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Lenalidomide plus rituximab (R^2) in previously untreated marginal zone lymphoma: subgroup analysis and long-term follow-up of an open-label phase 2 trial

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Summary

Lack of consensus for first-line marginal zone lymphoma (MZL) treatment and toxicities associated with currently available systemic therapies have inspired evaluation of immunotherapeutic agents yielding robust outcomes with improved tolerability. We previously reported durable efficacy with first-line lenalidomide and rituximab (R^2) in follicular lymphoma, MZL and small lymphocytic lymphoma with a subsequent long-term follow-up shown here in MZL patients. This phase 2 investigator-initiated study included previously untreated, stage III/IV MZL patients treated with lenalidomide 20 mg/day on days 1–21 and rituximab 375 mg/m^2 on day 1 of each 28-day cycle, continuing in responders for ≥6–12 cycles. The primary endpoint was overall response rate (ORR); secondary endpoints were complete and partial response (CR, PR), safety, and progression-free survival (PFS). The ORR was 93% with 70% attaining CR/CR unconfirmed. At median follow-up of 75·1 months, median PFS was 59·8 months and 5-year OS was 96%. Most non-haematological adverse events (AE) were grade 1/2. Grade 3 haematological AEs were neutropenia (33%) and leucopenia (7%), and grade 4 were leucopenia (3%) and thrombocytopenia (3%). Two patients died of secondary malignancies; no treatment-related fatalities occurred. With extended follow-up, outcomes for MZL patients receiving R^2 were robust with no unexpected late or delayed toxicities.

Keywords: marginal zone lymphoma, lenalidomide, non-Hodgkin lymphoma, phase 2, rituximab.

Marginal zone lymphoma (MZL) is a relatively rare variant of indolent non-Hodgkin lymphoma (NHL) that accounts for 10% of B-cell lymphomas (The Non-Hodgkin's Lymphoma Classification Project, 1997, Zucca & Bertoni, 2016). Subtypes include nodal, extranodal and splenic MZL, which comprise 2%, 5–8% and 1% of NHL patients, respectively (Zucca & Bertoni, 2016). MZL is a disease of older adults, and presents with a median age of approximately 65 years old at diagnosis (Thieblemont *et al*, 2016). Data from the Surveillance, Epidemiology, and End Results database report a 5-year relative survival rate of 84% for MZL as a whole, 77% for nodal, 89% for extranodal lymphoma and 80% for splenic MZL (Olszewski & Castillo, 2013).

The pathogenesis of MZL is largely associated with alterations in B-cell receptor signalling in association with the immune microenvironment. Therapeutic targeting of these aberrant pathways has identified promising treatment strategies for MZL. Lenalidomide, a second-generation immunomodulatory drug (IMiD®), has been effective in the treatment of various B-cell lymphomas (Kiesewetter *et al*, 2013; Fowler *et al*, 2014; Han *et al*, 2014). Lenalidomide enhances T-cell proliferation, upregulates costimulatory molecules on the surface of malignant cells and modulates the activation of oncogenic signalling pathways, such as nuclear factor (NF)-κB (Fowler *et al*, 2014).

Marginal zone lymphoma is often considered a chronic disease with a long natural history and no universally accepted standard of care. Typically, nodal MZL is treated similarly to follicular lymphoma (FL) with approaches such as observation, chemotherapy, immunotherapy and radiation, often selected

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based on such factors as comorbidity of the patient, and stage and pathogenesis of the disease (Kalpadakis *et al*, 2013; Fowler *et al*, 2014; Tadmor & Polliack, 2017).

