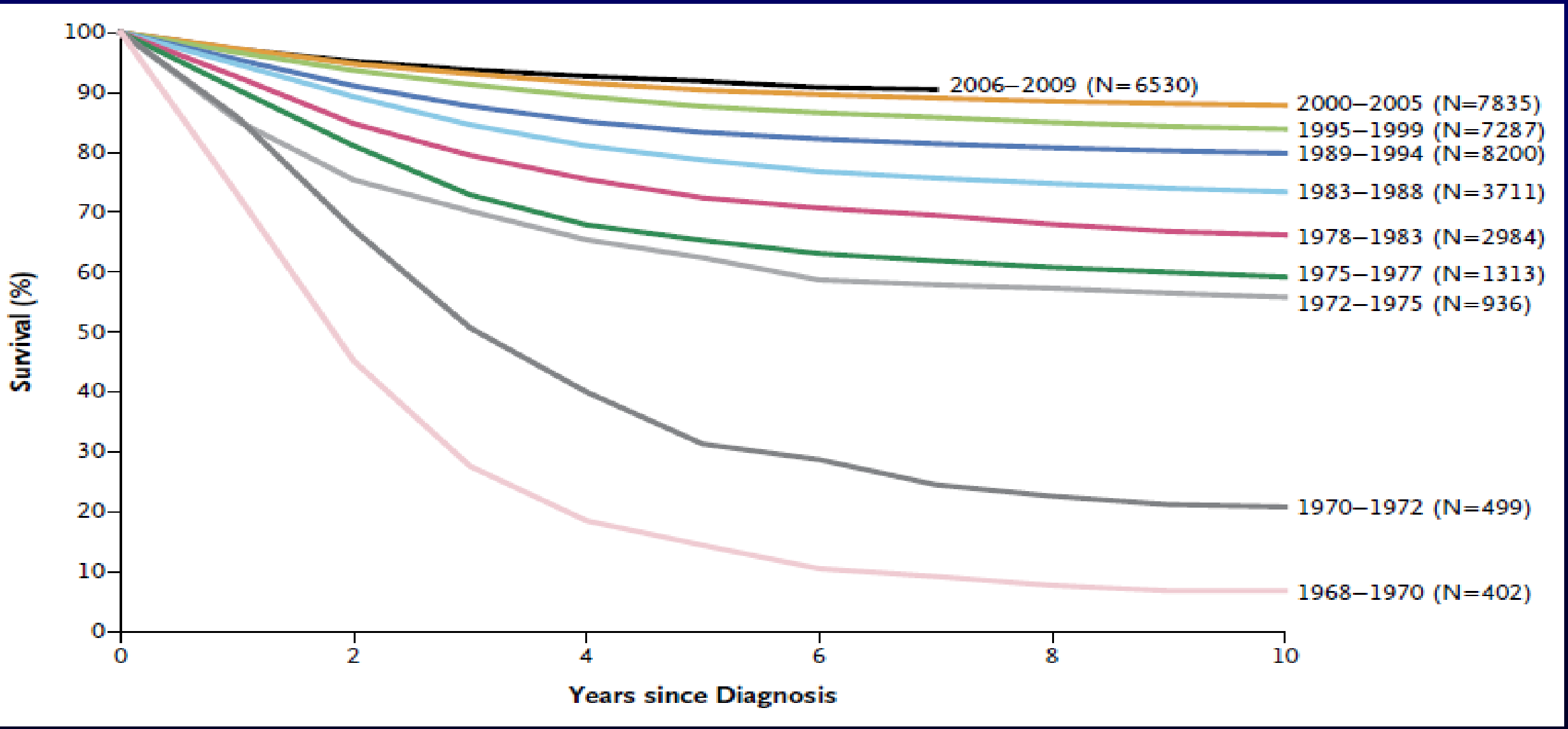
Adult ALL – Novel targeted Therapies in 2020

Hagop Kantarjian, M.D.

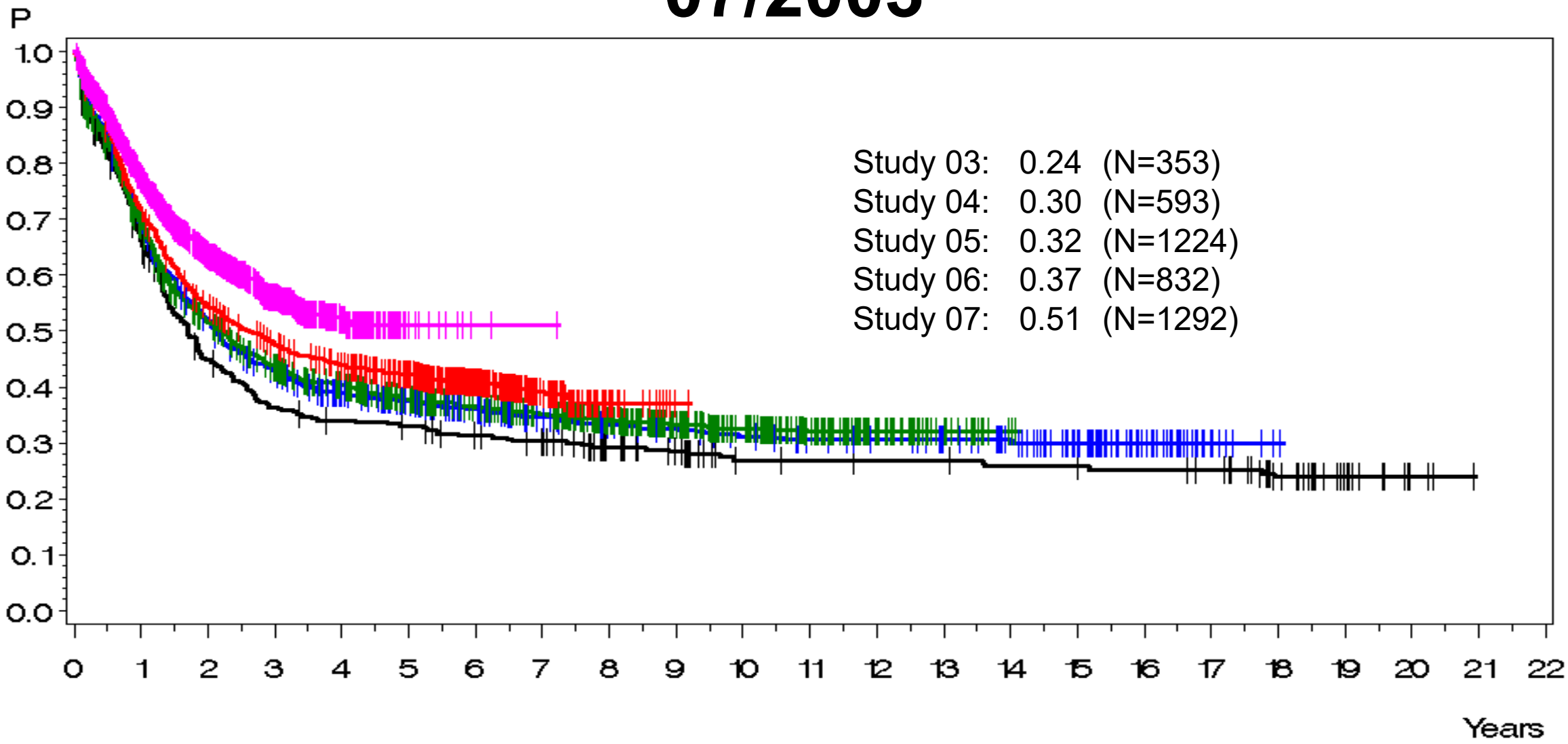
Indianapolis Hematology review, 2020

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

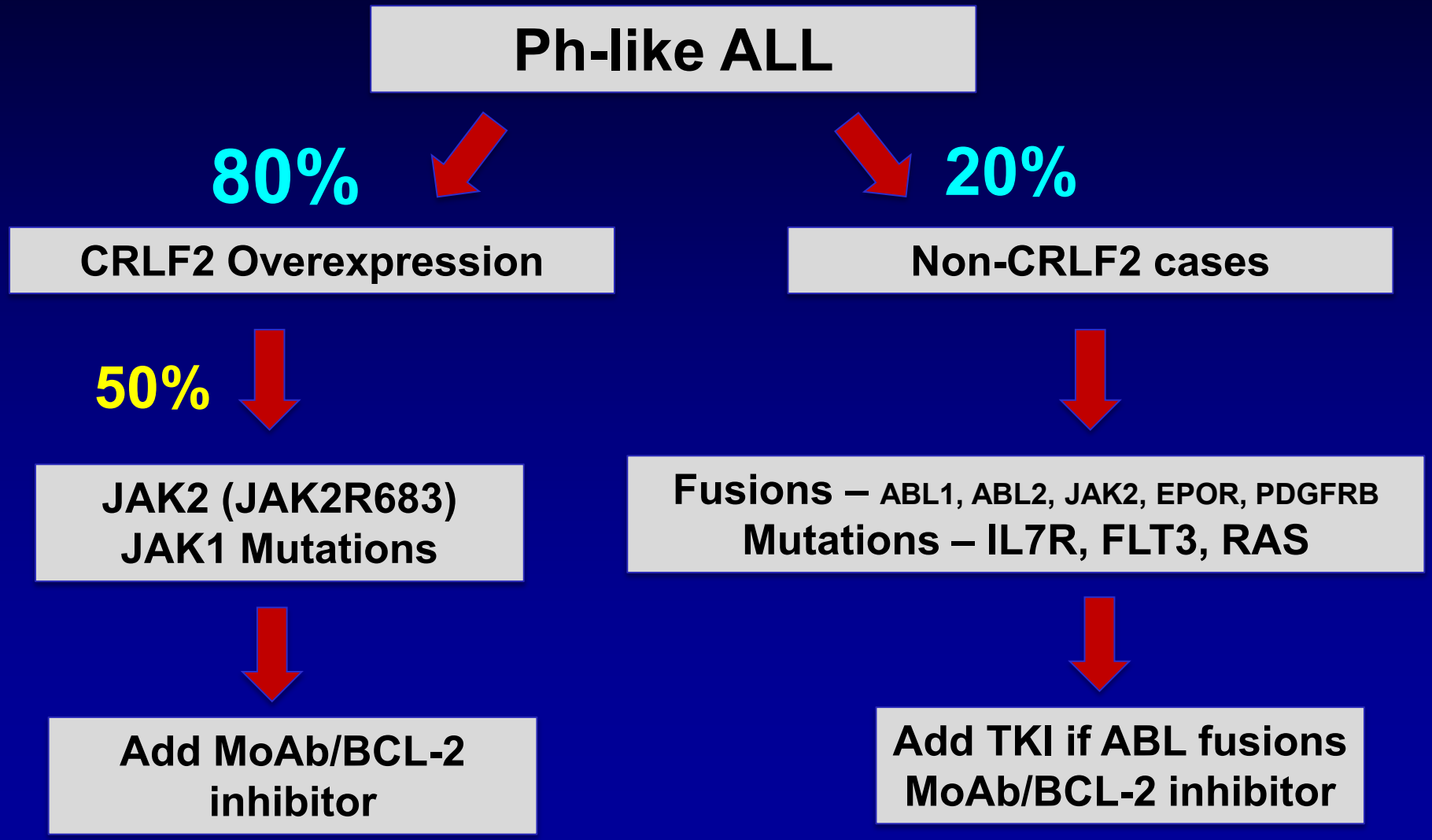


Reasons Why Pediatric ALL Does Better Than Adult ALL

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

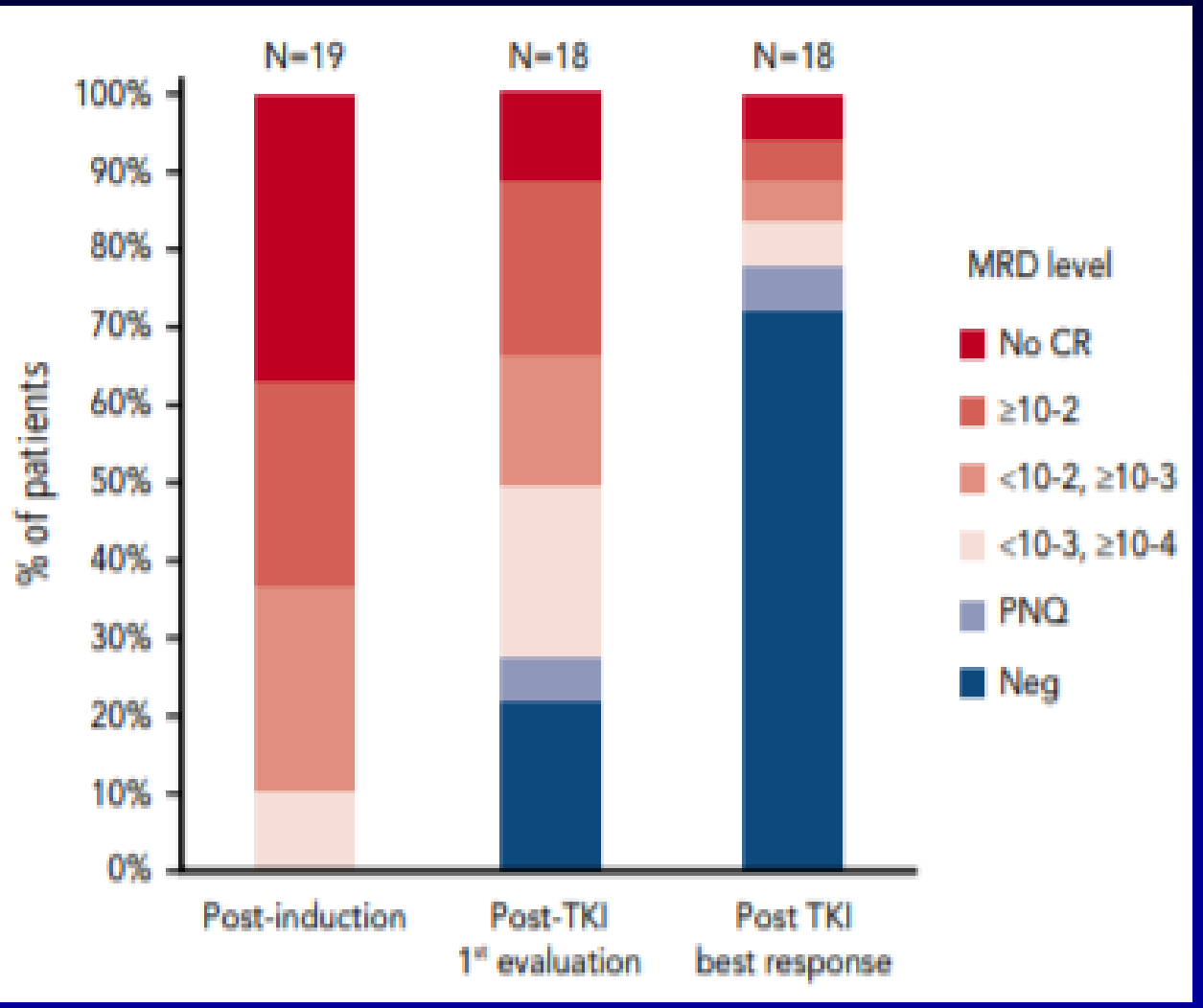
Ph-like ALL Molecular Lesions

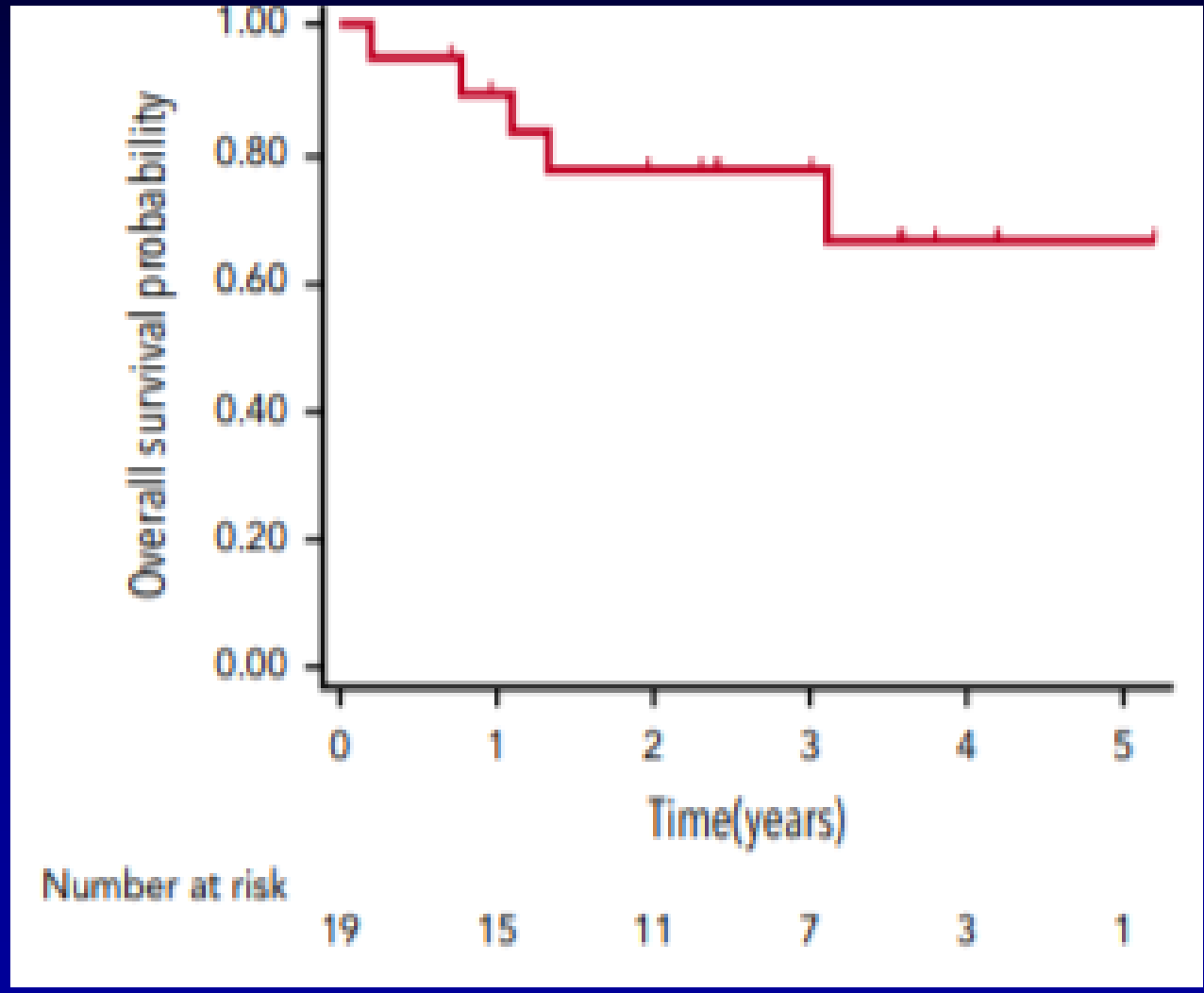
- Ph-like 25-30% of ALL; poor prognosis



BCR-ABL TKIs + Chemo Rx in Ph-like ALL

- 24 pts with Ph-like ALL: NUP214-ABL1-- 6, ETV6-ABL1-- 3, others -- 9. 19 frontline; 5 relapse.All Rx with chemo Rx + TKI



