Lenalidomide maintenance after autologous haematopoietic stem-cell transplantation in mantle cell lymphoma: results of a Fondazione Italiana Linfomi (FIL) multicentre, randomised, phase 3 trial

Marco Ladetto, Sergio Cortelazzo*, Simone Ferrero, Andrea Evangelista, Michael Mian, Rita Tavarozzi, Manuela Zanni, Federica Cavallo, Alice Di Rocco, Vittorio Stefoni, Chiara Pagani, Alessandro Re, Annalisa Chiappella, Monica Balzarotti, Vittorio R Zilioli, Maria Gomes da Silva, Luca Arcaini, Anna L Molinari, Filippo Ballerini, Andrés J M Ferreri, Benedetta Puccini, Fabio Benedetti, Piero M Stefani, Franco Narni, Ivana Casaroli, Caterina Stelitano, Giovannino Ciccone, Umberto Vitolo, Maurizio Martelli*

Lancet Haematol 2021; 8: e34–44

See **Comment** page e3

*These authors contributed equally

Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy (M Ladetto MD, R Tavarozzi MD, M Zanni PhD); **Unit of Oncology-Haematology, Humanitas Gavazzeni, Bergamo, Italy** (S Cortelazzo MD); **Department of Molecular Biotechnologies and Health Sciences** (S Ferrero MD, Prof F Cavallo MD), **Clinical Epidemiology** (A Evangelista MSc, G Ciccone MD), **Azienda Ospedaliero** (A Chiappella MD, U Vitolo MD), **Universitaria Città della Salute e della Scienza di Torino and Centre for Cancer Prevention Piemonte, Torino, Italy; Department of Haematology and CBMT, Bolzano Hospital, Bolzano, Italy** (M Mian MD); **Department of Translational and Precision Medicine, Sapienza University of Rome, Roma, Italy** (A Di Rocco PhD, Prof M Martelli MD); **Institute of Haematology L. e A. Seràgnoli, University of Bologna, Bologna, Italy** (V Stefoni MD); **Department of Haematology, ASST-Spedali Civili Hospital, Brescia, Italy** (C Pagani MD, A Re MD); **Haematology Unit, Humanitas Clinical and Research Center - IRCCS – Rozzano, Milano, Italy** (M Balzarotti MD); **Division of Haematology, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy** (V R Zilioli MD); **Haematology Unit, Instituto Portugues de Oncologia de Lisboa Francisco**

Summary

Background Fit patients with mantle cell lymphoma aged 18–65 years are usually given cytarabine and rituximab-based induction regimens followed by autologous haematopoetic stem-cell transplantation (HSCT). We investigated whether post-autologous HSCT maintenance with lenalidomide improves progression-free survival in this population.

Methods This open-label, randomised, multicentre, phase 3 trial was done at 49 haematology and oncology units in Italy and Portugal. Eligible patients had Ann Arbor stage III or IV treatment-naive mantle cell lymphoma (or stage II plus bulky disease [≥5 cm] or B symptoms), and had evidence of cyclin D1 overexpression or the translocation t(11;14)(q13;q32). Patients were aged 18–59 years with Eastern Cooperative Oncology Group (ECOG) performance status 0–3, or aged 60–65 years with ECOG 0–2. After an optional prephase with vincristine and steroids (intravenous vincristine 1·4 mg/m² on day 1, oral prednisone 100 mg [total dose] on days 1–5), patients were given three courses of R-CHOP (21-day cycle, intravenous rituximab 375 mg/m² on day 1; intravenous doxorubicin 50 mg/m², vincristine 1·4 mg/m², and cyclophosphamide 750 mg/m² on day 2; oral prednisone 100 mg/m² on day 2–6). Patients then received one cycle of high-dose CTX (intravenous cyclophosphamide 4 g/m² on day 1, intravenous rituximab 375 mg/m² on day 4). After restaging, patients received two cycles of R-HD-cytarabine (high-dose intravenous cytarabine 2 g/m² every 12 h on days 1–3, intravenous rituximab 375 mg/m² on days 4 and 10). Patients with complete remission or partial remission proceeded to autologous HSCT and responding patients (complete remission or partial remission) with haematological recovery were randomly assigned (1:1) to receive 24 courses of oral lenalidomide maintenance (15 mg per day for patients with platelets >100×10⁹ cells per L or 10 mg per day for platelets 60–100×10⁹ cells per L, days 1–21 every 28 days) for 24 months, or observation. The primary endpoint was progression-free survival, measured in the randomised population. This study is registered with EudraCT (2009–012807–25) and ClinicalTrials.gov (NCT02354313).

Findings Between May 4, 2010, and Aug 24, 2015, 303 patients were screened for inclusion and 300 patients were enrolled (median age 57 years, IQR 51–62; 235 [78%] male). 95 patients were excluded before randomisation, mostly due to disease progression, adverse events, and inadequate recovery. 104 patients were randomly assigned to the lenalidomide maintenance group and 101 patients to the observation group. 11 (11%) of 104 patients assigned to lenalidomide did not start treatment (3 withdrew, 6 adverse events or protocol breach, 2 lost to follow-up). At a median follow-up of 38 months after randomisation (IQR 24–50), 3-year progression-free survival was 80% (95% CI 70–87) in the lenalidomide group versus 64% (53–73) in the observation group (log-rank test p=0·012; hazard ratio 0·51, 95% CI 0·30–0·87). 41 (39%) of 104 patients discontinued lenalidomide for reasons including death or progression. Treatment-related deaths were recorded in two (2%) of 93 patients in the lenalidomide group (1 pneumonia, 1 thrombotic thrombocytopenic purpura), and one (1%) of 101 in the observation group (pneumonia). 59 (63%) of 93 patients in the lenalidomide group had grade 3–4 haematological adverse events versus 12 (12%) of 101 patients in the observation group (p<0·0001). 29 (31%) of 93 patients in the lenalidomide group and eight (8%) of 101 patients in the observation group had grade 3–4 non-haematological adverse events (p<0·0001), of which infections were the most common. Serious adverse events were reported in 22 (24%) of 93 patients in the lenalidomide group and five (5%) of 101 patients in the observation group. Pneumonia and other infections were the most common serious adverse events.

Interpretation Despite non-negligibile toxicity, lenalidomide after autologous HSCT improved progression-free survival in patients with mantle cell lymphoma, highlighting the role of maintenance in mantle cell lymphoma.

Funding Fondazione Italiana Linfomi and Celgene.

Research in context

Evidence before this study

We searched PubMed for full reports of clinical trials published in English before Dec 31, 2008, using the terms "mantle cell lymphoma" and "lenalidomide". No phase 3 randomised clinical trials focusing on young, untreated patients were found. Autologous haematopoietic stem-cell transplantation (HSCT) is considered the gold standard for these patients, and evidence arising from phase 2 studies indicated that inclusion of rituximab and high-dose cytarabine in the induction schedule was beneficial. We speculated that long-term maintenance treatment could be useful in delaying or reducing the pattern of constant relapse. We designed a phase 3 study to assess the benefit of oral maintenance with lenalidomide versus observation after autologous HSCT in patients aged 18–65 years with mantle cell lymphoma.

Added value of this study

Our results indicate that lenalidomide maintenance after first-line autologous HSCT can significantly improve progression-free survival in patients younger than 66 years with mantle cell lymphoma. The recorded toxicity did not preclude a clinically meaningful benefit.

Implications of all the available evidence

Progression-free survival in mantle cell lymphoma is improved by maintenance with several agents that have completely different mechanisms of action. This study, substantiated by results of a randomised phase 3 trial of rituximab maintenance that took place at the same time, provides further evidence of the crucial role of maintenance in the management of mantle cell lymphoma. With a clear benefit to overall and progression-free survival reported in two studies of rituximab maintenance, a combination of rituximab and lenalidomide compared with rituximab alone could be considered for future maintenance trials in both autologous HSCT and non-autologous HSCT-based settings.

