Annals of Hematology (2019) 98:897–907
https://doi.org/10.1007/s00277-018-3578-0

ORIGINAL ARTICLE

Six versus eight doses of rituximab in patients with aggressive B cell lymphoma receiving six cycles of CHOP: results from the "Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas" (PETAL) trial

Andreas Hüttmann[1] · Jan Rekowski[2] · Stefan P. Müller[3] · Bernd Hertenstein[4] · Christiane Franzius[5] · Rolf Mesters[6] · Matthias Weckesser[7] · Frank Kroschinsky[8] · Jörg Kotzerke[9] · Arnold Ganser[10] · Frank M. Bengel[11] · Paul La Rosée[12,13] · Martin Freesmeyer[14] · Heinz-Gert Höffkes[15] · Andreas Hertel[16] · Dirk Behringer[17] · Gabriele Prange-Krex[18] · Martin Griesshammer[19] · Jens Holzinger[20] · Stefan Wilop[21] · Thomas Krohn[22] · Aruna Raghavachar[23] · Georg Maschmeyer[24] · Ingo Brink[25] · Roland Schroers[26] · Tobias Gaska[27] · Helga Bernhard[28] · Aristoteles Giagounidis[29,30] · Jochen Schütte[31,32] · Ariane Dienst[33] · Hubertus Hautzel[34] · Ralph Naumann[35,36] · Alfred Klein[37] · Dennis Hahn[38] · Gabriele Pöpperl[39] · Matthias Grube[40] · Jörg Marienhagen[41] · Andreas Schwarzer[42] · Lars Kurch[43] · Thomas Höhler[44] · Heike Steiniger[45] · Holger Nückel[46] · Thomas Südhoff[47] · Wolfgang Römer[48] · Marcus Brinkmann[49] · Claudia Ose[49] · Ferras Alashkar[1] · Christine Schmitz[1] · Jan Dürig[1] · Dieter Hoelzer[50] · Karl-Heinz Jöckel[2] · Wolfram Klapper[51] · Ulrich Dührsen[1]

Received: 25 November 2018 / Accepted: 6 December 2018 / Published online: 4 January 2019

Abstract

Standard first-line treatment of aggressive B cell lymphoma comprises six or eight cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus eight doses of rituximab (R). Whether adding two doses of rituximab to six cycles of R-CHOP is of therapeutic benefit has not been systematically investigated. The Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas (PETAL) trial investigated the ability of [^{18}F]-fluorodesoxyglucose PET scanning to guide treatment in aggressive non-Hodgkin lymphomas. Patients with B cell lymphomas and a negative interim scan received six cycles of R-CHOP with or without two extra doses of rituximab. For reasons related to trial design, only about a third underwent randomization between the two options. Combining randomized and non-randomized patients enabled subgroup analyses for diffuse large B cell lymphoma (DLBCL; $n = 544$), primary mediastinal B cell lymphoma (PMBCL; $n = 37$), and follicular lymphoma (FL) grade 3 ($n = 35$). With a median follow-up of 52 months, increasing the number of rituximab administrations failed to improve outcome. A non-significant trend for improved event-free survival was seen in DLBCL high-risk patients, as defined by the International Prognostic Index, while inferior survival was observed in female patients below the age of 60 years. Long-term outcome in PMBCL was excellent. Differences between FL grade 3a and FL grade 3b were not apparent. The results were confirmed in a Cox proportional hazard regression model and a propensity score matching analysis. In conclusion, adding two doses of rituximab to six cycles of R-CHOP did not improve outcome in patients with aggressive B cell lymphomas and a fast metabolic treatment response.

Keywords Diffuse large B cell lymphoma · Primary mediastinal B cell lymphoma · Follicular lymphoma · Rituximab · R-CHOP · Survival

Introduction

The "Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas" (PETAL) trial investigated the ability of interim [^{18}F]-fluorodesoxyglucose (FDG) PET scanning to guide treatment in aggressive non-

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00277-018-3578-0) contains supplementary material, which is available to authorized users.

✉ Ulrich Dührsen
ulrich.duehrsen@uk-essen.de

Extended author information available on the last page of the article

Hodgkin lymphomas [1]. Patients whose scan remained positive after two cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (plus rituximab (R) in CD20-positive lymphomas) were randomly assigned to receive another six cycles of R-CHOP or an intensive methotrexate- and cytarabine-based protocol yielding excellent results in pediatric non-Hodgkin lymphomas [2] and adult Burkitt's lymphoma [3]. Using the ΔSUV_{max} method for PET evaluation [4], interim scanning reliably predicted outcome, but treatment intensification failed to improve survival in the study population as a whole and in all subgroups analyzed [1].

During the first 2 years of recruitment, patients with a negative interim scan uniformly received six cycles of R-CHOP (two cycles before and four after interim scanning). When publications suggested that increasing the cumulative dose of rituximab may improve outcome in CD20-positive lymphomas [5, 6], the protocol was amended, and patients with CD20-positive lymphomas and a negative interim scan were randomly assigned to receive six cycles of R-CHOP or the same treatment with two additional doses of rituximab. Because negative interim scans were more frequent than positive scans, randomization in the PET-negative part was terminated earlier than in the PET-positive part. After the end of randomization, interim PET-negative patients with CD20-positive lymphomas uniformly received eight doses of rituximab, which, by then, was considered the standard of care for aggressive B cell lymphomas [7].

Within the group of 255 randomized patients with interim PET-negative CD20-positive lymphomas, increasing the exposure to rituximab failed to improve outcome [1]. Because the trial included several histological entities, the group of randomized patients was too small for meaningful subgroup analyses. Adding the patients treated before or after the randomization period to the randomized group almost tripled the number of interim PET-negative patients with CD20-positive lymphomas. This allowed us to study rituximab exposure in three major subtypes of aggressive B cell lymphoma: diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL), and follicular lymphoma (FL) grade 3 [8].

Methods

Patients

Patients 18 to 80 years of age with newly diagnosed aggressive B cell or T cell lymphomas and an ECOG performance status ≤ 3 were eligible for registration. Lymphoblastic, Burkitt's, transformed indolent, and primary central nervous system lymphomas were excluded. A reference pathological review was obtained in 98% of cases [1]. All patients gave written informed consent.

Procedures

The PETAL trial was registered under EudraCT 2006-001641-33 and ClinicalTrials.gov NCT00554164 and performed according to the 1964 Declaration of Helsinki and its later amendments in 55 oncological and 23 nuclear medicine sites in Germany. The protocol was approved by the Federal Institute for Drugs and Medical Devices and the ethics committees of the participating sites. The trial design has been described previously [1]. This analysis is limited to patients with CD20-positive lymphomas and a negative interim PET scan. After baseline investigations, patients received a pre-phase [9] consisting of vincristine (1 mg, day 1) and prednisone (100 mg for 3–7 days) followed by two cycles of R-CHOP (rituximab, 375 mg/m^2, day 1; cyclophosphamide 750 mg/m^2, day 2; doxorubicin 50 mg/m^2, day 2; vincristine 2 mg, day 2; prednisone 100 mg, days 2–6; granulocyte colony-stimulating factor, 5 μg/kg, daily from day 5 until recovery of neutrophils > 1/nl). Patients with CD20-positive lymphomas and a negative interim scan received a further four cycles of R-CHOP with or without two additional doses of rituximab in 14-day intervals.

All efficacy and safety assessments were done by the primary investigators using the international response criteria for malignant lymphomas [10] and the Common Terminology Criteria for Adverse Events [11]. The end-of-treatment remission status was assessed by computed tomography (CT). Follow-up visits were scheduled according to international guidelines [10].

