Dose-adjusted EPOCH-Rituximab or intensified B-NHL therapy for pediatric primary mediastinal large B-cell lymphoma

Results from the study B-NHL-BFM 04 and the NHL-BFM registry 2012

Fabian Knörr[1], Martin Zimmermann[2], Andishe Attarbaschi[3], Edita Kabíčková[4], Britta Maecker-Kolhoff[2], Stephanie Ruf[5], Ingrid Kühnle[6], Martin Ebinger[7], Anne-Kathrin Garthe[8], Ingrid Simonitsch-Klupp[9], Ilske Oschlies[10], Wolfram Klapper[10], Birgit Burkhardt[8], Wilhelm Woessmann[1]

1 UKE, Department of Pediatric Hematology and Oncology, Hamburg, Germany

2 Hannover Medical School, Clinic for Pediatric Hematology and Oncology, Hannover, Germany

3 St. Anna Children's Hospital, Medical University of Vienna, Department of Pediatric Hematology and Oncology, Vienna, Austria

4 Charles University and University Hospital Motol, Department of Pediatric Hematology and Oncology, Prague, Czech Republic

5 University of Gießen, Pediatric Hematology and Oncology, Gießen, Germany

6 University Medical Center Göttingen, Division of Pediatric Hematology and Oncology, Göttingen, Germany

7 Children's University Hospital Tübingen, Department of General Pediatrics and Pediatric Hematology/Oncology, Tübingen, Germany

8 University-Hospital of Münster, Pediatric Hematology and Oncology, Münster, Germany

9 Clinical Institute of Pathology, Medical University of Vienna, Vienna, Austria

10 Universitätsklinikum Schleswig-Holstein, Campus Kiel, Institute of Pathology, Hematopathology Section and Lymph Node Registry, Kiel, Germany

Corresponding author

Address: Wilhelm Woessmann, Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Martinistraße 52, D-20246 Hamburg, Germany

Email: w.woessmann@uke.de
Phone: +49 (0) 40 7410 54270
Fax: +49 (0) 40 7410 54601

Disclosures

Andishe Attarbaschi received honoraria from Jazz Pharmaceuticals, Amgen, MSD, Novartis, travel grants from Jazz Pharmaceuticals, and has consulting or advisory roles for Jazz Pharmaceuticals, Amgen, MSD, Gilead and Novartis.
Martin Ebinger has received travel grants and honoraria from Amgen, MSD and Jazz Pharmaceuticals.
Wolfram Klapper received research funding by Roche, Amgen, Regeneron and Takeda.
The remaining authors have no conflicts of interest to disclose.

Contributions

WW, BB, AA, EK designed and supervised treatment in the NHL-BFM registry 2012. WW and FK designed the concept and the analysis; FK, MZ, SR and AG collected and assembled data; AA, EK, BMK, IK, ME provided patient data; ISK, IO, WK performed reference pathology review; FK and WW made the first draft of the manuscript; MZ and FK carried out the statistical analysis; WW and BB supervised the analysis; all authors critically revised the manuscript; all authors gave their approval of the final manuscript.

Acknowledgments

We thank all patients and their families for participating in the studies. We thank our colleagues in the hospitals and reference institutions, who contributed to this study, for their care for the children and families, and the supplied data.

Letter details
Word count (text): 1486
Tables/Figures: 1 Table, 2 Figures
Supplementary Tables/Figures: 1 Table, 2 Figures
References: 15

Treatment outcomes for children and adolescents with primary mediastinal large B-cell lymphoma (PMBCL) with chemotherapy designed for childhood mature B-Non-Hodgkin's Lymphoma (NHL) are inferior to those of children with other B-NHL-subtypes.[1-3] Consequently, B-NHL-type chemotherapy was first intensified and subsequently replaced by dose-adjusted chemo-immunotherapy with etoposide, prednisone, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) in the NHL- Berlin-Frankfurt-Münster (BFM)-study group. DA-EPOCH-R resulted in superior event-free (EFS) and overall survival (OS) compared to the previous B-NHL chemotherapy, however, in four patients CNS-relapses occurred.

