

Improved outcomes of acute lymphoblastic leukemia after allogeneic blood or marrow transplantation with high-dose post-transplantation cyclophosphamide in the era of more effective pre-transplant therapy

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Supplemental Methods

Conditioning

Conditioning regimens were defined as MAC or NMAC based on published definitions.¹ MAC consisted of busulfan and cyclophosphamide (Bu/Cy), cyclophosphamide and total body irradiation (Cy/TBI), or high-dose busulfan and fludarabine (Bu/Flu).² NMAC consisted of either fludarabine, cyclophosphamide and total body irradiation (Flu/Cy/TBI) or low-dose busulfan and fludarabine (Bu/Flu).³

References

1. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: Working definitions. *Biol Blood Marrow Transplant*. 2009;15(12):1628–1633.
2. Kanakry CG, Tsai HL, Bolanos-Meade J, et al. Single-agent GVHD prophylaxis with posttransplantation cyclophosphamide after myeloablative, HLA-matched BMT for AML, ALL, and MDS. *Blood*. 2014;124(25):3817–3827.
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Supplementary Table 1:
Additional demographic details for transplanted patients by era.

	2008-2014 (n=102)	2015-2022 (n=149)	p
BMI (Median, Range)	27.1 (18.2-55.2)	26 (14.6-48.8)	0.21
BMI			
<20	6 (5.9%)	8 (5.4%)	0.84
20-30	65 (63.7%)	101 (67.8%)	
30-35	18 (17.6%)	26 (17.4%)	
>35	13 (12.7%)	14 (9.4%)	
Race			
Asian	4 (3.9%)	16 (10.7%)	
Black or African American	10 (9.8%)	16 (10.7%)	
Other	9 (8.8%)	20 (13.4%)	
Other Pacific Islander	0	2 (1.3%)	
Unknown	1 (1%)	0	
White or Caucasian	78 (76.5%)	95 (63.8%)	
Ethnicity			
Hispanic	7 (6.8%)	19 (12.8%)	<0.0001
Non-Hispanic	63 (61.8%)	124 (83.2%)	
Unknown	32 (31.4%)	6 (4.0%)	

Supplementary Table 2: Details of transplant conditioning including total body irradiation doses by era.

	2008-2014 (n=102)	2015-2022 (n=149)
Conditioning Detail: MAC		
Bu/Cy	31 (30.4%)	4 (2.7%)
Cy/TBI 1200	14 (13.7%)	0
Bu/Flu	12 (11.8%)	0
Conditioning Detail: RIC		
Bu/Flu	1 (1.0%)	0
Flu/Cy/TBI 400	0	48 (32.2%)
Flu/Cy/TBI 200	44 (43.1%)	97 (65.1%)

Supplementary Table 3	1-year Graft Failure	GII-IV aGVHD at 1 year	GIII-IV aGVHD at 1 year	Mod-Sev cGVHD at 2 years
MAC	0%	34.4% (95% CI 23-46)	14.8% (95% CI 7-25)	14.8% (95% CI 7-25)
RIC	5.3% (95% CI 3-9)	24.7% (95% CI 19-31)	1.6% (95% CI 0-4)	10.0% (95% CI 6-15)
Conditioning Detail				
Bu/Cy	0%	34.3% (95% CI 19-50)	2.9 (95% CI 0-13)	11.4% (95% CI 4-24)
Flu/Cy/TBI 200	6.4% (95% CI 3-11)	25.5% (95% CI 19-33)	1.4% (95% CI 0-5)	10.7% (95% CI 6-16)
Cy/TBI 1200	0%	11.0% (95% CI 5-45)	21.4% (95% CI 5-45)	7.1% (95% CI 0-28)
Bu/Flu	0%	46.2% (95% CI 19-70)	38.5% (95% CI 14-63)	30.8% (95% CI 10-55)
Flu/Cy/TBI 400	2.1% (95% CI 0-10)	22.9% (95% CI 12-35)	2.1% (95% CI 0-10)	8.3% (95% CI 3-18)
Donor				
MSD	0%	22.0% (95% CI 12-34)	12.0% (95% CI 5-23)	12.0% (95% CI 5-23)
MUD	0%	34.2% (95% CI 20-49)	5.3% (95% CI 0-16)	13.2% (95% CI 5-26)
Haplo	6% (95% CI 3-11)	27.3% (95% CI 20-35)	2.7% (95% CI 1-6)	10.7% (95% CI 6-16)
mMUD	7.7% (95% CI 0-29)	23.1% (95% CI 6-47)	0%	7.7% (95% CI 0-29)
BMT	5.2% (95% CI 3-9)	28.7% (95% CI 22-35)	5.7% (95% CI 3-10)	9.9% (95% CI 6-15)
PBSCT	0%	22.0% (95% CI 13-33)	1.7% (95% CI 0-8)	15.3% (95% CI 8-26)
2008-2014	4.9% (95% CI 2-10)	31.4% (95% CI 23-40%)		12.8% (95% CI 7-20%)
2015-2022	3.4% (95% CI 1-7)	24.2% (95% CI 18-31%)	2.7% (95% CI 1-6%)	10.1% (95% CI 6-16%)

