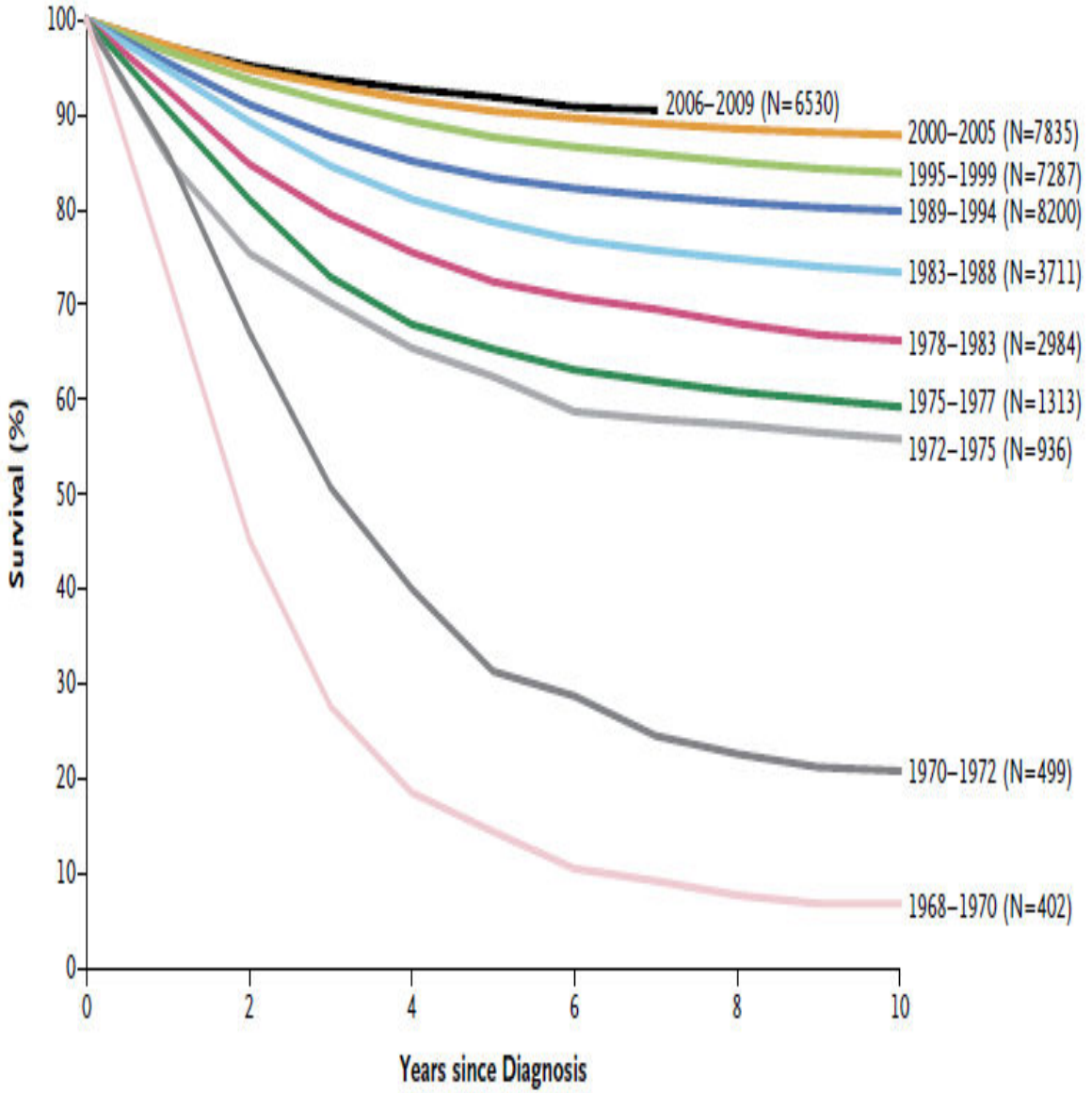
Current Treatment Strategies in Ph-Positive ALL

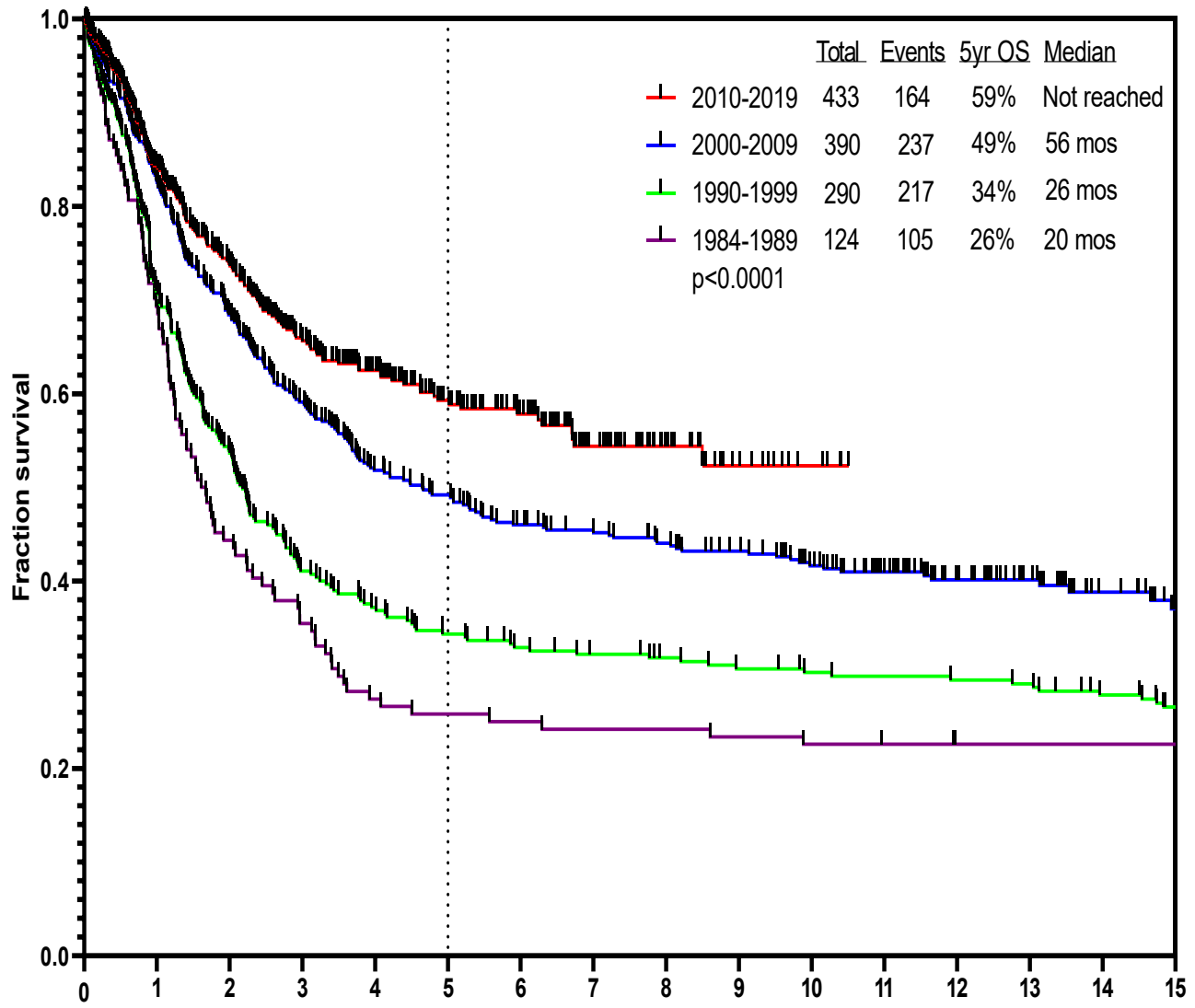
Hagop Kantarjian, M.D.

Emory Meeting
Sea Island; July 2026

Survival in Pediatric and Adult ALL with Classical Intensive ChemoRx Regimens



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

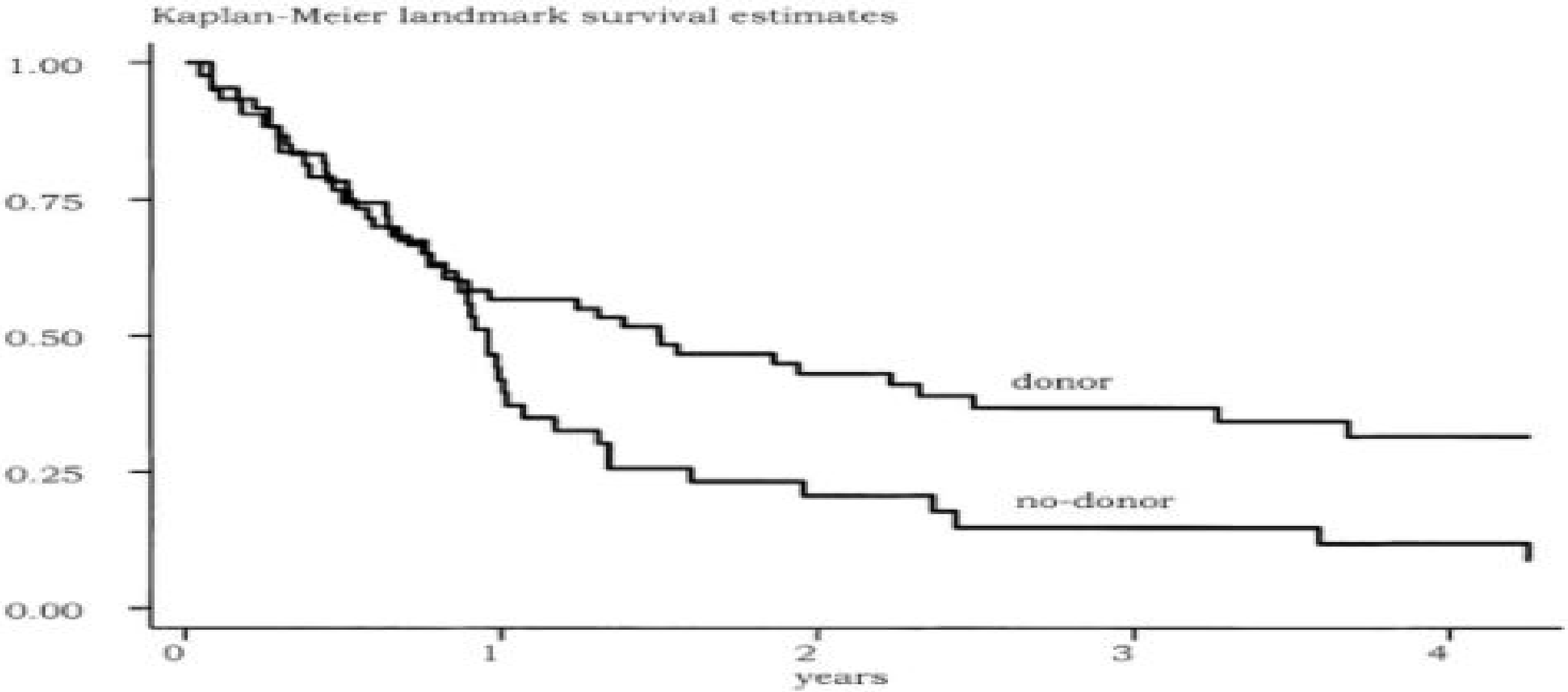


Kantarjian. Cancer 128: 240-259 ; 2022

What Should We Incorporate?

- Ph-positive ALL -- Ponatinib, blinatumomab. Novel BCR::ABL1 TKIs (asciminib; olverembatinib)
- Pre-B ALL -- Antibodies targeting CD19 (blinatumomab), CD22 (inotuzumab), and CD20 antibodies (rituximab, CD20 BiTEs)
- CARTs consolidation instead of allo SCT??
- MRD tracking by NGS clonoseq for IgHV– (analyzes >1 million cells) to decide on changes in Rx, and duration of Rx
- Goal maybe 5 years from now: Dose-dense mini-CVD-inotuzumab-blinatumomab +/-CARTs regimen – 7 months of Rx

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

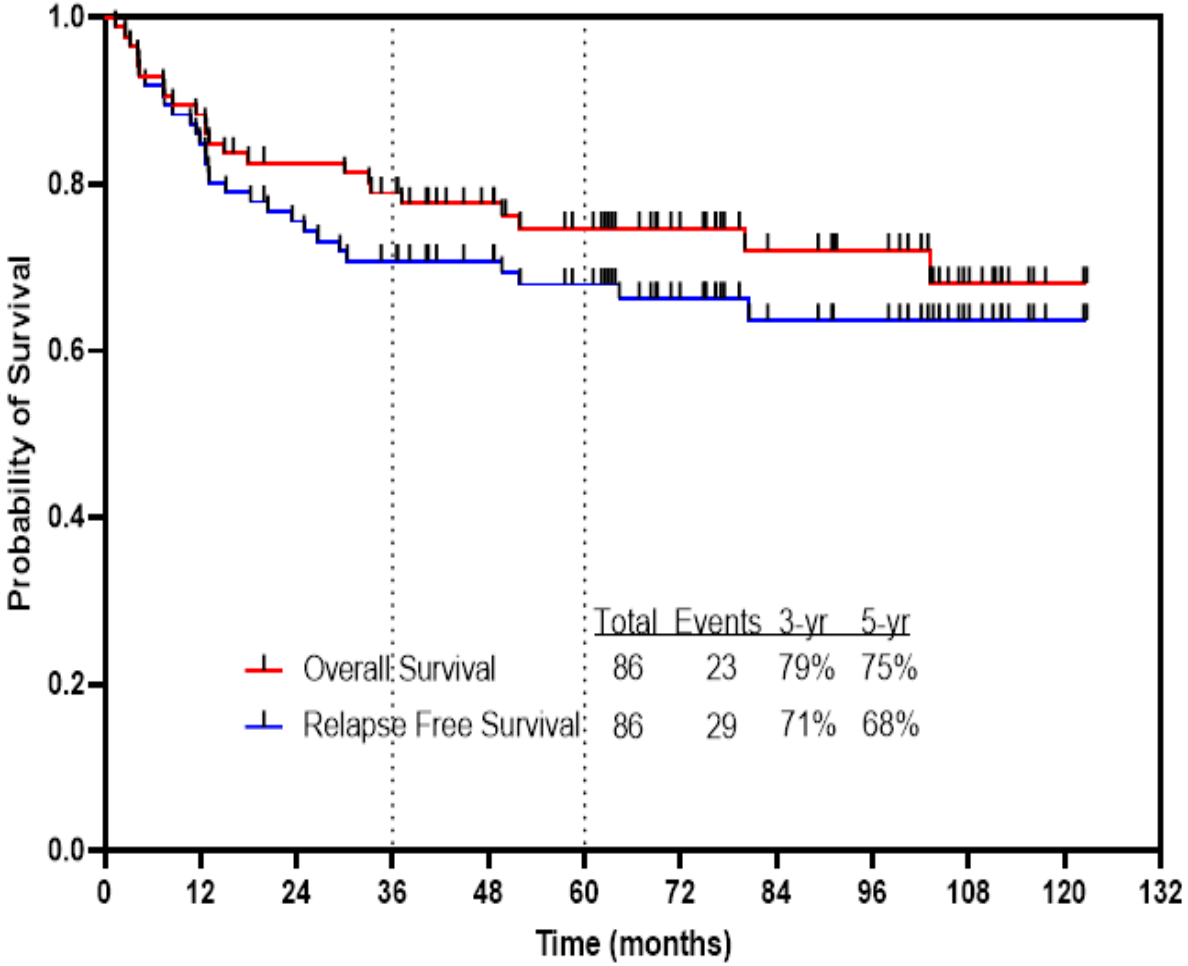
Evolution of Ph-Positive ALL Research and Rx at MDACC (1992-2024)

