Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial

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Summary

Background Six cycles of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) are the standard treatment for aggressive B-cell non-Hodgkin lymphoma. In the FLYER trial, we assessed whether four cycles of CHOP plus six applications of rituximab are non-inferior to six cycles of R-CHOP in a population of patients with B-cell non-Hodgkin lymphoma with favourable prognosis.

Methods This two-arm, open-label, international, multicentre, prospective, randomised phase 3 non-inferiority trial was done at 138 clinical sites in Denmark, Israel, Italy, Norway, and Germany. We enrolled patients aged 18–60 years, with stage I–II disease, normal serum lactate dehydrogenase concentration, ECOG performance status 0–1, and without bulky disease (maximal tumour diameter <7·5 cm). Randomisation was computer-based and done centrally in a 1:1 ratio using the Pocock minimisation algorithm after stratification for centres, stage (I *vs* II), and extralymphatic sites (no *vs* yes). Patients were assigned to receive either six cycles of R-CHOP or four cycles of R-CHOP plus two doses of rituximab. CHOP comprised cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), and vincristine (1·4 mg/m², with a maximum total dose of 2 mg), all administered intravenously on day 1, plus oral prednisone or prednisolone at the discretion of the investigator (100 mg) administered on days 1–5. Rituximab was given at a dose of 375 mg/m² of body surface area. Cycles were repeated every 21 days. No radiotherapy was planned except for testicular lymphoma treatment. The primary endpoint was progression-free survival after 3 years. The primary analysis was done in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of assigned treatment. A non-inferiority margin of –5·5% was chosen. The trial, which is completed, was prospectively registered at ClinicalTrials.gov, NCT00278421.

Findings Between Dec 2, 2005, and Oct 7, 2016, 592 patients were enrolled, of whom 295 patients were randomly assigned to receive six cycles of R-CHOP and 297 were assigned to receive four cycles of R-CHOP plus two doses of rituximab. Four patients in the four-cycles group withdrew informed consent before the start of treatment, so 588 patients were included in the intention-to-treat analysis. After a median follow-up of 66 months (IQR 42–100), 3-year progression-free survival of patients who had four cycles of R-CHOP plus two doses of rituximab was 96% (95% CI 94–99), which was 3% better (lower limit of the one-sided 95% CI for the difference was 0%) than six cycles of R-CHOP, demonstrating the non-inferiority of the four-cycles regimen. 294 haematological and 1036 non-haematological adverse events were documented in the four-cycles group compared with 426 haematological and 1280 non-haematological adverse events in the six-cycles group. Two patients, both in the six-cycles group, died during study therapy.

Interpretation In young patients with aggressive B-cell non-Hodgkin lymphoma and favourable prognosis, four cycles of R-CHOP is non-inferior to six cycles of R-CHOP, with relevant reduction of toxic effects. Thus, chemotherapy can be reduced without compromising outcomes in this population.

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Introduction

In aggressive B-cell non-Hodgkin lymphoma, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy in combination with rituximab is standard of care.[1–3] Although heterogeneous in its biology, the outcome of the disease can be predicted

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Research in context

Evidence before this study

Rituximab in combination with six to eight cycles of CHOP chemotherapy (R-CHOP) has been established as standard treatment for diffuse large B-cell lymphoma. We searched PubMed with the search terms "lymphoma", "DLBCL", "trial", and "rituximab", in English, published between Jan 1, 2002, and Dec 4, 2019. Three randomised trials demonstrated that rituximab improved event-free, progression-free, and overall survival compared with CHOP chemotherapy alone, resulting in a halving of lymphoma-related deaths in these trials. Since then, many trials have failed to improve therapy, suggesting that a plateau of efficacy has been reached with R-CHOP, especially in the subgroup of patients with good prognosis. Prognosis of aggressive non-Hodgkin lymphoma can be established by the International Prognostic Index (IPI), using the clinical parameters of age, tumour stage, serum lactate dehydrogenase concentration, performance status, and number of involved extralymphatic sites. The IPI was established in the pre-rituximab era. Pooled analyses of prospective, randomised trials confirmed the validity of IPI for R-CHOP regimens as well. Patients younger than 60 years without risk factors such as stage III–IV disease, increased serum lactate dehydrogenase concentration, poor performance status, and bulky disease (defined as maximum lymphoma diameter ≥7·5 cm) had a 3-year progression-free survival of 95% (95% CI 90–99) and an overall survival of 98% (95–100), when treated with six cycles of R-CHOP or R-CHOP-like regimens in the MInT trial.

Added value of this study

To our knowledge, this study is the first phase 3 study in aggressive B-cell lymphoma since rituximab was introduced, which showed that the treatment paradigm of six cycles of R-CHOP can be changed. It demonstrates that CHOP chemotherapy can be safely reduced to four cycles in young patients (≤60 years) with no risk factor according to the age-adjusted IPI and no bulky disease. Given this excellent outcome, it appears that some patients might be overtreated with six to eight cycles of R-CHOP.

Implications of all the available evidence

We consider these results to be potentially practice changing. Based on the current data, four cycles of CHOP combined with six doses of rituximab are non-inferior to six cycles of CHOP combined with six doses of rituximab in young low-risk patients with aggressive B-cell lymphoma.

by the clinical parameters of age, tumour stage, serum lactate dehydrogenase concentration, performance status, and number of involved extralymphatic sites. These characteristics have been subsumed in the international prognostic index (IPI),[4] which reliably separates patients into distinct prognostic subgroups.[5] For younger patients (≤60 years), the age-adjusted model of the IPI (including LDH, stage, and performance status) has been established. Patients without age-adjusted IPI risk factors and without bulky disease (ie, maximum lymphoma diameter <7·5 cm) have a very favourable prognosis with a 3-year progression-free survival of 95%, an event-free survival of 89%, and an overall survival of 98%, when treated with six cycles of combined immunochemotherapy with R-CHOP-like regimens.[2,6] However, very high cure rates with cytotoxic therapies suggest overtreatment of most patients at least. Accordingly, the benefit in efficacy might come at the cost of unnecessary and potentially severe toxic effects for all patients. Therefore, we hypothesised and tested whether only four cycles of CHOP plus six applications of rituximab are non-inferior to the standard treatment of six cycles of R-CHOP in this population.