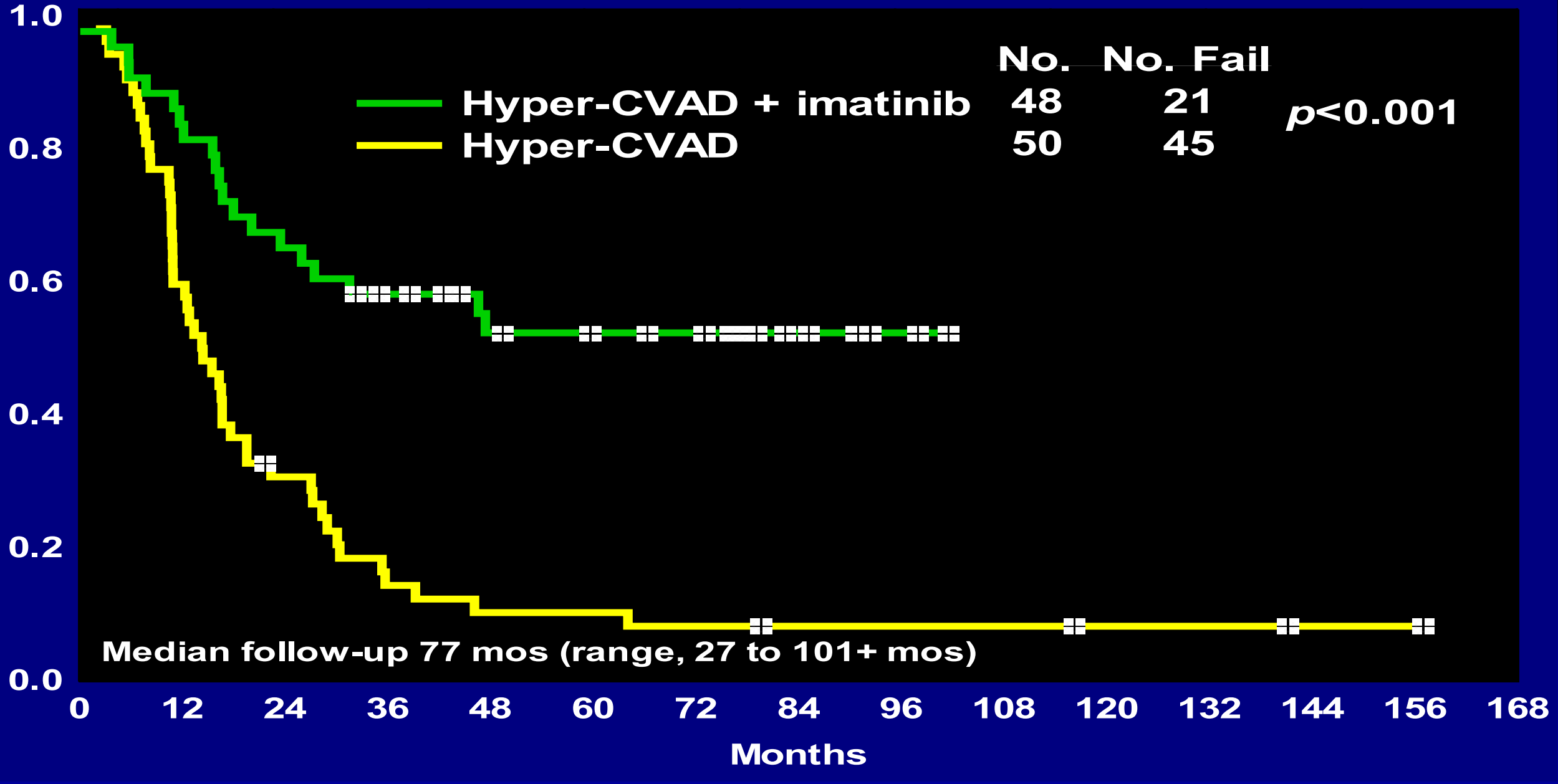


Tanasi. Blood 134: 1351; 2019

Reasons for Recent Success in Adult ALL Rx

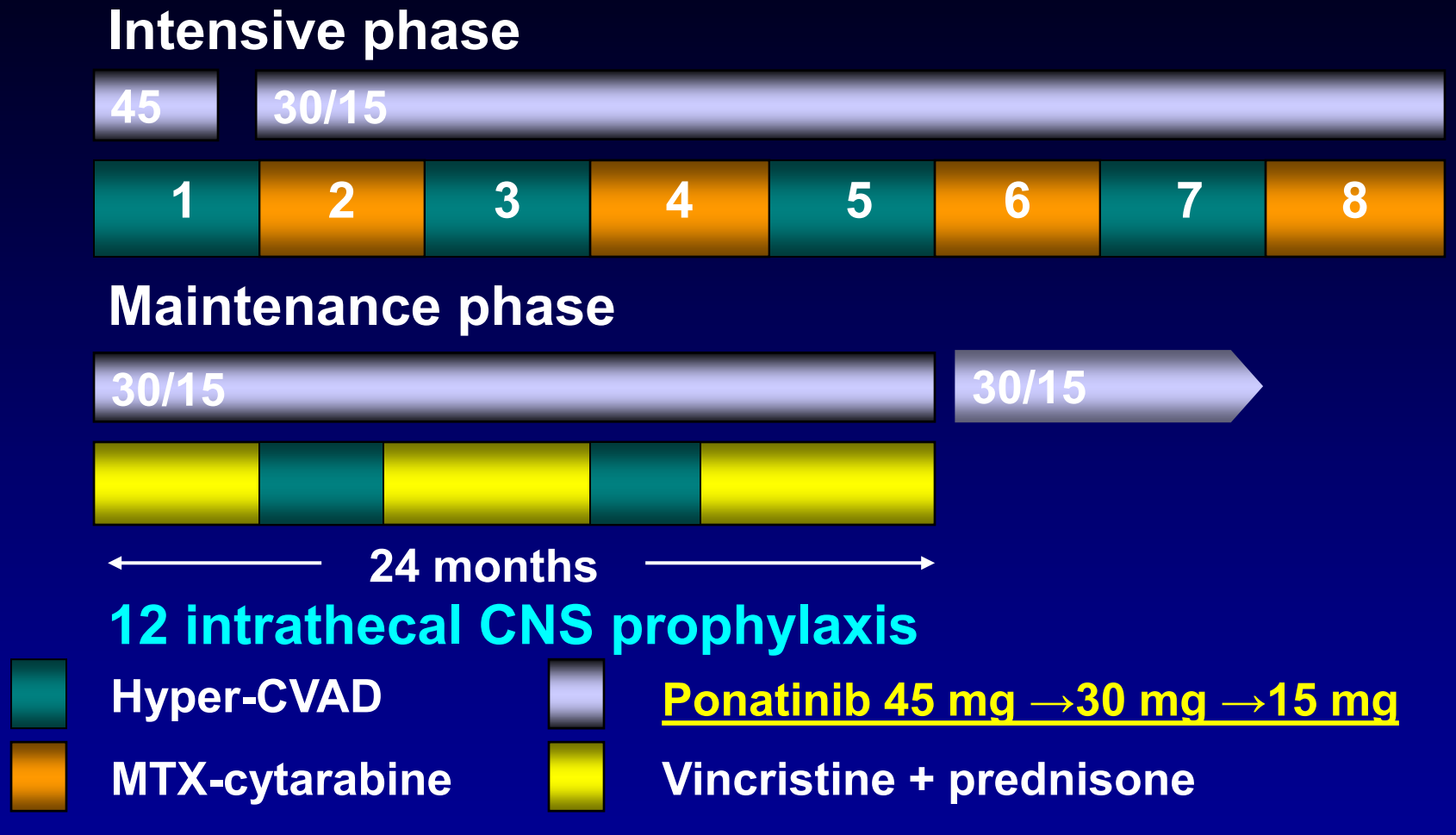
- Addition of TKIs to chemoRx in Ph-positive ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Potential benefit of addition of CD19 antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx
- CAR-T therapy

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



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

Hyper-CVAD + Ponatinib. Design

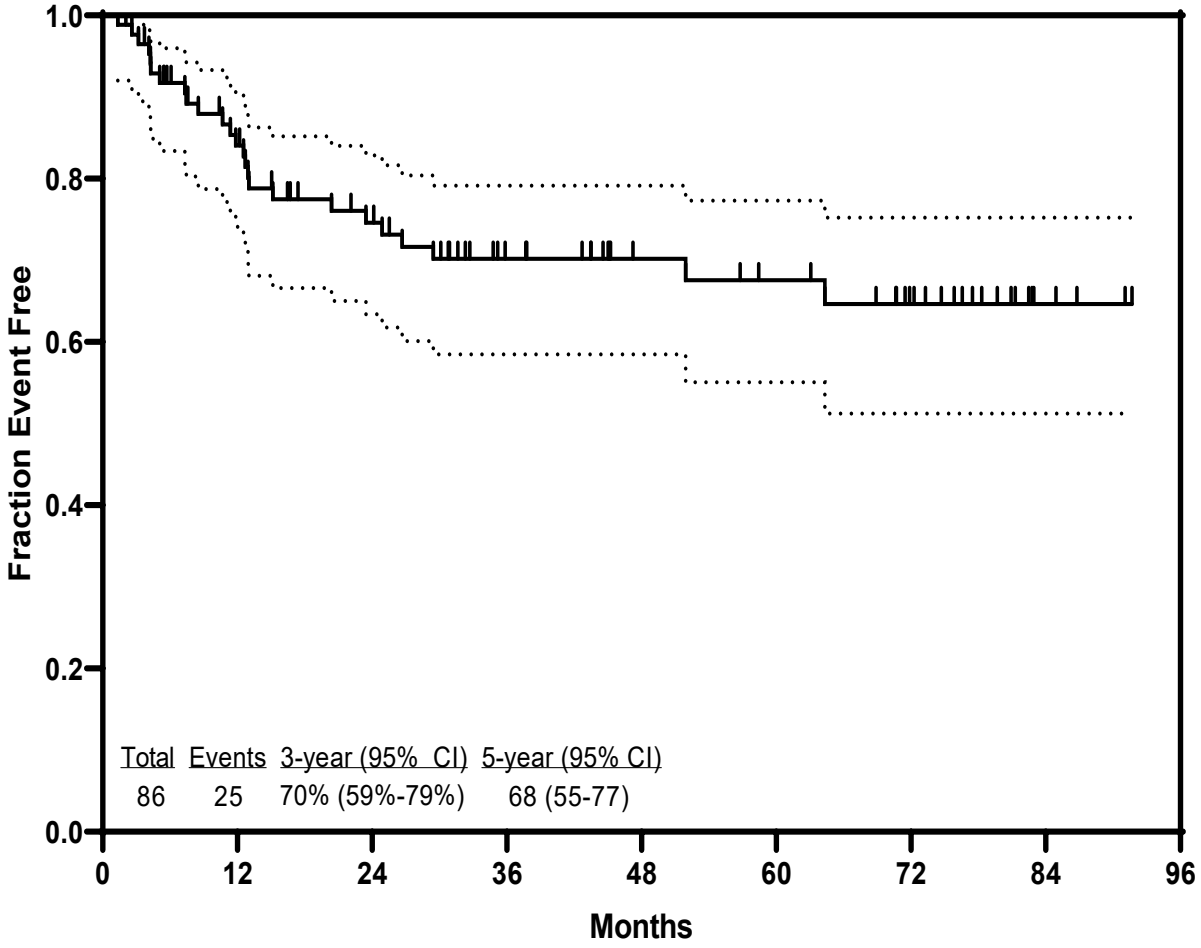


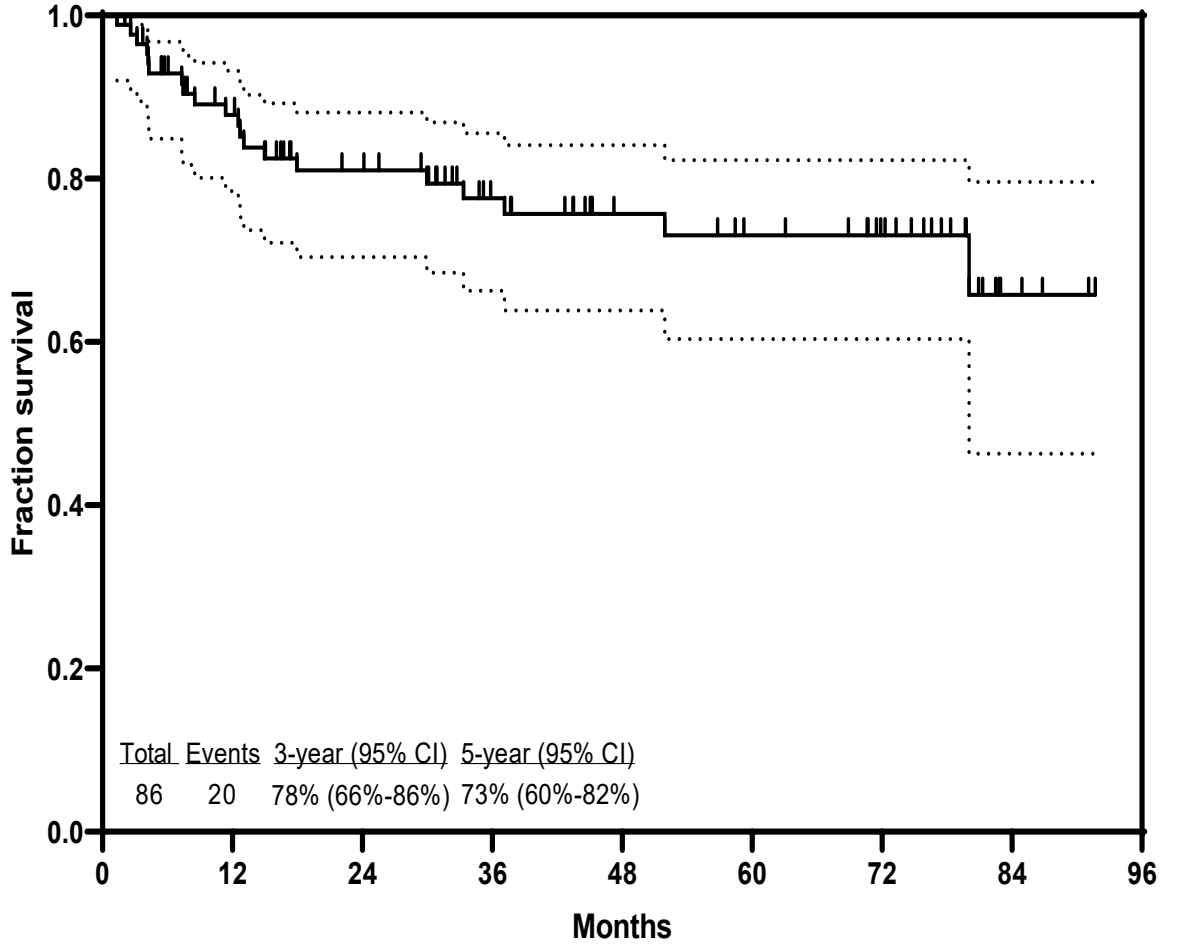
- After the emergence of vascular toxicity, protocol was amended: Beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

