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Frontline bortezomib and rituximab for the treatment of newly diagnosed high tumour burden indolent non-Hodgkin lymphoma: a multicentre phase II study

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Summary

There is a lack of published data examining non-cytotoxic options for the frontline treatment of patients with high-tumour burden (HTB) indolent non-Hodgkin lymphoma (iNHL). We completed a multicentre phase II study for patients with untreated HTB iNHL (NCT00369707) consisting of three induction cycles of weekly bortezomib and rituximab followed by an abbreviated consolidation. Forty-two patients were treated and all were evaluable; the most common histology was follicular lymphoma (FL) (n = 33, 79%). Patient characteristics included median age 62 years (40–86); 38% bulky disease; 19% malignant effusions; 91% advanced-stage disease; and median FL International Prognostic Index (FLIPI) score was 3. Therapy was well tolerated with few grade 3/4 toxicities including minimal neurotoxicity. On intent-to-treat, the overall response rate (ORR) at end of therapy was 70% with a complete remission (CR) rate of 40% (FL: ORR 76%, CR 44%). With 50-month median follow-up, 4-year progression-free survival (PFS) was 44% with 4-year overall survival (OS) of 87% (FL: 44% and 97%, respectively). Four-year PFS for FLIPI 0–2 vs. 3–5 was 60% vs. 26% respectively (P = 0·02), with corresponding OS rates of 92% and 81% respectively (P = 0·16). Collectively, bortezomib/rituximab is a non-cytotoxic therapeutic regimen that was well tolerated and resulted in long-term survival rates approximating prior rituximab/cytotoxic chemotherapy series for untreated HTB FL.

Keywords: follicular lymphoma, bortezomib, treatment, cancer, prognosis.

Indolent non-Hodgkin lymphoma (NHL) represents a treatable malignancy, but it is not curable in the vast majority of cases. Patient populations in most contemporary studies of untreated indolent NHL have been segregated into low (LTB) and high tumour burden (HTB) populations, with the latter representing higher risk disease and comparatively poorer outcomes (Ardeshna *et al*, 2003; Hiddemann *et al*, 2005; Marcus *et al*, 2005; Herold *et al*, 2007; Kahl *et al*, 2007; Salles *et al*, 2008, 2011; Federico *et al*, 2013; Rummel *et al*, 2013). The most common therapy for untreated HTB indolent NHL remains rituximab combined with cytotoxic chemotherapy (Solal-Celigny *et al*, 1998; Hiddemann *et al*, 2005; Marcus *et al*, 2005; Herold *et al*, 2007; Salles *et al*, 2008, 2011; Federico *et al*, 2013; Rummel *et al*, 2013). Notably, few of these HTB rituximab-chemotherapy series have reported long-term follow-up (i.e., median follow-up >4 years) (Marcus *et al*, 2008; Bachy *et al*, 2013). In these latter reports, the approximate 4-year time-to-progression and overall survival (OS) rates were 44–56% and 83–90%, respectively.

There remains a lack of published data examining non-cytotoxic therapy for untreated patients with HTB indolent NHL. Further, there is an unmet need to identify more tolerable therapeutic regimens for this patient population, particularly for patients with co-morbidities and other contraindications to chemotherapy. Bortezomib is a proteasome inhibitor with documented activity in relapsed or refractory indolent lymphoma (O'Connor *et al*, 2005, 2010; de Vos *et al*, 2009; Di Bella *et al*, 2010). The largest single-agent study conducted to date in indolent lymphoma showed an overall response rate (ORR) of 50% in patients with relapsed/refractory follicular lymphoma (FL) (O'Connor

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et al, 2005, 2010). A recent phase III study comparing bortezomib/rituximab *versus* rituximab for relapsed/refractory FL patients was reported (Coiffier *et al*, 2011), however, there are no data examining bortezomib in the frontline setting for indolent NHL.