Statistical analysis

The primary end-point was event-free survival, measured from the date of interim PET scanning to treatment failure (progression, relapse, change to a treatment inconsistent with the trial protocol, toxicity-related treatment termination, death from any cause). The randomized comparisons in the interim PET-positive and interim PET-negative parts of the trial have been reported previously [1]. This account covers interim PET-negative patients with CD20-positive lymphomas who were randomized or allocated to six cycles of R-CHOP with or without two additional doses of rituximab. The analysis was done in the intention-to-treat population, and included response, event-free, progression-free, overall survival, and safety. Planned subgroup analyses included lymphoma subtype, age, sex, and International Prognostic Index (IPI) risk group [12]. All analyses were exploratory. Time-to-event end-points were analyzed using the Kaplan-Meier estimator and the log-

Table 1 Characteristics of patients with aggressive B cell lymphomas and negative interim positron emission tomography findings treated with six or eight doses of rituximab

Characteristic	DLBCL		PMBCL		FL grade 3	
	6 × R	8 × R	6 × R	8 × R	6 × R	8 × R
No. of patients	292	252	22	15	21	14
Age, median (range) (years)	62 (18–80)	60 (18–79)	33 (18–80)	38 (20–59)	55 (29–80)	58 (29–72)
Age > 60 years	156 (53.4)	121 (48.0)	3 (13.6)	0	7 (33.3)	5 (35.7)
Male sex	175 (59.9)	128 (50.8)	11 (50.0)	4 (26.7)	14 (66.7)	8 (57.1)
ECOG performance status ≥ 2	26 (8.9)	20 (7.9)	3 (13.6)	1 (6.7)	2 (9.5)	0
Ann Arbor stage III or IV	167 (57.4)	143 (56.8)	11 (50.0)	5 (33.3)	13 (61.9)	7 (50.0)
Extranodal sites > 1	94 (32.3)	77 (30.6)	4 (18.2)	2 (13.3)	4 (19.1)	0
Lactate dehydrogenase > ULN	161 (55.3)	133 (52.8)	17 (77.3)	14 (93.3)	12 (57.1)	7 (50.0)
International Prognostic Index						
Low risk	113 (38.8)	97 (38.5)	11 (50.0)	10 (66.7)	11 (52.4)	8 (57.1)
Low-intermediate risk	71 (24.4)	68 (27.0)	6 (27.3)	2 (13.3)	4 (19.1)	4 (28.6)
High-intermediate risk	56 (19.2)	56 (22.2)	2 (9.1)	3 (20.0)	4 (19.1)	2 (14.3)
High risk	51 (17.5)	31 (12.3)	3 (13.6)	0	2 (9.5)	0

Data are given as number of patients affected (% of total number of patients with documented data), unless otherwise noted

DLBCL diffuse large B cell lymphoma, *ECOG* Eastern Cooperative Oncology Group, *FL* follicular lymphoma, *PMBCL* primary mediastinal B cell lymphoma, *R* rituximab, *ULN* upper limit of normal

rank test. All tests were two-sided applying an exploratory alpha of 0.05. Cox proportional hazard regression model was employed to adjust for effects of the stratification variables used at randomization (sex, age (18–50, 51–60, 61–70, 71–80 years), IPI risk group) [1]. The same factors were considered for propensity score matching which was carried out with a 1:1 case/control ratio.

Results

Demographic data

Between November 2007 and December 2012, 862 patients with aggressive non-Hodgkin lymphomas were treated in the PETAL trial. Six hundred seven had CD20-positive DLBCL,

Table 2 Remission and survival rates in patients with aggressive B cell lymphomas and negative interim positron emission tomography findings treated with six or eight doses of rituximab

Outcome	DLBCL		PMBCL		FL grade 3	
	6 × R	8 × R	6 × R	8 × R	6 × R	8 × R
No. of patients	292	252	22	15	21	14
Overall response rate[a]	258/271 (95.2)	219/234 (93.6)	19/22 (86.4)	14/15 (93.3)	20/21 (95.2)	11/11 (100)
Complete remission rate[a]	186/271 (68.6)	174/234 (74.4)	12/22 (54.6)	8/15 (53.3)	15/21 (71.4)	8/11 (72.7)
2-Year event-free survival rate[b]	75.1 (69.7–79.7)	74.9 (69.0–79.8)	90.9 (68.3–97.6)	86.7 (56.4–96.5)	100	78.6 (47.2–92.5)
2-Year progression-free survival rate[b]	77.5 (72.2–81.9)	80.9 (75.4–85.3)	100	93.3 (61.3–99.0)	100	85.7 (53.9–96.2)
2-Year overall survival rate[b]	87.4 (82.9–90.7)	88.9 (84.2–92.2)	100	93.3 (61.3–99.0)	100	100

DLBCL diffuse large B cell lymphoma, *FL* follicular lymphoma, *PMBCL* primary mediastinal B cell lymphoma, *R* rituximab

[a] No. of patients responding/total no. of patients reaching the end-of-treatment evaluation (%)

[b] Kaplan-Meier estimate of percentage of patients surviving after 2 years (95% confidence interval)

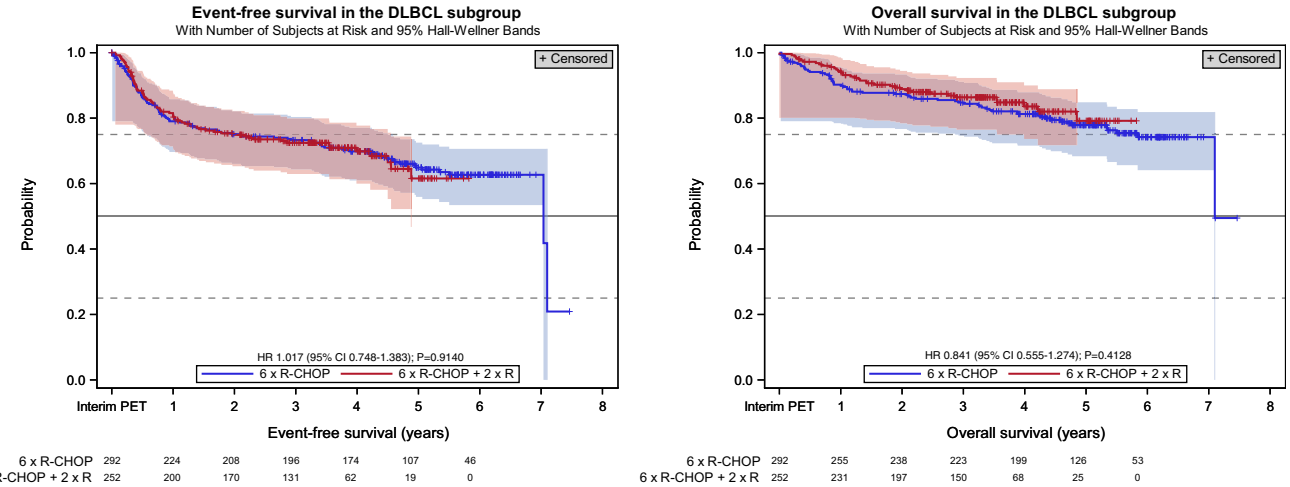


Fig. 1 Event-free survival and overall survival in interim positron emission tomography-negative patients with diffuse large B cell lymphoma. The patients were randomized or allocated to receive six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or the same treatment with two additional doses of rituximab. Survival started on the day of interim positron emission tomography (PET) scanning. Shaded areas correspond to 95% Hall-Wellner confidence bands

42 PMBCL, 25 FL grade 3a, and 17 FL grade 3b. Median baseline maximum standardized uptake values were 20.5 for DLBCL (range, 3.5–75.2), 21.6 for PMBCL (7.9–54.6), 12.8 for FL grade 3a (2.4–39.0), and 12.6 for FL grade 3b (6.5–53.8). The proportion of patients with a negative interim PET scan was 89.7% in DLBCL, 88.1% in PMBCL, and 83.3% in FL grade 3. In the interim PET-negative group, 197 of 544 DLBCL, 14 of 37 PMBCL, and 9 of 35 FL patients underwent randomization between six cycles of R-CHOP and six cycles of R-CHOP with two additional doses of rituximab. Randomization was restricted to the recruitment period between February 2010 and October 2011. Before that time, interim PET-negative patients with CD20-positive lymphomas uniformly received six R-CHOP cycles, and thereafter, they were uniformly treated with six R-CHOP cycles with two additional doses of rituximab. Because baseline data and treatment results (Electronic Supplementary Material, Tables S1 and S2) did not significantly differ between randomized and non-randomized patients, the groups were combined for this analysis.