Methods

Study design and participants

The investigator-initiated FLYER study was a two-arm, open-label, international, multicentre, prospective, randomised phase 3 trial from 138 clinical sites in Denmark, Israel, Italy, Norway, and Germany. It was coordinated by the German High-grade Non-Hodgkin's Lymphoma Study Group, which is now part of the German Lymphoma Alliance. The study was conducted in accordance with the Helsinki declaration. The protocol and its amendments were approved by the ethics committee of each participating centre. Additional information about trial oversight and amendments is provided in the appendix (p 11).

Patients aged 18–60 years were eligible for the study if they had previously untreated biopsy-confirmed aggressive, CD20-positive B-cell lymphoma according to WHO classification of tumours of haemopoietic and lymphoid tissues (third edition, 2001 and fourth edition, 2008) and if they had no risk factor according to age-adjusted IPI (serum lactate dehydrogenase less than upper limit of normal, Eastern Cooperative Oncology Group performance status 0 or 1, or Ann Arbor stage I or II), and no bulky disease (diameter of single or conglomerate tumour <7·5 cm). Exclusion criteria were CNS involvement or primary CNS lymphoma, marked impairment of cardiac, pulmonary, hepatic, or renal function; white blood cell count less than $2·5\times10^3$ cells per µL; initial platelet count less than 100×10^3 cells per µL; known hypersensitivity to the medication to be used; known HIV positivity; active hepatitis infection; previous chemotherapy or radiotherapy for past disorder; pregnancy and lactation period; simultaneous participation in other treatment studies; previous immunosuppressive treatment with cytostatics; other concomitant tumour disease or within the past 5 years; MALT lymphoma; planned radiotherapy of extranodal involvement; or inability to comply with study requirements. All patients gave written informed consent.

Randomisation and masking

Randomisation was done in a 1:1 ratio using the Pocock minimisation algorithm after stratification for centres, stage (Ann Arbor stage I *vs* II) and extralymphatic sites (no *vs* yes).[7] To ensure balanced group assignment at any time, patients were randomly assigned centrally by a data manager at the study centre (Homburg, Germany) by use of a computer program with an algorithm using a biased coin approach that accounted for previous randomisations. All eligible patients were randomly assigned to receive either six or four 21-day cycles of CHOP chemotherapy given concurrently with six applications of rituximab.

Procedures

CHOP comprised cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), and vincristine (1·4 mg/m², with a maximum total dose of 2 mg), all administered intravenously on day 1, plus oral prednisone or prednisolone at the discretion of the investigator (100 mg) administered on days 1–5. Rituximab was given at a dose of 375 mg/m² of body surface area. The first cycle of rituximab and first cycle of CHOP started concurrently (denoted R-CHOP). Thus, patients assigned to four cycles of CHOP received the fifth and sixth cycle of rituximab as monotherapy. Cycles were repeated every 21 days.

Lumbar puncture to exclude involvement of the CNS was mandatory in patients with testicular involvement. Prophylaxis for relapse in the CNS was planned to administer to patients with testicular, craniofacial, and upper cervical involvement and patients with Burkitt or Burkitt-like lymphoma. Prophylaxis consisted of four doses of intrathecal methotrexate, 15 mg per dose, administered at day 1 and day 5 of the first and second cycle of R-CHOP, or on day 1 only of the first four cycles of R-CHOP. CNS prophylaxis was stopped by the second amendment of the study protocol on Dec 12, 2011, when an analysis of a large clinical trial showed that intrathecal methotrexate did not lower the incidence of CNS relapse.[8] Prophylactic radiotherapy with 30·6 Gy to the contralateral testis in case of testicular involvement was mandatory since the second amendment of the study protocol. No radiotherapy was administered to other sites.

Response was assessed after three and six cycles according the 1999 consensus criteria.[9] First follow-up examination was done 3 months after the restaging after six cycles. Follow-up examinations thereafter took place during the initial 2 years every 3 months, in years 3–5 every 6 months and then subsequently on an annual basis. Follow-up examinations consisted of a clinical examination, laboratory analysis, imaging techniques, and documentation of remission status and of therapy-induced disorders, including secondary neoplasia.

Outcomes

Progression-free survival at 3 years was the primary endpoint, which was defined as the time from randomisation until one of the following events had occurred: progression during therapy, progressive disease after partial response, no change, unknown status at the end of study therapy, relapse after complete response or unconfirmed complete response or death from any cause, whichever came first. Response was assessed by local investigators. The key secondary endpoints were event-free survival and overall survival. Event-free survival was defined as the time from randomisation until one of the following events had occurred: progression during therapy, partial response, no change, unknown status at the end of study therapy, relapse after complete response or unconfirmed complete response, death from any cause; or additional treatment, whichever came first. Overall survival was defined as the time from randomisation until death from any cause. If no events occurred, patients were censored at the time of the last available information.

Other secondary endpoints were rate of complete remissions and progressive disease, safety (adverse events, serious adverse events, rate of secondary neoplasia, selected laboratory parameters, including leucocytes, thrombocytes, and haemoglobin), adherence to protocol (duration of cycles, cumulative dose, and dose intensity) and health-economic aspects (using the cumulative dose of chemotherapy drugs and rituximab). Other endpoints of health economic aspects (days in hospital, total number of days on which antibiotics were administered, total numbers of erythrocyte and platelet concentrates, and measures provided to treat serious adverse events) will be reported elsewhere. Adverse events were classified in accordance with the German version of the NCI common toxicity criteria prepared by the Deutsche Krebsgesellschaft (German Cancer Society). Severe adverse events had to be reported within 1 working day (if the event occurred during therapy) or within 10 working days (if the event occurred during the follow-up phase).

