Supplementary Design and Methods

Protocol stratification

Patient risk groups were defined as follows. The High risk group included patients with any of the following criteria: t(4;11) or MLL/AF4; prednisone poor response (≥ 1,000 blasts/µL on day 8 peripheral blood after 7 days of prednisone and one dose of intrathecal methotrexate on day 1); inability to achieve clinical remission after Induction Phase IA; high burden (≥ 10^{-3}) of PCR-Minimal Residual Disease (MRD) at day 78. The Standard risk group included patients who lacked high-risk criteria and tested negative to PCR-MRD performed by using two sensitive markers (≥ 1×10^{-4}) at both day 33 and day 78. The Intermediate risk group included the remaining patients, and those not evaluated by PCR-MRD.

PCR-MRD

PCR-MRD was detected by RQ-PCR of Immunoglobulin and/or T-cell receptor gene rearrangements in bone marrow samples collected at the end of the TP1 (day 33), and TP2 (day 78) induction phases; (17) data were interpreted according to EuroMRD published guidelines (van der Velden VHJ, Cazzaniga G, Schrauder A, Hancock J, Bader P, Panzer-Grumayer ER *et al*. On behalf of the European Study Group on MRD detection in ALL (ESG-MRD-ALL). Analysis of minimal residual disease by Ig/TCR gene rearrangements: Guidelines for interpretation of real-time quantitative PCR data. *Leukemia* 2007; **21**: 604-611).

Supplementary Tables

Supplementary Table 1. Clinical features of the study cohort patients *versus* not investigated patients.

	Analyzed for *IKZF1*		Not analyzed for *IKZF1*		*p-value*
	N	***%***	**N**	***%***	
All patients	410		472		
GENDER					
Male	214	*52.2*	252	*53.4*	*0.72*
Female	196	*47.8*	220	*46.6*	
AGE					
1-5 yrs	266	*64.9*	292	*61.9*	*0.60*
6-9 yrs	80	*19.5*	96	*20.3*	
10-17 yrs	64	*15.6*	84	*17.8*	
WBC(x1000/µl)					
<20	293	*71.5*	338	*71.6*	*0.92*
20-100	91	*22.2*	107	*22.7*	
≥100	26	*6.3*	27	*5.7*	
Translocations					
t(4;11)					
Positive	3	*0.7*	3	*0.7*	*0.98*
Negative	405	*99.3*	413	*99.3*	
Not known	2		56		
t(12;21)					
Positive	83	*21.3*	68	*16.7*	*0.10*
Negative	306	*78.7*	338	*83.3*	
Not known	21		66		
Prednisone response					
Good	386	*94.6*	425	*90.0*	*0.01*
Poor	22	*5.4*	47	*10.0*	
Not known	2		0		
MRD					
SR	124	*39.0*	134	*34.8*	
IR	189	*59.4*	214	*55.6*	*<0.001*
HR	5	*1.6*	37	*9.6*	
Not known	92		87		
Final protocol strata					
SR	117	*28.5*	129	*27.3*	
IR	264	*64.4*	266	*56.4*	*<0.001*
HR	29	*7.1*	77	*16.3*	
NCI criteria					
Standard	301	*73.4*	338	*71.6*	*0.55*
High	109	*26.6*	134	*28.4*	
DNA index					
≥1.16 and <1.6	81	*21.3*	110	*25.0*	*0.21*
<1.16 or ≥1.6	299	*78.7*	330	*75.0*	
Not known	30		32		

Supplementary Table 2. Additional genetic alterations in patients positive for an *IKZF1* deletion.

