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Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study

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Summary

The multicentre, open-label, two-stage, single-arm, phase 2, PILLAR (PIvotaL Lymphoma triAls of RAD001)-1 study (NCT00702052) assessed the efficacy and safety of everolimus 10 mg/d in adults with confirmed mantle cell lymphoma (MCL) refractory to or intolerant of bortezomib who received ≥1 other antineoplastic agent, either separately or in combination with bortezomib. Primary endpoint was overall response rate (ORR) per investigator review according to the response criteria for malignant lymphoma. Secondary endpoints included progression-free survival (PFS), overall survival (OS) and safety. Fifty-eight patients were enrolled from August 2008–January 2011. Five partial responses were observed (ORR 8·6%; 90% confidence interval [CI] 3·5–17·3%); the study did not meet the prespecified objective of ≥8 objective responses among 57 patients. Median PFS and OS were 4·4 months (95% CI 3·5–6·1) and 16·9 months (95% CI 14·4–29·9), respectively. Grade 3/4 non-haematological toxicities occurred in 70·7% of patients. Based on laboratory values, grade 3/4 thrombocytopenia, neutropenia and anaemia occurred in 13·8%, 13·8% and 8·6% of patients, respectively. Everolimus demonstrated modest activity and acceptable tolerability in heavily pretreated patients with MCL refractory to or intolerant of bortezomib. Future studies evaluating everolimus in a less refractory population or in combination with other targeted therapies in refractory MCL are warranted.

Keywords: bortezomib, everolimus, mantle cell lymphoma, mammalian target of rapamycin, relapsed/refractory disease.

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Mantle cell lymphoma (MCL) is a rare, often aggressive mature B-cell lymphoma representing 5–10% of all non-Hodgkin lymphomas (Perez-Galan *et al*, 2011). Most MCL are characterized by a t(11;14)(q13;q32) balanced chromosomal translocation of the cyclin D1 gene (*CCND1*) on chromosome 11 to the immunoglobulin heavy chain enhancer region on chromosome 14, resulting in cyclin D1 overexpression and increased cell proliferation (Perez-Galan *et al*, 2011). Aside from this hallmark translocation, MCL frequently involves secondary chromosomal alterations impacting other genes involved in cell cycle regulation and those implicated in DNA damage response, signal transduction and apoptosis (Perez-Galan *et al*, 2011).

MCL typically presents as advanced disease, with common extranodal manifestations in the gastrointestinal tract, bone marrow, liver, spleen and Waldeyer ring (Cohen *et al*, 1998; Romaguera *et al*, 2003). Recommended first-line therapy for advanced MCL is rituximab-based chemotherapy followed by autologous stem cell transplantation (ASCT) consolidation in eligible patients (Dreyling *et al*, 2013; National Comprehensive Cancer Network, Inc, 2013). Despite high response rates, many patients relapse and often develop chemoresistance. The response duration of conventional chemotherapy in relapsed/refractory MCL is typically short, even after high-dose therapy and ASCT (Perez-Galan *et al*, 2011). Although a small subset of patients may experience long-term disease-free survival after non-myeloablative allogeneic stem cell transplantation, curative therapy for MCL remains elusive for the majority of patients (National Comprehensive Cancer Network, Inc, 2013). The first novel agent approved by the United States Food and Drug Administration as second-line therapy for MCL was bortezomib (Fisher *et al*, 2006; Goy *et al*, 2009; O'Connor *et al*, 2009). In the phase 2 PINNACLE study of MCL patients previously treated with 1 or 2 lines of therapy ($N = 155$), bortezomib showed a 32% overall response rate (ORR), 9·2-month median duration of response and 6·7-month median time to progression (Goy *et al*, 2009). Based on the results of the phase II EMERGE study (Goy *et al*, 2013), lenalidomide was approved in the United States for the treatment of patients who relapsed after, or were refractory to, bortezomib. Although other cytotoxic regimens are used in this setting, no consensus regarding the optimal strategy exists.

Dysregulation of the mammalian target of rapamycin (mTOR) pathway is frequently observed in MCL (Rizzatti *et al*, 2005; Peponi *et al*, 2006; Rudelius *et al*, 2006; Dal *et al*, 2008), and the cap-dependent translation necessary for cyclin D1 expression is regulated by this pathway (Bjornsti & Houghton, 2004; Schatz, 2011). *In vitro* data have established that inhibiting mTOR with everolimus induces cell cycle arrest and reduces 4E-BP1 phosphorylation (Haritunians *et al*, 2007). Similar findings have been observed in other studies of everolimus and the mTOR inhibitors rapamycin and temsirolimus (Galimberti & Petrini, 2010; Rosich *et al*, 2012). In one phase 2 study ($N = 77$), oral everolimus 10 mg/d produced a 30% ORR in patients with relapsed, aggressive lymphoma, including a 32% ORR in patients with MCL ($n = 19$) (Witzig *et al*, 2011). Everolimus was generally well tolerated, and most toxicities were manageable with temporary dose adjustment. A second phase 2 study also found everolimus to be well tolerated with clinical activity against relapsed/refractory MCL (Renner *et al*, 2012). In a randomized, open-label, phase 3 study ($N = 162$), intravenous temsirolimus 175 mg/week for 3 weeks followed by 75 mg/week thereafter (175/75-mg regimen) significantly prolonged progression-free survival (PFS) compared with the investigator's choice of 1 of 11 prospectively defined single-agent treatment options (4·8 months vs. 1·9 months; $P = 0·009$) and increased ORR (22% vs. 2%; $P = 0·0019$) (Hess *et al*, 2009). Although thrombocytopenia, asthenia and diarrhoea occurred more often with temsirolimus than the investigator's choice ($P \leq 0·041$), the overall safety profile was considered manageable. Based on these results, temsirolimus was approved by the European Medicines Agency for the treatment of relapsed/refractory MCL (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000799/WC500039912.pdf).

This phase 2 study was designed to evaluate everolimus efficacy and safety in patients with MCL who were intolerant of or refractory to bortezomib.