- 1992 -- Hyper-CVAD; 8 IT; allo SCT when possible
- 2000 -- Hyper-CVAD + imatinib; 8 IT; allo SCT in CR
- 2006 – Hyper-CVAD + dasatinib; 8 IT; allo SCT in CR if no CMR by 3+ mos
- 2010 – Hyper-CVAD + ponatinib; 12 IT; allo SCT less and only if no MMR by 3+ mos
- 2017+ – Ponatinib dose-response adjusted + blinatumomab; 12-15 IT; allo SCT rare

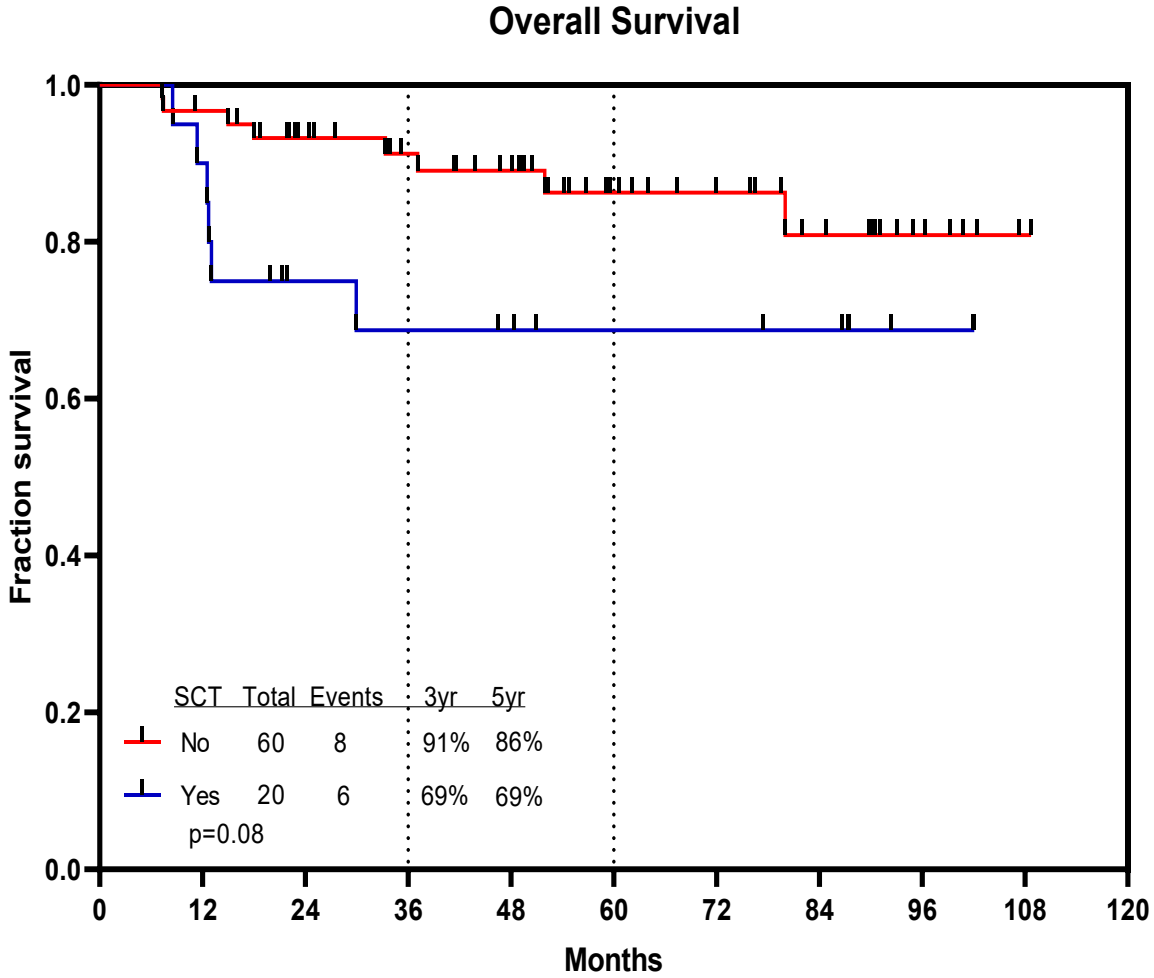
HyperCVAD + Ponatinib in Ph-positive ALL

- 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

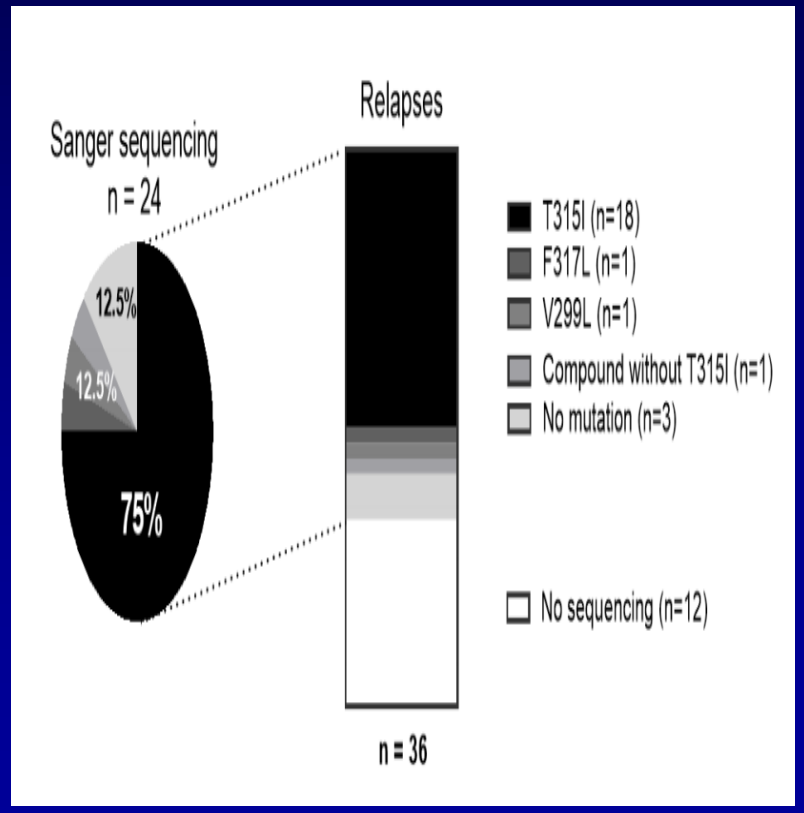


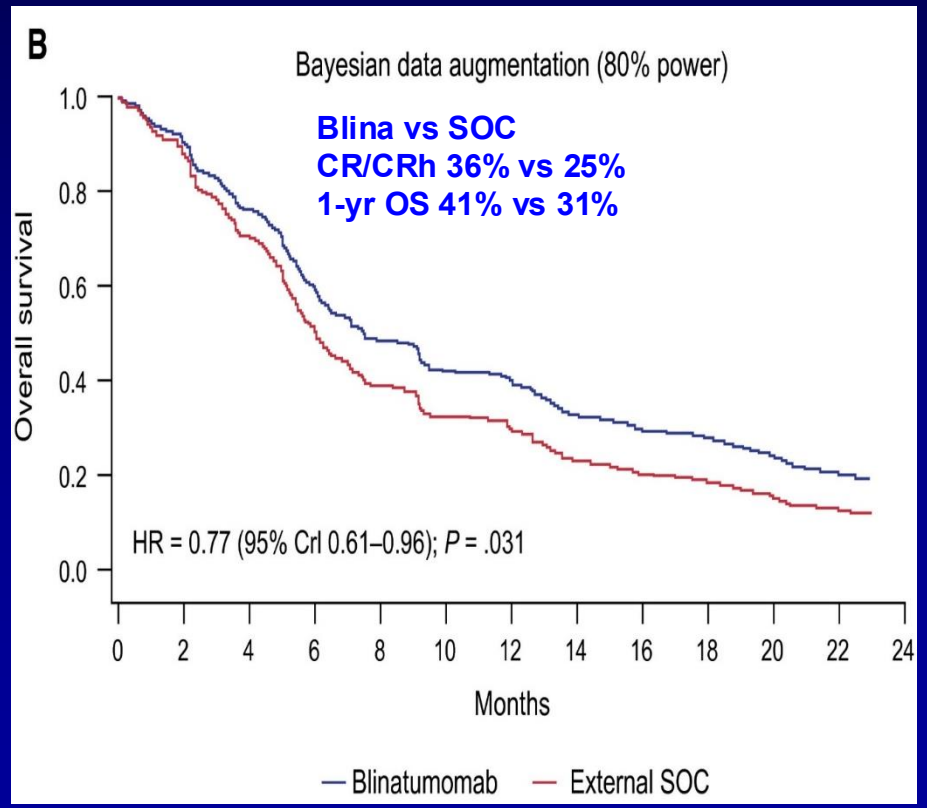
6-month Landmark

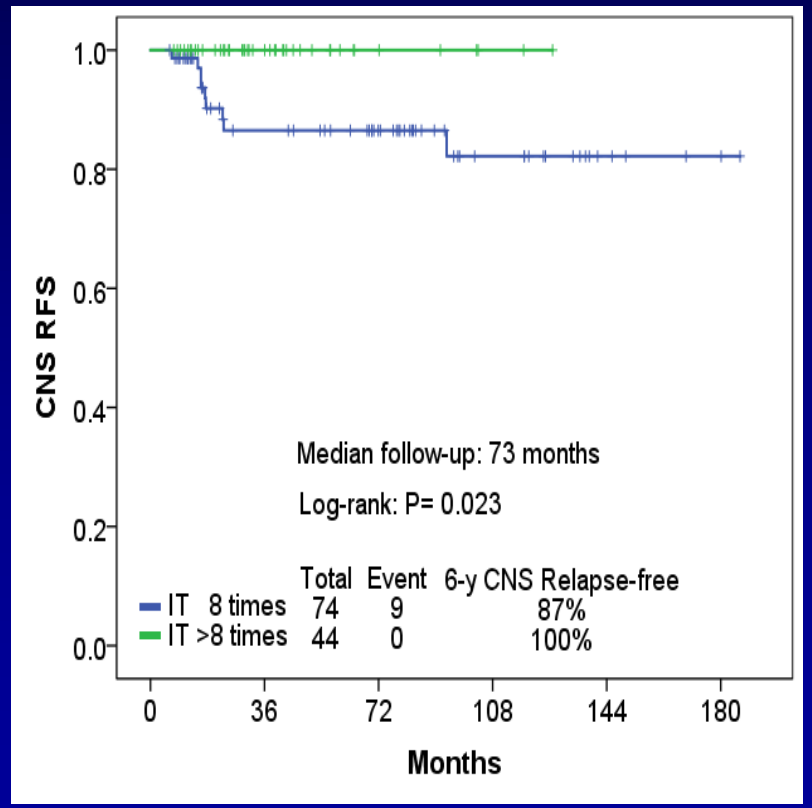


Ph-Positive ALL – Rationale for Changes

- 75% of relapses with T315I mutation = ponatinib
- Blinatumomab better than intensive chemoRx = blinatumomab replaces chemoRx and reduces need for allo SCT
- More CNS relapses with longer survival, and after elimination of HD araC = increase ITs from 8 to 12, and now to 15





