Global Leukemia Academy

Founding Sponsor
Platinum

AMGEN

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

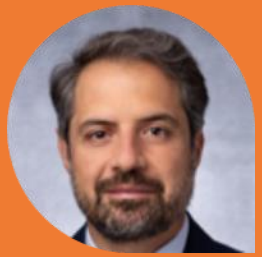
25 March 2022

APTITUDE HEALTH

Global Leukemia Academy

Welcome and Meeting Overview

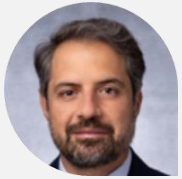
Elias Jabbour



APTITUDE HEALTH

Meet the Faculty

CO-CHAIRS



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

Franco Locatelli, MD
IRCCS Bambino Gesù
Children's Hospital, Rome, Italy

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

FACULTY

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

Sergio Giralt, MD
Memorial Sloan Kettering Cancer
Center, New York, NY, USA

Stephanie Dixon, MD, MPH
St. Jude Children's Research
Hospital, Memphis, TN, USA

Rob Pieters, MD, PhD
Princess Maxima Center for
Pediatric Oncology, Utrecht,
The Netherlands

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

Adriana Seber, MD
GRAACC, Federal University
of São Paulo, Brazil

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

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

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

Erica Almeida Viana, MD
GRAACC, Federal University of São
Paulo, Brazil

Objectives of the Program

- Understand current treatment patterns and recent developments in acute leukemias including incorporation of new technologies and immunotherapies
- Discuss the role of MRD in managing and monitoring acute leukemias
- Discuss optimal management of long-term toxicities in pediatric ALL
- Review treatment recommendations for AYA ALL patients
- Discuss risk stratification and treatment approaches for AML patients and high-risk subgroups

Virtual Plenary Sessions (Day 1)

Chair: Elias Jabbour

TIME (UTC-3)	TITLE	SPEAKER
18.00 – 18.10	Welcome and meeting overview; introduction to the voting system	Elias Jabbour
18.10 – 18.40	Recent developments in acute leukemias	Elias Jabbour
18.40 – 19.00	Review of prognostic value of MRD in acute leukemias	José Maria Ribera
19.00 – 19.20	Current and future role of transplantation in acute leukemias	Sergio Giralt
19.20 – 19.50	Leukemia board discussion • AYA ALL case plus discussion (15 min) – Erica Viana (Bra) • AML case plus discussion (15 min) – Paola Omaña (Col)	Moderator: Elias Jabbour All faculty
19.50 – 20.00	Break	
20.00 – 20.20	Optimal management and treatment coordination of long-term toxicities in pediatric leukemias	Stephanie Dixon
20.20 – 20.40	AYA ALL patients – what is the current treatment approach for this diverse patient population? Special considerations for adolescents and young adults	Rob Pieters
20.40 – 21.10	Debate on sequencing CD19-targeted approaches • Monoclonal antibodies and bispecifics first (10 min) • CAR T first (10 min) • Discussion and voting (10 min)	Moderator: Franco Locatelli Elias Jabbour José Maria Ribera All faculty
21.10 – 21.30	Genetic characterization and risk stratification of AML	Eunice Wang
21.30 – 21.50	Therapeutic approaches in high-risk and older AML patients	Naval Daver
21.50 – 22.00	Session close	Elias Jabbour

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

Virtual Breakout – Pediatric Leukemia Patients (Day 2)

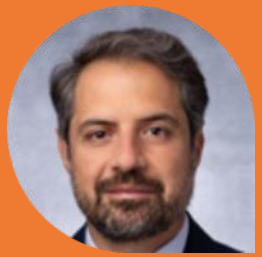
Co-chair: Franco Locatelli

TIME (UTC-3)	TITLE	SPEAKER
10.00 – 10.10	Session open	Franco Locatelli
10.10 – 10.30	The use of MRD and genetics for risk stratification and therapy guidance in pediatric ALL	Rob Pieters
10.30 – 10.50	First-line treatment of pediatric ALL, including HSCT	Christina Peters
10.50 – 11.10	Current treatment options for relapsed ALL in children, including HSCT	Franco Locatelli
11.10 – 11.25	Bispecifics for pediatric and AYA B-ALL	Christina Peters
11.25 – 11.55	ALL case-based panel discussion • Case 1 (10 min) – Irene Medina (Mex) • Case 2 (10 min) – Jorge Buitrago (Col) • Discussion (10 min) – Panelists: Maria Sara Felice, Oscar Gonzáles Ramella, Adriana Seber, Carlos Andrés Portilla	All
11.55 – 12.00	Break	
12.00 – 12.20	Current treatment options for pediatric AML	Franco Locatelli
12.20 – 12.50	AML case-based panel discussion • Case 1 (10 min) – Luisina Peruzzo (Arg) • Case 2 (10 min) – Erica Viana (Bra) • Discussion (10 min) – Panelists: Maria Sara Felice, Oscar Gonzáles Ramella, Adriana Seber, Carlos Andrés Portilla	All
12.50 – 13.00	Session close	Franco Locatelli

Global Leukemia Academy

Introduction to the Voting System

Elias Jabbour



APTITUDE HEALTH

Question 1

In which country do you practice?

1. Argentina
2. Brazil
3. Canada
4. Colombia
5. Chile
6. Mexico
7. Peru
8. Other

Question 2

Which patients do you treat?

1. Adults only
2. Children only
3. Adults and children
4. Other

Question 3

Which of the following is NOT true?

1. Inotuzumab and blinatumomab + chemotherapy is active in both frontline and salvage for ALL
2. ALK inhibitors can be combined with other therapy modalities in Ph+ ALL
3. MRD is highly prognostic for relapse and survival in Ph-negative ALL
4. CAR T approaches are active beyond 2L in Ph-negative ALL

Question 4

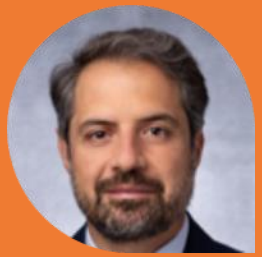
In AML the MRD assessment by RT-qPCR is especially useful for

1. *FLT3* ITD
2. *NPM1* mutation
3. Biallelic *CEBPA* mutation
4. *SF3B1* mutation
5. *ASXL1* mutation

Global Leukemia Academy

Recent developments in acute leukemias

Elias Jabbour



APTITUDE HEALTH

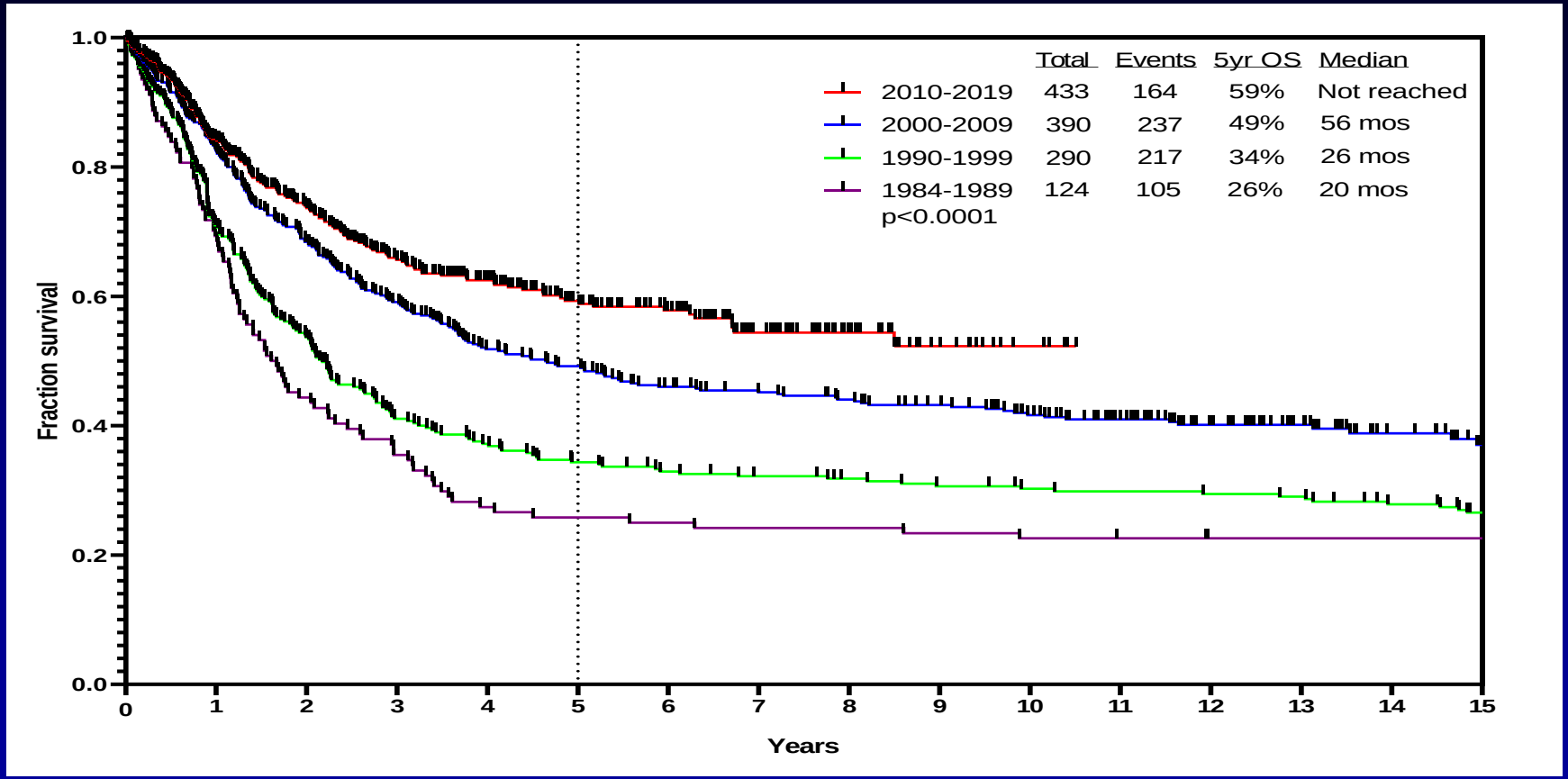
Recent Developments in Acute Leukemia

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

2022

ALL

ALL: Survival by Decade (MDACC 1985–2020)



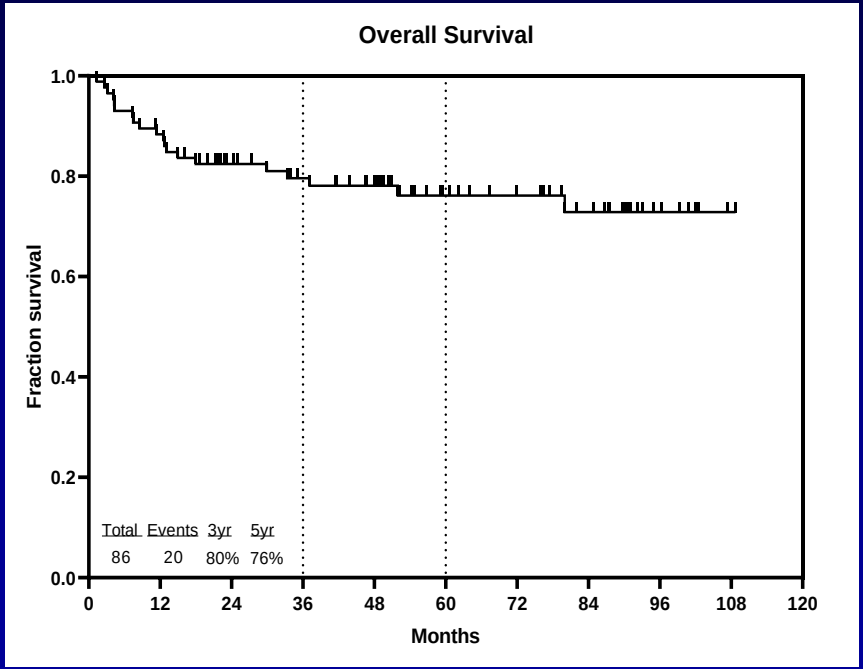
Reasons for Recent Success in Adult ALL

- 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)

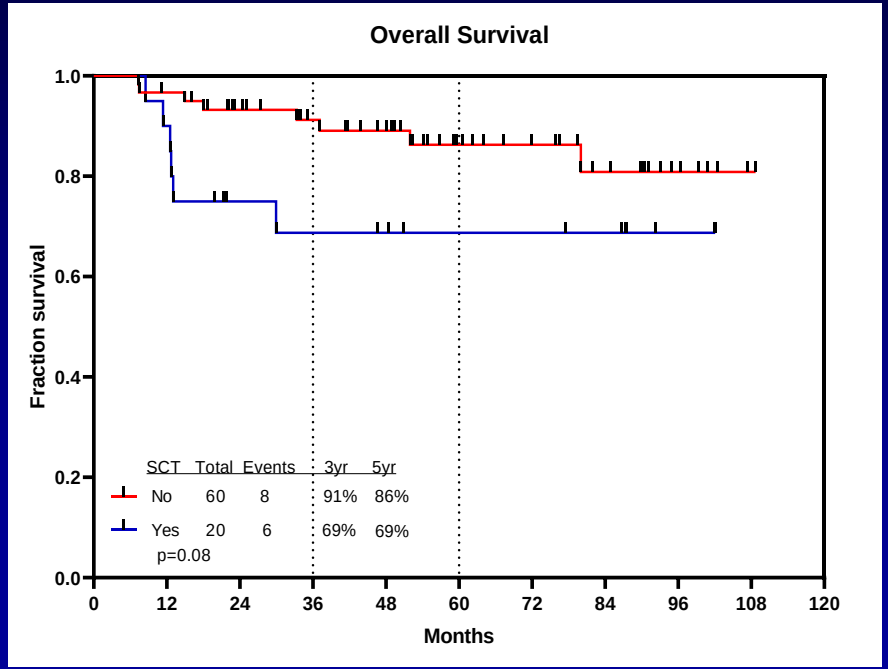
HyperCVAD + Ponatinib in Ph+ ALL

- 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

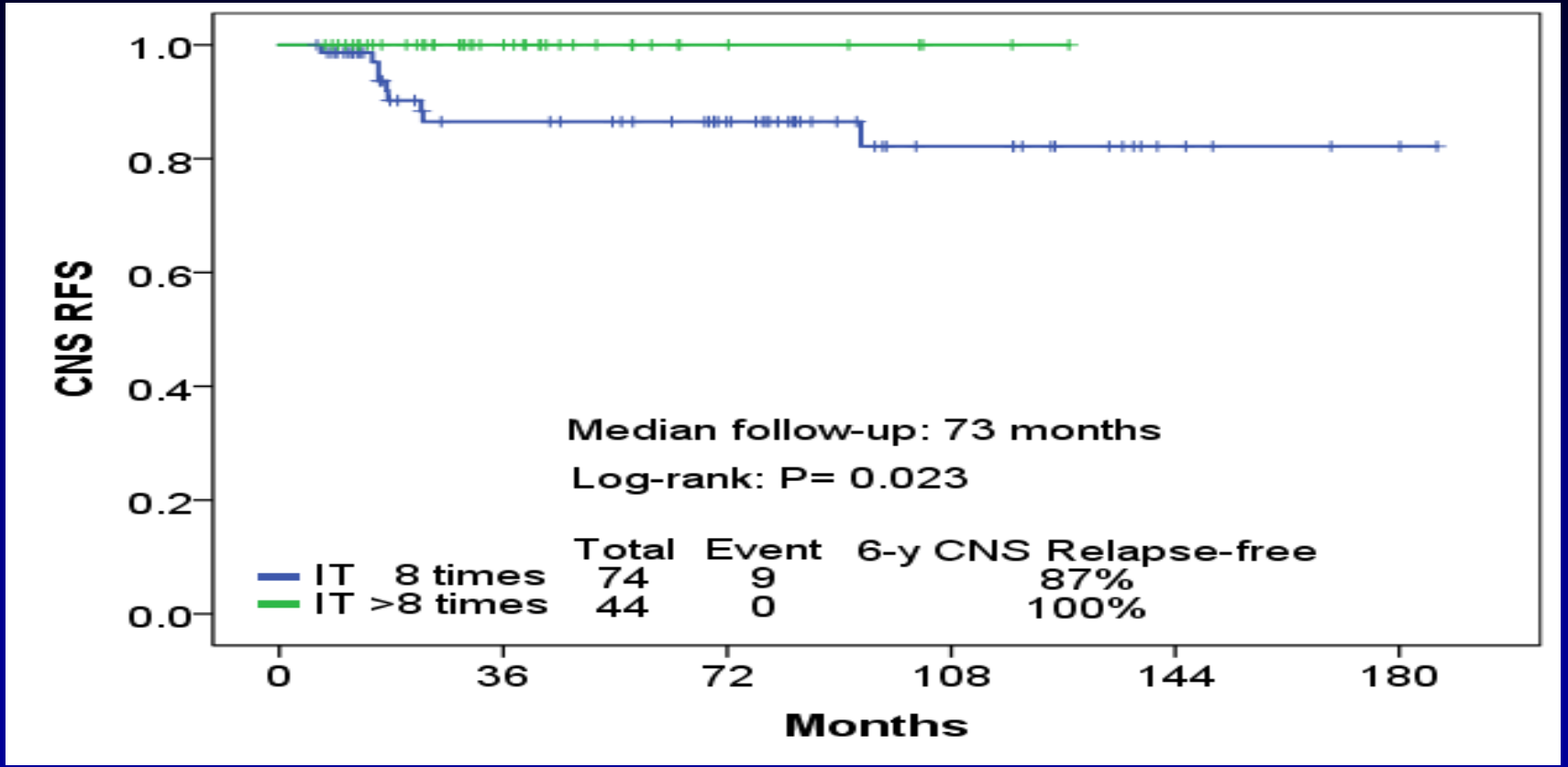


6-Month Landmark



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

IT ×8 vs IT ×12 in Ph+ ALL
6M Landmark: CNS Relapse-Free Survival

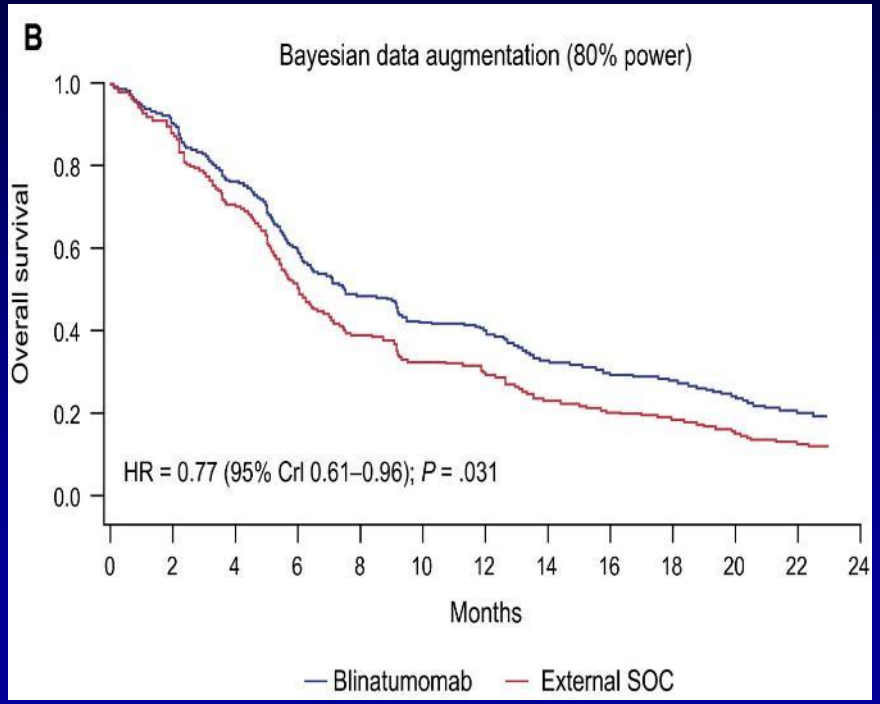


Paul et al. *Blood.* 2019;134:Abstract 3810.

Blinatumomab and Inotuzumab in R/R Ph+ ALL

Blina vs SOC

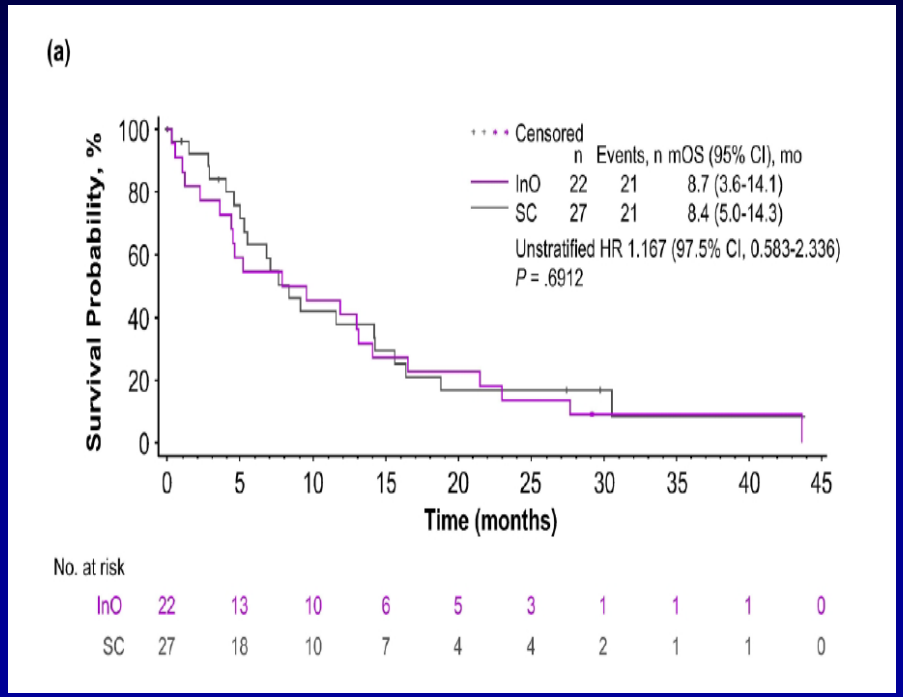
- CR/CRh 36% vs 25%
- 1-yr OS 41% vs 31%



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

Ino vs SOC

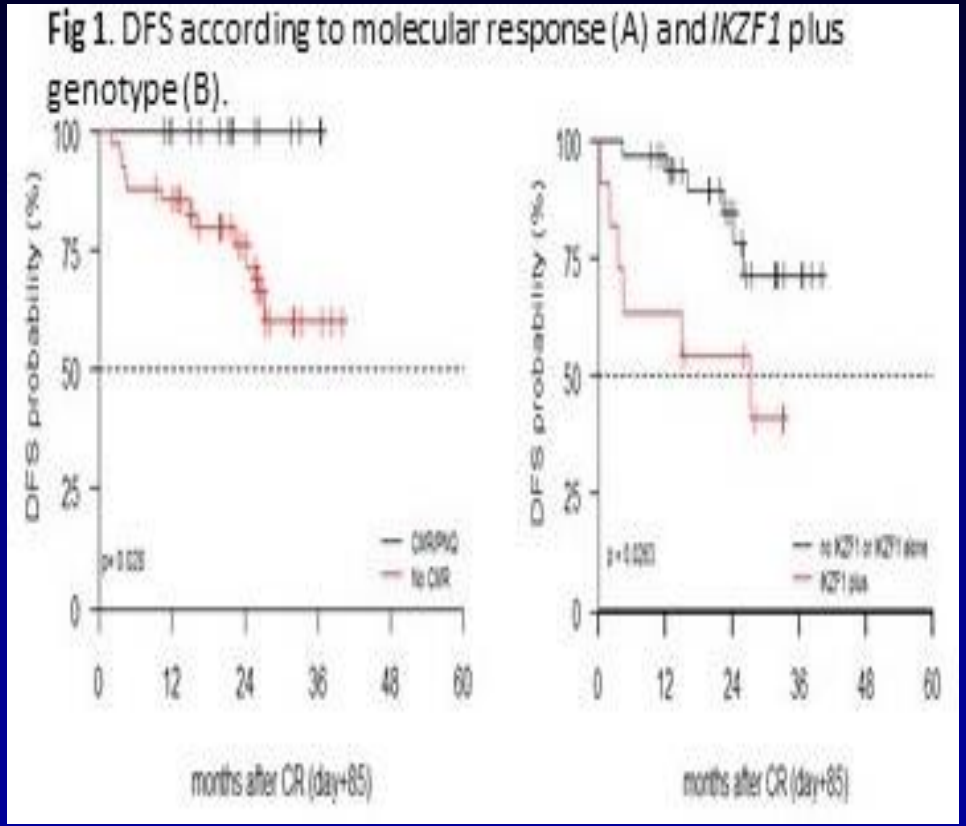
- CR/CRi 73% vs 56%
- 1-yr PFS 20% vs 4.8%



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

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

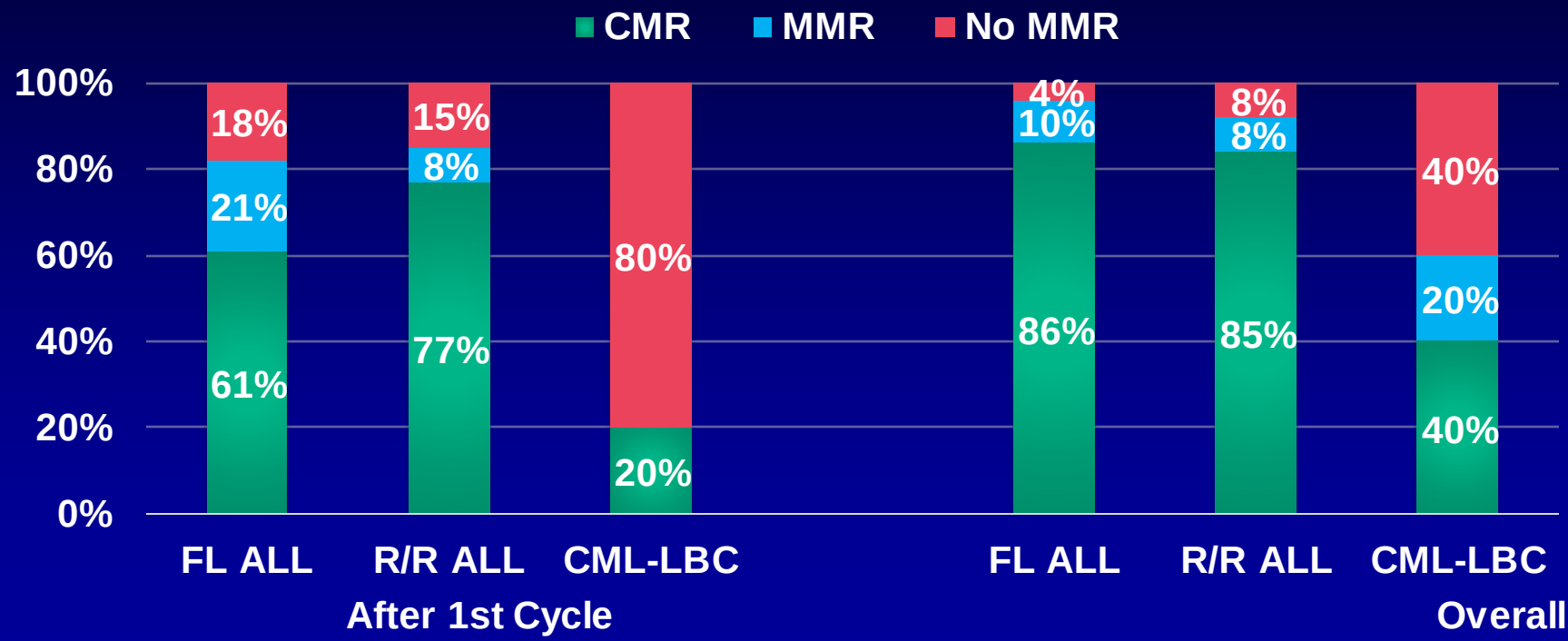
- 64 pts Rx; median age 54 yrs (24–82). Median FU 27 mos
- Molecular response (32/53 = 60%)
  - 22 CMR (41%)
- 29/58 (50%) who started blina have SCT
- 9 relapses: 4 hematologic, 4 CNS, 1 nodal
- 24-mos OS 88%, DFS 80%
- Outcome better if MR: DFS 100% vs 80% (*P* = .028)
- Outcome worse if IKZF1+: 2-yr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



Chiaretti et al. EHA 2021. Abstract S112.

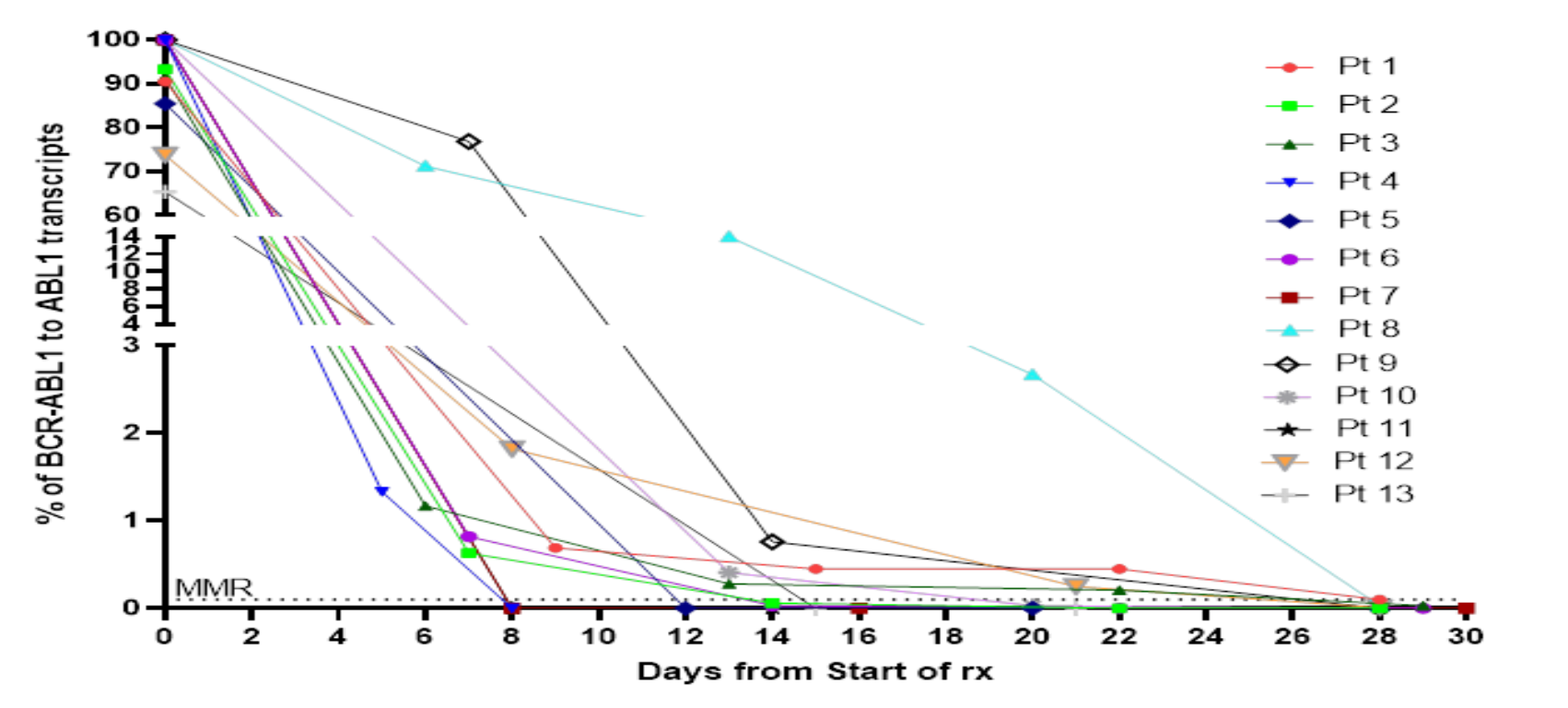
Ponatinib + Blinatumomab in Ph+ ALL: MRD Response Rates

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



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

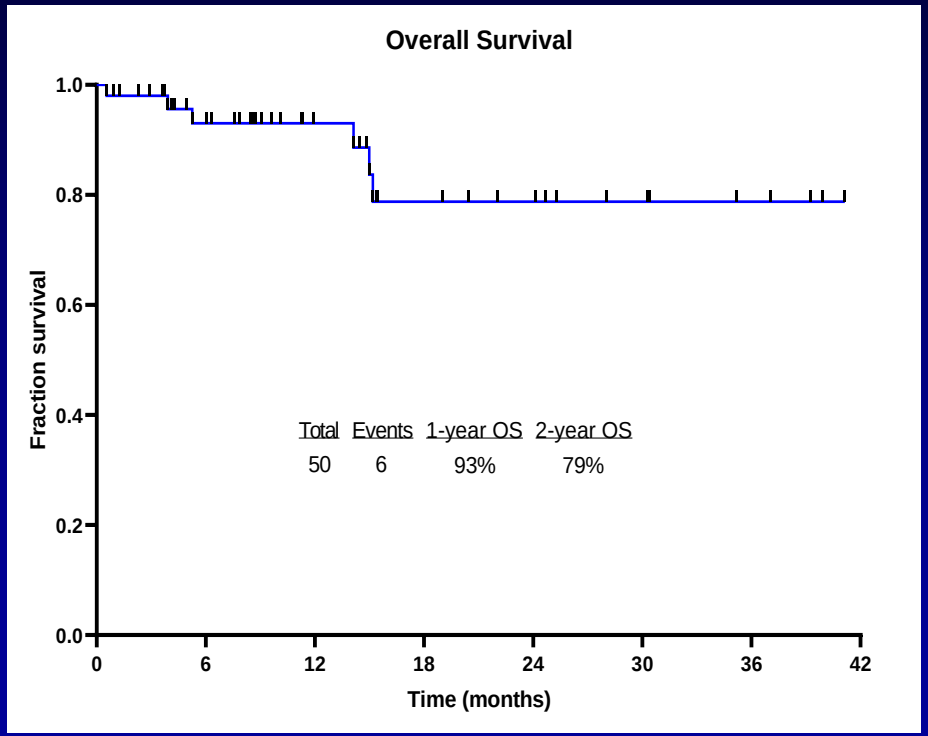
Ponatinib + Blinatumomab in Ph+ ALL: Dynamic of MRD Response



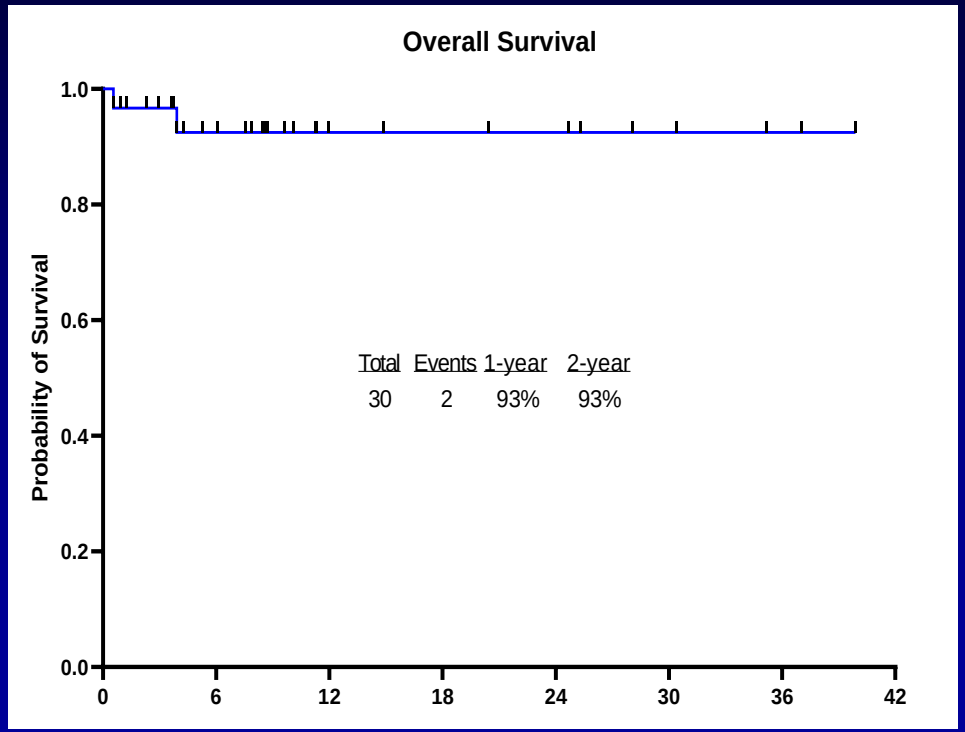
Ponatinib + Blinatumomab in Ph+ ALL: Survival

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

Overall Cohort

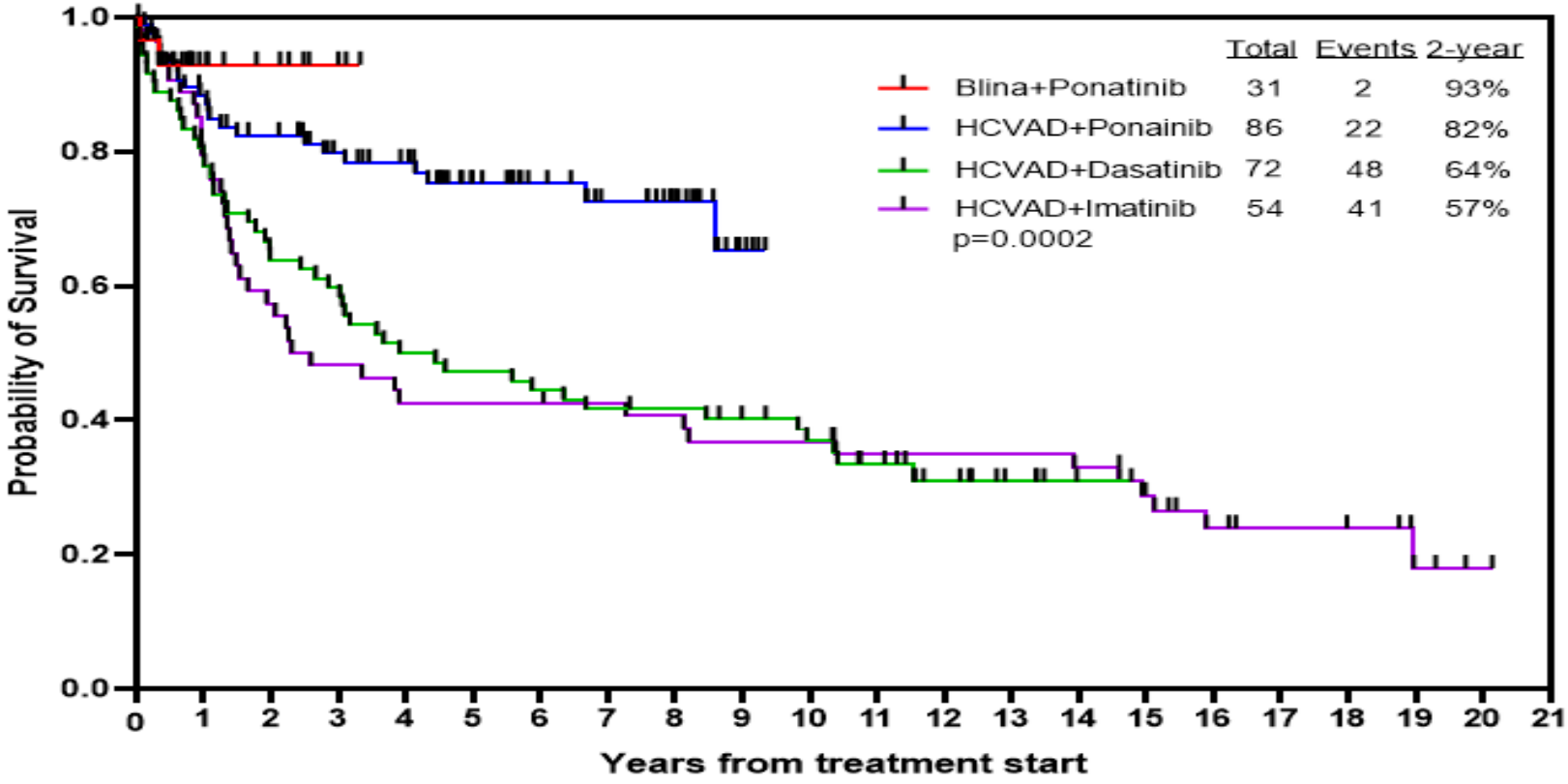


FL Cohort



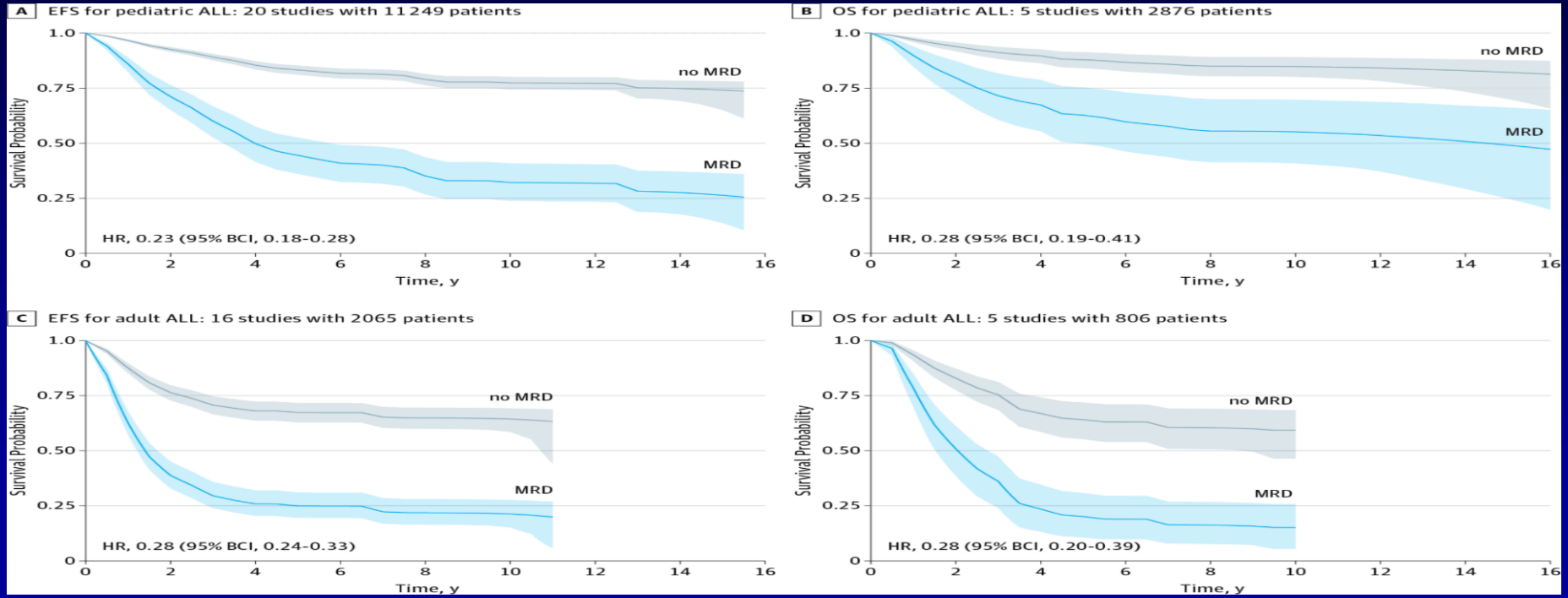
Short et al. *Blood.* 2021;140:abstract 2298.

Ponatinib-Blinatumomab in Ph+ ALL vs Historical Data



MRD in ALL

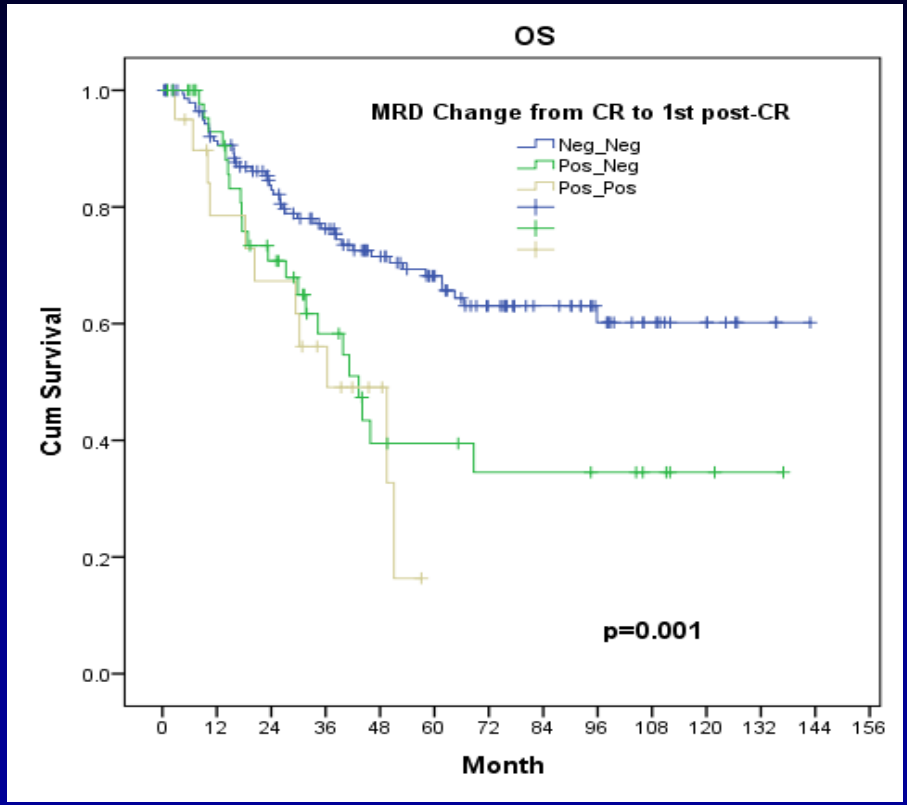
- Meta-analysis of 39 studies (pediatric and adult), including 13,637 patients with all ALL subtypes
- Prognostic impact of MRD clearance consistent across therapies, MRD method, timing, level of cutoff and subtypes



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

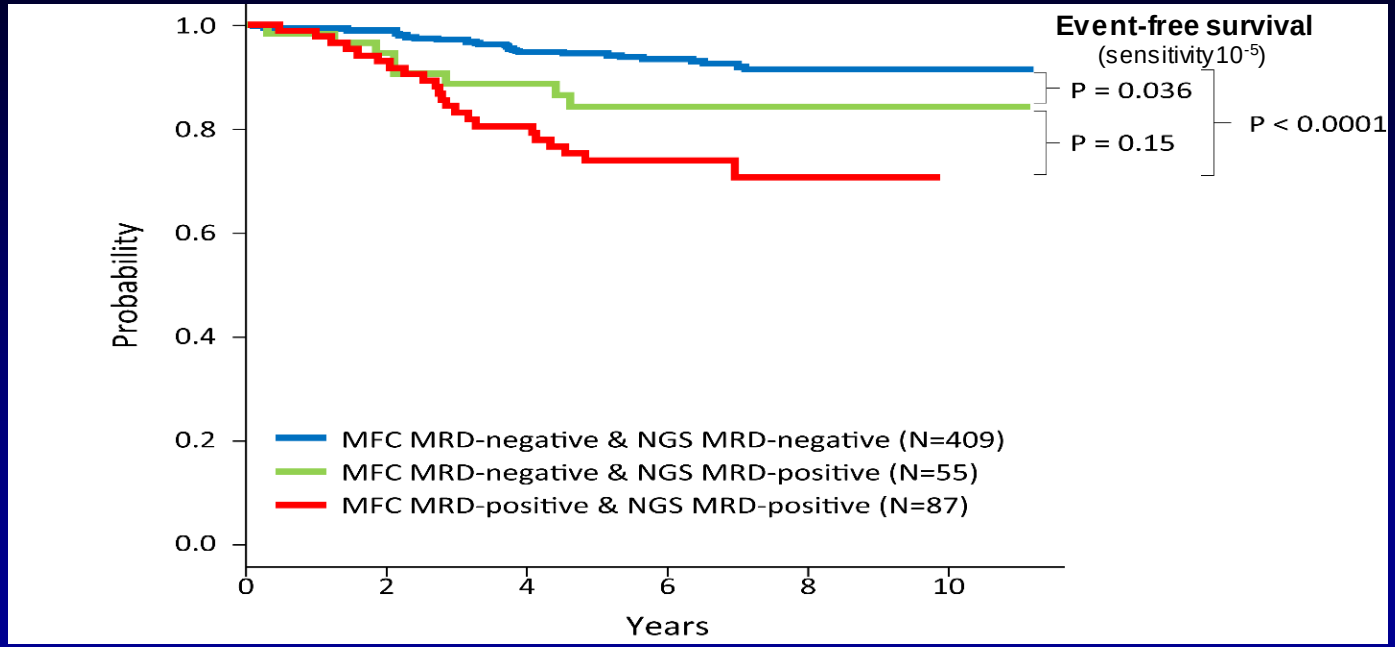
Dynamics of MRD: Outcomes

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.

NGS Identified Patients With Improved EFS

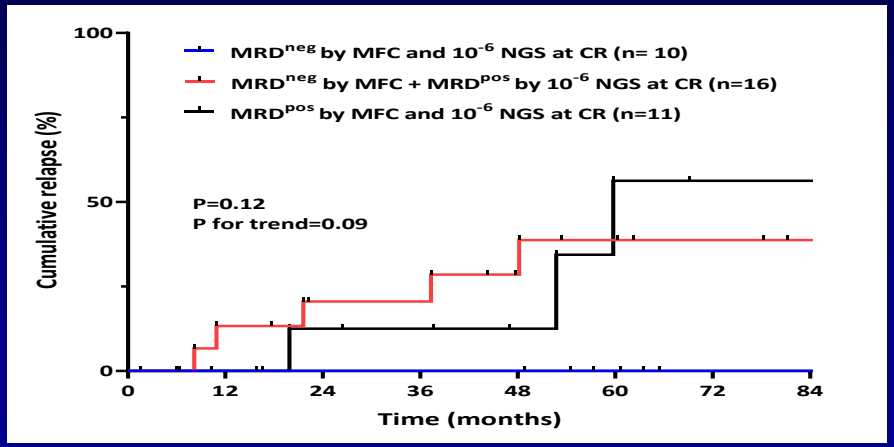


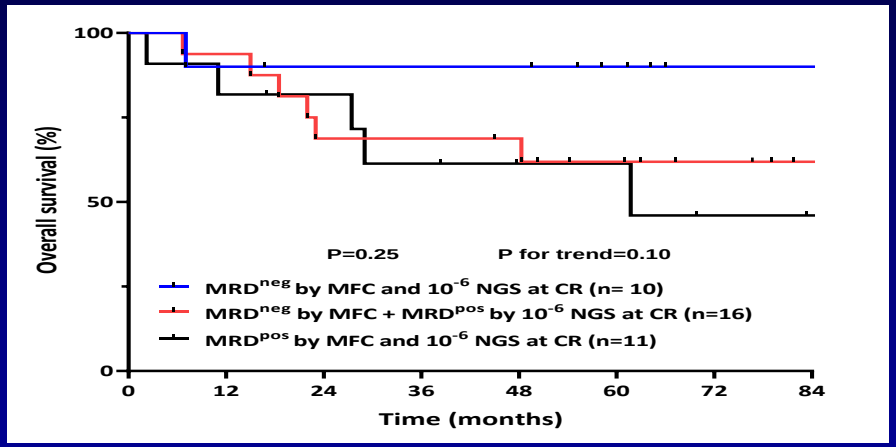
EFS was significantly worse in the NGS MRD+/flow cytometry MRD– group than patients who were MRD– by both methods (*P* = .036).
Six patients were identified as NGS MRD– and MFC MRD+.

Wood B, et al. *Blood*. 2018; 131(12):1350-1359.

MRD in ALL: NGS vs FCM

- 74 pts Rx (66% HCVAD; 34% mini-HCVD)
- 32/84 (38%) discordant (ie, MRD– by MFC but MRD+ by NGS)
  - 60% at CR and 25% @ midconsolidation
- MRD– by NGS highly predictive at CR





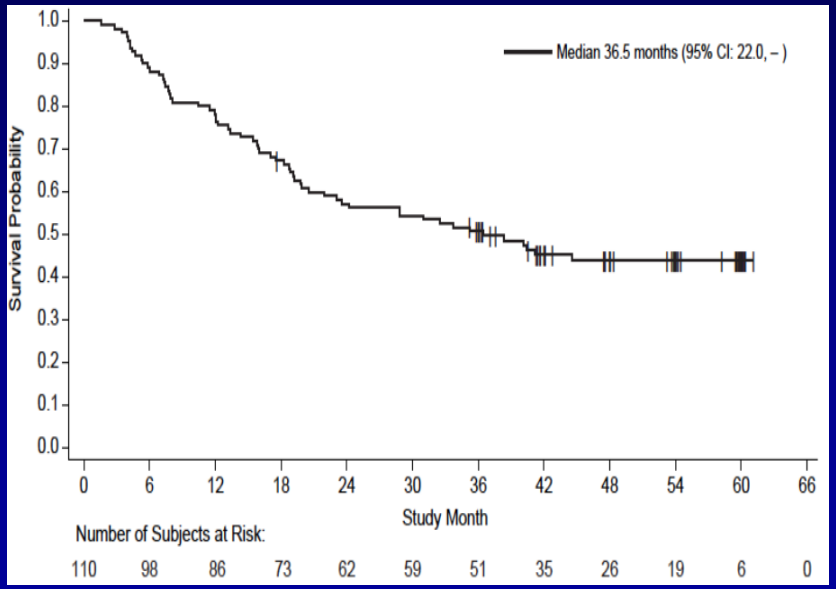
5-year CIR rates
MRD– by MFC and NGS: 0%
MRD– by MFC + MRD+ by NGS: 39%
MRD+ by MFC and NGS: 56%

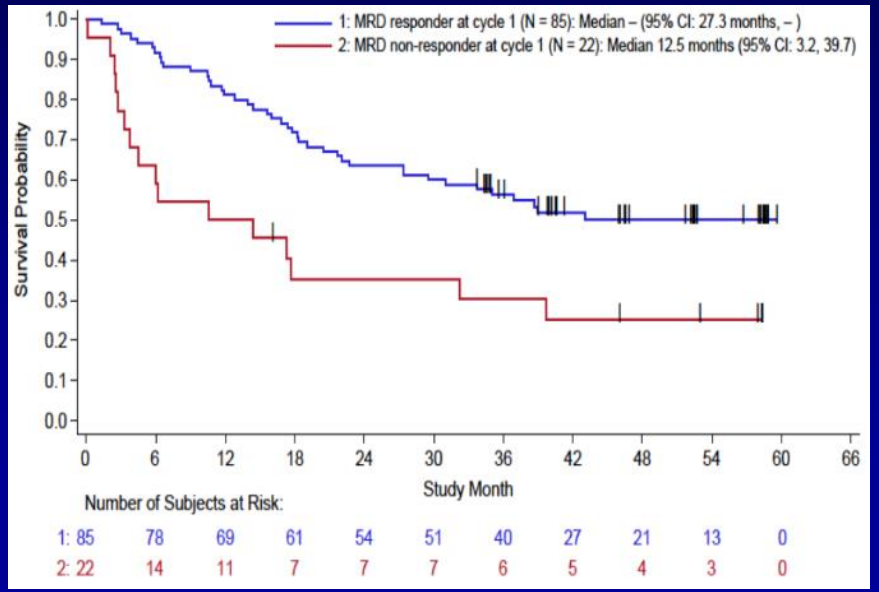
5-year OS rates
MRD– by MFC and NGS: 90%
MRD– by MFC + MRD+ by NGS: 62%
MRD+ by MFC and NGS: 61%

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

Blinatumomab for MRD+ ALL in CR1/CR2

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

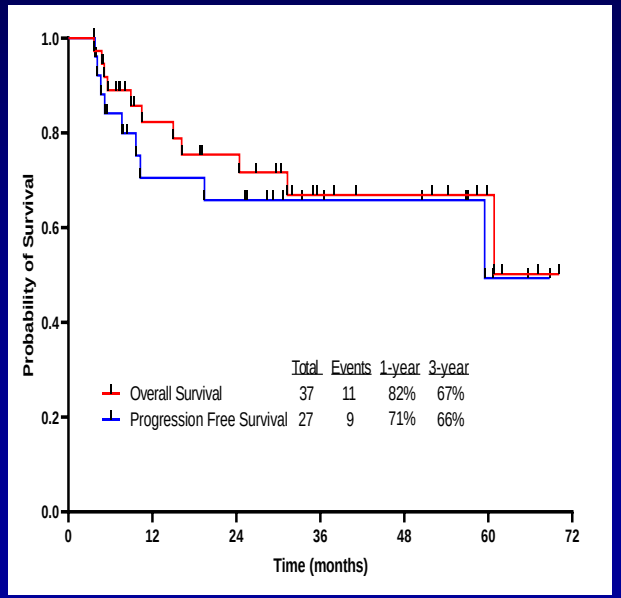


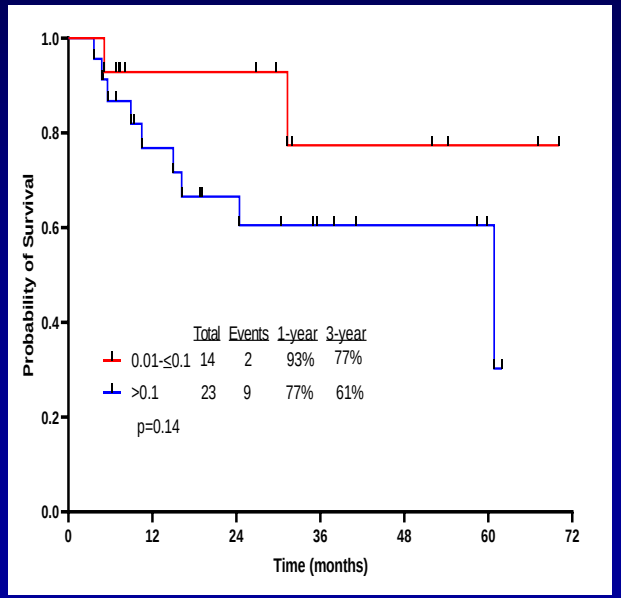


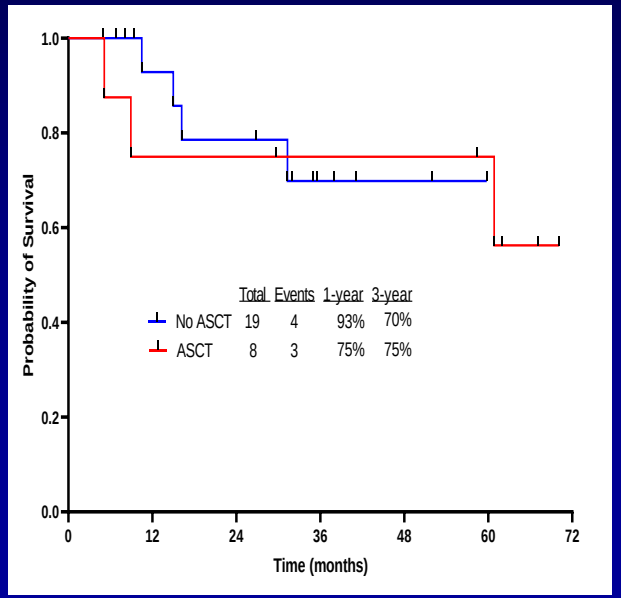
Goekbuget N, et al. *Blood*. 2018;132:abstract 554.

Blinatumomab for MRD+ ALL in CR1/CR2+

- 37 pts Rx. Post blina MRD– 27/37 = 73%; 83% in Ph– ALL
  - 70% after C1
- Median number of cycles 3 (1–9); Median F/U = 31 mos (5–70+)
- 14 pts 0.01 to <0.1%: 3-yr OS 77%; 23 pts ≥0.1%: 3-yr OS 61%
- 3-yr OS 67%; 3-yr OS if MRD– 72%





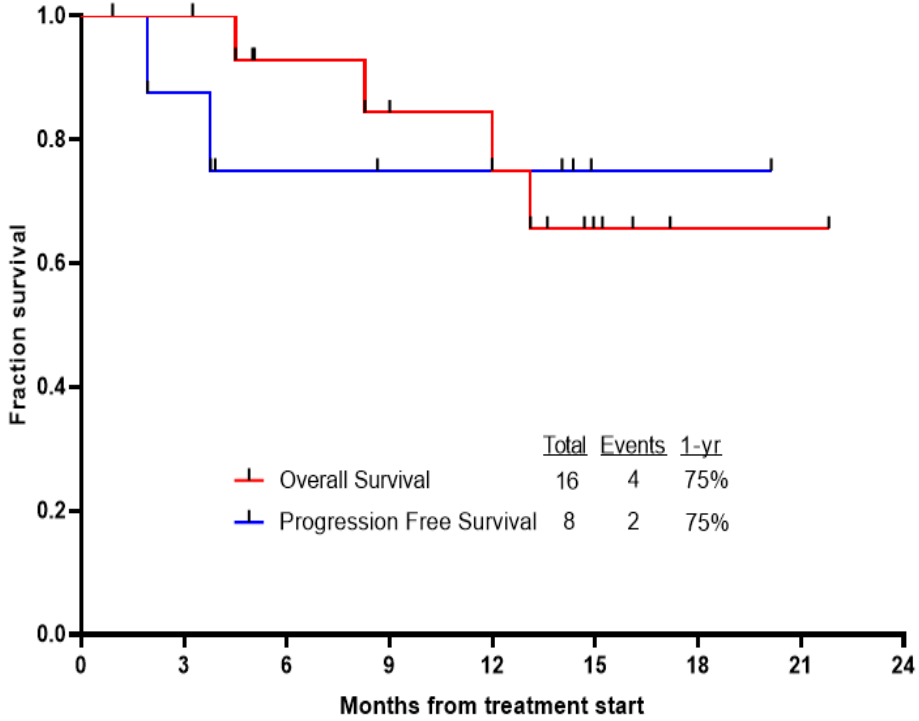


Short et al. EHA 2021.

Inotuzumab Ozogamicin in MRD+ ALL

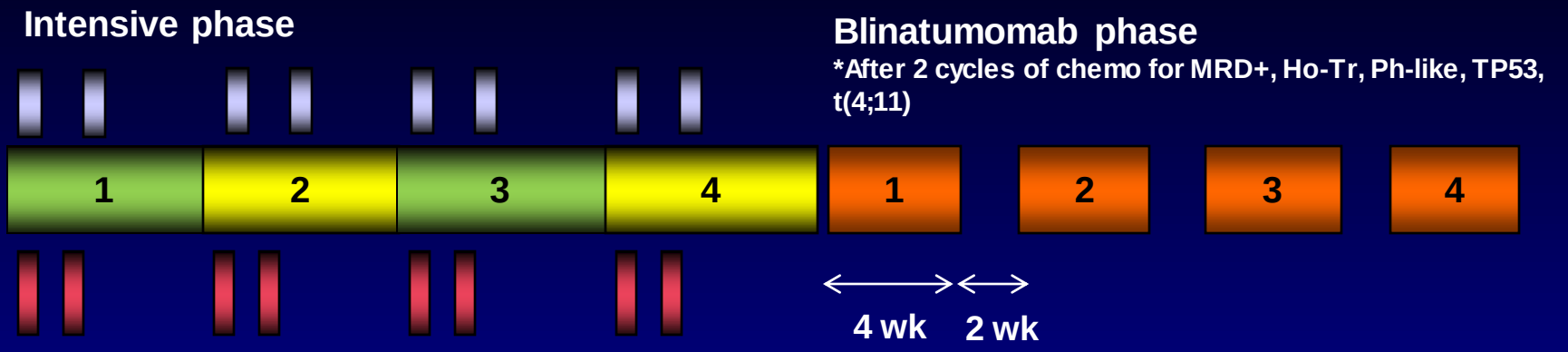
- 16 pts in CR1 (n = 11) or CR2 (n = 5) with FCM MRD >0.01
- Rx with INO 0.6 mg/m^2 D1, 0.3 mg/m^2 D8 and 0.3/0.3 D1/D8 in later courses. 10 had Ph+ ALL Rx with ponatinib (n = 9) or dasatinib (n = 1)
- Median INO 3 courses (1–6)
- Response – 8/16 (50%) MRD–: 4/6 (67%) by FCM, 4/10 Ph+ ALL (40%) by PCR—4 other Ph+ ALL had MMR
- Blina exposure – no: 5/7 (71%); yes: 3/9 (33%)
- 5 responders had later alloSCT
- 1 VOD post INO ×5

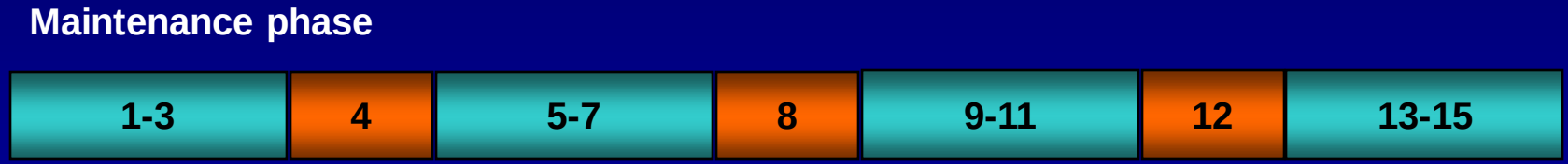
Figure 1: Overall survival and progression-free survival for the entire cohort (N=16)

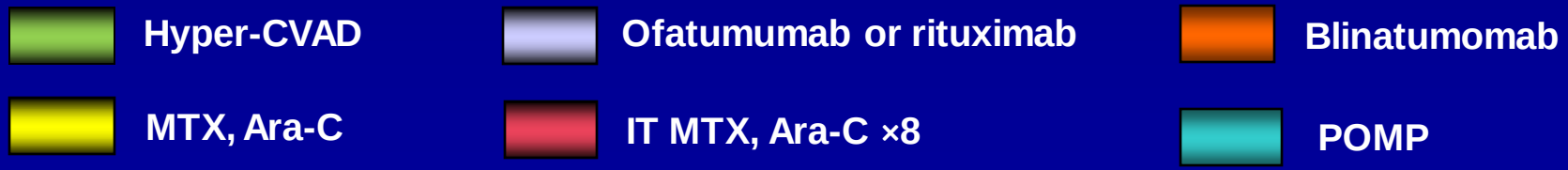


Short et al. *Blood.* 2021;138:abstract 2299.

Hyper-CVAD + Blinatumomab in B-ALL: Regimen





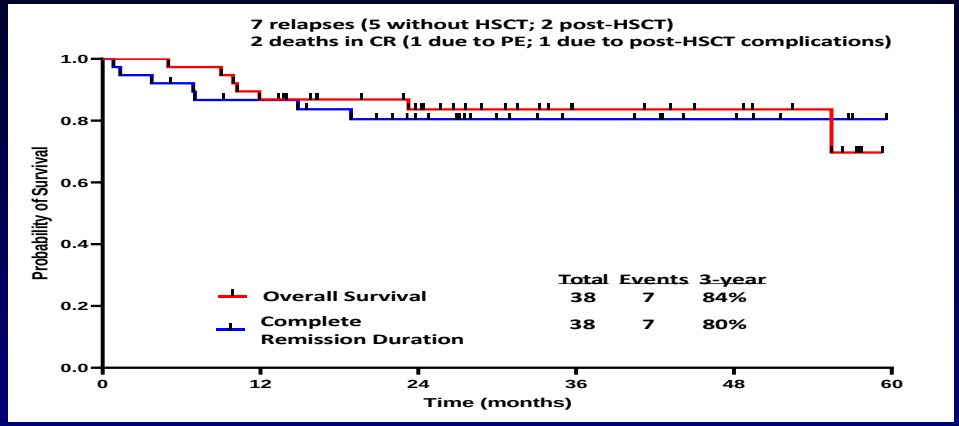


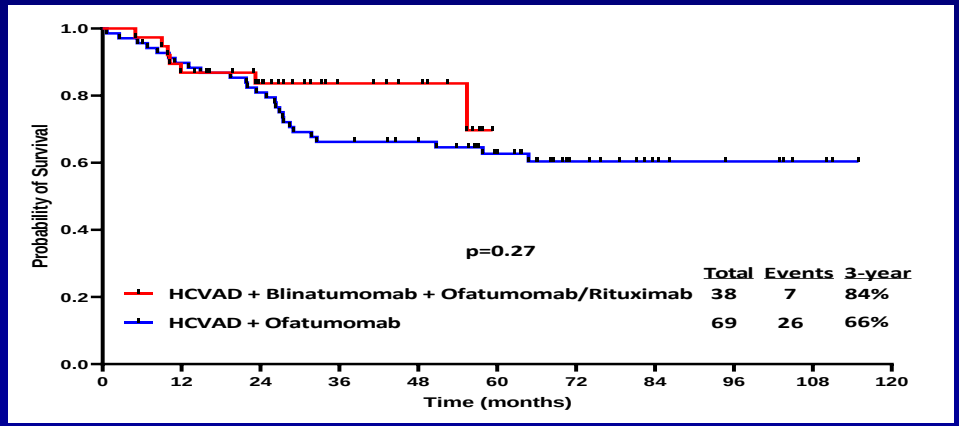
Short et al. *Blood.* 2021;136:abstract 1233.

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

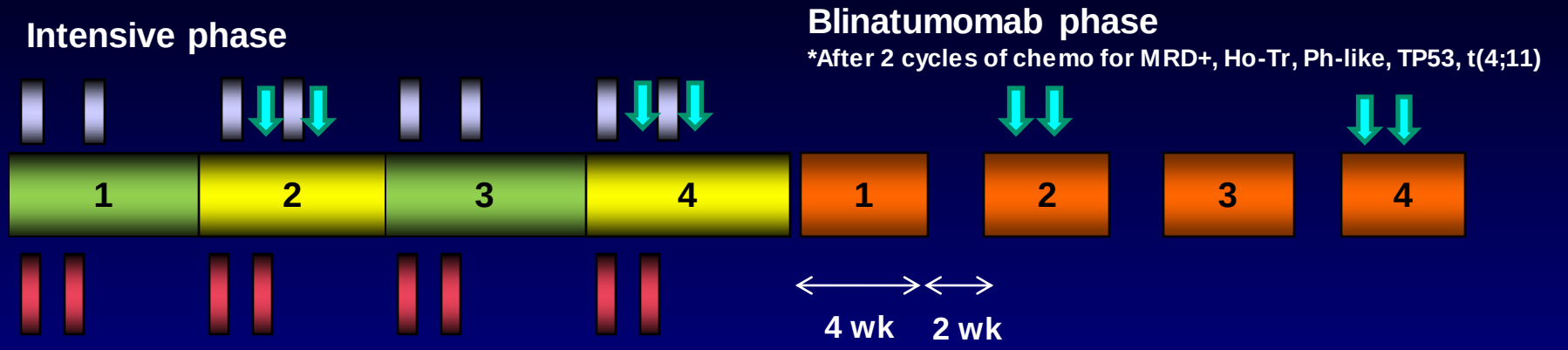
*6 pts in CR, 4 pts MRD– at start





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

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



Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

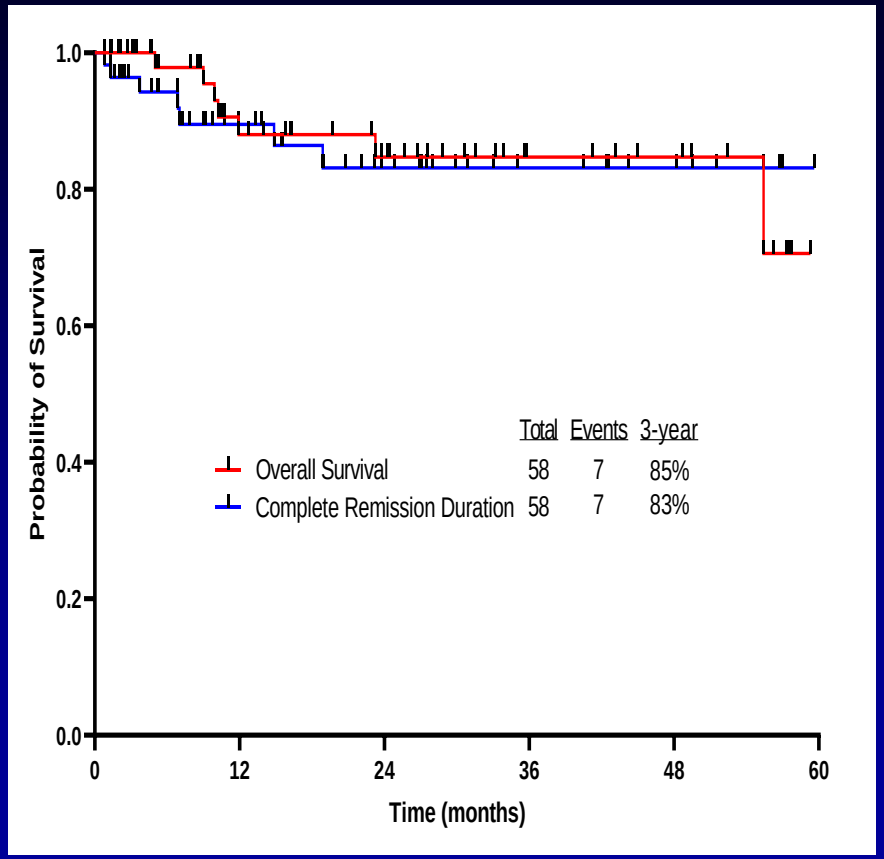
MTX (500 mg/m^2) + Ara-C (1 g/m^2)

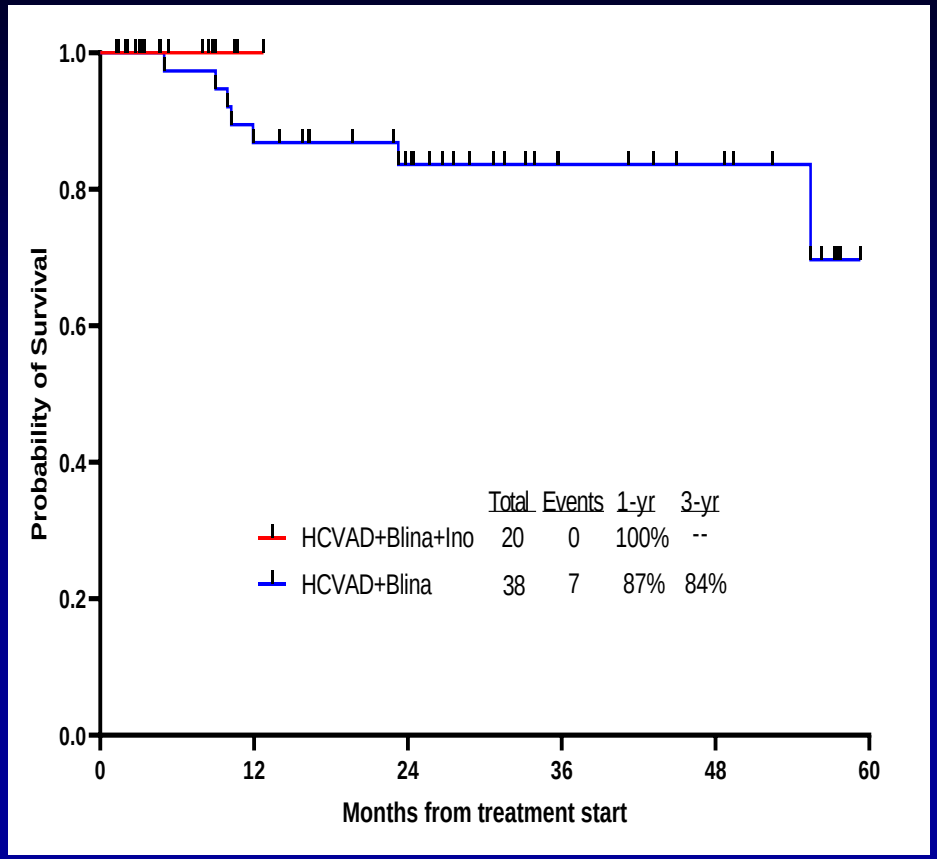
IT MTX, Ara-C ×8

POMP

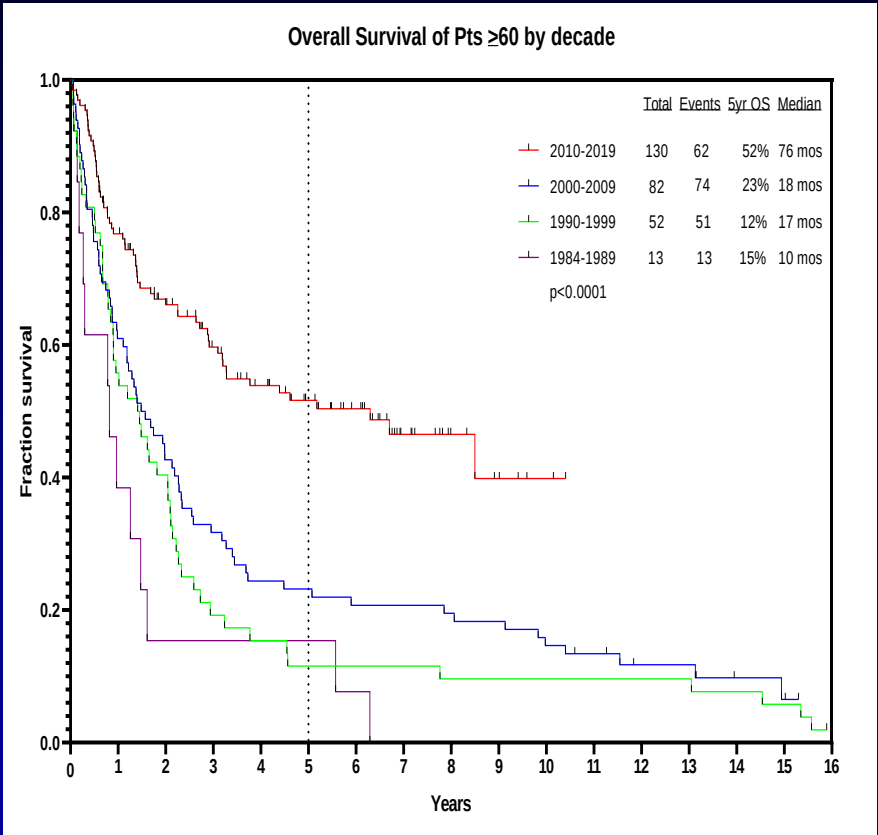
Inotuzumab 0.3 mg/m^2 on D1 and D8

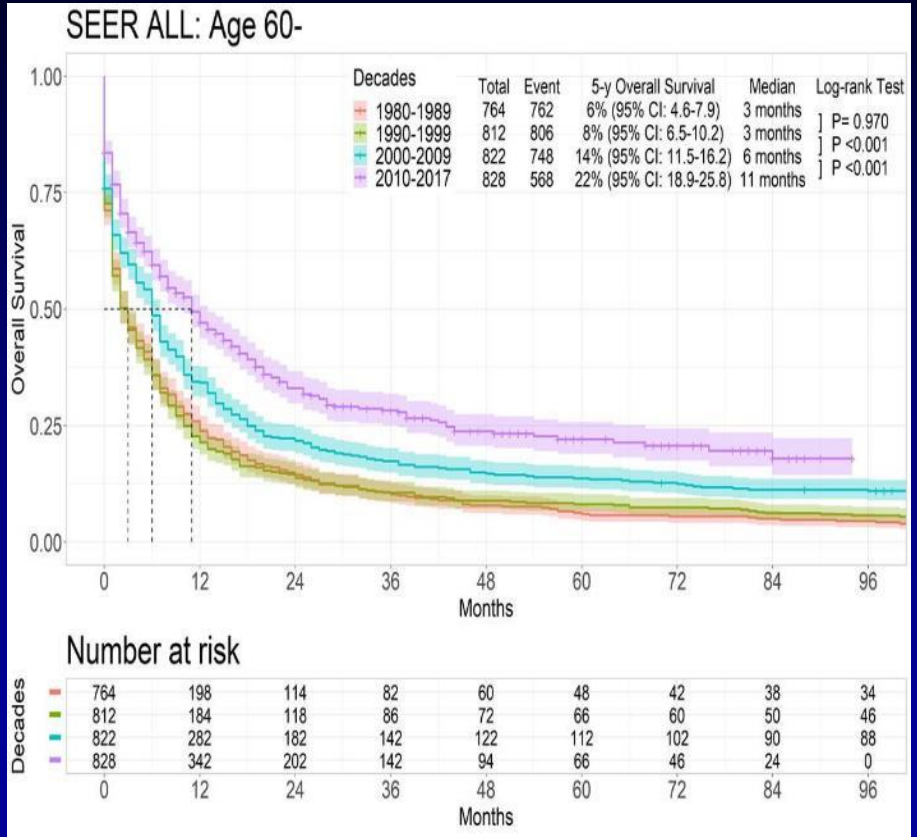
Hyper-CVAD + Blina + InO in B-ALL: Outcomes



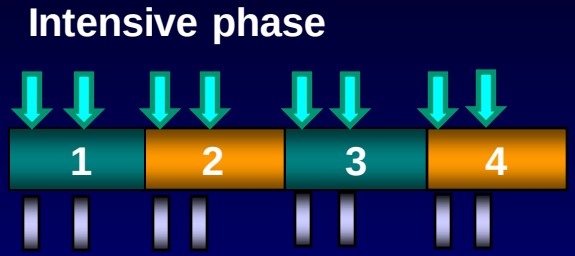


MDACC ALL: Survival by Decades for ≥60 Years





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

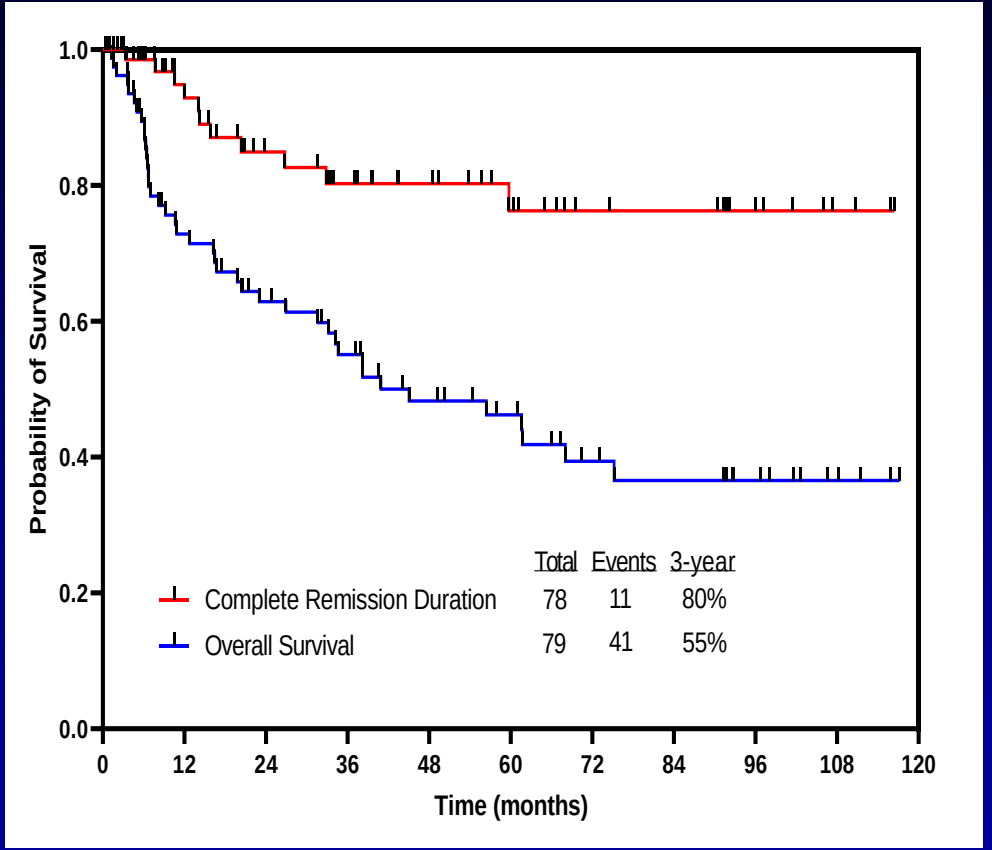
Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

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

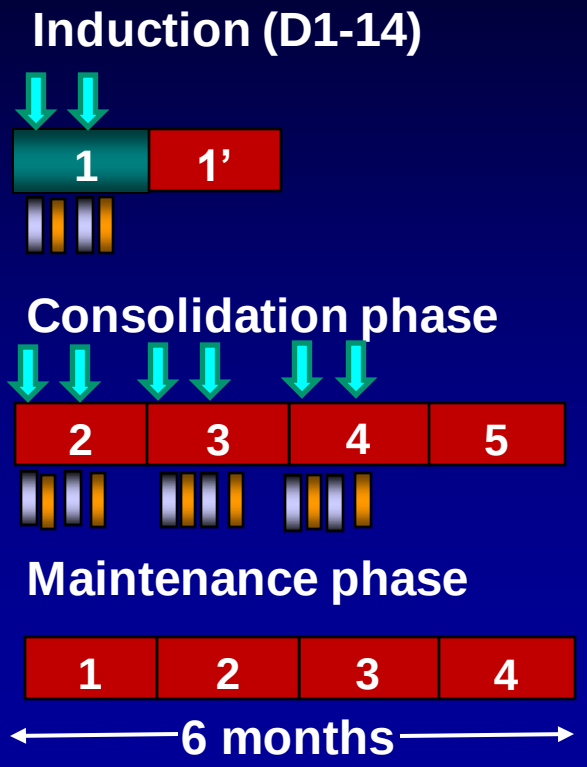
Mini-HCVD + Inotuzumab/Blinatumomab in Older ALL

- 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.

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

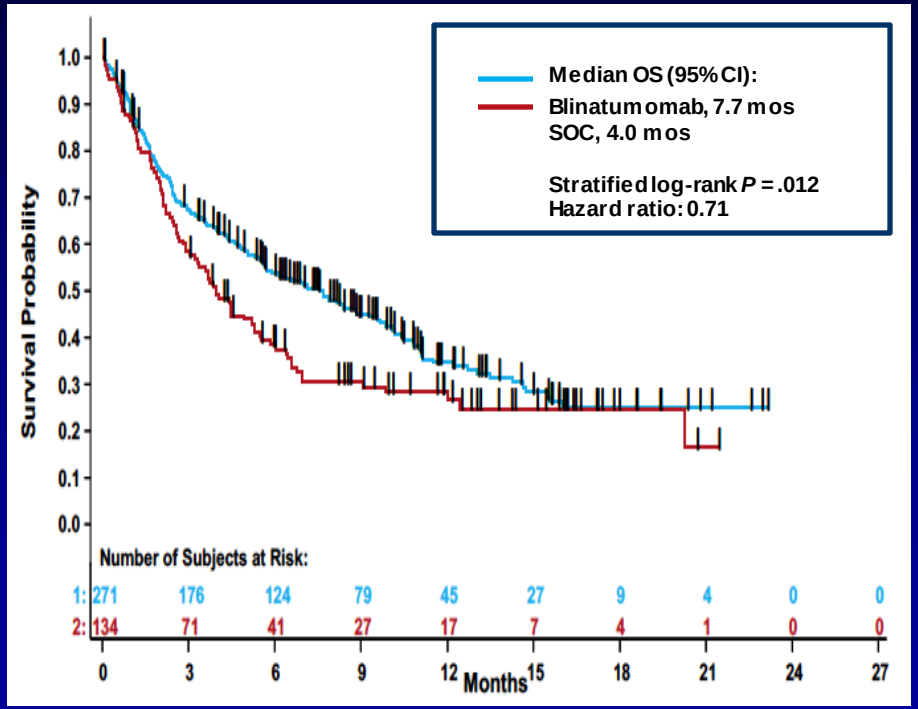
Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

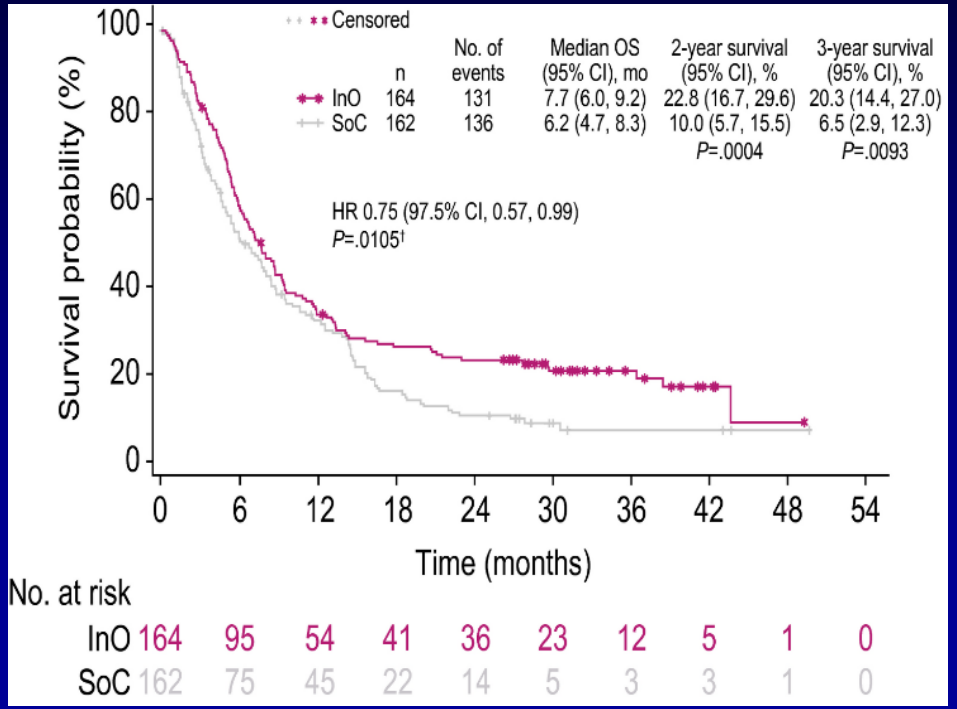
- **Marrow CR**

Blina vs SOC: 44% vs 25%



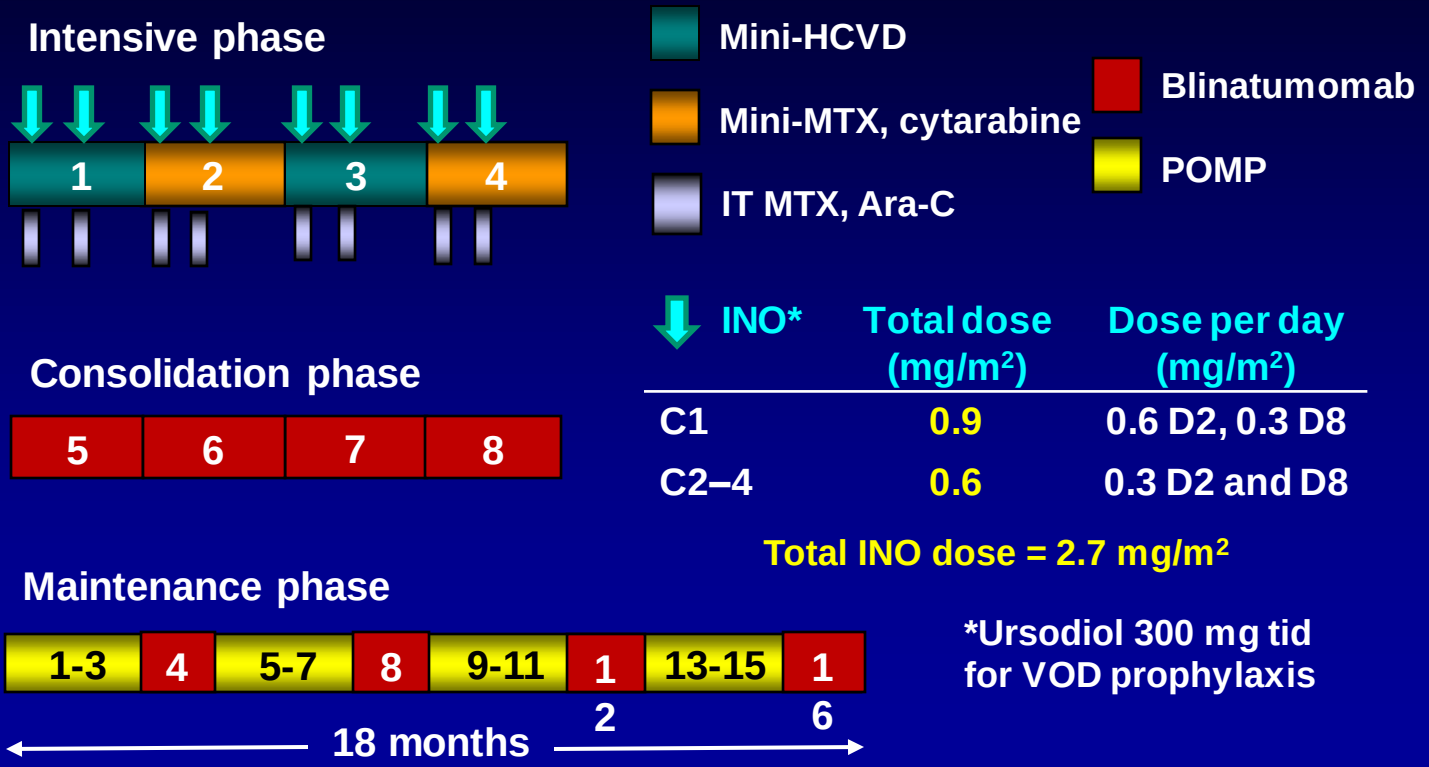
Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

Ino vs SOC: 74% vs 31%



Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

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



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

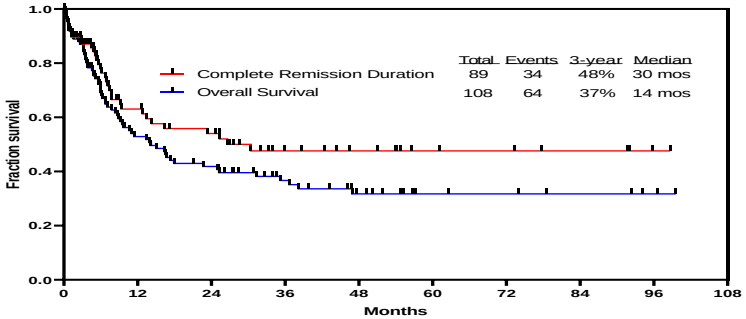
*Ursodiol 300 mg tid for VOD prophylaxis

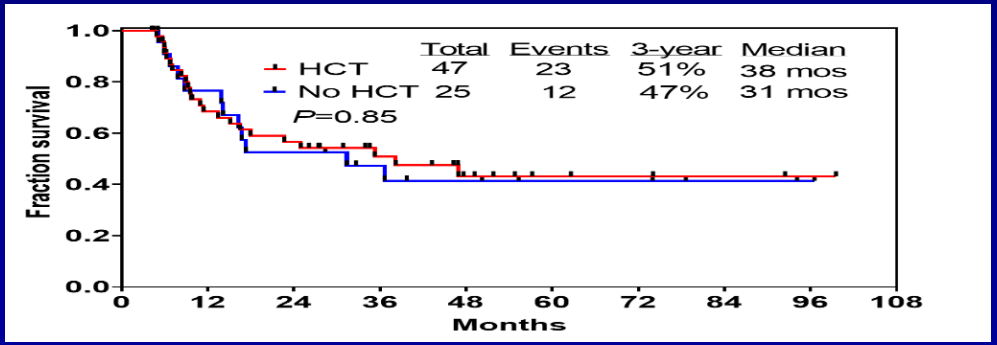
Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055.

