Online supplement S1

A) Additional information on patients and diagnosis

1. Exclusion criteria were irreversible severe cardiac, hepatic, or renal dysfunction unrelated to BL, a psychiatric disorder, pregnancy, or a lack of written informed consent.
2. Patients were not excluded from the clinical trial when c-myc rearrangement could not be assessed, and neither bcl-2 nor bcl-6 and EBV expression were within study objectives.
3. Pathology reports were reviewed centrally.
4. Diagnostic criteria for BL diagnosis were a monotonous proliferation of medium-sized, basophilic cells associated with a "starry sky" pattern, or a more pleomorphic morphology in the Burkitt-like variant; very high proliferative index by Ki-67 staining; expression of B-cell antigens CD19, CD20, CD22 with membrane IgM and light chain restriction, and negativity for nuclear TdT.
5. The pre-treatment evaluation included computed tomography (CT) of the chest and abdomen, bone marrow (BM) trephine biopsy, and cerebrospinal fluid (CSF) analysis in patients with neurological symptoms.

B) Additional information on treatment protocol (see enclosed Table)

1. The program consisted of a 5-day prednisone-cyclophosphamide pre-phase followed by four or six rituximab/chemotherapy cycles, depending on the disease stage.
2. Each chemotherapy course included a single rituximab infusion of 375 mg/m^2, and two more rituximab doses were planned at the end of chemotherapy (total 6-8 doses).
3. Each cycle was followed by the administration of granulocyte colony-stimulating factor (G-CSF) to shorten the neutropenic period and optimize the planned intercycle time.
4. Associated anti-infectious prophylaxis comprised continuous oral co-trimoxazole, acyclovir, and ciprofloxacin/fluconazole during neutropenic phases ($<0.5x10^9$/L).
5. Central nervous system (CNS) prophylaxis consisted of intrathecal chemotherapy, and cranial irradiation was administered only to patients with CNS involvement (24 Gy). Supplemental local radiotherapy (36 Gy) was delivered after the completion of chemotherapy in cases of initial mediastinal involvement or residual active tumor.

Table S1B. Treatment Protocol

Phase/Drug	Dose and units*	Route†	Days
Pre-phase			
Cyclophosphamide (CY)	200 mg/m^2	i.v.	from -5 to -1
Prednisone (PDN)	60 mg/m^2	p.o.	from -5 to -1
Course A1, A2			
Rituximab (R)	375 mg/m^2	i.v.	1
Dexamethasone (DXM)	10 mg/m^2	p.o.	2-6
Vincristine (VCR)	2 mg	i.v.	2
Methotrexate (HD-MTX)	1.5 g/m^2	i.v.	2 (10% in 30 min, 90% over 23.5 hr, folinic acid rescue starting 36 hours after beginning of MTX infusion to an MTX plasma concentration < 0.25 μM/L)
Ifosphamide (IF)	800 mg/m^2	i.v.	2-6
Cytarabine (Ara-C)	150 mg/m^2/bd#	i.v.	5-6
Teniposide/Etoposide (TP/VP)	100 mg/m^2	i.v.	5-6
G-CSF	5 mcg/kg	s.c.	from day 8 until neutrophil recovery
CNS prophylaxis:			
MTX	15 mg	i.t.	2,6
Ara-C	40 mg	i.t.	2,6
DXM	4 mg	i.t.	2,6
Course B1, B2			
Rituximab	375 mg/m^2	i.v.	1
VCR	2 mg	i.v.	2
DXM	10 mg/m^2	p.o.	2-6
CY	200 mg/m^2	i.v.	2-6
HD-MTX	1.5 g/m^2	i.v.	2 (folinic acid rescue as above)
Adriamycin (ADR)	25 mg/m^2	i.v.	5-6
G-CSF	5 mcg/kg	s.c.	from day 8 until neutrophil recovery

