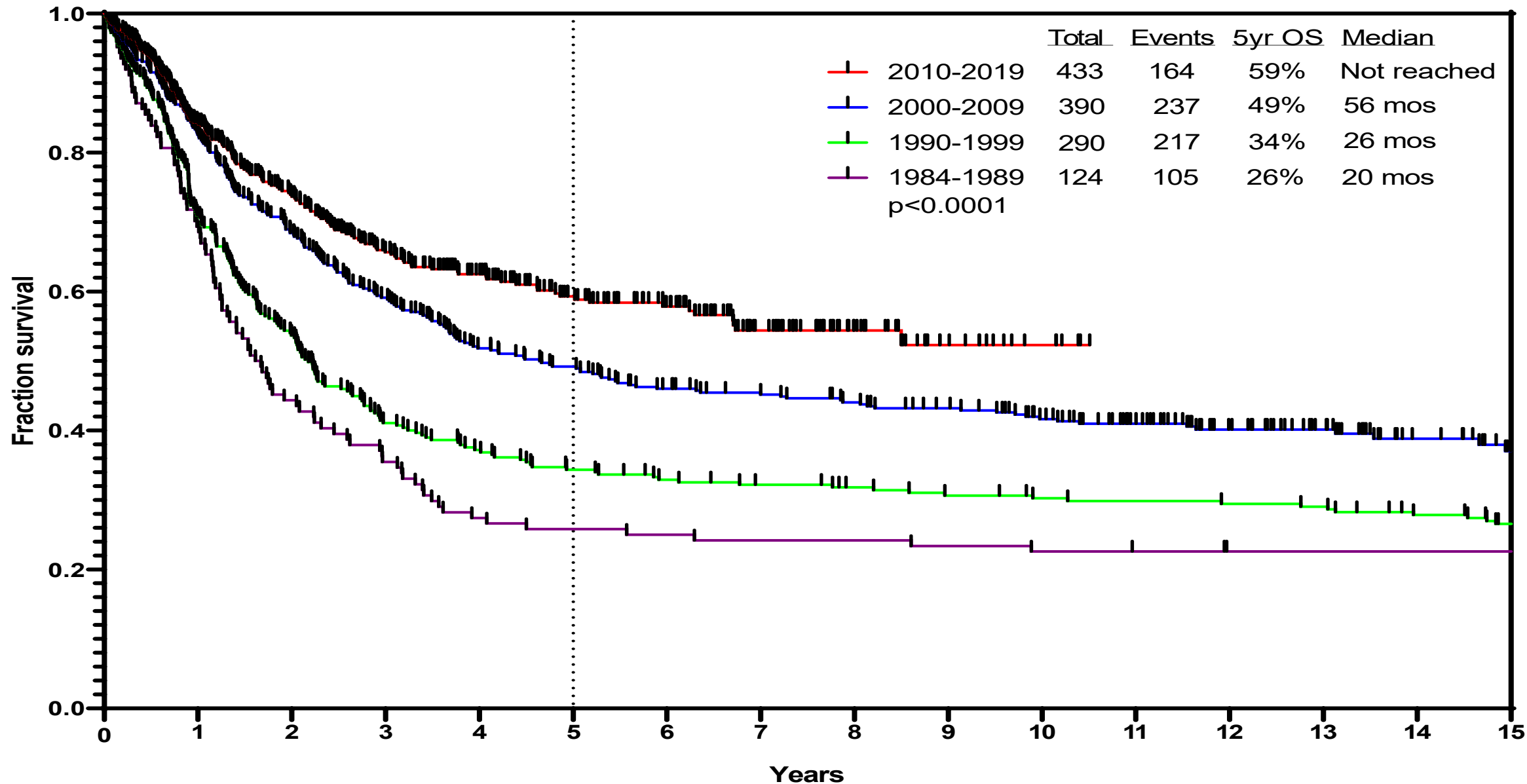


ALL Biologic And Targeted Therapies in 2021

Hagop Kantarjian, M.D.

Indianapolis – July 21, 2021

ALL. Survival by Decade (MDACC 1985-2020)



Why Pediatric ALL Does Better Than Adult ALL

Entity	Prognosis	% Pediatric	% Adult
Hyperdiploid	Favorable	25-30	5
t(12;21), <i>ETV6-RUNX1</i>	Favorable	20-25	2
Ph+ALL	Unfavorable historically (not today)	5	25
Ph-like ALL	Unfavorable	10	25

Reasons for Recent Success in Adult ALL

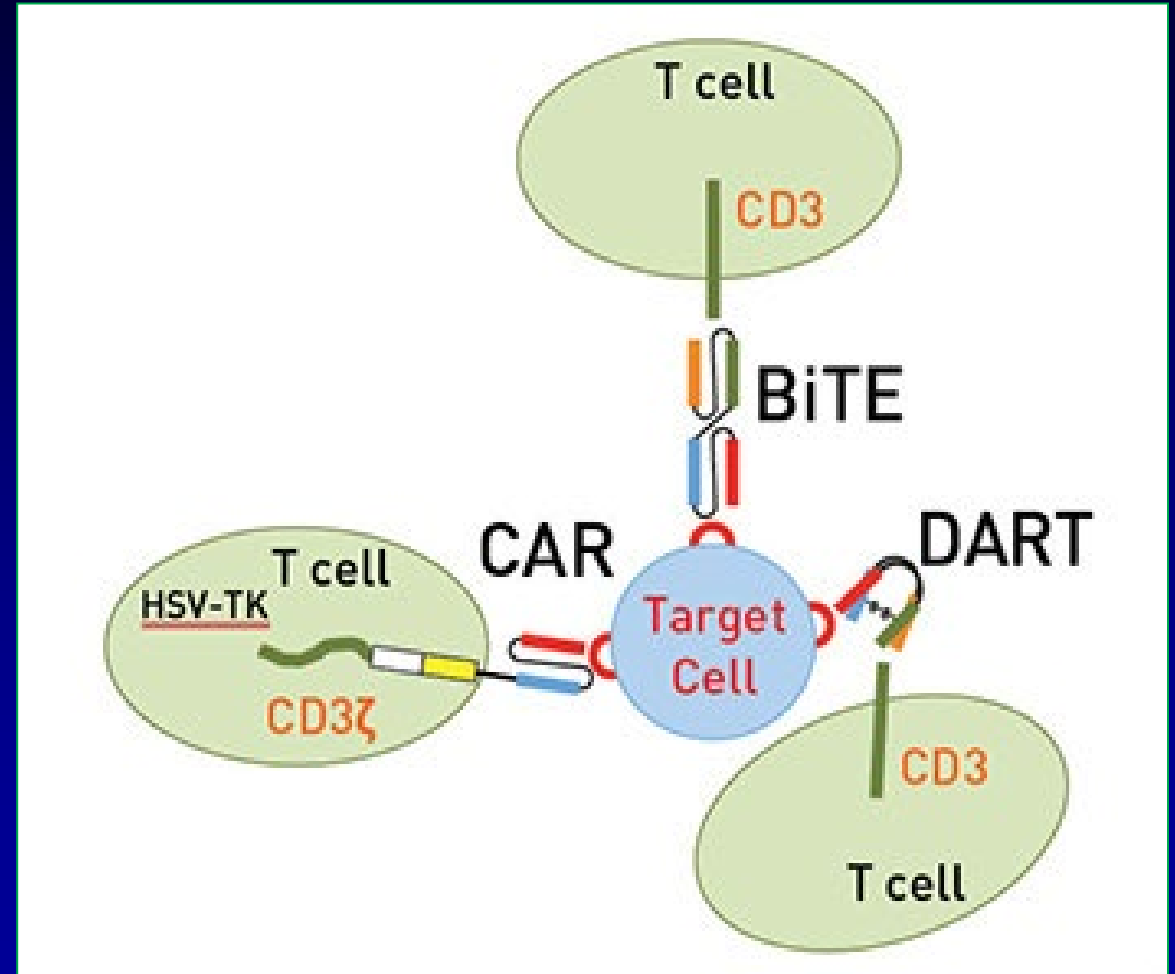
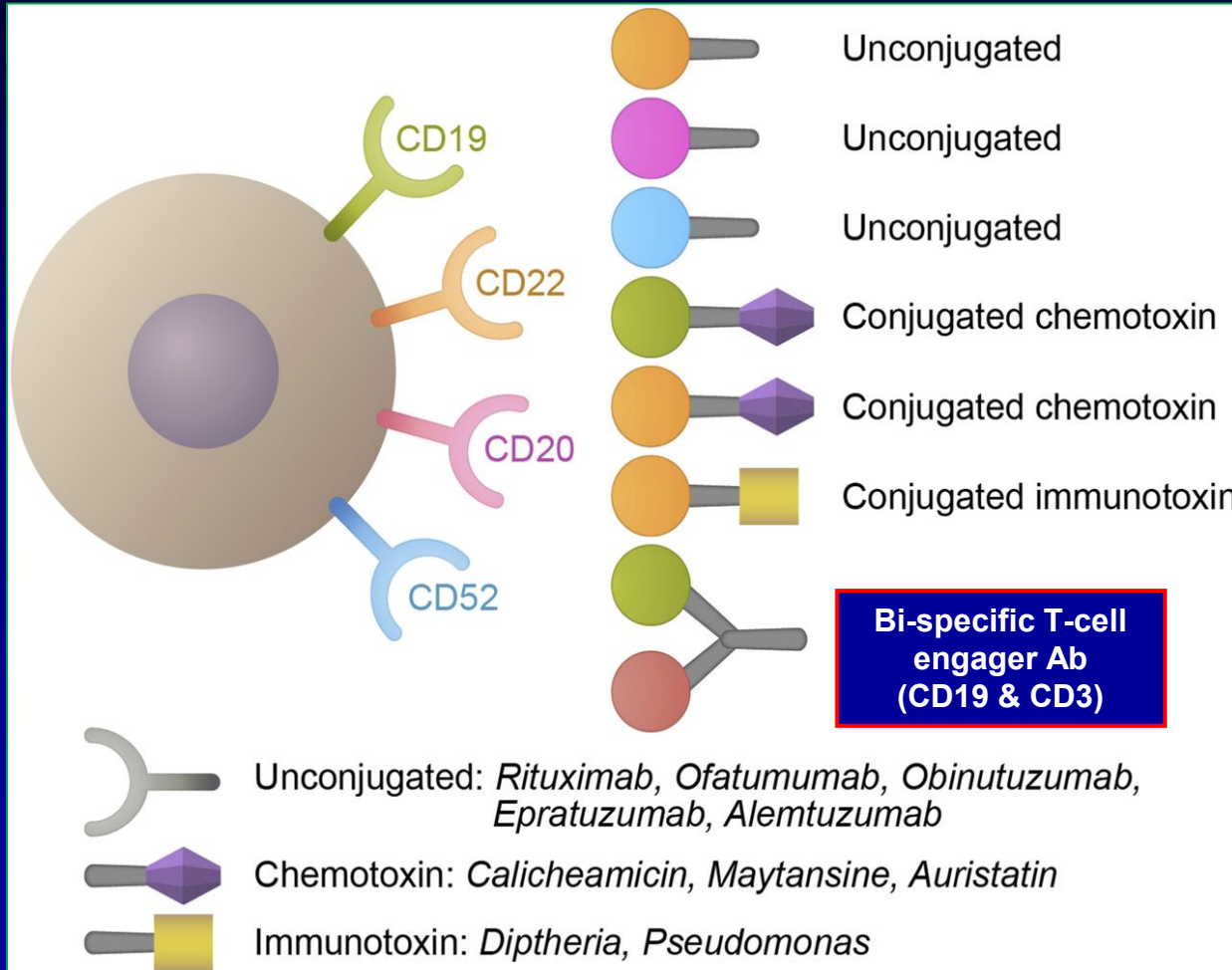
- Addition of TKIs (ponatinib) +/-blinatumomab to chemoRx in Ph-positive ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Addition of CD19 bispecific T-cell engager (BiTE) antibody blinatumomab, and of CD22 monoclonal antibody drug conjugate (ADC) inotuzumab to chemoRx in salvage and frontline ALL Rx
- CAR-T therapy
- Importance of MRD in CR (at CRvs 3 mos;NGS)

Biologic And Targeted Therapies in ALL

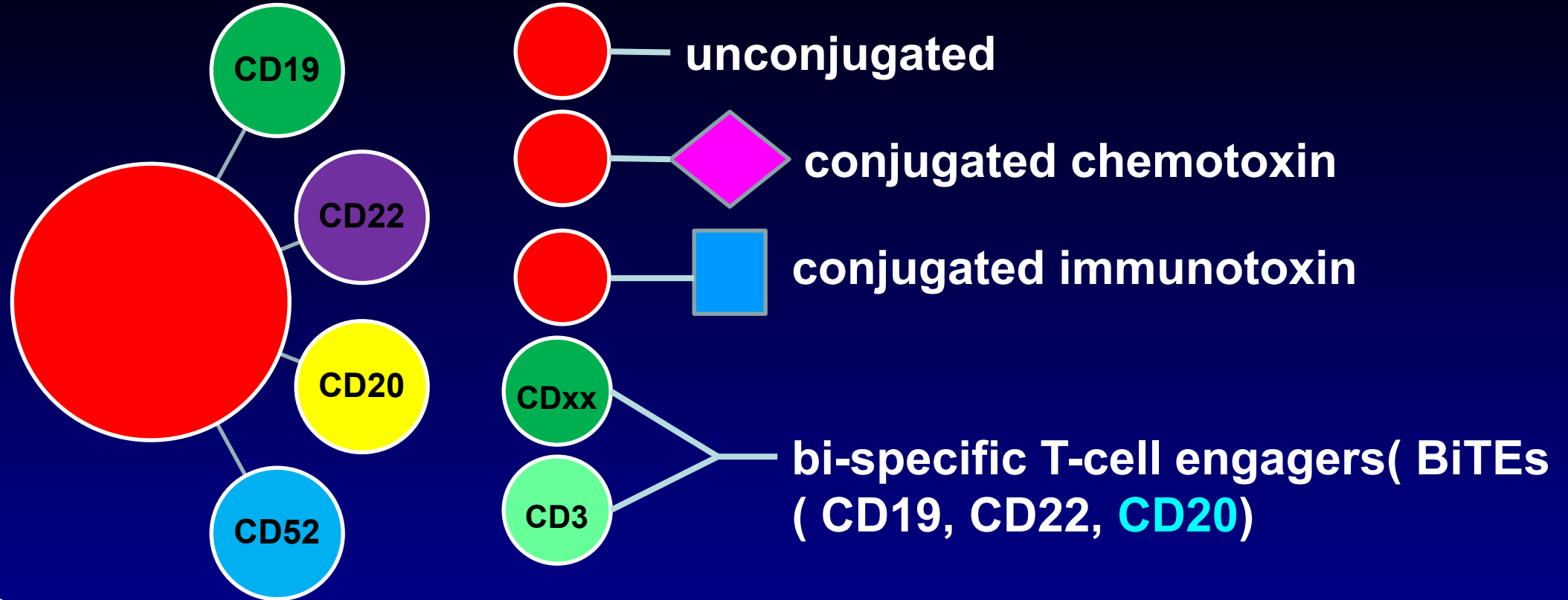
- **Ph-positive ALL --TKIs (dasatinib; ponatinib) + blinatumomab**
- **Burkitt leukemia – Rituximab + HCVAD/ DA-EPOCH**
- **PreB ALL frontline and salvage -- younger and older**
- **Treatment of MRD in CR**


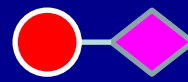
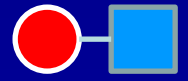
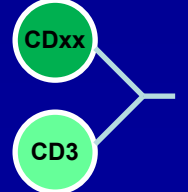
Immuno-oncology in ALL

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



Antibodies Different Flavors

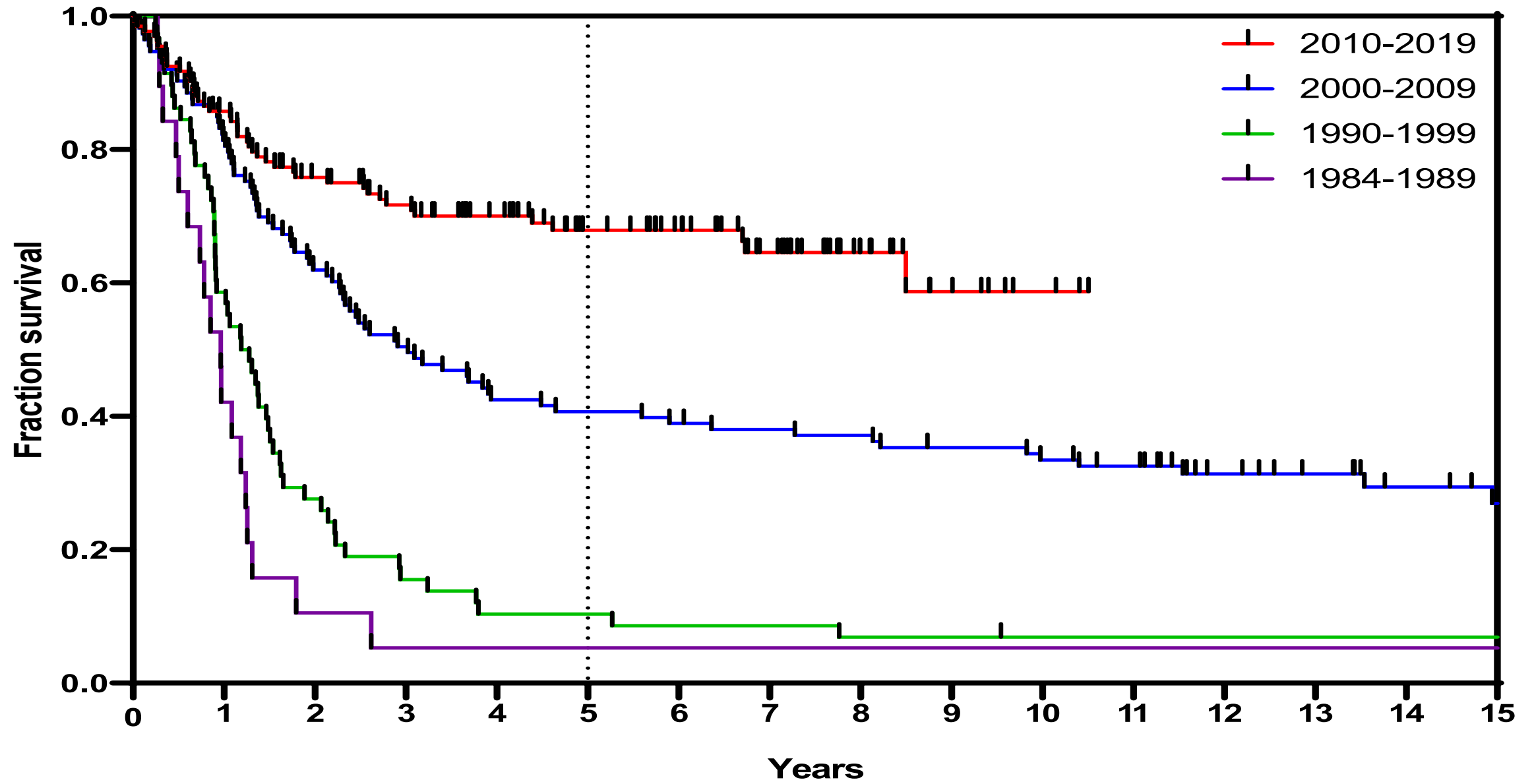


-  unconjugated: rituximab, ofatumumab, GA-101
-  chemotoxin: calicheamicin, maytansin, auristatin
-  immunotoxin: diphtheria, pseudomona
-  bi-specific: CD3 + CD19/20/22

