Frontline bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in transplantation-ineligible patients with newly diagnosed mantle cell lymphoma: final overall survival results of a randomised, open-label, phase 3 study

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Summary

Background In the LYM-3002 study, the efficacy and safety of frontline bortezomib plus rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) and rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) were compared in transplant-ineligible patients with untreated, newly diagnosed, mantle cell lymphoma. We report the final overall survival and safety outcomes for patients in the long-term follow-up phase after the primary progression-free-survival endpoint was met.

Methods LYM-3002 was a randomised, open-label, phase 3 study done at 128 clinical centres in 28 countries in Asia, Europe, North America, and South America. Adult patients with confirmed stage II–IV previously untreated mantle cell lymphoma, Eastern Cooperative Oncology Group performance status score of 2 or less, who were ineligible for bone marrow transplantation, were randomly assigned (1:1) to receive six or eight 21-day cycles of VR-CAP (intravenous rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and bortezomib 1·3 mg/m², plus oral prednisone 100 mg/m²) or R-CHOP (intravenous vincristine 1·4 mg/m² [2 mg maximum], rituximab 375 mg/m², cyclophosphamide 750 mg/m², and doxorubicin 50 mg/m², plus oral prednisone 100 mg/m²). Randomisation was done according to a computer-generated randomisation schedule prepared by the sponsor; permuted blocks central randomisation was used (block size of 4), and was stratified by International Prognostic Index score and disease stage at diagnosis. The primary endpoint of this final analysis was overall survival, which was analysed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00722137, and is closed to new participants with follow-up completed.

Findings Between May 22, 2008, and Dec 5, 2011, 487 patients were enrolled and randomly assigned. 268 patients (140 in the VR-CAP group and 128 in the R-CHOP group) were included in the follow-up analysis, which included patients with data available after the primary analysis clinical cutoff date of Dec 2, 2013. After median follow-up of 82·0 months (IQR 74·1–94·2), median overall survival was significantly longer in the VR-CAP group than in the R-CHOP group (90·7 months [95% CI 71·4 to not estimable] *vs* 55·7 months [47·2 to 68·9]; hazard ratio 0·66 [95% CI 0·51–0·85]; p=0·001). Three new adverse events were reported since the primary analysis cutoff (one each of grade 4 lung adenocarcinoma and grade 4 gastric cancer in the VR-CAP group, and one case of grade 2 pneumonia in the R-CHOP group). 103 (42%) of 243 patients in the VR-CAP group, and 138 (57%) of 244 in the R-CHOP group died; the most common cause of death was progressive disease.

Interpretations Compared with R-CHOP, VR-CAP was associated with significantly longer survival, and had a manageable and expected safety profile. Our results support further assessment of VR-CAP in patients with previously untreated mantle cell lymphoma.

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Introduction

Mantle cell lymphoma is an uncommon, incurable haematological malignancy that comprises 5–6% of all non-Hodgkin lymphomas, with approximately 3300 cases diagnosed annually in the USA.[1–3] The clinical behaviour of the disease is generally heterogeneous, varying from

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See Online for appendix

Research in context

Evidence before this study

We did not do a formal search to inform this study. Mantle cell lymphoma, an uncommon haematological malignancy, is associated with poor long-term survival despite initial favourable responses to treatment and evolving treatment modalities. Although stem-cell transplantation is indicated in some specific patient groups, most patients with mantle cell lymphoma are ineligible for the procedure. Combination therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is recommended in patients ineligible for transplantation, but the survival benefit is low. Bortezomib, a proteasome inhibitor, has been approved in the EU, the USA, and several other countries for treatment of mantle cell lymphoma. Bortezomib monotherapy was associated with durable responses and prolonged time to alternative therapy in patients with relapsed or relapsed, refractory mantle cell lymphoma in a phase 2, prospective, multicentre, single-group, three-stage study (M34103-053). An overall response to bortezomib was noted in 33% of participants, and the median duration of response was 9·2 months. The LYM-3002 study was designed to assess whether the benefits noted with bortezomib in patients with relapsed or refractory mantle cell lymphoma could be translated into the frontline setting and prolong progression-free survival and durable responses. The primary results of the study showed a significantly longer median progression-free survival in participants who received bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) compared with those who received R-CHOP (24·7 months *vs* 14·4 months; hazard ratio 0·63 [0·50–0·79]; p<0·001). Additionally, overall survival at 4 years was higher in the VR-CAP group than in the R-CHOP group, and the toxicity associated with VR-CAP was expected and manageable at the primary analysis.

Added value of this study

This follow-up study showed that replacement of vincristine with bortezomib in the R-CHOP regimen (ie, VR-CAP) significantly improved median overall survival in previously untreated patients with mantle cell lymphoma. Although haematological toxicities were more common and more severe with VR--CAP than with R-CHOP at the primary analysis, overall the safety profile of VR-CAP was acceptable at the final analysis. To the best of our knowledge, this study is the first to show the longterm survival benefits of bortezomib-based therapy in transplant-ineligible patients with mantle cell lymphoma compared with conventional R-CHOP treatment.