Introduction

Mantle cell lymphoma is an uncommon mature lymphoid neoplasm that accounts for approximately 6% of all non-Hodgkin lymphomas and is characterised by the *CCND1-IGH* translocation t(11;14)(q13;q32), which leads to cyclin D1 overexpression.[1] Despite substantial improvements in outcome,[2] mantle cell lymphoma is still considered an incurable disorder, with a continuous relapse pattern and median survival of approximately 5–7 years.[3]

Treatment for young, physically fit patients with mantle cell lymphoma consists of induction treatment with rituximab and cytarabine-based chemotherapy, followed by consolidation with autologous haematopoeitic stem-cell transplantation (HSCT).[4–6] Induction regimens are based either on standard dose regimens (such as alternating R-CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone] and R-DHAP [rituximab, dexamethasone, cytarabine, and cisplatin])[5] or on more intense regimens (such as that used by the Nordic group and the high-dose sequential [R-HDS] schedule).[7] R-HDS induced clinical and molecular remission in previous phase 2 studies.[8–10] Results from a study published in 2017[11] reported that rituximab maintenance every 2 months for 3 years after autologous HSCT can improve both progression-free survival and overall survival. Immunotherapy maintenance treatment was also efficacious in patients aged 60 years or older after conventional immunochemotherapy.[12,13] Several other agents are available for long-term maintenance, but the benefit of these treatments has not yet been investigated.

Lenalidomide is an oral agent with documented activity in mantle cell lymphoma[14–16] due to immunomodulatory, microenvironmental, and antiangiogenic mechanisms and direct effects on malignant cells.[17] Lenalidomide has been tested as maintenance treatment in several lymphoid malignancies, including diffuse large B-cell lymphoma and multiple myeloma, and in multiple myeloma it is now part of routine treatment,[18–20] but has not been tested in patients with mantle cell lymphoma after conventional treatment or autologous HSCT.

We aimed to assess the benefit of lenalidomide maintenance versus observation after intensive chemo-immunotherapy with R-HDS and autologous HSCT.

Methods

Study design and participants

This open-label, randomised, phase 3 trial was done at 49 haematology and oncology units (48 in Italy, 1 in Portugal; appendix pp 2–5). The protocol (appendix p 31) was reviewed and approved by the independent ethics committee of all participating centres.

Eligible patients were aged 18–59 years with Eastern Cooperative Oncology Group (ECOG) performance status 0–3, or aged 60–65 years with an ECOG performance status 0–2 (except when impairment of performance status was related to non-Hodgkin lymphoma). Eligible patients had treatment-naive advanced mantle cell lymphoma with Ann Arbor stage III or IV, or stage II plus bulky disease (≥5 cm) or B symptoms; had evidence of cyclin D1 overexpression or the translocation t(11;14)(q13;q32) by fluorescence in situ hybridisation or RT-PCR (evidence of overexpression of cyclin D2 or D3 by immunohistochemistry was acceptable for patients whose tumours were negative for the cyclin D1); had measurable disease (two diameters) in at least one site; were willing and able to comply with the protocol for the duration of the study; and understood that the study drug could have a potential teratogenic risk (and were counselled about pregnancy precautions and risks of fetal exposure). Patients were excluded if they had non-Hodgkin

Gentil, Lisbon, Portugal (M Gomes da Silva PhD); **Division of Haematology, Fondazione IRCCS Policlinico S Matteo and Department of Molecular Medicine, University of Pavia, Pavia, Italy** (Prof L Arcaini PhD); **Department of Haematology, Infermi Hospital, Rimini, Italy** (A L Molinari MD); **University of Genoa, Ospedale Policlinico San Martino, IRCCS per l'Oncologia, Genova, Italy** (F Ballerini MD); **Lymphoma Unit, Department of Onco-Haematology, IRCCS San Raffaele Scientific Institute, Milano, Italy** (A J M Ferreri MD); **Department of Haematology, University of Florence, Firenze, Italy** (B Puccini MD); **Haematology University Division, Verona Hospital, Verona, Italy** (F Benedetti MD); **SC di Ematologia - Presidio Ospedaliero Ca' Foncello, Treviso, Italy** (P M Stefani MD); **Department of Medical and Surgical Sciences, Section of Haematology, University of Modena and Reggio Emilia, Azienda Ospedaliero Universitaria Policlinico, Modena, Italy** (Prof F Narni MD); **Haematology Unit, ASST Monza San Gerardo, Monza, Italy** (I Casaroli MD); **Department of Haematology, Azienda Ospedaliera Bianchi Melacrino Morelli, Reggio Calabria, Italy** (C Stelitano MD)

Correspondence to:
Dr Marco Ladetto, Azienda Opedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
marco.ladetto@ospedale.al.it

See **Online** for appendix

lymphoma subtypes other than mantle cell lymphoma; clinical features of indolent mantle cell lymphoma; history of malignancy (other than squamous cell carcinoma, basal cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the breast, or incidental histological finding of prostate cancer [TNM stage T1a or T1b]) within the past 3 years; major surgery (other than diagnostic surgery) within the past 4 weeks; evidence of CNS involvement; clinically significant cardiac disease (ventricular ejection fraction <45%, congestive heart failure, symptomatic coronary artery disease, or cardiac arrhythmias not well controlled with medication) or myocardial infarction within the past 6 months; New York Heart Association class III or IV heart disease; marked impairment of pulmonary function (pulmonary diffusing capacity <50%); lymphoma-unrelated unacceptable haematologic values (haemoglobin <9 g/dL, white blood cells $<3\times10^9$ cells per L, platelets $<60\times10^9$ cells per L, absolute neutrophil count [ANC] $<1{\cdot}5\times10^9$ cells per L) in the week before the start of study; lymphoma-unrelated abnormal liver function tests (serum bilirubin >2 mg/dL, alanine aminotransferase or aspartate aminotransferase >3×upper limit of normal, alkaline phosphatase >2·5×upper limit of normal) in the week before the start of the study; lymphoma-unrelated abnormal renal function (serum creatinine >2·0 mg/dL); active opportunistic infections; known serological positivity or active infection with HIV, hepatitis C virus, or hepatitis B virus (except $HbsAg^-$ patients and $HbcAb^+$ patients, who could enter the trial under lamivudine prophylaxis; appendix p 5–7); or being pregnant or lactating. Diagnosis was obtained locally, followed by central pathological revision as detailed in the appendix (p 8).

This study was done according to the principles of the Declaration of Helsinki and in adherence with Good Clinical Practice Standards. Written informed consent was obtained from all patients.

Randomisation and masking

Patients were randomly assigned (1:1) in permuted blocks (size 2, 4, or 6) to lenalidomide or observation (appendix p 15). Placebo was not considered because patients receiving lenalidomide would be recognisable by history and laboratory examinations. Randomisation was stratified by centre and the presence of a clinical or molecular response (molecular response and clinical response *vs* absence of either or both). The randomisation sequence was generated by the statistician (AE) using the ralloc module in STATA (version 11.0) and implemented through a web-based procedure concealed from researchers. Investigators and patients were not masked to treatment.

Procedures

Eligible patients had clinical examination, complete blood count, and serum chemistry tests within 7 days before the first chemotherapy course. Patients had CT of the chest, abdomen, and pelvis and bone marrow specimens were obtained during the screening phase (and no longer than 1 month before the patient signed the written informed consent form). Tumour specimens were sent for central pathological revision as detailed in the appendix (p 8).