Antigen Expression Antigen in B-Cell Lineage ALL for Potential Antibody Therapy

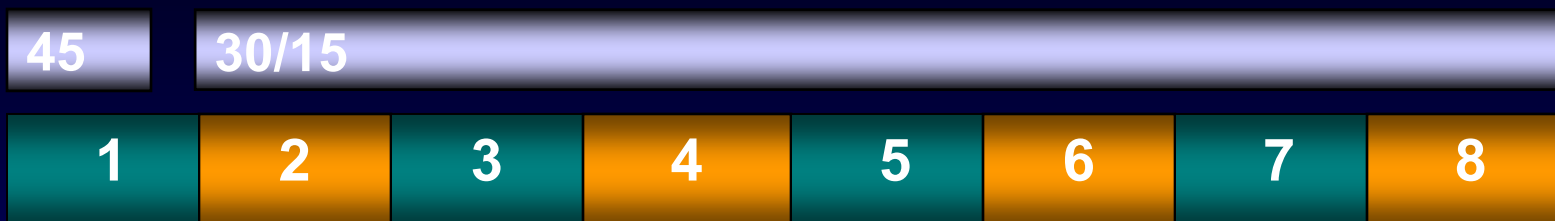
Surface antigen	ALL Subtype	Expression on LBC (%)	Therapeutic Potential
CD20	Burkitt	86-100	Rituximab
	B-precursor	30-40	Ofatumumab Novel CD20 BiTEs
CD19	B-precursor	95-<100	<ul style="list-style-type: none"> • Blinatumomab (bispecific CD3/CD19 T-cell engager ; BiTE) • CAR T cells
	Mature B-ALL	95-<100	
CD22	B-precursor	93-98	Inotuzumab ozogamicin Epratuzumab Moxetumomab pasudotox
	Mature B-ALL	≈100	

Ph-positive ALL Survival. MDACC 1985-2020

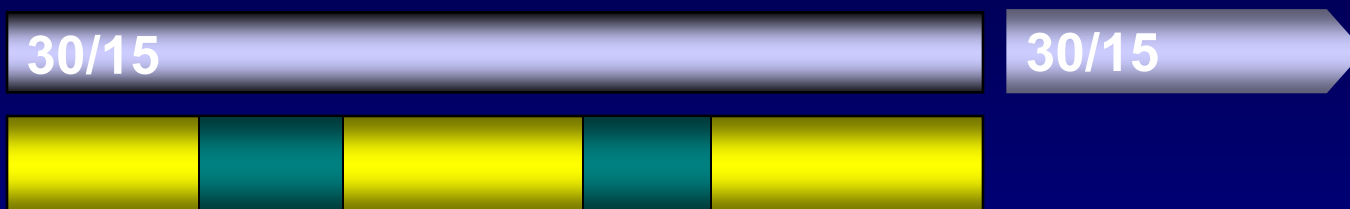


Hyper-CVAD + Ponatinib. Design

Intensive phase



Maintenance phase



← 24 months →

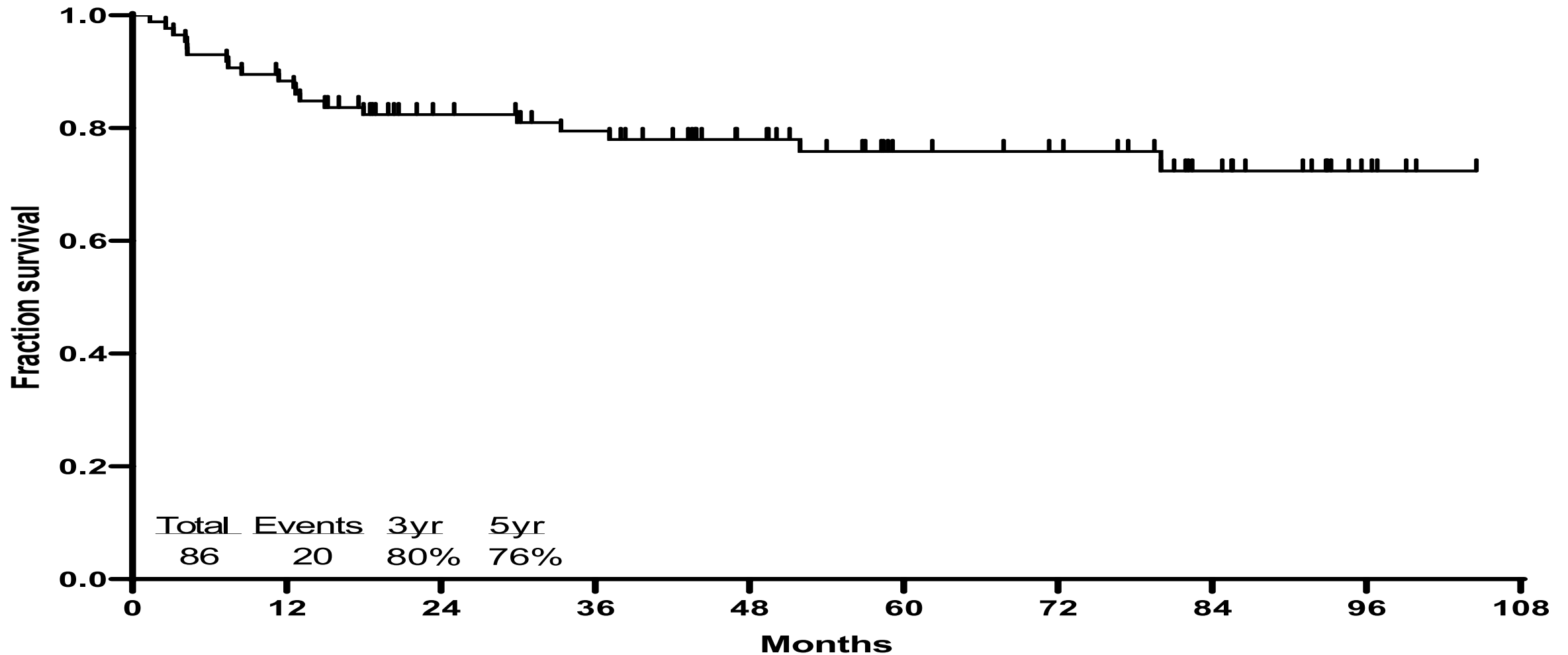
12 intrathecal CNS prophylaxis



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

HyperCVAD + Ponatinib in Ph-positive ALL

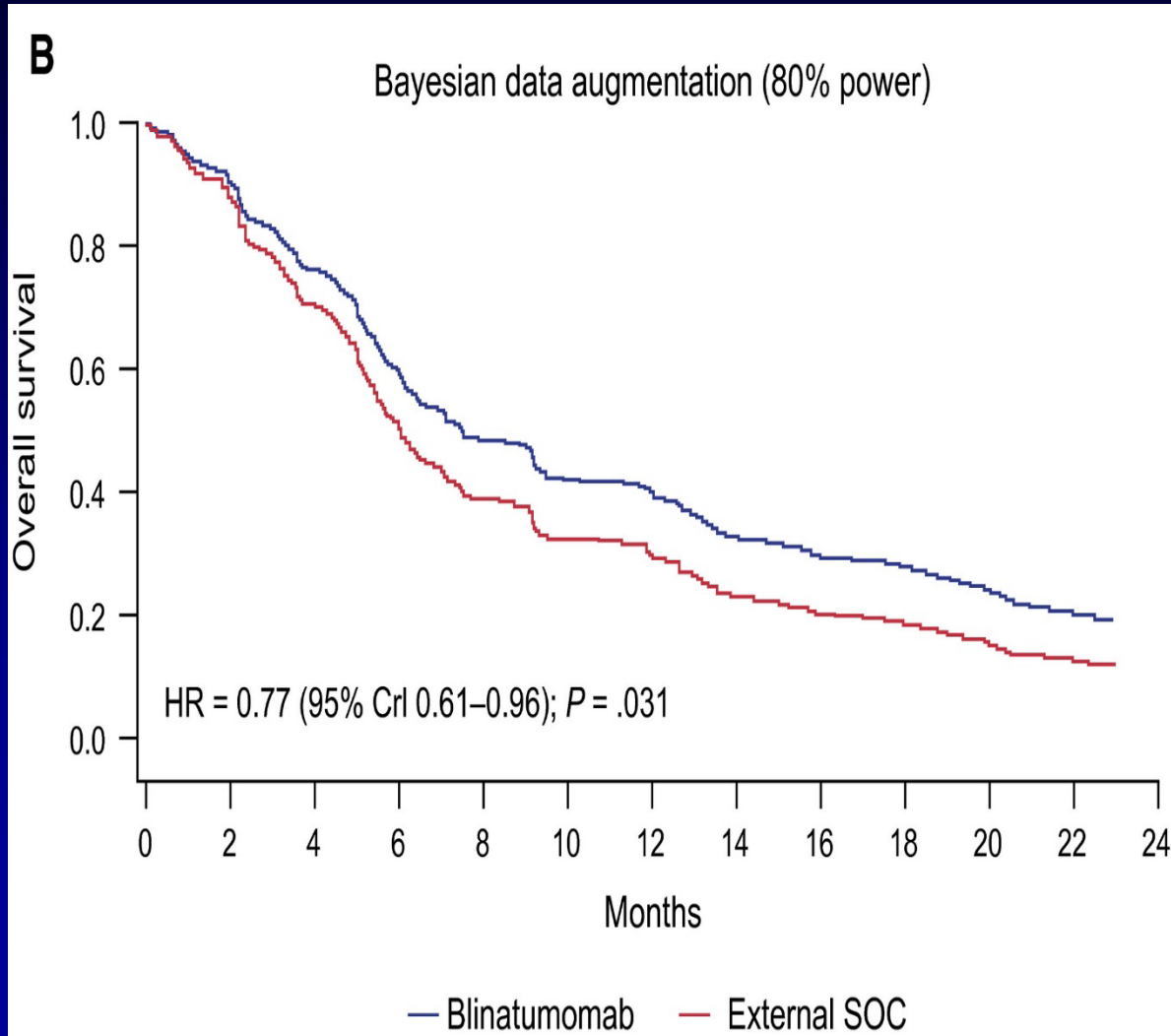
- 86 pts Rx; median age 47 yrs (39-61); median FU 43 mos(2-92)
- CR 68/68 (100%); FCM-MRD negative 85/86 (99%); **CMR 84%; 3/5-yr OS 80/76%,EFS 76/71%**



Blinatumomab and Inotuzumab in R-R Ph+ ALL

Blina vs SOC

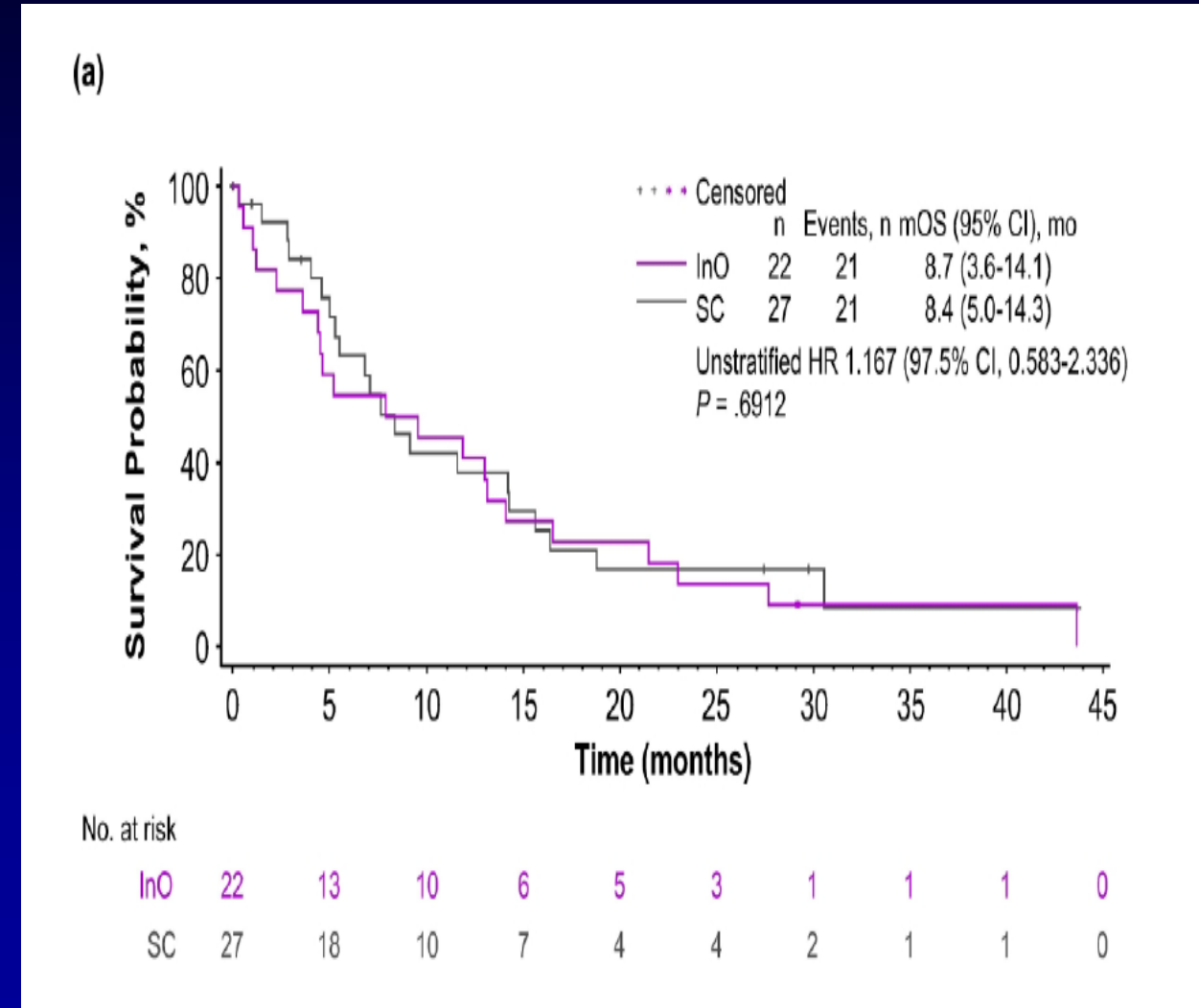
- CR/CRh 36% vs 25%
- 1-yr OS 41% vs 31%



Rambaldi. Cancer. 126: 304-310; 2019

Ino vs SOC

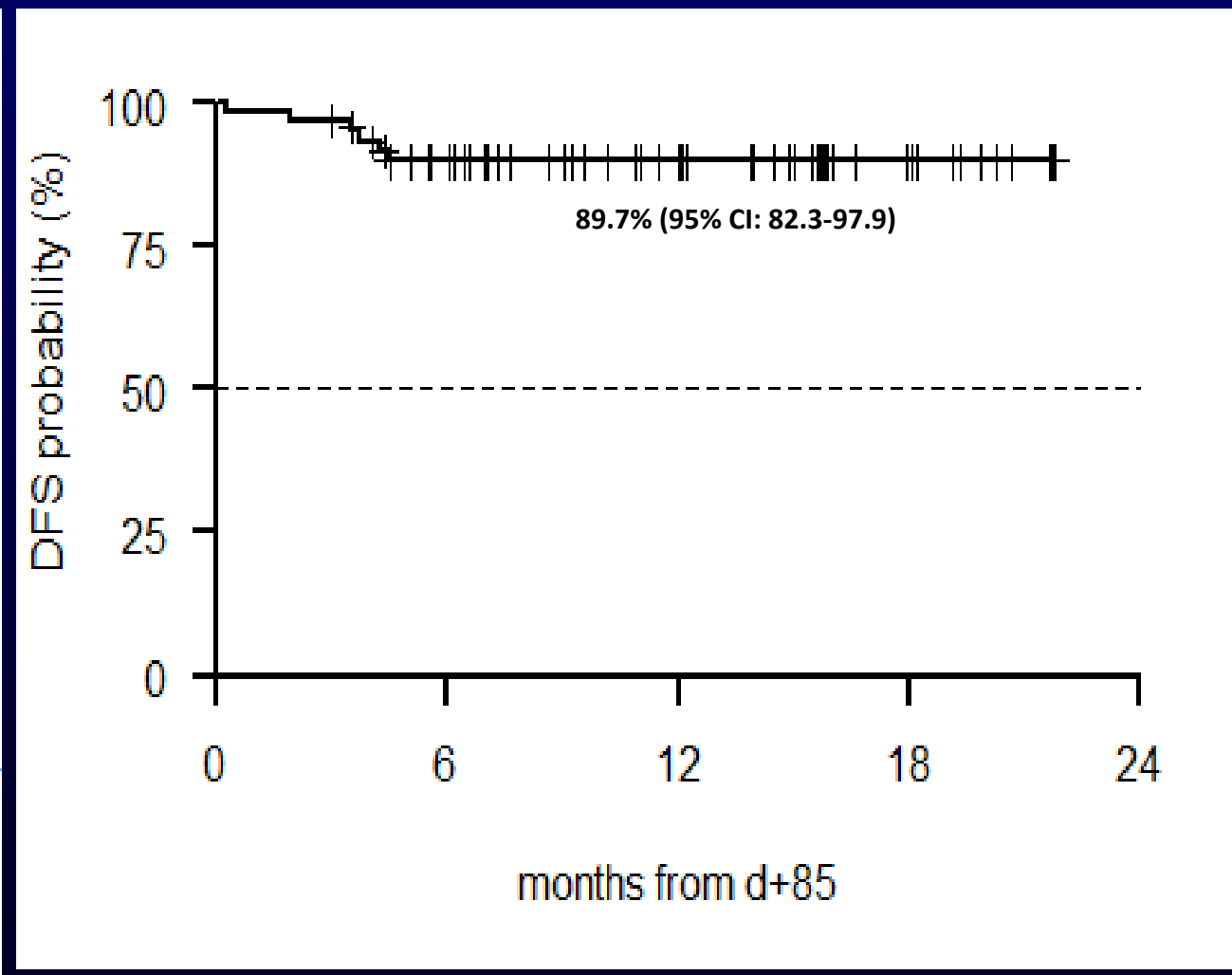
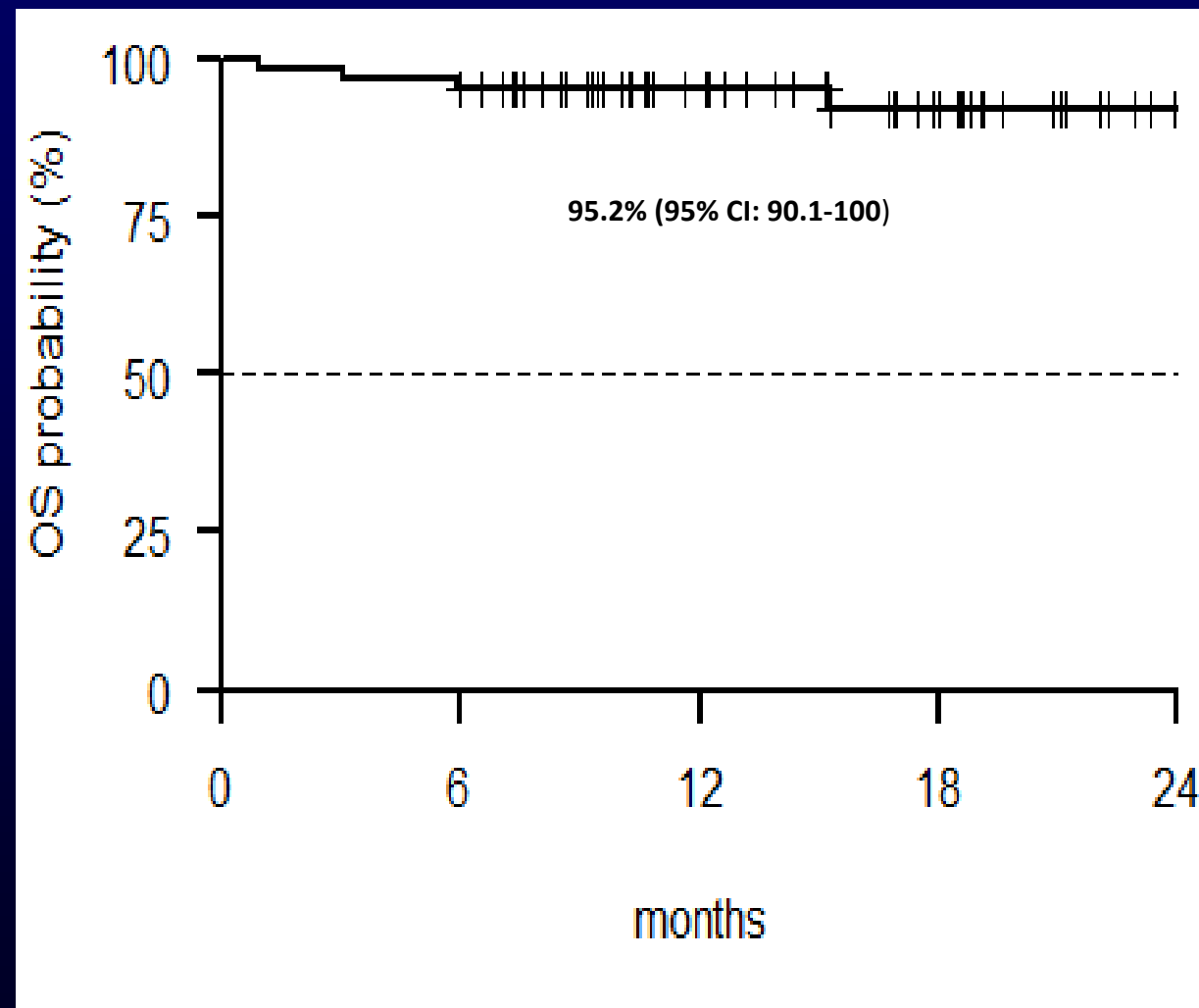
- CR/CRI 73% vs 56%
- 1-yr PFS 20% vs 4.8%



