Adult ALL – Emerging and Targeted Therapies

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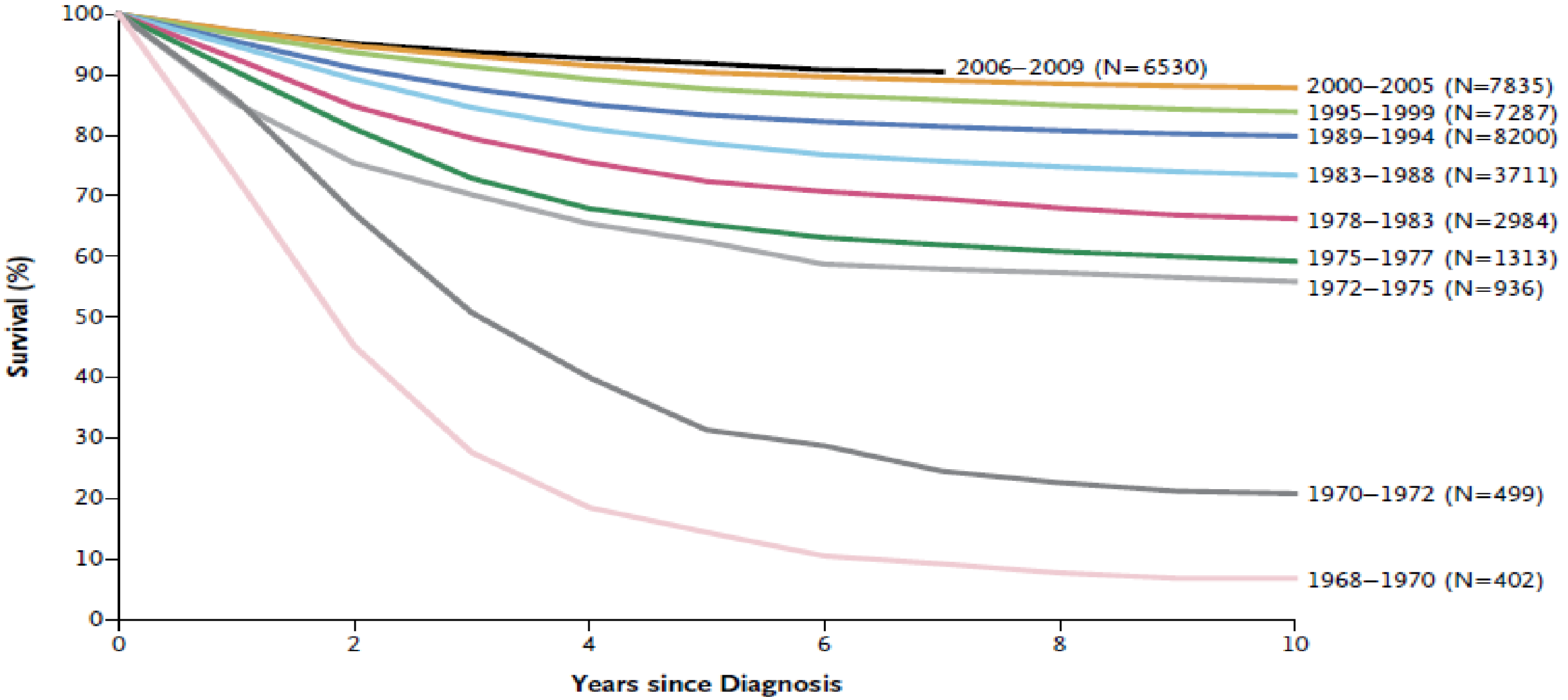
Indy Hematology Review

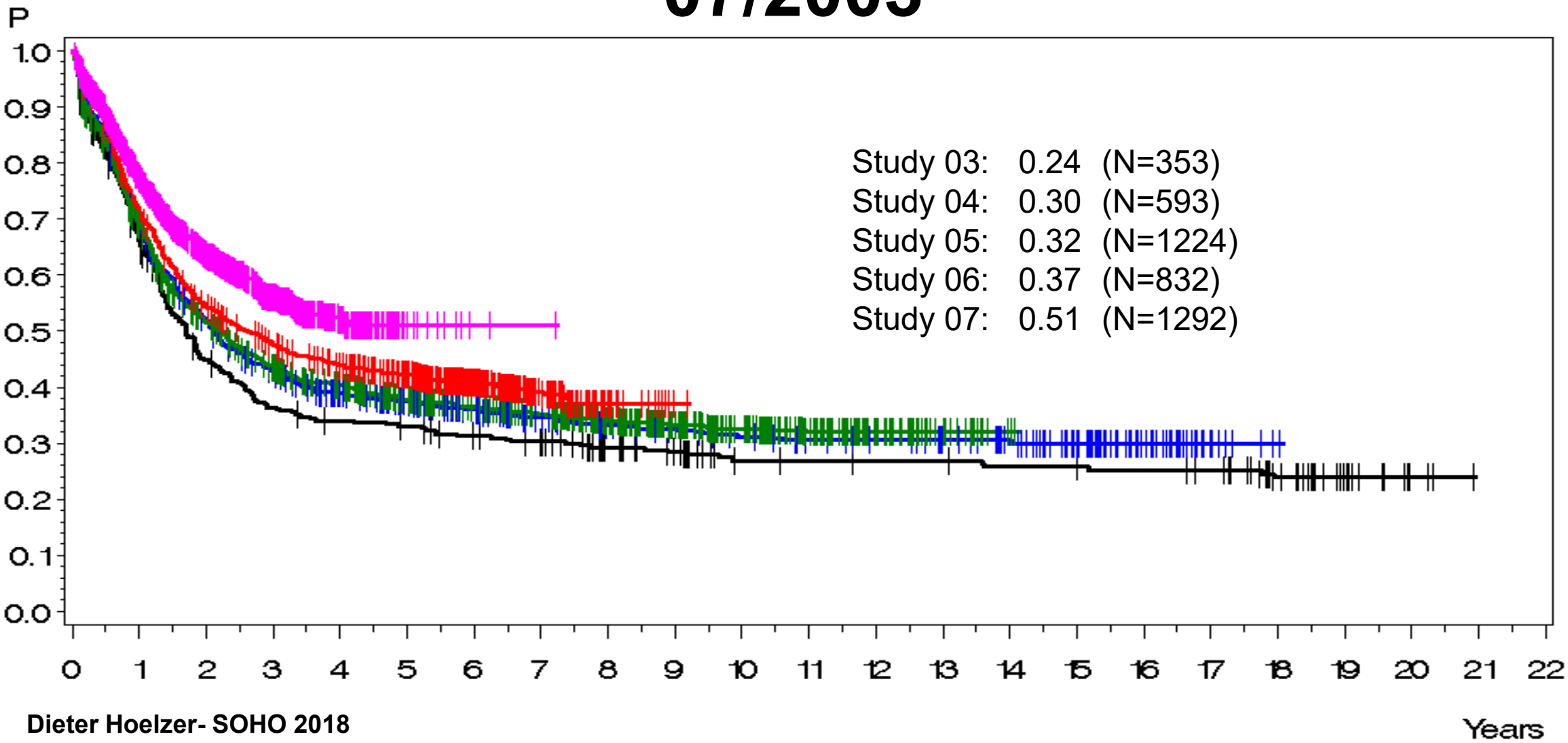
March 2019

Survival of 39,697 Children With ALL Treated on Sequential CCG/COG Clinical Trials



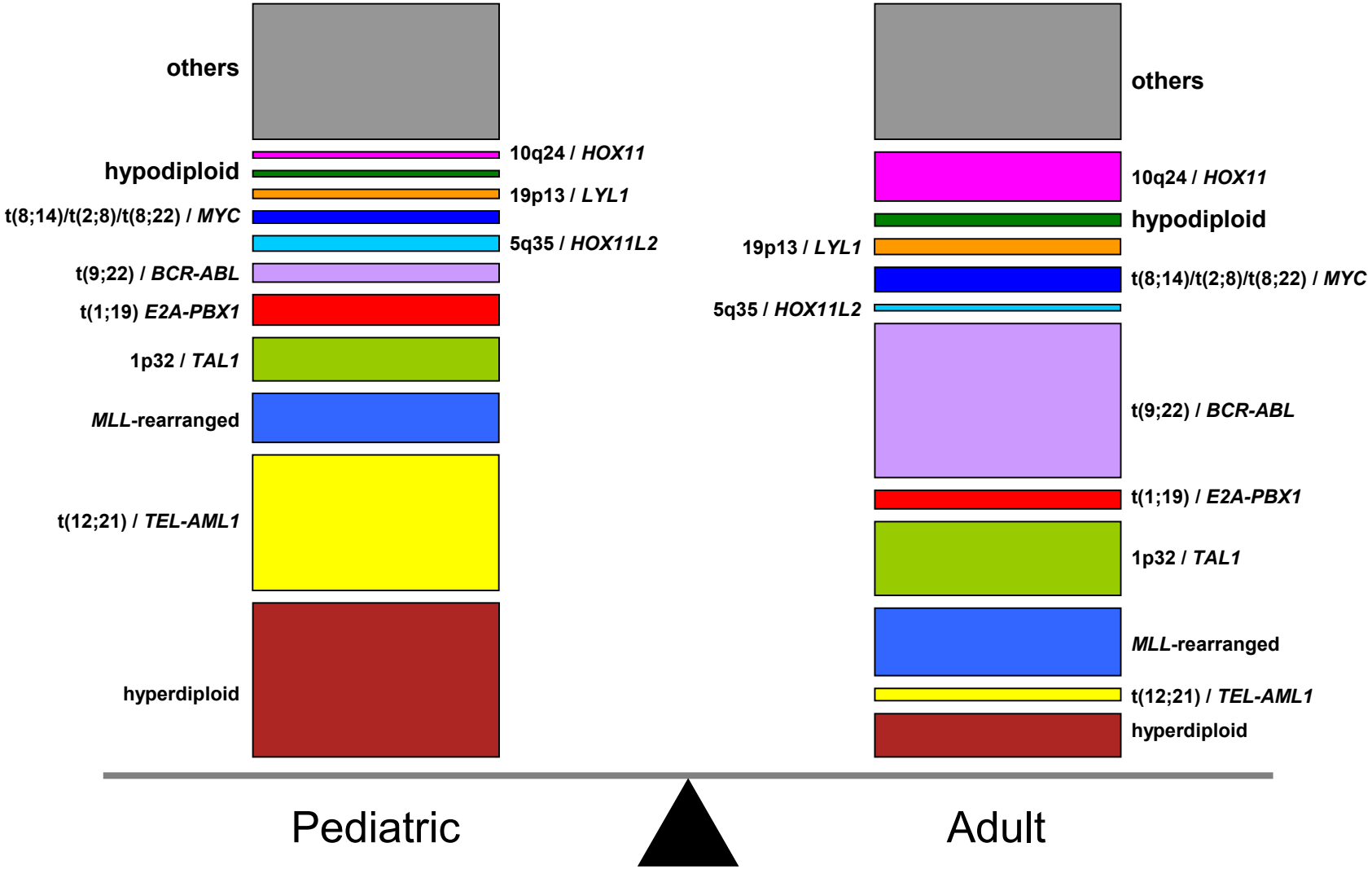
Hunger. NEJM. 2015;373(16):1541-1552

Overall Survival
Comparison of the GMALL studies 03/87 until 07/2003



Genetics in Pediatric vs. Adult ALL

Courtesy of T. Haferlach

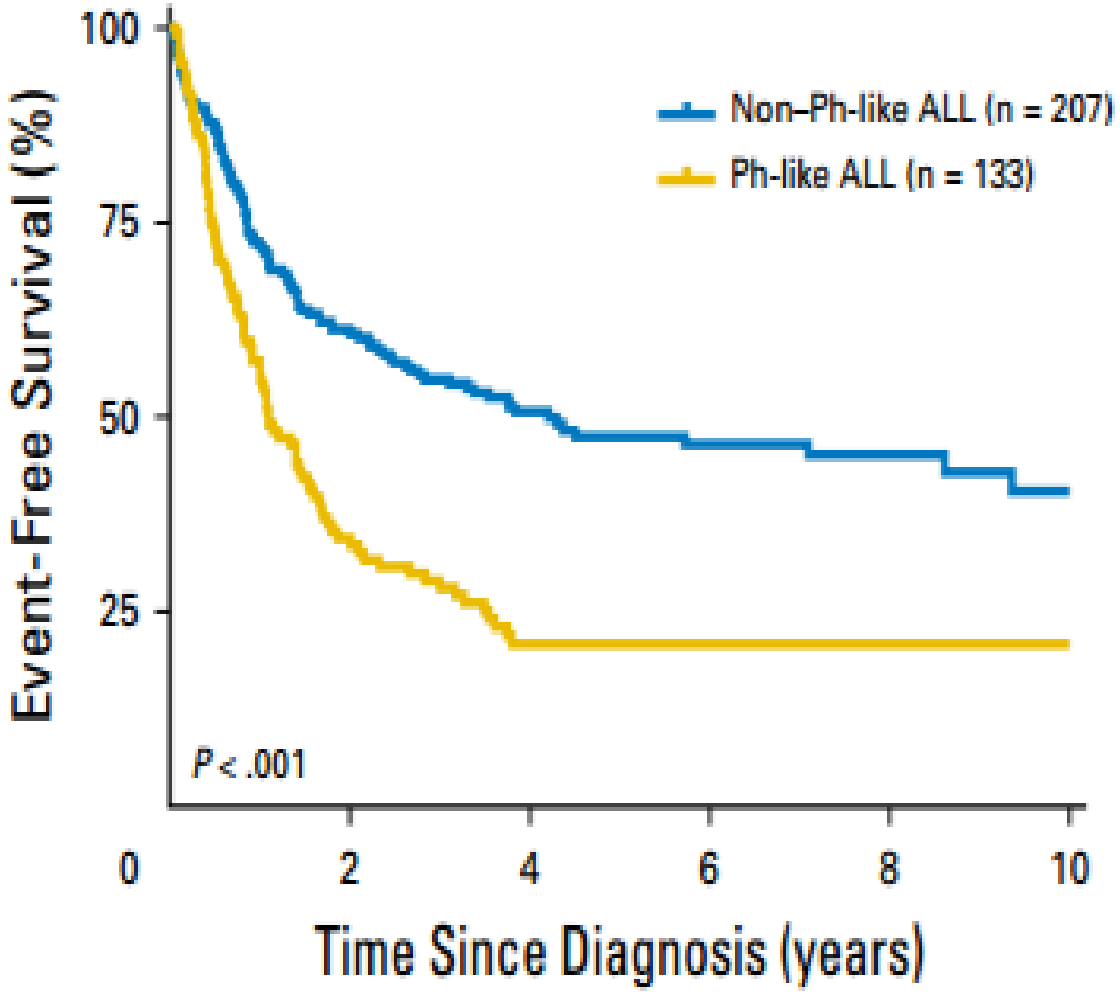


Pui . NEJM, 350, 1535-1548, 2004

Reasons Why Pediatric ALL Does Better Than Adult ALL

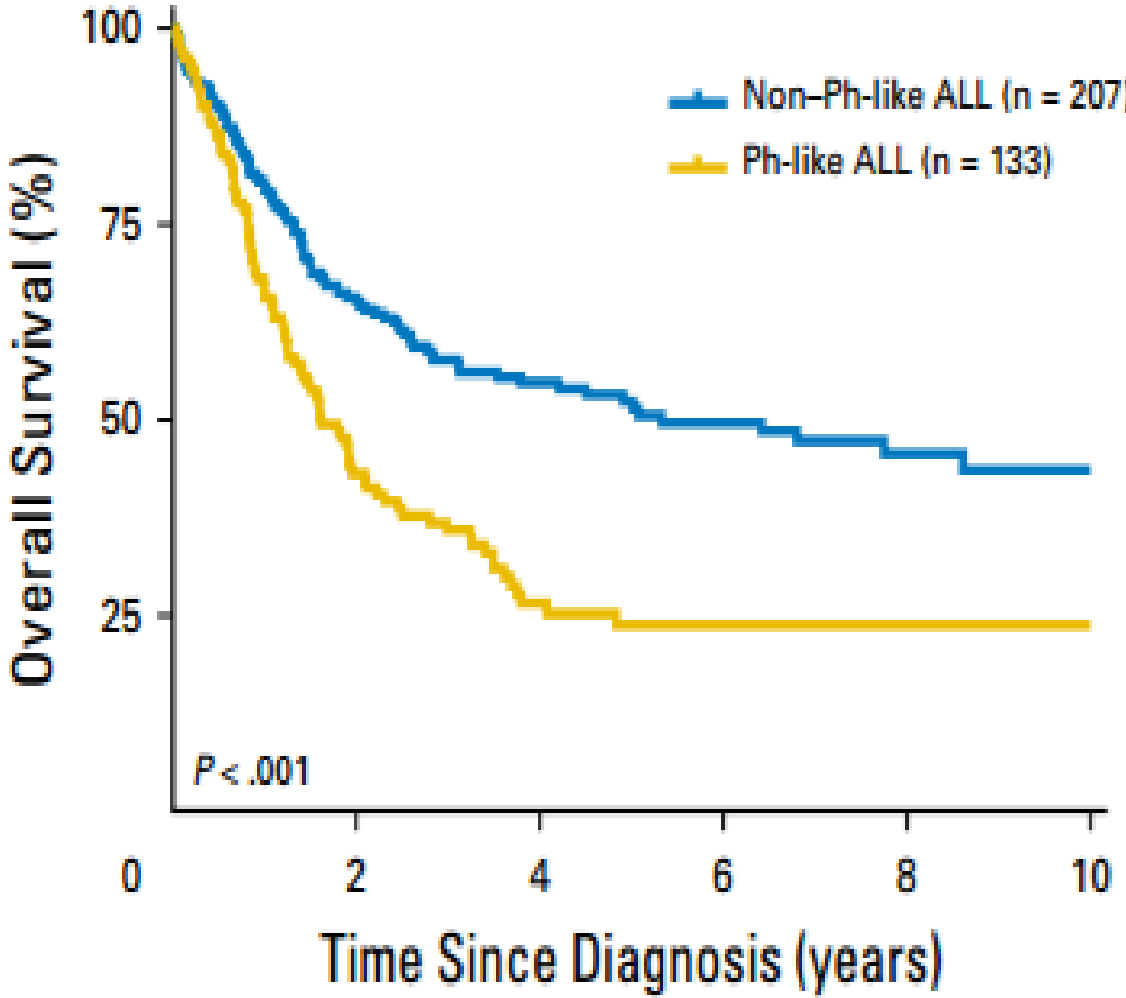
Entity	Prognosis	% Pediatric	% Adult
Hyperdiploid	Favorable	25-30	5
t(12;21), *ETV6-RUNX1*	Favorable	20-25	2
Ph+ALL	Unfavorable	5	25
Ph-like ALL	Unfavorable	10	25

Ph-Like ALL-- Survival and EFS



No. at risk:

Non–Ph-like ALL	207	146	117	102	73	53	47	35	28	20	13
Ph-like ALL	133	70	39	32	19	15	14	11	9	5	3



No. at risk:

Non–Ph-like ALL	207	162	127	107	80	60	51	37	29	20	14
Ph-like ALL	133	82	49	40	23	17	16	12	9	5	3

Roberts, et al. JCO 35:394; 2017

Ph-Like ALL: More Common in Hispanic Ethnicity

		B-ALL Categories (N=155)			
		Ph-Like	Ph+	B-other	p-value
	N				
Ethnicity					
Caucasian	60	13 (22)	20 (33)	27 (45)	
Hispanic	70	38 (54)	16 (23)	16 (23)	<0.001
African-American	16	2 (12)	8 (50)	6 (38)	
Asian	7	3 (44)	2 (28)	2 (28)	
Unclassified	2	-	-	2 (100)	

Jain. Blood 2017; 129:572-581

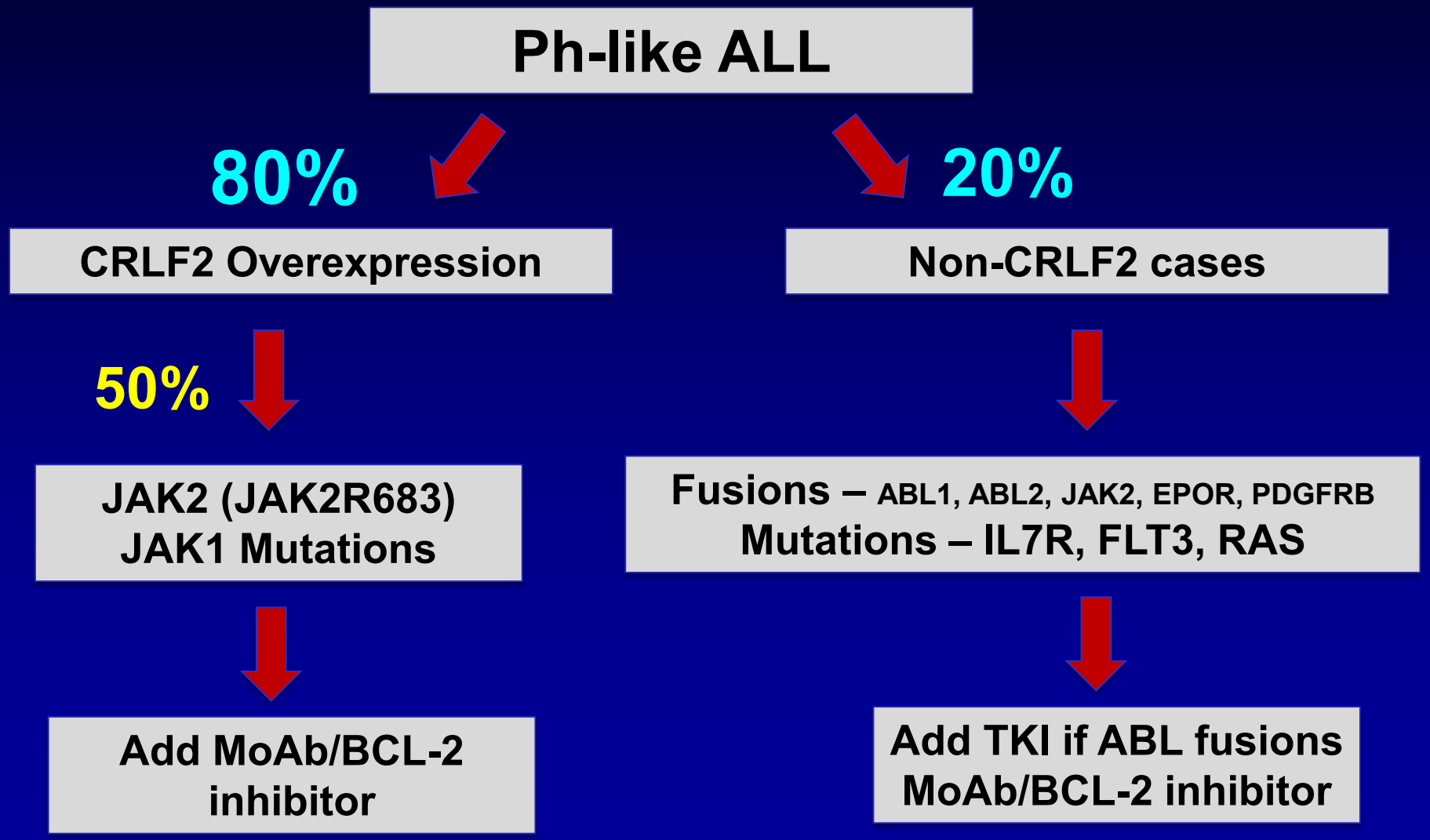
Ph-like ALL. Higher MRD + Rate

	B-ALL Categories (N=155)			
	Ph-Like	Ph+	B-other	p-value
N	56	46	53	
CR/CRp	50 (89)	43 (93)	50 (94)	0.57
MRD at CR				
Positive	23 (70)	15 (44)	4 (13)	<0.001
Negative	10 (30)	19 (56)	27(87)	

