Updates from ASH 2022

Acute Leukemias: Treatment (R)Evolution!

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With huge debt of gratitude to Dr. Geoff Uy

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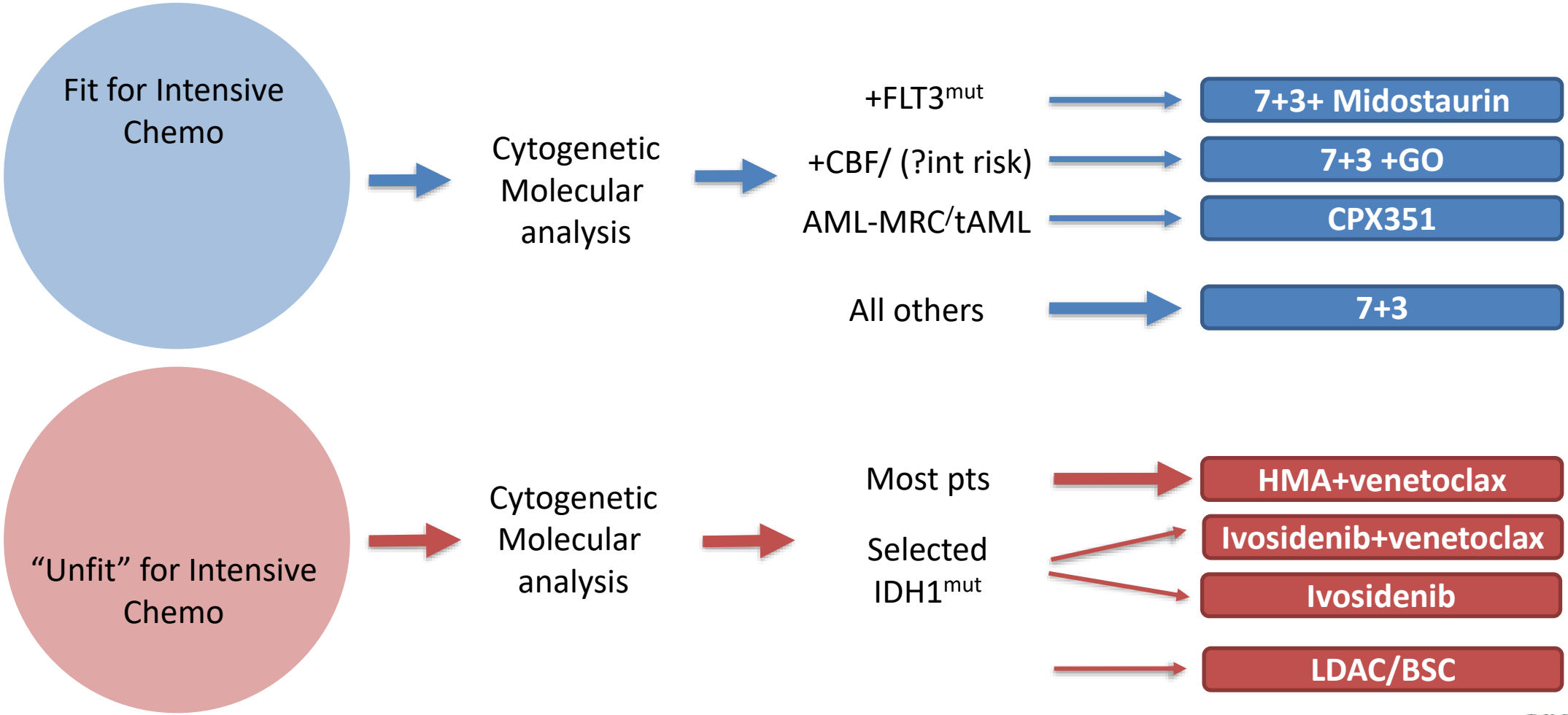
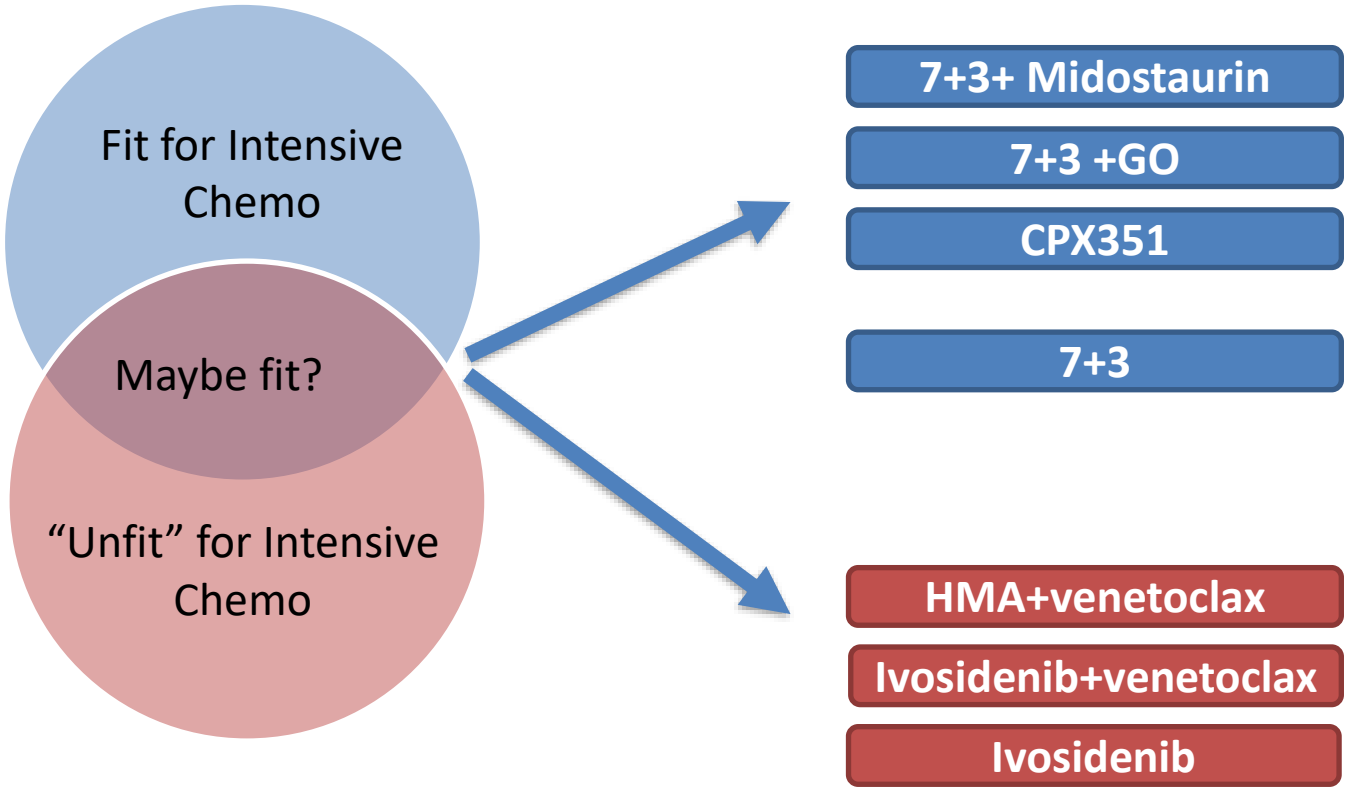
Outline:

- AML : The landscape shifts increasingly to AZA-VEN frontline
  - Longer term f/u still shows a survival advantage
  - Do all subsets respond equally?
- AML: How can we improve on Aza/VEN?
  - FLT3 mutant
  - TP53 mutant
- ALL: Importance of eradicating MRD, Changing paradigms
  - E1910 surprises us by showing power of blina in MRD ”neg” benefits
  - Ph+ ALL : TKI + Blinatumomab: outstanding early outcomes without transplant

Management of AML in 2023



Management of AML in 2023

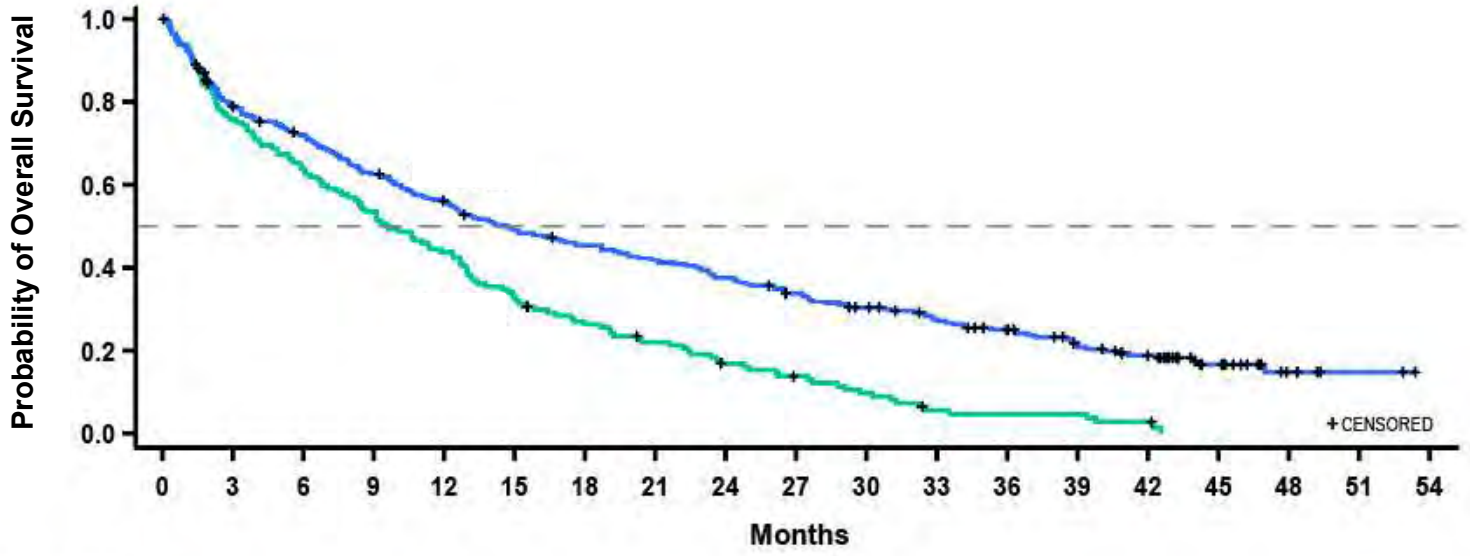


The reality

- Decisions for initial treatment of AML are frequently made with incomplete information
- Age is a poor predictor of treatment tolerance and validated measures of fitness and frailty do not exist
- Assessment of who is "appropriate" for what therapy is an evolving target
  - Outcomes of "less intensive" treatments are improving
  - "less intensive" treatments are becoming more "intense"
  - Improved understanding of how biologic subsets respond to specific treatments

Patients treated with Ven+Aza continue to show OS benefit over those on Aza monotherapy

Median follow-up time: 43.2 months (range: < 0.1 - 53.4)



Patients at Risk																			
Ven+Aza	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0
Pbo+Aza	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0	0	0	0

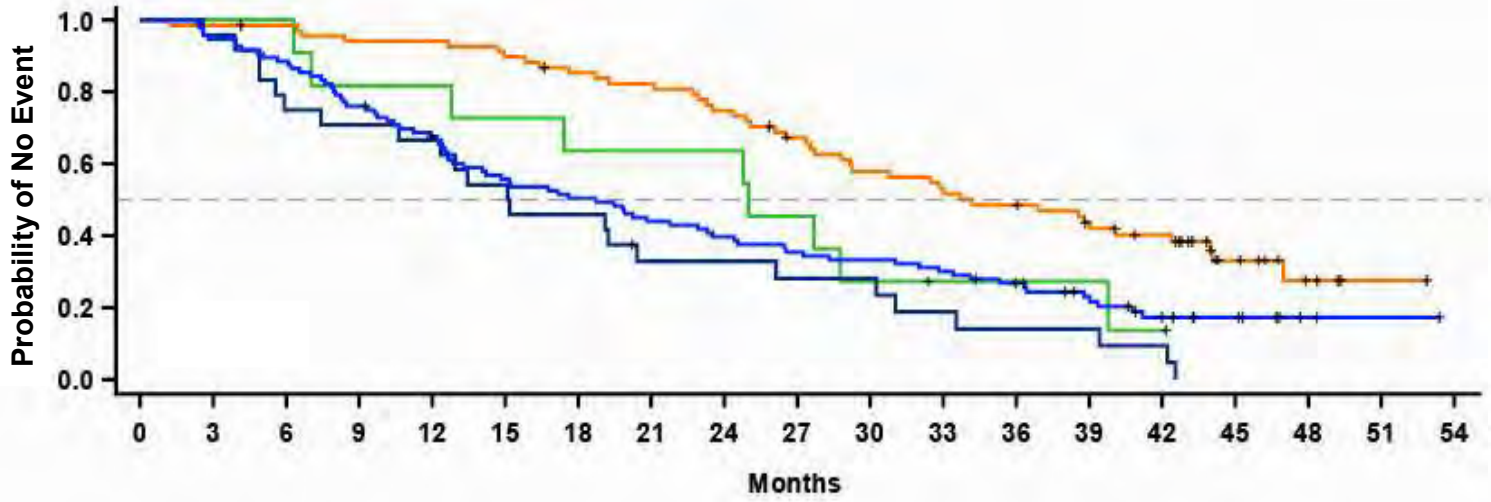
	No. of events/No. of patients (%)	OS (months) median (95% CI)
Ven+Aza	222/286 (77.6)	14.7 (12.1 - 18.7)
Pbo+Aza	138/145 (95.2)	9.6 (7.4 - 12.7)

Hazard ratio: 0.58 (95% CI, 0.465 - 0.723), P < 0.001

HR reduction from 0.66 (95% CI, 0.52 - 0.85) at 75% OS analysis

The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk); The hazard ratio between treatment arms were estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test; Data cutoff: 01 Dec 2021
Abbreviations: Aza, azacitidine; Pbo, placebo; Ven, venetoclax

Median OS is longer for MRD < 10^{-3} than MRD ≥ 10^{-3} in patients who achieved CR+CRi on Ven+Aza



	No. of events/No. of patients (%)	OS (months) median (95% CI)
Ven+Aza MRD < 10^{-3}	43/69 (62)	34.2 (27.7 - 44.0)
Ven+Aza MRD ≥ 10^{-3}	76/96 (79)	18.7 (12.9 - 23.5)

Patients at Risk

Ven+Aza MRD < 10^{-3}	69	68	67	64	64	61	57	55	50	43	37	34	31	26	22	10	4	1	0
Ven+Aza MRD ≥ 10^{-3}	96	91	85	73	63	52	47	41	37	33	31	28	23	17	10	7	2	1	0
Pbo+Aza MRD < 10^{-3}	11	11	11	9	9	8	7	7	7	5	3	2	2	2	1	0			
Pbo+Aza MRD ≥ 10^{-3}	24	23	18	17	16	13	11	7	7	6	6	4	3	3	2	0			

The distributions were estimated for each treatment arm using Kaplan-Meier methodology; Data cutoff: 01 Dec 2021;
Abbreviations: Aza; azacitidine; Pbo, placebo; MRD, minimal residual disease; Ven, venetoclax

Penn Medicine

American Society of Hematology 2022

Real World Effectiveness of “7 + 3” Intensive Chemotherapy Vs Venetoclax and Hypomethylating Agent for Initial Therapy in Adult Acute Myeloid Leukemia