We designed a biologically based treatment option, combining bortezomib with rituximab therapy for patients with untreated HTB FL. Outcomes were analysed by intent-to-treat (ITT) and long-term outcomes were examined. To the best of our knowledge, this represents one of the first studies to report long-term outcomes for untreated HTB indolent NHL patients utilizing a non-cytotoxic therapeutic regimen.

Methods

Study population and eligibility criteria

We conducted a multicentre prospective phase II clinical trial for untreated indolent NHL (NCT 00369707). Patients were >17 years of age (no upper limit) with no prior therapy for lymphoma. Patients had histologically confirmed small lymphocytic lymphoma (SLL); FL grade 1/2, or 3a; extranodal marginal zone B-cell lymphoma of mucosa- associated lymphoid tissue type, nodal marginal zone B-cell lymphoma, or Waldenstrom macroglobulinaemia. All patients were required to have HTB as defined by the Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria (Brice *et al*, 1997; Solal-Celigny *et al*, 1998). Prerequisite laboratory parameters included absolute neutrophil count $>1{\cdot}5 \times 10^9$/l ($>0{\cdot}75 \times 10^9$/l with bone marrow involvement), haemoglobin >80 g/l, and platelet count $>100 \times 10^9$/l ($>50 \times 10^9$/l with bone marrow involvement). Additionally, patients may not have had more than grade 1 peripheral neuropathy within 14 d prior to enrollment.

Study design

This was a phase II investigator-initiated clinical trial conducted at three universities. Institutional Review Board approval was obtained at all sites. Induction therapy consisted of three cycles of: rituximab at 375 mg/m^2 × 4 weekly doses for cycle 1, then only day 1 for cycles 2 and 3, combined with bortezomib 1·6 mg/m^2 intravenously days 1, 8, 15 and 22, given every 35 d for all three cycles. Bortezomib was given weekly based partly on available data suggesting similar efficacy in lymphoma when given twice weekly (de Vos *et al*, 2009). This was followed by an abbreviated consolidation with both drugs given once every 2 months × 8 months. Steroids were not used and prophylactic antibiotics were not required. Dose modifications for bortezomib-related neuropathy and other treatment-related toxicities are included in Table SI. Responses were assessed by computerized tomography (CT) according to International Working Group criteria (Cheson *et al*, 1999). Patients had CT scans at baseline, after one and three cycles of induction therapy, after two and four courses of abbreviated maintenance and then every 6 months thereafter up to 5 years of follow-up. Following completion of maintenance, physical examination and laboratory data were completed every 3 months up to the 5-year follow-up. In addition, neurological toxicity was assessed at baseline, after induction therapy, and after completion of consolidation (via FACT/GOG- Neurotoxicity Questionnaire, Version 4.0) (Petrucci *et al*, 2013).

Statistics

The primary objective of the study was to assess the ORR [complete response (CR) plus partial response (PR)] after three cycles of bortezomib/rituximab induction therapy. Secondary objectives included ORR after one cycle of bortezomib/rituximab induction and at end of all therapy. The optimal two-stage design tested the null hypothesis that the ORR at end of therapy was ≤0·5 *versus* the alternative that ORR was ≥0·7. The power was 0·8 with statistical significance declared at an alpha level of 0·05. In the planned Simon two-stage analysis, 15 patients were enrolled in stage I. At that interim analysis, if nine or more patients demonstrated response, the study proceeded to the second stage.

All efficacy endpoints and survival rates were analysed by ITT. We also assessed time to treatment failure (defined as time to disease progression, relapse, second tumour, death from any cause, treatment toxicity requiring termination from the study, or for any reason treatment was discontinued permanently), progression-free survival (PFS) (measured from the time of first induction infusion to disease progression, relapse or death from any cause and including responders and non-responders), and OS (measured from time of first induction infusion to death from any cause). Additionally, we examined the FL international prognostic index (FLIPI), disease histology (i.e., follicular *versus* non-follicular) and other clinical factors (i.e., gender, B symptoms, splenomegaly and cytopenias at diagnosis) for potential associations with PFS or OS on univariate analysis.