A detailed treatment description and schema is available in the appendix (pp 7–8, 20). After an optional prephase with vincristine and steroids (intravenous vincristine 1·4 mg/m² on day 1, oral prednisone 100 mg [total dose] on days 1–5), patients were given three courses of R-CHOP (21-day cycle, high-dose intravenous rituximab 375 mg/m² on day 1; intravenous doxorubicin 50 mg/m², vincristine 1·4 mg/m² [max 2 mg], and cyclophosphamide 750 mg/m² on day 2; oral prednisone 100 mg/m² on day 2–6). The R-HDS scheme was slightly modified from the original protocol to improve feasibility compared to the phase 2 study schedule.[8] In this study, R-HDS consisted of R-CTX (high-dose intravenous cyclophosphamide 4 g/m² on day 1, intravenous rituximab 375 mg/m² on day 4). After restaging (appendix p 20), patients received two cycles of R-HD-cytarabine (high-dose intravenous cytarabine 2 g/m² every 12 h on days 1–3; plus intravenous rituximab 375 mg/m² on days 4 and 10). $CD34^+$ peripheral blood stem cells (PBSCs) were harvested by local procedures after the first course of R-HD-cytarabine. At least $3{\cdot}5\times10^6$ $CD34^+$ cells per kg were required. PBSCs were only collected a second time in patients with inadequate harvesting or no documented minimal residual disease-negativity in the harvested PBSCs (centrally determined[21] at the University of Torino, Torino, Italy, and communicated to centres through Fondazione Italiana Linfomi operative offices). The induction programme included eight infusions of rituximab 375 mg/m² (appendix p 7).

After completing the whole R-HDS sequence [R-CTX and R-HD-cytarabine], patients with complete remission or partial remission (assessed by CT according to the 2007 International Working Group Criteria for non-PET avid lymphomas)[22] proceeded to autologous HSCT. The conditioning regimen was BEAM (intravenous carmustine 300 mg/m² on day –6; intravenous etoposide 200 mg/m² on days –5, –4, –3, and –2; intravenous cytarabine 400 mg/m² on days –5, –4, –3, and –2, intravenous melphalan 140 mg/m² on day –1, PBSC reinfusion on day 1, and granulocyte colony-stimulating factor [G-CSF] 5 µg/kg from day 2 until ANC $>1{\cdot}5\times10^9$ cells per L). At least $3{\cdot}5\times10^6$ PBSCs per kg were infused for autologous HSCT support. Subcutaneous G-CSF 5 µg/kg was given from the day after every high-dose chemotherapy course until recovery or completion of PBSC harvesting (appendix p 7).

Responding patients (complete remission or partial remission) with haematological recovery (ANC $>1{\cdot}5\times10^9$ cells per L and platelets $>60\times10^9$ cells per L) within 120 days after autologous HSCT were randomly assigned to receive oral lenalidomide (15 mg per day for patients with platelets $>100\times10^9$ cells per L or 10 mg per day for platelets $60–100\times10^9$ cells per L, days 1–21 every 28 days)

for 24 months, or observation. Treatment was continued for 24 months or until disease progression, unacceptable toxic effects, or voluntary withdrawal of the patient. If toxic effects occurred, lenalidomide treatment was interrupted or modified as described in the appendix (pp 9–12). The frequency and severity of adverse events were recorded on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. AEs were assessed during follow-up visits or when otherwise notified. Serious adverse events were defined as adverse events resulting in death, considered life-threatening by the investigators, those requiring hospitalisation or an extension of hospitalisation, those resulting in significant disability or incapacity (a substantial disruption of the patient's ability to conduct normal life functions), congenital anomaly or birth defects, and those constituting an important medical event. Prophylactic use of filgrastim was allowed, and used to support ANC recovery and to prevent febrile neutropenia even when not specifically recommended (appendix p 7). During the treatment and consolidation phases, safety was assessed before and after chemotherapy administration by haematology and blood chemistry including total protein, albumin, calcium, glucose, uric acid, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, creatinine, and lactate dehydrogenase; ECOG performance status; vital signs; physical examinations; bodyweight; and concomitant medications. During maintenance and in the observation group, patients had monthly physical examinations, ECOG performace status determination, complete blood counts and blood chemistry, and periodic quality of life assessments. These examinations were done at least every 3 months in the post-maintenance and observation follow-up period.

Response to therapy was assessed locally according to the 2007 Revised Criteria for Malignant Lymphoma for non-PET-avid disorders.[22] Response was assessed by CT after R-HD-CTX, before and after autologous HSCT, and then during maintenance or observation at 6, 12, 18, and 24 months, and during follow-up at 30 and 36 months. PET was not mandatory but suggested before and after autologous HSCT, but was not used for response assessment as established by response criteria.[22]

Data were centralised by the sponsor. The statistical analysis was done by the Unit of Clinical Epidemiology (CPO Piemonte, Italy), which also contributed to the design. The study protocol had four amendments that were approved by the institutional review boards of all participating centres (appendix pp 16–19). Two amendments were related to biological studies not described in

