Dose-adjusted EPOCH-rituximab or intensified B-non-Hodgkin lymphoma therapy for pediatric primary mediastinal large B-cell lymphoma. Results from the study B-NHL-BFM-04 and the NHL-BFM registry 2012

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Supplementary Data

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Supplementary Table 1: Treatment details

	Group	Criteria	Therapy courses							
N95[1]	**R2**	Stage III and LDH < 500 U/l	V	A^{24}	B^{24}	A^{24}	B^{24}			
	R2'		V	A^{4}	B^{4}	A^{4}	B^{4}			
	R3	Stage III and LDH 500 – 1000 U/l *or* Stage IV and LDH < 1000 U/l and CNS-neg.	V	AA^{24}	BB^{24}	CC	AA^{24}	BB^{24}		
	R3'		V	AA^{4}	BB^{4}	CC	AA^{4}	BB^{4}		
	R4	Stage III/IV and LDH ≥ 1000 U/l *or* CNS-pos.	V	AA^{24}	BB^{24}	CC	AA^{24}	BB^{24}	CC	
	R4'		V	AA^{4}	BB^{4}	CC	AA^{4}	BB^{4}	CC	
B04	**PMBCL6**	LDH < 500 U/l	V	A^{24}	B^{24}	A^{24}	B^{24}	A^{24}	B^{24}	
	PMBCL7	LDH ≥ 500 U/l	V	AA^{24}	BB^{24}	CC	AA^{24}	BB^{24}	CC	BB^{24}
DA-EPOCH-R		all patients	V	1	2	3	4	5	6	

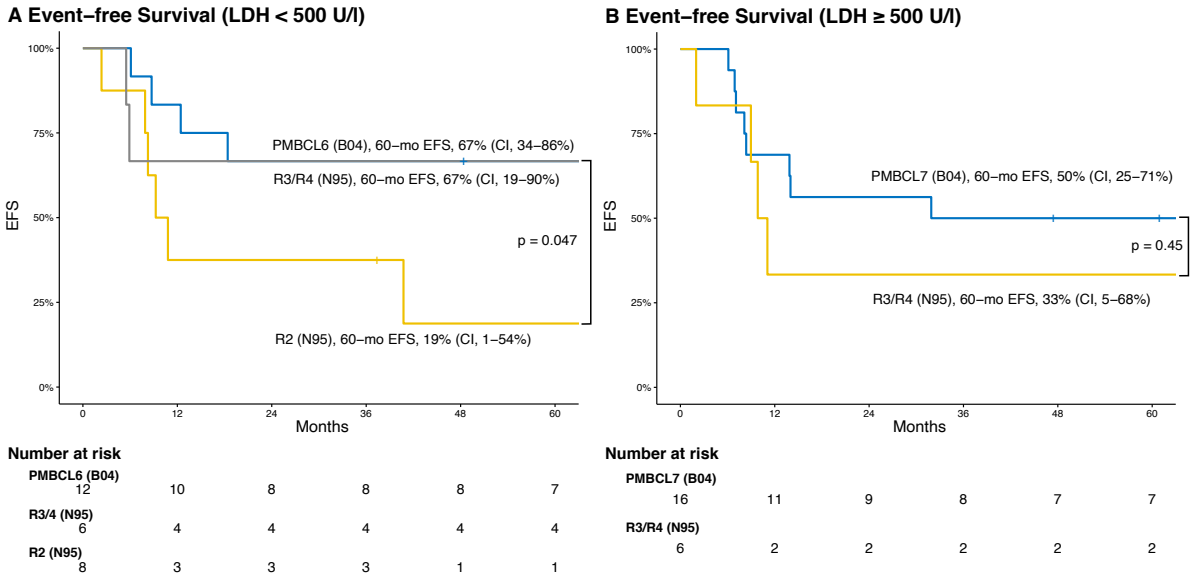
Course details

A4	Methotrexate 1 g/m2, 4 h infusion	Dexamethasone 5 x 10 mg/m²
A24	Methotrexate 1 g/m2, 24 h infusion	Etoposide 2 x 100 mg/m²
AA4	Methotrexate 5 g/m2, 4 h infusion	Ifosfamide 5 x 800 mg/m²
AA24	Methotrexate 5 g/m2, 24 h infusion	Vincristine 1 x 1.5 mg/m²
		Cytarabine 4 x 150 mg/m²
		ITT (prednisolone, cytarabine, methotrexate)
B4	Methotrexate 1 g/m2, 4 h infusion	Dexamethasone 5 x 10 mg/m²
B24	Methotrexate 1 g/m2, 24 h infusion	Doxorubicin 2 x 25 mg/m²
BB4	Methotrexate 5 g/m2, 4 h infusion	Cyclophosphamide 5 x 200 mg/m²
BB24	Methotrexate 5 g/m2, 24 h infusion	Vincristine 1 x 1.5 mg/m²
		ITT (prednisolone, cytarabine, methotrexate)
CC	dexamethasone 5 x 10 mg/m², vindesine 3 mg/m², cytarabine 4 x 3 g/m², etoposide 5 x 100 mg/m², ITT (prednisolone, cytarabine, methotrexate)	

