

Severe toxicity and poor efficacy of reinduction chemotherapy are associated with overall poor outcomes in relapsed B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group AALL1331 trial

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Supplemental Table 1. Definitions of Site of Relapse at Enrollment

Marrow relapse	M3 marrow (>25% BM blasts)
Isolated marrow relapse	M3 marrow (>25% blasts) without CNS or testicular disease
Central nervous system relapse	Positive cytomorphology and white blood cells $\geq 5/\mu\text{L}$ or clinical signs of CNS leukemia (CNS3)
Testicular leukemia	Documented by biopsy if not associated with marrow relapse
Isolated extramedullary relapse	Central nervous system or testicular relapse with M1 marrow (<5% blasts)
Combined relapse	$\geq 5\%$ blasts in the marrow with CNS or testicular relapse

Supplemental Table 2. Block 1 Reinduction Chemotherapy¹

Drug	Dose	Days
Dexamethasone	10 mg/m ² /dose twice daily	1-5,15-19
Vincristine	1.5 mg/m ² /dose (max 2mg)	1,8,15,22
Pegaspargase	2500 IU/m ² /dose	3,17
Mitoxantrone	10 mg/m ² /dose	1,2
IT methotrexate	Age based dosing	1,8 for CNS 1/2*
Triple IT	Age based dosing	8,15 and 22 for CNS 3

¹Modified Block 1 chemotherapy from UKR3 reinduction.

IT: intrathecal; Triple IT: methotrexate; cytarabine; hydrocortisone

*CNS2: weekly IT until 2 negative CSF samples (CNS1) obtained.

Supplemental Table 3. Characteristics of Patients with Treatment Failure after Block 1.

Number	Site of Relapse	Time to Relapse
23	BM±EM	< 18 months
10	BM±EM	18-36 months
7	BM±EM	≥ 36 months
2	IEM (iCNS)	≥ 18 months

BM: Bone marrow; EM: Extramedullary; IEM: Isolated extramedullary; iCNS: isolated central nervous system

Supplemental Table 4. Grade 3-5 adverse events that occurred in greater than 5% of patients in Block 1*.

Adverse Events (Grade 3-5)	Frequency (%)
Blood and lymphatic system disorders (total)	31.2%
Febrile neutropenia	30.3
Infections and infestations (total)	36.6
Infections and infestations – Other, specify	17.9
Sepsis	10.1
Lung infection	5.5
Metabolism and nutrition disorders (total)	37.4
Hyperglycemia	16.6
Hypokalemia	12.0
Hyponatremia	8.9
Hypophosphatemia	7.6
Anorexia	6.4
Hypoalbuminemia	6.2
Investigations (total)	26.3
Alanine aminotransferase increased	13.8
Blood bilirubin increased	7.1
Aspartate aminotransferase increased	7.0
Gastrointestinal disorders (total)	18
Mucositis oral	6.1
Vascular disorders (total)	9.5
Hypotension	5.9

*Does not include hematologic adverse events

Supplemental Table 5. Univariable and Multivariable logistic regression analysis of odds of having a grade 3+ or 4+ AE during Block 1 among BM±EM relapsed patients

