Rituximab-dose-dense chemotherapy with or without high-dose chemotherapy plus autologous stem-cell transplantation in high-risk diffuse large B-cell lymphoma (DLCL04): final results of a multicentre, open-label, randomised, controlled, phase 3 study

Annalisa Chiappella*, Maurizio Martelli*, Emanuele Angelucci, Ercole Brusamolino†, Andrea Evangelista, Angelo Michele Carella, Caterina Stelitano, Giuseppe Rossi, Monica Balzarotti, Francesco Merli, Gianluca Gaidano, Vincenzo Pavone, Luigi Rigacci, Francesco Zaja, Alfonso D'Arco, Nicola Cascavilla, Eleonora Russo, Alessia Castellino, Manuel Gotti, Angela Giovanna Congiu, Maria Giuseppina Cabras, Alessandra Tucci, Claudio Agostinelli, Giovannino Ciccone, Stefano A Pileri, Umberto Vitolo

Summary

Background The prognosis of young patients with diffuse large B-cell lymphoma at high risk (age-adjusted International Prognostic Index [aa-IPI] score 2 or 3) treated with R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone) is poor. The aim of this study was to investigate the possible benefit of intensification with high-dose chemotherapy and autologous stem-cell transplantation as part of first-line treatment in these patients.

Methods We did a multicentre, open-label, randomised, controlled, phase 3 trial with a 2×2 factorial design to compare, at two different R-CHOP dose levels, a full course of rituximab-dose-dense chemotherapy (no transplantation group) versus an abbreviated course of rituximab-dose-dense chemotherapy followed by consolidation with R-MAD (rituximab plus high-dose cytarabine plus mitoxantrone plus dexamethasone) and high-dose BEAM chemotherapy (carmustine, etoposide, cytarabine, and melphalan) plus autologous stem-cell transplantation (transplantation group) in young patients (18–65 years) with untreated high-risk diffuse large B-cell lymphoma (aa-IPI score 2–3). At enrolment, patients were stratified according to aa-IPI score and randomly assigned (1:1:1:1) to receive R-CHOP (intravenous rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1·4 mg/m² on day 1, plus oral prednisone 100 mg on days 1–5) delivered in a 14-day cycle (R-CHOP-14) for eight cycles; high-dose R-CHOP-14 (R-MegaCHOP-14; R-CHOP-14 except for cyclophosphamide 1200 mg/m² and doxorubicin 70 mg/m²) for six cycles; R-CHOP-14 for four cycles followed by R-MAD (intravenous rituximab 375 mg/m² on day 1 or 4 plus intravenous cytarabine 2000 mg/m² and dexamethasone 4 mg/m² every 12 h on days 1–3 plus intravenous mitoxantrone 8 mg/m² on days 1–3) plus BEAM (intravenous carmustine 300 mg/m² on day –7, intravenous cytarabine 200 mg/m² twice a day on days –6 to –3, intravenous etoposide 100 mg/m² twice a day on days –6 to –3, plus intravenous melphalan 140 mg/m² on day –2) and autologous stem-cell transplantation (day 0); or R-MegaCHOP-14 for four cycles followed by R-MAD plus BEAM and autologous stem-cell transplantation. The primary endpoint was failure-free survival at 2 years in the intention-to-treat population. This study is registered with EudraCT (2005-002181-14; 2007-000275-42) and with ClinicalTrials.gov, number NCT00499018.

Findings Between Jan 10, 2006, and Sept 8, 2010, 399 patients were randomly assigned to receive transplantation (n=199) or no transplantation (n=200); 203 patients were assigned to receive R-CHOP-14 and 196 were assigned to receive R-MegaCHOP-14. With a median follow-up of 72 months (IQR 57–88), 2-year failure-free survival was 71% (95% CI 64–77) in the transplantation group versus 62% (95% CI 55–68) in the no transplantation group (hazard ratio [HR] 0·65 [95% CI 0·47–0·91]; stratified log-rank test p=0·012). No difference in 5-year overall survival was observed between these groups (78% [95% CI 71–83] versus 77% [71–83]; HR 0·98 [0·65–1·48]; stratified log-rank test p=0·91). Grade 3 or worse haematological adverse events were reported in 183 (92%) of 199 patients in the transplantation group versus 135 (68%) of 200 patients in the no transplantation group. Grade 3 or worse non-haematological adverse events were reported in 90 (45%) versus 31 (16%); the most common grade 3 or worse non-haematological adverse event was gastrointestinal (49 [25%] *vs* 19 [10%]). Treatment-related deaths occurred in 13 (3%) patients; eight in the transplantation group and five in the no transplantation group.

Interpretation Abbreviated rituximab-dose-dense chemotherapy plus R-MAD plus BEAM and autologous stem-cell transplantation reduced the risk of treatment failure compared with full course rituximab-dose-dense chemotherapy in young patients with diffuse large B-cell lymphoma at high risk. However, these results might not be clinically meaningful, since this improvement did not reflect an improvement in overall survival. These results do not support

Department of Haematology, Istituto Clinico Humanitas, Rozzano, Italy (M Balzarotti MD); Department of Haematology, Arcispedale Santa Maria Nuova, IRCCS, Reggio Emilia, Italy (F Merli MD); Division of Haematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy (Prof G Gaidano MD); Department of Haematology and Transplantation, Azienda Ospedaliera Cardinal Panico, Tricase, Italy (V Pavone MD); Department of Haematology, Azienda Ospedaliero Universitaria Careggi, Firenze, Italy (L Rigacci MD); Department of Haematology, Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Udine, Italy (Prof F Zaja MD); Department of Haematology, Presidio Ospedaliero Umberto I, Nocera Inferiore, Italy (A D'Arco MD); Department of Haematology, Hospital Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy (N Cascavilla MD); Institute of Haematology L e A Seràgnoli, Università degli Studi di Bologna, Bologna, Italy (Prof C Agostinelli MD, Prof S A Pileri MD); and Haematopathology Unit, Istituto Europeo di Oncologia, Milan, Italy (Prof S A Pileri)

Correspondence to:
Dr Annalisa Chiappella, Department of Haematology, Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Corso Bramante 88, 10126 Turin, Italy
achiappella@cittadellasalute.to.it

See Online for appendix

further consideration of the use of intensification of R-CHOP as an upfront strategy in patients with diffuse large B-cell lymphoma with poor prognosis.

Introduction

Over the past decade, substantial improvements in long-term disease control and survival have been reported in the treatment of diffuse large B-cell lymphoma, with more than 50% of patients maintaining remissions beyond 5 years, largely as a result of routine incorporation of rituximab into the standard regimen of CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone).[1]

Patients younger than 60 years with newly diagnosed, diffuse large B-cell lymphoma at intermediate-high risk or high risk (age-adjusted International Prognostic Index [aa-IPI] score of 2 or 3)[2] have a poor prognosis, even when treated with standard rituximab plus CHOP (R-CHOP).[3] Several options have been investigated to improve outcomes in these patients, including the introduction of dose-dense chemotherapy or consolidation with high-dose chemotherapy plus autologous stem-cell transplantation as part of the first-line approach. In the pre-rituximab era, the potential benefit of intensification was investigated, with contradictory results;[4] on the contrary, subsequent phase 2 studies with the addition of rituximab to high-dose chemotherapy and autologous stem-cell transplantation or intensified chemotherapy (R-ACVBP; rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) showed favourable results.[5–8] In our previous phase 2 trial,[8] a brief course of dose-dense chemo-immunotherapy, followed by high-dose chemotherapy plus autologous stem-cell transplantation as consolidation, was administered in patients younger than 60 years with newly diagnosed, diffuse large B-cell lymphoma with poor prognosis, and showed a 4-year progression-free survival of 73%.

On the basis of these promising results, we did a randomised, phase 3 study with a 2×2 factorial design to investigate the possible benefit of intensification with high-dose chemotherapy and autologous stem-cell transplantation and two different doses of rituximab and doxorubicin-based chemoimmunotherapy as part of first-line treatment in young patients with diffuse large B-cell lymphoma with poor prognosis.

Methods

Study design and participants

The DLCL04 study was an open-label, randomised, controlled, phase 3 trial done by the Fondazione Italiana Linfomi at 52 hospitals and universities in Italy (appendix pp 2–4).

Eligible patients were aged 18–65 years with newly diagnosed, untreated, CD20-positive diffuse large B-cell lymphoma or follicular grade 3b lymphoma; patients

Research in context

Evidence before this study
During the planning of this study, we searched PubMed for full reports of clinical trials published in English before Nov 15, 2005, with the terms "lymphoma", "large B-cell", "diffuse", and "rituximab". No phase 3 randomised clinical trials focusing on young, untreated patients with poor prognosis in the rituximab era were published at that point. R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone) was listed as the standard treatment for young patients with diffuse large B-cell lymphoma with poor prognosis. Preliminary results presented at the 2004 and 2005 annual meetings of the American Society of Hematology suggested that rituximab dose-dense chemotherapy plus high-dose chemotherapy and autologous stem-cell transplantation showed significant activity in high-risk, untreated diffuse large B-cell lymphoma in phase 2 studies. These results have been subsequently confirmed. On the basis of the available evidence, in 2005 we designed a phase 3 study to assess the effect of R-MAD (rituximab plus high-dose cytarabine plus mitoxantrone plus dexamethasone) and high-dose BEAM chemotherapy (carmustine, etoposide, cytarabine, and melphalan) plus autologous stem-cell transplantation after an abbreviated course of rituximab-dose-dense chemotherapy versus a full course of dose-dense chemotherapy, and to assess the effect of chemoimmunotherapy intensification with two induction schemes at two different dose levels, specifically in untreated young patients with diffuse large B-cell lymphoma with poor prognosis.