Methods

Study design and patients

PILLAR (PIvotaL Lymphoma triAls of RAD001)-1 was a multicentre, open-label, two-stage, single-arm, phase 2 study conducted in the United States (ClinicalTrials.gov identifier NCT00702052). Inclusion criteria included age ≥18 years; histopathologically confirmed (central pathology review) MCL with staining for cyclin D1 overexpression or cytogenetic evidence of the t(11;14)(q13;q32) translocation, documented bortezomib-refractory disease or bortezomib intolerance and receipt of ≥1 other antineoplastic agent given either separately or with bortezomib. Patients were considered bortezomib refractory if they had documented radiological progression on or within 12 months of the last bortezomib dose when given alone or as the last component of combination therapy including bortezomib. Patients were considered bortezomib intolerant if they discontinued bortezomib due to documented toxicity. Other inclusion criteria included ≥1 nodal site of measurable disease >2·0 cm; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; life expectancy ≥3 months; and adequate bone marrow, hepatic and renal function. Exclusion criteria included unresolved grade 3/4 toxicity from antineoplastic therapies, anticancer therapy or other investigational agent taken within 4 weeks of study start, previous mTOR inhibitor treatment, previous allogeneic stem cell transplant, presence or history of central nervous system lymphoma, chronic immunosuppressive therapy

excluding topical or inhaled corticosteroids and any active bleeding diathesis or other serious and/or uncontrolled medical condition.

This study was conducted in accordance with the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice, applicable local regulations and the Declaration of Helsinki. The protocol and all amendments were reviewed and approved by the institutional review board of each centre. All patients provided written informed consent before enrolment.

Procedures

Patients received oral everolimus 10 mg once daily until disease progression per investigator review, unacceptable toxicity, death or discontinuation for other reason. Dose reductions and/or interruptions according to an algorithm outlined in the study protocol were permitted for intolerable toxicity.

Computed tomography scan of the chest, abdomen and pelvis with radiological tumour evaluation was performed at screening, every 8 weeks (±1 week) for the first year of study treatment and every 12 weeks (±1 week) thereafter until initiation of new anticancer therapy. Response was also assessed at end of treatment. Adverse events (AEs) were monitored continuously throughout the study and for 28 d after the last study drug dose. Serum chemistry, coagulation, complete blood count (CBC) and serum lipid profiles were assessed at baseline, every 4 weeks during treatment and at the end of treatment. Routine CBCs were also assessed every 2 weeks for the first 12 weeks. All patients were followed monthly for survival until the date of final analysis (20 April, 2012).

Venous blood samples (2 ml) for pharmacokinetic analysis were collected in EDTA-containing tubes pre-dose on day 15 and at times of tumour assessment to assess everolimus trough concentrations (C_{min}). Samples were also collected at 1 and 2 h post-dose on day 15 to capture the near-maximum everolimus concentration (C_{max}). If samples were not obtained at the specified visit, they were collected at the next scheduled visit. On days of sample collection, everolimus administration was supervised by study centre personnel. All blood samples were stored at −20°C within 1 h of collection. Everolimus concentrations in whole blood were determined at a central laboratory (WuXi Apptec, Shanghai, China) using a liquid chromatography-mass spectrometry method following liquid extraction (lower limit of quantification, 0·3 ng/ml).

Statistical analysis

Efficacy was assessed in the full analysis set (i.e. all patients who received ≥1 dose of study drug). Safety was assessed in the safety set (i.e. all patients who received ≥1 dose of study drug and had ≥1 valid postbaseline safety assessment).

The primary study endpoint was ORR, assessed by the investigator and defined as the percentage of patients with a complete response (CR) or partial response (PR) according to response criteria for malignant lymphoma based on Cheson (Cheson *et al*, 1999; Cheson, 2007). Sensitivity analyses were based on central radiology review. Secondary endpoints included duration of response (DOR), PFS, OS and safety and tolerability. DOR was defined as the time from first documented response (CR or PR) to the time of first documented progression or death due to lymphoma; patients without disease progression or who died from causes other than lymphoma were censored (indicated by "+") at the time of last valid tumour assessment. PFS was defined as the time from start of study treatment to the time of first documented disease progression or death due to any cause; patients were censored at the time of last valid tumour assessment in the absence of progression or death. OS was defined as the time from start of study treatment to the time of death due to any cause; patients lost to follow-up or alive at the analysis cut-off date were censored at their last contact date. AEs and laboratory abnormalities were assessed according to the Common Terminology Criteria for Adverse Events, version 3·0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

The Kaplan-Meier method was used to analyse time-to-event endpoints and to estimate median values and corresponding 95% confidence intervals (CIs). A Cox proportional model was used to analyse the relationship between average C_{min} and time to disease progression and select AEs. Average C_{min} was calculated as a time average over the trial period until the event, accounting for dose adjustments.

Simon's 2-stage minimax design was adopted to permit early termination for futility. The targeted ORR in the full analysis set was 20%; an ORR ≤7% would preclude further investigation. Assuming a 5% significance level and 90% power, 34 patients were to receive study treatment in the first stage. If ≤2 patients achieved response, the study was to be terminated. Otherwise, 23 additional patients were to be enrolled and receive treatment. If ≥8/57 enrolled patients experienced a response, everolimus would be considered of clinical interest in this population.

Role of the funding source

The sponsor helped to design the study and to collect, analyse and interpret the data and provided funding for medical writing assistance in the preparation of this report. As authors, employees of the sponsor contributed to the decision to submit the manuscript. All authors had access to the data and approved the manuscript for submission.

Results

Between 22 August, 2008, and 18 January, 2011, 58 patients were enrolled from 26 centres in the United States and

received ≥1 everolimus dose. Table I shows the baseline demographics and disease characteristics of the patients. Forty-nine patients (84·5%) were bortezomib refractory and eight patients (13·8%) were intolerant of bortezomib; one patient could not be classified as either because disease progression occurred >12 months after the last bortezomib dose. At initial diagnosis, 19·0% and 67·2% of patients presented with stage III and IV disease, respectively. Before enrolment, all patients received >1 antineoplastic therapy, including 74·1% who received ≥3 and 20·7% who received ASCT. All patients were included in both the full analysis and safety sets. Median follow-up duration (time from median treatment start date to final analysis date [20 April, 2012]) was 23·2 months. At final analysis, all patients discontinued treatment, most commonly because of disease progression or AEs (Table II). After study drug discontinuation, 42 patients (72·4%) received further antineoplastic therapy.