Andrew H. Matthews, MD[1]; Alexander E. Perl, MD[1]; Selina M. Luger, MD[1]; Saar I. Gill, MD, PhD[1]; Catherine Lai, MD, MPH[1]; David L. Porter, MD[1]; Sarah Skuli, MD, PhD[1]; Ximena Jordan Bruno MD[1]; Martin P. Carroll, MD[1]; Daria V. Babushok MD, PhD[1]; Noelle V. Frey, MD[1]; Elizabeth O. Hexner, MD[1]; Mary Ellen Martin MD[1]; Shannon R. McCurdy, MD[1]; Edward A. Stadtmauer MD[1]; Alison W. Loren, MD[1]; Vikram Paralkar, MD[1]; Ivana K. Maillard, MD, PhD[1]; Keith W. Pratz, MD[1]

December 11, 2022

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ELN Risk Stratification and Outcomes Among Treatment-Naïve Patients With Acute Myeloid Leukemia Treated With Venetoclax and Azacitidine

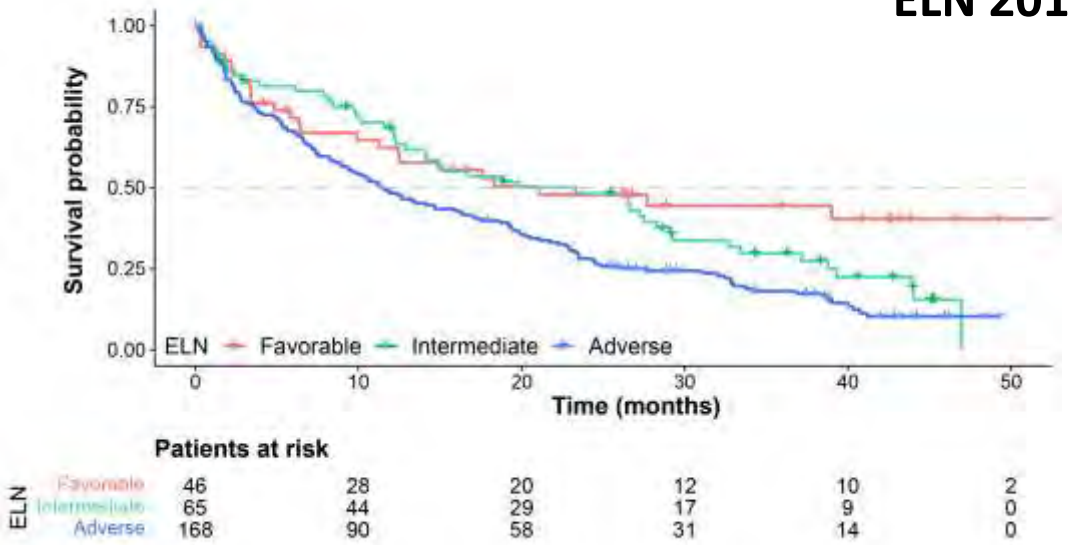
Hartmut Döhner[1], Keith W. Pratz[2], Courtney D. DiNardo[3], Brian A. Jonas[4], Vinod A. Pullarkat[5], Michael J. Thirman[6], Christian Recher[7], Andre C. Schuh[8], Sunil Babu[9], Monique Dail[10], Grace Ku[10], Yan Sun[11], Jalaja Potluri[11], Brenda Chyla[11], Daniel A. Pollyea[12]

[1]Department of Internal Medicine III, Ulm University Hospital, Ulm, Germany; [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Leukemia, Division of Cancer Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [4]Department of Internal Medicine, Division of Cellular Therapy, Bone Marrow Transplant and Malignant Hematology, University of California Davis School of Medicine, Sacramento, CA, USA; [5]Department of Hematology and Hematopoietic Cell Transplantation and Gehr Family Center for Leukemia Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [6]Section of Hematology and Oncology, Department of Medicine, University of Chicago Medicine, Chicago, IL, USA; [7]CHU de Toulouse; Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France; [8]Princess Margaret Cancer Centre, Toronto, Canada; [9]Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN, USA; [10]Genentech Inc., South San Francisco, CA, USA; [11]AbbVie Inc., North Chicago, IL, USA; [12]University of Colorado Division of Hematology, School of Medicine, Aurora, CO, USA

American Society for Hematology 2022, New Orleans, LA, USA

ELN recommendations do not provide clinically meaningful outcome stratification for patients treated with Ven+Aza

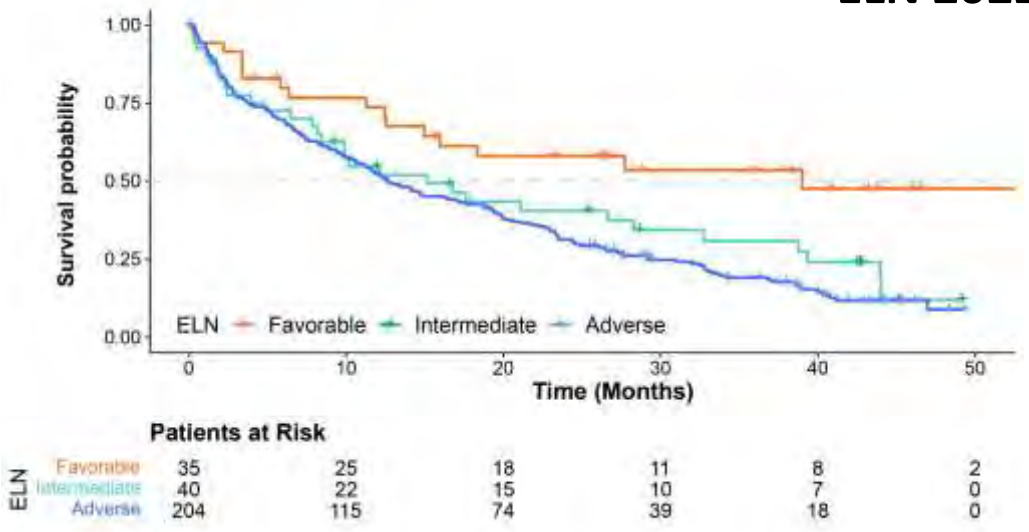
ELN 2017



ELN 2017	n	Events	Median OS, mo (95% CI)
Favorable	46	25	21.09 (9.92 – NE)
Intermediate	65	48	23.26 (12.85 – 28.29)
Adverse	168	141	11.53 (8.87 – 16.23)

- Overlapping outcomes to Ven+Aza for favorable and intermediate-risk patients

ELN 2022



ELN 2022	n	Events	Median OS, mo (95% CI)
Favorable	35	16	39.0 (12.52 – NE)
Intermediate	40	30	15.15 (8.18 – 28.29)
Adverse	204	168	12.65 (10.41 – 17.15)

- Overlapping outcomes to Ven+Aza for intermediate and adverse-risk pts;
- A small population of favorable-risk pts, primarily with *NPM1* mutations, show prolonged mOS of 39 months

Abbreviations: Aza, azacitidine; CI, confidence interval; ELN, European LeukemiaNet; HR, hazard ratio; mo, months; Pbo, placebo; NCCN, National Comprehensive Cancer Network; Ven, venetoclax

Pooled analysis of Ven+Aza treated patients to evaluate prognostic subgroups

Objective

Divide patients treated with Ven+Aza into three distinct groups based on OS, and then determine how these groups differ with respect to baseline cytogenetic/molecular data

Approach

Sequential-BATTing method[1] to derive algorithm

- Subgroup identification method to define subgroups as distinctive as possible from the remainder of the population.
- Minimize the *P* value of HR between the selected subgroup versus the remainder of the population

30 genetic markers as candidate predictors

- Included in the ELN 2022 recommendations and/or
- Genes with prevalence ≥ 10% in the analysis population of patients in the Ven+Aza arm

Limitation: 11 of the genetic markers have prevalence < 10% and may be too small to identify a signal

Cytogenetics	Ven+Aza (N=279)	Prev. (%)
Com. karyotype	72	25.8
del(5q)	49	17.6
del(7q)	48	17.2
del(17p)	15	5.4
t(v;11q23)	7	2.5
inv(3)	6	2.1

Mol. mutations detected	Ven+Aza (N=279)	Prevalence (%)
TET2	81	29.0
IDH1/2	77	27.6
DNMT3A	72	25.8
RUNX1	70	25.1
TP53	63	22.6
SRSF2	62	22.2
FLT3-TKD	59	21.1
IDH2	47	16.8
NPM1	46	16.5
FLT3-ITD	43	15.4
N/KRAS	42	15.0
ASXL1	35	12.5
STAG2	34	12.2
IDH1	32	11.5
BCOR	29	10.4
EZH2	16	5.7
SF3B1	23	8.2
U2AF1	26	9.3
CEBPA	13	4.7
ZRSR2	6	2.1
CEBPA-bZip	4	1.4

[1]Huang et. al. Stat. Med., 2017; Favorable-risk pts with CBF-AML [inv(16), t(8;21)] were excluded from the trials, except for one patient who was enrolled with poor cytogenetic risk; inv(6) and t(8;21) were included in the thirty genetic markers that were analyzed; Abbreviations: Aza, azacitidine; ELN, European LeukemiaNet; HR, hazard ratio; OS, overall survival; Ven, venetoclax

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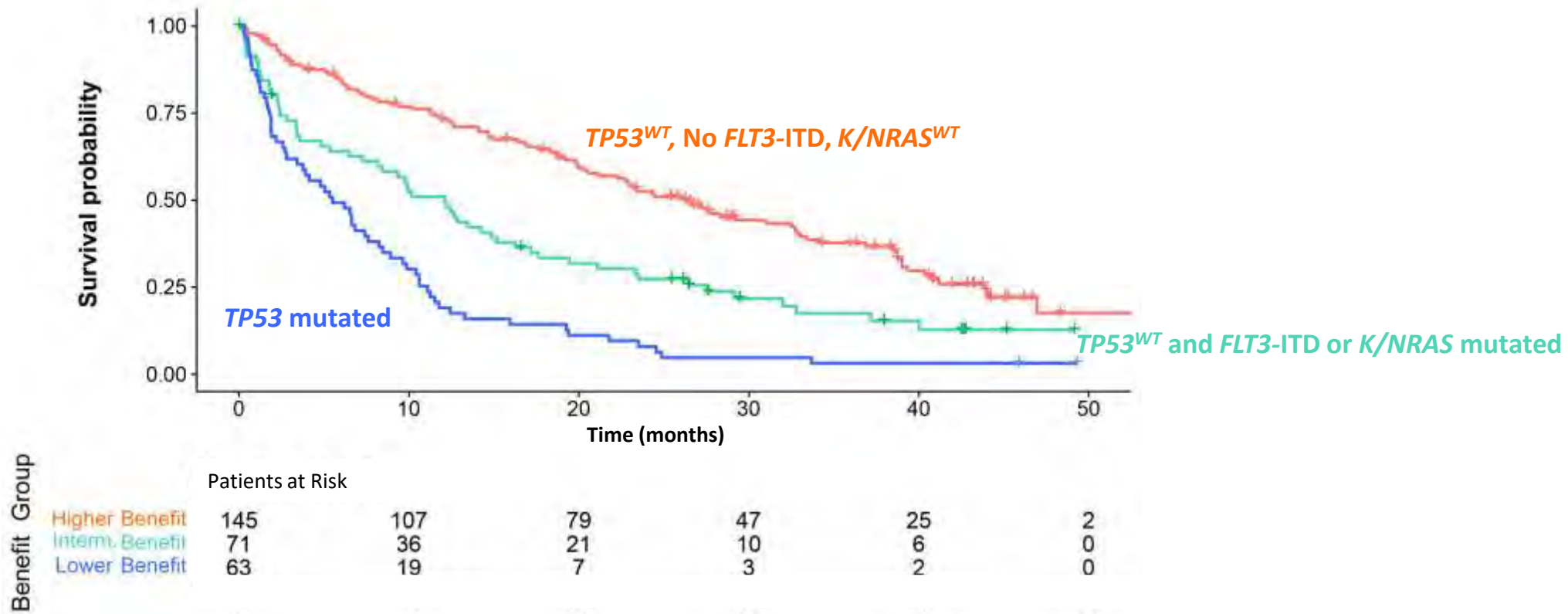
Three prognostic risk signatures derived to indicate higher, intermediate, and lower benefit from treatment with Ven+Aza



Abbreviations: Aza, azacitidine; OS, overall survival; Ven, venetoclax; WT, wild-type

Can we improve on the outcomes of Aza/ven?

- Addition of a targeted agent
  - FLT3, IDH1, IDH2
- Nontargeted novel agents for high risk subsets (*TP53*)
  - Anti-CD47 Ab (Magrolimab)

Updated results from a phase I/II study of the triplet combination of azacitidine, venetoclax and gilteritinib for patients with *FLT3*-mutated acute myeloid leukemia

NJ Short, CD Dinardo, N Daver, W Macaron, M Yilmaz, G Borthakur, G Montalban-Bravo, G Garcia-Manero, GC Issa, K Sasaki, P Thompson, J Burger, A Maiti, Y Alvarado, M Kwari, R Delumpa, J Thankachan, E Mayor, C Loiselle, A Milton, G Banks, T Kadia, M Konopleva, H Kantarjian, F Ravandi

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Aza+Ven+Gilteritinib in FLT3-mutated AML: Regimen

- Relapsed/refractory *FLT3*-mutated* AML or high-risk MDS or CMML

or

- Newly diagnosed *FLT3*-mutated* AML unfit for intensive chemotherapy

Induction

Azacitidine
75 mg/m² IV/SC on D1-7

Venetoclax#
D1-28 (bone marrow on D14)%

Gilteritinib
80-120 mg on D1-28

Consolidation

Azacitidine
75 mg/m² IV/SC on D1-5

Venetoclax
400mg on D1-7

Gilteritinib
80-120 mg on D1-28

Venetoclax ramp-up during cycle 1:
100mg on D1, 200mg on D2, 400mg on D3+

% If <5% blasts or insufficient on C1D14, venetoclax held (both cohorts) and gilteritinib held (frontline only)

Primary endpoints: MTD of gilteritinib in combination (phase I), CR/CRi rate (phase II)

Secondary endpoints: CR rate, MRD negativity rate, duration of response, OS, safety