Table 1 describes patients' baseline characteristics. PMBCL patients were more often female and tended to be younger than DLBCL and FL patients. The features of patients receiving six or eight doses of rituximab were well balanced.

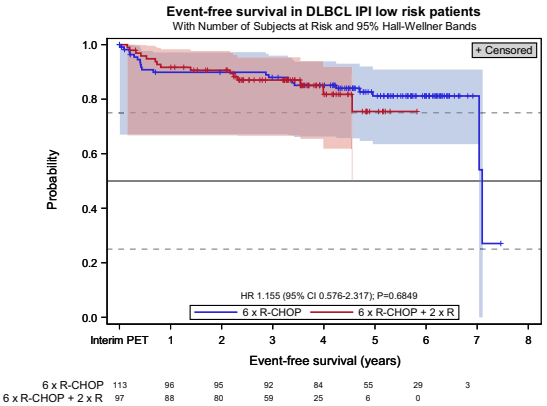
Treatment adherence was good. Five hundred and seventy-eight of a total of 616 interim PET-negative patients (93.8%) received six cycles of CHOP (range, 2–8), 304 of 335 patients (90.8%) allocated to six, and 255 of 281 patients (90.8%) allocated to eight doses of rituximab received the planned treatment. Among patients allocated to six rituximab doses, eight (2.4%) erroneously received seven or eight. Major reasons for premature treatment termination were toxicity ($n = 14$) and patient's preference ($n = 5$). Progression on therapy with a switch to an alternative regimen was rare ($n = 2$). The median follow-up time was 52 months (interquartile range, 40–64).

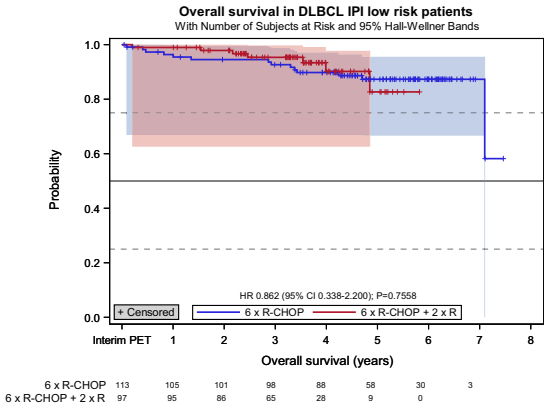
Outcome in diffuse large B cell lymphoma

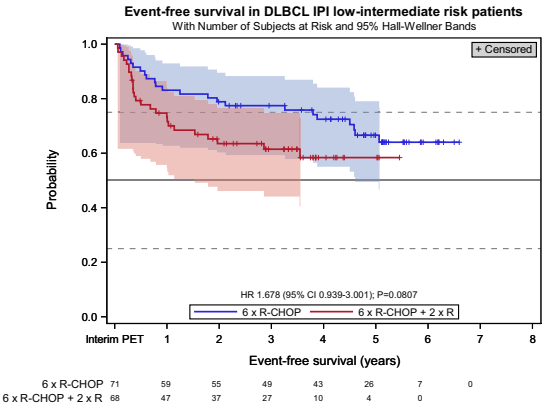
There were no statistically significant differences in response rate, event-free, progression-free, and overall survival between DLBCL patients receiving six or eight doses of rituximab (Table 2, Fig. 1). Stratification according to the IPI showed a statistically non-significant trend for improved event-free survival in the low-intermediate risk group favoring six and a similar trend in the high-risk group favoring eight doses of rituximab, with a weaker effect on overall survival (Fig. 2).

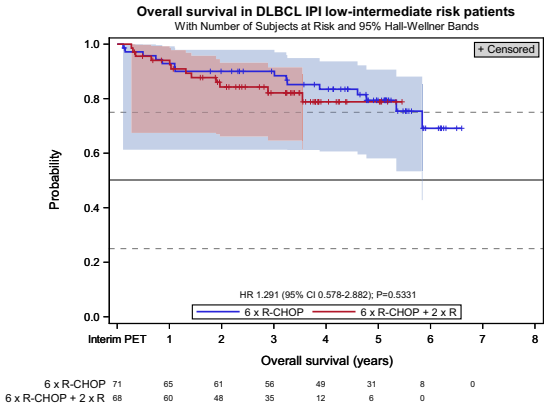
In subgroups defined by sex or age, survival differences between six and eight doses of rituximab were not observed (data not shown). However, when sex and age were combined, female patients below the age of 60 years had significantly inferior event-free survival when treated with eight as compared to six doses of rituximab, with a concomitant trend for decreased overall survival (Fig. 3). Fatal cases were restricted to patients 51 to 57 years of age. Causes of death included relapse ($n = 3$), infection ($n = 3$), and unknown

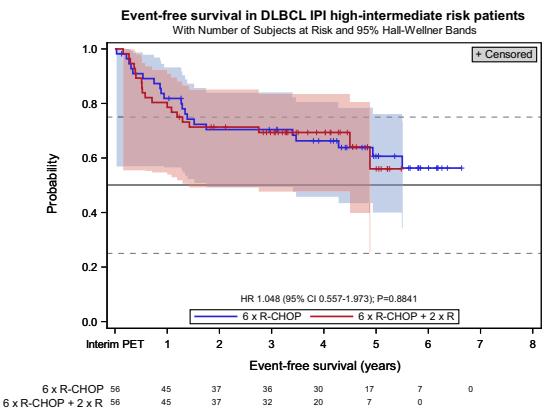
Fig. 2 Event-free survival and overall survival in interim positron emission tomography-negative patients with diffuse large B cell lymphoma in relation to the risk group of the International Prognostic Index. The patients were randomized or allocated to receive six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or the same treatment with two additional doses of rituximab. Survival started on the day of interim positron emission tomography (PET) scanning. Shaded areas correspond to 95% Hall-Wellner confidence bands

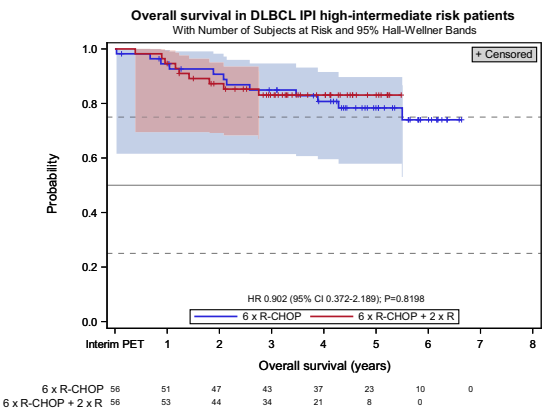

Event-free survival in DLBCL IPI low risk patients
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 1.155 (95% CI 0.576-2.317); P=0.6849
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Event-free survival (years)
6 x R-CHOP 113 96 95 92 84 55 29 3
6 x R-CHOP + 2 x R 97 88 80 59 25 6 0