Stock. Cancer 127: 905-13;2021

Dasatinib-blinatumomab in Ph-positive ALL

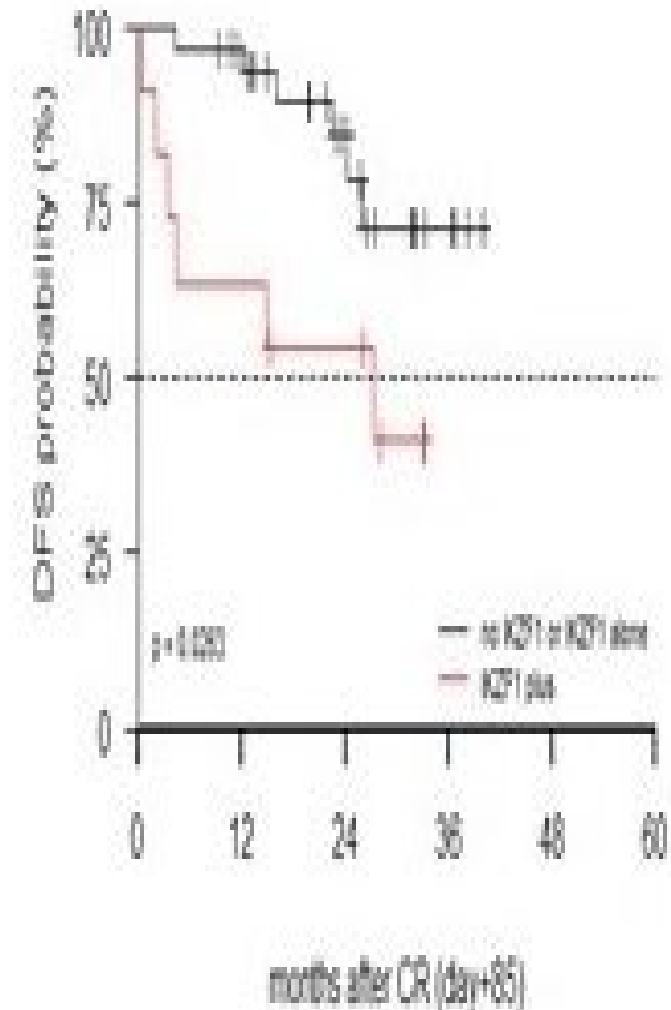
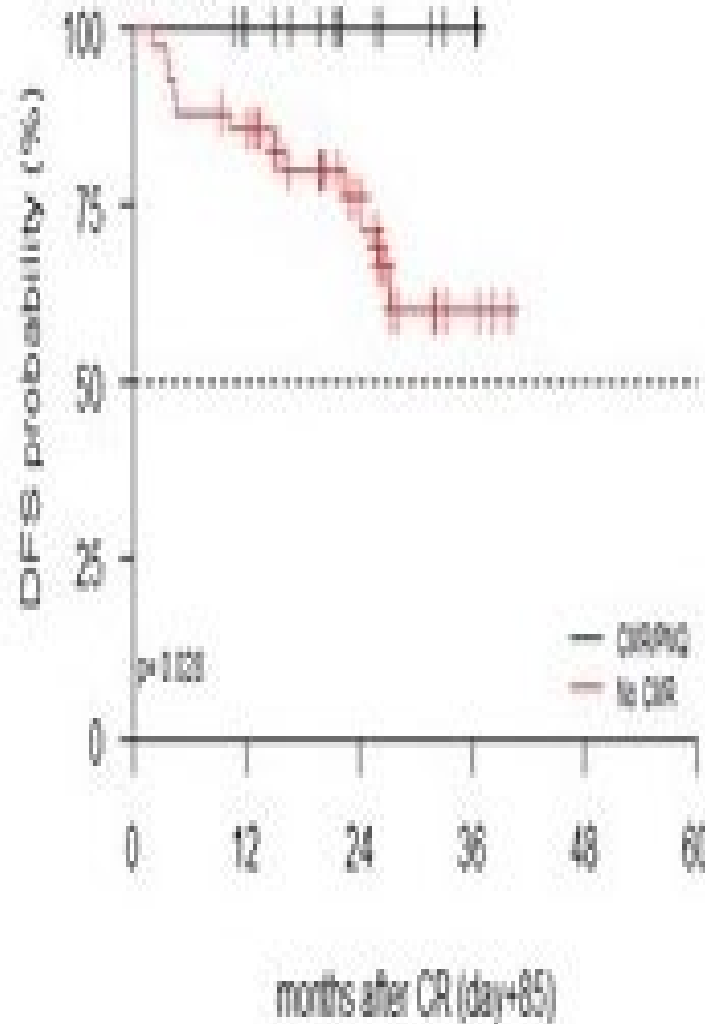
- 63 pts, median age 54 yrs (24-82). Dasatinib 140mg/D x 3 mos ; add blinatumomab x 2-5
- 53 post dasa-blina x 2--**molecular response 32/53 (60%), 22 CMR (41%)** . MRD ↑ in 15— 6 T315I; 2-yr OS 88%; DFS 80% . 29/58 (50%) allo SCT



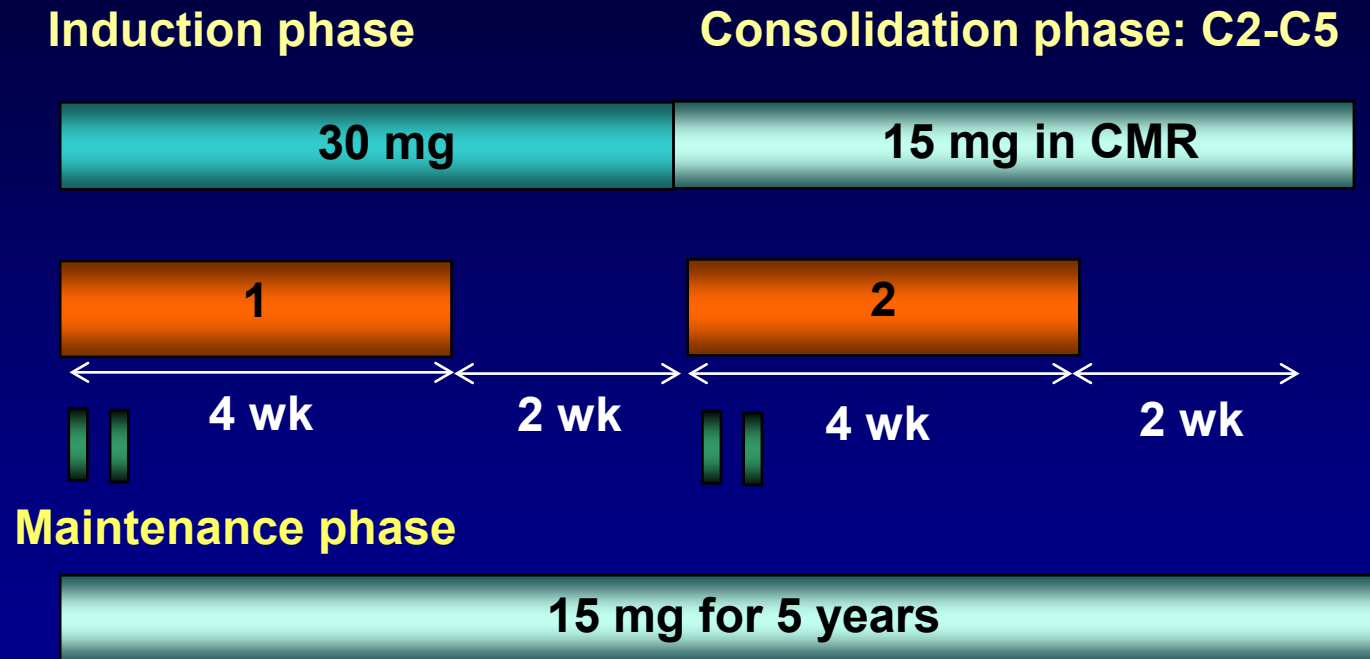
Dasatinib + Blinatumomab (D-ALBA) in Newly- Dx Ph+ ALL-- Update

- 64 pts Rx; median age 54 yrs (24-82). Median FU 27 mos
- 29/58 (50%) who started blina has 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)

Fig 1. DFS according to molecular response (A) and *IKZF1* plus genotype (B).



Blinatumomab-ponatinib in Ph-Positive ALL



 Blinatumomab  IT MTX, Ara-C  Ponatinib 30 mg  Ponatinib 15 mg

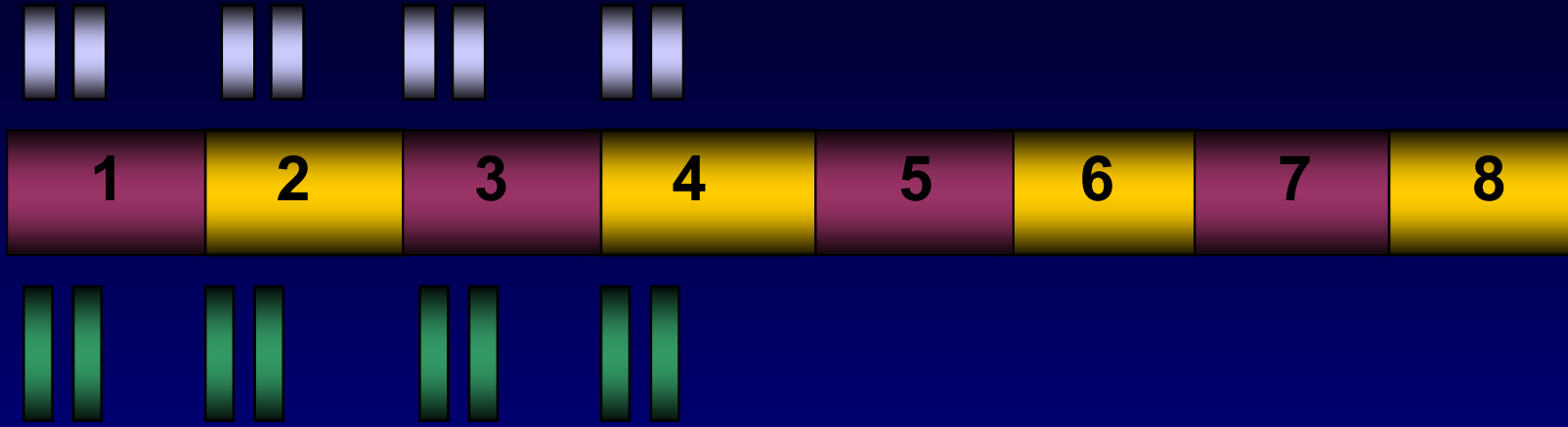
Ponatinib + Blinatumomab in Ph-positive ALL

- 28 pts Rx: 19 new Dx; 9 R-R.
Median age 59 yrs (25-83)
- P190 69% in ND
- Ponatinib 45-15 mg/D; blina standard starting D1
- Median time to CMR 1 mos (1-13)
- Allo SCT 0/19 ND, 4/9 R-R

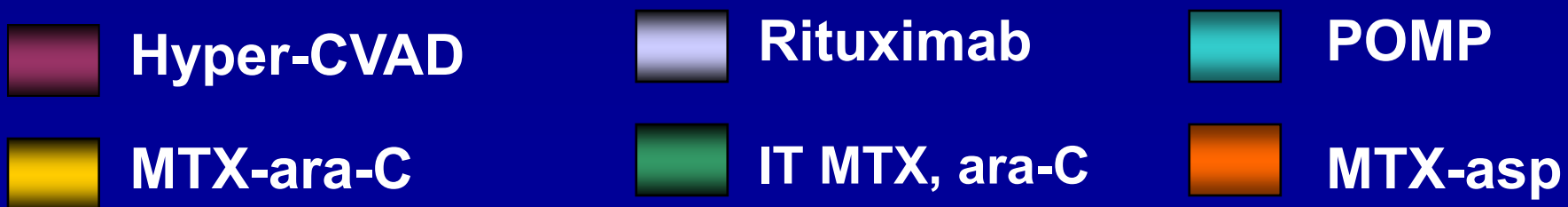
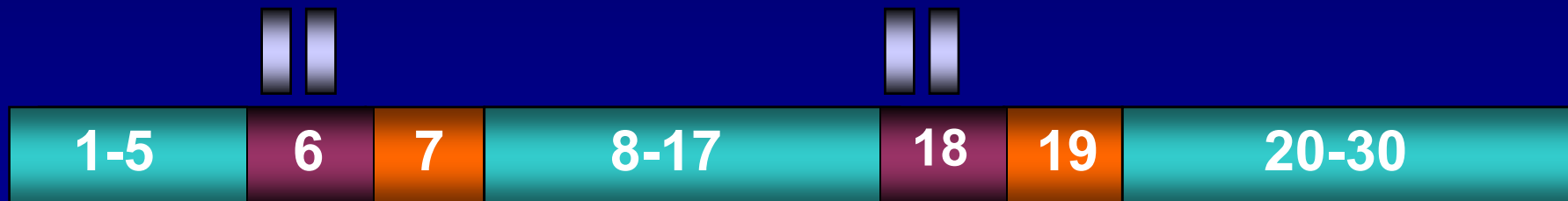
Parameter	New Dx	RR
% CR-CRi	100	88
% PCR negative	87	86
% 1-yr OS	100	88
% 1-yr EFS	100	55

Hyper-CVAD + Rituximab in Burkitt and Pre B-ALL

Intensive phase

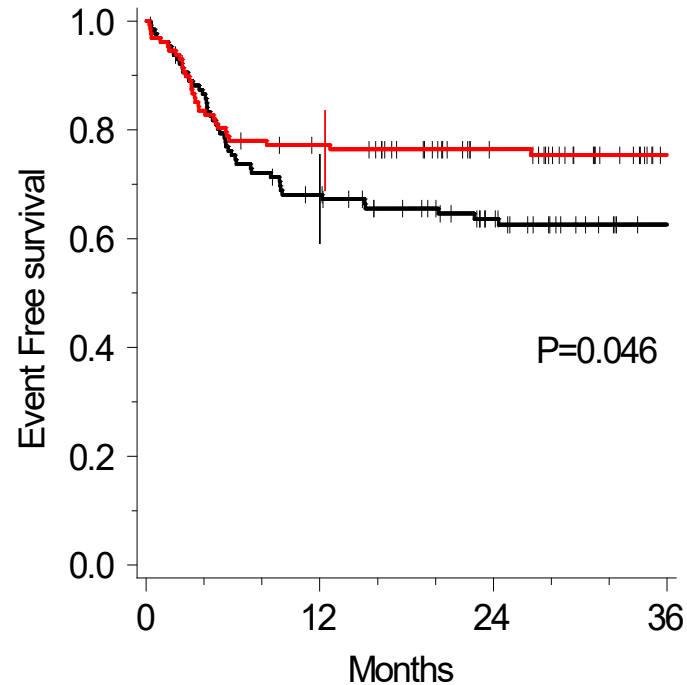


Maintenance phase



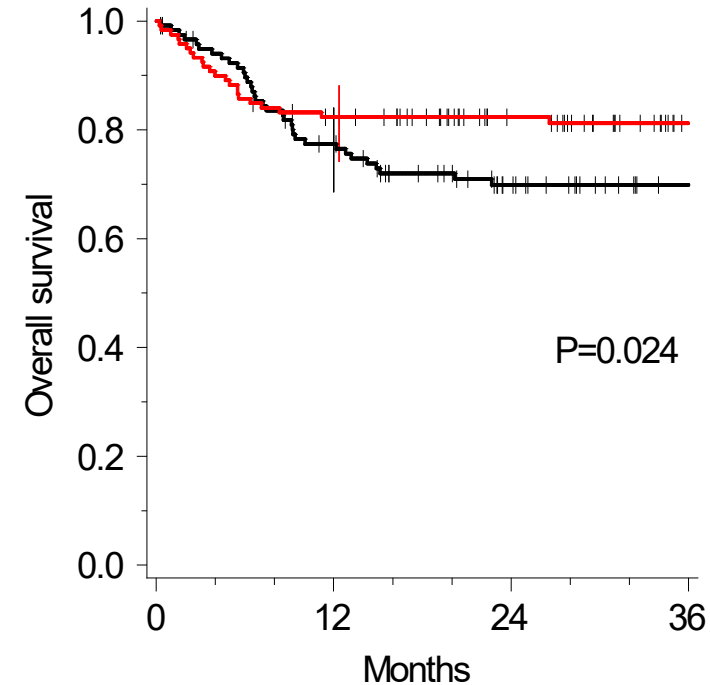
Results of the Randomized Intergroup (GRAALL-Lysa) LMBA02 Study.