Jain. Blood 2017; 129:572-581

Ph-like ALL Molecular Lesions

- Ph-like 25-30% of ALL; poor prognosis



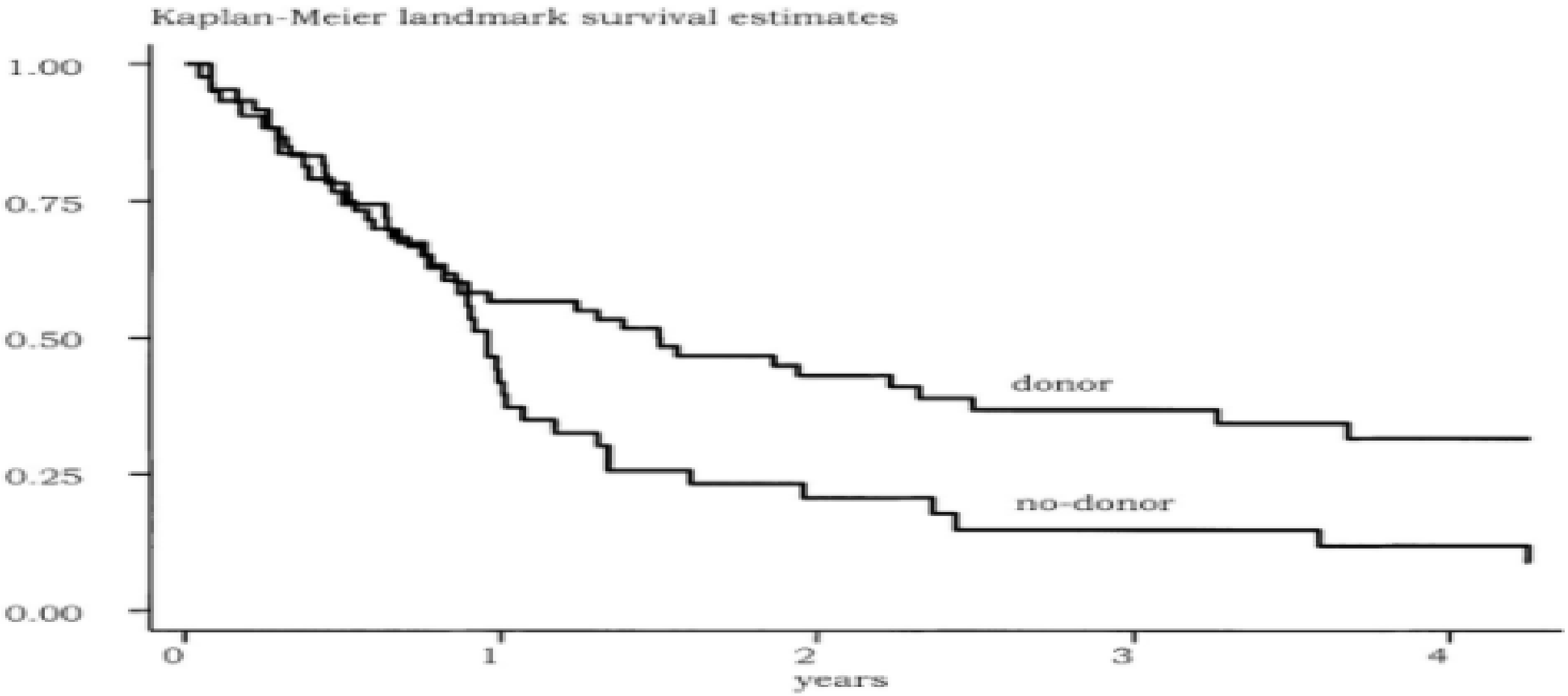
Ph-like ALL. Summary and Future Directions

- Ph-like 25-30% of ALL; poor prognosis
- 50-80% have CRLF2 rearrangement, of which 50% have JAK mutations
- ABL and JAK fusions in CRLF2 non-rearranged cases
- FISH and RT-PCR identifies fusions
- Plans: add TKI if ABL fusions, and antibodies/venetoclax if CRLF2+, to frontline and salvage ALL

Reasons for Recent Success in Adult ALL Rx

- Addition of TKIs to chemoRx in Ph+ ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Potential benefit of addition of CD19 bispecific antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx
- CAR-T Rx in salvage

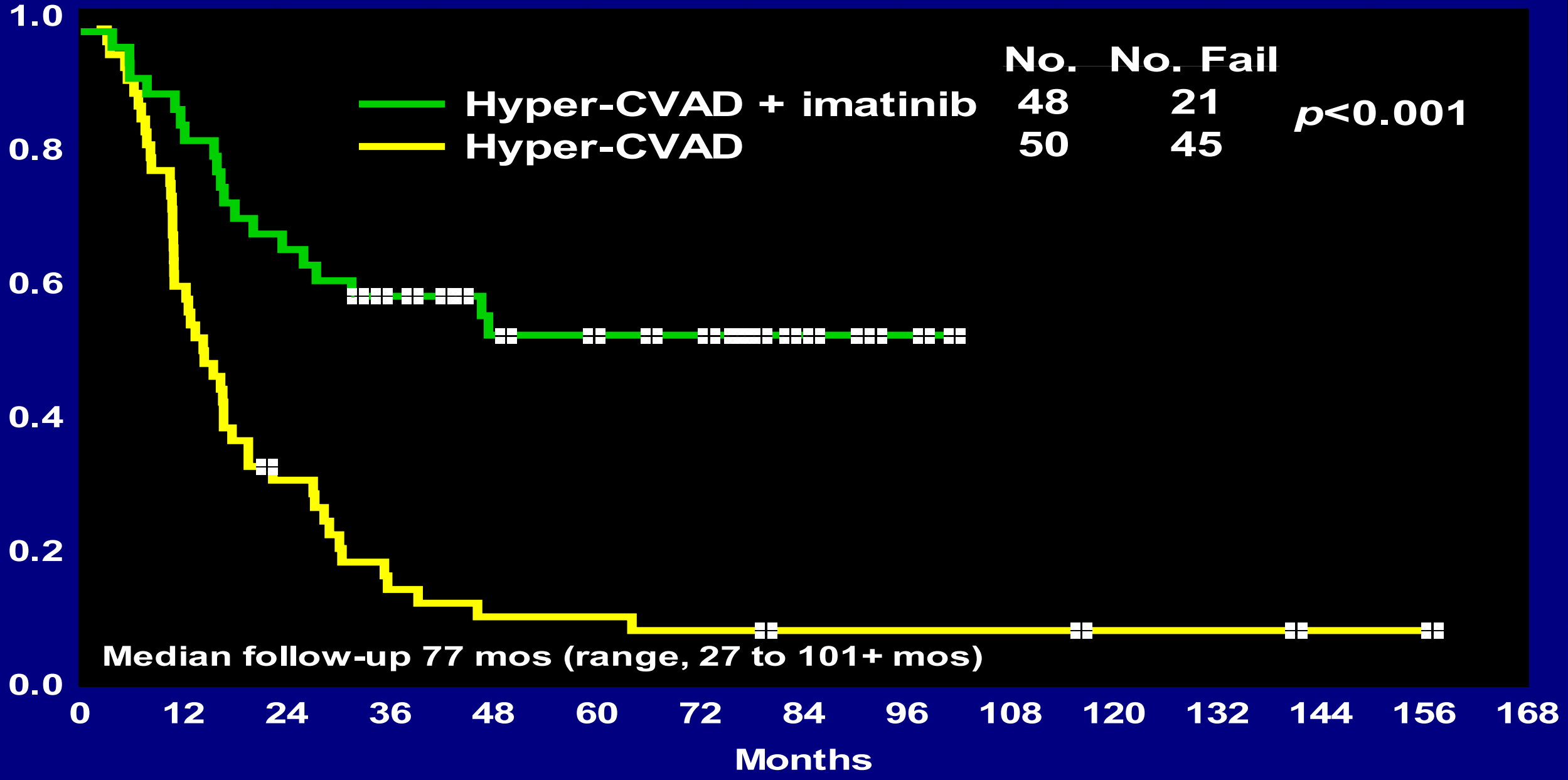
SCT for Ph+ ALL. Pre-TKI



- Donor (n=60) - 3-year OS: 37%
- No donor (n=43) – 3-year OS: 12%

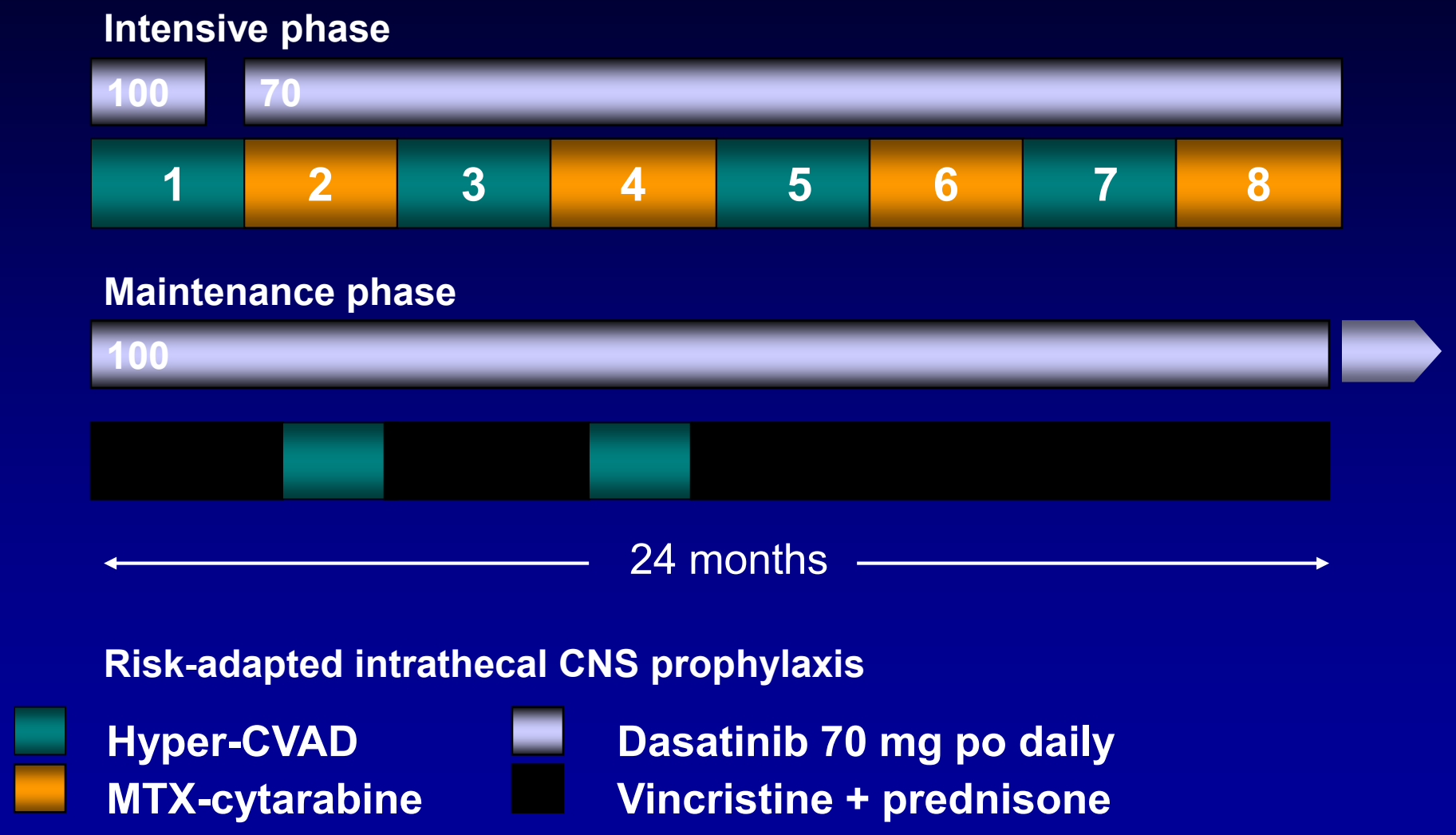
Dombret H et al *Blood* 2002

Survival in Ph-ALL by Regimen (Excluding Primary Refractory)



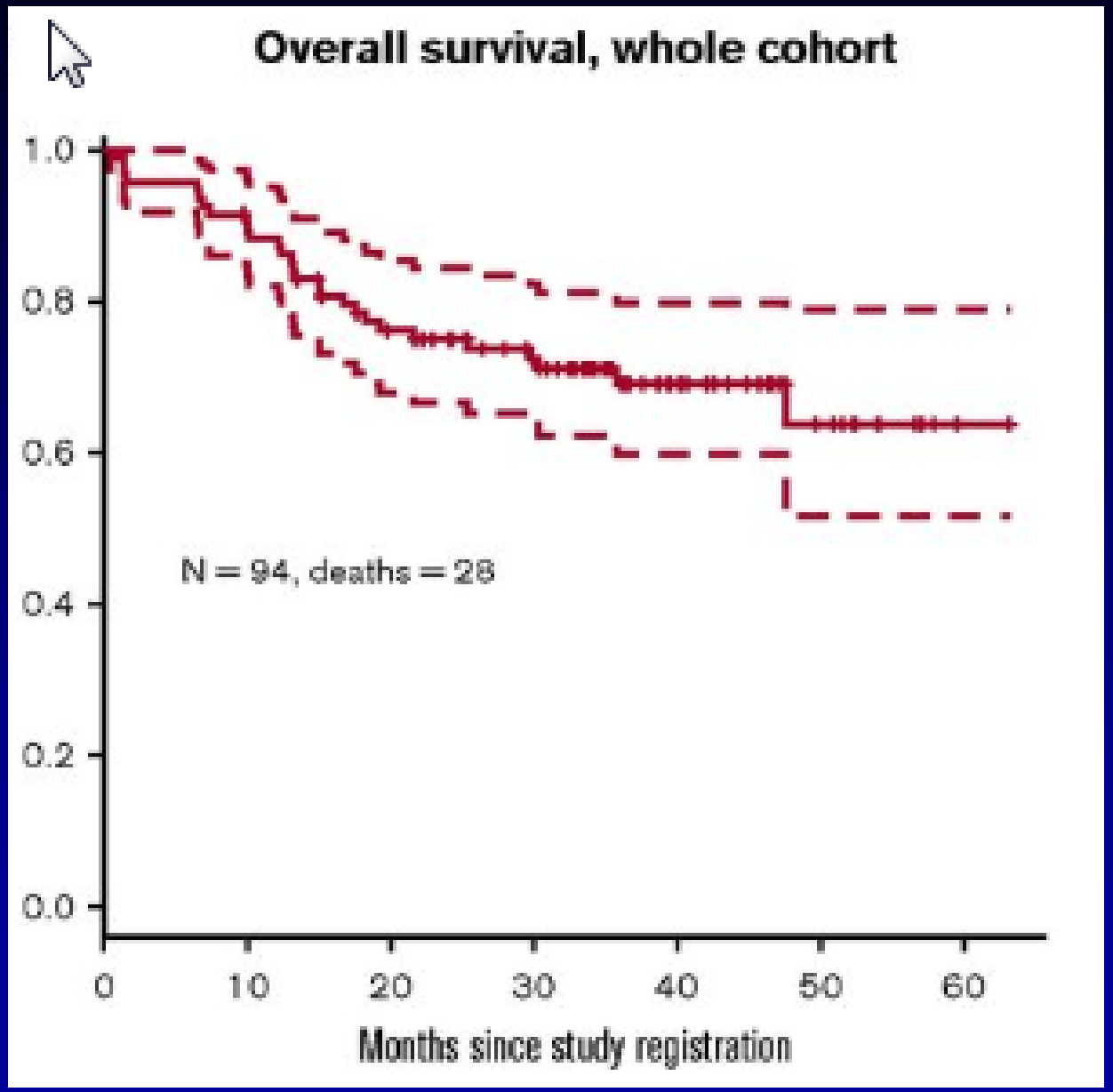
Daver . Haematologica. 2015;100(5):653-661.

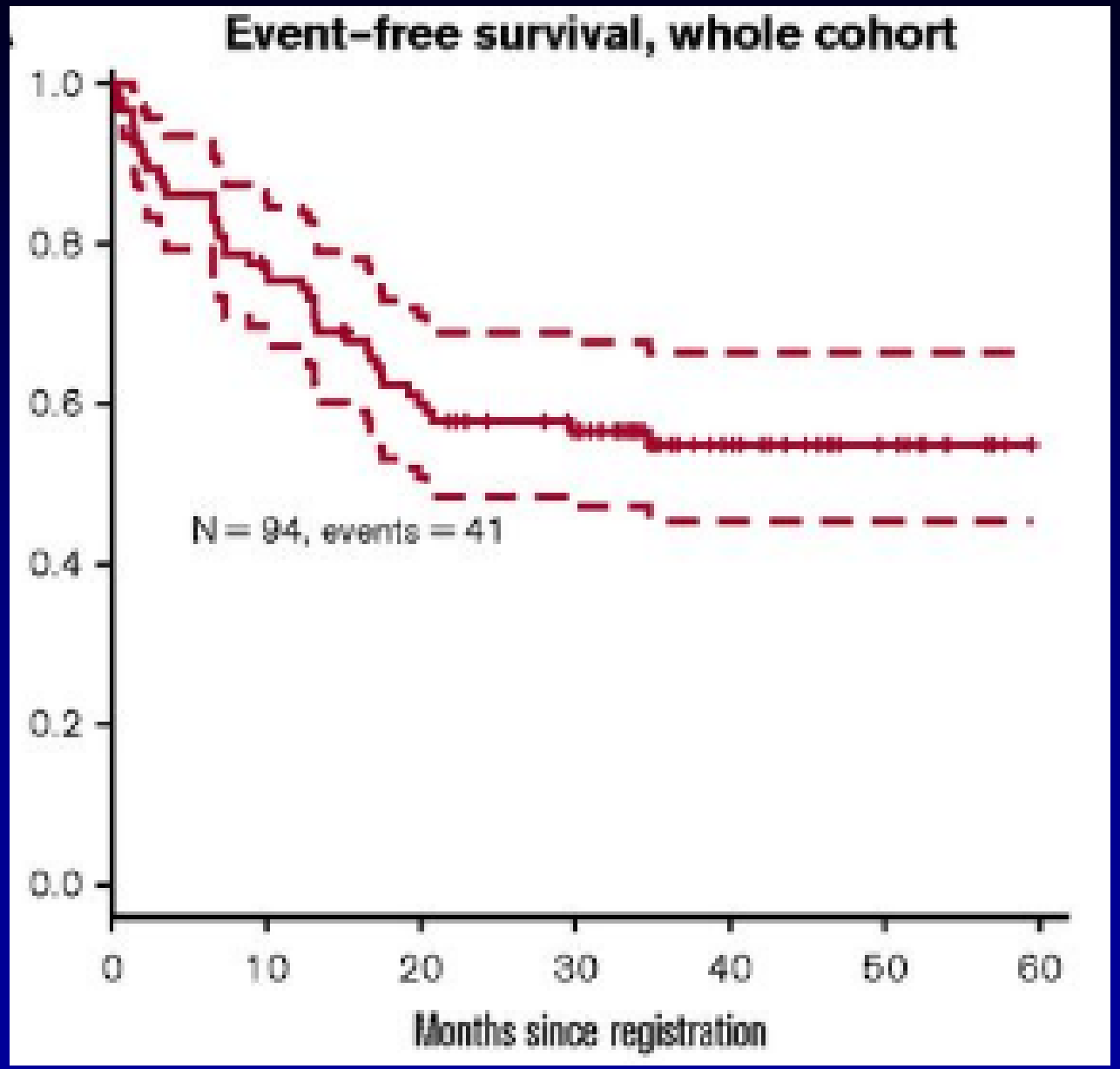
Hyper-CVAD + Dasatinib in Ph+ ALL: Regimen



Ravandi . Blood Advances. 2016;1:250-259.

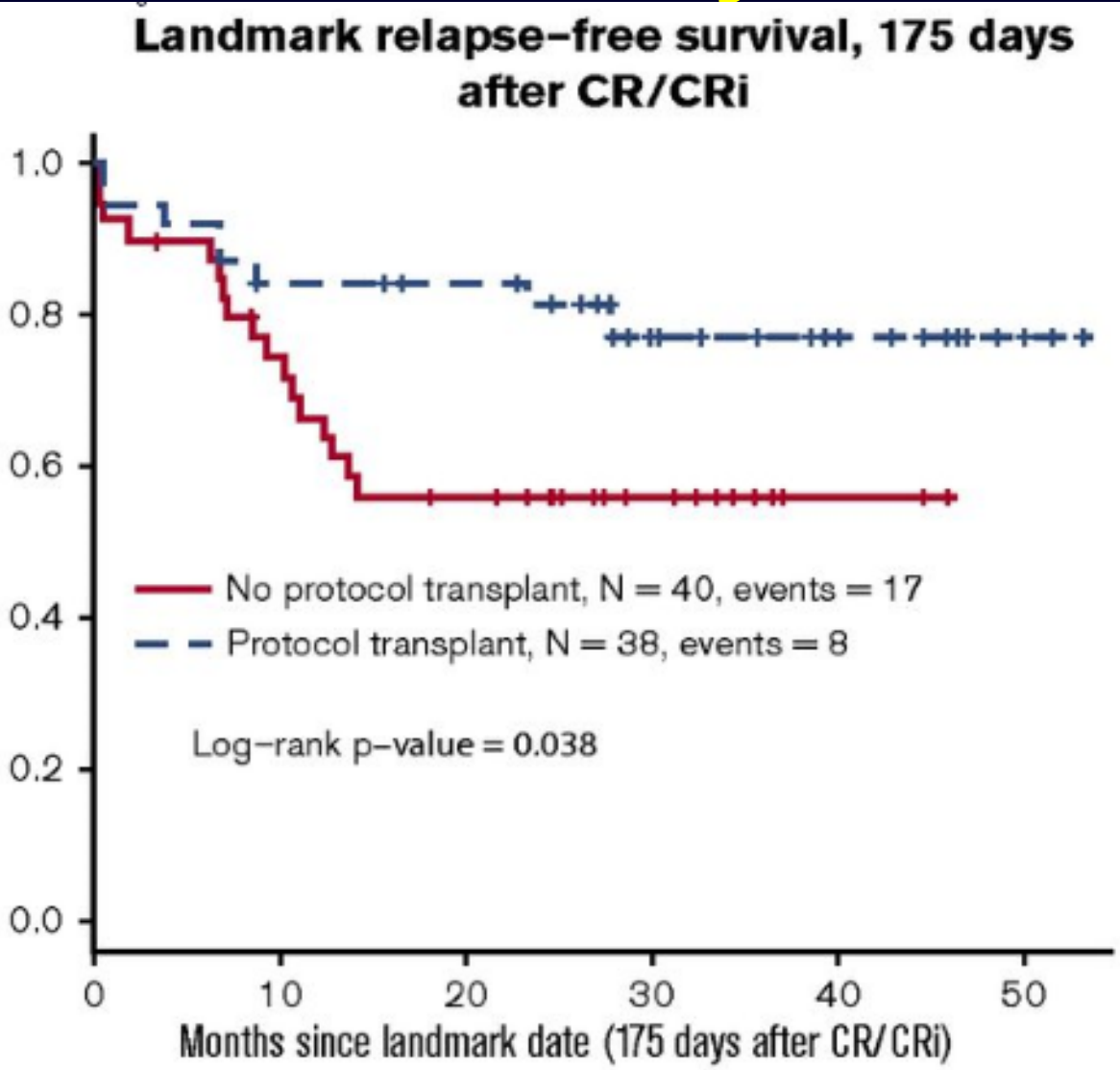
HyperCVAD+Dasatinib in Ph+ALL.

