

Phase II Window Study on Rituximab in Newly Diagnosed Pediatric Mature B-Cell Non-Hodgkin's Lymphoma and Burkitt Leukemia

Andrea Meinhardt, Birgit Burkhardt, Martin Zimmermann, Arndt Borkhardt, Udo Kontny, Thomas Klingebiel, Frank Berthold, Gritta Janka-Schaub, Christoph Klein, Edita Kabickova, Wolfram Klapper, Andishe Attarbaschi, Martin Schrappe, and Alfred Reiter

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ABSTRACT

Purpose

The activity of rituximab in pediatric B-cell non-Hodgkin's lymphoma (B-NHL) has not yet been determined. We conducted a phase II window study to examine activity and tolerability of rituximab in newly diagnosed pediatric B-NHL.

Patients and Methods

Patients younger than age 19 years with CD20⁺ B-NHL with at least one measurable site were eligible. Treatment consisted of rituximab at 375 mg/m² administered intravenously on day 1; concomitant therapy consisted of rasburicase, intrathecally (IT) triple drug (methotrexate, cytarabine, and prednisolone) on days 1 and 3 for CNS-positive patients and steroids only for anaphylaxis. Response criterion was the product of the two largest perpendicular diameters of one to three lesions and/or the percentage of blasts in bone marrow (BM) or peripheral blood (PB) within 24 hours before rituximab and on day 5. Responders had $\geq 25\%$ decrease of at least one lesion or BM or PB blasts and no disease progress at other sites. Response rate (RR) was set at 45% for unfavorable activity or at 65% for favorable activity.

Results

From April 2004 to August 2008, 136 patients were enrolled. National Cancer Institute Common Toxicity Criteria 3/4 toxicities attributable to rituximab were general condition, 15%; fatigue, 13%; anaphylaxis, 7%; infection, 3%; glutamic-oxaloacetic transaminase/glutamic-pyruvic transaminase, 8%; no capillary leakage; and no toxic death. Forty-nine patients were not evaluable for response because of withdrawal from the study ($n = 16$), IT therapy in CNS-negative patients ($n = 8$), corticosteroid treatment ($n = 3$), technical inadequacy of response evaluation ($n = 21$), or no evaluable lesion ($n = 1$). Of 87 evaluable patients, 36 were responders (RR, 41.4%; 95% CI, 31% to 52%); among them, 27 of 67 with Burkitt lymphoma and seven of 15 with diffuse large B-cell lymphoma. A response was more frequently observed in BM (12 of 18) compared with solid tumor lesions (36 of 108; $P = .007$).

Conclusion

Rituximab is active as a single-agent in pediatric B-NHL even though the RR was lower than requested in the phase II plan.

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INTRODUCTION

Since almost all pediatric mature B-cell non-Hodgkin's lymphoma (B-NHL) patients express CD20,^{1,2} rituximab, a monoclonal chimeric anti-CD20 antibody, may offer new treatment options. The addition of rituximab significantly improved outcome of adults with aggressive mature B-NHL³⁻⁶ and is considered the new standard of care.⁷ In contrast, rituximab is not yet established in the treat-

ment of pediatric B-NHL, mainly because of the lack of prospective studies determining its role. However, the beneficial effect of rituximab in the treatment of adults with aggressive B-NHL cannot simply be conferred to pediatric B-NHL. First, the outcome of pediatric B-NHL patients receiving chemotherapy alone is superior to that of adults.^{3-6,8-12} Second, the standard chemotherapy regimens differ significantly between pediatric and adult populations, and the beneficial effect of rituximab in adults

From the Non-Hodgkin's Lymphoma-Berlin-Frankfurt-Münster Study Center, Justus Liebig University Giessen, Giessen; University Hospital Schleswig-Holstein/Campus Kiel, Kiel; Center of Child and Adolescent Medicine, Hannover Medical School, Hannover; Center of Child and Adolescent Medicine, Heinrich Heine University, Düsseldorf; Center of Child and Adolescent Medicine, Albert Ludwigs University, Freiburg; Johann Wolfgang Goethe University, Frankfurt; University of Cologne, Cologne; University Medical Center Hamburg-Eppendorf, Hamburg; Charles University, University Hospital Motol, Prague, Czech Republic; and St. Anna Children's Hospital, Vienna, Austria.

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Corresponding author: Alfred Reiter, MD, Department of Pediatric Hematology and Oncology, Center of Child and Adolescent Medicine, Justus Liebig University, Feulgenstraße 12, 35392 Giessen, Germany; e-mail: alfred.reiter@paediat.med.uni-giessen.de.

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varies according to the intensity of chemotherapy.^{5,6,11} Third, pediatric B-NHL differs from that of adults in terms of biology. Approximately 70% of pediatric mature B-NHL patients have Burkitt lymphoma/leukemia (BL/B-AL), which is a rare subtype in adults in whom it represents < 10% of aggressive B-NHL cases. Although limited series reported favorable outcome of adult BL/B-AL patients when rituximab was added to hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone),¹¹ dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin),¹³ or GMALL (German Multicenter Study Group for Acute Lymphoblastic Leukemia) treatment,¹² no results from randomized trials are available regarding the beneficial effect of rituximab compared with chemotherapy alone. In those randomized trials proving the efficacy of rituximab in adult aggressive B-NHL, the vast majority of patients had diffuse large B-cell lymphoma (DLBCL),³⁻⁶ which accounts only for a minority of pediatric B-NHLs.^{14,15} Furthermore, recent studies indicate biologic differences between pediatric and adult DLBCL, with pediatric DLBCL being predominantly of the germinal center subtype, expressing Bcl-2 in only 40% and Bcl-6 in 90% of cases.² Interestingly, clinical data on adult DLBCL suggested that the beneficial effect of rituximab is more prominent in adult Bcl-2-positive and Bcl-6-negative DLBCL, while few or no positive effects were reported in Bcl-2-negative and Bcl-6-positive DLBCL.^{16,17}

Thus, the question arises of whether rituximab might be an effective drug in pediatric B-NHL. Phase II studies determining the activity in pediatric B-NHL are lacking, and testing the efficacy of rituximab as a single agent in a phase II study in children with recurrent B-NHL is difficult or even impossible because of the low number of cases. We therefore designed a phase II window study to evaluate the rituximab response in children with newly diagnosed B-NHL before beginning the established chemotherapy regimen. To avoid compromising the patients' chance of cure, we decided on a short window of only 5 days, with all patients starting chemotherapy at day 5 after rituximab administration.