Added value of this study
Our results show that intensification with R-MAD plus BEAM and autologous stem-cell transplantation after an abbreviated rituximab dose-dense chemotherapy in young patients with untreated diffuse large B-cell lymphoma with poor prognosis improved failure-free survival compared with a full course of rituximab dose-dense chemotherapy alone. However, this improvement did not translate into a difference in overall survival. Increasing the dose of standard R-CHOP did not lead to an improvement in failure-free survival or overall survival.

Implications of all the available evidence
On the basis of these results, early consolidation with high-dose chemotherapy and autologous stem-cell transplantation cannot be recommended, and R-CHOP should remain the standard treatment for diffuse large B-cell lymphoma in patients with poor prognosis.

with a diagnosis of primary mediastinal B-cell lymphoma were eligible only in the presence of extrathoracic dissemination of the disease. Other eligibility criteria were intermediate-high risk or high risk (aa-IPI score of 2 or 3); Eastern Cooperative Oncology Group (ECOG) performance status 0–2, and normal organ function.

Exclusion criteria included CNS involvement, any previous treatment for lymphoma, previous malignancies within 3 years before study entry, or the presence of HIV infection or an active hepatitis B or hepatitis C virus infection. A full list of exclusion criteria is provided in the appendix (pp 4–6).

Ethical approval was obtained from the independent ethics committees and institutional review boards of each site before trial initiation. The trial was done in accordance with the Declaration of Helsinki and good clinical practice. All patients gave written informed consent before enrolment.

The protocol for the DLCL04 study is available online.

Randomisation and masking
At enrolment, patients were stratified according to aa-IPI score (2 vs 3) and randomly assigned in permuted blocks (size 4, 8, or 12) to one of the four groups in a 1:1:1:1 ratio. The randomisation sequence was generated by the statistician (GC) by use of a computer program and implemented by means of a Web-based procedure, which was concealed to researchers. Investigators and patients were not blinded to the treatment assignment. Data were analysed by the Unit of Clinical Epidemiology, University of Turin, Turin, Italy, and CPO Piemonte, Turin, Italy.

Procedures
Patients were diagnosed by histology after lymph node or bone marrow biopsy. Patients were randomly assigned to receive one of four interventions: R-CHOP delivered in a 14-day cycle (R-CHOP-14) for eight cycles;[9] intensified R-CHOP delivered in a 14-day cycle (R-MegaCHOP-14) for six cycles; R-CHOP-14 for four cycles followed by R-MAD plus BEAM and autologous stem-cell transplantation; or R-MegaCHOP-14 for four cycles followed by R-MAD plus BEAM and autologous stem-cell transplantation. Patients who received the full course of rituximab-dose-dense chemotherapy were deemed to be in the no transplantation group; those who received abbreviated rituximab-dose dense chemotherapy followed by R-MAD plus BEAM and autologous stem-cell transplantation were in the transplantation group. R-CHOP-14 consisted of rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1·4 mg/m² [capped at 2 mg], all given intravenously on day 1 of a cycle, plus oral prednisone 100 mg on days 1–5 of a cycle. R-MegaCHOP-14 consisted of rituximab 375 mg/m², cyclophosphamide 1200 mg/m², doxorubicin 70 mg/m², and vincristine 1·4 mg/m² [capped at 2 mg], all given intravenously on day 1 of a cycle, plus oral prednisone 100 mg on days 1–5 of a cycle.

For patients in the transplantation groups, rituximab dose-dense chemotherapy was followed by two cycles of consolidation every 28 days, consisting of R-MAD (rituximab at a standard dose of 375 mg/m² on day 1 or 4 and before peripheral blood stem-cell harvest during the first course as an in-vivo purging, with MAD [cytarabine 2000 mg/m² every 12 h on days 1–3 plus mitoxantrone 8 mg/m² on days 1–3 plus dexamethasone 4 mg/m² every 12 h on days 1–3, all given intravenously]), plus a consolidation phase based on myeloablative chemotherapy according to the BEAM[10] regimen (intravenous carmustine 300 mg/m² on day –7, intravenous cytarabine 200 mg/m² twice a day on days –6 to –3, intravenous etoposide 100 mg/m² twice a day on days –6 to –3, plus intravenous melphalan 140 mg/m² on day –2), followed by autologous stem-cell transplantation with at least 3×10^6 peripheral blood CD34-positive cells per kg bodyweight.

Dosing schemes are shown in figure 1 and details are in the appendix (pp 6, 7).

Recovery of absolute neutrophil count to 1500 cells per μL and platelet count to 50 000 platelets per μL was required before starting each cycle of R-CHOP-14 or R-MegaCHOP-14. If the count of platelets was lower than 50 000, or the neutrophil count was lower than 1500, or both, on day 1 of the next cycle, the subsequent cycle was postponed for a maximum of 2 weeks, and doses of doxorubicin and cyclophosphamide or mitoxantrone and cytarabine reduced by 25%. If a delay of more than 2 weeks occurred, treatment was discontinued and patients were treated according to local practice. For stem-cell reinfusion, no dose reductions were scheduled in the BEAM course.

Patients at risk of CNS relapse[11] received CNS prophylaxis with intrathecal methotrexate (12 mg for four doses during the first four courses of chemoimmunotherapy in transplantation groups and 12 mg for six doses during the first six courses of chemoimmunotherapy in non-transplantation groups). At the end of the treatment, involved field radiotherapy was planned to isolated areas of residual uptake at the final 18-fluorodeoxyglucose PET (18FDG-PET) scan or to previous bulky disease or extranodal sites.

Granulocyte colony-stimulating factor (G-CSF; filgrastim or lenograstim or pegfilgrastim) and pneumocystis pneumonia prophylaxis were mandatory in all patients; prophylactic antibiotics were suggested in the transplantation groups and were given according to local practice. Details on G-CSF use, antibiotics, supportive care, delay, and dose reductions were allowed as specified by the protocol and are described in the appendix (pp 8–10). At baseline, all patients underwent a complete staging evaluation with complete blood cell counts and biochemistry, CT scan, and bone marrow biopsy. 18FDG-PET was recommended but not mandatory at baseline.

Tumour response was evaluated by local investigators. Intermediate response was assessed after four courses
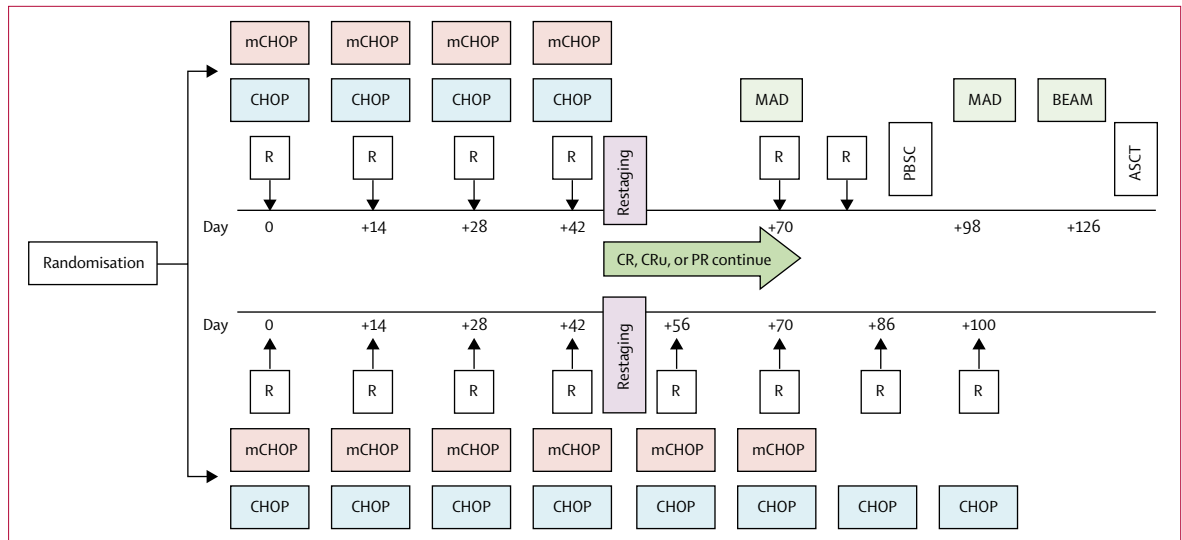
***Figure 1:* Study design**
R=rituximab 375 mg/m². CHOP=CHOP-14: cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1·4 mg/m² (capped at 2 mg), all given intravenously on day 1 of a cycle, plus oral prednisone 100 mg on days 1–5 of a cycle. mCHOP=MegaCHOP-14: cyclophosphamide 1200 mg/m², doxorubicin 70 mg/m², and vincristine 1·4 mg/m² capped at (2 mg), all given intravenously on day 1 of a cycle, plus oral prednisone 100 mg on days 1–5 of a cycle. MAD=cytarabine 2000 mg/m² every 12 h on days 1–3 plus mitoxantrone 8 mg/m² on days 1–3 plus dexamethasone 4 mg/m² every 12 h on days 1–3, all given intravenously. PBSC=peripheral blood stem-cell harvest as an in-vivo purging. BEAM=carmustine, cytarabine, etoposide, and melphalan (intravenous carmustine 300 mg/m² on day –7, intravenous cytarabine 200 mg/m² twice a day on days –6 to –3, intravenous etoposide 100 mg/m² twice a day on days –6 to –3, plus intravenous melphalan 140 mg/m² on day –2). ASCT=autologous stem-cell transplantation with at least 3 × 10⁶ peripheral blood CD34-positive cells per kg bodyweight. CR=complete response. CRu=unconfirmed complete response. PR=partial response. Patients who did not respond to the first four cycles of treatment were excluded from the study and treated according to clinical practice.