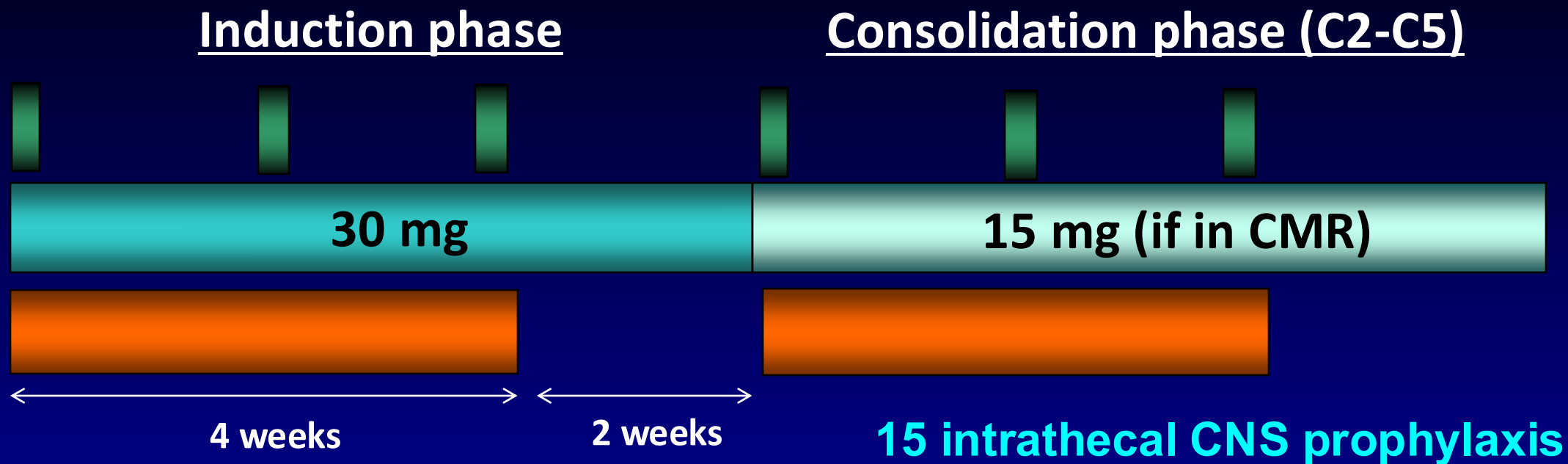


Rousselot. Blood 2016;128(6):774-82

Rambaldi. Cancer. 126: 304-310; 2019

Paul. Am J Hematol: 98:E11-E14;2023

Ponatinib + Blinatumomab in Ph+ ALL: Regimen



Jabbour. Lancet Haematology 10:e24-e34;2023 Kantarjian JCO: 4246-4251 ; 2024

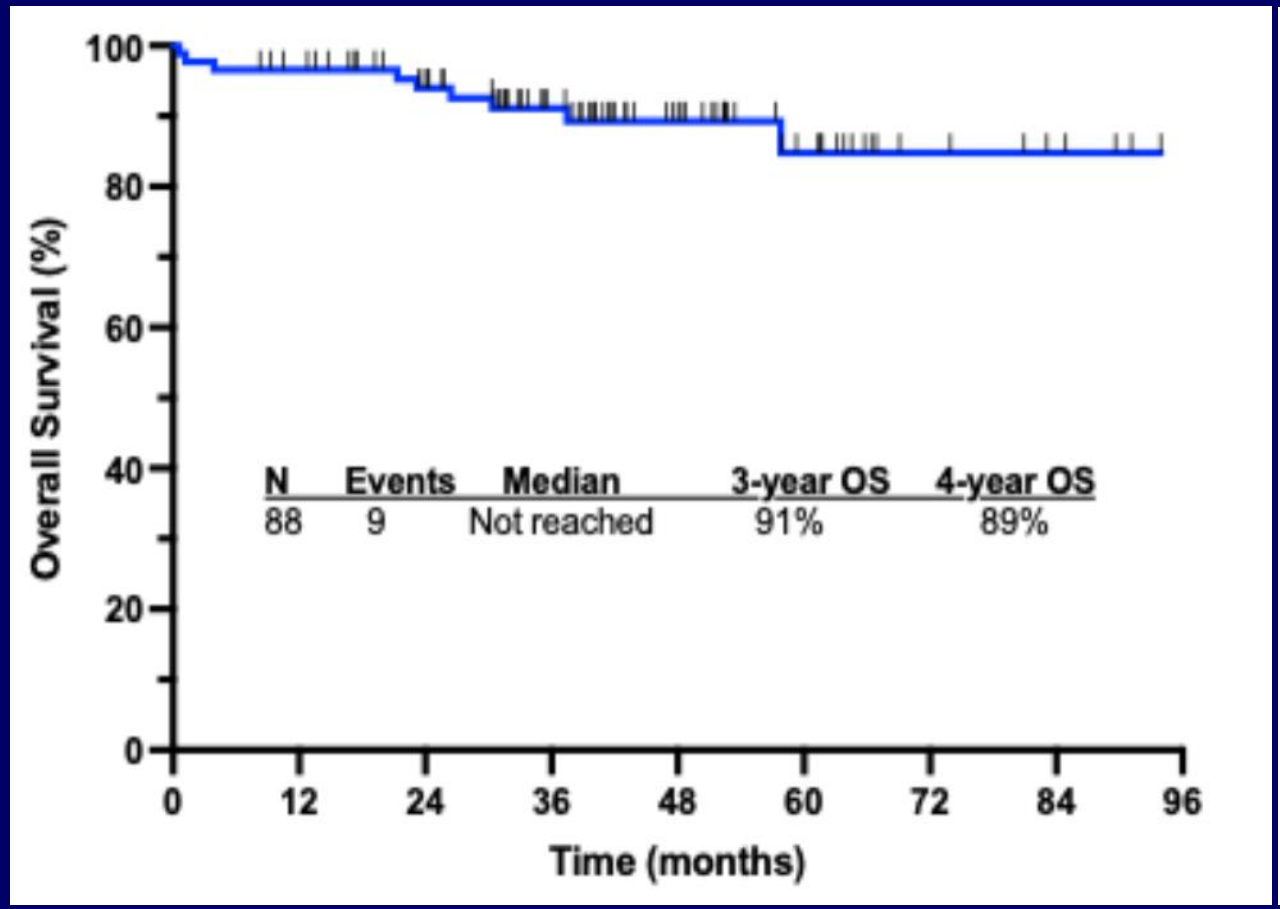
Ponatinib + Blinatumomab in Newly Dx Ph+ ALL

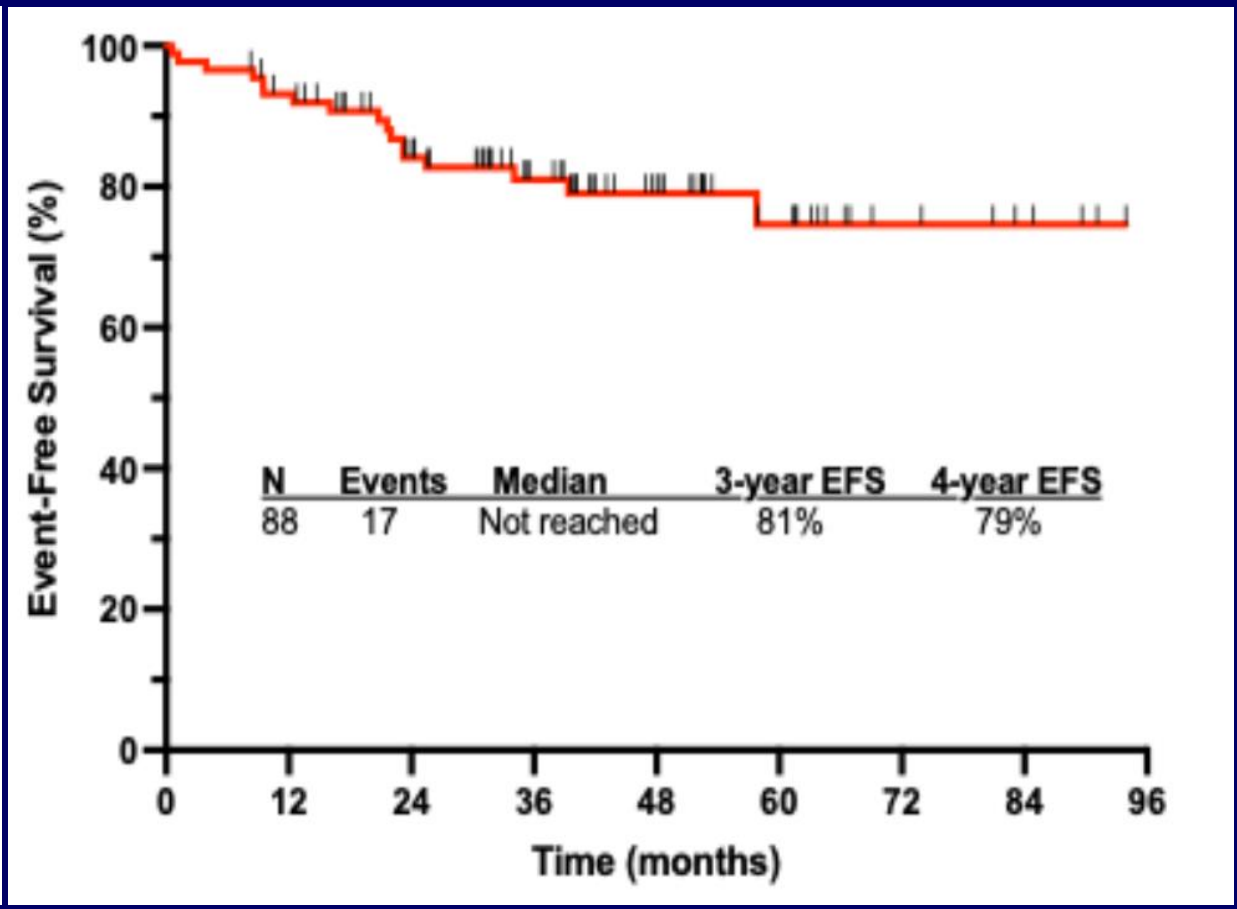
- 88 pts ; median age 50 yrs (18-83). P190 78%; *IKZF*+ 52%
- PONA 30 mg/D till DMR then 15 mg/D; BLINA with induction, 5 courses. Later, add MTX-araC x 2+blina in C3 and C4 if WBC > 70
- CR/CRi 96%; BCR::ABL1-neg 83%; NGS-MRD neg 95%
- Allo in CR 2 (2%); Relapse 12 (CNS only 5, BM only 6)
- 4-yr OS 89%, EFS 79%

Nasr. JCO 44 (suppl 16): abstr 4246; 2026

Kantarjian JCO. 2024;42(36):4246-4251

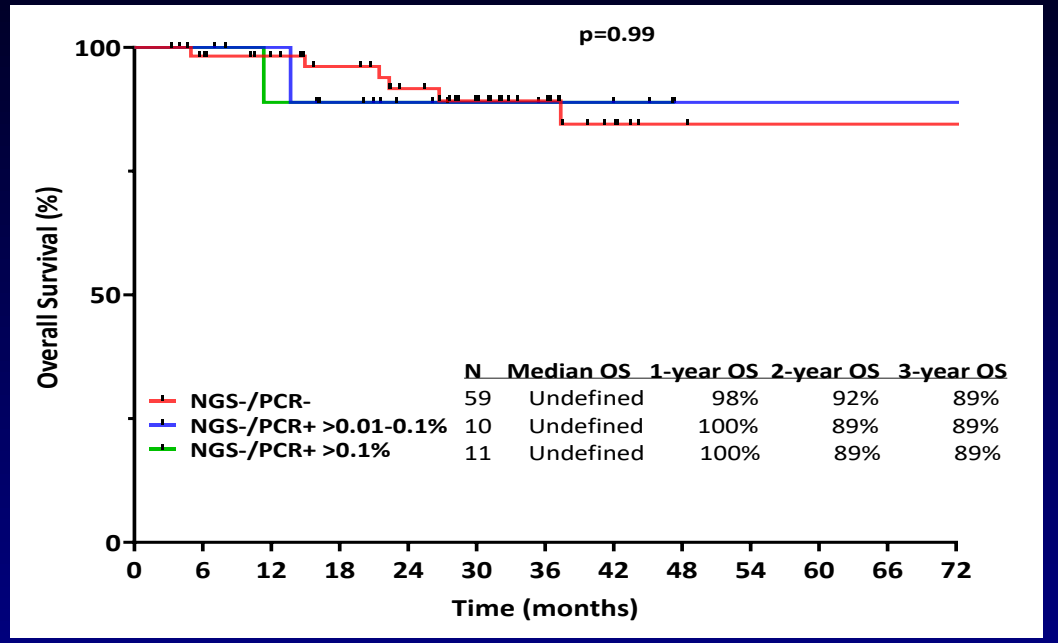
Jabbour. Lancet Haematol. 2023;10(1):e24-e34

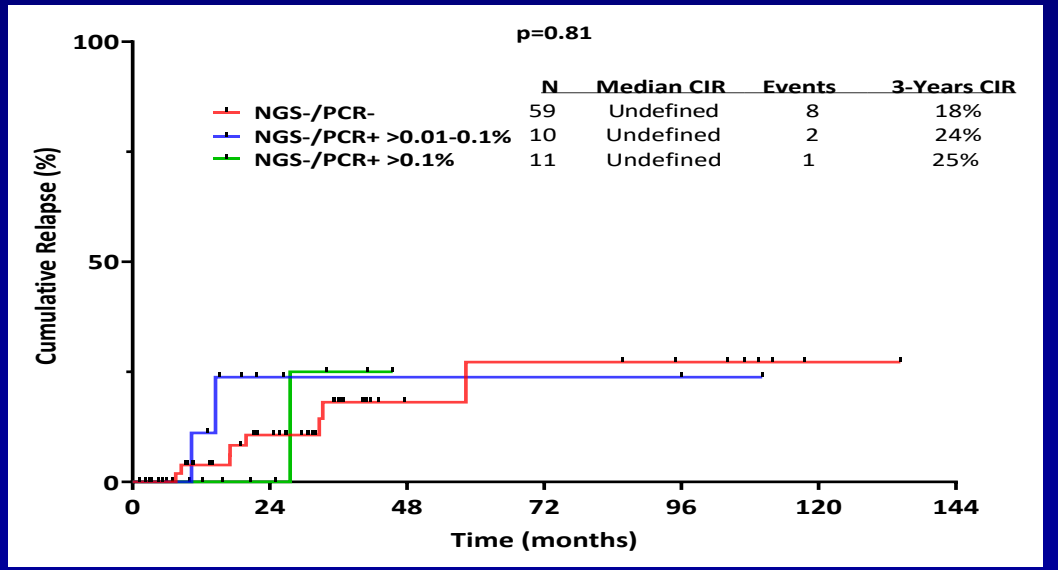




PCR for *BCR::ABL1* vs NGS for IG/TR in Ph+ ALL

- 187 pts who were NGS MRD neg and PCR for *BCR::ABL1* pos or neg
- Discordance (NGS-/PCR+) 23%
  - PCR >0.1% in ~50% of discordance cases
  - Similar rates in p190 and p210
  - High WBC = ↓ discordance
  - FISH+ in granulocytes = ↑ discordance
- No impact of discordance or level of *BCR::ABL1* PCR on relapse or OS
- 2 NGS-/PCR+ pts discontinued TKI → PCR >10% (but still NGS-)



