



SINTOMA'24

PARCERIA **soho**
society of hematologic oncology

APOIO
INSTITUCIONAL

bp Educação
e Pesquisa

How are target therapies (antibodies, TKIs) redefining the treatment paradigm in Acute Lymphoblastic Leukemia (ALL) in adults?

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Department of Leukemia

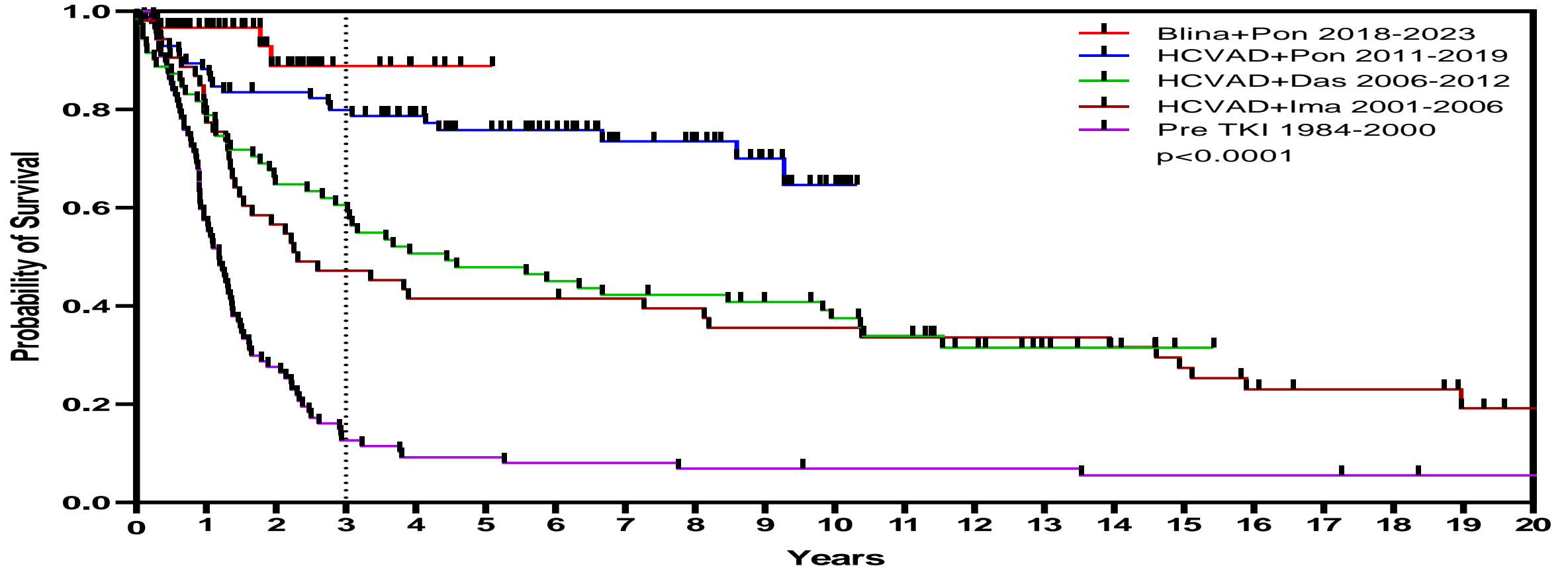
University of Texas MD Anderson Cancer Center

Houston, Texas

USA



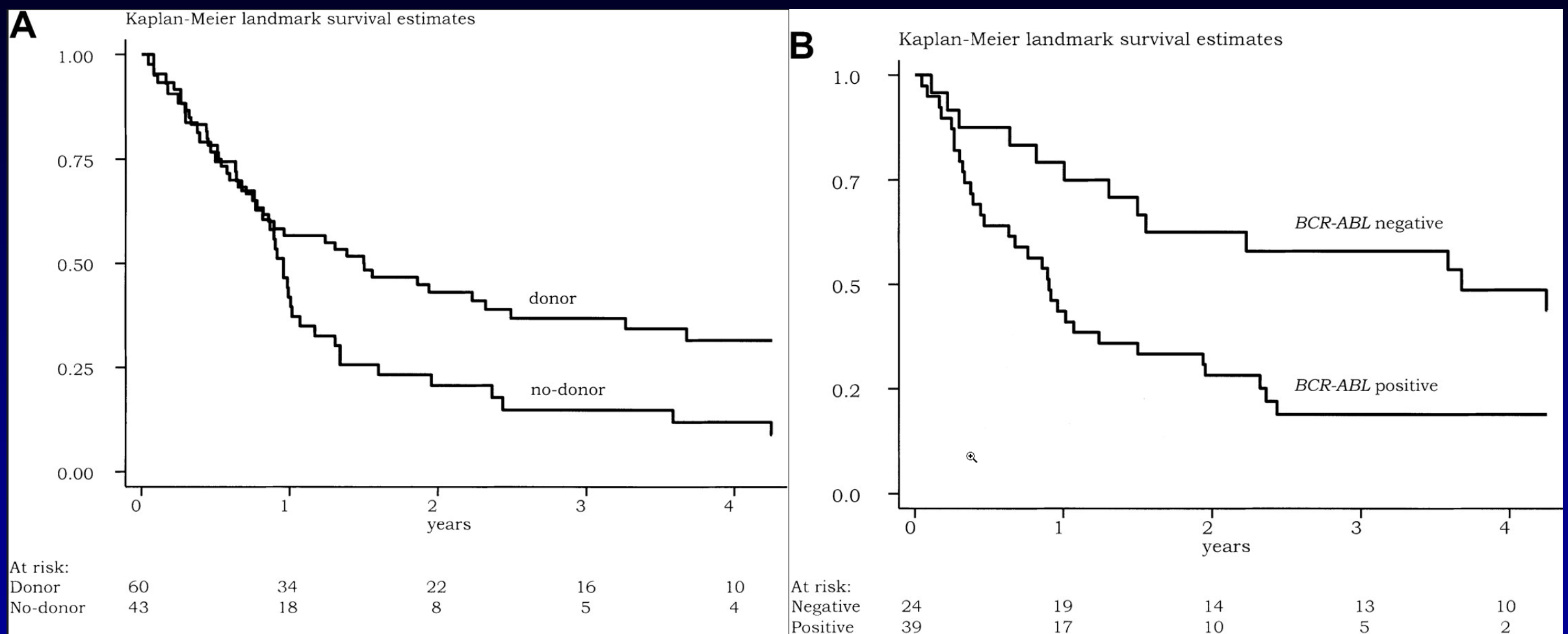
Ph-positive ALL. Survival by Decade (MDACC 1984-2023)



	Total	Events	3yr OS	5yr OS	Median
— Blina+Pon 2018-2022	62	4	89%	—	Not reached
— HCVAD+Pon 2011-2019	85	23	80%	76%	Not reached
— HCVAD+Das 2006-2012	71	47	61%	48%	53 mos
— HCVAD+Ima 2001-2006	53	41	47%	42%	28 mos
— Pre TKI 1984-2000	87	83	13%	9%	14 mos

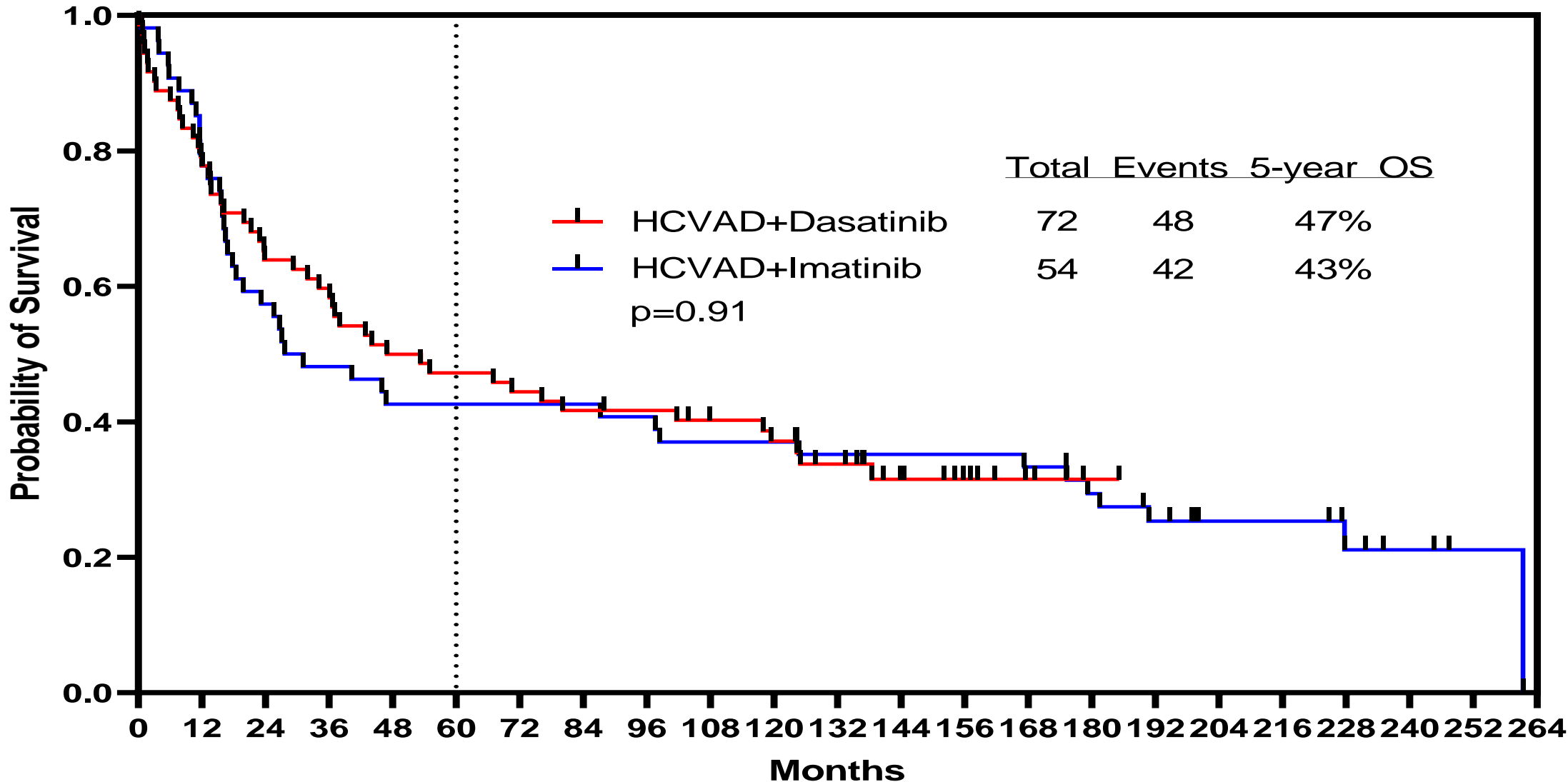
$p < 0.0001$

SCT for Ph⁺ ALL. Pre-TKI



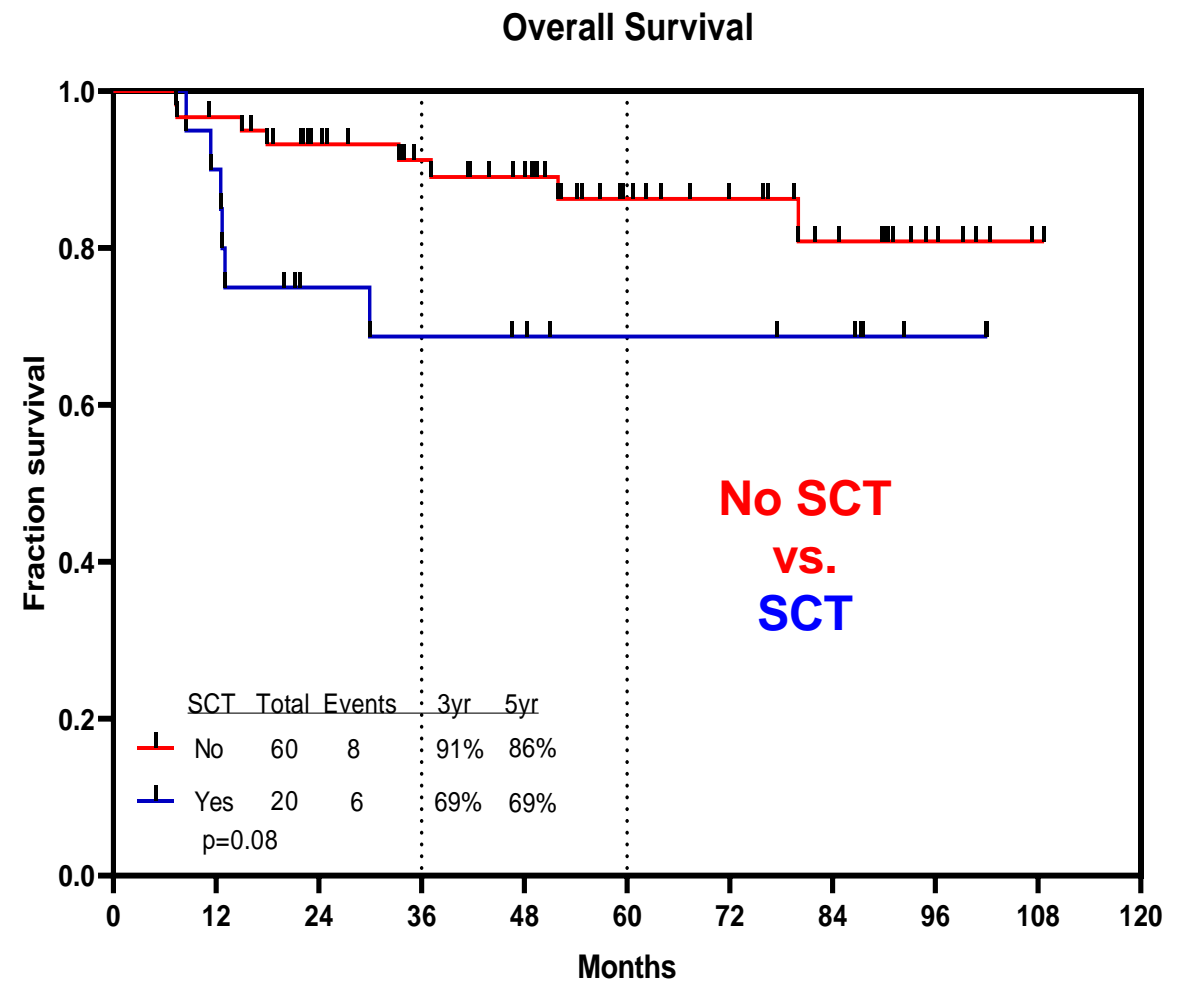
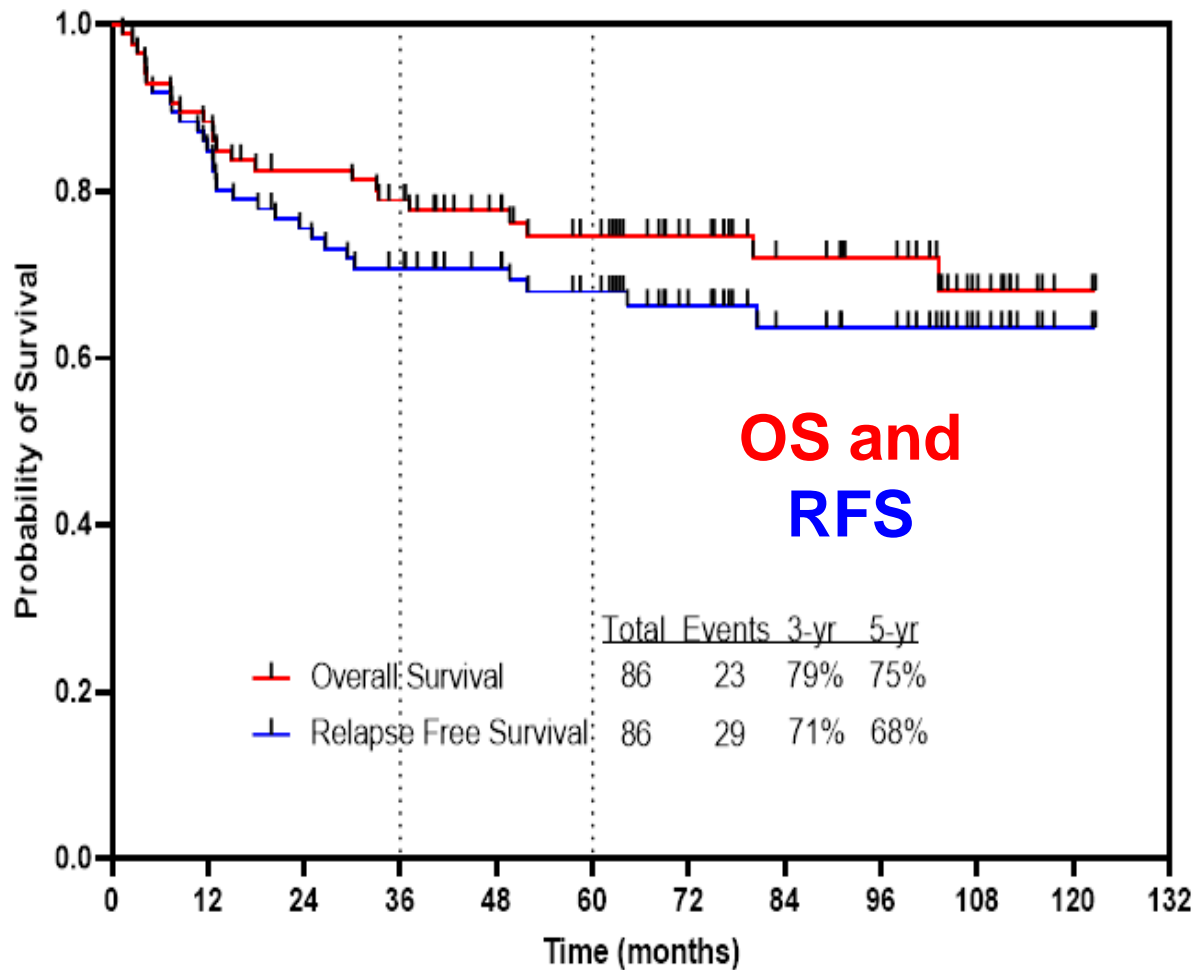
- Donor (n=60) - 3-year OS: 37%
- No donor (n=43) – 3-year OS: 12%