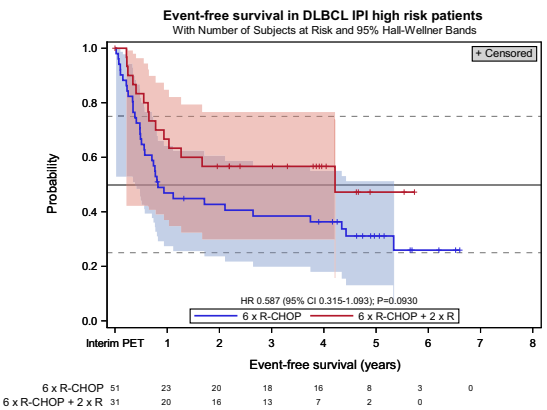

Overall survival in DLBCL IPI low risk patients
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 0.862 (95% CI 0.338-2.200); P=0.7558
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Overall survival (years)
6 x R-CHOP 113 105 101 98 88 58 30 3
6 x R-CHOP + 2 x R 97 95 86 65 28 9 0

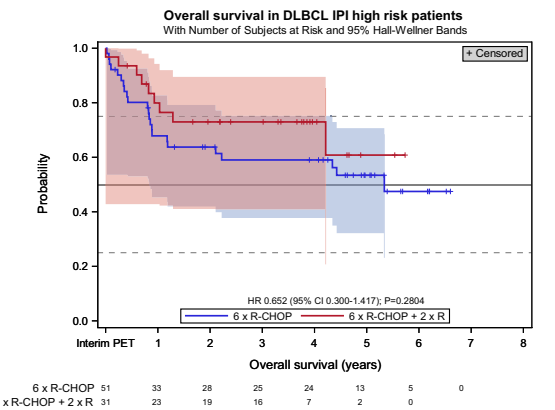

Event-free survival in DLBCL IPI low-intermediate risk patients
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 1.678 (95% CI 0.939-3.001); P=0.0807
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Event-free survival (years)
6 x R-CHOP 71 59 55 49 43 26 7 0
6 x R-CHOP + 2 x R 68 47 37 27 10 4 0


Overall survival in DLBCL IPI low-intermediate risk patients
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 1.291 (95% CI 0.578-2.882); P=0.5331
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Overall survival (years)
6 x R-CHOP 71 65 61 56 49 31 8 0
6 x R-CHOP + 2 x R 68 60 48 35 12 6 0


Event-free survival in DLBCL IPI high-intermediate risk patients
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 1.048 (95% CI 0.557-1.973); P=0.8841
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Event-free survival (years)
6 x R-CHOP 56 45 37 36 30 17 7 0
6 x R-CHOP + 2 x R 56 45 37 32 20 7 0


Overall survival in DLBCL IPI high-intermediate risk patients
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 0.902 (95% CI 0.372-2.189); P=0.8198
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Overall survival (years)
6 x R-CHOP 56 51 47 43 37 23 10 0
6 x R-CHOP + 2 x R 56 53 44 34 21 8 0


Event-free survival in DLBCL IPI high risk patients
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 0.587 (95% CI 0.315-1.093); P=0.0930
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Event-free survival (years)
6 x R-CHOP 51 23 20 18 16 8 3 0
6 x R-CHOP + 2 x R 31 20 16 13 7 2 0


Overall survival in DLBCL IPI high risk patients
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 0.652 (95% CI 0.300-1.417); P=0.2804
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Overall survival (years)
6 x R-CHOP 51 33 28 25 24 13 5 0
6 x R-CHOP + 2 x R 31 23 19 16 7 2 0

reason ($n = 1$) among 66 patients receiving eight doses of rituximab, as compared to relapse ($n = 1$) and unknown reason ($n = 1$) among 48 patients treated with six doses. Female patients above the age of 60 years and male patients of any age failed to show statistically significant survival differences between six and eight doses of rituximab (Fig. 3).

Stratification factors in the randomized subset included age, sex, and IPI risk group. To account for imbalances in these factors, the data were subjected to multivariable Cox regression analysis. The results obtained in the unadjusted population were confirmed after adjustment for confounding factors (Table S3). For further corroboration, the groups receiving six or eight doses of rituximab were harmonized by propensity score matching, yielding a total of 430 patients. The results in the matched population were similar to those obtained in the other analyses, but trends for subgroup-specific survival differences were less pronounced (Table S3, Figs. S1–S3).

Outcome in primary mediastinal B cell lymphoma

Although the rate of complete morphological remission, as assessed by CT, was lower in PMBCL than it was in DLBCL, event-free and overall survival tended to be superior (Table 2, Fig. 4). Two patients received consolidative mediastinal radiotherapy. There were no statistically significant differences between six or eight doses of rituximab (Table 2). This was confirmed in the Cox model and the propensity score matched population, but the validity of the results was limited by small numbers (data not shown).

Outcome in follicular lymphoma grade 3

As in DLBCL and PMBCL, the number of rituximab doses had no impact on outcome in FL (Table 2). This was confirmed in the Cox model and the propensity score matched population (data not shown). Statistically significant differences in the course of FL grade 3a and FL grade 3b were not observed (Fig. 4) which was confirmed by propensity score matching (Fig. S4).

Safety

The frequency and severity of side effects was similar in patients receiving six or eight doses of rituximab (Table S4). Grade 3 or 4 anemia ($P = 0.0001$), leukopenia ($P < 0.0001$), infection ($P < 0.0001$), diarrhea ($P = 0.0081$), and creatinine increase ($P = 0.0011$) were significantly more frequent above than below the age of 60 years. Treatment-related death (1.6%) also tended to occur more often in the older age group ($P = 0.0530$). Sex-related differences were limited to anemia ($P = 0.0086$) and leukopenia ($P = 0.0863$) which were more frequent in female than in male patients.

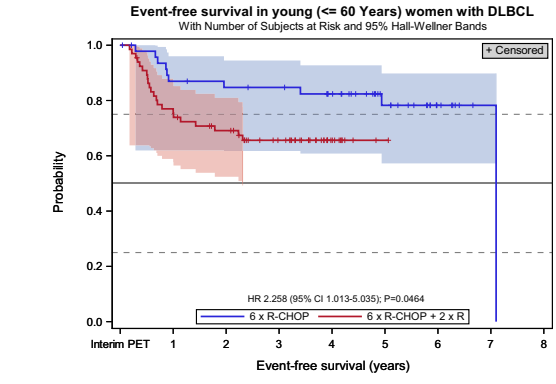
Fig. 3 Event-free survival and overall survival in interim positron emission tomography-negative patients with diffuse large B cell lymphoma in relation to sex and age. The patients were randomized or allocated to receive six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or the same treatment with two additional doses of rituximab. Survival started on the day of interim positron emission tomography (PET) scanning. Shaded areas correspond to 95% Hall-Wellner confidence bands

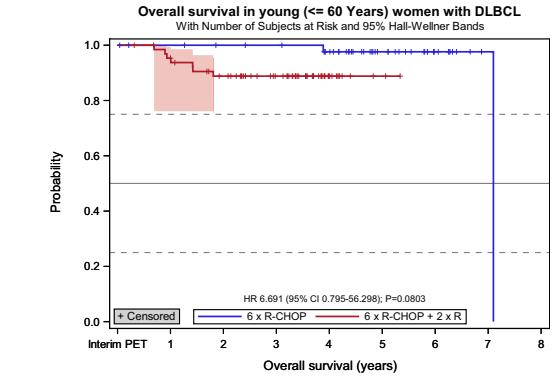
Discussion

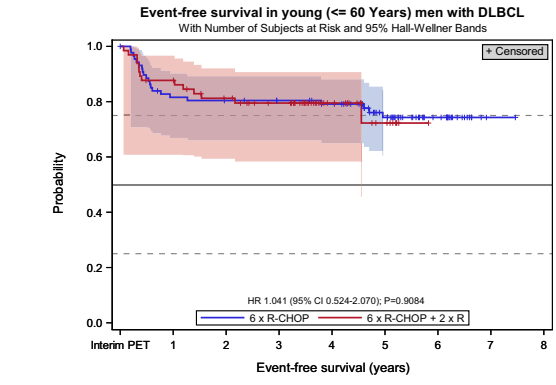
In the PETAL trial, two additional doses of rituximab failed to improve survival in interim PET-negative B cell lymphoma patients treated with six cycles of R-CHOP. A negative interim scan indicates chemotherapy sensitivity and translates into good long-term outcome [4]. Patients with a positive interim scan uniformly received eight doses of rituximab. Their outcome was poor, indicating therapy resistance [1]. Whether changes in rituximab exposure would impact survival in patients with resistant lymphoma was not investigated. Thus, our conclusions are limited to chemotherapy-sensitive lymphomas which comprised almost 90% of cases.