CNS prophylaxis :			
MTX	15 mg	i.t.	2,6
Ara-C	40 mg	i.t.	2,6
DXM	4 mg	i.t.	2,6
Course C1, C2			
Rituximab	375 mg/m^2	i.v.	1
DXM	10 mg/m^2	p.o.	2-6
Vindesine (VDS)	3 mg/m^2	i.v.	2
HD-MTX	1.5 g/m^2	i.v.	2 (folinic acid rescue as above)
HD-Ara-C	2 g/m^2/bd	i.v.	6
VP	250 mg/m^2	i.v.	5-6
G-CSF	5 mcg/kg	s.c.	from day 8 until neutrophil recovery

*Dose reductions in patients > 55 years: *Cycle A1-A2*: no VCR; MTX 500 mg/m^2; IF 400 mg/m^2; VM/VP 60 mg/m^2; Ara-C 60 mg/m^2; CY and IF day 2 and day 4 optional. *Cycle B1-B2*: VCR 1 mg; MTX 500 mg/m^2; CY 200 mg/m^2. *CNS prophylaxis:* only MTX 12 mg i.t. day 2. *Cycle C:* not administered.

[#]bd, twice daily

[†]i.v., intravenous; p.o., oral; s.c., subcutaneous; i.t., intrathecal.

C) Additional information on response evaluation and definitions

1. Complete remission (CR) was defined as resolution of all disease-related signs and symptoms. In B-ALL, CR required hemoglobin >10 g/dL with neutrophil and platelet counts of >1.0 and >100 × 10^9/L, respectively, and normocellular or regenerating bone marrow without Burkitt blast cells, evaluated after course 1.
2. Progressive disease was defined as the loss of CR status, confirmed by cytological or histological evidence.
3. Patients not achieving CR after three courses were considered non-responders (NR).
4. Early death (ED) was defined as death before the treatment response could be assessed.
5. Overall survival (OS) was calculated from the date of diagnosis to death, and disease-free survival (DFS) from the date of CR to relapse or death.
6. The cumulative incidence of relapse (CIR) was calculated from the date of CR to recurrence, and treatment-related mortality (TRM) from the date of diagnosis to death by treatment complications, during both induction and consolidation therapy.

D) Additional information on statistics

1. For statistical analysis, probabilities of CR were compared between groups using the chi-squared test with Yate's correction. DFS and survival curves were plotted using the Kaplan-Meier method and compared by the log-rank test.
2. Multivariate analyses were carried out using Cox's linear regression model and included all variables associated with a significant P value (< 0.05) in univariate prognostic analysis.