Ph-positive ALL 1st/2nd Generation TKI. Survival

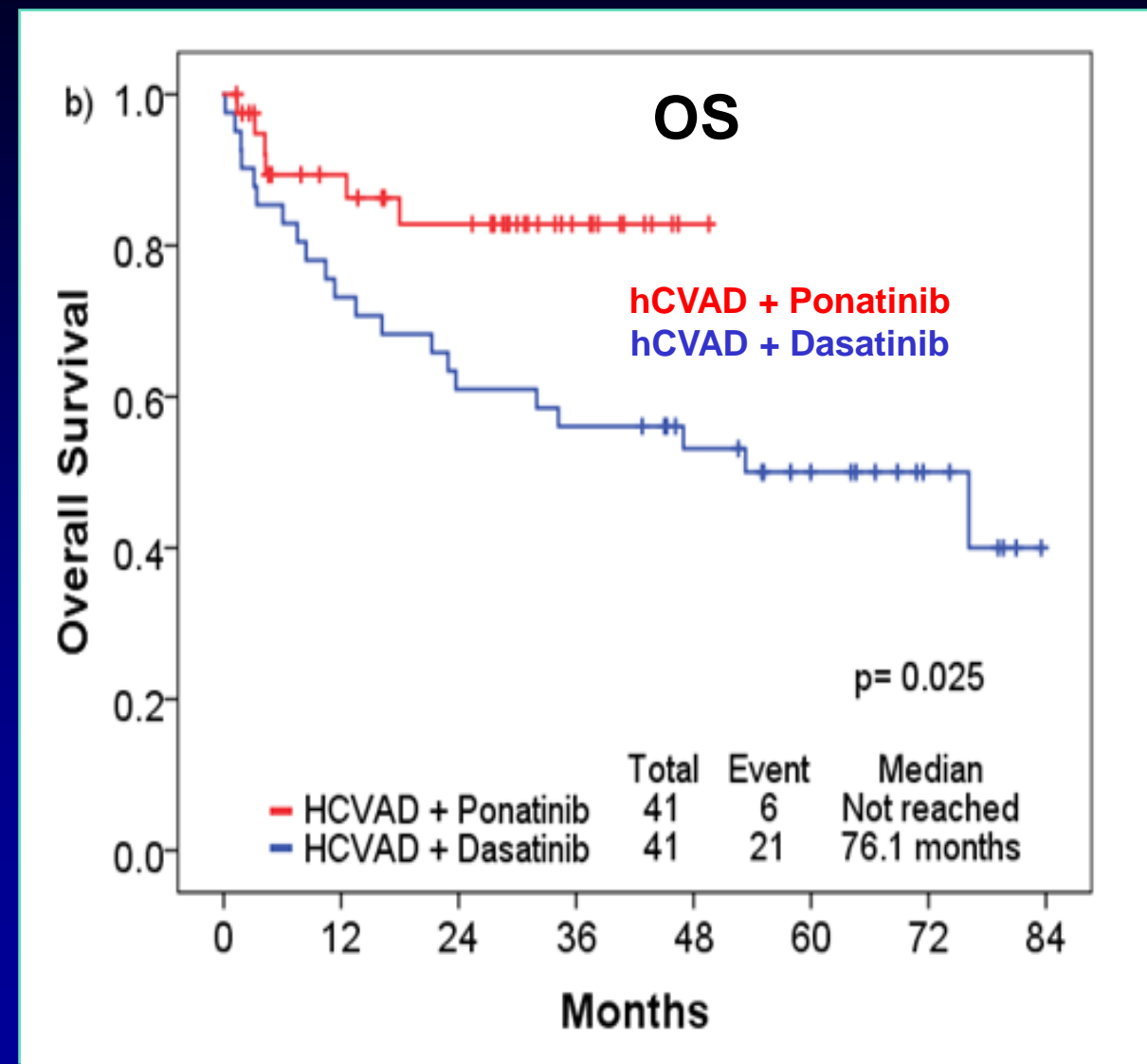
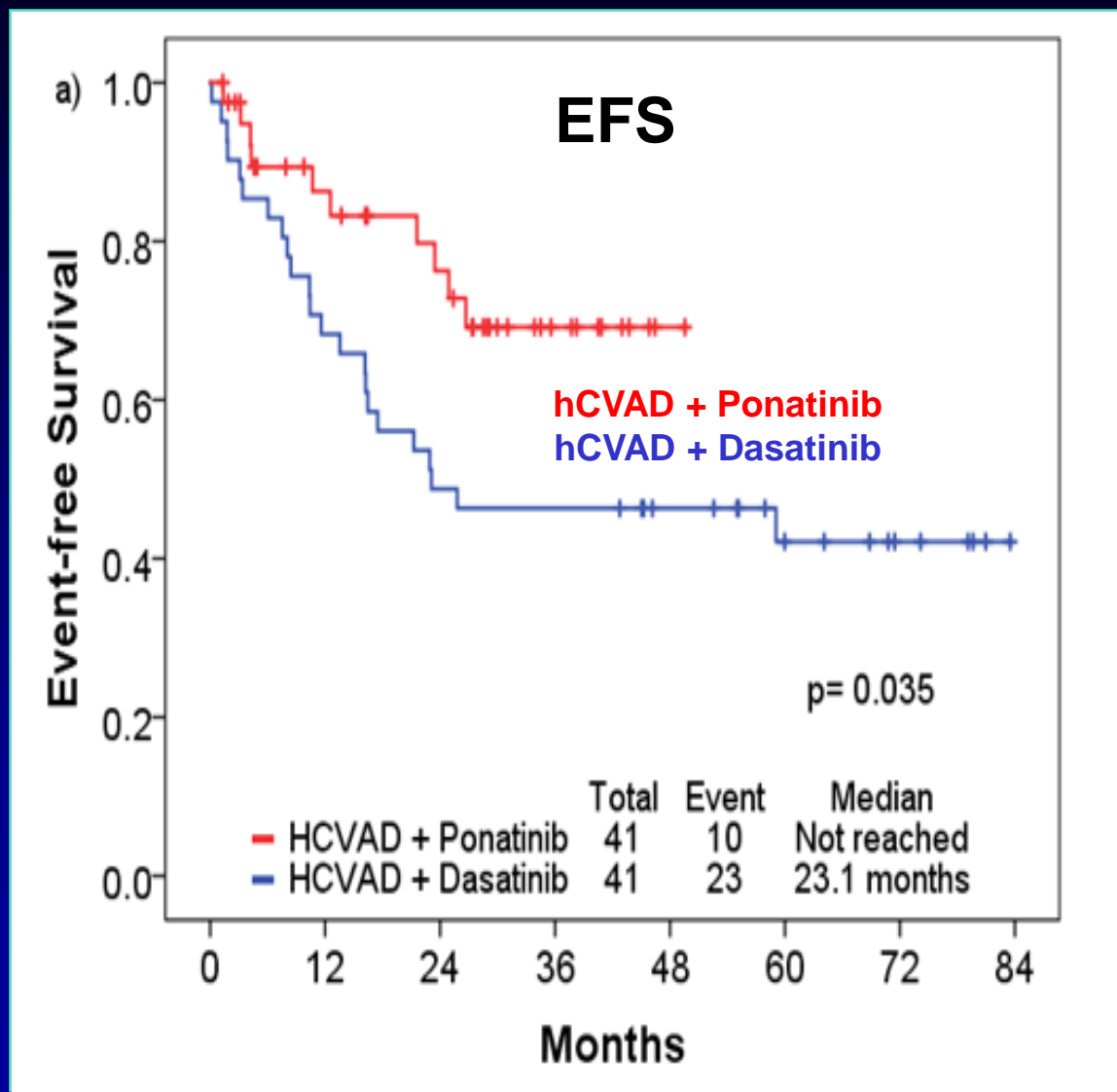


HyperCVAD + Ponatinib in Ph-positive ALL

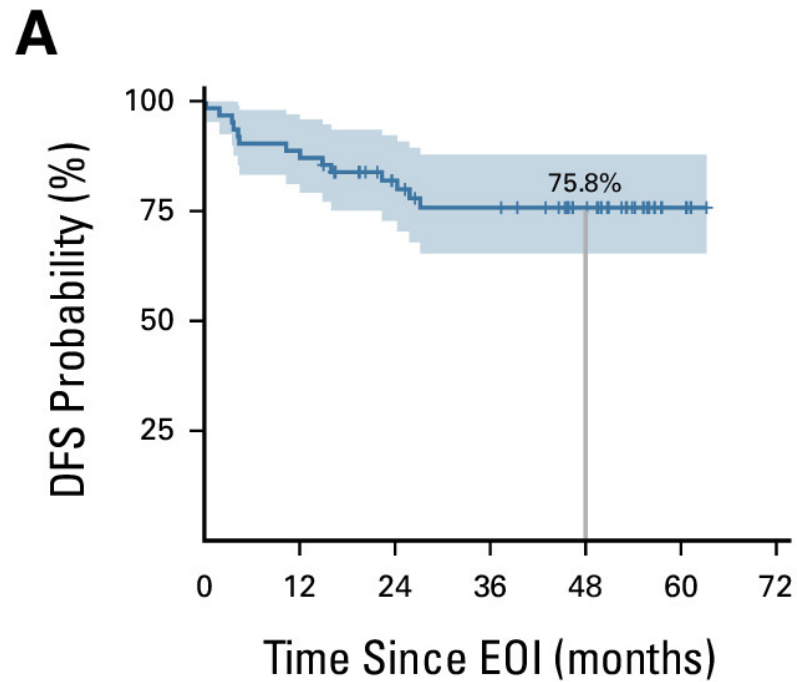
- 86 pts Rx; median age 47 yrs (39-61); median FU 75 mos (16-123)
- CR 68/68 (100%); FCM-MRD negative 85/86 (99%); **CMR 84%**; **5-yr OS 75%**, **EFS 68%**
RFS and survival 6-month Landmark



Propensity Score Analysis: HCVAD + Ponatinib vs HCVAD + Dasatinib in Ph-Positive ALL.

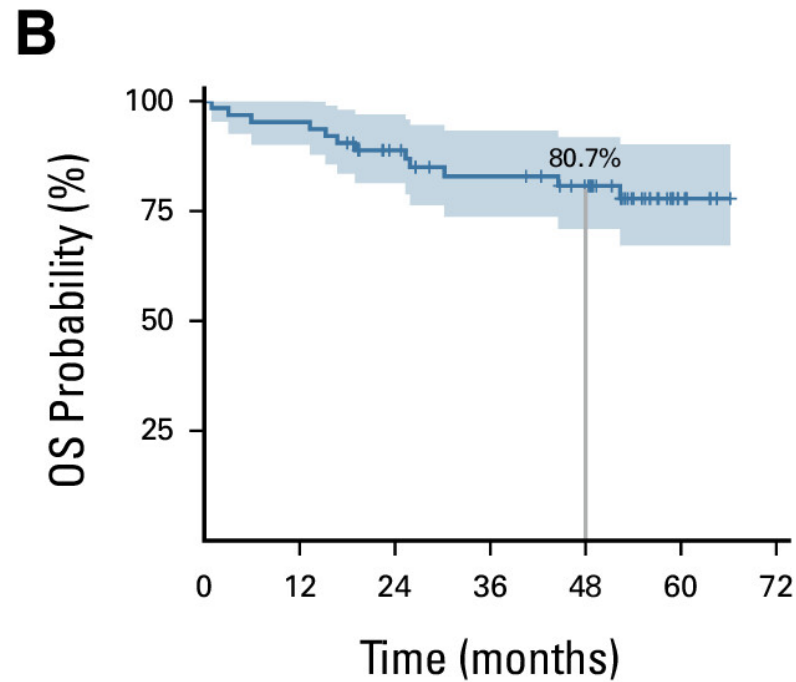


Long-Term Results of the Dasatinib-Blinatumomab in adult Ph⁺ ALL



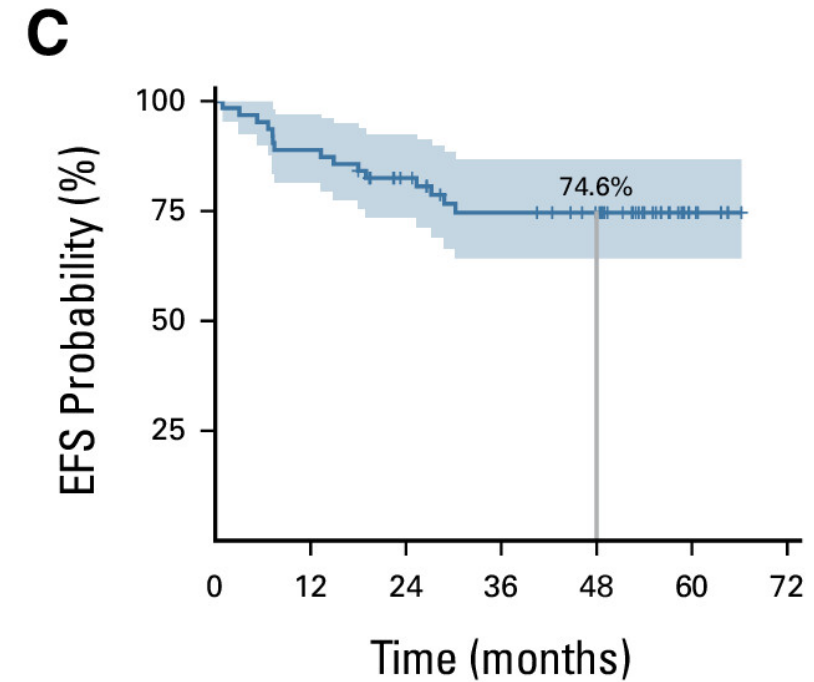
No. at risk:

Time (months)	No. at risk
0	62
12	55
24	41
36	36
48	26
60	5
72	0



No. at risk:

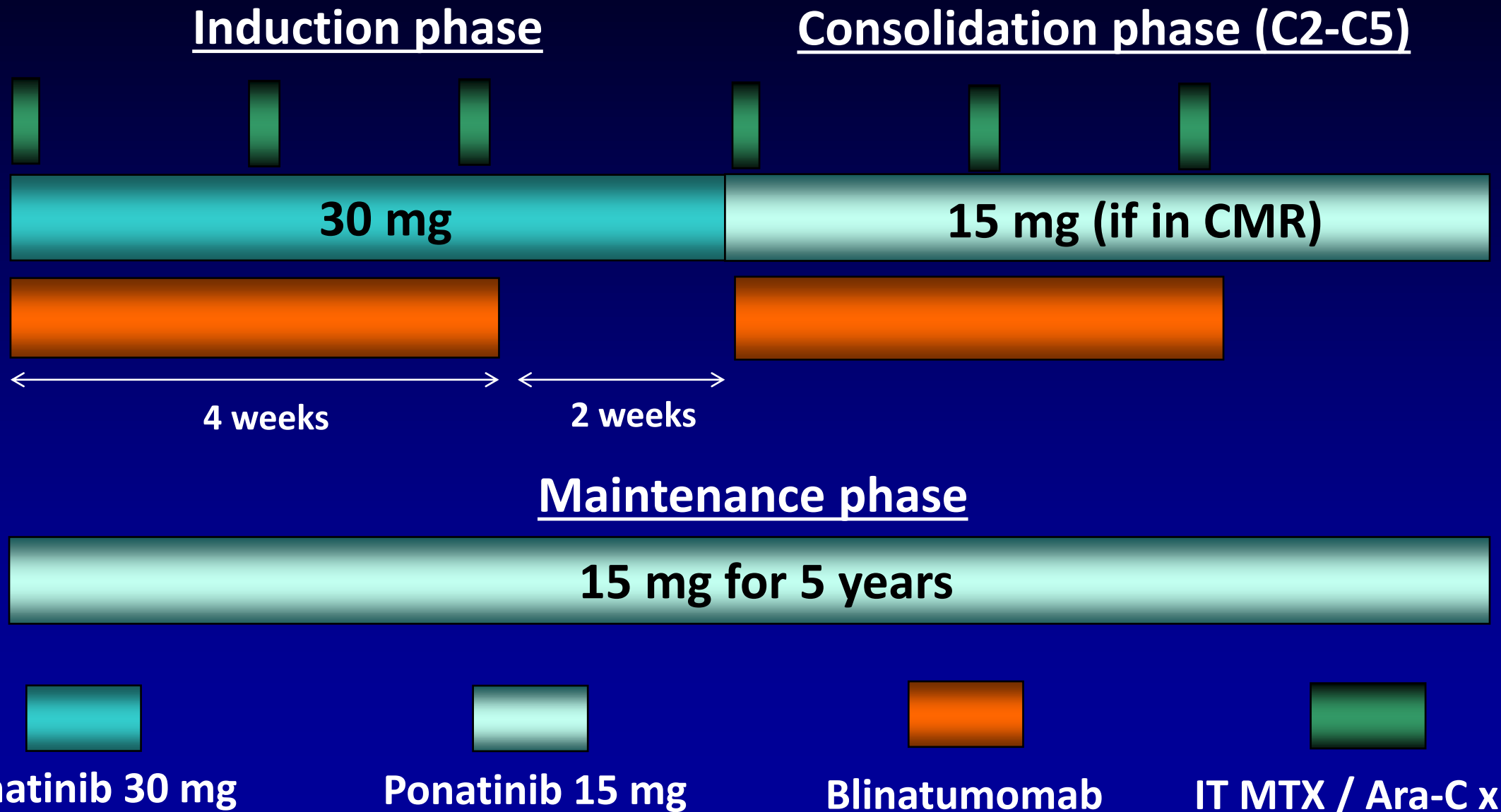
Time (months)	No. at risk
0	63
12	60
24	47
36	40
48	34
60	8
72	0



No. at risk:

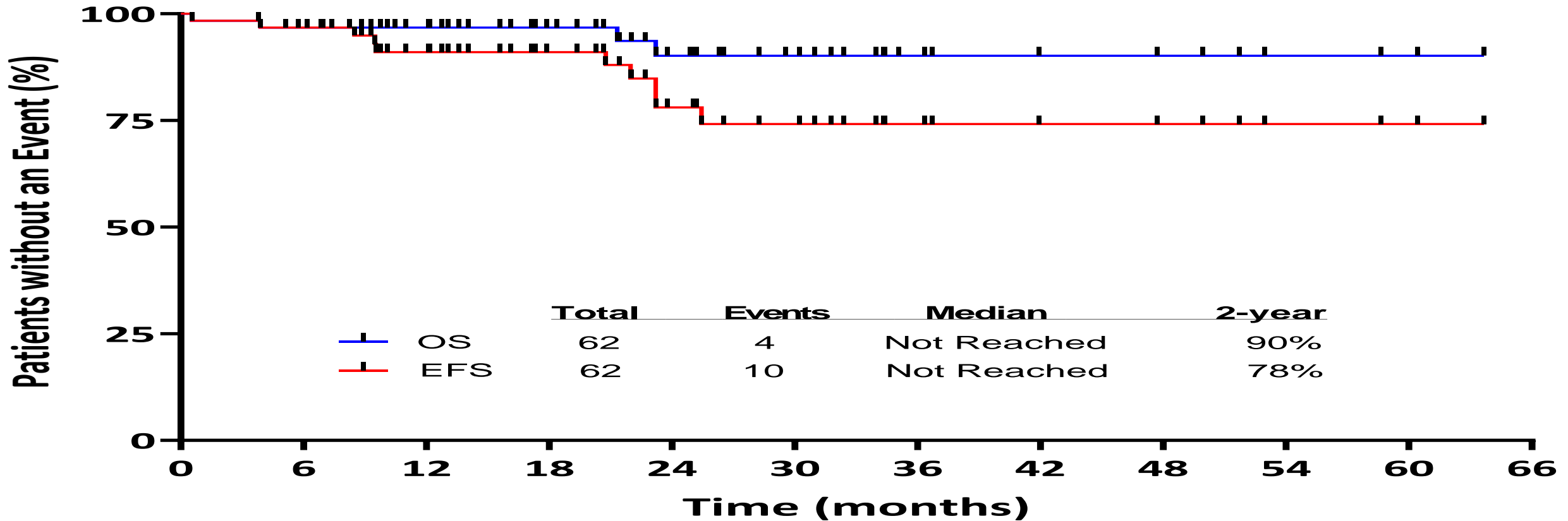
Time (months)	No. at risk
0	63
12	56
24	45
36	37
48	32
60	7
72	0

Ponatinib + Blinatumomab in Ph+ ALL. Regimen



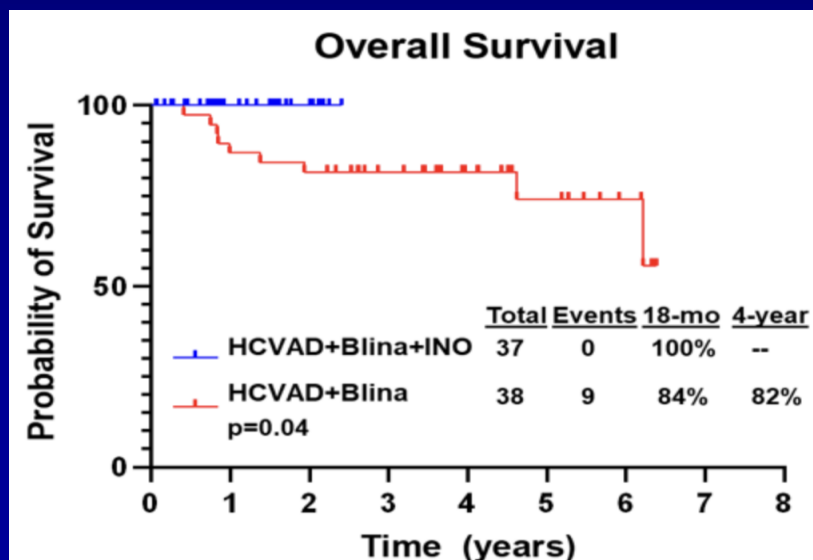
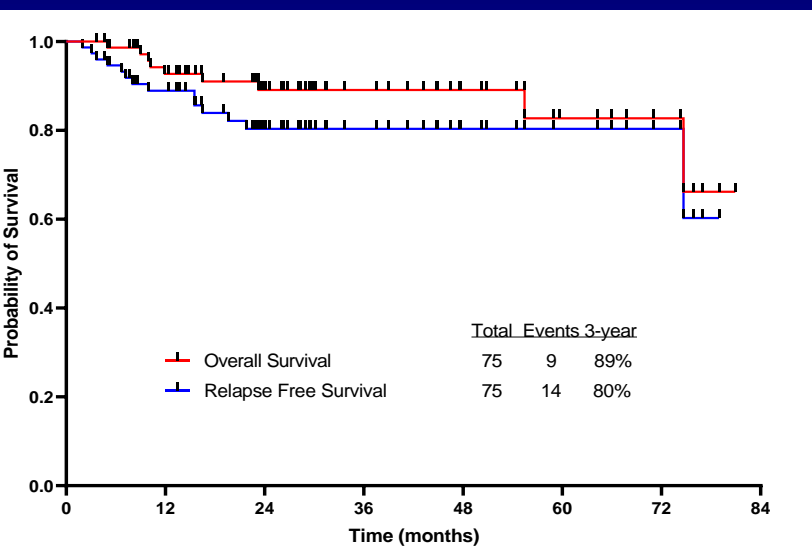
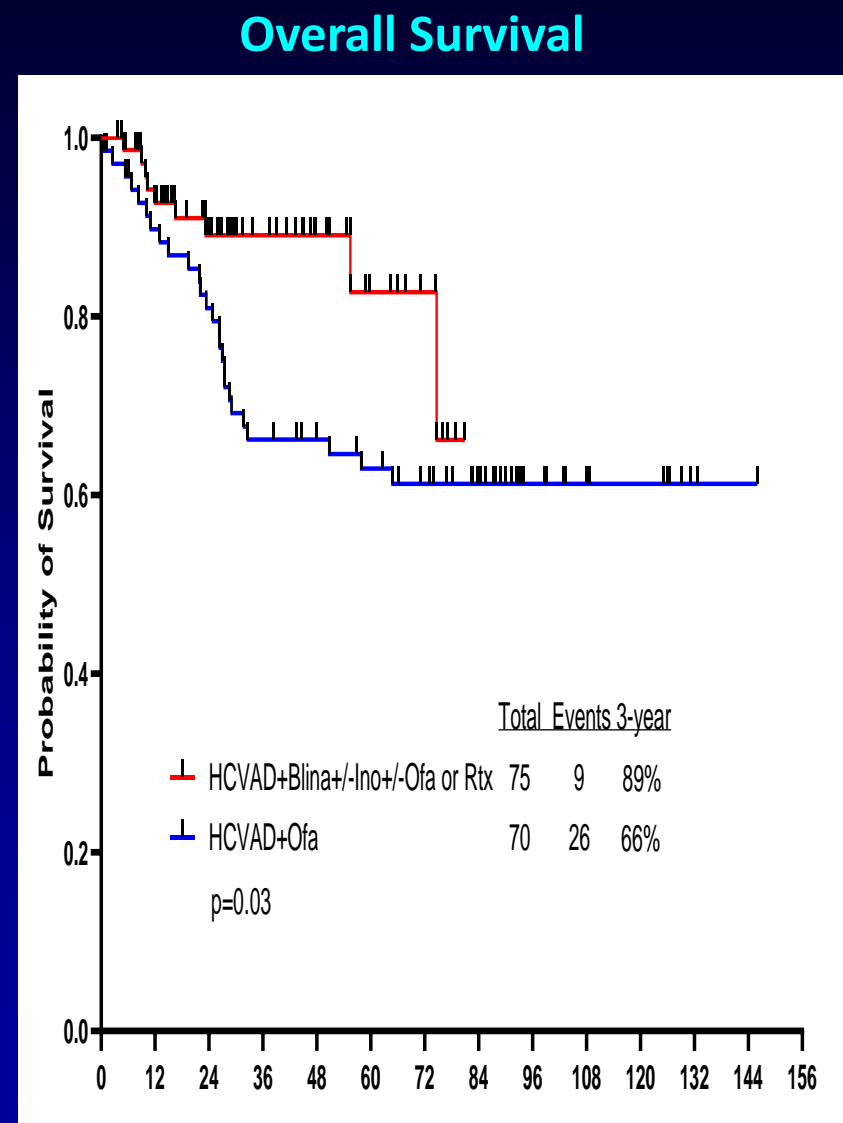
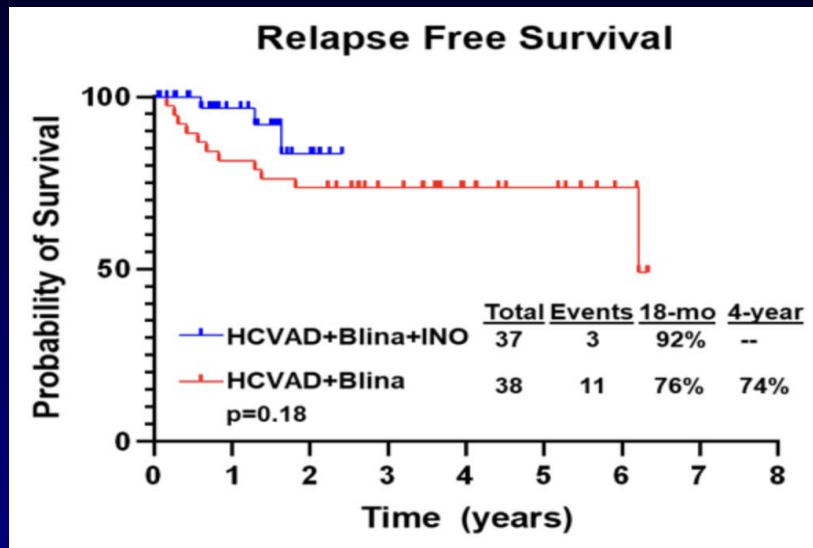
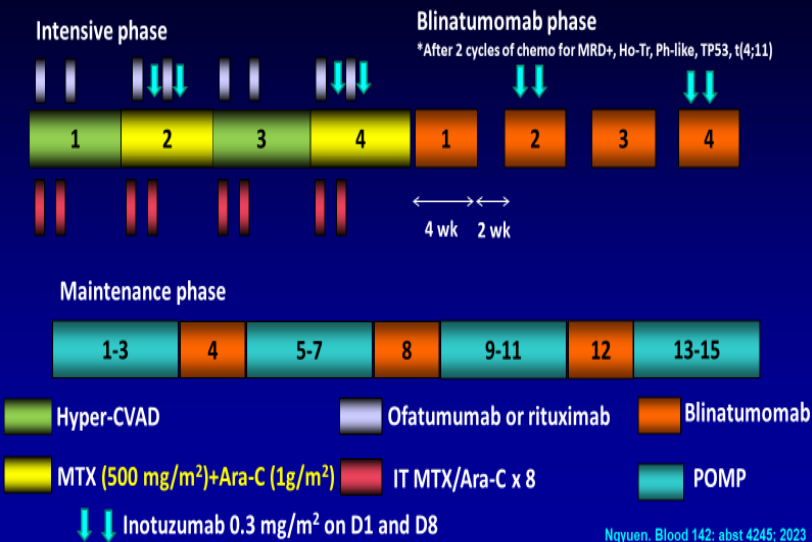
Ponatinib and Blinatumomab in Newly Dx Ph-Positive ALL

- 62 pts Rx with simultaneous ponatinib 30-15mg/D and blinatumomab x 5 courses. 12-15 ITs
- Only 1 pt had SCT(2%); Median F/U 17 months. **2-yr EFS 78%, OS 90%**
- CR/CRi 98% (CR 95%); **CMR 84% (67% after C1); NGS-MRD negativity 94%**
- 7 relapses (all p190): 4 CNS, 1 CRLF2+ (Ph-), 2 systemic; **5/7 WBC>75K**

