CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group

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Summary

Background **The role of rituximab in combination with different CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like chemotherapy regimens in young patients with good-prognosis diffuse large-B-cell lymphoma remains to be defined. We aimed to compare CHOP-like chemotherapy and rituximab with CHOP-like chemotherapy alone in these patients.**

Methods **824 patients who were from 18 countries; aged 18–60 years; and who had no risk factors or one risk factor according to age-adjusted International Prognostic Index (IPI), stage II–IV disease, or stage I disease with bulk were enrolled. These patients were randomly assigned to six cycles of CHOP-like chemotherapy and rituximab (n=413) or to six cycles of CHOP-like chemotherapy alone (n=411). Bulky and extranodal sites received additional radiotherapy. The primary endpoint was event-free survival; secondary endpoints were response, progression under therapy, progression-free survival, overall survival, and frequency of toxic effects. Analyses were done by intention to treat and per protocol. This trial is registered at http://www.clinicaltrials.gov, NCT 00064116.**

Findings **After a median follow-up of 34 months (range 0·03–61), patients assigned chemotherapy and rituximab had increased 3-year event-free survival compared with those assigned chemotherapy alone (79% [95% CI 75–83] *vs* 59% [54–64]; difference between groups 20% [13–27], log-rank p<0·0001), and had increased 3-year overall survival (93% [90–95] *vs* 84% [80–88]; difference between groups 9% [3–13], log-rank p=0·0001). Event-free survival was affected by treatment group, presence of bulky disease, and age-adjusted IPI: after chemotherapy and rituximab, a favourable subgroup (ie, IPI=0, no bulk) could be defined from a less-favourable subgroup (ie, IPI=1 or bulk, or both). Groups did not differ in the frequency of adverse events.**

Interpretation **Rituximab added to six cycles of CHOP is an effective treatment for young patients with good-prognosis diffuse large-B-cell lymphoma. The definition of two prognostic subgroups allows for a more refined therapeutic approach for these patients.**

Introduction

Young patients (ie, age 18–60 years) with low-risk (ie, no risk factor according to age-adjusted International Prognostic Index [IPI]) and low–intermediate risk (ie, one risk factor according to age-adjusted IPI) diffuse large-B-cell lymphoma[1] are thought to have a good outlook; by contrast, young patients with a poor outlook (ie, intermediate–high and high risk) present with two or three risk factors according to age-adjusted IPI.

A study by SWOG (Southwest Oncology Group)[2] reported that three cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by involved-field radiotherapy was more effective than eight cycles of CHOP alone in patients with limited stage diffuse large-B-cell lymphoma with regard to progression-free survival and overall survival. Furthermore, the Deutsche Studiengruppe für Hochmaligne Non-Hodgkin-Lymphome (DSHNHL) showed[3] that the addition of etoposide to CHOP—ie, CHOEP—improves the event-free survival of these patients. The Groupe d'Etude des Lymphomes de l'Adulte (GELA) noted[4] that dose-intensive doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) plus sequential consolidation chemotherapy was more effective than was combined chemoradiotherapy for patients with stage I or stage II aggressive lymphoma and no risk factor according to age-adjusted IPI.

In elderly patients, the GELA[5,6] and a US Intergroup study[7] showed that the addition of a monoclonal antibody to CD20—rituximab—to CHOP improved event-free survival and overall survival.[5–7] Because young patients who have good-prognosis disease have a better outlook than do elderly patients, whether young patients might benefit from rituximab is unclear, particularly if they receive more efficacious chemotherapy regimens such as

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	Regimen	Country
CHOP-21	750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, and 2 mg vincristine all given intravenously on days 1, 22, 43, 64, 85, and 106; and 100 mg prednisone given orally on days 1–5, 22–26, 43–47, 64–68, 85–89, and 106–110	Argentina, Australia, Austria, Brazil, Canada, Czech Republic, Denmark, Finland, France, Israel, Norway, Poland, Spain, Switzerland, and UK
CHOEP-21	As for CHOP-21, plus 100 mg/m² etoposide given intravenously or 200 mg/m² given orally on days 2–3, 23–24, 44–45, 65–66, 86–87, and 107–108	Germany and Sweden
MACOP-B	350 mg/m² cyclophosphamide and 50 mg/m² doxorubicin both given intravenously on days 1, 15, 29, 43, 57, and 71; 400 mg/m² methotrexate given intravenously on days 8, 36, and 64; 1·4 mg/m² vincristine given intravenously on days 8, 22, 36, 50, 64, and 78; 10 mg/m² bleomycin given intravenously on days 22, 50, and 78; and 40 mg/m² prednisone given orally or intramuscularly on days 1–84	Italy
PMitCEBO	7 mg/m² mitoxantrone, 300 mg/m² cyclophosphamide, and 150 mg/m² etoposide all given intravenously on days 1, 15, 29, 43, 57, and 71; 1·4 mg/m² vincristine (maximum 2 mg) and 10 mg/m² bleomycin both given intravenously on days 8, 22, 36, 50, 64, and 78; and 50 mg prednisone given orally on days 1–28 and on alternating days 29–84	UK

Table 1: **CHOP-like regimens used in trial**

CHOEP. To address these questions, and to reassess the role of age-adjusted IPI for treatment regimens with rituximab, the MabThera International Trial Group (MInT)—which consists of cooperative groups from 18 countries—designed the MInT study.

Methods

Patients

Eligible were patients aged 18–60 years with untreated CD20-positive diffuse large-B-cell lymphoma defined by the local pathologist according to WHO criteria,[8] and who had no risk factors or one risk factor according to age-adjusted IPI in stage II–IV disease or who had stage I disease with bulk; eligible patients had sufficient performance status as assessed by the treating physician (ie, 0–3 on Eastern Cooperative Oncology Group scale). Exclusion criteria were: life expectancy less than 3 months; missing written informed consent; participation in another clinical trial in the past 12 weeks; previous participation in this trial; secondary lymphoma after previous chemotherapy or radiotherapy for other disease; primary CNS lymphoma or gastrointestinal mucosa-associated lymphoid tissue (MALT) lymphoma as assessed by the local pathologist; previous lymphoma-specific treatment, including that with a mouse antibody but not that of prephase treatment; known allergic reactions against foreign proteins as assessed by medical history; concurrent disease that would exclude giving of treatment as outlined in the protocol; active infection needing systemic treatment with antibiotics or antiviral agents; non-compensated heart failure; dilatative cardiomyopathy; coronary heart disease with ST segment depression on electrocardiography; myocardial infarction in the past 6 months; chronic lung disease with hypoxaemia; severe non-compensated hypertension; severe non-compensated diabetes mellitus; renal insufficiency (ie, creatinine more than two-times normal value) not related to lymphoma; hepatic insufficiency (ie, transaminase more than three-times normal value or bilirubin >34·2 µmol/L, or both) not related to lymphoma; clinical signs of cerebral dysfunction; women who were lactating, pregnant, or of child-bearing potential and not using a reliable method of contraception; severe psychiatric disease; known infection with HIV or active chronic hepatitis B or C as assessed by medical history; post-transplantation lymphoproliferative disease; and substantial dysfunction of major organs as assessed by the treating physician (if cut-off points were not defined exactly by exclusion criteria).