Several studies have evaluated the activity and tolerability of chemoimmunotherapy in patients with previously untreated, stage III/IV MZL. A randomized study of patients with extranodal MZL demonstrated that the addition of rituximab to chlorambucil *versus* chlorambucil alone improved the overall response rate (ORR) with significant differences in complete response (CR) (Zucca *et al*, 2013). Long-term outcomes failed to show significant differences, questioning the need for treatment in asymptomatic MZL patients. The BRIGHT study, which included treatment-naïve patients with mixed indolent NHL, including MZL, demonstrated that bendamustine-rituximab (BR) was noninferior to rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) or cyclophosphamide, vincristine and prednisone (R-CVP) in terms of CR, and ORR favoured BR over R-CHOP/R-CVP (Flinn *et al*, 2014). The StiL study, which compared BR and R-CHOP in patients with mantle cell lymphoma and various types of indolent NHL (including 12–14% of MZL patients in each arm), showed a significant progression-free survival (PFS) benefit overall, but no significance between MZL arms (Rummel *et al*, 2013). Although these studies showed high initial responses, the lack of durable remissions in many patients supports the need for continued investigation of new agents and novel combinations to improve outcomes for these patients.

Lenalidomide has shown clinically significant efficacy both in the first-line and relapsed/refractory settings in multiple B-cell lymphomas (Wiernik *et al*, 2008; Habermann *et al*, 2009; Witzig *et al*, 2009, 2011; Badoux *et al*, 2011; Chen *et al*, 2011), including MZL (Kiesewetter *et al*, 2013). A phase 2 study showed that lenalidomide monotherapy in patients with extranodal MZL was well tolerated and demonstrated an ORR of 61% and a CR of 33% (Kiesewetter *et al*, 2013). In recent years, the anti-CD20 antibody rituximab has been the backbone of treatment for MZL. Kalpadakis *et al* (2013) reported a 5-year overall survival (OS) of 92% and PFS of 73% in splenic MZL patients treated with rituximab monotherapy.

We performed an investigator-initiated, open-label, phase 2 trial at MD Anderson Cancer Center to assess the efficacy and safety of R^2 in previously untreated patients with stage III or IV FL, MZL, or small lymphocytic lymphoma. The present report provides longer follow-up at a median of 75·1 months, with efficacy and safety outcomes for the 30 patients with MZL. This longer follow-up also allowed for assessment of the potential impact of patient subgroups on survival.

Patients and methods

Eligibility criteria

Patients had a diagnosis of stage III or IV MZL, were aged ≥18 years and had Eastern Cooperative Oncology Group performance status <2, absolute neutrophil count ≥1·5 × 10^9/l, platelet count ≥100 × 10^9/l and adequate organ function. Of note, patients were not required to meet Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria for treatment (Brice *et al*, 1997; Salles *et al*, 2011). Key exclusion criteria were a history of any malignancy within the previous 5 years, uncontrolled serious illness or comorbidities, human immunodeficiency virus infection, and active hepatitis B or C infection.

Study design

This was a single-institution phase 2 study of lenalidomide plus rituximab (i.e., R^2) in previously untreated patients with advanced-stage indolent NHL (ClinicalTrials.gov identifier: NCT00695786). Detailed methods have been previously described (Fowler *et al*, 2014) and are briefly summarized here. An institutional review board approved this study, which was performed in accordance with the Declaration of Helsinki and good clinical practice guidelines. All patients provided written informed consent.

Patients received oral lenalidomide at 20 mg/day on days 1–21 of each 28-day cycle and were given rituximab at 375 mg/m^2 as an intravenous infusion on day 1 of each cycle. Patients with a tumour response after six cycles could, but were not required to, continue treatment for a maximum of 12 cycles as tolerated. Prophylactic growth factor support was not permitted.

Responses were assessed according to 1999 International Working Group (IWG) criteria (Cheson *et al*, 1999). Two independent radiologists reviewed equivocal findings. Physical examinations and computed tomography imaging were performed at study entry, every 3 months for 2 years, every 6 months in the third year, and yearly thereafter. To confirm CR, bone marrow biopsies were performed at 3 and 6 months.