PATIENTS AND METHODS

Eligibility criteria included newly diagnosed CD20⁺ mature B-NHL or B-AL, age younger than 19 years, and at least one index lesion available for response evaluation and measured within 24 hours before rituximab. Exclusion criteria were complete resection; Karnofsky performance score ≤ 20%; pretreatment; impaired renal, heart, or liver function; ongoing or previous hepatitis B virus infection; pre-existing disease; known hypersensitivity to murine proteins; or pregnancy.

Between April 2004 and August 2008, 136 patients were enrolled from 42 centers in Germany, Austria, Switzerland, and the Czech Republic. They provided informed consent according to the Declaration of Helsinki. Approval of the study was obtained from the ethical committees of the principal investigator (A.R.) and the participating investigators.

Diagnosis

B-NHL subtypes were classified according to WHO classification¹⁸ and centrally reviewed. Staging according to St. Jude Staging System¹⁹ included physical examination, peripheral blood (PB) and bone marrow (BM) smears, cerebrospinal fluid (CSF) analyses, serum lactate dehydrogenase (LDH) level, and adequate imaging techniques. Initial CNS disease was diagnosed if lymphoma cells were present in the CSF, if there were intracerebral tumors, or if cranial nerve palsy not caused by extradural lymphoma was present.

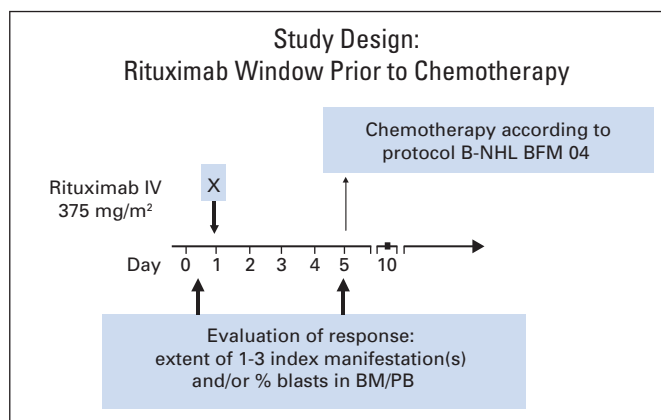


Fig 1. Outline of the treatment strategy for the B-Cell Non-Hodgkin's Lymphoma–Berlin-Frankfurt-Münster Group rituximab window study. IV, intravenously; BM, bone marrow; PB, peripheral blood.

Treatment

One dose of rituximab at 375 mg/m² was given intravenously on day 1 (Fig 1). Rituximab infusion started with 50 mg/h and increased every 30 minutes by 50 mg/h to a maximum of 200 mg/h. Because of infusion-associated fever and increased risk of tumor lysis syndrome (TLS), a protocol amendment was introduced with a slower infusion rate of 10 mg/m²/h for hours 1 and 2, 20 mg/m²/h for hours 3 to 5, 40 mg/m²/h for hours 6 to 9, and 80 mg/m²/h thereafter (infusion time amendment). Patients were to receive premedication with paracetamol and antihistamine, hydration, and rasburicase for TLS prevention.

Response Evaluation

Within 24 hours before starting rituximab, at least one index lesion accessible for restaging on day 5 was identified. For each lesion, the product of the two largest perpendicular diameters (PPD) was determined using the most appropriate imaging method: ultrasound, magnetic resonance imaging, or computed tomography (CT) for peripheral and abdominal sites; magnetic resonance imaging/CT for head/neck; and CT for thorax. Furthermore, the percentage of blasts in BM and PB was determined. On day 5 and before beginning chemotherapy, index lesions were restaged with identical imaging methods, investigators, and instrument settings. If there were initial BM and PB blasts, BM and PB were re-examined on day 5. Response criteria were as follows: complete remission (CR) was defined as complete disappearance of all lymphoma manifestations; partial response (PR) was defined as ≥ 50% reduction in the PPD of at least one index lesion; objective effect (OE) was defined as ≥ 25% but < 50% decrease of the PPD of at least one index lesion; and stable disease (SD) was defined as < 25% regression. For BM and PB, the same ranges for blast reduction applied. Progressive disease (PD) was defined as appearance of new lesions and/or ≥ 25% increase in the PPD of at least one index lesion and/or ≥ 25% increase of blasts in BM and PB. Patients were classified as responders if there was CR, PR, or OE of at least one index site and no signs of progression at other sites. Patients were classified as nonresponders in the absence of at least OE or in case of PD.

Patients should not receive any chemotherapy and/or corticosteroids during the window, except for (1) intrathecal (IT) therapy (methotrexate, cytarabin, prednisolone) on days 1 and 3 for CNS-positive patients only, while for CNS-negative patients, IT therapy was withheld until day 5 at the beginning of chemotherapy; (2) anaphylactic reactions to rituximab requiring corticosteroid therapy (these patients were excluded from response analysis); or (3) progression of lymphoma during the window, as defined above; in such cases, immediately beginning cytoreductive chemotherapy was recommended, and the patient was counted as a nonresponder.

Subsequent Chemotherapy

Following the 5-day rituximab window, patients were offered an opportunity to be enrolled onto the ongoing Berlin-Frankfurt-Münster (BFM)

Group phase IV study (B-NHL-BFM 04). The cytoreductive prephase of that study was to begin on day 5 following rituximab administration.

Toxicity

National Cancer Institute–Common Toxicity Criteria (NCI-CTC) scores were documented prior to and during the rituximab window and additionally during the prephase and the first course of chemotherapy. Serious adverse events (SAEs) were defined as any alteration within 30 days after initiation of rituximab therapy that could endanger the patient or act as a contraindication for continuation of therapy.

Study Design and Statistical Analysis

The primary objective was to study the response rate (RR) to rituximab in newly diagnosed pediatric B-NHL/B-AL. Secondary objectives were to

study the toxicity profile of rituximab and associations of RR with histologic subtypes, involved compartments (BM, PB, nodal tumor), pretherapeutic LDH, and outcome after chemotherapy. An optimal two-stage phase II design according to Simon was used.²⁰ An RR of 65% was defined as favorable while an RR of 45% was chosen as the upper limit of an unfavorable RR. With α and $\beta = 5\%$, more than 16 responders among the first 33 evaluable patients were required to continue with patient accrual. Final evaluation was planned after accrual of at least 79 evaluable patients, including at least 35 patients with low-risk features (LDH < 500 U/L) and at least 35 patients with high-risk features (LDH ≥ 500 U/L and/or BM and/or CNS involvement). With α and $\beta = 5\%$, more than 42 responders among 79 evaluable patients were required for a favorable RR. If there were 42 or fewer responders among 79 evaluable patients, an unfavorable RR would be stated. The RR calculation was based on patients treated and evaluated as specified under Response Evaluation.