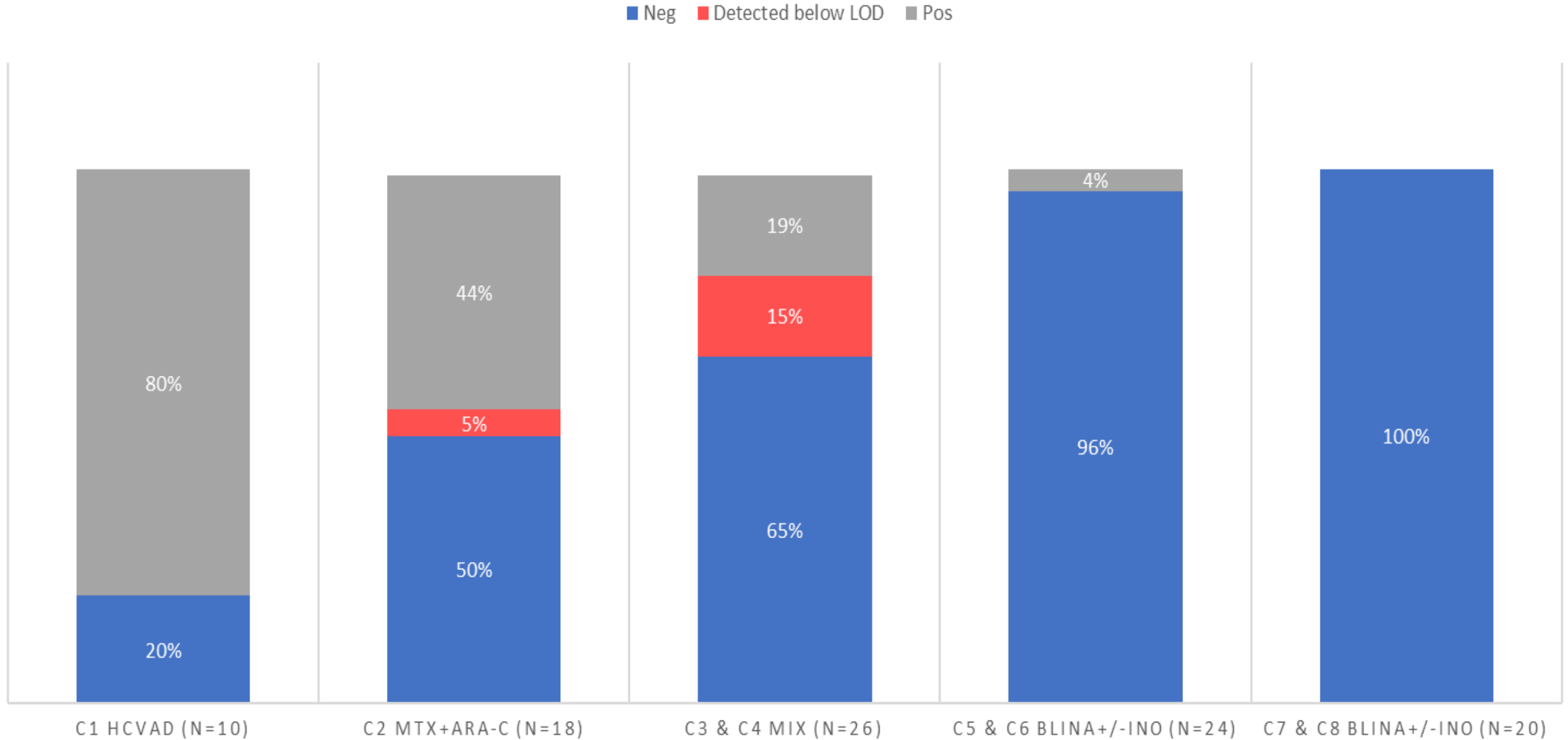


Hyper CVAD-Inotuzumab→Blinatumomab in Newly Dx Adult ALL

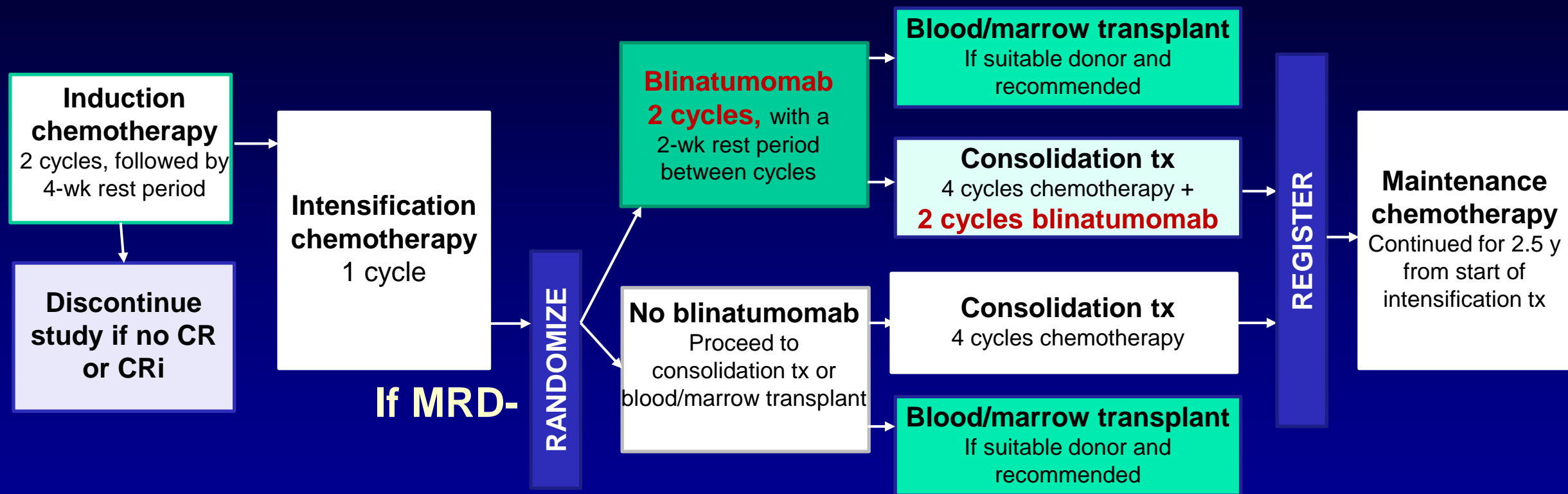
- 75 pts; median age 33 yrs (18-59); Median F/U 26 months (1-77)
- CR rate 100%; MRD negative 95% (66% at CR); NGS-MRD negative 73%; 60-day mortality 0%; 24 (32%) allo-SCT;



HCVAD-Blina-Ino in Newly Dx Ph-negative ALL. Dynamic of Molecular Response by NGS



E1910: Randomized Phase 3 Trial: Blinatumomab vs SOC as Consolidation in MRD-Negative CR

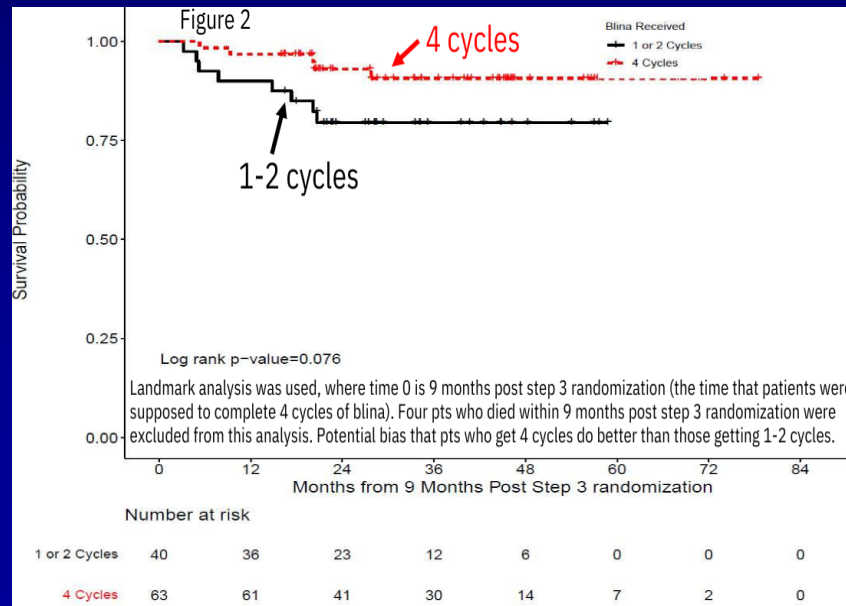
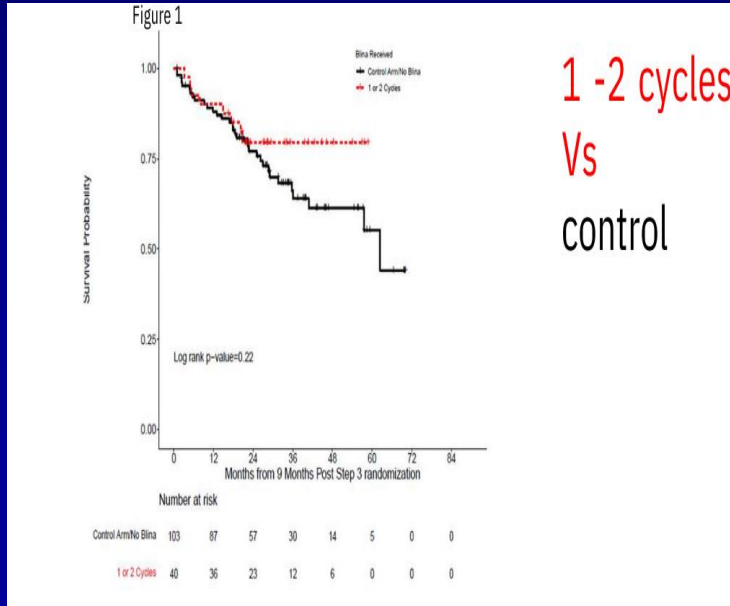
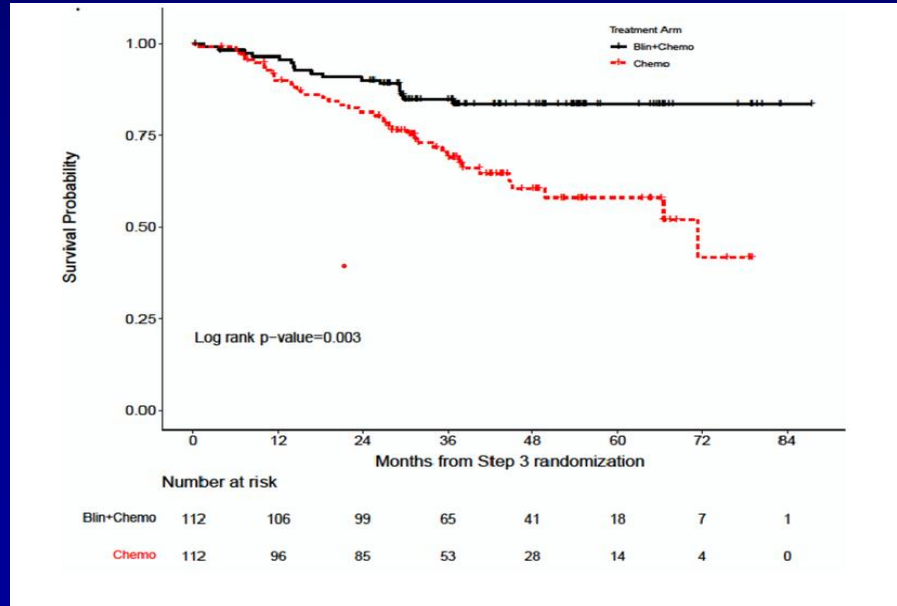


- Accrual = 488
- US intergroup study
- n = 265/360 (509) patients
- USA, Canada, Israel
- 1:1 randomization

E1910 Randomized Phase 3 Trial: Blina vs SOC as Consolidation in MRD-ve. Outcomes by Number of Cycles

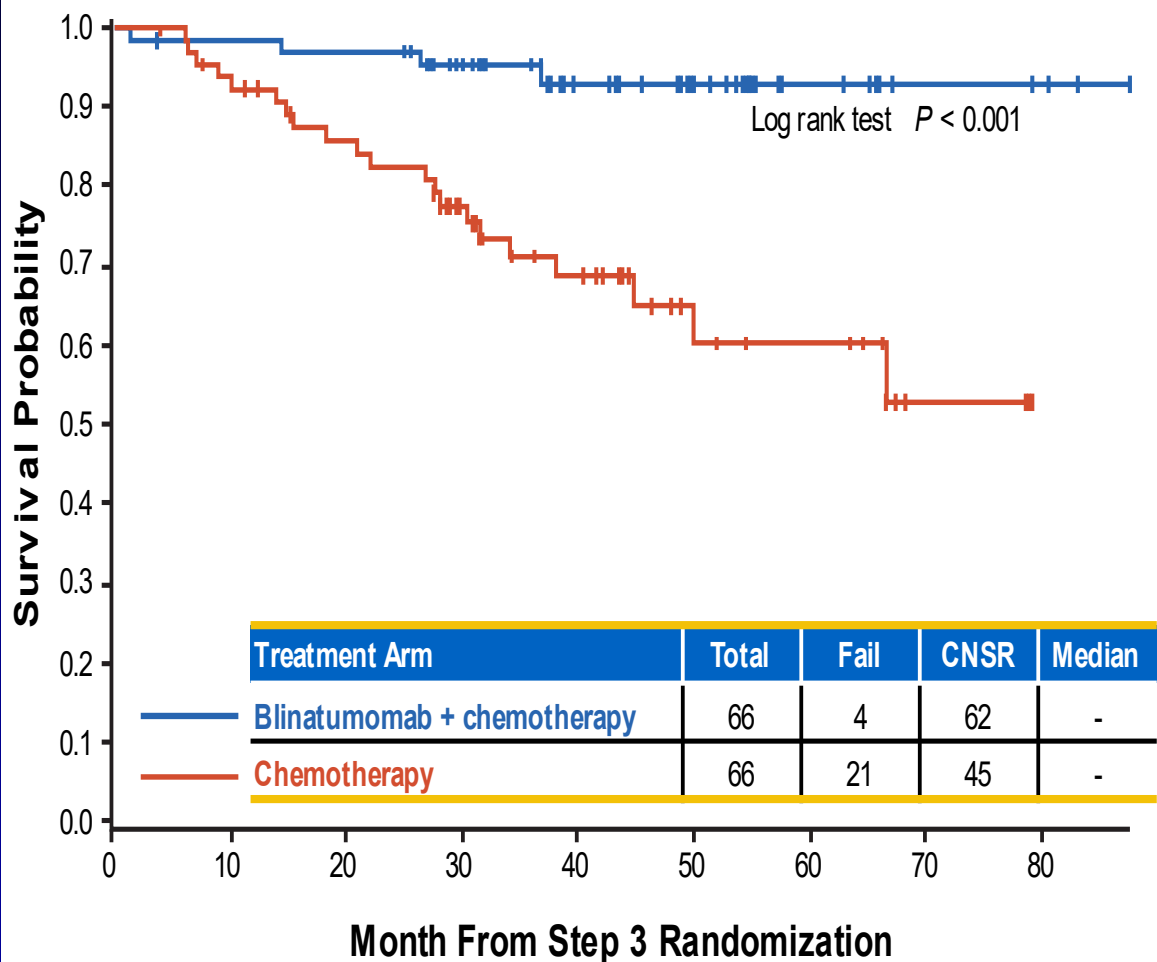
- 488 pts median age 51 yrs (30-70)
- 224 MRD-negative CR randomized 1:1
- 22 pts (20%) Rx ASCT in each arm
- Median F/U 43 months; **median OS NR vs 71.4 mos (HR=0.42; p=0.003)**
- No difference in OS if 1-2 cycles of blina vs control (HR: 0.62; p=0.22)
- OS: 1-2 cycles vs 4 cycles (HR: 0.39; p=0.07)

#cycles	121
1	12
2	32
3	4
4	63 (52%)



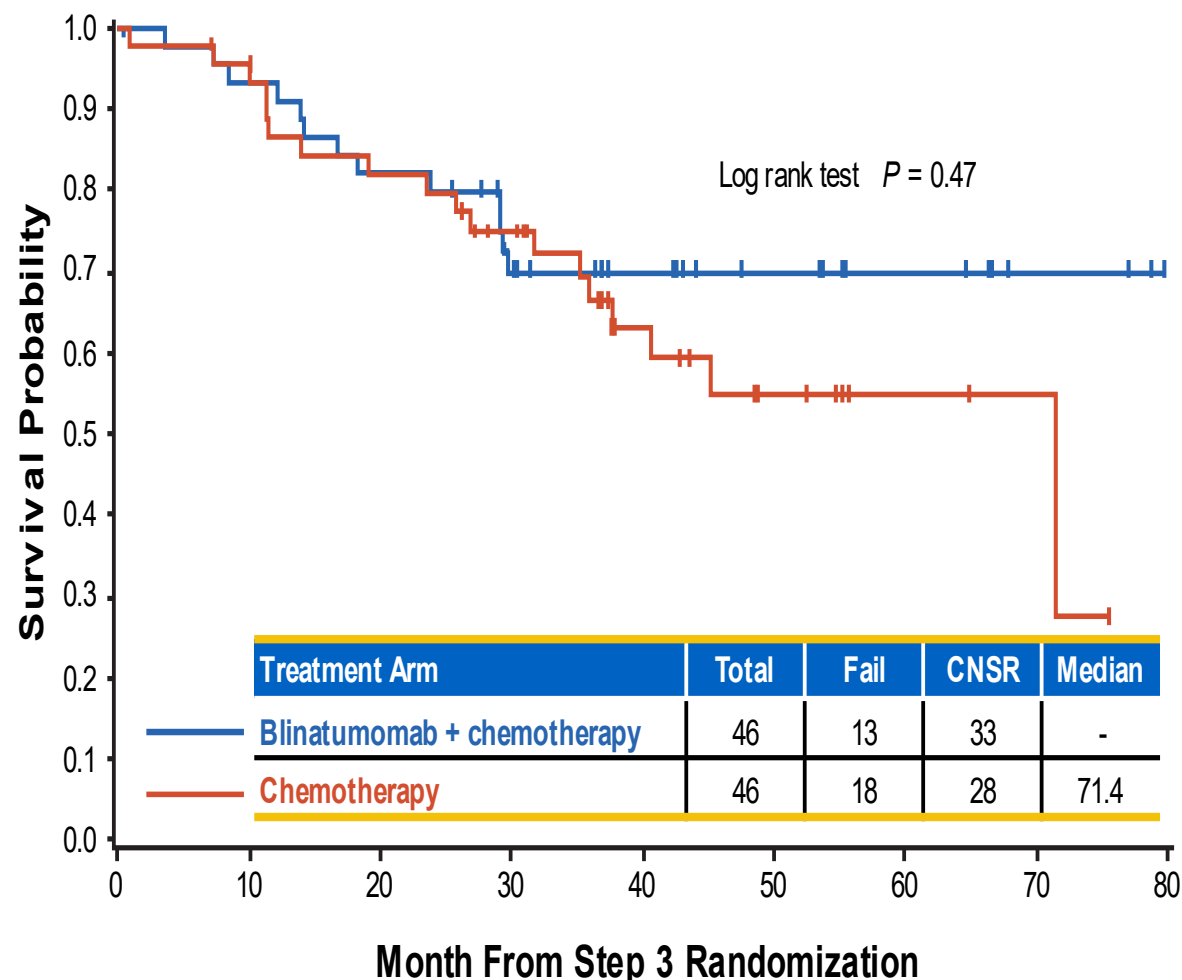
E1910 Randomized Phase 3 Trial: Blina vs SOC as Consolidation in MRD-ve. Outcomes by Age