Statistical analysis

The primary endpoint was ORR, defined as the proportion of patients who exhibited a CR, CR unconfirmed (CRu) or partial response (PR) as per 1999 IWG criteria (Cheson *et al*, 1999). Secondary endpoints included CR and PR rates, PFS (assessed from first treatment administration to disease progression or death due to any cause, whichever occurred first), OS (assessed from first treatment administration to death) and safety. Adverse events (AEs) were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0. (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

The trial was initially designed as a phase 2 pilot study with 30 patients, but was later expanded to enrol 156 patients (30 patients with MZL) to further examine safety and efficacy. For the MZL cohort, the null hypothesis predicted ORR in no more than 70% of patients. The 30-patient

sample size for MZL was expected to achieve a width of 0·23 for the posterior 90% credibility interval under the assumption of an 80% ORR. All patients with any post-baseline tumour assessment were assessed for response. Statistical assumptions based on MZL subtype and to compare among groups were not planned due to the small number of patients in each subgroup.

In this analysis, we evaluated the associations between various categorical patient characteristics (age, sex, stage, B symptoms, splenomegaly, effusions/ascites, haemoglobin, absolute lymphocyte count, high tumour burden and whether GELF criteria for treatment were met) with response to R^2, as well as the duration of disease control. Summary statistics, including mean, standard deviation, median and range for continuous variables, such as age and laboratory measurements, frequency counts and percentages for categorical variables, such as sex, stage, diagnosis and response, are provided. The chi-square test or Fisher's exact test were used to evaluate the association between two categorical variables. Kruskal–Wallis test or Wilcoxon rank sum test was used to evaluate the difference in a continuous variable among or between patient groups.

The Kaplan–Meier method was used for time-to-event analysis. For the PFS analysis, patients were censored at the last follow-up date if neither progression nor death had occurred. For the OS analysis, patients were censored at the last follow-up date if death had not occurred. Median time-to-event in months with 95% confidence interval (CI) was calculated. The log-rank test was used to evaluate the difference in time-to-event endpoints between patient groups. Statistical software SAS 9.1.3 (SAS Institute, Cary, NC, USA) and S-Plus 8.0 (TIBCO Software Inc. Palo Alto, CA, USA) were used for the analyses.

Table I. Patient demographics and clinical characteristics ($N = 30$).

Characteristic	*n*	%
Age, years		
Median	58	
Range	36–77	
Age		
<60 years	17	57
≥60 years	13	43
Sex		
Female	18	60
Male	12	40
Diagnosis		
Nodal MZL	18	60
Extranodal MZL/MALT lymphoma	11	37
Splenic MZL	1	3
Stage		
III	9	30
IV	21	70
B symptoms	3	10
Splenomegaly	4	13
Pleural effusion/ascites	2	7
Haemoglobin		
<120 g/l	8	27
≥120 g/l	22	73
Lactate dehydrogenase (≤618)	30	100
Absolute lymphocyte count		
$<1{\cdot}71 \times 10^9$/l	19	63
$\geq 1{\cdot}71 \times 10^9$/l	11	37
High tumour burden per GELF*	2	7
Met GELF criteria*	16	53

GELF, Groupe d'Etude des Lymphomes Folliculaires; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma.
*GELF criteria were defined according to previously published reports (Brice *et al*, 1997; Salles *et al*, 2011).

Results

Patient demographics

The trial enrolled patients from 30 June 2008 to 12 August 2011. For 30 MZL patients, the median age was 58 years (range, 36–77) and 60% were female (Table I). MZL subtypes included 18 (60%) patients with nodal MZL, 11 (37%) with extranodal MZL/mucosa-associated lymphoid tissue (MALT) lymphoma and 1 (3%) with splenic MZL. All MZL patients had stage III/IV disease, including 9 (30%) with stage III disease and 21 (70%) with stage IV.

Median follow-up for the study was 75·1 months (range, 16·2–100·2). The median duration of lenalidomide treatment was 6 months (range, 1–12 months; note, data for 1 patient were lost to follow-up). Twenty-four patients completed at least 6 cycles; 4 patients opted to proceed with 12 cycles of treatment; all 4 completed 12 cycles without early discontinuation. No patients discontinued therapy because of disease progression; 1 patient discontinued after 3 cycles secondary to stable disease, 3 (10%) discontinued secondary to AEs (rituximab intolerance), 2 discontinued due to patient preference based on intolerance to rituximab, and 4 were lost to long-term follow-up.