In a second analysis, patients with deviations from protocol prescriptions but available data on tumor size and percentage of blasts in BM/PB before rituximab and on day 5 were included as well as patients withdrawn from the window because of clinically suspected but not verified disease progression. Associations of the rituximab response with B-NHL subtypes, involved compartments, and LDH were analyzed using the χ^2 or Fisher's exact test. Associations of the RR to rituximab with treatment outcome of patients was analyzed by comparing the cumulative incidences of relapse, calculated according to Kalbfleisch and Prentice.²¹ The statistical analysis was carried out using SAS-PC, Version 9.12 (SAS Institute, Cary, NC). Data were updated as of February 23, 2009. Six monthly toxicity reports, interim analyses, and final analyses were approved by an external data safety and monitoring committee.

RESULTS

Patient Characteristics

Patient characteristics are given in Table 1. The distribution of age and sex in the 136 patients enrolled onto the study were comparable with those of 501 B-NHL patients simultaneously enrolled in the B-NHL-BFM 04 study, but patients diagnosed with BL/B-AL were overrepresented in the rituximab window study (75% v 58%; $P = .001$). According to the eligibility criteria, patients with resected stage I or II and patients with a low performance score were underrepresented in the rituximab study.

Toxicity

Table 2 summarizes CTC toxicities attributable to rituximab. Toxicities were considered attributable to rituximab if they appeared for the first time during the window or if there was aggravation of toxicities that existed before rituximab administration. Pre-existing toxicities before starting rituximab are shown in Appendix Table A1 (online only). Toxicities recorded during the rituximab window are depicted in Appendix Table A2 (online only). The most frequent stage III/IV toxicities attributable to rituximab were infusion-related reactions (Table 2). Furthermore, elevated liver enzymes and hematologic toxicities were reported in $> 5\%$ of patients. Eleven patients (8%) developed a TLS. After the infusion time amendment, the frequency of TLS decreased from 11% to 7%. There were no hepatitis B reactivations, no progressive multifocal leukoencephalopathy, no capillary leak syndrome, and no therapy-related deaths.

SAEs

Sixteen SAEs were reported (Table 3), 11 of which were probably or possibly caused by rituximab and/or lymphoma. One patient with renal failure, presenting with pretherapeutic infiltration of both kidneys, impaired renal function, hypertension, and hypertensive encephalopathy, was not eligible for the study. Five SAEs

Table 1. Patient Characteristics

Characteristic	All Rituximab Patients (n = 136)		Patients Not Evaluable for Response (n = 49)		Patients Evaluable For Response (n = 87)		P*
	No.	%	No.	%	No.	%	
Sex							
Female	28	21	10	20	18	21	1.000
Male	108	79	39	80	69	79	
Age, years							
Median	10.4		11.7		9.7		.004
Range	1.5-17.5		2.4-17.5		1.5-17.2		
< 10	67	49	21	43	46	53	
10-14	47	35	13	27	34	39	
≥ 15	22	16	15	31	7	8	
Stage							
I	4	3	—	—	4	5	.4
II	26	19	11	22	15	17	
III	67	49	23	47	44	50	
IV, CNS-negative	5	4	2	4	3	3	
IV, CNS-positive	4	3	1	2	3	3	
B-AL, CNS-negative	15	11	8	16	7	8	
B-AL, CNS-positive	11	8	2	4	9	10	
N/E†	4	3	2	4	2	2	
LDH, U/L							
< 500	72	53	26	53	46	53	.086
500-< 1,000	19	14	3	6	16	18	
$\geq 1,000$	45	33	20	41	25	29	
General condition (Karnofsky status, %)							
90-100	28	21	7	14	21	24	.252
70-80	69	51	24	49	45	52	
50-60	29	21	12	25	17	20	
30-40	9	7	5	10	4	5	
10-20	1	1	1	2	—	—	
Histology							
BL/B-AL	102	75	35	71	67	77	.680‡
DLBCL	27	20	12	24	15	17	
PMLBL	2	1	1	2	1	1	
B-NHL (DD: BL/DLBCL)	3	2	1	2	2	2	
Follicular lymphoma	2	1	—	—	2	2	

Abbreviations: B-AL, Burkitt leukemia; N/E, not evaluable; LDH, lactate dehydrogenase; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; PMLBL, primary mediastinal large B-cell lymphoma; B-NHL, B-cell non-Hodgkin's lymphoma; DD, differential diagnosis.

*Comparing not evaluable v evaluable patients.

†Most often due to missing initial lumbar puncture.

‡Burkitt lymphoma/leukemia (BL/B-AL) v other histologies.

Table 2. Number of Patients With Toxicities Attributable to Rituximab

Toxicity	Grade			
	I	II	III	IV
Physical symptoms				
General condition	17	14	12	9
Rigors, chills	25	18	1	—
Fatigue (lethargy, malaise, asthenia)	18	12	7	10
Hypotension	12	2	3	1
Hypertension	7	4	3	1
Hematologic				
Hemoglobin, g/L	16	20	11	3
Leukocytes $\times 10^9/L$	26	14	5	2
Granulocytes $\times 10^9/L$	9	5	2	6
Platelets $\times 10^9/L$	2	3	6	2
Infections				
Infection	4	10	3	1
Fever	28	17	1	—
Gastrointestinal				
Nausea	23	14	8	1
Vomiting	13	25	1	—
Stomatitis	—	2	—	—
Diarrhea	6	6	3	—
Kidney				
Creatinine elevation	8	3	1	—
Liver				
Bilirubin elevation	1	1	1	—
AST/ALT elevation	8	11	9	2
Cardiotoxicity				
Cardiac function	—	—	—	—
Arrhythmia	1	—	—	—
Skin				
Urticaria (hives, welts, wheals)	3	9	1	—
Other changes in the skin	5	1	—	—
Neurologic toxicity				
Central	10	—	—	2
Peripheral	3	1	—	—
Anaphylaxis	10	15	8	1
Pain				
Headache	14	8	6	1
Myalgia	5	2	4	1
Arthralgia	4	1	1	1
Other	7	7	8	5
Other				
Hyperglycemia	15	3	1	—
Bronchospasm	—	1	5	—
Angioedema	2	1	—	—
Peripheral edemas	5	4	2	—
Disseminated intravascular coagulation	—	—	1	—
Capillary leakage	—	1	—	—

NOTE. Toxicity first occurred during the window or aggravation of toxicities existing prior to rituximab administration.