Implications of all the available evidence

VR-CAP frontline therapy significantly improved overall survival compared with R-CHOP in transplant-ineligible patients with newly diagnosed mantle cell lymphoma, had a predictable and manageable safety profile, and was associated with a reduced need for subsequent therapies. Our findings support further asessment of VR-CAP in patients with mantle cell lymphoma, and suggest that combining bortezomib with newer drugs could be of clinical interest.

indolent to very aggressive, and often involves extranodal sites such as bone marrow, blood, and the gastrointestinal tract.[4,5] Despite favourable initial clinical and molecular responses, available treatment modalities are not curative, with median progression-free survival of 16·6 months and overall survival of 4–5 years from first diagnosis.[6] Frontline combination therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the standard of care for older patients (aged ≥65 years) who are ineligible for stem-cell transplantation or intensive chemotherapy.[7,8] However, the survival outcomes achieved with conventional R-CHOP therapy remain inadequate.

The proteasome inhibitor bortezomib has been approved in the EU, the USA, and several other countries for the treatment of both relapsed and previously untreated mantle cell lymphoma.[9] In LYM-3002, one of the largest, multicentre, randomised, phase 3 trials[9] of mantle cell lymphoma, the efficacy and safety of frontline bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) were compared with those of R-CHOP in transplant-ineligible patients with newly diagnosed mantle cell lymphoma. Primary results based on data from before the cutoff date (Dec 2, 2013) showed a significant improvement in median progression-free survival in the VR-CAP group compared with the R-CHOP group (24·7 months [95% CI 604·0 days to 969·0 days] *vs* 14·4 months [365·0 days to 513·0 days]; hazard ratio [HR] 0·63 [95% CI 0·50–0·79]; p<0·001).[9] Furthermore, VR-CAP was associated with clinically relevant improvements in secondary efficacy endpoints, including higher 4-year overall survival compared with R-CHOP (64·4% *vs* 53·9%), but overall survival data were not mature at the time of the primary report. Safety data showed that VR-CAP was associated with expected and manageable toxicities at the primary analysis. In this Article, we report results from the final analysis of the LYM-3002 study, which includes data for final overall survival and safety outcomes in patients with newly diagnosed mantle cell lymphoma after the primary progression-free-survival endpoint was met (ie, after the clinical cutoff date of Dec 2, 2013).

Methods

Study design and participants

The randomised, open-label phase 3 LYM-3002 study was done at 128 clinical centres in 28 countries in Asia, Europe, North America, and South America (appendix pp 6–8). Full details of the study design have been previously published.[9] Overall, the study had four phases: screening (up to 28 days—or 56 days for

bone marrow assessment—before treatment), treatment (six 21-day treatment cycles or eight cycles in case of documented response at cycle 6), short-term follow-up (from end of treatment to disease progression, initiation of another antineoplastic treatment, patient withdrawal, or death), and long-term follow-up (when clinical cutoff for the primary analysis was reached. After the clinical cutoff was reached, radiographic assessment of disease progression was stopped and all patients in short-term follow-up entered the long-term follow-up phase.

Eligible participants were aged 18 years or older; had histologically confirmed, newly diagnosed, previously untreated stage II, III or IV mantle cell lymphoma (according to the American Joint Committee on Cancer's staging system for non-Hodgkin lymphoma, and established by local expert pathologists and confirmed by central pathological review), Eastern Cooperative Oncology Group performance status scores of 2 or less, and either expression of cyclin D1 (in association with CD20 and CD5) or evidence of t(11;14) translocation (by cytogenetics, fluorescence in-situ hybridisation, or PCR); and were ineligible or not considered for stem-cell transplantation. Eligible patients had to have at least one measurable site of disease. Patients were excluded if they had received previous treatment with bortezomib, or any previous antineoplastics (including unconjugated therapeutic antibodies), experimental therapy, radiotherapy, or radio-immunoconjugates or toxin immunoconjugates to treat mantle cell lymphoma. Other exclusion criteria included diagnosis or treatment of a malignancy other than mantle cell lymphoma within 1 year of randomisation, previous diagnosis of another malignancy with radiographic or biochemical evidence of residual disease, active systemic infection requiring treatment, a known diagnosis of HIV, active hepatitis B virus infection, or a serious pre-existing medical condition. Detailed eligibility criteria for this study have been described previously.[9] A full list of all inclusion and exclusion criteria is in the appendix (pp 32–34).

The study was done according to ethical principles that have their origin in the Declaration of Helsinki (2013), consistent with good clinical practices and applicable regulatory requirements, and in compliance with the study protocol, which was approved by the local ethics committee or institutional review board at each site. All patients provided written, informed consent.

Randomisation and masking

Eligible patients were enrolled by study investigators and then randomly assigned (1:1) to either R-CHOP or VR-CAP with a computer-generated randomisation schedule prepared by the sponsor before the study. Patients were allocated to groups via an interactive voice–response system, which was operated by study staff. Permuted blocks (block size of 4) central randomisation was used, which was stratified by International Prognostic Index score (0–1 *vs* 2 *vs* 3 *vs* 4–5) and disease stage at diagnosis (II *vs* III *vs* IV). The stratified randomisation was intended to minimise the imbalance in the distribution of treatment numbers within the levels of each individual stratification factor. Patients were randomly assigned only when the central laboratory had confirmed that they had a diagnosis of mantle cell lymphoma. This study was open label, and thus patients and investigators were unmasked to treatment assignment. However, the radiologists who did all radiographic assessments were masked to treatment assignment.