Supplementary Table 3: Incidence of graft failure, Grade II-IV acute GVHD, Grade III-IV acute GVHD, and moderate-to-severe chronic GVHD by subgroups.

MVA2 OS:				
	HR	lowbd	upbd	p.value
I.year.bmt.2014	0.452	0.282	0.726	0.001
age.per10	1.365	1.141	1.632	0.001
factor(I.php.phn.t)1	1.561	0.938	2.596	0.086
factor(I.php.phn.t)2	1.602	0.769	3.336	0.208
I.mrd	2.262	1.242	4.119	0.008
I.hctci.3	1.720	0.956	3.096	0.070
I.notcr1	1.618	0.895	2.924	0.111

HCTCI: 4+ vs 0-3

CR status: not CR1 vs. CR1

MVA2 Relapse:				
	SDHR	lowbd	upbd	p.value
I.year.bmt.2014	0.473	0.286	0.782	0.004
age.per10	0.987	0.811	1.202	0.900
I.mrd	2.145	1.133	4.061	0.019
dumm.dis.phn	1.528	0.853	2.738	0.150
dumm.dis.t	1.951	0.916	4.156	0.083
I.hctci.3	0.465	0.177	1.217	0.120
I.notcr1	1.821	0.947	3.499	0.072

MVA2 RFS:				
	HR	lowbd	upbd	p.value
I.year.bmt.2014	0.455	0.299	0.691	0.000
age.per10	1.175	1.002	1.378	0.047
factor(I.php.phn.t)1	1.418	0.891	2.256	0.141
factor(I.php.phn.t)2	1.620	0.852	3.080	0.141
I.mrd	1.811	1.061	3.089	0.029
I.hctci.3	1.525	0.884	2.630	0.130
I.notcr1	1.868	1.112	3.136	0.018