Variables	Number of patients	Grade 3+ AE				Grade 4+ AE			
		Univariable		Multivariable		Univariable		Multivariable	
		OR (95% CI)	p ¹	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Site of relapse			0.050		0.77		0.22		0.96
Isolated BM	452	1.0		1.0		1.0		1.0	
BM+EM	80	1.82 (0.97-3.42)		0.85 (0.29-2.52)		1.38 (0.83-2.28)		1.03 (0.31-3.18)	
Testicular disease at first relapse			0.398	Excluded			0.50	Excluded	
No	514	1.0				1.0			
Yes	18	0.64 (0.24-1.75)				0.69 (0.22-2.12)			
CNS status at first relapse			0.016		0.099		0.061		0.16
CNS 1	404	1.0		1.0		1.0		1.0	
CNS 2	66	1.26 (0.68-2.33)		1.28 (0.67-2.44)		1.59 (0.92-2.74)		1.63 (0.91-2.89)	
CNS 3	62	2.9 (1.28-6.57)		3.95 (1.05-14.87)		1.75 (1-3.06)		1.93 (0.54-7.44)	
Age at enrollment			0.42		0.80		0.081		0.48
1-9 years	242	1.0		1.0		1.0		1.0	
10-17 years	200	1.33 (0.86-2.06)		1.19 (0.7-2.03)		1.27 (0.84-1.93)		1.13 (0.68-1.97)	
18+ years	90	1.23 (0.7-2.17)		1.07 (0.52-2.22)		1.8 (1.08-3.02)		1.5 (0.77-3.02)	
Time to relapse			0.20		0.47		0.11		0.22
<18 mo	84	1.0		1.0		1.0		1.0	
18-35 mo	125	1.79 (0.95-3.39)		1.54 (0.77-3.09)		0.8 (0.45-1.44)		0.74 (0.39-1.41)	
≥36 mo	323	1.36 (0.8-2.31)		1.33 (0.71-2.49)		0.6 (0.36-1)		0.59 (0.33-1.1)	
Sex			0.19		0.26		0.85		0.98
Male	278	1.0		1.0		1.0		1.0	
Female	254	1.31 (0.88-1.94)		1.28 (0.84-1.97)		0.96 (0.66-1.4)		1 (0.67-1.46)	
Race/ethnicity			0.017		0.017		0.002		0.005
Hispanic of all races	173	1.0		1.0		1.0		1.0	
Non-Hispanic White	244	0.58 (0.36-0.94)		0.57 (0.34-0.96)		0.68 (0.45-1.03)		0.73 (0.47-1.16)	
Non-Hispanic Black	48	0.42 (0.2-0.86)		0.42 (0.2-0.88)		0.33 (0.15-0.75)		0.31 (0.13-0.72)	
Non-Hispanic Asian	28	0.97 (0.34-2.74)		1.24 (0.41-3.72)		0.2 (0.06-0.69)		0.24 (0.07-0.84)	
Other/Unknown	39	0.34 (0.16-0.71)		0.34 (0.15-0.75)		0.43 (0.19-0.99)		0.44 (0.19-1.02)	
Obesity			0.55		0.66		0.24		0.63
Non-Obese	394	1.0		1.0		1.0		1.0	
Obese	133	1.15 (0.72-1.84)		0.9 (0.54-1.48)		1.29 (0.85-1.97)		1.12 (0.71-1.74)	
Unknown ¹	5	0.5 (0.08-3.05)		0.57 (0.07-4.82)		1.74 (0.29-10.58)		1.3 (0.16-10.48)	
NCI risk group at diagnosis			0.14		0.53		0.006		0.63
High Risk	241	1.0		1.0		1.0		1.0	
Standard Risk	285	0.74 (0.49-1.11)		0.79 (0.46-1.34)		0.59 (0.4-0.86)		0.85 (0.52-1.47)	
Unknown ¹	6	0.13 (0.02-0.75)		0.11 (0.01-0.82)		0.37 (0.04-3.19)		0.44 (0.04-3.67)	

Variables	Number of patients	Grade 3+ AE				Grade 4+ AE			
		Univariable		Multivariable		Univariable		Multivariable	
		OR (95% CI)	p ¹	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Cytogenetic group at initial diagnosis			0.61		0.63		0.36		0.97
<i>ETV6:RUNX1</i>	73	0.81 (0.45-1.45)		0.98 (0.52-1.86)		0.62 (0.34-1.13)		0.8 (0.42-0.89)	
DT/TT	53	0.6 (0.32-1.14)		0.59 (0.3-1.17)		0.64 (0.32-1.27)		0.91 (0.44-1.62)	
<i>KMT2A</i> rearranged	33	0.76 (0.34-1.71)		0.89 (0.34-2.38)		1.1 (0.51-2.35)		0.94 (0.38-1.91)	
Hypodiploidy	8	0.85 (0.17-4.32)		1.12 (0.21-5.93)		1.32 (0.31-5.61)		1.23 (0.27-2.2)	
None of the above	316	1.0		1.0		1.0		1.0	
Unknown ¹	49	0.71 (0.36-1.4)		0.7 (0.33-1.5)		0.88 (0.45-1.7)		0.86 (0.42-5.51)	

¹ "Unknown" category was excluded when calculating the P values.

BM: bone marrow; EM: extramedullary; CNS: central nervous system; Mo: months; AE: adverse events; OR: odd ratio; DT/TT: Double trisomy/triple trisomy

Supplemental Table 6. Univariable and Multivariable logistic regression analysis of odds of having a grade 3+ or 4+ AE during Block 1 among IEM relapsed patients