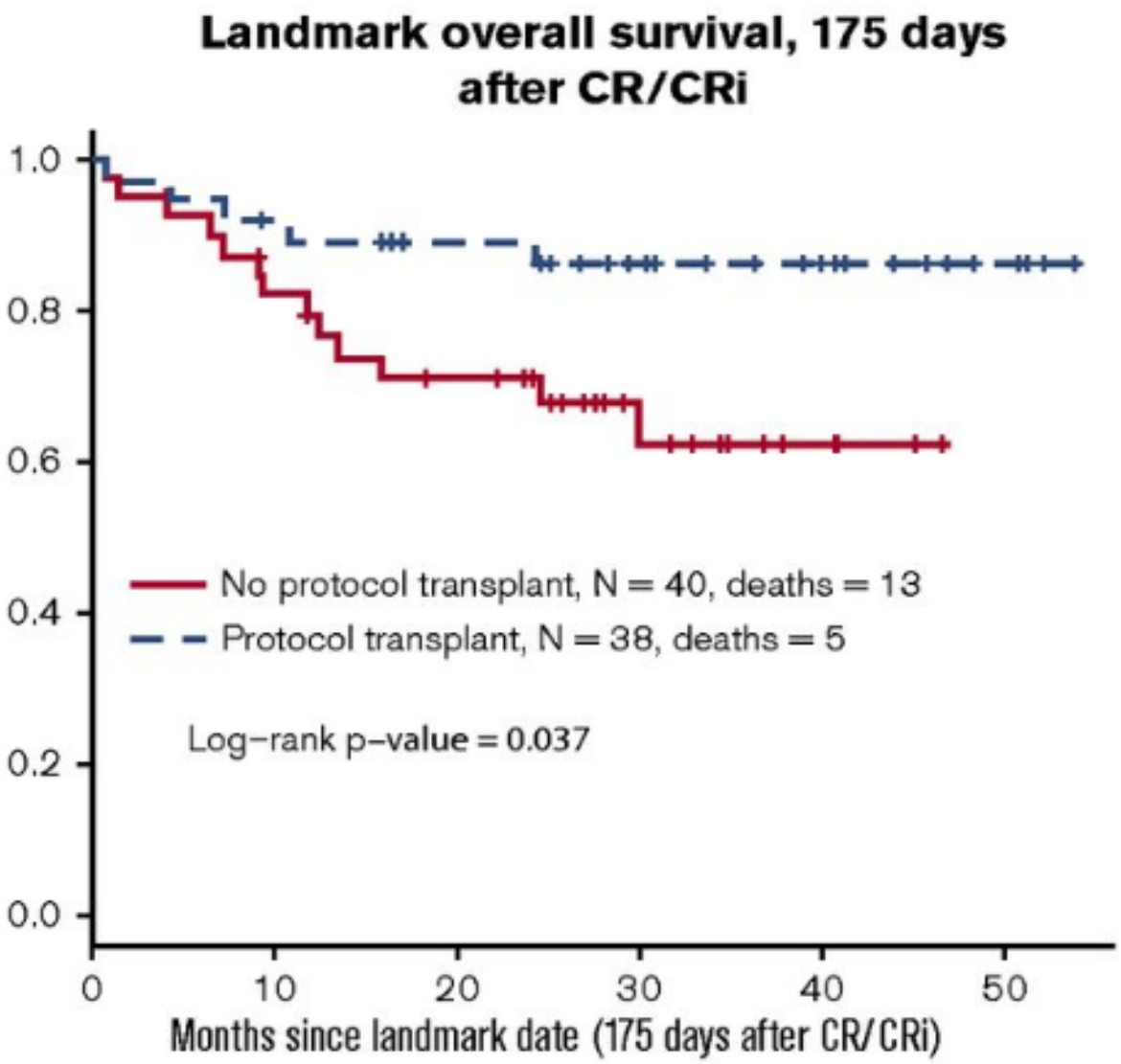




Ravandi. Blood Advances 1: 250; 2016

HyperCVAD+Dasatinib in Ph+ALL. Landmark Analysis: No ASCT vs. ASCT





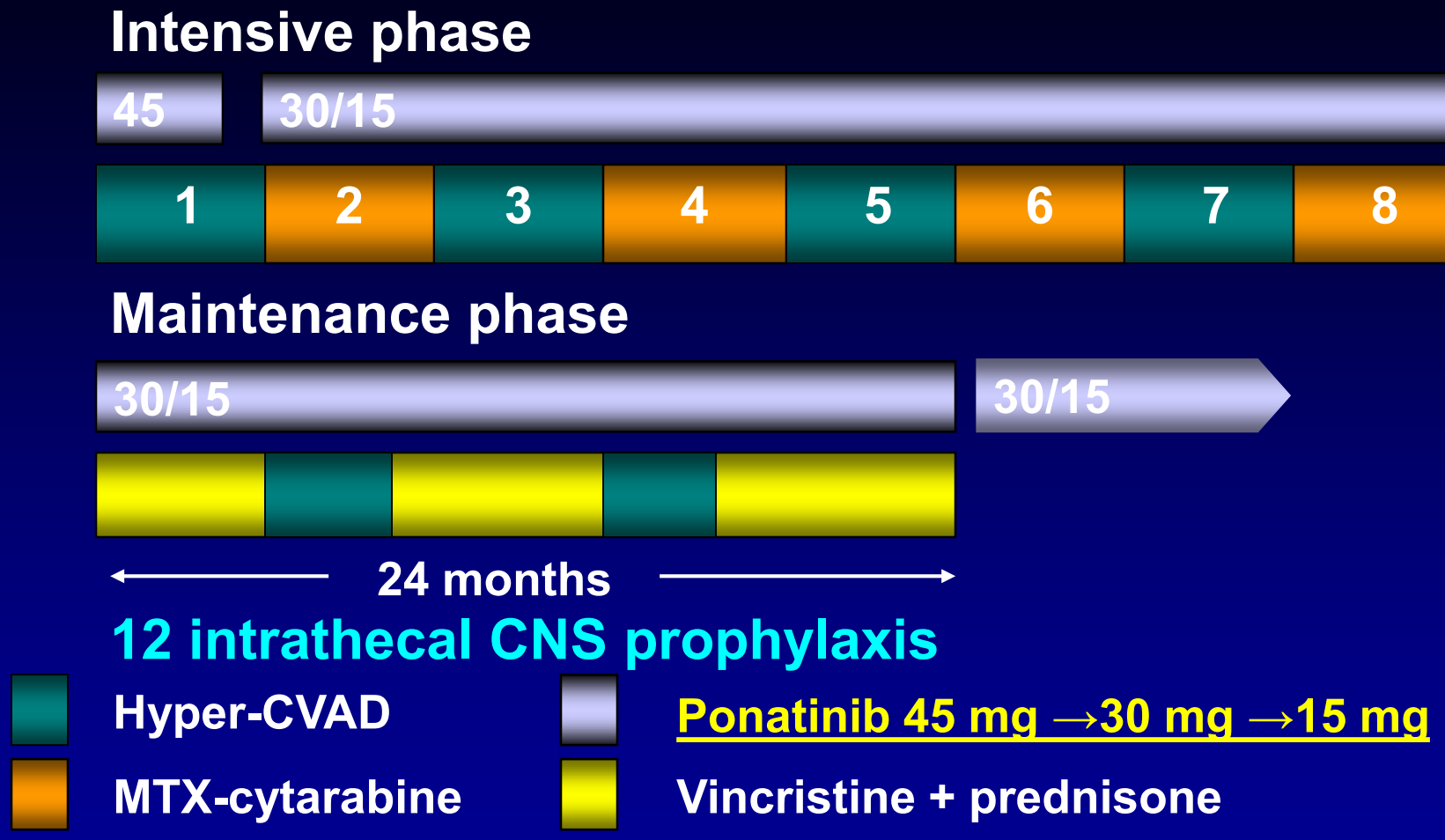
Ravandi. Blood Advances 1: 250; 2016

Low-intensity chemo Rx + Dasatinib in Ph + ALL ≥ 55 yrs

- 71 pts (2007-2010); median age 69 yrs (58-83)
- Dasatinib 100-140 mg/D, VCR 1mg Q wk, Dex 20-40 mg/D x 2, Qwk
- Consolidations: dasatinib 100 mg/D; MTX-Asp C1,3,5; ara-C C2,4,6. Maintenance: dasatinib + POMP
- CR 96%; MMR 65%; CMR 24%
- 5-yr survival 36%; EFS 25%
- T315I at Dx 23% by NGS
- 36 relapses; T315I in 75%

Rousselot. Blood 128: 774; 2016

Hyper-CVAD + Ponatinib. Design

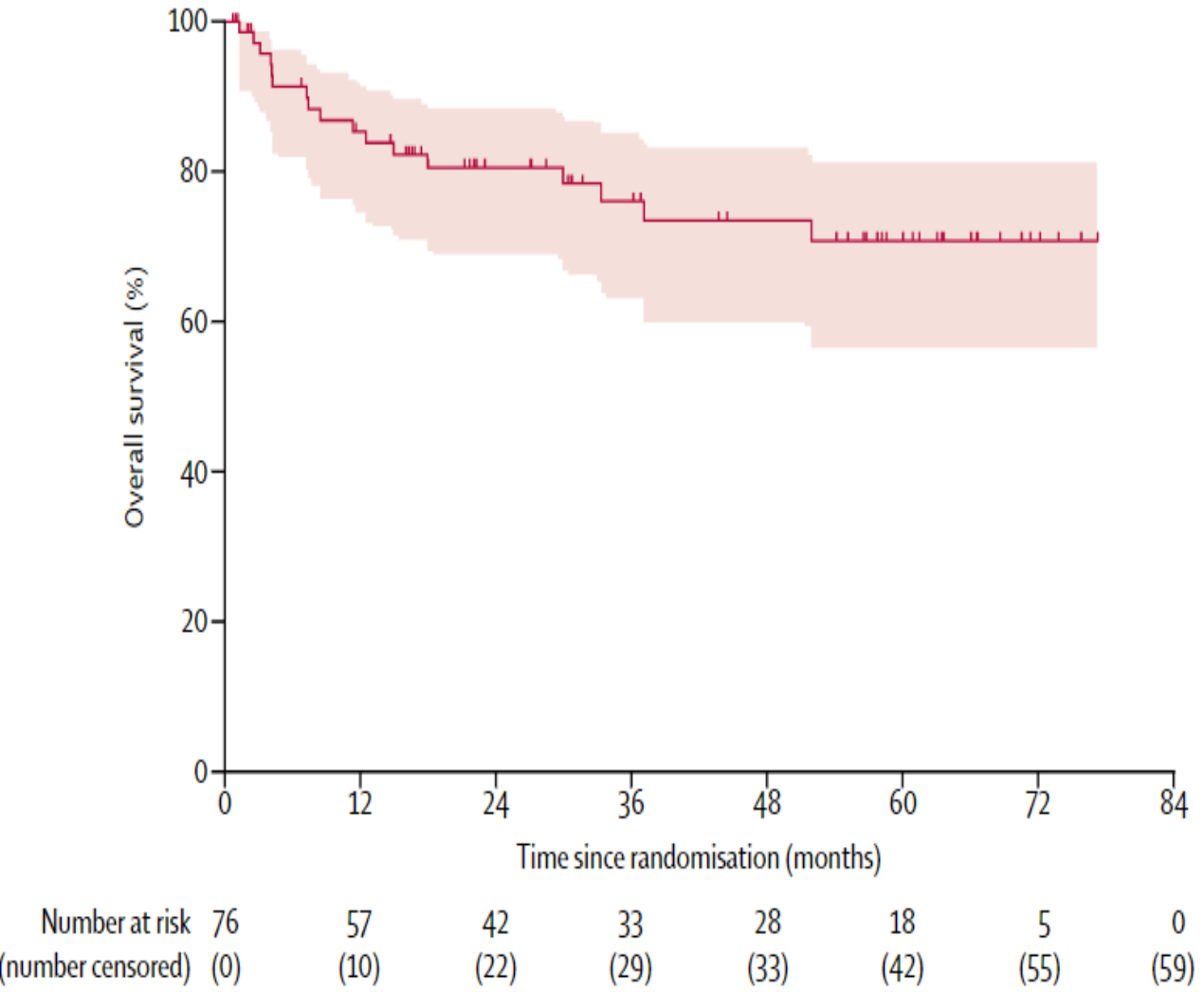


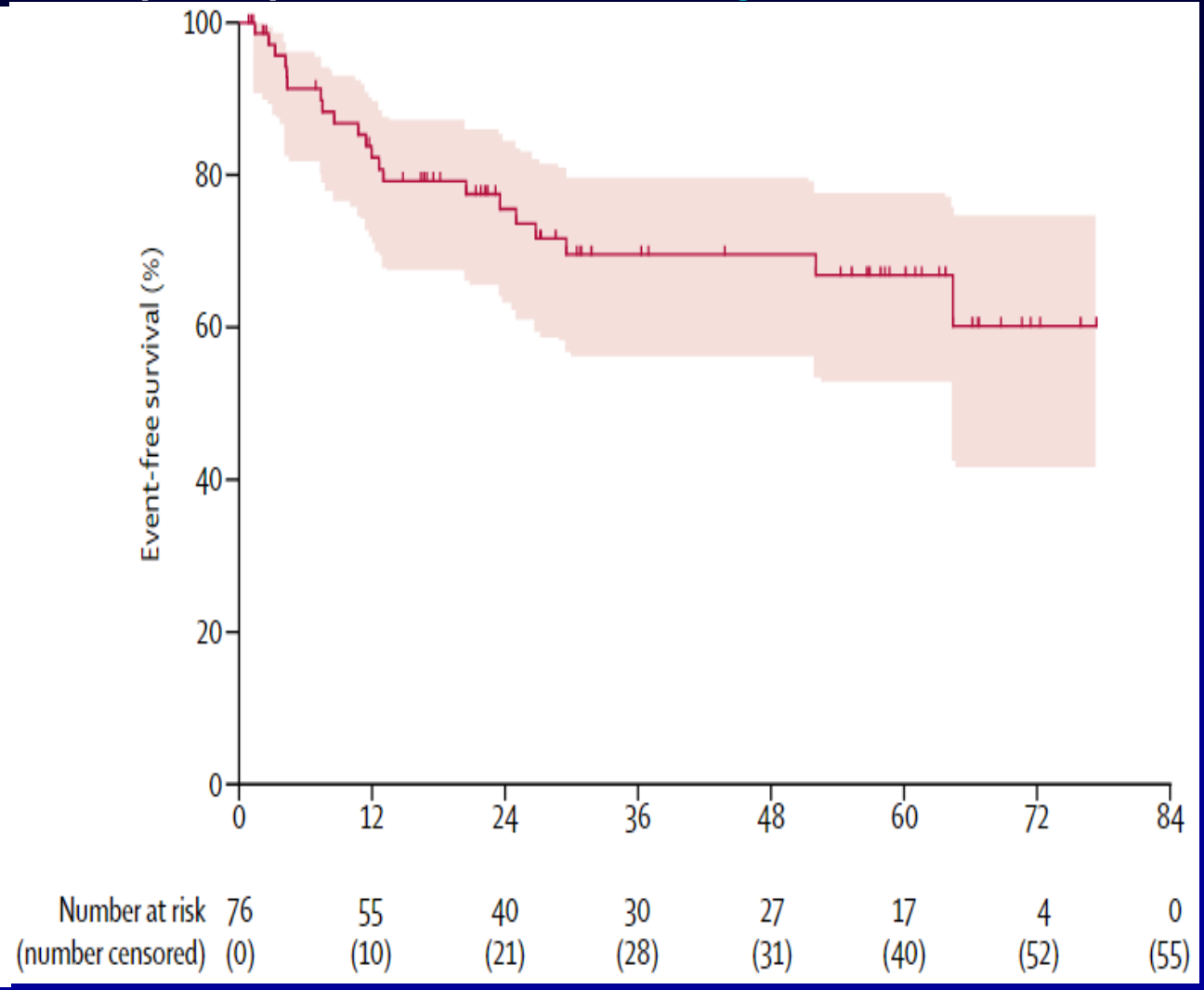
- After the emergence of vascular toxicity, protocol was amended: Beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

Jabbour. Lancet Onc. 16:1547;2015. Jabbour. Lancet Hematology 5: 618; 2018

HyperCVAD + Ponatinib in Ph-positive ALL

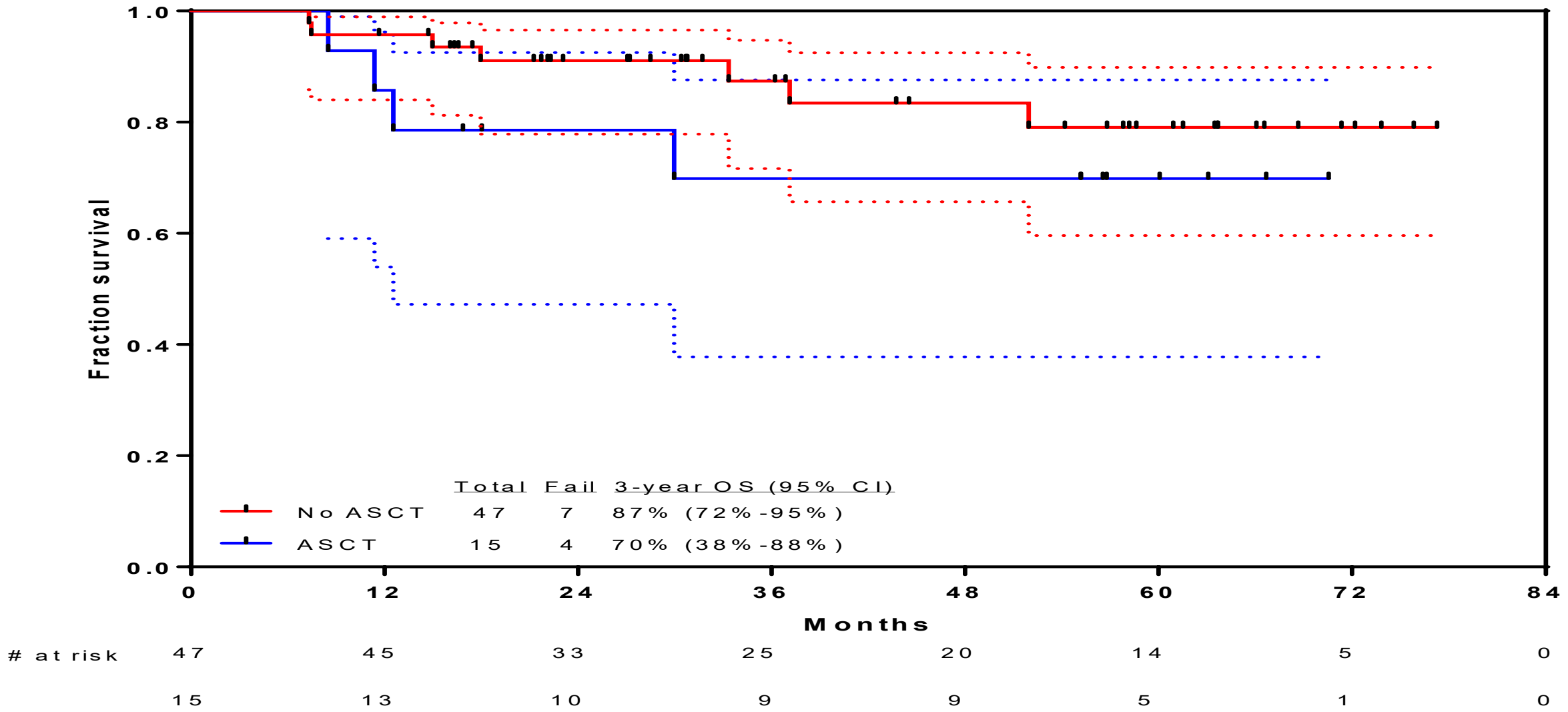
- 76 pts Rx; median age 47 yrs (39-61)
- CR 65/65 (100%); FCM-MRD negative 74/75 (99%); CMR 83%; 3/5-yr OS 76/71%





Jabbour. Lancet Hematology 5: 618; 2018

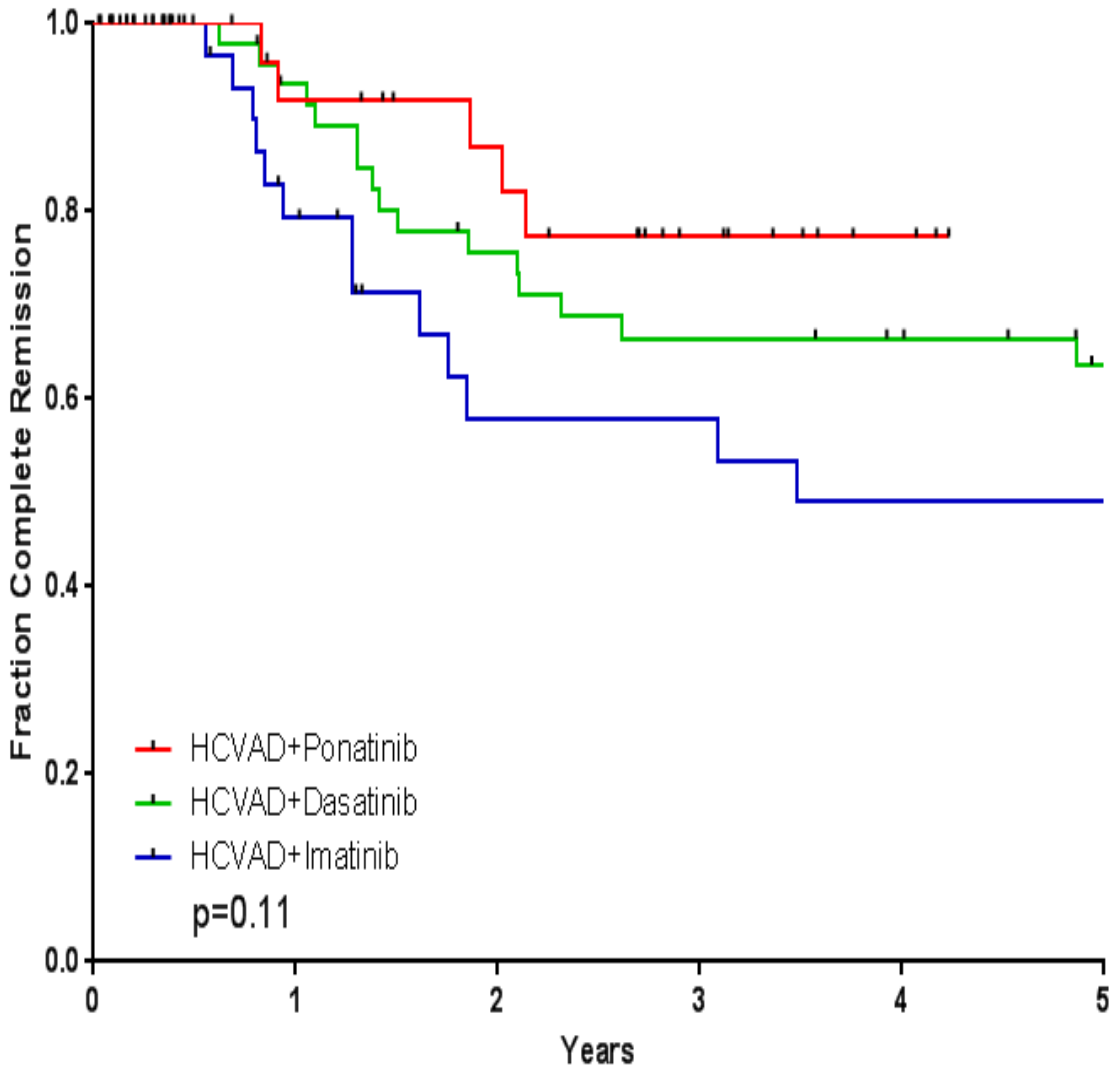
Hyper-CVAD + Ponatinib in Ph+ ALL. Landmark Analysis at 4 Months by SCT



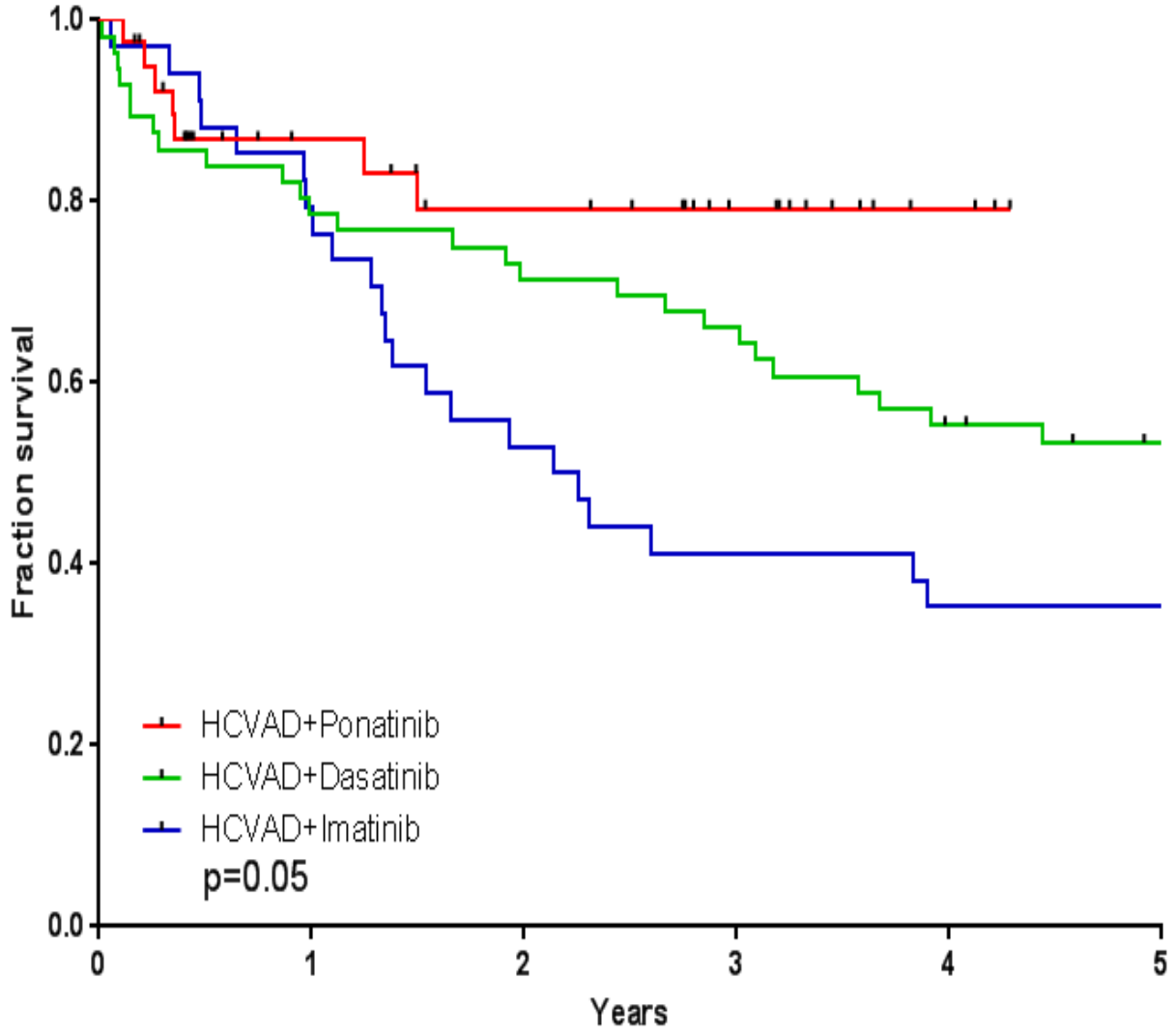
Jabbour. Lancet Hematology 5: 618; 2018

Hyper-CVAD + TKI in Ph-Positive ALL. Survival

CRD



OS



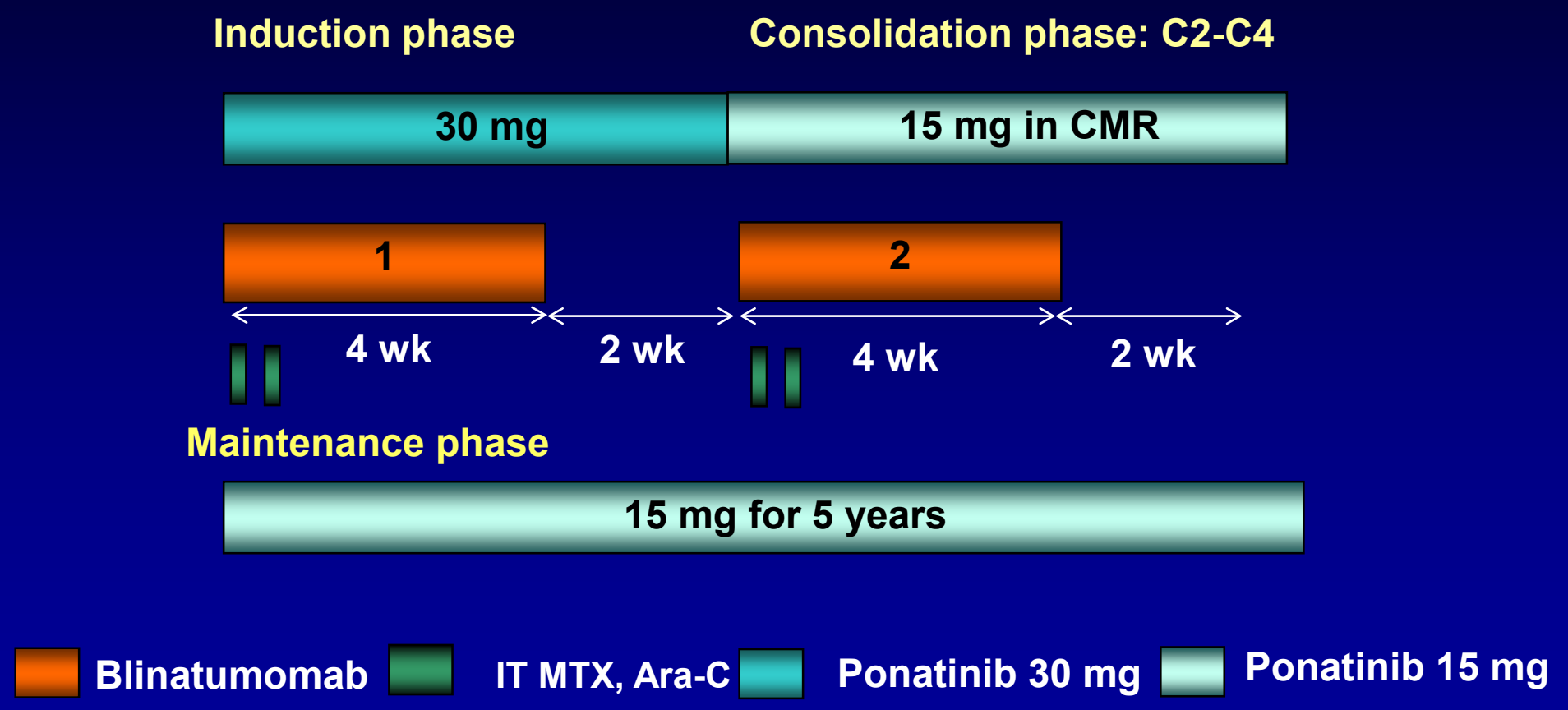
Jabbour. Lancet Oncology 16: 1547; 2016. Update April 2016