Statistical analysis

The trial was planned to show the non-inferiority of four cycles of R-CHOP plus two cycles of rituximab monotherapy versus six cycles of R-CHOP.

Progression-free survival at 3 years was selected as primary endpoint, assuming a rate of 93% for six cycles of R-CHOP and no difference between groups. With a prespecified non-inferiority margin of –5·5% and a 10% dropout rate, 592 patients are required to reach a power of 80%, at a significance level of 5% (one-sided).[10] The primary and secondary survival endpoints were analysed with the Kaplan-Meier method. To demonstrate non-inferiority we used the difference between the 3 years progression-free survival rate of four cycles versus six cycles of CHOP, each combined with six cycles of rituximab, calculated the one-sided 95% CI using the Kaplan-Meier estimates and Greenwood's estimates of the corresponding variance, and established whether it lies entirely on the positive side of the prespecified non-inferiority margin of –5·5%.[11] The primary analysis was

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See **Online** for appendix

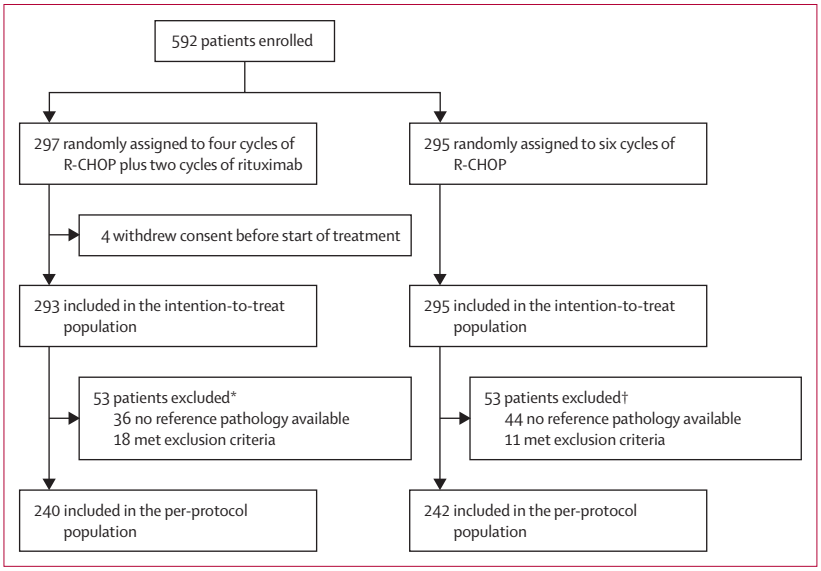

Figure 1: **Trial profile**
R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. IPI=international prognostic index. *One patient was excluded for both reasons stated. †Two patients were excluded for both reasons stated.

done in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of their assigned treatment. Per-protocol analysis was performed for patients with reference pathological diagnosis according to inclusion criteria and without exclusion criteria. In exploratory analyses, proportional hazard models were used for event-free, progression-free, and overall survival to adjust for the stratification variables (stage II *vs* I; extralymphatic involvement yes *vs* no) and for Ann Arbor lymphoma B symptoms.

We present as a post-hoc analysis the time from biopsy to start of therapy, also progression-free survival for patients with complete and partial remission at interim restaging separately. Progression-free survival is presented separately in patients who were recruited in the first half and the second half of the complete trial population.

Characteristics of patients between treatment regimens were compared by χ^2 tests and, if necessary, by Fisher's exact tests. The significance level was two-sided at 0·05. Dose reductions, treatment duration, relative dose, and relative dose intensity were assessed using a Kaplan-Meier-like estimator.[13] Response and relapse rates were presented with 95% CIs. Cumulative incidence curves for time to relapse were presented. Statistical analyses were done with SPSS, version 24/25, and R, version 3.1.0, package cuminc. The trial was overseen by a data safety monitoring committee and is registered at ClinicalTrials.gov, NCT00278421.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Four cycles of R-CHOP plus two cycles of rituximab group (n=293)	Six cycles of R-CHOP group (n=295)
Sex		
Female	118 (40%)	116 (39%)
Male	175 (60%)	179 (61%)
Age		
Median (IQR)	49 (40–55)	47 (41–54)
Range	18–60	19–60
Serum lactate dehydrogenase greater than upper limit of normal	0	0
Eastern Cooperative Oncology Group performance status >1	0	0
Stage III or IV*	2 (1%)	4 (1%)
Age-adjusted International Prognostic Index		
0	291 (99%)	291 (99%)
1*	2 (1%)	4 (1%)
Stage		
I	174 (59%)	172 (58%)
II	117 (40%)	119 (40%)
III*	1 (<1%)	2 (1%)
IV*	1 (<1%)	2 (1%)
Bulky disease*	1 (<1%)	1 (<1%)
Extralymphatic involvement	95 (32%)	96 (33%)
B-symptoms	27 (9%)	9 (3%)
Diffuse large B-cell lymphoma	252 (86%)	247 (84%)
Not otherwise specified	163 (56%)	172 (58%)
Centroblastic	73 (25%)	62 (21%)
Immunoblastic	4 (1%)	6 (2%)
Anaplastic large cell	5 (2%)	4 (1%)
T-cell-rich B-cell lymphoma	4 (1%)	3 (1%)
Primary mediastinal B-cell lymphoma	3 (1%)	0
Follicular lymphoma IIIB	17 (6%)	9 (3%)
Follicular lymphoma IIIB plus diffuse large B-cell lymphoma	17 (6%)	23 (8%)
Burkitt lymphoma	2 (1%)	2 (1%)
Burkitt-like lymphoma	1 (<1%)	3 (1%)
Aggressive marginal zone lymphoma	1 (<1%)	1 (<1%)
High-grade B-cell lymphoma not otherwise specified	3 (1%)	10 (3%)

Data are n (%) unless otherwise specified. R-CHOP=rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone. *Caused by retrospective changes, which were done by the investigators after data clearing.

