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Phase II trial of R-CHOP plus bortezomib induction therapy followed by bortezomib maintenance for newly diagnosed mantle cell lymphoma: SWOG S0601

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Summary

Bortezomib is active in mantle cell lymphoma (MCL), with approval in upfront and relapsed settings. Given inevitable recurrence following induction chemoimmunotherapy, maintenance approaches are a rational strategy to improve clinical outcomes. We conducted a phase II study to evaluate the safety and efficacy of six cycles of R-CHOP plus bortezomib (1.3 mg/m² days 1 and 4 of 21 day cycles) followed by bortezomib maintenance (1.3 mg/m² days 1, 4, 8, and 11 every 3 months for 2 years). Sixty-five eligible patients were enrolled. The treatment was well-tolerated and toxicities were mainly hematologic. The rate of grade 3 peripheral neuropathy was low (5%).

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Author Contributions

S.H.B, J.W.F, R.I.F. designed the study; B.G.T., H.L., S.H.B, R.I.F, W.R.B., L.M.R., J.D.F., M.A.D., D.F.M., O.P., S.M.S, M.L., and J.W.F. performed research; H.L. and M.L. performed statistical analyses; B.G.T., H.L., S.M.S., M.L., and J.W.F. analyzed and interpreted the data; B.G.T. wrote the manuscript, and all authors reviewed the draft manuscript and approved the final version for submission.

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Authors' Disclosures of Potential Conflicts of Interest

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With a median follow-up of 6.8 years, 2-year progression-free survival (PFS) was 62%, and 2-year overall survival (OS) was 85%. At 5 years, PFS was 28% and OS was 66%. MIPI scores were significantly associated with 2-year PFS, but did not predict long-term (5-year) PFS. Baseline Ki-67 index was significantly associated with survival. Combination R-CHOP with bortezomib followed by maintenance bortezomib appears to improve outcomes compared historically with R-CHOP alone, with prolonged remissions in a subset of patients. These results suggest that inclusion of bortezomib with induction chemotherapy and/or maintenance is promising in MCL and warrants further exploration.

Keywords

lymphoma; chemotherapy; mantle cell lymphoma; maintenance therapy; proteasome inhibition

Introduction

Mantle cell lymphoma (MCL) is a distinct subtype of B cell non-Hodgkin lymphoma characterised by the CCND1/IGH (t[11;14]) translocation leading to overexpression of cyclin D1. Although the survival of patients with MCL has improved over the last decade, much of this benefit is associated with selected populations of younger patients receiving intensive therapy (Delarue et al., 2013; Geisler et al., 2008; Hermine et al., 2010). Unfortunately, aggressive therapies are not feasible for many patients with MCL, and in population-based studies, where the median age at diagnosis is 70 or older, the median overall survival (OS) remains 3–5 years (Abrahamsson et al., 2014; Leux et al., 2014; van de Schans et al., 2010). The regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is a standard induction therapy for MCL that is associated with high response rates, but remissions are not durable, with a median progression-free survival (PFS) of 14 to 22 months (Howard et al., 2002; Lenz et al., 2005; Robak et al., 2015; Rummel et al., 2013). Thus, improved therapies are clearly needed, especially for the growing population of patients with MCL not eligible for intensive regimens (Aschebrook-Kilfoy et al., 2013).

Bortezomib is a low-molecular weight compound that inhibits the protease activity of the 26S proteasome, leading to important regulatory changes in many intracellular proteins relevant to MCL biology, including inhibition of NF- κ B activity (Pham et al., 2003), increased levels of p21 and p27, which regulate cyclin/cdk activity, resulting in cell cycle arrest (Bogner et al., 2003), and cleavage of the anti-apoptotic protein Bcl-2 via caspase 3 activation, leading to apoptosis (Bogner et al., 2006). The clinical activity of bortezomib in MCL has been demonstrated in several phase II trials, in which bortezomib as a single agent produced response rates ranging from 30–50% in patients with relapsed disease (Belch et al., 2007; Fisher et al., 2006; Gerecitano et al., 2009; Goy et al., 2009; Goy et al., 2005; O'Connor et al., 2005; Strauss et al., 2006), and a phase III trial recently showed a progression-free survival (PFS) benefit for bortezomib combined with frontline chemotherapy (Robak et al., 2015). Based on these studies, it is approved in the U.S. and Europe for the treatment of MCL in both the relapsed and upfront settings. The anti-CD20 antibody rituximab has been shown to be synergistic in vitro with bortezomib (Wang et al.,

2008). Additionally, anthracyclines induce NF- κ B in malignant cells, thus potentially increasing cellular dependency on NF- κ B for survival and sensitising cells to proteasome inhibition (Guzman et al., 2002). Combining bortezomib with R-CHOP is therefore a promising strategy to improve the frequency and quality of remissions with induction therapy for MCL.

The pattern of continuous relapse despite initial response that is characteristic of MCL has led to the hypothesis that maintenance therapy may be beneficial in prolonging remissions. A randomised phase III intergroup trial comparing two different maintenance approaches in elderly patients with MCL showed that rituximab maintenance after CHOP-based induction improved both progression-free and overall-survival compared to interferon maintenance (Kluin-Nelemans et al., 2012); thus, several recent or ongoing trials have incorporated a maintenance component to therapy. Given the single-agent activity of bortezomib and relatively low toxicity, maintenance therapy with this drug may be an effective approach to improve PFS duration.

