

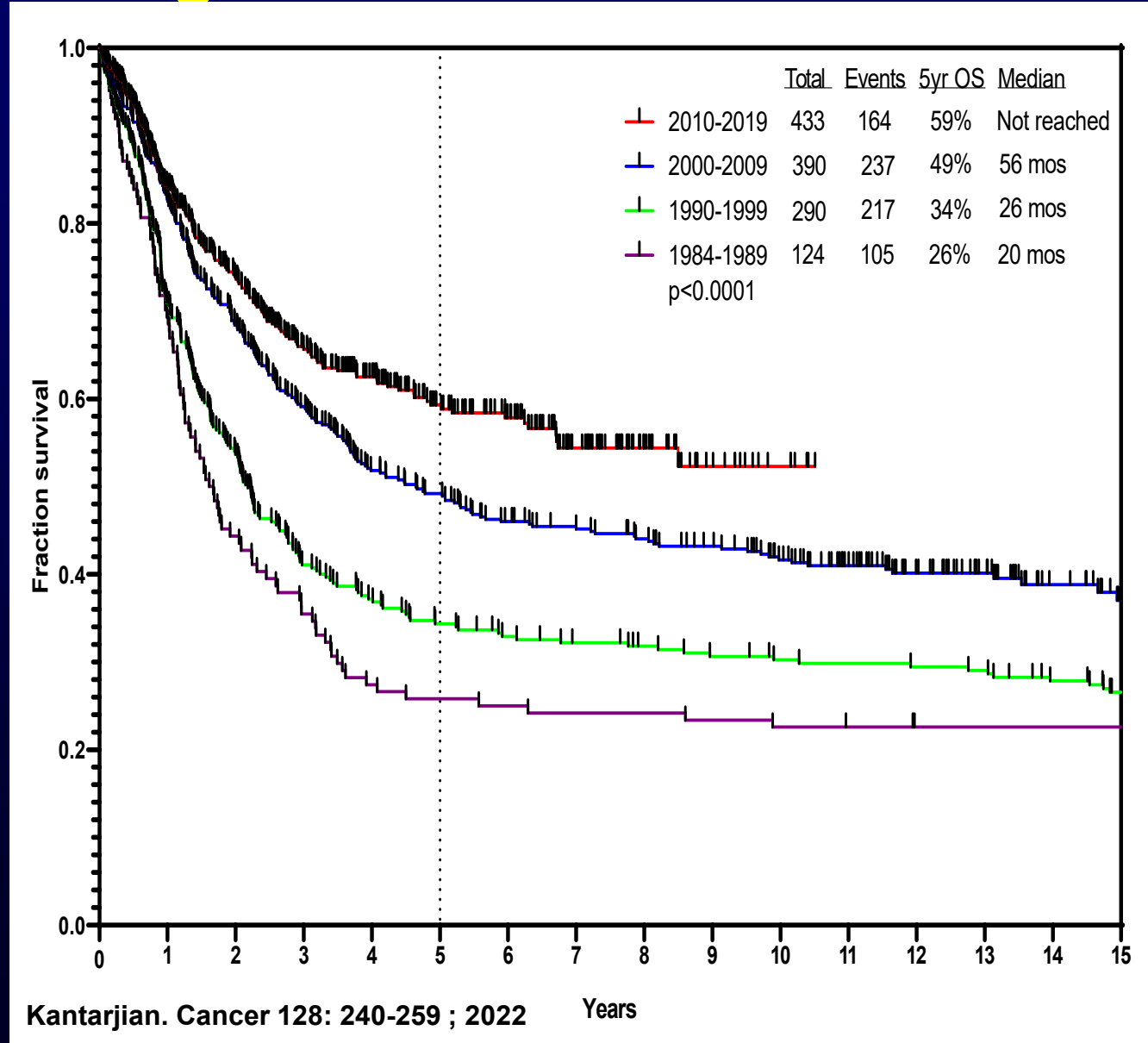
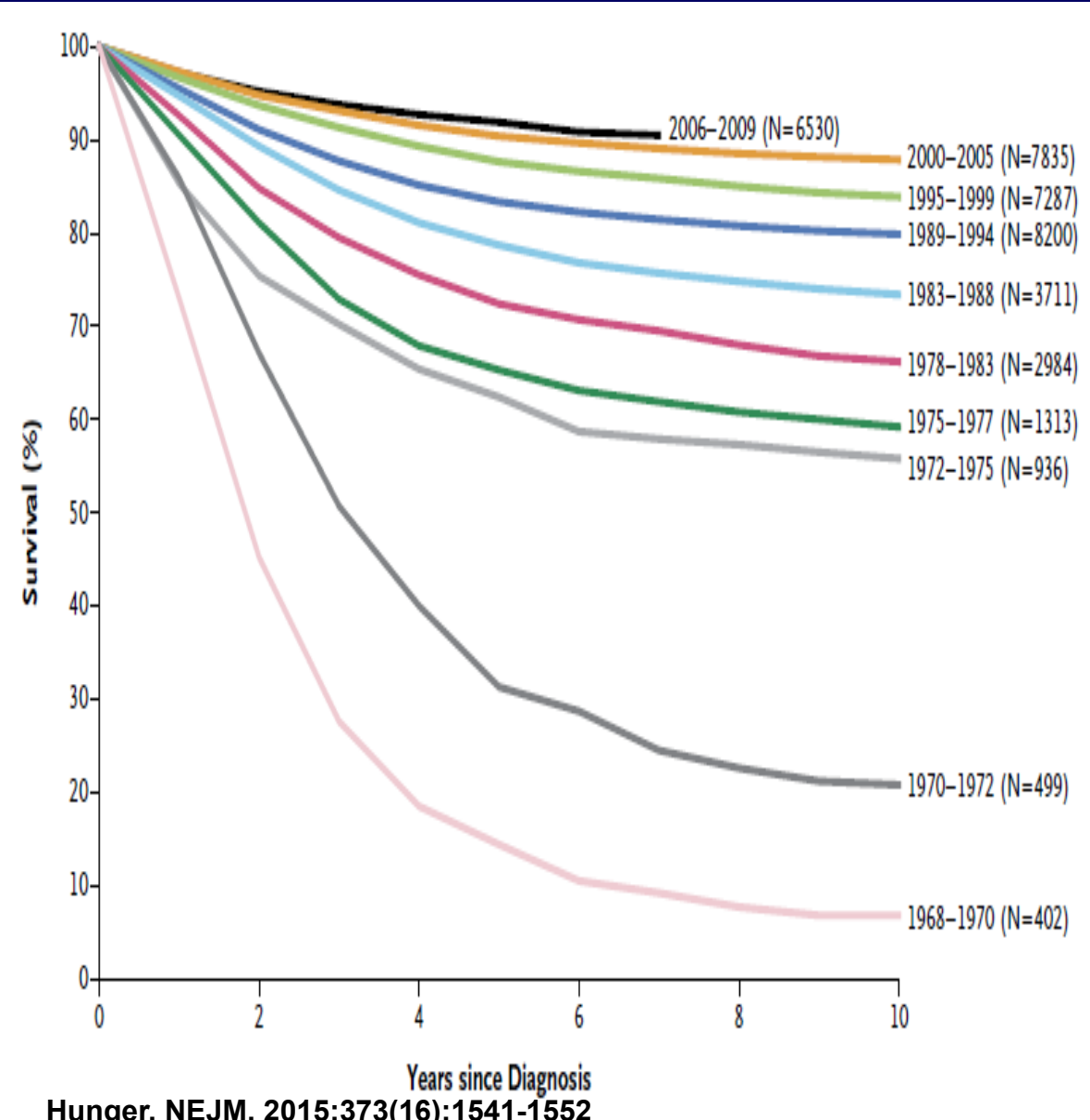
ALL – Biologic and Targeted Therapies in 2022

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Indianapolis -- September, 2022

Survival in Pediatric and Adult ALL with Classical Intensive ChemoRx Regimens



Reasons 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 (not anymore)	5	25
Ph-like ALL	Unfavorable (not in 2022+)	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)

Developmental Therapeutics in ALL

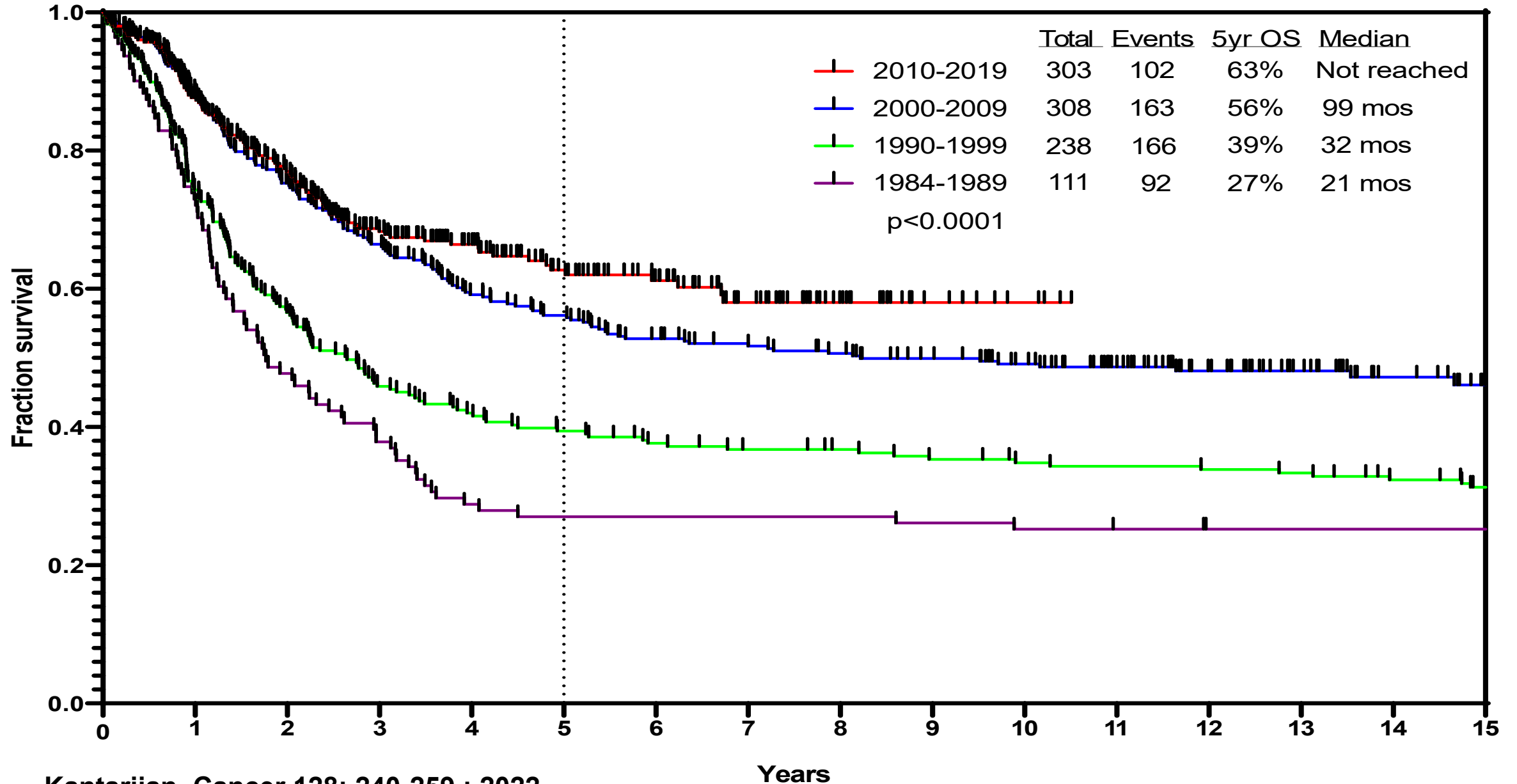
- Hyper CVAD regimen¹
- CNS prophylaxis with IT chemo Rx(no XRT)¹
- Hyper CVAD+rituximab in Burkitt ALL²
- Hyper CVAD+rituximab in pre-B ALL⁵
- Hyper CVAD+imatinib/dasatinib/ponatinib in Ph-positive ALL^{3,4}
- Clofarabine in pediatric ALL salvage (FDA approval 2004)⁶
- Liposomal vincristine (FDA approval 2012)⁷
- Activity of antibodies targeting CD19 and CD22 (blinatumomab; inotuzumab) in adult ALL^{8,9}

1. Kantarjian. JCO 18: 547; 2000 2. Thomas. Cancer 106: 1569; 2006 3. Thomas. Blood 103:4396; 2004

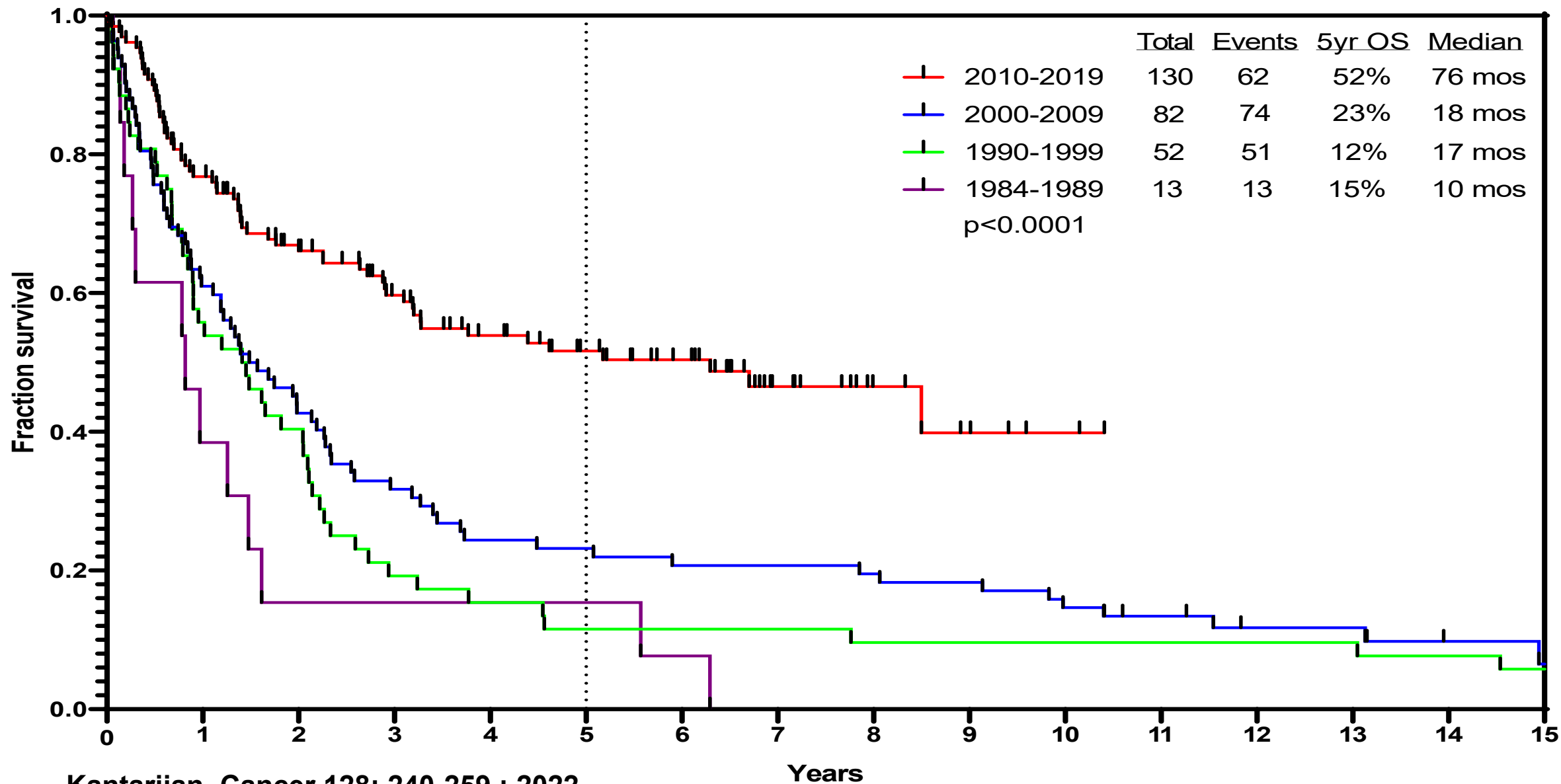
4. Ravandi. Blood 116: 2070; 2010 5. Thomas. JCO 28: 3880; 2010 6. Jeha. Blood 103: 784; 2004

7. O'Brien. JCO 31: 676; 2012 8. Kantarjian. JCO 30: 3876; 2012 9. Kantarjian. Lancet Oncol. 13: 403; 2012.

Survival in Younger ALL (16- 60 Yrs; MDACC 1985-2020)



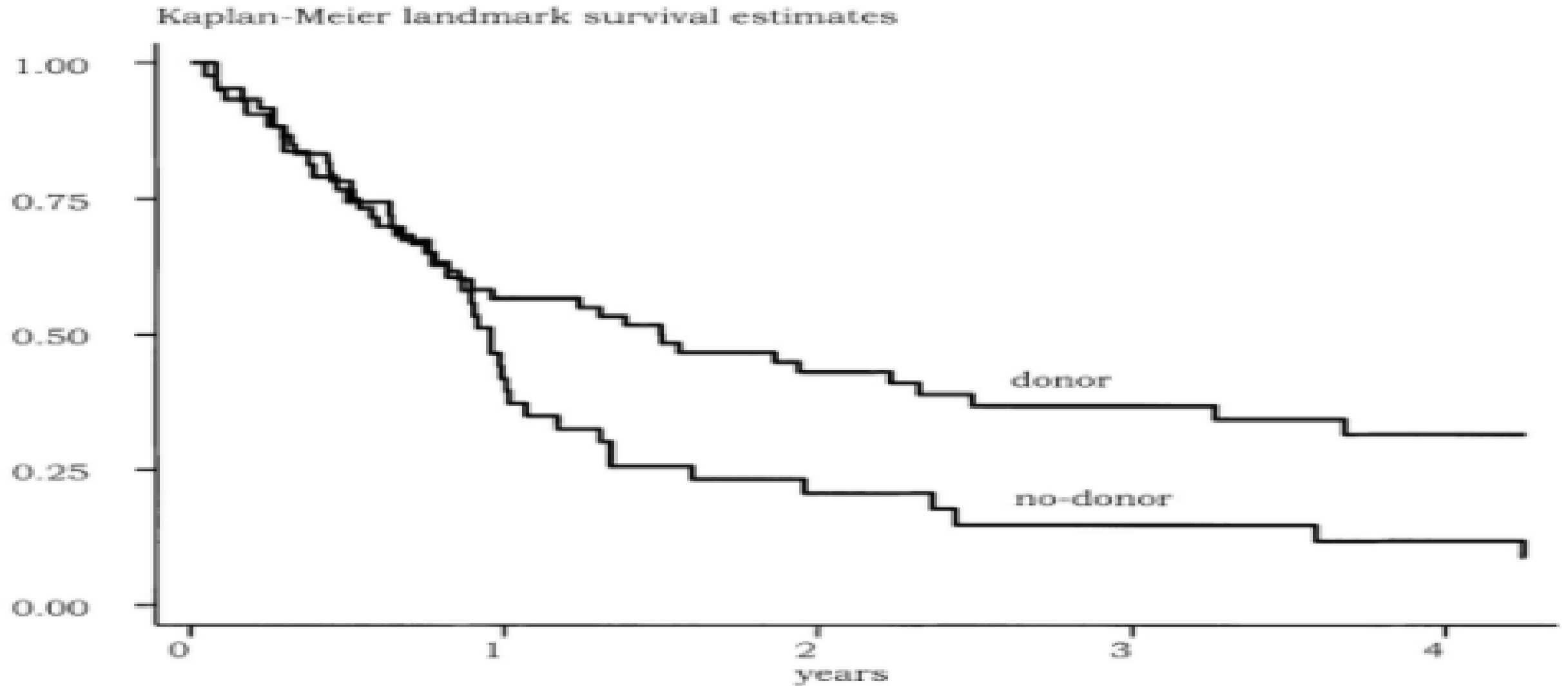
Survival in Older ALL (≥ 60 years; MDACC 1985-2020)



Hyper-CVAD in ALL – Pearls and Vignettes to Optimize Rx

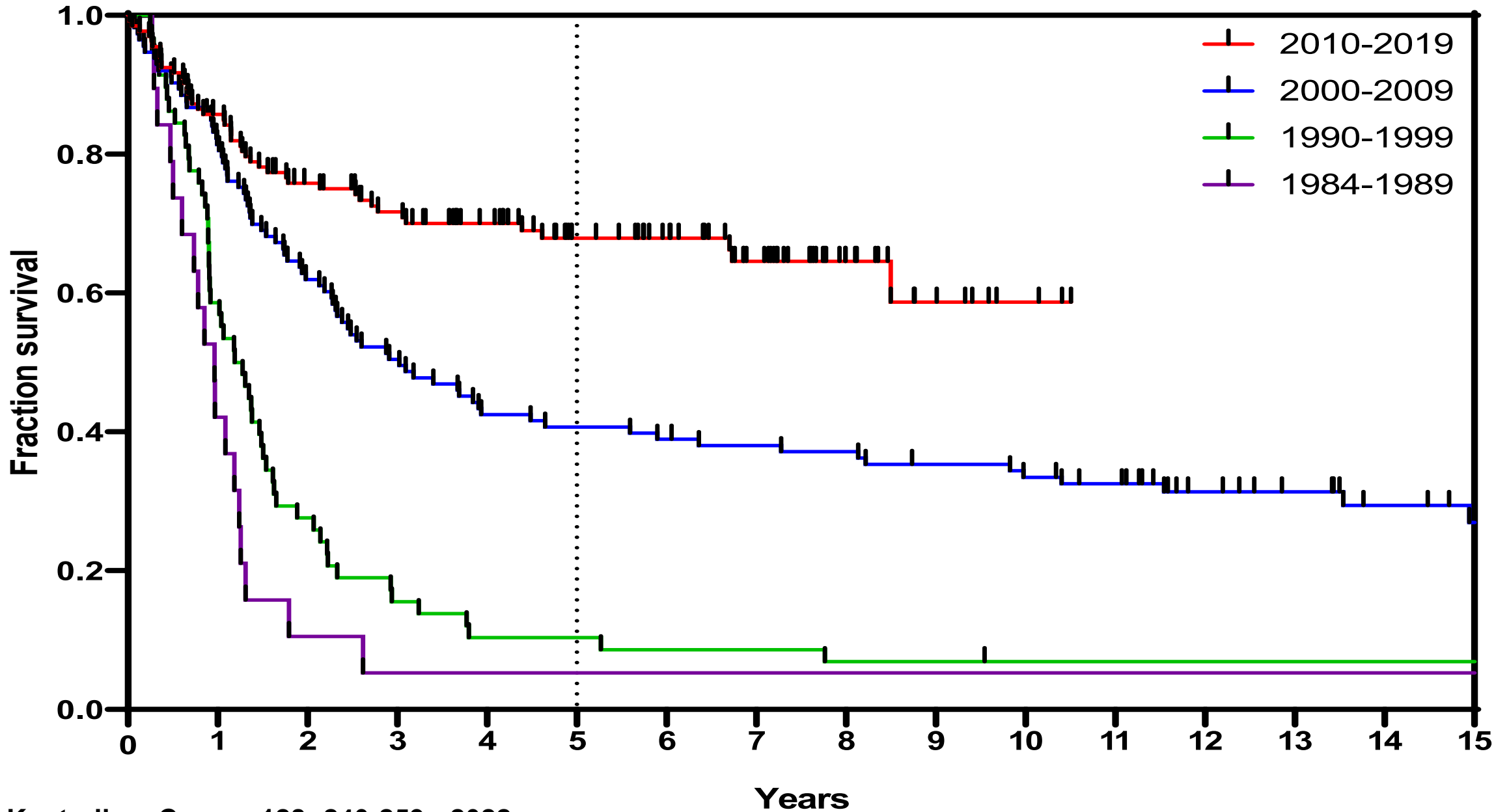
- **Even courses : MTX 750 mg/m²; ara-C 2 g/m². Dose adjust for older age**
- **Check Cr after MTX; if increase(>1.4), hold araC (avoid renal failure and cerebellar toxicity)**
- **VCR 2 mg flat dose (not 2 mg/m²). If constipation or neuropathy, omit VCR**
- **Prophylaxis : levo or vantin; posaconazole or voriconazole; Valtrex**
- **Hold azoles Day-1,0,+1 of VCR (avoid excess neurotoxicity)**
- **Switch IT Day 2 from MTX to araC in even courses (neurotoxicity with IT MTX and HD systemic MTX)**