Variables	Number of patient	Grade 3+ AE				Grade 4+ AE			
		Univariable		Multivariable		Univariable		Multivariable	
		OR (95% CI)	p ¹	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
CNS status at first relapse									
CNS 1	18	1.0	0.031	1.0	0.10	1.0	0.031	1.0	0.10
CNS 2	1	Small sample size		Small sample size		Small sample size		Small sample size	
CNS 3	110	2.19 (0.8-5.99)		1.38 (0.33-5.73)		5.26 (0.67-41.46)		5.47 (0.43-69.95)	
Age at enrollment									
1-9 years	66	1.0	0.782	1.0	0.94	1.0	0.78	1.0	0.94
10-17 years	50	1.57 (0.73-3.38)		1.23 (0.48-3.14)		1.17 (0.49-2.82)		1 (0.32-3.17)	
18+ years	13	0.86 (0.26-2.84)		0.8 (0.18-3.53)		0.68 (0.13-3.41)		1.41 (0.19-10.24)	
Time to relapse									
<18 mo	32	1.0	0.34	1.0	0.87	1.0	0.34	1.0	0.87
18-35 mo	61	0.93 (0.37-2.34)		1.1 (0.39-3.08)		1.27 (0.46-3.5)		1.36 (0.41-4.49)	
≥36 mo	36	0.36 (0.13-0.98)		0.55 (0.14-2.15)		0.58 (0.16-2.04)		1.13 (0.19-6.91)	
Sex									
Male	102	1.0	0.038	1.0	0.15	1.0	0.039	1.0	0.15
Female	27	1.66 (0.67-4.15)		1.15 (0.41-3.28)		2.75 (1.08-6.97)		2.28 (0.75-6.97)	
Race/ethnicity									
Hispanic of all races	43	1.0	0.11	1.0	0.19	1.0	0.11	1.0	0.19
Non-Hispanic White	61	0.5 (0.22-1.12)		0.62 (0.24-1.57)		0.35 (0.13-0.94)		0.32 (0.1-1.05)	
Non-Hispanic Black	8	3.38 (0.38-30.2)		3.91 (0.39-38.9)		0.33 (0.04-2.96)		0.27 (0.02-2.99)	
Non-Hispanic Asian	5	0.72 (0.11-4.84)		0.86 (0.11-6.76)		0.58 (0.06-5.67)		0.85 (0.07-9.84)	
Other/Unknown	12	1.45 (0.34-6.2)		1.37 (0.28-6.71)		1.65 (0.44-6.17)		1.47 (0.31-7.01)	
Obesity									
Non-Obese	93	1.0	0.70	1.0	0.98	1.0	0.053	1.0	0.085
Obese	36	1.17 (0.53-2.59)		1.01 (0.41-2.49)		2.41 (1-5.79)		2.54 (0.89-7.26)	
Unknown ¹	0								
NCI risk group at diagnosis									
High Risk	78	1.0	0.054	1.0	0.42	1.0	0.17	1.0	0.89
Standard Risk	51	0.49 (0.24-1.01)		0.65 (0.22-1.88)		0.54 (0.22-1.34)		1.11 (0.27-4.65)	
Unknown ¹	0								
Cytogenetic group at initial diagnosis									
<i>ETV6::RUNX1</i>	18	1.02 (0.36-2.88)	0.99	1.71 (0.49-6)	0.77	1.05 (0.31-3.57)	0.88	2.63 (0.53-12.95)	0.71
DT/TT	7	0.86 (0.18-4.1)		1.53 (0.27-8.53)		0.61 (0.07-5.41)		0.68 (0.05-8.66)	
<i>KMT2A</i> rearranged	6	1.3 (0.23-7.46)		1.49 (0.18-12.42)		1.84 (0.31-10.83)		1.9 (0.2-18.46)	
Hypodiploidy	0	NA		NA		NA		NA	
None of the above	89	1.0		1.0		1.0		1.0	

Variables	Number of patient	Grade 3+ AE				Grade 4+ AE			
		Univariable		Multivariable		Univariable		Multivariable	
		OR (95% CI)	p ¹	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Unknown ¹	9	1.3 (0.3-5.52)		1.55 (0.3-7.96)		1.05 (0.2-5.49)		1 (0.13-7.71)	

¹ "Unknown" category was excluded when calculating the P values.

CNS: central nervous system; Mo: months; AE: adverse events; OR: odd ratio; DT/TT: Double trisomy/triple trisomy

Supplemental Table 7. Univariable and Multivariable logistic regression analysis of odds of failing to achieve MRD negativity¹ at the end of Block 1 among BM±EM relapsed patients

Variables	Number of patients	MRD positive			
		Univariable		Multivariable	
		OR (95% CI)	p ¹	OR (95% CI)	p
Site of relapse			<0.0001		0.024
Isolated BM	452	1.0		1.0	
BM+EM	80	0.32 (0.2-0.52)		0.29 (0.1-0.87)	
Testicular disease at first relapse			0.053	Excluded	
No	514	1.0			
Yes	18	0.39 (0.15-1.03)			
CNS status at first relapse			0.0003		0.55
CNS 1	404	1.0		1.0	
CNS 2	66	0.97 (0.56-1.67)		0.72 (0.4-1.31)	
CNS 3	62	0.33 (0.19-0.57)		0.89 (0.27-2.9)	
Age at enrollment			0.31		0.95
1-9 years	242	1.0		1.0	
10-17 years	200	1.1 (0.75-1.61)		0.96 (0.59-1.54)	
18+ years	90	1.48 (0.89-2.47)		1.05 (0.53-2.08)	
Time to relapse			<0.0001		<0.0001
<18 mo	84	1.0		1.0	
18-35 mo	125	0.44 (0.22-0.88)		0.54 (0.25-1.15)	
≥36 mo	323	0.22 (0.12-0.41)		0.26 (0.13-0.52)	
Sex			0.27		0.053
Male	278	1.0		1.0	
Female	254	0.82 (0.58-1.17)		0.68 (0.46-1.01)	
Race/ethnicity			0.32		0.12
Hispanic of all races	173	1.0		1.0	
Non-Hispanic White	244	0.92 (0.62-1.37)		1.02 (0.65-1.59)	
Non-Hispanic Black	48	0.94 (0.49-1.81)		0.89 (0.43-1.85)	
Non-Hispanic Asian	28	0.62 (0.28-1.38)		0.74 (0.3-1.84)	
Other/Unknown	39	1.79 (0.82-3.91)		2.79 (1.15-6.73)	
Obesity			0.54		0.52
Non-Obese	394	1.0		1.0	
Obese	133	1.14 (0.76-1.7)		1.17 (0.74-1.85)	
Unknown ²	5	2.65 (0.29-23.93)		1.44 (0.12-17.33)	
NCI risk group at diagnosis			0.002		0.19
High Risk	241	1.0		1.0	
Standard Risk	285	0.56 (0.39-0.8)		0.73 (0.45-1.18)	
Unknown ²	6	0.09 (0.01-0.79)		0.05 (0-0.69)	
Cytogenetic group at initial diagnosis			0.002		0.069
<i>ETV6::RUNX1</i>	73	0.38 (0.23-0.64)		0.45 (0.25-0.81)	
DT/TT	53	0.84 (0.46-1.52)		1.14 (0.6-2.18)	
<i>KMT2A</i> rearranged	33	1.26 (0.58-2.75)		0.8 (0.32-2.03)	
Hypodiploidy	8	3.84 (0.47-31.59)		2.19 (0.25-19.36)	
None of the above	316	1.0		1.0	
Unknown ²	49	0.8 (0.43-1.47)		1.15 (0.57-2.32)	