S0601 was therefore designed with the goal of testing the feasibility and efficacy of adding bortezomib to an R-CHOP backbone, and prolonging PFS by incorporating a bortezomib maintenance strategy for patients with newly diagnosed MCL. The objective of this study was to estimate the 2 year PFS, with the goal of improving the rate and duration of remissions for patients with MCL without serious additive toxicity.

Patients and Methods

Study registration

This phase II multicenter trial was initiated in August 2006 and closed to accrual in June 2008. The protocol was approved by the Institutional Review Board at each site, and written consent was obtained from all patients prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki and was registered with ClinicalTrials.gov prior to enrolling patients (ClinicalTrials.gov Identifier: NCT00376961).

Eligibility

Patients with biopsy-proven, previously untreated mantle cell lymphoma were eligible if they were 18 years of age or older, had bi-dimensionally measurable stage III, IV, or bulky (> 10 cm) stage II disease, and a Zubrod performance status of 0–2. Patients were excluded if they received any prior therapy, were HIV-positive, had CNS involvement, had grade ≥ 2 peripheral neuropathy, were pregnant or nursing, or had a prior malignancy (except non-melanoma skin cancer, in situ cervical cancer, other stage I/II cancers in complete remission, or other cancers in remission ≥ 5 years). Investigators were counseled to adhere to good medical practice guidelines with regard to organ function, hematopoiesis, and hepatitis B virus screening, but results of these tests did not determine eligibility. All patients submitted written informed consent in accordance with institutional and federal guidelines.

Pathology Review

Representative paraffin-embedded sections from the original pre-treatment diagnostic biopsies were requested for central pathology review, which was required to determine eligibility. Diagnoses were established according to the World Health Organisation criteria (Jaffe et al., 2001). The characteristic morphologic features of MCL along with supporting documentation of co-expression of CD19 or CD20 and cyclin D1 protein, and/or the t(11;14)(q13;q32) translocation demonstrated by cytogenetics or fluorescent *in situ* hybridisation (FISH) were required for inclusion.

Baseline Studies

Baseline evaluation included a history and physical examination, radiographic imaging (computerised tomography of the chest, abdomen, and pelvis and fluorodeoxyglucose positron emission tomography [FDG-PET]), routine laboratory studies, bone marrow evaluation, and an echocardiogram.

Protocol Treatment

Patients were treated with six cycles of rituximab (375 mg/m² IV on day 1) plus standard CHOP chemotherapy (Press et al., 2003) (VR-CHOP) with the addition of bortezomib 1.3 mg/m² on days 1 and 4 of every 21 day cycle, consistent with a previously established tolerated dose of bortezomib with R-CHOP in a phase I/II trial (Furman et al., 2010). Day 1 rituximab was withheld if the circulating absolute lymphocyte count (i.e. leukemic mantle cells) was > 5000 cells/microliter to minimise the risk of tumor lysis and cytokine release syndrome. Patients achieving at least stable disease after induction were eligible for maintenance therapy, consisting of bortezomib 1.3 mg/m² IV days 1, 4, 8, and 11 every 3 months for 8 cycles (one cycle was defined as 3 months for the maintenance phase). Standard dose reductions were used for hematologic, hepatic, and renal toxicity. Bortezomib was dose-reduced to 1.0 mg/m² (dose level -1) and 0.7 mg/m² (dose level -2) for peripheral neuropathy or grade 3 non-hematologic toxicities. Myeloid and erythroid growth factors were permitted at the discretion of the treating physician. Patients were removed early from the protocol treatment for progressive disease, unacceptable toxicity, delay of treatment for more than three weeks, or patient preference.

Assessment of Clinical Responses and Toxicity

Data were centrally reviewed, and clinical responses (partial remission [PR], complete remission [CR], or unconfirmed CR [CRu]) were coded according to International Workshop NHL criteria (Cheson et al., 1999). Remission status was assessed 3–6 weeks after the 6th cycle of induction to determine eligibility for maintenance therapy, and subsequent restaging was performed every 6 months for 2 years. At each time point a patient history and physical examination, blood counts, and diagnostic CT scans were performed. An FDG-PET scan was required only for the first restaging after induction. National Cancer Institute Common toxicity criteria (version 3.0) were used to grade toxicities (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf).

Baseline tumor tissue biological correlates analysis

For studies of SOX11 expression, specimens were formalin-fixed paraffin-embedded tissues from diagnostic tumor biopsy specimens as either tissue microarrays (TMA) or unstained tissue slides. TMAs and slides were then stained with antibodies to SOX11 (MRQ-58; mouse monoclonal antibody, Cell Marque Corporation, Rocklin, CA) followed by PowerVision Homo-Mouse Poly HRP IHC Detection System (Leica Biosystems, Buffalo Grove, IL); For quantification of Ki-67, specimens were tissue slides which were stained with Ki-67 (Dako; diluted to 1:100) followed by Dako Flex HRP kit with a low pH retrieval with hematoxylin counterstain. To assess the fraction of Ki-67 positive cells, regions for analysis were selected per the European MCL Network consensus guidelines (Klapper et al., 2009) with the following necessary exceptions: extranodal specimens were included, TMAs were used in addition to biopsies, for several very small specimens the regions were selected non-randomly to ensure that they were not overlapping, and the number of total tumor cells evaluated exceeded 200 in all specimens. The association between the fraction of Ki-67 positive cells and PFS or OS was assessed using a Cox regression statistical analysis.