Histological diagnosis was reviewed by an experienced national haemopathologist in every participating country, and was available for 99% of patients. The study was done in accordance with the Helsinki declaration, the protocol was approved by the ethics-review committee of

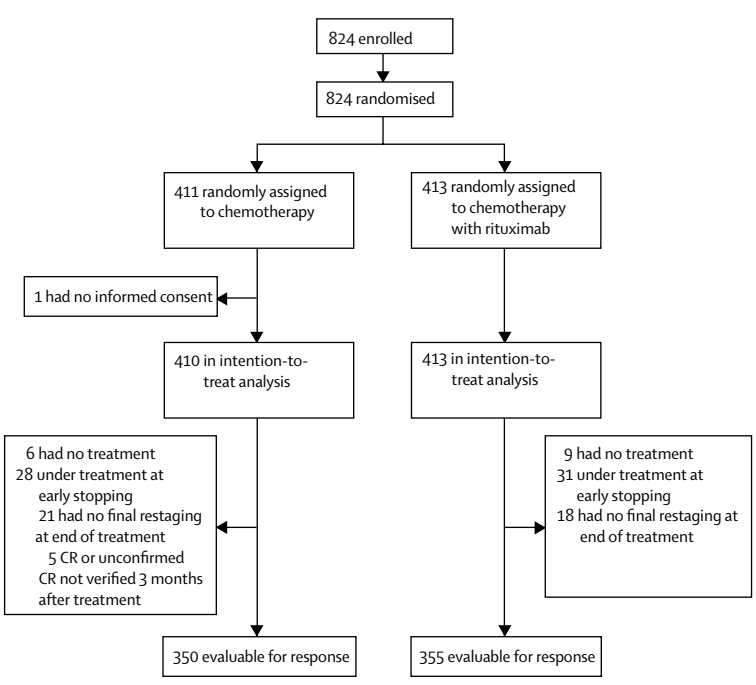

Figure 1: **Trial profile**
CR=complete remission.

every participating centre, and all patients gave written informed consent.

Staging

The stage of lymphoma was defined before enrolment by the referring physician on the basis of the Cotswolds modification of the Ann Arbor classification.[9] Stage was assessed by physical examination; relevant laboratory tests (ie, haemoglobin, platelets, total white-blood-cell count, differential white-blood-cell count, unmandatory immunophenotyping for B and T lymphocytes, total serum protein, albumin, serum creatinine, urea, uric acid, calcium, potassium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, lactate dehydrogenase, β2 microglobulin, and urinalysis); CT of the chest and abdomen; bone-marrow biopsy; and other investigational procedures depending on clinical symptoms. The results, which were recorded on clinical-report forms, were reviewed by a physician and statistician at the study centres in Homburg and Leipzig, Germany. For all patients, the local radiologist or treating physician measured maximum tumour mass, and bulky disease was defined as the presence of a tumour mass with a diameter of more than 5 cm, more than 7·5 cm, or more than 10 cm according to the cut-off points predefined by every cooperative group.

Treatment

Patients were randomly assigned to six cycles of CHOP-like chemotherapy and rituximab or to six cycles of CHOP-like chemotherapy alone. Table 1 shows the CHOP-like chemotherapy regimens used in the trial. Patients assigned chemotherapy plus rituximab were scheduled to receive a chemotherapy regimen shown in table 1, plus 375 mg/m^2 rituximab (MabThera™, Hoffmann-La Roche, Basel, Switzerland) given intravenously on days 1, 22, 43, 64, 85, and 106 of the chemotherapy regimen. Radiotherapy (30–40 Gy, according to national standards) was given to sites of primary bulky disease; radiotherapy (30–40 Gy) to primary extranodal disease was given at the physician's discretion. Filgrastim or lenograstim could also be given at the treating physician's discretion for alleviation or prophylaxis of neutropenia.

The trial was unmasked. Patients were randomised centrally by a data manager at the Intergroup Data Centre (Leipzig, Germany) using a computer-based randomisation tool with an algorithm that accounted for randomisations that had occurred previously to ensure balanced randomisation at any time; no blocks were used. Centres were informed of randomisation results by fax. The data manager was responsible for checking the data for discrepancies, raising queries, and archiving according to standard operating procedures. Patients were stratified by centre, bulky disease, age-adjusted IPI, and chemotherapy regimen by use of a modified minimisation algorithm that incorporated a stochastic (ie, random) component. Data were gathered by monitors employed by independent clinical-research organisations, and were sent directly to the Clinical Study Centre in Homburg for checking of clinical plausibility. From there, data were transferred to the Intergroup Study Centre in Leipzig for data-banking.

	Chemotherapy alone (n=410)	Chemotherapy and rituximab (n=413)
Age (years)		
Median (IQR)	47 (35–55)	47 (36–55)
Sex		
Men	221 (54%)	257 (62%)
Women	189 (46%)	156 (38%)
Histological analysis*		
Without central review	4 (1%)	4 (1%)
With central review	406 (99%)	409 (99%)
Eligible disease types*		
Diffuse large-B-cell lymphoma	355 (87%)	359 (87%)
CD20-positive	355 (87%)	357 (86%)
Not otherwise specified	181 (44%)	171 (41%)
Centroblastic	98 (24%)	110 (27%)
Immunoblastic	10 (2%)	6 (2%)
Plasmoblastic	1 (<1%)	2 (<1%)
Anaplastic large B-cell	10 (2%)	11 (3%)
T-cell-rich B-cell	11 (3%)	15 (4%)
Mediastinal B-cell lymphoma	43 (11%)	44 (11%)
Primary-effusion lymphoma	1 (<1%)	0
Inappropriate disease types*		
Burkitt's lymphoma	0	2 (<1%)
Burkitt-like lymphoma	4 (1%)	5 (1%)
Aggressive marginal-zone lymphoma	2 (<1%)	1 (<1%)
Follicular lymphoma III	5 (1%)	6 (2%)
Follicular lymphoma III and diffuse large-B-cell lymphoma	17 (4%)	11 (3%)
Cutaneous B-cell lymphoma	0	1 (<1%)
Precursor B lymphoblastic	3 (1%)	0
Mantle-cell lymphoma, blastic	1 (<1%)	1 (<1%)
Unclassified, B-cell related	5 (1%)	8 (2%)
Composite lymphoma	1 (<1%)	0
Low-grade non-Hodgkin lymphoma not otherwise specified	5 (1%)	7 (2%)
Hodgkin's disease	3 (1%)	3 (1%)
Unclassified	3 (1%)	2 (<1%)
Other lymphoma	1 (<1%)	0
No lymphoma	1 (<1%)	3 (1%)
CD20-positive*		
Yes	401 (98%)	400 (97%)
Extranodal involvement†		
Yes	144 (35%)	138 (33%)
B-symptoms‡		
Yes	105 (26%)	100 (24%)
Performance status		
0	287 (70%)	305 (74%)
1	119 (29%)	106 (26%)
2	2 (<1%)	1 (<1%)
3	2 (<1%)	1 (<1%)