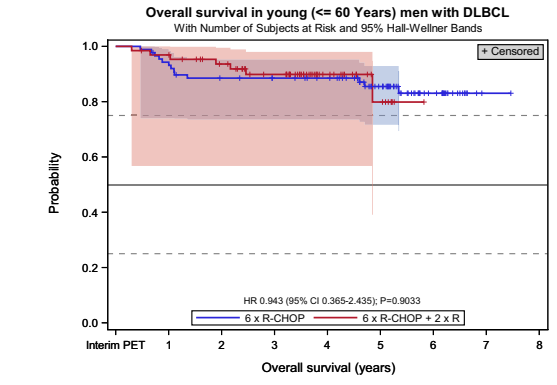
Several prospective trials have tested the impact of rituximab dose on outcome in aggressive B cell lymphomas. In the single-arm DENSE-R-CHOP-14 trial, tripling the number of rituximab doses in the first two of a total of six R-CHOP cycles led to a significant increase in infection-related morbidity and mortality, but had no impact on response rate or survival, as compared to a historical control treated with only one rituximab dose per cycle [13]. In the randomized HOVON84 trial, doubling the dose of rituximab in the first four R-CHOP cycles did not improve progression-free survival in the study population as a whole or in any of the sex- and age-related subgroups analyzed [14]. Likewise, in the GOYA trial, replacing eight standard doses of rituximab by ten more elevated doses of the novel CD20 antibody obinutuzumab failed to improve outcome [15]. In the PETAL trial, only DLBCL high-risk patients had a potential benefit of increased rituximab exposure. This, however, did not reach statistical significance and was less apparent in the propensity score matched population.

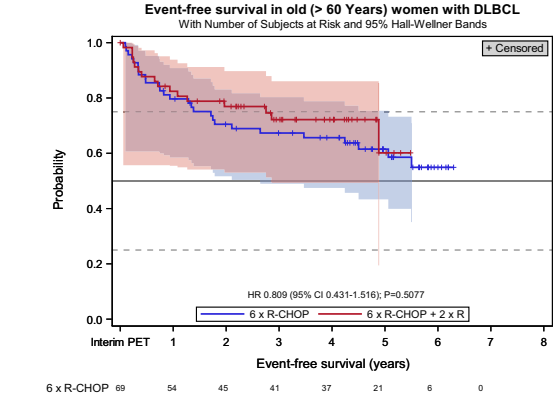
Further evidence of the limited value of increasing rituximab exposure in DLBCL is provided by randomized trials investigating maintenance therapy. In the US Intergroup study ECOG4494/CALGB9793, rituximab maintenance had no effect on outcome in newly diagnosed patients above the age of 60 years treated with rituximab and CHOP [16]. Similar observations were made in the LNH98-3 trial in which young high-risk patients received first-line high-dose chemotherapy with or without rituximab maintenance [17]. The AGMT-NHL13 trial included adult patients of any age in first complete remission after a rituximab-containing induction. In the trial population as a whole, rituximab maintenance did not improve outcome, but male patients had a statistically

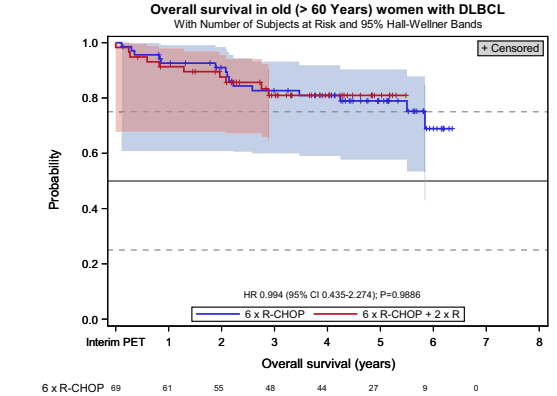

Event-free survival in young (<= 60 Years) women with DLBCL
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 2.258 (95% CI 1.013-5.035); P=0.0464
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Event-free survival (years)
6 x R-CHOP 48 40 38 37 32 19 7 1
6 x R-CHOP + 2 x R 66 50 42 30 10 1 0

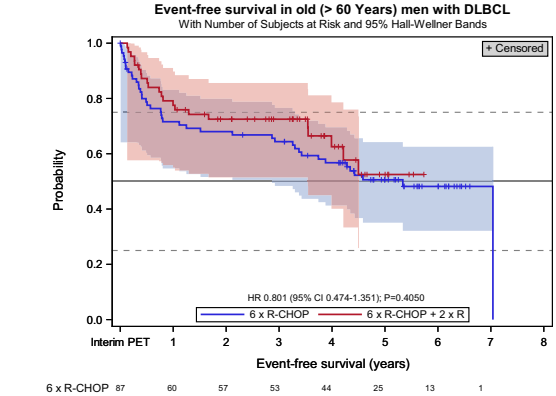

Overall survival in young (<= 60 Years) women with DLBCL
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 6.691 (95% CI 0.795-56.298); P=0.0803
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Overall survival (years)
6 x R-CHOP 48 46 44 43 38 22 9 1
6 x R-CHOP + 2 x R 66 61 52 39 11 2 0

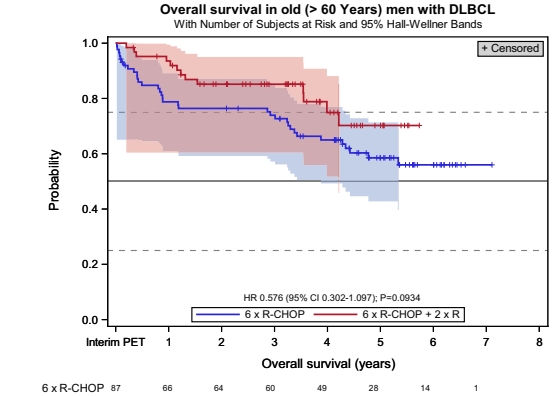

Event-free survival in young (<= 60 Years) men with DLBCL
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 1.041 (95% CI 0.524-2.070); P=0.9084
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Event-free survival (years)
6 x R-CHOP 88 70 68 65 61 42 20 1
6 x R-CHOP + 2 x R 65 56 48 41 18 8 0

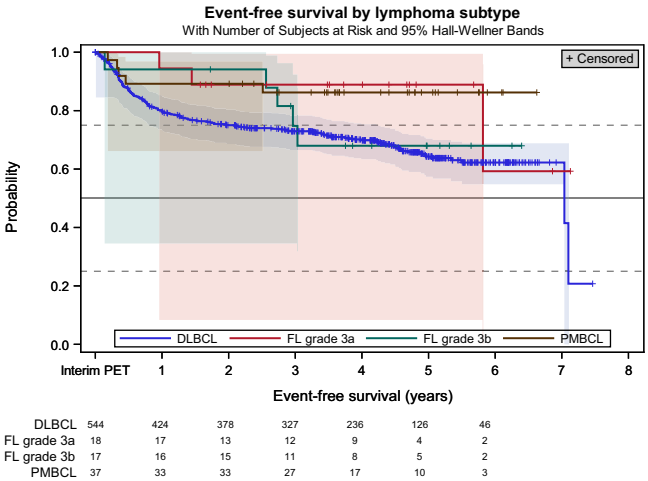

Overall survival in young (<= 60 Years) men with DLBCL
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 0.943 (95% CI 0.365-2.435); P=0.9033
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Overall survival (years)
6 x R-CHOP 88 82 75 72 68 49 21 1
6 x R-CHOP + 2 x R 65 62 54 43 19 8 0