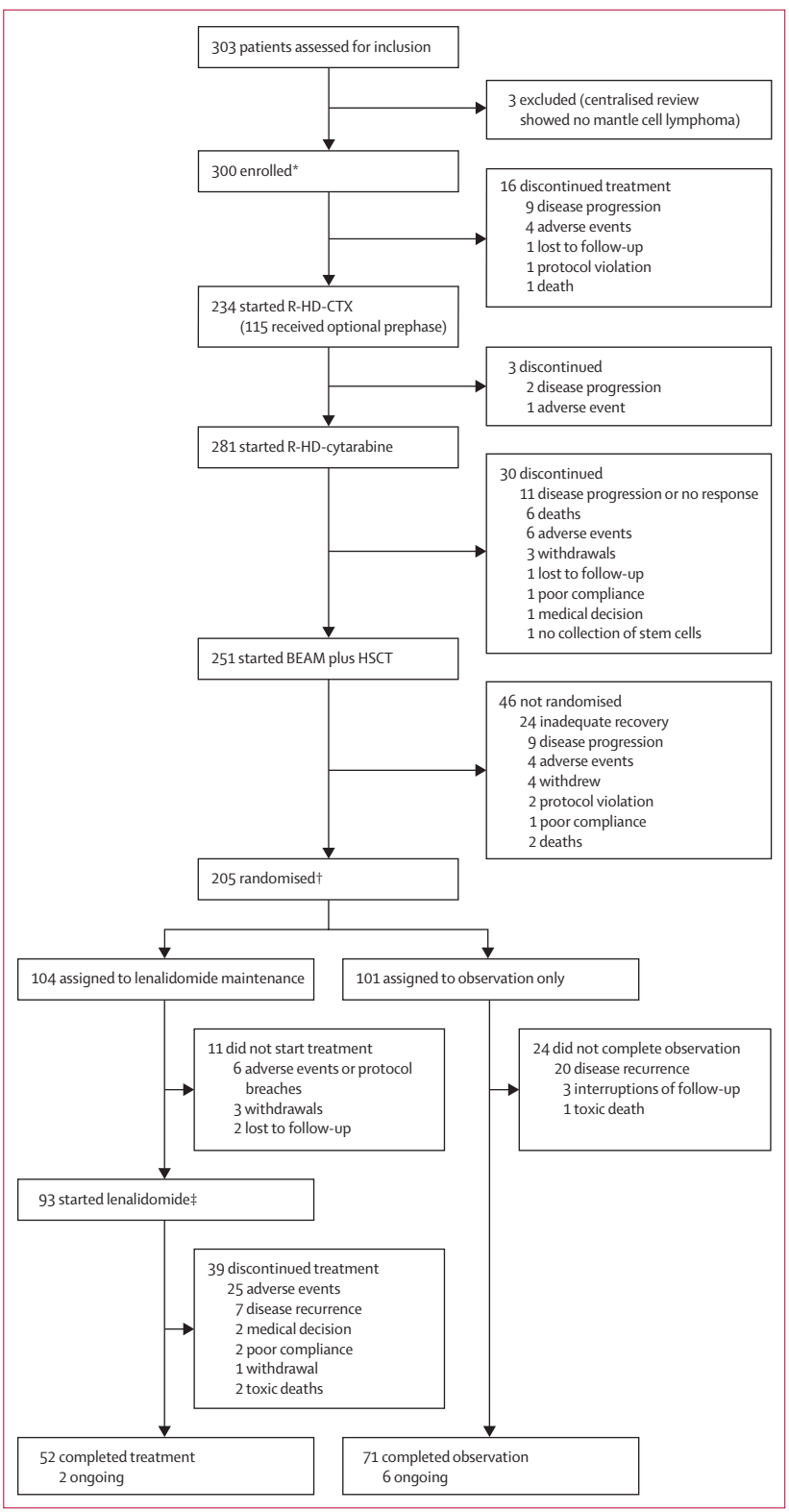

Figure 1: **Trial profile**
R-HD-CTX=high-dose cyclophosphamide + rituximab. R-HD-cytarabine=high-dose cytarabine + rituximab. BEAM=carmustine, etoposide, high-dose cytarabine, and melphalan. HSCT=haematopoetic stem-cell transplantation. *Included in intention-to-treat, enrolled population (n=300). †Included in intention-to-treat, randomised population (n=205). ‡Included in safety population (n=93).

this report, and modification of the informed consent due to accumulation of more knowledge on lenalidomide safety. The third amendment increased the sample size from 200 to 300 patients because of a higher than expected dropout rate during the pre-randomisation phase, extended the randomisation window after autologous HSCT, and increased the period of accrual. Amendement four introduced slight modifications in hepatitis B and varicella zoster virus monitoring and prophylaxis, as suggested by Italian regulatory authorities.

Outcomes

The primary endpoint was progression-free survival, measured from the date of randomisation to progression, relapse, or death from any cause, according to the 2007 Revised Criteria for Malignant Lymphoma for non-PET avid disorders.[22] Secondary endpoints were overall survival, event-free survival, disease-free survival, overall response rate, complete response rate,[22] safety, and incidence of secondary malignancies (defined in appendix pp 14–15). Additional secondary endpoints were minimal residual disease, prognostic impact of molecular response, molecular relapse and disease kinetics on progression-free survival, quality of life, and cost-effectiveness (results not shown; to be included in future reports).

Statistical analysis

We expected progression-free survival 30 months after randomisation in approximately 70% of patients in the observation group and at least 85% of patients in the lenalidomide group. According to the O'Brien and Fleming group sequential design with two interim analyses, 200 complete or partial responders should have been randomly assigned (100 per group) to ensure 60 progression-free survival events and detect the anticipated difference with α=5% and power=85%, assuming 3 years of accrual and a minimum follow-up of 2 years. As two interim analyses were done during the study, p was fixed at 0·045 for the final analysis. Because of a higher than expected dropout rate during the pre-randomisation phase (20% expected *vs* 30% actual), a protocol amendment in September, 2014, increased the sample size to 300. Statistical analyses were done in the enrolled population (all patients enrolled in the study), the intention-to-treat (ITT) population (all patients randomly assigned to lenalidomide or observation), and

	Enrolled population (N=300)	Non-randomised population (N=95)	Randomised population (N=205)	Lenalidomide maintenance group (N=104)	Observation group (N=101)
Age, years	57 (51–62)	58 (54–62)	57 (49–61)	57 (51–61)	57 (49–61)
Sex					
Female	65 (22%)	20 (21%)	45 (22%)	19 (18%)	26 (26%)
Male	235 (78%)	75 (79%)	160 (78%)	85 (82%)	75 (74%)
Lactate dehydrogenase >ULN	98 (33%)	45 (47%)	53 (26%)	25 (24%)	28 (28%)
ECOG-PS score >1	69 (23%)	29 (31%)	40 (20%)	18 (17%)	22 (22%)
Ann Arbor Stage III–IV	295 (98%)	95 (100%)	200 (98%)	102 (98%)	98 (97%)
MIPI score					
Low	162 (54%)	38 (40%)	124 (60%)	60 (58%)	64 (63%)
Intermediate	93 (31%)	38 (40%)	55 (27%)	29 (28%)	26 (26%)
High	45 (15%)	19 (20%)	26 (13%)	15 (14%)	11 (11%)
Bulky disease (>5 cm)	98 (33%)	39 (41%)	59 (29%)	29 (28%)	30 (30%)
Bone marrow involvement	233 (78%)	82 (86%)	151 (74%)	72 (69%)	79 (78%)
Ki67 index >30%	84/271 (31%)	30/81 (37%)	54/190 (28%)	24/94 (26%)	30/96 (31%)
MIPI-c					
Low risk	133/271 (49%)	32/81 (40%)	101/190 (53%)	46/94 (49%)	55/96 (57%)
Low–intermediate risk	79/271 (29%)	25/81 (31%)	54/190 (28%)	32/94 (34%)	22/96 (23%)
High–intermediate risk	36/271 (13%)	14/81 (17%)	22/190 (12%)	12/94 (13%)	10/96 (10%)
High risk	23/271 (8%)	10/81 (12%)	13/190 (7%)	4/94 (4%)	9/96 (9%)
Blastoid histology	26 (9%)	13 (14%)	13 (6%)	7 (7%)	6 (6%)
TP53^{mut} or del(17p)	31/186 (17%)	14/62 (23%)	17/124 (14%)	8/55 (15%)	9/69 (13%)
Clinical or molecular randomisation strata					
Group 1: CR with PCR negative	NA	NA	89 (43%)	42 (40%)	47 (47%)
Group 2: PR or CR with PCR positive	NA	NA	116 (57%)	62 (60%)	54 (53%)

Data are median (IQR), n (%), or n/total available (%). ULN=upper limit of normal. ECOG-PS=Eastern Cooperative Oncology Group Performance Status. MIPI=Mantle Cell Lymphoma International Prognostic Index. MIPI-c=combined Mantle Cell Lymphoma International Prognostic Index and Ki67 index.[13] CR=complete response. NA=not applicable. PR=partial response.

Table 1: **Demographic and clinical characteristics of patients at inclusion**

safety population (all patients who received at least one dose of the assigned treatment). Time-to-event efficacy endpoints (progression-free survival, overall survival, event-free survival, and disease-free survival) were estimated by the Kaplan-Meier method starting from the date of enrolment in the enrolled population, and the date of randomisation in the ITT population. Differences between groups were assessed in the ITT population by stratified log-rank test according to stratified randomisation by clinical and molecular response. Hazard ratios (HRs) were estimated using the stratified Cox model according to randomisation for clinical response and molecular response, and adjusting for Mantle Cell Lymphoma International Prognostic Index (MIPI) in an additional sensitivity analysis. To evaluate the heterogeneity of the maintenance effect on progression-free survival, planned (by stratification variable, age, and sex) and post hoc (by systemic symptoms, bulky disease, bone marrow involvement, Ki-67,[23] and MIPI score[24]) subgroup analyses were done. A Cox model was estimated for each subgroup, adjusting for the stratification variable. The presence of interaction was tested by including an interaction term between the randomised group and the subgroup covariate of interest. The cumulative incidence of secondary malignancies was estimated using the method proposed by Gooley and colleagues.[25] Death without secondary malignancy was defined as a competing event and comparisons between groups were done using the Fine and Gray model, adjusted for MIPI.[26] The proportion of patients who had grade 3–4 toxic effects was compared between groups using the Fisher's exact test, calculating the p value by doubling the one-tailed exact probability from exact test. See the appendix (pp 12–13) for the statistical analysis plan. This study is registered with EudraCT, 2009–012807–25, and ClinicalTrials.gov, NCT02354313. As detailed in the protocol (p 39) a data safety and monitoring committee was put in place for the entire duration of the study.