As of 26 April, 2010, stage 1 was declared successful, with 3/26 enrolled patients achieving PR per investigator review (before the 34-patient target); this permitted uninterrupted recruitment in stage 2. At final analysis and per investigator review, best overall response was PR in 5 patients (ORR 8·6%; 90% CI 3·5–17·3%) (Table III). DOR ranged from 0·7–11·1+ months. Four patients proceeded to stem cell transplantation following study completion (allogeneic transplantation, $n = 3$; unknown type, $n = 1$). Median PFS per investigator review was 4·4 months (95% CI 3·5–6·1 months) (Fig. 1A). Median OS was 16·9 months (95% CI 14·4–29·9) (Fig. 1B).

In a sensitivity analysis based on central radiology review, six patients achieved PR (ORR 10·3%; 90% CI 4·6–19·4%) (Table III). Per central review, DOR ranged from 1·6+ months to 13·2+ months and median PFS was 5·2 months (95% CI 4·0–7·1 months).

Median everolimus treatment duration and dose intensity were 87·0 d and 9·2 mg/d, respectively. Dose interruptions and/or reductions were required by 34 patients (58·6%), most commonly as the result of AEs (55·2%). All patients experienced ≥1 AE, including 81·0% who experienced ≥1 grade 3/4 AE (Table IV). Grade 3/4 non-haematological AEs occurred in 70·7% of patients and included pneumonia (8·6%), abdominal pain (8·6%) and fatigue (6·9%). Pneumonitis of all grades occurred in 7 patients (12·1%), with a greatest severity of grade 3 ($n = 3$; 5·2%); 3 of these 7 patients discontinued everolimus. Based on laboratory values, 57 patients (98·3%) experienced a haematological AE, including 23 (39·7%) who experienced a grade 3/4 event (Table V). The most frequently reported haematological laboratory abnormality was anaemia (84·5% any grade, 8·6% grade 3/4), followed by thrombocytopenia (75·9% any grade, 13·8% grade 3/4). Seven deaths (all due to lymphoma) occurred within 28 days of the last everolimus dose.

Everolimus C_{min} values, assessed by actual dose at time of assessment, were mostly stable over time, although fluctuation

Table I. Baseline patient demographics and disease history in the full analysis set.

	Everolimus $N = 58$
Age in years, median (range)	68·0 (50·0–83·0)
Age, years	
<65	23 (39·7)
≥65	35 (60·3)
Gender	
Male	45 (77·6)
Female	13 (22·4)
Race	
White	52 (89·7)
Black	3 (5·2)
Asian	1 (1·7)
Other	2 (3·4)
Eastern Cooperative Oncology Group performance status	
0	25 (43·1)
1	31 (53·4)
≥2	2 (3·5)
Bulk >10 cm at initial diagnosis	10 (17·2)
Bortezomib refractory or intolerant	
Refractory	49 (84·5)
Intolerant	8 (13·8)
Neither	1 (1·7)
Lactate dehydrogenase ≥ upper limit of normal	7 (12·1)
Time since initial diagnosis	
Median (range), months	55·5 (8·2–136·3)
>6 months to ≤2 years	8 (13·8)
>2 years to ≤5 years	24 (41·4)
>5 years	26 (44·8)
Time since most recent recurrence/relapse	
≤6 months	53 (91·4)
>6 months to ≤12 months	3 (5·2)
>12 months	2 (3·4)
Stage at initial diagnosis	
IA/IB	1 (1·7)/1 (1·7)
IIA	2 (3·4)
IIIA/B	9 (15·5)/2 (3·4)
IVA/B	30 (51·7)/9 (15·5)
Missing	4 (6·9)
MIPI risk	
Low (score <5·7)	28 (48·3)
Intermediate (score ≥5·7 to <6·2)	23 (39·7)
High (score ≥6·2)	7 (12·1)
Number of organs involved other than lymph nodes	
0	32 (55·2)
1	22 (37·9)
2	4 (6·9)
Prior lymphoma bone marrow tumour involvement	39 (67·2)
Number of previous treatment regimens	
1	0
2	15 (25·9)
3	20 (34·5)
>3	23 (39·7)

Table I. (*Continued*)

	Everolimus $N = 58$
Prior antineoplastic therapy	58 (100)
Chemotherapy	58 (100)
1 regimen	19 (32·8)
2 regimens	16 (27·6)
≥3 regimens	23 (39·7)
Surgery	12 (20·7)
Rituximab	57 (98·3)
Radiotherapy	14 (24·1)
Autologous stem cell transplant	12 (20·7)

MIPI, Mantle Cell Lymphoma International Prognostic Index.
Data are given as number (%) unless otherwise stated.

Table II. Patient disposition as of 20 April, 2012.

	Everolimus $N = 58$
Discontinued study treatment	58 (100)
Disease progression	30 (51·7)
Adverse events(s)	23 (39·7)
Subject withdrew consent	5 (8·6)
Entered post-treatment evaluation	40 (69·0)
Discontinued from post-treatment evaluation	40 (100*)
New anticancer therapy	32 (80·0*)
Death	5 (12·5*)
Administrative reasons	3 (7·5*)

Data are given as number (%).
*Denominator is the number of patients who discontinued the post-treatment evaluation period.

Table III. Best overall response per investigator and central review in the full analysis set.