Event-free survival in old (> 60 Years) women with DLBCL
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 0.809 (95% CI 0.431-1.516); P=0.5077
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Event-free survival (years)
6 x R-CHOP 69 54 45 41 37 21 6 0
6 x R-CHOP + 2 x R 58 46 40 28 18 4 0


Overall survival in old (> 60 Years) women with DLBCL
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 0.994 (95% CI 0.435-2.274); P=0.9886
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Overall survival (years)
6 x R-CHOP 69 61 55 48 44 27 9 0
6 x R-CHOP + 2 x R 58 51 45 32 19 6 0


Event-free survival in old (> 60 Years) men with DLBCL
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 0.801 (95% CI 0.474-1.351); P=0.4050
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Event-free survival (years)
6 x R-CHOP 87 60 57 53 44 25 13 1
6 x R-CHOP + 2 x R 63 48 40 32 16 6 0


Overall survival in old (> 60 Years) men with DLBCL
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Probability
HR 0.576 (95% CI 0.302-1.097); P=0.0934
6 x R-CHOP
6 x R-CHOP + 2 x R
Interim PET
Overall survival (years)
6 x R-CHOP 87 66 64 60 49 28 14 1
6 x R-CHOP + 2 x R 63 57 46 36 19 9 0



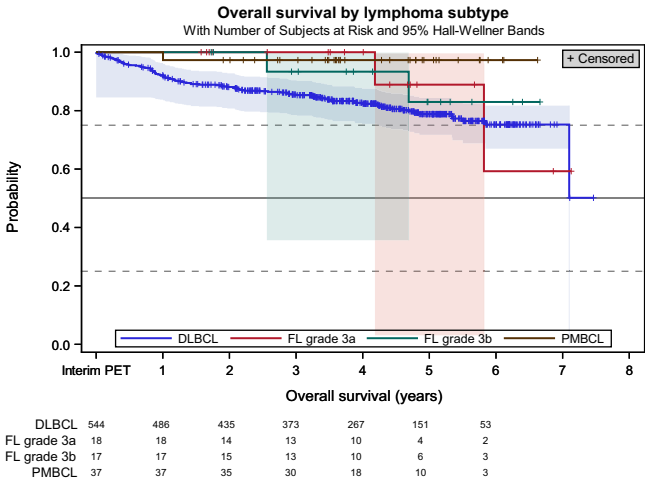


Fig. 4 Event-free survival and overall survival in interim positron emission tomography-negative patients with diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL), follicular lymphoma (FL) grade 3a, or follicular lymphoma grade 3b. The patients received six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) with or without two additional doses of rituximab. Survival started on the day of interim positron emission tomography (PET) scanning. Shaded areas correspond to 95% Hall-Wellner confidence bands

significant benefit with regard to event-free and progression-free survival [18]. Similar observations were made in the HD2002 trial [19]. By contrast, in the CORAL study exploring maintenance in relapse, only female patients appeared to benefit from prolonged rituximab exposure [20].

Male patients of any age and female patients below the age of 60 years eliminate rituximab faster than older female patients do. This has led to the assumption that the antibody may be under-dosed in the first-named patient groups [5, 6]. In the PETAL trial, none of these subgroups benefitted from increased rituximab exposure. Unexpectedly, female patients between 50 and 60 years of age fared worse with eight as compared to six rituximab doses. The increase in mortality was related to relapse and infection. Our conclusion that increased rituximab exposure may be hazardous in female patients is supported by safety data from the rituximab maintenance arm of the AGMT-NHL13 trial in which adverse events in general and infection in particular were more frequent in female patients than they were in male patients [18].

Long-term outcome in PMBCL was excellent, with only one of 37 patients dying within the observation period. Five patients with a positive interim PET scan were not included in the present analysis. Although two of them responded poorly to first-line therapy, none died (data not shown), raising the survival rate in the total PMBCL population to 98%. These results are in line with a subgroup analysis of the UK National Cancer Research Institute R-CHOP-14 versus R-CHOP-21 trial, which suggested that PMBCL patients may benefit from short treatment intervals [21]. In the PETAL trial, R-CHOP was given in 14-day intervals, except for the interval between cycles 2 and 3 which was 3 weeks (to avoid false-positive interim PET findings) [1]. In the UK trial, 58% of patients received additional radiotherapy. By contrast, in the PETAL trial, only two of 37 patients with a negative and one of five patients with a positive interim PET scan were subjected to mediastinal irradiation (7%). Thus, two-weekly R-CHOP is an excellent treatment option for PMBCL, and PET can identify patients who may be spared radiotherapy. Our results are similar to those reported in the dose-adjusted EPOCH-R trial in which the overall survival rate in PMBCL was 97%, and PET monitoring reduced the frequency of radiotherapy to 4% [22]. Administration of EPOCH-R, however, is cumbersome, with dose modifications from cycle to cycle and prolonged infusion of etoposide, vincristine, and doxorubicin, which may necessitate hospitalization. In addition, etoposide is a leukemogenic agent, putting patients with otherwise excellent prognosis at undue risk of developing a life-threatening secondary disease [23].

The PETAL trial included both grade 3a and grade 3b of FL. Whether these grades reflect differences in natural history remains controversial. Some studies suggest that the course of grade 3a is indolent, resembling grades 1 and 2, while grade 3b behaves like an aggressive lymphoma [24]. Others come to the conclusion that, although the biology of grade 3a and grade 3b may differ, their clinical course is largely indistinguishable [25–27]. Although our observations are limited by small numbers, with the R-CHOP regimen, clinical differences between grade 3a and grade 3b were not apparent.

In conclusion, increasing the exposure to rituximab did not improve outcome in B cell lymphomas with a fast metabolic response to R-CHOP. Irrespective of lymphoma entity, six doses of rituximab appear to be sufficient.

Acknowledgements We thank the patients, investigators, and PET centers from all parts of Germany for their participation.

Funding information This work was funded by Deutsche Krebshilfe (grant nos. 107592 and 110515 to Ulrich Dührsen), Amgen Germany, and Roche Pharma (institutional research funding to the University Hospital Essen).

Compliance with ethical standards

Conflict of interest Andreas Hüttmann: honoraria from Bristol-Myers Squibb, Takeda, Celgene, and Roche; travel reimbursement from Gilead and Amgen; Stefan P. Müller: institutional research funding from BTG Interventional Medicine; Frank Kroschinsky: honoraria and travel reimbursement from and consultancy for Roche, Celgene, Gilead, Pfizer, and Janssen; Paul La Rosée: honoraria and travel reimbursement from and consultancy for Roche; Martin Grieshammer: honoraria from, consultancy for, and speaker's bureau of Roche, Amgen, AOP, Novartis, Shire, and Janssen; Georg Maschmeyer: honoraria from Gilead, Pfizer, Merck Serono, Celgene, Bristol-Myers Squibb, and Boehringer Ingelheim; consultancy for Gilead; travel reimbursement from Bristol-Myers Squibb; Ingo Brink: honoraria from Siemens and Rotop; travel reimbursement from Bayer; Tobias Gaska: institutional research funding from Roche; travel reimbursement from Ipsen; Aristoteles Giagounidis: consultancy for Celgene; Matthias Grube: consultancy for Bristol-Myers Squibb and Sanofi; Claudia Ose: institutional research funding, honoraria, and travel reimbursement from Medice Arzneimittel Pütter; Jan Dürig: honoraria from and consultancy for Roche and Amgen; Wolfram Klapper: institutional research funding from Roche, Amgen, Regeneron, Novartis, and Takeda; Ulrich Dührsen: institutional research funding and honoraria from Roche and Amgen.