Procedures

Briefly, patients received either six or eight cycles of induction therapy (21-day cycles) with either R-CHOP (intravenous rituximab 375 mg/m² of body-surface area, cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1·4 mg/m² [up to 2 mg] on day 1 of each cycle, plus oral prednisone 100 mg/m² on days 1–5) or VR-CAP (intravenous bortezomib 1·3 mg/m² on days 1, 4, 8, and 11 of each cycle, followed by rituximab plus cyclophosphamide, doxorubicin, and prednisone, which were given at the same doses and on the same days as with the R-CHOP regimen). A short course of low-dose prednisone or equivalent corticosteroids (for a maximum duration of 10 days at a dose of ≤100 mg per day) was allowed to treat symptoms in patients with advanced disease before randomisation.

Toxicity-related dose adjustments were permitted as per each drug's recommended dose-modification guidelines. If the patient experienced grade 3 or worse neutropenia with fever, grade 4 neutropenia lasting more than 7 days, a platelet count of less than 10 000 per µL, or any grade 3 or worse non-haematological toxicity judged by the investigator to be related to bortezomib, the prespecified bortezomib dose reduction was to 1·0 mg/m², and subsequently, if necessary, to 0·7 mg/m². Doses of less than 0·7 mg/m² were not allowed, and instead bortezomib was discontinued. A 50% reduction in the rituximab infusion rate was permitted if patients had infusion-related reactions, as were 25–50% reductions in doxorubicin and vincristine doses if patients had impaired hepatic function (based on serum bilirubin concentrations), and reductions in prednisone doses to no less than 80 mg per day if patients had prednisone-associated adverse events. For cyclophosphamide, patients with absolute neutrophil counts of 1500 cells or more per µL and more than 100 000 platelets per µL received the full dose. Those with absolute neutrophil counts of 500 or more per µL, no febrile neutropenia, and more than 50 000 platelets per µL received the full dose of cyclophosphamide after recovery of the neutrophil and platelet counts to 1500 and 100 000 per µL, respectively. If counts did not recover, participants were either given reduced doses or discontinued cyclophosphamide (per criteria mentioned in the protocol, depending on the neutrophil count and

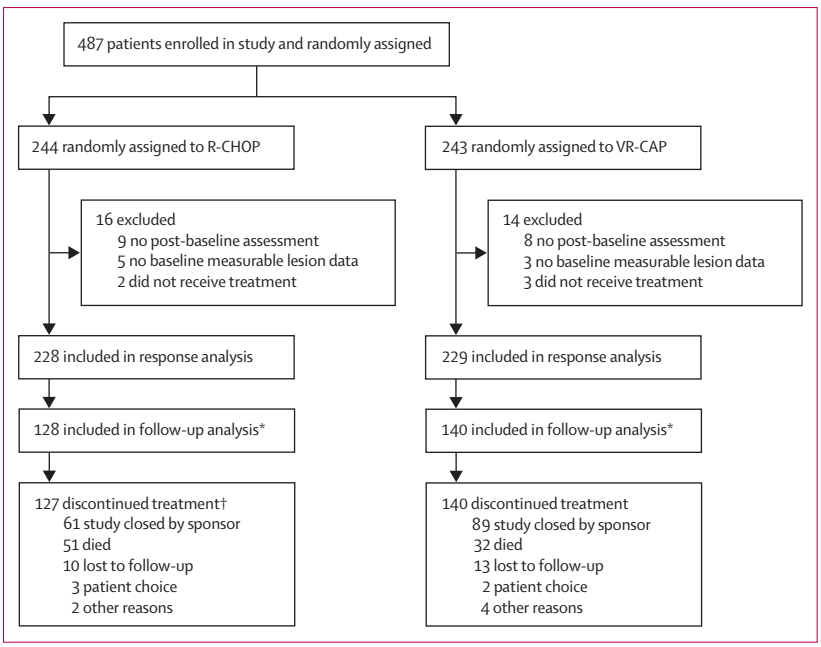

Figure 1: **Trial profile for the follow-up analysis**
R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. VR-CAP=bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone. *Follow-up analysis set included all patients with data collected after the primary analysis clinical cutoff date (Dec 2, 2013). †Discontinuation reason was missing for one patient; after final database lock, this patient was included in the group of patients who discontinued treatment due to study closure by the sponsor.

recurrence of febrile neutropenia). Patients with fewer than 500 neutrophils per μL or febrile neutropenia received granulocyte-colony-stimulating factor (the form used depended on each clinical centre's pharmacy) instead of cyclophosphamide for all subsequent cycles. Those with absolute counts of fewer than 500 neutrophils per μL or febrile neutropenia and platelet counts of less than 50 000 per μL received a 25% dose reduction in cyclophosphamide for subsequent cycles. Patients in whom absolute neutrophil counts of fewer than 500 cells per μL or febrile neutropenia and a platelet count of fewer than 50 000 per μL recurred underwent a further 25% dose reduction for subsequent cycles. Cyclophosphamide was discontinued in patients whose absolute neutrophil count fell to less than 500 cells per μL or who developed febrile neutropenia, and had a platelet count of fewer than 50 000 platelets per μL for a third time. Patients were withdrawn from the study if they were lost to follow-up, withdrew consent, or died during treatment. Adverse events judged to be related to the study drug were reported throughout the follow-up phase. After treatment, only grade 3 and 4 adverse events were recorded. Adverse events were reported in accordance with the US National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0).