of R-CHOP-14 or R-MegaCHOP-14 by CT scan. Patients with a complete response, unconfirmed complete response, or partial response were scheduled to complete the treatment according to the assigned group. At the end of treatment, response was assessed by CT scan, ¹⁸FDG-PET, and bone marrow biopsy if positive at baseline. Responses to treatment and standard outcome measures were defined according to a modification of Cheson 1999 criteria.[12,13] Follow-up continued from completion of treatment until disease progression, relapse, death, or withdrawal from the study as a result of the patient's decision or study completion. Pathological materials were collected and centrally reviewed by a panel of expert haematopathologists.

Safety evaluations were adverse events, vital signs, and laboratory safety assessments. Adverse events were categorised and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

On Jan 30, 2007, a protocol amendment was submitted to the ethical committee and approved. The changes were as follows: reduction of the doxorubicin dose from 75 mg/m² to 70 mg/m² in the R-MegaCHOP-14 groups to prevent cardiotoxicity; detailed prophylaxis with lamivudine in occult hepatitis B virus carrier patients; possibility of doing pre-phase with steroids with or without vincristine in patients with a high tumour burden at diagnosis; and revised pathological and biomarker analysis (central review of histology, definition

of analysis on cell of origin, fluorescence in-situ hybridisation [FISH]).

Outcomes

The primary endpoint was failure-free survival, which was measured from randomisation to any of the following events, whichever occurred first: progression, no response after four courses of R-CHOP-14 or R-MegaCHOP-14, relapse, or death from any cause. Secondary endpoints were overall survival (measured from randomisation to death from any cause) and response proportions after four courses of rituximab chemoimmunotherapy and at the end of treatment (complete remission, including complete response and unconfirmed complete response; and overall response, including complete response, unconfirmed complete response, and partial response).

According to the revised response criteria for malignant lymphoma,[14] progression-free survival was measured from randomisation to progression, relapse, or death from any cause.

Statistical analysis

The primary comparison was between the transplantation and no transplantation groups. With a two-sided alpha error of 0·05, 376 patients were required to have a statistical power of 80% to detect a 15% improvement in 2-year failure-free survival (from 50% to 65%) in the groups receiving transplantation compared with those who did not receive transplantation. The detailed

statistical analysis plan and sample size calculation is reported in the appendix (pp 10, 11). The primary efficacy analysis was done in the intention-to-treat population. A per-protocol analysis was done for failure-free survival, including all patients who, after restaging, had started the second treatment phase; and for safety.

Failure-free survival, overall survival, and progression-free survival were estimated with the Kaplan-Meier[15] product-limit method. Differences between randomised groups were assessed by stratified log-rank test and hazard ratios (HRs) were estimated with a Cox model,[16] including as primary variables the randomised groups (transplantation vs no transplantation) and (R-CHOP-14 vs R-MegaCHOP-14) and the aa-IPI score as a covariate according to the stratified randomisation. According to the Grambsch and Therneau test,[17] all variables met the proportional hazard assumption of the Cox model.

Response proportions were summarised as absolute frequencies and percentages, and compared between randomised groups by χ^2 test or Fisher's exact test, when required.

To test the homogeneity of treatment effects on failure-free survival, planned analyses (according to factorial design and stratified randomisation: type of dose-dense chemotherapy, aa-IPI score, age, and bone marrow involvement) and post-hoc subgroup analyses (sex and histology) were done. In each subgroup, transplantation was compared with no transplantation and R-CHOP-14 was compared with R-MegaCHOP-14 by use of the Cox proportional-hazards model and the presence of the interaction tested by including an interaction term between the randomised group and the subgroup covariate of interest. Statistical analyses were done with SAS software, version 8.2, and Stata software, version 11.2. No data monitoring committee oversaw the study.

In accordance with Italian regulations, this study was registered with the Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali registry of Agenzia Italiana del Farmaco (AIFA) in 2005, EudraCT number 2005-002181-14. In 2007, AIFA refreshed the registry and updated the EudraCT number (2007-000275-42). This study is also registered with ClinicalTrials.gov, number NCT00499018.

Role of the funding source

Results

Between Jan 10, 2006, and Sept 8, 2010, 412 patients were enrolled and 399 were randomly assigned as follows: 199 to the transplantation group and 200 to the no transplantation group; 203 were randomly assigned to R-CHOP-14 and 196 to R-MegaCHOP-14 (figure 2). The last day of follow-up (and the data cutoff date) was Jan 26, 2016. Histology was centrally reviewed in 359 (90%) of 399 patients. 13 patients were excluded before randomisation, because of different histological subtypes (ten patients) and active hepatitis B or C virus (three patients). All patients were included in the analysis.

The main clinical characteristics are summarised in table 1, and all characteristics were balanced between patients treated with or without transplantation.

All 399 randomised patients started the treatment: 148 (74%) of 199 patients completed the programme in the transplantation group and 177 (88%) of 200 in the no transplantation group. Four (2%) of 199 patients in the transplantation group did not undergo autologous stem-cell transplantation because of insufficient peripheral blood stem-cell harvest.

Dose reductions during chemotherapy occurred in 28 (7%) of 399 patients, all during the dose-dense chemo-immunotherapy phase, and were equally distributed among the four groups: doxorubicin and cyclophosphamide doses were reduced in seven patients because of neutropenia (one on R-CHOP-14 and six on R-MegaCHOP-14), and the vincristine dose was reduced or not given in 21 patients because of constipation or neurological adverse events (12 on R-CHOP-14 and ten on R-MegaCHOP-14).

The median relative dose intensities per patient for eight cycles of R-CHOP-14 and six cycles of R-MegaCHOP-14 were as follows: 91·4% (IQR 81·1–97·5) versus 88·1% (79·8–98·4) of the planned doses for rituximab, 89·9% (81·7–96·6) versus 87·7% (77·8–97·6) for cyclophosphamide, 89·0% (78·3–97·0) versus 88·8% (75·4–97·0) for doxorubicin, and 89·6% (78·1–98·8) versus 89·9% (78·9–100·0) for vincristine. 159 (89%) of 178 patients deemed at risk for CNS recurrence received the planned intrathecal chemotherapy prophylaxis. G-CSF support was given in 2308 (89%) of 2582 chemotherapy courses.

In the whole population, after a median follow-up of 72 months (IQR 57–88), 2-year failure-free survival was 66% (95% CI 62–71), overall survival 82% (78–86), and progression-free survival 69% (64–73); 5-year failure-free survival was 64% (95% CI 59–68), overall survival 77% (73–81), and progression-free survival 66% (61–70) for the whole population. When stratified according to aa-IPI score, 2-year failure-free survival was 70% (95% CI 64–75) for aa-IPI score 2 and 57% (47–66) for aa-IPI score 3; 5-year overall survival was 81% (95% CI 76–85) for aa-IPI score 2 and 69% (58–77) for aa-IPI score 3 (appendix pp 11, 12).

