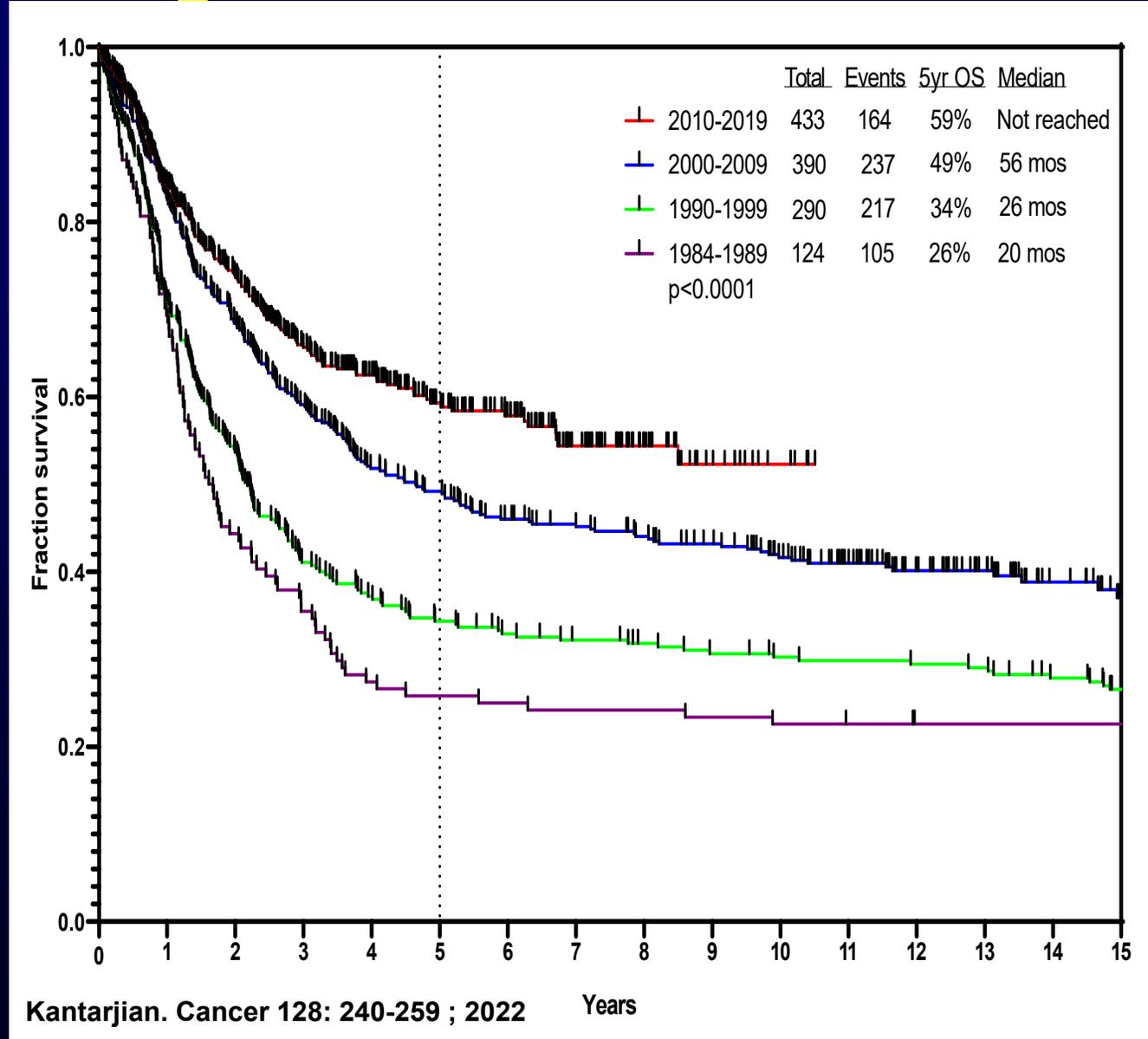
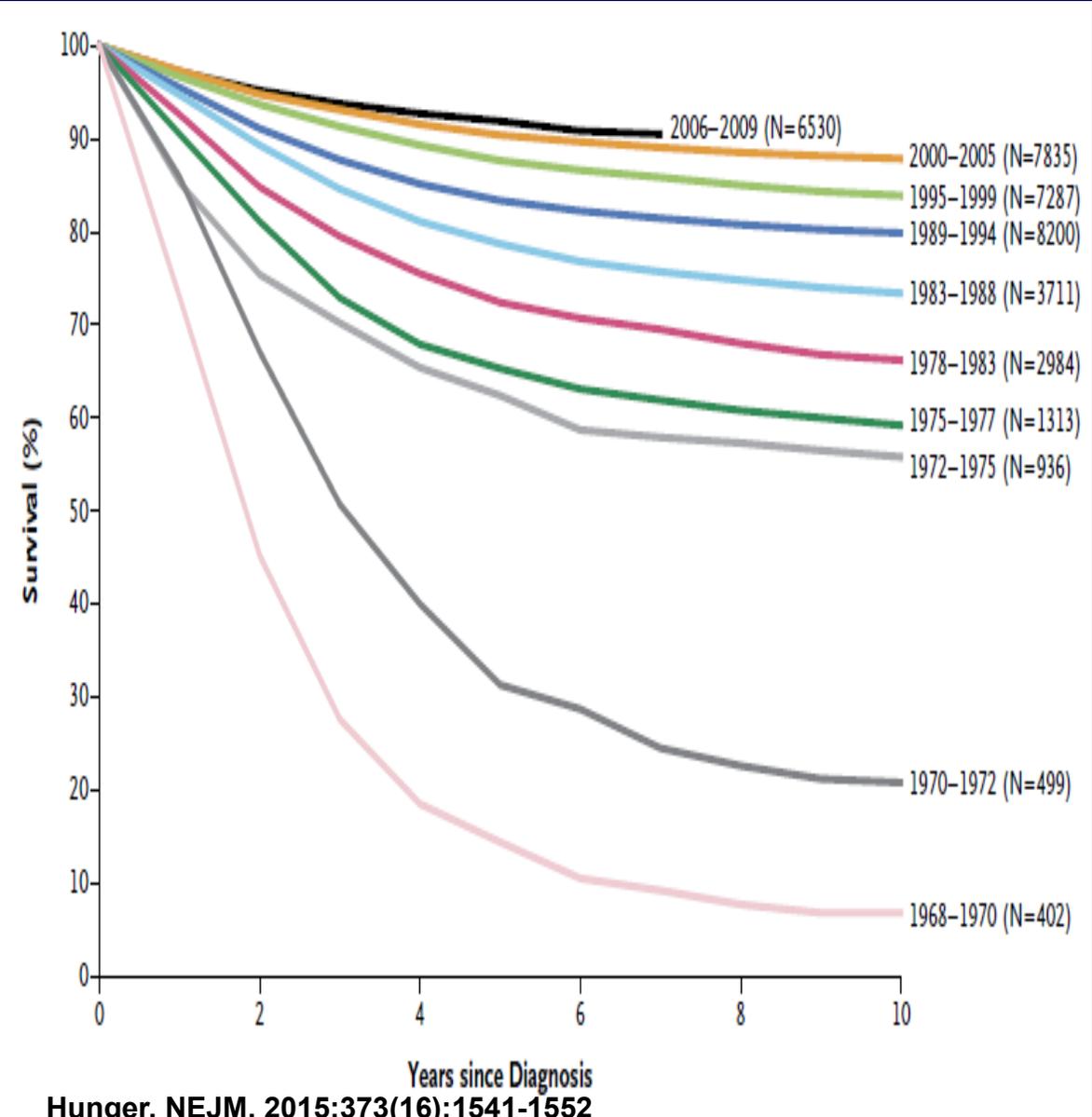


ALL – Progress in Research and Therapy in 2023

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**MD Anderson Cancer Center
July 2023**

Survival in Pediatric and Adult ALL with Classical Intensive ChemoRx Regimens



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

Adult ALL – The Cost of Traditional Intensive Chemotherapy

- **15 chemoRx agents used in intensive induction, consolidation, intensification, maintenance courses over 3 years**
- **Manageable in leukemia research “ivory towers”**
- **High dropout rates in practice/emerging nations, poorer and disadvantaged populations, due to socioeconomic and infrastructure/support hurdles**
- **Cost about \$ 0.5-1 million for frontline cure, \$2+ million if failure**
- **Long-term multiple organ problems, health care, psychological and social problems among cured patients**

ALL Outcome in Practice

Age	% 3-yr OS (Peru, n=378)	%4-yr EFS (India, n=273)
0-10	70	57
10-20	37	35-44
46-65	12	20-27

Adult ALL Therapy – The Solution

- **Shorter dose-dense curative regimens that combine traditional less intensive chemoRx with the novel targeted and immune therapies: new BCR::ABL1 TKIs; antibodies targeting CD19 (blinatumomab) CD22 (inotuzumab) and CD20 antibodies (rituximab, CD20 BiTEs); CARTs consolidation instead of allo SCT**
- **Measure residual disease by next-generation sequencing (NGS-MRD for IgHV; analyzes >1 million cells) to decide on changes in, and duration of, therapy**
- **Dose-dense mini-CVD-inotuzumab-blinatumomab +/- CARTs regimen –7 months of Rx**

Adult ALL – Time to Break With a Half-Century of Traditions

- **Ph-positive ALL -- Ponatinib-blinatumomab**
- **Pre-B ALL -- 1) Less chemoRx and shorter durations; 2) Addition of CD19/20/22 antibodies to chemoRx; 3) ? CARTs in MRD/CR instead of SCT; 4) NGS-MRD to monitor response and decide on change of Rx**
- **T-ALL -- Not sure yet; asparaginase-nelarabine; role of decitabine/HMAs, venetoclax**

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+ ALL^{3,4}
- Activity of antibodies targeting CD19 (blinatumomab; FDA approval 2014) and CD22 (inotuzumab; FDA approval 2017) in adult ALL^{6,7}
- Ponatinib-blinatumomab in Ph+ALL (2017) ⁸
- Mini CVD-ino-blina (2010).Hyper CVAD-ino-blina (2017) ⁹

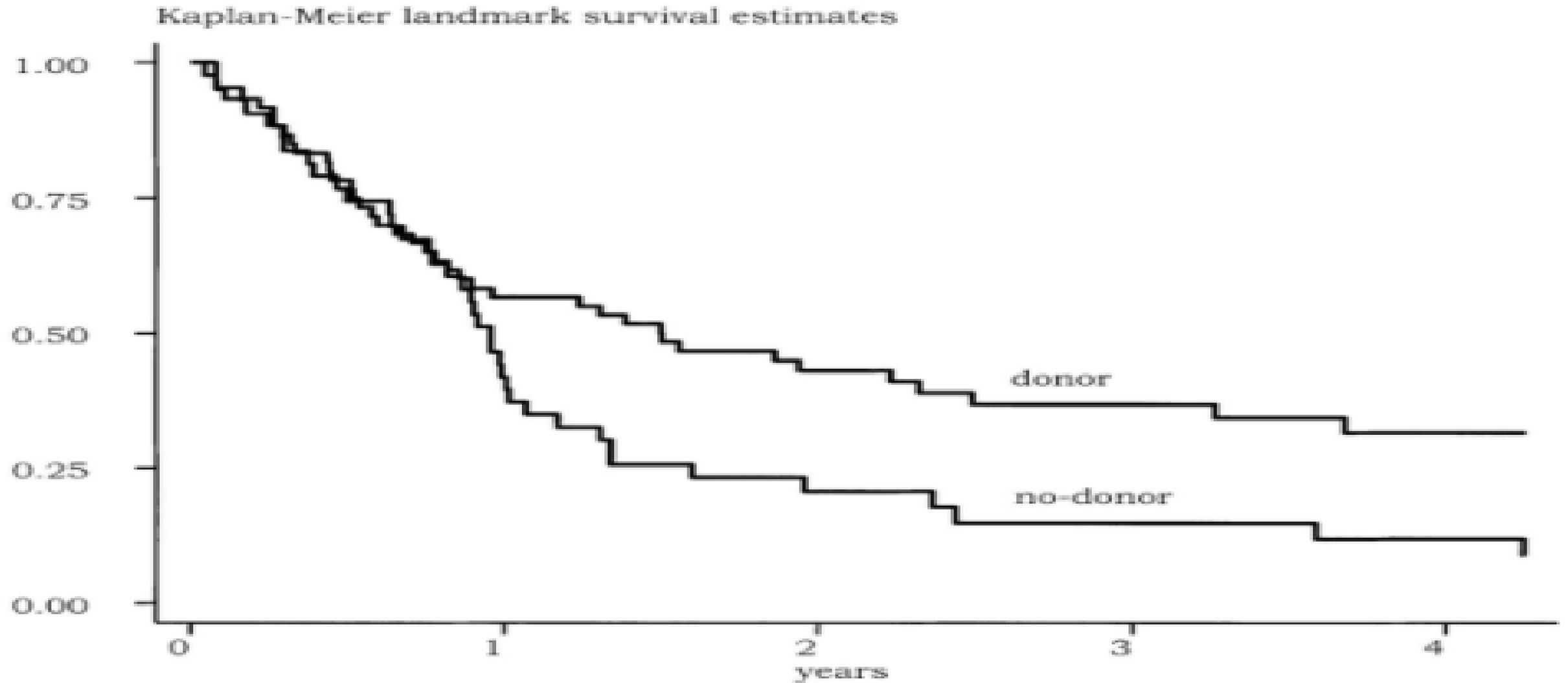
1. Kantarjian. JCO 18: 547; 2000 2. Thomas. Cancer 106: 1569; 2006 3.Thomas. Blood 103:4396; 2004

4. Ravandi. Blood 116: 2070; 2010 5. Thomas. JCO 28: 3880; 2010 6. Kantarjian. JCO 30: 3876; 2012 7. Kantarjian. Lancet Oncol. 13: 403; 2012 8. Jabbour. Lancet Haematology. November 2022 9. Jabbour. Lancet Haematology: October 21; 2022.

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 : levoquin 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%

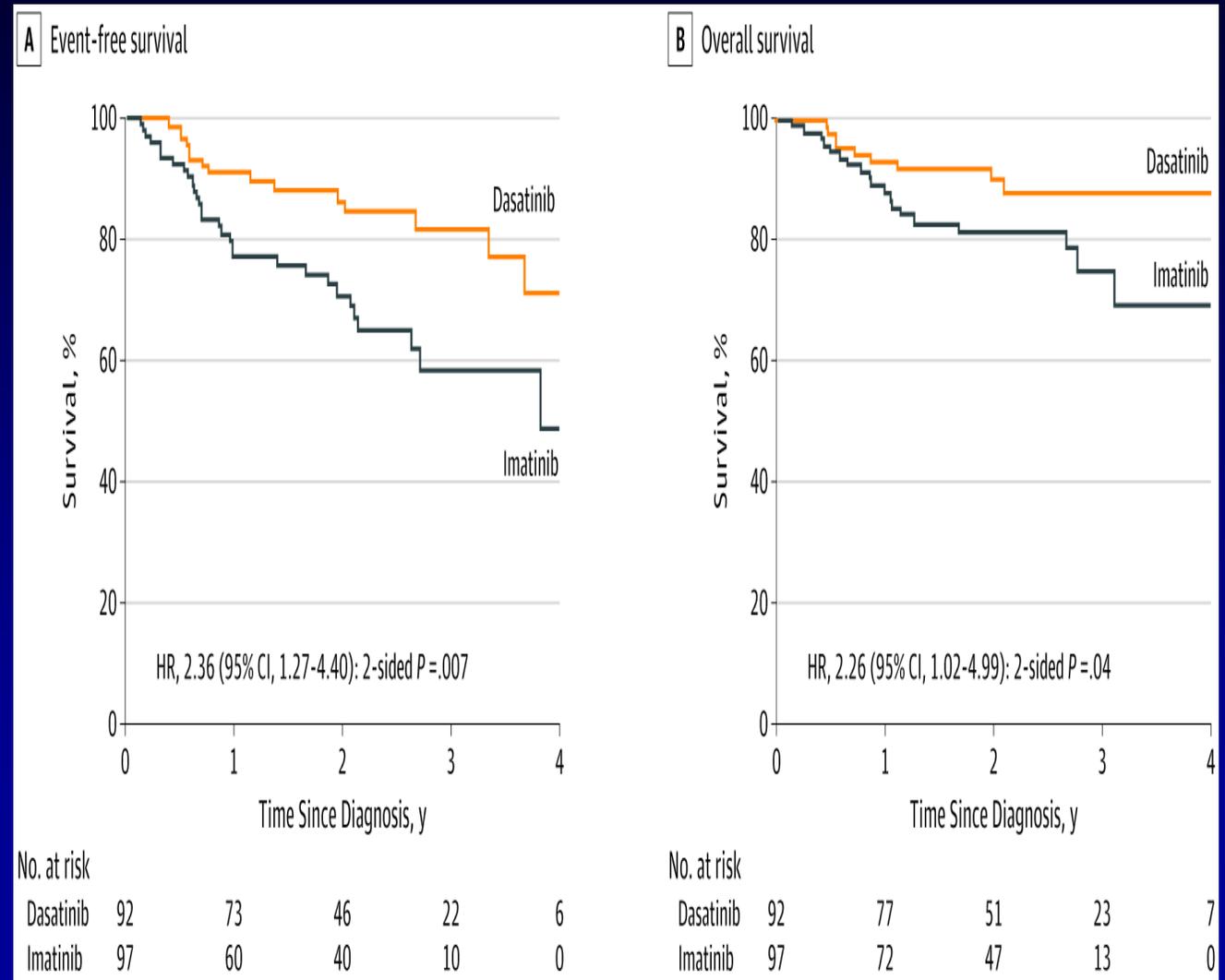
Evolution of Ph-positive ALL Research and Rx at MDACC (1992-2022)