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

HyperCVAD + Ponatinib in Ph-positive ALL

- 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 78/73%,EFS 76/71%

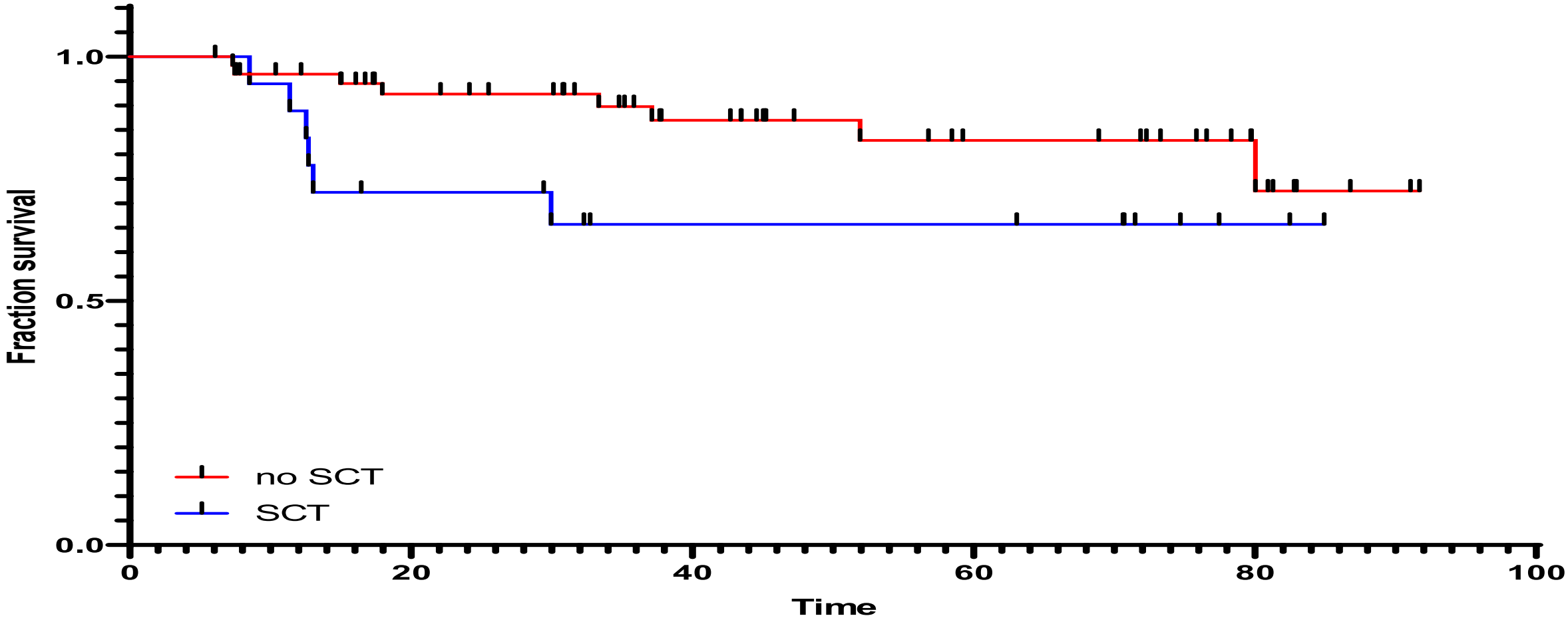




Jabbour. Lancet Hematology 5: 618; 2018 (and update July 2019) Short. Blood 134 : Abst 283; 2019

Hyper-CVAD + Ponatinib in Ph+ ALL. Landmark Analysis at 6 Months by HSCT

- 3-year OS rate was 66% for pts who underwent HSCT (n=18) and 90% for pts who did not undergo HSCT (n=57; P=0.07)



Jabbour. Lancet Hematology 5: 618; 2018 (and update July 2019)

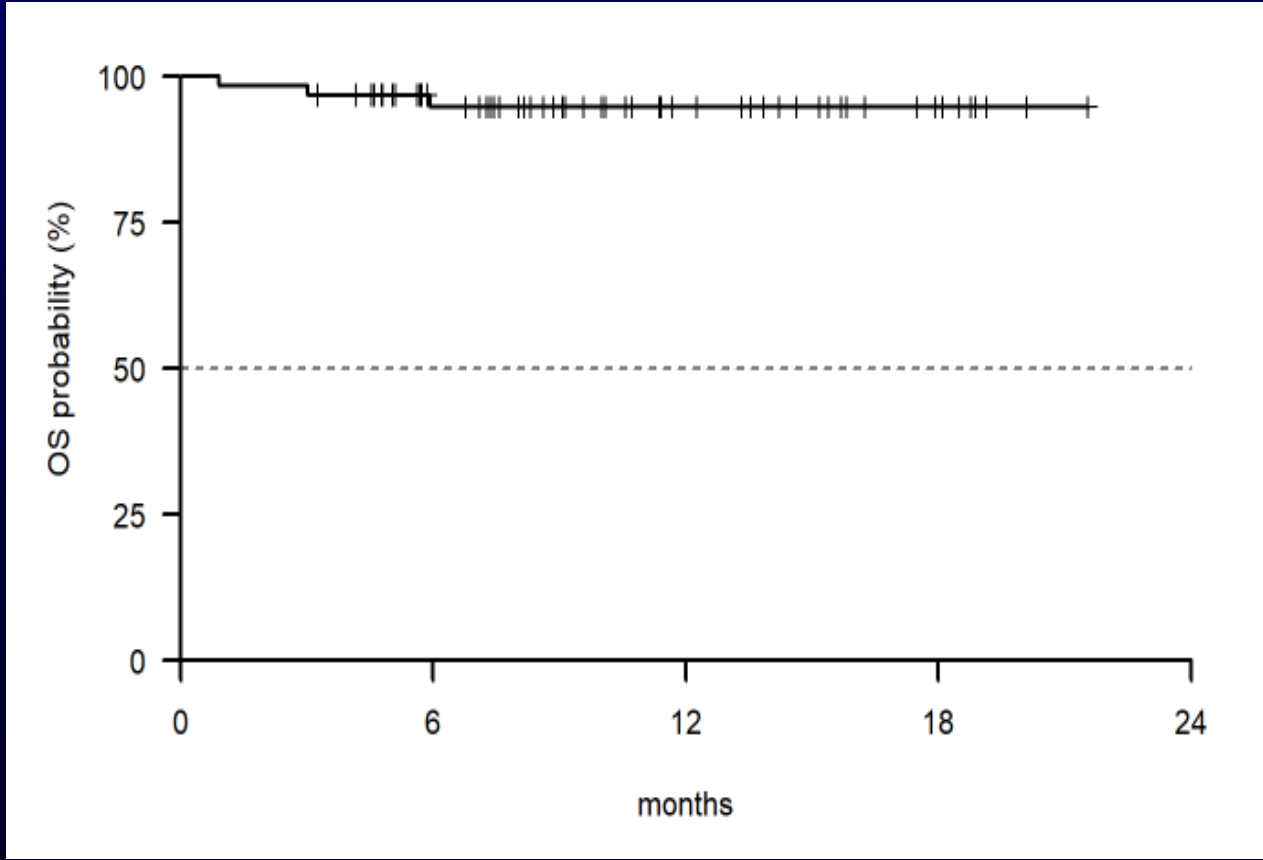
Blinatumomab and Inotuzumab in R-R Ph-positive ALL

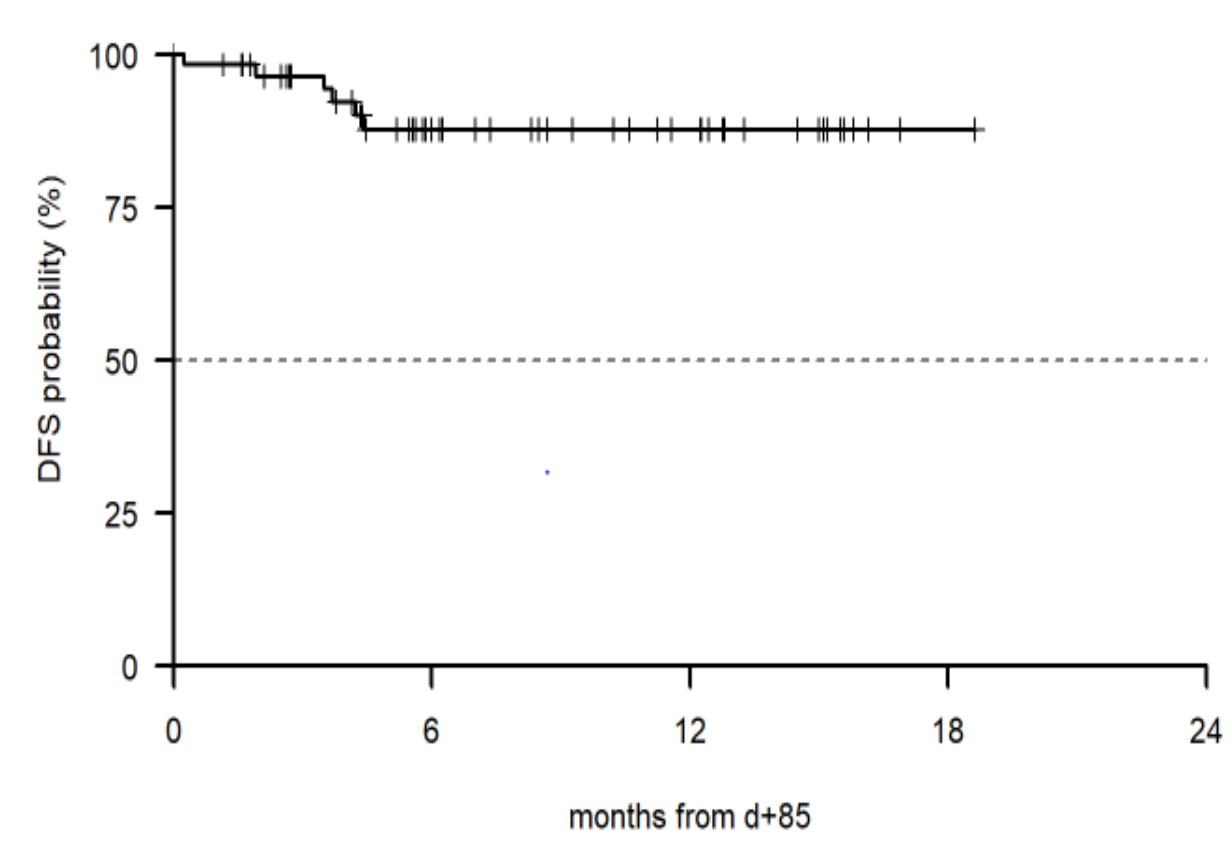
Parameter	Blinatumomab	Inotuzumab
No. Rx	45	38
No. CR/marrow CR (%)	16 (36)	25 (66)
% MRD negative in CR	88	63
Median OS (mos)	7.1	8.1
% later allo SCT	44	32

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

Dasatinib-blinatumomab in Ph-positive ALL

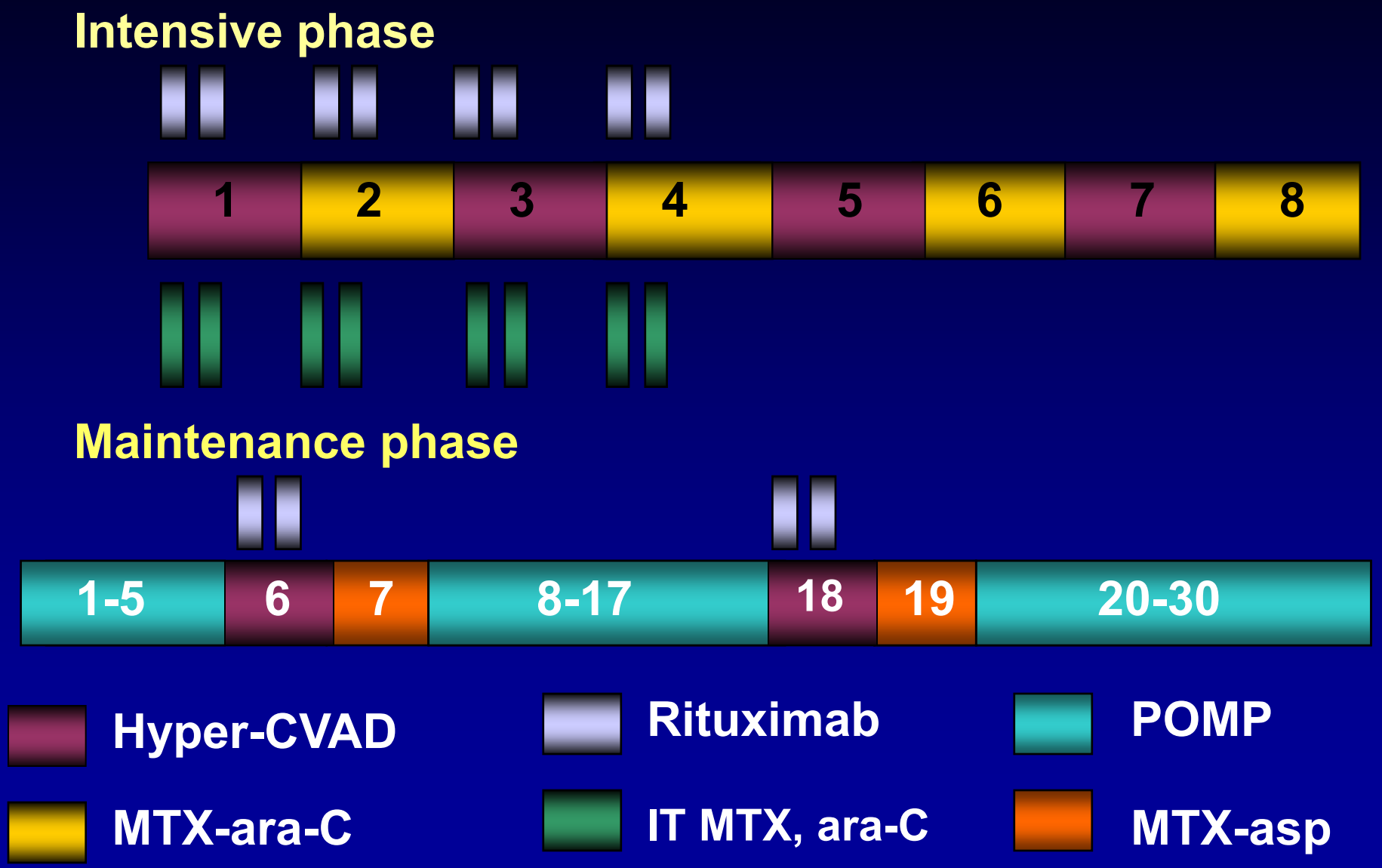
- 63 pts, median age 54 yrs (24-82)
- Dasatinib 140mg/D x 3 mos ; add blinatumomab x 2-5
- 35 post dasa-blina x 2--molecular response 19/35 (54%), 10 CMR (29%) . MRD ↑ in 11— 4 T315I;12-mos OS 96%; DFS 92%





Chiaretti. EHA; abst S1617; 2019

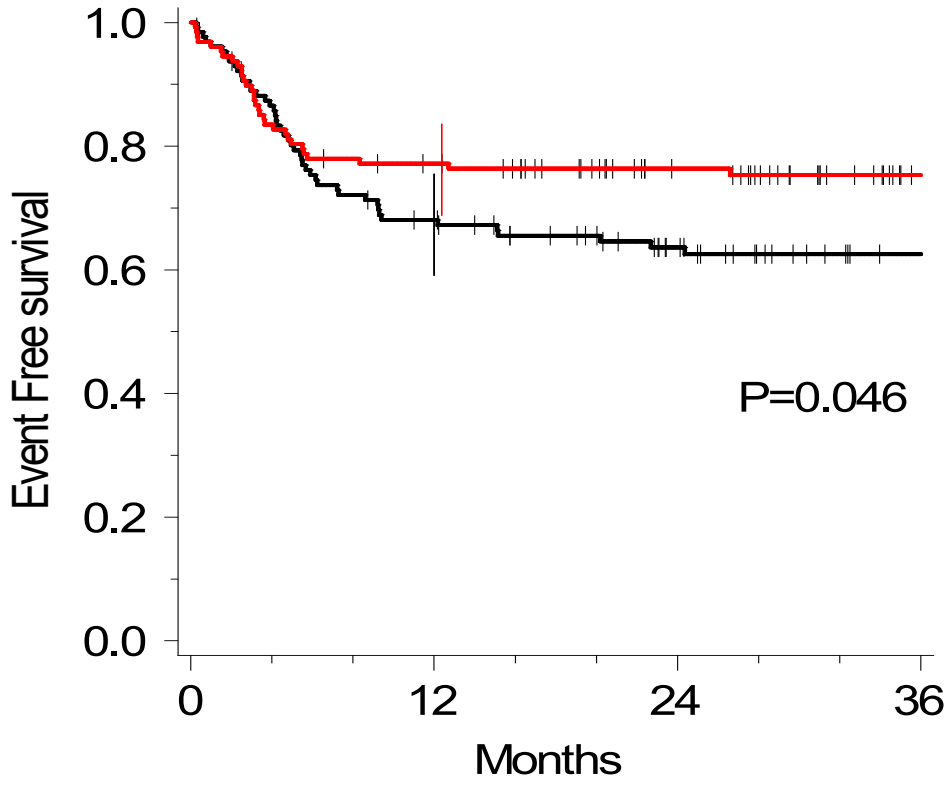
Hyper-CVAD + Rituximab in Precursor B-ALL