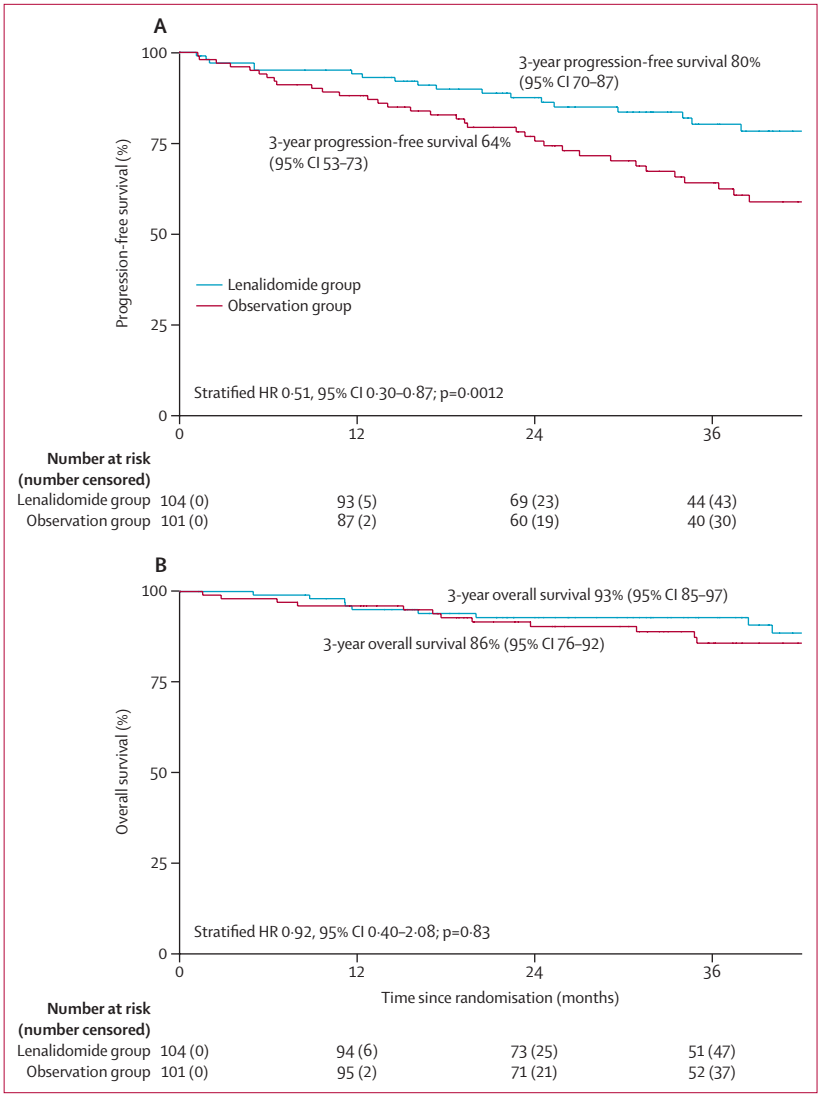

Figure 2: **Clinical outcomes in lenolidomide and observation groups**
(A) Progression-free survival. (B) Overall survival. HR=hazard ratio.

Role of the funding source

The funder provided lenalidomide for maintenance therapy and supported the study but did not contribute to study design, data collection, data analysis, interpretation, or to manuscript writing or submission. All authors contributed and reviewed subsequent drafts and jointly decided to submit the manuscript for publication. Data and statistical analyses were available to all authors, who controlled their accuracy, completion, integrity, and adhesion to protocol. The corresponding author had the final responsibility to submit for publication.

Results

Between May 4, 2010, and Aug 24, 2015, 303 patients were screened for inclusion (figure 1). Three patients were excluded as they did not have mantle cell lymphoma, and 300 patients were enrolled. Clinical characteristics at baseline are shown in table 1. Median age was 57 years (IQR 51–62), and 235 (78%) of 300 patients were male. All enrolled patients started treatment. 115 (38%) of 300 patients received the optional prephase and all others proceeded directly to R-CHOP. 284 (95%) patients started R-HD-CTX, and 281 (94%) started R-HD-cytarabine. 251 (84%) patients had autologous HSCT. Treatment was stopped in 95 (32%) of 300 patients due to disease progression (n=31, 10%), toxic death (n=9, 3%), and other causes (n=55, 18%; 15 adverse events [4 infectious, 2 gastrointestinal, 2 neurological, 2 cardiovascular, 2 pulmonary, and 3 other causes], 7 withdrew from treatment, 1 had poor mobilisation of stem cells, 2 were lost to follow-up, 3 had major protocol violations [1 delay in restaging after autologous HSCT, 1 not randomly assigned in time due to organisational problems, 1 switched to another therapeutic protocol with cytarabine],

1 medical decision, 2 poor compliance, and 24 could not be randomly assigned due to inadequate haematopoietic recovery after autologous HSCT).

After autologous HSCT, 205 (68%) of 300 patients had at least partial remission (191 complete remission and 14 partial remission) and met eligibility criteria for random assignment (figure 1). 104 patients were randomly assigned to lenalidomide maintenance treatment, and 101 patients were randomly assigned to observation only. Baseline characteristics of the patients randomised to each group are shown in table 1.

	Lenalidomide group (n=93)			Observation group (n=101)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Haematological*						
All	20 (22%)	27 (29%)	32 (34%)	22 (22%)	6 (6%)	6 (6%)
Granulocytes	15 (16%)	24 (26%)	31 (33%)	13 (13%)	6 (6%)	5 (5%)
Haemoglobin	43 (46%)	0	0	16 (16%)	1 (1%)	0
Platelets	45 (48%)	8 (9%)	0	19 (19%)	2 (2%)	1 (1%)
White blood cells	40 (43%)	17 (18%)	6 (6%)	13 (13%)	4 (4%)	3 (3%)
Non-haematological	44 (47%)	27 (29%)	2 (2%)	36 (36%)	6 (6%)	2 (2%)
Cardiac						
All	1 (1%)	0	0	1 (1%)	0	0
Hypertension	1 (1%)	0	0	1 (1%)	0	0
Febrile neutropenia	1 (1%)	5 (5%)	0	0	1 (1%)	1 (1%)
Gastrointestinal						
All	27 (29%)	2 (2%)	0	6 (6%)	2 (2%)	1 (1%)
Constipation	8 (9%)	0	0	1 (1%)	0	0
Diarrhoea	20 (22%)	2 (2%)	0	5 (5%)	0	0
Mucosal	2 (2%)	0	0	0	2 (2%)	1 (1%)
Haemorrhagic	2 (2%)	0	0	1 (1%)	0	0
Gastrointestinal haemorrhage	2 (2%)	0	0	0	0	0
Other haemorrhage	0	0	0	1 (1%)	0	0
Hepatic or pancreatic						
All	5 (5%)	0	0	0	1 (1%)	0
Hepatic dysfunction	4 (4%)	0	0	0	1 (1%)	0
Pancreatitis	1 (1%)	0	0	0	0	0
Infective						
All	17 (18%)	9 (10%)	1 (1%)	16 (16%)	3 (3%)	1 (1%)
Bacterial infection	11 (12%)	7 (8%)	1 (1%)	8 (8%)	2 (2%)	1 (1%)
Fungal infection	1 (1%)	0	0	1 (1%)	1 (1%)	0
Viral infection	6 (6%)	4 (4%)	0	10 (10%)	1 (1%)	0
Metabolic						
All	4 (4%)	1 (1%)	0	5 (5%)	1 (1%)	0
Hyperbilirubinaemia	0	0	0	1 (1%)	0	0
Hyperglycaemia	3 (3%)	1 (1%)	0	3 (3%)	0	0
Hyperuricaemia	1 (1%)	0	0	1 (1%)	0	0
Hypoglycaemia	0	0	0	0	1 (1%)	0
Neurological						
All	7 (8%)	2 (2%)	0	5 (5%)	0	0
Cranial nerve neuropathy	0	0	0	1 (1%)	0	0
Motor neuropathy	3 (3%)	1 (1%)	0	3 (3%)	0	0
Sensory neuropathy	5 (5%)	1 (1%)	0	2 (2%)	0	0
Pulmonary						
All	3 (3%)	1 (1%)	0	1 (1%)	0	0
Dyspnoea	3 (3%)	1 (1%)	0	1 (1%)	0	0
Renal failure	2 (2%)	1 (1%)	0	1 (1%)	0	0