Statistical Analysis

The primary endpoint of this phase II single arm study was to estimate progression-free survival (PFS). We planned to accrue 60 eligible patients, which gives sufficient power to estimate the 2-year PFS rate to within $\pm 13\%$ (95% CI). Given the historical 2-year PFS rate of 30% of R-CHOP alone in this patient population at the time the study was designed, we considered a 2-year PFS estimate of 42% to warrant further investigation of this therapy. Sixty patients would also provide 85% power at a 0.05 level (one-sided) to detect an improvement in CR/CRu rate from the historical rate of 48% with R-CHOP alone to 65%. Any adverse event occurring with at least 5% probability would be likely seen at least once (95% chance), and toxicity rates would be estimated to within $\pm 13\%$. Toxic effects were coded using the NCI's CTCAE, v3.0 and PFS was defined as the time from registration to the first observation of progressive disease or death due to any cause. Patients who were alive and progression-free at the time of final data analysis were censored at the last assessment. OS and PFS were estimated according to the Kaplan-Meier method (Kaplan and Meier, 1958) and all patients were included in these analyses regardless of whether they received maintenance therapy. Analyses of survival differences by prognostic factors were carried out using Cox regression (Cox, 1972). For univariate analyses, the factors evaluated included age, marrow involvement, bulky disease, extranodal involvement, hemoglobin, LDH, serum beta-2 microglobulin, MIPI risk group, performance status, gender, spleen involvement, stage, and presence of B symptoms. For multivariate analysis, stepwise selection and best subset selection methods were used for model selection. The above factors were included in the model selection, with the exception of factors used to calculate MIPI score (age, performance status, LDH, and WBC). The final model was selected based on minimum AIC from the subset selection. Four factors (bulky disease, spleen involvement, MIPI risk group, and serum beta-2 microglobulin) were included in the final model. Data as of March 30, 2015 were included in the analysis.

For the immunohistochemical analyses, the reviewing pathologists (WRB and OP) and technologists were blinded to all outcome data.

Results

Patient Characteristics

Between November 30, 2006 and May 30, 2008, 68 patients were registered. Central pathology review was performed on all patients. Three patients were determined to be ineligible due to incorrect histologic diagnosis; thus, 65 patients were included in the final analysis and were evaluable for both toxicity and efficacy. Baseline clinical characteristics are detailed in Table 1. The median age of enrolled patients was 61 years (range, 36 to 85), and 80% were male. All patients had advanced disease except one patient who had bulky stage II. The distribution of MIPI scores was 45% low risk, 43% intermediate risk, and 12% high risk.

Treatment

Sixty-one patients (94%) completed six cycles of VR-CHOP, and 27 patients (42%) completed the entire 2 years of maintenance bortezomib (Fig 1). Reasons for early termination included: progressive disease (1 patient during induction, 4 between induction and maintenance, and 18 during maintenance), toxicity (n = 3 during induction, due to fatigue and pneumonitis; n = 6 between induction and maintenance including 4 with peripheral neuropathy; and 1 during maintenance due to fatigue), withdrawal to pursue autologous stem cell transplantation (n = 2), or other reasons (n = 3). The median time on maintenance was 20.7 months (range 14 days – 24.8 months), with progressive disease being the most common reason for not completing the planned maintenance course.

During induction therapy, the mean dose intensity (total dose delivered/expected total dose) was 93% for bortezomib, 96% for doxorubicin, 96% for cyclophosphamide, and 96% for vincristine if based on capped dose of 2 mg, or 69% if calculated based on full 1.4 mg/m² dose. Bortezomib doses were reduced or omitted in 12 of 65 patients (18%), and one additional patient was dosed at 1 mg/m² for all 6 cycles contrary to protocol. Vincristine doses were reduced or omitted in 7 patients (11%). During maintenance, one patient did not receive any protocol maintenance therapy due to disease progression after registering to the maintenance step. Bortezomib doses were reduced or omitted during maintenance in 16 of 46 patients (35%), although these 16 patients still completed a median of 6 of the planned 8 cycles of maintenance, and overall maintenance dose intensity was fairly well preserved (91%), excluding cycles not given due to coming off study for disease progression, and excluding one patient who withdrew from the study due to insurance issues.

Safety

During induction therapy, grade 3–4 neutropenia and thrombocytopenia occurred in 52% and 17% of the patients, respectively. Twelve patients (17%) experienced febrile neutropenia. Details of the most significant toxicities are shown in Table 2. One treatment-related death occurred during the study in a patient who developed complete heart block in the setting of pneumonia, hypotension, and acute respiratory distress syndrome. The most common grade 1–2 non-hematologic toxicities during induction were fatigue (69%), alopecia (58%), sensory neuropathy (57%), nausea (51%), musculoskeletal pain (49%), and constipation (48%).