SCT for Ph+ ALL. Pre-TKI



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

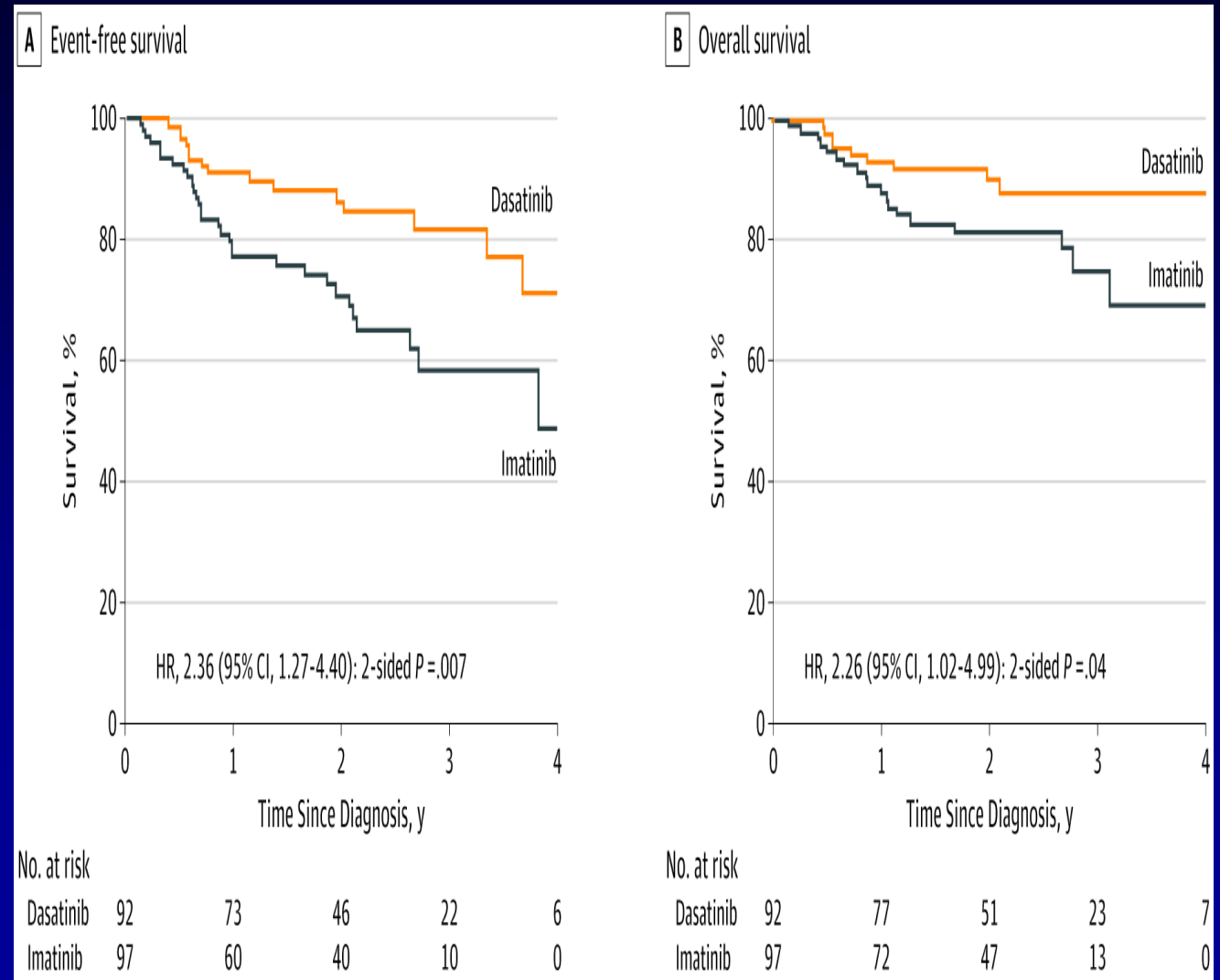
Ph-positive ALL Survival. MDACC 1985-2020



Dasatinib vs Imatinib in Pediatric Ph-positive ALL

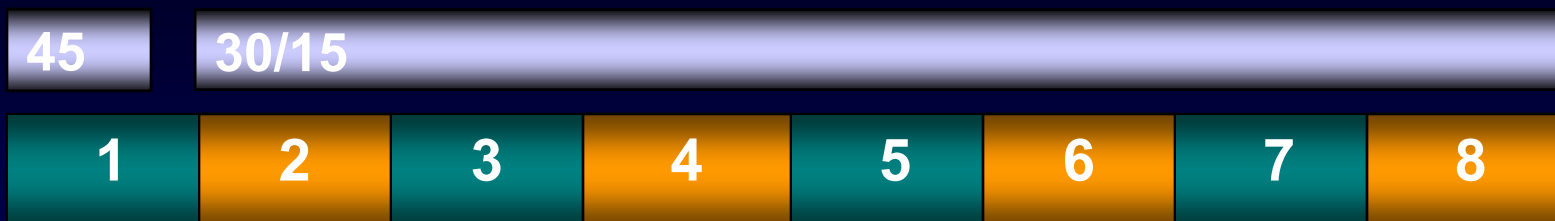
- 189 pts randomized Rx + dasatinib (n=92) or imatinib (n=97)
- Median F/U 26 mos; Triple IT 19 or 21

% 4-yr	Dasatinib	Imatinib	p-value
EFS	71	49	0.005
OS	88	69	0.04
Relapse	20	34	0.01
CNS	2.7	8.4	0.06

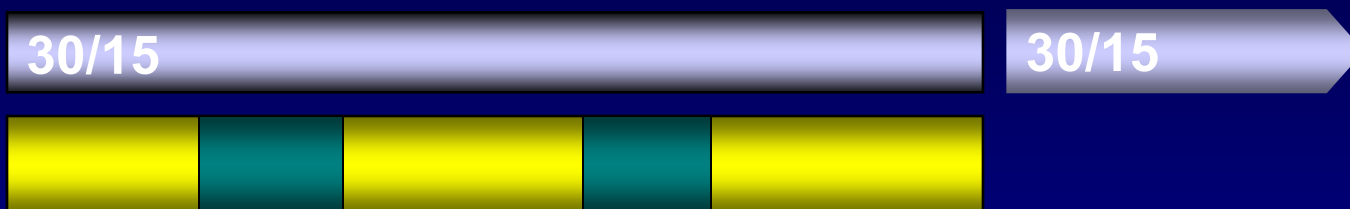


Hyper-CVAD + Ponatinib. Design

Intensive phase



Maintenance phase



← 24 months →

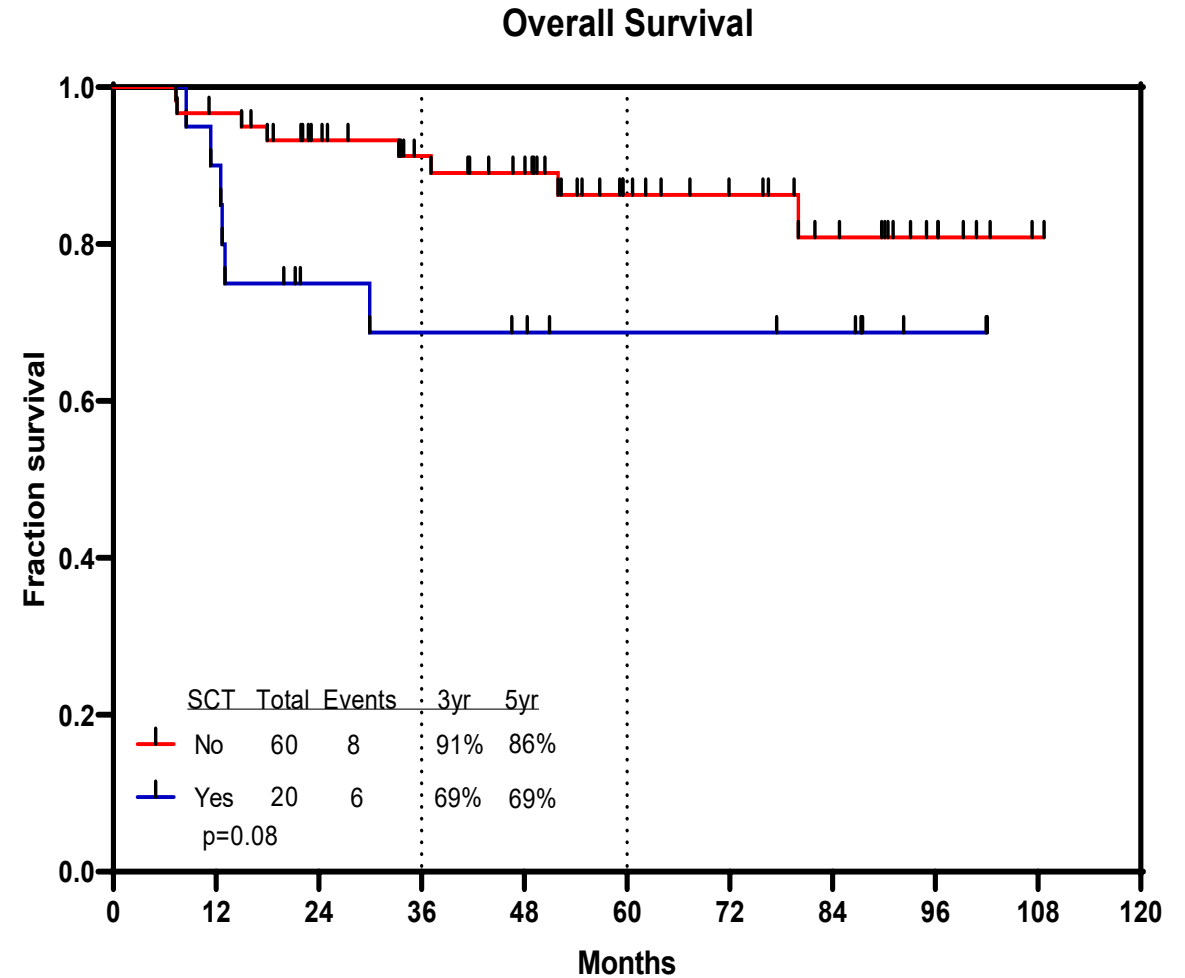
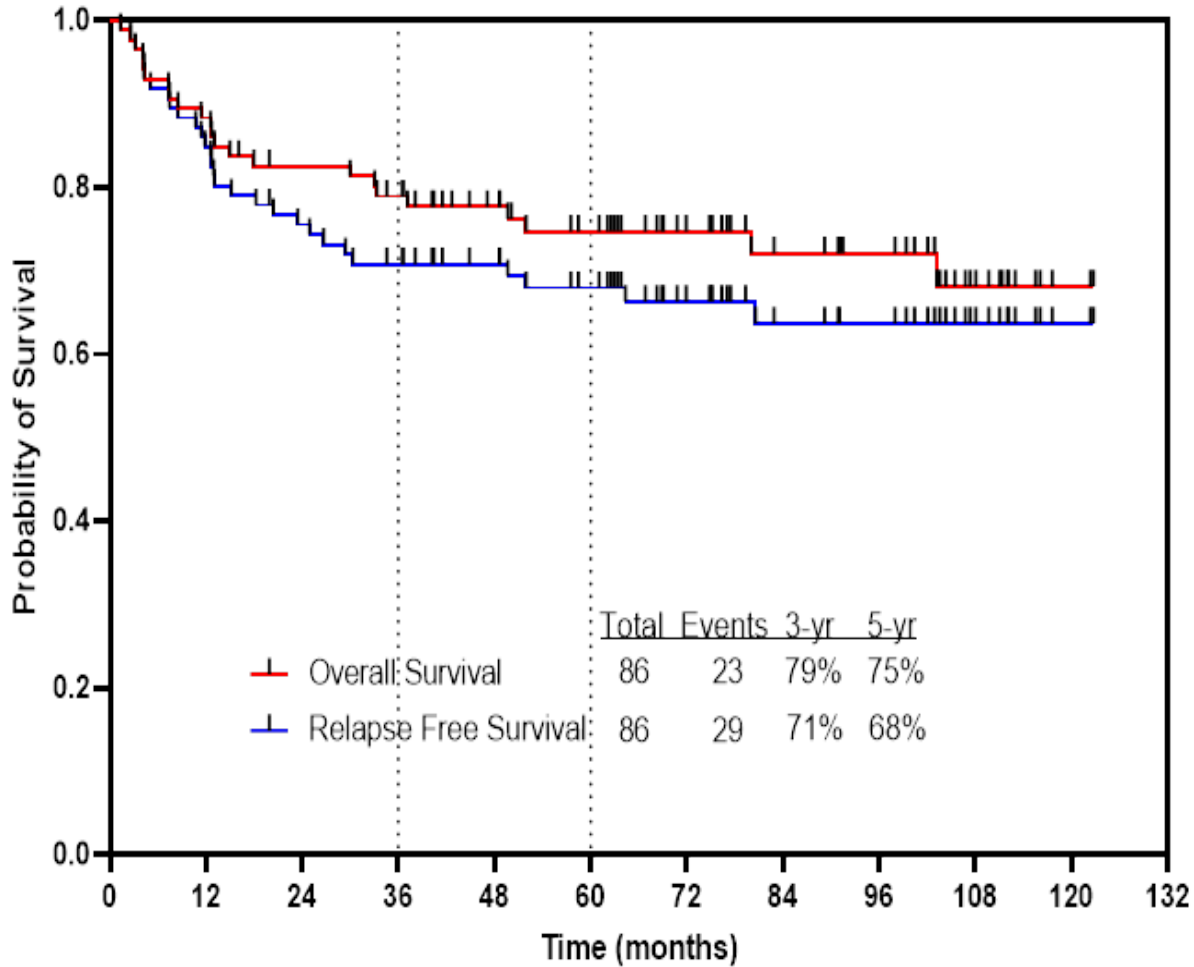
12 intrathecal CNS prophylaxis



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

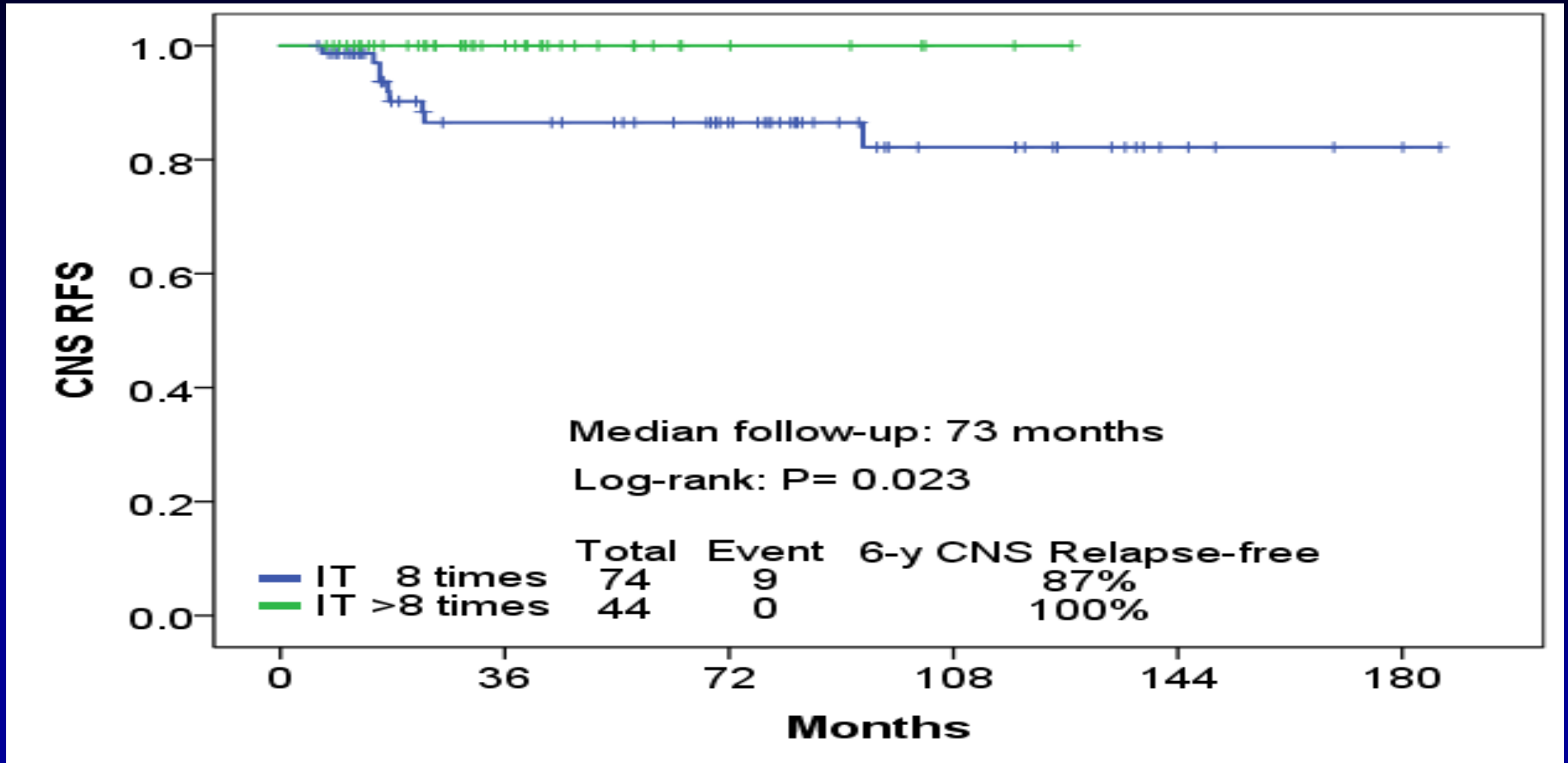
HyperCVAD + Ponatinib in Ph-positive ALL

- 86 pts Rx; median age 47 yrs (39-61); median FU 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