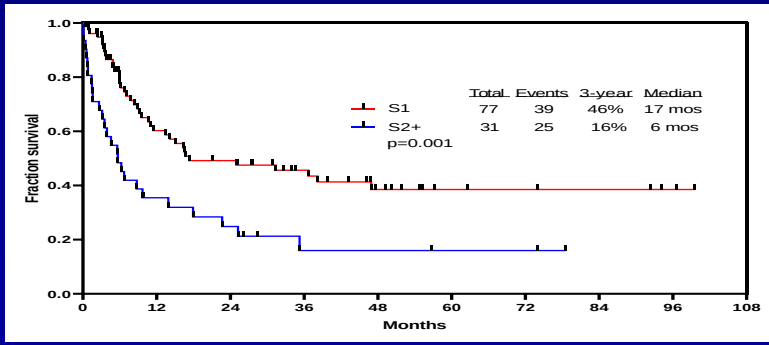
Mini-HCVD + INO in R/R ALL: Outcomes (N = 108)

Response	N (%)
Salvage 1	71/77 (93)
S1, primary refractory	14 (100)
S1, CRD1 <12 mos	21 (84)
S1, CRD1 ≥12 mos	36 (95)
S2	10 (59)
≥S3	8 (57)
ORR	89 (83)
MRD negativity	71/87 (82)
S1	59/69 (86)
≥S2	12/18 (67)
Early death	7 (6)*

	Single dose N = 67	Fractionated / reduced N = 41
VOD	9 (13)	1 (2)

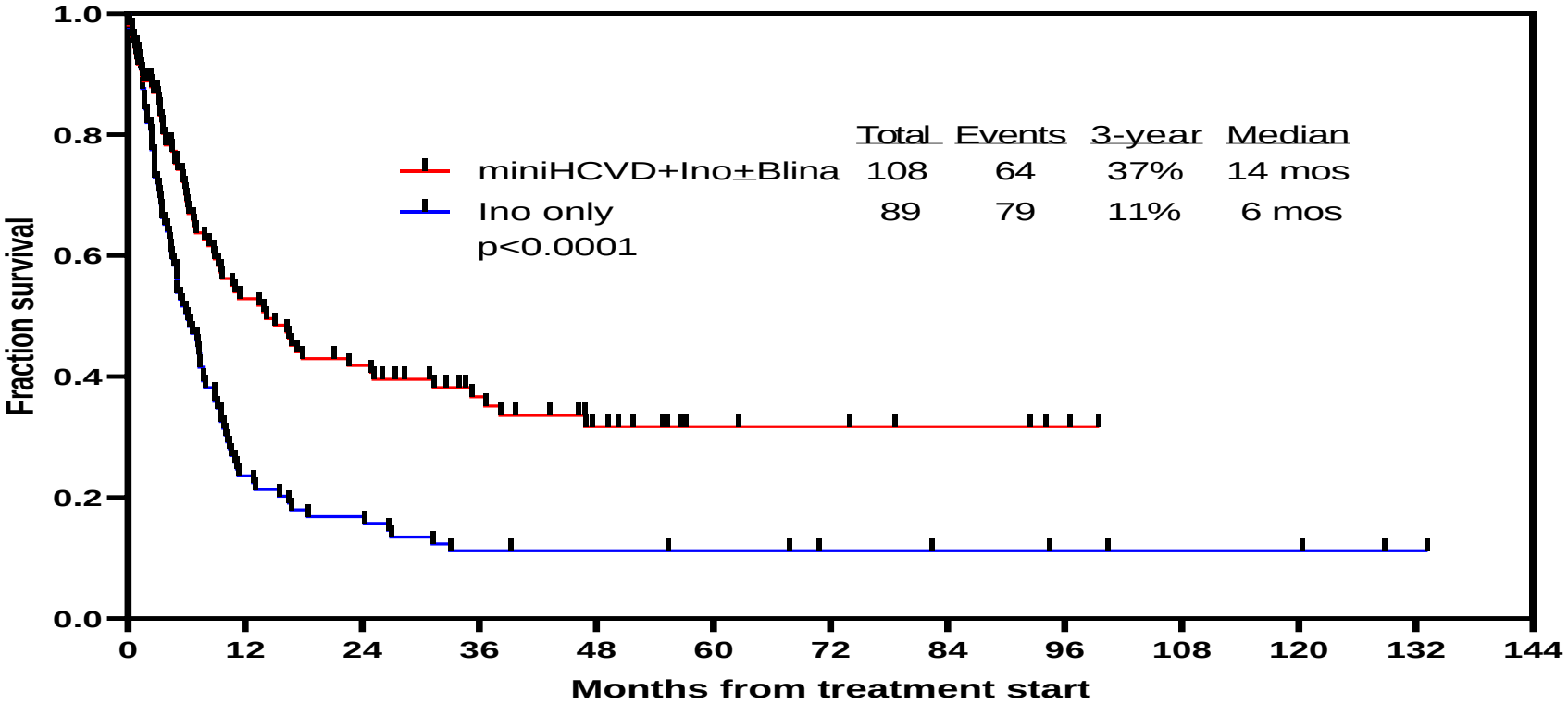






Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055.

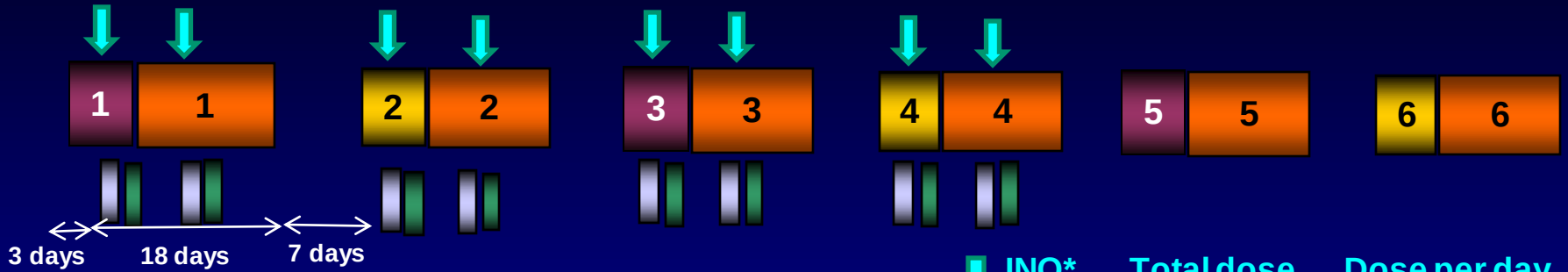
Mini-HCVD + INO ± Blina in R/R ALL: Historical Comparison



Jabbour E, et al. *JAMA Oncol.* 2018;4(2):230-234; Jabbour E, et al. *Cancer.* 2021;127(12):2025-2038.

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

Intensive phase: C1–C6



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

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Maintenance phase

Mini-HCVD

Rituximab

Blinatumomab

Mini-MTX, Ara-C

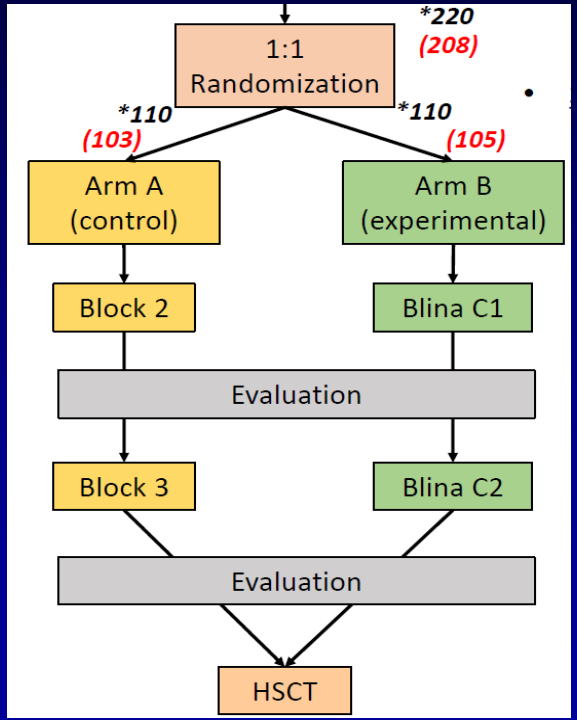
IT MTX, Ara-C

POMP

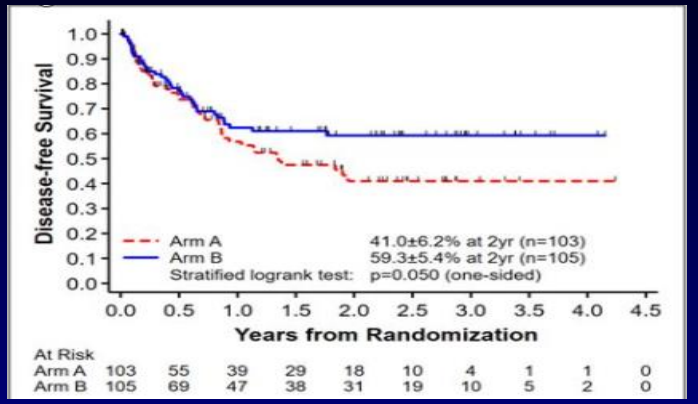
VCR/Steroid

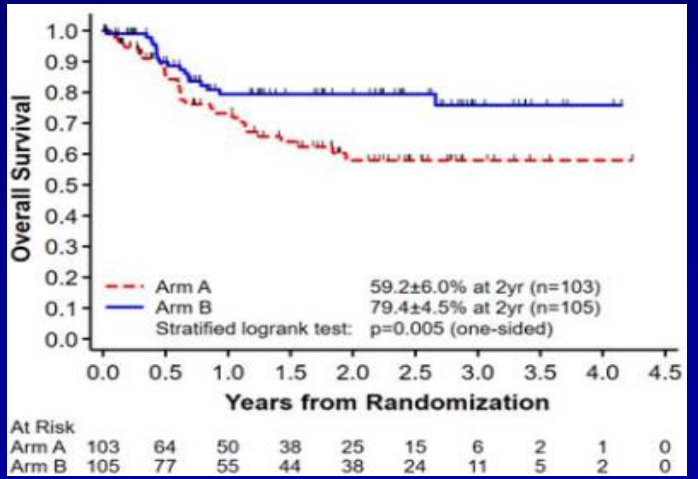
Phase III Study of Blinatumomab vs ChemoRx in Children-AYA in Salvage 1

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



Parameter	Blina	Chemo	*P*
% 2-yr DFS	59	41	.05
% 2-yr OS	79	59	.005
% SCT	73	49	<.001
% MRD clearance	79	21	<.001



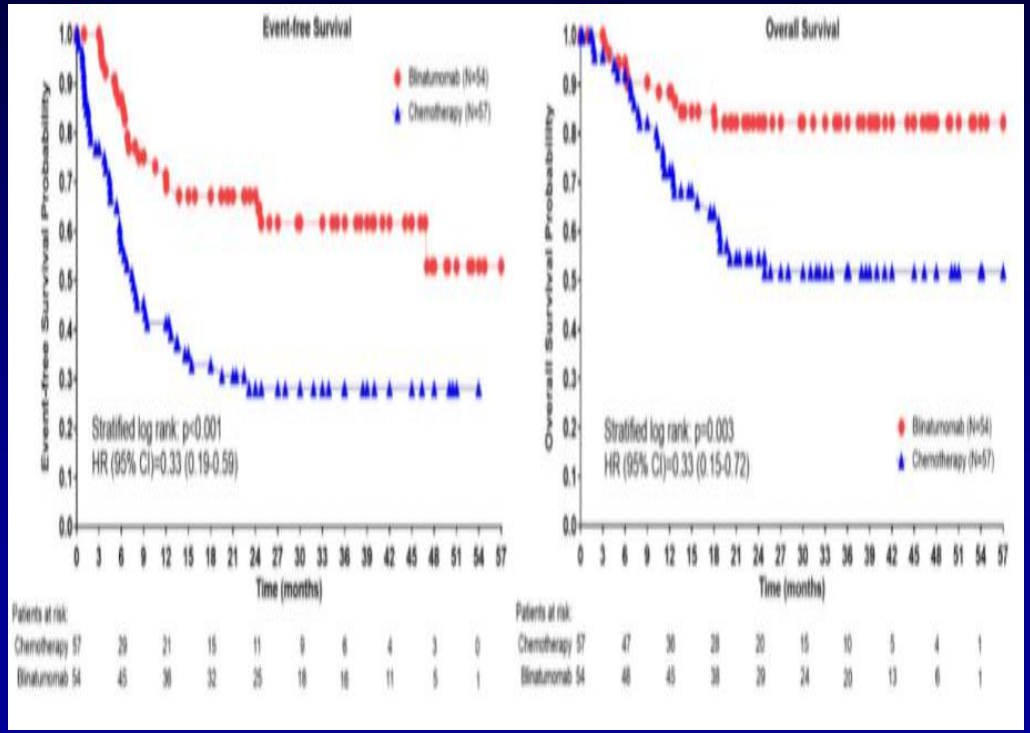


Brown et al. *JAMA*. 2021:325(9):833-842.

Blinatumomab vs Chemo Rx as Pre-SCT Consolidation

- 111 children in ALL S1 randomized post induction and 2 consolidations to blinatumomab (n = 54) or chemo Rx (n = 57)

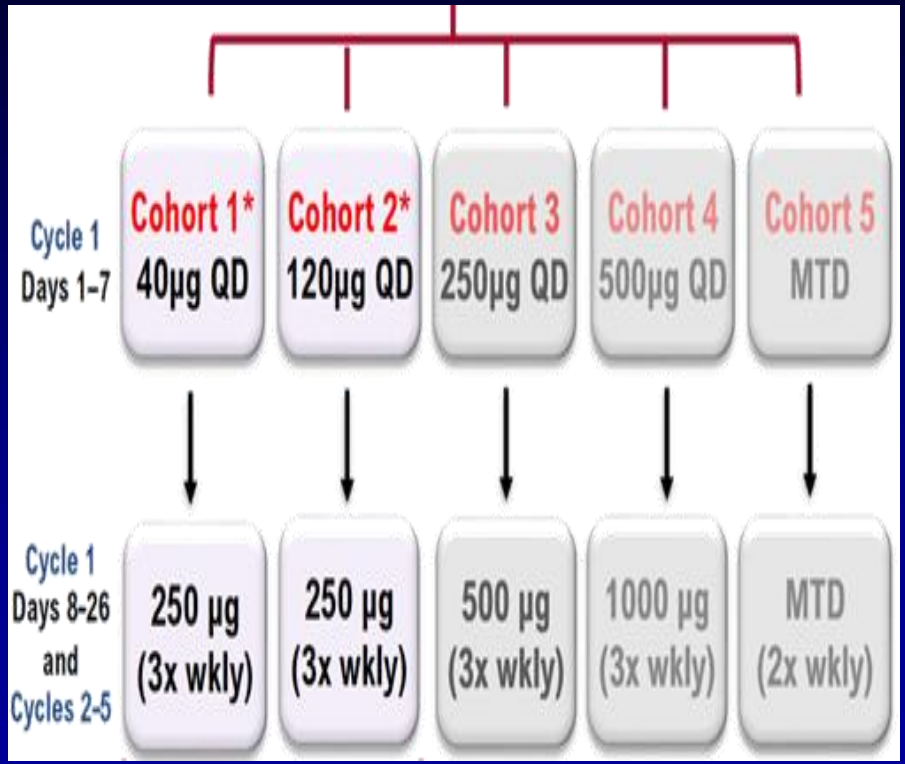
Parameter	Blina	Chemo Rx	*P* Value/ HR
% 2-yr EFS	63	37	<.001/.33
% 2-yr OS	83	60	.003/.33
% MRD–	91	48	-
AlloSCT	51/54	39/57	-



Locatelli F, et al. *Blood*. 2021;140:abstract 123.

Subcutaneous Blinatumomab in R/R B-ALL: Phase Ib Dose-Finding Study

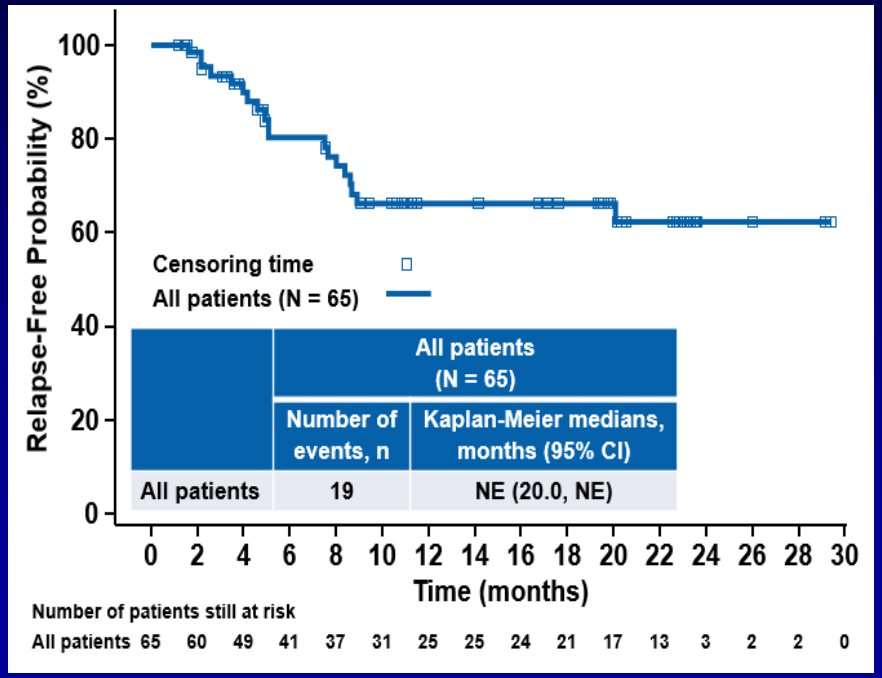
- 9 R/R pts, median age 64 yrs (38–83)
- Rx in with SC blinatumomab in 2 cohorts; median BM blast 79% (range, 28%–95%)
- Median prior therapies = 2 (range, 2–4)
- 5/9 achieved MRD-negative CR, 3 in Cohort 1 (3/6, 50%) and 2 in Cohort 2 (2/3, 66%)
- All patients who achieved CR did so within the first treatment cycle

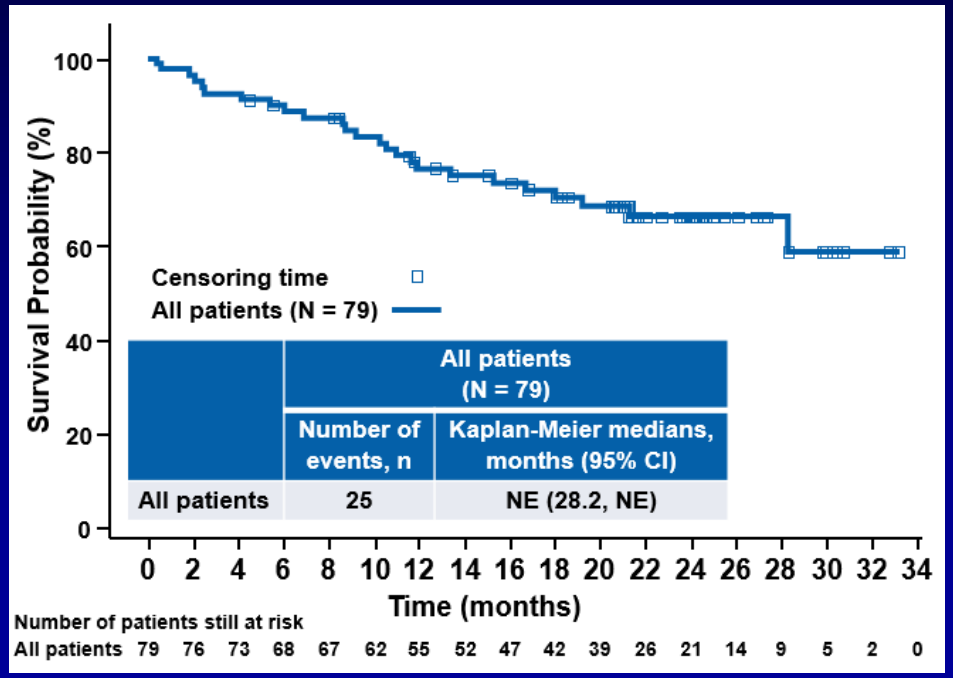


Martínez-Sánchez. *Blood*. 2021;138:abstract 2303.

ELIANA Trial Update

- 113 screened, 97 enrolled, 79 infused
- 3-mo CR 65/79 = 82%, or 65/97 = 67%
- 24-mos OS 66%; RFS 62%. Gr 3-4 CRS 49%. ICU 48%

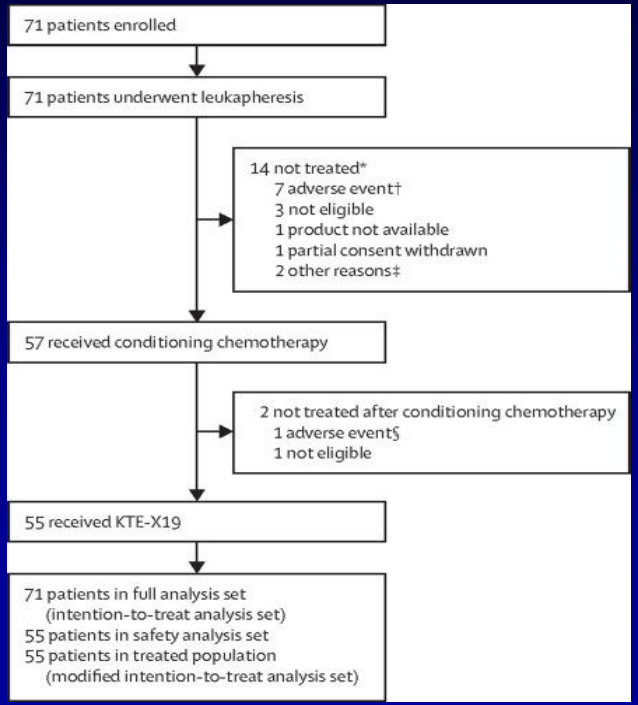


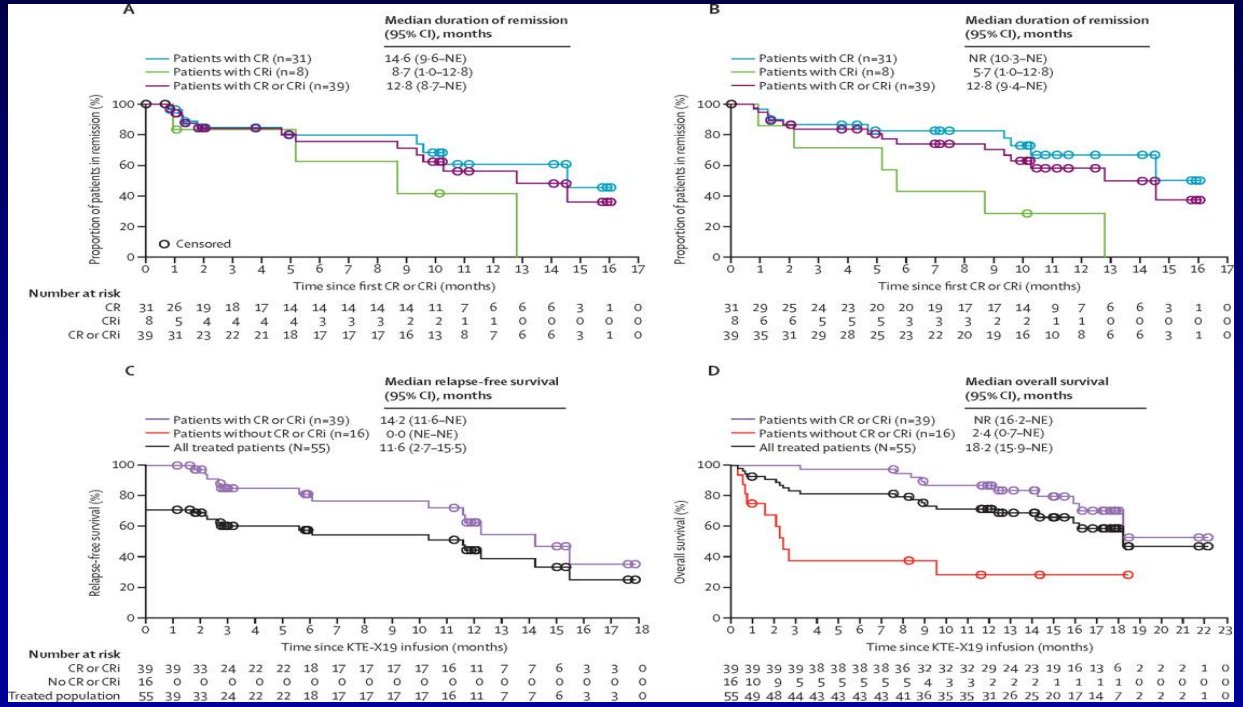


Grupp et al. EHA 2019. Abstract S1618.

KTE-X19 Anti-CD19 CAR T Cells RX (Kite) in R/R ALL: Phase II (ZUMA-3)

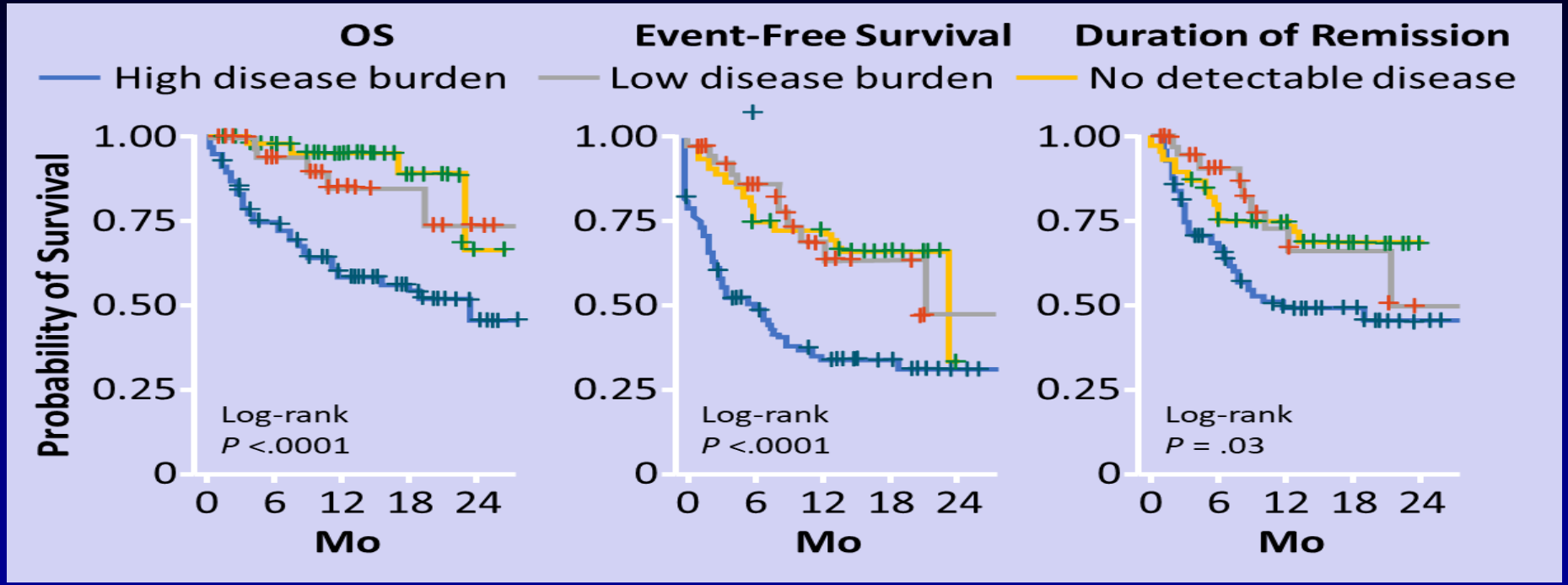
- 71 enrolled, 55 infused; median age 40 yrs (28–52)
- CR/CRi 39/55 (71%, CR 56%); ITT (39/71; 55% – CR 44%); MRD– response 76% (97% among responders); 10 pts (18% Rx ASCT)
- mDOR 12.8 mos; mRFS 11.6 mos; mOS 18.2 mos
- Grade ≥3: CRS 24%; NE 25%





Shah et al. *Lancet*. 2021;S0140-6736.

Real-Word CAR Consortium and Disease Burden



High Burden Disease (n = 94; 47%)

- 1-yr OS 58%
- 1-yr EFS 34%

Low Burden Disease (n = 60; 30%)

- 1-yr OS 85%
- 1-yr EFS 69%

Undetectable Disease (n = 46; 23%)

- 1-yr OS 95%
- 1-yr EFS 72%

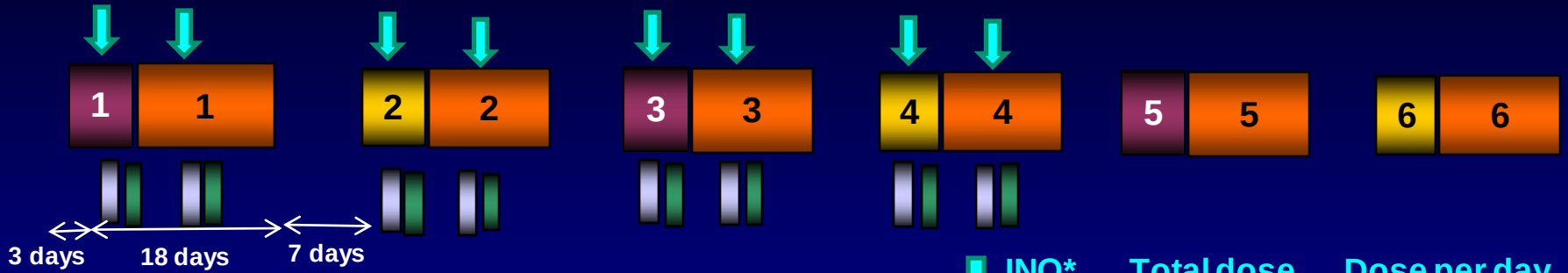
Schultz et al. *Blood*. 2020;136.abstract 468.

CAR T in ALL – The Beginning of a Great Journey

- CART Rx today is what allogeneic SCT was in 1980 – a great beginning
- Improved CAR T designs
- Dual CAR Ts targeting CD19, CD22, CD20
- Allogeneic off-the-shelf CAR Ts
- Smaller repeated allogeneic CAR Ts infusions (fractionated CAR Ts)
- CAR Ts in first CR in MRD to replace alloSCT

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 2022: Conclusions

- Significant progress and improved outcomes across all ALL categories: Ph+, Burkitt, younger and older pre-B ALL, T-ALL, ALL salvage. Rapidly evolving therapies
- Incorporation of Blina/Ino in FL therapy highly effective
  - HCVAD-Blina: MRD– CR 97%; 3-yr OS 84%
  - Mini-HCVD-INO-Blina: MRD– CR 96%; 3-yr OS 55%
  - Blina-ponatinib: CMR rate 85%; 2-yr OS 93%
- Early eradication of MRD predicts best overall survival
  - NGS-negative MRD at CR – 5-yr OS 100%
  - Tailoring therapy: "Treatment a la carte"
- 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) SQ blinatumomab; 4) CAR Ts in sequence in CR1 for MRD and replacing allo-SCT

AML

AML in 2017–2020, 10 Agents FDA Approved

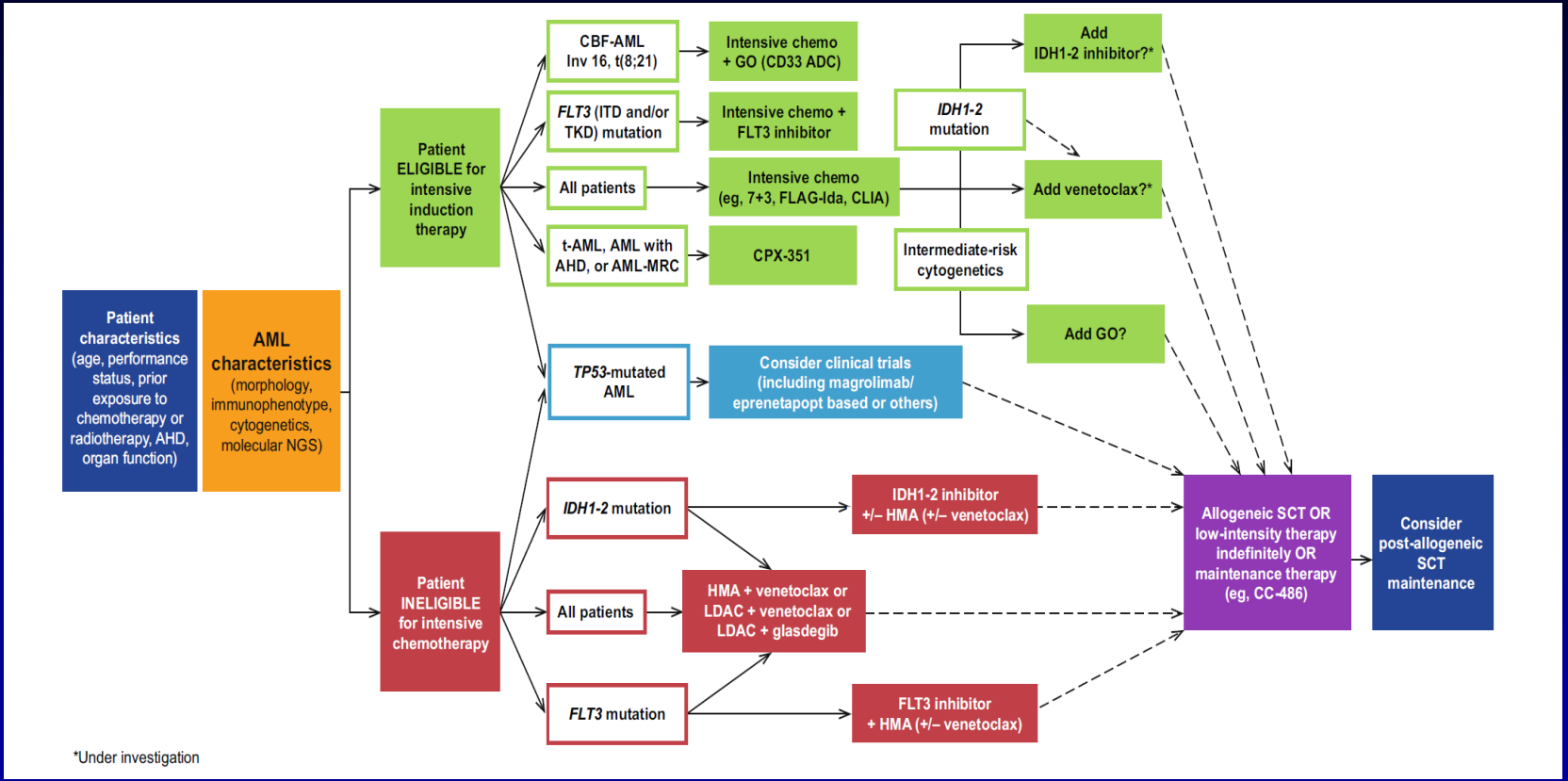
- **Midostaurin** (RYDAPT) for de novo younger AML (≤60 yr), *FLT3* mutation – April 2017
- **Gilteritinib** (*FLT3* inhibitor) for *FLT3*+ R/R AML
- **Enasidenib** (AG-221; IDHIFA) for R/R AML and *IDH2* mutation – August 2017
- **Ivosidenib** (AG-221) for R/R AML – August 2018
- **CPX-351** (Vyxeos) for newly Dx Rx-related AML and post-MDS AML – August 2017
- **Gemtuzumab ozogamicin** revival for frontline AML Rx – August 2017
- **Venetoclax** for newly Dx older/unfit for intensive chemo, with AZA/DAC, ara-C
- **Glasdegib** for newly Dx older/unfit, with ara-C
- **Oral decitabine – HMA Rx for MDS and CMML – August 2020**
- **Oral azacitidine** in AML maintenance – Sept 2020

Clinical Applications of Molecular Studies in AML

- *FLT3*-ITD mutations – add FLT3 inhibitor (midostaurin, sorafenib, gilteritinib), 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

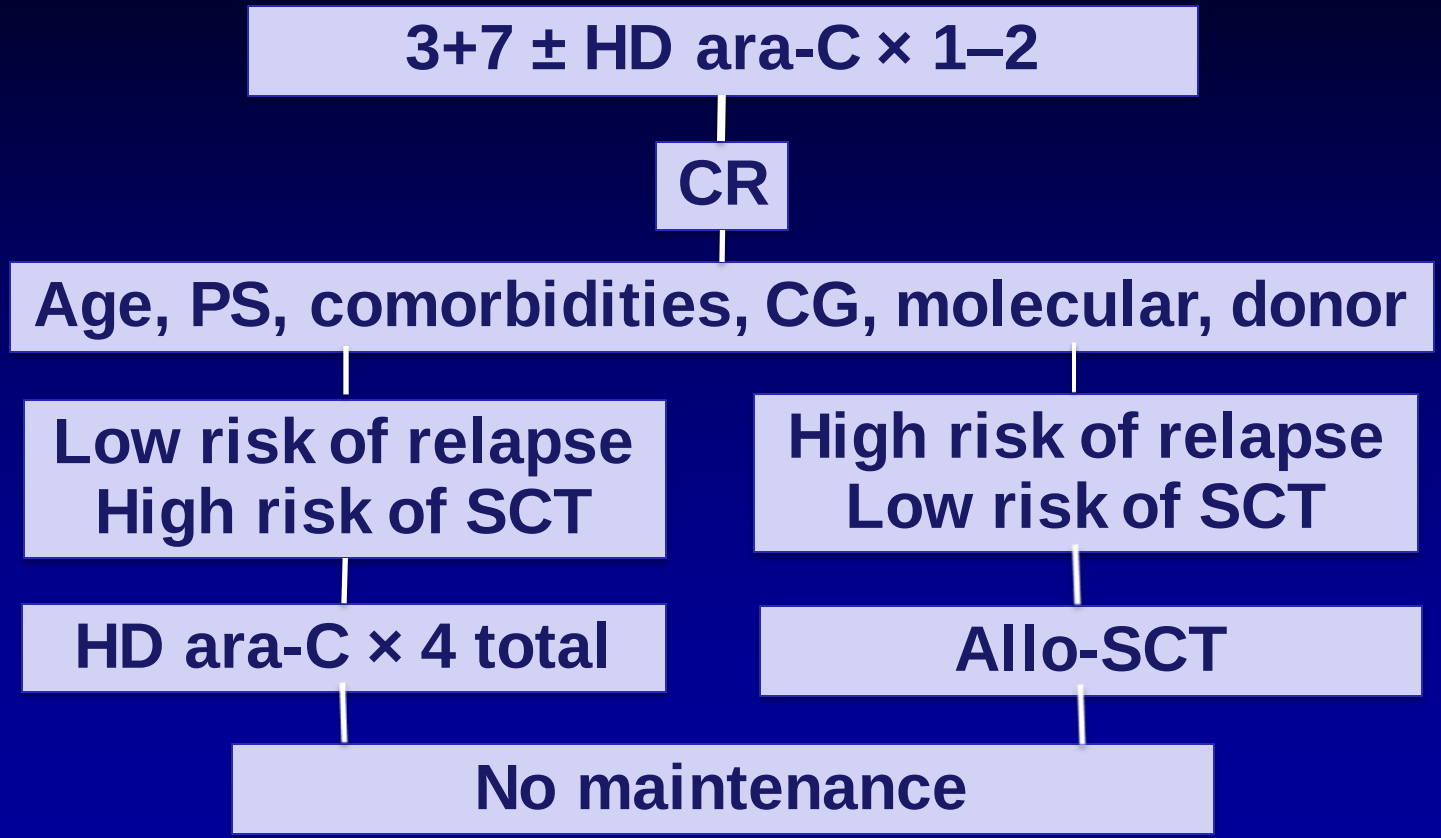
NCCN guidelines. Acute Myeloid Leukemia; v2.2018.

Evolving Diagnostic and Treatment Paradigm for Newly Dx AML

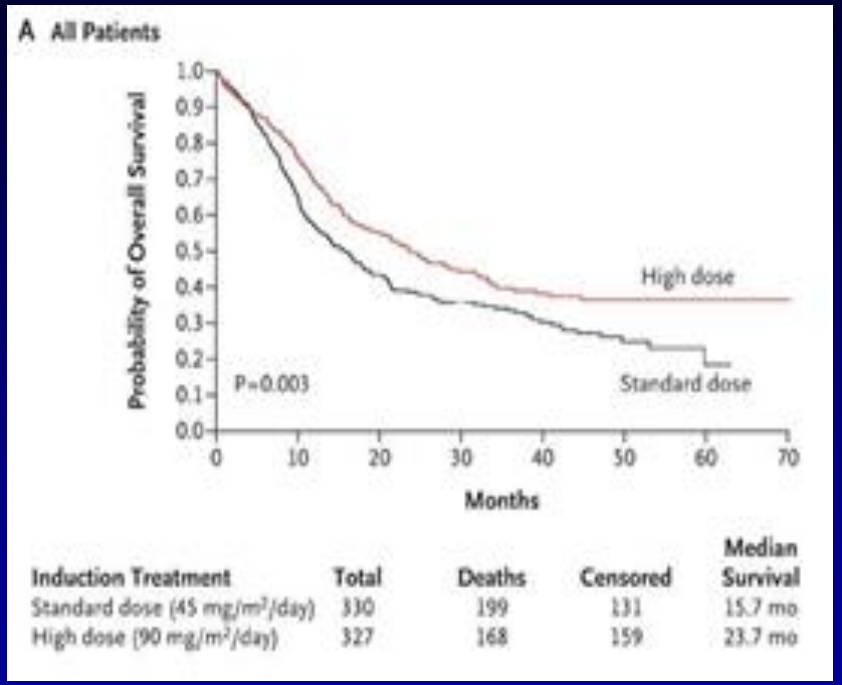


Daver N, et al. *Blood Cancer J.* 2020;10(10):107.

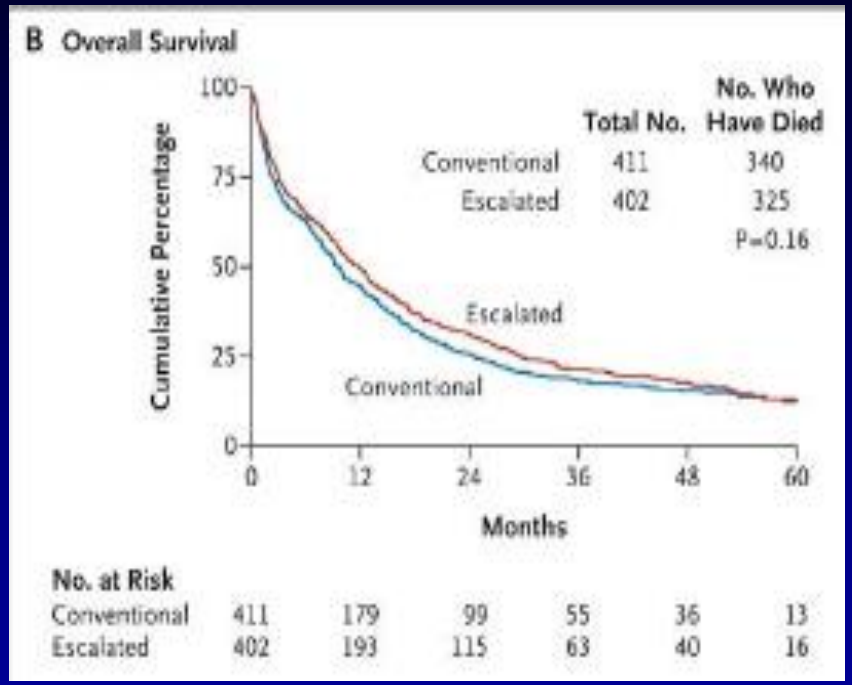
Therapy of AML: The Old Standard



Actual Results of “3+7”



Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m²/day)	330	199	131	15.7 mo
High dose (90 mg/m²/day)	327	168	159	23.7 mo



	Total No.	No. Who Have Died
Conventional	411	340
Escalated	402	325

P=0.16

No. at Risk						
Conventional	411	179	99	55	36	13
Escalated	402	193	115	63	40	16

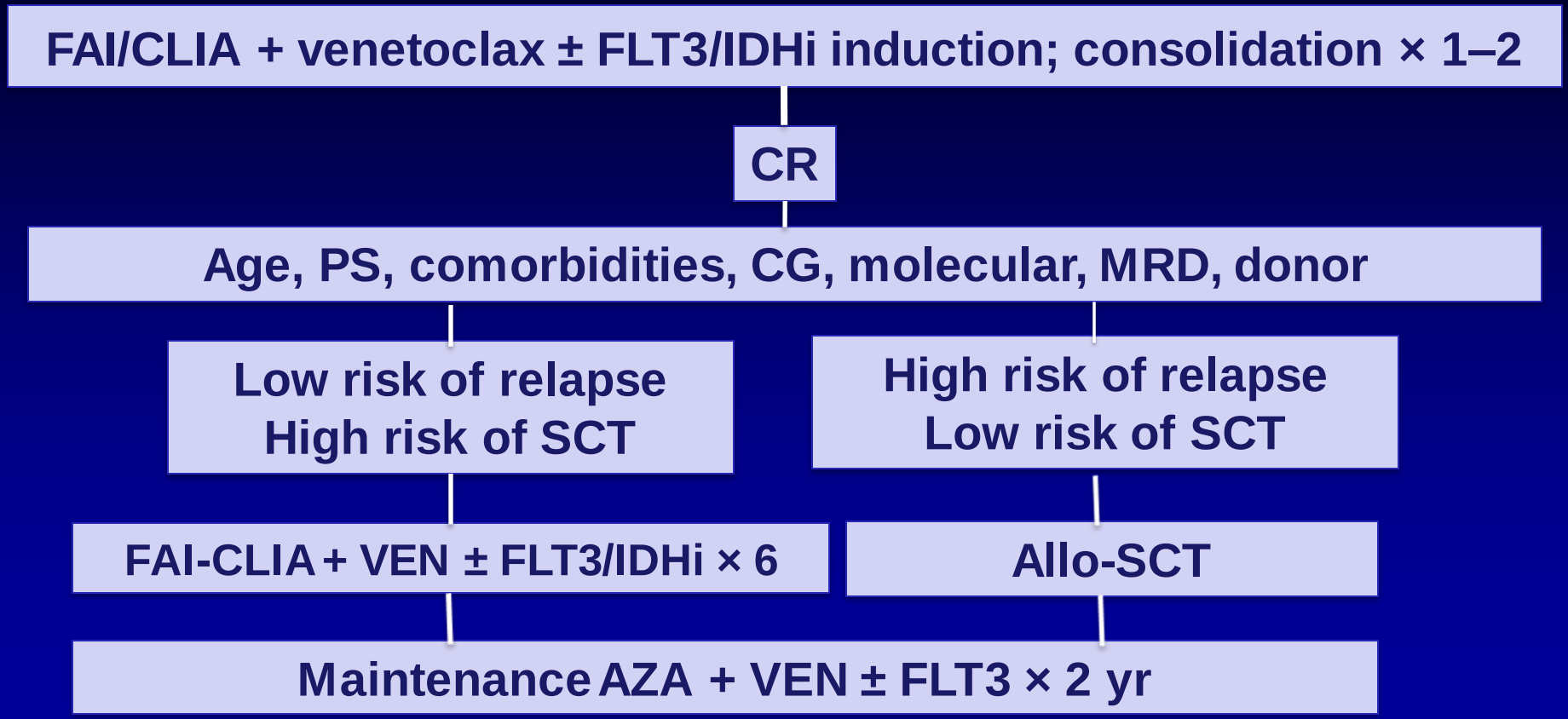
- 5-yr survival 20%–35% in young, 10% in old

Fernandez HF, et al. *N Engl J Med*. 2009;361:1249-1259; Löwenberg B, et al. *N Engl J Med*. 2009;3611235-1248.

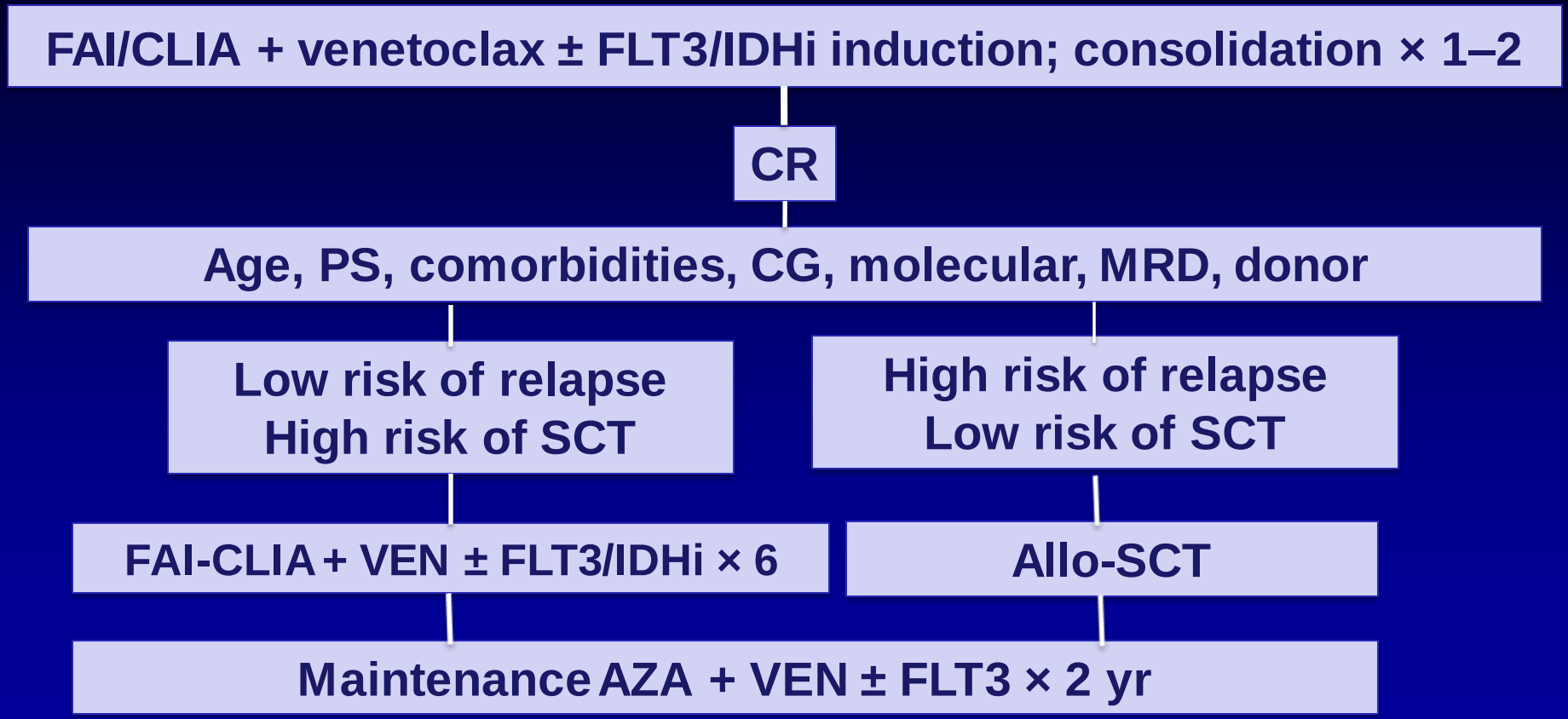
AML: What Definitely Works

- FLT3 inhibitors
- IDH1–2 inhibitors
- CD33 and CD123 antibodies
- Venetoclax
- Maintenance with oral azacitidine
- ? Oral decitabine-cedazuridine + venetoclax in older/unfit AML

Therapy of Younger AML at MD Anderson in 2022+



Therapy of Younger AML at MD Anderson in 2021+

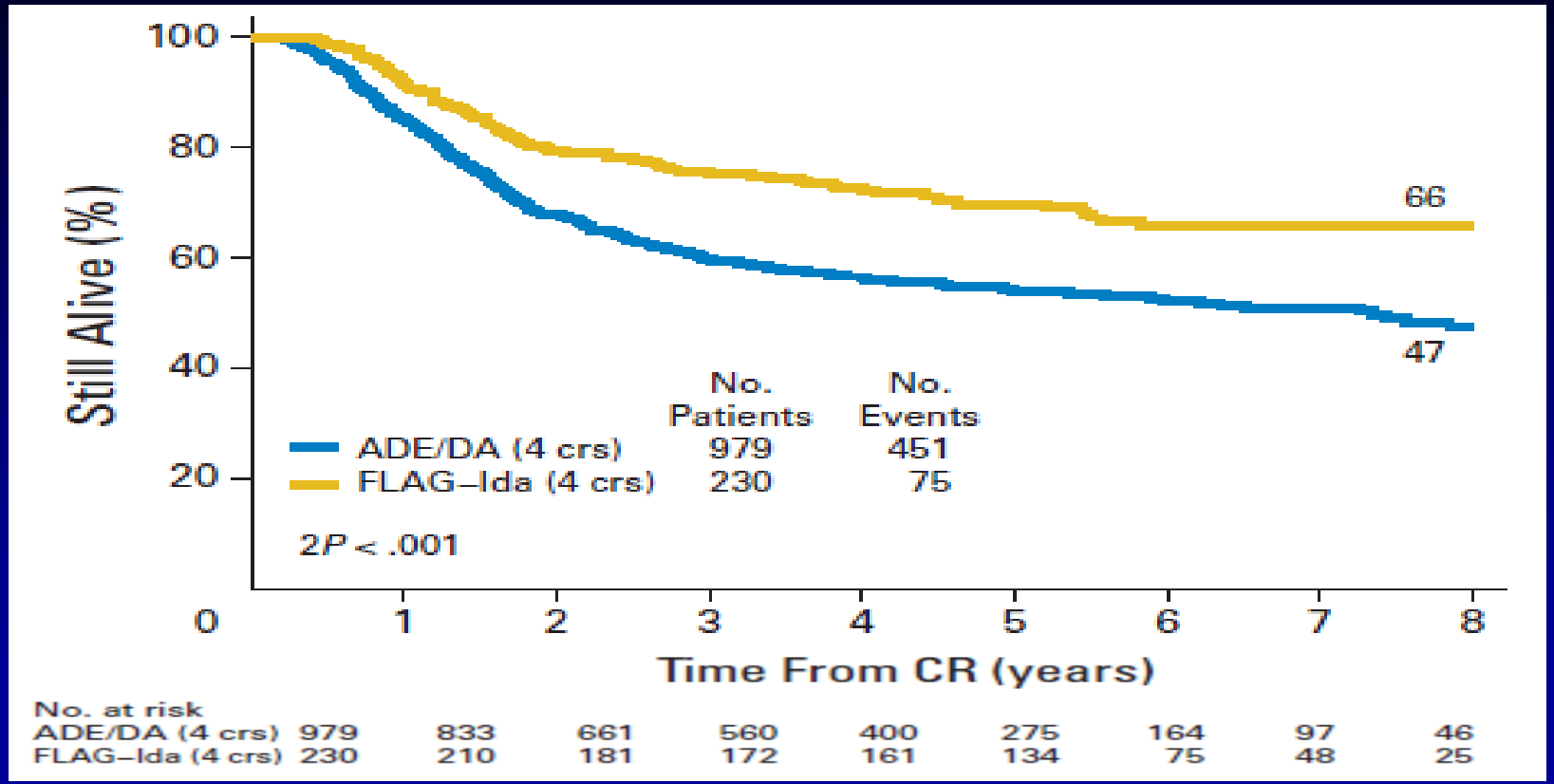


High-Dose Ara-C Induction Improves Outcomes in AML

- Meta-analysis of 3 randomized trials
- EORTC-GIMEMA: survival benefit in age ≤45 yr
- Chinese study
- MRC AML 15
- Italian study

Kern W, Estey EH. *Cancer*. 2006;107(1):116-124; Willemze R, et al. *J Clin Oncol*. 2014;32(3):219-228; Wei H, et al. *Blood*. 2017;130:abstract 146; Burnett AK, et al. *J Clin Oncol*. 2013;31:3360-3368; Bassan R, et al. *Blood Adv*. 2019;3(7):1103-1117.

MRC AML 15: ADE/DA vs FLAG-IDA – 4 Courses



Burnett AK, et al. *J Clin Oncol*. 2013;31:3360-3368.

FLAG-IDA and CLIA

- Fludarabine – 30 mg/m^2/D×5

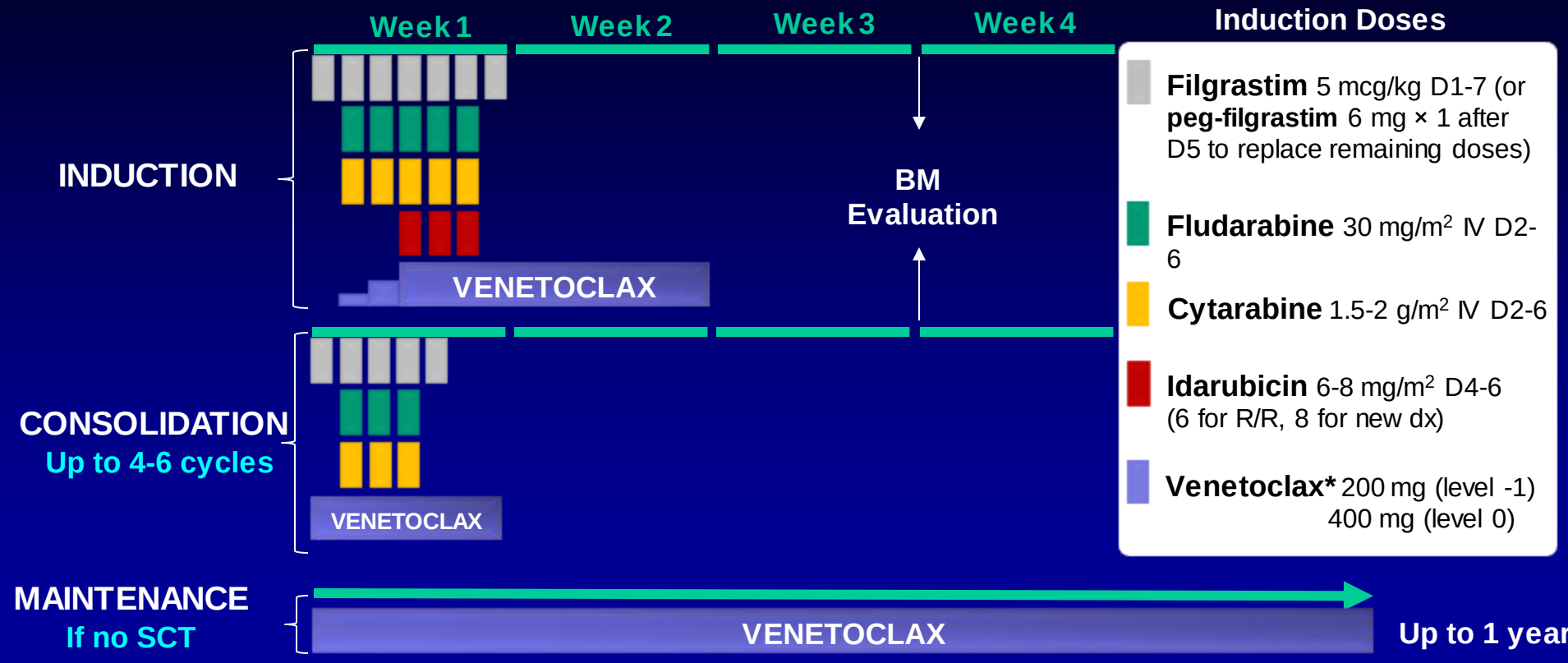
  AraC 2 g/m^2/D×5

  IDA 8–10 mg/m^2/D×3

  2 inductions
- FLAG-IDA × 2 → HD araC 1.5–3 g/m^2 Q12h D1, 3, 5 – ×2
- CLIA – F replaced with CDA 5 mg/m^2 daily × 5 in induction

Burnett AK, et al. *J Clin Oncol*. 2013;31:3360-3368.

FLAG-IDA-VEN Treatment Plan

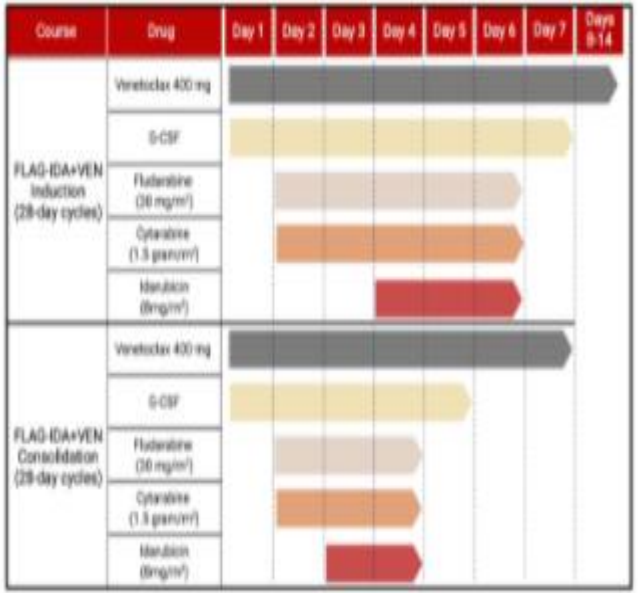


Abou Dalle, et al. *Blood.* 2019;134:abstract 176.

*Concomitant azole permitted with adequate dose reduction.

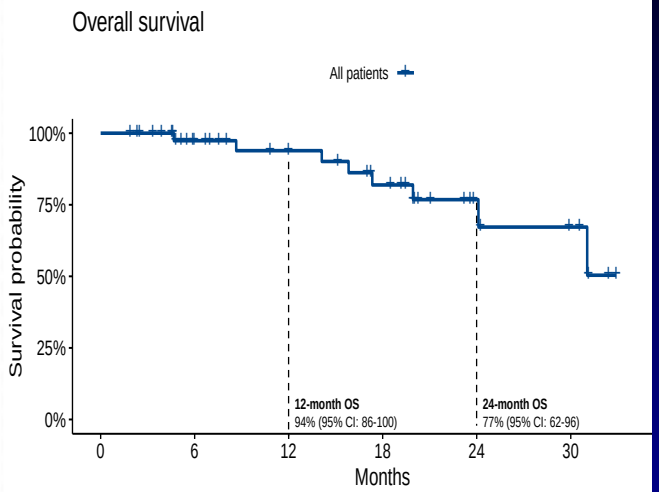
FLAG-IDA + Venetoclax in Newly Dx AML

- 41 pts (29 de novo, 7 sAML, 5 Rx-related)
- Median age 44 yrs (20–65)
- Rx with FLAG-IDA + VEN
- ORR 98%; CR 73%
- CR + Cri + CRh 88%
- 27/41 later SCT
- 2-yr OS 77%



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



	Median Months (95%CI)	12-month % (SE)	24-month % (SE)
Event-free survival	NR (18-NR)	77% (8)	60% (11)
Overall Survival	NR	96% (4)	87% (7)

Lachowiez C, et al. ASCO 2021. Abstract 7012.

CLIA-Venetoclax: Study Design

Venetoclax Dosing (PO daily on days 2–8 ± 1 day)				
Dose Level	Patients on posaconazole	Patients on strong CYP3A inhibitor	Patients on moderate CYP3A inhibitor	Patients not on CYP3A inhibitor
–1	50 mg	50 mg	100 mg	200 mg
1	70 mg	100 mg	200 mg	400 mg

Induction

Treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Cladribine 5 mg/m^2	X	X	X	X	X			
Cytarabine 1500 mg/m^2	X	X	X	X	X			
Idarubicin 10 mg/m^2	X	X	X					
Venetoclax		X	X	X	X	X	X	X

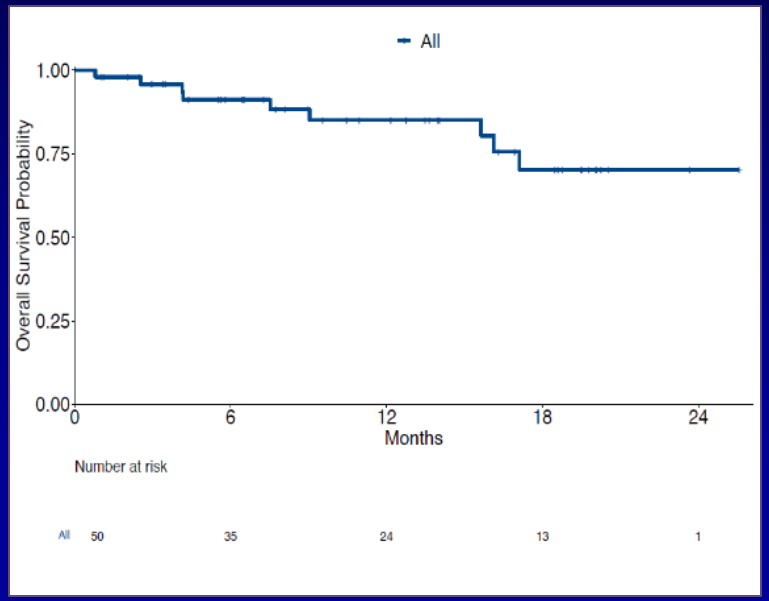
Consolidation

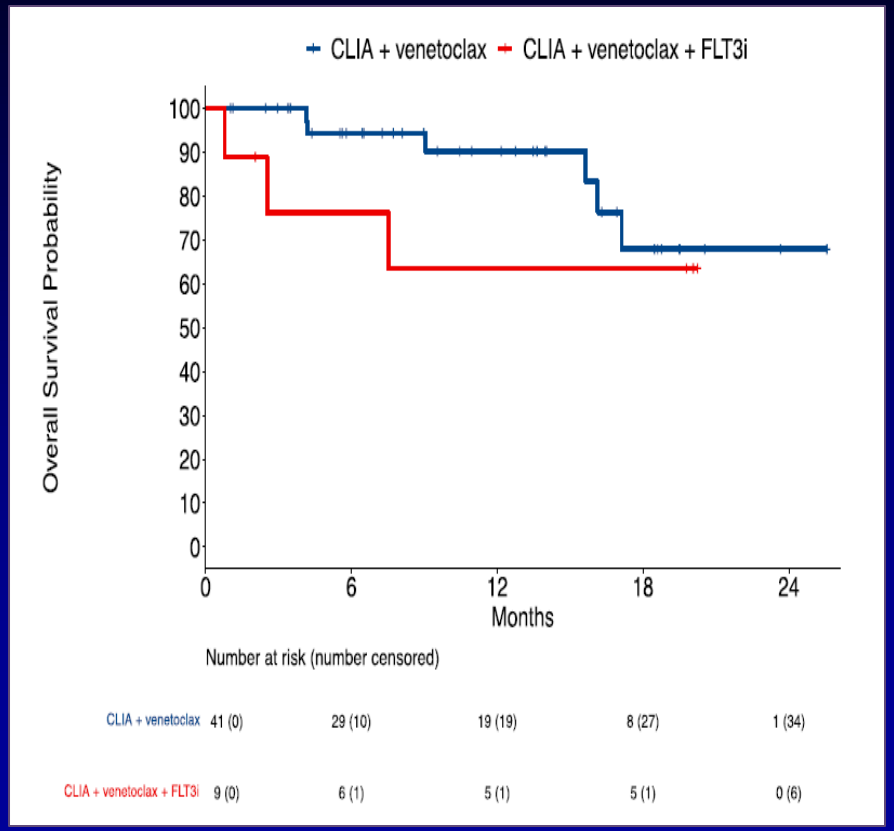
Treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Cladribine 5 mg/m^2	X	X	X					
Cytarabine 1000 mg/m^2	X	X	X					
Idarubicin 8 mg/m^2	X	X						
Venetoclax		X	X	X	X	X	X	X

Kadia T, et al. ASCO 2020. Abstract 7539.

CLIA + Venetoclax in Newly Dx AML

- 50 pts Rx with CLIA-VEN; median age 48 yr (18–64)
- CR + CRi 90%; early 4/8-wk mortality 3/3; 12-mo OS 81%

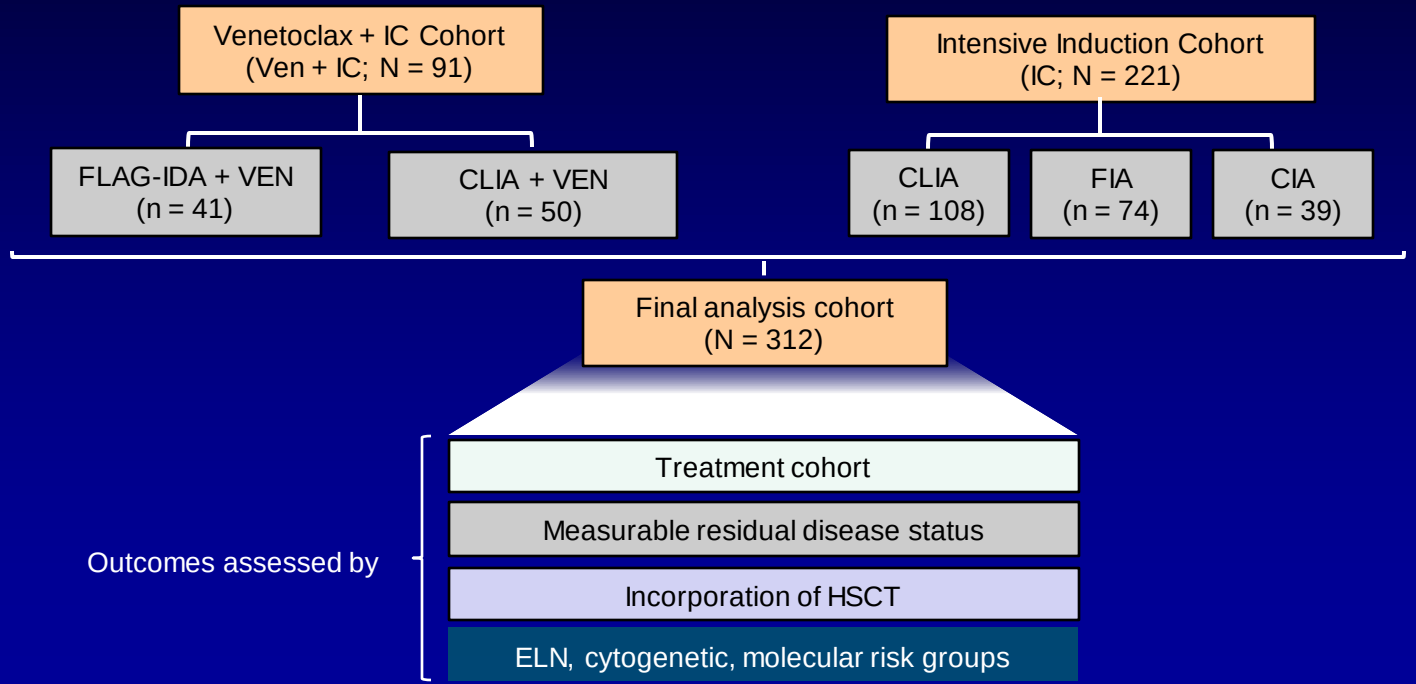




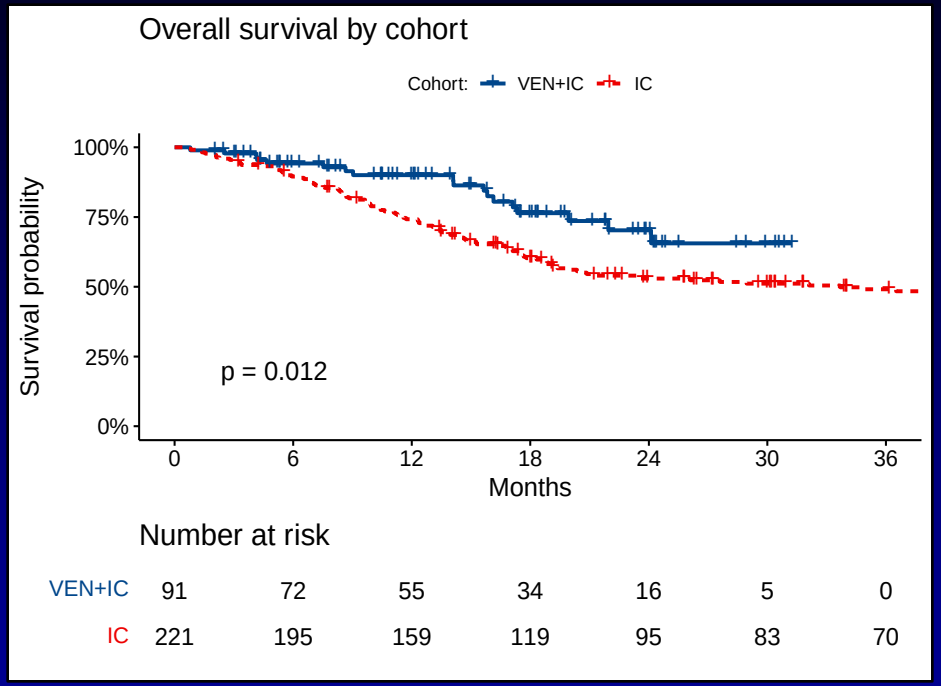
Kadia T, et al. *Lancet Hematol*. 2021;8:e522-e561.

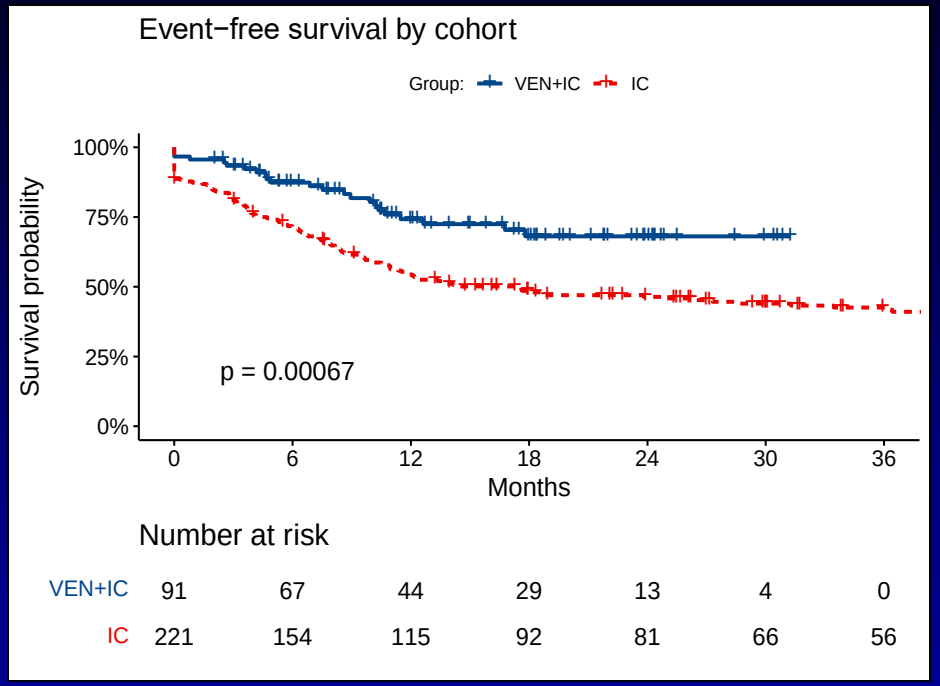
VEN + IC in AML – Study Design

Patients with ND-AML (de novo, sAML, tAML, st-AML) treated with intensive chemotherapy (IC) treated at MDACC on prospective clinical trial protocols



AML – Outcome With Intensive ChemoRx +/- Venetoclax



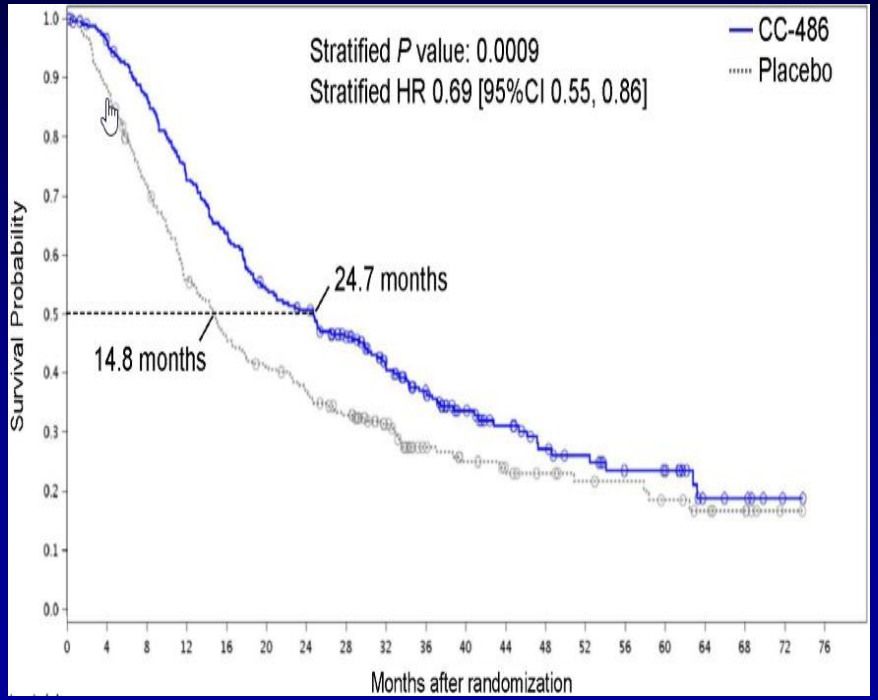


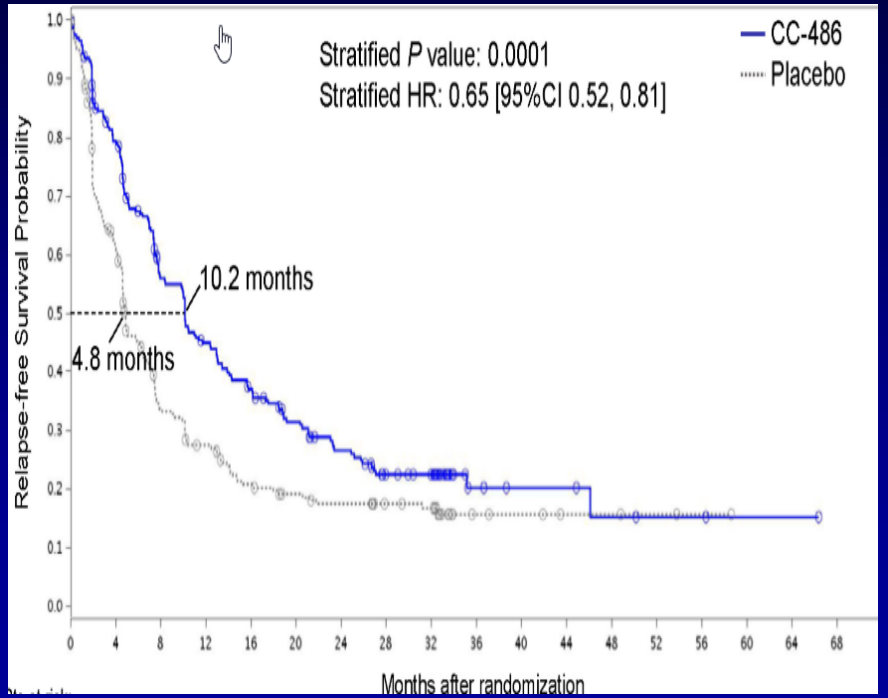
Demographic Median (95%CI) or %(SE)	Ven + IC	IC
Median OS, months	**NR (-)**	**34 (20-NR)**
12-Month OS	90 (3)	74 (3)
24-Month OS	70 (6)	52 (4)

Demographic Median (95%CI) or %(SE)	Ven + IC	IC
Median EFS, months	**NR (-)**	**17 (11-34)**
12-Month EFS	74 (5)	54 (3)
24-Month EFS	68 (6)	46 (3)

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

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



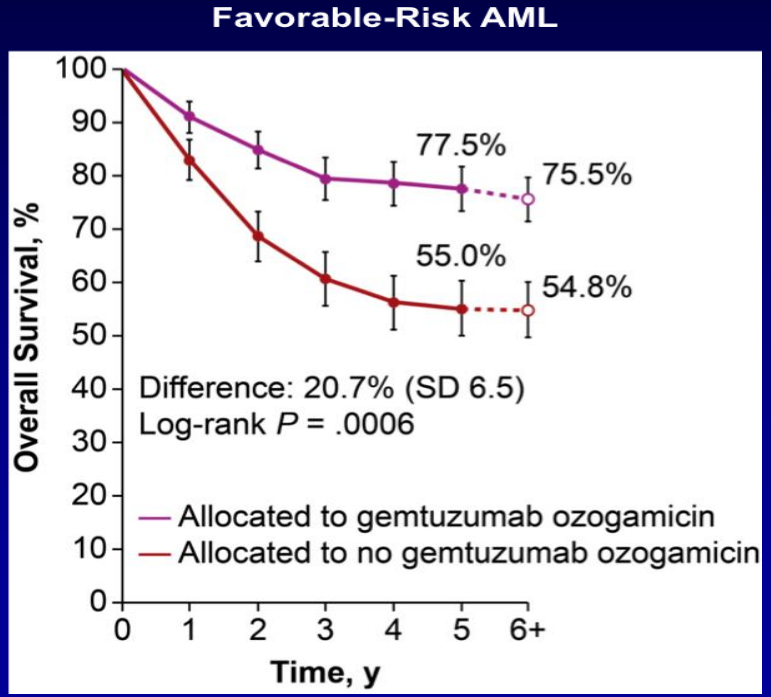


Wei H, et al. *Blood*. 2019;134:LBA 3.

Gemtuzumab Ozogamicin Meta-Analysis of 5 AML Randomized Trials

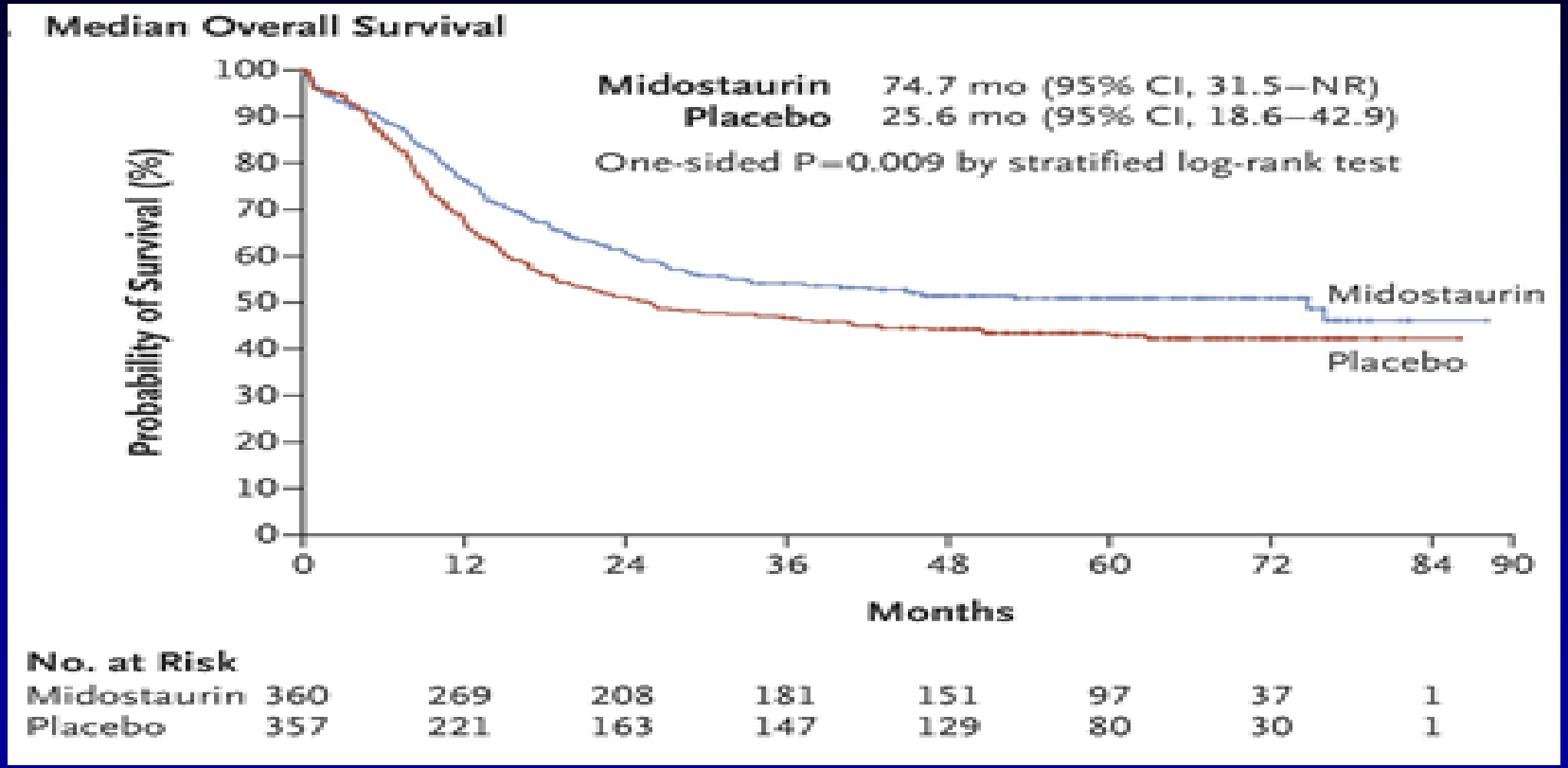
5 randomized trials of 3,325 pts: SWOG, ALFA, UK-MRC AML15 and 16, GOELAMS

Addition of GO
❑ No ↑ CR rate: OR, 0.91; *P* = .3
❑ Did not increase mortality: OR, 1.13; *P* = .4
❑ Improved survival: OR, 0.89; *P* = .01
❑ Reduced relapse: OR, 0.81; *P* = .001
❑ Highly significant survival benefit for favorable risk (OR, 0.47; P = .006) and intermediate risk (OR, 0.84; *P* = .005)



Hills RK. *Lancet Oncol*. 2014;15:986.

Chemo Rx ± Midostaurin in AML (RATIFY)



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

Intensive ChemoRx +/- Quizartinib in Newly Dx *FLT3*-ITD AML (QUANTUM)

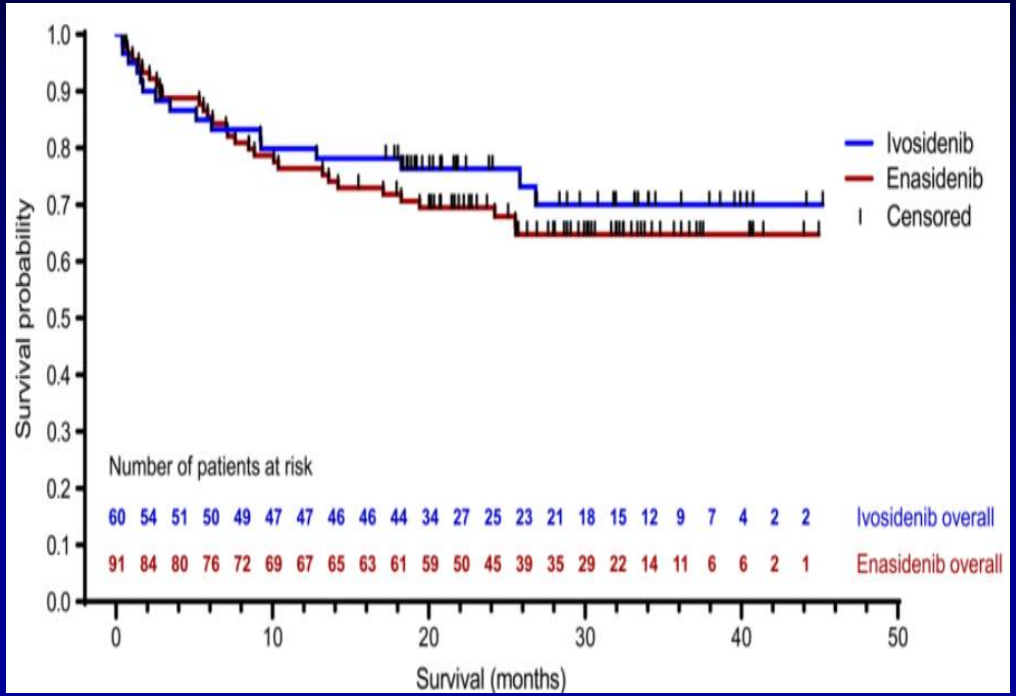
- 539 pts with *FLT3*-ITD AML randomized (1:1) to 3+7 chemoRx +/- QUIZ or placebo
- Post-chemoRx, continue QUIZ or placebo for up to 3 yr
- Primary endpoint overall survival met

Daiichi Sankyo. Public announcement, November 11, 2021

IDH Inhibitors With 3+7 in *IDH*-Mutated AML

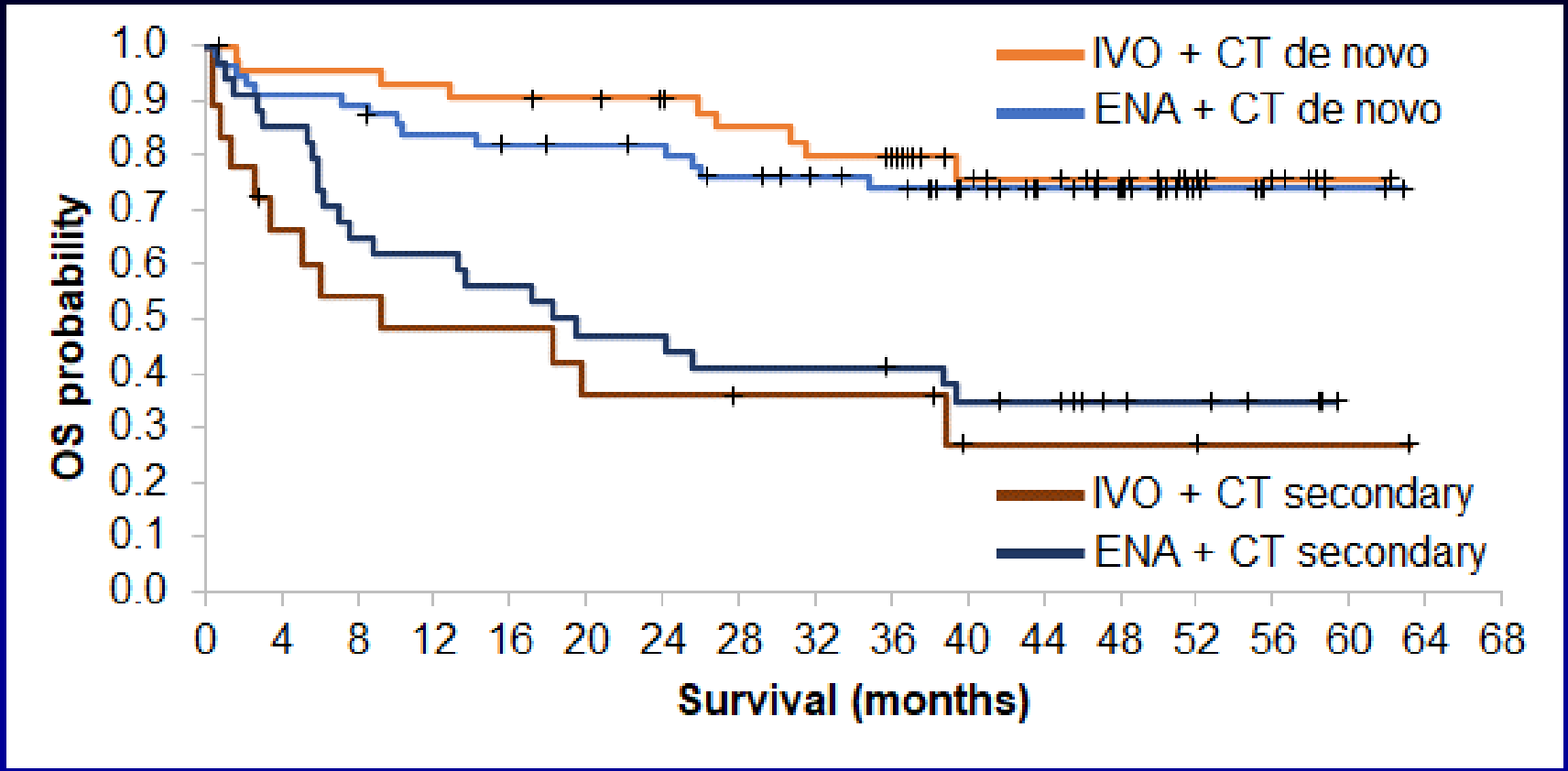
- 151 pts; median age 62 yr (24–73) Rx with 3+7 and ivosidenib (n = 60) or enasidenib (n = 93)

% Parameter	IVO	ENA
CR	70	57
CR + Cri + CRp	78	74
% 3-yr OS	67	61



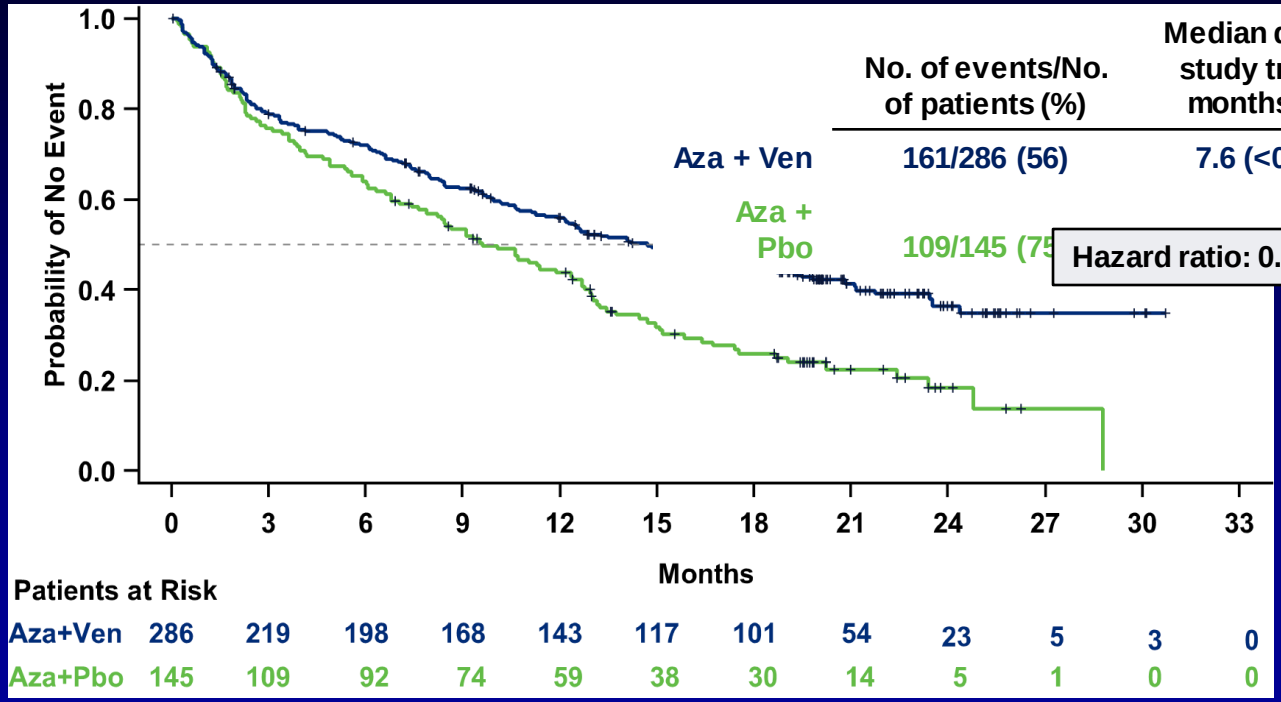
Stein E, et al. *Blood*. 2021;137(13):1792-1803; Stein E, et al. *Blood*. 2021;138:abstract 1276.