Patients randomly assigned to receive transplantation had significantly better 2-year failure-free survival than did those who did not receive transplantation (60 events; 71% [95% CI 64–77] vs 83 events; 62% [55–68]; HR 0·65

412 patients enrolled

13 excluded
  10 non DLBCL or FLG3b lymphoma
  3 active hepatitis

399 patients randomly assigned

n=96
R-MegaCHOP-14 (4 cycles) plus
R-MAD (2 cycles) plus BEAM plus ASCT

n=103
R-CHOP-14 (4 cycles) plus
R-MAD (2 cycles) plus BEAM plus ASCT

n=100
R-MegaCHOP-14 (6 cycles)

n=100
R-CHOP-14 (8 cycles)

96 began R-MegaCHOP (4 cycles)

103 began R-CHOP (4 cycles)

100 began R-MegaCHOP (4 cycles)

100 began R-CHOP (4 cycles)

10 discontinuations during
R-MegaCHOP
  2 deaths
  1 disease progression
  2 voluntary withdrawals
  4 adverse events
  1 investigator decision

9 discontinuations during
R-CHOP
  1 death
  5 disease progression
  2 voluntary withdrawals
  1 adverse event

15 discontinuations during
R-MegaCHOP
  4 deaths
  5 disease progression
  4 voluntary withdrawals
  1 adverse event
  1 investigator decision

6 discontinuations during
R-CHOP
  1 death
  4 disease progression
  1 investigator decision

86 began R-MAD (2 cycles)

94 began R-MAD (2 cycles)

85 began R-MegaCHOP (2 cycles)

94 began R-CHOP (4 cycles)

17 discontinuations during
R-MAD
  2 deaths
  8 disease progression
  3 adverse events
  3 investigator decision
  1 poor mobiliser

13 discontinuations during
R-MAD
  1 death
  2 disease progression
  2 voluntary withdrawals
  4 adverse events
  1 investigator decision
  3 poor mobilisers

2 discontinuations during
R-CHOP
  1 disease progression
  1 adverse event

69 began BEAM plus ASCT

81 began BEAM plus ASCT

1 death

1 death

68 completed treatment

80 completed treatment

85 completed treatment

92 completed treatment

96 included in the efficacy and safety analyses

103 included in the efficacy and safety analyses

100 included in the efficacy and safety analyses
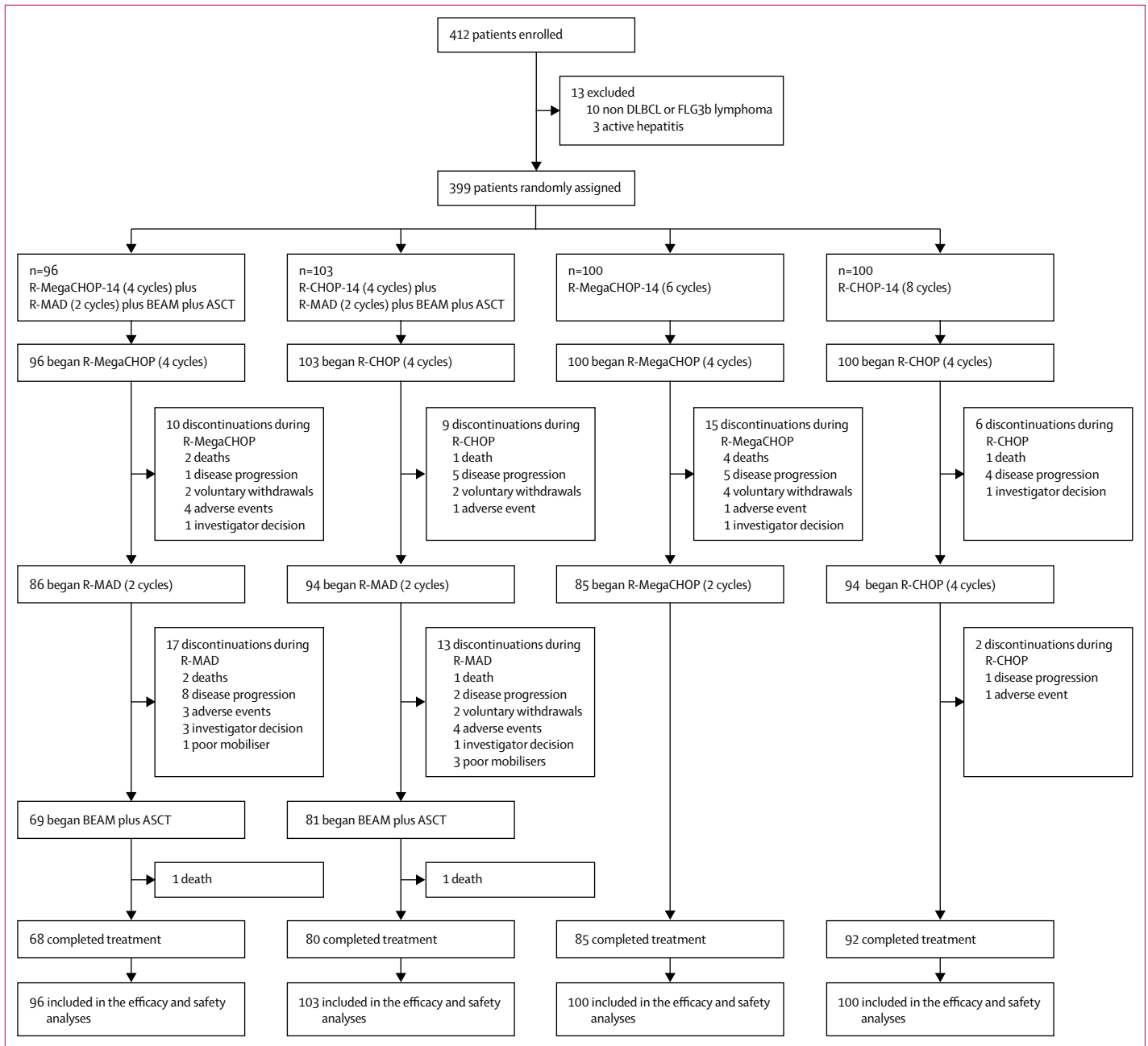
100 included in the efficacy and safety analyses

Figure 2: Patient flow

DLBC=diffuse large B-cell lymphoma. FLG3b=follicular grade 3b lymphoma. R-CHOP-14=dose-dense rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone delivered in a 14-day cycle. R-MegaCHOP-14=dose-dense intensified R-CHOP delivered in a 14-day cycle. R-MAD=rituximab plus high-dose cytarabine plus mitoxantrone plus dexamethasone. BEAM=carmustine, etoposide, cytarabine, and melphalan. ASCT=autologous stem-cell transplantation. Poor mobiliser=insufficient peripheral blood stem-cell harvest.

[95% CI, 0·47–0·91]; stratified log-rank test p=0·012; figure 3A). No difference in 2-year failure-free survival was observed between patients receiving R-CHOP-14 and those receiving R-MegaCHOP-14 (72 events; 67% [95% CI 60–73] vs 71 events; 66% [59–72]; HR 1·04 [95% CI 0·75–1·45]; stratified log-rank test p=0·77; figure 3B). At the time of this analysis, after 45 deaths in the transplantation group and 46 deaths in the no transplantation group, no differences in overall survival were observed: 5-year overall survival was 78% (95% CI 71–83) versus 77% (95% CI 71–83; HR 0·98 [95% CI 0·65–1·48]; stratified log-rank test p=0·91; figure 3A). After 44 deaths in the R-CHOP-14 group and 47 deaths in the R-MegaCHOP-14 group, 5-year overall survival was 79% (95% CI 73–84) versus 76% (69–81; HR 1·14 [95% CI 0·76–1·72]; stratified log-rank test p=0·54; figure 3B).

In aa-IPI score 2 patients, 2-year failure-free survival was 75% (95% CI 67–81, n=39 events) for those in the transplantation group versus 65% (57–72, n=54 events) for those in the no transplantation group (HR 0·65 [95% CI 0·43–0·98]; p=0·038); 5-year overall survival was 81% (95% CI 73–86, n=29 events) versus 81% (73–86, n=29 events; HR 0·99 [95% CI 0·59–1·66]; p=0·99; figure 3C). In aa-IPI score 3 patients, 2-year failure-free survival was 62% (95% CI 47–73, n=21 events) versus 52% (38–64, 29 events; HR 0·67 [95% CI 0·38–1·17]; p=0·16); 5-year overall survival was 69% (95% CI 55–80, n=16 events) versus 68% (53–79, n=17 events; HR 0·96 [0·48–1·90]; p=0·90; figure 3D).

A complete response or unconfirmed complete response at the end of treatment (at the end of 8 cycles of R-CHOP-14, 6 cycles of R-MegaCHOP-14, or R-CHOP-14/R-MegaCHOP-14 plus R-MAD plus BEAM plus autologous stem-cell transplantation) was achieved in 295 (74%) of 399 patients, a partial response in 27 (7%), and progressive disease during treatment or no response in 47 (12%); there were also 13 (3%) deaths during treatment and 17 patients (4%) were not evaluable for response because of voluntary withdrawal or investigator choice. 151 (76%) of 199 patients in the transplantation group achieved a complete response or unconfirmed complete response versus 144 (72%) of 200 in the no transplantation group (p=0·38); partial responses were achieved in six (3%) versus 21 (11%), and no responses were achieved in 23 (12%) versus 24 (12%).

After 58 progression events in the transplantation group and 76 progression events in the no transplantation group, 2-year progression-free survival was 72% (95% CI 65–78) versus 65% (95% CI 58–71; HR 0·72 [95% CI 0·51–1·01]; stratified log-rank test p=0·064).

Transplantation was favoured irrespective of which rituximab-dose-dense chemotherapy was received (figure 4). The benefit of transplantation on failure-free survival was maintained across all planned (type of rituximab-dose-dense chemotherapy, aa-IPI score, age, bone marrow involvement) and unplanned (sex and histology) subgroups (figure 4). The comparison between R-CHOP-14 and R-MegaCHOP-14 was homogeneous across patient subgroups.