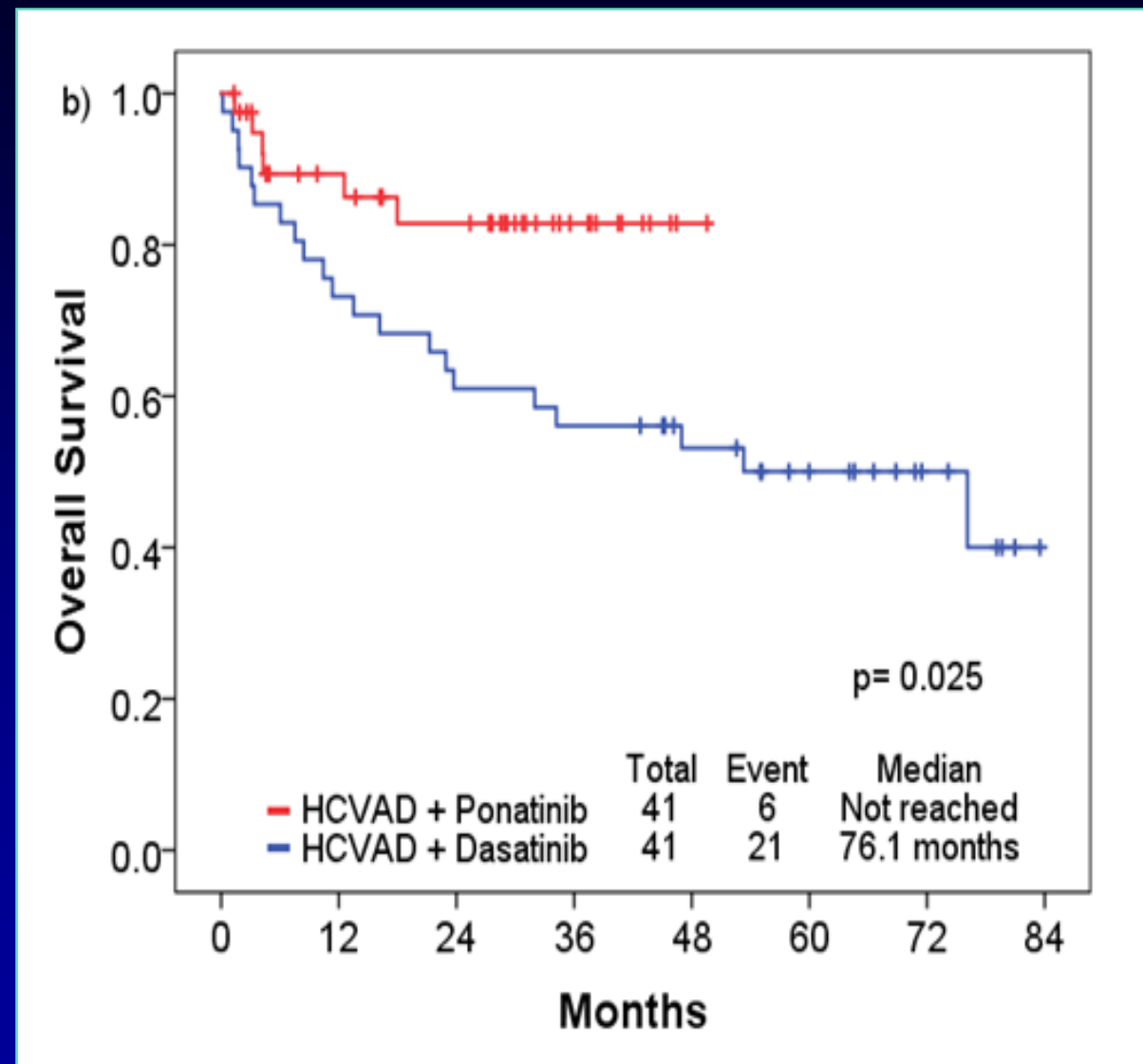
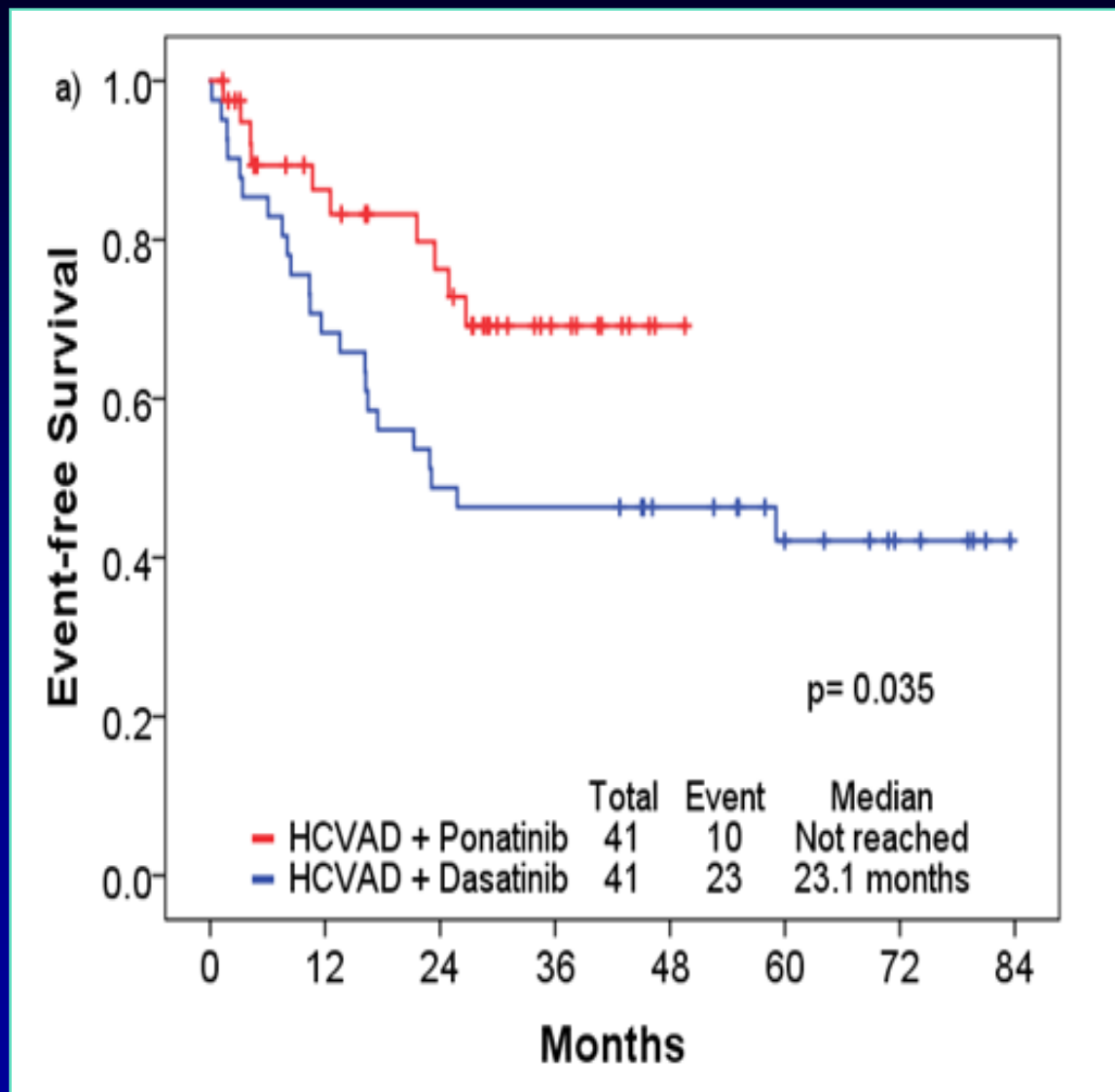


IT x8 vs. ITx12 in Ph+ ALL

6M Landmark: CNS Relapse-free Survival



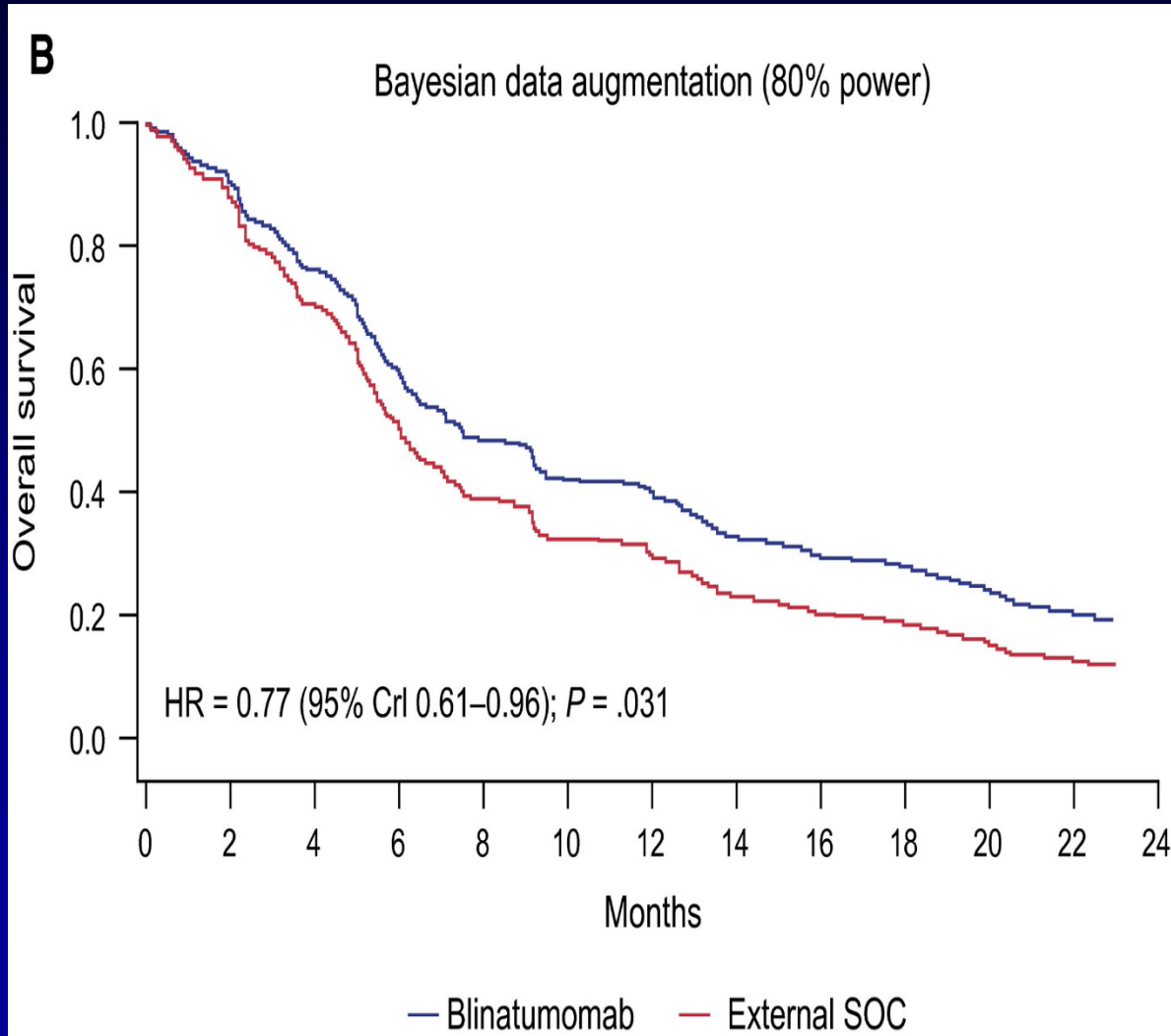
Propensity Score Analysis: HCVAD + Ponatinib vs HCVAD + Dasatinib in Ph-Positive ALL.



Blinatumomab and Inotuzumab in R-R Ph+ ALL

Blina vs SOC

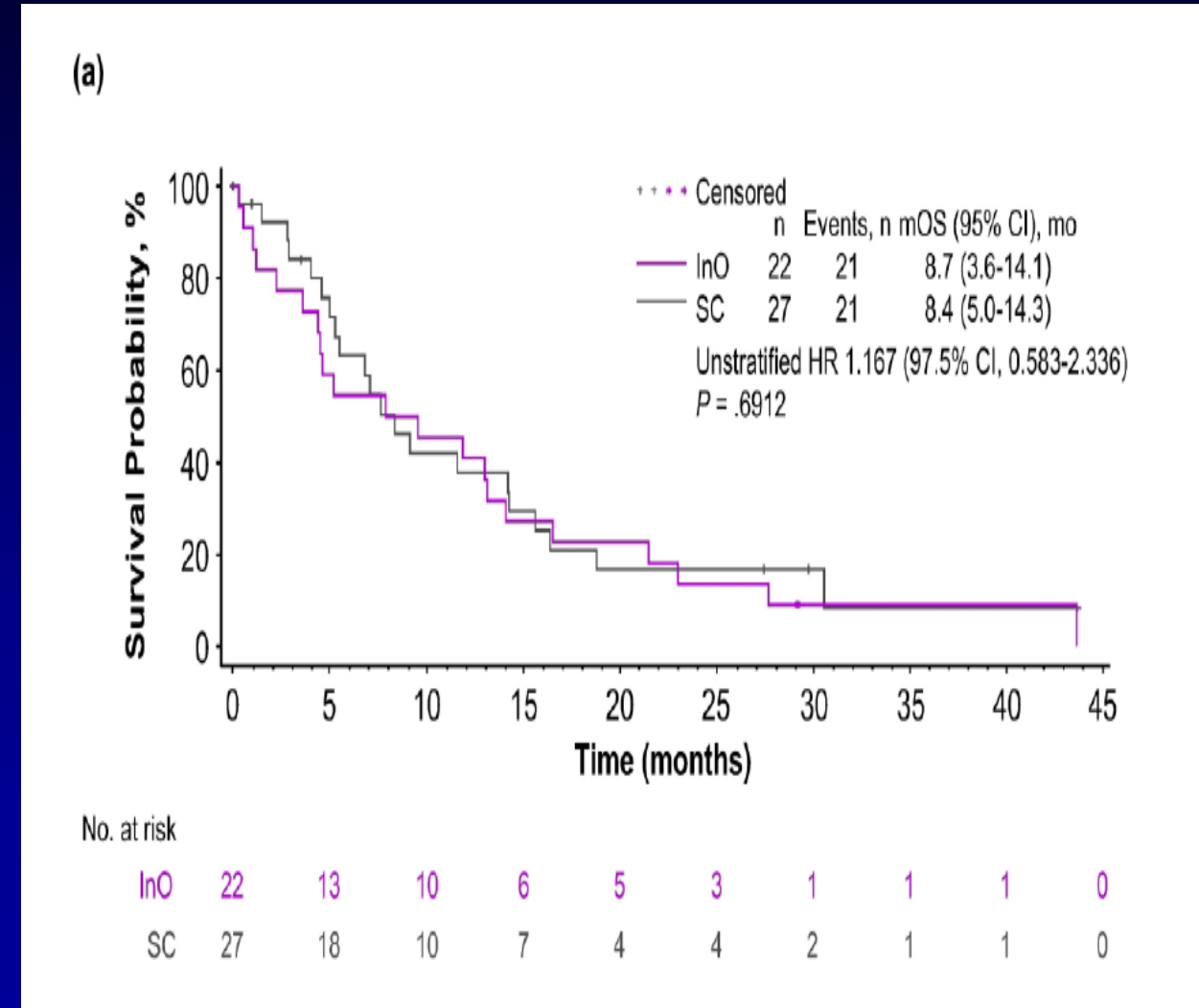
- CR/CRh 36% vs 25%
- 1-yr OS 41% vs 31%



Rambaldi. Cancer. 126: 304-310; 2019

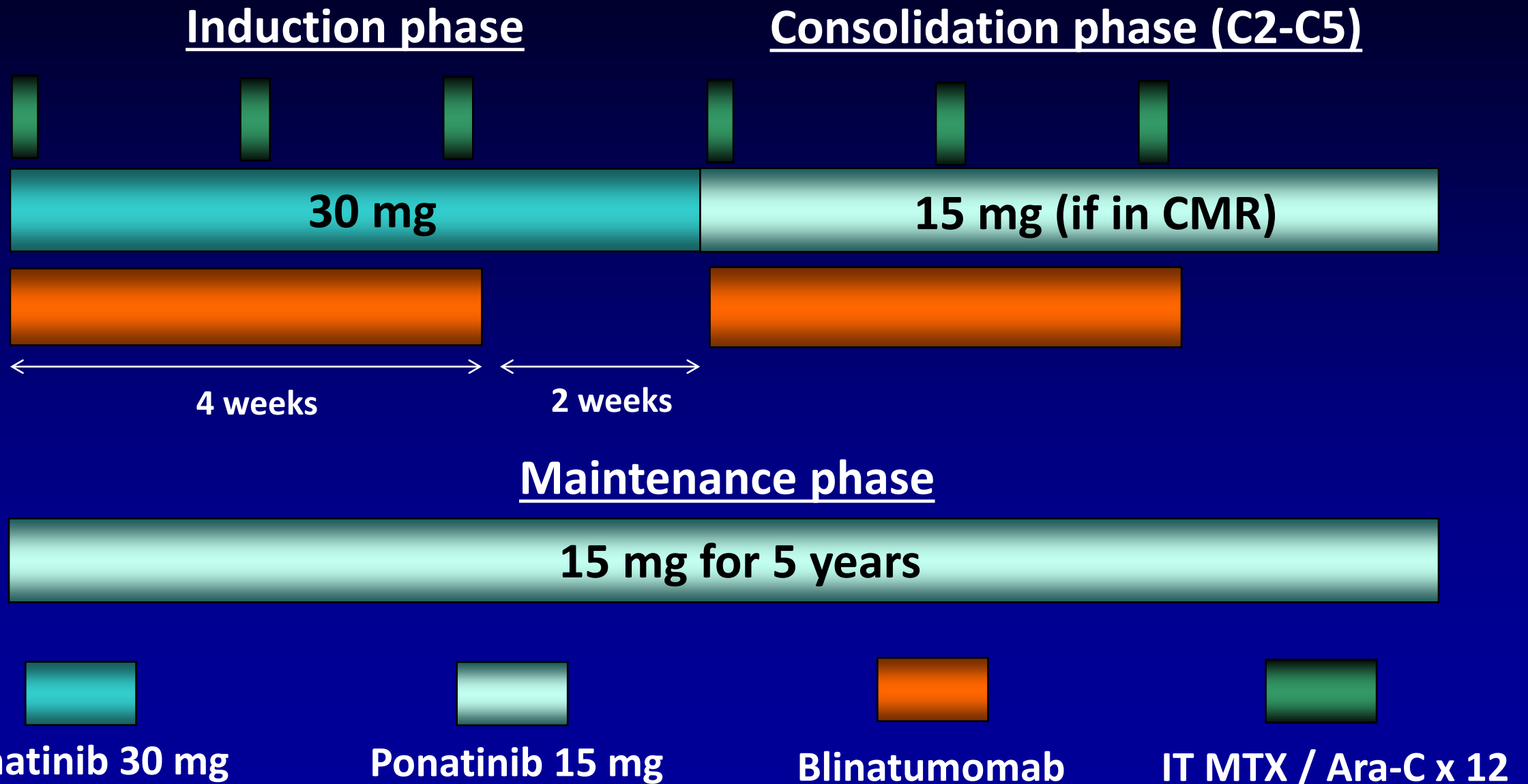
Ino vs SOC

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



Stock. Cancer 127: 905-13;2021

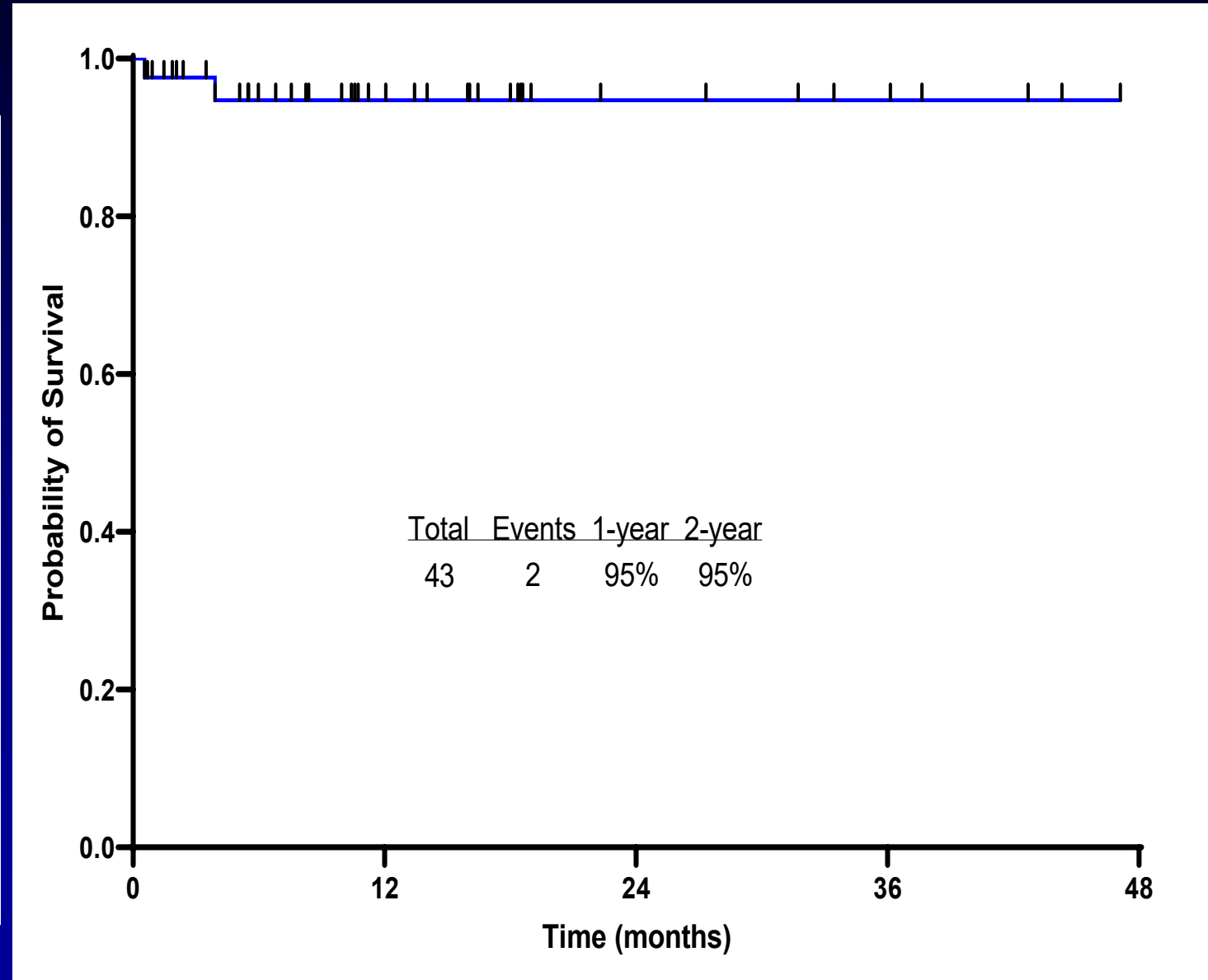
Ponatinib + Blinatumomab in Ph+ ALL: Regimen