IDH Inhibitors With 3+7 in *IDH*-Mutated AML



Stein E, et al. *Blood*. 2021;138:abstract 1276.

AZA ± VEN in AML – Overall Survival



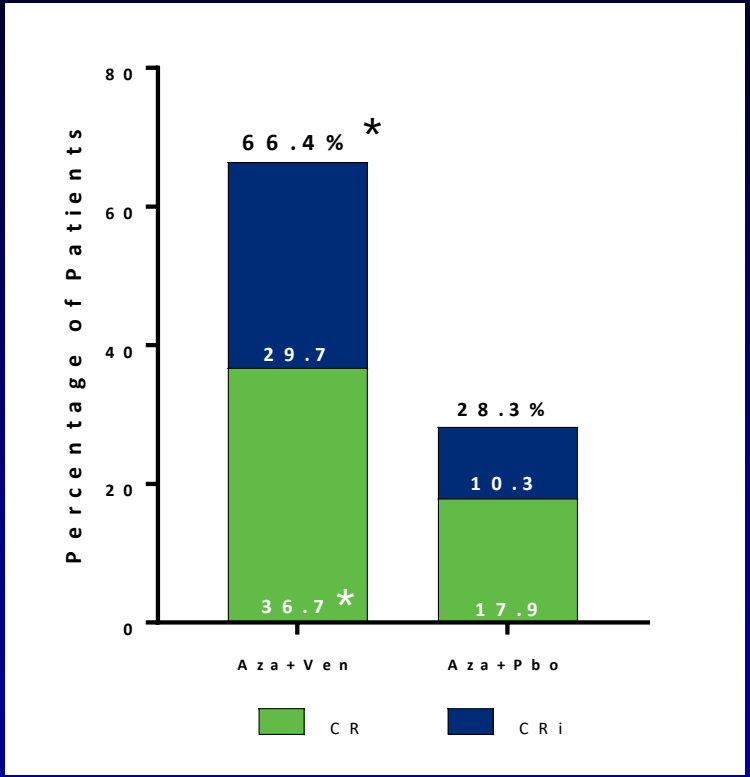
	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza + Ven	161/286 (56)	7.6 (<0.1–30.7)	14.7 (11.9–18.7)
Aza + Pbo	109/145 (75		

Hazard ratio: 0.66 (95% CI: 0.52–0.85), *P* <.001

Median follow-up time: 20.5 months (range: <0.1 – 30.7)

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

AZA ± VEN in AML – Composite Response Rate (CR + CRi)



	No. of treatment cycles, median (range)	Median time to CR/CRi, months (range)	*CR + CRi by initiation of cycle 2, n (%)
Aza + Ven (n = 286)	7.0 (1.0–30.0)	1.3 (0.6–9.9)	124 (43.4)
Aza + Pbo (n = 145)	4.5 (1.0–6.0)	2.8 (0.8–13.2)	11 (7.6)

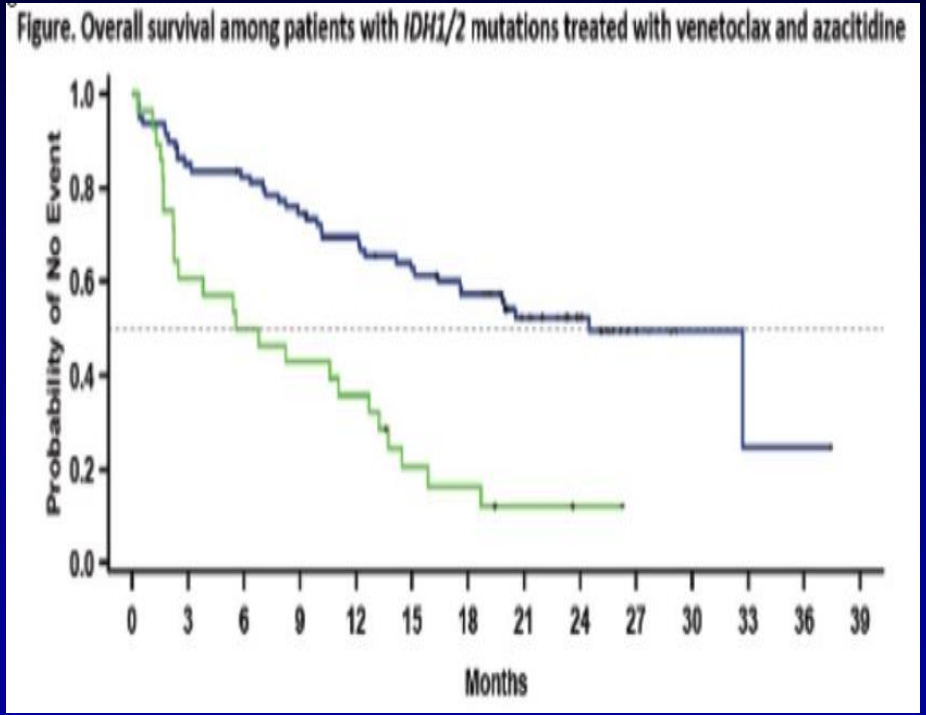
*CR + CRi rate, CR rate, and CR + CRi by initiation of cycle 2 are statistically significant with *P* <.001 by CMH test.

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

Azacitidine ± Venetoclax in Newly Dx *IDH2*-Mutated AML

- AZA ± ven given to 107 pts with older/unfit
- AML: 79 AZA + VEN; 28 AZA

No (%) Parameter	AZA-VEN (n = 79)	AZA (n = 28)
CR + CRi	62 (79)	3 (11)
CR + CRh	57 (72)	2 (7)
CR	35 (44)	1 (4)
Median DOR (mos)	29.5	17.5
Median OS (mos)	24.5	12.3



Pollyea D, et al. *Blood*. 2020;136:abstract 461.

Azacitidine ± Ivosidenib in *IDH1*-Mutated AML (AGILE)

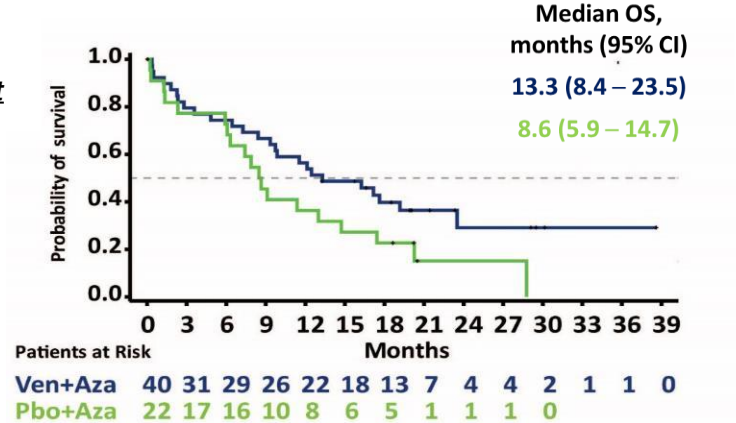
- 146 pts randomized to AZA + IVO (n = 72) or AZA (n = 74)

Parameter	AZA + IVO	AZA	*P* Value/HR
Median OS (mos)	24	7.9	.0005/.44
% CR	47	14.9	<.0001
% CR + CRh	52.8	17.6	<.0001
% ORR	62.5	18.9	<.0001

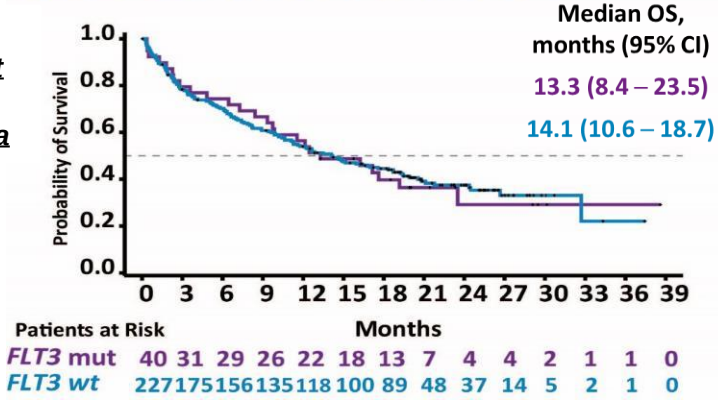
Montesinos. *Blood.* 2021;138:abstract 697.

AZA ± VEN in Older FLT3-Mutated AML: Survival Benefit With VEN Only in *FLT3-TKD*, Not *FLT3-ITD*

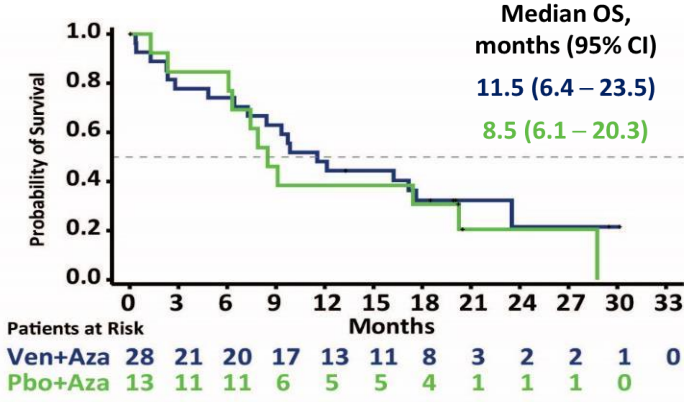
A. FLT3mut



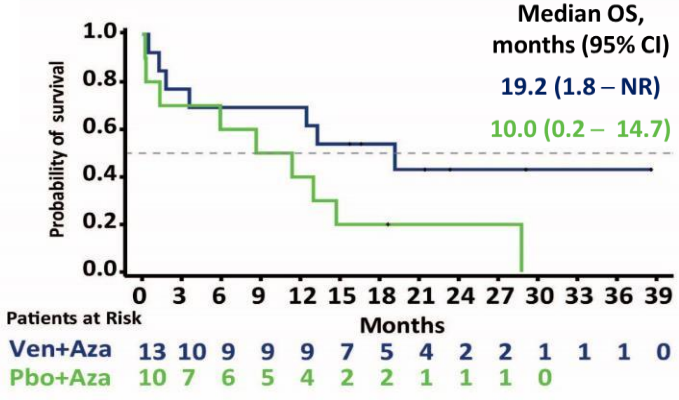
B. FLT3mut vs wt in Ven + Aza



C. FLT3-ITD



D. FLT3-TKD

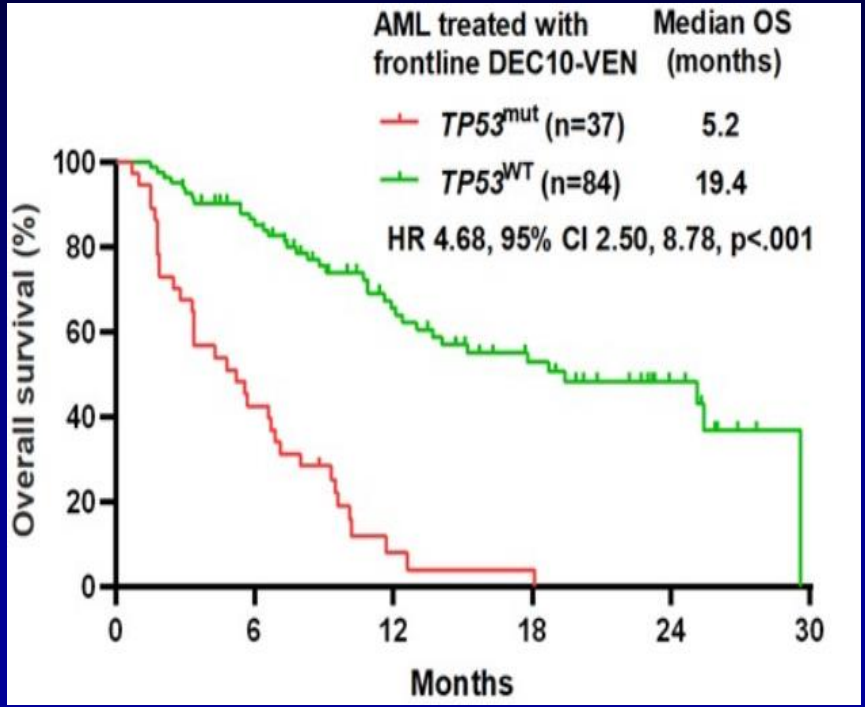


Konopleva M, et al. *Blood.* 2020;136(suppl 1): abstract 1904.

DAC + Venetoclax in *TP53* AML

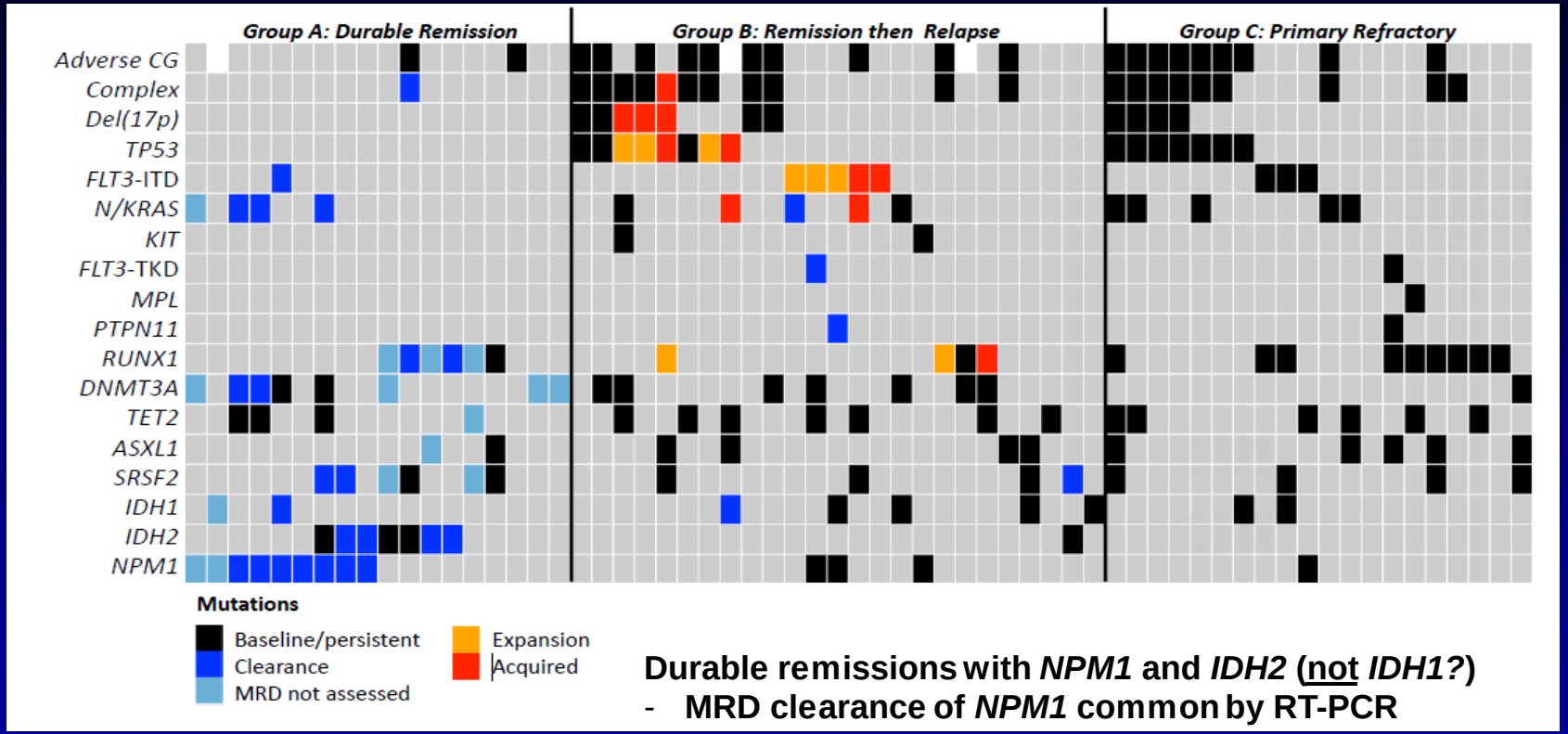
- 121 pts with newly Dx AML Rx with DAC10 + VEN. Median age 72 yrs (49–89); 37 (31%) with *TP53*-AML

Parameter	TP53 (n = 37)	Other (n = 84)	*P*
% ORR	65	88	.003
% CR	35	57	.02
% CR-CRi	54	76	.015
% MRD-negative	19	52	.001
% 30/60 D mortality	5/27	0/2	<.001
Median OS (mos)	5.2	19.4	<.001



Kim K, et al. *Blood*. 2020;136(suppl 1): abstract 693.

Molecular Determinants of Outcome With Venetoclax Combos



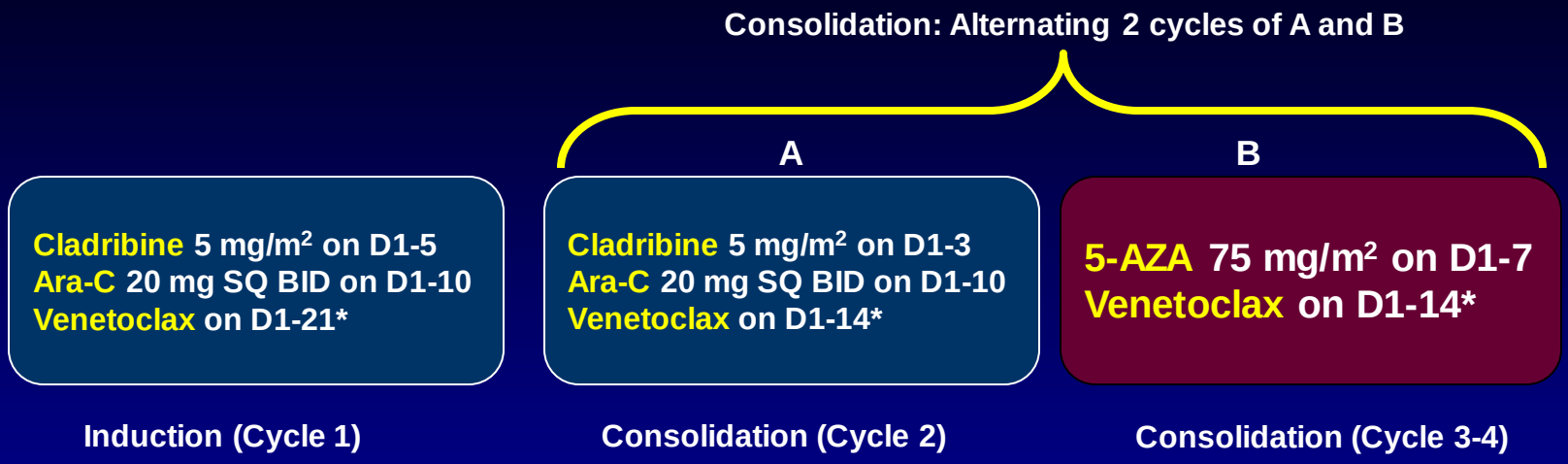
Durable remissions with *NPM1* and *IDH2* (not *IDH1?*)
- **MRD clearance of *NPM1* common by RT-PCR**

Patients treated at MDACC and The Alfred (n = 81)

DiNardo CD, et al. *Blood*. 2020;135(11):791-803.

Resistance commonly associated with expansion or acquisition of *TP53* or signaling mutations including *K/NRAS* and *FLT3*-ITD

Venetoclax Added to Cladribine/LDAC Alternating With 5-AZA

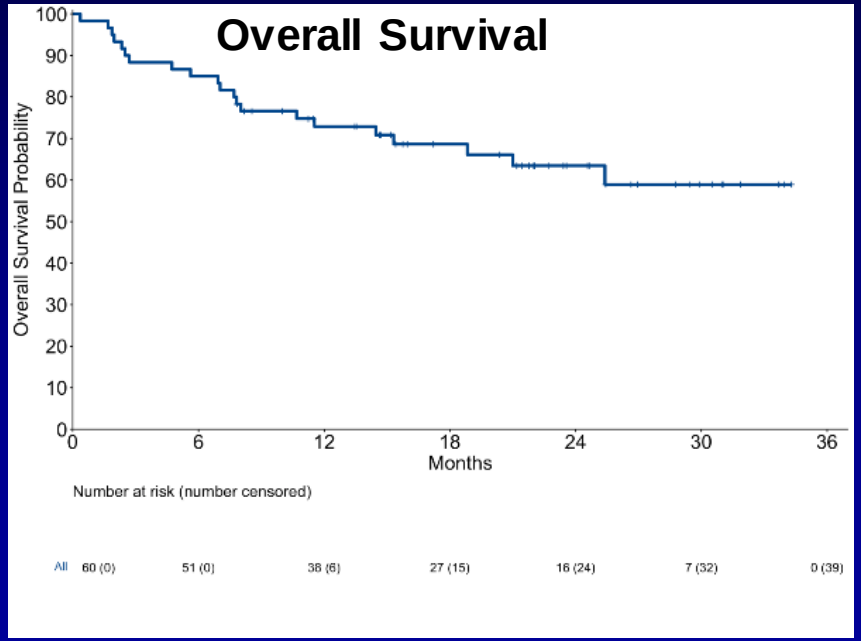


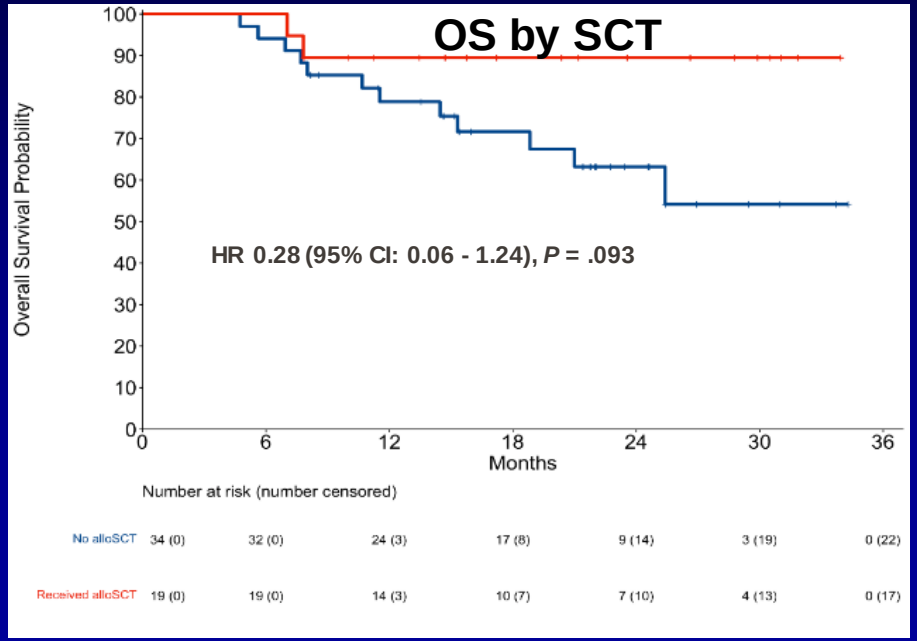
Venetoclax Dosing (PO Daily on Days 1–21)			
Dose Level	**Patients on strong CYP3A inhibitor**	**Patients on moderate CYP3A inhibitor**	**Patients not on CYP3A inhibitor**
-1	50 mg	100 mg	200 mg
1	100 mg	200 mg	400 mg

Kadia T, et al. *Blood.* 2020;136: abstract 25.

Triple-Nucleoside + Venetoclax in Older/Unfit AML

- 60 pts with newly Dx AML. Median age 68 yr (57–84)
- Rx with CDA-LD araC-Ven alternating with AZA-VEN
- CR 80%; CR+CRi 93%; early death 2%; MRD negative 84%
- 2-yr OS 64%. 19/60 (32%) had allo-SCT in CR

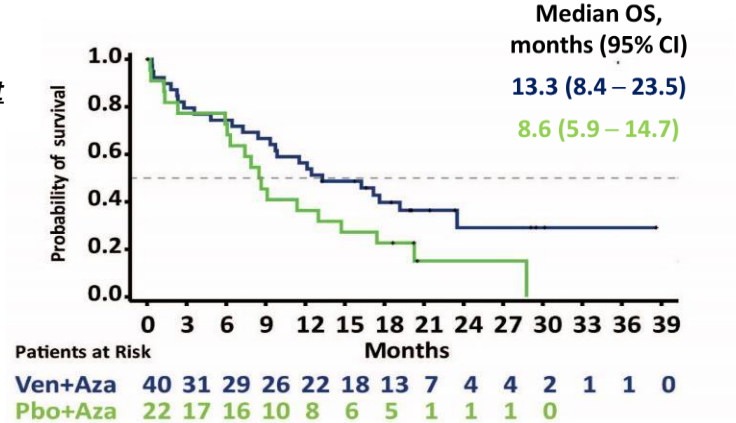




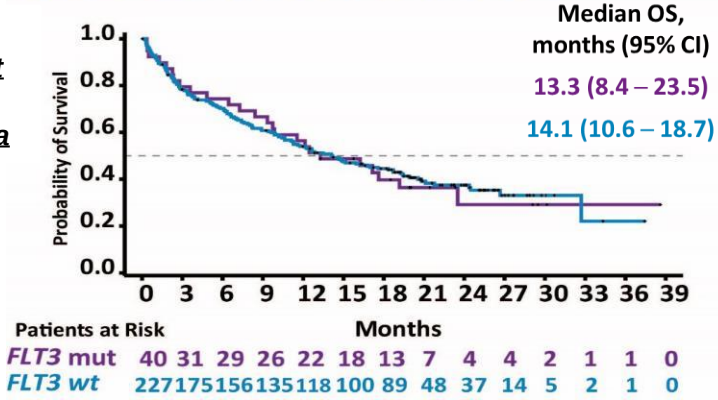
Reville et al. *Blood.* 2021;138:abstract 367.

AZA ± VEN in Older FLT3-Mutated AML: Survival Benefit With VEN Only in *FLT3-TKD*, Not *FLT3-ITD*

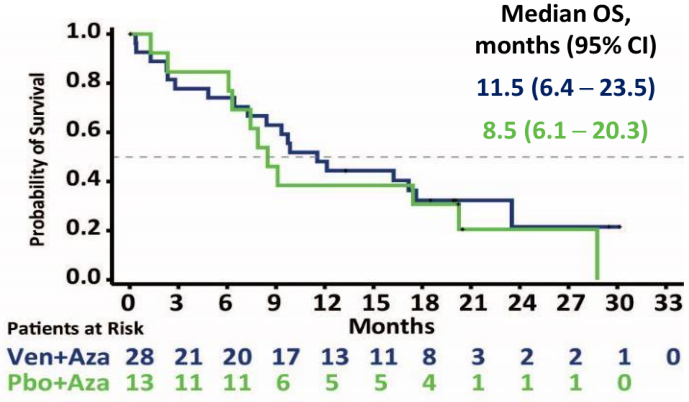
A. FLT3mut



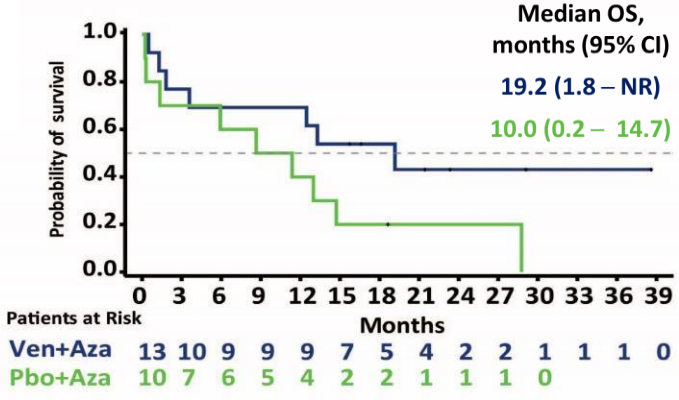
B. FLT3mut vs wt in Ven + Aza



C. FLT3-ITD



D. FLT3-TKD

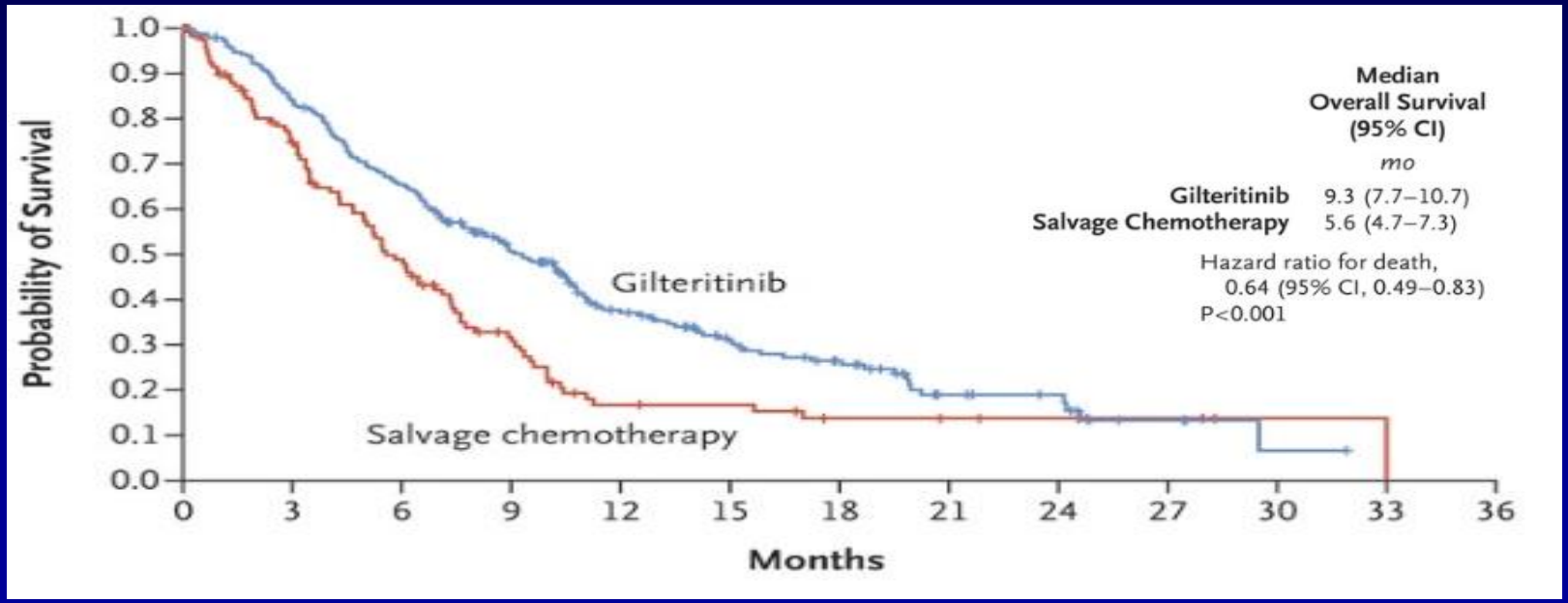


Konopleva M, et al. *Blood.* 2020;136(suppl 1): abstract 1904.

Gilteritinib vs Chemo Rx in R/R FLT3+ AML

- 371 pts randomized 2:1 to gilteritinib 120/D vs chemo Rx (n = 127)

Parameter	Gilt	Chemo Rx
% CR	21	10
% CR + CRi	34	15
Median OS (mos)	9.3	5.6

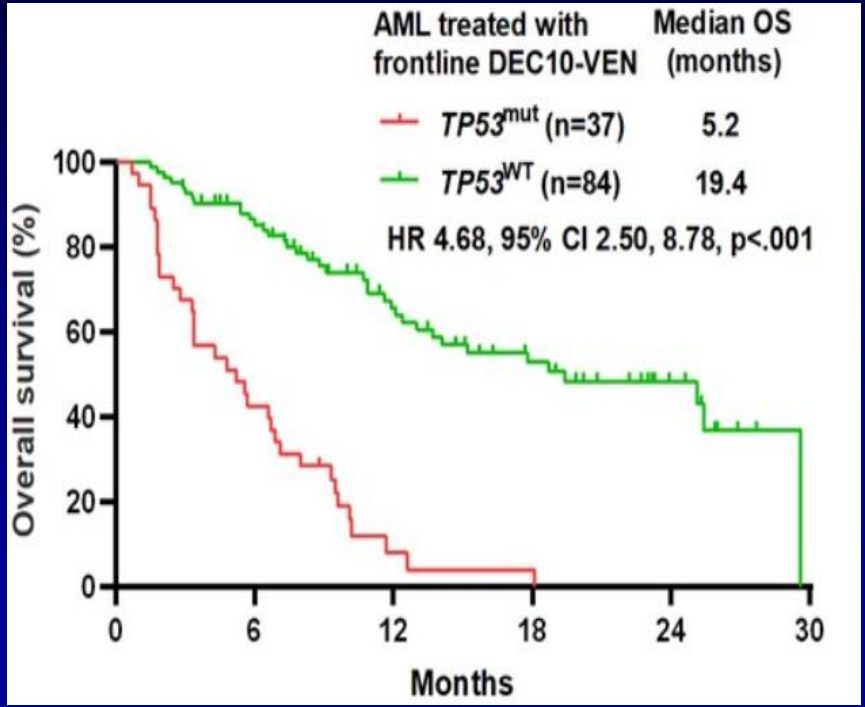


Perl AE, et al. *N Engl J Med.* 2019;381:1728-1740.

DAC + Venetoclax in *TP53* AML

- 121 pts with newly Dx AML Rx with DAC10 + VEN. Median age 72 yrs (49–89); 37 (31%) with *TP53*-AML

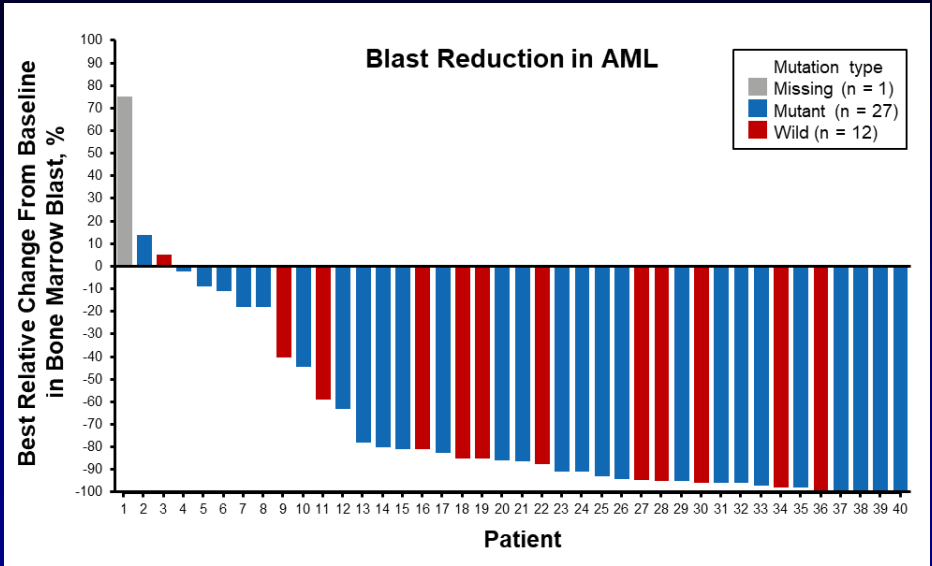
Parameter	TP53 (n = 37)	Other (n = 84)	*P*
% ORR	65	88	.003
% CR	35	57	.02
% CR-CRi	54	76	.015
% MRD-negative	19	52	.001
% 30/60 D mortality	5/27	0/2	<.001
Median OS (mos)	5.2	19.4	<.001



Kim K, et al. *Blood*. 2020;136(suppl 1): abstract 693.

Magrolimab + Aza in Newly Diagnosed AML[1,2]

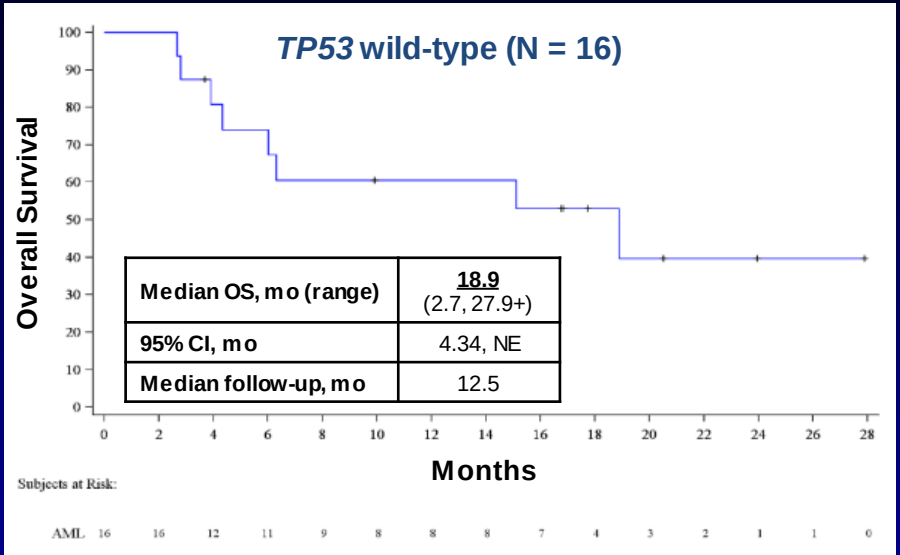
Best Overall Response	All AML (N = 43)	*TP53*-mutant AML (n = 29)
ORR	27 (63%)	20 (69%)
CR	**18 (42%)**	**13 (45%)**
CRi	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)

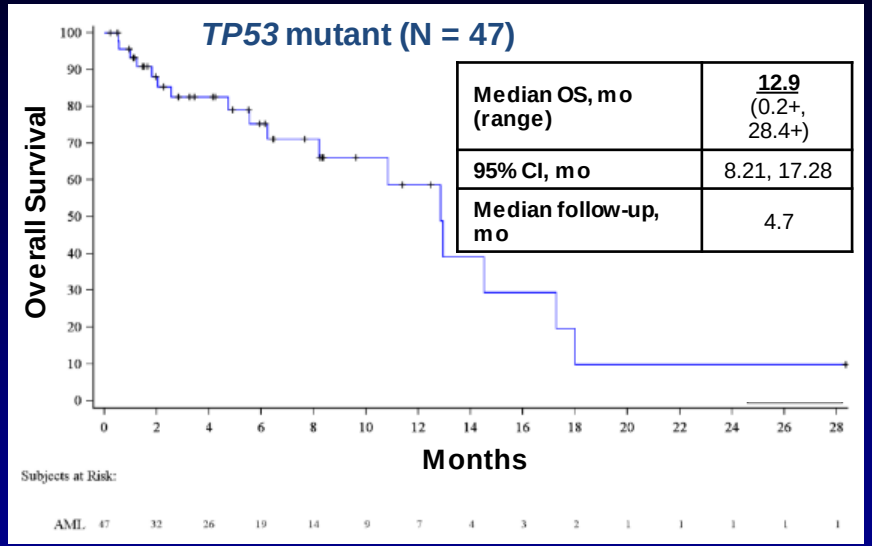


- Magrolimab + AZA with 63% ORR and **42% CR rate** in AML (similar responses in *TP53*-mutant disease)
- Median time to response is 1.95 months (range, 0.95–5.6 mo); more rapid than AZA monotherapy
- Magrolimab + AZA efficacy compares favorably with AZA monotherapy (CR rate: 18%–20%)
- No significant cytopenias, infections, or immune-related AEs were observed; on-target anemia
- Median TP53 VAF burden at baseline: **73.3% (range 23.1%–98.1%)**

1. Daver N, et al. EHA 2020; 2. Sallman DA, et al. ASH 2020. Abstract 330.

Preliminary Median Overall Survival Is Encouraging in Both *TP53*–Wild-Type and -Mutant Patients





- Median OS is 18.9 months in *TP53*–wild-type patients and 12.9 months in *TP53*-mutant patients
- Median OS with venetoclax + hypomethylating agent combinations (**14.7–18.0 mo** in all-comers,[1,3] **5.2–7.2 mo** in *TP53* mutant[2,3])
- Additional patients and longer follow-up are needed

NE, not evaluable.

1. DiNardo CD, et al. *N Engl J Med*. 2020;383(7):617-629; 2. Kim K, et al. ASH 2020. Poster; 3. DiNardo CD, et al. *Blood*. 2019;133(1):7-17.

SNDX-5613 in R-R AML (Mostly MLL)

- 54 pts Rx: 44 AML, 9 ALL, 1 MPAL. 35 (65%) MLL; 10 (19%) NPM1
- SNDX-5613 113–339 mg orally BID; phase II 163–276 mg BID
- ORR 28/51 = 55% – CR/CRh 12 (24%), CRp 7
- MRD-negative 14/51= 31%; 16/19 responders = 84%
- MLL – ORR 23/38 = 61%; CR/CRh 9/38 = 24%
- NPM1 – ORR 5/13 (38%); CR/CRh 3/13 = 23%
- Adverse events: QTc prolongation in 7 = 13%; TLS in 1

Stein. *Blood*. 2021;138:abstract 699.

Leukemia Research – Promising Combination Strategies in 2022

- FLT3 inhibitors
- IDH 1/2 inhibitors
- Gemtuzumab; other CD33 and CD123 MoAbs, Ab constructs; CAR T targeting CD33/123
- Venetoclax
- Oral azacitidine; oral decitabine
- CD47 Ab (macrophage stimulation)
- Menin inhibitors

Leukemia Questions?

- Email: ejabbour@mdanderson.org
- Cell: 713-498-2929
- Office: 713-792-4764

Global Leukemia Academy

Review of prognostic value of MRD in acute leukemias

José Maria Ribera

APTITUDE HEALTH

Global Leukemia Academy Latin American & Canada
Virtual Plenary Session
March 25, 2022

Review of the Prognostic Value of MRD in Acute Leukemias

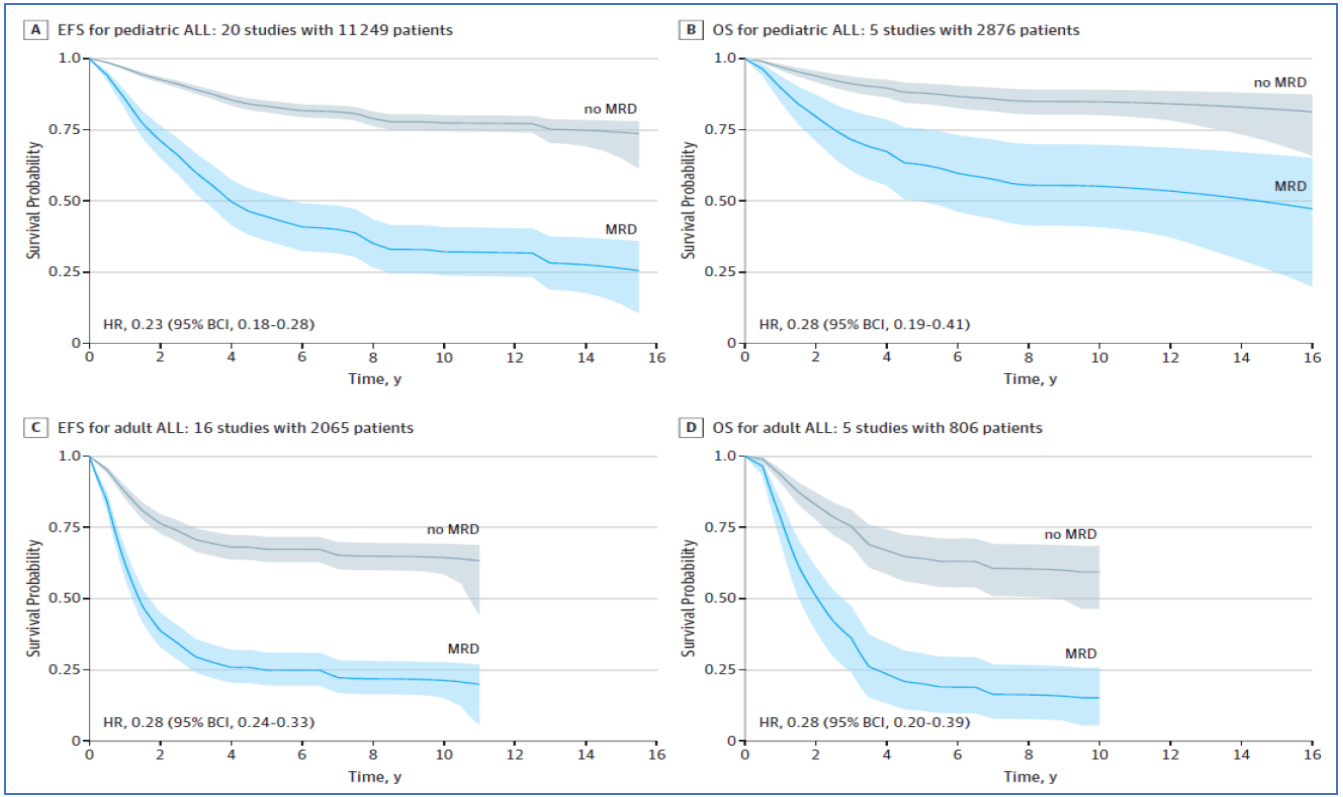
JM Ribera
Clinical Hematology Department
ICO-Hospital Germans Trias i Pujol
Josep Carreras Research Institute
Badalona, Spain

Disclosures

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

MRD in Acute Lymphoblastic Leukemia

Negative MRD Is Associated With Longer EFS and OS in Pediatric and Adult ALL

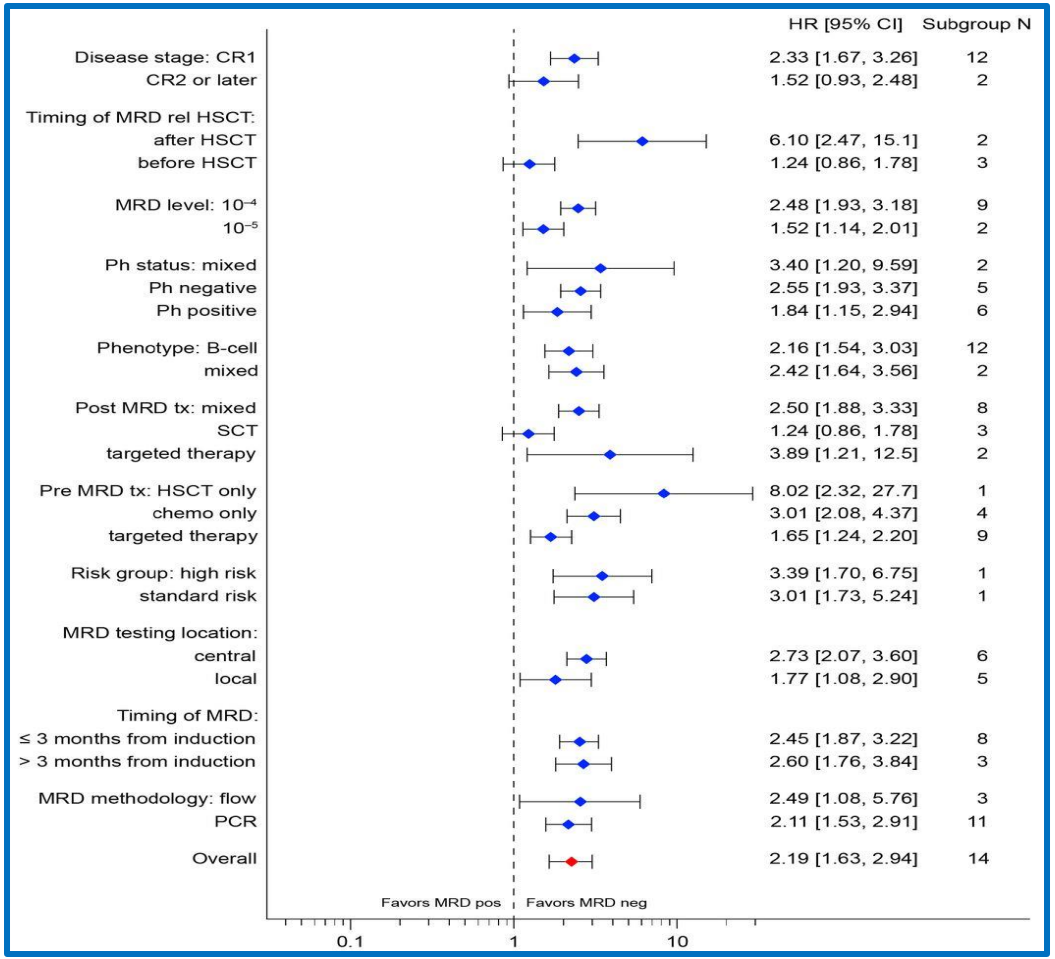


Meta-analysis of 20 pediatric ALL trials >11,000 patients

Meta-analysis of 16 adult ALL trials >2,000 patients

Berry DA, et al. *JAMA Oncol.* 2017;3:e170580.

Prognostic Value of MRD in All Situations

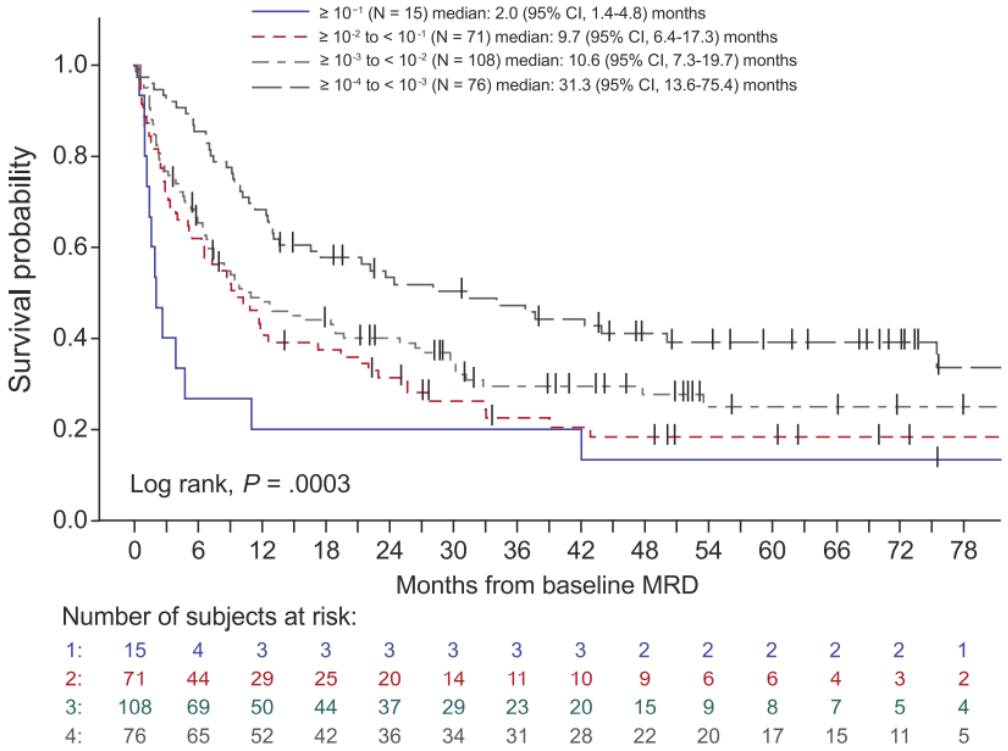


Bassan R, et al. *Haematologica*. 2019;104:2028-2039.

Impact of End-Induction MRD Level on Prognosis in Ph– ALL

Survey From 7 EU Cooperative Groups

- N = 270 patients with measurable MRD during first remission
  - 80% molecular failure
  - 19% molecular relapse
- Median DOR, 18.5 months (95% CI: 11.9, 27.2)
- Median RFS, 12.4 months (95% CI: 10.0, 19.0)
- Median OS, 32.5 months (95% CI: 23.6, 48.0)



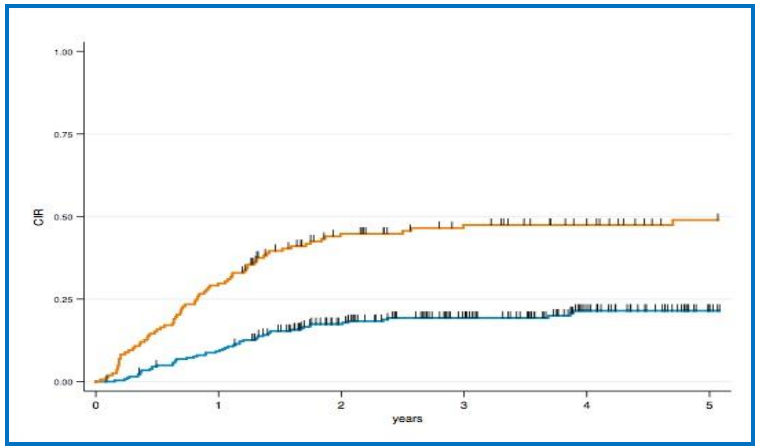
Gökbuget N, et al. *Hematology*. 2019;24:337-348.

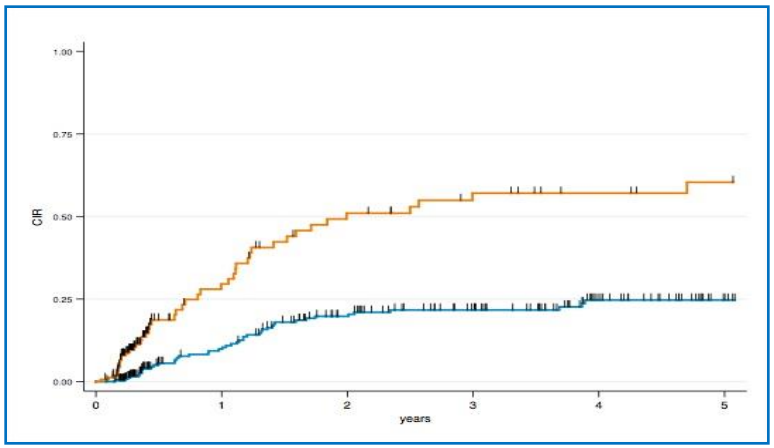
MRD Is Not a Perfect Predictive Factor in Adult Ph– ALL

Post-induction Ig-TCR MRD

$\geq 10^{-4}$

$< 10^{-4}$



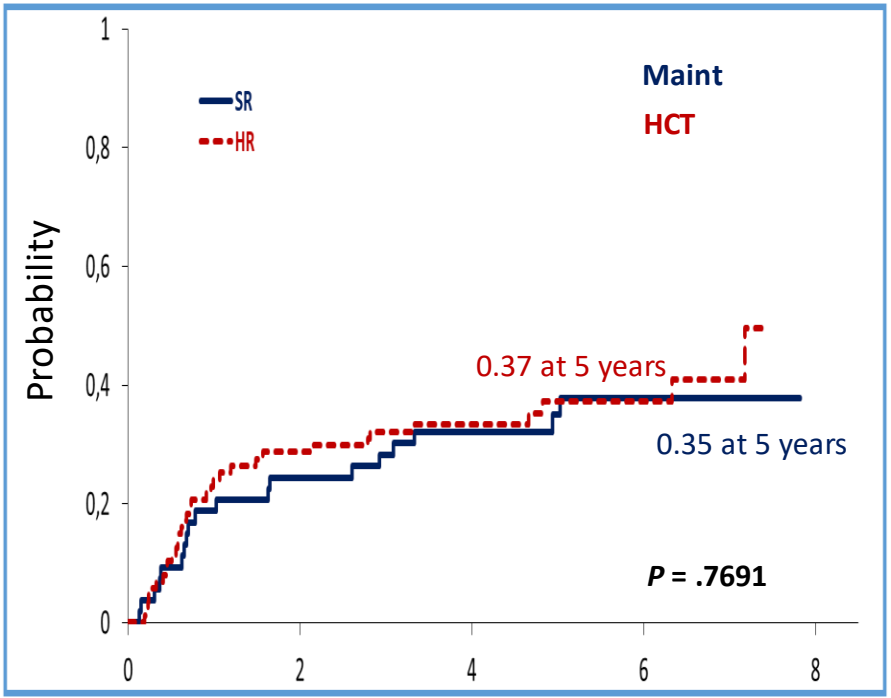


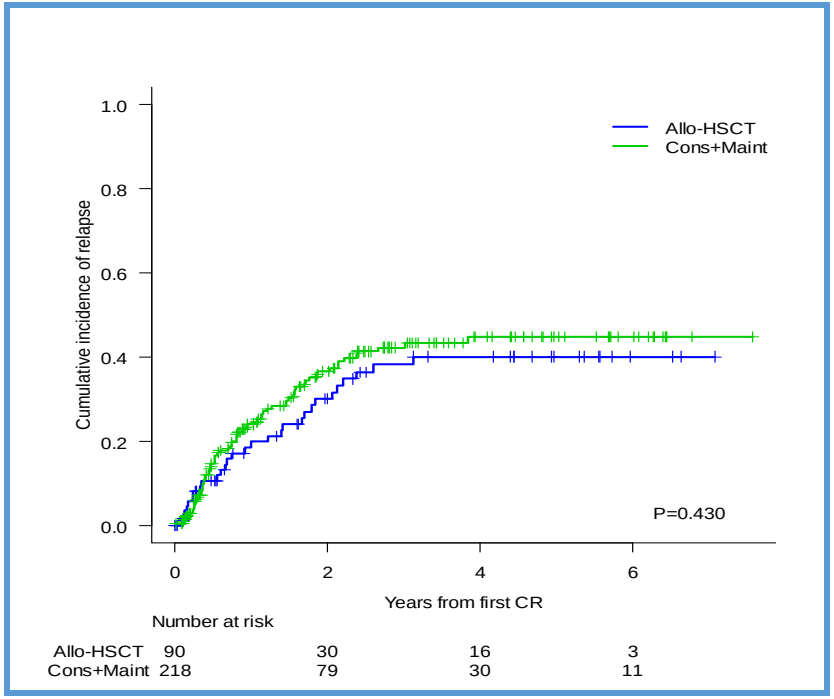
	Without AlloHSCT Censoring	With AlloHSCT Censoring
5-yr CCR in MRD+ pts	51.2%	39.6%
5-yr CIR in MRD– pts	21.2%	24.7%
Harrel's C-index	0.63	0.64

Courtesy of H. Dombret.

Beldjord K, et al. *Blood.* 2014;123:3739-3749; GRAALL data on file.

Cumulative Incidence of Relapse by Treatment Allocation (ITT analysis)

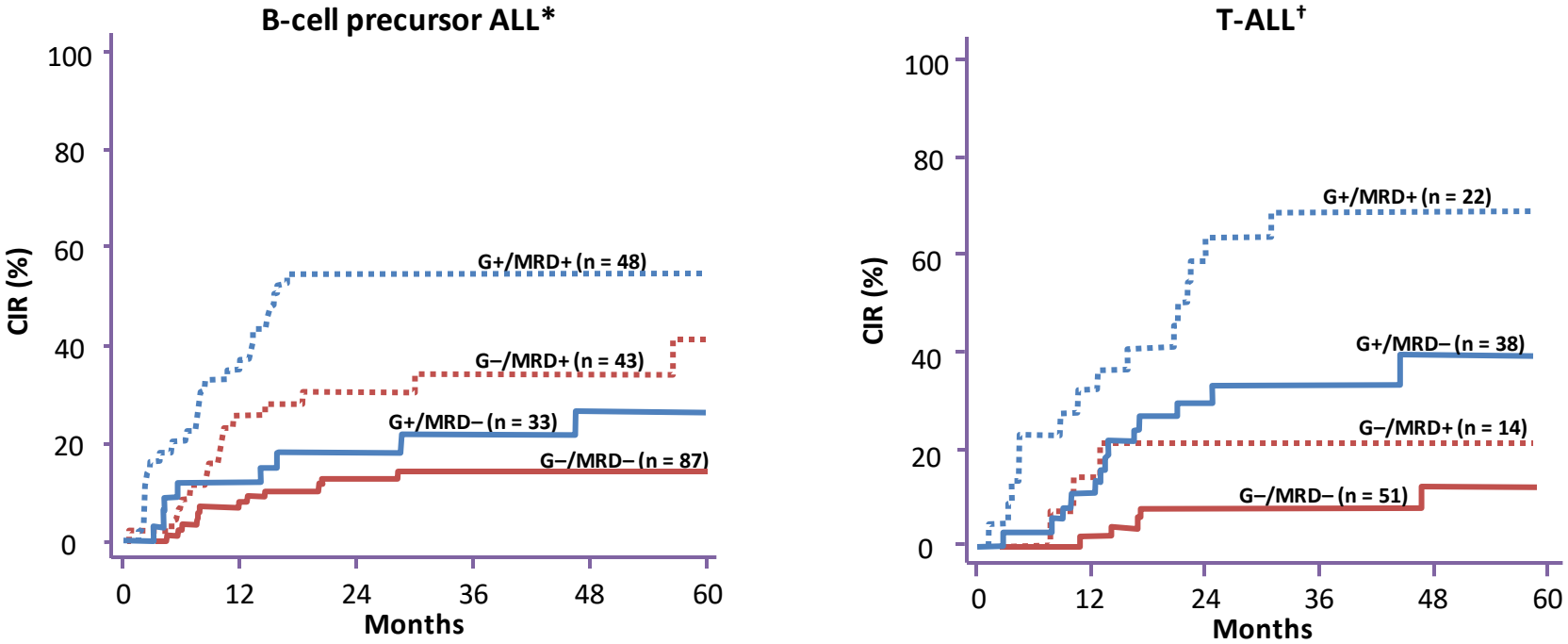




Bassan R, et al. *Blood Cancer J*. 2020;10(11):119.

Ribera JM, et al. *Blood*. 2021;137:1879-1894.

MRD Is Not the Only Prognostic Factor: Genetic Background Counts – GRAALL Data



GENETIC RISK: ***B-cell precursor ALL** – MLL and/or *IKZF1* mutation; †**T-ALL** – no *NOTCH* and/or *RAS*/*PTEN* mutation

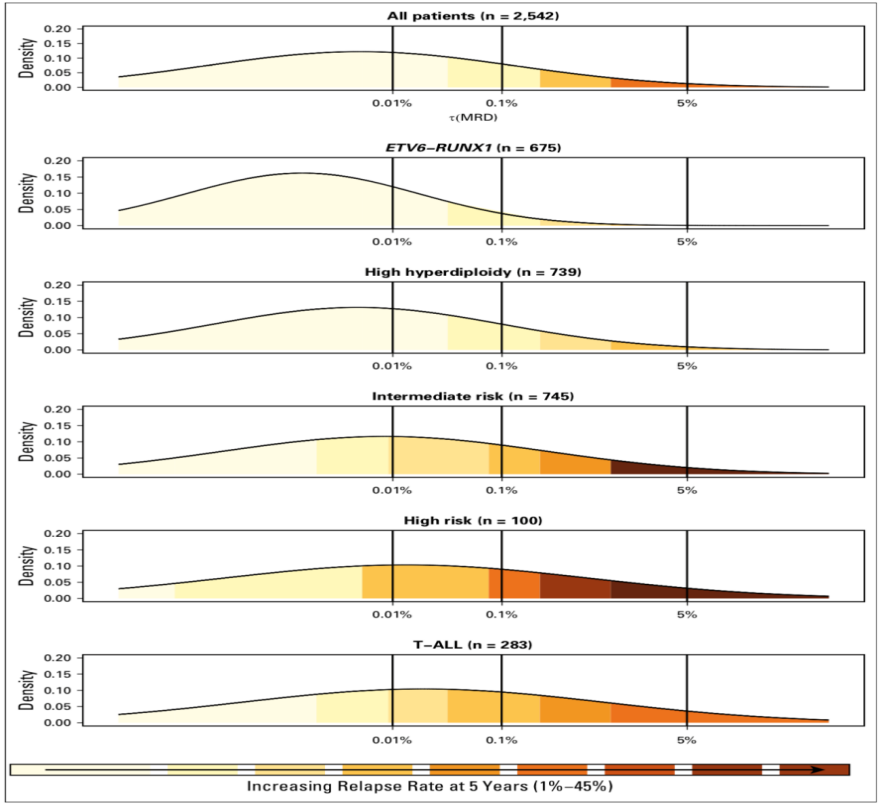
Adapted from Beldjord K, et al. *Blood.* 2014;123:3739-3749.

Value of MRD According to Genetic Subgroups

- **The value of MRD may depend on**
  - Response kinetics
  - Existence of resistant subclones

- Pediatric UKALL2003 study
  - The risk of relapse was proportional to the MRD level within each genetic risk group
  - However, absolute relapse rate that was associated with a specific MRD value varied significantly by genetic subtype

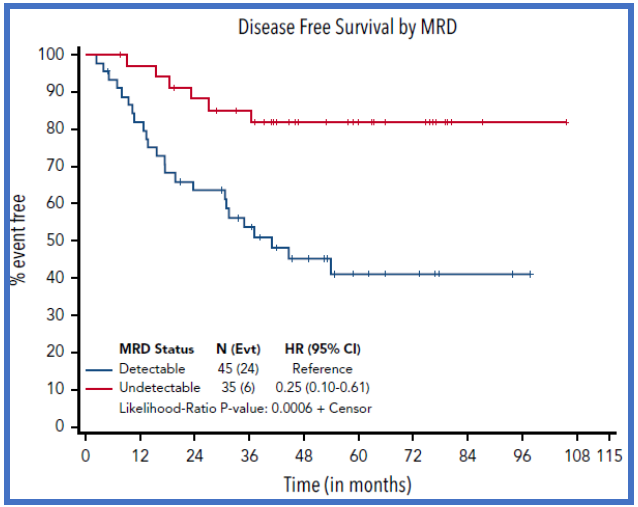
Integration of genetic subtype/subclone-specific MRD could allow a more refined risk stratification



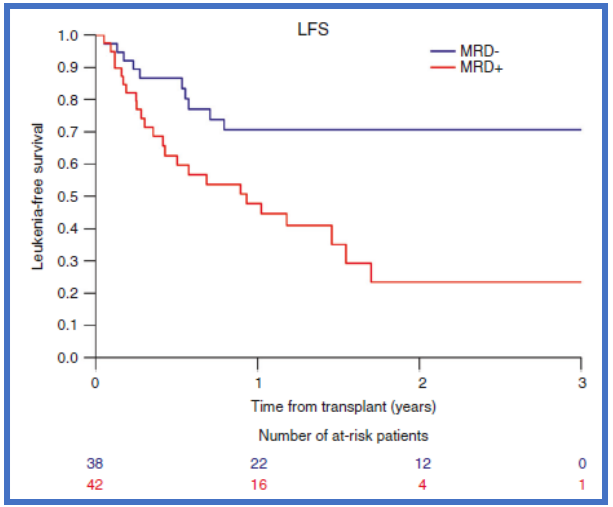
O'Connor D, et al. *J Clin Oncol*. 2018;36:34-43.

Impact of MRD in Some ALL Subtypes

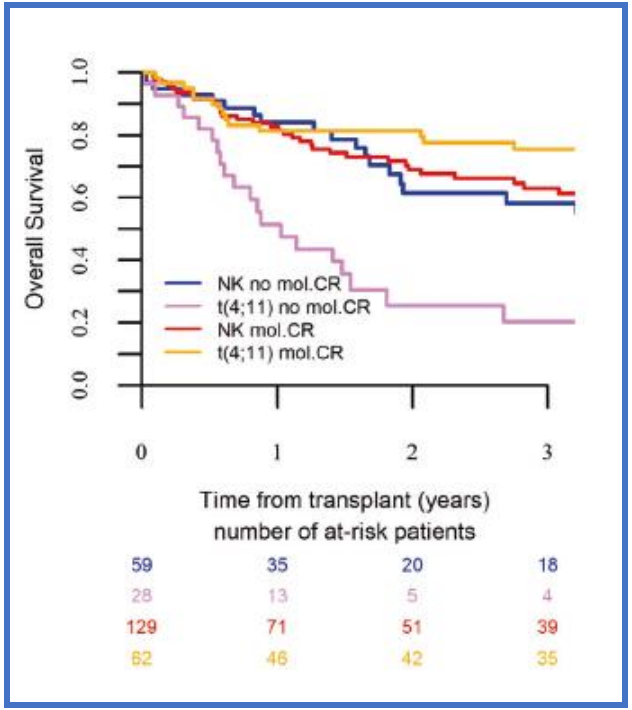
AYA[1]



IKZF1+[2]

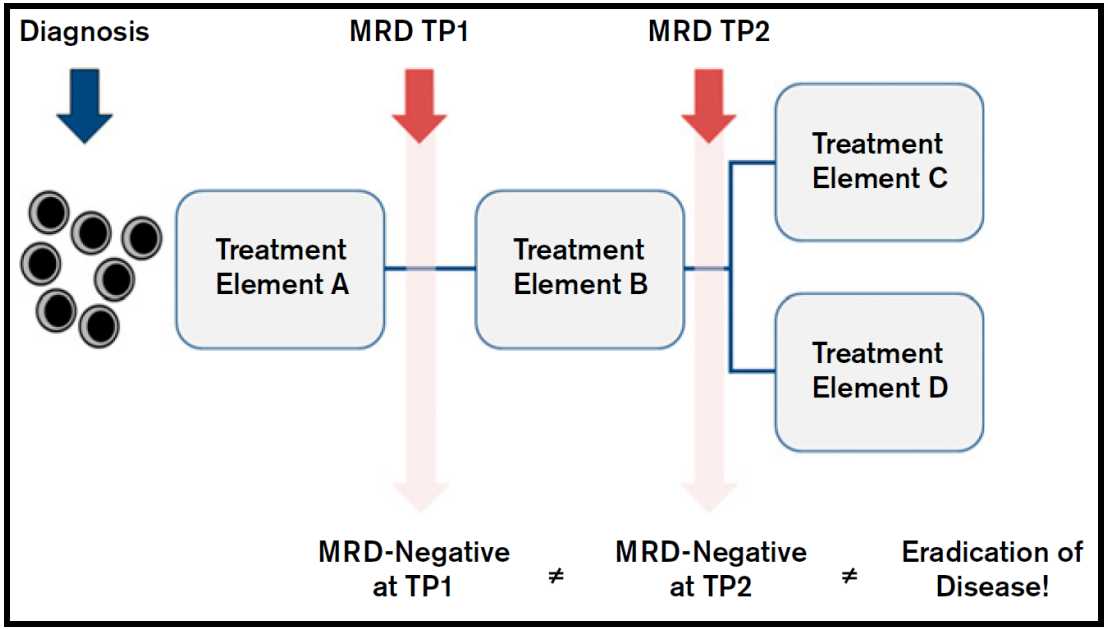


KMT2A+[3]



1. Stock W, et al. *Blood.* 2019;133:1548-1559; 2. Giebel S, et al. *Bone Marrow Transplant.* 2021;56(5):1047-1055; 3. Esteve J, et al. *Leukemia.* 2021;35(8):2232-2242.

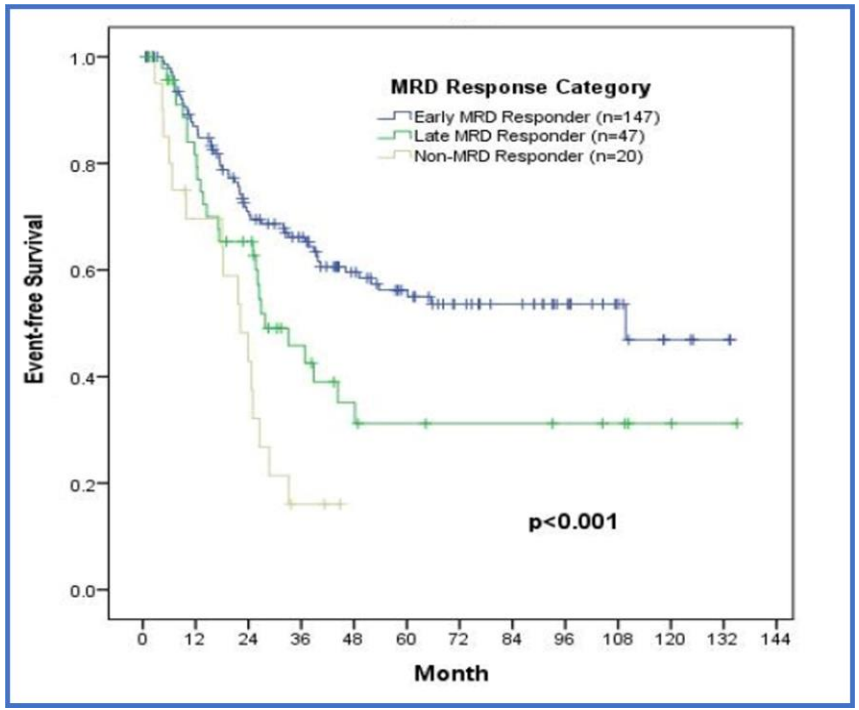
Importance of Time Points in MRD Assessment

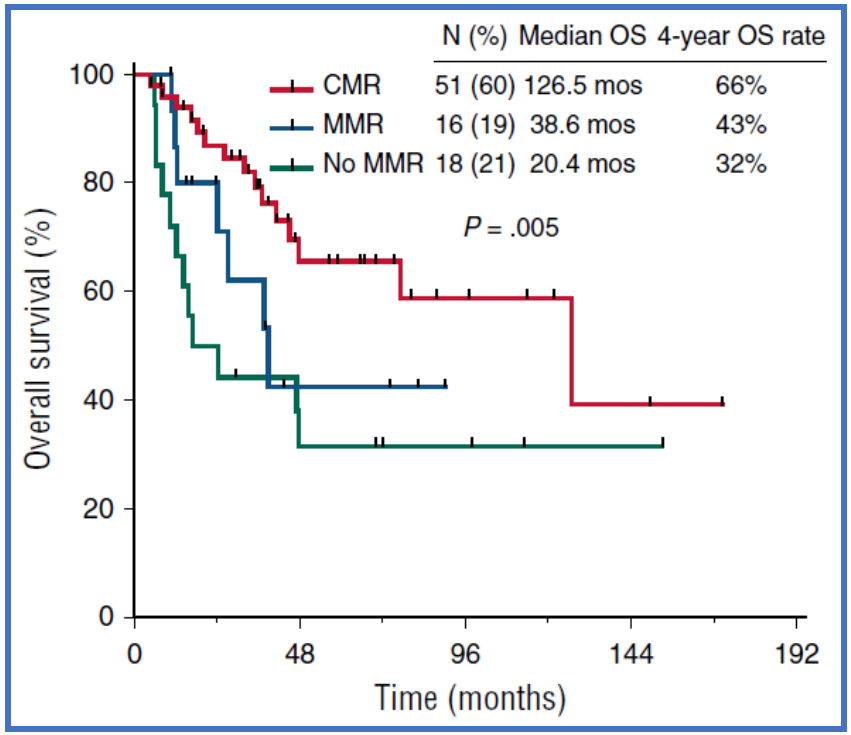


- **Negative** MRD at **TP1**: useful for recognizing patients with **low risk** of relapse
- **Positive** MRD at **TP2**: useful for recognizing patients with **high risk** of relapse

Brüggemann M, Kotrova M. *Blood Adv*. 2017;1:2456-2466.

Best Time Point for MRD Assessment: End-Induction for Ph– ALL, 3 Months for Ph+ ALL





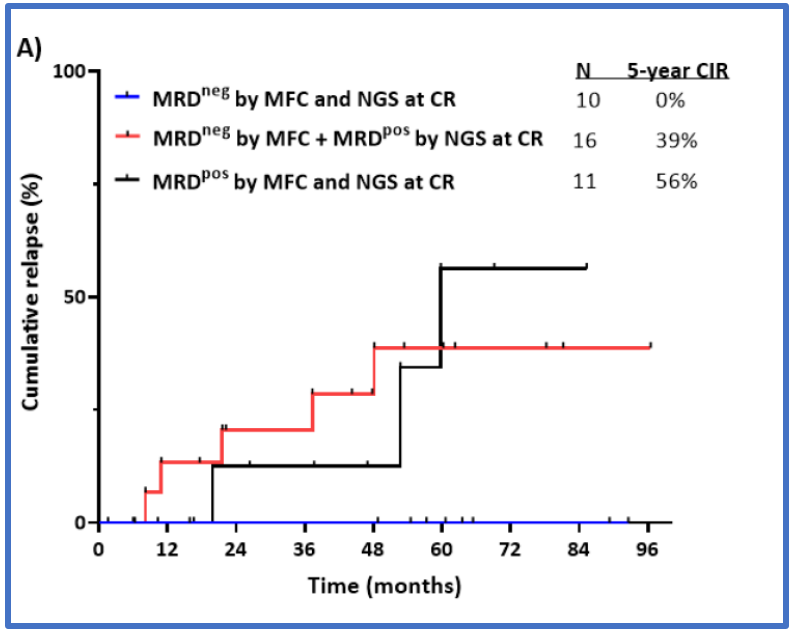
Yilmaz M, et al. *Am J Hematol*. 2020;95:144-150.

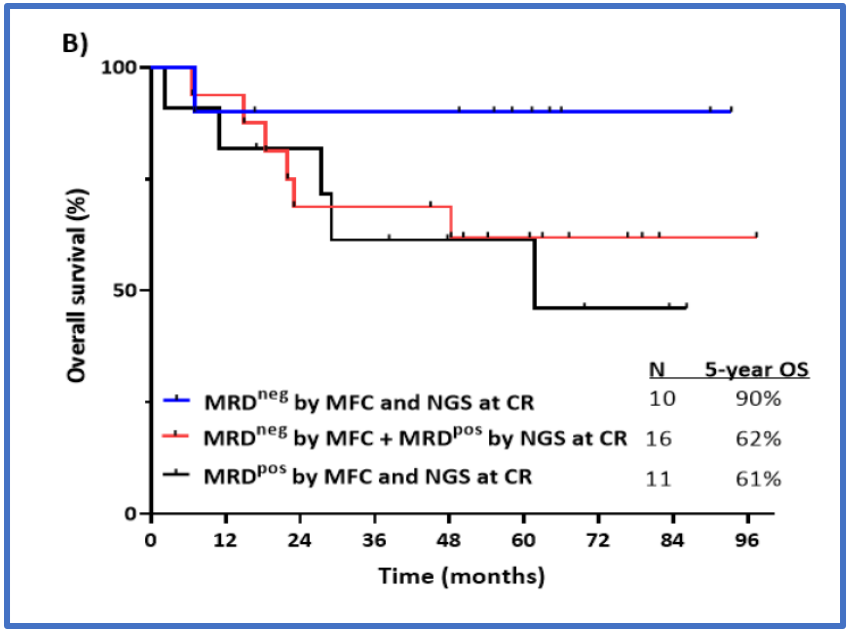
Short NJ, et al. *Blood*. 2016;128:504-507.

Impact of Sensitivity of the Method for MRD Assessment on Prognosis

Standard FCM (sensitivity 1×10^{-4}) vs ultrasensitive NGS (sensitivity 1×10^{-6})

End-induction MRD negative by MFC: 66%, by NGS: 23% of patients





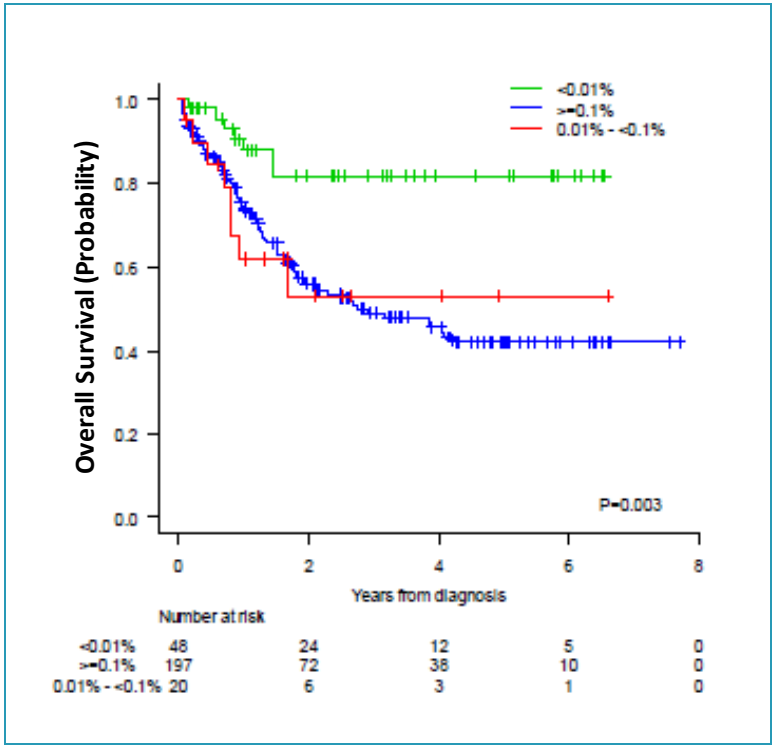
Early achievement of MRD negativity with NGS assay identifies patients with very low risk of relapse

Predictive value of MRD increases with increasing sensitivity!

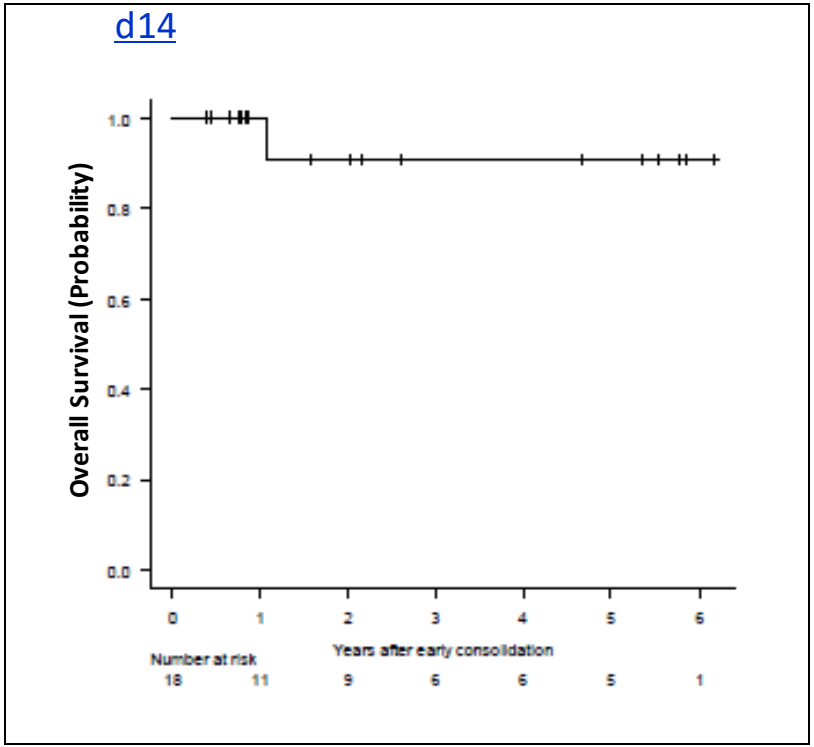
Short N, et al. ASH 2020. Abstract 583.

Outcomes by MRD Assessed by Next-Generation FCM (sensitivity 2 × 10^{-6})

According to post-induction MRD level



Patients with MRD <0.01% from d14

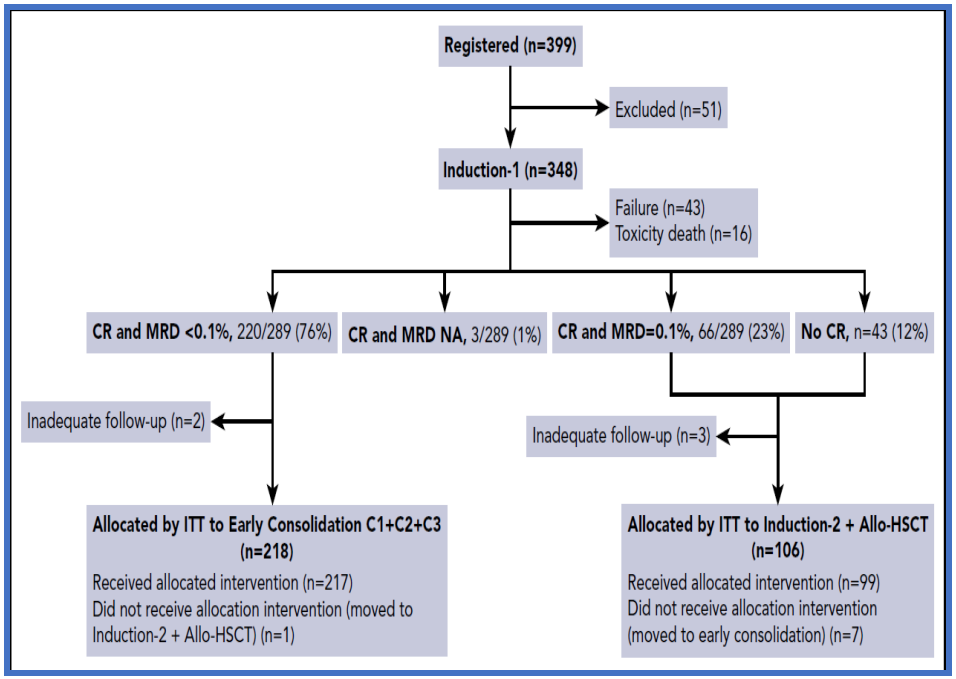


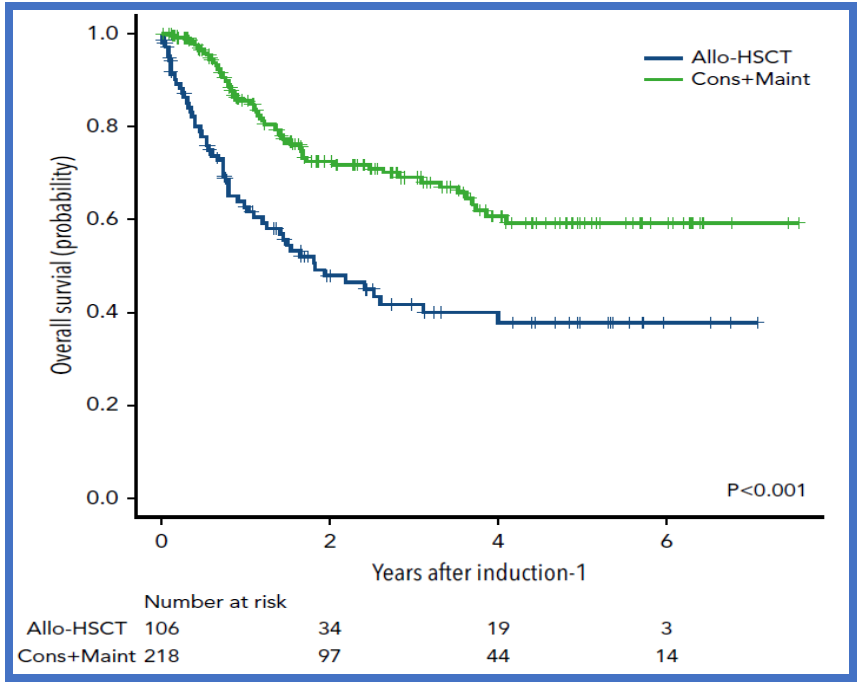
Ribera JM, et al. *Blood.* 2021;137(14):1879-1894.

Prospective Studies With Indication for HSCT on the Basis of MRD Data (adult Ph– ALL)

Trial	Risk Groups	MRD Assessment	Randomization Assignment	References
NILG	SR & HR	PCR	• No • Allo(auto)HSCT in MRD+ pts	Bassan R. *Blood.* 2009;113:4153-4162
PETHEMA HR03	HR	4-color flow	• No • AlloHSCT in poor early cytologic responders or MRD+ pts	Ribera JM. *J Clin Oncol.* 2014;32:1595-1604
NILG 10/07	SR & HR	PCR	• No • Allo(auto)HSCT in MRD+ pts	Bassan R. *Blood Cancer J.* 2020;10:119
PETHEMA HR11	HR	8-color flow	• No • AlloHSCT in MRD+ pts	Ribera JM, et al. *Blood*. 2021;137:1879-1894
GMALL 08/2013	SR & HR	PCR	• Yes. AlloHSCT vs chemo in MRD– HR pts • AlloHSCT in MRD+ pts	Ongoing; NCT02881086

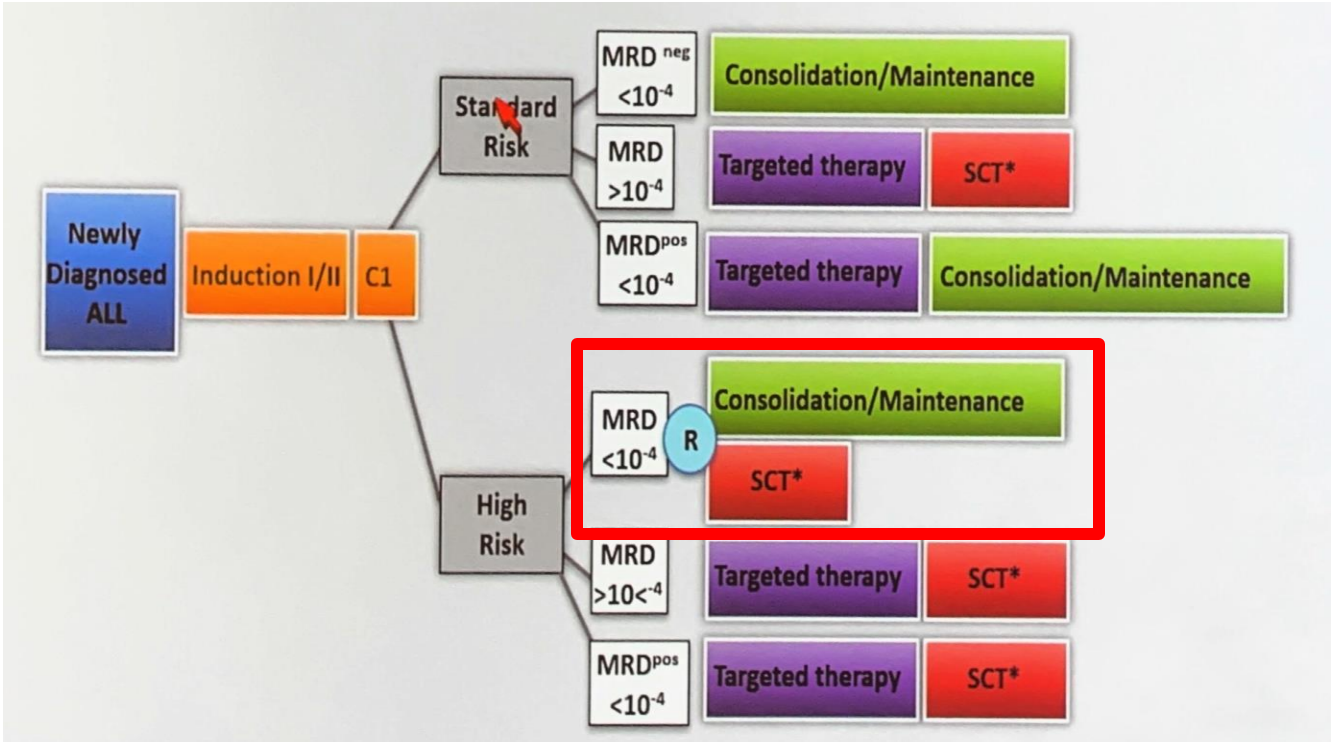
PETHEMA ALL HR11





Ribera JM, et al. *Blood*. 2021;137:1879-1894.

Current GMALL Strategy De Novo <55 Years: GMALL Trial 08/2013 — Ph– ALL



*Dose-reduced conditioning >45 yr.

Courtesy of N. Gokbuget.

NILG 10/07 Ph- ALL: ClinicalTrials.gov NCT-00795756.

Immunotherapy at Early Phases of ALL for Improving the MRD Negativity

Blinatumomab in MRD+ patients in CR: BLAST trial

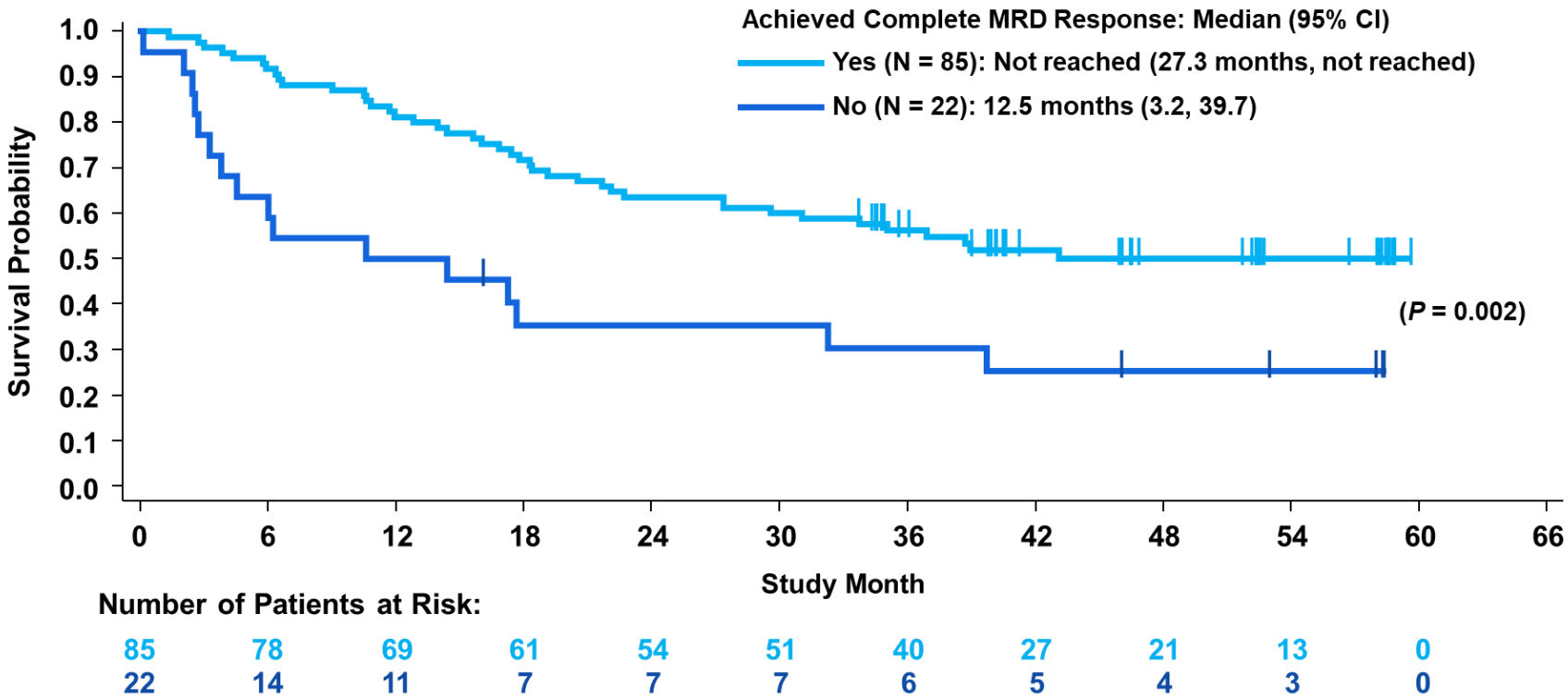
Blinatumomab or inotuzumab with chemotherapy in newly diagnosed Ph– ALL

Blinatumomab or inotuzumab with TKI in newly diagnosed Ph+ ALL

Overall Survival by Complete MRD Response

All Patients Analyzed

BLAST (MT103-203) STUDY



MRD, minimal residual disease.

