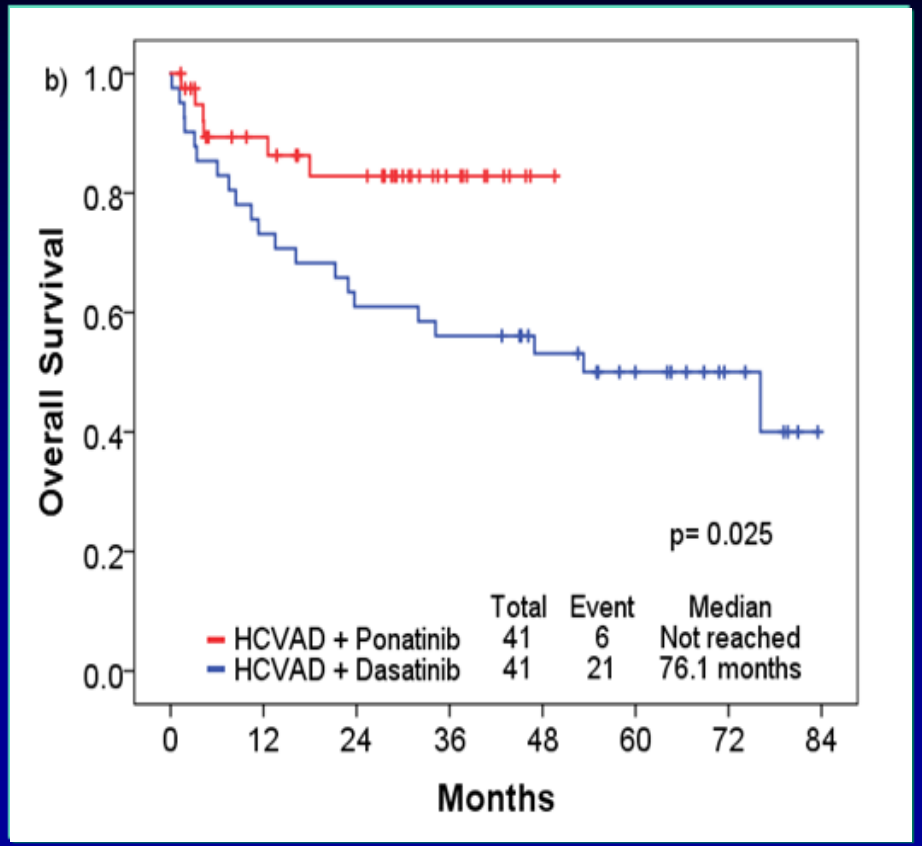
6-Month Landmark



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

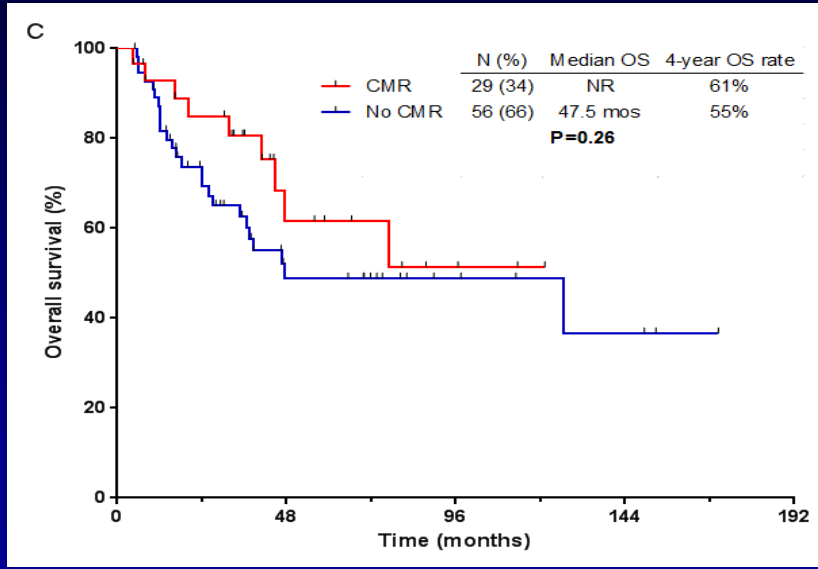




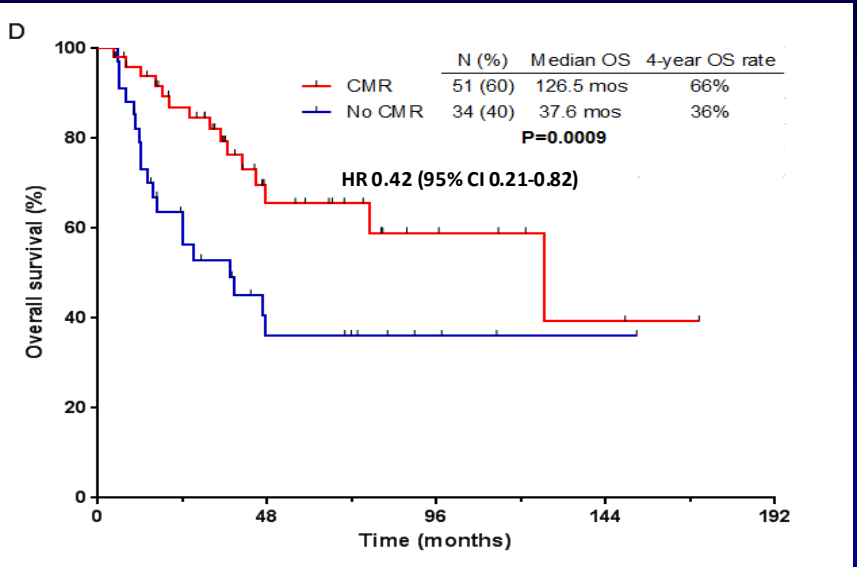
Sasaki et al. *Cancer*. 2016;122(23):3650-3656.

CMR in Ph+ ALL: OS for CMR vs Others

At CR



At 3 months



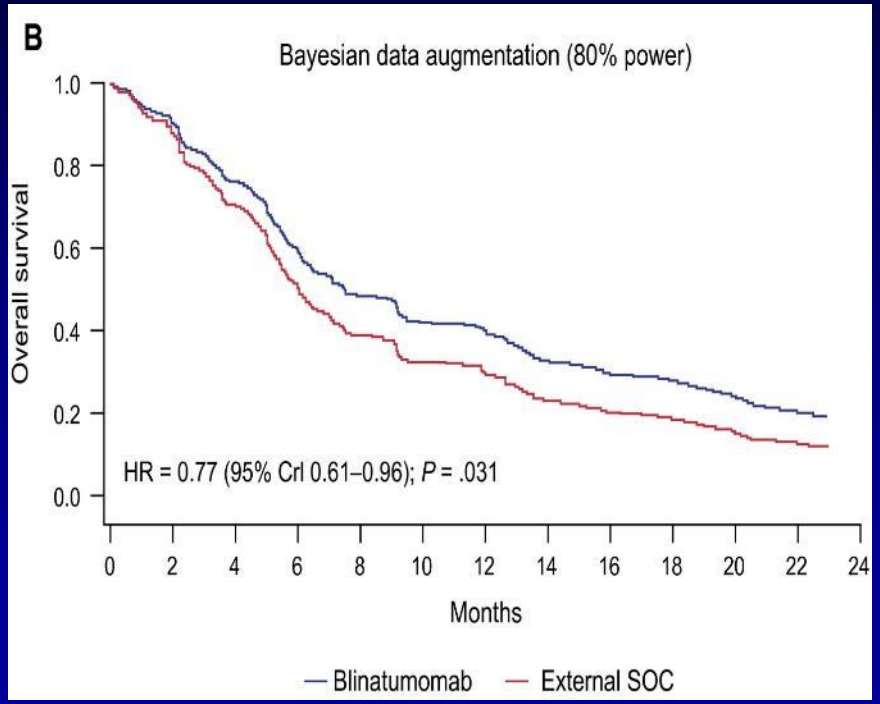
- **MVA for OS**
  CMR at 3 months (HR 0.42 [95% CI: 0.21-0.82]; *P* = .01)

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

Blinatumomab and Inotuzumab in R/R Ph+ ALL

Blina vs SOC

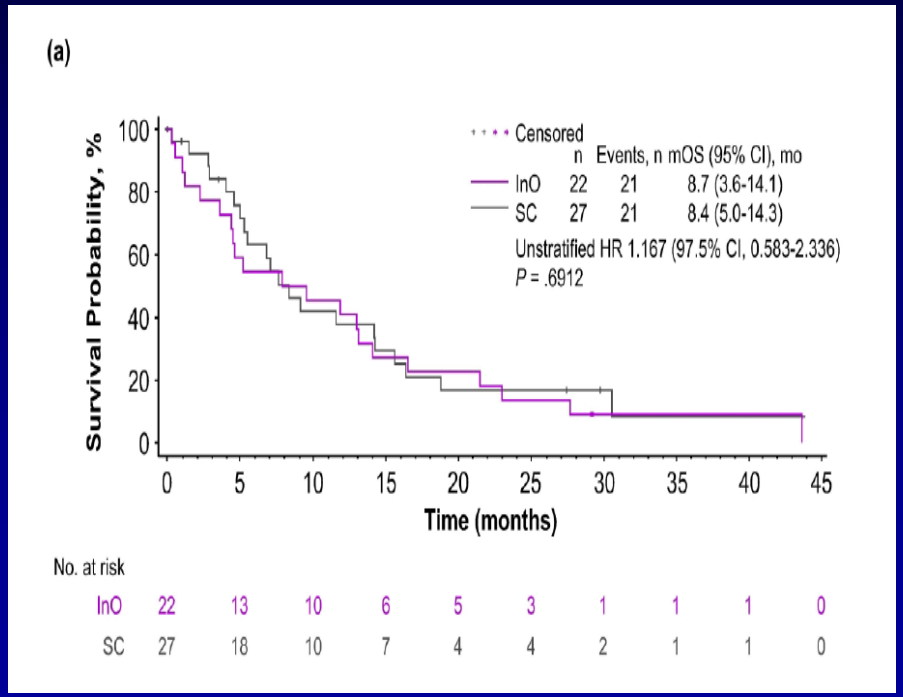
- CR/CRh 36% vs 25%
- 1-yr OS 41% vs 31%



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

Ino vs SOC

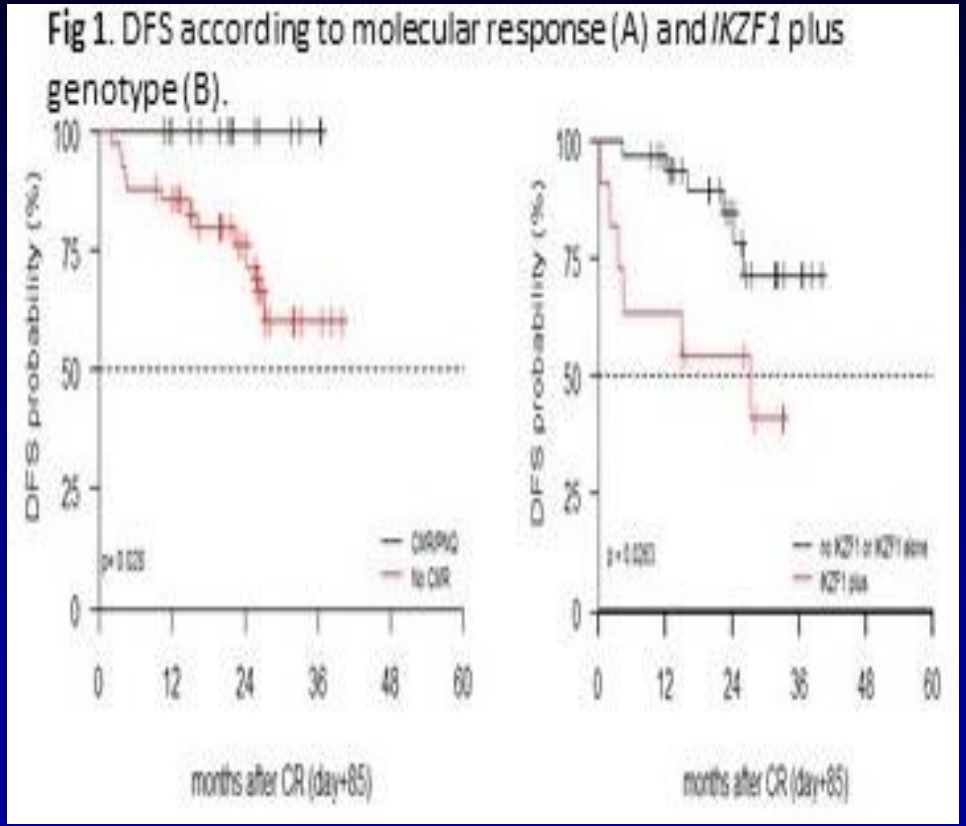
- CR/CRi 73% vs 56%
- 1-yr PFS 20% vs 4.8%



Stock W, et al. *Cancer*. 2020;127(6):905-913.

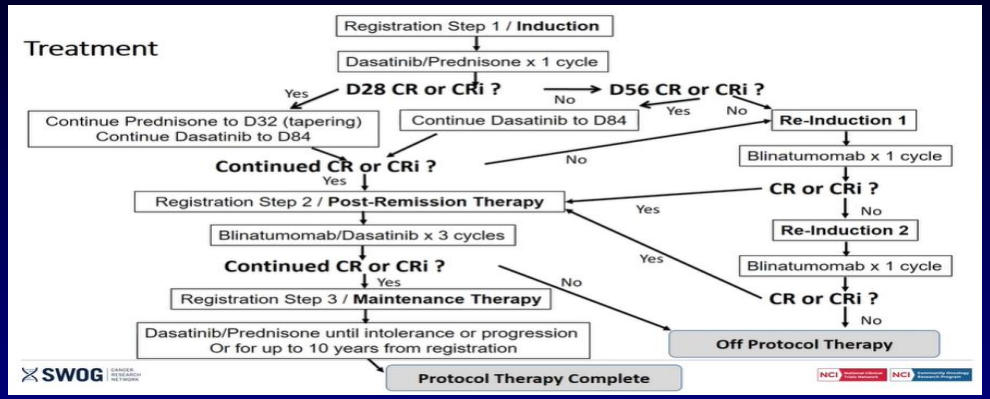
Dasatinib + Blinatumomab (D-ALBA) in Newly-Dx Ph+ ALL – Update

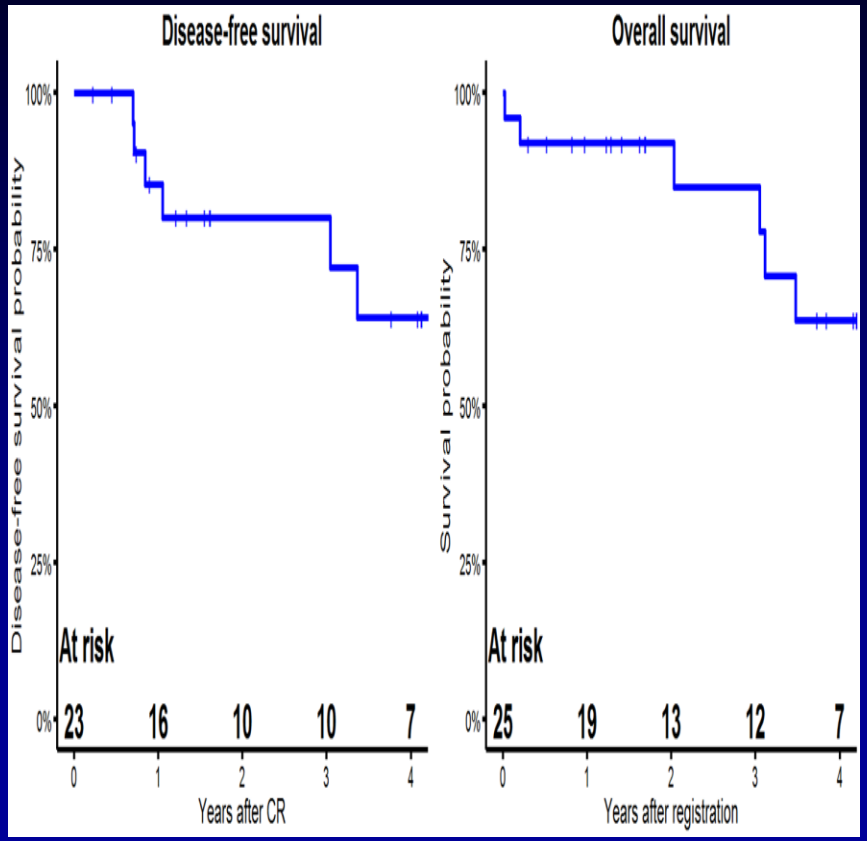
- 64 pts Rx; median age 54 yrs (24–82). Median FU 27 mos
- Molecular response (32/53 = 60%)
  - 22 CMR (41%)
- 29/58 (50%) who started blina have SCT
- 9 relapses: 4 hematologic, 4 CNS, 1 nodal
- 24-mos OS 88%, DFS 80%
- Outcome better if MR: DFS 100% vs 80% (*P* = .028)
- Outcome worse if IKZF1+: 2-yr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



Chiaretti et al. EHA 2021. Abstract S112.

Phase II SWOG1318 of Dasatinib, Prednisone, and Blinatumomab for Older Patients With Ph+ or Ph-Like ALL

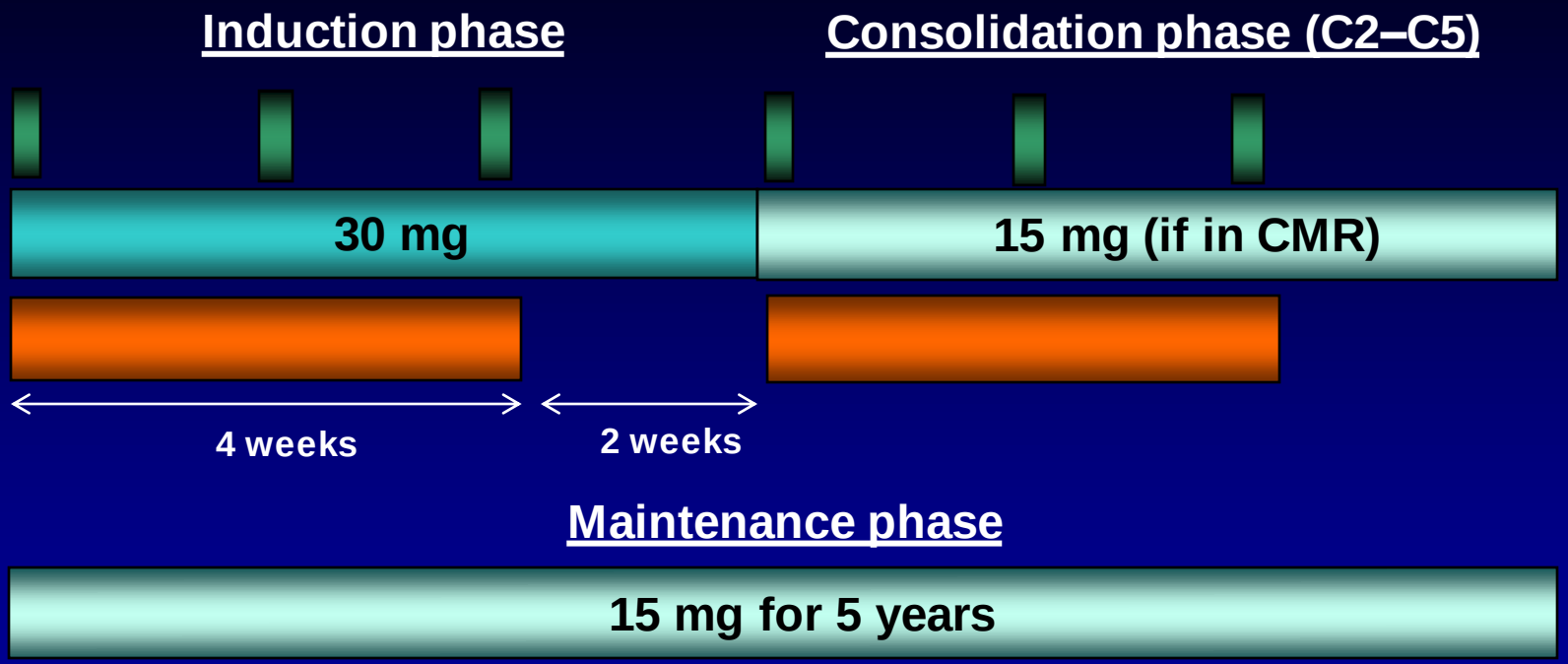




- 25 pts with ND Ph+ (n = 24) or Ph-like ALL (n = 1); median age 73 yrs (62–87)
- Rx dasatinib-steroids (+D84) then 3 cycles blinatumomab/dasatinib
- CR 23/25 pts = 92% during dasatinib-based induction therapy; 31% MRD-negative Day 28
- 3-year OS 85%; DFS 80%

Advani et al. *Blood.* 2021;138:abstract 3397.

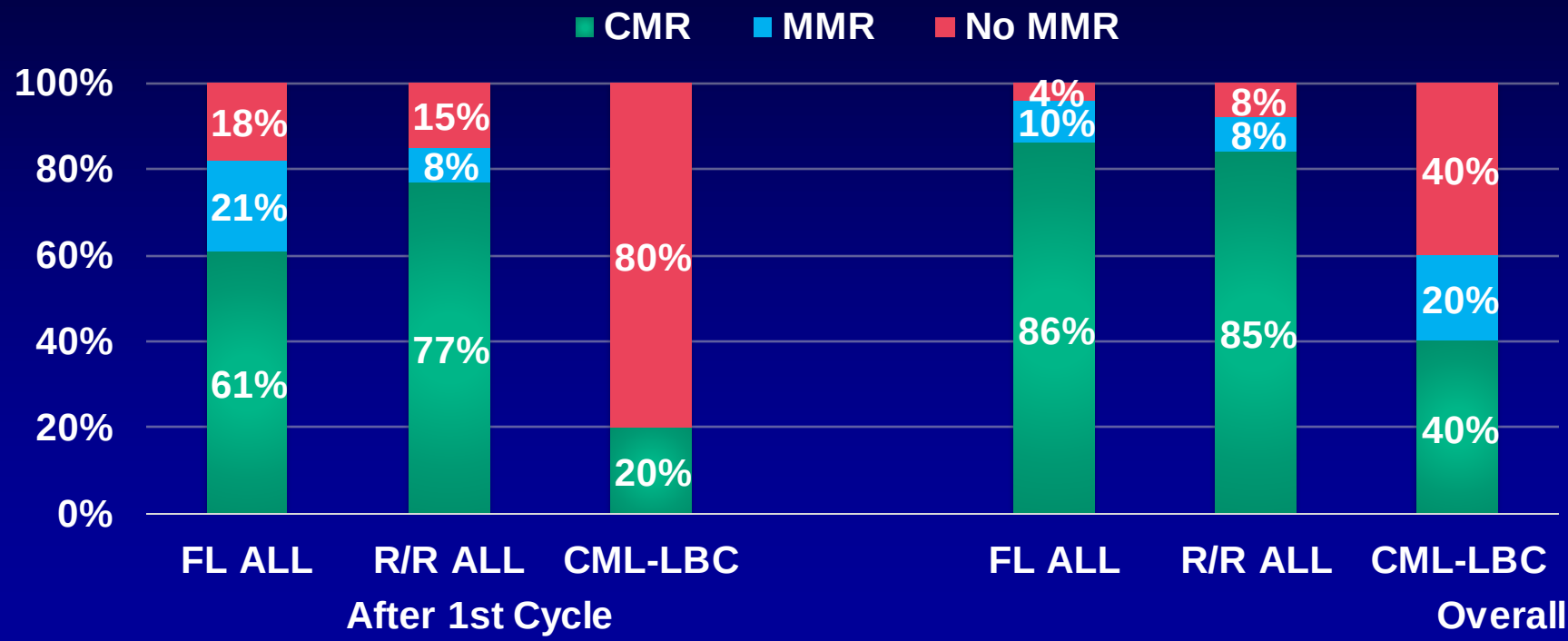
Ponatinib + Blinatumomab in Ph+ ALL: Regimen



Short NJ, et al. *Blood*. 2021;140:abstract 2298.

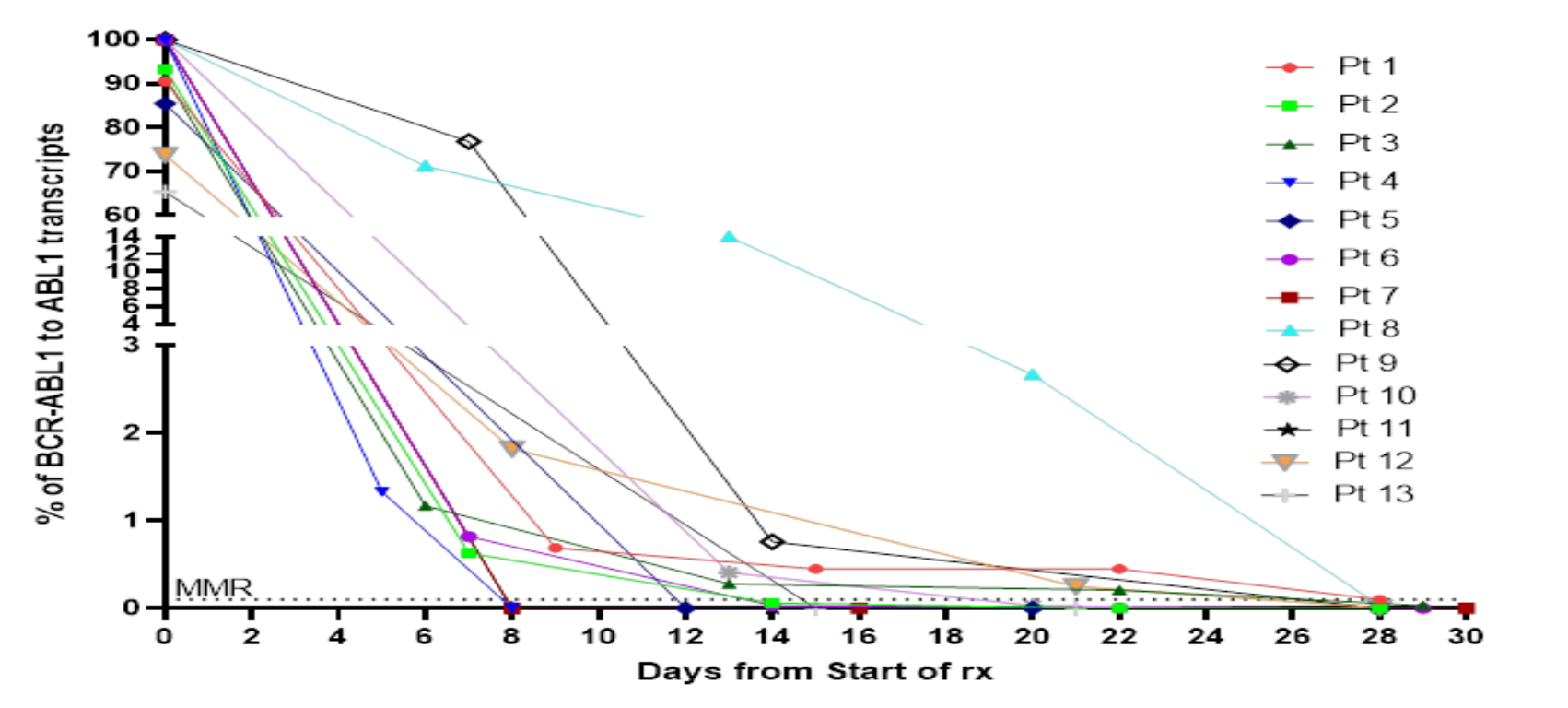
Ponatinib + Blinatumomab in Ph+ ALL: MRD Response Rates

- 50 pts with ND Ph+ (n=30) median age 73 yrs (22–83), R/R Ph+ ALL (n=14), CML-BP (n=6)



Short NJ, et al. *Blood*. 2021;140:abstract 2298.

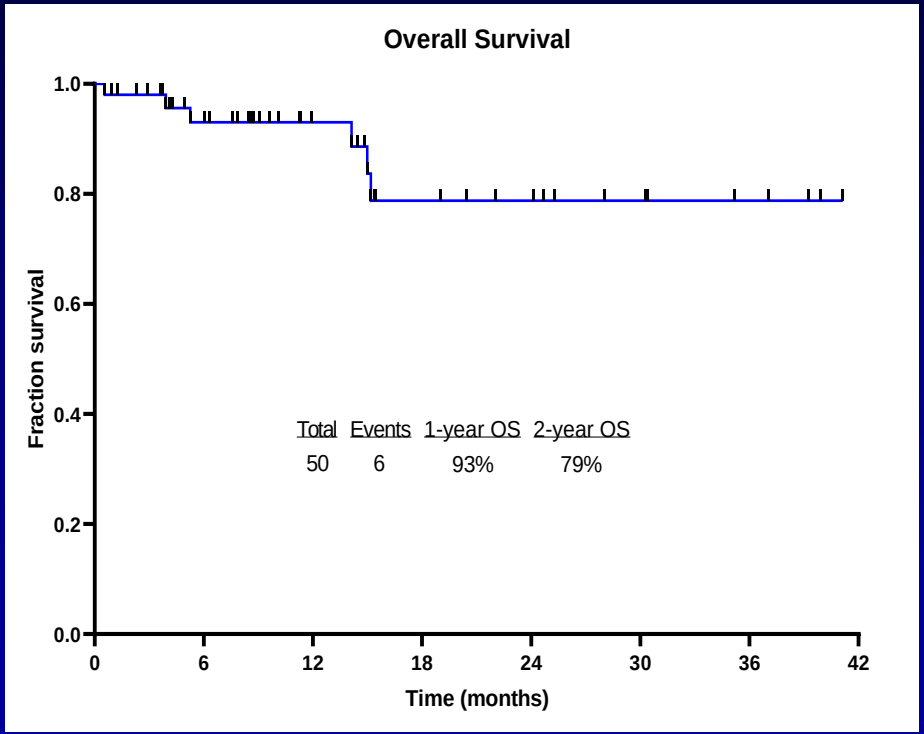
Ponatinib + Blinatumomab in Ph+ ALL: Dynamic of MRD Response



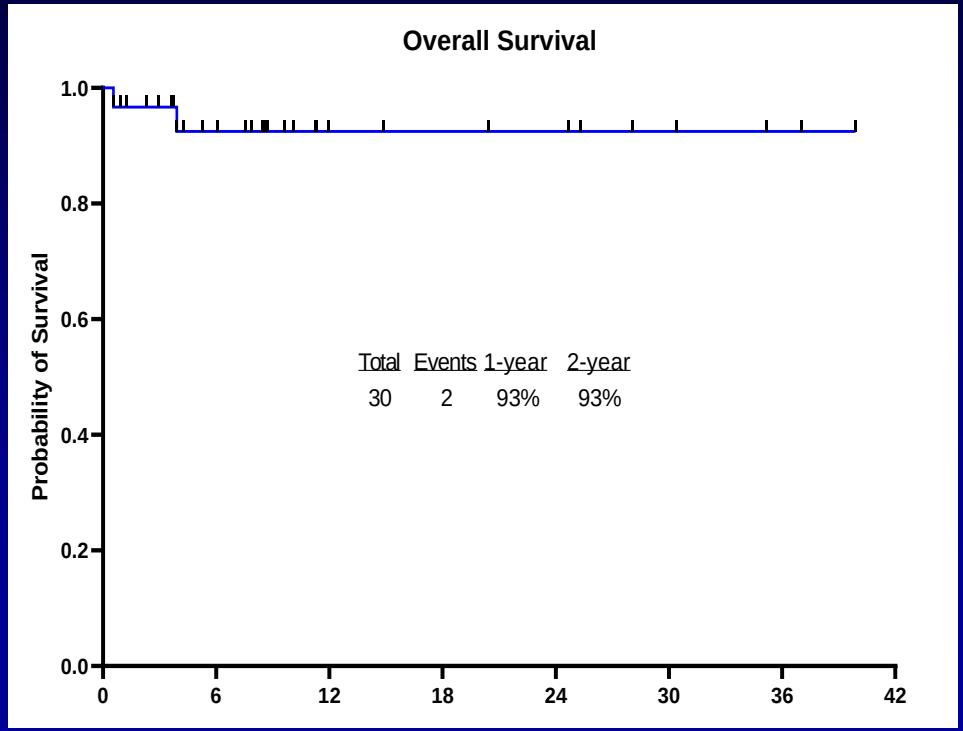
Ponatinib + Blinatumomab in Ph+ ALL: Survival

Median follow-up: 10 months (range, 1–41)

Overall Cohort

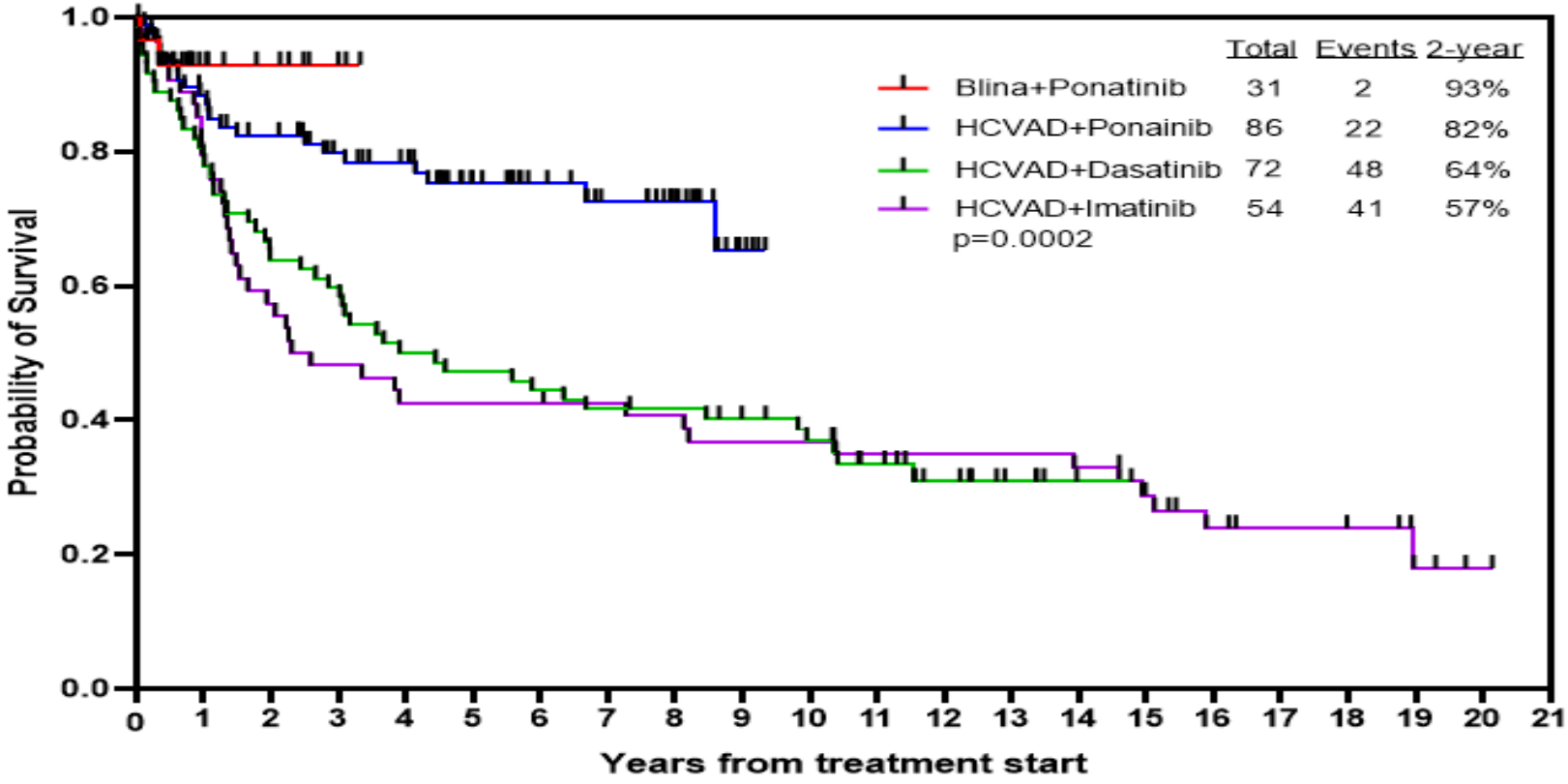


FL Cohort



Short NJ, et al. *Blood.* 2021;140:abstract 2298.

Ponatinib-Blinatumomab in Ph+ ALL vs Historical Data



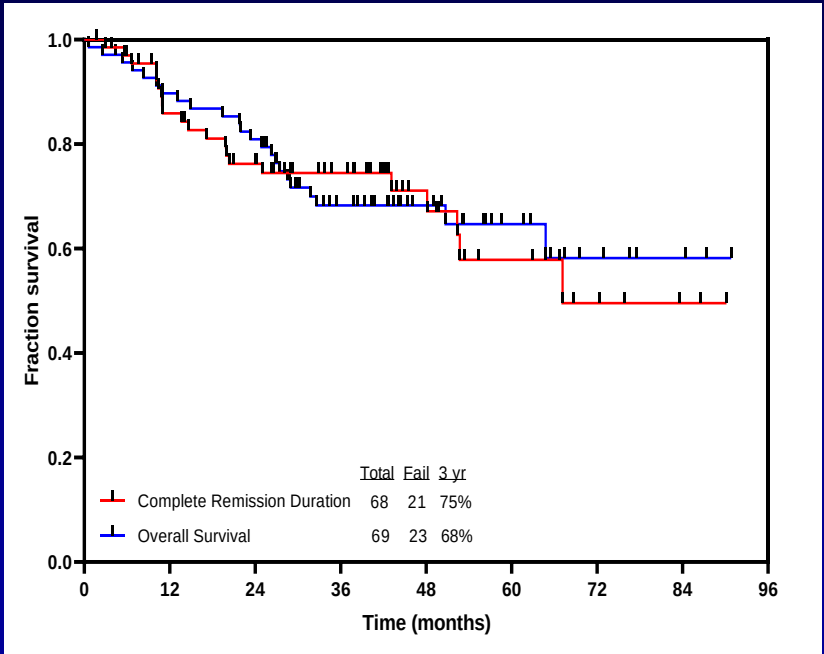
Future of Ph+ ALL

- Do we need allo-SCT? – not always; never?
  - Identify patients who can be cured without allo-SCT, eg, 3-mos CMR, MRD– by NGS
- Ponatinib best TKI? – 3 mos-CMR 86%; 5-year OS rate 76%
  - Phase III low-dose CT + imatinib vs low-dose CT + ponatinib
- How much chemoRx – low-intensity vs intensive chemoRx?
  - Mini-HCVD + ponatinib + blinatumomab for pts with P210 and CML-LBP
- Can we cure Ph+ ALL without chemoRx or allo SCT? – ponatinib + blinatumomab
- In pts with P210 transcripts – R/U CML-LBP: Chemo and allo-SCT needed
- Duration of TKI maintenance – TFR
  - At least 5 years
  - Driven by dynamic and depth of response (eg, CMR by 4 weeks)

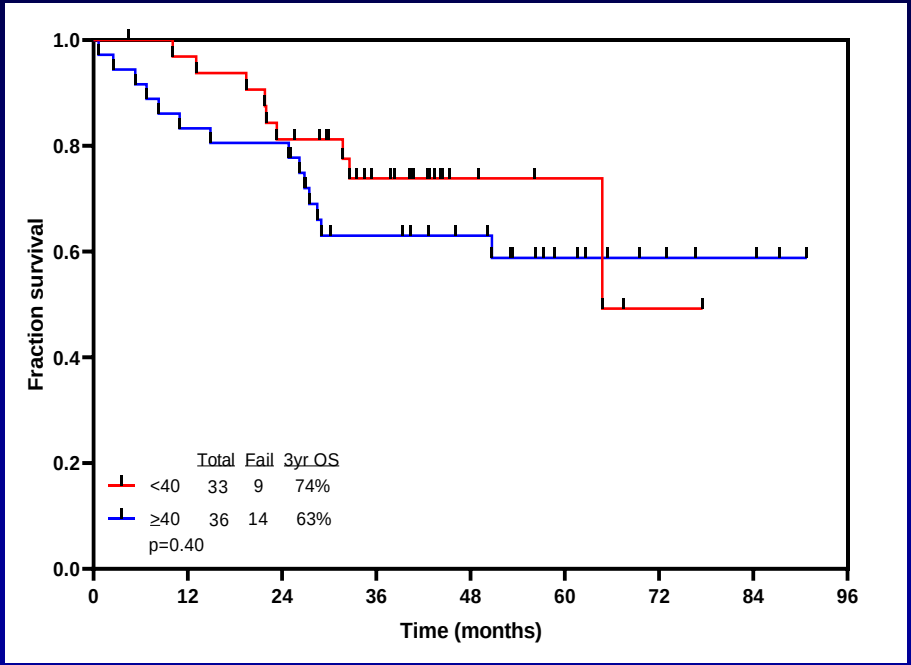
HCVAD + Ofatumumab: Outcomes (N = 69)

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

CRD and OS Overall

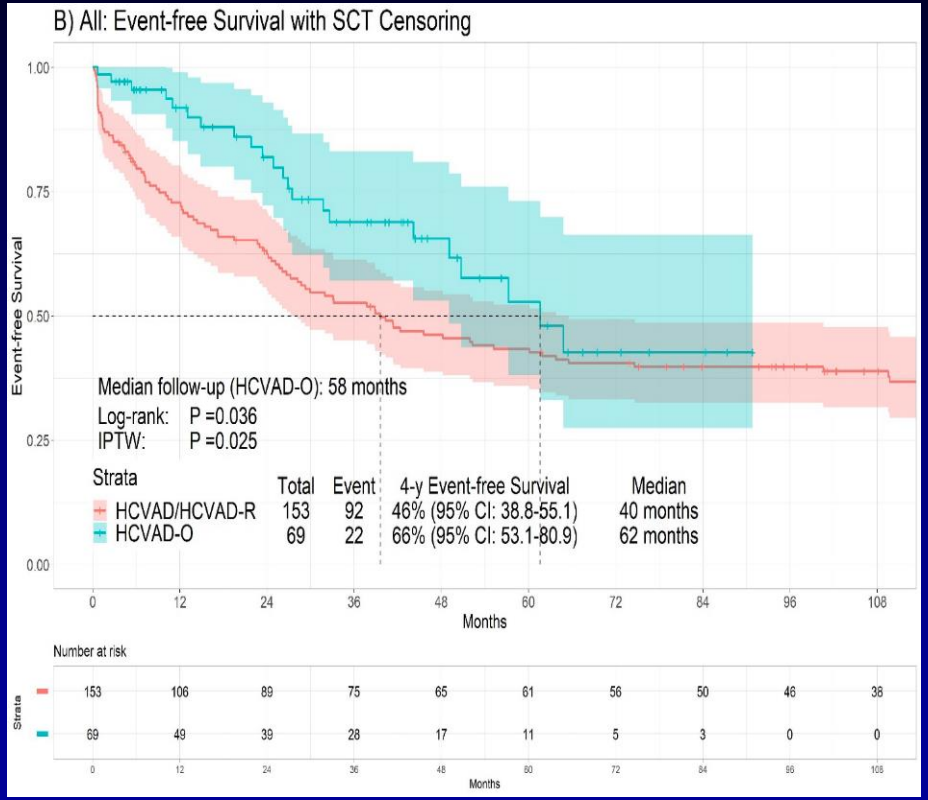


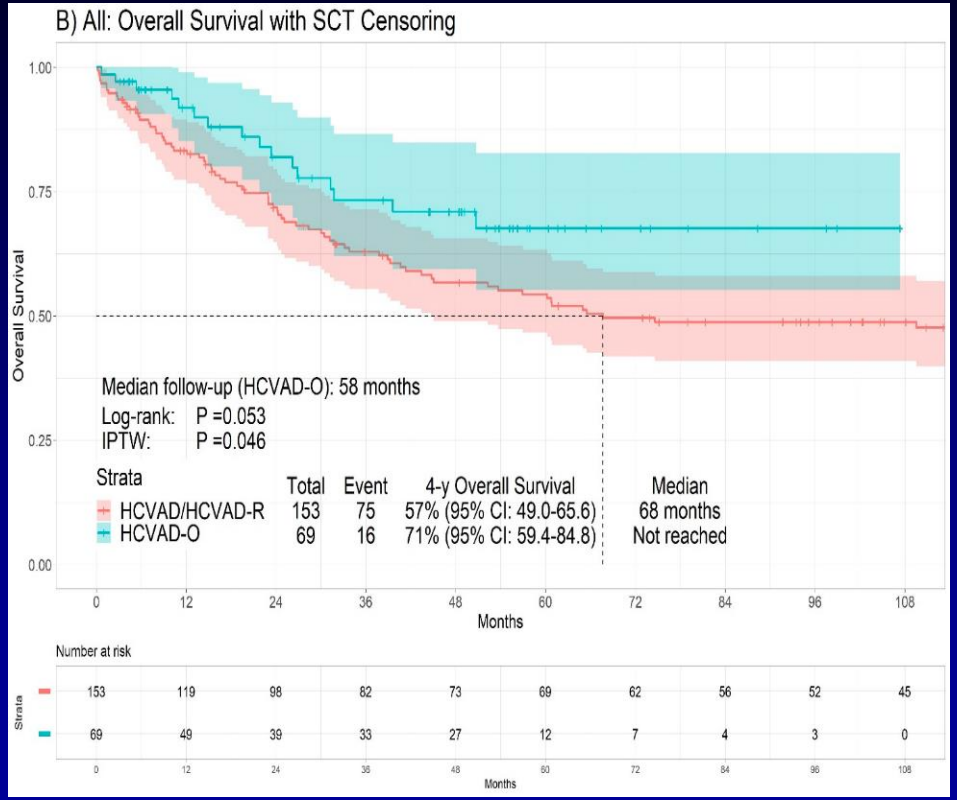
OS by Age



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

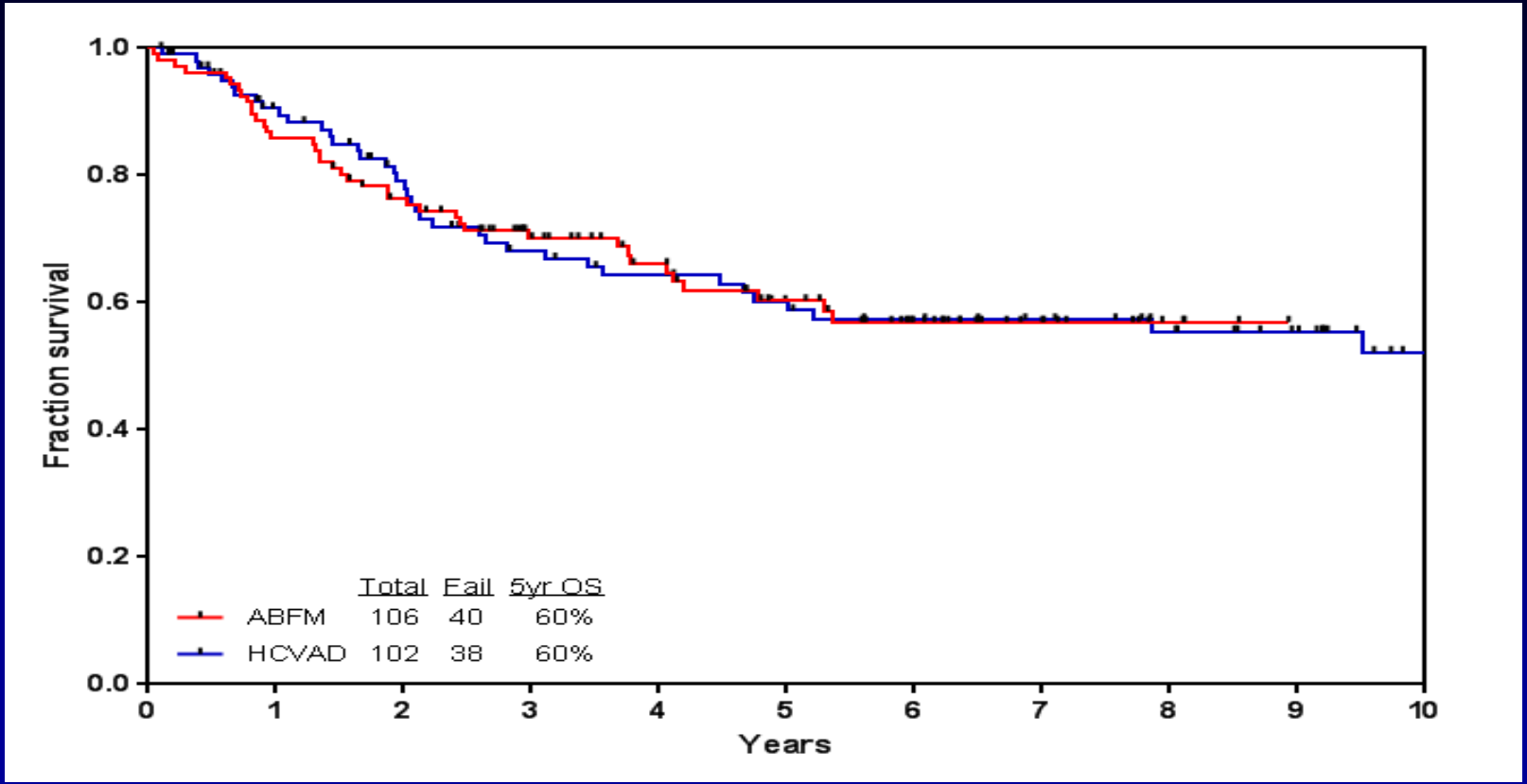
HCVAD-Rituximab vs HCVAD-Ofatumumab: Propensity Score Matching





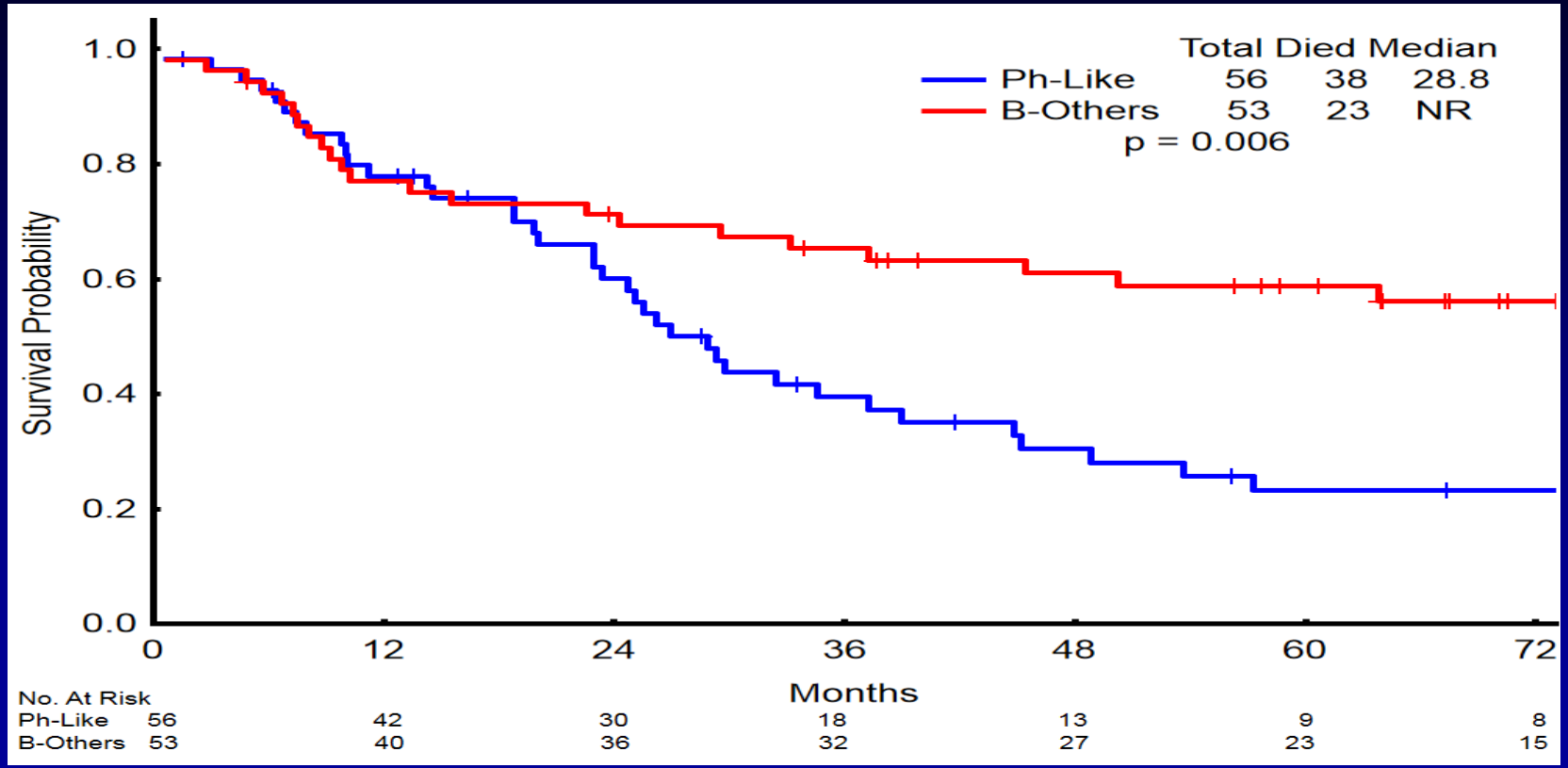
Morita et al. *Cancer.* 2021;127(18):3381-3389.