- 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 IT; allo SCT rare

Dasatinib vs Imatinib in Pediatric Ph-positive ALL

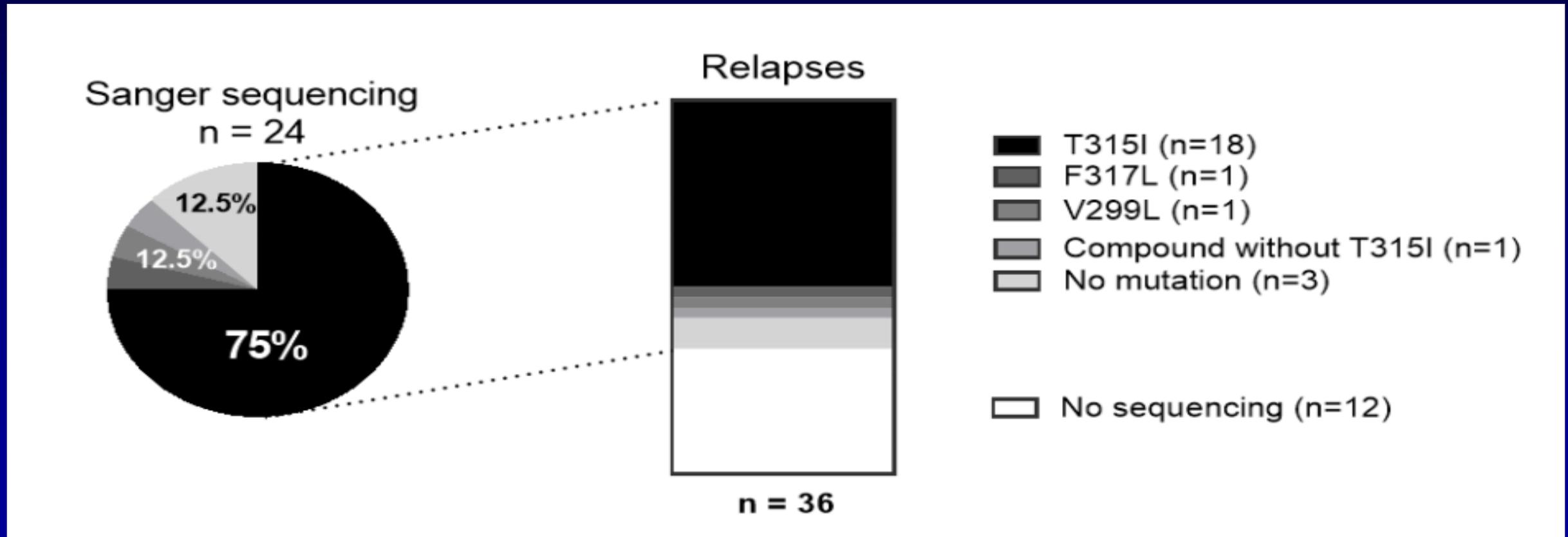
- 189 pts randomized Rx + dasatinib (n=92) or imatinib (n=97)
- Median F/U 26 mos; Triple IT 19 or 21

% 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



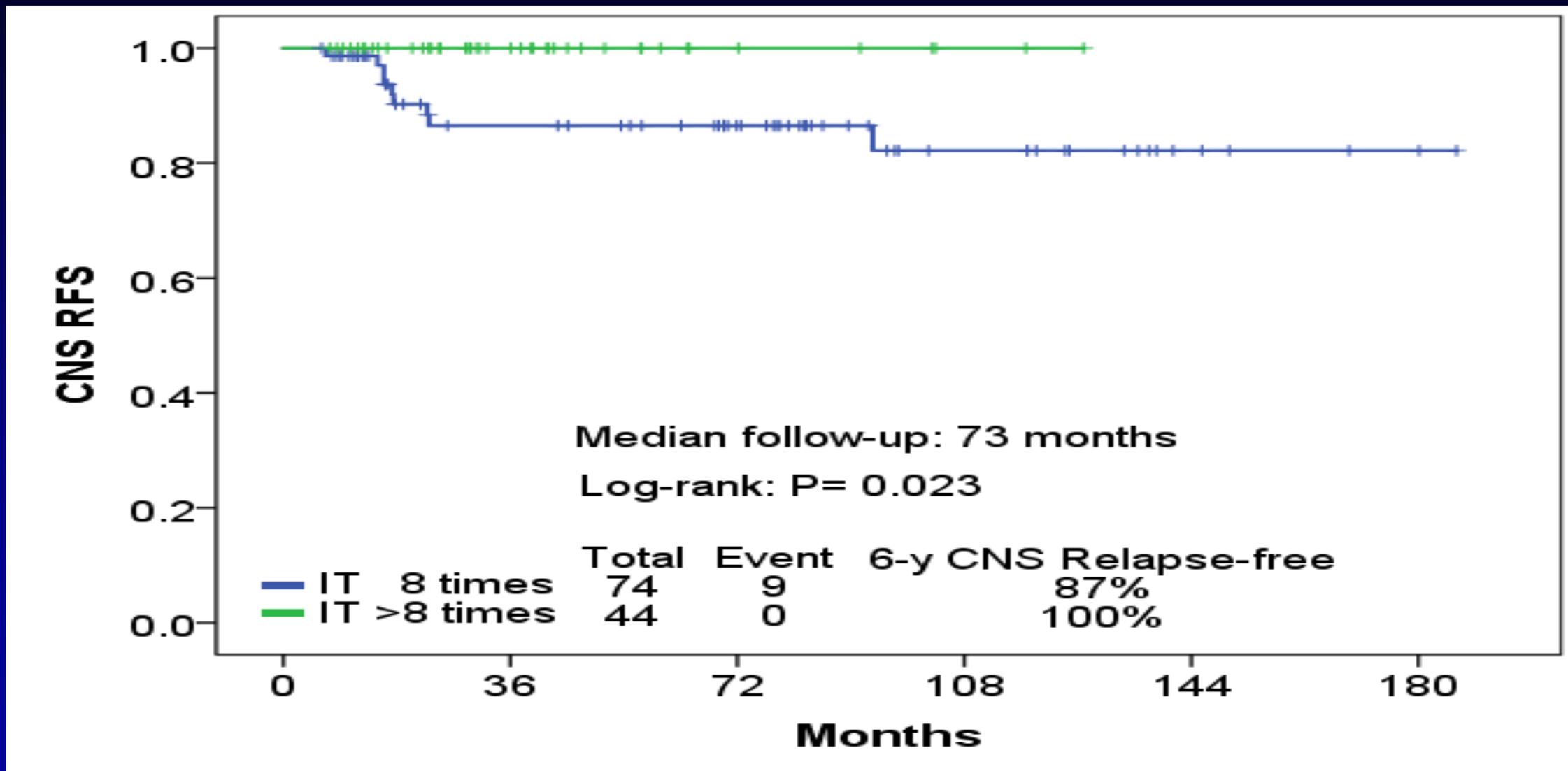
T315I Mutations at Diagnosis and Relapse in Ph+ ALL

- T315I kinase domain mutation present in 18/24 patients (75%) at time of relapse



IT x8 vs. ITx12 in Ph+ ALL

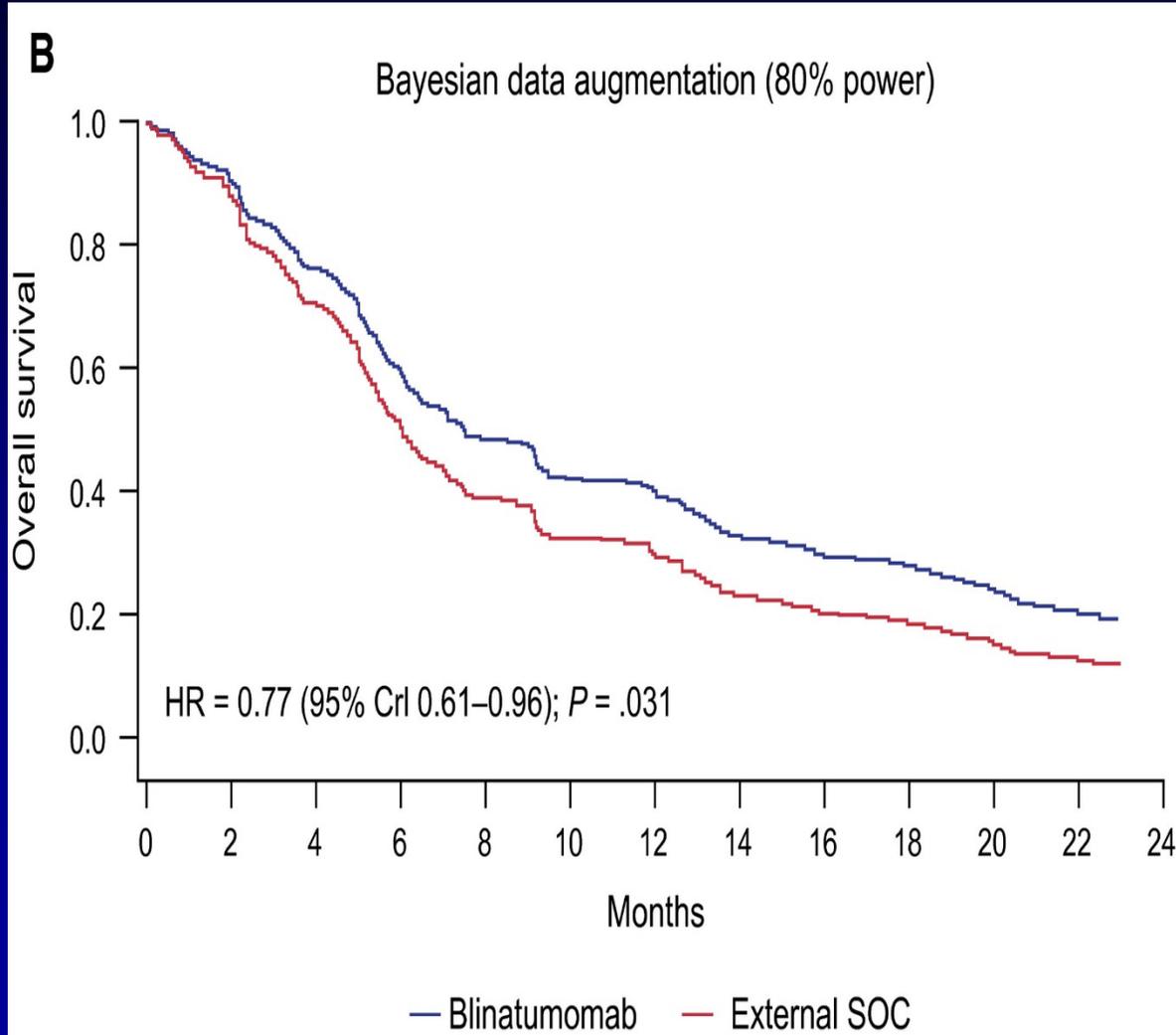
6M Landmark: CNS Relapse-free Survival



Blinatumomab and Inotuzumab in R-R Ph+ ALL

Blina vs SOC

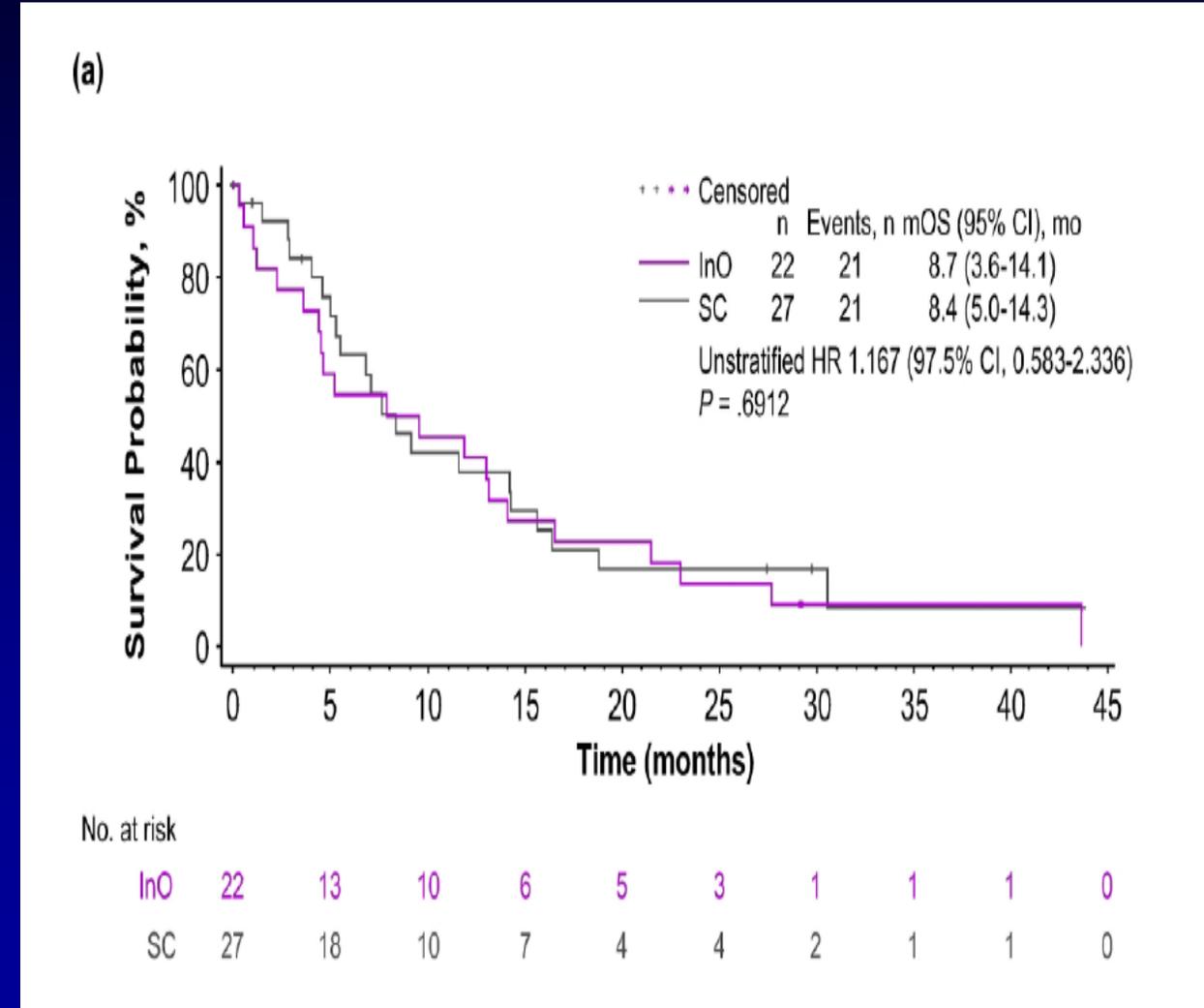
- CR/CRh 36% vs 25%
- 1-yr OS 41% vs 31%