Safety

A total of 6 patients required dose reductions of lenalidomide: 3 were reduced from 20 mg to 15 mg and the remaining 3 were reduced further to 10 mg. Adverse events experienced by all patients with MZL with mature follow-up data included non-haematological AEs (all grades) of fatigue (93%), nausea or vomiting (73%), cough/dyspnoea/pulmonary (63%), eye irritation (60%), pain or myalgia (60%), oedema (50%), constipation (47%), diarrhoea (47%) and rash (40%) (Fig 1). No grade 4 non-haematological AEs occurred. The most common grade 3 non-haematological AEs were pain or myalgia (10%), cough/dyspnoea/pulmonary (7%) and rash (7%). Most AEs were manageable with a temporary hold of the medication or with supportive measures. Two patients required dose reduction of lenalidomide secondary to rash.

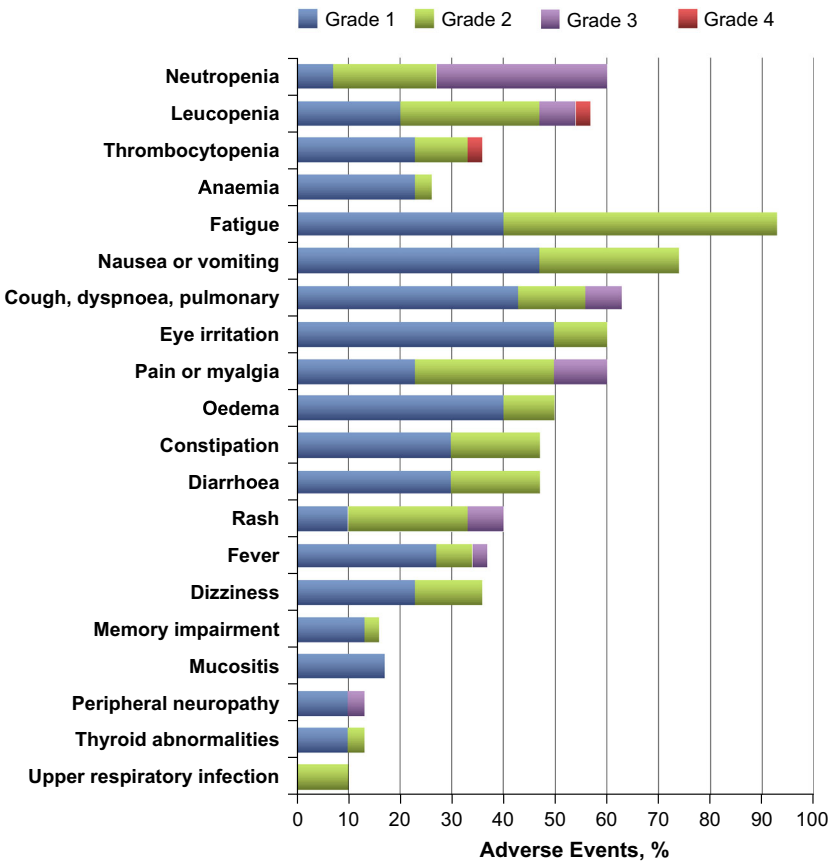

Fig 1. Adverse events for all patients and all grades (N = 30).

The most frequently reported any-grade haematological AEs were neutropenia (60%), leucopenia (57%) and thrombocytopenia (37%). The only grade 4 haematological AEs were thrombocytopenia (3%) and leucopenia (3%). The only grade 3 haematological AEs were neutropenia (33%) and leucopenia (7%). Neutropenia was, overall, transient and able to be managed with a short treatment hold or dose reduction. Six patients required dose reductions of lenalidomide secondary to neutropenia, although it should be noted that 5 of these 6 patients required reduction only after 5 or more cycles of treatment. Growth factor support was administered to 8 patients per the provider's discretion. Despite neutropenia, no serious or life-threatening infections were reported in any neutropenic patient. One patient developed sepsis secondary to pneumonia after cycle 2 but was not neutropenic at the time. No delayed infectious complications occurred after completion of treatment.