(Table 2 continues on next page)

11 (11%) of 104 patients randomly assigned to lenalidomide did not start the study drug, six of whom had a protocol violation (randomisation performed before haematological recovery). 52 (50%) of 104 patients completed the maintenance treatment, and 41 (39%) did not complete lenalidomide maintenance. Two (2%) of 104 patients died, seven (7%) relapsed, 25 (24%) had adverse events, and five (5%) discontinued for other reasons. In the observation group, observation was interrupted in 24 (24%) of 101 patients due to death (n=1 [1%]), relapse (n=20 [20%]), and other causes (n=3 [3%]). Two (2%) of 104 patients in the lenalidomide group were still on treatment at the time of analysis and six (6%) of 101 patients in the observation group were still followed up at the time of analysis. 25 (48%) of 52 patients who completed treatment with lenalidomide remained at the 15 mg dose throughout, and 27 patients (52%) reduced the dose (16 patients to 10 mg; 11 patients to 5 mg). Median time to first dose reduction was 3 months (IQR 2–9) and median time to interruption was 12 months (3–17).

Median follow-up for the enrolled population was 48 months (IQR 8·0–88·0) from enrolment and 38 months (24·0–50·0) from randomisation. 22 (21%) of 104 patients in the lenalidomide group had a progression-free survival event, compared with 38 (38%) of 101 patients in the observation group. After randomisation, six (80%) of eight patients with partial remission in the lenalidomide group converted to complete remission. The same occurred in one (25%) of four patients in the observation group. The median progression-free survival was not reached in either group. 3-year progression-free survival was 80% (95% CI 70–87) in patients given lenalinomide and 64% (53–73) in the observation group (stratified HR 0·51, 95% CI 0·30–0·87; stratified log-rank p=0·012, stratified MIPI-adjusted HR 0·48; 95% CI 0·28–0·81, p=0·0062; figure 2). Median overall survival was not reached in either group, and 3-year overall survival did not differ significantly between groups (93% [95% CI 85–97] in the lenalidomide group *vs* 86% [95% CI 76–92] in the observation group, stratified HR 0·92; 95% CI 0·40–2·08, stratified log-rank p=0·83; stratified MIPI-adjusted HR 0·75, 95% CI 0·33–1·73; p=0·5, figure 2). Progression-free survival and overall survival of the entire randomised population are shown in the appendix (p 21). 3-year disease-free survival was 83% (95% CI 72–90) in the lenalidomide group and 65% (53–75) in the observation group (stratified HR 0·44, 95% CI 0·24–0·80; stratified log-rank p=0·0055) and 3-year event-free survival in the lenalidomide group was 46% (35–57; appendix p 22). Because event-free survival includes discontinuation of therapy (and progression, death, adverse events) among

the outcomes, this outcome can only be seen in the lenalidomide group, and is therefore not presented for both groups with statistical comparison.

We did a subgroup post hoc analysis of progression-free survival to evaluate whether the benefit of lenalidomide was more prominent in specific subgroups. Patients with no bone marrow involvement at diagnosis seemed to benefit more from lenalidomide maintenance (HR 0·11 [95% CI 0·02–0·52]) than did those with bone marrow involvement at diagnosis (0·75 [0·43–1·32], interaction p=0·023; appendix p 23). Other investigated parameters (eg, response status, MIPI systemic symptoms, bulky disease, and Ki67) did not seem to have an effect on the efficacy of lenalidomide in terms of progression-free survival (appendix p 23).

An exploratory multivariable analysis indicated that only Ki67 proliferation index was associated with worse progression-free survival (HR 1·96, 95% CI 1·10–3·50; p=0·023). Moreover, treatment with lenalidomide was associated with better progression-free survival in patients with Ki67 (0·53, 0·31–0·90; p=0·020, appendix, p 26).[13]

Median progression-free survival and overall survival of the enrolled population calculated from study inclusion was also not reached. 4-year progression-free survival was 60% (95% CI 54–66), and 4-year overall survival was 82% (76–86) for the whole enrolled population (appendix p 24).

4-year progression-free survival according to MIPI was 71% (95% CI 62–78) in low-risk patients, 52% (41–62) in intermediate-risk patients, and 38% (23–53) in high-risk patients (log-rank test p<0·0001). Overall survival was 91% (95% CI 85–94) in low-risk patients, 75% (64–83) in intermediate-risk patients, and 60% (41–74) in high-risk patients (log-rank test p<0·0001). An exploratory multivariable analysis identified MIPI or MIPI-c, male sex, and bulky disease as independent adverse prognosticators of progression-free survival, whereas MIPI or MIPI-c, male sex, B-symptoms, and Ki-67 adversely affected overall survival (appendix p 26).

At the end of induction, or at study interruption for those not completing R-HDS for toxic effects or withdrawal, we recorded an overall response in 254 (85%) of 300 patients. 234 (78%) of 300 patients had complete remission and 20 (7%) patients had partial remission. 30 (10%) patients had disease progression.

During induction, nine (3%) of 300 patients in the enrolled population died (5 infections, 3 cardiovascular toxic effects, and 1 car accident). After randomisation, there were three treatment-related deaths; two (2%) of 104 patients in the lenalidomide safety population (1 pneumonia, 1 thrombotic thrombocytopenic purpura) and one (1%) of 101 patients in the observation group (pneumonia). During induction, 269 (90%) of 300 patients had grade 3–4 haematological adverse events, most frequently in the R-HD-cytarabine and autologous HSCT phases. Further details on the haematological adverse events during the induction and consolidation phases are shown in the appendix (p 27).

	Lenalidomide group (n=93)			Observation group (n=101)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
Vascular						
All	0	2 (2%)	0	0	0	0
Phlebitis	1 (1%)	0	0	0	0	0
Thrombosis or embolism	0	2 (2%)	0	0	0	0
Other toxic effects†	39 (42%)	11 (12%)	1 (1%)	24 (24%)	3 (3%)	1 (1%)

Data are n (%). CTCAE=Common Terminology Criteria for Adverse Events. *Reduction in blood values that define toxicity according to CTCAE v4.0. †General disorders and administration site conditions; and injury, poisoning, and procedural complications according to CTCAE v4.0.