Radiographic assessments (CT scans) were done every two cycles during treatment and every 6–8 weeks during follow-up until disease progression, study discontinuation, initiation of alternative therapy, or death. For radiographic assessments, patients had to have assessable disease (ie, objective evidence of disease that was identified by radiological imaging, physical examination, or other procedures as necessary, but was not measurable—eg, bone lesions; mucosal lesions in the gastrointestinal tract; effusions; pleural, peritoneal, or bowel-wall thickening; disease limited to bone marrow; and groups of lymph nodes that were not measurable but were thought to represent lymphoma). Additionally, if more than ten sites of disease were measurable, these other sites of measurable disease could be included as assessable disease.

During the long-term follow-up phase, patients were contacted every 12 weeks (or within 1 week either side of this timepoint) via telephone or physician visit to assess survival status until death. For patients who discontinued treatment before disease progression, end-of-treatment assessments were done and the patients entered short-term follow-up until disease progression or initiation of subsequent antilymphoma therapy. All patients then transitioned to the long-term follow-up phase, during which they were contacted every 12 weeks until death.

Outcomes

Protocol-defined efficacy outcomes assessed at the final analysis were overall survival (measured from date of randomisation to date of death), second primary malignancies (irrespective of onset date and relation to study drug), and subsequent antilymphoma therapy use during the entire study. Safety outcomes were assessed in patients who were followed up until the stopping date after the primary endpoint was achieved.

Statistical analysis

For the primary analysis of the LYM-3002 study, a data accrual period of 24 months and 18 months of follow-up was assumed and a sample size of 486 patients (243 per study group) was planned. Assuming that VR-CAP would improve median progression-free survival by 40%—ie, from 18 months to 25 months—295 events (ie, progressive disease or death) would provide 80% power with a two-sided α of 0·05 to detect such improvement. When the study was designed, the estimated median progression-free survival of eligible patients treated with the standard of care (ie, R-CHOP) was 16·6 months. An independent data and safety monitoring committee oversaw study conduct, reviewed results from the pre-defined interim analyses, and made appropriate recommendations to the sponsor.

For this final analysis of LYM-3002, formal statistical analysis was not planned separately for the data captured after the primary progression-free survival endpoint was achieved. The efficacy analysis was done in the intention-to-treat population, which included all patients who were randomly assigned to the two treatment groups. The safety analysis was done in the follow-up analysis set, which included patients with available data after the

clinical cutoff date for the primary analysis (Dec 2, 2013). Before the final analysis, three preplanned interim analyses were done as outlined in the study protocol. The first was done on April 23, 2009, when 100 patients were randomly assigned. The clinical cutoff for the second interim analysis was April 5, 2010, after 231 patients were randomly assigned. For the third interim analysis, the clinical cutoff was July 5, 2011, after 435 patients were randomly assigned and 173 progression-free-survival events had occurred.

The Kaplan-Meier method was used to estimate time-to-event distributions, with stratified log-rank tests and Cox models used for between-group comparisons of time-to-event endpoints. The stratification factors included International Prognostic Index (0–1 *vs* 2 *vs* 3, and 4–5) and disease stage at diagnosis (II *vs* III *vs* IV). The proportional hazards assumption of the primary effect was not checked when running the Cox proportional hazards model. A post-hoc analysis of overall survival was done according to mantle-cell- lymphoma-specific International Prognostic Index (MIPI) risk category, Ki-67 expression status (≤10% *vs* >10%), and MIPI with biological component (MIPIb) risk category in patients who underwent baseline Ki-67 assessments. Time-to-event analyses and analysis populations are defined in the appendix (p 2). We used SAS (versions 9.2 and 9.4) for all statistical analyses.

This trial is registered with ClinicalTrials.gov, number NCT00722137.

Role of the funding source

The study funder was involved in study design, and employees of the study funder had roles in data collection, analysis, and interpretation, and writing of the report. The corresponding author had access to all study data and had final responsibility for the decision to submit for publication.

Results

Between May 22, 2008, and Dec 5, 2011, 487 patients were enrolled and randomly assigned (intention-to-treat population): 243 to the VR-CAP group and 244 to the R-CHOP group (figure 1).[10] 482 patients were included in the safety population (240 in the VR-CAP group and 242 in the R-CHOP group), and 268 in the follow-up analysis set (140 in the VR-CAP group and 128 in the R-CHOP group). In the follow-up analysis set, 32 patients (23%) in the VR-CAP group discontinued because of death, compared with 51 (40%) in the R-CHOP group (figure 1). The main cause of these deaths was progressive disease (37 [29%] *vs* 19 [14%]).

Demographic and disease characteristics in the follow-up analysis set were generally balanced between treatment groups (table 1). Briefly, the median age of enrolled patients was 66 years (range 26–83), and 190 (71%) were men. 132 (49%) of the 268 patients included in the follow-up analysis were aged 65 years or younger.