Efficacy

The ORR among the 27 patients was 93%, including 19 (70%) patients with CR/CRu and 6 (22%) with PR (Table II). Patients underwent bone marrow biopsies to confirm responses. Among 16 patients with nodal MZL, 10 CRs/CRus occurred and ORR was 88%. Among 11 patients with extranodal MZL/MALT lymphoma, 8 CR/CRu responses contributed to an 80% ORR. The single patient with splenic MZL had a CR.

For all MZL patients, the median PFS was 59·8 months (95% CI, 50·6 to not reached) (Fig 2A) and 5-year PFS was 49% (95% CI, 32–73%), PFS rates were similar among various MZL subgroups (Fig 2B–H and Figure S1). Median OS was not reached (Figure S2) and 5-year OS was 96% (95% CI, 89–100%). OS rates were also similar among various MZL subgroups (Figure S2), with all subsets demonstrating an OS of at least 92% at 5 years. The current status of 27 patients at the last follow-up is as follows: 25 (93%) are alive, 14 (52%) are in remission, 11 (41%) demonstrated progression/relapse and 2 (7%) have died due to secondary malignancies. One patient developed metastatic gastroesophageal junction carcinoma, and one patient (who was receiving fludarabine at the time of relapse) developed 3 malignancies, including T-cell large granular lymphocytic leukaemia, smouldering multiple myeloma and carcinoma of unknown origin. Of the various patient characteristics assessed, none was significantly associated with ORR or CR outcome (data not shown).

Discussion

As first-line treatment for MZL, the combination of rituximab and lenalidomide was associated with favourable ORR, PFS and OS, and a manageable toxicity profile. Responses

Table II. Response status by subtype in evaluable patients (n = 27).

		ORR		CR/CRu		PR		SD	
Subtype	*n*	*n*	%	*n*	%	*n*	%	*n*	%
Nodal MZL*	16	16	88	10	56	4	22	2	11
Extranodal MZL/MALT lymphoma	10	10	80	8	73	0	0	2	18
Splenic MZL	1	1	100	1	100	0	0	0	0
All patients	27	25	93	19	70	6	22	2	7

CR, complete response; CRu, CR unconfirmed; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; ORR, overall response rate; PR, partial response; SD, stable disease.

*One patient with extranodal MZL and two patients with nodal MZL did not have a response analysis available.

achieved were durable. With a median follow-up of 75·1 months, the ORR was 93% for MZL patients, median PFS was 59·8 months and median OS has yet to be reached. With extended follow-up, nearly all MZL patients treated with R^2 remain alive, the majority with no unexpected long-term or delayed toxicity.

These results are comparable with results from other studies of previously untreated MZL patients, although relatively little MZL-specific data exist regarding the use of novel agents (Thieblemont *et al*, 2016; Zucca & Bertoni, 2016). The International Extranodal Lymphoma Study Group (IELSG)-19 study of rituximab combined with chlorambucil showed an ORR of 94%, 5-year OS of 89% and 5-year PFS of 71% (Zucca *et al*, 2013). As part of larger studies of mixed indolent lymphoma patients, MZL-specific data from the BRIGHT study of BR and R-CHOP/CVP reported ORRs of 92% and 71%, respectively (Flinn *et al*, 2014), whereas the StiL study reported a median PFS of 57·2 and 47·2 months for BR and R-CHOP, respectively (Rummel *et al*, 2013). Both lenalidomide and rituximab monotherapy have established activity in MZL patients. Lenalidomide monotherapy showed a 61% ORR (33% CR) in previously treated and treatment-naïve patients with extranodal MALT lymphoma (Kiesewetter *et al*, 2013). Five-year OS of 92% and PFS of 73% have been reported in splenic MZL patients treated with rituximab monotherapy (Kalpadakis *et al*, 2013). Results of the phase 3 Eastern Cooperative Oncology Group E4402 trial of rituximab maintenance versus retreatment strategies demonstrated an ORR for MZL patients of 52% and a superior time-to-treatment failure for maintenance rituximab over retreatment, but no difference in OS (Williams *et al*, 2016).