Results

Patient characteristics

A total of 42 patients, all with HTB, as defined by modified GELF criteria (Brice *et al*, 1997; Solal-Celigny *et al*, 1998) were enrolled. As detailed in Table I, the most common histology was FL, which constituted nearly 80% of all diagnoses. The median age was 63 years with 21% of patients aged >70 years. Ninety-one percent of patients had advanced-stage disease. Additional characteristics included B symptoms in 31%, bulky disease (i.e., >7 cm) was present in 38%, and malignant ascites or effusions were present in 19% of patients. The median FLIPI for all patients was 3 with 61% of patients having a FLIPI of 3–5 and 19% of patients with a FLIPI of 4/5; the FLIPI for specifically FL patients was nearly identical to these numbers (data not shown).

Table I. Patient characteristics.

Characteristics	Patients, *n* (%)
Age (years)	
Median	61
Range	40–86
Gender	
Male	22 (52)
Female	20 (48)
Race	
White	36 (87)
Black	4 (9)
Hispanic	2 (4)
Histology	
Follicular lymphoma	33 (79)
Marginal zone lymphoma	5 (12)
Small lymphocytic lymphoma	3 (7)
Waldenstrom macroglobulinaemia	1 (2)
ECOG performance status	
Median	1
Range	0–2
B symptoms present	13 (31)
Bulky disease (>7 cm)	16 (38)
Stage	
II	4 (9)
III	10 (24)
IV	28 (67)
Elevated LDH	26 (62)
Malignant ascites and/or effusions	8 (19)

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

Response

The ORR after three cycles of induction among the first 15 patients was 71% (CR rate 31%) and thus the study proceeded to the second stage. After one cycle of induction therapy among all 42 patients, the ORR was 33% (CR 5%) with 77% of patients having stable disease (SD). Following three induction cycles among all patients, the ORR on ITT was 71% with a CR rate of 24%. The ORR and CR rates after three induction cycles for FL patients were 72% and 25%, respectively. From cycle 1 to 3, 63% of FL patients improved response (17 SD to PR and three PR to CR). The ORR at end of therapy for all patients was 71% with 40% CR. For the FL cohort ($n = 33$), the ORR at end of therapy was 76% with a CR rate of 44%. After the brief consolidation phase, two SDs converted to PR and one PR to CR.

Toxicity

Therapy was overall well tolerated with minimal cytopenias noted. Severe adverse events (AEs) are depicted in Table II. Most AEs occurred during induction therapy. The only grade 4 AEs were neutropenia (5%) and thrombocytopenia (2%); only 7% experienced grade 1 neutropenia and 2% grade 2; 12% of patients had grade 1 and 5% had grade 2 thromobocytopenia.

Table II. Adverse events.

Event	G1 (*n*)	G2 (*n*)	G3 (*n*)	G4 (*n*)	% Grades 3/4*
Neutropenia	2	2	0	2	5
Fever	3	0	2	0	5
Infection	1	5	2	0	5
Infusion reaction (rituximab)	0	4	2	0	5
Cardiac	1	0	2	0	5
Fatigue	9	1	2	0	5
Thrombocytopenia	5	2	0	1	2
Diarrhoea	9	4	1	0	2
Hypokalemia	1	0	1	0	2
Bowel obstruction	0	0	1	0	2
Dehydration	0	1	1	0	2
Anaemia	10	5	0	0	0
Neurological (sensory)	6	1	0	0	0
Cough	5	2	0	0	0
Skin (rash)	4	2	0	0	0
Constipation	3	2	0	0	0
Loss of appetite	3	1	0	0	0

G1, Grade 1; G2, Grade 2; G3, Grade 3; G4, Grade 4.
*Percentage of grades 3 and 4 combined.