Table 1: **Baseline demographic and disease characteristics (intention-to-treat population)**

The corresponding authors had full access to all the data in the study and the final responsibility for the decision to submit for publication.

Results

From Dec 2, 2005, to Oct 7, 2016, 592 patients were enrolled and randomly assigned to either four cycles of R-CHOP plus two cycles of rituximab (n=297) or six cycles

of R-CHOP (n=295). Four patients in the four-cycles group withdrew their informed consent before the start of treatment, so 588 patients were included in the intention-to-treat analysis (figure 1).

Baseline characteristics were well balanced except B symptoms, with 27 (9%) of 293 patients in the four-cycles group and nine (3%) patients in the six-cycles group (p=0·002) initially presenting with B symptoms (table 1).

According to the primary pathology report, 499 (85%) of 588 patients had diffuse large B-cell lymphoma or one of its subtypes (table 1). Randomisation was done if diagnosis of the primary pathology was available. Reference pathology was done in 508 (86%) of 588 patients (appendix p 24).

The first planned interim analysis was done on July 5, 2013, in 408 patients. During the course of the trial, the efficacy endpoints for patients with aggressive lymphoma were internationally harmonised and published.[12] Additionally, progression-free survival was established as the preferred primary endpoint for clinical trials in aggressive lymphoma.[12] In the interim analysis of July, 2013, the initially planned primary endpoint of 3-year event-free survival showed a lower rate than assumed in the protocol, but the 3-year progression-free survival rate met that used for sample size calculation. The DSMB agreed to an amendment on 30 March, 2015, using progression-free survival as the primary endpoint.

Data cutoff for the final analysis was June 18, 2018. Median follow-up time was 66 months (IQR 42–100) for progression-free survival.

The median duration of chemotherapy from day one of the first cycle until day one of the last cycle of chemotherapy was 63 days (IQR 62–64) in the four cycle group and 105 days (105–107) in the six-cycles group. In both treatment groups the median duration of rituximab immunotherapy was 106 days (IQR 106–107 for four cycles and 106–108 for six cycles; appendix pp 16–17).

11 patients with testicular involvement were included (five in the four-cycles group and six in the six-cycles group; appendix p 26). Prophylactic radiotherapy with 30·6 Gy to the contralateral testis in case of testicular involvement was mandatory since the second amendment of the study protocol (appendix p 23). No radiotherapy was planned to be administered to other sites. Additional radiotherapy to the initially involved extralymphatic sites was given to 18 patients (seven in the four-cycles group and 11 in the six-cycles group; appendix p 27).

After a median follow-up of 66 months, 3-year progression-free survival was 96% (95% CI 94–99) with four cycles of R-CHOP plus two cycles of rituximab versus 94% (91–97) with six cycles of R-CHOP (figure 2A). The