OS Comparison: MRD- Age < 55 Years



Median OS: NR in both arms; HR: 0.18; 95% CI: 0.06-0.52; $P < 0.001$

OS Comparison: MRD- Age ≥ 55 Years



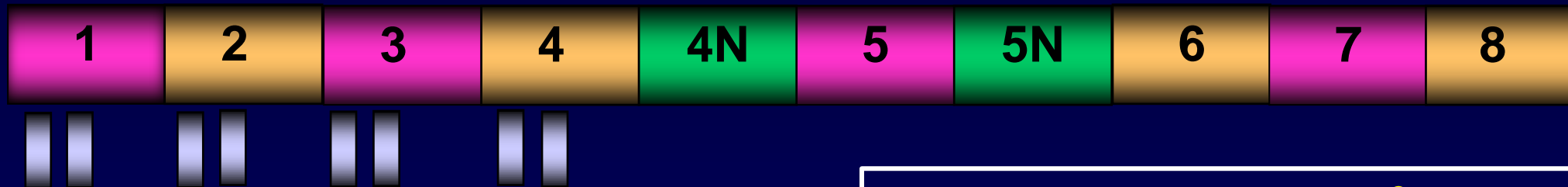
Median OS: NR vs 71.4 months; HR: 0.77; 95% CI: 0.37-1.58; $P = 0.47$

Hyper-CVAD + Nel in T-ALL/T-LL. Design

Regimen 4 (N=15)

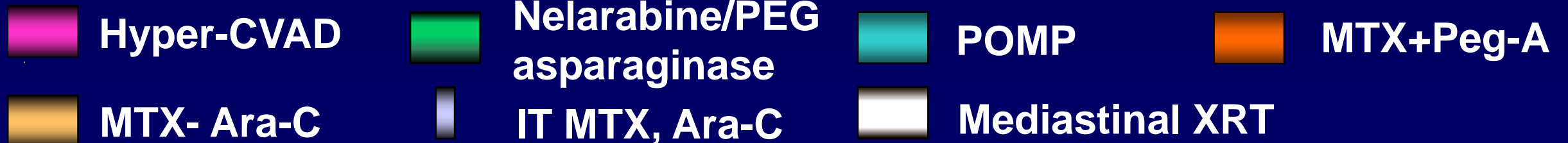
Venetoclax: initially two weeks per cycle
Then one week per subsequent cycles

Induction-Consolidation



Nelarabine: 650 mg/m² IV daily for 5 days
PEG asparaginase: 1500 IU/m²; capped

Maintenance



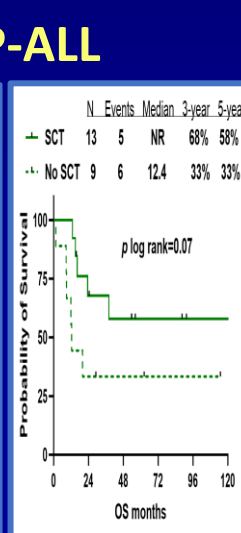
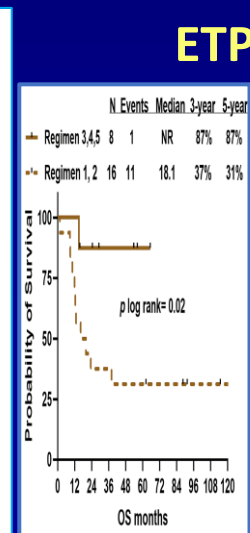
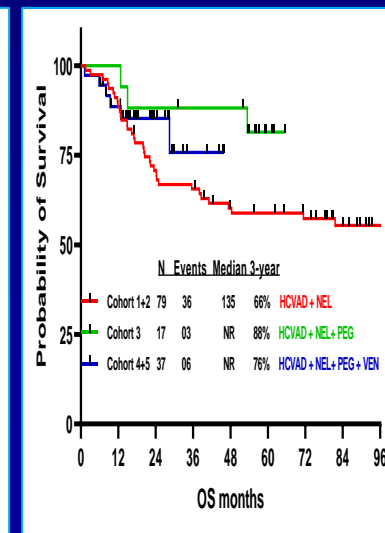
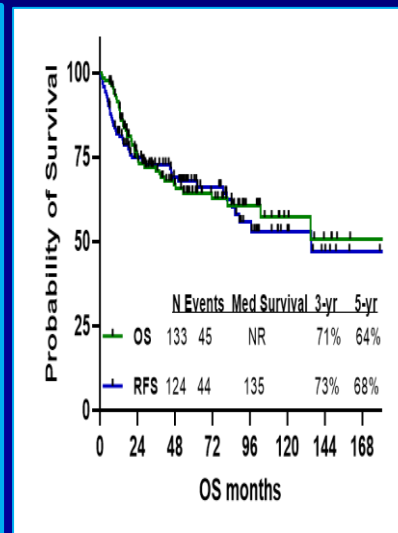
Hyper-CVAD, Venetoclax, Nelarabine-Peg Asp in T-ALL/LL

- 133 pts (7/2007-12/2022) on 5 cohorts; 60%T ALL; 18% ETP; Median FU 62 mos
- ORR 95%; CR 89%; 5-yr OS 64%
- Cohorts 3-5: 5-yr OS 87%
- OS shorter ETP/near-ETP vs non-ETP phenotype (71 mos vs. NR, p=0.08)

Regimens	N	Year	Hyper-CVAD	Nelarabine (NEL)	Pegasparaginase (PegAsp)	Venetoclax (Ven)
1	30	2007-2011	Hyper-CVAD 1,3,5,7 MTX/Ara-C 2,4,6,8	After C8 for 2 cycles Cycles 6-7 of maintenance	-	-
2	49	2011-2017		After C4 (4N) and C5 (5N) Cycles 6-7 of maintenance	-	-
3	17	2017-2019			PegAsp with NEL in Cycles 4N and 5N	-
4	16	2019-2021			PegAsp with NEL in Cycles 6-7 of maintenance	Days 1-7 of all Induction/ consolidation cycles
5	21	2021-2023				Days 1-7 of C1; Days 1-3 for C2-C8* only for ETP-ALL / MRD+

	Total N=133	Regimen 1 n=30	Regimen 2 n=49	Regimen 3 n=17	Regimen 4 n=16	Regimen 5 n=21
ORR	109/113 (96)	25/26 (96)	39/40 (98)	16/16 (100)	13/13 (100)	16/18 (89)
CR/CRp	104/113 (92)	25/26 (96)	38/40 (95)	15/16 (94)	12/13 (92)	14/18 (78)
PR	5/113 (4)	0	1/40 (3)	1/16 (6)	1/13 (8)	2/18 (11)
NR	4/113 (4)	1/26 (4)	1/40 (3)	0	0	2/18 (11)
CR at start	20	4	9	1	3	3

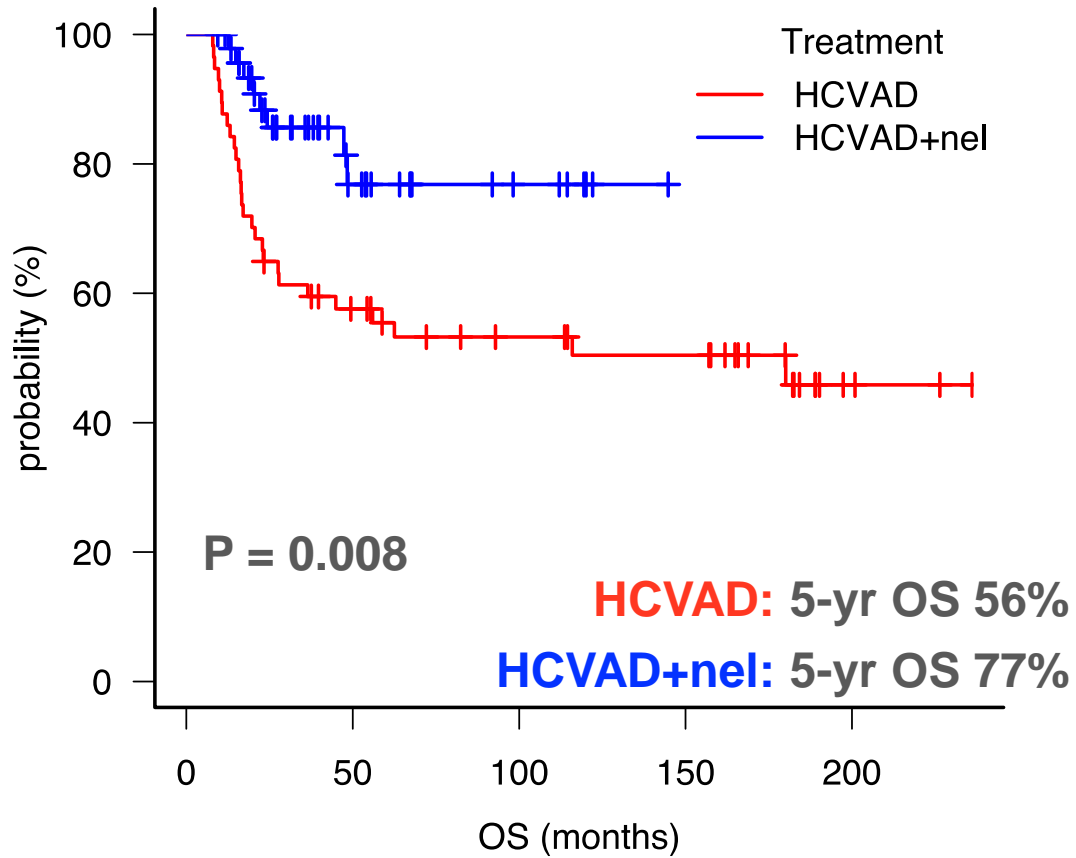
	Total	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Regimen 5
Number of patients	133	30	49	17	16	21
Median age [Range] Age ≥60 yrs	35 [18-78] 12 (9)	38 [19-76] 2 (7)	33 [18-78] 6 (12)	31 [18-65] 2 (12)	38 [18-52] 0	33 [20-62] 2 (10)
Male	102 (77)	22 (73)	39 (80)	14 (82)	12 (75)	15 (71)
ECOG PS 2-3	18 (14)	3 (10)	7 (14)	3 (18)	3 (19)	2 (10)
T-ALL	81 (61)	19 (63)	29 (59)	9 (53)	11 (69)	13 (62)
T-LBL	52 (39)	11 (37)	20 (41)	8 (47)	5 (31)	8 (38)
CNS+ at Dx	6 (5)	2 (7)	2 (4)	1 (6)	1 (6)	0
Mediastinal disease	72 (54)	16 (53)	24 (49)	8 (47)	8 (50)	16 (76)
Median WBC [Range]	7.8 [0.5-344.3]	7.6 [0.6-241.4]	7.7 [1.2-309.2]	7.4 [0.5-86.3]	9.3 [1.4-344.3]	11.3 [1.7-150.7]
BM Blast % [Range]	20 [0-97]	19.5 [0-95]	9 [0-96]	30 [1-94]	39 [0-90]	25 [1-97]
Immunophenotype						
Thymic	59 (44)	10 (33)	20 (41)	9 (53)	10 (63)	10 (48)
ETP	24 (18)	6 (20)	10 (20)	5 (29)	2 (13)	1 (5)
ETP+CD5	20 (15)	7 (23)	7 (14)	1 (6)	2 (13)	3 (14)
Early, non-ETP	3 (2)	0	1 (2)	0	2 (13)	0
Mature	15 (11)	3 (10)	6 (12)	1 (6)	0	5 (24)
NOS/NA	12 (9)	4 (13)	5 (10)	1 (6)	0	2 (10)



ETP-ALL

HCVAD +/- Nelarabine in non-ETP ALL. Landmark at 6 Months (post 8 courses)