Three patients were taken off study early (each after one cycle of induction therapy) due to grade 3 diarrhoea, fatigue and cardiac AE (the latter due to congestive heart failure exacerbation unrelated to study therapy). There was one other grade 3 cardiac event of diastolic heart failure that was possibly related to study drugs; this patient expired due to progressive disease 5 months after study entry. Two additional patients were taken off study at physician discretion (both with SD). The rates of neurotoxicity were overall modest; there was no motor toxicity noted, no grade 3 or 4 sensory neuropathy, and the rates of grade 1 and 2 sensory neuropathy were 14% and 2%, respectively.

Survival and prognosis

With a median follow-up of 50 months (range, 12–78) and on ITT, the 4-year PFS for all patients was 44% with a 4-year OS rate of 87%. The 4-year PFS and OS rates for FL patients were 46% and 97% respectively (Fig 1). Further, 4-year OS for FL patients was significantly better compared with non-FL patients [97% (95% confidence interval (CI) 80·4%, 99·6%) vs. 43% (95% CI 5·8%, 77·7%) respectively ($P = 0·003$)], while there was no difference in PFS [44% (95% CI 25·2%, 60·8%) vs. 47% (95% CI 11·5%, 76·5%) respectively, $P = 0·99$]. The time-to-treatment failure (TTF) rate at 4 years for all patients was 26%, which was primarily due to the aforementioned AEs resulting in study removal of several patients as well as several non-progressing patients who were taken off study at physician discretion. Additionally, one patient experienced transformation to diffuse large B-cell lymphoma (64-year-old patient who obtained partial