Rambaldi. Cancer. 126: 304-310; 2019

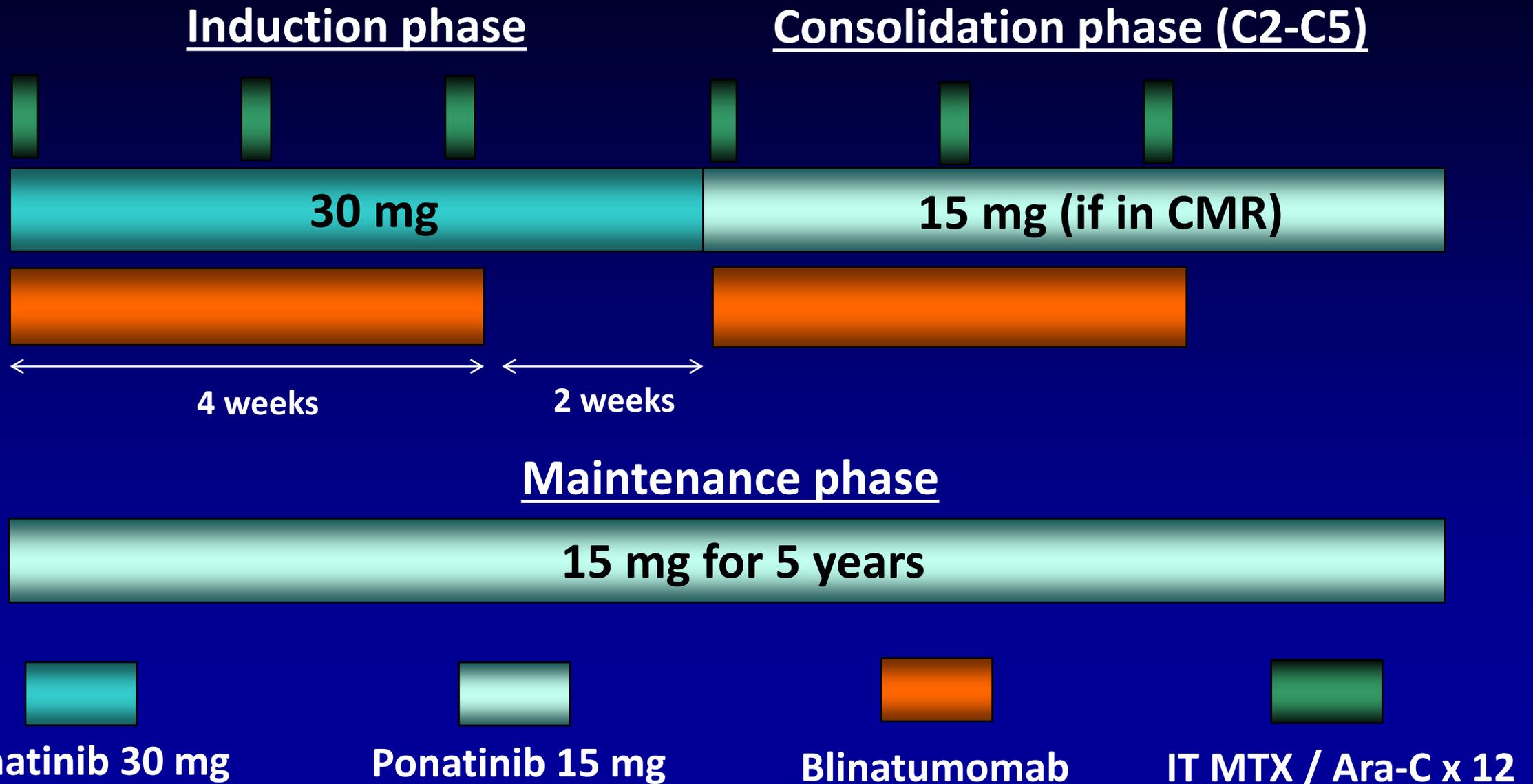
Ino vs SOC

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



Stock. Cancer 127: 905-13;2021

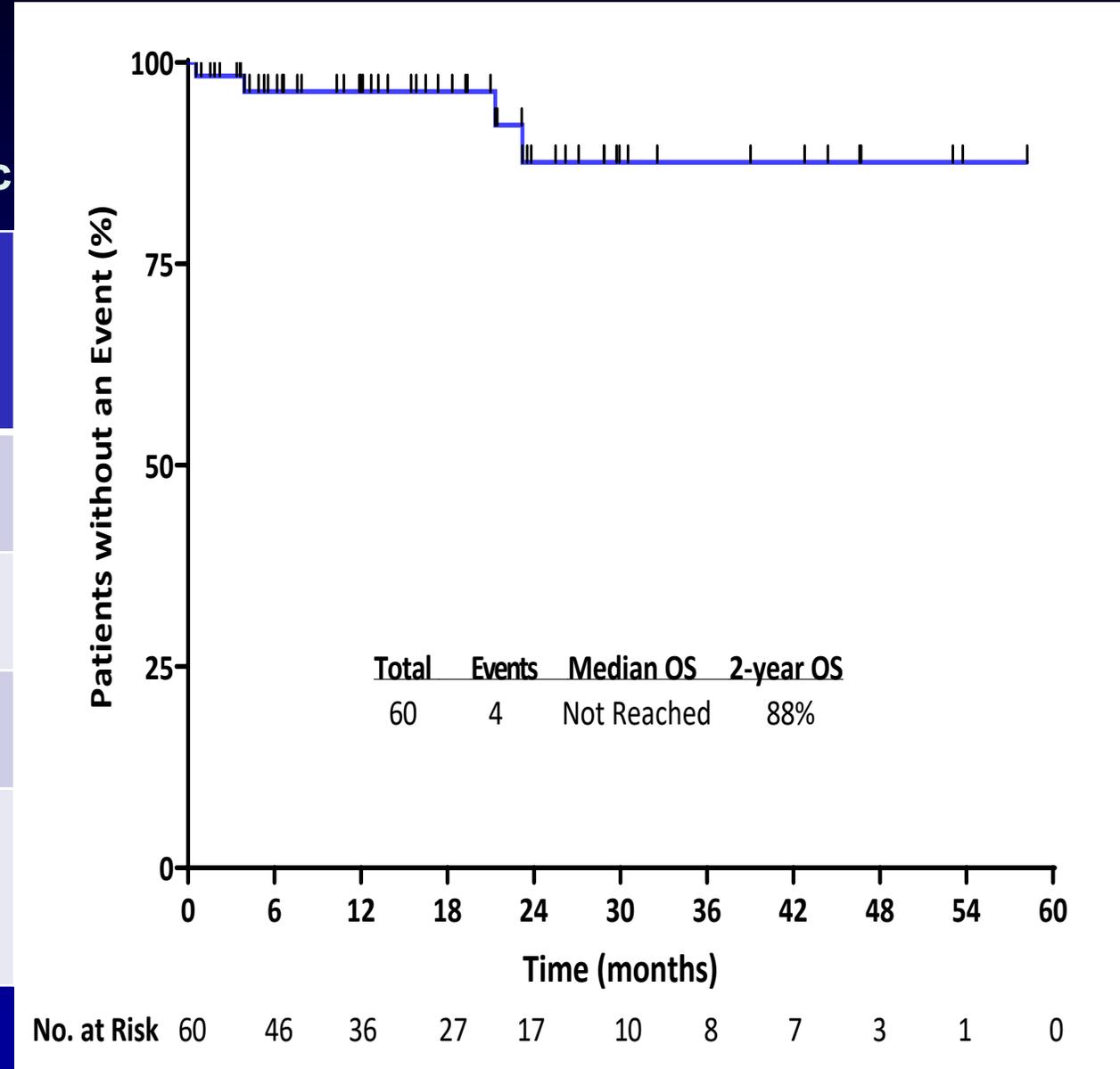
Ponatinib + Blinatumomab in Ph+ ALL: Regimen



Ponatinib and Blinatumomab in Newly Dx Ph-Positive ALL

- 60 pts Rx with simultaneous ponatinib 30-15mg/D and blinatumomab x 5 courses. 12 ITs
- Only 1 pt had SCT(3%)
- Median F/U 16 months. 3-yr EFS 79%, OS 88%
- 4 relapses: 2 CNS, 1 CRLF2+ (Ph-), 1 systemic

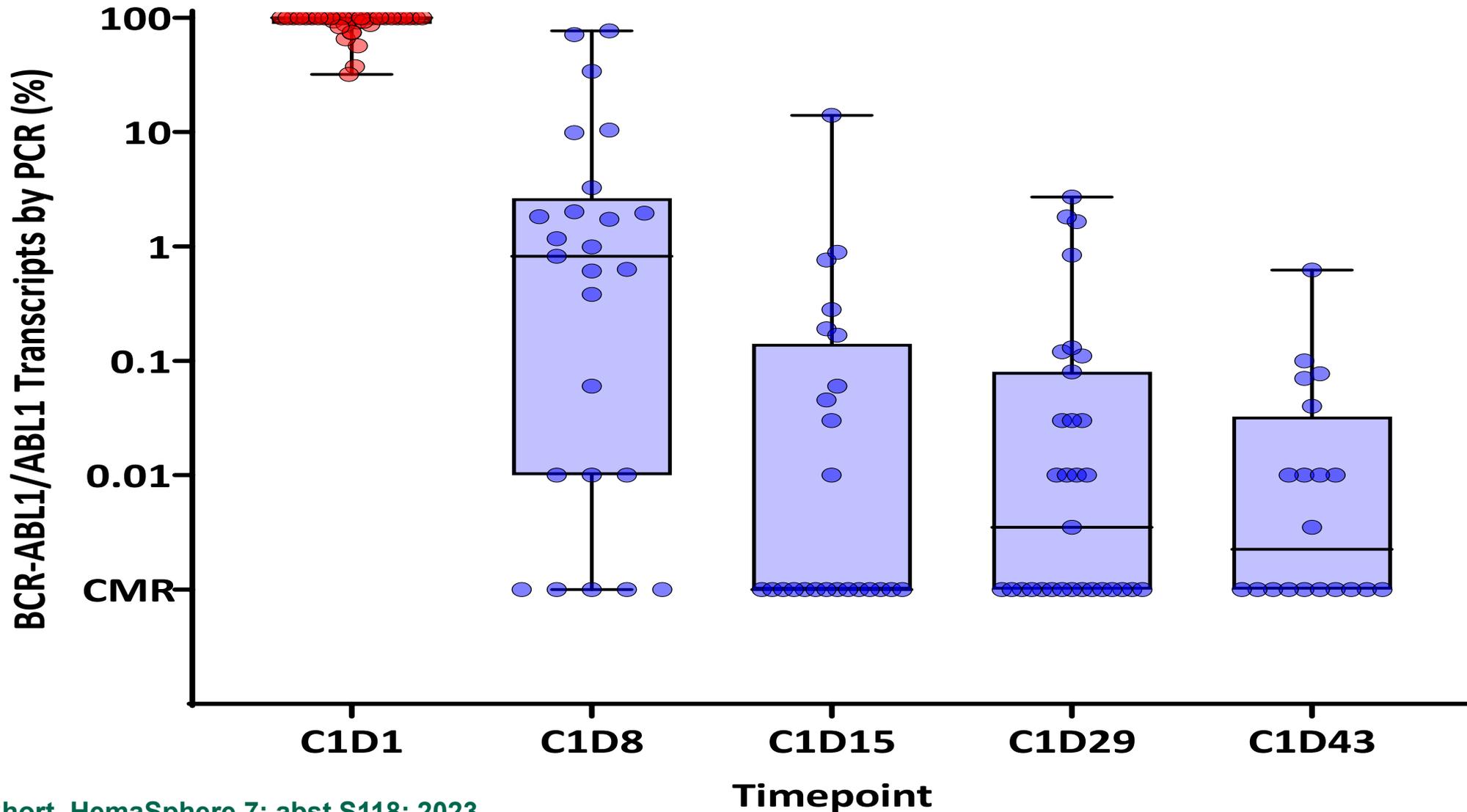
Parameter	%
CR-CRi	97
% CMR	83
% NGS-MRD negative	89
% 2-yr OS	88



Short. HemaSphere 7: abst S118: 2023

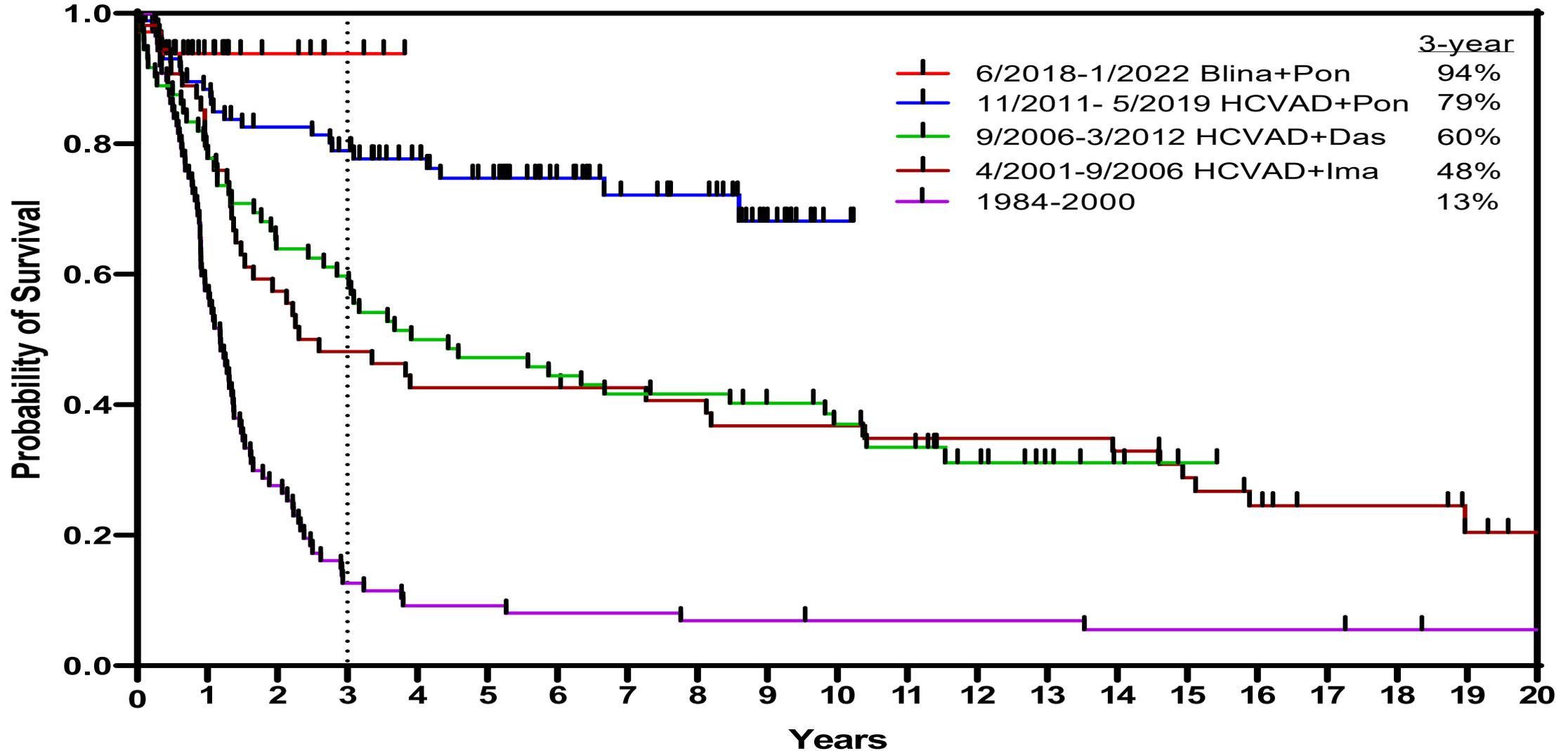
Jabbour. Lancet Haematol. 2023;10(1):e24-e34.