Hyper-CVAD vs ABFM: Overall Survival



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

Ph-like ALL – Worse Survival



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

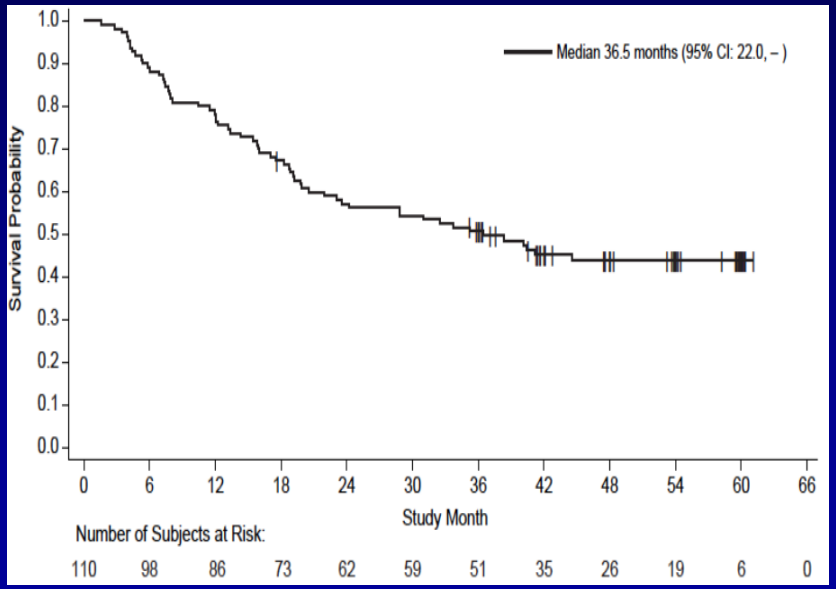
Ph-Like ALL: Higher MRD+ Rate

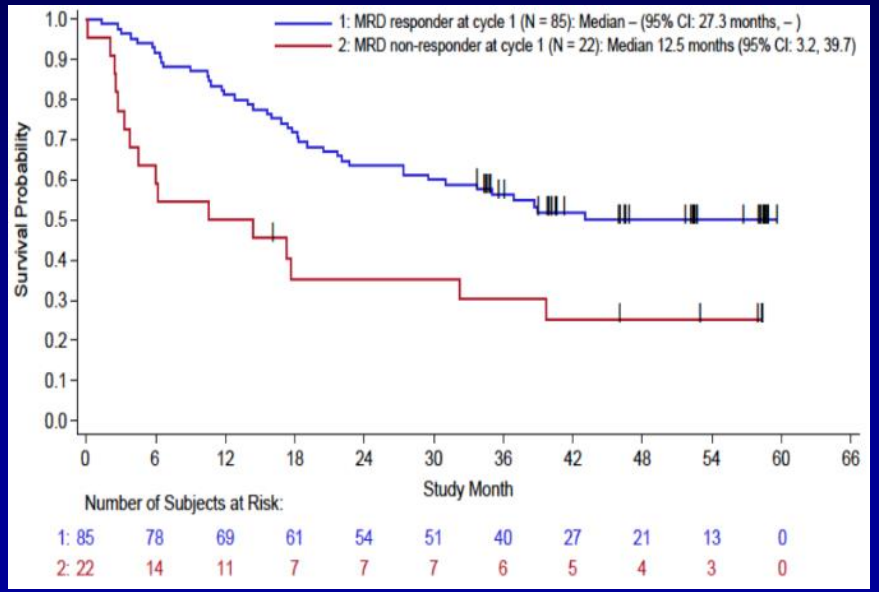
	B-ALL Categories (N = 155)			
	Ph-like	Ph+	B – other	*P* value
N	56	46	53	
CR/CRp	50 (89)	43 (93)	50 (94)	.57
MRD at CR				
Positive	**23 (70)**	**15 (44)**	**4 (13)**	**<.001**
Negative	10 (30)	19 (56)	27(87)	

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

Blinatumomab for MRD+ ALL in CR1/CR2

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

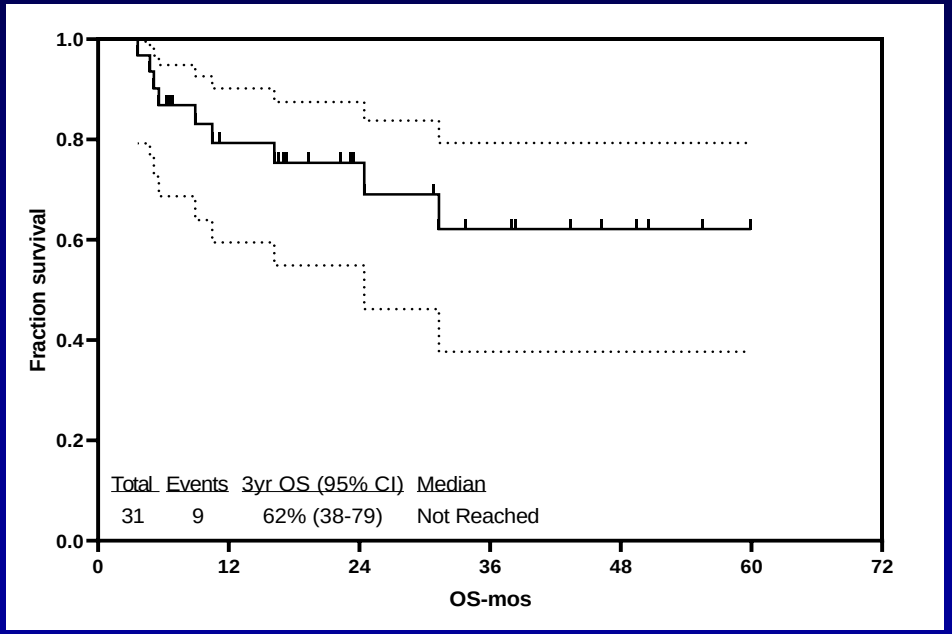


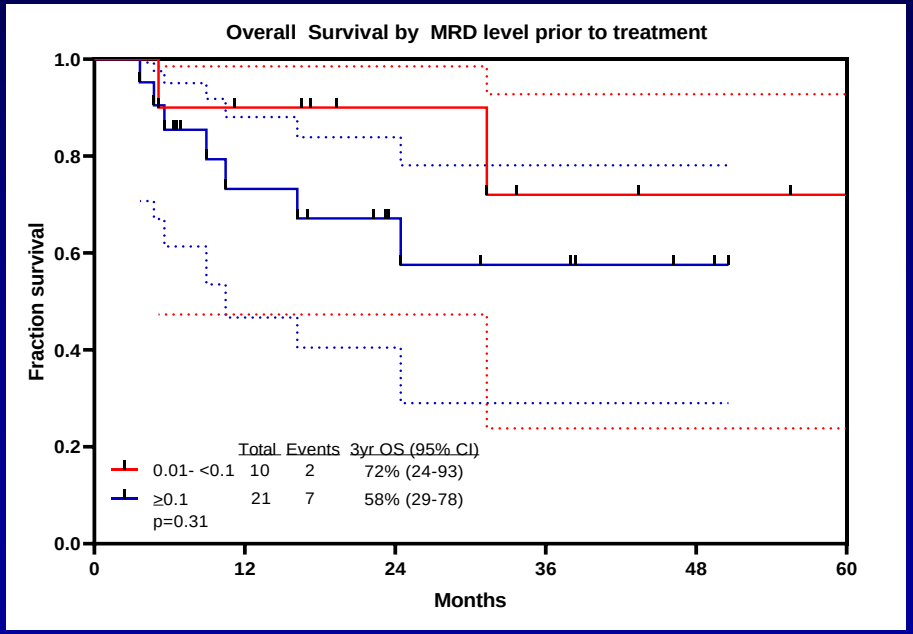


Goekbuget N, et al. *Blood*. 2018;132:abstract 554.

Blinatumomab for MRD+ ALL in CR1/CR2+

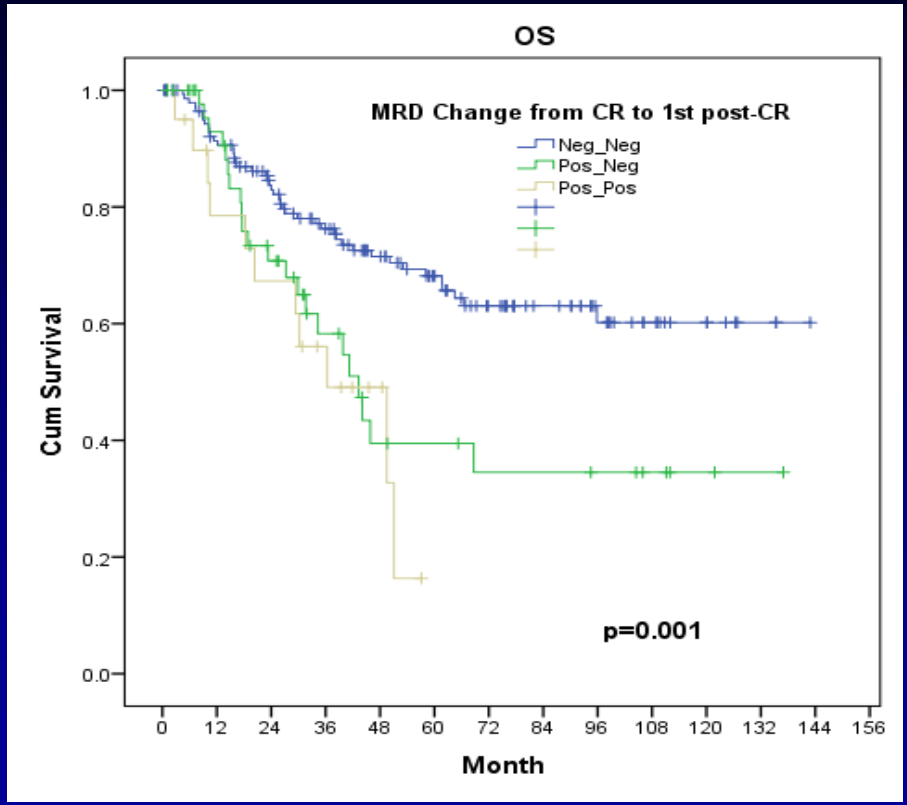
- 31 pts Rx. Post blina MRD-negative 23/31 = 74%
- 10 pts 0.01 to <0.1% RR = 90%; 21 pts ≥0.1% RR = 67%
- Median OS not reached; 3-yr OS 62%; 3-yr OS if MRD-negative 72%
- Continuous CR 6/8 post alloSCT (75%); 9/15 without SCT (60%)





Dynamics of MRD: Outcomes

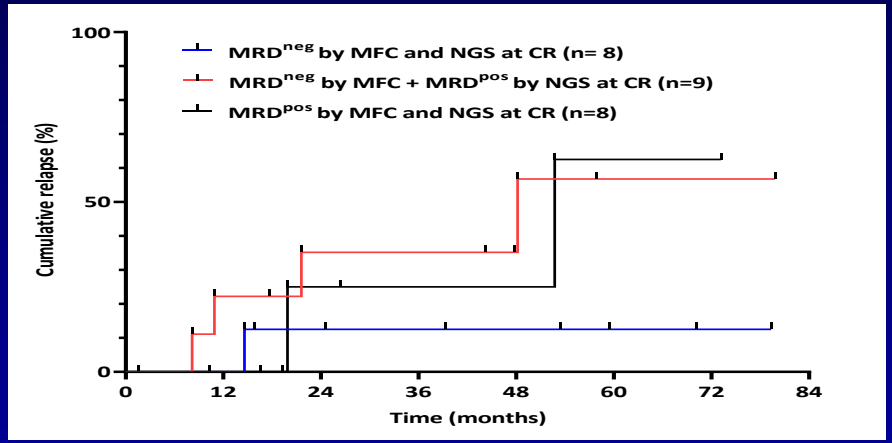
MRD Status		Patients (%) n = 214	5-yr EFS, %	5-yr OS, %
@CR	@ First post-CR			
Negative	**Negative**	**147 (69)**	**56**	**68**
≤0.1%	Negative	14 (7)	31	46
>0.1%	Negative	33 (15)	32	38
Positive	Positive	20 (9)	NA	NA

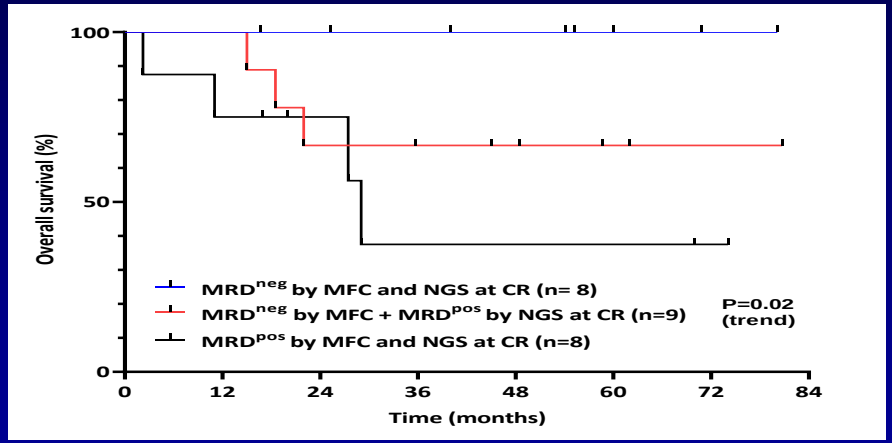


Yilmaz et al. *Am J Hematol.* 2020;95(2):144-150.

MRD in ALL: NGS vs FCM

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





5-year CIR rates

MRD– by MFC and NGS: 13%

MRD– by MFC + MRD+ by NGS: 57%

MRD+ by MFC and NGS: 63%

5-year OS rates

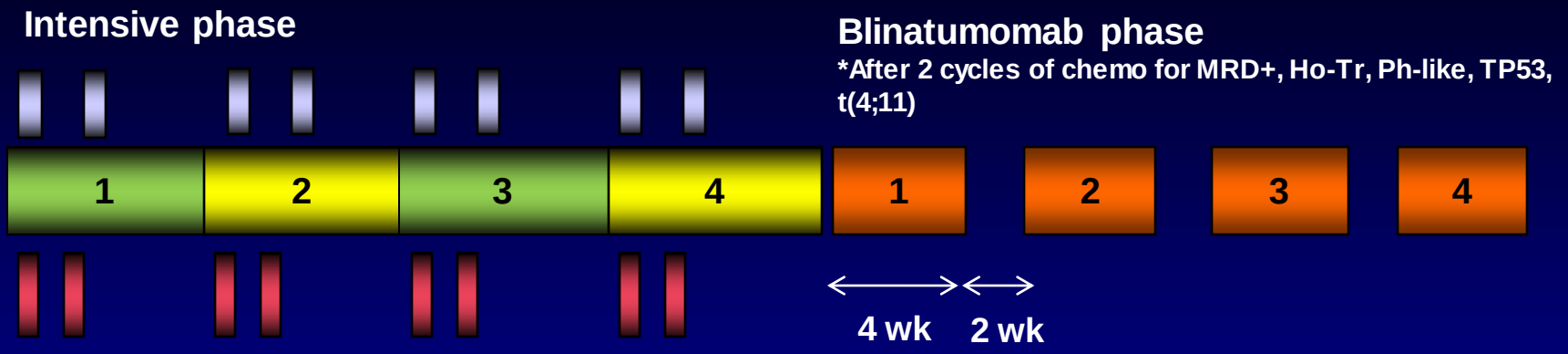
MRD– by MFC and NGS: 100%

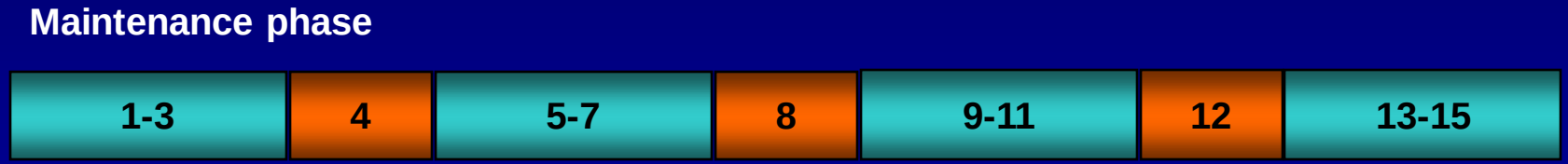
MRD– by MFC + MRD+ by NGS: 67%

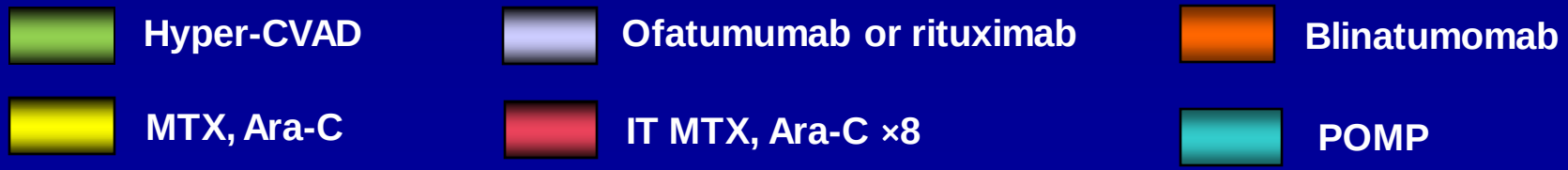
MRD+ by MFC and NGS: 38%

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

Hyper-CVAD + Blinatumomab in B-ALL: Regimen





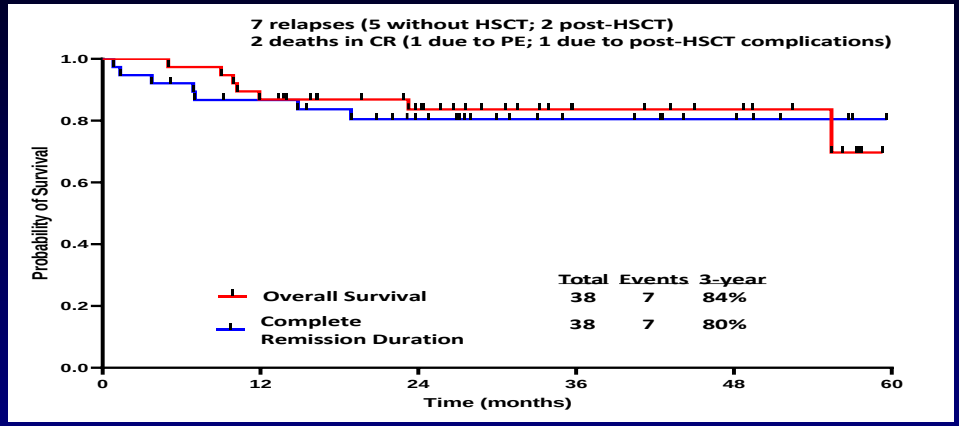


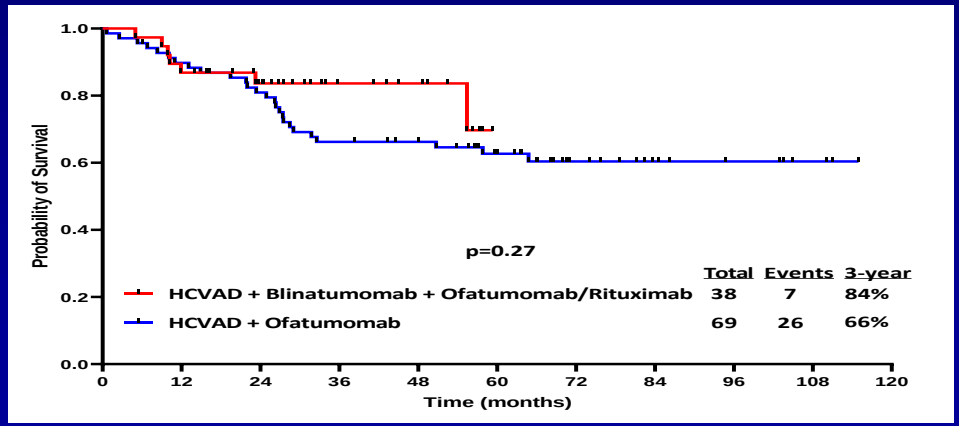
Short et al. *Blood.* 2021;138:abstract 1233.

Hyper-CVAD + Blinatumomab in B-ALL

Response	n/N (%)
CR post induction	26/32 (81)
CR any time	32/32 (100)
MRD– post induction	24/34 (71)
MRD– anytime	33/34 (97)
30-day mortality	0

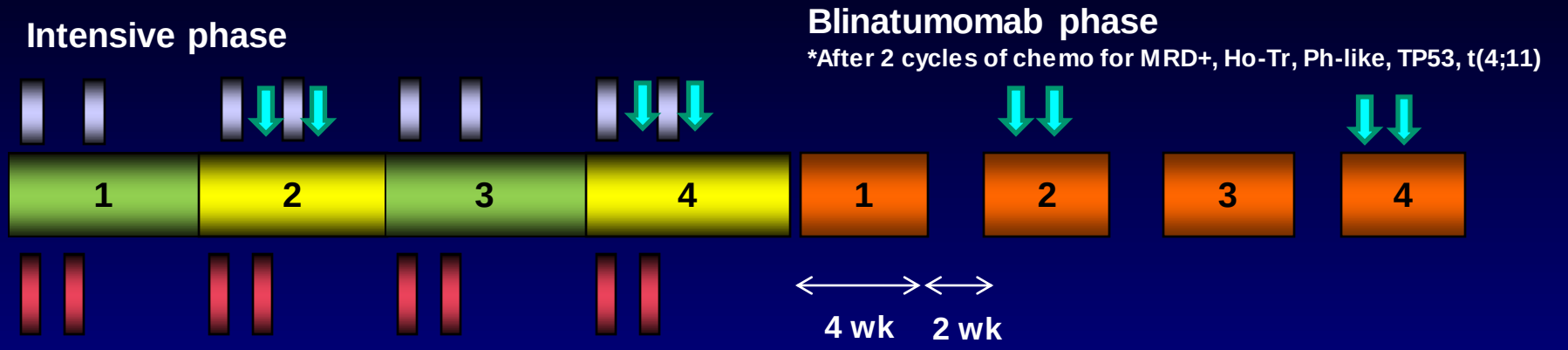
*6 pts in CR, 4 pts MRD– at start





Short et al. *Blood.* 2021;138:abstract 1233.

Hyper-CVAD + Blina + InO in B-ALL: Regimen



Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

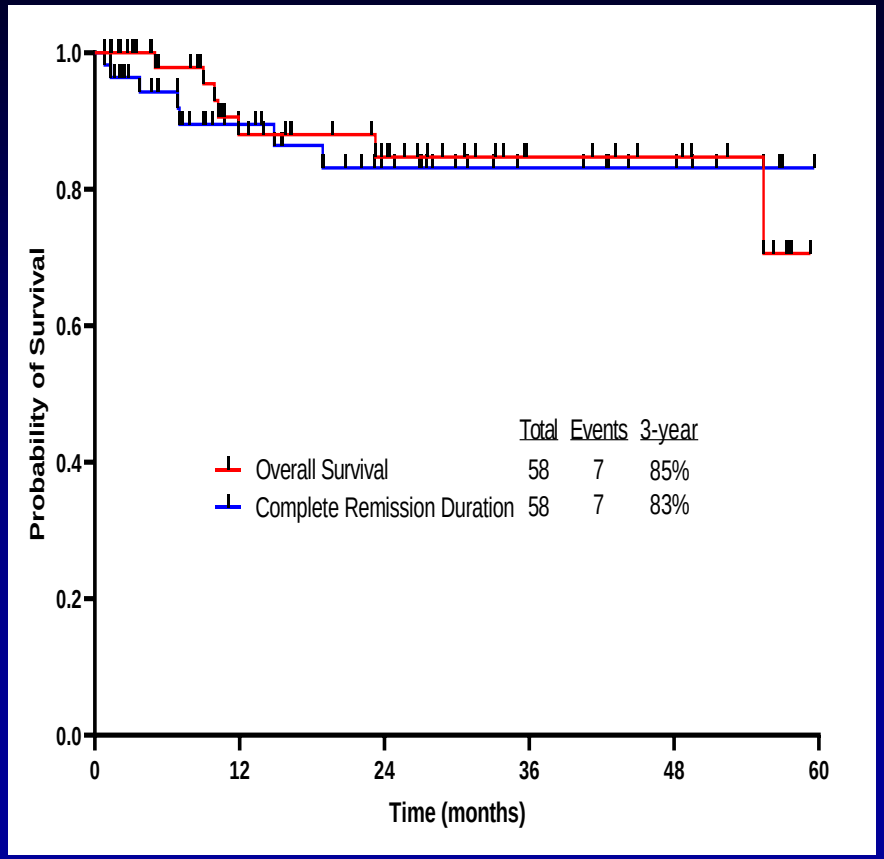
MTX (500 mg/m^2) + Ara-C (1 g/m^2)

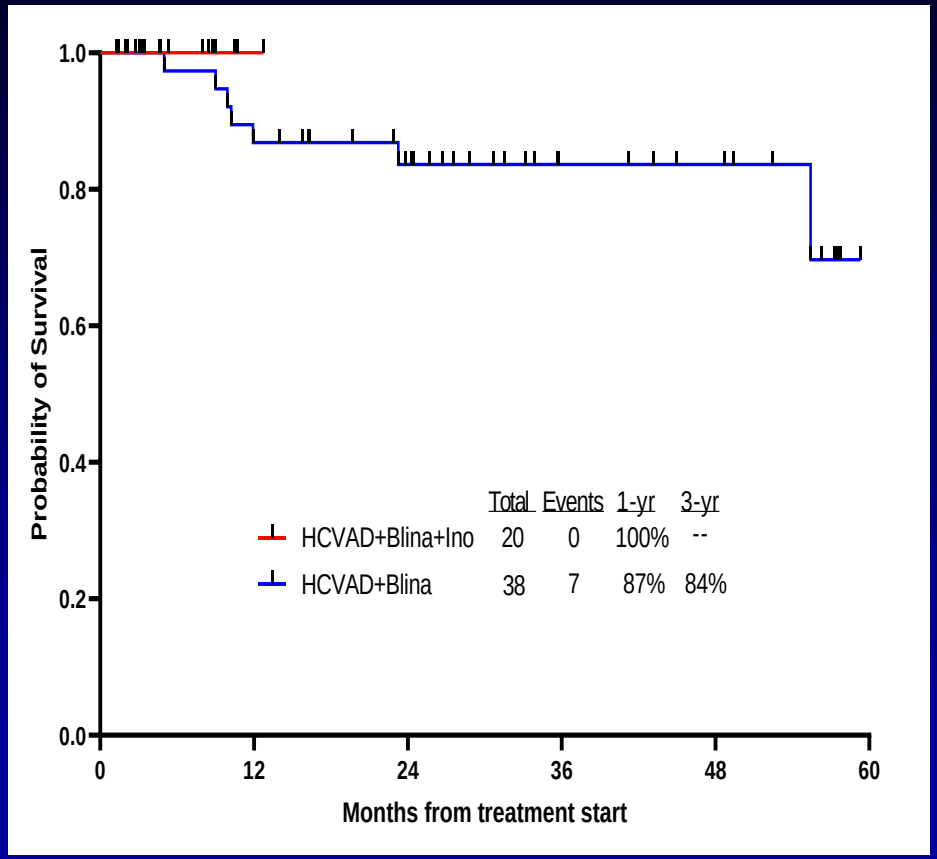
IT MTX, Ara-C ×8

POMP

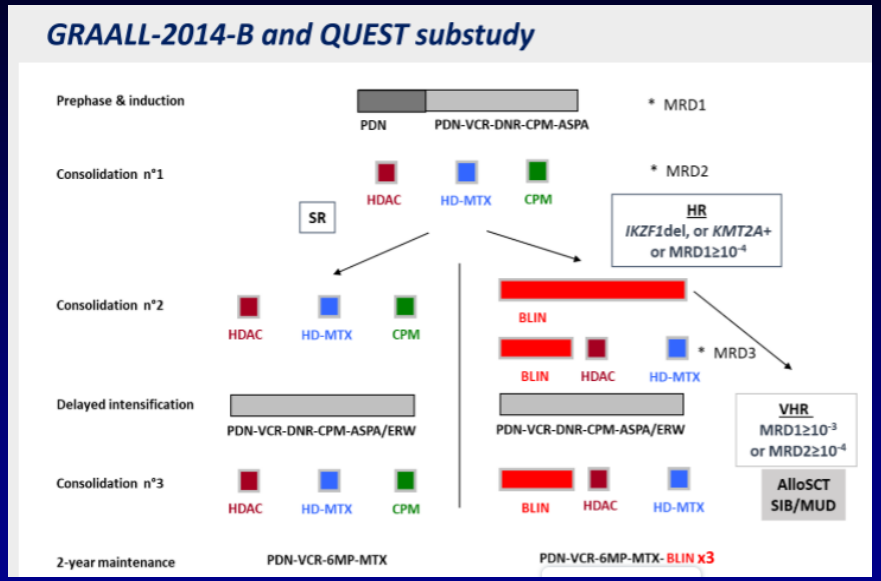
Inotuzumab 0.3 mg/m^2 on D1 and D8

Hyper-CVAD + Blina + InO in B-ALL: Outcomes

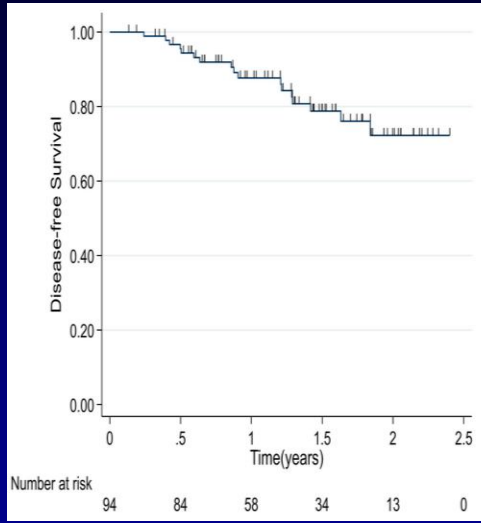




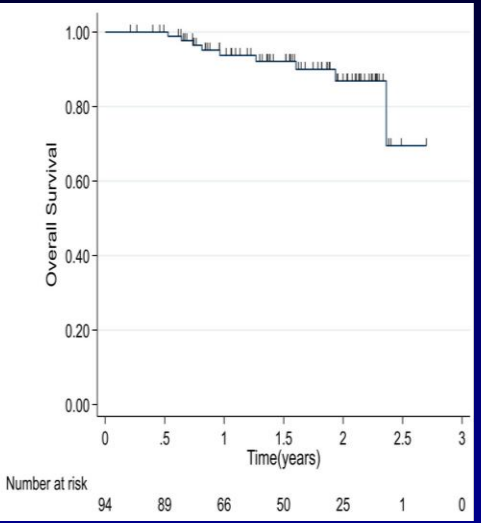
Blinatumomab Consolidation for HR Frontline Adult B-ALL: GRAALL-2014-QUEST Phase II Study



Disease-Free Survival



Overall Survival

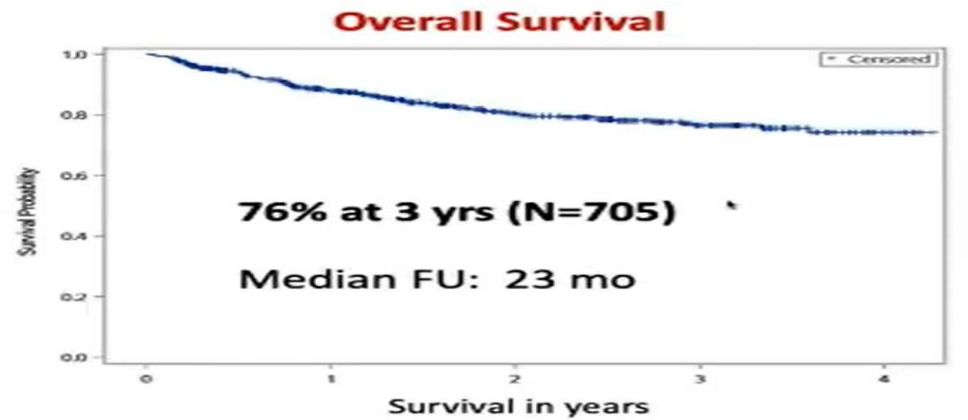


- 95 pts HR Ph– B-ALL Rx blinatumomab at week 12; 42% of patients received allo-HSCT
- After blinatumomab, MRD response in 61/82 (74%)
- With a median follow-up of 20 months, 18-month DFS 79% and OS 92%
- AE: 1 CRS (Gr2), 8 neurotoxicities (1 Gr2, 3 Gr3, 3Gr4, 1Gr5)

Boissel et al. Blood. 2021;140:abstract 1232.

First Results of the Risk-Adapted, MRD-Stratified GMALL Phase III Trial in Newly Diagnosed B-ALL/LBL

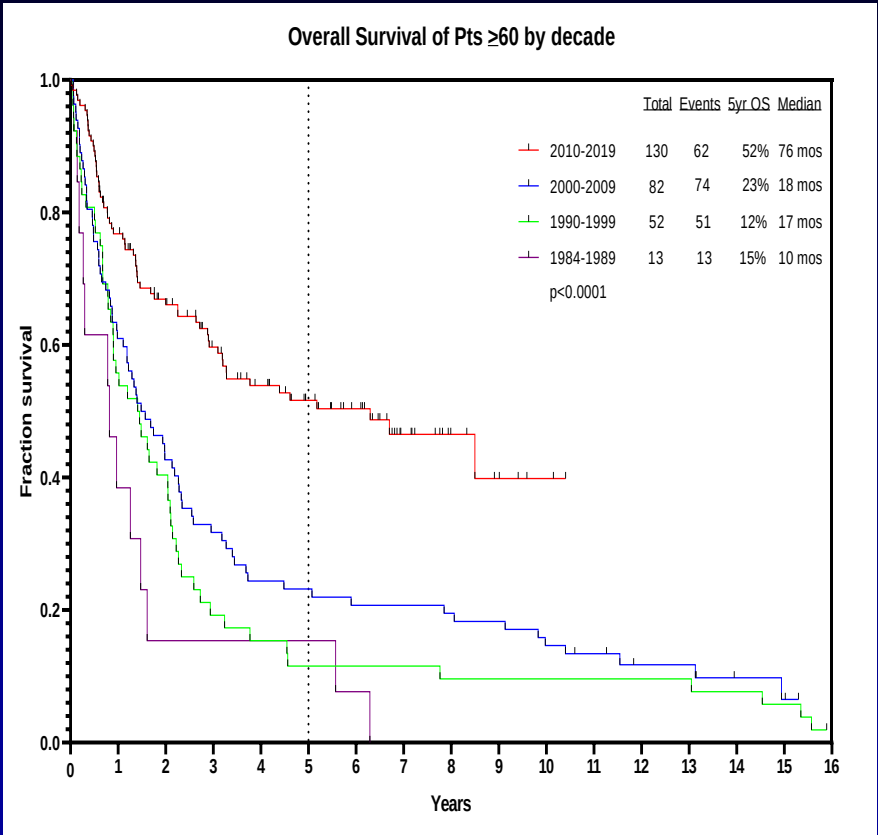
- 638 pts with ALL and 67 with LBL; median age 35 yrs (18–55)
- CR 93%, MolCR 61%, 3-yr OS 76%
- 63 pts with MolFail:
  - MRD clearance with blinatumomab in 55% (n = 40)

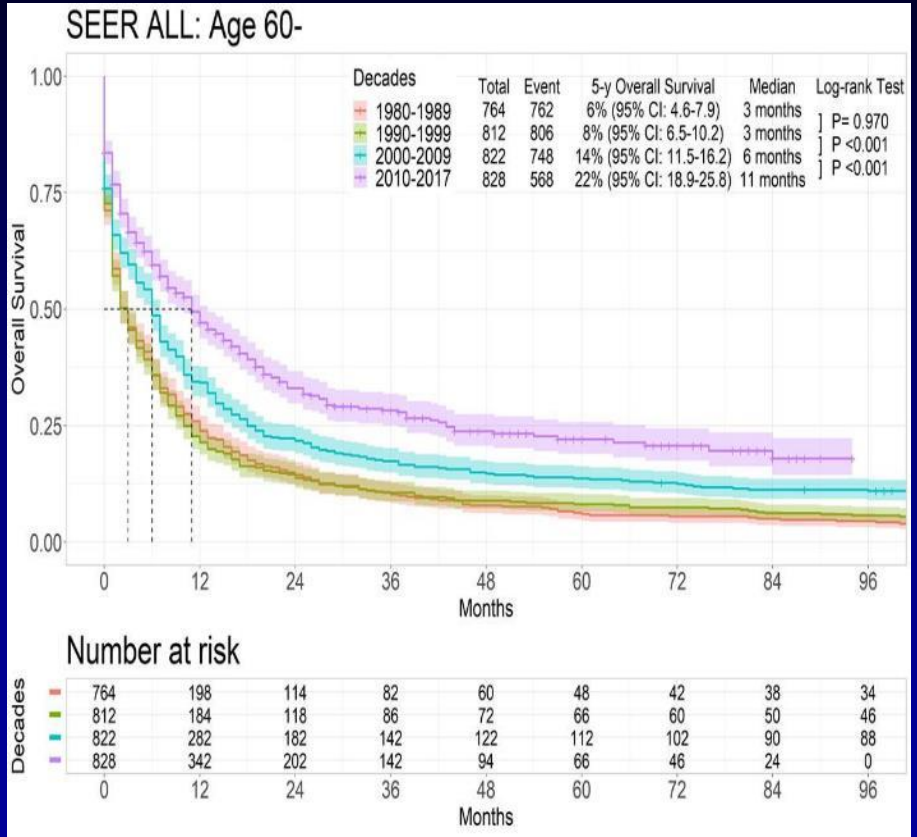


	Total	B-ALL/Ph-	B-ALL/PH+	T-ALL	B/T SR[4]	B/T HR[4]
Evaluable for Hematologic Response (N) [1]	599	326	122	151	261	217
Hematologic CR	93%	94%	95%	89%	96%	88%
Early death	4%	5%	3%	5%	3%	7%
Failure/PR[2]	3%	1%	2%	7%	1%	4%
Evaluable for Molecular Response (N) [3]	542	306	116	120	248	178
Molecular CR	61%	65%	41%	67%	74%	54%
Molecular Failure	19%	18%	28%	11%	10%	25%
Molecular Low positive	14%	11%	17%	20%	12%	16%
Molecular not evaluable	6%	6%	13%	3%	4%	5%
N Overall Survival	638	350	128	160	276	234
Overall Survival 1y	88%	88%	85%	88%	94%	81%
Overall Survival 3y	76%	77%	74%	74%	85%	65%

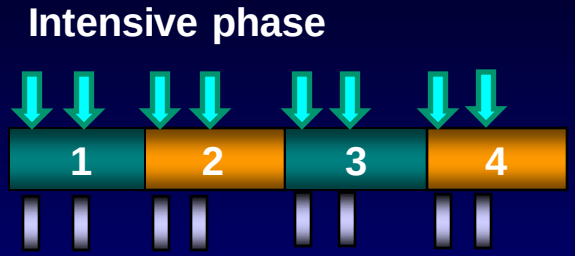
Goekbuget N, et al. *Blood.* 2021;138:abstract 362.

MDACC ALL: Survival by Decades for ≥60 Years





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



Mini-HCVD

Mini-MTX-cytarabine

IT MTX, Ara-C

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

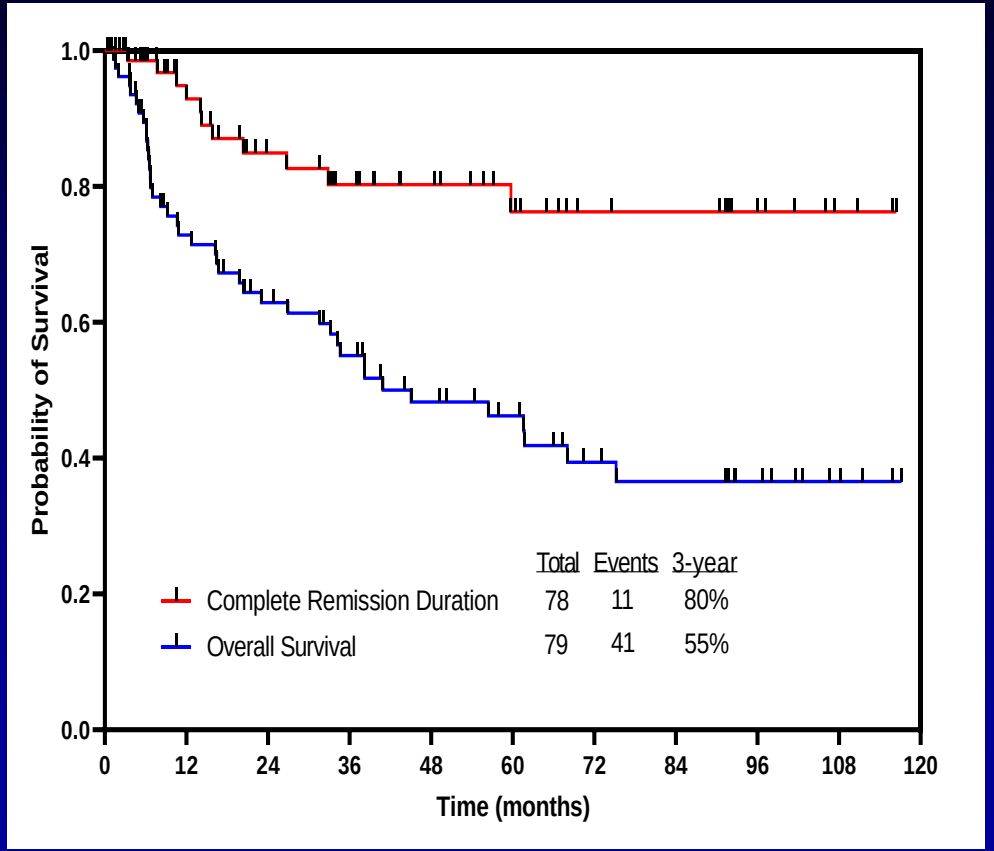
Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

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

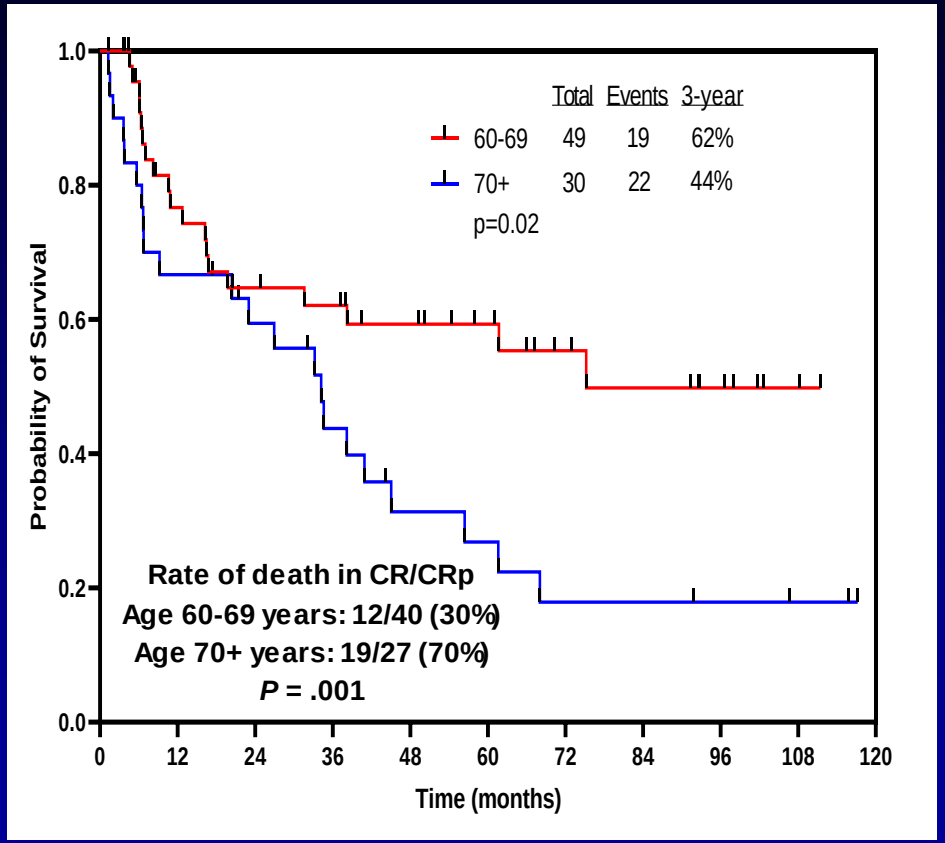
Mini-HCVD + Inotuzumab/Blinatumomab in Older ALL

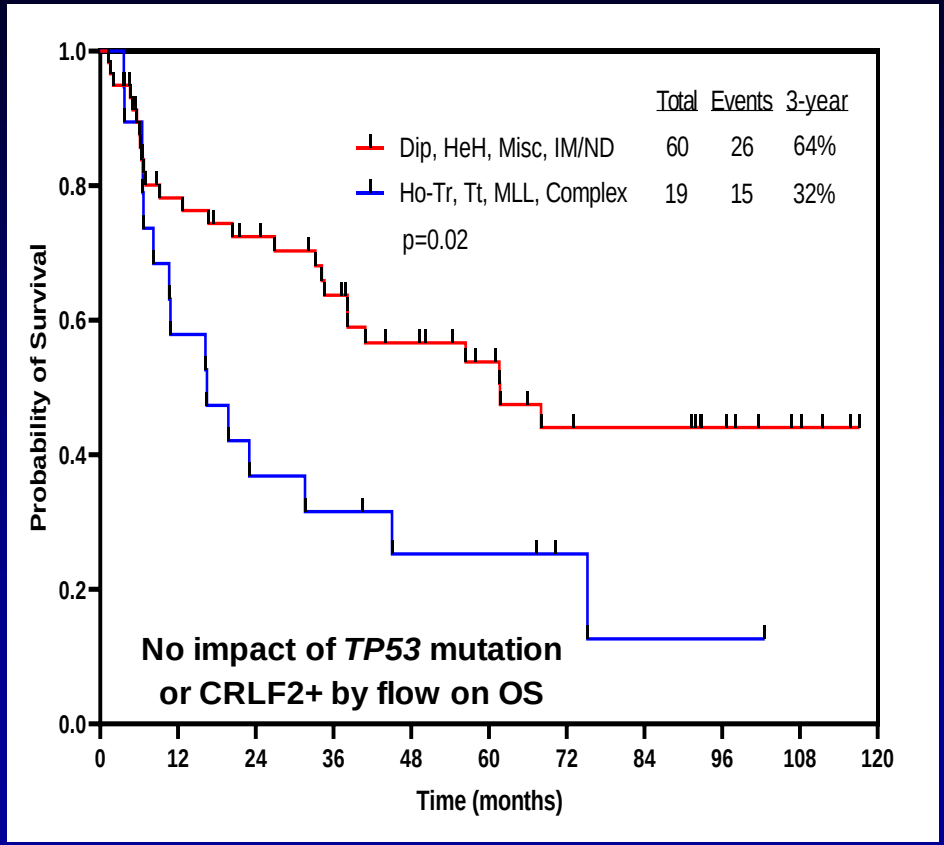
- 79 pts; median age 68 yrs (60–87)
- ORR 72/73 = 99%; CR 65/73 = 89%; MRD– 73/78 = 94%
- 9 MDS/AML (12%)—7/9 had *TP53*-mutated ALL (all 70+ yrs)
- 28 deaths in CR (38%); 7 from sepsis
- 10 relapses (14%)
- VOD 6/75 = 8%



Short et al. *Blood.* 2021;138:abstract 3400.