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Bulky disease at randomisation§		
All	197 (48%)	205 (50%)
Maximum diameter >5·0 cm (median 10·0 cm [range 5·1–20·0])	20 (5%)	18 (4%)
Maximum diameter >7·5 cm (median 10·0 cm [7·6–25·0])	166 (40%)	173 (42%)
Maximum diameter >10·0 cm (median 12·0 cm [10·1–16·8])	11 (3%)	14 (3%)
Stage		
I	74 (18%)	75 (18%)
II	223 (54%)	225 (55%)
III	61 (15%)	68 (16%)
IV	52 (13%)	45 (11%)
Lactate dehydrogenase		
Concentration higher than upper normal value	118 (29%)	124 (30%)
Age-adjusted IPI¶		
0	178 (43%)	174 (42%)
1	229 (56%)	239 (58%)
2	3 (<1%)	0
Subgroup		
Favourable subgroup (ie, IPI=0, no bulk)	108 (26%)	101 (24%)
Less-favourable subgroup (ie, IPI=1, bulk, or both)	302 (74%)	312 (76%)

*Assessed after pathological review: histological review may change original diagnosis into one not eligible for trial inclusion; nevertheless, these patients were included in intention-to-treat analysis. †Involvement by sites other than lymph nodes and spleen. ‡Ann Arobor criteria. §Assessed by physical examination or CT: median maximum diameter of all bulky disease 10·0 cm (range 5·1–25·0). ¶For all analyses, patients with one or two risk factors according to age-adjusted IPI were pooled.

Table 2: **Baseline characteristics of intention-to-treat population (n=823)**

Endpoints and assessment of response

The primary endpoint was event-free survival; secondary endpoints were response, progression under therapy, progression-free survival, overall survival, and frequency of toxic effects. Event-free survival was defined as time to progressive disease under therapy, the events for which were: progressive disease; no achievement of complete remission; no achievement of unconfirmed complete remission; partial remission associated with treatment in excess of that stipulated in the protocol (eg, more than six cycles of chemotherapy, radiotherapy to non-bulky areas, or use of rituximab in chemotherapy-only group); no change; relapse after achievement of complete remission or unconfirmed complete remission; or death from any cause, whichever came first.

Response was defined as the proportion of patients with complete remission or unconfirmed complete remission after study treatment for all patients evaluable for response. Progression under therapy was defined as the proportion of patients with progressive disease during treatment and within 3 months after the end of treatment for all patients evaluable for response. Progression-free survival was defined as time to progression under therapy, relapse, or death from any cause; additional treatment was censored for this endpoint. Overall survival was defined as time to death from any cause. Patients without an event in event-free survival, progression-free survival, or overall survival were censored at the last day of having valid information for that endpoint.

Response was assessed according to the International Workshop criteria[10] by the treating physician on day 155 after starting treatment. Methods of assessment were: physical examination; relevant laboratory tests (as those done for staging); CT of the chest and abdomen; bone-marrow biopsy for previous involvement by lymphoma; and the control of all other previous pathological findings by adequate investigational procedures.

Follow-up was done by the referring physician every 3 months for the first 2 years after treatment and every 6 months thereafter by use of physical examination, relevant laboratory tests (as those done for staging), and CT of the chest and abdomen. No functional imaging (ie, gallium or PET) was used to define response. Complete remission and unconfirmed complete remission were defined according to the International Workshop criteria,[10] and were classified as progression if they lasted less than 3 months. Furthermore, we planned to do a subgroup analysis to assess CHOP-21 chemotherapy compared with that of CHOEP-21.

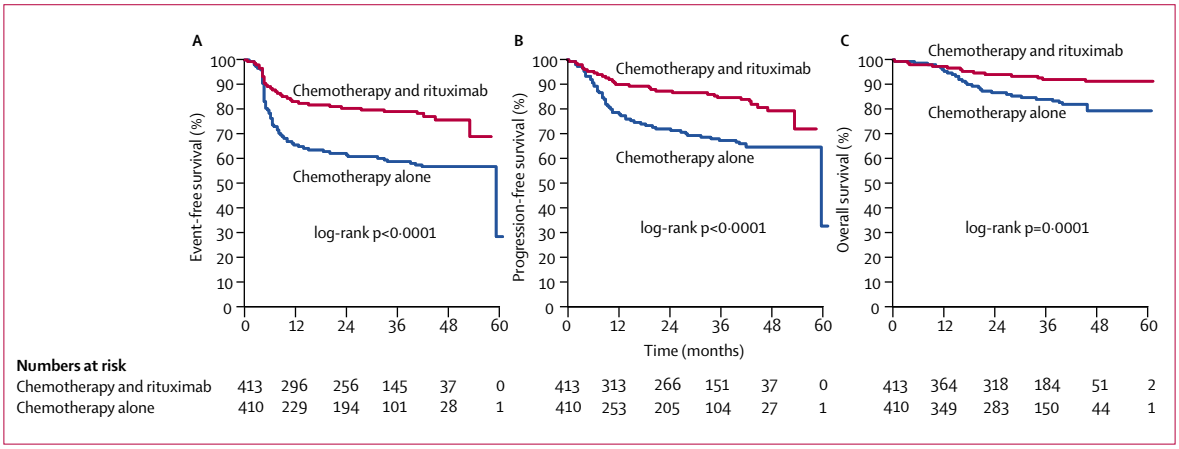

Figure 2: **(A) Event-free survival, (B) progression-free survival, and (C) overall survival of 823 patients assigned to CHOP-like chemotherapy alone (n=410) or to CHOP-like chemotherapy and rituximab (n=413)**