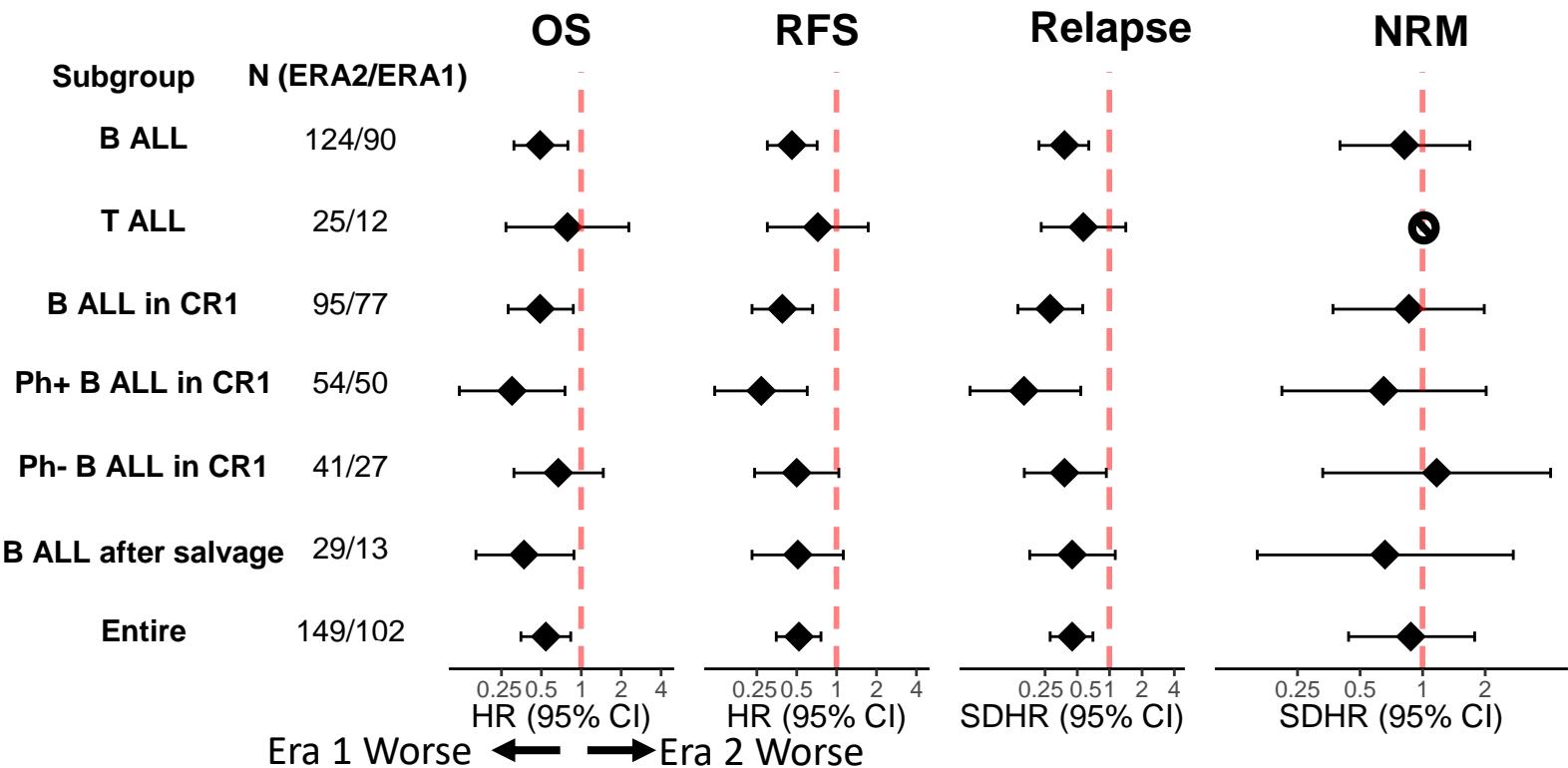
MVA2 NRM:				
	SDHR	lowbd	upbd	p.value
I.year.bmt.2014	0.554	0.248	1.235	0.150
age.per10	1.612	1.106	2.351	0.013
I.mrd	0.474	0.090	2.501	0.380
dumm.dis.phn	1.078	0.470	2.473	0.860
dumm.dis.t	0.668	0.129	3.464	0.630
I.hctci.3	3.452	1.438	8.291	0.006
I.notcr1	1.624	0.560	4.710	0.370

Supplementary Tables 4: Multivariate analysis of OS, RFS, relapse incidence, and non-relapse mortality including clinically significant variables: transplant in ERA1 vs. ERA2, age by 10 years, Ph+ ALL vs. T ALL, Ph+ ALL vs. Ph- B ALL, MRD, HCT-CI 0-3 vs. 4+, and CR1 without salvage vs. transplant after salvage.