Maintenance therapy was well tolerated, with almost all toxicities limited to grade 1 or 2. Sensory peripheral neuropathy was experienced during induction as grade 1 in 48% of patients, grade 2 in 9%, and grade 3 in 3%. Four patients (6%) experienced motor neuropathy during induction, two as grade 2 and two as grade 3. During maintenance bortezomib, sensory neuropathy occurred as grade 1, 2, and 3 in 36%, 34%, and 2% of patients, and two patients (4%) experienced grade 1 motor neuropathy.

Clinical Responses

Of the 65 patients assessed for response following induction therapy with VR-CHOP, 52 (80%) achieved an objective response to therapy, including partial response (PR; n = 23) or a confirmed (CR; n = 20) or unconfirmed (CRu; n = 9) complete response based upon prespecified criteria (Cheson et al., 1999). Nine additional patients (14%) did not have adequate assessments to determine response but were included in the denominator as nonresponders. Following maintenance therapy, 7 partial responders to induction therapy plus one patient with inadequate assessment after induction converted to a CR/CRu, and one patient with stable disease converted to a PR, for an overall best response rate of 83% (57% CR/CRu and 26% PR) during the study. Median duration of response was 27.7 months, and median duration of CR/CRu was 30.3 months.

Progression-free and overall survival

The median follow up of the patients still alive is 6.8 years. To date, 52 patients have either manifested progressive disease or died, with a median PFS of 29.5 months. The Kaplan-Meier estimate of 2-year PFS is 62% (95% CI: 48.6 – 72.1%), and the estimate of 5-year PFS is 28% (95% CI: 18.0 – 39.7%). Twenty-seven patients died, with a median OS not yet reached. The Kaplan-Meier estimate of 2-year OS is 85% (95% CI: 73.3 – 91.4%) and 5-year OS of 66% (95% CI: 52.9 – 76.0%). Survival curves of the entire cohort are shown in Fig 2.

Prognostic Factor Analysis

We conducted univariate and multivariate Cox regression analyses to identify baseline clinical characteristics associated with PFS and OS. In the univariate analysis (Table 3), bulky disease, MIPI risk group, and performance score > 0 were significantly associated with inferior PFS and OS, and spleen involvement was significantly associated with inferior PFS. The MIPI was not defined at the time this study was initiated, but we reviewed the database for all 65 eligible patients to assign MIPI scores retroactively according to published criteria (Hoster et al., 2008). In a multivariate analysis (excluding performance score since it is included in the calculation of the MIPI score), bulky disease remained statistically significantly associated with both PFS and OS, whereas splenic involvement was associated with PFS but not OS. High-risk MIPI score was associated with a worse OS and a trend towards worse PFS. Beta-2 microglobulin was also significantly associated with OS (Table 4).

Given the relatively high number of patients with long-term disease-free survival compared with historical rates with R-CHOP alone, we attempted to define baseline clinical characteristics predictive of long-term remissions by comparing patients with 5 or more

years of PFS with those with a PFS of less than 5 years. In this univariate logistic regression analysis, only absence of splenic involvement was significantly associated with a PFS of 5 years (odds ratio 3.9, $P = 0.02$). MIPI score was not significantly associated with 5 year PFS, with the distribution of MIPI risk categories amongst patients with long-term PFS being similar to the baseline distribution.

Biological correlates

Baseline tumor characteristics were assessed by evaluating for blastoid morphology and immunohistochemical analysis for Ki-67 and SOX11. Of 48 eligible patients who consented to correlative studies, 23 had a Ki-67 score of 0–10%, 9 had a score of 11–30%, and 6 had a score of >30%, with a median score of 5.5%, somewhat lower than that reported in other studies (15–20%) (Geisler et al., 2008; Hoster et al., 2014; Tiemann et al., 2005) potentially due to technical differences. Ten patients who could not have Ki-67 scored were excluded from the analysis. Tumor samples from 45 patients (94%) expressed SOX11, with any staining scored as positive, and 3 patients (6%) had no SOX11 expression, comparable to the rates reported in other studies (Nordstrom et al., 2014; Nygren et al., 2012). Of 57 patients with available tissue, four (7%) had blastoid variant morphology, also consistent with expected rates (Tiemann et al., 2005).

A Cox regression analysis was performed to assess for an association between continuous Ki-67 score and PFS and OS. Given that Ki-67 scores were skewed towards lower scores, the analysis was performed using a log[Ki-67] score to normalise the distribution. There was a significant association between higher Ki-67 score and mortality (HR 1.47, $P = 0.018$), although the association with PFS was not significant (HR 1.2, $P = 0.07$). Kaplan-Meier estimates of PFS and OS stratified by Ki-67 score are shown (Fig 4). An analysis of the association of SOX11 and blastoid morphology with clinical outcome was not possible due to the small numbers of patients (only 3 SOX11-negative patients and 4 patients with blastoid morphology).