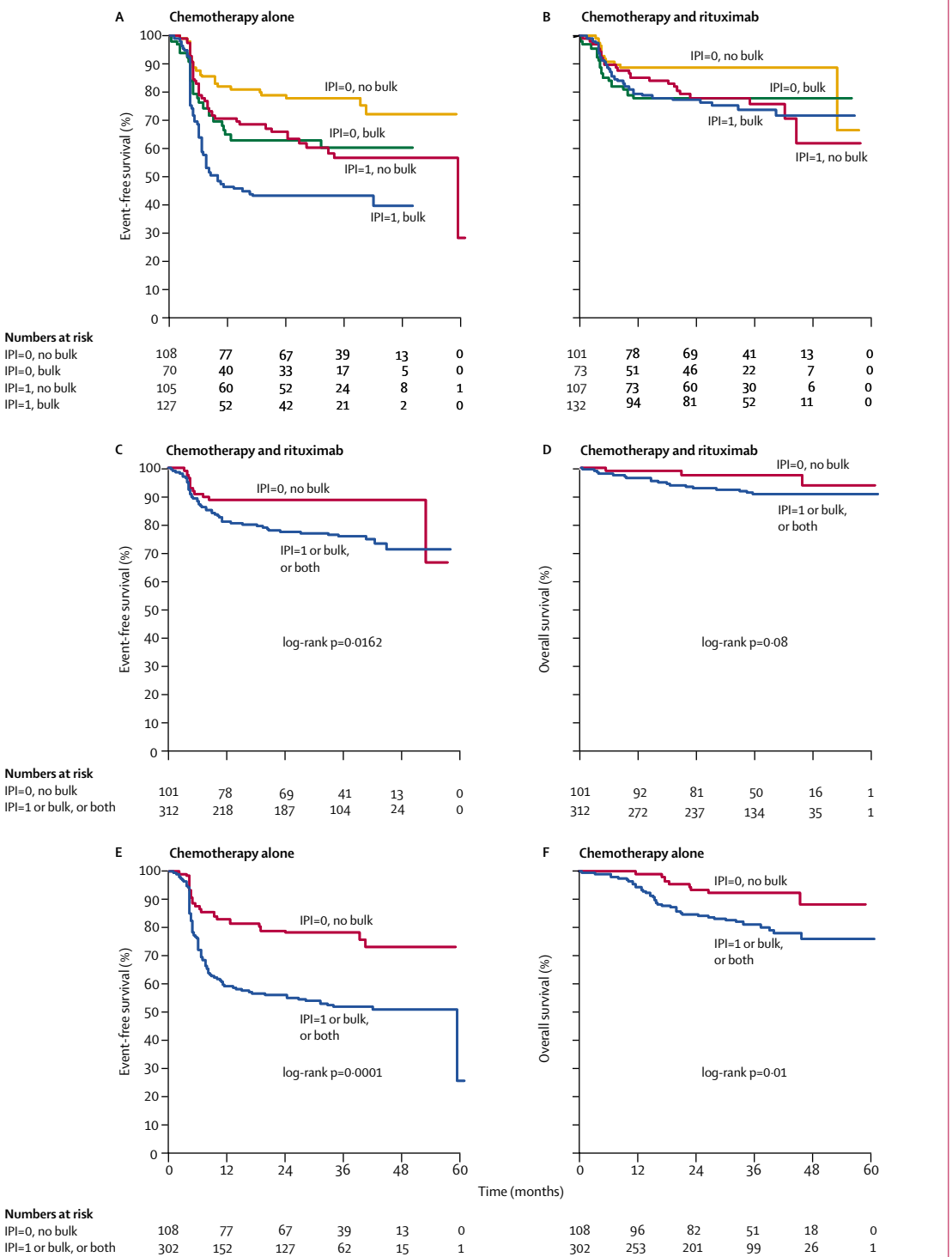

***Figure 3*: Event-free survival and overall survival of prognostic subgroups of young patients with good-prognosis diffuse large-B-cell lymphoma**
Three subgroups can be defined with regard to event-free survival after chemotherapy alone (A: no bulk, no age-adjusted IPI risk factor; one age-adjusted IPI risk factor or bulk; and bulk and age-adjusted IPI risk factor), two subgroups emerge after chemotherapy plus rituximab (B: age-adjusted IPI=0, no bulk [favourable subgroup] and IPI=1 or bulk, or both [unfavourable subgroup]). In patients assigned chemotherapy plus rituximab, the favourable subgroup had significantly better event-free survival (C), but not overall survival (D) than did the less-favourable subgroup. However, after chemotherapy alone, the favourable subgroup had better event-free survival (E) and overall survival (F) than did the less-favourable subgroups.

	3-year event-free survival (95% CI)		Log-rank p
	Chemotherapy alone	Chemotherapy and rituximab	
IPI=0 and no bulk	78% (70–86)	89% (82–95)	0·054
IPI=0 and bulk	61% (48–73)	78% (68–88)	0·064
IPI=1 and no bulk	57% (46–68)	76% (67–86)	0·034
IPI=1 and bulk	44% (34–53)	74% (66–82)	<0·0001

Table 3: 3-year event-free survival by treatment group, according to prognostic factors

Statistical analysis

We aimed to identify a difference of 10% in 3-year event-free survival with a two-sided significance level of 5% and a power of 80%, requiring 820 patients. A 10% difference was regarded as clinically relevant and as justifying the additional costs of rituximab. Interim analysis was planned after the recording of 100 events according to an α-spending approach, where α used at the point of interim analysis depends on the amount of information already accumulated.

Main analyses were done by intention to treat. Response and progression under therapy were analysed by use of Fisher's exact test. Event-free survival, progression-free survival, and overall survival were measured from the date of randomisation, estimated according to Kaplan-Meier, and the differences between groups compared by use of log-rank test. Differences between groups were calculated on the basis of rounded estimates, whereas 95% CI for these differences were calculated on the basis of exact estimates. Kaplan-Meier estimates at 3 years, with 95% CI, were calculated for the probability of not having an event in the endpoints of event-free survival, progression-free survival, and overall survival. Multivariable analyses were done by use of Cox proportional-hazard models to estimate hazard ratios (HR) for having an event. Sensitivity analyses (ie, per-protocol analyses) of the primary and secondary endpoints were done to assess the robustness of the results. Differences between groups were regarded as significant for p values less than 0·05. For subgroup analyses of event-free survival and overall survival, interaction terms were included and tested in the Cox proportional-hazard models. Interaction terms were: treatment group and IPI; treatment group and bulky disease; treatment group and chemotherapy regimen; IPI and bulk; IPI and chemotherapy regimen; and bulk and chemotherapy regimen. Statistical analyses of efficacy were done with SPSS version 11.5 and StatXact version 5; safety analyses were done with SAS software version 8.2.