Event Free Survival



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

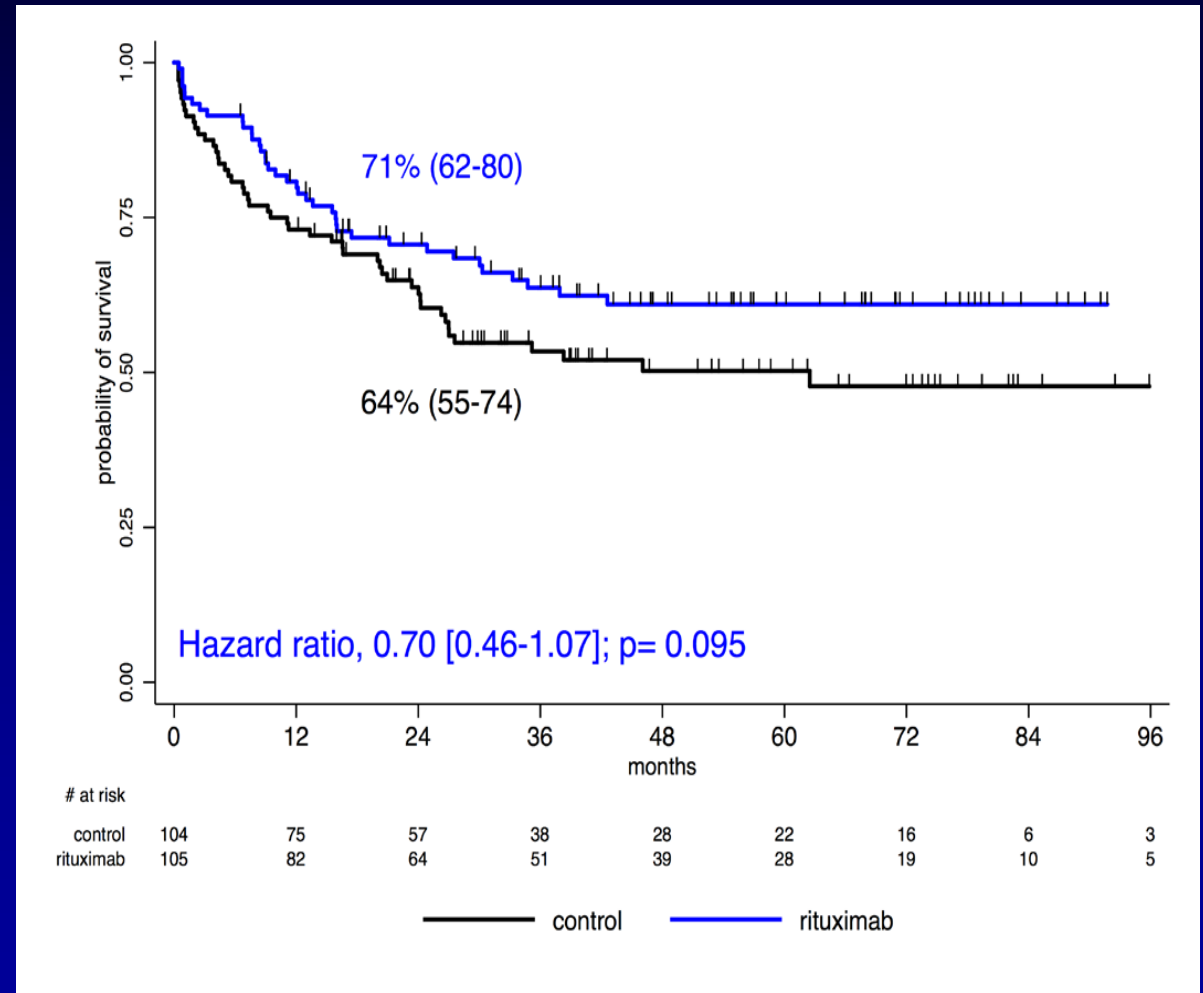
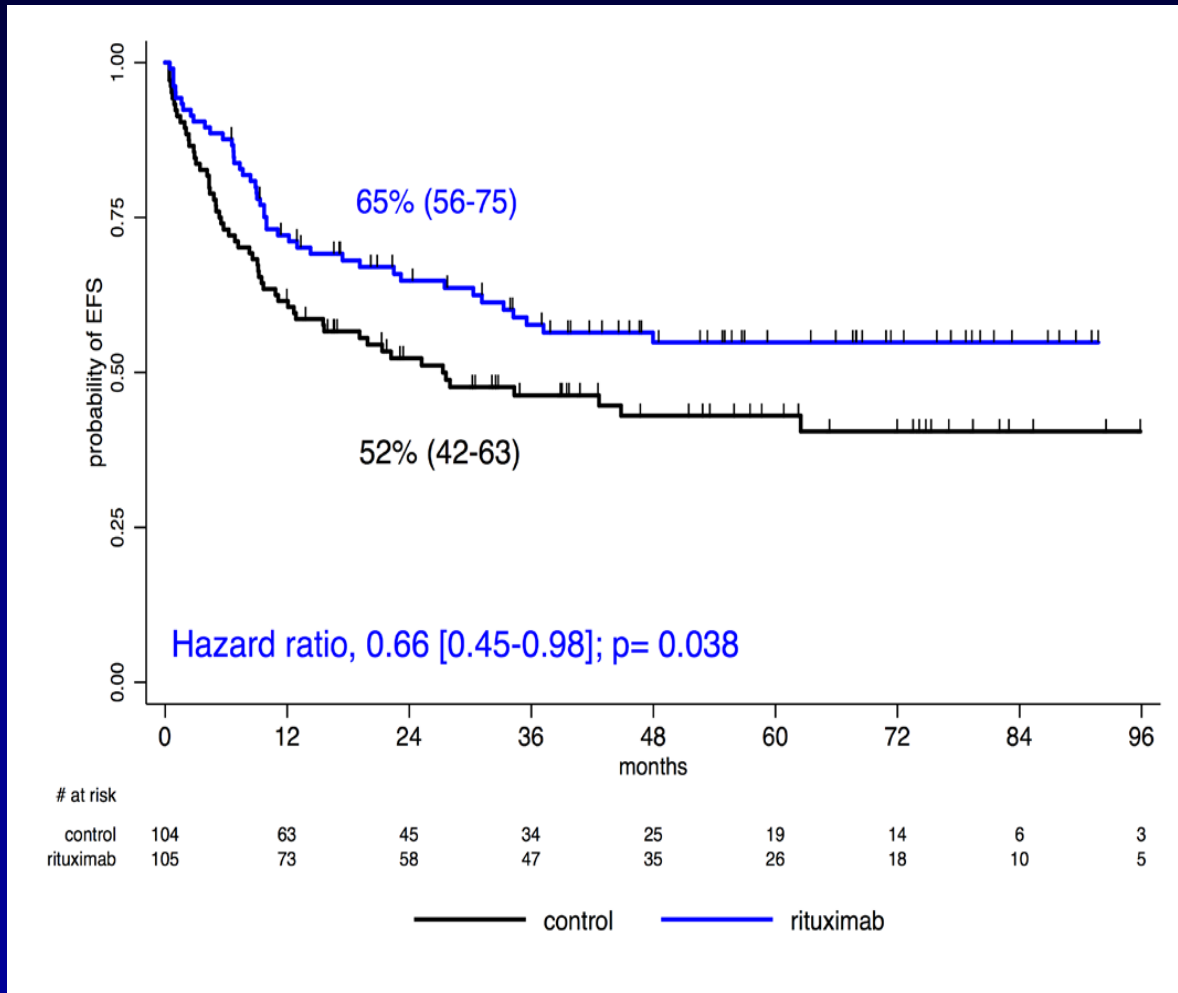
Overall Survival



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

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

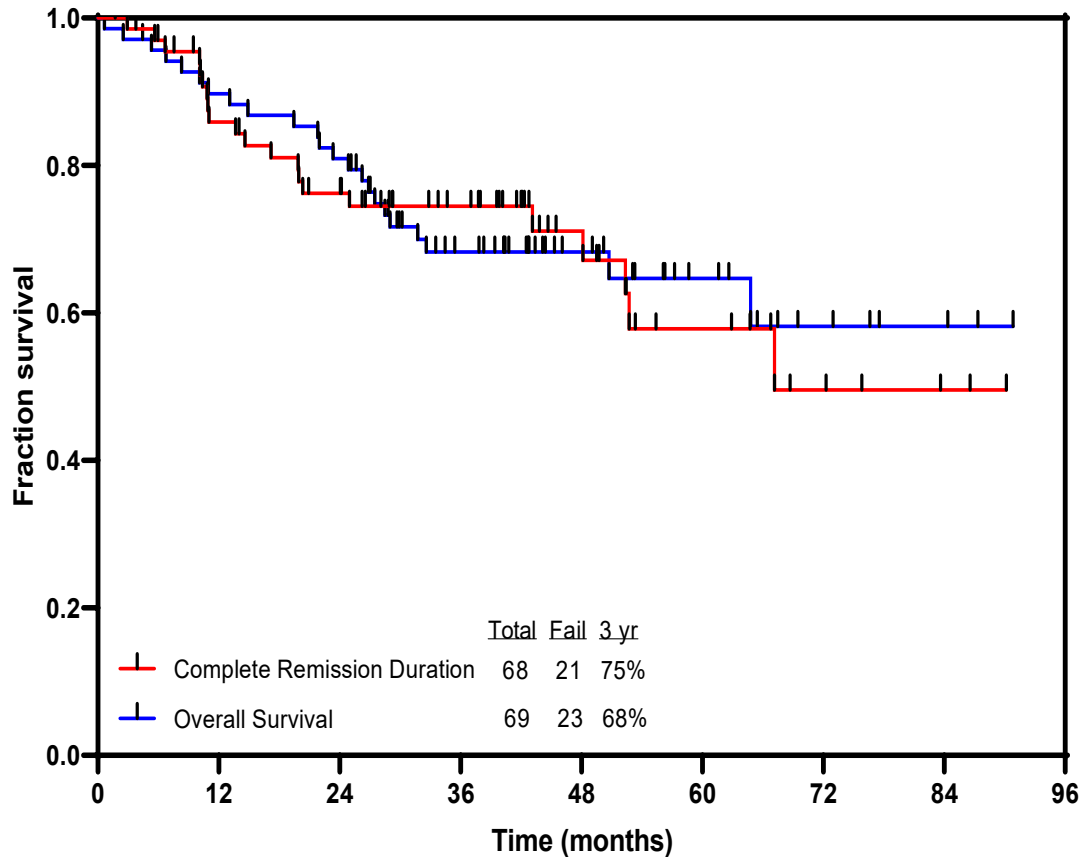
- Median follow-up 30 months



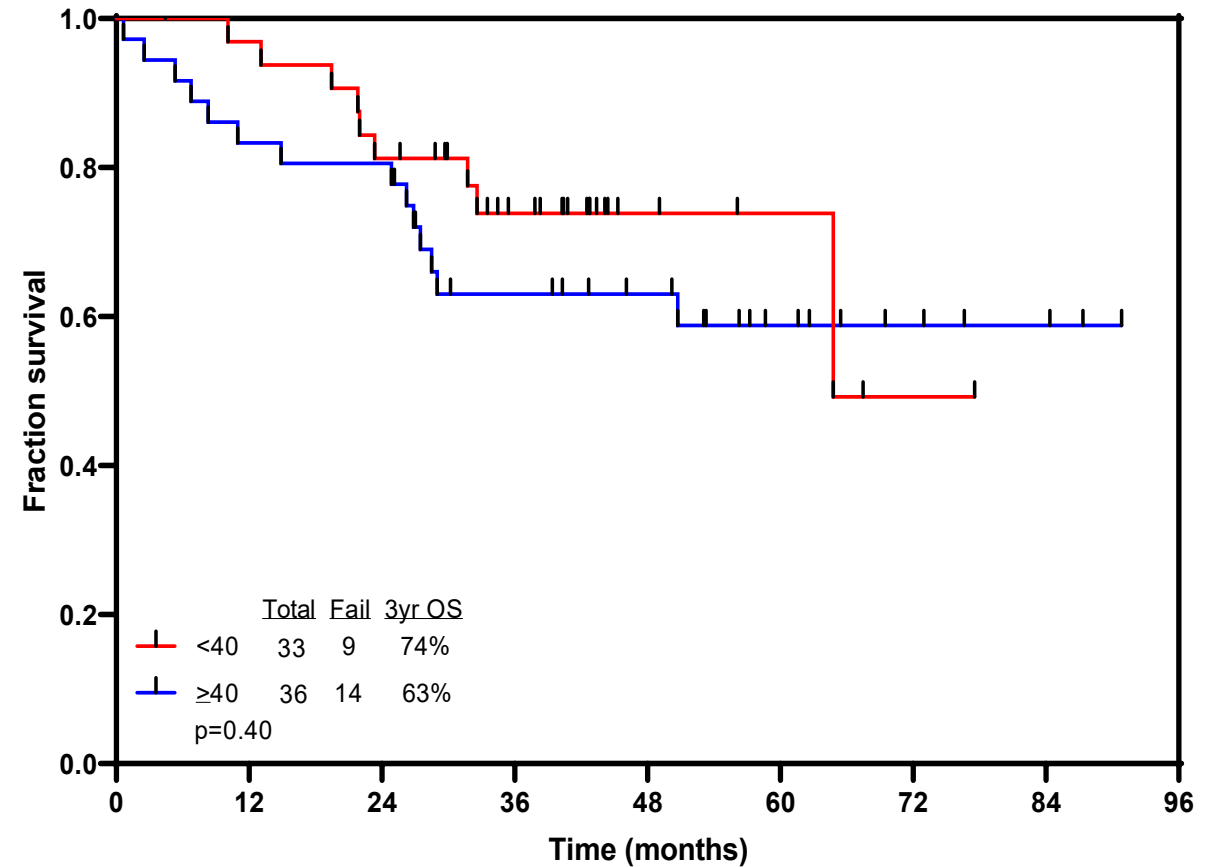
HCVAD + Ofatumumab. Outcome (N=69)