Thomas. JCO 2010; 28:3880-9

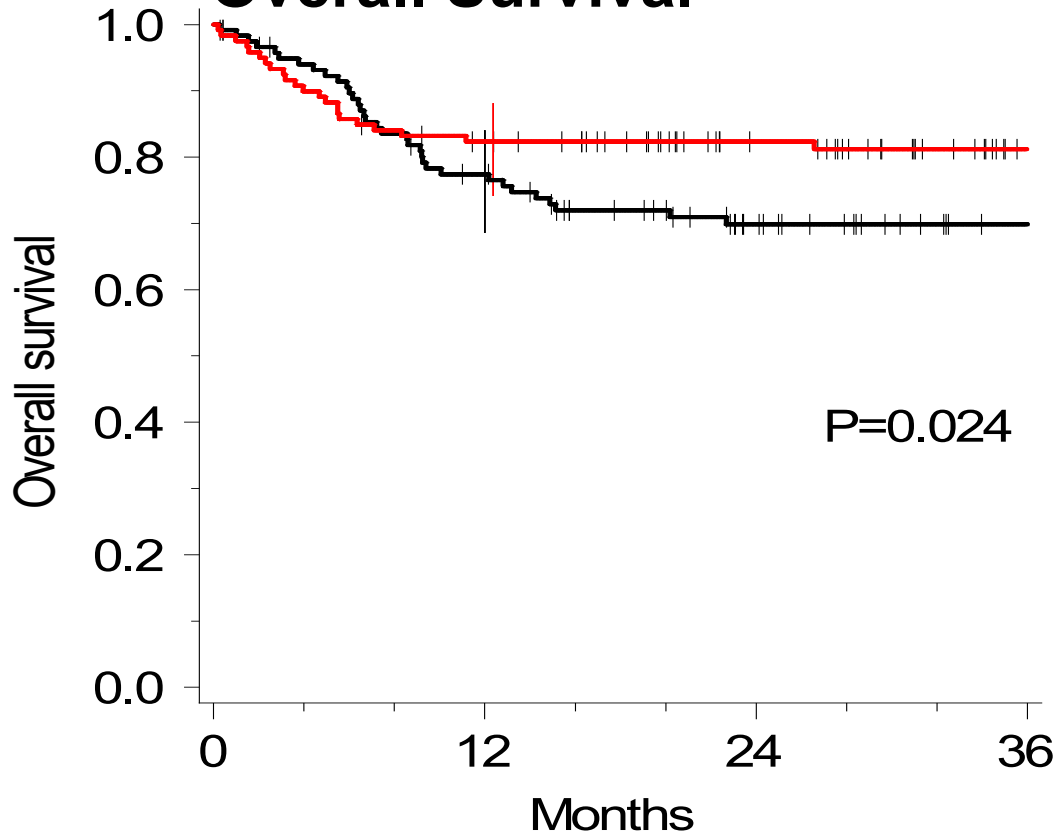
ChemoRx +/- Rituximab in Burkitt Disease--Results of the Randomized Intergroup (GRAALL-Lysa) LMBA02 Study

Event Free Survival



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

Overall Survival

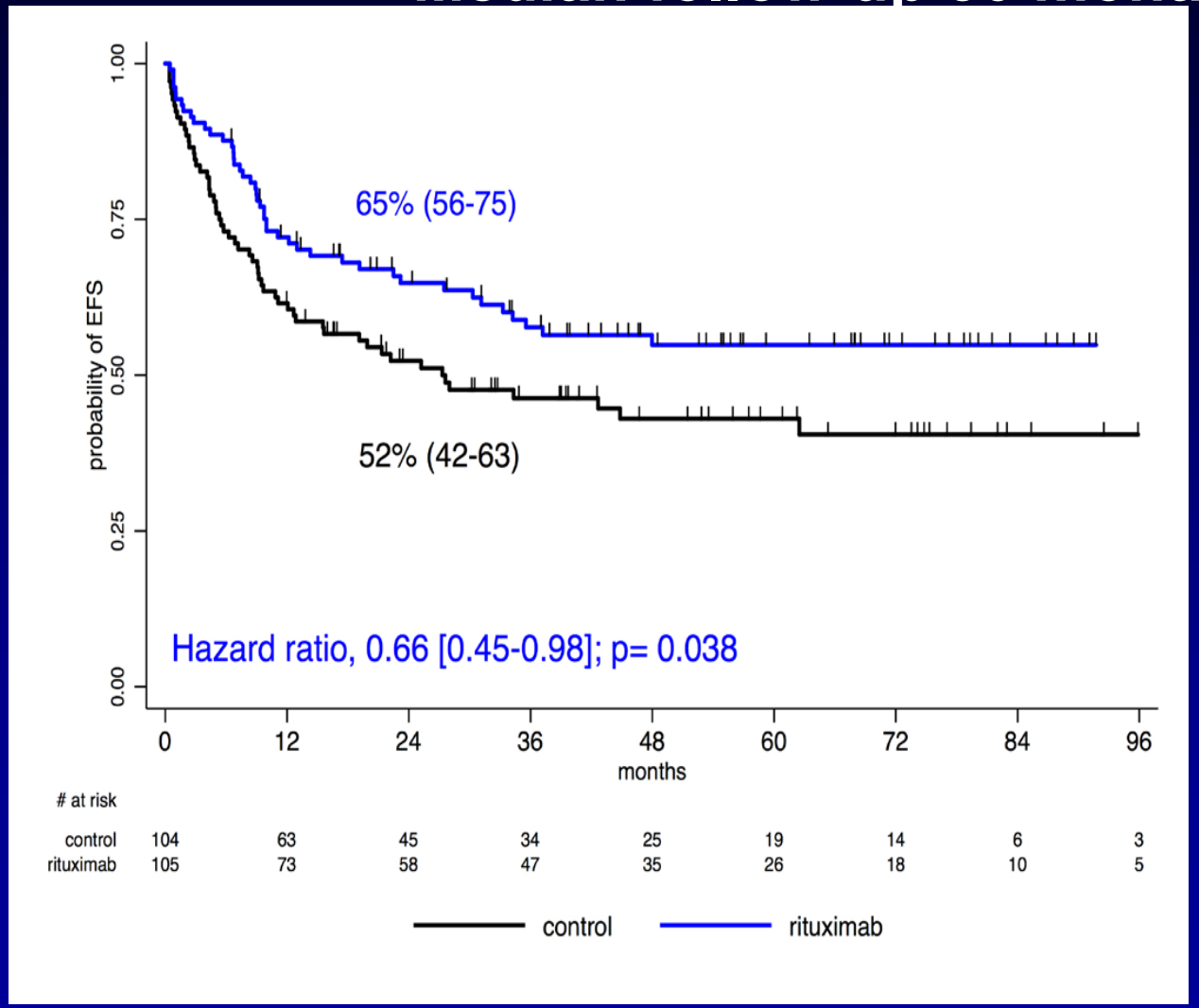


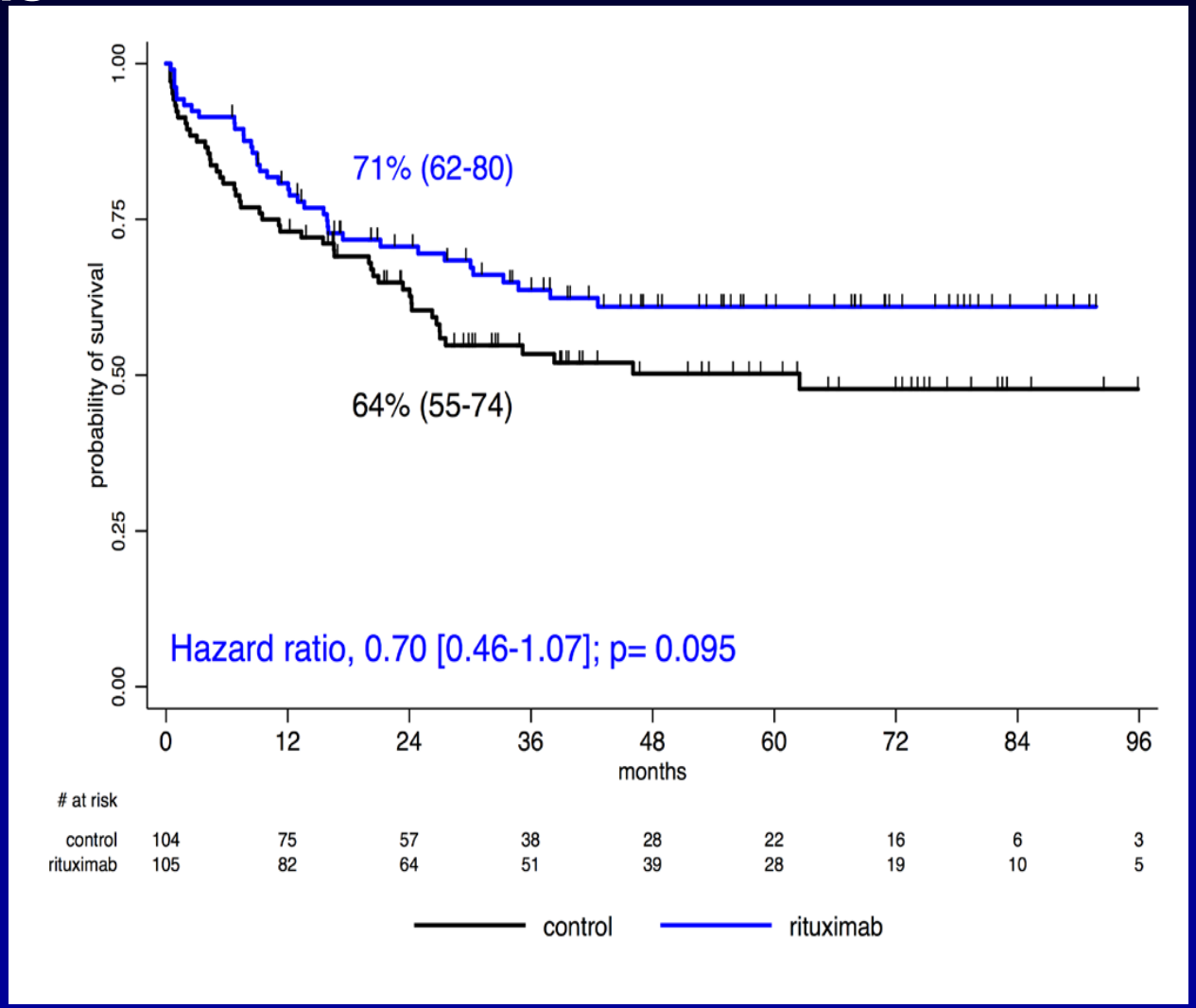
Treatment arm		Patients at risk		
No Rituximab	119	87	60	44
Rituximab	120	95	73	50

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

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

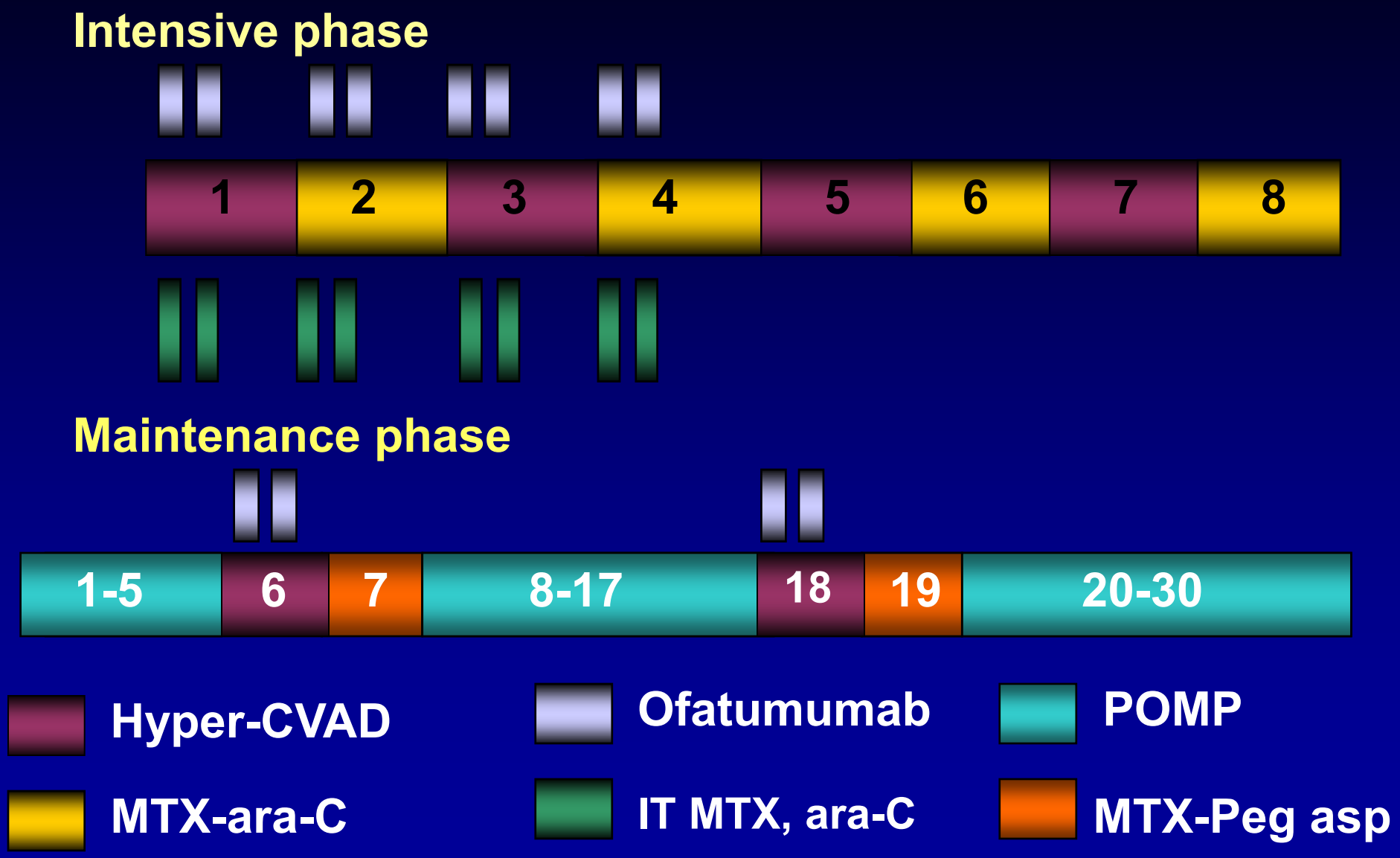
- Median follow-up 30 months





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

Hyper-CVAD + Ofatumumab. Design



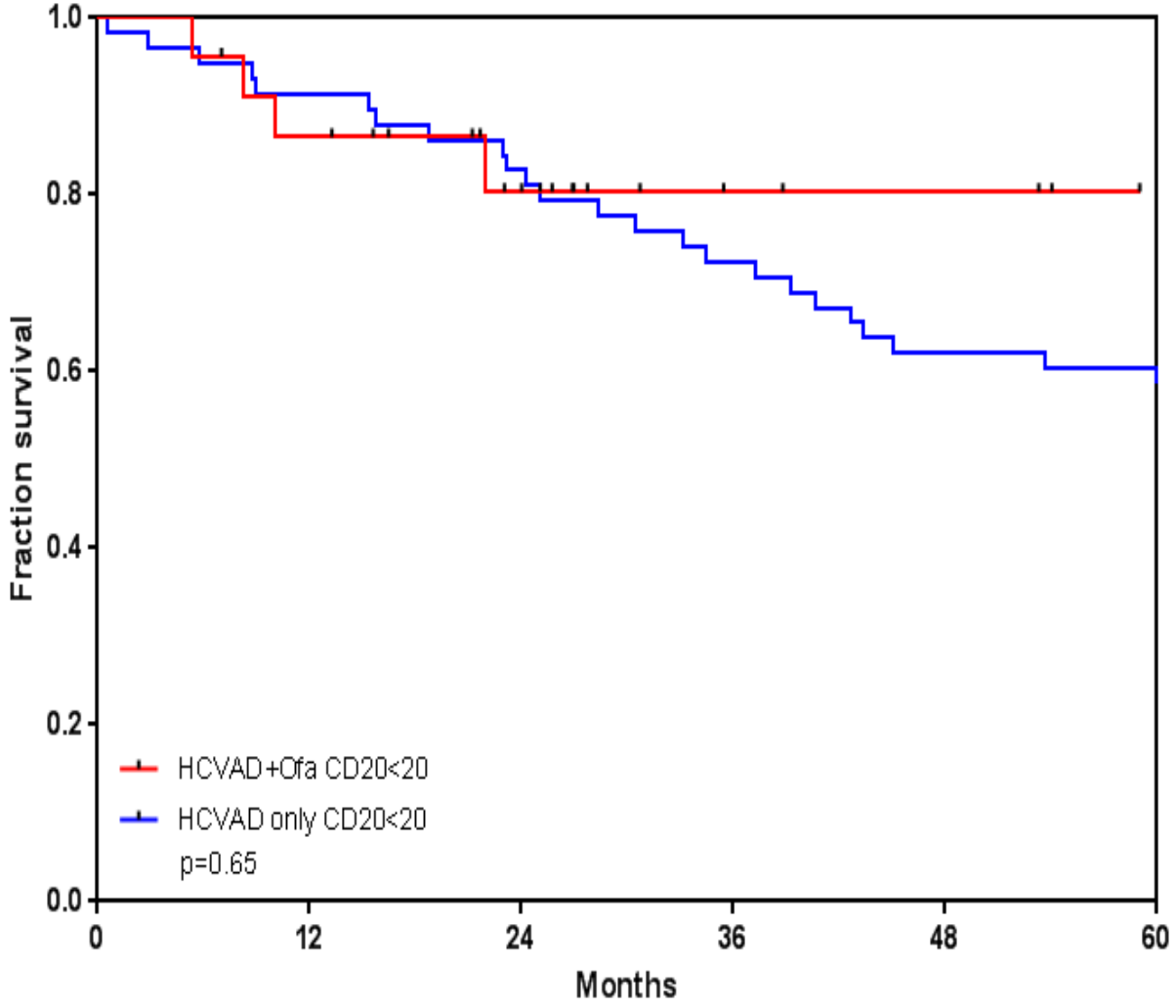
Hyper-CVAD + Ofatumumab. Overall Results