A phase 2 study of ibritumomab tiuxetan monotherapy in patients with previously untreated, non-gastric, extranodal MZLs reported an 88% ORR at 12 weeks of therapy; with a median follow-up of 65·6 months, median PFS was 47·6 months, median OS was not reached, 5-year PFS was 40% and 5-year OS was 72% (Lossos *et al*, 2015). A phase 2 study of bortezomib added to R-CHOP (VR-CHOP) reported a 100% ORR, including 66% CR, 4-year PFS of 83%, 4-year OS of 93%, and 2 cases of grade 3 peripheral neuropathy (no grade 4) in 29 patients with previously untreated indolent NHL (Cohen *et al*, 2015).

Our results suggest that the combination of lenalidomide and rituximab as first-line therapy for MZL achieves similar efficacy to that of currently available first-line combinations. Additionally, R^2 treatment is well tolerated and responses are durable. These results suggest that rituximab can be combined with lenalidomide rather than standard chemotherapy without compromising efficacy.

Notable limitations of this study include the small sample size and the inherent weaknesses of this being a single-arm, non-randomized study that was performed at a single centre located in the United States. MZL is a rare disease and, as such, the low number of patients limits the statistical power of these analyses. Additionally, response was assessed using 1999 IWG response criteria, which has advanced to include additional assessments (e.g., positron emission tomography imaging) to improve these analyses. Future global, randomized studies with a higher number of and more diverse patient population, and with updated response assessments, are needed to accurately compare R^2 with other first-line treatment regimens for MZL.

Ongoing phase 3 studies have been designed to continue to address the feasibility of R^2 in first-line and relapsed/refractory indolent NHL. The AUGMENT study is examining R^2 *versus* rituximab/placebo in patients with relapsed/refractory MZL and grade 1–3a FL (NCT01938001) to identify the potential additive benefit of R^2 over R. The MAGNIFY study adds in an analysis of lenalidomide or rituximab maintenance, while building more depth to the R^2 initial treatment data in relapsed/refractory FL, MZL, or mantle cell lymphoma (NCT01996865). An early look at the effects of the initial treatment phase of R^2 in MZL patients supports its efficacy and tolerability in this patient cohort (Coleman *et al*, 2017). Phase 1 studies of single-agent ibrutinib, a Bruton tyrosine kinase inhibitor, in relapsed/refractory patients with various B-cell malignancies demonstrated an ORR of 60% with minimal AEs (Advani *et al*, 2013). Noy *et al* (2017) reported an ORR of 48% in patients with MZL previously treated with rituximab. Additionally, *in vitro* combination of lenalidomide and ibrutinib demonstrated synergy via the downregulation of the transcription factor IRF4, which is important in NF-κB signalling, a pathway vital in the pathogenesis of MZL (Yang *et al*, 2012). Based on this information,