	VR-CAP group (n=140)	R-CHOP group (n=128)
Age, years		
Median (IQR)	65 (58–71)	66 (60–70)
≤65	75 (54%)	57 (45%)
>65	65 (46%)	71 (556%)
Median weight (range), kg	70 (40–135)	69 (40–109)
Sex		
Male	100 (71%)	90 (70%)
Female	40 (29%)	38 (30%)
Ethnic origin		
White	87 (62%)	91 (71%)
Asian	49 (35%)	35 (27%)
Black or African American	3 (2%)	0
Other	1 (1%)	2 (2%)
ECOG performance status		
0	72 (51%)	52 (41%)
1	58 (41%)	69 (54%)
2	10 (7%)	7 (56%)
International Prognostic Index score*		
0–1 (low risk)	30 (21%)	25 (20%)
2 (low–intermediate risk)	46 (33%)	39 (3130%)
3 (high–intermediate risk)	45 (32%)	50 (39%)
4–5 (high risk)	19 (14%)	14 (11%)
Disease stage at diagnosis		
II	8 (6%)	10 (8%)
III	27 (19%)	24 (19%)
IV	105 (75%)	94 (73%)
Median time since initial diagnosis (range), months	1 (0–36)	1 (0–28)
Increased lactate dehydrogenase	41 (29%)	36 (28%)
Bone marrow involvement	91 (65%)	86 (67%)
Cellularity		
Blastoid	9/134 (7%)	10/126 (8%)
Nodular	65/134 (49%)	62/126 (49%)
Other	60/134 (45%)	54/126 (43%)
Reason for transplantation ineligibility†		
Age	101 (72%)	95 (74%)
Intolerant to high-dose intensive chemotherapy regimens	9 (6%)	10 (8%)
Comorbidity	19 (14%)	20 (16%)
Investigator decision‡	14 (10%)	11 (9%)
Other§	19 (14%)	11 (9%)

Data are n (%), unless otherwise specified. Because of rounding, the sum of percentages might not equal 100%. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. VR-CAP=bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone. ECOG=Eastern Cooperative Oncology Group. *Data from stratification. †Based on the sponsor's medical monitor assessment; patients might have met more than one reason for transplantation ineligibility. ‡Because of older age, comorbidity, an inability to tolerate high-dose chemotherapy. §Socioeconomic reasons, unavailability of stem-cell transplantation, or patient refusal.

Table 1: **Patient demographics and baseline characteristics (follow-up analysis set)**

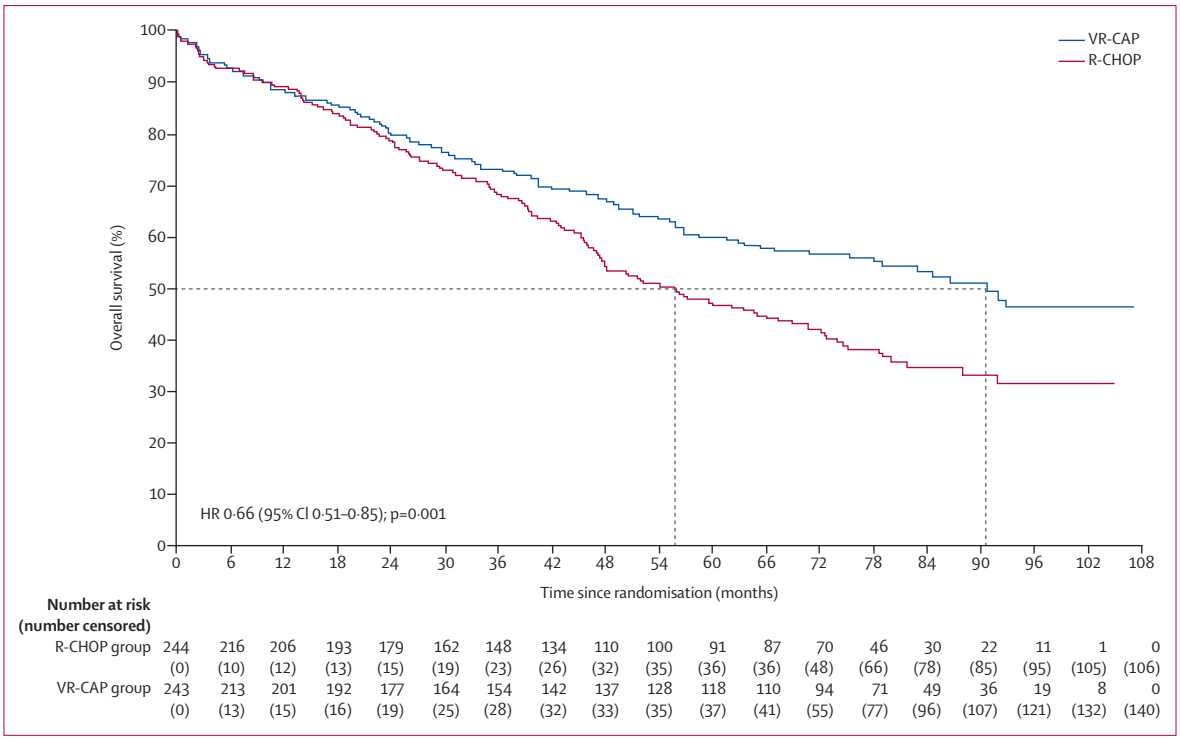

Figure 2: **Final analysis of overall survival in the intention-to-treat population**
R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. VR-CAP=bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone. HR=hazard ratio.

	VR-CAP group (n=243)	R-CHOP group (n=244)	Hazard ratio (95% CI)*
Number of patients censored	140 (58%)	106 (43%)	..
Number of events	103 (42%)	138 (57%)	..
Median overall survival, months (95% CI)	90·7 (71·4–NE)	55·7 (47·2–68·9)	0·66 (0·51–0·85)†
Overall survival at 4 years, % (95% CI)	67·3% (60·6–73·0)	54·3% (47·5–60·7)	NA
Overall survival at 6 years, % (95% CI)	56·6% (49·6–63·0)	42·0% (35·2–48·6)	NA

Data are n (%), unless otherwise specified. VR-CAP=bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. NE=not estimable. NA=not applicable. *Estimated based on a Cox´s model stratified by International Prognostic Index risk and disease stage. †p=0·001.