The per-protocol analysis of failure-free survival, comprising 359 (90%) of 399 patients who started the second treatment phase (180 in the transplantation group, 179 in the no transplantation group), was consistent with the intention-to-treat analysis: 2-year failure-free survival in the transplant group was 74% (95% CI 67–80, n=49 events) and 68% (60–74, n=65 events) in the no transplantation group (HR 0·68 [95% CI 0·47–0·99]; stratified log-rank test p=0·039).
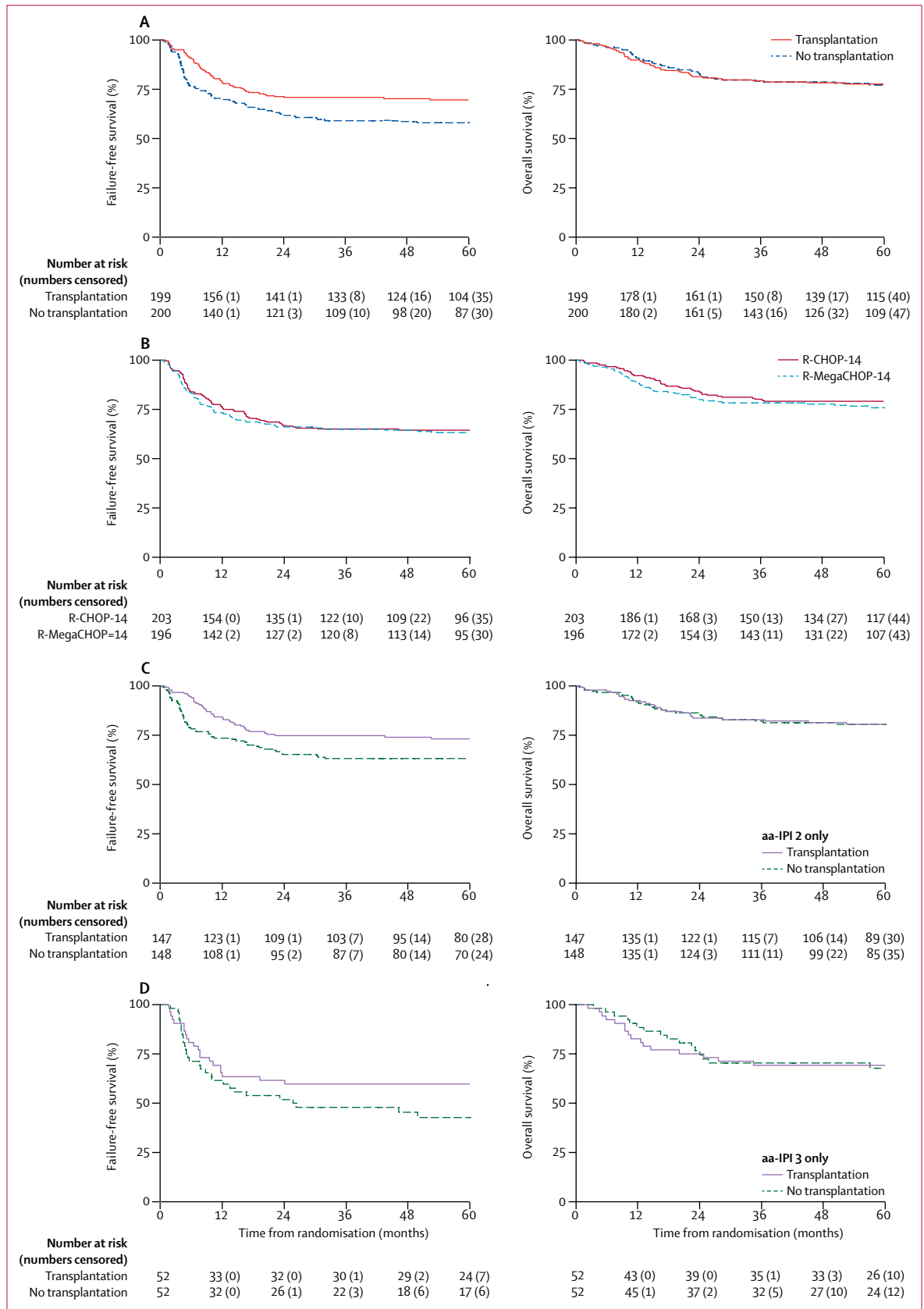
Of the 199 patients randomly assigned to receive transplantation, treatment was unsuccessful in 43 (22%); salvage regimens were chemotherapy in all patients,

	No transplantation* (n=200)	Transplantation† (n=199)	R-CHOP-14 (n=203)	R-MegaCHOP-14 (n=196)
Age at enrolment, years (median, IQR)	49 (38–56)	48 (36–56)	48 (37–55)	50 (38–56)
Sex				
Male	107 (54%)	108 (54%)	99 (49%)	116 (59%)
Female	93 (46%)	91 (46%)	104 (51%)	80 (41%)
Age-adjusted IPI score				
2	148 (74%)	147 (74%)	151 (74%)	144 (73%)
3	52 (26%)	52 (26%)	52 (26%)	52 (27%)
Histology				
Diffuse large B-cell lymphoma	181 (90%)	172 (86%)	188 (93%)	165 (84%)
Primary mediastinal B-cell lymphoma	4 (2%)	12 (6%)	5 (2%)	11 (6%)
Non-Hodgkin lymphoma follicular grade 3b	5 (2%)	5 (3%)	3 (1%)	7 (4%)
Transformed diffuse large B-cell lymphoma	10 (5%)	9 (5%)	6 (3%)	13 (7%)
Missing data	0	1 (1%)	1 (0%)	0 (0%)
Ann Arbor staging				
II	16 (8%)	9 (5%)	10 (5%)	15 (8%)
III	49 (24%)	66 (33%)	59 (29%)	56 (29%)
IV	135 (68%)	124 (62%)	134 (66%)	125 (64%)
ECOG performance status				
0	45 (22%)	55 (28%)	53 (26%)	47 (24%)
1	64 (32%)	62 (31%)	61 (30%)	65 (33%)
2	79 (40%)	72 (36%)	78 (38%)	73 (37%)
3	11 (6%)	10 (5%)	10 (5%)	11 (6%)
4	1 (<1%)	..	1 (<1%)	0
Bulky disease	64 (32%)	60 (30%)	59 (29%)	65 (33%)
Number of extranodal sites (>1)	63 (32%)	64 (32%)	64 (32%)	63 (32%)
Systemic symptoms				
A	103 (52%)	102 (51%)	108 (53%)	97 (49%)
B	97 (48%)	96 (48%)	94 (46%)	99 (51%)
Missing data	0	1 (1%)	1 (<1%)	0
Abnormal lactate dehydrogenase	178 (89%)	179 (90%)	178 (88%)	179 (91%)
Bone marrow involvement				
No	155 (78%)	159 (80%)	159 (78%)	155 (79%)
Yes	45 (22%)	39 (20%)	43 (21%)	41 (21%)
Missing data	0	1 (1%)	1 (<1%)	0

Diagnosis made on the basis of the WHO classification and includes diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and non-Hodgkin lymphoma follicular grade 3b. R-CHOP-14=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. R-MegaCHOP-14=R-CHOP-14 with higher-dose cyclophosphamide and doxorubicin. IPI=International Prognostic Index. ECOG=Eastern Cooperative Oncology Group. A=absence of systemic symptoms. B=presence of systemic symptoms. *Full course of rituximab-dose-dense chemotherapy. †Abbreviated rituximab-dose-dense chemotherapy plus R-MAD (rituximab plus high-dose cytarabine plus mitoxantrone and dexamethasone) plus BEAM (carmustine, etoposide, cytarabine, and melphalan) and autologous stem-cell transplantation.