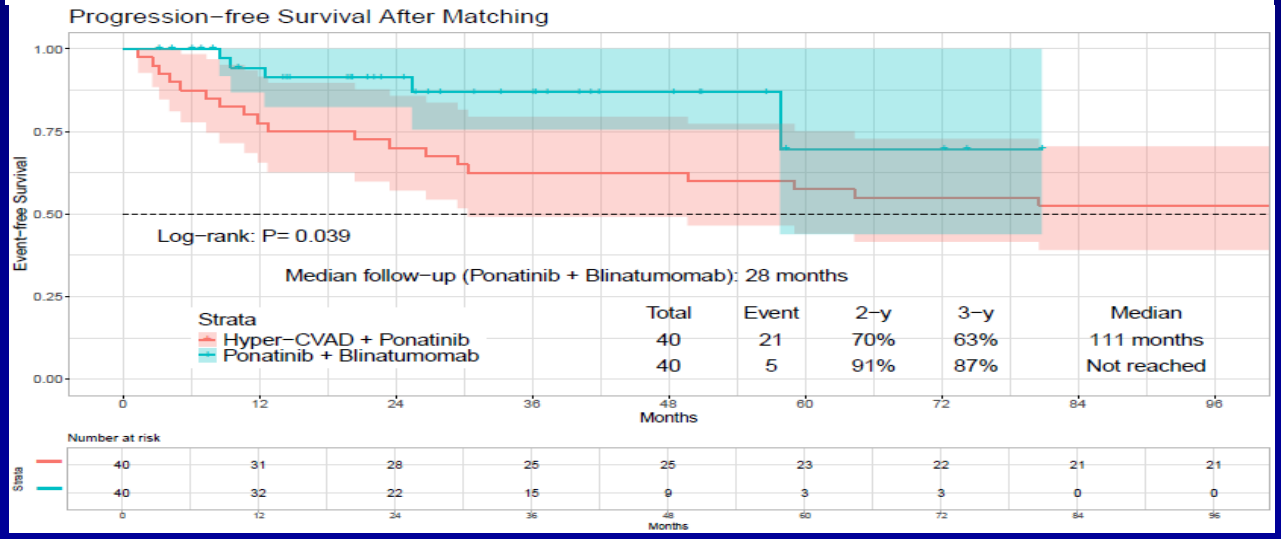


Maroun. Blood 146: abst 551; 2025

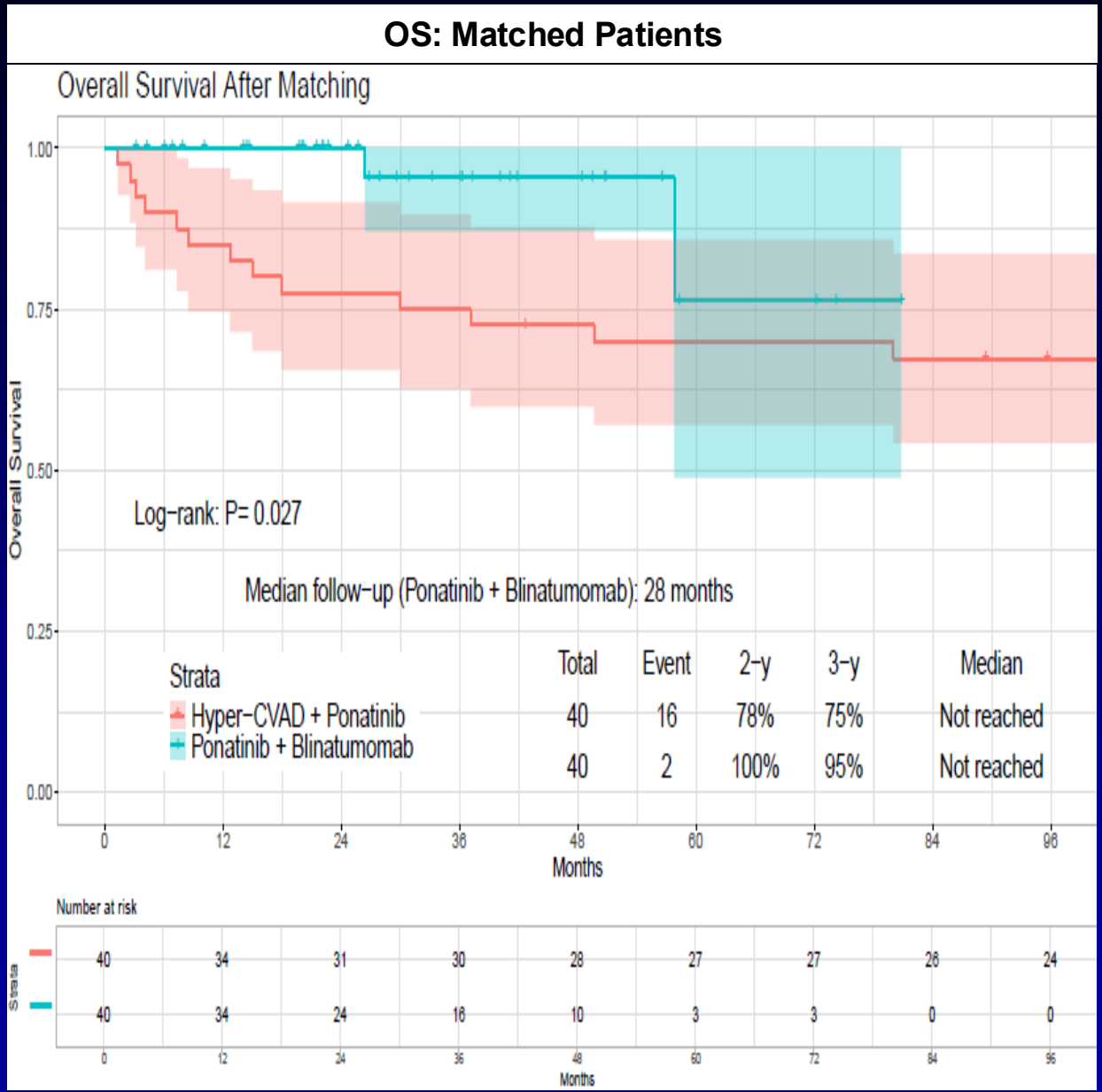
Blinatumomab-Ponatinib vs HCVAD-Ponatinib Propensity Matched Analysis

Parameter	Blina-Ponat (N=40)	HCVAD-Ponat (N=40)	P value
ORR	100%	100%	--
C1 CMR	56%	38%	0.115
Overall CMR	80%	90%	0.348
NGS-MRD Neg	53/55 (96%)	--	--
Relapse Rate	10%	28%	0.083
Death in CR	3%	25%	0.007
Allo-SCT	1 (3%)	8 (20%)	0.029

PFS: Matched Patients

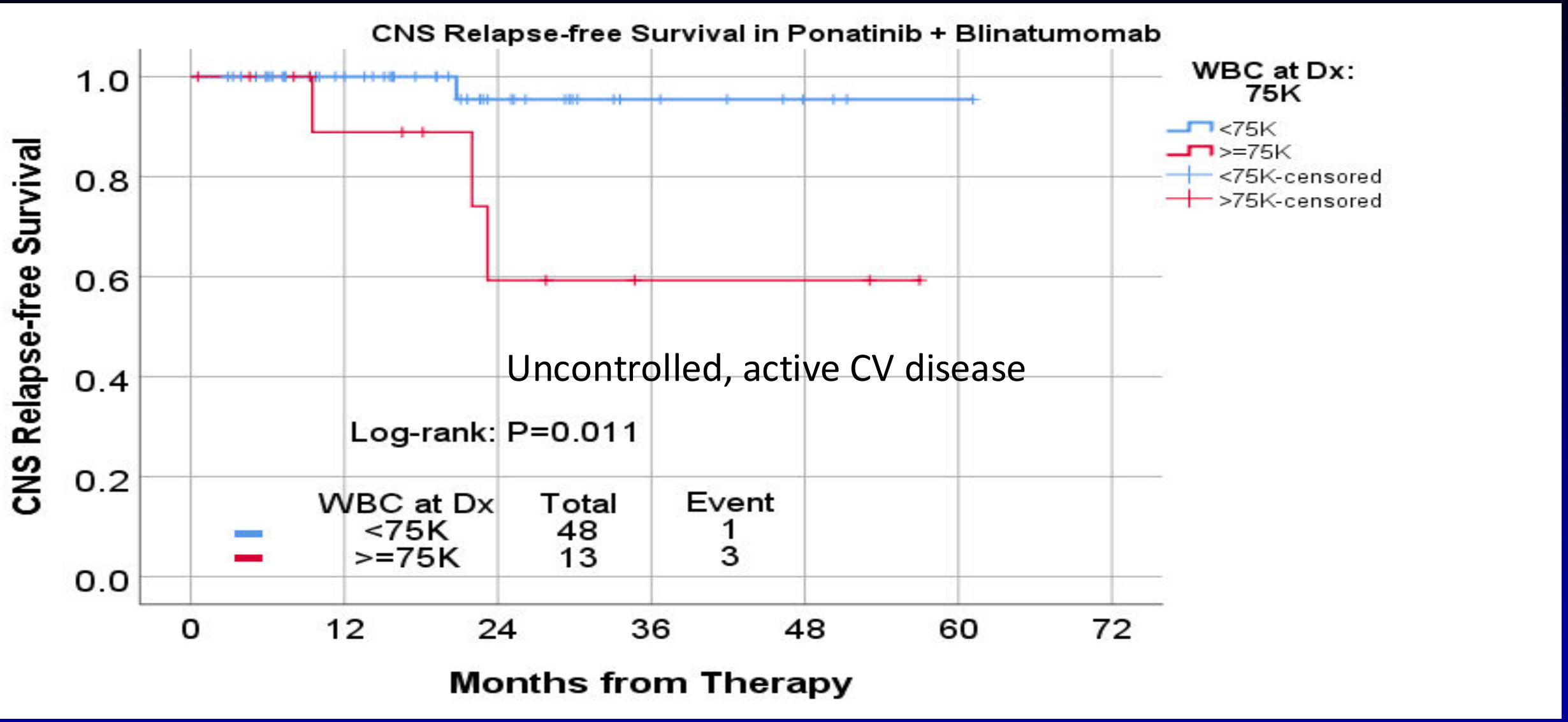


OS: Matched Patients



Sasaki. Blood 146: abst 1578; 2025

Ponatinib + Blinatumomab in Ph+ ALL. CNS Relapses

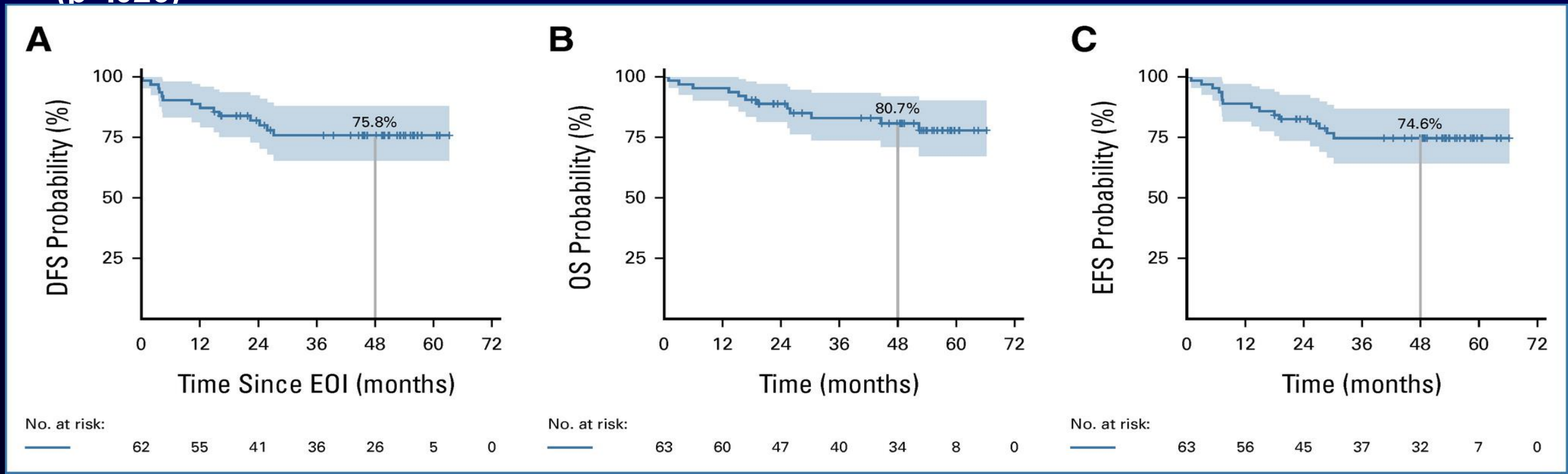


- By MVA, high WBC only predictive for CNS relapses (OR=10.3; p=0.047)

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

Foa. JCO online, December 23; 2023

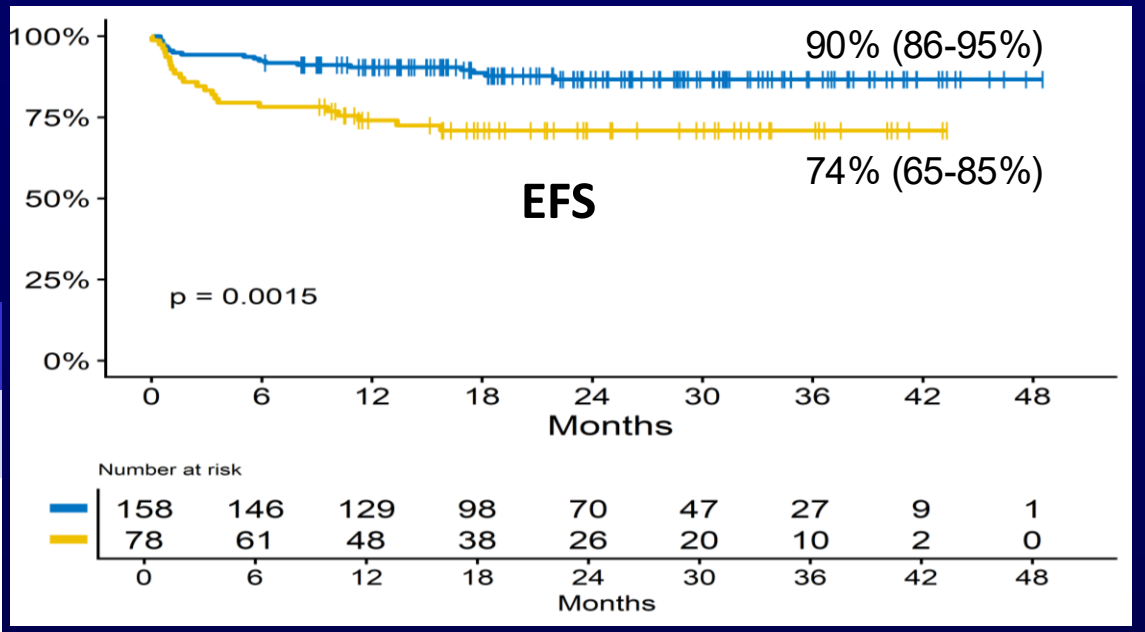
- 63 pts Rx; median age 54 yrs (24-82). Median FU 53 mos
- Molecular response (CMR/PNQ) 27/29 non-SCT = 93%
- 30/63 (48%) allo SCT– 6 allo SCT in CR2
- 9 relapses: 4 hematologic, 4 CNS, 1 nodal. 6 deaths
- 4-yr OS 81%, DFS 76%, EFS 75%
- Outcome better if MR (EOI): DFS 100% vs 69% (p=.016); worse if IKZF1+: DFS 82% vs 45% (p=.026)

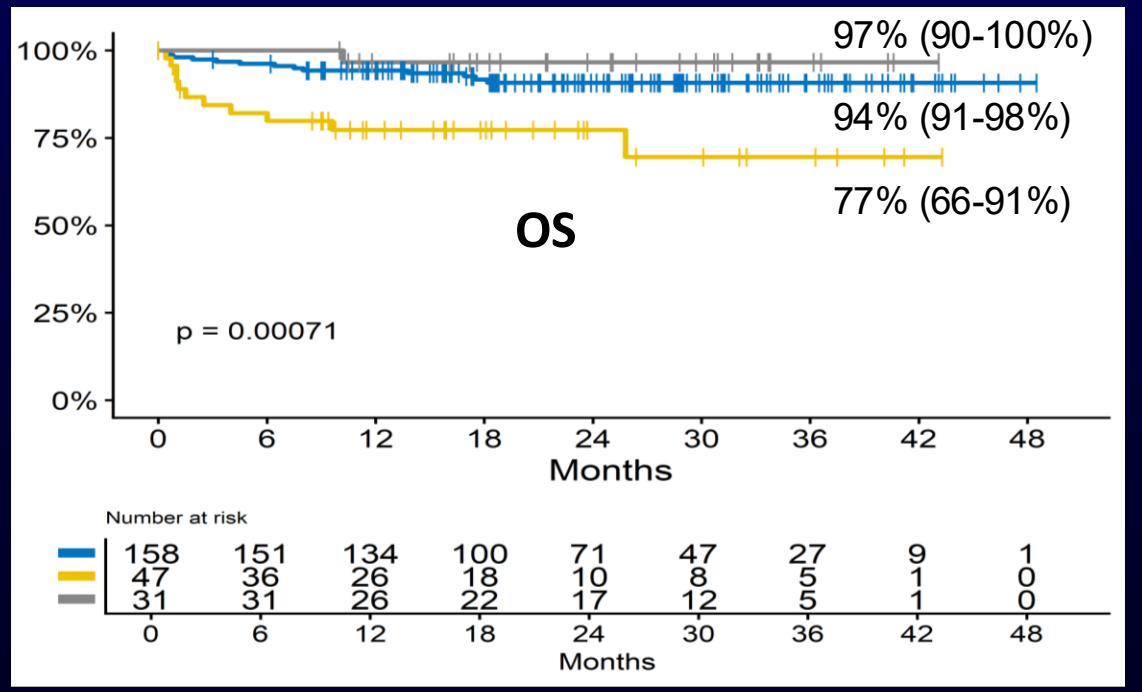


Blina-Ponatinib vs Imatinib-ChemoRx in ND Ph+ ALL (GIMEMA)

- 236 pts randomized 2:1 to Blina-PONA (n=158) or ChemoRx-IMA (n=78). Induction 70 D (2 courses) or 3 ChemoRx . Median age 57 yrs. Median FU 23.4 mos