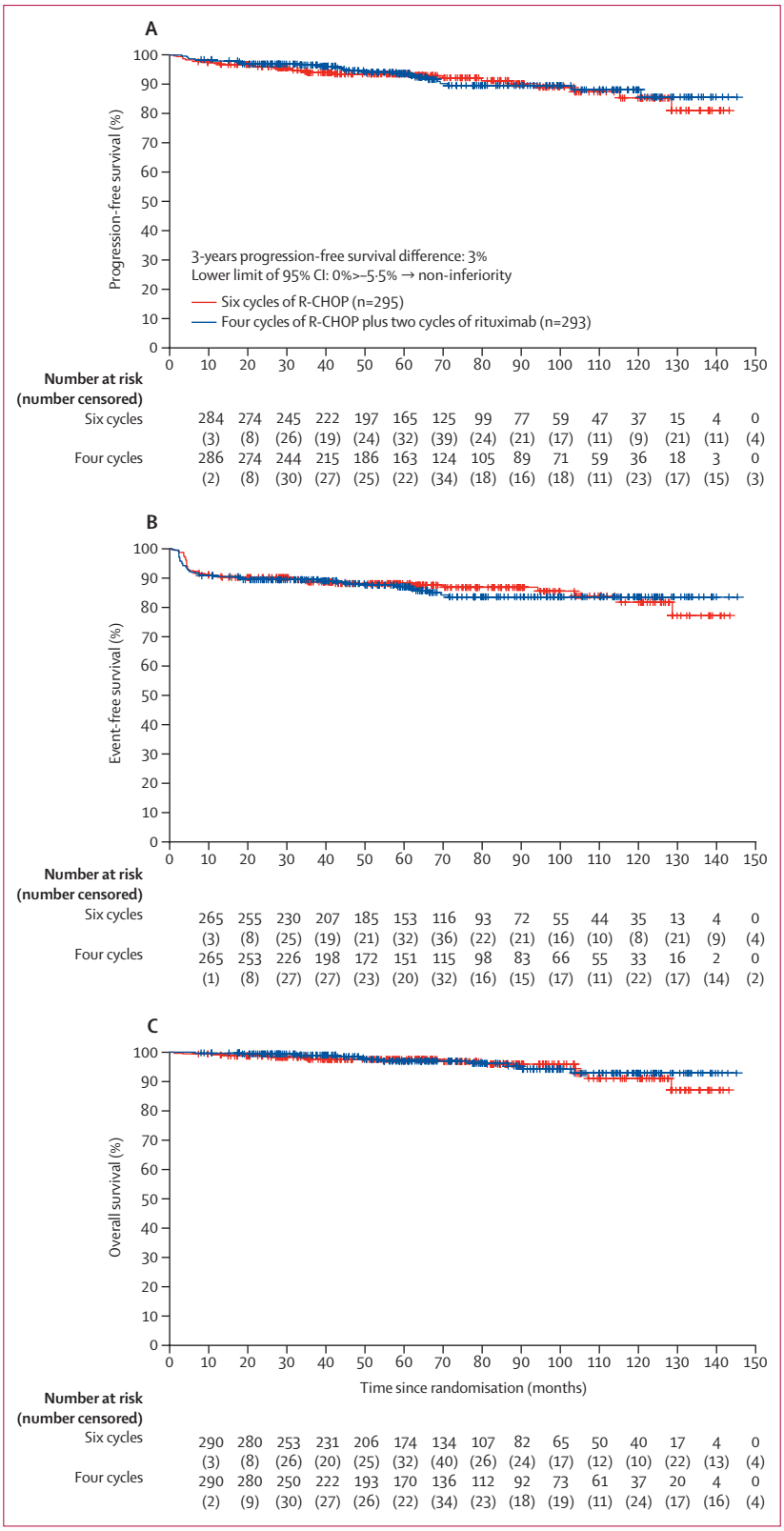

Figure 2: **Progression-free survival (A), event-free survival (B), and overall survival (C) in the intention-to-treat population**

	Four cycles of R-CHOP plus two cycles of rituximab group (n=293)	Six cycles of R-CHOP group (n=295)
Complete response or unconfirmed complete response	267 (91%; 87–94)	271 (92%; 88–95)
Partial response*	8 (3%)	11 (4%)
No change	0	1 (<1%)
Progressive disease	3 (1%)	3 (1%)
Not evaluated or missing data†	15 (5%)	9 (3%)
Relapse after complete response or unconfirmed complete response	11/267 (4%; 2–7)	13/271 (5%; 3–8)
Relapse after partial response	2/8 (25%)	2/11 (18%)
Relapse after no change	0	1/1 (100%)
Relapse after not evaluated or missing data	3/15 (20%)	2/9 (22%)

Data are n (%; 95% CI), n (%), n/N (%; 95% CI), or n/N (%). R-CHOP=rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone. *Five patients with partial response in the four-cycles group and six in the six-cycles group had complete response or unconfirmed complete response but received additional treatment outside study protocol. †Six patients in the six-cycles group prematurely discontinued chemotherapy, including two therapy-associated deaths in the six-cycles group, without having a response assessment; 18 patients started subsequent treatment without having a response assessment.

Table 2: **Response and relapse rates (intention-to-treat population)**

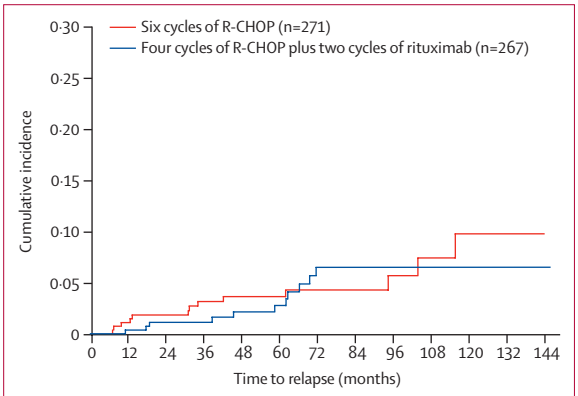

Figure 3: **Cumulative incidence of relapse**

absolute difference between groups in 3-year progression-free survival was 3% (lower limit of the one-sided 95% CI 0%). Thus, the 95% CI is on the positive side of the prespecified non-inferiority margin of –5·5%, demonstrating the non-inferiority of four cycles of R-CHOP plus two cycles of rituximab versus six cycles of R-CHOP.

A detailed description of absolute and relative dose and relative dose intensity is in the appendix (appendix pp 18–19). Protocol deviations occurred in six patients in the six-cycles group and eight in the four-cycles group (nine were rituximab deviations and seven were chemotherapy deviations (appendix p 25).

In both treatment groups, remission rates were high. At the end of therapy, 267 (91%) of 293 patients in the four-cycles group versus 271 (92%) of 295 patients in the six-cycles group had a complete response or unconfirmed complete response (table 2). Eight (3%) patients in the four-cycles group versus 11 (4%) in the six-cycles group had a partial response. None of the patients in the four-cycles group and one (<1%) patient in the six-cycles group had no change. In both groups, three (1%) patients progressed while on therapy. A more detailed description of patients with partial response or an unknown response is provided in the appendix (pp 45–47).

3-year event-free survival was 89% (95% CI 86–93) in the four-cycles group versus 89% (85–92) in the six-cycles group (figure 2B). 3-year overall survival was 99% (98–100) in the four-cycles group versus 98% (96–99) in the six-cycles group (figure 2C).

In a post-hoc analysis, median time from biopsy to start of prephase treatment was 23 days (IQR 15–31), to first application of rituximab it was 32 days (23–43), and to first cycle of CHOP it was 32 days (23–43; appendix p 15).

In a post-hoc analysis of patients with progression-free survival who had complete and partial remission at interim restaging, progression-free survival did not differ between the treatment groups (appendix p 20). In post-hoc analyses of progression-free survival in patients who were recruited in the first half of the trial and those recruited in the last half, results were similar between treatment groups (appendix pp 21–22). The multivariate analysis for progression-free survival comparing four cycles with six cycles after adjusting for strata and B symptoms showed a hazard ratio of 0·9 (95% CI 0·5–1·6; p=0·810; appendix p 28).

The long median follow-up allowed us to estimate 5-year outcomes in post-hoc analyses. Progression-free survival was 94% (95% CI 91–97) in the four-cycles group versus 94% (91–96) in the six-cycles group. 5-year event-free survival was 87% (83–91) in the four-cycles group versus 88% (84–92) in the six-cycles group. 5-year overall survival was 97% (94–99) in the four-cycles group versus 98% (96–100) in the six-cycles group.