Table 2: **Overall survival in the intention-to-treat population**

199 (74%) patients had stage IV disease and almost half (49%) of patients in each group had disease with nodular morphology (65 patients in the VR-CAP group and 62 in the R-CHOP group; table 1). Median treatment duration was 17·7 weeks (IQR 17·0–20·0) in the VR-CAP group and 16·7 weeks (16·0–19·0) in the R-CHOP group. Baseline Ki-67 expression and MIPIb risk categories were similar between groups (appendix p 3).

After median follow-up of 82·0 months (IQR 74·1–94·2) among surviving patients (82·5 months [74·1–94·6] in the VR-CAP group *vs* 81·5 months [74·4–93·6] in the R-CHOP group), median overall survival was 90·7 months (95% CI 71·4 to not estimable) in the VR-CAP group and 55·7 months (47·2 to 68·9) in the R-CHOP group (HR 0·66 [95% CI 0·51–0·85]; p=0·001; figure 2; table 2).

At final analysis, 103 (42%) of 243 patients in the VR-CAP group had died, compared with 138 (57%) of 244 in the R-CHOP group. Progressive disease was the main cause of death in both groups (64 [26%] of 243 patients in the VR-CAP group *vs* 92 [13%] of 244 in the R-CHOP group). 18 (7%) patients in each group died from adverse events. Adverse events leading to death in the VR-CAP group were infections and infestations (seven [3%]) and respiratory, thoracic, and mediastinal disorders (five [2%]). In the R-CHOP group, adverse events leading to death were cardiac disorders (six [2%]), infections and infestations (six [2%]), and respiratory, thoracic, and mediastinal disorders (eight [3%]). Nine (4%) patients in the VR-CAP group and ten (4%) in the R-CHOP group died from treatment-related adverse events. Other causes led to 21 (9%) deaths in the VR-CAP group (septic shock [n=2], cardiogenic shock [n=1], stroke [n=1], uraemic encephalopathy secondary to acute renal failure [n=1], general deterioration [n=1] pulmonary carcinoma [n=1], melanoblastoma [n=1], lung cancer [n=1], septicaemia and intracerebral bleeding [n=1], myelodysplastic syndrome [n=1], acute coronary syndrome [n=1], pneumonia [n=2], sudden death caused by a fall [n=1], neurological worsening and internal comorbidities [n=1], and unknown [n=5]) and 28 (11%) deaths in the R-CHOP group (septic shock [n=1], brain haemorrhage [n=1], secondary malignancies [acute

myeloid leukaemia and myelodysplastic syndrome [n=1]; lung cancer [n=1]), diffuse cardiosclerosis [n=1], acute cardiovascular collapse [n=1], pulmonary infection [n=1], acute leukaemia [n=1], repeated syncopes and ventricular arrhythmia [n=1], renal failure and respiratory insufficiency [n=1], multiorgan failure [n=1], sepsis [n=1], acute heart failure [n=1], pneumonia [n=1], interstitial pulmonary disease [n=1], head injury caused by a fall [n=1], cardiovascular collapse due to tumour intoxication [n=1], unknown cause probably related to disease [n=1], case unknown [n=1], heart attack [n=1], ischaemic heart disease [n=1], sudden death at home, [n=1], sudden death with absence of disease progression or previous signs of worsening condition [n=1]; main cause unknown [died in another hospital; n=1], and unknown [n=4]).

The point difference in overall survival at 4 years was 13·0% (67·3% in the VR-CAP group *vs* 54·3% in the R-CHOP group) and 14·6% at 6 years (56·6% *vs* 42·0%), suggesting consistent improvements in survival outcomes in patients receiving VR-CAP compared with those receiving R-CHOP. In a post-hoc exploratory subgroup analysis, VR-CAP was associated with significantly improved overall survival compared with R-CHOP in Ki-67-positive patients (ie, those with Ki-67 expression in >10% tumour cells) irrespective of Ki-67 expression level, but not in Ki-67-negative patients (appendix p 4), and in patients in low MIPIb risk categories (appendix p 4). When analysed according to MIPI risk category, VR-CAP was associated with significantly improved overall survival compared with R-CHOP in the low-risk and intermediate-risk categories, but not in the high-risk category (appendix p 4).

During the entire 9 years since the start of the study, 255 (52%) of 487 patients received subsequent therapies, 104 (43%) in the VR-CAP group and 151 (62%) in the R-CHOP group. 80 (77%) of 104 patients in the VR-CAP group and 123 (81%) of 151 in the R-CHOP group received subsequent antineoplastic therapy, and 55 (53%) and 89 (59%), respectively, received rituximab as second-line therapy (table 3). Alkylating agents and systemic corticosteroids were also commonly used in both groups (table 3).

Second primary malignancies were reported in ten patients in each group throughout the study duration. In the VR-CAP group, these second malignancies were basal cell carcinoma, gastric cancer, hepatocellular carcinoma, lung adenocarcinoma, malignant lung neoplasm, malignant melanoma, myelodysplastic syndrome, non-small-cell lung cancer, rectal adenocarcinoma, and small intestine adenocarcinoma (all in one patient each). In the R-CHOP group, the second primary malignancies were acute leukaemia, clear cell renal cell carcinoma, gastric cancer, lung adenocarcinoma, malignant melanoma, and squamous cell carcinoma (all in one patient each), myelodysplastic syndrome (in two patients), and prostate cancer (in three patients). We noted no patterns in the type of second primary malignancies that occurred.