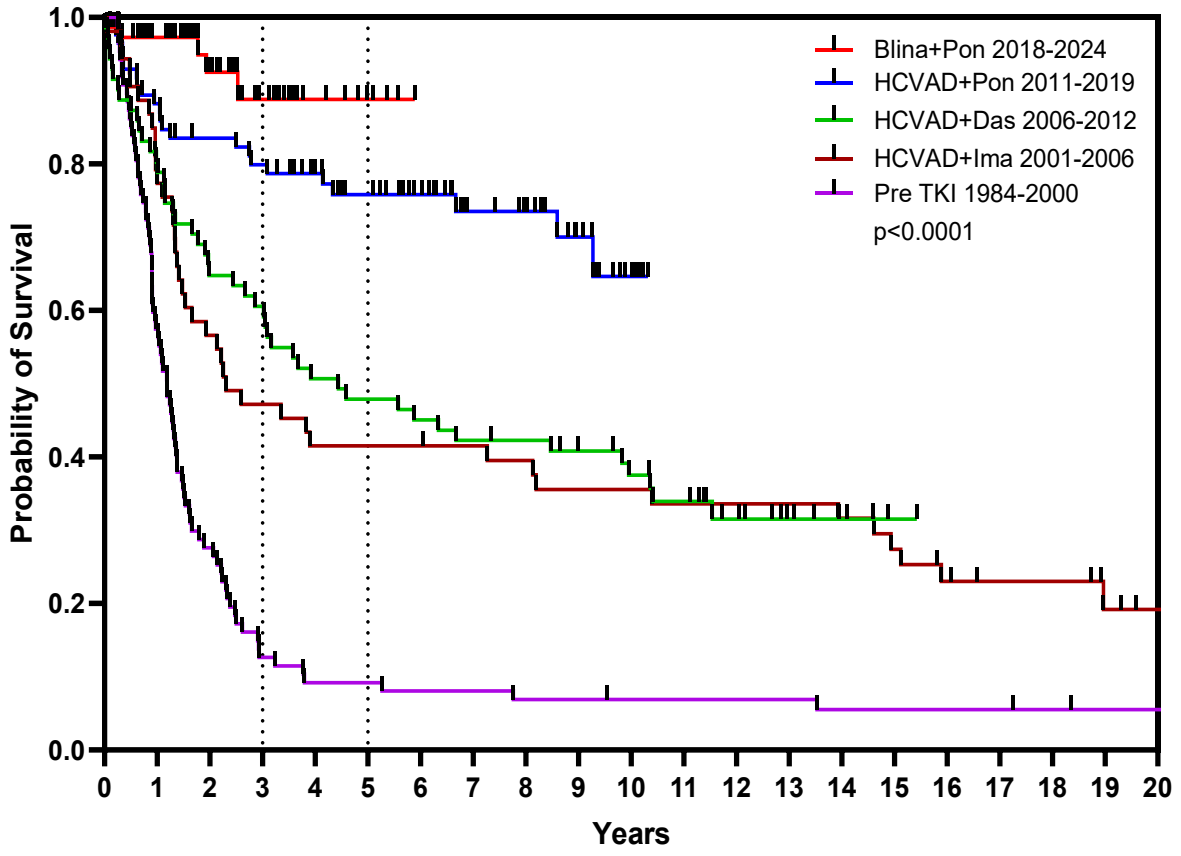
Parameter	Blina-PON; %	ChemoRx-IM; %	
CHR (D70)	94	79	P=0.001
Induction death	4	10	
MRD-neg (D133)	71	59	P=0.009
MRD-neg post cross-over	NA	62 (18/29)	
Relapses	6 (n=9; 1 CNS)	8 (n=5; 0 CNS)	
N (%) cross-over	NA	29 (37)	
ASCT	19	19	
18-mo EFS	90	77	P=0.01





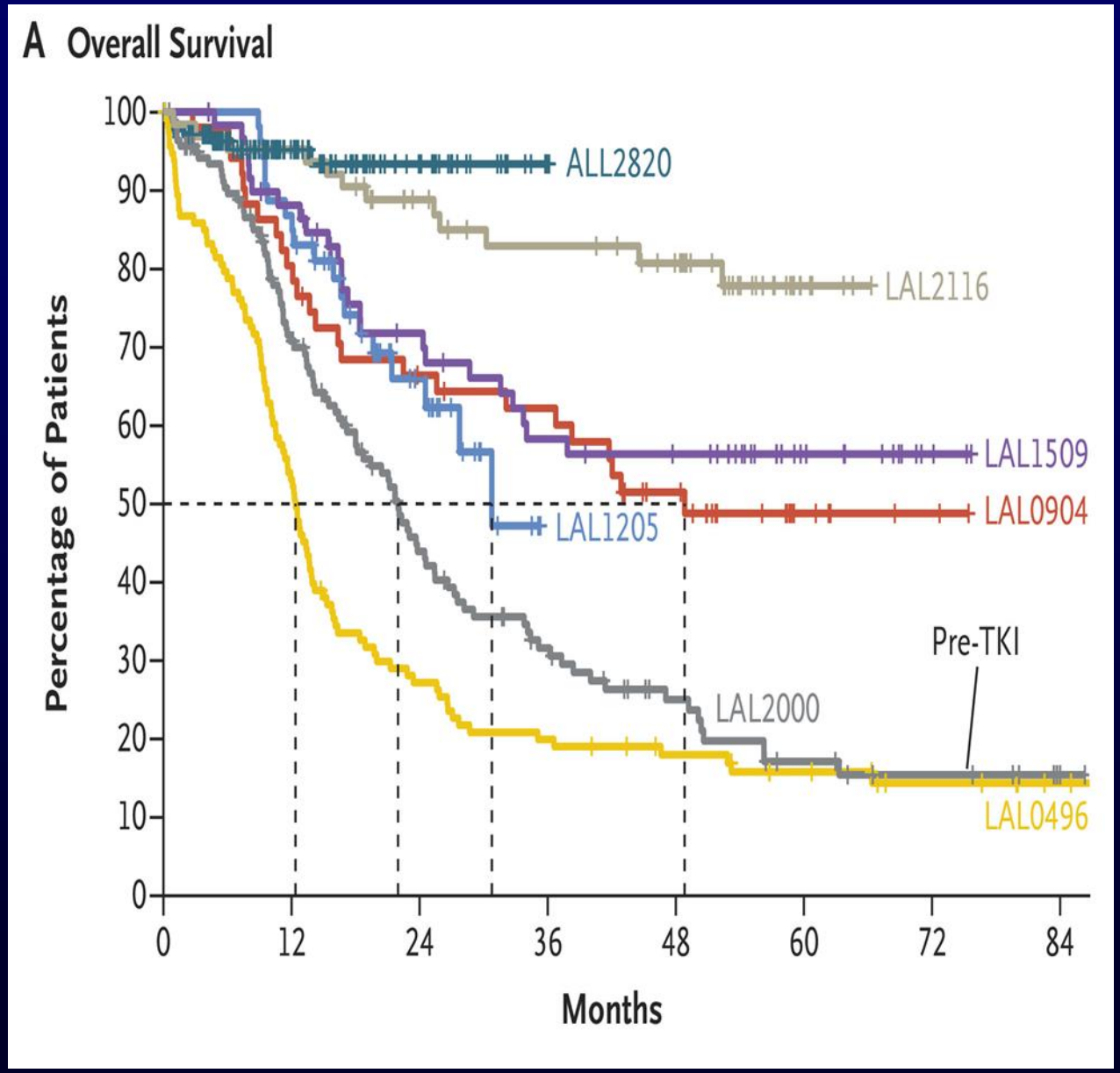
Chiaretti. Blood 146: abst 439; 2025

Ph+ALL. Survival Since 2000



	Total	Events	3yr OS	5yr OS	Median
Blina+Pon 2018-2024	76	5	89%	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

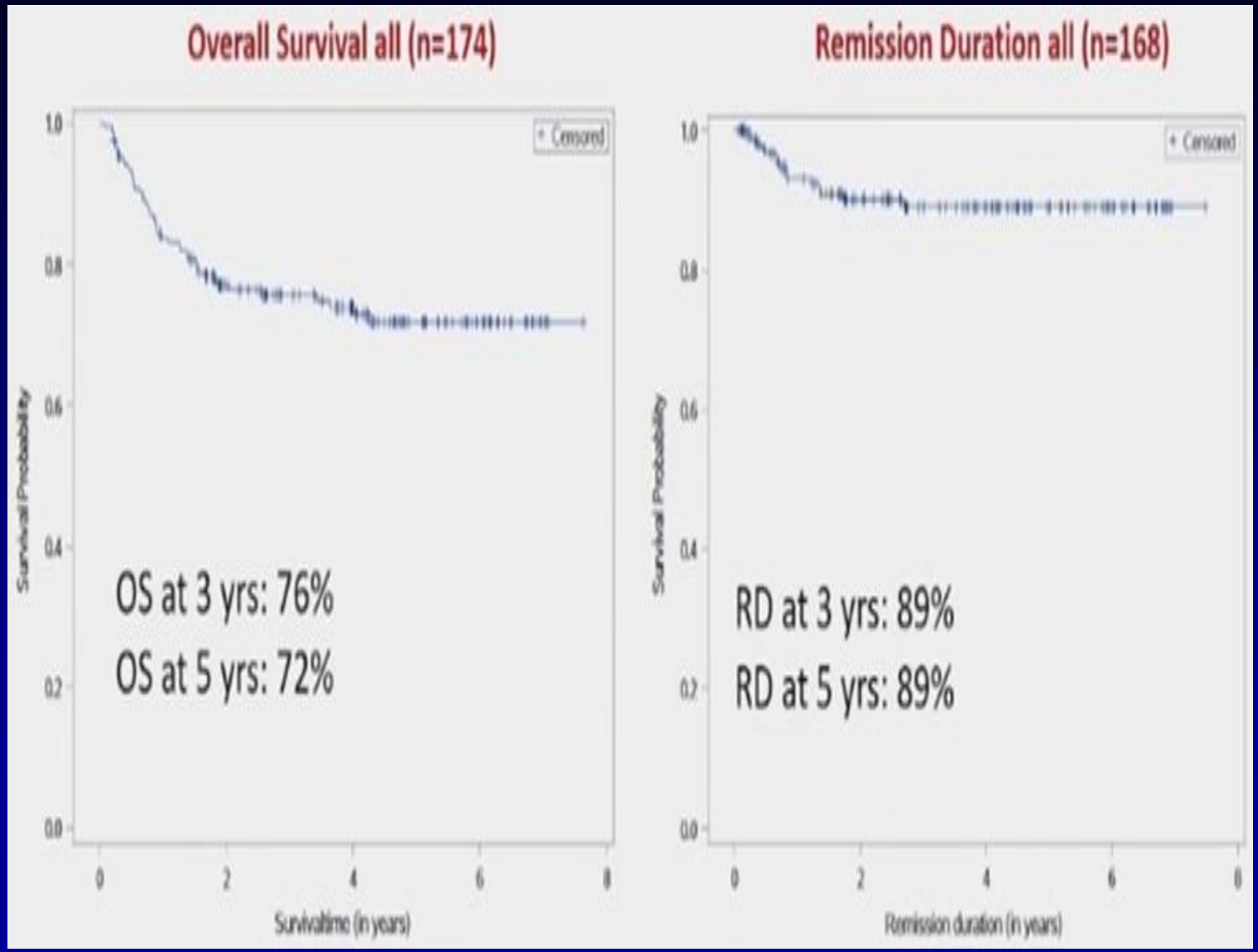
p<0.0001



Foa. NEJM 391:1941-1952; 2025

Ph-Positive ALL on GMALL

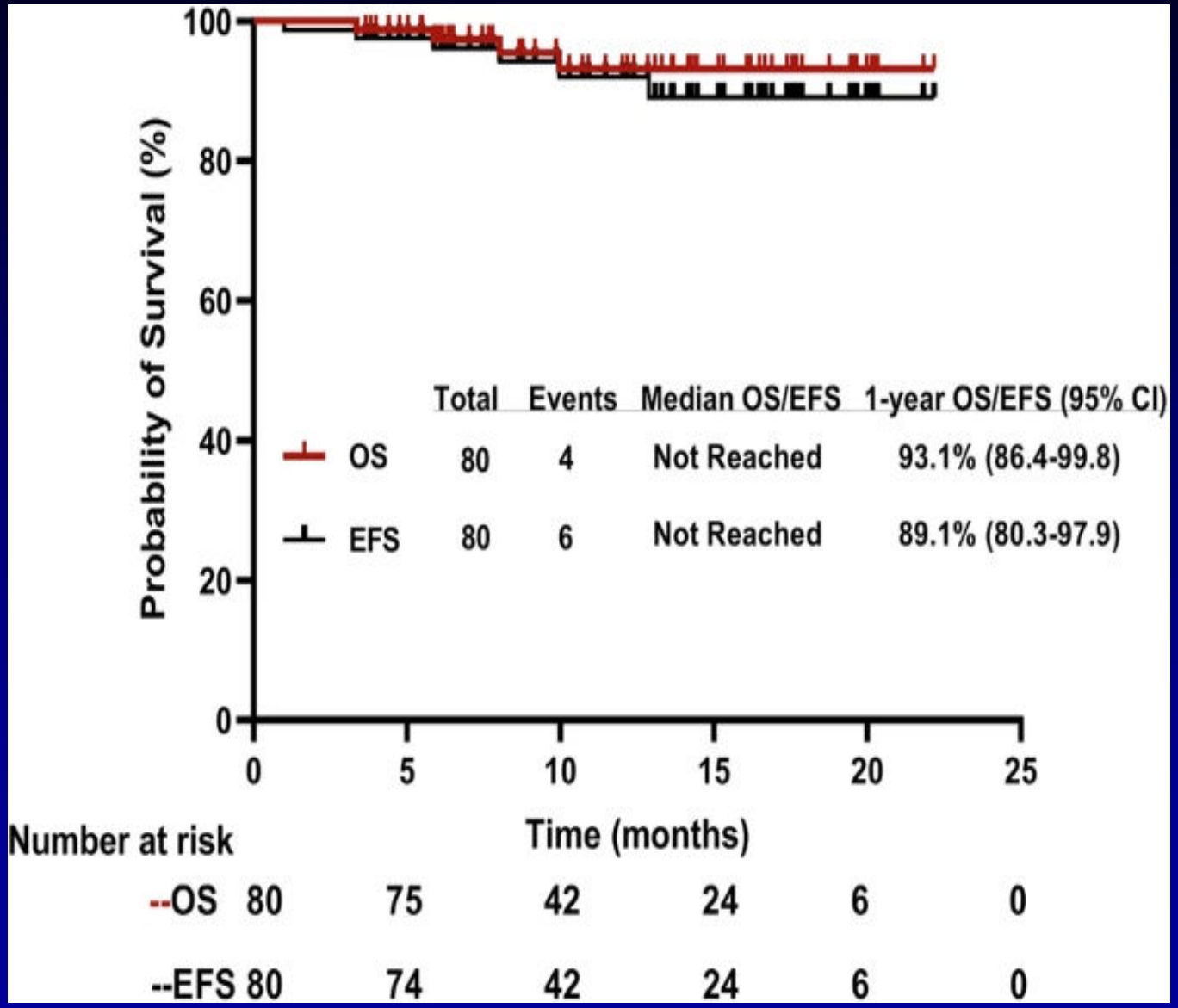
- 174 pts; median age 42 yrs (18-55)
- Imatinib 600mg/D + LI ChemoRx; then allo HSCT 159/174 (91%; 98% of CRs; median time to SCT 4 mos)
- CR 85% post induction; CR 95% overall
- Molecular CR 9% post induction, 42% post C3
- 3-yr OS 76%; 3-yr OS post HSCT 81%; Rx mortality 16%