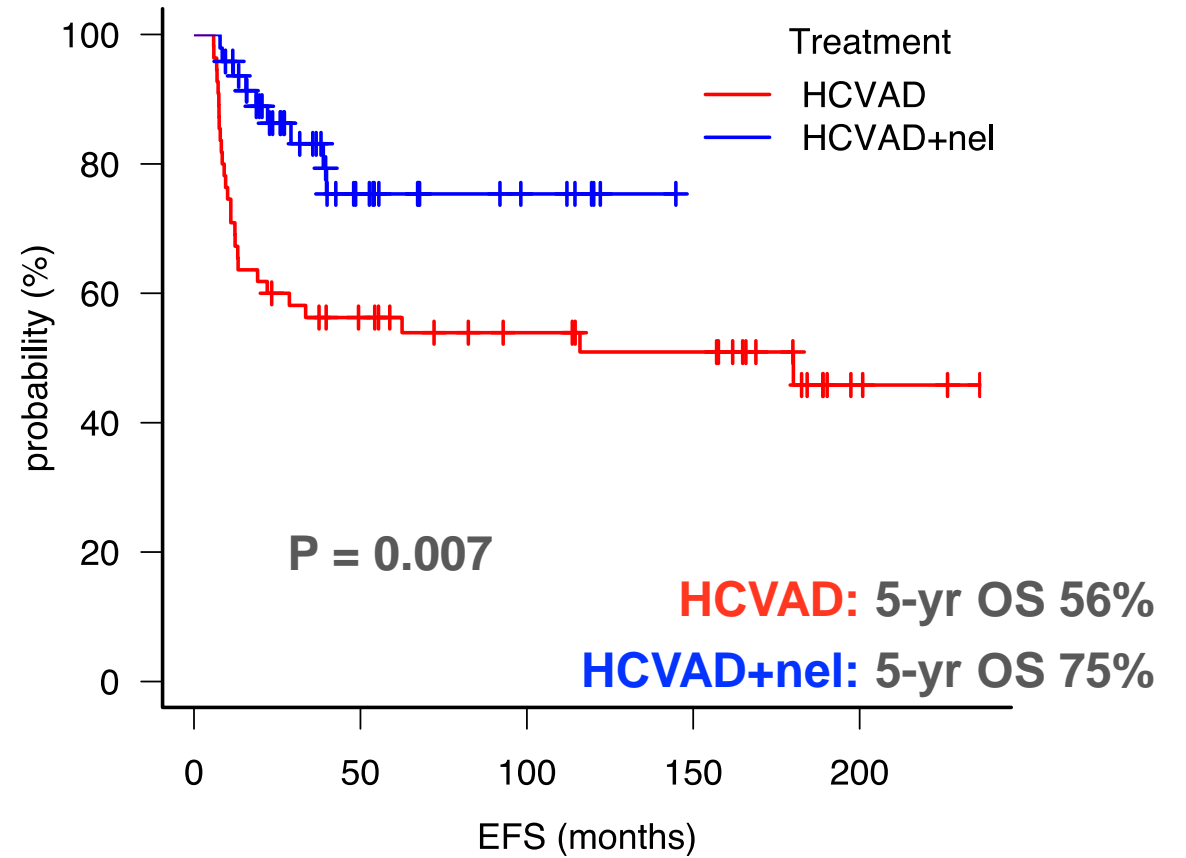
OS



Number at risk

HCVAD	57	29	21	18	3
HCVAD+nel	49	16	6	0	0

EFS

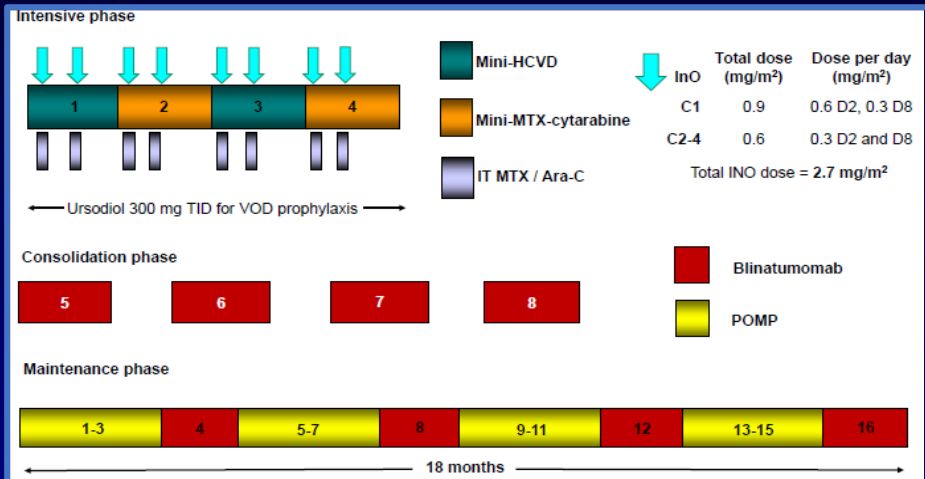


Number at risk

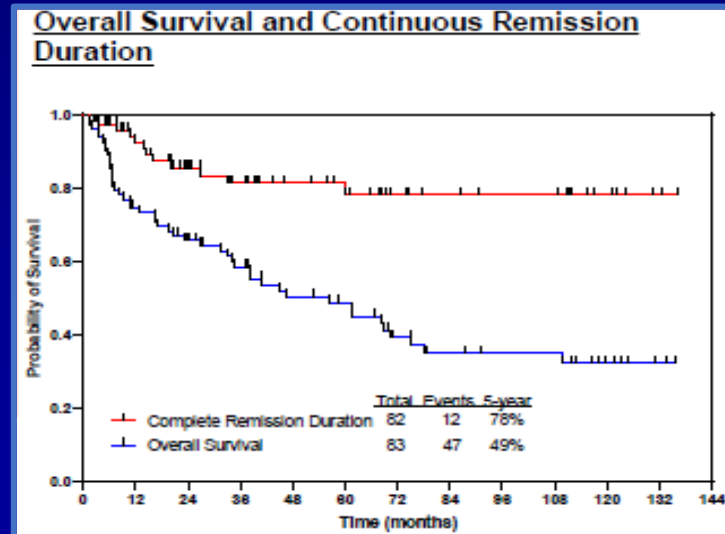
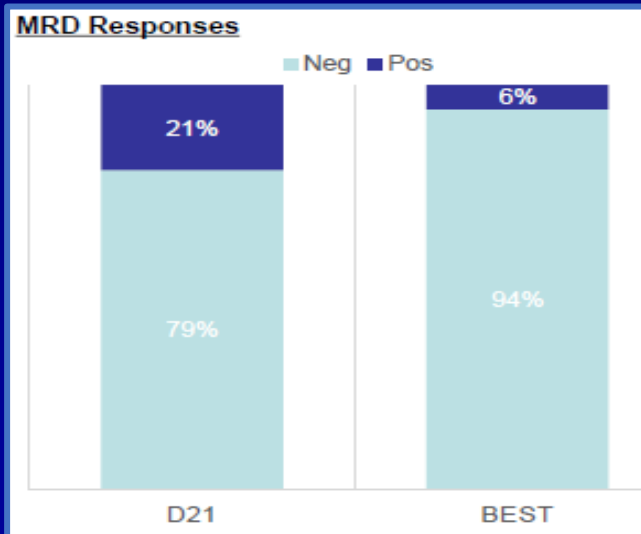
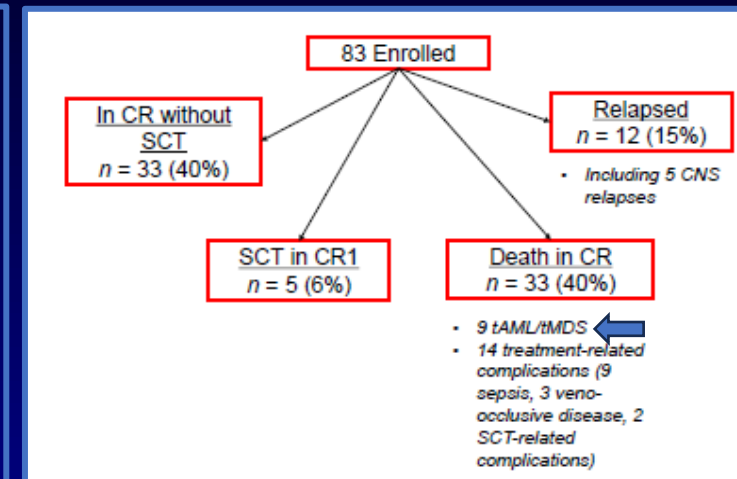
HCVAD	55	27	20	17	3
HCVAD+nel	48	15	6	0	0

Mini-HCVD + INO ± Blina in Older ALL (N=83)

- Median age 68 years (range, 60-87; 34% ≥ 70 years)
- High-risk features: **TP53 39%**; Ph-like **18%**; poor cytogenetics **23%**
- **ORR 99%** (CR 90%); **MRD negativity 94%** (79% at CR)



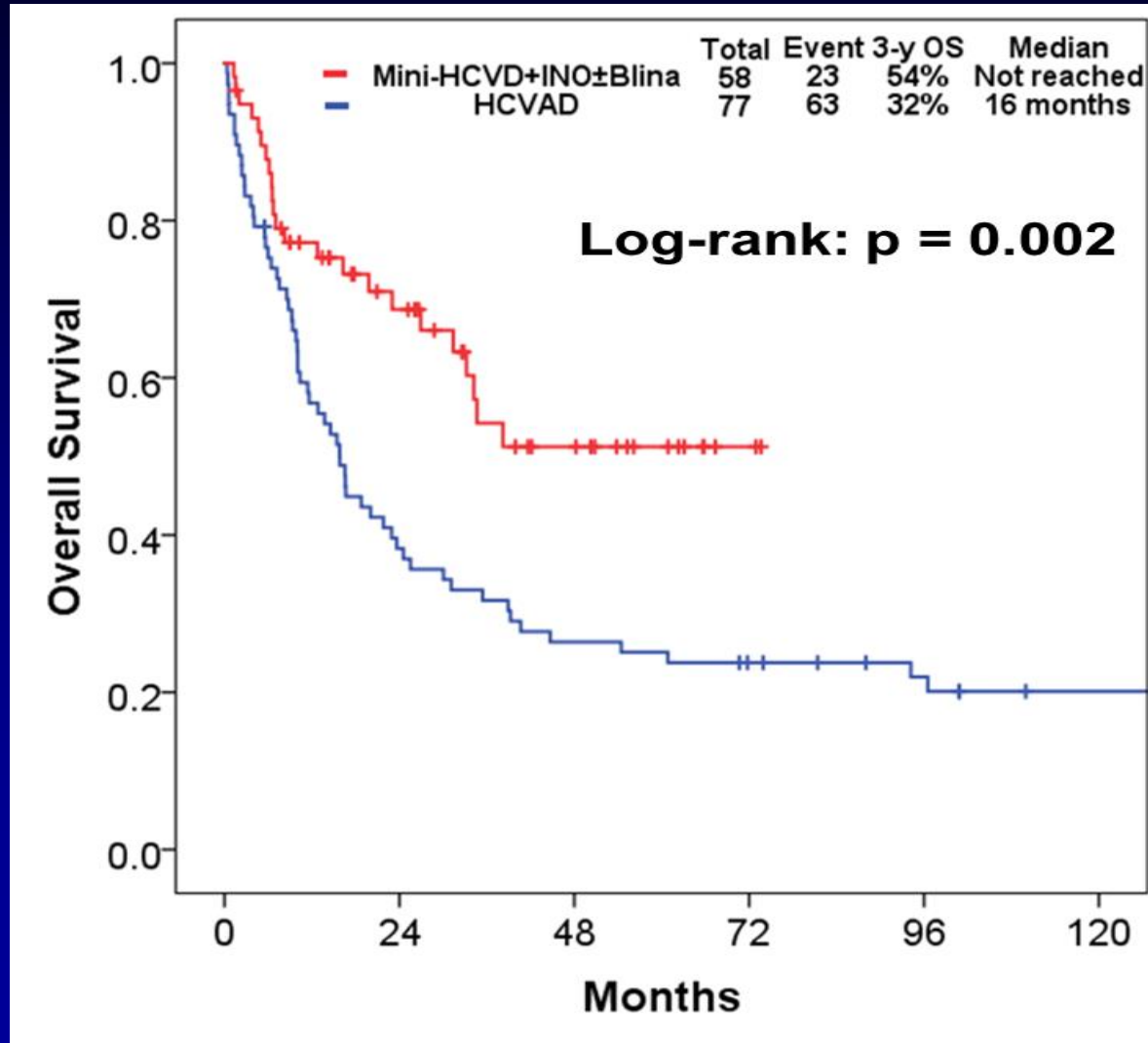
Characteristic	Category	N (%) / Median [range]
Age (years)	≥70	28 (34)
Cytogenetics	Diploid	27 (33)
	HeH	5 (6)
	Ho-Tr	12 (14)
	Tetraploidy	3 (4)
	Complex t(4;11)	3 (4)
CD19 (%)	Misc	1 (1)
	IM/ND	16 (19)
		16 (19)
CD22 (%)		99.6 [26-100]
CD20	≥20%	46/76 (61)
Ph-like ALL		9/50 (18)
TP53 mutation		25/64 (39)



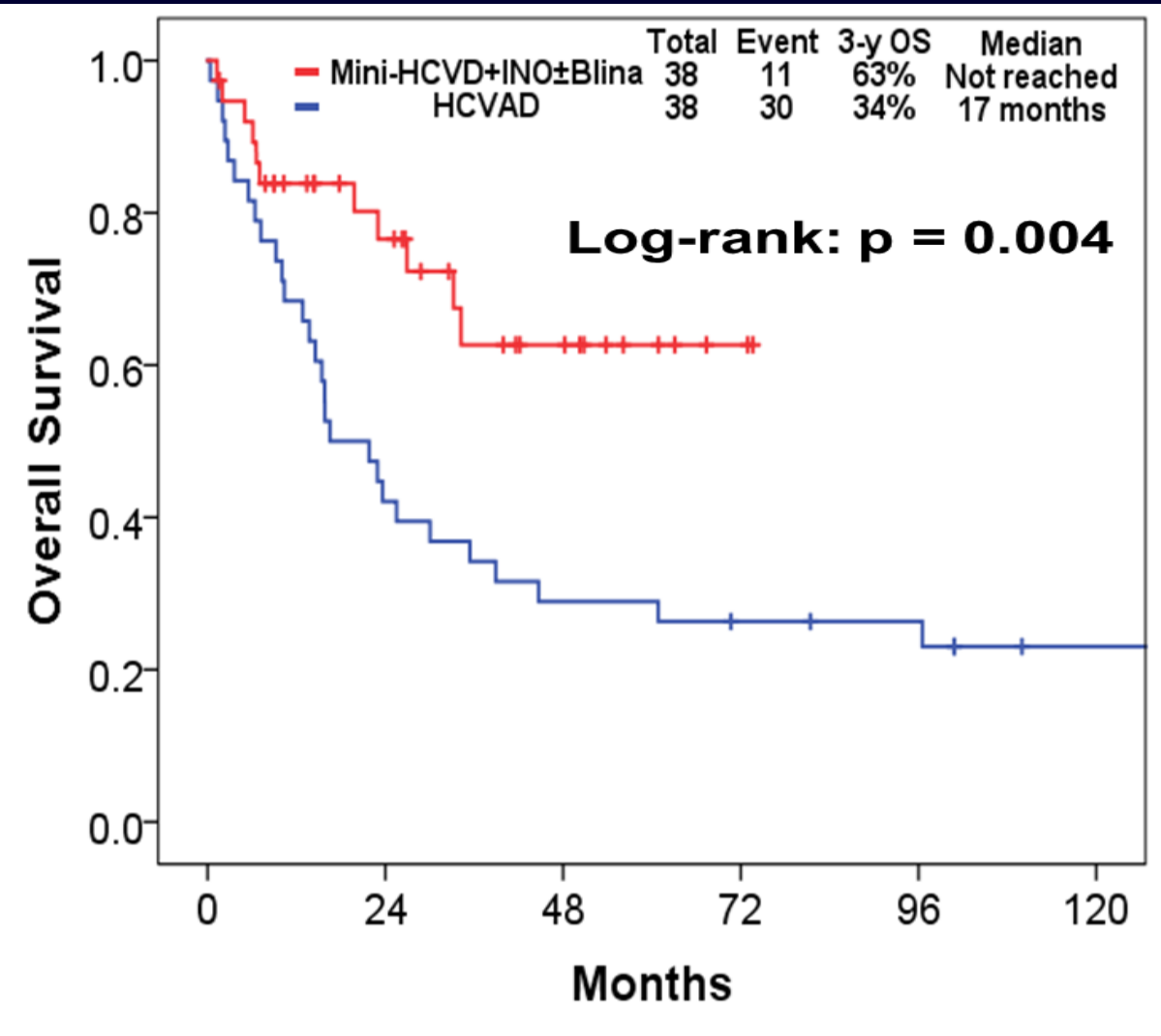
- **Median F/U 88 months**
- 5/12 pts with relapse (42%) had EMD (1 concurrent BM relapse), all with CNS involvement (5/83; **6%**)
- Death due PD/NR: 12/83 (**15%**); median 23 mos (2-78); median age 64 yrs (60-79)
- Death due to AML/MDS: 9/83 (**11%**); median 34 mos (7-75); median age 71 yrs (64-87)
- Death in CR: 33/83 (**40%**); 11/28 (39%) in pts ≥70 yrs
- 14/33 deaths (42%) Rx related (9 sepsis, 3 VOD, 2 ASCT)

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

Pre-matched

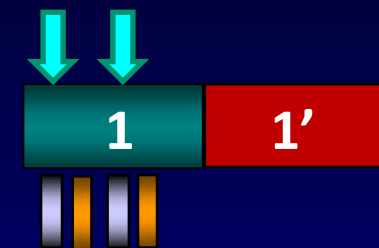


Matched

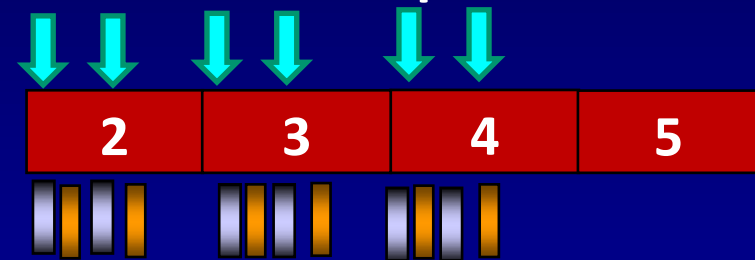


INO + Blina in Older ALL. Amended Design (Pts ≥70 years)

Induction (D1-14)



Consolidation phase



Maintenance phase

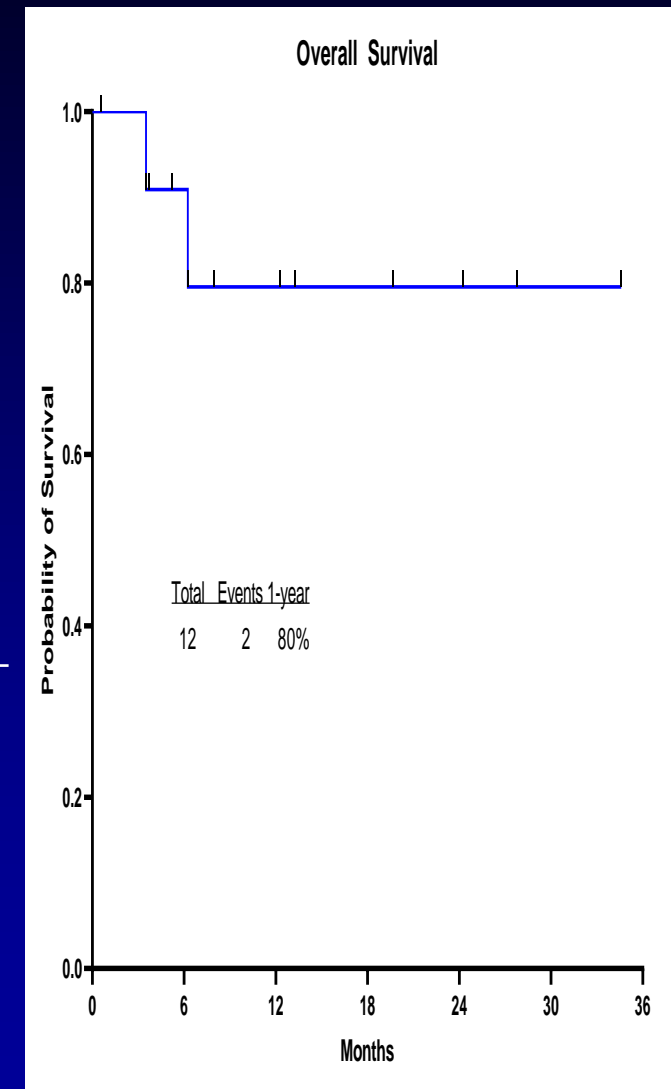


- Dexa 20 mg D1-4 and VCR 1 mg D4
- Blinatumomab
- IT MTX, Ara-C
- Rituximab if CD20+
- 1' Blinatumomab for 2 weeks

INO*	Total dose (mg/m ²)	Dose per day (mg/m ²)
C1	0.9	0.6 D1, 0.3 D8
C2-C4	0.6	0.3 D1 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300mg tid for VOD prophylaxis