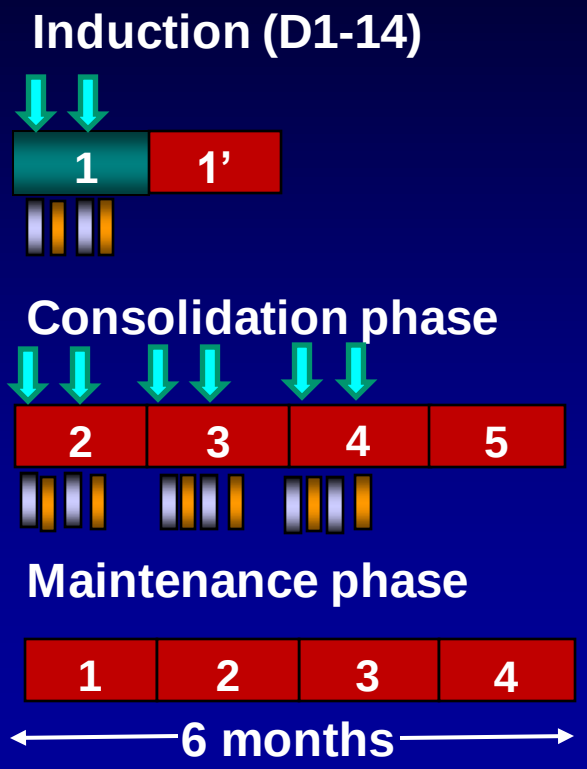
Mini-HCVD + INO ± Blina in Older ALL: Impact of Age and CG (OS)





Short et al. *Blood.* 2021;138:abstract 3400.

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



Dexa 20 mg D1–4 and VCR 1 mg D4

Blinatumomab

IT MTX, Ara-C Rituximab if CD20+

1' Blinatumomab for 2 weeks

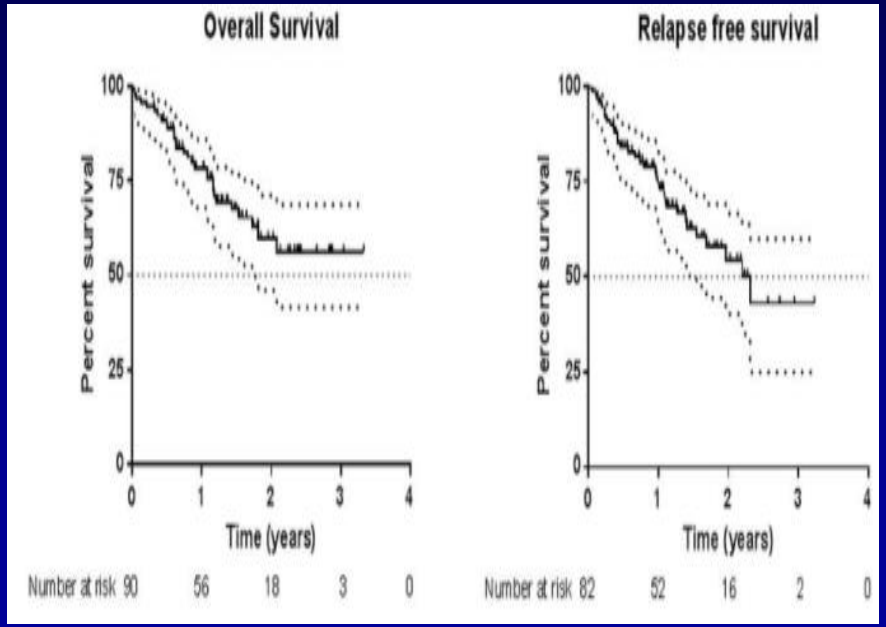
	INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1		0.9	0.6 D1, 0.3 D8
C2–C4		0.6	0.3 D1 and D8

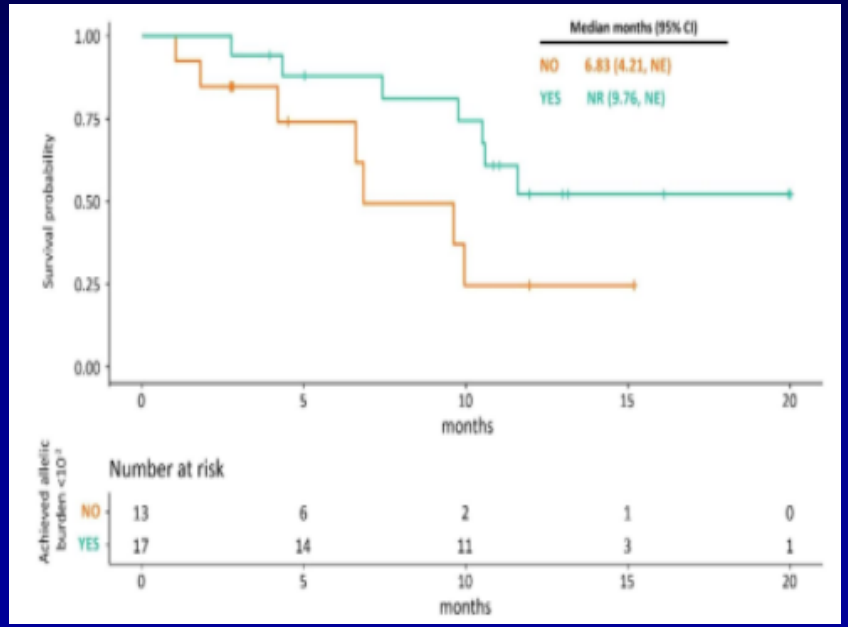
Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Inotuzumab + Low-Intensity ChemoRx in Older Pre-B ALL: EWALL-INO Phase II

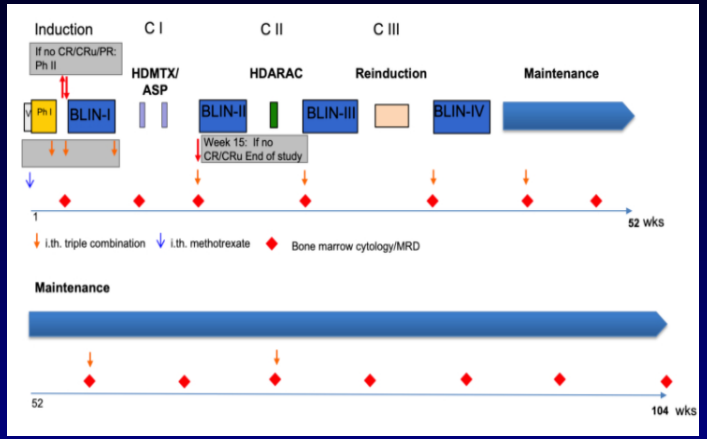
- 115 pts; median age 69 yrs (55–84)
- Pre phase dex 10 mg/D ×5. Induction 1: VCR weekly ×4 + dex 20 mg ×2D weekly ×4; ino 0.8 mg/m² D1, 0.5 mg/m² D8 and D15. Induction 2: dex + CTX + ino – In CR– 6 consolidation blocks: ara C-Dex (C1 and C4); MTX-VCR-6MP (C2 and C5); CTX-VP16 (C3 and C6). Then POMP ×1.5 yrs
- CR + CRp 77/90 = 88%. 1-yr OS 78%. 13 relapses (18%). 3 pts (3.3%) SOS





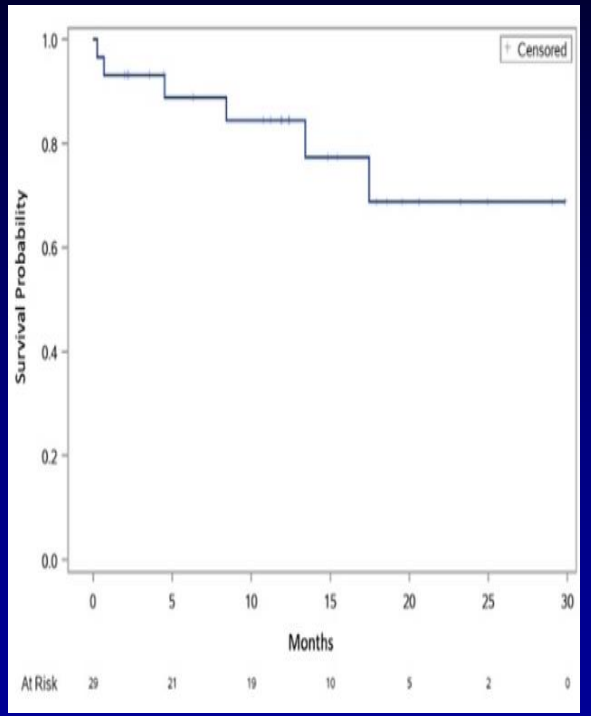
Chevallier. *Blood*. 2021;140:abstract 511.

Dose-Reduced ChemoRx and Blinatumomab in Older Pre-B ALL: Phase II GMALL Bold Trial



- 34 pts, median age 65 yrs (56–76)
- Therapy—5D pre phase CTX-Dex-VCR-IDA. In CR blina ×1 then alternate MTX-Asp-Ara-C and blina ×3 then 6MP + MTX for 2 yrs. 9 TIT
- CR-CRu 76%; PR 9%
- 1-yr survival 89% – 100% if age 55–65, 66% if age 65+

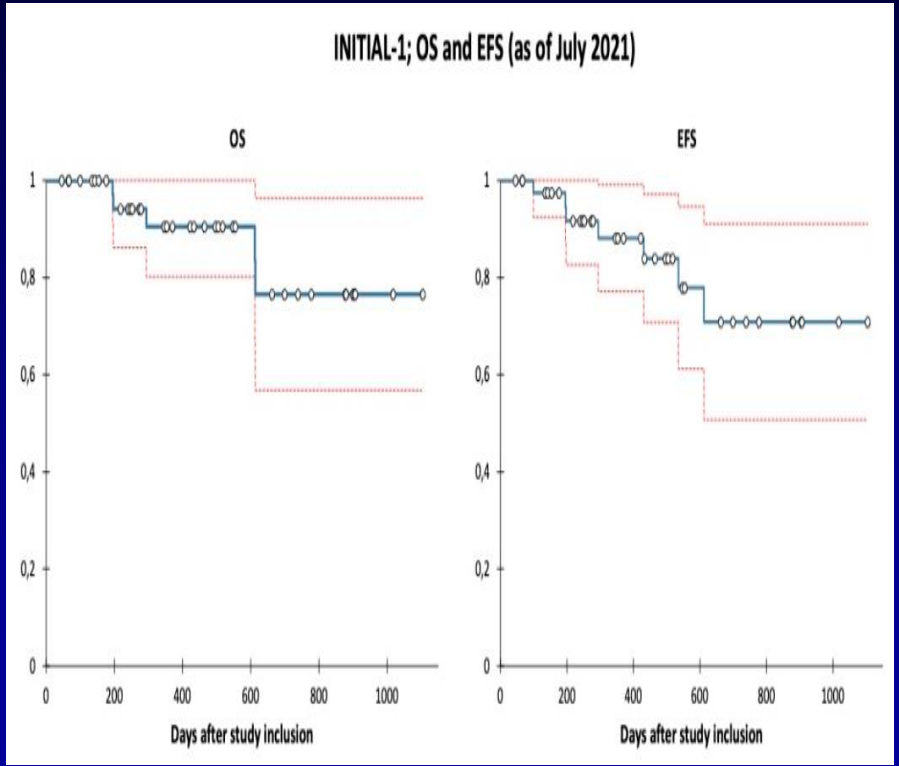
	Induction I	Blina I
Evaluable for Hematologic Response (N)[1]	33	29
Hematologic CR	25 (76%)	24 (83%)
Early death	2 (6%)	2 (7%)[3]
Failure/PR/Relapse	6 (18%)	3 (10%)
Evaluable for Molecular Response (N)[2]	24	23
Molecular CR	4 (17%)	16 (69%)
Molecular Low positive	3 (12%)	3 (13%)
Molecular Failure	14 (58%)	2 (9%)
Molecular not evaluable	3 (12%)	2 (9%)



Goekbuget N, et al. *Blood*. 2021;140:abstract 3399.

Inotuzumab Followed by Chemo Rx in ALL 55+ Yrs

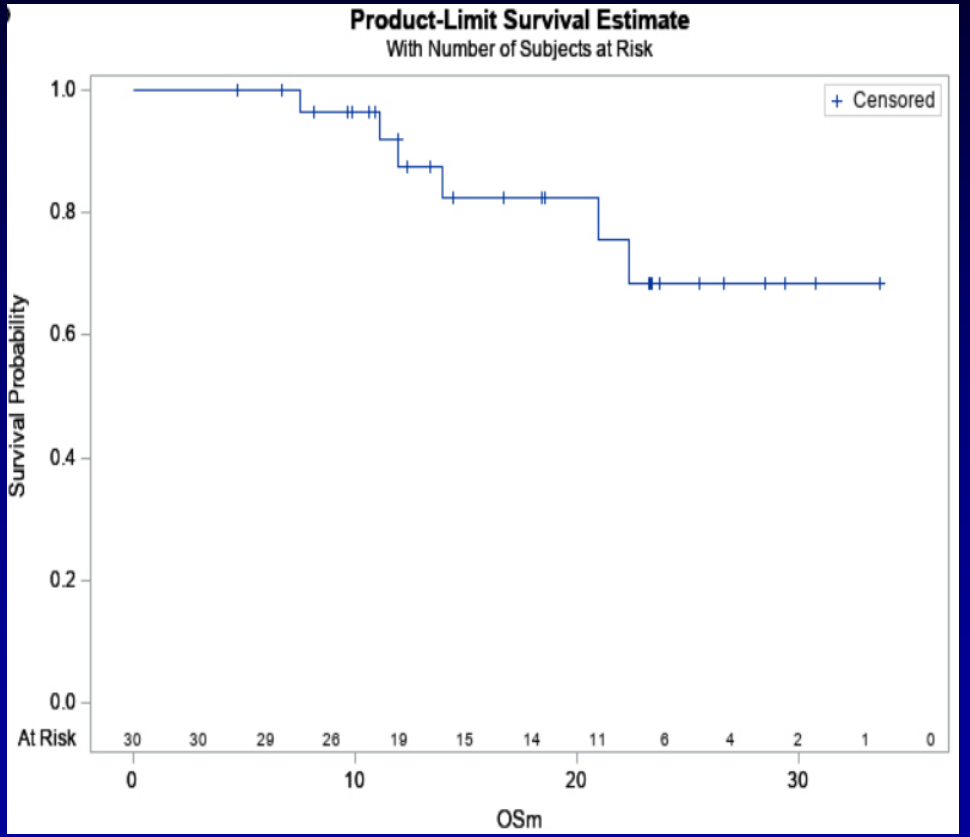
- Course 1: Ino 0.8 mg/m^2 D1, 0.5 g/m^2 D8 and 15 (1.8 mg/m^2) in Course 1
  - CTX-VCR-steroids pre phase – TIT ×1/course
- Courses 2 and 3: Ino 0.5 mg/m^2 Days 1, 8, 15 (1.5 mg/m^2)
  - 5 consolidations: 3 MTX/Asp, 2 ID-Ara-C → 1 reinduction IDA-Ara-C-CTX-Dex
  - 6MP-MTX maintenance ×1 yr
- 45 Rx, results in 43; median age 65 years (56–80)
- CR/CRi 100%; MRD– 23/43 (53%) post IND 2 and 31/42 (74%) post IND 3
- 2-yr OS 77%; 2-yr EFS 74%
- 1 VOD



Stelljes et al. *Blood.* 2021;140:abstract 2300.

Sequential Blinatumomab and Low-intensity Chemo Rx in Older ALL

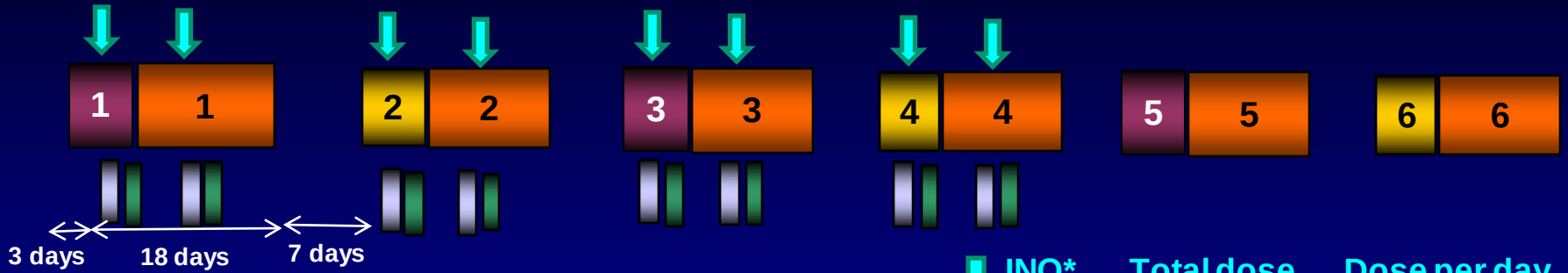
- 30 pts, median age 52 yrs (39–66)
- Therapy: Prednisone 5D → CTX-VCR-Dex → blinatumomab alternating with HD MTX-Ara-C – Total 6 (3 blina – 3 MTX ara C) → POMP ×2 yrs
- CR 30/30 (100%), MRD– 83%. 7 PD (23%)
- 2-yr OS 69%, EFS 62%



Fleming. *Blood*. 2021;138:abstract 1234.

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

Induction phase: C1–C6



Consolidation phase

CAR T Consolidation

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

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Mini-HCVD

Mini-MTX, Ara-C

Rituximab

IT MTX, Ara-C

Blinatumomab

ALL Summary

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

The Future of ALL Therapy…

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

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

Thank You

Elias Jabbour, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX
Email: ejabbour@mdanderson.org
Cell: 001.713.498.2929

Global Leukemia Academy

Current treatment options for relapsed ALL in adult and elderly patients

José Maria Ribera

APTITUDE HEALTH

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

Chemotherapy for Older Patients With ALL: Historical Studies

Author	Year	Age	Ph+	Pts (N)	CR rate	Early death	Failure	CCR	DFS	OS
Delannoy et al	2002	65 (55–81)	Yes	58	43%	10%	47%	5	10	NR
Offidani et al	2004	69 (61–79)	Yes	17	76%	17%	6%	20	21	38% (2 y)
Sancho et al	2007	65 (56–77)	No	33	58%	36%	6%	46% (2 y)	7	39% (1 y)
Kao et al	2008	66 (60–78)	Yes	17	71%	29%	0%	82% (1 y)	NR	71% (1 y)
Gökbuget et al	2008	66 (56–73)	No	54	85%	0%	15%	9	NR	61% (1 y)
Hunault-Berger et al	2010 Arm 1 Arm 2	 68 (55–77) 66 (60–80)	No	 31 29	 90% 72%	 7% 10%	 3% 17%	 32% (2 y) 52% (2 y)	NR	 35% (2 y) 24% (2 y)
Gökbuget et al	2012	57 (55–85)	No	268	76%	14%	10%	32% (5 y)	NR	23% (5 y)
Fathi et al	2016	58 (51–72)	Yes	30	67%	3%	30%	NR	52% (2 y)	52% (2 y)
Ribera et al	2016	66 (56–79)	No	54	74%	14%	14%	NR	24% (2 y)	30% (2 y)
Kozlowski et al	2017	69 (62–82)	Yes	35	71%	20%	9%	NR	NR	20% (3 y)
Kozlowski et al	2017	63 (55–79)	Yes	79	89%	13%	NR	NR	NR	39% (3 y)

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

Ph+ ALL

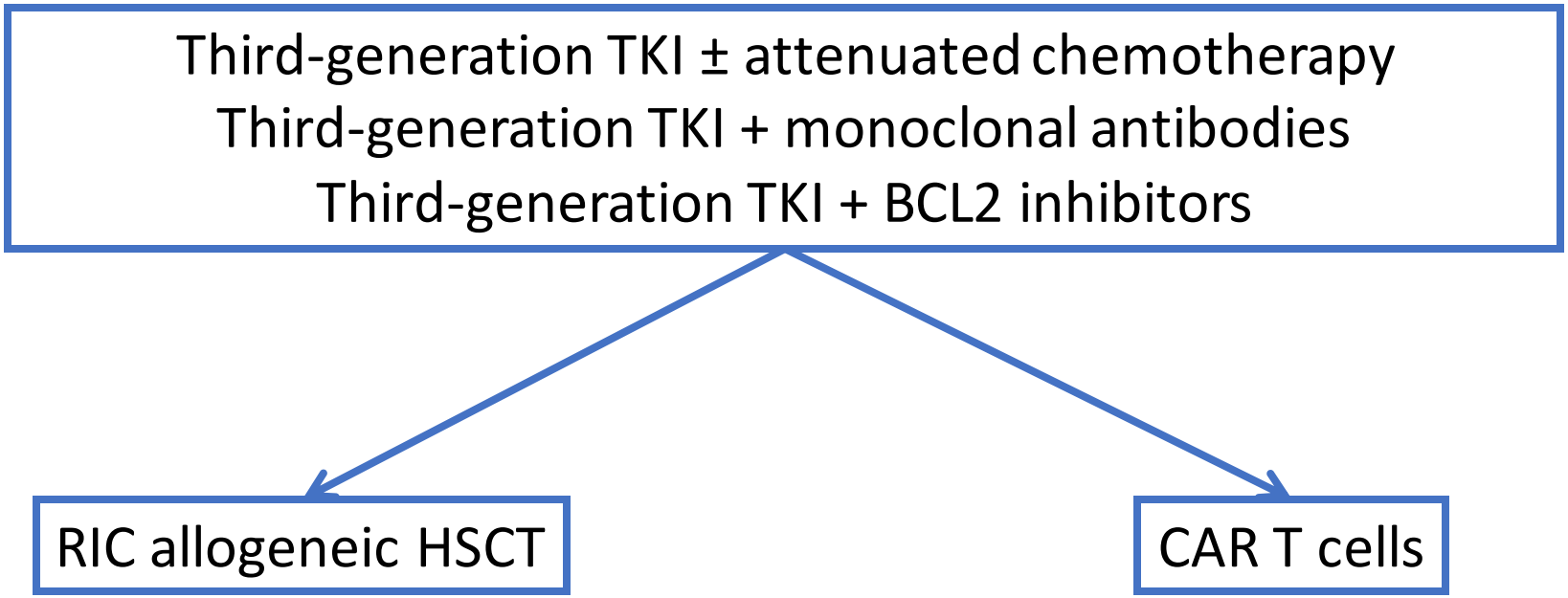
Ph– ALL

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	66 (26–85)	**PONA**	**PONA**	86	55 (3 y)
Foa*	2020	63	54	DASA	DASA + **BLINA**	98	87 (2 y)
Jabbour*	2020	30		**PONA + BLINA**	**PONA + BLINA**	100	100 (1 y)

*Not specifically designed for elderly patients.

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



Blinatumomab and Inotuzumab in R/R Ph+ ALL

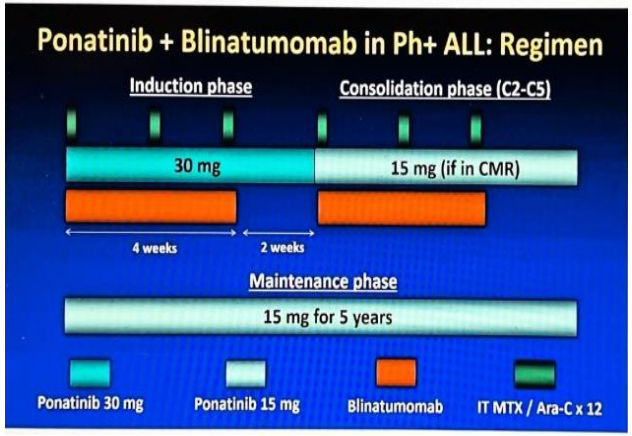
Parameter	Blinatumomab	Inotuzumab
No. Rx	45	38
No. CR/marrow CR (%)	16 (36)	25 (66)
MRD negative in CR, %	88	63
Median OS (mo)	7.1	8.1
Later alloSCT, %	44	32

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

Ponatinib and Blinatumomab for Patients With Ph+ ALL

Phase II study: newly diagnosed (ND) Ph+ ALL, R/R Ph+ ALL, or CML-LBP

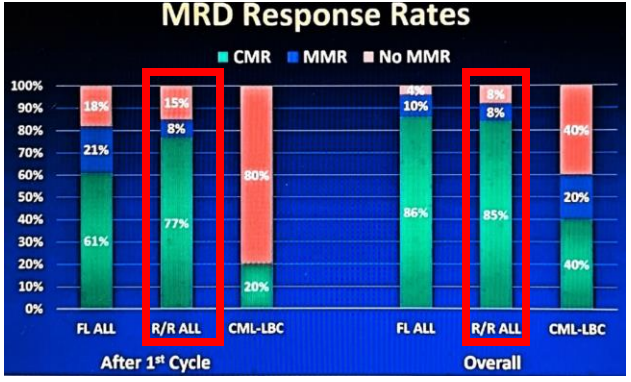
Treatment: Up to 5 cycles of blina. Ponatinib 30 mg/d during cycle 1, 15 mg/d once CMR. Ponatinib at least 5 y. IT × 12 cycles

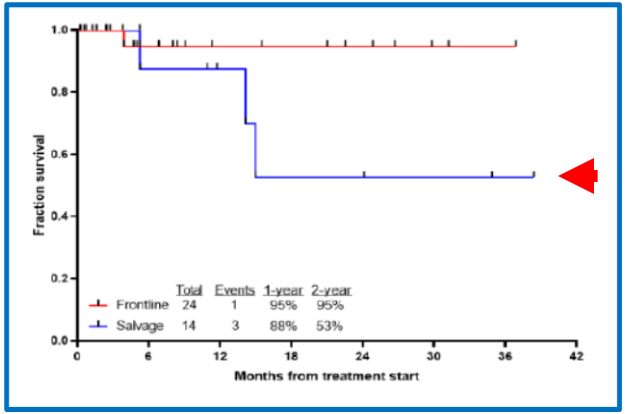


Response Rates

Response, n/N (%)	All N = 50	Frontline Ph+ ALL N = 30	R/R Ph+ ALL N = 14	CML-LBC N=6
CR/CRp/CRi*	36/39 (92)	19/20 (95)	12/13 (92)	/6 (83)
CR	33 (85)	18 (94)	11 (85)	4 (67)
CRp	2 (5)	1 (6)	0	1 (17)
CRi	1 (3)	0	1 (8)	0
PR	1 (3)	0	0	1 (17)
MMR	43/47 (91)	28/29 (97)	12/13 (92)	3/5 (60)
CMR	38/47 (81)	25/29 (86)	11/13 (85)	2/5 (40)
Early death	1 (3)	1 (6)	0	0

* 10 frontline pts and 1 salvage pt in MRD+ CR at start





Short N, et al. ASH 2021. Abstract 2298.

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

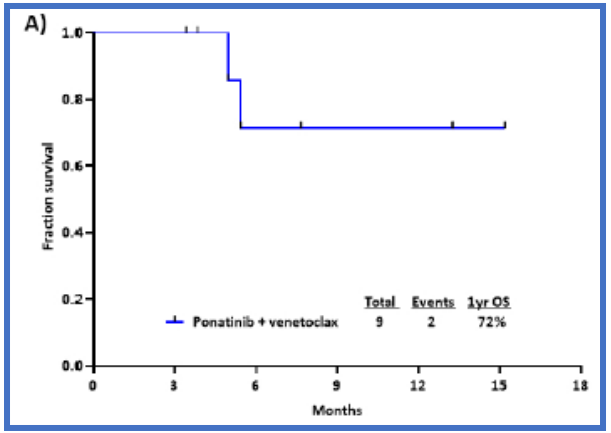
Venetoclax 400–800 mg

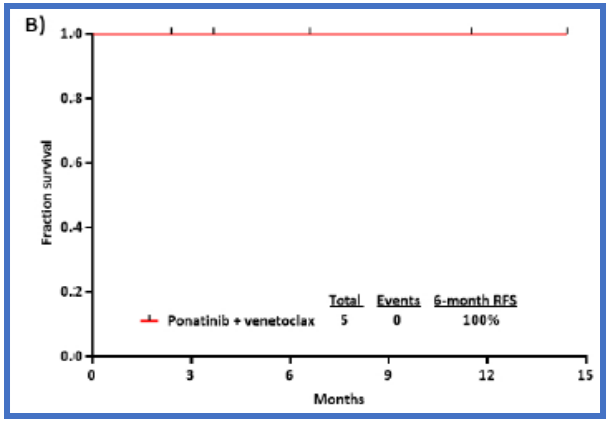
9 pts; *T315I* (4/8); prior therapies 3 (2–4)

CR/CRi: 56%

CMR: 44%

1-yr OS: 72% (2 deaths)





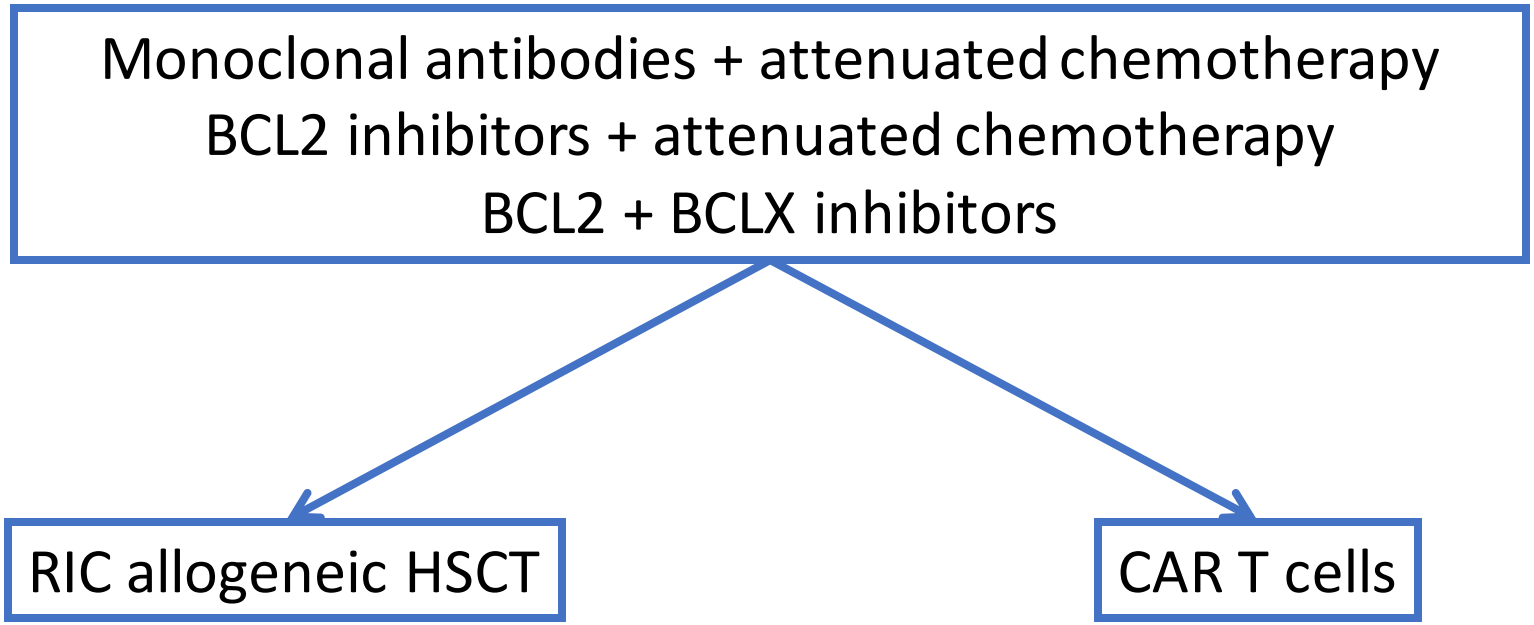
Short NJ, et al. *Am J Hematol*. 2021;96(7):E229-E232.

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

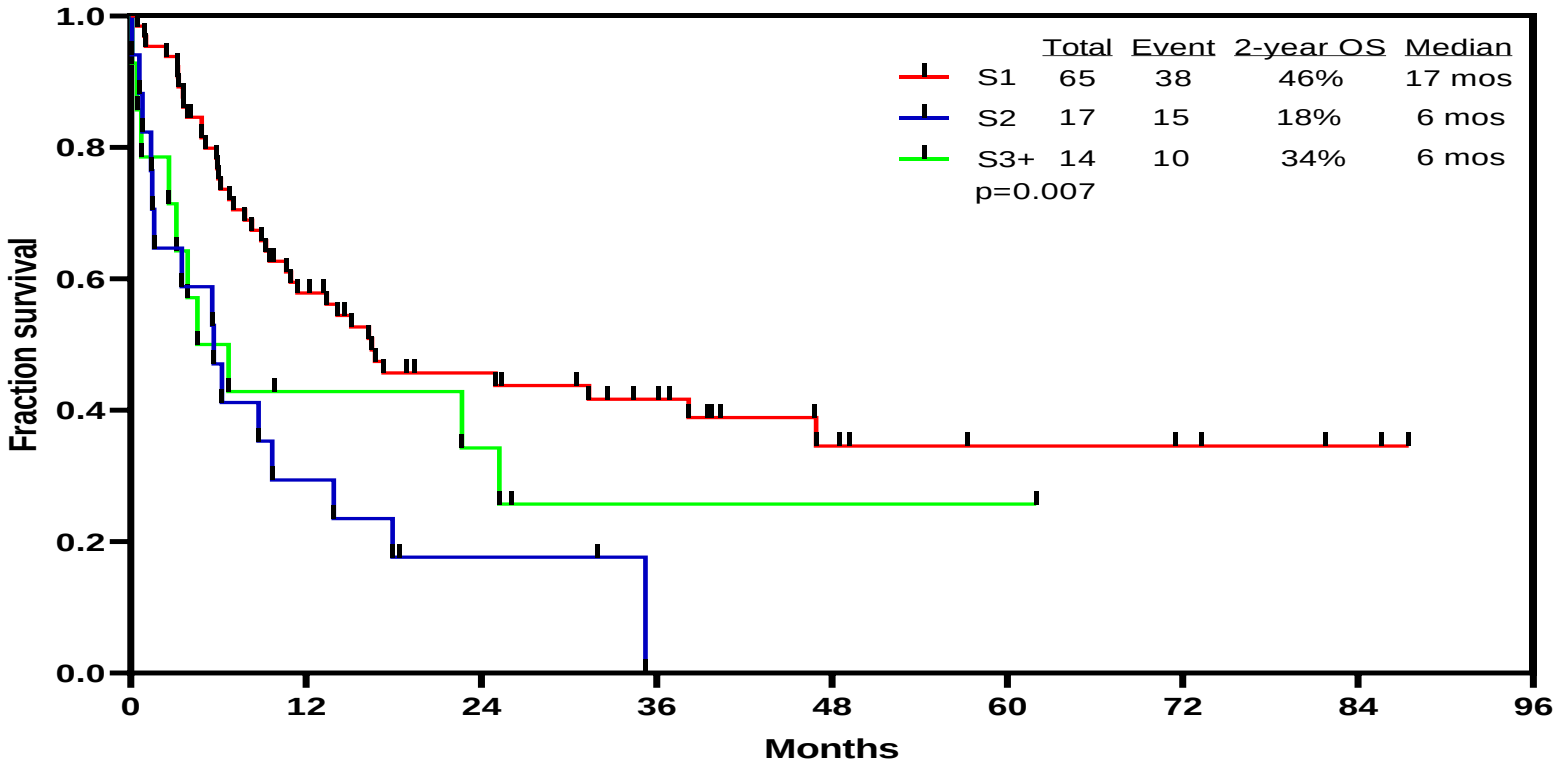


Mini-HCVD + INO ± Blinatumomab in R/R ALL: Response by Salvage (N = 96)

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.

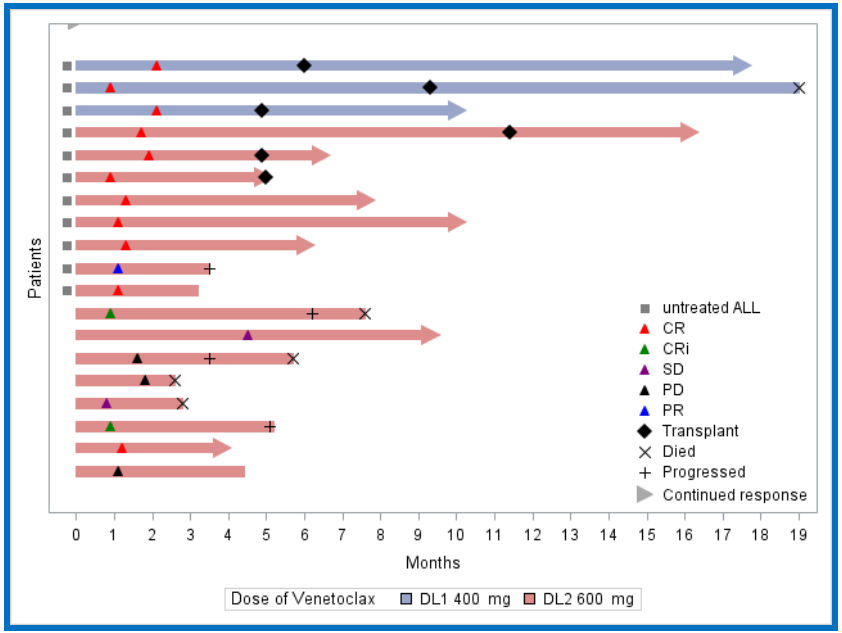
Mini-HCVD + INO ± Blinatumomab in R/R ALL: OS by Salvage Status



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

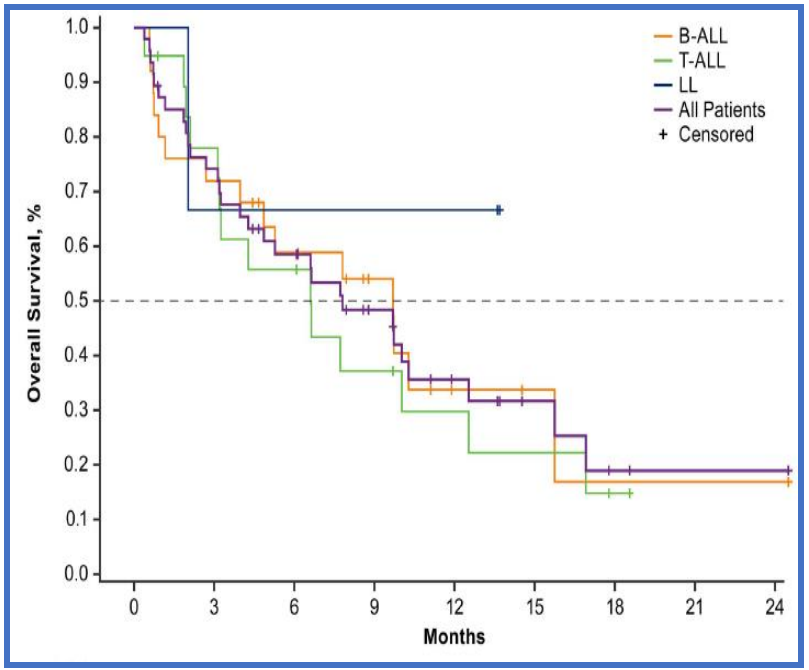
Mini HCVD + Venetoclax

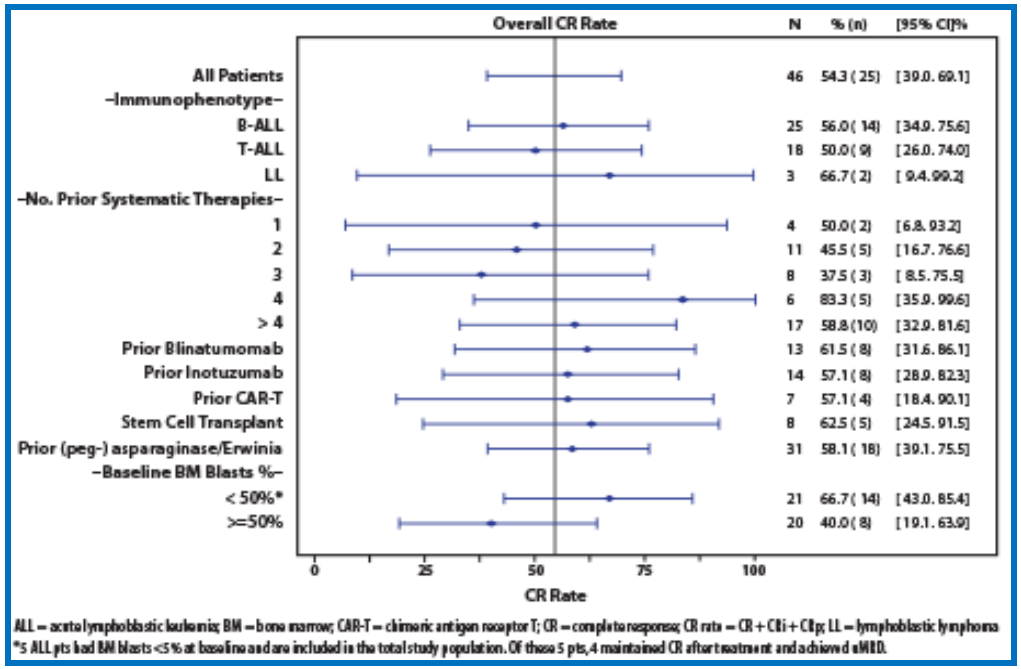
	Response n, (%)	MRD– n, (%)	Duration of response
Untreated ALL (N = 11)	10 CR/CRi (91%) 1 PR (9%)	10 (91%)	5.7 mos (1.6–16.5)
R/R ALL (N = 8)	3 CR/CRi (38%)	2 (25%)	4.2 mos (1.8–5.3)



Jain N, et al. ASH 2019.

Venetoclax and Navitoclax in R/R ALL and LBL





B-ALL: 25, T-ALL: 19, LL: 3

CR: 60%

Recommended dose for phase II: 400 mg Ven + 50 mg Nav (25 for <45 kg)

Pullarkat VA, et al. *Cancer Discov.* 2021;11(6):1440-1453.

Second-Generation CD19 CAR T in R/R Adult ALL

Study	N*	Age, Median (range)	CR, %	MRD– in CR, %	Relapse (%)	PFS	OS
UPenn	35	33 (20–70) Single dose, low: 9 Single dose, high: 6 Fractionated dose, high: 20	33 50 90			0% 17% 49% (24 mo)	22% 17% 73% (24 mo)
MSKCC	53	44 (23–74)	83	67	57	Median: 6.1 mo	Median: 12.1 mo
FHCRC	53	39 (20–76)	85	85	49	Median: 7.6 mo	Median: 20 mo
City of Hope	13	33 (24–72)	100	91	NR	NR	NR
UCL	19	43 (18–72)	84	84	26	62% (6 mo)	NR
HCB-HSJD	27	35 (18–69)	85	85	15	Median: 9.4 mo	Median: 20.2 mo
KTE-X19 phase I	45	46 (18–77)	83	100		Median: 17.6 mo	Median: 16.1 mo
KTE-X19 phase II	55	40 (19–84)	71	97		Median 11.6 mo	Median 18.2 mo

*Infused.

Conclusion

- Treatment of R/R elderly patients with ALL: promising options
- Better approach for salvage therapy
  - Ph– ALL: attenuated chemotherapy + immunotherapy (Ino, Blina), BH3 mimetics
  - Ph+ ALL
    - Third-generation TKI + immunotherapy
    - Third-generation TKI + BCL2 inhibitors
- Do not forget cell therapy
  - RIC alloHSCT
  - CAR T

Question 1

Regarding CAR T for R/R ALL, indicate the incorrect sentence:

1. Are effective in both relapsed and refractory patients
2. Are effective in R/R Ph+ ALL
3. Are effective in Ph– ALL
4. Are not effective in elderly patients with R/R ALL
5. Can be followed by non-myeloablative allogeneic HSCT

Question 2

Venetoclax has demonstrated activity in:

1. Ph+ ALL only
2. Ph– ALL only
3. Ph+ and Ph– ALL
4. T-ALL
5. 3 and 4 answers are correct

Global Leukemia Academy

Case 1: Adult ALL

Paola Omaña

APTITUDE HEALTH

Olga Paola Omaña Orduz

Colombia

March 26, 2022

Adult ALL Case

Disclosures

- Amgen: Speaker honoraria, ad board consultancy
- Janssen: Speaker honoraria, ad board consultancy
- AbbVie: Speaker honoraria
- AstraZeneca: Speaker honoraria
- Bristol Myers Squibb: Speaker honoraria, ad board consultancy

General Information

Male
57 years
Lawyer

- Hypertension
- Morbid obesity

Shortness of breath, weakness

Hemogram: leukopenia, anemia, and thrombocytopenia. Blasts in PB

Bone Marrow

- Flow cytometry: B lymphoblasts CD19+, CD10++, CD34+, CD45-/+ (68%), CD20-/+ (57%), CD81+, HLADR + heterogeneous CD38+, CD123-/+ (45%)

- Biopsy: cellularity close to 100%. This is massively infiltrated by a hematolymphoid neoplasm with intermediate cells of immature characteristics, with little cytoplasm, arranged in sheets and accompanied by some histiocytes with cellular debris in their cytoplasm. Neoplastic cells show expression for CD99, CD20, and weakly for CD34. Expression for CD20 is found in approximately 60% of neoplastic cells. There is no expression of CD3, TDT, CD1a, CD2, CD45, PAX-5, or CD79a

Question 1

In your country, do you have medical coverage for rituximab for this indication?

1. Yes
2. No

P210 FISH negative

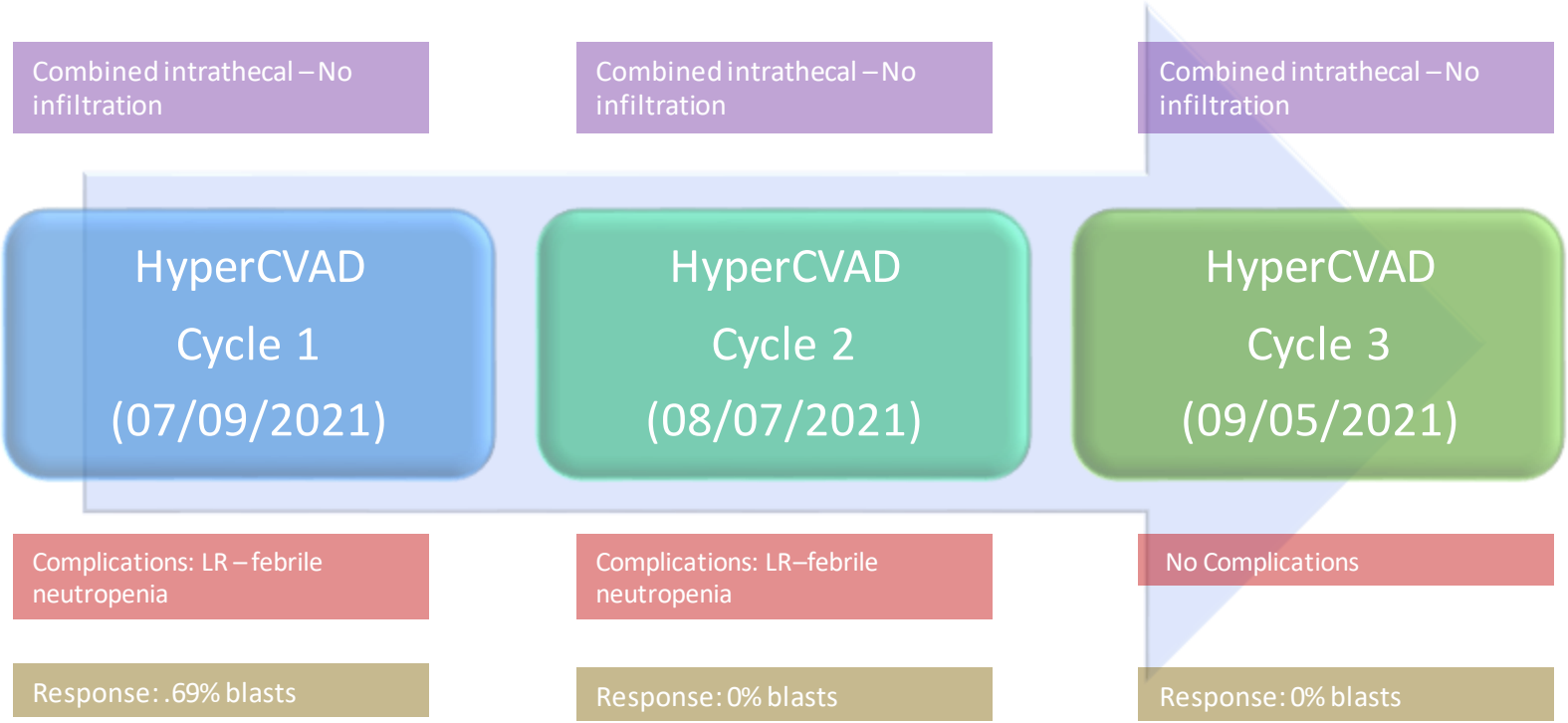
High Risk

- Age
- CD20 expression
- MRD(+) post-induction

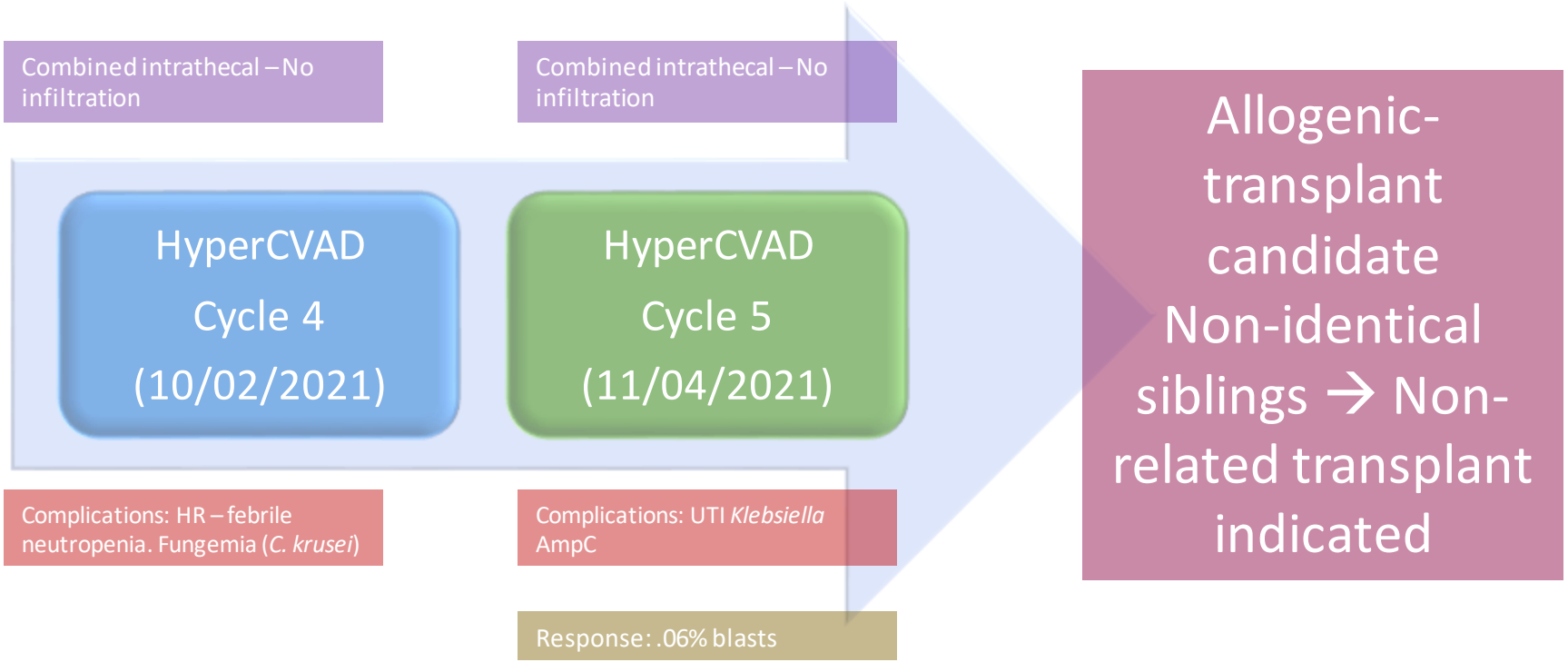
Asparaginase-based regimen??