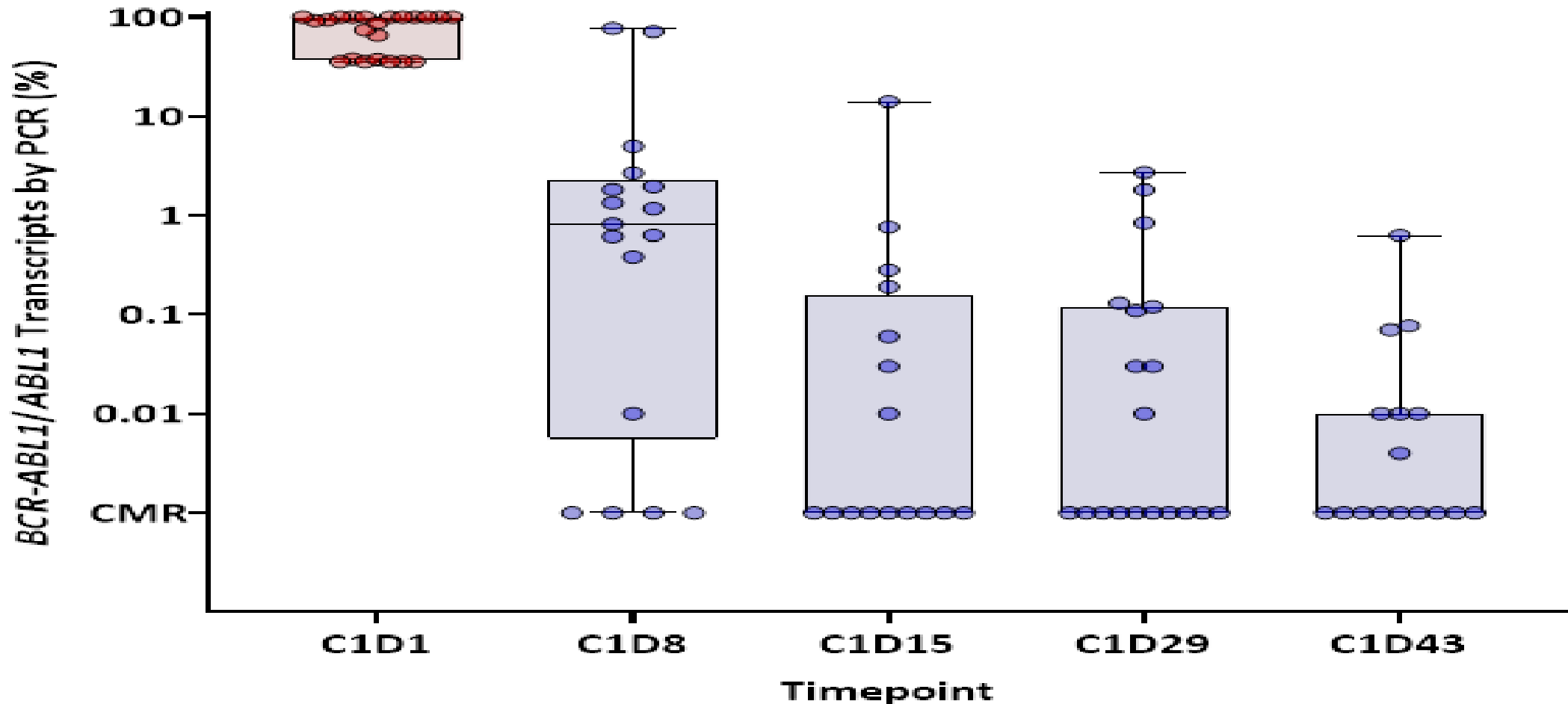
Ponatinib and Blinatumomab in Ph-positive ALL

- 63 pts (43 newly Dx, 14 R-R, 6 CML-LBP) Rx with simultaneous Ponatinib 45-15mg/D and blinatumomab x 5 courses
- Only 1 newly Dx pt had SCT(3%)

Parameter	New Dx	R-R	CML-LBP
% CR-CRi	97	92	83
% CMR	79	91	33
% 2-yr OS	95	59	60

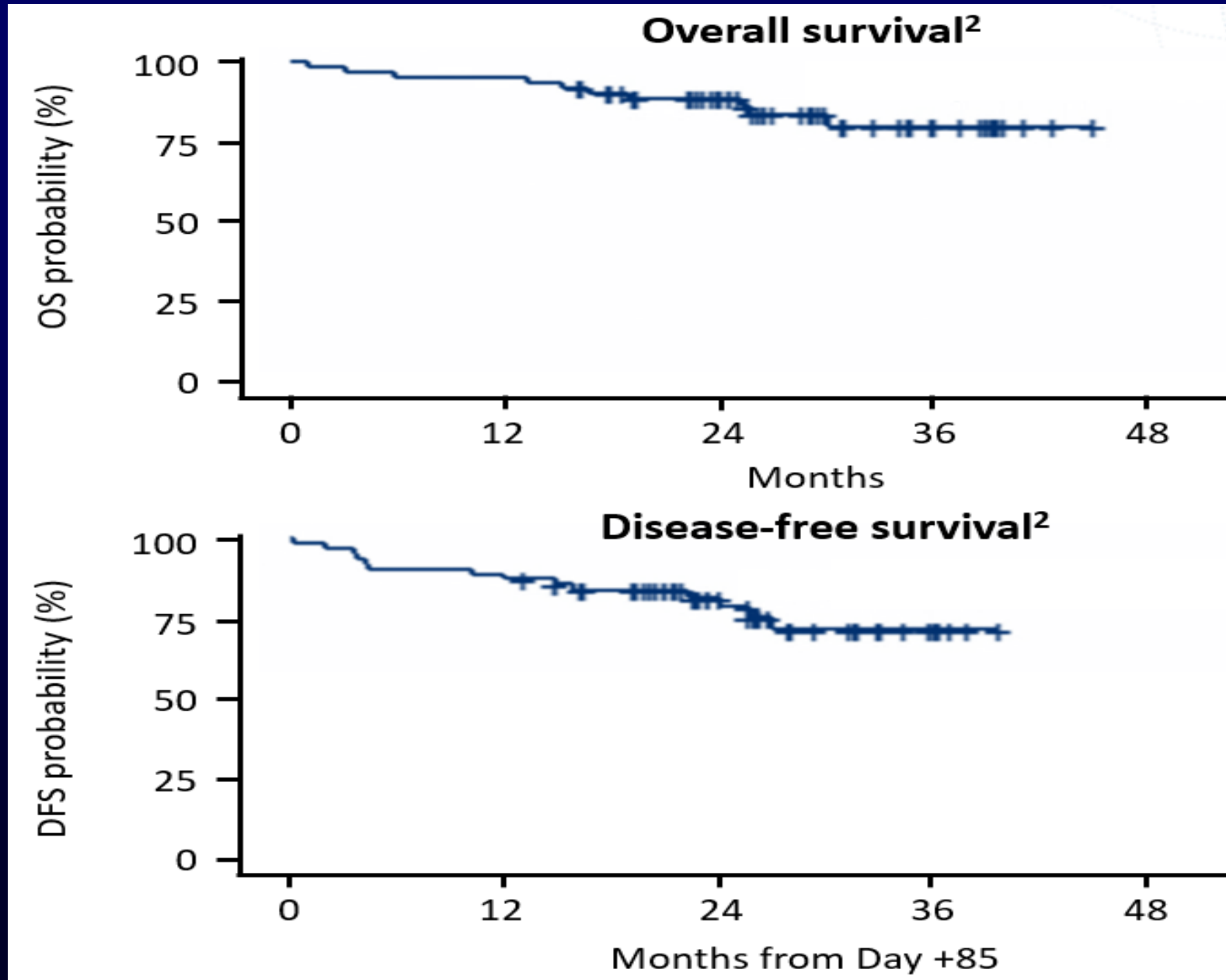


Ponatinib + Blinatumomab in Ph+ ALL. Early MRD Responses in Frontline Cohort



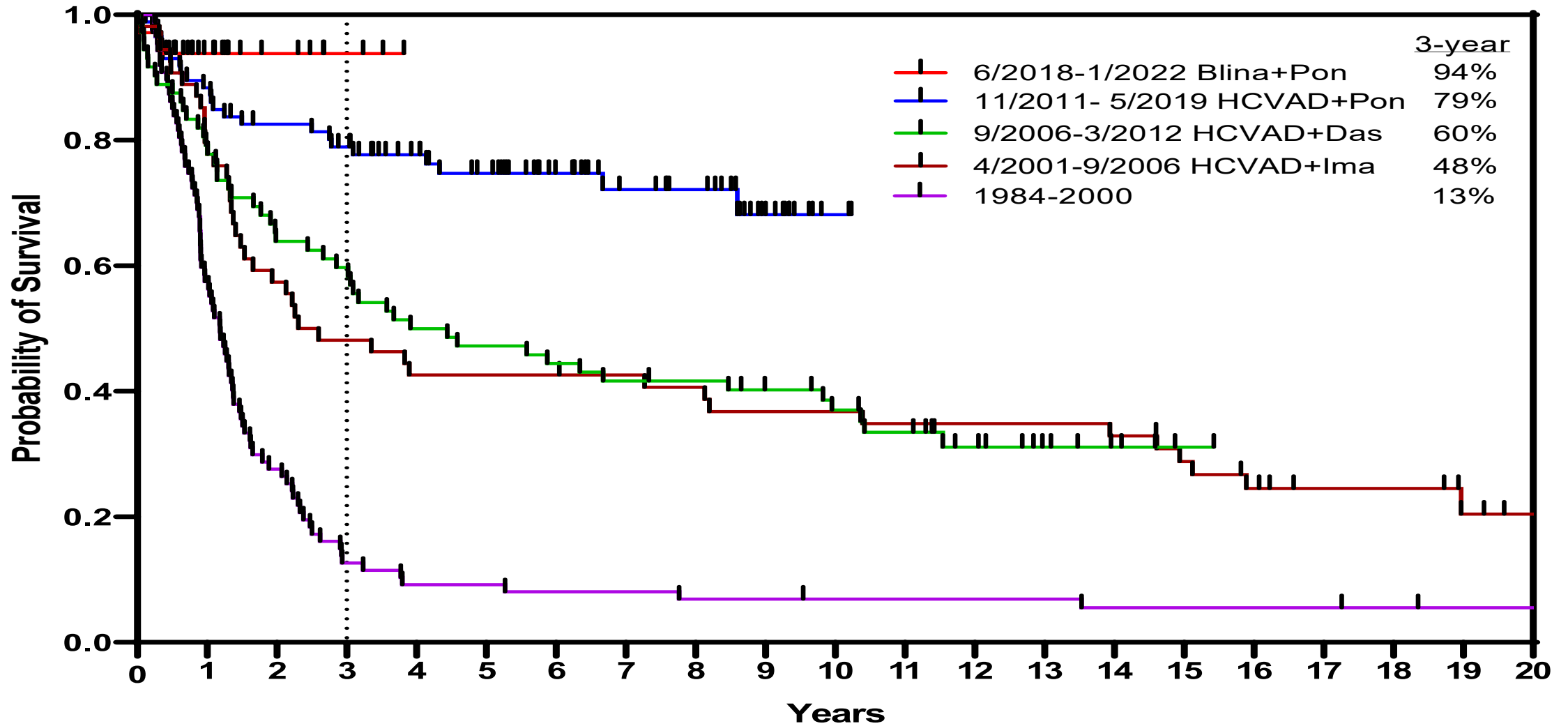
Dasatinib-blinatumomab in Ph-positive ALL

- 63 pts, median age 54 yrs (24-82).
- Dasatinib 140mg/D x 3 mos ; add blina x 2-5
- 53 post dasa-blina x 2--
molecular response 32/53 (60%), 23CMR (42%) . MRD ↑ in 15— 6 T315I; **3-yr OS 77%; DFS 71%** . 29/58 (50%) allo SCT

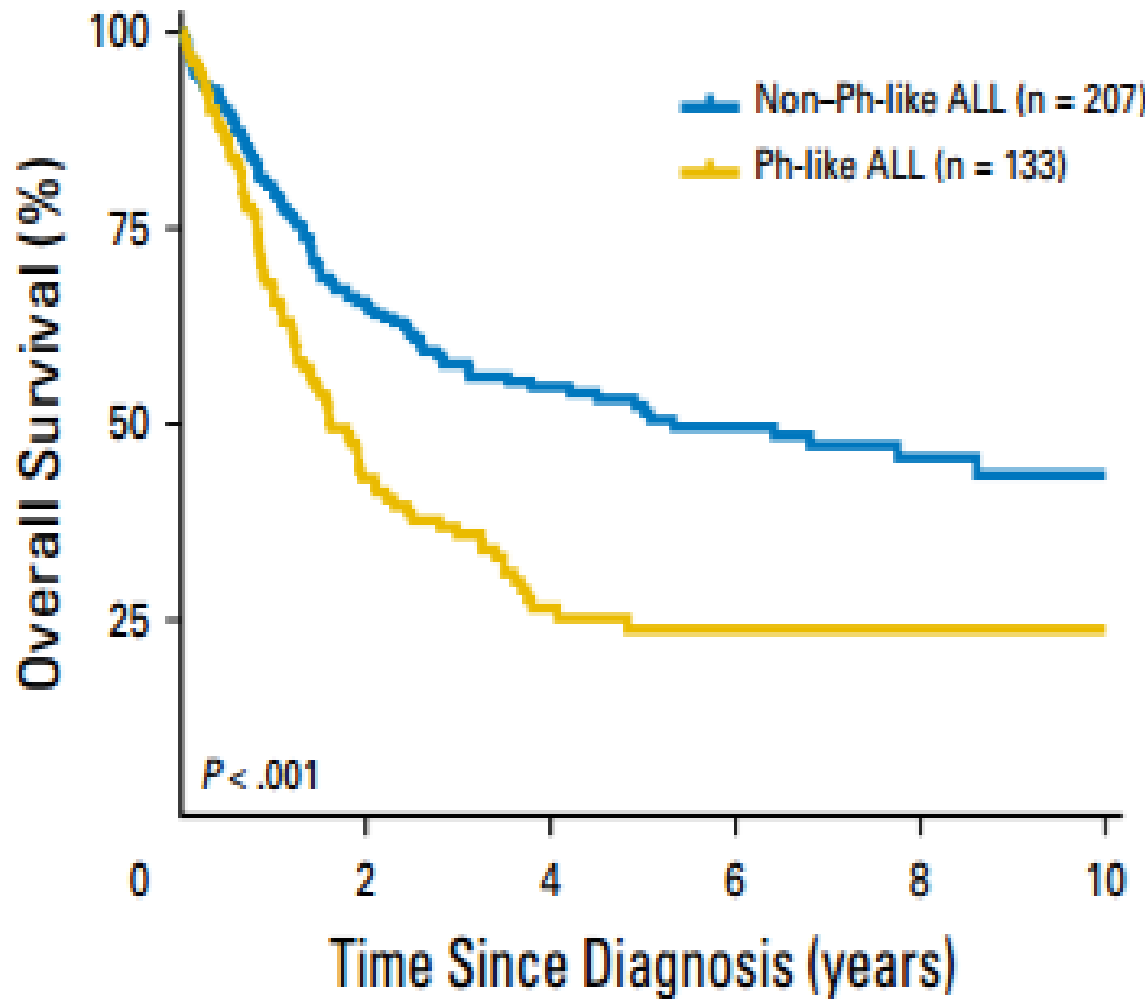


ALL. Survival by Decade (MDACC 1985-2022)

Overall Survival of Ph+ patients

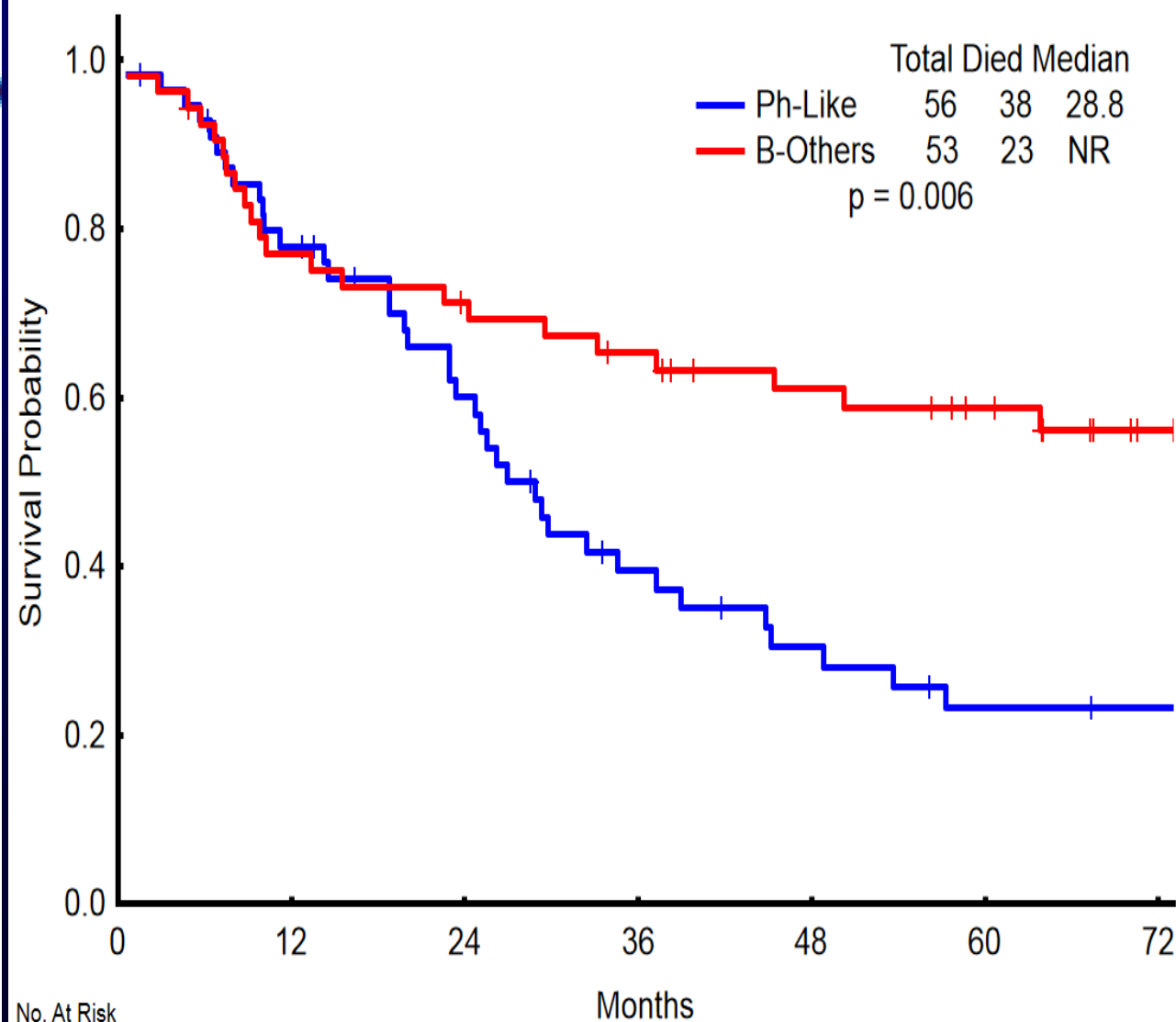


Ph-Like ALL-- Survival and EFS



No. at risk:

	0	2	4	6	8	10
Non-Ph-like ALL	207	162	127	107	80	60
Ph-like ALL	133	82	49	40	23	17