	VR-CAP group (n=243)	R-CHOP group (n=244)
Received subsequent therapy	104 (43%)	151 (62%)
Received other antineoplastic drugs	80 (77%)	123 (82%)
Rituximab		
Frontline maintenance	0	2 (1%)
Second-line and beyond	55 (53%)	89 (59%)
Cisplatin	16 (15%)	19 (13%)
Bortezomib	4 (4%)	28 (19%)
Ibrutinib	12 (12%)	16 (11%)
Temsirolimus	6 (6%)	12 (8%)
Protein kinase inhibitors	9 (9%)	8 (5%)
Oxaliplatin	5 (5%)	9 (6%)
Carboplatin	2 (2%)	9 (6%)
Alkylating agents		
Any	67 (64%)	109 (72%)
Cyclophosphamide	37 (36%)	64 (42%)
Bendamustine	25 (24%)	45 (30%)
Ifosfamide	11 (11%)	11 (7%)
Corticosteroids for systemic use	56 (54%)	80 (53%)
Dexamethasone	29 (28%)	45 (30%)
Prednisone	16 (15%)	26 (17%)
Prednisolone	10 (10%)	22 (15%)
Methylprednisolone	9 (9%)	8 (5%)
Antimetabolites	43 (41%)	66 (44%)
Cytarabine	24 (23%)	34 (23%)
Fludarabine	16 (15%)	30 (20%)
Gemcitabine	12 (12%)	21 (14%)
Methotrexate	8 (8%)	7 (5%)
Plant alkaloids and other natural products	46 (44%)	52 (34%)
Vincristine	27 (26%)	35 (23%)
Etoposide	23 (22%)	33 (22%)
Cytotoxic antibiotics and related substances	30 (29%)	47 (31%)
Doxorubicin	16 (15%)	35 (23%)
Mitoxantrone	11 (11%)	16 (11%)
Immunosuppressants	14 (13%)	16 (11%)
Lenalidomide	11 (11%)	14 (9%)
All other treatments	8 (8%)	17 (11%)
Radiotherapy	5 (5%)	10 (7%)

Treatments used in ≥5% of patients in either group are included. In each column, the denominator used to calculate the percentages is the number of patients who received subsequent therapy in that treatment group (n=151 in the R-CHOP group; n=104 in the VR-CAP group). VR-CAP=bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Table 3: **Most commonly used subsequent therapies in the intention-to-treat population**

Of these 20 patients with second primary malignancies, 19 had only one second primary malignancy. One patient in the R-CHOP group had two different metachronous second primary malignancies—clear cell renal cell carcinoma, and prostate cancer. The patient underwent curative surgeries for both cancers. Three patients in the

VR-CAP group (one patient each with malignant melanoma, lung adenocarcinoma and myelodysplastic syndrome) and five in the R-CHOP group (one patient each with malignant melanoma, myelodysplastic syndrome, acute leukaemia, lung adenocarcinoma, and prostate cancer) died as a result of their second primary malignancy.

Acute toxicities resulting from both treatment regimens have been summarised in detail previously.[9] 19 (8%) of 240 patients in the VR-CAP group, and 14 (6%) of 242 in the R-CHOP group, discontinued the study because of drug-related adverse events (some patients had more than one): blood and lymphatic system disorders (five [2%] of 240 in the VR-CAP group *vs* two [1%] of 242 in the R-CHOP group), infections and infestations (five [2%] *vs* five [2%]), nervous system disorders (four [2%] *vs* two [1%]), cardiac disorders (three [1%] *vs* two [1%]), general disorders and administration site conditions (three [1%] *vs* one [<1%]), gastrointestinal disorders and hepatobiliary disorders (one [<1%] *vs* one [<1%]), vascular disorders (one [<1%] *vs* none), injury, poisoning, and procedural complications (none *vs* two [1%]), metabolism and nutrition disorders (none *vs* three [1%]), and musculoskeletal and connective tissue disorders (none *vs* one [<1%]). Since Dec 2, 2013, adverse events were reported in two (1%) of 140 patients in the VR-CAP group and one (1%) of 128 in the R-CHOP group. Grade 4 lung adenocarcinoma (stage IV) was reported in a patient receiving VR-CAP, who subsequently received cisplatin, vinorelbine, and palliative supportive care. Grade 2 pneumonia was reported in a patient receiving R-CHOP treatment, who was treated with amoxicillin and recovered without sequelae. Neither of these events was judged to be related to the administered study drugs. The other patient in the VR-CAP group had a serious adverse event: grade 4 gastric cancer (stage IV). The patient was treated with systemic therapy of S-1 and cisplatin, but did not recover. This event was judged to be possibly attributable to cyclophosphamide, doxorubicin, or bortezomib use. No late toxicities (including haematological toxicities) were reported in the remaining patients. A subtype statistical analysis of efficacy and safety in patients with blastoid mantle cell lymphoma was not feasible because the sample was too small.