	Everolimus $N = 58$	
Best overall response	Investigator review	Central review
Overall response rate, % (90% CI*)	8·6 (3·5–17·3)	10·3 (4·6–19·4)
Complete response	0	0
Partial response	5 (8·6)	6 (10·3)
Stable disease	35 (60·3)	30 (51·7)
Progressive disease	8 (13·8)	9 (15·5)
Unknown	10 (17·2)	13 (22·4)

Data are given as number (%) unless otherwise stated.
*Exact (Clopper Pearson) 90% confidence interval (CI).

during the first 12 weeks was observed among patients receiving everolimus 10 mg/d (Fig. 2). An approximately dose-proportional increase in steady state C_{max} from everolimus 5 mg/d to 10 mg/d was noted (median [range] 23·7 [17·1–30·2] ng/ml and 49·0 [17·2–103·0] ng/ml, respectively). Cox proportional hazards analysis showed no significant

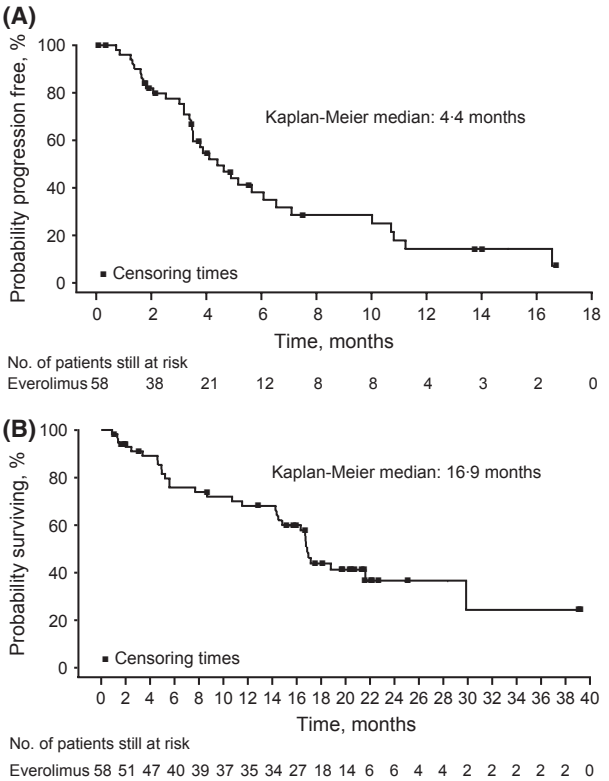

Fig 1. Progression-free survival based on local radiology review (A) and overall survival (B) in the full analysis set.

relationship between time-normalized C_{min} and risk of disease progression (risk ratio for twofold C_{min} increase 0·708; 95% CI 0·297–1·685) or risk of experiencing selected clinically notable AEs (i.e. elevated creatinine, infections and infestations, neutropenia, non-infectious pneumonitis, renal events, stomatitis and thrombocytopenia [data not shown]). Caution should be used when the exposure-safety results are interpreted because of the low incidence of certain AEs.

Discussion

In the phase 2 PILLAR-1 study of 58 patients with heavily pretreated MCL refractory to or intolerant of bortezomib, 5 patients experienced PR with everolimus, which was below the targeted ≥8 responses out of 57 patients required to declare everolimus worthy of further study in this population. The ORR was 8·6% (90% CI 3·5–17·3%), which was lower than the 32% (Witzig *et al*, 2011) and 20% (Renner *et al*, 2012) ORRs reported in other phase 2 studies of everolimus for previously treated MCL, the 41% (Ansell *et al*, 2008) and 38% (Witzig *et al*, 2005) ORRs reported in the phase 2 studies of temsirolimus and the 22% ORR reported in the phase 3 temsirolimus study (Hess *et al*, 2009). It is interesting to note that, although median PFS in PILLAR-1 was less than that reported in the phase 2 study of temsirolimus published by Witzig *et al* (2005) (4·4 months and 6·5 months, respectively), it was similar to

Table IV. Non-haematological adverse events occurring in >10% of patients regardless of relationship to study drug in the safety set.

	Everolimus $N = 58$		
	All grades	Grade 3	Grade 4
Any adverse event	58 (100)	35 (60·3)	12 (20·7)
Diarrhoea	26 (44·8)	3 (5·2)	0
Fatigue	25 (43·1)	4 (6·9)	0
Nausea	16 (27·6)	0	0
Peripheral oedema	16 (27·6)	1 (1·7)	0
Rash	16 (27·6)	2 (3·4)	0
Dyspnoea	14 (24·1)	3 (5·2)	0
Decreased appetite	13 (22·4)	1 (1·7)	0
Abdominal pain	12 (20·7)	4 (6·9)	1 (1·7)
Cough	12 (20·7)	0	0
Pyrexia	12 (20·7)	1 (1·7)	0
Stomatitis	12 (20·7)	1 (1·7)	0
Headache	11 (19·0)	2 (3·4)	0
Pneumonia	10 (17·2)	5 (8·6)	0
Vomiting	10 (17·2)	1 (1·7)	0
Arthralgia	9 (15·5)	0	0
Asthenia	9 (15·5)	3 (5·2)	0
Constipation	9 (15·5)	0	0
Dizziness	9 (15·5)	0	0
Dysgeusia	8 (13·8)	0	0
Hyperglycaemia	8 (13·8)	3 (5·2)	1 (1·7)
Weight decreased	8 (13·8)	1 (1·7)	0
Dry mouth	7 (12·1)	0	0
Epistaxis	7 (12·1)	0	0
Pneumonitis	7 (12·1)	3 (5·2)	0
Upper respiratory tract infection	7 (12·1)	0	0
Back pain	6 (10·3)	1 (1·7)	0
Dehydration	6 (10·3)	2 (3·4)	0
Hypercholesterolaemia	6 (10·3)	1 (1·7)	1 (1·7)
Insomnia	6 (10·3)	0	0
Oropharyngeal pain	6 (10·3)	0	0
Pain in extremity	6 (10·3)	0	0
Blurred vision	6 (10·3)	0	0

Data are given as number (%).

Table V. Haematological laboratory abnormalities regardless of relationship to study drug in the safety set.