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

CRD and OS Overall



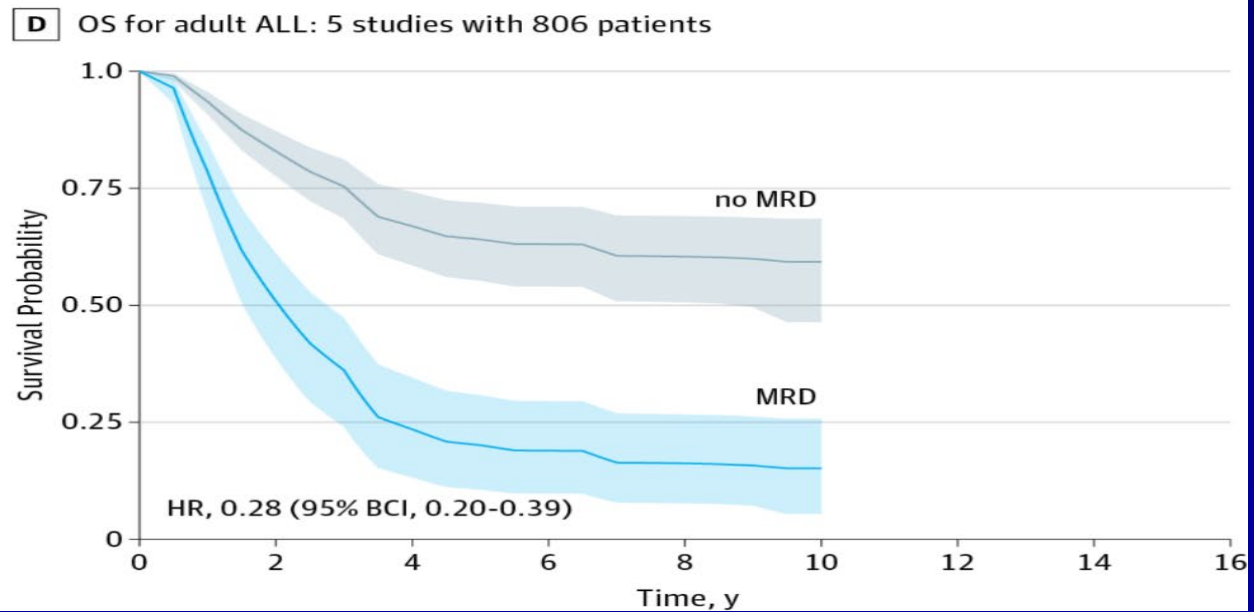
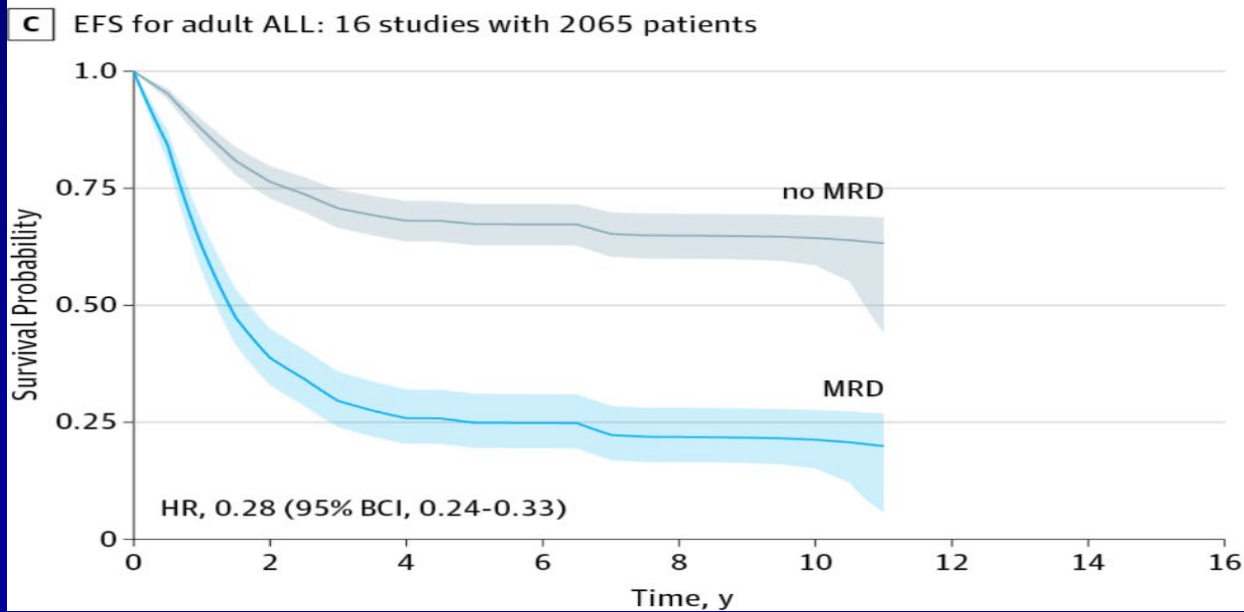
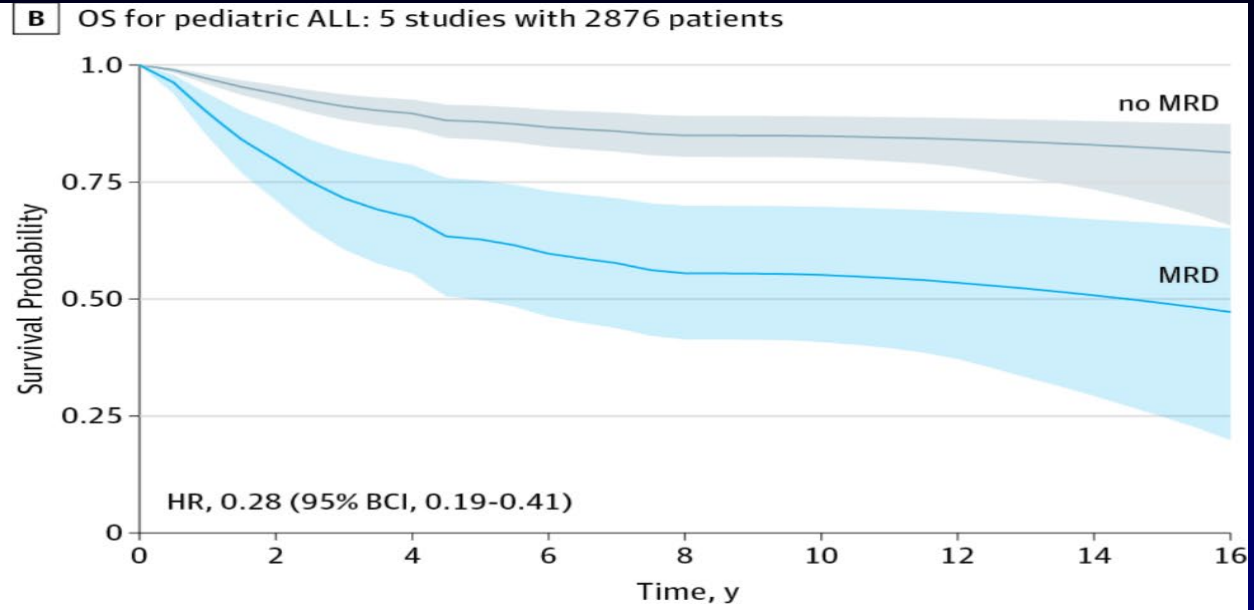
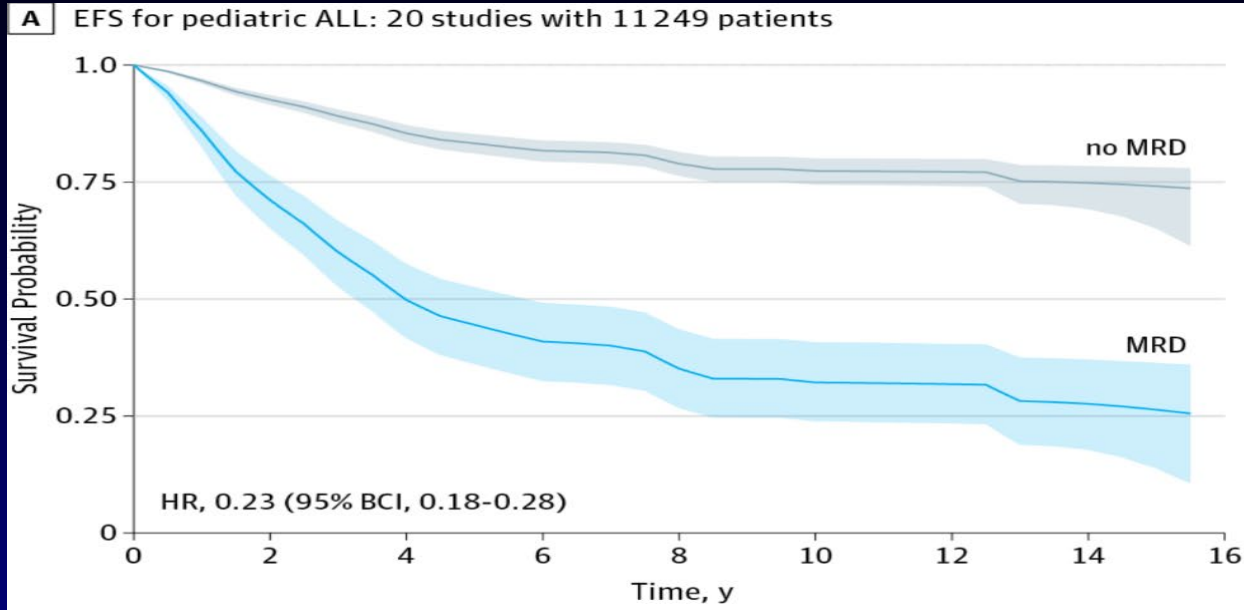
OS by Age



CD20-CD3 BiTEs in DLBCL (ASH 2020)

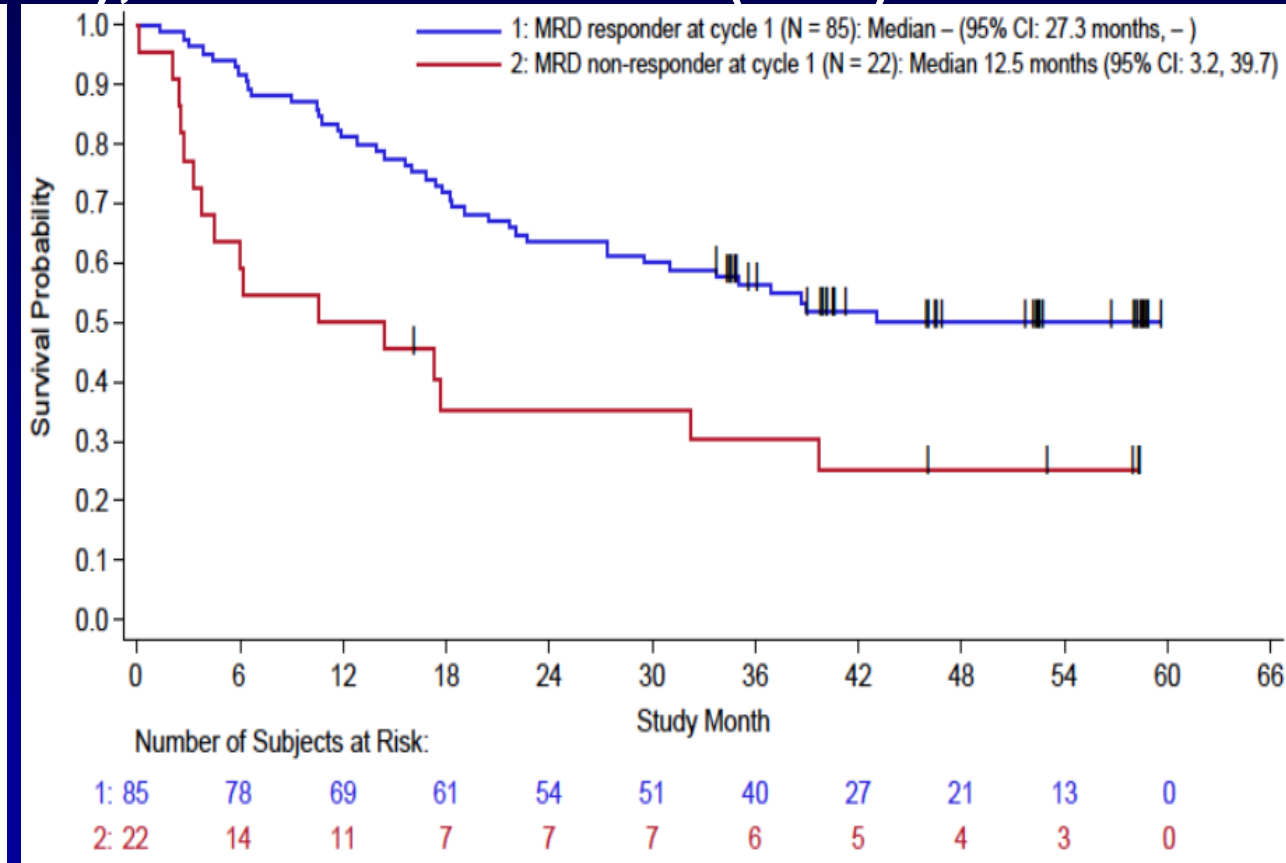
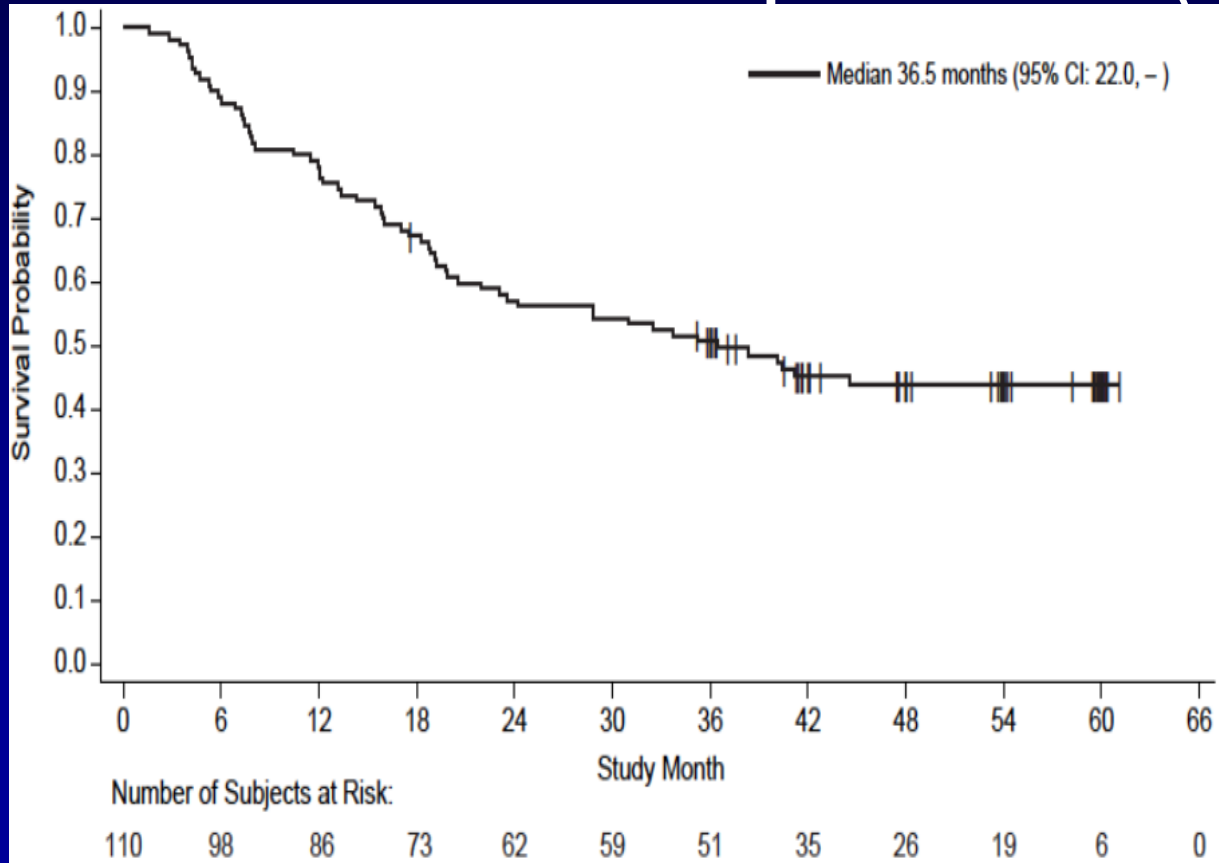
	Mosunetuzumab (Genentech) Olszewski (N=29)	Odronextamab (REGN1979) Bannerji (N=78)	Glofitamab (Roche/Genentech) Hutchings (N=28)	Epcoritamab (Genmab/AbbVie) Hutchings (N=46)
Patient population	Frontline DLBCL (older adults)	R/R DLBCL	R/R DLBCL	R/R DLBCL
Administration	IV	IV	IV (+obinutuzumab)	SQ
Median age	82 (67-100)	67 (27-89)	68 (44-85)	68 (21-82)
Median prior therapies	none	3	3	3
ORR (CR)	63% (45%) n=22	40% (31%) n=35	61% (54%) n=28	68% (46%) n=22
CRS	G1-2: 21% G3-4: 0%	G1-2: 54% G3-4: 7%	G1-2: 62% G3-4: 2%	G1-2: 59% G3-4: 0%

MRD in ALL

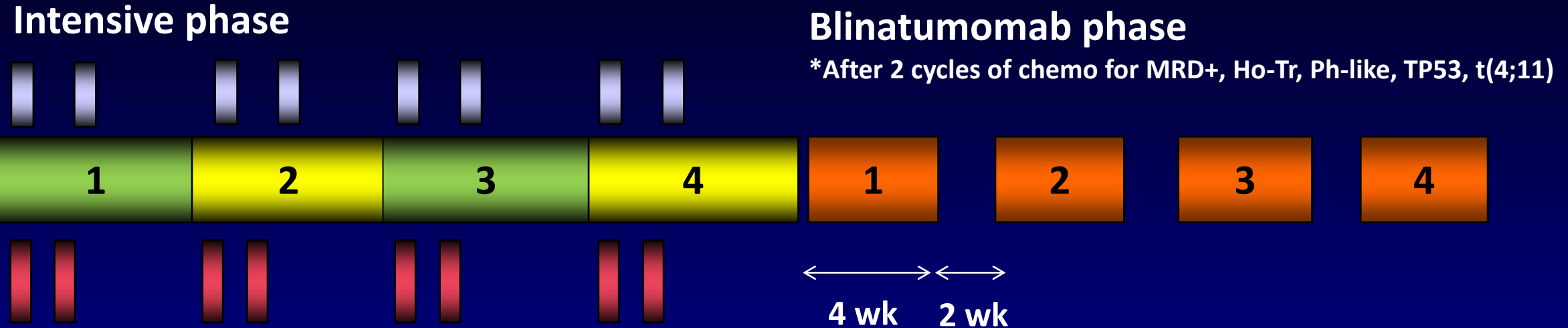


Blinatumomab for MRD-positive ALL in CR1/CR2

- 113 pts Rx. Post blina MRD-negative 88/113=78%
- 110 evaluated (blasts <5%, MRD+≥0.1%). 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%)**









Hyper-CVAD + Blinatumomab in B-ALL: Regimen



Maintenance phase

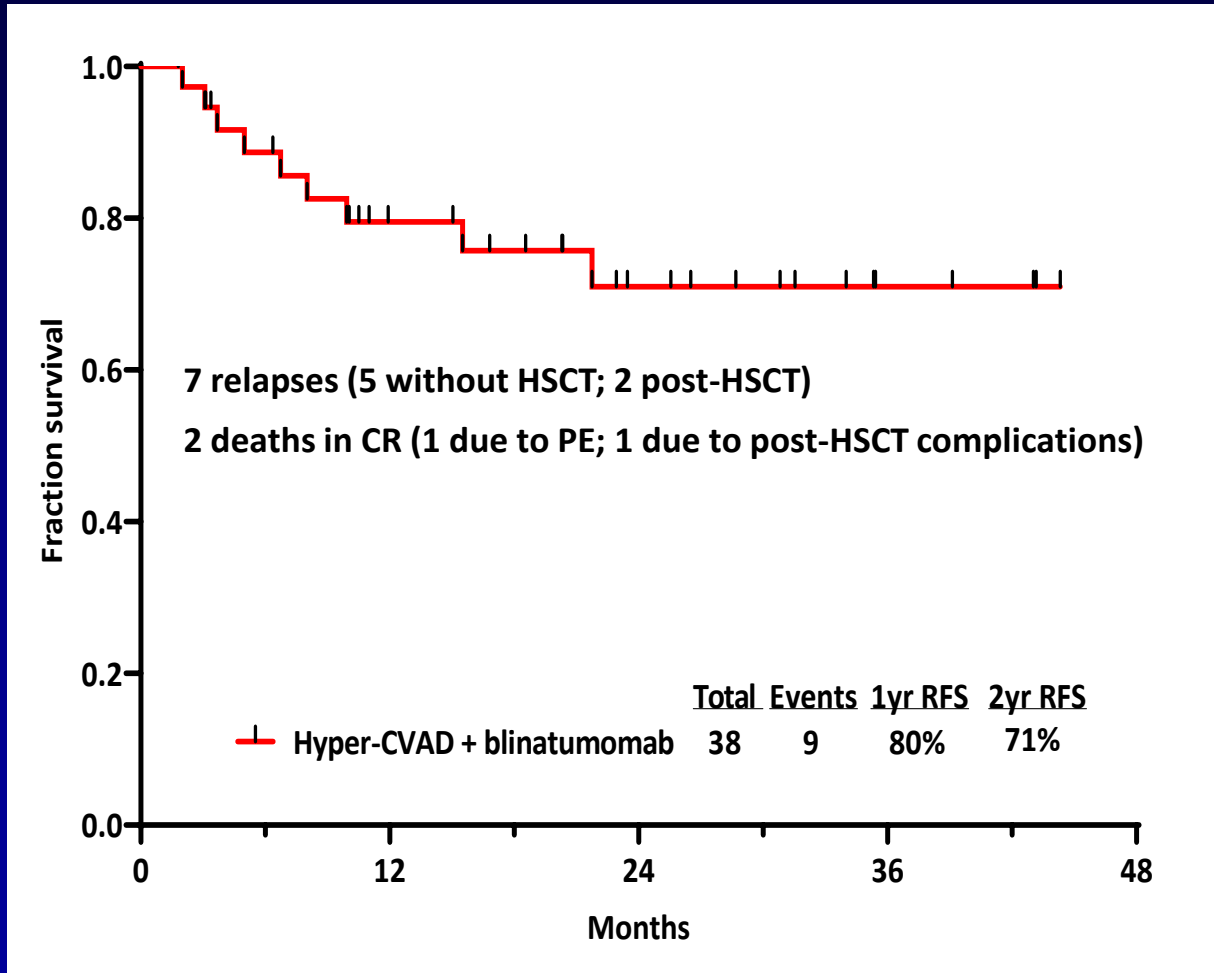


-  **Hyper-CVAD**
-  **Ofatumumab or rituximab**
-  **Blinatumomab**
-  **MTX + Ara-C**
-  **IT MTX / Ara-C x 8**
-  **POMP**