Pt.	Deletions								Final Risk	Relapse
	IKZF1	*CDKN2A/B*	*PAX5*	*ETV6*	*BTG1*	*RB1*	*EBF1*	*P-CRLF2*		
Pt. #1	Δ 1-8	**pos**	**pos**	neg	**pos**	neg	neg	neg	IR	yes
Pt. #2	Δ 1-8	neg	neg	**pos**	neg	neg	neg	neg	IR	no
Pt. #3	Δ 1-8	**pos**	neg	neg	neg	neg	neg	nd	IR	no
Pt. #4	Δ 1-8	neg	neg	**pos**	neg	neg	neg	neg	IR	no
Pt. #5	Δ 1-8	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #6	Δ 1-8	neg	neg	**pos**	neg	neg	**pos**	neg	HR	no
Pt. #7	Δ 1-8	**pos**	**pos**	**pos**	neg	neg	neg	neg	SR	no
Pt. #8	Δ 1-8	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #9	Δ 1-8	**pos**	**pos**	neg	**pos**	neg	neg	neg	IR	no
Pt. #10	Δ 1-8	neg	neg	**pos**	neg	neg	neg	neg	HR	yes
Pt. #11	Δ 1-8	neg	neg	**pos**	neg	neg	neg	nd	IR	no
Pt. #12	Δ 1-8	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #13	Δ 1-8	neg	neg	**pos**	neg	neg	neg	nd	IR	no
Pt. #14	Δ 1-8	neg	neg	**pos**	neg	neg	neg	neg	SR	no
Pt. #15	Δ 1-8	neg	neg	**pos**	neg	neg	neg	nd	IR	no
Pt. #16	Δ 1-8	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #17	Δ 1-8	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #18	Δ 1-8	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #19	Δ 1-8	**pos**	**pos**	**pos**	neg	neg	neg	neg	IR	no
Pt. #20	Δ 1-8	neg	neg	neg	neg	neg	neg	neg	SR	no
Pt. #21	Δ 1-8	**pos**	**pos**	neg	neg	neg	neg	neg	IR	no
Pt. #22	Δ 1-8	neg	neg	neg	neg	neg	neg	neg	IR	yes
Pt. #23	Δ 1-8	neg	neg	neg	neg	neg	neg	neg	IR	yes
Pt. #24	Δ 1-8	**pos**	neg	neg	neg	neg	neg	neg	IR	no
Pt. #25	Δ 1-8	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #26	Δ 1-8	**pos**	**pos**	neg	neg	neg	neg	neg	IR	no
Pt. #27	Δ 1-8	neg	neg	**pos**	neg	neg	neg	neg	IR	no
Pt. #28	Δ 1-8	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #29	Δ 1-8	neg	neg	**pos**	neg	neg	neg	neg	IR	yes
Pt. #30	Δ 1-3	neg	**pos**	**pos**	neg	neg	neg	neg	SR	no
Pt. #31	Δ 1-3	neg	neg	**pos**	neg	neg	neg	neg	IR	no
Pt. #32	Δ 1-4	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #33	Δ 2	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #34	Δ 2-3	neg	neg	**pos**	neg	neg	neg	neg	IR	no
Pt. #35	Δ 2-3	**pos**	**pos**	neg	**pos**	neg	neg	neg	IR	yes
Pt. #36	Δ 2-7	neg	neg	neg	**pos**	neg	neg	**pos**	IR	yes
Pt. #37	Δ 2-7	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #38	Δ 2-8	**pos**	neg	neg	neg	neg	neg	neg	SR	no
Pt. #39	Δ 2-8	neg	neg	neg	neg	neg	neg	nd	HR	yes
Pt. #40	Δ 2-8	neg	neg	neg	neg	neg	neg	**pos**	IR	yes
Pt. #41	Δ 4-5	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #42	Δ 4-6	neg	neg	neg	neg	neg	neg	neg	SR	no
Pt. #43	Δ 4-7	neg	neg	neg	neg	neg	neg	neg	IR	yes
Pt. #44	Δ 4-7	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #45	Δ 4-7	neg	neg	neg	neg	neg	neg	neg	SR	no
Pt. #46	Δ 4-7	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #47	Δ 4-7	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #48	Δ 4-7	**pos**	**pos**	neg	neg	neg	neg	neg	IR	yes
Pt. #49	Δ 4-7	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #50	Δ 4-7	**pos**	**pos**	neg	neg	neg	neg	**pos**	IR	yes
Pt. #51	Δ 4-7	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #52	Δ 4-8	neg	neg	neg	neg	neg	neg	neg	IR	no
Pt. #53	Δ 4-8	neg	neg	neg	**pos**	neg	neg	neg	HR	yes
Pt. #54	Δ 6-8	neg	neg	neg	neg	neg	neg	neg	SR	no