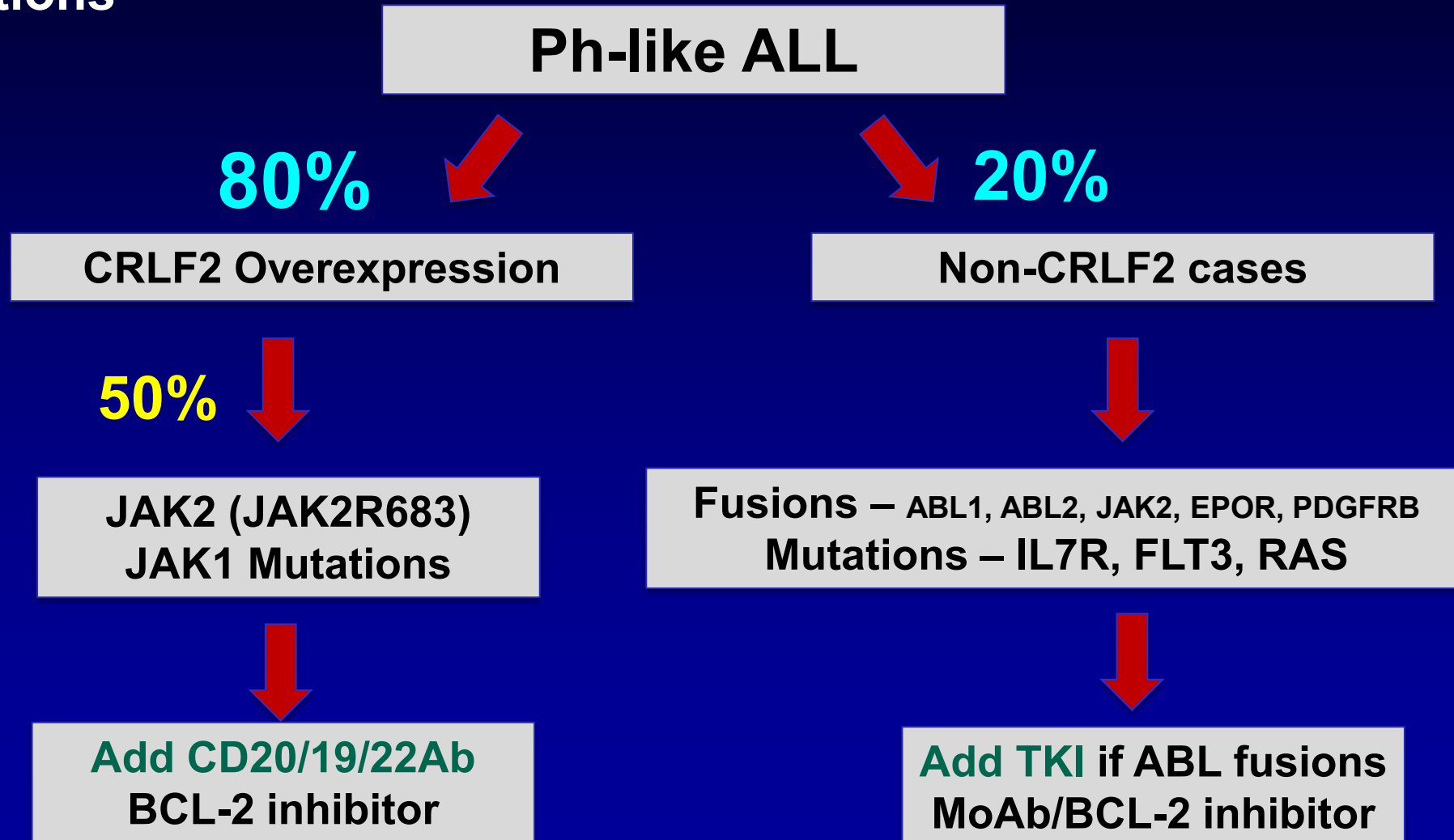


No. At Risk

	0	12	24	36	48	60	72
Ph-Like	56	42	30	18	13	9	8
B-Others	53	40	36	32	27	23	15

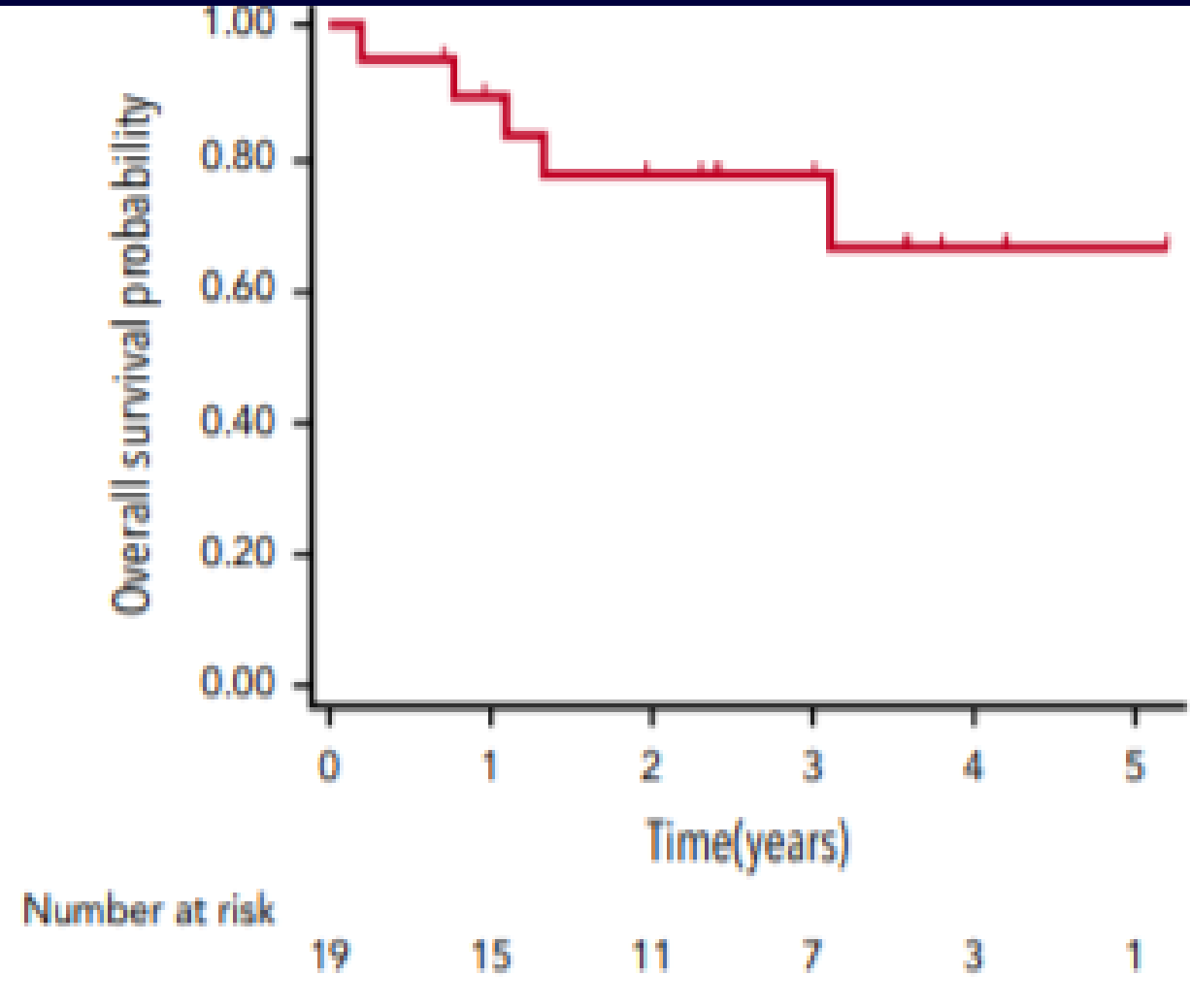
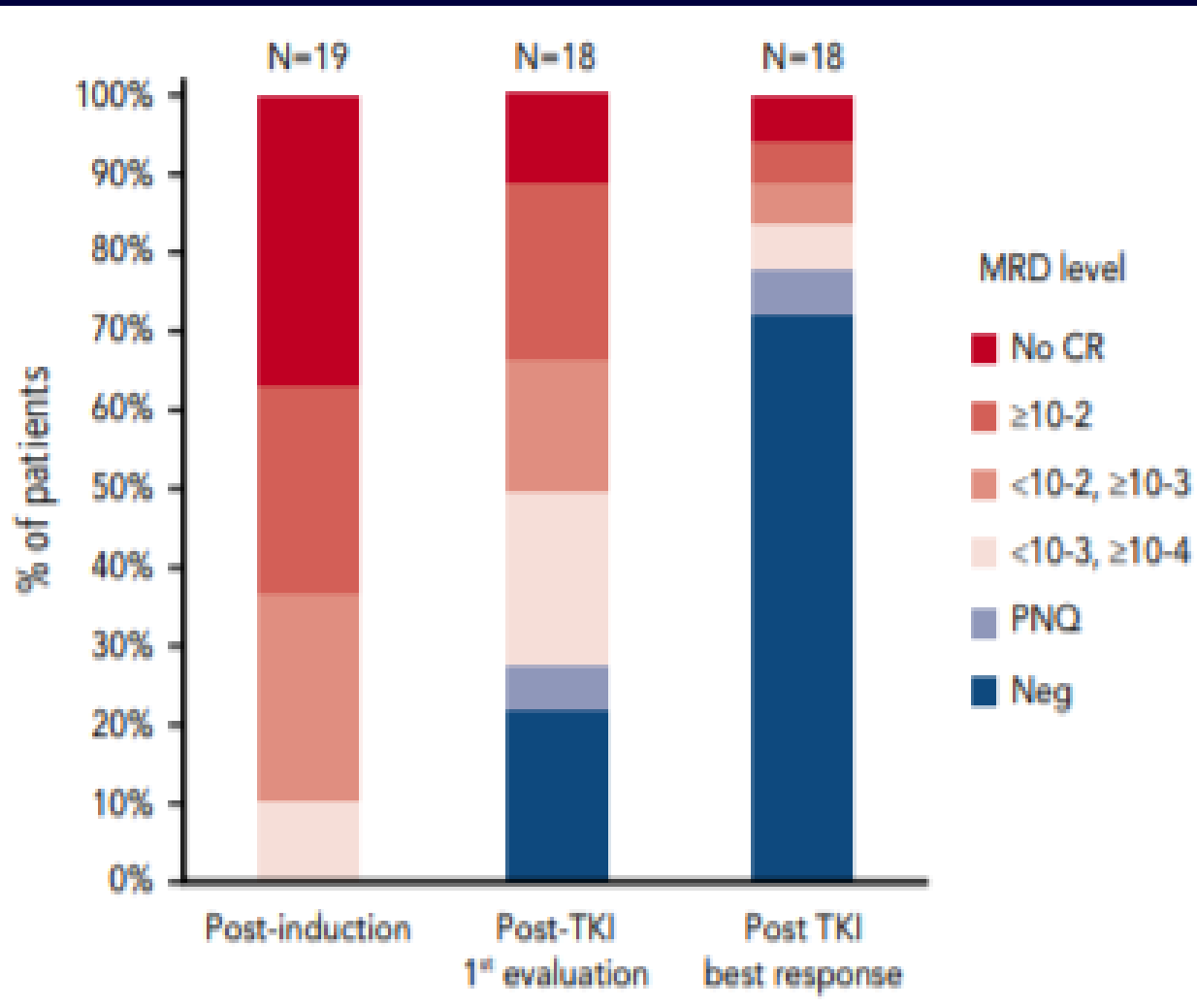
Ph-like ALL Molecular Lesions

- Ph-like 25-30% of ALL; poor prognosis
- Ph-like ALL misleading. Better : CRLF2+ ALL; true Ph ALL with ABL1/PDGFR translocations



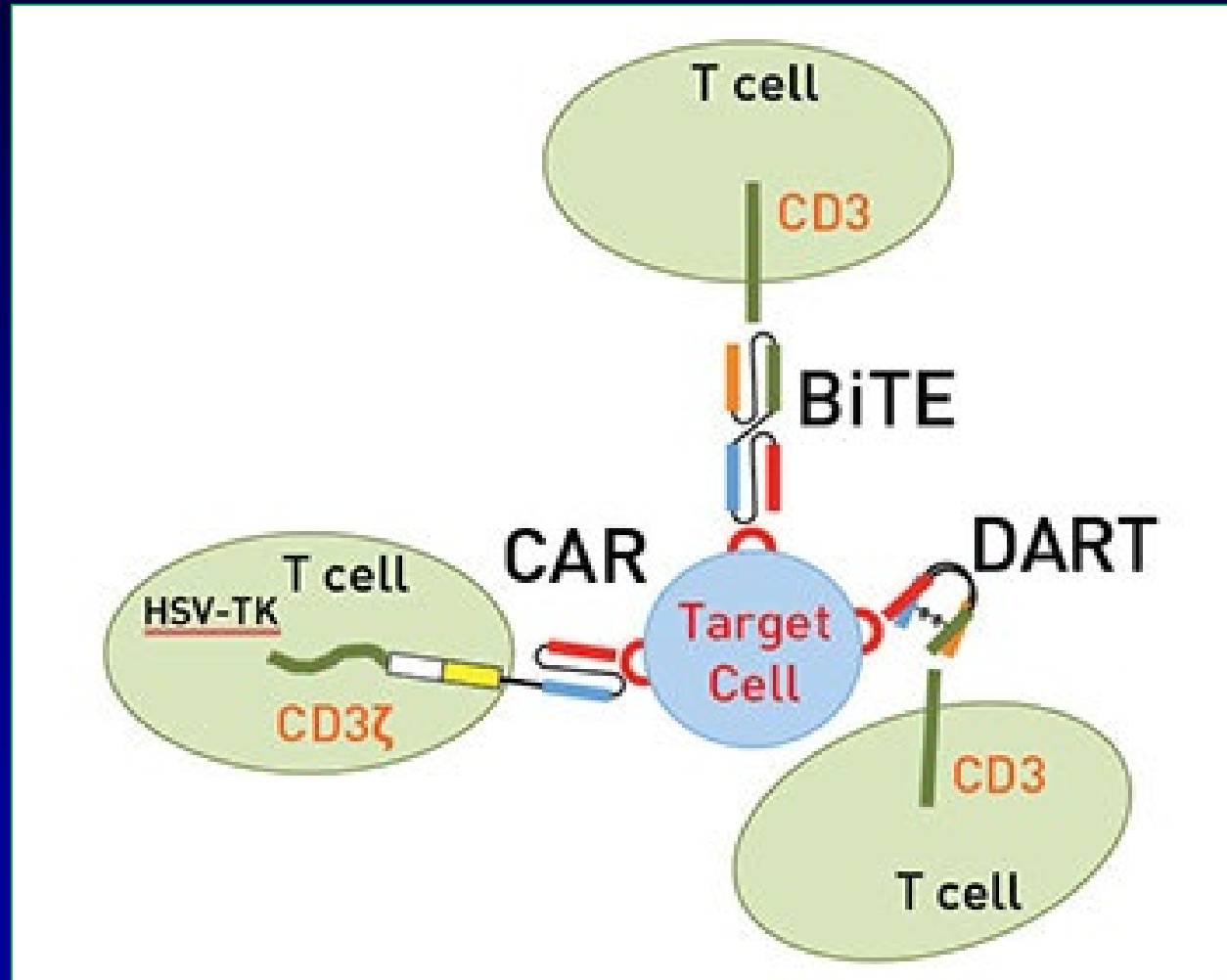
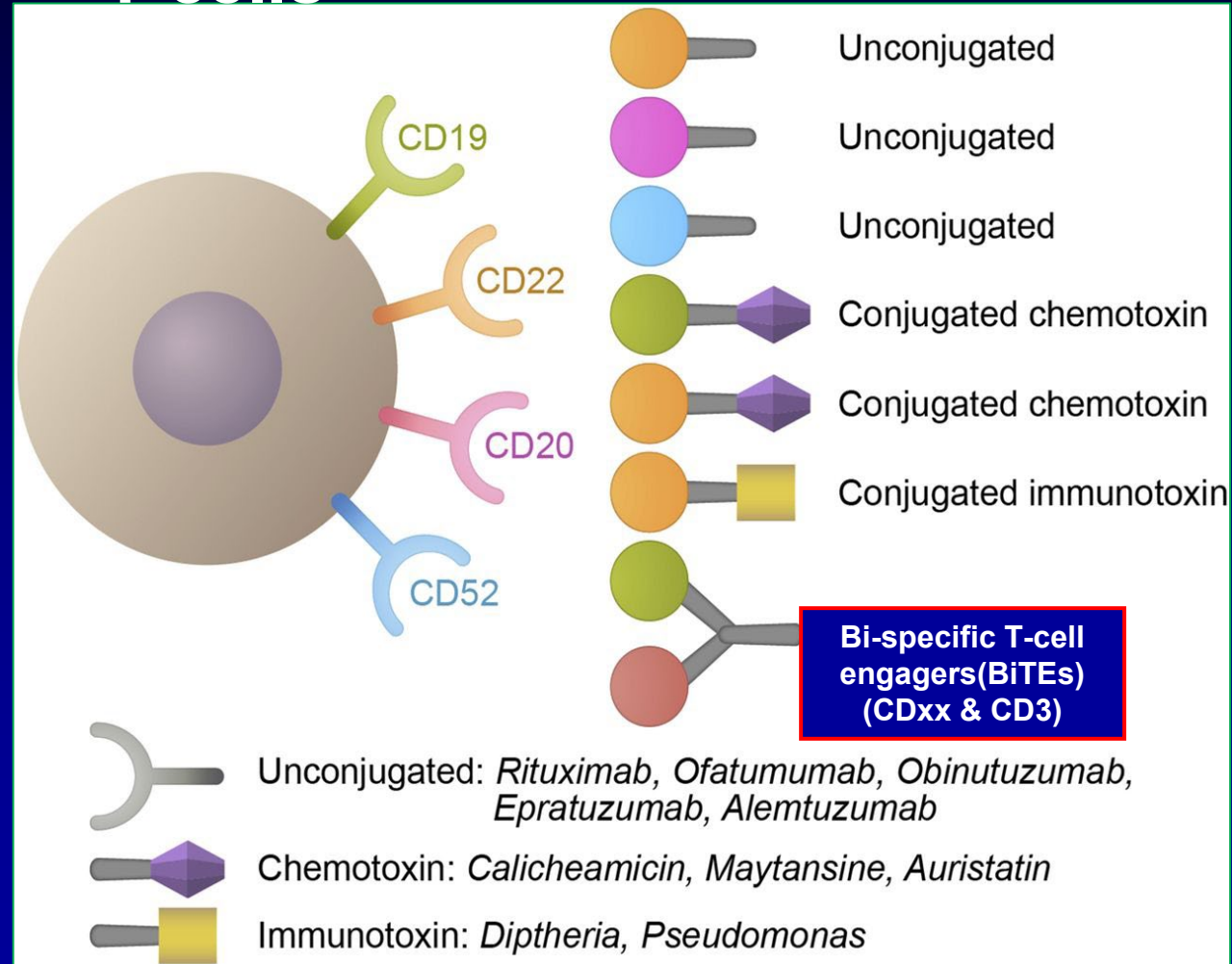
BCR-ABL TKIs + Chemo Rx in Ph-like ALL

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



Immuno-oncology in ALL

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

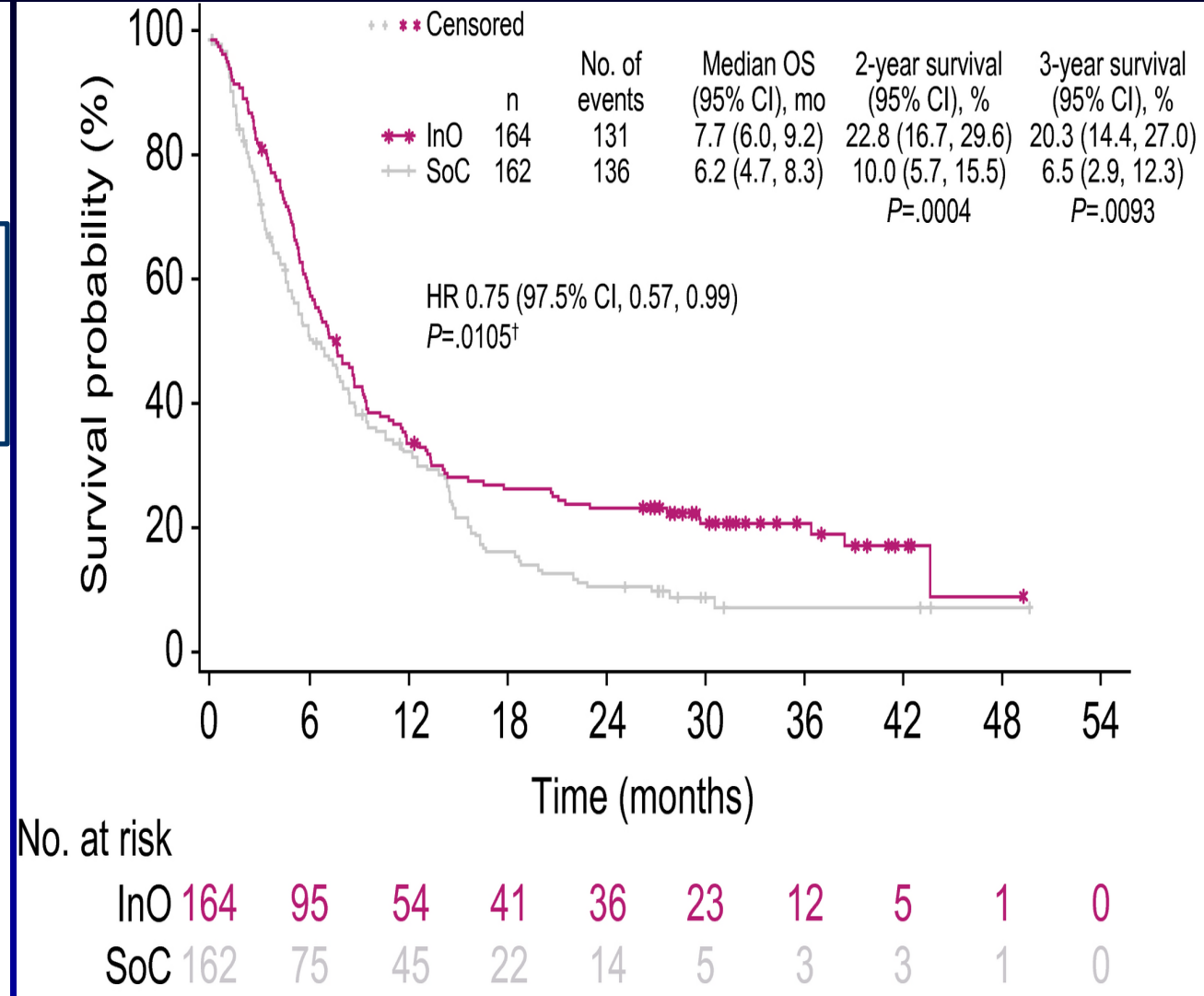
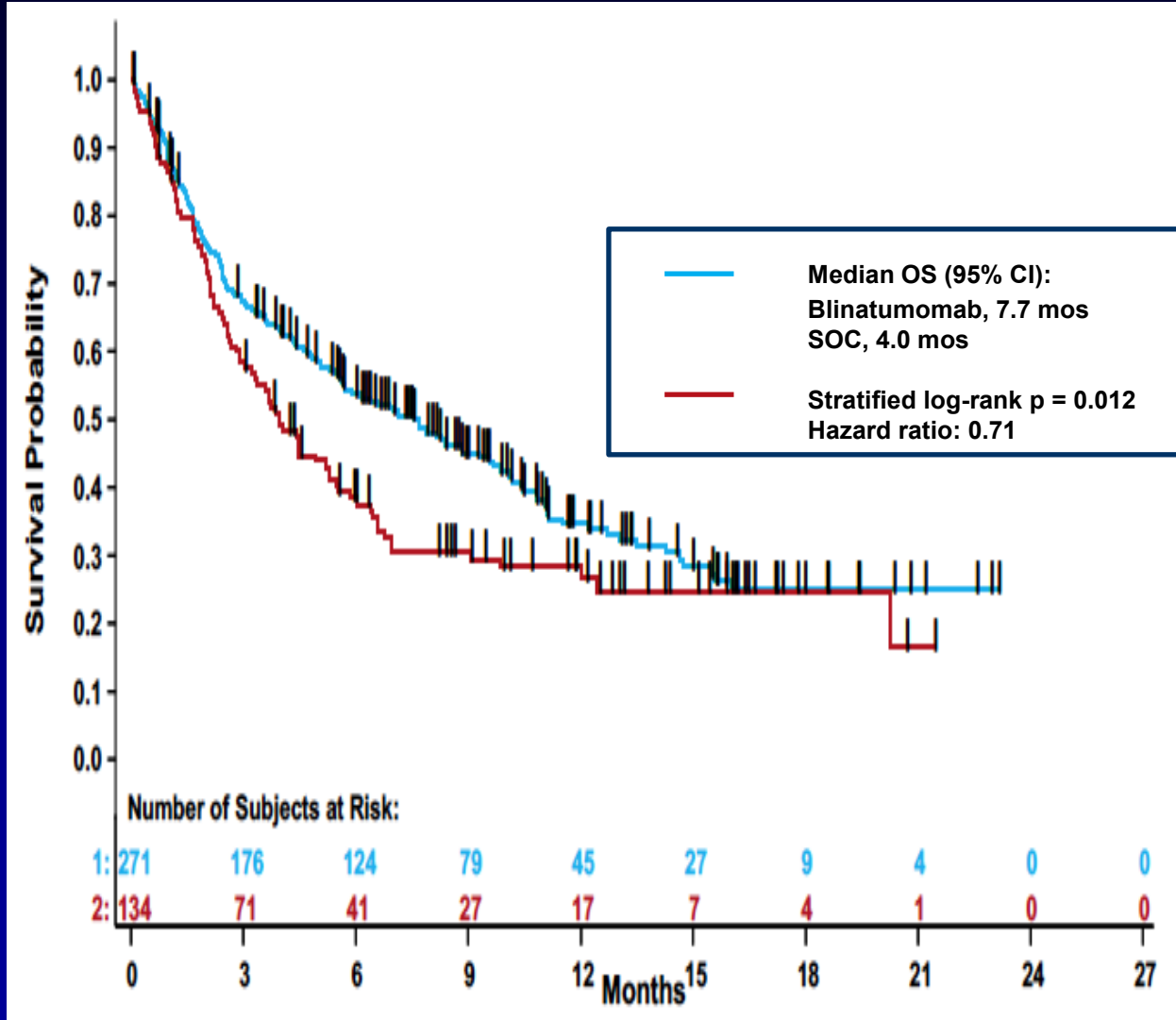