Table 3. SAEs Reported for the Rituximab Window or Within 30 Days After Rituximab Administration

No. of Patients	Time Point	SAE	Course
7	Day 1	Allergic reaction*	Recovery without late effects
1	Day 2	Toxic hepatopathy with elevated AST, ALT, no clinical symptoms*	Recovery without late effects
1	Day 1	Focal seizure with secondary generalization*	Recovery without late effects
1	Day 3	Intestinal perforation (tumor infiltration of the intestine) with subsequent peritonitis; therapy: partial ileum resection, ileostoma†	Recovery without late effects
1	Day 3	Renal failure due to acute cell lysis,* requiring dialysis; hypertension, generalized seizure requiring antihypertensive and antiepileptic medication; patient had tumor infiltration of both kidneys, impaired renal function, and hypertensive leucoencephalopathy prior to rituximab†	Recovery without late effects
2	Days 16-21	Severe mucositis after first course of chemotherapy according to protocol B-NHL-BFM 04‡	Recovery without late effects
3	Days 19-25	Severe infection after first course of chemotherapy according to protocol B-NHL-BFM 04‡	Recovery without late effects

Abbreviations: SAE, severe adverse event; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; B-NHL-BFM 04, B-Cell Non-Hodgkin's Lymphoma-Berlin-Frankfurt-Münster Group phase IV study.

*Probably related to rituximab.

†Probably related to rituximab and/or lymphoma.

‡Probably related to the following B-NHL-BFM 04 chemotherapy.

(severe mucositis or infection in aplasia) were reported between day 16 and day 25 after rituximab administration—thus after the first course of chemotherapy—and might therefore be attributable to chemotherapy.

Response to Rituximab

Of the first 33 patients evaluable for response and enrolled between April 2004 and May 2006, 17 were responders, meaning that patient accrual could be continued as planned. By August 2008, 87 of

the 136 patients enrolled were evaluable for response, including 41 low-risk patients, 43 high-risk patients, and three patients with unspecified risk group. In 33 patients, the response was not evaluable per protocol because PPD was not determined ($n = 10$), time points of measurements were not correct ($n = 9$), the BM smear at day 5 was not representative ($n = 2$), CNS-negative patients had IT therapy ($n = 8$), corticosteroids were used ($n = 3$), or there was no measurable lesion ($n = 1$; Appendix Table A3, online only). Sixteen patients were withdrawn from the study because of allergic reactions ($n = 8$), TLS ($n = 2$), clinically suspected but not verified PD ($n = 4$), lymphoma-associated ileus ($n = 1$), or incorrect diagnosis ($n = 1$; Appendix Table A4, online only). Eighty-seven patients were evaluable per protocol for response to rituximab. Characteristics of patients evaluable for response and of those not evaluable did not significantly differ except evaluable patients had younger age (median of 9.7 years [range, 1.5 to 17.2 years] v median of 11.7 years [range 2.4 to 17.5 years]; $P = .004$; Table 1).

Thirty-six of 87 patients who were evaluable per protocol were responders and 51 were nonresponders, (Table 4) resulting in an RR of 41.4% (95% CI, 31% to 52%). In 50 patients, response evaluation was based on one index tumor lesion, and in 10 patients, response evaluation was based on BM alone. In 14 patients, two index lesions were evaluated, and in 13 patients, three sites were evaluated. In one of the latter, PR and SD were observed in two solid lesions but the

Table 4. Evaluation of Response to Rituximab

Table 4. Evaluation of Response to Mitoximab										
No. and Type of Lesions Evaluated	Response per Lesion	Response per Patient			Response in Solid Lesions			Response in BM/PB		
		No. of Patients	No. of Responders	%	No. of Lesions	No. of Responses	%	No. of Samples	No. of Responses	%
1 lesion (n = 60)										
Tumor	CR	1	1		1	1				
	PR	8	8		8	8				
	OE	6	6		6	6				
	SD	33	0		33	0				
	PD	2	0		2	0				
BM	CR	3	3					3	3	
	PR	2	2					2	2	
	OE	2	2					2	2	
	SD	3	0					3	0	
	PD	0	0					0	0	
2 lesions (n = 14)										
Tumor/tumor	PR/PR	1	1		2	2				
	PR/OE	1	1		2	2				
	OE/SD	2	2		4	2				
	SD/SD	5	0		10	0				
	PD/SD	1	0		2	0				
Tumor/BM	PR/CR	3	3		3	3		3	3	
PB/BM	CR/SD	1	1					2	1	
3 lesions (n = 13)										
Tumor/tumor/tumor	OE/PR/PR	1	1		3	3				
	OE/SD/SD	2	2		6	2				
	SD/SD/SD	3	0		9	0				
	PD/SD/OE	1	0		3	1				
	PD/SD/SD	1	0		3	0				
	PD/PD/SD	1	0		3	0				
Tumor/tumor/BM	PR/OE/CR	1	1		2	2		1	1	
	CR/PR/SD	1	1		2	2		1	0	
	OE/SD/SD	1	1		2	1		1	0	
Tumor/tumor/CNS	PR/SD/PD	1	0		2	1		0	0	
Total		87	36		108	36		18	12	
Percent				41			33			67
Abbreviations: BM, bone marrow; PB, peripheral blood; CR, complete remission; PR, partial response; OE, objective effect; SD, stable disease; PD, progressive disease.										

Abbreviations: BM, bone marrow; PB, peripheral blood; CR, complete remission; PR, partial response; OE, objective effect; SD, stable disease; PD, progressive disease.

patients had single L3 blasts in the CSF on day 5, although CSF had initially been negative. This patient was classified as a nonresponder. Details of the responses per evaluated sites and patients are depicted in Table 4.

The RR to rituximab was not significantly different concerning sex, age, histologic subtype, and LDH, but in B-AL patients, the RR was higher (13 of 16; Table 5). Seven of nine B-AL patients without IT therapy and six of seven B-AL patients with IT therapy, respectively, were responders. However, the RR differed concerning the compartments evaluated comparing BM and PB with solid lymphoma (Table 4). A response was observed in 12 of 18 BM and PB samples evaluated (67%) and in 36 of 108 solid lesions evaluated (33%; $P = .007$). In six patients, BM and solid lesions were evaluated for response to rituximab. The response was PR-solid/CR-BM in three patients, PR-solid/OE-solid/CR-BM in one, CR-solid/PR-solid/SD-BM in one, and OE-solid/SD-solid/SD-BM in one.