HyperCVAD?

Treatment


Combined intrathecal – No infiltration
Combined intrathecal – No infiltration
Combined intrathecal – No infiltration
HyperCVAD Cycle 1 (07/09/2021)
HyperCVAD Cycle 2 (08/07/2021)
HyperCVAD Cycle 3 (09/05/2021)
Complications: LR – febrile neutropenia
Complications: LR–febrile neutropenia
No Complications
Response: .69% blasts
Response: 0% blasts
Response: 0% blasts

Treatment

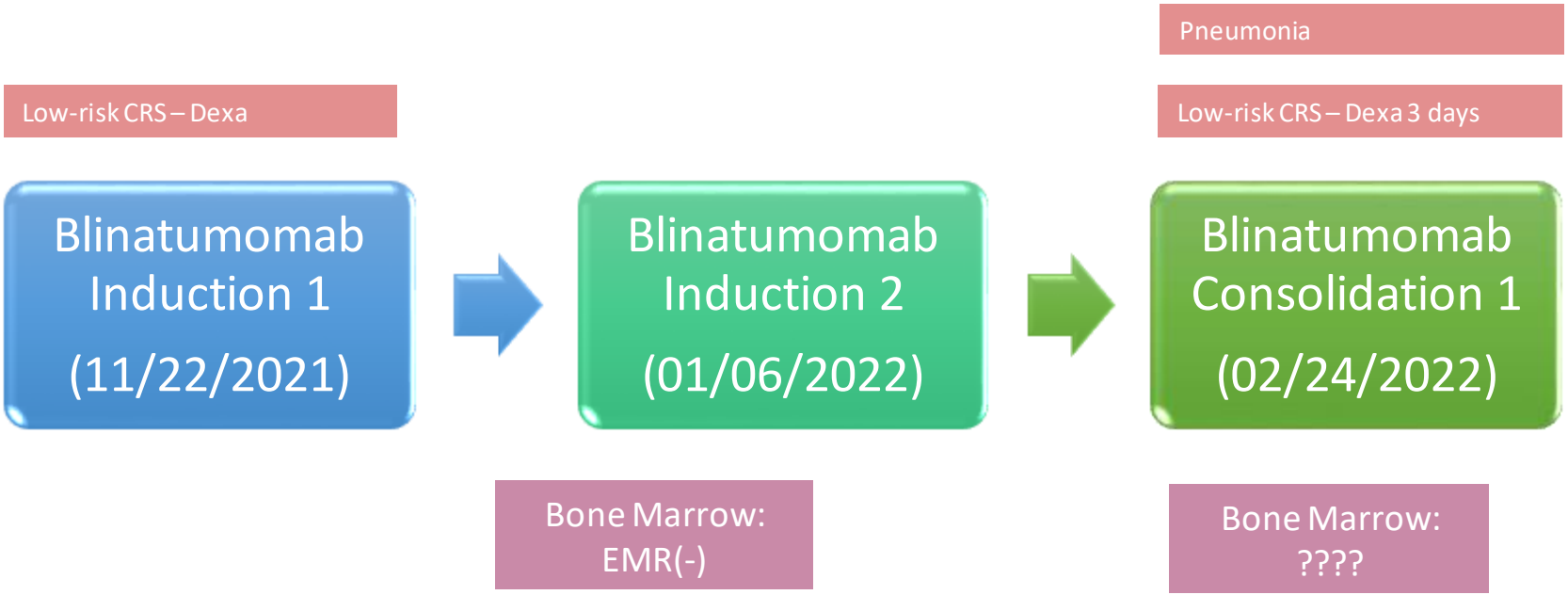

Combined intrathecal – No infiltration
Combined intrathecal – No infiltration
HyperCVAD Cycle 4 (10/02/2021)
HyperCVAD Cycle 5 (11/04/2021)
Complications: HR – febrile neutropenia. Fungemia (*C. krusei*)
Complications: UTI *Klebsiella* AmpC
Response: .06% blasts
Allogenic-transplant candidate Non-identical siblings → Non-related transplant indicated

Question 2

What do you think is the best next step?

1. Continue with HyperCVAD 8 cycles, followed by transplant
2. Change to blinatumomab and then transplant
3. Continue with HyperCVAD until finished 8 cycles, followed by POMP maintenance
4. Change to FLAG IDA and then consider transplant

We Decided Blinatumomab Was the Better Choice . . .



Key Points – Discussion

- Early interventions can change prognosis
- Insurance problems in our region
  - Rituximab for CD20(+) ALL
  - Blinatumomab as second line/MRD(+)
- Role of FLAG IDA and repercussions if used before blinatumomab in the R/R setting

paolaomanaorduz@gmail.com


Clínica
del
Country

Global Leukemia Academy

Case 2: Adult ALL

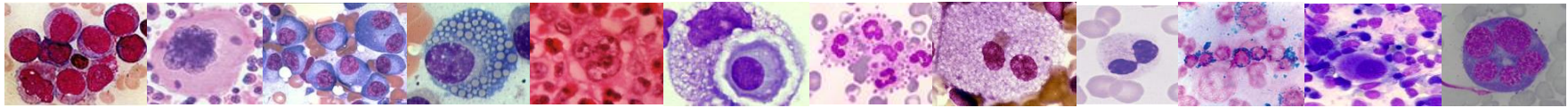
Roberta Demichelis

APTITUDE HEALTH

Global Leukemia Academy

Adult ALL Case

Roberta Demichelis, MD
Acute Leukemia Clinic – INCMNSZ
Mexico City

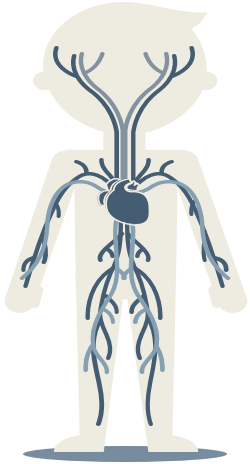


Disclosures

- Consulting: AbbVie, Amgen, Bristol/Celgene, Jazz, Novartis, Gilead, Astellas
- Research grants: Novartis, ASH
- Honoraria: AbbVie, Amgen, Bristol/Celgene, Jazz, Novartis

Case presentation

35-year-old man
Diabetes (March 2021)



Weight loss 14 kg in 3 months

ECOG: 0

BMI: 29.5

Hgb: 11.7 g/dL
WBC: 2.1 × 10^9/L
Plat: 309 × 10^9/L
2% blasts

Fatigue and diaphoresis

June 2021

July 2021
High WBC

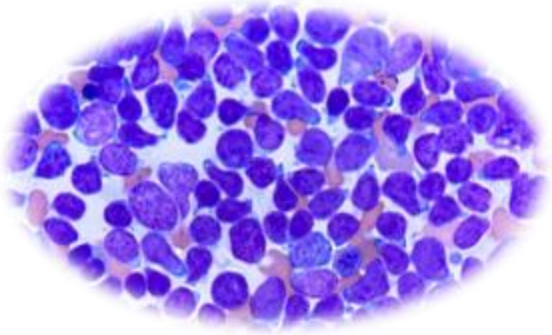
31 August 2021

Case presentation

BMA: 69% blasts

CD34+, CD10+, CD19+, CD79a+, TdT+
Aberrant CD33+
CD20 17%

46XY
Negative: t(9;22) and 11q23

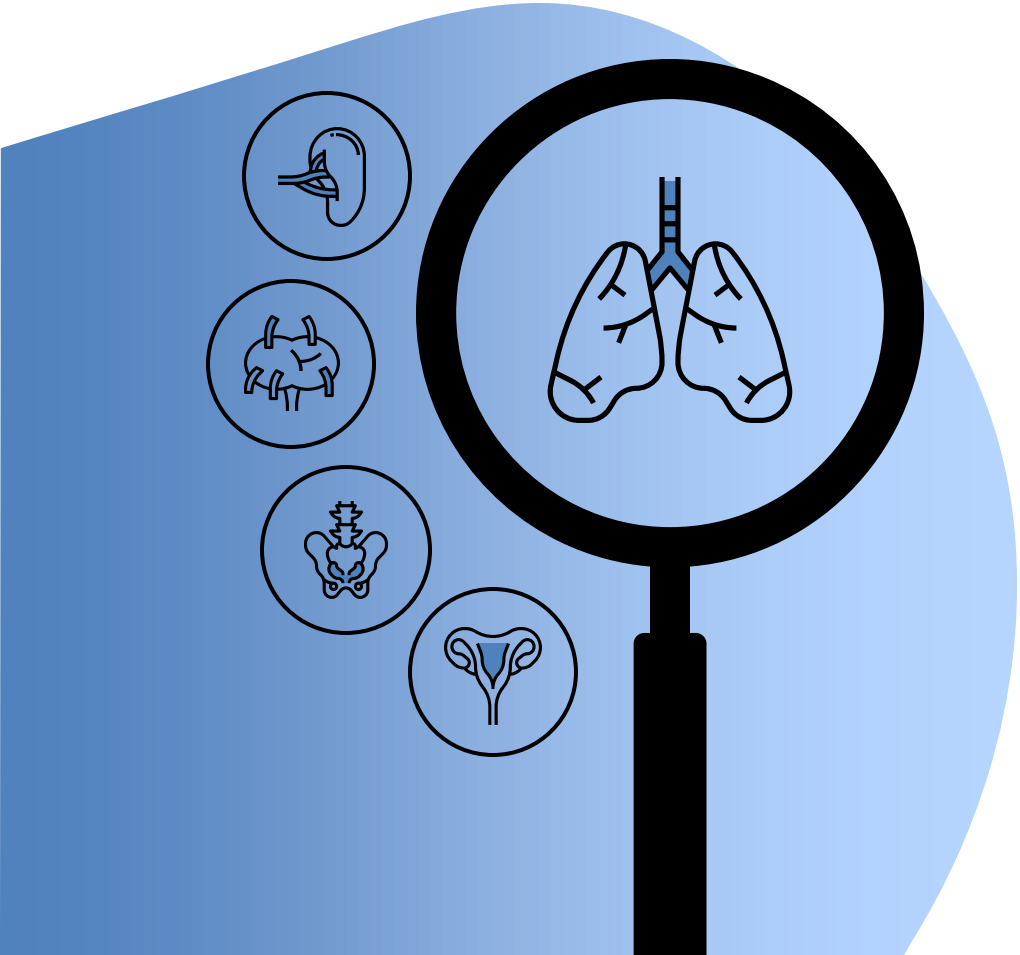


Fibroscan F0 S2

TT eco: LVEF 58%

Normal kidney and liver function

Controlled diabetes



How to treat?

Treatment

Pediatric inspired

- ✓ Retrospective comparisons: better outcomes
- ✓ Less hematologic toxicity
- ✧ More hepatotoxicity/ metabolic toxicity
- ✧ More thrombosis
- ✧ Concerns with overweight/steatosis

B-cell Ph– ALL
AYA
Overweight
Controlled diabetes
Steatosis

HyperCVAD

- ✓ We feel comfortable
- ✓ MDACC comparison: PIR not superior
- ✧ More hematologic toxicity
- ✧ Treatment-related mortality in LMIC

Question 1

In your practice, how would you treat this patient?

1. **A pediatric-inspired regimen**
2. **A pediatric-insipred regimen + rituximab**
3. **HyperCVAD**
4. **HyperCVAD + rituximab**
5. **Other**

Case presentation

Modified
CALGB 10403
(PIR)
+ rituximab

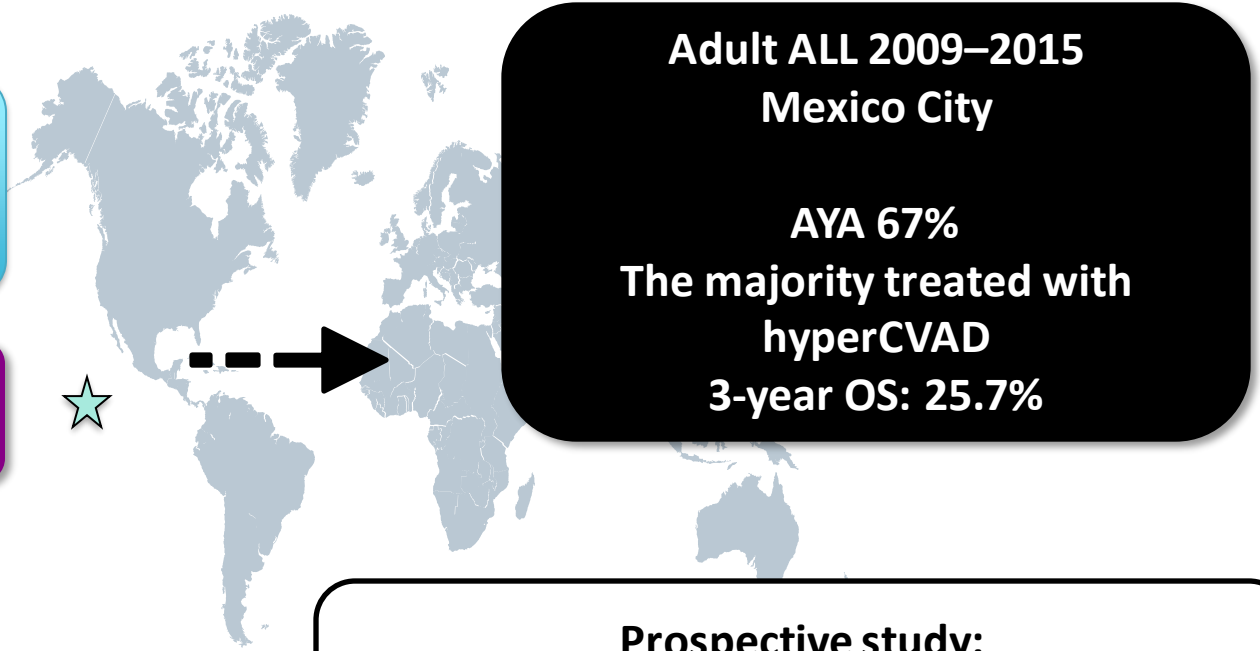
What is the rationale behind this decision?

Drug	Dose	Schedule
Vincristine	1.5 mg/m^2 (max 2)	Days 1, 8, 15, 22
Daunorubicin	25 mg/m^2	Days 1, 8, 15, 22
E. coli asparaginase	6000 UI/m^2	Days 3, 5, 7, 9, 11, 13
Dexamethasone	5 mg/m^2 every 12 hr	Days 1 to 7 and 15 to 21
Rituximab	375 mg/m^2	Day 8
Intrathecal CT		Day 1 and 29

Adult ALL in Mexico

USA
Hispanic: 2.2–2.9/100,000
Non-Hispanic: 1.5–2/100,000

Mexico:
5/100,000



Adult ALL 2009–2015
Mexico City

AYA 67%
The majority treated with hyperCVAD
3-year OS: 25.7%

Mexico and Central America: high prevalence of ALL in AYA

Prospective study:
4 centers in Mexico and 1 in Guatemala
Modified CALGB 10403

AYA, adolescents and young adults.

National Cancer Institute. Cancer stat facts: Leukemia – acute lymphocytic leukemia (ALL). https://seer.cancer.gov/statfacts/html/alyl.html; Ferlay J, et al. Globocan 2000. Version 1.0. Lyon, France: IARC Press; Crespo-Solis E, et al. *Cancer Med*. 2018;7(6):2423-2433.

Results: 95 patients until Dec 2020

Induction toxicity

Adverse event	Grade 3 or 4, %
Hypofibrinogenemia	44.1
Bilirubin elevation	21.1
ALT/AST elevation	14.7
Hyperglycemia	14.7
Thrombosis	10.5
Hypersensitivity	2.2
Pancreatitis	2.2

Febrile neutropenia

Induction: 55.8%
Consolidation: 32.9%
63%: 1 episode
37%: 2 or 3 episodes

TRM:
7.4%

TRM, treatment-related mortality.

Results

CR: 87.8%

MRD <0.1% after induction: 75.4%

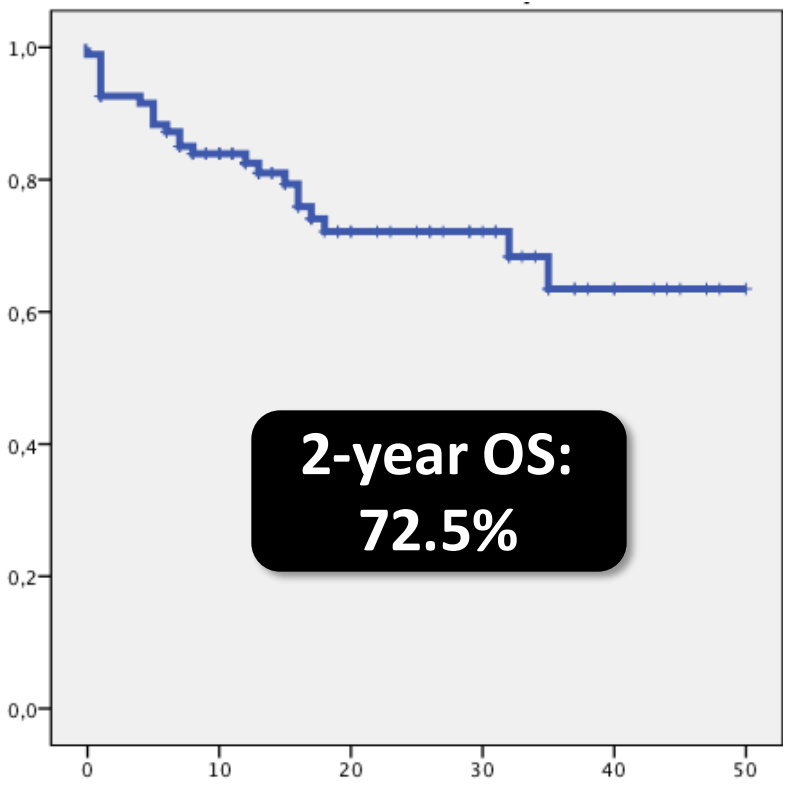
MRD <0.01% after induction: 36.2%

AlloHCT: 8.4%

Relapse: 28.2%

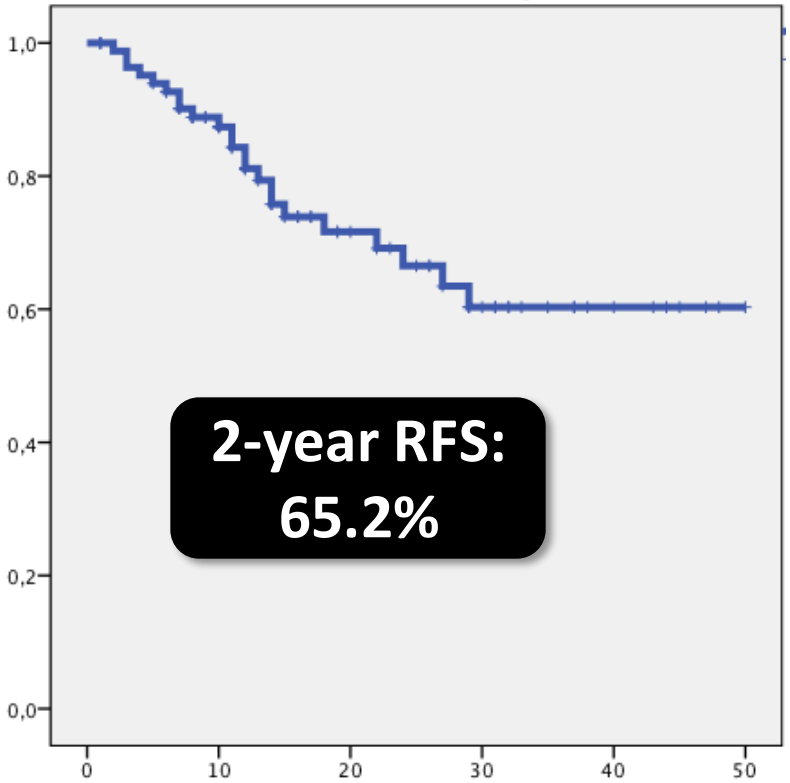
CR, complete remission; MRD, minimal residual disease; alloHCT, allogeneic hematopoietic cell transplantation.

Survival



2-year OS: 72.5%

Overall survival



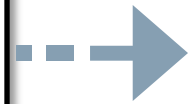
2-year RFS: 65.2%

Relapse-free survival

Our experience with PIR

When compared with historical = better outcomes

RC: 80.1%
TRM: 17.3%
Relapse: 61.7%
Median OS: 16.9 mo
3-year OS: 25.7%

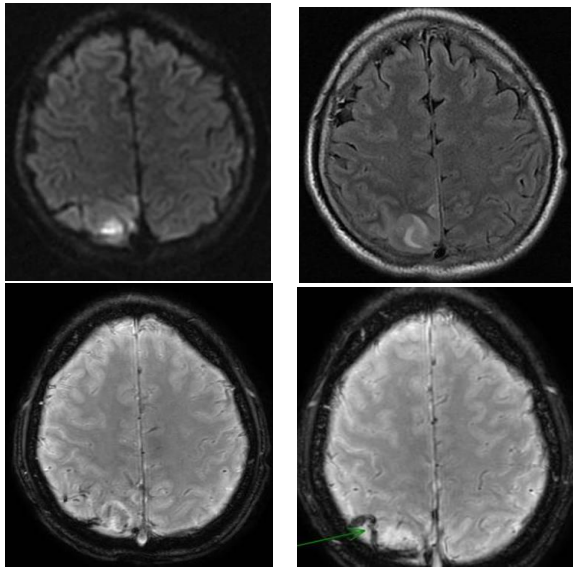


CC: 87.8%
TRM: 7.4%
Relapse: 28.2%
Median OS: NR
2-year OS: 72.1%

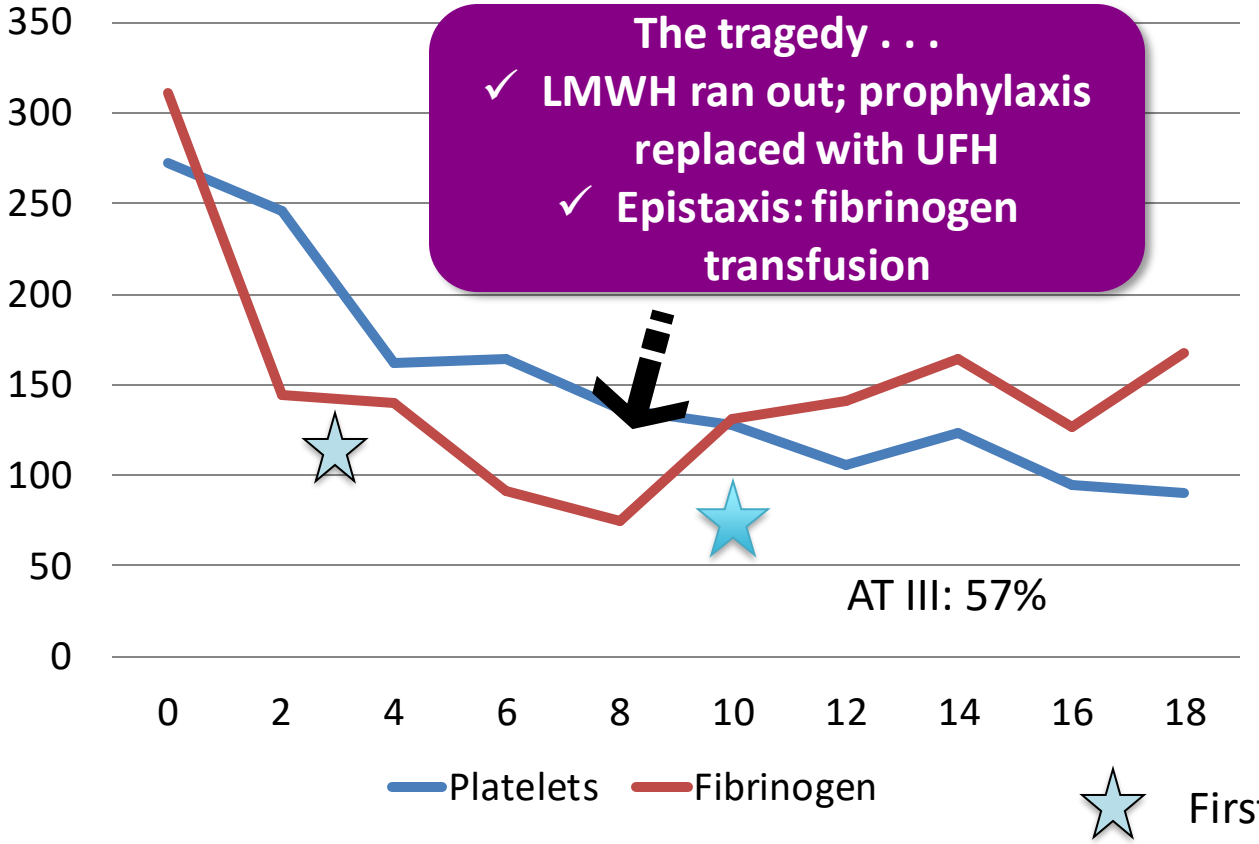
Original CALGB
CR: 89%
TRM: 3%
Median OS: NR
3-year OS: 73%

Case continuation: Induction

Seizures

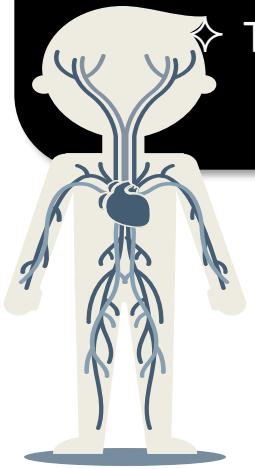


Cerebral vein thrombosis



Case continuation

- We stopped asparaginase (4/6 doses)
- Full anticoagulation with LMWH
- Treatment with levetiracetam



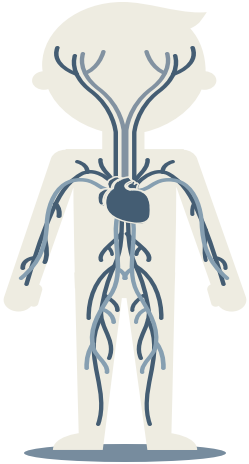
No neurologic sequelae or further seizures

Question 2

Which of the following actions would you consider?

1. **No more asparaginase. Continue the same regimen without asparaginase**
2. **No more asparaginase. Change to an asparaginase-free regimen (hyperCVAD)**
3. **Resume asparaginase (+ anticoagulation) in consolidation**
4. **Now that the patient is stable with no sequelae or another seizure episode, resume asparaginase (+ anticoagulation) and complete the induction regimen**

Case continuation



72 hr later

Resume asparaginase + full-dose enoxaparin

Grade 1 hepatotoxicity

Other EA

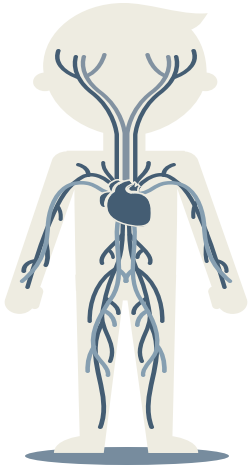
+29

CR with MRD: <0.01%

Grade 3 hypertriglyceridemia

Consolidation

Case continuation

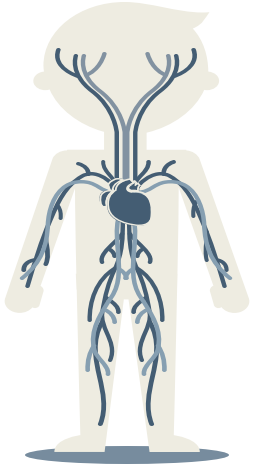


March 2022

- Receiving the last cycle of intensive chemotherapy
- No hospitalizations
- Received complete CALGB 10403 regimen without delays
- Undetectable MRD
- Still on treatment with rivaroxaban and levetiracetam

Messages to remember and questions

- Thromboprophylaxis with LMWH unless contraindication
- Restrictive fibrinogen/cryoprecipitate tranfusions



- Role of AT III concentrates?
- Should asparaginase be permanently stopped in CVT?
- Long-term management?

Thank you

Contacto roberta.demichelis@incmnsz.mx @RobertaDemiche3

Global Leukemia Academy

ALL case-based panel discussion

Panelists: Roberta Demichelis, Wellington Silva Fernandes, Paola Omaña



APTITUDE HEALTH

Question 1

What age group is considered elderly ALL patients?

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

Question 2

Which of the following is NOT true for treating ALL?

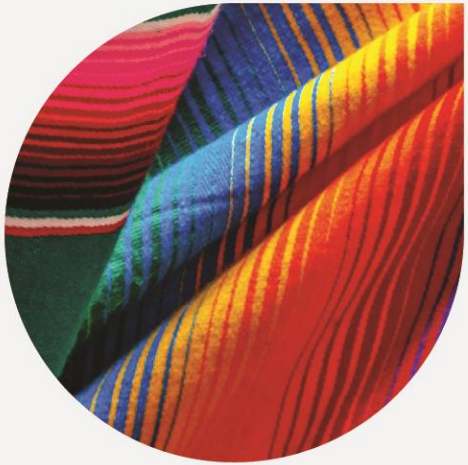
1. Inotuzumab and blinatumomab plus chemotherapy has produced 90% CR rates in salvage therapy and in first line in older patients
2. Blinatumomab and ponatinib can be used as a chemotherapy-free regimen in Ph+ ALL
3. MRD-negative CR does not correlate strongly with outcome
4. Since 1999, median survival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

Global Leukemia Academy

BREAK

APTITUDE HEALTH

Global Multiple Myeloma Academy



PLEASE JOIN US FOR OUR OTHER ACADEMY!

Global Multiple Myeloma Academy
- focusing on LATAM region

23 – 24 June 2022

- 2.00 PM – 5.00 PM EDT (Central Daylight Time)
- 3.00 PM – 6.00 PM EDT (Easter Daylight Time)
- 4.00 PM – 7.00 PM GMT-3 (San Paulo time)

For more information, please visit the website:
https://globalmmacademy.com

APTITUDE HEALTH®

Global Leukemia Academy

AML session open

Naval Daver

APTITUDE HEALTH

Question 1

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

1) Adverse genetic alterations
2) Age
3) Comorbidities
4) Performance status
5) Prior cytotoxic therapy
6) Prior myelodysplasia

Question 2

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

1) Patients >75 years of age
2) Patients <75 years of age with ECOG PS 3
3) Patients <75 years of age with significant cardiac co-morbidity
4) Patients <75 years of age with significant pulmonary comorbidities
5) Patients <75 years of age with adverse cytogenetics

Question 3

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

1) The CR/CRi with HMA+VEN in the VIALE-A was >65%
2) HMA+VEN improved median OS compared with HMA alone
3) Lab or clinical TLS is not seen with HMA+VEN in AML
4) The recommended daily dose of venetoclax (without azoles) was 400mg PO Qday in VIALE-A study
5) Neutropenia is commonly seen with HMA+VEN regimen

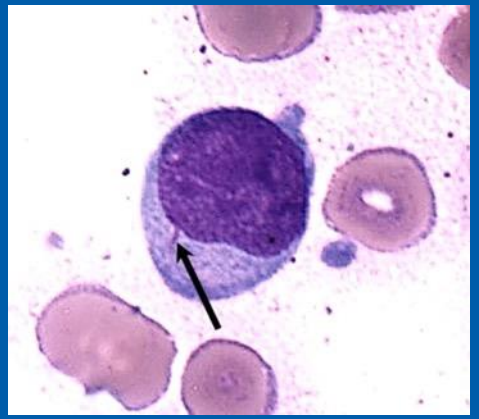
Global Leukemia Academy

Personalized induction and maintenance approaches for AML

Eunice Wang

APTITUDE HEALTH

Personalized induction and maintenance approaches for AML



ROSWELL PARK
COMPREHENSIVE CANCER CENTER

Eunice S. Wang MD
Chief, Leukemia Service

Disclosures

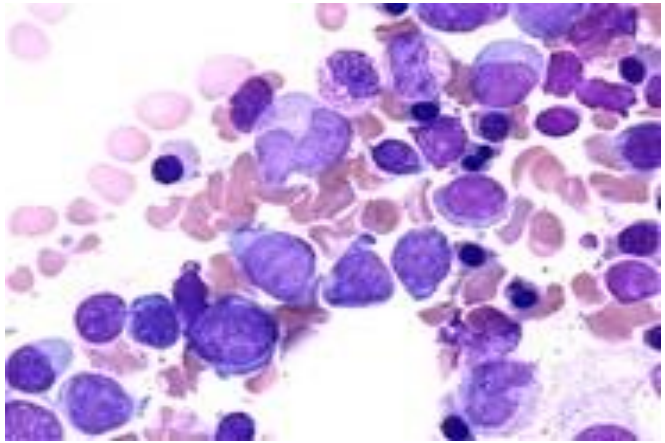
- Consulting/Advisory board: Abbvie, Amgen, Astellas, BMS, Genentech, Gilead, GSK, Jazz, Kite, Novartis, Pfizer, PharmaEssentia, Takeda
- Speaker role: Abbvie, Stemline, Pfizer, Dava Oncology
- Data monitoring committee: Abbvie, Rafael Pharmaceuticals, Gilead

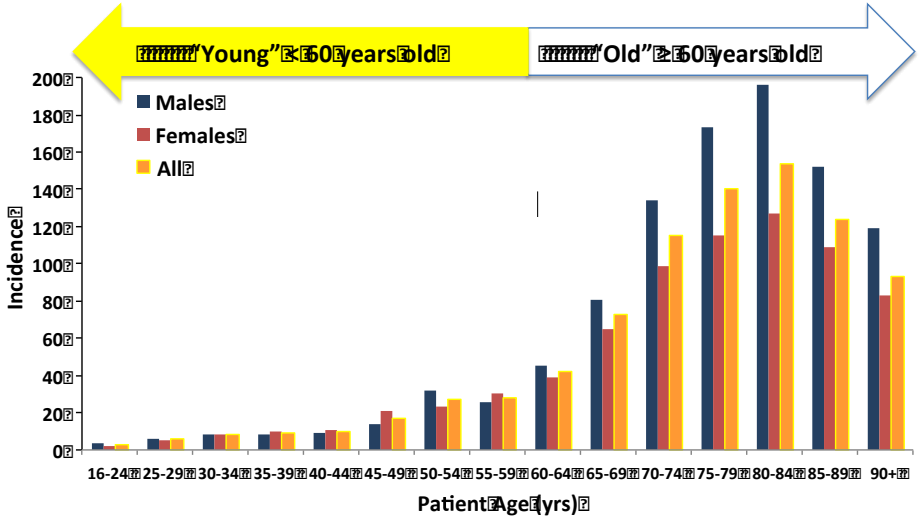
Personalized AML therapy in 2022

1. Overview of AML treatment approach
2. Intensive chemotherapy (7+3 based)
3. Non-intensive chemotherapy
4. Maintenance strategies

Acute Myeloid Leukemia (AML)

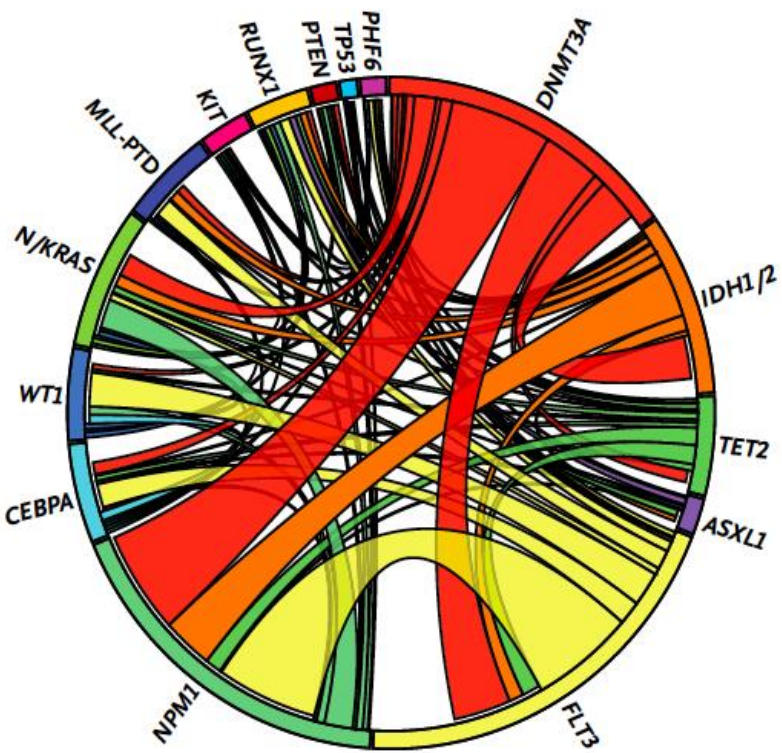
Disease of older adults (median 67-70 years)
Biologically diverse (karyotype, mutations, antigens)
Clinically aggressive disease with survival in weeks-months





Lee et al Blood 129(2): 257, 2017.

Mutational complexity of AML

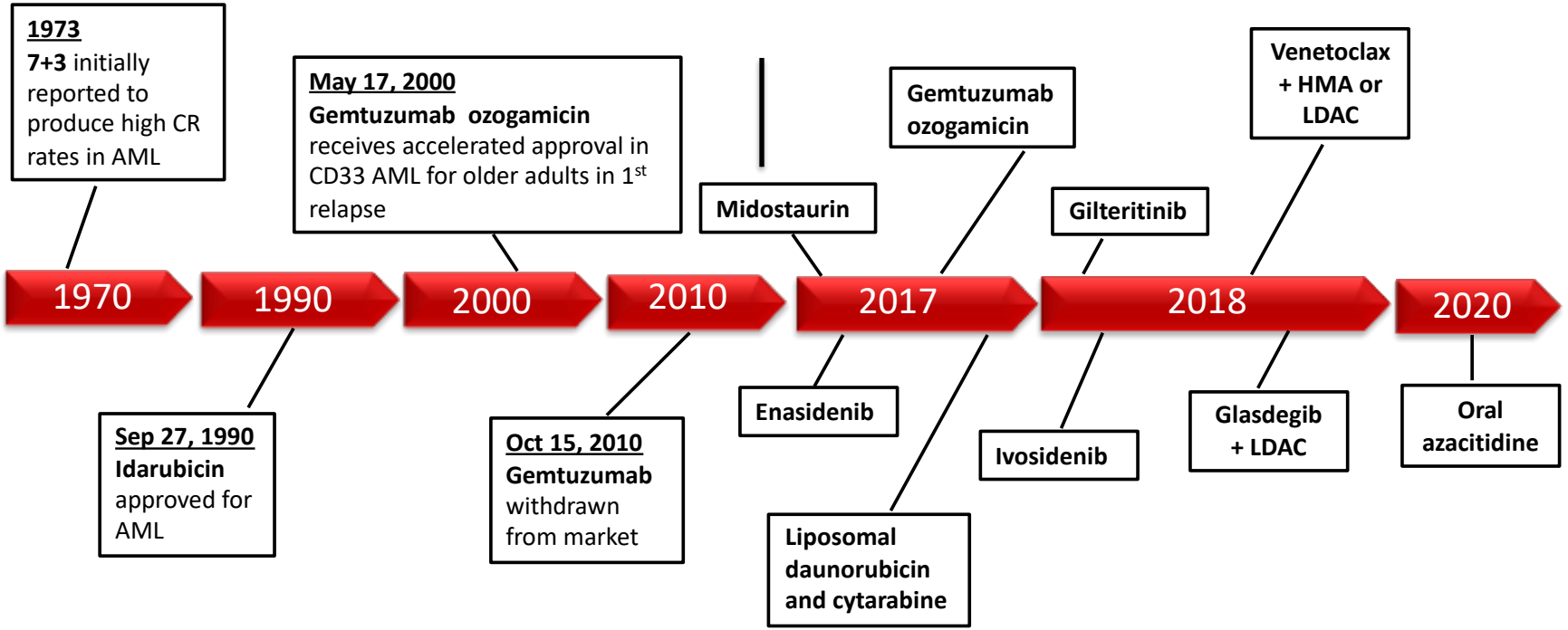


Gene	Overall Frequency, %
FLT3 (ITD, TKD)	37 (30,7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6

Gene	Overall Frequency, %
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

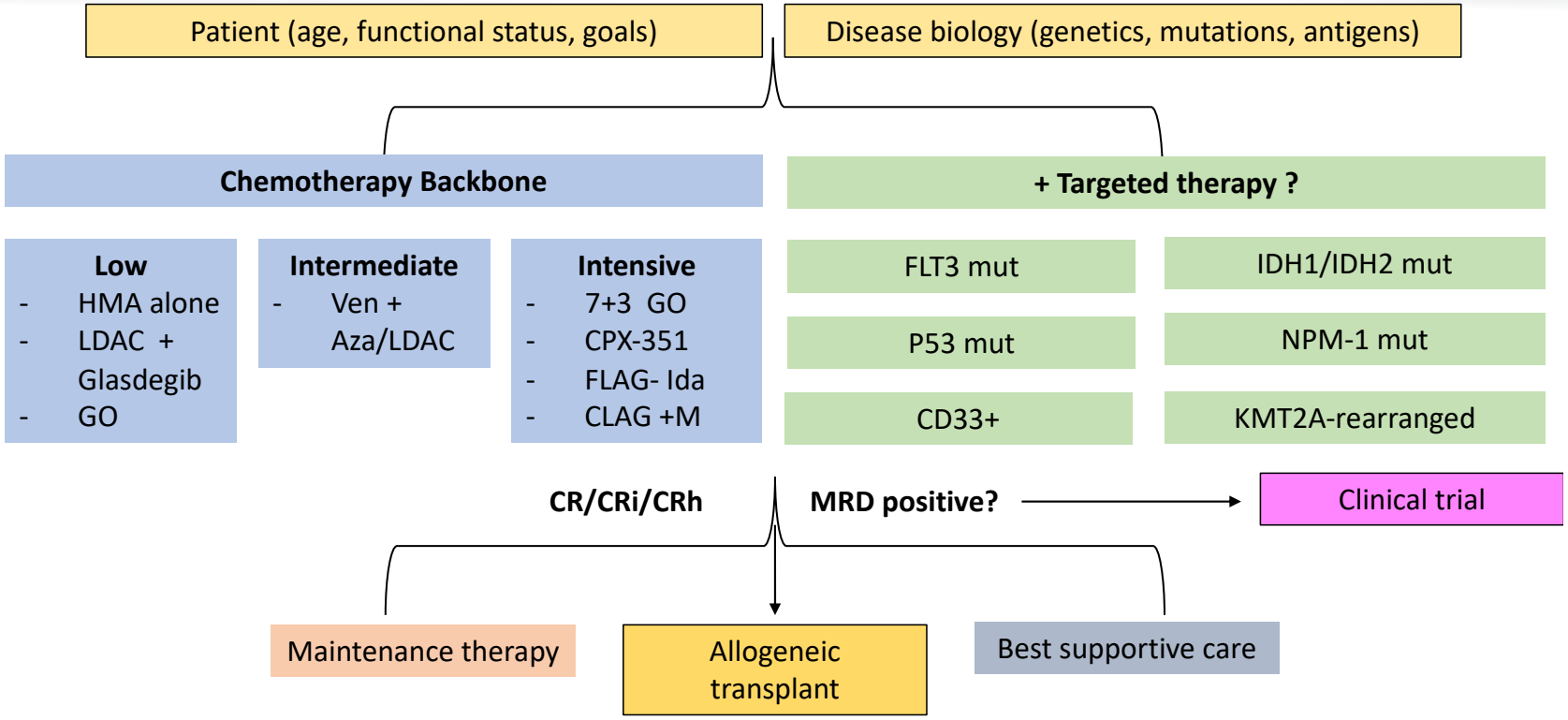
Papaemmanuil E et al NEJM 374(23): 2209-221, 2016

Drugs approved for AML therapy



Slide courtesy of Alison Walker MD

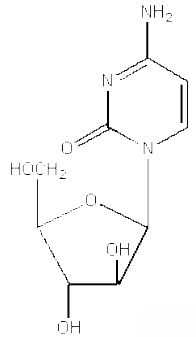
Personalized approach to AML therapy

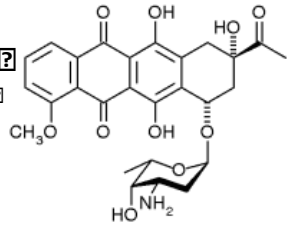


1973: 7+3 intensive chemotherapy= gold standard

7 days - 3 days

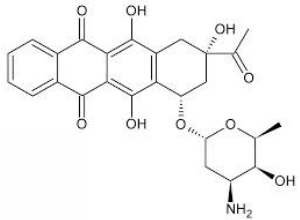
Cytarabine + Daunorubicin 60-90 mg/m²





OR

Idarubicin 12 mg/m²



Cytosine Arabinoside (NSC-63878) and Daunorubicin (NSC-83142) Therapy in Acute Nonlymphocytic Leukemia [1,2,3]

Brief Reports and Preliminary Communications

Jerome W. Yates, H. James Wallace, Jr., Rose Ruth Ellison, and James F. Holland [4]

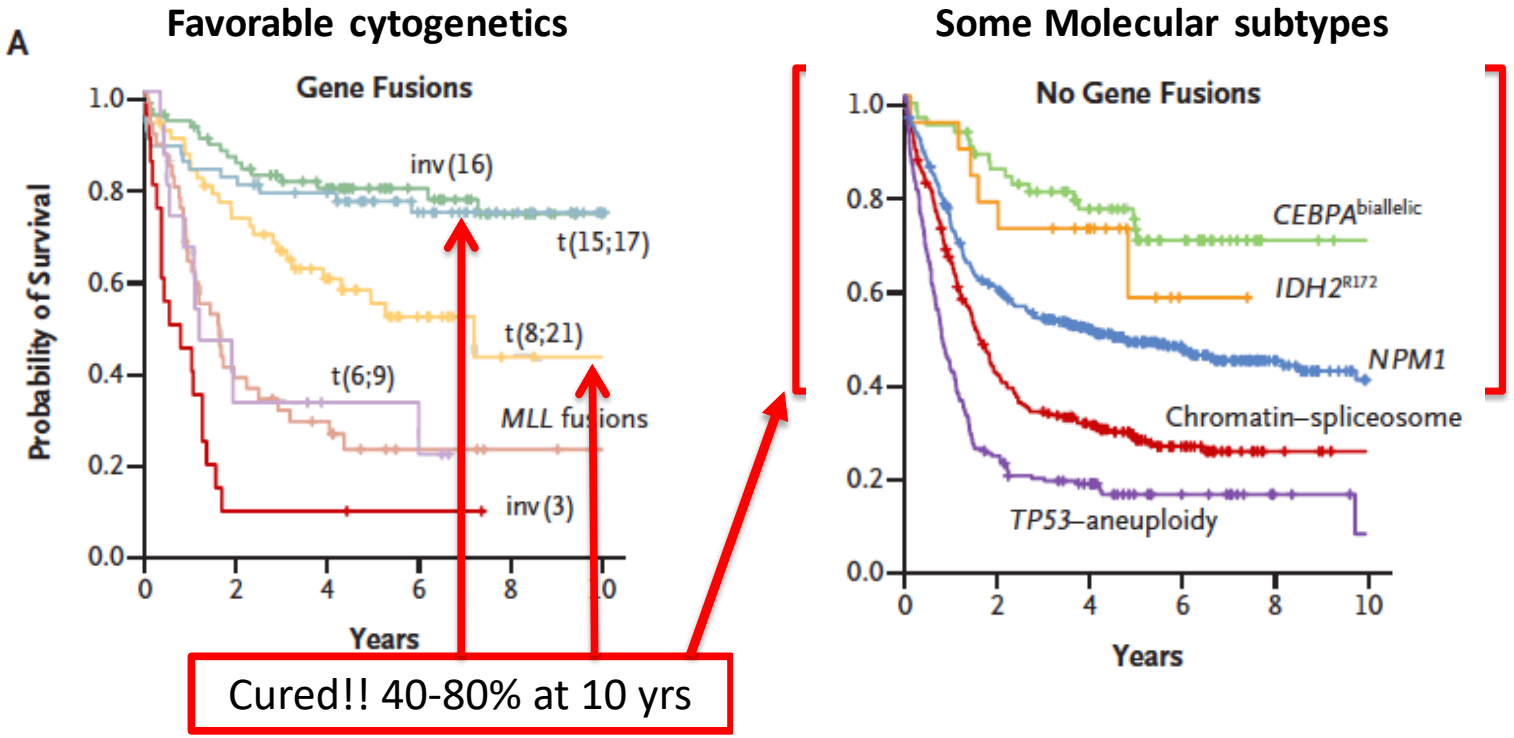
Early destruction of leukemic infiltration in the induction phase of treatment may reduce the duration of time most hazardous for infection as well as the total period of necessary hospitalization. Daunorubicin produces rapid bone marrow depression, and when administered as a single agent it is active in acute myelocytic leukemia, producing 43% remissions after a 5-day course (1). At the effective dose, however, the mortality and morbidity rates are high. The combination of daunorubicin and cytosine arabinoside appears to be quite active in the treatment of acute myelo- intensify the effects of cytosine arabinoside and daunorubicin thereby producing rapid destruction of leukemic cells. Such an effect might attain more remissions and earlier discharges from the hospital.