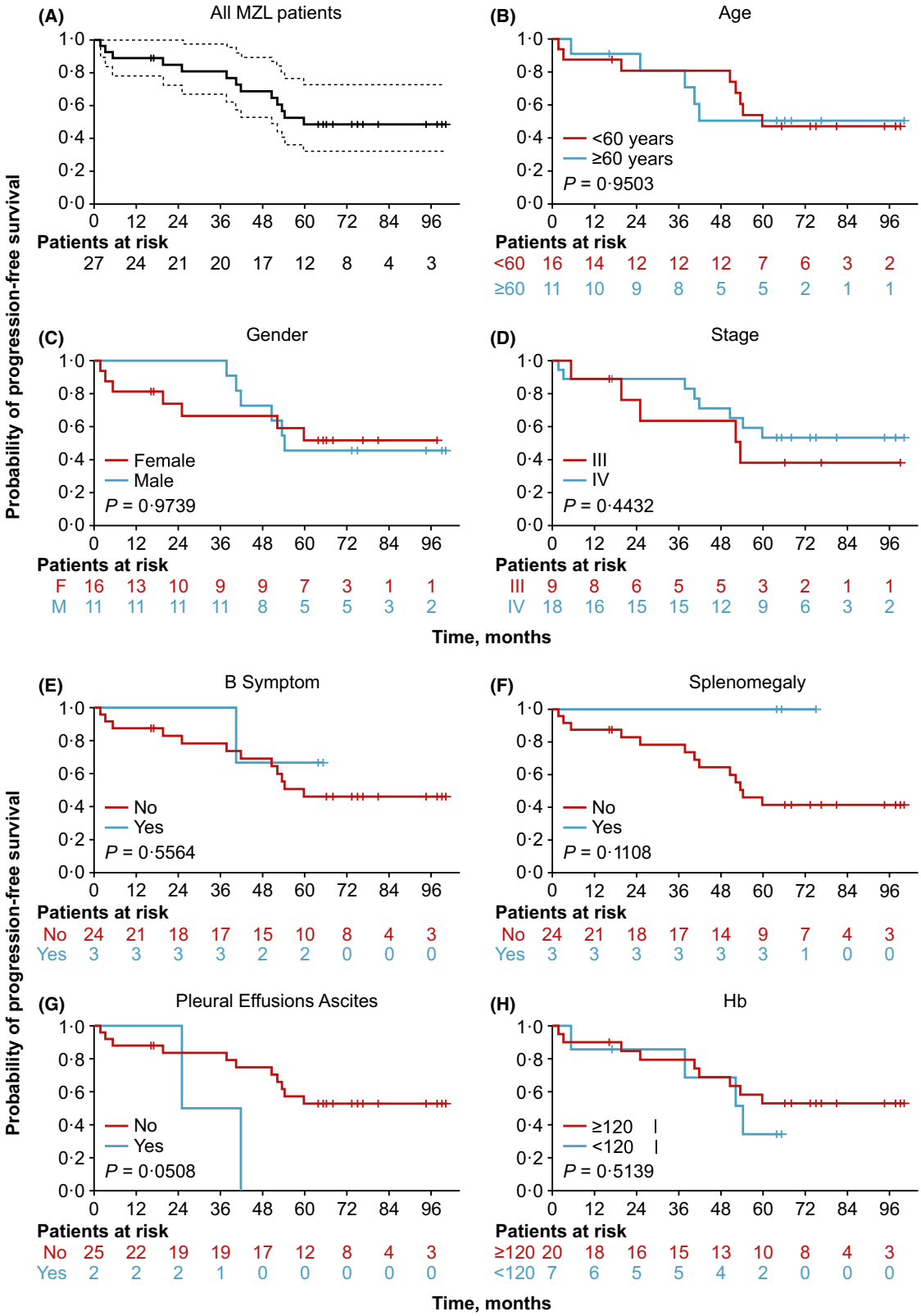

Fig 2. Kaplan–Meier curves for progression-free survival (in all marginal zone lymphoma patients (A), by age (B), gender (C), disease stage (D), B symptoms (E), splenomegaly (F), pleural effusion/ascites (G) and haemoglobin [Hb] status (g/l; H). Time was calculated in months from the treatment start date to the progression date or death, whichever occurred first. Patients were censored at the last follow-up date if neither progression nor death occurred. 95% confidence intervals are shown as broken lines in (A).

our group has initiated an open-label, phase 2 trial of the combination of R^2 and ibrutinib as first-line treatment in MZL patients (NCT02532257).