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)

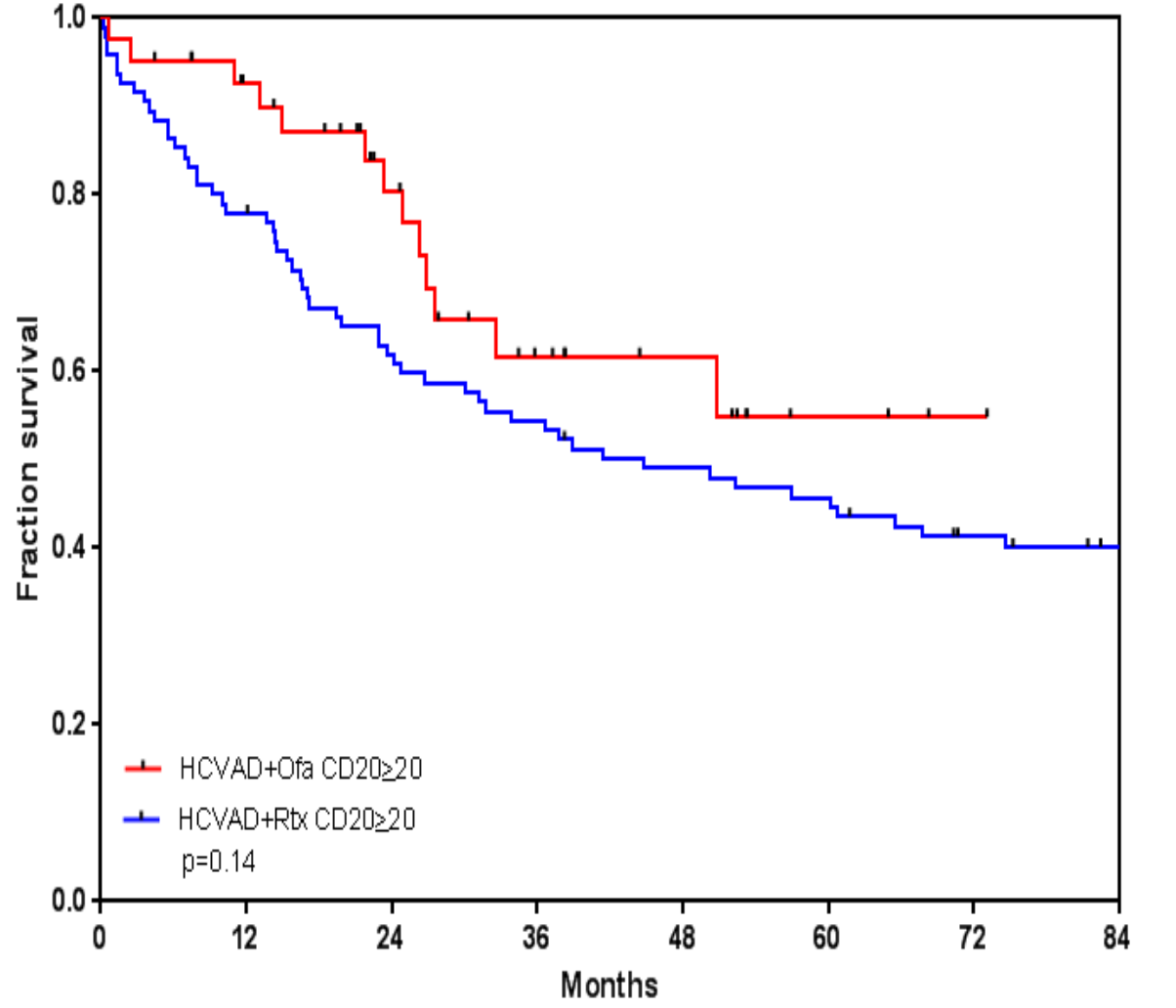
- * 3 pt in CR at start
- Median time to negative MRD 0.7 mos

Hyper-CVAD + Ofa vs Hyper-CVAD +/- R.
OS by CD20 expression

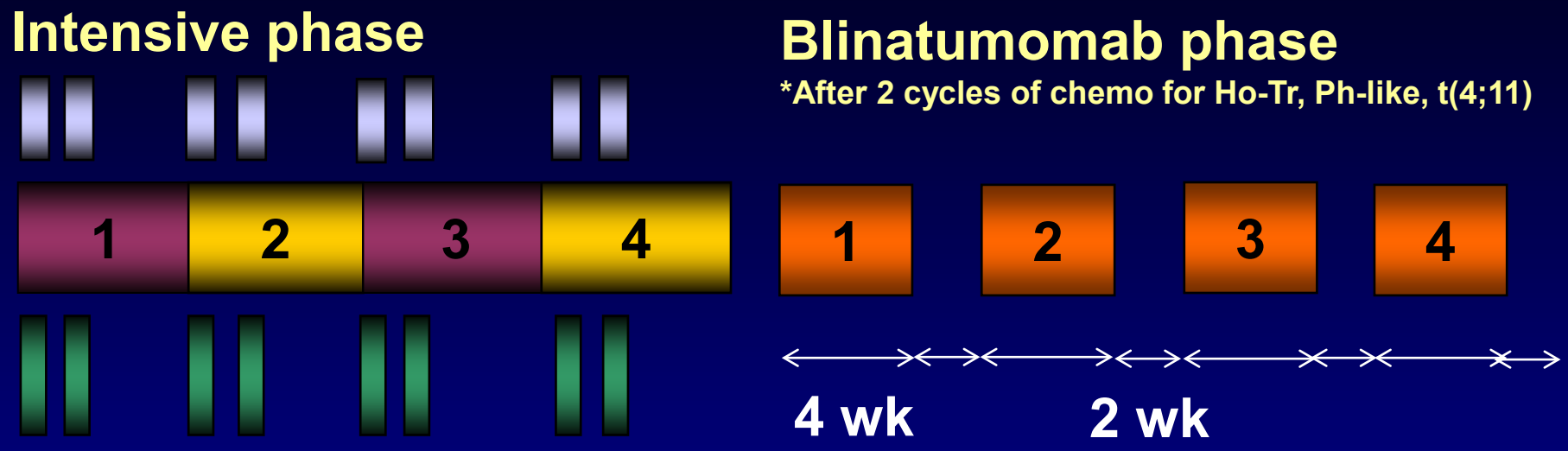
CD<20%

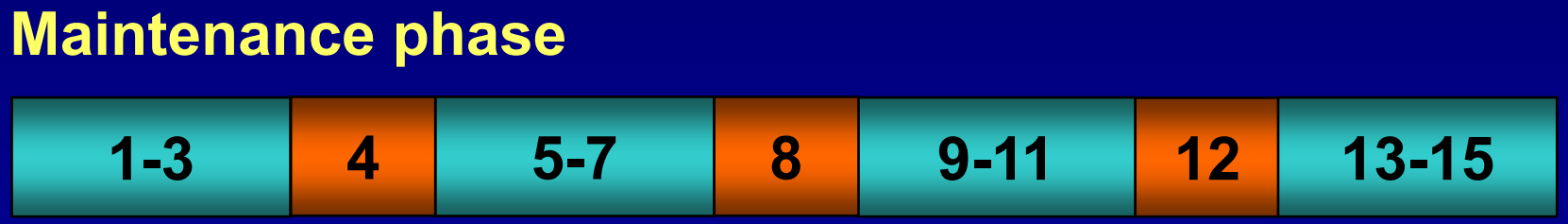


CD≥20%



Hyper-CVAD + Blinatumomab in Frontline B-ALL
Treatment schedule





Hyper-CVAD

Ofatumumab or Rituximab

MTX-Ara-C

8 x IT MTX, Ara-C

POMP

Blinatumomab

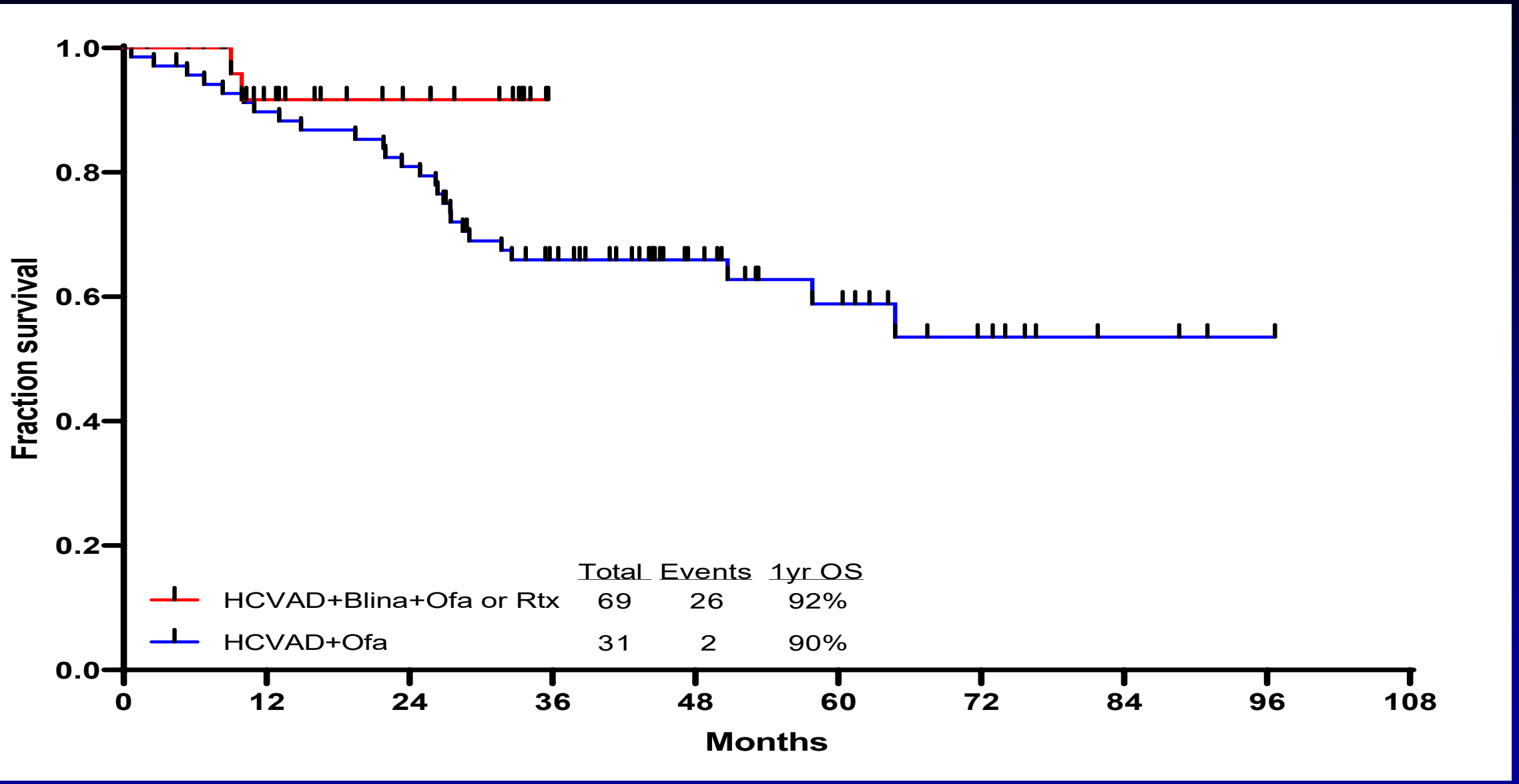
Hyper-CVAD + Blinatumomab in FL B-ALL . Response rates

Response assessment	N (%)
CR after induction	20/24 (83)
CR at any time	24/24 (100)
MRD negativity after induction	17/20 (85)
MRD negativity at any time	28/29 (97)
Early death (30-day)	0/24 (0)

* 2 are too early, 5 are CRs at start
Median time to MRD negativity : 20 days

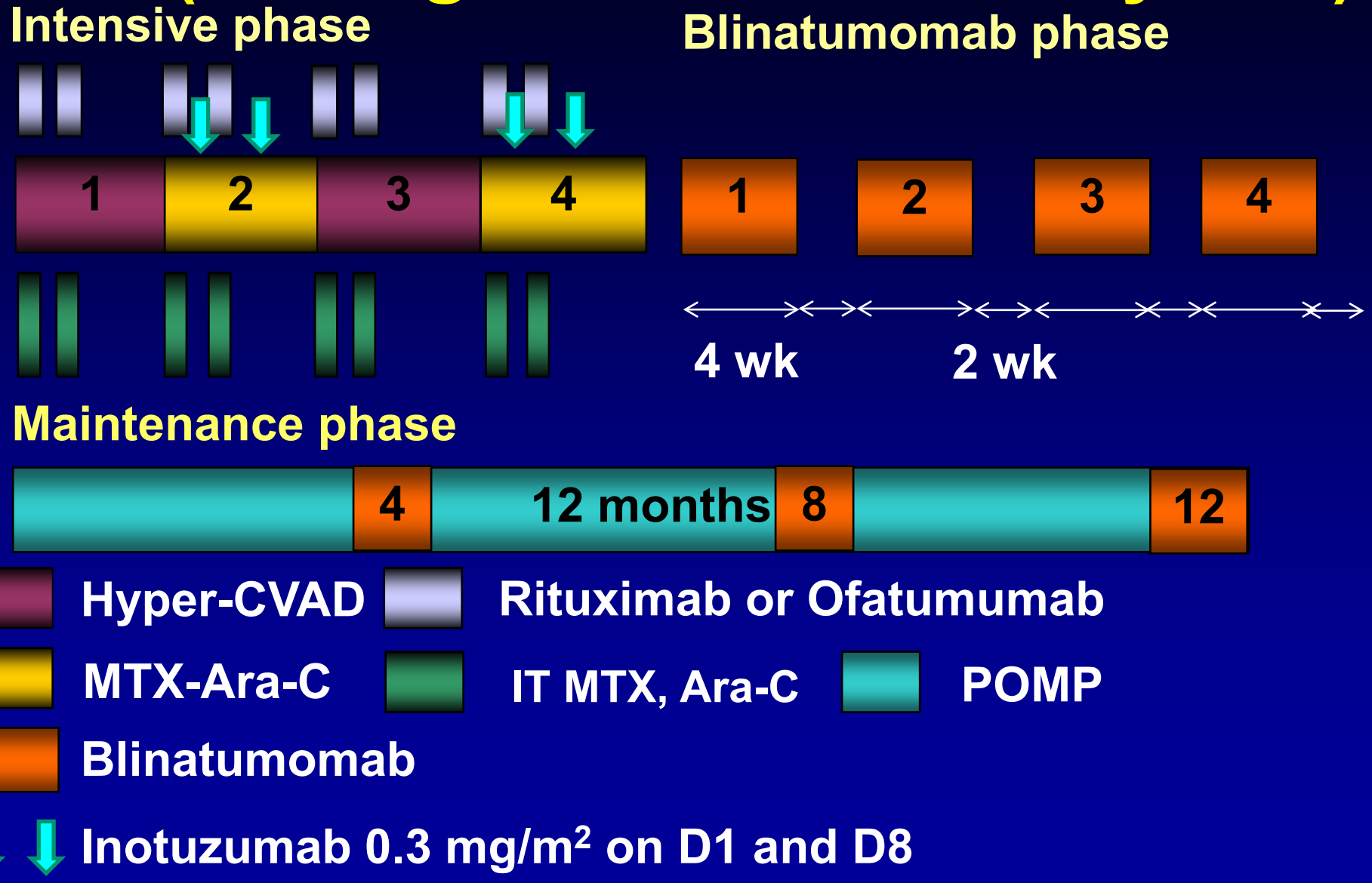
Richard-Carpentier. Blood 134: abst 3807; 2019