Table 1: Baseline characteristics of patients

followed by further autologous or allogeneic transplantation in 12. Of the 200 patients in the no transplantation group, treatment was unsuccessful in 67 (34%); all patients underwent second-line treatment with chemotherapy, followed by transplantation in 37

***Figure 3*: Kaplan-Meier estimates of failure-free survival and overall survival**
(A) Failure-free survival and overall survival in the abbreviated rituximab-dose-dense chemotherapy plus R-MAD (rituximab plus high-dose cytarabine plus mitoxantrone plus dexamethasone) plus BEAM (carmustine, etoposide, cytarabine, and melphalan) and autologous stem-cell transplantation (ASCT) group (transplantation) versus the full-course rituximab-dose-dense chemotherapy group (no transplantation). (B) Failure-free survival and overall survival in the full-course rituximab-dose-dense chemotherapy groups: R-CHOP-14 (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) versus R-MegaCHOP-14 (intensified R-CHOP-14). (C) Failure-free survival and overall survival for age-adjusted International Prognostic Index (aa-IPI) score 2 patients within the transplantation and no transplantation groups. (D) Failure-free survival and overall survival for aa-IPI score 3 patients within the transplantation and no transplantation groups.
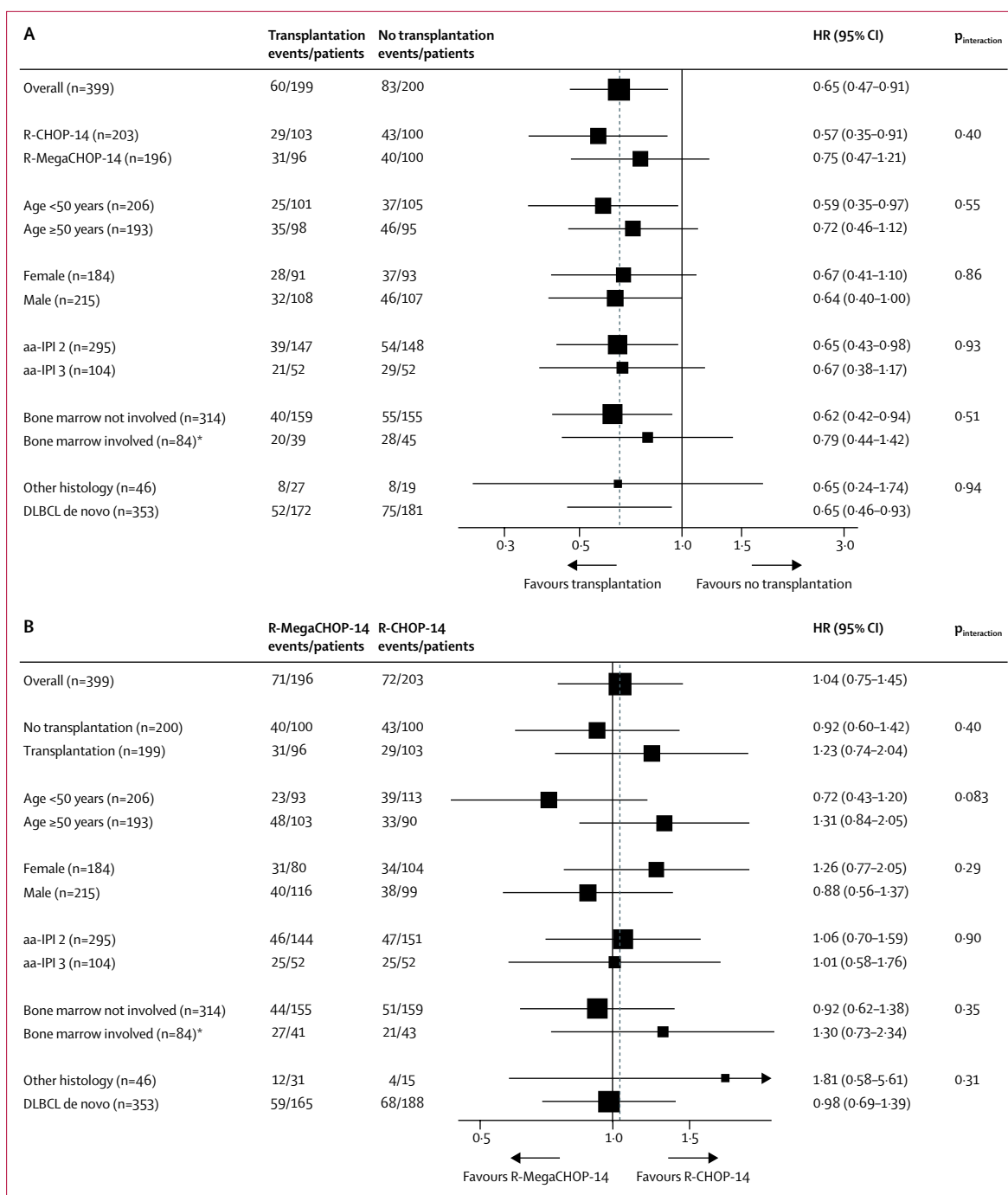
A

	Transplantation events/patients	No transplantation events/patients	HR (95% CI)	$p_{interaction}$
Overall (n=399)	60/199	83/200	0·65 (0·47–0·91)	
R-CHOP-14 (n=203)	29/103	43/100	0·57 (0·35–0·91)	0·40
R-MegaCHOP-14 (n=196)	31/96	40/100	0·75 (0·47–1·21)	
Age <50 years (n=206)	25/101	37/105	0·59 (0·35–0·97)	0·55
Age ≥50 years (n=193)	35/98	46/95	0·72 (0·46–1·12)	
Female (n=184)	28/91	37/93	0·67 (0·41–1·10)	0·86
Male (n=215)	32/108	46/107	0·64 (0·40–1·00)	
aa-IPI 2 (n=295)	39/147	54/148	0·65 (0·43–0·98)	0·93
aa-IPI 3 (n=104)	21/52	29/52	0·67 (0·38–1·17)	
Bone marrow not involved (n=314)	40/159	55/155	0·62 (0·42–0·94)	0·51
Bone marrow involved (n=84)*	20/39	28/45	0·79 (0·44–1·42)	
Other histology (n=46)	8/27	8/19	0·65 (0·24–1·74)	0·94
DLBCL de novo (n=353)	52/172	75/181	0·65 (0·46–0·93)	

0·3 0·5 1·0 1·5 3·0
←Favours transplantation   Favours no transplantation→

B

	R-MegaCHOP-14 events/patients	R-CHOP-14 events/patients	HR (95% CI)	$p_{interaction}$
Overall (n=399)	71/196	72/203	1·04 (0·75–1·45)	
No transplantation (n=200)	40/100	43/100	0·92 (0·60–1·42)	0·40
Transplantation (n=199)	31/96	29/103	1·23 (0·74–2·04)	
Age <50 years (n=206)	23/93	39/113	0·72 (0·43–1·20)	0·083
Age ≥50 years (n=193)	48/103	33/90	1·31 (0·84–2·05)	
Female (n=184)	31/80	34/104	1·26 (0·77–2·05)	0·29
Male (n=215)	40/116	38/99	0·88 (0·56–1·37)	
aa-IPI 2 (n=295)	46/144	47/151	1·06 (0·70–1·59)	0·90
aa-IPI 3 (n=104)	25/52	25/52	1·01 (0·58–1·76)	
Bone marrow not involved (n=314)	44/155	51/159	0·92 (0·62–1·38)	0·35
Bone marrow involved (n=84)*	27/41	21/43	1·30 (0·73–2·34)	
Other histology (n=46)	12/31	4/15	1·81 (0·58–5·61)	0·31
DLBCL de novo (n=353)	59/165	68/188	0·98 (0·69–1·39)	

0·5 1·0 1·5
←Favours R-MegaCHOP-14   Favours R-CHOP-14→

Figure 4: Subgroup analysis of failure-free survival
(A) Failure-free survival in subgroups comparing the abbreviated rituximab-dose-dense chemotherapy plus R-MAD (rituximab plus high-dose cytarabine plus mitoxantrone plus dexamethasone) plus BEAM (carmustine, etoposide, cytarabine, and melphalan) and autologous stem-cell transplantation (ASCT) group (transplant) versus the full-course rituximab-dose-dense chemotherapy group (no transplant). (B) Failure-free survival in subgroups comparing R-MegaCHOP-14 (intensified R-CHOP-14) versus R-CHOP-14 (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). The area of the squares is proportional to the sample size. The vertical dashed line is the hazard ratio (HR) of the comparison in the whole population. aa-IPI=age-adjusted International Prognostic Index. DLBCL=diffuse large B-cell lymphoma. *Missing data for bone marrow involvement (see table 1).

(36 autologous, one allogeneic). CNS relapses were observed in eight patients, two in the transplantation group and six in the no transplantation group.

Grade 3 or worse haematological adverse events were reported in 183 (92%) of 199 patients in the transplantation group versus 135 (68%) of 200 patients in the no

transplantation group. Grade 3 or worse non-haematological adverse events were reported in 90 (45%) versus 31 (16%); the most common grade 3 or worse non-haematological adverse event was gastrointestinal (49 [25%] vs 19 [10%]). Adverse events are shown in table 2.

Adverse events resulted in treatment discontinuation for 12 patients in the transplantation group (infections in six patients, prolonged neutropenia in four, gastrointestinal in one, and cardiac in one) and two patients in the no transplantation group (infection in one patient, prolonged neutropenia in one patient).

Treatment-related deaths occurred in 13 (3%) of 399 patients: eight (4%) of 199 patients in the transplantation group versus five (3%) of 200 patients in the no transplantation group. Causes of treatment-related deaths were Gram-negative pneumonia complicated by septic shock (n=7), gastrointestinal complications (toxic megacolon or haemorrhagic colitis; n=2), cachexia (n=1), cardiac failure (n=1), encephalitis (n=1), and multiorgan failure (n=1).

Secondary malignancies were reported in five (1%) of 399 patients: two solid tumours (one osteogenic sarcoma in a non-irradiated area and one not specified) in the 199 patients in the transplantation group; and one acute myeloid leukaemia 1 year after therapy while in complete remission and two solid tumours (one thyroid and one urothelial carcinoma, both in non-irradiated areas) in the 200 patients in the no transplantation group.