Supp Table 5	HR OS	HR RFS	HR CIR	HR NRM
Diagnosis vs. Ph+ ALL (n=113)				
Ph- B ALL (n=101)	1.47 (0.93-2.32), p=0.1	1.48 (0.97-2.25), p=0.07	1.64 (0.98-2.76), p=0.06	1.01 (0.49-2.07), p=0.98
T ALL (n=37)	1.67 (0.91-3.08), p=0.1	1.98 (1.17-3.36), p=0.01	2.97 (1.66-5.31), p=0.0002	0.38 (0.09-1.65), p=0.20
B v. T ALL	0.72 (0.41-1.26), p=0.25	0.61 (0.38-0.99), p=0.04	0.43 (0.26-0.72), p=0.001	2.63 (0.63-10.97), p=0.18
Age vs. <40 (n=81)				
40-54 (n=86)	1.04 (0.59-1.81), p=0.13	0.74 (0.46-1.19), p=0.21	0.75 (0.45-1.26), p=0.28	0.91 (0.26-3.16), p=0.89
>55 (n=84)	1.84 (1.10-3.08), p=0.02	1.07 (0.68-1.67), p=0.78	0.51 (0.29-0.91), p=0.02	4.76 (1.77-12.82), p=0.002
MRD+ (n=33) vs. MRD- (n=216)	3.13 (1.94-5.05), p<0.0001	2.90 (1.85-4.56), p<0.0001	4.16 (2.56-6.74), p<0.0001	0.42 (0.10-1.77), p=0.24
CR Status vs. CR1 (n=186)				
CR1 after salvage (n=15)	1.13 (0.41-3.13), p=0.81	1.33 (0.58-3.05), p=0.51	1.64 (0.62-4.39), p=0.32	0.54 (0.07-4.14), p=0.55
CR2+/No CR (n=50)	2.61 (1.65-4.12), p<0.0001	2.92 (1.92-4.42), p<0.0001	3.16 (1.95-5.13), p<0.0001	1.16 (0.50-2.69), p=0.73
HCT-Cl vs. 0 (n=68)				
1-3 (n=138)	1.54 (0.91-2.61), p=0.11	1.52 (0.95-2433), p=0.08	1.32 (0.79-2.21), p=0.29	2.00 (0.68-5.88), p=0.21
4+ (n=40)	1.97 (1.01-3.84), p=0.05	1.65 (0.89-3.04), p=0.11	0.49 (0.20-1.23), p=0.13	6.95 (2.30-21.02), p=0.001
MAC (n=61) v. RIC (n=190)	1.55 (1.00-2.42), p=0.05	1.46 (0.97-2.20), p=0.07	1.55 (0.96-2.49), p=0.07	1.10 (0.50-2.43), p=0.81
2015-2022 (n=149) vs 2008-2014 (n=102)	0.54 (0.35-0.83), p=0.005	0.52 (0.35-0.76), p=0.001	0.45 (0.28-0.70), p=0.0005	0.88 (0.44-1.78), p=0.73
PBSCT vs. BMT(n=191)	1.19 (0.72-1.98), p=0.49	0.99 (0.62-1.57), p=0.97	0.68 (0.37-1.25), p=0.22	1.74 (0.83-3.68), p=0.15
Donor vs Haplo (n=150)				
MSD (n=50)	0.73 (0.41-1.27), p=0.26	0.84 (0.52-1.37), p=0.49	0.98 (0.56-1.73), p=0.95	0.64 (0.24-1.67), p=0.36
MUD (n=38)	0.86 (0.49-1.52), p=0.60	0.72 (0.41-1.26), p=0.25	0.84 (0.43-1.61), p=0.59	0.63 (0.22-1.83), p=0.40
mMUD (n=13)	0.19 (0.03-1.35), p=0.10	0.28 (0.07-1.15), p=0.08	0.22 (0.03-1.53), p=0.13	0.55 (0.08-4.00), p=0.56