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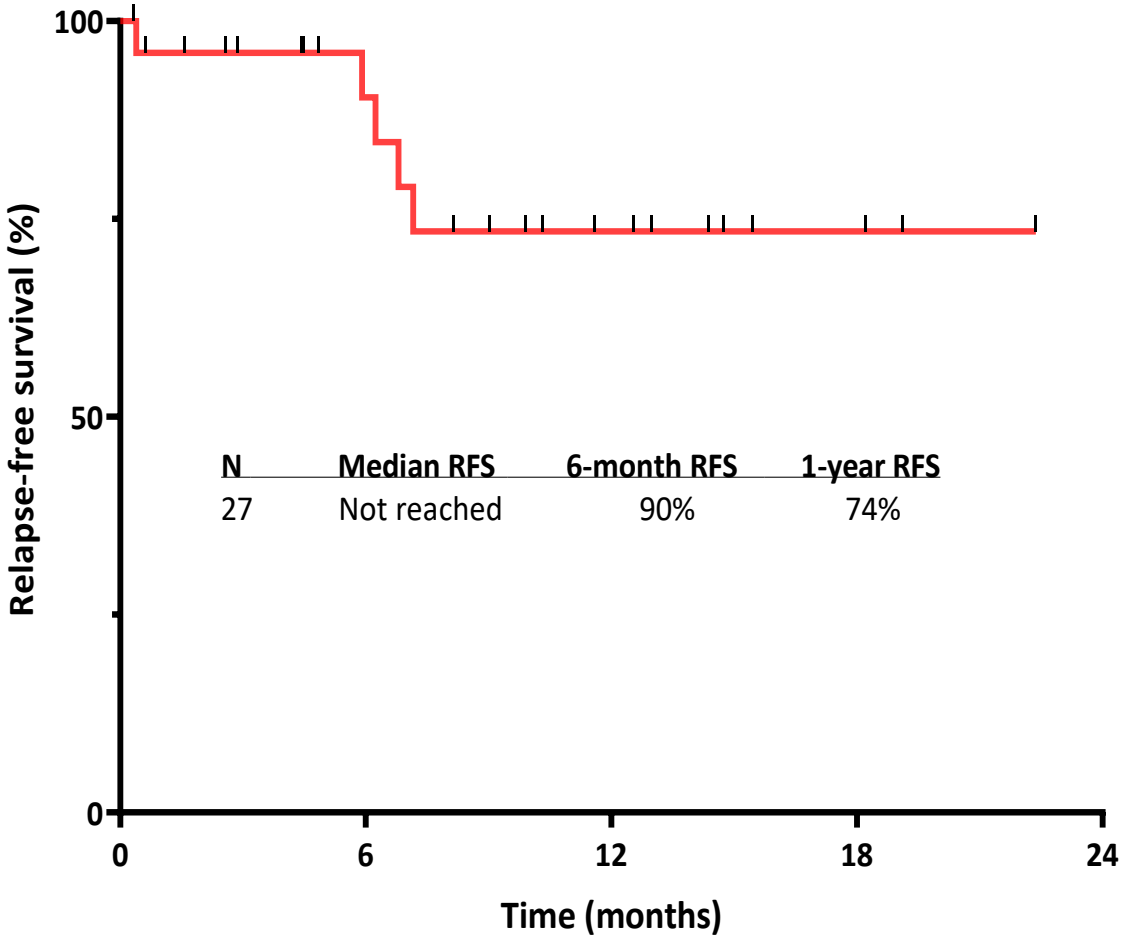
Aza+Ven+Gilteritinib in FLT3-mutated AML: Responses

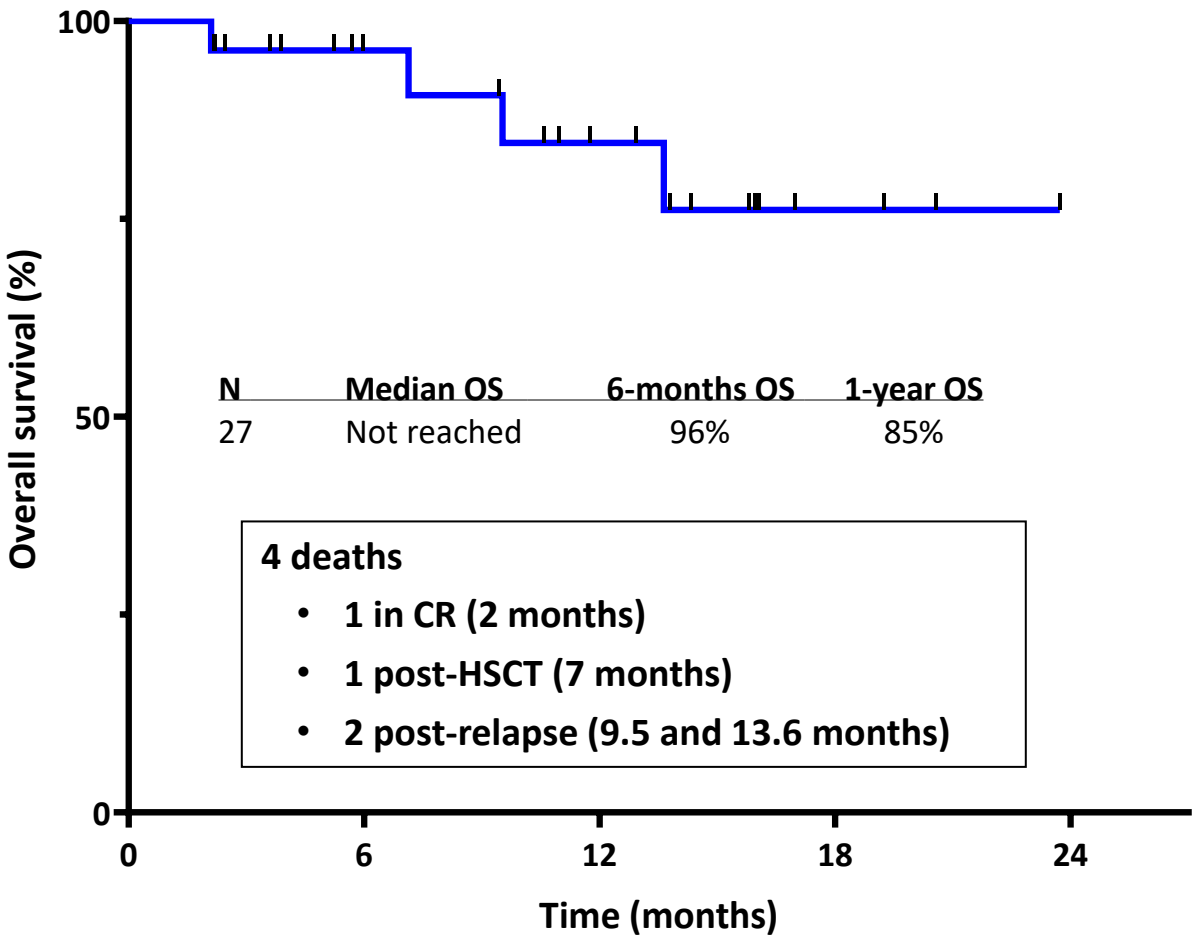
Response, n/N (%)	Frontline N = 27	R/R N = 20
mCRc (CR/CRi/MLFS)	27 (100)	14 (70)
CR	25 (92)	4 (20)
CRi	1 (4)	3 (15)
MLFS	1 (4)	7 (35)
PR*	0	1 (5)
No response	0	5 (25)
Early death	0	0

Aza+Ven+Gilteritinib in FLT3-mutated AML: RFS and OS in Frontline Cohort

Median follow-up: 12 months (range, 1.5-24+ months)



N	Median RFS	6-month RFS	1-year RFS
27	Not reached	90%	74%



N	Median OS	6-months OS	1-year OS
27	Not reached	96%	85%

4 deaths

- **1 in CR (2 months)**
- **1 post-HSCT (7 months)**
- **2 post-relapse (9.5 and 13.6 months)**

TP53 mutations in AML patients

- Epidemiology
  - Occurs in 5-10% of patients with de novo AML
  - 20-30% of patients with therapy-related AML
  - Often associated with complex / monosomal karyotype
- Poor outcomes irrespective of treatment with median OS (<1 yr)
  - No clear benefit with newer approved agents
  - AlloHCT still the best modality but post-transplant outcomes are also poor with a median posttransplant OS of <1 year and 2 year OS rate of <30%

1.Bowen D, et al Leukemia 2009
2.Grossman V, et al Blood 2012
3. Short NJ, et al. Lancet Haematol 2019
4. Ciurea SO, et al Blood 2018

sAML therapy options

Regimen	Response rates		Overall survival	
	All groups	*TP53*	All groups	*TP53*
Intensive regimens				
7+3 (cytarabine and anthracycline)[2,11,12,37]	CR: 35%-71% CR/CRi: 40%-71% sAML subset: CR: 26%-52% CR/CRi: 33%-55%	CR: 30%-34% CR/CRi: 40%	sAML subset: 5–10 mo	5–6 mo
CPX-351 (liposomal cytarabine and daunorubicin)[12,16,37]	sAML subset: CR: 7%-12% CR/CRi: 45%-48%	CR: 29% CR/CRi: 29%	sAML subset: 10–13 mo	4–6 mo
Nonintensive regimens				
Azacitidine and venetoclax[16,17,21]	CR: 40% CR/CRi: 65% sAML subset: CR/CRi: 60%	CR: NA CR/CRi: 50%-55%	11–16 mo sAML subset: 11–16 mo	5–7 mo
Azacitidine or decitabine monotherapy[21,38]	CR: 13%-24% CR/CRi: 18%-27% sAML subset: CR/CRi: 25%	CR: 24%-40% CR/CRi: 0%-40%	6–11 mo sAML subset: 7–8 mo	2–7 mo

Matthews and Pratz Hematology 2022

Phase I/II Study of Azacitidine, Venetoclax and Magrolimab for Newly Diagnosed and Relapsed/Refractory AML

N.G. Daver[1], J. Senapati[1], A. Maiti[1], M.Y. Konopleva[1], C.D. DiNardo[1], G. Borthakur[1], K. Chien[1], G.C. Issa[1], E.J. Jabbour[1], S.M. Kornblau[1], L. Masarova[1], T.M. Kadia[1], Y. Alvarado[1], N. Jain[1], S. Loghavi[2], K. Sasaki[1], N. Pemmaraju[1], H. Abbas[1], P. Bose[1], J.A. Burger[1], A. Ferrajoli[1], G. Montalban-Bravo[1], M. Yilmaz[1], M. Ohanian[1], N.J. Short[1], K. Takahashi[1], P.A. Thompson[1], W.W. Weirda[1], G. Tang[2], M. Golez[1], K.P. Patel[2], S. Pierce[1], G. Nogueras-Gonzalez[3], J. Ning[3], F. Ravandi[1], G. Garcia-Manero[1], H.M. Kantarjian[1].

[1]Department of Leukemia, [2]Department of Hematopathology, [3]Department of Biostatistics

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ABSTRACT#616 American Society of Hematology Meeting, 2022

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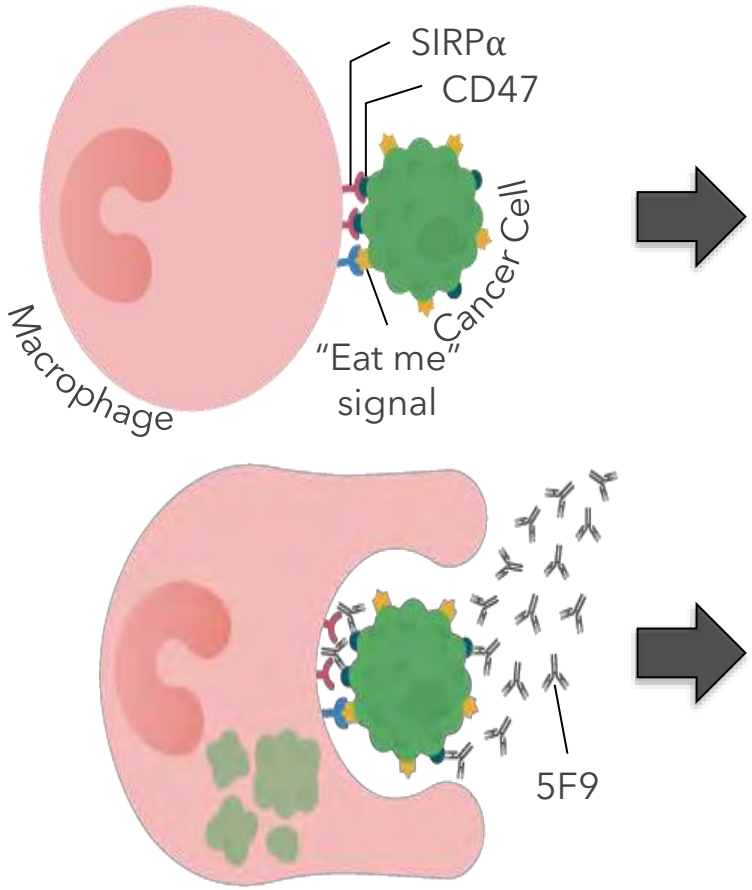
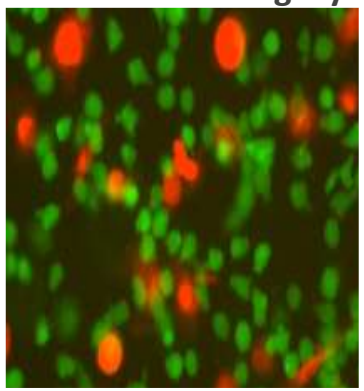
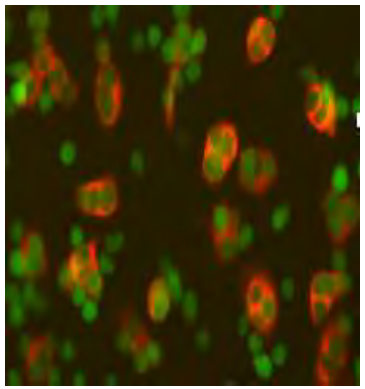
Magrolimab: Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



Macrophages
Cancer cells

- Magrolimab enables macrophages to phagocytose cancer cells by blocking the binding of the "don't eat me" signal CD47 to its receptor SIRPα
- Normal cells are not phagocytosed as they do not express "eat me" signals, except for aged red blood cells

Courtesy of D. Sallman

Responses per ITT FRONTLINE (n=43): CR/CRi rates similar in TP53m and TP53wt

Parameters		Full Frontline	De novo		Secondary AML	
		N=43	TP53^{mut} (N=22)	TP53^{WT} (N=11)	TP53^{mut} (N=5)	TP53^{WT} (N=5)
				N (%), Median [range]		
Overall response	CR	21 (49)	10 (46)	6 (55)	2 (40)	3 (60)
	CRi	10 (23)	4 (18)	4 (36)	1 (20)	1 (20)
	CR + CRi	31 (72)	14 (64)	10 (91)	3 (60)	4 (80)
	MLFS	4 (9)	1 (5)	1 (9)	2 (40)	0 (0)
MRD-ve best responses#	FCM-CR/CRi	16/28 (67)#	8/14 (64)	6/10 (60)	0 (0)	2/4 (50)
Time to response (days)	First response	23 [19-105]	24 [20-81]	20 [20-29]	20 [19-105]	27 [20-73]
	Best response	51 [20-130]	49 [20-130]	33 [20-63]	48 [20-105]	62 [20-88]
Counts recovery (days)	ANC ≥ 500/cu mm	36 [16-88]	36 [16- 88]	34 [26-62]	34 [31-36]	39 [23-59]
	Platelet ≥ 100 x 10^9/L	32 [0-74]	31 [15-55]	33 [19-74]	28 [22-49]	33 [0-46]
Cycles on therapy		3 [1-17]	3 [2-6]	3 [1-17]	1 [1-3]	2 [1-3]
Mortality:						
- **4 week**		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
- **8 week**		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Amongst CR/CRi patients with longitudinally MRD evaluable samples
Amongst responders with baseline clonal CTG abnormality