¹ Failing to achieve MRD negativity includes patients known to be MRD ≥0.01% or unknown.

² "Unknown" category was excluded when calculating the P values.

BM: bone marrow; EM: extramedullary; CNS: central nervous system; OR: odd ratio; DT/TT:
Double trisomy/triple trisomy

Supplemental Table 8. Univariable and multivariable analysis of EFS from enrollment among BM±EM relapsed patients

Variables	Number of patients	EFS from enrollment					
		Univariable		Multivariable		Multivariable Reduced	
		HR (95% CI)	p ¹	HR (95% CI)	p	HR (95% CI)	p
Site of relapse			0.33		0.11		0.11
Isolated BM	452	1.0		1.0		1.0	
BM+EM	80	0.85 (0.6-1.19)		1.76 (0.92-3.39)		1.75 (0.93-3.29)	
Testicular disease at first relapse			0.69	Excluded		Excluded	
No	514	1.0					
Yes	18	1.13 (0.62, 2.07)					
CNS status at first relapse			0.27		0.10		0.12
CNS 1	404	1.0		1.0		1.0	
CNS 2	66	1.18 (0.84, 1.65)		1.08 (0.76-1.55)		1.12 (0.79-1.58)	
CNS 3	62	0.79 (0.53, 1.17)		0.44 (0.21-0.91)		0.47 (0.23-0.96)	
Age at enrollment			0.14		0.40		0.038
1-9 years	242	1.0		1.0		1.0	
10-17 years	200	0.92 (0.71, 1.2)		1 (0.73-1.37)		1.17 (0.89-1.54)	
18+ years	90	1.29 (0.94, 1.77)		1.26 (0.84-1.89)		1.55 (1.12-2.16)	
Time to relapse			<0.0001		<0.0001		<0.0001
<18 mo	84	1.0		1.0		1.0	
18-35 mo	125	0.4 (0.29, 0.55)		0.39 (0.28-0.54)		0.4 (0.29-0.55)	
≥36 mo	323	0.15 (0.11, 0.2)		0.13 (0.09-0.18)		0.12 (0.09-0.17)	
Sex			0.012		0.003		0.006
Male	278	1.0		1.0		1.0	
Female	254	0.74 (0.59, 0.94)		0.69 (0.54-0.88)		0.71 (0.56-0.91)	
Race/ethnicity			0.096		0.001		0.003
Hispanic of all races	173	1.0		1.0		1.0	
Non-Hispanic White	244	0.95 (0.73, 1.23)		1.32 (0.99-1.75)		1.27 (0.97-1.66)	
Non-Hispanic Black	48	0.93 (0.6, 1.45)		0.77 (0.49-1.22)		0.79 (0.5-1.23)	
Non-Hispanic Asian	28	0.89 (0.51, 1.57)		1.2 (0.67-2.15)		1.19 (0.67-2.11)	
Other/Unknown	39	0.47 (0.26, 0.85)		0.47 (0.25-0.88)		0.47 (0.25-0.87)	
Obesity			0.33		0.13		
Non-Obese	394	1.0		1.0			
Obese	133	1.14 (0.88, 1.48)		1.24 (0.94-1.65)			
Unknown ¹	5	2.8 (1.04, 7.55)		0.98 (0.31-3.06)			
NCI risk group at diagnosis			<0.0001		0.45		
High Risk	241	1.0		1.0			
Standard Risk	285	0.6 (0.47, 0.75)		0.89 (0.66-1.21)			
Unknown ¹	6	0.42 (0.1, 1.69)		0.51 (0.12-2.2)			
Cytogenetic group at initial diagnosis			0.0002		0.23		
<i>ETV6::RUNX1</i>	73	0.56 (0.38, 0.82)		0.64 (0.42-0.98)			
DT/TT	53	0.56 (0.36, 0.88)		0.83 (0.52-1.32)			
<i>KMT2A</i> rearranged	33	1.55 (0.99, 2.44)		0.83 (0.48-1.42)			
Hypodiploidy	8	1.65 (0.68, 4.01)		1.44 (0.58-3.58)			
None of the above	316	1.0		1.0			
Unknown ¹	49	0.93 (0.62, 1.4)		1 (0.64-1.55)			

¹ "Unknown" category was excluded when calculating the P values.