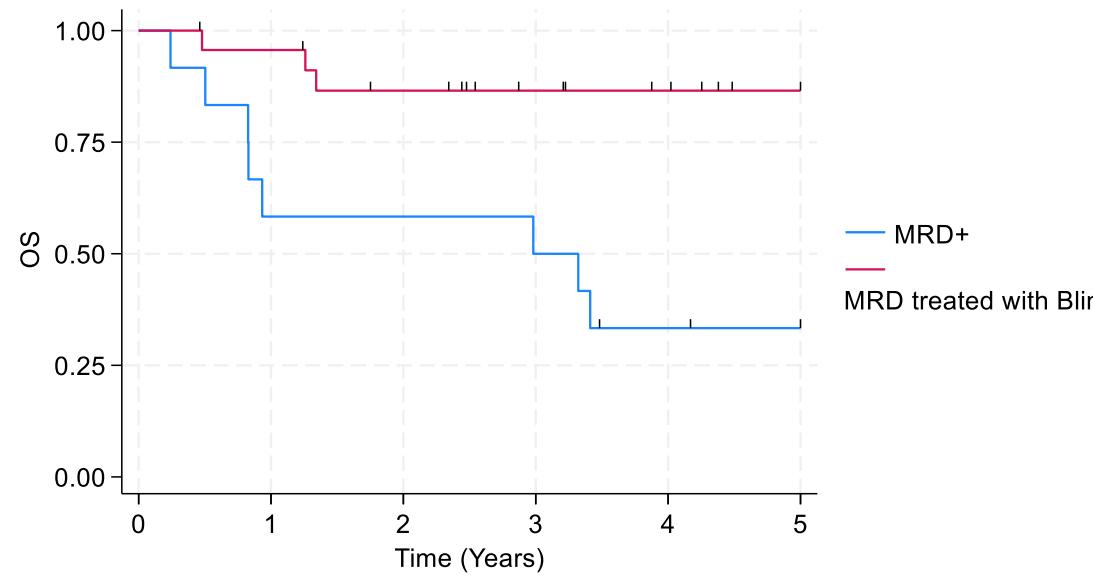
Supplementary Table 5: HR for OS, RFS, relapse (CIR), and NRM by subgroup.

Supplementary Figure 1: Forest plot comparing OS, RFS, relapse incidence and NRM across eras by disease subtype and remission status at transplant.

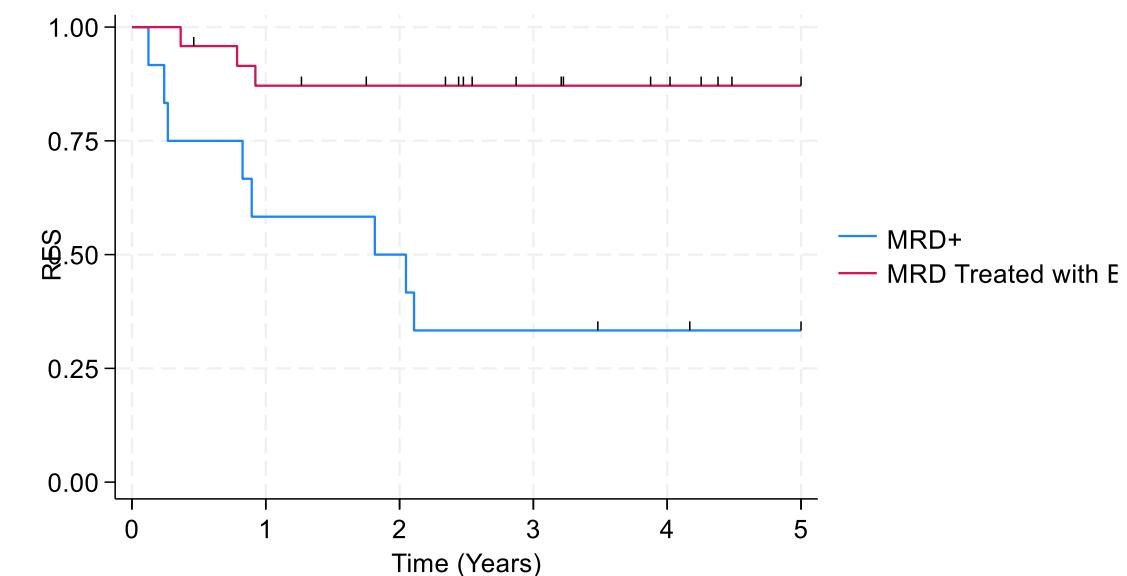


Supplementary Table 6:
Demographics and transplant characteristics by receipt of pre-transplant blinatumomab for B ALL patients transplanted in CR1.