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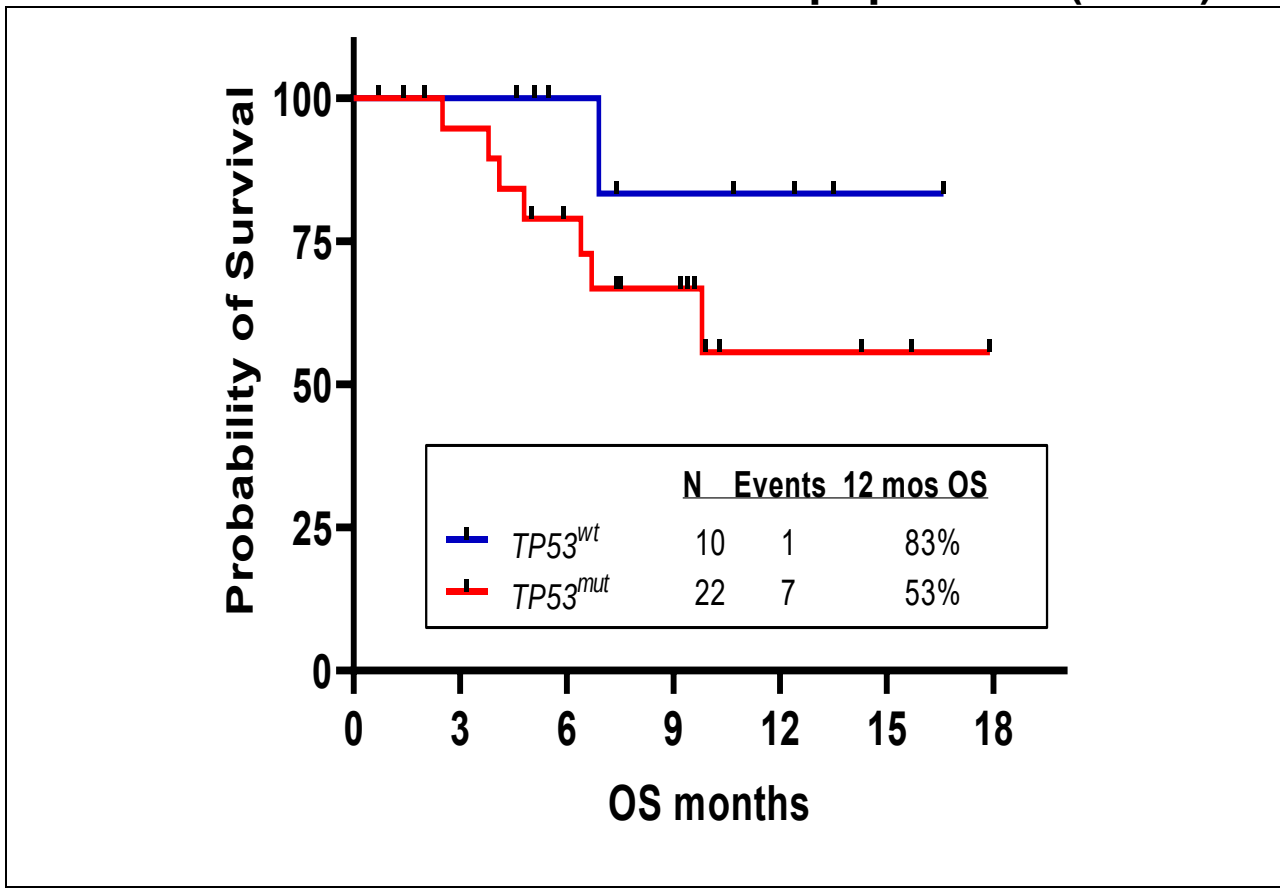
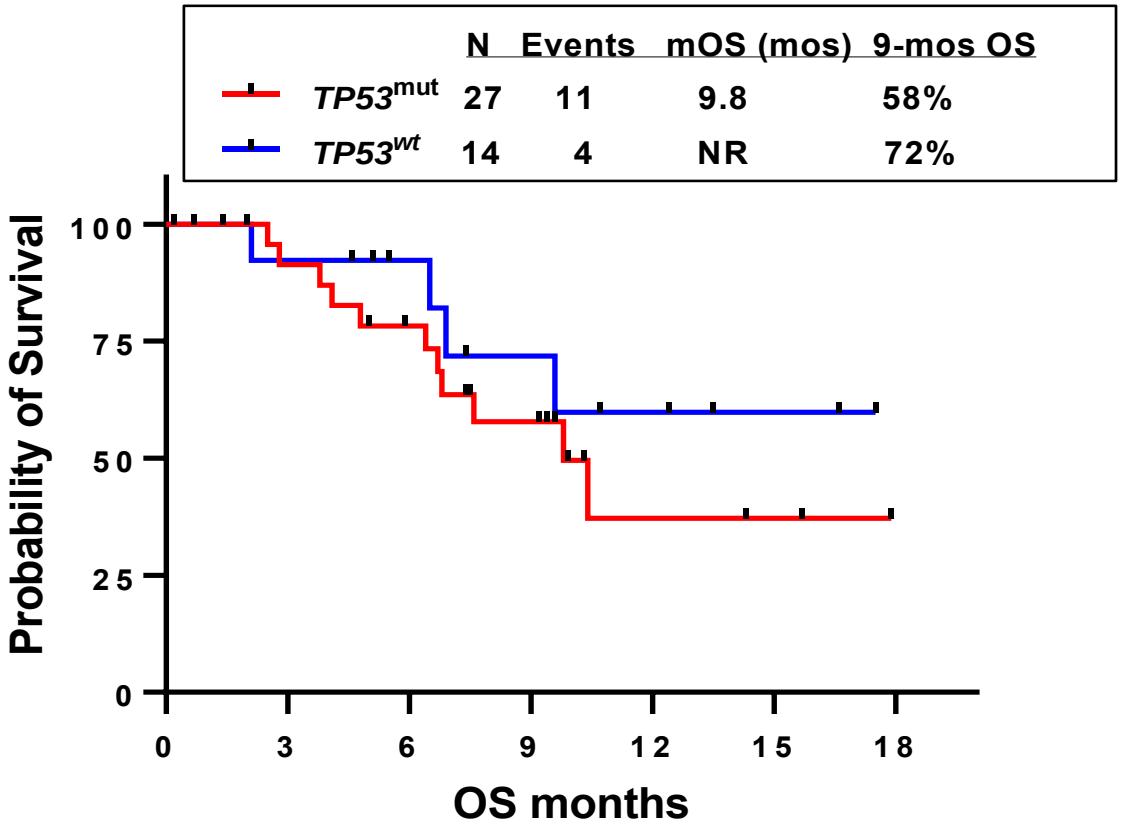
Results: Survival outcomes FRONTLINE (n=41)* cohort

Median follow up: 9.9 months

Median OS in frontline De Novo population (N=32)*



Median OS in FRONTLINE population (N=41)*



*1 patient is < 3months on study and too early

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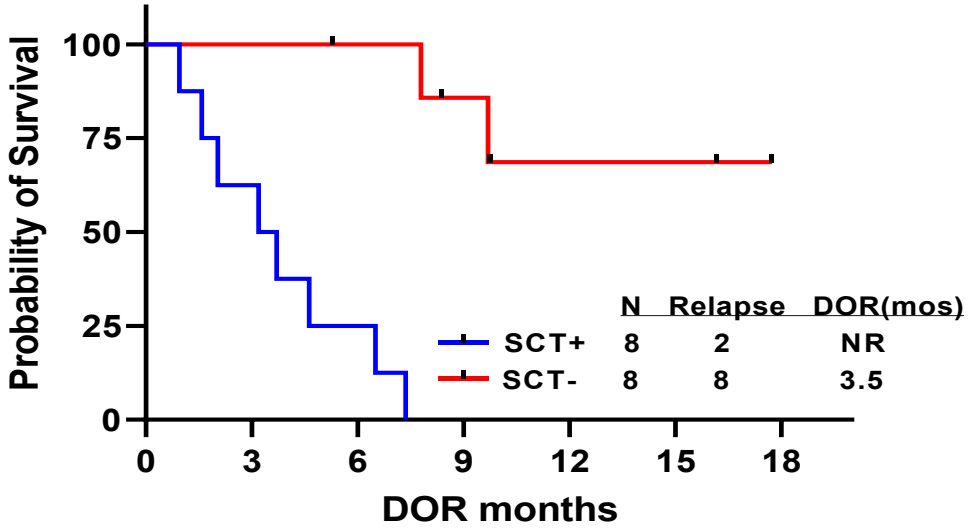
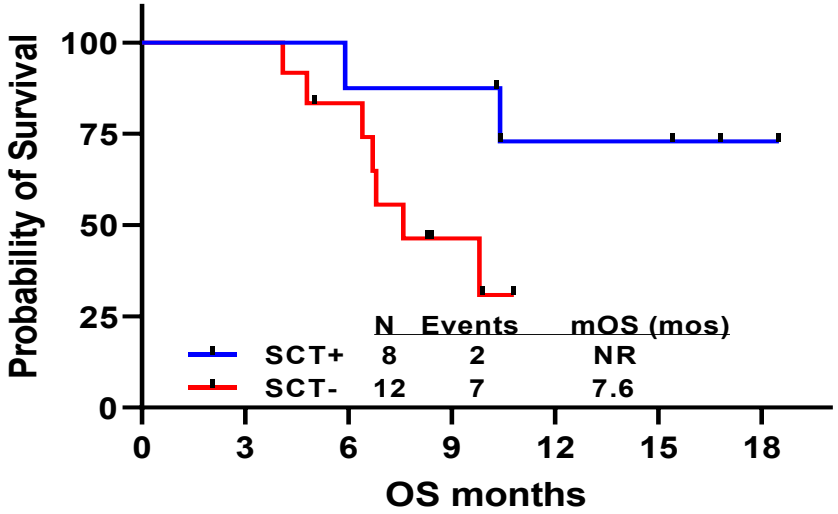
Results: Impact of SCT in the frontline setting in *TP53*^{mut} patients

No. of *TP53*^{mut} patients transplanted	8 (7 denovo+ 1 secondary untreated)
Age of the SCT patients	64 years (range, 46-69 years)
Median time to SCT from trial therapy initiation	4.2 months (range, 2.6-5.8 months)
Median cycles on therapy to SCT	3 (range, 2-4 cycles)
Disease status at SCT *	CR=6; CRi=2; MRD-ve = 5/8

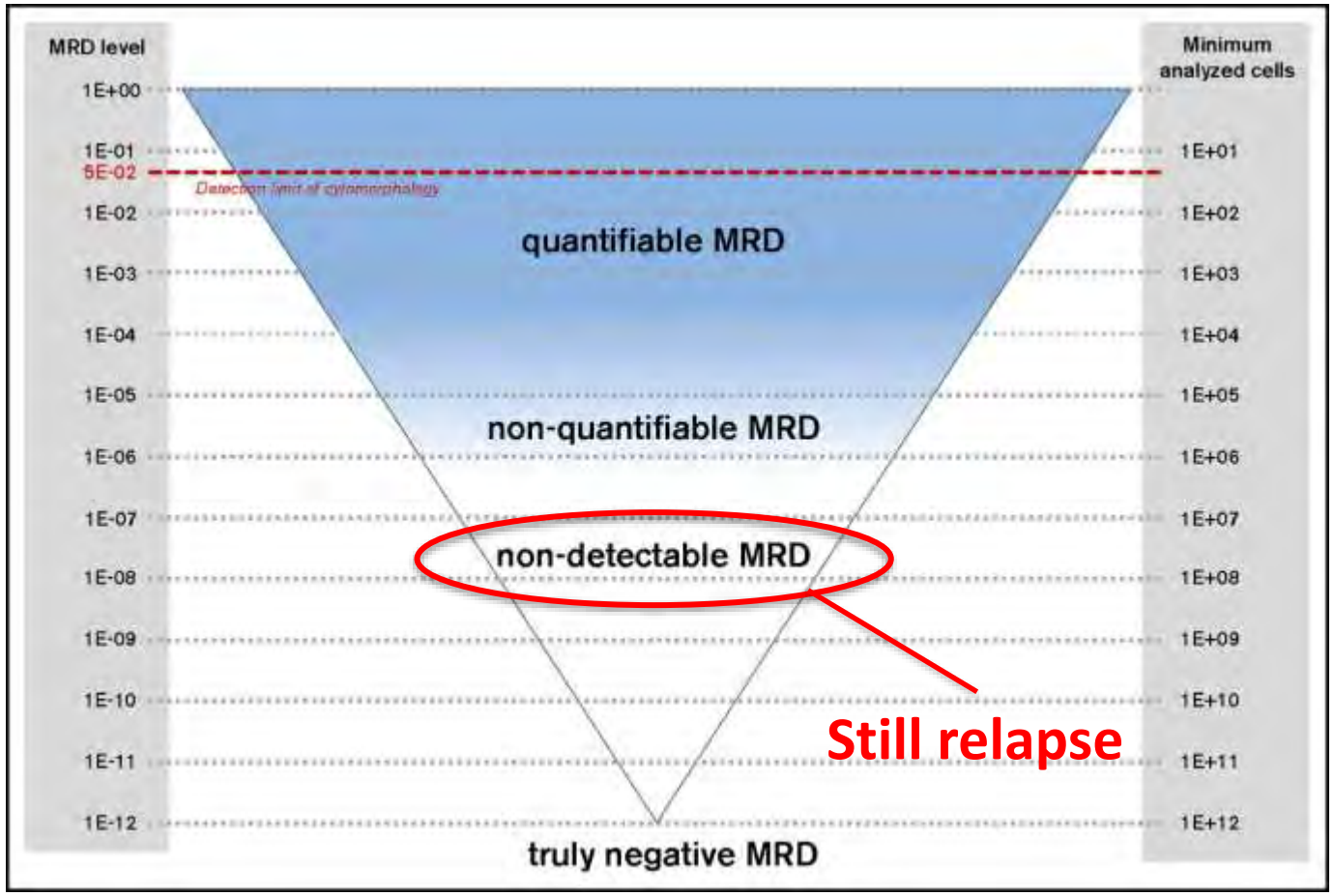




Landmark analysis of SCT vs. No SCT in frontline setting with *TP53*^{mut} mutated AML

*Median age of landmark comparator "**No SCT**" arm= 67 years (range, 32-84 years)

MRD: “Minimal” or “Measurable” Residual Disease



- **Multiparameter Flow Cytometry (MFC)**
  - Sensitivity: 10^{-4}
- **Allele-Specific Oligonucleotide PCR (ASO-PCR)**
  - Sensitivity 10^{-5} to 10^{-6}
- **Next Generation Sequencing (NGS)**
  - Sensitivity: 10^{-6}