Ponatinib + Blinatumomab in Ph+ ALL: Early MRD Responses



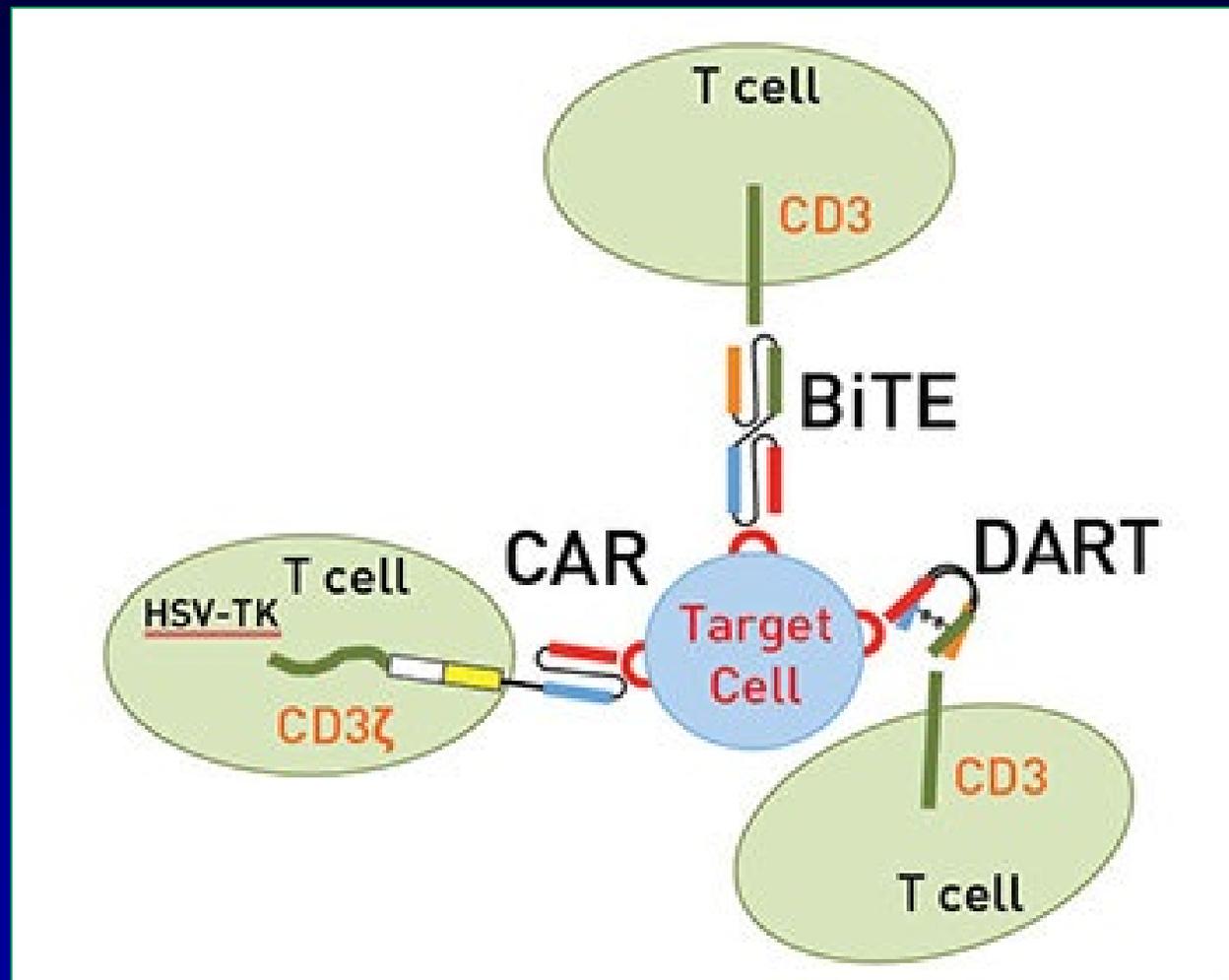
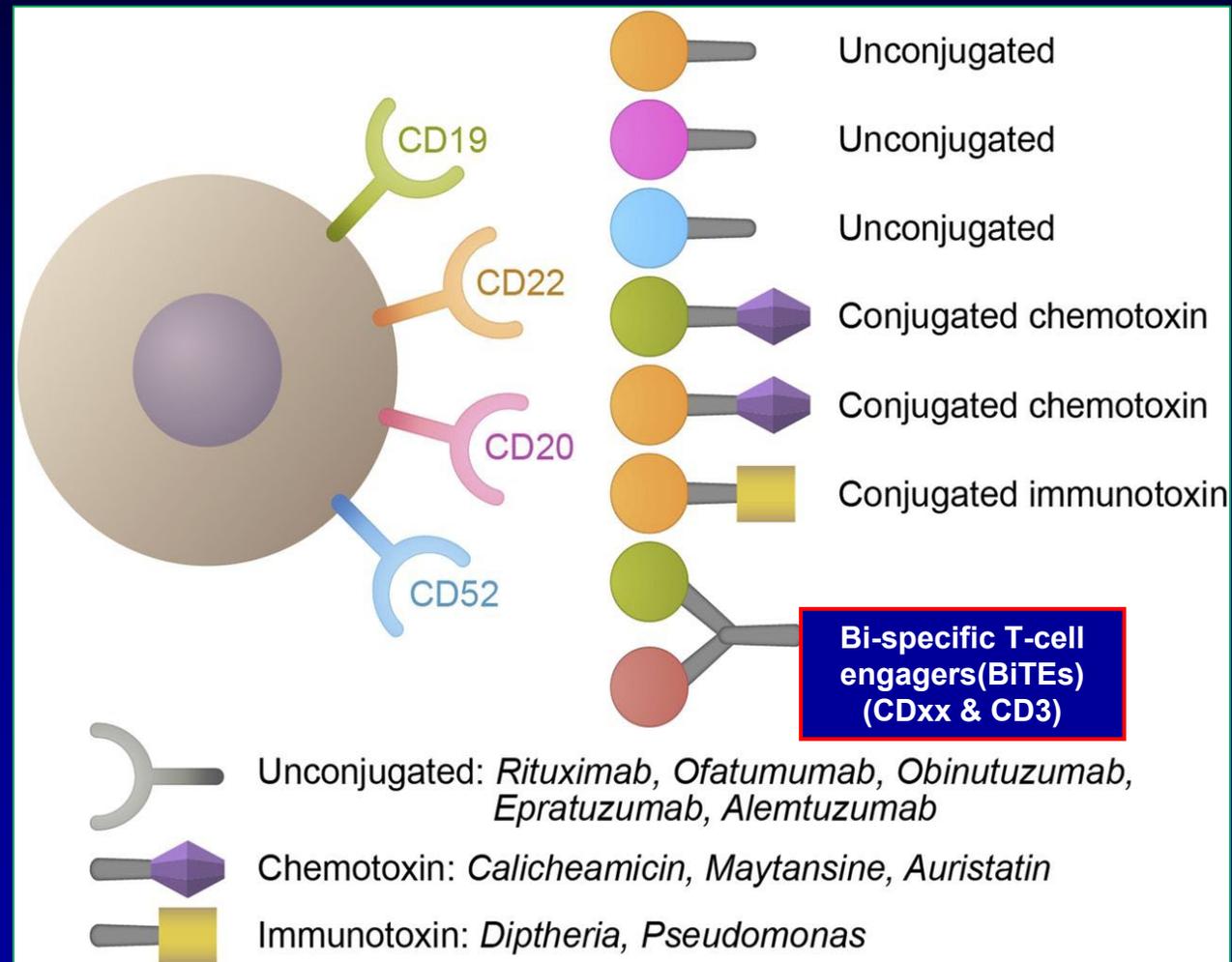
Ph+ ALL. Survival by Decade (MDACC 1985-2022)

Overall Survival of Ph+ patients



Immuno-oncology in ALL

- Antibodies, ADCs, immunotoxins, BiTEs, CARTcells

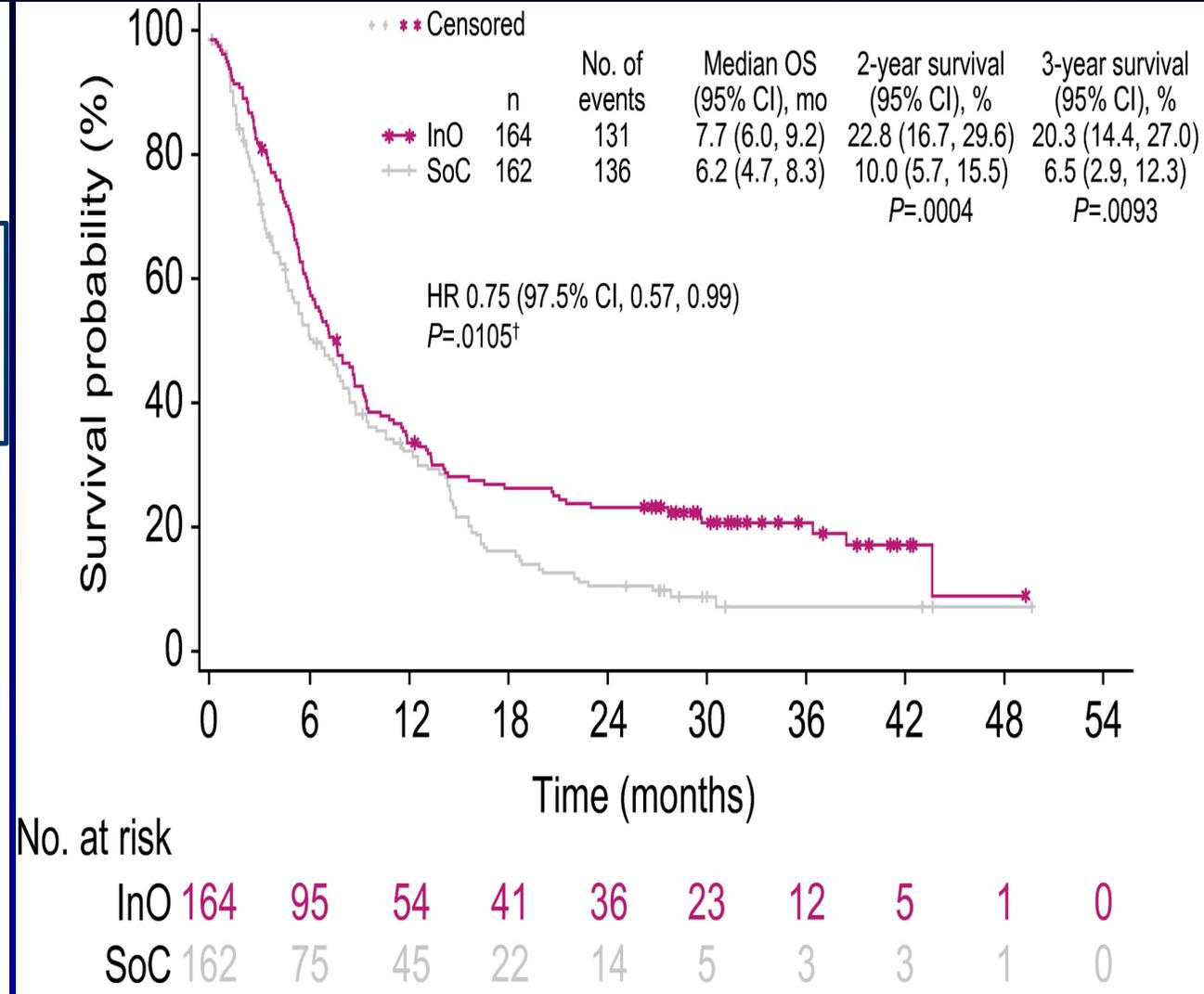
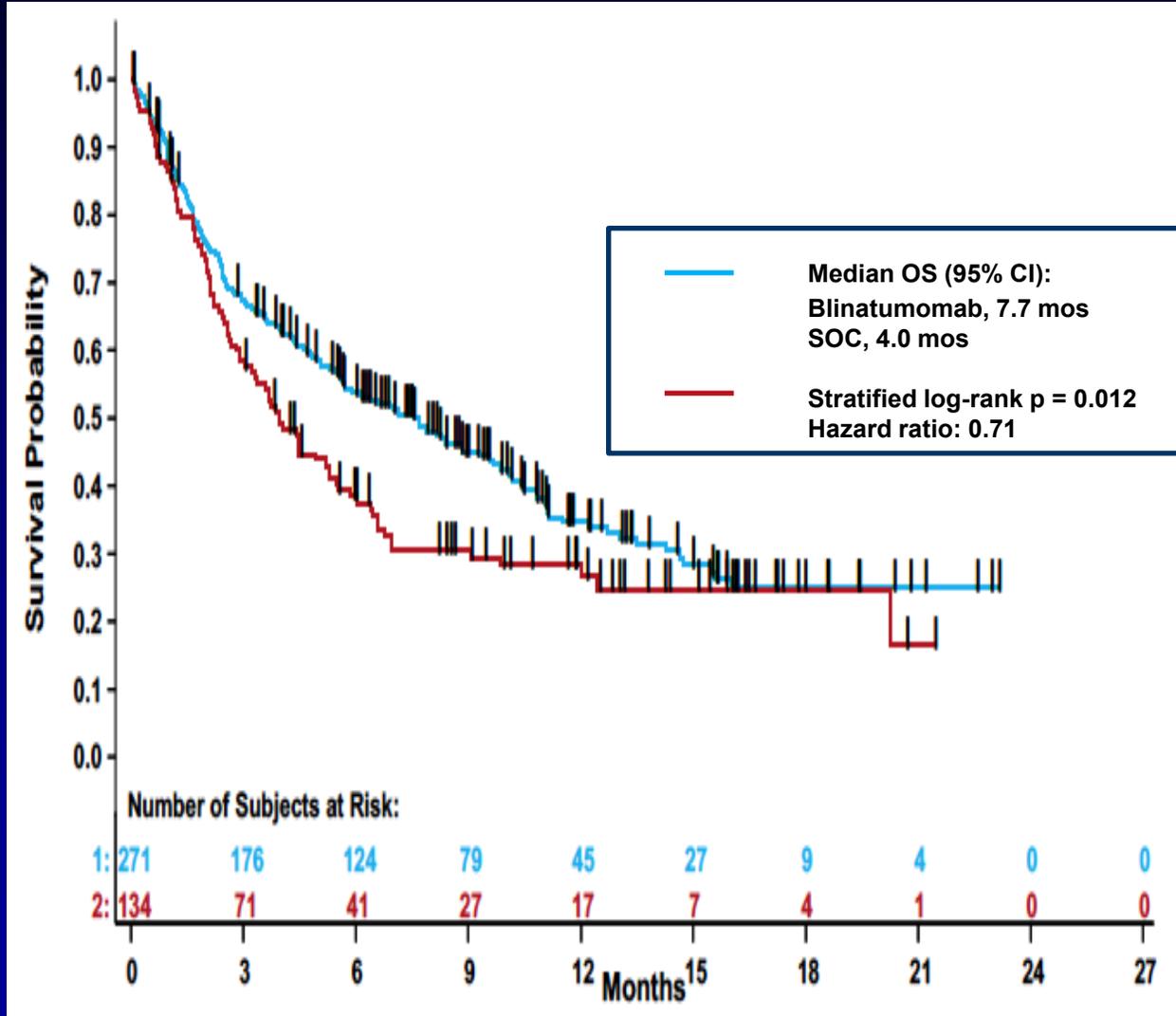


Blinatumomab/Inotuzumab vs ChemoRx in R-R ALL

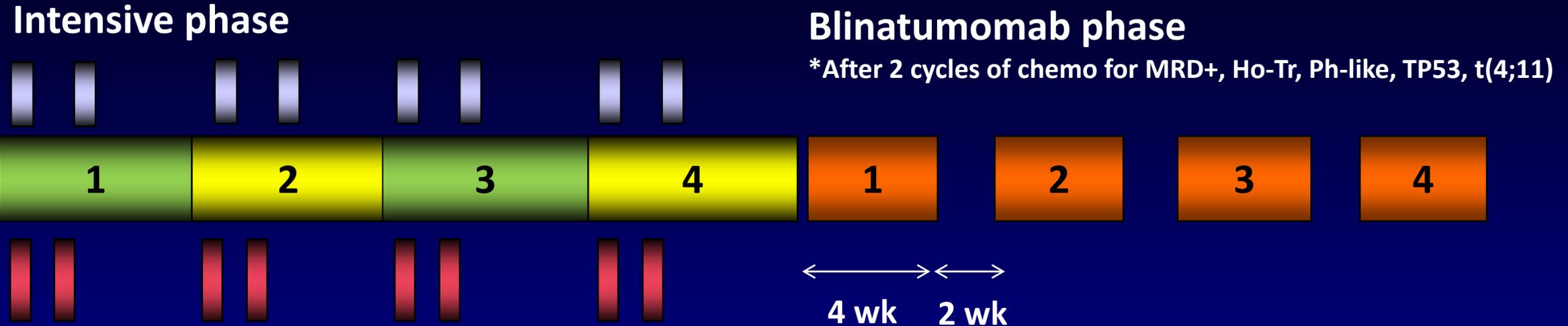
- Marrow CR

Blina vs SOC: 44% vs 25%

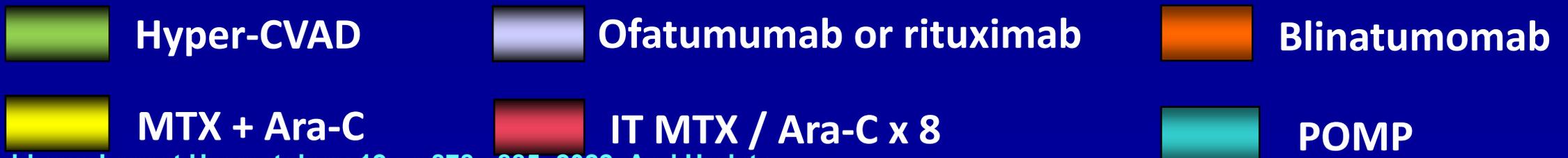
Ino vs SOC: 74% vs 31%



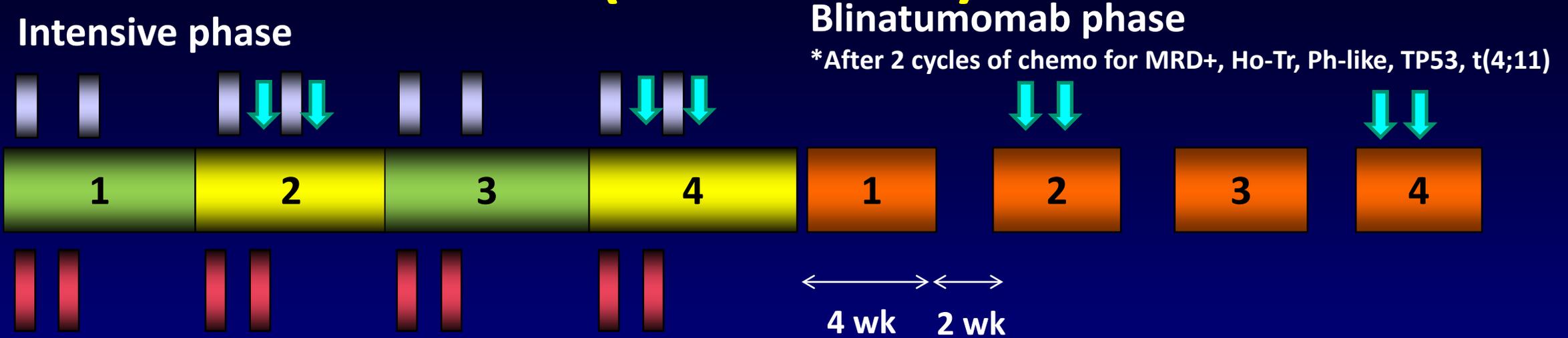
Hyper-CVAD + Blinatumomab in B-ALL: Regimen