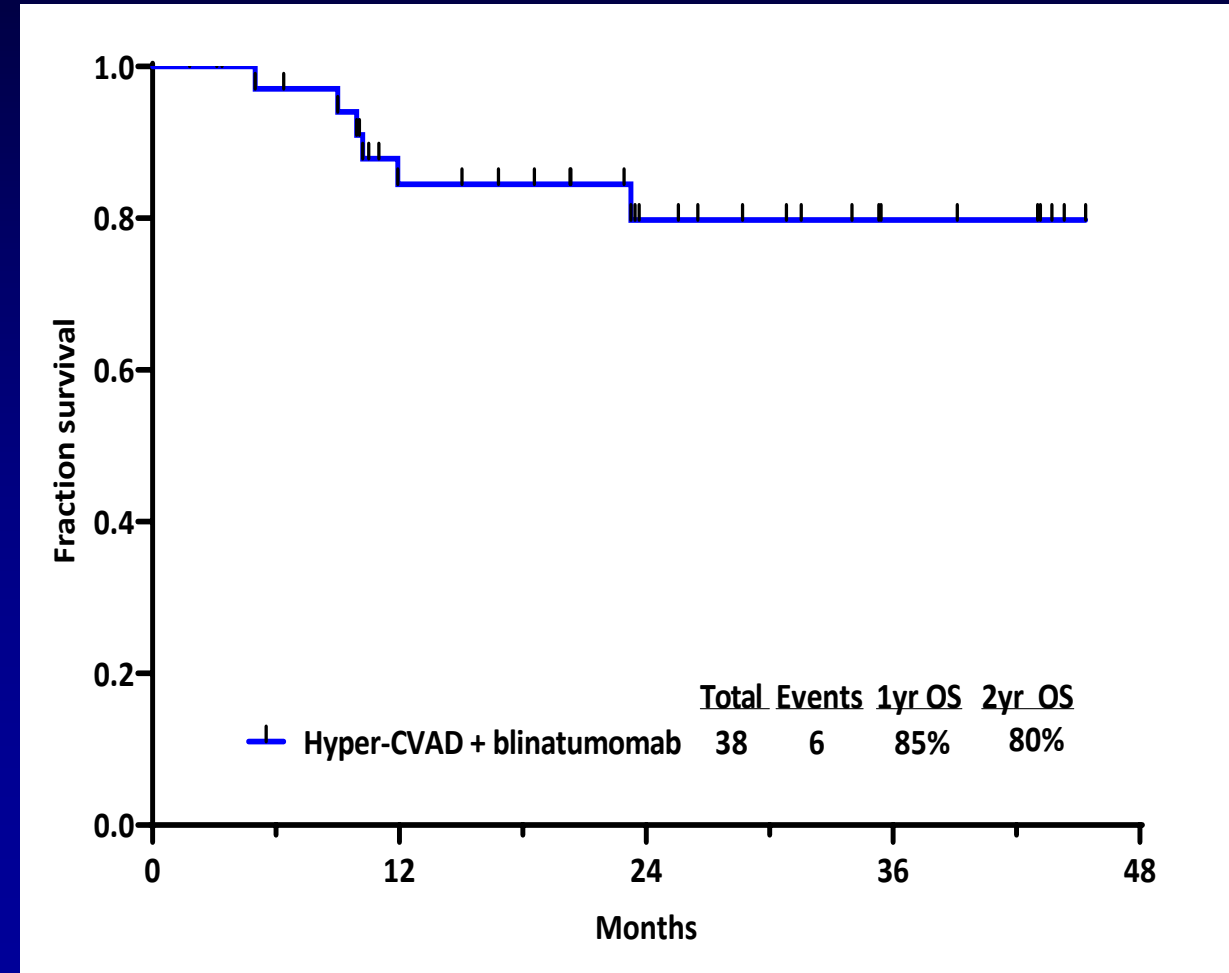
Hyper CVAD → Blinatumomab in Newly Dx Adult ALL

- 38 pts; median age 36 yrs (17-59 yrs). Rx with O-HCVAD x 4 → POMP 1 yr with blina Q3 mos
- CR rate 100%; MRD negative 97% (71% at CR); **60-day mortality 0%**; 12 (32%) allo-SCT; F/U 24 mos

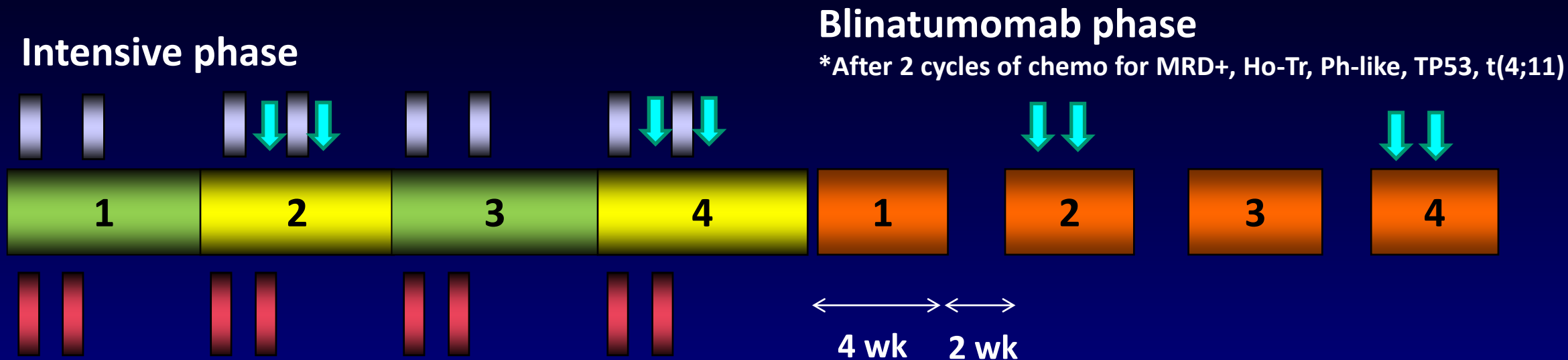
RFS



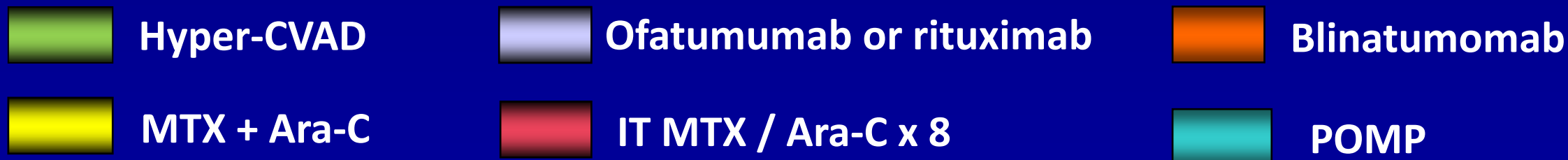
OS



Hyper-CVAD + Blinatumomab/Inotuzumab in B-ALL



Maintenance phase



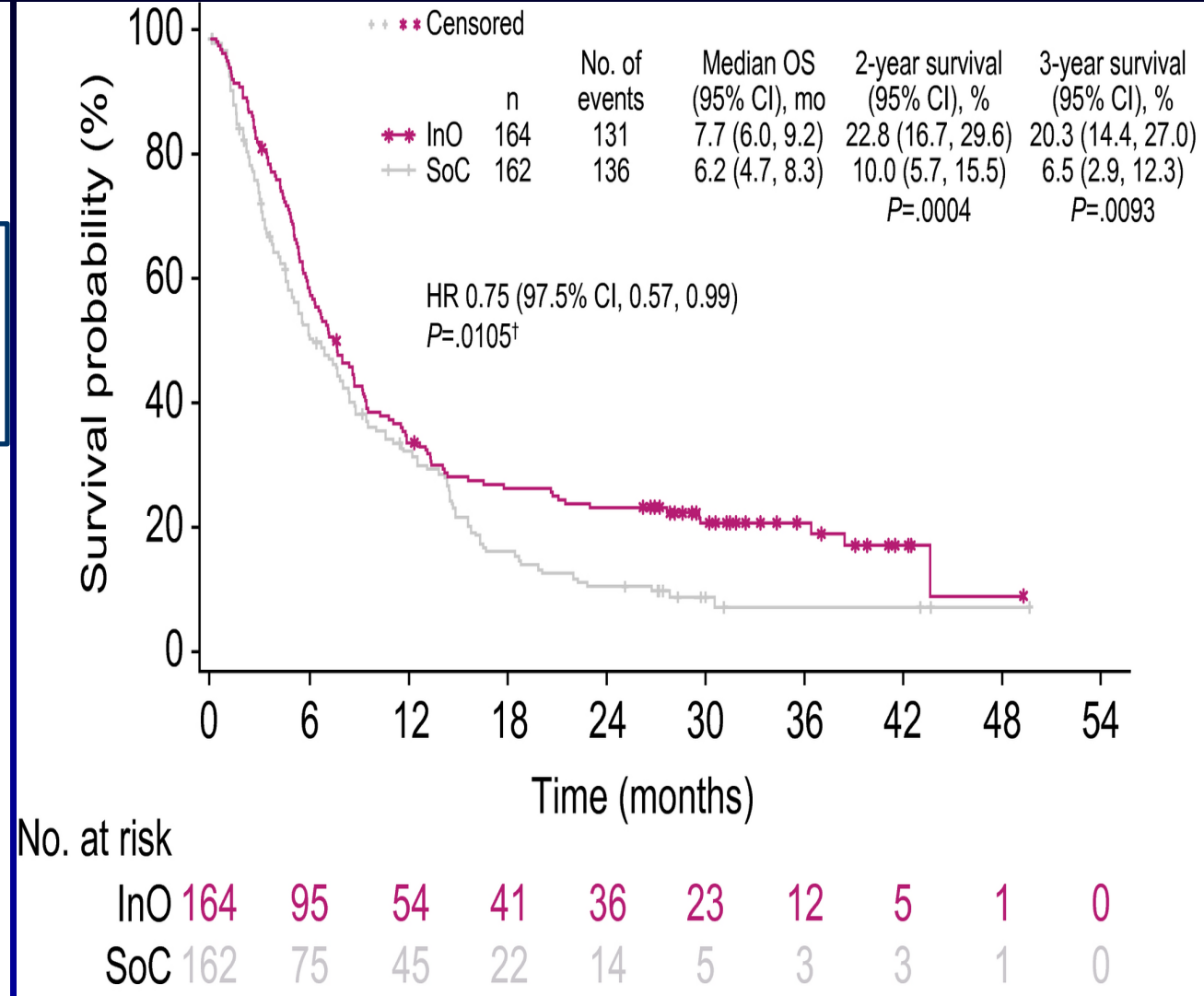
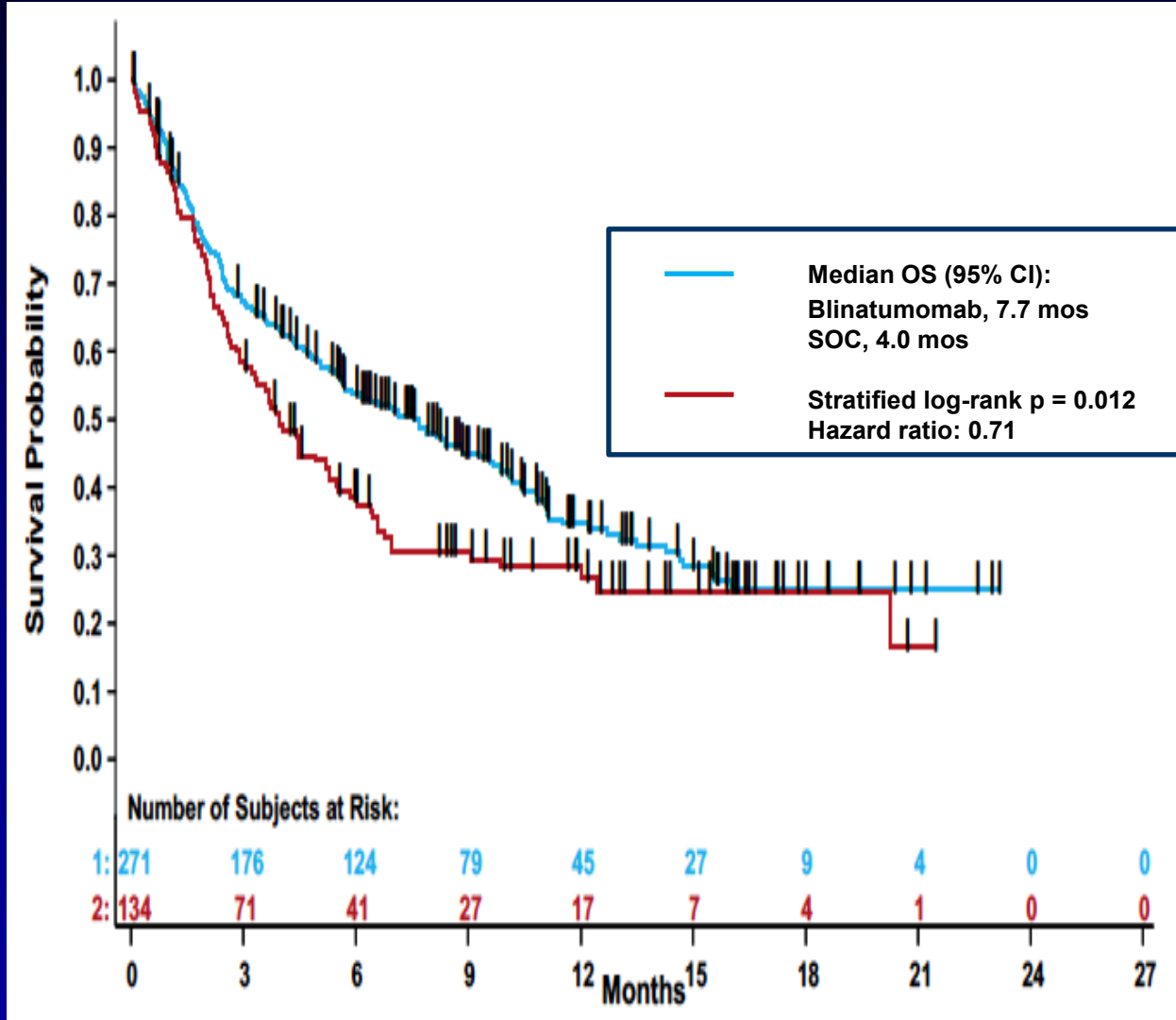
  Inotuzumab 0.3 mg/m² on D1 and D8

Blinatumomab/Inotuzumab vs ChemoRx in R-R ALL

- Marrow CR

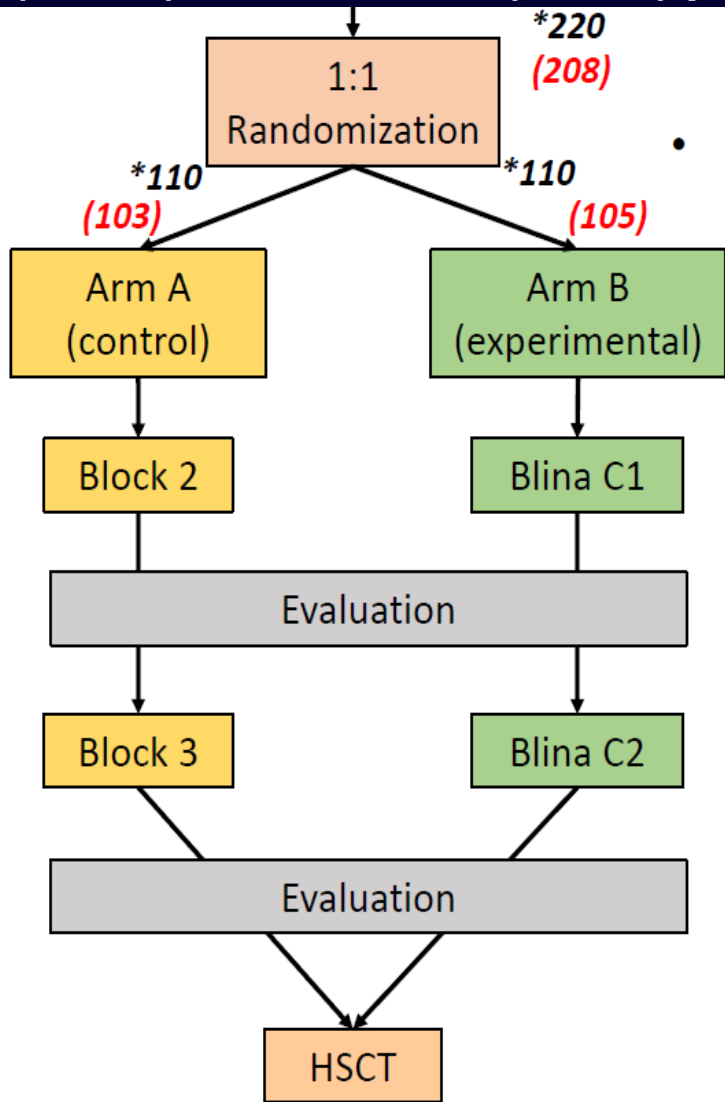
Blina vs SOC: 44% vs 25%

Ino vs SOC: 74% 31%

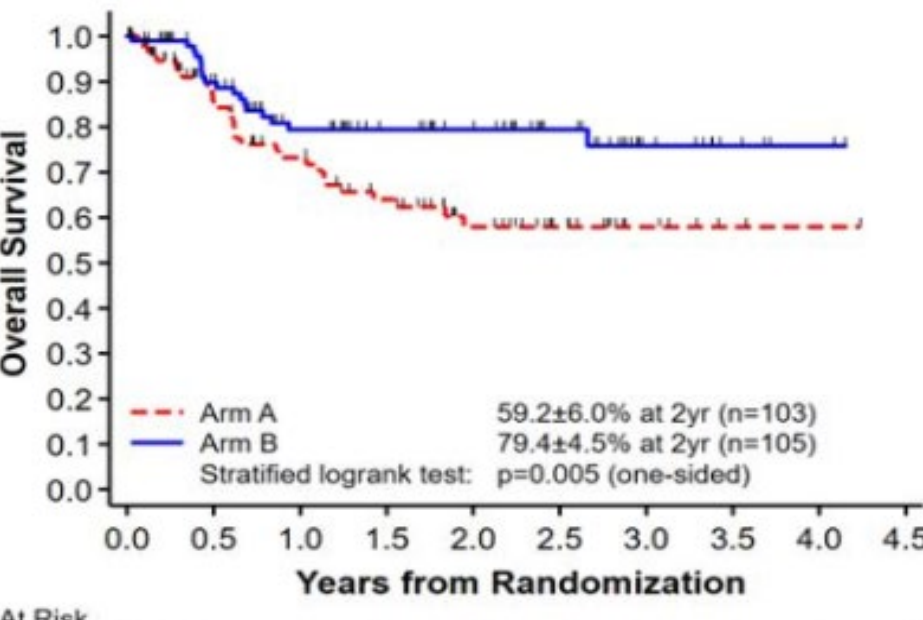
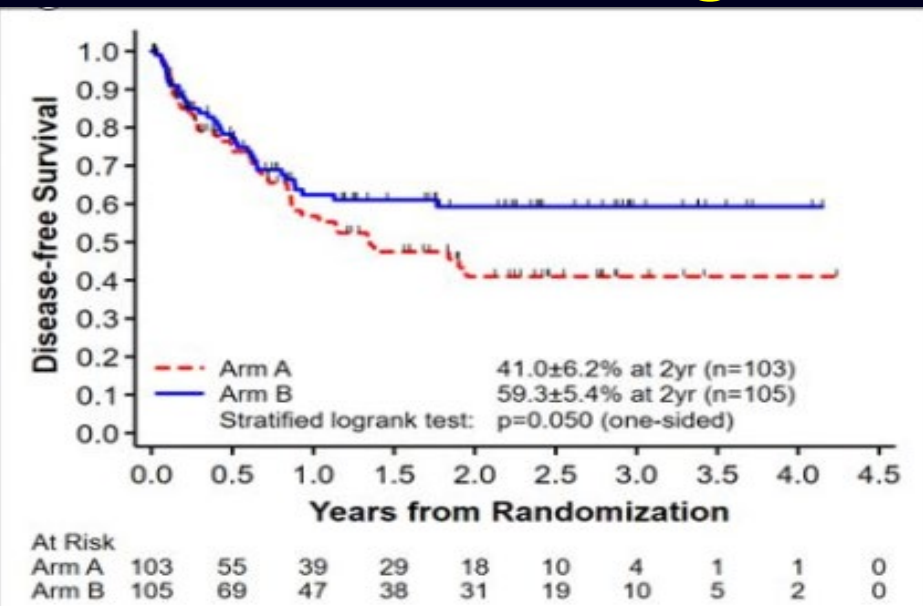