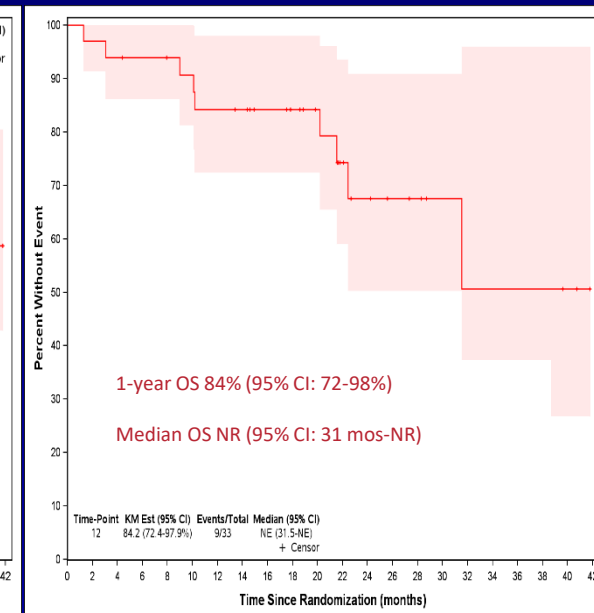
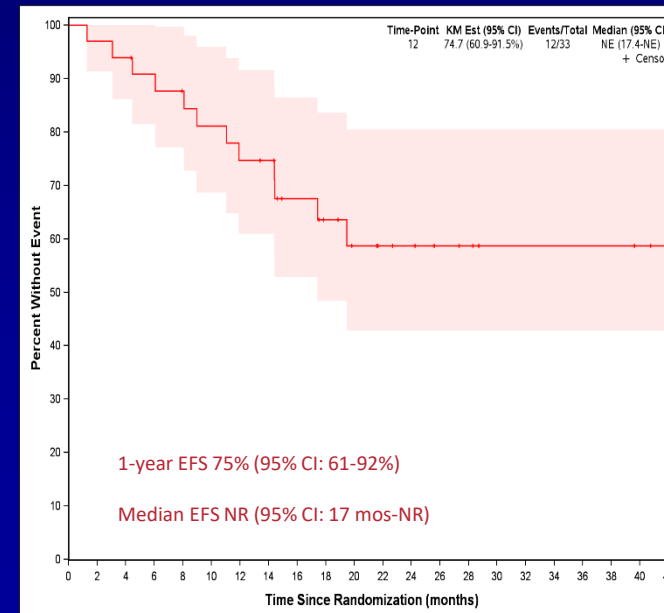
Chemo Rx-Free Inotuzumab+Blinatumomab in Pre B-ALL (Alliance A 041703)

- 33 pts; median age 71 yrs (60-84). Median CD22 92%. **F/U 22 months**
- Induction: INO 0.8mg/m² D1, 0.5mg/m² D8 &15 (1.8mg/m²)
- Maintenance: If CR-CRi INO 0.5mg/m² D1,8,15 (1.5mg/m²) x 2 then BLINAx2
- If no CR-CRi—BLINA 28mcg/Dx21 then x 28 x 3
- IT x 8
- CR 85% post INO x 3; cumulative CR 97%
- 1-yr EFS 75%; **1-yr OS 84%**
- 9 relapses; 2 deaths in CR. 9 deaths, 6 post relapse

	Induction with Inotuzumab (IA/B/C)	Consolidation with Blinatumomab
Cumulative CR (CR+CRh+CRi)	28/33 (85 %)	32/33 (97 %)
CR	15/33 (45%)	19/33 (58 %)
CRh	11/33 (33 %)	12/33 (36 %)
CRi	2/33 (6 %)	1/33 (3 %)
Refractory	3/33 (9 %) [#]	-

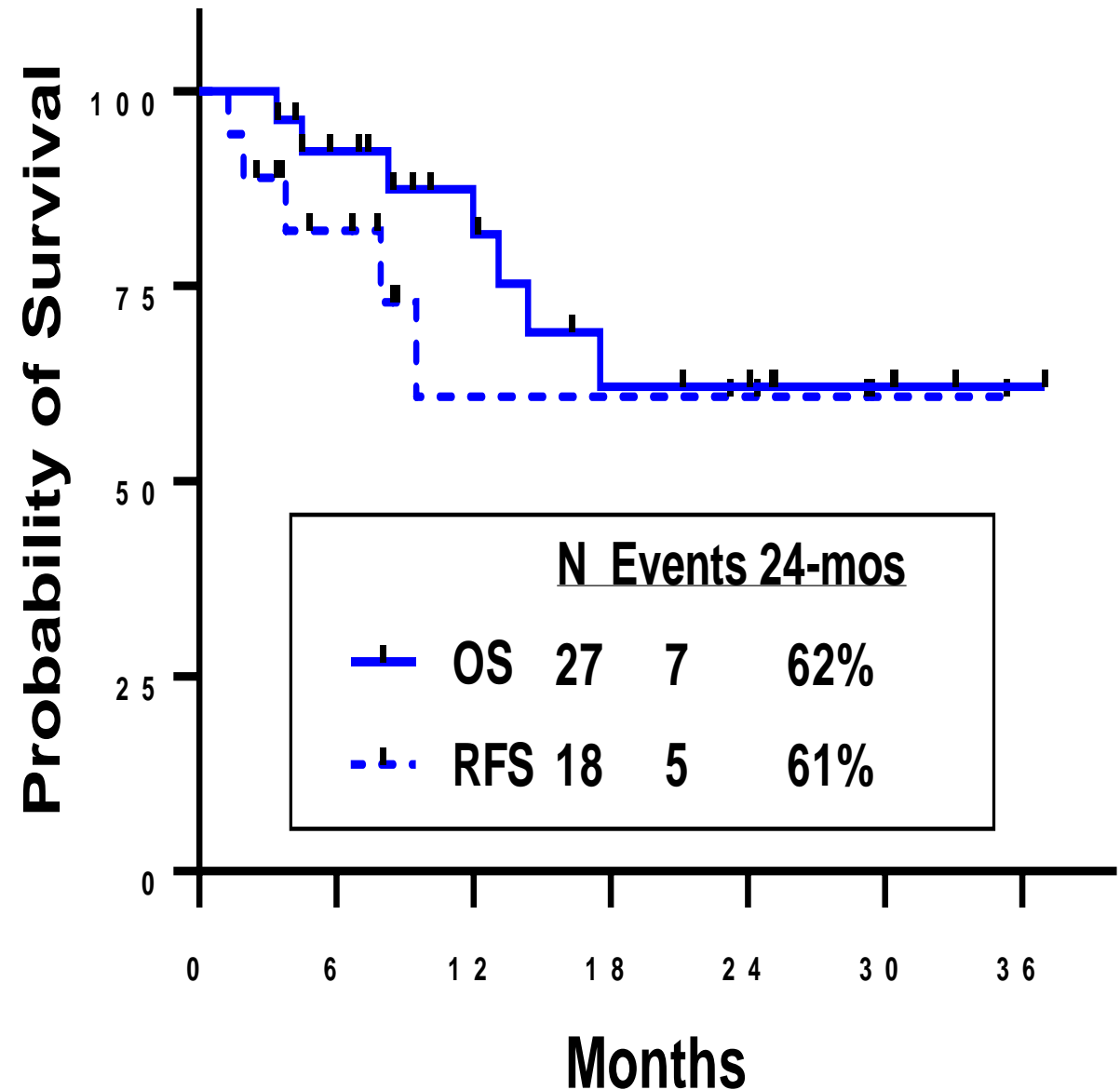
EFS

OS



Inotuzumab Ozogamicin for MRD in B-Cell ALL

- 27 adults with B-cell ALL in MRD+ CR ($\geq 0.01\%$ by flow, PCR for *BCR::ABL1* and/or NGS)
- INO 0.6 mg/m² Day 1 and 0.3 mg/m² Day 8 (Course 1); 0.3 mg/m² Day 1 and 8 (Courses 2-6); Combined with TKI in pts with Ph+ ALL (ponatinib in 15/17 pts)
- **MRD negativity 67% overall** (59% in Ph+ ALL, 80% in Ph-negative ALL)
- 6/18 responders (33%) proceeded to HSCT
- **VOD/SOS in 2 pts (7%)**

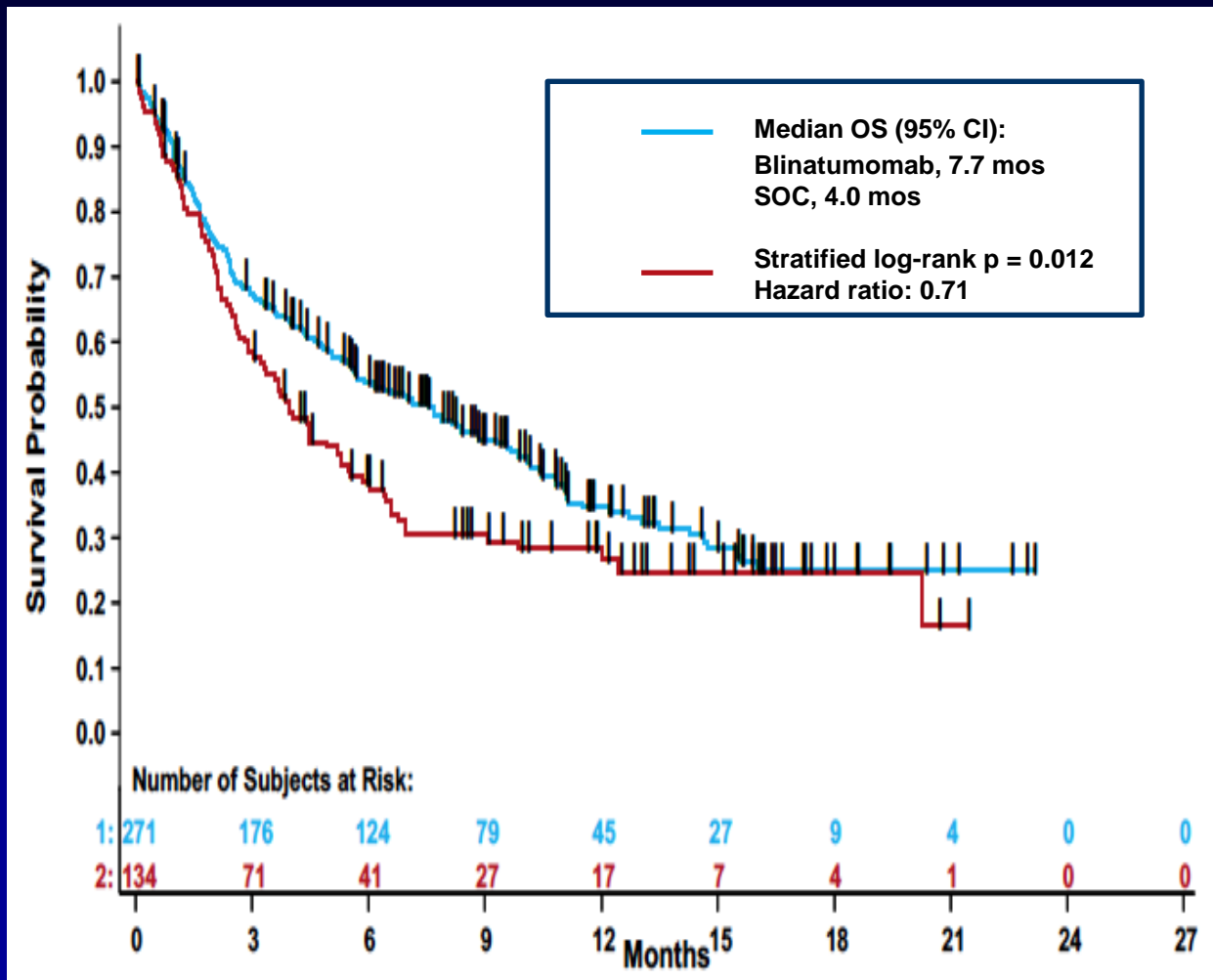


Blinatumomab/Inotuzumab vs ChemoRx in R-R ALL

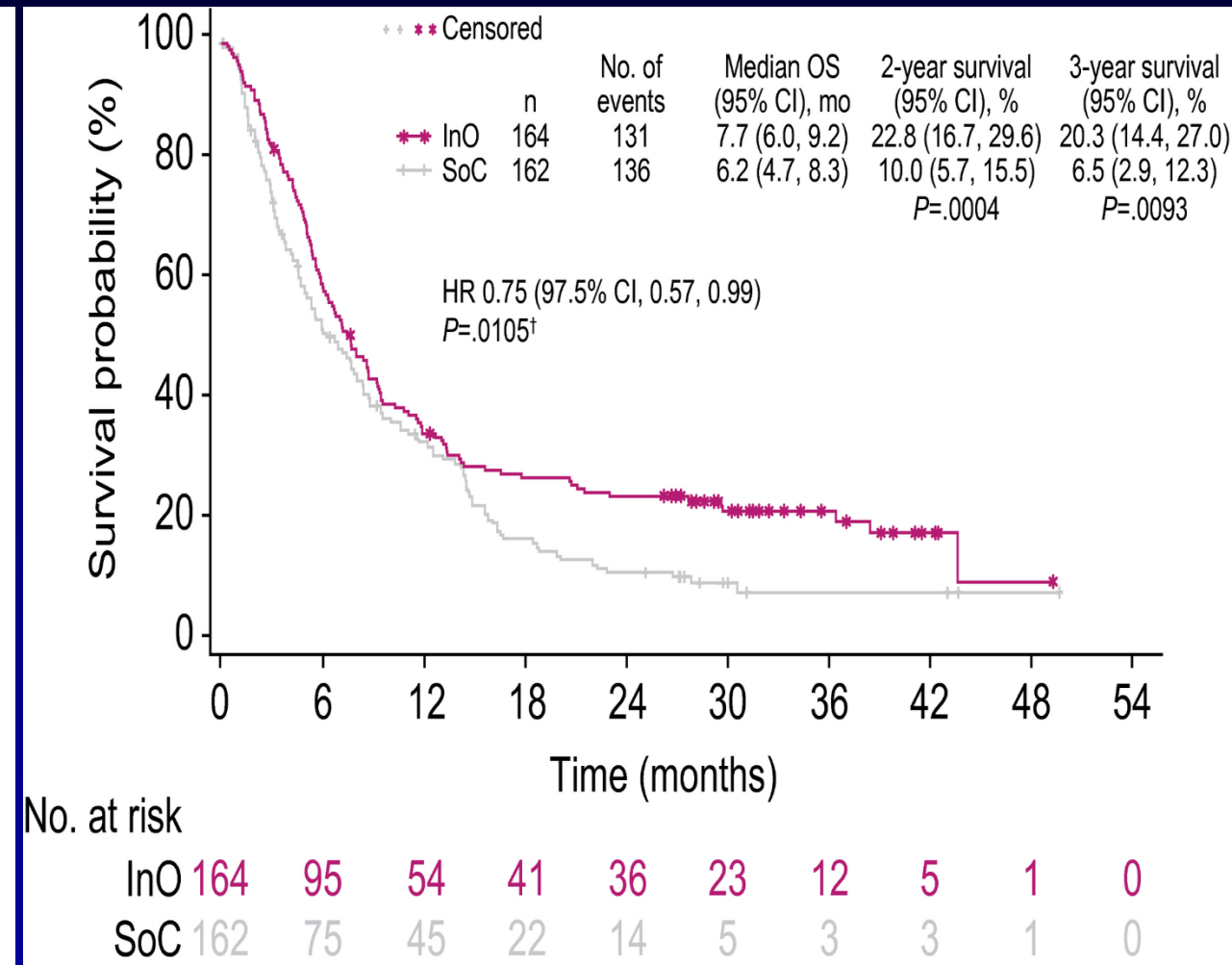
- Marrow CR

Blina vs SOC: 44% vs 25%

Ino vs SOC: 74% vs 31%

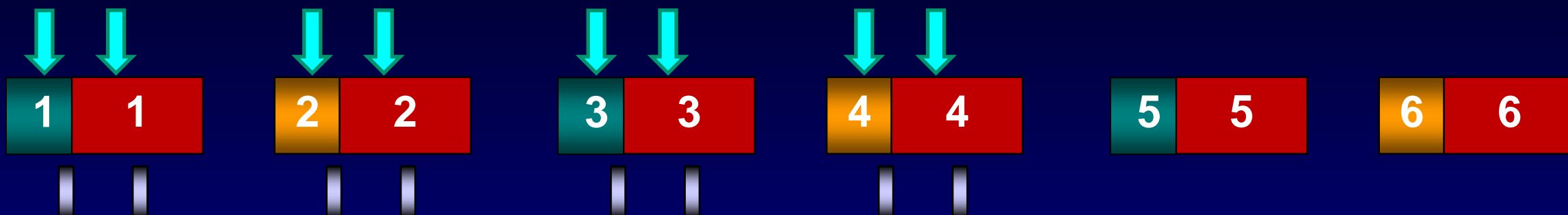


Kantarjian. NEJM. 376: 836-47; 2017



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

Mini-HCVD + INO ± Blina in R/R B-ALL: “Dose-Dense” Design (Pts #111-125+)