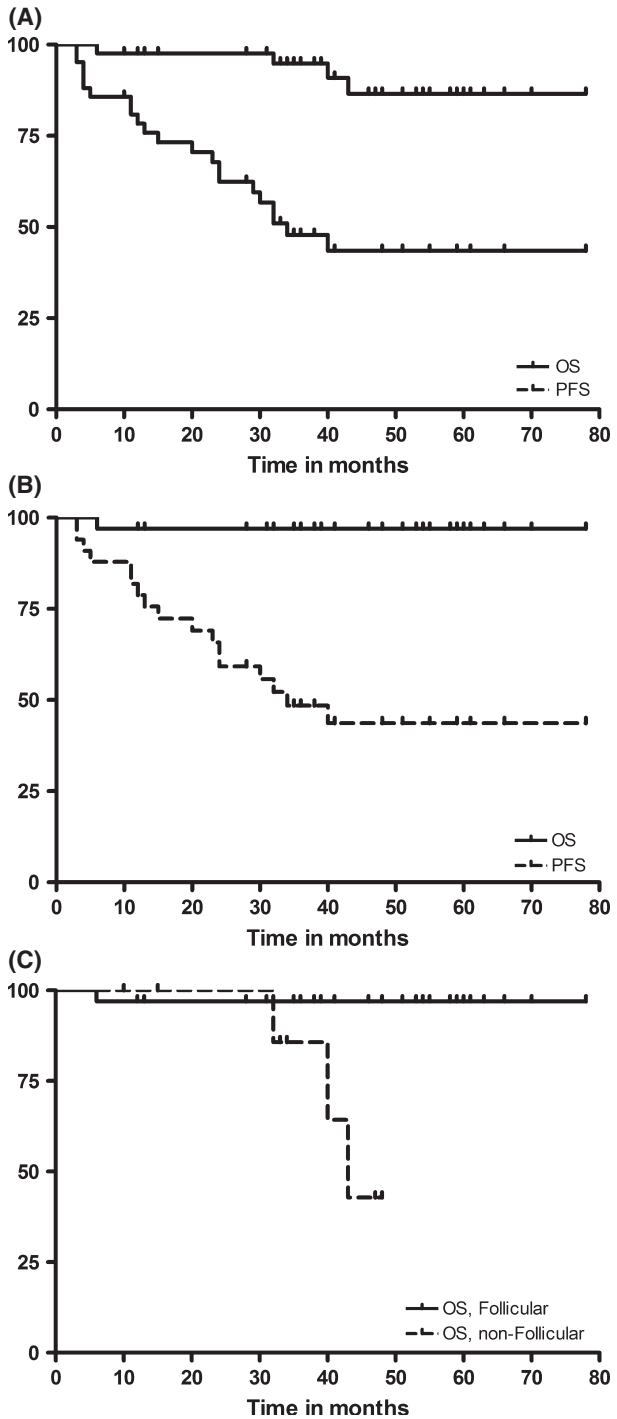

Fig 1. Survival for newly diagnosed high-tumour burden indolent non-Hodgkin lymphoma patients. (A) The 4-year progression-free survival (PFS) and overall survival (OS) in 42 high-tumour burden (HTB) indolent non-Hodgkin lymphoma patients on intent-to-treat analysis were 44% and 48%, respectively. (B) The 4-year PFS and OS rates for follicular lymphoma (FL) patients was 47% and 97% respectively, while (C) the 4-year OS rates were improved for patients with FL *versus* non-FL histologies [97% (95% confidence interval (CI) 80·4%, 99·6%) vs. 43% (95% CI 5·8%, 77·7%) respectively, $P = 0·003$].

remission with transformation at 13 months) and there was 1-s malignancy identified; a 70-year-old man with SLL was diagnosed with squamous cell anal cancer 13 months after study entry. The median TTF rate for FL patients was 32 months (range, 2–78) and the 4-year TTF for FL patients who achieved CR was 53%.

There were four total deaths on study; one FL patient died 31 months after study entry due to lymphoma. This was a 61-year-old man with stage IVB disease who experienced progressive disease after one cycle of bortezomib/rituximab. There were three non-FL deaths ($n = 2$ SLL and $n = 1$ marginal zone lymphoma), all due to lymphoma, occurring at 32, 40 and 43 months. PFS and OS rates according to low and high-risk FLIPI groups (i.e., 0–2 and 3–5 respectively) are shown in Fig 2. On univariate analysis for survival, there was a trend for the FLIPI predicting outcomes of PFS [hazard ratio (HR): 1·48, 95% CI 0·95–2·32, $P = 0·08$] as well as

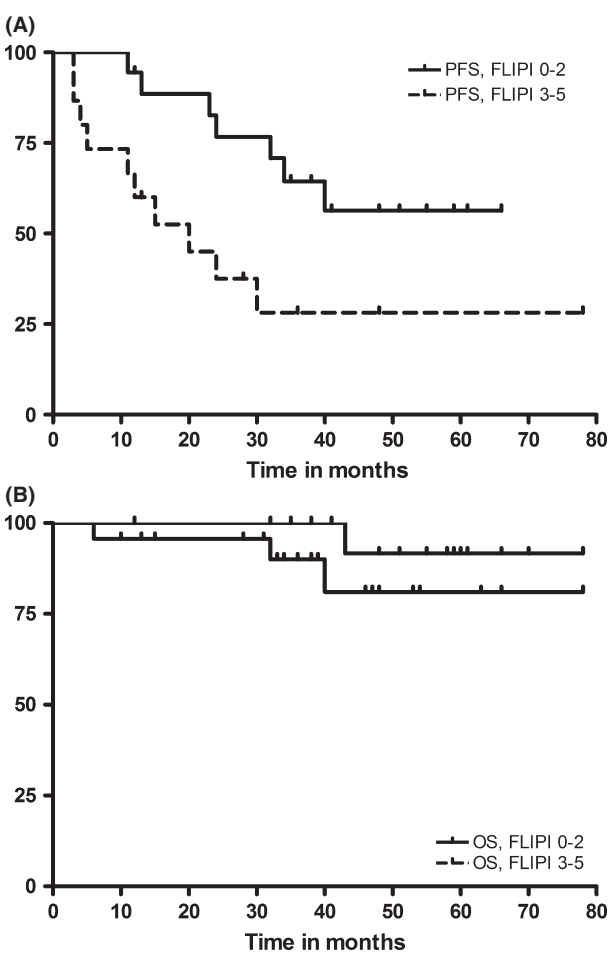

Fig 2. Survival according to the Follicular Lymphoma International Prognostic Index. The progression-free survival (PFS) and overall survival (OS) rates by low and high-risk FLIPI groups (0–2 and 3–5 respectively) are shown. (A) The 4-year PFS rates for patients with low and high Follicular Lymphoma International Prognostic Index (FLIPI) were 60% vs. 26% respectively ($P = 0·02$), while (B) the corresponding OS rates were 92% and 81% respectively ($P = 0·26$).