Landmark analysis from day 45; complete MRD response was defined as no target amplification, with a minimum sensitivity of 10^{-4}.

Gökbuget N, et al. ASH 2018. Presentation 554.

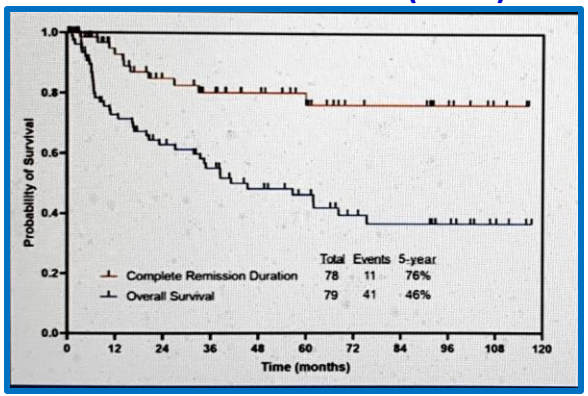
Immunotherapy in Early Phases of Ph– ALL: Results From Phase II Trials

Group	Chemotherapy	MoAb	N pts	Median age (range)	CR after induction	MRD– after induction	OS (y)
MDACC[1]	Mini HyperCVD	Ino ± Blin	78	68 (60–87)	86%	80%	46% (5y)
EWALL[2]	EWALL backbone	Ino	90	69 (55–84)	88.8%	73%	78.5% (1y)
GMALL[3]	EWALL backbone (in consolidation)	Ino (single-drug induction)	43	64 (56–80)	100%	74%	77% (2y)
SWOG[4]	POMP (maintenance only)	Blin (single-drug induction)	29	75 (66–84)	65.5%	NA	37% (3y)
GRAALL[5]	Standard induction + consolidation	Blin	94	35 (18–60)	NR	74%	92% (1y)
GMALL[6]	EWALL backbone	Blin	33	65 (56–76)	83%	69%	84% (1y)
MDACC[7]	HyperCVAD	Blin	38	37 (17–59)	81%	85%	83% (3y)

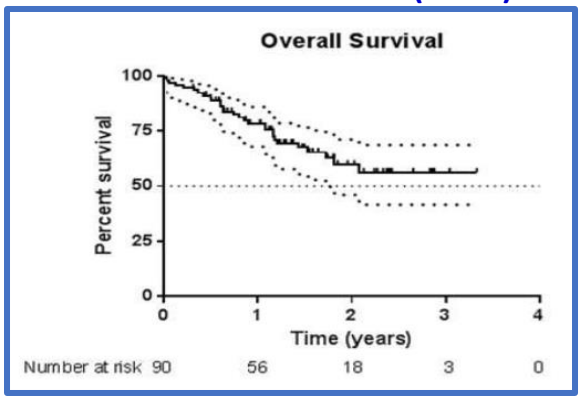
1. Short N, et al. ASH 2021. Abstract 3400; 2. Chevalier P, et al. ASH 2021. Abstract 511; 3. Stelljes M, et al. ASH 2021. Abstract 2300; 4. Advani A, et al. *J Clin Oncol.* 2022 DOI: 10.1200/JCO.21.01766; 5. Boissel N, et al. ASH 2021. Abstract 1232; 6. Gokbuget N, et al. ASH 2021. Abstract 3399; 7. Short N, et al. ASH 2021. Abstract 1233.

Immunotherapy in First-Line ALL: Phase II Trials

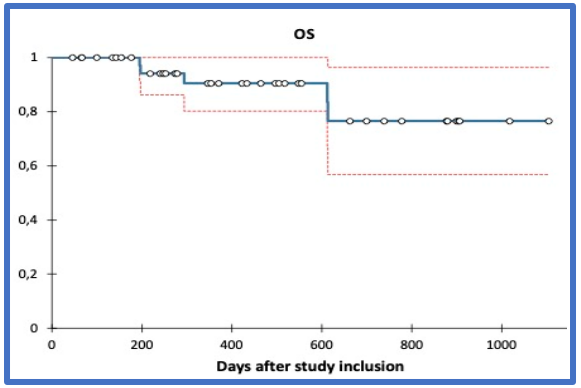
MiniHCVD + Ino ± Blin (older)[1]



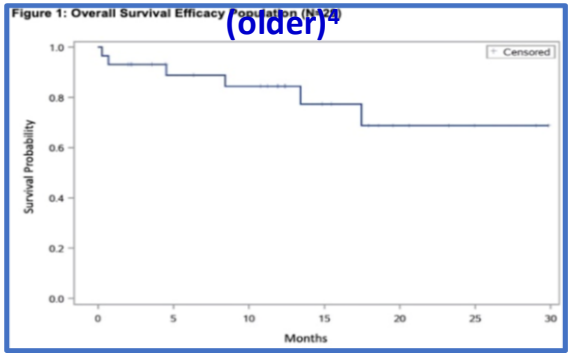
Ino + low induction CHT (older)[2]



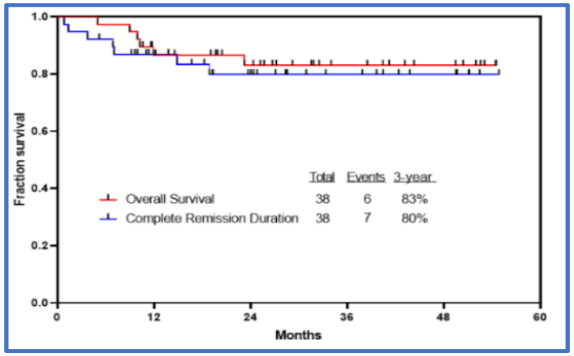
Ino induction + CHT consol (older)[3]



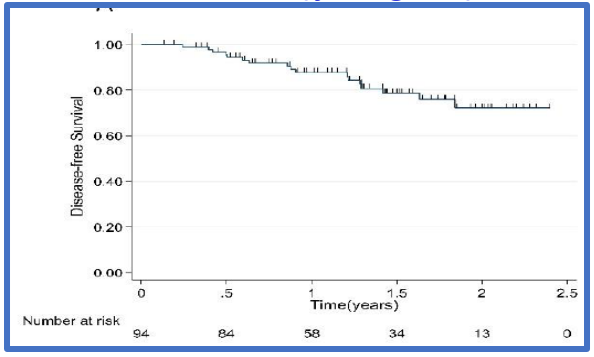
Low induction + Blin consol (older)[4]



HCVAD + Blin (young)[5]



Std CHT + Blin (young, HR)[6]



1. Short N, et al. ASH 2021. Abstract 3400; 2. Chevalier P, et al. ASH 2021. Abstract 511; 3. Stelljes M, et al. ASH 2021. Abstract 2300; 4. Gokbuget N, et al. ASH 2021. Abstract 3399; 5. Short N, et al. ASH 2021. Abstract 1233; 6. Boissel N, et al. ASH 2021. Abstract 1232; .

Immunotherapy in Early Phases of Ph+ ALL: Results From Phase II Trials

Reference	TKI	Immunotherapy	N	Median age (range)	CR, %	CMR, %	OS, % (95% CI) years
Foa et al[1]	Dasatinib	Blinatumomab	63	54 (24–82)	98	29 (ponatinib) 60 (blinatumomab)	80 (68–93) 2-yr
Short et al[2]	Ponatinib	Blinatumomab	30	62 (34–83)	94	81 (CMR + MMR)	93 2-yr
Advani et al[3]	Dasatinib	Blinatumomab	24	73 (62–87)	92	31	85 (58–95) 3-yr

1. Foa R, et al. *N Engl J Med.* 2020;383:1613-1623; 2. Short N, et al. *Blood.* 2021;138(suppl 1): abstract 2299; 3. Advani A, et al. *Blood.* 2021; 138(suppl 1): abstract 3397.

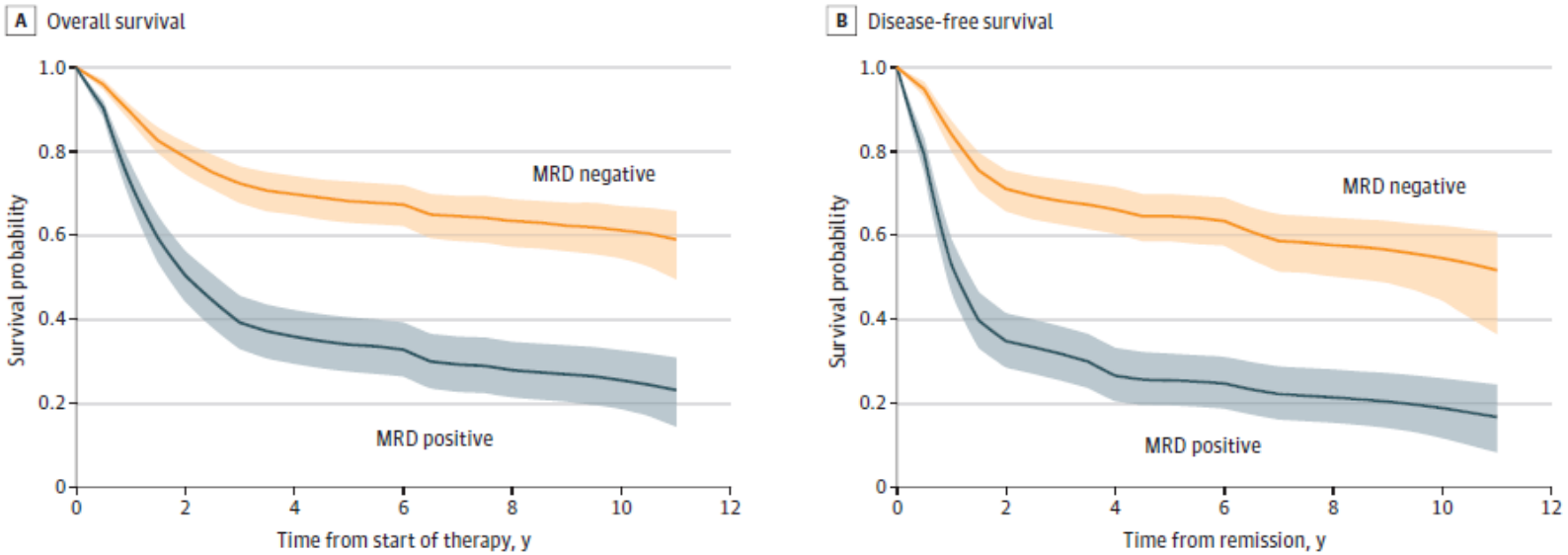
Conclusions (ALL)

- MRD is the best prognostic factor in children and adults with ALL
- Prognostic significance at any time point (after induction, consolidation, before and after HSCT)
- Limited predictive value. Possible additional influence of oncogenetic factors
- MRD must de assessed within specific trials
- Possible early interventions to decrease the MRD level
  - Immunotherapy with MoAb (blinatumomab, inotuzumab)(Ph– ALL)
  - Combination of MoAb with targeted therapy (Ph+ ALL)

Acute Myeloid Leukemia

Outcomes Stratified by MRD Status in AML

Systematic review and meta-analysis of 81 publications including 11151 patients



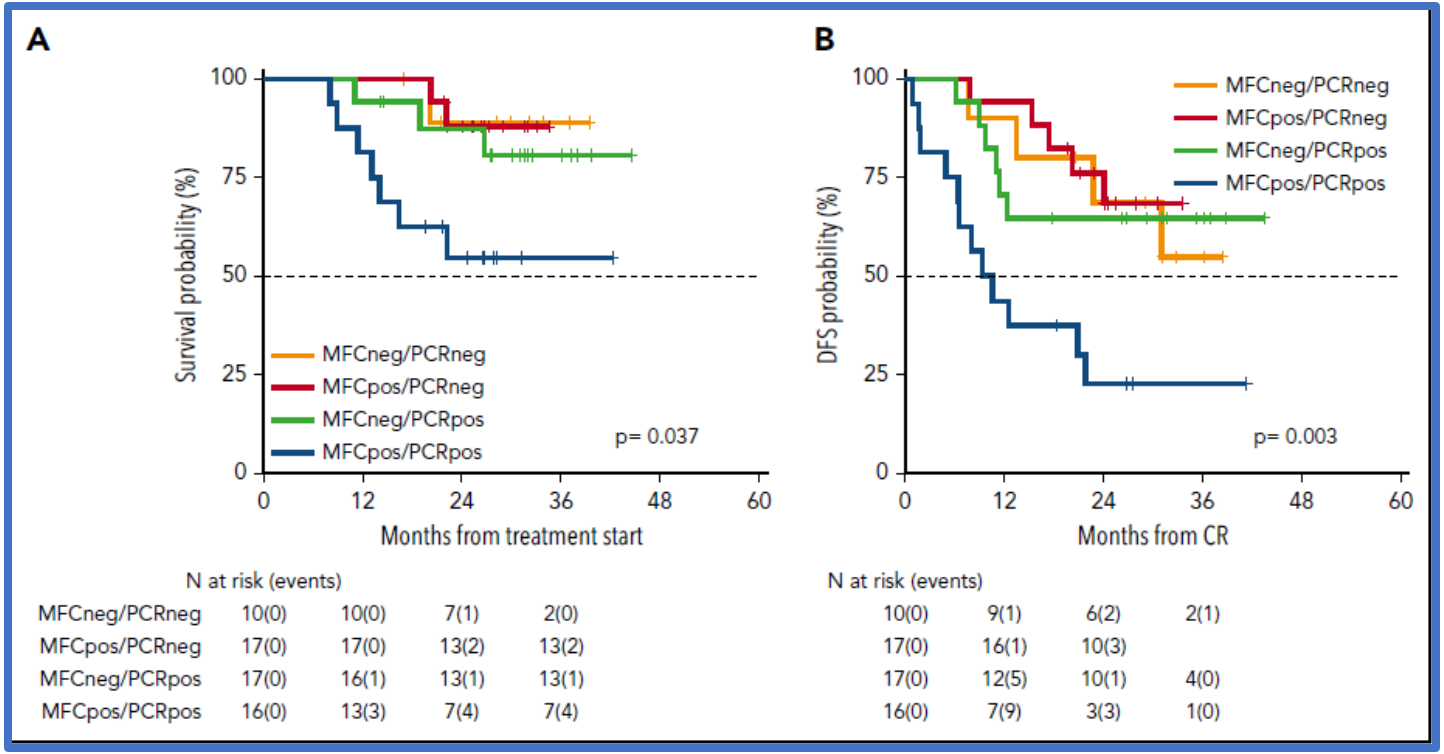
Short NJ, et al. *JAMA Oncol.* 2020;6:1890-1899.

MRD in AML: Techniques

Technique	Advantages	Disadvantages
Multiparameter flow cytometry	• Most commonly used method • Applicable to >90% of patients • Sensitivity 1×10^{-4} to 1×10^{-5} • Identification of leukemia-associated immunophenotypes (LAIP) and/or different from normal approach	• High level of expertise needed – Selection of right antibody panel – Standardization of analyses – Extensive knowledge about normal and regenerative BM expression of CD
Molecular measurable MRD	• Higher sensitivity of RT-qPCR • Novel developments of higher-sensitivity techniques – Droplet digital PCR – NGS (under investigation)	• Limited to specific stable genes during disease progression – *NPM1* – *RUNX1-RUNX1* – *CBF-MY11*

MFC vs PCR for MRD Assessment in AML

GIMEMA AML 1310



N at risk (events)				
MFCneg/PCRneg	10(0)	10(0)	7(1)	2(0)
MFCpos/PCRneg	17(0)	17(0)	13(2)	13(2)
MFCneg/PCRpos	17(0)	16(1)	13(1)	13(1)
MFCpos/PCRpos	16(0)	13(3)	7(4)	7(4)

N at risk (events)				
	10(0)	9(1)	6(2)	2(1)
	17(0)	16(1)	10(3)	
	17(0)	12(5)	10(1)	4(0)
	16(0)	7(9)	3(3)	1(0)

Venditti A, et al. *Blood.* 2019;134:935-945.

Where to Measure MRD in AML?

- **Standard approach**: bone marrow
- **Peripheral blood**
  - MFC: probably 1 log less sensitive
  - RT-qPCR: similar sensitivity?

Prognostic and Predictive Value of MRD in AML

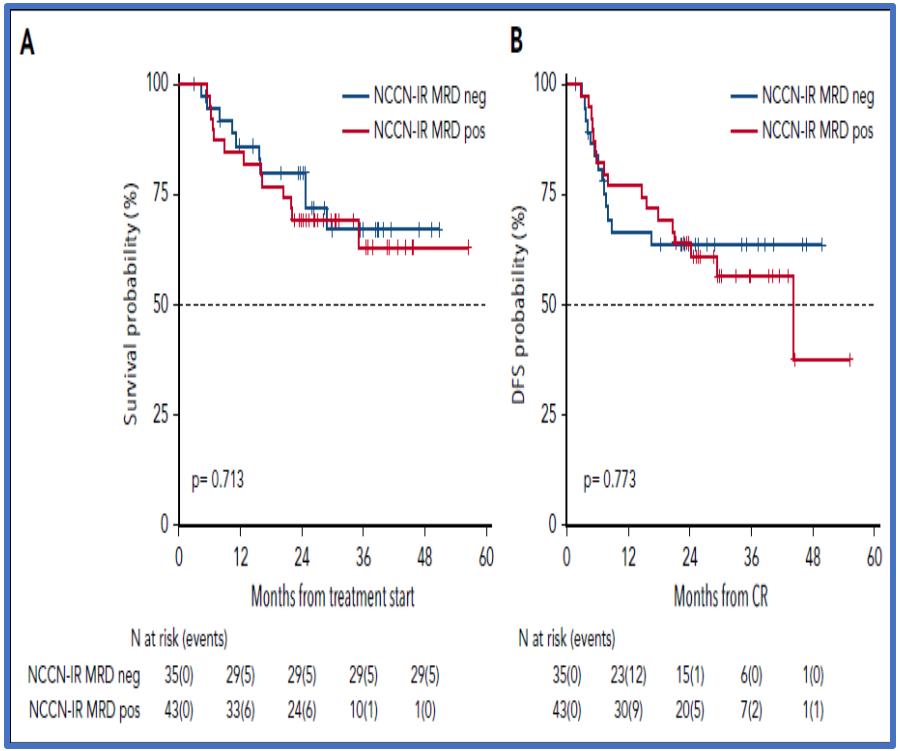
- **Growing evidence on the prognostic value** of MRD in
  - Post-remission
  - After consolidation
  - Before HSCT
- **Poor predictive value** (as in ALL)
  - 30% of MRD– patients relapse

(Potential) Use of MRD in the Clinic

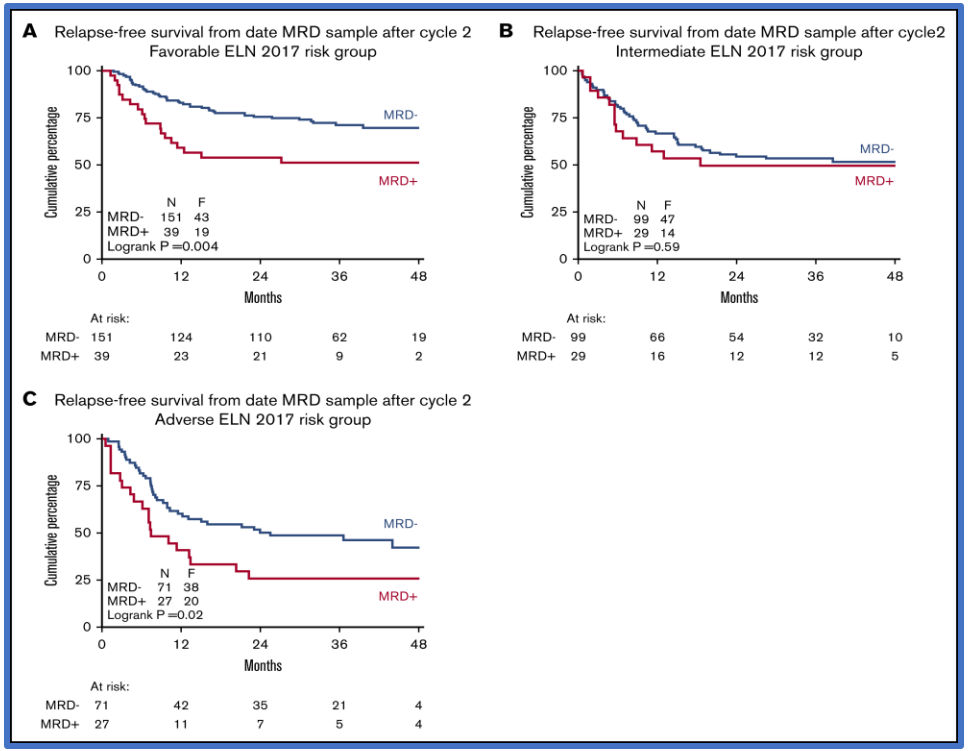
Potential Use	Comment
• **Refine the CR status**	• MRD not officially recognized as surrogate endpoint
• **Choose targeted therapy at induction**	• Under research
• **Intensifying induction therapy in MRD+ pts**	• Several trials with new drugs and targeted therapies
• **Choice of consolidation therapy**	• Incorporation of new drugs in this phase
• **Defining the need and type of HSCT**	• Potentially useful for selecting allo/auto in intermediate-risk group
• **Pre-emptive therapy before HSCT**	• Intensification of consolidation vs new drugs before HSCT
• **Post-transplant interventions**	• Hypomethylating agents, DLI, immunotherapy, targeted therapy . . .

Allogeneic HSCT Abrogates the Poor Prognosis of MRD+ in Intermediate-Risk AML

GIMEMA AML 1310



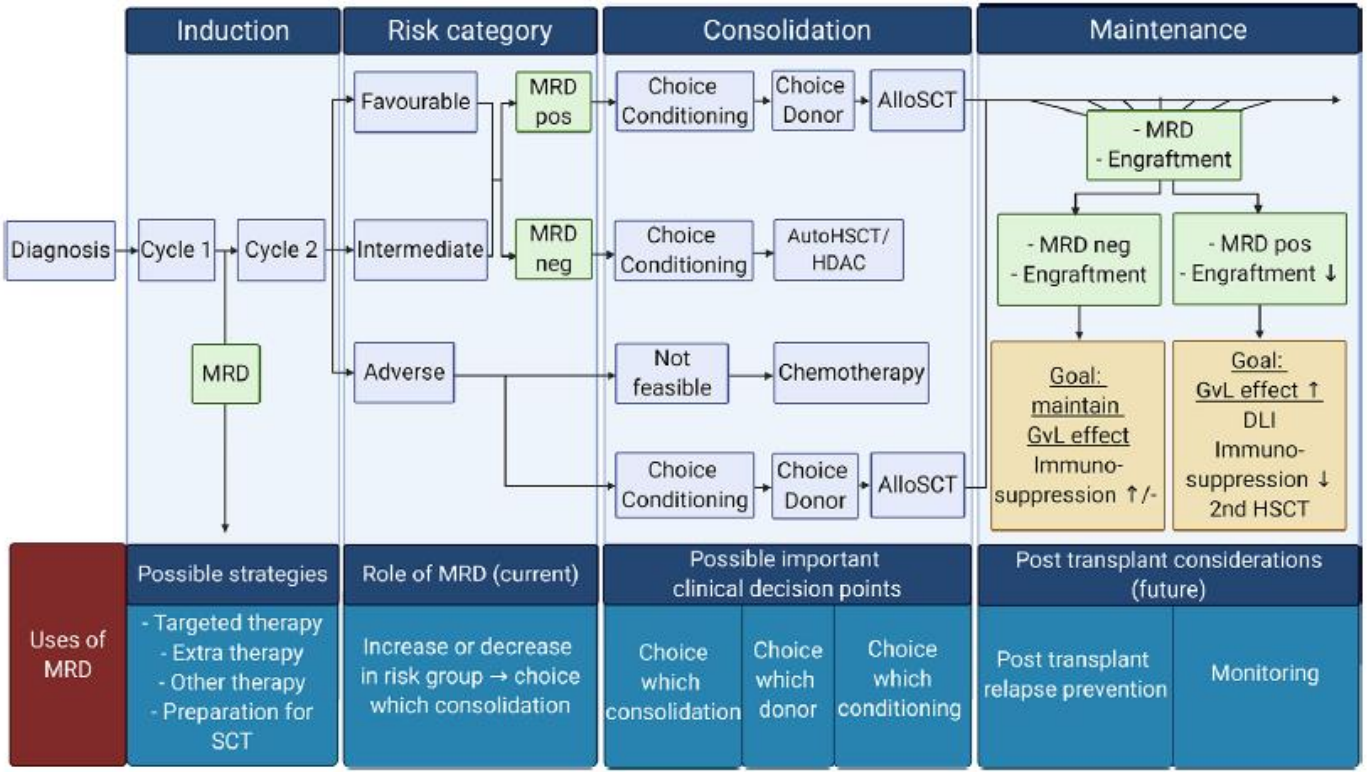
HOVON SAKK



Venditti A, et al. *Blood.* 2019;134:935-945.

Löwenberg B, et al. *Blood Adv.* 2021;5:1110-1121.

Possible MRD Tailored Therapy in Different AML Phases



Ngai LL, et al. *Front Oncol*. 2021;10:603636.

Conclusions (AML)

- MRD has prognostic value in AML
- Techniques for MRD assessment less standardized than in ALL
- MRD increasingly recognized as surrogate endpoint
- MRD is a decision tool for incorporation of new therapies and for selection of HSCT
- As in ALL, MRD has poor predictive value

Question 1

The best moment of MRD assessment for prognosis in Ph+ ALL is:

1. At diagnosis
2. After induction (1 month from diagnosis)
3. After consolidation (3 months from diagnosis)
4. After autologous HSCT
5. After allogeneic HSCT

Question 2

In AML, one of the following techniques is not used for MRD assessment:

1. Flow cytometry
2. Fluorescence in situ hybridization
3. Quantitative PCR
4. Droplet-digital PCR
5. NGS

Global Leukemia Academy

Current and future role of transplantation in acute leukemias

Sergio Giralt

APTITUDE HEALTH

Memorial Sloan Kettering Cancer Center

Allogeneic HCT for AML and ALL: Current State of the Science Global Leukemia Academy

Sergio Giralt, MD
Melvin Berlin Chair in Myeloma Research
Professor of Medicine
Weill Cornell Medical College
Deputy Head, Division of Hematologic Malignancies
Attending Physician, Adult BMT Service
Memorial Sloan Kettering Cancer Center
New York, New York

Memorial Sloan Kettering Cancer Center

Disclosures

- Research support
  - Celgene, Sanofi, Johnson & Johnson, Actinuum, Millennium, Amgen, Takeda, Omeros
- Consulting fees
  - Celgene, Sanofi, Johnson & Johnson, Actinuum, Millennium, Amgen, Kite (Gilead), Novartis, BMS, Jazz, Pfizer, CSL Behring, Omeros
- I am a transplanter

Memorial Sloan Kettering Cancer Center

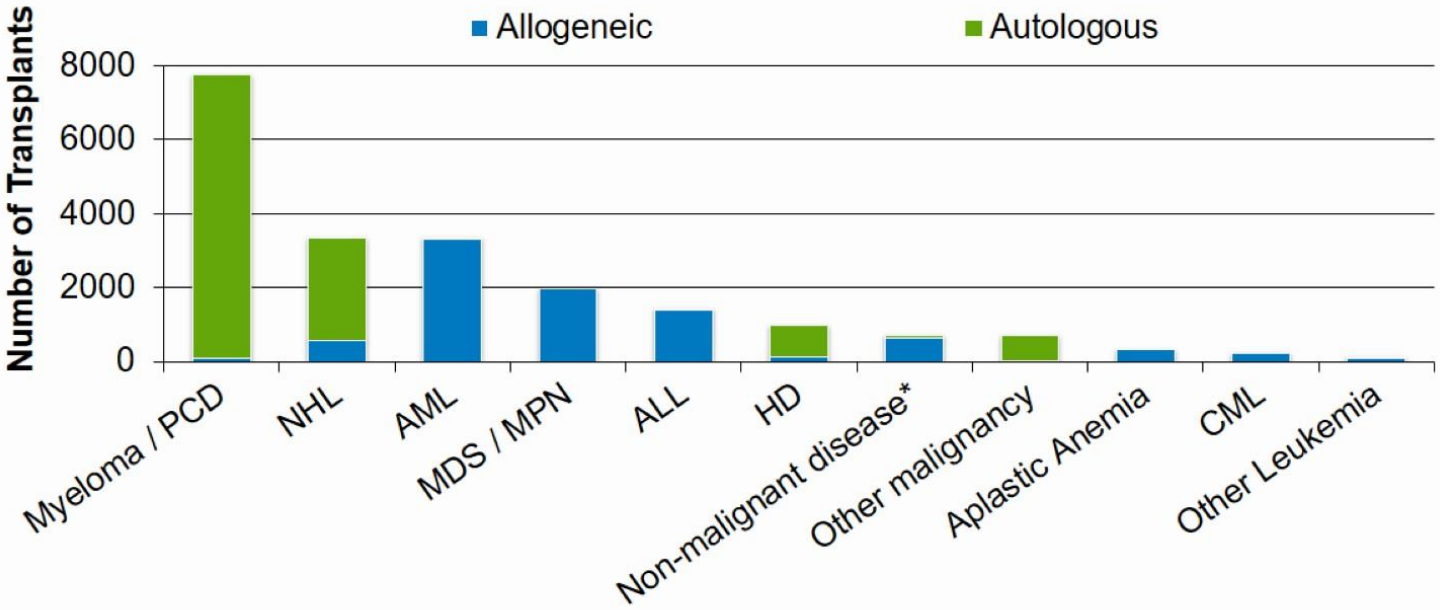
Agenda

- Current State of Allo-HCT in AML and ALL
- Indication for HCT in AML
- Planning HCT for AML Patients
- Future Directions in HCT for AML
- Indication for HCT in ALL
- Planning HCT for ALL Patients
- Future Directions in HCT for ALL

Memorial Sloan Kettering Cancer Center

Current State of Allogeneic HCT for AML/ALL

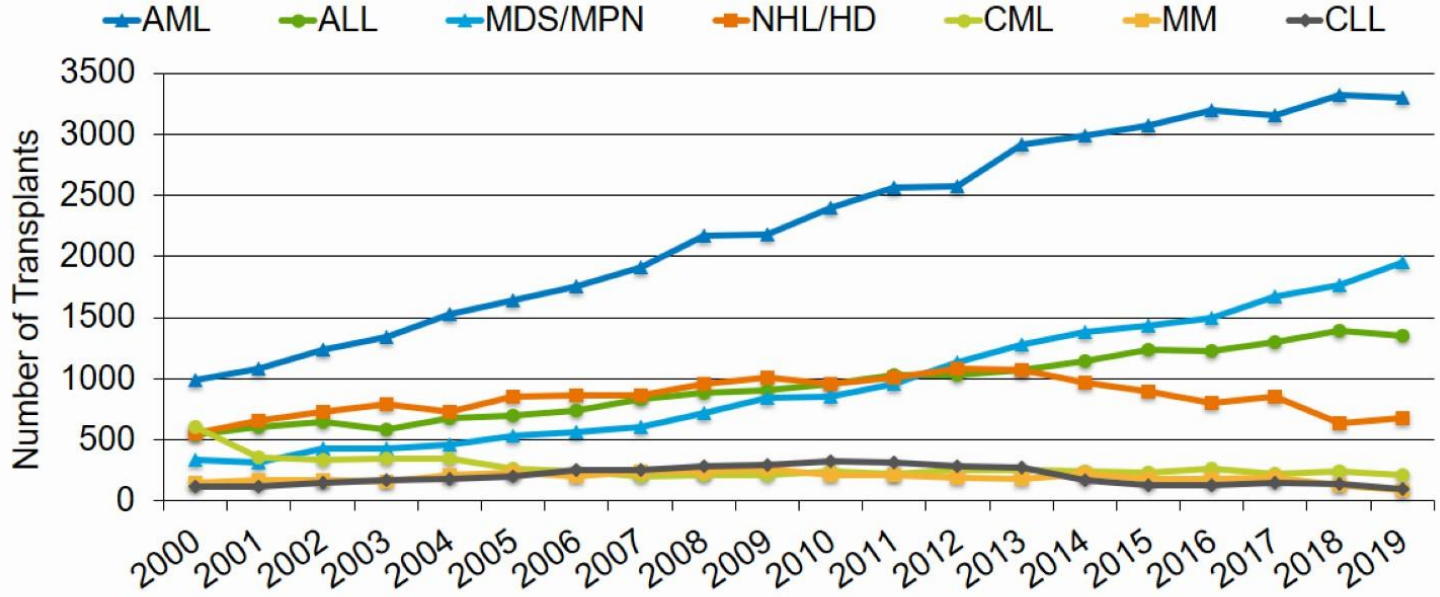
Indications for Hematopoietic Cell Transplant in the US, 2019



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

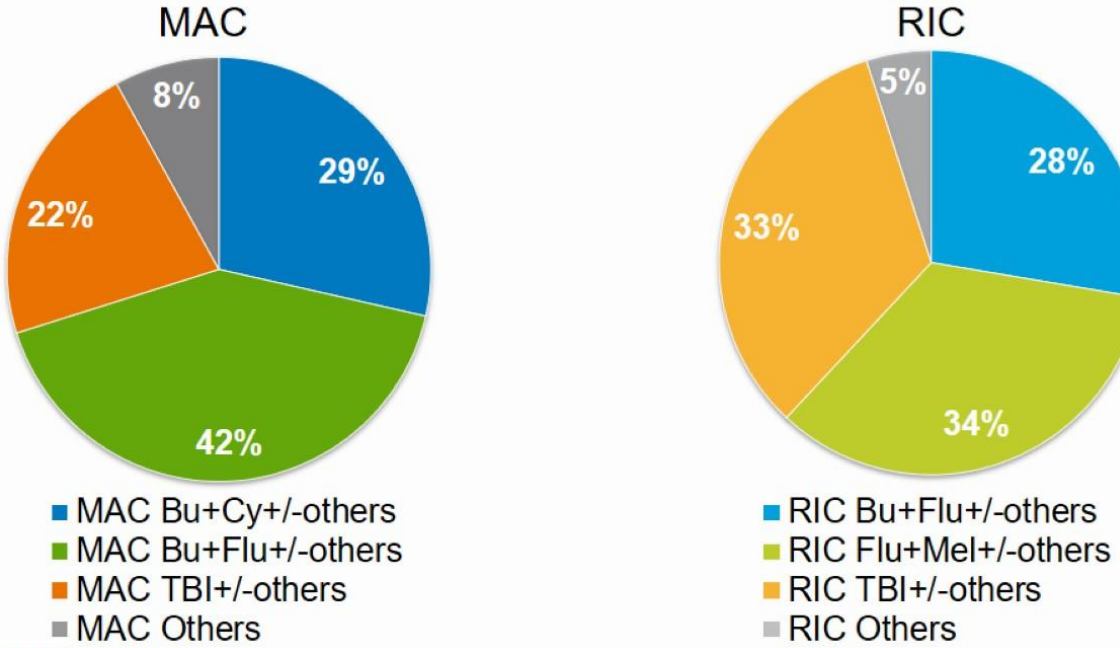
*excludes aplastic anemia

Selected Disease Trends for Allogeneic HCT in the US



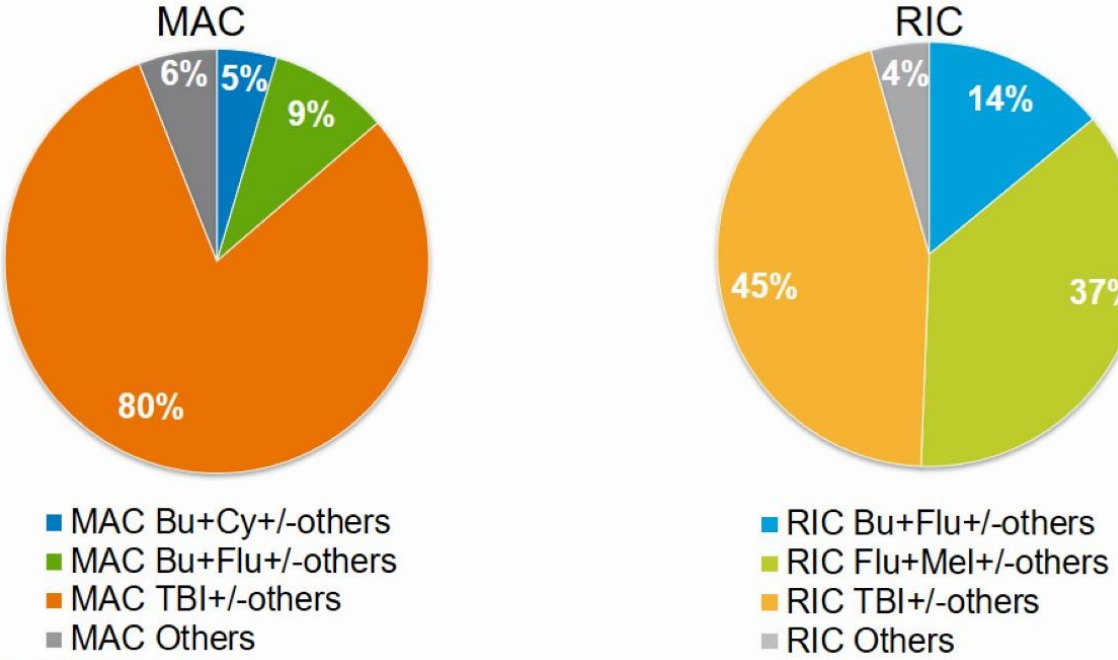
CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Common Conditioning Regimens in Acute Myelogenous Leukemia (AML) or Myelodysplastic Syndrome (MDS) Allogeneic HCT in the US, 2009-2019



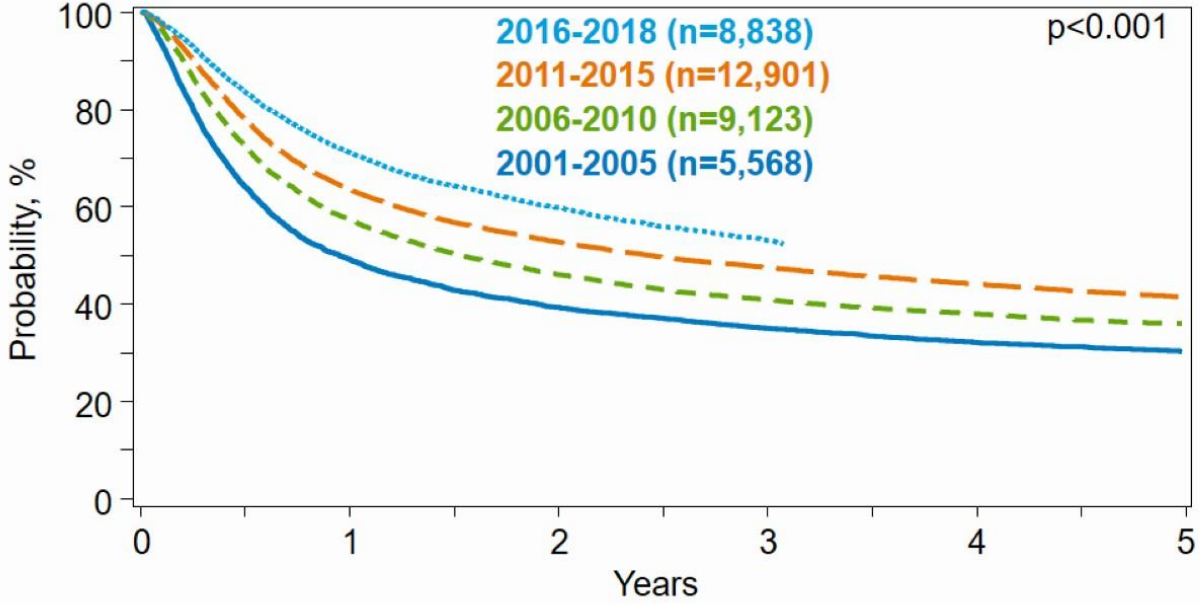
CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Common Conditioning Regimens in Acute Lymphoblastic Leukemia (ALL) Allogeneic HCT in the US, 2009-2019



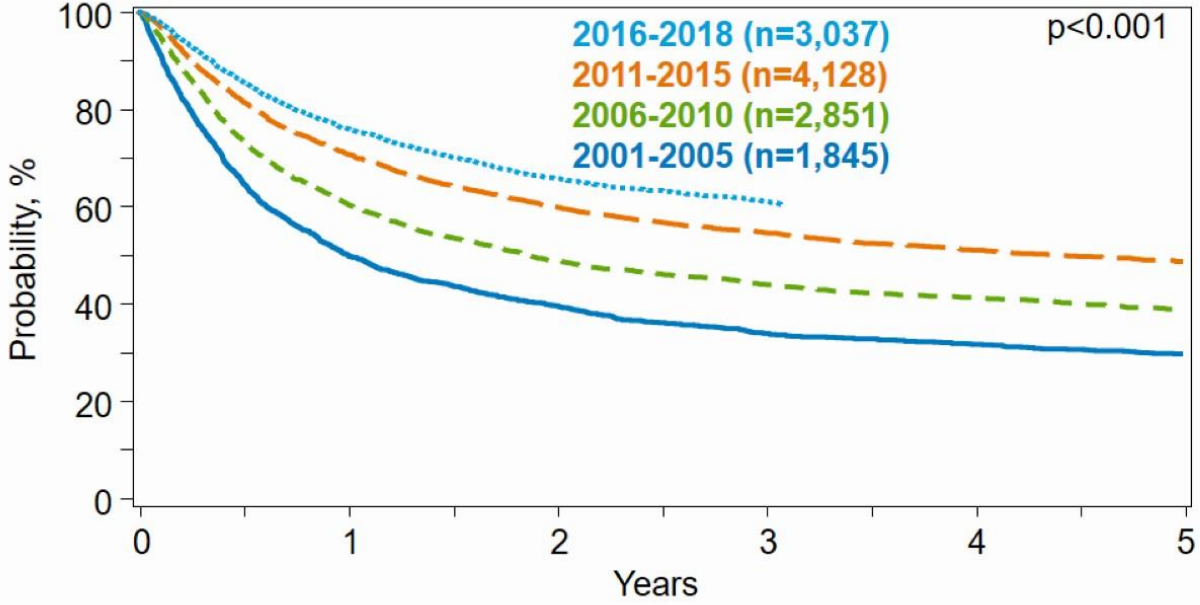
CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Trends in Survival after Allogeneic HCT for Acute Myelogenous Leukemia (AML), Age ≥18 Years, in the US, 2001-2018



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Trends in Survival after Allogeneic HCT for Acute Lymphoblastic Leukemia (ALL), Age ≥18 Years, in the US, 2001-2018



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Memorial Sloan Kettering Cancer Center

Who Should Be Referred for Allo-HCT in AML?

Memorial Sloan Kettering Cancer Center

Who Should Be Referred for Allo-HCT?

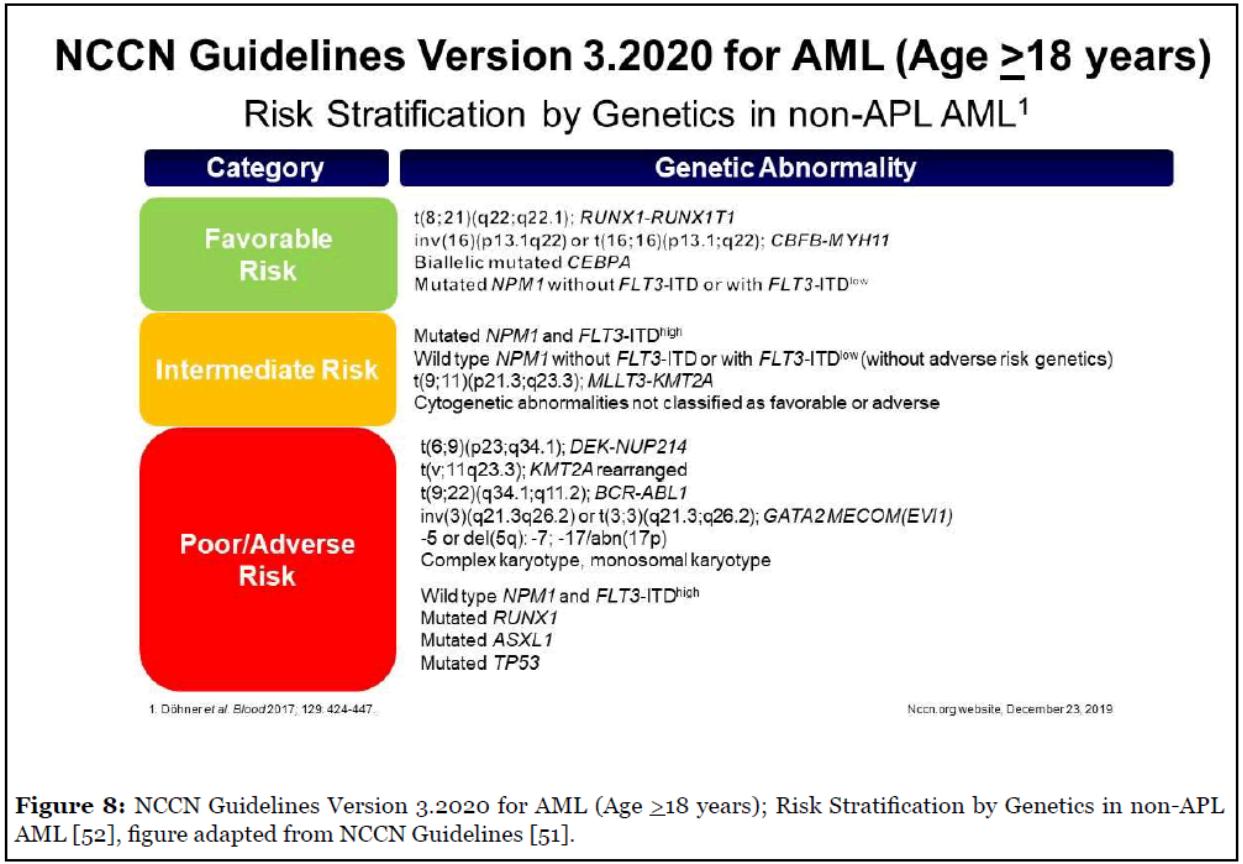


Figure 8: NCCN Guidelines Version 3.2020 for AML (Age ≥18 years); Risk Stratification by Genetics in non-APL AML [52], figure adapted from NCCN Guidelines [51].

Memorial Sloan Kettering Cancer Center

Who Should Be Referred for Allo-HCT With ALL?

Memorial Sloan Kettering Cancer Center

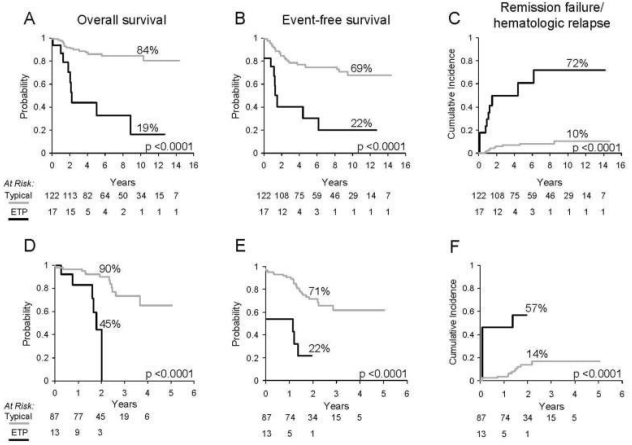
Indications for Transplant in Adult ALL

- CR1
  - High-risk karyotype: complex, hypodiploid, 11q23, iAMP21 (pedi)
  - High-risk immune phenotype: ETP, Ph-like
  - Poor Rx response: MRD
  - Ph?
    - HCT if persistent MRD after 3 months of therapy
- CR2 and greater remission
  - All patients

<u>Disease status remains a powerful prognosticator.</u>

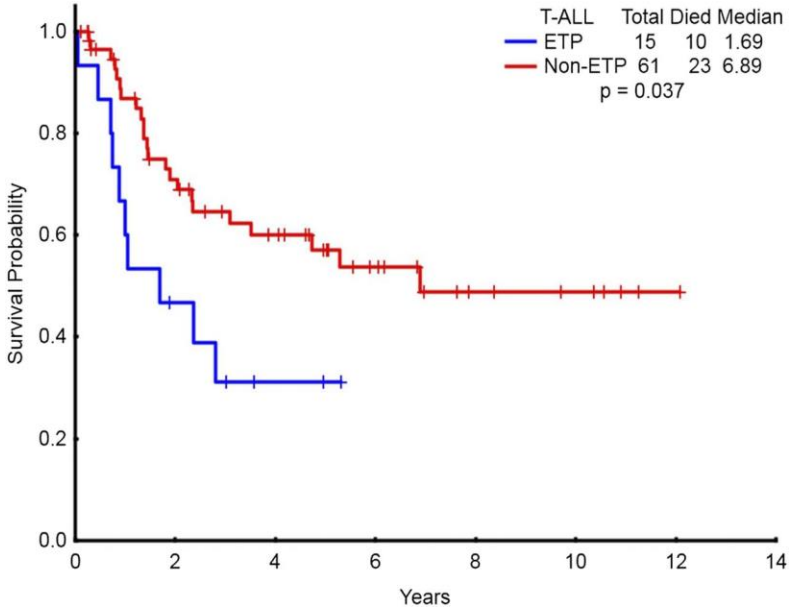
Poor Outcome for ETP ALL

- T-ALL originating from early T-cell precursors
- Distinct gene expression profile
- Distinct immunophenotype: $CD1a^{neg}$, $CD8^{neg}$, $CD5^{weak}$, ± myeloid markers



N = 239 children treated on St Jude's, A–C (n = 139) or AIEOP, D–F (n = 100) protocols.
Black line: ETP; Gray line: other T

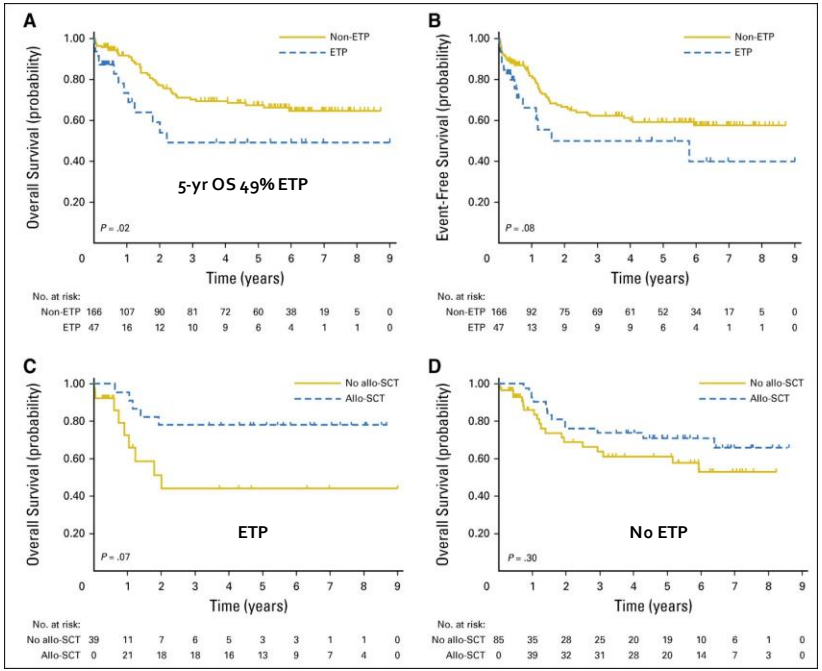
Coustan-Smith E, et al. *Lancet.* 2009;10:147-156.



Jain N, et al. *Blood.* 2016;127:1863-1869.

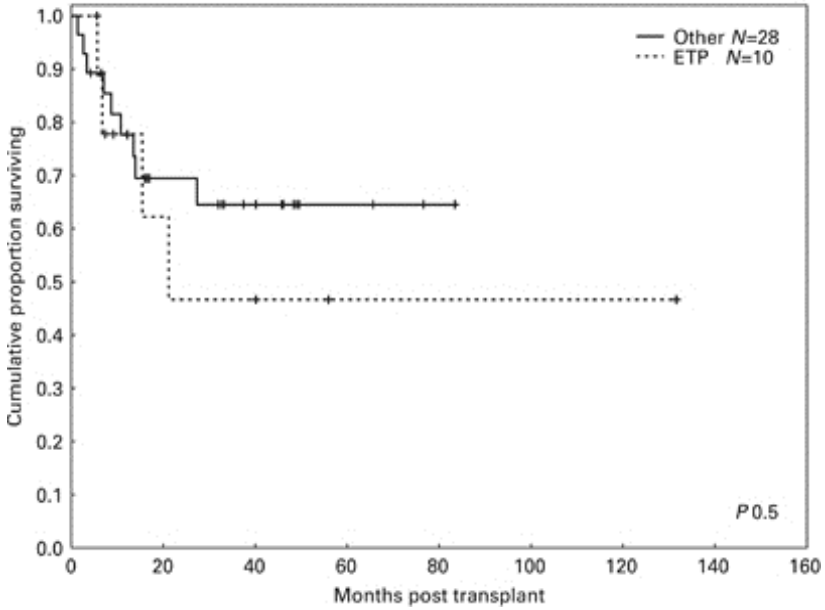
Poor Outcome for ETP ALL Abrogated by HCT

GRAALL, N = 213 adults, 47 ETP; HCT in CR1



Bond J, et al. *J Clin Oncol.* 2017;35(23):2683-2691.

HCT in CR1; 3-yr OS 47% for ETP

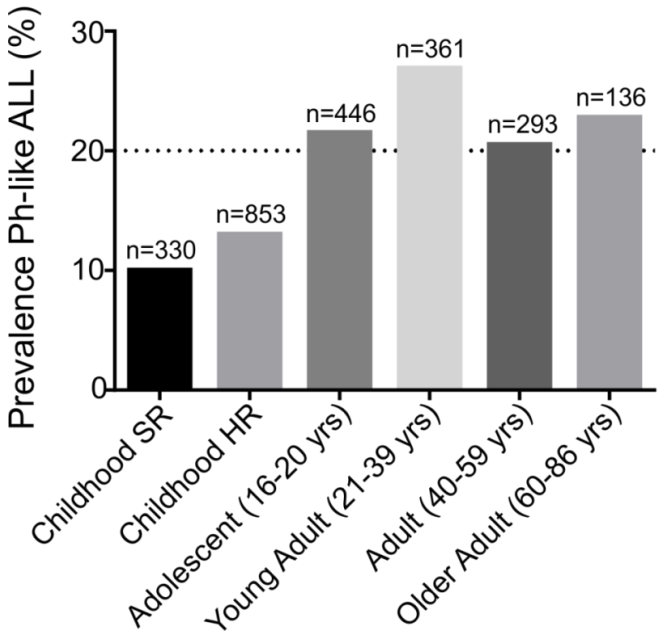


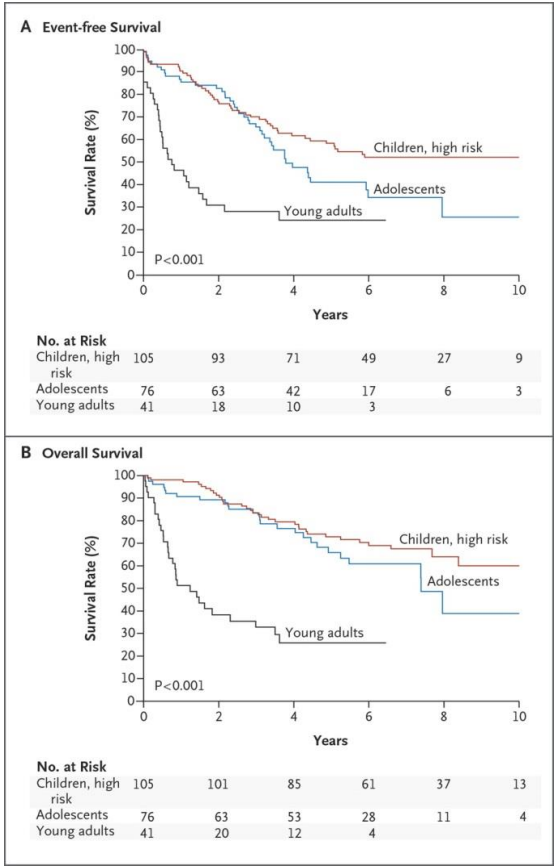
Brammer JE, et al. *Bone Marrow Transplant.* 2017;52(1):20-27.

Memorial Sloan Kettering Cancer Center

Ph-Like ALL

Peaks in AYAs



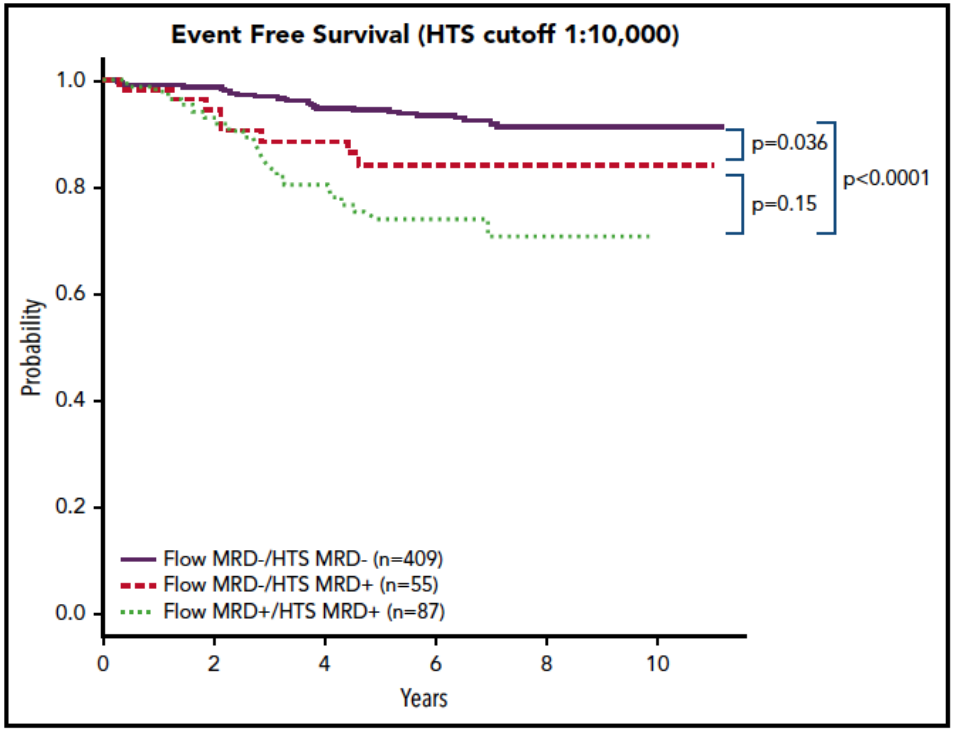


Poor outcome

Courtesy Dr Roberts *NEJM* 2014 and unpublished.

Memorial Sloan Kettering Cancer Center

MRD Allows Precise Risk Stratification



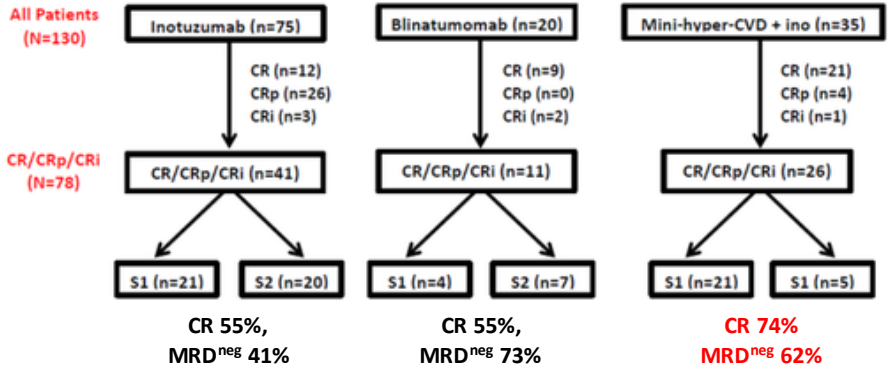
- Next-generation sequencing (NGS) MRD testing more accurately predicts outcomes
  - NGS MRD identified a subgroup with NGS+/flow MRD– with an intermediate prognosis
  - Low-risk characteristics + NGS MRD negativity (20% of pts) identified very good survival (EFS 98.1%, OS 100%)

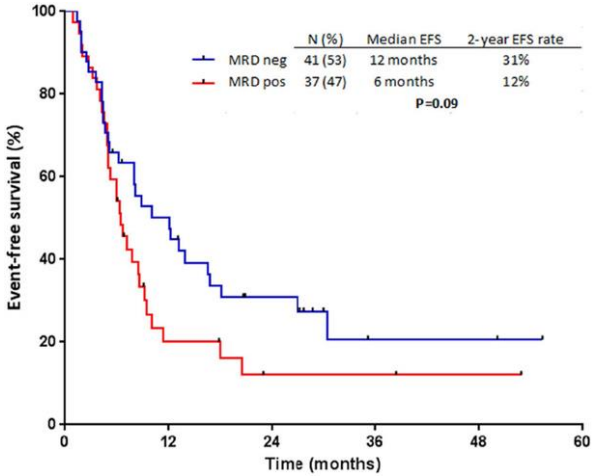
Wood B, et al. *Blood.* 2018;131:1350-1359.

Memorial Sloan Kettering Cancer Center

Now: Probability of Survival From Relapse

- 130 adults with ALL received therapy in salvage 1 (SI) or 2 (S2) at MDACC between 2010–2015
- ORR 60%, MRD^{neg} 32% by MFC; best response in chemo-immunotherapy group
- Med 27 mo FU, stratified by MRD and salvage
  - 2-yr EFS and OS rates were 31% vs 12%, p = .09, and 40% vs 26%, p = .18, respectively
  - MRD significantly impacts EFS in salvage 1 only





Jabbour E, et al. *Cancer*. 2017;23:294-302.

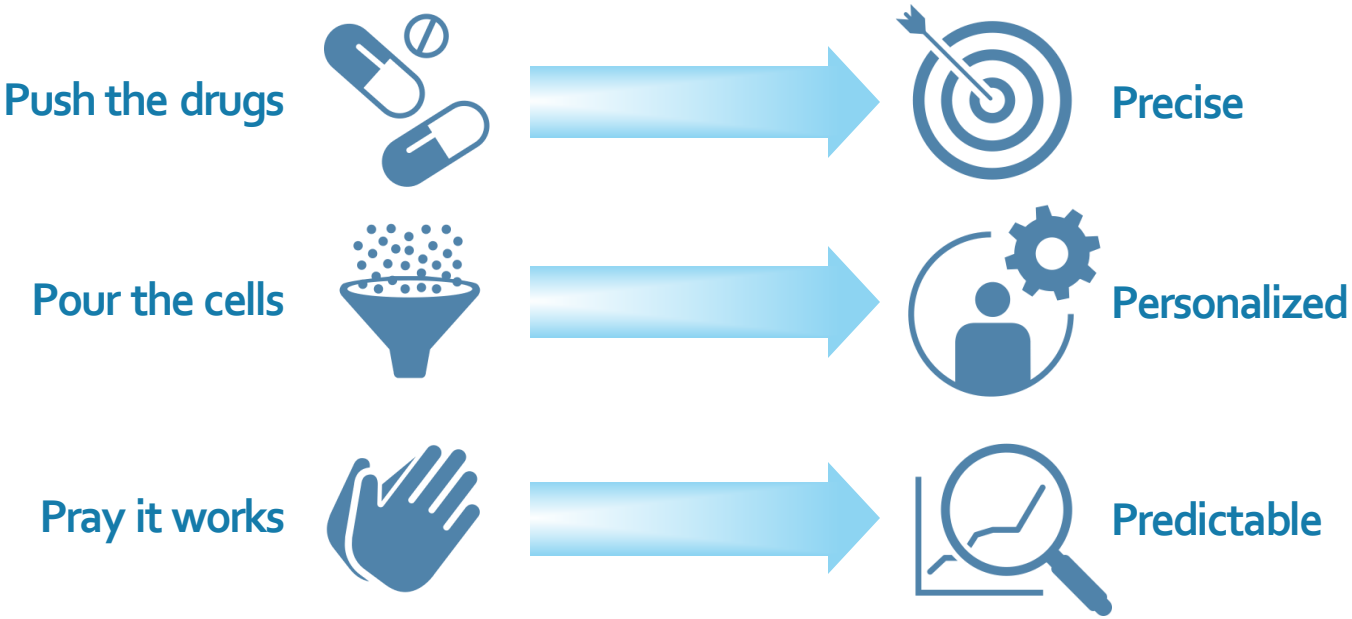
Memorial Sloan Kettering Cancer Center

Summary

- Progressive improvement in patient outcomes compared with historical data
  - CR rates up to 80% (c/w ~30%); notably majority MRD^{neg}
  - Survival ~50% (c/w ~20%)
- Blinatumomab, inotuzumab
  - Median OS <12 months
  - Improved CR rates and durability noted when used earlier in disease course, combined with chemotherapy
  - Studies ongoing

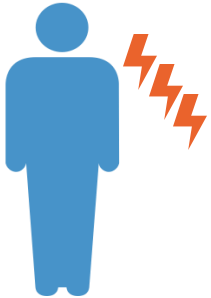
Memorial Sloan Kettering Cancer Center

Triple P Transplants



Memorial Sloan Kettering Cancer Center

Improving HCT Outcomes

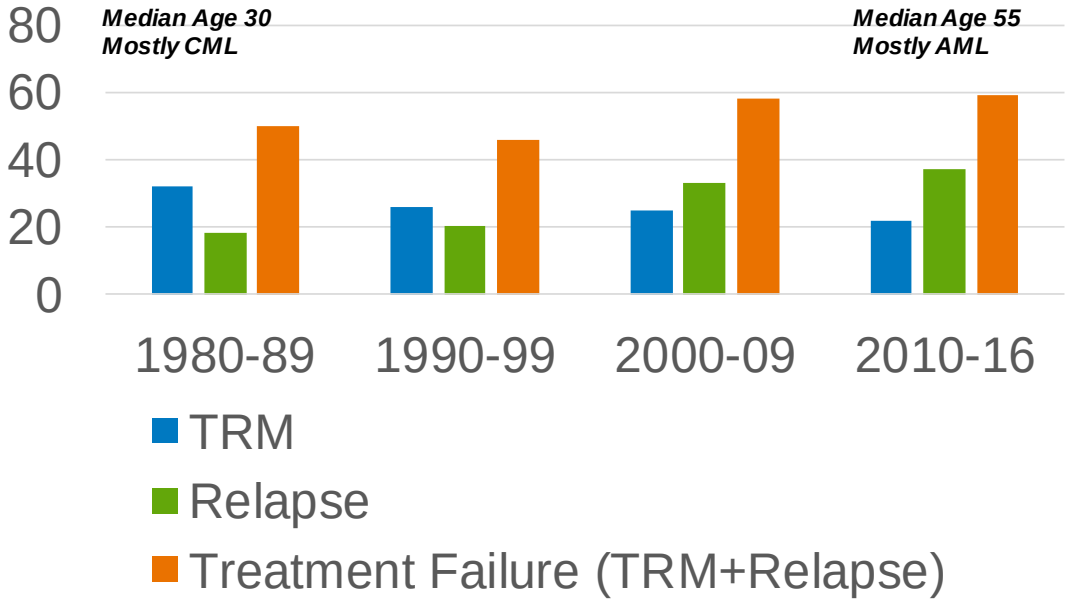


Pre-HCT therapy

Pre-HCT early referral

Memorial Sloan Kettering Cancer Center

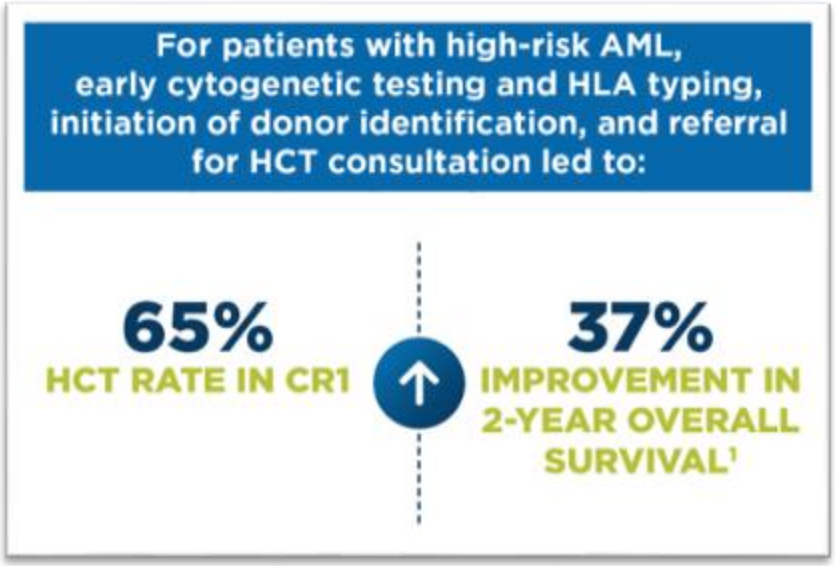
Are We Making Progress? Five-Year Outcomes After HCT for AML in CR1



Memorial Sloan Kettering Cancer Center

Early Referral Makes a Difference

Performing HLA typing and cytogenetic testing at the time of diagnosis increases the chance of receiving HCT in early-stage disease, which **leads to improved patient outcomes.**



1. Pagel JM, et al. *JCO Oncology Practice.* 2020;16(6):e464-e475.

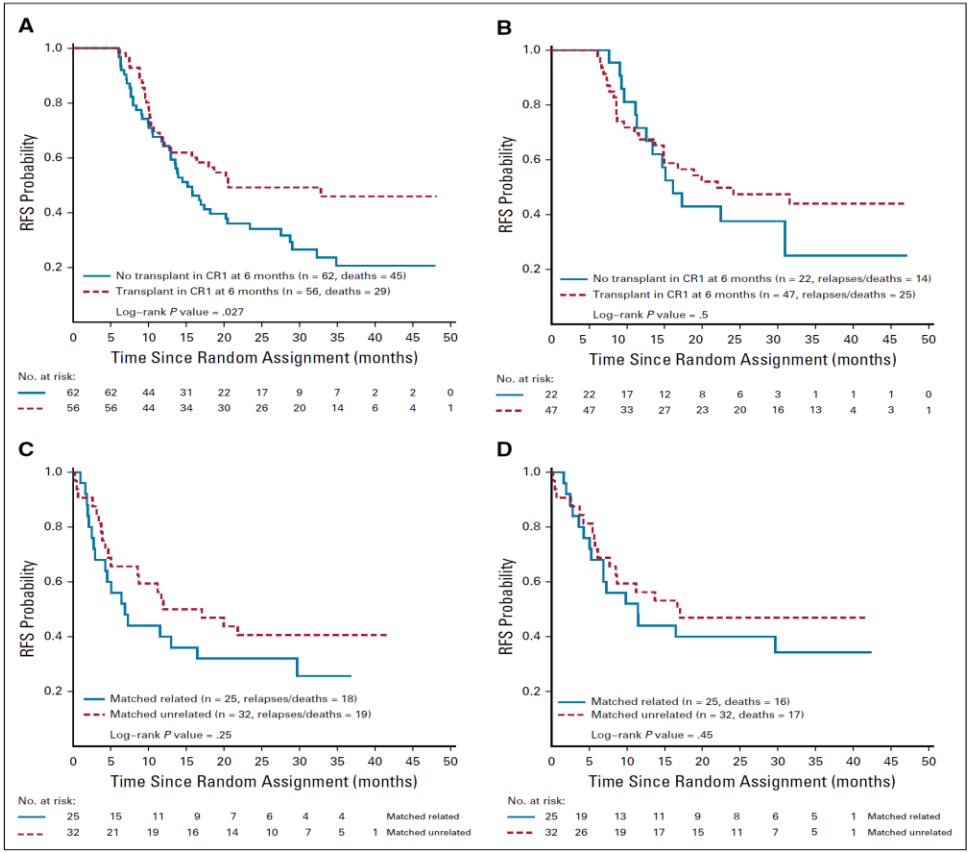
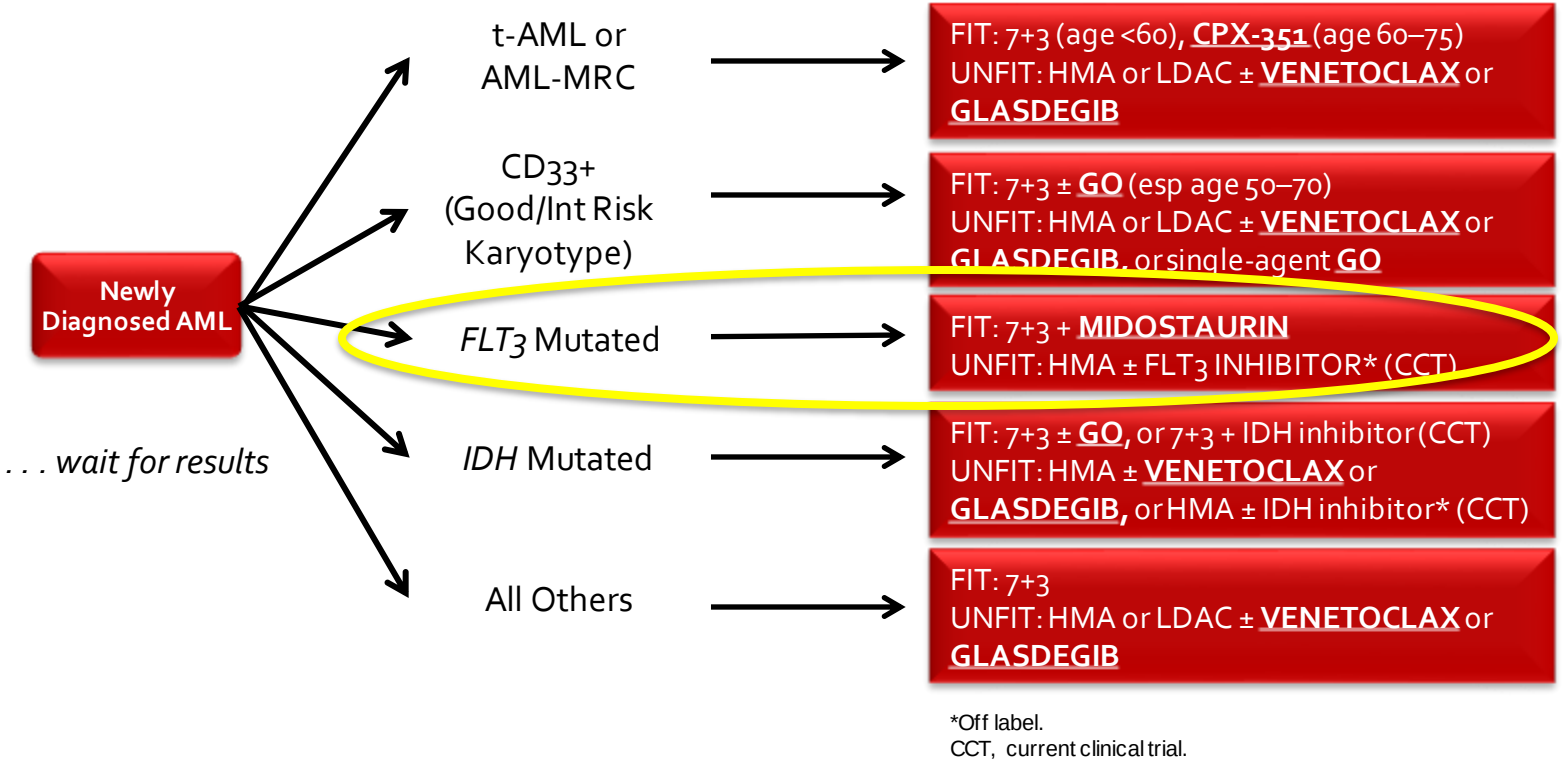


FIG 3. Survival outcomes for patients transplanted in CR1. (A) Landmark analysis for OS and (B) RFS among patients alive after 6 months after randomization. (C) RFS and (D) OS among CR1 high-risk patients who were treated using a matched related donor *v* a matched unrelated donor. CR1, first complete remission; OS, overall survival; RFS, relapse-free survival.

Memorial Sloan Kettering Cancer Center

AML Induction Therapy: A More Complicated Landscape

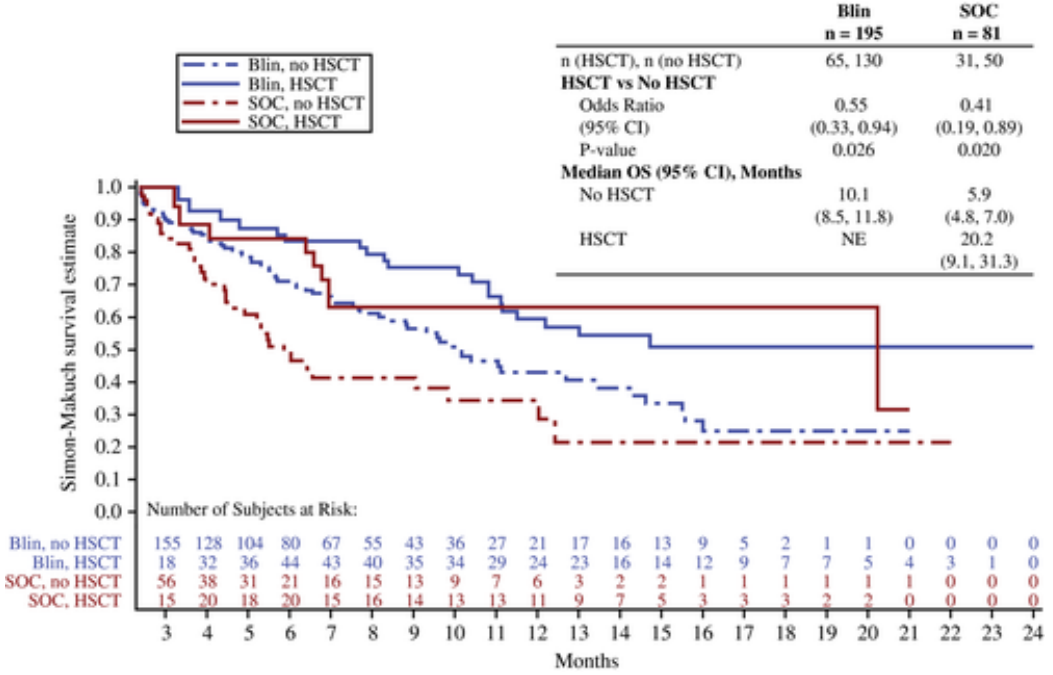


*Off label.
CCT, current clinical trial.

Memorial Sloan Kettering Cancer Center

TOWER: Impact of HCT in Blin and SOC Groups

- HCT significantly improved survival in both Blin and SOC groups
- No difference in HCT benefit by treatment group



	Blin n = 195	SOC n = 81
n (HSCT), n (no HSCT)	65, 130	31, 50
HSCT vs No HSCT		
Odds Ratio	0.55	0.41
(95% CI)	(0.33, 0.94)	(0.19, 0.89)
P-value	0.026	0.020
Median OS (95% CI), Months		
No HSCT	10.1 (8.5, 11.8)	5.9 (4.8, 7.0)
HSCT	NE	20.2 (9.1, 31.3)

Jabbour E, et al. *Cancer*. 2019;125:4181-4192.

Memorial Sloan Kettering Cancer Center

Optimize IO With HCT

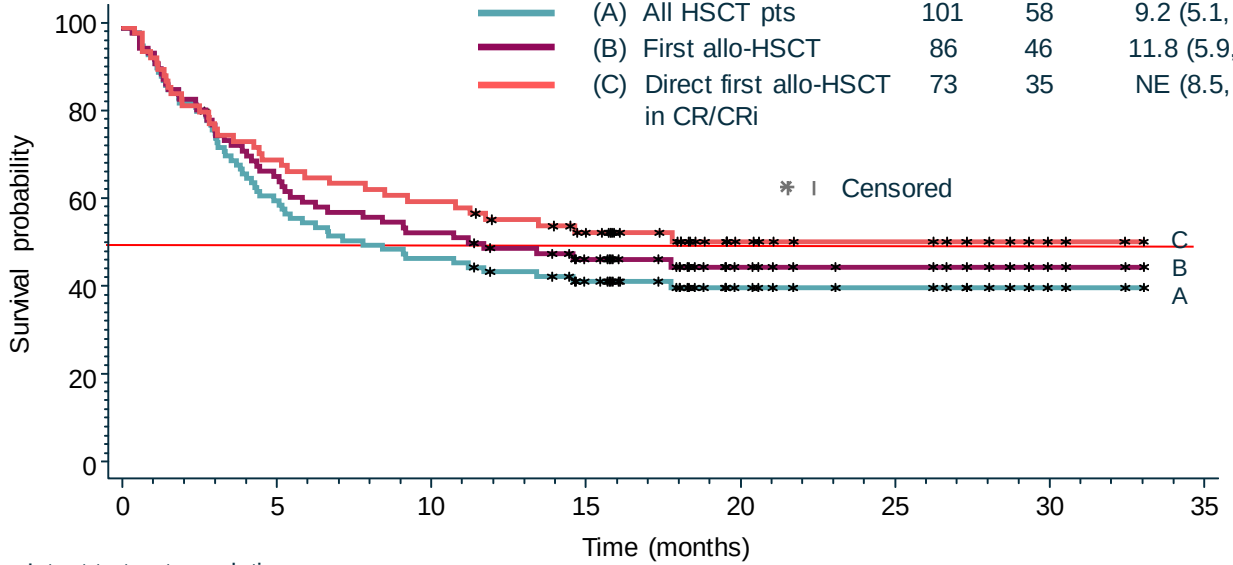
- Analyzed R/R ALL pts who were treated with IO and went to HCT as part of 2 clinical trials: NCT01363297, phase I/II trial, and NCT01564784, phase III trial
- N = 236 patients Rx on 2 studies; 101 went to HCT
- Median age 37 yr, 62% received IO as first salvage and 85% had no prior SCT
- 70% matched grafts; 60% MAC regimens
- MVA
  - Factors predicting better survival: MRD^{neg} during IO, no prior HCT associated with lower risk of mortality post-HCT
  - Factors predicting worse OS: older age, higher baseline LDH, higher bili prior to HCT, thiotepa

Marks DI, et al. *Biol Blood Marrow Transplant.* 2019;25:1720-1729.

Memorial Sloan Kettering Cancer Center

Survival for Patients Who Received IO and Proceeded to HCT

	n	No of events	Median OS, mo (95% CI)	Percentage of 24-month survival, (95% CI)
(A) All HSCT pts	101	58	9.2 (5.1, NE)	41.4 (31.5, 51.0)
(B) First allo-HSCT	86	46	11.8 (5.9, NE)	45.7 (34.7, 56.0)
(C) Direct first allo-HSCT in CR/CRi	73	35	NE (8.5, NE)	51.1 (38.9, 62.1)



Intent-to-treat population.

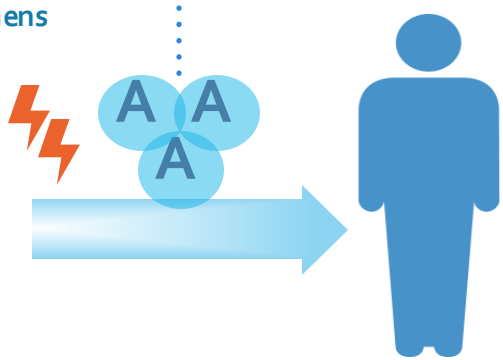
Marks DI, et al. *Biol Blood Marrow Transplant.* 2019;25:1720-1729.

Memorial Sloan Kettering Cancer Center

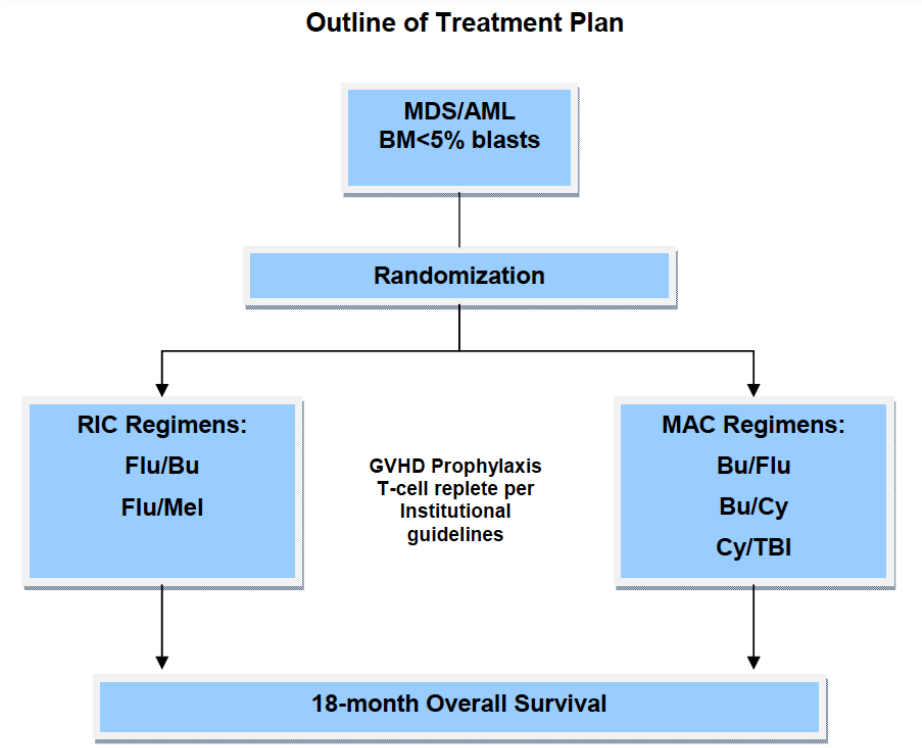
Improving HCT Outcomes

New graft sources
Cord Blood
Haplo

Precision drug dosing
Novel regimens



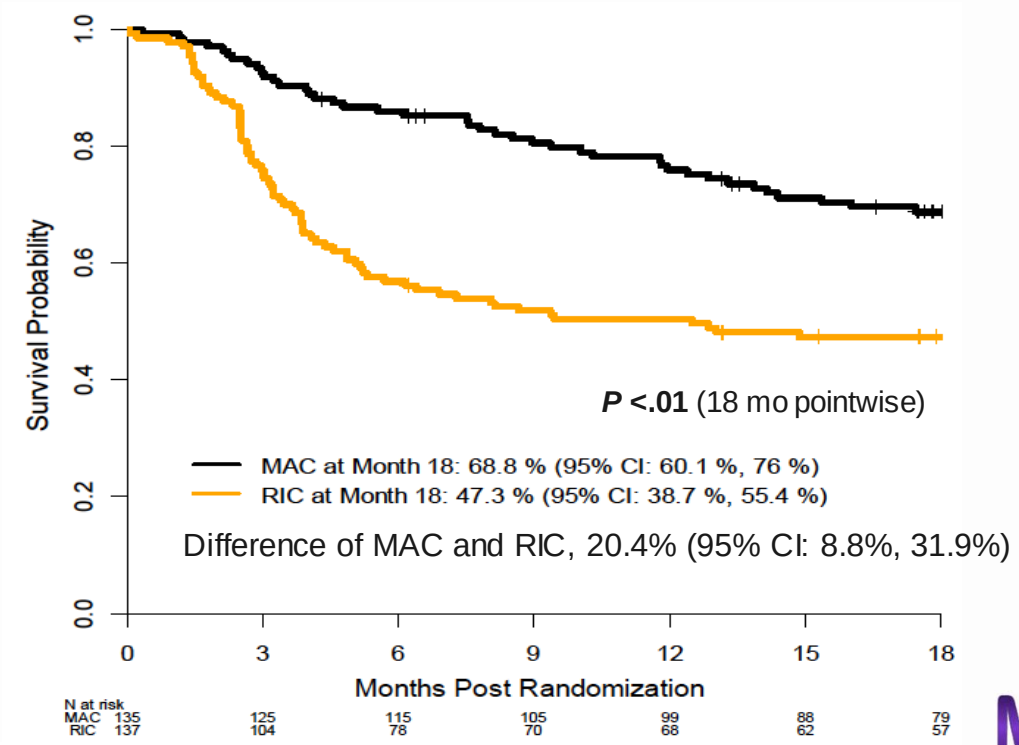
BMT CTN 0901: Randomized Phase III Design



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

MAvRIC

Relapse-Free Survival by Treatment Arm

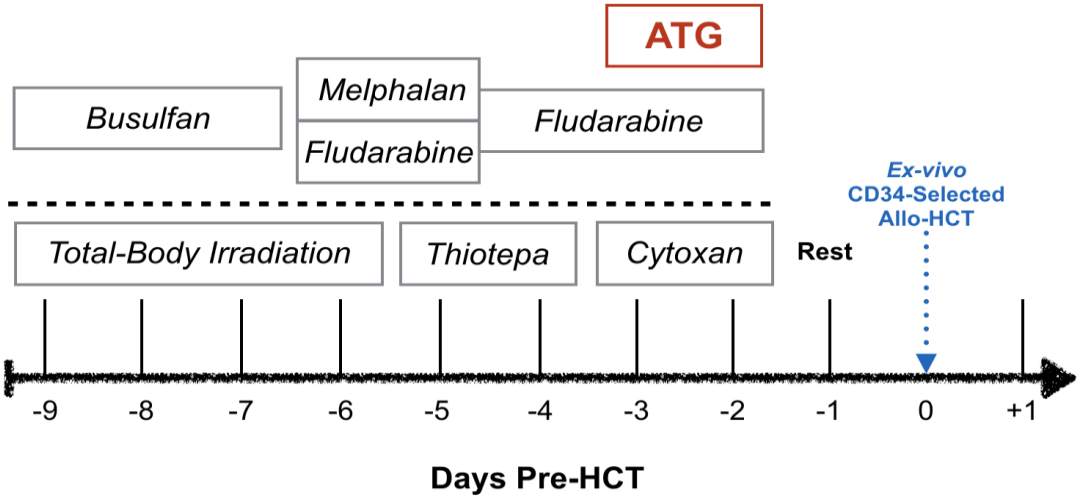


BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

MAvRIC

Memorial Sloan Kettering Cancer Center

Our Ex Vivo CD34-Selected Platform Uses Weight-Based ATG to Reduce the Risk of Graft Rejection

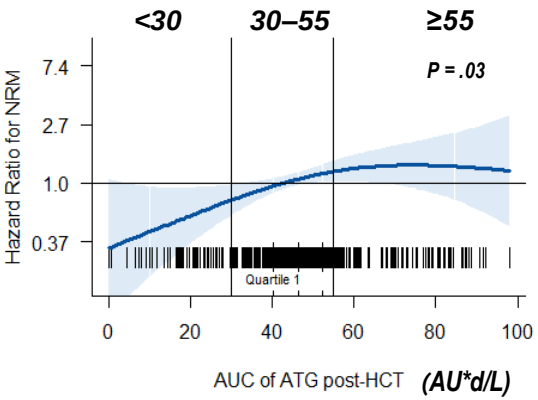


ATG [Thymoglobulin] = 2.5 mg/kg IV on days –3, –2 (–1)

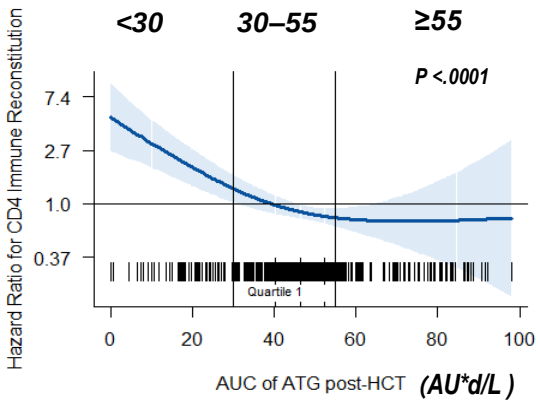
Memorial Sloan Kettering Cancer Center

Post-HCT ATG Exposure and Outcomes

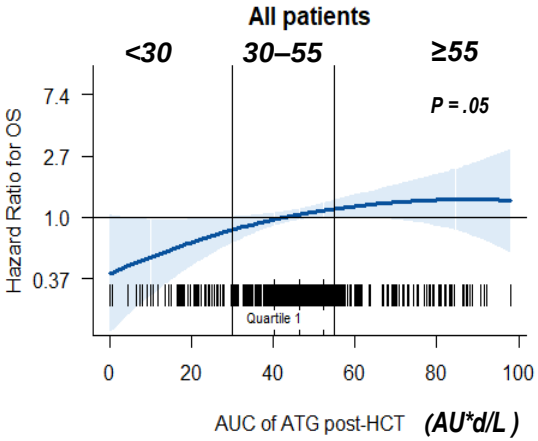
rATG exposure and NRM



rATG exposure and CD4+IR



rATG exposure and OS

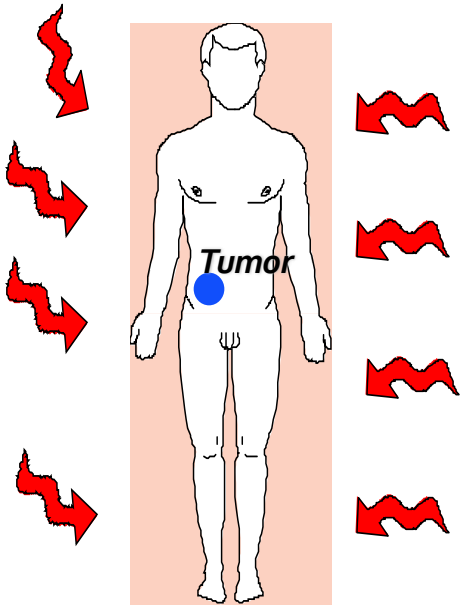


rATG, rabbit antithymocyte globulin; OS, overall survival; NRM, nonrelapse mortality; CD4+ IR, CD4+ immune reconstitution defined as CD4+ levels twice above 50/μL at 2 consecutive measures within 100 days.