3 days 18 days 7 days

Maintenance phase



18 months

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/m²

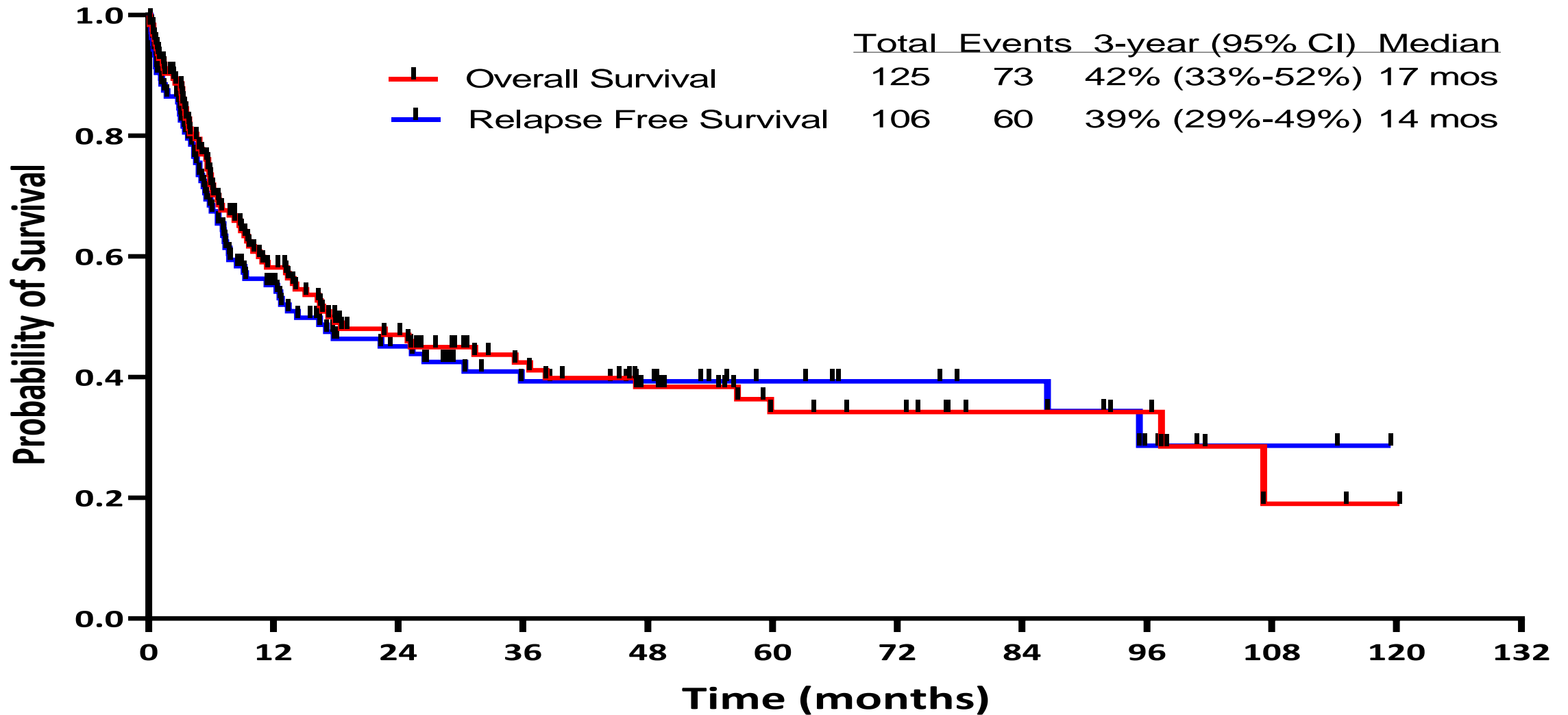
*Ursodiol 300mg tid for VOD prophylaxis

- Mini-HCVD
- Blinatumomab
- Mini-MTX-Ara-C
- IT MTX, Ara-C
- POMP

Mini-HCVD + INO ± Blina in R/R B-ALL: MRD Negativity Rates

MRD negativity by flow cytometry	N (%)			
	Overall (n=125)	Before blinatumomab (n=67)	After blinatumomab (n=43)	Dose-dense (n=15)
All patients				
End of cycle 1	53/100 (53)	25/49 (51)	18/38 (47)	10/13 (77)
Overall	87/102 (85)	41/50 (82)	34/39 (87)	12/13 (92)
Salvage 1				
End of cycle 1	45/82 (55)	22/34 (65)	17/37 (46)	8/11 (73)
Overall	73/83 (88)	31/35 (89)	32/37 (86)	10/11 (91)
Salvage 2+				
End of cycle 1	6/18 (33)	3/15 (20)	1/1 (100)	2/2 (100)
Overall	14/19 (74)	10/15 (67)	2/2 (100)	2/2 (100)

Mini-HCVD + INO ± Blina in R/R B-ALL: RFS and OS (Entire Cohort)



Single Agent Subcutaneous Blinatumomab for Advanced Acute Lymphoblastic Leukemia

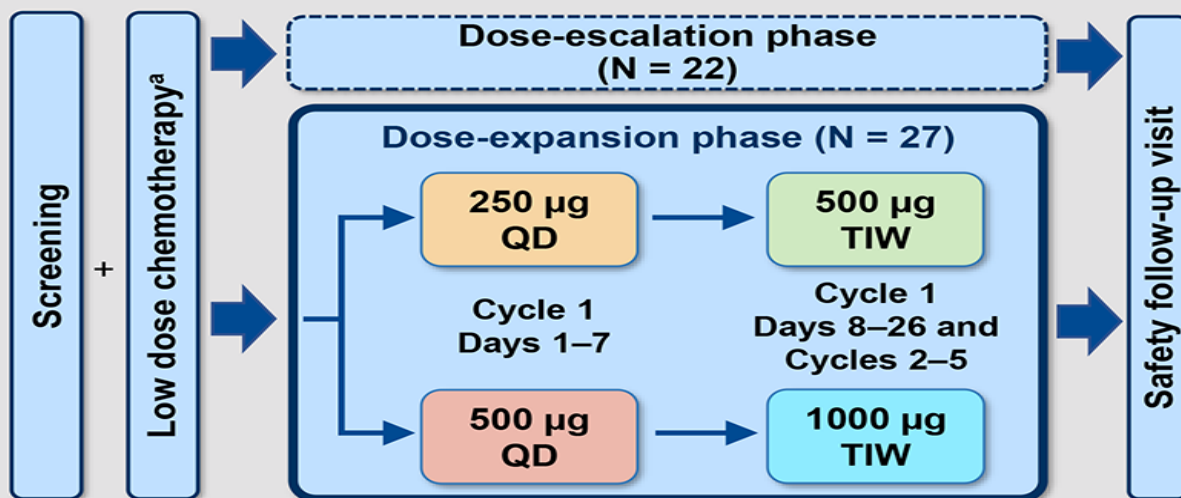
Results from the expansion phase of a phase 1b trial

Objective



To assess the efficacy and safety of subcutaneous blinatumomab in heavily pretreated adults with R/R B-ALL at two doses

Study Schema



Results

Efficacy



250 µg QD/500 µg TIW (N = 14)

- CR/CRh: 85.7%
- MRD-neg CR/CRh: 75%

500 µg QD/1000 µg TIW (N = 13)

- CR/CRh: 92.3%
- MRD-neg CR/CRh: 100%

Dosing regimen 500 µg QD/1000 µg TIW demonstrated higher MRD-negative CR/CRh within 2 cycles (100%) compared with dosing regimen 250 µg QD/500 µg TIW (75%)

Safety



250 µg QD/500 µg TIW (N = 14)

- Grade ≥3 CRS^b: 21.4%
- Grade ≥3 NE^b: 42.9%

500 µg QD/1000 µg TIW (N = 13)

- Grade ≥3 CRS^b: 23.1%
- Grade ≥3 NE^b: 23.1%

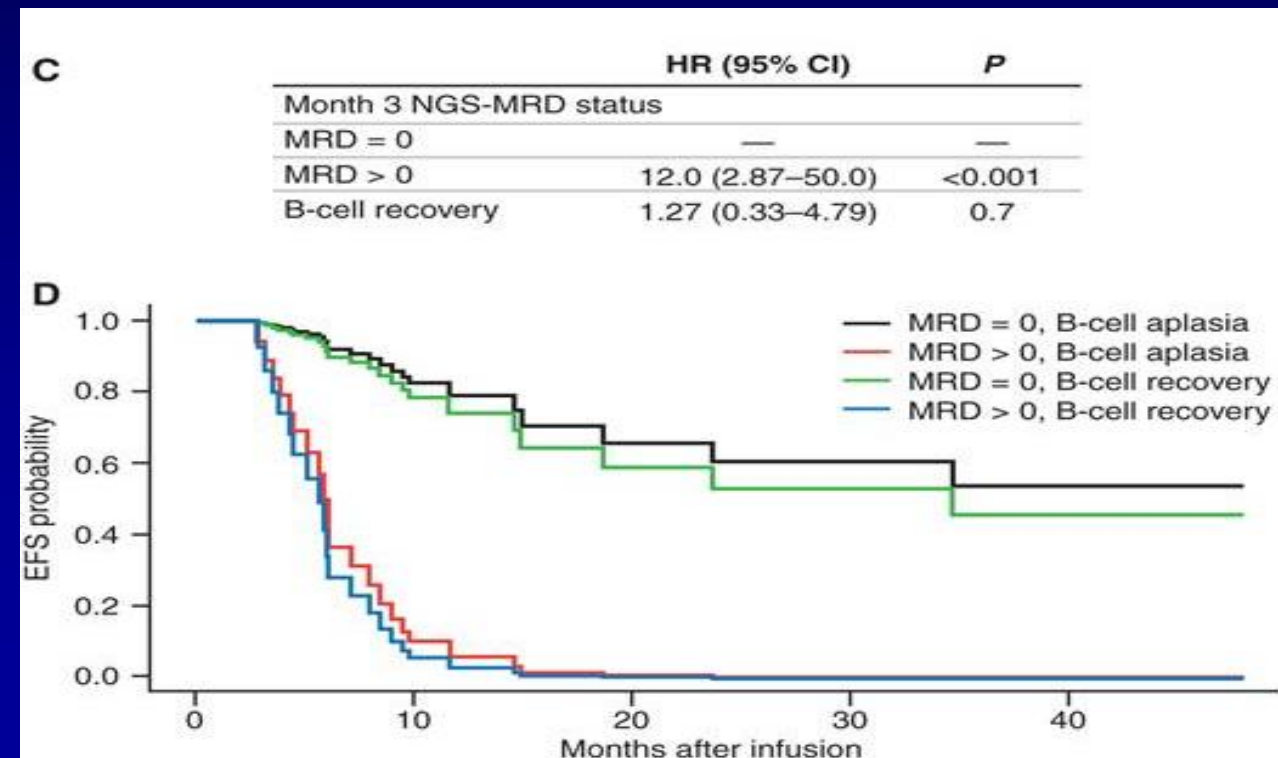
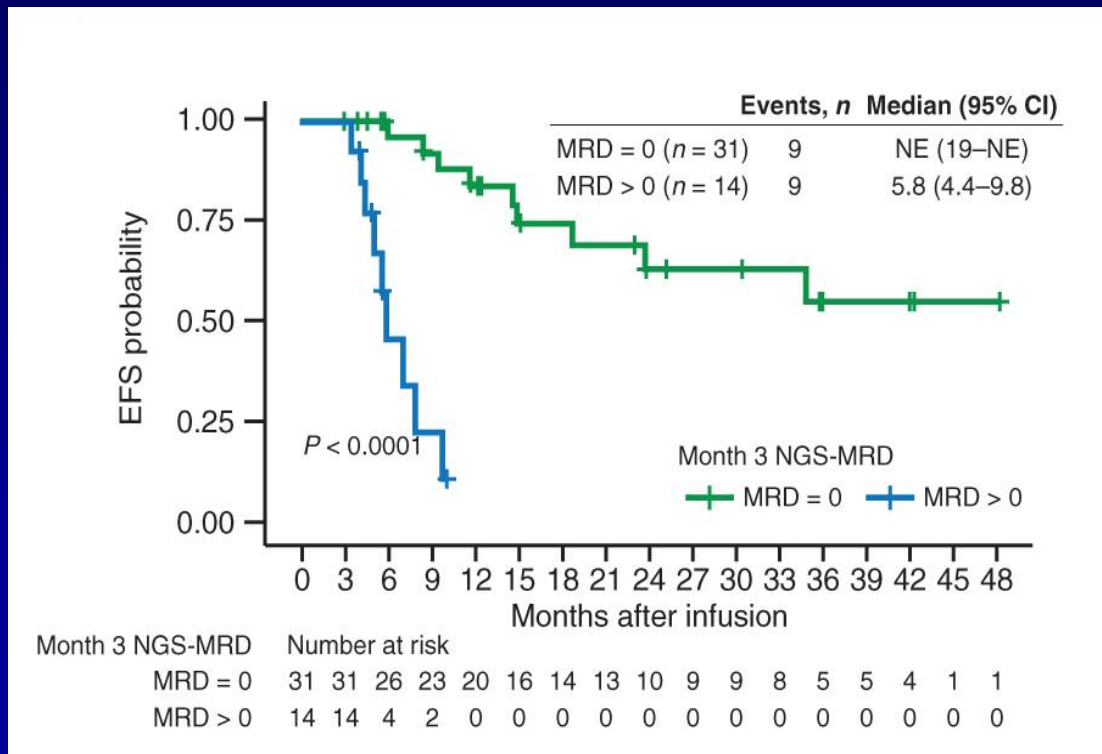
- SC injections were well tolerated
- No treatment-related grade 4 CRS or NE

Conclusion

Treatment with single agent SC blinatumomab resulted in a high CR rate, high MRD-negativity rate, and an acceptable safety profile in heavily pretreated adults with R/R B-ALL

NGS MRD negativity after CAR T-cell Therapy for ALL

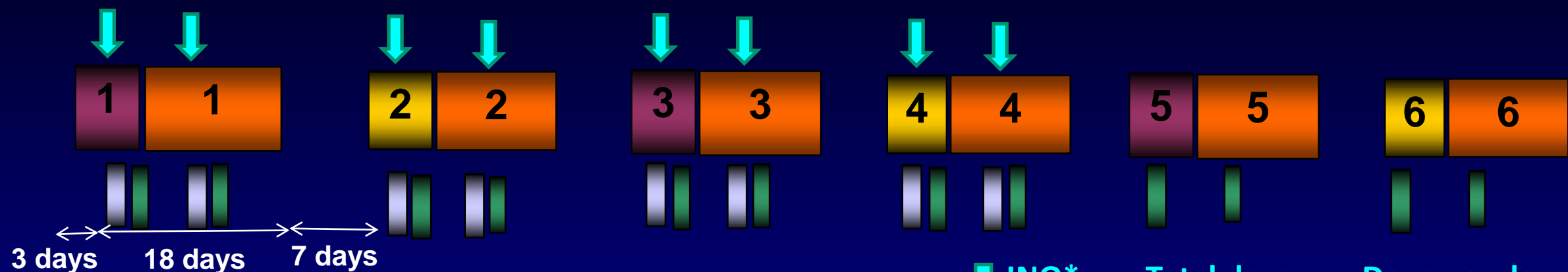
- Detectable MRD after tisagenlecleucel by NGS independently predicted for EFS and OS on multivariate analysis
- NGS MRD status at 3-months was superior to B-cell aplasia/recovery at predicting relapse/survival



Dose Dense Mini-HCVD + INO + Blina + CAR T-cells in ALL.

The CURE

Induction phase: C1-C6



Consolidation phase

CAR T Consolidation

INO*

Total dose
(mg/m²)

Dose per day
(mg/m²)

C1	0.9	0.6 D2, 0.3 D8
C2-4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300mg tid for
VOD prophylaxis

Mini-Hyper-CVD

Rituximab

Blinatumomab

Mini-MTX-Ara-C

IT MTX, Ara-C

ALL 2024+. Conclusions

- Significant improvements across all ALL categories
- Ph-positive ALL
 - Ponatinib > imatinib--- evaluating newer TKI (olverembatinib, asciminib)
 - Blina-ponatinib: 3-year OS 90%, rarely allo-SCT
 - CNS relapses: 15 IT vs systemic chemotherapy in WBC>70K
- Incorporation of Blina/INO in FL therapy highly effective and improves survival
 - HCVAD-blina-ino: 3-year OS 88%
 - Mini-HCVD-INO in older ALL: 5-year OS 50%
 - Exploring chemotherapy-free approach to reduce death in CR in older ALL
- Early eradication of MRD predicts best overall survival
 - NGS> FCM in Ph-negative ALL, NGS> PCR in Ph-positive
- Antibody based Rxs and CARTs both outstanding; not mutually exclusive/competitive (versus); rather complementary
 - CAR T as consolidation post Blina/Ino based regimen
- Future of ALL Rx:
 - 1) less chemotherapy and shorter durations
 - 2) combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22, CD79
 - 3) SQ Blinatumomab
 - 4) **CARTs CD19 and CD19 allo and auto in sequence in CR1 for MRD and replacing ASCT**

Thank You

Jan Burger

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