METHODS

All adult patients admitted to Roswell Park Memorial Institute with acute nonlymphocytic leukemia who had received no prior daunorubicin therapy and who were not in remission were studied during a 6-month period. All

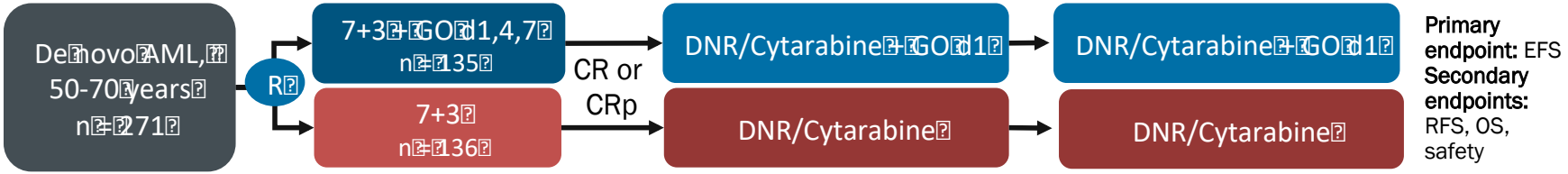
Yates JW et al Cancer Chemo Rep 57(4): 485-488, 1973

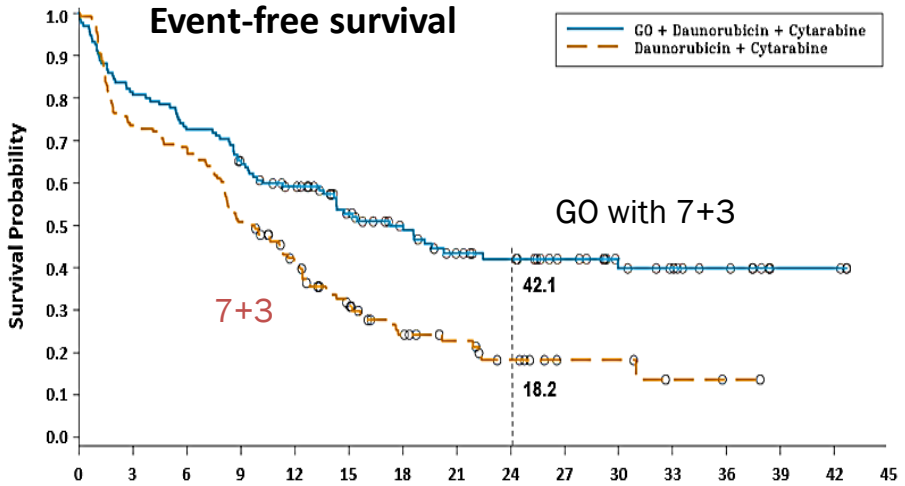
In 2022, who should still get 7+3?



Papaemmanuil E et al NEJM 374(23): 2209-221, 2016

Addition of GO to 7+3 improves event-free survival





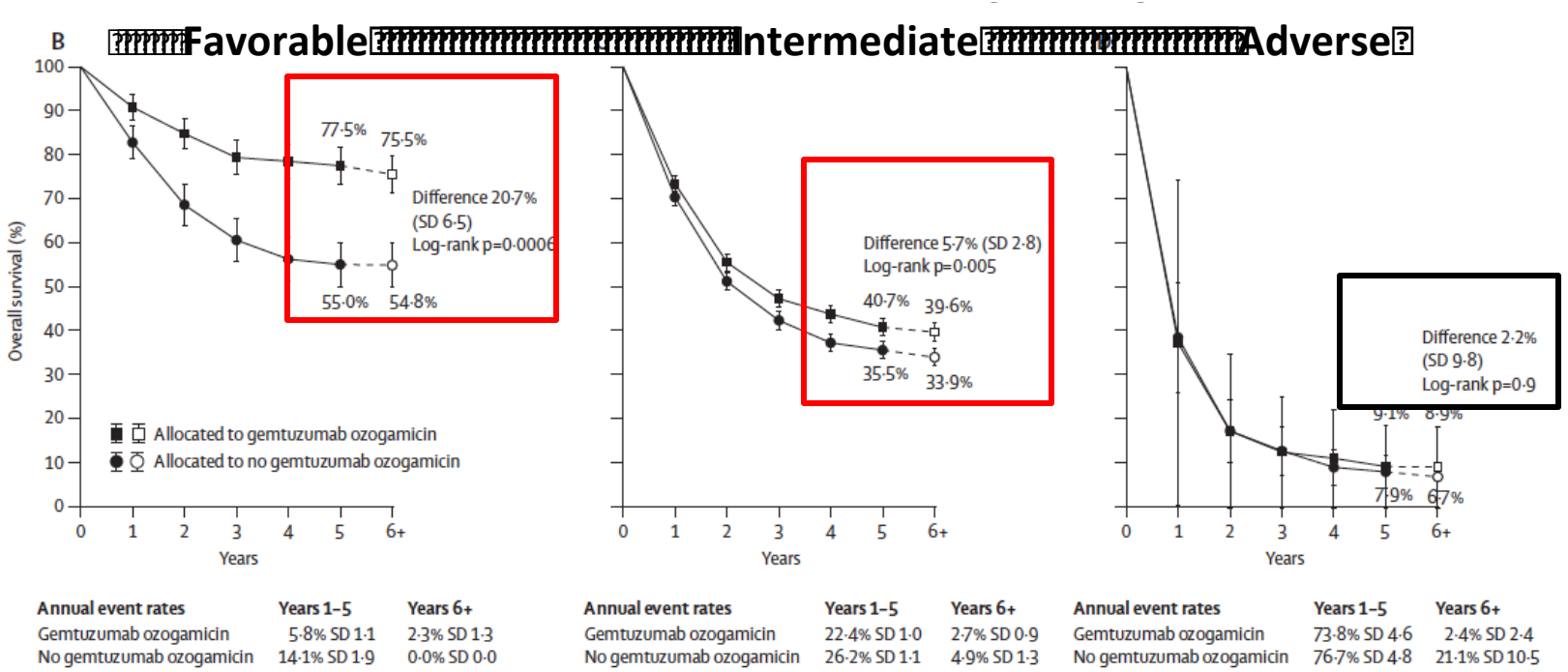
- GO better for favorable/intermediate risk

- Increased Gr3 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. 2018

GO improves 7+3 outcomes for favorable/intermediate risk

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



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

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

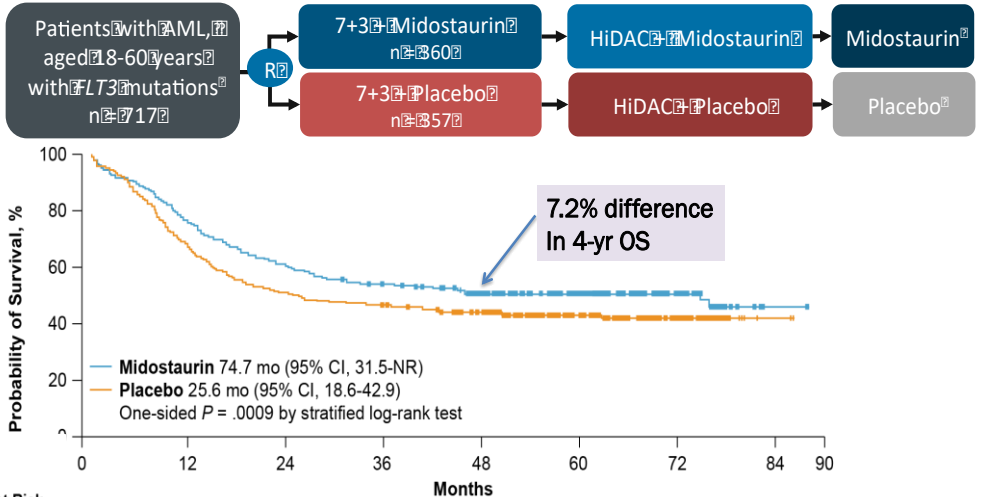
Addition of FLT3 inhibitor to 7+3 in FLT3 mutant AML

Midostaurin targets:

cKIT, PKC, PDGFR, VEGFR, FLT3 TKD FLT3 ITD

	Midostaurin Group (N=360)	Placebo Group (N=357)	P Value†
CR	212 (59)	191 (54)	0.15

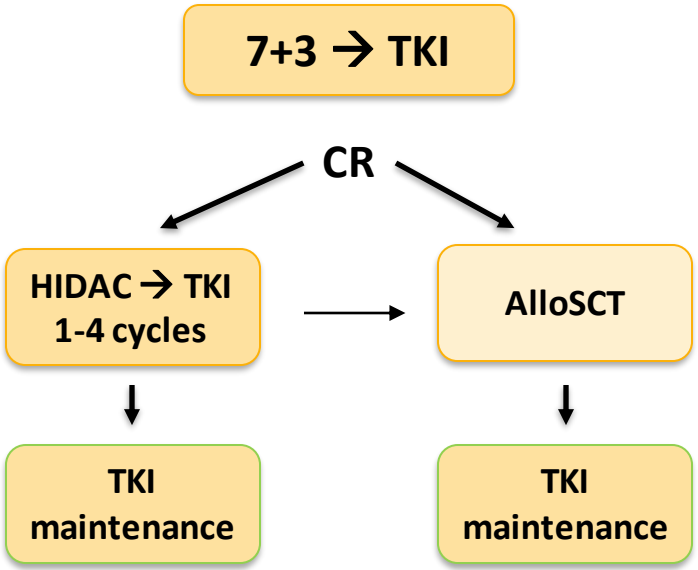
De novo FLT3 mutant AML (18-60 yo)



- 7+3: Cytarabine 200 mg/m²/d, days 1-7; daunorubicin 60 mg/m²/d, days 1-3; HiDAC: High-dose cytarabine at 3 g/m²/d twice daily, days 1, 3, 5; Midostaurin induction/consolidation: 50 mg or placebo orally twice daily, days 8-21, with each cycle; Midostaurin maintenance: 50 mg or placebo orally twice daily for twelve 28-day cycles.
- Stone RM, et al. *N Engl J Med.* 2017;377:454-464.

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

Second generation FLT3 inhibitor added to 7+3

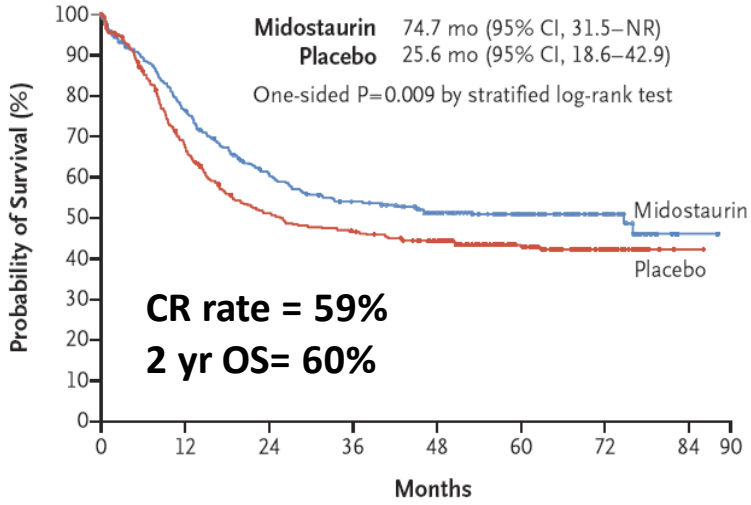


Regimen	N	CR/CRi /CRh	Overall survival
Midostaurin/7+3	717	59%	2 yr OS= 50%
Quizartinib/7+3	16	84%	NA
Crenolanib/7+3	38	88%	2 yr OS = 79%
Gilteritinib/7+3	38	89%	2 yr OS approx. 70%

Stone R et al NEJM 377(5): 454, 2017; Wang E et al ASH 2017; Altman J et al AJH 93(2): 213, 2018; Pratz K et al ASH 2020

Outcomes of 1st vs 2nd generation FLT3 inhibitors plus 7+3

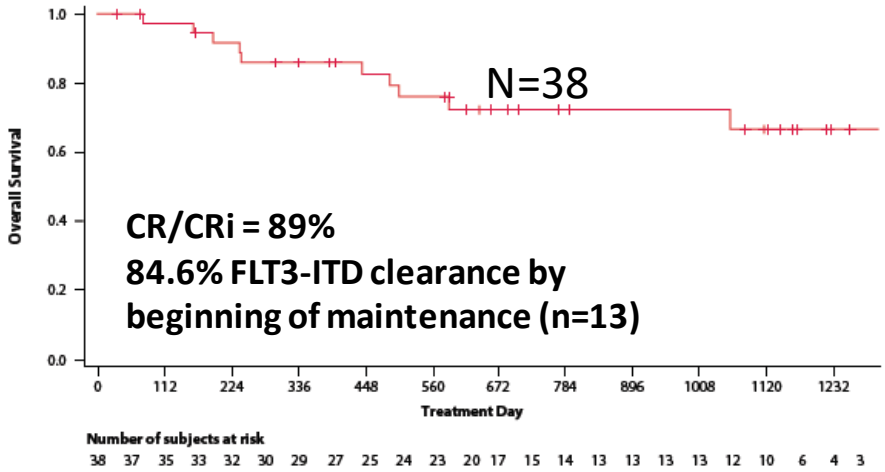
Midostaurin/ 7+3 (RATIFY)



No. at Risk

Midostaurin	360	269	208	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1

Gilteritinib/ 7+3



Stone R et al NEJM 2017; Pratz et al 2021 EHA Abstract EP437

Quantum-FIRST trial (Press release Nov 22, 2021)

- QuANTUM-First trial (NCT02668653): Double blind, placebo controlled, multicenter global trial assessed quizartinib, an oral, highly potent and selective type II FLT3 inhibitor, combined with chemotherapy in a population of adult patients between the ages of 18 and 75 years. Patients who enrolled on the study (n = 539) were randomized 1:1 to received either quizartinib and chemotherapy or placebo plus standard anthracycline- and cytarabine-based induction and consolidation chemotherapy.

- Quizartinib combined with standard induction and consolidation chemotherapy followed by quizartinib monotherapy resulted in a **statistically significant and clinically meaningful improvement in OS, meeting the study's primary end point**. Moreover, the agent's safety profile proved to be manageable and was consistent with what has been previously observed. Findings from the trial will be presented at an upcoming medical meeting.

AML-MRC: AML with MDS related changes

Definition: AML with a history of MDS or myelodysplasia-related cytogenetic findings, specifically ≥ 20% blasts in the peripheral blood or bone marrow and any of the following:

- Prior known MDS or MDS/MPN
- MDS-related **cytogenetic** abnormalities
- Morphologic **multilineage dysplasia**

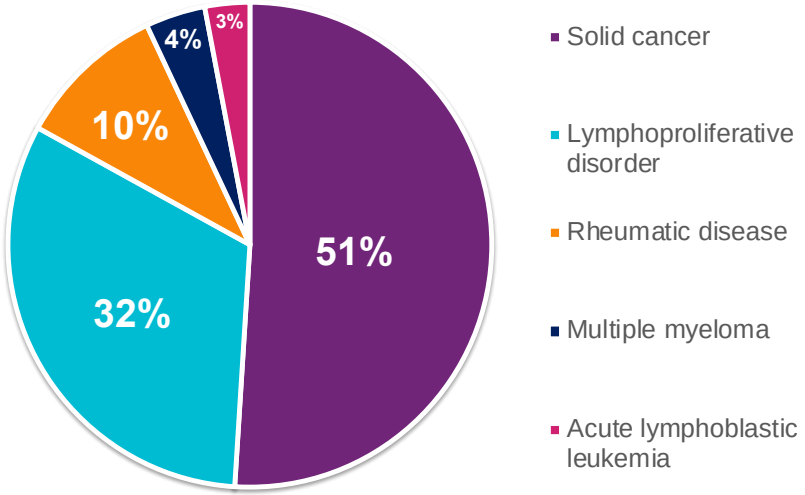
1. ***Complex karyotype*** *(3 or more abnormalities).*
2. ***Unbalanced abnormalities****: -7/del(7q), del(5q)/t(5q), i(17q)/t(17p), -13/del(13q), del(11q), del(12p)/t(12p), idic(X)(q13).*
3. ***Balanced abnormalities****: t(11;16)(q23.3;p13.3), t(3:21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23.3), t(5;12)(q32;p13.2), t(5;7)(q32;q11.2), t(5;17)(q32;p13.2), t(5;10)(q32;q21.2), t(3;5)(q25.3;q35.1)*

Footnote 1. The presence of 50% or more dysplastic cells in at least 2 cell lines, ***excluding cases when a mutation of NPM1 or biallelic mutation of CEBPA is present.***

Therapy related AML (tAML)

The WHO defines t-AML as AML that arises from prior cytotoxic therapy or ionizing radiotherapy for an unrelated disease. Estimated to account for 5-10% of all AML cases.

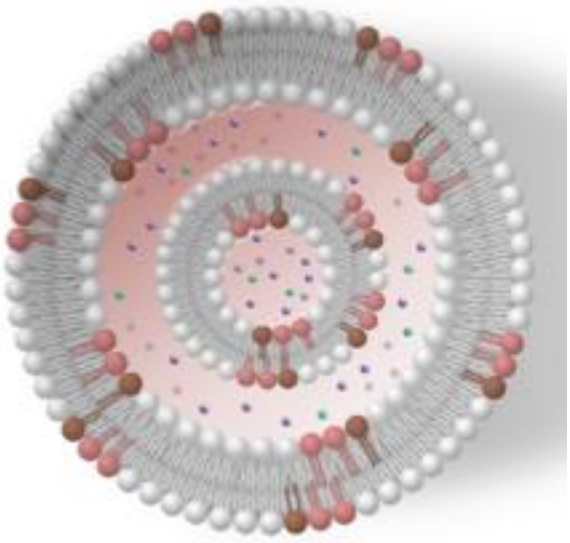
Primary malignancy prior to tAML



Cytotoxic therapy[a]	MOA	Examples	Latency period
Alkylating agents and radiation	Induce chromosomal deletions, commonly in 5 and/or 7	Cyclophosphamide, mechlorethamine, procarbazine, chlorambucil, melphalan, carmustine, busulfan	5-10 years
Topoisomerase II inhibitors	Induce chromosomal translocations	Etoposide, teniposide, mitoxantrone, epirubicin, and doxorubicin	2-3 years

Bhatia S. *Semin Oncol.* 2013;40(6):666-675. 2. Czader M, et al. *Am J Clin Pathol*. 2009;132(3):410-425. 3. Leone G, et al. *Haematologica.* 1999;84(10):937-945.

Liposomal 7+3 (CPX-351): Drug formulation

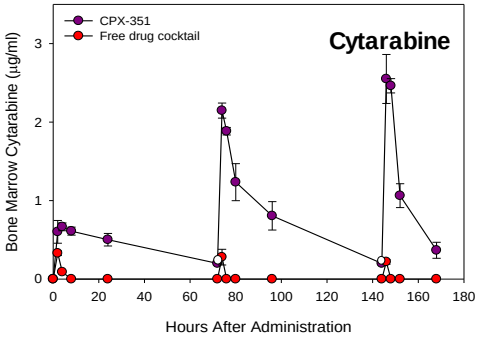


Liposomal formulation of cytarabine and daunorubicin

Fixed 5:1 molar ratio of cytarabine: daunorubicin provides synergistic leukemia cell killing *in vitro*

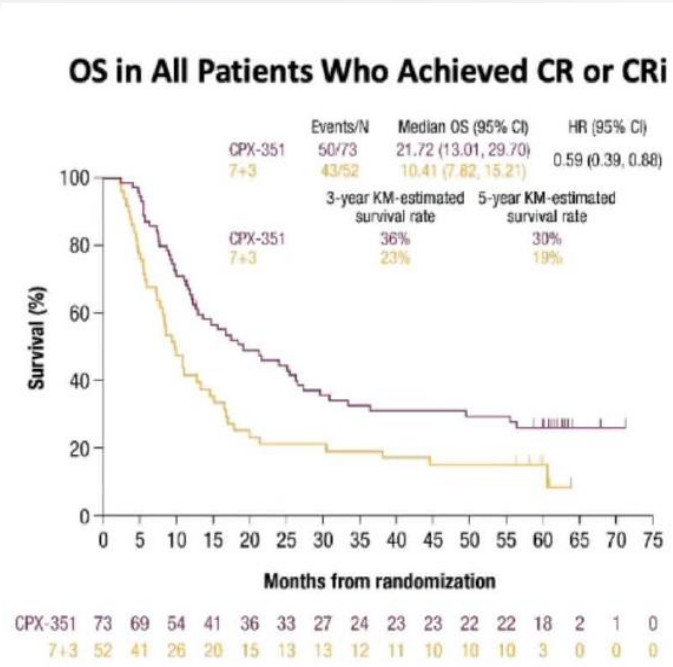
In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days

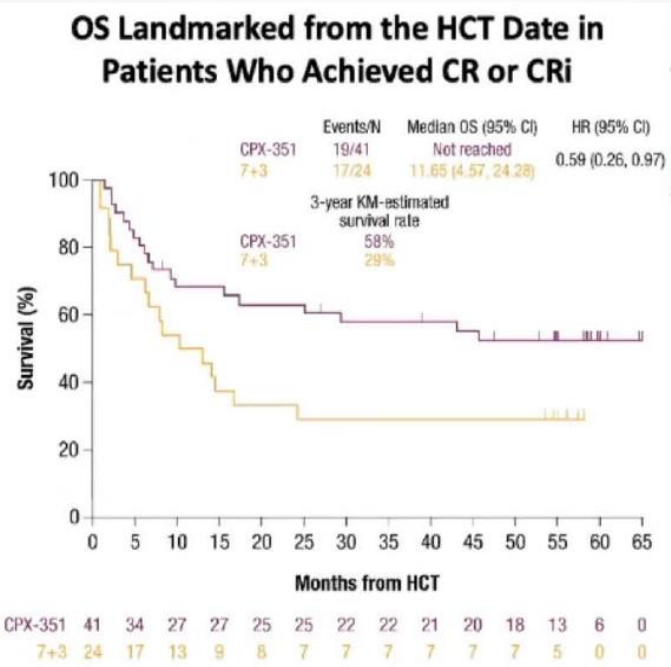
Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]



Lancet JE, et al. J Clin Oncol. 2018;36:2684-2692.

Outcomes of CPX-351 in AML-MRC and t-AML





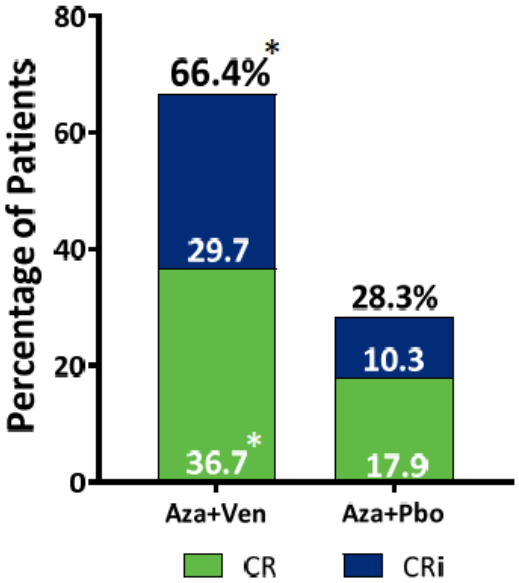
	CPX-351	7+3
% CR-CRi	48	33
mOS	9.6	5.9
mOS in pts w CR/CRi	21.7	10.4
% SCT	35	25
% 5-yr OS post SCT	56	23

Long term data confirms impressive 5-yr OS in responding patients s/p SCT with CPX-351

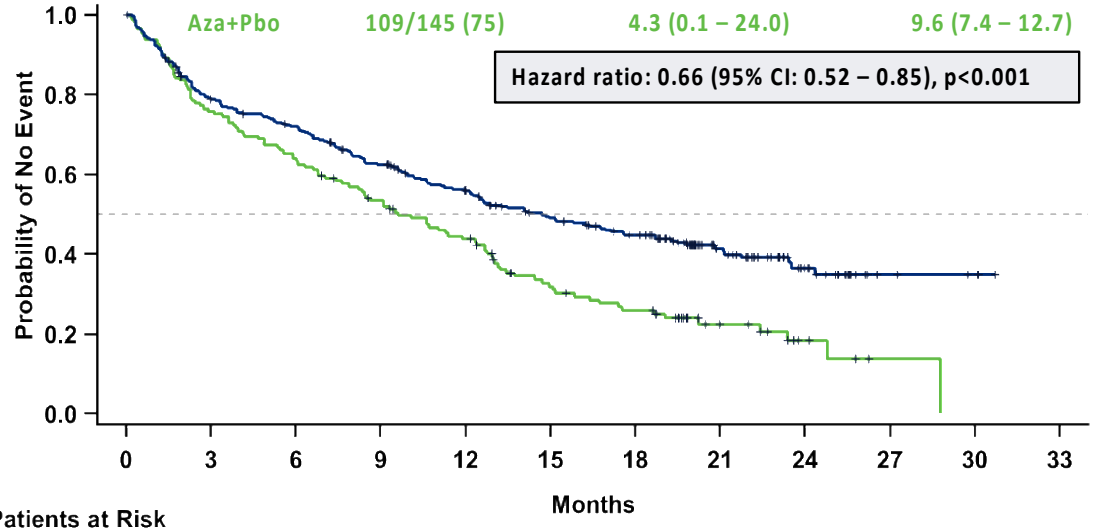
Lancet J et al, Blood Advances

Outcomes of Venetoclax + Azacitidine for older unfit AML

Overall Responses



	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)



Patients at Risk

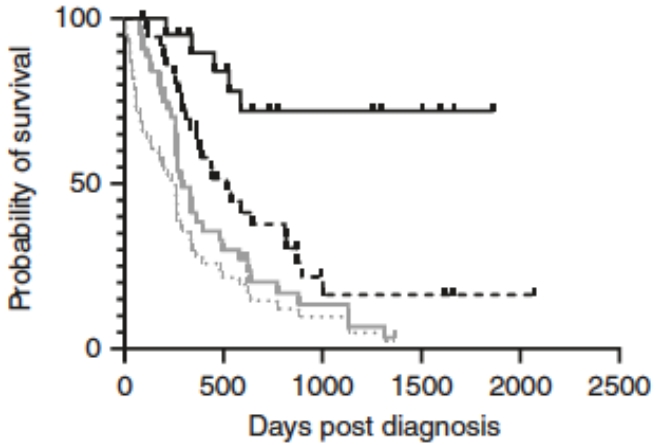
Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

Dinardo C et al NEJM 2020

Single center outcomes of transplant following Ven + Aza

Transplant *N*=21
Consistent with strong transplant recommendation per guidelines *N*=18
Maintenance recommendation reasonable per guidelines *N*=3

No transplant *N*=31
Consistent with maintenance recommendation reasonable per guidelines *N*=14
Due to patient preference in spite of strong transplant recommendation per guidelines *N*=17



SCT
SCT eligible, no SCT
Not SCT candidate, survived at least 60 days from diagnosis
No SCT consult

SCT versus SCT eligible, no SCT *P*=0.002

SCT eligible, no SCT versus not SCT candidate survived 60 days *P*=0.035

	SCT patients	SCTETD patients	P value
n	21	31	
Age (median (range))	65 (60–73)	72 (64–78)	<0.01

Pollyea D et al Bone Marrow Transplant Oct 2021

Real world comparison of CPX-351 vs Ven+Aza in AML

UPenn study

Patient Characteristics		CPX-351 (n=217)	Ven+Aza (n=439)	*P* value
Median age (range), years		67 (21-82)	75 (36-88)	<0.001
High-risk mutations, n (%)	*ASXL1*	14 (6)	42 (10)	0.17
	TP53	33 (15)	57 (13)	
Gender, n (%)	Male	105 (48)	248 (56)	0.056
AML type, n (%)	De Novo	63 (29)	226 (51)	<0.001
	Prior MDS/MPN	104 (48)	150 (34)	
	Therapy-related	50 (23)	63 (14)	
ELN risk group, n (%)	Favorable	15 (7)	34 (8)	0.84
	Intermediate	64 (29)	117 (27)	
	Adverse	92 (42)	172 (39)	
	Favorable	15 (7)	34 (8)	

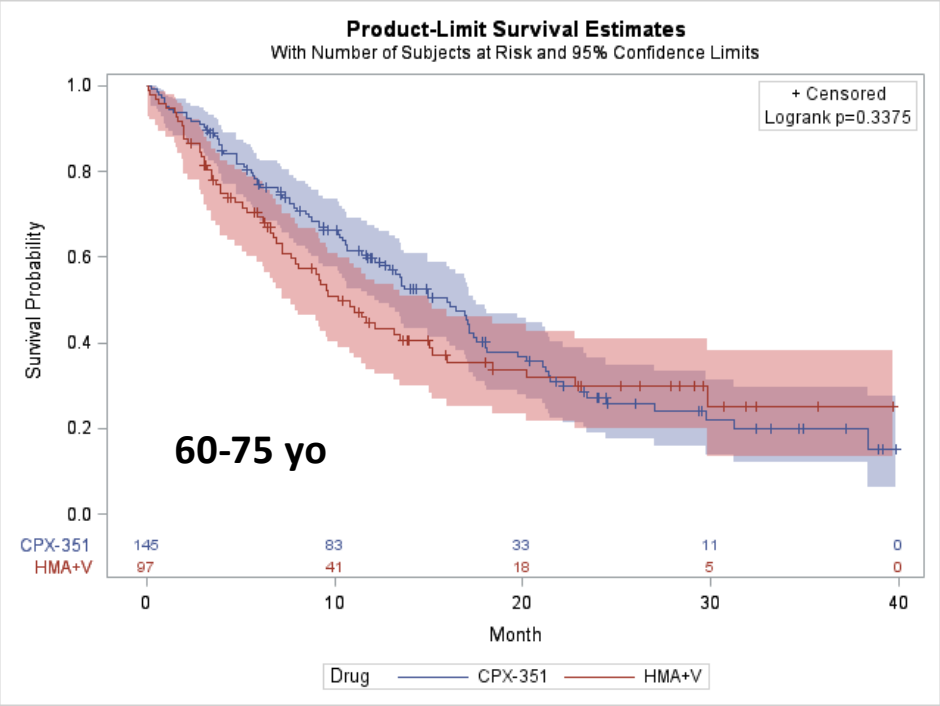
Matthews A, et al. ASH 2021. Abstract 795.

Weil- Cornell study

	CPX-351 Frontline	HMA+V Frontline	p-value
n	211	226	
Demographics			
Age, Median (IQR)	66.8 (60.8, 71.6)	75.2 (69.7, 78.8)	$p < 0.001$
Male, N (%)	121 (57.4%)	138 (61.1%)	$p = 0.430$
AML ELN Risk, N (%)			$p = 0.020$
Favorable/Intermediate	82 (38.9)	64 (28.3)	
Adverse	129 (61.1)	162 (71.7)	
Mutations			
TP53 (n=411), N (%)	37 (19.1)	58 (26.7)	$p = 0.066$
FLT3 (n=413), N (%)	12 (6.10)	19 (8.87)	$p = 0.311$
NPM1 (n=412), N (%)	13 (6.63)	23 (10.7)	$p = 0.150$
RUNX1 (n=411), N (%)	44 (22.7)	54 (24.9)	$p = 0.601$
ASXL1 (n=412), N (%)	32 (16.5)	59 (27.1)	$p = 0.010$
IDH1/IDH2 (n=411), N (%)	38 (19.7)	40 (18.4)	$p = 0.729$
Antecedent Hematologic Malignancy			
Prior myeloid disorder, N (%)	114 (54.0)	92 (40.7)	$p = 0.005$
Prior HMA therapy			$p = 0.001$
Yes, N (%)	43 (20.4)	22 (9.73)	
No, N (%)	136 (64.5)	180 (79.7)	
Other, N (%)	32 (15.2)	24 (10.6)	

Grenet J et al ASH 2021

Outcomes of Pts 60-75 yo with CPX-351 vs Ven + HMA



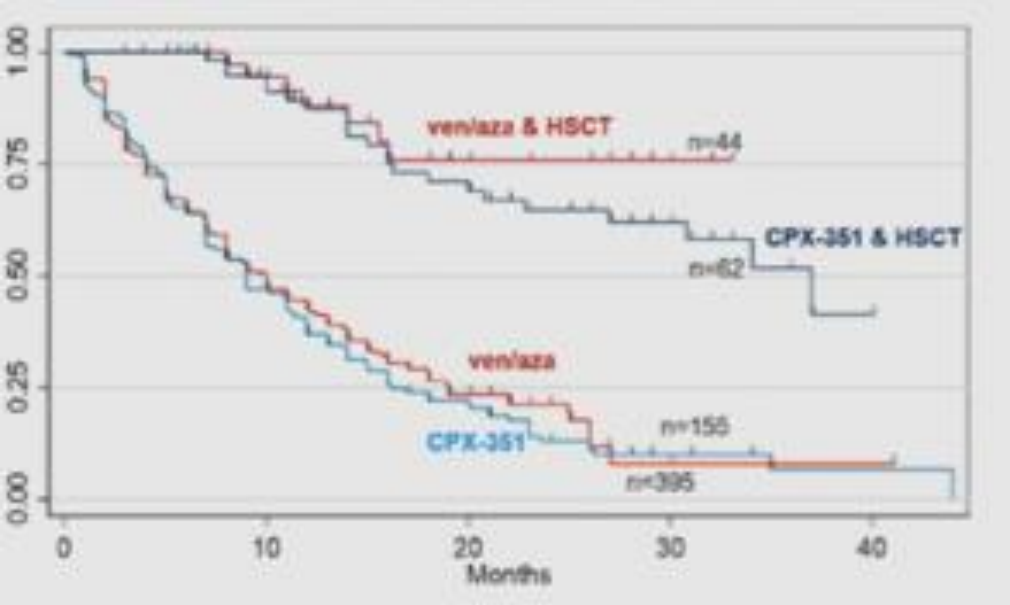
CR+CRi, 60-75yo
CPX-351: 59.2%
HMA+V: 54.0%
***p* = 0.41**

Total "n" and HSCT rates, 60-75yo
CPX-351: n = 152 (47.7% underwent HSCT)
HMA+V: n = 100 (19% underwent HSCT)
p <0.001

- No significant difference in OS in 60-75yo only, despite more than double the rate of HSCT in CPX-351 cohort
- No significant difference in OS in 60-75yo, censoring for HSCT

Grenet J et al ASH 2021 oral presentation

Transplant improved OS following CPX-351 vs Ven + HMA



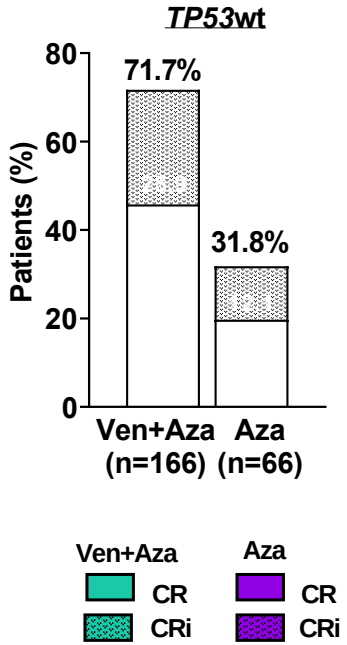
Transplant Outcomes	Ven+Aza	CPX-351
n, (%)	44 (10)	61 (28)
Median time to HSCT (range), days	186 (87-578)	171 (34-903)
Median OS with HSCT, months	NR	37
Median OS without HSCT, months	10	9

- **Transplanted pts had improved OS regardless of induction regimen (CPX-351 vs Ven+Aza)**
- **No difference in OS between CPX-351 vs Ven/Aza in these different pt populations**

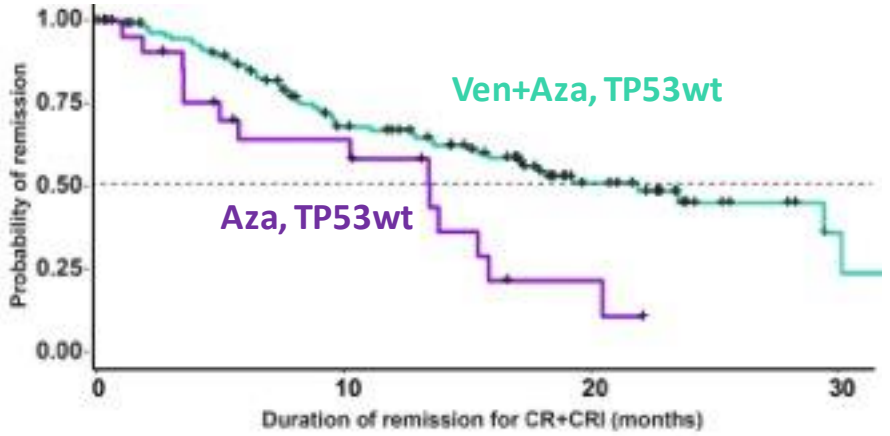
Matthews A, et al. ASH 2021. Abstract 795.

Ven + Aza in intermediate risk cytogenetics

Remissions



Duration of remission



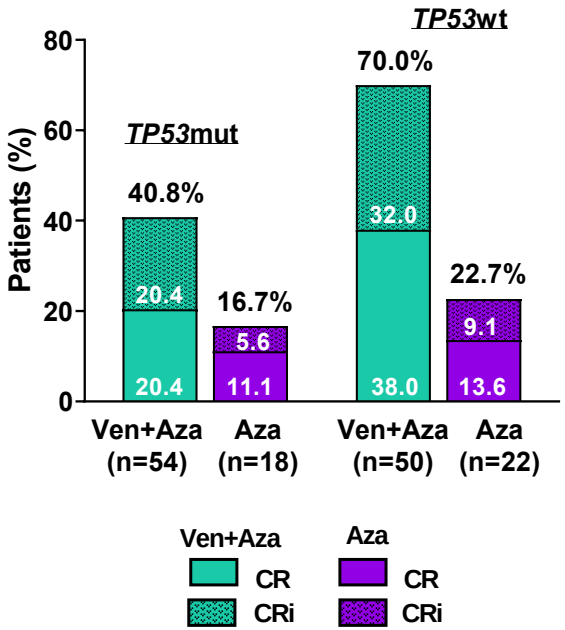
Patients with intermediate-risk cytogenetics at risk

Ven+Aza, TP53wt	119	66	25	3
Aza, TP53wt	21	11	2	0

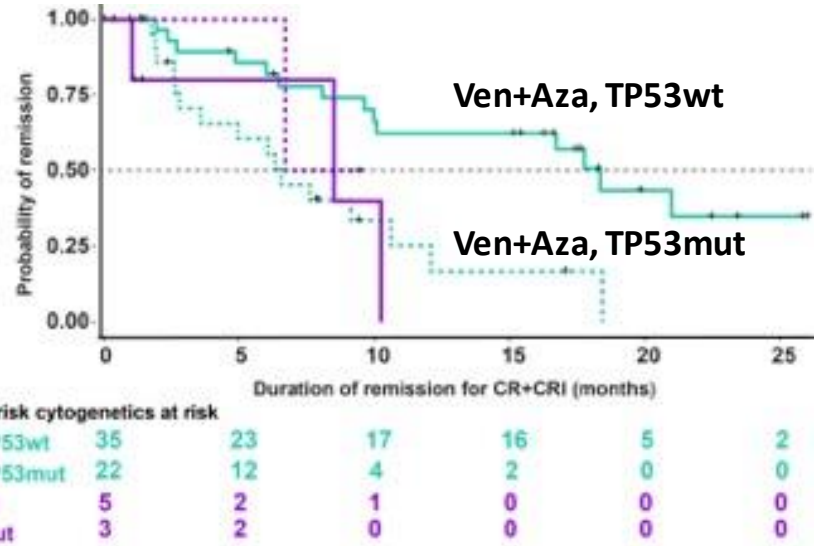
Pollyea et al 2021 ASH abstract

Ven + Aza in poor risk cytogenetics and p53 mutation

Remissions



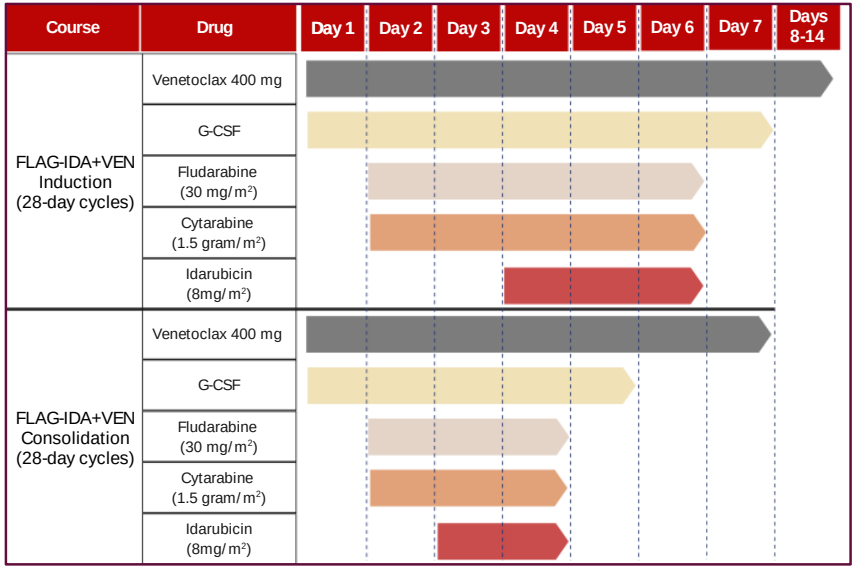
Duration of remission



Patients with poor-risk cytogenetics at risk						
Ven+Aza, TP53wt	35	23	17	16	5	2
Ven+Aza, TP53mut	22	12	4	2	0	0
Aza, TP53wt	5	2	1	0	0	0
Aza, TP53mut	3	2	0	0	0	0

Pollyea et al 2021 ASH abstract

Phase 1b/2 trial of Venetoclax + FLAG-IDA



G-CSF: 5 mcg/kg the day prior to and days of IV chemotherapy followed by 1 dose of pegfilgrastim or biosimilar the day following chemotherapy each 28 D cycle

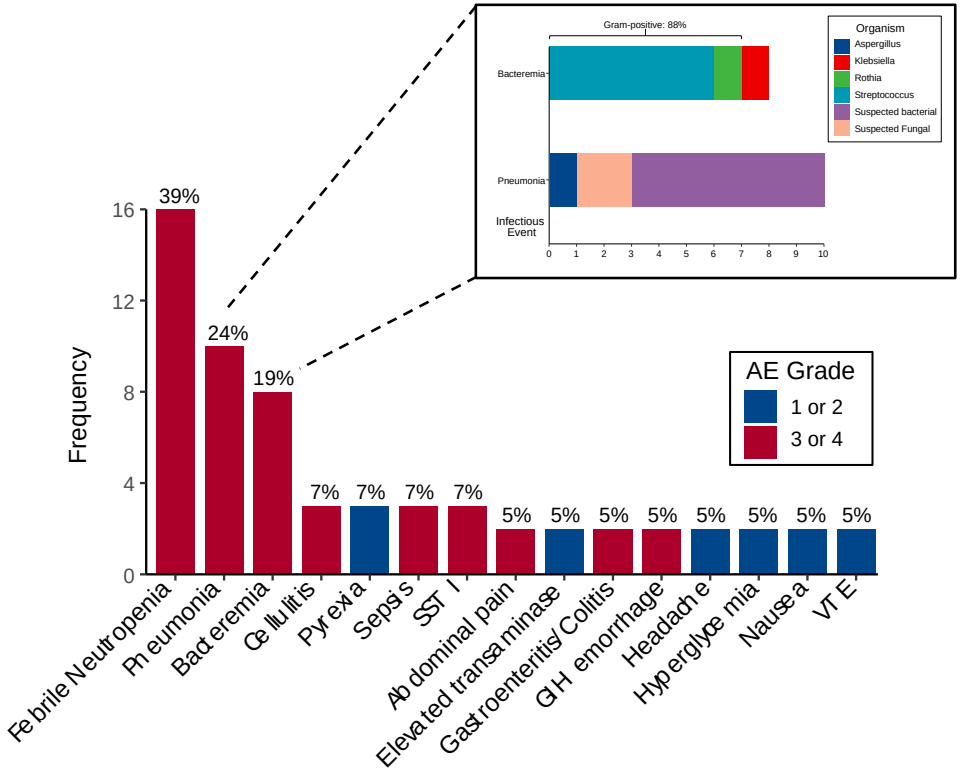
Consolidation: Idarubicin permitted on days 3 and 4 in 2 post-remission cycles (ie. C2 or C3 and C5 or C6) at physician discretion

Patient demographics

Demographic*	N=45
Age, years median (range)	44 (20-65)
Sex, male N(%)	20 (44)
Median blast % at enrollment	46 (4-85)**
AML Type	
De Novo AML	33 (73)
Secondary AML (sAML)	7 (16)
Therapy-related AML (tAML)	5 (11)
Treated sAML/tAML	6 (13)
ELN Risk Group	
Favorable	8 (18)
Intermediate	18 (40)
Adverse	19 (42)
Cytogenetics	
Intermediate risk	32 (71)
Diploid	19
Other intermediate risk	12
KMT2A-rearranged	1
Adverse risk/Complex	12 (27)
Complex karyotype	5
del(7)	1
inv(3)	2
KMT2A-rearranged	4
Insufficient mitoses	1 (2)

Lachowiez CA et al 2021 ASH abstract 701

Ven + FLAG-IDA: Adverse events



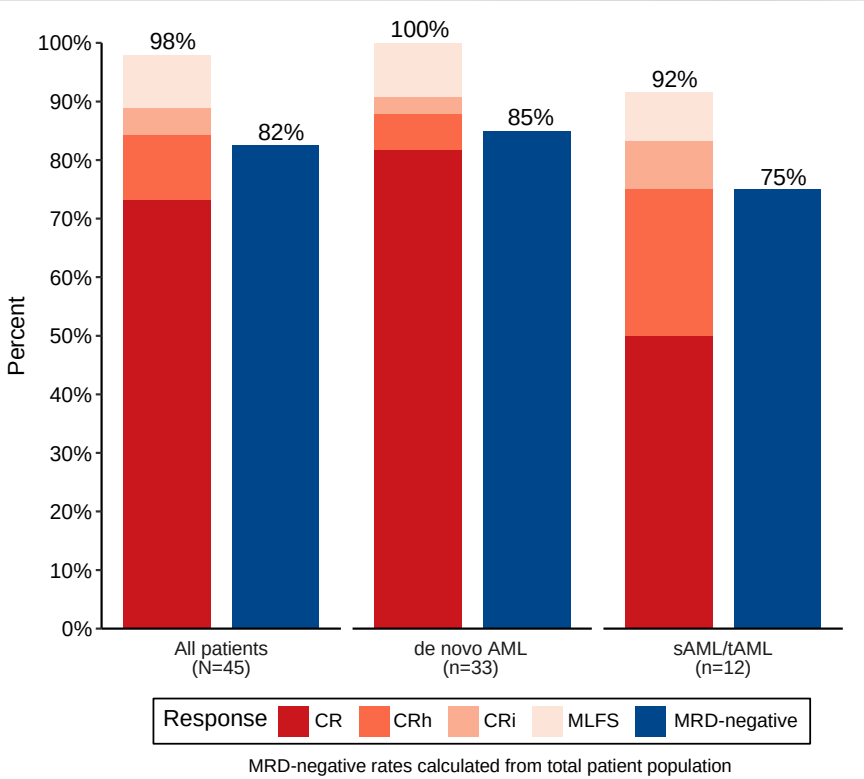
Adverse Event	Total N (%)	Grade 1/2	Grade 3	Grade 4
Febrile Neutropenia	**16 (39%)**	-	16	-
Pneumonia	**10 (24%)**	-	10	-
Bacteremia	**8 (19%)**	-	8	-
Cellulitis	**3 (7%)**	-	3	
Pyrexia	**3 (7%)**	3	-	-
Sepsis	**3 (7%)**	-	-	3
SSTI*	**3 (7%)**	-	3	-
Abdominal pain	**2 (5%)**	-	3	-
Elevated LFT	**2 (5%)**	2	-	-
Gastroenteritis/ Colitis	**2 (5%)**	-	2	-
GI Hemorrhage	**2 (5%)**	-	-	2
Headache	**2 (5%)**	2	-	-
Hyperglycemia	**2 (5%)**	2	-	-
Nausea	**2 (5%)**	2	-	-
VTE	**2 (5%)**	2	-	-

Lachowiez CA et al 2021 ASH abstract 701

Ven + FLAG-IDA: Responses

Demographic Median (range)/ N (%)	All (N=45)	De novo AML (n=33)	sAML/tAML (n=12)	*P-value*
Overall Response Rate	44 (98%)	33 (100%)	11 (92%)	0.26
Composite CR	**40 (89%)**	**30 (91%)**	**10 (83%)**	1.0
Complete Response	33 (73%)	27 (82%)	6 (50%)	*0.06*
CRh	5 (11%)	2 (6%)	3 (25%)	-
CRi	2 (4%)	1 (3%)	1 (8%)	-
MRD-Negative CRc*	**37 (93%)**	**28 (93%)**	**9 (90%)**	1.0
MLFS	4 (9%)	3 (9%)	1 (8%)	-
NR/PD	1	-	1 (8%)	-

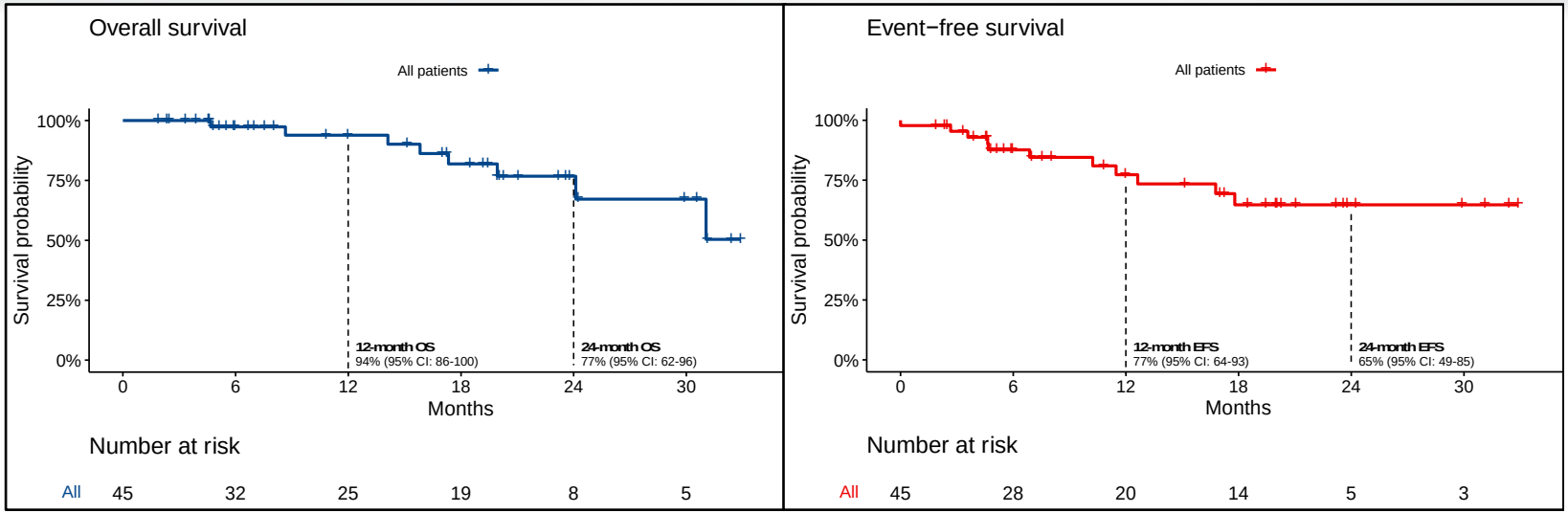
*Measured using multiparameter flow cytometry in evaluable patients with a sensitivity of 0.1-0.01%. Patients with unavailable or limited specimens were considered positive