Treatment of children with PMBCL by chemotherapy protocols without rituximab including high-dose methotrexate, etoposide, ifosfamide, cyclophosphamide, cytarabine, vincristine, and corticosteroids, combined with intrathecal chemotherapy resulted in EFS rates at 5 years of 53–70%.[1-3] To improve outcome, treatment was intensified for patients with PMBCL in the trial B-NHL-BFM 04 (B04) by adding two courses of chemotherapy and prolonging the infusion time of high-dose methotrexate. In 2010, a modified DA-EPOCH-R regimen was recommended for PMBCL by the NHL-BFM study committee on the basis of a 5-year-EFS of 93% in adults with PMBCL in a phase II study.[4] The modifications included the addition of a least one dose of intrathecal triple therapy (ITT), and a cumulative doxorubicin dose limit at 360 mg/m^2 of body-surface area (BSA). A first analysis by our group of 15 patients treated with DA-EPOCH-R showed an EFS and OS of 92±8% after 2 years.[5] A retrospective analysis of 156 adults and children with PMBCL treated with DA-EPOCH-R reports an EFS at 3 years of 86%.[6] However, in the prospective Intergroup trial testing DA-EPOCH-R, the 2-year EFS of children and adolescents with PMBCL was 72%, not different from the historical control.[7]

We analyzed children and adolescents with PMBCL confirmed by central histopathological review, excluding mediastinal grey zone lymphoma, enrolled in the B04 trial (German clinical trial registry, DRKS00009436) or the NHL-BFM Registry 2012 between 2004 and 2019 to assess the efficacy of intensified B-NHL-BFM chemotherapy (n=29 patients) and modified DA-EPOCH-R (n=67 patients), compare it retrospectively to the treatment regimen in the NHL-BFM 95 trial (N95, n=20 patients) and to identify risk factors for treatment failure with DA-EPOCH-R.

Treatment details for N95, B04 and DA-EPOCH-R are summarized in the Supplementary Table 1. N95 treatment was stratified by LDH and stage to risk groups R2–R4, as previously reported.[8] In B04, treatment was intensified by adding two courses: Patients with LDH <500 U/l received six (PMBCL6), those with LDH ≥500 U/l seven (PMBCL7) 5-day courses of chemotherapy including high-dose methotrexate infused over 24h and ITT. Outside the protocol, three patients received one or two doses of rituximab and one patient initial emergency-mediastinal radiotherapy. One patient each after B04 and DA-EPOCH-R received radiotherapy for a persisting mediastinal mass. From September 2010, DA-EPOCH-R was recommended with the described modifications. Erroneously, 60 mg/m² prednisone was used instead of 120 mg/m² as protocol-specified for 26 patients.

The primary endpoint was the EFS at 5 years, defined as time from diagnosis to death, relapse, progressive disease, or secondary malignancy, estimated using the Kaplan-Meier method. OS was defined as time from diagnosis to death. Survival and

competing risk comparisons were performed by log-rank analysis and Gray´s test.[9] Data were updated as of January 3, 2021.

For this analysis, 116 of 118 registered patients were included (Fig 1). Their median age was 16.2 years, 53% were female. Patient characteristics are summarized in Table 1.

Fifteen patients in the trial N95 and 15 patients treated by DA-EPOCH-R enrolled in B04 have been reported previously.[2,5,8]

Of 20 patients treated according to N95, six patients with LDH levels at diagnosis ≥500 U/l received the intended treatment (R3/R4). Of 14 patients with LDH <500 U/l, 8 received the protocol-intended treatment with four courses (R2) and 6 were treated more intensively (R3/R4). B04-therapy was used for 29 patients, of whom 12 with LDH <500 U/l were scheduled for six courses, one for seven. All 16 patients with LDH ≥500 U/l received the intended treatment with seven courses.

Among 67 patients treated by DA-EPOCH-R, 15 received pretreatment other than one dose of rituximab or a BFM-type pre-phase (B04 chemotherapy in 13 patients - one course A24 in two, one course AA24 in ten patients, two courses AA24 and BB24 in one patient, two courses of OEPA and one course of R-CHOEP in one patient each). Fifty-two patients without pretreatment received 6 (n=50) or 8 (n=2) courses of DA-EPOCH-R. The mean cumulative doxorubicin dose was 310 mg/m^2 of BSA (range, 200–415 mg/m^2). The median number of ITT was 2.5 (range, 0–8) in 50 patients with available data. The maximal dose levels reached were 1, 2, 3, 4, and 5 in 5 (10%), 6 (12%), 17 (34%), 17 (34%) and 5 (10%) patients, respectively, and unknown in 2 patients.