Discussion

This multicenter study has demonstrated the safety and efficacy of administering combination R-CHOP plus bortezomib induction followed by bortezomib maintenance in patients with previously untreated MCL. The observed 2-year PFS of 62% exceeded our pre-defined threshold (2-year PFS of 42%) for further evaluation, despite this being an older patient population with the majority of patients having intermediate or high risk MIPI scores. Several prospective trials of R-CHOP have reported the median PFS for previously untreated MCL to be 14–22 months (Howard et al., 2002; Lenz et al., 2005; Robak et al., 2015; Rummel et al., 2013). While the current study was not randomised, the median PFS of 30 months in a comparable population of patients (based on similar median age, gender ratio, performance status, and number of patients with elevated LDH, B symptoms, and stage IV disease) suggests that the addition of bortezomib to R-CHOP improves clinical outcomes. These findings support the results recently reported from the phase III LYM-3002 trial in which newly diagnosed patients with MCL randomised to VR-CAP (R-CHOP plus

bortezomib, omitting vincristine) had a superior PFS compared to patients who received R-CHOP (median 24.7 vs. 14.4 months) (Robak et al., 2015).

The long follow-up in this study allowed us to assess the frequency of long-term remissions, and we found that nearly one-third of patients remained progression-free at 5 years, a rate significantly higher than has been reported with R-CHOP alone. Perhaps somewhat surprisingly, prolonged responders could not be identified simply on the basis of a low MIPI score, suggesting a potential biological underpinning for this observation that warrants future study. It is also worth noting the durable overall survival in this study, with median OS not yet reached despite nearly 7 years of follow-up. This attests to the progress in therapy for relapsed/refractory in MCL in general and also specifically the ability to salvage relapsed patients following this regimen.

The Ki-67 proliferation index is a well-established prognostic factor for MCL, and consistent with prior studies (Goy et al., 2010; Tiemann et al., 2005), we found that a higher Ki-67 was significantly associated with an inferior overall survival. The lack of separation of the PFS curves at late timepoints (> 5 years) suggests that this regimen may overcome the poor prognosis of a high Ki-67 index in a subset of patients, and that other biologic features may be contributing to outcome.

VR-CHOP with bortezomib maintenance was generally well-tolerated, with toxicities being primarily hematologic, occurring during induction, and comparable to those historically seen with R-CHOP alone (Flinn et al., 2014; Howard et al., 2002; Lenz et al., 2005; Rummel et al., 2013). There was little apparent additive toxicity from inclusion of bortezomib, with the exception of increased rates of peripheral neuropathy. This required some dose reductions of bortezomib, but dose intensity was nevertheless fairly well preserved. It is likely that the rate of neurotoxicity could be reduced by subcutaneous administration of bortezomib, or potentially substitution of newer proteasome inhibitors. Additionally, omission of vincristine may also be helpful in this regard, though it is possible that this could have a small negative impact on efficacy. Interestingly, the rate of grade 3–4 thrombocytopenia was significantly lower (17%) with VR-CHOP than with the rate reported with VR-CAP (57%), suggesting that the lower dose (2.6 mg/m²/cycle vs 5.2 mg/m²/cycle in VR-CAP) and duration (ending day 4 vs day 11) of bortezomib used in our study is important in preserving thrombopoiesis, consistent with the known effects of proteasome inhibition on platelet production (Lonial et al., 2005; Shi et al., 2014).

Recently reported randomised trials have demonstrated a benefit for maintenance rituximab following R-CHOP or autologous stem cell transplantation (Kluin-Nelemans et al., 2012; Le Gouill et al., 2014), supporting a potential role for maintenance strategies in MCL. In the absence of a control arm, our data cannot determine the contribution of maintenance bortezomib to prolonging PFS and/ or OS relative to induction alone. Interim results of a small randomised study did not indicate a benefit of bortezomib maintenance after DA-EPOCH-R plus bortezomib (Dunleavy et al., 2012). While direct comparisons across studies is not feasible, the observation of a slightly longer median PFS, as well as a higher 5-year PFS rate, in our study as compared to the very similar VR-CAP regimen which lacked a

maintenance component is provocative, suggesting that prolonged proteasome inhibition may be beneficial, at least in a subset of patients.

Since the initiation of this study in 2006 it has become clear that R-CHOP may not be the optimal induction regimen for MCL, and other therapies such as R-bendamustine (Flinn et al., 2014; Rummel et al., 2013), or, in younger patients, high-dose cytarabine-containing regimens (Delarue et al., 2013; Geisler et al., 2008; Hermine et al., 2010; Romaguera et al., 2005) are more promising and may serve as superior platforms for combination therapy with proteasome inhibitors (Chang et al., 2014; Friedberg et al., 2011). Based in part on our findings, an ongoing randomised U.S. Intergroup study (E1411) is evaluating the role of adding bortezomib to R-bendamustine induction.

In summary, our results support the feasibility and efficacy of including bortezomib as part of induction and maintenance on an R-CHOP backbone for the treatment of newly diagnosed MCL. The high overall survival rate is noteworthy in this elderly population with more than 50% of patients with intermediate or high risk MIPI scores. Therapy for MCL is a rapidly evolving field, with many exciting new agents being tested in clinical trials, and it remains to be determined how best to combine bortezomib or newer proteasome inhibitors with other therapies. Despite the many active treatments for MCL, it is likely that proteasome inhibition will continue to play a role given the distinct mechanism of action and expected lack of cross-resistance with other therapies.