Discussion

In this study, the final follow-up outcomes from the pivotal LYM-3002 trial show that replacement of vincristine with bortezomib in the R-CHOP chemotherapy regimen significantly improved median overall survival in previously untreated patients with mantle cell lymphoma, with a manageable safety profile. The ultimate therapeutic goal for patients with mantle cell lymphoma is potential extension of survival and improved quality of life via long-term treatments associated with minimal toxicities.[11] The patients included in this trial, with newly diagnosed mantle cell lymphoma who were ineligible for intensive therapy or bone marrow transplantation, are representative of the broader patient population with mantle cell lymphoma in the clinical setting.[10,12–15] To the best of our knowledge, ours is the first study to show that bortezomib-based therapy is associated with long-term survival benefits compared with standard R-CHOP in this patient population.

At the time of the primary analysis,[9] overall survival data were not mature after 158 (32%) deaths, and median overall survival had not been reached for VR-CAP versus R-CHOP (not reached *vs* 56·3 months; HR 0·80 [95% CI 0·59–1·10]; p=0·17). However, 4-year overall survival estimates with VR-CAP compared with R-CHOP seemed promising (64% *vs* 54%).[9] In this follow-up analysis, 67% of patients in the VR-CAP group were alive at 4 years, compared with 54% in the R-CHOP group. This outcome seems plausible in the context of 4-year survival data reported in phase 3 studies of other conventional first-line cytotoxic chemotherapies for mantle cell lymphoma: R-CHOP versus R-fludarabine plus cyclophosphamide (62% *vs* 47%),[14] R-CHOP versus bendamustine plus rituximab (no difference [actual percentages not reported]),[10] and melphalan, chlorambucil, and prednisone versus rituximab, melphalan, chlorambucil, and prednisone (52% *vs* 55%).[16]

Previously published exploratory analyses[17] of bortezomib dose intensity in this trial suggested that overall survival from the landmark point at the end of cycle 6 was significantly longer in the high-dose-intensity group (n=93) than in the low-dose-intensity group (n=88; HR 0·43 [95% CI 0·23–0·80]; p=0·0059), when a median bortezomib dose of 4·6 mg/m² per cycle during the first six cycles was used as the cutoff to define low versus high dose intensity.

Patients in this follow-up analysis had a median age of 66 years, and almost three quarters had stage IV (advanced) disease. In a post-hoc subgroup analysis, VR-CAP was associated with improved overall survival compared with R-CHOP in patients positive for Ki-67, especially in patients with high (>30%) Ki-67 expression. VR-CAP was also associated with a generally favourable effect across all MIPIb categories, strengthening the prognostic value of the Ki-67 index together with MIPIb as a standard biomarker in mantle cell lymphoma.[18,19]

Induction therapy with VR-CAP resulted in worse haematological toxicity than that with R-CHOP at the time of the primary analysis.[9] However, in this final analysis, no further haematological toxicities were reported, and no increases in peripheral neuropathy or second primary malignancies were noted. The only clinically meaningful long-term toxicity was a serious event of stage IV gastric cancer that was possibly attributable to use of cyclophosphamide, doxorubicin, or bortezomib. Of note, a higher proportion of patients in the R-CHOP than in the VR-CAP group discontinued the study because of death (40% *vs* 23%). Furthermore,

subsequent therapies were used less often by patients in the VR-CAP group than by those in the R-CHOP group (43% *vs* 62%).

Overall, the safety profile of VR-CAP was as expected during this follow-up period on the basis of previously reported acute toxicities at primary analysis,[9] data for the use of bortezomib plus R-CHOP in non-Hodgkin lymphoma,[20–22] and data for bortezomib monotherapy in relapsed or refractory mantle cell lymphoma.[23,24] In accordance with past experience in patients with multiple myeloma or B-cell lymphoma, modification of the dose frequency to weekly or exploration of alternative routes of administration (eg, subcutaneous) along with suitable supportive treatments could reduce toxicities and result in an improved safety profile after chronic treatment.[25] Compared with intravenous administration, subcutaneous administration of bortezomib is associated with less peripheral neuropathy and has non-inferior efficacy.[25]

A limitation of this study is that maintenance therapy with rituximab, which could have further improved progression-free survival and overall survival in both groups, was not included in the study. Maintenance rituximab was not recommended as a standard of care at the time of study initiation. Another limitation of our study is that new treatment guidelines for mantle cell lymphoma were introduced in 2018, in which use of Bruton tyrosine kinase inhibitors and other targeted therapies was recommended.[26]

In conclusion, VR-CAP frontline therapy was associated with significantly improved overall survival compared with R-CHOP in transplant-ineligible patients with newly diagnosed mantle cell lymphoma. The safety profile of VR-CAP was manageable and predictable. Our data support further assessment of the VR-CAP regimen, and the combination of bortezomib with newer agents[27] to treat mantle cell lymphoma.

Contributors

TR and FC designed the study. TR, JJ, HP, GV, NS, JD, MR, JM, JP, GT, RO, and FC were involved in data collection, including patient accrual, enrolment, recruitment, and treatment. TR, SNa, PH, CA, SNe, and FC were involved in data analysis and interpretation. All authors participated in drafting or review of the Article and approval of the submitted version.

Declaration of interests

TR and JM have received research grants from Janssen Research & Development. NS has received research grants from Roche and Janssen-Cilag. MR has received research grants from Celgene and personal fees from Ipsen and Novartis. SNa, PH, CA, and SNe are employees of Janssen and hold stock in Johnson & Johnson. All other authors declare no competing interests.

Data sharing

The data sharing policy of the study sponsor is available online. Requests for access to the study data can be submitted through the Yale Open Data Access Project.

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