BM: bone marrow; EM: extramedullary; CNS: central nervous system; Mo: months; HR: hazard ratio; DT/TT: Double trisomy/triple trisomy

Supplemental Table 9. Univariable and multivariable analysis of EFS from enrollment among iCNS relapsed patients

Variables	Number of patients	EFS from enrollment					
		Univariable		Multivariable		Multivariable Reduced	
		HR (95% CI)	p ¹	HR (95% CI)	p	HR (95% CI)	p
Age at enrollment			0.11		0.53		
1-9 years	54	1.0		1.0			
10-17 years	44	1.45 (0.91, 2.29)		1.22 (0.71-2.11)			
18+ years	12	1.96 (0.97, 3.96)		1.63 (0.69-3.88)			
Time to relapse			0.053		0.22		0.056
<18 mo	31	1.0		1.0		1.0	
18-35 mo	61	1.18 (0.71, 1.96)		1.24 (0.69-2.24)		1.23 (0.74-2.04)	
≥36 mo	18	0.54 (0.26, 1.15)		0.68 (0.28-1.65)		0.57 (0.27-1.21)	
Sex			0.43		0.43		
Male	83	1.0		1.0			
Female	27	1.22 (0.75, 1.99)		1.26 (0.72-2.2)			
Race/ethnicity			0.76		0.90		
Hispanic of all races	34	1.0		1.0			
Non-Hispanic White	54	0.77 (0.47, 1.26)		1.19 (0.66-2.13)			
Non-Hispanic Black	7	1.24 (0.51, 3.02)		1.53 (0.57-4.11)			
Non-Hispanic Asian	4	0.83 (0.25, 2.75)		1.37 (0.39-4.82)			
Other/Unknown	11	0.8 (0.38, 1.71)		0.94 (0.4-2.18)			
Obesity			0.002		0.008		0.002
Non-Obese	79	1.0		1.0		1.0	
Obese	31	2.14 (1.34, 3.4)		2.12 (1.23-3.67)		2.13 (1.34-3.39)	
Unknown ¹	0						
NCI risk group at diagnosis			0.014		0.42		
High Risk	73	1.0		1.0			
Standard Risk	37	0.56 (0.35, 0.9)		0.75 (0.37-1.51)			
Unknown ¹	0						
Cytogenetic group at initial diagnosis			0.28		0.93		
<i>ETV6::RUNX1</i>	12	0.57 (0.26, 1.25)		0.94 (0.4-2.22)			
DT/TT	5	0.65 (0.2, 2.08)		0.94 (0.26-3.39)			
<i>KMT2A</i> rearranged	5	1.66 (0.6, 4.57)		1.5 (0.42-5.4)			
Hypodiploidy	0						
None of the above	82	1.0		1.0			
Unknown ¹	6	1.4 (0.56, 3.48)		1.09 (0.39-3.05)			

¹ "Unknown" category was excluded when calculating the P values.

Mo: months; HR: hazard ratio; DT/TT: Double trisomy/triple trisomy

Supplemental Table 10. Univariable and multivariable analysis of OS from enrollment among BM±EM relapsed patients