The levels reached were slightly lower than reported by Dunleavy and colleagues.[4] Dose decisions were at the discretion of the treating physicians, and reasons for non-

escalation might include concerns for sequelae, overestimation of hematological toxicity due too frequent blood counts for dose decisions, or the fact that G-CSF was not administered to all patients (only 39 of 46 (85%) of patients with available data).

In 15 pretreated patients, the median number of DA-EPOCH-R-courses was 5, the median number of ITT 5, and the mean cumulative dose of doxorubicin 260 mg/m^2 BSA.

For treatment by DA-EPOCH-R, B04 and N95, estimates for EFS at 5 years were 84% (95%-confidence interval (CI), 72–91%), 59% (CI, 39–74%), and 39% (CI, 19–60%), respectively (Figure 2). Overall survival was 90% (CI, 79–95%), 72% (CI, 51–85%) and 70% (CI, 45–85%), respectively (Figure 2). EFS and OS with DA-EPOCH-R were significant superior to treatment with B04 (p=.016 for EFS, p=.039 for OS) and N95 (p<.001 for EFS and p=.026 for OS).

The observed EFS with DA-EPOCH-R was comparable to that of other trials ranging from 72% to 93%.[4,6,7,10,11] To what extent rituximab alone contributed to the superior outcome cannot be answered by our data. The addition of rituximab to CHOP improved outcomes in adult patients with PMBCL.[12] Recent preliminary data from the non-randomized, prospective IELSG37 trial suggest similar efficacy for DA-EPOCH-R and R-CHOP14.[13] The AEIOP reported 13 pediatric PMBCL patients treated with a modified MTX-based BFM-type backbone combined with rituximab resulting in an EFS of 84%.[14] These data indicate that addition of rituximab contributed substantially to the improved outcome.

Estimated EFS at 5 years for patients with LDH <500 U/l receiving PMBCL6, R3/R4, and R2 in B04/N95 were 67% (CI, 34–86%), 67% (CI, 19–90%), and 19% (CI, 1–54%), respectively (Supplementary Figure 1A), with a significant difference between PMBCL6 and R2 (p=.047). PMBCL7 was given to 16 patients with LDH ≥500 U/l in

B04, R3/R4 in N95 to 8 patients. The estimated EFS was 50% (CI, 25–71%) and 33% (CI, 5–68%), respectively (p=.45, Supplementary Figure 1B). The improvement with intensified B-NHL therapy in patients with LDH levels <500 U/l but not among those with LDH levels ≥500 U/l indicates a possible limit for further improvements by modifying standard B-NHL chemotherapy for PMBCL.

In patients treated by DA-EPOCH-R without pretreatment, EFS and OS at 5 years were 87% (CI, 74–93%) and 91% (CI, 78–97%), not significantly different from the outcome for 15 patients receiving DA-EPOCH-R after pretreatment (EFS and OS 73% (CI, 44–89%) and 86% (CI, 55–96%), respectively (p=.2 for EFS, p=.54 for OS, Supplementary Figure 2). The heterogeneity in treatment with pretreatment in about 20% of patients is a limitation of our analysis, but likely reflects real-world diagnostic uncertainties, with a final diagnosis of PMBCL only made by central histopathological review in conjunction with the typical location.

There was no significant difference in EFS according to sex, initial LDH, extra-thoracic involvement, prednisone dose or the maximal dose-level reached in DA-EPOCH-R. Mean age was lower in patients experiencing relapse (HR 0.74, p=.012), resulting in an EFS of 90% (CI, 76–96%) for 41 patients ≥16 years, compared with 73% (CI, 52–86%) for 26 patients <16 years (p=.07). The limited number of patients might explain that we could not identify risk factors for treatment failure with DA-EPOCH-R except for younger age.

At relapse 4/11 (37%) patients treated by DA-EPOCH-R had parenchymal CNS involvement compared to 0/22 after B04 chemotherapy (Gray´s test, p=.08).

Three of the patients had received only 60 mg/m^2 prednisolone, two reached only dose level 1 or 2 and one received only one ITT for CNS prophylaxis. Further explanations for a possibly higher risk of CNS-relapse after DA-EPOCH-R include

the use of prednisone instead of dexamethasone and the omission of high-dose methotrexate, both part of the B-NHL therapy.

In conclusion, our prospective data confirmed DA-EPOCH-R as effective treatment for children and adolescents with PMBCL with only one patient receiving consolidation radiotherapy. Further trials on PMBCL should address the risk of CNS relapse and identify prognostic markers. Low patient numbers in this orphan disease call for collaborative, international trials including patients of the whole age spectrum.