Blinatumomab/Inotuzumab vs ChemoRx in R-R ALL

- Marrow CR

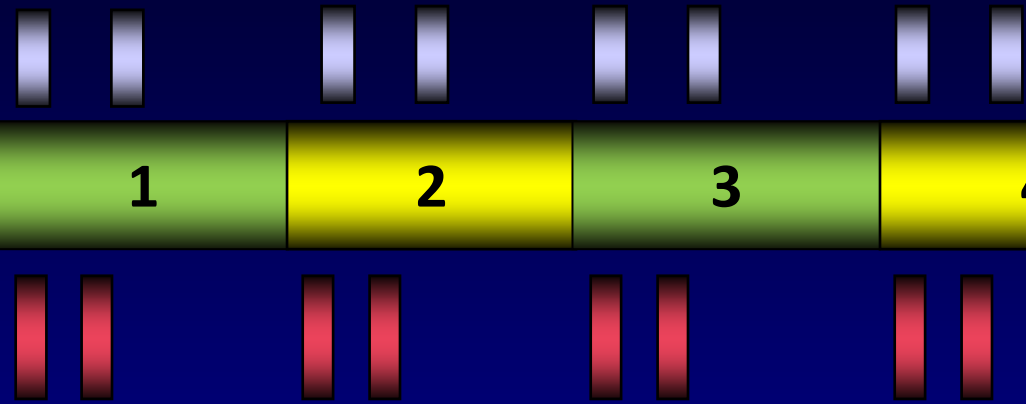
Blina vs SOC: 44% vs 25%

Ino vs SOC: 74% vs 31%



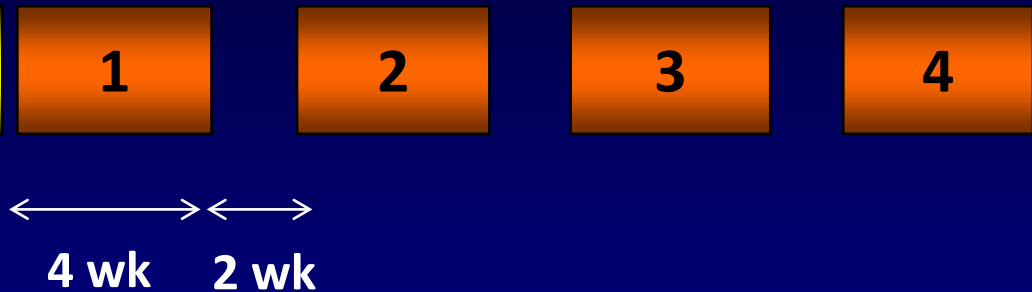
Hyper-CVAD + Blinatumomab in B-ALL: Regimen

Intensive phase



Blinatumomab phase

*After 2 cycles of chemo for MRD+, Ho-Tr, Ph-like, TP53, t(4;11)



Maintenance phase



 Hyper-CVAD

 Ofatumumab or rituximab

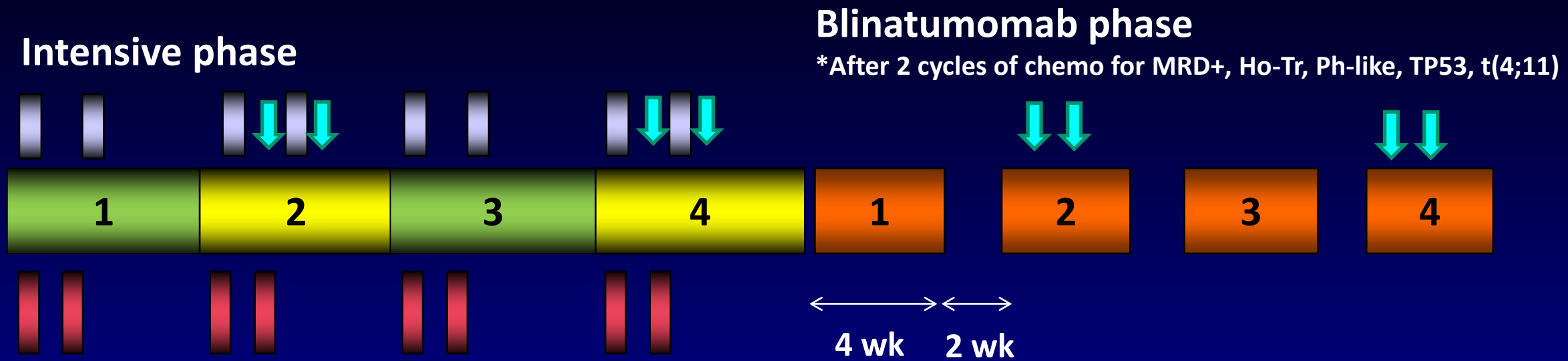
 Blinatumomab

 MTX + Ara-C

 IT MTX / Ara-C x 8



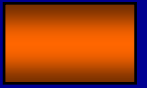



 POMP

Hyper-CVAD + Blinatumomab/Inotuzumab in B-ALL



Maintenance phase

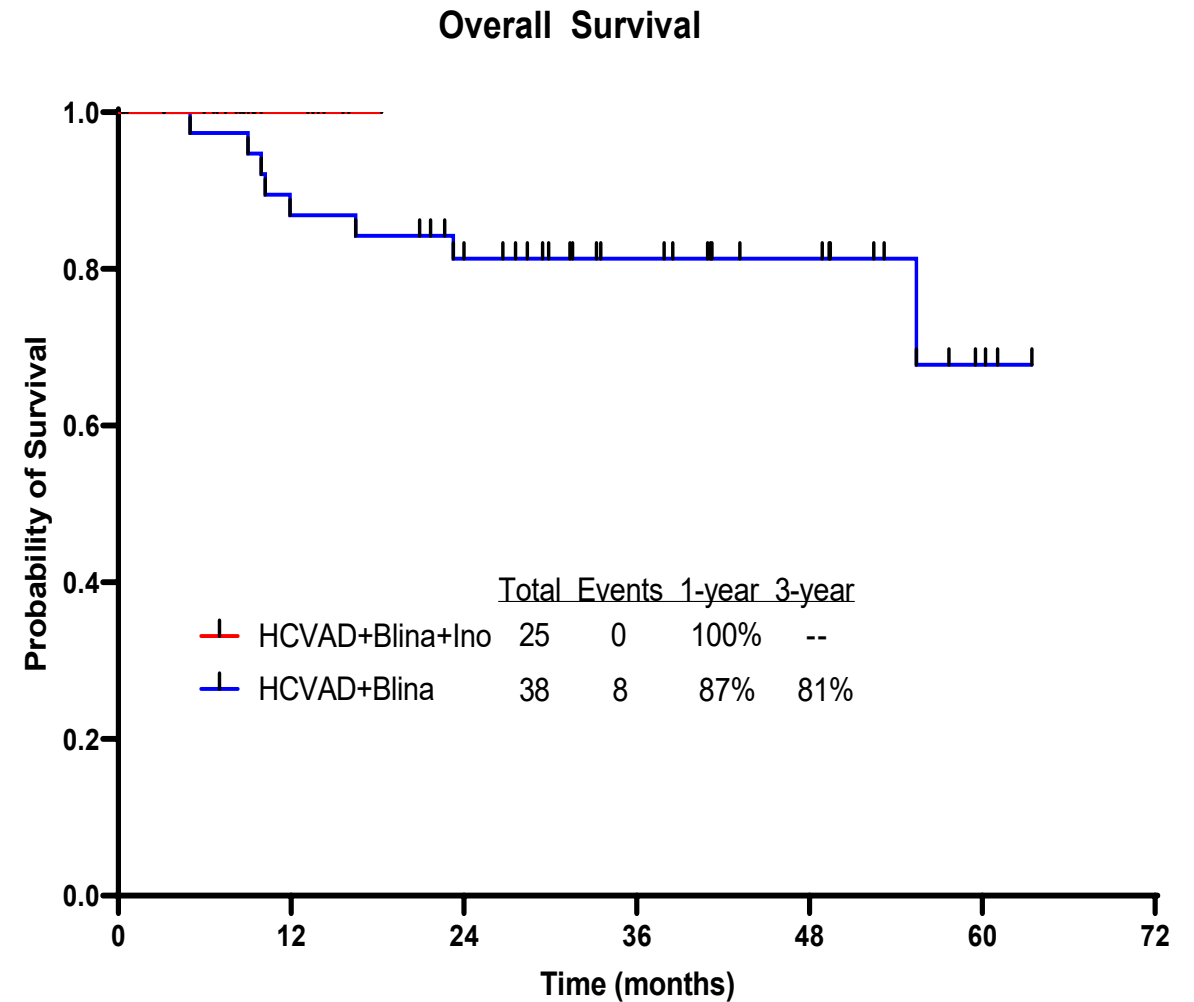
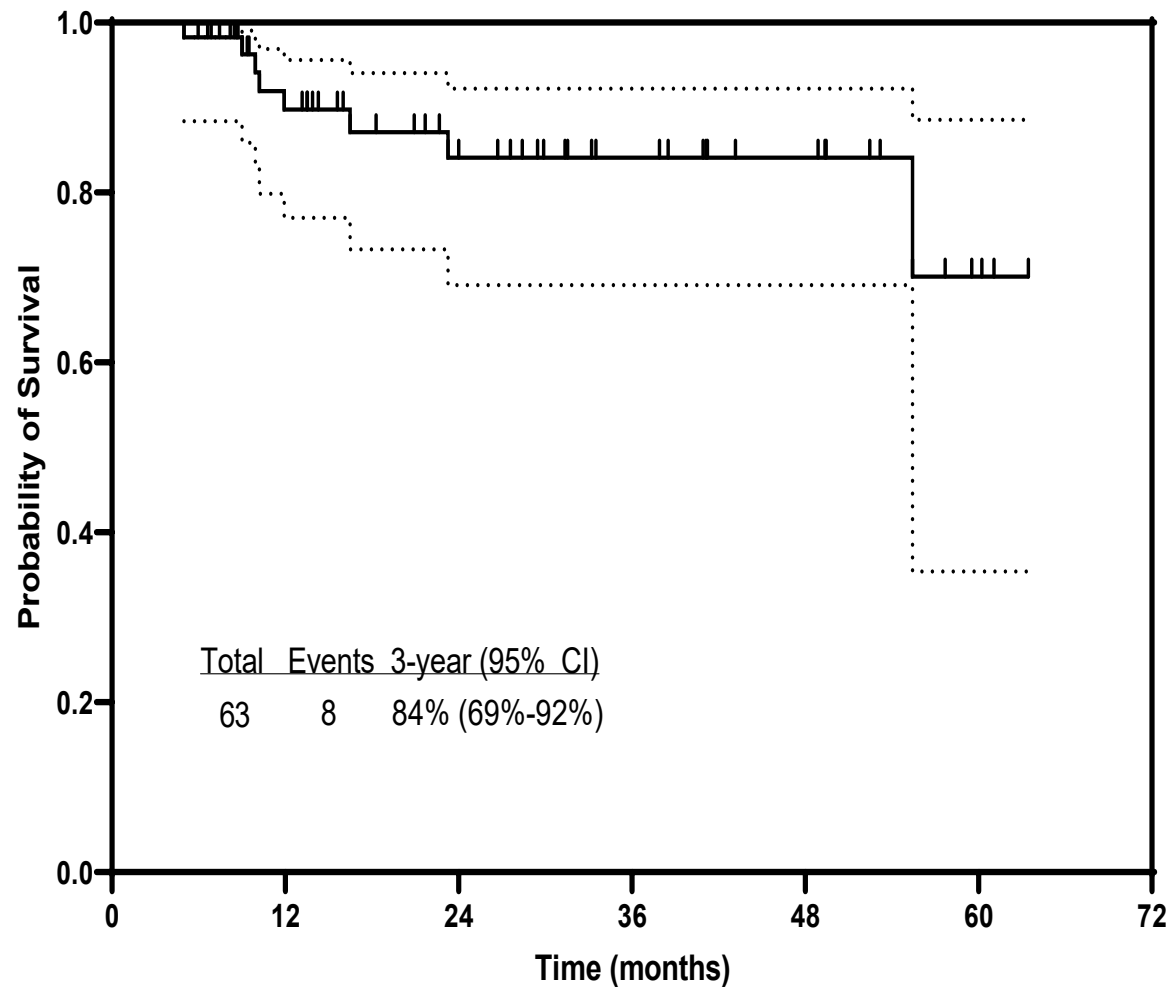


 Hyper-CVAD	 Ofatumumab or rituximab	 Blinatumomab
 MTX + Ara-C	 IT MTX / Ara-C x 8	 POMP

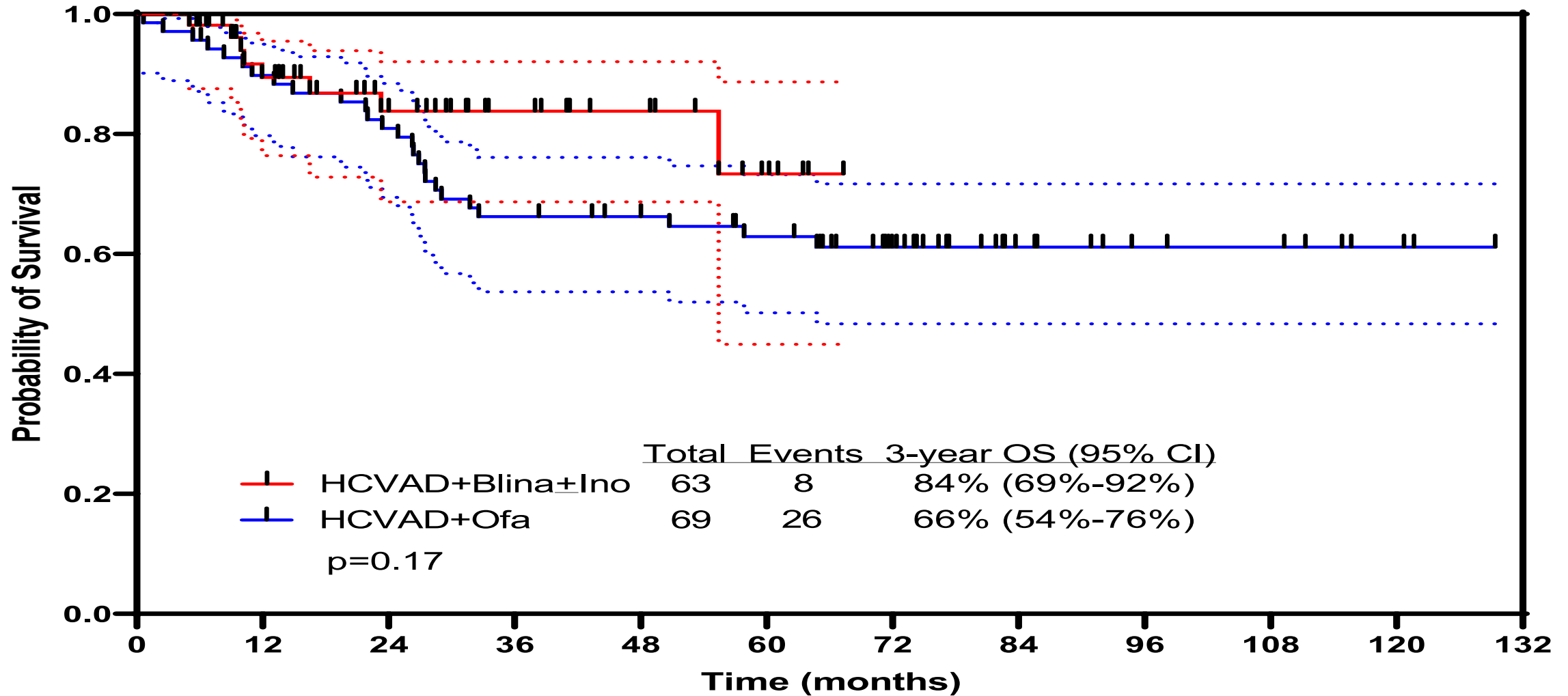
  Inotuzumab 0.3 mg/m² on D1 and D8

Hyper CVAD → Blinatumomab in Newly Dx Adult ALL

- 63 pts; median age 33 yrs (18-59). Rx with O-HCVAD x 4; Blinax4 → POMP 1 yr with blina Q3 mos
- CR rate 100%; MRD negative 95% (75% at CR); 60-day mortality 0%; 12 (32%) allo-SCT; F/U 24 mos



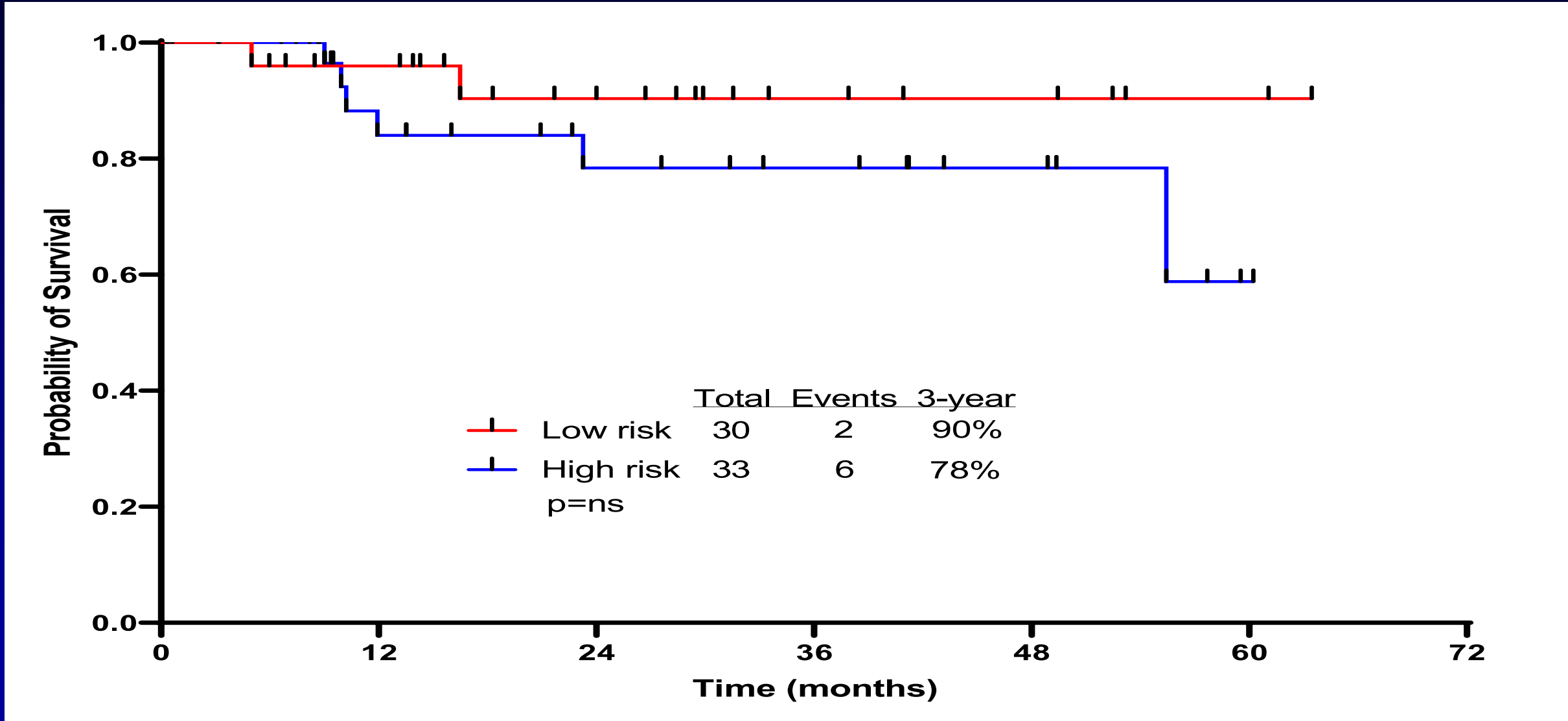
Hyper-CVAD + Blinatumomab + InO in B-ALL. Outcome vs Historical Control