Discussion

The results of this randomised, phase 3 study show an improvement in failure-free survival for patients who received abbreviated rituximab-dose-dense chemotherapy plus R-MAD plus BEAM and autologous stem-cell transplantation (transplantation group) compared with patients who received full course rituximab-dose-dense chemotherapy (no transplantation group), although the hypothesised absolute improvement of 15% was not observed. This statistically significant but not clinically meaningful improvement in failure-free survival did not translate into any overall survival advantage. Increasing

	No transplantation* (1309 cycles, 200 patients)				Transplantation† (1273 cycles, 199 patients)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Number of cycles in which haematological adverse events and febrile neutropenia were reported								
Haematological	378 (29%)	144 (11%)	234 (18%)	1 (0%)	229 (19%)	136 (11%)	517 (40%)	1 (0%)
Granulocytes	171 (13%)	105 (8%)	215 (16%)	1 (0%)	113 (9%)	111 (9%)	492 (38%)	0
Haemoglobin	499 (38%)	43 (3%)	8 (1%)	0	518 (42%)	137 (11%)	46 (4%)	0
Platelets	119 (9%)	19 (1%)	11 (1%)	1 (0%)	120 (10%)	76 (6%)	348 (27%)	1 (0%)
White blood counts	219 (17%)	158 (12%)	177 (14%)	1 (0%)	155 (13%)	126 (10%)	471 (37%)	0
Febrile neutropenia	19 (1%)	4 (0%)	1 (0%)	0	61 (5%)	28 (2%)	2 (0%)	0 (0%)
Number of patients with haematological adverse events or febrile neutropenia								
Haematological	40 (20%)	37 (19%)	97 (49%)	1 (1%)‡	3 (2%)	19 (10%)	163 (82%)	1 (1%)‡
Granulocytes	28 (14%)	27 (14%)	93 (47%)	1 (1%)‡	4 (2%)	20 (10%)	158 (79%)	0
Haemoglobin	113 (57%)	31 (16%)	5 (3%)	0	70 (35%)	78 (39%)	33 (17%)	0
Platelets	48 (24%)	7 (4%)	11 (6%)	1 (1%)‡	9 (5%)	16 (8%)	150 (75%)	1 (1%)‡
White blood counts	35 (18%)	38 (19%)	84 (42%)	1 (1%)‡	3 (2%)	22 (11%)	160 (80%)	0
Febrile neutropenia	14 (7%)	4 (2%)	1 (1%)	0	39 (20%)	22 (11%)	2 (1%)	0
Number of patients with non-haematological adverse events								
Non-haematological	98 (49%)	24 (12%)	6 (3%)	1 (1%)‡	74 (37%)	68 (34%)	18 (9%)	4 (2%)‡
Cardiac	10 (5%)	1 (1%)	0	0	12 (6%)	2 (1%)	1 (1%)	0
Gastrointestinal	63 (32%)	16 (8%)	2 (1%)	1 (1%)‡	66 (33%)	37 (19%)	12 (6%)	0
Haemorrhagic	3 (2%)	0	0	0	5 (3%)	5 (3%)	1 (1%)	2 (1%)‡
Hepatic or pancreatic, or both	15 (8%)	3 (2%)	0	0	15 (8%)	4 (2%)	0	0
Infective	21 (11%)	0	2 (1%)	0	14 (7%)	18 (9%)	2 (1%)	2 (1%)‡
Metabolic	5 (3%)	0	0	0	10 (5%)	2 (1%)	0	0
Neurological	58 (29%)	2 (1%)	1 (1%)	0	26 (13%)	2 (1%)	0	0
Pulmonary	3 (2%)	1 (1%)	1 (1%)	0	8 (4%)	4 (2%)	3 (2%)	1 (1%)‡
Renal failure	0	0	0	1 (1%)‡	4 (2%)	0	0	0
Vascular	10 (5%)	2 (1%)	0	0	8 (4%)	2 (1%)	1 (1%)	0

*Full course of rituximab-dose-dense chemotherapy. †Abbreviated rituximab-dose-dense chemotherapy plus R-MAD (rituximab plus high-dose cytarabine plus mitoxantrone and dexamethasone) plus BEAM (carmustine, etoposide, cytarabine, and melphalan) and autologous stem-cell transplantation. ‡13 treatment-related deaths; more than one adverse event occurred in each patient.

Table 2: **Haematological and non-haematological adverse events**

the dose of standard R-CHOP did not have an effect on failure-free survival or overall survival.

We used failure-free survival as a primary endpoint because it has been used as a primary endpoint in the majority of diffuse large B-cell lymphoma randomised trials,[1,4] with the assumption that a difference in progression-free survival, failure-free survival, or event-free survival usually translates into a difference in overall survival. The absence of an effect on overall survival in our study could have several causes. First, failure-free survival is usually similar to overall survival in a general diffuse large B-cell lymphoma population that includes elderly patients (older than 65 years), and it therefore might not be a valid surrogate of overall survival in patients younger than 65 years in whom salvage chemotherapy with autologous stem-cell transplantation is more likely to be feasible and effective, which could abrogate the difference in overall survival. Second, a significant improvement in failure-free survival in the transplantation group was seen only in patients at intermediate-high risk (aa-IPI score 2) and not in the high-risk (aa-IPI score 3) group, possibly lowering the power of the comparison; however, the number of patients in the high-risk group was too small to provide a definite conclusion. Moreover, in our study, we aimed to achieve a 15% improvement in 2-year failure-free survival for the transplantation group compared with the no transplantation group; the treatment groups were significantly different, but the improvement was only 9%. Salvage treatment was also more intensive in the control group than in the transplantation group, since roughly 50% of relapsed patients underwent transplant as second-line treatment. This observation is reassuring, suggesting that high-dose chemotherapy plus autologous stem-cell transplantation could be selectively given only when needed and not to every high-risk patient.

The other primary objective of our study was the comparison of two different dose levels of chemotherapy (R-CHOP-14 *vs* R-MegaCHOP-14). No difference in efficacy was shown between the two regimens, and R-MegaCHOP-14 was more affected by side-effects than R-CHOP-14 (appendix p 13). The frequency of febrile neutropenia in this study was lower than reported in the literature; this was probably because the use of G-CSF and pneumocystis pneumonia prophylaxis were mandatory in our trial. Although better results with an intensified R-CHOP-like regimen (ie, ACVBP followed by sequential consolidation) have been reported, they were seen only in low-risk patients.[18] Our study enrolled only intermediate-high-risk or high-risk patients, and the findings do not support the hypothesis that increasing the dose of R-CHOP improves outcomes in patients with diffuse large B-cell lymphoma who are at high risk.

It is difficult to assess which component of the high-dose approach was most likely to be responsible for the high efficacy of the transplantation treatment. In our view, the efficacy of this scheme might be explained by the rapid tumour reduction during the first part of dose-dense chemoimmunotherapy, and by the addition of non-cross-resistant high-dose cytarabine chemotherapy supplemented with rituximab, which further increases the response and avoids the onset of resistant clones. However, the protocol required intermediate assessment of response after the abbreviated rituximab-dose-dense chemotherapy phase and only responding patients proceeded to R-MAD and BEAM plus autologous stem-cell transplantation, so there were not enough data to make definite conclusions.

The role of intensification with autologous stem-cell transplantation as first-line treatment in high risk diffuse large B-cell lymphoma has been a matter of debate for several years. Several phase 2 and phase 3 trials were done in this setting; intensification with upfront autologous transplantation showed improved progression-free survival compared with standard chemoimmunotherapy in some studies, without differences in overall survival probably because of the effectiveness of transplantation in the salvage setting. In the SWOG-9704 trial,[19] 253 complete responders (after receiving CHOP with or without rituximab) were randomly assigned to receive autologous stem-cell transplantation or to continuation of the same chemotherapy. 2-year progression-free survival was 69% in the transplantation group versus 55% in the control group, but overall survival was not improved by transplantation except in true high-risk patients (aa-IPI score 3) in a subgroup analysis.[19] As acknowledged by the authors, this analysis was not preplanned and the study was not powered for this subgroup analysis. However, these results suggest that high-dose chemotherapy plus consolidation with autologous stem-cell transplantation might benefit selected high-risk patients, as recognised by some guidelines.[20,21]

In the DSHNHL 2002-1 trial,[22] young untreated patients with diffuse large B-cell lymphoma with poor prognosis were randomly assigned to receive R-CHOP-14 plus etoposide (R-CHOEP-14) or R-MegaCHOEP-14. In this trial, patients with an aa-IPI score of 2 had significantly better outcomes in the R-CHOEP-14 group than in the R-MegaCHOEP-14 group, while no differences were reported in patients with an aa-IPI score of 3. The study concluded that R-MegaCHOEP-14 was not superior to conventional R-CHOEP-14 in terms of efficacy and was associated with significantly increased toxicity. A proper comparison with our results is difficult because the control group of the German trial was different as a result of the addition of etoposide to R-CHOP-14. Whether R-CHOEP is superior to R-CHOP in patients with diffuse large B-cell lymphoma is an unanswered question.