Multivariate analysis comparing overall survival between the treatment groups after adjusting for strata and B symptoms showed a hazard ratio of 0·9 (95% CI 0·4–1·9; p=0·722; appendix p 28). Cause of death was related to progression or relapse of lymphoma in five patients in the four-cycles group versus seven patients in the six-cycles group (appendix p 28).

The per-protocol analysis of 482 patients who fulfilled inclusion criteria showed similar results for 3-year progression-free survival, which was 98% (95% CI 96–100) in the four-cycles group versus 94% (91–97) in the six-cycles group.

40 patients progressed or relapsed. The relapse rates for patients with complete response or unconfirmed complete response at the end of therapy were similar in both treatment groups (table 2; appendix pp 29–44). Three of 11 patients with testicular involvement relapsed (appendix p 26). Four (17%) of 24 relapses after complete

response or unconfirmed complete response occurred in the first year after enrolment. Eight (33%) occurred in the 2 years after study inclusion but continued to occur with longer follow-up in both groups (figure 3). No patient relapsed in the CNS.

The safety population included 293 patients in the four-cycles group and 295 patients in the six-cycles group. Fewer adverse events were documented during therapy in the four-cycles group, with 294 haematological adverse events, than in the six-cycles group, with 426 haematological adverse events (table 3).

Fewer non-haematological adverse events occurred in the four-cycles group (1036 events) than in the six-cycles group (1280 events; table 3). 48 serious adverse events occurred in the four-cycles group compared with 45 in the six-cycles group.

In the four-cycles group, 116 infections were reported, 22 of which were grade 3 or grade 4. 156 infections were reported in the six-cycles group, of which 23 were grade 3 or grade 4. Two patients, both in the six-cycles group, died during study therapy (table 3). Seven cardiac events as atrial fibrillation, heart failure, and coronary artery disease have been reported during therapy and follow-up: four events in the four-cycles group and three events in the six-cycles group.

18 (6%) of 293 patients in the four-cycles group versus 14 (5%) of 295 in the six-cycles group developed a secondary neoplasm (appendix p 48). Cause of death was related to secondary neoplasm in three (1%) patients in the four-cycles group versus four (1%) patients in the six-cycles group (appendix p 28).

	Four cycles of R-CHOP plus two cycles of rituximab group (n=293)		Six cycles of R-CHOP group (n=295)	
	Any grade	Grades 3–4	Any grade	Grades 3–4
Leucocytopenia*	171	80	237	110
Anaemia†	107	2	172	8
Thrombocytopenia‡	16	5	17	7
Non-haematological adverse event	1036	52	1280	71
Infection	116	22	156	23
Paresthesia	342	16	370	14
Nausea	221	6	319	12
Vomiting	61	1	117	7
Mucositis	80	1	105	3
Constipation	100	4	69	2
Mood alteration	59	1	60	0
Diarrhoea	33	0	40	6
Arrhythmia	8	1	24	0
Allergy	16	0	19	3
Paraplegia	..	..	1§	1
Therapy-associated deaths	..	..	2¶	..

Leucocytopenia, anaemia, and thrombocytopenia were documented only during the chemotherapy. R-CHOP=rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone. *Relevant leucocyte counts between cycles, on days 11–14, were available in 192 of 1161 cycles in the four-cycles group and 267 of 1746 cycles in the six-cycles group. †Haemoglobin values were documented in 839 of 1161 cycles in the four-cycles group and in 1207 of 1746 cycles in the six-cycles group. ‡Thrombocyte counts were documented in 848 of 1161 cycles in the four-cycles group and 1205 of 1746 cycles in the six-cycles group. §After the first application of 15 mg intrathecal methotrexate administered as CNS prophylaxis in a patient with stage II disease and testicular involvement. ¶Two patients, both in the six-cycles group, died during study therapy; one patient died after the second cycle of R-CHOP from pneumonia caused by influenza H1N1 virus; the other patient died after the fifth cycle of R-CHOP from an atypical pneumonia after having herpes zoster ophthalmicus.

Table 3: **Adverse events during treatment period (safety population)**

Discussion

Young patients with aggressive B-cell non-Hodgkin lymphoma and no IPI risk factors, such as the population included in our study, have an excellent prognosis. We showed that reduction of chemotherapy to four cycles of R-CHOP plus two cycles of rituximab from the standard six cycles of R-CHOP results in similar progression-free survival after 3 years, which was the primary endpoint of this study, demonstrating the non-inferiority of four cycles compared with the six cycles. Also, no difference in event-free survival or overall survival was detected, neither after 3 years nor after 5 years of follow-up. Reliability of the results is provided by the multicentre setting of this large international trial. In these patients, four cycles of CHOP in combination with six applications of rituximab are non-inferior in eradicating the malignant lymphoma clone. This conclusion is confirmed by the observation of similar responses and relapse rates.

To provide benefit to patients with aggressive B-cell non-Hodgkin lymphoma with such a favourable risk profile, our trial studied the reduction of cytostatic drugs rather than rituximab, which has only minor toxic effects.[1–3] In fact, some evidence suggests increased efficacy when rituximab is administered over a prolonged period of time in aggressive non-Hodgkin lymphoma. Rituximab maintenance tested in the NHL13 trial[14] increased event-free survival as well as progression-free survival in the subgroup of male patients. In elderly patients, a phase 2 trial[15] demonstrated superior survival after six cycles of CHOP-14 in combination with an extended rituximab exposure time compared with a historical control. Thus, we do not recommend less than six applications of rituximab, which led to excellent outcomes in the pivotal MInT trial.[2]