	CHOP-21 (n=197)	CHOEP-21 (n=180)	CHOP-21 and rituximab (n=199)	CHOEP-21 and rituximab (n=181)
Age (years)				
Median (IQR)	48 (35–55)	47 (37–55)	49 (38–55)	47 (35–54)
Bulky disease				
Yes	97 (49%)	85 (47%)	108 (54%)	83 (46%)
Stage				
III or IV	53 (27%)	52 (29%)	58 (29%)	48 (27%)
Lactate dehydrogenase				
Raised	58 (29%)	53 (29%)	58 (29%)	56 (31%)
Performance status				
≥1	62 (32%)	56 (31%)	49 (25%)	54 (30%)
IPI				
>0	112 (57%)	105 (58%)	118 (59%)	104 (58%)
Less-favourable subgroup				
IPI=1, bulk, or both	147 (75%)	133 (74%)	160 (80%)	130 (72%)

Table 4: Characteristics of patients assigned CHOP and CHOEP, with or without rituximab

Role of the funding source

The sponsor of the study had no role in the study design; in the collection, analysis, or interpretation of the data; or in the writing of the report. The corresponding author had full access to all data in the study, and had final responsibility to submit the paper for publication. The sponsor was not involved in the decision of the data safety and monitoring committee to stop the trial early. Safety analyses were done by the sponsor after the Intergroup Data Centre had gathered and viewed the raw data for adverse events, and there was full disclosure of all adverse events by the employees of the sponsor of this study to the other authors.

Results

Between May 16, 2000, and Oct 22, 2003, 824 patients were enrolled at 172 participating institutions from 18 countries. 410 patients were randomly assigned to CHOP-like chemotherapy alone and 413 to CHOP-like chemotherapy plus rituximab. One patient was excluded because of missing informed consent. Figure 1 shows the trial profile; table 2 shows the baseline characteristics of patients.

The first planned interim analysis was started after 100 events were recorded on Nov 7, 2003, and was completed on Nov 19, 2003, by the Intergroup Data Centre. At that time, 326 patients were evaluable (ie, were randomised before Aug 1, 2002 with confirmed CD20-positive diffuse large-B-cell lymphoma and data for the first follow-up after restaging). The median observation time of these patients was 15 months (range 0·03–31·5 months) on Nov 7, 2003. 15-month event-free survival was 63% (95% CI 55–70) for patients allocated chemotherapy alone and 84% (78–90) for those allocated chemotherapy plus rituximab (difference between groups 21% [12–31]). Because the significance of this difference (p<0·0001) was beyond the critical α-spending level (p=0·00105), the data safety and monitoring committee recommended the stopping of the trial, which became effective on Dec 5, 2003. 59 patients still under treatment at this time were censored on this date in analyses for all time-to-event endpoints.

The median relative dose intensity of cytotoxic drugs was 97% (97–98) of the planned relative dose intensity,

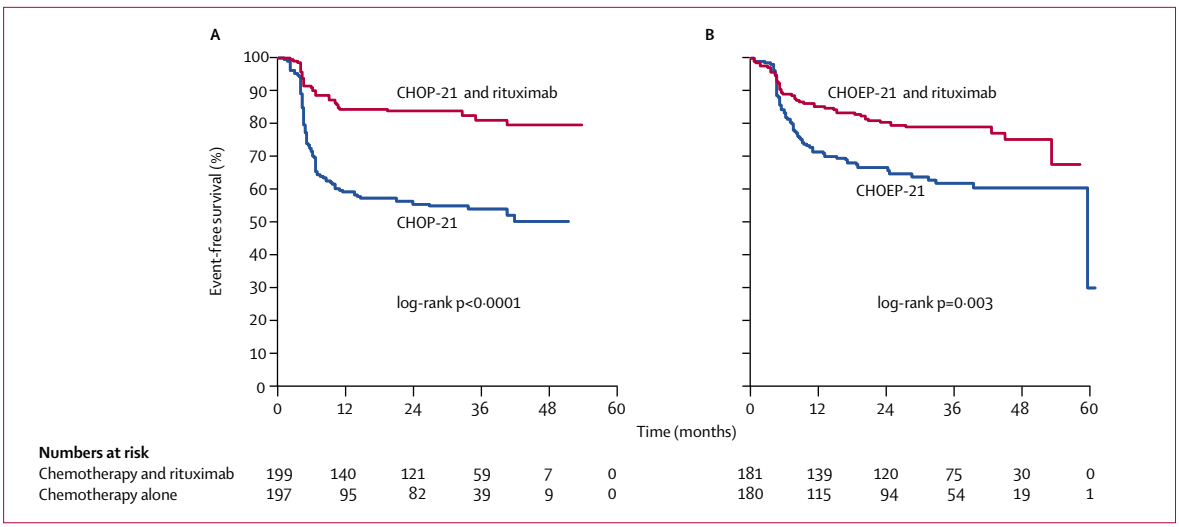

Figure 4: **Event-free survival of patients given CHOP with or without rituximab (A) compared with CHOEP with or without rituximab (B)**

with no differences between treatment groups. Filgrastim was given at the treating physician's discretion, with no difference between treatment groups: 107 (27%) of 404 patients allocated chemotherapy alone and 106 (26%) of 404 patients allocated chemotherapy plus rituximab received at least one application of filgrastim after chemotherapy; 15 patients (six in the chemotherapy-alone group and nine in the chemotherapy-and-rituximab group) did not receive allocated treatment because of adverse events. Groups did not differ in the numbers of patients who: received radiotherapy (159 after chemotherapy alone *vs* 169 after chemotherapy and rituximab); did not receive per-protocol radiotherapy (41 *vs* 33, respectively); or who received additional (ie, unplanned) radiotherapy (15 *vs* 14, respectively).

More patients assigned chemotherapy and rituximab had complete remission or unconfirmed complete remission 155 days after starting treatment than did those assigned chemotherapy alone (304 [86%] of 355 [82–89]) *vs* 239 [68%] of 350 [63–73]; difference between groups 18% [11–23], p<0·0001, Fisher's exact test). Fewer patients allocated chemotherapy and rituximab had progressive disease compared with those allocated chemotherapy alone (13 [4%] of 355 [2–6] *vs* 40 [11%] of 350 [8–15]; difference between groups –7% [–12 to –4], p<0·0001, Fisher's exact test).

After a median follow-up of 34 months (range 0·03–61), 3-year event-free survival was 59% (54–64; 147 events) for patients assigned chemotherapy alone and was 79% (75–83; 79 events) for those assigned chemotherapy plus rituximab (difference between groups 20% [13–27], log-rank p<0·0001; figure 2A).

Sensitivity (ie, per-protocol) analyses of patients who met the eligibility criteria of CD20-positive diffuse large-B-cell lymphoma that was confirmed by histopathological review, and who met all eligibility criteria or did not have a major protocol violation, confirmed the results of intention-to-treat analyses with regard to all endpoints. Moreover, results remained unchanged if the 59 patients who were still under therapy when the trial was stopped were not censored.

3-year progression-free survival was significantly lower for the chemotherapy-alone group than for the chemotherapy-and-rituximab group (68% [62–73] *vs* 85% [81–89]; difference between groups 17% [11–24], log-rank p<0·0001); figure 2B).

We recorded 57 relapses—33 after allocation to chemotherapy alone and 24 after allocation to chemotherapy plus rituximab. 30-month relapse-free survival after achieving complete remission or unconfirmed complete remission for patients allocated chemotherapy alone was significantly lower compared with those allocated combined rituximab and chemotherapy (86% [82–91]) *vs* 94% [91–96]; difference between groups 8% [2–13], log-rank p=0·02).