Variables	Number of patients	OS from enrollment					
		Univariable		Multivariable		Multivariable Reduced	
		HR (95% CI)	p ¹	HR (95% CI)	p	HR (95% CI)	p
Site of relapse			0.009		0.096		0.005
Isolated BM	452	1.0		1.0		1.0	
BM+EM	80	0.56 (0.35-0.90)		0.42 (0.13-1.35)		0.53 (0.32-0.85)	
Testicular disease at first relapse			0.046	Excluded			
No	514	1.0					
Yes	18	0.38 (0.12, 1.18)					
CNS status at first relapse			0.094		0.85		
CNS 1	404	1.0		1.0			
CNS 2	66	1.29 (0.87, 1.93)		0.99 (0.65-1.52)			
CNS 3	62	0.67 (0.4, 1.12)		1.41 (0.4-4.94)			
Age at enrollment			0.20		0.34		
1-9 years	242	1.0		1.0			
10-17 years	200	0.96 (0.7, 1.32)		1.22 (0.81-1.84)			
18+ years	90	1.37 (0.94, 2.01)		1.46 (0.88-2.4)			
Time to relapse			<0.0001		<0.0001		<0.0001
<18 mo	84	1.0		1.0		1.0	
18-35 mo	125	0.41 (0.29, 0.57)		0.45 (0.32-0.65)		0.49 (0.34-0.68)	
≥36 mo	323	0.08 (0.06, 0.12)		0.09 (0.06-0.13)		0.09 (0.06-0.14)	
Sex			0.063		0.004		0.012
Male	278	1.0		1.0		1.0	
Female	254	0.76 (0.57, 1.02)		0.64 (0.47-0.87)		0.69 (0.52-0.92)	
Race/ethnicity			0.63		0.64		
Hispanic of all races	173	1.0		1.0			
Non-Hispanic White	244	0.84 (0.61, 1.16)		1.18 (0.83-1.69)			
Non-Hispanic Black	48	1.08 (0.65, 1.78)		0.99 (0.59-1.66)			
Non-Hispanic Asian	28	0.9 (0.46, 1.75)		1.37 (0.67-2.82)			
Other/Unknown	39	0.69 (0.36, 1.3)		0.81 (0.41-1.58)			
Obesity			0.39		0.31		
Non-Obese	394	1.0		1.0			
Obese	133	1.15 (0.84, 1.59)		1.18 (0.84-1.65)			
Unknown ¹	5	2.6 (0.83, 8.15)		0.44 (0.12-1.57)			
NCI risk group at diagnosis			<0.0001		0.097		0.0003
High Risk	241	1.0		1.0		1.0	
Standard Risk	285	0.42 (0.32, 0.57)		0.72 (0.49-1.06)		0.58 (0.43-0.78)	
Unknown ¹	6	0.3 (0.04, 2.14)		0.32 (0.04-2.49)		0.22 (0.03-1.59)	
Cytogenetic group at initial diagnosis			<0.0001		0.094		
<i>ETV6::RUNX1</i>	73	0.42 (0.25, 0.72)		0.67 (0.38-1.18)			
DT/TT	53	0.27 (0.13, 0.59)		0.5 (0.23-1.09)			
<i>KMT2A</i> rearranged	33	1.99 (1.23, 3.22)		1.33 (0.75-2.36)			
Hypodiploidy	8	1.34 (0.5, 3.64)		0.63 (0.23-1.77)			
None of the above	316	1.0		1.0			
Unknown ¹	49	0.77 (0.45, 1.31)		0.92 (0.51-1.66)			

¹ "Unknown" category was excluded when calculating the P values.

BM: bone marrow; EM: extramedullary; CNS: central nervous system; Mo: months; HR: hazard ratio; DT/TT: Double trisomy/triple trisomy

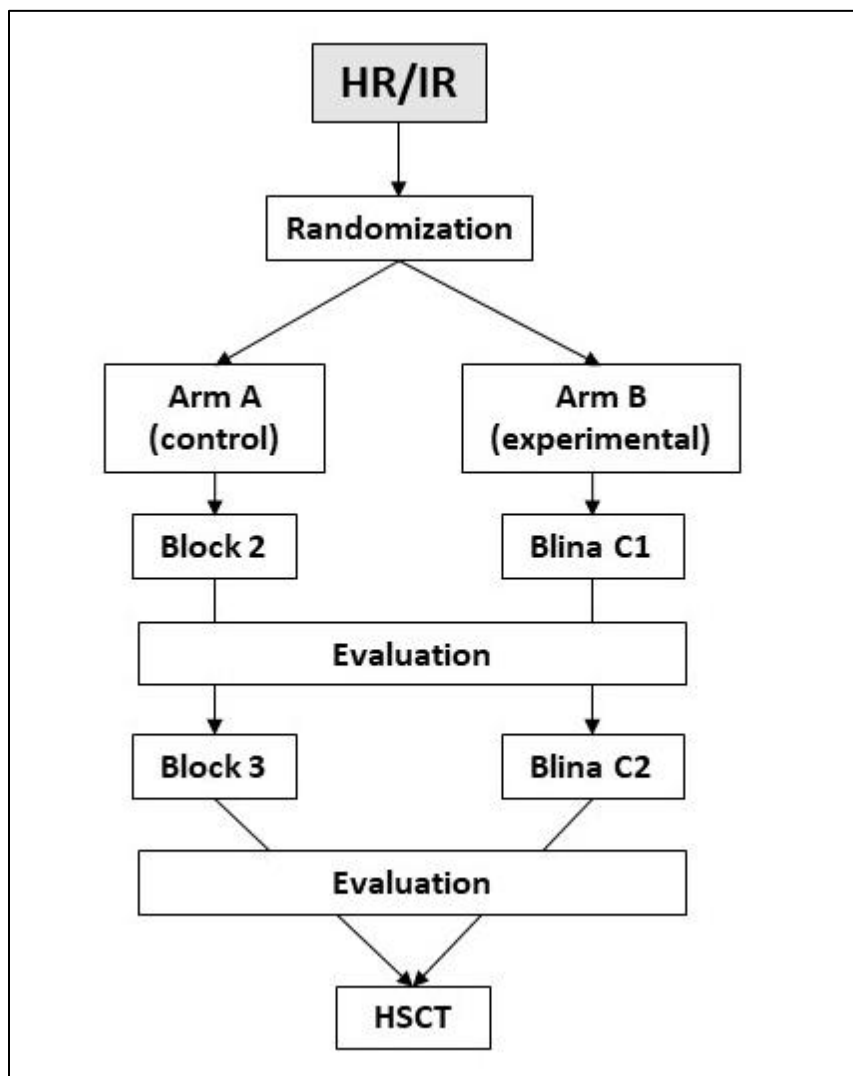
Supplemental Table 11. Univariable and multivariable analysis of OS from enrollment among iCNS relapsed patients