	Everolimus $N = 58$		
	All grades	Grade 3	Grade 4
Any	57 (98·3)	12 (20·7)	11 (19·0)
Anaemia	49 (84·5)	4 (6·9)	1 (1·7)
Thrombocytopenia	44 (75·9)	4 (6·9)	4 (6·9)
White blood cells decreased	37 (63·8)	7 (12·1)	1 (1·7)
Lymphopenia	32 (55·2)	9 (15·5)	4 (6·9)
Neutropenia	28 (48·3)	4 (6·9)	4 (6·9)

Data are given as number (%).

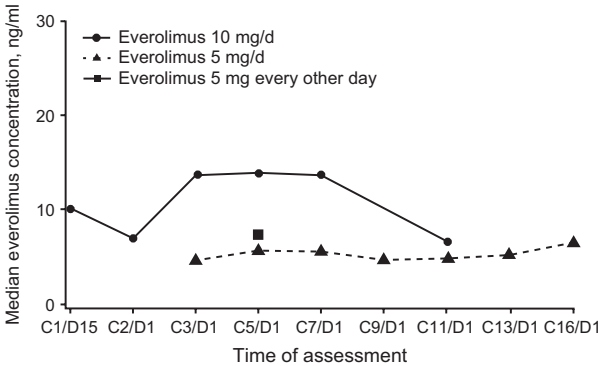

Fig 2. Longitudinal everolimus C_{min} values by actual dose at the time of sampling in the safety set. Aside from Cycle (C) 5, Day (D) 1, no patients were receiving everolimus 5 mg every other day at the time of assessment; therefore, only 1 data point is available for this dosage.

that reported by Hess *et al* (2009) for the 175/75-mg temsirolimus regimen in the phase 3 trial (4·8 months). The PFS observed in PILLAR-1 was also similar to the 4·0-month median PFS recently reported in the phase 2 EMERGE study of lenalidomide for patients who relapsed after or were refractory to bortezomib (Goy *et al*, 2013). Additionally, the median OS in PILLAR-1 was longer than that reported in any of the temsirolimus trials (16·9 months vs. 12 months (Witzig *et al*, 2005), 14 months (Ansell *et al*, 2008) and 12·8 months with temsirolimus 175/75 mg (Hess *et al*, 2009)). Although it is not clear why the PILLAR-1 ORR was lower than in other studies of mTOR inhibitors in this setting, it is possible that the enrolment of a high percentage of patients with bortezomib-refractory disease (84·5%) resulted in a more heavily pretreated, higher-risk population than that enrolled in previous studies of mTOR inhibitors for relapsed/refractory MCL. Only 23% of patients in the phase 3 temsirolimus study had prior bortezomib therapy (Hess *et al*, 2009). Although not reported, the percentage of patients previously treated with bortezomib in the phase 2 temsirolimus trials was probably very low because these studies were conducted before bortezomib was approved for treating MCL (Witzig *et al*, 2005; Ansell *et al*, 2008). In PILLAR-1, 74·1% of patients received ≥3 previous treatment regimens, similar to the 78·3% of patients enrolled in the EMERGE study who received ≥3 previous treatment regimens (Goy *et al*, 2013). In the trials of temsirolimus, the median number of therapies ranged from 3 (Witzig *et al*, 2005; Hess *et al*, 2009) to 4 (Ansell *et al*, 2008). Compared with the phase 2 temsirolimus trial published by Witzig *et al* (2005), almost twice as many patients in PILLAR-1 had undergone previous ASCT (11% vs. 20·7%).

It is also clear that MCL is a very heterogeneous disease. Previous studies (Rosenwald *et al*, 2003; Katzenberger *et al*, 2008) have shown that the proliferation index can be used to sub-classify MCL into different clinical and prognostic entities. Patients with more proliferative disease, as determined

by gene expression profiling or Ki-67 staining, are known to have a worse prognosis and more aggressive disease. Patients with a lower proliferative index are known to have a substantially better prognosis and may be managed in a manner similar to those with other indolent lymphomas (Martin & Leonard, 2011). Given this biological diversity, it is conceivable that variability in the proportion of patients with highly versus less proliferative disease could influence the outcome of a drug known to have a marked impact on this underlying biology.

Another possible explanation related to MCL heterogeneity is that fewer patients in PILLAR-1 may have had disease with constitutive mTOR pathway activation, rendering them less responsive to mTOR inhibition with everolimus. Although predictive biomarkers for efficacy of mTOR inhibitors in lymphoma have not been clearly established, preclinical data suggest that tumour cells with constitutive mTOR pathway activation are more responsive to mTOR inhibitors (Di Nicolantonio *et al*, 2010; Weigelt *et al*, 2011; Meric-Bernstam *et al*, 2012). Supportive clinical data come from whole genome and capture-based sequencing performed on DNA samples collected from 14 patients enrolled in a phase 2 study of everolimus for metastatic bladder cancer (Iyer *et al*, 2012). In that study, patients whose tumours harboured mutations in *TSC1*, a gene encoding one half of the hamartin/tuberin tumour suppressor complex that lies upstream of mTOR, had a longer duration of everolimus therapy than those with *TSC1* wild-type tumours (7·7 vs. 2·0 months; $P = 0{\cdot}004$) and a significantly longer time to recurrence (4·1 vs. 1·8 months; $P = 0{\cdot}001$).

Everolimus demonstrated acceptable tolerability in this heavily pretreated, bortezomib-refractory/intolerant population, with no new safety findings. The toxicities observed were similar to those previously reported in patients receiving mTOR inhibitors, were reversible and were effectively managed with either dose adjustment or use of supportive therapies. The incidence of grade 3/4 non-haematological AEs in this study (70·7%) was somewhat higher than that reported by Witzig *et al* (2011) (53%), although the incidence of the most commonly observed grade 3/4 AEs was similar (Witzig *et al*, 2011). Conversely, the incidence of grade 3/4 haematological AEs in this study (39·7% as assessed by laboratory abnormalities) was somewhat less than the 56% incidence reported by Witzig *et al* (2011). Additionally, rates of grade 3/4 thrombocytopenia, neutropenia and anaemia in PILLAR-1 (13·8%, 13·8% and 8·6%, respectively) compare favourably with those reported previously (38%, 18% and 14%, respectively) (Witzig *et al*, 2011). Individual grade 3/4 haematological AEs were also more common in the trials of temsirolimus for MCL, with 39–66% of patients experiencing thrombocytopenia, 14–26% experiencing anaemia and 15–29% experiencing neutropenia (Witzig *et al*, 2005; Ansell *et al*, 2008; Hess *et al*, 2009).