Phase 3 Blinatumomab vs ChemoRx in Children-AYA in Salvage 1

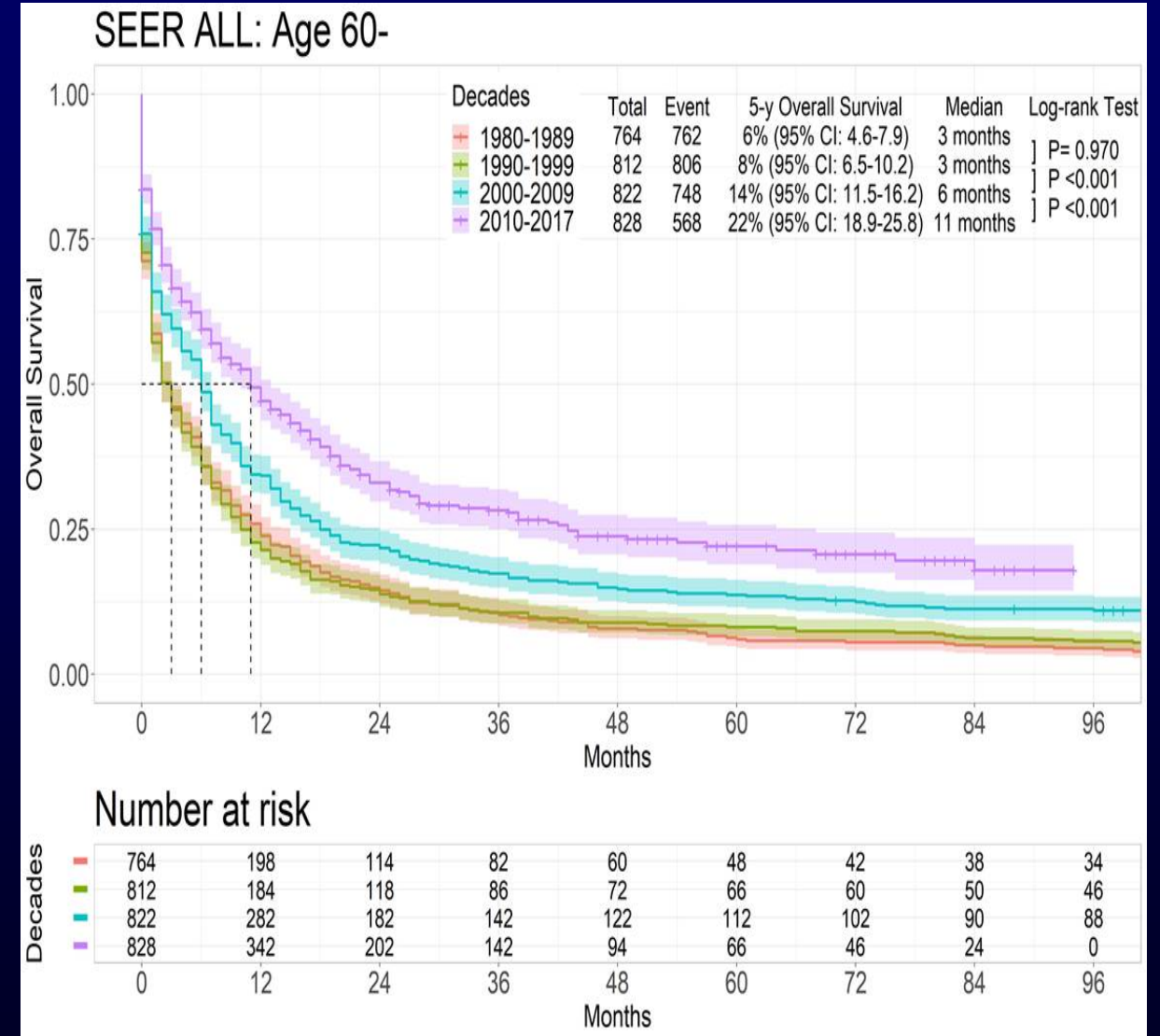
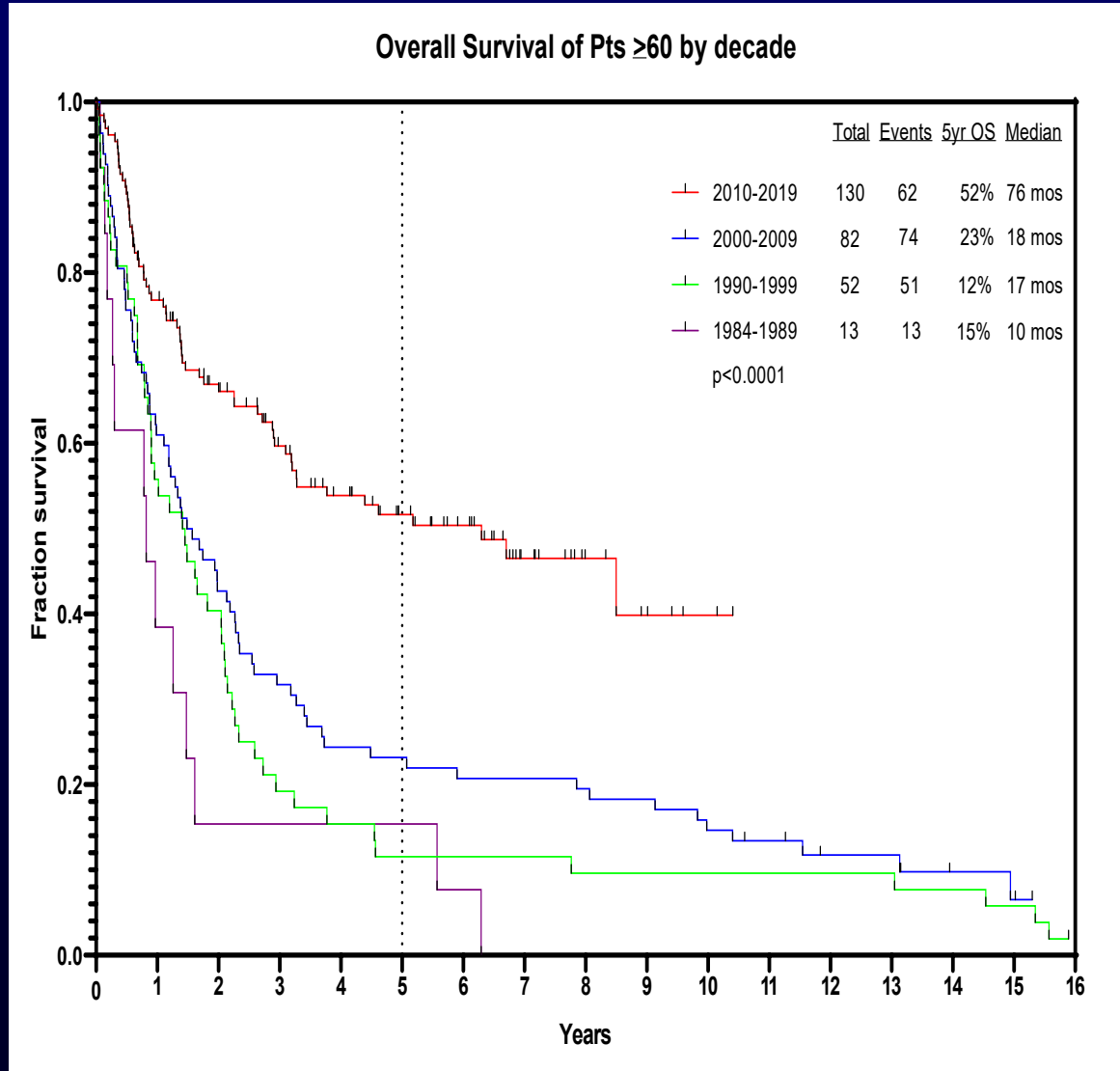
- 208 pts HR/IR randomized 1:1 to blina (n=105) vs chemo Rx (n=103) post Block 1 reinduction



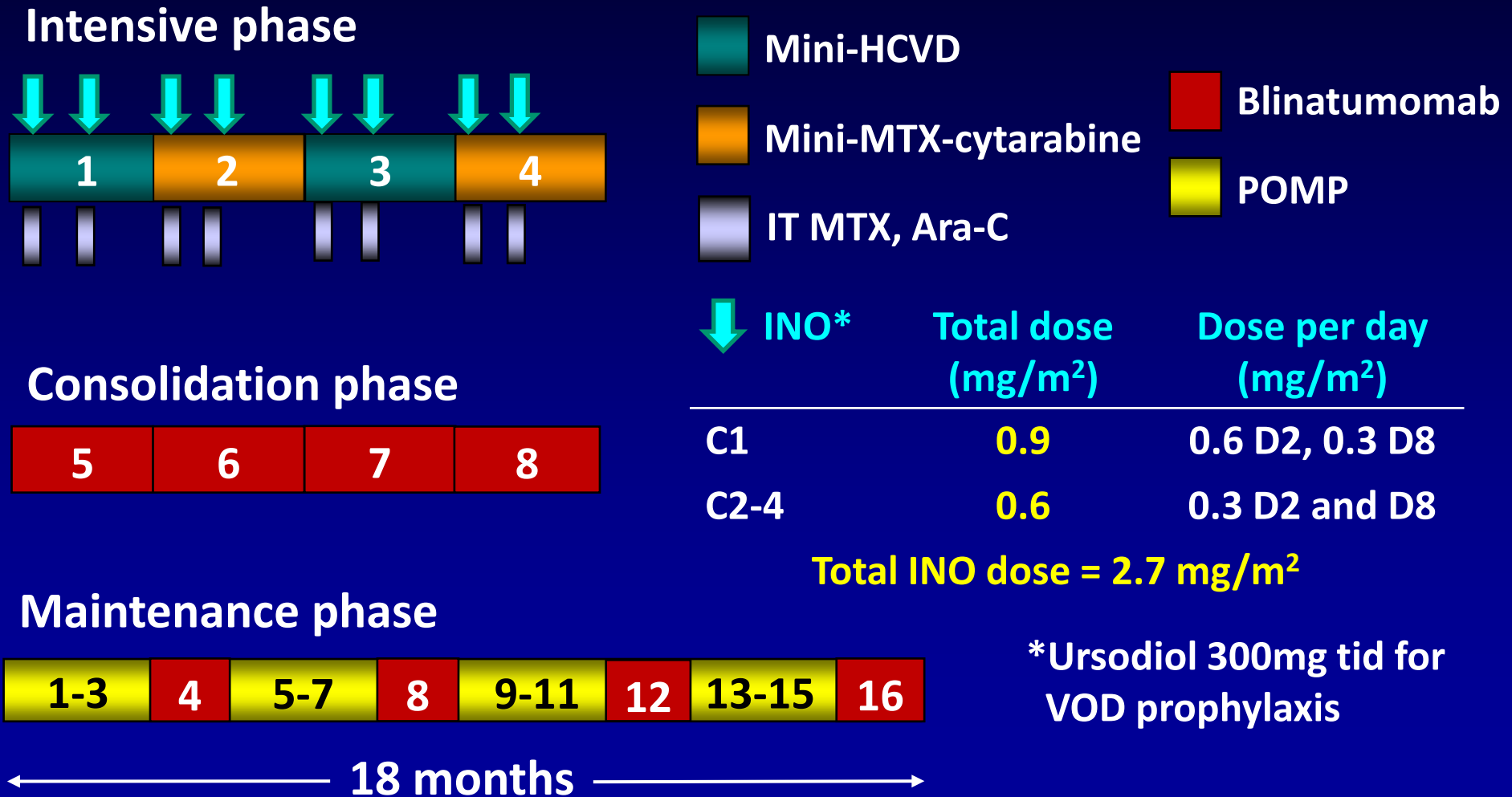
Parameter	Blina	Chemo	p
%2-yr DFS	59	41	.05
%2-yr OS	79	59	.005
% SCT	73	49	<.001
% MRD clearance	79	21	<.001



MDACC ALL. Survival by Decades for ≥ 60 years



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



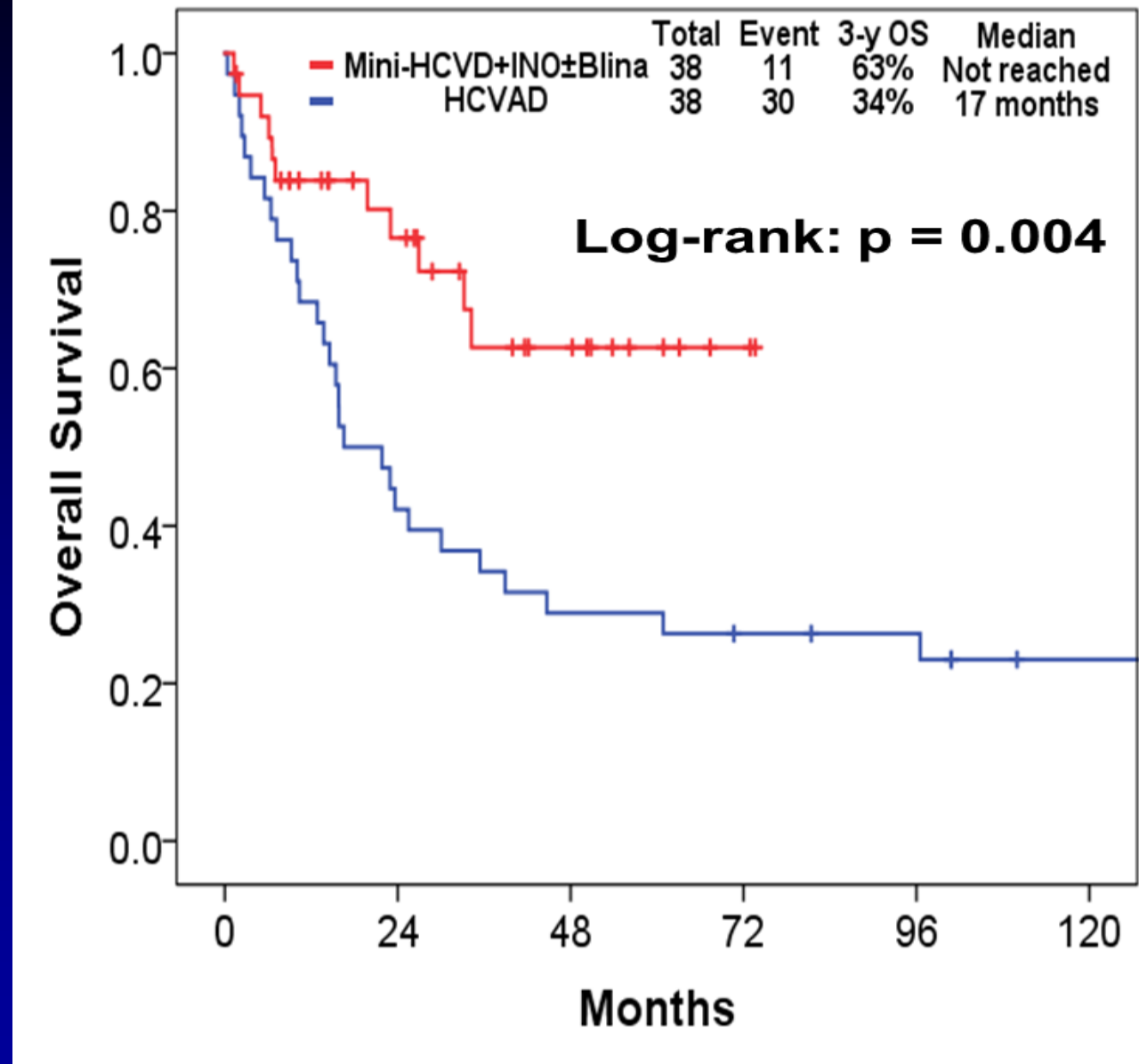
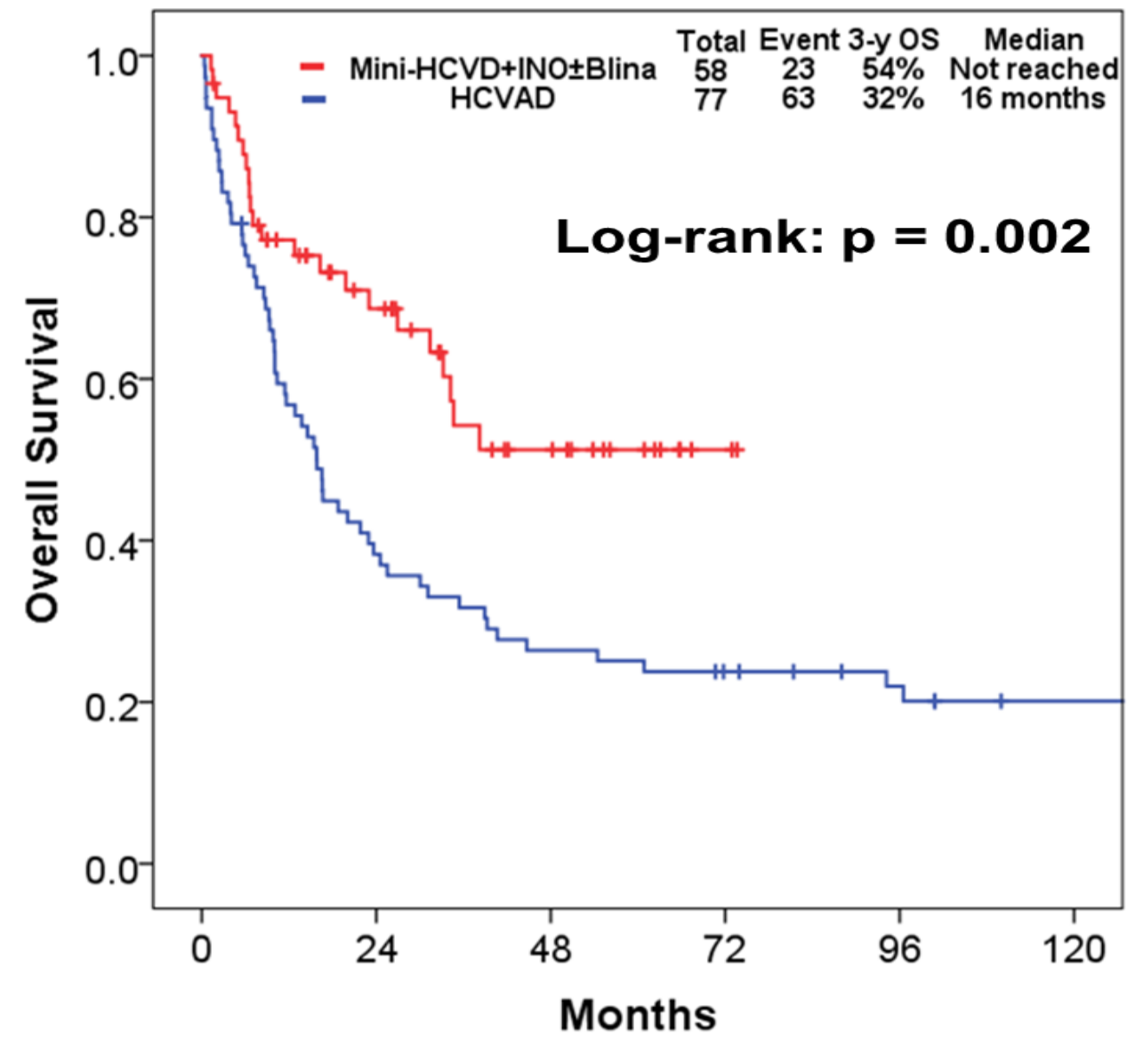
Mini-HCVD + INO ± Blina in Older ALL. (N=70)