Blinatumomab and Inotuzumab in R-R Ph-positive ALL

Parameter	Blinatumomab	Inotuzumab
No. Rx	45	38
No. CR/marrow CR (%)	16 (36)	25 (66)
% MRD negative in CR	88	63
Median OS (mos)	7.1	8.1
% later allo SCT	44	32

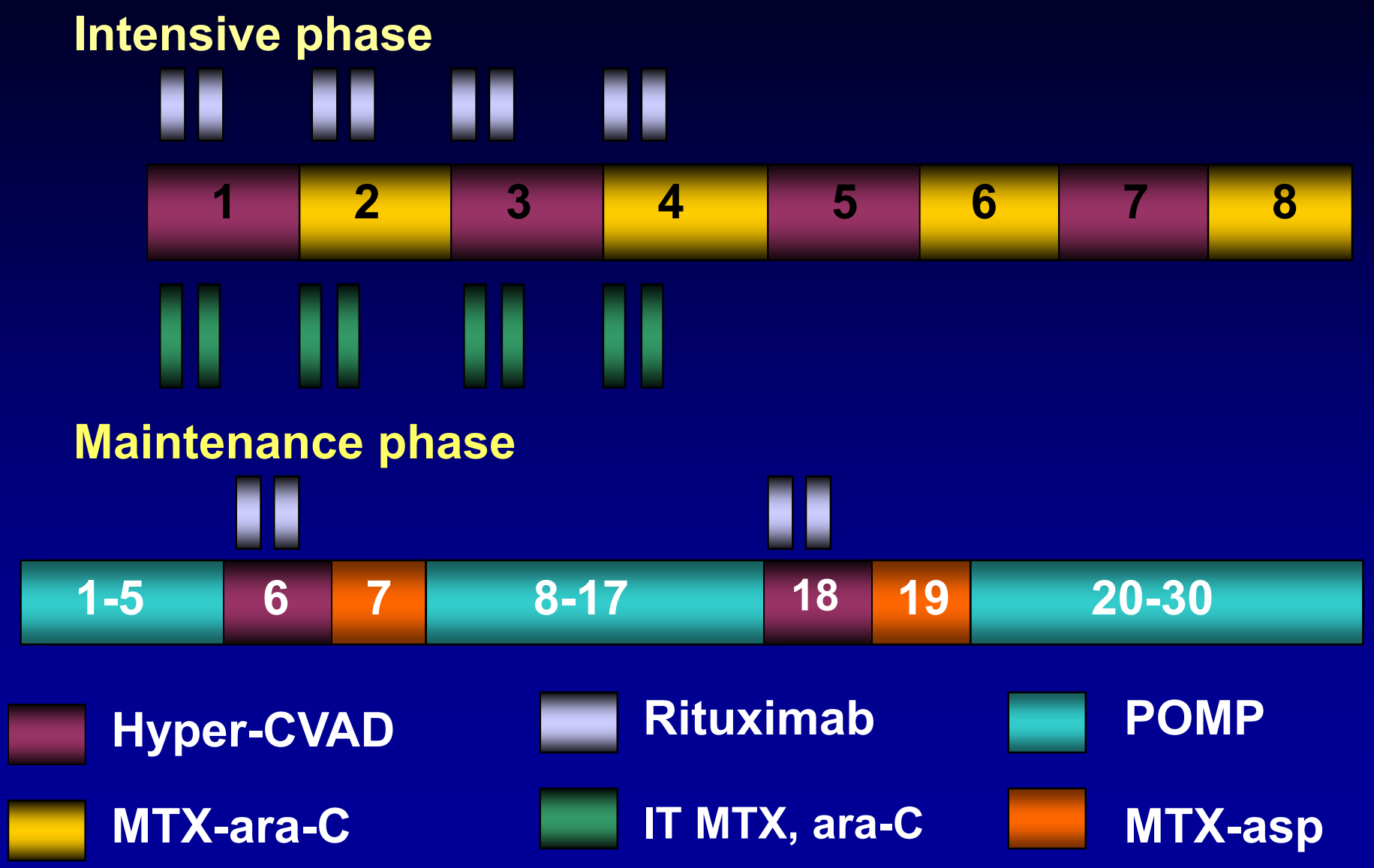
Martinelli. JCO 35: 1795; 2017. Stock. Proceedings ASCO 2018

Blinatumomab-ponatinib in Ph-Positive ALL



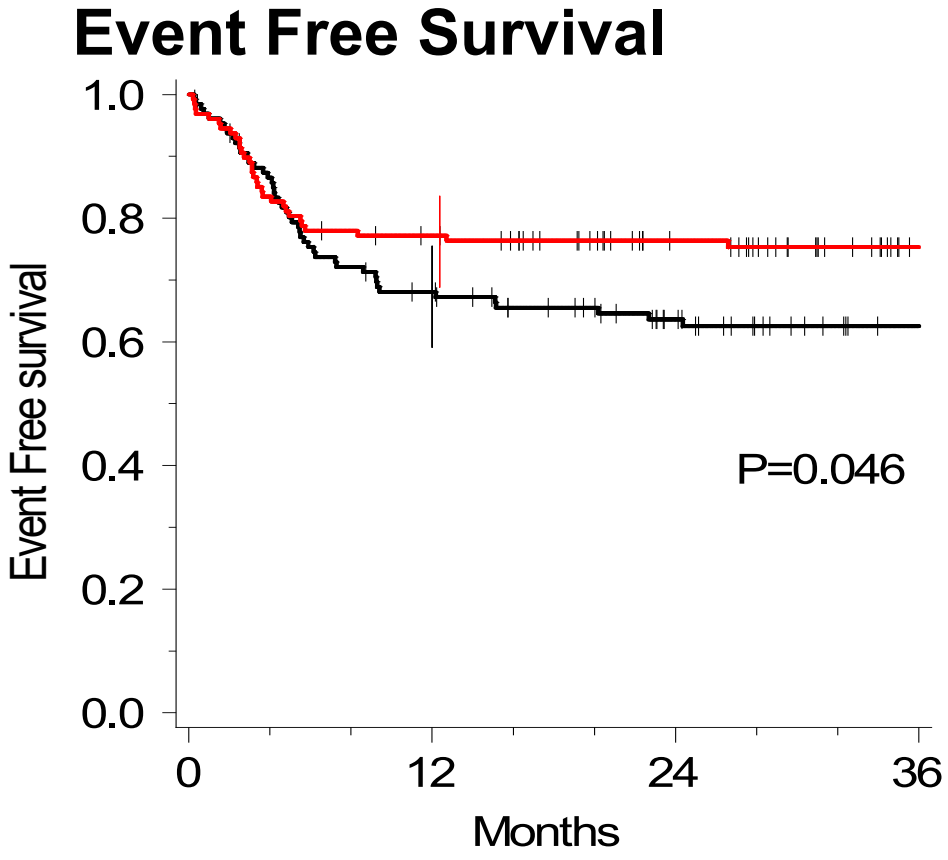
Assi. Clin Lymphoma Myeloma Leuk. 2017;17(12):897-901

Hyper-CVAD + Rituximab in Precursor B-ALL

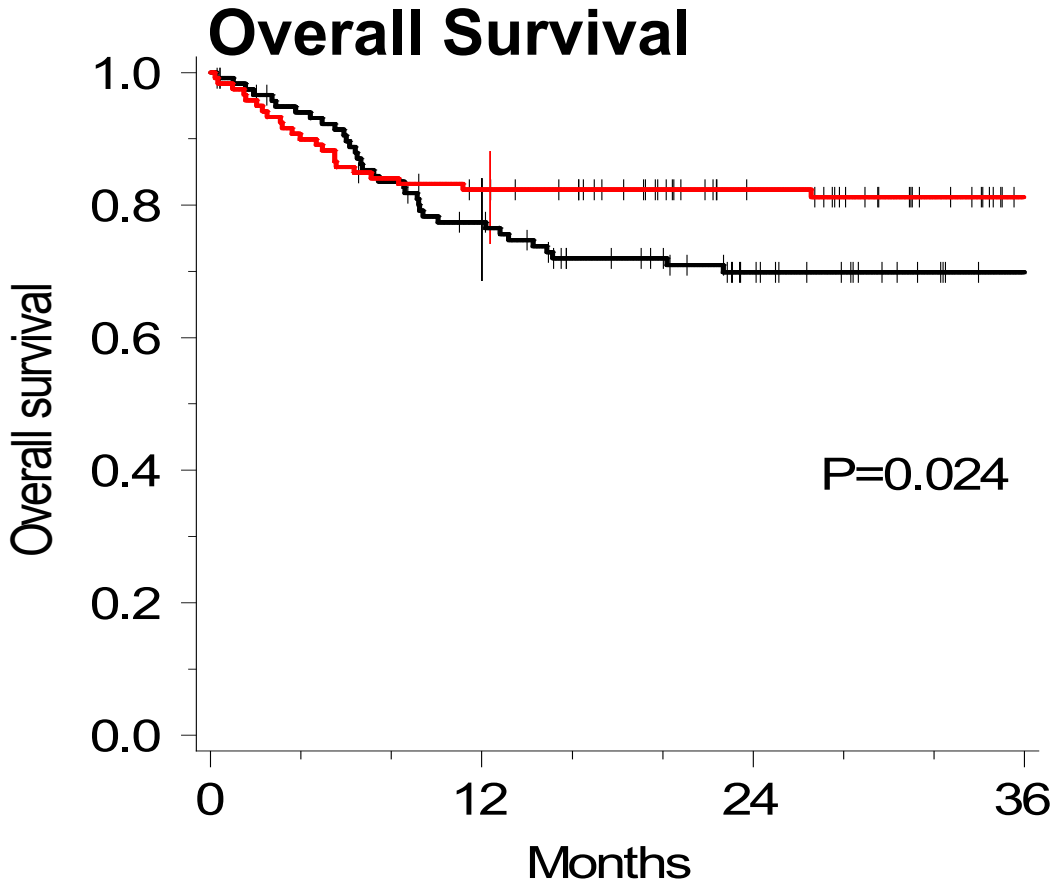


Thomas. JCO 2010; 28:3880-9

ChemoRx +/- Rituximab in Burkitt Disease--Results of the Randomized Intergroup (GRAALL-Lysa) LMBA02 Study



Treatment arm		Patients at risk		
No Rituximab	129	83	61	43
Rituximab	128	95	74	50

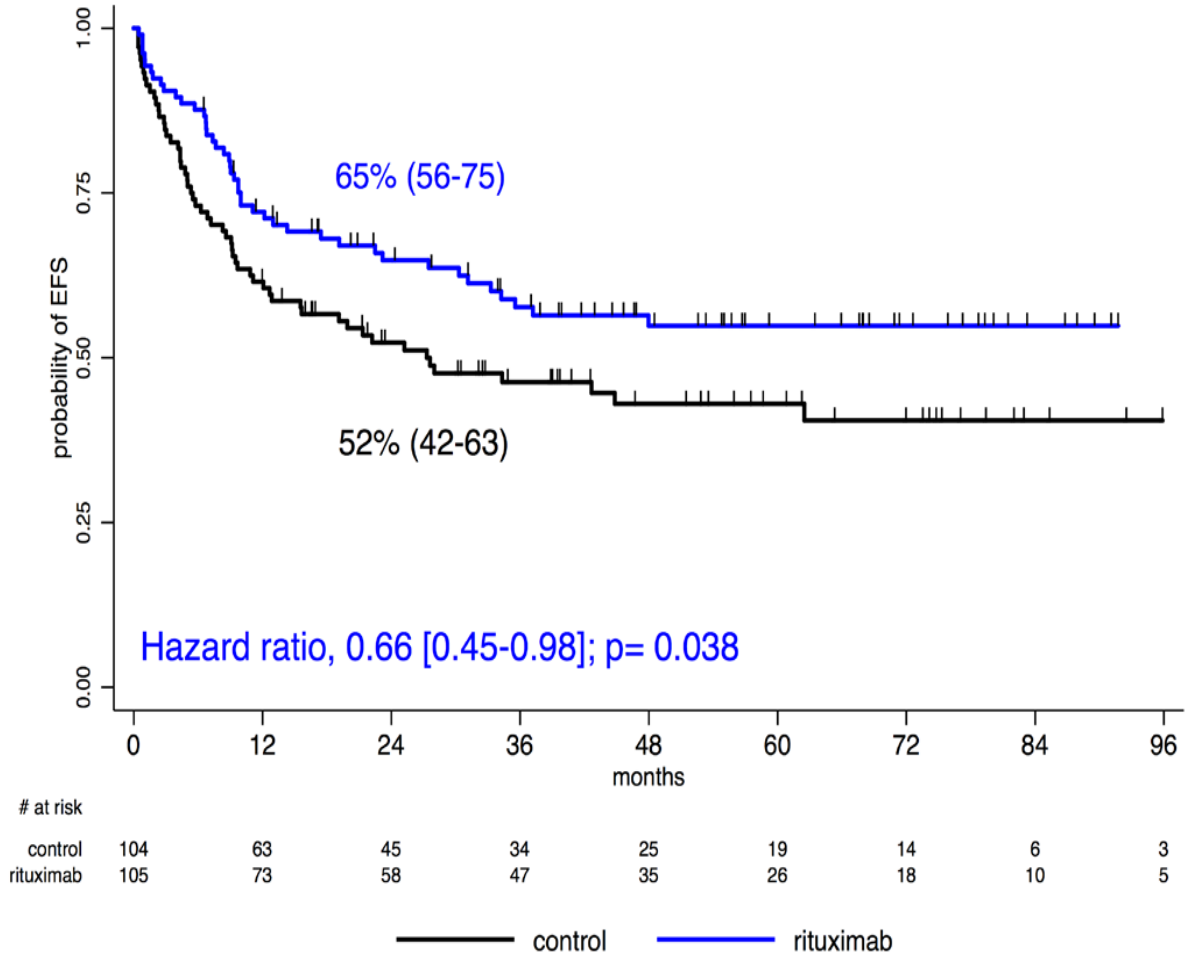


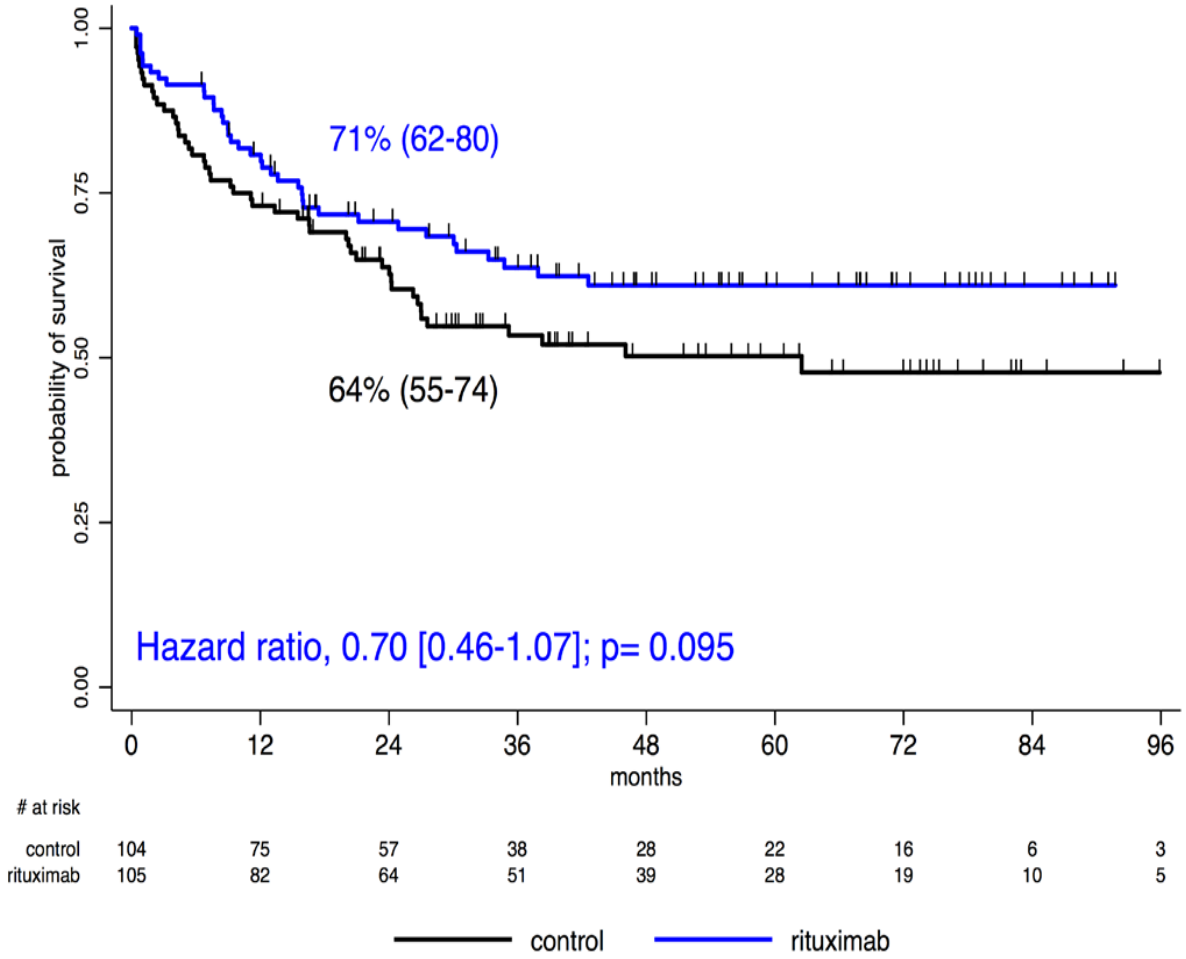
Treatment arm		Patients at risk		
No Rituximab	119	87	60	44
Rituximab	120	95	73	50

Ribrag. Lancet. 2016;387:2402-11.

Chemo Rx +/- Rituximab: Results of the Randomized GRAALL-R 2005 in Pre B-ALL

- Median follow-up 30 months





Maury. N Engl J Med. 2016;375:1044-53

US Intergroup Study for AYA: A041501
Randomized Phase III trial, 18-39 yrs

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
VCR	VCR	VCR	Cyclo	VCR
Dex	Dex	Peg-ASP	Dex	6MP
Peg-Asp	Peg-Asp	IT-MTX	Peg-Asp	MTX
IT-MTX	Ara-C		Ara-C	IT-MTX
IT-AraC	6MP		6-TG	
	IT-MTX		IT-MTX	

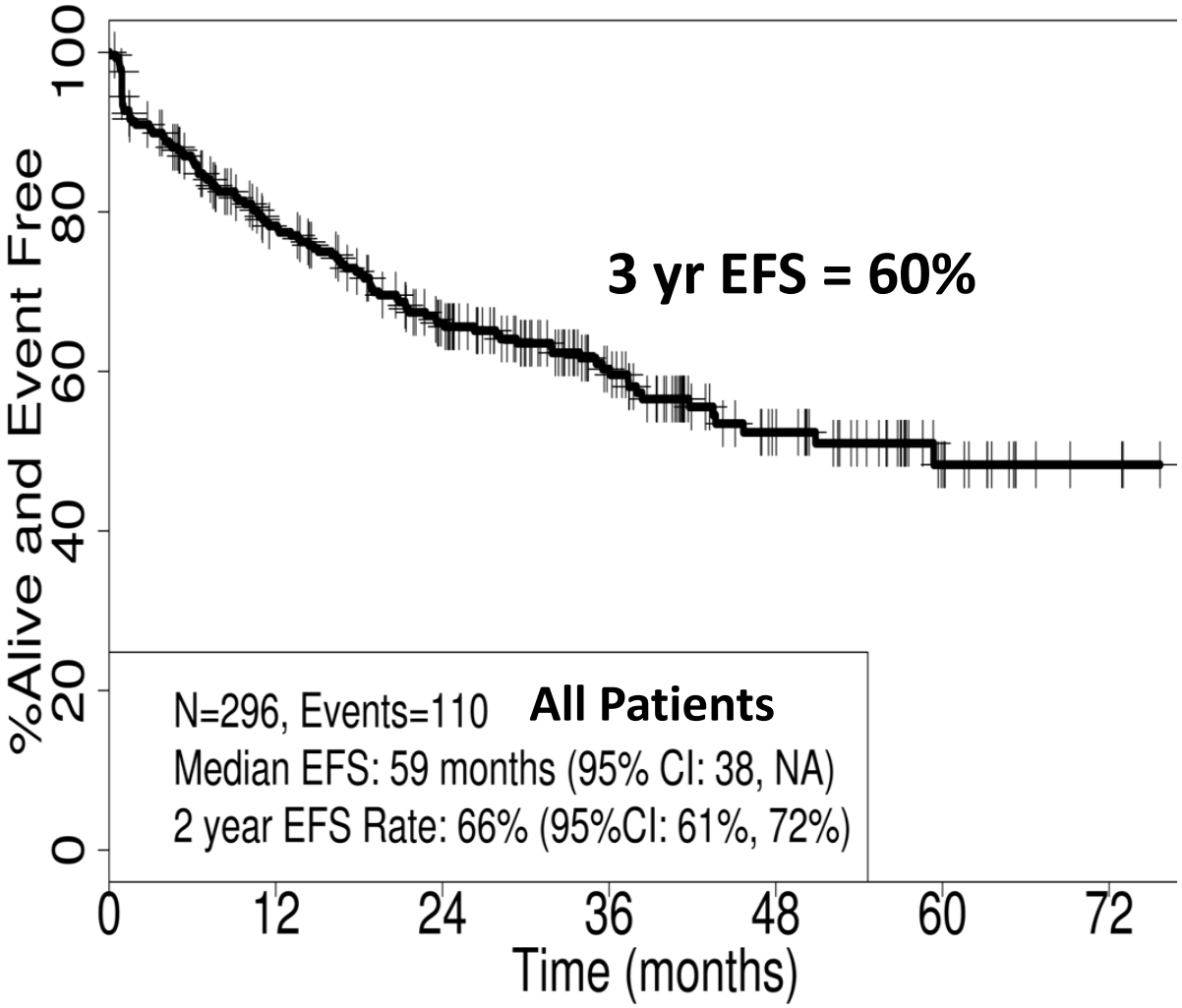
Inotuzumab

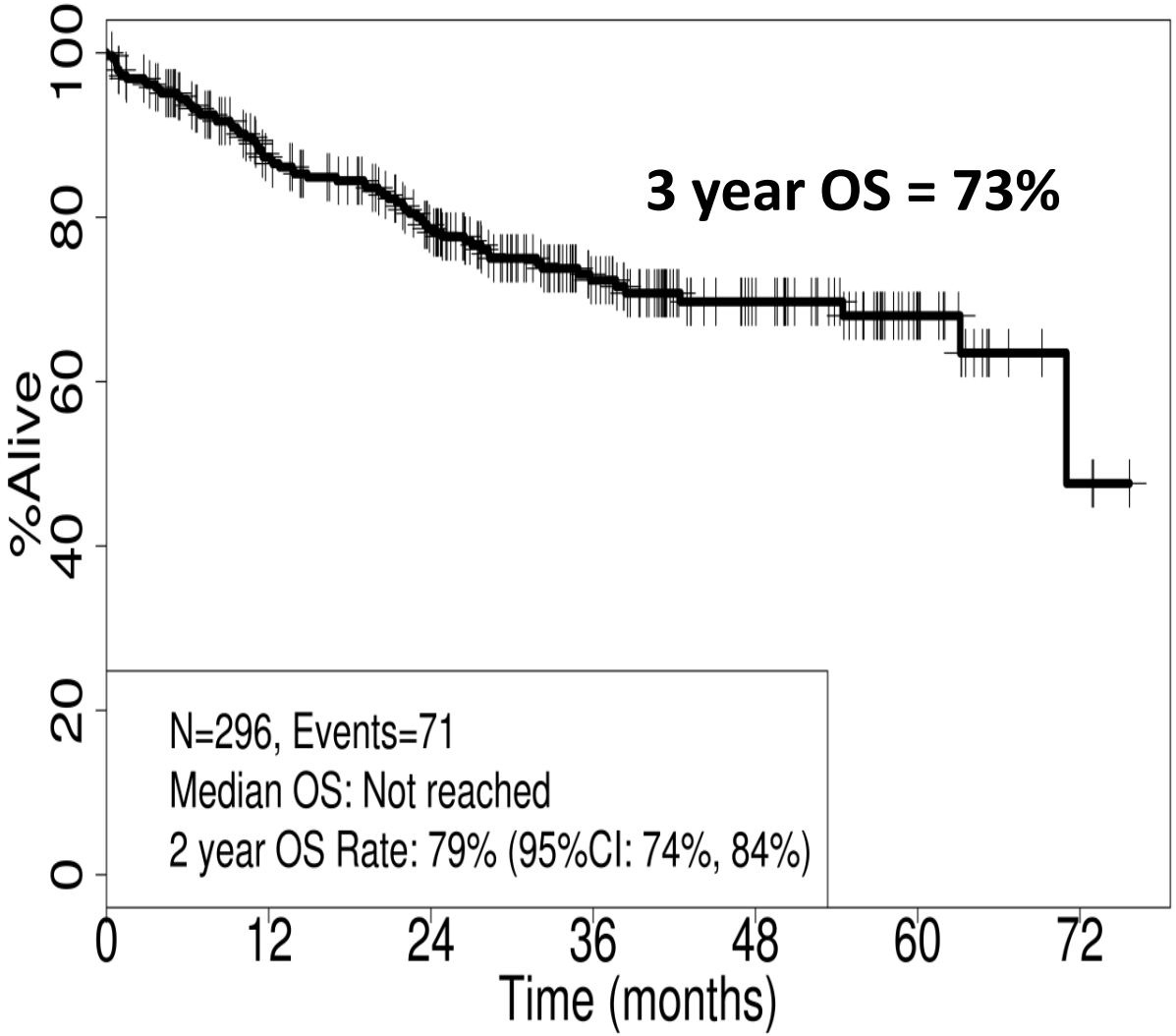
CD20+ Patients will Receive Rituximab with I, C, IM, DI