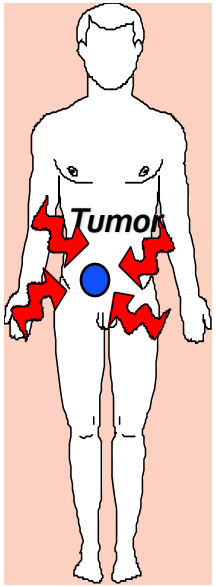
Memorial Sloan Kettering Cancer Center

Radioimmunotherapy: Delivering High Doses of Radiation Therapy Safely to the Tumor

Total body irradiation



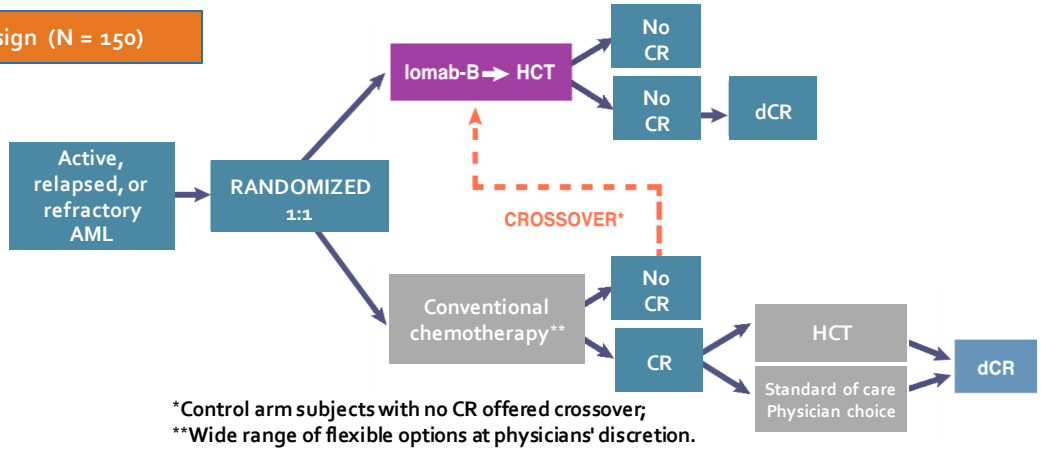
Radioimmunotherapy



Memorial Sloan Kettering Cancer Center

SIERRA Phase III Trial Design

Study Design (N = 150)



*Control arm subjects with no CR offered crossover;
**Wide range of flexible options at physicians' discretion.

Primary endpoint:	Durable complete response rate (dCR) – morphologic CR lasting ≥180 days
Secondary endpoint:	1-year overall survival

Key Eligibility Criteria

Active, relapsed, or refractory AML defined as

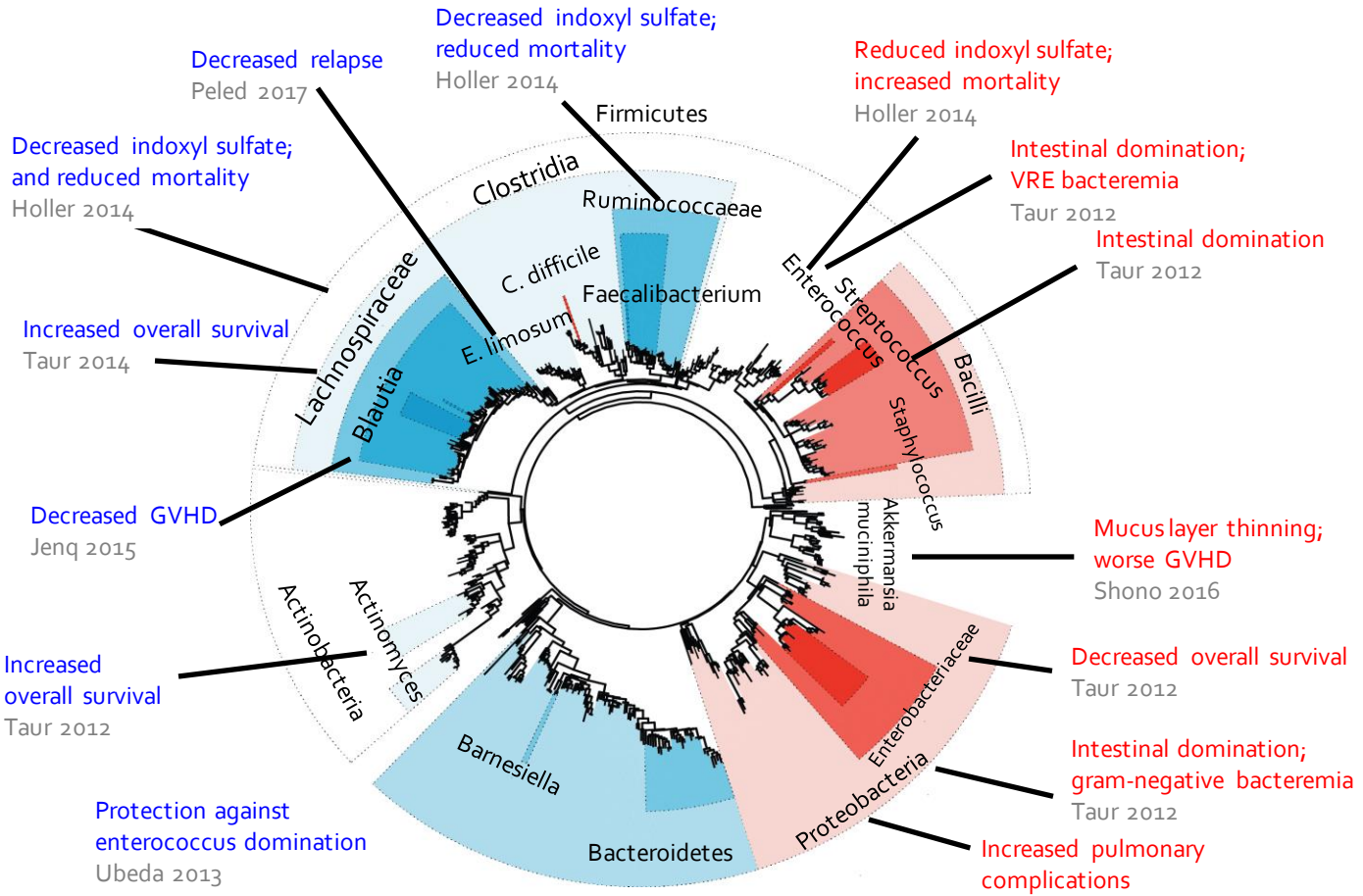
- Primary induction failure (PIF) after ≥2 cycles of chemotherapy
- First early relapse after remission <6 months
- Refractory to salvage combination chemotherapy with high-dose cytarabine
- Second or subsequent relapse

- Bone marrow blast count ≥5% or the presence of peripheral blasts
- ≥55 years of age
- Karnofsky score ≥70
- An 8/8 allele-level, related or unrelated, medically cleared HSC donor matching at HLA-A, HLA-B, HLA-C, and DRB-1

Agura E, et al. *Blood.* 2018;132: abstract 1017.

Memorial Sloan Kettering Cancer Center

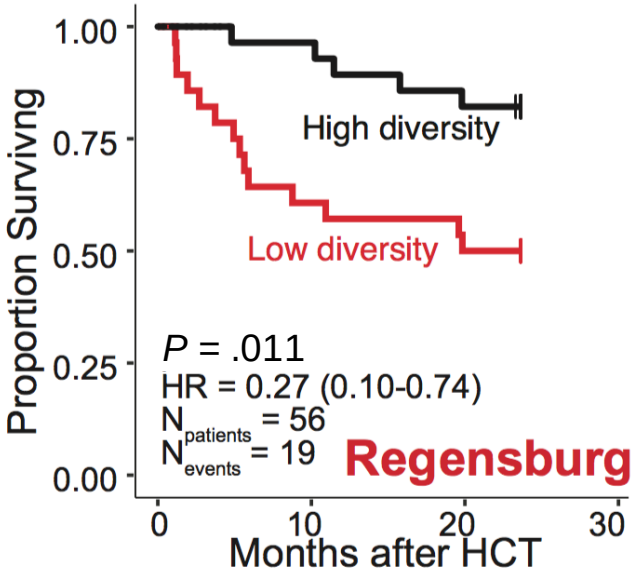
Gut Bacteria Associated With Allo-HSCT Outcomes

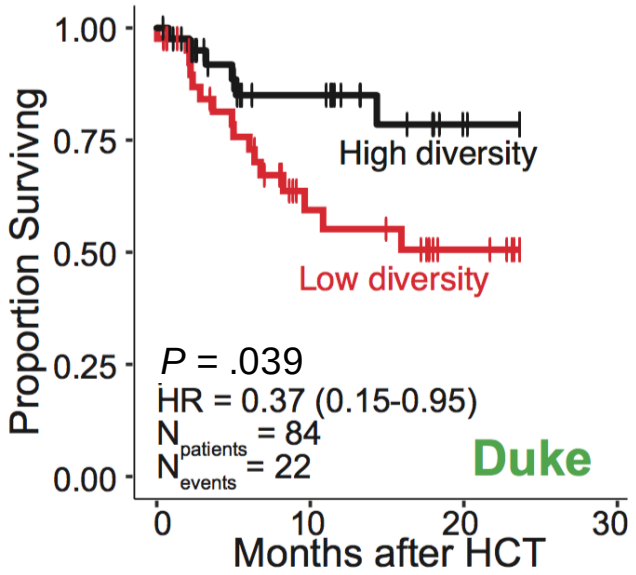


Adapted from Taur 2016.

Memorial Sloan Kettering Cancer Center

The Association of OS With Intestinal Microbial Diversity: Perineutrophil Engraftment Is Reproducible

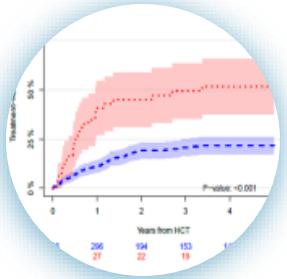


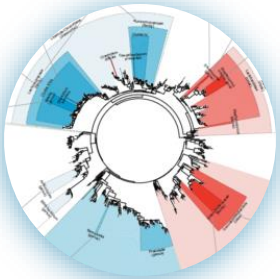


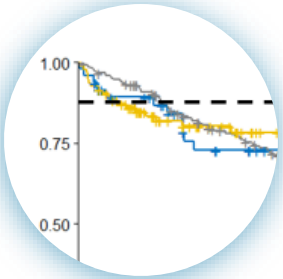
Stratified by above- and below-median Simpson reciprocal index in each cohort.
Single sample per patient, collected day 14 ± 7.
Confirms prior single-center analysis of n = 80.

Taur Y, et al. *Blood.* 2014;124(7):1174-1182.

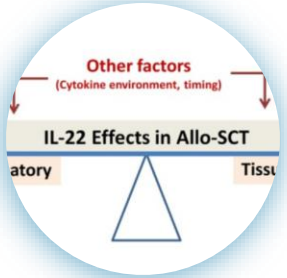
Memorial Sloan Kettering Cancer Center





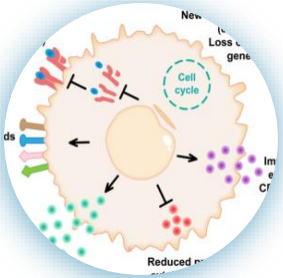


Donor selection and alternative-donor SCT



GVHD and immune-reconstitution Graft composition

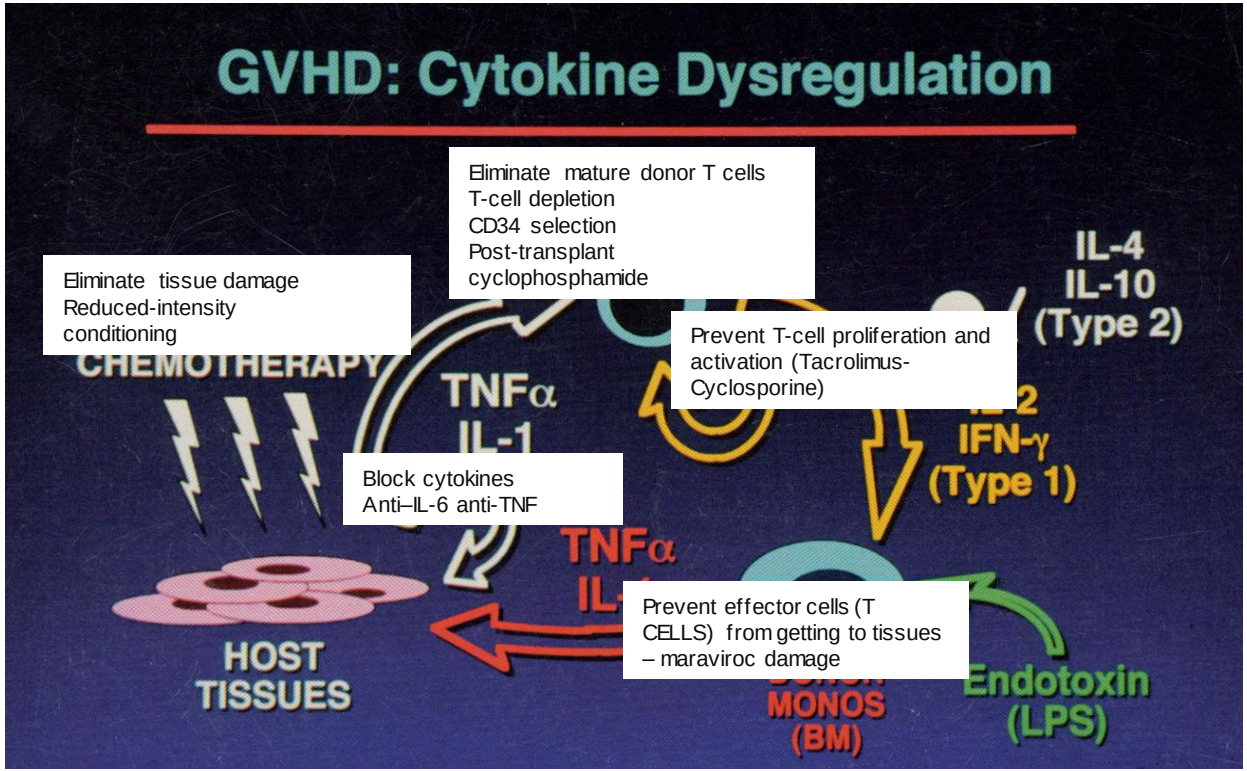
Toxicity, supportive care, and survivorship



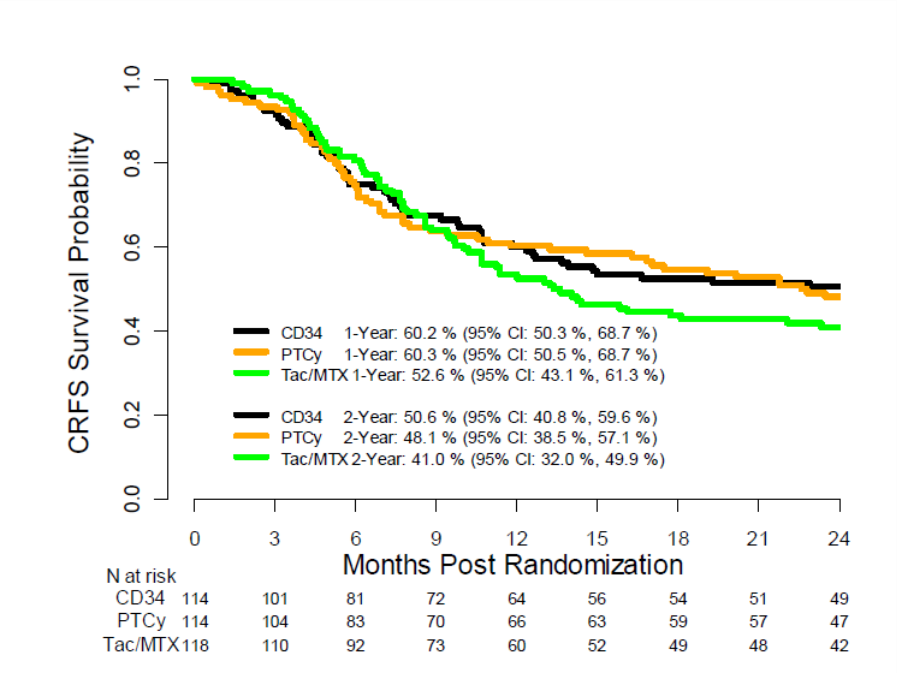
Relapse prevention Strategies cellular and non-cellular

Memorial Sloan Kettering Cancer Center

What Other Strategies to Prevent GVHD Are Being Explored?



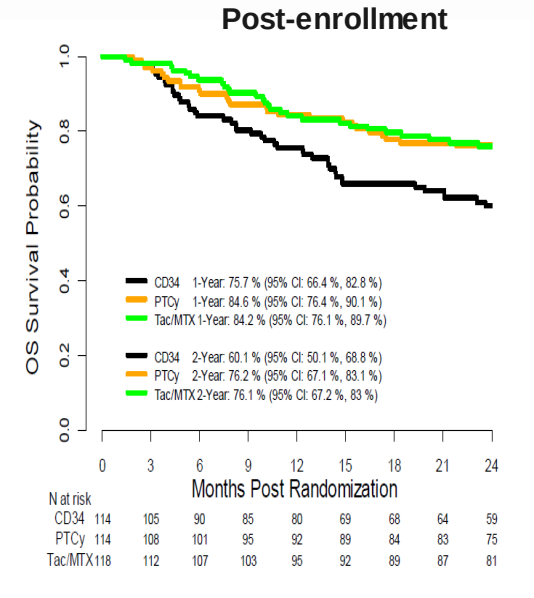
No Difference in Primary Endpoint: CRFS

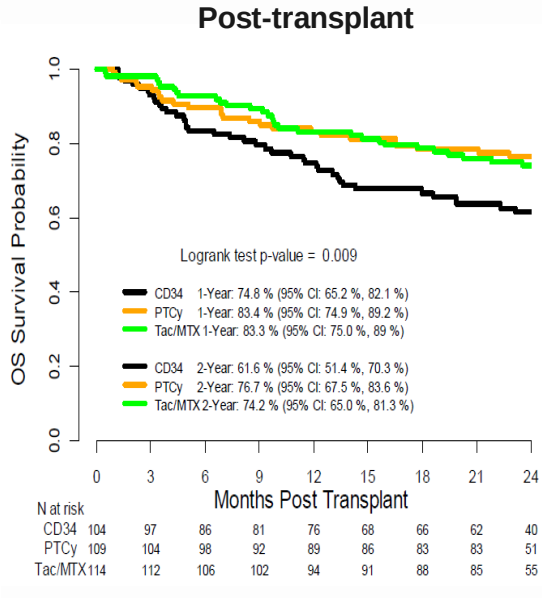


	Events for the Pair	HR	95% CI	*P* Value
CD34 Vs Tac/MTX	122 (232)	0.81	(0.56, 1.15)	.27
PTCY vs Tac/MTX	127 (232)	0.86	(0.61, 1.23)	.41
CD34 vs PTCY	111 (228)	0.93	(0.64, 1.36)	.72

*Log-rank test.

Overall Survival Decreased in CD34+



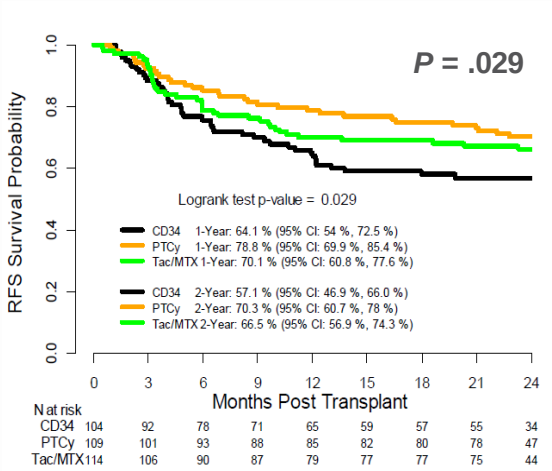


	Events for the Pair	HR	95% CI	*P* Value
CD34 Vs Tac/MTX	71 (232)	1.74	(1.09, 2.80)	.02
PTCY vs Tac/MTX	56 (232)	1.02	(0.60, 1.72)	.95
CD34 vs PTCY	69 (228)	1.78	(1.09, 2.89)	.02

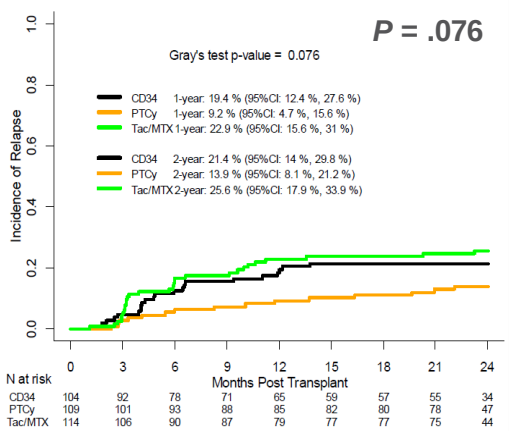
RFS and TRM, but Not Relapse, Showed Significant Differences Between the 3 Arms

Progress
Prevention and Reduction Of Gvhd and Relapse and Enhancing Survival after Stem cell transplantation

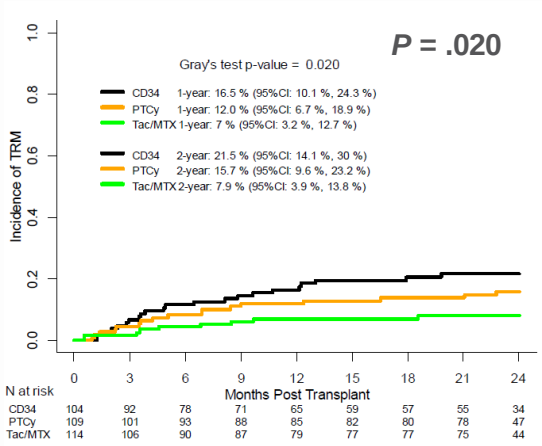
Relapse-free survival



Relapse



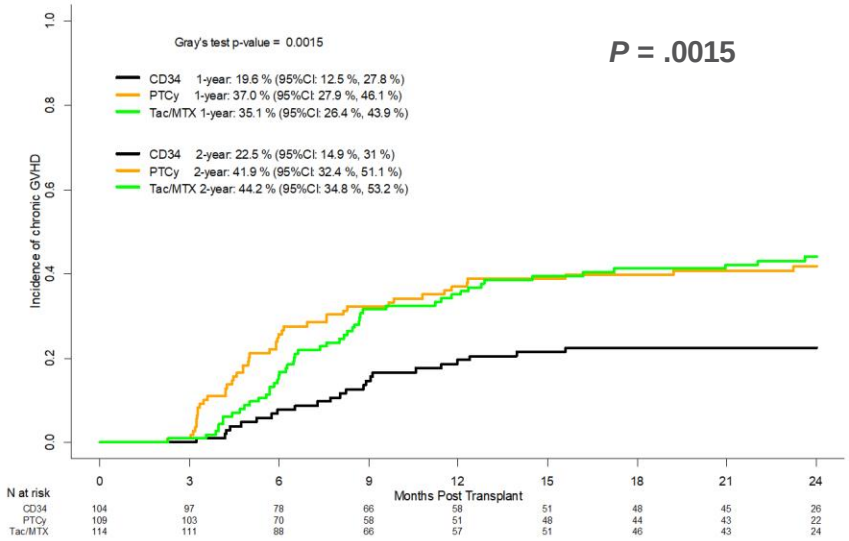
Transplant-related mortality



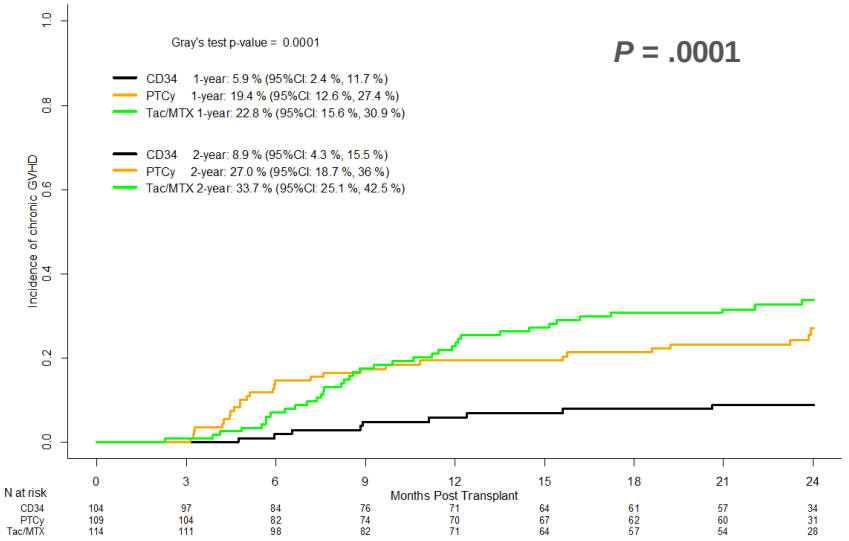
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Chronic GVHD Was Reduced in CD34+

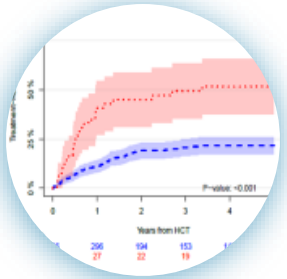
Chronic GVHD

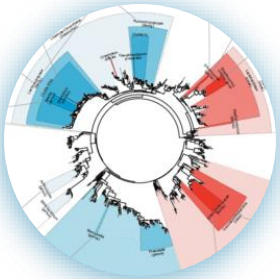


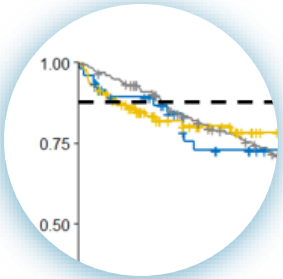
Moderate to severe chronic GVHD



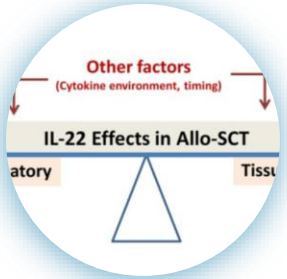
Memorial Sloan Kettering Cancer Center





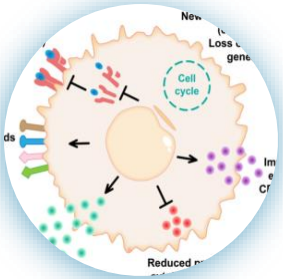


Donor selection and alternative-donor SCT



GVHD and immune-reconstitution Graft composition

Toxicity, supportive care, and survivorship



Relapse prevention Strategies cellular and non-cellular

Memorial Sloan Kettering Cancer Center

Targeted vs Non-targeted Approaches

Targeted approaches

- Exploit a specific mutation or surface antigen expression as the therapeutic target
  - *BCR/ABL*
  - *FLT3*
  - CD19, CD20, CD30, CD33, CD22
- Pros
  - Less toxicity
  - Known efficacy
  - Both drugs/cells can be used
- Cons
  - Emergence of resistance

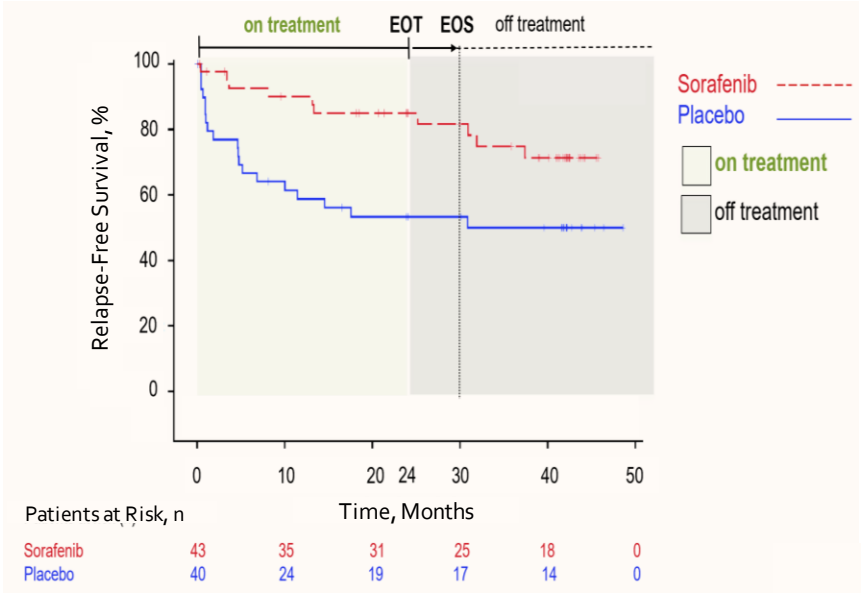
Non-targeted approaches

- Exploits the GVT effect and differential sensitivity of tumor cells over normal cells to therapeutic agents
- Immune-therapeutics
  - DLI
  - Hypomethylating agents
  - IMiDs
- Cytotoxic agents
  - Conventional chemo
- Pros
  - More broad-based
- Cons
  - Potentially more toxic
  - May trigger GVHD

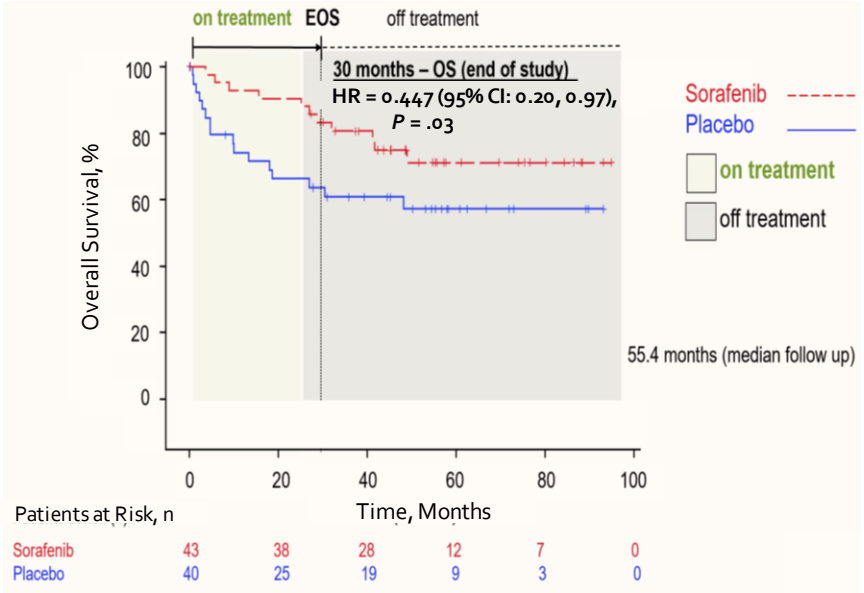
Memorial Sloan Kettering Cancer Center

SORMAIN: Results

Progression-Free Survival



Overall Survival

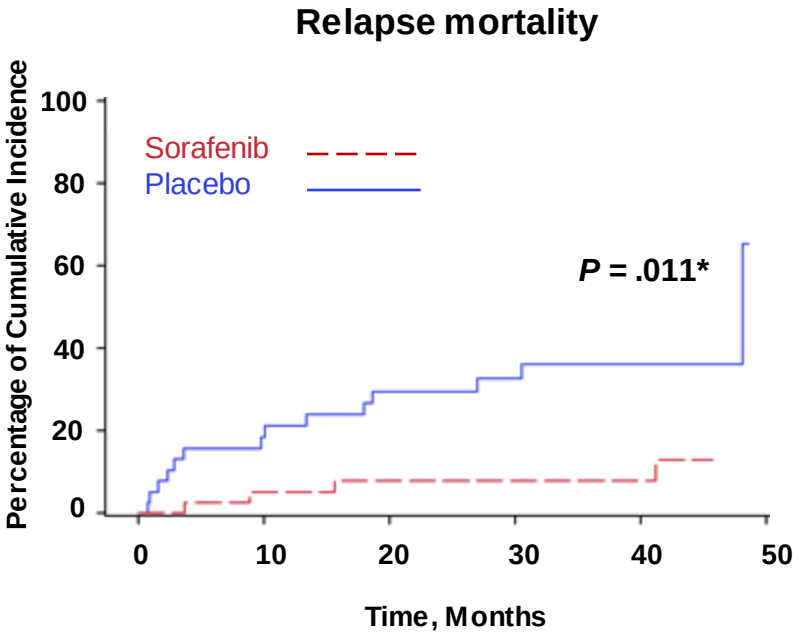


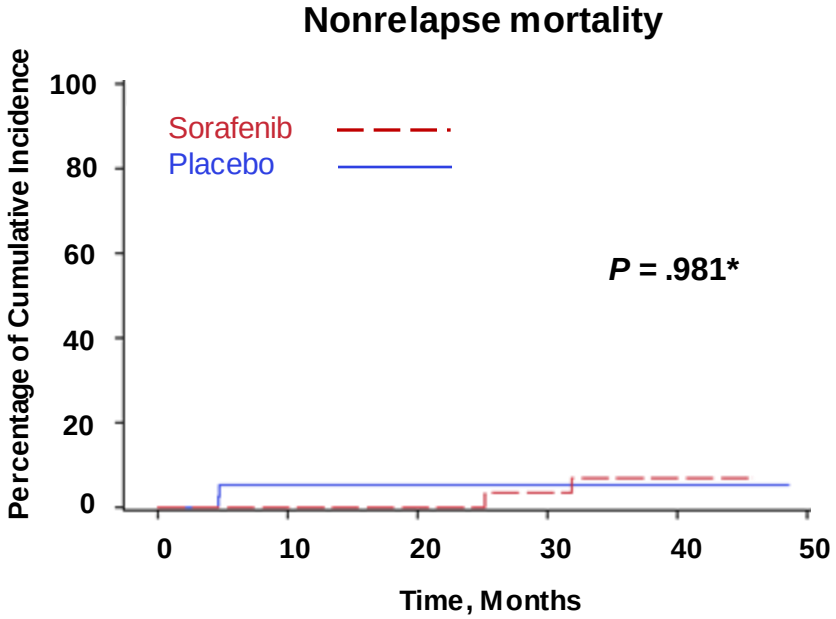
EOT, end of treatment; EOS, end of study.

Burchert A, et al. *Blood*. 2018;132: abstract 661.

Memorial Sloan Kettering Cancer Center

SORMAIN: Results – Relapse Mortality at 2 Years

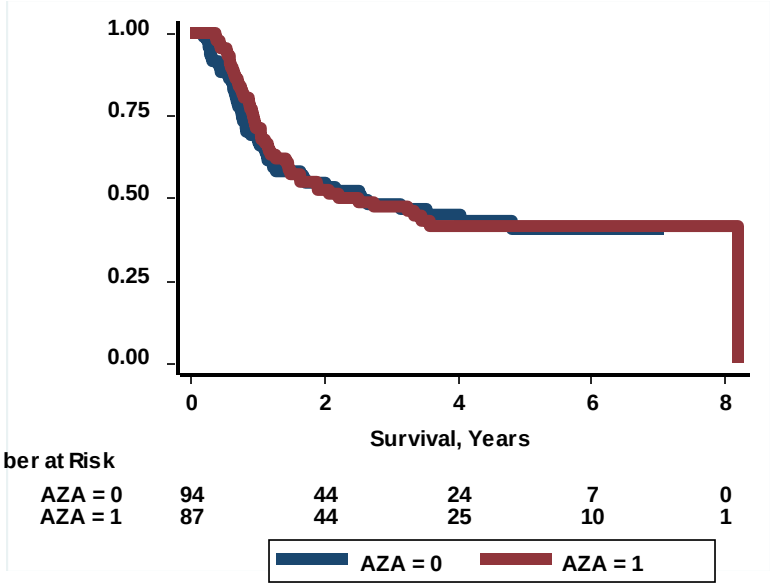




*Gray's test.

Burchert A, et al. *Blood*. 2018;132: abstract 661.

Overall Survival



Cox regression for RFS by stratification

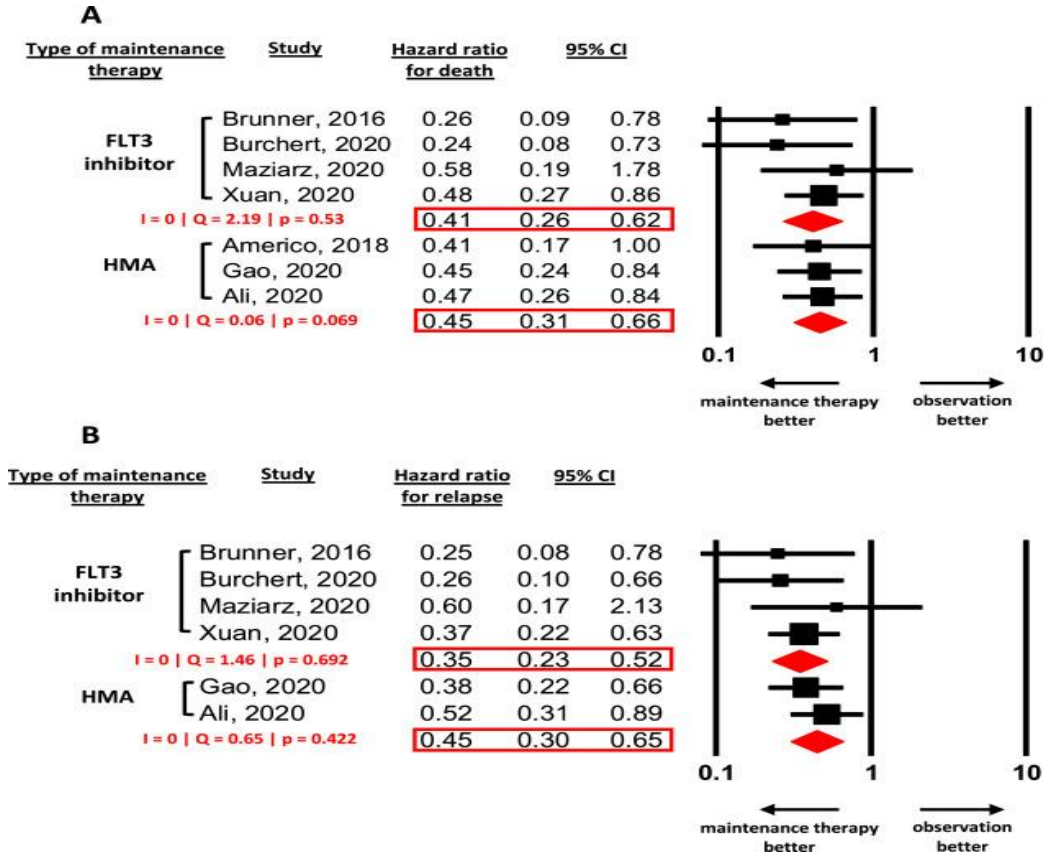
		Median, Years	*P* Value	HR* (95%CI)	*P* Value*
RFS, stratified analysis					
Group 1	Obs	1.28		Ref	
	AZA, 1–4 cycles	0.54	.04	1.5 (0.94–4.42)	.09
Group 2	Obs	3.40		Ref	
	AZA, 5–8 cycles	1.06	.21	0.81 (1.23–0.35)	.64
Group 3	Obs	NA		Ref	
	AZA, 9–12 cycles	7.64	.16	0.47 (0.19–1.17)	.11

*Adjusted for disease type, cytogenetic risk groups, disease status at HSCT, conditioning, intensity, stem cell source, donor type, HCT-CI and second SCT.

Cox regression analyses showed improvement in RFS in AZA group if they received ≥9 cycles of AZA, but the effect was not significant (*P* = .11)

Oran B, et al. *Blood.* 2018;132: abstract 971.

HMA and FLT3 Inhibitors as Maintenance

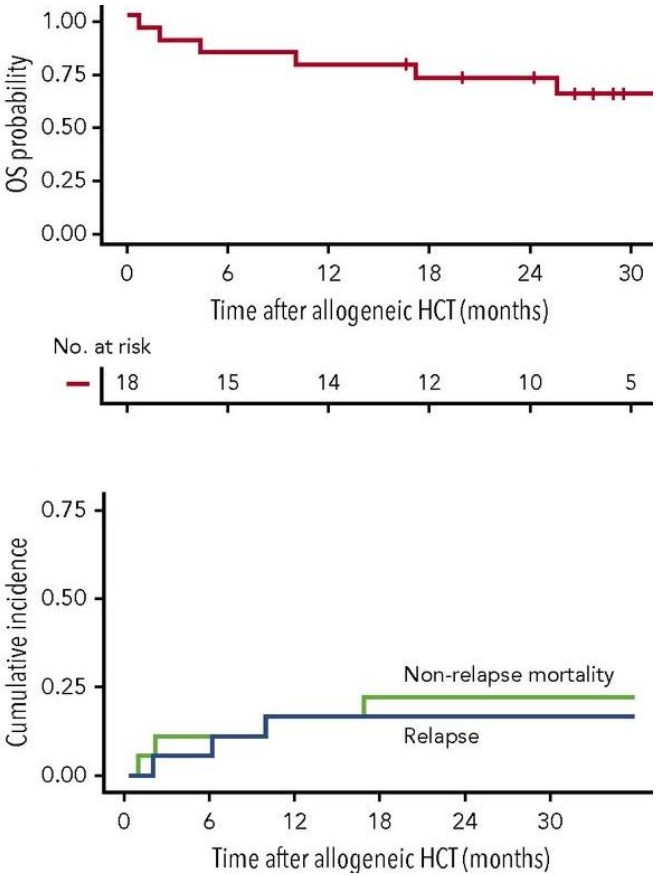


Bewersdorf, et al. *Transplant Cell Ther.* 2021;27:997.

Memorial Sloan Kettering Cancer Center

FHCRC: HCT Post-CAR Improves EFS

- 18/45 patients received HCT consolidation at median 70 days post-CAR
- Median 28 mo post-HCT, 2-yr EFS 61%, OS 72%, CIR 17% (all CD19+), NRM 23%
- 17% grade 3–4 aGVHD; 44% cGVHD
  - No correlation b/w CRS and GVHD
- HCT independent predictor of better EFS on MVA, HR 0.39, *P* = .088



Hay KA, et al. *Blood*. 2019;133:1652-1663.

Memorial Sloan Kettering Cancer Center

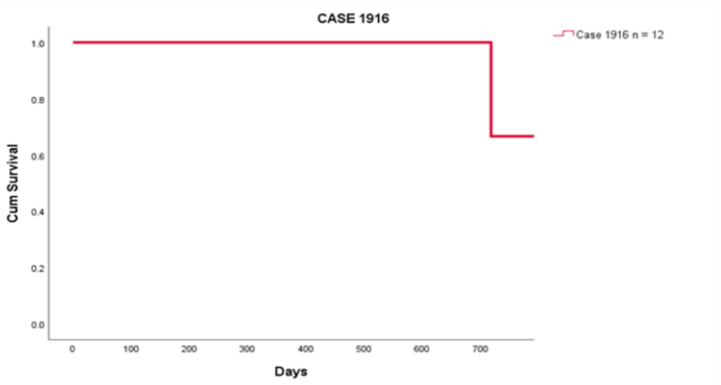
Blinatumomab Maintenance Post-HCT: Trial at MDACC

- Study group: ALL with MRD^{pos}, and/or beyond CR1
- Treatment plan: 4 cycles of blinatumomab as a 4-week continuous infusion at 28 µg/m²/24 hours at 2–3, 6, 9, and 12 months following HCT
- N = 12 patients, med age 30 years (range, 21–65); cumulative 26 cycles Blin administered
  - Toxicity: seven grade 3 or 4 AEs reported (leukopenia n = 4, transaminitis n = 2, rash n = 1). No CRS. One grade 2 neurotoxicity
  - Response, with med follow-up 8.5 months post-HCT (range 2–35): all 4 patients who were MRD+ prior to start of Blin have progressed and 2 have died. None of the 8 patients who were MRD negative post-transplant have relapsed

Memorial Sloan Kettering Cancer Center

Low-Dose Inotuzumab Maintenance Post-HCT: Trial at UH

- Study group: ALL with MRD^{pos}, and/or beyond CR1, recipients of RIC
- Treatment plan: 4 cycles of inotuzumab, single-dose monthly, starting at 40–100 days post-transplant
- N = 12 patients, med age 48 years (range, 17–67); cumulative 34 cycles ino administered (0.3, 0.4, 0.5, 0.6 mg/m^2)
  - Toxicity: mostly thrombocytopenia; no VOD
  - Day 100 and 1-year non-relapse mortality is zero
  - Median follow-up of 16 months post-HCT (range 3–40): 11/12 patients are alive
  - One patient relapsed during first year and 1 patient relapsed 2 yr after HCT
  - One-year PFS is 91%



Memorial Sloan Kettering Cancer Center

Summary

- Allo-HCT remains the most effective therapy for patients with RELAPSED AML or ALL and all efforts should be taken to get these patients to allo-HCT
- For patients in CR1, risk-stratification is essential to guide the decision of proceeding to allo-HCT or not
- Early referral is essential to optimize transplantation rates
- In 2022, everybody has a donor and donor selection may be a strategy to improve outcomes. However, we are uncertain if a younger unrelated donor is superior to an older related donor
- Improvements in supportive care have reduced NRM and allowed us to transplant older patients
- Relapse remains the most important cause of treatment failure, and prospective trials of maintenance therapies are currently ongoing

Memorial Sloan Kettering Cancer Center

ACKNOWLEDGMENTS

Adult BMT Service
Juliet Barker, MBBS
Hugo Castro-Malaspina, MD
Christina Cho, MD
David Chung, MD
Parastoo Dahi, MD
Sergio Giralt, MD
Jenna D. Goldberg, MD
Boglarka Gyurkocza, MD
Katharine Hsu, MD, PhD
Ann A. Jakubowski, MD, PhD
Robert J. Jenq, MD
Guenther Koehne, MD
Molly Maloy
Jimmy Nieves, RN
Esperanza Papadopoulos, MD
Tsoni Peled, MD
Brian Shaffer, MD
Gunjan Shah, MD
Roni Tamari, MD
Marcel van den Brink, MD, PhD
James W. Young, MD

Pediatric BMT Service
Farid Boulad, MD
Nancy A Kernan, MD
Richard J. O'Reilly, MD
Susan Prockop, MD
Trudy N. Small, MD

Biostatistics
Junting Zheng, PhD
Glenn Heller, PhD
Sean Devlin, PhD

Marcel van den Brink, MD, PhD
Onder Alpdogan, MD
Arnab Ghosh, MD, PhD
Lauren Young
Johannes Zakrzewski, MD

Eric Pamer, MD
Jeroen Van Heijst, PhD
Ying Taur, MD

Immune Monitoring
Jianda Yuan, MD
Jedd D. Wolchok, MD, PhD
Hulimidad Gallardo
Ryan Kendle
Cailian Liu, MD
Theresa Rasalan
Yingyan Xu
Bushra Zaid

Cytheris
Therese Croughs, MD
Michel Morre, MD

Support
Cytheris, Inc
NIH, NY Community Trust, Experimental Therapeutics Center (MSKCC), Cycle for Survival (MSKCC), Translational and Integrative Medicine Research Fund (MSKCC)

Memorial Sloan Kettering Cancer Center

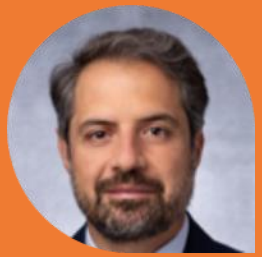
Questions?

giralts@mskcc.org

Global Leukemia Academy

Leukemia Board Discussion

Elias Jabbour



APTITUDE HEALTH

Global Leukemia Academy

Leukemia Board Discussion: Case 1 – AYA ALL

Erica Almeida Viana

APTITUDE HEALTH

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

Latin America and Canada

IKZF1 Deletion in ALL: What Is the Best Strategy?

Clinical Case

Speaker Brief:
Érica Almeida Viana
Fellow GRAACC, Sao Paulo, Brazil

Medical History

male, 16 years old

No prior comorbidities

Abdominal pain, weakness/asthenia, sore throat, and sweating

Adenomegaly, gingival bleeding, petechiae, and fever

Medical History

Bone Marrow Aspirate: 96% blasts

Flow cytometry → pre-B acute lymphoblastic leukemia

- Karyotype: 46,XY [20]
- Molecular Biology (PCR)
  - Negative for t(1:19)(q23;p13.3) E2A/PBX1
  - Negative for t(4;11)(q21;q23) AF4/MLL
  - Negative for t(9;22)(q34;q11.2) BCR/ABL1
  - Negative for t(12;21)(q12;22) ETV6-TEL/RUNX-AML1
  - **Positive for *IKZF1* deletion (7p12.2)**
- CNS 1

ALL With *IKZF1* Deletion

- Frequency of ~15% in pediatric and 40% in adult ALL cases
- Older pediatric age at diagnosis
- Higher white blood cell count
- Higher MRD after induction and consolidation
- HR Treatment Protocols (BFM: *IKZF1*plus)
  - 2/3 of pediatric ALL with *IKZF1* deletion also have *BCR-ABL1* mutations

IKZF1 deletions in pediatric acute lymphoblastic leukemia: still a poor prognostic marker? Stanulla M, et al. *Blood.* 2020;135(4):252-260.

Therapies for Del *IKZF1* ALL

1. BFM 2009 Protocol
2. GRALL
3. COG AALL
4. CALGB
5. HyperCVAD
6. ESPHALL

Therapy

RELLA Brazilian HR Protocol

Alto Risco (duração 120 semanas)

Indução	Consolidação	Manut Primária	Reindução I	Manut A	Reindução II
PVDA Ciclo+ AraC+MP +Asparaginase 7 Semanas 1 - 7	HDMTX MP 8 Semanas 8 - 16	MP+MTX DEXA+VCR 6 semanas 1 - 6	Linhagem B DVA+Dauno MP+HDMTX 6 semanas 7 - 12	MP+MTX DVA 12 semanas 13 - 24	DVA+MP HDMTX 4 semanas 25 - 28

Manut A	Manut B
MP+MTX Dexa+VCR 24 semanas 29 - 52	MP+MTX DEXA+VCR (55-100) 52 semanas 53-104

PVDA=prednisona, vincristina, daunoblastina e asparaginase
DVA=dexametasona, vincristina e asparaginase
HDMTX=Alta dose de metrotrexate

Grupo	Indução	Intensif.	Consolidação MTX (2.5 G)	Consolid MTX (5 G)	Re-Ind I	Re-Ind II	Manutenção A e B
Baixo	28 dias	não	Sim	Não	Sim	Não	Sim
Intermediário	20 dias	29 dias	Sim	Não	Sim	Não	Sim
Alto	20 dias	29 dias	Não	Sim	Sim	Sim	Sim

Therapy

RELLA Brazilian HR Protocol

- D19: hypocellular bone marrow aspirate
  - MRD 8.6% blasts
- D49: MRD 4.3% blasts
- Consolidation MRD: 0.9% blasts

 # Discussion with St Jude Team and initiated imatinib due to the *IKZF1* deletion

- Week 17 Maint A – MRD: 0.08%
- Week 30 Maint A – MRD: negative

Do I Need a Bridge to Transplant?

1. Blinatumomab
2. Dasatinib
3. TACL-Bortezomib
4. REZ BFM
5. R17

Therapies

Blinatumomab

- First cycle: MRD negative
- Second cycle: MRD negative

Haplo SCT

- Fludarabine 90 mg/m^2 + TBI 1200cGy
- Pt-Cy 50 mg/kg (D +3 to +4)
- Mycophenolate 45 mg/kg/d + tacrolimus 0,05 mg/kg/d
- Father, minor ABO mismatch
- Engraftment: D +14
- D +60: Imatinib 100 mg/d progressively increased to 400 mg/d

Actual Status

Bone Marrow Evaluation

- D +30: negative MRD/full donor chimerism
- D +75: negative MRD/full donor chimerism
- D +100: negative MRD/full donor chimerism
- 4 mo: negative MRD/full donor chimerism
- 5 mo: full donor chimerism
- 7 mo: full donor chimerism
- 10 mo: full donor chimerism
- 12 mo: full donor chimerism

Actual Status

- Is imatinib really needed in this case?
- For how long should imatinib be continued in post-SCT for ALL with del *IKZF1*?

For how long should the imatinib prophylaxis continuate post-SCT?

1. 6 months
2. 12 months
3. 24 months
4. 36 months

Actual Status

1 yr, 5 mo post-SCT

- Imatinib discontinued on D +120
- Tacrolimus discontinued on D +126
- No GVHD


O tratamento contra o **câncer**
não pode esperar a
pandemia passar
GRAACC

Thank you!

Global Leukemia Academy

Leukemia Board Discussion: Case 2 – AML

Paola Omaña

APTITUDE HEALTH

Clinical case: Acute myeloid leukemia

Olga Paola Omaña Orduz

March 2022

General data

- Female
- 62 years old

- MC: Abnormalities in laboratories

- AI: Sent by another hematologist before abnormalities were found in her hemogram. She doesn´t have symptoms

Clinical history

- Time of diagnosis: 07/29/2021

- Bone marrow studies
  - Morphology: Diluted sample without spicule that gives off good cellularity. Sample infiltrated by 47% intermediate to large sized blasts, loose chromatin, very evident nucleolus, some granular. Acute myeloid leukemia M2 vs M5 a
  - Flow cytometry: myeloblast CD34+, CD117+, HLADR+, CD45+, CD56–, CD64±, CD38+, CD13+, MPO± (30%), CD19–

Clinical history

Clínica del Country

Bone marrow studies

- Biopsy: Adequate cylinder with 10 intertrabecular spaces for evaluation. Bone marrow with an average cellularity of 80% is observed, diffusely infiltrated by a monotonous population of medium-sized cells with loose chromatin and evident nucleoli, some molded with clefts; the residual population is minimal, represented by few megakaryocytes, lymphocytes, and erythroids in small groups. Histochemistry for reticulum shows a diffuse increase in the MF(1 and 2/3) plot. PATHOLOGICAL DIAGNOSIS BONE MARROW BIOPSY: INFILTRATED BY A HEMATOPOIETIC NEOPLASM, MORPHOLOGICALLY CONSISTENT WITH AML

Clinical history

- Molecular studies

04/08/2021

  - NPM1 negative
  - FLT3 negative
  - CEBPA negative
  - t(8:21) negative
  - inv16 negative

Induction

Clínica del Country

Protocol: 7+3

- 07/30/2021
- Complications
  - Febrile neutropenia MASCC 23 points – low risk
    - First episode: No clinic focus. Received Pip Taz
  - Febrile neutropenia
    - Second episode: *E. cloacae* bacteremia

- Reevaluation day 15: Bone marrow with 9% promonocytes al 10% blast

Question 1

With the 15th day bone marrow result, what do you think will be your next step?

1. Reinduction with protocol of your choice
2. Continue with consolidations with high-dose AraC
3. Move to best supportive care
4. Rescue with FLAG IDA

Re-induction

Clínica del Country

GOELAMS

- 09/02/2021
- Complications
  - Febrile neutropenia MASCC 21 pts – low risk
- Response: Morphologic response with EMR(–) status

Consolidation

Clínica del Country

High-dose cytarabine

- Cycle 1: 10/02/2021
  - Complications: Febrile neutropenia – low risk
  - Response: Complete remission with EMR(–)
- Cycle 2: 11/03/2021
  - Complications: *E. coli* bacteremia – cefepime 14 days
- Cycle 3: 11/30/2021
  - Complications: Febrile neutropenia
  - Response
    - FC: Promonocytes 9.8% with abnormal expression of CD56 myeloblasts 0.26%
    - Myelogram: 6.3% promonocytes and 14% monocytes

Question 2

If this was your patient, what would have been your next step?

1. Reinduction with another 7+3
2. Rescue with FLAG IDA
3. Best supportive care

Consolidation

Clínica del Country

FLAG IDA

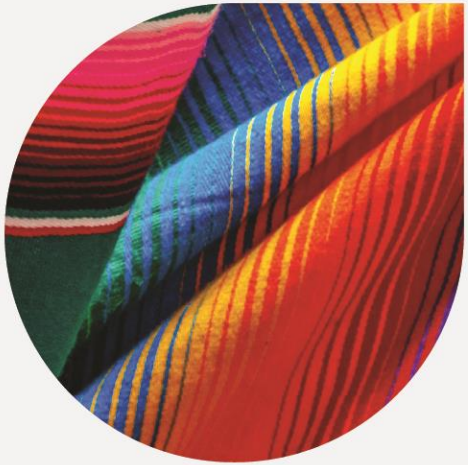
- Date: 12/24/2021
- Complications at day +10
  - Febrile neutropenia
  - KPC *K. pneumoniae* bacteremia
- Needs monitoring in intensive care unit
- Multiorgan failure
- Death

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

Optimal management and treatment coordination of long-term toxicities in pediatric leukemias

Stephanie Dixon

APTITUDE HEALTH

Optimal Management and Treatment Coordination of Long-Term Toxicities in Pediatric Leukemia

Stephanie Dixon, MD, MPH
Cancer Survivorship Division, St. Jude Children's Research Hospital

St. Jude Children's Research Hospital

Objectives

- Describe prevalent late health outcomes among survivors of childhood leukemia
- Identify resources to help guide survivorship care
- Introduce survivorship care plans and models of survivorship care

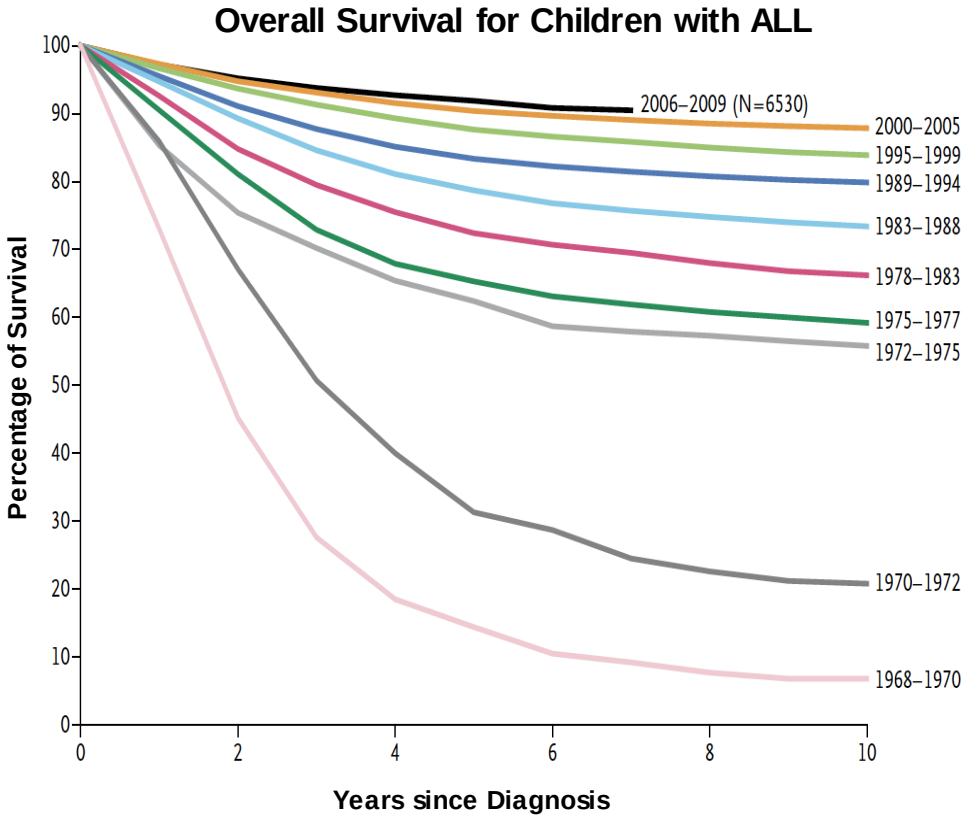
Q1: Which of the Following Groups of Survivors Have the Highest Risk for Cardiomyopathy?

1. Survivors of ALL treated with conventional chemotherapy including moderate-doses of anthracyclines
2. Survivors of ALL requiring hematopoietic cell transplant
3. Survivors of AML treated with conventional chemotherapy including high doses of anthracyclines (>250 mg/m^2)
4. Survivors of AML treated with hematopoietic cell transplant

Q2: Which of the Following Statements Is False?

1. Survivorship care plans can be useful tools to summarize treatment and follow-up recommendations
2. The risk-stratified care model is optimal for survivorship care
3. Many barriers to optimal survivorship care exist and may be unique to specific regions or healthcare systems
4. Survivorship care includes transition planning for return to community practice and/or adult providers

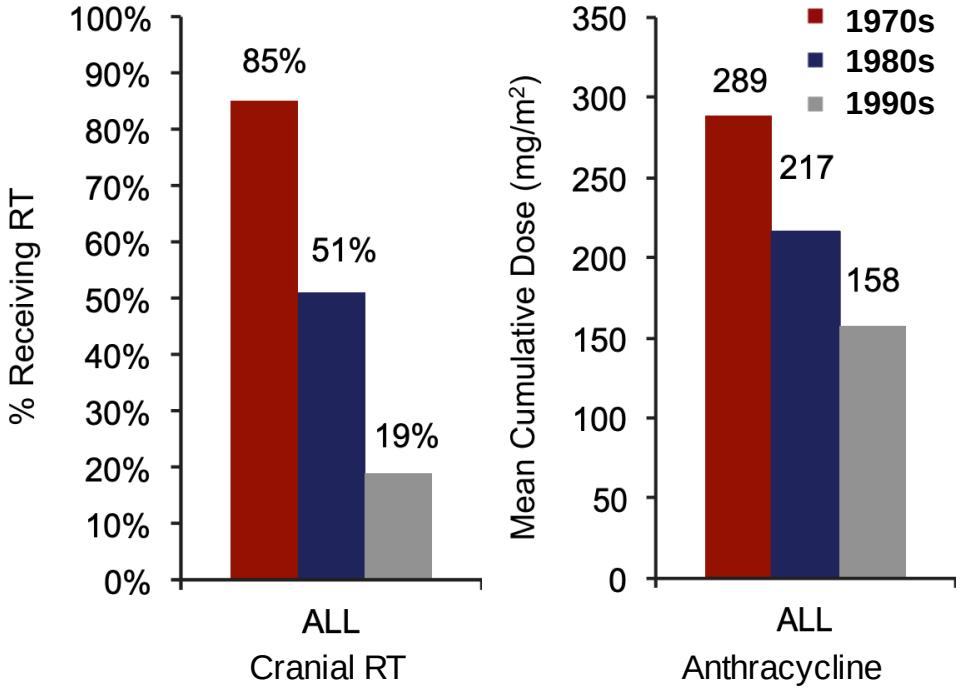
Improved Overall Survival for Childhood ALL



- ALL cure rates have dramatically improved since the 1970s
- 5-year survival now exceeds 90%
- Risk-stratification to adjust treatment intensity to clinical and biologic risk factors is continually improving

Hunger and Mullighan. *N Engl J Med.* 2015.

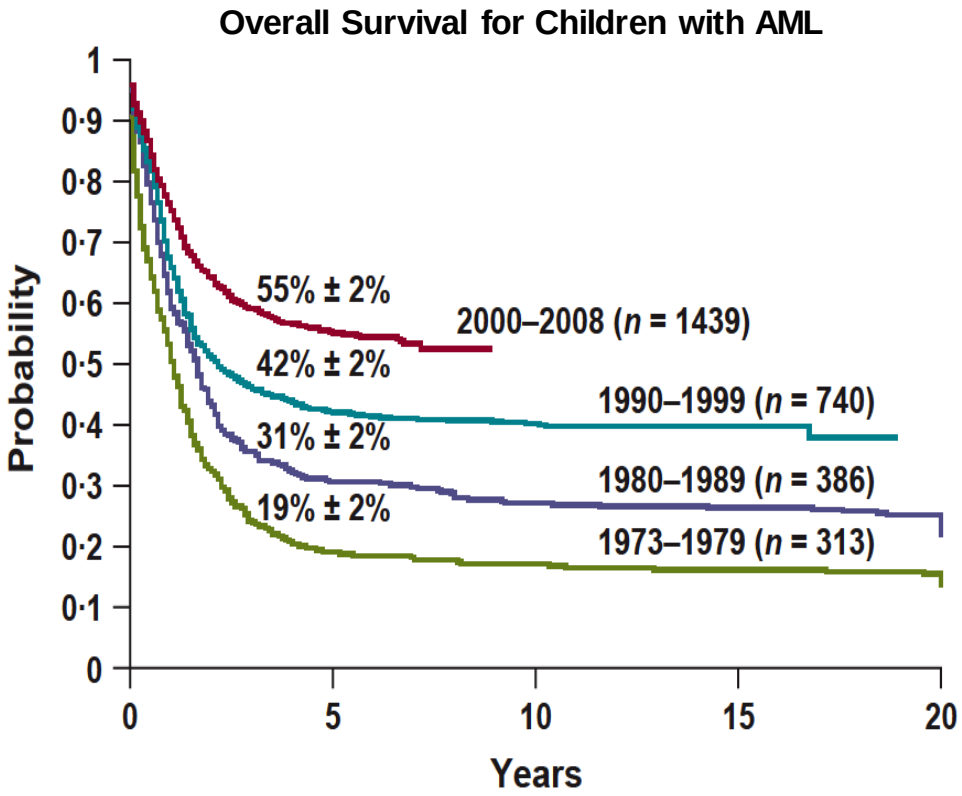
Therapy Exposures Among ALL Survivors by Era



- Reduction in use and dose of prophylactic cranial radiation
- Reduction in cumulative dose of anthracycline chemotherapy
- Concurrent increase in use of asparaginase, dexamethasone, and high-dose methotrexate

Armstrong et al. *N Engl J Med.* 2016.

Improved Overall Survival for Childhood AML

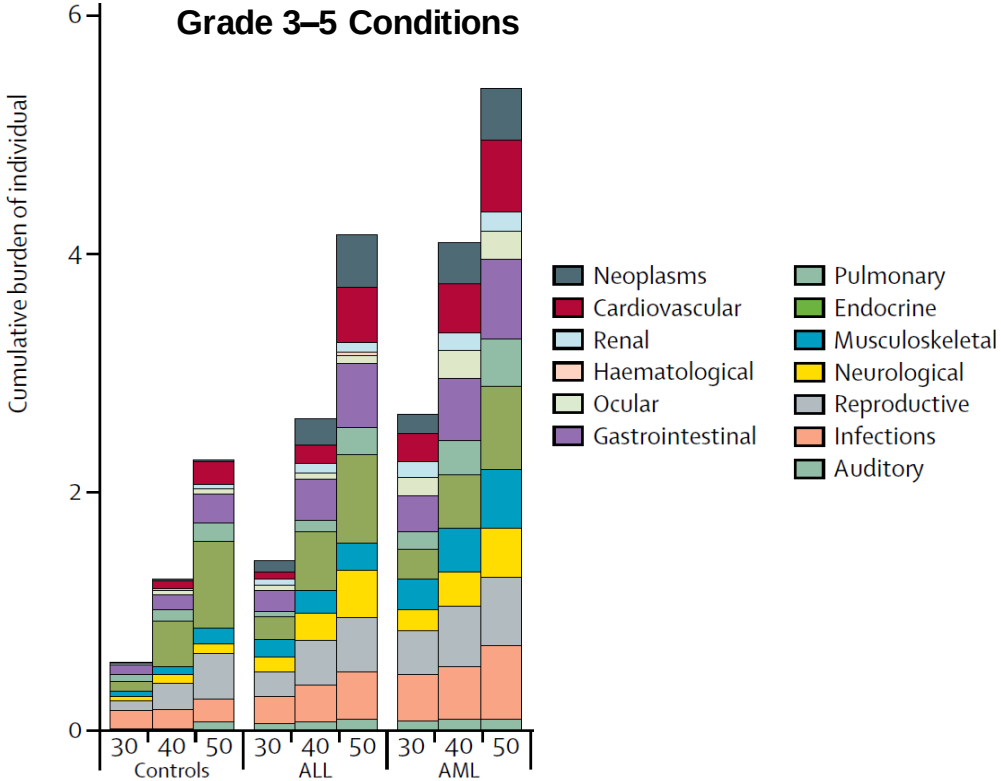


- AML cure rates have dramatically improved since the 1970s
- Overall outcomes remain suboptimal
- Effective regimens have been largely dependent upon higher doses of anthracyclines

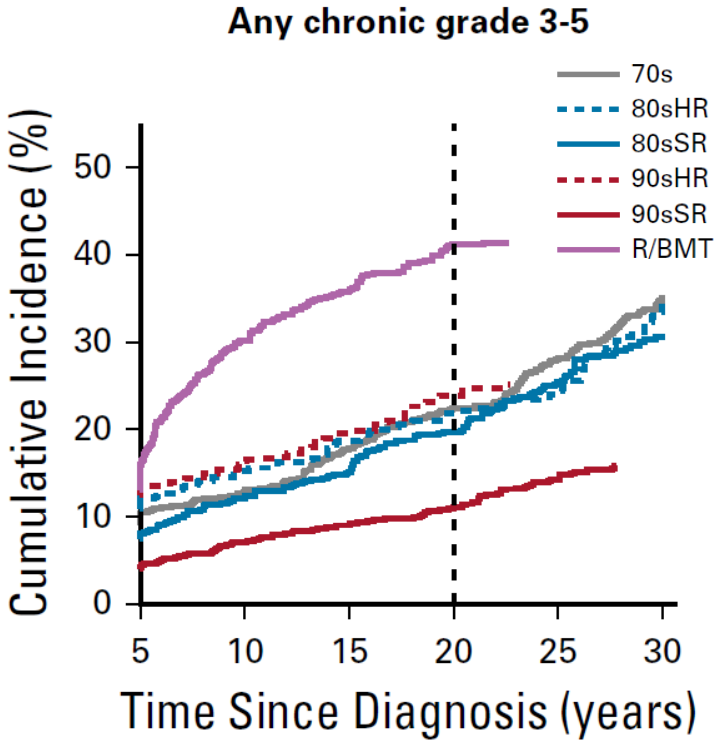
Rubnitz and Inaba. *Brit J Haematol*. 2012.

High Burden of Health Conditions in Leukemia Survivors

- Most leukemia survivors develop chronic health conditions related to treatment
- At least 20% self-report a severe condition by 20 years from diagnosis



Outcomes by Risk-Stratified Groups in ALL



20-year cumulative incidence

70s: 22.5%

80sHR: 22.2%

80sSR: 19.8%

90sHR: 23.9%

90sSR: 11.0%

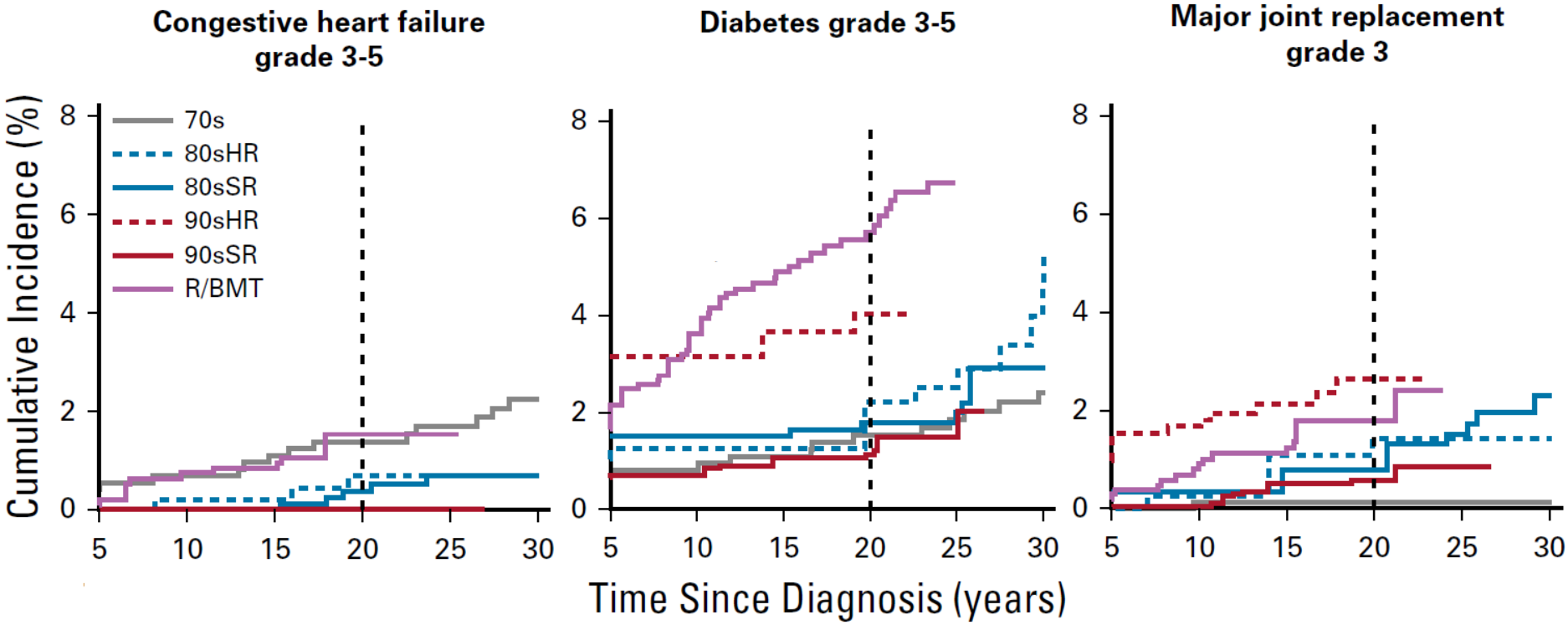
R/BMT: 41.2%

No CRT

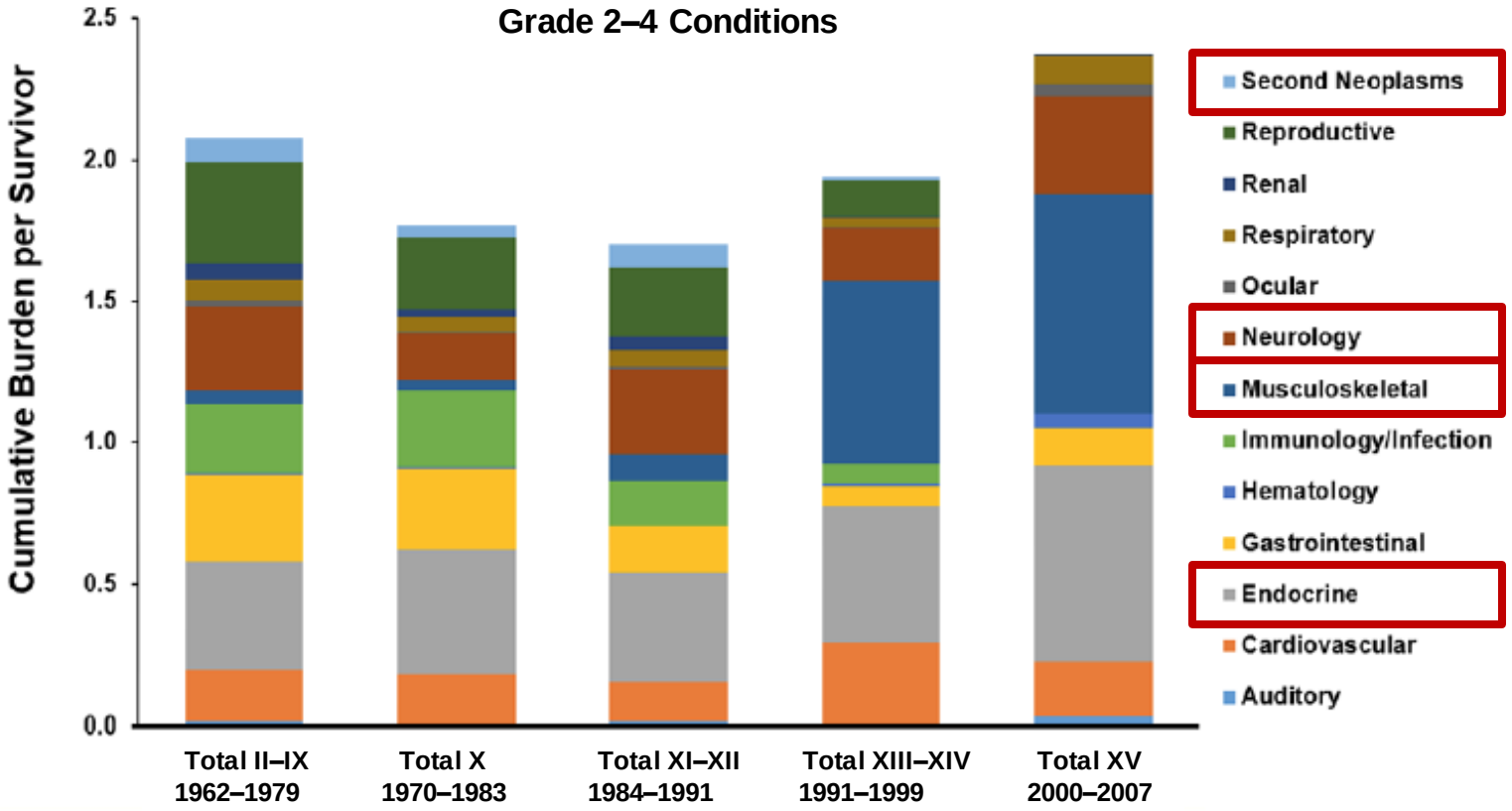
<120 mg/m^2 anthracycline

<1000 mg/m^2 cyclophosphamide

Outcomes by Risk-Stratified Groups in ALL



Cumulative Burden of Conditions in ALL by Era



Chronic Conditions in Survivors of AML

Survivors of AML treated with transplant have a higher burden of complications

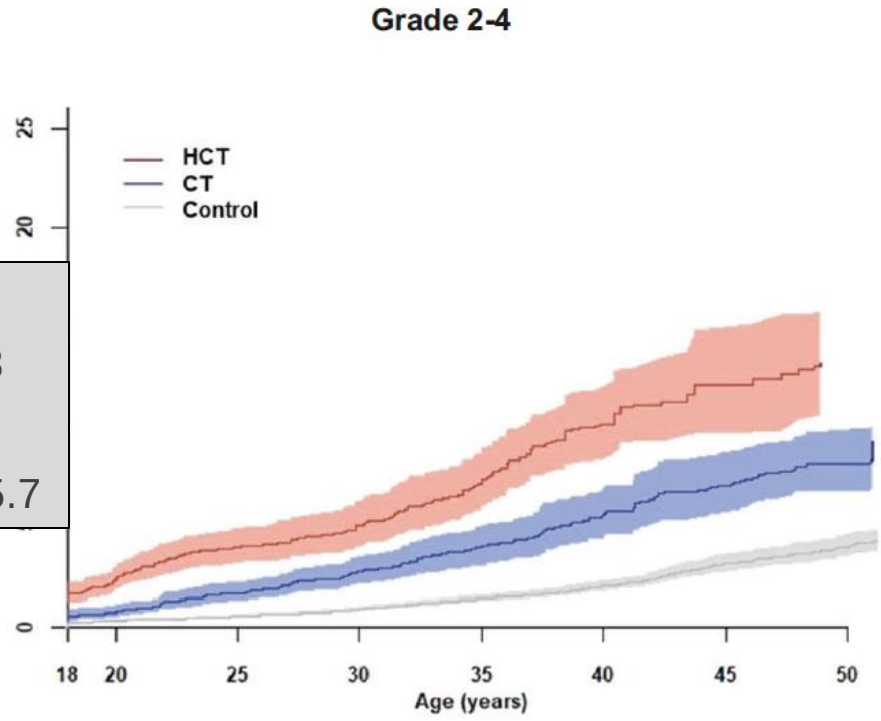
Prevalence select conditions:

Subsequent neoplasm 13.5%

Cardiomyopathy 9.0%

HCT 6.1% vs CT 11.9%, *p* = .001

SMR
SMN = 8.8
Cardiac = 15.7



Chronic Conditions in Survivors of HSCT

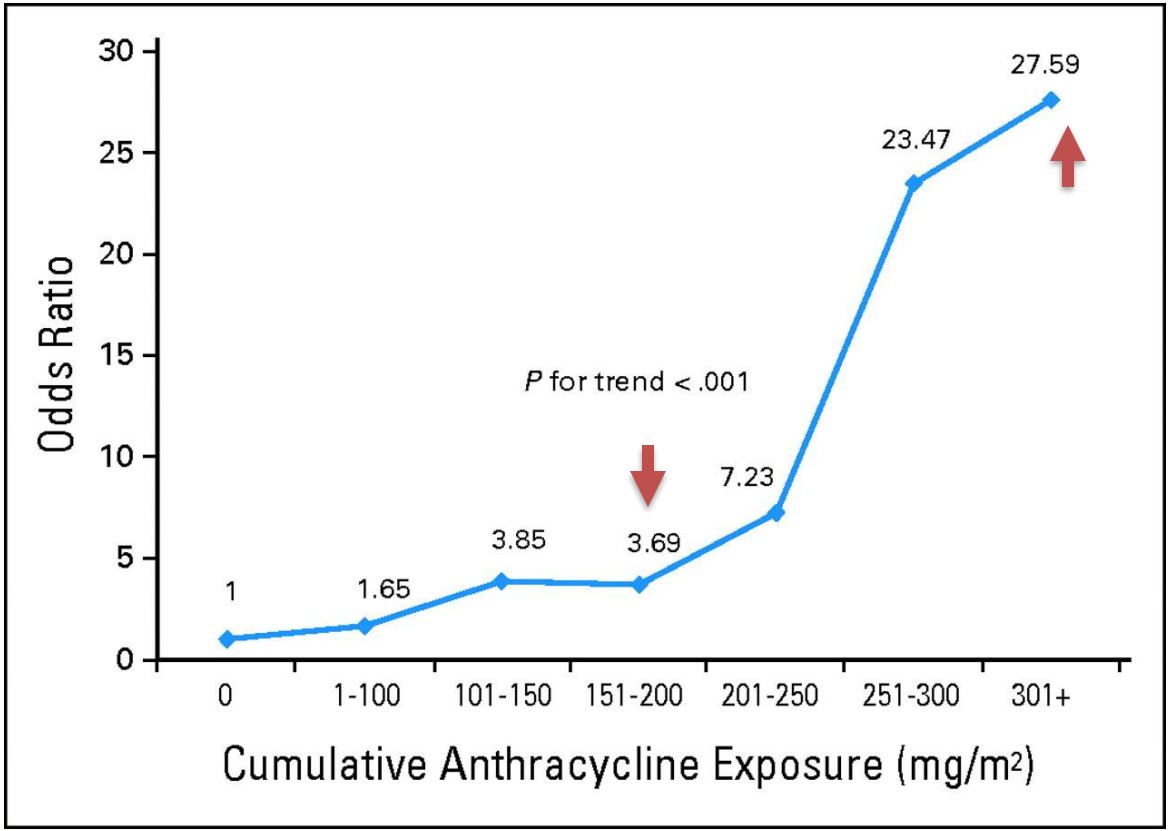
Survivors of transplant have an increased risk for chronic conditions compared to those treated with chemotherapy alone.

Relative risk of second cancers and endocrine or metabolic conditions is highest.

	Relative risk grade 3-5 conditions		
	BMTSS (N = 145), %	Conventionally treated, CCSS (N = 7207), %	RR (95% CI)*
Second malignant neoplasm‡	6.9	3.1	8.6 (2.9-25.3)
Endocrine	29.7	4.9	7.7 (4.2-14.3)
Musculoskeletal	2.1	0.5	7.4 (2.4-23.1)
Gastrointestinal	2.8	2.0	4.8 (1.0-21.7)
Neurosensory impairment	9.0	3.9	3.8 (1.4-10.3)
Genitourinary	1.4	0.3	2.9 (1.1-7.8)
Cardiovascular	4.8	3.2	0.5 (0.1-2.5)

Armenian et al. *Blood.* 2011.

Anthracycline Exposure and Cardiomyopathy



Blanco et al. *J Clin Oncol.* 2012.

Goals for Optimal Survivorship Care Delivery

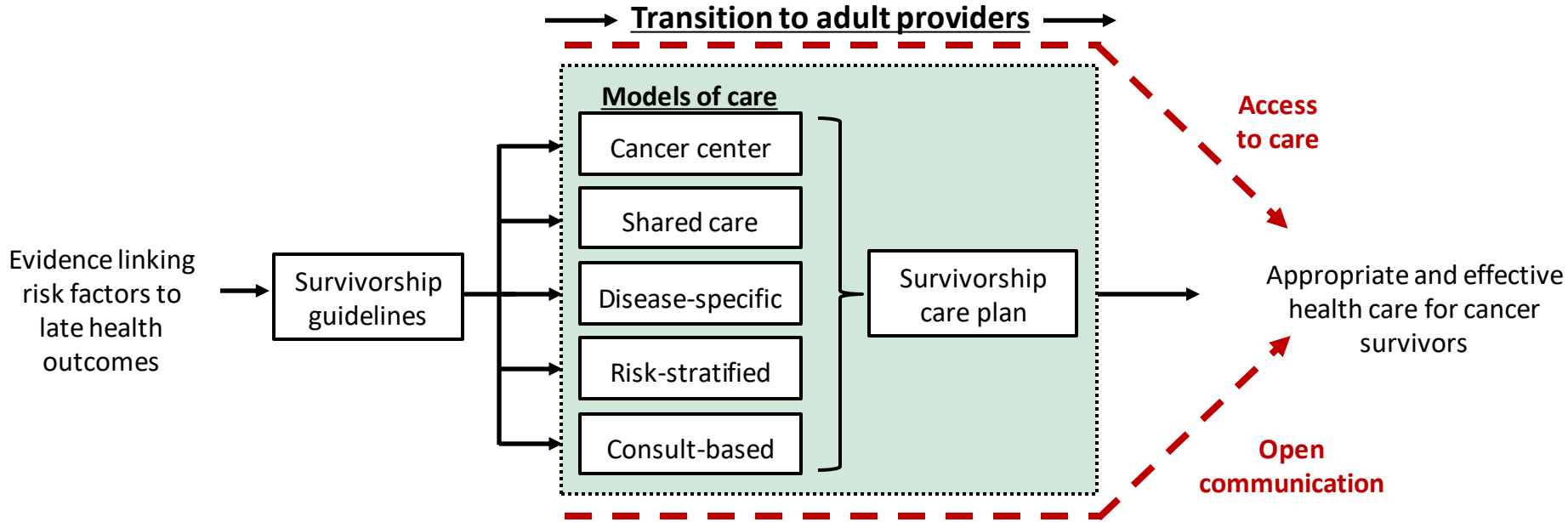
- Survivors are a medically complex and diverse population
- Medical and psychosocial late effects of treatment continue to evolve

Goals of survivorship care

- Prevention of recurrent/new cancer and late effects
- Cancer surveillance
- Assessment of medical and psychosocial late effects
- Intervention for consequences of cancer and its treatment
- Coordination between specialists and primary care providers

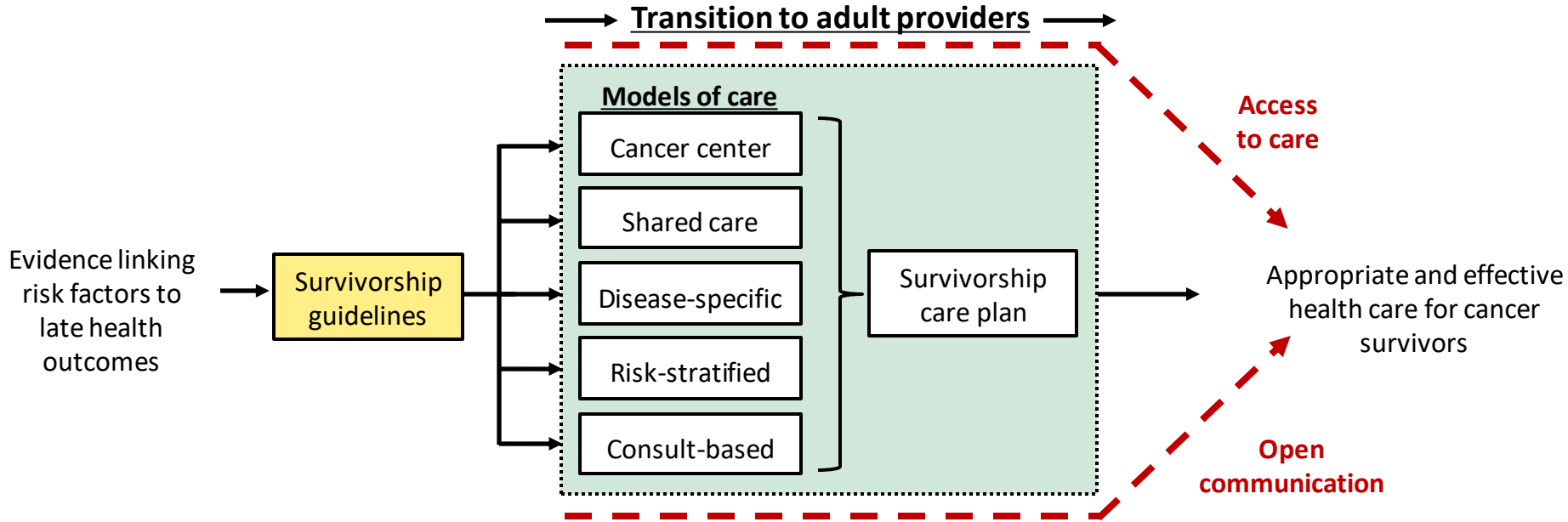
Hewitt et al. *From Cancer Patient to Cancer Survivor: Lost in Transition*. 2005.

Survivorship Care Continuum



Dixon et al. *CA Cancer J Clin.* 2016.

Survivorship Care Continuum

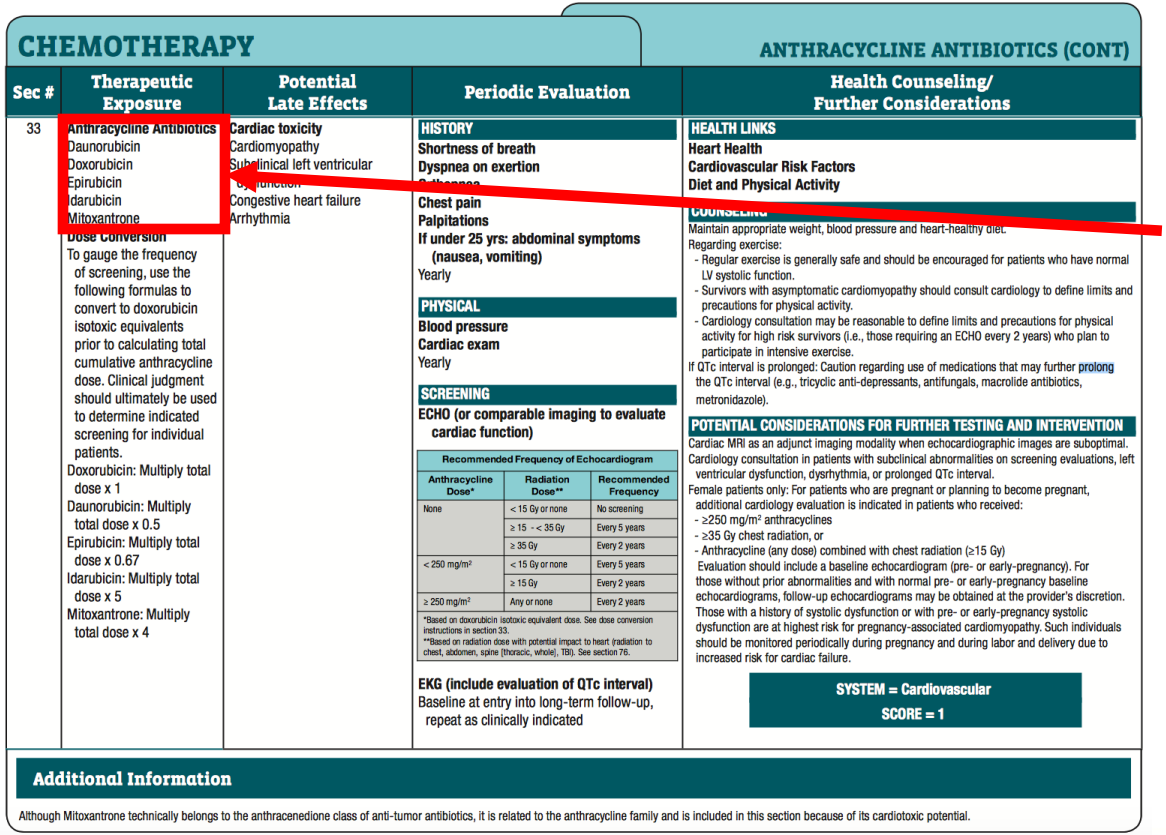


Dixon et al. *CA Cancer J Clin.* 2016.