In a further analysis, in addition to the 87 patients evaluable per protocol for response, nine patients who were not evaluable for response (eg, corticosteroid or IT therapy during the window, although they were CNS-negative) were included (patients 34, 38, 39, 72, 94, 95, 98, 120, and 123; Appendix Table A3); five were counted as responders

and four as nonresponders. Four patients withdrawn from the window because of clinically suspected but not verified disease progression were included as nonresponders (patients 23, 42, 113, and 116; Appendix Table A4). Of these 100 patients, 41 were responders (RR, 41%; 95% CI, 31% to 51%).

All 136 patients enrolled in the rituximab window study were subsequently treated according to B-NHL-BFM 04 study protocols (median follow-up of 1.8 years; range, 0.2 to 4.4 years). Seven patients suffered from relapse. No patient suffered from toxic death. Among the 87 patients evaluable for response to rituximab, there was no significant difference in the cumulative incidence of relapses at 3 years between rituximab responders and nonresponders ($P = .37$). Two of 36 rituximab responders relapsed (cumulative incidence of relapse, 0.06; SE, 0.04) compared with one of 51 rituximab nonresponders (cumulative incidence of relapse, 0.02; SE, 0.02).

DISCUSSION

To the best of our knowledge, this is the first phase II study determining the activity of rituximab in pediatric mature B-NHL. Data on

Table 5. Patient Characteristics of Rituximab Nonresponders Compared With Responders

Characteristic	Non-responder (n = 51)		Responder (n = 36)		P
	No.	%	No.	%	
Sex					
Female	12	24	6	17	.592
Male	39	77	30	83	
Age, years					
Median	9.2		10.0		.535
Range	1.5-16.1		3.4-17.2		
< 10	29	57	17	47	
10-15	19	37	15	42	
≥ 15	3	6	4	11	
Stage					
I	2	4	2	6	< .001
II	12	24	3	8	
III	31	61	13	36	
IV, CNS-negative	1	2	2	6	
IV, CNS-positive	0	0	3	8	
B-AL, CNS-negative	2	4	5	14	
B-AL, CNS-positive	1	2	8*	22	
N/D†	2	4	—	—	
LDH, U/L					
< 500	28	55	18	50	.877
500-< 1,000	9	18	7	19	
≥ 1,000	14	28	11	31	
Histology					
BL/B-AL	40	78	27	75	.798‡
DLBCL	8	16	7	19	
PMLBL	—	—	1	3	
B-NHL (DD: BL/DLBCL)	2	4	—	—	
Follicular lymphoma	1	2	1	3	

Abbreviations: B-AL, Burkitt leukemia; N/D, not determined; LDH, lactate dehydrogenase; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; PMLBL, primary mediastinal large B-cell lymphoma; B-NHL, B-cell non-Hodgkin's lymphoma; DD, differential diagnosis.

*Two of the eight responders did not receive intrathecal therapy during the window although they were CNS-positive.

†Due to missing initial lumbar puncture.

‡BL/B-AL v other histologies.

Abbreviations: B-AL, Burkitt leukemia; N/D, not determined; LDH, lactate dehydrogenase; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; PMLBL, primary mediastinal large B-cell lymphoma; B-NHL, B-cell non-Hodgkin's lymphoma; DD, differential diagnosis.

*Two of the eight responders did not receive intrathecal therapy during the window although they were CNS-positive.

†Due to missing initial lumbar puncture.

‡BL/B-AL v other histologies.

rituximab in pediatric B-NHL are limited and include case reports and retrospective studies hampered by the possibility of a positive reporting bias and of limited value for validating efficacy.²² Prospective studies so far have evaluated rituximab only in combination with chemotherapy in nonrandomized studies.²³ The objectives of an ongoing Children's Oncology Group (COG) phase II study²⁴ on newly diagnosed pediatric intermediate-risk B-NHL are pharmacokinetics and safety of rituximab when added to chemotherapy. Interim analysis of 48 patients showed that rituximab can safely be added to French-American-British Mature B-Cell Lymphoma/Leukemia 96 (FAB-LMB96) chemotherapy.

The design of this study allowed the evaluation of the activity of rituximab as a single agent in an upfront window before chemotherapy. In view of a possible subsequent phase III trial testing whether rituximab can substitute for chemotherapy drugs, we predefined rather high RRs as "favorable" and "unfavorable" in the study plan. Although this ambitious RR was not achieved, the study clearly shows that rituximab is active as a single agent in pediatric mature B-NHL

and B-AL. A comparable RR to rituximab was observed in BL/B-AL and DLBCL patients. There was also no significant difference in the RR according to sex, age, or initial LDH level. Interestingly, a higher RR of rituximab was observed in BM and PB compared with solid tumor manifestations. Whether this observation reflects methodologic differences in measuring the response rather than real differences in the kinetics of the response in the different compartments remains unclear. The rapid blast clearance in the BM is in line with earlier studies in a murine model. That study focused on in vivo factors influencing B-cell depletion after rituximab. The examinations showed a distinct hierarchical kinetic of B-cell depletion, which was first achieved for circulating B-cells in blood, followed by lymph nodes.²⁵ These data suggest that the effect of rituximab might be fast in PB and BM but might require more time to induce a measurable response in different compartments or bulky disease.

In our study, the extremely short window of only 5 days was chosen to avoid withholding the beginning of chemotherapy for an undue time. Thus, the full effect of a single dose of rituximab might not have been measurable at such an early time point after administration, meaning the real RR to rituximab might be underestimated in our study. In addition, pharmacokinetic data suggest that multiple doses of rituximab are necessary to reach a plateau in the serum level that correlates with rituximab response.²⁶

The mechanisms of action of rituximab have not been completely elucidated, but they include antibody-dependent cellular cytotoxicity,²⁷ complement-dependent cytotoxicity,²⁷ and induction of apoptosis.²⁸ Data on additional mechanisms are derived from in vitro studies, which showed a sensitization of B-NHL cell lines to chemotherapeutic drugs via selective downregulation of antiapoptotic proteins Bcl-2 and Bcl-xL.^{29,30} Therefore, the combination of rituximab with chemotherapy may have additive, if not synergistic, effects.