References

1. Gerrard M, Waxman IM, Sposto R, et al. Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/LMB96 mature B-NHL therapy. Blood. 2013;121(2):278-285.
2. Seidemann K, Tiemann M, Lauterbach I, et al. Primary mediastinal large B-cell lymphoma with sclerosis in pediatric and adolescent patients: treatment and results from three therapeutic studies of the Berlin-Frankfurt-Münster Group. J Clin Oncol. 2003;21(9):1782-1789.
3. Cairo MS, Sposto R, Gerrard M, et al. Advanced stage, increased lactate dehydrogenase, and primary site, but not adolescent age (≥ 15 years), are associated with an increased risk of treatment failure in children and adolescents with mature B-cell non-Hodgkin's lymphoma: results of the FAB LMB 96 study. J Clin Oncol. 2012;30(4):387-393.
4. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma. N Engl J Med. 2013;368(15):1408-1416.
5. Woessmann W, Lisfeld J, Burkhardt B. Therapy in Primary Mediastinal B-Cell Lymphoma. N Engl J Med. 2013;369(3):282-284.
6. Giulino-Roth L, O'Donohue T, Chen Z, et al. Outcomes of adults and children with primary mediastinal B-cell lymphoma treated with dose-adjusted EPOCH-R. Br J Haematol. 2017;179(5):739-747.
7. Burke GAA, Gross TG, Pillon M, et al. Results of Inter-B-NHL Ritux 2010 - Phase II Study of DA-EPOCH-R for Children and Adolescents with Primary Mediastinal Large B-Cell Lymphoma (PMLBL) on Behalf of European Intergroup for Childhood Non Hodgkin's Lymphoma (EICNHL) and Children's Oncology Group (COG). Blood. 2017;130(Supplement 1):4124.
8. Woessmann W, Seidemann K, Mann G, et al. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. Blood. 2005;105(3):948-958.
9. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. Ann Stat. 1988;16(3):1141-1154.
10. Shah NN, Szabo A, Huntington SF, et al. R-CHOP versus dose-adjusted R-EPOCH in frontline management of primary mediastinal B-cell lymphoma: a multi-centre analysis. Br J Haematol. 2018;180(4):534-544.
11. Melani C, Advani R, Roschewski M, et al. End-of-treatment and serial PET imaging in primary mediastinal B-cell lymphoma following dose-adjusted EPOCH-R: a paradigm shift in clinical decision making. Haematologica. 2018;103(8):1337-1344.
12. Rieger M, Österborg A, Pettengell R, et al. Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: results of the Mabthera International Trial Group study. Ann Oncol. 2011;22(3):664-670.
13. Martelli M, Zucca E, Botto B, et al. Impact of Different Induction Regimens on the Outcome of Primary Mediastinal B Cell Lymphoma in the Prospective Ielsg 37 Trial. Hematol Oncol. 2021;39(S2):90-92.
14. Pillon M, Carraro E, Mussolin L, et al. Primary mediastinal large B-cell lymphoma: Outcome of a series of pediatric patients treated with high-dose methotrexate and cytarabine plus anti-CD20. Pediatr Blood Cancer. 2018;65(2).

15. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. Semin Oncol. 1980;7(3):332-339.

Tables

Table 1 Clinical characteristics of the children and adolescents with primary mediastinal large B cell lymphoma (PMBCL)

		All eligible Patients (n=116)	Treatment		
			N95 (n=20)	B04 (n=29)	DA-EPOCH-R (n=67)
Study	B04	45	.	29	16
	N95	19	19	.	.
	REG12	52	1	.	51
Sex	f	62	7	17	38
	m	54	13	12	29
Stage**	III	94	20	19	55
	IV	1	.	1	.
	not evaluable*	19	.	9	10
	unknown	2	.	.	2
CNS involvement	not analyzed	16	.	8	8
	No	100	20	21	59
Bone marrow involvement	not analyzed	11	.	4	7
	no	104	20	24	60
	yes	1	.	1	.
Age at diagnosis (years)	mean	15,8	14,7	15,7	16,2
	range	1,4–21,7	1,4–17,9	10,3–18,6	8,4–21,7
LDH at diagnosis (U/l)	mean	562	445	608	578
	range	187–1698	187–1267	252–1322	188–1698
	above normal range	89/96	unknown***	25/29 (86%)	64/67 (96%)
	< 500 U/l	56	14	13	29
	500 – <1000 U/l	47	5	12	30
	≥ 1000 U/l	13	1	4	8
Duration of follow-up (months)	mean	59	77	73	48
	range	2–211,8	2–211,8	12,5–144,2	7,6–123,2