Hyper-CVAD + Blinatumomab + InO in B-ALL. Outcome by Risk

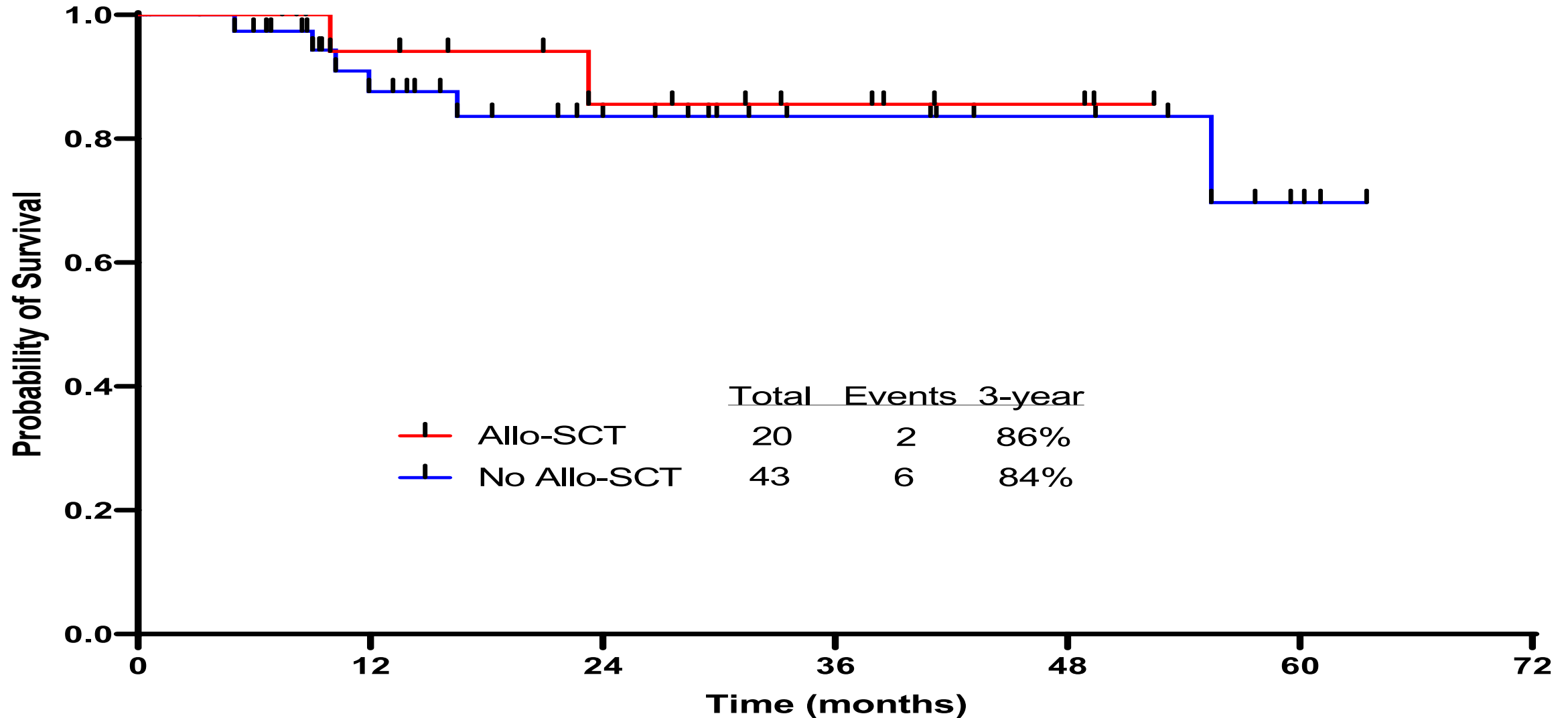
Short. HemaSphere: abst P371; 2022

- High-risk defined as CRLF2+/JAK2+/TP53-mutated and poor-risk CG



Hyper-CVAD + Blinatumomab + InO in B-ALL. Outcome by Allo-SCT

Short. HemaSphere: abst P371; 2022



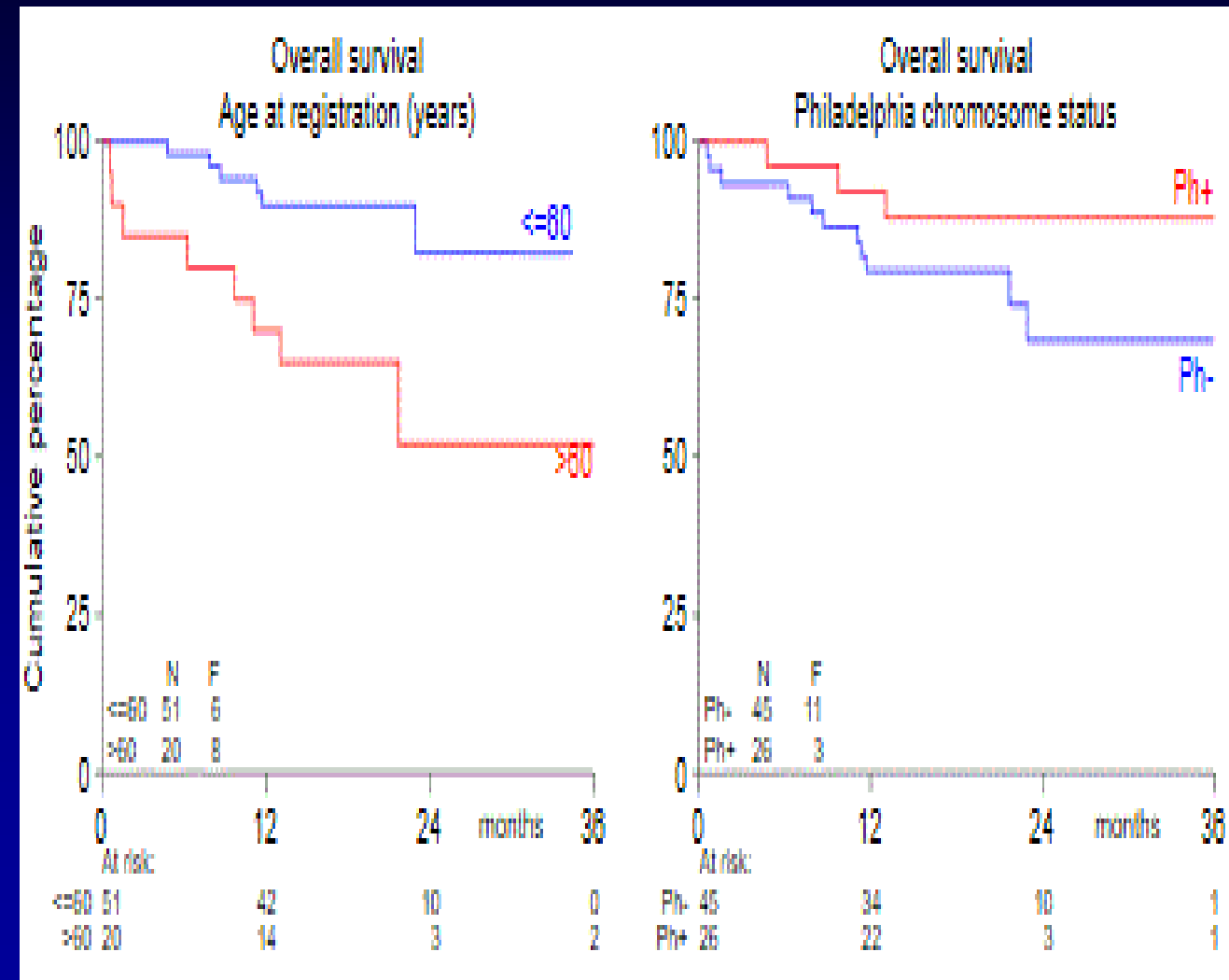
Frontline Blina and Inotuzumab Combinations in Adults with Newly Dx ALL

	Agent	N	Median Age (yrs, range)	% CR	% MRD negativity	% OS (x-yr)
HCVAD-Blina	Blinatumomab	38	37 (17-59)	100	97	85 (3-yr)
HCVAD-blina-inotuzumab	Blinatumomab and Inotuzumab	20	24 (18-47)	100	90	100 (1-yr)
GIMEMA LAL1913	Blinatumomab	149	41 (18-65)	90	96	84 (1-yr)
GRAALL-2014-Quest	Blinatumomab	95	35 (18-60)	NA	74	92 (1.5 yr)
Low-intensity-Blinatumomab	Blinatumomab	30	52 (39-66)	100	73	69 (2-yr)

Blinatumomab Pre-phase then 2 Consolidations in ALL (HOVON)

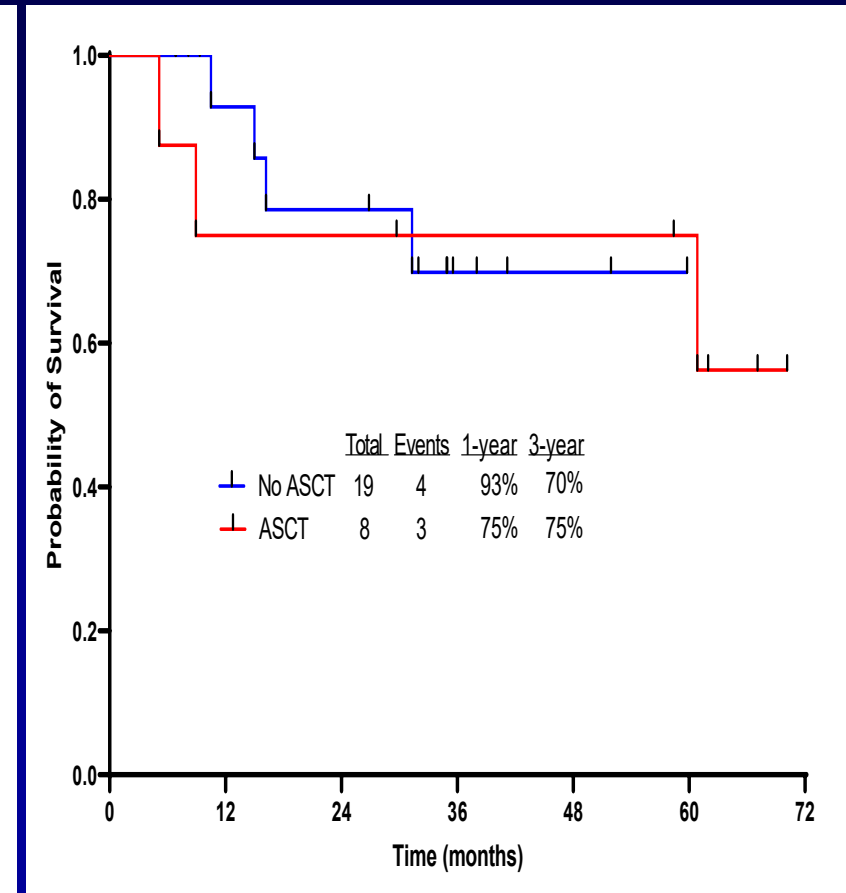
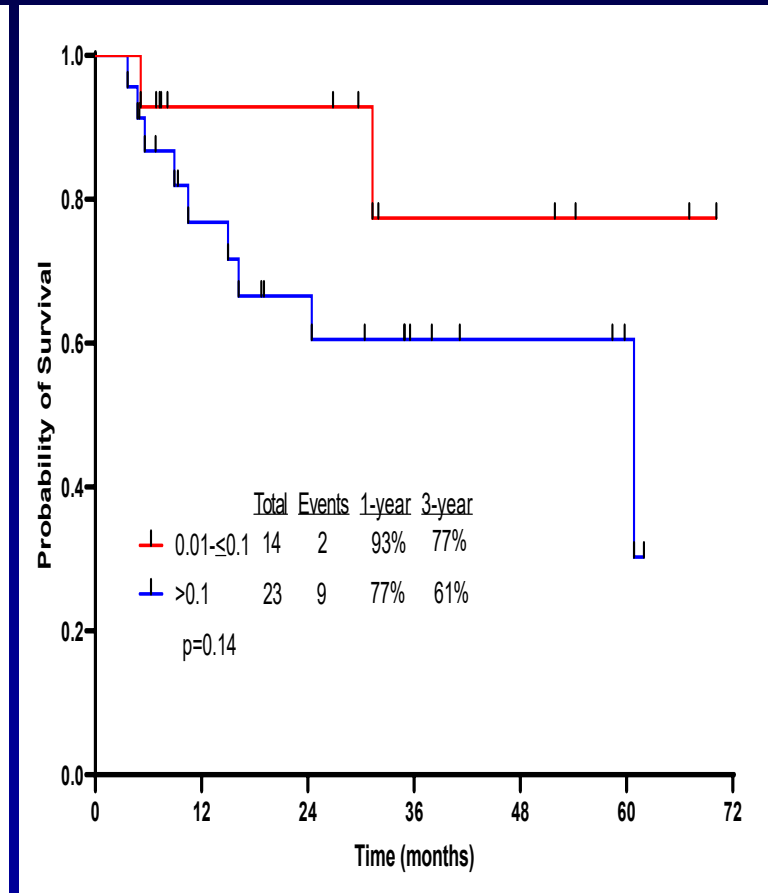
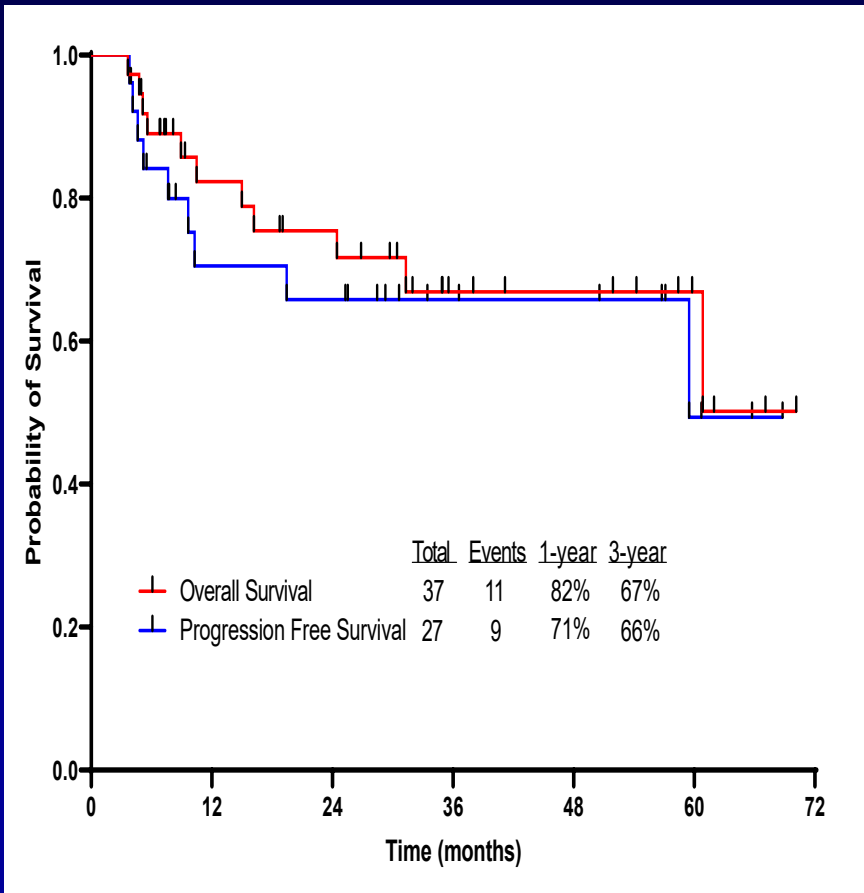
- 71 pts, age 18-70 yrs Rx
- Pre-phase 10 days steroids+blina x 14d. ChemoRx HOVON 70 (amended 2x to ↓ PEG-ASP & reduce Int 1) .Consolidation-Intensification. Blina x 2 (4-wk courses). Ph-positive ALL- Add imatinib
- **Post-pre phase CR 63%**
- 60/71 achieved CR = 85%
- CR 55/56 = 98%; MRD-negativity 50/55=91%
- 9 pts DC blina due to toxicity!!
- Ph+ALL -- 2-yr OS 88%
- 22 pts had allo SCT
- 5 relapses (8%), 6 deaths (10%)

Parameter	Overall	Age < 60	Age 60+
% 2-yr EFS	64	71	47
% 2-yr OS	73	82	52



Blinatumomab for MRD-positive ALL in CR1/CR2+

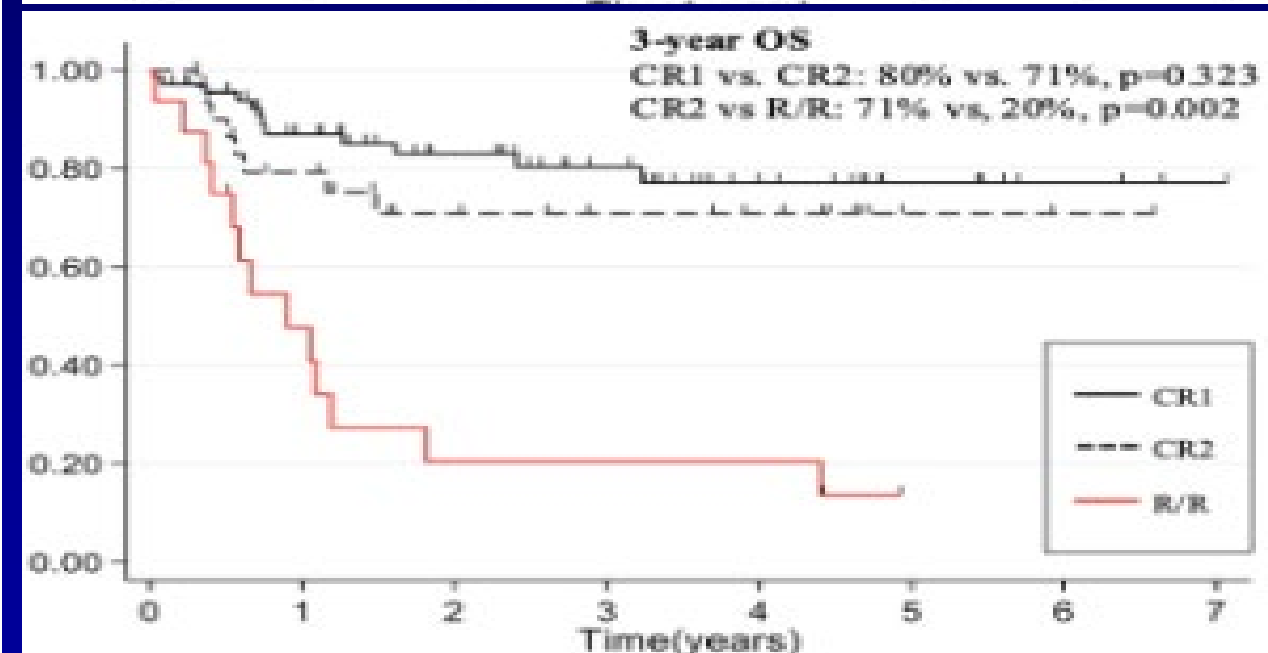
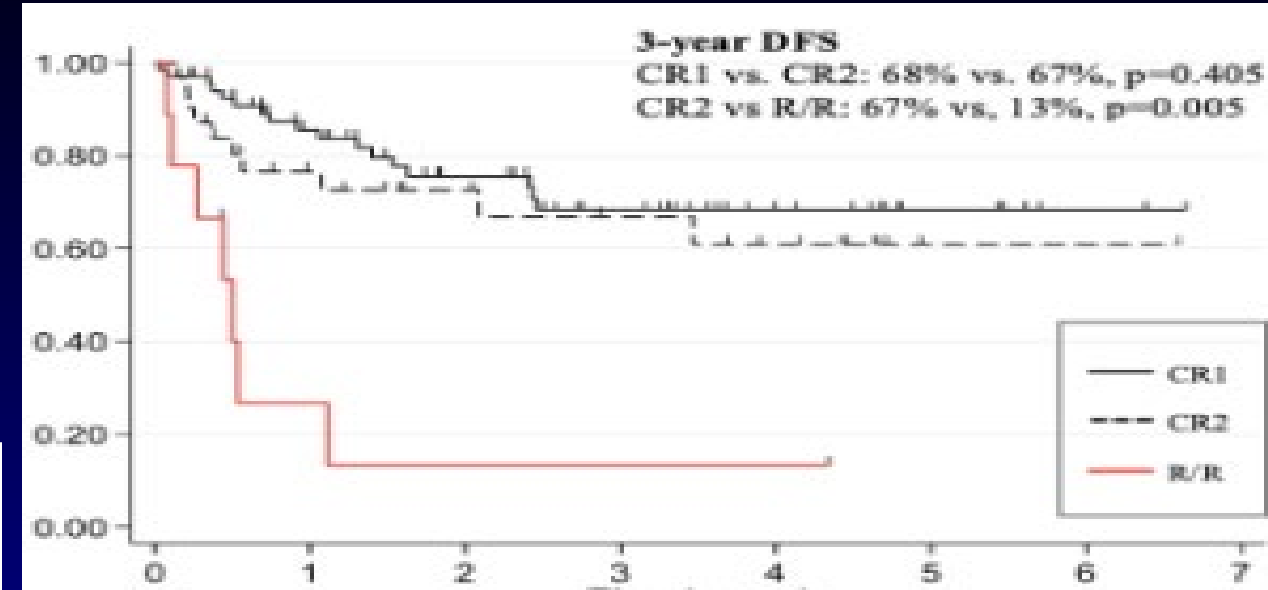
- 37 pts Rx. Post blina MRD-negative 27/37=73%; 83% in Ph-negative ALL
 - 70% after C1
- Median number of cycles 3 (1-9); Median F/U= 31 mos (5-70+)
- 14 pts 0.01-<0.1%: 3-yr OS 77%; 23 pts ≥0.1%: 3-yr OS 61%
- 3-yr OS 67%; 3-yr OS if MRD- negative 72%



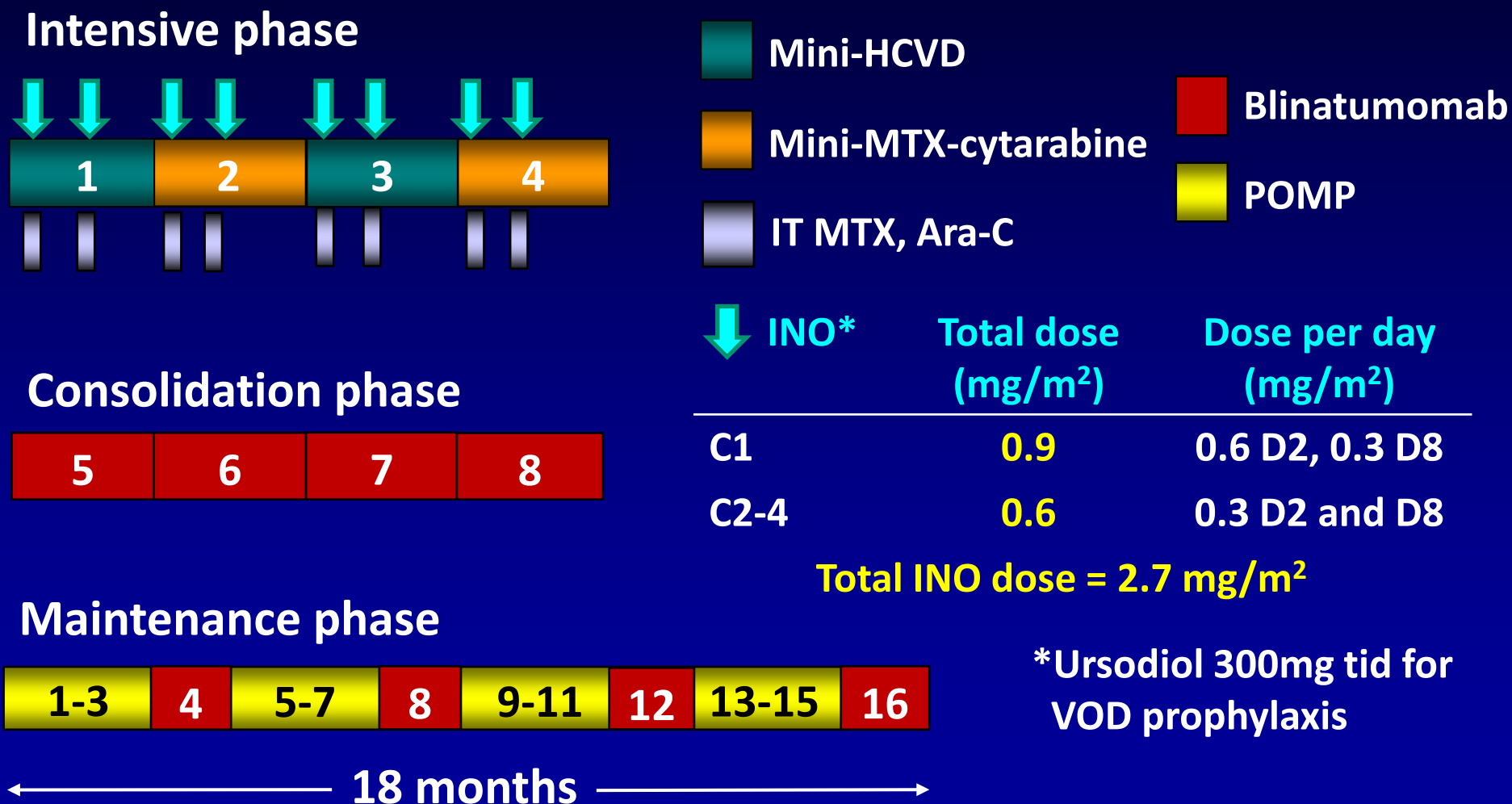
Blinatumomab Consolidation in ALL-France