Characteristic	Category	N (%) / median [range]
Age (years)		68 [60-81]
	≥70	29 (41)
Performance status	≥2	10 (14)
WBC (x10 ⁹ /L)		3.1 [0.6-111.0]
Karyotype	Diploid	23 (33)
	HeH	5 (7)
	Ho-Tr	12 (17)
	Tetraploidy	3 (4)
	Complex	3 (4)
	t(4;11)	1 (1)
	Misc	10 (14)
	IM/ND	13 (19)
CNS disease at diagnosis		4 (6)
CD19 expression (%)		99.6 [30-100]
CD22 expression (%)		96.7 [27-100]
CD20 expression	≥ 20%	38/64 (59)
CRLF2+ by flow		7/38 (18)
TP53 mutation		21/51 (41)

Response (N=64*)	N (%)
ORR	63 (98)
CR	56 (88)
CRp	6 (9)
CRi	1 (2)
No response	1 (2)
Early death	0
Flow MRD response	N (%)
D21	53/66 (80)
Overall	65/68 (96)

Mini-HCVD + INO ± Blina vs. HCVD in elderly ALL. Survival

Pre-matched Matched



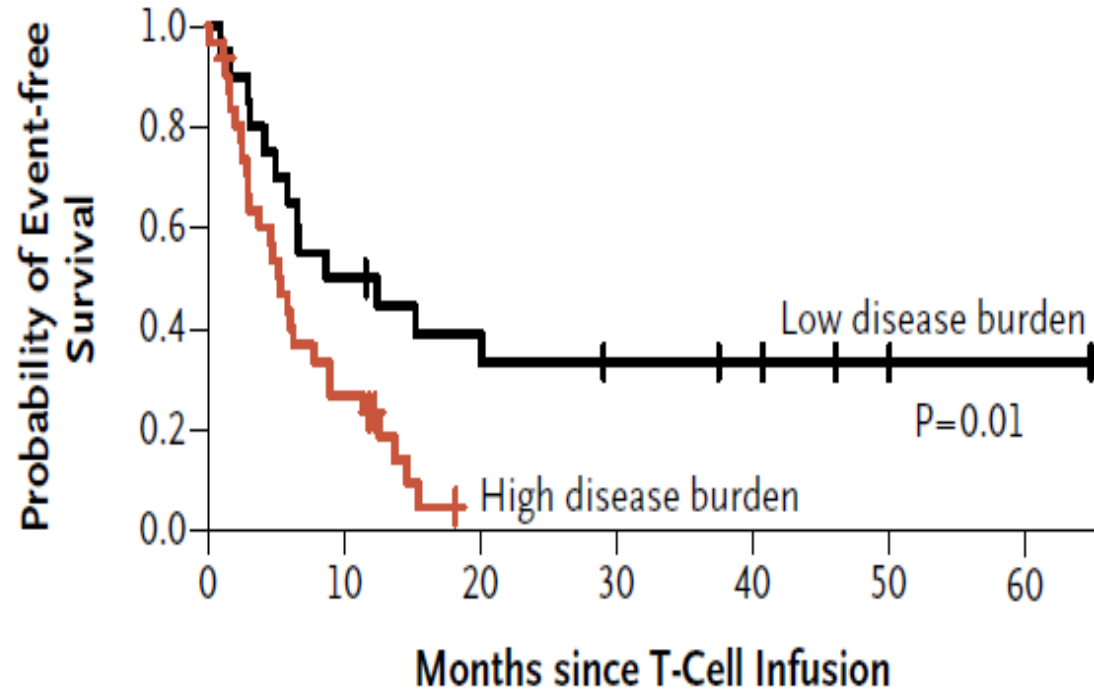
Inotuzumab Followed by Chemo Rx in ALL 55+ Yrs

- Course 1- Ino 0.8mg/m² D1, 0.5g/m² D8 and 15 (1.8mg/m²) in Course 1
 - CTX-VCR-steroids pre phase – TIT x 1/course
- Courses 2 & 3- Ino 0.5 mg/m² Days 1, 8, 15 (1.5 mg/m²)
 - 5 consolidations: 3 MTX/Asp, 2 ID-ara-C→1 reinduction IDA-ara-C-CTX-Dex
 - 6MP-MTX maintenance x 1.5 yr
- 36 Rx, results in 31; Median age 65 years (56-80)
- **CR/CRI 31/31 (100%); MRD negative 21/27 (78%)**
- **1-yr OS 87%; 1-yr EFS 87%**
- **No VOD**

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

- High tumor burden : BM blasts $\geq 5\%$ (n=27) ; BM blasts $< 5\%$ + EM disease (n=5)
- Low tumor burden (MRD+ disease) (n=21)

A Event-free Survival, According to Disease Burden



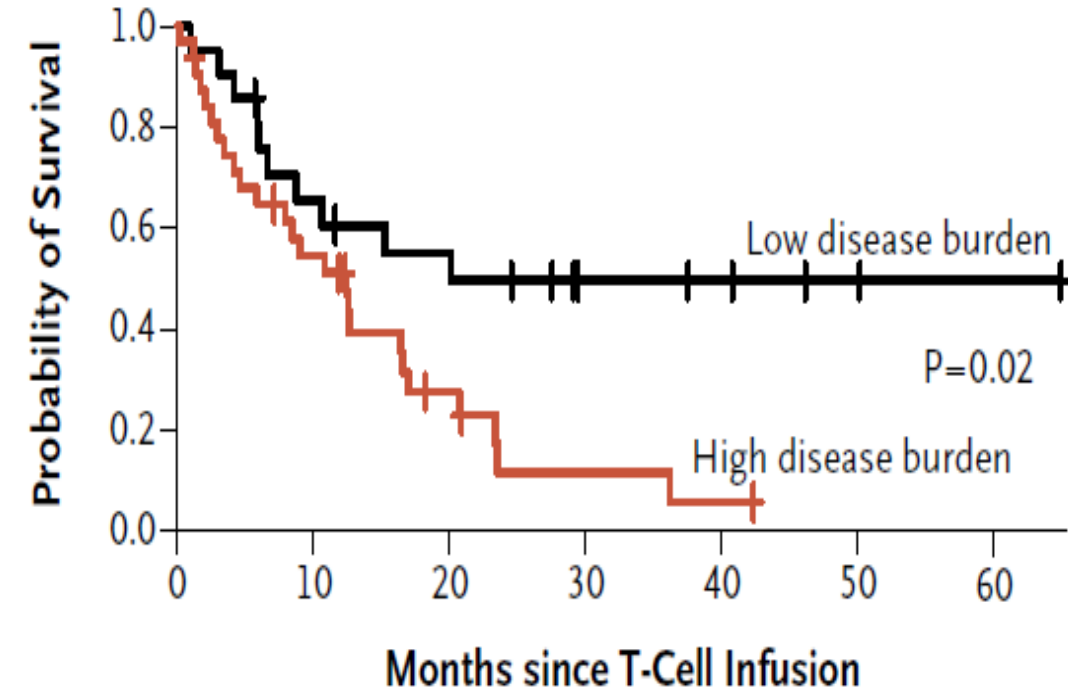
No. at Risk

Low burden	20	10	7	5	4	2	1
High burden	31	8	0	0	0	0	0

Median EFS

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

B Overall Survival, According to Disease Burden



No. at Risk

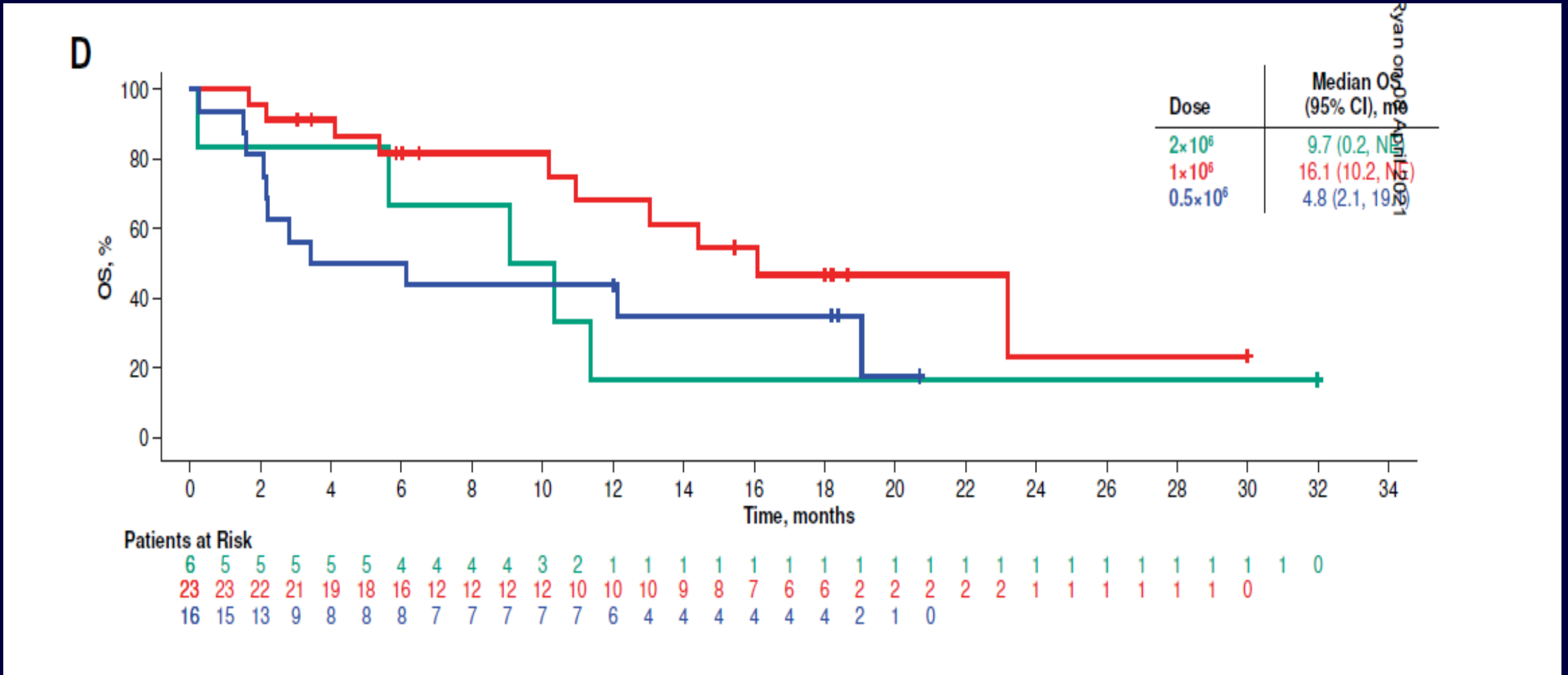
Low burden	21	13	10	5	4	2	1
High burden	32	16	6	2	1	0	0

Median OS

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

KTE-X19 anti-CD19 CAR T-cells (Kite) in R-R ALL. Phase 1/2 (ZUMA-3)

- 54 screened, 49 enrolled, 45 infused
- **ORR 31/45 = 69% (31/49 enrolled = 63%). CR 24/45= 53% MRD- 100% of responders**
- **mDOR 17.6 mos; mRFS 7.7 mos; mOS 16.1 mos . Grade ≥ 3 : CRS 31%; CNS 38%**

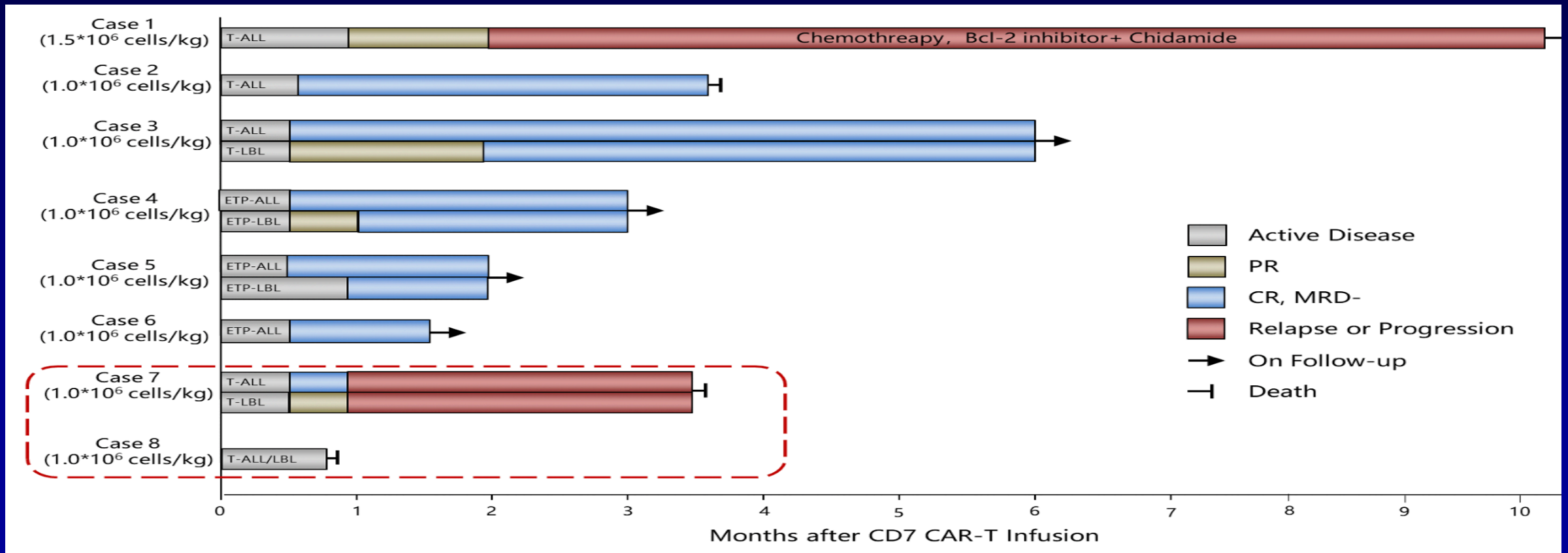


Dual-Targeting (CD19-CD22) CAR T in R/R ALL

- GC022F (auto CD19 x CD22 CAR-T): 24-hour manufacturing turnaround time
- 10 patients (9 pediatric and 1 adult); 3 had prior CD19 CAR-T, 1 had prior ASCT
- No $G \geq 3$ CRS or neurotoxicity
- 6 patients with $>5\%$ blasts at baseline : CR 100%, MRD- 83% (5/6)
- 4 patients with MRD+ disease at baseline : MRD- 75% (3/4)
- At last follow up, 50% of patients in MRD- CR

CD7 CAR T in R/R T-ALL/LBL

- 8 pts (3 ETP-ALL) Rx
- 5/8 CR; all 3 ETP-ALL achieved CR, all neg MRD CR
- No G \geq 3 CRS (1 Grade 2 and 2 Grade 1)
- No NT observed



Antibodies vs CART in ALL. Comparing Apples to Apples

Age Group	Salvage	Rx	%CR	% OS (x yr)
Pedi	S1	Blinatumomab	79	79(2)
	S2	Inotuzumab	62	40(1)
	S2	CART	67(82% of infused)	66(2)
Adult	S1	Mini-CVD-ino-blina	91	40(3)
	S2-S3	Mini-CVD-ino-blina	57-61	20-40(2)
	S2+	CART (Active ALL)	65	10-20(2)

CAR-T in ALL – The Beginning of a Great Journey

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

Antibodies and CAR-T in ALL – Summary

- Antibody based Rxs and CARTs both outstanding
- Not mutually exclusive/competitive (versus); 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) CARTs in sequence in CR1 for MRD and replacing allo SCT
- SQ easily deliverable BiTEs

Leukemia Questions?

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