Children's Oncology Group Survivorship Guidelines

- survivorshipguidelines.org
- Comprehensive literature search and grading of evidence
- Recommendations are consensus based
- Late effects linked with therapy exposure and screening recommendations

Children's Oncology Group Survivorship Guidelines



CHEMOTHERAPY

ANTHRACYCLINE ANTIBIOTICS (CONT)

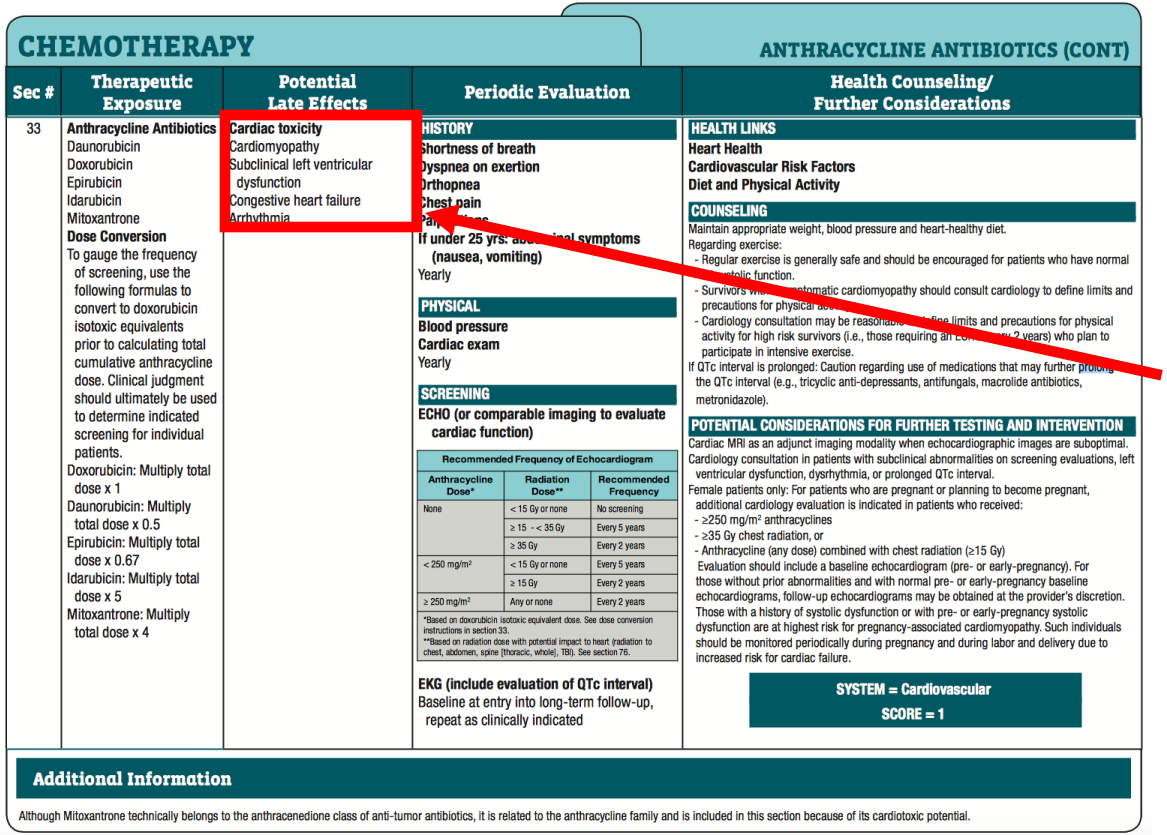
Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
33	**Anthracycline Antibiotics** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **Dose Conversion** To gauge the frequency of screening, use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. Clinical judgment should ultimately be used to determine indicated screening for individual patients. Doxorubicin: Multiply total dose x 1 Daunorubicin: Multiply total dose x 0.5 Epirubicin: Multiply total dose x 0.67 Idarubicin: Multiply total dose x 5 Mitoxantrone: Multiply total dose x 4	**Cardiac toxicity** Cardiomyopathy Subclinical left ventricular [illegible] Congestive heart failure Arrhythmia	**HISTORY** **Shortness of breath** **Dyspnea on exertion** **Chest pain** **Palpitations** **If under 25 yrs: abdominal symptoms (nausea, vomiting)** Yearly **PHYSICAL** **Blood pressure** **Cardiac exam** Yearly **SCREENING** **ECHO (or comparable imaging to evaluate cardiac function)** **Recommended Frequency of Echocardiogram** Anthracycline Dose* / Radiation Dose** / Recommended Frequency None / < 15 Gy or none / No screening ≥ 15 - < 35 Gy / Every 5 years ≥ 35 Gy / Every 2 years < 250 mg/m² / < 15 Gy or none / Every 5 years ≥ 15 Gy / Every 2 years ≥ 250 mg/m² / Any or none / Every 2 years *Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33. **Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76. **EKG (include evaluation of QTc interval)** Baseline at entry into long-term follow-up, repeat as clinically indicated	**HEALTH LINKS** **Heart Health** **Cardiovascular Risk Factors** **Diet and Physical Activity** **COUNSELING** Maintain appropriate weight, blood pressure and heart-healthy diet. Regarding exercise: - Regular exercise is generally safe and should be encouraged for patients who have normal LV systolic function. - Survivors with asymptomatic cardiomyopathy should consult cardiology to define limits and precautions for physical activity. - Cardiology consultation may be reasonable to define limits and precautions for physical activity for high risk survivors (i.e., those requiring an ECHO every 2 years) who plan to participate in intensive exercise. If QTc interval is prolonged: Caution regarding use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Cardiac MRI as an adjunct imaging modality when echocardiographic images are suboptimal. Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Female patients only: For patients who are pregnant or planning to become pregnant, additional cardiology evaluation is indicated in patients who received: - ≥250 mg/m² anthracyclines - ≥35 Gy chest radiation, or - Anthracycline (any dose) combined with chest radiation (≥15 Gy) Evaluation should include a baseline echocardiogram (pre- or early-pregnancy). For those without prior abnormalities and with normal pre- or early-pregnancy baseline echocardiograms, follow-up echocardiograms may be obtained at the provider's discretion. Those with a history of systolic dysfunction or with pre- or early-pregnancy systolic dysfunction are at highest risk for pregnancy-associated cardiomyopathy. Such individuals should be monitored periodically during pregnancy and during labor and delivery due to increased risk for cardiac failure. **SYSTEM = Cardiovascular** **SCORE = 1**

Additional Information

Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family and is included in this section because of its cardiotoxic potential.

- Organized by risk-based exposure and follow-up care
- Exposure-specific sections list relevant agents

Children's Oncology Group Survivorship Guidelines



CHEMOTHERAPY

ANTHRACYCLINE ANTIBIOTICS (CONT)

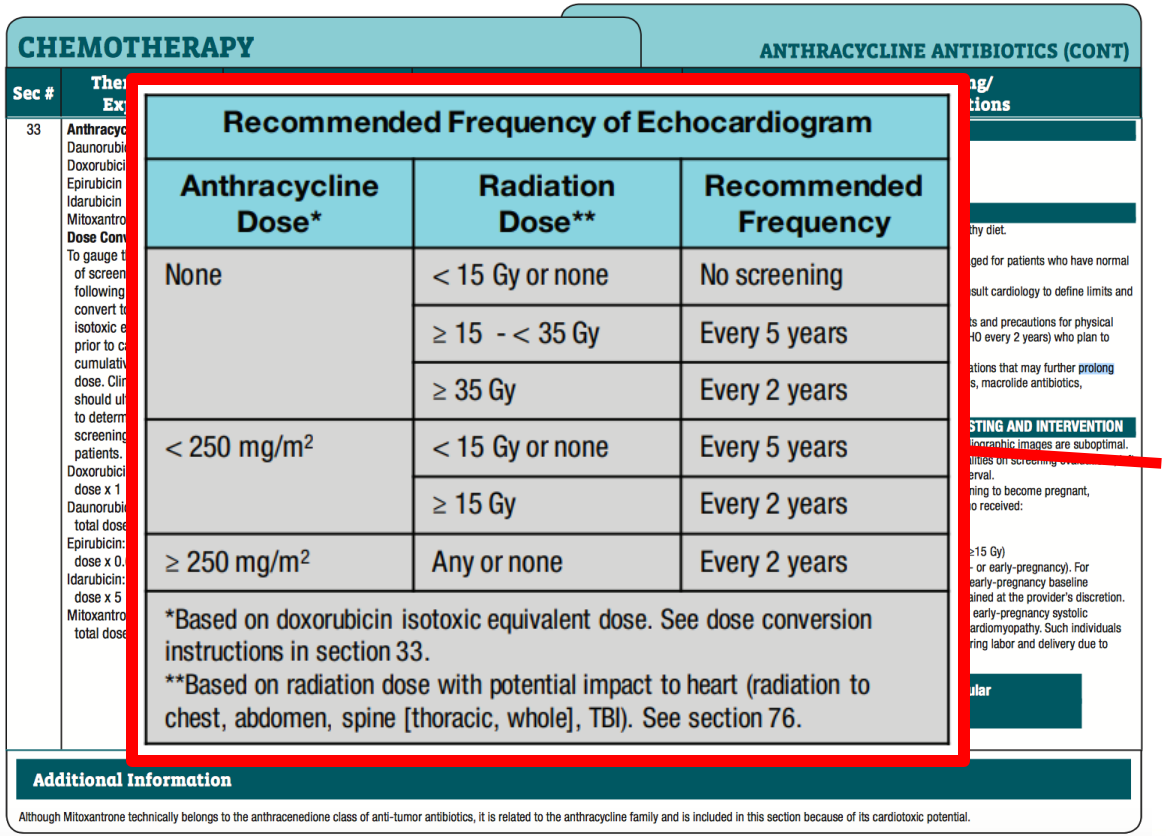
Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
33	**Anthracycline Antibiotics** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **Dose Conversion** To gauge the frequency of screening, use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. Clinical judgment should ultimately be used to determine indicated screening for individual patients. Doxorubicin: Multiply total dose x 1 Daunorubicin: Multiply total dose x 0.5 Epirubicin: Multiply total dose x 0.67 Idarubicin: Multiply total dose x 5 Mitoxantrone: Multiply total dose x 4	**Cardiac toxicity** Cardiomyopathy Subclinical left ventricular dysfunction Congestive heart failure Arrhythmia	**HISTORY** **Shortness of breath** **Dyspnea on exertion** **Orthopnea** **Chest pain** **Pa[illegible]** **If under 25 yrs: abn[illegible]inal symptoms (nausea, vomiting)** Yearly **PHYSICAL** **Blood pressure** **Cardiac exam** Yearly **SCREENING** **ECHO (or comparable imaging to evaluate cardiac function)** **Recommended Frequency of Echocardiogram** Anthracycline Dose* / Radiation Dose** / Recommended Frequency None / < 15 Gy or none / No screening ≥ 15 - < 35 Gy / Every 5 years ≥ 35 Gy / Every 2 years < 250 mg/m² / < 15 Gy or none / Every 5 years ≥ 15 Gy / Every 2 years ≥ 250 mg/m² / Any or none / Every 2 years *Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33. **Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76. **EKG (include evaluation of QTc interval)** Baseline at entry into long-term follow-up, repeat as clinically indicated	**HEALTH LINKS** **Heart Health** **Cardiovascular Risk Factors** **Diet and Physical Activity** **COUNSELING** Maintain appropriate weight, blood pressure and heart-healthy diet. Regarding exercise: - Regular exercise is generally safe and should be encouraged for patients who have normal [illegible]tolic function. - Survivors wi[illegible]tomatic cardiomyopathy should consult cardiology to define limits and precautions for physical ac[illegible] - Cardiology consultation may be reasonable to define limits and precautions for physical activity for high risk survivors (i.e., those requiring an LV[illegible] 2 years) who plan to participate in intensive exercise. If QTc interval is prolonged: Caution regarding use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Cardiac MRI as an adjunct imaging modality when echocardiographic images are suboptimal. Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Female patients only: For patients who are pregnant or planning to become pregnant, additional cardiology evaluation is indicated in patients who received: - ≥250 mg/m² anthracyclines - ≥35 Gy chest radiation, or - Anthracycline (any dose) combined with chest radiation (≥15 Gy) Evaluation should include a baseline echocardiogram (pre- or early-pregnancy). For those without prior abnormalities and with normal pre- or early-pregnancy baseline echocardiograms, follow-up echocardiograms may be obtained at the provider's discretion. Those with a history of systolic dysfunction or with pre- or early-pregnancy systolic dysfunction are at highest risk for pregnancy-associated cardiomyopathy. Such individuals should be monitored periodically during pregnancy and during labor and delivery due to increased risk for cardiac failure. **SYSTEM = Cardiovascular** **SCORE = 1**

Additional Information

Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family and is included in this section because of its cardiotoxic potential.

- Organized by risk-based exposure and follow-up care
- Exposure-specific sections list relevant agents
- Late effects are listed

Children's Oncology Group Survivorship Guidelines



CHEMOTHERAPY

ANTHRACYCLINE ANTIBIOTICS (CONT)

Sec #

33

Recommended Frequency of Echocardiogram

Anthracycline Dose*	Radiation Dose**	Recommended Frequency
None	< 15 Gy or none	No screening
	≥ 15 - < 35 Gy	Every 5 years
	≥ 35 Gy	Every 2 years
< 250 mg/m²	< 15 Gy or none	Every 5 years
	≥ 15 Gy	Every 2 years
≥ 250 mg/m²	Any or none	Every 2 years

*Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33.

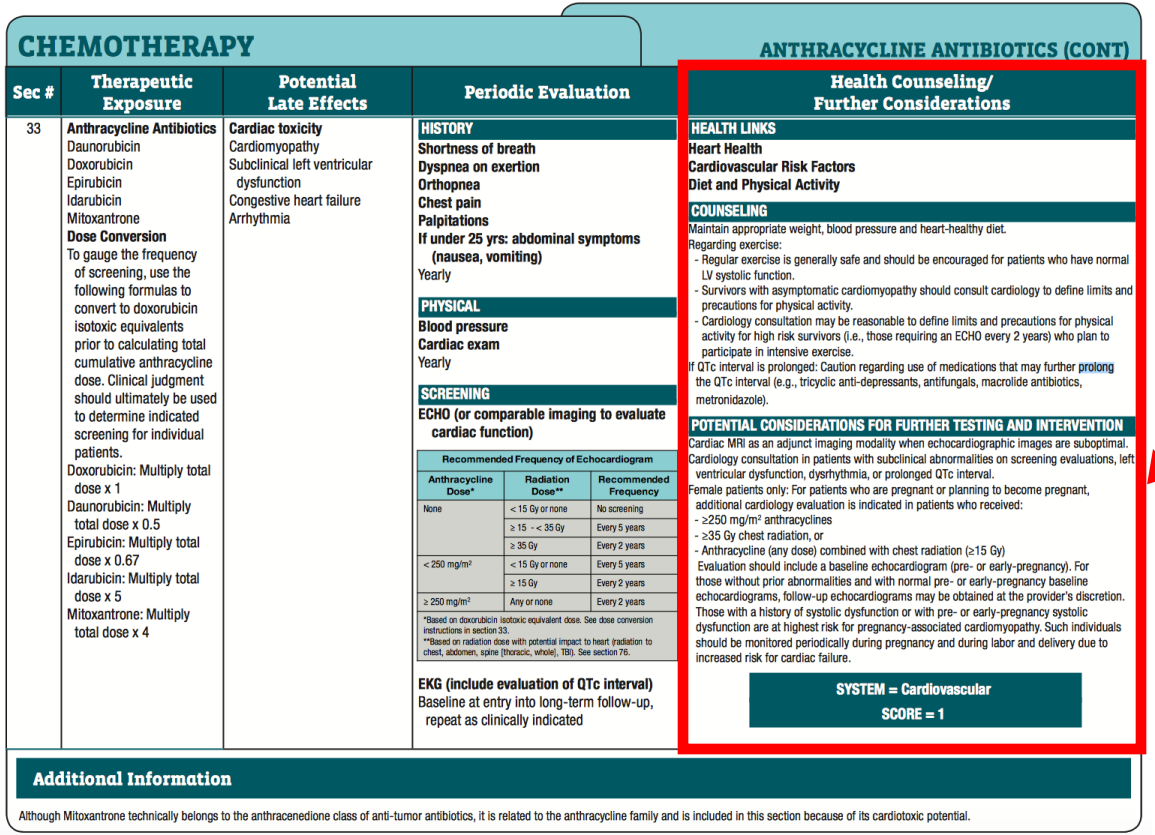
**Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76.

Additional Information

Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family and is included in this section because of its cardiotoxic potential.

- Organized by risk-based exposure and follow-up care
- Exposure-specific sections list relevant agents
- Late effects are listed
- Screening evaluations are outlined with consideration of exposure and level of risk

Children's Oncology Group Survivorship Guidelines



CHEMOTHERAPY

ANTHRACYCLINE ANTIBIOTICS (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
33	**Anthracycline Antibiotics** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **Dose Conversion** To gauge the frequency of screening, use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. Clinical judgment should ultimately be used to determine indicated screening for individual patients. Doxorubicin: Multiply total dose x 1 Daunorubicin: Multiply total dose x 0.5 Epirubicin: Multiply total dose x 0.67 Idarubicin: Multiply total dose x 5 Mitoxantrone: Multiply total dose x 4	**Cardiac toxicity** Cardiomyopathy Subclinical left ventricular dysfunction Congestive heart failure Arrhythmia	**HISTORY** **Shortness of breath** **Dyspnea on exertion** **Orthopnea** **Chest pain** **Palpitations** **If under 25 yrs: abdominal symptoms (nausea, vomiting)** Yearly **PHYSICAL** **Blood pressure** **Cardiac exam** Yearly **SCREENING** **ECHO (or comparable imaging to evaluate cardiac function)**	**HEALTH LINKS** **Heart Health** **Cardiovascular Risk Factors** **Diet and Physical Activity** **COUNSELING** Maintain appropriate weight, blood pressure and heart-healthy diet. Regarding exercise: - Regular exercise is generally safe and should be encouraged for patients who have normal LV systolic function. - Survivors with asymptomatic cardiomyopathy should consult cardiology to define limits and precautions for physical activity. - Cardiology consultation may be reasonable to define limits and precautions for physical activity for high risk survivors (i.e., those requiring an ECHO every 2 years) who plan to participate in intensive exercise. If QTc interval is prolonged: Caution regarding use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Cardiac MRI as an adjunct imaging modality when echocardiographic images are suboptimal. Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Female patients only: For patients who are pregnant or planning to become pregnant, additional cardiology evaluation is indicated in patients who received: - ≥250 mg/m² anthracyclines - ≥35 Gy chest radiation, or - Anthracycline (any dose) combined with chest radiation (≥15 Gy) Evaluation should include a baseline echocardiogram (pre- or early-pregnancy). For those without prior abnormalities and with normal pre- or early-pregnancy baseline echocardiograms, follow-up echocardiograms may be obtained at the provider's discretion. Those with a history of systolic dysfunction or with pre- or early-pregnancy systolic dysfunction are at highest risk for pregnancy-associated cardiomyopathy. Such individuals should be monitored periodically during pregnancy and during labor and delivery due to increased risk for cardiac failure. **SYSTEM = Cardiovascular** **SCORE = 1**

Recommended Frequency of Echocardiogram

Anthracycline Dose*	Radiation Dose**	Recommended Frequency
None	< 15 Gy or none	No screening
	≥ 15 - < 35 Gy	Every 5 years
	≥ 35 Gy	Every 2 years
< 250 mg/m²	< 15 Gy or none	Every 5 years
	≥ 15 Gy	Every 2 years
≥ 250 mg/m²	Any or none	Every 2 years

*Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33.
**Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76.

EKG (include evaluation of QTc interval)
Baseline at entry into long-term follow-up, repeat as clinically indicated

Additional Information

Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family and is included in this section because of its cardiotoxic potential.

- Organized by risk-based exposure and follow-up care
- Exposure-specific sections list relevant agents
- Late effects are listed
- Screening evaluations are outlined with consideration of exposure and level of risk
- Other considerations of level of evidence

St. Jude Children's Research Hospital

Guidelines Harmonization Across Groups

Pancare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies

PanCareSurFup

CHILDREN'S ONCOLOGY GROUP *Foundation*

International Guideline Harmonization Group

for Late Effects of Childhood Cancer

Children's Cancer and Leukaemia Group

Working together to beat childhood cancer

DCOG LATER

Longterm effects after childhood cancer

SIGN

Scottish Intercollegiate Guidelines Network

International Guideline Harmonization Group (IGHG)

- The IGHG established consensus guidelines for cardiomyopathy surveillance in 2015

Risk	Surveillance	Suggested interval
High	Yes	5-year
		≤5-year
Moderate	Maybe	5-year
Low	Maybe	5-year

Strong recommendation, high quality evidence

Moderate recommendation, moderate quality evidence

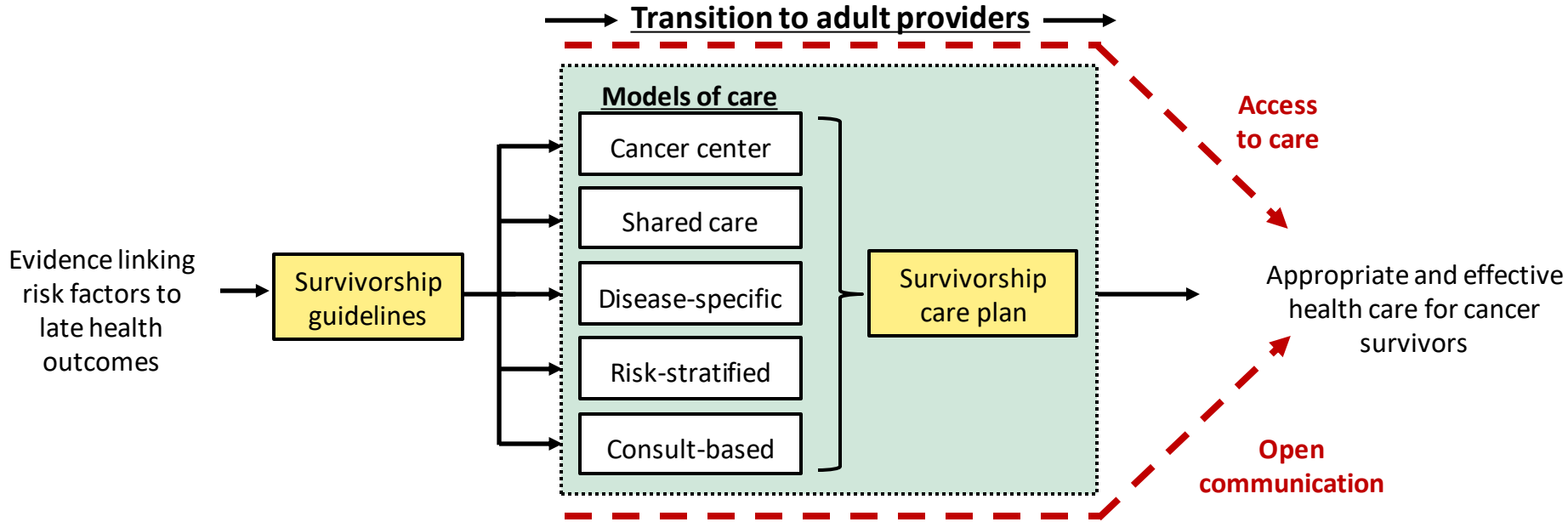
Moderate recommendation, weak quality evidence

Armenian et al. *Lancet Oncol.* 2015.

IGHG Publications and Considerations for Leukemia Survivors

- Methodology (*Pediatr Blood Cancer* 2013)
- Breast cancer (*Lancet Oncol* 2013, *J Clin Oncol* 2020)
- Cardiomyopathy (*Lancet Onc*ol 2015)
- Premature ovarian insufficiency (*J Clin Oncol* 2016)
- Fertility preservation (*Cancer* 2016)
- Male *gonadotoxicity (Lancet Oncol 2017)*
- *Thyroid cancer (Cancer Treat Rev 2018)*
- *Ototoxicity (Lancet Oncol* 2019)
- Meningioma surveillance (*J Neuro-Oncol* 2020)
- Cancer-related fatigue (*J Cancer Surviv* 2020)
- Obstetrical care (*Am J Obstet Gynecol* 2020)
- COVID-19 survivorship statement (*Pediatr Blood Cancer* 2020)
- Fertility preservation series (female, male, ethics) (*Lancet Oncol* 2021)
- Meningioma (*Lancet Oncol* 2021)
- Coronary artery disease (*Eur J Cancer* 2021)
- Bone mineral density (*Lancet Diabetes Endocrinol* 2021)
- Hepatotoxicity (*Cancer Treat Rev* 2021)
- Education/employment (*In press*, *Cancer*)
- Pituitary deficiencies (*In press*)
- Impact of COVID-19 on survivorship providers (*In press*)
- Mental health (*In press*)

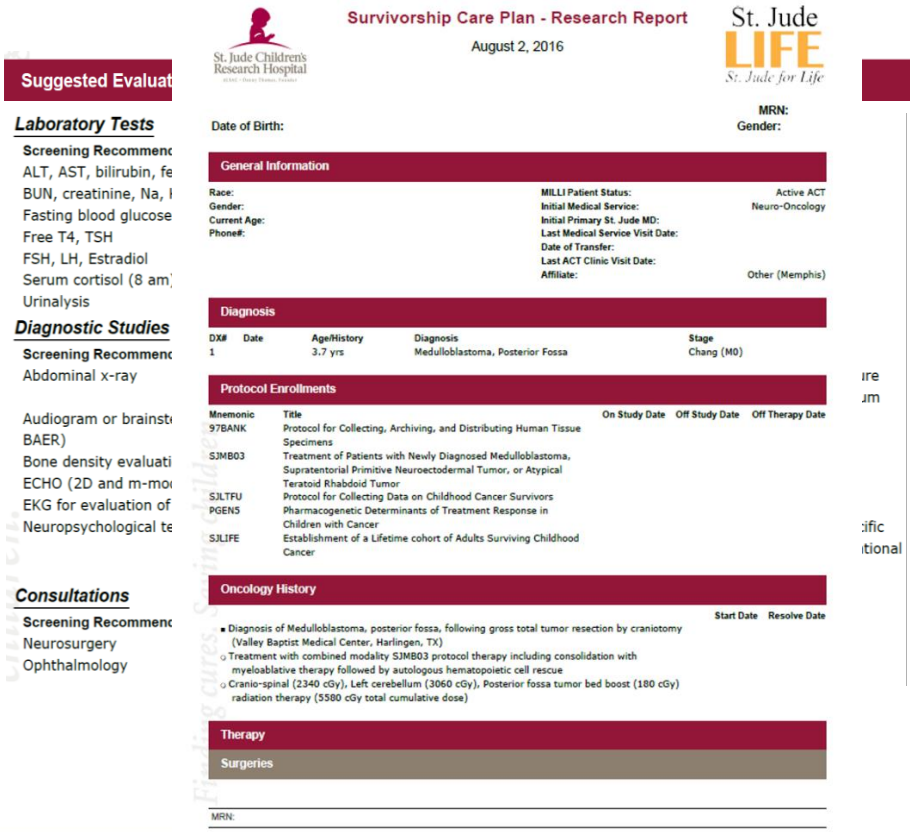
Survivorship Care Continuum



Dixon et al. *CA Cancer J Clin.* 2016.

Survivorship Care Plans (SCPs)

- Cancer diagnostic information
- Cumulative treatment exposures
- Cancer-related health risks
- Risk-based screening recommendations
- Major clinical events
- Transfusion history
- Health behaviors modifying risk
- Family history



Suggested Evaluat

Laboratory Tests

Screening Recommenc
ALT, AST, bilirubin, fe
BUN, creatinine, Na, I
Fasting blood glucose
Free T4, TSH
FSH, LH, Estradiol
Serum cortisol (8 am)
Urinalysis

Diagnostic Studies

Screening Recommenc
Abdominal x-ray

Audiogram or brainste
BAER)
Bone density evaluati
ECHO (2D and m-mo
EKG for evaluation of
Neuropsychological te

Consultations

Screening Recommenc
Neurosurgery
Ophthalmology

St. Jude Children's Research Hospital

Survivorship Care Plan - Research Report

August 2, 2016

St. Jude LIFE — St. Jude for Life

Date of Birth:

MRN:
Gender:

General Information

Race:
Gender:
Current Age:
Phone#:

MILLI Patient Status: Active ACT
Initial Medical Service: Neuro-Oncology
Initial Primary St. Jude MD:
Last Medical Service Visit Date:
Date of Transfer:
Last ACT Clinic Visit Date:
Affiliate: Other (Memphis)

Diagnosis

DX#	Date	Age/History	Diagnosis	Stage
1		3.7 yrs	Medulloblastoma, Posterior Fossa	Chang (M0)

Protocol Enrollments

Mnemonic	Title	On Study Date	Off Study Date	Off Therapy Date
97BANK	Protocol for Collecting, Archiving, and Distributing Human Tissue Specimens			
SJMB03	Treatment of Patients with Newly Diagnosed Medulloblastoma, Supratentorial Primitive Neuroectodermal Tumor, or Atypical Teratoid Rhabdoid Tumor			
SJLTFU	Protocol for Collecting Data on Childhood Cancer Survivors			
PGEN5	Pharmacogenetic Determinants of Treatment Response in Children with Cancer			
SJLIFE	Establishment of a Lifetime cohort of Adults Surviving Childhood Cancer			

Oncology History

Start Date Resolve Date

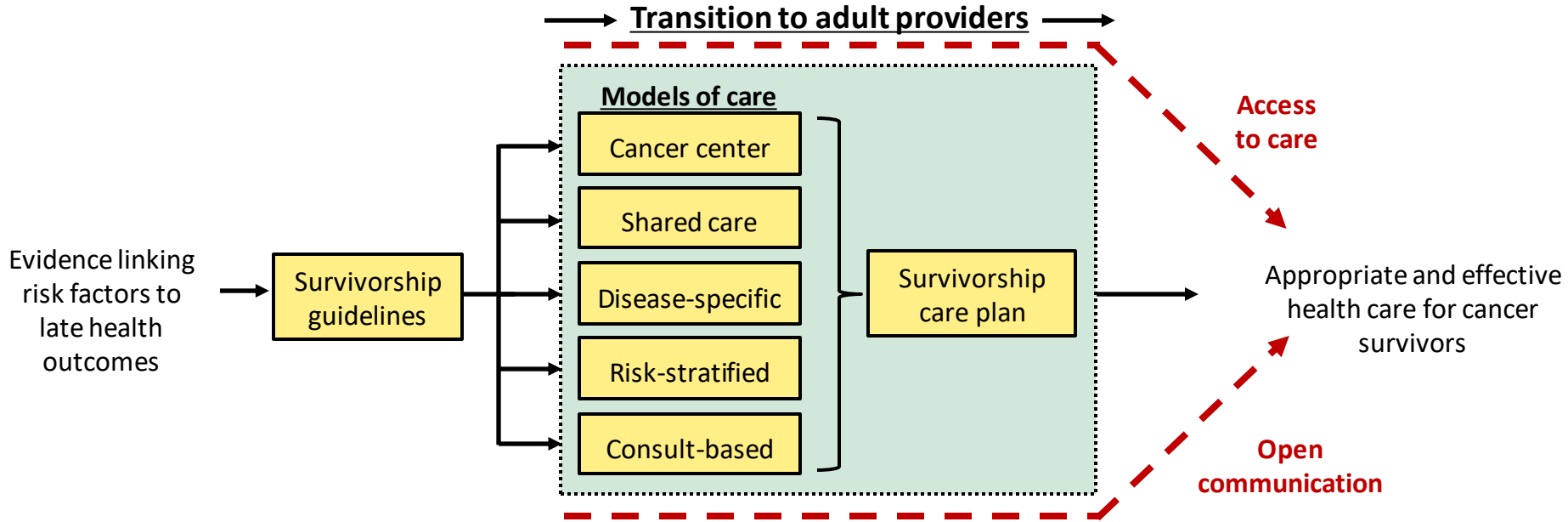
- Diagnosis of Medulloblastoma, posterior fossa, following gross total tumor resection by craniotomy (Valley Baptist Medical Center, Harlingen, TX)
  - Treatment with combined modality SJMB03 protocol therapy including consolidation with myeloablative therapy followed by autologous hematopoietic cell rescue
  - Cranio-spinal (2340 cGy), Left cerebellum (3060 cGy), Posterior fossa tumor bed boost (180 cGy) radiation therapy (5580 cGy total cumulative dose)

Therapy

Surgeries

MRN:

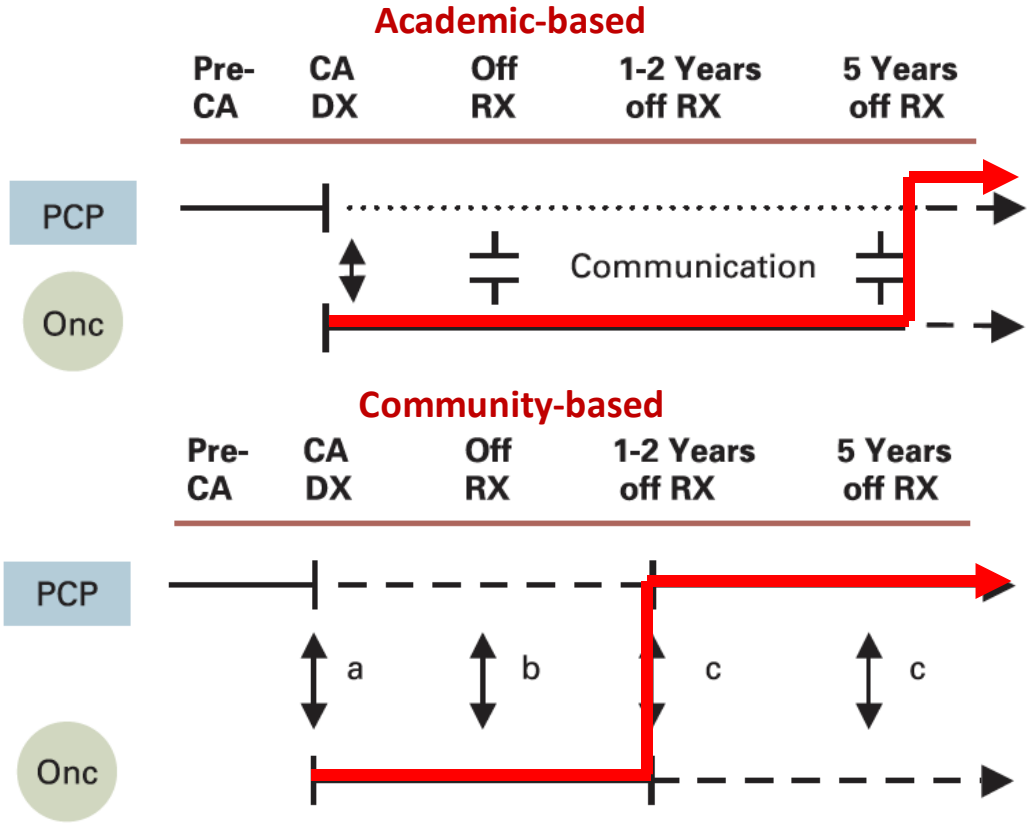
Survivorship Care Continuum



Dixon et al. *CA Cancer J Clin.* 2016.

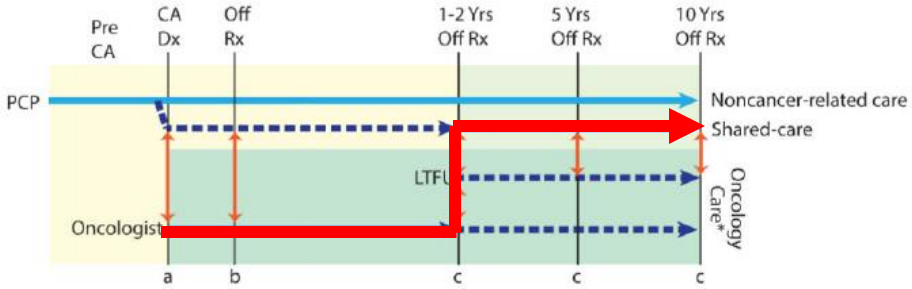
Shared-Care Model of Survivorship Care

- Communication begins at dx and continues through transition
- Survivorship-focused extension of cancer care continuum
- Nurse practitioners and physician assistant visits

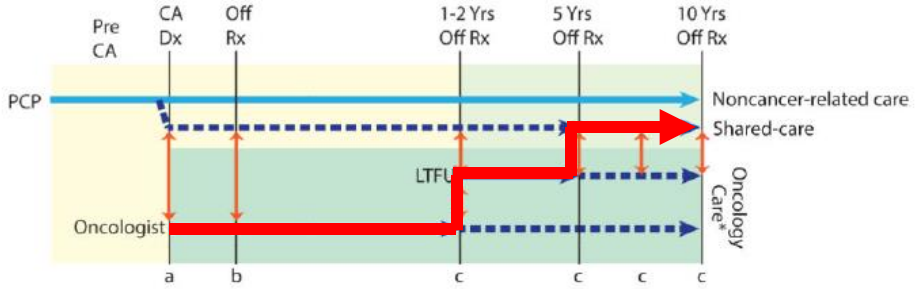


Risk-Stratified Model of Survivorship Care

Low Risk

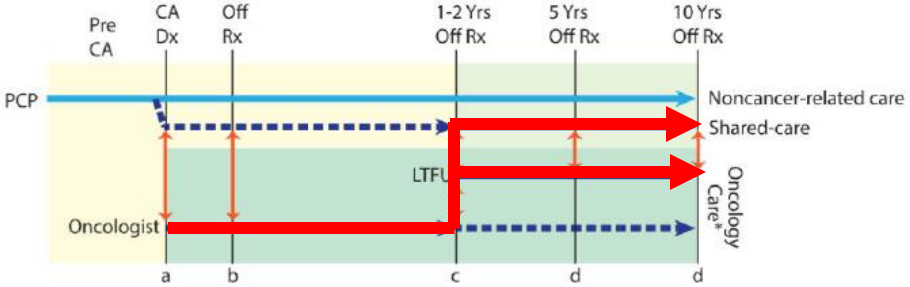


Moderate Risk

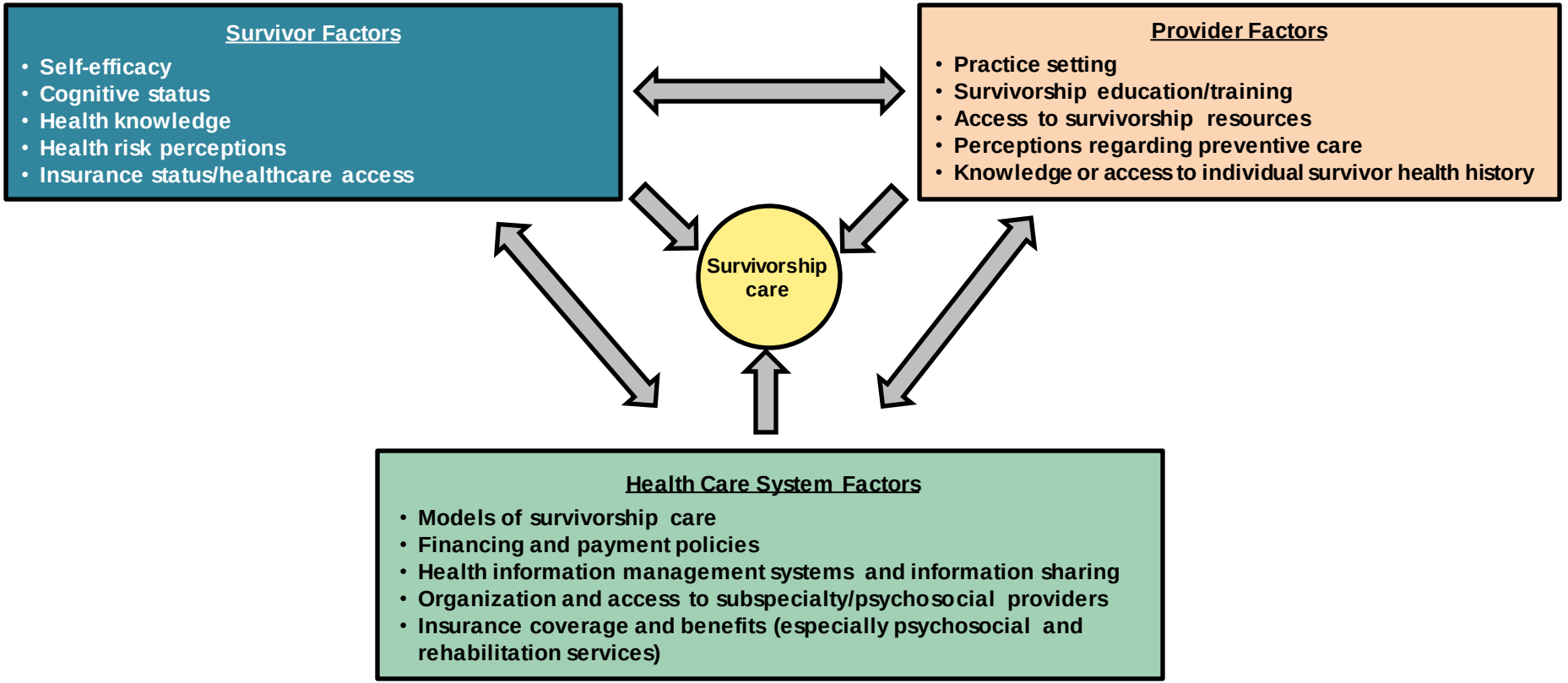


- Risk-stratified and shared care
  - Care based upon low, moderate, and high risk for late effects
  - Coordination between oncology and primary care with differential transition to primary care

High Risk



Barriers to Survivorship Care Delivery



Dixon et al. *CA Cancer J Clin.* 2016.

St. Jude Children's Research Hospital

Summary

- Survivors of childhood leukemia are a medically complex and diverse population
- As medical and psychosocial late effects of treatment continue to evolve, so will care needs and recommended screening
- Survivorship guidelines and survivorship care plans can support delivery of survivorship care
- Optimal survivor care must be tailored to the risk of the patient and the availability of resources in the region and health system

Q1: Which of the Following Groups of Survivors Have the Highest Risk for Cardiomyopathy?

1. Survivors of ALL treated with conventional chemotherapy including moderate-doses of anthracyclines
2. Survivors of ALL requiring hematopoietic cell transplant
3. Survivors of AML treated with conventional chemotherapy including high doses of anthracyclines (>250 mg/m^2)
4. Survivors of AML treated with hematopoietic cell transplant

Q2: Which of the Following Statements Is False?

1. Survivorship care plans can be useful tools to summarize treatment and follow-up recommendations
2. The risk-stratified care model is optimal for survivorship care
3. Many barriers to optimal survivorship care exist and may be unique to specific regions or healthcare systems
4. Survivorship care includes transition planning for return to community practice and/or adult providers

St. Jude Children's Research Hospital

Questions?

Global Leukemia Academy

AYA ALL patients – what is the current treatment approach for this diverse patient population?

Special considerations for adolescents and young adults

Rob Pieters

APTITUDE HEALTH

Adolescents/young adults (AYA) with ALL

Rob Pieters
Chief Medical Officer

Question

Which assertion is NOT correct for adolescent and young adult ALL patients?

1. Pediatric-inspired protocols lead to a better outcome than adult-inspired protocols
2. Osteonecrosis and anaphylactic reactions to asparaginase are more often seen in adults than in children and teenagers
3. AYA patients experience more liver toxicity and thrombosis than children <10 years old
4. *BCR-ABL1*–like ALL is more frequent in AYA ALL than in children <10 years old with ALL

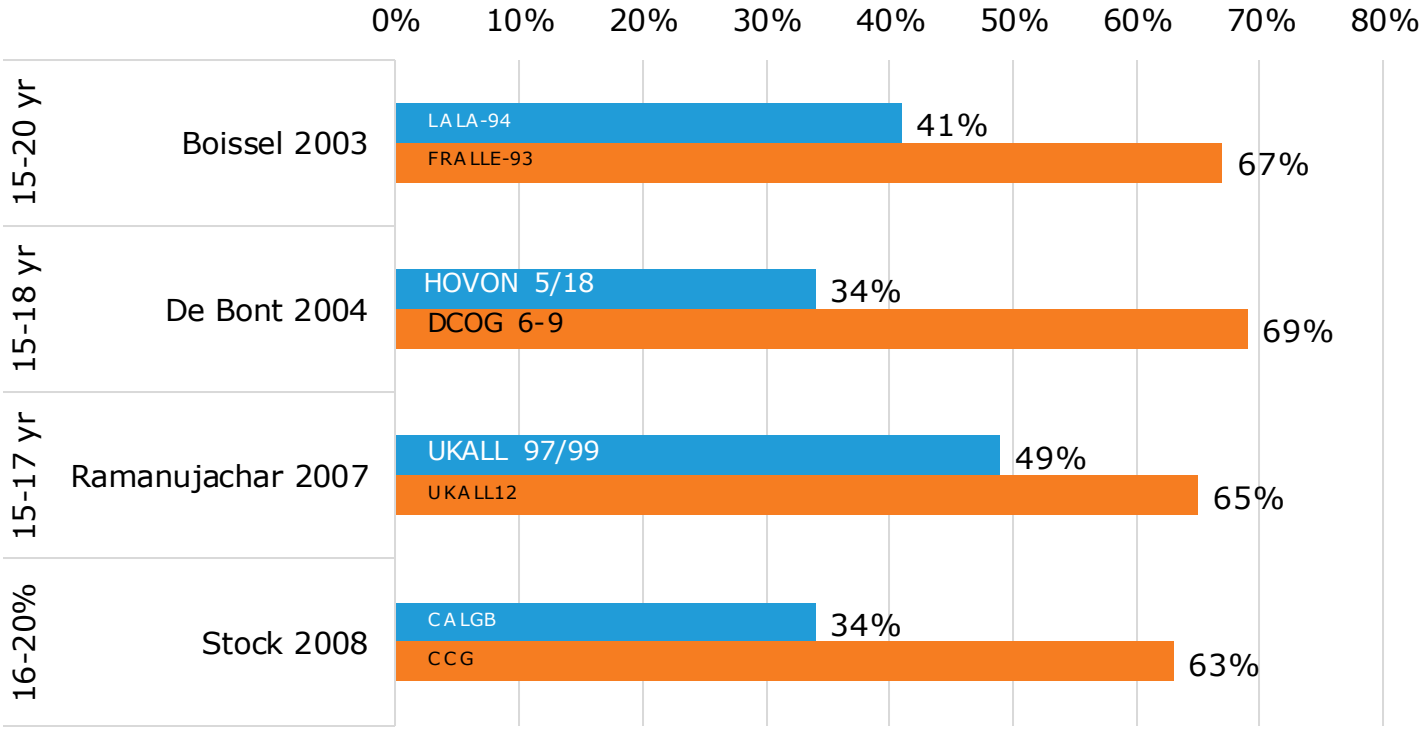
Inferior outcome for AYA patients: Why?

- Role of “pediatric-“ vs “adult-inspired” treatment protocols
- Site of treatment
- Trial enrollment
- Toxicity profile
- Biology/genetics of the leukemia
- Adherence

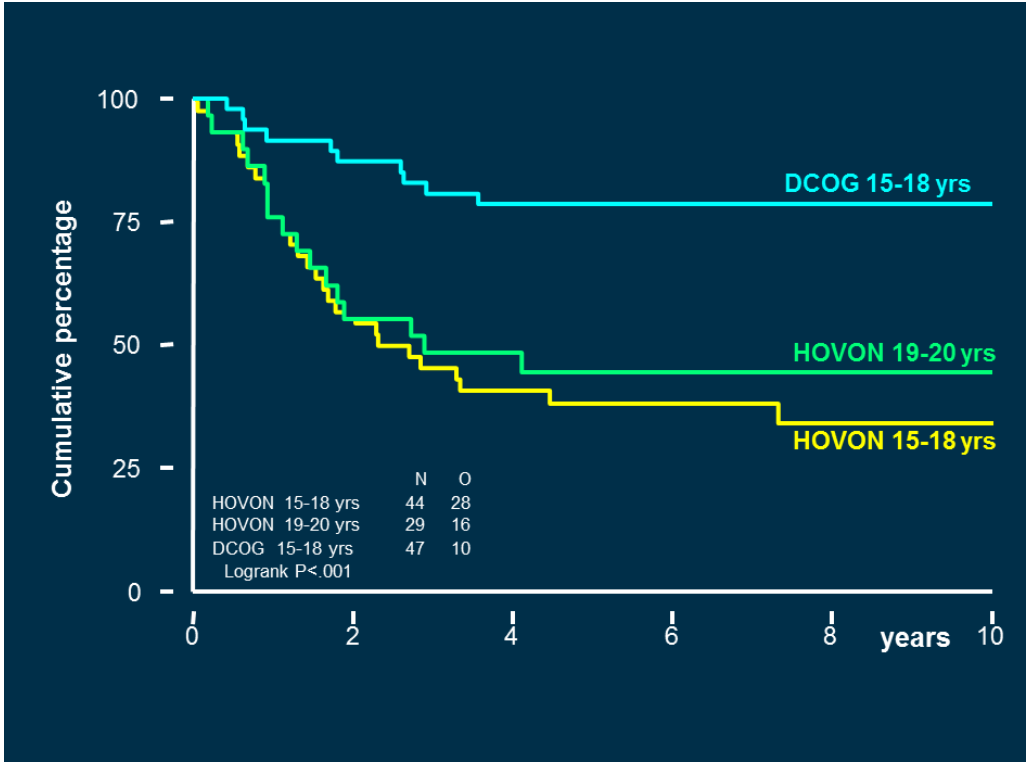
Pediatric vs adult treatment protocols

- More intensive use of
  - Glucocorticoids
  - Vincristine
  - Asparaginase
  - Methotrexate
  - 6-mercaptopurine
- Less intensive use of
  - Anthracyclines
  - Cyclophosphamide
- Less frequent use of alloSCT
- Prolonged maintenance, delayed intensification, CNS-directed therapy

Comparison of 5-year EFS in adolescent and young adult (AYA) patients treated on pediatric and adult protocols



Adolescent ALL on pediatric DCOG vs adult HOVON protocol in the Netherlands



De Bont, Leukemia 2004

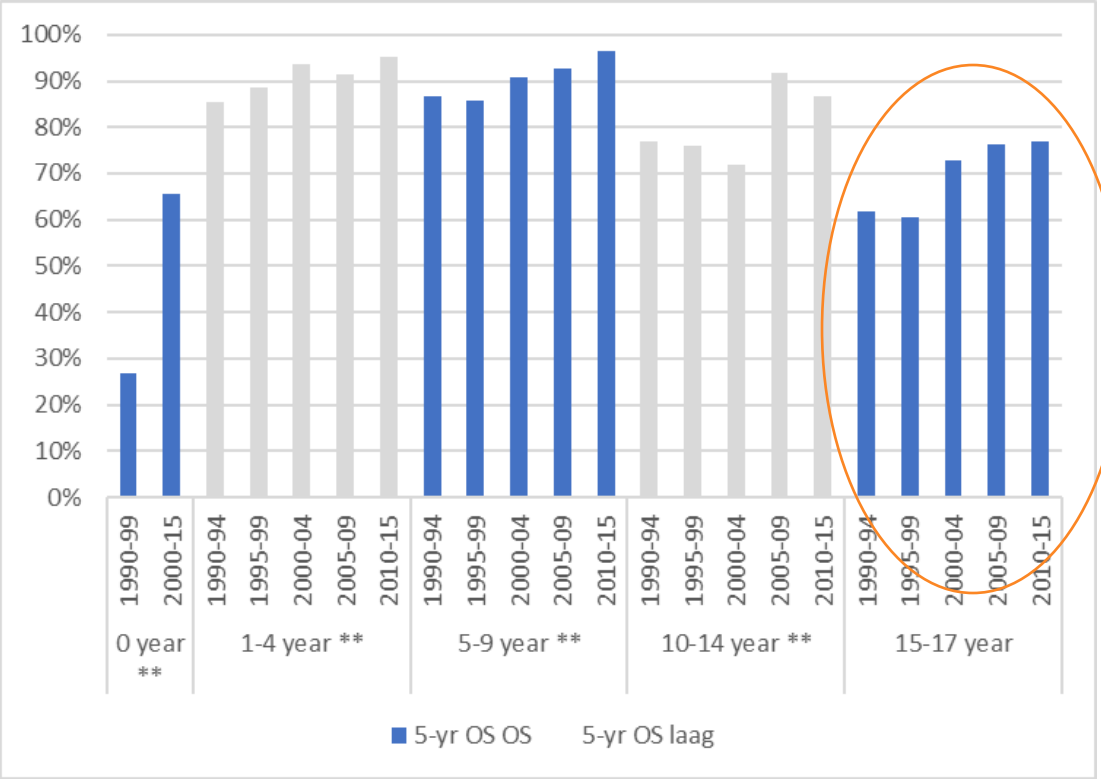
Adolescent ALL on pediatric DCOG vs adult HOVON protocol in the Netherlands

5 yrs actuarial probabilities

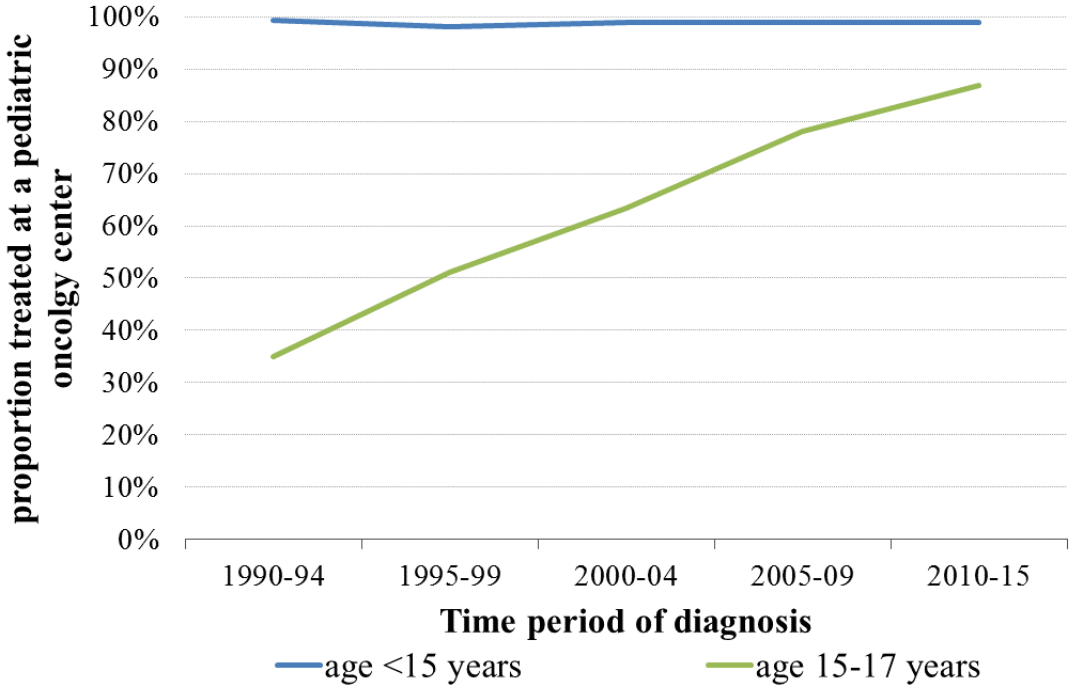
	CR	OS (sd)	EFS (sd)	DFS (sd)	pREL (sd)	TRM (sd)
DCOG 15-18 yrs (n=47)	**98%**	**79%** (±6)	**69%** (±7)	**71%** (±7)	**27%** (±7)	**4%** (±3)
HOVON 15-18 yrs (n=44)	**91%**	**38%** (±7)	**34%** (±7)	**37%** (±8)	**55%** (±8)	**25%** (±7)
HOVON 19-20 yrs (n=29)	**90%**	**44%** (±9)	**34%** (±9)	**38%** (±10)	**50%** (±10)	**21%** (±8)
p-value	***0.24***	***0.0001***	***<0.0001***	***0.0002***		

De Bont, Leukemia 2004

5-year overall survival by age group over time in the Netherlands



Proportion of patients with ALL treated at a pediatric oncology center in the Netherlands



Reedijk, Leukemia 2020

Multivariate analysis of risk of death: Patients 15–17 years old with ALL in the Netherlands between 1990 and 2015

		Hazard risk	95% CI	95% CI	*P* value
Period	1990–94	Reference			
	1995–99	0.97	0.50	1.91	.94
	2000–04	0.67	0.32	1.42	.30
	2005–09	0.64	0.30	1.37	.25
	2010–15	0.80	0.38	1.68	.56
Sex	Male	Reference			
	Female	1.45	0.89	2.37	.14
Immunophenotype	Precursor B cell	Reference			
	Precursor T cell	1.59	0.97	2.62	.07
Site of treatment	Outside pediatric oncology center	Reference			
	Pediatric oncology center	0.32	0.20	0.53	<.01

Outcomes of older adolescents treated on recent pediatric trials

Trial	No. of patients	Age range, yr	Early death, %	Death in CR, %	HSCT, %	EFS		OS	
						Y	%	Y	%
CCG 1961	262	16–21	2	3	4	5	72	5	78
DFCI 9101/9501	51	15–18	4	2	NR	5	78	5	81
Total Therapy XV	45	15–18	0	7	11	5	86	5	88
UKALL 2003	229	16–24	NR	6	6.1	5	72	5	76
FRALLE 2000	186	15–19	2	2	12	5	74	5	80
DCOG ALL-10	57	15–18	3.5	3.5	12	5	79	5	82

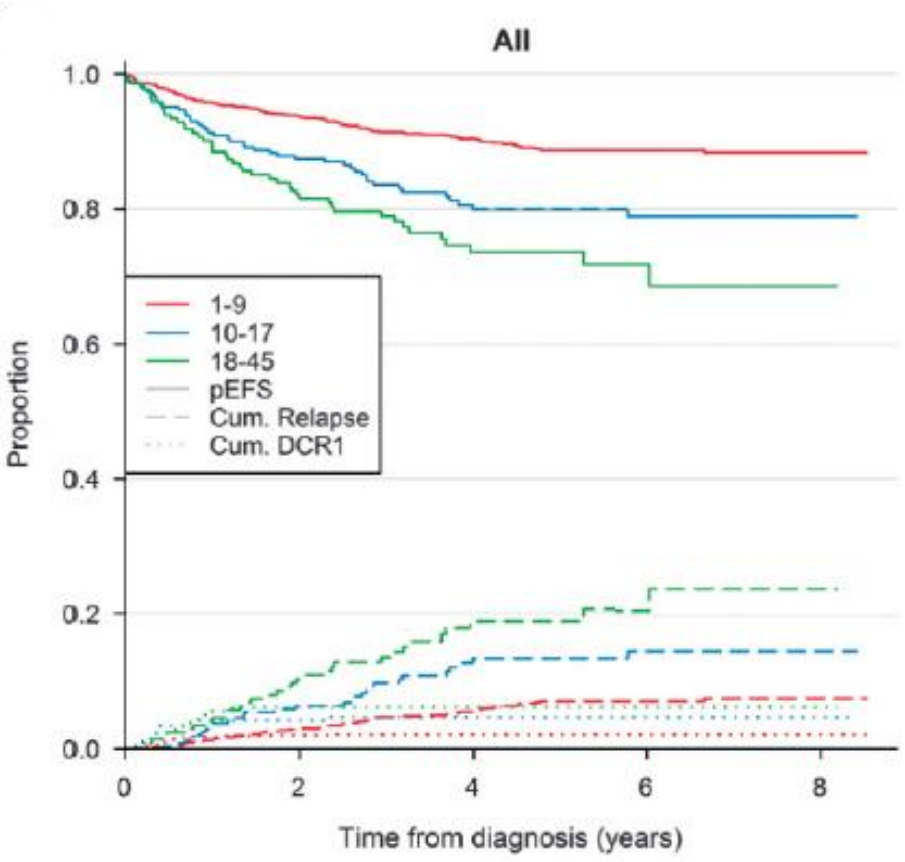
Adapted from Boissel, 2018 and Pieters, 2016

Outcomes of young adults on recent pediatric-inspired protocol (HOVON)

Trial	No. of pts	Age range, yr	Early death, %	Death in CR, %	HSCT, %	EFS		OS	
						Y	%	Y	%
CCG 1961	262	16–21	2	3	4	5	72	5	78
DFCI 9101/9501	51	15–18	4	2	NR	5	78	5	81
Total Therapy XV	45	15–18	0	7	11	5	86	5	88
UKALL 2003	229	16–24	NR	6	6.1	5	72	5	76
FRALLE 2000	186	15–19	2	2	12	5	74	5	80
DCOG ALL-10	57	15–18	2.5	2.5	12	5	79	5	82
HOVON 100	***77***	***18–25***			***44%***	***5***	***59***	***5***	***77***
HOVON 100	***82***	***26–40***			***41%***	***5***	***61***	***5***	***72***

Courtesy of Anita Rijneveld and Lotte van der Wagen (HOVON study group)

EFS, relapse, and death in first remission by age



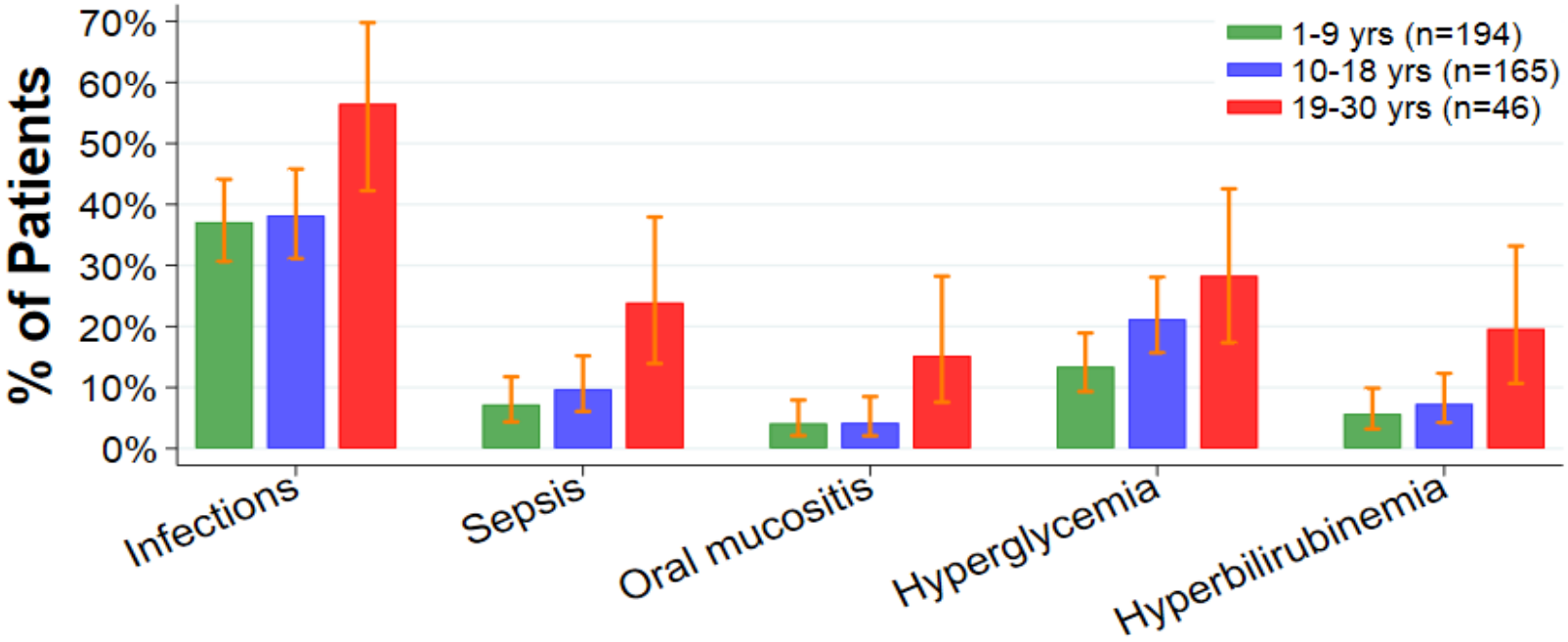
Toft N, 2018

Toxicity by age

	Y/N (%)	OR (95% CI)	P
Intensive care w/wo assisted ventilation			
1-9	145 / 864 (14.4%)	1.0 (1.0- 1.0)	
10-17	54 / 208 (20.6%)	1.3 (0.9- 1.9)	0.14
18-45	40 / 172 (18.9%)	1.1 (0.7- 1.6)	0.68
Anaphylatic reaction to asparaginase			
1-9	146 / 863 (14.5%)	1.0 (1.0- 1.0)	
10-17	25 / 237 (9.5%)	0.6 (0.4- 0.9)	0.016
18-45	11 / 201 (5.2%)	0.3 (0.1- 0.5)	<0.001
Invasive Fungal infection			
1-9	98 / 911 (9.7%)	1.0 (1.0- 1.0)	
10-17	32 / 230 (12.2%)	0.9 (0.6- 1.4)	0.68
18-45	28 / 184 (13.2%)	0.9 (0.5- 1.4)	0.54
Peripheral paralysis			
1-9	100 / 909 (9.9%)	1.0 (1.0- 1.0)	
10-17	30 / 232 (11.5%)	1.3 (0.8- 2.1)	0.21
18-45	20 / 192 (9.4%)	1.1 (0.7- 1.9)	0.61
Pancreatitis			
1-9	60 / 949 (5.9%)	1.0 (1.0- 1.0)	
10-17	29 / 233 (11.1%)	2.2 (1.3- 3.5)	0.001
18-45	24 / 188 (11.3%)	2.4 (1.4- 4.0)	0.001
Hyperlipidemia			
1-9	72 / 937 (7.1%)	1.0 (1.0- 1.0)	
10-17	26 / 236 (9.9%)	1.7 (1.0- 2.8)	0.027
18-45	15 / 197 (7.1%)	1.3 (0.7- 2.3)	0.37
Thrombosis			
1-9	36 / 973 (3.6%)	1.0 (1.0- 1.0)	
10-17	40 / 222 (15.3%)	5.0 (3.1- 8.2)	<0.001
18-45	37 / 175 (17.5%)	6.0 (3.6-10.1)	<0.001
Osteonecrosis			
1-9	23 / 986 (2.3%)	1.0 (1.0- 1.0)	
10-17	35 / 227 (13.4%)	8.0 (4.6-14.1)	<0.001
18-45	18 / 194 (8.5%)	5.3 (2.7-10.3)	<0.001
Seizures			
1-9	38 / 971 (3.8%)	1.0 (1.0- 1.0)	
10-17	16 / 246 (6.1%)	1.7 (0.9- 3.1)	0.086
18-45	5 / 207 (2.4%)	0.7 (0.2- 1.6)	0.39
PCP			
1-9	29 / 980 (2.9%)	1.0 (1.0- 1.0)	
10-17	11 / 251 (4.2%)	1.3 (0.6- 2.6)	0.48
18-45	13 / 199 (6.1%)	1.8 (0.9- 3.7)	0.089
PRES			
1-9	37 / 972 (3.7%)	1.0 (1.0- 1.0)	
10-17	9 / 253 (3.4%)	0.8 (0.4- 1.7)	0.60
18-45	5 / 207 (2.4%)	0.5 (0.2- 1.3)	0.18

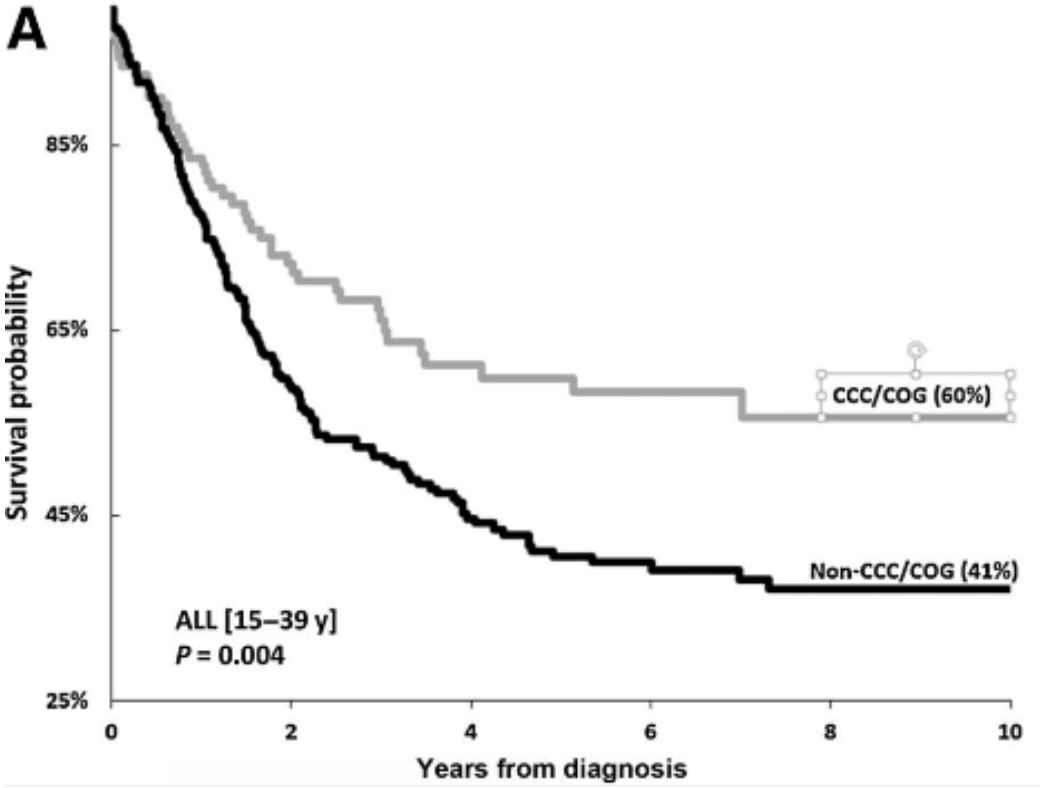
Toft N, 2018

Induction toxicities by age (COG first-relapse B-ALL clinical trial AALL1331)



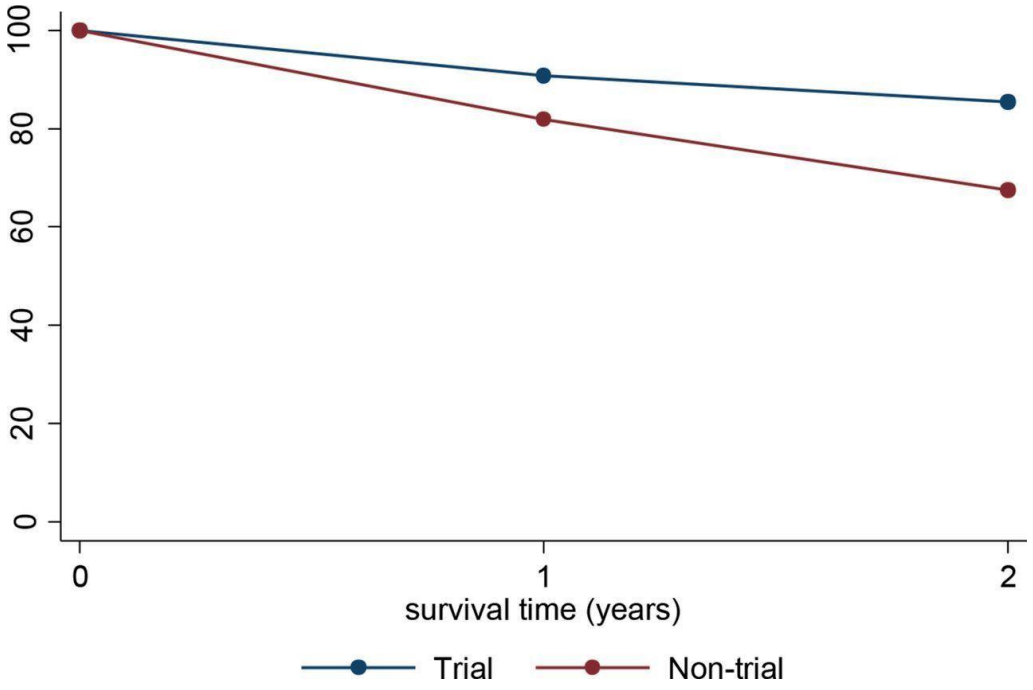
Hogan et al. *Blood.* 2018;132:1382 (courtesy of Mignon Loh)

Survival in AYA with ALL by treatment site in North America



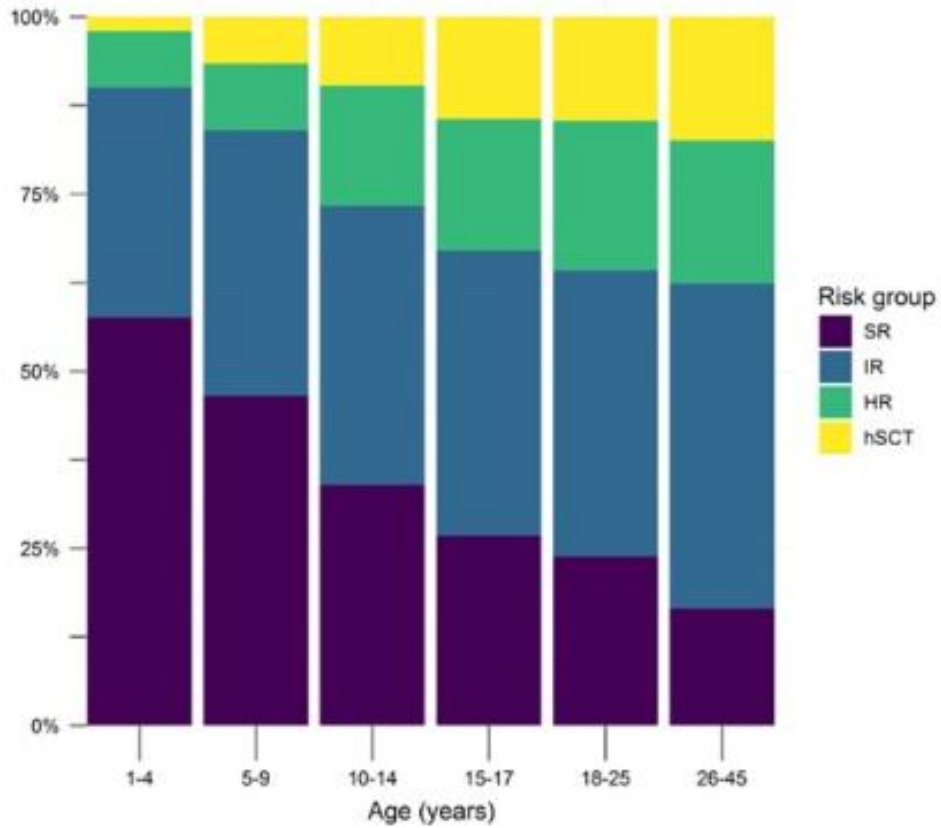
Wolfson J, 2017

Survival in 15- to 24-year-old ALL patients (n = 503) by trial status



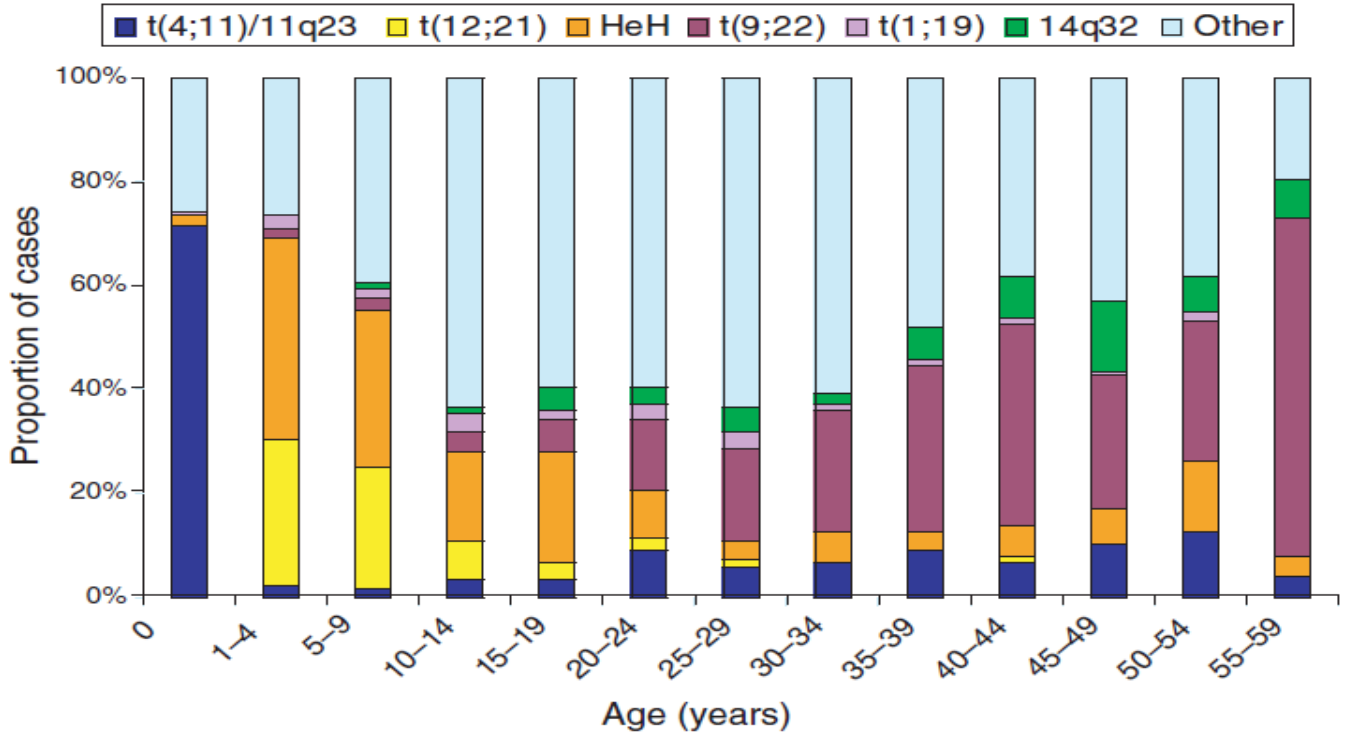
Hough R, 2017

Risk group distribution (MRD based) by age



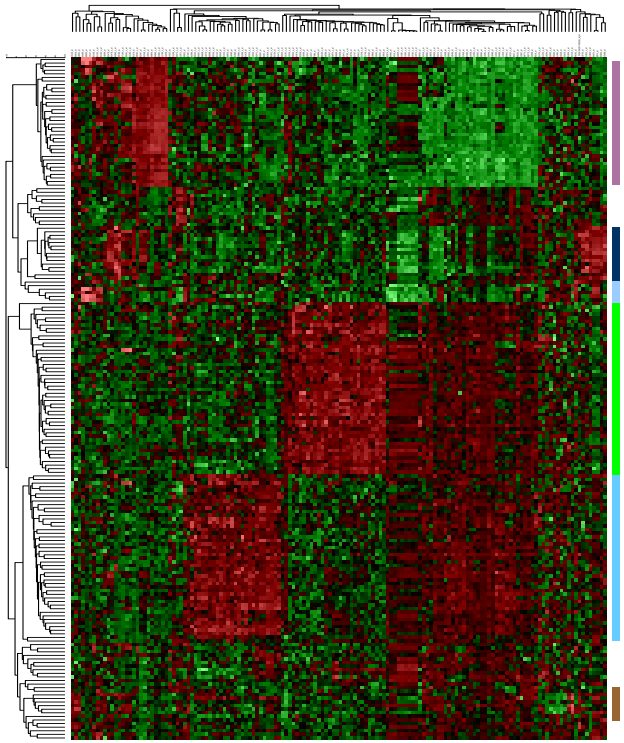
Toft N, 2018

Distribution of cytogenetic subtypes of ALL by age



Harrison, 2008

Discovery of *BCR-ABL1*–like ALL in 2009



T-ALL

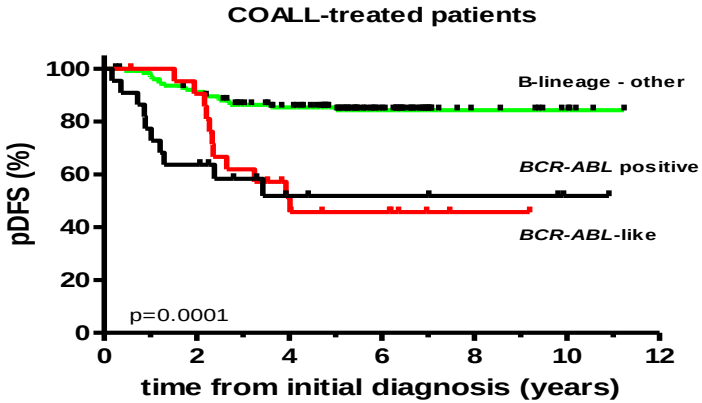
E2A-rearranged

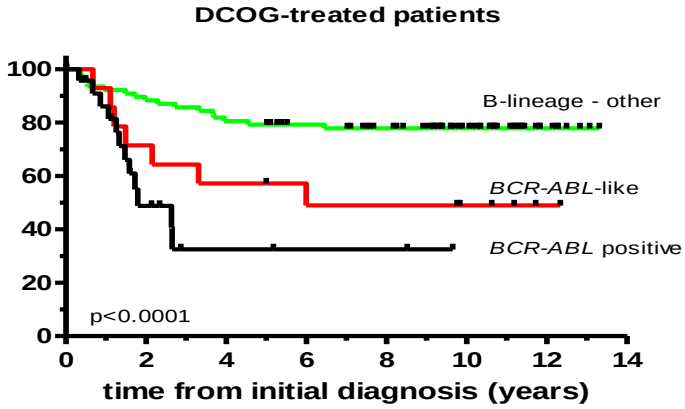
MLL-rearranged

TEL-AML1

Hyperdiploid

BCR-ABL1 } 5 real *BCR-ABL1*
30 *BCR-ABL1*–like





Den Boer et al. Lancet Oncol. 2009

Frequency of identified tyrosine kinase fusion genes in *BCR-ABL1*–like ALL and remaining B-other ALL

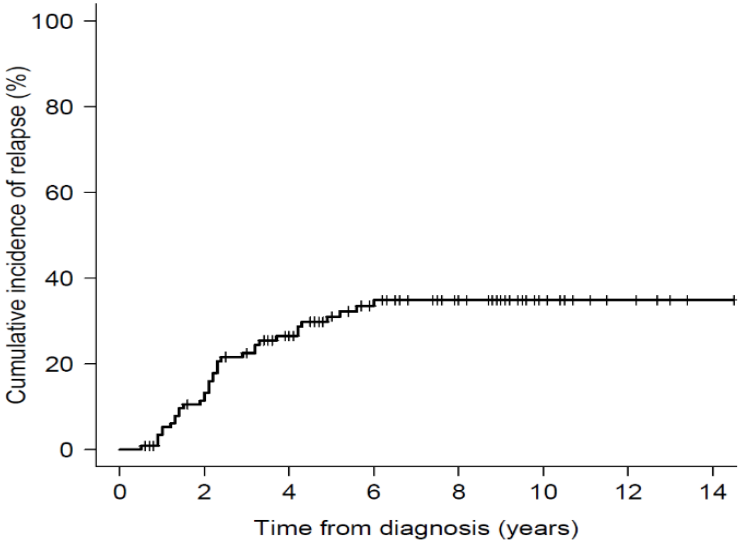
Marker	*BCR-ABL1*-like (n=77)	Remaining B-other (n=76)
***ABL1/ABL2* fusion**	**3.9%**	0%
ZMIZ1-ABL1	1	
FOXP1-ABL1	1	
RCSD1-ABL2	1	
***PDGFRB* fusion**	**5.2%**	0%
EBF1-PDGFRB	4	
***CSF1R* fusion**	**2.6%**	0%
SSBP2-CSF1R	2	
***JAK2* fusion**	**6.5%**	0%
PAX5-JAK2	3	
BCR-JAK2	1	
TERF2-JAK2	1	
CRLF2* high expression	15.6%	15.8%
PAR1 deletion**	10.5%	10.7%

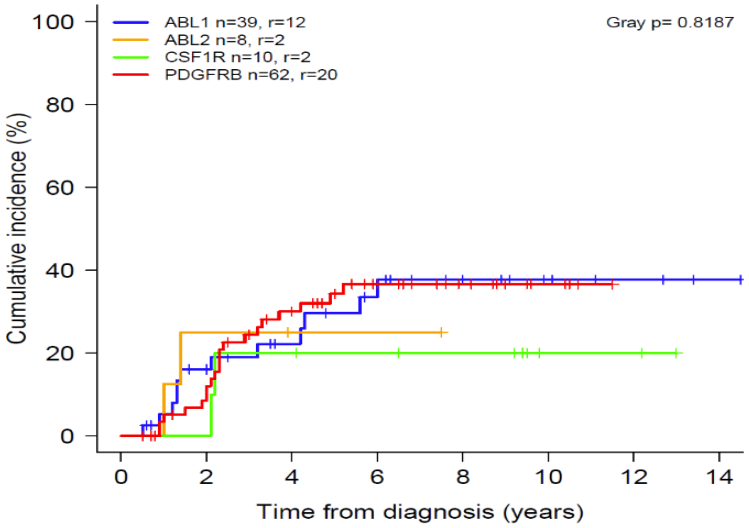
12% with **ABL-class** fusions
Targetable with TKI, eg, imatinib/dasatinib

6% with *JAK2* fusions
Targetable with ruxolitinib????

Boer, Oncotarget 2016

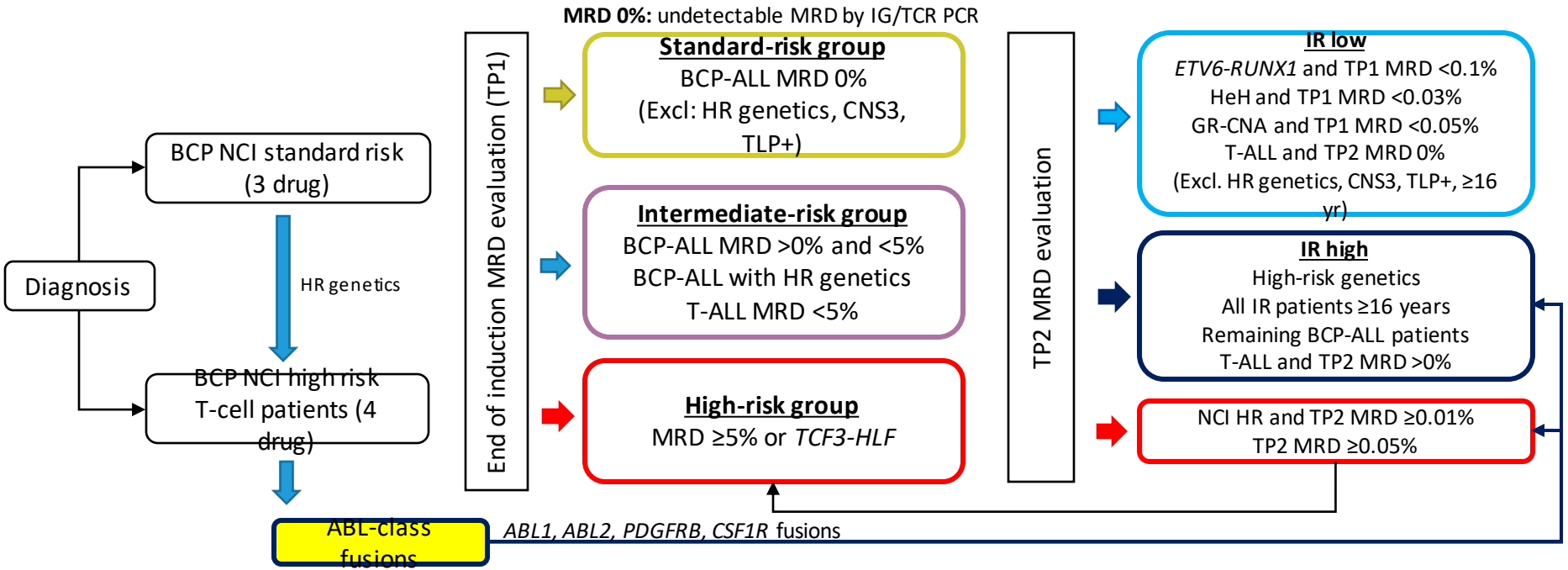
Cumulative incidence of relapse in ABL-class patients





Den Boer ML, Lancet Haematol 2020

Risk-stratification algorithm

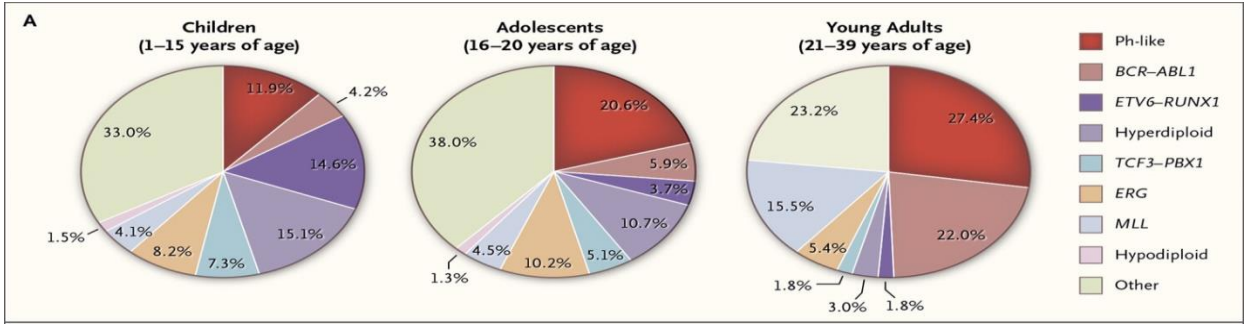


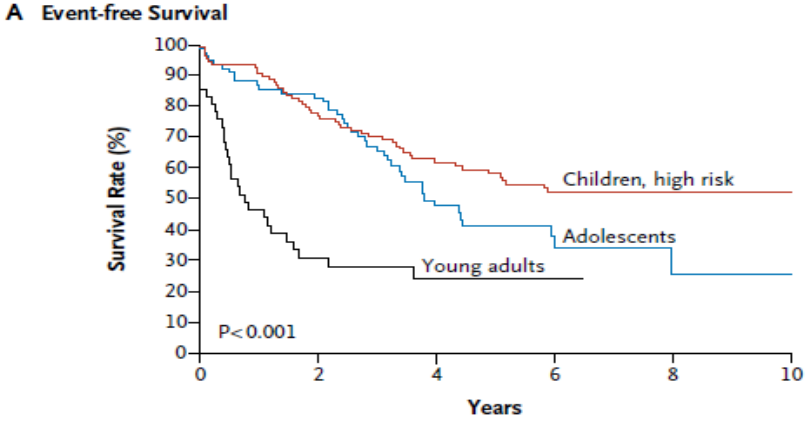
High-risk genetics: *KMT2A/MLL* fusions, near haploidy, low hypodiploidy, iAMP21

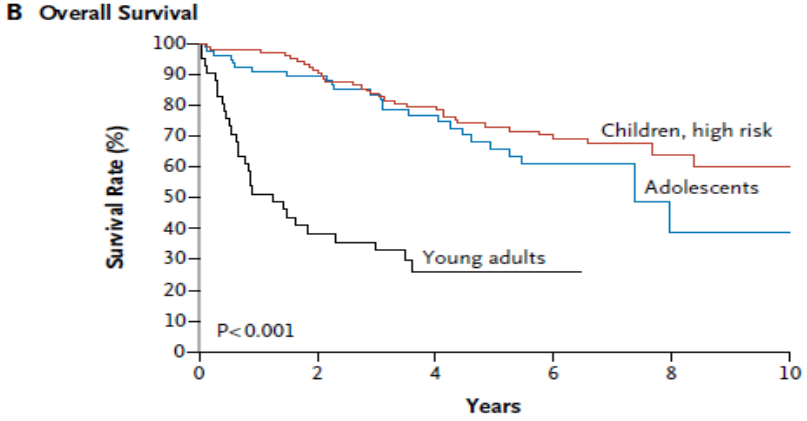
GR-CNA profile

- No deletion of *IKZF1, CDKN2A/B, PAR1, BTG1, EBF1, PAX5, ETV6, RB1*
- Isolated deletions of *ETV6, PAX5, BTG1*
- *ETV6* deletions with a single additional deletion of *BTG1, PAX5, CDKN2A/B*

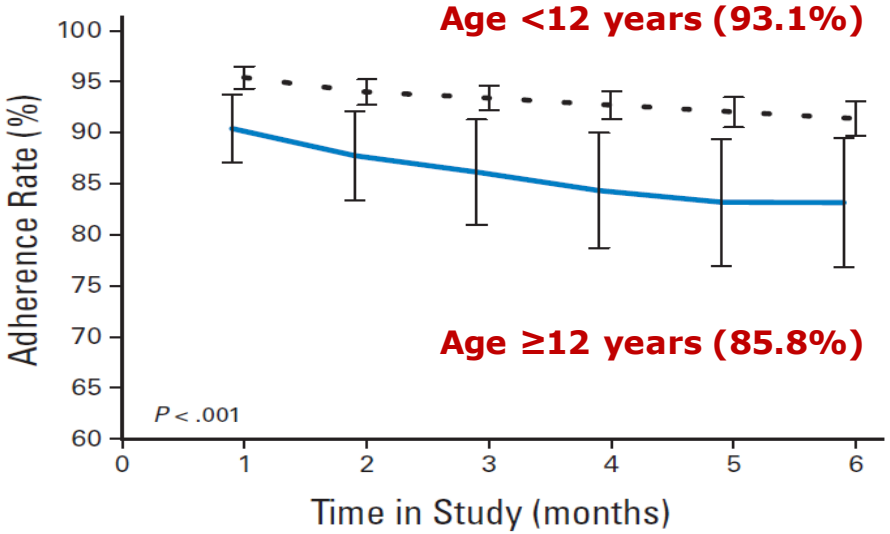
Ph-like ALL: Prevalence and outcomes

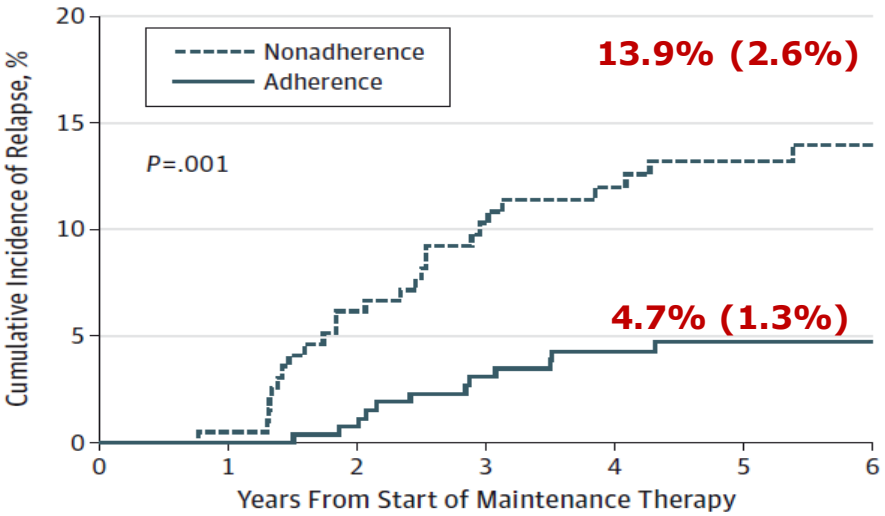






Low adherence to oral 6-MP significantly increases relapse risk and depends on age





Bhatia et al. *J Clin Oncol.* 2012;30:2094-2102 and *JAMA Oncol.* 2015;3:287–295 (courtesy of Mignon Loh)

AYA conclusions

- Outcomes improved but still inferior to those in younger children
- Pediatric-inspired protocols better than adult-inspired protocols
- Treatment within trials – better outcomes
- Higher toxicity in AYA than in younger children, but manageable
- Higher incidence of unfavorable biology/genetics
- Lower adherence to medication

Answer to Question:
Which assertion is NOT correct for adolescent and young adult ALL patients?

1. Pediatric-inspired protocols lead to a better outcome than adult-inspired protocols
2. Osteonecrosis and anaphylactic reactions to asparaginase are more often seen in adults than in children and teenagers
3. AYA patients experience more liver toxicity and thrombosis than children <10 years old
4. *BCR-ABL1*–like ALL is more frequent in AYA ALL than in children <10 years old with ALL

Thank you

Global Leukemia Academy

Debate on sequencing CD19-targeted approaches in ALL

Franco Locatelli

APTITUDE HEALTH

Question

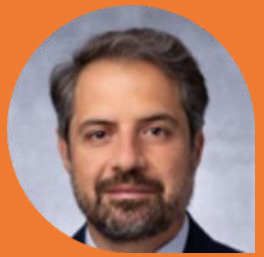
What is your preferred ALL treatment choice in salvage if all these therapies were available in your country?