CR1 B ALL	All (N=172)	No Blina (n=141)	Blini (n=31)	p
Age (Median, Range)	49.4 (20.4-73.6)	49.8 (20.4-73.6)	46.3 (27.2-73.1)	0.76
Age				
<40	45 (26.2%)	36 (25.5%)	9 (29.0%)	0.92
40-54	63 (36.6%)	52 (36.9%)	11 (35.5%)	
>55	64 (37.2%)	53 (37.6%)	11 (35.5%)	
Male Gender (Percent)	85 (49.4%)	68 (48.2%)	17 (54.8%)	0.55
Ph Status				
Ph+	104 (60.4%)	90 (63.8%)	14 (45.2%)	0.07
Ph-	68 (39.5%)	51 (36.2%)	17 (54.8%)	
MRD+	11/171 (6.4%)	11/140 (7.9%)	0 (0%)	0.22
HCT-CI	N=169	N=139	N=30	
0	41 (24.3%)	35 (25.2%)	6 (20%)	0.83
1-4	113 (66.9%)	92 (66.2%)	21 (70%)	
5+	15 (8.9%)	12 (8.6%)	3 (10%)	
Myeloablative Conditioning	44 (25.6%)	44 (31.2%)	0 (0%)	0.0001
PBSCT	30 (17.4%)	18 (12.8%)	12 (38.7%)	0.003
2008-2014	77 (44.8%)	77 (54.6%)	0 (0%)	0.0001
Blina Indication				
Frontline	1 (0.5%)	N/A	1 (3.2%)	
MRD+	24 (14.0%)	N/A	24 (77.4%)	
MRD-	6 (3.5%)	N/A	6 (19.4%)	

A

Number at risk						
ivedblinatumomab = 0	12	7	7	6	3	2
ivedblinatumomab = 1	24	22	18	13	9	6

B

Number at risk						
ivedblinatumomab = 0	12	7	6	4	3	2
ivedblinatumomab = 1	24	20	18	13	9	6

C

	5-year OS	5-year RFS	5-year CIR	5-year NRM
MRD+	31.8% (95% CI 9-58)	33.3% (95% CI 10-59)	58.3% (95% CI 27-80)	8.3% (95% CI 1-31)
MRD Treated with Blina Pre-Transplant	86.6% (95% CI 64-95)	87.2% (95% CI 65-96)	12.9% (95% CI 3-29)	0

D

	HR OS	HR RFS	HR CIR	HR NRM
Blina-treated vs. MRD+	0.16 (0.04-0.62), p=0.008	0.14 (0.04-0.55), p=0.004	0.18 (0.05-0.66), p=0.01	-

Supplementary Figure 2: A. OS for B ALL patients transplanted in CR1 comparing those transplanted with persistent MRD vs. those who received blinatumomab for persistent MRD prior to transplant. B. RFS for B ALL patients transplanted in CR1 comparing those transplanted with persistent MRD vs. those who received blinatumomab for persistent MRD prior to transplant. C. Table of 5-year OS, RFS, relapse incidence, and NRM for B ALL patients in CR1 transplanted with persistent MRD vs. those who received blinatumomab for persistent MRD prior to transplant. D. HRs for OS, RFS, and relapse for B ALL patients in CR1 transplanted with persistent MRD vs. those who received blinatumomab for persistent MRD prior to transplant.

Supplementary Table 7:
Demographics and transplant characteristics by receipt of pre-transplant TKI for Ph+ B ALL patients transplanted in CR1.

