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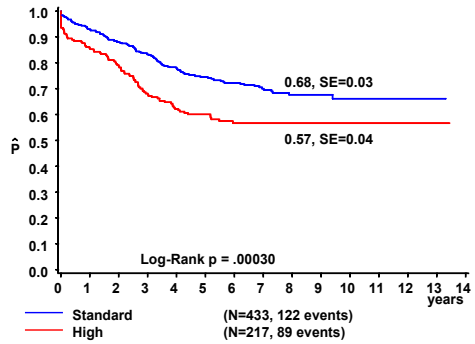
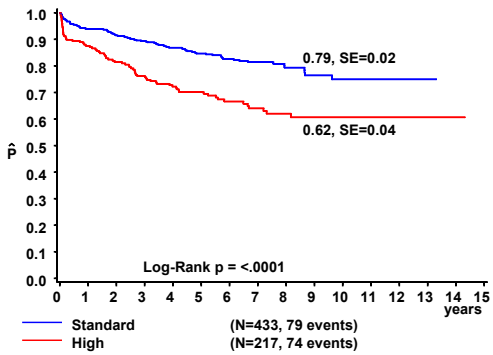
Supplementary Figure 1. Treatment outcome according to standard- and high-risk NCI criteria in DS-ALL patients.

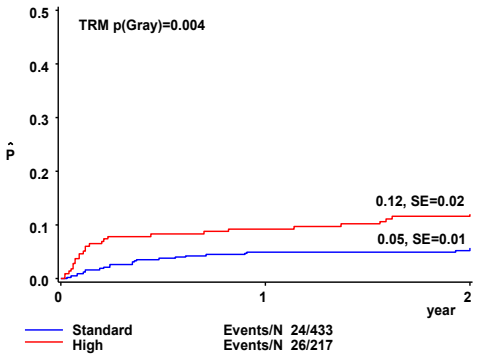
A)



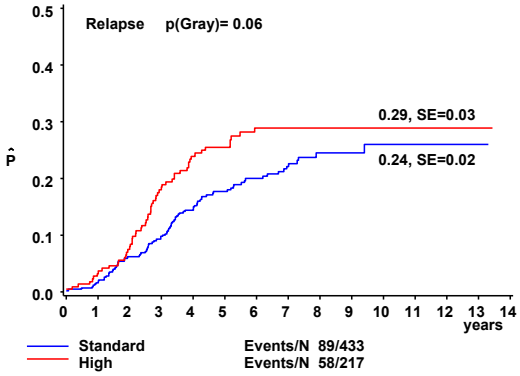
B)



C)



D)



The overall survival (A), event-free survival (B), cumulative risk of mortality (C) and cumulative risk of relapse (D) depicted for patients with NCI standard-risk and high-risk patients with cut off values for WBC < or ≥ $50x10^9$/L and age < or ≥10 years. The numbers on the curves for overall survival and event-free survival represent results at 8 years. The numbers on the curves for treatment-related mortality are 2-year results and those for relapse are results at 8 years.

Supplementary Table 1. Participating study groups

Name study group	Number of patients
North American Children's Oncology Group including the Children's Cancer Group and the Pediatric Oncology Group studies	202
German Berlin-Frankfurt-Münster Study Group	109
UK Medical Research Council	66
Italian Associazione Italiana di Ematologia ed Oncologia Pediatrica	63
Scandinavian Nordic Society for Pediatric Hematology and Oncology	43
Belgian European Organization for Research and Treatment of Cancer	31
Dutch Childhood Oncology Group	30
North American Dana Faber Cancer Institute	27
Japan Association of Childhood Leukemia Study	18
German Cooperative study-group for childhood acute lymphoblastic leukemia	16
St. Jude Children's Research Hospital	13
Tokyo Children's Cancer Study Group	10
Taiwan Pediatric Oncology Group	9
Polish Paediatric Leukaemia and Lymphoma Study Group	8
Israel National Study group for Childhood ALL	8