1. CAR T therapies
2. Monoclonal antibodies or bispecifics

Global Leukemia Academy

Monoclonal antibodies and bispecifics first

Elias Jabbour



APTITUDE HEALTH

Management of R/R B-Cell Acute Lymphocytic Leukemia: Bispecifics and ADC

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

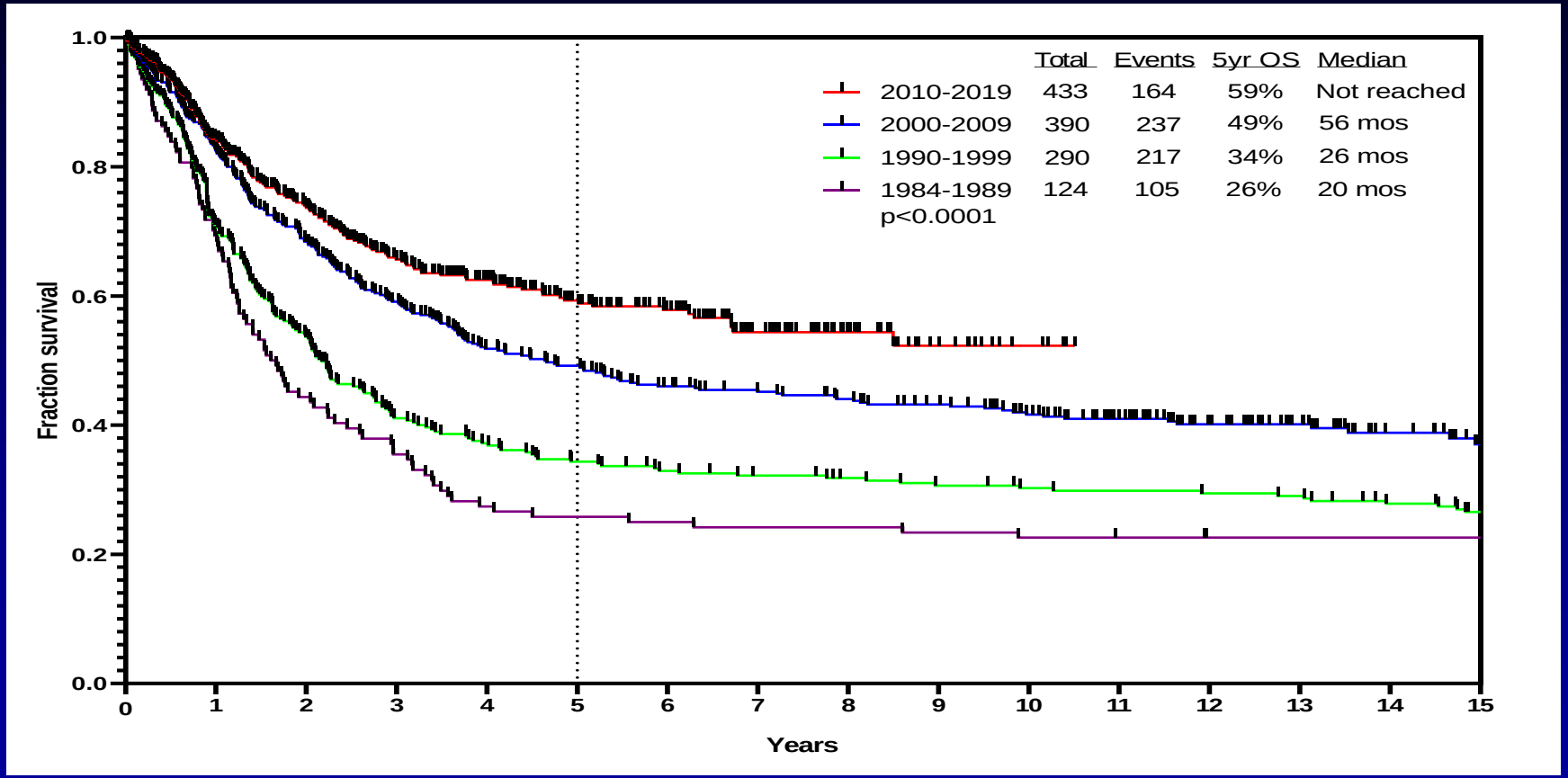
GLA, 2022

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)

Historical Results in R/R ALL

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

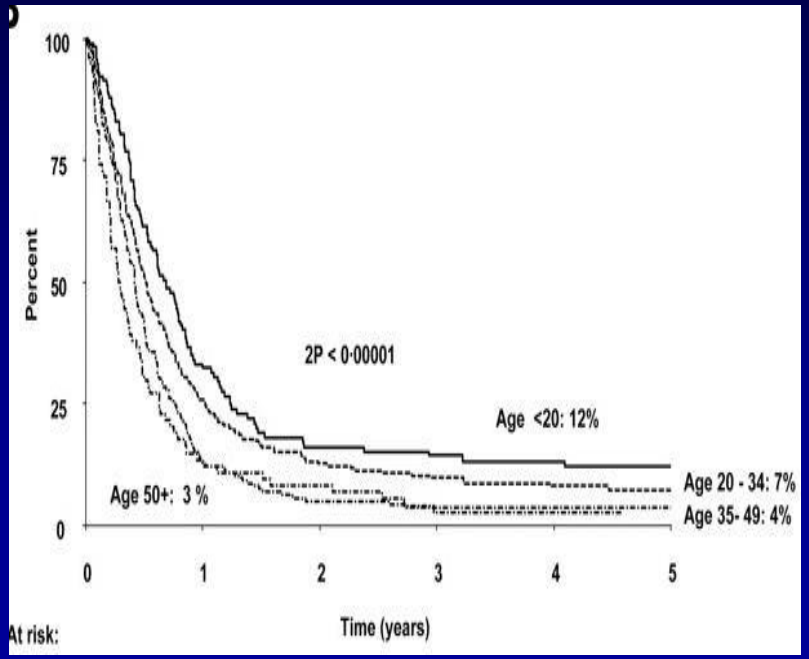
Rate (95% CI)	No prior salvage (S1)	One prior salvage (S2)	≥2 prior salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.8	3.4	2.9

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

ALL – Historical Survival Rates After First Relapse

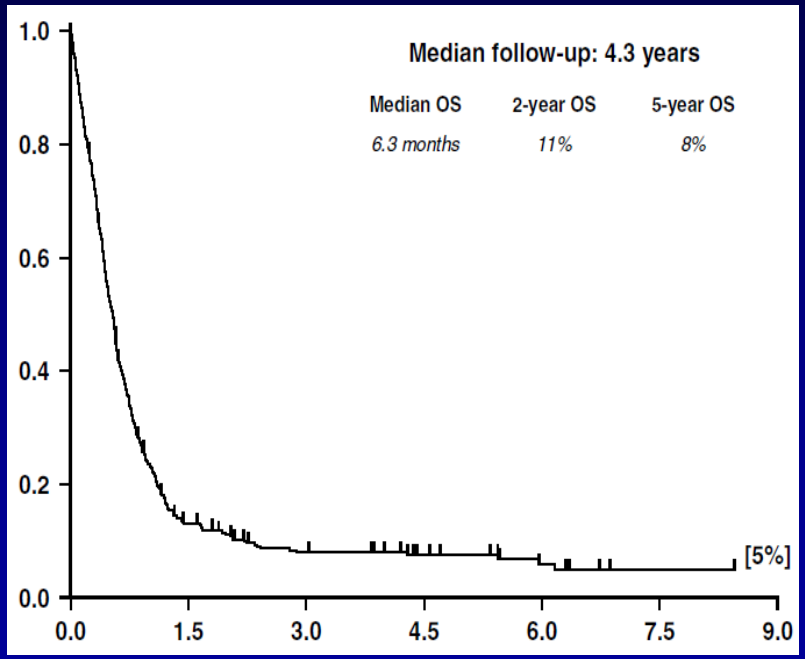
MRC UKALL2/ ECOG2993 Study (n = 609)

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



LALA-94 Study (n = 421)

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



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

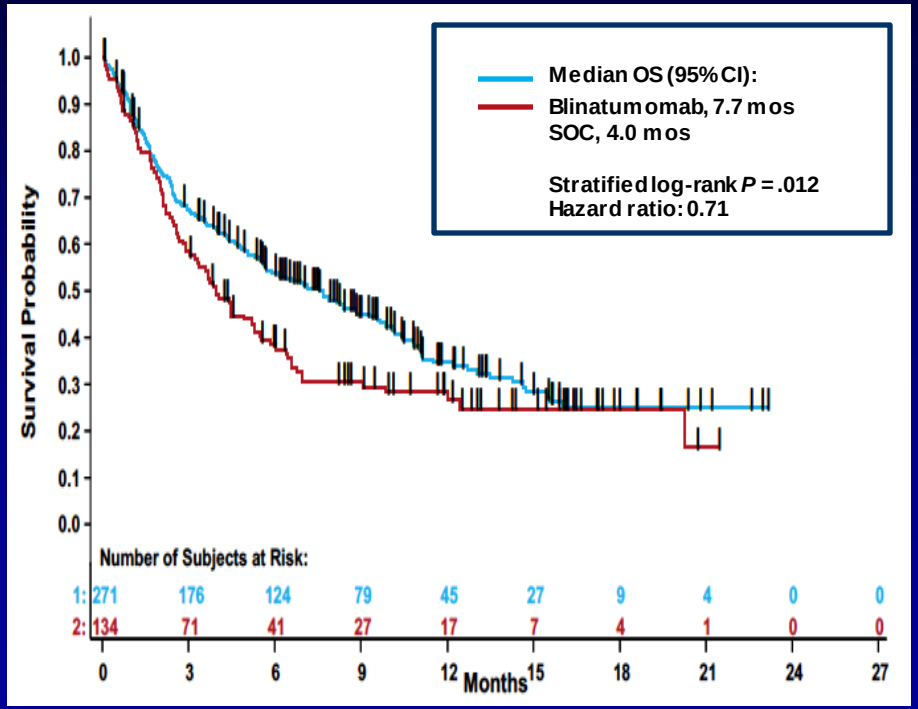
ALL Salvage Standards of Care in 2022

- Refer for investigational therapies – mini-CVD-ino-blina; CAR T
- Ph+ ALL – TKIs (ponatinib preferred) + chemoRx/blinatumomab
- Pre-B ALL
  - Blinatumomab (FDA approval 12.2014)
  - Inotuzumab (FDA approval 8.2017)
  - CAR Ts (FDA approvals 8.2017 and 10.2021)
- T ALL: nelarabine
- ChemoRx: FLAG IDA, Hyper CVAD, augmented HCVAD, MOAD
- BUT – very promising new therapies with chemoRx + TKIs/BCL2i (venetoclax; navitoclax)/ADCs/BiTEs/CAR Ts

Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

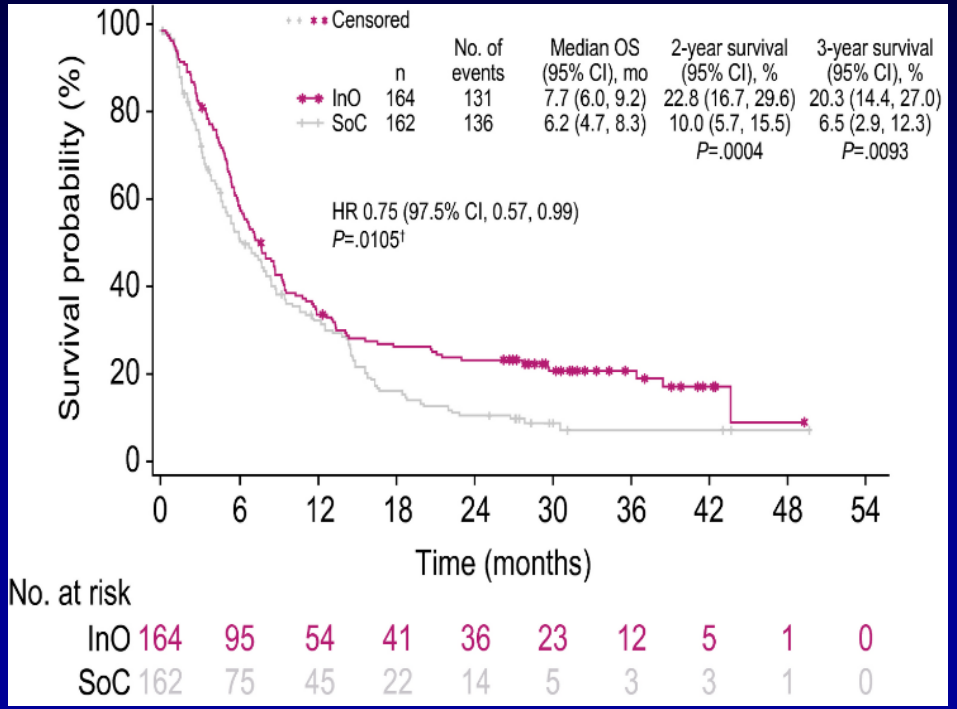
- **Marrow CR**

Blina vs SOC: 44% vs 25%



Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

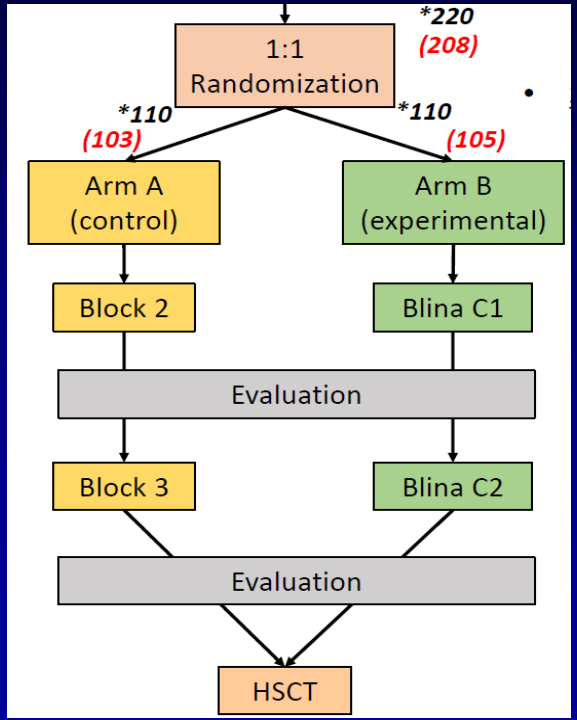
Ino vs SOC: 74% vs 31%



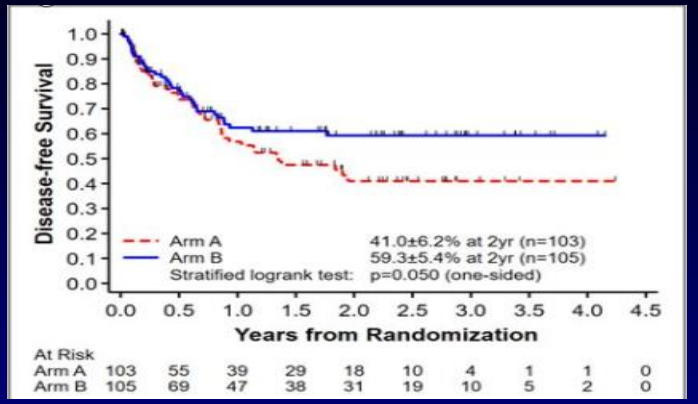
Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

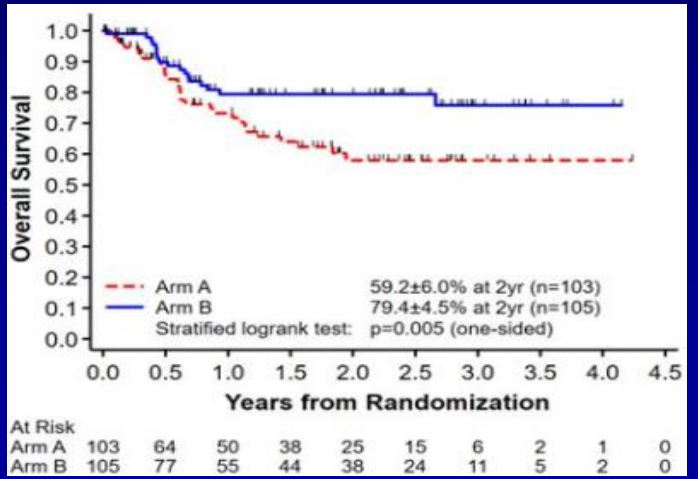
Phase III Study of Blinatumomab vs ChemoRx in Children-AYA in Salvage 1

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



Parameter	Blina	Chemo	*P*
% 2-yr DFS	59	41	.05
% 2-yr OS	79	59	.005
% SCT	73	49	<.001
% MRD clearance	79	21	<.001





Brown et al. *JAMA*. 2021:325(9):833-842.

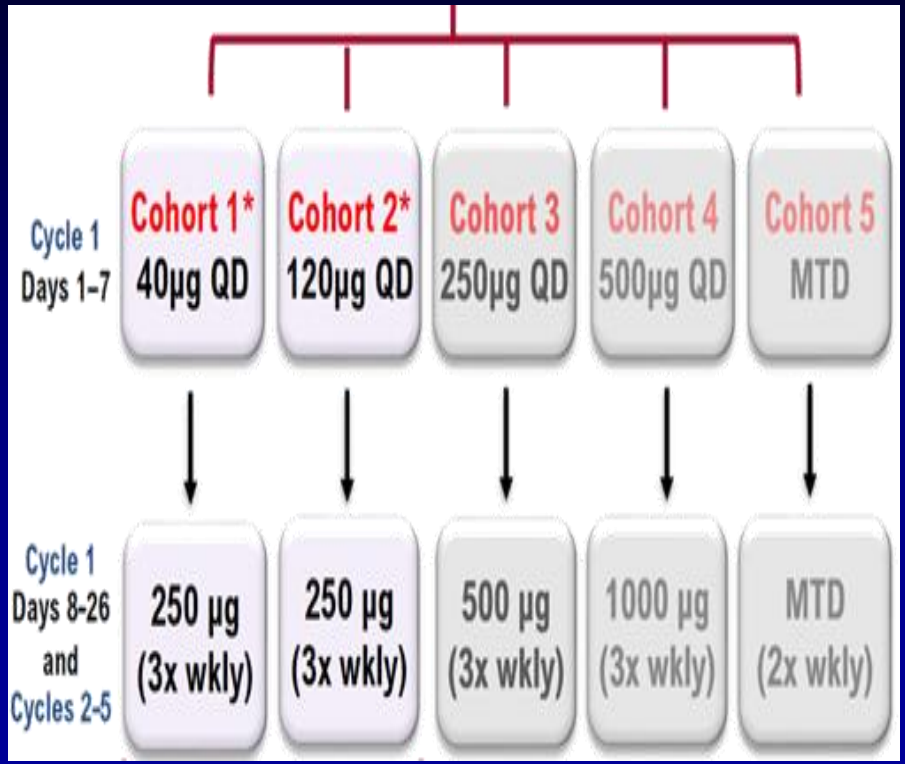
Phase II Study of Inotuzumab in R/R Pediatric ALL

- 32 pts enrolled, 28 Rx, 27 evaluable
- Median age 7.5 yrs (1.7–17). S2+ 57%. Prior blina 25%; prior ASCT 50%; prior CAR T Rx 11%
- Inotuzumab weekly ×3 up to 6 courses
  - RP2D 1.8 mg/m^2 (0.8-0.5-0.5)
- ORR = 81.5% (CR 50%); MRD– 95% (82% after C1)
- 64% proceeded to ASCT and 14% to CAR T Rx
- 12-mos EFS 23%; 12-mos OS 46.5%
- 6 VOD (22%): 1 during InO; 5/14 post ASCT (36%)

Brivio et al. *Blood*. 2020;136:abstract 164.

Subcutaneous Blinatumomab in R/R B-ALL: Phase Ib Dose-Finding Study

- 9 R/R pts, median age 64 yrs (38–83)
- Rx in with SC blinatumomab in 2 cohorts; median BM blast 79% (range, 28%–95%)
- Median prior therapies = 2 (range, 2–4)
- 5/9 achieved MRD-negative CR, 3 in Cohort 1 (3/6, 50%) and 2 in Cohort 2 (2/3, 66%)
- All patients who achieved CR did so within the first treatment cycle



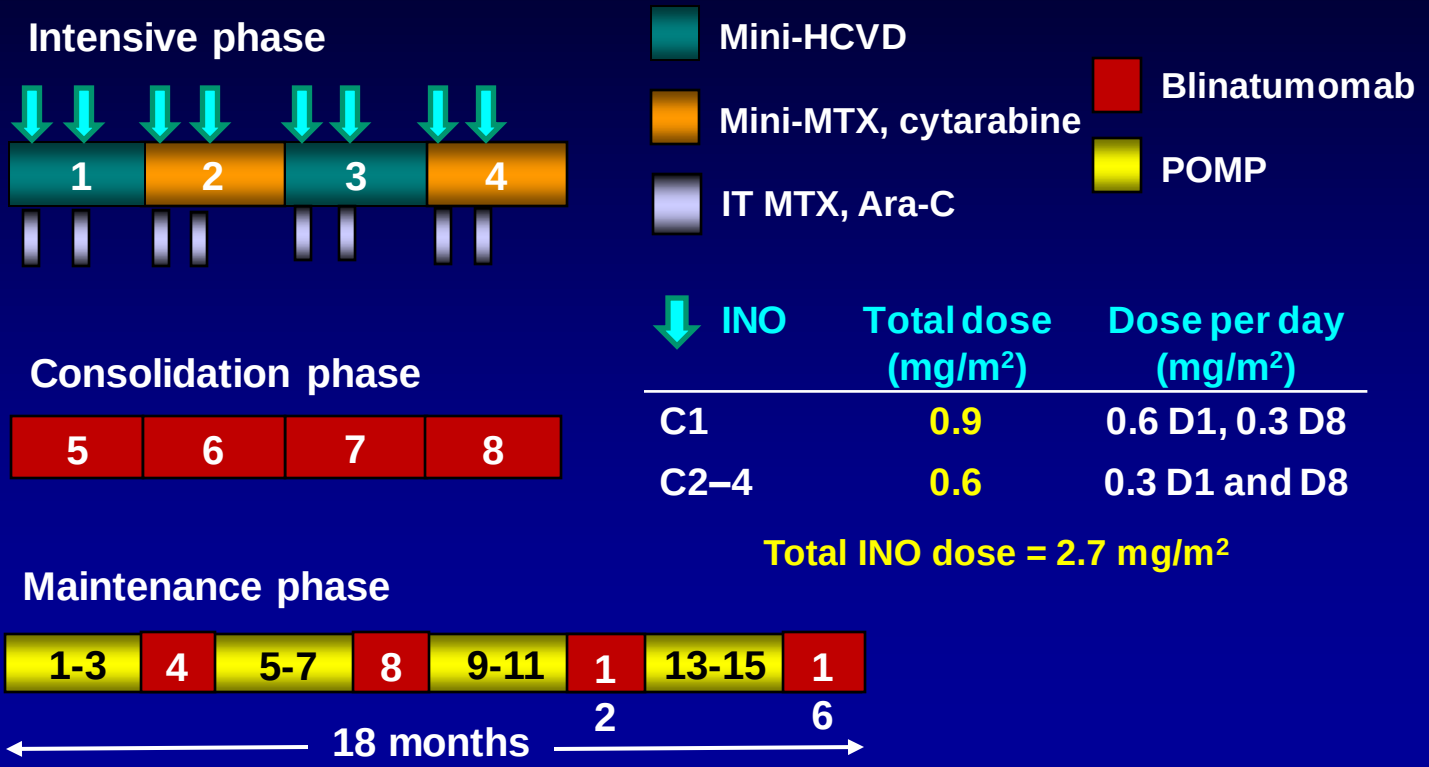
Martínez-Sánchez. *Blood*. 2021;138:abstract 2303.

Mini-HCVD-INO ± Blina in ALL: Design

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

Jabbour E, et al. *JAMA Oncol*. 2018;4(2):230-234; Jabbour E, et al. *Cancer*. 2021;127(12):2025-2038.

Mini-HCVD + INO ± Blina in R/R ALL: Long-Term Follow-Up



INO	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D1, 0.3 D8
C2–4	0.6	0.3 D1 and D8

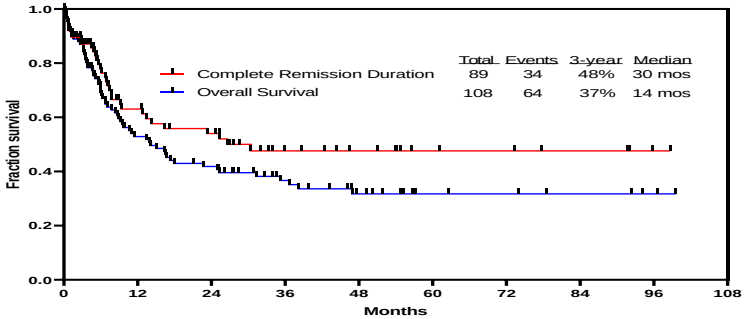
Total INO dose = 2.7 mg/m²

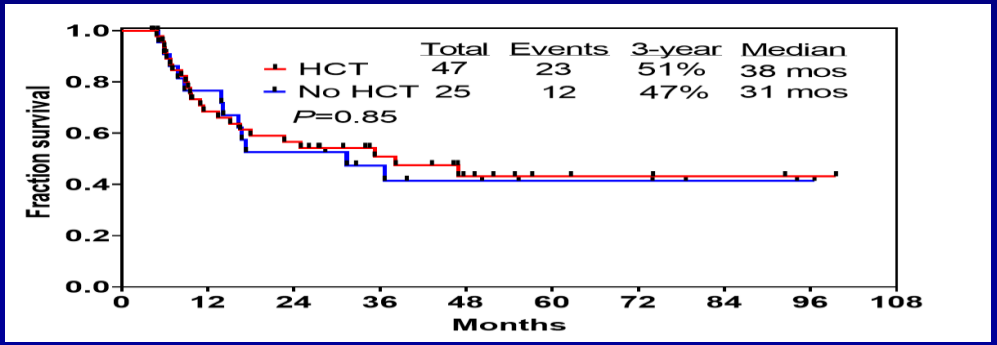
Sasaki et al. *Blood*. 2020;136:abstract 1895.

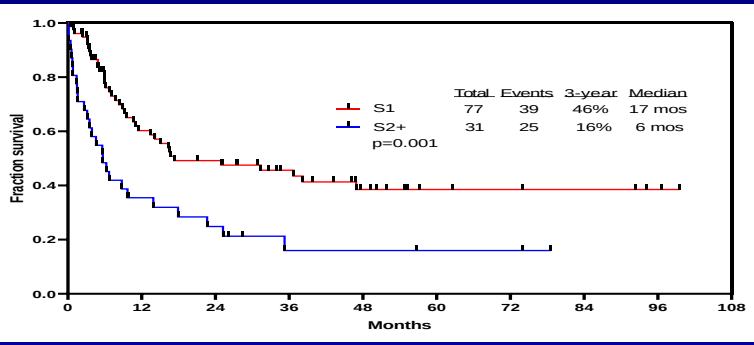
Mini-HCVD + INO in R/R ALL: Outcomes (N = 108)

Response	N (%)
Salvage 1	71/77 (93)
S1, primary refractory	14 (100)
S1, CRD1 <12 mos	21 (84)
S1, CRD1 ≥12 mos	36 (95)
S2	10 (59)
≥S3	8 (57)
ORR	89 (83)
MRD negativity	71/87 (82)
S1	59/69 (86)
≥S2	12/18 (67)
Early death	7 (6)*

	Single dose N = 67	Fractionated / reduced N = 41
VOD	9 (13)	1 (2)

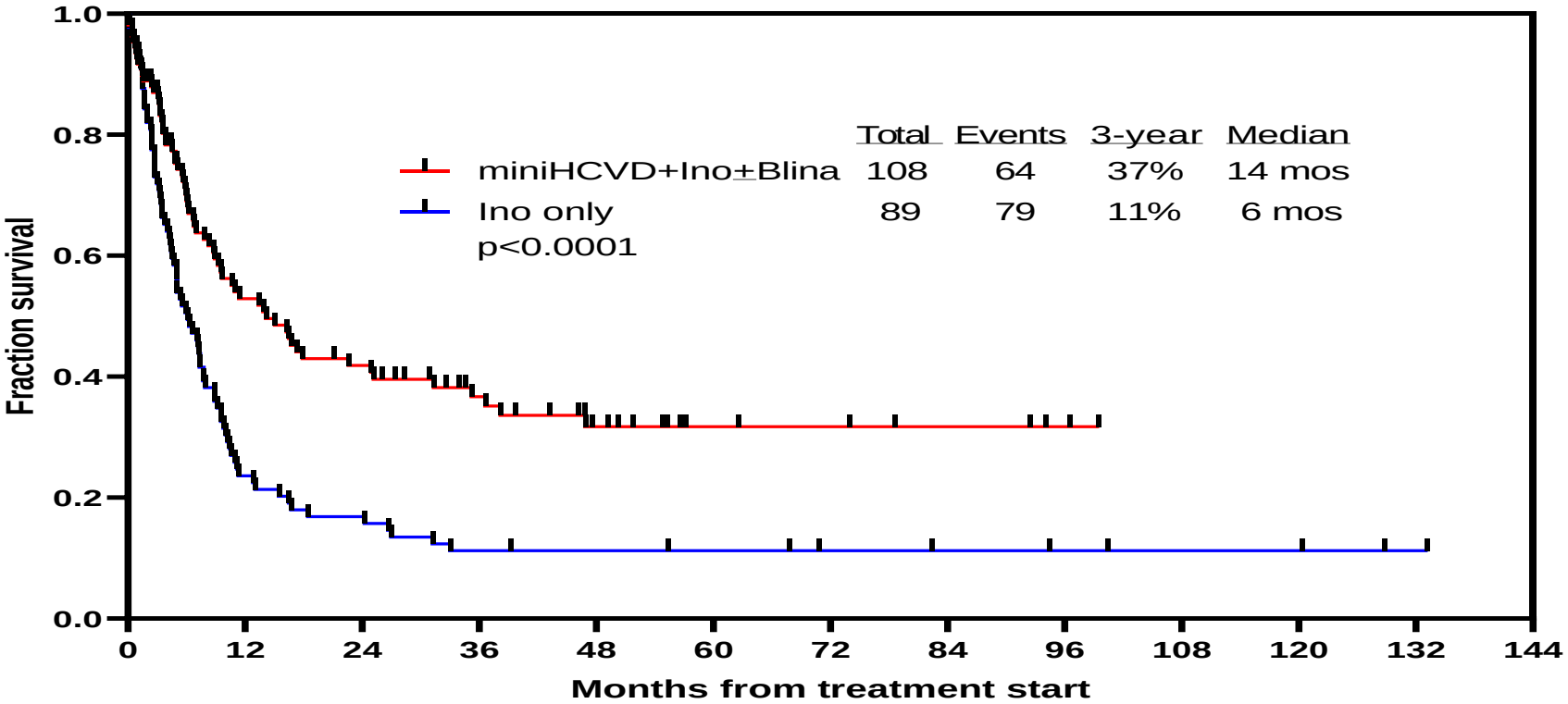






Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055.

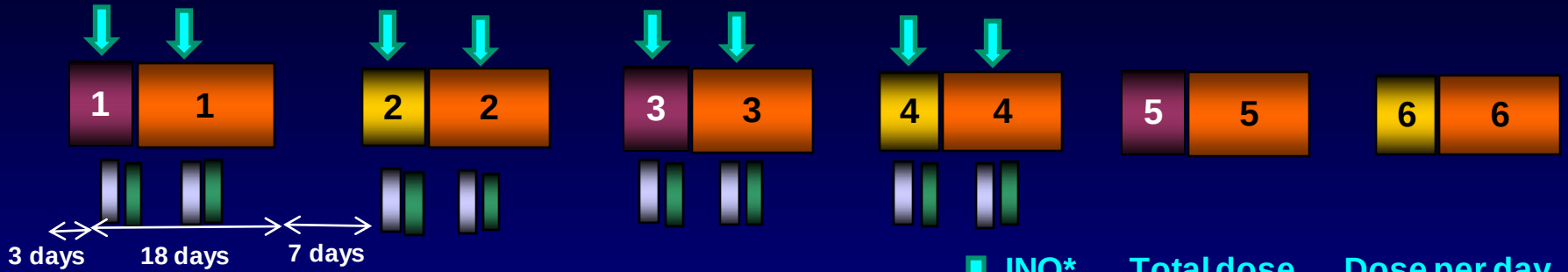
Mini-HCVD + INO ± Blina in R/R ALL: Historical Comparison



Jabbour E, et al. *JAMA Oncol.* 2018;4(2):230-234; Jabbour E, et al. *Cancer.* 2021;127(12):2025-2038.

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

Intensive phase: C1–C6



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

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Maintenance phase

Mini-HCVD

Rituximab

Blinatumomab

Mini-MTX, Ara-C

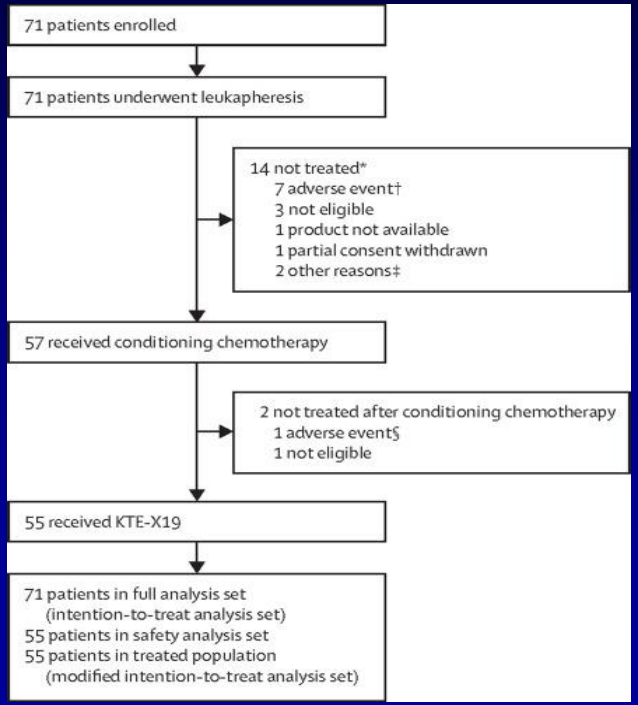
IT MTX, Ara-C

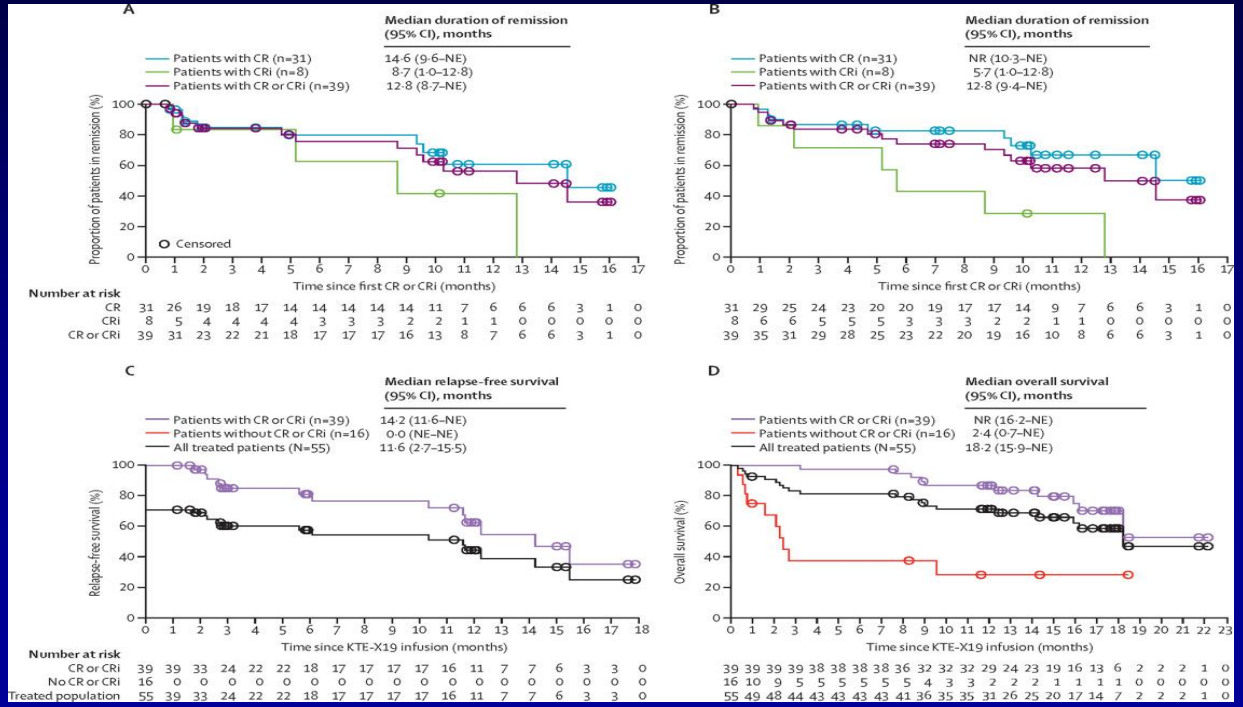
POMP

VCR/Steroid

KTE-X19 Anti-CD19 CAR T Cells RX (Kite) in R/R ALL: Phase II (ZUMA-3)

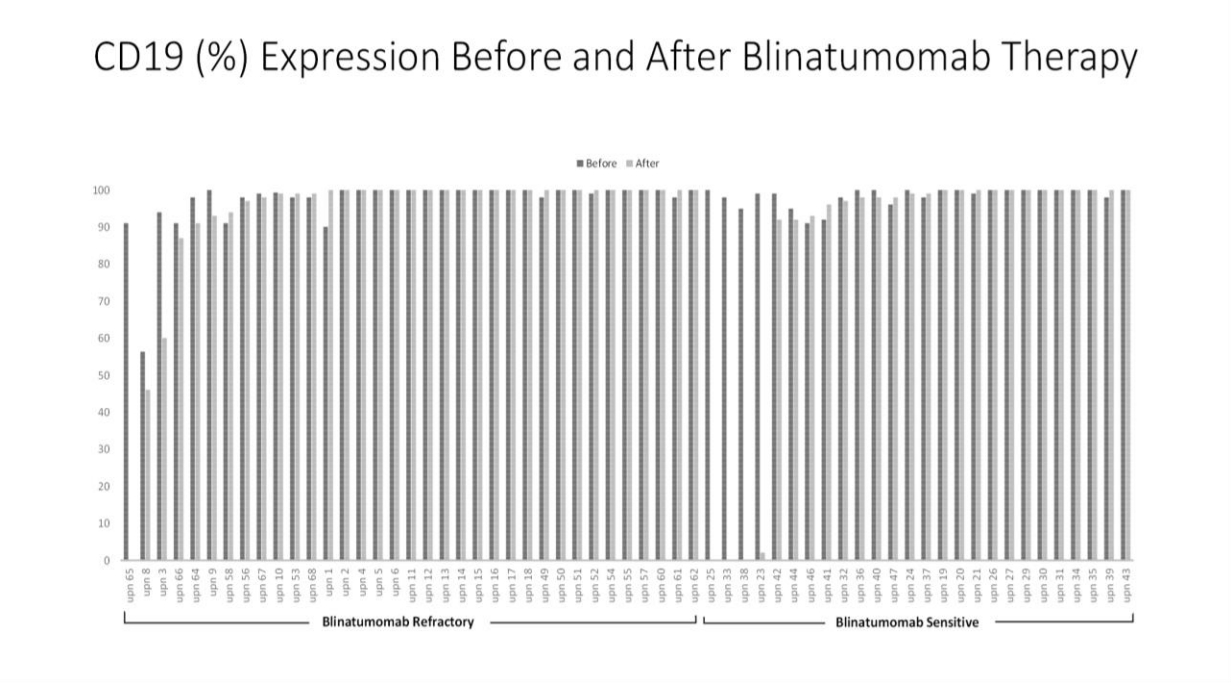
- 71 enrolled, 55 infused; median age 40 yrs (28–52)
- CR/CRi 39/55 (71%, CR 56%); ITT (39/71; 55% – CR 44%); MRD– response 76% (97% among responders); 10 pts (18% Rx ASCT)
- mDOR 12.8 mos; mRFS 11.6 mos; mOS 18.2 mos
- Grade ≥3: CRS 24%; NE 25%





Shah et al. *Lancet*. 2021;S0140-6736.

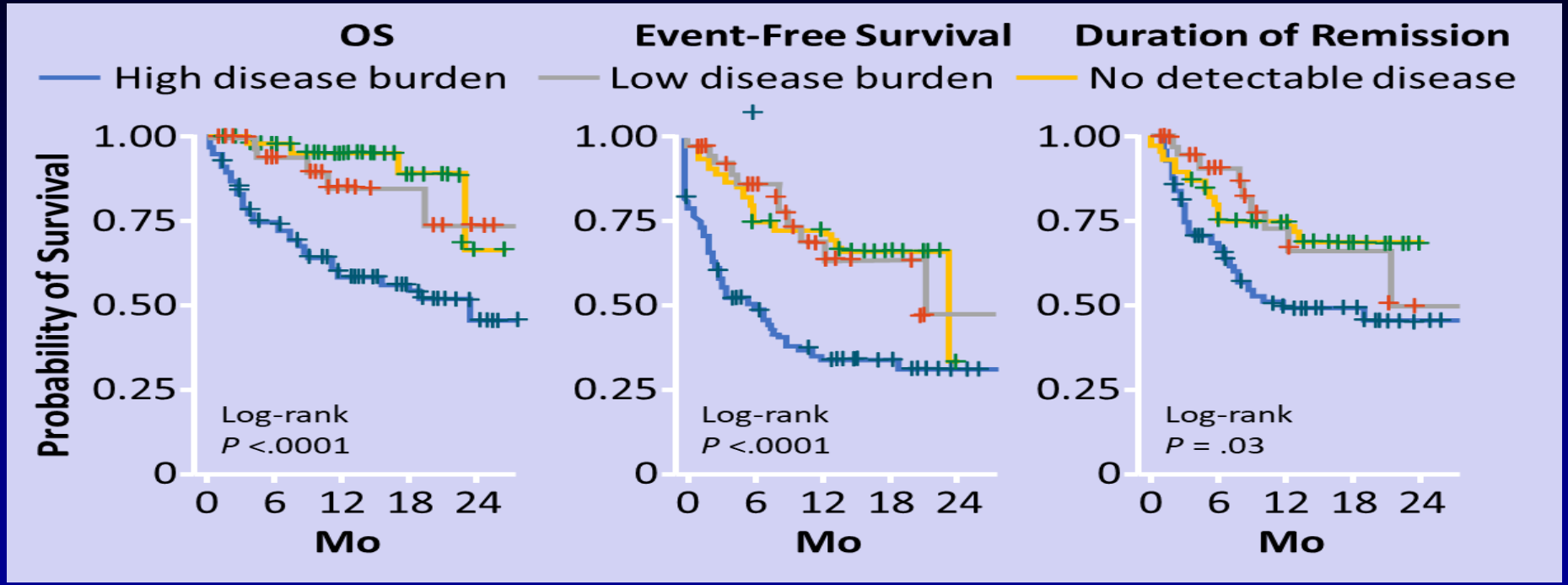
CD19 (%) Expression Before and After Blinatumomab Therapy



- 61 patients evaluated for immunophenotype, 56 (92%) had CD19-positive disease
  - 5 (8%) had ALL recurrence with CD19-negative disease
  - 2 patients progressed with lower CD19-positive disease

Jabbour et al. *Am J Hematol.* 2018;376:836-847.

Real-Word CAR Consortium and Disease Burden



High Burden Disease (n = 94; 47%)

- 1-yr OS 58%
- 1-yr EFS 34%

Low Burden Disease (n = 60; 30%)

- 1-yr OS 85%
- 1-yr EFS 69%

Undetectable Disease (n = 46; 23%)

- 1-yr OS 95%
- 1-yr EFS 72%

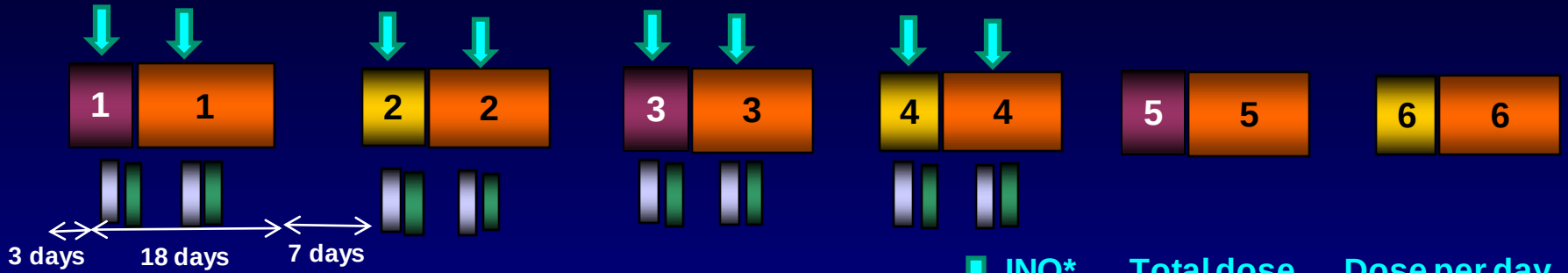
Schultz et al. *Blood*. 2020;136.abstract 468.

CAR T in ALL – The Beginning of a Great Journey

- CART Rx today is what allogeneic SCT was in 1980 – a great beginning
- Improved CAR T designs
- Dual CAR Ts targeting CD19, CD22, CD20
- Allogeneic off-the-shelf CAR Ts
- Smaller repeated allogeneic CAR Ts infusions (fractionated CAR Ts)
- CAR Ts in first CR in MRD to replace alloSCT

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

Salvage Therapies in ALL: Conclusions

- Very effective salvage therapy in R/R ALL
  - High MRD negativity rate
  - Best outcome in Salvage 1
- Combination with low-dose chemotherapy
  - Safe and effective
  - Median survival 14 months
  - Salvage-1: 24 months (2-year OS rate >50%)
- AE better controlled
  - CRS: debulk with sequential chemotherapy
  - VOD lower doses explored
- CAR T cells RX offered post blinatumomab and inotuzumab failure – Complementary
  - Salvage-2 and high-risk Salvage-1 (eg, MLL)
  - Consolidation in high-risk patients (replacing allo-SCT)
- Better "blinatumomab" and "inotuzumab" needed
  - Better "Blina": Long half-life; SQ; no neurotoxicities
  - Better "InO": no VOD

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

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

CAR T first

José Maria Ribera

APTITUDE HEALTH

Recent Improvements in ALL Therapy

ALL Subtype	Improvements
Ph+	More potent TKI upfront: ponatinib Attenuation of chemotherapy **Immunotherapy in first line combined with TKI** **CAR T for R/R**
Ph–	HSCT vs CHT according to MRD Rituximab in first line **Blinatumomab in first line (MRD+, elderly, young adults)** TKI, JAK-2 inhibitors in Ph-like ALL (clinical trials) **CAR T for R/R**
T-ALL	Nelarabine upfront (children, adults?) BCL2/BCLX inhibitors (venetoclax, navitoclax) in R/R **MoAb (daratumumab, isatuximab) in R/R** **CAR T (early phases of development) in R/R**
All subtypes	Drug profiling for R/R pts

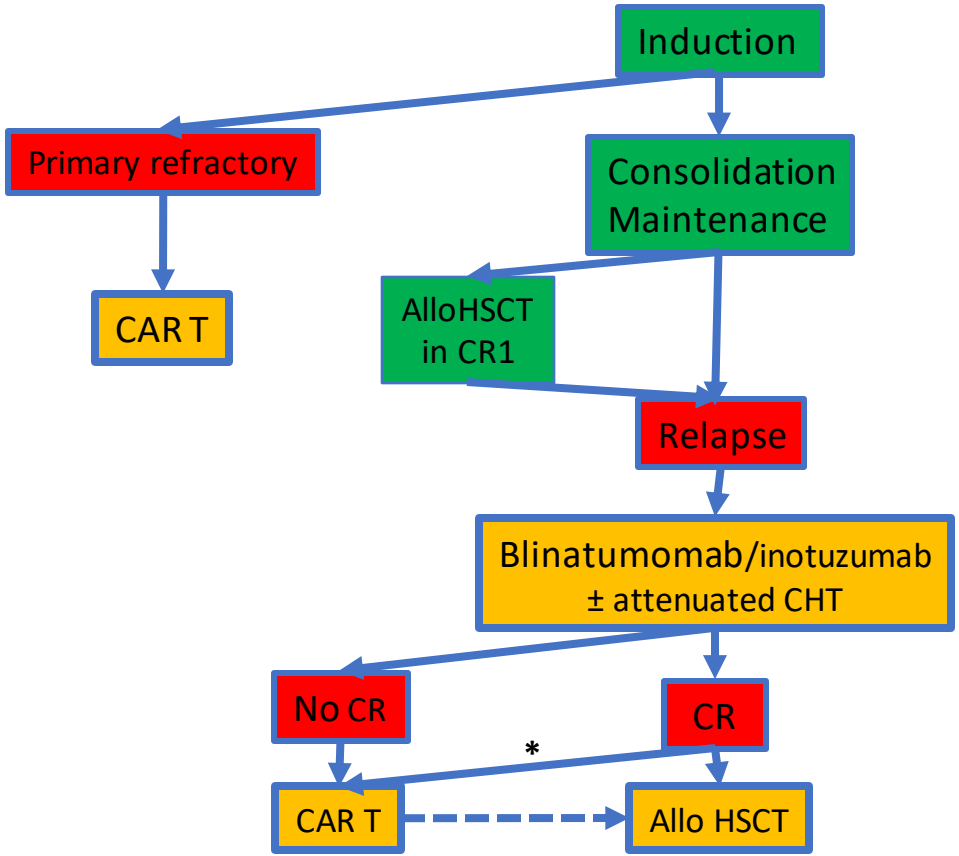
Approved Immunological Therapies for B-Cell Precursor ALL

	Blinatumomab		Inotuzumab	Brexucabtagene autoleucel	Tisa-cel
FDA approval	2014		2017	2021	2017
Approved indication	CD19+ BCP R/R adults & children MRD+ BCP CD19+ ALL		R/R CD22+ ALL in adults	Adults R/R BCP ALL	BCP children & AYA (≤25 yr)
Clinical trial	BLAST	TOWER	INO-VATE	ZUMA-3	ELIANA
N Pts (ITT)	118	405	326	71	97
N (evaluable)	113/110	376	326 (OS/PFS) 218 (CR)	55	79
CR/CRi (%)	-	43.9 vs 24.6 (ITT)	80.7 vs. 29.4 (evaluable)	71 (evaluable)	82.3 (evaluable)
RFS/PFS/EFS	mRFS 18.9 m (evaluable)	6m EFS: 31% v. 12% (ITT)	mPFS: 5.0 vs 1.8 m (ITT)	mRFS 11.6 m (evaluable)	18m RFS: 66% (evaluable)
OS	mOS 36.5 (evaluable)	mOS 7.7 vs 4.0 (ITT)	mOS 7.7 vs 6.7 (ITT)	mOS 18.2 m (evaluable)	18m OS: 70% (evaluable)
G ≥3 AE (%)	60	86.5 vs 91.7	46 vs 43	95	-
G ≥3 CRS (%)	1.7	4.9 vs 0.0	-	24	48
G ≥3 neurol ev.	13	9.4 vs 8.3	-	25	13

MoAb vs CAR T Cells in ALL

There is no (or little) debate

The Present



*In previously transplanted patients.

The Future

MoAb

- **Ph+ ALL**
  - TKI+ MoAb in newly diagnosed patients
  - Reduced use of HSCT
- **Ph– ALL**
  - Attenuated chemotherapy + MoAb as first-line therapy
  - HSCT for MRD+ patients

CAR T cells

- **B-cell precursor ALL**
  - Use in first line in very-high risk patients (poor genetics and MRD+)
- **T-ALL**
  - CAR T in R/R status

Immunotherapy in Early Phases of Ph– ALL: Results From Phase II Trials

Group	Chemotherapy	MoAb	N pts	Median age (range)	CR after induction	MRD– after induction	OS (y)
MDACC[1]	Mini HyperCVD	Ino ± Blin	78	68 (60–87)	86%	80%	46% (5y)
EWALL[2]	EWALL backbone	Ino	90	69 (55–84)	88.8%	73%	78.5% (1y)
GMALL[3]	EWALL backbone (in consolidation)	Ino (single-drug induction)	43	64 (56–80)	100%	74%	77% (2y)
SWOG[4]	POMP (maintenance only)	Blin (single-drug induction)	29	75 (66–84)	65.5%	NA	37% (3y)
GRAALL[5]	Standard induction + consolidation	Blin	94	35 (18–60)	NR	74%	92% (1y)
GMALL[6]	EWALL backbone	Blin	33	65 (56–76)	83%	69%	84% (1y)
MDACC[7]	HyperCVAD	Blin	38	37 (17–59)	81%	85%	83% (3y)

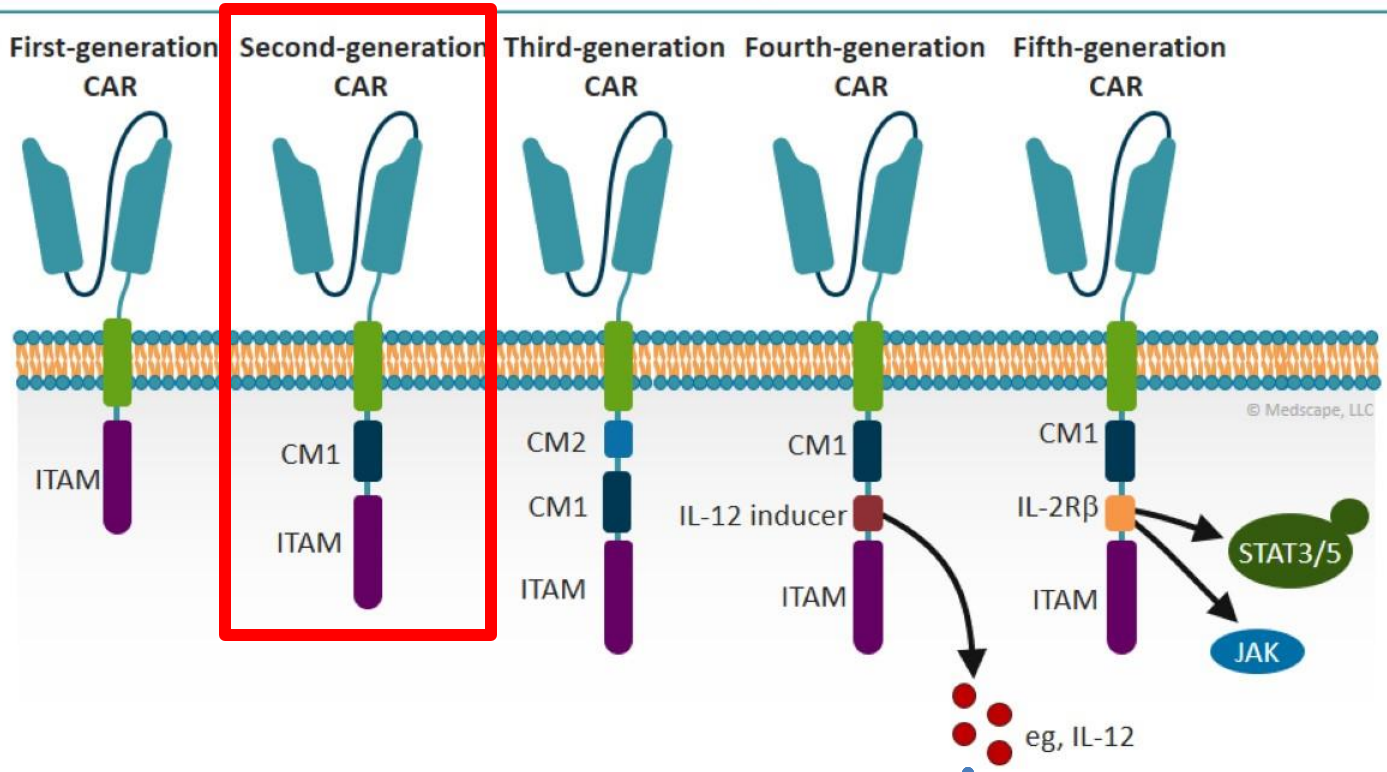
1. Short N, et al. ASH 2021. Abstract 3400; 2. Chevalier P, et al. ASH 2021. Abstract 511; 3. Stelljes M, et al. ASH 2021. Abstract 2300; 4. Advani A, et al. *J Clin Oncol.* 2022 DOI: 10.1200/JCO.21.01766; 5. Boissel N, et al. ASH 2021. Abstract 1232; 6. Gokbuget N, et al. ASH 2021. Abstract 3399; 7. Short N, et al. ASH 2021. Abstract 1233.

Immunotherapy in Early Phases of Ph+ ALL: Results From Phase II Trials

Reference	TKI	Immunotherapy	N	Median age (range)	CR, %	CMR, %	OS, % (95% CI) years
Foa et al[1]	Dasatinib	Blinatumomab	63	54 (24–82)	98	29 (ponatinib) 60 (blinatumomab)	80 (68–93) 2-yr
Short et al[2]	Ponatinib	Blinatumomab	30	62 (34–83)	94	81 (CMR + MMR)	93 2-yr
Advani et al[3]	Dasatinib	Blinatumomab	24	73 (62–87)	92	31	85 (58–95) 3-yr

1. Foa R, et al. *N Engl J Med.* 2020;383:1613-1623; 2. Short N, et al. *Blood.* 2021;138(suppl 1): abstract 2299; 3. Advani A, et al. *Blood.* 2021; 138(suppl 1): abstract 3397.

Differences in CAR T Cell Therapies



Tokarew N, et al. *Br J Cancer.* 2019;120:26-37.

Possibilities of improvement in efficacy

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; **Approved by FDA in October 2021.

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

- Still limited experience, short-term results
- High CR rate (80%–90%), MRD– in >80%, mortality <5%
- Short duration of response (median 8–18 mo)
- Better results in pts with low tumor mass, promising in MRD+ pts
- Need for subsequent alloHSCT unclear, good results in some series
- Early MRD assessment by NGS sequencing predicts outcome

Challenges and Possible Solutions

Challenge	Possible Solution
Broad and immediate availability	Off the shelf CAR T
Manufacturing failure	Not a problem currently
Persistence	Humanized CAR T, improvements in construct
Toxicity	Early use of anti–IL-6, construct with low affinity . . .
CD19-neg relapses	CD22, CD19+22 (bispecific, bicistronic) . . .
Need for subsequent alloHSCT	Better definition of patient candidates
Indication outside BCP-ALL	CAR T for T-ALL (phase I–II clinical trials)
Economic issues	Wide use, academic CAR T . . .

My Current View

- The best place for MoAb will be in first-line therapy, in combination with chemotherapy (Ph– ALL) or TKI (Ph+ ALL)
- MoAb also useful for cytoreductive therapy before CAR T or even in relapse after CAR T (cytoreduction before HSCT)
- The best current place for CAR T is primary refractory ALL and R/R after HSCT
- A future area for CAR T will be first-line therapy for very high-risk subsets of ALL and R/R T-ALL

Question

What is your preferred ALL treatment choice in salvage if all these therapies were available in your country?

1. CAR T therapies
2. Monoclonal antibodies or bispecifics

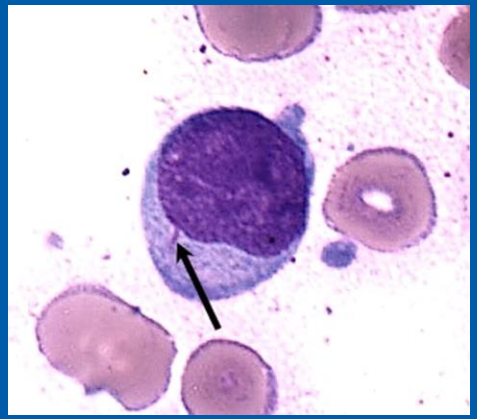
Global Leukemia Academy

Genetic characterization and risk stratification of AML

Eunice Wang

APTITUDE HEALTH

Genetic characterization and risk stratification of AML



ROSWELL PARK
COMPREHENSIVE CANCER CENTER

Eunice S. Wang, MD
Chief, Leukemia Service

Disclosures

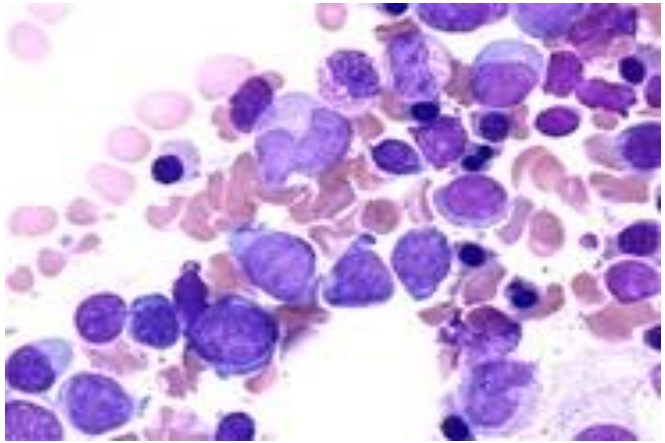
- Consulting/Advisory board: AbbVie, Amgen, Astellas, BMS, Genentech, Gilead, GSK, Jazz, Kite, Novartis, Pfizer, PharmaEssentia, Takeda
- Speaker role: AbbVie, Stemline, Pfizer, Dava Oncology
- Data monitoring committee: AbbVie, Rafael Pharmaceuticals, Gilead

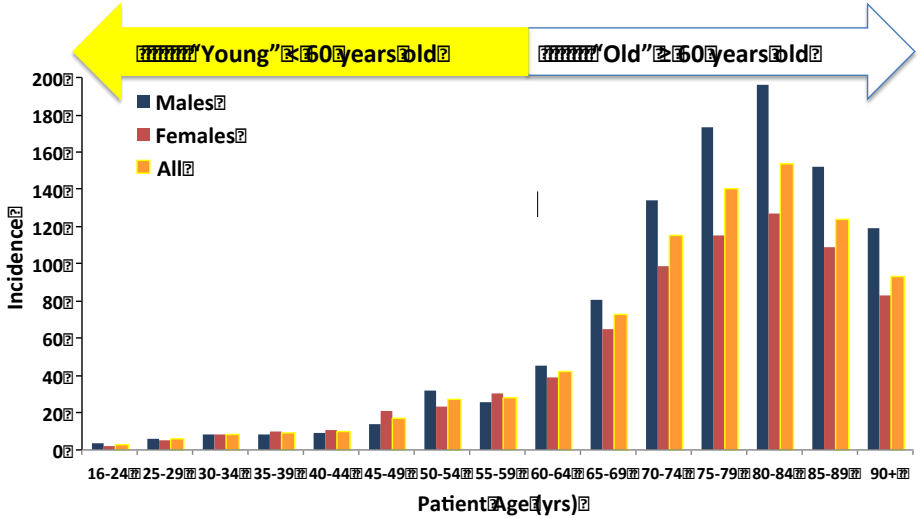
Genetic characterizations and risk stratification

1. Overview of AML
2. ELN classification (2017)
3. Actionable mutations
    1. *FLT3*-ITD and -TKD
    2. Biallelic *CEBPalpha*
    3. *IDH1/IDH2*
    4. *TP53*
    5. *NPM1*

Acute myeloid leukemia (AML)

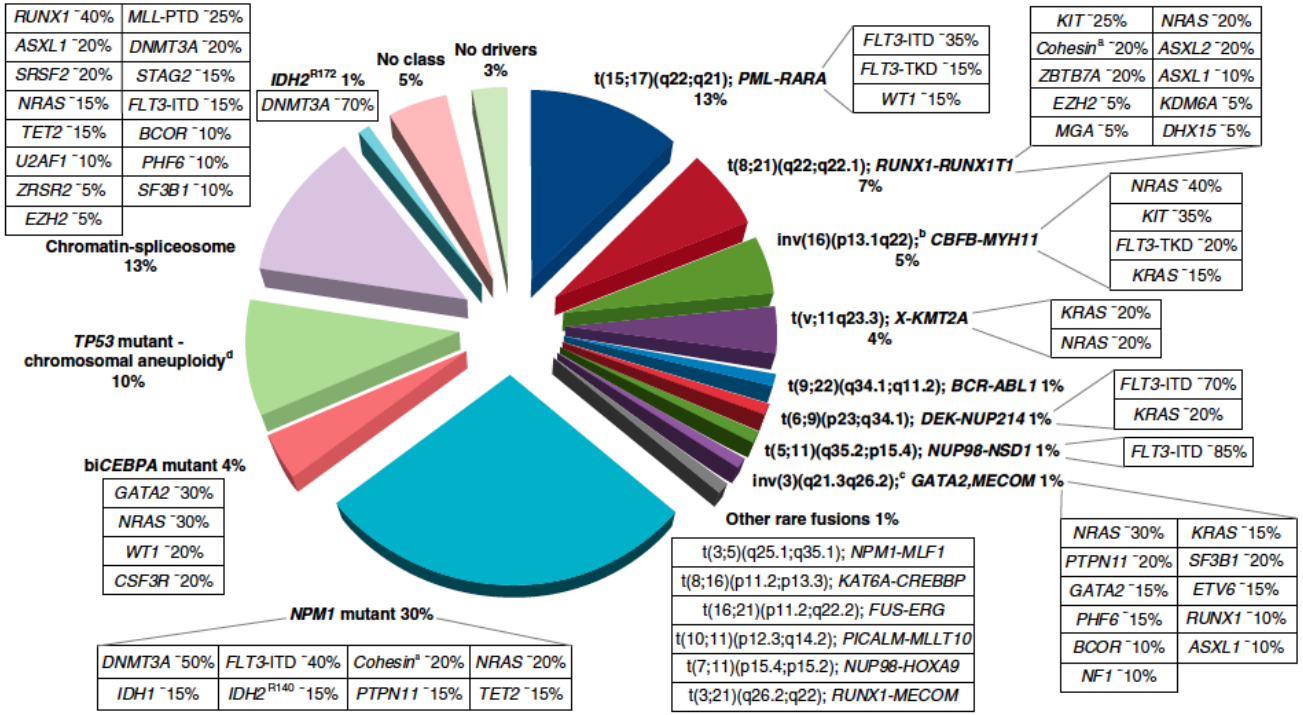
Disease of older adults (median 67–70 years)
Biologically diverse (karyotype, mutations, antigens)
Clinically aggressive disease with survival in weeks-months





Lee LY, et al. *Blood*. 2017;129(2):257-260.

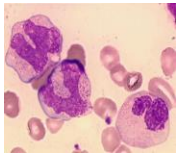
AML is a biologically diverse malignancy

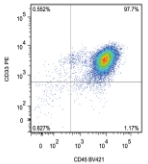


Döhner H, et al. *Blood*. 2017;129(4):424-447.

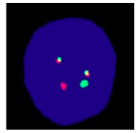
“Ideal” diagnostic workup for AML

Morphology (BM, PB), Flow cytometry (CD33)





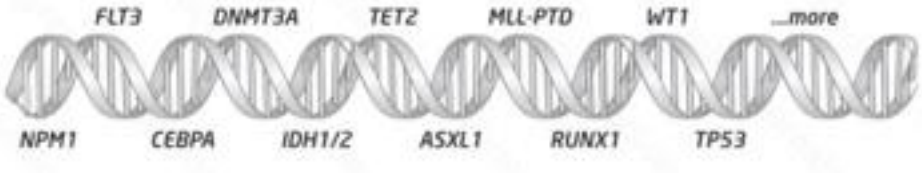
Conventional cytogenetics, FISH (per request), marrow IHC



Mutation results (*FLT3-ITD*, *FLT3-D835 TKD*, *IDH1*, *IDH2*)

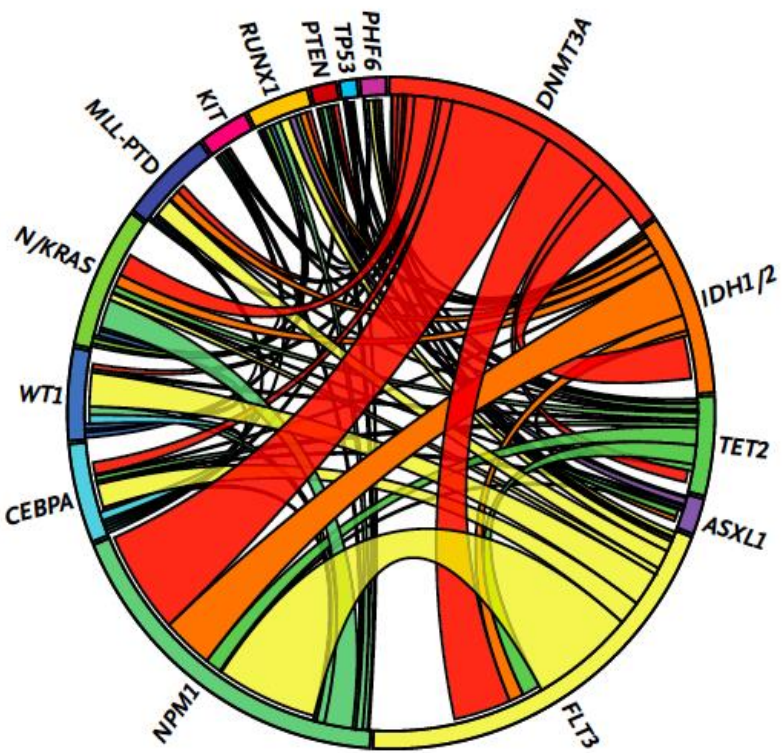
10-17 days

Next gen sequencing
(400 mutations)



Typically, we wait for the top 3 test results to report to initiate treatment

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

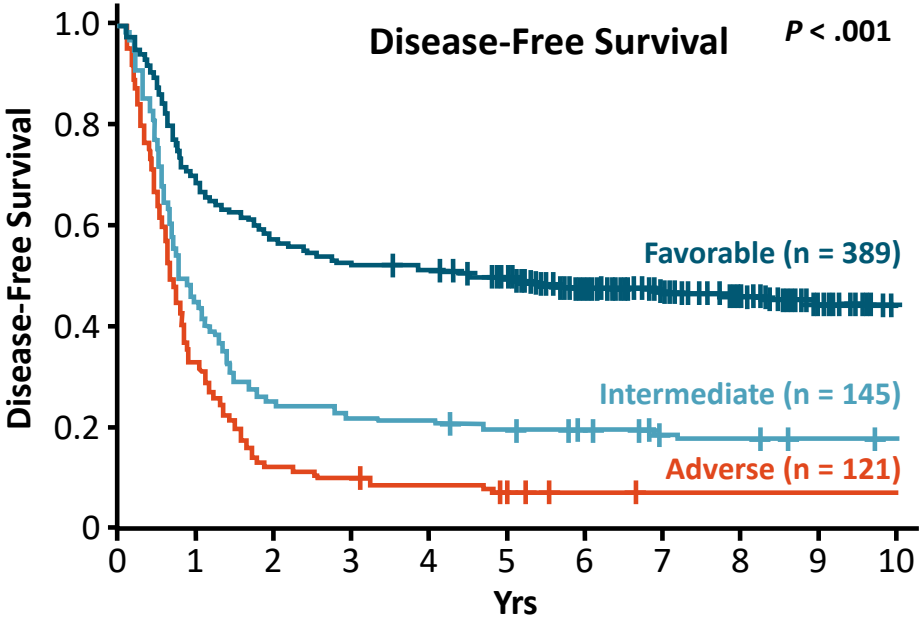
European LeukemiaNet (ELN 2017): AML classification

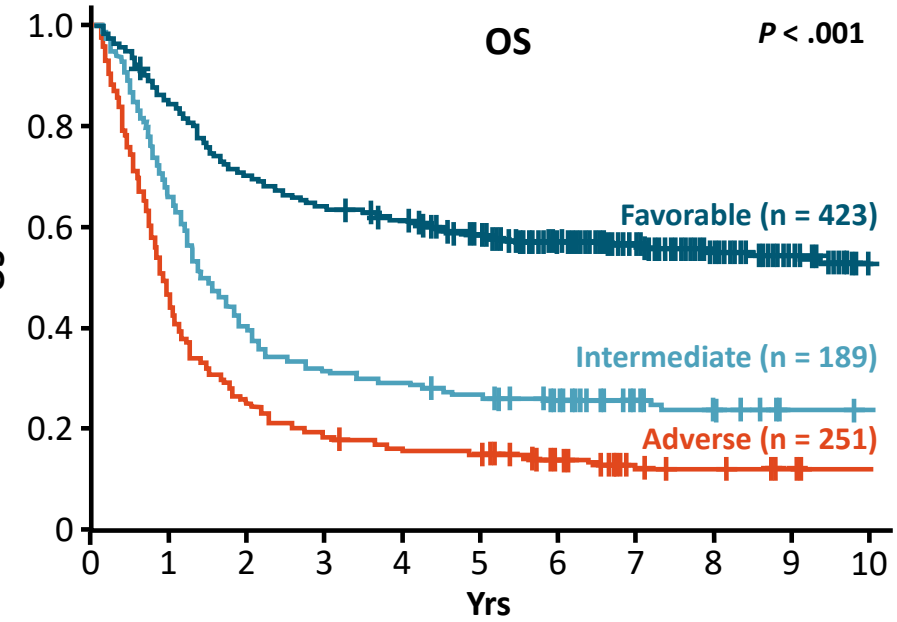
Risk Status	Cytogenetics	Molecular Abnormalities
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} or Biallelic mutated *CEBPA*
Intermediate	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse	Mutated *NPM1* and *FLT3*-ITD^{high} Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions)
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* −5 or del(5q); −7; −17/abn(17p) Complex karyotype, monosomal karyotype	Wild-type *NPM1* and *FLT3*-ITD^{high} Mutated *RUNX1* Mutated *ASXL1* Mutated *TP53*

Döhner H, et al. *Blood*. 2017;129(4):424-447.
Papaemmanuil E, et al. *N Engl J Med*. 2016;374(23):2209-2221.

Survival of patients <60 years of age by risk group

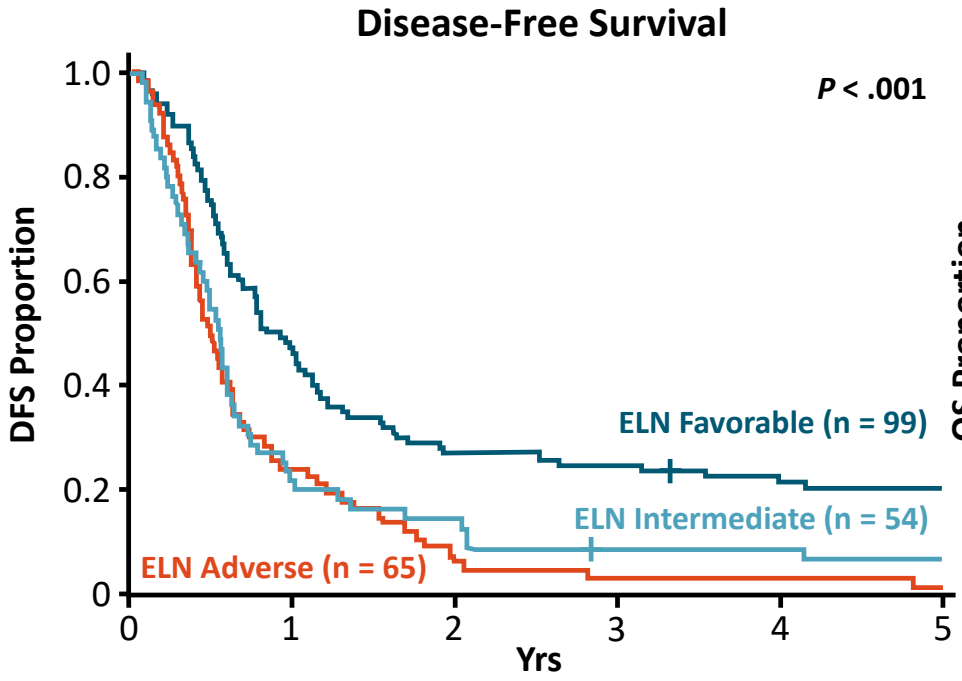
§ Retrospective analysis of data from CALGB/Alliance clinical trials (N = 863; median age: 45 years)

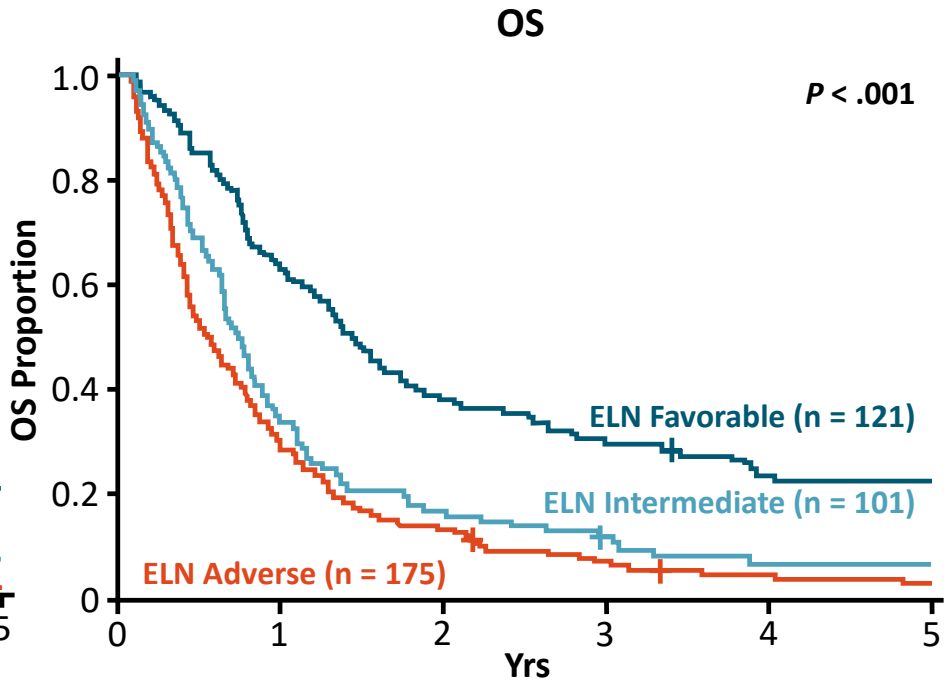




Bill M, et al. EHA 2019. Abstract PF232.

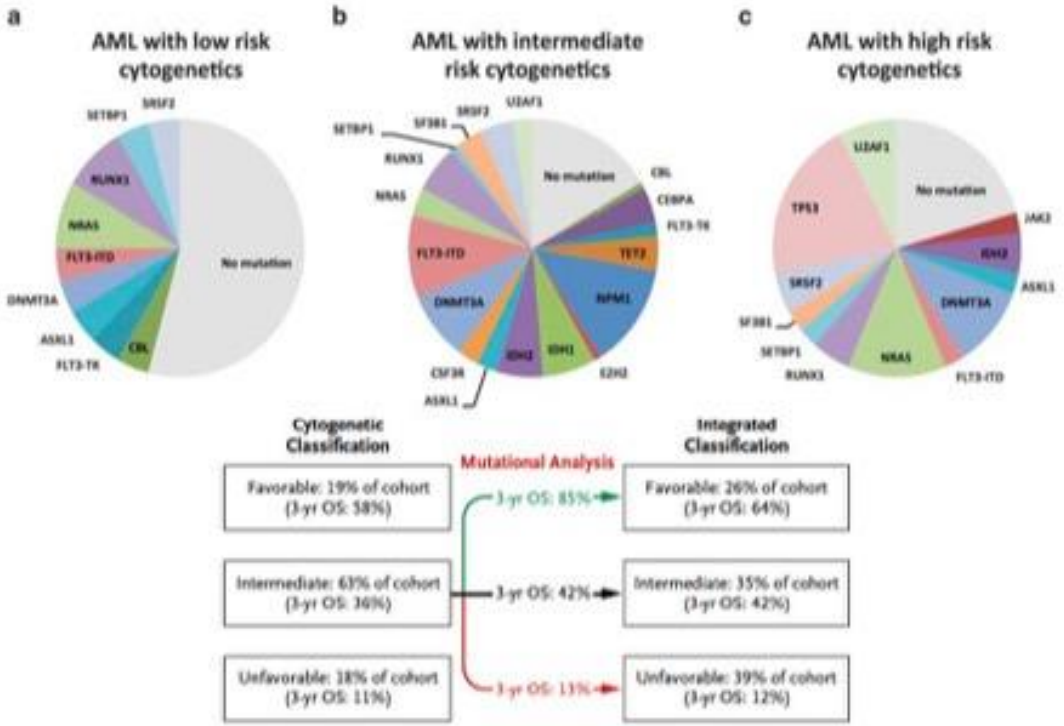
Survival of patients ≥60 years of age by risk group





Eisfeld AK, et al. *Leukemia*. 2018;32(6):1338-1348.

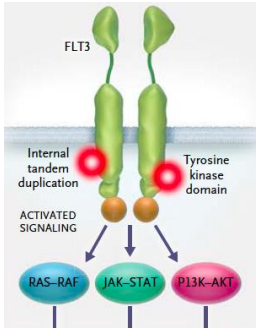
Impact of mutational profiling on prognosis

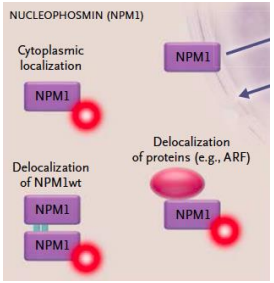


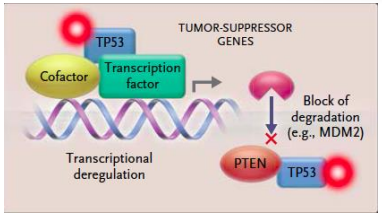
Ohgami RS, et al. *Mod Pathol*. 2014;28(5):706-714;
Patel JP, et al. *N Engl J Med*. 2012;366(12):1079-1089.

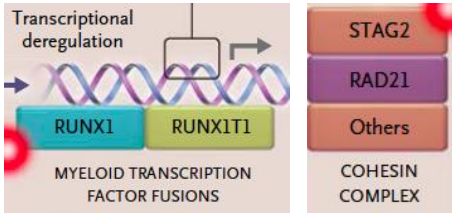
Classes of mutations in AML

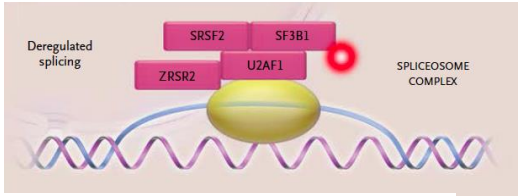
1. *FLT3*
2. Nucleophosmin (*NPM1*)
3. Spliceosome complex
4. Myeloid transcription factor fusions
5. Chromatin modification
6. DNA methylation
7. Cohesin complex
8. Tumor supressor genes

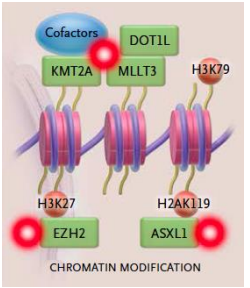


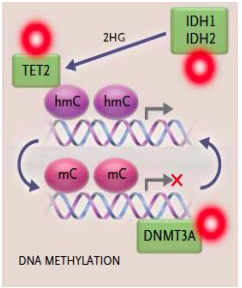








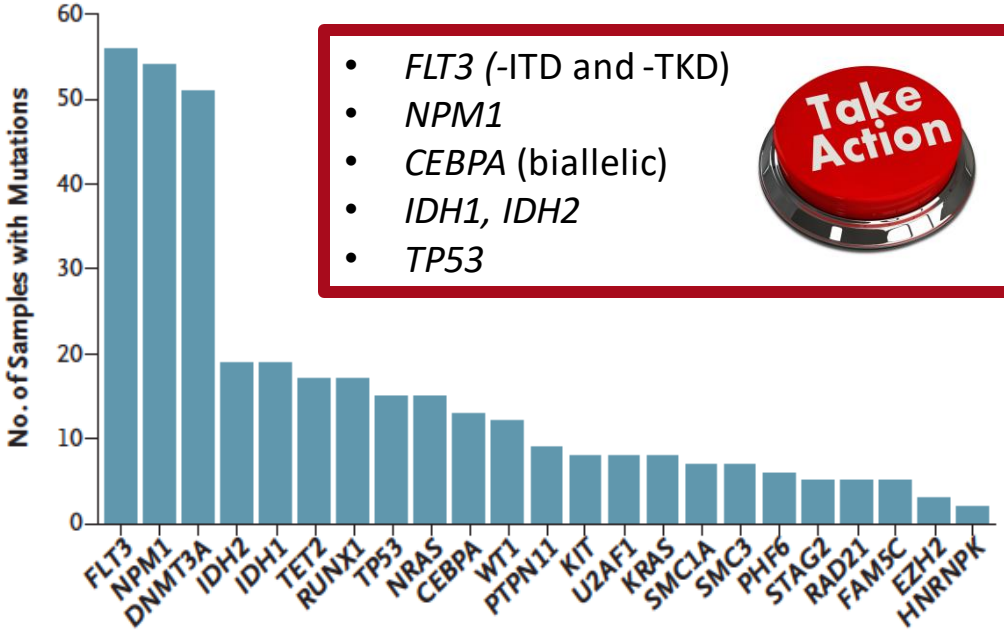




Döhner H, et al. *N Engl J Med*. 2015;373(12):1136-1152.

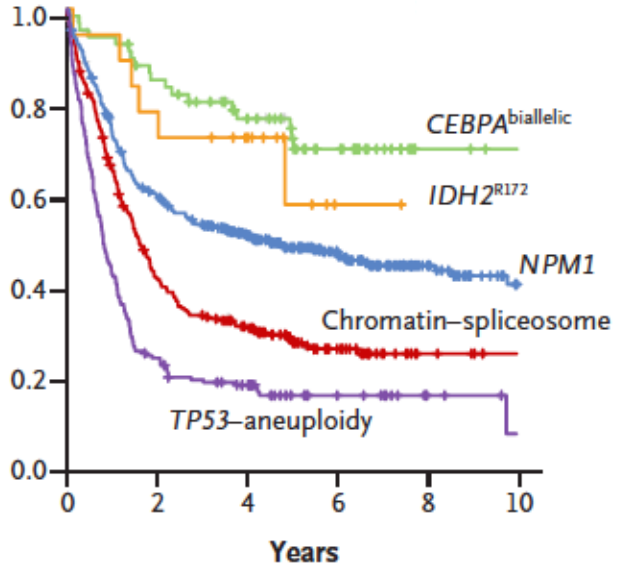
What are the actionable mutations in AML?

Frequency of mutated genes in AML



- *FLT3 (*-ITD and -TKD)
- *NPM1*
- *CEBPA* (biallelic)
- *IDH1, IDH2*
- *TP53*

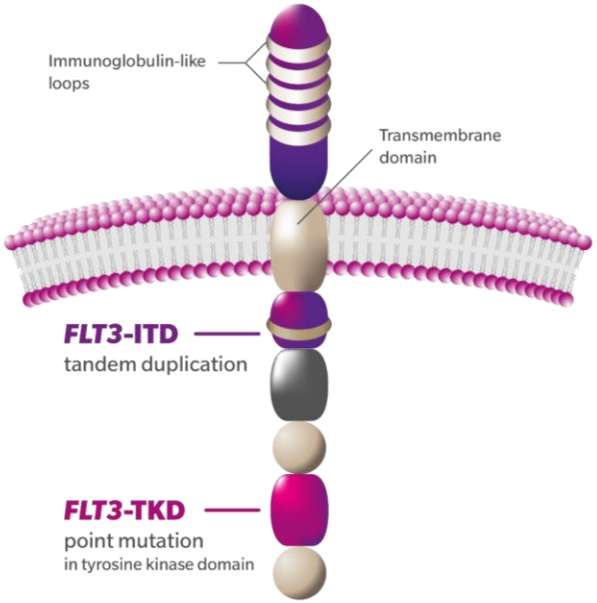
Mutations in NK AML



CGARN. *N Engl J Med.* 2013;368:2059;
Papaemmanuil E, et al. *N Engl J Med.* 2016;374:2209.

FLT3 mutations are the most common mutations in AML[1]

The FLT3 receptor promotes cell proliferation and blocks differentiation[2,3]



There are 2 classes of *FLT3* mutations[1]

***FLT3*-ITD**
mutations are found in **30%** of patients with AML

***FLT3*-TKD**
mutations are found in **7%** of patients with AML

Patients with *FLT3*$^{mut+}$ AML tend to

- Have highly proliferative disease[3]
- Be younger[5]
  - In a study evaluating 250 adult patients with *FLT3*-ITD^{mut+} AML, the median age was 59 years (range 18–80 years)

Figure adapted from Litzow MR. *Blood.* 2005;106(10):3331-3332.

FLT3-ITD mutations negatively impact OS at diagnosis and relapse

OS in patients with AML

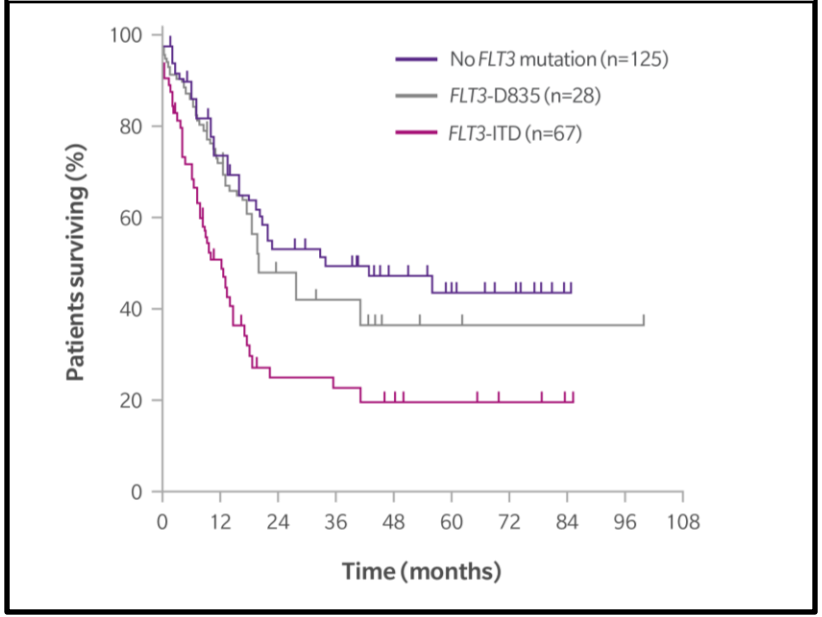


Figure adapted from Fröhling S, et al. *Blood.* 2002;100(13):4372-4380.

OS in patients with AML after first relapse

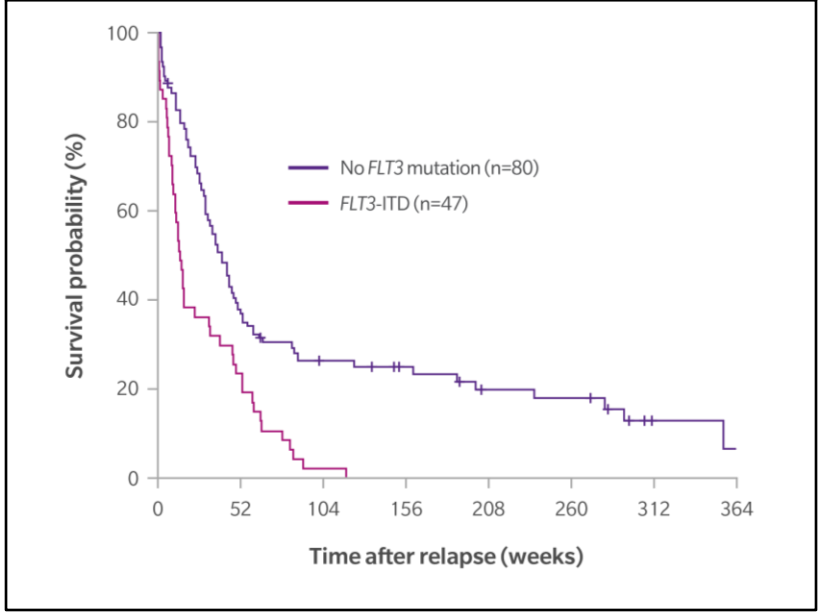


Figure adapted from Ravandi F, et al. *Leuk Res.* 2010;34(6):752-756.

FLT3 mutation testing at Dx and each disease progression

AML mutations can emerge after diagnosis[1]

65% of patients
(n = 35/54)

treated with a FLT3 inhibitor had a mutation emerge at relapse, including *FLT3* (retrospective analysis)

***FLT3* mutation status can change over the course of AML treatment[2,3]**

22% of patients
(n = 11/50)

had their mutation status change between diagnosis and disease progression in an analysis of several trials

Among patients with *FLT3*-ITD mutations at diagnosis, *FLT3*-TKD mutations may be present after treatment*[4]

25% of patients
(n = 15/60)

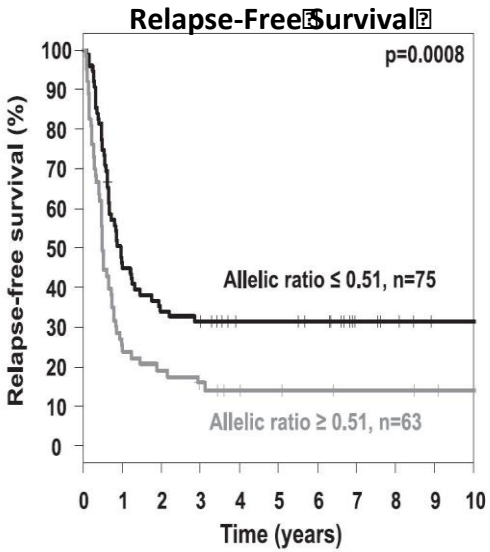
had both *FLT3*-ITD and *FLT3*-TKD mutations at the end of therapy (retrospective analysis)

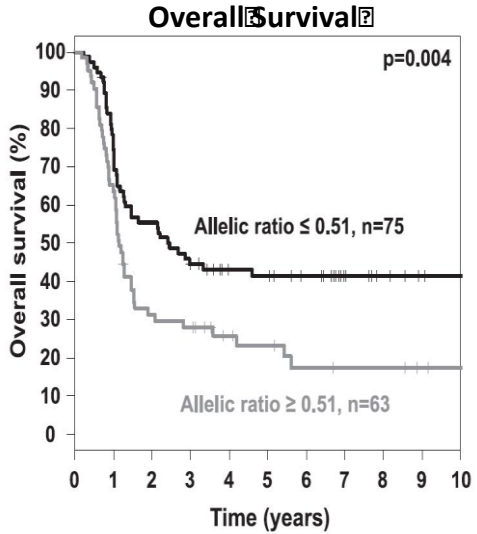
*Quizartinib,† sorafenib,† and lestaurtinib.†

NCCN and ESMO guidelines recommend retesting all AML patients for *FLT3* mutations at relapse[5,6]

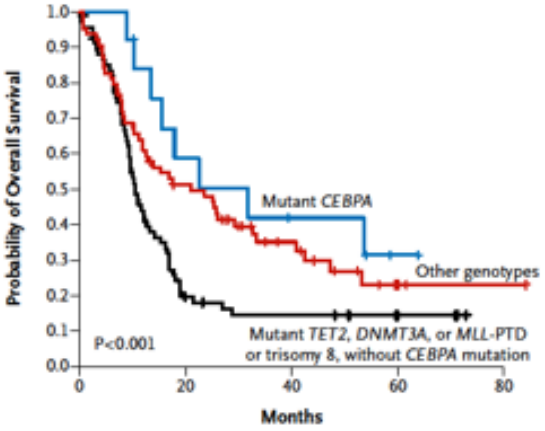
FLT3 allelic ratio and impact of co-mutations

Poor prognosis associated with high *FLT3*-ITD AR





***FLT3* mutations + other mutations**



No. at Risk					Prognosis
Mutant *CEBPA*	13	7	4	1	Intermediate
Other genotypes	64	31	14	3	Intermediate
Mutant *TET2*, *DNMT3A*, or *MLL*-PTD or trisomy 8, without *CEBPA* mutation	67	12	8	3	Poor

Patel J, et al. *N Engl J Med.* 2012;366(12):1079-1089;
Schlenk R, et al. *Blood.* 2014;124(23):3441-3449.