Maintenance phase



Hyper-CVAD + Blina + InO in B-ALL: Regimen (2nd Cohort)



Maintenance phase

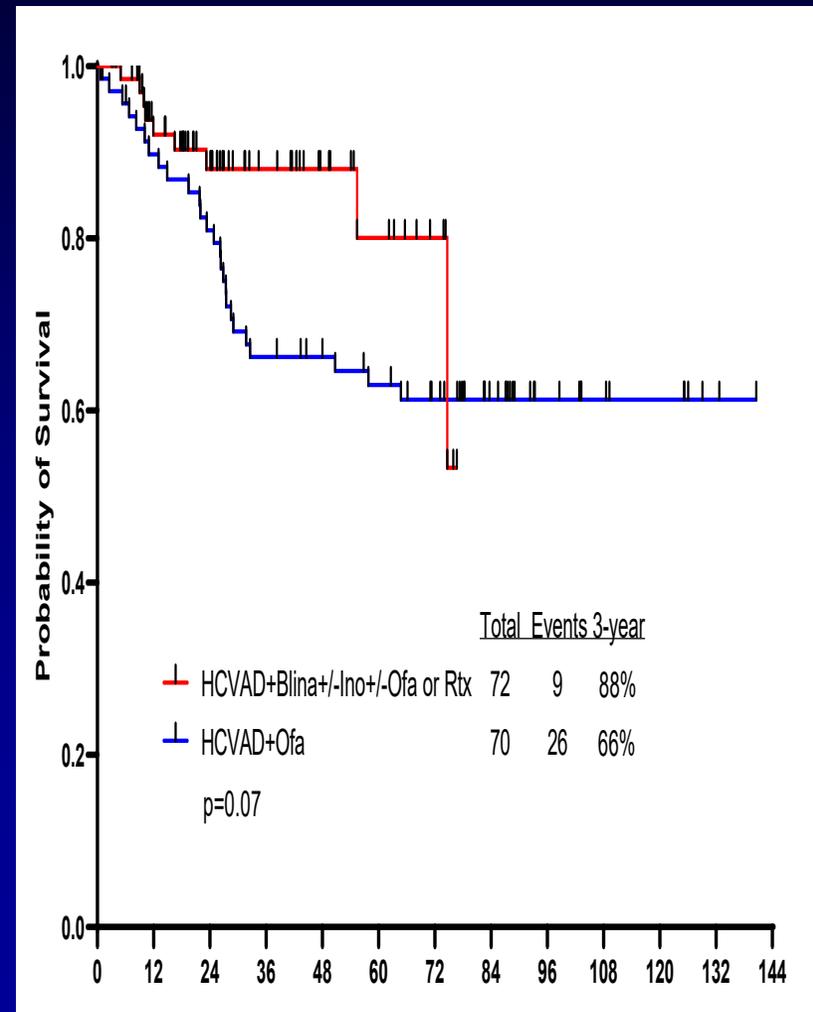
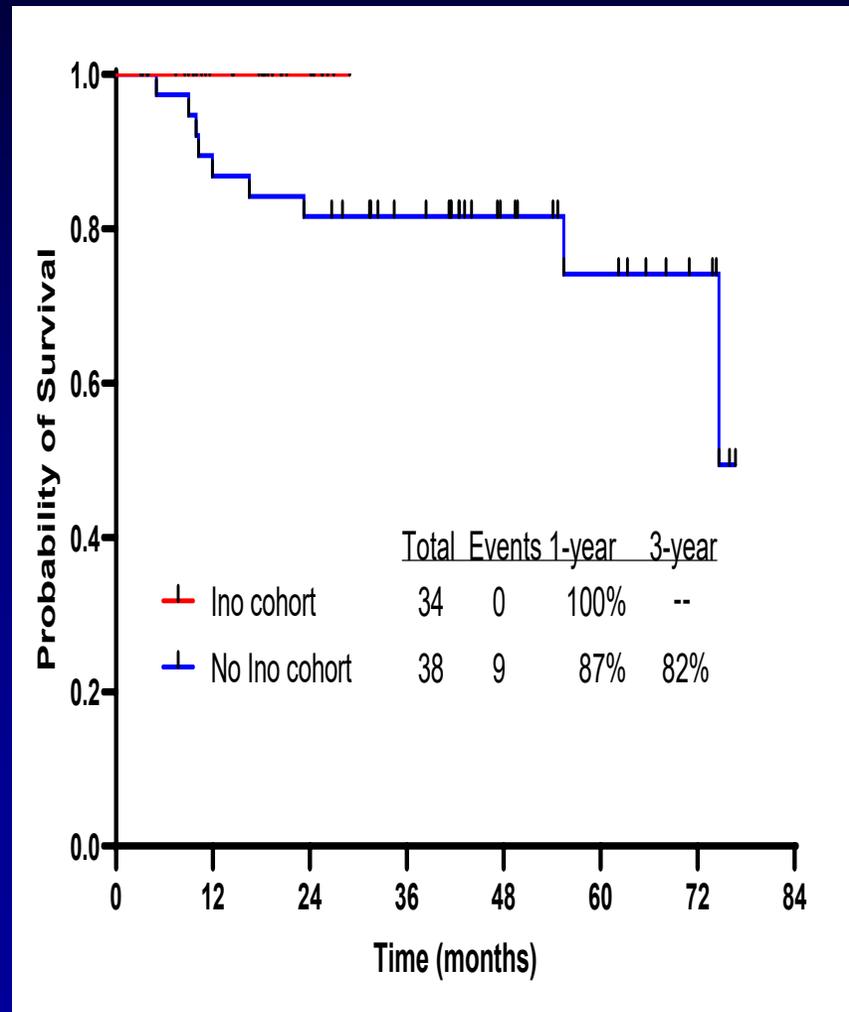
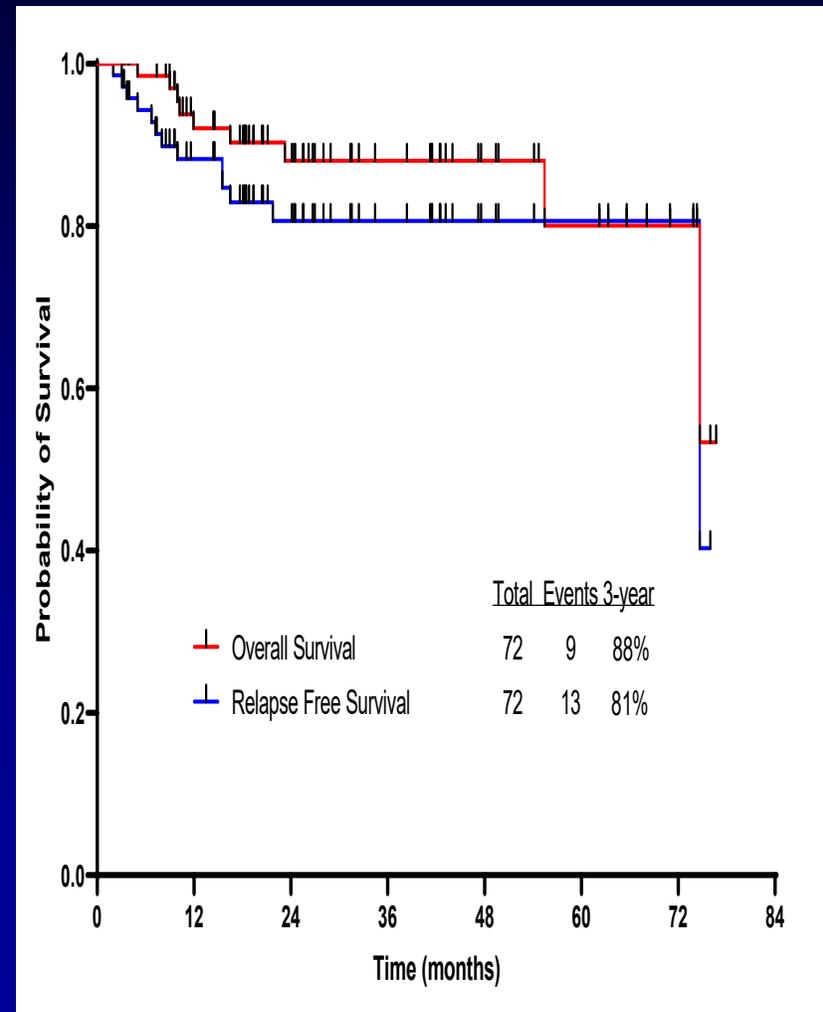


 Hyper-CVAD	 Ofatumumab or rituximab	 Blinatumomab
 MTX (500 mg/m ²)+Ara-C (1g/m ²)	 IT MTX/Ara-C x 8	 POMP

  Inotuzumab 0.3 mg/m² on D1 and D8 Jabbour. Lancet Haematology 12 : e 878-e885; 2022. And Update

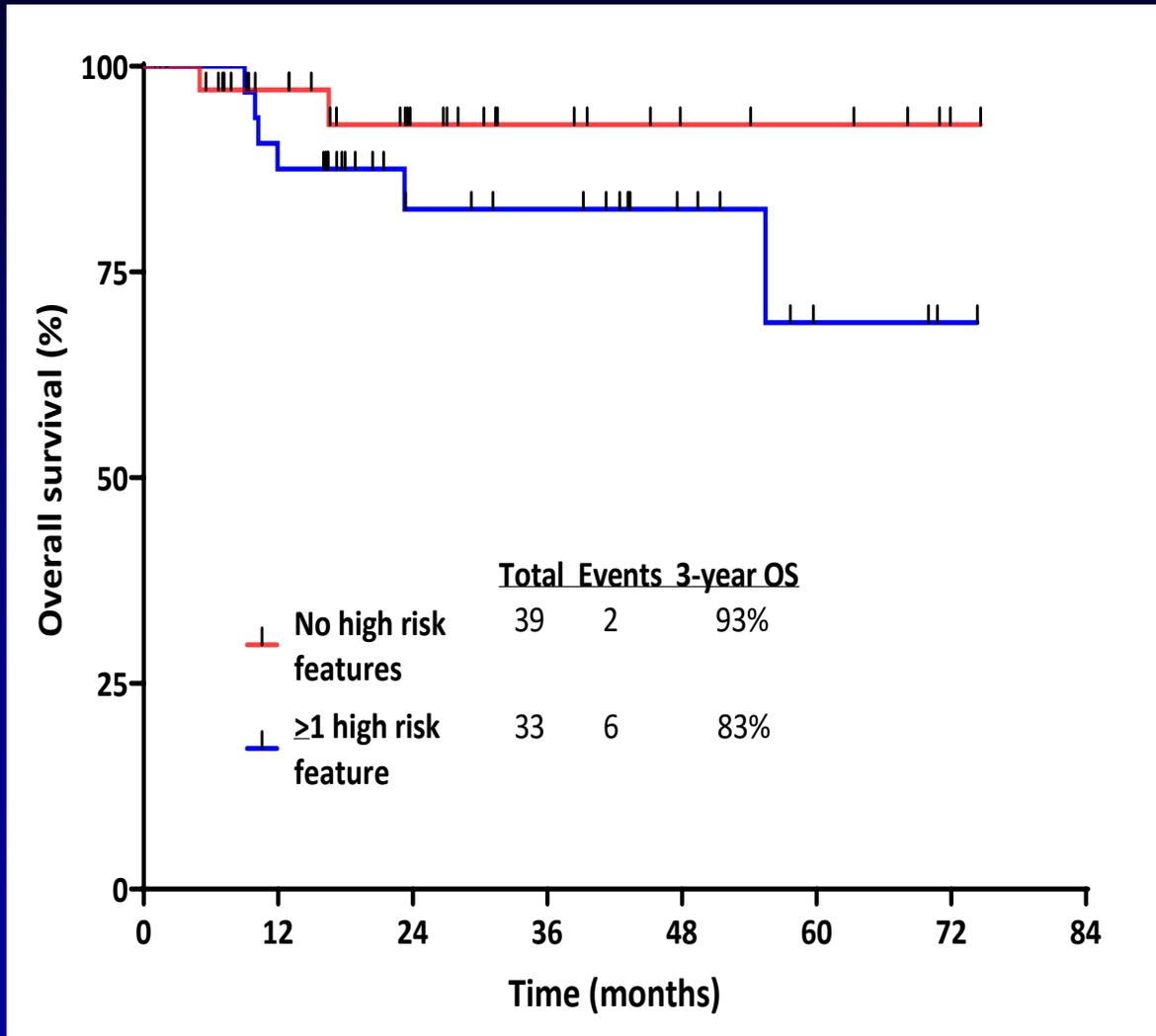
Hyper CVAD-Inotuzumab → Blinatumomab in Newly Dx Adult ALL

- 72 pts; median age 34 yrs (18-59).
- Rx with O-HCVAD x 4; Blinax4 → POMP 1 yr with blina Q3 mos; Ino 0.3 mg/m² D1&8 C2,4,6,8 (2.4 mg/m²)
- CR rate 100%; MRD negative 95% (69% at CR); NGS-MRD negative 74%; 60-day mortality 0%; 21 (32%) allo-SCT;

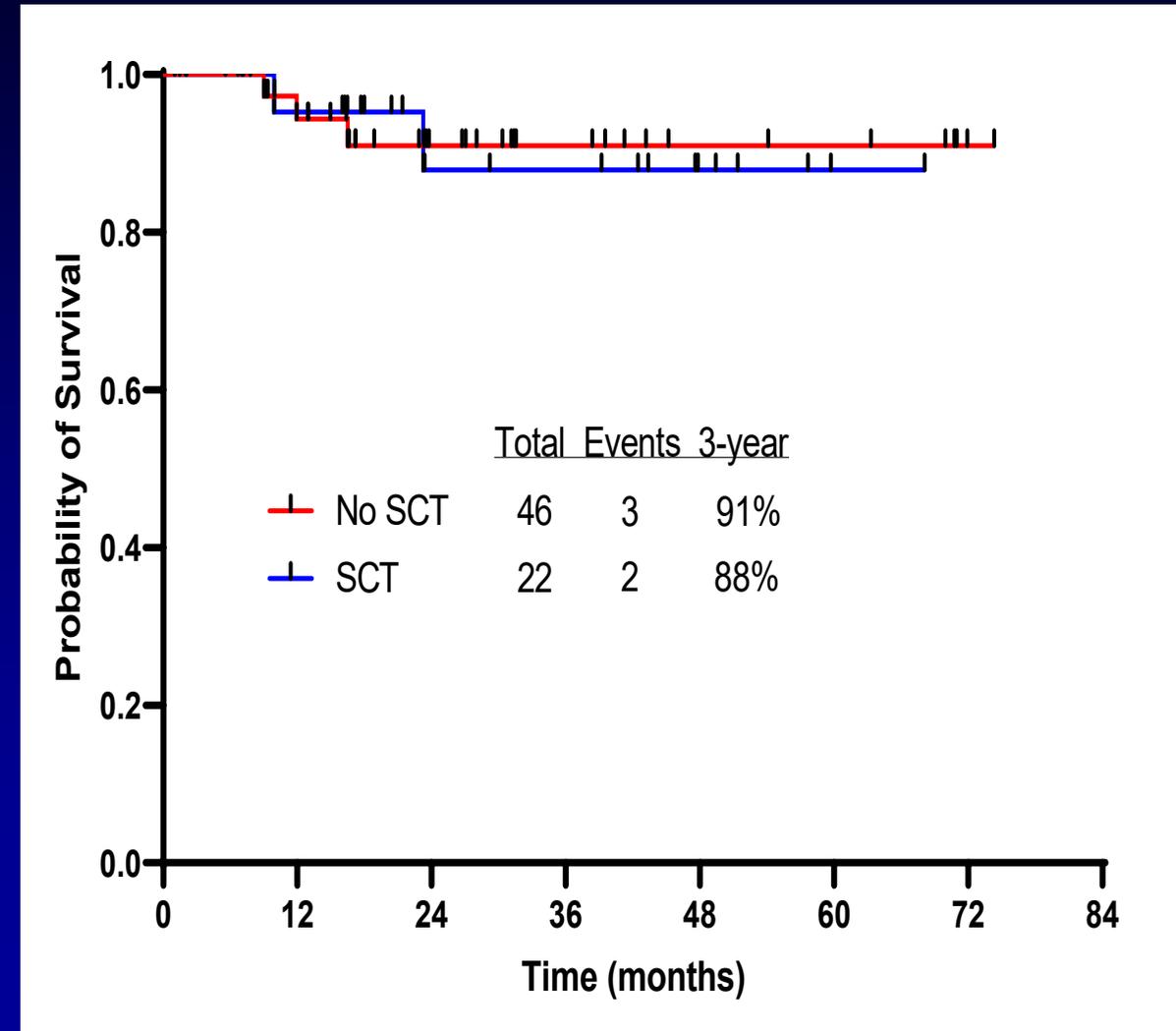


Hyper-CVAD + Blinatumomab + Inotuzumab in B-ALL

Outcome by ALL Risk



Outcome by ASCT (5-mo landmark)