R/O-Hyper-CVAD + Blina vs O-Hyper-CVAD . Survival



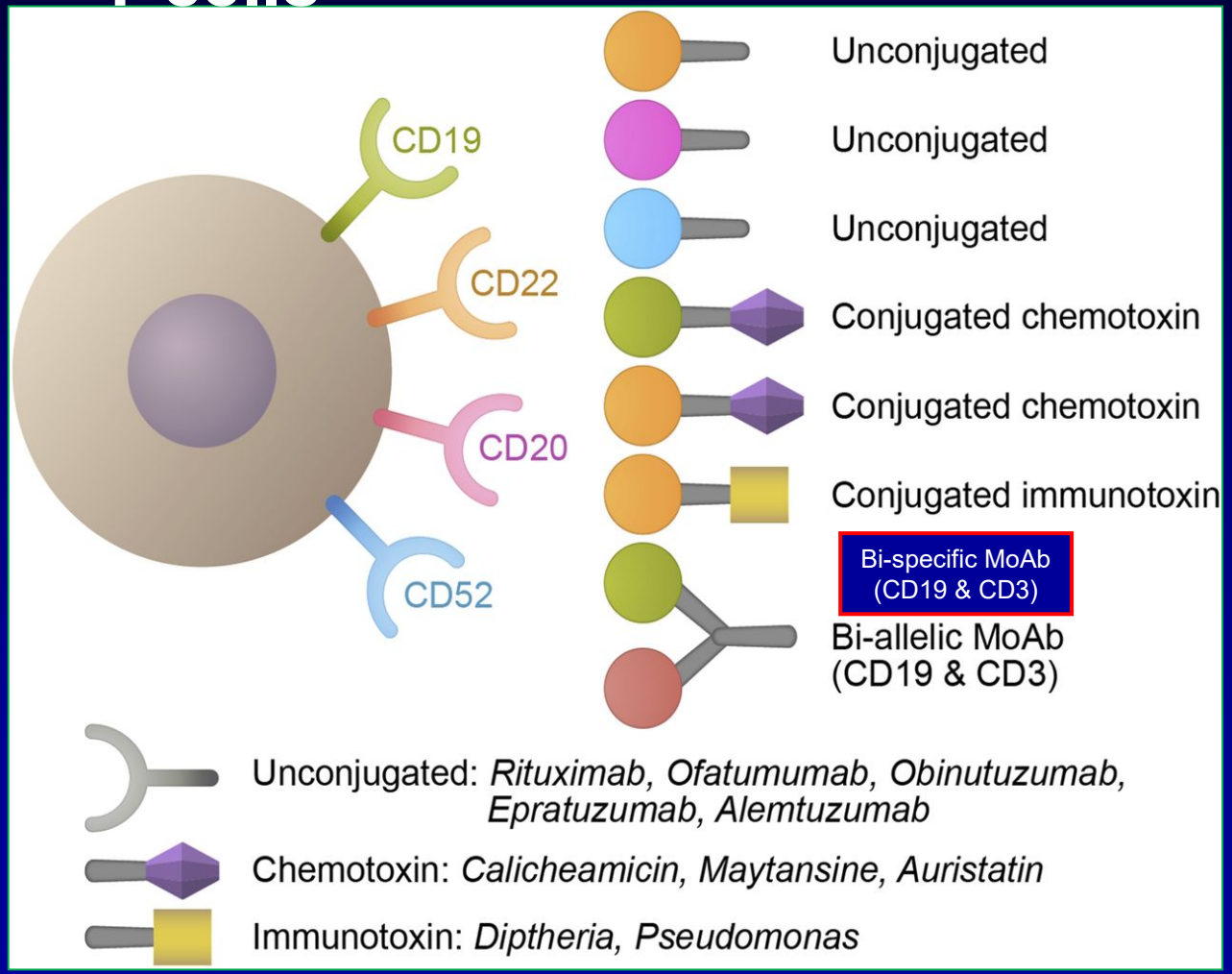
Richard-Carpentier. Blood 134: abst 3807; 2019

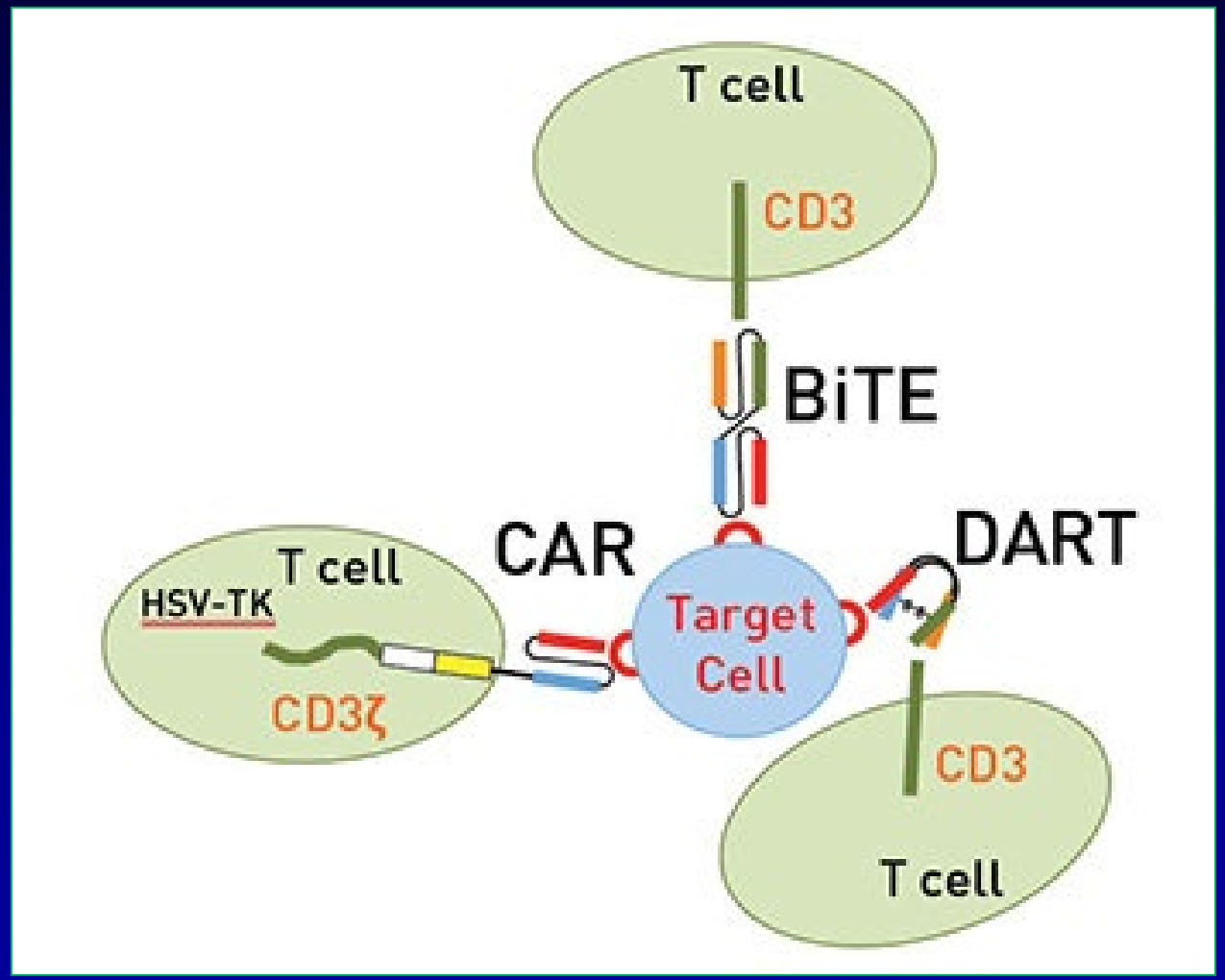
Hyper-CVAD + Inotuzumab + Blinatumomab in B-ALL (Ph-negative B-ALL < 60 years)



Immuno-oncology in ALL

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



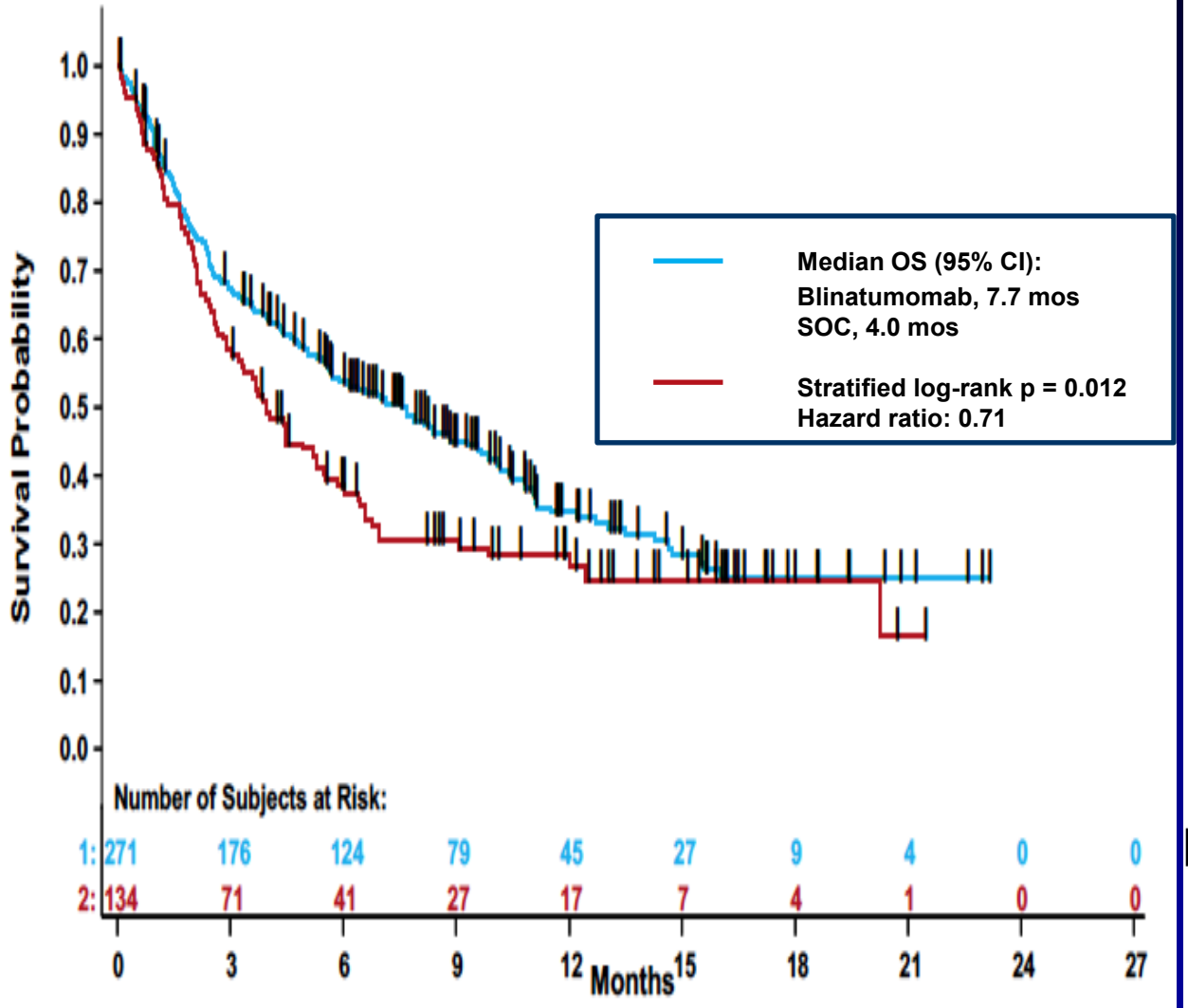


Jabbour E. Blood 125: 4010; 2015

Blinatumomab/Inotuzumab vs ChemoRx in R-R ALL

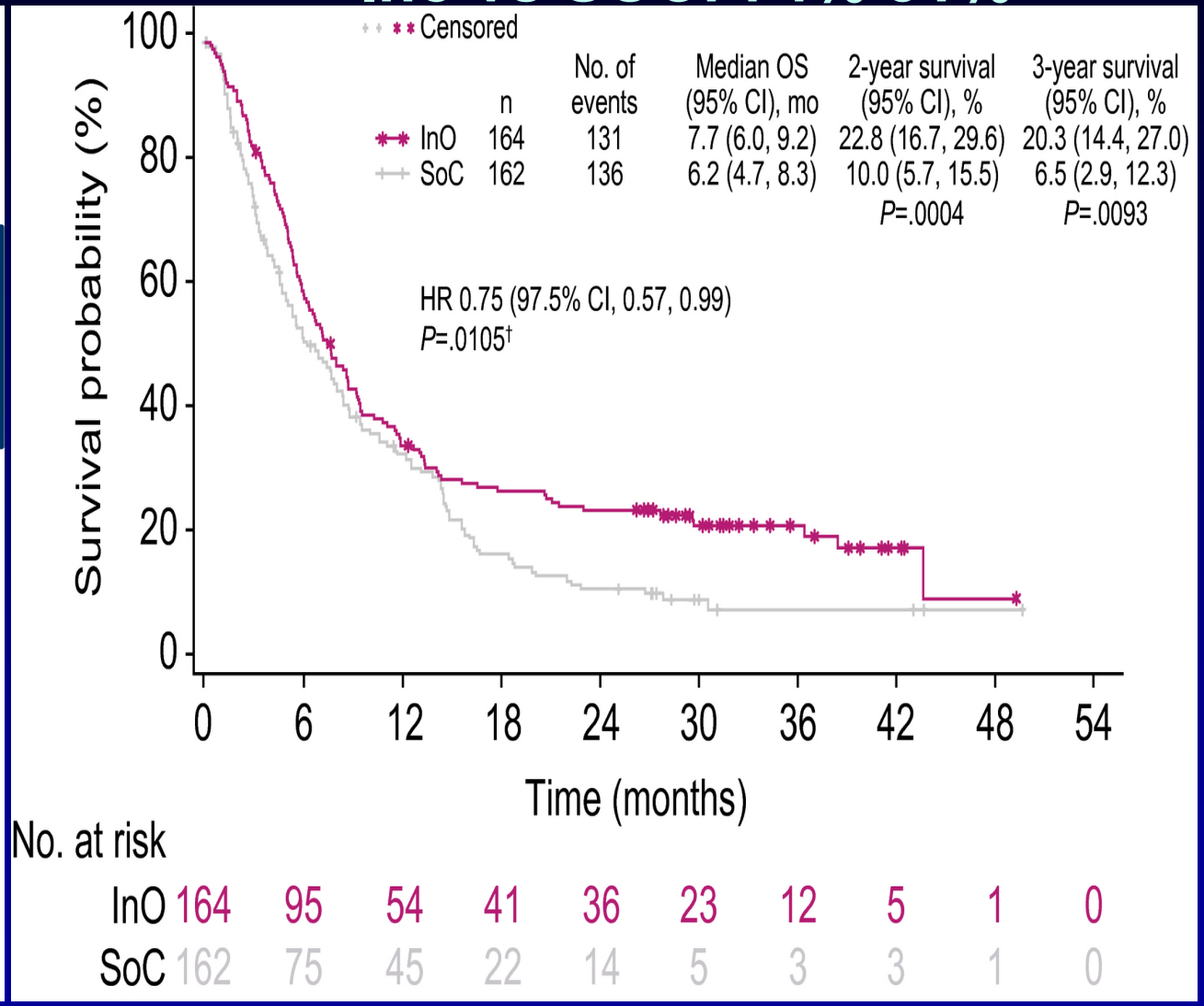
- **Marrow CR**

Blina vs SOC: 44% vs 25%



Kantarjian. NEJM. 376: 836-47; 2017

Ino vs SOC: 74% 31%

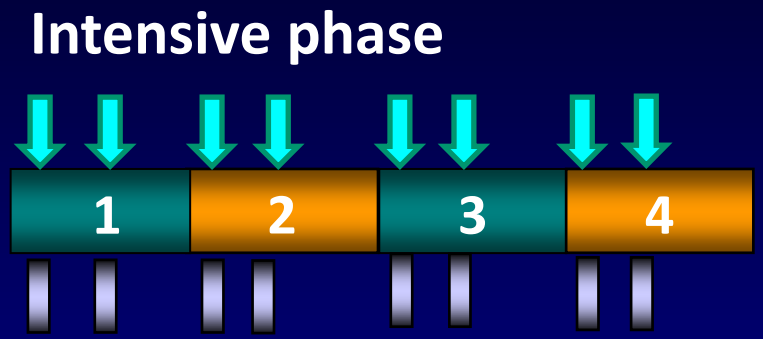


Kantarjian. NEJM. 375: 740; 2016 . Cancer. May 2019

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

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



Mini-HCVD

Mini-MTX-cytarabine

IT MTX, Ara-C

Blinatumomab

POMP

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

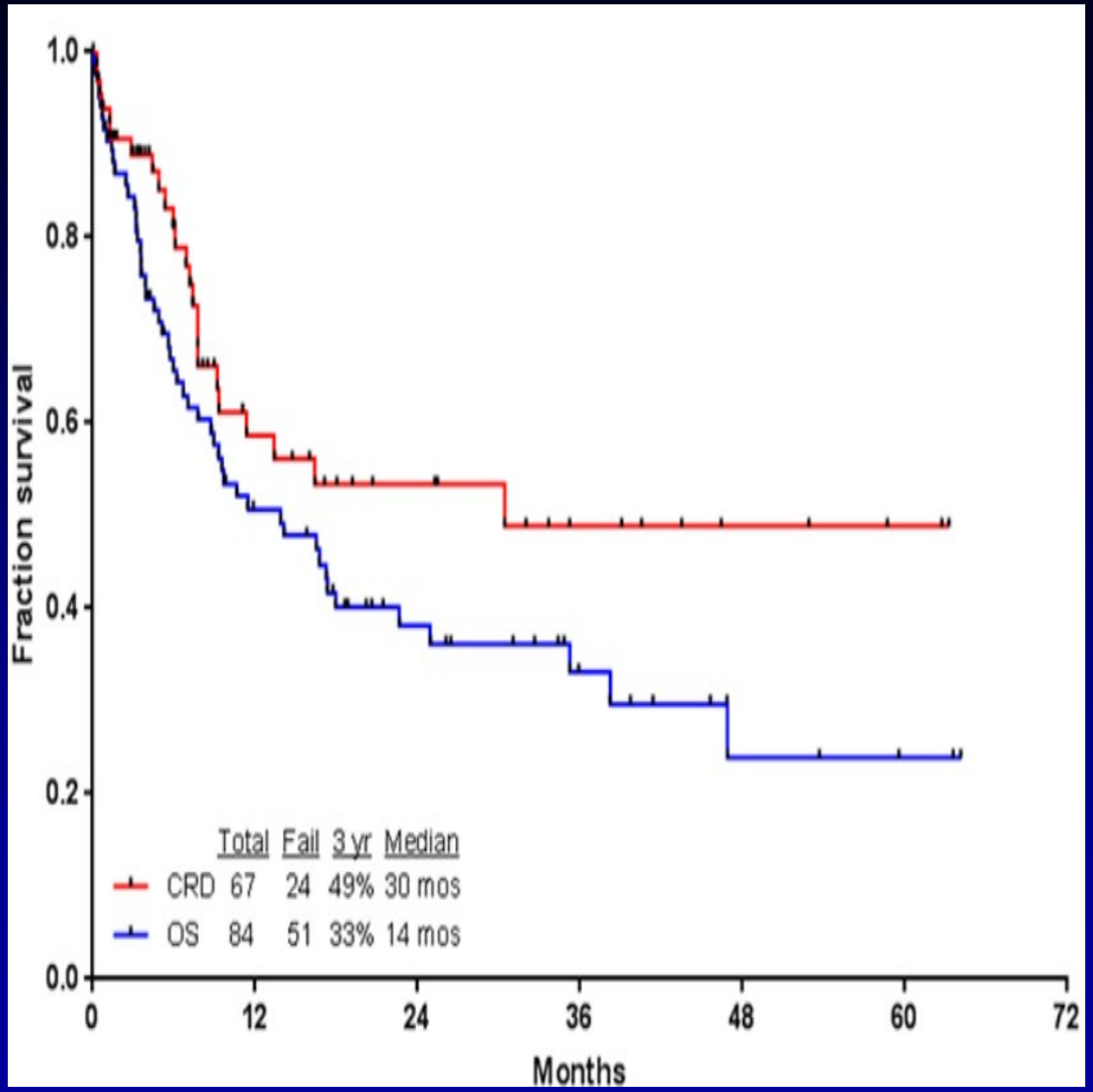
Mini-HCVD + INO ± Blinatumomab in R/R ALL
Response by Salvage (N=89)