EPOCH-R	etoposide	d1–4	**DA** 50 mg/m²	cyclophosphamide	d5	**DA** 750 mg/m²
	prednisolone	d1–5	2 x 60 mg/m²	doxorubicin	d1–4	**DA** 10 mg/m²
	vincristine	d1–4	0,4 mg/m²	rituximab	d1	375 mg/m²
	application of at least one ITT (prednisolone, cytarabine, methotrexate), limit of cumulative dosis for doxorubicin at 360 mg/m², dose level decisions based on blood counts twice weekly:					

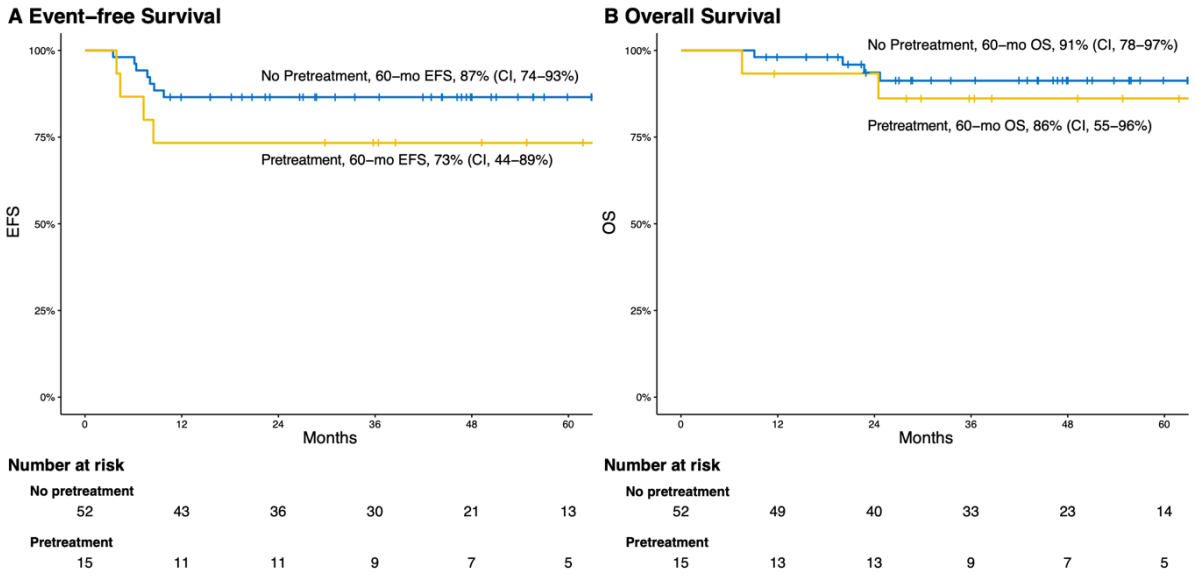
	Increase the doses of etoposide, cyclophosphamide, doxorubicin by 20% if: • ANC > 500/µl on all blood counts *and* • platelet count > 25/nl *and* absence of dose-limiting side effects	Decrease the doses of etoposide, cyclophosphamide, doxorubicin by 20% if: • ANC < 500/µl on at least two blood counts • Platelet count < 25/nl *or* presence of dose-limiting side effects

1–duration of intravenous MTX infusion was randomized to 24 hours or 4 hours



Supplementary Figure 1: Event-free survival in patients treated by NHL-BFM 95 or B-NHL-BFM 04 according to treatment arm and LDH level at time of diagnosis

Treatment in the NHL-BFM 95 (N95) and B-NHL 04 (B04) trials was stratified by stage and initial LDH level. Patients in N95 with PMBCL, stage III, and LDH < 500 U/l (A) were intended for four courses (R2). Patients with stage III and LDH ≥ 500 U/l (B) were intended for five (R3), or six (LDH ≥ 1000 U/l, R4) courses of B-NHL BFM-type chemotherapy, respectively. For this figure, R3 and R4 are combined. Six patients with an LDH < 500 U/l were treated more intensively and received R3 or R4.
Patients in B04 with initial LDH < 500 U/l (A) received R2 with two additional courses (PMBCL6); patients with LDH ≥ 500 U/l (B) received 7 courses (R4 with one additional course) and MTX infusion duration was 24 hours for all patients.



Supplementary Figure 2: Event-free survival and overall survival in patients with PMBCL treated with DA-EPOCH-R by pretreatment

Event-free survival (EFS, A) and overall survival (OS, B) for patients with PMBCL depending on whether the patients had received pretreatment other than one dose of rituximab prior to the start of DA-EPOCH-R. EFS in patients without pretreatment was 87%, compared to 73% in patients with pretreatment (p =.2). OS was not significantly different (p=.54).