We noted 86 deaths—59 in the chemotherapy-alone group (57 lymphoma-associated, one treatment-related, and one due to a second neoplasm), and 27 in the chemotherapy-and-rituximab group (19 lymphoma-associated, six treatment-related, and two due to concomitant disease). 3-year overall survival was higher for patients allocated chemotherapy plus rituximab than for those allocated chemotherapy alone (93% [90–95] *vs* 84% [80–88]; difference between groups 9% [3–13], log-rank p=0·0001; figure 2C).

In multivariable analyses done by intention to treat, the occurrence of events in the primary-endpoint measure event-free survival was affected by treatment with rituximab (HR 0·44 [0·34–0·59]; p<0·0001, Wald test), bulky disease (1·57 [1·20–2·05], p=0·001), and the presence of at least one age-adjusted IPI risk factor (1·68 [1·27–2·23], p=0·0003). We found no interactions between treatment group and bulky disease (0·71

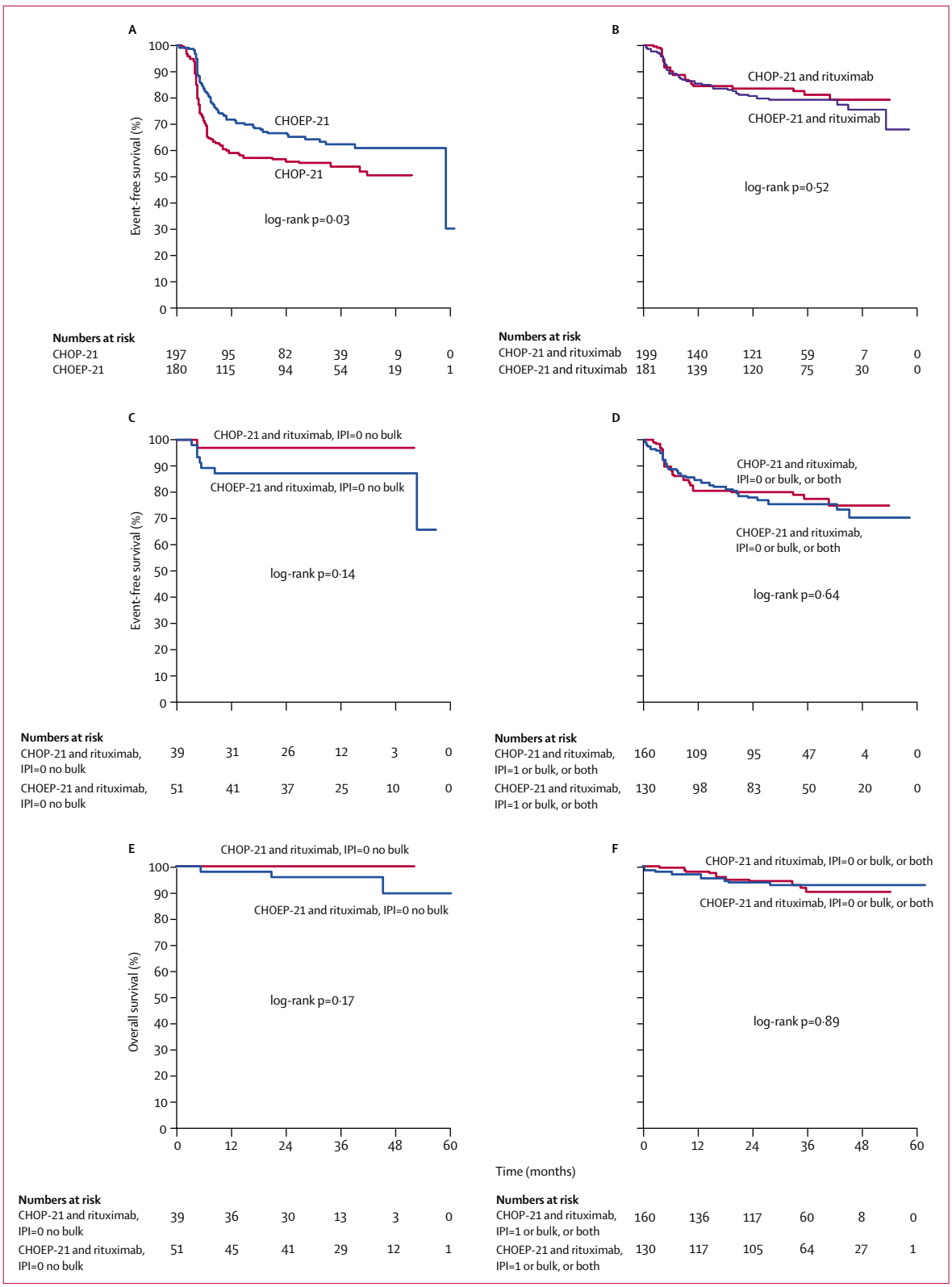

Figure 5: **Addition of rituximab to CHOP and CHOEP**
The benefit with regard to event-free survival with the more-intensive regimen of CHOEP over that of CHOP (A) is not present on addition of rituximab (B) for event-free survival of the favourable subgroup (C) and unfavourable subgroups (D), and for overall survival of the favourable subgroup (E) and unfavourable subgroups (F).

	Chemotherapy (n=403)*	Chemotherapy and rituximab (n=404)*
All body systems	166 (41%)	150 (37%)
Leucocytopenia†	23 (6%)	29 (7%)
Thrombocytopenia†	2 (<1%)	1 (<1%)
Anaemia†	2 (<1%)	3 (<1%)
Infection	31 (8%)	30 (7%)
Nausea	6 (1%)	4 (<1%)
Vomiting	8 (2%)	8 (2%)
Cardiotoxicity	5 (1%)	10 (2%)
Neurotoxicity	13 (3%)	13 (3%)
Renal toxic effects	3 (<1%)	0
Lung toxic effects	6 (1%)	2 (<1%)

Data are number (%) of patients with US National Cancer Institute-Common Toxicity Criteria grade 3 and 4 toxic effects. *Data excludes one patient assigned to chemotherapy alone who had no data for toxic effects, and 15 who did not have treatment: six in chemotherapy-alone group (two without CD20+ diffuse large-B-cell lymphoma on histological review, three as a result of patient's decision, and one as a result of treating physician's decision); and nine in the chemotherapy-and-rituximab group (seven without CD20+ diffuse large-B-cell lymphoma on histological review, and two as a result of patient's decision). †Haematological toxic effects were grade 4, together with clinical signs or symptoms, with or without a change in treatment or concomitant therapy.