- 115 pts Rx with Blina—68 in CR1, 31 in CR2, 16 in R-R
- Median 2 courses (1-6); 42% later allo SCT

Parameter	CR1	CR2	R-R
% MRD-negative	83	86	CR9/15 = 60%
% 3-yr DFS	68	67	13
% 3-yr OS	80	71	20

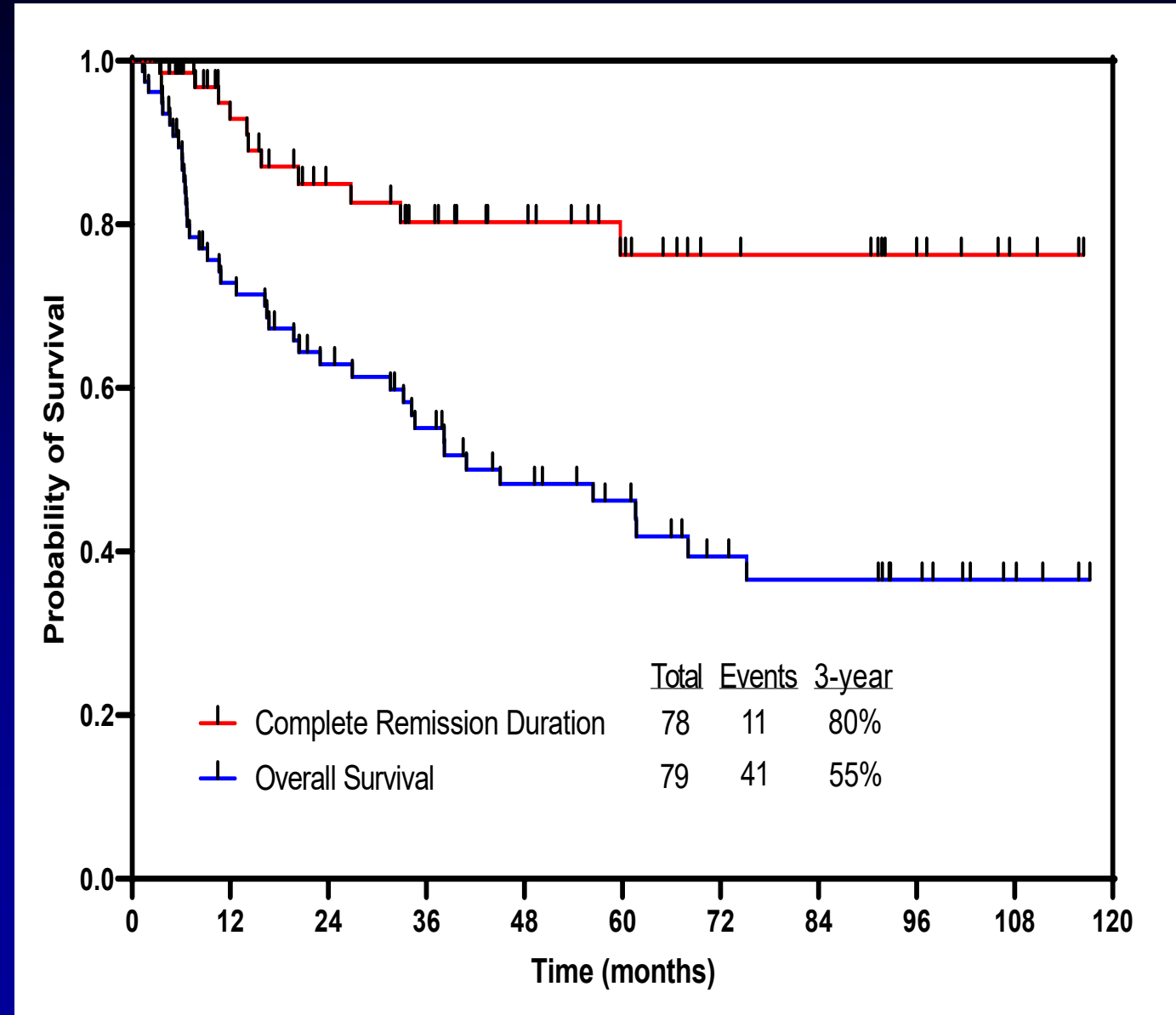


Mini-HCVD + INO ± Blina in Older ALL: Modified Design (Pts #50+)



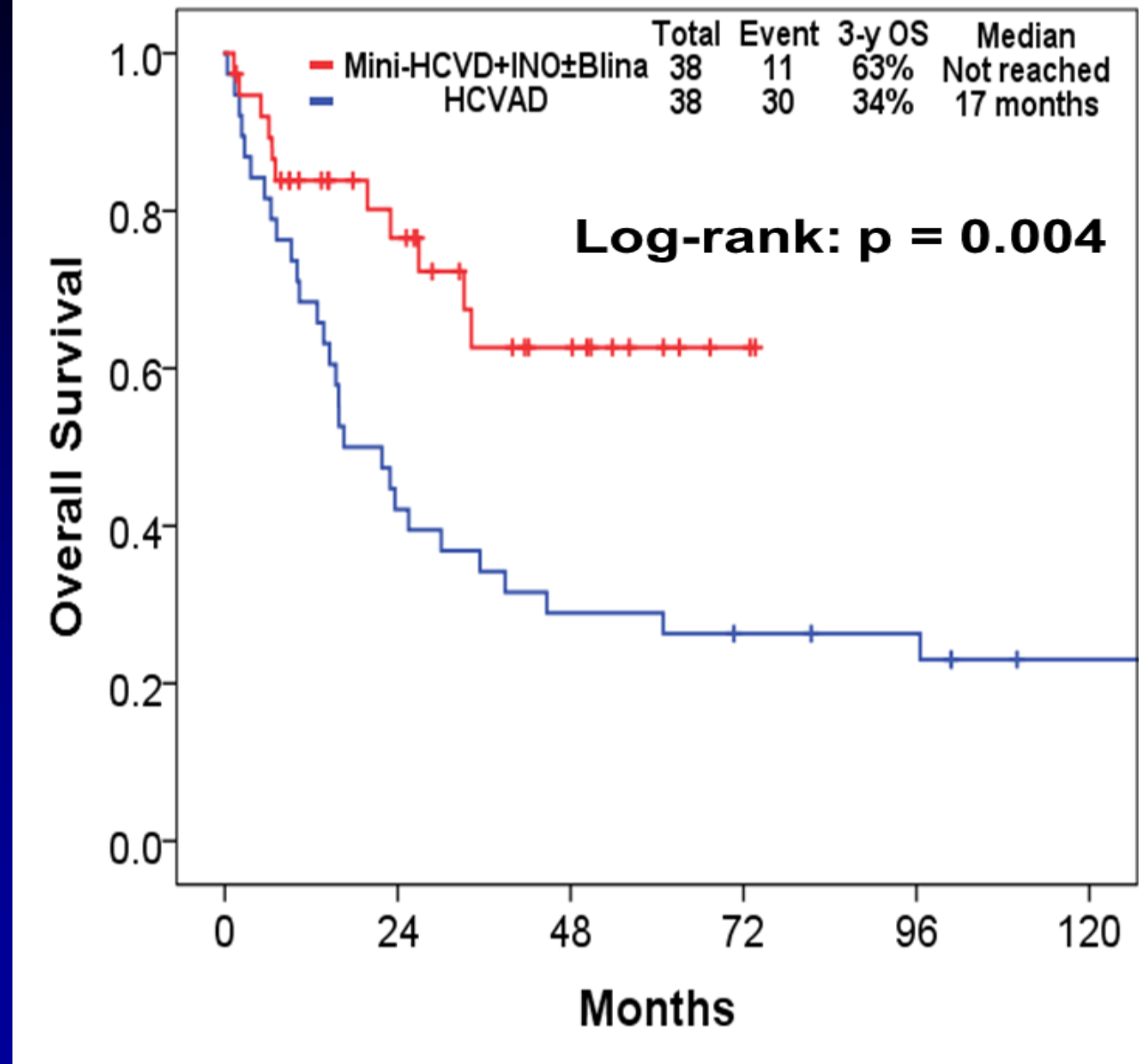
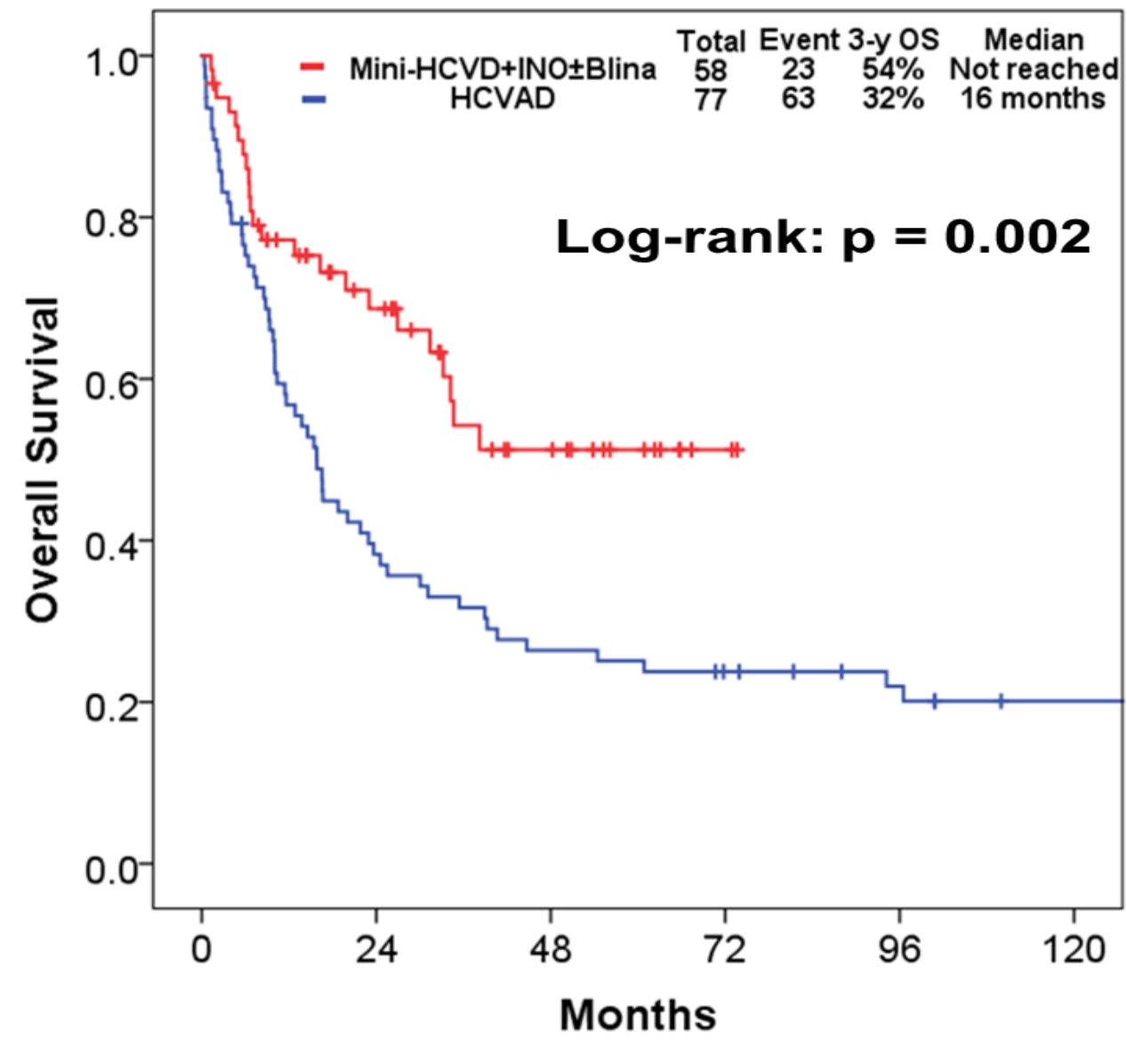
Mini-Hyper-CVD + Inotuzumab/Blinatumomab in Older ALL

- 79 pts; median age 68 yrs (60-87)
- ORR 72/73=99%; CR 65/73 =89%; MRD-NEG 73/78 = 94%
- 9 MDS/AML (12%)—7/9 had *TP53*-mutated ALL (all 70+ yrs)
- 28 deaths in CR (38%); 7 from sepsis
- 10 relapses (14%)
- VOD 6/75=8%



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

Pre-matched Matched



Frontline Blina and Inotuzumab Combinations in Newly Dx Older ALL

	Agent	N	Median Age (yrs, range)	% CR	% MRD negativity	% OS (x-yr)
Mini-HCVD-Inotuzumab-blinatumomab	Blinatumomab and Inotuzumab	79	68 (60-87)	89	94	55 (3-yr)
SWOG-1318	Blinatumomab	31	73 (66-86)	66	92	37 (3-yr)
EWALL-INO	Inotuzumab	115	69 (55-84)	88	73	78 (1-yr)
GMALL Bold	Blinatumomab	34	65 (56-76)	76	69	89 (1-yr)
INITIAL-1	Inotuzumab	45	65 (56-80)	100	74	77 (2-yr)

T-ALL – A separate Disease and Dilemma

- **What works -- ALL chemoRx + lots of MTX, HD araC, asparaginase**
- **No active Abs yet (like in pre B-ALL)**
- **New effective Rxs -- Venetoclax, decitabine, Novel T CARTs**
- **Precursor T-ALL – Adverse; genomic-epigenetic more like AML; AML regimens work: FAI, DAC10-ven, GO**

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

Regimen 4 (N=15)

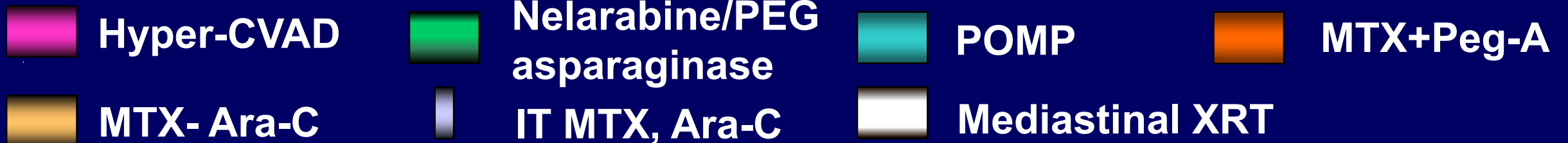
Venetoclax: initially two weeks per cycle
Then one week per subsequent cycles

Induction-Consolidation

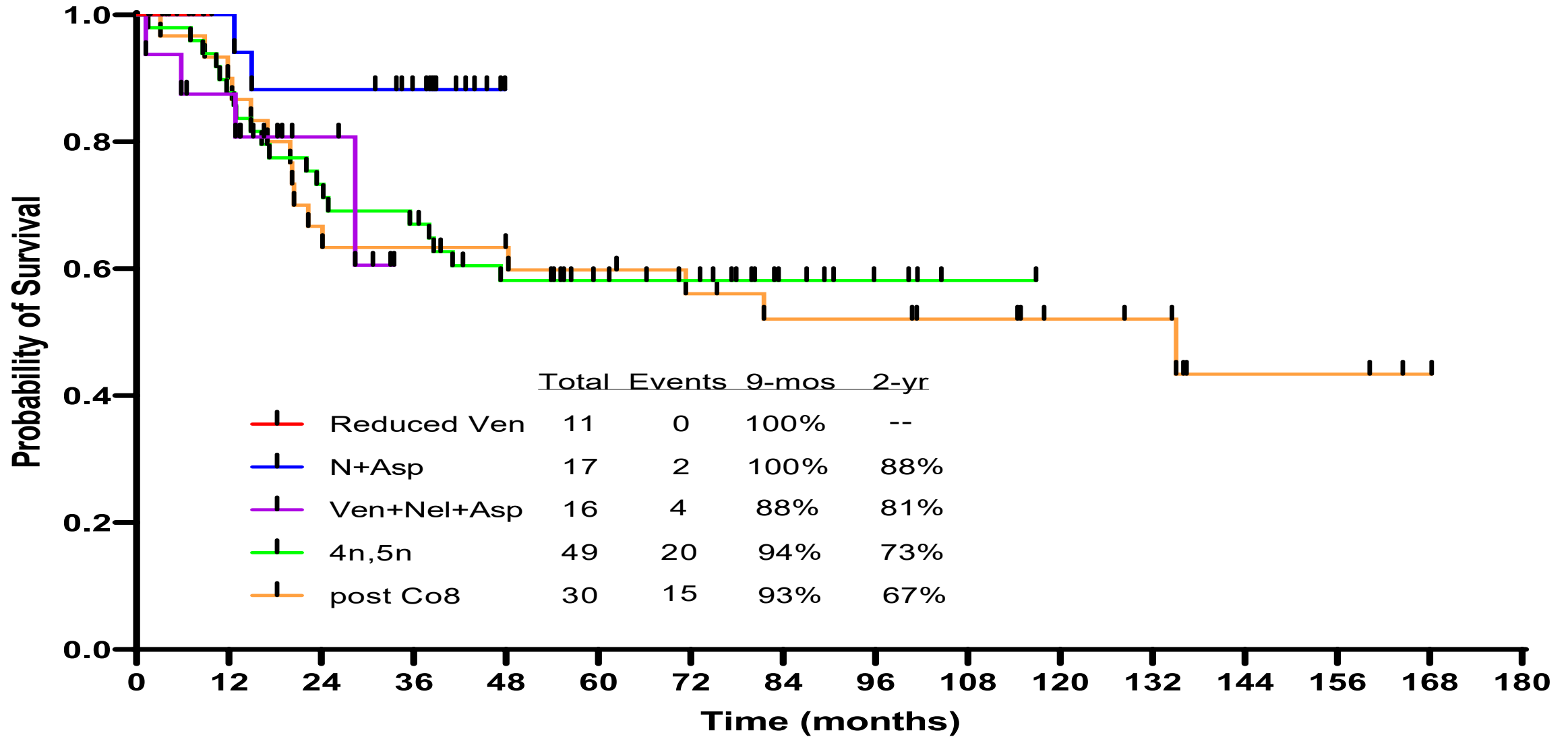


Nelarabine: 650 mg/m² IV daily for 5 days
PEG asparaginase: 1500 IU/m²; capped

Maintenance



T-ALL -- Overall Survival with Modified H-CVAD Regimens

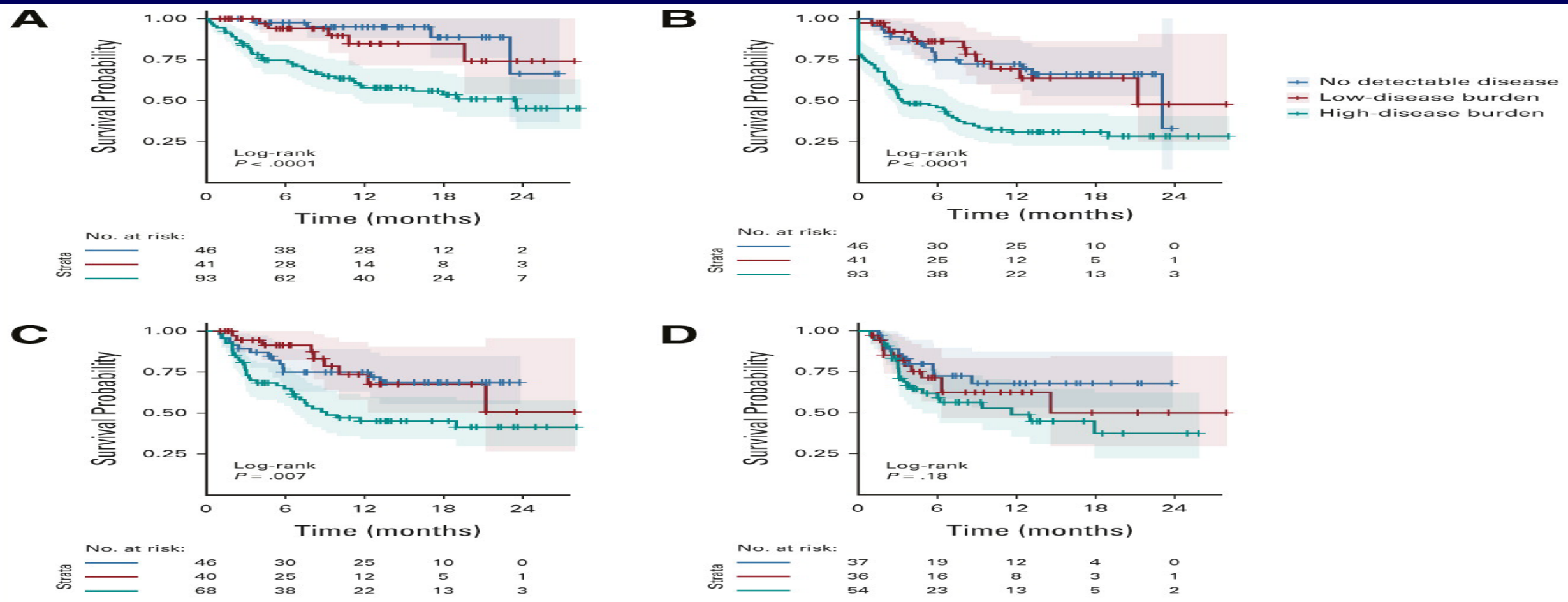


ALL – Role of Allogeneic SCT

- **ALL-MLL; t(11q23; ---)**
- **Precursor T ALL**
- **Complex CG ≥ 5 abn; near hypoploid+p53**
- **Ph-like if CRLF2 + JAK2 mutation**
- **Others: Ph-positive ALL PCR+ in CR3 mos; other Ph-like ALL; ALL CR1 MRD+---may be managed with blina-ino**

Real Word CAR Consortium and Disease Burden

- 200 pts (185 pts infused); median age 12 yrs (0-26 yrs); CR=85%
- High disease burden n=94 (47%); Low disease burden n=60 (30%); No detectable disease n=46 (23%)
- 12-mos EFS=50%, 12 mos OS=72%
- G3 CRS=21% (35% in HDB); G3 CNS=7% (9% in HDB)



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
- Monitor MRD by NGS (MRD in 1 million cells) to decide on Rx changes and Rx duration

Leukemia Questions?

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