Bruggemann & Kotrova Blood Adv 2017

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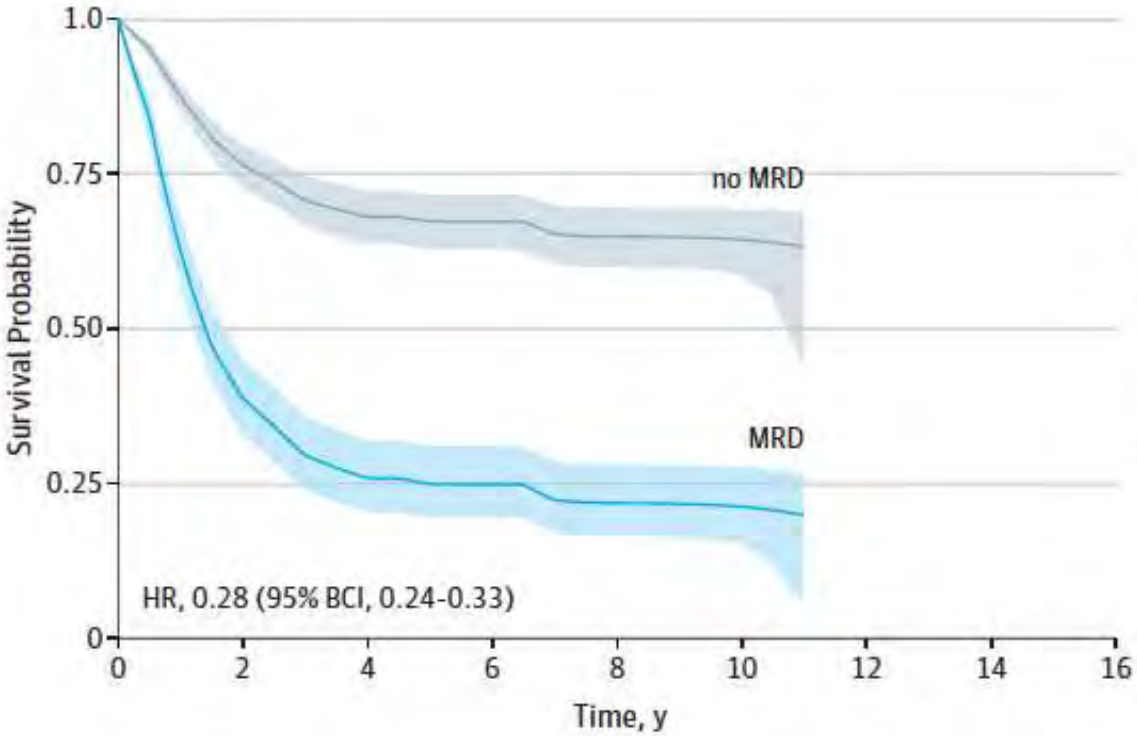
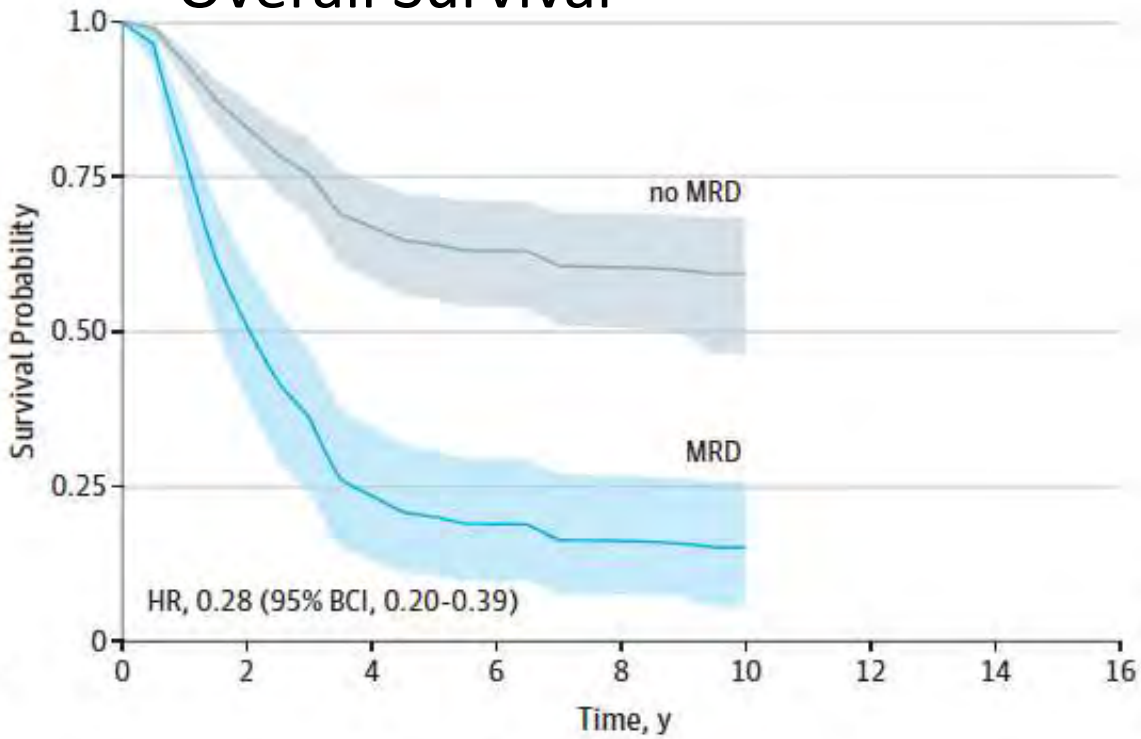
MRD associated with inferior EFS and OS in adult ALL

Event-Free Survival

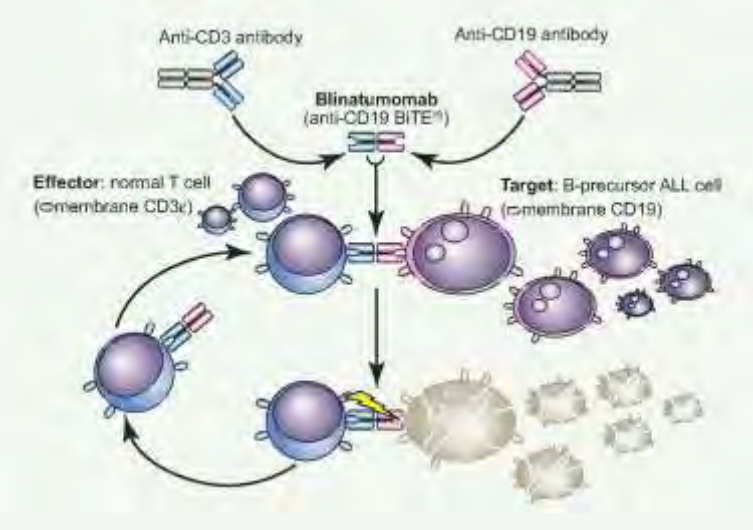


Overall Survival



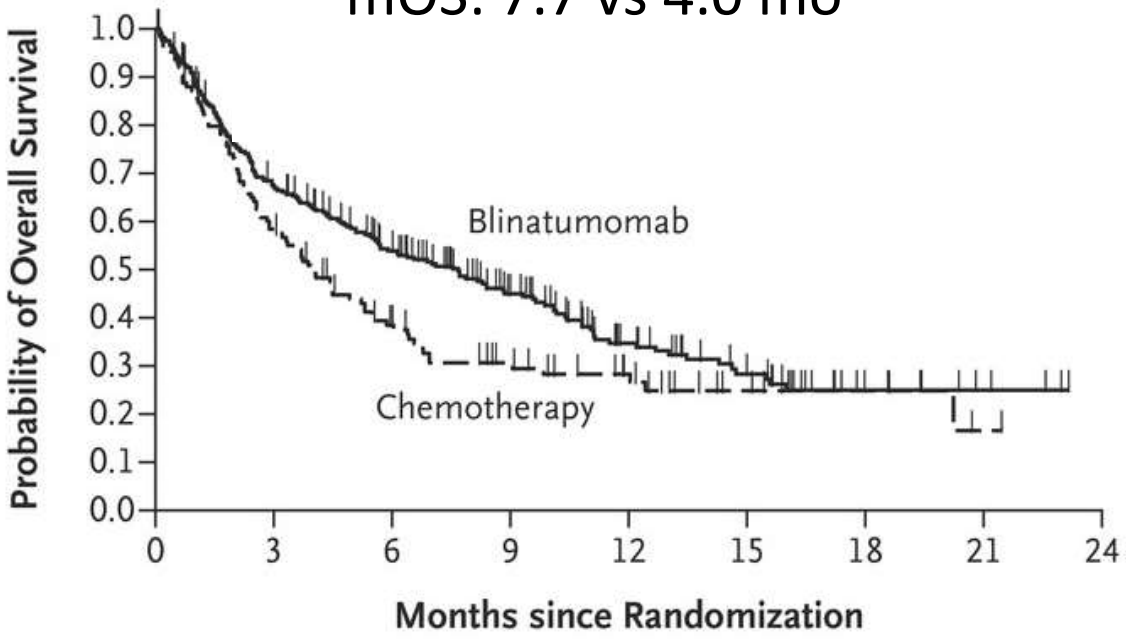
Berry, et al. JAMA Oncol 2017

Blinatumomab is a novel agent effective in treatment of R/R disease - Phase 3 (TOWER)



- 405 patients with R/R Ph- B-cell ALL, including prior HSCT
- Randomized 2:1 to blinatumomab or SOC

mOS: 7.7 vs 4.0 mo



Kantarjian et al, N Engl J Med. 2017

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Blinatumomab is approved for R/R disease - Phase 3 (TOWER)

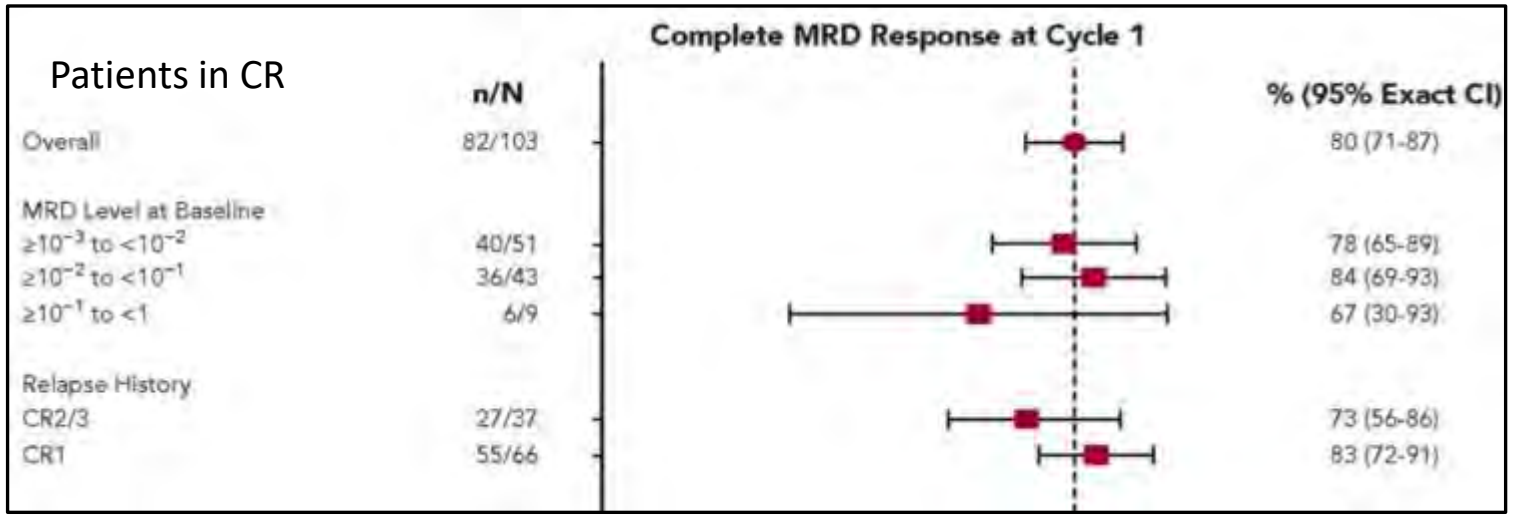
Response (12 weeks)	Blinatumomab	Chemotherapy	p-value
CR/CRh (*MRD-neg*)	44% (119/271) (*76%*)	25% (33/134) (*48%*)	<0.001
CR/CRh <50% blasts	**66%**	34%	<0.05
CR/CRh >50% blasts	**34%**	21%	<0.05

Blinatumomab is less effective with high burden disease

Kantarjian et al, N Engl J Med. 2017

BLAST trial - blinatumomab for MRD+ disease

- 116 patients, age ≥18 years old
  - B-cell ALL in first or later hematologic CR
  - Persistent or recurrent MRD $\geq 10^{-3}$ after 3+ blocks of chemotherapy
- Received up to 4 cycles of blinatumomab



Complete MRD response

- 88/113 (**78%**) after C1
- 2 more after C2

Gökbuget, et al. Blood 2018

ASH 2022: Late Breaking Abstract

ECOG-ACRIN-E1910 NCTN Clinical Trial: A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed BCR::ABL-negative B lineage Acute Lymphoblastic Leukemia in Adults

Mark R. Litzow, MD

Zhuoxin Sun, Elisabeth Paietta, Ryan Mattison, Hillard Lazarus, Jacob Rowe, Daniel Arber, Charles Mullighan, Cheryl Willman, Yanming Zhang, Matthew Wieduwilt, Michaela Liedtke, Julie Bergeron, Keith Pratz, Shira Dinner, Noelle Frey, Steven Gore, Bhavana Bhatnagar, Ehab Atallah, Geoffrey Uy, Deepa Jeyakumar, Tara Lin, Daniel DeAngelo, Richard Stone, Harry Erba, Richard Little, Selina Luger, Martin Tallman

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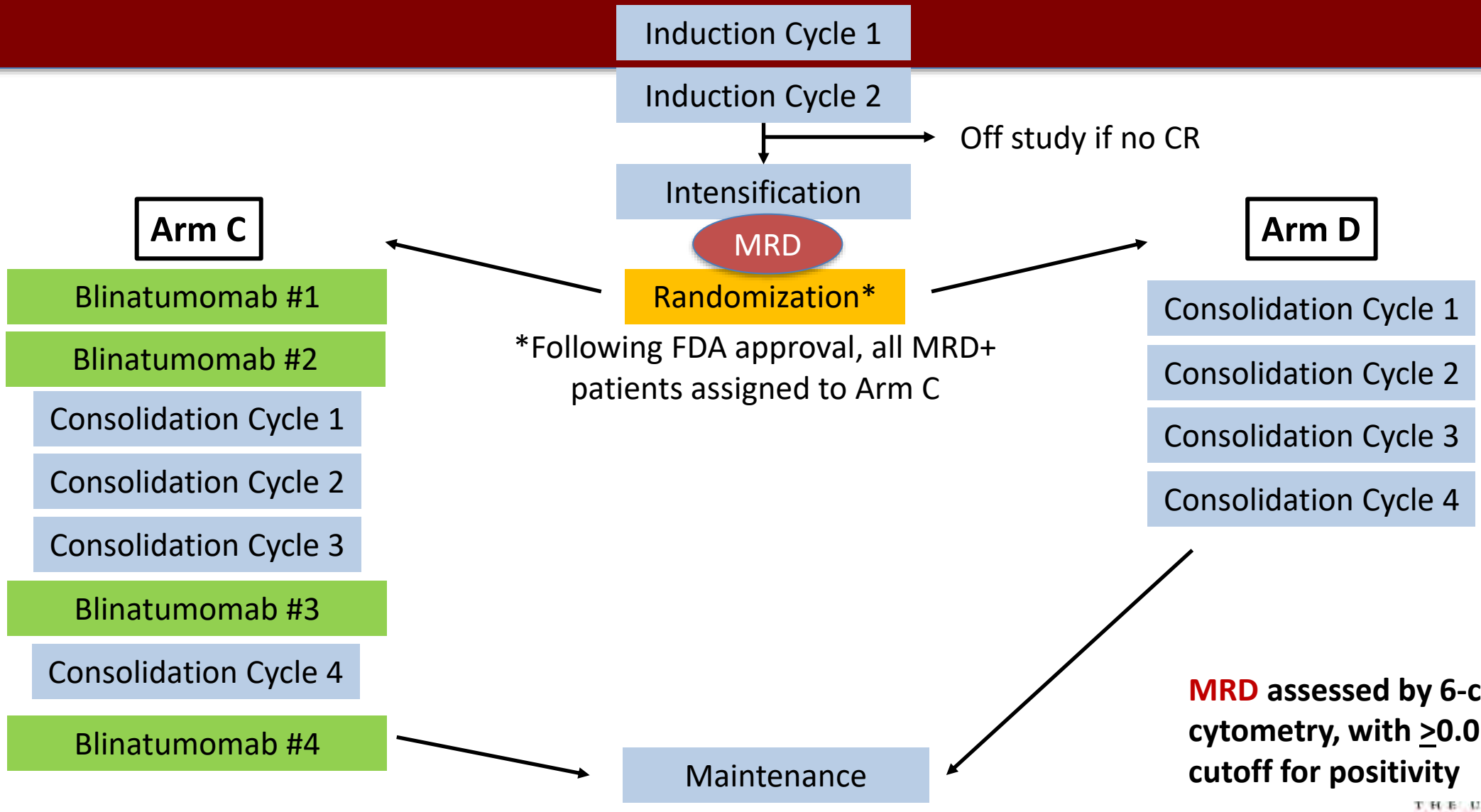
E1910:

- **The E1910 chemotherapy regimen consisted of:**
  - **2.5 months of a BFM type induction regimen modified from the E2993/UKALLXII protocol**
  - **Pts in CR/CRi then received CNS intensification with high dose methotrexate & pegaspargase**
  - **MRD status was assessed and patients (pts) were randomized to receive 4 cycles of combination consolidation chemotherapy +/- four 4 week cycles of IV blinatumomab by continuous infusion followed by 2.5 years of POMP maintenance chemotherapy timed from the start of intensification**

Slides provided by Mark Litzow, MD

E1910: Randomized CD19+ B- ALL



*Following FDA approval, all MRD+ patients assigned to Arm C

MRD assessed by 6-color flow cytometry, with ≥0.01% as the cutoff for positivity

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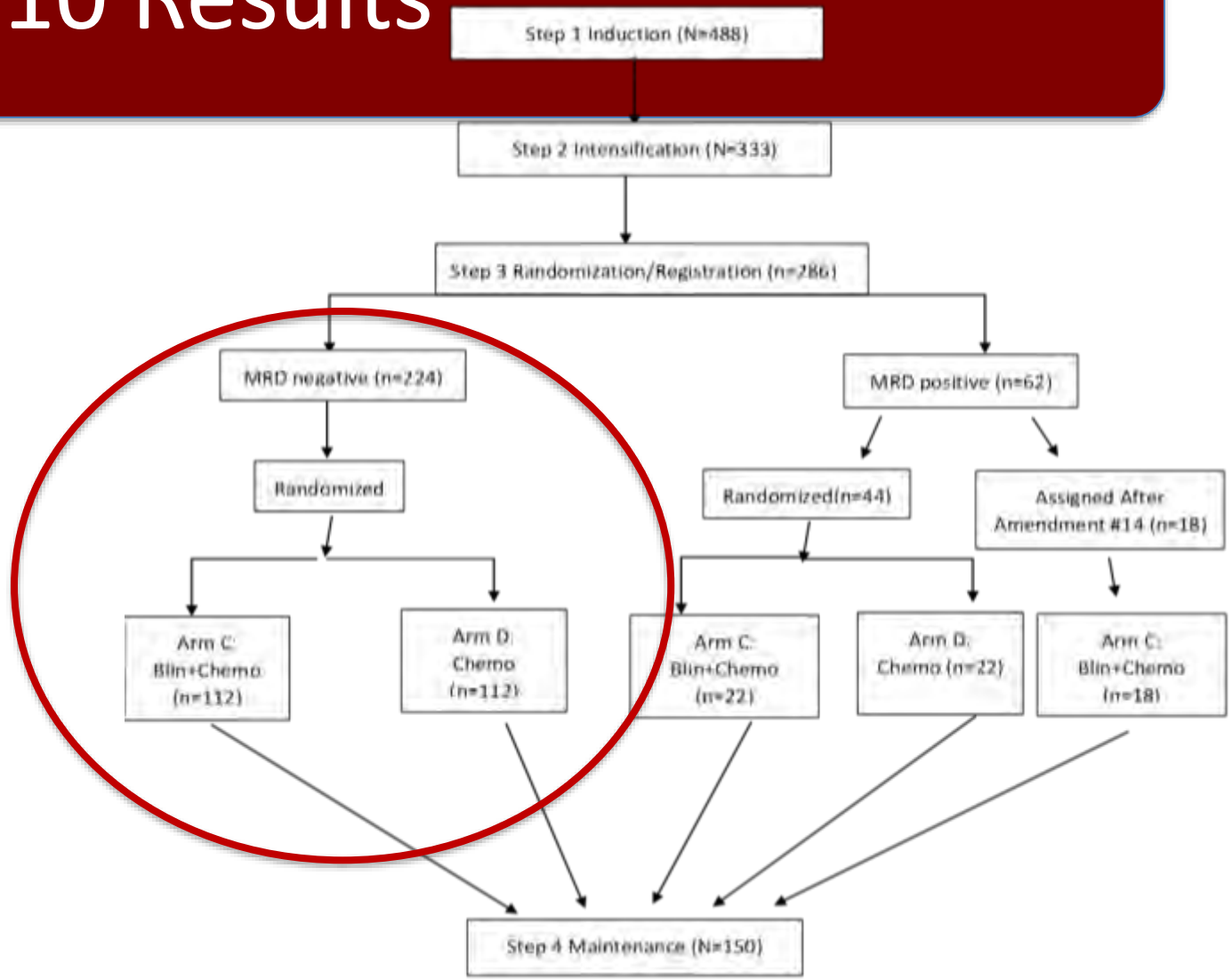
E1910 Results

- 488 pts enrolled
- Median age: 51yrs (range 30-70yrs)
- Median follow-up 3.6 yrs
- CR/CRi rate 81% (395/488 pts)
  - CR 75% (364 pts)
  - CRi 6% (31 pts)
- 224 MRD – patients
  - Among MRD-neg, 22 patients in each arm underwent alloHSCT
  - 80% of pts received ≥2 cycles of blinatumomab



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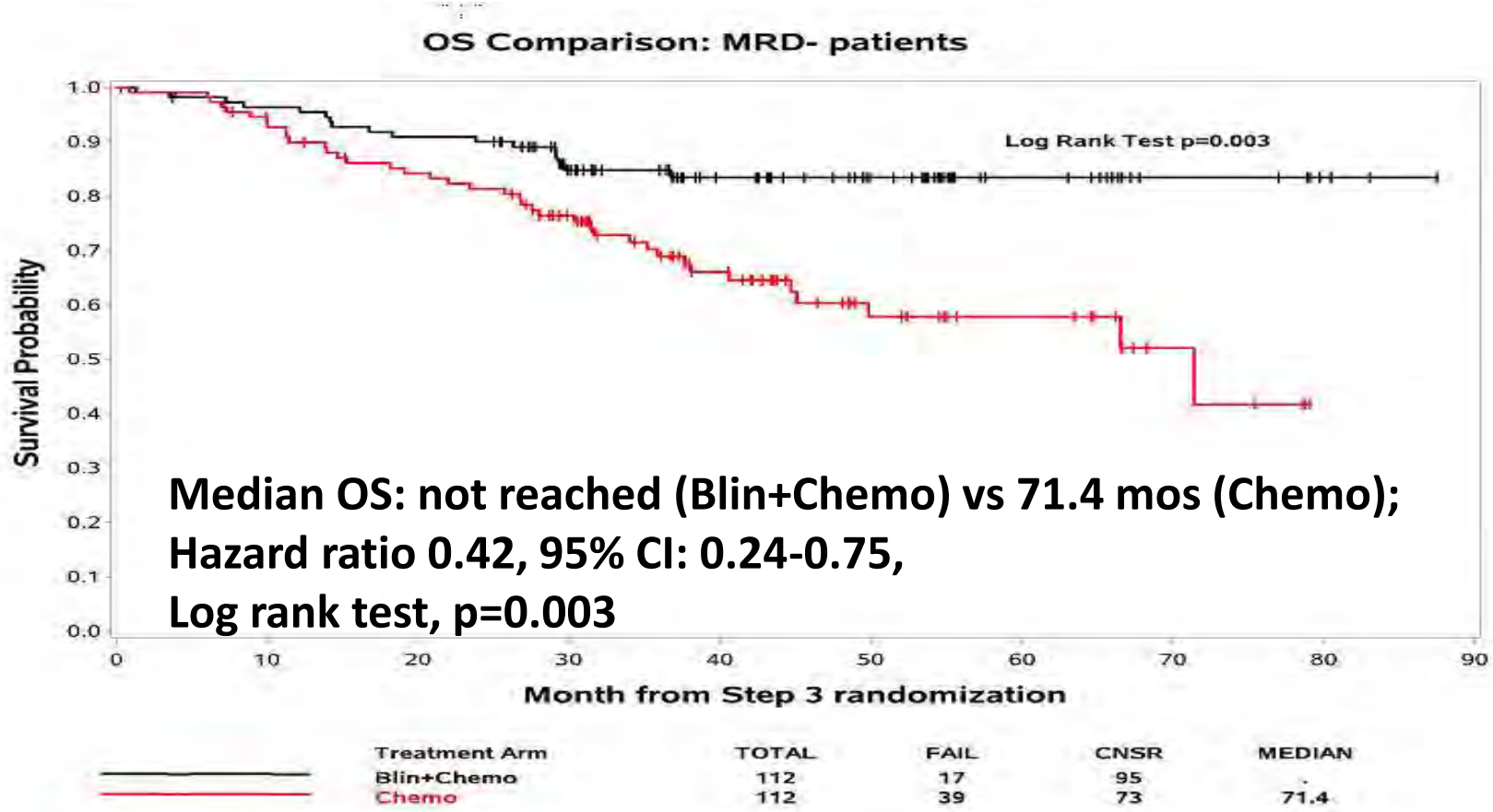
Methods & Results

- MRD assessed centrally by standardized 6 color flow cytometry with ≥0.01% as the cutoff for positivity
- Age: median 51, range (30, 70)
- CR/CRi rate 395/488 (81%); CR 364 (75%), CRi 31 (6%)
- 224 MRD- patients; 12 in each arm transplanted
  - 80% received at least 2 cycles of Blina
- Median F/U: 43 months (3.6 yrs)

Overall Survival : MRD negative patients



Median OS: not reached (Blin+Chemo) vs 71.4 mos (Chemo);
Hazard ratio 0.42, 95% CI: 0.24-0.75,
Log rank test, p=0.003

Deaths on Blin+Chemo Arm=17 (2° to ALL=8, NRM=9), Chemo Arm=39 (2° to ALL=20, NRM=17, Unknown=2)

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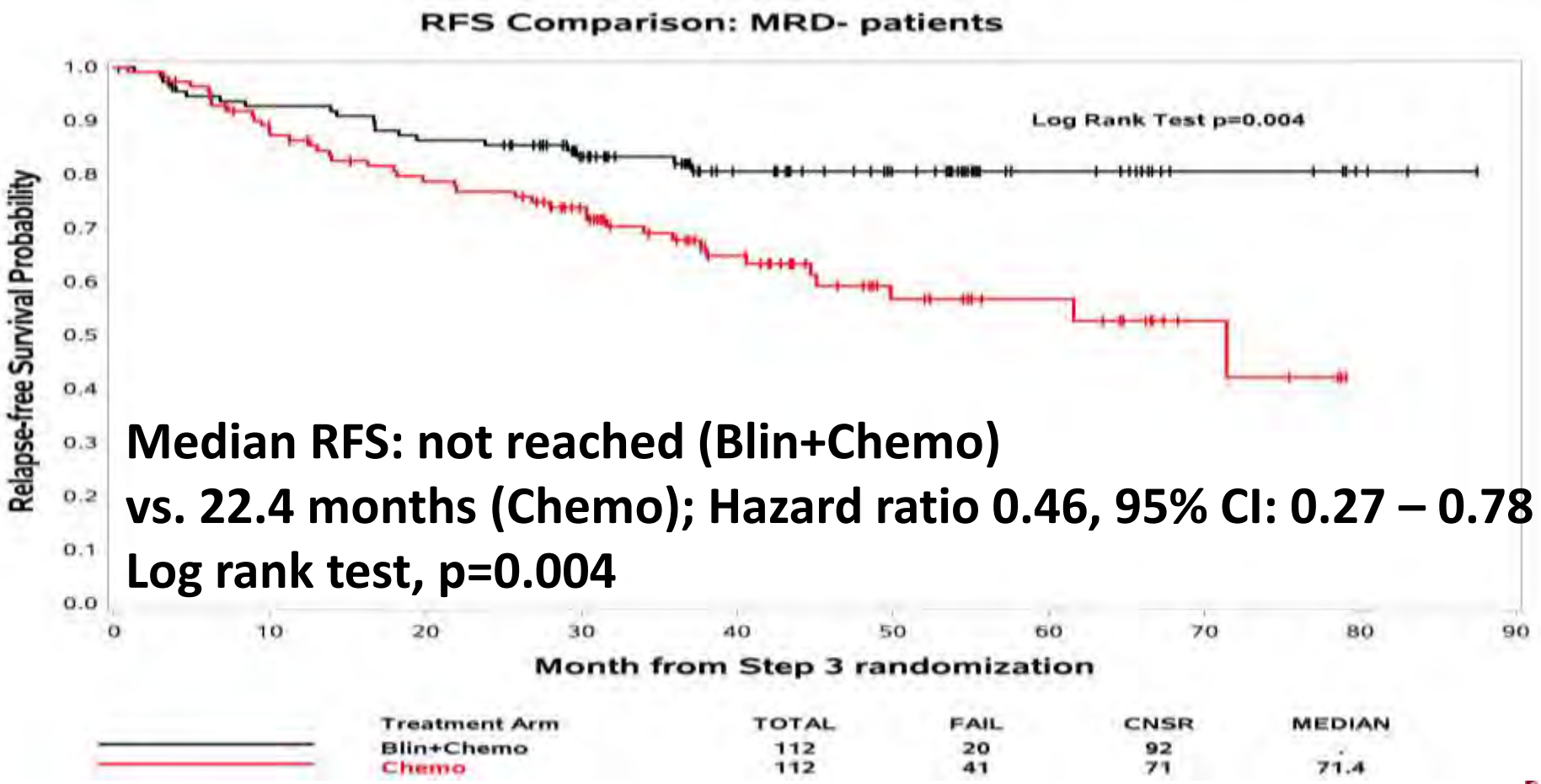
Relapse-Free Survival : MRD negative patients



Median RFS: not reached (Blin+Chemo)
vs. 22.4 months (Chemo); Hazard ratio 0.46, 95% CI: 0.27 – 0.78
Log rank test, p=0.004

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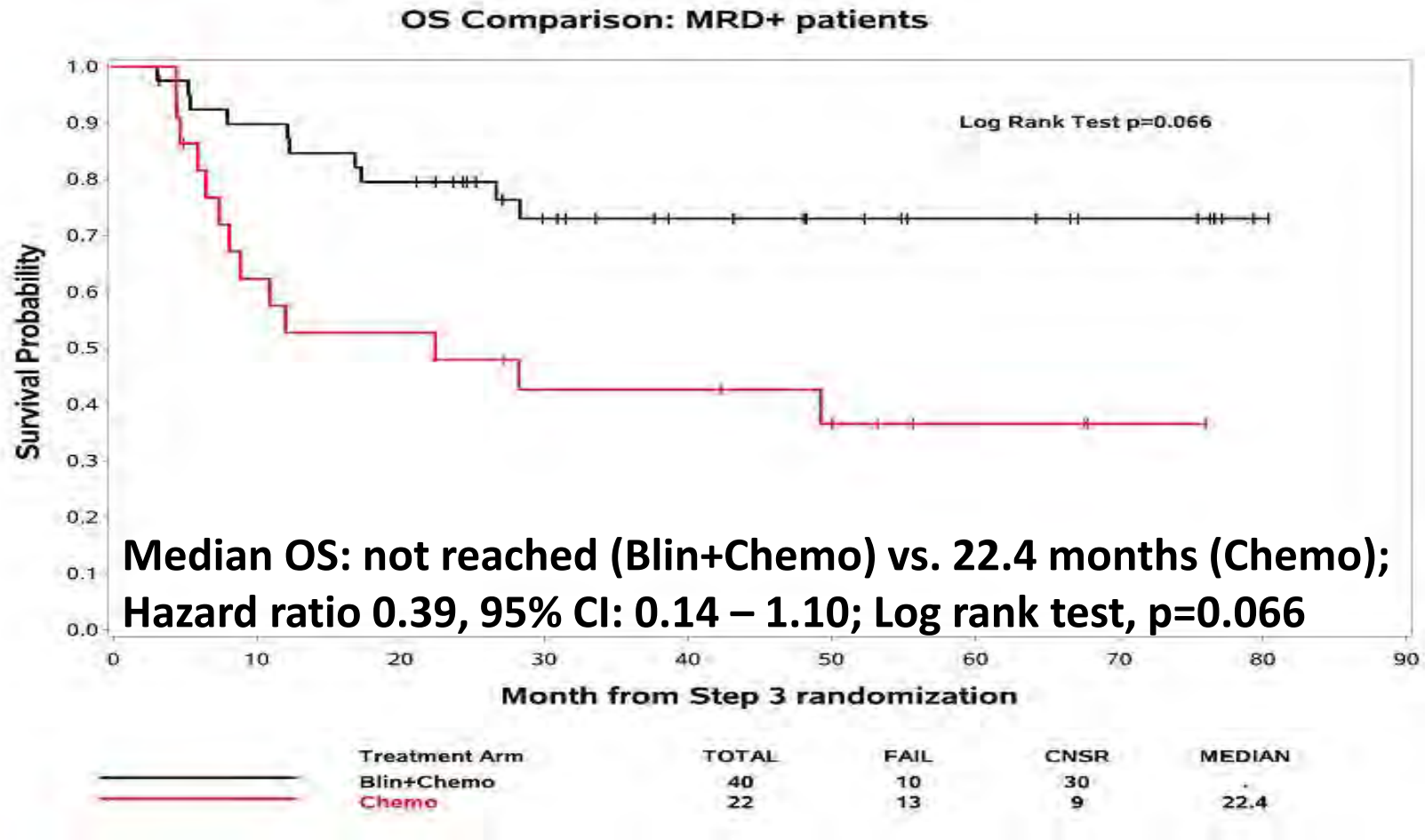
Overall Survival : MRD positive patients