Pfeifer. Blood 144: abst 840; 2024

Olverembatinib, Venetoclax, Low-Dose ChemoRx in ND Ph-Positive ALL

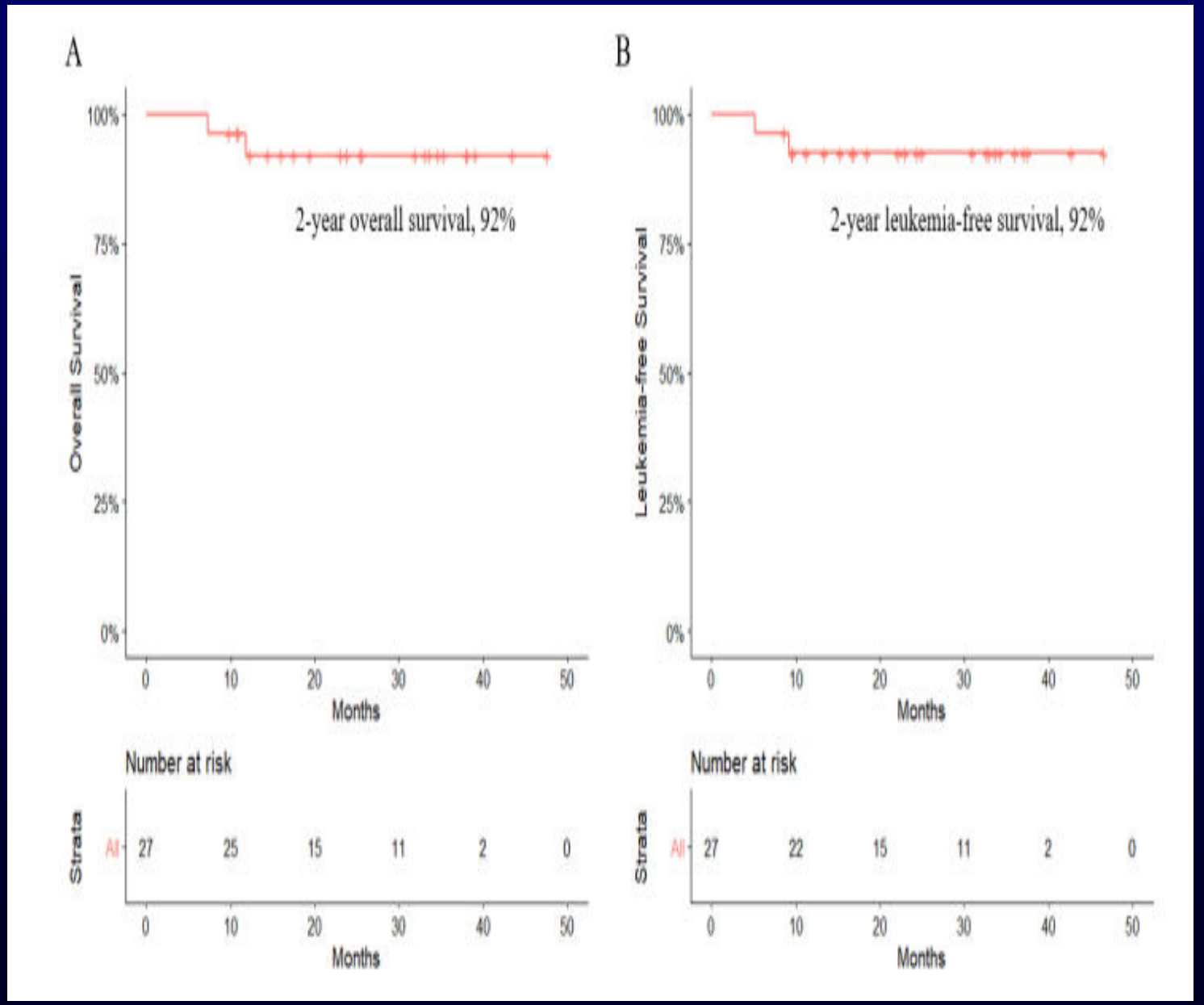
- 79 pts; median age 42 yrs (15-76); median FU 12 mos
- Rx OLVER 40mg QoD, VEN x 28 days, VCR-pred
- 3-mo CMR 62%
- 1-yr OS 93%, 1-yr EFS 89%



Gong. Leukemia 39: 1838-1847; 2025

Dasatinib + Sequential CD19 and CD22 CARTs in Ph+ ALL

- 28 pts; median age 48.5 yrs (18-69); Rx with dasatinib 100 mg/D, then sequential CD19 and CD22 CARTs; median FU 24 mos
- CMR 25% post induction; 85% post CD19(n=27) CART; 76% post CD22 CART (n=25)
- CD22 CART given for normal B-cell reappearance in 18, and PCR+ in 7
- 2-yr OS and LFS 92%
- 2 relapses/deaths; 21 in CMR, 4 PCR+



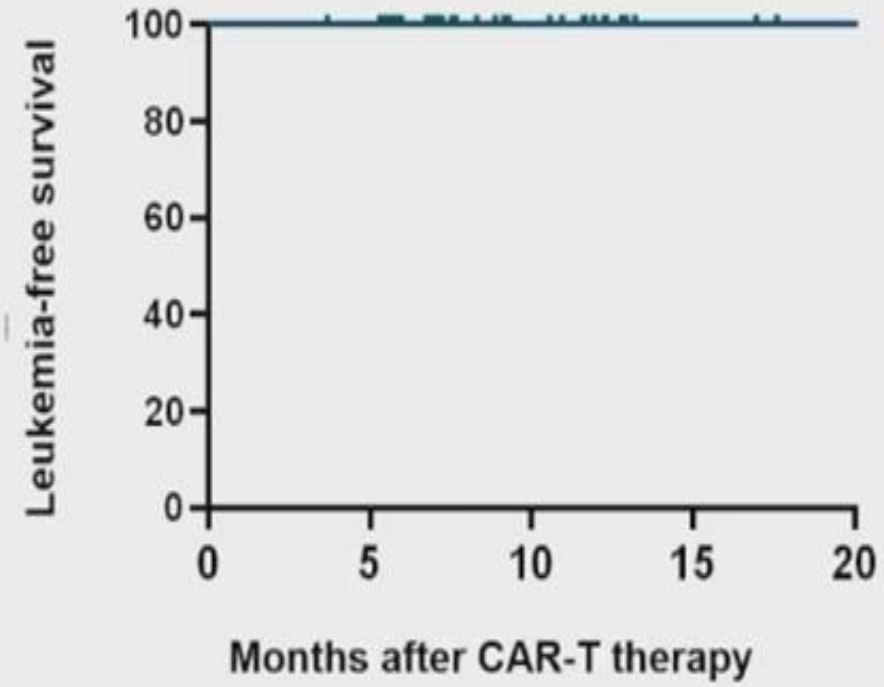
Zhang. JAMA Oncology. Online; April 17, 2025

CART Consolidation in Ph-Positive ALL

- Rx-- olverembatinib-vcr pred-VEN x 1-2; then CD19 CART in CR1; then olverembatinib
- 35 pts Ph+ ALL in CR— 8 PCR+; 4 NGS-MRD pos
- Post CART 35/35 NGS-MRD neg
- Median FU 11 mos. 1-yr OS 100%; 1-yr LFS 100%

Gu. Blood 146: abst 442; 2025

- After a median follow-up of 10.9 months, the 1-year estimate LFS rate was 100%



- No patients experienced bone marrow or extramedullary relapse
- Three patients underwent hematopoietic stem cell transplantation during CR1 by personal choice

CART for CNS Relapse (U-PENN)

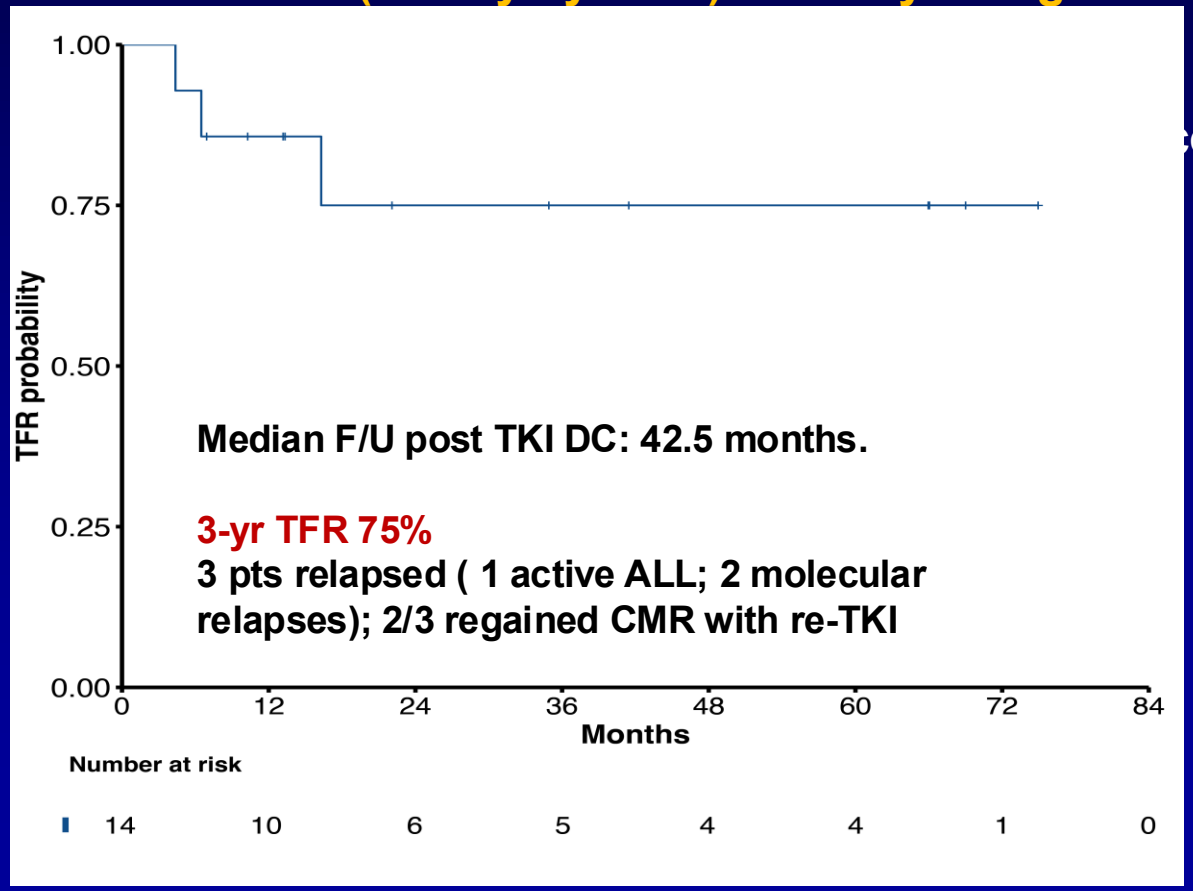
- 42 pts with CNS disease: 8 CNS 2, 2 by imaging; no CNS 3. Median age 8 yrs (1-26)
- CAR $5x10^6$/kg
- CNS CR 41/42=98%
- Median FU 12 mos. 2-yr EFS 90%
- 4-yr EFS 71%. 4-yr OS 93%

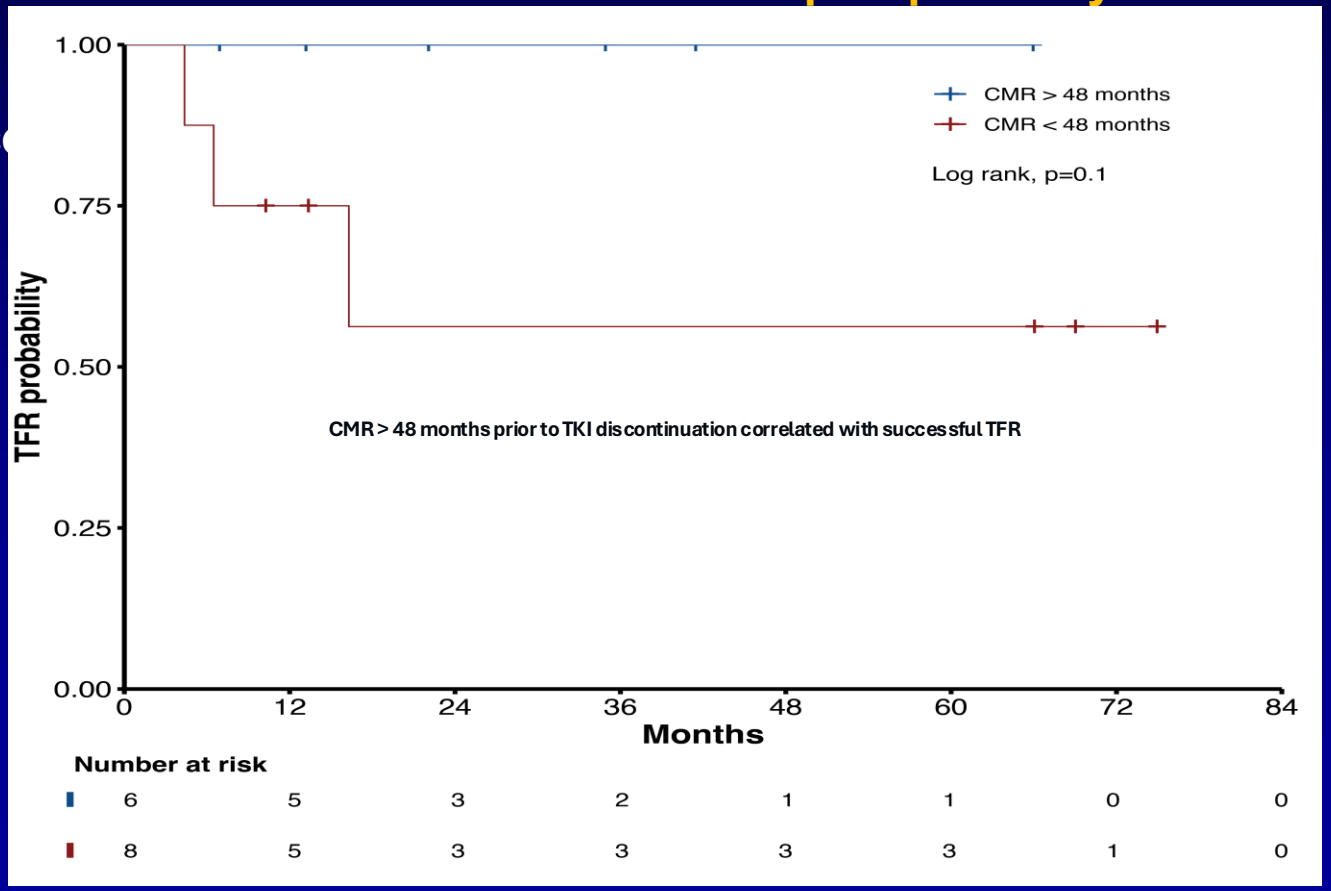
DiNofia. Blood 146: abst 25-8174; 2025

TKI DC/TFR in Ph+ ALL Without Allo HSCT

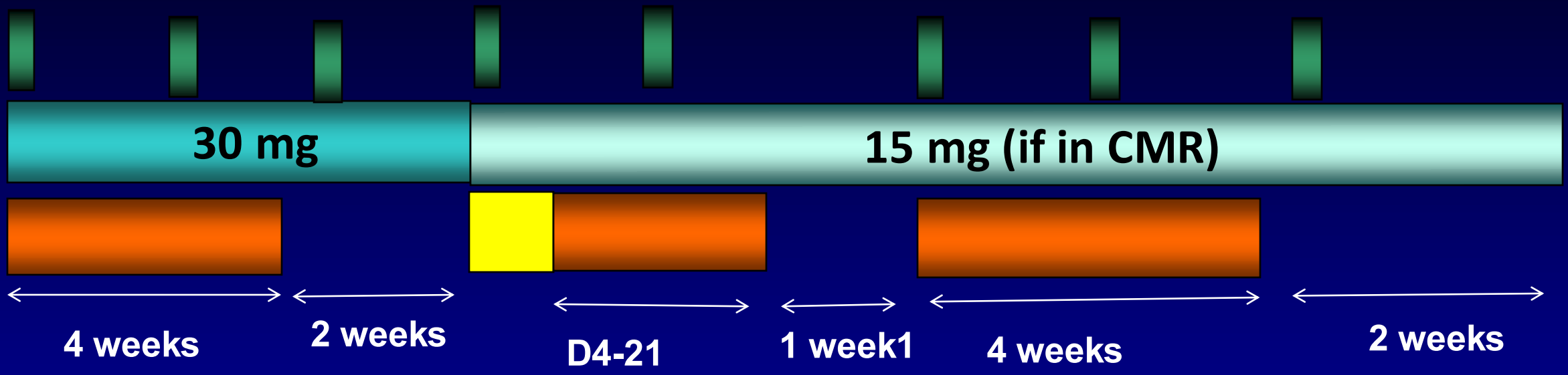
- 14/238 pts (6%); median age 61 yrs; Median time on TKI 60 mos (31-125); median time in CMR 46 mos (2.7-121). Median FU post DC TKI 51 mos
- Rx HCVAD + added TKI: Ima 2, dasa 6, pona 4, blina-pona 2
- Reason for TKI DC: pleural effusions 4, AOE/VOE 4, pulmonary hypertension 2, pancreatitis 1, cytopenia 1, other 2
- 11pts (79%) remained in TFR. None of 8 in CMR 4+yrs prior to TKI DC had relapse
- Plan --DMR (ideally by NGS) for 4-5 years good to consider TFR trial --- to be tested prospectively