Online supplement S2

Table S2A. Characteristics of patients with treatment failure

UPN	*Age*	*ECOG*	HIV	Diagnosis	Stage	Cause of death	Survival/remission duration	Cycle
Induction death								
84	40	0	neg	Lymphoma	IV	Encephalopathy	40 (days)	A1
88	43	2	pos	Lymphoma	IV	Infection	32	A1
92	48	2	neg	Lymphoma	II	Infection	31	A1
13	48	2	neg	Lymphoma	IV	Infection	62	A1
66	48	4	neg	Leukemia	NA	Infection/MOF	28	A1
89	51	0	neg	Lymphoma	IV	Infection	52	B1
51	55	2	pos	Leukemia	NA	Infection	49	A1
114	57	1	neg	Leukemia	NA	Infection/Respiratory failure	22	A1
2	57	0	neg	Lymphoma	III	Infection	43	A1
18	60	3	neg	Leukemia	NA	Infection	50	A1
63	64	1	neg	Leukemia	NA	Ictus cerebri	21	A1
100	65	2	pos	Leukemia	NA	Infection	22	A1
60	73	1	neg	Leukemia	NA	Hemorrhage	42	A1
93	73	0	neg	Lymphoma	III	Infection	33	A1
Refractory disease								
47	24	0	neg	Lymphoma	IV		45.7 (months)	
76	38	1	pos	Leukemia	IV	Disease	7	
102	40	1	neg	Lymphoma	IV		8.6	
21	47	2	neg	Leukemia	IV	Disease	4.6	
36	47	3	neg	Leukemia	IV	Disease	4.7	
82	59	3	neg	Lymphoma	IV	Disease	5.5	
46	63	2	neg	Leukemia	IV	Disease	7.7	
67	68	1	neg	Lymphoma	III	Disease	7.13	
Death in remission								
50	45	3	neg	Lymphoma	II	Infection	7.3 (months)	
48	55	0	neg	Lymphoma	III	Secondary AML	42.0	
68	56	3	neg	Leukemia	NA	Infection	1.1	
85	60	2	neg	Leukemia	NA	Infection	2.9	
4	60	2	neg	Lymphoma	I	Sudden death	29.5	
116	62	1	neg	Lymphoma	I	Infection	4.6	
64	70	2	neg	Leukemia	NA	Infection	1.4	
Relapse						**Mean intercycle time (days)**		
15	17	1	neg	Leukemia	NA	26	5.0 (months)	
74	30	2	pos	Leukemia	NA	32.6	5.5	
39	31	1	neg	Lymphoma	III	25.8	4.9	
49	43	0	neg	Lymphoma	IV	30.6	6.8	
94	44	3	neg	Leukemia	NA	23.6	4.2	
112	45	2	pos	Leukemia	NA	50.5	3.6	
30	58	2	neg	Leukemia	NA	29.2	5.5	
61	62	1	neg	Leukemia	NA	30.6	5.9	
52	66	3	neg	Leukemia	NA	28	3.0	
23	69	1	neg	Lymphoma	II	28	24.3*	
35	78	4	neg	Lymphoma	IV	48	5.4	

Abbreviations: MOF, multiorgan failure; AML, acute myeloid leukemia; NA, not applicable or not available.

*Single late relapse observed in a patient with Burkitt-like lymphoma (CD10+ CD20+ with 100% proliferative index determined by Ki-67 staining at diagnosis); recurrence documented by fine needle biopsy of abdominal mass, described as large B-cell lymphoma

Table S2B. Drug dose reductions in patients failing therapy, according to treatment phase/cycles

	Induction cycles A1-B1 (N 38)	**Postinduction cycles A2/C1-A3/C3 (N 56)**
NR patients (n=8)		
Dose reduced	0 (0%)	2 (3.5%), VDS 17%
Dose omitted	1 (3%), R	3 (5%), R
Relapse patients (n=11)		
Dose reduced	4 (10.5%), MTX 34%, DOX 50%, IFO 50%, VCR 50%	6 (11%), 3 MTX 50%, 2 IFO 50%, VCR 50%
Dose omitted	6 (16%), R 3, MTX 3	0 (0%)
Total patients (n=19)		
Dose reduced	4 (10.5%)	8 (14.5%)
Dose omitted	7 (18%)	3 (5%)

Abbreviations: R, rituximab; VDS, vindesine; MTX, methotrexate; DOX, doxorubicin; IFO, ifosfamide; VCR, vincristine (no. and per cent reductions indicated for each drug)

Online supplement S3

Table S3A. Toxicity of first induction course (A1) and subsequent courses (B1- C2/B3) according to treatment intensity