The type of mutation testing can make a difference

FLT3-ITD is an actionable mutation, but can be challenging for some tests to detect[1,2]*

- *FLT3*-ITD mutations may present at relapse and are associated with more negative patient outcomes[3,4]

PCR detects *FLT3*-ITD mutations with greater reliability compared with multiple NGS tools[2]

In an evaluation, **only 2 out of 9 NGS tools** detected *FLT3*-ITD mutations with

- 100% sensitivity (95% CI: 83–100)
- 100% specificity (95% CI: 88–100)

among 20 subjects with *FLT3*-ITD mutations and 29 subjects without *FLT3*-ITD mutations, as confirmed by PCR[2]

Confirming an actionable mutation at each disease progression is critical for choosing the right targeted therapy[1,5]

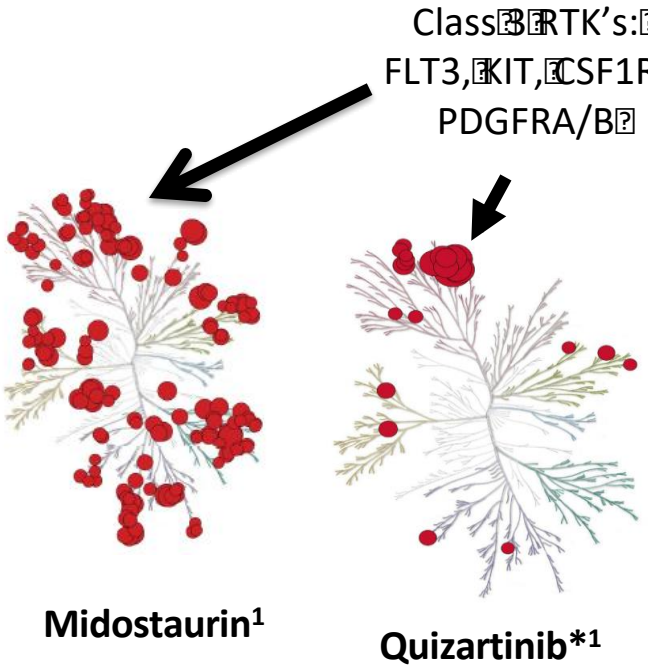
Differences in *FLT3* mutation testing by PCR and NGS

	PCR	Targeted NGS/gene panel
How many genes assessed?	**Targeted assessment** • Detects mutations on **single gene** of interest[1]	**Broader assessment** • Allows the **full genome** to be sequenced • Simultaneously assesses **multiple** genes[2–4]
Which *FLT3* mutations are detected?	**Good sensitivity** • Standard testing method for *FLT3* assessment[2] • *FLT3*-ITD can be reliably determined with standardized protocols[4,5] • *FLT3*-TKD can be detected	**Sensitivity may vary** • Detects both *FLT3*-ITD and -TKD mutations • May give false-negative results for *FLT3*-ITD due to variable size, insertion point, and allelic burden[2,4,6] • May required "add-on" technology to gene panel to ensure detection[3,7]
How quickly are results available?	**Relatively faster** • Turnaround time = 2–3 days[1]	**Relatively slower** • Turnaround time = 3–20 days[1]

FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; NGS, next-generation sequencing; PCR, polymerase chain reaction; R/R, relapsed/refractory; TKD, tyrosine kinase domain.

1. Patnaik MM. *Leuk Lymphoma.* 2018;59:2273-2286; 2. He R, et al. *Mod Pathol.* 2020;33:334-343; 3. Au CH, et al. *Diagn Pathol.* 2016;11:11; 4. Levine RL, et al. *Haematologica.* 2019;104:868-871; 5. Murphy KM, et al. *J Mol Diagn.* 2003;5:96-102; 6. Mack EKM, et al. *Haematologica* 2019;104:277-287; 7. Spencer DH, et al. *J Mol Diagn.* 2013;15:81-93.

FLT3 inhibitors in clinical development for AML



Midostaurin[1]

Quizartinib*[1]

	Other kinases (inhibited)	IC_{50} (plasma)
Lestaurtinib*[2]	JAK2, TrkA	700 nM
Midostaurin[2]	cKIT, PKC, PDGFR, VEGFR	1000 nM
Sorafenib†[2]	cKIT, PDGFR, RAF, VEGFR	265 nM
Quizartinib*[2]	cKIT, PDGFR, RET	18 nM
Crenolanib*[3]	PDGFR	48 nM
Gilteritinib[4]	AXL	43 nM

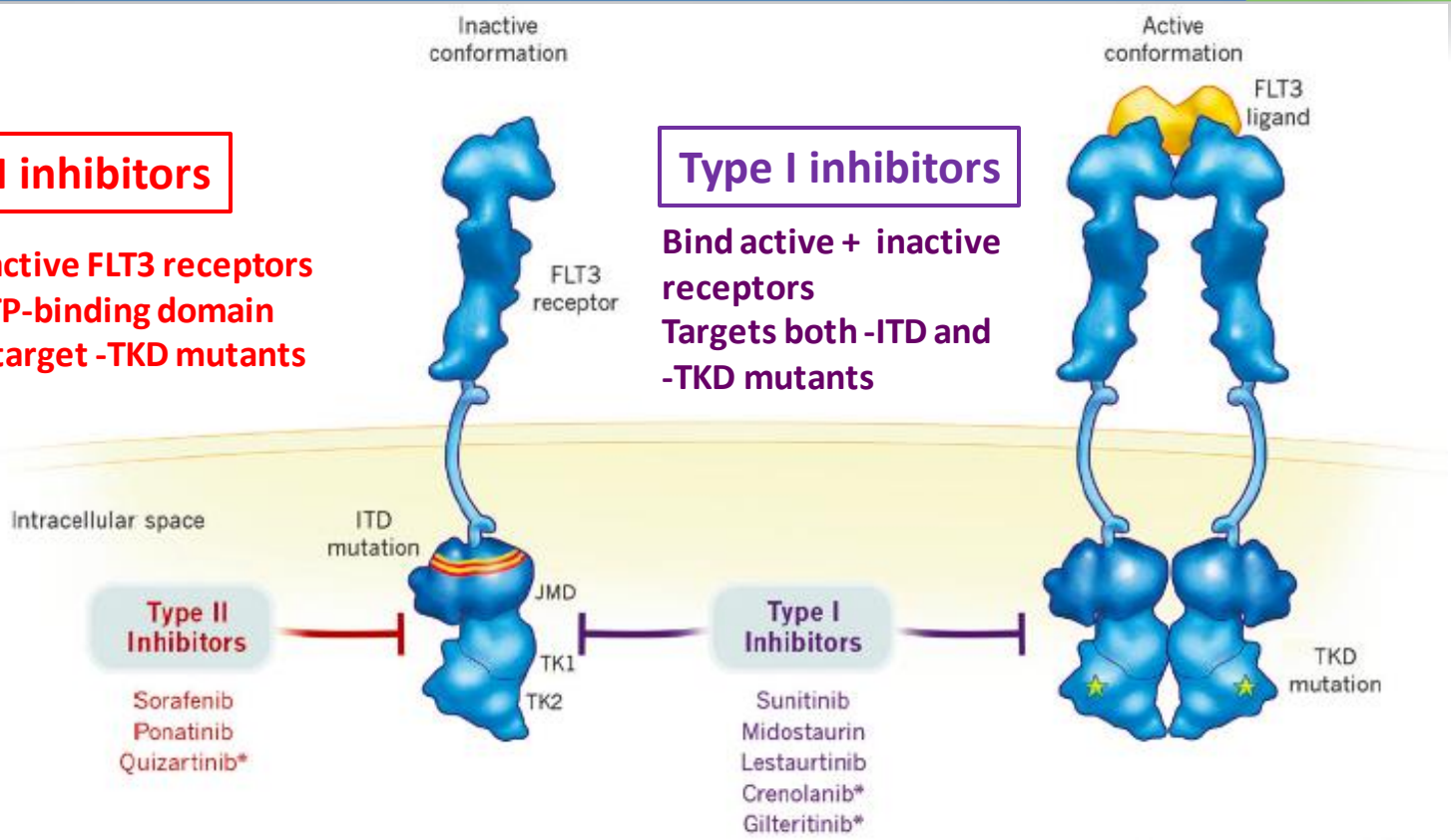
FLT3 TKIs differ in binding mutant *FLT3*

Type II inhibitors

Bind inactive FLT3 receptors
Near ATP-binding domain
Do not target -TKD mutants

Type I inhibitors

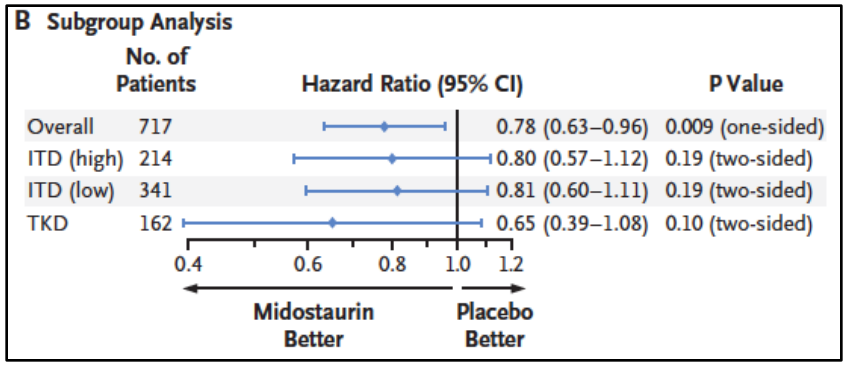
Bind active + inactive receptors
Targets both -ITD and -TKD mutants



Daver N, et al. *Leukemia*. 2019;33(2):299-312.

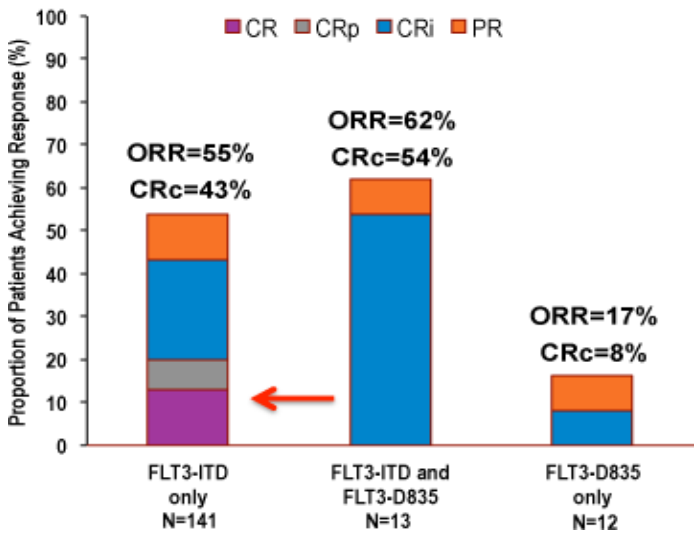
Response to FLT3 TKI therapy on the basis of *FLT3* mutation

Midostaurin plus 7+3



Benefit in *FLT3*-ITD *regardless of AR* and in *FLT3*-TKD mutation

Gilteritinib in R/R AML

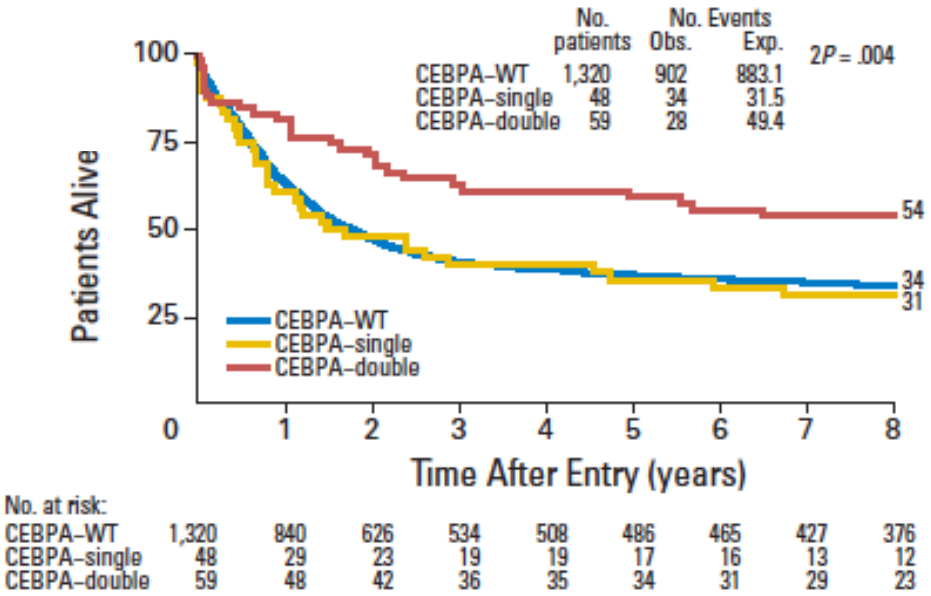


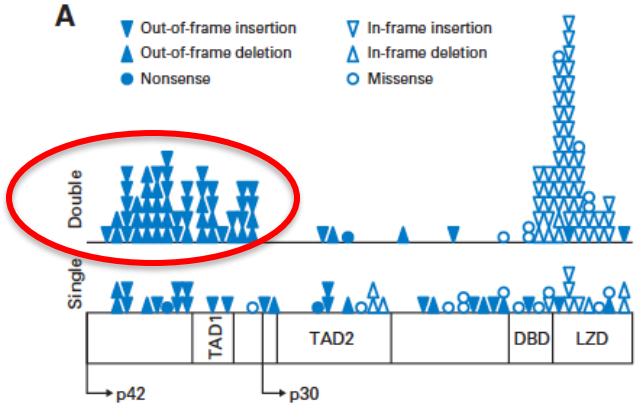
Lower ORR in *FLT3*-TKD only

Stone RM, et al. *N Engl J Med*. 2017;377(5):454-464; 2017; Perl A, et al. *Lancet Oncol*. 2017;18(8):1061-1075.

Daver N, et al. *Leukemia*. 2019;33(2):299-312.

Biallelic *CEBP*alpha mutations confer favorable risk





7%–11% of AML cases
13%–15% of normal karyotype
Double (not single) mutation is considered favorable risk

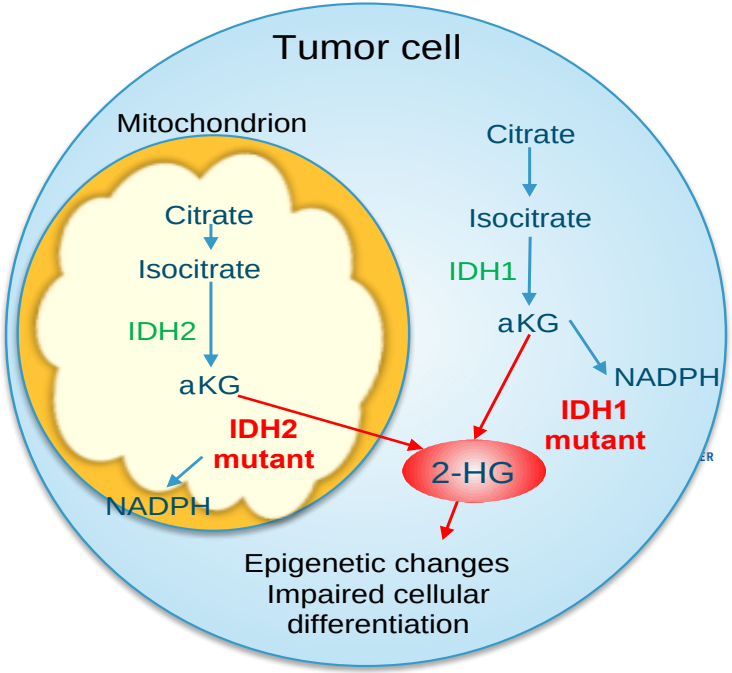
Green CL, et al. *J Clin Oncol*. 2010;28(16):2739-2747.

IDH mutations in AML

- **Isocitrate dehydrogenase (IDH)** is a critical enzyme of the citric acid cycle

- *IDH* mutations are mutually exclusive in AML
  - *IDH1* mut: 6–9% of AML (8–16% NK AML)
  - *IDH2* mut: 8–12% of AML (19% of NK AML)

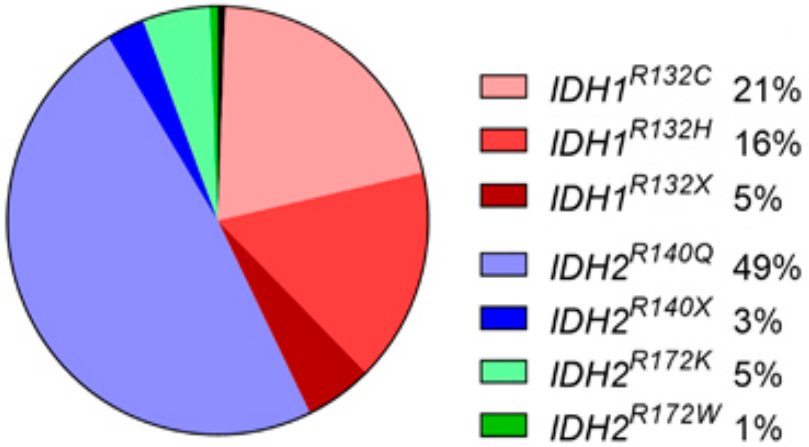
- *IDH1/2* mutations confer a gain of function[2]
  - Increased histone and DNA methylation
  - Impaired cellular differentiation



Dang L, et al. *Nature*. 2009;462:739-744.

IDH mutations in AML

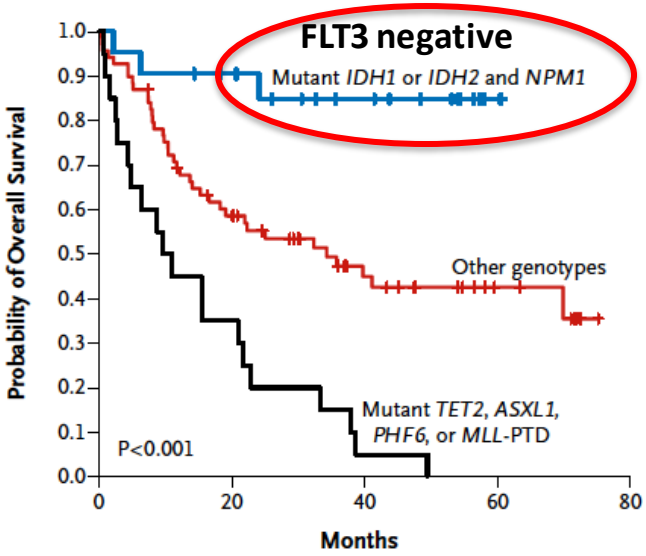
- **IDH mutations occur in ~ 20% of AML**
  - Most (~85%) occur in *de novo* diploid or +8 AML
  - IDH1 in ~8% AML, IDH2 in ~ 12% AML
  - ↑ prevalence with ↑ patient age
- **Hot-Spot mutations in enzymatic active site**
  - **IDH1-R132, IDH2-R140 or IDH2-R172**
- **Often early mutational events**
  - Ancestral in **20% IDH1** and **35% IDH2** cases
- **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.

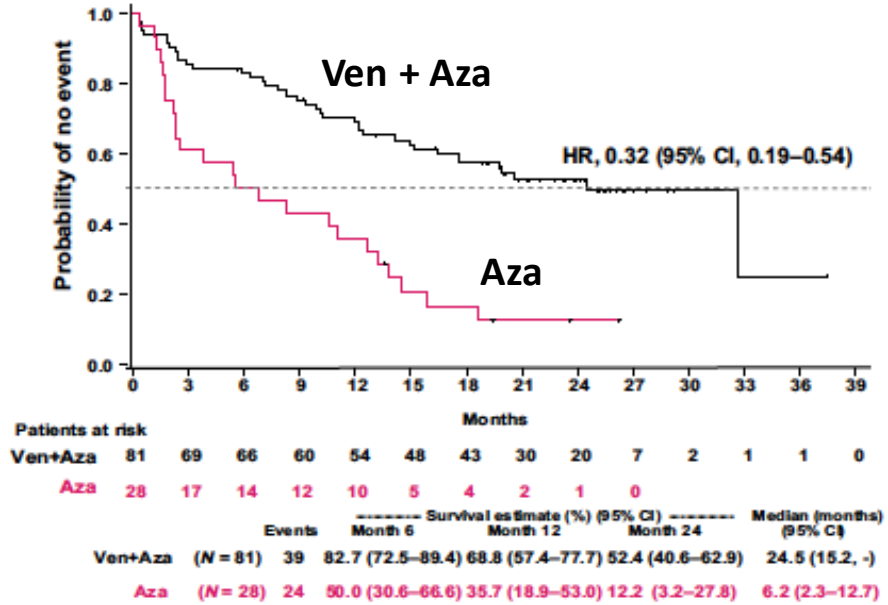
IDH mutations in AML

Intensive chemotherapy



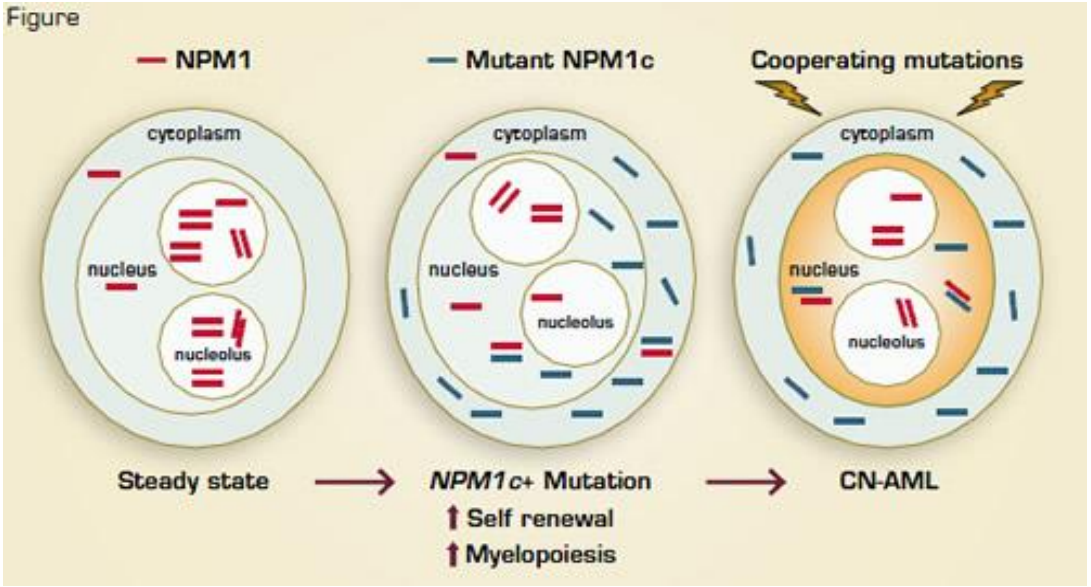
Favorable risk: *IDH*^{mut}*NPM1*^{mut}*FLT3*^{wt}

Venetoclax-Aza vs Aza



Patel J, et al. *N Engl J Med*. 2012;366(12):1079-1089;
Pollyea DA, et al. *Clin Cancer Res*. 2022. Epub ahead of print.

Nucleophosmin-1 (*NPM1*) mutations in AML



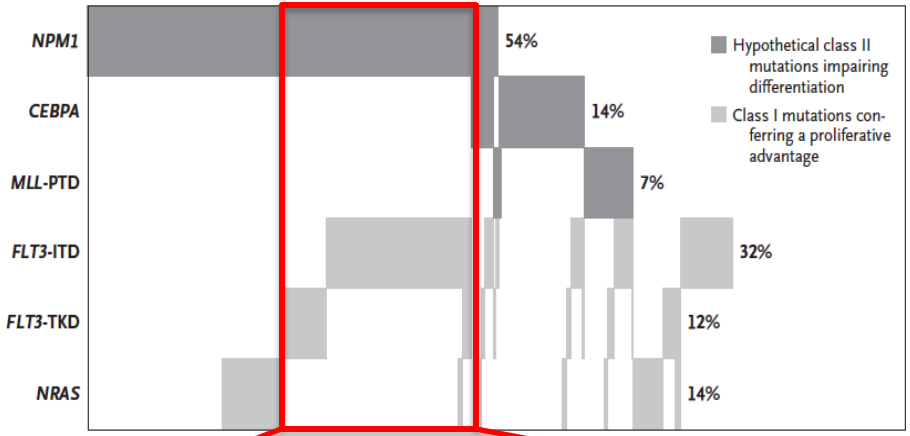
Nuclear export protein
28%–35% of AML cases
48%–53% of normal karyotype AML

Common co-mutations
Confers better prognosis to 7+3

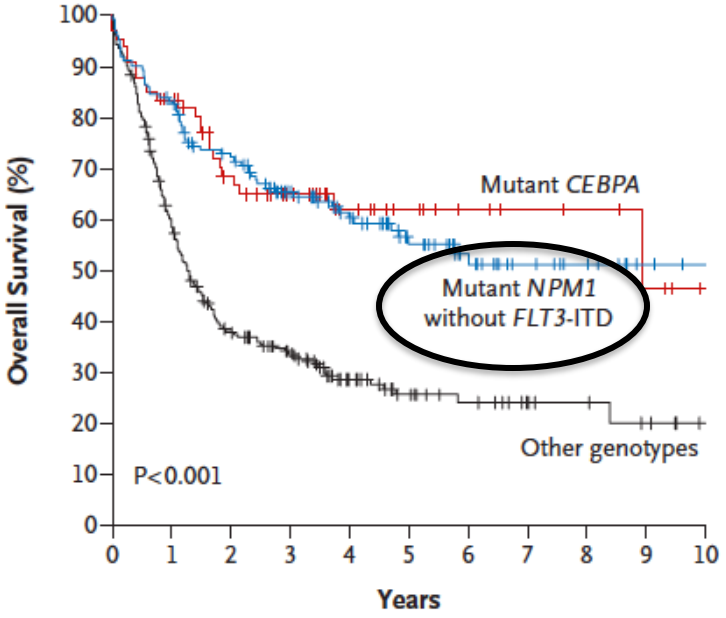
- *FLT3*-ITD–mutant AML
- *IDH1/2*–mutant AML

Linenberger M, Ostronoff F. *Hematologist*. 2011;8(6).

NPM1-mutant AML: Favorable prognosis without *FLT3* mutation

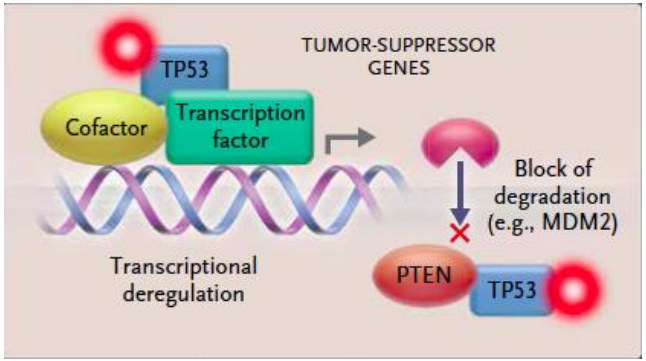


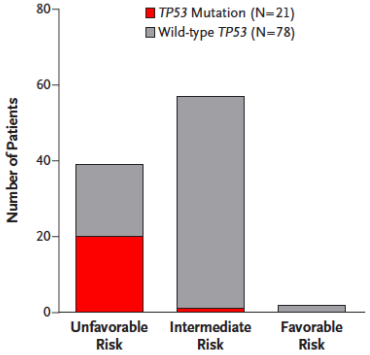
Half of *NPM1*-mutant AML has *FLT3* mutation

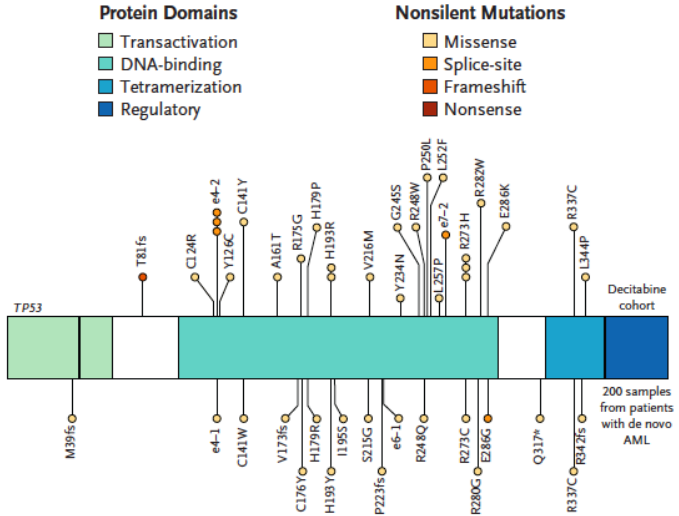


Schlenk RF, et al. *N Engl J Med*. 2008;358(18):1909-1920.

TP53 mutations in AML







~12%–13% AML, primarily unfavorable karyotype

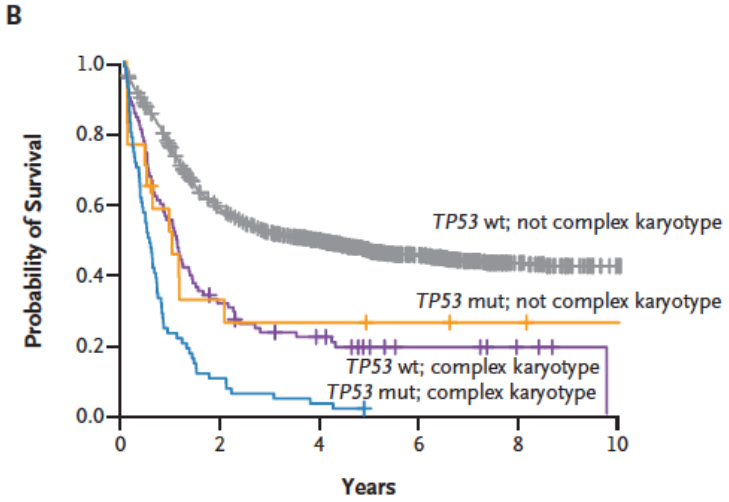
Higher incidence in

- Older (9%) vs younger (2%) patients
- Therapy-related AML (23%)
- Monosomal karyotype, chr 5 and 7 abnormalities

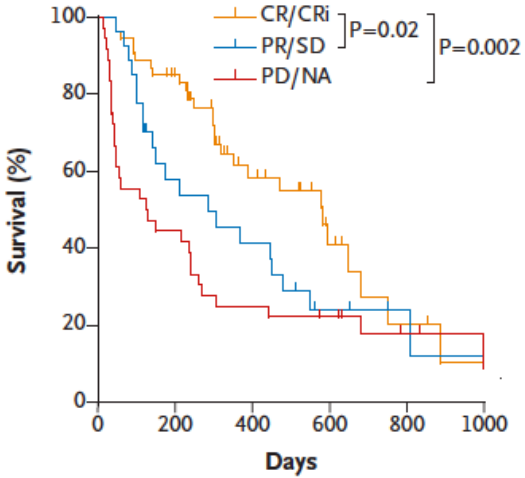
Döhner H, et al. *N Engl J Med*. 2015;373(12):1136-1152;
Welch J, et al. *N Engl J Med*. 2016;375(21):2023-2036.

TP53-mutant AML: Treatment outcomes

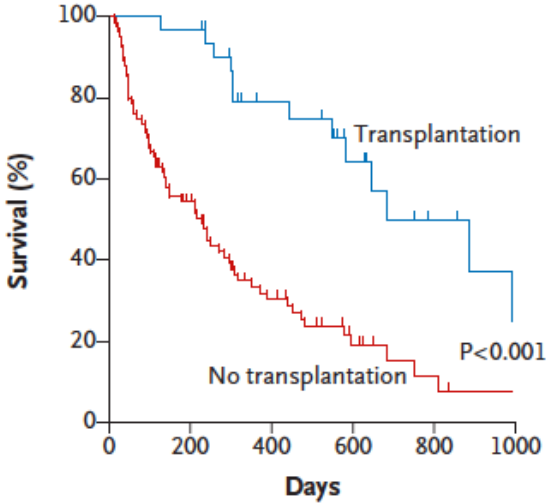
7+3 chemotherapy



Decitabine (10-day)



Allo transplantation



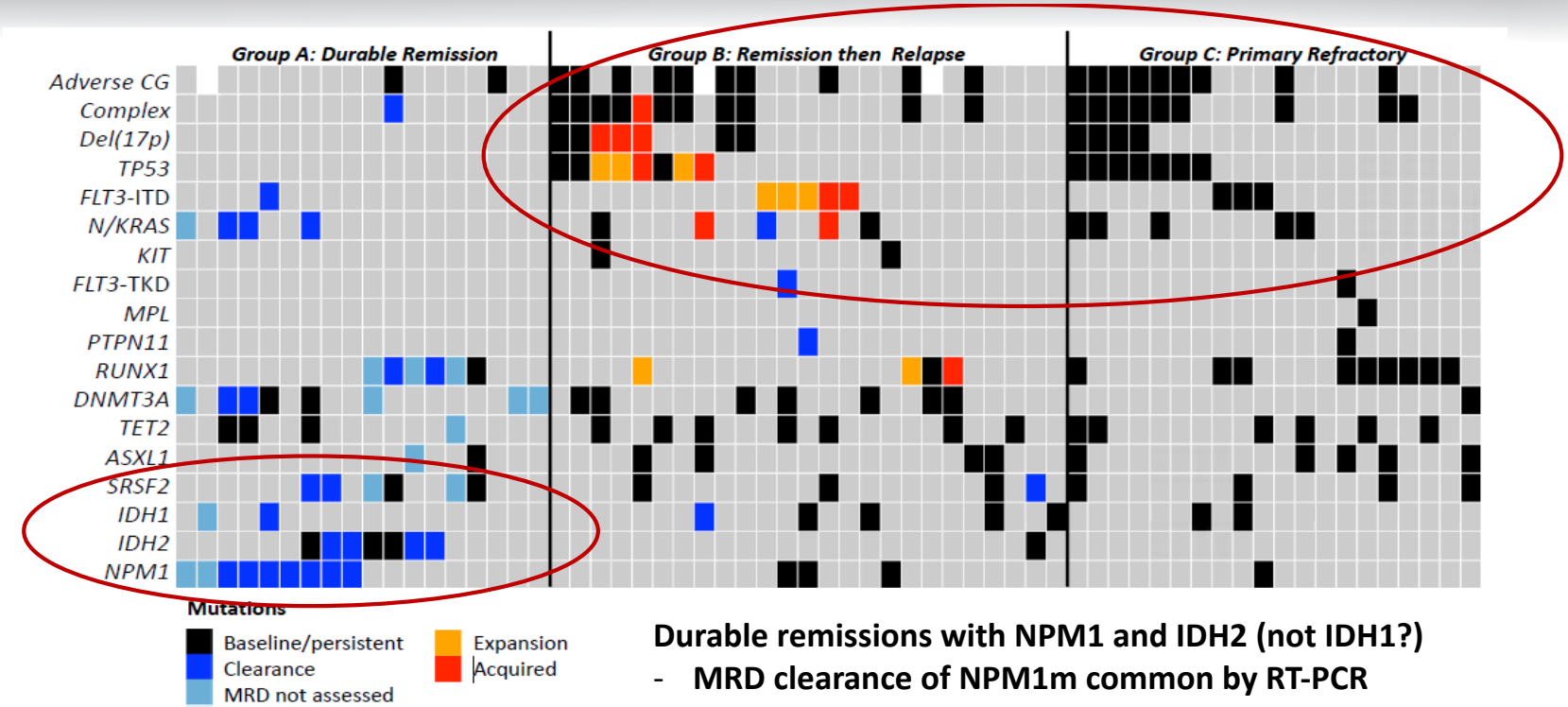
Papaemmanuil E, et al. N Engl J Med. 2016;374(23):2209-2221;
Welch J, et al. *N Engl J Med.* 2016;375(21):2023-2036.

European LeukemiaNet (ELN 2017): AML classification

Risk Status	Cytogenetics	Molecular Abnormalities
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} or Biallelic mutated *CEBPA*
Intermediate	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse	Mutated *NPM1* and *FLT3*-ITD^{high} Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions)
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* −5 or del(5q); −7; −17/abn(17p) Complex karyotype, monosomal karyotype	Wild-type *NPM1* and *FLT3*-ITD^{high} Mutated *RUNX1* Mutated *ASXL1* Mutated *TP53*

Döhner H, et al. *Blood*. 2017;129(4):424-447.
Papaemmanuil E, et al. *N Engl J Med*. 2016;374(23):2209-2221.

Response to Ven + Aza varies on the basis of AML biology



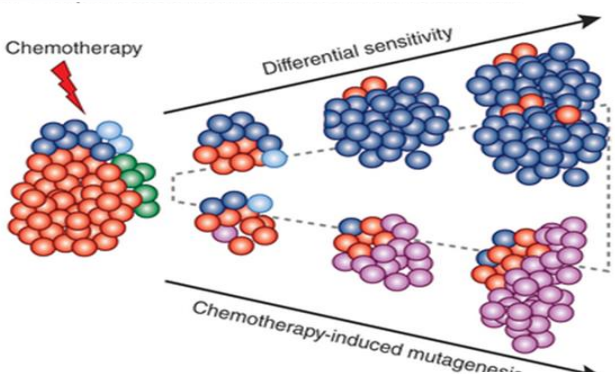
Durable remissions with NPM1 and IDH2 (not IDH1?)

- **MRD clearance of NPM1m common by RT-PCR**

Resistance commonly associated with expansion or acquisition of TP53 or FLT3-ITD

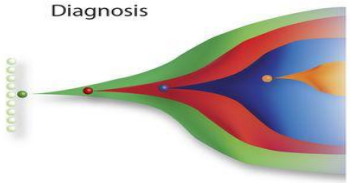
DiNardo CD, et al. *Blood*. 2020;135(11):791-803.

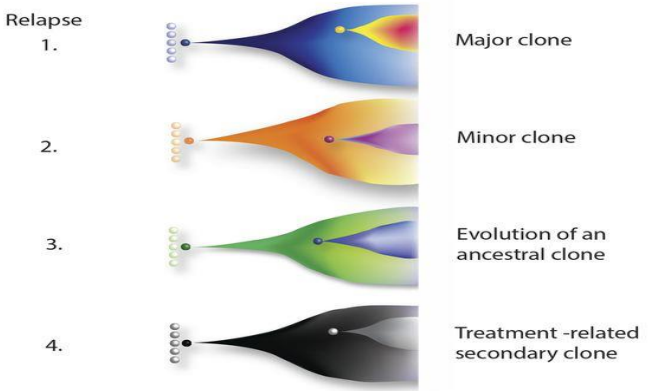
Relapsed/refractory AML: Clonal evolution



Leukemia is not a static condition!

Repeat genomic analysis at relapse is necessary



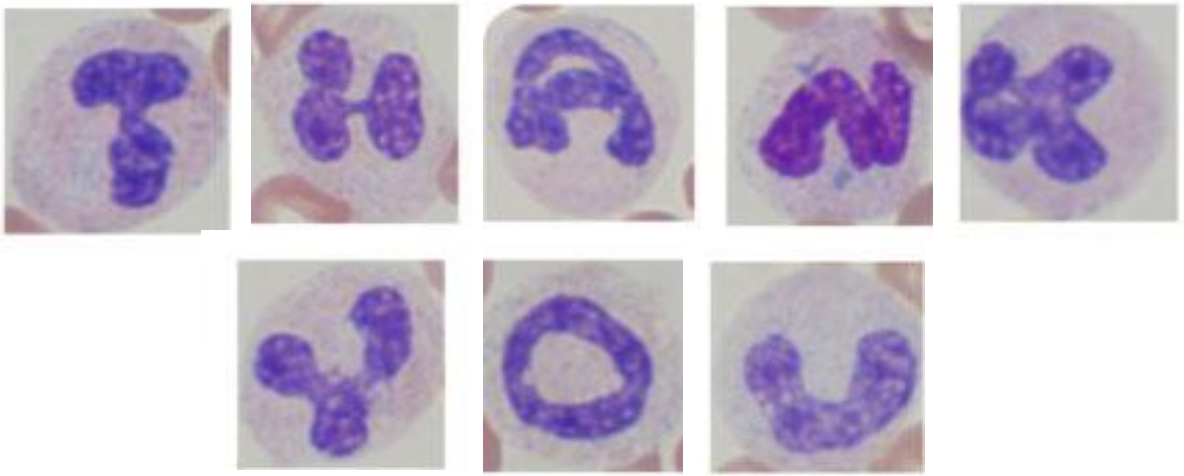


Kleppe M, Levine RL. *Nat Med*. 2014;20(4):342-344;
Grimwade D, et al. *Blood*. 2016;127(1):29-41.

Genetic characterizations and risk stratification

1. Overview of AML
2. ELN classification (2017)
3. Actionable mutations
    1. *FLT3*-ITD and -TKD
    2. Biallelic *CEBPalpha*
    3. *IDH1/IDH2*
    4. *TP53*
    5. *NPM1*

Questions?



Email: Eunice.wang@roswellpark.org

ROSWELL PARK
COMPREHENSIVE CANCER CENTER

Global Leukemia Academy

Therapeutic approaches in high-risk and older AML patients

Naval Daver

APTITUDE HEALTH

Therapeutic Approaches in High-Risk and Older AML Patients

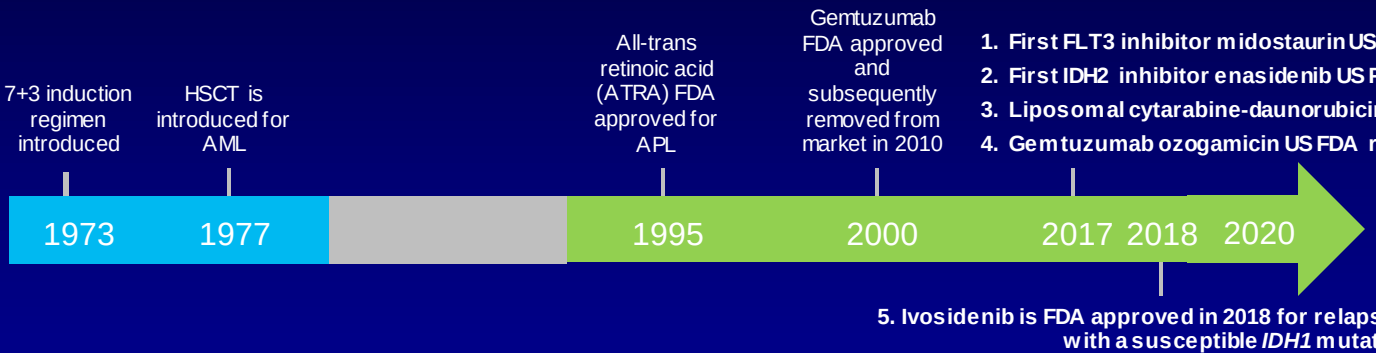
Global Leukemia Academy

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

Treatment of AML (accelerated progress 2017–2020): History

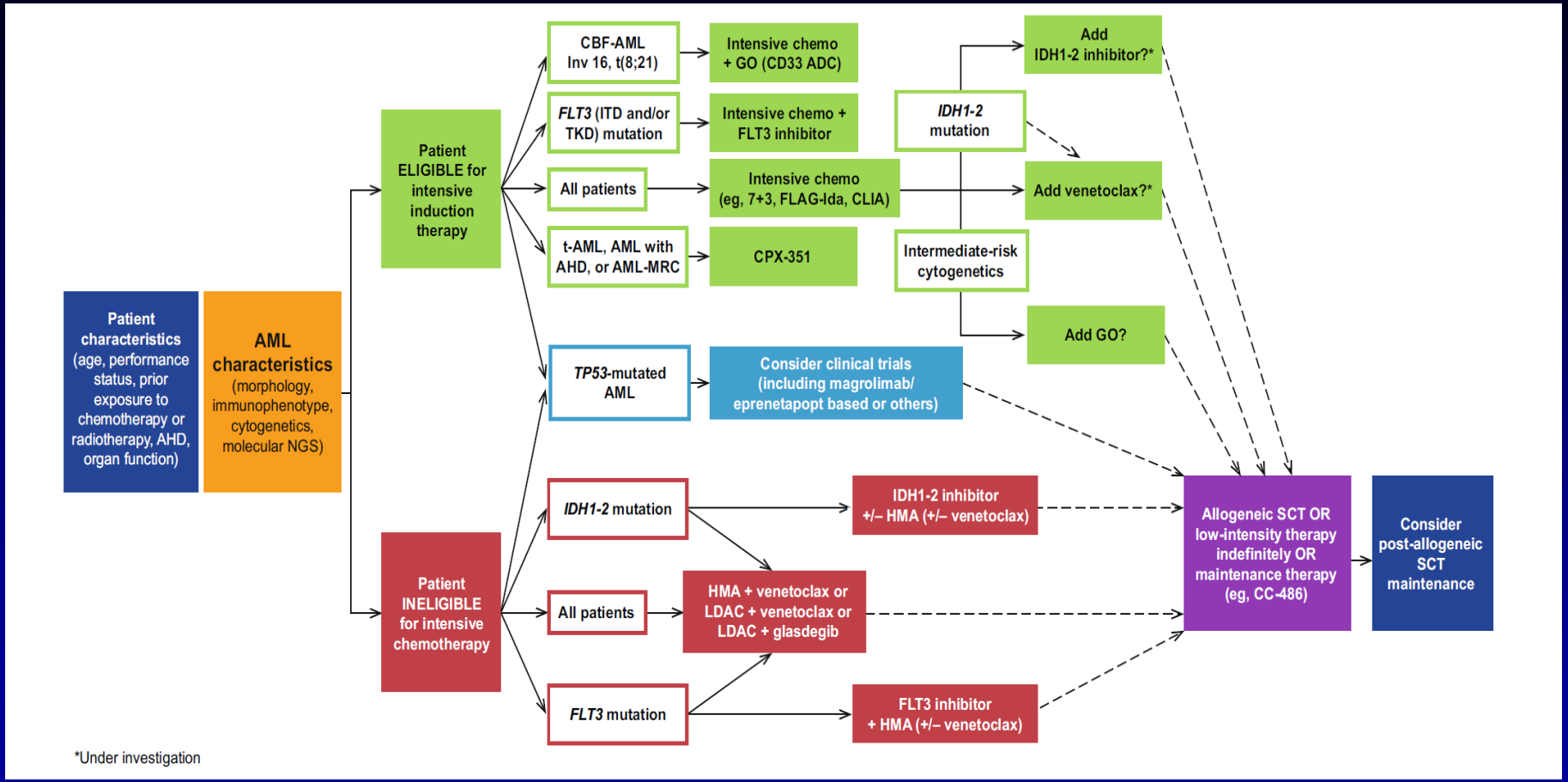
Since its introduction in the early 1970s, 7+3 therapy (cytarabine for 7 days + anthracycline for 3 days) has been the standard of care for AML

US FDA approvals



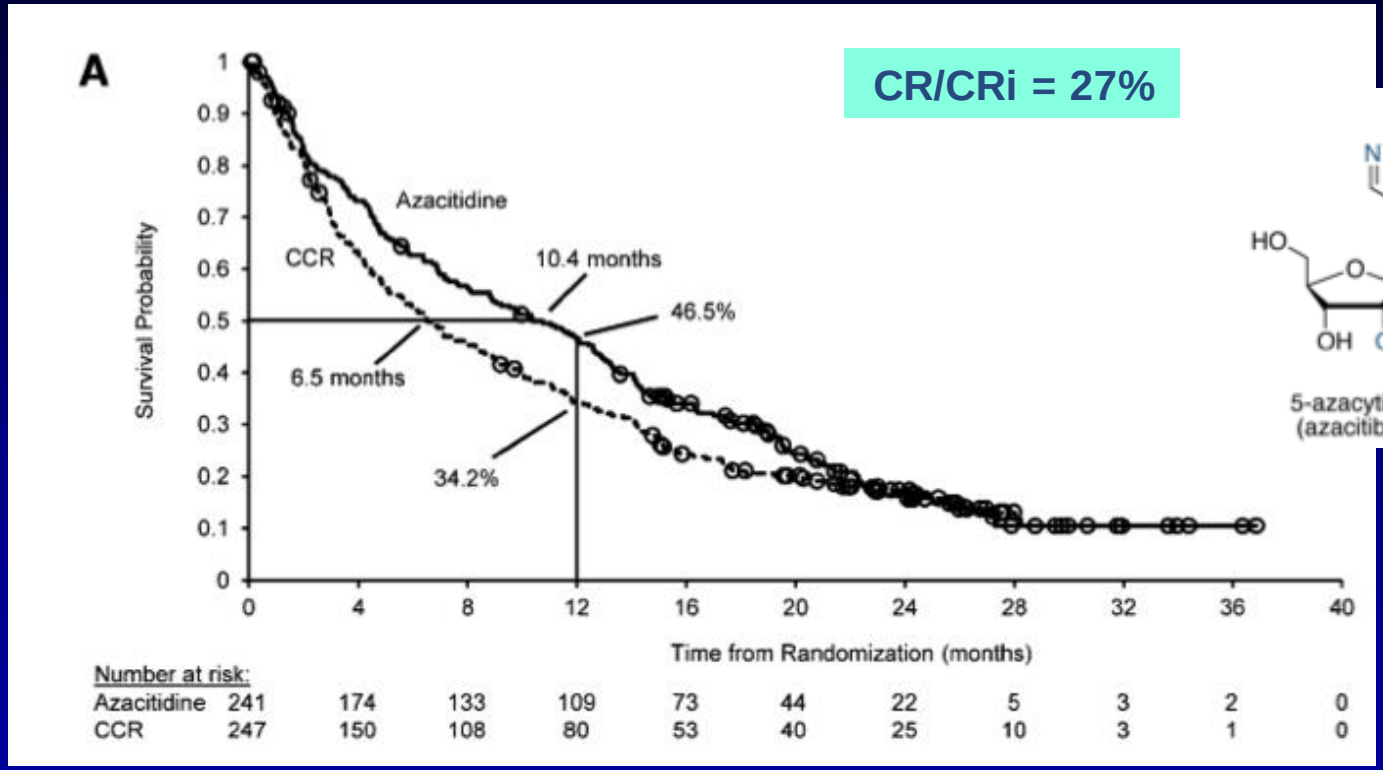
Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

Evolving Diagnostic and Treatment Paradigm for Newly Dx AML

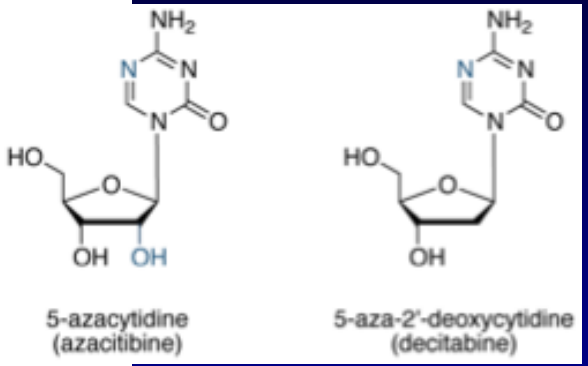


Daver N, et al. *Blood Cancer J.* 2020;10(10):107.

HMA-Based Therapies for Older AML: Hypomethylating Agents Are Well Tolerated and Safe in Older Patients, but Modest Single-Agent CR/CRi



CR/CRi = 27%



Dombret H, et al. *Blood*. 2015;36126(3):291-299.

Azacitidine +/– Venetoclax (VIALE-A) Study Design

Eligibility

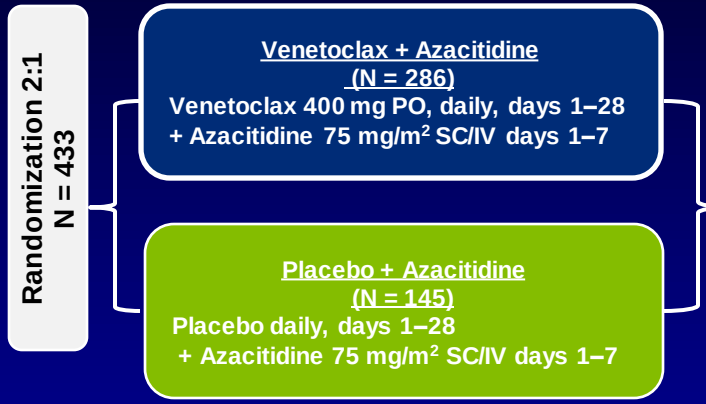
Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least 1 of the comorbidities
    - CHF requiring treatment or ejection fraction ≤50%
    - Chronic stable angina
    - DLCO ≤65% or FEV1 ≤65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable-risk cytogenetics per NCCN
- Active CNS involvement

Treatment



Endpoints

Primary

- Overall survival

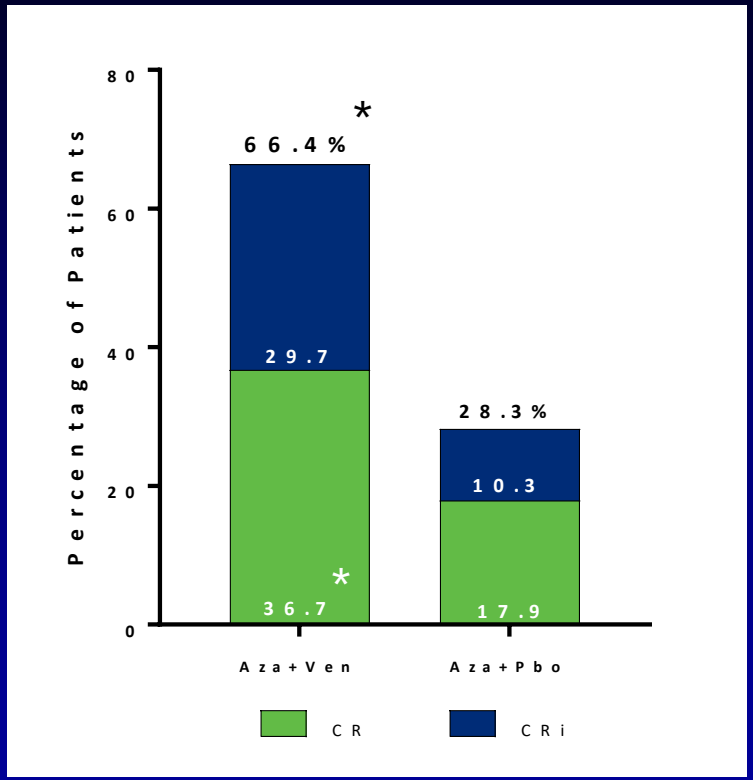
Secondary

- CR + CRi rate
- CR + CRh rate
- CR + CRi and CR + CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR + CRi rates and OS in molecular subgroups
- Event-free survival

Randomization stratification factors	Age (<75 vs ≥75 years); cytogenetic risk (intermediate, poor); region
Venetoclax dosing ramp-up	**Cycle 1 ramp-up** Day 1: 100 mg, day 2: 200 mg, day 3–28: 400 mg **Cycle 2** → Day 1–28: 400 mg

DiNardo CD, et al. EHA 2020. Abstract LB2601.

Aza +/– Ven in AML: Composite Response Rate (CR + CRi)

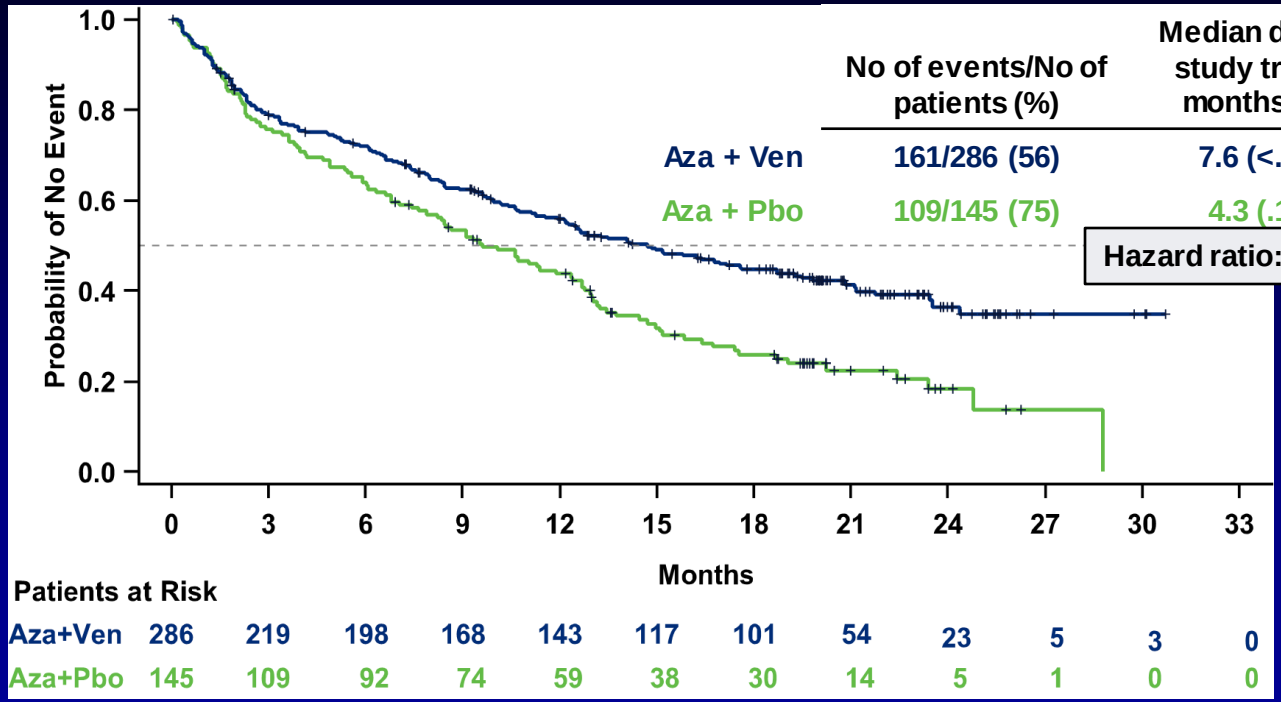


	No of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR + CRi by initiation of Cycle 2, n (%)
Aza + Ven (n = 286)	7.0 (1.0–30.0)	1.3 (.6–9.9)	124 (43.4)
Aza + Pbo (n = 145)	4.5 (1.0–26.0)	2.8 (.8–13.2)	11 (7.6)

*CR + CRi rate, CR rate, and CR + CRi by initiation of cycle 2 are statistically significant with *P* <.001 by CMH test.

DiNardo CD, et al. EHA 2020. Abstract LB2601.

AZA +/- VEN in AML: Overall Survival



	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 (<.1–30.7)	14.7 (11.9–18.7)
Aza + Pbo	109/145 (75)	4.3 (.1–24.0)	9.6 (7.4–12.7)

Hazard ratio: .66 (95% CI: .52–.85), *P* <.001

Median follow-up time: 20.5 months (range: <.1–30.7)

DiNardo CD, et al. EHA 2020. Abstract LB2601.

Pratz 1944: Cytopenia Management in Patients With Newly Diagnosed Acute Myeloid Leukemia Treated With Venetoclax Plus Azacitidine in the VIALE-A Study

Protocol (VIALE-A – NCT02993523)

- Phase III, double-blind, placebo controlled, 2:1 randomization of Ven + Aza vs Pbo + Aza
- Analysis of frequency and management of cytopenia in patients with CR or CRh

Population

- Patients with newly diagnosed AML ineligible for intensive chemotherapy due to age ≥75 years or comorbidities

Authors' conclusions

- Majority of Ven + Aza responders required dosing modifications to manage cytopenia, particularly delays between cycles or within-cycle reductions of Ven dosing days
- Post-remission cytopenia and dosing modifications were more frequent with Ven + Aza vs Pbo + Aza

CR/CRh rate: **66%** (Ven + Aza) vs **23%** (Pbo + Aza)

Cytopenia and dose adjustments in responders (CR/CRh)	Ven + Aza (n = 186)	Pbo + Aza (n = 33)
Post-remission grade 4 cytopenia lasting ≥1 week, %	**87**	**45**
1 episode	19	24
≥2 episodes	68	21
In-cycle dose interruptions for any reason, %	**26**	**24**
Median duration per cycle (range), days	2.0 (1–20)	1.0 (1–13)
Post-remission cycle delays due to cytopenia, %	**77**	**30**
Median duration per cycle delay (range), days	14.0 (1–129)	11.0 (3–63)
Post-remission reduction of Ven/Pbo dosing days and/or cycle delay totaling ≥7 days due to neutropenia, %	**75**	**27**
Median number of cycles (range)	2.0 (0–15)	0 (0–7)
Post-remission Ven/Pbo dosing ≤21-day cycles, %	69	30
Median time from remission to first ≤21-day cycle (range), days	92.0 (1–480)	74.0 (6–405)

AZA, azacitidine; CRh, CR with partial hematologic recovery; Pbo, placebo; Ven, venetoclax.

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

MDACC-Recommended Dosing Schema

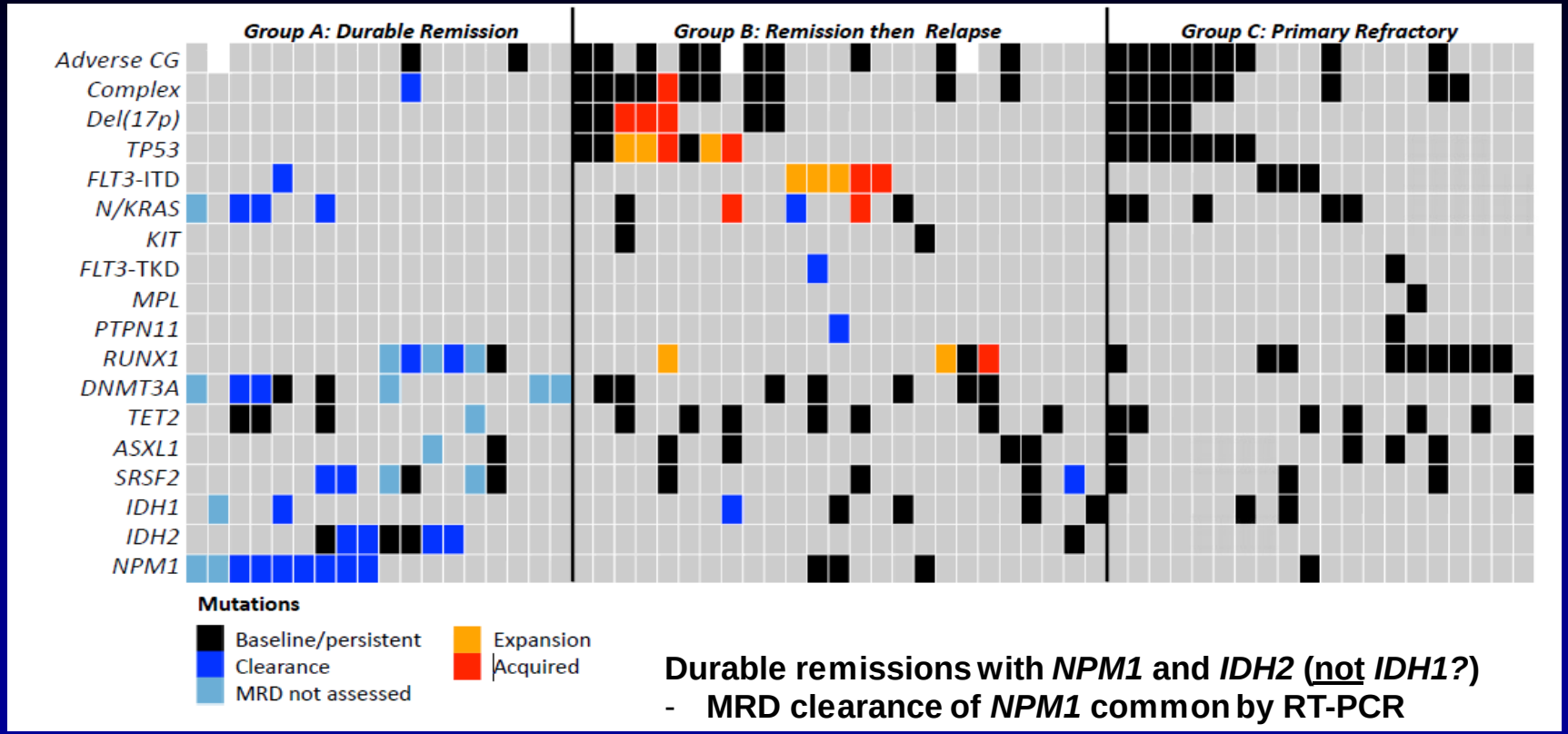
- Ven D1–21 in cycle 1
- Bone marrow EOC1 (D21–D28) for all patients: if BM blasts <5% or <10% cellularity/acellular (majority of patients) – hold VEN 10–14 days for count recovery
- If needed, use G-CSF (usually if no spontaneous recovery after 14 days of Ven interruption)
- Cycle 2 onward: Ven D1–21 (or Ven D1–14) for most (subsequently may be further reduced to 7–10 days if cumulative myelosuppression observed)
- Cycles every 4–6 weeks on the basis of count recovery
- Continue second-generation azole prophylaxis, antibiotic, and antiviral until ANC >1.0 without fluctuations (usually after 4–5 cycles)

KEY: Reducing Ven duration does not seem to impact efficacy, but significantly improves neutropenia; more CR/CRh

Recommended Venetoclax Dose-Adjustments With Azoles

Antifungal	Package Insert Recommendation (Ven mg/d)	MDACC Dose Adjustment (Ven mg/d)
Posaconazole	70	50–100
Voriconazole	100	100
Isavuconazole	200	200
Caspofungin, echinocandins	400	400

Molecular Determinants of Outcome With Venetoclax Combos



Durable remissions with *NPM1* and *IDH2* (not *IDH1?*)
- **MRD clearance of *NPM1* common by RT-PCR**

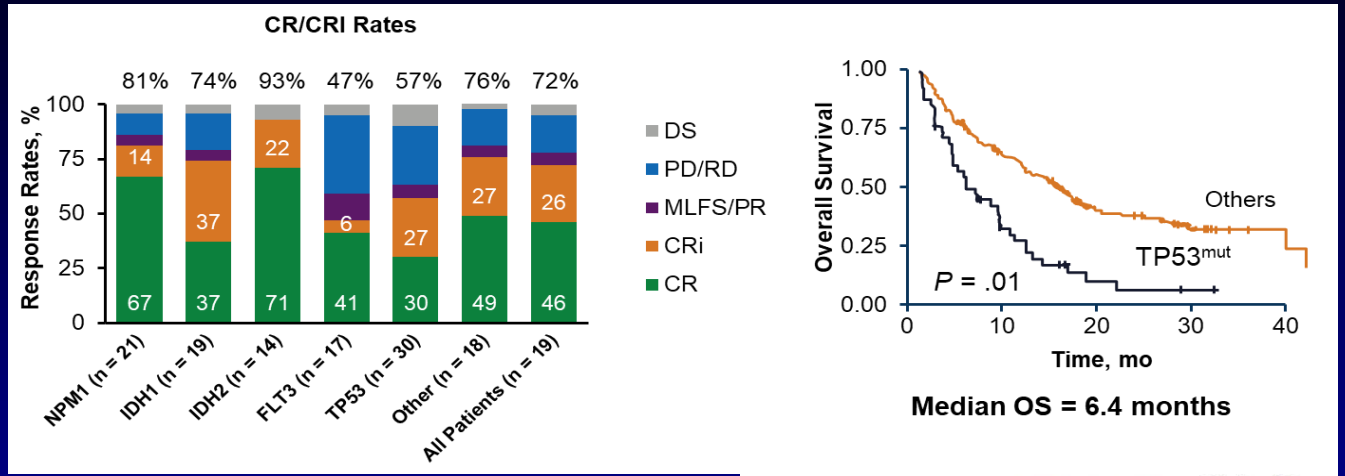
Patients treated at MDACC and The Alfred (n = 81)

Resistance commonly associated with expansion or acquisition of *TP53* or signaling mutations including *K/NRAS* and *FLT3*-ITD

DiNardo CD, et al. *Blood*. 2020;135(11):791-803.

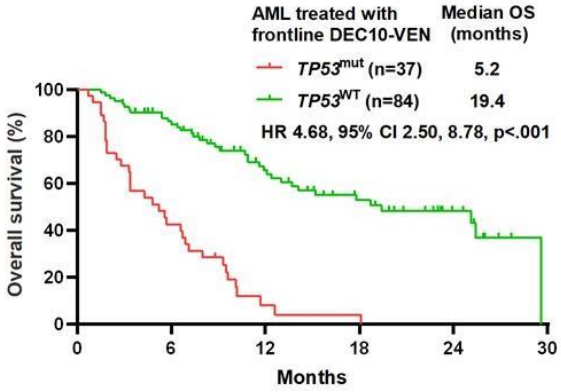
1. Poor Outcomes in *TP53*-Mutant AML, Even With Venetoclax-Based Treatment

Venetoclax + LDAC or HMA[1]



N = 121 patients with newly diagnosed AML receiving decitabine + venetoclax[2]

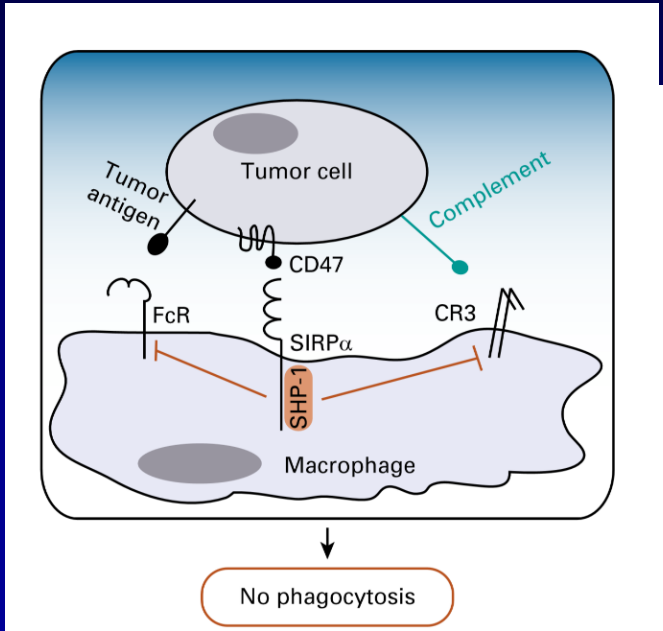
- **Those with *TP53*^{mut} had a lower rate of CR at 35% vs 57% in pts with *TP53*^{WT} (*P* = .026)**
- Lower rate of CR/CRi (54% vs 76%; *P* .015)



1. Chyla BJ, et al. ASH 2019. Abstract 546; 2. Kim K, et al. ASH 2020. Abstract 693.

CD47 Is a Major Macrophage Immune Checkpoint and "Do Not Eat Me" Signal in Myeloid Malignancies, Including AML

- CD47 is a "do not eat me" signal in cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in AML patients



CD47 Expression in AML Patients

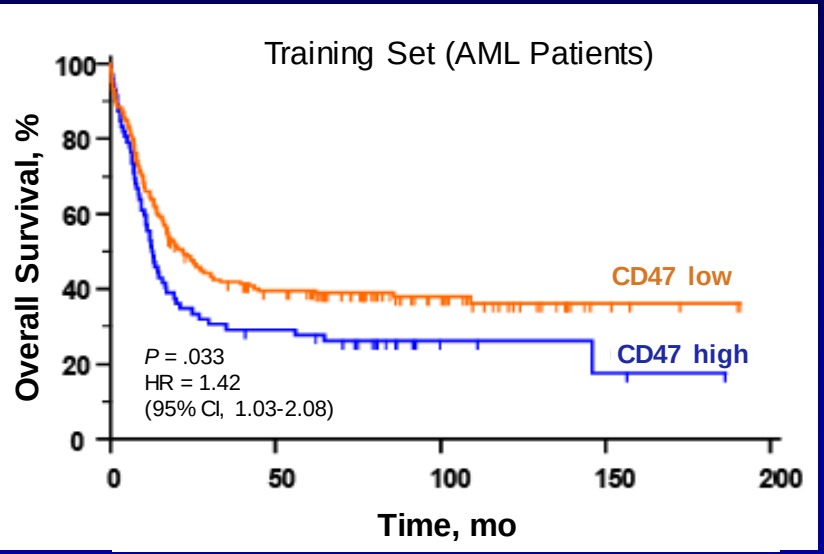
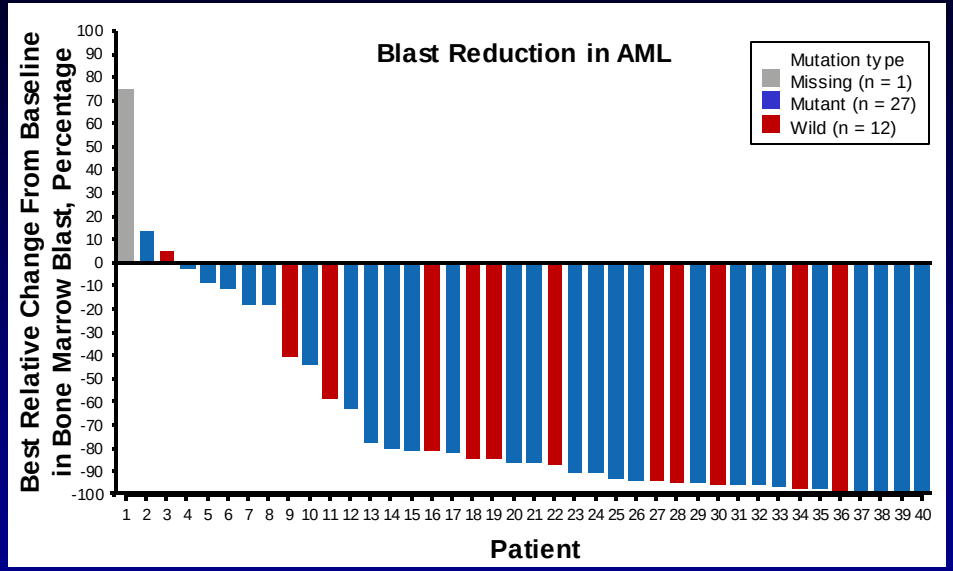


Figure at left adapted from Veillette A, Tang Z. *J Clin Oncol*. 2019;37:1012-1014 and Chao MP, et al. *Curr Opin Immunol*. 2012;24:225-232.
Figure at right adapted from Majeti R, et al. *Cell*. 2009;138:286-299.

Magrolimab + AZA in Newly Diagnosed AML[1,2]

Best Overall Response	All AML (N = 43), n (%)	*TP53*-Mutant AML (n = 29), n (%)
ORR	27 (63)	20 (69)
CR	**18 (42)**	**13 (45)**
CRi	5 (12)	4 (14)
PR	1 (2)	1 (3)
MLFS	3 (7)	2 (7)
SD	14 (33)	8 (28)
PD	2 (5)	1 (3)



- Magrolimab + AZA with 63% ORR and **42% CR rate** in AML (similar responses in *TP53*-mutant disease)
- Median time to response is 1.95 months (range, 0.95–5.6 mo); more rapid than AZA monotherapy
- Magrolimab + AZA efficacy compares favorably with AZA monotherapy (CR rate: 18%–20%)
- No significant cytopenias, infections, or immune-related AEs were observed; on-target anemia
- Median *TP53* VAF burden at baseline: **73.3% (range 23.1%–98.1%)**

1. Daver N, et al. EHA 2020. Abstract S144; Sallman D, et al. ASH 2020. Abstract 330.

AZA-VEN-Magro in Frontline and R/R AML Results: Response Rates per ITT (n = 48)

Outcomes	Frontline Cohort (n = 25)		R/R Cohort (n = 23)	
	TP53 mutated (n = 14)	*TP53* wild type (n = 11)	VEN-naive (n = 8)	Prior VEN (n = 15)
ORR	**12 (86)**	**11 (100)**	**6 (75)**	**3 (20)**
CR/Cri	9 (64)	10 (91)	5 (63)	3 (20)
CR	**9 (64)**	**7 (64)**	**3 (38)**	**0**
CRi	0	3 (27)	2 (25)	3 (20)
MLFS/PR[1]	3 (21)	1 (9)	1 (13)	0
MRD neg FCM	5/9* (55)	4/9 (45)	2/6 (33)	0
CCyR	4/9‡ (44)	5/6 (83)	3/5 (60)	1/2 (50)
No response	2 (14)	0	2 (25)	12 (80)
TT First response	**.7 [.6–1.9]**	**.7 [.7–1.5]**	.7 [.6–4.1]	2.2 [1.8–2.6]
TT Best response	1.5 [.7–3.2]	1.1 [.7–2.9]	1.5 [1.0–4.1]	2.0 [1.2–3.9]
Med TT ANC >500	**28 (20–41) days**			
Med TT Plt >50K	**24 (18–41) days**			
8-wk mortality	**0**	**0**	**1 (13)**	**3 (20)**

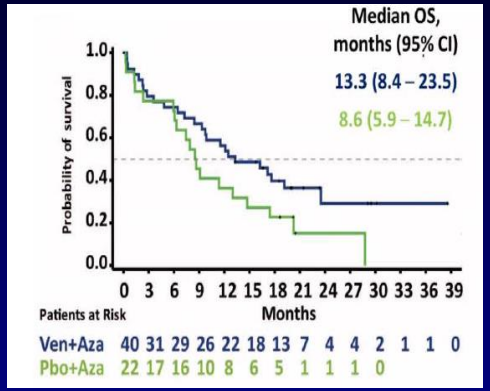
Results expressed as n (%), n/N (%) or median [range]. FCM = multiparametric FCM, sensitivity .1–.01%, *Only among pts with evaluable longitudinal samples; ‡Only among patients with baseline cytogenetic aberrations and longitudinal cytogenetic samples; 1Two with PR per ELN2017

2. FLT3: AZA + VEN Improved Responses vs AZA in *FLT3*-Mutated Newly Diagnosed AML, But Median OS Was <12 Months

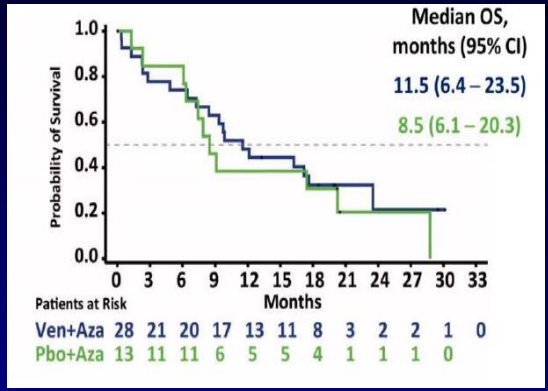
CR + CRi, n/N (%)	VEN + AZA	PBO + AZA
FLT3 mutation	28/40 (70)	8/22 (36)
FLT3 WT	150/227 (66)	21/86 (24)
***FLT3*-ITD**	**19/28 (68)**	**6/13 (46)**
FLT3-ITD AR <0.5	14/19 (74)	4/8 (50)
FLT3-ITD AR ≥0.5	5/9 (56)	2/5 (40)
***FLT3*-TKD**	**10/13 (77)**	**3/10 (30)**
FLT3 and *NPM1* comutation	10/14 (71)	2/7 (29)

Median Duration of CR + CRi	VEN + AZA		PBO + AZA	
	N	Months (95% CI)	N	Months (95% CI)
FLT3 mutation	28	17.3 (10.1–NR)	8	5.0 (1.0–15.9)
FLT3 WT	150	18.2 (14.0–NR)	21	13.4 (5.8–15.6)

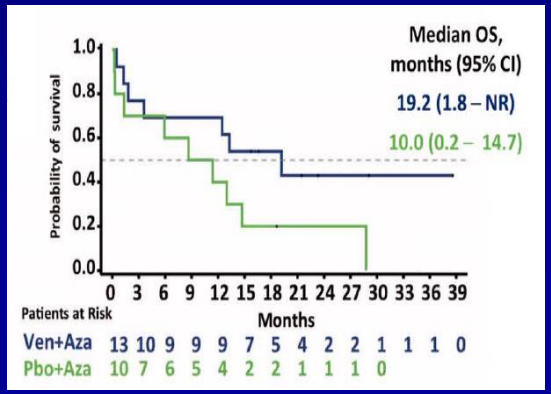
FLT3



***FLT3*-ITD**

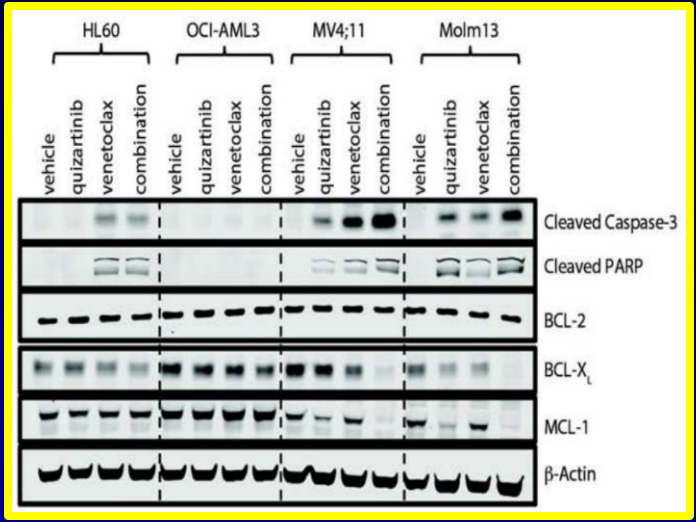


***FLT3*-TKD**

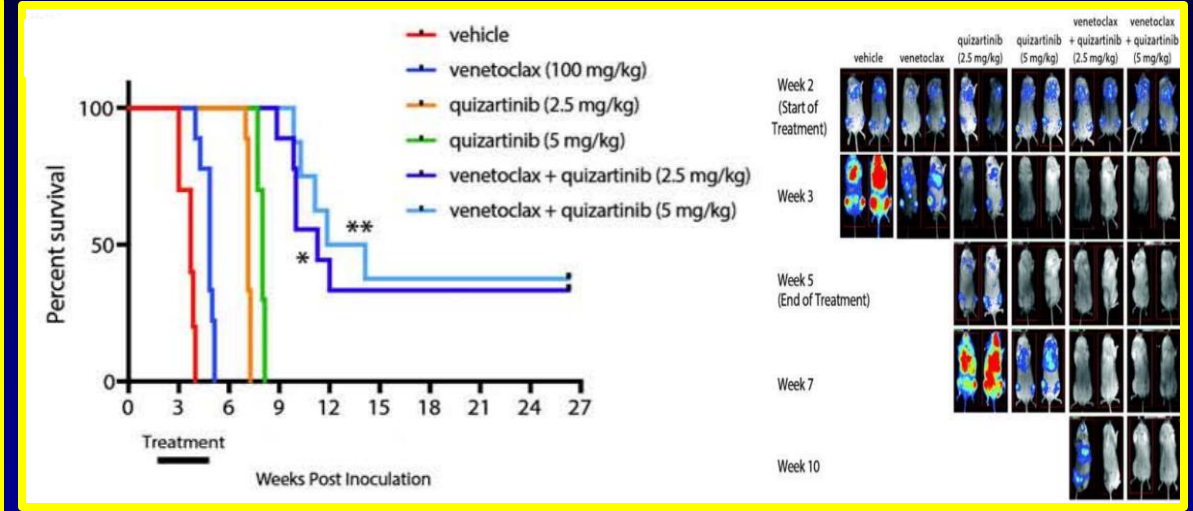


Konopleva M, et al. *Blood.* 2020;136:abstract 1904.

Venetoclax Combines Synergistically With Quizartinib



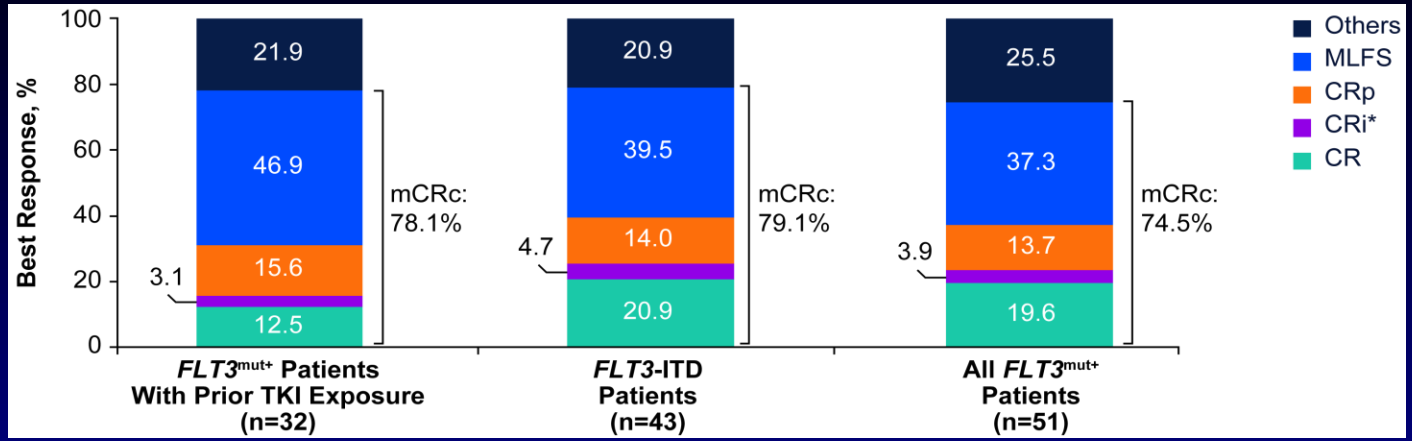
Cell lines were treated with combination – ↓ MCL-1, ↓ BCL-X_L



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.

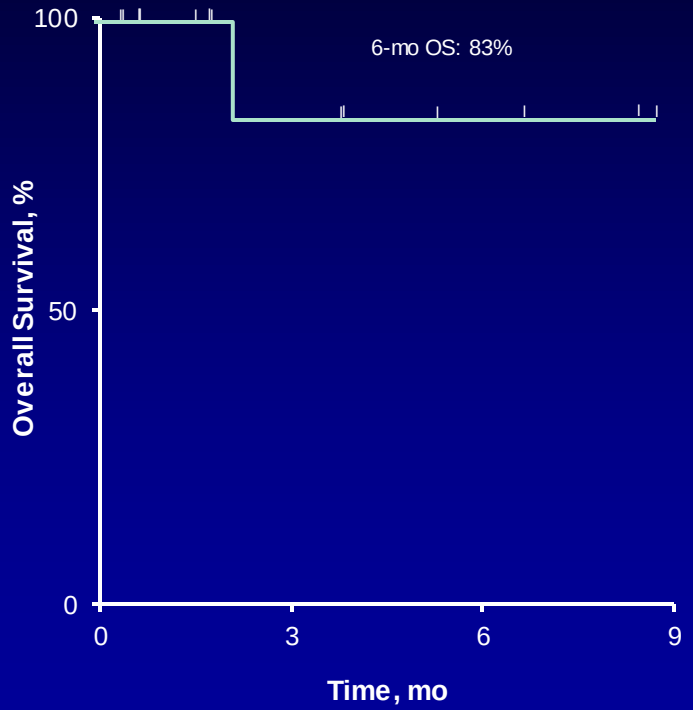
Novel Triplets (Azacitidine, Venetoclax, and Gilteritinib) Show Promising Early Activity in Newly Diagnosed AML

ASH 2021: phase I/II study of AZA, venetoclax, and gilteritinib in patients with a *FLT3* mutation (n = 26)

- R/R *FLT3*-mutated AML
- High-risk MDS/CMML
- Newly diagnosed *FLT3*-mutated AML unsuitable for intensive chemotherapy were eligible

Results: The triplet was effective in this *FLT3*-mutated AML population

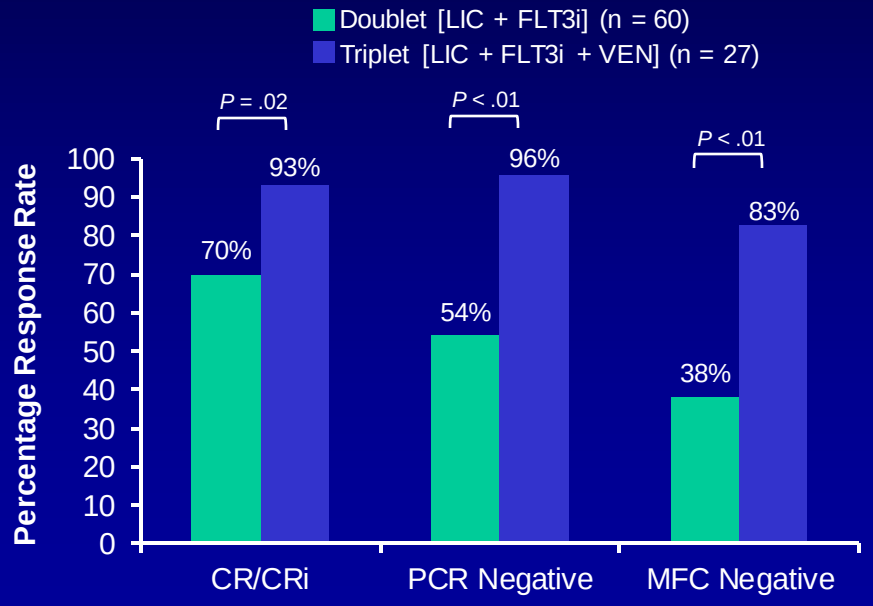
- CRc of 100% in the frontline setting (n = 11)
- Gilteritinib dosing at 80 mg daily was associated with a better safety/efficacy profile (especially myelosuppression) and was selected for future study



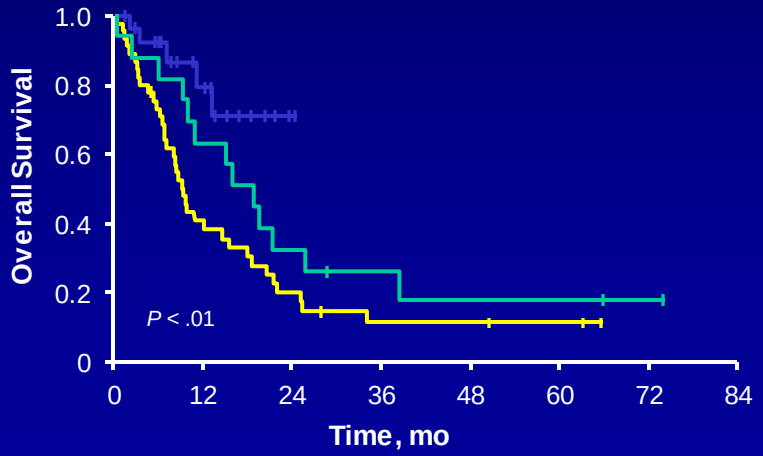
Short N, et al. ASH 2021. Abstract 696.

Retrospective Pooled Analysis Suggests That Frontline Triplets May Be Highly Active in *FLT3*-Mutant AML

- First- and second-generation FLT3i-based doublet and triplet regimens in older/unfit adults with newly diagnosed *FLT3*-mutated AML (N = 87)
  - Doublets (FLT3i + low-intensity chemotherapy): CRc: 70%; survival of 9–16 mo
  - HMA/VEN/FLT3i combination significantly improved CR/CRi rates, CR rates, *FLT3*-PCR and MFC MRD rates, as well as OS, without increasing 60-day mortality (7% vs 10%)



Treatment Regimen	N = 87	Median Age	Median OS, mo
Triplet (LIC + FLT3i + VEN)	27	69 (40–85)	NR
Doublet (LIC + 2nd generation FLT3i)	16	71 (64–83)	15.7
Doublet (LIC + 1st generation FLT3i)	44	70 (51–83)	8.7



Yilmaz M, et al. ASH 2021. Abstract 798.

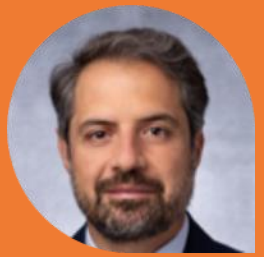
Leukemia Questions?

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

Global Leukemia Academy

Session close

Elias Jabbour



APTITUDE HEALTH

Question 1

Which of the following is NOT true?

1. Inotuzumab and blinatumomab + chemotherapy is active in both frontline and salvage for ALL
2. ALK inhibitors can be combined with other therapy modalities in Ph+ ALL
3. MRD is highly prognostic for relapse and survival in Ph-negative ALL
4. CAR T approaches are active beyond 2L in Ph-negative ALL

Question 2

In AML the MRD assessment by RT-qPCR is especially useful for

1. *FLT3* ITD
2. *NPM1* mutation
3. Biallelic *CEBPA* mutation
4. *SF3B1* mutation
5. *ASXL1* mutation

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

Virtual Breakout – Pediatric Leukemia Patients (Day 2)

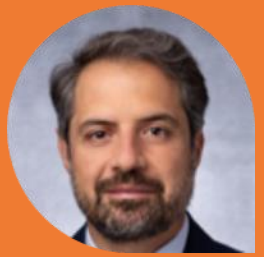
Co-chair: Franco Locatelli

TIME (UTC-3)	TITLE	SPEAKER
10.00 – 10.10	Session open	Franco Locatelli
10.10 – 10.30	The use of MRD and genetics for risk stratification and therapy guidance in pediatric ALL	Rob Pieters
10.30 – 10.50	First-line treatment of pediatric ALL, including HSCT	Christina Peters
10.50 – 11.10	Current treatment options for relapsed ALL in children, including HSCT	Franco Locatelli
11.10 – 11.25	Bispecifics for pediatric and AYA B-ALL	Christina Peters
11.25 – 11.55	ALL case-based panel discussion • Case 1 (10 min) – Irene Medina (Mex) • Case 2 (10 min) – Jorge Buitrago (Col) • Discussion (10 min) – Panelists: Maria Sara Felice, Oscar Gonzáles Ramella, Adriana Seber, Carlos Andrés Portilla	All
11.55 – 12.00	Break	
12.00 – 12.20	Current treatment options for pediatric AML	Franco Locatelli
12.20 – 12.50	AML case-based panel discussion • Case 1 (10 min) – Luisina Peruzzo (Arg) • Case 2 (10 min) – Erica Viana (Bra) • Discussion (10 min) – Panelists: Maria Sara Felice, Oscar Gonzáles Ramella, Adriana Seber, Carlos Andrés Portilla	All
12.50 – 13.00	Session close	Franco Locatelli

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

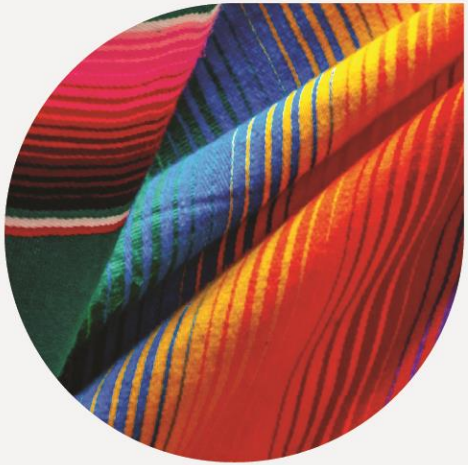
Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

SEE YOU TOMORROW!

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®