A different strategy in stage I or II aggressive B-cell non-Hodgkin lymphoma based on three cycles of R-CHOP plus involved-field radiotherapy was investigated in a smaller phase 2 trial.[16] The SWOG 0014 study included patients with stage I or II disease, but with a more unfavourable prognostic profile with at least one adverse risk factor for non-bulky stage II disease, age older than 60 years, WHO performance status of 2, or increased serum lactate dehydrogenase. The treatment resulted in a progression-free survival of 93% and an overall survival of 95% at 2 years and a progression-free survival of 88% and an overall survival of 92% at 4 years.[16] However, in light of a 3-year overall survival of 99% after four cycles of R-CHOP plus rituximab in our trial, it seems unlikely that radiotherapy is providing an improvement in outcome in patients with such a

favourable prognostic profile who were included in our phase 3 trial. Indeed, a phase 3 trial in non-bulky stage I or II diffuse large B-cell lymphoma did not show any improvement in event-free survival and overall survival with additive involved-field radiotherapy after R-CHOP compared with R-CHOP alone.[17] Thus, radiotherapy seems to not be relevant a priori, but might be confined to a minority of patients who are responding poorly. FDG-PET-CT scan has become standard in response assessment of lymphoma.[18] When FDG-PET scanning is performed, it is more prognostic the later it is applied during the course of immunochemotherapy.[19] However, the positive predictive value of the method is low, ranging only from 20–74%, which makes it difficult to predict a relapse for an individual patient.[20] But it remains a valid tool to allocate patients into subgroups with different outcomes. Radiotherapy might be given to those who are still positive in FDG-PET after two to four cycles of R-CHOP. Radiotherapy is feasible, because in these patients with a maximal Ann Arbor stage II disease and the absence of bulky disease, only small irradiation volumes will be needed. Indeed, when patients aged 61–80 years with an age-adjusted IPI of 0 and a positive FDG-PET after four cycles of R-CHOP-14 are treated with six cycles of R-CHOP-14 followed by modified involved-site radiotherapy, they have similar progression-free survival and overall survival to those patients with a negative FDG-PET scan.[21] Thus, positive FDG-PET-CT scan potentially might identify patients whose inferior prognosis can be compensated for by radiotherapy. These results have been obtained from the interim analysis of a still ongoing and recruiting clinical trial (NCT01478542). Therefore, the final results have to be awaited before this strategy can be estimated as safe and effective with the appropriate methodical and scientific validity.

We did not include patients older than 60 years, because age is an independent risk factor for inferior survival.[4,5] The additional risk factors of the IPI still accurately separate elderly patients to distinct prognostic subgroups and interim FDG-PET predicts survival independent of the IPI.[22] The result of two ongoing clinical trials (LNH 2009–1B [NCT01285765] and OPTIMAL>60 [NCT01478542]), which are testing FDG-PET-based, response-adapted reduction of chemotherapy in patients with good prognosis according to IPI might answer the question of whether the number of cycles of CHOP chemotherapy can also be reduced in patients older than 60 years.

We also did not include patients with bulky disease, which is associated with inferior prognosis in a population of young patients with an otherwise good prognosis.[6] Primary mediastinal B-cell lymphoma is a distinct pathogenetic subtype of aggressive lymphoma, which typically presents in young patients with an isolated manifestation as bulky anterior mediastinal mass.[23] Only three patients with primary mediastinal B-cell lymphoma have been included, because bulky disease, defined as maximal tumour diameter of 7·5 cm or more was an exclusion criterion. Therefore, our conclusion can't be extended to this particular entity.

Relapse rates after complete response or unconfirmed complete response were low in patients included in this trial. Relapse rate in the low number of included patients with testicular involvement was similar to that reported before.[24] Notably, cumulative incidence of relapse increased linearly during follow-up, similar to indolent non-Hodgkin lymphoma.[25] This pattern differs from that observed in an unselected population of patients with diffuse large B-cell lymphoma, where 70% of relapses occurred within the first year after diagnosis with a continued declining rate as the time from diagnosis increased.[26] The observation suggests that lymphoma, which present with good prognostic features without risk factors according to the age-adjusted IPI, and whose malignant clone is not eradicated by R-CHOP, might have a different biological background driving this unique pattern of relapse. A thorough and accurate molecular analysis of the lymphoma at primary diagnosis and late relapse is warranted to decipher mechanisms of chemotherapy resistance, evolution of relapse, or eventually, de-novo lymphoma genesis.

Notably, no progression or relapse in the CNS occurred among the 588 patients of the FLYER study. This observation confirms a recently developed risk model for CNS relapse of diffuse large B-cell lymphoma.[27] The so-called CNS-IPI consists of the IPI risk factors in addition to involvement of kidneys or adrenal glands. The CNS-IPI predicts a risk for CNS relapse of 0% for the population of the FLYER study, which included only patients with no risk factor according to the IPI and CNS-IPI (only one of 588 patients had involvement of the kidney). Therefore, the prediction of the CNS-IPI is in line with the results observed. Also, patients presenting such a favourable risk profile do not need a CNS-directed prophylaxis.

We observed less acute haematological and non-haematological toxicities with the reduced number of chemotherapy cycles, as expected, but no relevant differences in secondary neoplasia. This is probably because of the very low incidence of second primary malignancies in both treatment groups. However, to assess long-term toxicity of curative immunochemotherapy, a longer follow-up than that in our study is necessary.