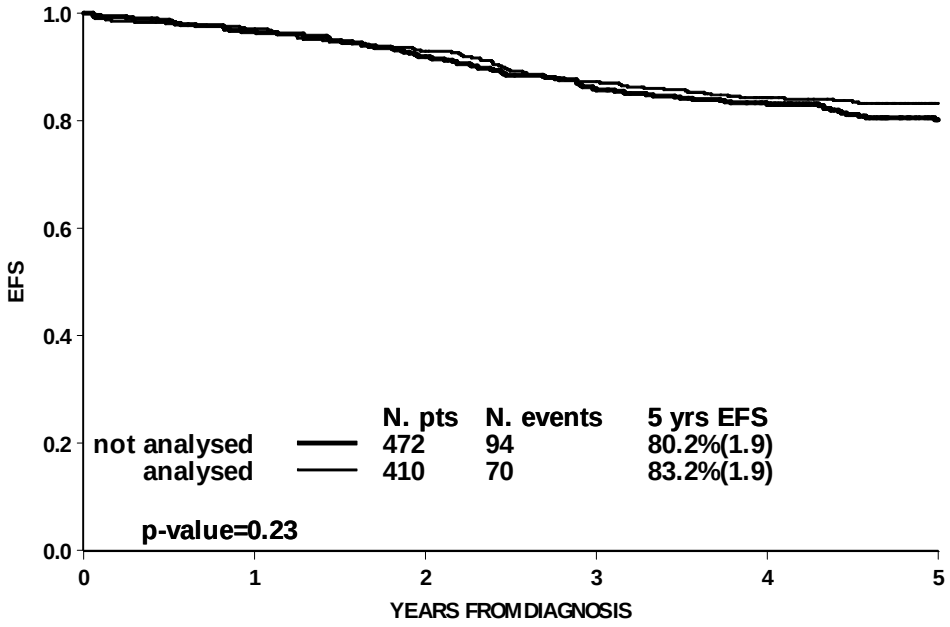
P-CRLF2 , *P2RY8-CRLF2* .

Supplementary Table 3. Additional genomic alterations of study cohort patients positive or negative for an *IKZF1* deletion.

Characteristics	P-value	*IKZF1 deletions*			
		No		Yes	
		N	%	N	%
All patients		356	*100,00*	54	*100,00*
***CDKN2A/B* deletion**	0,96				
No		278	*78,1*	42	*77,8*
Yes		78	*21,9*	12	*22,2*
***PAX5* deletion**	0,24				
No		311	*87,4*	44	*81,5*
Yes		45	*12,6*	10	*18,5*
***ETV6* deletion**	0,08				
No		293	*82,3*	39	*72,2*
Yes		63	*17,7*	15	*27,8*
***BTG1* deletion**	0,37				
No		335	*94,1*	49	*90,7*
Yes		21	*5,9*	5	*9,3*
***RB1* deletion**	0,06				
No		331	*93,0*	54	*100,0*
Yes		25	*7,0*	0	*0,0*
EBF1 deletion	0,99				
No		350	*98,3*	53	*98,2*
Yes		6	*1,7*	1	*1,8*

Supplementary Figures

Supplementary Figure 1. **Treatment outcome of study cohort.** Event-free survival (EFS) between patients included and non-included in the study cohort.



Supplementary Figure 2. Association of *IKZF1* deletions to treatment outcome in the absence of the favorable prognostic factors t(12;21) or hyperdiploidy. Event Free survival, EFS (A, C) and Cumulative Incidence of Relapse, CIR (B, D) of the study cohort for the presence or absence of *IKZF1* deletions, excluding t(12;21) positive (A, B) or hyperdiploid patients, respectively.