Although PILLAR-1 demonstrated moderate clinical activity for everolimus monotherapy in bortezomib-refractory or intolerant MCL, the activity observed in this study and previously noted with other mTOR inhibitors (Witzig *et al*, 2005, 2011; Ansell *et al*, 2008; Hess *et al*, 2009; Renner *et al*, 2012) suggests a possible role for mTOR inhibition in MCL. It is possible that everolimus may demonstrate improved efficacy in a less refractory population or in patients whose disease demonstrates constitutive mTOR pathway activity. Given the profound prognostic impact of the proliferation index in MCL and the likelihood that different MCL subsets will respond differently to drugs targeting pathways involved in cellular proliferation, future MCL studies should include some measurement of the proliferation index. Combination therapy with everolimus should also be considered. In human MCL cell lines, synergistic cytotoxic activity was observed when everolimus was combined with various agents already used to treat MCL, including doxorubicin, vincristine, paclitaxel, rituximab, bortezomib and vorinostat (Haritunians *et al*, 2007). Preclinical data from human MCL cell lines also suggest that simultaneously inhibiting PI3K and mTOR could lead to more effective MCL treatment (Civallero *et al*, 2012; Kim *et al*, 2012). Data from clinical trials of temsirolimus-based combination therapy appear to confirm the merit of assessing everolimus-based combinations. In a phase 2 study of patients with relapsed or refractory MCL, temsirolimus plus rituximab was associated with acceptable tolerability, provided an ORR of 59·4% and median time to progression of 9·7 months and was associated with a median OS of 29·5 months (Ansell *et al*, 2011). Preliminary data from a phase I/II study also suggest a possible benefit for the combination of temsirolimus, bendamustine and rituximab (Hess *et al*, 2011). Ongoing trials are assessing temsirolimus in combination with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), R-FC (rituximab, fludarabine, cyclophosphamide) or R-DHA (rituximab, high-dose cytarabine, dexamethasone (NCT01389427); bortezomib, rituximab and dexamethasone (NCT01381692); and lenalidomide (NCT01076543); everolimus is being assessed in combination with panobinostat (NCT00918333 and NCT00967044), idelalisib (NCT01088048) and lenalidomide (NCT01075321).

In conclusion, everolimus monotherapy demonstrated modest activity and acceptable tolerability in patients with heavily pretreated, bortezomib-refractory or -intolerant MCL. Future studies exploring everolimus as monotherapy in a less refractory population or in combination with chemotherapy or other targeted therapies for refractory MCL are warranted.

Author contributions

Designed the study: MW, PBJ, AR, WC, OAO; Conducted research: MW, NLB, JL, JTB, OAO; Conducted literature search: MW, MSK, OAO; Recruited/enrolled/treated patients: MW, LLP, RHC, JNW, AG, MSK, NLB, PBJ, JL, SRF, JMT, JTB, HK, OAO; Participated in trial conduct: JF; Oversaw data collection: MW, JL, JTB, AR, AC; Collected data: MW,

LLP, RHC, JNW, AG, NLB, PBJ, JL, JTB, JK, OAO; Analysed data: MW, LLP, NLB, JL, JTB, JK, WC, AC, OAO; Interpreted data: MW, LLP, JTB, AR, JF, JK, AC, OAO; Wrote manuscript: MW, LLP, AR, JF, WC, AC, OAO; Edited/reviewed manuscript: MW, LLP, RHC, JNW, AG, MSK, NLB, PBJ, JL, SRF, JMT, JTB, HK, AR, JF, JK, WC, AC, OAO; All authors approved the final draft of the manuscript.

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Conflict of interest

Funding for this work was provided by Novartis Pharmaceuticals Corporation. MW has received research grants from Celgene, Novartis, Janssen, Pharmacyclics, Millennium and Onyx. JNW's institution has received research funding from Novartis, and her spouse has a consultancy relationship with Novartis. NLB's institution has received a research grant from Novartis. PBJ has participated on an advisory board for Novartis. JTB's institution has received a research grant from Novartis. AR, JF, WC and AC are employees of and own stock in Novartis. JK is an employee of Novartis. OAO has received research grants from Celgene, Novartis, Janssen, Pharmcyclics, Millennium and Onyx; has participated on an advisory committee for Allos Therapeutics, Millennium, Mundipharma International Ltd, Onyx Pharmaceuticals and Spectrum Pharmaceuticals; and has a consulting agreement with Celgene and Millennium. LLP, RHC, AG, MSK, JL, SRF and HK declare no conflicts of interest.

References

Ansell, S.M., Inwards, D.J., Rowland, K.M. Jr, Flynn, P.J., Morton, R.F., Moore, D.F. Jr, Kaufmann, S.H., Ghobrial, I., Kurtin, P.J., Maurer, M., Allmer, C. & Witzig, T.E. (2008) Low-dose, single-agent temsirolimus for relapsed mantle cell lymphoma: a phase 2 trial in the North Central Cancer Treatment Group. *Cancer*, **113**, 508–514.

Ansell, S.M., Tang, H., Kurtin, P.J., Koenig, P.A., Inwards, D.J., Shah, K., Ziesmer, S.C., Feldman, A.L., Rao, R., Gupta, M., Erlichman, C. & Witzig, T.E. (2011) Temsirolimus and rituximab in patients with relapsed or refractory mantle cell lymphoma: a multi-center phase 2 study. *Lancet Oncology*, **12**, 361–368.

Bjornsti, M.A. & Houghton, P.J. (2004) The TOR pathway: a target for cancer therapy. *Nature Reviews – Cancer*, **4**, 335–348.

Cheson, B.D. (2007) The International Harmonization Project for response criteria in lymphoma clinical trials. *Hematology and Oncology Clinics of North America*, **21**, 841–854.