MRD-negative rates calculated from total patient population

Lachowiez CA et al 2021 ASH abstract 701

Ven + FLAG-IDA: Survival

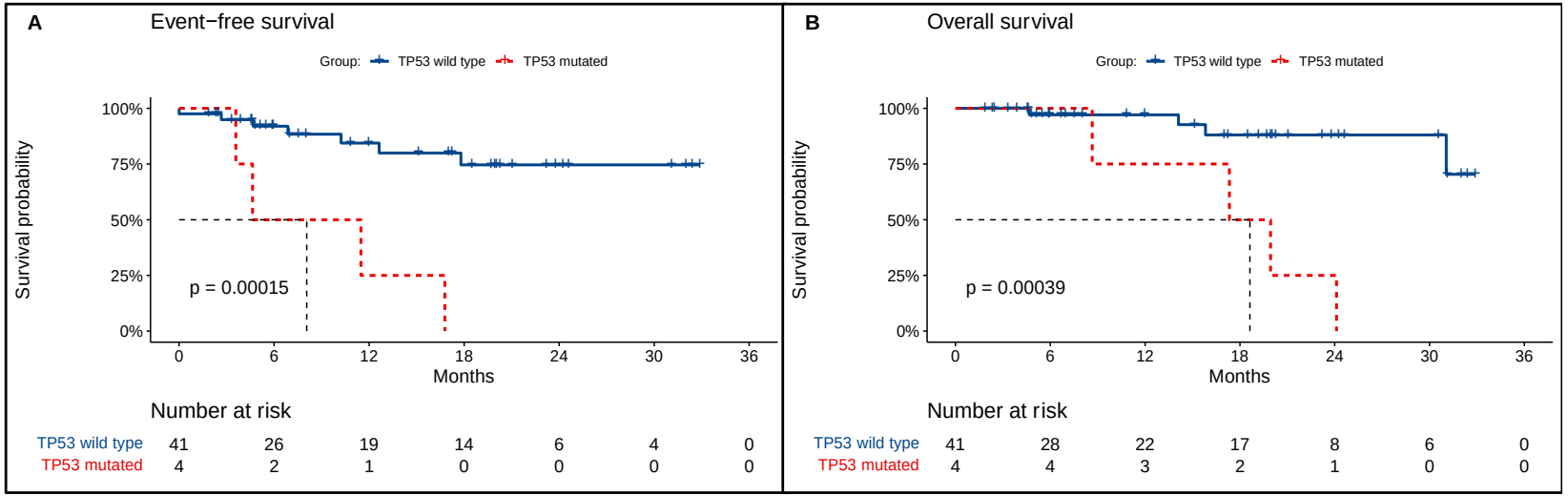


Demographic Median (95% CI) or %(SE)	All patients (N=45)	De Novo AML (n=33)	sAML/tAML (n=12)
Median EFS, months	**NR (18-NR)**	**NR (13-NR)**	**NR (18-NR)**
12-Month EFS	77% (8)	72% (10)	83% (11)
24-Month EFS	65% (9)	65% (11)	62% (16)
Median OS	**NR (-)**	**NR (20-NR)**	**31.1 (24-NR)**
12-Month OS	94% (4)	96% (4)	92% (8)
24-Month OS	77% (9)	68% (11)	92% (8)
Median Follow Up, months	19 (11-23)	11 (6-23)	21 (19-NR)

Lachowiez CA et al 2021 ASH abstract 701

Ven + FLAG-IDA: TP53 mutant AML

TP53 mutations correlated with significantly inferior event-free (**A**) and overall (**B**) survival compared to *TP53* wild type patients

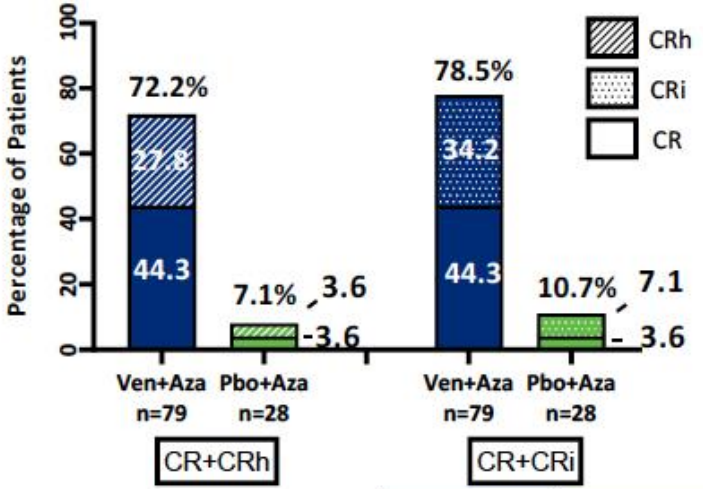


Variable Months (95% CI)	No *TP53* (N=40)	*TP53* (N=4)	*P-value*
Median event-free survival	NR (-)	8 (4-NR)	*< 0.001*

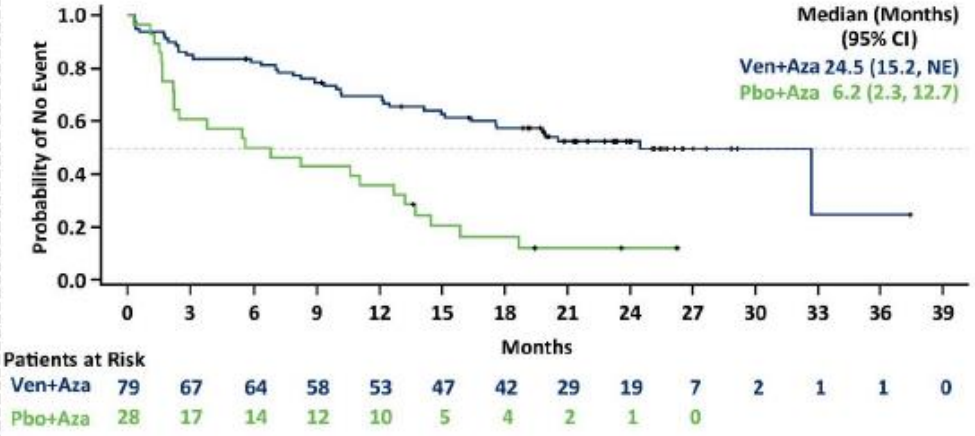
Variable Months (95% CI)	No *TP53* (N=40)	*TP53* (N=4)	*P-value*
Median overall survival	NR (31-NR)	19 (9-NR)	*< 0.001*

Lachowiez CA et al 2021 ASH abstract 701

Outcomes of Ven+ Aza in IDH1/2 mutant AML



	Ven + Aza n = 79	Pbo + Aza n = 28
CR+CRh:		
Median time to first response, mo. (min, max)	1.0 (0.7, 9.6)	2.6 (2.1, 3.1)
Median DoR, mo. (95% CI)*	29.6 (16.7, NE)	15.5 (NE)
CR + CRi:		
Median time to first response, mo. (min, max)	1.1 (0.7, 8.8)	3.4 (2.1, 7.1)
Median DoR, mo. (95% CI)*	29.5 (16.7, NE)	9.5 (3.5, 15.5)
Median treatment cycles (min,max)	8.0 (1, 37)	2.5 (1, 18)

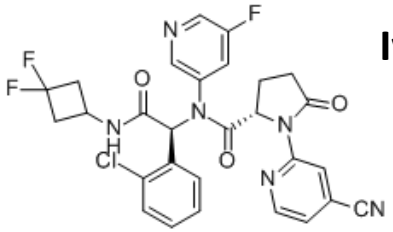


Survival Estimate (%) (95% CI)

	Month 6	Month 12	Month 24
Ven+Aza	82.3 (71.9, 89.1)	69.3 (57.8, 78.3)	52.4 (40.4, 63.1)
Pbo+Aza	50.0 (30.6, 66.6)	35.7 (18.9, 53.0)	12.2 (3.2, 27.8)

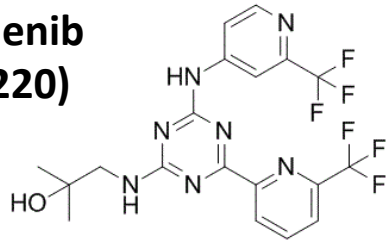
Pratz K, et al. ASH 2020. Abstract 1944.

Small molecule inhibitors of IDH1/2 mutant AML



AG-120
1448347-49-6

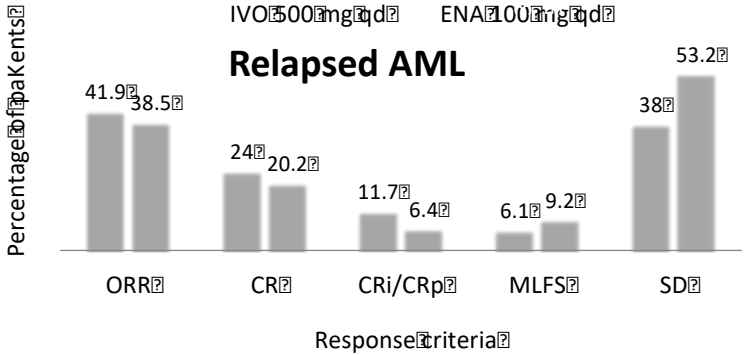
Ivosidenib (AG-120)



Enasidenib (AG-220)

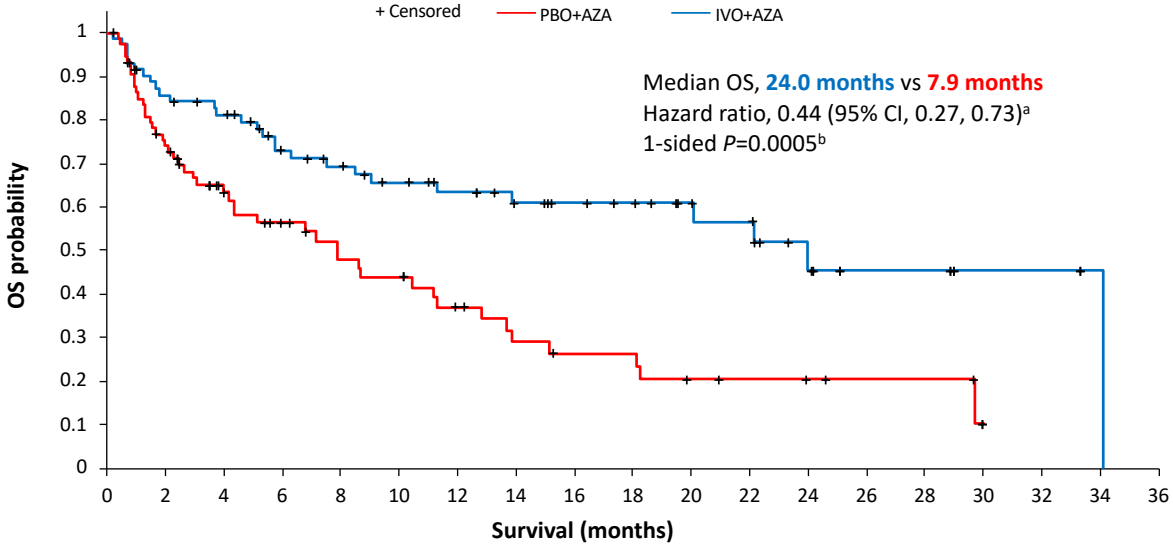
De novo AML

Single agent	IVO 500 mg qd (N=33)	ENA 100 mg qd (N=39)
CR/CRh	14 (42.4%)	12 (30.8%)
Median OS	12.6 mos	11.3 mos



DiNardo CD, et al. N Engl J Med. 2018;378(25):2386-2398.; Stein EM, et al. Blood. 2017;130(6):722-731.

Ivo + Aza improves Overall Survival over Aza alone



Number of patients at risk:

PBO+AZA	74	53	38	29	23	21	15	11	9	9	6	5	4	3	3	0	
IVO+AZA	72	58	53	42	38	33	29	24	21	19	15	13	7	4	4	2	2	1

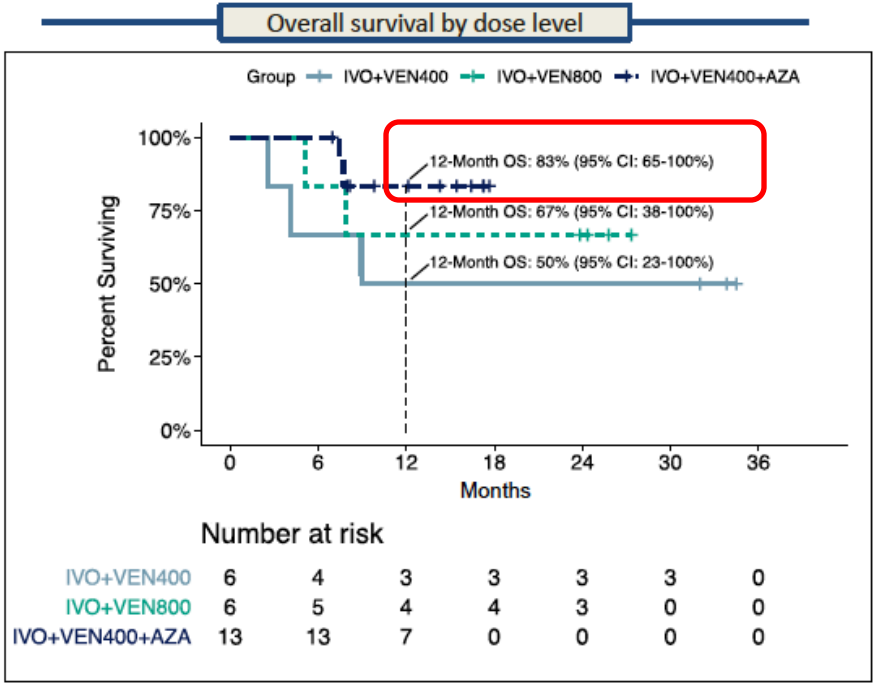
- OS benefit was consistent across subgroups: de novo status, region, age, baseline ECOG PS score, sex, race, baseline cytogenetic risk status, WHO classification of AML, baseline white blood cell count, baseline percentage of bone marrow blasts.

Montesinos P et al ASH oral abstract 2021

Ivosidenib + Ven +/- Aza in IDH1 mutant AML

- High composite CR rates in ND and R/R-AML
  - ND-AML: **92%**
  - R/R-AML: **63%**
- MRD-negative remissions in ND and R/R-AML
  - ND-AML: **60%**
  - R/R-AML: **60%**
- Durable responses and prolonged survival across disease groups

Outcome (mo)*	All (N=25)	DL #1 (N=6)	DL #2 (N=6)	DL #3 (N=13)	MDS or MPN (N=4)	ND-AML (N=13)	R/R-AML (N=8)
Median OS	NR	9 (4-NR)	NR (8-NR)	NR	NR	NR	9 (8-NR)
Median DOR	NR (13-NR)	13 (1-NR)	7 (4-NR)	NR	13 (7-NR)	NR (7-NR)	NR (5-NR)

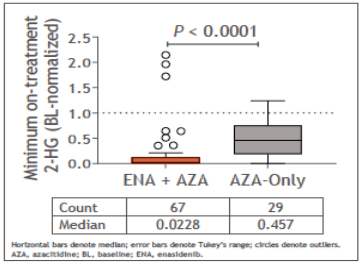


Lachowiez et al EHA 2021 abstract

Enasidenib + Azacitidine in IDH2 mutant AML

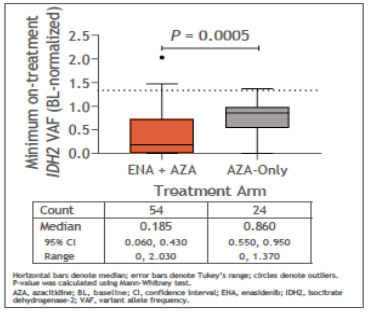
2-HG

Figure 3. Maximum reductions from baseline in 2-HG concentrations on-study



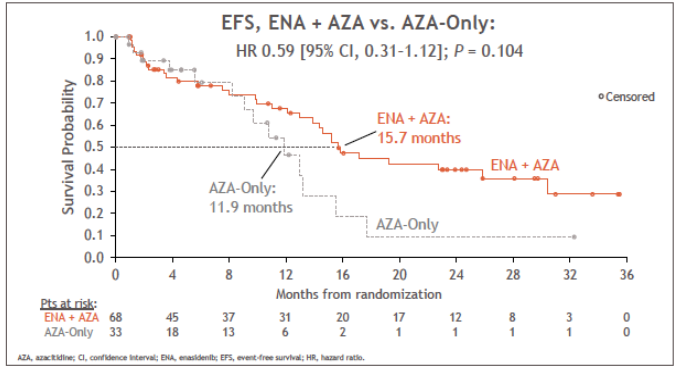
IDH2 VAF

Figure 5. Maximum reductions from baseline in *IDH2* variant allele frequency on-study



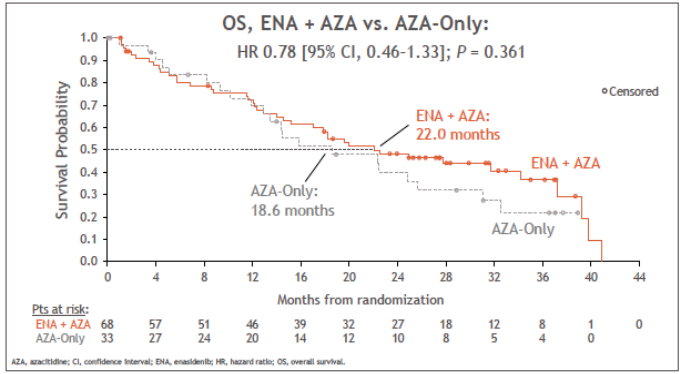
EFS

Figure 7. Event-free survival (Aug 2020 cutoff)



OS

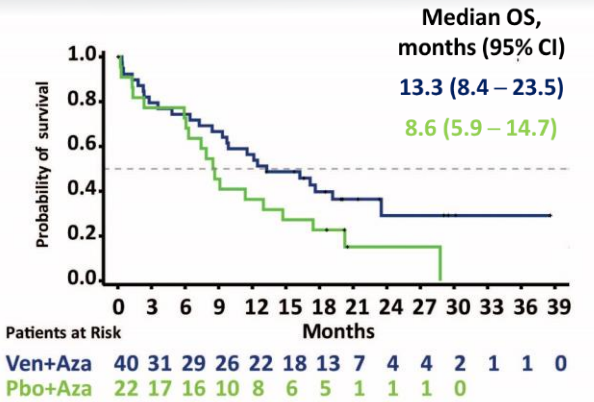
Figure 8. Overall survival (Aug 2020 cutoff)



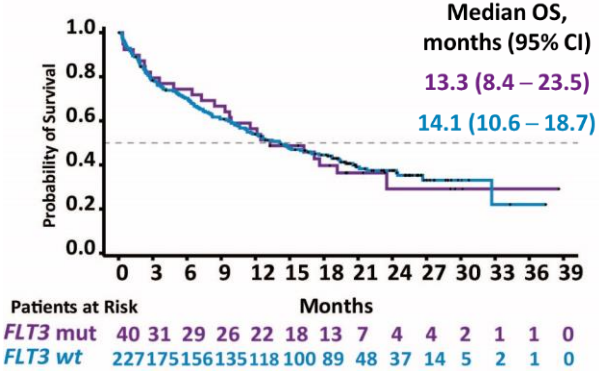
Dinardo C et al 2021 EHA Abstract EP465

Outcomes of Ven + Aza in FLT3 mut AML (Post hoc)

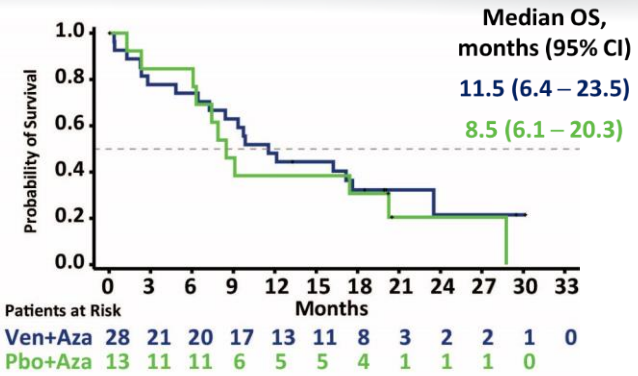
A. FLT3mut



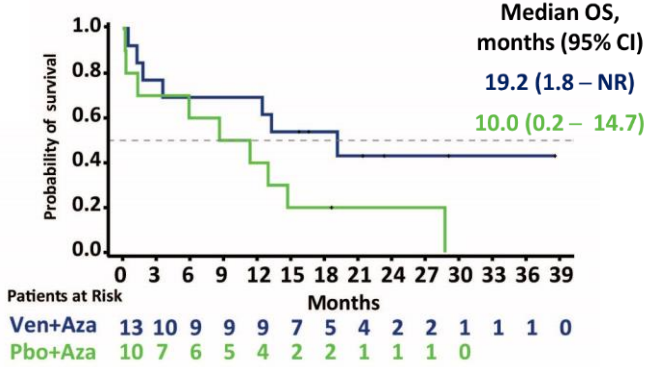
B. FLT3mut vs. wt in Ven+Aza



C. FLT3-ITD



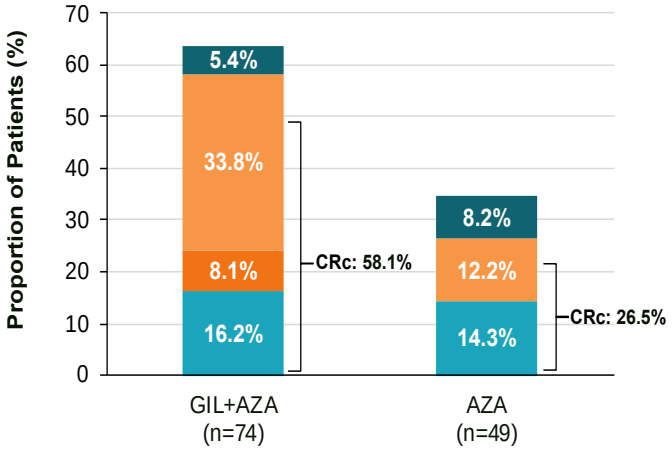
D. FLT3-TKD



Konopleva M et al, ASH 2020 abst #1904

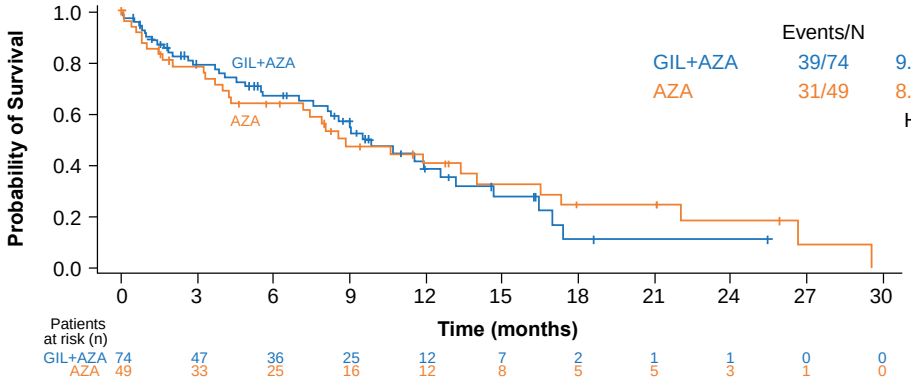
Outcomes of Gilt+Aza vs Aza (phase 3 LACEWING)

Response rate



Overall survival

- Median follow-up[a] was 9.76 months for GIL+AZA and 17.97 months for AZA

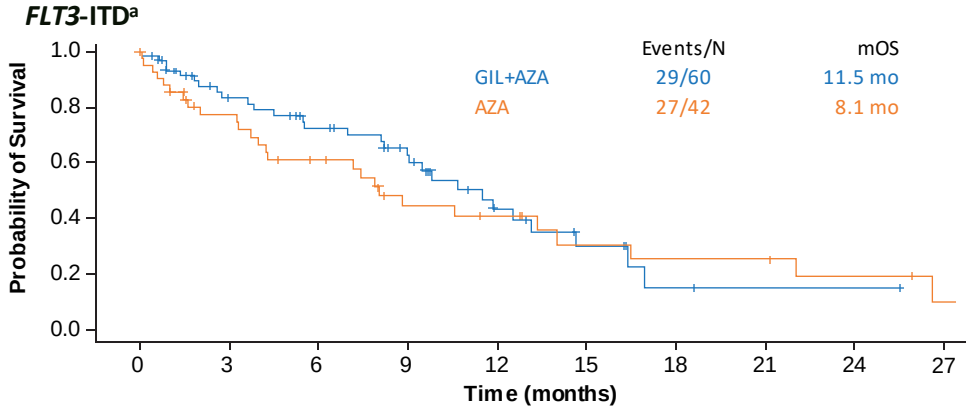


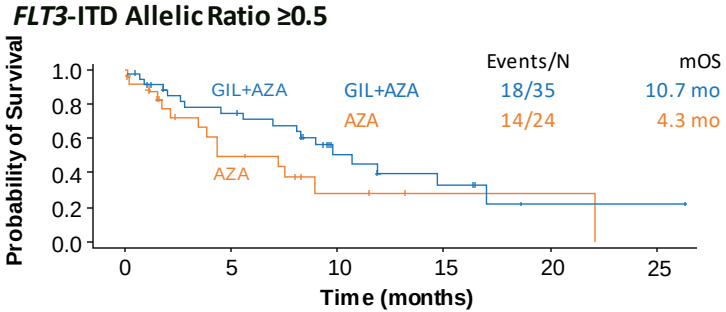
The intention-to-treat population included all randomized patients.
[a]Based on reverse Kaplan-Meier estimates.
Abbreviations: AZA, azacitidine; CI, confidence interval; GIL+AZA, gilteritinib plus azacitidine; HR, hazard ratio.

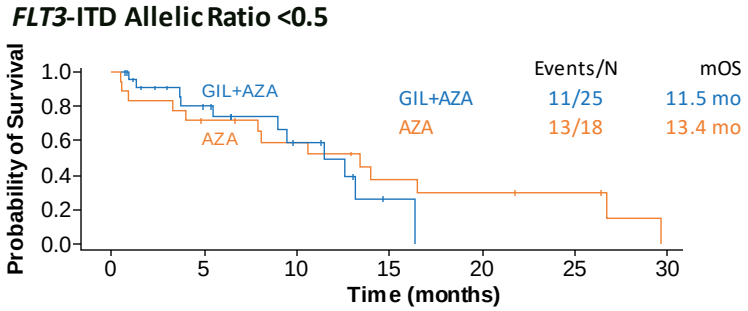
Overall and grade ≥3 adverse event rates were similar in both arms

Wang ES et al ASH 2021 abstract #700

Trend to improved OS with Gilt+Aza in FLT3 mutant AML





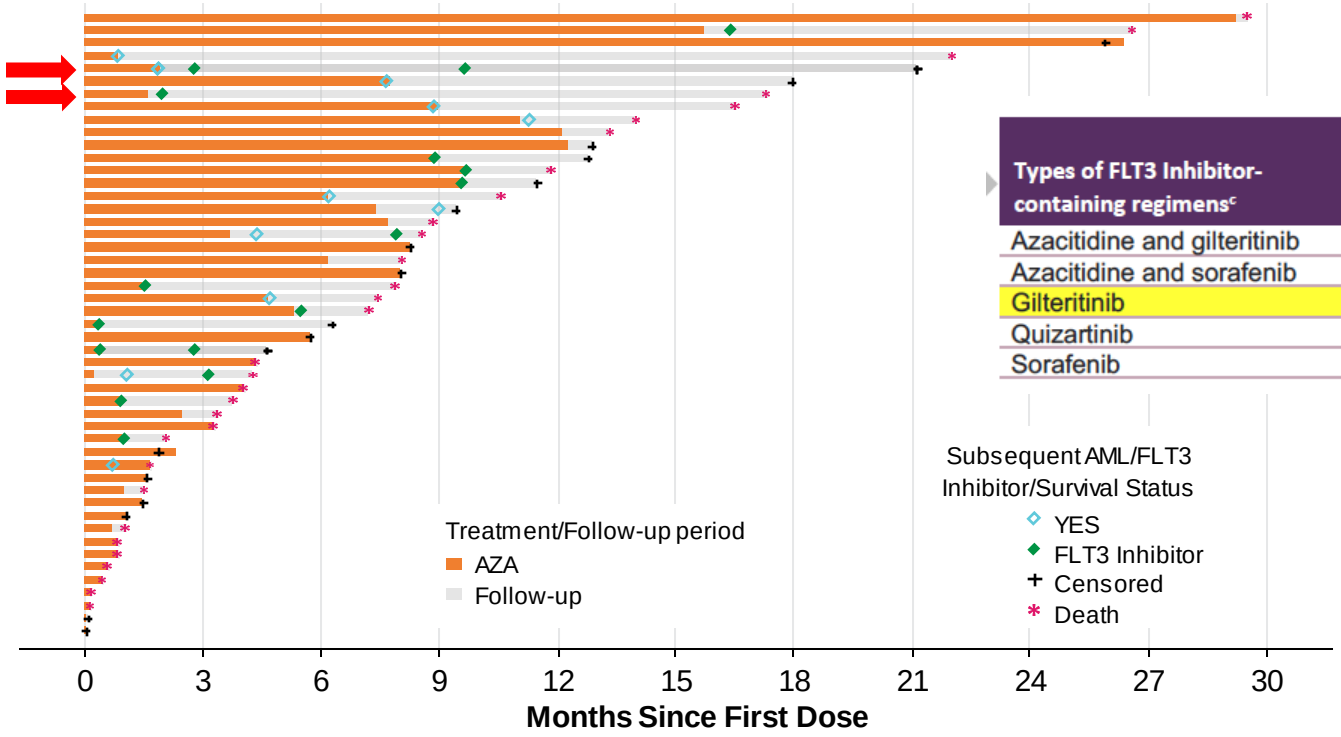


[a]Includes patients ITD alone and ITD with TKD mutations.

Abbreviations: AZA, azacitidine; CI, confidence interval; *FLT3*, FMS-like tyrosine kinase 3; GIL+AZA, gilteritinib plus azacitidine; HR, hazard ratio; ITD, internal tandem duplication; mOS, median overall survival; TKD, tyrosine kinase domain.

Wang ES et al ASH 2021 abstract #700

Subsequent AML therapy in Aza only arm

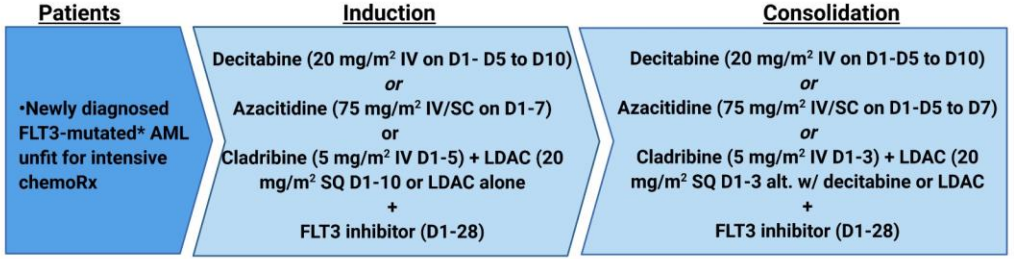


Types of FLT3 Inhibitor-containing regimens[c]	GIL+AZA (n=3) n[b] (%)	AZA (n=14) n[b] (%)
Azacitidine and gilteritinib	1 (33.3)	0
Azacitidine and sorafenib	0	1 (7.1)
Gilteritinib	2 (66.7)	10 (71.4)
Quizartinib	0	2 (14.2)
Sorafenib	0	3 (21.4)

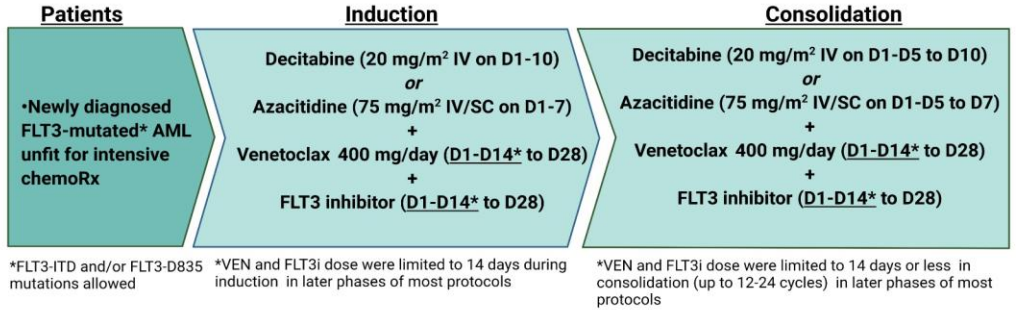
Wang ES et al ASH 2021 abstract #700

Regimens for older/unfit FLT3 mutant AML

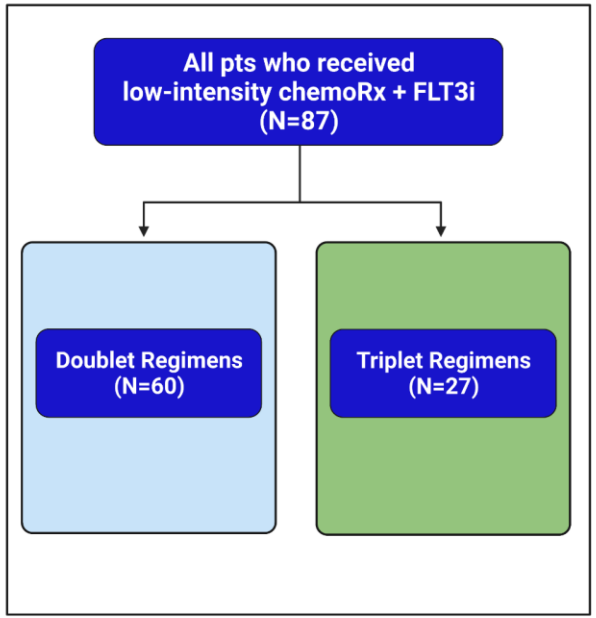
Doublets – Low-Intensity ChemoRx + FLT3 Inhibitors

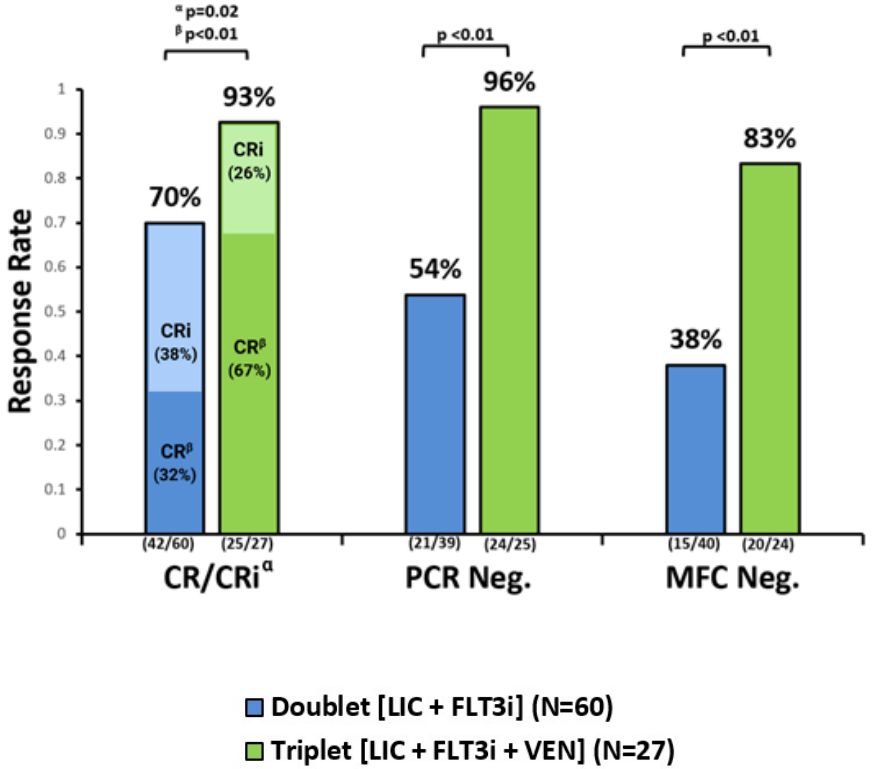


Triplets – Low-intensity ChemoRx + Venetoclax + FLT3 Inhibitors



Doublet vs Triplet therapy in Newly Dx FLT3 mutant AML

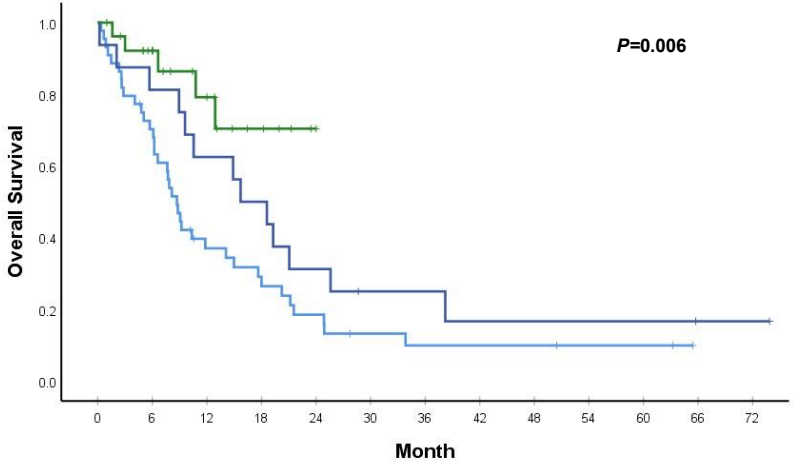




Yilmaz et al ASH 2021

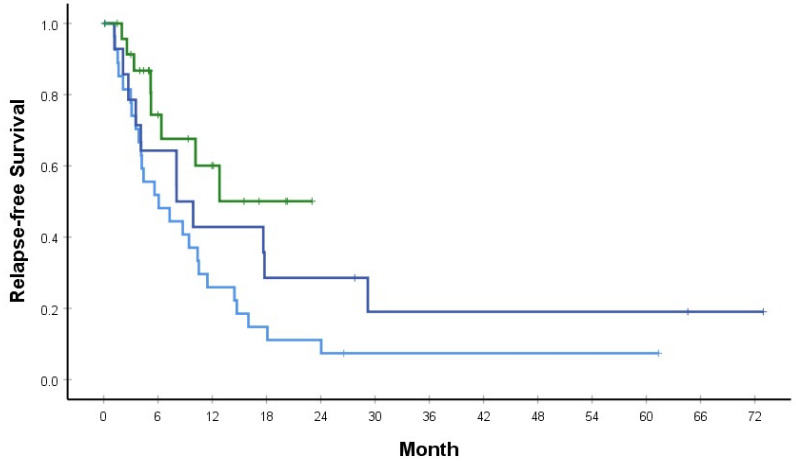
Doublet vs Triplet therapy in Newly Dx FLT3 mutant AML

Overall survival



Treatment Regimen	N=87	Median Follow-up	Median OS
Triplet (LIC + FLT3i + VEN)	27	12m	NR
Doublet (LIC + 2nd gen. FLT3i)	16	65m	15.7m
Doublet (LIC + 1st gen. FLT3i)	44	50m	8.7m

Relapse-free survival

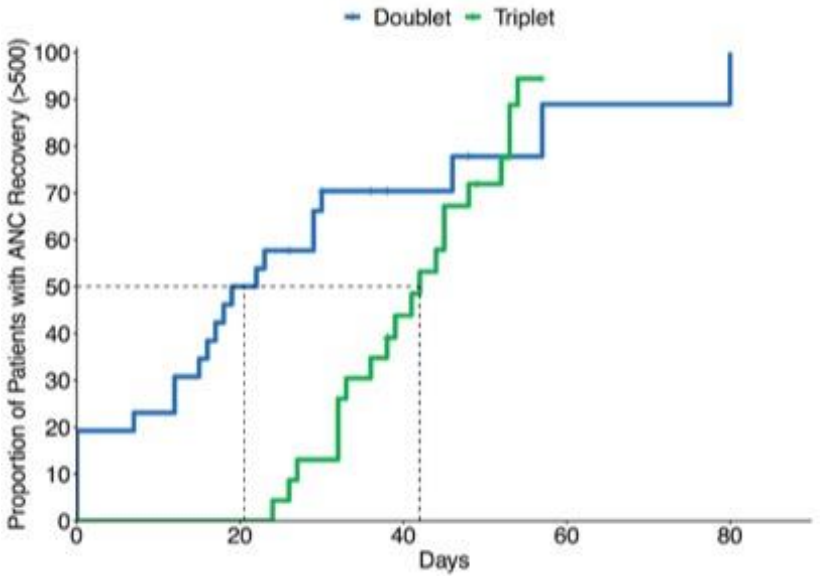


Treatment Regimen	N=67	Median RFS
Triplet (LIC + FLT3i + VEN)	25	NR
Doublet (LIC + 2nd gen. FLT3i)	14	8 m
Doublet (LIC + 1st gen. FLT3i)	28	6 m

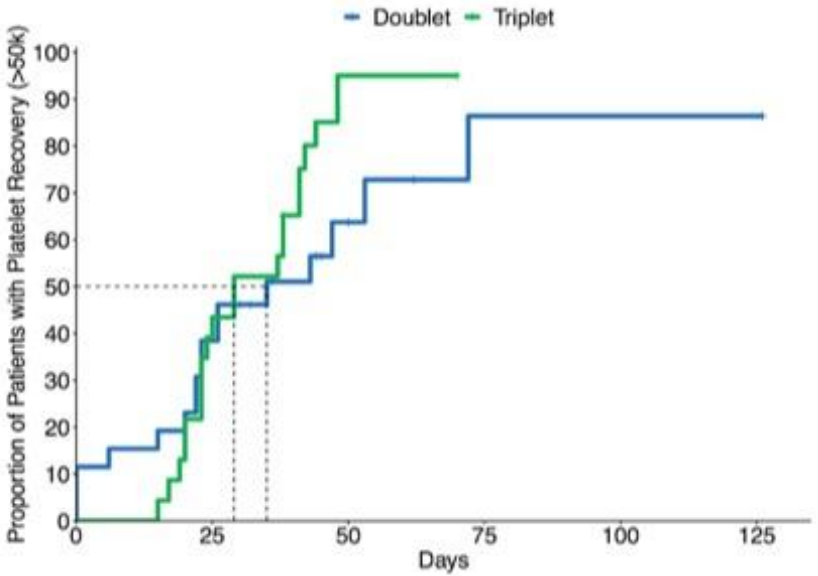
Yilmaz et al ASH 2021

Doublet vs Triplet therapy in Newly Dx FLT3 mutant AML

ANC >500



Platelets >50K



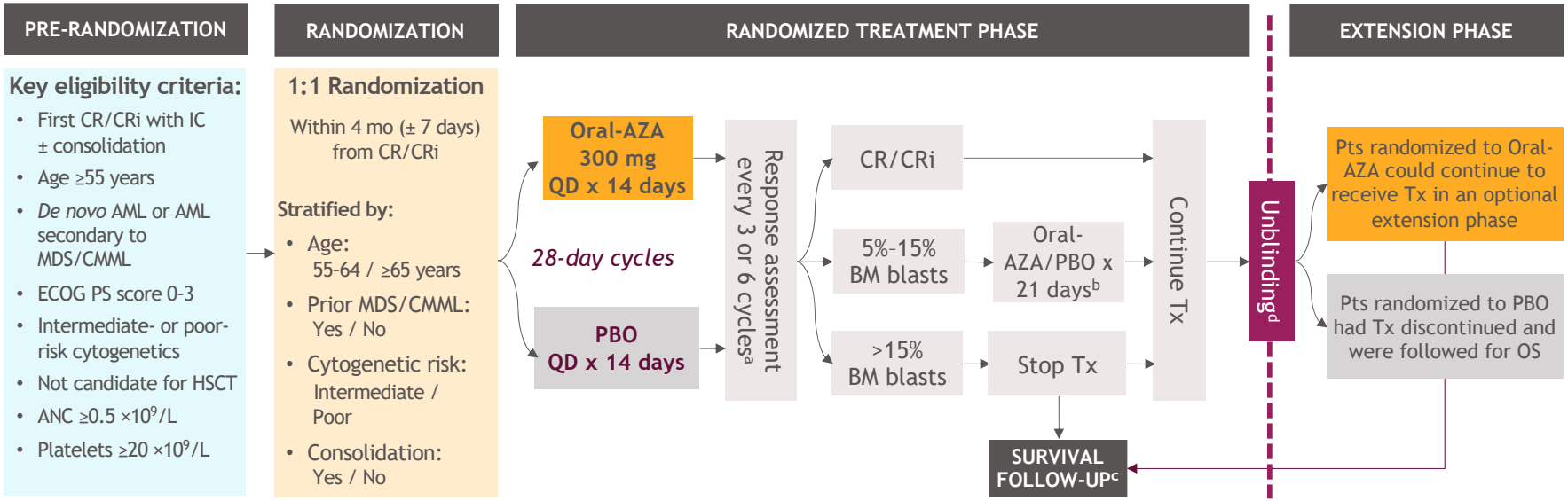
ANC, absolute neutrophil count (per mm^3), Platelet (per microliter)

ANC recovery: doublet median 21 days (95% CI: 15 – NE days); triplet median 42 days (95% CI: 36 – 53 days). P=0.075. Platelet recovery: doublet median 35 days (95% CI: 23 – NE days); triplet median 29 days (95% CI: 23 – 42 days). P=0.20.

Yilmaz et al ASH 2021

Phase 3 : Oral azacitidine vs placebo following IC

International, multicenter, PBO-controlled, double-blind, randomized, phase 3 trial

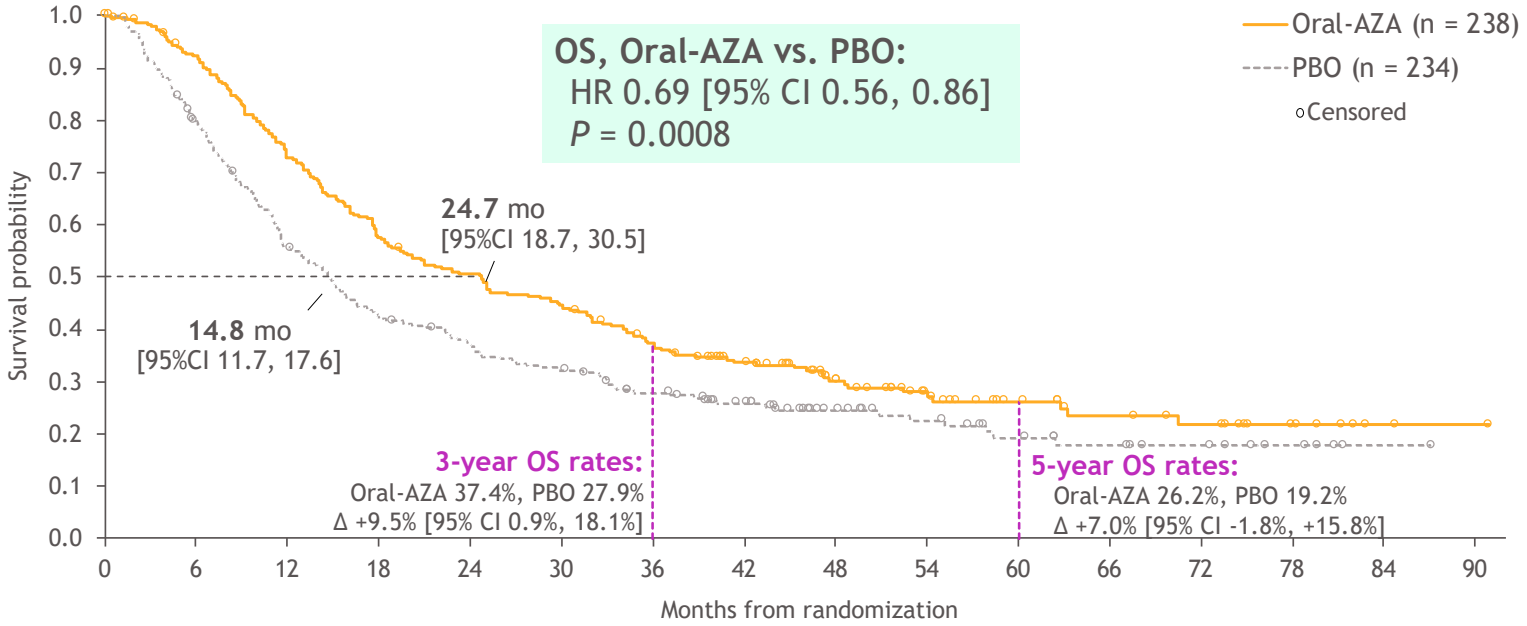


Wei AH, et al. ASH 2021. Abstract 871.

Long-term follow-up of Oral Azacitidine

Updated OS at Sep 2020 Data Cutoff

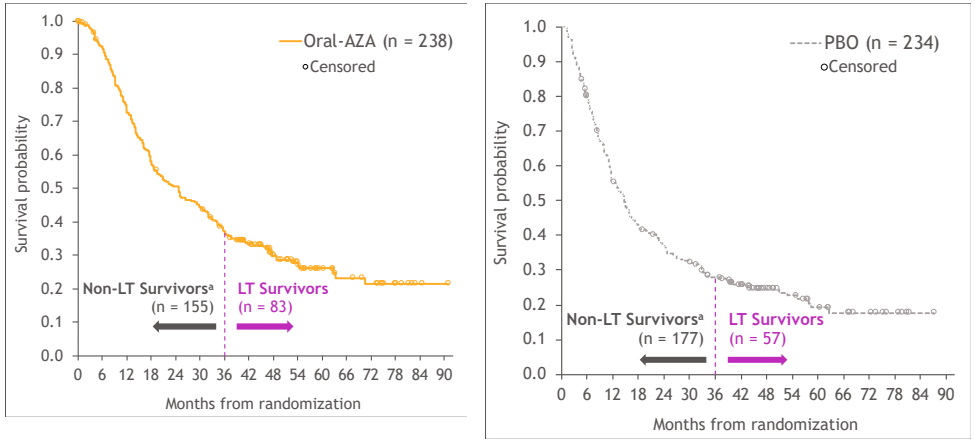
Median follow-up: 51.7 mo



Wei AH, et al. ASH 2021. Abstract 871.