Variables	Number of patients	OS from enrollment					
		Univariable		Multivariable		Multivariable Reduced	
		HR (95% CI)	p ¹	HR (95% CI)	p	HR (95% CI)	p
Age at enrollment			0.24		0.66		
1-9 years	54	1.0		1.0			
10-17 years	44	1.55 (0.8, 3.02)		1.24 (0.54-2.81)			
18+ years	12	2.05 (0.8, 5.22)		1.75 (0.53-5.8)			
Time to relapse			0.61		0.92		
<18 mo	31	1.0		1.0			
18-35 mo	61	1 (0.49, 2.04)		1.01 (0.44-2.32)			
≥36 mo	18	0.64 (0.22, 1.84)		0.8 (0.22-2.95)			
Sex			0.87		0.93		
Male	83	1.0		1.0			
Female	27	1.06 (0.52, 2.16)		0.96 (0.42-2.2)			
Race/ethnicity			0.71		0.67		
Hispanic of all races	34	1.0		1.0			
Non-Hispanic White	54	0.8 (0.39, 1.64)		1.05 (0.45-2.47)			
Non-Hispanic Black	7	0.61 (0.14, 2.69)		0.82 (0.17-3.88)			
Non-Hispanic Asian	4	1.25 (0.28, 5.53)		1.64 (0.35-7.79)			
Other/Unknown	11	1.48 (0.56, 3.91)		2.12 (0.72-6.25)			
Obesity			0.072		0.19		0.089
Non-Obese	79	1.0		1.0		1.0	
Obese	31	1.83 (0.97, 3.46)		1.62 (0.79-3.31)		1.77 (0.93-3.37)	
Unknown ¹	0						
NCI risk group at diagnosis			0.018		0.42		0.022
High Risk	73	1.0		1.0		1.0	
Standard Risk	37	0.43 (0.21, 0.91)		0.64 (0.21-1.91)		0.44 (0.21-0.93)	
Unknown ¹	0						
Cytogenetic group at initial diagnosis			0.098		0.29		
<i>ETV6::RUNX1</i>	12	0.16 (0.02, 1.17)		0.22 (0.03-1.74)			
DT/TT	5	1.04 (0.25, 4.34)		1.74 (0.34-8.97)			
<i>KMT2A</i> rearranged	5	1.08 (0.26, 4.52)		1.18 (0.2-7.07)			
Hypodiploidy	0						
None of the above	82	1.0		1.0			
Unknown ¹	6	1.74 (0.53, 5.69)		1.22 (0.32-4.61)			

¹ "Unknown" category was excluded when calculating the P values.

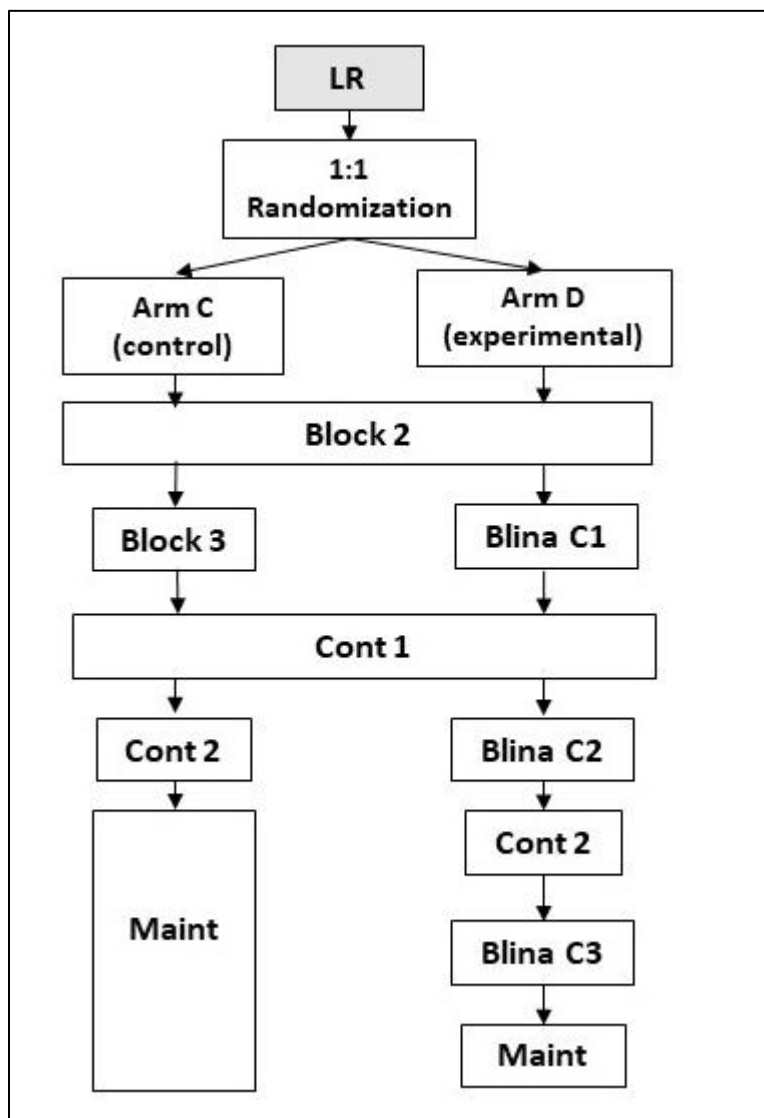
Mo: months; OR: odd ratio; DT/TT: Double trisomy/triple trisomy