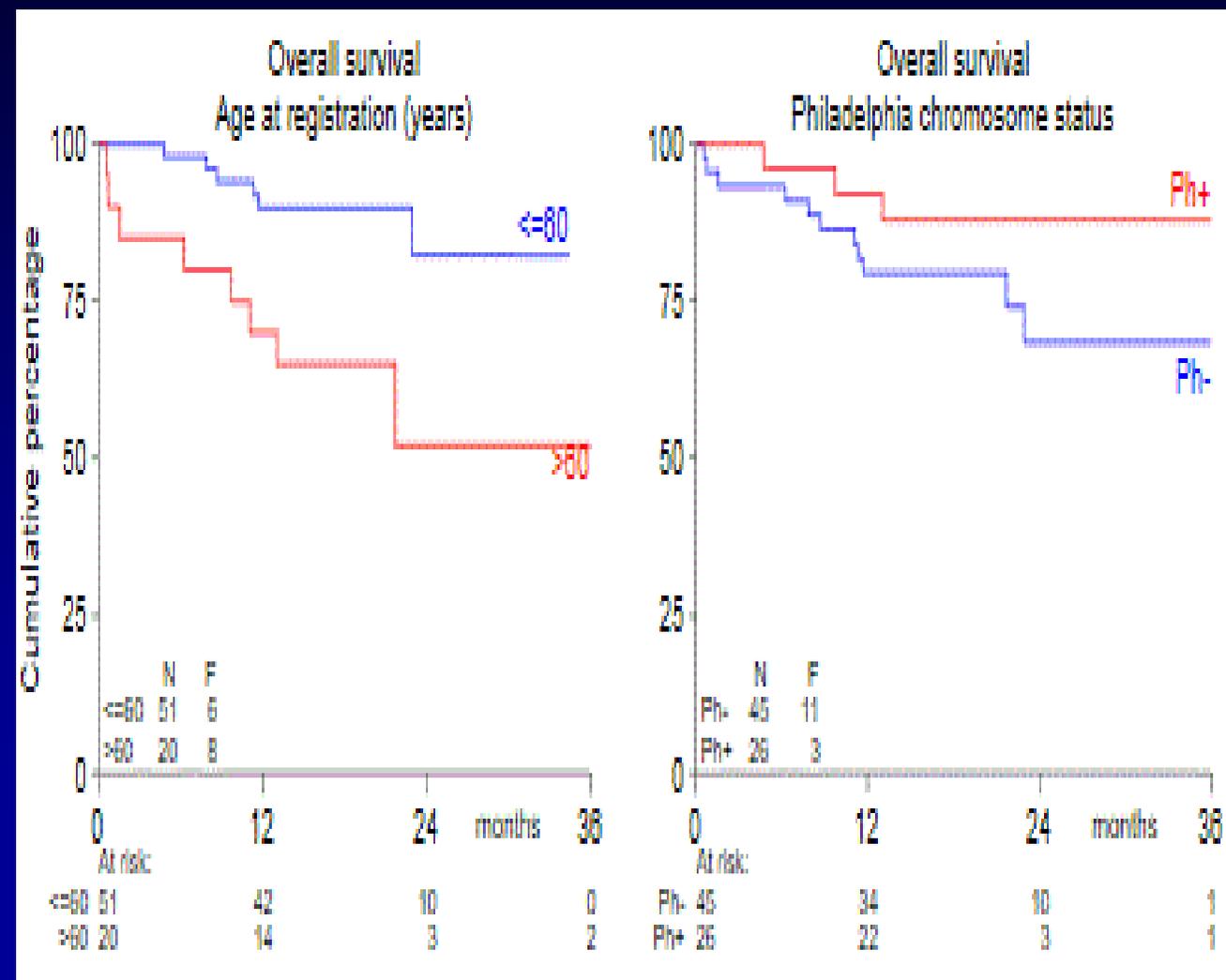
Frontline Blinatumomab and Inotuzumab Combinations in Adult Newly Dx ALL

	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)

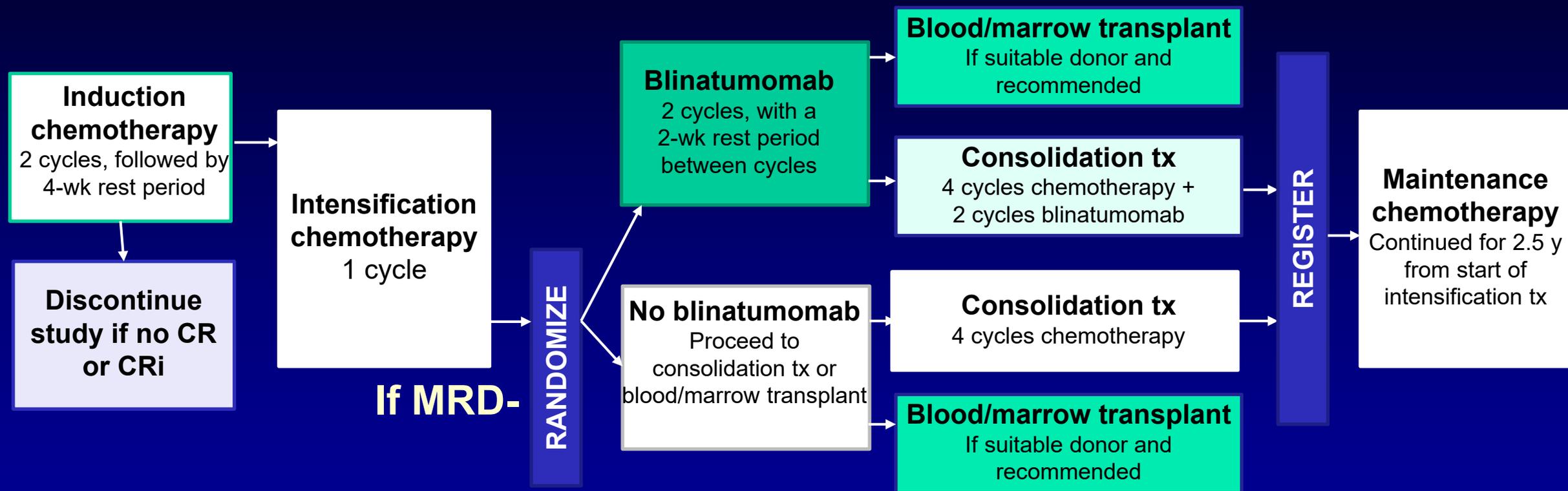
Blinatumomab Pre-phase then 2 Consolidations in ALL (HOVON)

- 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



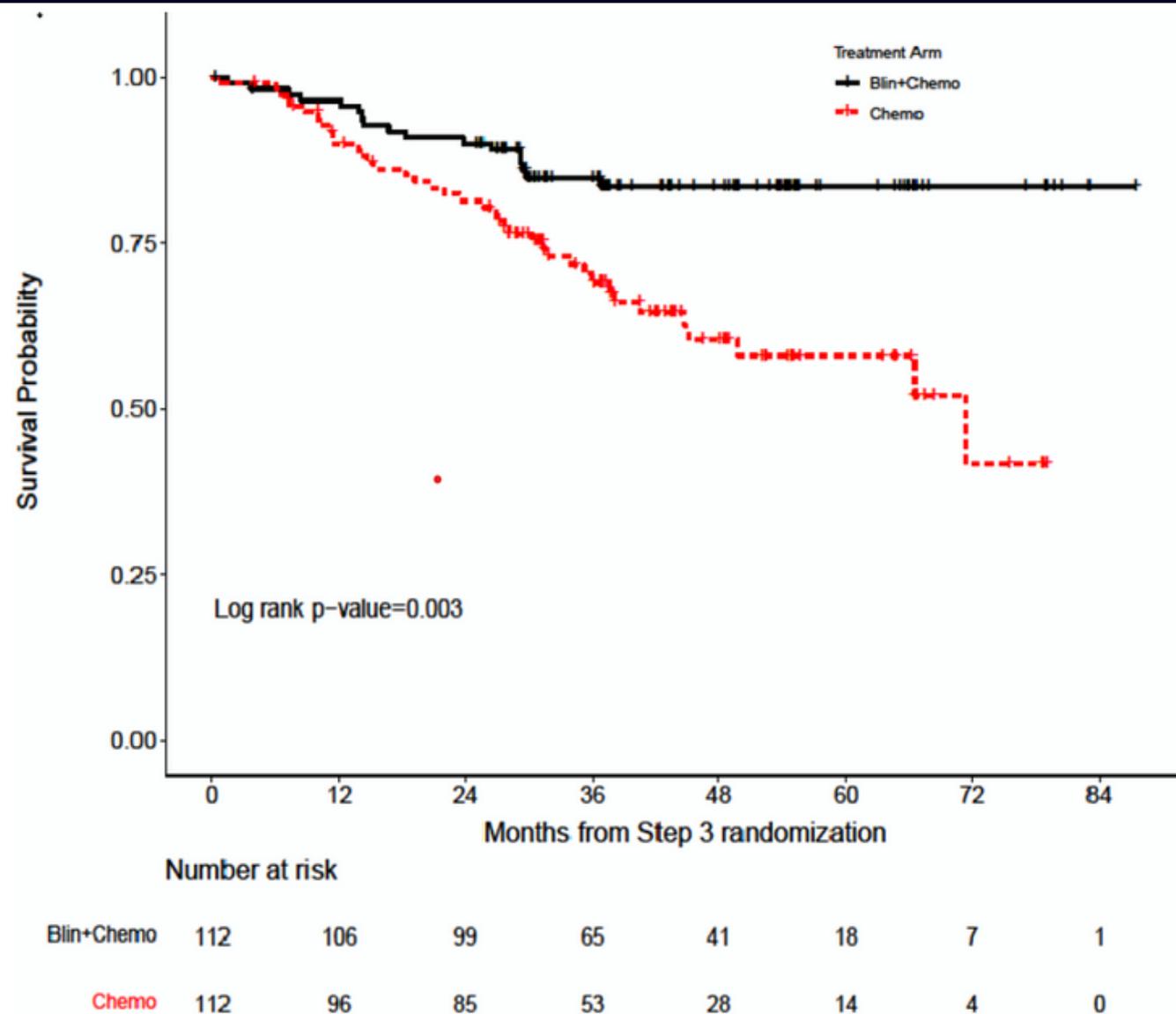
E1910: Randomized Phase 3 Trial: Blina vs SOC as Consolidation in MRD-Negative CR



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

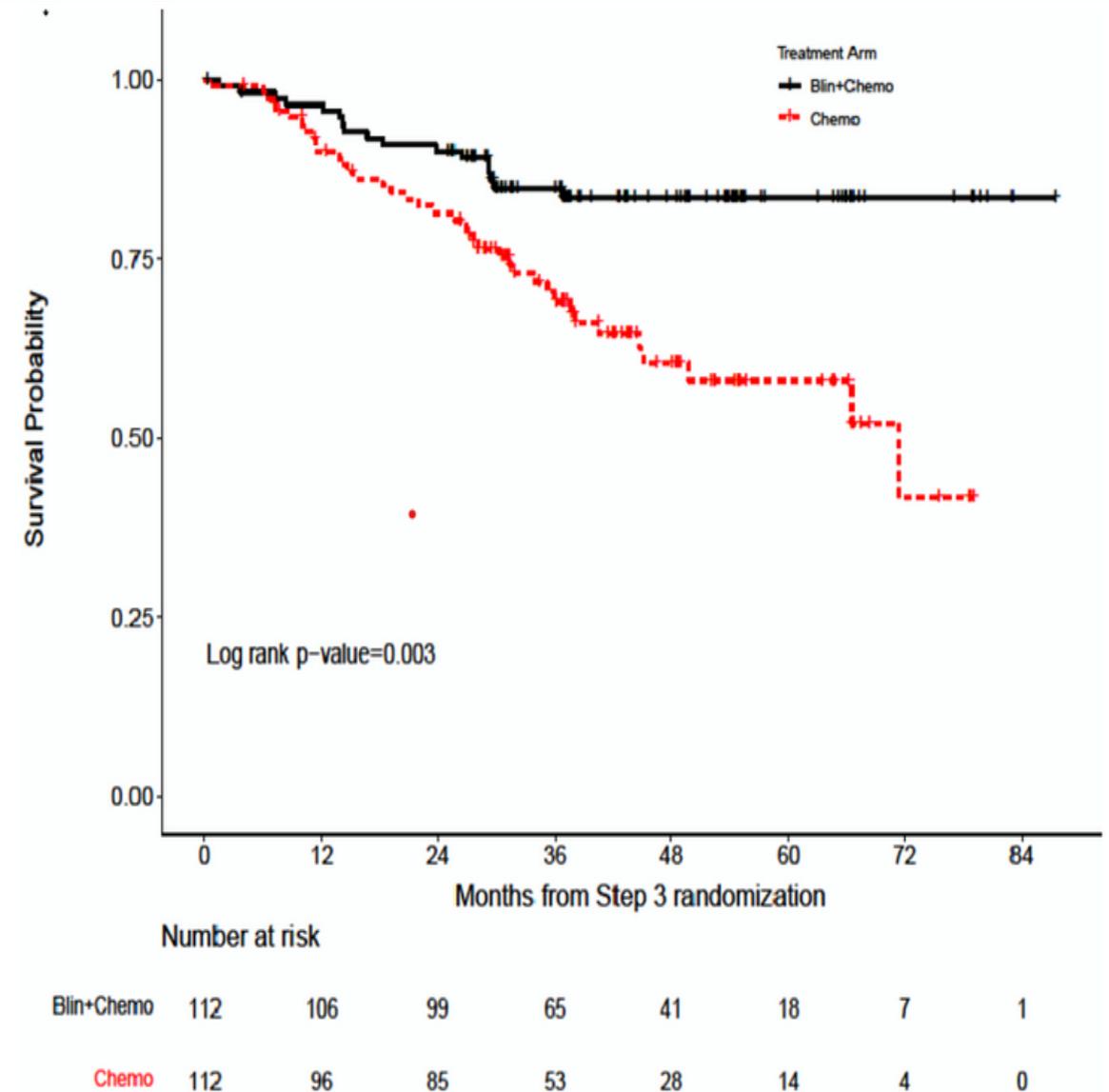
Adult Frontline ALL Rx-- E1910 Randomized Phase 3 Trial: Blin vs SOC Consolidation in MRD-Negative CR

- 488 pts median age 51 yrs (30-70)
- 224 MRD-negative CR randomized 1:1 to blina vs SOC
- 22 pts (20%) had allo SCT in each arm
- Median F/U 43 mos; median OS NR vs 71.4 mos (HR=0.42; p=0.003)

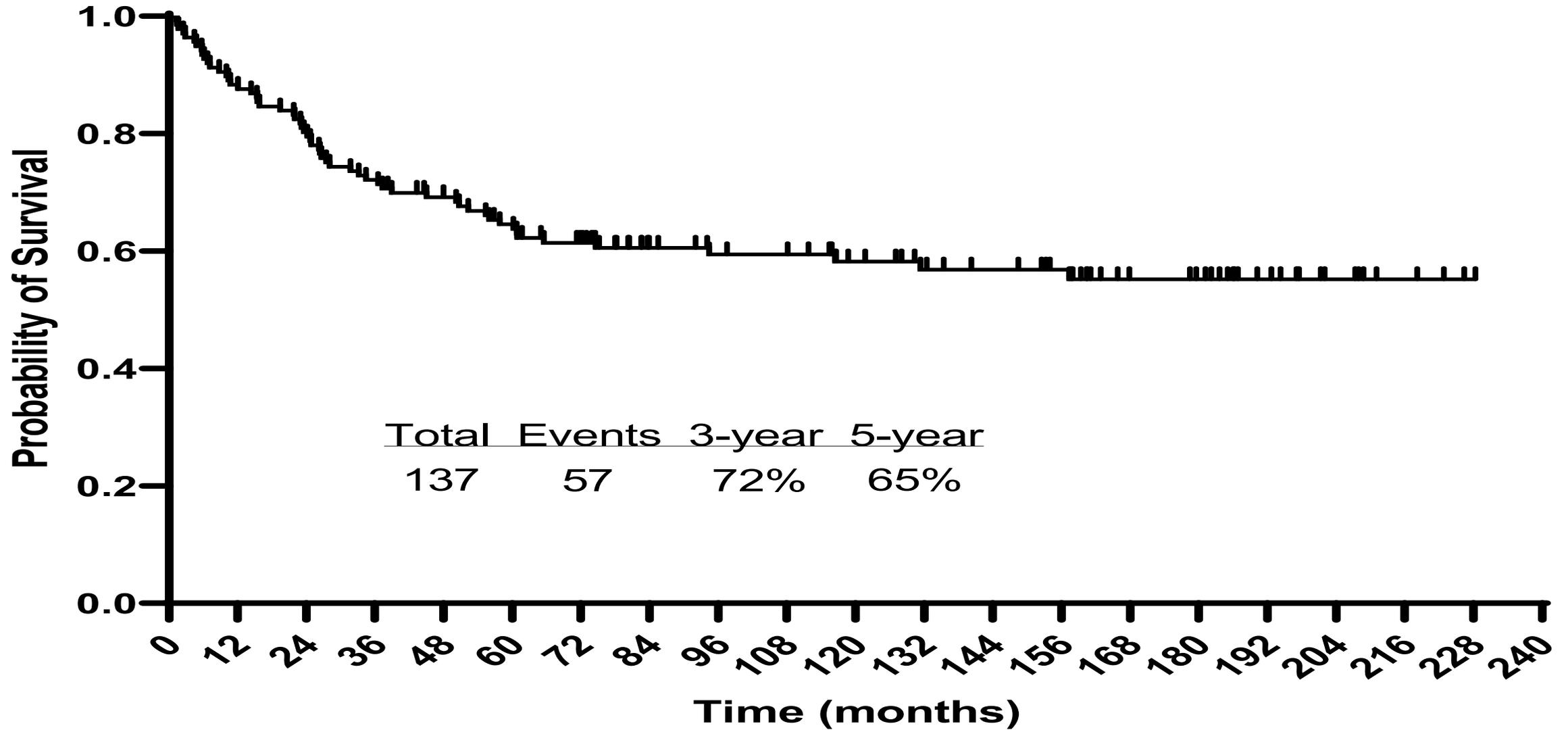


Adult Frontline ALL Rx-- E1910 Randomized Phase 3 Trial: Blin vs SOC Consolidation in MRD-Negative CR -- Discussion