In the GITIL trial[23] and the GOELAMS 075 trial,[24] no differences in progression-free survival and overall survival were reported in the autologous stem-cell transplantation groups versus standard groups.

Some limitations of this study include the selection of failure-free survival as primary endpoint, which might not have been appropriate in a young population

(younger than 65 years), and the small number of aa-IPI 3 patients enrolled.

On the basis of the findings of all this and other phase 3 studies, the available data do not support further consideration of the use of high-dose chemotherapy with upfront autologous stem-cell transplantation in young, intermediate-high-risk or high-risk patients with diffuse large B-cell lymphoma.

The pathological and molecular heterogeneity of diffuse large B-cell lymphoma has now been better elucidated, leading to the study of new agents that might have different activity in molecular subtypes or have specific efficacy on molecular targets involved in disease pathogenesis.[25–27] Biomarker studies, including cell-of-origin analysis based on immunohistochemistry and gene expression profiling with nanostring assay, and FISH analysis for *MYC*, *BCL2*, and *BCL6*, are still ongoing for the DLCL04 study.

A better knowledge of the disease could represent a new era aimed at selecting tailored treatment based not only on IPI risk score but also targeting the biological complexity and molecular genetics of patients with diffuse large B-cell lymphoma. The addition of novel drugs such as lenalidomide, ibrutinib, bortezomib, and others to standard R-CHOP regimens has been reported in phase 1 or 2 studies with promising results in high-risk patients as well, leading to ongoing phase 3 randomised trials to assess the efficacy of these strategies.[28–32] While awaiting the results of these randomised studies, the standard treatment in patients with diffuse large B-cell lymphoma at intermediate-high and high risk remains chemoimmunotherapy based on the standard R-CHOP regimen.

Contributors
UV, ACh, MM, EA, EB, MB, and GC designed the study. ACh, MM, EA, EB, AMC, CS, GR, MB, FM, GG, VP, LR, FZ, AD'A, NC, ER, ACa, MG, AGC, MGC, and AT recruited patients and obtained study data. CA and SAP were responsible for histological review. AE and GC did the biometric analyses. ACh, MM, EA, GC, and UV analysed and interpreted data, and wrote the report. All authors reviewed and approved the final report.

Declaration of interests
ACh is on the advisory board of Celgene, and reports lecture fees from Amgen, Celgene, Janssen, Nanostring, Pfizer, Roche, and Teva. MM is on the advisory board of Roche, Janssen, Celgene, Mundipharma, and Teva, and reports lecture fees from Roche, Celgene, and Janssen. EA is on the advisory board of Novartis, Roche, Jazz, and Amgen, on the steering committee of Novartis Oncology, data monitoring committee of Celgene, and has received consultancy fees from Celgene. GR is on the advisory board of Celgene, Roche, Janssen, Gilead, Teva, and Amgen. MB is on the advisory board of Celgene, Takeda, and Teva, and reports lecture fees from Roche. FM is on the advisory board of Roche and Celgene, and reports lecture fees from Gilead, Janssen, Mundipharma, Pfizer, Roche, Takeda, and Teva. GG is on the advisory board of Roche, Janssen, Gilead, Amgen, and AbbVie. FZ is on the advisory board of Janssen, Novartis, Sandoz, Roche, and Celgene; reports lecture fees from Roche, Novartis, Gilead, Teva, and BMS; and reports study research funding from Roche, Novartis, and Celgene. SAP reports lecture fees from Takeda. UV is on the advisory board of Roche, Janssen, and Celgene, and reports lecture fees from Roche, Celgene, Janssen, Gilead, and Takeda. All other authors declare no competing interests.

References
1 Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; **346:** 235–42.
2 The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993; **329:** 987–94.
3 Ziepert M, Hasenclever D, Kuhnt E, et al. Standard international prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010; **28:** 2373–80.
4 Greb A, Bohlius J, Trelle S, et al. High-dose chemotherapy with autologous stem cell support in first-line treatment of aggressive non-Hodgkin lymphoma—results of a comprehensive meta-analysis. *Cancer Treat Rev* 2007; **33:** 338–46.
5 Tarella C, Zanni M, Di Nicola M, et al. Prolonged survival in poor-risk diffuse large B-cell lymphoma following front-line treatment with rituximab-supplemented, early intensified chemotherapy with multiple autologous hematopoietic stem cell support: a multicenter study by GITIL (Gruppo Italiano Terapie Innovative nei Linfomi). *Leukemia* 2007; **21:** 1802–11.
6 Fitoussi O, Belhadj K, Mounier N, et al. Survival impact of rituximab combined with ACVBP panel upfront consolidation autotransplantation in high risk diffuse large B-cell lymphoma for GELA. *Haematologica* 2011; **96:** 1136–43.
7 Glass B, Kloess M, Reisen M, et al. Repetitive high-dose therapy followed by autologous stem cell transplantation (MegaCHOEP) for primary treatment of aggressive NHL: the impact of Rituximab on outcome and toxicity. *Bone Marrow Transpl* 2006; **37:** S27.
8 Vitolo U, Chiappella A, Angelucci E, et al. Dose-dense and high-dose chemotherapy plus rituximab with autologous stem cell transplantation for primary treatment of diffuse large B-cell lymphoma with a poor prognosis: a phase II multicenter study. *Haematologica* 2009; **94:** 1250–58.
9 Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol* 2008; **9:** 105–16.
10 Mills W, Chopra R, McMillan A, et al. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol* 1995; **13:** 588–95.
11 Barosi G, Carella A, Lazzarino M, et al. Management of nodal indolent (non marginal-zone) non-Hodgkin's lymphomas: practice guidelines from the Italian Society of Hematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation. *Haematologica* 2005; **90:** 1236–57.
12 Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non Hodgkin's lymphomas. *J Clin Oncol* 1999; **17:** 1244–53.
13 Dixon DO, McLaughlin P, Hagemeister FB, et al. Reporting outcomes in Hodgkin's disease and lymphoma. *J Clin Oncol* 1987; **5:** 1670–72.
14 Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25:** 579–86.
15 Kaplan EL, Meier P. Nonparametric estimation from incomplete information. *J Am Stat Assoc* 1958; **53:** 547–81.
16 Cox DR. Regression model and life tables (with discussion). *J R Stat Soc* 1972; **34:** 187–222.
17 Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994; **81:** 515–26.
18 Reyes F, Lepage E, Ganem G, et al. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. *N Engl J Med* 2005; **352:** 1197–205.
19 Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 2013; **369:** 1681–90.
20 Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26** (suppl 5)**:** v116–25.

21   Zelenetz AD, Gordon LI, Wierda WG, et al. Diffuse large B-cell lymphoma version 1.2016. *J Natl Compr Canc Netw* 2016; **14:** 196–231.

22   Schmitz N, Nickelsen M, Ziepert M, et al, for the German High-Grade Lymphoma Study Group (DSHNHL). Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: an open-label, randomised, phase 3 trial (DSHNHL 2002-1). *Lancet Oncol* 2012; **13:** 1250–59.

23   Cortelazzo S, Tarella C, Gianni AM, et al. Randomized trial comparing R-CHOP versus high-dose sequential chemotherapy in high-risk patients with diffuse large B-cell lymphomas. *J Clin Oncol* 2016; **34:** 4015–22.

24   Le Gouill S, Milpied NJ, Lamy T, et al. First-line rituximab (R) high-dose therapy (R-HDT) versus R-CHOP14 for young adults with diffuse large B-cell lymphoma: preliminary results of the GOELAMS 075 prospective multicenter randomized trial [abstract]. *Proc Am Soc Clin Oncol* 2011; **29** (suppl)**:** abstr 8003.

25   Bachy E, Salles G. Treatment approach to newly diagnosed diffuse large B-cell lymphoma. *Semin Hematol* 2015; **52:** 107–18.

26   Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. *Blood* 2015; **125:** 22–32.

27   Scott DW, Mottok A, Ennishi D, et al. Prognostic significance of diffuse large B-cell lymphoma cell of origin determined by digital gene expression in formalin-fixed paraffin-embedded tissue biopsies. *J Clin Oncol* 2015; **33:** 2848–56.

28   Vitolo U, Chiappella A, Franceschetti S, et al. Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial. *Lancet Oncol* 2014; **15:** 730–37.

29   Nowakowski GS, Laplant B, Macon WR, et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-cell lymphoma: a phase II study. *J Clin Oncol* 2015; **33:** 251–57.

30   Nowakowsky GS, Chiappella A, Witzig TE, et al. ROBUST: lenalidomide-R-CHOP versus placebo-R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. *Future Oncol* 2016; **12:** 1553–63.

31   Younes A, Thieblemont C, Morschhauser F, et al. Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B-cell non Hodgkin lymphoma: a non-randomised, phase 1b study. *Lancet Oncol* 2014; **15:** 1019–26.

32   Ruan J, Martin P, Furman RR, et al. Bortezomib plus CHOP-rituximab for previously untreated diffuse large B-cell lymphoma and mantle cell lymphoma. *J Clin Oncol* 2011; **29:** 690–97.