Supplementary Table 2. Collected variables in the dataset

Collected variables in the dataset	
Patient ID	Name of protocol
Study group	Use of Anthracylines in induction: yes/no
Lab ID cytogenetic lab	Steroids in induction: Prednisone or Dexamethasone
Date of birth	L' asparaginase in induction: yes or no
Gender	Dose of Methotrexate: gram/m2
Age at diagnosis	Therapy reduction: yes/no, agent, dose
Date of diagnosis	Day 6-9 BM evaluated
Hepatomegaly	Day 6-9 BM evaluated
Splenomegaly	Day 6-9 PB evaluated
Lymphnodes	Day 6-9 PB evaluated
Mediastinal involvement	Day 12-16 BM evaluated
Testicular infiltration	Day 12-16 BM evaluated
Hemoglobine	Start date and name of therapy block 1
Platelets	Start date and name of therapy block 2
White bloodcell count	Start date and name of therapy block 3
CNS involvement	Start date and name of therapy block 4
Percentage blasts in PB by morphology	Start date and name of therapy block 5
Percentage blasts in PB by immunology	Start date and name of therapy block 6
BM aspirate: percentage blasts morphologically	Start date and name of therapy block 7
BM aspirate: percentage blasts immunological	Start date and name of therapy block 8
Trephine % blasts morphologically	Irradiation and dose
Trephine % blasts immunology	Therapy Comments
Immunophenotype determined on PB or BM	Stemcell transplantation, type and date
Immunophenotype	Date of CR
Date karyotype	Date of relapse
Karyotype on PB or BM	Date and type of secondary malignancy
Karyotype (ISCN 1995 nomenclature)	Date and status at last follow up
Number of metaphases	Date of death
Ploidy	Cause of death
FISH for *ETV6-RUNX1*, *BCR-ABL*, *MLL-AF4*, and any other FISH performed.	General comments
Percentage of positive cells in FISH	
Number of assessed nuclei in FISH	
PCR for *ETV6-RUNX1*, *BCR-ABL*, *MLL-AF4*, and any other PCR performed.	
CRLF2 gene rearrangement	
JAK 1-3 mutation	
DNA index	
If available percentage of positive cells of CD33, CD 117, TdT, HLA-DR, CD19, CD10, CD20, CD22, CD79a, CD1, TCR a/b, TCR g/d, CD13, CD33, cylgM, CD2, CD3m, CD3cy, CD4, CD5, CD7, CD8	

Supplementary Table 3. Details of the various treatment protocols used in this study.

Study group	Protocol	Methotrexate (gram/m^2)	Anthracycline	Induction steroids	L-asparaginase
AIEOP	AIEOP ALL 95 SR	1[1]	No	Prednisone	Yes
AIEOP	AIEOP ALL 95 MR	1[1]	Yes	Prednisone	Yes
AIEOP	AIEOP ALL 95 HR	1[1]	Yes	Prednisone	Yes
AIEOP	AIEOP ALL 2000	1[1]	Yes	Prednisone	Yes
AIEOP	AIEOP ALL 2000 (SR1)	1[1]	Yes	Prednisone	Yes
AIEOP	AIEOP ALL 2000 (SR2)	1[1]	Yes	Prednisone	Yes
AIEOP	AIEOP ALL 2000 (MR1)	1[1]	Yes	Prednisone	Yes
AIEOP	AIEOP ALL 2000 (MR2)	1[1]	Yes	Prednisone	Yes
AIEOP	AIEOP ALL 2000 (DXM)	1[1]	Yes	Dexamethasone	Yes
AIEOP	AIEOP ALL 2000 (DXM-SR1)	1[1]	Yes	Dexamethasone	Yes
AIEOP	AIEOP ALL 2000 (PDN-MR1)	1[1]	Yes	Prednisone	Yes
AIEOP	AIEOP ALL 2000 (DXM-MR2)	1[1]	Yes	Dexamethasone	Yes
AIEOP	AIEOP ALL 2000 (PDN-MR2)	1[1]	Yes	Prednisone	Yes
BFM-A	ALL-BFM 95 SR	5	Yes	Prednisone	Yes
BFM-A	ALL-BFM 95 MR	5	Yes	Prednisone	Yes
BFM-A	ALL-BFM 2000 SR	5	Yes	Prednisone	Yes
BFM-A	ALL-BFM 2000 MR	5	Yes	Prednisone	Yes
BFM-G	ALL-BFM 95 SR	5	Yes	Prednisone	Yes
BFM-G	ALL-BFM 95 MR	5	Yes	Prednisone	Yes
BFM-G	ALL-BFM 2000 SR	5.0[2]	Yes	Prednisone	Yes
BFM-G	ALL-BFM 2000 MR	5.0[2]	Yes	Prednisone	Yes
BFM-G	ALL-BFM 2000 HR	5.0[2]	Yes	Prednisone	Yes
CCG	1952	No HD MTX	No	Prednisone	Yes
CCG	1961	No HD MTX	Yes	Prednisone	Yes
CCG	1991	No HD MTX	No	Dexamethasone	Yes
POG	9201	0.5[3]	No	No	No
POG	9405	1[4]	No	Prednisone	Yes
POG	9406	1[4]	No	Prednisone	Yes
POG	9605	0.5[3]	No	Prednisone	Yes
POG	9904	0.5[3]	No	Dexamethasone	Yes
POG	9905*	0.5[3]	No	Dexamethasone	Yes
POG	9906*	0.5[3]	No	Prednisone	Yes
DCOG	ALL8	5	Yes	Prednisone	Yes
DCOG	ALL9 NHR	3	No	Dexamethasone	Yes
DCOG	ALL9 HR	5	Yes	Dexamethasone	Yes
DCOG	ALL10	5	Yes	Prednisone	Yes
DFCI	95001 (SR)	4	Yes	Prednisone	Yes
DFCI	95001 (HR)	4	Yes	Prednisone	Yes
DFCI	00001 (SR)	4	Yes	Prednisone	Yes
DFCI	00001 (HR)	4	Yes	Prednisone	Yes
EORTC	EORTC CLG 58881	5	Yes	Prednisone	Yes
EORTC	EORTC CLG 58951	5[5]	Yes	Randomized trial	Yes
Israel	93-01(ALL -BFM 90 mod)	5	Yes	Prednisone	Yes
Israel	98-01(ALL-BFM 95 SR)	5	Yes	Prednisone	Yes
Israel	98-02(ALL-BFM 95 MR)	5	Yes	Prednisone	Yes
Israel	03-02-00(IC-BFM 2002)	5	Yes	Prednisone	Yes