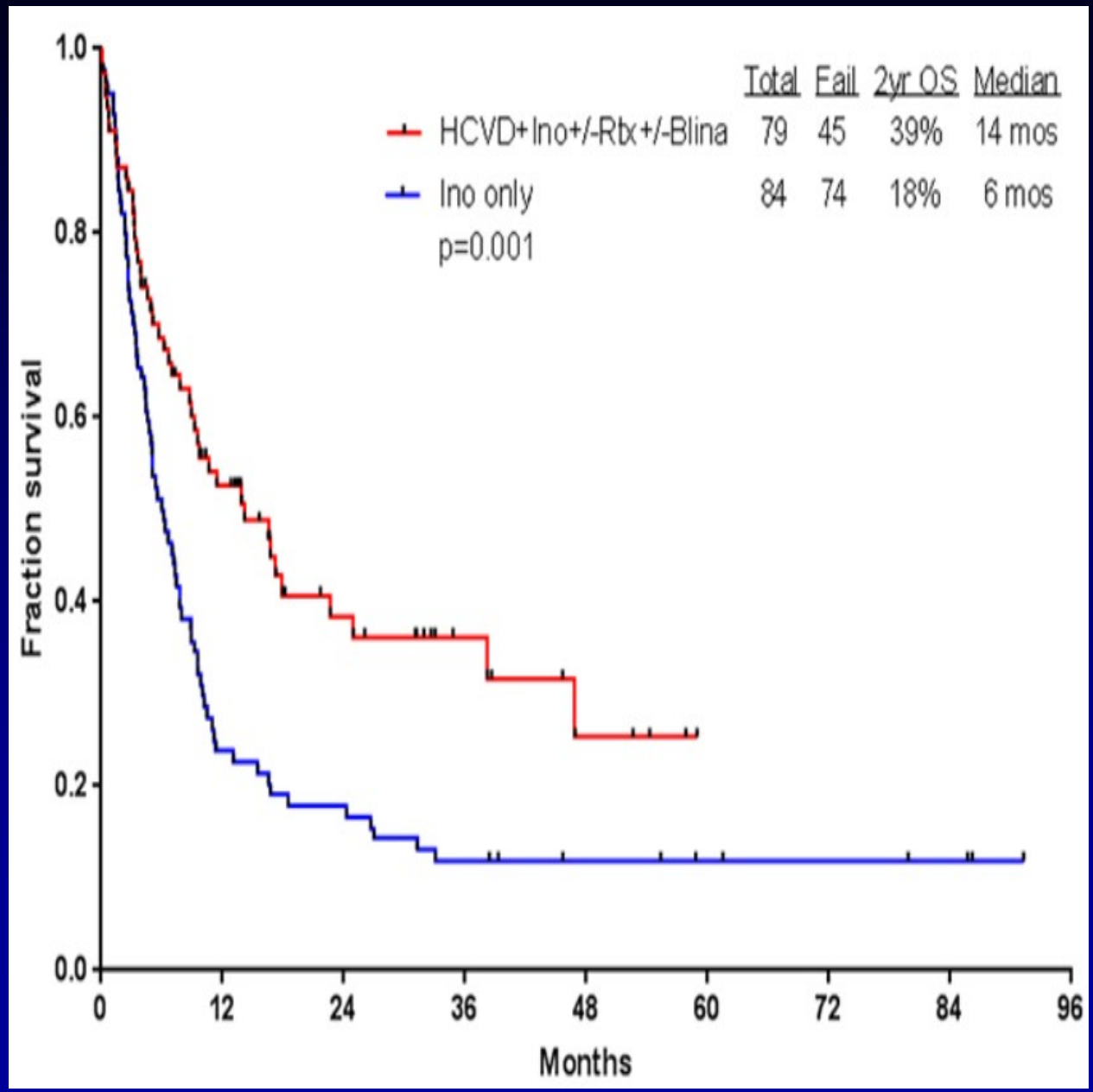
Response	N	(%)
Salvage 1	**51/56**	**91**
S1, Primary refractory	5/5	100
S1, CRD1 < 12 mos	19/23	83
S1, CRD1 ≥ 12 mos	27/28	96
Salvage 2	9/16	56
≥ Salvage 3	9/15	60
Overall	**69/87**	**79**
MRD negativity	55/67	82
Salvage 1	**42/49**	**86**
≥ Salvage 2	13/18	72
Early death	7/87	8

Sasaki. Blood 132: abst 553; 2018

Jabbour. JAMA Oncology 4: 230; 2018

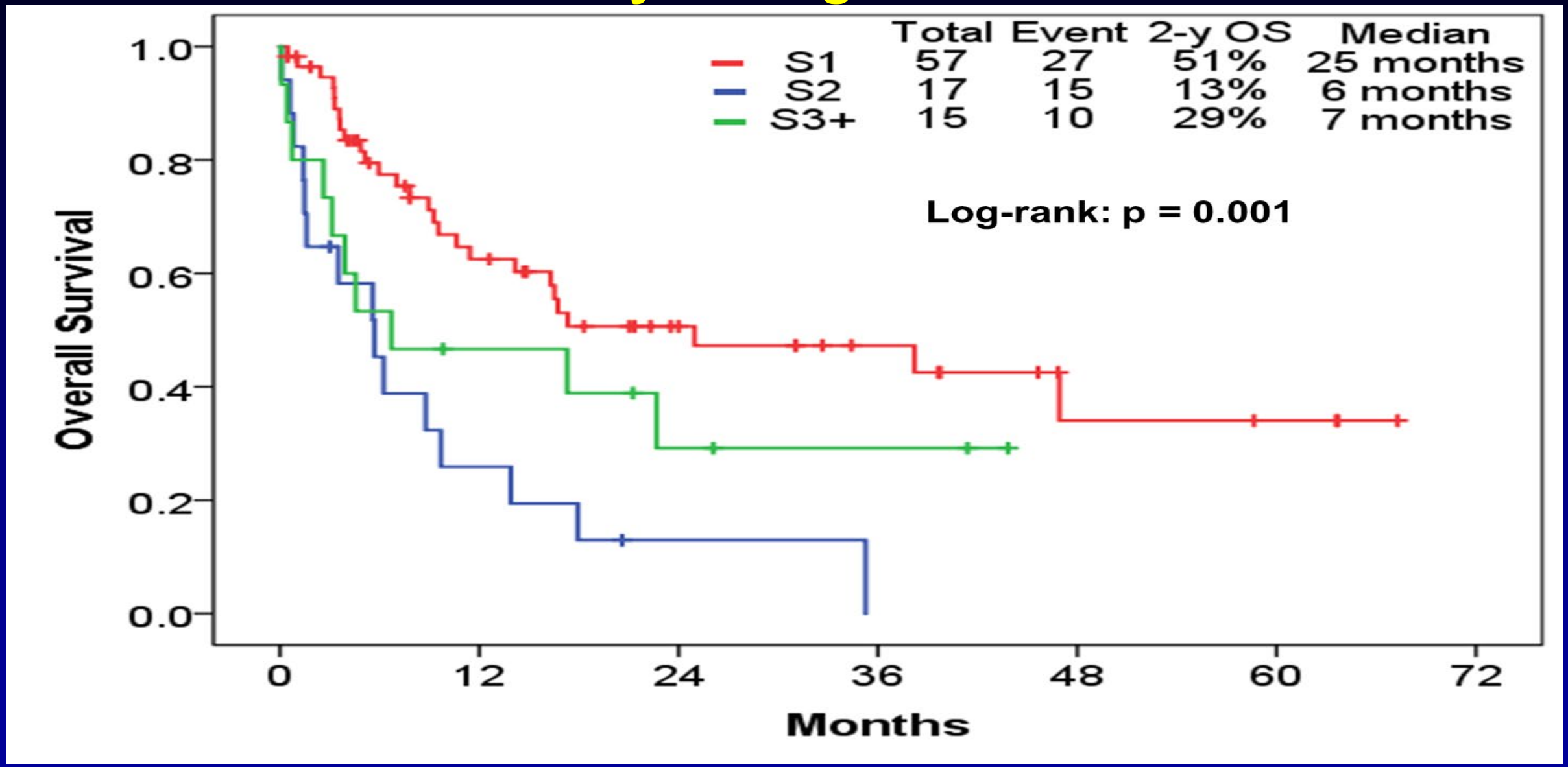
Mini-HCVD+Inotuzumab/Blinatumomab in R-R ALL





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

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

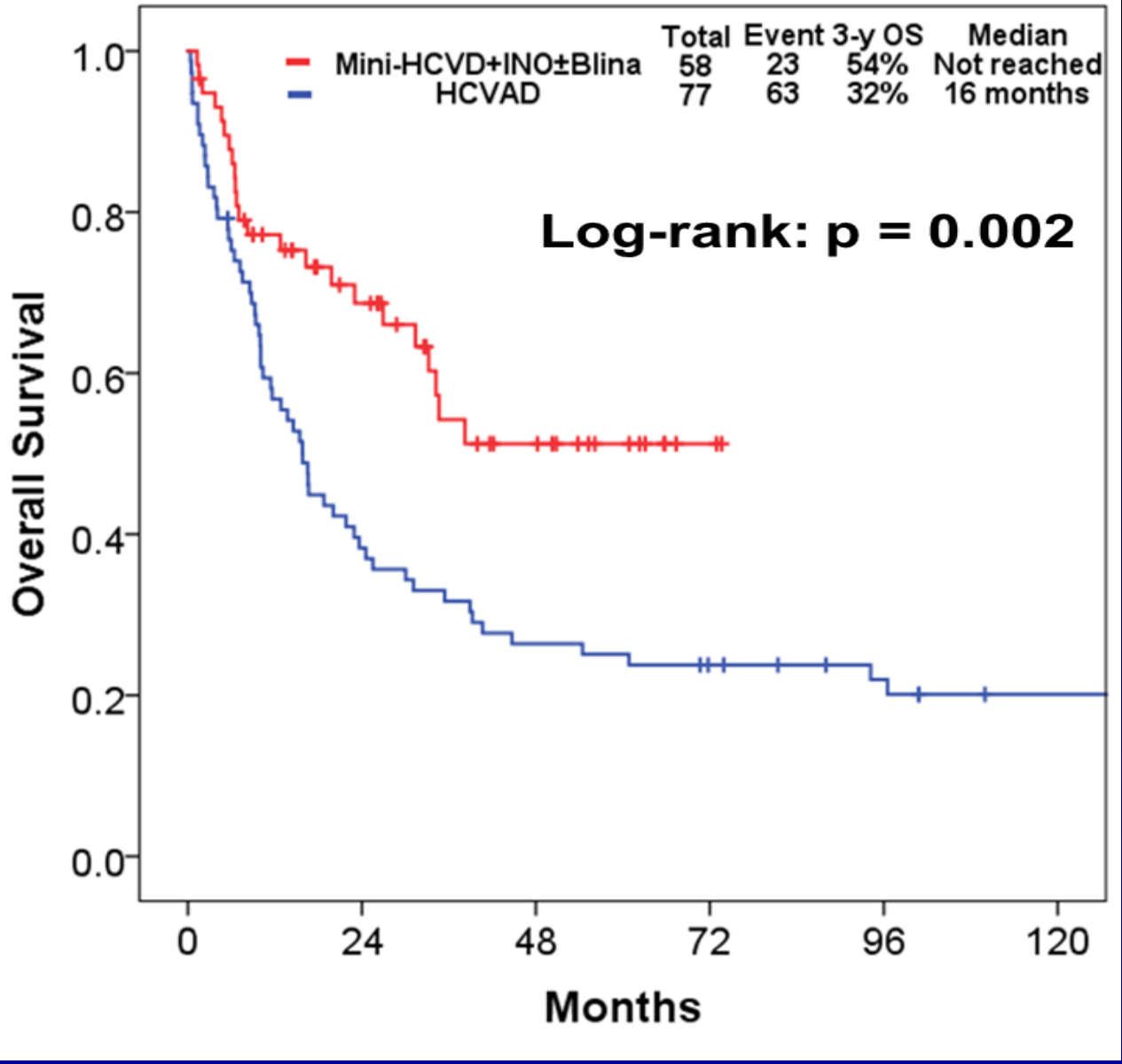
Mini-HCVD + INO ± Blina in Older ALL . Response

Response (N=59)	N (%)
ORR	58 (98)
CR	51 (86)
CRp	6 (10)
CRi	1 (2)
No response	1 (2)
Early death	0

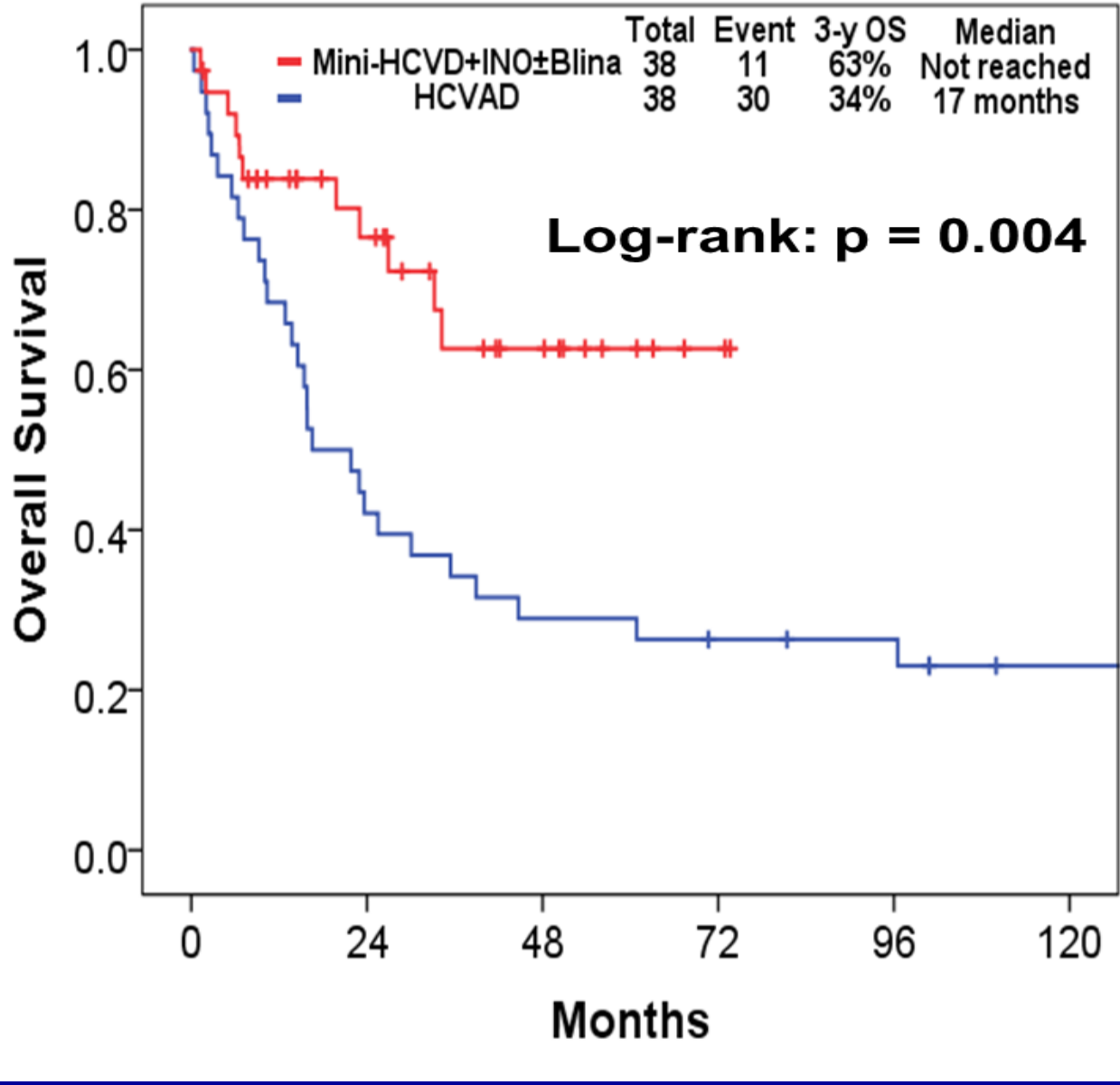
Flow MRD response	N (%)
D21	50/62 (81)
Overall	60/63 (95)