References

1. Dührsen U, Müller S, Hertenstein B et al (2018) Positron-emission tomography-guided therapy of aggressive non-Hodgkin lymphomas (PETAL): a multicenter, randomized phase 3 trial. J Clin Oncol 36:2024–2034
2. Woessmann W, Seidemann K, Mann G, Zimmermann M, Burkhardt B, Oschlies I, Ludwig WD, Klingebiel T, Graf N, Gruhn B, Juergens H, Niggli F, Parwaresch R, Gadner H, Riehm H, Schrappe M, Reiter A, BFM Group (2005) 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 105:948–958
3. Hoelzer D, Walewski J, Döhner H et al (2014) Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: report of a large prospective multicenter trial. Blood 124:3870–3879
4. Lin C, Itti E, Haioun C, Petegnief Y, Luciani A, Dupuis J, Paone G, Talbot JN, Rahmouni A, Meignan M (2007) Early 18F-FDG PET for prediction of prognosis in patients with diffuse large B-cell lymphoma: SUV-based assessment versus visual analysis. J Nucl Med 48:1626–1632
5. Müller C, Murawski N, Wiesen MH et al (2012) The role of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. Blood 119:3276–3284
6. Pfreundschuh M, Müller C, Zeynalova S et al (2014) Suboptimal dosing of rituximab in male and female patients with DLBCL. Blood 123:640–646
7. Cunningham D, Hawkes EA, Jack A, Qian W, Smith P, Mouncey P, Pocock C, Ardeshna KM, Radford JA, McMillan A, Davies J, Turner D, Kruger A, Johnson P, Gambell J, Linch D (2013) Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 381:1817–1826
8. Swerdlow SH, Campo E, Harris NL et al (2008) WHO classification of tumours of the haematopoetic and lymphoid tissues. IARC Press, Lyon
9. Pfreundschuh M, Schubert J, Ziepert M, Schmits R, Mohren M, Lengfelder E, Reiser M, Nickenig C, Clemens M, Peter N, Bokemeyer C, Eimermacher H, Ho A, Hoffmann M, Mertelsmann R, Trümper L, Balleisen L, Liersch R, Metzner B, Hartmann F, Glass B, Poeschel V, Schmitz N, Ruebe C, Feller AC, Loeffler M, German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) (2008) Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 9:105–116
10. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V, International Harmonization Project on Lymphoma (2007) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579–586
11. National Cancer Institute (2006) Common Terminology Criteria for Adverse Events v3.0 (CTCAE); https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed 1 Oct 2007 and Accessed 14 Feb 2008
12. International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993) A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329:987–994
13. Murawski N, Pfreundschuh M, Zeynalova S, Poeschel V, Hänel M, Held G, Schmitz N, Viardot A, Schmidt C, Hallek M, Witzens-Harig M, Trümper L, Rixecker T, Zwick C (2014) Optimization of rituximab for the treatment of DLBCL (I): dose-dense rituximab in the DENSE-R-CHOP-14 trial of the DSHNHL. Ann Oncol 25:1800–1806
14. Lugtenburg PJ, de Nully Brown P, van der Holt B et al (2016) Randomized phase III study on the effect of early intensification of rituximab in combination with 2-weekly CHOP chemotherapy followed by rituximab or no maintenance in patients with diffuse large B-cell lymphoma: results from a HOVON-Nordic lymphoma group study. J Clin Oncol 34(suppl):abstract 7504
15. Vitolo U, Trněný M, Belada D, Burke JM, Carella AM, Chua N, Abrisqueta P, Demeter J, Flinn I, Hong X, Kim WS, Pinto A, Shi YK, Tatsumi Y, Oestergaard MZ, Wenger M, Fingerle-Rowson G, Catalani O, Nielsen T, Martelli M, Sehn LH (2017) Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. J Clin Oncol 35:3529–3537
16. Habermann TM, Weller EA, Morrison VA, Gascoyne RD, Cassileth PA, Cohn JB, Dakhil SR, Woda B, Fisher RI, Peterson BA, Horning SJ (2006) Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 24:3121–3127
17. Haioun C, Mounier N, Emile JF, Ranta D, Coiffier B, Tilly H, Recher C, Ferme C, Gabarre J, Herbrecht R, Morchhauser F, Gisselbrecht C (2009) Rituximab versus observation after high-dose consolidative first-line chemotherapy with autologous stem-cell transplantation in patients with poor-risk diffuse large B-cell lymphoma. Ann Oncol 20:1985–1992
18. Jaeger U, Trneny M, Melzer H, Praxmarer M, Nawarawong W, Ben Yehuda D, Goldstein D, Mihaljevic B, Ilhan O, Ballova V, Hedenus M, Hsiao LT, Au WY, Burgstaller S, Weidinger G, Keil F, Dittrich C, Skrabs C, Klingler A, Chott A, Fridrik MA, Greil R, for the AGMT-NHL13 Investigators (2015) Rituximab maintenance for

patients with aggressive B-cell lymphoma in first remission: results of the randomized NHL13 trial. Haematologica 100:955–963
19. Witzens-Harig M, Benner A, McClanahan F, Klemmer J, Brandt J, Brants E, Rieger M, Meissner J, Hensel M, Neben K, Dreger P, Lengfelder E, Schmidt-Wolf I, Krämer A, Ho AD (2015) Rituximab maintenance improves survival in male patients with diffuse large B-cell lymphoma. Results of the HD2002 prospective multicentre randomized phase III trial. Br J Haematol 171:710–719
20. Gisselbrecht C, Schmitz N, Mounier N, Singh Gill D, Linch DC, Trneny M, Bosly A, Milpied NJ, Radford J, Ketterer N, Shpilberg O, Dührsen U, Hagberg H, Ma DD, Viardot A, Lowenthal R, Brière J, Salles G, Moskowitz CH, Glass B (2012) Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. J Clin Oncol 30:4462–4469
21. Gleeson M, Hawkes EA, Cunningham D, Chadwick N, Counsell N, Lawrie A, Jack A, Smith P, Mouncey P, Pocock C, Ardeshna KM, Radford J, McMillan A, Davies J, Turner D, Kruger A, Johnson PWM, Gambell J, Linch D (2016) Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) in the management of primary mediastinal B-cell lymphoma: a subgroup analysis of the UK NCRI R-CHOP 14 versus 21 trial. Br J Haematol 175:668–672
22. Dunleavy K, Pittaluga S, Maeda LS, Advani R, Chen CC, Hessler J, Steinberg SM, Grant C, Wright G, Varma G, Staudt LM, Jaffe ES, Wilson WH (2013) Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 368:1408–1416
23. Ezoe S (2012) Secondary leukemia associated with the anti-cancer agent, etoposide, a topoisomerase II inhibitor. Int J Environ Res Public Health 9:2444–2453
24. Wahlin BE, Yri OE, Kimby E, Holte H, Delabie J, Smeland EB, Sundström C, Christensson B, Sander B (2012) Clinical significance of the WHO grades of follicular lymphoma in a population-based cohort of 505 patients with long follow-up times. Br J Haematol 156:225–233
25. Hans CP, Weisenburger DD, Vose JM, Hock LM, Lynch JC, Aoun P, Greiner TC, Chan WC, Bociek RG, Bierman PJ, Armitage JO (2003) A significant diffuse component predicts for inferior survival in grade 3 follicular lymphoma, but cytologic subtypes do not predict survival. Blood 101:2363–2367
26. Shustik J, Quinn M, Connors JM, Gascoyne RD, Skinnider B, Sehn LH (2011) Follicular non-Hodgkin lymphoma grades 3A and 3B have a similar outcome and appear incurable with anthracycline-based therapy. Ann Oncol 22:1164–1169
27. Koch K, Hoster E, Ziepert M, Unterhalt M, Ott G, Rosenwald A, Hansmann ML, Bernd W, Stein H, Pöschel V, Dreyling M, Trümper L, Löffler M, Schmitz N, Hiddemann W, Pfreundschuh M, Klapper W (2016) Clinical, pathological and genetic features of follicular lymphoma grade 3A: a joint analysis of the German low-grade and high-grade lymphoma study groups GLSG and DSHNHL. Ann Oncol 27:1323–1329