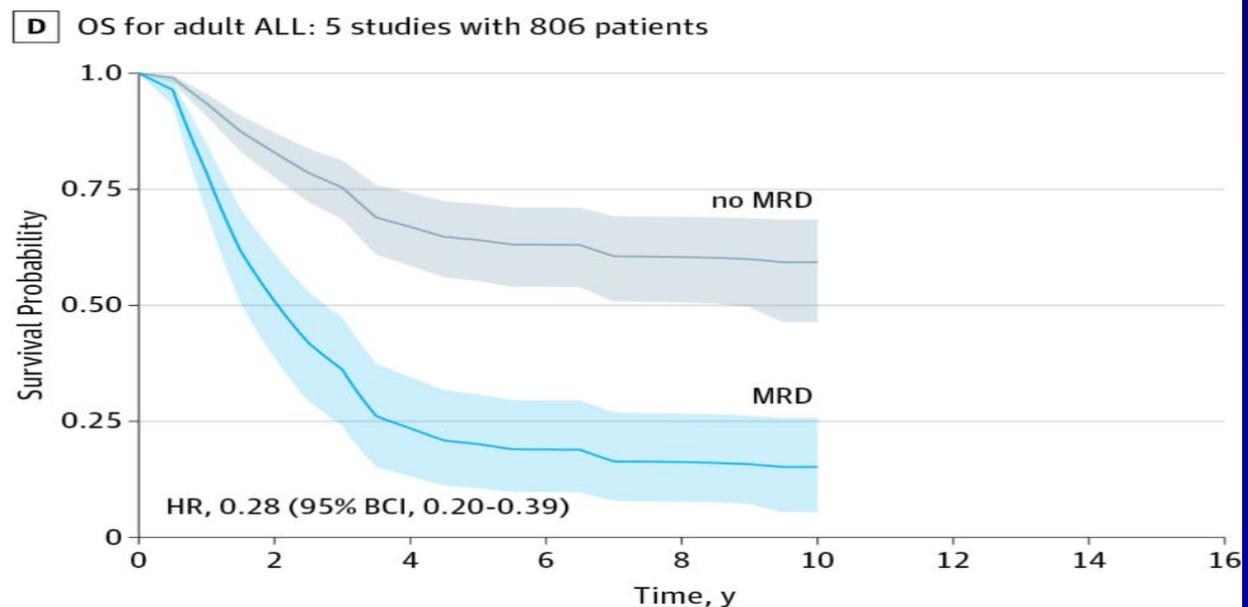
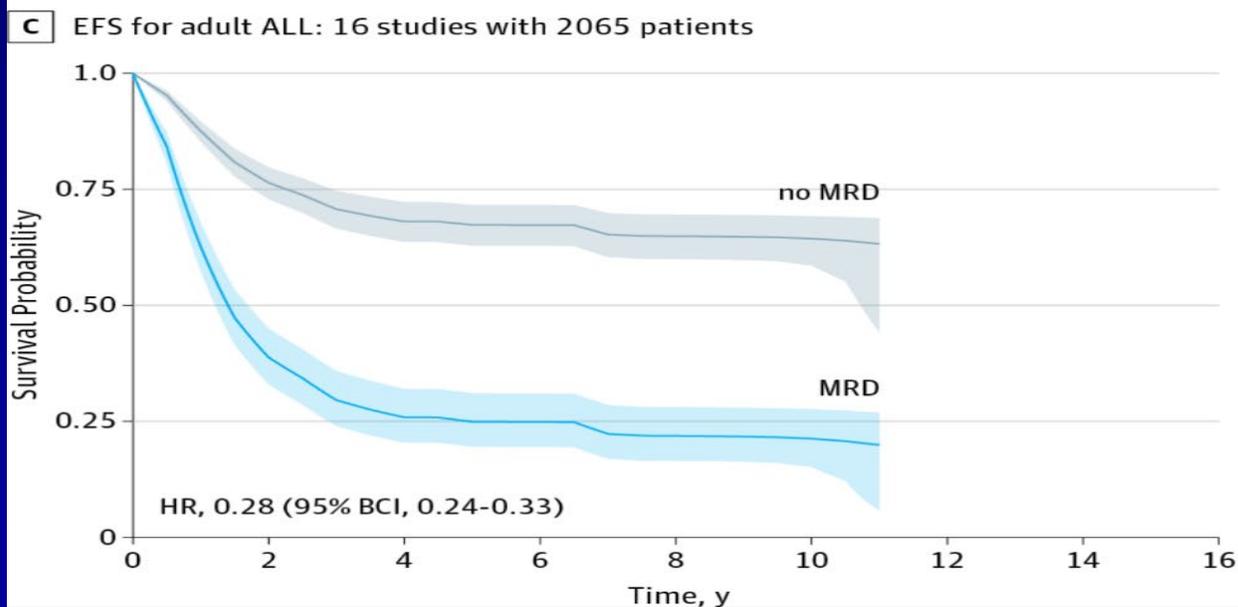
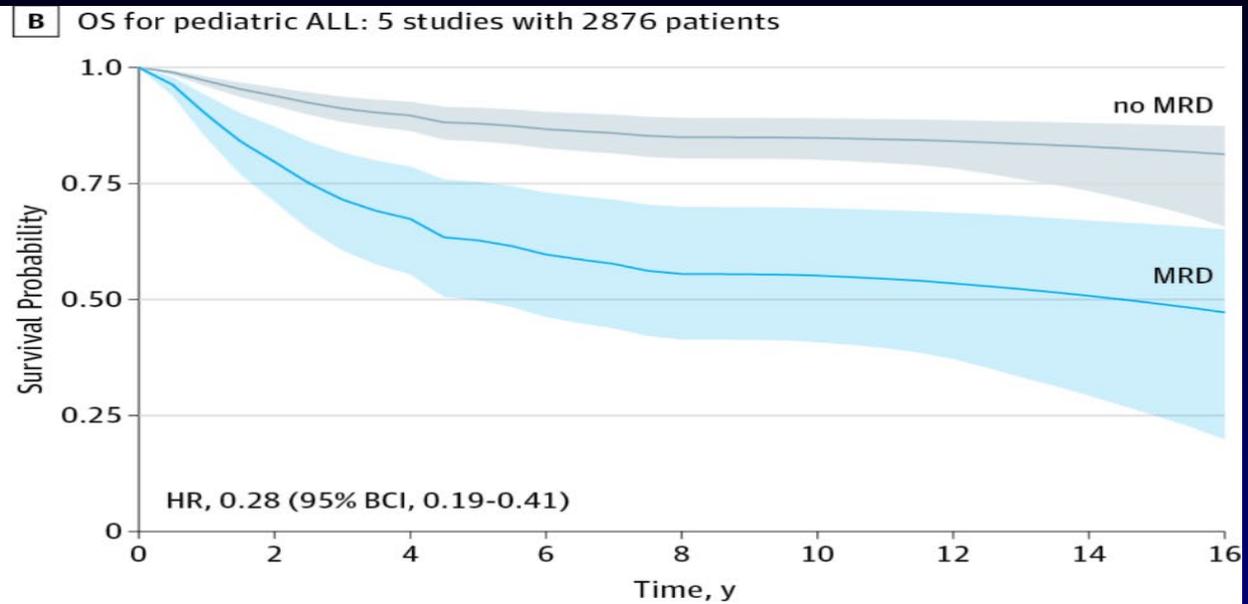
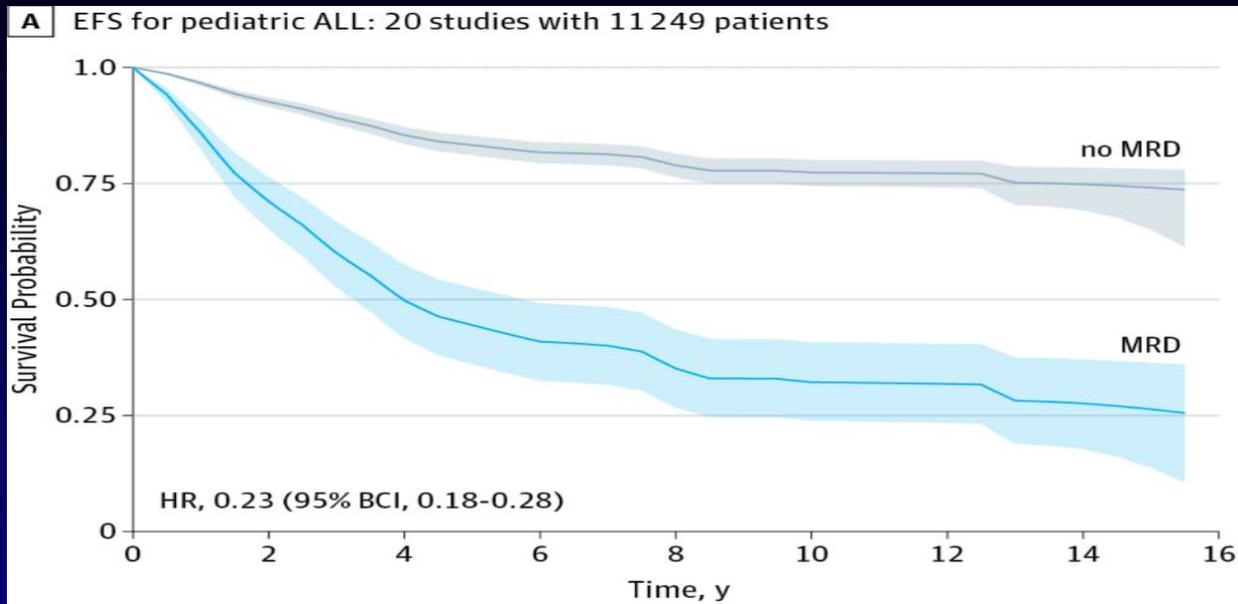
- Benefit even though MRD-MFC negative because many pts may have NGS-MRD at 1/million-1/10,000, and benefit
- Blinatumomab benefit in ALL in CR1 whether FMC-MRD + or –
- Control arm are pts who are MRD-negative (supposed to have OS>70+% with pediatric regimens). YET, 5-yr OS 55%



Hyper-CVAD-R/O: Outcomes of MRD-neg CR by 3 months

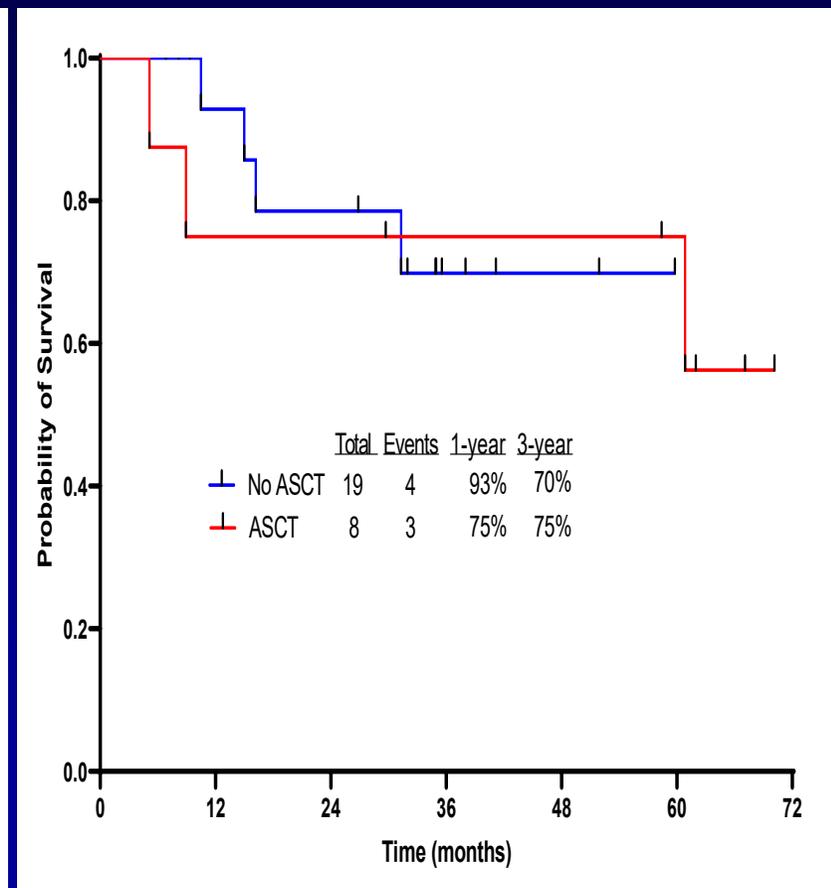
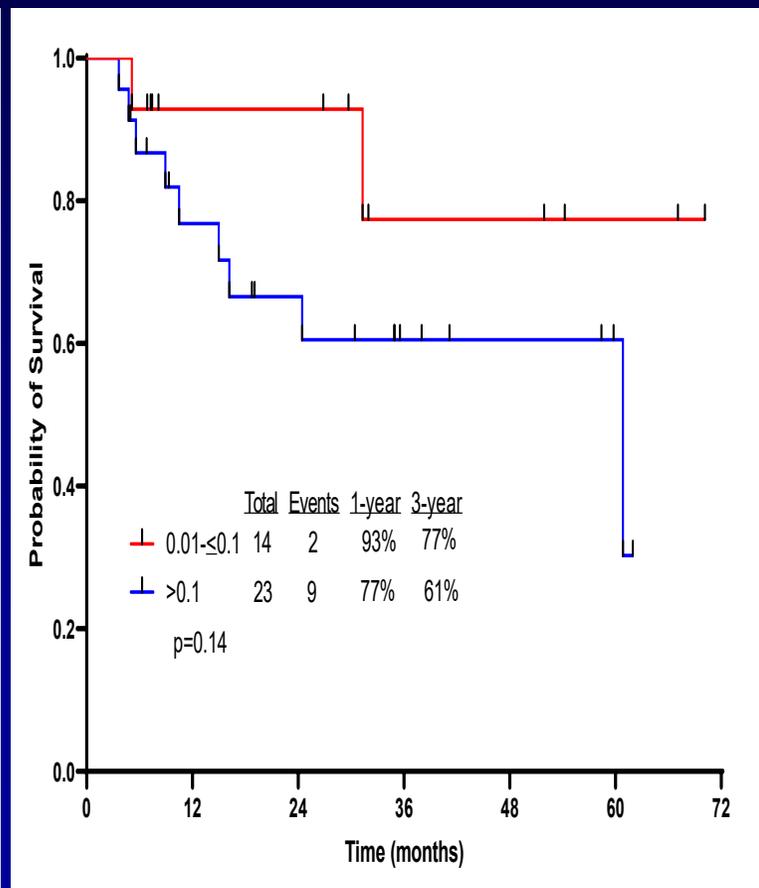
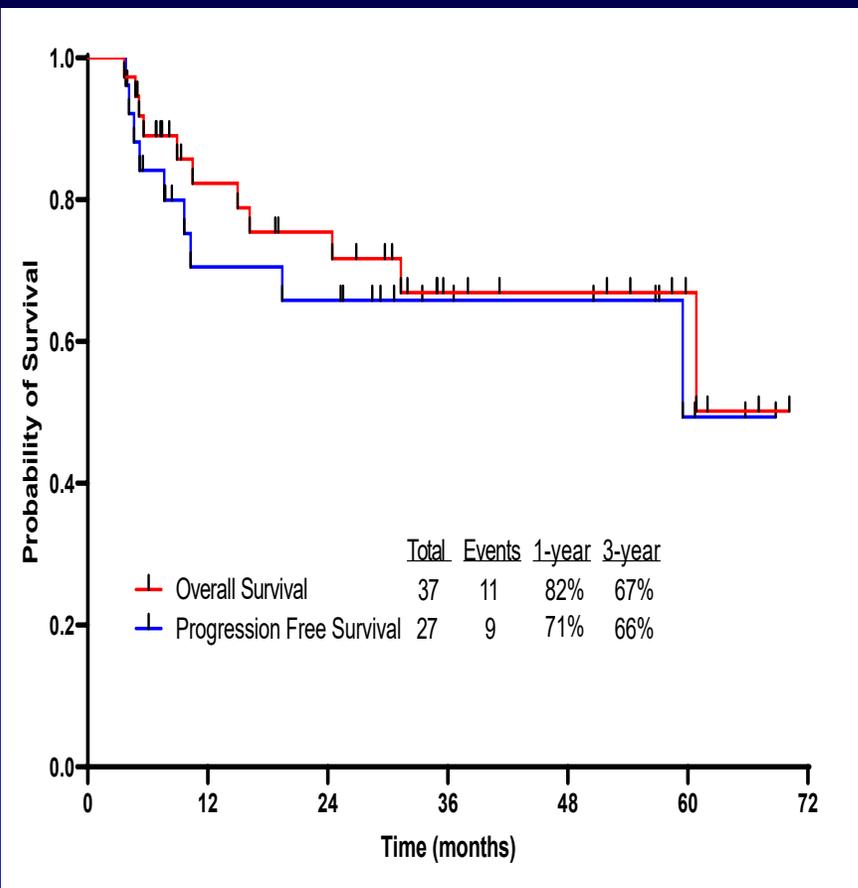