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

Pre-matched



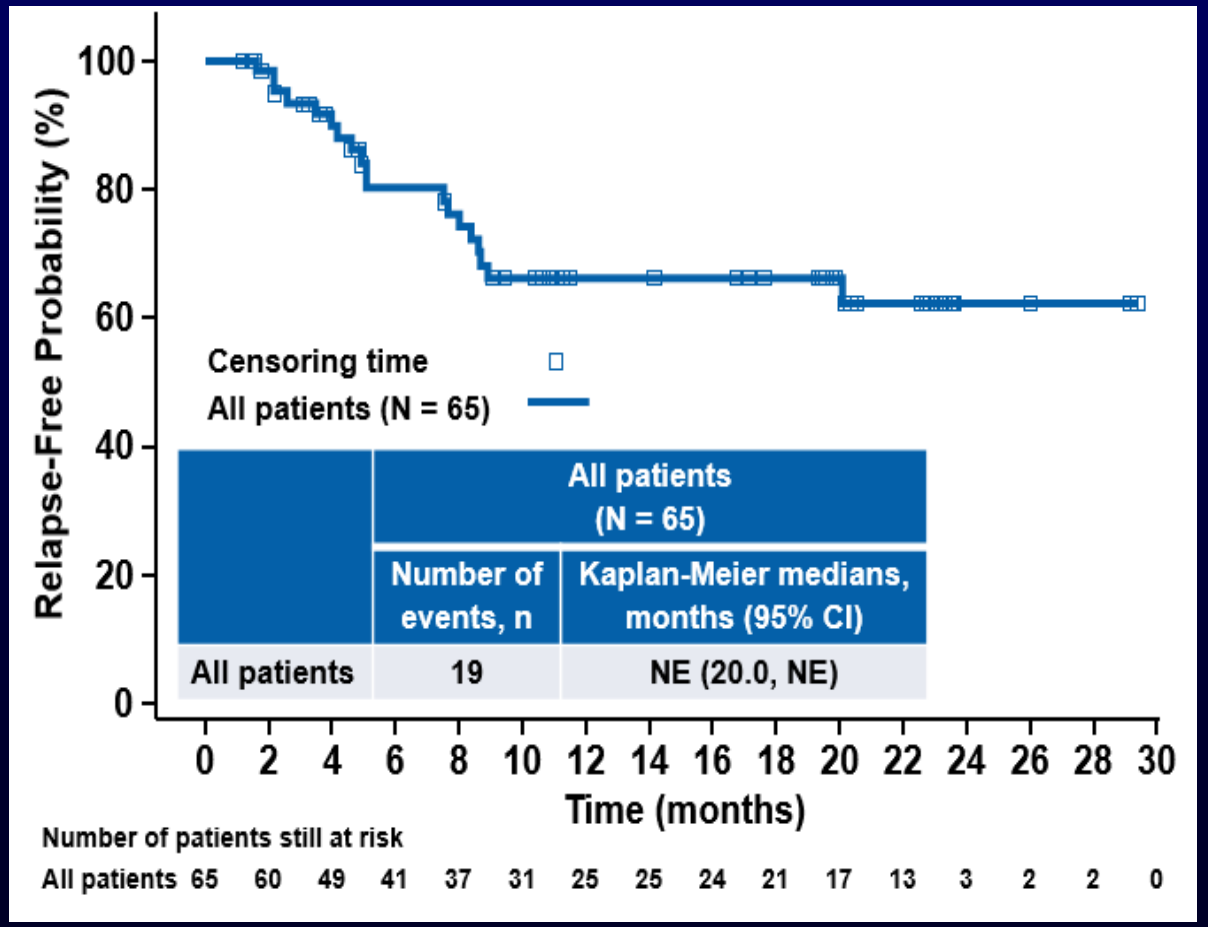
Matched

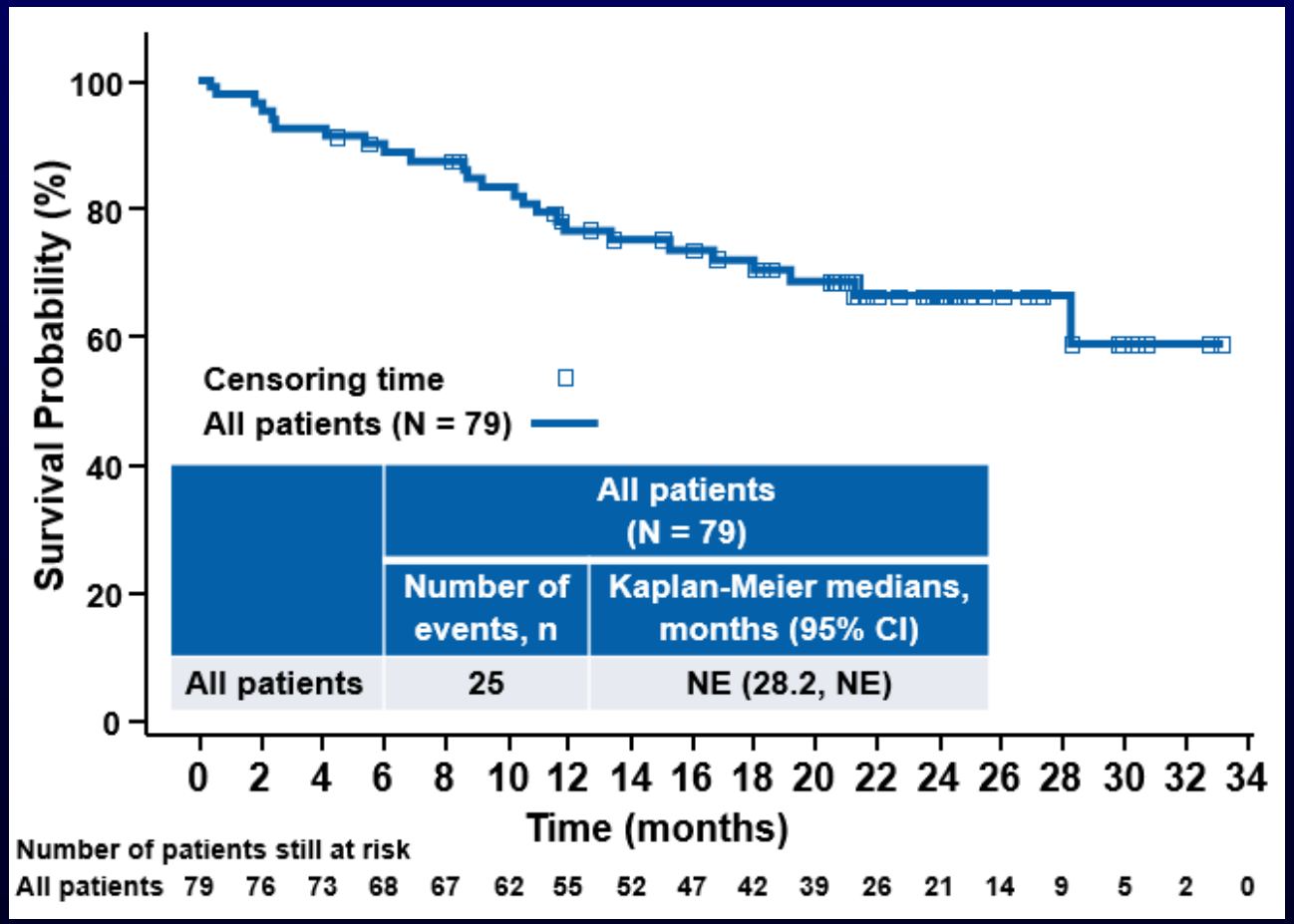


Sasaki. Blood 132: abst 34; 2018

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%. G 3-4 CRS 49%. ICU 48%

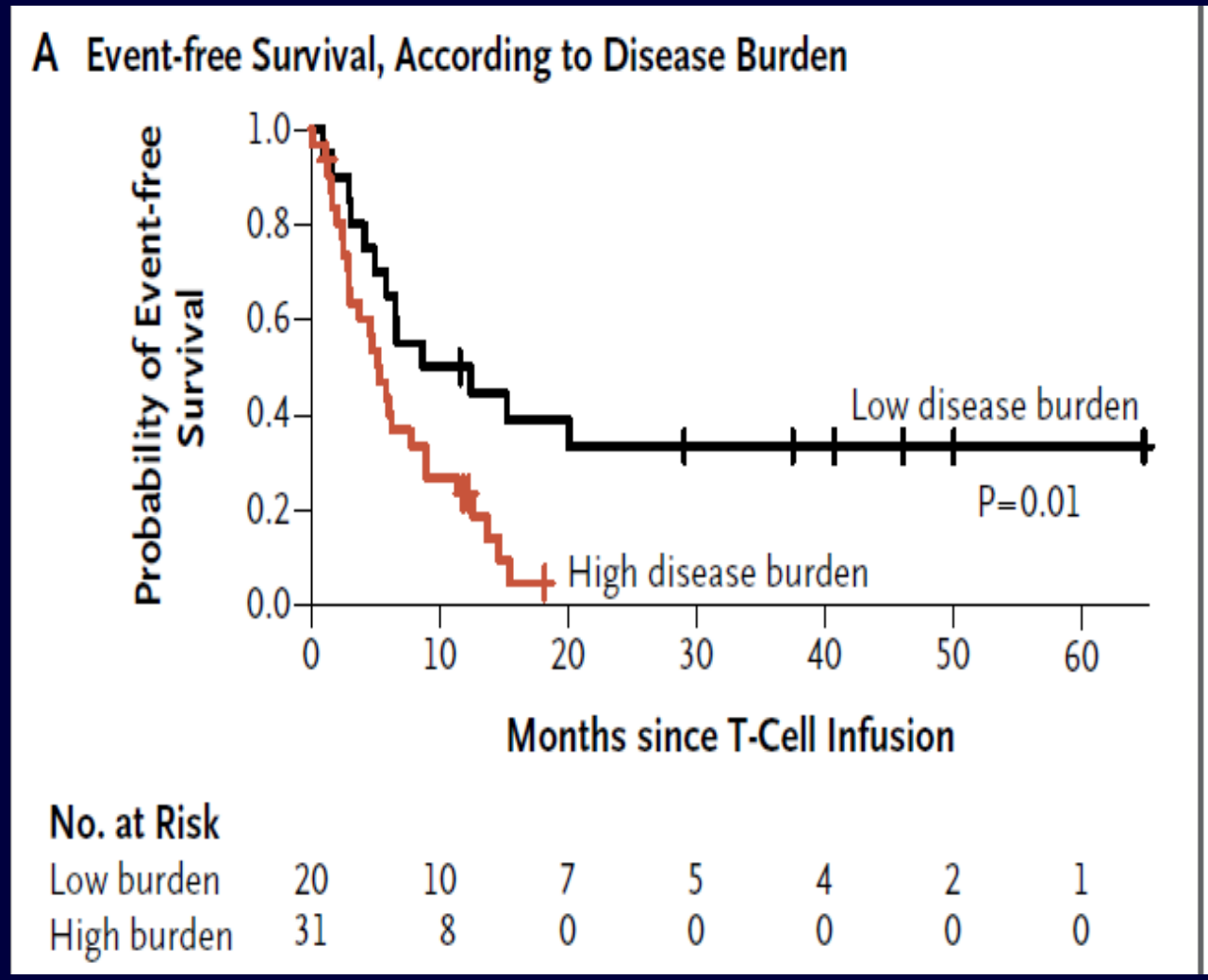


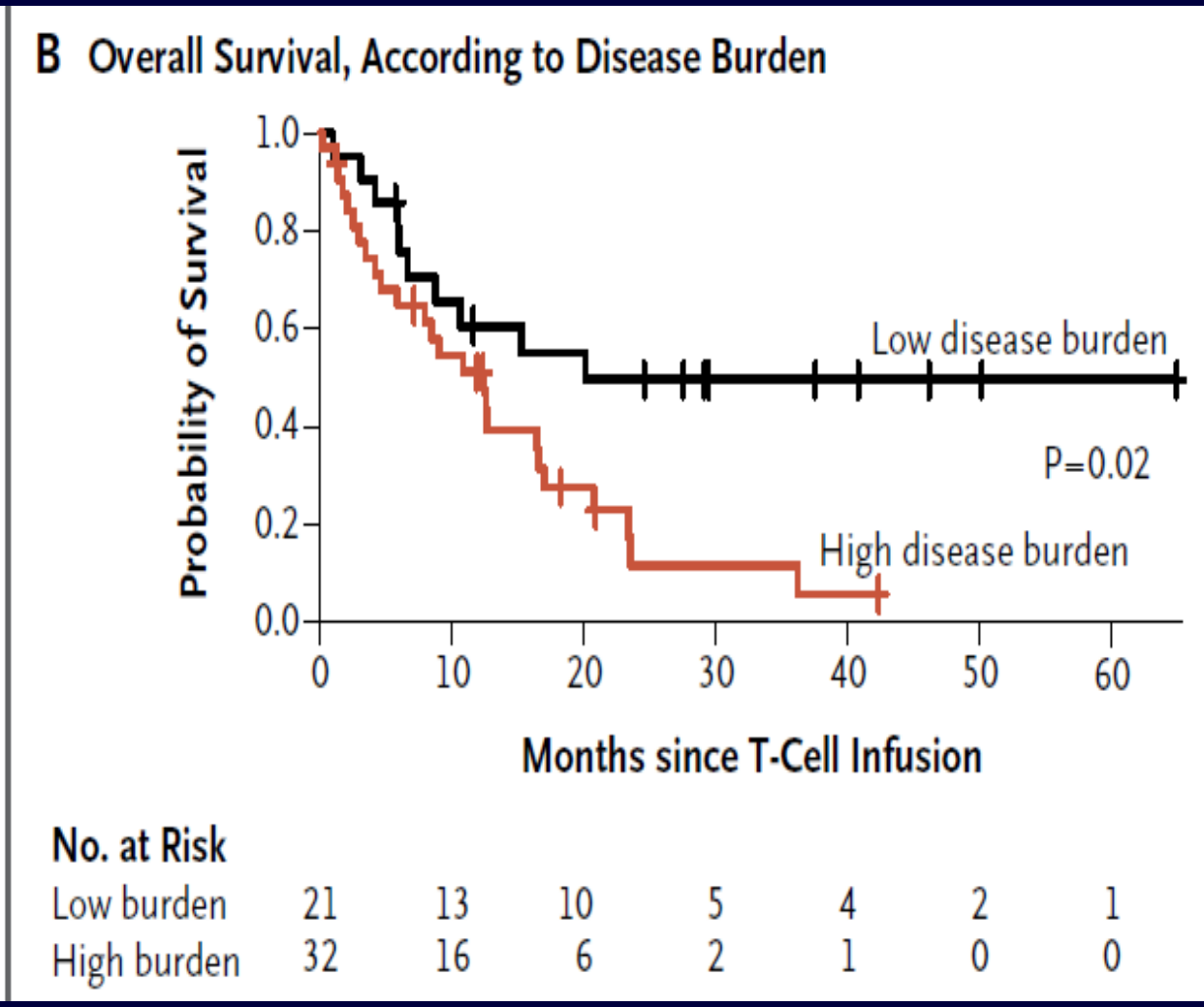


Grupp. EHA. Abst S1618; 2019

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.

Phase I trial using CD19/CD22 Bispecific CAR T cells in Pediatric and Adult ALL

Safety & Efficacy

Dose Level 1: 1 x 10^6 CAR T cells/kg: 8 patients

Dose Level 2: 3 x 10^6 CAR T cells/kg: 13 patients

86% CR;
MRD neg CR = 17/21 (81%)

ALL Pt ID	P-1	P-2	P-3	P-4	P-5	P-6	P-7	P-10	7	8	9	13	24	26	29	30	32	33	34	35
Age	17	2	16	13	2	12	11	8	35	69	48	58	35	26	27	59	36	26	48	31
Max CRS Grade	1	1	0	2	2	1	0	2	1	1	0	4	2	1	1	2	2	1	0	2
Max ICANs Grade	1	0	0	0	0	0	0	0	0	2	0	4	0	0	0	0	0	3	0	1
CR (Best response)	CR	CR	CR	CR	PD	CR	CR	CR	CR	CR	CR	CR	CR	CR	PR	CR	CR	CR	CR	CR
MRD $<10^4$	Neg	Neg	Neg	Pos		Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg		Neg	Neg	Neg	Neg	Neg

Schultz. Blood 134: abst 744; 2019

ALL Next Questions. Future

- Optimal regimens—less chemo;chemo+ino-blina-venetoclax; SQ blina
- More CNS prophylaxis (since less HD ara C and HDMTX, and longer survival)
- Improve ino schedule— 50% cumulative dose (2.7mg/m^2); ursadiol
- Improve blina schedules— 8 vs 4 courses; SQ blina
- Interject blina between last ino dose and SCT when needed (3 mos?)
- Incorporate new strategies—SQ blina, “better inos” ,venetoclax, navitoclax
- Role of CARTs and alloSCT—redefine in frontline Rx

Leukemia Questions?

Cell– 281-705-7207

Email-
hkantarjian@mdanderson.org