Samra. Acta Haematol. 2021;144:285-292.
Kugler. Cancer. On-line, February 21, 2025





Ponatinib + Blinatumomab in Ph-Positive ALL. Regimen (WBC≥70K)



Maintenance phase

15 mg for 5 years

Ponatinib 30 mg

Ponatinib 15 mg

HDAC/MTX x1-2

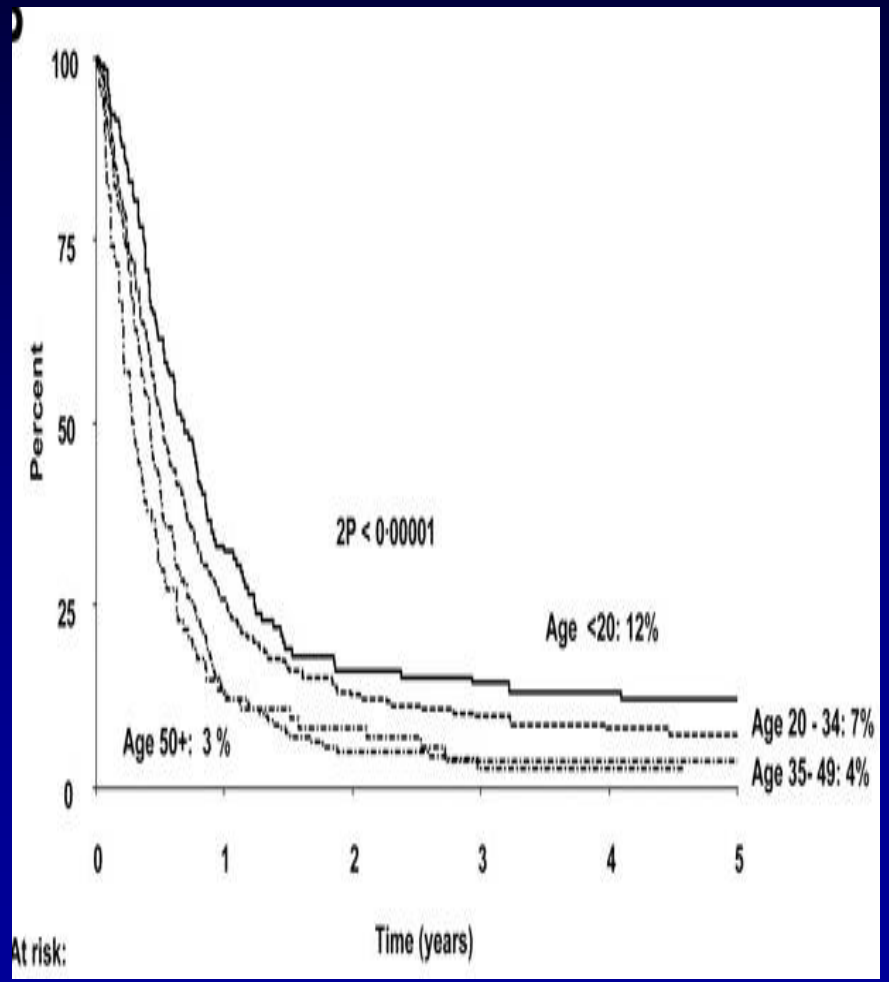
Blinatumomab

IT MTX / Ara-C x 15

ALL -- Historical Survival Rates after 1st Relapse

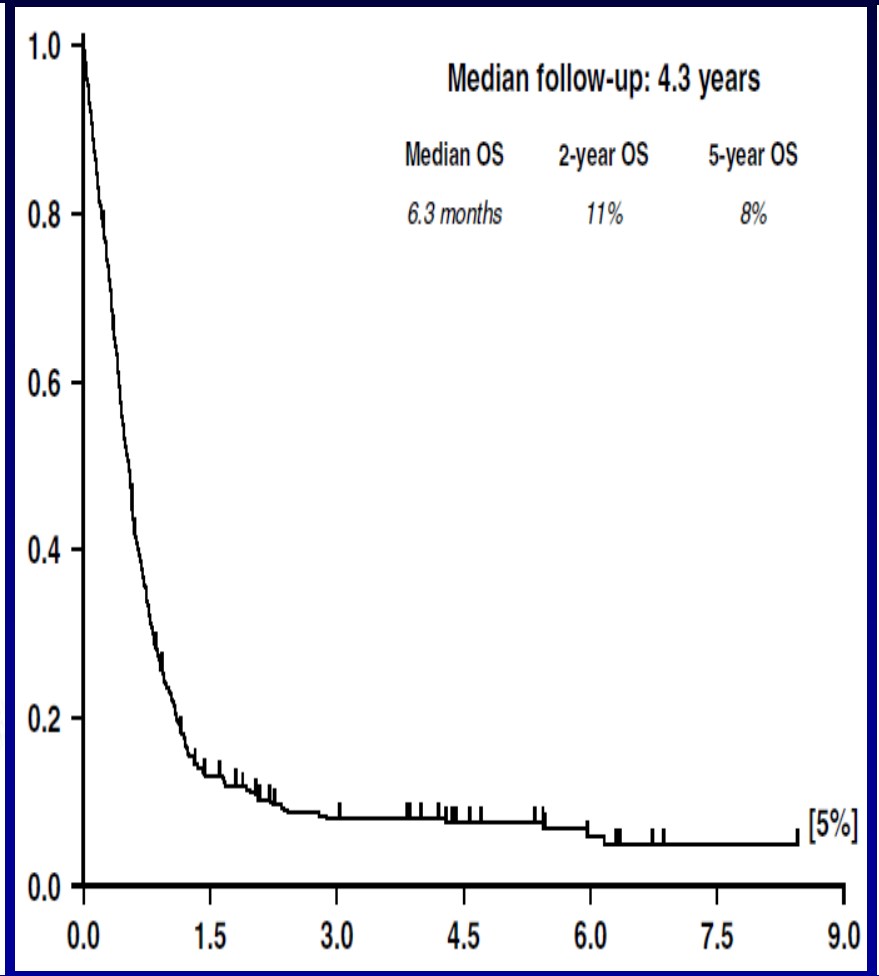
MRC UKALL2/ ECOG2993 Study (n=609)

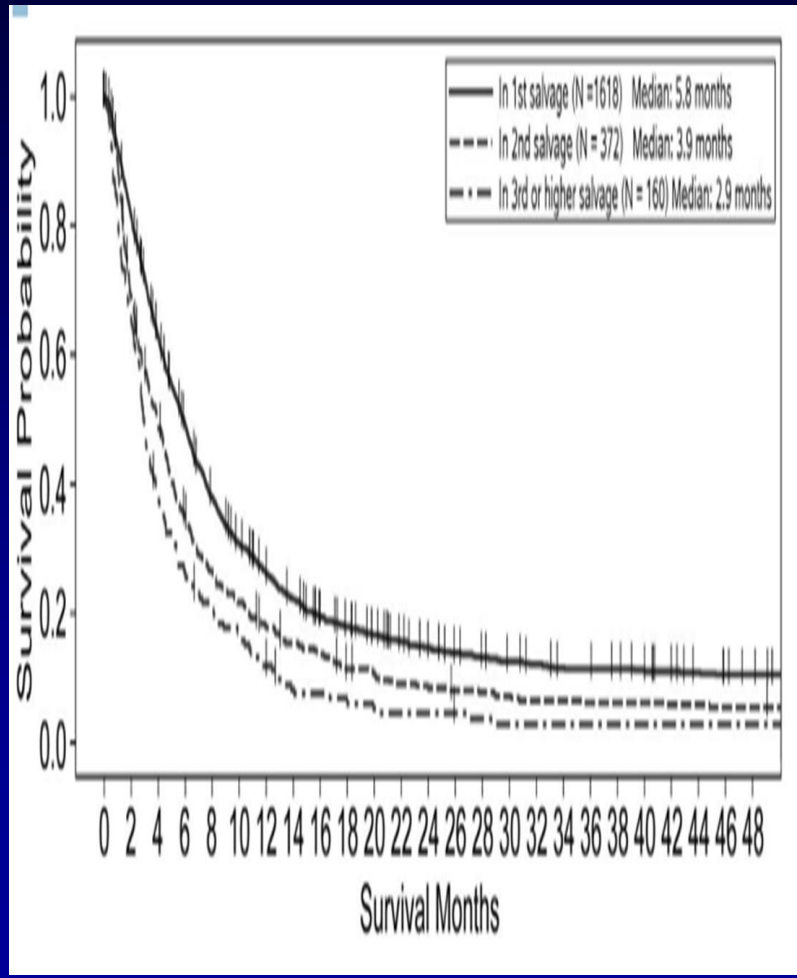
Outcome of patients after 1st relapse
5-yr OS: 7%



LALA-94 Study (n=421)

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





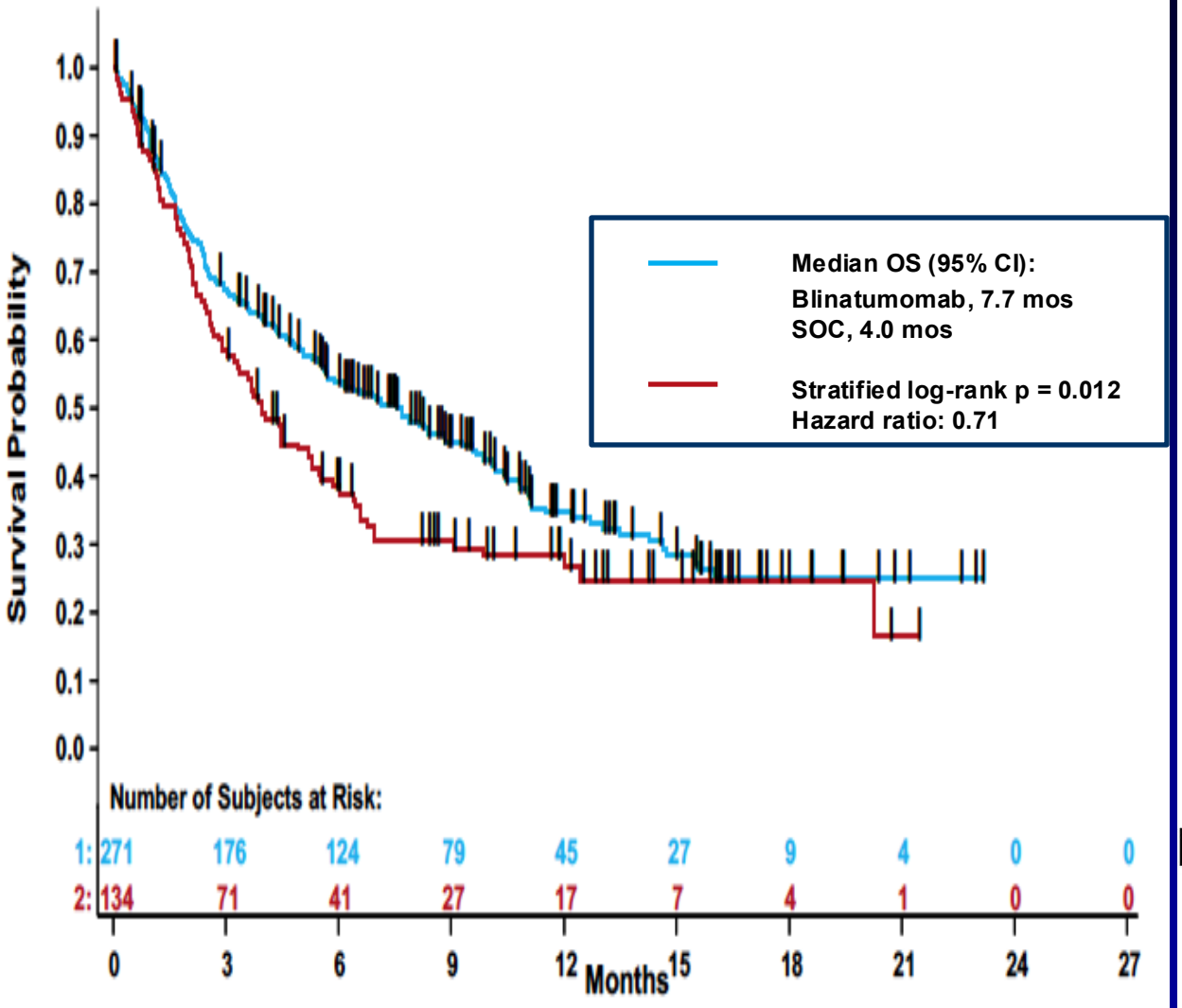
Fielding. Blood. 2007;109:944-950. Tavernier. Leukemia 2007;21:1907-1914