Maintenance therapy continues for 2 (F) – 3 (M) years

Stock. Under review, 2018

C10403 in AYA. Outcome





CALGB Historical Control EFS = 34%

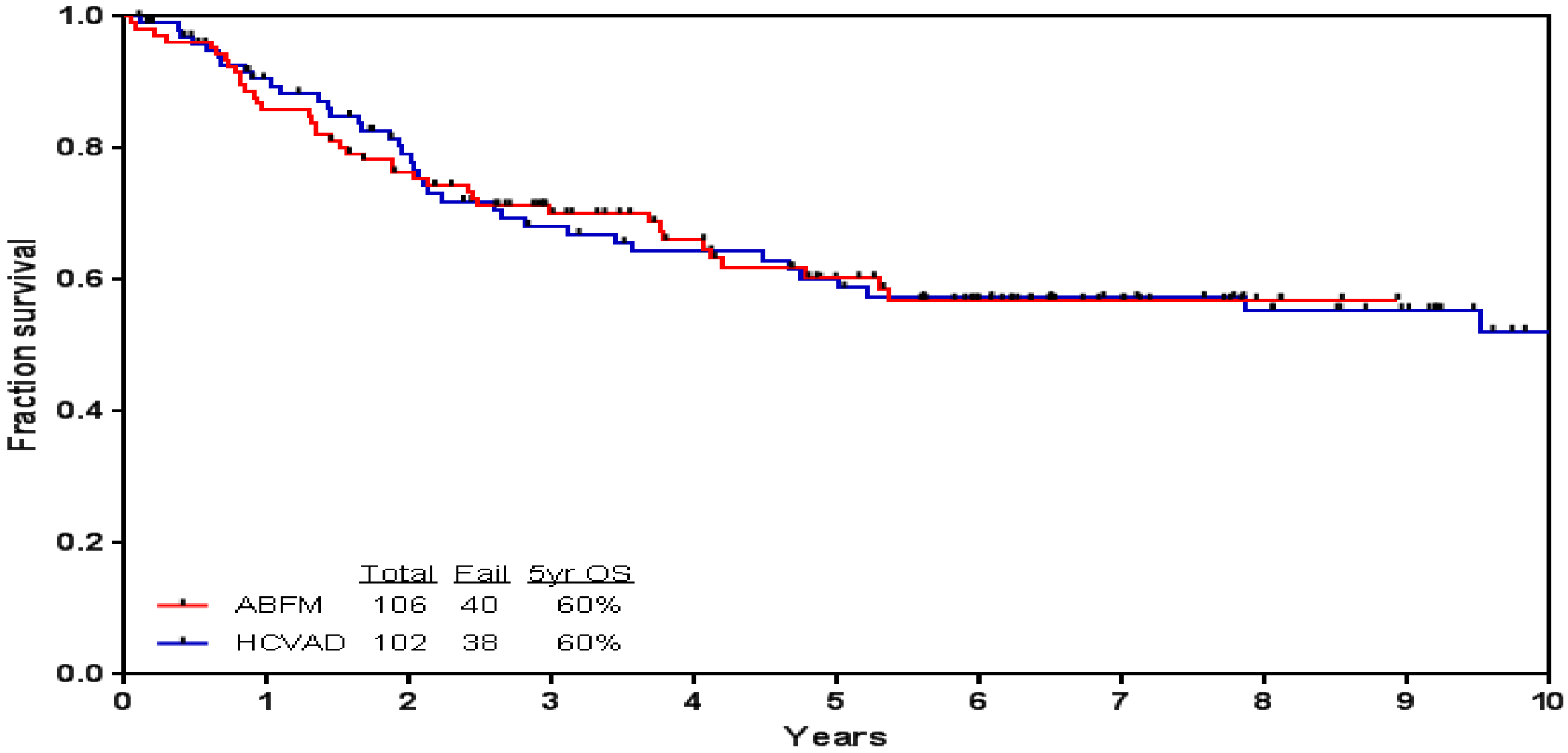
Stock. Under review, 2018

Augmented BFM and Hyper-CVAD

Response	No. (Percent)	
	ABFM (n=106)	Hyper-CVAD (n=102)
• Complete response	99 (93)	100 (98)
• Induction mortality	1 (1)	1 (1)
• Resistant disease	6 (6)	1 (1)

Rytting. Cancer 120: 3660-8; 2014 .Rytting.AJH 91: 819; 2016

Hyper-CVAD vs. ABFM.Overall Survival



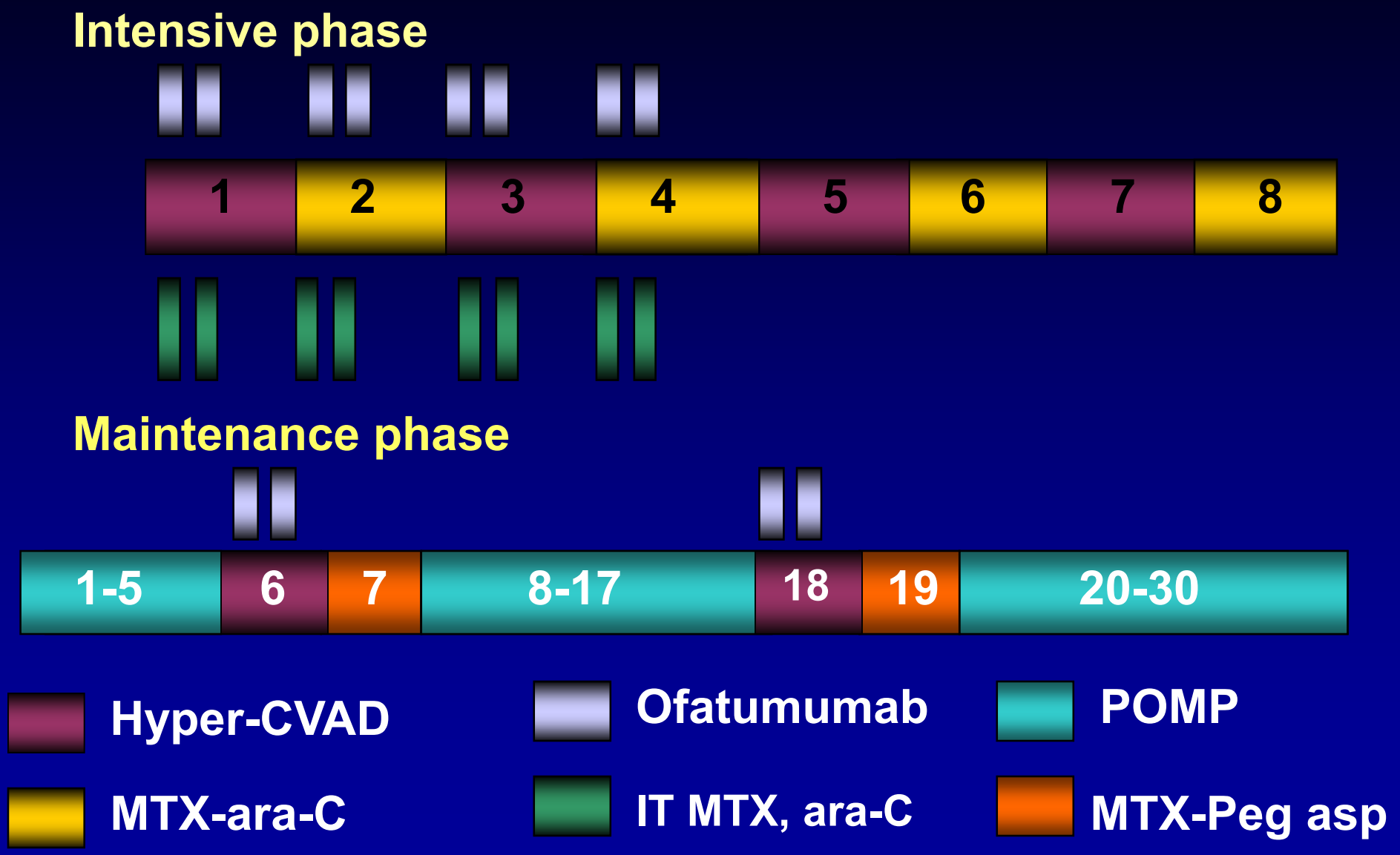
Rytting. Cancer 120: 3660-8; 2014 . Rytting. AJH 91: 819; 2016

ABFM vs HyperCVAD. Severe Toxicities

% Toxicity	ABFM (n=106)	Hyper-CVAD (n=102)	p value
Asparaginase allergy	19	N/A	NS
Hypofibrinogenemia	35	14	<0.001
Pancreatitis	11	3	0.02
↑LFTs	41	44	0.60
↑ Bili	38	18	0.001
Osteonecrosis	9	8	0.68
Thrombosis	19	12	0.16
Stroke	3	0	0.09
Induction infections	22	45	<0.001
Induction bleeding	1	5	0.09
Infections in CR first 60 days	30	60	<0.001
Bleeding in CR first 60 days	1	5	0.09
Deaths in CR	8	7	.85

Rytting. Cancer 120: 3660-8; 2014 .AJH 91: 819; 2016

Hyper-CVAD + Ofatumumab. Design



Jabbour. Unpublished . 2019

Hyper-CVAD + Ofatumumab. Overall Results

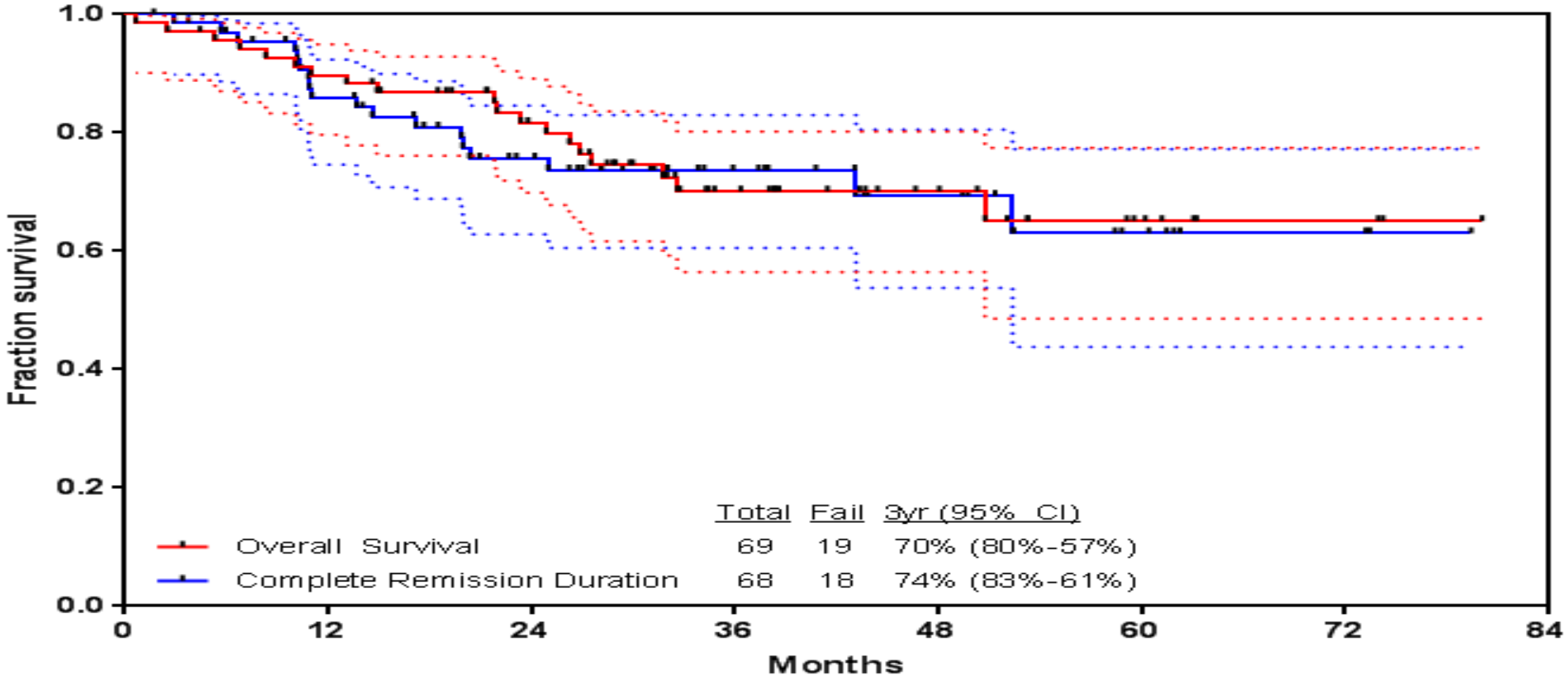
Parameter	N (%)
CR/CRp*	65/66 (98)
CR after induction	63/66 (95)
MRD negativity at CR	40/63 (63)
MRD overall	63/68 (93)
Early death	1/69 (1)

- * 3 pt in CR at start
- Median time to negative MRD 0.7 mos

Jabbour. Unpublished . 2019

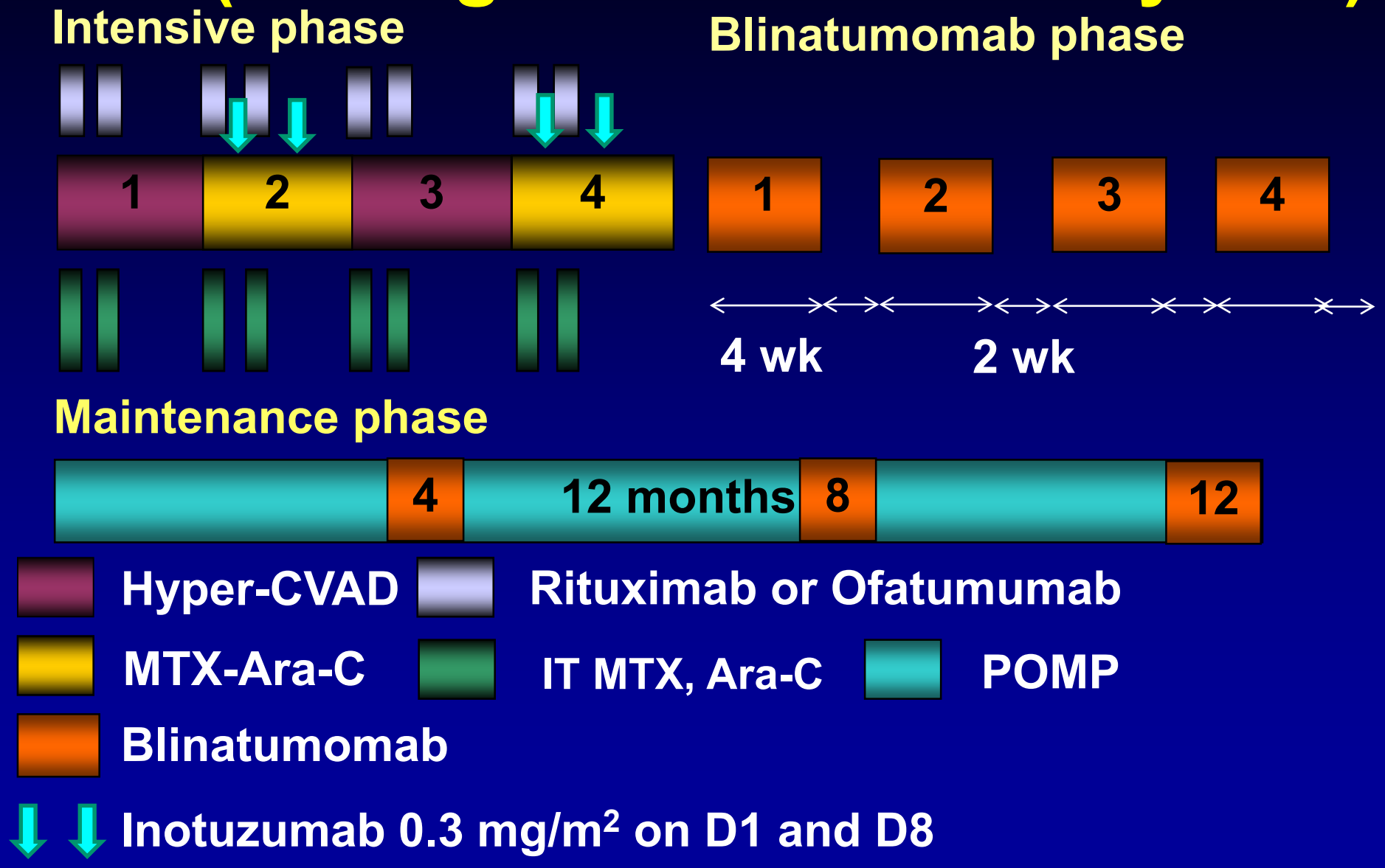
Hyper-CVAD + Ofatumumab.
Overall Survival and Complete Remission Duration

- Median follow up of 36 months (4-80)

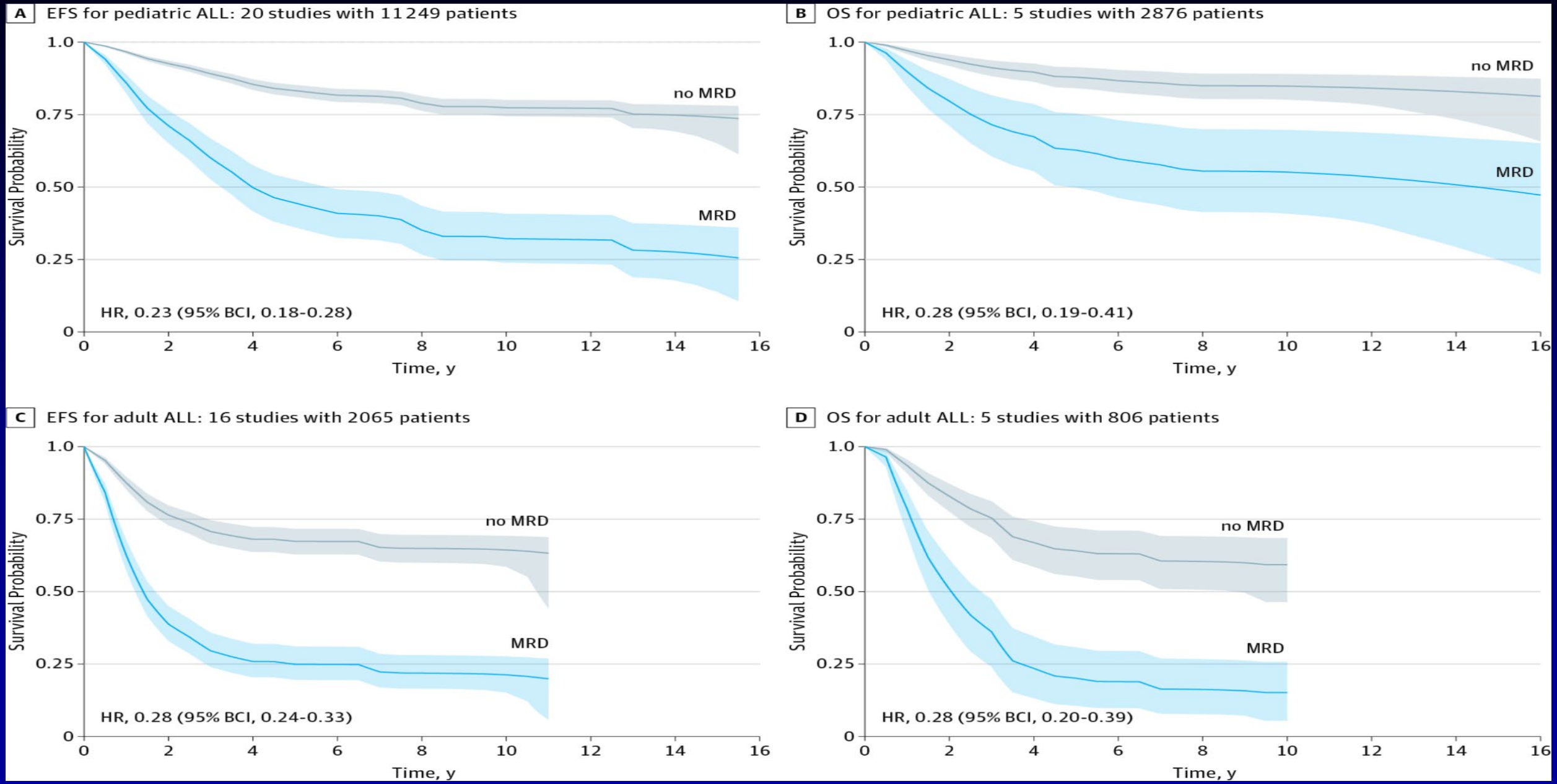


Jabbour- Unpublished . 2019

Hyper-CVAD + Inotuzumab + Blinatumomab in B-ALL (Ph-negative B-ALL < 60 years)