Results from this analysis also show that R^2 is well tolerated in patients with MZL. The most common non-haematological AEs were grade 1 or 2, with a low number of grade 3 and no grade 4 non-haematological AEs. Grade 3 haematological AEs consisted of neutropenia (33%) and leucopenia (7%), and the only grade 4 haematological AEs were thrombocytopenia (3%) and leucopenia (3%). Overall, these toxicities were manageable with supportive measures, and only a few patients required dose reductions of lenalidomide, mainly after 5 cycles or more. Despite this degree of neutropenia, no patient developed serious infectious complications, and the occurrences of neutropenia were transient in nature. To date, no patient has developed delayed infectious complications or marrow failure. We plan to further analyse the difference in the toxicity profile and efficacy among patients treated with 6 vs. 12 cycles of R^2. To date, no long-term toxicities related to treatment have been reported. Two patients developed secondary malignancies, but, based on the tumour histologies and additional patient risk factors, these were unlikely to be due to treatment with R^2.

In conclusion, the combination of R^2 has demonstrated significant efficacy, with an expected and manageable toxicity profile, in patients with previously untreated MZL. With extended follow-up, most MZL patients receiving R^2 remain alive, with a median PFS of approximately 5 years, and no unexpected long-term or delayed toxicities. Although first-line R^2 treatment in treatment-naïve MZL patients is well tolerated and associated with high response rates that are durable, further prospective studies are warranted to determine the potential biological rationale that could explain the differences in PFS and response in MZL compared with those seen in patients with FL.

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Author contributions

LJN, FS, RED, JY, FBH, MAF, LEF, JRW, MW, YO, SSN and NHF designed the study. MRB, LJN, RED, JY, SGF, FBH, JRW, MW, LF, SSN and NHF contributed to writing of the manuscript. All authors provided study materials and/or patients, collected and assembled the data, analysed and interpreted the data, and provided final approval of the manuscript.

Competing interests

LJ Nastoupil reports honoraria, consulting or advisory role, and research funding from Celgene and Genentech. MA Fanale reports grants and personal consulting fees up to 4 June 2018 from Seattle Genetics and salary and stocks from 1 October 2018 following the start of her employment with Seattle Genetics. Grants and personal fees from Takeda, Celgene, BMS and Merck up to 4 June 2018, grants from ADC Therapeutics, Molecular Templates, MedImmune, Gilead and Genentech up to 4 June 2018, personal fees from Bayer and Spectrum up to 4 June 2018.JR Westin reports research funding from Janssen, Novartis, Kite Pharma, Celgene and Genentech. M Wang reports stock or other ownership from MoreHealth, honoraria from Janssen, AstraZeneca, Pharmacyclics, Dava Oncology and Celgene; consulting or advisory role from Janssen, AstraZeneca, MoreHealth, Medscape, IO Biotech, Nordic Biotech and BioInvent; research funding from Janssen, Pharmacyclics, AstraZeneca, Kite Pharma, Juno, BeiGene, Novartis, Celgene and Oncternal Therapeutics; and travel, accommodations, expenses from Janssen, Pharmacyclics, AstraZeneca and Celgene. Y Oki reports employment from Jazz Pharmaceuticals. SG Forbes reports consulting or advisory role from Gilead and Bayer. SS Neelapu reports consulting or advisory role and research funding from Celgene. NH Fowler reports consulting or advisory role from AbbVie, Janssen, Celgene and TG Therapeutics; research funding from AbbVie, Celgene, Janssen, and Roche and TG Therapeutics; and travel, accommodations, expenses from Celgene and Janssen. MR Becnel, F Samaniego, RE Davis, MJ You, M Green, FB Hagemeister, LE Fayad, and L Feng report no conflicts of interests.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Kaplan–Meier curves for progression-free survival (PFS) in all MZL patients by absolute lymphocyte count (ALC) status (A), high tumor burden (B), and Groupe d'Etude des Lymphomes Folliculaires (GELF) (C).

Fig S2. Kaplan–Meier curve for overall survival (OS) in all MZL patients (A), by age (B), gender (C), stage (D), B symptoms (E), splenomegaly (F), pleural effusion/ascites (G), hemoglobin status (H), absolute lymphocyte count (ALC) status (I), high tumor burden (J), and Groupe d'Etude des Lymphomes Folliculaires (GELF) (K).

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