Median OS: not reached (Blin+Chemo) vs. 22.4 months (Chemo);
Hazard ratio 0.39, 95% CI: 0.14 – 1.10; Log rank test, p=0.066

Deaths on Blin+Chemo Arm=9 (2° to ALL=6, NRM=1, Unknown=3), Chemo Arm=13 (2° to ALL=7, NRM=6)

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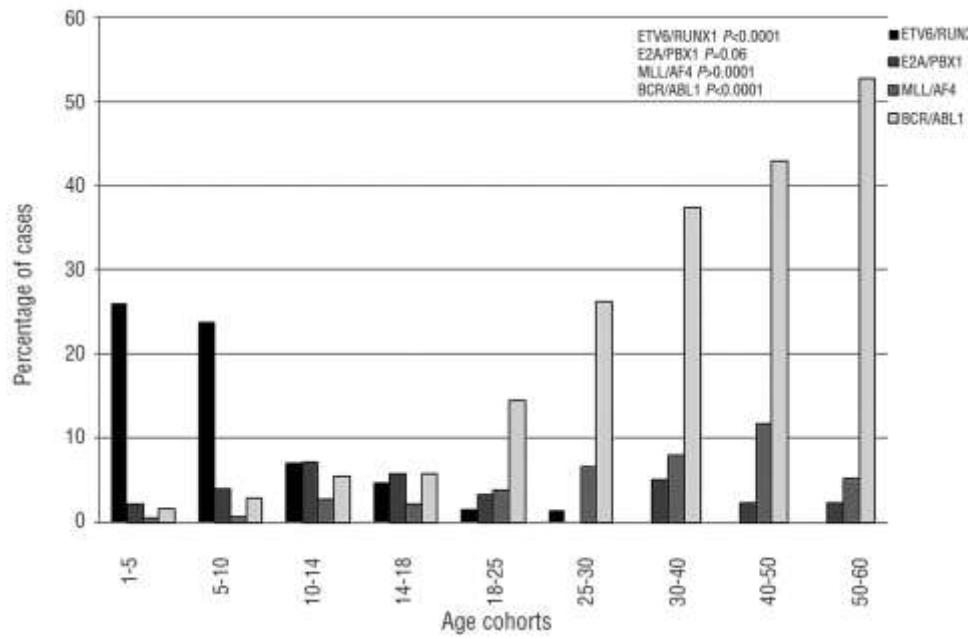
Conclusions/Commentary

- First evidence that Blina significantly improves survival for MRD negative patients in CR1: IMPRESSIVE!
- Likely new standard of care for CD19+ ALL in CR1
- Comments:
  - MRD method in E1910 was less sensitive flow cytometry
    - Wonder about impact of blina if MRD neg using more sensitive methods of detection
  - Many patients were lost prior to blina – relapse, transplant, alternative therapies, toxicity
    - Likely more useful to introduce blina earlier in treatment

Ph+ ALL, Historically Adverse Outcomes

- Philadelphia chromosome/BCR-ABL1 fusion present in ~1/3 of ALL cases.
- Prevalence increases with age (>50% in patients >50 years).
- Historically adverse prognosis prior to 2nd and 3rd generation TKIs.



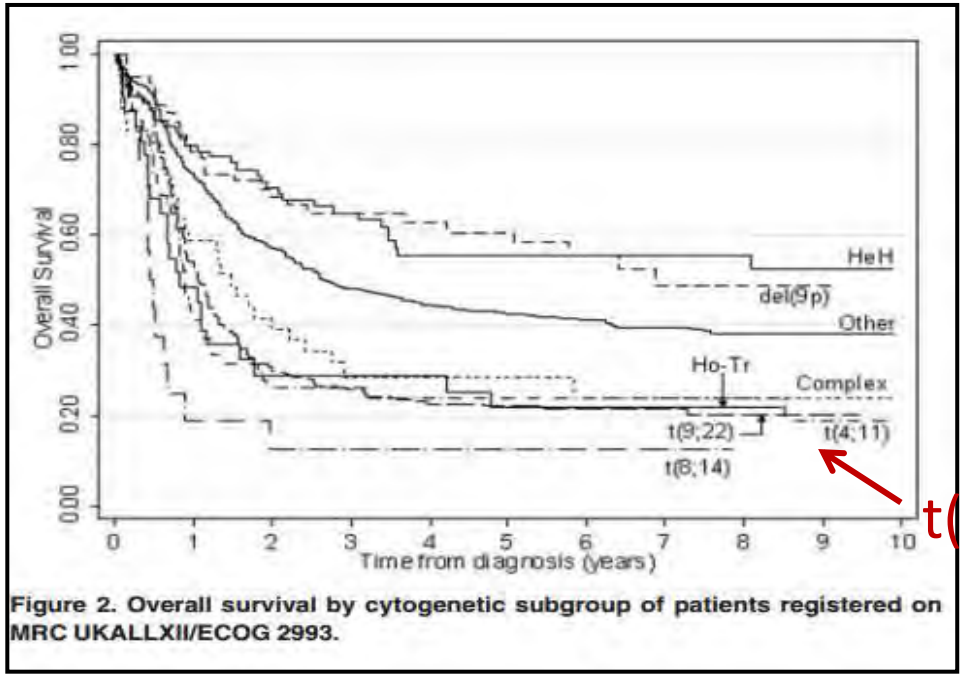


Figure 2. Overall survival by cytogenetic subgroup of patients registered on MRC UKALLXII/ECOG 2993.

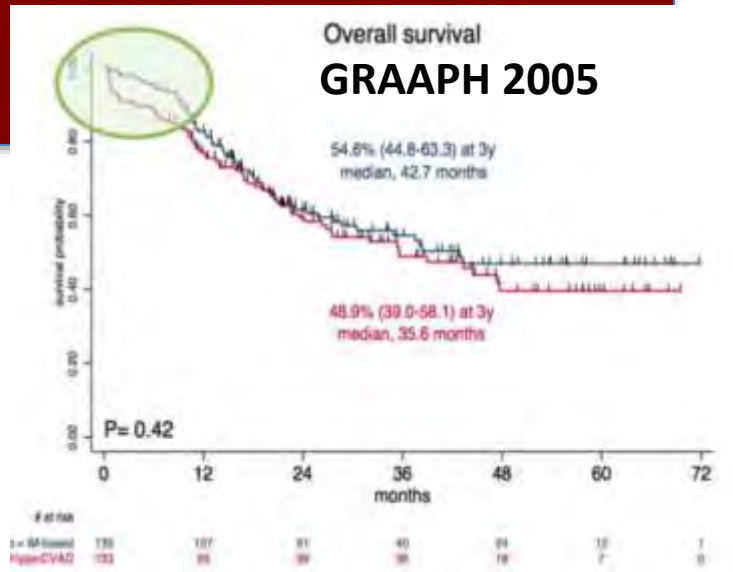
Chiaretti S, et al. *Haematologica* 2013;98:1702–10; Burmeister T, et al. *Blood* 2008;112:918–9; Ribera JM, et al. *Br J Haematol* 2012;159:485–8; Moorman AV, et al. *Blood* 2007;109:3189–97; Rowe JM, et al. *Blood* 2005;106:3760–7.

Ph+ ALL, recent context

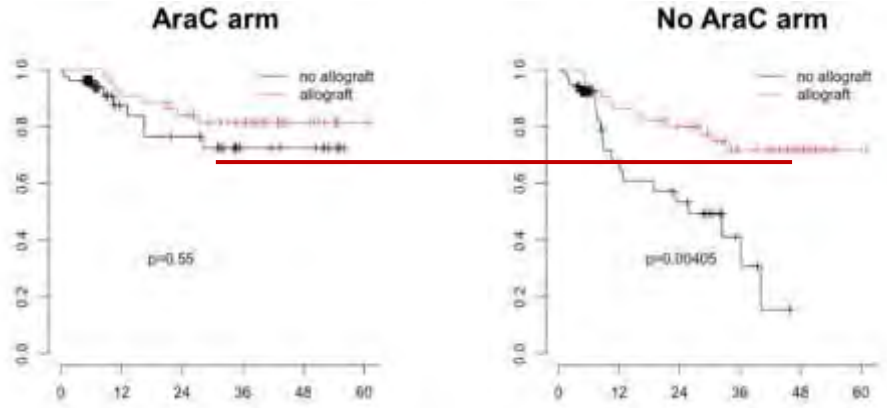
- **GRAAPH 2005 (IMATINIB)** → IM + VCR/Dex: ↑CR rate and ↓mortality compared to IM + hyperCVAD (**lesson**: reduce chemo in induction)

- **GIMEMA** → "chemotherapy-free" induction (imatinib LAL 0201-B; dasatinib LAL 1205, ponatinib LAL 1811).
  - High CR rates (>90%); (**lesson: 2G**/3G TKIs - Deeper and more durable); minimal toxicity

- **GRAAPH-2014 (NILOTINIB)** → Omission of HiDAC consolidation associated with more relapse in non-transplanted patients (**lesson:** still need intensive conventional chemo or BMT *in context of 2G TKI*)



GRAAPH 2014



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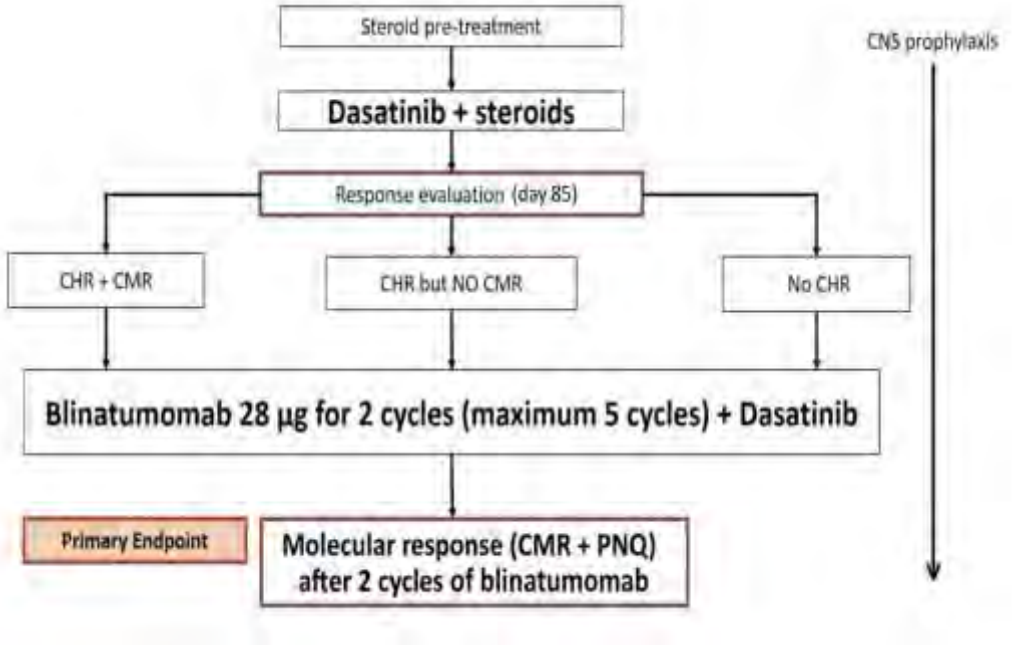
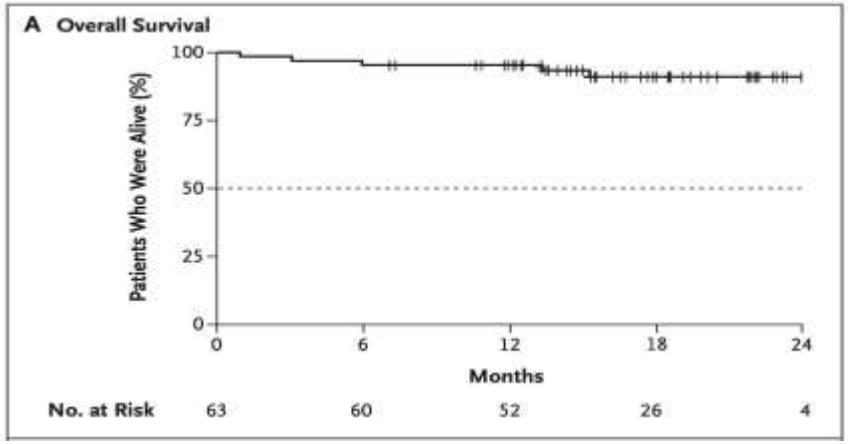
Chalandon et al. *Blood* 2015;125:3711-9; Rousselot ASH 2021 Abstract 614

Dasatinib + blinatumomab (D-ALBA)



- Day 85 – 29% Molecular Response
- Blina C2 (n=55) – 60% Molecular Response
- Blina C4 – 81% Molecular Response



N=63, median age 54 (range 24-82) yrs

Note: Approximately half transplanted

- 18-mo DFS was 88%
- Worse outcomes in *IKZF1* deletion
- T315I in 5/6 relapses tested

Foa et al. *N Eng J Med* 2020;383:1613-23

T315 drives most relapses after 2nd generation TKIs, role for novel agents and ponatinib?

- *BCR::ABL1* T315I KD mutation common at relapse after dasatinib (~70-75%).
- Ponatinib is a 3rd gen TKI active against T315I.
- Ponatinib associated with serious arterial thrombotic events, hepatotoxicity, and pancreatitis (unrandomized).