Affiliations

Andreas Hüttmann[1] · Jan Rekowski[2] · Stefan P. Müller[3] · Bernd Hertenstein[4] · Christiane Franzius[5] · Rolf Mesters[6] · Matthias Weckesser[7] · Frank Kroschinsky[8] · Jörg Kotzerke[9] · Arnold Ganser[10] · Frank M. Bengel[11] · Paul La Rosée[12,13] · Martin Freesmeyer[14] · Heinz-Gert Höffkes[15] · Andreas Hertel[16] · Dirk Behringer[17] · Gabriele Prange-Krex[18] · Martin Griesshammer[19] · Jens Holzinger[20] · Stefan Wilop[21] · Thomas Krohn[22] · Aruna Raghavachar[23] · Georg Maschmeyer[24] · Ingo Brink[25] · Roland Schroers[26] · Tobias Gaska[27] · Helga Bernhard[28] · Aristoteles Giagounidis[29,30] · Jochen Schütte[31,32] · Ariane Dienst[33] · Hubertus Hautzel[34] · Ralph Naumann[35,36] · Alfred Klein[37] · Dennis Hahn[38] · Gabriele Pöpperl[39] · Matthias Grube[40] · Jörg Marienhagen[41] · Andreas Schwarzer[42] · Lars Kurch[43] · Thomas Höhler[44] · Heike Steiniger[45] · Holger Nückel[46] · Thomas Südhoff[47] · Wolfgang Römer[48] · Marcus Brinkmann[49] · Claudia Ose[49] · Ferras Alashkar[1] · Christine Schmitz[1] · Jan Dürig[1] · Dieter Hoelzer[50] · Karl-Heinz Jöckel[2] · Wolfram Klapper[51] · Ulrich Dührsen[1]

1 Klinik für Hämatologie, Universitätsklinikum Essen, Essen, Germany

2 Institut für Medizinische Informatik, Biometrie und Epidemiologie, Universität Duisburg-Essen, Essen, Germany

3 Klinik für Nuklearmedizin, Universitätsklinikum Essen, Essen, Germany

4 Medizinische Klinik I, Klinikum Bremen-Mitte, Bremen, Germany

5 Zentrum für moderne Diagnostik (Zemodi), Zentrum für Nuklearmedizin und PET/CT, Bremen, Germany

6 Medizinische Klinik A, Universitätsklinikum Münster, Münster, Germany

7 Klinik für Nuklearmedizin, Universitätsklinikum Münster, Münster, Germany

8 Medizinische Klinik I, Universitätsklinikum Carl Gustav Carus, Dresden, Germany

9 Klinik für Nuklearmedizin, Universitätsklinikum Carl Gustav Carus, Dresden, Germany

10 Klinik für Hämatologie, Hämostaseologie, Onkologie und Stammzelltransplantation, Medizinische Hochschule Hannover, Hannover, Germany

11 Klinik für Nuklearmedizin, Medizinische Hochschule Hannover, Hannover, Germany

12 Klinik für Innere Medizin II, Universitätsklinikum Jena, Jena, Germany

13 Klinik für Innere Medizin II, Schwarzwald-Baar-Klinikum, Villingen-Schwenningen, Germany

[14] Klinik für Nuklearmedizin, Universitätsklinikum Jena, Jena, Germany

[15] Tumorklinik, Klinikum Fulda, Fulda, Germany

[16] Klinik für Diagnostische und Therapeutische Nuklearmedizin, Klinikum Fulda, Fulda, Germany

[17] Klinik für Hämatologie, Onkologie und Palliativmedizin, Augusta-Kranken-Anstalt, Bochum, Germany

[18] Onkologische Gemeinschaftspraxis, Dresden, Germany

[19] Universitätsklinik für Hämatologie, Onkologie, Gerinnungsstörungen und Palliativmedizin, Johannes Wesling Klinikum, Minden, Germany

[20] Institut für Diagnostische Radiologie, Neuroradiologie und Nuklearmedizin, Johannes Wesling Klinikum, Minden, Germany

[21] Klinik für Hämatologie, Onkologie, Hämostaseologie und Stammzelltransplantation, Universitätsklinikum Aachen, Aachen, Germany

[22] Klinik für Nuklearmedizin, Universitätsklinikum Aachen, Aachen, Germany

[23] Medizinische Klinik 1, Helios Universitätsklinikum Wuppertal, Wuppertal, Germany

[24] Klinik für Hämatologie, Onkologie und Palliativmedizin, Klinikum Ernst von Bergmann, Potsdam, Germany

[25] Klinik für nuklearmedizinische Diagnostik und Therapie, Ernst von Bergmann Klinikum, Potsdam, Germany

[26] Medizinische Klinik, Knappschaftskrankenhaus, Ruhr-Universität Bochum, Bochum, Germany

[27] Klinik für Hämatologie und Onkologie, Brüderkrankenhaus St. Josef, Paderborn, Germany

[28] Medizinische Klinik V, Klinikum Darmstadt, Darmstadt, Germany

[29] Klinik für Onkologie und Hämatologie, Helios St. Johannes Klinik, Duisburg, Germany

[30] Present Address: Klinik für Onkologie, Hämatologie und Palliativmedizin, Marien Hospital, Düsseldorf, Germany

[31] Klinik für Onkologie, Hämatologie und Palliativmedizin, Marien Hospital, Düsseldorf, Germany

[32] Present Address: Überörtliche Schwerpunktpraxis für Onkologie, Hämatologie und ambulante Tumortherapie, Düsseldorf, Germany

[33] Klinik für Hämatologie, Onkologie und Klinische Immunologie, Universitätsklinikum Düsseldorf, Düsseldorf, Germany

[34] Klinik für Nuklearmedizin, Universitätsklinikum Düsseldorf, Düsseldorf, Germany

[35] Gemeinschaftsklinikum Mittelrhein, Klinik für Innere Medizin, Hämatologie/Onkologie, Palliativmedizin, Koblenz, Germany

[36] St. Marienkrankhaus, Medizinische Klinik III, Hämatologie, Medizinische Onkologie und Palliativmedizin, Siegen, Germany

[37] Klinik für Nuklearmedizin, Bundeswehrkrankenhaus, Koblenz, Germany

[38] Klinik für Hämatologie, Onkologie und Palliativmedizin, Klinikum Stuttgart, Stuttgart, Germany

[39] Klinik für Nuklearmedizin, Klinikum Stuttgart, Stuttgart, Germany

[40] Klinik für Innere Medizin III, Universitätsklinikum Regensburg, Regensburg, Germany

[41] Abteilung für Nuklearmedizin, Universitätsklinikum Regensburg, Regensburg, Germany

[42] Onkopraxis Probstheida, Leipzig, Germany

[43] Klinik und Poliklinik für Nuklearmedizin, Universitätsklinikum Leipzig, Leipzig, Germany

[44] Medizinische Klinik I, Prosper-Hospital, Recklinghausen, Germany

[45] Praxis für Hämatologie und Onkologie, Oberhausen, Germany

[46] Gemeinschaftspraxis für Hämatologie, Onkologie, Hämostaseologie und Palliativmedizin, Bochum, Germany

[47] 2. Medizinische Klinik, Klinikum Passau, Passau, Germany

[48] Nuklearmedizinische Gemeinschaftspraxis, Klinikum Passau, Passau, Germany

[49] Zentrum für Klinische Studien Essen (ZKSE), Universität Duisburg-Essen, Essen, Germany

[50] Onkologikum, Frankfurt/Main, Germany

[51] Institut für Pathologie, Sektion für Hämatopathologie, Universitätsklinikum Schleswig-Holstein, Kiel, Germany