Cheson, B.D., Horning, S.J., Coiffier, B., Shipp, M.A., Fisher, R.I., Connors, J.M., Lister, T.A., Vose, J., Grillo-Lopez, A., Hagenbeek, A., Cabanillas, F., Klippensten, D., Hiddemann, W., Castellino, R., Harris, N.L., Armitage, J.O., Carter, W., Hoppe, R. & Canellos, G.P. (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *Journal of Clinical Oncology*, **17**, 1244.

Civallero, M., Cosenza, M., Marcheselli, L., Pozzi, S. & Sacchi, S. (2012) NVP-BEZ235 alone and in combination in mantle cell lymphoma: an effective therapeutic strategy. *Expert Opinion on Investigational Drugs*, **21**, 1597–1606.

Cohen, P.L., Kurtin, P.J., Donovan, K.A. & Hanson, C.A. (1998) Bone marrow and peripheral blood involvement in mantle cell lymphoma. *British Journal of Haematology*, **101**, 302–310.

Dal, C.J., Zancai, P., Terrin, L., Guidoboni, M., Ponzoni, M., Pavan, A., Spina, M., Bergamin, S., Rizzo, S., Tirelli, U., De Rossi, A., Doglioni, C. & Dolcetti, R. (2008) Distinct functional significance of Akt and mTOR constitutive activation in mantle cell lymphoma. *Blood*, **111**, 5142–5151.

Di Nicolantonio, F., Arena, S., Tabernero, J., Grosso, S., Molinari, F., Macarulla, T., Russo, M., Cancelliere, C., Zecchin, D., Mazzucchelli, L., Sasazuki, T., Shirasawa, S., Geuna, M., Frattini, M., Baselga, J., Gallicchio, M., Biffo, S. & Bardelli, A. (2010) Deregulation of the PI3K and KRAS signaling pathways in human cancer cells determines their response to everolimus. *Journal of Clinical Investigation*, **120**, 2858–2866.

Dreyling, M., Thieblemont, C., Gallamini, A., Arcaini, L., Campo, E., Hermine, O., Kluin-Nelemans, J.C., Ladetto, M., Le Gouill, S., Iannitto, E., Pileri, S., Rodriguez, J., Schmitz, N., Wotherspoon, A., Zinzani, P. & Zucca, E. (2013) ESMO consensus conferences: guidelines on malignant lymphoma. Part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. *Annals of Oncology*, **24**, 857–877.

Fisher, R.I., Bernstein, S.H., Kahl, B.S., Djulbegovic, B., Robertson, M.J., de Vos, S., Epner, E., Krishnan, A., Leonard, J.P., Lonial, S., Stadtmauer, E.A., O'Connor, O.A., Shi, H., Boral, A.L. & Goy, A. (2006) Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *Journal of Clinical Oncology*, **24**, 4867–4874.

Galimberti, S. & Petrini, M. (2010) Temsirolimus in the treatment of relapsed and/or refractory mantle cell lymphoma. *Cancer Management and Research*, **2**, 181–189.

Goy, A., Bernstein, S.H., Kahl, B.S., Djulbegovic, B., Robertson, M.J., de Vos, S., Epner, E., Krishnan, A., Leonard, J.P., Lonial, S., Nasta, S., O'Connor, O.A., Shi, H., Boral, A.L. & Fisher, R.I. (2009) Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. *Annals of Oncology*, **20**, 520–525.

Goy, A., Sinha, R., Williams, M.E., Besisik, S.K., Drach, J., Ramchandren, R., Zhang, L., Cicero, S., Fu, T. & Witzig, T.E. (2013) Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. *Journal of Clinical Oncology*, **31**, 3688–3695.

Haritunians, T., Mori, A., O'Kelly, J., Luong, Q.T., Giles, F.J. & Koeffler, H.P. (2007) Antiproliferative activity of RAD001 (everolimus) as a single agent and combined with other agents in mantle cell lymphoma. *Leukemia*, **21**, 333–339.

Hess, G., Herbrecht, R., Romaguera, J., Verhoef, G., Crump, M., Gisselbrecht, C., Laurell, A., Offner, F., Strahs, A., Berkenblit, A., Hanushevsky, O., Clancy, J., Hewes, B., Moore, L. & Coiffier, B. (2009) Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. *Journal of Clinical Oncology*, **27**, 3822–3829.

Hess, G., Keller, U., Atta, J., Buske, C., Borchmann, P., Medler, C., Witzens-Harig, M. & Dreyling, M.H. (2011) Temsirolimus in combination with bendamustine and rituximab for the treatment of relapsed mantle cell and follicular lymphoma: report of an ongoing phase I/II trial. *Blood* (ASH Annual Meeting Abstracts), **118**, 2697.

Iyer, G., Hanrahan, A.J., Milowsky, M.I., Al-Ahmadie, H., Scott, S.N., Janakiraman, M., Pirun, M., Sander, C., Socci, N.D., Ostrovnaya, I., Viale, A., Heguy, A., Peng, L., Chan, T.A., Bochner, B., Bajorin, D.F., Berger, M.F., Taylor, B.S. & Solit, D.B. (2012) Genome sequencing identifies a basis for everolimus sensitivity. *Science*, **338**, 221.

Katzenberger, T., Kienle, D., Stilgenbauer, S., Holler, S., Schilling, C., Mader, U., Puppe, B., Petzoldt, C., Sander, S., Bullinger, L., Stocklein, H., Kalla, J., Hartmann, E., Adam, P., Ott, M.M., Muller-Hermelink, H.K., Rosenwald, A. & Ott, G. (2008) Delineation of distinct tumour profiles in mantle cell lymphoma by detailed cytogenetic, interphase genetic and morphological analysis. *British Journal of Haematology*, **142**, 538–550.

Kim, A., Park, S., Lee, J.E., Jang, W.S., Lee, S.J., Kang, H.J. & Lee, S.S. (2012) The dual PI3K and mTOR inhibitor NVP-BEZ235 exhibits anti-proliferative activity and overcomes bortezomib resistance in mantle cell lymphoma cells. *Leukemia Research*, **36**, 912–920.