CR1 Ph+ B ALL	All (N=104)	Imatinib at Dx (n=32)	2 nd or 3 rd gen TKI at Dx (n=72)	p
Age (Median, Range)	49.4 (21.0-72)	49.7 (25-71.9)	47.9 (21-72)	0.82
Age				
<40	27 (26.0%)	8 (25.0%)	19 (26.4%)	0.63
40-54	42 (40.4%)	15 (46.9%)	27 (37.5%)	
>55	35 (33.7%)	9 (28.1%)	26 (36.1%)	
Male Gender (Percent)	45 (43.3%)	11 (34.4%)	34 (47.2%)	0.28
Received Blina	14 (13.5%)	1 (3.1%)	13 (18.1%)	0.06
MRD+	8/103 (7.8%)	2/31 (6.5%)	6 (8.3%)	0.72
HCT-CI	N=102	N=32	N=70	
0	30 (29.4%)	10 (31.3%)	20 (28.6%)	0.93
1-4	61 (59.8%)	19 (59.4%)	42 (60.0%)	
5+	11 (10.8%)	3 (9.4%)	8 (11.4%)	
Myeloablative Conditioning	27 (26.0%)	16 (50.0%)	11 (15.3%)	0.0005
PBSCT	18 (17.3%)	1 (3.1%)	17 (23.6%)	0.01
2008-2014	50 (48.1%)	28 (87.5%)	22 (30.6%)	0.0001
TKI at Diagnosis				
Imatinib	32 (30.8%)	32 (100%)		
Dasatinib	62 (59.6%)		62 (86.1%)	
Nilotinib	8 (7.7%)		8 (11.1%)	
Ponatinib	2 (1.9%)		2 (2.8%)	

Salvage B ALL	All (N=42)	No Blina/INO (n=16)	Received Blina (n=25)	Received INO (n=9)	p
Age (Median, Range)	47.4 (25-74)	47.4 (25-64)	47.6 (29-74)	54.0 (30-63)	
Age					
<40	14 (33.3%)	4 (25.0%)	9 (36.0%)	4 (44.4%)	
40-54	15 (35.7%)	9 (56.3%)	6 (24.0%)	1 (11.1%)	
>55	13 (31.0%)	3 (18.8%)	10 (40.0%)	4 (44.4%)	
Male Gender (Percent)	25 (59.5%)	9 (56.3%)	16 (64.0%)	6 (66.7%)	
Ph-negative B ALL	33 (78.6%)	9 (56.3%)	23 (92%)	9 (100%)	0.006
CR Status					
CR1 after salvage	11 (26.2%)	1 (6.3%)	10 (40%)	4 (44.4%)	
CR2/CR3	31 (73.8%)	15 (93.8%)	15 (60%)	5 (55.5%)	
MRD+	10/41 (24.4%)	7/15 (46.7%)	3 (12.0%)	1 (11.1%)	0.04
Myeloablative Conditioning	8 (19.0%)	6 (37.5%)	2 (8.0%)	0	0.02
PBSCT	12 (28.6%)	0	11 (44.0%)	6 (66.7%)	0.0003
2008-2014	13 (31.0%)	13 (81.3%)	0	0	<0.0001

Supplementary Table 8: Demographics and transplant characteristics by receipt of pre-transplant therapy for B ALL patients transplanted following salvage for relapsed or primary refractory disease.

Salvage B ALL	2008-2014 (n=13)	2015-2022 (n=29)	p
Conditioning			0.006
MAC	6 (46.2%)	2 (6.9%)	
RIC	7 (53.8%)	27 (93.1%)	
MRD			0.02
MRD-	6 (46.2%)	25 (86.2%)	
MRD+	6 (46.2%)	4 (13.8%)	
MRD Unknown	1 (7.7%)		
Ph Status			0.02
Ph-positive	6 (46.2%)	3 (10.3%)	
Ph-negative	7 (53.8%)	26 (89.7%)	

Supplementary Table 9: Transplant and disease characteristics by era for B ALL patients undergoing transplant following salvage treatment for relapsed or primary refractory disease.