The observed side effects of rituximab monotherapy were in accordance with those in adults. The effects were usually mild and mainly infusion-related. No unexpected SAE was reported. The interim analyses of the COG phase II trial showed that rituximab can safely be added to a pediatric chemotherapeutic regimen,²⁴ which is in line with recent experiences in adults.³¹

With this report, which determined the activity of rituximab in pediatric B-NHL, and the safety, feasibility, and pharmacokinetic data from the COG trial,²⁴ all prerequisites are now available for including rituximab in phase III trials to test its efficacy in combination with chemotherapy. However, the fact that intravenously administered rituximab reaches the CSF poorly needs to be taken into account when planning future studies.^{32,33} Determining the possible roles of rituximab in the treatment of pediatric B-NHL may include studies in two directions: to test whether rituximab can improve the outcome of patients with increased risk for treatment failure by recruiting additional mechanisms of lymphoma-directed treatment and to test whether rituximab can substitute for chemotherapy drugs in the treatment of low-risk patients. Most importantly, only controlled clinical trials will allow for careful monitoring of possible late effects of rituximab, especially in the pediatric population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

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AUTHOR CONTRIBUTIONS

Conception and design: Birgit Burkhardt, Martin Zimmermann, Arndt Borkhardt, Udo Kontny, Thomas Klingebiel, Gritta Janka-Schaub, Edit Kabickova, Martin Schrappe, Alfred Reiter

Administrative support: Andrea Meinhardt, Birgit Burkhardt, Andishe Attarbaschi, Alfred Reiter

Provision of study materials or patients: Andrea Meinhardt, Birgit Burkhardt, Arndt Borkhardt, Udo Kontny, Thomas Klingebiel, Frank Berthold, Gritta Janka-Schaub, Christoph Klein, Edit Kabickova, Wolfram Klapper, Andishe Attarbaschi, Martin Schrappe, Alfred Reiter

Collection and assembly of data: Andrea Meinhardt, Birgit Burkhardt, Martin Zimmermann, Andishe Attarbaschi, Alfred Reiter

Data analysis and interpretation: Andrea Meinhardt, Birgit Burkhardt, Martin Zimmermann, Udo Kontny, Gritta Janka-Schaub, Alfred Reiter

Manuscript writing: Andrea Meinhardt, Birgit Burkhardt, Martin Zimmermann, Alfred Reiter

Final approval of manuscript: Andrea Meinhardt, Birgit Burkhardt, Martin Zimmermann, Arndt Borkhardt, Udo Kontny, Thomas Klingebiel, Frank Berthold, Gritta Janka-Schaub, Christoph Klein, Edit Kabickova, Wolfram Klapper, Andishe Attarbaschi, Martin Schrappe, Alfred Reiter

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Appendix

Principal investigators in this study include the following: R. Mertens (Aachen); A. Gnekow (Augsburg); G. Henze (Berlin, Charité); N. Jorch (Bielefeld); A. Pekrun (Bremen); M. Suttrop (Dresden); A. Borkhardt (Düsseldorf); A. Sauerbrey (Erfurt); W. Holter (Erlangen); B. Kremens (Essen); Th. Klingebiel (Frankfurt); C. Niemeyer (Freiburg); A. Reiter (Gießen); C. Urban (Graz); J.F. Beck (Greifswald); St. Burdach and D. Körholz (Halle); G. Janka-Schaub (Hamburg); K. Welte and C. Klein (Hannover); A. Kulozik (Heidelberg); N. Graf (Homburg); F.M. Fink (Innsbruck); F. Zintl and J.F. Beck (Jena); W. Dupuis and A. Leipold (Karlsruhe); F.K. Tegtmeyer and M. Nathrath (Kassel); M. Schrappe (Kiel); F. Berthold (Köln); D. Körholz (Leipzig); P. Bucszy (Lübeck); U. Mittler (Magdeburg); S. Burdach (München); A. Borkhardt and I. Schmidt (München); H. Jürgens (Münster); A. Jobke and W. Scheuerlen (Nürnberg); E. Kabickova (Prag); O. Peters (Regensburg); S. Bielack (Stuttgart); J. Greiner (St. Gallen); R. Handgretinger (Tübingen); K.M. Debatin (Ulm); H. Gadner (Wien, St. Anna Kinderspital); P.G. Schlegel (Würzburg); F. Niggli (Zurich).

Table A1. National Cancer Institute Common Toxicity Criteria Toxicities Evaluated Prior to the Start of Rituximab

Table 10. All National Cancer Institute Common Toxicity Criteria Toxicities Evaluated Prior to the Start of Metastasis						
Toxicity	No.	Patients With Grade (%)				
		0	I	II	III	IV
Physical symptoms						
General condition	128	25.0	37.5	22.7	12.5	2.3
Rigors, chills	124	98.4	1.6	0	0	0
Fatigue (ie, lethargy, malaise, asthenia)	123	55.3	16.3	18.7	4.9	4.9
Hypotension	124	95.2	4.0	0.8	0	0
Hypertension	123	95.1	2.4	0.8	1.6	0
Hematologic						
Hemoglobin, g/L	127	48.0	22.0	19.7	8.7	1.6
Leukocytes ×10 ⁹ /L	124	93.5	5.6	0.8	0	0
Granulocytes ×10 ⁹ /L	106	93.4	1.9	0	3.8	0.9
Thrombocytes ×10 ⁹ /L	124	94.4	0.8	1.6	3.2	0
Infections						
Infection	122	78.7	9.8	6.6	4.9	0
Fever	124	82.3	12.1	5.6	0	0
Gastrointestinal						
Nausea	122	77.9	13.9	7.4	0.8	0
Vomiting	123	80.5	10.6	8.1	0.8	0
Stomatitis	123	99.2	0.8	0	0	0
Diarrhea	124	87.9	8.9	2.4	0.8	0
Kidney						
Creatinine elevation	125	92.0	7.2	0.8	0	0
Liver						
Bilirubin elevation	120	95.0	3.3	1.7	0	0
AST/ALT elevation	125	65.6	22.4	9.6	2.4	0
Cardiotoxicity						
Cardiac function	111	95.5	3.6	0.9	0	0
Arrhythmia	118	96.6	2.5	0	0.8	0
Skin						
Urticaria (ie, hives, welts, wheals)	124	100	0	0	0	0
Other skin alterations	124	97.6	2.4	0	0	0
Neurologic						
Central	124	96.0	3.2	0	0	0.8
Peripheral	126	96.8	3.2	0	0	0
Anaphylaxis	124	99.2	0.8	0	0	0
Pain						
Headache	123	90.2	3.3	5.7	0.8	0
Myalgia	124	93.5	1.6	2.4	2.4	0
Arthralgia	123	92.7	1.6	3.3	2.4	0
Other	128	51.6	15.6	20.3	10.9	1.6
Other						
Hyperglycemia	112	89.3	8.9	0.9	0.9	0
Bronchospasm	123	98.4	1.6	0	0	0
Angioedema	122	100	0	0	0	0
Peripheral edema	124	95.2	2.4	1.6	0.8	0
Disseminated intravascular coagulation	115	99.1	0	0	0.9	0
Capillary leakage	108	100	0	0	0	0

Table A2. National Cancer Institute Common Toxicity Criteria Toxicities Evaluated During the 5-Day Rituximab Window