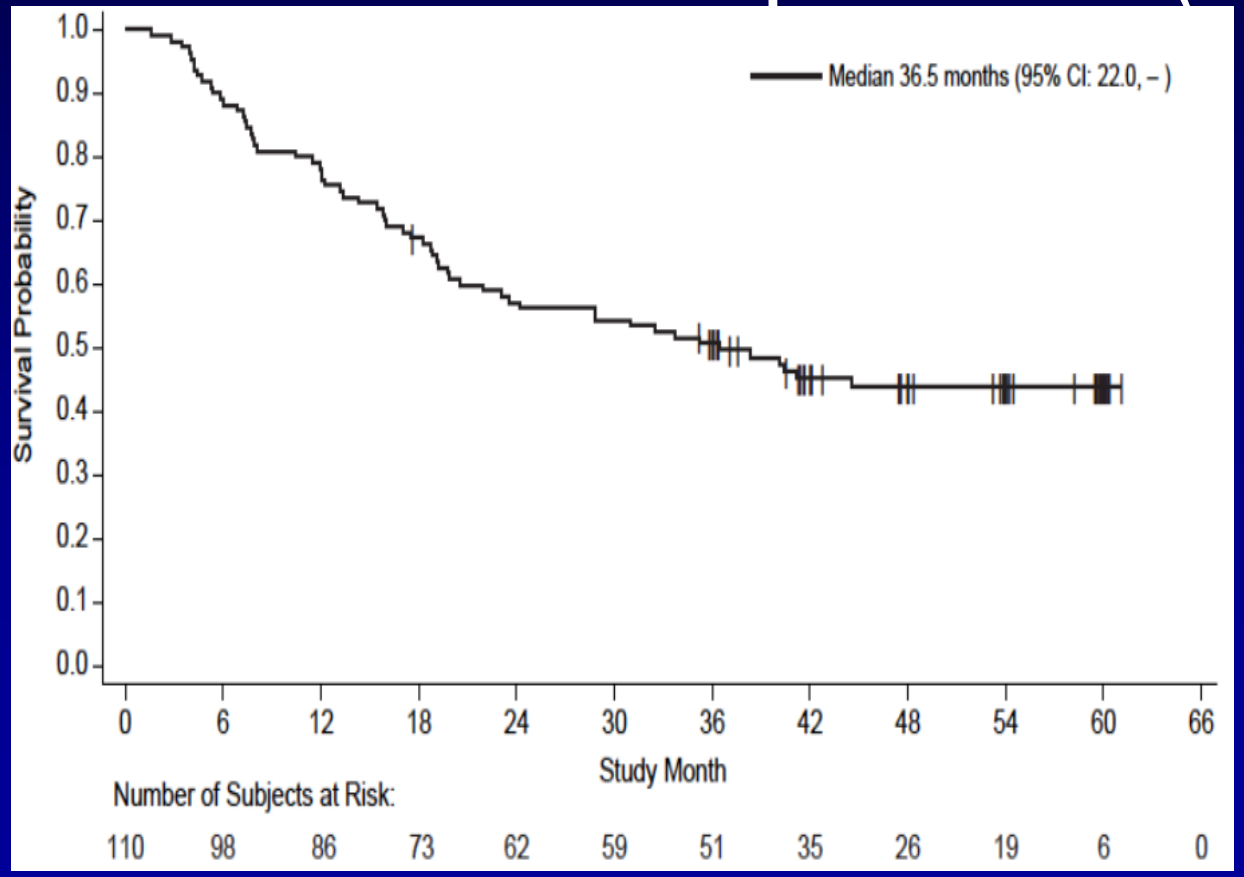
MRD in ALL

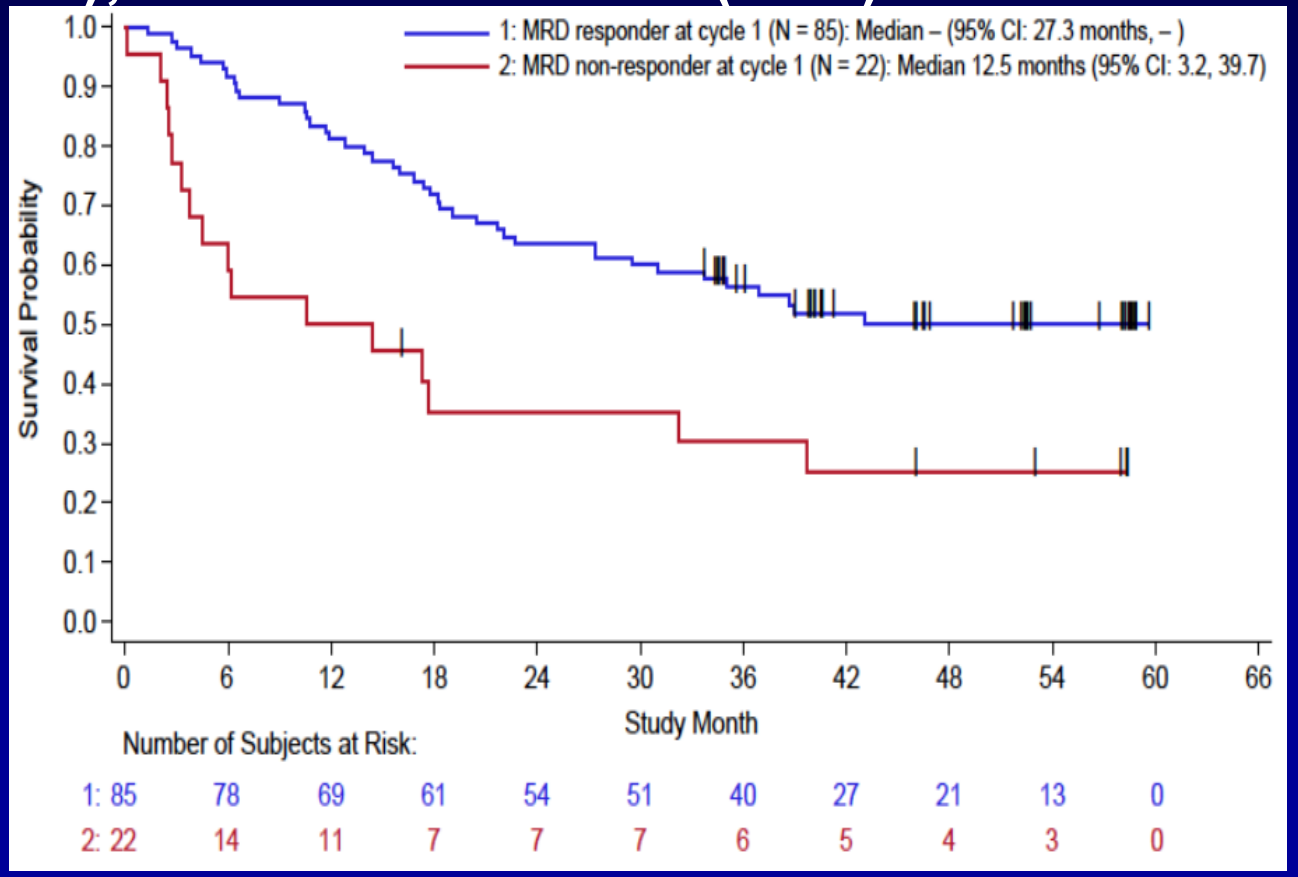


Berry DA. JAMA Oncol. 2017 Jul 13;3(7):e170580

Blinatumomab for MRD-positive ALL in CR1/CR2

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





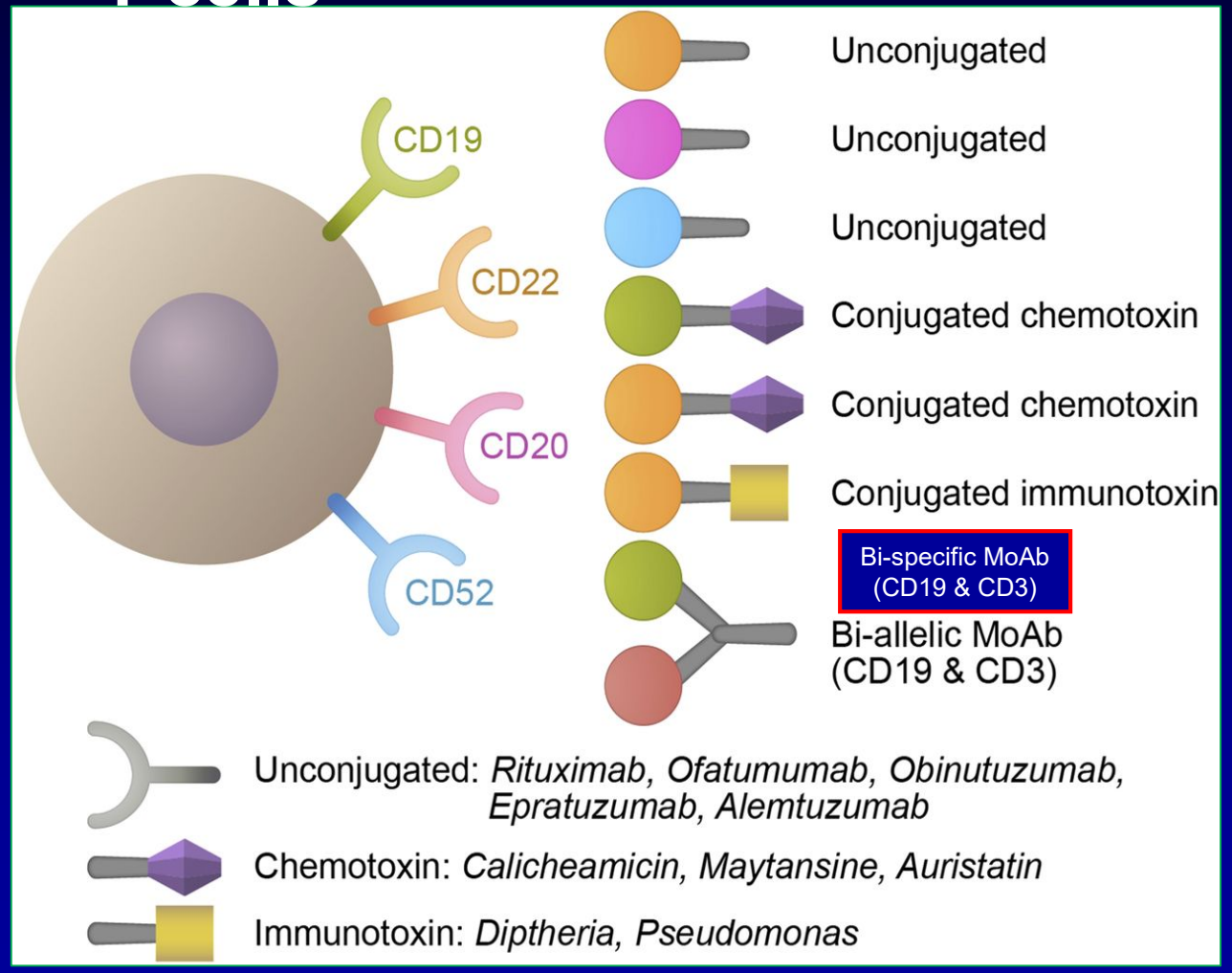
Goekbuget. Blood 132: abst 554; 2018

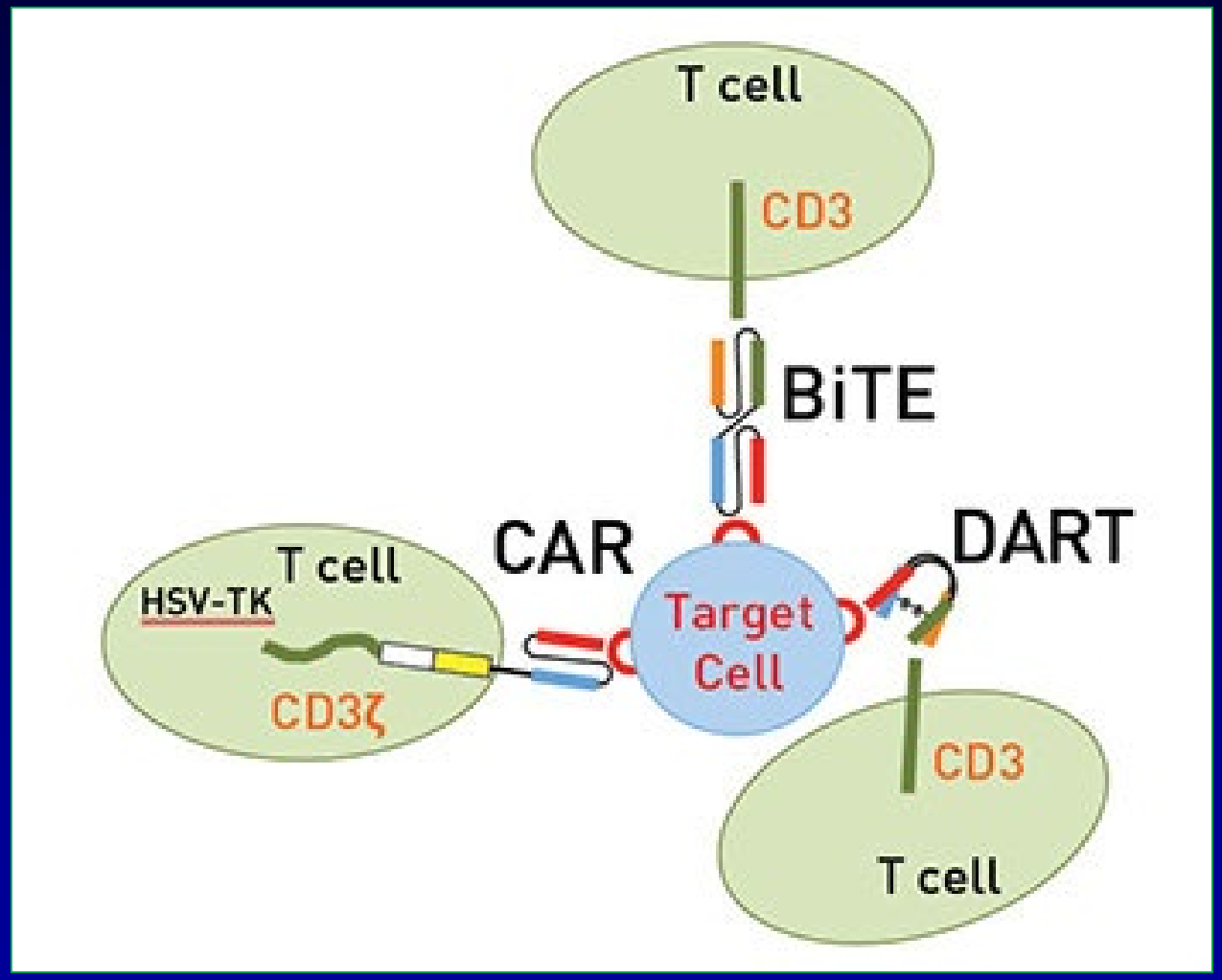
Indications for Allogeneic SCT in CR1

- T (4;11); MLL rearranged
- Ph+ ALL with PCR > 0.1% at 3+mo in CR
- Ph-like ALL?
- FCM MRD+ > 0.05% at 2-3 + mo in CR
- Precursor T-ALL
- Complex CG; near hypoploid + p53

Immuno-oncology in ALL

- Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR-T cells





Jabbour E. Blood 125: 4010; 2015

Historical Results in R/R ALL

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

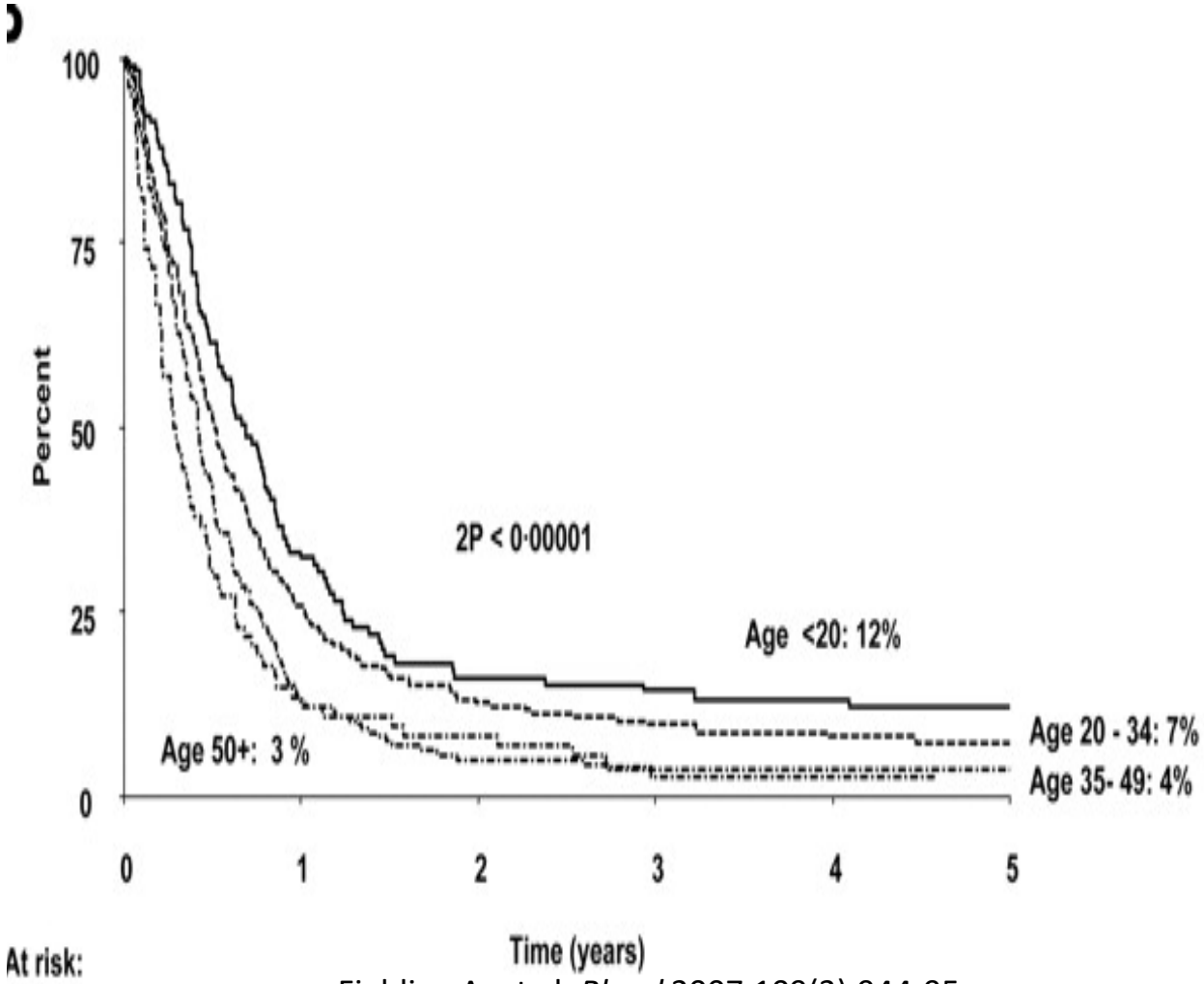
Rate (95% CI)	No prior salvage (S1)	One prior salvage (S2)	≥2 prior salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.8	3.4	2.9

Gökbuget N, et al. *Haematologica*. 2016;101:1524–33.

ALL ---Historical Survival Rates after Relapse

MRC UKALL2/ ECOG2993 Study (n=609)

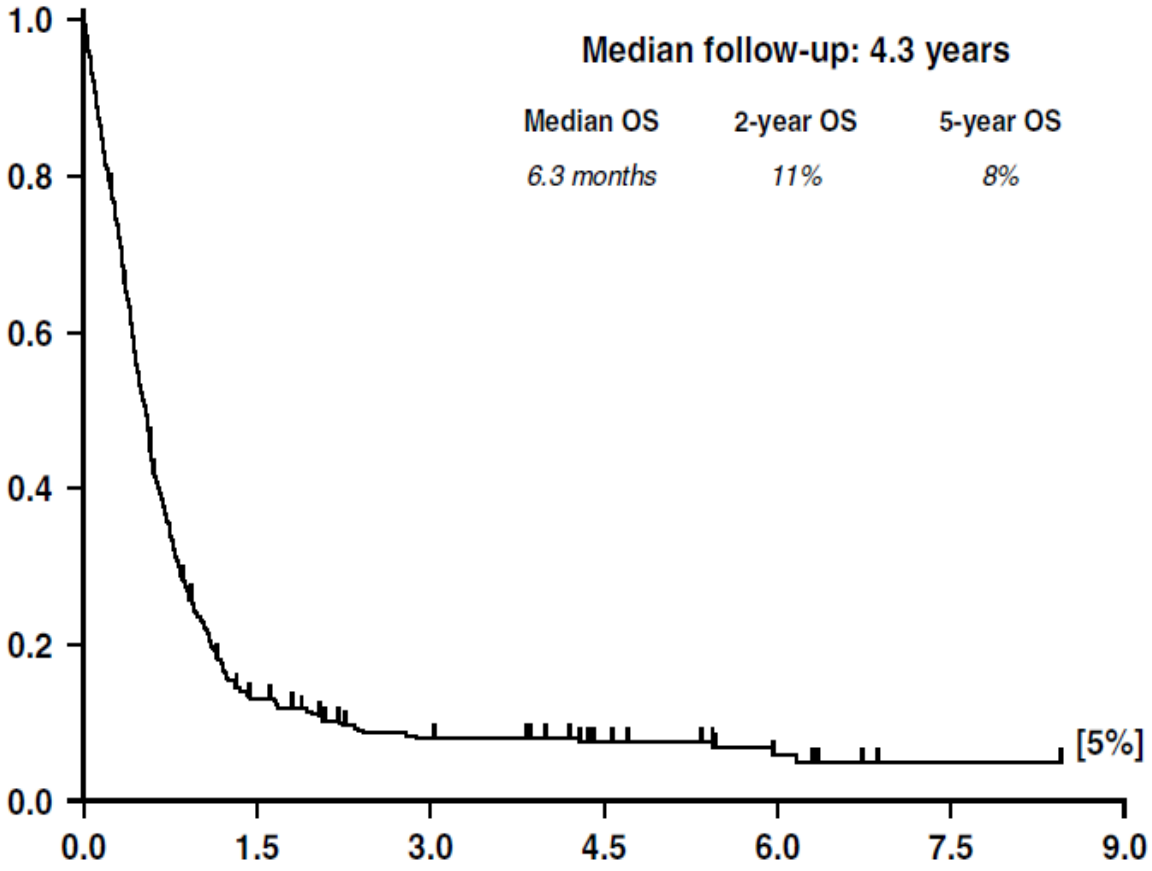
Outcome of patients after 1st relapse
5-yr OS: 7%



Fielding A, et al. *Blood* 2007;109(3):944-95.

