The long-term impact of *in vitro* drug sensitivity on risk stratification and treatment outcome in acute lymphoblastic leukemia of childhood (CoALL 06-97)

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Online Supplementary Table S1. Characteristics of patients in the CoALL 06 – 97 trial.

	All patients (n)	Low risk (n) [standard/reduced/ intensified]	High risk (n) [standard/reduced]
Number of patients	667	[183/93/47]	[270 / 74]
Gender:			
Male	381	[102/46/31]	[160 / 42]
Female	286	[81/47/16]	[110 / 32]
Age at diagnosis (years)			
≥ 1 year < 5 years	329	[123/64/27]	[81 / 34]
≥ 5 years < 10 years	184	[60/29/20]	[57 / 18]
≥ 10 years < 15 years	119		[102 / 17]
≥ 15 years	35		[30 / 5]
WBC at diagnosis (×10⁹/L)			
< 10	311	[132/ 62/ 31]	[72 / 14]
≥ 10 to < 25	129	[51/ 31/ 16]	[24 / 7]
≥ 25 to < 50	87		[71/ 16]
≥ 50 to <100	60		[45 / 15]
≥ 100	80		[58 / 22]
Lineage:			
Common-ALL	415	[143 /71 / 43]	[131/ 27]
PreB-ALL	134	[39/ 22/ 4]	[50/ 19]
Pro-B-ALL	23		[21/ 2]
T lineage	94		[68/ 26]
Not determined	1	[1/ /]	

Online Supplementary Table S2. Treatment schedule of patients in the CoALL-06-97 trial.

Element	Drug	Dose	Day(s) given in low risk therapy	Day(s) given in high risk therapy
Prephase	Daunorubicin (24h) i.v. Methotrexate (i.t.)[§]	36 mg/m² 8/10/12 mg	day -7	day -7
Induction	Vincristine (i.v.) Daunorubicin (i.v.) Methylprednisolone (p.o.)	1,5 mg/m² (max.2 mg) 36 mg/m² 60 mg/m²	day 1, 8, 15, 22 day 1, 8, 15 day 1 - 28	day 1, 8, 15, 22 day 1, 8, 15 day 1 - 28
Consolidation	Cyclophosphamide (i.v.) Methotrexate (24h i.v.) L-Asparaginase (i.v.) VM-26 (i.v.) Cytarabine (i.v.) High-dose cytarabine (i.v.) Mercaptopurine (p.o.) Thioguanine (p.o.) Methotrexate (i.t.)[§]	900 mg/m² 1000 mg/m² 45000 U/m² 165 mg/m² 300 mg/m² 3000 mg/m² 100 mg/m² 100 mg/m² 8/10/12 mg	None day 29, 43, 78 day 31, 59, 80 day 45 day 45 day 57, 58 q12 h x 4 day 29 - 35, 78 - 84 day 43 - 49 day -7, 29, 43, 57, 78	day 29, 43 day 30, 44, 57, 71 day 31, 45, 87, 108 day 59, 73 day 59, 73 day 85, 86 q12 hrs.x 4 106,107 q 12hrs.x 4 day 43 - 49, 57 - 64, day 71 - 77 day -7, 30, 44, 57, 71
CNS prophylaxis	Mercaptopurine (p.o.) Methotrexate (i.t.)[§] Cranial irradiation	50 mg/m² 8/10/12 mg	day 92 - 120 day 92, 95, 106, 109 none	day 127 - 155 day 127,130, 134, 137 #
Reinduction	Vincristine (i.v.) Doxorubicin (i.v.) L-Asparaginase (i.v.) Dexamethasone (p.o.) Cyclophosphamide (i.v.) Cytarabine (i.v.) Thioguanine (p.o.) Methotrexate (i.t.)[§]	1,5 mg/m² (max.2 mg) 30 mg/m² 45000 U/m² 10 mg/m² 900 mg/m² 90 mg/m² 100 mg/m² 8/10/12 mg	day 1, 8 day 1, **8*** day 9 day 1 - 14 **(1 - 8**)** day 15 day 16 - 19 day 15 - 22 day 1, 15, 29	day 1, 8, 22, 29 day 1, **8***, 22, **29*** day 9, 30 day 1 - 14 **(1 - 8**)** + 22 - 36 **(22 - 29**)** day 36, 50 day 37 - 40, 51 - 54 day 36 - 42, 50 - 56 day 1, 22, 36

*[§]age-related dose; [#]all T – ALL patients and B-Precursor-ALL WBC > 200x10⁹/L (before 2001 > 100x10⁹/L) or with 100-200x10⁹/L and >1000 blasts/µL at day 7 after prephase; *in bold: doxorubicin omitted in patients with treatment reduction; **in bold: days on which dexamethasone was given to patients receiving treatment reduction*

Online Supplementary Table S3. Probability of 10-year event-free survival according to the results of *in vitro* sensitivity testing in the CoALL 06–97 and 05-92 trials.

	All patients		Low Risk		High Risk	
	COALL 97	COALL 92	COALL 97	COALL 92	COALL 97	COALL 92
Score 3+4	0.79 (SE 0.03) n = 167	0.81 (SE 0.06) n = 39	0.87 (SE 0.04) n = 93	0.81 (SE 0.10) n = 16	0.71 (SE 0.06) n = 74*	0.82 (SE 0.08) n = 23
Score 5+6	0.74 (SE 0.03) n = 226	0.78 (SE 0.04) n = 101	0.80 (SE 0.04) n = 114	0.85 (SE 0.05) n = 46	0.66 (SE 0.04) n = 112	0.73 (SE 0.06) n = 45
Score 7-9	0.69 (SE 0.05) n = 105	0.68 (SE 0.06) n = 63	0.79 (SE 0.06) n = 47	0.75 (SE 0.12) n = 12	0.57 (SE 0.07) n = 58	0.66 (SE 0.07) n = 51
Score 8+9	0.67 (SE 0.08) n = 41	0.53 (SE 0.09) n = 32	0.81 (SE 0.09) n = 16	0.50 (SE 0.21) n = 4	0.47 (SE 0.11) n = 25	0.53 (SE 0.09) n = 28
(Score 3-9)	0.75 (SE 0.02) n = 510	0.76 (SE 0.03) n = 203	0.83 (SE 0.02) n = 254	0.82 (SE 0.03) n = 74	0.66 (SE 0.03) n = 244	0.73 (SE 0.04) n = 129

Without 12 high-risk patients with a score of 3 or 4 who were not allocated to reduced therapy according to PVA score. Comparison within the score groups (3+4, 5+6, 7-9) showed no significant difference between the two studies for all patients, or low-risk and high-risk patients separately.

Online Supplementary Table S4. Participating investigors and centers involved in the CoALL 06-97 trial.

Participating investigator	Address		Phone/Fax
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Online Supplementary Figure S1. Ten-year probability of event-free survival in CoALL 06-97 patients. (A) According to prednisolone (PRED) score (log-rank test: PVA score 1 *versus* 3 *P*=0.049). (B) According to vincristine (VCR) score.