MRD in ALL



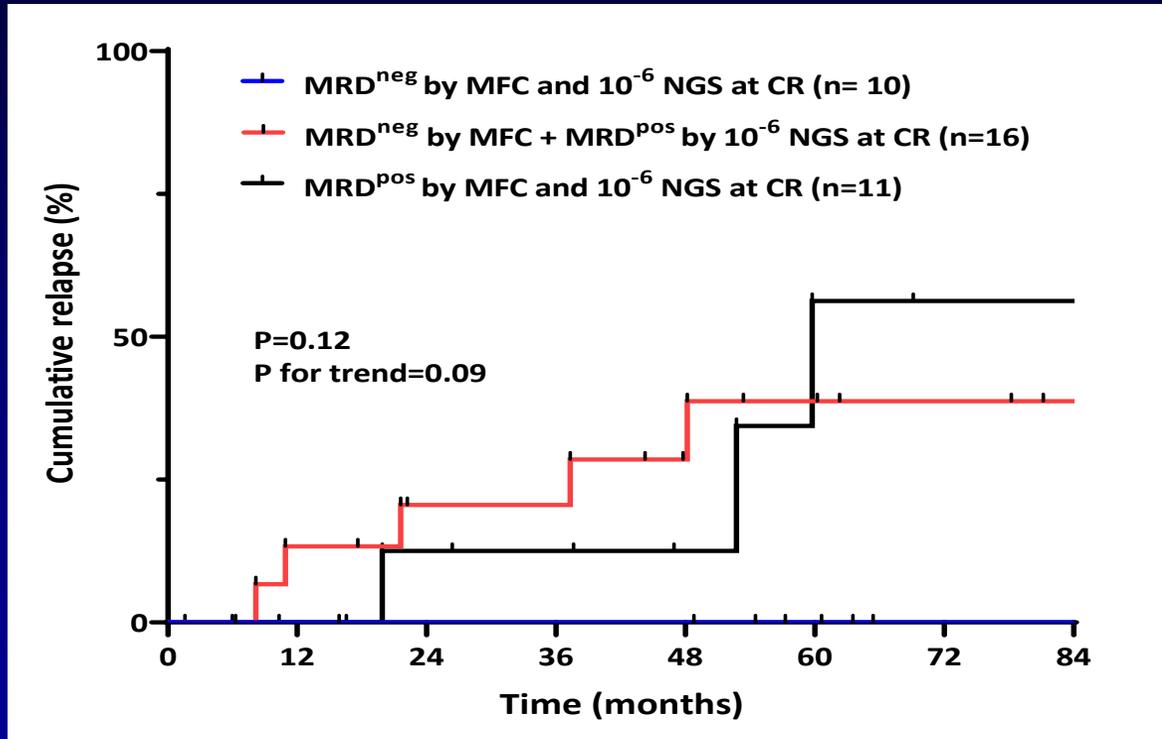
Blinatumomab for MRD-positive ALL in CR1/CR2+

- 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%



MRD in ALL. NGS vs FCM

- 74 pts Rx (66% HCVAD; 34% mini-hcvd)
- 32/84 (38%) discordant (i.e. MRD neg by MFC but MRDpos by NGS)
- MRDneg by NGS highly predictive at CR

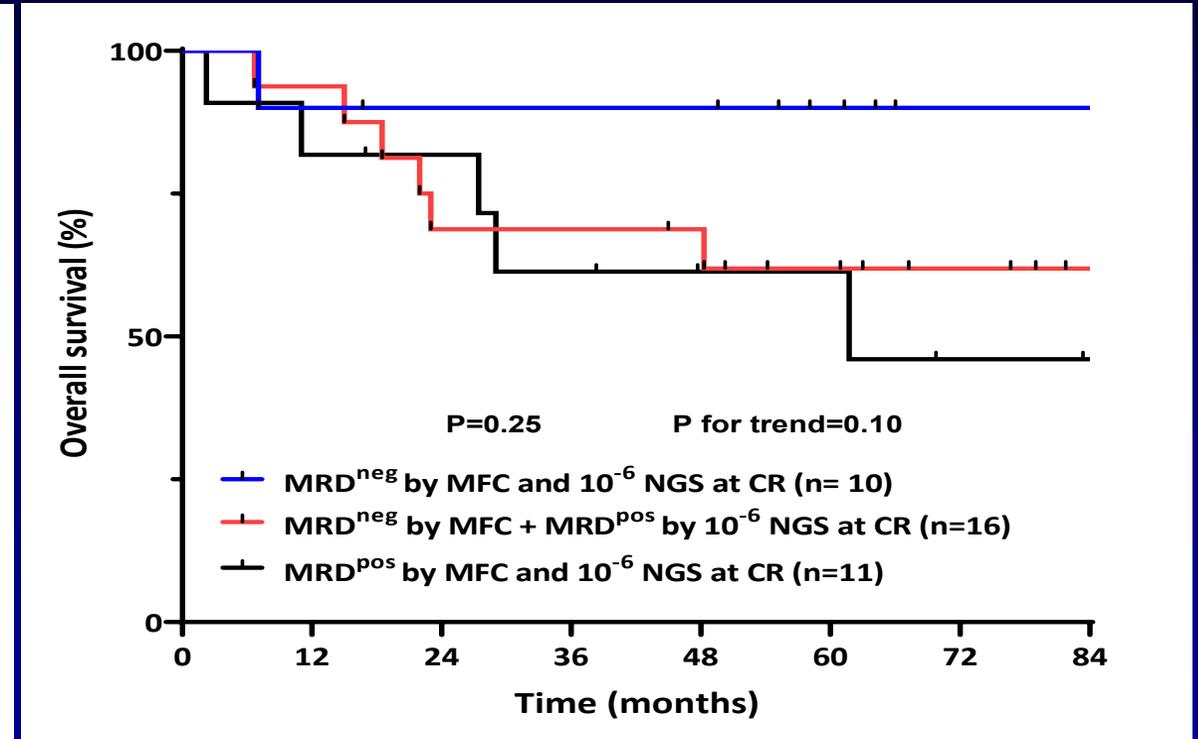


5-year CIR rates

MRD^{neg} by MFC and NGS: 0%

MRD^{neg} by MFC + MRD^{pos} by NGS: 39%

MRD^{pos} by MFC and NGS: 56%



5-year OS rates

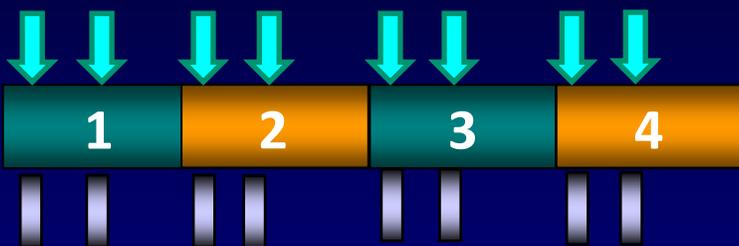
MRD^{neg} by MFC and NGS: 90%

MRD^{neg} by MFC + MRD^{pos} by NGS: 62%

MRD^{pos} by MFC and NGS: 61%

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

Intensive phase



Consolidation phase



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

Maintenance phase

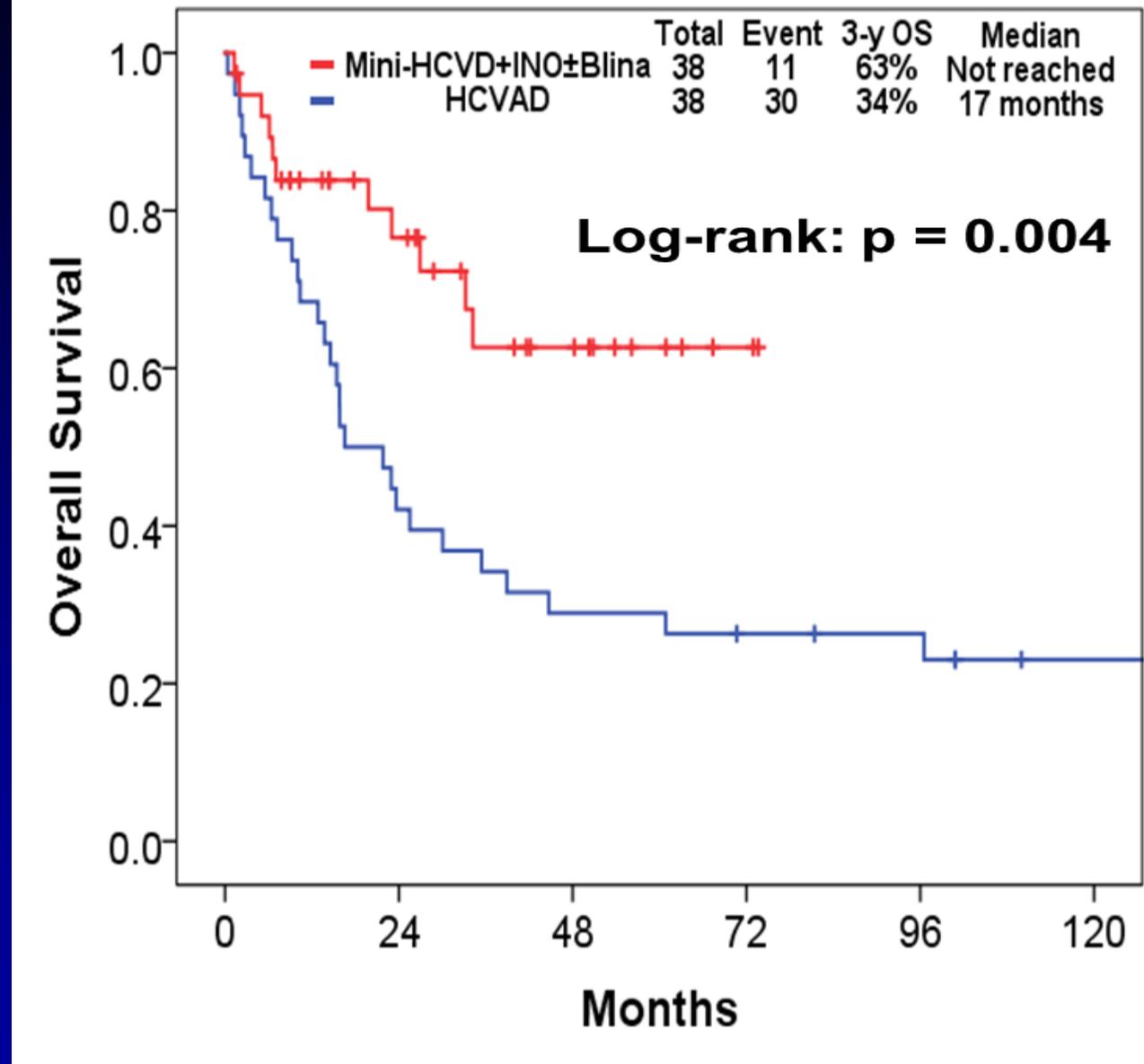
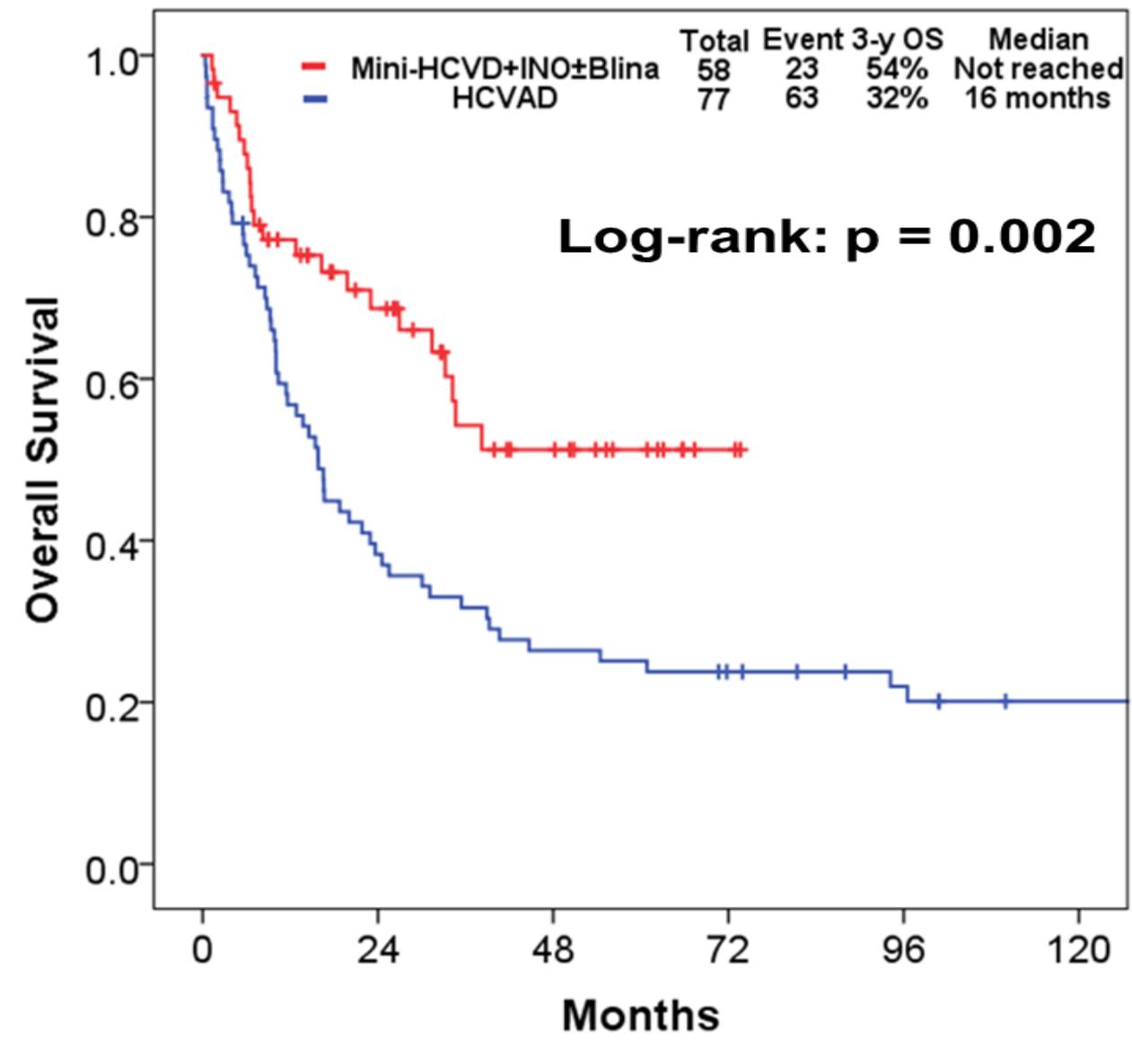


*Ursodiol 300mg tid for VOD prophylaxis

← 18 months →

Mini-HCVD + INO ± Blina vs. HCVAD 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	131	69 (55-84)	88	57	54 (2-yr)
GMALL Bold	Blinatumomab	34	65 (56-76)	76	69	89 (1-yr)
INITIAL-1	Inotuzumab	45	65 (56-80)	100	74	81 (2-yr)

ALL – Summary

- Ph-positive ALL – Ponatinib (dasatinib)-blinatumomab
- Antibody based Rxs and CARTs both outstanding. But uses different from FDA approvals
- Future of pre-B 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; 4) Monitor MRD by NGS (MRD in 1 million cells) to decide on Rx changes and Rx duration
- SQ easily deliverable BiTEs; CD20 BiTEs

Leukemia Questions?

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- **Office: 713-792-7026**