Gokbuget. Haematologica 101: 1524-1533; 2016

Blinatumomab/Inotuzumab vs ChemoRx in R-R ALL

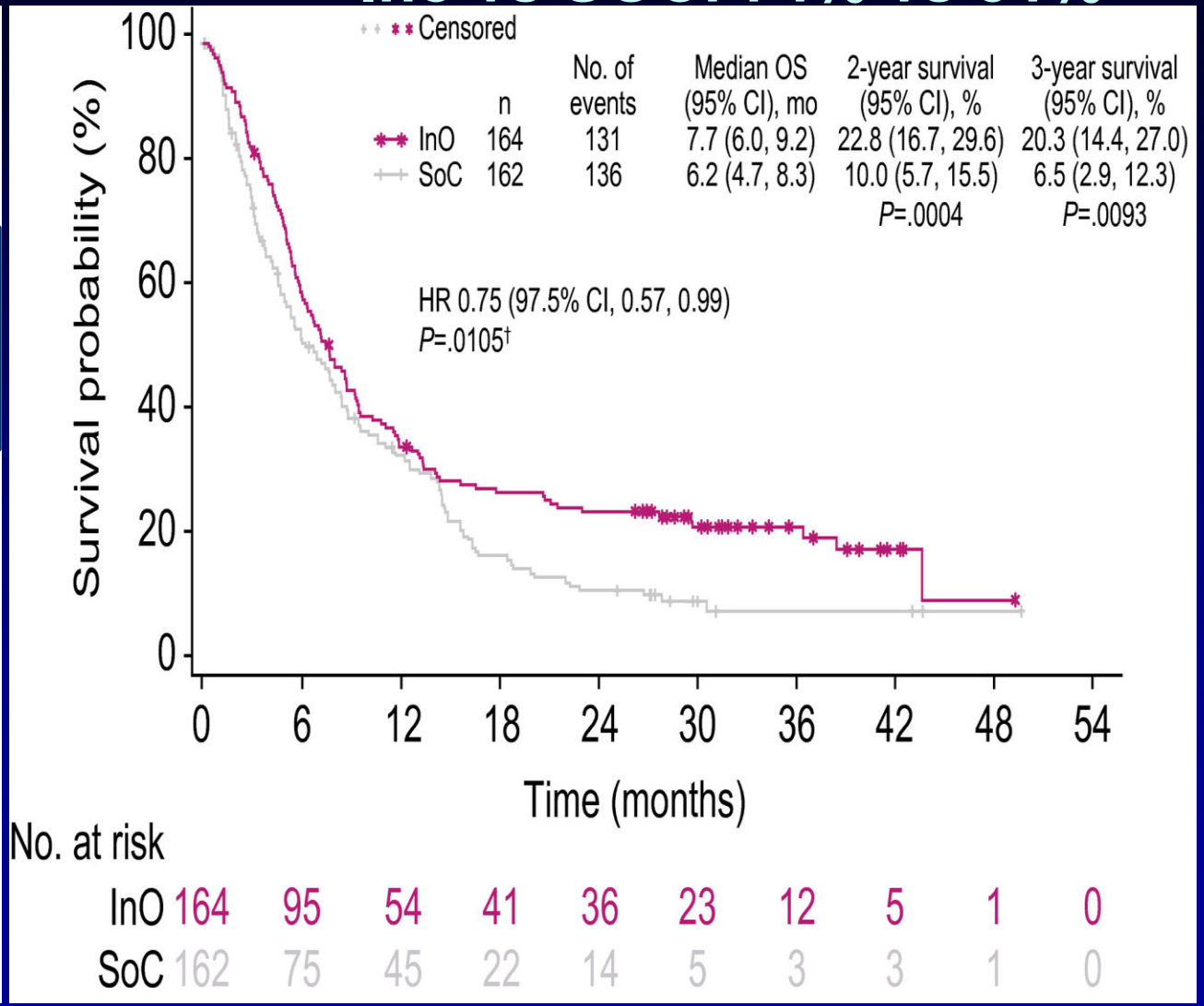
- Marrow CR

Blina vs SOC: 44% vs 25%



Kantarjian. NEJM. 376: 836-47; 2017

Ino vs SOC: 74% vs 31%



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

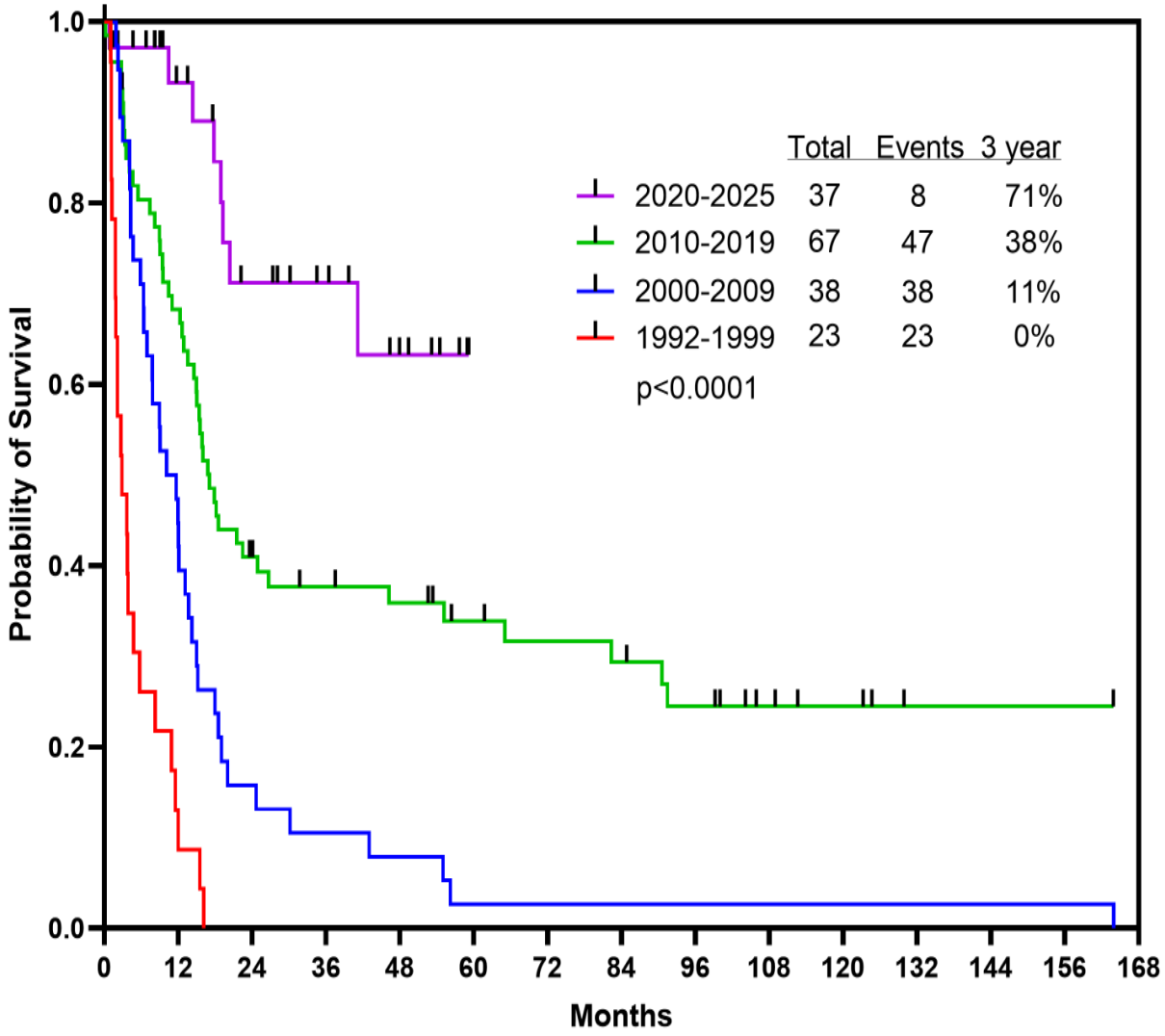
ALL Salvage Strategies Increasing Survival/Cure

- Blinatumomab IV and SQ
- Inotuzumab
- BRICK regimen = D-D miniCVD-ino-blina
- CART
- ChemoRx
- Allogeneic HSCT
- BCR::ABL1 inhibitors in Ph+ALL
- Venetoclax
- Any of above not used optimally, or at all, in frontline Rx

Second-Line Therapy in Ph-Positive ALL

- 165 pts with Ph-positive ALL treated with second-line Rx

Parameter	% CR	% 3-yr OS
No TKIs (<2000/2000+)	30/58	0/0
IMA combo	92	8
2nd GEN TKI combo	93	38
3rd GEN TKI combo	86	58
2020+ (PONA-BLINA)	84	71

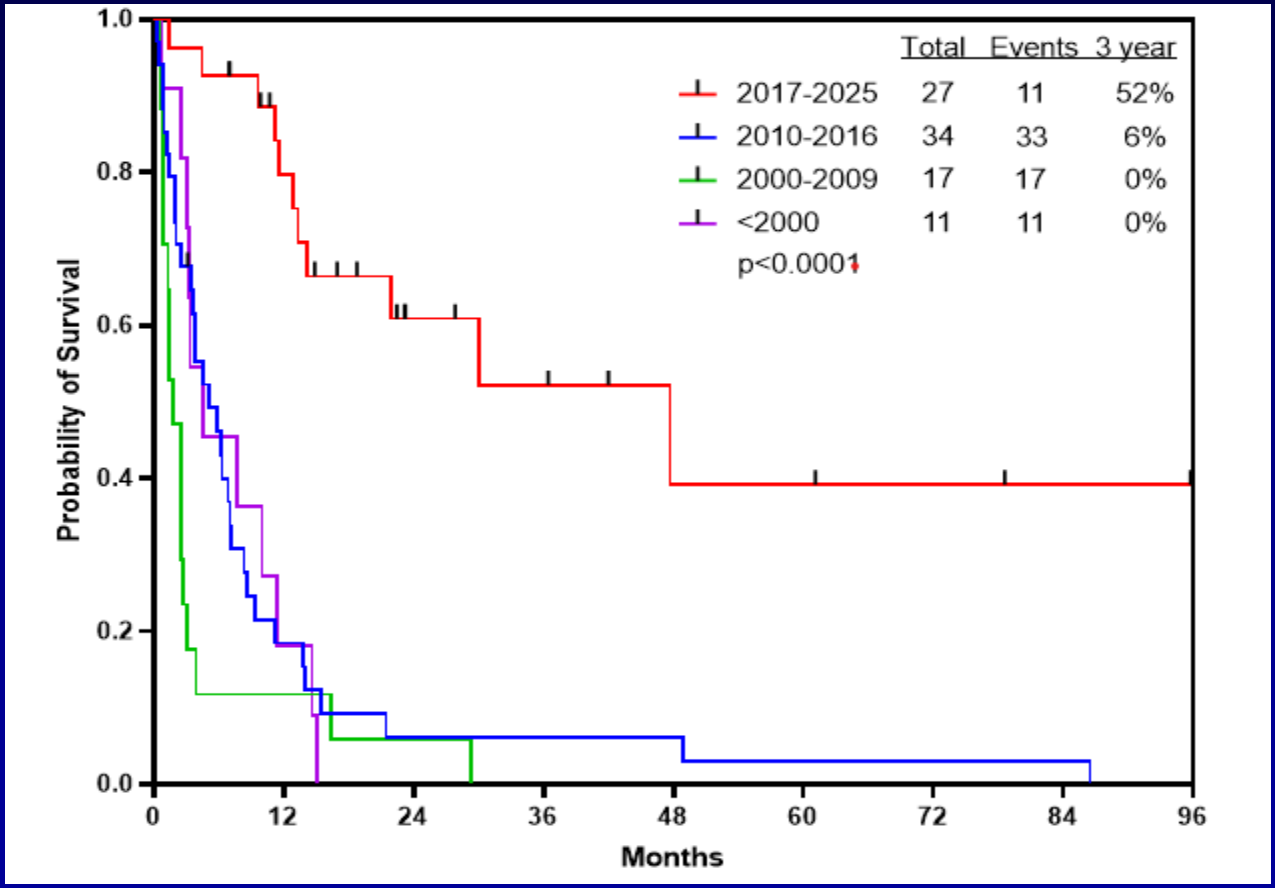


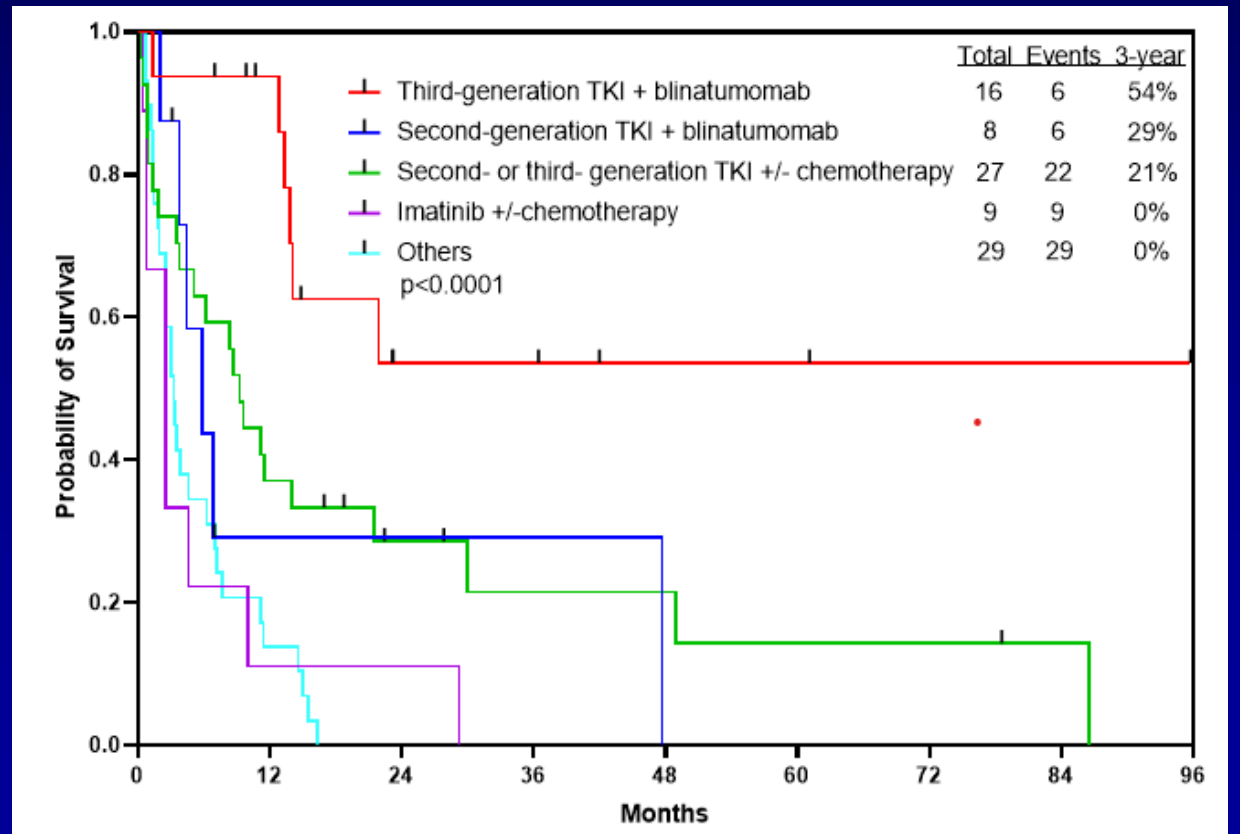
Kantarjian. Cancer; in press . July 2026

Third-Line Therapy in Ph-Positive ALL

- 89 pts with Ph-positive ALL treated with third-line Rx
- CR 58%; 3-yr OS 17%

Parameter	% CR	% 3-yr OS
<2000/ 2000-2009	55/18	0/0
2010-2016	56	6
2017-2025	89	52
3rd GEN TK-BLINA combo (n=16)	100	54





Jen. CLML ; in press . July 2026

Ph-Positive ALL 2026 – How Much ChemoRx Needed?

- Ponatinib 30/15 –blinatumomab x5. Pona 5 yrs; blina 5 courses. 15 ITs
- Monitor by both NGS-MRD and PCR. SCT only if NGS-MRD +
- Add MTX-HDaraC if high WBC; or CARTs
- 4-yr OS 90%
- CART if high risk for both CNS/systemic prevention
- Consider stopping TKI after 5 years of PCR and NGS-MRD negative
- Role of CART in CR1/CR2; for CNS leukemia

Leukemia Questions?

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