***Table 2*: Adverse events in patients receiving lenalidomide maintenance or assigned to observation after autologous haematopoetic stem-cell transplantation**

During induction, 205 (68%) of 300 enrolled patients had grade 3–4 non-haematological adverse events, mostly during the autologous HSCT phase (154 [61%] of 251 patients, appendix p 28). The most frequent non-haematological adverse event was febrile neutropenia, which occurred in 146 (49%) of 300 patients overall and 106 (42%) of 251 patients during the autologous HSCT phase (appendix p 28). After randomisation, 59 (63%) of 93 patients in the lenalidomide safety population had grade 3–4 haematological adverse events, compared with 12 (12%) of 101 patients in the observation group (Fisher's exact test p<0·0001; table 2). Grade 3–4 non-haematological adverse events occurred in 29 (31%) of 93 patients in the lenalidomide safety population and eight (8%) of 101 patients in the observation group (p<0·0001), mostly caused by infections (10 [11%] of 93 patients in the lenalidomide group *vs* 4 [4%] of 101 patients in the observation group, p=0·12; table 2). After randomisation, serious adverse events occurred in 22 (24%) of 93 patients in the lenalidomide group (7 pneumonia, 6 other infections, 2 neurological, 2 gastrointestinal, 5 other toxic effects) and five (5%) of 101 patients in the observation group (1 pneumonia, 2 other infections, two other toxic effects).

We recorded non-cutaneous solid tumours in 13 (4%) of 300 patients, skin cancers in two (1%) of 300 patients, and secondary myelodysplastic syndrome or acute myeloid leukaemia in a total of four (1%) of 300 patients. Nine (9%) of 95 patients in the non-randomised population had secondary malignancy (incidence 15·6% [95% CI 7·1–27·1] 48 months after enrolment) compared with ten (5%) of 93 patients in the randomised population (incidence 6·2% [3·5–13·6] 48 months after enrolment). Two of these ten secondary tumours were fatal. Secondary malignancies were reported in five (5%) of 93 patients in the lenalidomide safety population and in three (3%) of 101 patients in the observation group. The cumulative incidence of any secondary malignancy at 48 months was 10·3% (95% CI 3·2–22·3) in the lenalidomide safety population versus 3·2% (0·5–10·5) in the observation

group (MIPI-adjusted HR 2·00, 95% CI 0·50–8·03; p=0·33, appendix p 25).

Discussion

In this multicentre, randomised, phase 3 trial, we report a substantial improvement in progression-free survival among patients with mantle cell lymphoma given lenalidomide maintenance after autologous HSCT. The 15 mg dosing schedule had a non-negligible proportion of treatment stoppings, and many patients required dose reductions. However, the reduced treatment intensity did not preclude a clinically meaningful improvement in progression-free survival. Our data also suggest that R-HDS[8] is feasible for induction, despite its intensity, but has substantial toxicity, which prevented a proportion of patients from being randomly assigned after autologous HSCT. Finally, the follow-up is still too brief to draw definitive conclusions about overall survival and late toxic effects, including secondary malignancies.

The study did not include a placebo, as the active treatment has easily recognisable effects on blood counts, making it difficult to mask clinicians in the treatment group. The improved progression-free survival result was achieved despite stoppings and dose reductions, suggesting remarkable clinical activity and low tolerance of the maintenance scheme. We recorded objective difficulties in delivering the planned dose of lenalidomide, mostly due to haematological adverse events and infections, which can be explained, at least in part, by the presence of a particularly stressed haematopoietic compartment due to R-HDS and autologous HSCT. Almost 10% of patients who had HSCT could not be randomly assigned due to inadequate haematopoietic recovery, which largely explains the increased rate of randomisation failures compared with the LYMA trial[11] of post-autologous HSCT rituximab maintenance in a similar patient population. On the other hand, lenalidomide has well known myelotoxic properties that might have been amplified by the intensive induction treatment. A broad ancillary substudy on clonal haematopoiesis and stem-cell damage to try to clarify these issues is ongoing (see protocol). However, haematological adverse events (particularly neutropenia) were frequently observed in trials investigating post-autologous HSCT lenalidomide maintenance in multiple myeloma,[18] even if induction and consolidation were less chemo-intensive than R-HDS. Nevertheless, lenalidomide toxicity did not preclude the clinical benefit in both settings.

Ours is the second study to show the benefit of adding a maintenance regimen after autologous HSCT in mantle cell lymphoma. Previous studies have already established the value of a maintenance regimen in the non-transplantation setting.[12] The LYMA study[11] reported a benefit in both progression-free survival and overall survival of post-autologous HSCT rituximab maintenance compared with observation in 2017, after the completion of enrolment for our study. The notion that both rituximab and lenalidomide, despite different mechanisms of action, had a substantial effect on the residual mantle cell lymphoma clone strengthens the value of maintenance for the successful management of mantle cell lymphoma. The main differences between our trial and the LYMA trial[11] are related to the superior feasibility and inferior toxicity of rituximab compared with lenalidomide. Moreover, the progression-free survival advantage observed in the LYMA trial translated into a significant overall survival benefit that was not observed in our study with the current length of follow-up (LYMA 4-year overall survival in rituximab group 88·7% [95% CI 80·7–93·5] *vs* 81·4% in the observation group [72·3–87·7], p=0·0413). There are several possible explanations, including shorter follow-up (50 *vs* 39 months from randomisation), the nature and duration of treatment, higher rate of early lenalidomide stopping, the availability of better salvage regimens, and the effect of late adverse events. Long-term results will help clarify these issues.

One major concern associated with lenalidomide treatment is the occurrence of secondary malignancies. We recorded 19 secondary malignancies, including 13 non-cutaneous solid cancers, two skin cancers, and four cases of secondary myelodysplastic syndrome or acute myeloid leukaemia. Nine of these secondary malignancies occurred in the non-randomised population. Of the ten cases in the randomised population, two were fatal, with a 48-month cumulative incidence of 6·2%. More secondary malignancies were reported in the lenalidomide group than in the observation group and, although this difference was not significant, careful monitoring of future secondary malignancies is crucial. In the MCL Younger trial,[5] the cumulative incidence of secondary tumours was 4·8% in the group given R-CHOP+DHAP and 4·3% in the group given R-CHOP.

In the LYMA trial,[11] three patients died from secondary malignancies in the rituximab group and one patient died from secondary malignancies in the observation group. This is in line with our findings, in which only two cases in the enrolled population were fatal. Again, long-term analysis will help clarify this important safety aspect.

Patients in our study uniformly had R-HDS[8] as induction therapy before randomisation. This regimen, similar to that used by the Nordic group,[7] does not contain platinum derivatives and is characterised by an intense induction phase before autologous HSCT, with delivery of an R-HD-cytarabine dose that is considerably higher than other commonly used schedules, such as the classic CHOP+DHAP regimen.[5] Overall, the R-HDS schedule proved to be feasible, with an overall response rate of 85%, a rate of toxic deaths similar to that of less intense regimens, and a high rate of successful stem-cell mobilisation. However, the programme was more cumbersome, particularly because of the need for hospital admission for R-HD-cytarabine delivery. This necessity was a problem for both patients and institutions, but no superior disease control was recorded compared with easier and more manageable programmes.

Our results indicate that lenalidomide improves progression-free survival in patients with mantle cell lymphoma, at the cost of an increased rate of adverse events. We are waiting to see if this improvement will translate into improved overall survival, which will be included in a later report. The toxicity profile observed in the lenalidomide population suggests that either a reduction of lenalidomide dosing or a less intense induction is needed. Nevertheless, the encouraging progression-free survival finding suggests the need to further improve maintenance programmes in mantle cell lymphoma, including the option of combining lenalidomide and rituximab, or use of ibrutinib as maintenance. Both of these approaches are under investigation within European MCL network phase 3 trials (NCT01865110 and NCT02858258).