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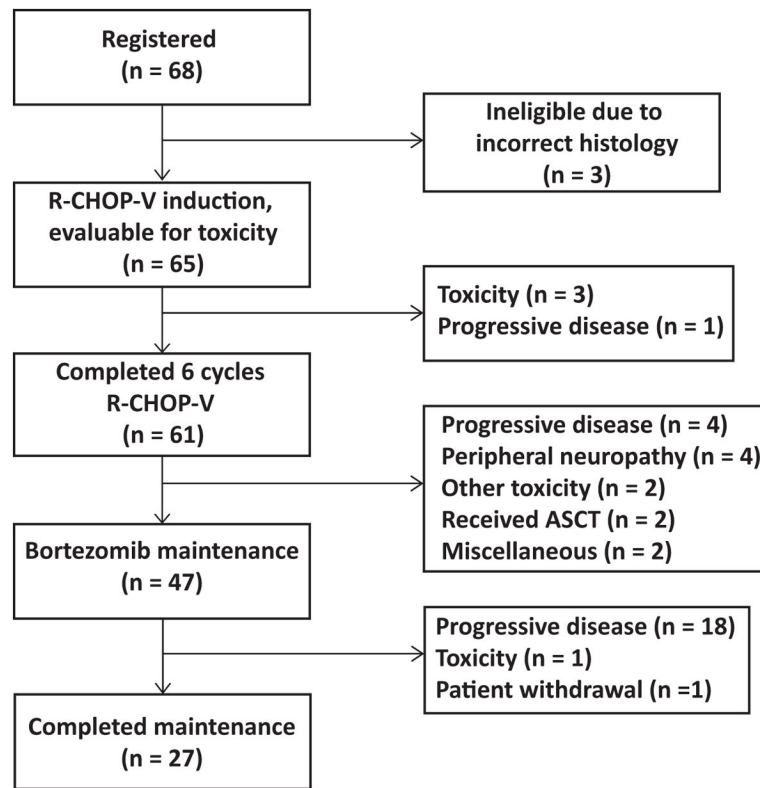


Figure 1. CONSORT diagram of patients enrolled in S0601. VR-CHOP: bortezomib, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ASCT: autologous stem cell transplantation