Table 5: **Adverse events**

[0·40–1·23], p=0·219), and between treatment group and age-adjusted IPI (0·77 [0·43–1·38], p=0·384). In a Cox-regression model restricted to patients assigned rituximab, we found no interactions between bulky disease and age-adjusted IPI (0·53 [0·20–1·38], p=0·192). Events in progression-free survival were affected by: treatment with rituximab (0·42 [0·31–0·59, p<0·0001); bulky disease (1·46 [1·06–2·00], p=0·02); and by an age-adjusted IPI risk factor (1·79 [1·28–2·51, p=0·001). Events in overall survival were affected by treatment with rituximab (0·40 [0·26–0·64], p=0·0001), and by bulky disease (2·82 [1·75–4·54], p<0·0001).

Figure 3 and table 3 show Kaplan-Meier estimates for the four stratified risk groups in intention-to-treat analysis (ie, presence or absence of bulky disease; IPI=0 or 1) in both treatment groups for event-free survival and overall survival. Patients with no bulky disease and IPI=0 have a favourable 3-year event-free survival after chemotherapy plus rituximab compared with the other three subgroups (ie, IPI=1 or bulk, or both; 89% [82–95] *vs* 76% [70–81], log-rank p=0·0162; figure 3C), but not with regard to 3-year overall survival (98% [95–100] *vs* 91% [87–94], log-rank p=0·08; figure 3D). After chemotherapy alone, event-free survival was higher for patients with no bulky disease and IPI=0 compared with the less-favourable subgroups with IPI=1 or bulky disease, or both (78% [70–86] *vs* 52% [46–58], log-rank p=0·0001; figure 3E), as was 3-year overall survival (92% [87–98] *vs* 81% [76–86], log-rank p=0·01; figure 3F).

48% of patients received CHOP-21, 44% received CHOEP-21, and a small number received MACOP-B (n=34; 4%) or PMitCEBO (n=32; 4%). Table 4 shows the characteristics of patients who received CHOP-21 or CHOEP-21 chemotherapy, with or without rituximab. Patients treated with CHOP-21 and CHOEP-21 benefited from the addition of rituximab. 3-year event-free survival was 54% [46–62] for patients allocated CHOP-21 alone compared with 81% [75–88] for those allocated CHOP-21 with rituximab (log-rank p<0·0001), and was 62% [55–70] for patients allocated CHOEP-21 alone compared with 79% [73–85] for those allocated CHOEP-21 with rituximab (log-rank p=0·003; figure 4). Use of CHOEP-21 alone resulted in a higher 3-year event-free survival than did CHOP-21 alone (log-rank p=0·03; figure 5A). However, there was no difference in 3-year event-free survival between CHOP-21 plus rituximab and CHOEP-21 plus rituximab (log-rank p=0·52; figure 5B).

Cox-regression analyses by intention to treat of patients assigned CHOP-21 or CHOEP-21 with or without rituximab showed a significant risk reduction in 3-year event free survival due to etoposide in the chemotherapy-alone group (HR for etoposide 0·69 [0·49–0·97], p=0·033), and a significant interaction compensating for this benefit in the rituximab group (HR for interaction between rituximab and etoposide 1·81 [1·01–3·25], p=0·047).

Intention-to-treat analysis showed that for the favourable subgroup (ie, age-adjusted IPI=0, no bulky disease) and unfavourable subgroups (ie, bulky disease or age-adjusted IPI=1, or both), CHOP-21 and rituximab were much the same as CHOEP-21 and rituximab in terms of event-free survival and overall survival. In the 39 patients in the favourable subgroup who received CHOP-21 and rituximab, one event occurred—after 4·4 months—in analyses of event-free survival. In the favourable subgroup, 3-year event-free survival was 97% (91–100) for patients who received CHOP-21 and rituximab and was 87% (78–97) for those who received CHOEP-21 and rituximab (log-rank p=0·14; figure 5C). In the less-favourable subgroups, 3-year event-free survival was 78% (70–85) for patients who received CHOP-21 and rituximab, and was 76% (68–84) for those who received CHOEP-21 and rituximab (log-rank p=0·64; figure 5D). 3-year overall survival in the favourable subgroup was 100% with CHOP-21 and rituximab and was 96% (90–100) with CHOEP-21 and rituximab (log-rank p=0·17; figure 5E); 3-year overall survival in the less-favourable subgroups was 90% (85–96) with CHOP-21 and rituximab and was 93% (88–97) with CHOEP-21 and rituximab (log-rank p=0·89; figure 5F)

Groups did not differ in the frequency of adverse events (table 5). There were seven treatment-related deaths: one sepsis in the chemotherapy-alone group (CHOEP-21 regimen); and two myocardial infarctions (CHOP-21 and CHOEP-21 regimens), one intrathecal vincristine application (CHOEP-21 regimen), and three septicaemias (two CHOEP-21 and one MACOP-B regimens) in the chemotherapy-and-rituximab group (p for difference between groups=0·123, Fisher's exact test). To date, four second neoplasms have been reported: one acute myelogenous leukaemia in the chemotherapy-

alone group; and one melanoma and two acute myelogenous leukaemias in the chemotherapy-and-rituximab group.

Discussion

We have shown that the addition of rituximab to six cycles of a CHOP-like chemotherapy improves the outcome of all subgroups of patients with good-prognosis diffuse large-B-cell lymphoma without increased toxic effects. To our knowledge, these findings are the best reported for this group of patients to date in a randomised trial. Furthermore, our findings lend support to the previously reported therapeutic benefit of the more-intensive CHOEP regimen over that of CHOP;[3] however, we noted that such benefit was not present after the addition of rituximab. Moreover, we found that bulky disease with a maximum diameter of more than 7·5 cm is a strong prognostic factor, and that new prognostic subgroups emerge after treatment with a CHOP-like regimen plus rituximab that allow for a more-refined therapeutic approach to young good-prognosis patients with diffuse large-B-cell lymphoma. Our data do not suggest that the open-label randomisation affected our findings: adherence to the protocol, both with respect to chemotherapy and radiotherapy, was the same for both treatment groups.

The effect of rituximab in our study with young good-prognosis patients was larger than that expected on the basis of the GELA study in elderly patients.[6] In our study, nearly twice as many patients failed after chemotherapy compared with chemotherapy plus rituximab (41% *vs* 21%). Thus, the proportion of young patients who need salvage treatment—usually high-dose chemotherapy with haemopoietic stem-cell transplantation—could be halved by the addition of rituximab.

Even with the exclusion of patients with stage I disease, no risk factors, and no bulky disease from the MInT trial, the results achieved with six cycles of CHOP-like chemotherapy plus rituximab without radiotherapy in the favourable subgroup (ie, those with no risk factor according to age-adjusted IPI, no bulky disease, and all stage II) compare favourably with the results obtained with the more-aggressive and more-toxic ACVBP chemotherapy,[4] even though two-thirds of patients in this study[4] of ACVBP had stage I disease. On designing our study, the question of six or eight cycles was debated because in the absence of data from appropriate randomised trials, some countries had six cycles and others had eight as standard treatment. However, six cycles of CHOP plus rituximab in the MInT trial has led to use of this regimen as a new standard treatment in many parts of the world for young patients who have a good outlook .