Supplemental Figure 1. High Risk/Intermediate Risk Treatment Schema



HR: high risk; IR: intermediate risk; Blina: blinatumomab; C:cycle, HSCT: hematopoietic stem cell transplant

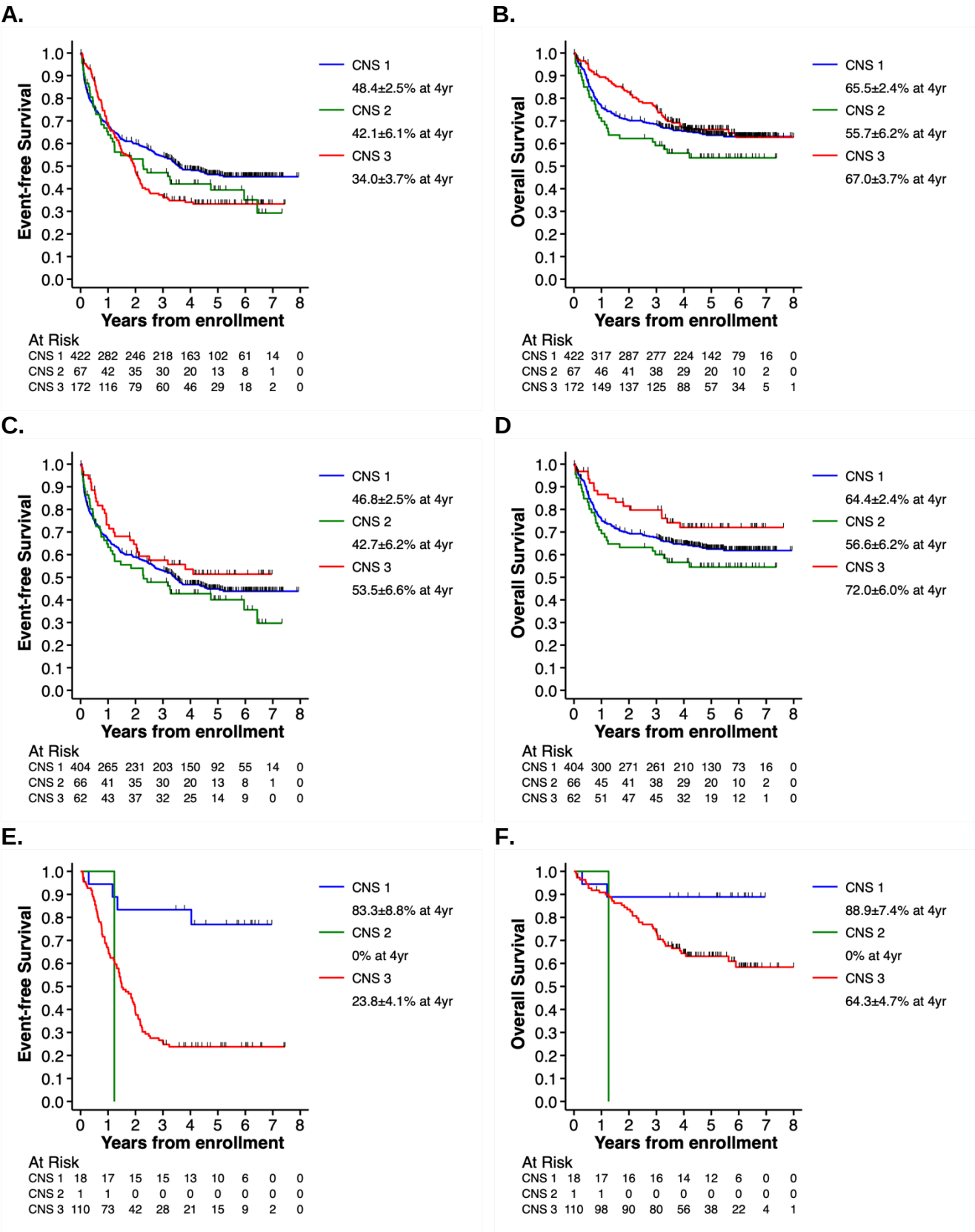
Supplemental Figure 2. Low Risk Treatment Schema



LR: low risk; Blina: Blinatumomab; C:cycle ,Cont: continuation; Maint: Maintenance

Therapy Given for a total of 2 years from the start of Block 1.

Supplemental Figure 3. EFS and OS from enrollment by CNS status at first relapse for all relapsed patients (A/B), BM±EM (C/D) and IEM (E/F).



CNS: central nervous system; Yr: year