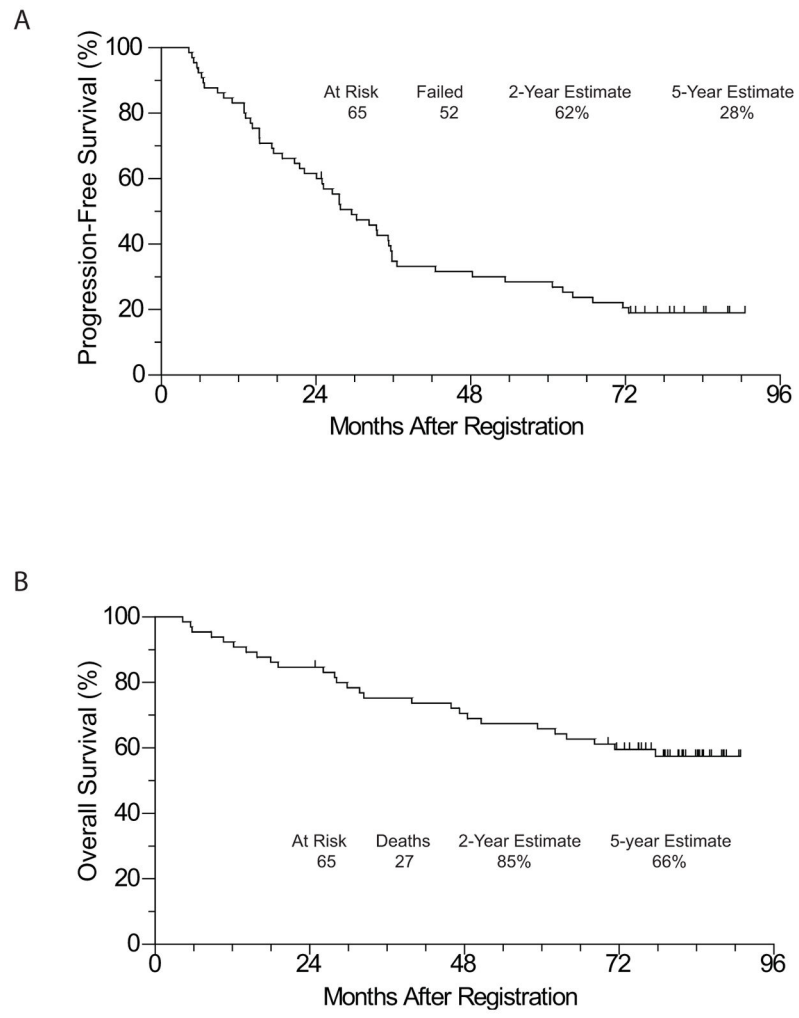


Figure 2.
(A) PFS and (B) OS of the entire cohort

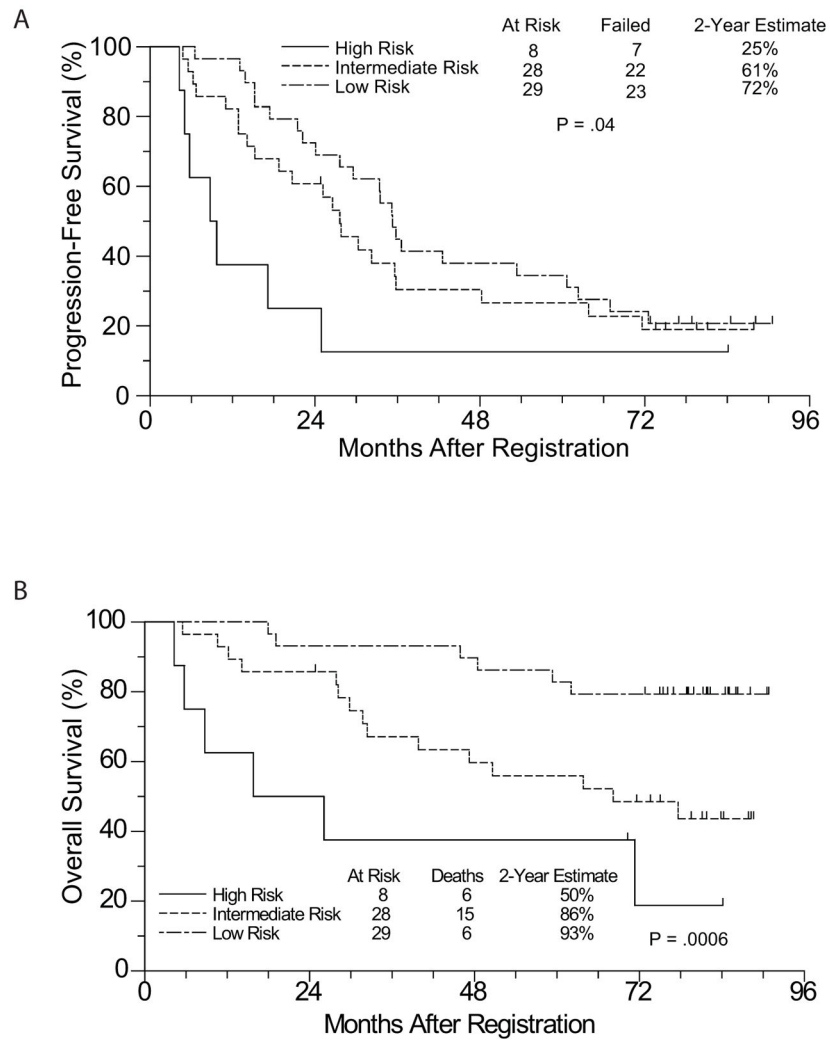


Figure 3.
(A) PFS and (B) OS by MIPI score

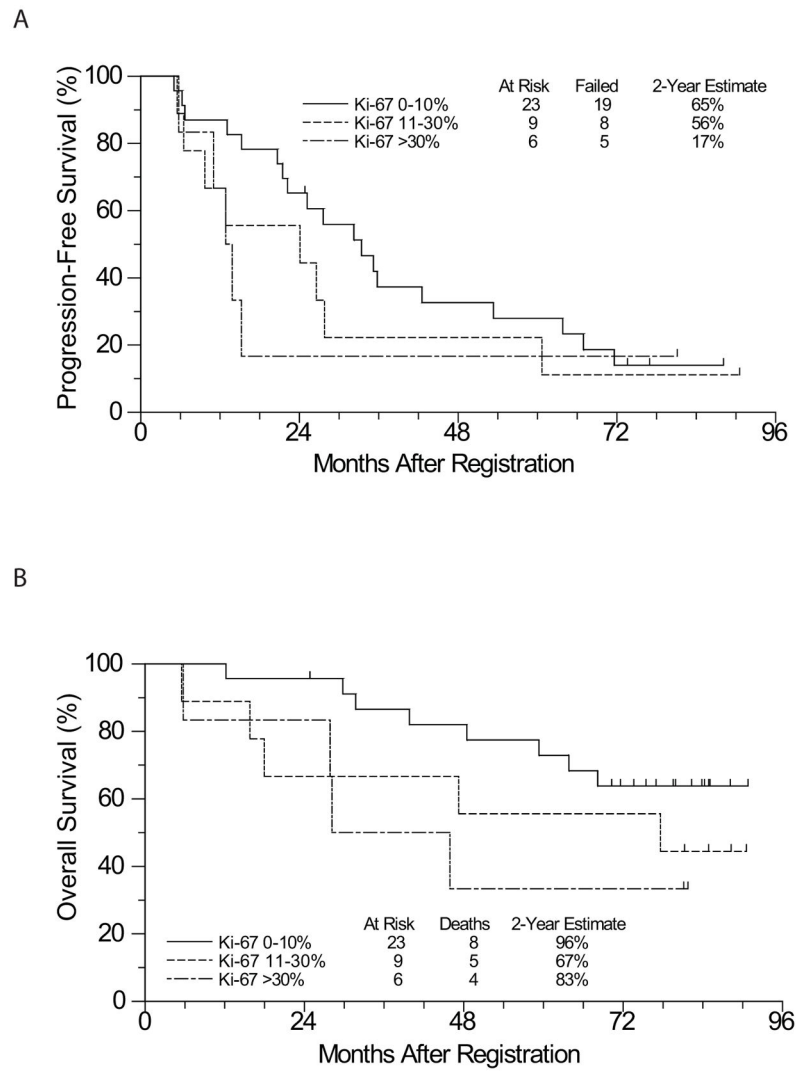


Figure 4.
 (A) PFS and (B) OS by Ki-67 proliferation index from baseline tumor samples