Study group	Protocol	Methotrexate (gram/m2)	Anthracycline	Induction steroids	L'asparaginase
JACLS	JACLS ALL 97-SR	No HD MTX	Yes	Dexamethasone and Prednisone	Yes
JACLS	JACLS ALL 97-IR	No HD MTX	Yes	Dexamethasone and Prednisone	Yes
JACLS	JACLS ALL 97-HR	No HD MTX	Yes	Dexamethasone and Prednisone	Yes
JACLS	JACLS ALL 02-SR	No HD MTX	Yes	Prednisone	Yes
JACLS	JACLS ALL 02-ER	No HD MTX	Yes	Prednisone	Yes
JACLS	JACLS ALL 02-HR	No HD MTX	Yes	Prednisone	Yes
UKCLWP	ALL97	6-8	No	Randomized trial	Yes
UKCLWP	ALL97 HR1	6-8	No	Randomized trial	Yes
UKCLWP	ALL9799 B	No HD MTX	Yes	Randomized trial	Yes
UKCLWP	UKALLXI92	No HD MTX	No	Prednisone	Yes
UKCLWP	UKALL2003 A	No HD MTX	No	Dexamethasone	No
UKCLWP	UKALL2003 B	No HD MTX	Yes	Dexamethasone	Yes
UKCLWP	UKALL2003 C	No HD MTX	Yes	Dexamethasone	Yes
NOPHO	ALL92	5-8	Yes	Prednisone	Yes
NOPHO	Protocol mix (92-2000 or 2000 to Pilot)	5-8	Yes	Prednisone	Yes
NOPHO	ALL2000	5-8	Yes	Prednisone	Yes
PPLLSG	ALL IC2002	No HD MTX	Yes	Prednisone	Yes
SJCRH	Total 13BH	0.5[7]	Yes	Prednisone	Yes
SJCRH	Total 13BL	0.5[7]	Yes	Prednisone	Yes
SJCRH	Total XIV	0.5[7]	Yes	Prednisone	Yes
TCCSG	TCCSG L99-15 SR	3	Yes	Prednisone	Yes
TCCSG	TCCSG L99-15 HR	3	Yes	Prednisone	Yes
TCCSG	TCCSG L99-1502 HR	3	Yes	Prednisone	Yes
TCCSG	TCCSG L99-15 HEX18	3	Yes	Prednisone	Yes
TCCSG	TCCSG L99-15HEX0	3	Yes	Prednisone	Yes
CoALL	COALL92	1	Yes	Prednisone	Yes
CoALL	COALL92 HR	1	Yes	Prednisone	Yes
CoALL	COALL 97 Low Risk	1	Yes	Dexamethasone	Yes
CoALL	COALL 97 High Risk	1	Yes	Dexamethasone	Yes
CoALL	COALL 03 Low risk	1	Yes	No	No
TPOG	TPOG ALL97-SRE	1	Yes	Prednisone	Yes
TPOG	TPOG ALL97-HR	1	Yes	Prednisone	Yes
TPOG	TPOG ALL97-VHR	1	Yes	Prednisone	Yes
TPOG	TPOG-911	1	Yes	Prednisone	Yes
TPOG	TPOG ALL2002-SR	0.5[8]	Yes	Prednisone	No
TPOG	TPOG ALL2002-HR	0.5[8]	Yes	Prednisone	Yes