Moreover, a DSHNHL trial[11] of elderly patients found no difference between six and eight cycles of CHOP-14 with rituximab. Results reported by SWOG for a phase II trial[12] of three cycles of CHOP with rituximab followed by involved-field radiotherapy are difficult to interpret because the number of patients in the SWOG trial[12] is small (n=62), the median follow-up is short (2·4 years), and because a non-randomised phase II trial carries the risk of uncontrolled selection—as shown by the Intergroup trial,[13] which showed that for many years patients with diffuse large-B-cell lymphoma had been exposed to more-toxic, but not more-efficacious, regimens on the basis of promising phase II results.

We permitted every participating country to choose their preferred CHOP-like regimen because we postulated that a clinically important effect of rituximab should become evident with various chemotherapy regimens. This idea was confirmed because patients receiving CHOP-21 and CHOEP-21 benefited from the addition of rituximab. After CHOEP had been reported to be more effective than CHOP in young good-prognosis patients,[3] CHOEP became the standard chemotherapy regimen for these patients in several countries participating in this trial. Therefore, we planned to compare CHOP-21 with that of CHOEP-21 in the MInT trial because of clinical interest in these regimens, even though this comparison was not an explicit endpoint of the trial because we could not anticipate how many patients would be recruited by every country. Although we confirmed the previously reported[3] efficacy of CHOEP-21 over that of CHOP-21, the benefit was not present after the addition of rituximab. Therefore, an improvement similar to that reported for young patients in a cancer-registry study[14] after the regionwide introduction of rituximab could have been expected if the more efficacious CHOEP-21 had been used as the chemotherapy-only comparator.

Because it has fewer toxic effects[3] and is easier to handle (ie, is a 1-day regimen), CHOP-21 plus rituximab may be preferred over that of CHOEP-21 plus rituximab. The lack of effectiveness of CHOEP-21 plus rituximab over that of CHOP-21 plus rituximab might be explained by an equalising effect of rituximab on the chemotherapy regimen. Alternatively, the lack of effectiveness might be due to the greater haemological toxic effects of CHOEP-21,[3] which might compromise the efficacy of rituximab by impairing necessary immune effector mechanisms (eg, natural killer cells) that are essential for rituximab-mediated antibody-dependent cellular cytotoxicity. The latter idea would not only explain why the addition of rituximab to a high-dose chemotherapy (ie, mega-CHOEP) regimen did not improve the outcome of young patients with poor-prognosis diffuse large-B-cell lymphoma,[15] but would also caution against combining rituximab with more-aggressive chemotherapy regimens (eg, ACVBP) outside appropriately controlled clinical trials.

We identified new prognostic subgroups after treatment with chemotherapy plus rituximab that are only partly identified by age-adjusted IPI. That the best prognostic group of patients with diffuse large-B-cell lymphoma (ie, stage I without bulky disease) were excluded from the MInT trial does not weaken the

prognostic model emerging after treatment with CHOP-like chemotherapy and rituximab: 3-year event-free survival was 97% (with the last event occurring after 4·4 months) after six cycles of CHOP plus rituximab, and 3-year overall survival was 98% after any chemotherapy and rituximab and 100% after six cycles of CHOP plus rituximab in patients with stage II disease, no age-adjusted IPI risk factor, and no bulky disease. Moreover, separation of patients with stage I disease, no age-adjusted IPI risk factor, and no bulky disease from the respective patients in stage II no longer seems justifiable; rather, these patients should be grouped with respect to prognosis and therapeutic strategy. The excellent results achieved with CHOP plus rituximab in this favourable subgroup justify, perhaps for the first time in the history of treatment of diffuse large-B-cell lymphoma, a reduction in the number of chemotherapy cycles for these patients. In a continuing randomised trial, four cycles of CHOP plus rituximab are under comparison with the MInT standard of six cycles.

The less-favourable subgroups had a 3-year event-free survival of 76% after chemotherapy plus rituximab, and warrants further improvement. The main feature of these subgroups is bulky disease, which is expected in three-quarters of these patients. Although a cut-off point of 10 cm for bulky disease is commonly used, the margins present in the MInT trial from the different cooperative groups ranged from 5 cm to 10 cm. Because most patients were recruited by cooperative groups that used a cut-off point of 7·5 cm for bulky disease, it is not surprising that most patients qualified as having bulky disease on the basis of this cut-off. The median maximum diameter of the largest tumour mass in patients who qualified to have bulky disease, as defined by their centre-defined cut-off, was 10·0 cm. That bulky disease—which is not represented in the IPI—emerged as a strong and independent prognostic factor with respect to event-free survival, progression-free survival, and overall survival, with 94% of patients with bulky disease qualifying as such because they fulfilled a preset cut-off point of 7·5 cm or 5 cm, suggests that 7·5 cm rather than 10 cm defines bulky disease as a prognostic marker. Because the median maximum diameter of all bulky disease qualifying as such in the MInT trial was 10·0 cm, half the population at increased risk not responding after chemotherapy plus rituximab would be missed by applying a cut-off point of 10·0 cm. Because of the paucity of patients in the MInT trial qualifying for having bulky disease due to a mass larger than 5 cm but smaller than 7·5 cm, we have no data to analyse a cut-off point of less than 7·5 cm for the definition of bulky disease. A more detailed analysis of the role of bulky disease in this trial is in preparation.

A subgroup analysis of the NHL-B1[3] and NHL-B2[16] trials of the DSHNHL group showed that apart from patients with raised lactate dehydrogenase, those with bulky disease had the greatest benefit from reducing CHO(E)P-21 every 3 weeks to CHO(E)P-14 every 2 weeks. Because half the patients in the less-favourable subgroup in the MInT study presented with raised lactate dehydrogenase and two-thirds with bulky disease, these patients might benefit from dose-dense treatment, and CHOP-14 plus rituximab is currently under assessment with CHOP-21 plus rituximab in a DSHNHL trial for young patients with bulky disease or one age-adjusted IPI, or both. Our finding that bulky disease emerged as a prominent risk factor in the MInT study, even though patients with bulky disease received additional radiotherapy, questions the role of radiotherapy in this setting. Therefore, patients with bulky disease in the continuing DSHNHL study will receive a second randomisation into additional radiotherapy or not.

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Conflicts of interest

M Pfreundschuh, K Imrie, and N Milpied are members of the MabThera advisory board of Roche. J Walewski has received travel grants from Roche for travel during the past 5 years. K Imrie and J Walewski have received honoraria from Roche for presentations at Roche-sponsored symposia. M Rashford and M Mendila, who is Clinical Science Leader of Global Drug Development, are full-time employees of Roche.

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