TABLE 12. National Cancer Institute Common Toxicity Criteria Toxicities Evaluated During the 6-Day Maximum Window						
Toxicity	No.	Percent of Patients With Grade:				
		0	I	II	III	IV
Physical symptoms						
General condition	130	14.6	40.8	18.5	18.5	7.7
Rigors, chills	125	64.0	20.8	14.4	0.8	0
Fatigue (ie, lethargy, malaise, asthenia)	130	37.7	25.4	18.5	9.2	9.2
Hypotension	124	83.1	12.1	1.6	2.4	0.8
Hypertension	123	84.6	7.3	4.1	3.3	0.8
Hematology						
Hemoglobin, g/L	129	28.7	28.7	27.1	13.2	2.3
Leukocytes ×10 ⁹ /L	128	61.7	21.9	10.9	3.9	1.6
Granulocytes ×10 ⁹ /L	101	77.2	8.9	5.0	3.0	5.9
Platelets ×10 ⁹ /L	124	87.9	1.6	2.4	6.5	1.6
Infections						
Infection	127	74.8	7.1	11.0	6.3	0.8
Fever	129	57.4	27.9	14.0	0.8	0
Gastrointestinal						
Nausea	128	55.5	23.4	13.3	7.0	0.8
Vomiting	130	63.8	13.8	21.5	0.8	0
Stomatitis	125	97.6	0.8	1.6	0	0
Diarrhea	125	84.8	7.2	5.6	2.4	0
Kidney						
Creatinine elevation	126	84.1	11.9	3.2	0.8	0
Liver						
Bilirubin elevation	111	97.3	0.9	0.9	0.9	0
AST/ALT elevation	119	58.0	17.6	12.6	10.1	1.7
Cardiotoxicity						
Cardiac function	77	97.4	1.3	1.3	0	0
Arrhythmia	111	98.2	1.8	0	0	0
Skin						
Urticaria (ie, hives, welts, wheals)	126	89.7	2.4	7.1	0.8	0
Other changes in the skin	124	94.4	4.8	0.8	0	0
Neurologic toxicity						
Central	125	89.6	8.8	0	0	1.6
Peripheral	124	96.8	2.4	0.8	0	0
Anaphylaxis	126	73.0	7.9	11.9	6.3	0.8
Pain						
Headache	124	71.0	15.3	8.1	4.8	0.8
Myalgia	124	87.9	4.8	2.4	4.0	0.8
Arthralgia	124	91.9	4.8	1.6	0.8	0.8
Other pain	129	58.1	14.7	14.0	8.5	4.7
Other						
Hyperglycemia	107	78.5	17.8	2.8	0.9	0
Bronchospasm	122	95.1	0	0.8	4.1	0
Angioedema	119	97.5	1.7	0.8	0	0
Peripheral edemas	122	86.9	7.4	4.1	1.6	0
Disseminated intravascular coagulation	109	99.1	0	0	0.9	0
Capillary leakage	104	99.0	0	1.0	0	0

Table A3. Response Not Evaluable per Protocol (n = 33)

Patient ID No.	Age (years)	Stage	LDH (U/L)	Histology	Reason	Remarks	Best Estimation of Response
2	13	II	250	BL	PPD not determined	No diameters defined	Not possible
7	2	II	234	DLBCL	PPD not determined	Only one diameter defined (maximum, 4 cm on day 0 and 1.5 cm on day 4); initial measurement on day -6; response evaluation on day 4	Not possible
52	11	III	353	DLBCL	PPD not determined	No diameters defined (volume, 860 mL on day 0 and 831 mL on day 5)	Not possible
55	7	III	1,152	BL	PPD not determined	No diameters defined	Not possible
59	4	III	1,137	BL	PPD not determined	No diameters defined	Not possible
76	11	III	3,574	BL	PPD not determined	No diameters defined	Not possible
91	4	II	382	BL	PPD not determined	No diameters defined (volume, 2 mL on day 0 and 1.3 mL on day 5)	Not possible
106	10	III	308	BL	PPD not determined	No diameters defined (3.0 × 1.8 cm on day 0 and not evaluated on day 5)	Not possible
107	15	III	168	DLBCL	PPD not determined	Only one diameter measured (5.8 cm on day 0 and 5.0 cm on day 5); corticosteroids on day -3 because of an allergic reaction	Not possible
127	14	III	280	DLBCL	PPD not determined	No diameters defined	Not possible
26	16	III	441	PMLBL	Incorrect time point of measurement	Initial measurement on day -3 (1.5 × 1.5 cm on day 3 and 1.5 × 1.5 cm on day 5); corticosteroids on day 1 because of chills and fever	Not possible
38	15	N/E	309	BL	Incorrect time point of measurement	Initial measurement on day -4; iliac LN (ultrasound): OE on day 5	Response
65	5	III	165	B-NHL (BL; DD: DLBCL)	Incorrect time point of measurement	Initial measurement on day -6; index lesion on day 5: SD	Not possible
80	9	II	241	BL	Incorrect time point of measurement	Initial measurement on day -7; only one diameter defined	Not possible
96	15	II	182	DLBCL	Incorrect time point of measurement	Initial measurement on day -5; no diameters defined	Not possible
99	8	III	472	BL	Incorrect time point of measurement	Initial measurement on day -9, right cervical LN (MRI) on day 5: SD	Not possible
69	4	II	250	BL	Incorrect time point of measurement	Measurement on day 7 after starting chemotherapy on day 5	Not possible
71	16	IV, CNS-negative	631	BL	Incorrect time point of measurement	Measurement on day 6 after starting chemotherapy on day 5	Not possible
6	6	III	442	BL	Incorrect time point of measurement	Day 5 response not evaluable because of intestinal perforation (tumor infiltration of the intestine) on day 3	Not possible
10	10	IV, CNS-negative	7,890	B-AL	Not evaluable on day 5	BM, 79% blasts on day 0 and not representative* on day 5	Not possible
92	6	IV, CNS-positive	2,940	B-AL	Not evaluable on day 5	BM, 94% blasts on day 0 and not representative* on day 5; LDH, 2,780 U/L on day 1 and 12,450 U/L on day 2	Not possible
79	11	II	224	BL	No measurable index lesion	Measurable index lesion initially completely resected	Not possible
9	14	II	260	DLBCL	Corticosteroids before/during window	Corticosteroids on day 1 because of prolonged cerebral seizure; no imaging	Not possible
98	12	IV, CNS-negative	1,128	B-AL	Corticosteroids before/during window	Corticosteroids on day 1 because of chills; BM, 87% on day 0 and 4% on day 5: PR	Response

(continued on following page)