Contributors

ML, SC, AE, UV, MMi, and GC designed the study. ML, SC, SF, AE, MMi, RT, GC, UV, and MMa analysed and interpreted the data. ML, SC, AE, GC, UV, and MMa drafted the manuscript. ML, AE, and RT created the figures. ML, SC, and RT did the literature search. All authors contributed and reviewed subsequent drafts and jointly decided to submit the manuscript for publication. Data and statistical analyses were available to all authors, who controlled their accuracy, completion, integrity, and adhesion to protocol.

Declaration of interests

ML has received invitations to scientific meetings, institutional research support, and contracts with AbbVie, Acerta, Amgen, Archigen, ADC Therapeutics, BeiGene Celgene, Gilead, J&J, Jazz, Roche, Sandoz, and Takeda. SF has done consultancy work for Janssen; advisory board work for Janssen and EUSA Pharma; has received speaker honoraria from Janssen, EUSA Pharma, and Servier; and research funding from Gilead. AC has served on advisory boards for Celgene, Iqone, Janssen, and Takeda; and received lecture fees from Celgene, Gilead-Kite, Janssen, Roche, and Servier. VRZ has acted as an adviser for Janssen and MSD, and received honoraria from Italfarmaco and Roche. MGdS has received research grants from Gilead; has served on advisory boards member for Janssen, AbbVie, Roche, Celgene, Gilead, and AstraZeneca; has been a speaker for Janssen, BMS, AbbVie, Gilead, and Takeda; and has received travel support from Janssen, Roche, AbbVie, Celgene, and Gilead. AJMF has served on advisory boards for Gilead, Juno, Novartis, and PletixaPharm; has received research grants from BMS, Beigene, Pharmacyclics, Hutchison Medipharma, Amgen, Genmab, ADC Therapeutics, Gilead, Novartis, and Pfizer; and has patents on NGR-hTNF/RCHOP in relapsed or refractory PCNSL and SNGR-hTNF in brain tumours with San Raffaele Scientific Institute. UV has served on advisory boards for Celgene, Janssen, and Gilead; and received honoraria for lectures from Celgene, AbbVie, Roche, Janssen, and Gilead. MMa has acted as a consultant for and received honoraria from Roche, Celgene, Janssen, Sandoz, Novartis, and Gilead; and has served as a member of the advisory board for Roche, Celgene, Janssen, Sandoz, Novartis, and Gilead. All other authors declare no competing interests.

Acknowledgments

The study was sponsored by Fondazione Italiana Linfomi and endorsed by the European Mantle Cell Lymphoma network. We are grateful to the Fondazione Italiana Linfomi personnel for their management of the study, particularly Antonella Ferranti, Daniela Gioia, and Alessandro Levis. We are grateful to the European Mantle Cell Lymphoma Network for scientific support and useful discussions during study design and conduct. We are indebited to Alberto Zamò, Domenico Novero, and Marco Paulli for the histological revision of patient specimens.

Data sharing

Qualified researchers may contact the Fondazione Italiana Linfomi board at segreteriadirezione@filinf.it for individual-level patients' clinical data reported in this manuscript (for the avoidance of doubt, no identifiable data, such as name, address, hospital name, date of birth, or any other identifying data, will be shared and should not be requested). For each data sharing request, it is essential that a proforma is completed that describes the purpose, scope, data items requested, analysis plan and acknowledgment of the trial management team. Requests will be reviewed on the basis of scientific merit. Requesters who are granted access to the data will be required to complete a data sharing agreement that will be signed by the requester and Fondazione Italiana Linfomi. In compliance with the domestic ethics guideline and applicable legislation, individual de-indentified patients' data underlying the results reported in this Article can be shared under the approval of each institutional review board until 5 years after the end of this study. The study protocol and statistical analysis plan will be available to anyone who wants access for what is not already available in the appendix by contacting Fondazione Italiana Linfomi offices at segreteriadirezione@filinf.it.

References

1 Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th edn, vol 2. Lyon: International Agency for Research on Cancer, 2008.
2 Pérez-Galán P, Dreyling M, Wiestner A. Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. *Blood* 2011; **117:** 26–38.
3 Herrmann A, Hoster E, Zwingers T, et al. Improvement of overall survival in advanced stage mantle cell lymphoma. *J Clin Oncol* 2009; **27:** 511–18.
4 Dreyling M, Geisler C, Hermine O, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014; **25** (suppl 3)**:** iii83–92.
5 Hermine O, Hoster E, Walewski J, et al. Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network. *Lancet* 2016; **388:** 565–67.
6 Gerson JN, Handorf E, Villa D, et al. Survival outcomes of younger patients with mantle cell lymphoma treated in the rituximab era. *J Clin Oncol* 2019; **37:** 471–80.
7 Eskelund CW, Kolstad A, Jerkeman M, et al. 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau. *Br J Haematol* 2016; **175:** 410–18.
8 Gianni AM, Magni M, Martelli M, et al. Long-term remission in mantle cell lymphoma following high-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting (R-HDS regimen). *Blood* 2003; **102:** 749–55.
9 Magni M, Di Nicola M, Carlo-Stella C, et al. High-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting in mantle cell lymphoma: a 10-year update of the R-HDS regimen. *Bone Marrow Transplant* 2009; **43:** 509–11.
10 Cortelazzo S, Magni M, Tarella C, et al. Update of a GITIL cohort study: frontline high dose sequential chemotherapy with rituximab and autologous stem cell transplantation induces a high rate of long-term remissions in patients with mantle cell lymphoma. *Blood* 2006; **110:** 1282 (abstr).
11 Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. *N Engl J Med* 2017; **377:** 1250–60.
12 Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med* 2012; **367:** 520–31.
13 Hoster E, Rosenwald A, Berger F, et al. Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: results from randomised trials of the European Mantle Cell Lymphoma Network. *J Clin Oncol* 2016; **34:** 1386–94.
14 Desai M, Newberry K, Ou Z, Wang M, Zhang L. Lenalidomide in relapsed or refractory mantle cell lymphoma: overview and perspective. *Ther Adv Haematol* 2014; **5:** 91–101.
15 Wang M, Martin P, Phillip T. Effectiveness of lenalidomide in patients with mantle cell lymphoma who relapsed/progressed after or were refractory/intolerant to ibrutinib: the MCL-004 study. *Blood* 2016; **128:** 1786 (abstr).

16 Trneny M, Lamy T, Walewski J, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2 randomised, multicenter trial. *Lancet Oncol* 2016; **17:** 319–31.

17 Gribben JG, Fowler N, Morschhauser F. Mechanisms of action of Lenalidomide in B-cell non-Hodgkin lymphoma. *J Clin Oncol* 2015; **33:** 2803–11.

18 Holstein SA, Jung SH, Richardson PG, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. *Lancet Haematol* 2017; **4:** e431–44.

19 Thieblemont C, Tilly H, Gomes da Silva M et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol* 2017; **35:** 2473–81.

20 Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines. *Ann Oncol* 2017; **28** (suppl 4)**:** iv52–61.

21 Della Starza I, Cavalli M, De Novi LA, et al. Minimal residual disease (MRD) in non-Hodgkin lymphomas: interlaboratory reproducibility on marrow samples with very low levels of disease within the FIL (Fondazione Italiana Linfomi) MRD Network. *Haematol Oncol* 2019; **37:** 368–74.

22 Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25:** 579–86.

23 Klapper W, Hoster E, Determann O, et al. Ki-67 as a prognostic marker in mantle cell lymphoma—consensus guidelines of the pathology panel of the European MCL Network. *J Hematopathol* 2009; **2:** 103–11.

24 Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood* 2008; **111:** 558–65.

25 Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999; **18:** 695–706.

26 Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94:** 496–97.