LALA-94 Study (n=421)

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



Tavernier E, et al. *Leukemia* 2007;21:1907-1914

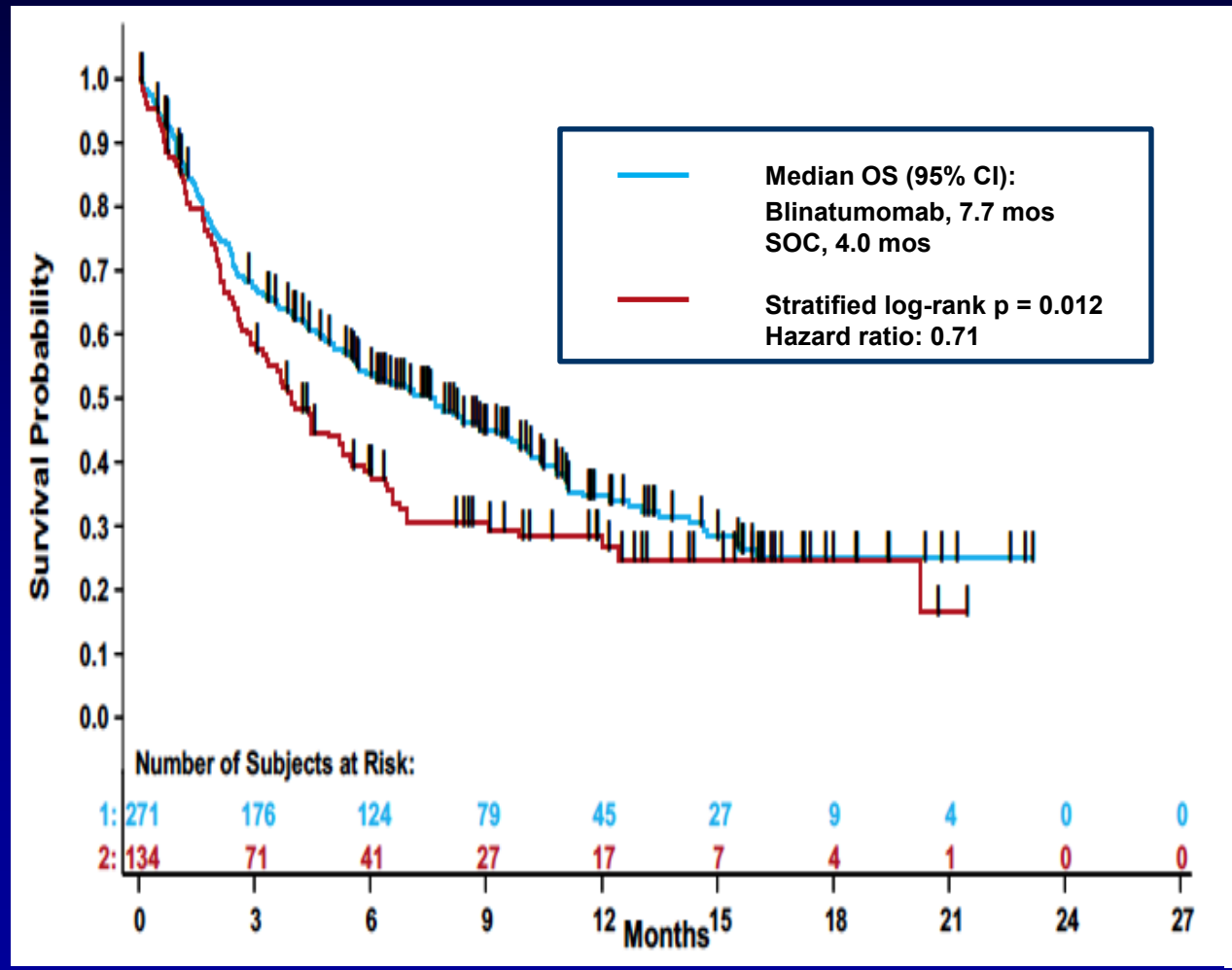
ALL Salvage Standards of Care in 2018

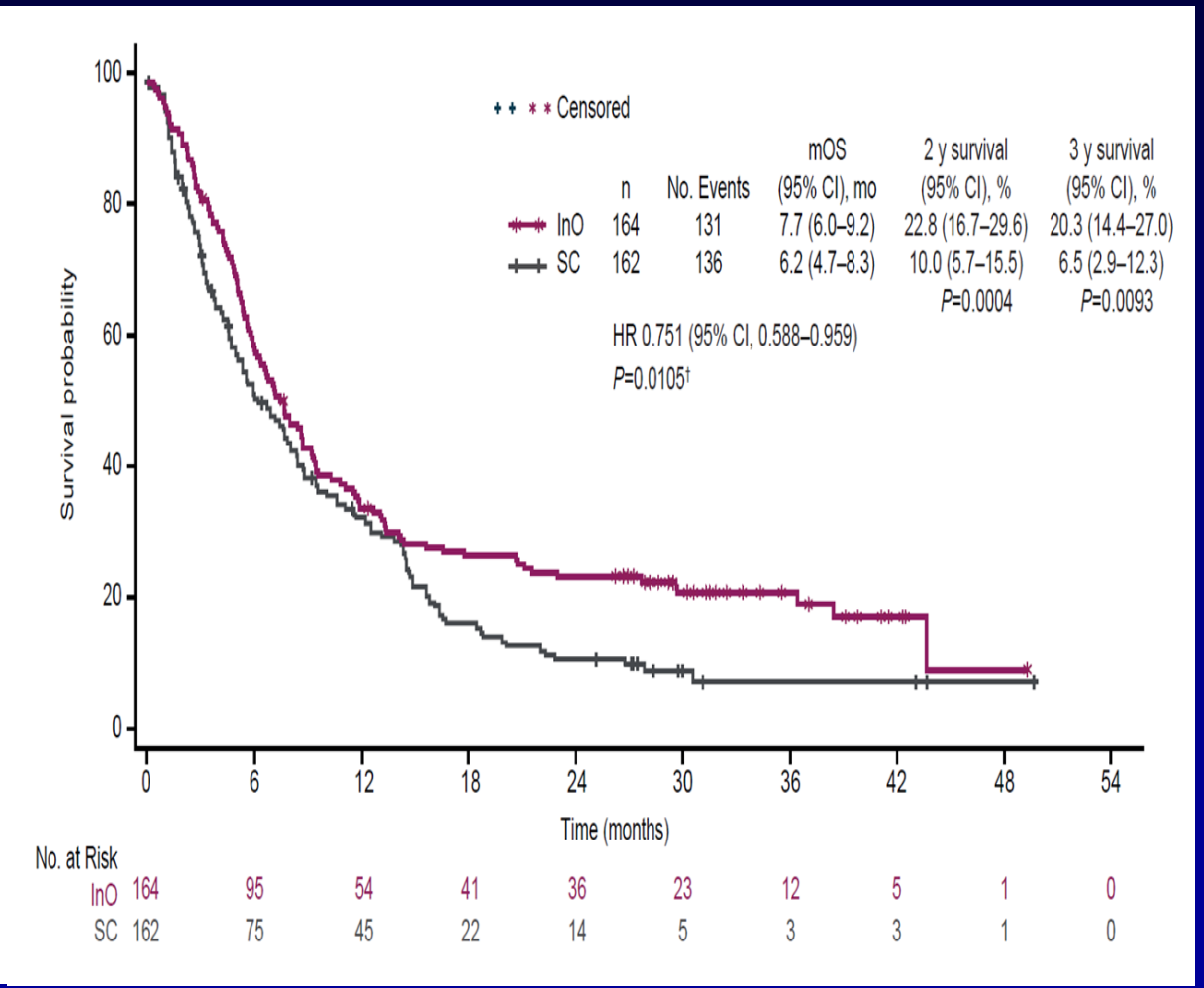
- Refer for investigational therapies-- MoAb + ChemoRx; CAR-T
- Ph-positive ALL-- TKIs+ chemoRx; blinatumomab
- Pre-B ALL--
  - Blinatumomab (FDA approval 12.2015)
  - Inotuzumab (FDA approval 8.2017)
  - 2 CARTs (FDA approvals 8.2017 and 10.2017)
- T ALL: nelarabine
- ChemoRx: FLAG IDA, Hyper CVAD, augmented HCVAD, MOAD

Blinatumomab/Inotuzumab vs ChemoRx in R-R ALL

- **Marrow CR**

  Blina vs SOC: 44% vs 25% **Ino vs SOC: 81% 29%**





Kantarjian. NEJM. 376: 836-47; 2017

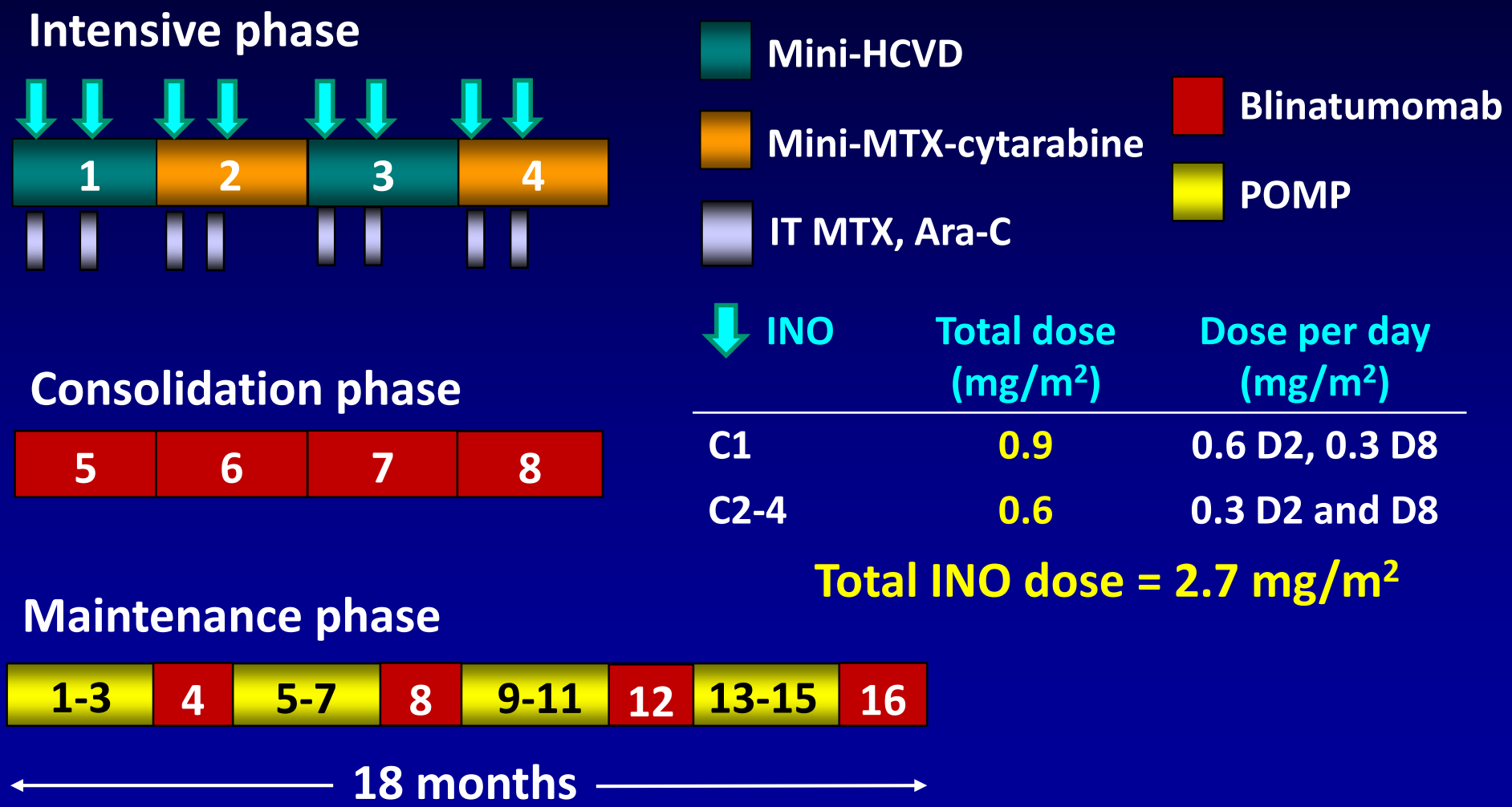
Kantarjian. NEJM. 375: 740; 2016

MiniHCVD-INO-Blina in ALL. Design

- Dose reduced HyperCVD for 4-8 courses
  - Cyclophosphamide (150 mg/m^2 x 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 x 4) 83% dose reduction
- Inotuzumab on D3 (first 4 courses)
  - Modified to 0.9 mg/m^2 C1 (0.6 and 0.3 on D1&8) and 0.6 mg/m^2 C2-4 (0.3 and 0.3 on D1&8)
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- Blinatumomab 4 courses and 3 courses during maintenance
- POMP maintenance for 3 years, reduced to 1 year

Sasaki. Blood 132: abst 553; 2018

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



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

Total INO dose = 2.7 mg/m^2

Jabbour E et al. *Cancer* 2018;124(20):4044-55; Short. Blood 132: abst 36; 2018

Mini-HCVD + INO ± Blinatumomab in R/R ALL
Response by Salvage (N=89)

Response	N	(%)
Salvage 1	51/56	91
S1, Primary refractory	5/5	100
S1, CRD1 < 12 mos	19/23	83
S1, CRD1 ≥ 12 mos	27/28	96
Salvage 2	9/16	56
≥ Salvage 3	9/15	60
Overall	69/87	79
MRD negativity	55/67	82
Salvage 1	42/49	86
≥ Salvage 2	13/18	72
Early death	7/87	8

Sasaki. Blood 132: abst 553; 2018

Jabbour. JAMA Oncology 4: 230; 2018

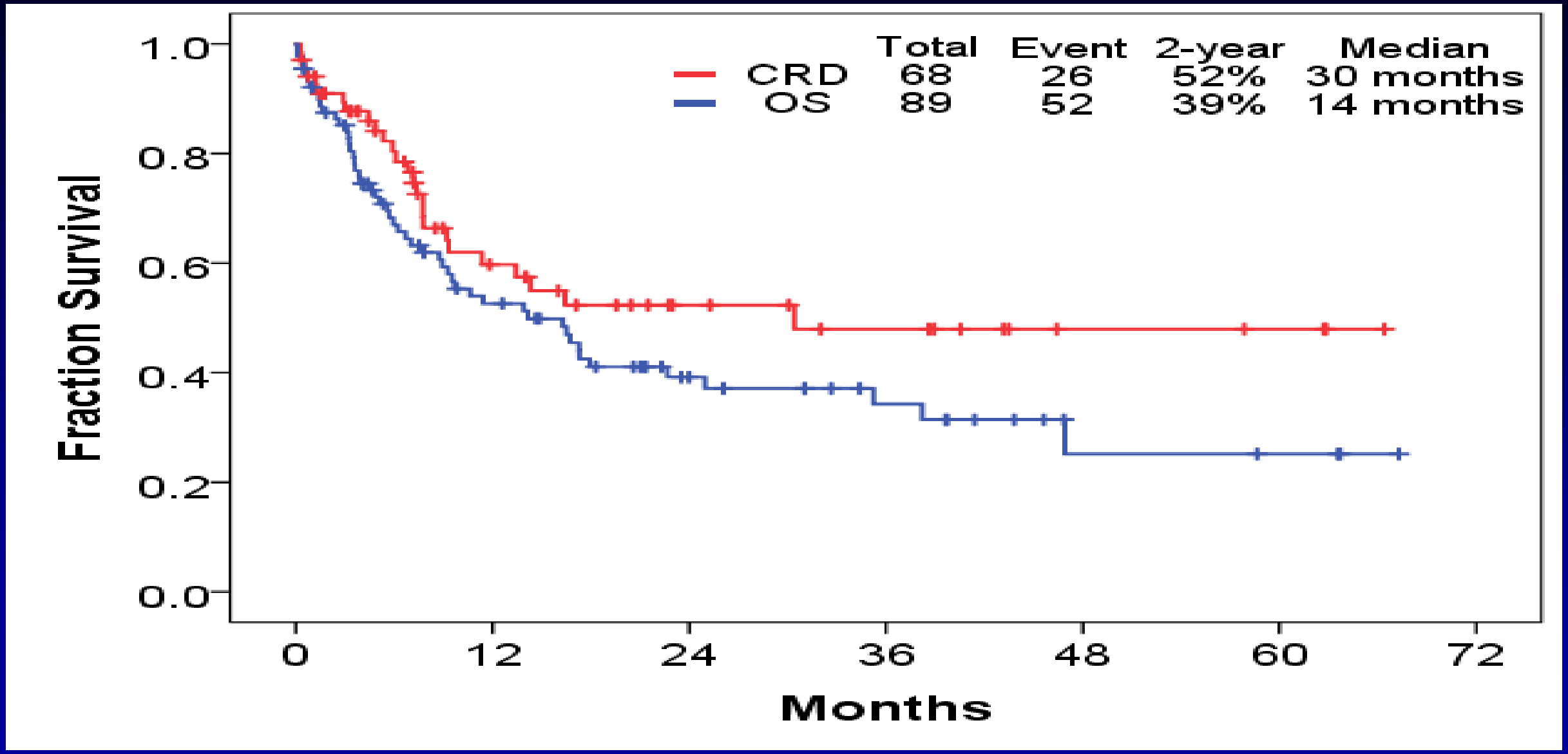
Mini-HCVD + INO ± Blinatumomab in R/R ALL
Early Death by Salvage

Early death	4-week		8-week	
	N	(%)	N	(%)
Overall	7/87	8	11/87	13
Salvage 1	1/56	2	2/56	4
S1, Primary refractory	0/5	0	0/5	0
S1, CRD1 < 12 mos	1/23	4	1/23	4
S1, CRD1 ≥ 12 mos	0/28	0	1/28	4
Salvage 2	3/16	19	6/16	38
≥ Salvage 3	3/15	20	3/15	20

Sasaki. Blood 132: abst 553; 2018

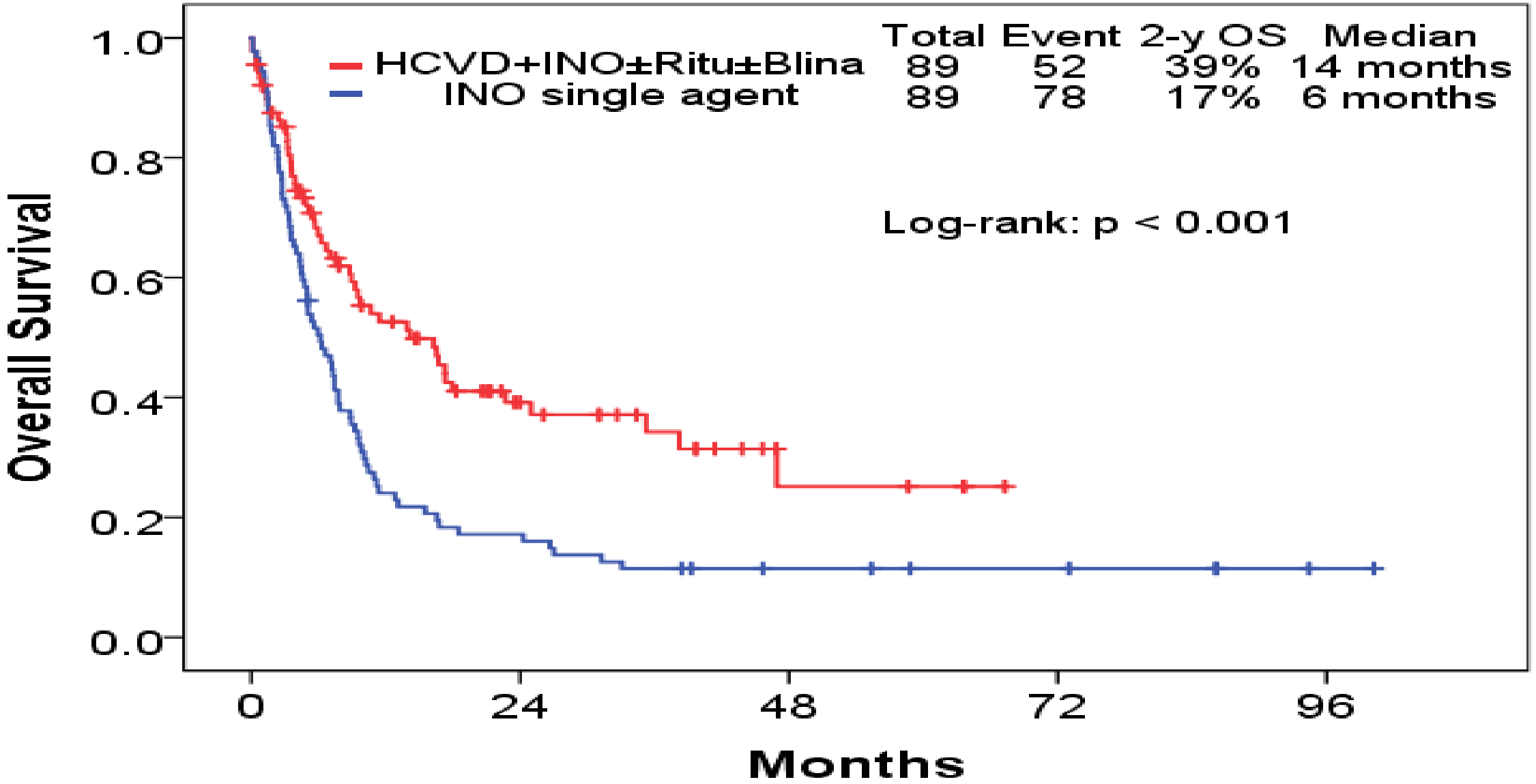
Jabbour. JAMA Oncology 4: 230; 2018

Mini-HCVD + INO ± Blinatumomab in R/R ALL
CR duration and OS (Median F/U 31 months)



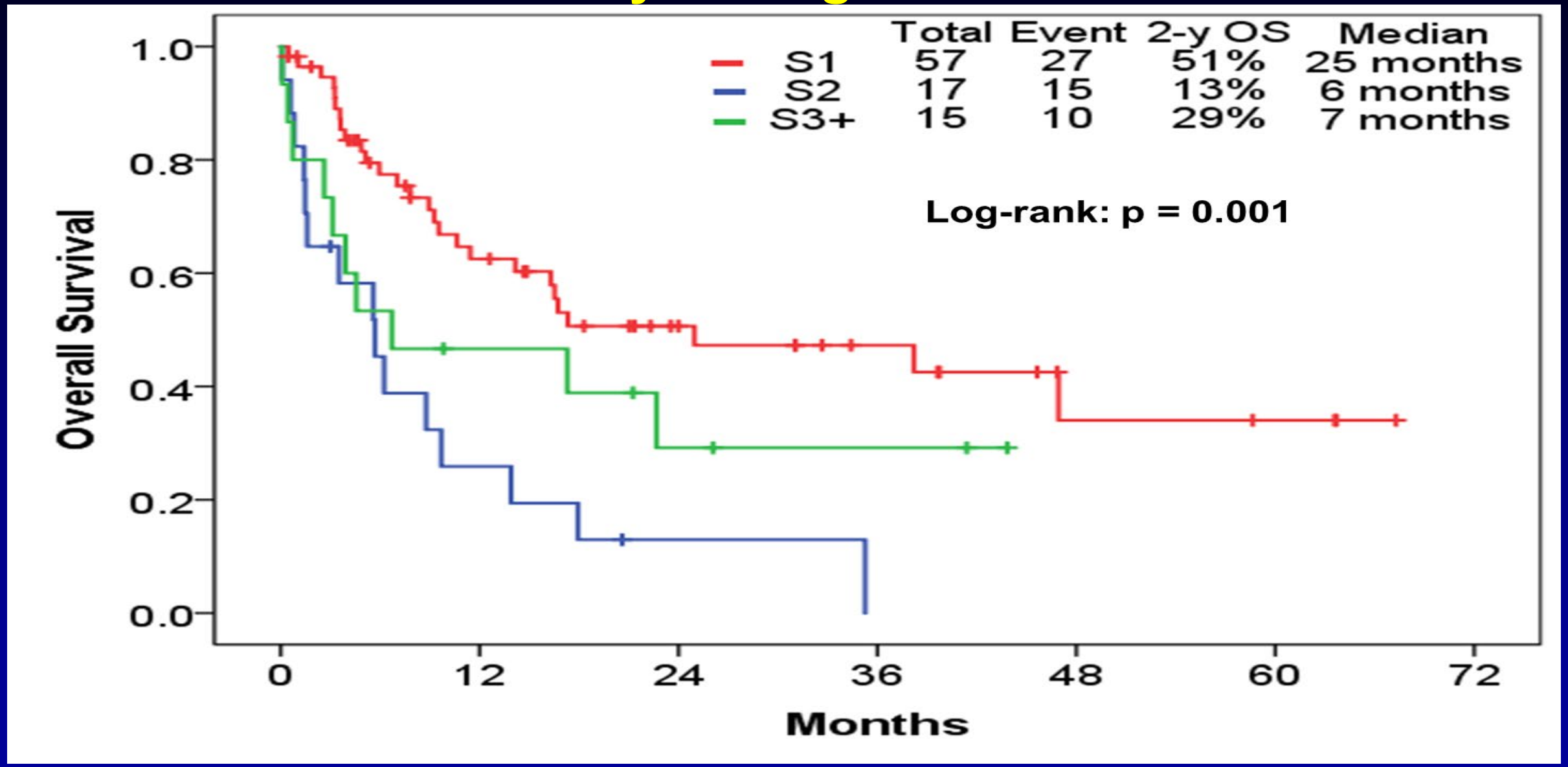
Sasaki. Blood 132: abst 553; 2018 Jabbour. JAMA Oncology 4: 230; 2018

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



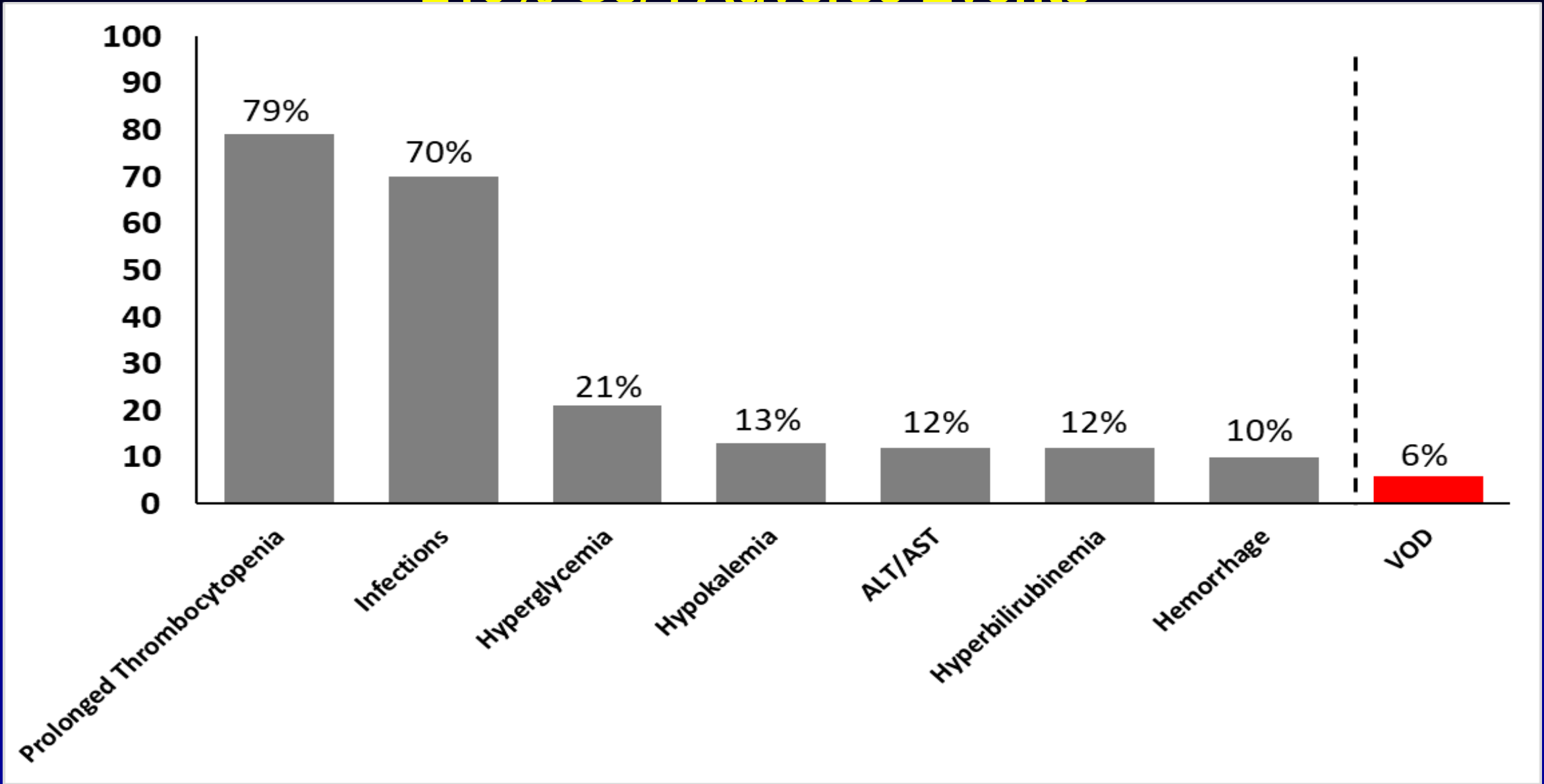
Sasaki. Blood 132: abst 553; 2018 Jabbour. JAMA Oncology 4: 230; 2018