*Induction therapy (type of steroid, asparaginase, anthracycline) was based on initial NCI risk stratification, but subsequent treatment assignment was based on additional genetic and day 29 response criteria.

[1] First high dose MTX course is 1g/m^2, if tolerated 2nd course 2g/m^2.

[2] First high dose MTX course 0.5g/m^2, if tolerated 2nd course 2g/m^2, if tolerated following course 5g/m^2.

[3] First course of MTX 0.5g/m^2, if tolerated 2nd course 1g/m^2. If not tolerated, continue to reduce each dose by 25% until tolerated.
[4] DS patients not eligible for randomization to 2.5 mg/m^2 MTX.
[5] From September 2002, DS ALL patients were only enrolled in VLR and AR1 risk groups, and received 0.5g.m^2 MTX.
[6] Children <4 years of age receive 8 g/m^2, and those older received 6g/m^2.
[7]High dose MTX is limited to 0.5g/m^2 for all course, leucovorin rescue from T=30 and vigorous hydration.
[8] High dose MTX is limited to 0.5g/m^2, normal dose is 2.5 g/m^2 for SR and 5.0 g/m^2 for HR patients.

Supplementary Table 4. Patient characteristics and outcome parameters of the 5 excluded T cell DS-ALL patients.

ID	Age, y	Sex	WBC	CNS	Lymph nodes	Hepato megaly	Testis infiltration	Karyotype	CR	Relapse (RFS)	Dead (OS)
1	13.6	M	55.9	No	No	No	No	47,XY,+21c	Yes	No	No (101)
2	9.1	F	231.6	No	No	No	NK	47,XX,+21c	Yes	No	No (78)
3	2.2	M	50.2	No	No	No	No	47,XY,t(1;16)(p34),t(3;6)(q24;p12),del(4)(q34),der(7)t(1;7)(q32;q36),+21c[18]	Yes	Yes (13.2)	Yes (18.5)
4	11.2	M	0.6	No	Yes	Yes	No	NK	NK	NK	No (60)
5	3.5	M	5.5	No	NK	Yes	NK	47,XY,+21c[10]	Yes	No	No (154)

WBC, white blood cell count x 10^9/L; CNS, central nervous system; CR, complete remission; RFS, relapse free survival in months; OS, overall survival in months; M, male; F, female; NK, not known.

Supplementary Table 5. *JAK2* and *CRLF2* subgroup analysis

	***JAK2*/*CRLF2* cohort (n=182)**	**Residual cohort (n=471)**	**P-value**
Age at diagnosis (range)	5.1 (1.2-17.2)	5.0 (1.2-17.9)	0,6
Sex			
Male (%)	98 (54)	245 (52)	
Female (%)	84 (46)	226 (48)	0,68
Median initial WBC x 10^9/L (range)	11.7 (1.0-322)	9.5 (0.2-459)	0,15
Extra medullary disease			
CNS (%)	8/176* (4.5)	8/440* (1.8)	0.06
Molecular aberrations			
JAK1	2/141* (1.4)		
JAK2 R683	30/141* (21.3)		
IGH@-CRLF2	6/134* (4.5)		
P2RY8-CRLF2	87/134* (69.4)		
8-year OS	73 ± 5%	83 ± 8%	0,13
8-year EFS	62 ± 6%	71 ± 8%	0,21
8-year CIR	26 ± 6%	22 ± 8%	0,44

*Number of patients available for analysis.

Supplementary Table 6. Patient characteristics of NCI-SR DS-ALL patients considered HR by PdL DS risk group criteria.