- **Additional therapy needed to limit relapse further – is there a "best" post remission strategy?**

Foa et al. *Blood* 2011;118:6521-28; Rousselot et al. *Blood* 2016; 128:774-82; Wieduwilt et al. *Blood Advances* 2021;4691-700; Moslehi et al. *J Clin Oncol* 2015;33:4210-8; Martinelli et al. *Blood Advances* 2022;6:1742-53

Ponatinib and Blinatumomab for Patients with Newly Diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Subgroup Analysis from a Phase II Study

NJ Short, H Kantarjian, N Jain, X Huang, G Montalban-Bravo, TM Kadia, N Daver, K Chien, Y Alvarado, G Garcia-Manero, GC Issa, W Macaron, FG Haddad,
M Kwari, R Delumpa, E Mayor, W Deen, J Thankachan, C Loiselle, J Rivera,
A Milton, L Waller, G Banks, R Garris, MY Konopleva, F Ravandi, E Jabbour

Department of Leukemia

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

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Abstract 213 (Short et al.) – Ponatinib/Blinatumomab for Newly-diagnosed Ph+ ALL

Patient Characteristics (N=40)

Characteristic	Category	N (%) / median [range]
Age (years)		57 [20-83]
≥1 CV risk factor		24 (60)
WBC (x10^9/L)		4.5 [0.4-23.7]
CNS involvement		2 (6)
BCR::ABL1 transcript	p190	30 (75)
	p210	10 (25)

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Abstract 213 (Short et al.) – Ponatinib/Blinatumomab for Newly-diagnosed Ph+ ALL

Eligibility

Adults

Newly-diagnosed Ph+ ALL

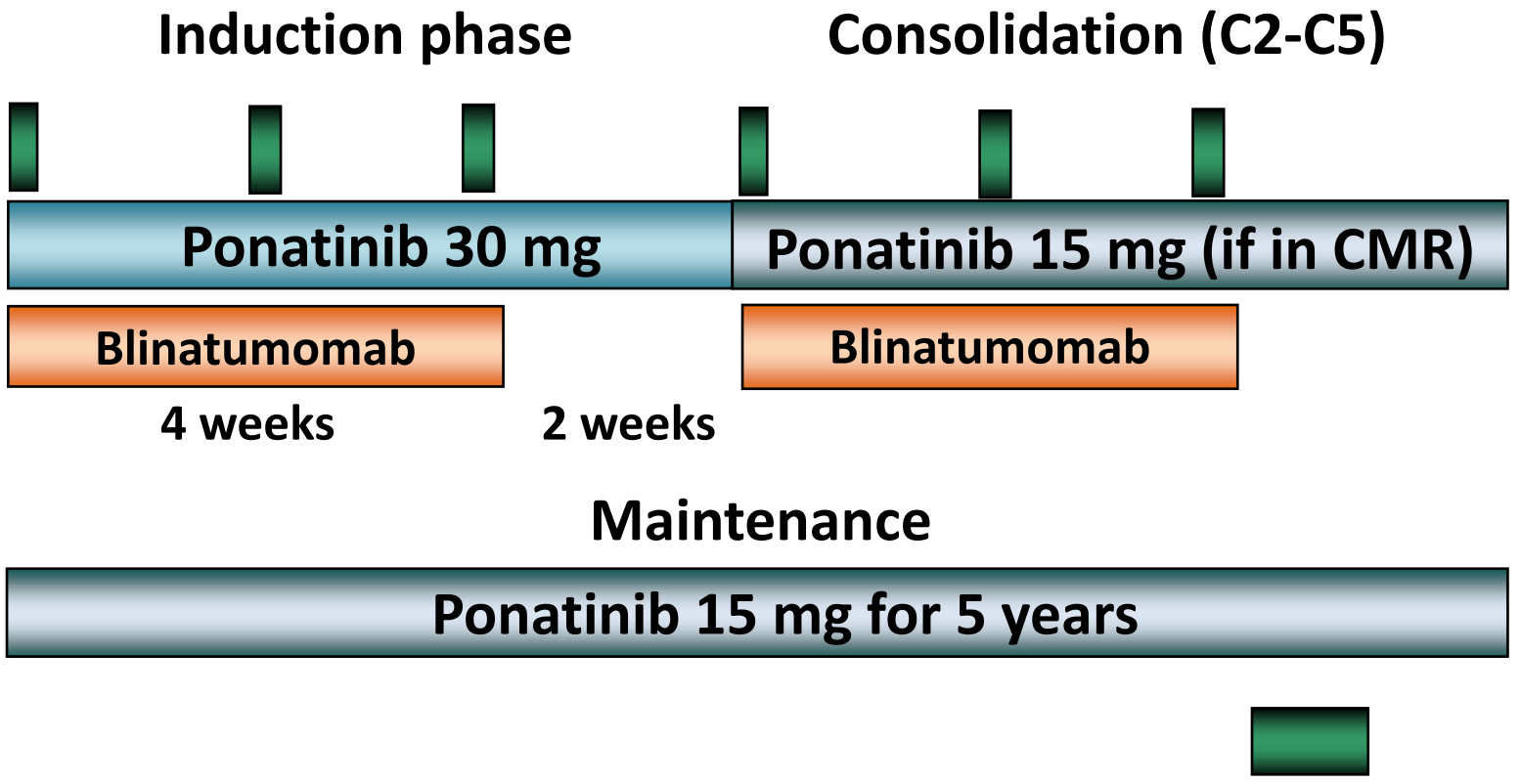
ECOG PS 0-2

No active CV disease

No CNS pathology

Primary endpoint

CMR rate



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Ponatinib + Blinatumomab : Response Rates

Response, n/N (%)	Frontline Ph+ ALL N = 40
CR/CRi*	27/28 (96)
CR	26/28 (93)
CRi	1/28 (4)
Early death	1/40 (3)
MMR**	36/37 (97)
CMR**	33/38 (87)
After 1 cycle	26/38 (68)
NGS MRD negative	22/25 (88)

NGS MRD$^-$ pts had low-level *BCR::ABL1* by PCR (0.01-0.05%)

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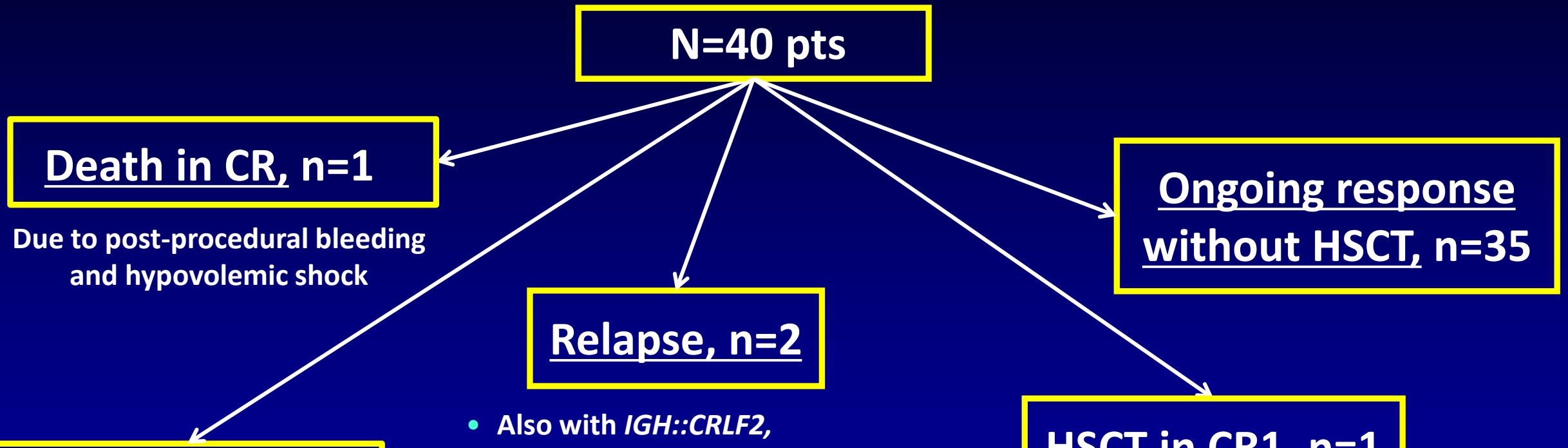
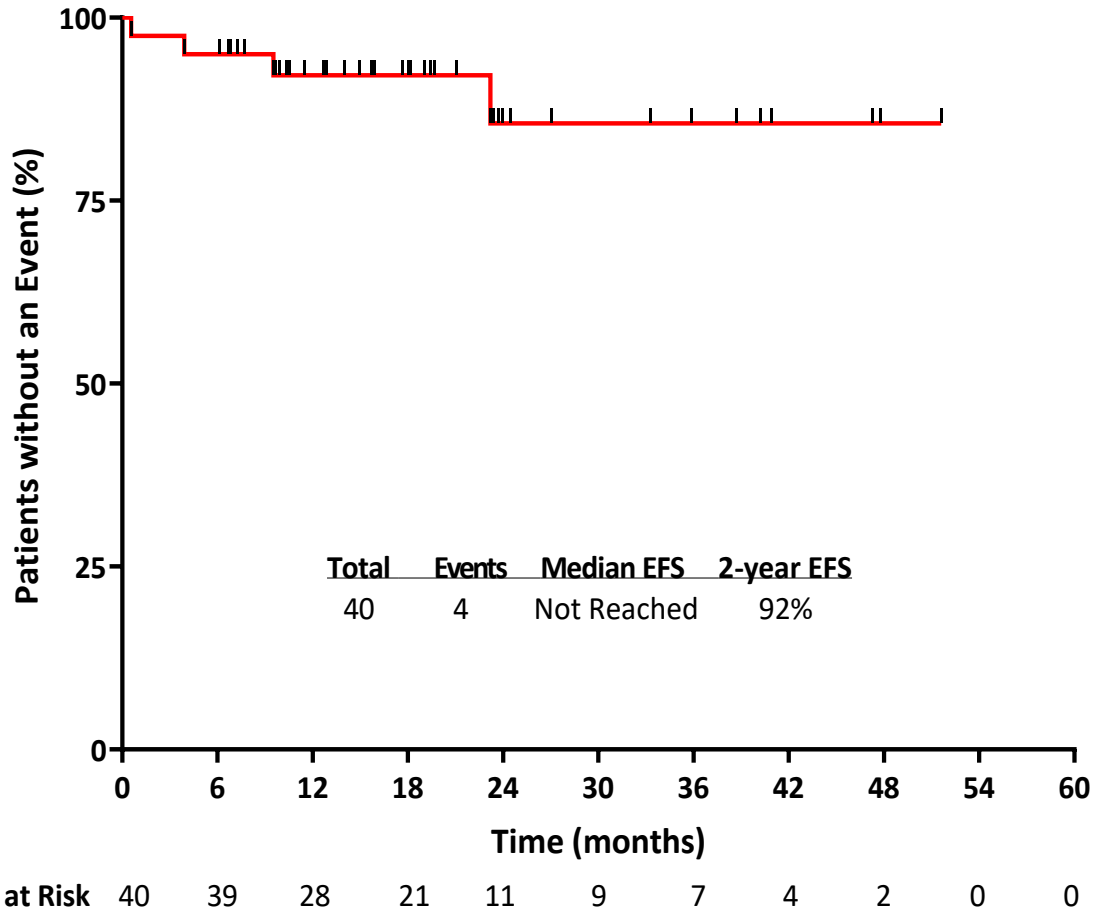
Ponatinib + Blinatumomab in Ph+ ALL:

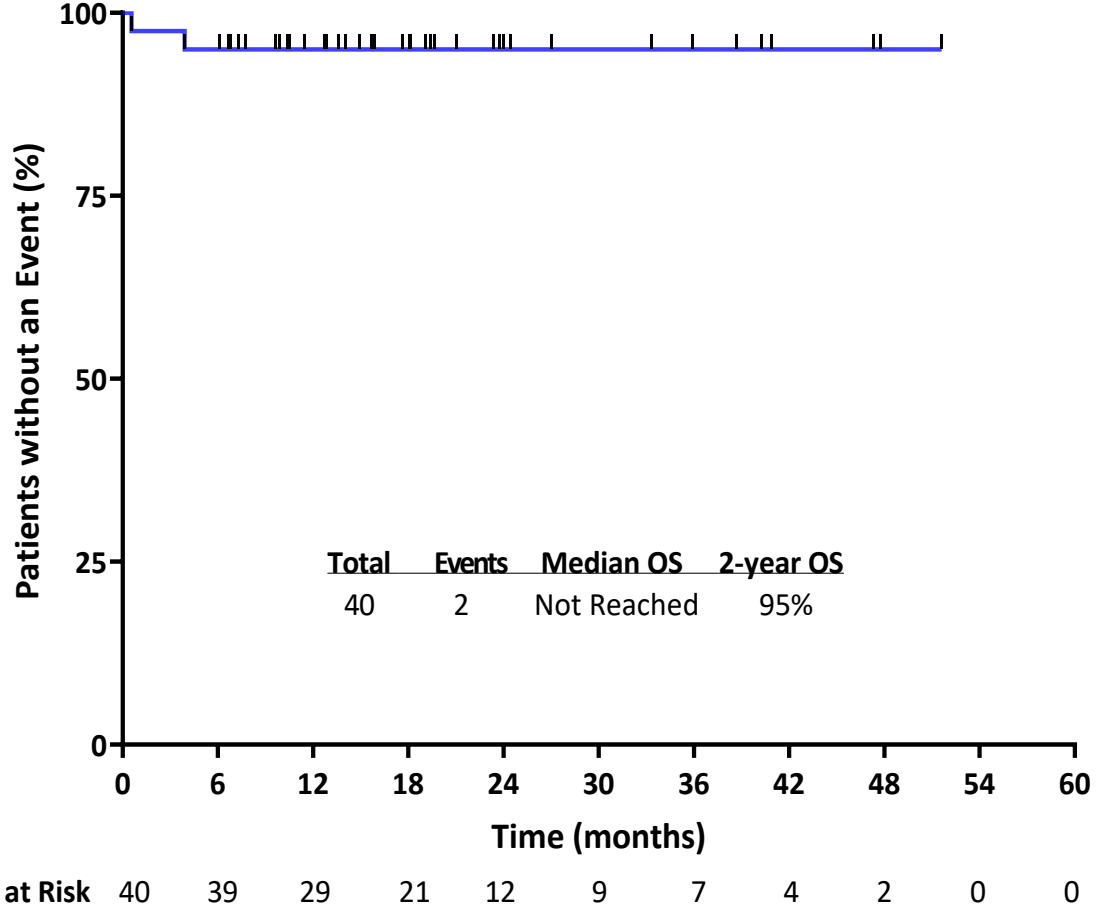


- Also with *IGH::CRLF2,* extramedullary-only (peritoneal and lymphomatous) Ph-negative relapse (MYC rearranged) after 9 months
- CNS-only relapse after 23 months

Survival: Median F/U 18 months

Estimated 2 year EFS: 92%- 4 events include 1 early death, 1 death in remission and 2 relapses; only 1 pt transplanted





Conclusions/Comments: Ph+ ALL

- Ponatinib + blinatumomab safe and effective
  - No ≥ Grade 4 events; 3 ponatinib discontinuations due to toxicity
- Deep and rapid responses
  - CR/CRi 96%, CMR 87%, NGS MRD negativity 88%
  - Most pts achieved CMR within 2-4 weeks of treatment
- Durable remissions: 2 relapses to date
  - (both extramedullary-only, 1 in pt with *CRLF2* rearrangement)
- EXCITING – **need longer follow-up**, May spare transplant!
  - Only 1 patient received alloSCT in CR1

Final Thoughts

- Aza/ven : our ”go to” regimen for many patients with AML
  - Testing in frontline in younger patients in randomized trials to start in NCTN myelomatch: COMING OUR WAY SPRING 2023!
- High risk AML subsets with low response rates to Aza/Ven have been identified and prognostic system developed
  - TP53 remains the huge challenge – Magrolimab responses ”hopeful”!
- Targeted therapies for ALL are changing treatment paradigm!
  - Less chemotherapy, better targets lead to TRM, decreasing transplant ”need” and resulting in significantly improved OS