OS (HR: 3·34, 95% CI 0·89–12·56, $P = 0·08$) for FL patients. Interestingly, FL histology had a significant effect, favouring lower risk of death *versus* patients with non-FL histology (OS HR: 0·07, 95% CI 0·01–0·70, $P = 0·02$). Besides histology, there were no other predictive factors for survival.

Discussion

Rituximab in combination with cytotoxic chemotherapy remains the standard therapy for the majority of patients with untreated indolent NHL patients with HTB. There remains an unmet need to identify more tolerable non-cytotoxic frontline treatment regimens. We completed a multicentre phase II study for previously untreated FL and other indolent NHLs with HTB. Treatment was well tolerated with minimal cytopenias or other severe AEs noted. Further, ORR and PFS rates in FL patients here approximated that of rituximab/chemotherapy series and the OS was excellent. In interpreting these findings, several factors should be considered.

Rituximab has been examined as a single agent in patients with untreated indolent NHL, however most patients in these reports had LTB. In these LTB series, the ORR and CR rates following one cycle (i.e., 4 weeks) of rituximab were 47–74% and 9–20% respectively (Colombat *et al*, 2001; Hainsworth *et al*, 2002; Ghielmini *et al*, 2004; Martinelli *et al*, 2010) with median PFS of approximately 2 years without maintenance therapy (Colombat *et al*, 2001) or 3 years with abbreviated post-induction rituximab (Ghielmini *et al*, 2004; Martinelli *et al*, 2010). The ORR and CR rates seen here after 4 weeks (one cycle) of rituximab/bortezomib were 33% and 5% respectively, with 77% of patients having SD. These comparatively lower rates were probably due to the HTB of patients in the current series, which included a number of high-risk features, including bulky disease in nearly 40% and malignant ascites or effusions in approximately one-fifth of patients. In addition, it has previously been documented that the time to response of bortezomib in indolent NHLs may be up to 10–12 weeks (i.e., three cycles) (O'Connor *et al*, 2010). Accordingly, there were a number of successive conversions of response with ORR and CR rates in FL patients after three cycles of rituximab/bortezomib of 70% and 23%, respectively. The only prognostic factors identified that predicted outcome/survival were the FLIPI for PFS and non-FL histology for OS. The significant inferior OS for non-FL patients may in part reflect the more modest activity of bortezomib in SLL (O'Connor *et al*, 2010), however this result should not be over-interpreted as the non-FL numbers were small.

The response rates with rituximab/bortezomib here appeared lower compared with frontline rituximab/chemotherapy regimens where ORR and CR rates in prior HTB FL series have ranged from 81–96% and 20–50% respectively (Hiddemann *et al*, 2005; Marcus *et al*, 2005; Herold *et al*, 2007; Salles *et al*, 2008). This should be balanced by the comparatively lower toxicity and better tolerability with rituximab/bortezomib. In addition, it is important to note that these latter response rates were documented after six to eight cycles of induction rituximab and chemotherapy, while the response rates in the current report were after three cycles. The three cycles of induction therapy in the current series were probably not sufficient for a HTB patient population; a more protracted therapeutic course (induction and/or maintenance) is recommended in future studies.