Predictors of long-term survival following oral Azacitidine

OS for LT vs Non-LT Survivors With Oral Aza and Placebo

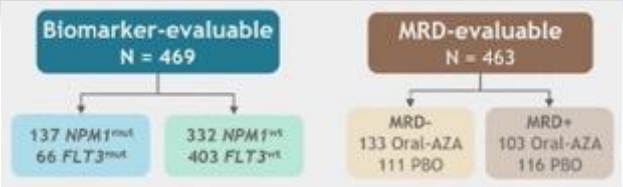


Patient Characteristics by LT Survivor Status	Oral Aza (n=238)		Placebo (n=234)	
	LT (n=83)	Non-LT (n=155)	LT (n=57)	Non-LT (n=177)
Median age (range), years	67 (55-80)	69 (55-86)	67 (55-79)	69 (55-82)
Intermed cytogenetic risk, %	94	81	96	84
NPM1 mut, %	45	19	46	26
CR/CRi after induction, %	80/20	78/22	84/16	84/16
Received consolidation, %	77	79	88	80
MRD+ at randomization, %	35 (n=29)	48 (n=74)	30 (n=17)	56 (n=99)
Became MRD-on-study, %	76 (22/29)	22 (16/74)	71 (12/17)	10 (10/99)
MRD response,[a] %	37 (38/103)		19 (22/116)	

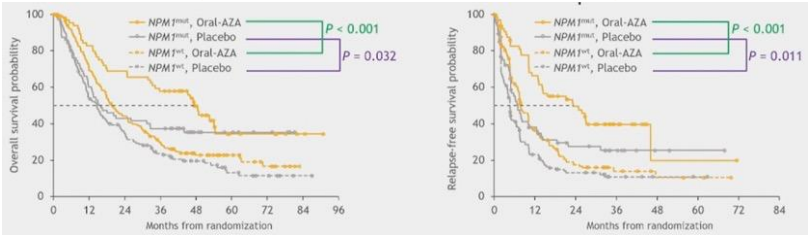
- LT Survivors: patients alive in survival follow-up ≥3 years from randomization
- Non-LT Survivors: patients who died or were censored for OS before 3 years

Wei AH, et al. ASH 2021. Abstract 871.

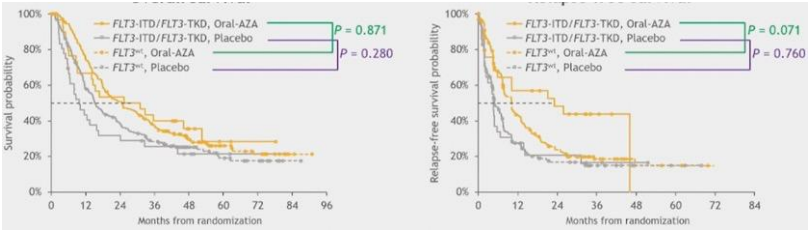
Outcomes of Oral Aza by mutational and MRD status



OS and RFS by *NPM1* Mutation Status at Diagnosis



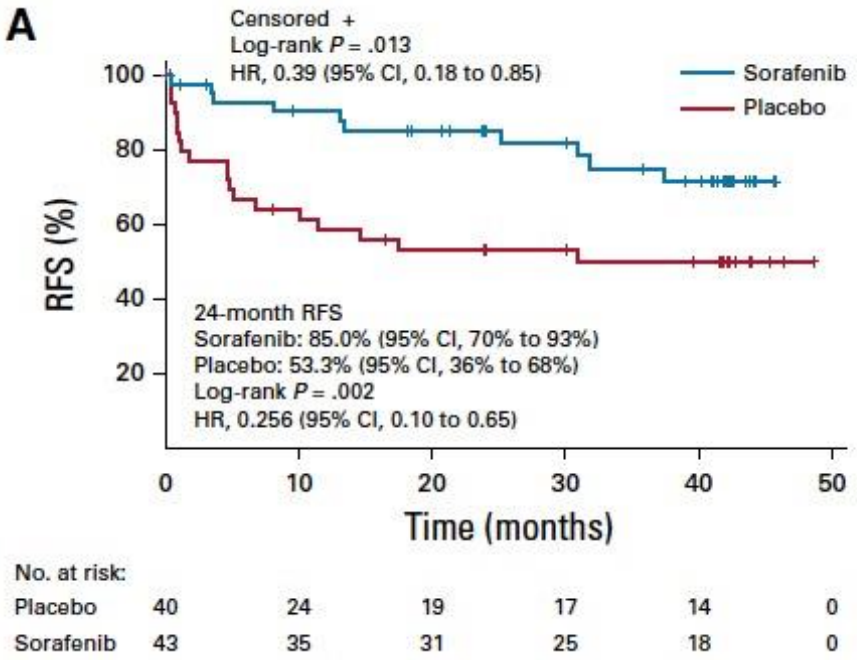
OS and RFS by *FLT3* Mutation Status at Diagnosis

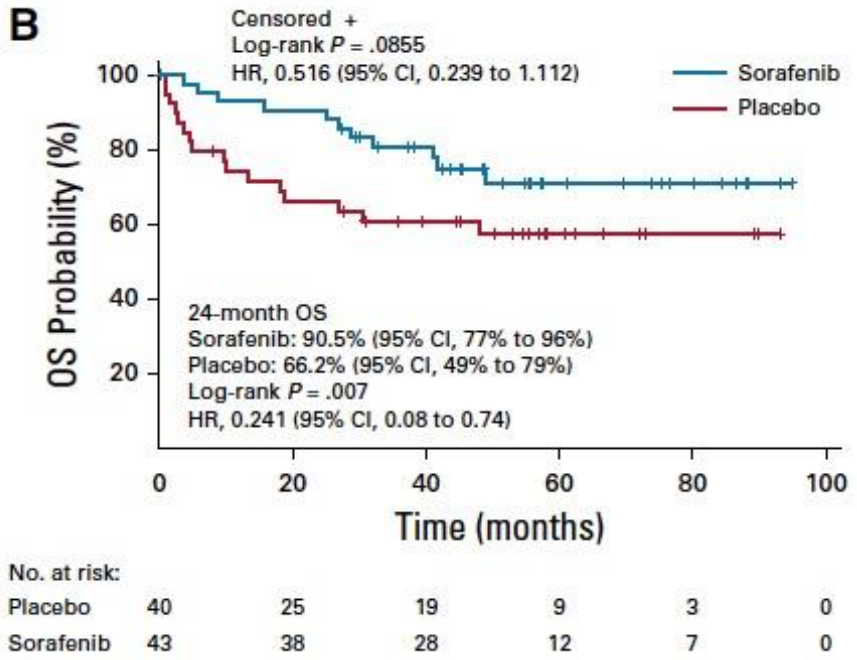


OS via Multivariate Analysis	HR [Exp[coef.)]	*P* Value
Oral Aza vs Placebo	0.78	=0.028
*NPM1*mut vs *NPM1*wt	0.62	=0.002
*FLT3*mut (ITD/TKD) vs. *FLT3*wt	1.48	=0.032
Poor vs intermediate cytogenetic risk	2.01	<0.001
MRD+ vs MRD- at BL (post-IC)	1.65	<0.001
RFS via Multivariate Analysis		
Oral Aza vs Placebo	0.65	<0.001
*NPM1*mut vs *NPM1*wt	0.60	<0.001
*FLT3*mut (ITD/TKD) vs. *FLT3*wt	1.06	=0.737
Poor vs intermediate cytogenetic risk	1.82	<0.001
MRD+ vs MRD- at BL (post-IC)	1.94	<0.001

Wei AH, et al. ASH 2021. Abstract 871.
Dohner H, et al. ASH 2021. Abstract 804.

Sorafenib maintenance for FLT3 mut AML after transplant

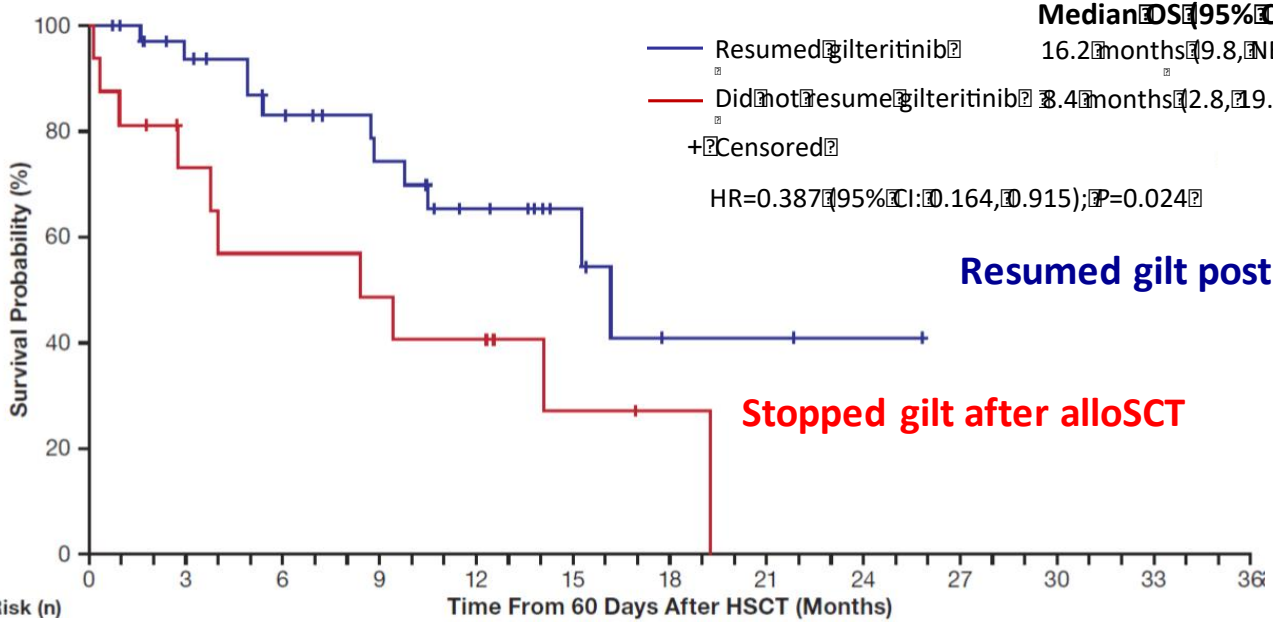




Burchert A et al J Clin Oncol 38(26): 2993, 2020

Gilteritinib maintenance after transplant for RR-AML

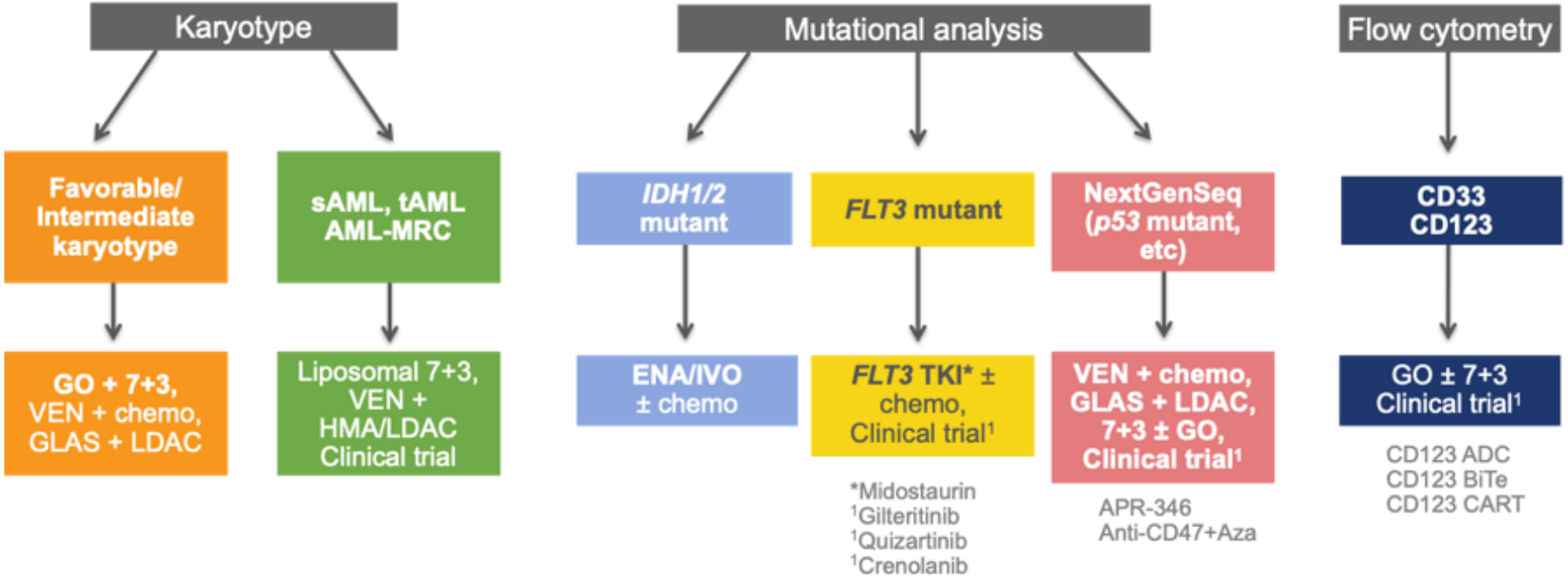
Landmark Analysis Day 60 Post-HSCT (n=51)



Two-sided P-values were determined according to the log-rank test; the Kaplan-Meier method in combination with the Greenwood formula were used to determine overall survival and corresponding 95% confidence intervals.
Abbreviations: CI, confidence interval; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ITT, intention-to-treat; NE, not estimable; OS, overall survival.

Perl A et al NEJM 2019

Choice of AML therapy based on biology



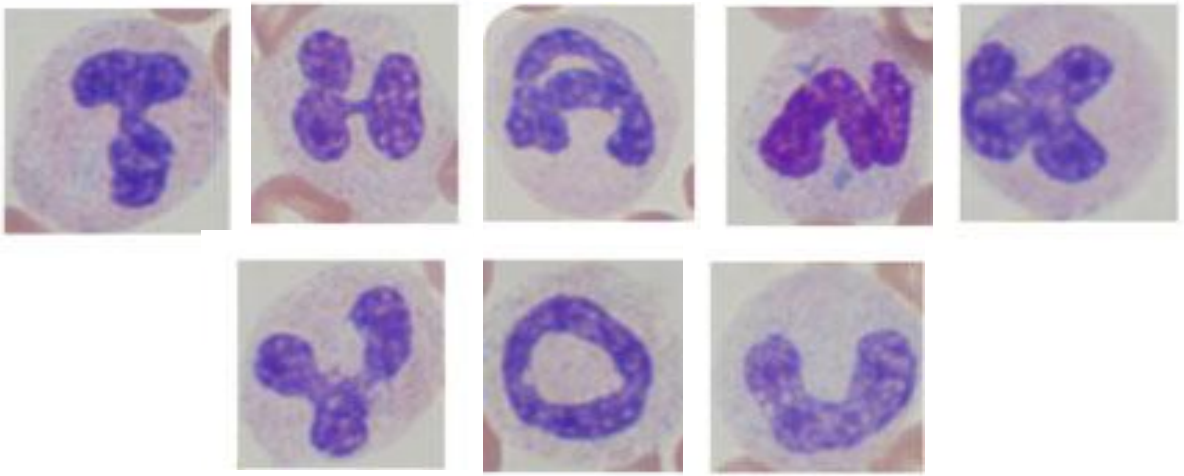
Summary: Personalized therapy for AML

1. 7+3 backbone + another agent
    1. Favorable/intermediate risk: GO plus 7+3
    2. FLT3 mutant AML: FLT3 inhibitor plus 7+3

2. Older and/or unfit AML
    1. Mutation agnostic, p53 wildtype: Ven/Aza
    2. FLT3 mutant: Ven/Aza, Gilt/Aza, Ven/Gilt, triplet therapy
    3. IDH1/2 mutant: Ven/Aza, IDH inhibitor + Aza +/- Ven
    4. P53 mutant: Clinical trial = first choice

3. Secondary/therapy-related AML: CPX-351 vs Ven/Aza
4. Adverse cytogenetics: Ven/Aza (p53 wildtype)
5. Maintenance therapy: Oral aza, FLT3 inhibitors

Questions?



Email: Eunice.wang@roswellpark.org

ROSWELL PARK
COMPREHENSIVE CANCER CENTER

Global Leukemia Academy

Optimizing management of relapsed/refractory AML

Naval Daver

APTITUDE HEALTH

Optimizing the Management of Relapsed/Refractory AML: 2022

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

Options for R/R AML With *IDH* Mutations

NCCN Recommendations, 2021

Targeted therapy

- Therapy for AML with *FLT3*-ITD mutation
  - Gilteritinib (category 1)
  - Hypomethylating agents (azacitidine or decitabine) + sorafenib
- Therapy for AML with *FLT3*-TKD mutation
  - Gilteritinib (category 1)
- Therapy for AML with *IDH2* mutation
  - Enasidenib
- Therapy for AML with *IDH1* mutation
  - Ivosidenib
- Therapy for *CD33*-positive AML
  - Gemtuzumab ozogamicin

Aggressive therapy for appropriate patients

- Cladribine + cytarabine + G-CSF ± mitoxantrone or idarubicin
- HiDAC (if not received previously in treatment ± idarubicin or daunorubicin or mitoxantrone)
- Fludarabine + cytarabine + G-CSF ± idarubicin
- Etoposide + cytarabine ± mitoxantrone
- Clofarabine ± cytarabine ± idarubicin

Less-aggressive therapy

- Hypomethylating agents (azacitidine or decitabine)
- LDAC (category 2B)
- Venetoclax + HMA/LDAC

Clinical trials are always recommended as an option

NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.

Clinical Applications of Molecular Studies in AML

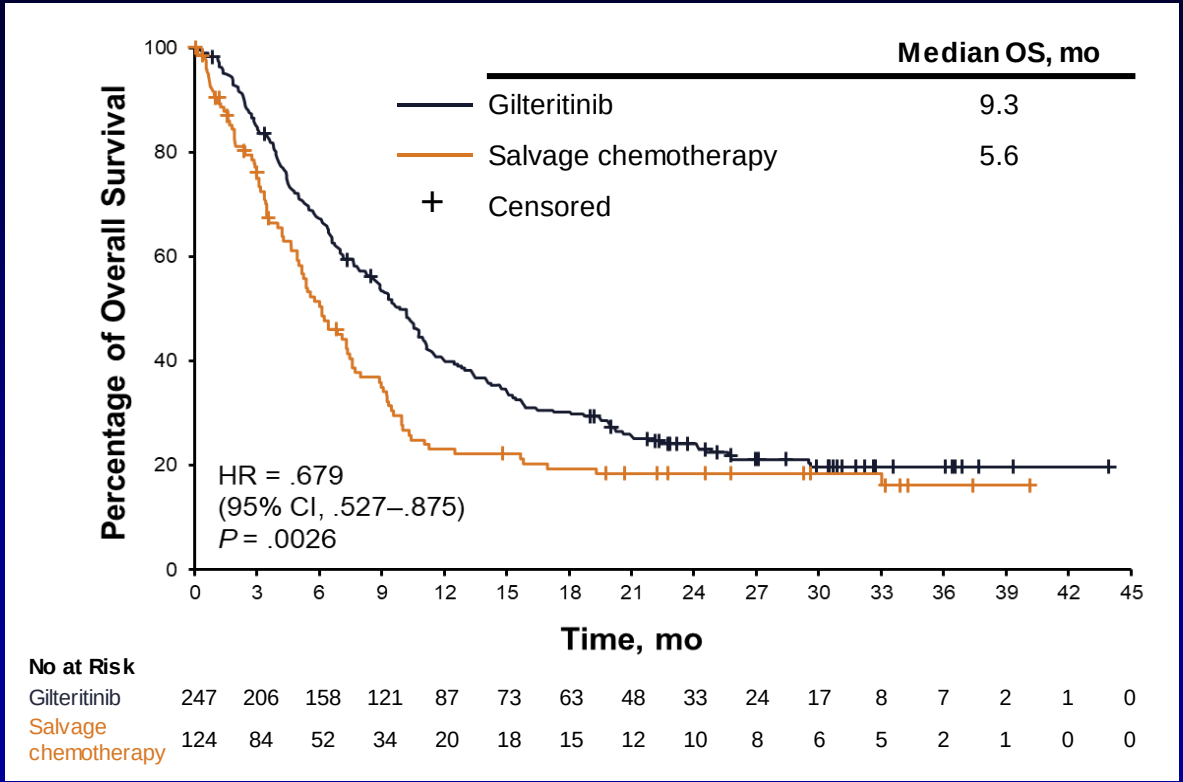
- ***FLT3-ITD* mutations – Add FLT3 inhibitor (gilteritinib, midostaurin, sorafenib), consider allo-SCT and post-SCT FLT3i**
- ***IDH1-2* mutations – Add IDH inhibitor: enasidenib (AG-221/IDH2 inhibitor), ivosidenib (AG-120/IDH1 inhibitor)**
- ***NPM1* mutation in diploid CG – ara-C sensitivity**
- ***TP53* mutation – Consider decitabine 10 days ± others (GO, venetoclax); refer to allo-SCT; role of CD47 Ab (magrolimab)**
- **MLL-AML; t (11q23;---) – Menin inhibitors**

NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 2.2018.

1. *FLT3*-mutated AML – ADMIRAL: Longer Follow-Up Continues to Show OS Benefit With Gilteritinib in R/R *FLT3*-Mutated AML

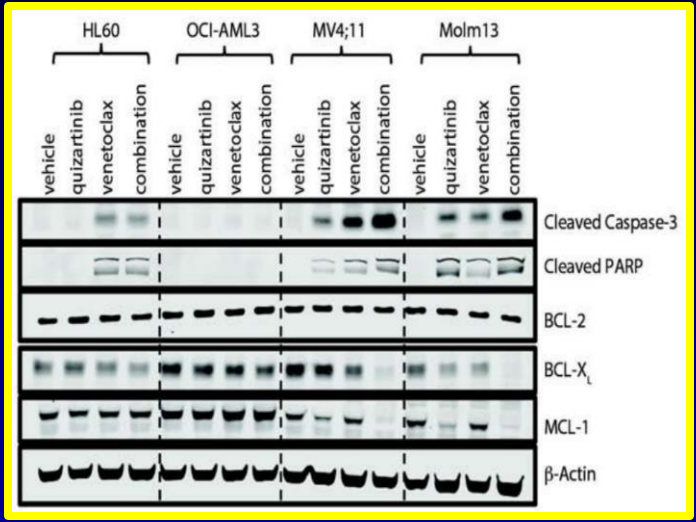
Median duration of follow-up: 29.2 mo

- **Continued prolonged median OS with gilteritinib vs salvage chemotherapy**
- **Long-term survivors typically remained in remission, frequently proceeded to HCT, and received post-HCT gilteritinib**

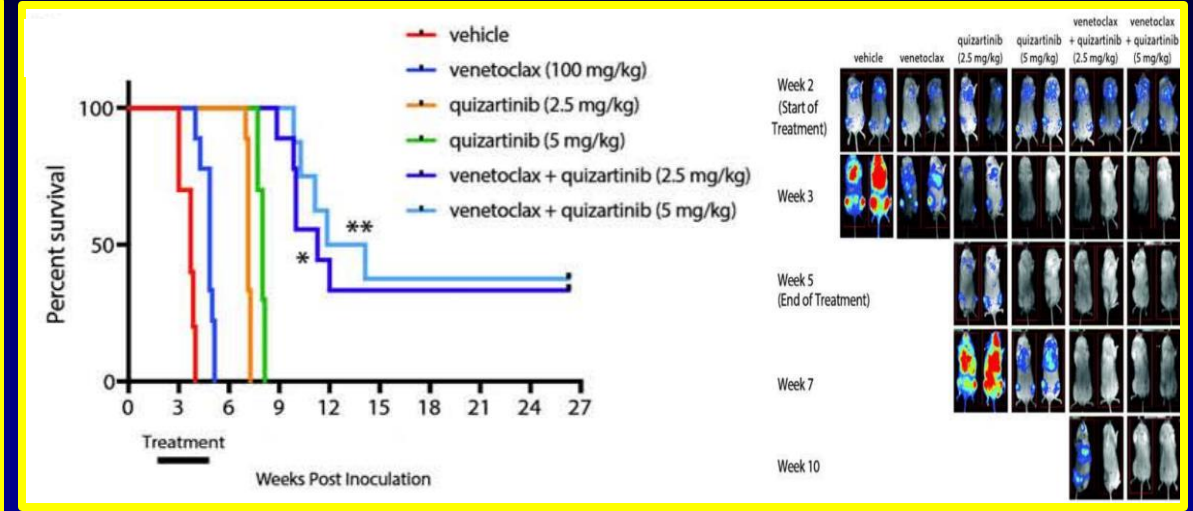


Perl A, et al. EHA 2021. Abstract EP543.

Venetoclax Combines Synergistically With Quizartinib



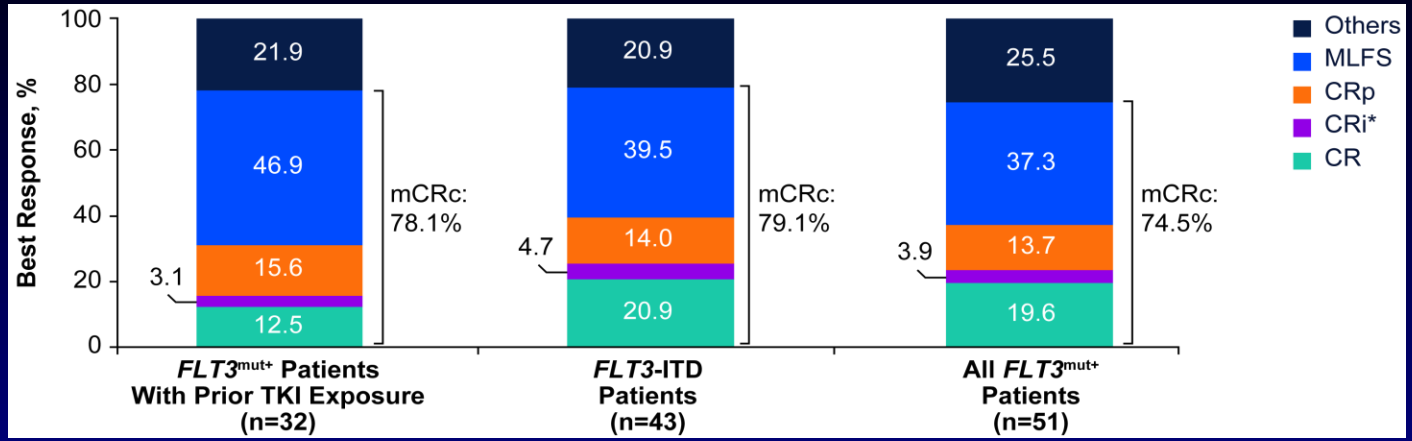
Cell lines were treated with combination – ↓ MCL-1, ↓ BCL-X_L



Venetoclax combined with quizartinib prolonged survival and reduced tumor burden in *FLT3*-ITD+ xenograft models

Mali RS, et al. *Haematologica*. 2021;106. doi:10.3324/haematol.2019.244020

Summary of Best Responses



	FLT3^{mut+} Patients With Prior TKI Exposure (n = 32)	*FLT3*-ITD Patients (n = 43)	All *FLT3*$^{mut+}$ Patients (n = 51)
mCRc[a], n (%)	25 (78.1)	34 (79.1)	38 (74.5)
CR+CRp+CRi*[b]	10 (31.3)	17 (39.5)	19 (37.3)
MLFS	15 (46.9)	17 (39.5)	19 (37.3)

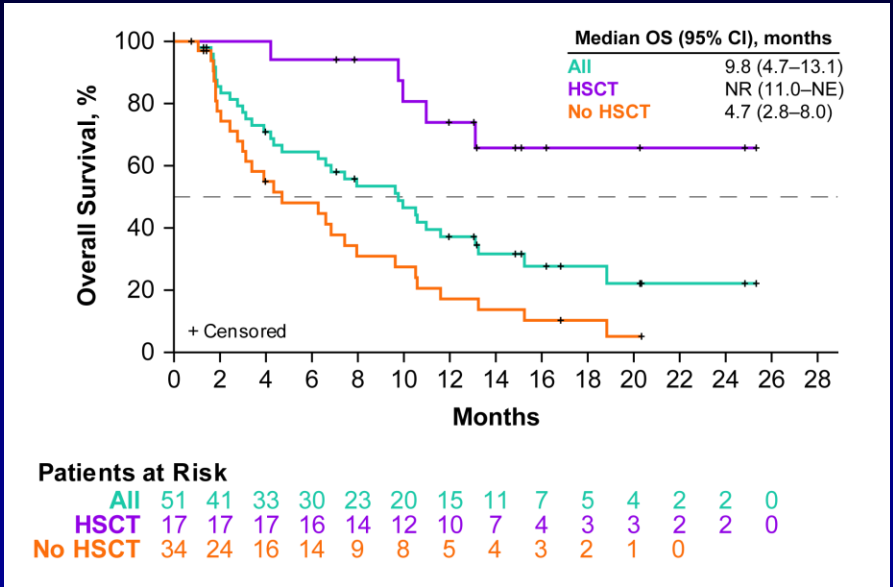
The mCRc rate in this study was **74.5**%. The CRc rate in the ADMIRAL phase III study for single-agent Gilt was 54.3% (using the same response parameters).

[a]mCRc defined as CR+CRp+CRi*+MLFS, per modified IWG response criteria. [b]Hematology criteria for CRi* is ANC ≤1×10^9/L and platelet >100×10^9/L, which is mutually exclusive with IWG response CRp. CR, complete remission; CRi*, complete remission with incomplete neutrophil count recovery; CRp, complete remission with incomplete platelet recovery; ITD, internal tandem duplication; IWG, International Working Group; mCRc, modified composite complete remission; MLFS, morphologic leukemia-free state; TKI, tyrosine kinase inhibitor.

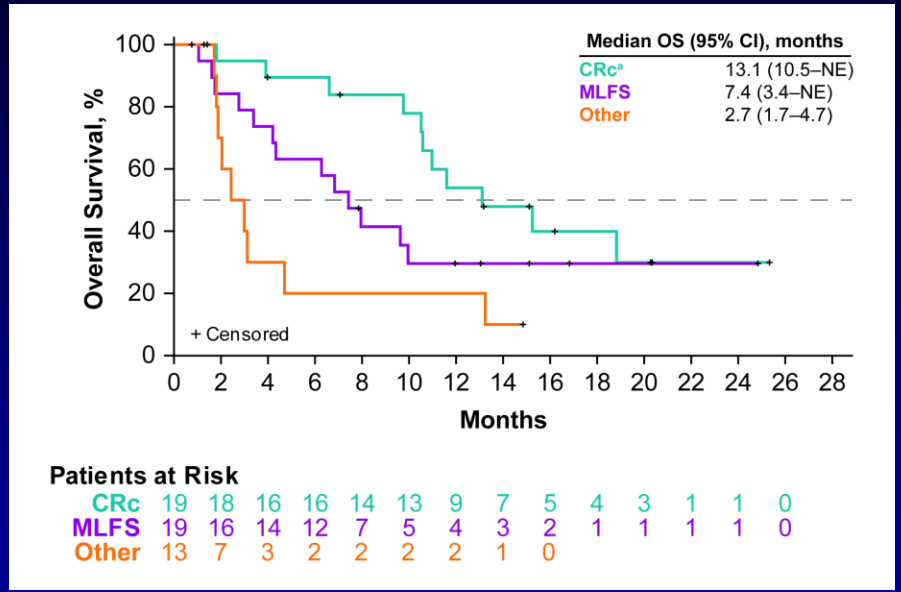
Perl A, et al. *N Engl J Med*. 2019;381:1728-1740.

OS by Transplant or Response Status

OS by Transplant Status (*FLT3*$^{mut+}$ Patients)



OS by Best Response Status (*FLT3*$^{mut+}$ Patients)



- Median duration of follow-up was 15.1 months (range, .8–25.3)
- Median OS for *FLT3*-ITD patients was 10.0 months (95% CI, 6.6–13.2)

[a]CRc defined as CR+CRp+CRi*.

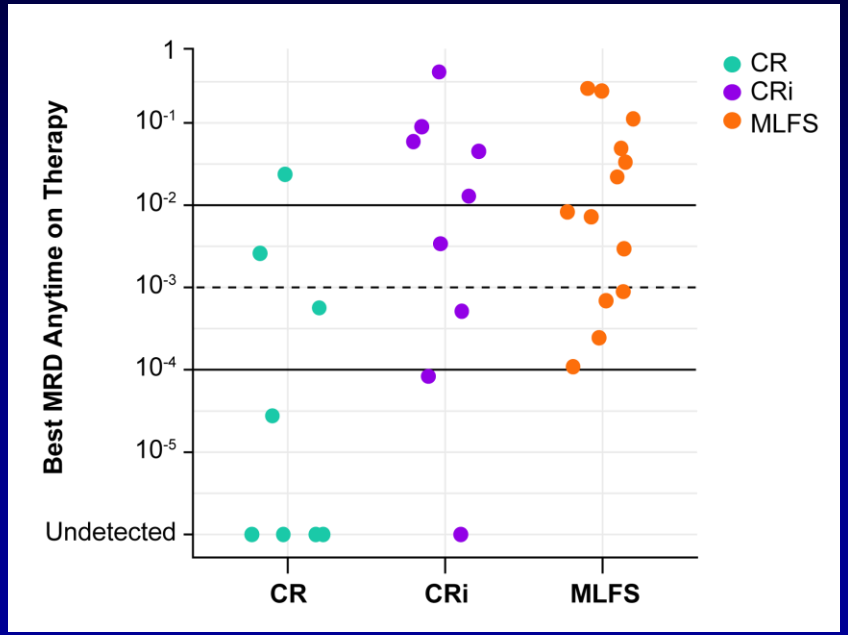
CR, complete remission; CRc, composite complete remission; CRi*, complete remission with incomplete neutrophil count recovery; CRp, complete remission with incomplete platelet recovery; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; MLFS, morphologic leukemia-free state; NE, not estimable; NR, not reached; OS, overall survival.

Ven + Gilt Demonstrated Deep Reductions in *FLT3* Allelic Burden in Patients Achieving mCRc

FLT3-ITD burden, n (%)	<10^{-2} (1%)	<10^{-3}	<10^{-4}
Cycle 1, Day 28	9 (30.0)	3 (10)	0
Any time on therapy	18 (60.0)*	13 (43.3)	7 (23.3)

**The molecular best response (<10^{-2}) of Ven + Gilt was 60.0% in FLT3-ITD patients achieving mCRc*
The molecular best response (<10^{-2}) for Gilt alone in a subset analysis from CHRYSALIS was 25%

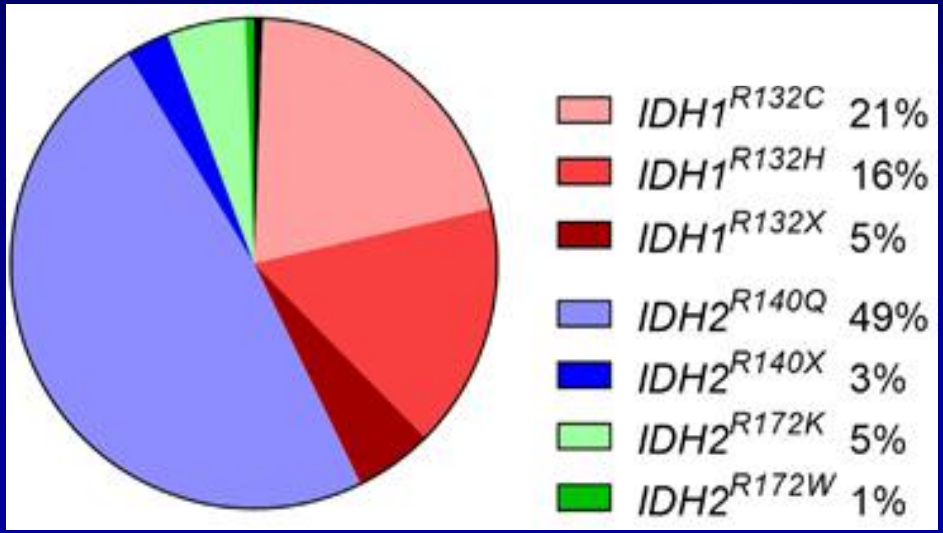
- **30/34 *FLT3*-ITD mCRc patients were evaluable for longitudinal reduction in *FLT3*-ITD using an assay with sensitivity of 10^{-6}**



Gilt, gilteritinib; ITD, internal tandem duplication; mCRc, modified composite complete remission; RP2D, recommended Phase 2 dose; Ven, venetoclax.
Levis MJ, et al. *Blood Adv.* 2018;2(8):825–31.

2. IDH Inhibitors in R/R and Newly Diagnosed AML
Characteristics of mIDH AML

- *IDH* mutations occur in ~20% of AML
  - *IDH1* in ~8% AML, *IDH2* in ~12% AML
  - ↑ prevalence with ↑ patient age
- Hot-spot mutations in enzymatic active site
  - *IDH1*-R132, *IDH2*-R140, or *IDH2*-R172
- Can be acquired at progression
  - ~10%–15% of AML from MDS
  - ~20%–25% of AML from MPN

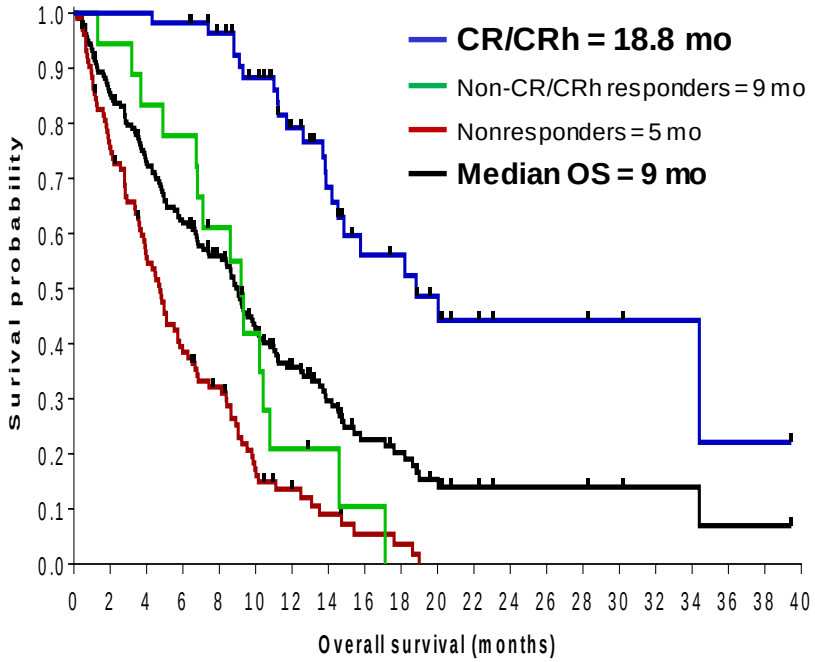


Dang L, et al. *Trends Mol Med*. 2010;16(9):387-397; Chou WC, et al. *Leukemia*. 2011;25(2):246-253; Molenaar RJ, et al. *Leukemia*. 2015;29(11):2134-2142.

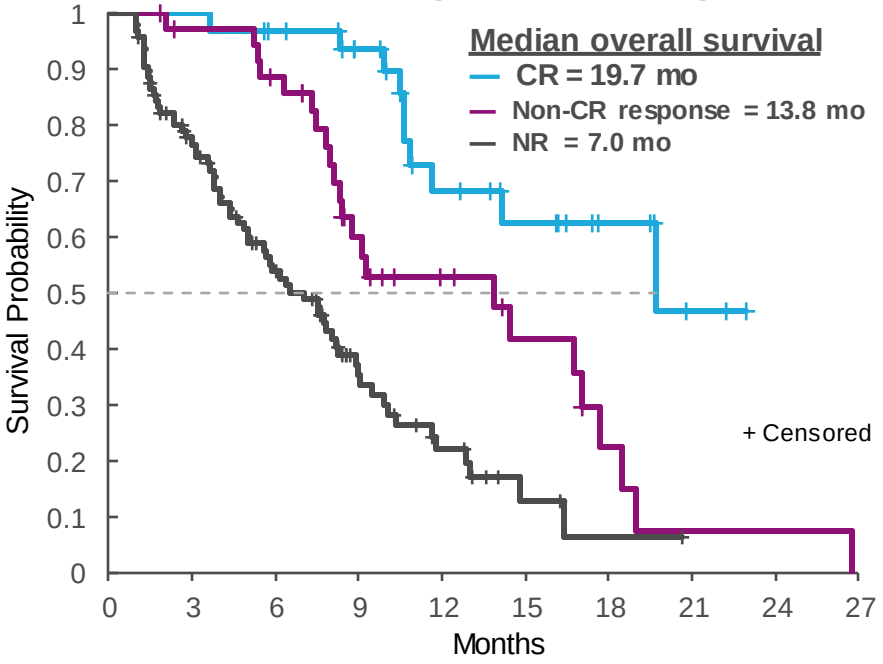
IDH1 or IDH2 Inhibitor Monotherapy

CR rate ~20%
CR/CRh rate ~30%
ORR ~40%

Ivosidenib (IDH1 inhibitor)[1]



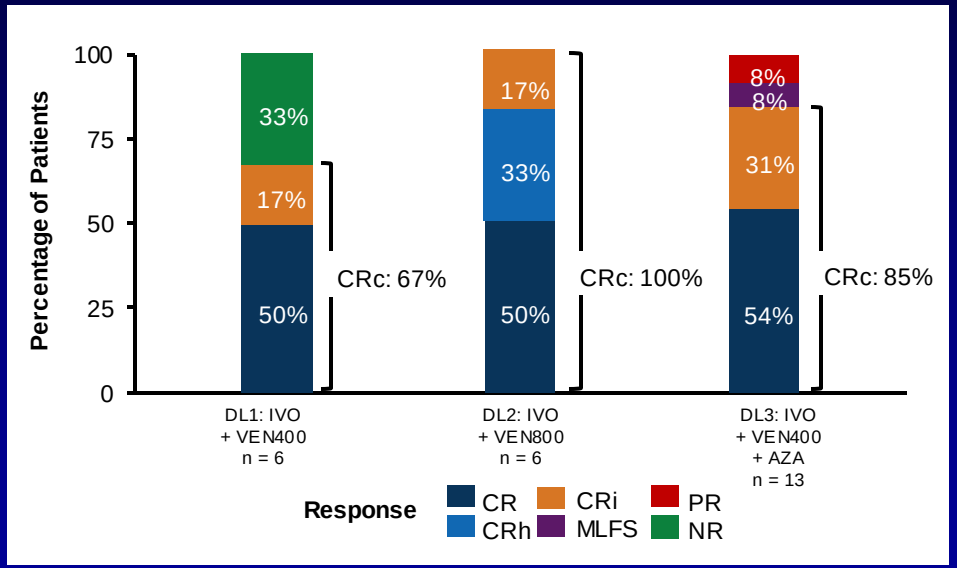
Enasidenib (IDH2 inhibitor)[2]

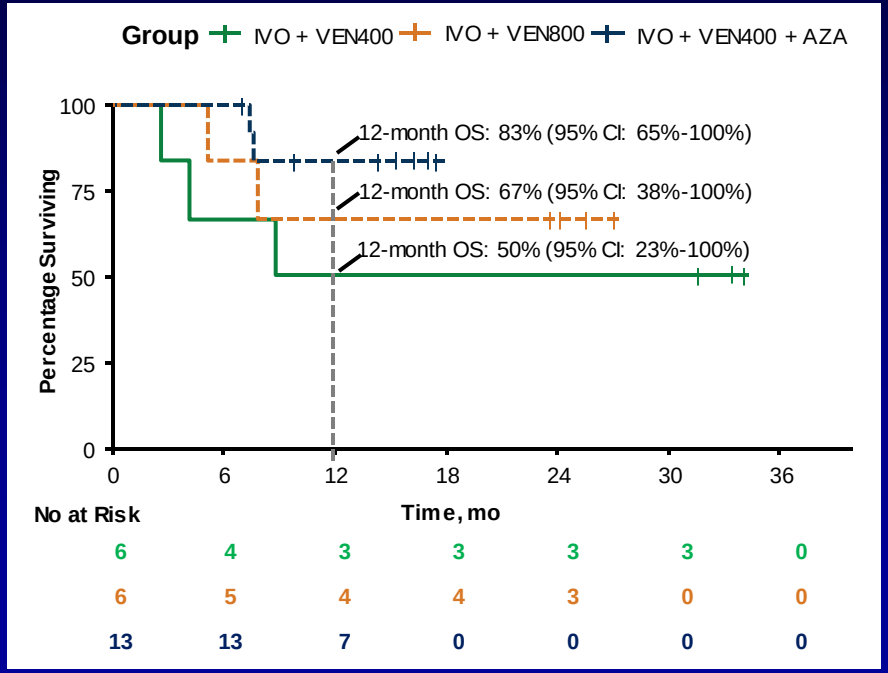


1. DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398; 2. Stein EM, et al. *Blood*. 2017;130(6):722-731.

A Role for Doublet and Triplet Therapy in *IDH1*-Mutant AML? Ivosidenib and Venetoclax ± AZA

- N = 25 patients with newly diagnosed AML, R/R AML, or MDS/MPN
- IVO + VEN ± AZA is active against *IDH1*-mutated myeloid malignancies, with an acceptable and expected toxicity profile and high rates of MRD-negative CRc in AML





Lachowiez C et al. ASCO 2021. Abstract 7012.

3. MLL and *NPM1*-Mutated AML: SNDX-5613 Is a Potent, Selective Protein–Protein Interaction Inhibitor of Menin

Currently being evaluated in the phase I/II AUGMENT-101 study (N = 54)

Median age was 49 years

- 82% (n = 44) of patients had AML
- 65% (n = 35) had MLLr leukemia
- 19% (n = 10) had mutated *NPM1* leukemia

Two parallel dose-escalation cohorts

- Arm A: patients not taking strong CYP3A4 inhibitors
- Arm B: patients taking strong CYP3A4 inhibitors
- SYNDX-5613 dosing: orally Q12h in continuous 28-day cycles

MTD was 276 mg Q12h in arm A and 163 mg Q12h in arm B

Best Overall Response	Overall (N = 54), n (%)
CRc (CR + CRh + CRp + CRi/MLFS)	20 (44.4)
CR + CRh	10 (22.2)
CR	7 (15.6)
CRh	3 (6.7)
CRp	3 (6.7)
CRi/MLFS	7 (15.6)

ASH 2021: Monday, December 13: 2:45 PM

Stein E, et al. ASH 2021. Abstract 699.

In AUGMENT, SNDX-5613 Was Safe and Tolerable Across Treatment Cohorts

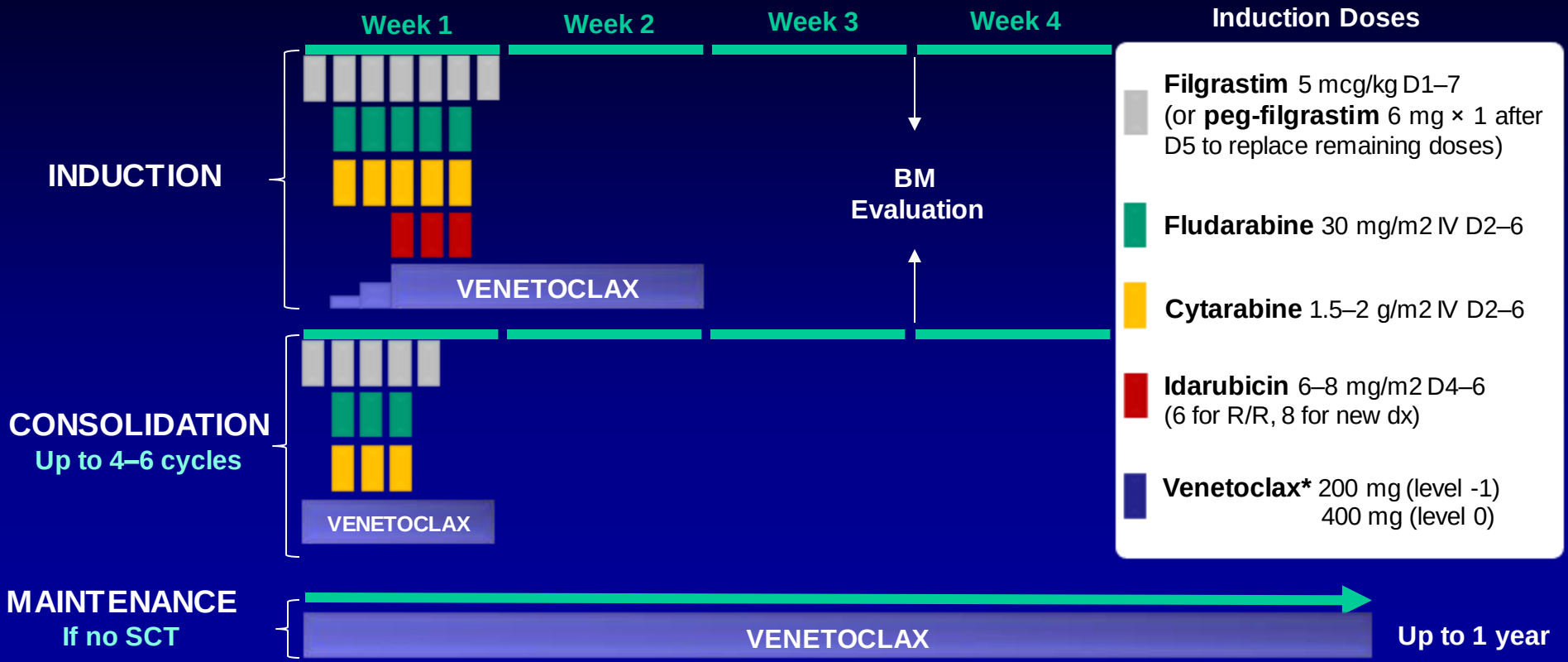
- The frequency of grade 3 prolonged QTc at these doses was 8% (3/38)
- No ventricular arrhythmias were reported, and no patients discontinued 5613 due to a treatment-related event

	Arm A Overall (n = 25), n (%)	Arm B Overall (n = 29), n (%)	Overall (N = 54), n (%)
Subjects with ≥1 grade 3 or greater related TEAE	5 (20)	5 (17.2)	10 (18.5)
ECG QT prolonged	4 (16)	3 (10.3)	7 (13)
Anemia	0	1 (3.4)	1 (1.9)
Asthenia	0	1 (3.4)	1 (1.9)
Diarrhea	0	1 (3.4)	1 (1.9)
Fatigue	0	1 (3.4)	1 (1.9)
Hypokalemia	0	1 (3.4)	1 (1.9)
Neutropenia	0	1 (3.4)	1 (1.9)
Thrombocytopenia	0	1 (3.4)	1 (1.9)
Tumor lysis syndrome	1 (4.0)	0	1 (1.9)

ASH 2021: Monday, December 13: 2:45 PM

Stein E, et al. ASH 2021. Abstract 699.