Our study has some limitations. The recruitment extended over a period of more than 10 years. However, treatment did not change over time, but was confirmed because numerous randomised trials did not improve on R-CHOP.[28–30] Also, we found no evidence for a treatment by time interaction (appendix pp 21–22). The WHO classification of lymphoma was modified three times since the study was started: the WHO classification of tumours of haemopoietic and lymphoid

tissues revised fourth edition in 2017, made it essential to assign diffuse large B-cell lymphoma—not otherwise specified according to its cell of origin, either germinal centre B-cell-like or activated B-cell-like. However, the concept of cell of origin does not affect R-CHOP as standard of care in aggressive B-cell lymphoma.[30,31] Response assessment of lymphoma changed, making an FDG-PET scan mandatory to distinguish between complete response and partial response.[9,18] But the changes would not have affected progression-free survival, which was the primary endpoint of our study, nor overall survival. Therefore, these modifications, which were introduced to the standard care of patients with lymphoma, have no influence on the primary endpoint and conclusions of our study. Biological risk factors need special consideration, especially translocations of *MYC*, which might occur in combination with *BCL2* or *BCL6* translocation as so-called double-hit or triple-hit lymphoma. It requires FISH testing and was implemented in the fourth edition of the WHO classification of tumours of haemopoietic and lymphoid tissues, which was published when accrual of the FLYER trial was already finished. When *MYC* is rearranged with an immunoglobulin gene it confers to an inferior prognosis.[32] We do not know whether in patients with an *MYC* translocation reduction of cycles of chemotherapy is safe. But applying an age-adjusted IPI of 0 as an inclusion criterion and bulky disease as an exclusion criterion results in a 3-year progression-free survival of 96% and overall survival of 99% after four cycles of R-CHOP with six applications of rituximab, clearly selecting patients with good prognosis and excluding those with poor prognosis. A detailed analysis of biological risk factors is warranted, ongoing, and will be reported. Another limitation is that quality of life was not assessed systematically. However, toxicity was reduced, which is associated with better quality of life. Besides reduced toxicity, returning to an unrestricted family and professional life quicker is a very important benefit.

The strengths of the study are its clear phase 3 design. The large number of patients is an adequate sample size to address the objective. Patients have been recruited at 138 sites across five countries, represented by private practice-based oncologists, primary, secondary, tertiary, and university hospitals, reflecting a real world scenario of the health-care systems. Furthermore, the analysis of primary and secondary endpoints provides definite results, also in predefined and post-hoc subgroups.

In conclusion, treatment of young patients with aggressive B-cell lymphoma and a favourable risk profile can be reduced to four cycles of CHOP chemotherapy plus six cycles of rituximab without compromising efficacy.

Contributors

MP was the study chairman and designed and oversaw the study. VP and GH oversaw the study and contributed to study design, data monitoring, data interpretation, and writing and approval of the report. MZ and ML did the statistical analysis and contributed to study design, data interpretation, and writing and approval of the report. AR coordinated the reference pathology. CB coordinated and assessed the imaging review. OS was the principal investigator in Israel and recruited patients. HH was the principal investigator in Norway and recruited patients. FM was the principal investigator in Italy and recruited patients. PdNB was the principal investigator in Denmark and recruited patients. JA and KC contributed to data monitoring. FH contributed to study design. NM contributed to study oversight and data monitoring. SS contributed to data interpretation and recruited patients. MN, GW, BG, NS, and LTr contributed to study design and recruited patients. BA contributed to statistical analysis and data interpretation. MP, GH, MW-H, LTh, PB, AV, MS, UK, CS, RMah, RMar, H-GH, BM, JD, NF, MH, AN, MK, AT, MF, EL, AdR, RT, and MM recruited patients. All authors have reviewed and approved the final version of the report.

Declaration of interests

VP and HH report grants from the non-profit organisation Deutsche Krebshilfe; HH and MN report grants from Roche; and UK and MN report personal fees from Roche, during the conduct of the study. VP reports personal fees from Hexal and non-financial support from AbbVie, Amgen, and Roche. GH reports personal fees from Bristol-Myers Squibb (BMS), Roche, Amgen, Spectrum, and Merck Sharp & Dohme (MSD) and grants from BMS and Roche. AV reports personal fees from Roche, Kite/Gilead, Pfizer, BMS, and Amgen. CS reports personal fees from Novartis AG, Gilead, and Takeda and grants and non-financial support from Janssen Cilag, Gilead, and Takeda. LTr reports personal fees from Takeda. UK reports personal fees from Janssen Cilag, BMS, Gilead, Takeda, Amgen, Hexal, Celgene, AstraZeneca, and MSD; advisory board, travel support, and speaker honoraria from Janssen Cilag, BMS, Takeda, Celgene, and MSD; advisory board and travel support from Gilead; and speaker honoraria from Amgen. RM reports personal fees from Roche, Servier, and Merck. MK reports personal fees from AstraZeneca. FM reports personal fees from Roche, Takeda, Celgene, Janssen, Gilead, and Mundipharma and non-financial support from Takeda and Celgene. PdNB reports personal fees from Roche. FH reports personal fees from BMS, Roche, Boehringer Ingelheim, Sanofi, Celgene, Novartis, Ipsen, Janssen, and Gilead. SS reports personal fees, grants, and non-financial support from AbbVie, Amgen, AstraZeneca, Celgene, Gilead, GlaxoSmithKline (GSK), Roche, Janssen, Novartis, Pharmacyclics, and Sunesis. MN reports personal fees and grants from Roche. BG reports personal fees from Roche, Janssen Cilag, Celgene, and Sandoz/Hexal, grants from Roche and Celgene, non-financial support from Roche, and travel expenses from Roche, Janssen Cilag, and Sandoz/Hexal. RT reports grants from Roche; advisory board for AbbVie and Atara; and travel support for Celgene, Janssen, Gilead, and AbbVie. All other authors declare no competing interests.

Data sharing

Individual data will be made available as well as data dictionaries. Data that underlie the main results reported in this Article, will be shared after de-identification. The study protocol is available in the appendix (pp 49–160). Pseudonymised data will be available upon request up to 5 years after publication of this Article to researchers who provide a data sharing agreement that describes a methodically sound proposal and the data necessary for the purpose of the approved proposal. Proposals should be directed to dshnhl@uks.eu. Data will be shared once all relevant parties approve and sign the data sharing agreement. Selected data will be also available on the Leipzig Health Atlas website.

For the **Leipzig Health Atlas website** see www.health-atlas.de

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