	High risk modified model
Number	246
Age at diagnosis (range)	5.2 (1.2 - 9.9)
Sex	
Male	136
Female	110
Median initial WBC x 10^9/L (range)	16.4 (0.5 - 48.8)
Extra medullary disease	
CNS (%)	6/234* (2.6)
Lymph nodes (%)	64/159* (40.3)
Hepatomegaly (%)	100/171* (58.5)
Testis (%)	1/117* (<1)
Survival	
10-year OS	73±3%
10-year EFS	63±4%
10-year TRM	7±2%
2-year CIR	30±4%
Median time to relapse in years (range)	3.2 (4.4 months - 9.3 years)
Cytogenetic subgroups	171*
Normal karyotype (%)	71 (41.5)
MLL (%)	1 (<1)
ETV6-RUNX1 (%)	11 (6.4)
High hyperdiploidy (%)	18 (10.5)
Other (%)	70 (40.9)

WBC, white blood cell count; CNS, central nervous system; OS, overall survival; EFS, event-free survival; TRM, treatment-related mortality; CIR, cumulative incidence of relapse, *Number of patients available for analysis.

Supplementary Table 7. Specified cause of death for TRM.

Patient ID	Cause of death	Treatment phase	Study group
1	Infection	Induction	DFCI
2	Infection	Induction	AIEOP
3	Infection	Induction	UKCLWP
4	Suspected infection, unknown organism	Induction	NOPHO
5	Suspected infection, unknown organism	Induction	NOPHO
6	Infection and Epidermolysis Bullosa	Induction	UKCLWP
7	Gram positive infection: Streptococcus alpha	Induction	CCG
8	Pseudomonas aeruginosa	Induction	NOPHO
9	Pseudomonal aeruginosa septicaemia	Induction	TPOG
10	Serratia marcescens in blood and urine	Induction	CCG
11	Para-influenza pneumonitis	Induction	UKCLWP
12	Adenovirus during leukopenia	Induction	COALL
13	Candida Albicans pneumonia	Induction	SJCRH
14	Chemotherapy related toxcity	Induction	NOPHO
15	Chemotherapy related toxcity	Induction	BFM-Austria
16	Central nervous system toxicity	Induction	CCG
17	Coagulation disturbances (trombosis in oment to intestinal ischemia)	Induction	NOPHO
18	Haemorrhage	Induction	UKCLWP
19	Pseudomonal septicaemia	Delayed intensification	UKCLWP
20	Gram negative septicaemia, aspiration and septic shock	Delayed intensification	UKCLWP
21	Rhinovirus	Delayed intensification	UKCLWP
22	Respiratory syncytial virus	Delayed intensification	CCG
23	Sepsis	Interim maintenance	BFM-Germany
24	Cardiopulmonal decompensation	Interim maintenance	BFM-Germany
25	Infection during aplasia	Consolidation	BFM-Germany
26	Infection and neutropenia	Consolidation	UKCLWP
27	Haemorrhage	Consolidation	UKCLWP
28	Atypical pneumonia during aplasia	Consolidation	BFM-Germany
29	Candida septicaemia	Intsified consolidation	POG
30	Infection	Maintenance	DFCI
31	Fulminant sepsis, multi organ faillure	Maintenance	BFM-Germany
32	Detection of adenovirus in stool and serum, acute liver failure	Maintenance	BFM-Germany
33	Infection, pneumonia	Maintenance	BFM-Germany
34	Sepsis, aplasia	Maintenance	BFM-Germany
35	Septic shock	Maintenance	UKCLWP
36	Septic shock	Maintenance	TPOG
37	Septic shock, Acute Respiratory Distress Syndrome	Maintenance	DCOG
38	Pseudomonal septicaemia	Maintenance	UKCLWP
39	Pneumonia, septicaemia, acute renal failure	Maintenance	UKCLWP
40	Infection and lympho proliferative disease (EBV associated)	Maintenance	POG
41	Bacterial pneumonia	Maintenance	UKCLWP
42	Bacillus meningitis	Maintenance	CCG
43	Aspergillus pneumonia	Maintenance	UKCLWP
44	RSV pneumonitis	Maintenance	UKCLWP
45	Influenza	Maintenance	UKCLWP
46	Cardiopulmonary failure secondary to overwhelming sepsis, presumed viral etiology	Maintenance	POG
47	Cardiopulmonal circulatory failure during conditioning for SCT	Maintenance	BFM-Germany
48	Chemotherapy related toxcity	Maintenance	CCG
49	Renal insuffiency	Maintenance	EORTC-CLG
50	Haemorrhage	Maintenance	UKCLWP