4. Venetoclax-Based Options in R/R AML: FLAG-IDA-VEN Treatment Plan

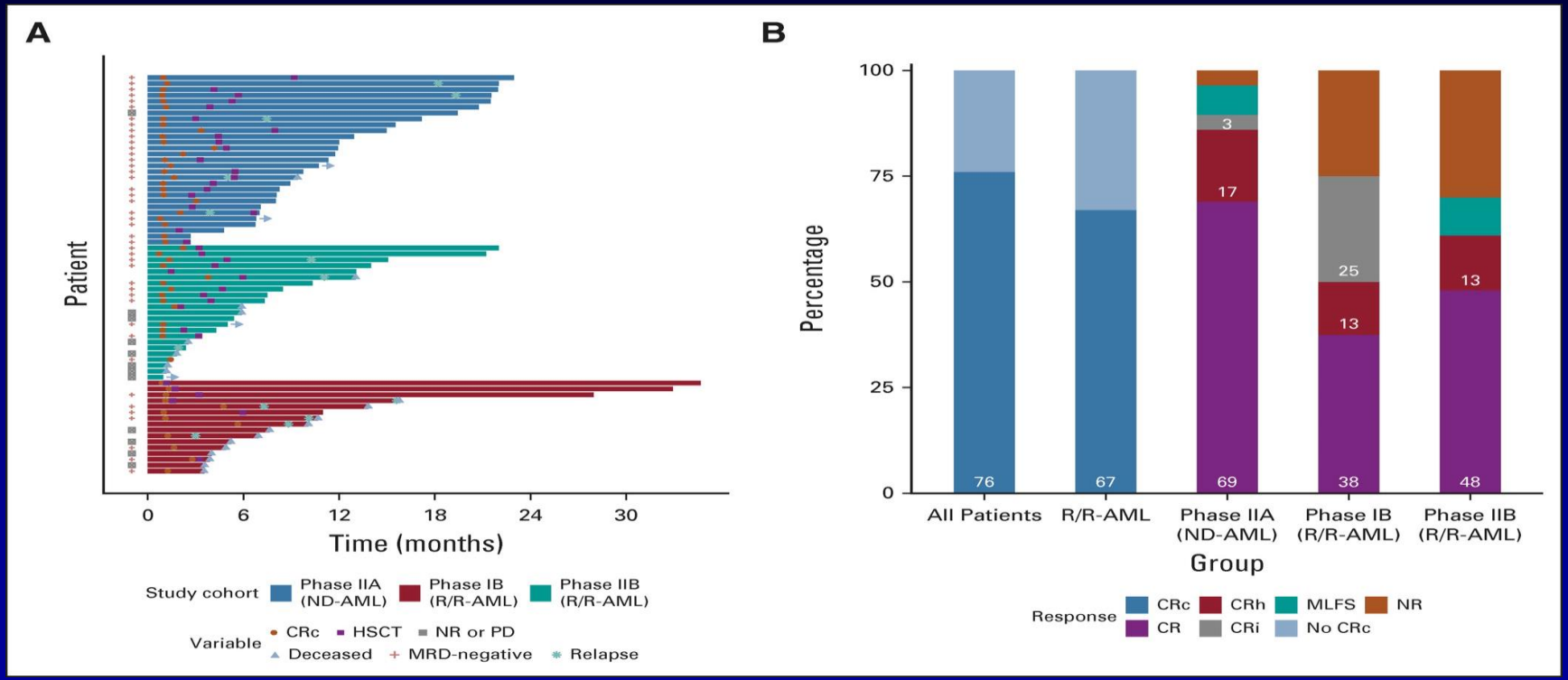


DiNardo CD, et al. *J Clin Oncol.* 2021;39(25):2768-2778.

*Concomitant azole permitted with adequate dose reduction

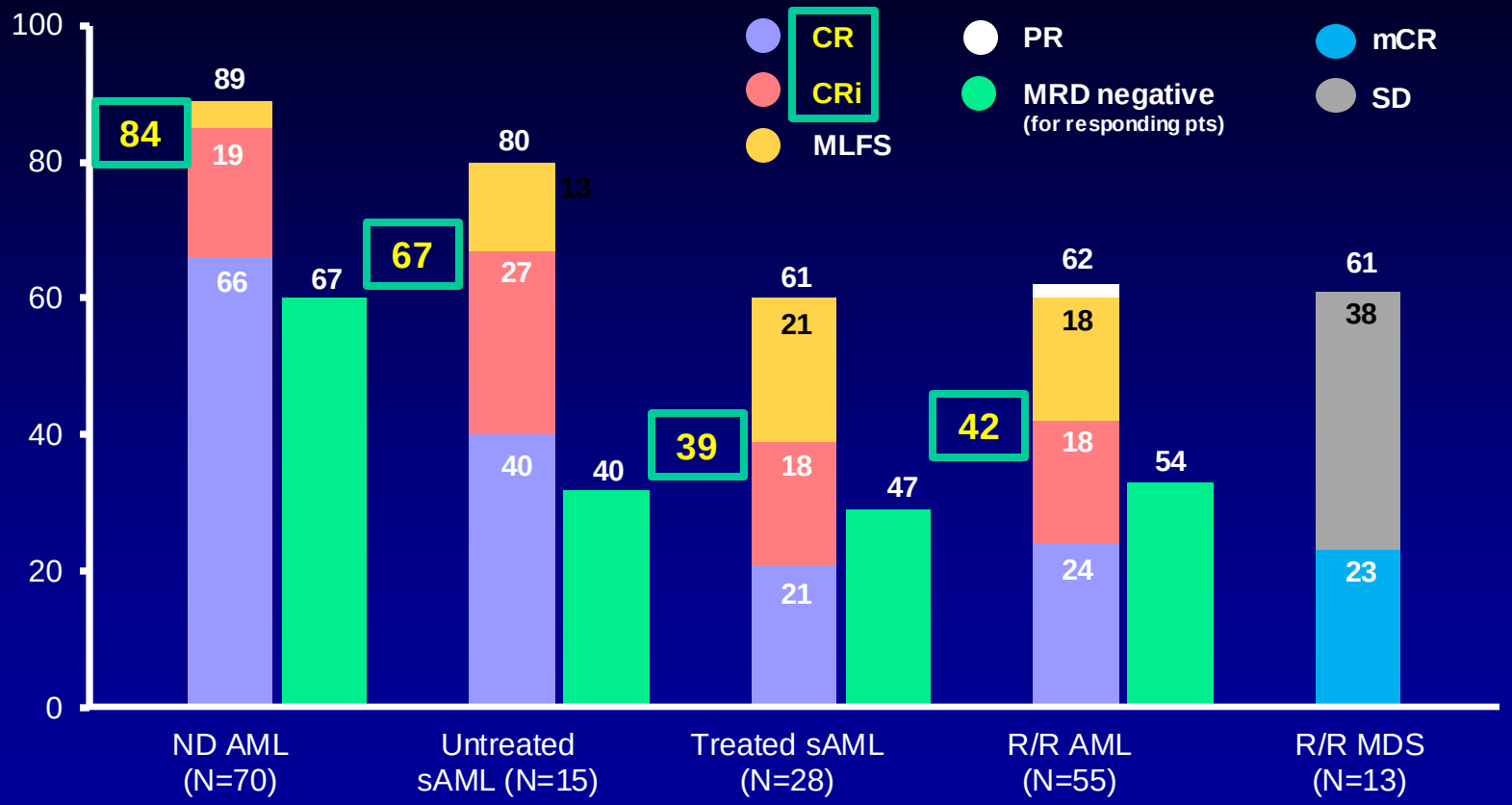
FLAG-IDA + Venetoclax in Frontline and R/R AML

- FLAG-IDA + VEN evaluated in R-R AML, then newly Dx AML
- 68 pts Rx: ND AML 29; R-R AML 39



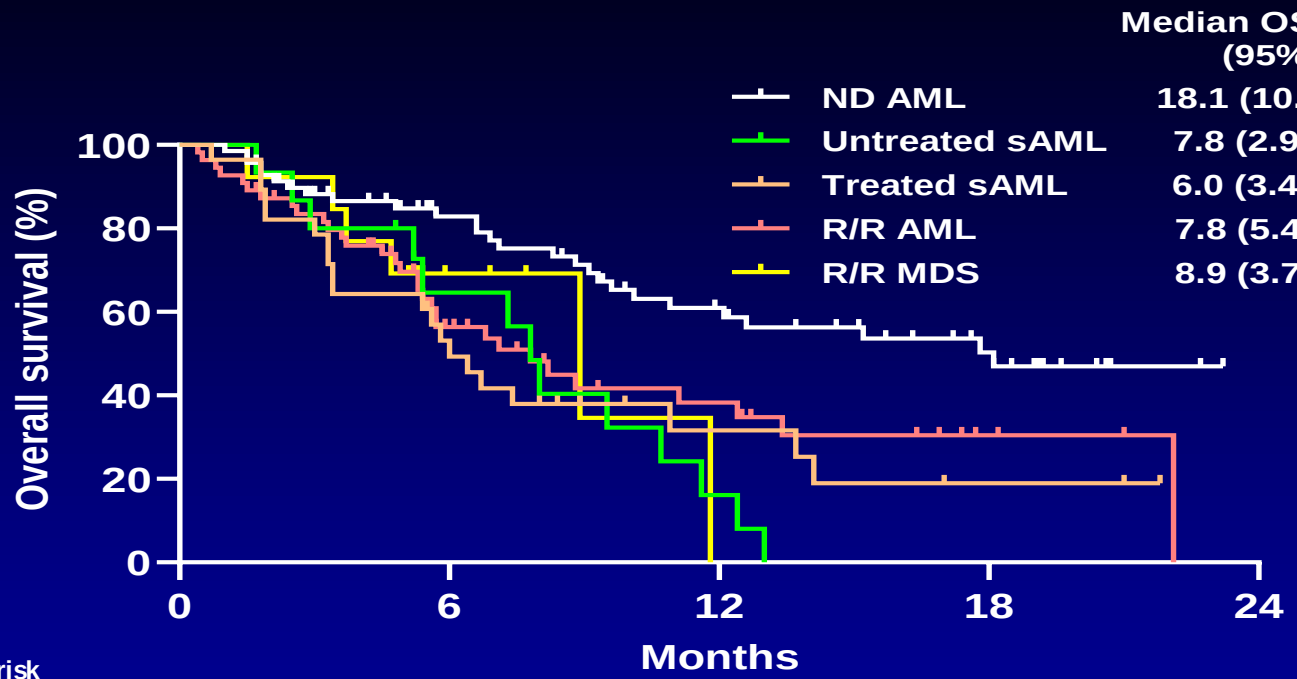
DiNardo CD, et al. *J Clin Oncol.* 2021;39(25):2768-2778.

DEC10-VEN in AML and HR MDS: Results



DiNardo CD, et al. *Lancet Haematol.* 2020;7(10):e724-e736.

DEC10-VEN in AML and HR MDS: Results

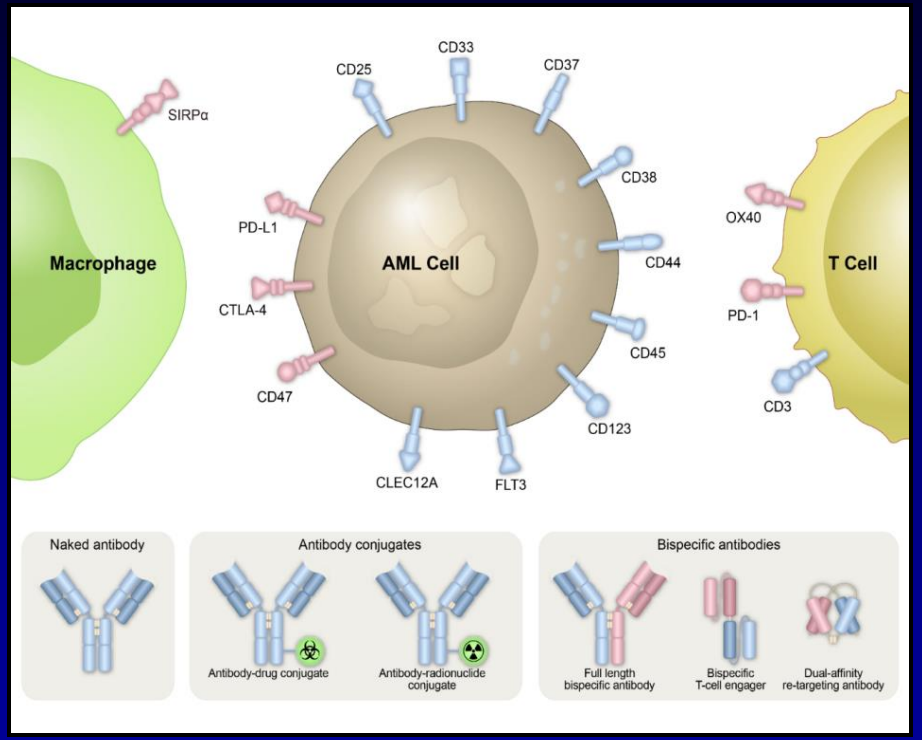


No at risk					
ND AML	70	45	28	15	0
Untreated sAML	15	9	3	0	0
Treated sAML	28	14	6	2	0
R/R AML	55	24	12	3	0
R/R MDS	13	4	0	0	0

DiNardo CD, et al. *Lancet Haematol.* 2020;7(10):e724-e736.

5. Immune-Based Approaches in AML May Soon Provide Another Treatment Modality[1]

- **Two major approaches**
  - Antibody-drug conjugates (CD33, CD123, CLL1)
  - Adaptive or innate immune system-harnessing therapies
- **Bispecific antibodies (CD3 × AML antigen, CD47 × CD3, others)**
- **Immune checkpoint-based approaches: T-cell and macrophage checkpoints**
- **CAR-T, CAR NK, high-volume hn-NK cells**
- **Vaccines**



Short N, et al. *Cancer Discov*. 2020;10:506-525.

A Number of Immunotherapy Options Are in Development for AML, With Applications in R/R Disease

IMGN632 (CD123): ADC with novel single-strand alkylating payload

Flotetuzumab (MGD006): CD123xCD3 dual-affinity retargeting (DART) molecule

XmAb 14045: CD3xCD123 bispecific

AMG330 and AMG673: CD3xCD33

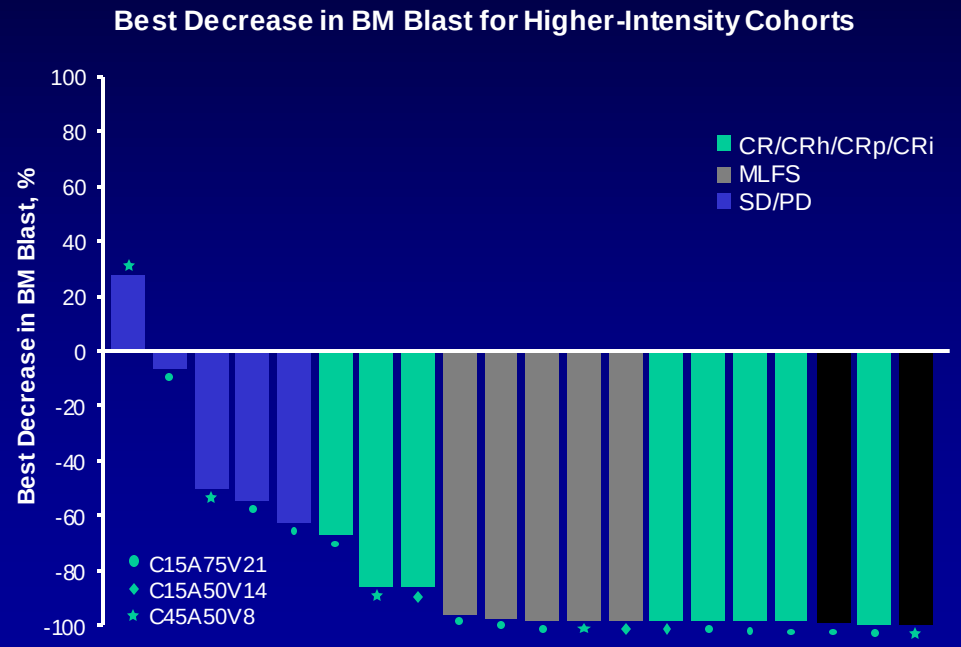
AMV564: CD3xCD33 bispecific

Novel IMGN632 Triplet Is Safe and Highly Active in CD123-Positive R/R AML

Phase Ib/II study designed to determine the safety, tolerability, and activity of IMGN632 combined with AZA and VEN in CD123-positive AML

Results

- Efficacy was seen across all cohorts/doses and schedules (N = 29)
  - ORR: 55%; cCR rate: 31%
- Higher-intensity cohorts (n = 20)
  - ORR: 75%; cCR rate: 40%
- No TLS, VOD, capillary leak, or cytokine release were observed
- 30-day mortality: 0%



Daver N, et al. ASH 2021. Abstract 372.

Immune Strategies to Kill AML

- Recruiting CD3 T cell – BiTEs linking to CD3 and targeting CD33/123; CAR Ts with modified CD3 killer cells
- Recruiting macrophages – targeting CD47 on AML (magrolimab, ALX) or SIRP alpha on macrophages (Trillium, CC95251)
- Recruiting NK cells – allo–NK-CAR Ts; NK-engineered cells/repeated infusions
- Targets other than CD33/123; eg, CLL1

Leukemia Questions?

- Email: ndaver@mdanderson.org
- Cell: 832-573-7080
- Office: 713-794-4392

Global Leukemia Academy

Case 1: Adult AML

Wellington Silva Fernandes

APTITUDE HEALTH

AML in Latin America

Clinical Case

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

DISCLOSURES

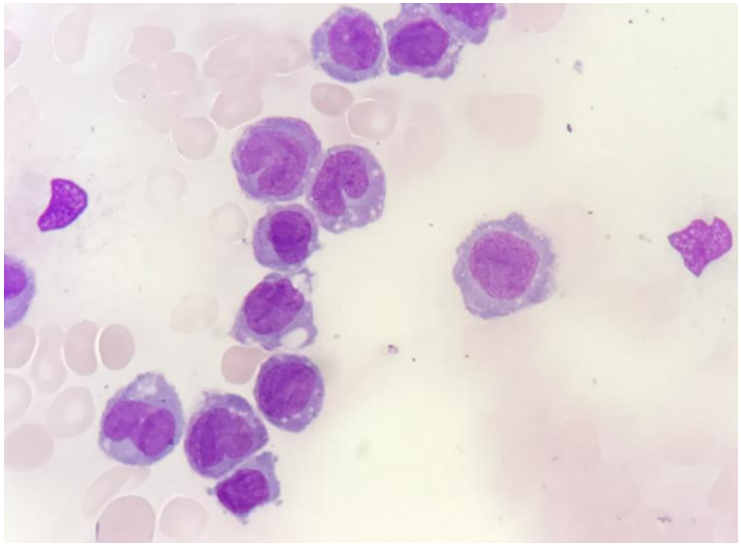
Advisory: Pfizer, Amgen, Daiichi Sankyo, Takeda

Speaker: Pfizer, Amgen, Servier, Pint-Pharma

Research funding: AbbVie, Amgen

Medical History

- 59-year-old female
- No prior comorbidities



- **Oral ulcer for 15 days**
- **Fever and easy bruising**

Peripheral blood: Hb 9.4 g/dl, WBC 163.2×10^9/L (59% blasts), Plat 50×10^9/L
Immunophenotyping → **AML with monocytic component**

- **My: CD33+, CD13+, CD38+, CD117+, MPO+, HLA-DR+, CD34–**
- **Mono: CD4+, CD11b+, CD33+, CD64+, IREM2+**

Medical History

- BM karyotype: 46,XX [20]
- **Molecular evaluation**
  - ***NPM1* mut**
  - ***FLT3*-ITD mut (allelic ratio = 0.2)**
  - ***FLT3*-TKD mut (allelic ratio = 0.3)**

- AML fusions and CEBPA resulted negative

AML With *NPM1*^{mut} and *FLT3*-ITD–low AR

Question 1

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

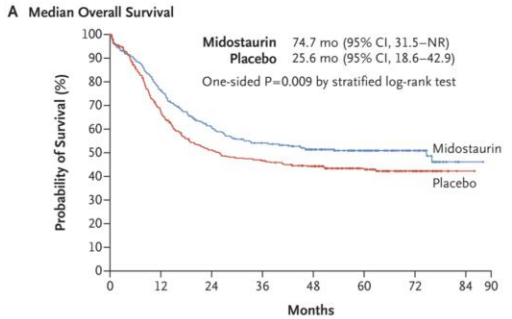
1. **“7+3” (anthracycline + low-dose cytarabine)**
2. **“7+3” plus gemtuzumab ozogamicin**
3. **“7+3” plus midostaurin**
4. **“7+3” plus gilteritinib**
5. **Other**

AML With *NPM1*^{mut} and *FLT3*-ITD–low AR

Question

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

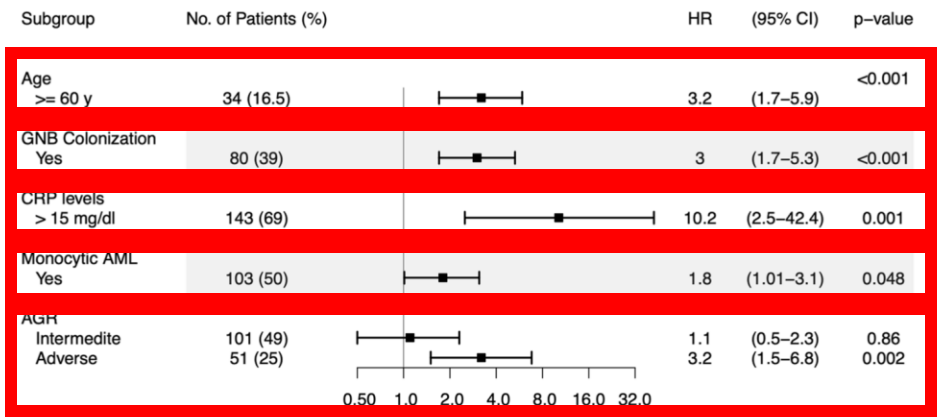
1. **"7+3" (anthracycline + low-dose cytarabine)**
2. **"7+3" plus gemtuzumab ozogamicin**
3. **"7+3" plus midostaurin**
4. **"7+3" plus gilteritinib**
5. **Other**



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

AML Remission Induction in Brazil

- N = 206 pts – Institute of Cancer of Sao Paulo – “7+3”
- Early (6 weeks) mortality after intensive induction = Mortality 25.8%
- ≥60 yr → 41.4%
  - Carbapenem-resistant Enterobacteriaceae (CRE) colonization during induction = 44.5%
  - Invasive fungal infection rate = 26%



Silva WF, Mendes F, et al. *Ann Hematol.* 2022;101(1):147-154.

AML *FLT3* in Brazil

- Midostaurin approved by the regulatory agency – not available in the public health setting
- Gilteritinib also approved for R/R AML with *FLT3*^{mut} – not available in the public health setting

Clinical Case

***NPM1* with *FLT3*low – Favorable category in ELN-2017**
Shortage of HSCT beds at that time
Post-remission therapy – HiDAC for pts >50 yr

Complete response after "7+3" – qPCR *NPM1* = 0.29%

Lumbar puncture – No CSF infiltration

Matched sibling donor

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

qPCR *NPM1* = 0 (after 2 HiDAC courses)

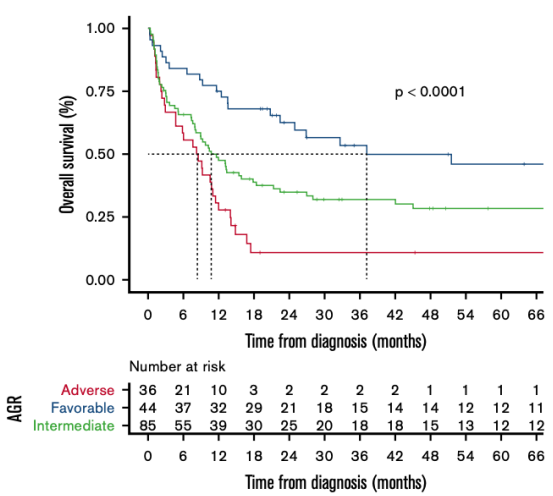
Question 2

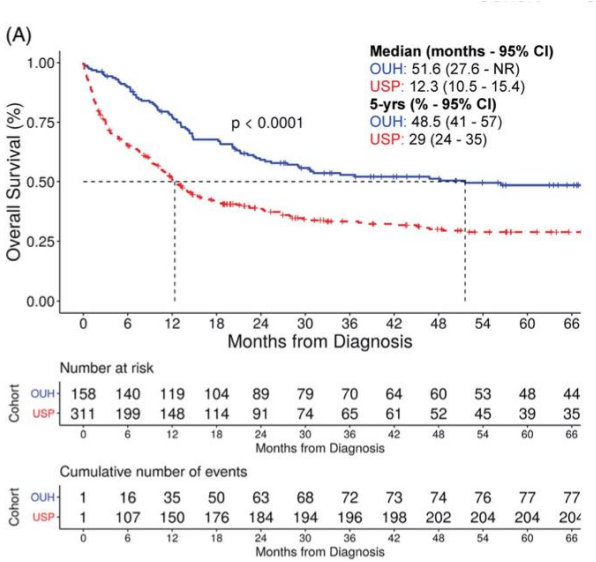
In your practice, what would be the post-remission therapy?

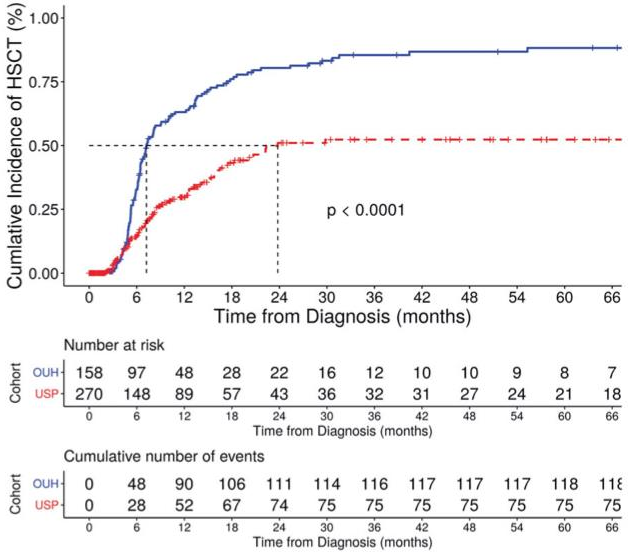
1. **Intermediate- or high-dose cytarabine only, if MRD negative**
2. **Autologous transplant**
3. **Chemo plus FLT3 inhibitor**
4. **Allogeneic stem-cell transplant followed by FLT3 inhibitor regardless of MRD**
5. **Other**

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

Molecular 3 months after the end of IDAC

qPCR *NPM1* 2.1% (Peripheral blood) – confirmed in 2 samples
BM: 2% myeloblasts/*FLT3*-ITD+ 0.5 (AR)

HiDAC – 1 course

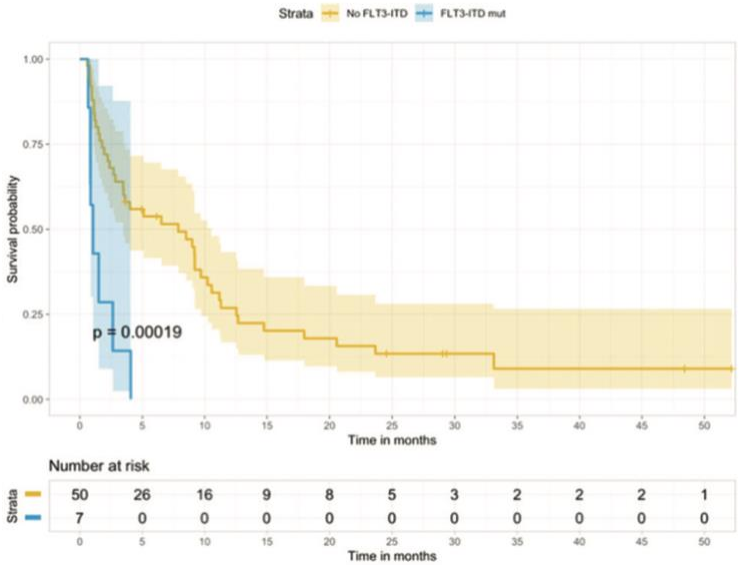
qPCR *NPM1* = 0

AlloHSCT – RIC conditioning (BuFlu) – MSD – June 2020

- Compassionate use of quizartinib
- Remission until now

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 mut on response and survival



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

Question 3

In your practice, how do you perform the surveillance of patients with AML *NPM1* mut?

1. **3-month BM aspirate with MRD by flow**
2. **3-month BM aspirate with MRD by qPCR**
3. **Peripheral blood – qPCR for *NPM1***
4. **Only clinical and blood counts assessment**
5. **Other**

To the panelists – how have you interpreted *NPM1* quantitative results in your clinical practice?

ACKNOWLEDGMENTS

Disciplina de Hematologia
- Prof Dr Eduardo Rego
- Prof Dr Vanderson Rocha

Serviço de Leucemias Agudas
ICESP/HCFMUSP
- Dra Fernandes Mendes
- Dr Raphael Bandeira
- Dra Valéria Buccheri
- Prof Dra Elvira Velloso

Thank you!

wellington.fernandes@hc.fm.usp.br

Global Leukemia Academy

Case 2: Adult AML

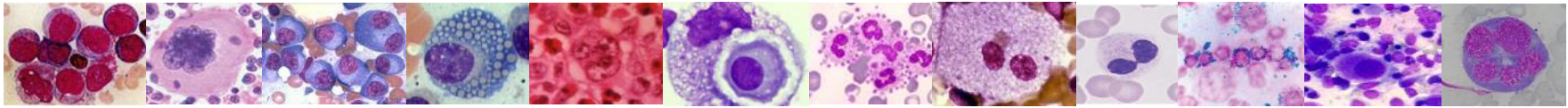
Roberta Demichelis

APTITUDE HEALTH

Global Leukemia Academy

Adult AML Case

Roberta Demichelis, MD
Acute Leukemia Clinic – INCMNSZ
Mexico City



Disclosures

- Consulting: AbbVie, Amgen, Bristol/Celgene, Jazz, Novartis, Gilead, Astellas
- Research grants: Novartis, ASH
- Honoraria: AbbVie, Amgen, Bristol/Celgene, Jazz, Novartis

Case

73-year-old man

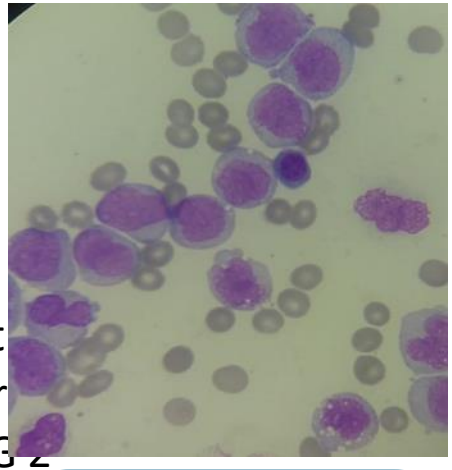
Unemployed lawyer. No social security or insurance

ALCOHOL USE DISORDER

PRE-DIABETES

GOUT

History



Fatigue and hyporexia

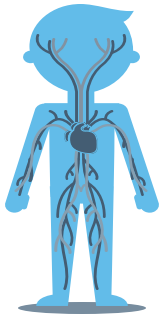
April 2021

Fever and disorientation.
Labs: high WBC, anemia, and thrombocytopenia

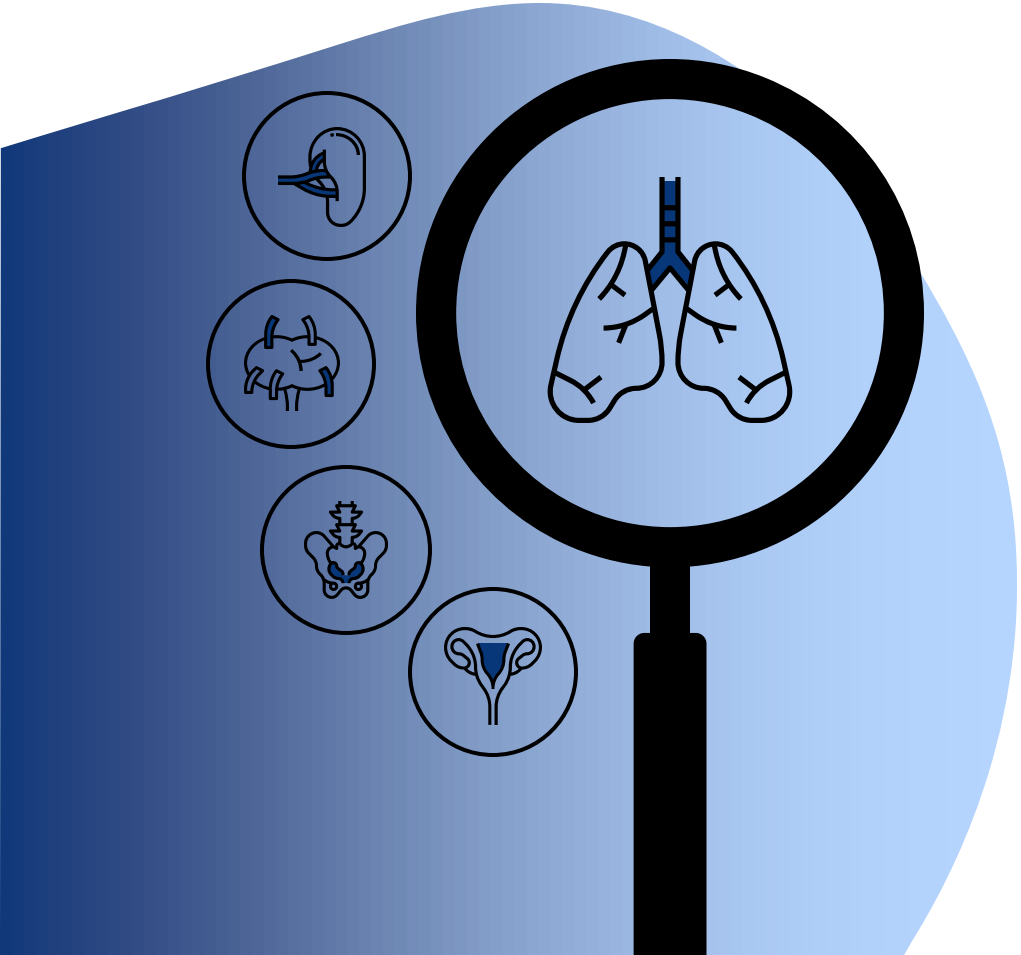
May 2021

ER at
Disor
ECOG 2
Diarr

May 17, 2021



Hb: 5.6 g/dL
WBC 146 × 10^9/L
Plat 66 × 10^9/L
Blood smear: 87% blasts/promonocytes
Creat: 2.03 g/dL, Uric ac. 16 mg/dL, LDH 692 UI/L



Challenges in the Diagnosis and Treatment of AML in Mexico?

AML in Mexico

Retrospective registry: 2013–2017, 13 public institutions

- ✓ Median age: **47 years**
- ✓ 80.2% intensive chemotherapy
- ✓ 3-year OS: 34.8%
- ✓ Non-candidates for intensive chemotherapy: **median OS 31 days**

CHALLENGES

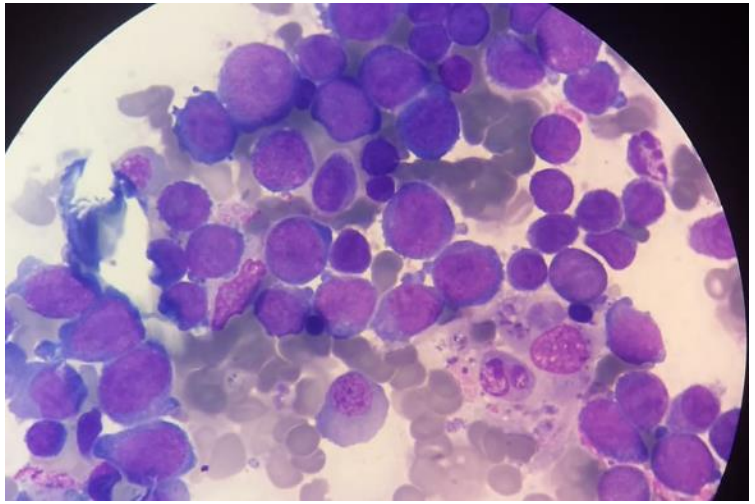
1. 30% karyotype unavailable or non-evaluable
2. Molecular testing only in 12.2% (*FLT3*)
3. Induction-related mortality: 17.8%
4. AlloHSCT: 8.2%

01.
Prospective registry with centralized genetic/molecular testing

02.
Acute leukemia monthly virtual sessions focused on support treatment

Demichelis R, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20(06):e295-e303.

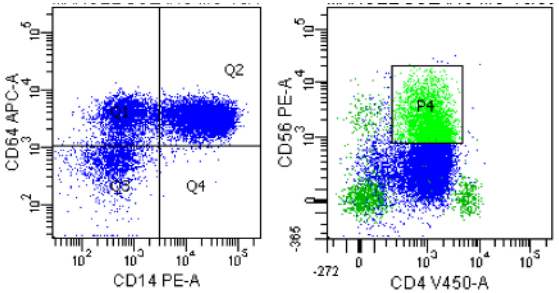
Case: Bone Marrow



BMA

- 57% blasts and promonocytes

Flow cytometry



Genetics

- Karyotype: 46XX, del(21p)
- Molecular: *IDH1+*, *FLT3–* TKD+, *NPM1+*

Question 1

What genetic/molecular tests do you have access to when diagnosing AML?

- Only cytogenetics/FISH
- Cytogenetics/FISH and *FLT3*
- Cytogenetics/FISH and a reduced molecular panel
- Cytogenetics/FISH and a complete NGS panel

Question 2

In your practice, how would you treat this patient?

- Standard intensive chemotherapy (7+3)
- Low-dose cytarabine (LDAC) or hypomethylating agents (HMA)
- Venetoclax + LDAC or HMA
- Ivosidenib +/- HMA
- Supportive care

Case

73-year-old de novo AML
IDH1*/*FLT3*-TKD/*NPM1

- ✓ ECOG 2
- ✓ No significant comorbidities
- ✓ Geriatric assessment = frail
- ✓ Active infection
- ✓ Delirium

Financial considerations

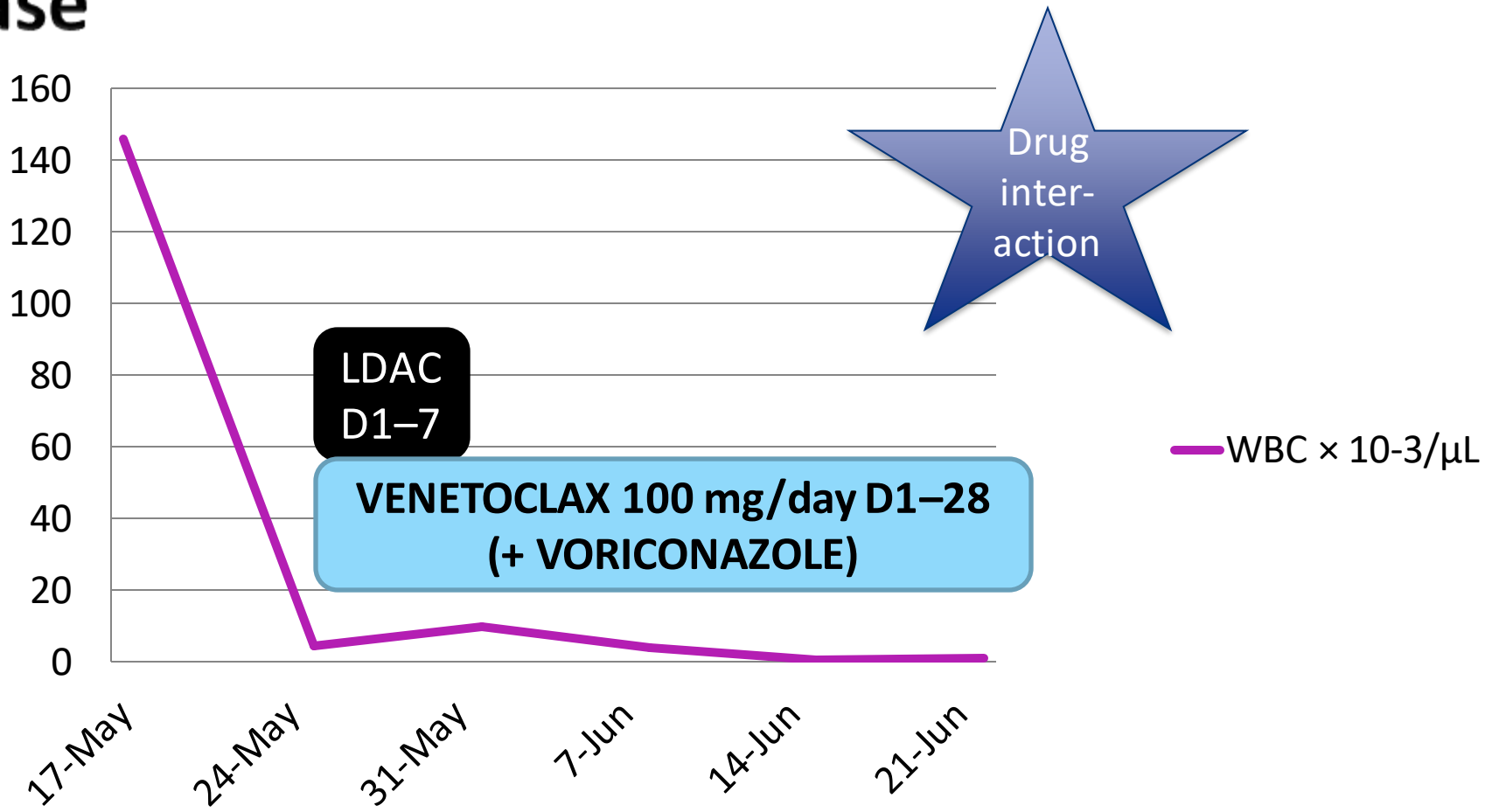
01. Phase III clinical trial: Aza + Ivo vs Aza + placebo

02. *IDH/NPM1* mutations: good outcomes with VEN

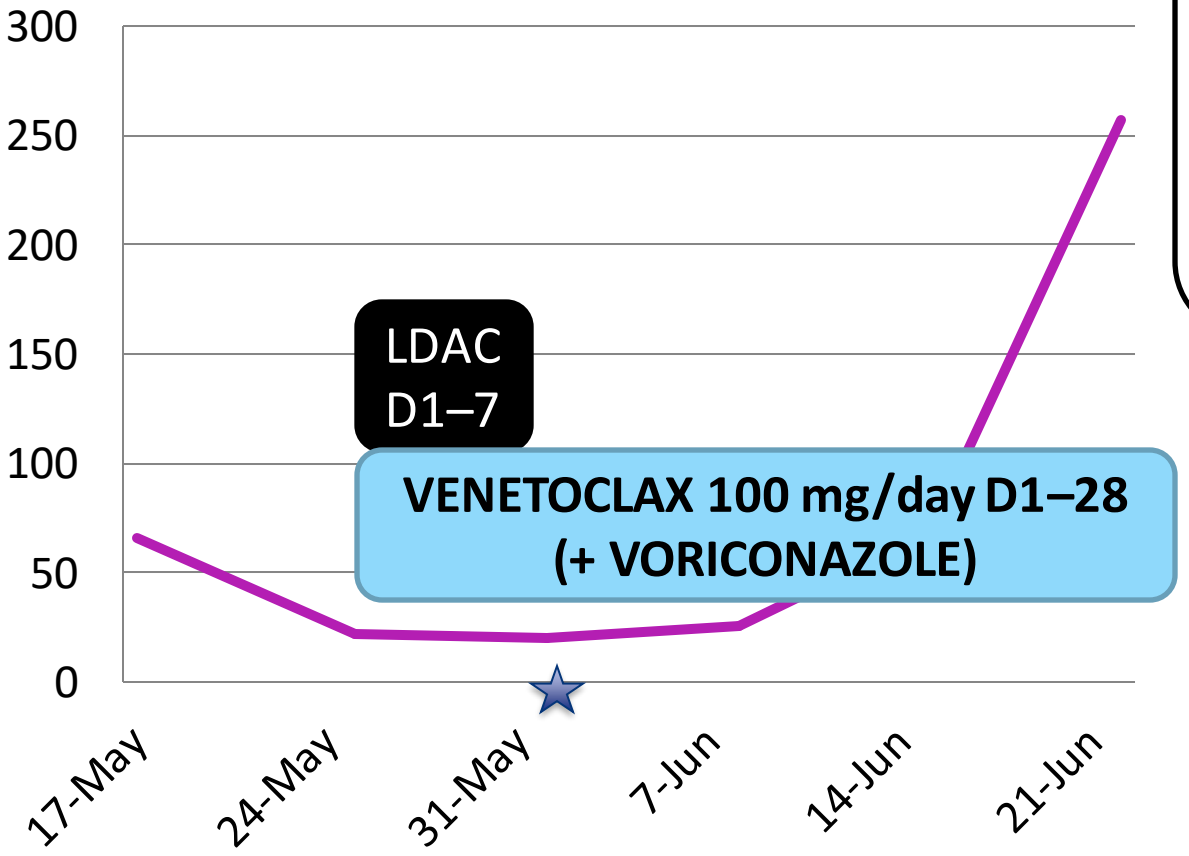
LDAC + VEN

NON-INTENSIVE REGIMEN

Case


160
140
120
100
80
60
40
20
0
17-May
24-May
31-May
7-Jun
14-Jun
21-Jun
Drug inter-action
LDAC D1–7
VENETOCLAX 100 mg/day D1–28 (+ VORICONAZOLE)
WBC × 10-3/µL

Case



+28
Afebrile, stable, no delirium

Hb 7.1, WBC 0.7, ANC 300, platelets 257

Evolution

73-year-old de novo AML
Genetics: del21
NPM1/IDH1/FLT3-TKD
Frail

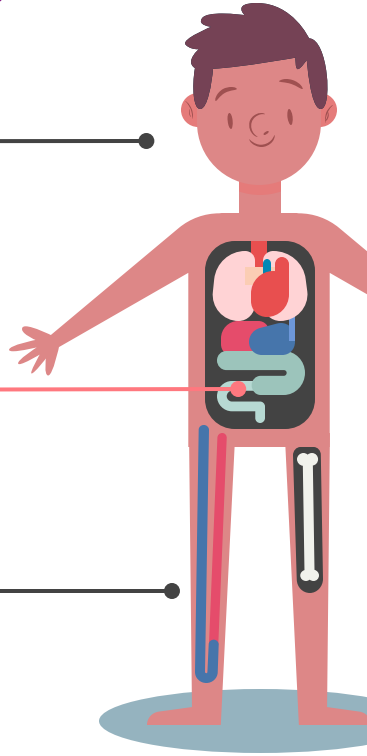
Day 28:
BMA <5% blasts

G-CSF

Complete hematologic recovery

CR

9º cycle



- ✓ MRD: *NPM1* every 3 months → negative
- ✓ Transfusion independent
- ✓ ECOG PS 0
- ✓ No further hospitalizations

Open Questions for the Panelists

1. **What is the role of MRD measurement with non-intensive regimens?**

2. **Is there a possibility of a finite treatment with venetoclax based-combinations? Patient profile?**

Thank you

Contact: roberta.demichelis@incmnsz.mx @RobertaDemiche3

Global Leukemia Academy

AML case-based panel discussion

Panelists: Roberta Demichelis, Wellington Silva Fernandes, Paola Omaña



APTITUDE HEALTH

Question 1

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

1) Adverse genetic alterations
2) Age
3) Comorbidities
4) Performance status
5) Prior cytotoxic therapy
6) Prior myelodysplasia

Question 2

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

1) Patients >75 years of age
2) Patients <75 years of age with ECOG PS 3
3) Patients <75 years of age with significant cardiac co-morbidity
4) Patients <75 years of age with significant pulmonary comorbidities
5) Patients <75 years of age with adverse cytogenetics

Question 3

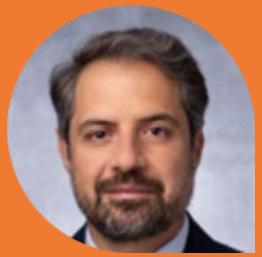
Which of the following is not true regarding HMA + venetoclax in AML?

1) The CR/CRi with HMA+VEN in the VIALE-A was >65%
2) HMA+VEN improved median OS compared with HMA alone
3) Lab or clinical TLS is not seen with HMA+VEN in AML
4) The recommended daily dose of venetoclax (without azoles) was 400mg PO Qday in VIALE-A study
5) Neutropenia is commonly seen with HMA+VEN regimen

Global Leukemia Academy

Session close

Elias Jabbour and Naval Daver

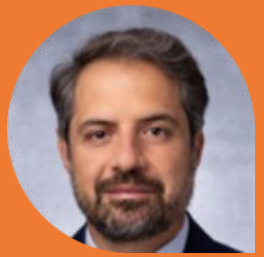


APTITUDE HEALTH

Global Leukemia Academy

Closing remarks

Elias Jabbour



APTITUDE HEALTH

Thank you!

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

THANK YOU!

Global Leukemia Academy

Founding Sponsor
Platinum

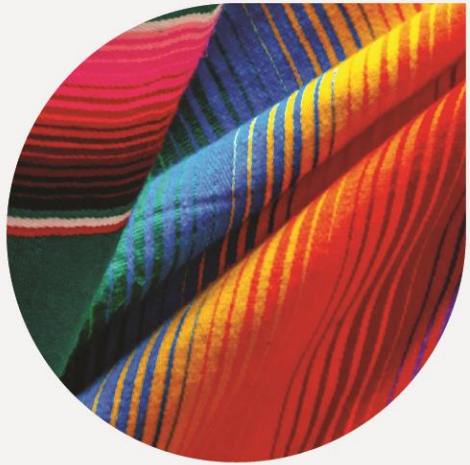
AMGEN

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

APTITUDE HEALTH

Global Multiple Myeloma Academy



PLEASE JOIN US FOR OUR OTHER ACADEMY!

Global Multiple Myeloma Academy
- focusing on LATAM region

23 – 24 June 2022

- 2.00 PM – 5.00 PM EDT (Central Daylight Time)
- 3.00 PM – 6.00 PM EDT (Easter Daylight Time)
- 4.00 PM – 7.00 PM GMT-3 (San Paulo time)

For more information, please visit the website:
https://globalmmacademy.com

APTITUDE HEALTH®