	Protocol A	**Protocol B**	**P**
First induction course (A1)			
No. of patients	76	29	-
Median age, years (range)	41 (17-66)	65 (45-78)	.0001
Hematologic toxicity			
neutrophils < $0.5x10^9$/L, median days (range)	7 (0-25)	8 (0-23)	.46
neutrophils <$0.5x10^9$/L >10 days, no. (%)	20/72 (28)	11/27 (41)	.21
platelets < $20x10^9$/L, median days (range)	3 (0-45)	5 (0-32)	.36
Nonhematologic toxicity grade >2, no. (%)			
gastrointestinal	16 (21)	8 (27)	.45
liver	21 (28)	11 (38)	.3
metabolic	8 (10)	11 (38)	.001
renal	4 (5)	2 (7)	.7
neurological	3 (4)	4 (14)	.7
cardiovascular	2 (3)	2 (7)	.3
respiratory	3 (4)	2 (7)	.5
other	4 (5)	5 (17)	.05
Fever > 38°C, median days (range)	2 (0-18)	1 (0-11)	.4
Infections, no. (%)			
sepsis/bacteriemia	23 (30)	10 (34)	.7
pneumonia	10 (13)	8 (28)	.08
other	14 (18)	8 (28)	.3
Other courses (B1-C2/B3)			
No. of patients	70	21	-
No. of courses	302	72	-
Hematologic toxicity			
neutrophils < $0.5x10^9$/L, median days (range)	2 (0-15)	2 (0-34)	.12
platelets < $20x10^9$/L, median days (range)	0 (0-38)	0 (0-29)	.02
Nonhematologic toxicity grade >2, no. (%)			
gastrointestinal	39 (13)	8 (11)	.678
liver	21 (7)	3 (4)	.38
metabolic	5 (2)	4 (5)	.05
renal	0	1 (1)	.04
neurological	2 (0.6)	0	.49
cardiovascular	1 (0.3)	2 (3)	.03
respiratory	1 (0.3)	1 (1)	.27
other	3 (1)	3 (4)	.054
Fever > 38°C, median days (range)	0 (0-12)	0 (0-6)	.65
Infections, no. (%)			
sepsis/bacteriemia	24 (8)	3 (4)	.26
pneumonia	9 (3)	5 (7)	.11
other	27 (9)	9 (12)	.36

Protocol A, age ≤55 years; Protocol B, age >55 years.

Table S3B. Toxicity of first induction course (A1) and subsequent courses (B1-C2/B3) according to HIV status

	HIV negative	HIV positive	P
First induction course (A1)			
No. of patients	90	15	-
Median age, years (range)	48 (17-78)	38 (30-65)	.0051
Hematologic toxicity			
neutrophils < $0.5x10^9$/L, median days (range)	6 (0-25)	8 (0-22)	.34
neutrophils <$0.5x10^9$/L >10 days, no. (%)	26/90 (29)	5/14 (36)	.60
platelets < $20x10^9$/L, median days (range)	3 (0-32)	3.5 (0-45)	.67
Nonhematologic toxicity grade >2, no. (%)			
gastrointestinal	21 (23)	3 (20)	.78
liver	24 (27)	8 (53)	.04
metabolic	15 (17)	4 (27)	.35
renal	5 (6)	1 (7)	.86
neurological	5 (6)	2 (13)	.26
cardiovascular	4 (4)	0	.40
respiratory	4 (4)	1 (7)	.71
other	8 (9)	1 (7)	.78
Fever > 38°C, median days (range)	2 (0-18)	2 (0-7)	.53
Infections, no. (%)			
sepsis/bacteriemia	27 (30)	6 (40)	.44
pneumonia	14 (16)	4 (27)	.29
other	18 (20)	4 (27)	.56
Other courses (B1-C2/B3)			
No. of patients	79	12	-
No. of courses	329	45	-
Hematologic toxicity			
neutrophils < $0.5x10^9$/L, median days (range)	2 (0-34)	2 (0-15)	.02
platelets < $20x10^9$/L, median days (range)	0 (0-38)	0 (0-16)	.23
Nonhematologic toxicity grade >2, no. (%)			
gastrointestinal	37 (11)	10 (22)	.04
liver	18 (5)	6 (13)	.04
metabolic	9 (3)	0	.26
renal	1 (0.3)	0	.71
neurological	2 (0.6)	0	.60
cardiovascular	3 (0.9)	0	.52
respiratory	2 (0.6)	0	.60
other	6 (1.8)	0	.36
Fever > 38°C, median days (range)	0 (0-9)	0 (0-12)	.01
Infections, no. (%)			
sepsis/bacteremia	25 (8)	2 (4)	.44
pneumonia	11 (3)	3 (7)	.27
other	26 (8)	10 (22)	.002