Table A3. Response Not Evaluable per Protocol (n = 33) (continued)

Patient ID No.	Age (years)	Stage	LDH (U/L)	Histology	Reason	Remarks	Best Estimation of Response
120	15	IV, CNS-negative	2,224	BL	Corticosteroids before/during window	Corticosteroids on days -23, -18, and -9; left thigh (MRI) on day 5: PD; BM: SD	Nonresponse
29	12	IV, CNS-negative	2,075	B-AL	IT therapy before/during window	BM, 90% blasts on day 0 and not representative* on day 5	Not possible
34	15	IV, CNS-negative	15,071	B-AL	IT therapy before/during window	BM, 95% blasts on day 0 and 95% blasts on day 5	Nonresponse
39	12	IV, CNS-negative	262	B-AL	IT therapy before/during window	IT therapy (MTX, ARA-C, no steroids) on day 1; tonsil (ultrasound) on day 5: SD	Nonresponse
72	16	III	471	DLBCL	IT therapy before/during window	IT therapy (MTX) on day -2; mediastinal lymphoma (CT) on day 5: OE	Response
75	8	III	3,900	BL	IT therapy before/during window	IT therapy (MTX, ARA-C, PDN) on day 1; no diameters defined	Not possible
94	12	II	246	DLBCL	IT therapy before/during window	IT therapy (MTX, ARA-C, PDN) on day 1; cervical LN (ultrasound) on day 5: OE; dorsal LN on day 5: SD	Response
95	4	IV, CNS-negative	311	B-AL	IT therapy before/during window	IT therapy (MTX, ARA-C, PDN) on day -1; initial measurement on day -4; response evaluation on day 6 before starting chemotherapy: PR	Response
123	8	III	3,112	BL	IT therapy before/during window	IT therapy (MTX, ARA-C, PDN) on day 4; retroversal LN (ultrasound) on day 5: SD	Nonresponse

Abbreviations: ID, identification; LDH, lactate dehydrogenase; BL, Burkitt lymphoma; PPD, product of the two largest perpendicular diameters; DLBCL, diffuse large B-cell lymphoma; PMLBL, primary mediastinal B-cell lymphoma; N/E, not evaluable; LN, lymph node; OE, objective effect; B-NHL, B-cell non-Hodgkin's lymphoma; DD, differential diagnosis; SD, stable disease; MRI, magnetic resonance imaging; B-AL, Burkitt leukemia; BM, bone marrow; PR, partial response; PD, progressive disease; IT, intrathecal; MTX, methotrexate; ARA-C, cytarabine; CT, computed tomography; PDN, prednisolone.

*BM without crumbles, questionable blood-diluted marrow.

Table A4. Response Not Evaluable per Protocol Due to Withdrawal From Study (n = 16)

Patient ID No.	Age (years)	Stage	LDH (U/L)	Histology	Day of Withdrawal	Cause for Withdrawal	Remarks	Best Estimation of Response
13	5	II	404	DLBCL	1	Allergic reaction	Corticosteroids to treat allergic reaction, start of chemotherapy on day 5, no imaging	Not possible
14	13	IV, CNS-positive	1,235	B-AL	1	Allergic reaction	Corticosteroids to treat allergic reaction, start of chemotherapy on day 1, no imaging	Not possible
27	15	II	169	DLBCL	1	Allergic reaction	Withdrawal after ≈10% of the rituximab target dose, corticosteroids to treat allergic reaction, start of chemotherapy on day 2, no imaging	Not possible
73	17	III	226	DLBCL	1	Allergic reaction	Withdrawal after ≈8% of the rituximab target dose, corticosteroids to treat allergic reaction, start of chemotherapy on day 1, measurement of one index lesion on day 6: SD	Not possible
83	9	III	4,897	BL	1	Allergic reaction	Corticosteroids to treat allergic reaction, start of chemotherapy on day 2, no imaging	Not possible
103	10	IV, CNS-negative	1,372	B-AL	1	Allergic reaction	Withdrawal after ≈5% of the rituximab target dose, corticosteroids to treat allergic reaction, start of chemotherapy on day 1	Not possible
105	16	III	150	BL	1	Allergic reaction	Withdrawal after ≈7% of the rituximab target dose, corticosteroids to treat allergic reaction, start of chemotherapy on day 3, no imaging	Not possible
109	16	IV, CNS-positive	3,704	BL	1	Allergic reaction	Withdrawal after ≈3% of the rituximab target dose, corticosteroids to treat allergic reaction, start of chemotherapy on day 2, no imaging	Not possible
23	17	III	1,100	BL	4	Suspicion of progression	Worsening of general condition, abdominal girth 81 cm on day 0 and 86 cm on day 5, start of chemotherapy on day 5, no imaging	Nonresponse
42	8	III	2,311	BL	3	Suspicion of progression	Worsening of general condition because of a large abdominal lymphoma, pleural effusion, and ascites with respiratory insufficiency; start of chemotherapy on day 3, measurement of three index lesions on day 6: all SD	Nonresponse
113	13	III	1,624	BL	3	Suspicion of progression	No imaging	Nonresponse
116	15	N/E	381	DLBCL	3	Suspicion of progression	Worsening of general condition, increasing oxygen demand, start of chemotherapy on day 3, imaging on day 3: increase of pleural effusions, marginal increase of lymphoma, no specification by diameters	Nonresponse
77	6	IV, CNS-negative	1,904	B-AL	1	Tumor lysis syndrome	Withdrawal after ≈15% of the rituximab target dose, start of chemotherapy on day 5, measurement of one index lesion on day 5: PD	Not possible
118	15	III	602	BL	1	Tumor lysis syndrome	Withdrawal after ≈7% of the rituximab target dose, start of chemotherapy on day 3, imaging on day 5: OE	Not possible
53	16	III	566	BL	2	Lymphoma-associated ileus	Start of chemotherapy on day 2, no imaging	Not possible
112	4	III	1,042	BL	2	Temporary change of diagnosis	Initially, FAB-L3 blasts in ascites were diagnosed locally; later on, morphologic results were interpreted as FAB-L2 blasts (locally) and therefore a precursor B-cell lymphoblastic lymphoma was diagnosed and therapy was changed according to the protocol for lymphoblastic lymphomas (EURO-LB02); reference morphology confirmed FAB-L3 blasts, no imaging	Not possible

Abbreviations: ID, identification; LDH, lactate dehydrogenase; DLBCL, diffuse large B-cell lymphoma; B-AL, Burkitt leukemia; SD, stable disease; BL, Burkitt lymphoma; N/E, not evaluable; PD, progressive disease; OE, objective effect; FAB, French-American-British.