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



Sasaki. Blood 132: abst 553; 2018 Jabbour. JAMA Oncology 4: 230; 2018

Mini-HCVD + INO ± Blinatumomab in R/R ALL
≥10% G3/4 Adverse Events



Sasaki. Blood 132: abst 553; 2018

Jabbour. JAMA Oncology 4: 230; 2018

Elderly ALL. Historical Results

	MDACC	GMALL	SEER	Medicare
N	122	268	1675	727
Median OS (mos)	15	NA	4	10
%OS (x-yr)	20 (3)	23 (5)	13 (3)	NA

O'Brien. Cancer 113: 2097, 2008; Gökbuget. Blood. 2013;122:1336; Li S. Blood. 2016;128:3981; Geyer. Blood 2017;129:1878

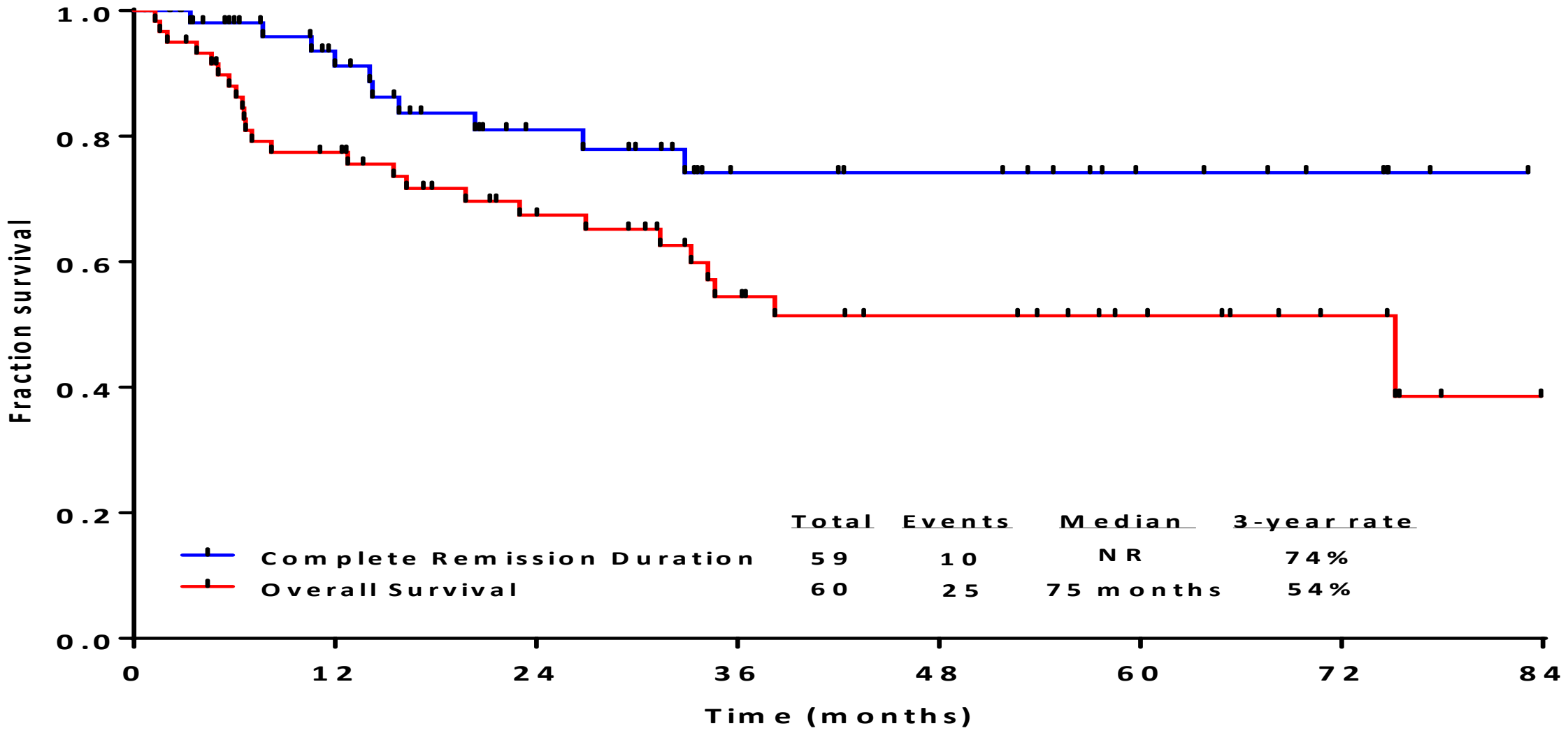
MiniHCVD-INO in Older ALL. Response (N=60)

Response	N	(%)
CR	51	(85)
CRp	6	(10)
CRi	2	(3)
ORR	59	(98)
No response	1	(2)
Early death	0	0

- Median age 68yrs (60-81)
- 4 patients were enrolled with CR

Kantarjian. Lancet Oncology 19: 240; 2018

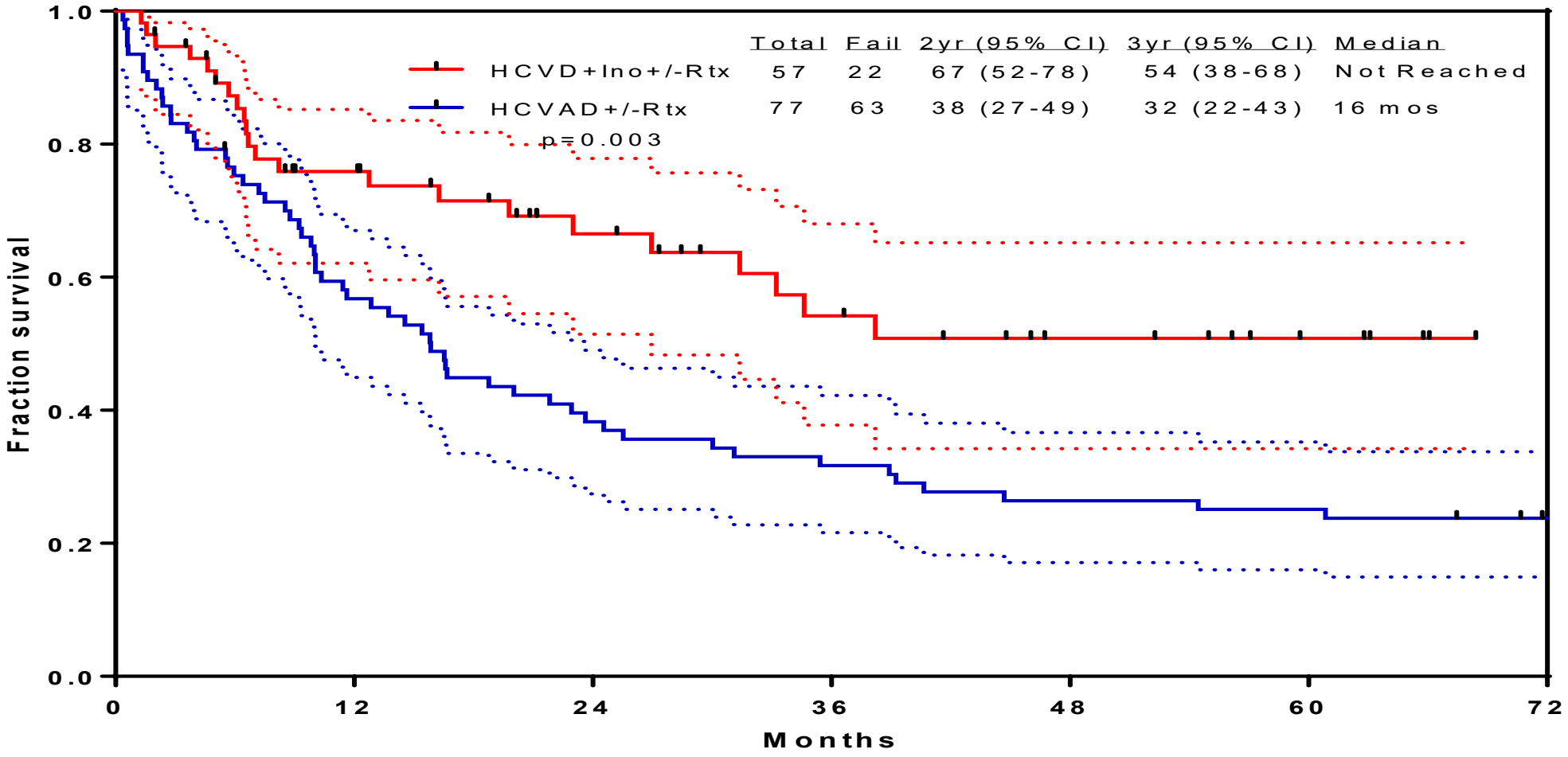
Mini-HCVD + INO ± Blina in Older ALL: CRD and OS (Entire Cohort)



Kantarjian. Lancet Oncology 19: 240; 2018

Short. Blood 132: abst 36; 2018

MiniHCVD-INO vs HCVAD in ALL.



Number at Risk

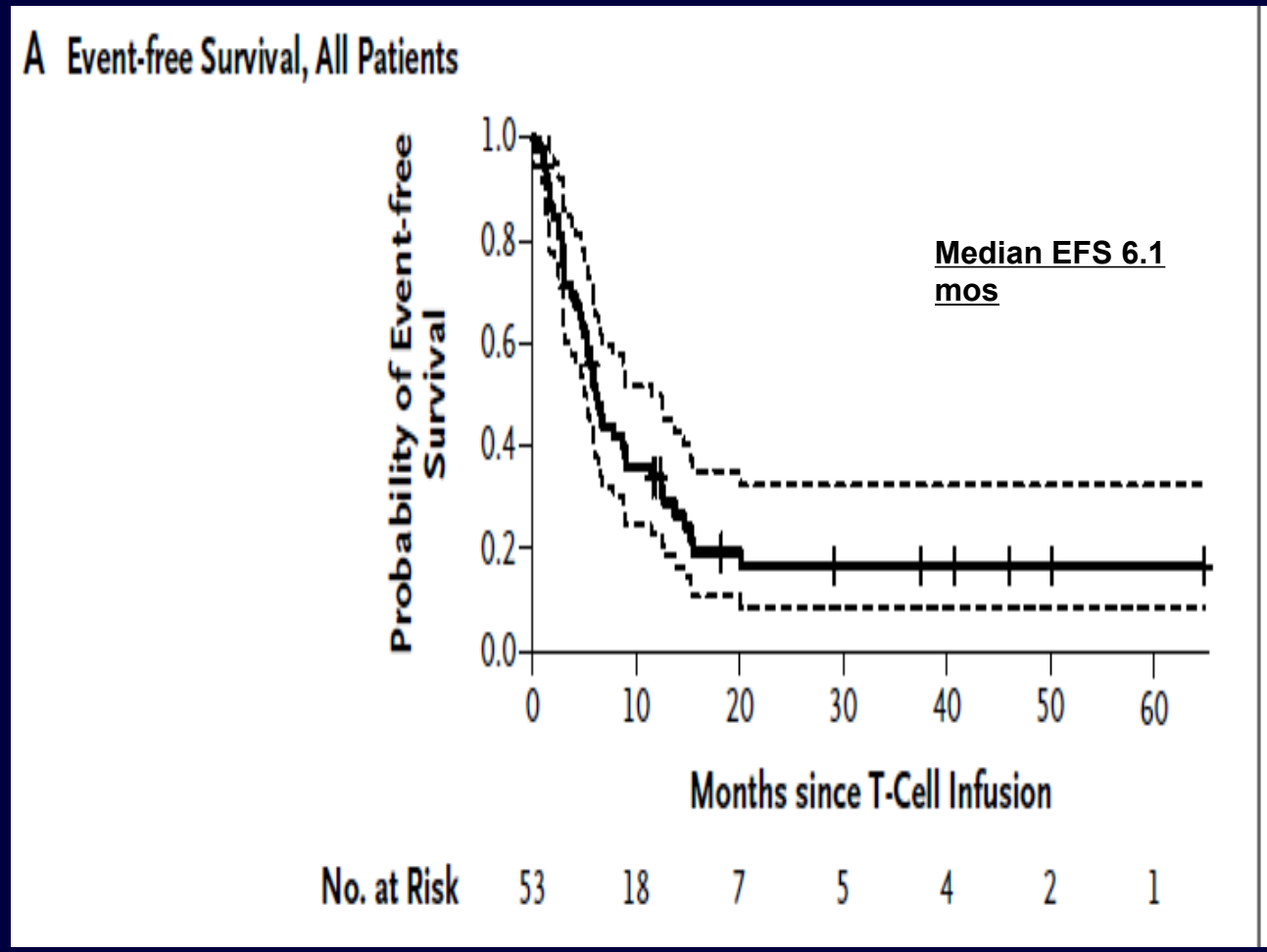
HCVD+Ino+/-Rtx	57	38	26	18	11	6	0
HCVAD+/-Rtx	77	43	29	24	20	19	15

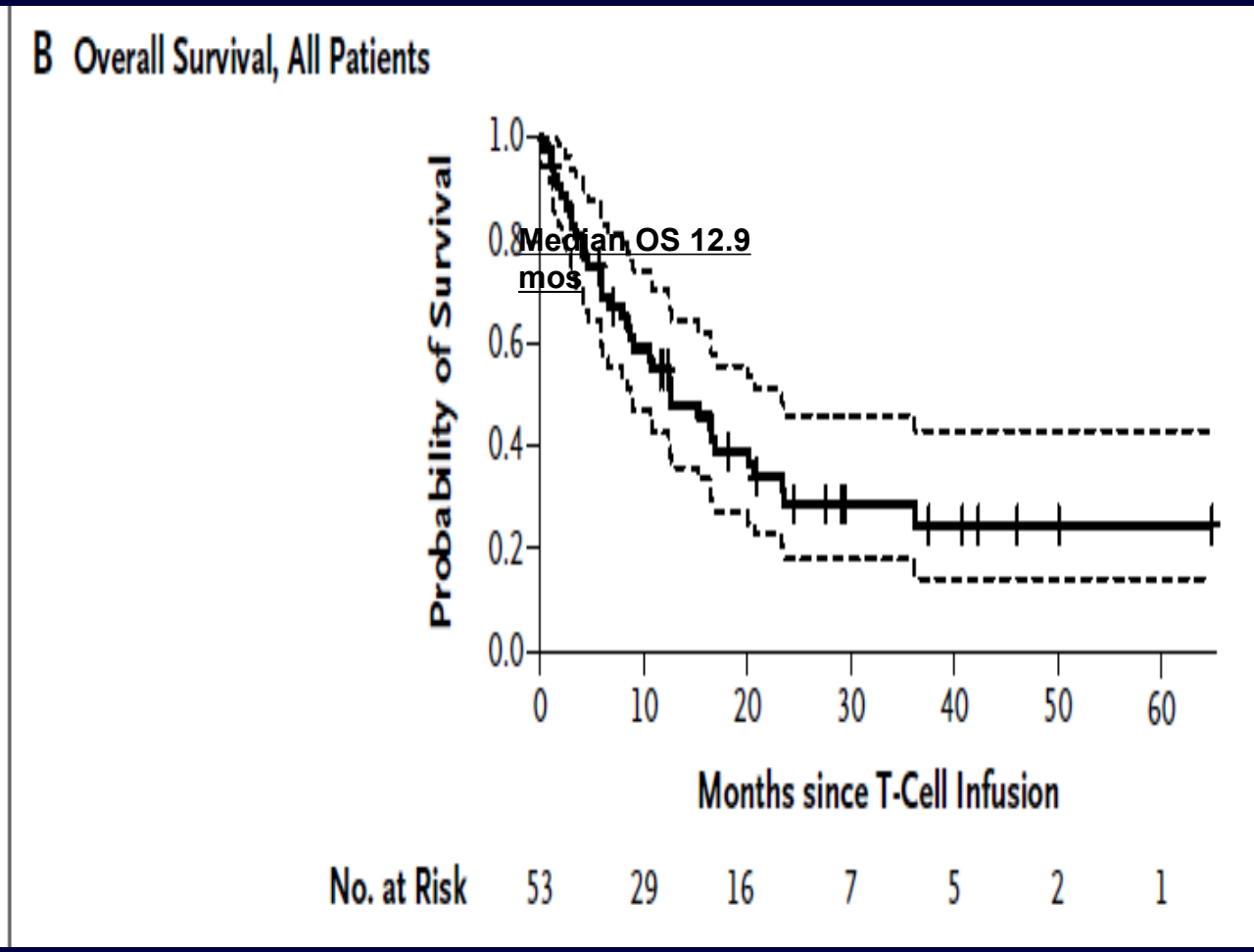
Kantarjian. Lancet Oncology 19: 240; 2018

MSKCC-Long-term Data with CD19-CD28z CAR

CR 44/53 = 83%; ITT overall CR 44/78 = 56%

Response (n=53) : CR 83%, MRD- CR 60%

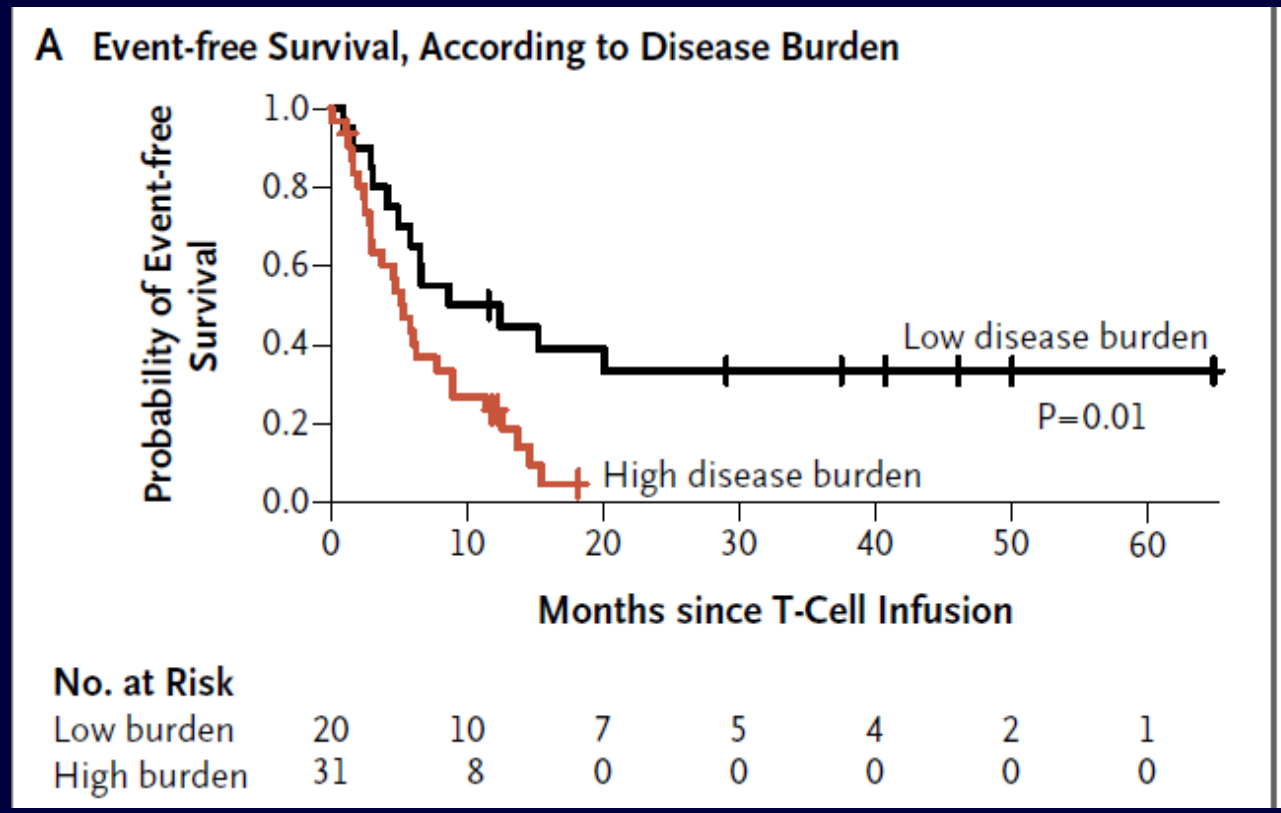


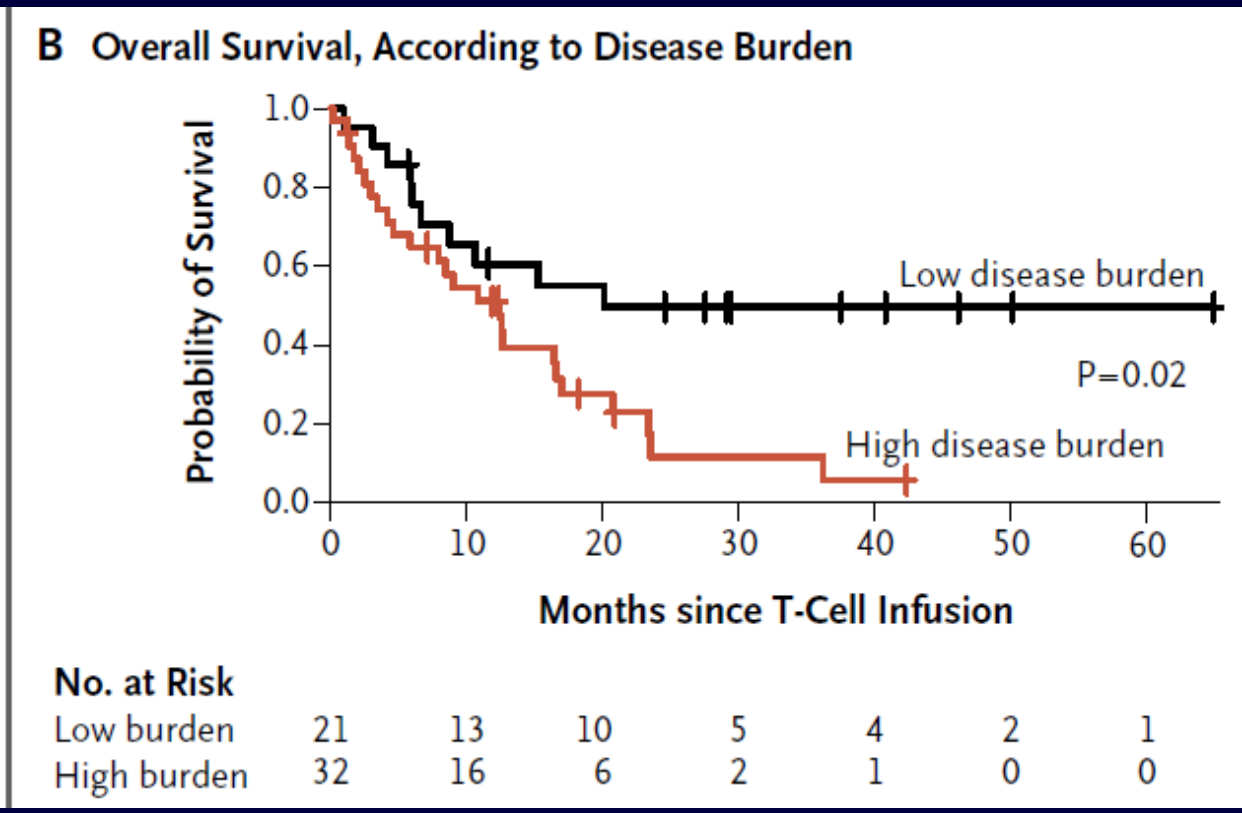


Park. NEJM. 2018 ;378:449

CD19-CD28z CAR (MSKCC). Responses by Tumor Burden

- **High tumor burden**
  - BM blasts ≥5% (n=27)
  - BM blasts <5% + EM disease (n=5)
- **Low tumor burden (MRD+ disease) (n=21)**





Median EFS
Low tumor burden: 10.6 mos
High tumor burden: 5.3 mos

Median OS
Low tumor burden: 20.1 mos
High tumor burden: 12.4 mos

Park et al. NEJM. 2018;378:449.

HyperCVAD in ALL- Dynamic Bayesian Strategy to Answer Multiple Questions

- Ph-positive ALL: HCVAD+ponatinib vs miniCVD+ponatinib vs ponatinib+blinatumomab
- Dose of inotuzumab: 1.8 vs 0.9mg/m^2 (0.6/0.3); number of courses (not to exceed 5.4mg/m^2 total)
- Courses of blinatumomab: 4 vs 7-8
- Schedules combining chemoRx with inotuzumab and blinatumomab
- Duration and intensity of chemoRx: 3 vs 1 year; HCVAD vs miniCVD
- Role of allo SCT; CAR-T to replace SCT as consolidation in CR1
- IT prophylaxis: 8 vs more
- Venetoclax in T and pre-B ALL

Leukemia Questions?

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