Martin, P. & Leonard, J. (2011) Is there a role for "watch and wait" in patients with mantle cell lymphoma? *Seminars in Hematology*, **48**, 189–193.

Meric-Bernstam, F., Akcakanat, A., Chen, H., Do, K.A., Sangai, T., Adkins, F., Gonzalez-Angulo, A.M., Rashid, A., Crosby, K., Dong, M., Phan, A.T., Wolff, R.A., Gupta, S., Mills, G.B. & Yao, J. (2012) PIK3CA/PTEN mutations and Akt activation as markers of sensitivity to allosteric mTOR inhibitors. *Clinical Cancer Research*, **18**, 1777–1789.

National Comprehensive Cancer Network, Inc. *NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas*. Version 1. 2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf. Accessed June 27, 2013.

O'Connor, O.A., Moskowitz, C., Portlock, C., Hamlin, P., Straus, D., Dumitrescu, O., Sarasohn, D., Gonen, M., Butos, J., Neylon, E., Hamelers, R., Mac-Gregor, C.B., Blumel, S., Zelenetz, A.D., Gordon, L., Wright, J.J., Vose, J., Cooper, B. & Winter, J. (2009) Patients with chemotherapy-refractory mantle cell lymphoma experience high response rates and identical progression-free survivals compared with patients with relapsed disease following treatment with single agent bortezomib: results of a multicentre Phase 2 clinical trial. *British Journal of Haematology*, **145**, 34–39.

Peponi, E., Drakos, E., Reyes, G., Leventaki, V., Rassidakis, G.Z. & Medeiros, L.J. (2006) Activation of mammalian target of rapamycin signaling promotes cell cycle progression and protects cells from apoptosis in mantle cell lymphoma. *American Journal of Pathology*, **169**, 2171–2180.

Perez-Galan, P., Dreyling, M. & Wiestner, A. (2011) Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. *Blood*, **117**, 26–38.

Renner, C., Zinzani, P.L., Gressin, R., Klingbiel, D., Dietrich, P.Y., Hitz, F., Bargetzi, M., Mingrone, W., Martinelli, G., Trojan, A., Bouabdallah, K., Lohri, A., Gyan, E., Biaggi, C., Cogliatti, S., Bertoni, F., Ghielmini, M., Brauchli, P. & Ketterer, N. (2012) A multicenter phase II trial (SAKK 36/06) of single-agent everolimus (RAD001) in patients with relapsed or refractory mantle cell lymphoma. *Haematologica*, **97**, 1085–1091.

Rizzatti, E.G., Falcão, R.P., Panepucci, R.A., Proto-Siqueira, R., Anselmo-Lima, W.T., Okamoto, O.K. & Zago, M.A. (2005) Gene expression profiling of mantle cell lymphoma cells reveals aberrant expression of genes from the PI3K-AKT, WNT and TGFbeta signalling pathways. *British Journal of Haematology*, **130**, 516–526.

Romaguera, J.E., Medeiros, L.J., Hagemeister, F.B., Fayad, L.E., Rodriguez, M.A., Pro, B., Younes, A., McLaughlin, P., Goy, A., Sarris, A.H., Dang, N.H., Samaniego, F., Brown, H.M., Gagneja, H.K. & Cabanillas, F. (2003) Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. *Cancer*, **97**, 586–591.

Rosenwald, A., Wright, G., Wiestner, A., Chan, W.C., Connors, J.M., Campo, E., Gascoyne, R.D., Grogan, T.M., Muller-Hermelink, H.K., Smeland, E.B., Chiorazzi, M., Giltnane, J.M., Hurt, E.M., Zhao, H., Averett, L., Henrickson, S., Yang, L., Powell, J., Wilson, W.H., Jaffe, E.S., Simon, R., Klausner, R.D., Montserrat, E., Bosch, F., Greiner, T.C., Weisenburger, D.D., Sanger, W.G., Dave, B.J., Lynch, J.C., Vose, J., Armitage, J.O., Fisher, R.I., Miller, T.P., Leblanc, M., Ott, G., Kvaloy, S., Holte, H., Delabie, J. & Staudt, L.M. (2003) The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. *Cancer Cell*, **3**, 185–197.

Rosich, L., Xargay-Torrent, S., Lopez-Guerra, M., Campo, E., Colomer, D. & Roue, G. (2012) Counteracting autophagy overcomes resistance to everolimus in mantle cell lymphoma. *Clinical Cancer Research*, **18**, 5278–5289.

Rudelius, M., Pittaluga, S., Nishizuka, S., Pham, T.H., Fend, F., Jaffe, E.S., Quintanilla-Martinez, L. & Raffeld, M. (2006) Constitutive activation of Akt contributes to the pathogenesis and survival of mantle cell lymphoma. *Blood*, **108**, 1668–1676.

Schatz, J.H. (2011) Targeting the PI3K/AKT/mTOR pathway in non-Hodgkin's lymphoma: results, biology, and development strategies. *Current Oncology Reports*, **13**, 398–406.

Weigelt, B., Warne, P.H. & Downward, J. (2011) PIK3CA mutation, but not PTEN loss of function, determines the sensitivity of breast cancer cells to mTOR inhibitory drugs. *Oncogene*, **2011**, 3222–3233.

Witzig, T.E., Geyer, S.M., Ghobrial, I., Inwards, D.J., Fonseca, R., Kurtin, P., Ansell, S.M., Luyrun, R., Flynn, P.J., Morton, R.F., Dakhil, S.R., Gross, H. & Kaufmann, S.H. (2005) Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. *Journal of Clinical Oncology*, **2005**, 5347–5356.

Witzig, T.E., Reeder, C.B., Laplant, B.R., Gupta, M., Johnston, P.B., Micallef, I.N., Porrata, L.F., Ansell, S.M., Colgan, J.P., Jacobsen, E.D., Ghobrial, I.M. & Habermann, T.M. (2011) A phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma. *Leukemia*, **25**, 341–347.