Table 1

Baseline characteristics of eligible patients (N = 65)

Characteristic	N	%
Age		
Median, y (range)	61 (36–85)	
Sex		
Female	13	20
Race		
White	61	94
Black	2	3
Asian	1	2
Pacific Islander	1	2
B symptoms		
Present	18	28
LDH		
Elevated	24	37
Bulky disease (> 10 cm)		
Present	10	15
Marrow involvement		
Present	51	78
Disease stage		
Bulky II	1	2
III	10	15
IV	54	83
Performance status		
0	39	60
1	24	37
2	2	3
MIPI risk score		
Low	29	45
Intermediate	28	43
High	8	12
Blastoid histology		
No	53	81
Yes	4	6
Not assessed [†]	8	12
SOX11 expression		
Yes	45	69
No	3	5

Characteristic	N	%
Not assessed [†]	17	26
Ki-67 index		
10%	23	35
> 10%	15	23
Not assessed [†]	27	42

[†]Tissue was not available to assess blastoid morphology in 8 patients. Reasons for not assessing Ki-67 or SOX11 included: patients not consenting for correlative studies (n = 7), no tissue available or insufficient specimen (n= 20 for Ki-67, n = 10 for SOX11)

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Table 2

Adverse events at least possibly related to study treatment. All Grade 4 or 5 adverse events, as well as common (5% of patients) Grade 3 events are included.

Adverse Event (grade 3)	Associated with VR-CHOP n (%) of eligible patients (total n = 65)			Associated with bortezomib maintenance n (%) of eligible patients (total n = 47)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Hematologic/infection						
Neutropenia	9 (14)	25 (38)	-	-	-	-
Febrile neutropenia	11 (17)	1 (2)	-	-	-	-
Thrombocytopenia	5 (8)	6 (9)	-	-	-	-
Anemia	3 (5)	-	-	-	-	-
Lymphopenia	11 (17)	4 (6)	-	1 (2)	1 (2)	-
Leukopenia	16 (25)	10 (15)	-	-	-	-
Lung infection	4 (6)	-	-	1 (2)	-	-
Cardiovascular	-	-	1 (2)	-	-	-
Diarrhea	3 (5)	-	-	-	-	-
Fatigue	4 (6)	2 (3)	-	1 (2)	-	-
Hyperglycemia	3 (5)	-	-	-	-	-
Hyperuricemia	-	1 (2)	-	-	-	-
Sensory neuropathy	3 (5)	-	-	1 (2)	-	-

Table 3

Univariate Cox regression analysis of baseline factors for PFS and OS in the 65 eligible patients

Factor	Progression-Free Survival HR (95% CI) P=.	Overall Survival HR (95% CI) P=.
Age > 60	0.61 (0.35–1.06) P=.08	1.65 (0.74–3.68) P=.22
Bone marrow Involvement	1.12 (0.59–2.13) P=.74	1.06 (0.43–2.63) P=.90
Bulky disease	2.30 (1.12–4.75) P=.0240	3.66 (1.53–8.75) P=.0035
Extranodal involvement	0.69 (0.34–1.37) P=.29	0.58 (0.24–1.45) P=.25
Hemoglobin median (13.6 g/dl)	1.29 (0.74–2.22) P=.37	1.52 (0.69–3.32) P=.30
Elevated LDH	1.68 (0.96–2.93) P=.07	1.86 (0.87–3.96) P=.11
Beta-2 microglobulin > median (2.55 mg/L)	1.31 (0.75–2.28) P=.34	0.89 (0.42–1.89) P=.76
High risk MIPI	2.60 (1.16–5.81) P=.0201	3.63 (1.46–9.04) P=.0057
Performance status 1 or 2	2.07 (1.19–3.60) P=.0096	3.38 (1.56–7.32) P=.0020
Male sex	1.09 (0.53–2.24) P=.82	0.74 (0.30–1.84) P=.52
Spleen involvement	2.07 (1.19–3.61) P=.0103	1.46 (0.68–3.11) P=.33
Stage IV	0.75 (0.37–1.49) P=.41	0.45 (0.19–1.06) P=.07
B symptoms	1.42 (0.79–2.56) P=.25	1.37 (0.61–3.05) P=.44

Table 4

Multivariate Cox regression analysis of baseline factors for PFS and OS in the 65 eligible patients

Factor	Progression-Free Survival HR (95% CI)	Overall Survival HR (95% CI)
Bulky disease	3.16 (1.41–7.09) P=.0045	6.62 (2.45–17.90) P=.0002
Spleen involvement	2.23 (1.21–4.08) P=.0097	1.48 (0.65–3.39) P=.35
High risk MIPI	2.38 (0.96–5.89) P = 0.0604	7.35 (2.24–24.05) P = 0.0010
Serum beta-2 microglobulin > median (2.55)	1.33 (0.70–2.55) P=.39	2.94 (1.12–7.71) P=.0289

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