Only a handful of rituximab/chemotherapy series for untreated indolent NHL with HTB have reported long-term outcomes (Marcus *et al*, 2008; Bachy *et al*, 2013). Among HTB FL patients treated with rituximab and cyclophosphamide, vincristine, prednisone (R-CVP), Marcus *et al* (2008) noted a median time to progression (TTP) of 37 months, and 4-year OS was 83% at a median follow-up of 53 months. In the series recently reported by Bachy *et al* (2013), the median EFS was 5·5 years and the 8-year EFS was 44% for patients who received R-CHVP (rituximab with cyclophosphamide, adriamycin, etoposide and prednisolone). With a median follow-up of 50 months, the median PFS for FL patients with rituximab/bortezomib therapy in the present study was 31 months with an excellent 4-year OS rate of 97%. The median TTF was 22 months, which compares with 27 months in the series reported by Marcus *et al* (2008).

This rituximab/bortezomib regimen was well tolerated with minimal cytopenias seen and few serious non-haematological AEs. The rates and severity of neurotoxicity were less than prior data that added bortezomib to therapy, where, after four cycles of therapy, 48%, 12% and 3% of patients had grade 1, 2 and 3 neurotoxicity respectively (Sehn *et al*, 2011). Additionally, Sehn *et al* (2011) reported that 3% of patients had grade 2 motor neuropathy after three cycles of therapy. The weekly dosing schedule probably resulted in the low rates of neuropathy seen here. Several studies have also suggested comparable outcomes and decreased toxicity (particularly neurological events) in relapsed/refractory indolent NHL using a weekly *versus* bi-weekly bortezomib schedule (de Vos *et al*, 2009; Ribrag *et al*, 2013). We did not identify any significant clinical factors that predicted for toxicity.

Results from a recent large randomized phase III study of rituximab alone *versus* rituximab and bortezomib for relapsed/refractory lymphoma showed a statistically significant longer PFS for the latter, but the absolute clinical improvement was modest (Coiffier *et al*, 2013). Correlative tumour and host studies associated with that study, however, detected several strongly predictive biomarkers. Patients who had a particular host single-nucleotide polymorphism genotype (i.e., *PSMB1* P11A C/G heterozygote) in combination with low CD68 tissue expression had significantly improved PFS (HR 0·47, $P < 0·0001$) and superior OS (HR 0·49, $P = 0·04$). For future studies that incorporate novel therapeutic agents into lymphoma treatment paradigms, it will be critical to investigate tissue- and host-based biomarker studies so that response and survival rates may be maximally enriched.

In summary, rituximab/bortezomib, at the dose and schedule reported here, is a well-tolerated therapeutic regimen for patients with untreated HTB indolent NHL. Despite having lower remission rates compared with prior rituximab/cytotoxic chemotherapy series, rituximab/bortezomib, at the dose and scheduled utilized here, it resulted in comparable PFS rates for HTB FL. Moreover, OS rates for FL patients were excellent. For future studies incorporating front-line bortezomib (or other novel therapy), a more protracted induction course is likely warranted. There is an ongoing randomized phase II study that includes a study arm examining the integration of bortezomib into rituximab/bendamustine induction therapy for untreated HTB FL patients (http://www.clinicaltrials.gov/ct2/show/NCT01216683); this study was based in part on encouraging data utilizing this therapeutic combination in the relapsed/refractory setting (Fowler *et al*, 2011; Friedberg *et al*, 2011). Continued strategies to incorporate novel therapeutic agents into frontline FL are warranted to delineate untreated HTB indolent NHL patient populations that may achieve long-term survival without use of cytotoxic therapy and via integration of biologically-based therapy.

Authorship

AME, ISL, LI: designed the study, collected data, analysed results, performed the statistical analysis and wrote the manuscript; MRS: collected data, analysed results, performed the statistical analysis and wrote the manuscript; IH, MM: analysed results, performed the statistical analysis and wrote the manuscript; JNW, STR: analysed results and wrote the manuscript.

Conflict of interest

AME: research support and advisory board/honorarium- Millennium; MRS, ISL, JNW: research support- Millennium; IH, MM, STR: none; LIG: research support and advisory board/honorarium- Genentech.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. Management of Bortezomib-Related Toxicities.

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