* no initial assessment of CNS or bone marrow involvement
**St. Jude staging system[15]
***Upper limit of normal not reported in the study N95
N95, study NHL-BFM 95; B04, study B-NHL BFM 04, REG12, NHL-BFM Registry 2012; CNS, central nervous system; LDH, lactate dehydrogenase

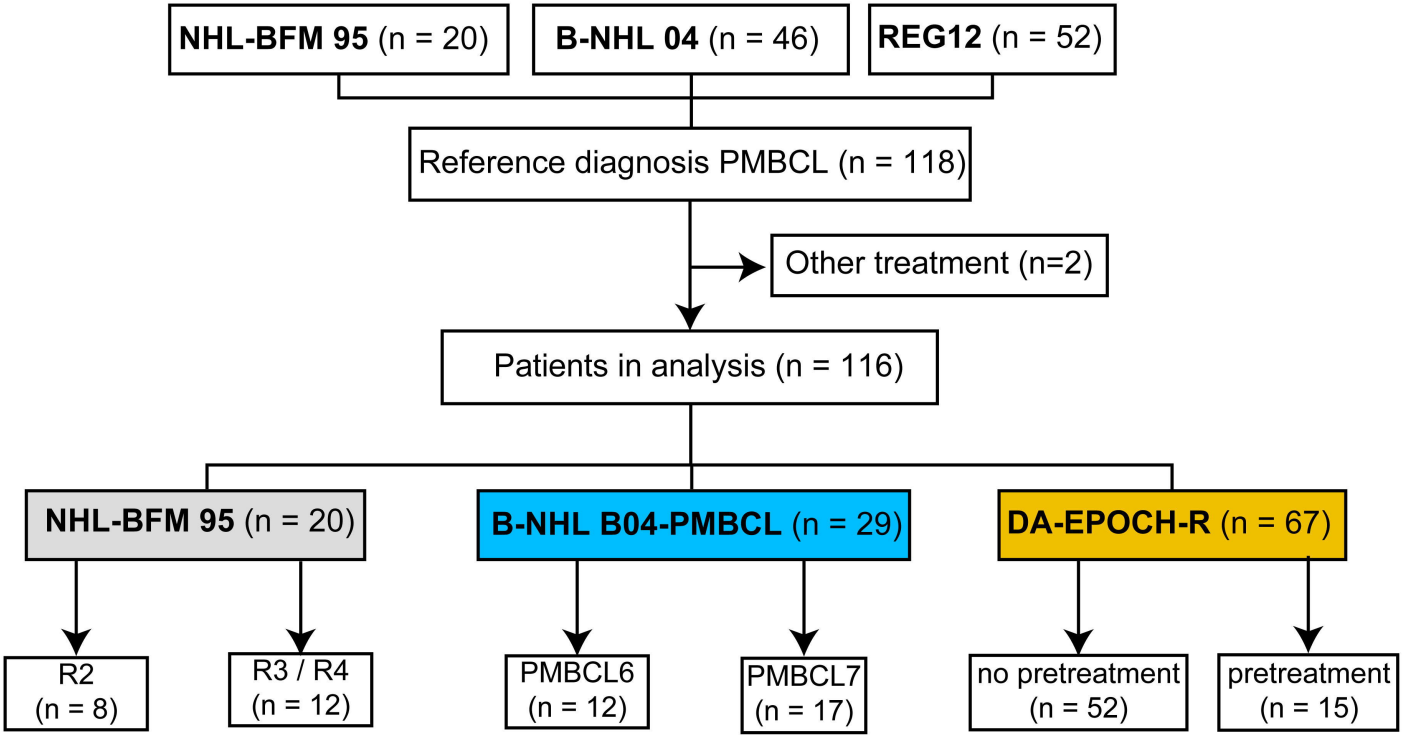
Figures

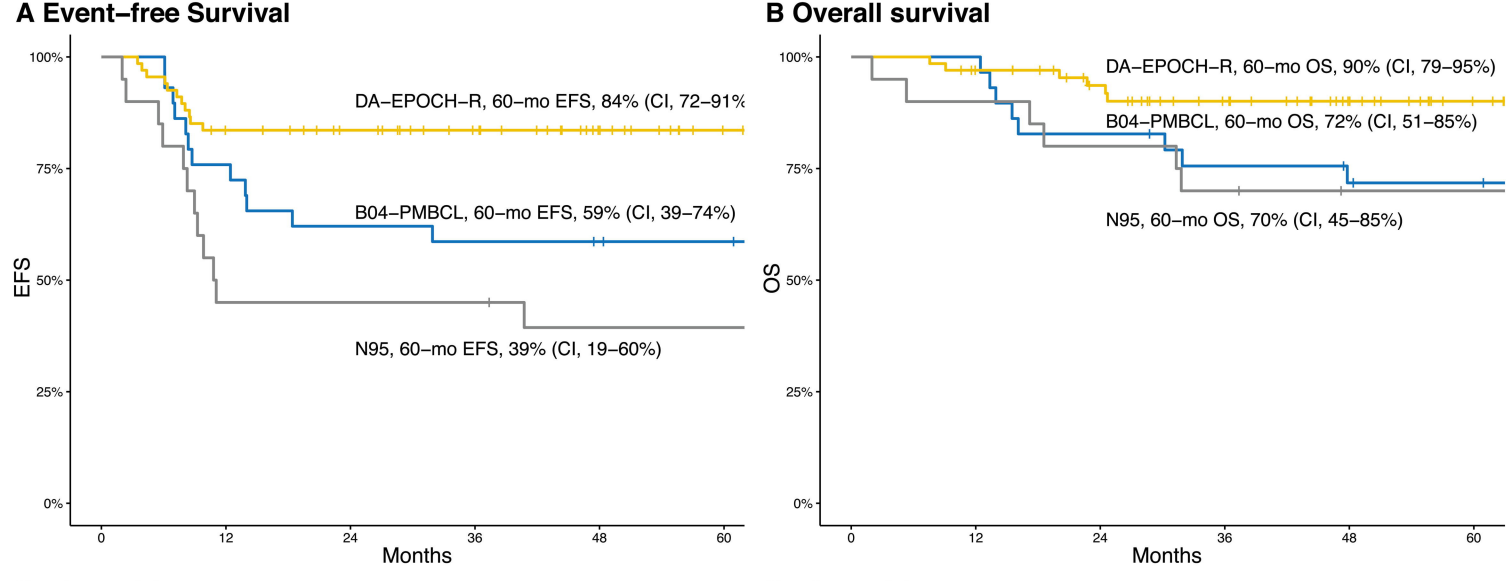
Fig 1. Patient allocation and treatment assignment

Patients with diagnosis of primary mediastinal large B cell lymphoma (PMBCL) were identified from three trials. Two patients received treatment not according to protocol and were excluded from the analysis. One patient from the NHL-BFM registry 2012 (REG12) received treatment according to the NHL-BFM 95 treatment strategy (R2).

Fig 2. Event-free survival and overall survival at 5 years for patients with PMBCL treated with the treatment regimen NHL-BFM 95, B-NHL-BFM 04 or DA-EPOCH-R

Event-free survival (EFS, A) and overall survival (OS, B) for patients with PMBCL according to the type of treatment. EFS was significantly different between DA-EPOCH-R and B-NHL-BFM 04 (p=.024) and DA-EPOCH-R and N95 (p<.001). The difference between BNHL-04 and N95 was not significant (p=.142).


NHL-BFM 95 (n = 20)
B-NHL 04 (n = 46)
REG12 (n = 52)
Reference diagnosis PMBCL (n = 118)
Other treatment (n=2)
Patients in analysis (n = 116)
NHL-BFM 95 (n = 20)
B-NHL B04-PMBCL (n = 29)
DA-EPOCH-R (n = 67)
R2 (n = 8)
R3 / R4 (n = 12)
PMBCL6 (n = 12)
PMBCL7 (n = 17)
no pretreatment (n = 52)
pretreatment (n = 15)



Number at risk

B04-PMBCL					
29	22	18	17	16	15
DA-EPOCH-R					
67	54	47	39	28	18
N95					
20	9	9	9	7	7

Number at risk

B04-PMBCL					
29	29	24	21	19	18
DA-EPOCH-R					
67	62	53	42	30	19
N95					
20	18	16	14	12	12

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).